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Contents

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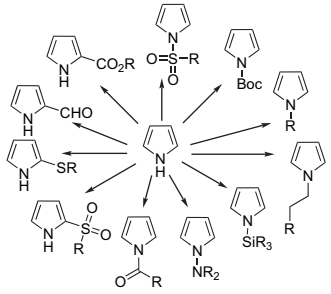

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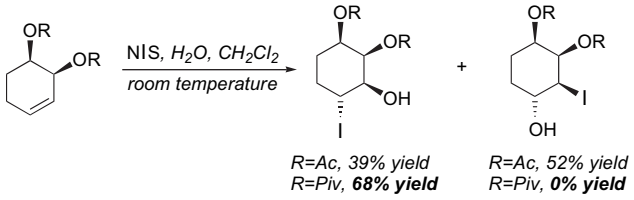
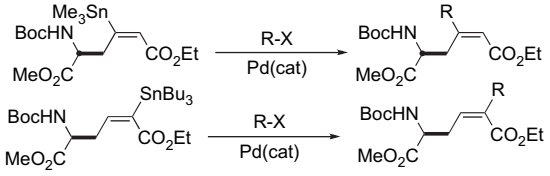
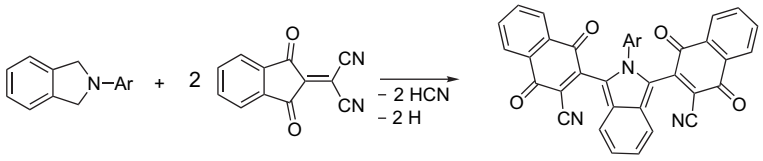
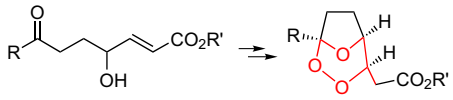
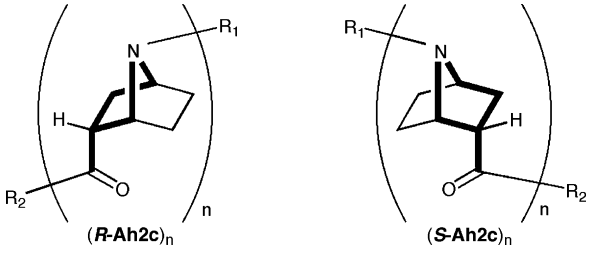
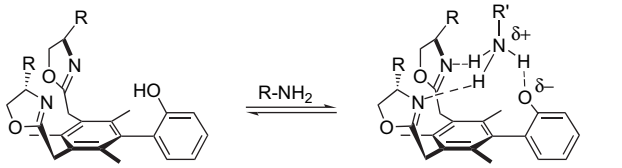


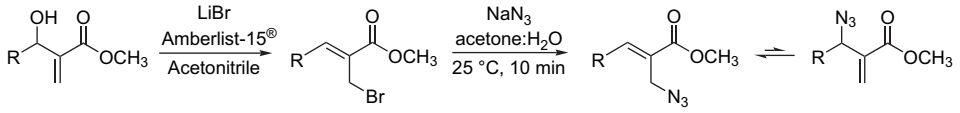




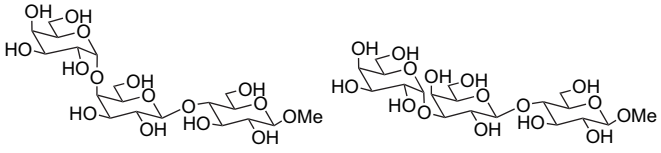


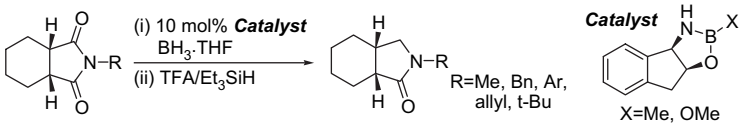


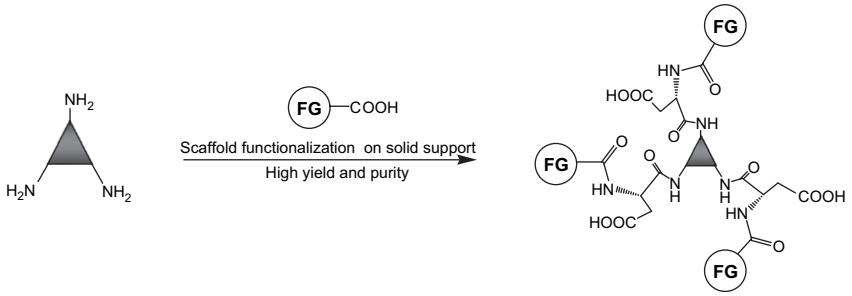


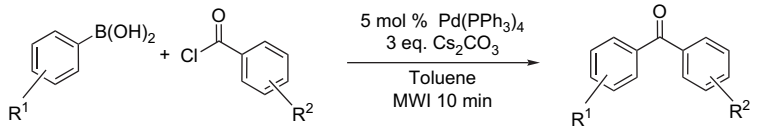


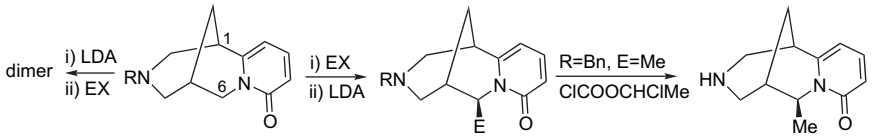
A practical access to alkyl- and aryl-substituted (*E*)-2-(azidomethyl)alkenoates and related azido compounds from the corresponding allylic bromides in aqueous acetone is described. An alternative method to obtain the starting bromides based on heterogeneous catalysis under mild conditions was also investigated.



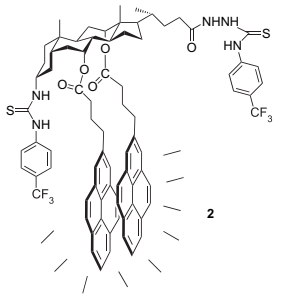


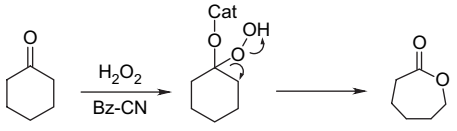


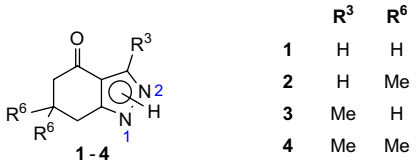




9 examples; yields: 42-98%, 100% C-6β

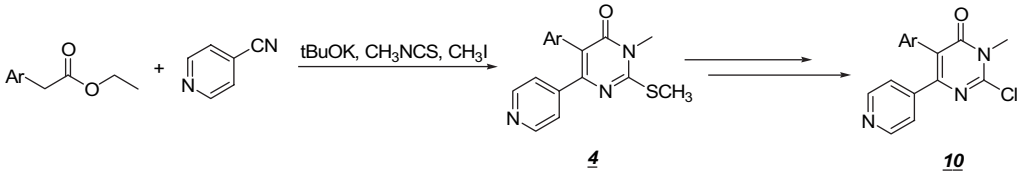


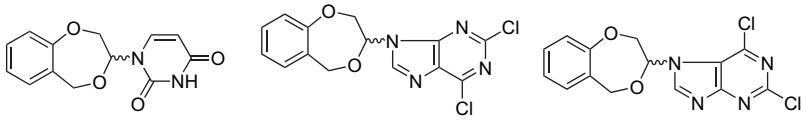


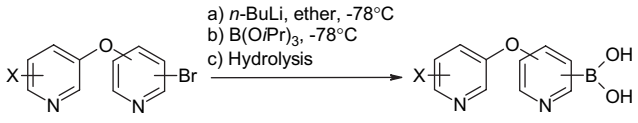


	R^3	R^6
1	H	H
2	H	Me
3	Me	H
4	Me	Me

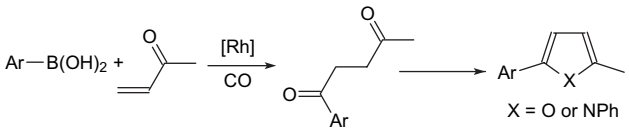
Will 1*H* tautomers be more stable than 2*H* forms?

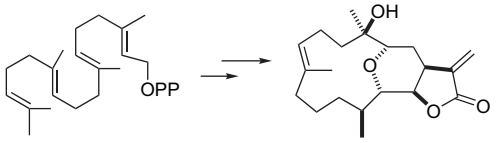




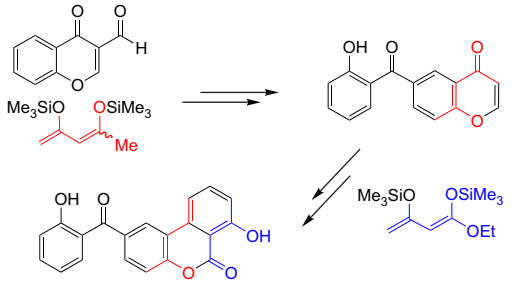


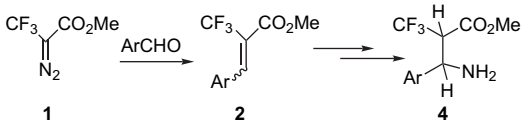
This paper describes the synthesis of novel oxybispyridylboronic acids, which are involved in Suzuki-type cross-coupling reactions leading to pyridylethers of interest in cholinergic medicinal chemistry.

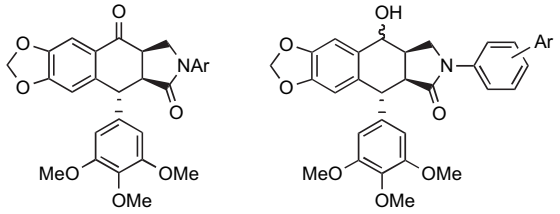


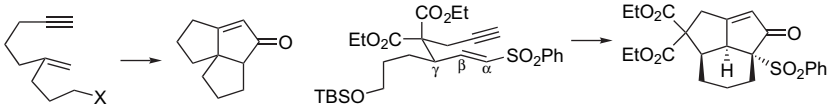


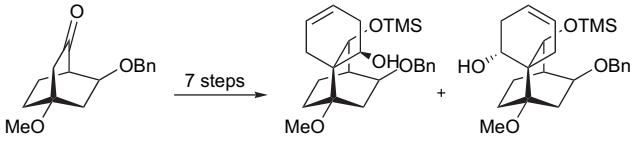
New cytotoxic diterpene cembranes were isolated from *Eunicea mammosa*. Several biogenetic studies using its cell-free extract were performed and a series of analogues were synthesized and evaluated for their cytotoxicity against several cancer cell lines.

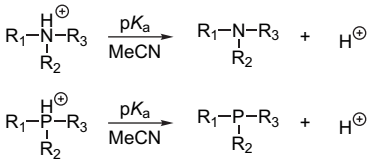


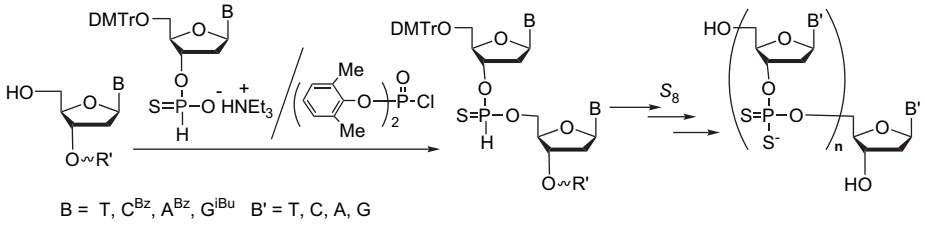


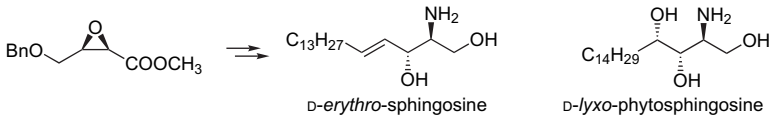












*Corresponding author
Supplementary data available via ScienceDirect

COVER

The photo on the cover represents the leaves and flowers of the leguminosae *Laburnum anagyroïdes* from the seeds of which (−)-cytisine is easily extracted. During the last decade, this alkaloid has been the focus of intense research as a template for the synthesis of new compounds with pharmaceutical interest or as chiral sources for asymmetric synthesis. We report in this article an original regio- and diastereoselective functionalization of (−)-cytisine based on the in situ trapping of a carbanion formed via a carbonyl directed deprotonation. *Tetrahedron* **2006**, *62*, 11679–11686.

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Pyrrole protection

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Contents

1. Introduction

The chemistry of pyrrole and its derivatives is enjoying a relative renaissance of interest due to the growing abundance of pyrrolic components in natural products, pharmaceuticals, and new materials. Pyrrole is the major constituent of naturally occurring tetrapyrroles, such as heme and chlorophyll, the tripyrrolic prodigiosin skeleton, and many alkaloid natural products of varying complexity and biological activity.[1–6] Increasingly, pyrroles are being investigated as potential pharmaceuticals because of their less restricted patent position relative to more common heterocycle skeletons such as indole and imidazole. Moreover, the blockbuster atorvastatin calcium (Lipocor, Lipitor®) is a pentasubstituted pyrrole, and is, the most-prescribed prescription drug for cholesterol lowering.[7] Furthermore, pyrrolic molecules exhibit a wide variety of useful and emerging optical and electronic properties.[1,8–11]

The synthetic chemistry of the pyrrolic unit is dominated by electrophilic aromatic substitution and pyrrole is much more reactive than benzene in this respect, as a result of the lone pair at nitrogen and the consequent stability of σ-complexes (Wheland intermediates, Fig. 1).[10] Polymerization of pyrrole, and substituted pyrroles, is acid-catalyzed and polypyrroles (dark tars) are often the result of the careless management of reactions involving pyrroles. Such reactivity necessitates that a delicate balance[12] be achieved between

Keywords: Pyrrole; Pyrrolic; Protecting group; Protection; Deprotection; Electron withdrawing; Blocking.
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doi:10.1016/j.tet.2006.08.071

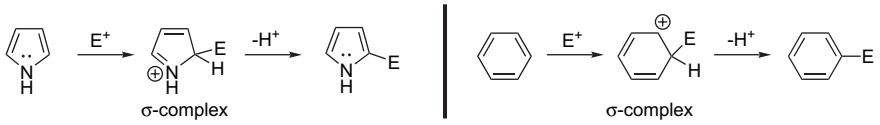


Figure 1. Electrophilic substitution of pyrrole and benzene.

the exploitation of nucleophilicity for required electrophilic aromatic substitution, and the containment of nucleophilicity (through electronic or steric means) to inhibit over-substitution and/or unwanted transformations. Harnessing the reactivity of pyrrole is often achieved by the use of protecting and blocking groups, most usually involving N-substitution (1-substitution) and 2-substitution. Electron-withdrawing groups serve to both lessen nucleophilicity and block certain positions from unwanted substitution. Sterically bulky protecting groups can block the pyrrole to prevent alpha-substitution. Certain groups have been shown to activate the pyrrolic core. As with any useful synthetic protecting group, three criteria must be met: facile introduction; robust reactivity of the protected moiety; and efficient deprotection.

Over the last century, synthetic pyrrole chemistry has played a crucial role in the preparation of porphyrins. The final steps to prepare the porphyrinogenic skeleton typically require large quantities of pyrroles as starting materials, as the reactions can be low yielding and give complex product mixtures. Consequently syntheses and derivatizations of functionalized pyrroles are routinely achieved on multimolar scales using modest laboratory facilities. Many traditional reactions involving pyrroles incorporate harsh acidic or caustic conditions, as well as high reaction temperatures. With the absolute goal of synthesizing porphyrins, the moderate yields from such reaction conditions were tolerated; however, as other needs for pyrroles have surfaced, more elegant syntheses and manipulations of pyrroles have been required to achieve more effective and selective chemistry. Although protecting groups suitable for pyrroles[13] have been included within comprehensive sources,[14,15] and many authorities of synthetic pyrrole and porphyrin chemistry have necessarily included protected pyrroles in the discussion of synthetic strategies,[10,16–18] a modern and comprehensive survey is desirable. This review embraces the gamut of protecting groups for pyrroles, including the availability, utility, and deprotection of protected pyrroles. Without a doubt this review does not include every report of protected pyrroles, nor does it fully summarize all aspects of the cited references. Instead, examples have been chosen based on their demonstrated and potential usefulness, in the opinion of the authors. The aim of this review is to provide practicing and aspirant pyrrole chemists with a survey and flavor of the types of groups used to protect pyrroles, and insight into why certain groups are advantageous under particular circumstances.

2. Pyrroles protection by N-substitution

2.1. *N*-Sulfonyl protecting groups

The sulfonyl groups are among the more common protecting groups for pyrrole protection at nitrogen because of their strong electron-withdrawing effect. Their ability to reduce the reactivity of pyrrole allows a wider range of reactions and higher yields in regioselective alkenylation[19] and acylation[20] at the alpha and beta positions. Some representative sulfonyl protecting groups that have been used in pyrrole chemistry are presented in Figure 2.

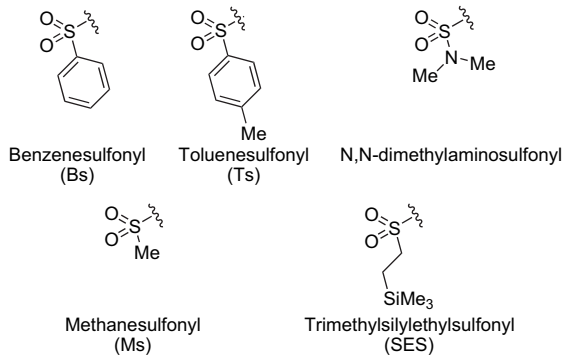


Figure 2. Sulfonyl groups for pyrrole chemistry.

The effect of the sulfonyl group on the electron density distribution in pyrrole has been evaluated by analysis of ^{13}C NMR chemical shift data and X-ray crystal structure analysis.[21] The four major resonance forms **A**–**D** of 3,5-dimethylpyrrole-2-carboxylate are shown in Figure 3. The introduction of an electron-withdrawing group (EWG) on the nitrogen of the pyrrole significantly changes the distribution of the resonance contributors by decreasing the availability of the nitrogen lone pair, favoring **A**. As the strength of the EWG was increased (N–H<*N*-Boc<*N*-Ms<*N*-Tf), the aromatic carbons were proportionally deshielded in the respective pyrrole ^{13}C NMR spectra (Fig. 3).[21]

N-Phenylsulfonylpyrroles react regioselectively under Friedel–Crafts acylation conditions contingent on Lewis acid.[22,23] For example, benzoylation of *N*-phenylsulfonylpyrrole **1** with benzoyl chloride gave only 3-benzoyl-1-phenylsulfonylpyrrole **4b** using $AlCl_3$ as Lewis acid in DCM. Highly regioselective acylation at the 2-position of *N*-phenylsulfonylpyrrole with benzoyl chloride was later

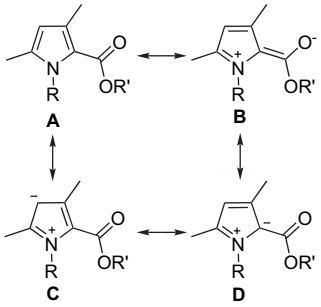


Figure 3. Major resonance forms **A**–**D**.

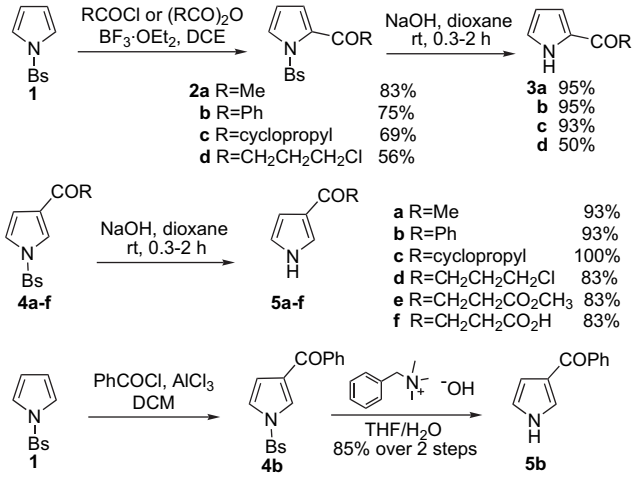


Figure 4. Alkaline hydrolysis of *N*-sulfonylacylpyrroles.

obtained by using $BF_3 \cdot OEt_2$ as Lewis acid in 1,2-dichloroethane to give **2b** (Fig. 4).[20]

The introduction of a sulfonyl group on the nitrogen of pyrrole is generally accomplished by reacting the pyrrolyl anion with the corresponding sulfonyl halide. The counter ion, the solvent, and the electrophile are all important for avoiding electrophilic substitution at the 2-position. Some of the common bases and solvents for *N*-sulfonyl protection include metal hydrides (NaH or KH) in THF, DCM or DMF, as well as trialkylamines in DCM or MeCN. Alternatively, regioselective protection of unsubstituted pyrrole with BsCl or TsCl in ionic liquids [1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim][PF_6]) and 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4])] in the presence of KOH afforded *N*-sulfonylpyrroles in quantitative yields.[24]

The removal of *N*-aryl and *N*-alkylsulfonyl groups has been typically achieved using alkaline hydrolysis with NaOH or KOH (Figs. 4 and 5). For example, sodium hydroxide in dioxane at room temperature effectively deprotected pyrroles **2a**–**d** and **4a**–**f**, which possess acyl groups either at the alpha or beta position, to provide pyrroles **3a**–**d** and **5a**–**f** in variable yields.[20] Alternatively, benzyltrimethylammonium hydroxide (Triton B) was used to hydrolyze *N*-benzenesulfonyl-3-benzoylpyrrole **4b**, with similar results.[22]

Unsubstituted *N*-sulfonyl protected terpyrroles **6a**–**b** and bispyrrylthiophenes **7a**–**b** were deprotected effectively in refluxing MeOH with NaOH.[25] Similarly, the *N*-methanesulfonyl group was cleaved from dipyrrolylmethane **10** using NaOH.[26] The *p*-toluenesulfonyl group was easily removed from **12** and **13** by treatment with KOH in MeOH, giving the corresponding deprotected pyrroles **14** and **15**, respectively.[27] 2-Furanyl-*N*-toluenesulfonylpyrrole **16** has also been deprotected successfully using K_2CO_3 at room temperature to yield pyrrole **17** (Fig. 5).[28]

Other moieties may be affected during deprotection of *N*-sulfonylpyrroles under alkaline hydrolysis. For example, in the preparation of an intermediate for the synthesis of

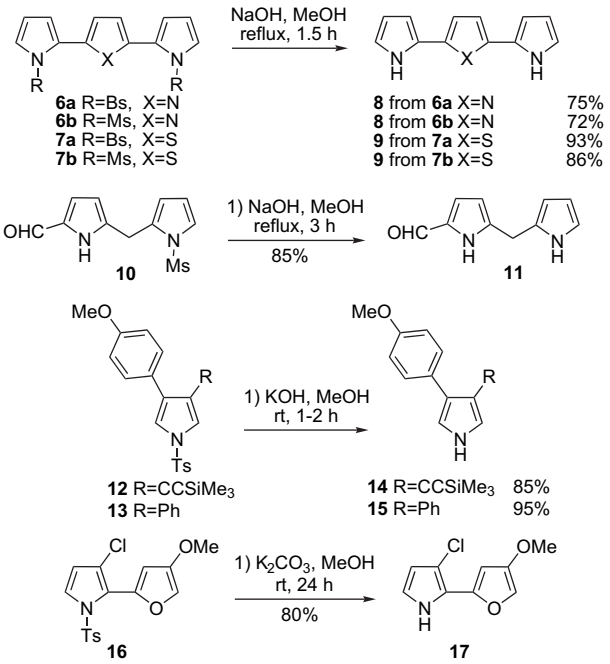


Figure 5. Alkaline hydrolysis of *N*-sulfonylpyrroles.

porphyrins, alkaline hydrolysis of *N*-methanesulfonylpyrrole **18** with potassium hydroxide in MeOH caused simultaneous N-demesylation, elimination of methanesulfenic acid, and attack of MeOH to afford 2-(methoxymethyl)pyrrole **19**[29] in quantitative yield in one step. Deprotection of *N*-benzenesulfonylpyrrole **20** with ethanolic sodium hydroxide was accompanied by ester saponification to provide acid **21** (Fig. 6).[30]

The relatively harsh conditions of alkaline hydrolysis and lack of selectivity encouraged synthetic chemists to find alternative methods for *N*-sulfonyl deprotection. For example, under relatively mild reaction conditions, *N*-tosyl pyrrole **23** was desulfonylated with magnesium in MeOH to give pyrrole **24**.[31] In comparison, alkaline hydrolysis of **23** with KOH gave a very poor yield of the deprotected pyrrole **24**, together with 60% recovery of the starting material. Ammonium chloride was later shown to be useful for activation of the magnesium surface for the deprotection of *N*-phenylsulfonylpyrrole **25**. Furthermore, improved selectivity for deprotection was observed with pyrroles possessing a variety of functional groups compared to alkaline hydrolysis (i.e., **23**

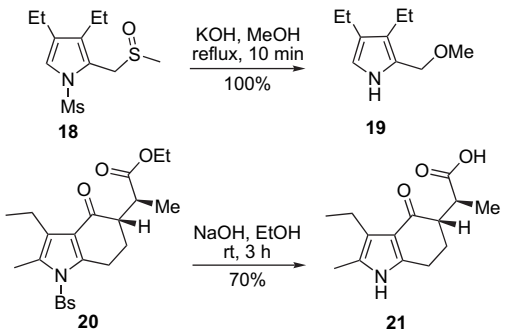


Figure 6. Alkaline hydrolysis of *N*-sulfonylpyrroles.

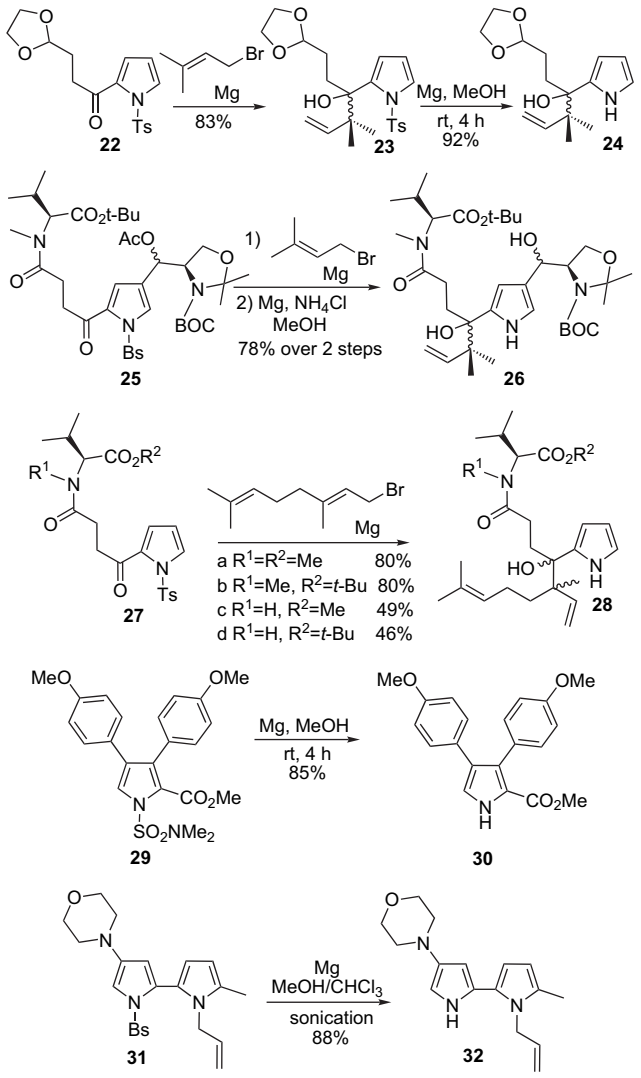


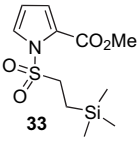
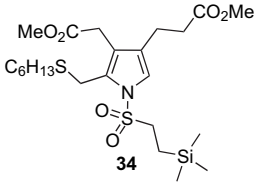
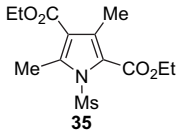
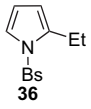
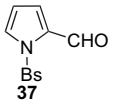
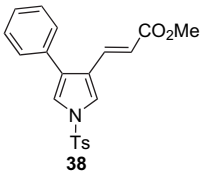
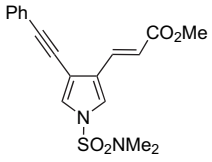
Figure 7. Deprotection of *N*-sulfonylpyrroles with Mg in MeOH.

and **25**).[31,32] Moreover, elimination of the tosyl group of pyrroles **27a–d** occurred concurrently with the Grignard reaction with geranyl bromide and magnesium. The same Grignard reagent was reacted with *N*-tosyl pyrrole **22** without cleaving the protecting group.[33] The magnesium/MeOH conditions have also been used for the deprotection of *N*,*N*-dimethylaminosulfonylpyrrole **29** to provide **30**, an advanced intermediate for the synthesis of the natural product lamellarin O. Deprotection of pyrrole **29** with tetrabutylammonium fluoride (TBAF) gave **30** in moderate yield.[27] 4-Amino-2,2′-bipyrrole **31** failed to react under similar conditions (Mg, NH_4Cl, MeOH) even with heating. However, sonication of bipyrrole **31** and magnesium in MeOH/$CHCl_3$ (99:1) caused complete deprotection in 15 min to give **32** (Fig. 7).[34]

The *N*-trimethylsilylethanesulfonyl (SES) group was developed for pyrrole protection because it can be removed under mild conditions using tetrabutylammonium fluoride (TBAF) in THF at room temperature.[35,36] With additional heating, this methodology was extended to the removal of *N*-methylsulfonyl,[37] *N*-phenylsulfonyl,[37] *N*-*p*-toluenesulfonyl,[38] and *N*,*N*-dimethylaminosulfonyl[38] groups without affecting formyl (i.e., **37**) and carboxylate (i.e., **35**, **38**, and **39**) ring substituents (Table 1).

$$N\text{-sulfonylpyrrole} \xrightarrow[\text{THF}]{\text{TBAF}} \text{pyrrole}$$

Table 1. Desulfonylation of *N*-sulfonylpyrrole with TBAF in THF

N-Sulfonylpyrrole	Time (h)	Temperature (°C)	Yield (%)	Ref.
 **33**	1.5	rt	98	35
 **34**	0.5	rt	89	36
 **35**	0.5	Reflux	96	37
 **36**	24	Reflux	64	37
 **37**	6	Reflux	90	37
 **38**	3	60	96	38
 **39**	2	60	60	38

In addition, deoxygenation by reductive removal of xanthate **40** with triphenyl tinhydride proceeded with cleavage of the tosyl moiety to provide the tricyclic core of the natural product roseophilin **41** (Fig. 8).[39]

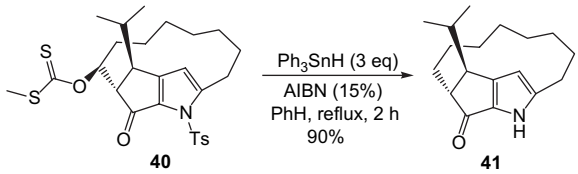


Figure 8. Concomitant xanthate deoxygenation and *N*-toluenesulfonyl group cleavage.

2.2. *N*-Boc protection

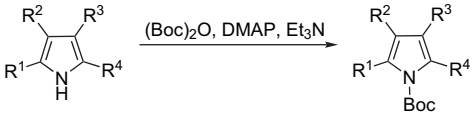
The *tert*-butoxycarbonyl (Boc) moiety has been useful for pyrrole chemistry, because of its electron-withdrawing effect and ease of removal under a variety of conditions. The protection of the pyrrole nitrogen has been performed using different sources of the *tert*-butoxycarbonyl moiety including $(Boc)_2O$, BocOPh, and Boc–ON. For example, pyrroles **42a–j** were protected in the presence of di-*tert*-butyl dicarbonate [$(Boc)_2O$], catalytic 4-(dimethylamino)-pyridine (DMAP), and Et_3N in good yields (Table 2).[40,41]

Employing *tert*-butyl phenyl carbonate (BocOPh) and sodium hydride in THF, pyrrole **42a** and 2,5-dimethylpyrrole **44** were converted to *N*-Boc-protected pyrroles **43a** and **45**, respectively.[43] The N-protection of pyrrole-2-carboxaldehyde **46** using 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc–ON) and similar conditions gave the Boc analog **47** (Fig. 9).[44]

Although the reactivity of certain pyrroles may limit the use of acidic conditions for Boc group deprotection, success has been achieved with relatively electron-deficient pyrroles. For example, in the pursuit of novel biologically active heteroaromatic thiophenes, thiophenyl pyrrole **49** was obtained by mixing *N*-Boc pyrrole **48** in trifluoroacetic acid (TFA) for 30 min (Fig. 10).[45]

In a study of TFA-induced and thermolytic cleavage of *N*-Boc pyrroles **50a** and **50b**, optimum thermolytic conditions at 180 and 155 °C, respectively, yielded acrylate

Table 2. *N*-Boc protection with $(Boc)_2O$



42 **43**

Entry	R^1	R^2	R^3	R^4	Solvent	Yield (%)	Ref.
a	H	H	H	H	DCM	81	40
b	CO_2Et	H	H	H	DCM	85	40
c	$COCCl_3$	H	H	H	DCM	81	40
d	CO_2Et	H	H	Me	DCM	94	40
e	CO_2Et	Me	H	Me	DCM	94	40
f	CO_2Et	Me	CO_2Et	Me	DCM	81	40
g	CO_2Bz	H	NO_2	H	DCM	87	40
h	CO_2Bz	H	NH(Boc)	H	DCM	80	40
i	CO_2t-Bu	Me	Me	H	MeCN	100	41
j	H	TMS	H	TMS	DCM	100	42

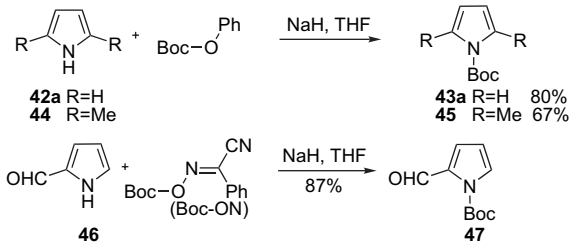


Figure 9. *N*-Boc pyrrole protection.

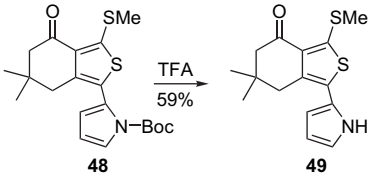


Figure 10. Acidic deprotection of *N*-Boc pyrrole.

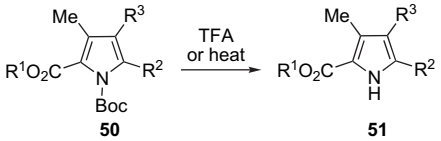
pyrroles **51a** and **51b**. Pyrrole **51a** could be obtained in similar yield when *N*-Boc pyrrole **50b** was exposed to TFA; however, acrylate **50b** decomposed in the presence of TFA in DCM (Table 3).[41]

Thermolytic removal of the *N*-Boc group from neat pyrrole, at 180 °C for 30 min, was reported to give high yields in the deprotection of a series of pyrrole and bipyrrole analogs, **52**, **54**, and **56**.[46] Similar thermolysis conditions were later used for the selective Boc deprotection of pyrrole amino esters **58a–e** to afford pyrroloprolines **59a–e**.[47] Recently, thermally induced decarboxylation by heating Boc-protected bipyrrole **60** at 230 °C under reduced pressure (10^{-3} Torr) for 30 min produced 1,3-bis(2-pyrrolyl)azulene **61**, a luminescent chemosensor for fluoride ions (Fig. 11).[48]

The Boc group can also be cleaved from the pyrrole nitrogen under basic conditions. For example, *N*-Boc 2-substituted pyrroles **62a–d** were deprotected with sodium methoxide in a mixture of methanol and THF.[49] Furthermore, *N*-Boc deprotection of 3,4-disubstituted pyrrole **64** produced 3,4-bis(trimethylsilyl)pyrrole **65** (Fig. 12).[42]

The utility of the Boc group in natural product synthesis was demonstrated in the synthesis of prodigiosin **75**. Hydroboration and oxidation of olefin **66** furnished ketone **67** as the substrate for the subsequent Wittig olefination. Hydrogenation of olefin **68** and oxidation of the methyl group on

Table 3. Comparison of TFA and thermolysis for *N*-Boc removal



50 **51**

Entry	R^1	R^2	R^3	Method	Yield (%)
a	Et	Me	CH=CHCO$_2$Me	TFA/DCM	85
				180 °C, neat	86
b	*t*-Bu	CH=CHCO$_2$Me	Me	TFA/DCM	Decomposition
				155 °C, neat	96

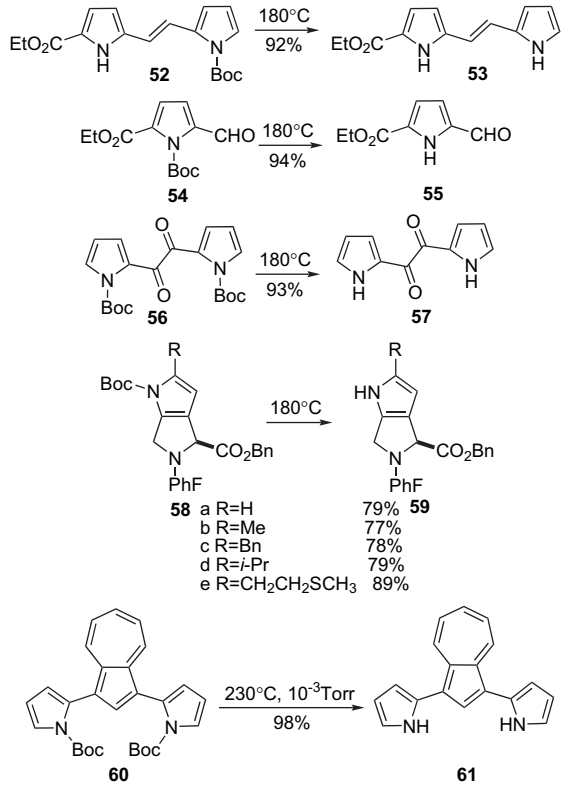


Figure 11. Thermolysis of *N*-Boc pyrroles.

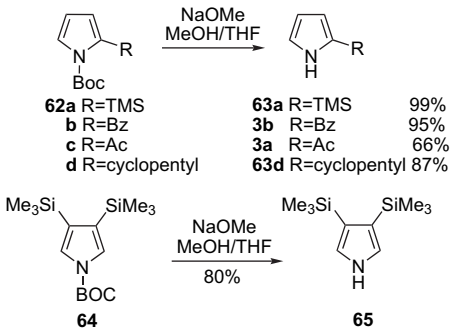


Figure 12. *N*-Boc group removal under alkaline conditions.

pyrrole **69** with cerium ammonium nitrate (CAN) afforded *N*-Boc-protected pyrrole-2-carboxaldehyde **70**. Base-induced condensation of aldehyde **70** with lactam **71** was accompanied with Boc removal such that unprotected dipyrromethene **72** was isolated. Treatment of **72** with Tf_2O produced triflate **73** suitable for the cross-coupling with boronic acid **74** delivering prodigiosin **75** (Fig. 13).[50]

The cleavage of the Boc group has also been observed during Suzuki reactions on bromopyrrole **76**, presumably due to heating under alkaline conditions.[51] Taking advantage of this one-step process, 4-arylpyrroles **77a–d** were prepared from *N*-Boc-4-bromopyrrole **76** and different arylboronic acids at 110 °C (Table 4).[51]

It is noteworthy that a series of *N*-(Boc)-2-arylpyrroles **78a–k** were prepared by Suzuki coupling at 85 °C in 1,2-dimethoxyethane (DME) with retention of the Boc moiety in variable yields (Table 5).[52]

However, palladium-catalyzed cross-coupling reactions of the same pyrrole boronic acid **74** at 130 °C in DMF induced removal of the Boc group, such that 2-arylpyrroles **80a–b** were isolated (Fig. 14).[53]

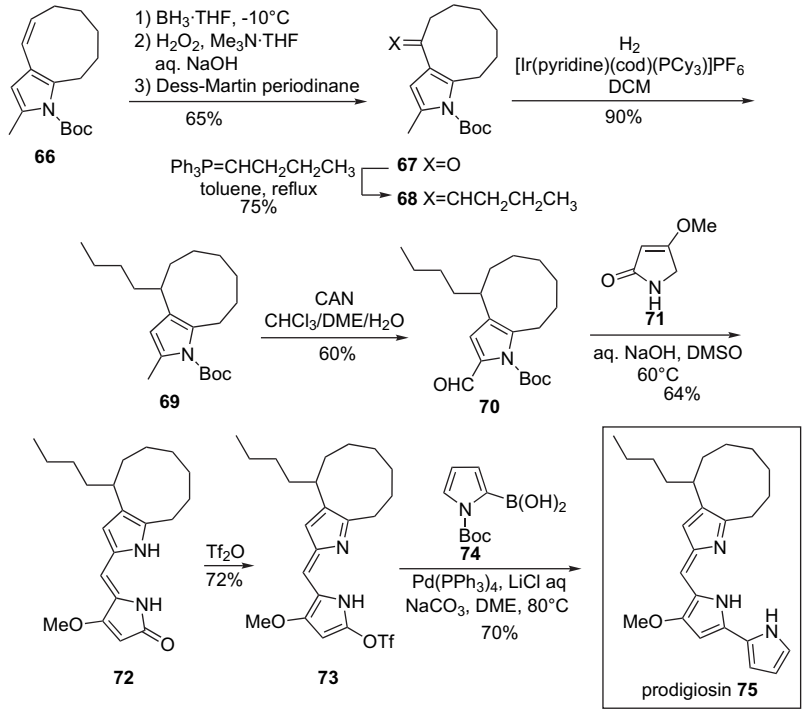
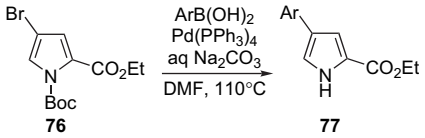


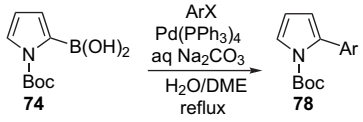
Figure 13. Boc group use in the synthesis of butylcycloheptylprodigiosin **75**.

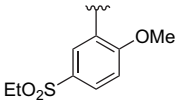
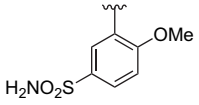
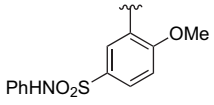
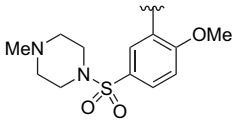
Table 4. *N*-Boc removal during Suzuki coupling



Entry	Ar	Yield (%)
a	3,4-Dimethoxyphenyl	80
b	4-Fluorophenyl	68
c	3-Isopropoxy-4-methoxyphenyl	82
d	2,3,4-Trimethoxyphenyl	84

Table 5. Suzuki coupling with retention of the *N*-Boc moiety



Entry	Ar	X	Yield (%)
a	Ph	I	55
b	Ph	Br	16
c	4-MeC_6H_5	Br	15
d	4-ClC_6H_5	Br	34
e	1-Naphthyl	Br	34
f	2-Thienyl	Br	35
g	3-Pyridyl	Br	72
h		Br	98
i		Br	83
j		Br	63
k		Br	70

Alternative methods for Boc deprotection have been developed in recent years. For example, 3-pyrrolylalanine **82** was liberated by simultaneous deprotection of the *N*-(Boc) and *N*-carboxybenzyloxy (Cbz) amino protecting groups using trimethylsilyl iodide (TMSI) and pyridine (Fig. 15).[54] In pursuit of the synthesis of marine alkaloids, *N*-(Boc)pyrrole diester **83** was treated with Br_2, which caused bromination of the 3- and 4-positions, and in situ Boc removal to afford dibromopyrrole **84**[54] (Fig. 15). Moreover, selective deprotection of *N*-Boc pyrrole *tert*-butyl ester **85** was achieved

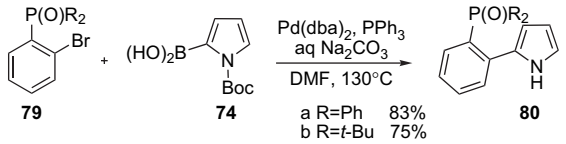


Figure 14. *N*-Boc cleavage under Suzuki reaction conditions.

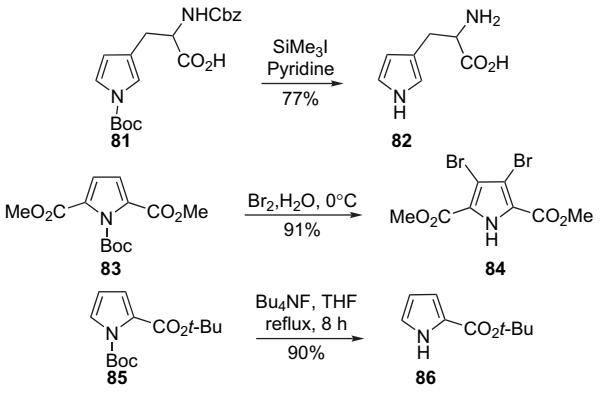


Figure 15. Various conditions for *N*-Boc deprotection.

with TBAF in THF at reflux. The proposed mechanism for the deprotection involves nucleophilic attack by fluoride on the carbonyl group to release the pyrrole anion and Boc–F (Fig. 15).[55]

2.3. *N*-Benzyl, alkyl, and allyl protection

The N-benzylation and alkylation of pyrrole, rather than substitution at the 2-position, is enhanced by the use of soft pyrrolyl anions (e.g., potassium, ammonium, and thallium) and polar aprotic solvents.[56–59] Phase-transfer catalysis has been a useful strategy for the N-benzylation of pyrrole, making use of the soft trialkylammonium cation.[59] This method was shown to be applicable to the N-benzylation of pyrroles with electron-withdrawing groups at the 2-position. Ionic liquids[24] and phase-transfer catalysis conditions with polyethylene glycols[60] have also been reported to be advantageous for the preparation of *N*-benzyl pyrrole. A synthesis of *N*-benzyl pyrroles bearing 2-morpholino substituents has been developed featuring the reaction of an imine **87**, as its enamine, with a diimmonium salt **88** (Fig. 16).[61] In electrophilic substitution reactions, the effects of the *N*-benzyl group on the regioselectivity have been investigated in pyrrole bromination, nitration, and Vilsmeier–Haack formylation. Bromination and nitration gave 3-substituted pyrroles as major products (66 and 60%, respectively). On the contrary, formylation gave the pyrrole-2-carboxaldehyde as the major product, with an increased amount of pyrrole-3-carboxaldehyde (15%) compared to product from Vilsmeier–Haack formylation of *N*-methylpyrrole under the same conditions.[62] Debenzylation of *N*-benzyl pyrroles was originally found to be problematic[63] as catalytic hydrogenation methods resulted in reduction of the phenyl ring to give *N*-cyclohexylmethyl derivatives, and acid-catalyzed deprotection conditions induced migration of the benzyl group to an unsubstituted 2-position. Debenzylation via hydrogenation over Raney nickel was also unsuccessful, with only starting material being recovered.[62] Effective removal of the benzyl group has been achieved by reaction with a reducing metal such as sodium in liquid ammonia (Fig. 16).

En route to indoles, *N*-benzyl pyrroles have been employed in the synthesis of 4-oxo-4,5,6,7-tetrahydroindole derivatives (Fig. 17).[64] The *N*-benzyl group proved stable to conditions for a variety of synthetic steps, including reduction

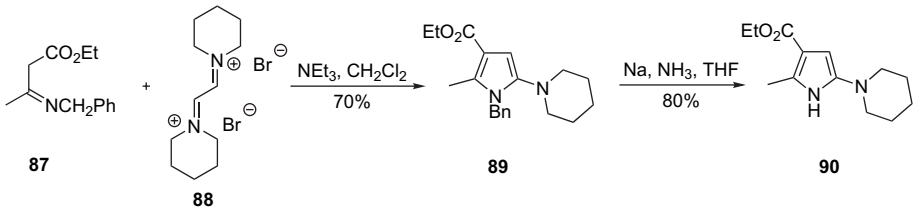


Figure 16. Synthesis and deprotection of **89**.

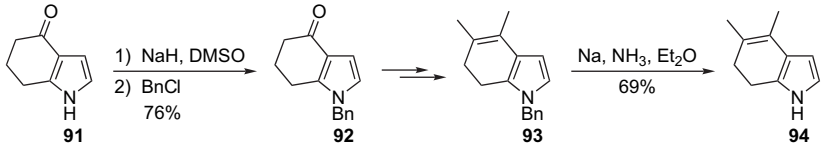


Figure 17. Use of the benzyl group in the synthesis of dihydroindole **94**.

($NaBH_4$ and Wolff–Kishner), Wittig, aldol and alkylation reactions. Final removal of the benzyl group from dihydroindole **93** was performed using sodium in liquid ammonia.

In the synthesis of indole **100**, *N*-benzyl pyrroles were employed in a sequence featuring a Stille cross-coupling reaction, Grignard addition to aldehyde **97**, alkylation, and electrocyclization (Fig. 18).[65] Removal of the benzyl group from indole **99** was found to be problematic, and best achieved by transalkylation.

In the synthesis of the macrotricyclic segment **41** of the antitumor agent roseophilin, a benzyl group was used to protect the pyrrole nitrogen during the intramolecular acylation, sulfone elimination, and conjugate addition reactions to provide the protected intermediate **103** (Fig. 19).[28] The benzyl group was first introduced by a palladium-catalyzed amination to form pyrrole **102**. Model debenzylation studies with 2-acetyl-1-benzyl pyrrole revealed that deprotection could be achieved by transalkylation ($AlCl_3$, benzene);[66] however, these conditions were not effective for the deprotection of *N*-benzyl pyrrole **103**. Instead, the benzyl group was removed from pyrrole **103** by reductive cleavage using calcium in liquid ammonia, which caused concurrent ketone reduction such that oxidation was necessary to reinstall the carbonyl group.

In the synthesis of alkoxyporphyrins (Fig. 20),[67] the benzyl group prevented N-alkylation during the synthesis of dimethoxypyrrole **107**. Benzyl group removal from pentasubstituted **107** was achieved both by hydrogenation and by exposure to acid in the presence of anisole to trap the benzyl carbonium ion. Related debenzylation of *N*-protected 3,4-dialkoxy pyrroles has been achieved using sodium in liquid ammonia.[68]

The 2,4-dimethoxybenzyl (DMB) group has been employed to N-protect pyrrolo[2,3-*d*]pyrimidines, en route to the

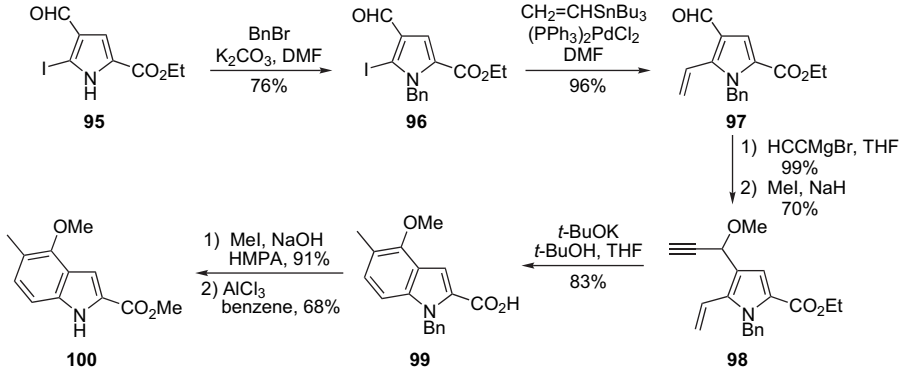


Figure 18. Use of the benzyl group in the synthesis of indole **100**.

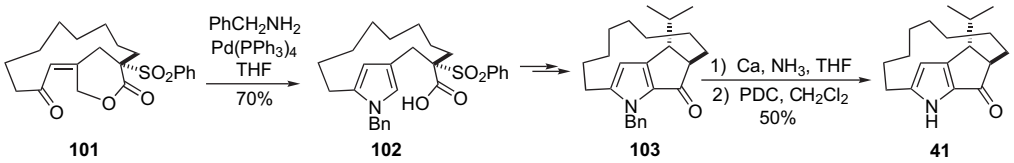


Figure 19. Use of the benzyl group in the synthesis of macrotricyclic segment **41**.

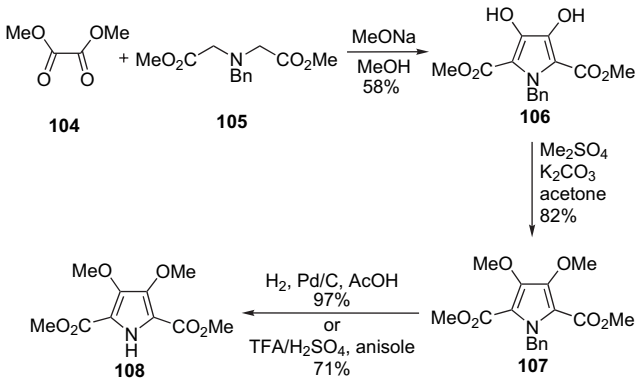


Figure 20. Use of the benzyl group in the synthesis of dimethoxypyrrole **108**.

natural product rigidin (Fig. 21).[69] The pyrrolo[2,3-*d*]pyrimidine **110** was prepared by ring closure of pyrimidinone **109**, via intramolecular acylation. Conversion to the corresponding triflate **111**, Stille cross-coupling and then TFAA-promoted acylation gave a mixture of DMB-protected product **112** (18%) and pyrrolopyrimidine **113** (47%), from loss of the DMB group under the acidic conditions. Complete removal of the DMB group was then achieved by treating **112** with TFA. Deprotection of the DMB group in this way surmounted difficulties encountered with the related *N*-benzyl analog of **112**, which had resisted deprotection by a number of methods, including hydrogenation, BBr_3, HBr/AcOH, TMSI/CH_3CN, and Na/NH_3.[69]

The 3,4-dimethoxybenzyl group was also used in the synthesis of porphobilinogen (Fig. 22).[63] Annulation of vinylogous amide **114** gave *N*-DMB pyrrole **115**, which was deprotected cleanly with acid to afford pyrrole triester **116**. Although *N*-benzyl and *N*-*p*-methoxybenzyl pyrrole derivatives of **115** could be prepared, their deprotection was troublesome since hydrogenative methods led to reduction of the benzyl units and acidic methods led to migration of the *N*-substituent to the free α-position.

In a total synthesis of prodigiosin, alkenyl vicinal tricarbonyl compound **117** served in the construction of dipyrrole **119** (Fig. 23).[70] Protected dipyrrole **118** was constructed by condensation of **117** with 3,4-dimethoxybenzyl amine, and subsequently *O*-methylated and *N*-deprotected to provide dipyrrole **119**, after removal of the *N*-tosyl group.[63]

The *N*-(4-methoxybenzyl) (MPM) group has been incorporated into *N*-substituted-2-vinylpyrroles evaluated as potential anti-HIV agents.[71] *N*-(MPM)pyrroles have also served in the synthesis of indoles by an analogous manner to that

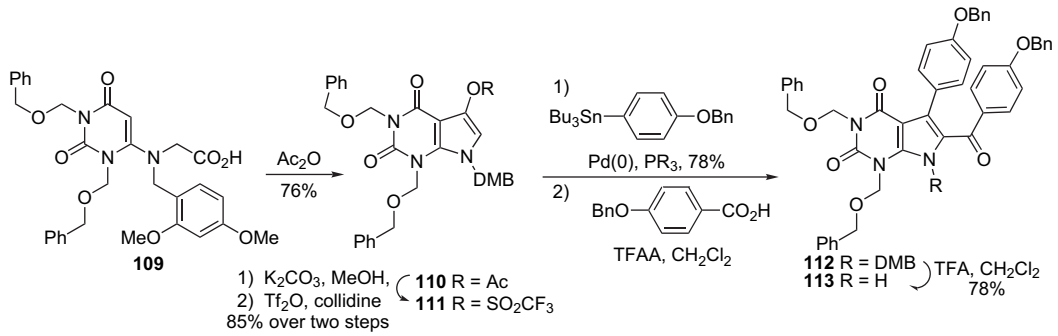


Figure 21. Synthesis of pyrrolo[2,3-*d*]pyrimidine **113**.

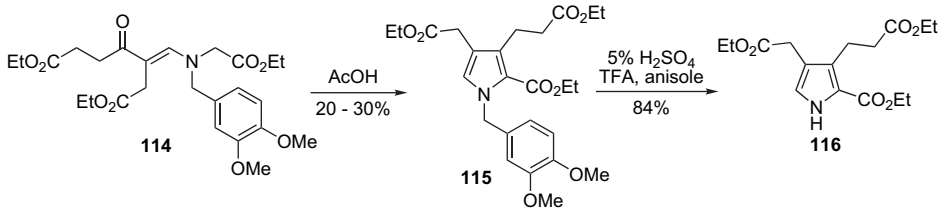


Figure 22. Synthesis of precursor to porphobilinogen.

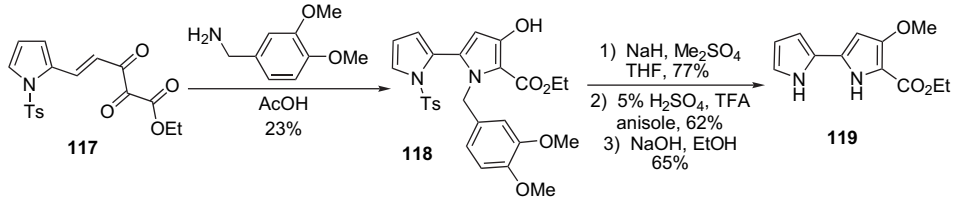


Figure 23. Synthesis of bipyrrole **119**.

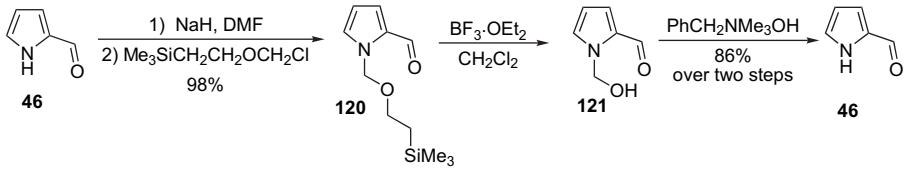


Figure 24. Installation and removal of SEM group.

detailed in Figure 18 for the benzyl group.[65] In a synthesis of porphobilinogen akin to that shown in Figure 22,[63] attempts at hydrogenolytic and acidic deprotection of the corresponding *N*-MPM pyrrole caused reduction of the benzene ring and migration of the protecting group to the free α-position, respectively.

The 2-(trimethylsilyl)ethoxymethyl (SEM) group has been demonstrated to be a useful *N*-protecting group for pyrroles, conferring resistance to reductive, oxidative, acidic, and basic conditions.[72,73] Treatment of the sodium anion of pyrrole-2-carboxaldehyde with SEM-chloride gave *N*-(SEM)-pyrrole **120** in excellent yield (Fig. 24), and pyrroles substituted with formyl, keto, and benzyl groups were also *N*-protected in this manner. Deprotection occurred upon treatment with $BF_3 \cdot OEt_2$, to give the corresponding *N*-(hydroxymethyl)-pyrrole **121**. In situ treatment of **121** with catalytic amounts of Triton B caused loss of formaldehyde. Alternatively, the SEM group has been removed directly using TBAF albeit in lower yields, which are enhanced in the presence of amines; however attempts using $LiBF_4$/MeCN and CsF/HMPA failed to remove the SEM group.[73]

The SEM group has been particularly useful as a directing group for pyrrole metalation. For example, α-lithiation of *N*-(SEM)pyrrole **122** was best accomplished using *n*-BuLi/DME to furnish chelated 2-lithio-SEM-pyrrole **123**.[73] α-Lithiated pyrrole **123** reacted with a series of alkyl halides, acid chlorides, silyl chlorides, aldehydes, and lactones in moderate–good yield.[72,73] In essence the SEM group acts as both an *N*-protecting group and a directing group for substitution. This approach to acylation has been used in the preparation of ketone **126** en route to the ionophore X-14547 A (**127**) (Fig. 25).[74] Halopyrroles have also been protected with the SEM group prior to halogen–lithium exchange and acylation at the β-position.[75,76]

The employment of SEM protection has been critical in two total syntheses of roseophilin.[28,77] N-Protection of pyrrole **41** with the SEM group minimized steric bulk during the addition to the ketone **128**, and provided means for simultaneous removal of the SEM and the triisopropylsilyl (TIPS) groups (Fig. 26). The SEM protection enabled the organocerium addition to ketone **128** to provide protected roseophilin (**130**), which was subsequently deprotected with TBAF. In an alternative synthesis of *ent*-roseophilin[78] employing *N*-(SEM)pyrrole **133**, the SEM group proved robust throughout steps including lactone hydrolysis, reduction, oxidation, Wittig olefination, alkylation (TMS, diazomethane), and ring-closing metathesis (Fig. 27). Organo-cerium addition, followed by removal of the SEM group using TBAF gave *ent*-rosoephilin. A SEM-protected pyrrole was also used in the synthesis of (+)-dragmacidin F.[79]

N-Pivaloyloxymethyl (POM) pyrrole[13] has been prepared in good yield from chloromethylpivalate and the sodium anion of pyrrole. Although removal of the POM group from pyrrole has yet to be reported, deprotection of POM-protected indole with sodium methoxide gave a mixture of indole (50%) and *N*-(hydroxymethyl)indole (30%), and treatment with sodium methoxide followed by KOH gave 95% yield for the deprotection.

The benzylmethyl ether (benzyloxymethyl, BME) group has been introduced to N-protect pyrroles to alleviate problems during functional group manipulations that would occur if the acidic N–H were present.[80] The sodium anion of 3,4-disubstituted pyrrole **134** reacted with benzyl chloromethyl ether to give *N*-(BME)-pyrrole **135** in excellent yield (Fig. 28). Stable to acidic, basic, and acylating conditions, the *N*-BME group has been removed from pyrroles by either hydrogenation or treatment with $AlCl_3$ to give the corresponding 1-(hydroxymethyl)-pyrrole, which as described

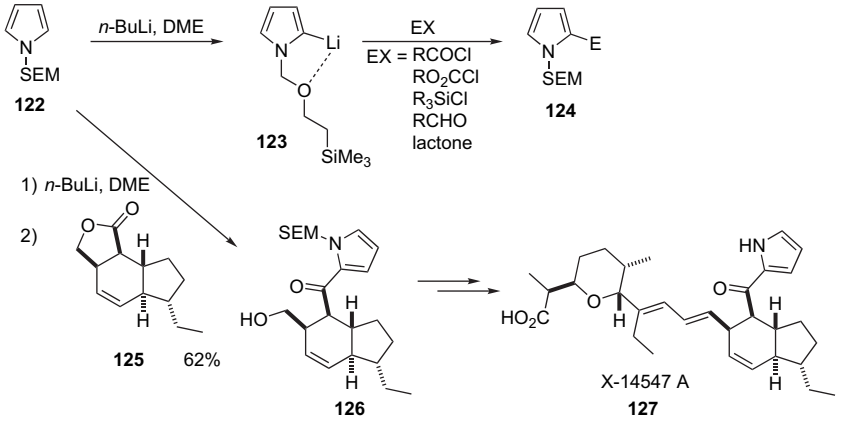


Figure 25. Regioselective acylation of *N*-SEM pyrrole **122**.

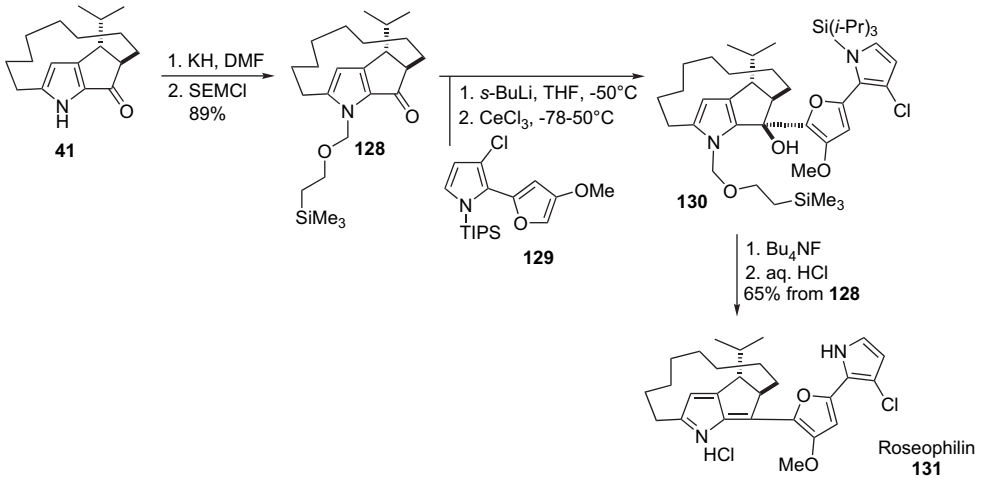


Figure 26. Roseophilin synthesis.

for SEM group removal, can be cleaved with catalytic amounts of Triton B to effect the loss of formaldehyde. In the synthesis of verrucarin E (**139**),[81] the BME group demonstrated utility both for nitrogen protection and for improving the solubility of the pyrrole 3,4-dicarboxylates.

The BME group has been used to N-protect pyrroles involved in mercuration reactions. Difficulties with the deprotection of *N*-benzyl pyrroles and complications with pyrroles bearing electron-withdrawing *N*-protecting groups (benzoyl and tosyl) were surmounted by the electron-donating ability of the BME group, which enhanced nucleophilicity and facilitated β-mercuration of *N*-(BME)-pyrrole **140** (Fig. 29).[41] With the BME group, higher yields of organomercuration were obtained than with the corresponding

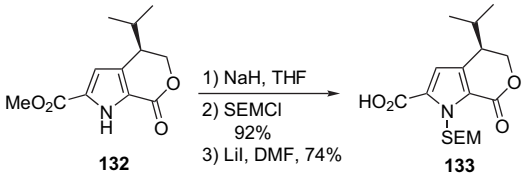


Figure 27. Alternative route toward *ent*-roseophilin using *N*-(SEM) pyrrole **133**.

N-methylpyrrole.[41] Subsequent Heck-type coupling of **141** with methyl acrylate gave pentasubstituted pyrrole **142**. N-Deprotection occurred with concurrent reduction of the alkene in the hydrogenation step.[80] In the removal of the BME group, the solvent was key for successful hydrogenation (use of THF was prohibitively slow), and the addition of NEt_3 to the reaction mixture gave the *N*-(ethoxymethyl)-pyrrole. The use of more than catalytic amounts of Triton B for deformylation resulted in partial hydrolysis of the 3-methylpropanoate. α-Mercuration of *N*-BME-2-unsubstituted pyrroles has also been demonstrated.[41]

The trityl group may act as both a nitrogen blocking group and a bulky directing group.[82] Pyrrole N-protection with the triphenylmethyl (trityl, CPh_3) group has been particularly used to favor substitution at the 3-position. *N*-Tritylpyrrole (**145**) was synthesized by condensation of 2,5-dimethoxytetrahydrofuran and triphenylmethylamine (Fig. 30). *N*-Tritylpyrroles have also been prepared by treating the potassium salt of the pyrrolyl anion with trityl chloride, albeit with variable yields due to difficulties in product purification. Formylation of *N*-tritylpyrrole (**145**) proceeded with reasonable selectivity for the 3-position, and the regioselectivity was improved by modification of the formylating agent. Bromine and triphenylphosphine in DMF gave better selectivity than

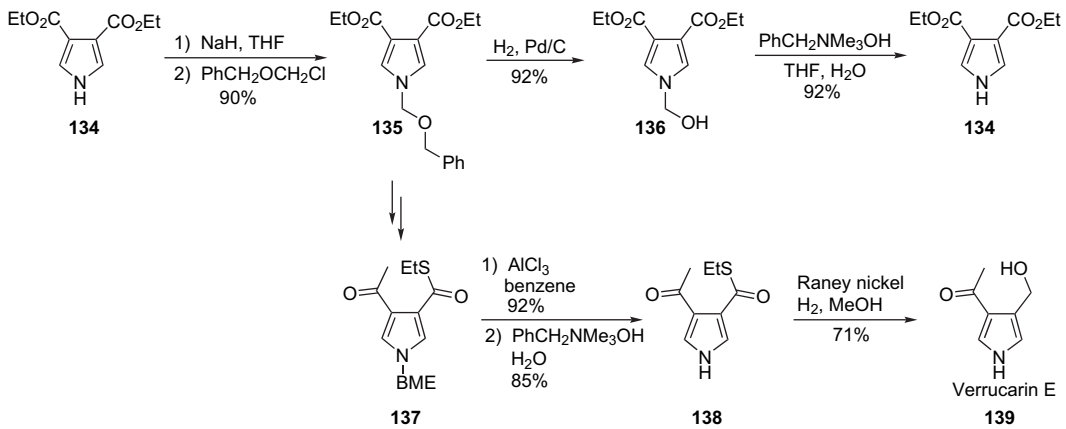


Figure 28. Use of BME protecting group.

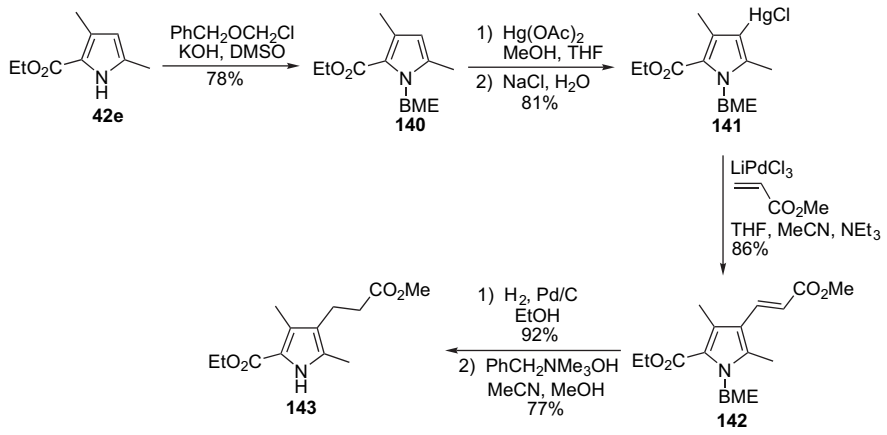


Figure 29. Use of the BME group during mercuration.

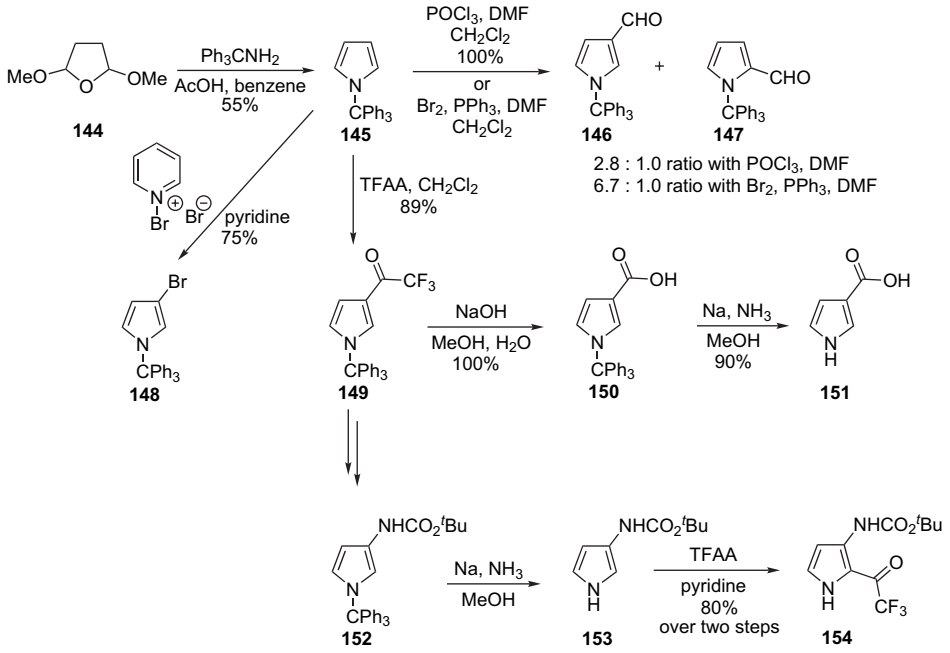


Figure 30. Trityl group as nitrogen blocking group.

$POCl_3$ in DMF (Fig. 30). Trifluoroacetylation of **145** proceeded with high regioselectivity for the 3-position, as did bromination. Pyrrole-3-carboxylic acid (**151**), which was difficult to prepare by other routes, was synthesized from 3-trifluoroacetylpyrrole **149** by a haloform reaction using sodium hydroxide in methanol and deprotection of the trityl group with sodium in liquid ammonia. 3-Trifluoroacetylpyrrole **149** was also used to synthesize 3-amino pyrroles **152**–**154**, by way of a sequence featuring a Curtius rearrangement. An electrochemical method for the deprotection of the trityl group has also been briefly investigated.[82]

N-Tritylpyrrole (**145**) has been shown to undergo regioselective Friedel–Crafts 3-position acylation with an *N*-protected β-lactam to provide aminoketone **155** (Fig. 31).[83] In comparison, *N*-phenylsulfonylpyrrole underwent acylation solely at the 2-position. The Diels–Alder reaction of *N*-tritylpyrrole (**145**) with acetylenedicarboxylic acid gave the required product in the same yield as for *N*-benzyl pyrrole[84] as part of a study that deduced that steric factors alone do not control the reactivity of *N*-substituted pyrroles.

Allyl (2-propenyl) groups have been used in the N-protection of pyrrole, although with little synthetic application. *N*-Allyl pyrrole (**156**) has been prepared in good yield by alkylation of pyrrole with allyl bromide and potassium hydroxide in DMSO (Fig. 32).[85] Other solvent systems that have been effective for N-allylation include ionic liquids[24] and the application of aqueous/organic mixtures

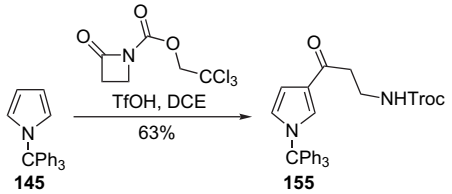


Figure 31. Acylation of *N*-tritylpyrrole.

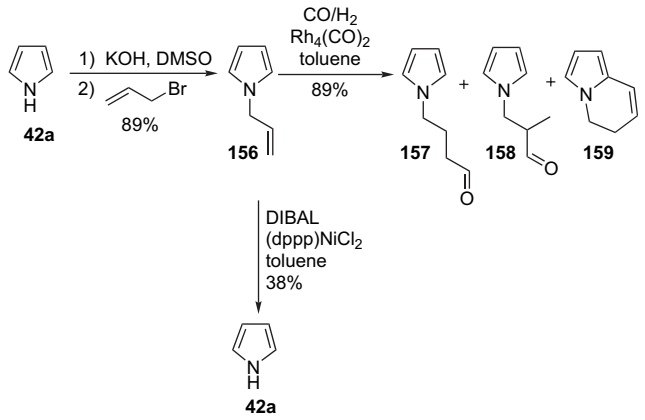


Figure 32. Synthesis, deprotection, and reaction of *N*-allyl pyrrole (**156**).

with polyethylene glycols as phase-transfer catalysts.[60] Subjection of *N*-allyl pyrrole **156** to rhodium-catalyzed hydroformylation gave excellent conversion to furnish a mixture of three products (**157–159**), the ratio of which varied with temperature and reaction time. Removal of the *N*-allyl group from pyrrole has been achieved by treatment with DIBAL in the presence of dichloro[bis(diphenylphosphino)propane]nickel [(dppp)$NiCl_2$], which has been claimed to be vital for success (Fig. 32). This method has not been applied to substituted pyrroles and with *N*-allyl pyrrole (**156**) the low isolated yield after allyl group removal may be due to difficulties in product isolation.[86]

In the synthesis of 3,4-dialkoxy pyrroles for the construction of alkoxy-substituted porphyrins (Fig. 33),[68] *N*-allyl protection was introduced by the condensation of allyl amine with dimethoxy dialdehyde **161**, which was produced in situ from hydrolysis of tetrahydrofuran **160**. The *N*-allyl group was removed by treatment with sodium in liquid ammonia. Deallylation of **162** was also achieved with stoichiometric amounts of methyl Grignard reagent in the presence of a nickel catalyst. With *O*-allyl and *O*-benzyl derivatives of **162**, all of the protecting groups were removed by treatment with either sodium in liquid ammonia or methyl Grignard reagent with nickel catalyst.

2.4. Beta-eliminating protecting groups

N-Ethyl groups possessing a terminal electron-withdrawing group have been used effectively for the protection of the pyrrole nitrogen atom because of their capacity to liberate the negatively charged heterocycle by beta-elimination in a reverse Michael reaction under basic conditions.

The introduction of such beta-eliminating ethyl group protection onto pyrrole has been achieved by alkylation, after nitrogen deprotonation with sodium hydride in DMF.[59] For example, 2-phenylsulfonylethyl chloride reacted with pyrrole-2-carboxaldehyde **46**, 2-methylthio pyrrole (**164**), and 4-oxo-4,5,6,7-tetrahydroindole **91** under these conditions (Fig. 34).[87] Alternatively, pyrrole alkylation has been achieved using phase-transfer conditions with tetrabutylammonium iodide in a benzene/aqueous sodium hydroxide mixture. In this way, 2-phenylsulfinylethyl and 2-phenylsulfonylethyl chlorides reacted with 2-benzoylpyrrole **3b** to provide *N*-alkylpyrroles **176** and **167** (Figs. 34 and 38).[87] Under modified conditions, 1-cyanoethylpyrrole **169** was prepared by alkylation of pyrrole **42a** with 3-chloropropionitrile using tetrabutylammonium bromide in a dichloromethane/aqueous sodium hydroxide mixture (Fig. 35).[59]

Various conditions have also been developed for performing the Michael addition of pyrrole **42a** onto α,β-unsaturated esters, nitriles, ketones, and sulfones in order to protect the heterocycle nitrogen. For example, using KOH in the ionic liquid [Bmim][PF_6], pyrrole **42a** reacted respectively with acrylonitrile, methyl acrylate, and methyl vinyl ketone to provide *N*-alkylpyrroles **169–171** (Fig. 36).[24] Reduced reaction times and higher yields were typically obtained in the respective syntheses of *N*-alkylpyrroles **169**, **170**, and **172** by employing ultrasound irradiation in the attack of pyrrole

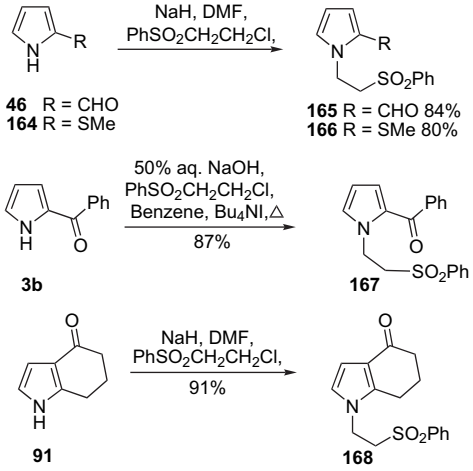


Figure 34. Pyrrole alkylation with 2-phenylsulfonylethyl chloride.

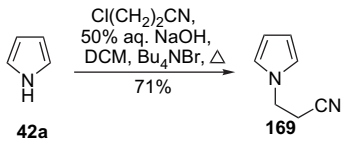


Figure 35. Pyrrole alkylation with 3-chloropropionitrile.

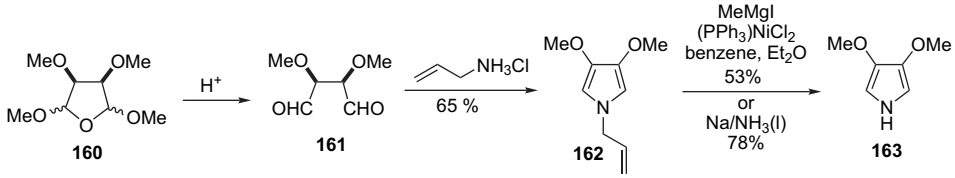


Figure 33. Synthesis of pyrrole **163** from tetrahydrofuran **160**.

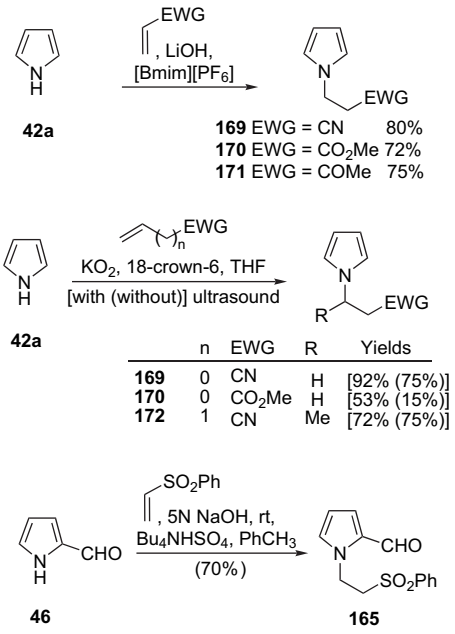


Figure 36. Pyrrole alkylations by Michael additions.

onto acrylonitrile, methyl acrylate, and allylcyanide using potassium superoxide as base in the presence of catalytic 18-crown-6 in THF (Fig. 36).[88] The alkylation of pyrrole-2-carboxaldehyde **46** with phenylvinylsulfone provided *N*-alkylpyrrole **165** using tetrabutylammonium bisulfate as phase-transfer catalyst in a toluene/aqueous sodium hydroxide mixture for 24 h at room temperature (Fig. 36).[89] At reflux, after 1 h, these same conditions provided a mixture from which *N*-alkylpyrrole **165** was isolated in only 27% yield contaminated with three pyrrolizines **173–175** each of which was isolated in <5% yield (Fig. 37).[89]

Oxidation of phenylthioethyl ether to its corresponding sulfoxide and sulfone has been used to generate the respective phenylsulfinylethyl- and phenylsulfonylethyl-protection for the subsequent alkaline induced beta-elimination. For example, *N*-(2-phenylsulfinylethyl)pyrrole **176** has been synthesized in two steps from *N*-(2-chloroethyl)-2-benzoylpyrrole **177** by nucleophilic displacement of the chloride with sodium thiophenolate in DMF, followed by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane (Fig. 38).[87] Treatment of *N*-(2-phenylthioethyl)pyrrole **194** in EtOH with a pH=5 buffered NaOAc/AcOH solution containing oxone oxidized thioether **194** to provide *N*-(2-phenylsulfonylethyl)pyrrole **195** (Fig. 41).[90]

As mentioned, the advantage of *N*-ethyl groups possessing a terminal electron-withdrawing group as pyrrole protection

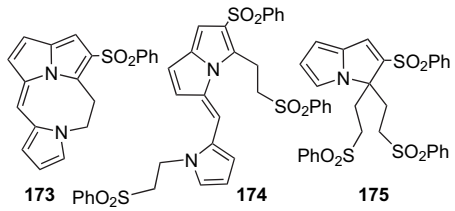


Figure 37. Pyrrolizines **173–175**.

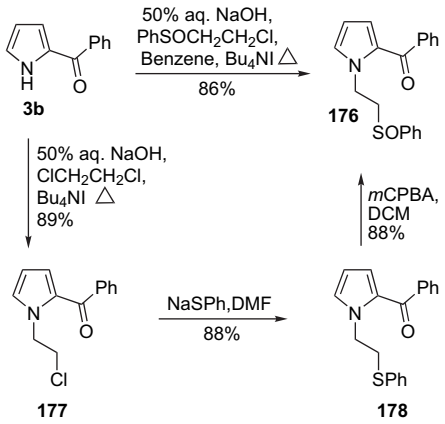


Figure 38. Oxidation of phenylthioethyl pyrrole **178** to sulfoxide **176**.

is their effective removal under basic conditions. For example, *N*-(2-phenylsulfinylethyl)pyrrole **176** was deprotected using sodium hydride in DMF at room temperature (Fig. 39).[87] Similar conditions were used to remove the phenylsulfonylethyl group from the tetrahydroindole **185** in the synthesis of aziridinomitosene **187** (Fig. 40).[91] Diazabicyclo-[4.3.0]non-5-ene (DBN) has been employed successfully as a non-nucleophilic base in the presence of diethylamine as a scavenger for the removal of 2-phenylsulfonylethyl groups from pyrroles **165** and **167** at room temperature (Fig. 39). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been similarly employed in DMF to remove 2-*p*-nitrophenylethyl groups from benzoylpyrrole **210** at 100 °C and pyrrolopyrimidines **203** and **205** at 25 °C, respectively (Figs. 42 and 43).[92–94] Furthermore, the phenylsulfonylethyl group has been removed from the tetrahydroindole **195** using potassium *tert*-butoxide in a dichloromethane/THF mixed solvent system (Fig. 41).

The 2-phenylsulfonylethyl and 2-*p*-nitrophenylethyl groups have both been employed in the total syntheses of various pyrroles. For example, in the synthesis of aziridinomitosene **187**, alkylation of oxazole **179** with the crystalline triflate **180** (derived from 2-phenylsulfonylethanol and triflic anhydride in pyridine) gave the corresponding oxazolium salt **181** (Fig. 40). Electrocyclic ring opening of the oxazoline on treatment of **181** with cyanide ion provided the azomethine ylide **183**, which reacted in an intramolecular dipolar cycloaddition to furnish tetrahydroindole **185**. Subsequent removal of the 2-phenylsulfonylethyl group with sodium hydride in DMF gave pyrrole **186**, which was converted to the target aziridinomitosene **187**.[91]

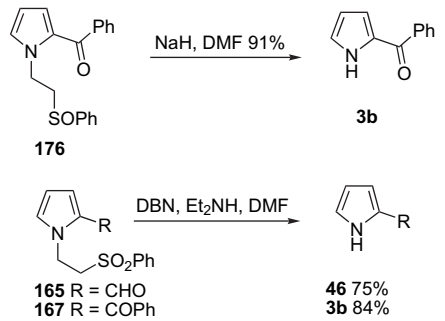


Figure 39. Deprotection by beta-elimination.

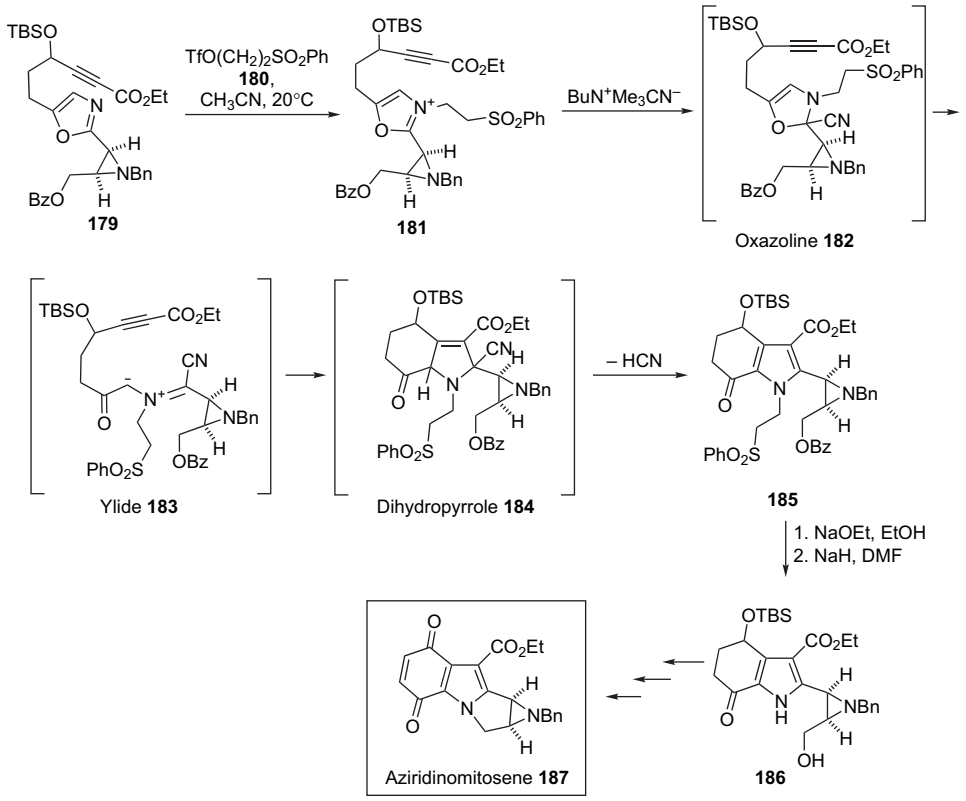


Figure 40. Application of 2-phenylsulfonylethyl group in aziridinomitosene synthesis.

In an alternative approach to the aziridinomitosene skeleton, 4-oxo-4,5,6,7-tetrahydroindole **196** was prepared by an oxaza-Claisen rearrangement and subsequent ring closure of the aldehyde intermediate (Fig. 41).[90] The key vinylogous hydroxamate **190** starting material was produced by condensation of 1,3-cyclohexanedione with the hydroxylamine product **189** from reduction of oxime **188** with sodium cyanoborohydride in methanol acidified with 10% HCl. Michael addition, rearrangement, and pyrrole annulation, all were performed in the same pot by treating vinylogous hydroxamate **190** with ethyl propiolate and Hünig's base to provide aminol **193** that eliminated water on exposure to TsOH to give *N*-protected tetrahydroindole **194**. Removal of the *N*-protecting group was then achieved by oxidation of sulfide **194** to sulfone **195** using oxone, and beta-elimination with potassium *tert*-butoxide to give tetrahydroindole **196** in two steps.[90]

The *p*-nitrophenylethyl group has been employed in the synthesis of pyrrolopyrimidines.[93,94] Introduced as the sodium salt of *N*-(*p*-nitrophenylethyl)glycinate (**197**) during the step to form 4-acetoxypyrrole **199**, which featured substitution onto chloride **198** and annulation using acetic anhydride (Fig. 42), the *p*-nitrophenylethyl group was tolerant to subsequent steps involving hydrolysis of the acetate, activation of the resulting 4-hydroxypyrrole **200** as its corresponding triflate, and Pd-catalyzed methoxycarbonylation to provide ester **202**. Both acetoxypyrrole **199** and its corresponding methyl ester **202** could be effectively deprotected with DBU in acetonitrile at 25 °C to provide the pyrrole nitrogen suitable for alkylation with a carbohydrate moiety.[93,94]

In the preparation of the potent activator of L-type calcium channels, FPL 64176 (**211**), the *p*-nitrophenylethyl group played a key role in preventing destruction of the pyrrole

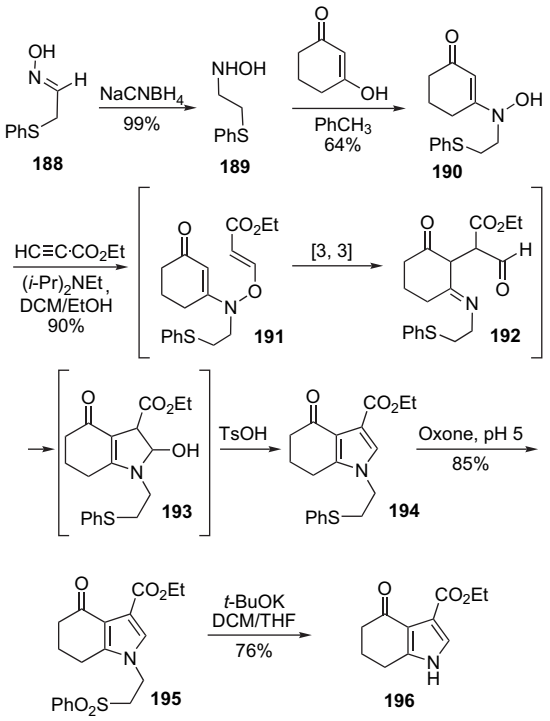


Figure 41. 2-Phenylsulfonylethyl group use in the synthesis of tetrahydroindole **196**.

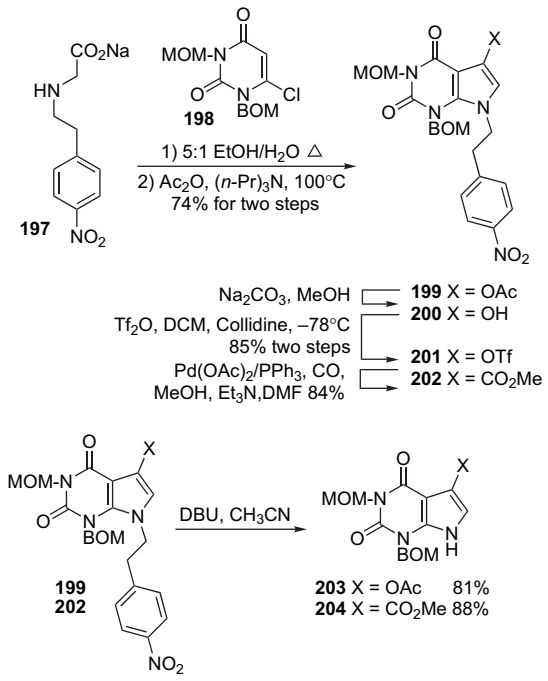


Figure 42. *p*-Nitrophenylethyl group use in the synthesis of pyrrolopyrimidines.

product by Michael attack on dipolarophile **209** during the cycloaddition of azomethine ylide **208** (Fig. 43).[92] Alkylation of *p*-nitrophenylethylamine with ethyl 2-bromopropionate and hydrolysis gave amino acid **207**, which on treatment with acetic anhydride and triethylamine at 70 °C underwent acetylation and dehydration to form oxazolium intermediate **208**. Cycloaddition of the oxazolium onto electron-deficient acetylene **209** yielded the protected pyrrole **210**. Removal of the *p*-nitrophenylethyl group was then accomplished with DBU in DMF at 100 °C giving the desired benzoylpyrrole **211**.[92]

The pyridylethyl group has been developed as a safety-catch[95] *N*-protecting group for pyrrole. Alkylation of the

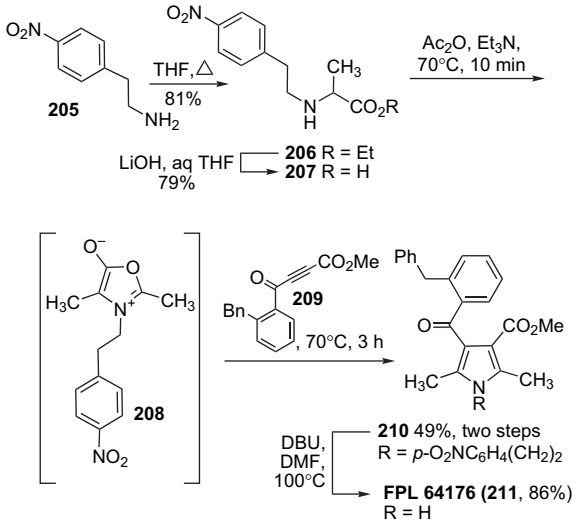


Figure 43. *p*-Nitrophenylethyl group use in the synthesis of FPL 64176.

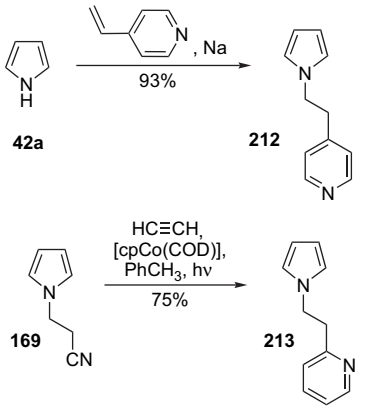


Figure 44. Syntheses of pyridylethylpyrroles **212** and **213**.

pyridine nitrogen of this group generates the corresponding *N*-alkyl pyridinium salt, which on exposure to alkaline conditions undergoes beta-elimination of the *N*-alkyl vinylpyridinium salt to liberate the pyrrole. *N*-(2-Pyrid-4-ylethyl)pyrrole (**212**) has been synthesized by reaction of pyrrole and 4-vinylpyridine in the presence of sodium metal (Fig. 44).[96,97] Isomeric 2-(2-pyrrol-1-yl-ethyl)pyridine (**213**) was made by the photocatalyzed [2+2+2]-cycloaddition of 2-cyanoethylpyrrole **169** with acetylene in the presence of a cobalt catalyst (Fig. 44).[98]

Removal of the pyridylethyl group from *N*-(2-pyrid-4-ylethyl)pyrrole (**212**) was performed in two steps.[97] First, alkylation with iodomethane in acetone at 25 °C for 24 h gave a solid, which, after recrystallization, afforded the pyridinium iodide **214** as prisms. Exposure of the pyridinium salt **214** to sodium hydroxide in a 10:1 acetone/water solution released 1-methyl-4-vinylpyridinium iodide (**215**), which precipitated, and delivered pyrrole **42a** (Fig. 45).

N-Vinylpyrroles are relatively stable, but can be hydrated using strong acid to provide the corresponding 1-hydroxyethylpyrroles that can be deprotected with loss of acetaldehyde. The 2-chloroethyl and 2-hydroxyethyl groups have been employed as pyrrole protecting groups because of their ability to be removed by conversion into vinylpyrroles.[87,99]

As mentioned, chloroethylation of pyrrole can be achieved in high yield under phase-transfer conditions with tetrabutylammonium iodide as catalyst in a mixture of 1,2-dichloroethane and 50% aqueous sodium hydroxide (Figs. 38 and 46).[87] Removal of the chloroethyl group involves beta-elimination to the corresponding vinylpyrrole. In the case of 2-chloroethylpyrroles **217a** and **177**, sodium hydride in acetonitrile at 50 °C was employed to generate the

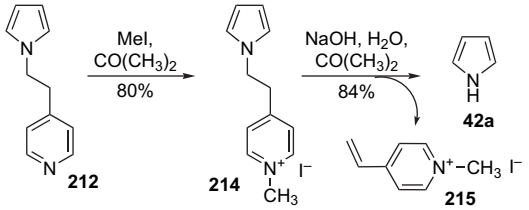


Figure 45. Deprotection of pyridylethylpyrrole **212**.

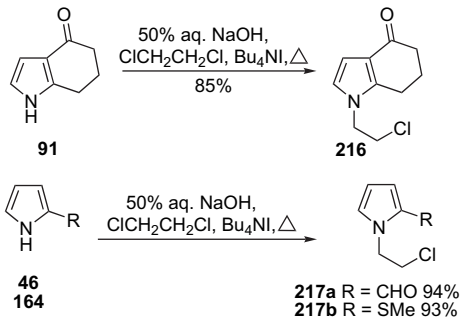


Figure 46. Synthesis of chloroethylpyrroles.

respective vinylpyrroles **218a** and **218b** (Fig. 47).[87] Alternatively, heating 2-chloroethylpyrrole **233** with potassium hydroxide in a methanol/2-propanol solution gave vinylpyrrole **234** (Fig. 50).[100] Moreover, elimination occurred concurrently with the formylation of ketone **216** using sodium methoxide and ethyl formate in methanol to produce vinylpyrrole **220** (Fig. 48).[87]

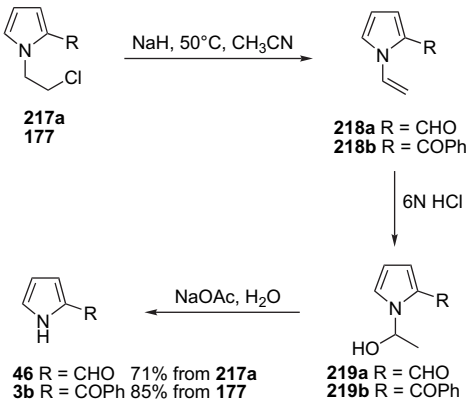


Figure 47. Removal of the 2-chloroethyl group via a vinylpyrrole intermediate.

Vinylpyrroles **218a** and **218b** were subsequently solvolyzed in a two-step process featuring hydration of the enamine with 6 N HCl and hydrolysis of the resulting 1-hydroxyethylpyrroles **219a** and **219b** with aqueous sodium acetate.[87] The three-step deprotections of 2-chloroethylpyrroles **217a** and **177** thus furnished 2-formyl and 2-benzoylpyrroles **46** and **3b**, respectively (Fig. 47). Additionally, vinylpyrrole **234** was hydrated using 12 N HCl and solvolyzed by heating with silver benzoate in wet acetonitrile to provide trisubstituted pyrrole **236** (Fig. 50).[100]

Alternatively, the vinyl group has been used as protection in pyrrole synthesis. For example, vinylpyrrole **220** was employed in the four-step synthesis of benzyl 1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-4-carboxylate (**223**) featuring rearrangement of alpha-diazoketone **221** to the vinyl protected tetrahydrocyclopenta[*b*]pyrrole-4-carboxylate **222** (Fig. 48).[87] For such pyrroles without electron-withdrawing substituents, the acidic conditions for hydration of vinylpyrroles were claimed to be 'too vigorous to permit survival of the pyrrole moiety'. To liberate the tetrahydrocyclopenta[*b*]-pyrrole **223**, vinylpyrrole **222** was, instead, deprotected using mercuric acetate in aqueous acetonitrile. The supposed acetoxy mercury intermediate was reduced in situ with sodium borohydride (Fig. 48).[87] In addition, 1,1′-divinyl-[3,3′]bipyrrole **227** and 1,5-divinyl-4,8-dihydropyrrolo[2,3-*f*]-indole **229** were respectively synthesized by treatment of dioximes **224** and **228** with acetylene and potassium hydroxide in DMSO in an autoclave at 100 °C and at 14 atm of initial pressure (Fig. 49).[99]

Installed by using ethanolamine in a Hantzsch synthesis with α-bromoketone **230** and dimethyl acetone dicarboxylate, the 2-hydroxyethyl group has been employed as a precursor to the 2-chloroethyl group in the synthesis of trisubstituted pyrrole **236** (Fig. 50).[100] 2-Chloroethylpyrrole **233** was synthesized by the activation of 2-hydroxyethylpyrrole **231** as the methanesulfonate **232**, using methanesulfonylchloride and trimethylamine in DCM, followed by displacement with lithium chloride in DMF. Removal of the 2-chloroethyl

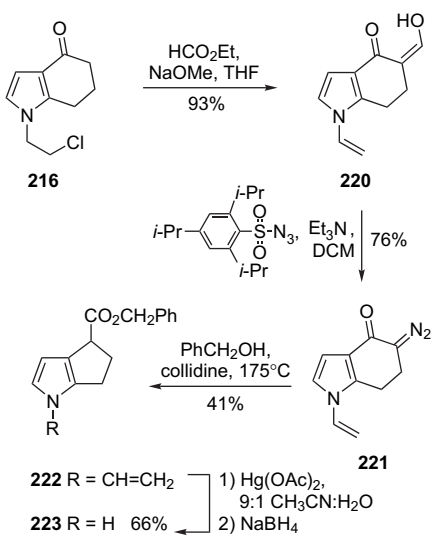


Figure 48. Synthesis of benzyl cyclopenta[*b*]pyrrole-5-carboxylate **223**.

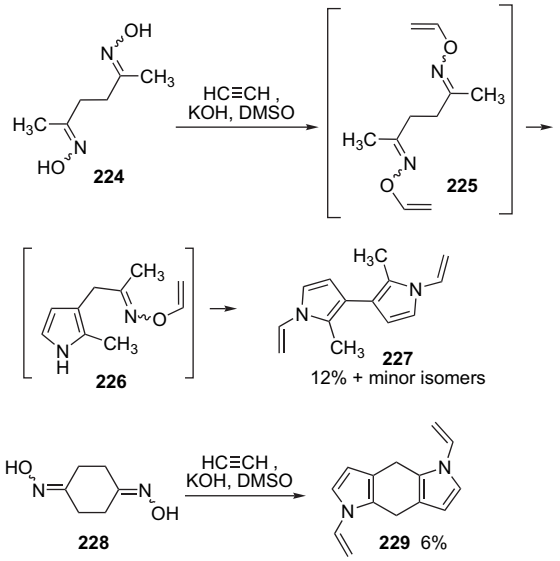


Figure 49. Synthesis of bipyrrole **227** and dihydropyrrolo[2,3-*f*]indole **229**.

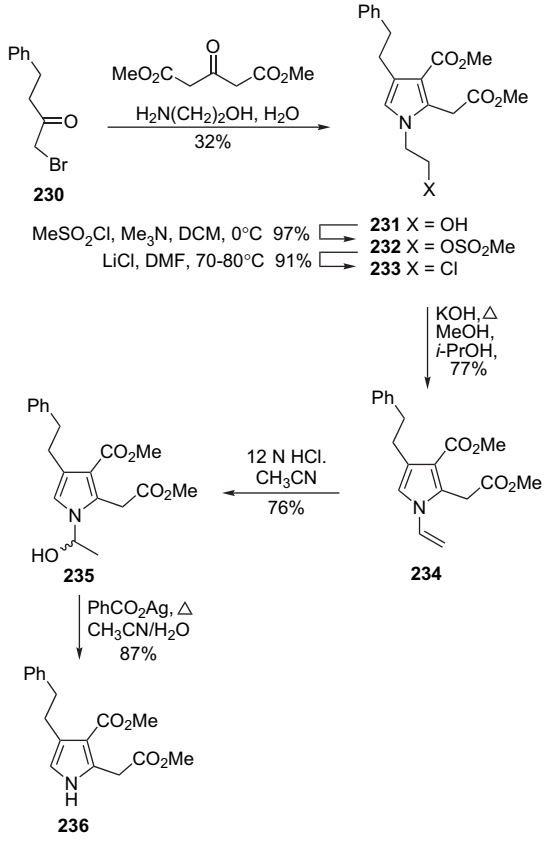


Figure 50. 2-Hydroxyethyl group use in the synthesis of trisubstituted pyrrole **236**.

group was then achieved by way of vinylpyrrole **234** in three steps, as described above.[100]

2.5. *N*-Trialkylsilyl protecting groups

The silyl family of protecting groups has found use in pyrrole chemistry as its members meet the requirements for a relatively stable yet easily removable *N*-substituent. *N*-Trialkylsilylpyrroles are generally prepared from the sodium salt of pyrrole and the corresponding silyl chloride. For example, pyrroles **42a** and **44** were reacted with sodium hydride in THF, and treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) to afford *N*-protected pyrroles **237a–b**.[43] Similarly, 2-(2-phenylsulfinylvinyl)pyrrole **238** was converted to TIPS-protected pyrrole **239** using sodium hydride and triisopropylsilyltrifluoromethane sulfonate (TIPSOTf) in DMF (Fig. 51).[101]

The triisopropylsilyl (TIPS) group was found to be particularly useful for the synthesis of 3-substituted pyrroles. In

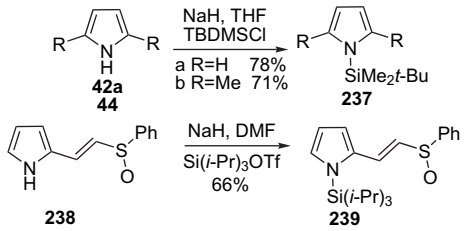


Figure 51. N-Silylation of pyrroles **42a**, **44**, and **238**.

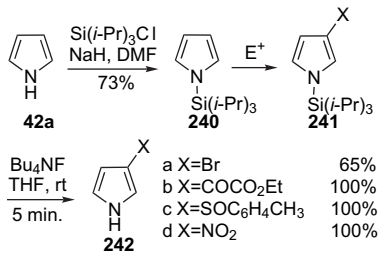


Figure 52. Synthesis of 3-substituted pyrroles based on the use of TIPS protecting group.

CPK models of *N*-triisopropylsilylpyrrole **240**, the alpha positions of the pyrrole were sterically hindered. Competitive trifluoroacetylation experiments showed that substitution at the alpha position of TIPS-pyrrole **240** was $>10^4$ times slower than for pyrrole itself. However, reactivity at the beta position was not changed. Reactions of TIPS-pyrrole **240** with different electrophiles have produced predominantly or exclusively products from substitution at the beta position. Desilylation of **241a–d** was performed using TBAF in THF to afford 3-substituted pyrroles **242a–d** (Fig. 52).[102,103]

Furthermore, regioselective alkenylation at the beta position was performed on TIPS-pyrrole **240**. This is in contrast to pyrroles possessing Bn, SEM, Ac, BOC, and Ts N-protection, which afforded only, or predominantly, alpha-substitution products (Fig. 53).[19]

A series of 3-aryl, 3-ethynyl and 3,4-diethynylpyrroles **244a–j** were efficiently desilylated using TBAF (Table 6).[104]

N-Silyl protection of pyrrole has been employed in natural product synthesis. The cross-coupling reaction of organozinc **246** with 3,4-dibromo-*N*-TIPS-pyrrole **247** in the

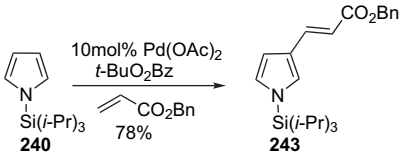
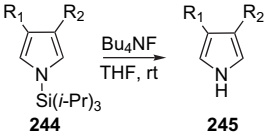


Figure 53. Regioselective alkenylation on *N*-silylpyrrole **240**.

Table 6. Deprotection of *N*-TIPS-pyrroles



Entry	R^1	R^2	Yield (%)
a	H	Ph	92
b	H	4-MePh	90
c	H	4-OmePh	91
d	H	4-ClPh	93
e	H	3-Pyridyl	96
f	H	C≡CH	62
g	H	C≡CC_5H_{11}	74
h	H	C≡CPh	85
i	C≡CH	C≡CH	82
j	C≡CPh	C≡CPh	85

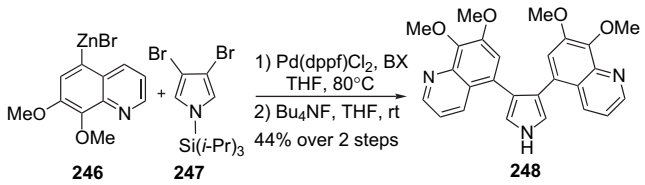


Figure 54. Utilization of TIPS-pyrroles in natural product synthesis.

presence of palladium catalyst gave access to the core of the marine alkaloid halitulin **248** after deprotection with TBAF (Fig. 54).[105] The total synthesis of roseophilin was completed by treating **128** with TBAF in THF to cleave the TIPS group at ambient temperature, whereas the 2-trimethylsilylethoxymethyl (SEM) substituent was removed upon warming to 60 °C. Addition of aqueous HCl caused dehydration and roseophilin hydrochloride **129** was obtained (Fig. 26).[28]

Although tetrabutylammonium fluoride (TBAF) is commonly used as a source of fluoride for silylpyrrole deprotection, sodium fluoride has also been successfully employed in a few cases. For example, *N*-TBDMS-pyrroles **249a–c** were deprotected in 3 h with NaF in a THF/water (1:1) solution at reflux to give 3-acylpyrroles **5a**, **5b**, and **250** (Fig. 55).[106]

It is noteworthy that 1,3,4-tris(trimethylsilyl)pyrrole **251** was selectively *N*-deprotected using methanol to furnish pyrrole **65**. Similarly, desilylation of *N*-TIPS-pyrrole **252** with sodium methoxide in methanol at reflux afforded 3,4-disubstituted pyrrole **253** (Fig. 56).[42]

Finally, it should be mentioned that a rearrangement of the triethylsilyl group (TES) was observed when *N*-triethylsilylpyrrole **254** was exposed to an excess of *t*-BuLi followed by carboxylation and methylation. A mixture of three 2-triethylsilylpyrroles (**255**, **256**, and **257**) was obtained in a ratio of 4:1.5:1, respectively, and each component was isolated and individually treated with TFA to cleave the TES groups (Fig. 57).[107]

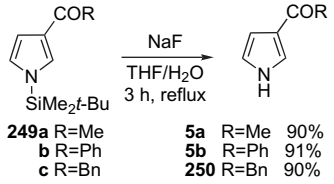


Figure 55. Deprotection of TBDMS-pyrroles with sodium fluoride.

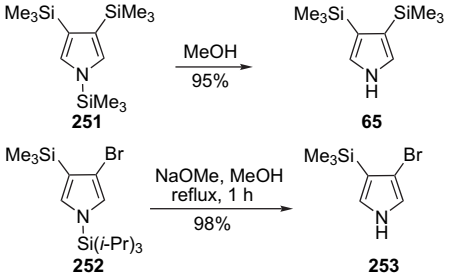


Figure 56. Deprotection of TIPS and TMS-pyrroles using methanol and methoxide.

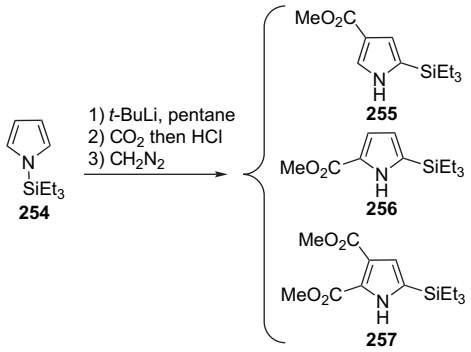


Figure 57. Triethylsilyl group rearrangement.

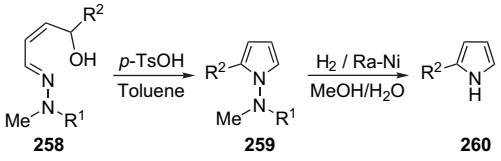
2.6. *N*-Amino protecting groups

N-(Amino)pyrroles are generally formed by intramolecular or intermolecular annulations onto *N*,*N*-disubstituted hydrazines and hydrazones. The most common *N*-aminopyrrole protecting group is *N*,*N*-dimethylamine; however, *N*-methyl-*N*-phenylamine has also been used for pyrrole protection.

N-Aminopyrroles **259** were obtained by intramolecular cyclization with dehydration of hydrazones **258** using *p*-toluenesulfonic acid (*p*-TsOH) in toluene at room temperature. Cleavage of the N–N bond was achieved by hydrogenolysis using Raney nickel in aqueous methanol under hydrogen atmosphere to afford the deprotected pyrroles **260** after 48 h in good yields (Table 7).[108]

2-Substituted *N*,*N*-dimethylaminopyrrole **263** was synthesized by a three-step reaction sequence featuring selective C-alkylation of *N*,*N*-dimethylhydrazone **261** with 2-iodomethyl-1,3-dioxolane, followed by acid-catalyzed dehydration of iminoacetal derivative **262**. Removal of the dimethylamino group by hydrogenation over Raney nickel as catalyst provided pyrrole **264** (Fig. 58).[109]

Table 7. Formation of *N*-aminopyrroles and deprotection of *N*-amino groups



Entry	R^1	R^2	Yield of **259** (%)	Yield of **260** (%)
a	C_6H_5	*p*-$CH_3C_6H_4$	94	89
b	Me	*p*-$CH_3C_6H_4$	87	92
c	Me	*p*-$CH_3OC_6H_4$	n/d	90

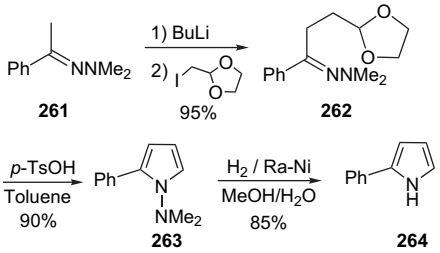


Figure 58. Synthesis of 2-phenylpyrrole **264** from hydrazone **261**.

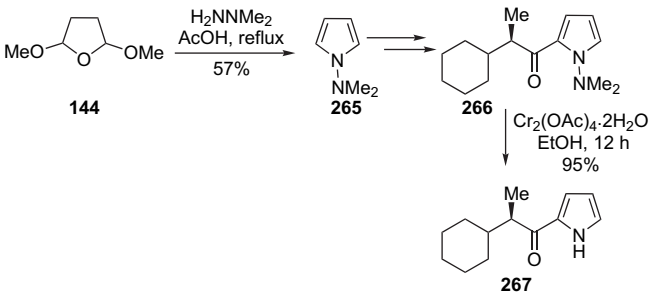


Figure 59. Synthesis of 2-acylpyrrole from 2,5-dimethoxytetrahydrofuran.

N-(*N*,*N*-Dimethylamino)pyrrole **265** was synthesized from 2,5-dimethoxytetrahydrofuran **144** and *N*,*N*-dimethylhydrazine in acetic acid at reflux for 3 h. After C-acylation of the protected pyrrole, reductive cleavage of the N–N bond with chromous acetate gave 2-acylpyrrole **267** (Fig. 59).[110]

Similarly, in the last steps of the synthesis of calcimycin **269**, the *N*,*N*-dimethylamino group was cleaved from 2-acylpyrrole **268** using chromous acetate. Subsequent hydrolysis of the trifluoroacetamide and ester with potassium carbonate in aqueous methanol delivered the targeted pyrrole natural product **269** (Fig. 60).[111]

A one-pot synthesis of 1,2,3-trisubstituted pyrroles (**273**) from hydrazones **270** has been achieved using the carbometalation of vinylstannane, followed by aerobic oxygenation of the *gem*-Zn/Sn dimetallic species **272** (Table 8). In this case, the *N*,*N*-dimethylamino group was removed from **273a** under Birch conditions (Na in liquid NH_3) to afford the corresponding 2,3-disubstituted pyrrole **274** (Fig. 61).[112]

The reaction of hydrazone **275** with silylenol ether **276** in the presence of titanium tetrachloride for 1–3 days afforded

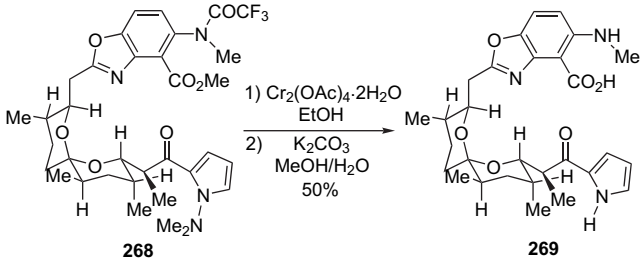


Figure 60. Synthesis of calcimycin **269** by *N*,*N*-dimethylamino group cleavage.

Table 8. Formation of *N*-aminopyrroles **273**

Entry	R^1	R^2	Yields of **273** (%)
a	CH_2Ph	CH_2CH_2Ph	63
b	Pr	*i*-Pr	77
c	CH_2Ph	CH_2Ph	53
d		$-(CH_2)_{10}-$	67
e		$-(CH_2)_6-$	50
f		$-(CH_2)_4-$	29

N-aminopyrroles **277** (Fig. 62).[113] Alkyl- and aryl-substituted as well as ring-fused pyrroles **278** were obtained after reductive cleavage of the dimethylamino group under Birch conditions (Table 9).[113,114]

2.7. *N*-Amido protecting groups

N-Acylpyrroles exhibit different properties from their respective saturated pyrrolidine amides due to the aromatic ring restricting the ability for the nitrogen lone pair of electrons to conjugate with the carbonyl. For example, lithium aluminum hydride reduction of *N*-acylpyrroles liberates the pyrrole and the respective aldehyde or alcohol, contingent on stoichiometry and order of hydride addition. In contrast, the *N*-alkylheterocycle is typically the major product from reduction of the corresponding *N*-acylpyrrolidines.[115] Moreover, *N*-acylpyrroles are much more labile to alkaline hydrolysis than their pyrrolidine counterparts, by a mechanism that can be first or second order in hydroxide ion, contingent on concentration (Fig. 63).[116] In addition, the acetyl group proved more effective in suppressing azafulvene intermediate (**281**, EWG=Ac) than no protection, yet less

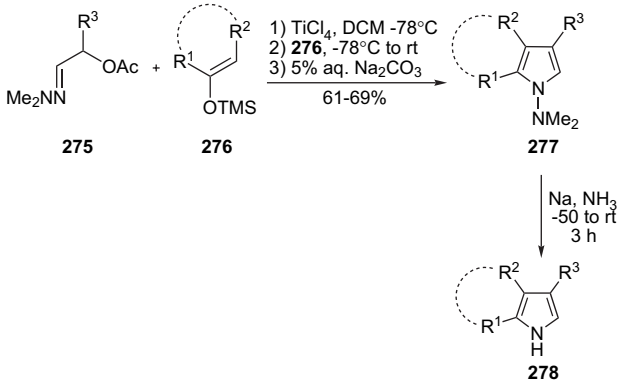


Figure 62. Synthesis of 2,3,4-trisubstituted pyrroles.

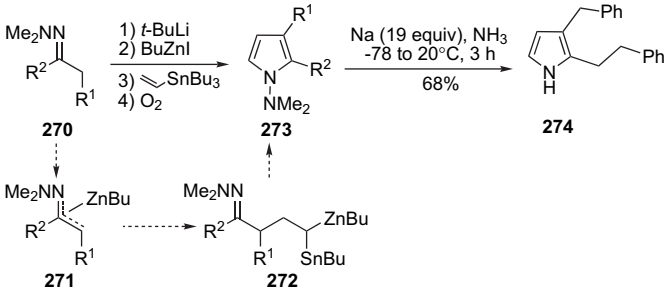
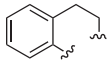


Figure 61. Synthesis of 2,3-disubstituted pyrroles **274**.

Table 9. Synthesis of pyrroles **278** by reductive cleavage of N–N bond

Entry	R^1	R^2	R^3	Yield (%)	Ref.
a	Me	H	Me	32	113
b	*t*-Bu	H	Me	42	114
c	C_6H_5	H	Me	85	113
d	C_6H_5	Me	Me	82	113
e	Et	Me	Me	70	114
f	$-(CH_2)_3-$		Me	90	113
g	$-(CH_2)_4-$		Me	86	114
h	$-(CH_2)_5-$		Me	82	113
i			Me	89	113
j	C_6H_5	H	Et	44	114
k	C_6H_5	Me	Et	51	114
l	C_6H_5	H	*i*-Pr	65	114

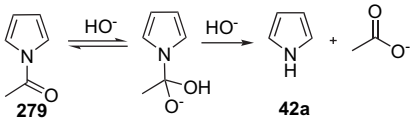


Figure 63. Alkaline hydrolysis of *N*-acetylpyrrole **279**.

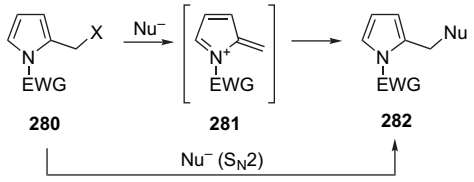


Figure 64. Nucleophilic displacement of 2-hydroxymethylpyrrole **280**.

effective than sulfonyl protection (EWG=mesyl and triflyl), during displacement of 2-hydroxymethylpyrroles **280** (X=OH) with camphanic acid as nucleophile under Mitsunobu reactions (Fig. 64).[44]

Amide protection is usually installed by treating the pyrrolyl anion with the corresponding acyl chloride. For example, pyrrole-2-carboxaldehyde **46** was converted to its acetamide derivative by treating a solution of the pyrrole and sodium hydride in THF with acetyl chloride.[44] Similarly, treatment of a mixture of pyrrole **91** and potassium *tert*-butoxide in benzene with benzoyl chloride at reflux gave benzamide **283** after recrystallization (Fig. 65).[64] Recently, acylation of pyrrole itself (**42a**) with benzoyl chloride has been achieved by heating with KOH in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphonate, [Bmim][PF_6], at 80 °C.[24] Finally, diamine **287** was converted to diacetate **288** without discernable selectivity for either the pyrrole or enamide nitrogens using acetic anhydride in DMF (Fig. 66).[117]

Amides have been generally used less often for pyrrole protection than the Boc or sulfonyl groups, because of their greater reactivity to nucleophiles. On the other hand, the application of benzamide protection proved more advantageous than benzenesulfonyl protection in the synthesis of pyrrolo[3,2-*e*]benzothiazole **286**. This is because the former could be removed using sodium hydroxide in methanol, conditions that had no effect on the corresponding sulfonamide

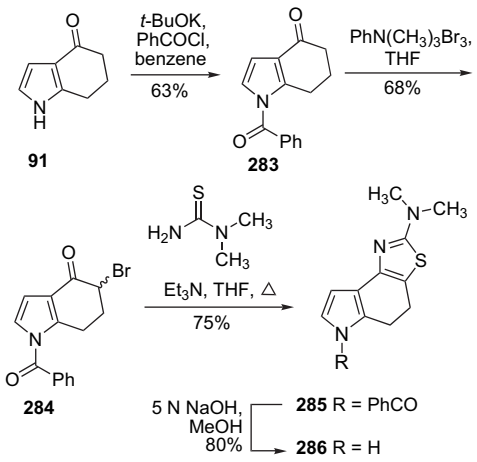


Figure 65. Synthesis of pyrrolo[3,2-*e*]benzothiazole **286**.

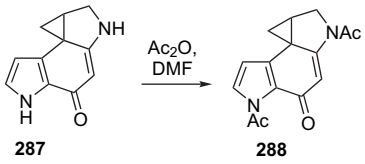


Figure 66. Acetylation of diamine **287**.

derivative, which decomposed under stronger alkaline conditions (Fig. 65).[64] Acetamide protection was abandoned in the synthesis of **286**, after protection of pyrrole **91** with acetic anhydride and sodium acetate, because solvolysis of the acetyl group on attempted recrystallization from methanol returned the starting pyrrole.[64]

3. Pyrrole protection by C-substitution

3.1. Introduction to C-2 protection

As discussed, protection of pyrroles through substitution at nitrogen is well documented and the field benefits directly from advances in amine protection.[15,118] Placing an EWG on the 2-position of the pyrrole ring has proven to be another successful strategy for tempering pyrrole reactivity during the synthesis of substituted porphyrins and other synthetic targets. By utilizing the doubly vinylogous[10] amino-nature of the 2-position, as shown in Figure 67 for carboxylate substitution, a suitable group can serve to diminish pyrrole reactivity. Moreover, by blocking the 2-position such groups can direct catalyzed substitution to the other positions. The natural tendency for pyrrole to undergo 2- (and 5-) substitution is altered by the presence of EWG at the 2-position. In this case, substitution can favor the 4-position. The extent of selectivity is dependent upon the nature of the 2-position substituent and the conditions of the substitution reaction. 2-Position substituents with electron-donating groups can activate the pyrrolic core toward electrophilic aromatic substitution. Careful manipulation and removal of the 2-position substituent has been important for the preparation of a wide range of functionalized pyrroles. The directing effects of various 2-position substituents upon electrophilic substitution of 2-protected pyrroles have been previously reviewed

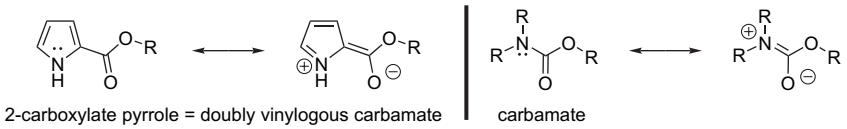


Figure 67. Resonance forms of pyrrole-2-carboxylate and carbamate.

by Anderson.[119] In addition, Trofimov has reviewed the use of 2-vinyl-substituted pyrroles as building blocks within synthesis.[120]

3.2. Pyrrole-2-carboxylates

Pyrrole-2-carboxylates exhibit doubly vinylogous carbamate character[10] (Fig. 67), and the pyrrolic lone pair is stabilized through resonance. Indeed, pyrrole-2-carboxylates are usually air- and moisture-stable crystalline solids, making purification through crystallization or chromatography facile. Furthermore, the 2-carboxylate functionality is stable to oxidation, reduction, and nucleophilic substitution conditions that are often required for the derivatization of other substituents of the pyrrole ring. In these two respects, the carboxylate group at the 2-position of pyrroles represents an ideal protecting group and has widespread application in dipyrromethene[121,122] and porphyrin[17,18] synthesis. Furthermore, the electron-withdrawing ability of the ester[123] and the stability of pyrrole-2-carboxylates render this structural motif useful within pyrrolic targets for the pharmaceutical industry, for example, pyrroles with antiviral,[124] antibacterial,[125] and anticancer[3,126] capabilities.

Courtesy of the Knorr reaction and its modifications (Fig. 68)[18] substituted pyrrole-2-carboxylates are readily available on grand scales from acyclic materials. Typical Zanetti-modified[127] Knorr reaction conditions involve the oxime of an alkylacetoacetate (**289**) and 2,4-pentanedione (acetylacetone). The oxime **290a** is reduced with zinc dust to the corresponding α-aminoketone, which can undergo self-condensation rather than react as desired with the 2,4-pentanedione. Consequently, the modern procedure[18] involves the dropwise addition of the oxime to the acetylacetone with concurrent slow addition of zinc powder, thereby limiting the concentrations of α-aminoketone generated in situ. With practice, the exothermic reaction can be performed on multi-molar scales to obtain moderate–good yields of crystalline pyrroles **291** of very high purity. The ketone functionality can be reduced using diborane[128] and thus the familiar ethyl–methyl substitution pattern of many porphyrin skeletons[129] is created.

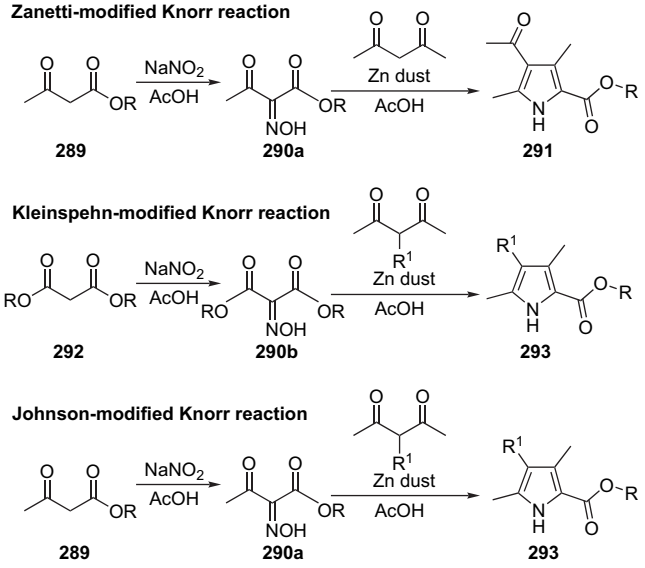


Figure 68. Knorr reactions.

The Kleinspehn-modified[130] Knorr reaction replaces alkylacetoacetate with a dialkyl malonate (**292**). Condensation involves an alternative conformation and the resulting pyrrole-2-carboxylate **293** is unsubstituted at the 4-position (R^1=H) if 2,4-pentanedione is used. Alternatively, use of 3-substituted 2,4-pentanediones gives 4-substituted pyrrole-2-carboxylates. The Johnson-modified[131] Knorr reaction also gives 4-substituted pyrrole-2-carboxylates and it uses alkylacetoacetates and 3-substituted 2,4-pentanediones. Although the Kleinspehn modification typically gives higher pyrrole yields than the Johnson modification, the nitrosation of alkylacetoacetates proceeds more readily than the nitrosation of dialkyl malonates.[18] A variety of other Knorr-type reactions, and alternatives, have been reviewed previously.[18] The Barton–Zard route[132] (Fig. 69) to pyrrole-2-carboxylates (**296**) is particularly advantageous in that pyrroles unsubstituted at the 5-position are produced.

Pyrrole-2-carboxylates are the traditional mainstay of synthetic routes to porphyrins and dipyrromethenes. The carboxylate group serves to deactivate the pyrrole ring, thus protecting it from over-reaction and facilitating isolation and purification procedures. The 3-, 4- and 5-positions of pyrroles are typically manipulated with the carboxylate group serving to block the 2-position. Pyrrole-2-carboxylates generated through Knorr-type syntheses are robust under the reaction conditions required for derivatization at the other positions (Fig. 70). By no means comprehensive, Figure 70 serves to show a range of synthetic steps typically encountered in routes to porphyrins and dipyrromethenes. For example, 5-methyl groups of pyrroles protected with 2-carboxylate groups can be mono-oxidized, and the products (**304**) can be either isolated (X=OAc) or self-condensed in situ to give 2,2′-dipyrromethanes (**305**).[133] Trioxidation of the 5-methyl group, followed by decarboxylation gives the 5-unsubstituted pyrrole-2-carboxylate (**307**), the same as the product produced directly via the Barton–Zard procedure. This trioxidation and thermal or iodinative[134]

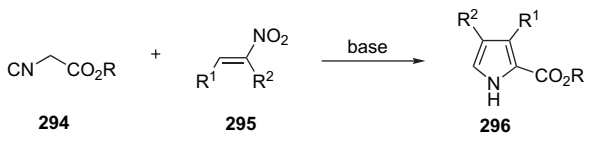


Figure 69. The Barton–Zard reaction.

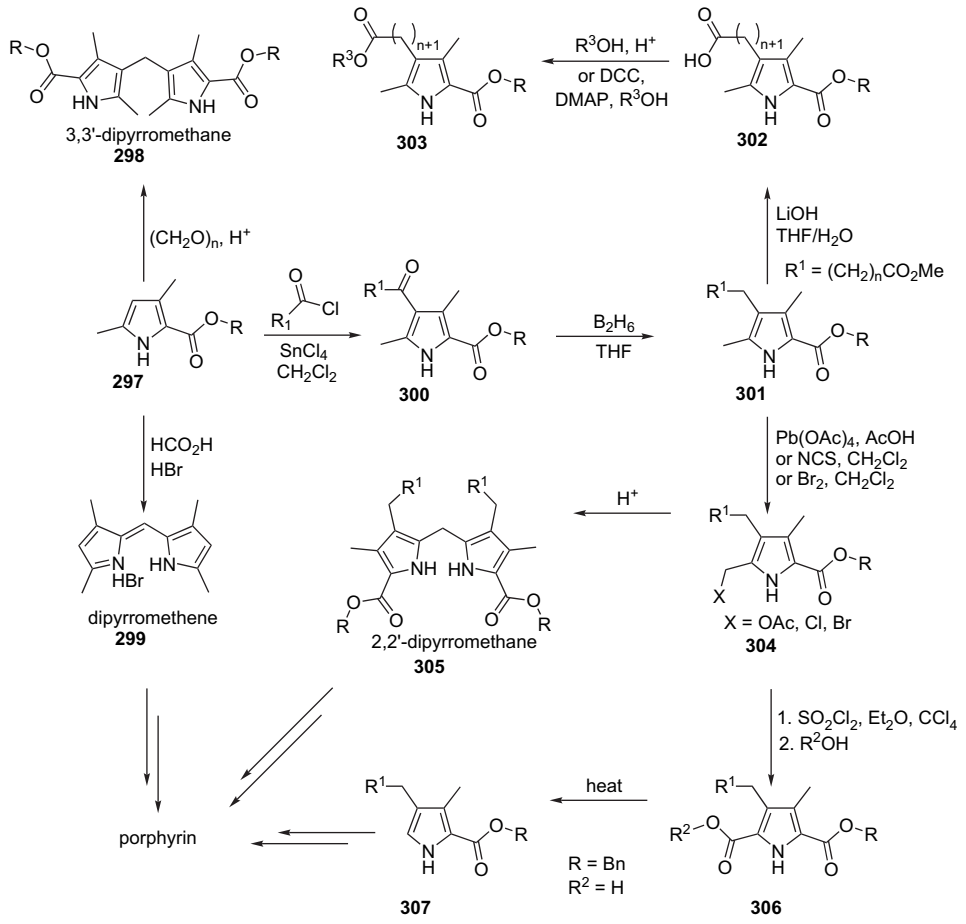


Figure 70. Syntheses involving Knorr pyrroles.

decarboxylation effectively permits a reversal of the orientation of substituents, and is crucial in the synthesis of protoporphyrin IX.[135,136] The 2-carboxylate group is stable under mild hydrolysis conditions giving **302**, and thus alkanoates at other positions can be hydrolyzed and transesterified to give **303**.[137] In many cases, acids are required to catalyze the reaction (e.g., acylation,[138,139] self-condensation[133]) as the electron-withdrawing 2-carboxylate group greatly reduces the nucleophilicity of the pyrrolic core.[21] Without such protection over-reaction and side-reactions leading to dark tars would likely result from exposure of related pyrroles to acidic conditions.

The deprotection and application of the three most popular pyrrole-2-carboxylates (ethyl, benzyl, and *tert*-butyl) will be discussed. Diethylmalonate and ethylacetoacetate are commercially available at very modest cost. Consequently, Knorr-type reactions often utilize these esters. Ethyl pyrrole-2-carboxylates can be saponified by treatment with aqueous KOH, whereby the resulting carboxylic acid undergoes acid-catalyzed decarboxylation to give the corresponding 2-unsubstituted (alpha-free) pyrrole. For example, cryptopyrrole (**310**, Fig. 71) has been used as a common starting material for porphyrin synthesis, despite its relative instability and propensity to give tars under acidic conditions. Cryptopyrrole is best prepared by large-scale saponification of ethyl 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylate (**308**), followed by decarboxylation and steam-distillation (Fig. 71).[138] Exposure to high temperatures has been commonly used for the decarboxylation of pyrrole-2-carboxylic acids,[140,141] and so has treatment with TFA.[142] For example, 3,4-dialkoxypyrroles were made by saponification and decarboxylation of dimethyl-3,4-dialkoxypyrrole-2,5-dicarboxylates.[67] In the presence of formic acid, alpha-free pyrroles were produced by decarboxylation and condensed in situ to give the dipyrromethene hydrobromide salt (**299**, Fig. 70).[143] Such reactions are also applicable to 2,2′- and 3,3′-dipyrromethanes, molecules containing more than one pyrrolic unit.[18,137]

The terpyrrole **312**, protected as its tetra(ethyl carboxylate), was synthesized from **311** by condensation with ammonia.

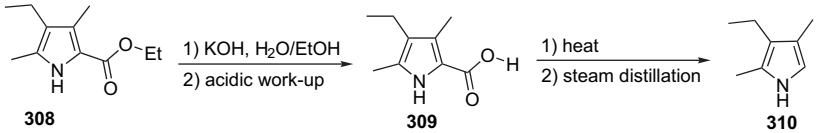


Figure 71. Synthesis of cryptopyrrole.

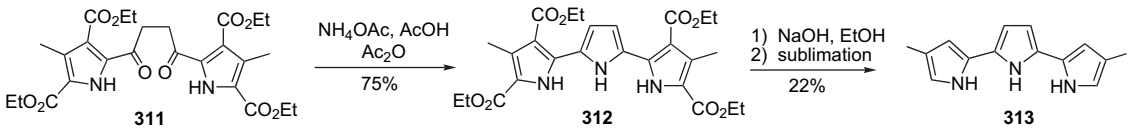


Figure 72. Synthesis of terpyrrole **313**.

Removal of all four ethyl esters, to give **313**, was achieved by hydrolysis followed by decarboxylation under sublimation conditions (Fig. 72).

Following saponification of ethyl esters, acidification is required to give the carboxylic acid. This acidification process must be very carefully controlled, because excess acid can cause side reactions such as polymerization, which may result in the discoloration of the product and formation of dark tars. Trans-esterification of ethyl pyrrole-2-carboxylates such as **308** in benzyl alcohol at reflux with stoichiometric amounts of sodium benzoxide gave benzyl ester **314** (Fig. 73).[144] Trans-esterification can be promoted by microwave energy using catalytic amounts of sodium methoxide in benzyl alcohol.[145] Benzyl pyrrole-2-carboxylates have the advantage that hydrogenolysis catalyzed by Pd/C proceeds very readily and the carboxylic acids prepared in this way are generally less prone to discoloration and polymerization than those prepared by saponification of ethyl pyrrole-2-carboxylates.[18]

tert-Butyl pyrrole-2-carboxylates cannot be prepared by trans-esterification of ethyl or benzyl pyrrole-2-carboxylates. The synthesis of such *tert*-butyl esters has been achieved by Knorr-type reactions employing di-*tert*-butyl malonate and *tert*-butyl acetoacetate.[18,146] *tert*-Butyl pyrrole-2-carboxylates are advantageous in that deprotection can be achieved by treatment of the pyrrole with TFA, although these conditions are not always tolerated by other substituents. Furthermore, *tert*-butyl acetoacetate is less readily available than the ethyl and benzyl analogues.[147] Given the difficulties encountered with the decarboxylation of pyrrole-2-carboxylates, it might appear rather tedious to persevere with their use. However as the Knorr reaction is so adept at providing such pyrroles, and the starting materials for the reaction are inexpensive, the bulk of synthetic chemistry toward porphyrins and dipyrromethenes still uses these pyrroles as building blocks.

The methyl pyrrole-2-carboxylate **316** was prepared in order to temporarily protect the pyrrole **315** (Fig. 74). After a number of steps the methyl ester was hydrolyzed and in situ decarboxylation under acidic conditions gave (−)-rhazinilam **318**.[148]

3.3. Pyrrole-2-carboxaldehydes

Formyl groups are often used to stabilize electron-rich pyrroles within extended synthetic sequences, with the Vilsmeier–Haack reaction[18,147] (e.g., DMF/$POCl_3$[134] or DMF/PhCOCl[149]) and the Clezy formylation reaction ($CH(OMe)_3$/TFA[150,151]) being extremely useful for the preparation of pyrrole-2-carboxaldehydes in situ from pyrrole-2-carboxylates. Although pyrrole-2-carboxaldehydes are key intermediates en route to porphyrins and dipyrromethenes, they are often susceptible to oxidation, reduction, and acid-induced decomposition. This can lead to complex reaction mixtures and unpleasant tars, often making for extremely difficult purification procedures when pyrrole-2-carboxaldehydes are involved. Consequently, the formyl group is often protected as an oxime, hydrazone, acetal or related functionality,[18] among which one of the more useful protecting groups has been the corresponding 2-cyanovinyl pyrroles.[152–154] The cyanovinyl group has acted as an electron-withdrawing protecting group for the pyrrole during mono-oxidation of the 5-methyl group, and isolation of the 5-chloromethyl pyrrole **321** (Fig. 75). 2-Cyanovinyl pyrroles can be readily prepared by treating pyrrole-2-carboxaldehydes with malonitrile or cyanoacetate esters via the Knoevenagel reaction. For example, protection of 3,4,5-trimethylpyrrole-2-carboxaldehyde (**319**), with methyl cyanoacetate gave excellent yields of 2-(2-cyano-2-methoxycarbonylvinyl)-3,4-5-trimethylpyrrole (**320**, Fig. 75).

Coupling of chloromethylpyrrole **321** with 2-cyanovinyl-protected pyrrole **322**[155] under Lewis acid-catalyzed conditions gave the 2,2′-dipyrromethane **323**, which was

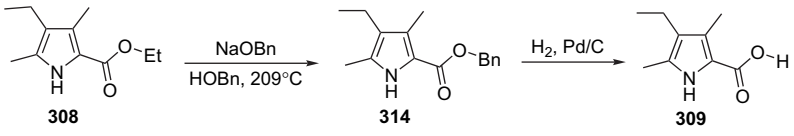


Figure 73. Trans-esterification with benzoxide and hydrogenolytic ester cleavage.

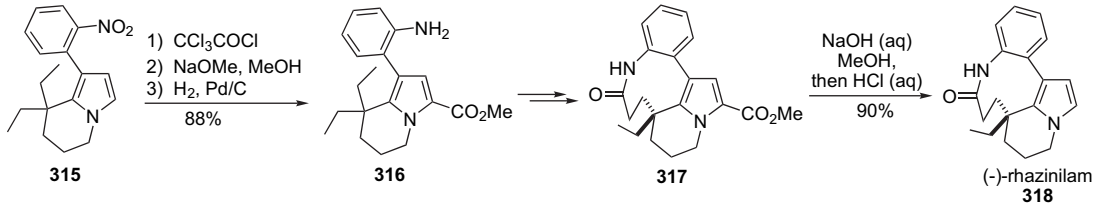


Figure 74. Use of methyl carboxylate in the synthesis of (−)-rhazinilam **318**.

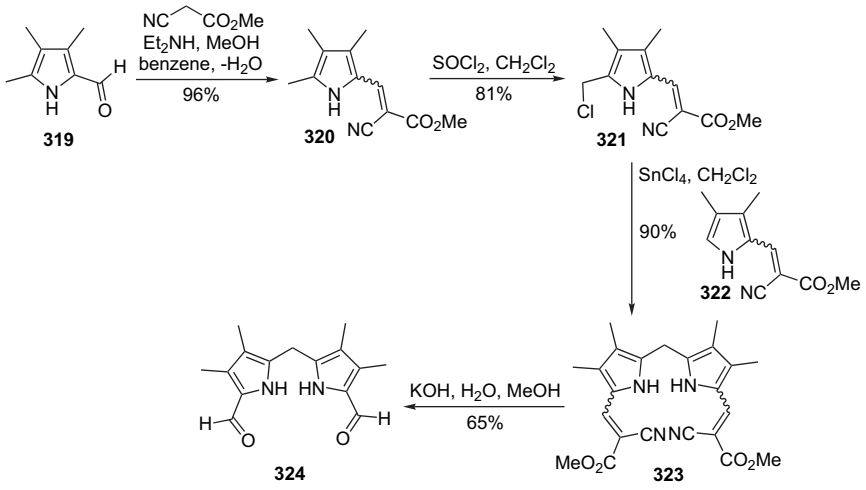


Figure 75. Synthesis of 5,5′-cyanovinyl-protected-2,2′-dipyrromethane (**323**).

hydrolyzed to release the two formyl groups. 2-Cyanovinyl pyrroles are recognizably bright yellow and often crystalline solids. They are quite nonpolar relative to pyrrole-2-carboxaldehydes and simpler to purify using silica-gel chromatography. Due to their easy crystallization and facile chromatographic purification, dicyanovinyl derivatives of pyrrole-2-carboxaldehydes are sometimes made purely for the purposes of facilitating purification. Furthermore, the cyanovinyl group is resistant to oxidation and thus protects pyrrole aldehydes from oxidation to carboxylic acid. This is especially important in the synthesis of strapped porphyrins, etc. whereby both the 2- and 5-positions of the pyrrole must be functionalized. Methyl cyanoacrylates have been reported[155] to be the most useful cyanovinyl group for this purpose, as these are more reactive and more soluble than their 2-dicyanovinyl analogues. However *E*/*Z* isomers, of variable ratio, unnecessarily complicate NMR spectra and so many practitioners favor using 2-dicyanovinyl-protected pyrroles. Disadvantages of cyanovinyl groups include their susceptibility toward hydrogenation, the low reactivity of cyanovinyl-protected pyrroles as a result of the very electron-withdrawing group, and the strongly alkaline conditions required for their hydrolysis (Fig. 75).[155]

5-Substituted pyrrole-2-carboxaldehydes have been efficiently synthesized by protection of pyrrole-2-carboxaldehyde as the dimer **325**. Deprotonation of **325**, followed by treatment with a range of electrophiles and subsequent hydrolysis gave good yields of the required 5-substituted pyrrole-2-carboxaldehydes (**326**, Fig. 76). Protection of the 2-formyl group in this way avoided the mixtures of 4- and 5-substituted products that would likely result from electrophilic aromatic substitution of pyrrole-2-carboxaldehyde, due to the poor regioselectivity induced by the formyl group.[18]

Pyrrole-2-carboxaldehyde has been protected as various iminium salts that have increased selectivity for 4-substitution, compared to pyrrole-2-carboxaldehyde.[156] The electron-withdrawing iminium substituent often limits pyrrole reactivity to only the more reactive electrophilic reactions, for example, bromination and acylation (Fig. 77).[157] After regioselective acylation and subsequent hydrolysis, the formyl group has been removed from disubstituted pyrrole **328** by oxidation to the carboxylic acid and then heat-induced decarboxylation, thus giving ketone **329**.[157]

Acetals have also been used to protect formyl groups. Difficulty was encountered in preparing simple acetal derivatives of pyrrole-2-carboxaldehydes (e.g., with methanol or ethylene glycol) as a result of acid instability and the reduced nucleophilicity of the doubly vinylic amide carbonyl

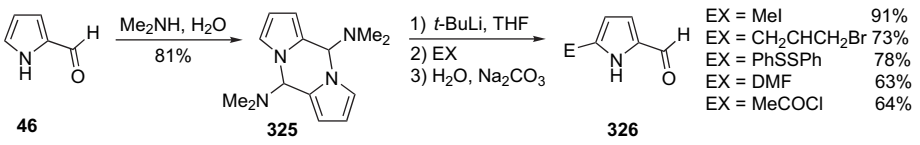


Figure 76. Synthesis and acylation of **325**.

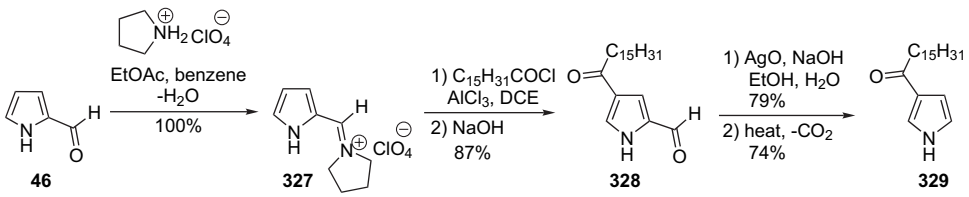


Figure 77. Protection of the formyl group using an iminium salt.

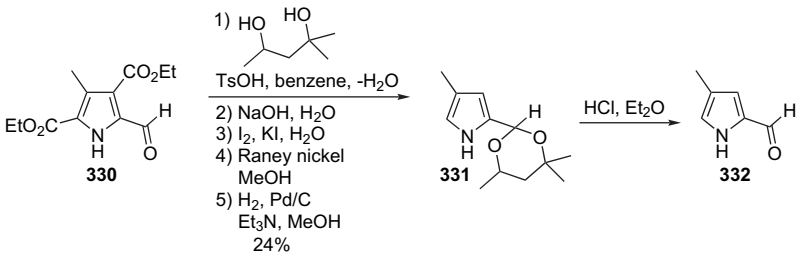


Figure 78. Use of a formyl group protected as an acetal.

group.[140] Acetals of 2-methylpentane-2,4-diol were, however, isolable in cases when the pyrrole bore an EWG in addition to the formyl group. For example, acetylation of pyrrole-2-carboxaldehyde **330** (bearing three EWGs), hydrolysis and decarboxylation yielded acetalpyrrole **331** (Fig. 78).

Thioacetals have also proven to be useful protecting groups for the carbonyl group of pyrrole-2-carboxaldehydes (Fig. 79),[140] with successful condensation again being reliant upon the presence of a second electron-withdrawing substituent (in addition to the formyl group). Reaction of ethanedithiol with the appropriate 2-(dichloromethyl)-pyrrole has also provided the thioacetal directly from the dichloride precursor to the aldehyde. Such thioacetals (**334**) do not introduce chiral centers and have been used effectively in the synthesis of dipyrromethanes (e.g., **337**), preventing self-condensation of 5-unsubstituted pyrrole-2-carboxaldehyde. Removal of the thioacetal has been achieved by treatment with red mercuric oxide and $BF_3 \cdot Et_2O$.

3.4. Blocking and activating groups at the 2-position

Introduction of an electron-rich blocking group at the 2-position of pyrrole group is an alternative and useful strategy for promoting the pyrrole reactivity. For example, the electron-donating[158] thio substituent in 2-sulfenyl pyrroles[159,160] has been used to block the 2-position and activate the other positions toward electrophilic substitution reactions. The 2-methylthio substituent in pyrrole **164** promoted regioselective Vilsmeier–Haack acylation at the 5-position (Fig. 80),[161] exclusively giving ketone **340**. For the synthesis of pyrrolizine **343**, the sulfide was oxidized to the corresponding sulfone (**341**). *N*-Alkylpyrrole **342** was then synthesized by reaction with spiro-activated cyclopropane **344**. Hydrolysis to the dimethyl malonate, deprotonation with sodium hydride, and intramolecular addition with elimination of the sulfinate gave pyrrolizine **343**, an intermediate en route to a potent anti-inflammatory and analgesic agent. In this synthetic sequence, the methylthio substituent served to block the 2-position of the pyrrole toward electrophilic attack, and activated the 5-position toward acylation. On oxidation to the sulfone, a leaving group was generated for intramolecular displacement in the annulation step. The procedure for the preparation of methylthio pyrrole **164** was somewhat general and extended to the syntheses of 2-(alkylthio)- and 2-(arylthio)-pyrroles. Furthermore, the addition–elimination of sulfinate in the annulation was only successful with pyrroles bearing electron-withdrawing ring substituents, and other leaving groups (e.g., Br) also underwent displacement in related cyclizations.

The use of alkylthio groups as masking and activating groups for pyrroles has been extended by the preparation of methylthio, ethylthio, *n*-decylthio, and phenylthio substituents.[160] 2-(Methylthio)-pyrrole (**164**) was prepared by the reaction of pyrrole with dimethyldisulfide under acidic conditions;[160] however this procedure could not be extended to give good yields of the other sulfides (Fig. 81). Instead, the treatment of 2-thiocyanatopyrrole with Grignard reagents gave 2-(ethylthio)-, 2-(decylthio)-, and 2-(phenylthio)pyrrole (**347**, **348**, and **346**, respectively).[162] Deuterium exchange studies showed that the three alkylthio substituents all activated the 3- and 5-positions toward substitution (relative to pyrrole itself), and that these 2-(alkylthio)-pyrroles were intermediate in reactivity between pyrrole and 2-methylpyrrole.

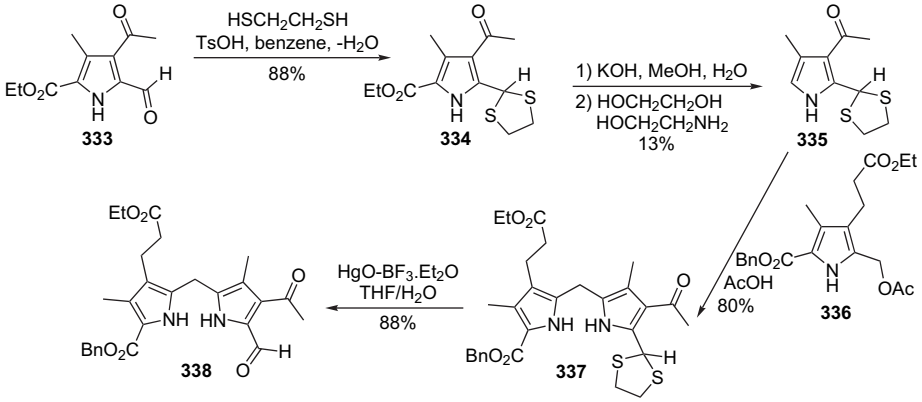


Figure 79. Thioacetal employment in the synthesis of dipyrromethane **338**.

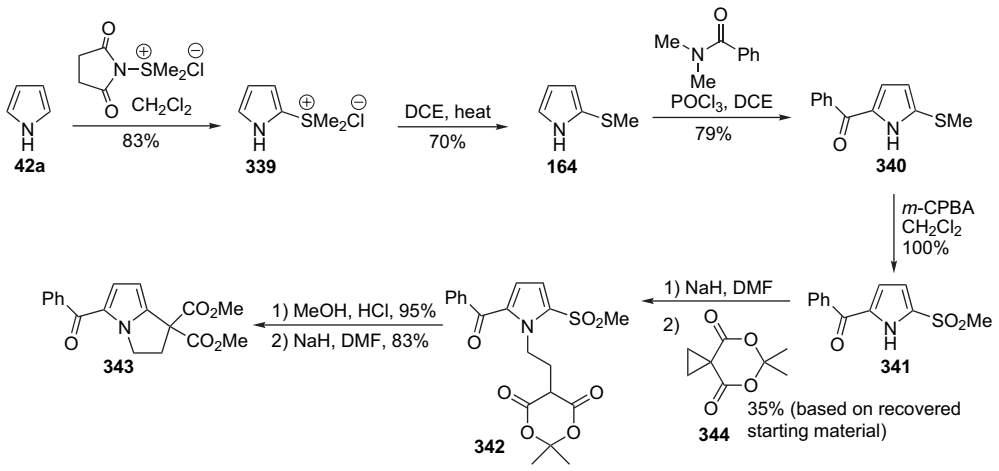


Figure 80. Synthesis of **343** using 2-sulfonium pyrrole **339**.

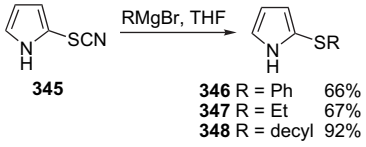


Figure 81. Synthesis of 2-thio-pyrroles.

Significantly, the electron-donating alkylthio substituent deactivated the 4-position (relative to pyrrole itself). In contrast, 2-(phenylthio)-pyrrole was found to deactivate all positions of the pyrrolic ring toward deuterium exchange.

Reaction of 2-(methylthio)-pyrrole (**164**) with pseudo-stoichiometric amounts of benzaldehyde under acid-catalyzed conditions gave the corresponding *meso*-substituted dipyrromethane **349** in moderate yield (Fig. 82), with $InCl_3$ proving to be the best Lewis acid for effecting good regioselectivity between the desired dipyrromethane and its *N*-confused alternative (not shown). This procedure was applied to the ethyl, decyl, and phenyl analogues and represented a significant improvement over existing routes to *meso*-substituted dipyrromethenes, which had typically required the use of a large excess of the pyrrole.[163] Desulfurization of thioether **349** proceeded smoothly with Raney nickel to give dipyrromethane **351**; similar results were obtained for the decyl analog. For the phenyl analog, incomplete reaction and several products resulted from the use of Raney nickel, and nickel boride did not improve the desulfurization process. Oxidation of dipyrromethane **349** with DDQ gave the required dipyrromethene (**350**), and treatment of the decyl and phenyl analogues with *m*-CPBA gave the corresponding sulfones, which proved difficult to purify. A potential route to unsymmetrical dipyrromethanes was also demonstrated, whereby the acylated 2-(methylthio)-pyrrole **340** was reduced and the resulting alcohol was reacted with **164**, as shown in Figure 82.

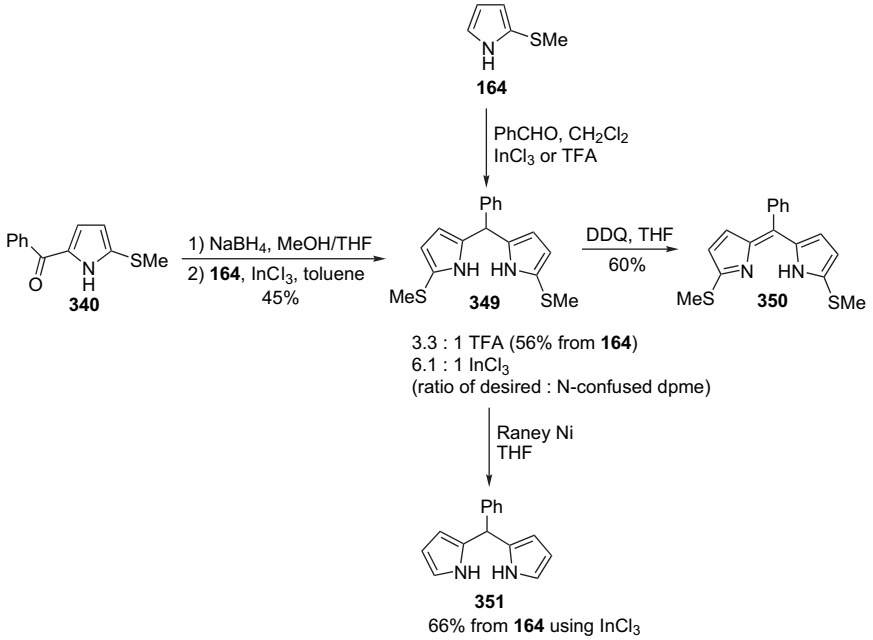


Figure 82. 2-Methylthio-pyrrole in the synthesis of dipyrromethanes and dipyrromethenes.

3.5. 2-Sulfinyl and 2-sulfonyl protecting groups

Sulfonium, sulfinyl, and sulfonyl groups at the 2-position, all stabilize the electron-excessive[119] pyrrolic ring as demonstrated by ^{13}C NMR spectroscopic and X-ray crystallographic studies.[12] Some 2-(arylsulfinyl)-pyrroles rearrange under acidic conditions to give the 3-substituted isomer.[164] 2-(Alkylsulfinyl)-pyrroles also rearrange at slower rates. Although desulfonylation reactions occur usually via treatment with Raney nickel, 2-(arylsulfonyl)-pyrroles undergo radical-induced reductive desulfonylation on treatment with Bu_3SnH/AIBN (Fig. 83).[161] This procedure was used to effect annulation by intramolecular trapping of the radical intermediate with aryl and alkyl bromides to form pyrrolizine and indolizine analogs **355** and **357**, respectively (Fig. 83). The related 3-(arylsulfonyl)-pyrroles were reported to be inert under such conditions.

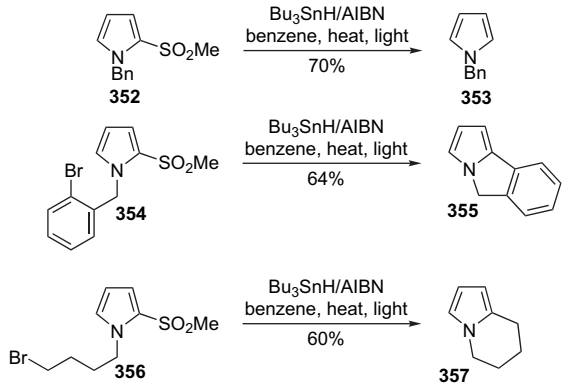


Figure 83. Radical-induced desulfonylation and annulation of 2-sulfonyl pyrroles.

2,4-Dinitrobenzenesulfinyl and sulfonyl groups are effective stabilizing groups for pyrrole. In analogous fashion to the liberation of amines from protection as nitrobenzenesulfonylamides,[165] 2,4-dinitrobenzenesulfinyl and sulfonyl groups can be removed by treatment of the pyrrole with thiol, which produces the thioether **359** as byproduct (Fig. 84).[12]

Figure 84. Cleavage of 2,4-dinitrobenzenesulfonyl group from pyrrole.

4. Concluding remarks

Pyrrole chemistry presents particular challenges for mediating the reactivity of this archetypal pi-excessive heterocycle.[166] Innovative strategies have been developed for controlling reactivity and selectivity by modulation of the electron density and steric environment through use of different protecting groups at the pyrrole nitrogen and its 2-position carbon. Growing interest in pyrrolic products for applications in medicine and materials science evokes the need for more selective chemistry and improved methods to effectively introduce, apply, and remove protection for the functionalization of pyrrole. By presenting a survey of these different protection strategies and their application in the synthesis of pyrrolic targets, we hope that this review will facilitate the application of existing methods and inspire creativity for the development of new approaches for performing practical, effective, and selective pyrrole chemistry.

Acknowledgements

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References and notes

1. Sternberg, E. D.; Dolphin, D.; Brückner, C. *Tetrahedron* **1998**, *54*, 4151–4202.
2. Melvin, M. S.; Tomlinson, J. T.; Saluta, G. R.; Kucera, G. L.; Lindquist, N.; Manderville, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 6333–6334.
3. Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603.
4. D'Alessio, R.; Margiotti, A.; Carlini, O.; Colotta, F.; Ferrari, M.; Gnocchi, P.; Isetta, A. M.; Mongelli, N.; Motta, P.; Rossi, A.; Rossi, M.; Tibolla, M.; Vanotti, E. *J. Med. Chem.* **2000**, *43*, 2557–2565.
5. O'Hagen, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
6. Sato, A.; McNulty, L.; Cox, K.; Kim, S.; Scott, A.; Daniell, K.; Summerville, K.; Price, C.; Hudson, S.; Kiakos, K.; Hartley, J. A.; Asao, T.; Lee, M. *J. Med. Chem.* **2005**, *48*, 3903–3918.
7. *Drug Topics* **2006**, *150*, 26.
8. Taylor, E. C.; Jones, R. A. *Pyrroles*; Wiley: New York, NY, 1990.
9. Ketcha, D. M. *Prog. Heterocycl. Chem.* **2001**, 111–129.
10. *The Chemistry of Pyrroles*; Jones, A. R., Bean, G. P., Eds.; Academic: London, 1977.
11. Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411–454.
12. Thompson, A.; Butler, R. J.; Grundy, M. N.; Laltoo, A. B. E.; Robertson, K. N.; Cameron, T. S. *J. Org. Chem.* **2005**, *70*, 3753–3756.
13. Dashyant, D.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2181–2186.
14. Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
15. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, NY, 1999.
16. Gossauer, A. *Houben-Weyl*; Kreher, R. P., Von Backes, J., Eds.; Thieme: Stuttgart, 1994; Vol. E 6a, Part 1, pp 556–798.
17. Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*; Springer: New York, NY, 1989.
18. Paine, J. B., III. *The Porphyrins*; Dolphin, D., Ed.; Academic: 1978; Vol. I, Chapter 4.
19. Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529.
20. Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214–3219.
21. Thompson, A.; Gao, S.; Modzelewska, G.; Hughes, D. S.; Patrick, B.; Dolphin, D. *Org. Lett.* **2000**, *2*, 3587–3590.

22. Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; Mcdonald, R. *Tetrahedron Lett.* **1981**, *22*, 4899–4900.
23. Rokach, J.; Hamel, P.; Kakushima, M.; Smith, G. M. *Tetrahedron Lett.* **1981**, *22*, 4901–4904.
24. Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, *12*, 1951–1954.
25. Merrill, B. A.; LeGoff, E. *J. Org. Chem.* **1990**, *55*, 2904–2908.
26. Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Org. Chem.* **1998**, *63*, 8163–8169.
27. Liu, J. H.; Yang, Q. C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587–3595.
28. Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825.
29. Kinoshita, H.; Tanaka, S.; Inomata, K. *Chem. Lett.* **1989**, 1107–1108.
30. Masaguer, C. F.; Ravina, E.; Fueyo, J. *Heterocycles* **1992**, *34*, 1303–1309.
31. Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783–794.
32. Okabe, K.; Natsume, M. *Tetrahedron* **1991**, *47*, 7615–7624.
33. Muratake, H.; Natsume, M. *Tetrahedron* **1991**, *47*, 8535–8544.
34. Jolicoeur, B.; Lubell, W. D. *Org. Chem. Div. Am. Chem. Soc. Meeting*, Abstract ORGN 61: Atlanta, GA, March 26–30, 2006.
35. Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099–2102.
36. Miller, A. D.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1943–1956.
37. Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595–596.
38. Liu, J. H.; Chan, H. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274–3283.
39. Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601–2604.
40. Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296–301.
41. Ganske, J. A.; Pandey, R. K.; Postich, M. J.; Snow, K. M.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 4801–4807.
42. Chan, H. W.; Chan, P. C.; Liu, J. H.; Wong, H. N. C. *Chem. Commun.* **1997**, 1515–1516.
43. Dhanak, D.; Reese, C. B.; Romana, S.; Zappia, G. *J. Chem. Soc., Chem. Commun.* **1986**, 903–904.
44. Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Am. Chem. Soc.* **1998**, *120*, 1741–1746.
45. Chambers, M. S.; Atack, J. R.; Broughton, H. B.; Collinson, N.; Cook, S.; Dawson, G. R.; Hobbs, S. C.; Marshall, G.; Maubach, K. A.; Pillai, G. V.; Reeve, A. J.; MacLeod, A. M. *J. Med. Chem.* **2003**, *46*, 2227–2240.
46. Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141–6142.
47. Jeannotte, G.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 4656–4662.
48. Salman, H.; Abraham, Y.; Tal, S.; Meltzman, S.; Kapon, M.; Tessler, N.; Speiser, S.; Eichen, Y. *Eur. J. Org. Chem.* **2005**, 2207–2212.
49. Hasan, I.; Marinelli, E. R.; Lin, L. C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157–164.
50. Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2777–2781.
51. Handy, S. T.; Bregman, H.; Lewis, J.; Zhang, X. L.; Zhang, Y. N. *Tetrahedron Lett.* **2003**, *44*, 427–430.
52. Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025–1027.
53. Baillie, C.; Xiao, J. L. *Tetrahedron* **2004**, *60*, 4159–4168.
54. Beecher, J. E.; Tirrell, D. A. *Tetrahedron Lett.* **1998**, *39*, 3927–3930.
55. Routier, S.; Sauge, L.; Ayerbe, N.; Coudert, G.; Merour, J. Y. *Tetrahedron Lett.* **2002**, *43*, 589–591.
56. Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499–500.
57. Candy, C. F.; Jones, R. A. *J. Org. Chem.* **1971**, *36*, 3993–3994.
58. Hobbs, C. F.; McMillin, C. K.; Papadopoulos, E. P.; VanderWerf, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 43–51.
59. Wang, N.-C.; Teo, K.-E.; Anderson, H. J. *Can. J. Chem.* **1977**, *55*, 4112–4116.
60. Sukata, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 280–284.
61. Baroni, S.; Stradi, R. *J. Heterocycl. Chem.* **1980**, *17*, 1221–1223.
62. Anderson, H. J.; Griffiths, S. J. *Can. J. Chem.* **1967**, *45*, 2227–2234.
63. Jones, M. I.; Froussios, C.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 472–473.
64. Remers, W. A.; Roth, R. H.; Gibs, G. J.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 1232–1240.
65. Hirayama, M.; Choshi, T.; Kumemura, T.; Tohyama, S.; Nobuhiro, J.; Hibino, S. *Heterocycles* **2004**, *63*, 1765–1770.
66. Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738–739.
67. Merz, A.; Schropp, R.; Dötterl, E. *Synthesis* **1995**, 795–800.
68. Merz, A.; Meyer, T. *Synthesis* **1999**, 94–99.
69. Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1993**, *58*, 403–407.
70. Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725–1728.
71. Costi, R.; Di Santo, R.; Artico, M.; Roux, A.; Ragno, R.; Massa, S.; Tramontano, E.; La Colla, M.; Loddo, R.; Marongiu, M. E.; Pani, A.; La Colla, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1745–1749.
72. Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203–205.
73. Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723–3729.
74. Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630–633.
75. Dixon, J.; Baxter, A. J. G.; Manners, C. N.; Teague, S. *Chem. Abstr.* **1989**, *111*.
76. Dalton, C. R.; Kane, J. M.; Rampe, D. *Tetrahedron Lett.* **1992**, *39*, 5713–5716.
77. Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.
78. Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515–8519.
79. Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553.
80. Anderson, H. J. *Tetrahedron Lett.* **1971**, *34*, 3165–3166.
81. Groves, J. K.; Cundasawmy, N. E.; Anderson, H. J. *Can. J. Chem.* **1973**, *51*, 1089–1099.
82. Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 93–102.
83. Anderson, K. W.; Tepe, J. J. *Tetrahedron* **2002**, *58*, 8475–8481.
84. Mandell, L.; Piper, J. U.; Pesterfield, C. E. *J. Org. Chem.* **1963**, 574–575.
85. Lazzaroni, R.; Settembolo, R.; Caiazzo, A.; Pontorno, L. *J. Organomet. Chem.* **2000**, *601*, 320–323.
86. Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679–4682.

87. Gonzalez, C.; Greenhouse, R.; Tallabs, R. *Can. J. Chem.* **1983**, *61*, 1697–1702.
88. Yim, E. S.; Park, M. K.; Han, B. H. *Ultrason. Sonochem.* **1997**, *4*, 95–98.
89. Flitsch, W.; Lubisch, W. *Chem. Ber.* **1984**, *117*, 1424–1435.
90. Vedejs, E.; Little, J. D.; Seaney, L. M. *J. Org. Chem.* **2004**, *69*, 1788–1793.
91. Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498–5505.
92. Santiago, B.; Dalton, C. R.; Huber, E. W.; Kane, J. M. *J. Org. Chem.* **1995**, *60*, 4947–4950.
93. Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1995**, *60*, 5069–5076.
94. Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1994**, *59*, 6902–6903.
95. Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636–637.
96. Magnus, G.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 4127–4130.
97. Katritzky, A. R.; Khan, G. R.; Marson, C. M. *J. Heterocycl. Chem.* **1987**, *24*, 641–644.
98. Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H. J.; You, J. S.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414–4422.
99. Trofimov, B. A.; Zaitsev, A. B.; Schmidt, E. Y.; Vasil'tsov, A. M.; Mikhaleva, A. I.; Ushakov, I. A.; Vashchenko, A. V.; Zorina, N. V. *Tetrahedron Lett.* **2004**, *45*, 3789–3791.
100. Ackrell, J.; Franco, F.; Greenhouse, R.; Guzmãn, A.; Muchowski, J. M. *J. Heterocycl. Chem.* **1980**, *17*, 1081–1085.
101. Muchowski, J. M.; Scheller, M. E. *Tetrahedron Lett.* **1987**, *28*, 3453–3456.
102. Muchowski, J. M.; Solas, D. R. *Tetrahedron Lett.* **1983**, *24*, 3455–3456.
103. Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317–6328.
104. Alvarez, A.; Guzmãn, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653–1656.
105. Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373–6380.
106. Simchen, G.; Majchrzak, M. W. *Tetrahedron Lett.* **1985**, *26*, 5035–5036.
107. Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1833–1836.
108. Severin, T.; Poehlmann, H. *Chem. Ber.* **1977**, *110*, 491–499.
109. Chelucci, G.; Marchetti, M. *J. Heterocycl. Chem.* **1988**, *25*, 1135–1137.
110. Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3760–3761.
111. Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivasan, C. V. *J. Am. Chem. Soc.* **1982**, *104*, 1436–1438.
112. Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505–1507.
113. Enders, D.; Han, S. H.; Maaβen, R. *Tetrahedron Lett.* **1995**, *36*, 8007–8010.
114. Enders, D.; Maaβen, R.; Han, S. H. *Liebigs Ann.* **1996**, 1565–1574.
115. Mićović, V. M.; Mihailović, M. L. *J. Org. Chem.* **1953**, *18*, 1190–1200.
116. Cipiciani, A.; Savelli, G.; Bunton, C. A. *J. Heterocycl. Chem.* **1984**, *21*, 975–976.
117. Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y. S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706–2711.
118. Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2495–2527.
119. Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353–364.
120. Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev.* **2004**, *104*, 2481–2506.
121. Zhang, Y.; Ma, J. S. *Org. Prep. Proced. Int.* **2001**, *33*, 81–86.
122. Wood, T. E.; Dalgleish, N. D.; Power, E. D.; Thompson, A.; Chen, X.; Okamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5740–5741.
123. Paine, J. B., III; Dolphin, D.; Trotter, J.; Greenhough, T. J. *Can. J. Chem.* **1985**, *63*, 2683–2690.
124. Zimmermann, H.; Brueckner, D.; Heimbach, D.; Henninger, K.; Hewlett, G.; Rosentreter, U.; Schohe-Loop, R.; Baumeister, J.; Schmidt, T.; Reefschlaeger, J.; Lang, D.; Lin, T.-I.; Radtke, M. In WO 2004052852 A1 20040624 CAN 141:71440 AN 2004:515480, 2004; p 108.
125. Breeze, A. L.; Green, O. M.; Hull, K. G.; Ni, H.; Hauck, S. I.; Mullen, G. B.; Hales, N. J.; Timms, D. In WO 2005026149 A1 20050324 CAN 142:336239, 2005; p 250.
126. Martyn, D. C.; Abell, A. D. *Aust. J. Chem.* **2004**, *57*, 1073–1077.
127. Zanetti, C. U.; Levi, E. *Gazz. Chim. Ital.* **1894**, *24*, 546–554.
128. Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1968**, *24*, 1145–1162.
129. Sternberg, E.; Dolphin, D. *Curr. Med. Chem. Anticancer Agents* **1996**, *3*, 239–272.
130. Kleinspehn, G. G. *J. Am. Chem. Soc.* **1955**, *77*, 1546–1548.
131. Bullock, E.; Johnson, A. W.; Markham, E.; Shaw, K. B. *J. Chem. Soc. C* **1958**, 1430–1440.
132. Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098–1100.
133. Jackson, A. H.; Pandey, R. K.; Nagaraja Rao, K. R.; Roberts, E. *Tetrahedron Lett.* **1985**, *26*, 793–796.
134. Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 2826–2835.
135. Cavaleiro, J. A. S.; d'A Rocha Gonslaves, A. M.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2471–2478.
136. Smith, K. M.; Eivazi, F.; Martynenko, Z. *J. Org. Chem.* **1981**, *46*, 2189–2193.
137. Wood, T. E.; Ross, A. C.; Dalgleish, N. D.; Power, E. D.; Thompson, A.; Chen, X.; Okamoto, Y. *J. Org. Chem.* **2005**, *70*, 9967–9974.
138. Wijesekera, T. P.; Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1988**, *53*, 1345–1352.
139. Beshara, C. S.; Thompson, A. *J. Org. Chem.* **2006**, *70*, 10607–10610.
140. Clezy, P. S.; Fookes, C. J. R.; Lau, D. Y. K.; Nichol, A. W.; Smythe, G. A. *Aust. J. Chem.* **1974**, *27*, 357–369.
141. Brown, D.; Griffiths, D.; Rider, M. E.; Smith, R. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 455–463.
142. Al-Hazimi, H. M. G.; Jackson, A. H.; Knight, D. W.; Lash, T. D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 265–276.
143. Markovac, A.; MacDonald, S. F. *Can. J. Chem.* **1965**, *43*, 3364–3371.
144. Hayes, A.; Kenner, G. W.; Williams, N. R. *J. Chem. Soc.* **1958**, 3779–3788.
145. Regourd, R.; Comeau, I. M.; Beshara, C. S.; Thompson, A. *J. Heterocycl. Chem.*, in press.
146. Clezy, P. S.; Fookes, C. J. R.; Prashar, J. K. *Aust. J. Chem.* **1989**, *42*, 775–786.
147. Silverstein, R. M.; Ryskiewicz, E. E.; Willard, C. *Organic Syntheses Collective Volume IV*; Rabjohn, N., Ed.; Wiley: New York, NY, 1963; p 831.
148. Johnson, J. A.; Ning, L.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900–6903.

149. Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *22*, 229–238.
150. Clezy, P. S.; Fookes, C. J. R.; Liepa, A. J. *Aust. J. Chem.* **1972**, *25*, 1979–1990.
151. Clezy, P. S.; Fookes, C. J. R.; Hai, T. T. *Aust. J. Chem.* **1978**, *31*, 365–379.
152. Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. P.; Ito, S.; Langemann, A.; LeGoff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Voltz, H. *J. Am. Chem. Soc*. **1960**, *82*, 3800–3802.
153. Badger, G. M.; Harris, R. L. N.; Jones, R. A. *Aust. J. Chem.* **1964**, *17*, 987–1001.
154. Fischer, H.; Orth, H. *Die Chemie des Pyrrols*; Akademische: Leipzig, 1937; Vol. II, Part 1.
155. Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1988**, *53*, 2787–2795.
156. Sonnet, P. E. *J. Org. Chem.* **1971**, *36*, 1005–1007.
157. Sonnet, P. E. *J. Org. Chem.* **1972**, *37*, 925–929.
158. David, S.; Dolphin, D.; James, B. R.; Paine, J. B., III; Wijesekera, T. P.; Einstein, F. W. B.; Jones, T. *Can. J. Chem.* **1986**, *64*, 208–212.
159. Franco, F.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 1682–1688.
160. Thamyongkit, P.; Bhise, A. D.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 903–910.
161. Antonio, Y.; De La Cruz, E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15–22.
162. Semmelhack, M. F.; Chlenov, A.; Ho, D. M. *J. Am. Chem. Soc.* **2005**, *127*, 7759–7773.
163. Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799–812.
164. Carmona, O.; Greenhouse, R.; Landeros, R.; Muchowski, J. M. *J. Org. Chem.* **1980**, *45*, 5336–5339.
165. Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
166. Albert, A. *Heterocyclic Chemistry*; Athlone: London, 1959.

Biographical sketch

Benoit Jolicoeur was born in Montreal, Canada in 1980. He received his B.Sc. degree in 2003 from the Université de Montréal. He performed undergraduate research under the guidance of Professor William D. Lubell on the synthesis of indolizidin-9-one amino acids as peptide mimics. Presently he is pursuing graduate study in the laboratory of Professor Lubell at the Université de Montréal on the synthesis of prodigiosin analogs.

Erin Chapman received her Bachelor of Science degree with honors in chemistry from Mount Allison University in 2005. While at Mount Allison, Erin conducted her Honors Research Project with Dr. Richard Langler in the area of organosulfur chemistry. She also completed a special topics research project with Dr. Stephen Westcott exploring new rhodium catalysts for hydroboration reactions. Erin is currently a graduate student at Dalhousie University in Halifax, Nova Scotia under the supervision of Dr. Alison Thompson. Dr. Thompson's research group focuses on pyrrole chemistry and Erin's research projects at Dalhousie have included various aspects of dipyrromethene reactivity and synthesis.

Dr. Alison Thompson's research interests include the synthesis and applications of helical dipyrromethene complexes, the development of new methodology for the efficient synthesis of functionalized pyrroles, and the design and synthesis of prodigiosins for evaluation as anti-cancer treatments. Born in Nottingham, England, Dr. Thompson obtained her B.Sc. (Hons. Class I) from the University of Leicester in 1993. In 1996 she gained her Ph.D. from the University of Sheffield for research on the development of catalytic asymmetric aziridination and epoxidation reactions with Professor Varinder Aggarwal. She then moved to Strasbourg, France and worked with Professeur Arlette Solladié Cavallo for a year as a postdoctoral fellow with a Royal Society/NATO award. In 1997 Dr. Thompson joined the University of British Columbia, Canada to work with Professor David Dolphin. In 2001 she moved to Halifax, Nova Scotia to take up a faculty position at Dalhousie University with an NSERC University Faculty Award. In 2006 she was awarded the AstraZeneca Award in Chemistry.

Professor William D. Lubell received his B.A. degree in Chemistry in 1984 from Columbia College and his Ph.D. in 1989 from the University of California in Berkeley under the supervision of Professor Henry Rapoport. As a fellow of the Japan Society for the Promotion of Science, he studied enantioselective hydrogenation with Professor Ryoji Noyori at Nagoya University in Nagoya, Japan. In September of 1991, he joined the faculty at l'Universite de Montreal in Quebec, Canada where he is now Full Professor.

Studying the synthesis of heterocycles, amino acids, and peptide mimics, Lubell's interests lie in making these novel structures for drug discovery and in their use to explore protein folding and molecular recognition. His laboratory has developed effective protocols for creating conformationally biased peptide surrogates, and solid-phase processes for making and

introducing these scaffolds into peptide mimic libraries in order to study a spectrum of biologically relevant targets.

Co-author of more than 100 scientific publications, his honors include the Bio-Méga/Boehringer Ingelheim Young Investigator Award (1994), the DuPont Canada Educational Aid Grant (1997), the Danish National Bank Award (1999) and the Merck Frosst Centre for Therapeutic Research Award (2002). Associate Editor of *Organic Letters*, he is a Member of the Editorial Boards of *Biopolymers*, *Peptide Science* and *Chemical Biology and Drug Design*. Council Member of the American Peptide Society, he will co-chair the 20th American Peptide Symposium to be held in Montreal, Canada from June 26–30, 2007.

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Substituent effects in hydroxyiodination of 1,2-diacyloxycyclohex-3-enes

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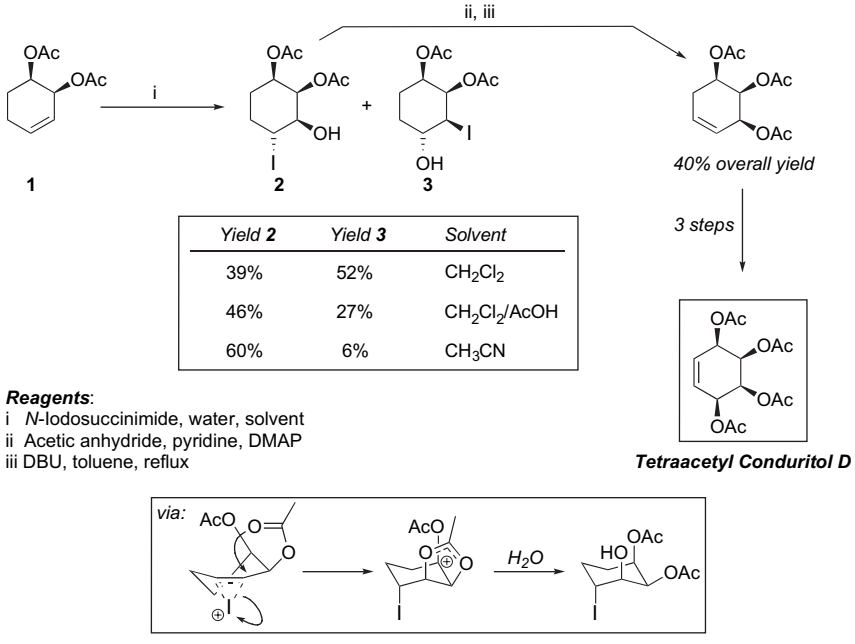
Abstract—The reaction of 1,2-diacyloxycyclohex-3-enes with iodinating agents in the presence of water has been investigated. The process is inherently diastereoselective, with many reactions giving only two of the four possible diastereoisomers which could be obtained. However, the regiocontrol is variable: highest selectivities are observed when pivalates are present on the periphery of the cycloalkene, when single regio- and diastereoisomers are obtained from the reactions.

1. Introduction

We have previously described[1] the use of iterative 1,2-hydroxyiodination reactions of acetoxycyclohexenes to prepare a conduritol D derivative;[2] during the course of that work we experienced difficulty in obtaining the desired regioselectivity in one of the crucial steps of the synthetic route to this cyclitol. Thus, the reaction of 1,2-diacetoxycyclohex-3-ene **1** with NIS in CH_2Cl_2/H_2O solvent initially gave key intermediate **2** as the minor component isolated, with diastereoisomer **3** being the primary product (Scheme 1). In other words, the diastereoselectivity of the reaction was reasonable (only two of the four possible stereoisomers were obtained) but the regioselectivity was poor and of the wrong type for our strategy. When wet acetic acid was used as cosolvent (following the precedent of



Yield **2**	Yield **3**	Solvent
39%	52%	CH_2Cl_2
46%	27%	CH_2Cl_2/AcOH
60%	6%	CH_3CN

Scheme 1.

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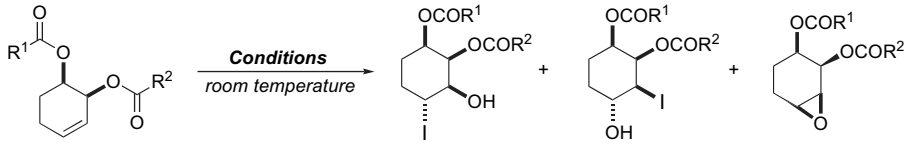
Table 1

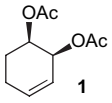
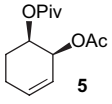
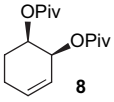


1 $R^1=R^2=Me$
5 $R^1={}^tBu$, $R^2=Me$
8 $R^1=R^2={}^tBu$

2 $R^1=R^2=Me$
6 $R^1={}^tBu$, $R^2=Me$
9 $R^1=R^2={}^tBu$

3 $R^1=R^2=Me$
7 $R^1={}^tBu$, $R^2=Me$
10 $R^1=R^2={}^tBu$

4 $R^1=R^2=Me$
11 $R^1=R^2={}^tBu$

Entry	Substrate	Conditions	Time/h	**Product** yield (%)			
1[a]	 **1**	NIS, H_2O, CH_2Cl_2	240	—	**2** 39	**3** 52	—
2[a]	**1**	NIS, H_2O, MeCN	72	—	**2** 60	**3** 6	—
3	**1**	NIS, 4 Å sieves, MeCN	144	**1** 80	**2** 1	**3** 2	—
4[a]	**1**	NIS, AcOH, CH_2Cl_2[3]	48	—	**2** 46	**3** 27	—
5	**1**	NIS, AcOH, 4 Å sieves, CH_2Cl_2	96	**1** 30	**2** 20	**3** 15	—
6	**1**	NIS, $Pb(OAc)_3\cdot H_2O$, AcOH[5]	5	—	**2** 30[b]	**3** 30[b]	—
7	**1**	I_2, AgOAc; H_2O, AcOH[6]	21	**1** 79	—	—	**4** 21
8	**2**	I_2, AgOAc; H_2O, MeCN	168	**1** 41	—	—	**4** 4
9	 **5**	NIS, H_2O, CH_2Cl_2	96	**5** 20	**6** 68	—	—
10	**5**	NIS, H_2O, MeCN	96	**5** 17	**6** 58	—	—
11	 **8**	NIS, H_2O, CH_2Cl_2	102	**8** 30	**9** 68	—	—
12	**8**	NIS, H_2O, MeCN	144	**8** 3	**9** 29	—	—
13	**8**	I_2, H_2O, CH_2Cl_2[7]	96	**8** 58	**9** 29	—	—
14	**8**	I_2, AgOAc; H_2O, AcOH	20	—	**9** 17[c]	—	**11** 25
15	**8**	I_2, AgOAc; H_2O, MeCN	24	—	**9** 26[d]	—	—

[a] Ref. 2.
[b] Inter alia.
[c] 3-Iodo-4-acetoxy analogue also obtained (55% yield).
[d] 3-Iodo-4-acetoxy analogue also obtained (27% yield).

Danishefsky et al.[3]) in the same reaction, an improvement in regiochemistry was observed, along with an inversion of selectivity: compound **2** was now obtained as the *major* isomer. Our best result was obtained when the reaction was performed using wet acetonitrile as solvent, in which case the regiocontrol was good (**2**:**3**=10:1) and the diastereocontrol maintained.

Since **2** was separable chromatographically from its diastereoisomer, the presence of by-product **3** did not seriously hinder our progression along the synthetic path leading to conduritol D, but we were of course motivated to explore the factors responsible for the variation in regioselectivity we had observed. Having briefly examined solvent effects, we next sought to investigate the effect of both alternative iodonium sources and the acyl substituent. We here describe in full[4] the results of these investigations.

2. Results and discussion

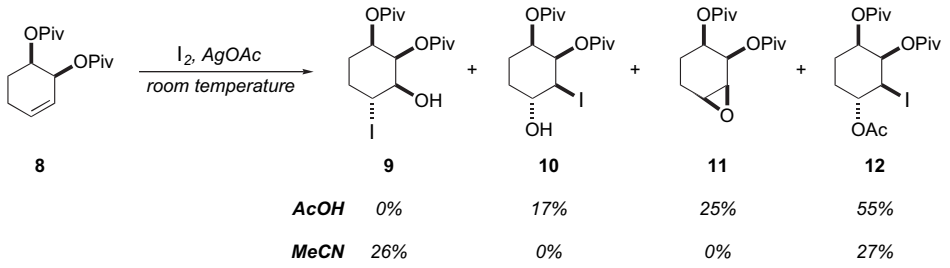
2.1. The effect of other sources of iodonium ion

We started our optimization study (Table 1) by varying the reagents employed in the reaction, but quickly found that any alteration in the source of iodonium had a deleterious effect on the process. Thus, reaction with a range of iodinating reagents proceeded very slowly, with starting materials being returned as the major constituent of the reactions. Reaction in the presence of lead acetate proceeded more rapidly than the original process, but there was no preference for **2** over **3** (Table 1, entry 6) and the reaction was difficult to work-up, returning significant amounts of intractable materials. Reaction under Prévost conditions (entries 7 and 8) was inefficient, with only **1** and epoxide **4**[†] being retrieved from the reaction mixture. Presumably the latter is formed via **2** by ring closure, under the influence of the silver(I) salt. Thus, the original source of iodonium was optimal.

2.2. The effect of 1,3-diaxial interactions

To study the effect of 1,3-diaxial interactions, we next varied the nature of the acyl substituents on the periphery of the alkene. Thus, mixed diester **5** (prepared from pivaloxycyclohexene by a sequence of hydroxyiodination, acetylation and elimination of hydroiodic acid) reacted under the conditions found to be optimal in hydroxyiodination of **1** to give a single product, *trans*-3,4-hydroxyiodide **6**, in 58% yield (or 70%, based on recovery of starting material). Now the reaction

[†] The structure of **4** was confirmed by chemical correlation with the minor epoxide obtained from epoxidation of **1** with mCPBA.



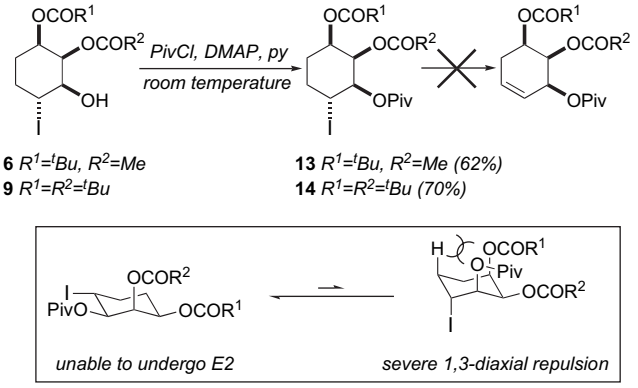
Scheme 2.

using dichloromethane as solvent was also highly selective (in contrast to the hydroxyiodination of diacetate **1**): a 68% yield (85%, based on recovered starting material) of **6** was obtained. Thus, as might be expected, it seems that increasing the steric bulk of the axial ester substituent favours formation of the α-iodonium ion, necessarily leading to **6**. What is also notable is the return of unreacted starting material from these reactions; this had been observed in similar reactions of diacetate **1** only for reactions conducted in the presence of a dessicant (entries 3 and 5) or using iodine itself as an iodinating reagent, perhaps suggesting that the crowded steric environment now retards formation of iodonium ion.

To probe this phenomenon further, we prepared dipivalate **8**, by a similar sequence to that used previously for **5**. This compound, the bulkiest diester used to date, was not completely consumed upon exposure to NIS (two portions, 2.5 equiv in total) in dichloromethane after more than 4 days at room temperature (Table 1, entry 11) and the yield of product was significantly diminished if the reaction was left past this stage. However, the reaction was highly selective, providing only the desired (from the perspective of conduritol synthesis) iodoalcohol **9** in 68% yield (entry 11, 97% yield based on recovered **8**). This process stands in stark contrast to the reaction of diacetate **1**, which proceeded with much inferior regiocontrol, although in higher yield (73–91%).

When the reaction of **8** with NIS was carried out in acetonitrile, the process was again highly selective, but not efficient: though the only product was **9**, the mass balance was poor (29% yield, 3% returned starting material). Other iodinating reagents did not efficiently produce **9**: reaction with elemental iodine gave predominantly starting material (entry 13), whilst Prévost reaction gave a mixture of products, depending upon the solvent (entries 14 and 15, Scheme 2). Thus, reaction in acetic acid proceeded in good yield (overall yield 97%) but did not give **9**, yielding instead isomer **10** and two other products, epoxide **11**[‡] (presumably formed from **9**) and (as the major product) *trans*-3,4-iodoacetate **12**. In acetonitrile solvent, **9** and **12** were formed in roughly equal amounts, implying ring opening of both α- and β-iodonium ions to be similar in energy.

Armed with a more efficient entry to the 1,2-*cis*-2,3-*cis*-3,4-*trans*-hydroxyiodides needed for conduritol synthesis, we proceeded to investigate the elimination reaction next in the synthetic sequence for conduritols. However, both mixed triester **13** and trispivalate **14** did not undergo elimination of hydroiodic acid upon treatment with a range of bases (Scheme 3). Instead, decomposition was generally observed, producing unidentifiable aromatic products. Only when the P_4-^{t}Bu base was used could products be isolated in pure form: epoxide **11** was obtained from **14** in 57% yield. Presumably in this case the *trans*-diaxial conformer required for E2 elimination is energetically inaccessible due to the crowded periphery.



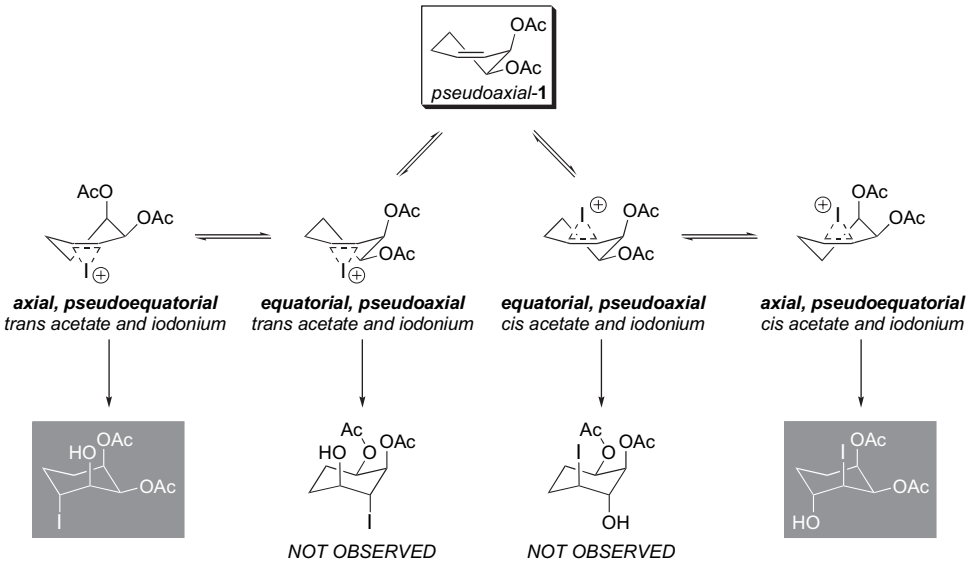
Scheme 3.

2.3. Mechanistic discussion

It is interesting to note that these reactions often proceed via apparently less stable intermediates, in Curtin–Hammett-like processes.[8] Diacetate **1** reacts through iodonium ions in which the 1-acetoxy substituent is axial, and the 2-acetoxy pseudoequatorial (Scheme 4). Thus, although one might predict that the 1-equatorial, 2-pseudoaxial conformers would be favoured, no product arising from *trans*-diaxial ring opening of such iodonium ions is obtained. It seems that the primary requirement is a pseudoequatorial allylic acyloxy group: when this condition is satisfied, formation of iodonium ion either *cis*- or *trans*-to the ring substituents is feasible and under solvent control. In a nonpolar solvent, β-iodonium is favoured, leading to 3,4-iodoalcohol product as the major product (Table 1, entry 1). When a more polar solvent, or a polar additive, is used (entries 2 and 4), α-iodonium is the favoured intermediate, leading to preferentially to *trans*-3,4-hydroxyiodides. We have previously rationalized this observation by means of nucleophilic attack of the carbonyl oxygen onto the α-iodonium, or an electrostatic stabilization of the β-iodonium ion.

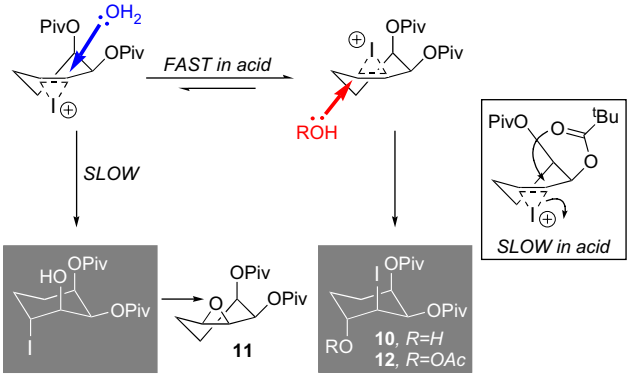
In the case of bispivalate **8**, there is a much greater preference for the α-iodonium ion, except in the Prévost reaction in acetic acid where the β-iodonium dominates. We propose

[‡] The structure of **11** was confirmed by chemical correlation with the minor epoxide obtained from epoxidation of **8** with mCPBA.



Scheme 4.

that there are two reasons for the latter observation: firstly, the equilibrium between the iodonium ions is facilitated in acid and secondly, intramolecular ring opening by the adjacent acyl group is disfavoured. Thus, the more rapid (because less hindered) diaxial ring opening to give **10** and **12** dominates, rather than the relatively slow diaxial opening of the α-iodonium by water (Scheme 5).



Scheme 5.

3. Conclusion

We have investigated the 1,2-hydoxyiodination reactions of 1,2-diacyloxycyclohex-3-enes and found them to highly selective when bulky acyl substituents are present. We are currently engaged in a detailed study of the precise mechanistic factors underlying these phenomena and we shall report in due course the results of our further studies in this arena.

4. Experimental

4.1. General techniques

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[9] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40–60 °C and 'ether' refers to diethyl ether. Ether was distilled from sodium benzophenone ketyl; dichloromethane from calcium hydride. Other chemicals were purchased from Aldrich Chemical Co. or prepared by literature methods.

Melting points were recorded on either a Kofler hot-stage apparatus and are corrected, or an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 881 spectrophotometer. Mass spectra were recorded on a Fisons Autospec spectrometer. NMR spectra were recorded on a Jeol GX-270 spectrometer, a Jeol GX-400 spectrometer or a Jeol Λ-300 spectrometer, using tetramethylsilane or chloroform as the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as parts per million downfield from tetramethylsilane, and, in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (J) are quoted in Hz.

Reactions involving chemicals or intermediates sensitive to air and/or moisture were conducted under a nitrogen or argon atmosphere in flame- or oven-dried apparatus. Column chromatography was performed using Merck Kieselgel 60 or Fluka Kieselgel 60 silica gel. Analytical thin layer chromatography was carried out using either precoated Merck Kieselgel 60 F_{254} glass backed plates, or precoated Merck Kieselgel 60 F_{254} aluminium backed plates and were visualized under UV at 346 nm and/or by staining with iodine and an acidic ammonium molybdate stain (20% w/v ammonium molybdate(VI) tetrahydrate in 10% sulfuric acid).

4.1.1. (±)-*cis*-2-Acetoxy-1-(2,2-dimethylpropionyloxy)-cyclohex-3-ene (5). 1. To a solution of (±)-1,2-*cis*-2,3-*trans*-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexan-2-ol[2] (1.30 g, 3.99 mmol) in pyridine (12 mL) was added acetic anhydride (0.42 mL, 4.44 mmol). The mixture was stirred at room temperature (27 h), diluted with ethyl acetate (30 mL) and washed with saturated copper(II)sulfate solution (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded 1,2-*cis*-2,3-*trans*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexane as a colourless solid (0.96 g, 65%); R_f 0.40

[ether/petrol, 1:4]; mp 52–53 °C (Found: C, 42.63; H, 6.18; I, 34.37. $C_{13}H_{21}IO_4$ requires C, 42.40; H, 5.75; I, 34.46%); ν_{max} (CCl_4)/cm^{-1} 2954, 1754 (C=O), 1734 (C=O); δ_H (270 MHz, $CDCl_3$) 1.22 (9H, s), 1.51–2.03 (5H, m), 2.04 (3H, s), 2.46–2.51 (1H, m), 4.31 (1H, ddd, *J* 11.4, 10.3, 4.4), 5.01 (1H, dd, *J* 10.2, 3.0), 5.29–5.31 (1H, m); δ_C (67.5 MHz, $CDCl_3$) 177.29, 169.58, 76.14, 69.06, 39.03, 37.22, 28.46, 27.16, 26.20, 22.04, 20.77; *m/z* (CI) 309 (100.0), 241 ([M−I]$^+$, 13.3), 225 (5.2), 207 (9.2), 199 (5.5).

2. (±)-1,2-*cis*-2,3-*trans*-2-Acetoxy-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexane (937 mg, 2.54 mmol) and DBU (0.76 mL, 5.08 mmol) in toluene (15 mL) were heated at reflux for 3 days, to yield **5** after column chromatography (ether/petrol, 1:4) as a colourless oil (469 mg, 77%); R_f 0.40 [ether/petrol, 1:4] (Found: C, 64.13; H, 8.80. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.39%); ν_{max} (CCl_4)/cm^{-1} 2973, 1732 (C=O); δ_H (270 MHz, $CDCl_3$) 1.19 (9H, s), 1.80–2.28 (4H, m), 2.05 (3H, s), 5.09 (1H, ddd, *J* 9.9, 3.5, 3.5), 5.48 (1H, m), 5.64 (1H, dddd, *J* 9.9, 4.2, 2.0, 2.0), 5.98 (1H, dddd, *J* 9.9, 4.0, 4.0, 1.0); δ_C (67.5 MHz, $CDCl_3$) 177.29, 169.96, 132.21, 123.26, 68.555, 66.365, 38.55, 26.775, 23.22, 23.06, 20.68; *m/z* (CI) 241 (MH$^+$, 2.2%), 181 (85.4), 153 (8.6), 131 (7.7), 103 (74.5) (Found 241.1451. $C_{13}H_{21}O_4$ (MH$^+$) requires 241.1440).

4.1.2. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-Acetoxy-1-(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol 6 (Table 1, entries 9 and 10).

4.1.2.1. Method 1. To a solution of (±)-*cis*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-cyclohex-3-ene **1** (100 mg, 0.416 mmol) in dichloromethane (5 mL) were added *N*-iodosuccinimide (122 mg, 0.542 mmol) and water (five drops). The mixture was stirred at room temperature (2 days), then further *N*-iodosuccinimide (94 mg, 0.418 mmol) was added and stirring continued (2 days). The mixture was washed with saturated sodium thiosulfate solution (4 mL) and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate/petrol, 1:4) yielded unreacted **1** (20 mg, 20%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **6** as a colourless solid (109 mg, 68%); R_f 0.36 [ethyl acetate/petrol, 1:4]; mp 106–107 °C (Found: C, 40.70; H, 5.70; I, 33.20%. $C_{13}H_{21}IO_5$ requires C, 40.64; H, 5.51; I, 33.03%); ν_{max} (CCl_4)/cm^{-1} 3583 (OH), 2973, 1756 (C=O), 1736 (C=O); δ_H (270 MHz, $CDCl_3$) 1.15 (9H, s), 1.69–2.03 (3H, m), 2.13 (3H, s), 2.42–2.52 (1H, m), 2.87 (1H, d, *J* 4.8), 3.85 (1H, ddd, *J* 9.9, 4.4, 3.1), 4.21 (1H, ddd, *J* 11.5, 10.2, 4.4), 4.90 (1H, ddd, *J* 10.6, 4.8, 2.75), 5.53 (1H, ddd, *J* 2.75, 2.75, 1.1); δ_C (67.5 MHz, $CDCl_3$) 177.23, 170.18, 74.52, 70.87, 69.98, 38.62, 32.78, 31.00, 26.87, 25.92, 20.77; *m/z* (CI) 385 (0.8%), 325 (34.5), 283 (5.7), 257 (18.4) (Found 385.0514. $C_{13}H_{22}IO_5$ requires 385.0512).

4.1.2.2. Method 2. To a solution of (±)-*cis*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-cyclohex-3-ene **1** (100 mg, 0.416 mmol) in acetonitrile (5 mL) was added *N*-iodosuccinimide (122 mg, 0.542 mmol). The mixture was stirred at room temperature (22 h), then further *N*-iodosuccinimide (94 mg, 0.418 mmol) was added and stirring continued (4 days). Acetonitrile was removed in vacuo, the residue dissolved in dichloromethane (10 mL), and washed with saturated sodium thiosulfate solution (8 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate/petrol, 1:4) yielded unreacted **1** (17 mg, 17%) and **6** (93 mg, 58%).

4.1.3. (±)-*cis*-1,2-Bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene 8.

1. To a solution of (±)-1,2-*cis*-2,3-*trans*-1-(2,2-dimethylpropionyloxy)-3-iodocyclohexan-2-ol[2] (3.05 g, 9.35 mmol) in pyridine (35 mL) were added pivaloyl chloride (1.27 mL, 10.31 mmol) and DMAP (50 mg). The mixture was stirred at room temperature (2 days), at which time further pivaloyl chloride (1.15 mL, 9.34 mmol) was added and stirring continued (24 h). The mixture was then diluted with ethyl acetate (50 mL) and washed with saturated copper(II)sulfate solution (30 mL) and water (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded unreacted starting material (124) (0.39 g, 13%) and 1,2-*cis*-2,3-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane (2.83 g, 74%) as a colourless oil; R_f 0.70 [ether/petrol, 1:4] (Found: C, 46.54; H, 7.17; I, 31.21. $C_{16}H_{27}IO_4$ requires C, 46.84; H, 6.63; I, 30.93%); ν_{max} (CCl_4)/cm^{-1} 2935, 1736 (C=O); δ_H (270 MHz, $CDCl_3$) 1.214 and 1.215 (18H, 2×s), 1.40–2.48 (6H, m), 4.35 (1H, ddd, *J* 10.1, 10.1, 4.2), 5.00 (1H, dd, *J* 9.9, 2.7), 5.29–5.31 (1H, m); δ_C (67.5 MHz, $CDCl_3$) 176.88, 176.69, 75.57, 69.13, 40.08, 38.74, 36.935, 28.36, 27.12, 26.43, 26.17, 21.89; *m/z* (EI) 283 ([M−I]$^+$, 22.0%), 207 (3.7), 129 (4.7), 97 (12.6) (Found 283.1891. $C_{16}H_{27}O_4$ ([M−I]$^+$) requires 283.1909).

2. To a solution of (±)-1,2-*cis*-2,3-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane (2.44 g, 5.95 mmol) in toluene (30 mL) was added DBU (1.78 mL, 11.90 mmol). The mixture was heated to reflux (30 h) until the reaction had gone to completion as evinced by ^1H NMR spectroscopy. The toluene was removed in vacuo, and the residue dissolved in dichloromethane (50 mL) and washed with 5% hydrochloric acid (30 mL) and saturated sodium hydrogen carbonate solution (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded **8** as a colourless oil (1.33 g, 79%); R_f 0.70 [ether/petrol, 1:4] (Found: C, 67.59; H, 9.23. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28%); ν_{max} (CCl_4)/cm^{-1} 2972, 1733 (C=O), 1619 (C=C); δ_H (270 MHz, $CDCl_3$) 1.19 and 1.21 (18H, 2×s), 1.75–2.31 (4H, m), 5.08 (1H, ddd, *J* 10.3, 3.4, 3.4), 5.41 (1H, m), 5.67 (1H, dddd, *J* 9.9, 4.4, 2.2, 2.2), 5.94 (1H, ddd, *J* 9.9, 3.2, 3.2); δ_C (67.5 MHz, $CDCl_3$) 177.39, 132.08, 123.54, 69.22, 66.43, 38.58, 27.03, 26.97, 23.66, 23.09; *m/z* (CI) 283 (MH$^+$, 24.5%), 181 (100.0), 149 (6.3) (Found 283.1899. $C_{16}H_{27}O_4$ (MH$^+$) requires 283.1909).

4.1.4. NIS/water addition to (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene 8 in dichloromethane (Table 1, entry 11); preparation of (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-Bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol 9.

To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (100 mg, 0.35 mmol) in dichloromethane (5 mL) were added *N*-iodosuccinimide (120 mg, 0.53 mmol) and water (two drops). The mixture

was stirred at room temperature for 30 h, then further *N*-iodosuccinimide (79 mg, 1.00 mmol) and water (two drops) were added, and stirring continued for 3 days. The mixture was washed with saturated sodium thiosulfate solution (4 mL), and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 3:7 to 1:1) yielded unreacted **8** (30 mg, 30%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **9** as a colourless solid (102 mg, 60%); R_f 0.38 [ether/petrol, 3:7]; mp 137–138 °C; ν_{max} (CCl_4)/cm^{-1} 3583 (OH), 2974, 1743 (C=O); δ_H (270 MHz, $CDCl_3$) 1.15 and 1.25 (18H, 2×s), 1.70–1.87 (2H, m), 1.97–2.12 (1H, m), 2.43–2.50 (1H, m), 2.51 (1H, br s), 3.85 (1H, ddd, *J* 10.1, 3.5, 2.9), 4.16 (1H, ddd, *J* 11.5, 10.3, 4.4), 4.91 (1H, ddd, *J* 10.9, 4.6, 2.4), 5.49 (1H, ddd, *J* 2.75, 2.75, 1.1); δ_C (67.5 MHz, $CDCl_3$) 177.48, 177.29, 75.03, 70.65, 70.21, 39.04, 38.65, 32.63, 31.38, 27.25, 27.16, 27.00; *m/z* (CI) 427 (MH^+, 8.5%), 325 (100.0), 299 (24.9) (Found 427.0982. $C_{16}H_{28}IO_5$ (MH^+) requires 427.0982).

4.1.5. I_2/water addition to (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene 8 in dichloromethane (Table 1, entry 13). To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (50 mg, 0.177 mmol) in dichloromethane (2 mL) were added iodine (67 mg, 0.264 mmol) and water (five drops). The mixture was stirred at room temperature (23 h), then further iodine (50 mg, 0.197 mmol) and water (two drops) was added and stirring continued for 3 days. The mixture was washed with saturated sodium thiosulfate solution (2 mL), and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 3:7) yielded (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **9** (22 mg, 29%) and unreacted **8** (29 mg, 58%).

4.1.6. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-4-Acetoxy-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane 12 (Table 1, entries 14 and 15).

4.1.6.1. Method 1. To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (50 mg, 0.177 mmol) in acetonitrile (2 mL) were added acetic acid (0.02 mL, 0.354 mmol) and silver(I)acetate (59 mg, 0.354 mmol) followed by iodine pellets (67 mg, 0.264 mmol). The mixture was stirred at room temperature (24 h), filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL), washed with saturated sodium hydrogen carbonate solution (6 mL) and brine (6 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20%-ether/petrol, 3:7) yielded **9** (20 mg, 26%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-4-acetoxy-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexane **12** as a colourless solid (22 mg, 27%); R_f 0.50 [ether/petrol, 1:4]; mp 116–117 °C (corrected) (Found: C, 45.53; H, 6.40; I, 26.90. $C_{18}H_{29}IO_6$ requires C, 46.16; H, 6.24; I, 27.10%); ν_{max} (CCl_4)/cm^{-1} 2975, 1747 (C=O), 1737 (C=O); δ_H (270 MHz, $CDCl_3$) 1.14 and 1.31 (18H, 2×s), 1.40–1.55 (1H, m), 1.85–1.99 (1H, m), 2.10 (3H, s), 2.14–2.34 (1H, m), 4.21 (1H, dd, *J* 11.0, 2.6), 4.91 (1H, ddd, *J* 11.2, 5.3, 2.75), 5.09 (1H, ddd, *J* 10.8, 10.8, 4.8), 5.65–5.67 (1H, m); δ_C (75 MHz, $CDCl_3$) 177.47, 176.29, 169.90, 72.70, 72.40, 70.05, 39.19, 38.67, 28.82, 28.49, 27.46, 27.04, 23.65, 21.11; *m/z* (EI) 341 ($[M-I]^+$, 4.5%), 306 (4.4), 281 (7.8), 197 (12.5) (Found 341.1977. $C_{18}H_{29}O_5$ ($[M-I]^+$) requires 341.1964).

4.1.6.2. Method 2. To a solution of (±)-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-cyclohex-3-ene **8** (50 mg, 0.177 mmol) in acetic acid (2 mL) was added silver(I) acetate (59 mg, 0.354 mmol) and water (five drops) followed by iodine (67 mg, 0.264 mmol). The mixture was stirred at room temperature (20 h), filtered and concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL), washed with saturated sodium hydrogen carbonate solution (6 mL) and brine (6 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded **12** (46 mg, 55%), (±)-1,2-*cis*-2,3-*cis*-3,4-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-3,4-epoxycyclohexane **11** (13 mg, 25%) and (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-3-iodocyclohexan-4-ol **12** (13 mg, 17%).

4.1.7. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-Tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane 14. To a solution of (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **9** (455 mg, 1.067 mmol) in pyridine (5 mL) were added pivaloyl chloride (0.2 mL, 1.624 mmol) and DMAP (30 mg). The mixture was stirred at room temperature (24 h), then further pivaloyl chloride (0.2 mL, 1.624 mmol) was added and stirring continued for 3 days. The mixture was then diluted with ethyl acetate (30 mL) and washed with saturated copper(II)sulfate solution (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (ether/petrol, 1:4) yielded **14** as a colourless solid (380 mg, 70%); R_f 0.57 [ether/petrol, 1:4]; mp 176–177 °C (corrected) (Found: C, 49.87; H, 6.74; I, 24.26. $C_{21}H_{35}IO_6$ requires C, 49.42; H, 6.71; I, 24.86%); ν_{max} (CCl_4)/cm^{-1} 2976, 1745 (C=O); δ_H (270 MHz, $CDCl_3$) 1.14, 1.21 and 1.27 (27H, 3×s), 1.60–1.88 (2H, m), 2.04–2.20 (1H, m), 2.52–2.61 (1H, m), 4.20 (1H, ddd, *J* 12.6, 11.3, 4.6), 4.94 (1H, ddd, *J* 11.5, 5.5, 2.6), 5.01 (1H, dd, *J* 11.4, 2.6), 5.47 (1H, ddd, *J* 2.75, 2.75, 1.3); δ_C (67.5 MHz, $CDCl_3$) 176.89, 176.39, 176.32, 74.95, 69.62, 69.44, 38.90, 38.68, 38.54, 33.81, 27.24, 27.04, 26.90, 26.43, 23.00; *m/z* (EI) 409 (0.7%), 393 (1.1), 385 (1.5), 383 ($[M-I]^+$, 40.6), 197 (9.1) (Found 383.2430. $C_{21}H_{35}O_6$ ($[M-I]^+$) requires 383.2434).

4.1.8. (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-Acetoxy-1,3-bis(2,2-dimethylpropionyloxy)-4-iodocyclohexane 13. Prepared as for (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane **14**, but from (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-2-acetoxy-1-(2,2-dimethylpropionyloxy)-4-iodocyclohexan-3-ol **6** (205 mg, 0.534 mmol), pivaloyl chloride (0.07 mL initially, then an additional 0.07 mL after 19 h, 1.136 mmol total) and DMAP (20 mg) in pyridine (4 mL) with stirring at room temperature (2 days) to yield unreacted alcohol **6** (21 mg, 10%) and **15** as a colourless solid (155 mg, 62%); R_f 0.54 [ethyl acetate/petrol, 1:4]; mp 129.5–130.5 °C (corrected); ν_{max} (CCl_4)/cm^{-1} 2978, 1757 (C=O), 1744 (C=O); δ_H (270 MHz, $CDCl_3$) 1.13 and 1.20 (18H, 2×s), 1.65–1.90 (2H, m), 2.00–2.13 (1H, m), 2.12 (3H, s), 2.49–2.58 (1H, m), 4.22

(1H, ddd, *J* 12.8, 11.6, 4.6), 4.91 (1H, ddd, *J* 11.7, 5.1, 2.9), 4.97 (1H, dd, *J* 11.4, 2.8), 5.49 (1H, ddd, *J* 2.75, 2.75, 1.3); δ_C (67.5 MHz, $CDCl_3$) 176.97, 176.39, 169.40, 74.71, 69.57, 69.28, 38.71, 38.58, 33.66, 27.08, 26.97, 26.85, 26.43, 22.92; *m/z* (EI) 341 ([M−I]$^+$, 15.5%), 264 (1.4), 193 (4.2), 189 (5.1), 137 (8.7), 113 (4.6) (Found 341.1962. $C_{18}H_{29}O_6$ ([M−I]$^+$) requires 341.1964).

4.1.9. Attempted elimination of HI from (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-Tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane 14. To a solution of (±)-1,2-*cis*-2,3-*cis*-3,4-*trans*-1,2,3-tris(2,2-dimethylpropionyloxy)-4-iodocyclohexane **14** (60 mg, 0.118 mmol) in THF (2 mL) at −78 °C was added, dropwise, a solution of phosphazene P_4-^{t}Bu base (152) (0.12 mL of a 1 M solution in hexane, 0.12 mmol) in THF (0.5 mL). The mixture was stirred at −78 °C (2 h), then to room temperature (20 h). Solvent was removed in vacuo, and ether (10 mL) was added to the residue. The resultant precipitate was filtered and washed with ether (4×10 mL). The combined filtrates were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20%-ether/petrol, 3:7) yielded (±)-1,2-*cis*-2,3-*cis*-3,4-*cis*-1,2-bis(2,2-dimethylpropionyloxy)-3,4-epoxycyclohexane **11** (20 mg, 57%) as the only isolable product.

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References and notes

1. Bange, J.; Haughan, A. F.; Knight, J. R.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1039.
2. For a review of syntheses of conduritols and other cyclitols, see: Gultekin, M. S.; Celik, M.; Balci, M. *Curr. Org. Chem.* **2004**, *8*, 1159; for recent syntheses, see: Cere, V.; Minzoni, M.; Pollicino, S.; Ricci, A.; Gasparrini, F.; Ciogli, A.; D'Acquarica, I. *J. Comb. Chem.* **2006**, *8*, 74; Serrano, P.; Llebaria, A.; Delgado, A. *J. Org. Chem.* **2005**, *70*, 7829; Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H. J. *Eur. J. Org. Chem.* **2005**, 3116; Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H. J. *Eur. J. Org. Chem.* **2005**, 3101; Orsini, F.; Sello, G.; Bernasconi, S.; Fallacara, G. *Tetrahedron Lett.* **2004**, *45*, 9253; Saito, S.; Shimazawa, R.; Shirai, R. *Chem. Pharm. Bull.* **2004**, *52*, 727; Freeman, S.; Hudlicky, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1209 and references contained therein.
3. Danishefsky, S. J.; Selnick, H. G.; Armstead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119.
4. Knight, J.; Sweeney, J. B. *Tetrahedron Lett.* **1998**, *39*, 8703.
5. Bedekar, A. V.; Nair, K. B.; Soman, R. *Synth. Commun.* **1994**, 2299.
6. Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 6403.
7. Cornforth, R. H. *J. Chem. Soc. C* **1970**, 928.
8. For recent discussion of reactions controlled by the Curtin–Hammett principle, see: Wu, H.; Loeppky, R. N.; Glaser, R. *J. Org. Chem.* **2005**, *70*, 6790; Yoon, U. C.; Kwon, H. C.; Hyung, T. G.; Choi, K. H.; Oh, S. W.; Yang, S. R.; Zhao, Z. M.; Mariano, P. S. *J. Am. Chem. Soc.* **2004**, *126*, 1110; Adam, W.; Librera, C.; Trofimov, A. V. *J. Am. Chem. Soc.* **2004**, *125*, 5741; Adam, W.; Librera, C.; Trofimov, A. V. *J. Am. Chem. Soc.* **2002**, *124*, 11936; Howell, S. J.; Ashton, P. R.; Spencer, N.; Philp, D. *Org. Lett.* **2001**, *3*, 353; Chandrasekhar, S. *Res. Chem. Intermed.* **1998**, *24*, 625; Cavalier, J. F.; Fotiadu, F.; Verger, R.; Buono, G. *Synlett* **1998**, 73; Chandrasekhar, S. *Res. Chem. Intermed.* **1997**, *23*, 55; Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351; Pearson, A. J.; Neagu, I. B.; Pinkerton, A. A.; Kirschbaum, K.; Hardie, M. J. *Organometallics* **1997**, *16*, 4346.
9. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1988.

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Syntheses of highly functionalized δ,γ-unsaturated-α-amino acids

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Abstract—The synthesis of several γ,δ-unsaturated-α-amino acid derivatives is described. The method features regioselective stannylation of propargylglycine derivatives followed by Stille coupling reactions.

1. Introduction

Non-proteinogenic α-amino acids are important nitrogenous building blocks that are useful for the synthesis of natural products and a multitude of biologically significant substances.[1] There has been a continuing interest in the development of new methods for the synthesis of enantiomerically pure amino acids with substituents strategically placed at side-chain positions including the capacity to install unsaturation. Many methods have been developed for the asymmetric synthesis of amino acids.[2,3] Despite the plethora of methodologies extant, many reactive functionalities remain incompatible with existing templates.[2]

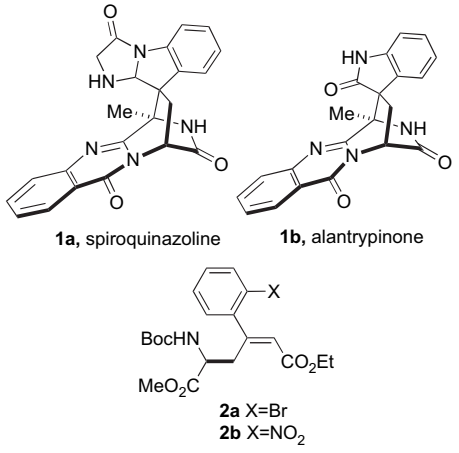

Figure 1. Structures of spiroquinazoline, alantrypinone, and γ,δ-unsaturated amino acid derivatives **2**.

As part of a strategy to synthesize the natural metabolites spiroquinazoline (**1a**)[4] and alantrypinone (**1b**),[5] we required access to γ-aryl-γ,δ-unsaturated-α-amino acids such as **2**. Several reported methods to prepare this type of amino acid were attempted but we were unsuccessful in constructing the target substances **2**.[6] Jackson et al. have reported the synthesis of enantiomerically pure unsaturated α-amino acids via coupling with readily available serine-derived β-iodoalanine derivatives using zinc/copper reagents.[7] We have adapted this approach to prepare a variety of γ-aryl-γ,δ-unsaturated-α-amino acids (Fig. 1).

2. Results and discussion

Our approach commenced with *N*-(*tert*-butoxycarbonyl)-L-iodoalanine methyl ester **3**, which is commercially available or can be prepared on a large scale by using the reported procedure with serine as the starting material.[8] Iodide **3** was converted into the corresponding Zn/Cu complex and then coupled with ethyl 3-bromopropiolate or *tert*-butyl 3-bromopropiolate.[7] The Zn/Cu complex **4** reacted with ethyl-3-bromopropiolate to produce the propargyl species **5a** and **5b** in 77 and 48% yields, respectively (Scheme 1).

Next, we examined the conjugate stannylation of organocopper(I) reagents to the γ,δ-alkynyl residue of **5**. The addition of compound **5a** to the solution of $Bu_3SnCu\cdot SMe_2$ or $[Bu_3SnCuCN]Li$[9,10] in THF resulted in no reaction. When **5a** was added to $Me_3SnCu\cdot SMe_2$ in THF, compound **6** was obtained in 23% yield with 40% recovery of **5a**. Piers et al. reported that (trimethylstannyl)copper(I)

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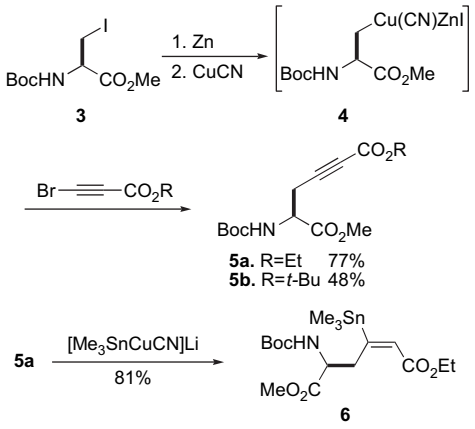


Scheme 1. Preparation of stannane **6**.

dimethylsulfide complex was relatively unreactive toward α,β-unsaturated carbonyl compounds.[9] When a more reactive species [$Me_3SnCuCN$]Li[10] was used in the place of $Me_3SnCu\cdot SMe_2$ for this reaction we observed that the yield was dramatically improved. When **5a** was added to [Me_3Sn-CuCN]Li in dry THF at −78 °C, compound **6** and the corresponding *Z*-isomer were produced in a nearly 1:1 ratio with no recovery of the starting material. Separation of the two isomers by flash chromatography proved to be very difficult and synthetically intractable. When [$Me_3SnCuCN$]Li was treated with EtOH prior to the addition of **5a**, the product obtained was exclusively the desired *E*-isomer. The geometric configuration of the product was determined by the coupling constant between the α-olefinic proton and the tin atom (^{117}Sn, ^{119}Sn) of the Me_3Sn group. It is well-known that when a trialkylstannyl group and a proton are vicinal on a C=C bond, the $^3J_{Sn-H}$ values are much larger when these moieties are trans- as opposed to cis-configuration.[11] The $^3J_{Sn-H}$ value in the present case of 69 Hz, falls into the expected range for the *E*-stereochemistry. The observation of a significant ^1H NOE between the vinyl proton and the Me_3Sn protons provided corroborating evidence to support the *E*-stereochemistry assigned for **6** (Fig. 2). The optical integrity of **6** was determined by ^1H NMR analysis of the derived Mosher's amide,[12] which revealed that **6** was obtained in at least 99.5:0.5 er. Compound **6** proved to be a stable substance and can be kept as an oil, exposed to air at ambient temperature for several weeks without detectable decomposition.

Compound **6** was then coupled with a variety of aryl and heterocyclic halides under Stille cross-coupling conditions (Table 1).[13] Our initial efforts examined $Pd(PPh_3)_4$ as the catalyst in the presence of CuI[14] at room temperature. But under these conditions either no product or trace amount

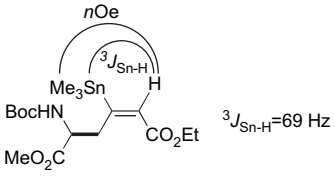
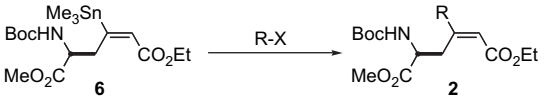
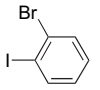
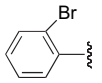
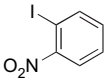
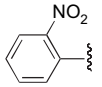
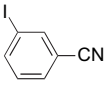
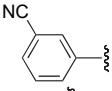
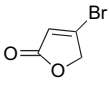
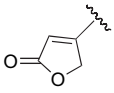
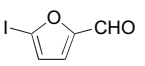
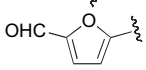
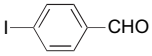
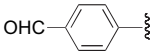


Figure 2. *E*-Stereochemical assignment for **6**.

Table 1. Stille coupling reactions of stannane **6**



Entry	R-X	Conditions	Yield (%)	R
a		Pd_2dba_3, CuI, $AsPh_3$, DMF	68	
b		$Pd_2Cl_2(CH_3CN)_2$, Bu_3SnH	79 (brsm)	
c		Pd_2dba_3, CuI, $AsPh_3$, DMF	71	
d		Pd_2dba_3, CuI, $AsPh_3$, DMF	77	
e		Pd_2dba_3, CuI, $AsPh_3$, DMF	57	
f		Pd_2dba_3, CuI, $AsPh_3$, DMF	80	
g		Pd_2dba_3, CuI, $AsPh_3$, DMF	84	
h		$Pd_2Cl_2(CH_3CN)_2$, Bu_3SnH, 45 °C	67	

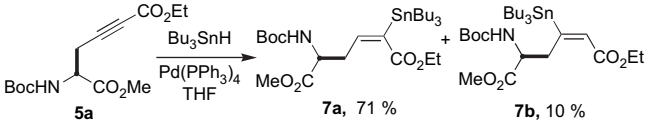
of product was obtained. Higher temperature only led to the decomposition of compound **6**. Amino acid **2a** was successfully prepared by coupling *o*-bromoiodobenzene with compound **6** by using Pd_2dba_3 in the presence of $AsPh_3$ and CuI.[15] Only the bromide product **2a** was observed as evidenced by ^{13}C NMR and MS; the corresponding iodide was not observed. The 3-cyanophenyl moiety can be introduced under similar conditions (entry c). Heterocyclic species such as 2-bromocyclopent-2-enone and 4-bromofuran-2(5*H*)-one were also successfully coupled with compound **6** to yield **2d** and **2e** in 77 and 57% yields, respectively (entries d and e). The coupling of **6** with 3-iodothiophene or 5-iodofuran-2-carboxaldehyde also provided the cross-coupling products in useful yields (entries f and g).

In all cases, the reaction was complete in just 2 h and no loss of optical integrity was observed by chiral HPLC analysis.[16] *o*-Iodonitrobenzene coupled with compound **6** to deliver **2b**, however in very poor yield. When $PdCl_2(CH_3CN)_2$ was used as the catalyst, incomplete reaction was observed. We found that the yields could be improved by increasing the catalyst loading, but this also caused more homocoupling. Eventually, it was found that treatment of $PdCl_2(CH_3CN)_2$ with tri-*n*-butyltin hydride followed by the addition of compound **6** and *o*-iodonitrobenzene portionwise resulted in a 79% yield of **2b** (based on a small amount of unreacted starting material).

It proved unnecessary to employ dry, deoxygenated solvent (DMF) and the reaction can be manipulated in air at ambient temperature. It should be noted that no reaction occurred when commercially available Pd-black was

used. This system also proved effective for the coupling of *p*-iodobenzaldehyde with compound **6** (entry h). In this case the catalyst could be added in one portion and heating to 45 °C was required. It is known that for aryl iodide substrates, the oxidative addition of Pd(0) in the Stille reaction cycle is accelerated by electron-withdrawing substituents.[17] Strong electron-withdrawing groups, such as the aldehyde or nitro group consequently accelerates the oxidative addition step so that no ligand is needed (entries b and h). For the other halides examined, which were devoid of strong electron-withdrawing substituents, the ligand has to be added to facilitate the oxidative addition.[18]

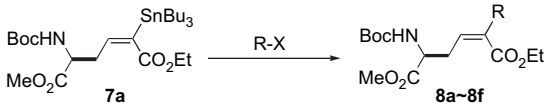
In contrast to the copper(I) chemistry described above, compound **5a** underwent a Pd-catalyzed hydrostannylation reaction[19] with tri-*n*-butyltin hydride providing **7a** as the major product in 71% yield along with regioisomer **7b** (10%) as shown in Scheme 2.

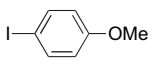
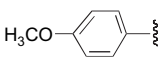
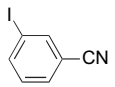
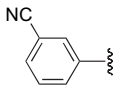
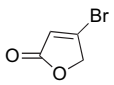
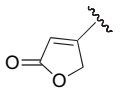
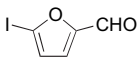
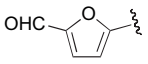


Scheme 2.

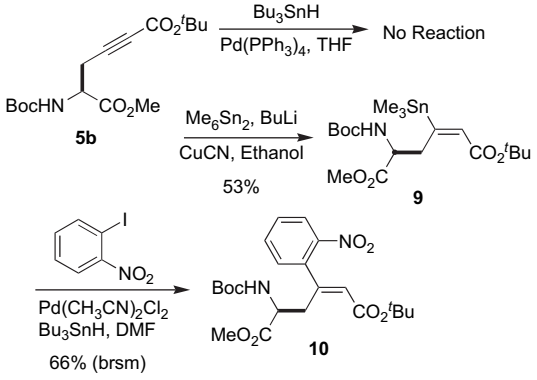
The two regioisomers **7a** and **7b** can be separated by flash chromatography and may be stored by exposing to air for weeks without significant decomposition. The major isomer **7a** can couple with a variety of halides to give the amino acids listed in Table 2. The catalytic system Pd_2dba_3/CuI/$AsPh_3$ works quite well for the Stille coupling reactions of **7a** and the halides that are listed in Table 2. It does not appear to matter whether the substituent on the phenyl group is an electron-withdrawing group such as cyano or an electron-donating group such as methoxy. 2-Bromocyclopent-2-enone and 4-bromofuran-2(5*H*)-one can couple with compound **7a** to yield **8c** and **8d**, respectively. The coupling of **7a** with 3-iodothiophene or 5-iodofuran-2-carboxaldehyde delivered **8e** and **8f**, respectively, in good yields.

Table 2. Stille coupling reactions of stannane **7a**



Entry	R-X	Conditions	Yield (%)	R
a		Pd_2dba_3, CuI, $AsPh_3$, DMF	74	
b		Pd_2dba_3, CuI, $AsPh_3$, DMF	79	
c		Pd_2dba_3, CuI, $AsPh_3$, DMF	72	
d		Pd_2dba_3, CuI, $AsPh_3$, DMF	69	
e		Pd_2dba_3, CuI, $AsPh_3$, DMF	84	
f		Pd_2dba_3, CuI, $AsPh_3$, DMF	76	

Compound **5a** underwent hydrostannylation with good regioselectivity favoring the δ-stannane **7a**. We also examined the reaction conditions by using a hindered *tert*-butyl ester that would favor the γ-stannane-type regioisomer **7b**. Compound **5b** underwent conjugate addition with [Me_3Sn-CuCN]Li to yield the γ-substituted stannane **9** in 53% yield (Scheme 3). As a preliminary demonstration of the utility of this species, compound **9** underwent Stille cross-coupling with *o*-iodonitrobenzene to produce the γ-aryl-γ,δ-unsaturated amino acid derivative **10** in which the two ester groups are differentiated. This amino acid and related derivatives are currently being examined for their utility in an intramolecular S_N2'-type strategy to access the core ring systems of spiroquinazoline and alantrypinone.



Scheme 3. Synthesis of **10** via **9**.

3. Conclusion

In summary, we have developed an efficient strategy to synthesize two types of γ,δ-unsaturated-α-amino acids bearing substitution at either γ- or δ-position. Further applications of this methodology toward the total synthesis of spiroquinazoline and other nitrogen-rich substances are currently underway and will be reported on in due course.

4. Experimental

4.1. General

All anhydrous reactions were conducted under an inert argon atmosphere. Dry solvents were obtained from a glass contour solvent purification system. Flash column chromatography was carried out using silica gel 60. All chemical shifts (δ) are reported in parts per million. Ethyl 3-bromopropiolate and *tert*-butyl 3-bromopropiolate were prepared by Leory's method.[20] 2-Bromocyclopent-2-enone[21] and 4-bromofuran-2(5*H*)-one[22] were prepared by literature procedures.

4.1.1. (*S*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)hex-2-ynedioate (5a).[7] A suspension of zinc (9.83 g, 150.4 mmol) in 11.2 mL dry THF and 1,2-dibromoethane

(0.65 mL, 7.53 mmol) was heated under Ar to 60 °C for 3 min. After cooling the mixture to 35 °C, trimethylsilyl chloride (0.194 mL, 1.53 mmol) was added and the mixture was vigorously stirred for 30 min. At this point the reaction vessel was warmed to 35 °C, compound **3** (8.25 g, 25.1 mmol) in 50 mL dry THF was slowly added, and the mixture was stirred for 15–40 min until no starting material remained. The solution of zinc reagent was then converted to the zinc/copper reagent **4** by the following procedure. The solution of zinc reagent was cooled to −10 °C, and a solution prepared from CuCN (2.27 g, 25.1 mmol) and LiCl (2.15 g, 50.2 mmol) in 50 mL dry THF was added. The mixture was stirred at 0 °C for 10 min and then cooled to −55 °C. A solution of ethyl 3-bromoprop-2-ynoate (5.91 g, 33.4 mmol) in 67 mL dry THF was introduced followed by stirring at this temperature for 20 h. After quenching with saturated aqueous NH_4Cl, the mixture was extracted with ethyl acetate (3×400 mL), the combined organic layers were washed with 400 mL water, dried ($MgSO_4$), and concentrated in vacuo. The residue was separated by silica gel flash chromatography (eluted with 20% ethyl acetate/hexane) to give 6.2 g of **5a** as a yellow oil (yield 77%). $[\alpha]_D^{20}$ +55.7 (*c* 0.670, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.79 (3H, t, *J*=7.2 Hz), 1.38 (9H, s), 2.39 (1H, dd, *J*=17.4, 5.4 Hz), 2.54 (1H, dd, *J*=17.4, 5.1 Hz), 3.18 (3H, s), 3.81 (2H, q, *J*=7.2 Hz), 4.34 (1H, ddd, *J*=7.8, 5.4, 5.1 Hz), 5.29 (1H, d, *J*=7.8 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.3, 23.3, 28.7, 52.5, 52.6, 62.1, 76.6, 80.3, 83.6, 153.5, 155.4, 170.7. IR (NaCl, neat) 3366, 2980, 2240, 1748, 1712, 1507. HRMS (FAB+) calcd mass for $C_{14}H_{22}NO_6$ 300.1447 (M+1), found: 300.1453. R_f 0.33 (eluted with 20% ethyl acetate/hexane).

4.1.2. (*S*)-1-*tert*-Butyl 6-methyl 5-(*tert*-butoxycarbonylamino)hex-2-ynedioate (5b). A procedure similar to the one described above for the preparation of **5a** was used for the synthesis of **5b** starting from 2.1 g (6.38 mmol) of compound **3** and 1.44 g (7.02 mmol) of *tert*-butyl 3-bromoprop-2-ynoate. Yield: 1.0 g (48%). $[\alpha]_D^{20}$ +52.5 (*c* 1.46, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.24 (9H, s), 1.37 (9H, s), 2.39 (1H, dd, *J*=17.1, 5.4 Hz), 2.53 (1H, dd, *J*=17.1, 5.1 Hz), 3.15 (3H, s), 4.34 (1H, ddd, *J*=7.8, 5.4, 5.1 Hz), 5.26 (1H, d, *J*=7.8 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 23.1, 28.1, 28.6, 52.3, 52.5, 77.8, 80.2, 81.3, 83.0, 152.7, 155.4, 170.8. IR (NaCl, neat) 3366, 2980, 2244, 1750, 1709, 1505. HRMS (FAB+) calcd mass for $C_{16}H_{26}NO_6$ 328.1760 (M+1), found 328.1746. R_f 0.33 (eluted with 20% ethyl acetate/hexane).

4.1.3. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(trimethylstannyl)hex-2-enedioate (6).[9] To a cold (−20 °C), stirred solution of 5.2 g of hexamethylditin (15.87 mmol) in 150 mL dry THF was added a solution of 10.7 mL (17.12 mmol) of a 1.6 M solution of methyl lithium in ether. The mixture was stirred at −20 °C for 15 min to afford a pale yellow solution of Me_3SnLi. This solution was then cooled to −78 °C and 1.66 g (18.52 mmol) of solid CuCN was added in one portion. The mixture was stirred at −78 °C for 5 min and at −48 °C for 15 min to afford a bright orange solution. This solution was then cooled to −78 °C and 0.95 mL (16.0 mmol) of dry ethanol was added. After 5 min, a solution of compound **5a** in 50 mL dry THF was added dropwise and the mixture was stirred at −78 °C for 4 h. NH_4Cl–NH_4OH buffer (200 mL, consisting of a 9:1 ratio of saturated aqueous NH_4Cl/28–30% NH_4OH, pH=8) was added, the mixture was opened to the atmosphere, allowed to warm to room temperature, and stirred vigorously until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted thoroughly with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel flash column chromatography (eluted with 15% ethyl acetate/hexane) to give 5.0 g of compound **6** as a yellow oil (81% yield). $[\alpha]_D^{20}$ +60.8 (*c* 2.65, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.18 (9H, s), 0.95 (3H, t, *J*=7.2 Hz), 1.36 (9H, s, $^2J_{Sn-H}$= 54.3 Hz), 2.89 (1H, dd, *J*=12.0, 3.9 Hz), 3.28 (3H, s), 3.90 (1H, t, *J*=12.0 Hz), 3.95 (2H, q, *J*=7.2 Hz), 4.68 (1H, *J*= 12.0, 8.1, 3.9 Hz), 6.09 (1H, d, *J*=8.1 Hz), 6.22 (1H, s, $^3J_{Sn-H}$=69.0 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ −8.7, 28.7, 28.9, 37.2, 52.3, 54.5, 79.5, 81.0, 133.4, 156.2, 164.9, 165.5, 172.8. IR (NaCl, neat) 3371, 2977, 1751, 1717, 1598, 1507, 1446 cm^{-1}. HRMS (FAB+) calcd mass for $C_{19}H_{36}NO_6Sn$: 494.1565 (M+1), found: 494.1557. R_f 0.33 (eluted with 15% ethyl acetate/hexane).

4.1.4. (*S*,*E*)-1-Ethyl 6-methyl 3-(2-bromophenyl)-5-(*tert*-butoxycarbonylamino)hex-2-enedioate (2a). A solution of *o*-iodobromobenzene (41.2 mg, 0.146 mmol), CuI (6.67 mg, 35 μmol), $AsPh_3$ (10.7 mg, 35 μmol), and Pd_2dba_3 (9.45 mg, 8.74 μmol) in 1.2 mL dry DMF under Ar was treated with compound **6** (61.3 mg, 0.132 mmol). The reaction mixture was then stirred for 2 h. The solution was then diluted with EtOAc (5 mL) and washed with water. The combined aqueous layers were back-extracted with EtOAc (2×5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting oil was purified by silica gel chromatography (eluted with 25% EtOAc in hexanes) to yield 41.0 mg of **2a** as a yellow oil (yield 68%). $[\alpha]_D^{20}$ +53.2 (*c* 1.17, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 0.91 (3H, t, *J*=7.2 Hz), 1.41 (9H, s), 3.13 (3H, s), 3.33 (1H, dd, *J*=12.4, 4.0 Hz), 3.88 (2H, q, *J*=7.2 Hz), 4.02 (1H, t, *J*=12.4 Hz), 4.70 (1H, ddd, *J*=12.4, 6.6, 4.0 Hz), 5.89 (1H, s), 5.96 (1H, d, *J*=6.6 Hz), 6.58–7.25 (4H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.7, 35.4, 52.1, 53.3, 60.9, 79.6, 121.8, 124.6, 127.9, 128.9, 130.1, 130.9, 133.6, 142.5, 156.2, 167.0, 172.5. IR (NaCl, neat) 3382, 2978, 1748, 1717, 1645, 1507, 1436 cm^{-1}. HRMS (FAB+) calcd mass for $C_{20}H_{27}NO_6Br$: 456.1021 (M+1, ^{80}Br), found: 456.1005. R_f 0.30 (eluted with 25% ethyl acetate/hexane).

4.1.5. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(2-nitrophenyl)hex-2-enedioate (2b). A 25 mL flask, equipped with a magnetic stir bar was charged with 80 mg (0.308 mmol) of $PdCl_2(CH_3CN)_2$ and 10 mL of DMF. Tri-*n*-butyltin hydride (182 μL, 0.339 mmol) was added dropwise and a black precipitate was formed immediately. The mixture was stirred for 10 min and then added to a solution of compound **6** (1.98 g, 4.27 mmol) and 1.12 g (4.49 mmol) of *o*-iodonitrobenzene in DMF (50 mL) in three portions (one portion every 5 h). The mixture was stirred overnight. The reaction was then quenched with water and the mixture was extracted with ether (3×100 mL). The combined organic extracts were washed with 300 mL water, dried over Na_2SO_4, and concentrated in vacuo. The residue

was separated by silica gel flash column chromatography (eluted with 25% ethyl acetate/hexane) to give 850 mg (47% conversion and 79% yield based on recovered **6**) of **2b** as a yellow oil along with 800 mg of unreacted **6**. $[\alpha]_D^{20}$ +17.8 (*c* 0.835, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.89 (3H, t, *J*=7.2 Hz), 1.42 (9H, s), 3.11 (3H, s), 3.16 (1H, dd, *J*=12.9, 3.6 Hz), 3.85 (2H, q, *J*=7.2 Hz), 4.03 (1H, t, *J*=12.9 Hz), 4.64 (1H, ddd, *J*=12.9, 9.0, 3.6 Hz), 5.75 (1H, s), 5.9 (1H, d, *J*=9.0 Hz), 6.5–7.6 (4H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 14.8, 28.4, 35.6, 52.1, 53.3, 79.6, 81.4, 124.2, 125.3, 128.9, 131.7, 133.6, 137.3, 147.4, 153.4, 156.3, 166.3, 172.4. IR (NaCl, neat) 3389, 2979, 1747, 1716, 1640, 1608, 1528, 1367, 1347 cm^{-1}. HRMS (FAB+) calcd mass for $C_{22}H_{31}N_2O_8$: 451.2080 (M+1), found: 451.2086. R_f 0.30 (eluted with 25% ethyl acetate/hexane).

4.1.6. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(3-cyanophenyl)hex-2-enedioate (2c). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **2c** starting from 19.5 mg (0.0421 mmol) of compound **6** and 10.6 mg (0.0464 mmol) of 3-iodobenzonitrile. Yield: 12.0 mg (71%). $[\alpha]_D^{20}$ +46.7 (*c* 0.405, CH_2Cl_2). ^1H NMR (400 MHz, C_6D_6): δ 0.99 (3H, t, *J*=7.0 Hz), 1.36 (9H, s), 3.16 (3H, s), 3.20 (1H, dd, *J*=13.4, 10.0 Hz), 3.59 (1H, dd, *J*=13.4, 9.6 Hz), 3.96 (2H, q, *J*=7.0 Hz), 4.46 (1H, ddd, *J*=10.0, 9.6, 8.4 Hz), 5.71 (1H, d, *J*=8.4 Hz), 5.81 (1H, s), 6.40–7.20 (3H, m), 7.21 (1H, s). ^{13}C NMR (100 MHz, C_6D_6): δ 14.5, 28.6, 33.4, 52.1, 53.5, 60.9, 79.8, 113.9, 118.7, 122.8, 129.7, 130.9, 131.1, 132.6, 141.5, 153.0, 155.9, 166.7, 172.2. IR (NaCl, neat) 3371, 2878, 2231, 1744, 1713, 1632, 1510 cm^{-1}. HRMS (FAB+) calcd mass for $C_{21}H_{27}N_2O_6$ 403.1869 (M+1), found 403.1869. R_f 0.30 (eluted with 25% ethyl acetate/hexane).

4.1.7. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(5-oxocyclopent-1-enyl)hex-2-enedioate (2d). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **2d** starting from 21.0 mg (0.0454 mmol) of compound **6** and 8.05 mg (0.05 mmol) of 4-bromocyclopent-2-enone. Yield: 13.3 mg (77%). $[\alpha]_D^{20}$ +46.5 (*c* 0.550, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.91 (3H, t, *J*=6.9 Hz), 1.39 (9H, s), 1.58 (2H, m), 1.78 (2H, t, *J*=4.5 Hz), 3.07 (1H, dd, *J*=13.5, 5.1 Hz), 3.33 (3H, s), 3.74 (1H, *J*=13.5, 10.8 Hz), 3.91 (2H, q, *J*=6.9 Hz), 4.70 (1H, ddd, *J*=10.8, 8.1, 6.9 Hz), 6.37 (1H, d, *J*=8.1 Hz), 7.41 (1H, t, *J*=3.0 Hz), 7.66 (1H, s). ^{13}C NMR (100 MHz, C_6D_6): δ 14.7, 26.3, 28.9, 32.6, 36.2, 52.4, 54.5, 61.0, 79.8, 122.5, 140.5, 144.0, 156.4, 163.0, 168.4, 172.8, 205.7. IR (NaCl, neat) 3371, 2978, 1746, 1708, 1625, 1510, 1367 cm^{-1}. HRMS (FAB+) calcd mass for $C_{19}H_{28}NO_7$ 382.1866 (M+1), found 382.1873. R_f 0.30 (eluted with 50% ethyl acetate/hexane).

4.1.8. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(5-oxo-2,5-dihydrofuran-3-yl)hex-2-enedioate (2e). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **2e** starting from 45.0 mg (0.097 mmol) of compound **6** and 17.4 mg (0.107 mmol) of 4-bromofuran-2(5*H*)-one. Yield: 21.1 mg (57%). $[\alpha]_D^{20}$ +36.0 (*c* 2.19, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.93 (3H, t, *J*=7.2 Hz), 1.35 (9H, s), 2.90 (1H, dd, *J*=13.2, 4.8 Hz), 3.21 (1H, dd, *J*=13.2, 9.6 Hz), 3.24 (3H, s), 3.87 (2H, q, *J*=7.2 Hz), 3.96 (2H, s), 4.69 (1H, ddd, *J*=9.6, 8.1, 4.8 Hz), 5.34 (1H, s), 5.62 (1H, d, *J*=8.1 Hz), 6.15 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.6, 32.3, 52.4, 53.9, 61.3, 70.0, 80.0, 120.3, 123.2, 143.9, 155.9, 162.1, 166.0, 171.9, 172.2. IR (NaCl, neat) 3376, 2979, 1789, 1752, 1714, 1630, 1599, 1507 cm^{-1}. HRMS (FAB+) calcd mass for $C_{18}H_{26}NO_8$ 384.1658 (M+1), found 384.1673. R_f 0.30 (eluted with 50% ethyl acetate/hexane).

4.1.9. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(thiophen-3-yl)hex-2-enedioate (2f). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **2f** starting from 19.6 mg (0.0423 mmol) of compound **6** and 9.8 mg (0.0466 mmol) of 3-iodothiophene. Yield: 13.0 mg (80%). $[\alpha]_D^{20}$ +46.1 (*c* 0.460, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.99 (3H, t, *J*=7.1 Hz), 1.38 (9H, s), 3.27 (1H, dd, *J*=12.9, 5.1 Hz), 3.28 (3H, s), 3.76 (1H, dd, *J*=12.9, 9.9 Hz), 3.96 (2H, q, *J*=6.9 Hz), 4.77 (1H, ddd, *J*=7.8, 6.9, 5.1 Hz), 6.22 (1H, d, *J*=7.8 Hz), 6.26 (1H, s), 6.65 (1H, dd, *J*=5.1, 3.0 Hz), 6.88 (1H, dd, *J*=5.1, 1.5 Hz), 7.35 (1H, dd, *J*=3.0, 1.5 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 14.8, 28.9, 33.4, 52.3, 54.9, 60.8, 79.7, 118.5, 125.8, 125.9, 126.9, 141.3, 148.7, 156.1, 167.8, 172.6. IR (NaCl, neat) 3366, 2978, 1745, 1711, 1698, 1619, 1503, 1450 cm^{-1}. HRMS (FAB+) calcd mass for $C_{18}H_{26}NO_6S$ 384.1481 (M+1), found 384.1489. R_f 0.40 (eluted with 20% ethyl acetate/hexane).

4.1.10. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(5-formylfuran-2-yl)hex-2-enedioate (2g). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **2g** starting from 53.5 mg (0.116 mmol) of compound **6** and 28.2 mg (0.127 mmol) of 5-iodofuran-2-carbaldehyde. Yield: 38.4 mg (84%). $[\alpha]_D^{20}$ +27.2 (*c* 1.13, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.94 (3H, t, *J*=7.1 Hz), 1.36 (9H, s), 3.17 (1H, dd, *J*=13.2, 5.7 Hz), 3.29 (3H, s), 3.50 (1H, dd, *J*=13.2, 9.9 Hz), 3.90 (2H, q, *J*=7.1 Hz), 4.69 (1H, ddd, *J*=9.9, 8.1, 5.7 Hz), 6.02 (1H, d, *J*=8.1 Hz), 6.37 (1H, d, *J*=4.2 Hz), 6.55 (1H, d, *J*=4.2 Hz), 6.67 (1H, s), 9.13 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.6, 31.1, 52.3, 54.7, 61.0, 79.9, 113.9, 119.6, 121.1, 140.6, 153.4, 156.2, 156.7, 167.2, 172.2, 177.7. IR (NaCl, neat) 3366, 2978, 1746, 1713, 1683, 1623, 1500, 1447 cm^{-1}. HRMS (FAB+) calcd mass for $C_{19}H_{26}NO_8$ 396.1658 (M+1), found 396.1649. R_f 0.25 (eluted with 25% ethyl acetate/hexane).

4.1.11. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(4-formylphenyl)hex-2-enedioate (2h). A procedure similar to the one described above for the preparation of **2b** was used for the synthesis of **2h** starting from 45.0 mg (0.0972 mmol) of compound **6** and 21.6 mg (0.117 mmol) of 4-iodobenzaldehyde. Yield: 26.4 mg (67%). $[\alpha]_D^{20}$ +66.8 (*c* 0.467, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.99 (3H, t, *J*=6.9 Hz), 1.37 (9H, s), 3.19 (3H, s), 3.28 (1H, dd, *J*=13.2, 5.1 Hz), 3.75 (1H, dd, *J*=13.2, 9.9 Hz), 3.87 (2H, q, *J*=6.9 Hz), 4.55 (1H, ddd, *J*=9.9, 8.4, 5.1 Hz), 5.80 (1H, d, *J*=8.4 Hz), 6.03 (1H, s), 7.12 (2H, d, *J*=4.8 Hz), 7.39 (2H, d, *J*=4.8 Hz), 9.59 (1H, s). ^{13}C NMR (400 MHz,

C_6D_6): δ 14.5, 28.7, 33.4, 52.1, 53.7, 60.9, 79.7, 122.7, 130.0, 130.2, 137.4, 145.7, 154.2, 155.9, 166.9, 172.4, 191.0. IR (NaCl, neat) 3371, 2979, 1745, 1704, 1604, 1511 cm^{-1}. HRMS (FAB+) calcd mass for $C_{21}H_{28}NO_7$ 406.1866 (M+1), found 406.1874. R_f 0.30 (eluted with 33% ethyl acetate/hexane).

4.1.12. (*S*,*E*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(tri-*n*-butylstannyl)hex-2-enedioate (7a) and (*S*,*E*)-1-ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(tri-*n*-butylstannyl)hex-2-enedioate (7b).[18] A solution of compound **5a** (347.8 mg, 022 mmol) and $Pd(PPh_3)_4$ (5 mg, 4.3 mmol) in dry THF (10 mL) under Ar was treated with tri-*n*-butyltin hydride (343 mmol, 0.24 mmol). The reaction mixture was then stirred for 2 h and the solvent was evaporated to dryness. The resulting oil was purified by silica gel chromatography (eluted with 5% ethyl acetate, 95% hexane). The fast eluting compound was **7b** (66 mg, 10%) and the slower eluting substance was **7a** (487 mg, yield 71%). Data for **7a**: $[\alpha]_D^{20}$ +33.5 (*c* 1.10, CH_2Cl_2). ^1H NMR (400 MHz, C_6D_6): δ 0.96 (9H, t, *J*=7.6 Hz), 1.01 (3H, t, *J*=7.2 Hz), 1.02 (6H, t, *J*=8.8 Hz), 1.37 (6H, m), 1.42 (9H, s), 1.59 (6H, m), 2.90 (2H, m), 3.28 (3H, s), 3.95 (2H, q, *J*=7.2 Hz), 4.58 (1H, ddd, *J*=13.2, 7.2, 0.4 Hz), 5.76 (1H, d, *J*=7.2 Hz), 6.09 (1H, t, *J*=7.4 Hz, $^3J_{Sn-H}$= 45.0 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 11.0, 14.3, 14.7, 28.0, 28.7, 29.6, 35.2, 52.1, 54.0, 60.8, 79.6, 141.1, 146.9, 156.1, 171.1, 172.8. IR (NaCl, neat) 3364, 2957, 2928, 2872, 2854, 1754, 1719, 1607, 1500 cm^{-1}. HRMS (FAB+) calcd mass for $C_{26}H_{50}NO_6Sn$: 591.2671 (M+1), found: 591.2647. R_f 0.33 (eluted with 10% ethyl acetate/hexane). Data for **7b**: $[\alpha]_D^{20}$ +54.3 (*c* 3.30, CH_2Cl_2). ^1H NMR (400 MHz, C_6D_6): δ 0.93 (9H, t, *J*=7.4 Hz), 0.94 (3H, t, *J*=7.0 Hz), 1.02 (6H, t, *J*=8.2 Hz), 1.36 (6H, m), 1.41 (9H, s), 1.58 (6H, m), 2.97 (1H, dd, *J*=12.4, 3.6 Hz), 3.31 (3H, s), 3.92 (2H, q, *J*=7.0 Hz), 4.02 (1H, t, *J*=12.4 Hz), 4.71 (1H, ddd, *J*=12.4, 12.4, 8.4 Hz), 6.23 (1H, d, *J*=8.4 Hz), 6.34 (1H, s, $^3J_{Sn-H}$=60.0 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 10.7, 14.2, 14.5, 28.1, 28.8, 29.7, 37.6, 52.2, 54.6, 60.6, 79.5, 132.1, 156.5, 165.3, 168.1, 173.0. IR (NaCl, neat) 3364, 2957, 2929, 2872, 2854, 1754, 1719, 1607, 1503 cm^{-1}. HRMS (FAB+) calcd mass for $C_{26}H_{50}NO_6Sn$: 591.2671 (M+1), found: 591.2671. R_f 0.30 (eluted with 15% ethyl acetate/hexanes).

4.1.13. (*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(4-methoxyphenyl)hex-2-enedioate (8a). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **8a** starting from 40.0 mg (0.0678 mmol) of compound **7a** and 17.4 mg (0.0745 mmol) of 1-iodo-4-methoxybenzene. Yield: 20.4 mg (74%). $[\alpha]_D^{20}$ +20.9 (*c* 0.675, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.94 (3H, t, *J*=7.1 Hz), 1.42 (9H, s), 2.81 (2H, t, *J*=7.2 Hz), 3.25 (3H, s), 3.28 (3H, s), 4.01 (2H, q, *J*=7.1 Hz), 4.61 (1H, q, *J*=7.5 Hz), 5.71 (1H, d, *J*= 7.5 Hz), 5.89 (1H, t, *J*=7.5 Hz), 6.72 (2H, d, *J*=8.7 Hz), 7.23 (2H, d, *J*=8.7 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.4, 28.7, 33.5, 52.1, 54.1, 55.1, 61.2, 79.8, 114.4, 129.3, 130.6, 131.6, 138.5, 156.1, 160.4, 168.6, 172.8. IR (NaCl, neat) 3371, 2978, 1745, 1715, 1608, 1513 cm^{-1}. HRMS (FAB+) calcd mass for $C_{21}H_{30}NO_7$ 408.2022 (M+1), found 408.2003. R_f 0.33 (eluted with 33% ethyl acetate/hexane).

4.1.14. (*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(3-cyanophenyl)hex-2-enedioate (8b). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **8b** starting from 41.3 mg (0.070 mmol) of compound **7a** and 17.6 mg (0.077 mmol) of 3-iodobenzonitrile. Yield: 22.0 mg (79%). $[\alpha]_D^{20}$ +27.4 (*c* 0.625, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.84 (3H, t, *J*=6.9 Hz), 1.41 (9H, s), 2.82 (1H, t, *J*=7.5 Hz), 3.25 (3H, s), 3.88 (2H, q, *J*=6.9 Hz), 4.57 (1H, q, *J*=7.5 Hz), 5.53 (1H, d, *J*=7.2 Hz), 5.75 (1H, t, *J*=7.8 Hz), 6.61 (1H, t, *J*=7.5 Hz), 6.8–7.4 (4H, m). ^{13}C NMR (100 MHz, C_6D_6): δ 14.3, 28.7, 33.7, 52.3, 53.8, 61.5, 80.1, 113.5, 118.9, 129.2, 131.5, 131.8, 132.1, 136.1, 138.1, 139.5, 156.0, 166.8, 172.5. IR (NaCl, neat) 3373, 2979, 2231, 1745, 1716, 1511, 1438 cm^{-1}. HRMS (FAB+) calcd mass for $C_{21}H_{27}N_2O_6$ 403.1869 (M+1), found 403.1864. R_f 0.30 (eluted with 25% ethyl acetate/hexane).

4.1.15. (*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(5-oxocyclopent-1-enyl)hex-2-enedioate (8c). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **8c** starting from 42.4 mg (0.0718 mmol) of compound **7a** and 12.7 mg (0.079 mmol) of 4-bromocyclopent-2-enone. Yield: 19.7 mg (72%). $[\alpha]_D^{20}$ +20.2 (*c* 0.130, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 1.01 (3H, t, *J*=7.2 Hz), 1.66 (9H, s), 1.68 (2H, m), 1.85 (2H, m), 2.83 (2H, m), 3.30 (3H, s), 4.05 (2H, q, *J*=7.2 Hz), 4.59 (1H, m), 5.64 (1H, d, *J*=6.9 Hz), 6.82 (1H, t, *J*=7.8 Hz), 6.96 (1H, t, *J*=2.9 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.5, 26.3, 28.7, 33.2, 35.3, 52.2, 53.9, 61.4, 79.7, 130.0, 135.6, 140.5, 156.0, 160.0, 167.0, 172.6, 205.6. IR (NaCl, neat) 3367, 2978, 1745, 1709, 1509, 1367 cm^{-1}. HRMS (FAB+) calcd mass for $C_{19}H_{28}NO_7$ 382.1866 (M+1), found 382.1874. R_f 0.33 (eluted with 50% ethyl acetate/hexane).

4.1.16. (*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(5-oxo-2,5-dihydrofuran-3-yl)hex-2-enedioate (8d). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **8e** starting from 36.0 mg (0.061 mmol) of compound **7a** and 10.93 mg (0.0671 mmol) of 4-bromofuran-2(5*H*)-one. Yield: 16.0 mg (69%). $[\alpha]_D^{20}$ +20.8 (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.82 (3H, t, *J*=7.2 Hz), 1.37 (9H, s), 2.65 (1H, m), 2.66 (1H, t, *J*=8.1 Hz), 3.21 (3H, s), 3.81 (2H, q, *J*=7.2 Hz), 4.11 (2H, s), 4.40 (1H, dd, *J*=14.1, 8.1 Hz), 5.36 (1H, d, *J*=8.1 Hz), 5.54 (1H, t, *J*=7.8 Hz), 5.98 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.2, 28.6, 33.7, 52.4, 53.5, 61.8, 70.5, 80.3, 117.5, 129.5, 140.4, 155.9, 158.7, 164.9, 172.1, 172.9. IR (NaCl, neat) 3364, 2979, 1785, 1750, 1716, 1634, 1516 cm^{-1}. HRMS (FAB+) calcd mass for $C_{18}H_{26}NO_8$ 384.1658 (M+1), found 384.1649. R_f 0.30 (eluted with 50% ethyl acetate/hexane).

4.1.17. (*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(thiophen-3-yl)hex-2-enedioate (8e). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **8e** starting from 35.6 mg (0.0603 mmol) of compound **7a** and 13.9 mg (0.0633 mmol) of 3-iodothiophene. Yield: 19.4 mg (84%). $[\alpha]_D^{20}$ +17.0 (*c* 0.635, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6): δ 0.91 (3H, t, *J*=7.1 Hz), 1.40 (9H, s), 2.76 (2H, t,

J=7.5 Hz), 3.25 (3H, s), 3.96 (2H, q, J=7.1 Hz), 4.57 (1H, q, J=7.5 Hz), 5.64 (1H, d, J=7.5 Hz), 5.95 (1H, t, J=8.1 Hz), 6.77 (1H, dd, J=5.1, 3.3 Hz), 6.94 (1H, dd, J=5.1, 1.2 Hz), 7.08 (1H, dd, J=3.3, 1.2 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ 14.6, 28.9, 33.5, 52.3, 54.2, 61.5, 79.9, 123.2, 125.9, 127.2, 132.3, 133.4, 138.6, 156.0, 168.5, 172.6. IR (NaCl, neat) 3372, 2978, 1743, 1717, 1506, 1436, 1366 cm^{-1}. HRMS (FAB+) calcd mass for $C_{18}H_{26}NO_6S$ 384.1481 (M+1), found 384.1486. R_f 0.30 (eluted with 25% ethyl acetate/hexane).

4.1.18. (*S*,*Z*)-1-Ethyl 6-methyl 5-(*tert*-butoxycarbonylamino)-2-(5-formylfuran-2-yl)hex-2-enedioate (8f). A procedure similar to the one described above for the preparation of **2a** was used for the synthesis of **8f** starting from 40.3 mg (0.0683 mmol) of compound **7a** and 16.7 mg (0.0751 mmol) of 5-iodofuran-2-carbaldehyde. Yield: 20.5 mg (76%). $[\alpha]_D^{20}$ −1.3 (*c* 0.555, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.92 (3H, t, J=7.2 Hz), 1.39 (9H, s), 2.78 (2H, t, m), 3.23 (3H, s), 3.93 (2H, q, J=7.2 Hz), 4.50 (1H, m), 5.42 (1H, d, J=7.8 Hz), 6.36 (1H, d, J=3.6 Hz), 6.46 (1H, d, J=3.6 Hz), 6.66 (1H, t, J=7.95 Hz), 9.22 (1H, s). ^{13}C NMR (75 MHz, C_6D_6): δ 14.3, 28.6, 33.2, 52.2, 53.7, 61.8, 80.0, 111.8, 121.8, 127.0, 137.5, 152.8, 154.9, 155.9, 165.0, 172.4, 177.0. IR (NaCl, neat) 3365, 2979, 1742, 1716, 1678, 1500, 1439 cm^{-1}. HRMS (FAB+) calcd mass for $C_{19}H_{26}NO_8$ 396.1658 (M+1), found 396.1640. R_f 0.30 (eluted with 33% ethyl acetate/hexane).

4.1.19. (*S*,*E*)-1-*tert*-Butyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(trimethylstannyl)hex-2-enedioate (9). A procedure similar to the one described above for the preparation of **6** was used for the synthesis of **9** starting from 0.91 mg (2.78 mmol) of compound **5b** and 1.09 g (3.34 mmol) of hexamethylditin. Yield: 729 mg (53%). $[\alpha]_D^{20}$ +60.8 (*c* 2.65, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 0.13 (9H, s, $^2J_{Sn-H}$= 54.3 Hz), 1.36 (9H, s), 1.42 (9H, s), 2.89 (1H, dd, J=12.0, 3.9 Hz), 3.28 (3H, s), 3.95 (1H, t, J=12.0 Hz), 4.68 (1H, J=12.0, 8.1, 3.9 Hz), 6.09 (1H, d, J=8.1 Hz), 6.22 (1H, s, $^3J_{Sn-H}$=69.0 Hz). ^{13}C NMR (75 MHz, C_6D_6): δ −8.7, 28.7, 28.9, 37.2, 52.3, 54.5, 79.5, 81.0, 133.4, 156.2, 164.9, 165.5, 172.8. IR (NaCl, neat) 3371, 2977, 1751, 1717, 1598, 1507, 1446 cm^{-1}. HRMS (FAB+) calcd mass for $C_{19}H_{36}NO_6Sn$ 494.1565 (M+1), found 494.1557. R_f 0.33 (eluted with 15% ethyl acetate/hexane).

4.1.20. (*S*,*E*)-1-*tert*-Butyl 6-methyl 5-(*tert*-butoxycarbonylamino)-3-(2-nitrophenyl)hex-2-enedioate (10). A procedure similar to the one described above for the preparation of **2b** was used for the synthesis of **10** starting from 404 mg (1.03 mmol) of compound **9** and 284 mg (1.14 mmol) of *o*-iodonitrobenzene. Product of 94.9 mg was obtained along with the recovery of 246 mg compound **9** (25% conversion and 66% yield based on recovered **9**). $[\alpha]_D^{20}$ +17.8 (*c* 0.835, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.36 (9H, s), 1.42 (9H, s), 3.11 (3H, s), 3.16 (1H, dd, J=12.9, 3.6 Hz), 4.03 (1H, t, J=12.9 Hz), 4.64 (1H, ddd, J=12.9, 9.0, 3.6 Hz), 5.75 (1H, s), 6.02 (1H, d, J=9.0 Hz), 6.5–7.6 (4H, m). ^{13}C NMR (75 MHz, C_6D_6): δ 28.4, 28.8, 35.6, 52.1, 53.3, 79.6, 81.4, 124.2, 125.3, 128.9, 131.7, 133.6, 137.3, 147.4, 153.4, 156.3, 166.3, 172.4. IR (NaCl, neat) 3389, 2979, 1747, 1716, 1640, 1608, 1528, 1367, 1347 cm^{-1}. HRMS (FAB+) calcd mass for $C_{22}H_{31}N_2O_8$ 451.2080 (M+1), found 451.2086. R_f 0.30 (eluted with 25% ethyl acetate/hexane).

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References and notes

1. For a few representative examples of amino acid-containing natural products see: (a) Kaneko, I.; Kamoshida, K.; Takahashi, S. *J. Antibiot.* **1989**, *42*, 236–241; (b) Matasunaga, S.; Fusetani, N.; Hashimoto, K.; Walchi, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582–2588; (c) Helms, H. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298–1307; (d) McMillan, J. A.; Paul, I. C.; Goo, Y. M.; Rinehart, K. L. *Tetrahedron Lett.* **1981**, *22*, 39–42.
2. For reviews see: (a) Williams, R. M. *Synthesis of Optically Active Amino Acids*, 1st ed.; Pergamon: Oxford, England; New York, NY, 1989; (b) O'donnell, M. J., Ed.; *Tetrahedron* **1988**, *44*, 5253–5614; (c) Izumi, Y.; Chibata, I.; Itoh, T. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 176–183.
3. For examples of amino acids natural products that have been synthesized, see: (a) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690; (b) White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 738–743; (c) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559–562.
4. Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471–476.
5. (a) Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1998**, *61*, 1154–1157; For total syntheses of alantrypinone, see: (b) Hart, D. J.; Magomedov, N. *J. Am. Chem. Soc.* **2001**, *123*, 5892–5899; (c) Hart, D. J.; Magomedov, N. *Tetrahedron Lett.* **1999**, *40*, 5429–5432; (d) Chen, Z.; Fan, J.; Kende, A. S. *J. Org. Chem.* **2004**, *69*, 79–85.
6. (a) Schollkopf, U.; Hartwig, W.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 863–864; (b) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104; (c) Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1992**, *57*, 6532–6536; (d) Genet, J. P.; Feroud, D.; Judge, S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573–4576.
7. (a) Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210–2215; (b) Reißer, M.; Maas, G. *Synthesis* **1998**, 1129–1132; For related work on propargylglycine, see: (c) van Esseveldt, B. C. J.; van Delft, F. L.; de Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717–1720.
8. Jackson, R. F. W.; Perez-Gonzalez, M. *Org. Synth.* **2005**, *81*, 77–88.
9. Piers, E.; Wong, T.; Howard, E. M.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78–87.
10. Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058–2064.
11. Leusink, A. J.; Budding, H. A.; Marsamn, J. W. *J. Organomet. Chem.* **1967**, *9*, 285–294.
12. The *N*-*t*-Boc residue was first removed from compound **6** by treatment with $Et_2O{\cdot}BF_3$ in EtOAc. The free amine thus obtained was then coupled with Mosher's acid chloride

to yield the corresponding Mosher's amide. See: Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543–2549.
13. Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, NY, 1998.
14. Scott, W.; Crisp, G. G. T.; Stille, J. K. *Org. Synth.* **1989**, *68*, 116–129.
15. Farina, V.; Krishna, B.; Marshall, D. R.; Roth, G. P. J. *J. Org. Chem.* **1993**, *58*, 5434–5444.
16. Racemic products were prepared and separated on chiral HPLC. Conditions: Chiralcel OD (Column No. OD00CE-DL010), Chiral Technologies, Inc. Eluent: hexanes/IPA (90/10); flow rate: 1.0 mL/min; detection: UV270. For all products listed in Table 1, >99:1 er values were obtained.
17. Fauvarque, J. F.; Pflüger, f.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419–427.
18. Ugo, R.; Pasini, A.; Cenini, S. *J. Am. Chem. Soc.* **1972**, *94*, 7364–7370.
19. Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.
20. Leroy, J. *Synth. Commun.* **1992**, *22*, 567–572.
21. Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462–4471.
22. Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31–32.

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A palladium-catalyzed tandem cyclization-cross-coupling reaction using indolylborate as a transfer agent

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Abstract—Investigation of the palladium-catalyzed tandem cyclization-cross-coupling reaction using indolylborate (**2**) as a transfer agent has been carried out. Furthermore, the cross-coupling reaction performed under carbon monoxide led to the generation of indolyl ketones.

1. Introduction

Metal-catalyzed cross-coupling reactions have now become a quite significant synthetic tool for the carbon–carbon bond formation, and have furnished an enormous variety of fascinating transformations.[1] Within this research, the search for palladium-catalyzed tandem Heck-type carbocyclization-cross-coupling reactions has provided a vast development that complex entities can be built up in a one-pot protocol,[2] in which various organometallic reagents such as zinc, tin, and magnesium compounds were adapted as transfer agents to take advantage of their high reactivity. The Suzuki cross-coupling protocol has now emerged as the method of choice in various chemical transformations,[3] for which phenylboronic acid is ranked among the premier transfer agents, whereas the use of organoboron compounds in the tandem process is of limited significance.[4] Notably, tetravalent organoboron compounds (ate complexes) have proven to offer less practical advantages over other agents.[5]

In connection with our project to elucidate indolylborate (**2**) as a potential synthetic intermediate,[6] we have previously disclosed that **2** is highly effective, though nevertheless an ate complex, in the palladium-catalyzed cross-coupling process.[7] By taking advantage of the attractive features of **2** in the cross-coupling reaction, we have interested in whether **2** might also be valid as a transfer agent in the palladium-catalyzed tandem cyclization-cross-coupling process, and herein, we report the detailed results of our investigation.[8]

Keywords: Indolylborate; Cascade reaction; Cross-coupling reaction; Carbonylation; Palladium catalyst.
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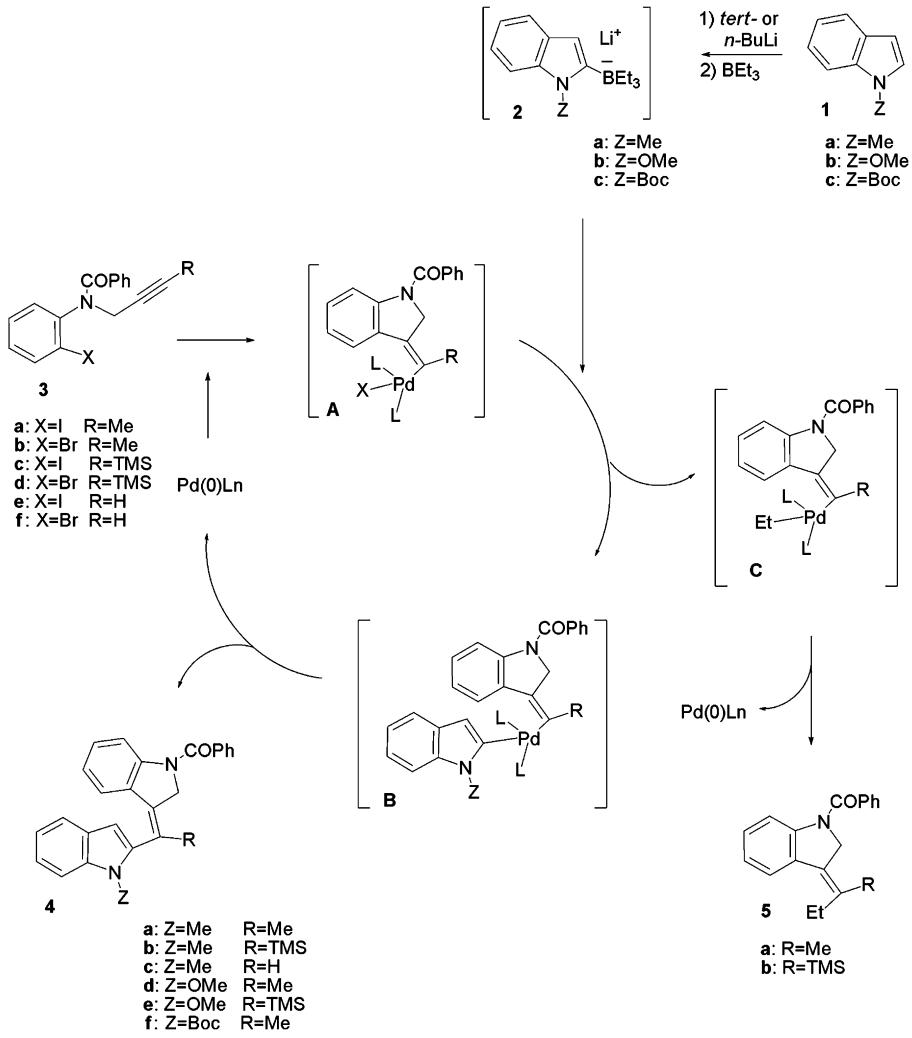
2. Results and discussion

At first, we have set about our study by reacting **2**, generated from the corresponding indole (**1**) and triethylborane in situ,[9] with **3** in the presence of a catalytic amount of palladium complex (5 mol %). The following common mechanistic scheme might account for the present reaction (Scheme 1); (1) the palladium-catalyzed Heck-type cyclization of **3**, (2) the transmetalation between complex (**A**) and **2** possibly involving transfer of the indole ring and/or the Et group, and (3) the subsequent reductive elimination. The implementation of the present protocol requires a potent transfer of the indole ring of **2** (**A**→**B**) to produce **4**, while competitive transfer of the ethyl group of **2** (**A**→**C**) should account for the formation of **5**.

On treating **2a** with 1 and 2 equiv of **3a** in the presence of $Pd(OAc)_2$, **4a** was obtained in 60 and 53% yields, respectively, along with substantial amounts of **5a** as a byproduct. Eventually, the successful reaction of **2a** with **3a** could be achieved using an excess amount of **2a** (ca. 2 equiv) in the presence of $Pd(OAc)_2$ in THF at 60 °C, which proceeded to completion within 30 min, allowing the isolation of **4a** in 78% yield along with trace amounts of **5a** (Table 1). On the other hand, marked retardation in the yield of **4a** and the appreciable appearance of **5a** were observed in the reaction with PPh_3. Under the same conditions, treatment of **2a** with bromide (**3b**) resulted in a lower yield of **4a** together with substantial amounts of **5a**.

The (*E*)-configuration in **4a** was firmly established based on NOE experiments, in which irradiation of the H2′-proton at δ 4.82 gave NOE enhancement of the methyl group at δ 2.04 (Chart 1).



Scheme 1.

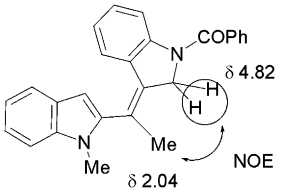


Chart 1.

It is possible that the increased steric bulkiness on the Pd in **A** (L=PPh_3) or the decrease in the positive charge on the Pd in **A** (X=Br)[10] might hamper the coordination–transmetalation step, thus allowing enough time for side reactions and resulting in the formation of **4a** and **5a** with the observed selectivity.

A clear steric effect was observed during the reaction of *N*-Boc-indolylborate (**2c**). The reaction of **2c** with **3a** became sluggish, giving **4f** in 23% yield along with **5a** (20%) and unreacted **3a** (18%) after heating for 2 h. With **3c** having a bulky TMS group on the alkyne terminus, the reaction of **2c** failed to isolate cross-coupling products, resulting in substantial amounts of **3c** and other unidentified compounds.

The reaction of **2a** with **3e** and **3f** was messy, allowing the isolation of **4c** only in a low yield. This is likely due to the lower stability of complex (**A**) (R=H) during the transmetalation step.

A closely related reaction outcome could be observed on the reaction of **2** with **6** (Table 2). When the reaction was performed in the presence of PPh_3, a decrease in the yield of **7** and the appearance of **8** were observed.

Subjection of iodides (**9**)[11] to the reaction with **2a** under the same conditions also afforded cross-coupling products (**10**) in good yields (Scheme 2).

To explore the advantage of this reaction, we next investigated the reaction of **2** with **11** having an olefin moiety under the same conditions. The initially attempted reaction of **2a** with **11** was messy, and resulted in the isolation of **12** and **13** in low yields (Table 3).

Due to the possible presence of multiple paths acting simultaneously in the decomposition of the σ-alkyl palladium complex (**D**),[12] there is no clear account for the formation of **12**. One possibility suggests that the homolytic cleavage

Table 1. Tandem cyclization-cross-coupling reaction of **2** with **3**[a]

2	3	PdLn	Time (h)	Yield (%)[b] of **4**	Yield (%)[b] of 5
2a	**3a**	$Pd(OAc)_2$	1	53 (**4a**)[c]	13 (**5a**)[c]
2a	**3a**	$Pd(OAc)_2$	1	60 (**4a**)[d]	10 (**5a**)[d]
2a	**3a**	$Pd(OAc)_2$	0.5	78 (**4a**)	—
2a	**3a**	$Pd(OAc)_2$+2PPh_3	1	37 (**4a**)	30 (**5a**)
2a	**3a**	$Pd_2(dba)_3CHCl_3$	0.5	75 (**4a**)	—
2a	**3a**	$Pd_2(dba)_3CHCl_3$+4PPh_3	1	34 (**4a**)	31 (**5a**)
2a	**3a**	$PdCl_2(CH_3CN)_2$	0.5	75 (**4a**)	—
2a	**3b**	$Pd(OAc)_2$	1	53 (**4a**)	15 (**5a**)
2a	**3b**	$Pd(OAc)_2$+2PPh_3	1	35 (**4a**)	23 (**5a**)
2a	**3b**	$Pd_2(dba)_3CHCl_3$	1	50 (**4a**)	20 (**5a**)
2a	**3b**	$Pd_2(dba)_3CHCl_3$+4PPh_3	2	29 (**4a**)	35 (**5a**)
2a	**3b**	$PdCl_2(CH_3CN)_2$	1	53 (**4a**)	15 (**5a**)
2a	**3b**	$PdCl_2(CH_3CN)_2$+2PPh_3	2	35 (**4a**)	25 (**5a**)
2a	**3c**	$Pd(OAc)_2$	0.5	71 (**4b**)	—
2a	**3c**	$PdCl_2(CH_3CN)_2$	0.5	71 (**4b**)	—
2a	**3c**	$Pd_2(dba)_3CHCl_3$	0.5	72 (**4b**)	—
2a	**3d**	$Pd(OAc)_2$	1	55 (**4b**)	15 (**5b**)
2a	**3d**	$PdCl_2(CH_3CN)_2$	1	51 (**4b**)	15 (**5b**)
2a	**3e**	$Pd(OAc)_2$	0.5	34 (**4c**)	—
2a	**3e**	$Pd(OAc)_2$+2PPh_3	1	24 (**4c**)	—
2a	**3e**	$Pd_2(dba)_3CHCl_3$	0.5	29 (**4c**)	—
2a	**3e**	$Pd_2(dba)_3CHCl_3$+4PPh_3	1	12 (**4c**)	—
2a	**3f**	$Pd(OAc)_2$	1	27 (**4c**)	—
2a	**3f**	$Pd(OAc)_2$+2PPh_3	1	18 (**4c**)	—
2b	**3a**	$Pd(OAc)_2$	1	70 (**4d**)	—
2b	**3c**	$Pd(OAc)_2$	1	65 (**4e**)	10 (**5b**)
2b	**3b**	$Pd(OAc)_2$	1	55 (**4d**)	10 (**5a**)
2b	**3d**	$Pd(OAc)_2$	1	43 (**4e**)	15 (**5b**)
2c	**3a**	$Pd(OAc)_2$	3	23 (**4f**)	20 (**5a**)
2c	**3c**	$Pd(OAc)_2$	3	—	—

[a] The reaction was carried out using indole (**1**) (2 equiv), **3** (1 equiv), and palladium complex (5 mol %) in THF under argon atmosphere at 60 °C.
[b] Yields based on **3**.
[c] Indole (**1a**) (1 equiv) and **3a** (2 equiv) and yield based on **1a**.
[d] Indole (**1a**) (1 equiv) and **3a** (1 equiv).

of the C–Pd bond, a commonly observable side reaction, is responsible for the generation of **12** (Scheme 3).[13] On the other hand, the nucleophilic attack of **2a** with a spontaneous intramolecular alkyl migration to complex (**D**) could have produced **13**.[14]

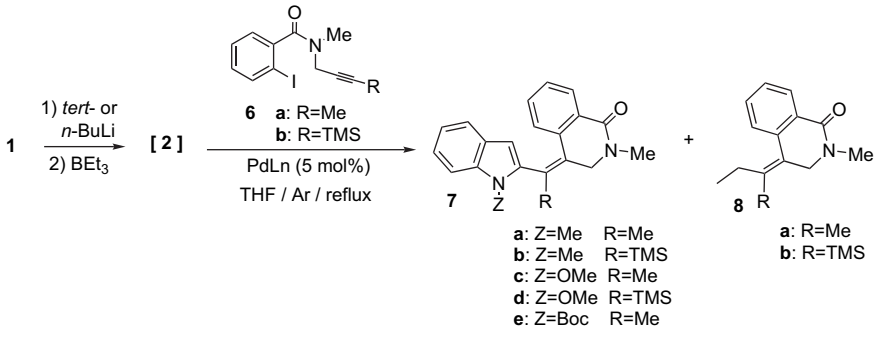
As several factors are generally known to enhance the stability of the σ-monoalkyl palladium complex, an increase in sterical hindrance was envisioned to exert an influence on the stability of σ-alkyl palladium intermediate, enabling the cross-coupling reaction to proceed.

Then, we next carried out the reaction using **14** under the same conditions (Table 4). As was expected, treatment of **2a**,**b** with **14** in the presence of $Pd(OAc)_2$ smoothly produced the cross-coupling product (**15**) in good yields. However, the presence of PPh_3 markedly altered the reaction outcome by resulting in a lower yield of **15** along with **16**.[15] A reason for this result is that the σ-alkyl palladium intermediate, generated from **14** by the way of carbopalladation, might possibly undergo homolytic cleavage of the C–Pd bond to give **16**.

Otherwise, treatment of **2a** with **17** allowed the isolation of two kinds of cross-coupling products **18a** and **19a**, in which a marked propensity for the yield of **18a** to exceed that of **19a** in the presence of PPh_3 was observed (Table 5). To our surprise, **19b** was exclusively obtained in the reaction of **2b** with **17**, and no additional products by way of the cascade reaction were isolated. The reaction of **2c** was also sluggish, giving rise to lower yield of **18b** together with the recovery of unreacted **17**.

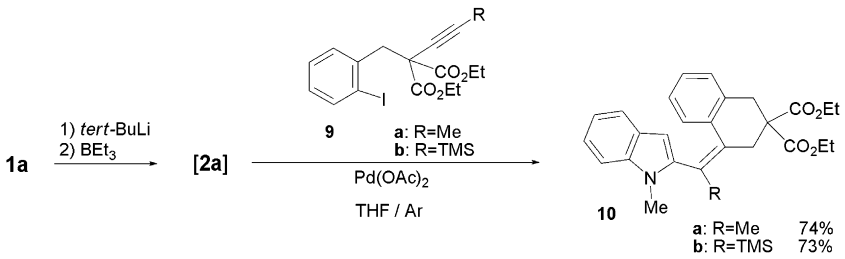
The conformational space of **14** is restricted by the presence of carbonyl sp^2 carbon involved in the tether, which enforces

Table 2. Tandem cyclization-cross-coupling reaction of **2** with **6**



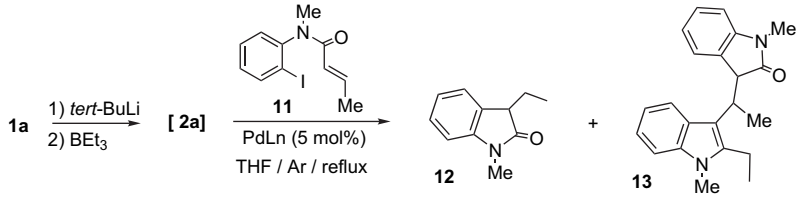
2	6	PdLn	Time (h)	Yield (%)[a] of **7**	Yield (%)[a] of **8**
2a	**6a**	$Pd(OAc)_2$	0.5	74 (**7a**)	—
2a	**6a**	$Pd(OAc)_2$+2PPh_3	0.5	55 (**7a**)	18 (**8a**)
2a	**6a**	$Pd_2(dba)_3CHCl_3$	0.5	71 (**7a**)	—
2a	**6a**	$PdCl_2(CH_3CN)_2$	0.5	70 (**7a**)	—
2a	**6a**	$PdCl_2(CH_3CN)_2$+2PPh_3	0.5	55 (**7a**)	10 (**8a**)
2a	**6b**	$Pd(OAc)_2$	0.5	73 (**7b**)	—
2a	**6b**	$PdCl_2(CH_3CN)_2$	0.5	63 (**7b**)	5 (**8b**)
2b	**6a**	$Pd(OAc)_2$	0.5	43 (**7c**)	—
2b	**6b**	$Pd(OAc)_2$	0.5	45 (**7d**)	—
2c	**6a**	$Pd(OAc)_2$	2	23 (**7e**)	15 (**8a**)[b]
2c	**6b**	$Pd(OAc)_2$	4	—	20 (**8b**)[c]

[a] Yields based on **6**.
[b] Recovery of **6a** (20%).
[c] Recovery of **6b** (30%) with unidentified products.



Scheme 2.

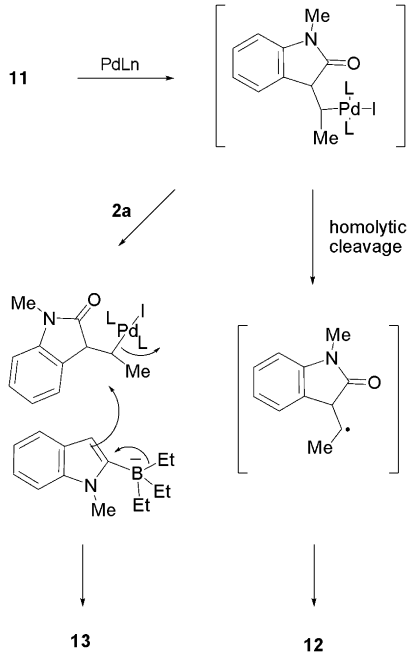
Table 3. Tandem cyclization-cross-coupling reaction of **2** with **11**



PdLn	Time (h)	Yield (%)[a] of **12**	Yield (%)[a] of **13**
$Pd(OAc)_2$	0.5	26	4
$Pd(OAc)_2$+2PPh_3	0.5	—[b]	—[b]
$Pd_2(dba)_3CHCl_3$	0.5	29	5
$PdCl_2(CH_3CN)_2$	0.5	24	2

[a] Yields based on **11**.
[b] Unidentified products.

Heck-type cyclization path. On the other hand, the lack of conformational restriction in **17** and free rotation around the C–N bond before the cyclization now made the direct cross-coupling process more favorable. Stabilization through the coordination of PPh_3 seems to be enough to minimize the transmetalation, so that the tandem cyclization-cross-coupling process might proceed.



Scheme 3.

Upon treatment of **2** with **20** under the same conditions, cross-coupling products **21** and **22** were similarly obtained, where the yield of **21** was greater than that of **22** in the absence of PPh_3 (Table 6).

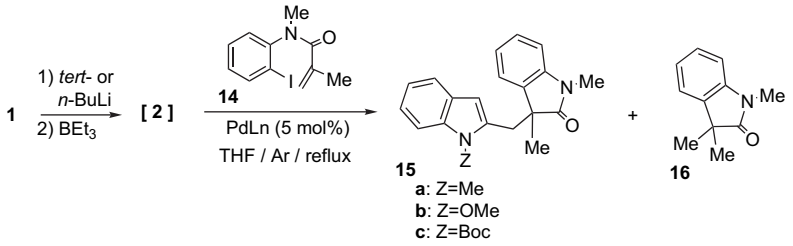
These results demonstrate that indolylborate (**2**) successfully serves as a transfer agent in the tandem cyclization-cross-coupling reaction. As we have previously reported the successful use of **2** for indolyl ketone synthesis by the way of the palladium-catalyzed carbonylative-cross-coupling reaction,[16] we then wondered if this protocol could be expanded to the cascade of cyclization–carbonylation-cross-coupling process.

When **2a** was simply treated with **14** in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) in THF at 60 °C under carbon monoxide (10 atm), a 65% yield of ketone (**23a**) was obtained together with a small amount of **15a** (Table 7). The reaction using **2c** was less effective, producing ketone (**23b**) in 51% yield accompanied by the recovery of unreacted **14**.

Under the same conditions, the reaction of **2a** with **17** also proceeded to afford ketone (**24**) along with **18a** and **19a**. Unfortunately, on the treatment of **2a** with **20**, ketone (**25**) was obtained but in low a yield allowing the isolation of ketone (**26**) along with **22** (Scheme 4).

In summary, we have disclosed that **2**, which is a tetravalent organoboron compound, could offer practical advantages as a transfer agent in the palladium-catalyzed tandem cyclization-cross-coupling reaction. Moreover, it was also shown that **2** is effective for tandem cyclization–carbonylation-cross-coupling reactions, providing indolyl ketones.

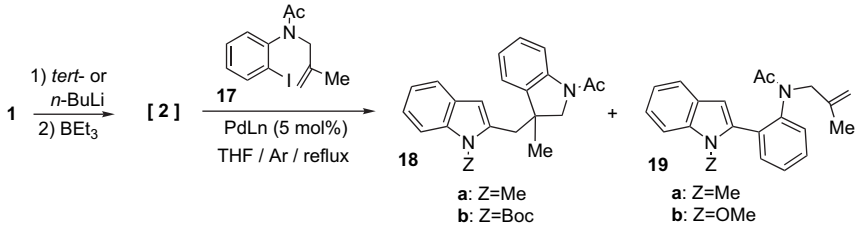
Table 4. Tandem cyclization-cross-coupling reaction of **2** with **14**



2	PdLn	Time (h)	Yield (%)[a] of **15**	Yield (%)[a] of **16**
2a	$Pd(OAc)_2$	0.5	75 (**15a**)	—
2a	$Pd(OAc)_2$+2PPh_3	0.5	53 (**15a**)	16
2b	$Pd(OAc)_2$	0.5	74 (**15b**)	—
2b	$PdCl_2(CH_3CN)_2$	0.5	70 (**15b**)	—
2c	$Pd(OAc)_2$	6	12 (**15c**)	30
2c	$Pd(OAc)_2$+2PPh_3	6	—	45

[a] Yields based on **14**.

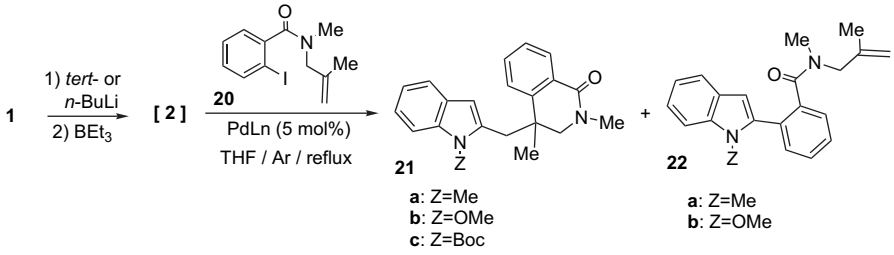
Table 5. Tandem cyclization-cross-coupling reaction of **2** with **17**



2	PdLn	Time (h)	Yield (%)[a] of **18**	Yield (%)[a] of **19**
2a	$Pd(OAc)_2$	0.5	13 (**18a**)	60 (**19a**)
2a	$Pd(OAc)_2$+2PPh_3	0.5	65 (**18a**)	10 (**19a**)
2a	$Pd_2(dba)_3CHCl_3$	0.5	12 (**18a**)	72 (**19a**)
2a	$PdCl_2(CH_3CN)_2$	0.5	10 (**18a**)	75 (**19a**)
2b	$Pd(OAc)_2$	0.5	—	80 (**19b**)
2b	$Pd(OAc)_2$+2PPh_3	0.5	—	70 (**19b**)
2c	$Pd(OAc)_2$	6	31 (**18b**)	—[b]
2c	$Pd(OAc)_2$+2PPh_3	6	51 (**18b**)	—[c]

[a] Yields based on **17**.
[b] Recovery of **17** (20%).
[c] Recovery of **17** (10%).

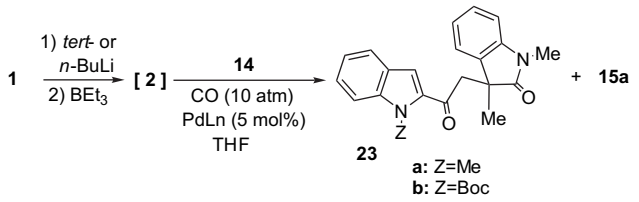
Table 6. Tandem cyclization-cross-coupling reaction of **2** with **20**



2	PdLn	Time (h)	Yield (%)[a] of **21**	Yield (%)[a] of **22**
2a	$Pd(OAc)_2$	1	26 (**21a**)	54 (**22a**)
2a	$Pd(OAc)_2$+2PPh_3	1	68 (**21a**)	5 (**22a**)
2b	$Pd(OAc)_2$	1	35 (**21b**)	20 (**22b**)
2b	$Pd(OAc)_2$+2PPh_3	1	63 (**21b**)	5 (**22b**)
2c	$Pd(OAc)_2$	5	32 (**21c**)	—[b]
2c	$Pd(OAc)_2$+2PPh_3	5	57 (**21c**)	—[c]

[a] Yields based on **20**.
[b] Recovery of **20** (20%) and unidentified products.
[c] Recovery of **20** (10%) and unidentified products.

Table 7. Tandem cyclization–carbonylation-cross-coupling reaction of **2** with **14**



2	PdLn	Yield (%)[a] of **23**	Yield (%)[a] of **15**
2a	$Pd(OAc)_2$	36 (**23a**)	31 (**15a**)
2a	$PdCl_2(Ph_3P)_2$	65 (**23a**)	5 (**15a**)
2c	$Pd(OAc)_2$	22 (**23b**)	—[b]
2c	$PdCl_2(Ph_3P)_2$	51 (**23b**)	—[c]

[a] Yields based on **14**.
[b] Recovery of **14** (30%).
[c] Recovery of **14** (10%).

3. Experimental

3.1. General

Melting points were recorded on a Yamato MP21 apparatus and are uncorrected. MS and high-resolution MS spectra were recorded on a Micromass AutoSpec 3100 mass spectrometer. IR spectra were measured on a Hitachi Model 270-30 spectrometer. The NMR experiments were performed with a JEOL JNM-LA300 or JNM-ECA500 spectrometer, and chemical shifts are expressed in parts per million (δ) with TMS as an internal reference. Medium pressure liquid chromatography (MPLC) was performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.).

3.1.1. *N*-(2-Iodophenyl)-*N*-but-2-yn-1-ylbenzamide (3a). Treatment of **3e** (2 g, 5.5 mmol) with iodomethane (0.5 mL, 8 mmol) according to the literature[10] produced **3a** in 70% yield after separation by MPLC with hexane–AcOEt (10:1) as an eluent.

Colorless crystals. Mp 73–74 °C (hexane–AcOEt). IR ($CHCl_3$): 1642 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.76 (s, 3H), 4.07 (qd, 1H, J=2.0, 17.2 Hz), 5.09 (d, 1H, J=17.2 Hz), 6.90–6.93 (m, 1H), 7.12–7.25 (m, 5H), 7.38 (d, 2H, J=7.5 Hz), 7.80 (d, 1H, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 3.7, 38.9, 73.7, 80.6, 99.9, 127.7, 128.3, 128.4, 128.5, 128.9, 129.4, 130.1, 132.1, 135.3, 140.0, 144.2, 170.3. MS *m/z*: 375 (M^+). Anal. Calcd for $C_{17}H_{14}INO$: C, 54.42; H, 3.76; N, 3.73. Found: C, 54.30; H, 3.87; N, 3.68.

3.1.2. *N*-(2-Bromophenyl)-*N*-but-2-yn-1-ylbenzamide (3b). Treatment of **3f** (2 g, 6.3 mmol) with iodomethane (0.5 mL, 8 mmol) according to the literature[10] produced **3b** in 71% yield after separation by MPLC with hexane–AcOEt (10:1) as an eluent.

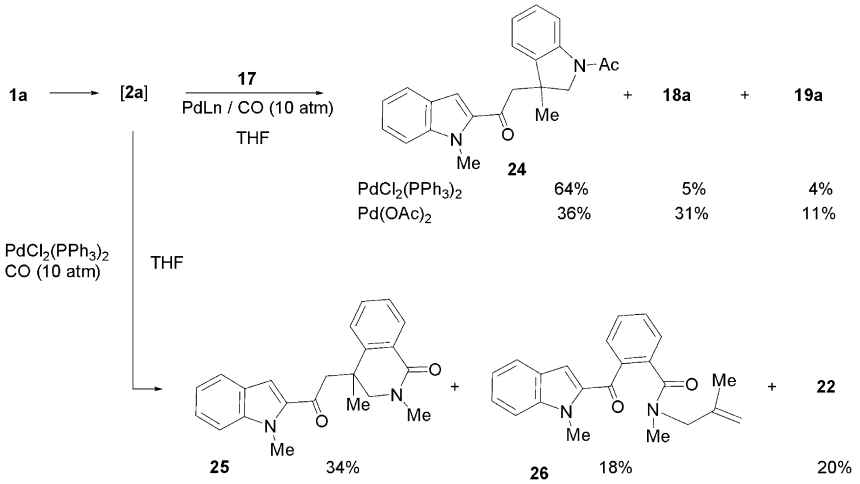
Viscous oil. IR ($CHCl_3$): 1646 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.76 (s, 3H), 4.09 (qd, 1H, J=2.0, 17.2 Hz), 5.09 (d, 1H, J=17.2 Hz), 7.05–7.25 (m, 6H), 7.36 (d, 2H, J=7.5 Hz), 7.54 (d, 1H, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 3.69, 38.5, 73.8, 80.5, 123.2, 127.8, 128.1, 128.3, 129.4, 130.1, 132.5, 133.6, 135.3, 141.3, 170.5. HRMS *m/z* Calcd for $C_{17}H_{14}BrNO$: 327.0259 and 329.0238. Found: 327.0264 and 329.0225.

3.1.3. *N*-(2-Iodophenyl)-*N*-[3-(trimethylsilyl)prop-2-yn-1-yl]benzamide (3c). Treatment of **3e** (2 g, 5.5 mmol) with chlorotrimethylsilane (1 mL, 8 mmol) according to the literature[10] produced **3c** in 68% yield after separation by MPLC with hexane–AcOEt (10:1) as an eluent.

Viscous oil. IR ($CHCl_3$): 2340, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.09 (s, 9H), 4.16 (d, 1H, J=17.2 Hz), 5.20 (d, 1H, J=17.2 Hz), 6.91–6.94 (m, 1H), 7.10–7.28 (m, 5H), 7.38 (d, 2H, J=7.5 Hz), 7.78 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 0.1, 39.0, 90.2, 100.2, 127.2, 128.5, 128.7, 129.6, 130.1, 132.5, 135.3, 139.9, 143.9, 170.1. HRMS *m/z* Calcd for $C_{19}H_{20}INOSi$: 433.0358. Found: 433.0348.

3.1.4. *N*-(2-Bromophenyl)-*N*-[3-(trimethylsilyl)prop-2-yn-1-yl]benzamide (3d). Treatment of **3f** (2 g, 6.3 mmol) with chlorotrimethylsilane (1 mL, 8 mmol) according to the literature[10] produced **3d** in 69% yield after separation by MPLC with hexane–AcOEt (10:1) as an eluent.

Colorless crystals. Mp 82–83 °C (hexane–AcOEt). IR ($CHCl_3$): 2320, 1646 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.08 (s, 9H), 4.19 (d, 1H, J=17.2 Hz), 5.20 (d, 1H, J=17.2 Hz),



Scheme 4.

7.04–7.25 (m, 6H), 7.34–7.40 (m, 2H), 7.52 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: −0.2, 38.5, 90.1, 100.2, 123.5, 127.7, 127.9, 128.2, 129.5, 130.1, 132.8, 133.5, 135.3, 140.7, 170.3. MS m/z: 385, 387 (M^+). Anal. Calcd for $C_{19}H_{20}BrNOSi$: C, 59.07; H, 5.22; N, 3.63. Found: C, 58.89; H, 5.28; N, 3.49.

3.1.5. *N*-But-2-yn-1-yl-2-iodo-*N*-methylbenzamide (6a). Treatment of 2-iodo-*N*-methyl-*N*-prop-2-yn-1-ylbenzamide (1.8 g, 6.3 mmol) with iodomethane (0.5 mL, 8 mmol) according to the literature[10] produced **6a** in 65% yield after separation by MPLC with hexane–AcOEt (3:1) as an eluent.

Viscous oil. IR ($CHCl_3$): 1632 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.79 and 1.83 (two s, 3H), 4.07 (dd, 1H, J=2.3, 16.7 Hz), 5.09 (d, 1H, J=16.7 Hz), 6.90–6.93 (m, 1H), 7.15–7.22 (m, 5H), 7.38 (d, 2H, J=7.5 Hz), 7.80 (d, 1H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 3.7, 32.1, 35.5, 35.9, 36.4, 41.1, 72.6, 73.1, 80.3, 81.3, 92.3, 92.6, 127.1, 128.5, 130.3, 139.3, 142.1, 142.3, 170.3. HRMS m/z Calcd for $C_{12}H_{12}INO$: 312.9964. Found: 312.9953.

3.1.6. 2-Iodo-*N*-methyl-*N*-[3-(trimethylsilyl)prop-2-yn-1-yl]benzamide (6b). Treatment of 2-iodo-*N*-methyl-*N*-prop-2-yn-1-ylbenzamide (1.8 g, 6.3 mmol) with chlorotrimethylsilane (1 mL, 8 mmol) according to the literature[10] produced **6b** in 60% yield after separation by MPLC with hexane–AcOEt (3:1) as an eluent.

Colorless crystals. Mp 53–54 °C (hexane–AcOEt). IR ($CHCl_3$): 1634 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.15 and 0.17 (two s, 9H), 2.88 and 3.18 (two s, 3H), 3.86 (d, 1H, J=7.5 Hz), 4.43 (s, 1H), 7.05–7.09 (m, 1H), 7.22 (dd, 1H, J=1.5, 8.0 Hz), 7.27 (dd, 1H, J=1.5, 8.0 Hz), 7.37–7.41 (m, 1H), 7.82 (dd, 1H, J=2.9, 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: −0.1, 32.2, 35.4, 36.9, 41.7, 89.6, 90.5, 92.3, 92.6, 99.2, 99.5, 127.1, 127.3, 128.4, 128.5, 130.3, 130.4, 139.3, 142.1, 170.3. MS m/z: 371 (M^+). MS m/z: 371 (M^+). Anal. Calcd for $C_{14}H_{18}INOSi$: C, 45.29; H, 4.89; N, 3.77. Found: C, 45.30; H, 4.74; N, 3.76.

3.1.7. (2*E*)-*N*-(2-Iodophenyl)-*N*-methylbut-2-enamide (11). Treatment of (2*E*)-*N*-(2-iodophenyl)but-2-enamide, readily available from 2-iodoaniline and *trans*-crotonyl chloride in 80% yield, with iodomethane according to a common procedure using sodium hydride gave **11** in 85% yield.

Colorless crystals. Mp 107–108 °C (hexane–AcOEt). IR ($CHCl_3$): 1664, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.73 (dd, 3H, J=1.8, 6.9 Hz), 3.21 (s, 3H), 5.48 (dd, 1H, J=1.8, 15.5 Hz), 6.94 (dq, 1H, J=6.9, 15.5 Hz), 7.08 (dt, 1H, J=1.8, 8.0 Hz), 7.24 (dd, 1H, J=1.8, 8.0 Hz), 7.41 (dt, 1H, J=1.8, 8.0 Hz), 7.93 (dd, 1H, J=1.8, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.1, 36.1, 99.8, 122.2, 129.5, 129.7, 129.9, 140.2, 142.0, 145.9, 165.9. MS m/z: 301 (M^+). Anal. Calcd for $C_{11}H_{12}INO$: C, 43.87; H, 4.02; N, 4.65. Found: C, 43.83; H, 4.05; N, 4.54.

3.1.8. *N*,2-Dimethyl-*N*-(2-methylphenyl)acrylamide (14). Treatment of *N*-(2-iodophenyl)-2-methylacrylamide, readily available from 2-iodoaniline and methacryl chloride in 85% yield, with iodomethane according to a common procedure using sodium hydride gave **14** in 90% yield.

Colorless crystals. Mp 79–80 °C (hexane–AcOEt). IR ($CHCl_3$): 1648, 1622 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.81 (s, 3H), 3.23 (s, 3H), 4.97 (s, 1H), 5.04 (s, 1H), 7.00 (dt, 1H, J=1.2, 8.0 Hz), 7.16 (d, 1H, J=7.5 Hz), 7.34 (t, 1H, J=7.5 Hz), 7.86 (dd, 1H, J=1.2, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.6, 36.9, 99.1, 119.1, 129.3, 129.4, 129.5, 140.3, 147.0, 171.8. MS m/z: 301 (M^+). Anal. Calcd for $C_{11}H_{12}INO$: C, 43.87; H, 4.02; N, 4.65. Found: C, 43.77; H, 4.02; N, 4.56.

3.1.9. *N*-(2-Iodophenyl)-*N*-(2-methylprop-2-en-1-yl)-acetamide (17). Treatment of *N*-(2-iodophenyl)acetamide, readily available from 2-iodoaniline and acetyl chloride, with methallyl chloride according to a common procedure using sodium hydride gave **17** in 80% yield.

Colorless crystals. Mp 68–69 °C (hexane–AcOEt). IR ($CHCl_3$): 1655 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.79 (s, 3H), 1.80 (s, 3H), 3.32 (d, 1H, J=14.9 Hz), 4.64 (s, 1H), 4.82 (s, 1H), 4.97 (d, 1H, J=14.9 Hz), 7.05 (t, 1H, J=7.5 Hz), 7.16 (dd, 1H, J=1.5, 7.5 Hz), 7.36 (t, 1H, J=7.5 Hz), 7.93 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.7, 22.9, 54.0, 100.2, 114.2, 129.4, 129.8, 130.3, 140.4, 140.5, 144.8, 170.2. MS m/z: 315 (M^+). Anal. Calcd for $C_{12}H_{14}INO$: C, 45.73; H, 4.48; N, 4.44. Found: C, 45.88; H, 4.50; N, 4.31.

3.1.10. 2-Iodo-*N*-methyl-*N*-(2-methylprop-2-en-1-yl)benzamide (20). Treatment of 2-iodo-*N*-methylbenzamide, readily available from 2-iodobenzoyl chloride and methylamine, with methallyl chloride according to a common procedure using sodium hydride gave **20** in 78% yield.

Viscous oil. IR ($CHCl_3$): 1638 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.57 and 1.82 (two s, 3H), 2.73 and 3.04 (two s, 3H), 3.58 and 3.68 (two d, 1H, J=14.9 Hz), 4.12 (s, 1H), 4.85 and 4.90 (two s, 1H), 4.95 (s, 1H), 7.00–7.08 (m, 1H), 7.15–7.22 (m, 1H), 7.30–7.40 (m, 1H), 7.73–7.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 20.0, 20.5, 32.3, 35.6, 52.4, 56.8, 92.2, 92.9, 113.3, 113.4, 127.1, 127.3, 128.2, 128.4, 130.1, 130.2, 139.1, 139.3, 140.0, 140.2, 142.3, 143.0, 170.7, 171.2. HRMS m/z Calcd for $C_{12}H_{14}INO$: 315.0120. Found: 315.0133.

3.2. General procedure for the tandem cross-coupling reaction of indolylborate (2) with 3, 6, 9,[11] 11, 14, 17, and 20

To a THF solution of indolylborate (**2**) generated from indole (**1**) (2 mmol) in situ under an argon atmosphere, **3**, **6**, **9**, **11**, **14**, **17**, or **20** (1 mmol) and the palladium complex (0.05 mmol) were added at room temperature, and then, the whole was heated at 60 °C for the time indicated in Table 1. The mixture was ice-cooled, and 10% NaOH (10 mL) and 30% H_2O_2 (2 mL) were added. After stirring for 10 min, the mixture was diluted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane–AcOEt.

3.2.1. 2-[(1*E*)-1-(1-Benzoyl-1,2-dihydro-3*H*-indol-3-ylidene)ethyl]-1-methyl-1*H*-indole (4a). Colorless crystals. Mp 180–181 °C (hexane–AcOEt). IR ($CHCl_3$): 1642 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.04 (br s, 3H), 3.53 (s, 3H), 4.82

(br s, 2H), 6.14 (d, 1H, J=7.8 Hz), 6.39 (s, 1H), 6.60–6.75 (m, 1H), 6.90–7.15 (m, 1H), 7.16 (t, 1H, J=7.8 Hz), 7.25 (t, 1H, J=7.8 Hz), 7.36 (d, 1H, J=7.8 Hz), 7.48–7.56 (m, 4H), 7.57–7.62 (m, 2H), 7.64 (d, 1H, J=7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.0, 29.6, 55.1, 99.1, 109.5, 118.4, 119.6, 120.5, 121.3, 122.8, 124.1, 126.7, 128.1, 128.5, 128.6, 129.0, 130.3, 133.4, 136.7, 136.8, 140.3, 168.4. MS m/z: 378 (M^+). Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.31; H, 5.99; N, 7.25.

3.2.2. 2-[(*Z*)-(1-Benzoyl-1,2-dihydro-3*H*-indol-3-ylidene)(trimethylsilyl)methyl]-1-methyl-1*H*-indole (4b). Colorless crystals. Mp 190–191 °C (hexane–AcOEt). IR ($CHCl_3$): 1642, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.06 (s, 9H), 3.49 (s, 3H), 4.90 (br s, 2H), 5.91 (d, 1H, J=8.3 Hz), 6.15 (s, 1H), 6.60–6.70 (m, 1H), 7.00–7.18 (m, 1H), 7.14 (t, 1H, J=7.8 Hz), 7.21 (t, 1H, J=7.8 Hz), 7.34 (d, 1H, J=8.3 Hz), 7.42–7.56 (m, 4H), 7.56–7.61 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: −1.1, 29.6, 56.4, 97.8, 109.5, 119.4, 120.0, 120.6, 124.4, 126.8, 128.6, 128.7, 129.9, 130.0, 130.6, 136.7, 136.9, 140.0, 147.0, 168.3. MS m/z: 436 (M^+). Anal. Calcd for $C_{28}H_{28}N_2OSi$: C, 74.02; H, 6.46; N, 6.42. Found: C, 76.87; H, 6.46; N, 6.49.

3.2.3. 2-[(*E*)-(1-Benzoyl-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-1-methyl-1*H*-indole (4c). Colorless crystals. Mp 171–172 °C (hexane–AcOEt). IR ($CHCl_3$): 1642, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.65 (s, 3H), 4.86 (br s, 2H), 6.40 (br s, 1H), 6.65 (s, 1H), 6.80–6.90 (m, 1H), 7.14 (dt, 1H, J=1.2, 7.8 Hz), 7.20–7.25 (m, 1H), 7.23 (dt, 1H, J=1.0, 7.8 Hz), 7.33 (d, 1H, J=7.8 Hz), 7.46–7.56 (m, 5H), 7.57–7.62 (m, 2H), 7.62 (d, 1H, J=7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 30.3, 57.2, 101.7, 109.5, 109.7, 119.9, 120.6, 121.8, 123.9, 124.1, 127.1, 128.0, 128.6, 128.9, 130.5, 130.6, 135.4, 136.9, 137.4, 137.7, 137.8, 168.6. MS m/z: 364 (M^+). Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.45; H, 5.72; N, 7.69.

3.2.4. 2-[(1*E*)-1-(1-Benzoyl-1,2-dihydro-3*H*-indol-3-ylidene)ethyl]-1-methoxy-1*H*-indole (4d). Colorless crystals. Mp 124–125 °C (hexane–AcOEt). IR ($CHCl_3$): 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.16 (br s, 3H), 3.89 (s, 3H), 4.81 (br s, 2H), 6.30 (s, 1H), 6.73 (br s, 1H), 6.83 (d, 1H, J=8.0 Hz), 7.05–7.15 (m, 1H), 7.15 (t, 1H, J=7.5 Hz), 7.27 (t, 1H, J=7.5 Hz), 7.46 (d, 1H, J=8.0 Hz), 7.49–7.55 (m, 4H), 7.57–7.69 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 22.4, 55.4, 65.8, 97.3, 108.6, 117.2, 120.4, 121.1, 122.4, 123.5, 124.0, 127.0, 128.8, 129.2, 129.3, 129.5, 130.6, 132.4, 133.5, 136.4, 136.9, 168.7. MS m/z: 394 (M^+). Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.10; H, 5.78; N, 6.97.

3.2.5. 2-[(*Z*)-(1-Benzoyl-1,2-dihydro-3*H*-indol-3-ylidene)(trimethylsilyl)methyl]-1-methoxy-1*H*-indole (4e). Viscous oil. IR (neat): 1646, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.06 (s, 9H), 3.90 (s, 3H), 4.84 (br s, 2H), 6.02 (s, 1H), 6.60 (d, 1H, J=7.5 Hz), 6.67–6.74 (m, 1H), 7.08–7.18 (m, 1H), 7.13 (t, 1H, J=7.5 Hz), 7.22 (t, 1H, J=7.5 Hz), 7.45 (d, 1H, J=8.0 Hz), 7.35–7.65 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: −0.12, 56.8, 65.8, 94.7, 108.3, 120.0, 120.7, 121.4, 124.1, 124.3, 124.9, 127.0, 128.8, 130.7, 132.2, 136.8, 137.0, 146.6, 168.4. HRMS m/z Calcd for $C_{28}H_{28}N_2O_2$: 452.1920. Found: 452.1916.

3.2.6. *tert*-Butyl 2-[(1*E*)-1-(1-Benzoyl-1,2-dihydro-3*H*-indol-3-ylidene)ethyl]-1*H*-indole-1-carboxylate (4f). Colorless crystals. Mp 177–178 °C (AcOEt–hexane). IR ($CHCl_3$): 1724, 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.98 (br s, 3H), 4.73 (br s, 2H), 6.45 (s, 1H), 6.57 (d, 1H, J=8.0 Hz), 6.69 (br s, 1H), 7.26 (t, 1H, J=7.5 Hz), 7.34 (t, 1H, J=7.5 Hz), 7.48–7.60 (m, 7H), 8.24 (d, 1H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.9, 28.1, 50.5, 83.6, 107.9, 115.9, 120.7, 123.0, 123.1, 124.2, 124.3, 127.0, 128.7, 128.9, 129.6, 130.5, 136.4, 137.1, 139.5, 149.8, 168.8. MS m/z: 464 (M^+). Anal. Calcd for $C_{30}H_{28}N_2O_3$: C, 77.56; H, 6.08; N, 6.03. Found: C, 77.48; H, 6.20; N, 5.87.

3.2.7. (3*E*)-1-Benzoyl-3-(1-methylpropylidene)indoline (5a). Viscous oil. IR (neat): 1666, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.13 (t, 3H, J=7.4 Hz), 1.71 (br s, 3H), 2.46 (q, 2H, J=7.4 Hz), 4.56 (br s, 2H), 7.04 (br s, 1H), 7.43–7.58 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 11.7, 21.3, 27.5, 55.7, 117.3, 123.5, 123.9, 124.1, 125.1, 126.9, 127.4, 128.7, 137.1, 145.5, 168.5. HRMS m/z Calcd for $C_{19}H_{19}NO$: 277.1467. Found: 277.1470.

3.2.8. (3*Z*)-1-Benzoyl-3-[1-(trimethylsilyl)propylidene]-indoline (5b). Viscous oil. IR ($CHCl_3$): 1636, 1598 cm^{-1}. ^{1}H NMR (acetone-d_6) δ: 0.05 (s, 9H), 1.09 (t, 3H, J=7.5 Hz), 2.55 (q, 2H, J=7.5 Hz), 4.67 (s, 2H), 7.08 (t, 1H, J=8.0 Hz), 7.38 (br s, 1H), 7.45–7.54 (m, 4H), 7.58–7.64 (m, 2H), 7.68 (d, 1H, J=7.5 Hz). ^{13}C NMR (acetone-d_6) δ: −1.1, 13.1, 24.2, 57.1, 117.3, 123.9, 125.4, 126.8, 128.5, 128.8, 130.1, 130.6, 135.4, 137.6, 140.2, 146.1, 167.8. HRMS m/z Calcd for $C_{21}H_{25}NOSi$: 335.1705. Found: 335.1701.

3.2.9. (4*E*)-2-Methyl-4-[1-(1-methyl-1*H*-indol-2-yl)ethylidene]-3,4-dihydroisoquinolin-1(2*H*)-one (7a). Colorless crystals. Mp 181–182 °C (hexane–AcOEt). IR ($CHCl_3$): 1638 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.31 (s, 3H), 3.05 (s, 3H), 3.27 (s, 3H), 4.36 (d, 2H, J=5.2 Hz), 6.38 (d, 1H, J=7.5 Hz), 6.51 (s, 1H), 6.95 (dt, 1H, J=1.2, 7.5 Hz), 7.11–7.14 (m, 2H), 7.17–7.22 (m, 2H), 7.60 (d, 1H, J=8.0 Hz), 8.07 (dd, 1H, J=1.2, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.6, 30.0, 35.0, 51.4, 101.6, 109.7, 119.9, 120.4, 121.8, 125.8, 126.3, 127.6, 127.7, 127.8, 128.8, 131.1, 136.4, 137.2, 140.7, 164.1. MS m/z: 316 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.71; H, 6.37; N, 8.85. Found: C, 79.51; H, 6.61; N, 8.82.

3.2.10. (4*Z*)-2-Methyl-4-[(1-methyl-1*H*-indol-2-yl)(trimethylsilyl)methylene]-3,4-dihydroisoquinolin-1(2*H*)-one (7b). Viscous oil. IR (neat): 1646 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 9H), 3.00 (s, 3H), 3.59 (s, 3H), 3.65 (d, 1H, J=13.5 Hz), 3.98 (d, 1H, J=13.5 Hz), 6.18 (s, 1H), 7.14 (t, 1H, J=7.5 Hz), 7.22 (t, 1H, J=7.5 Hz), 7.33 (d, 1H, J=8.0 Hz), 7.51–7.53 (m, 2H), 7.59–7.63 (m, 2H), 8.10–8.12 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 0.44, 30.1, 34.9, 54.0, 99.8, 109.4, 119.8, 120.2, 121.0, 126.9, 128.1, 128.5, 129.7, 129.9, 130.7, 136.0, 137.1, 137.2, 140.6, 146.6, 164.5. HRMS m/z Calcd for $C_{23}H_{26}N_2OSi$: 374.1814. Found: 374.1805.

3.2.11. (4*E*)-4-[1-(1-Methoxy-1*H*-indol-2-yl)ethylidene]-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (7c). Colorless crystals. Mp 170–171 °C (hexane–AcOEt). IR ($CHCl_3$): 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.32 (s, 3H),

3.26 (s, 3H), 3.78 (s, 3H), 4.33 (s, 2H), 6.23 (s, 1H), 6.72 (d, 1H, *J*=8.0 Hz), 7.01 (t, 1H, *J*=7.5 Hz), 7.10 (t, 1H, *J*=7.5 Hz), 7.19–7.24 (m, 2H), 7.31 (d, 1H, *J*=8.0 Hz), 7.51 (d, 1H, *J*=8.0 Hz), 8.07 (d, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.4, 35.2, 51.5, 65.2, 99.0, 108.6, 120.4, 121.0, 122.6, 123.4, 123.8, 126.4, 127.7, 127.9, 128.8, 128.9, 130.8, 132.7, 136.8, 136.9, 164.5. MS *m/z*: 332 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O_2\cdot 1/10H_2O$: C, 75.47; H, 6.09; N, 8.38. Found: C, 75.51; H, 6.19; N, 8.28.

3.2.12. (4*Z*)-4-[(1-Methoxy-1*H*-indol-2-yl)(trimethylsilyl)methylene]-2-methyl-3,4-dihydro-isoquinolin-1(2*H*)-one (7d). Viscous oil. IR ($CHCl_3$): 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.00 (s, 9H), 3.04 (s, 3H), 3.98 (s, 3H), 3.95–4.01 (m, 1H), 4.09–4.15 (m, 1H), 6.05 (s, 1H), 7.13 (t, 1H, *J*=7.5 Hz), 7.23 (t, 1H, *J*=7.5 Hz), 7.42 (d, 1H, *J*=8.0 Hz), 7.45–7.55 (m, 2H), 7.56 (d, 1H, *J*=8.0 Hz), 7.65–7.69 (m, 1H), 8.08–8.14 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 0.98, 34.6, 54.0, 65.3, 96.9, 108.2, 120.4, 120.5, 121.8, 124.1, 126.7, 128.1, 129.6, 129.9, 130.6, 132.4, 133.5, 137.3, 137.5, 146.5, 164.4. HRMS *m/z* Calcd for $C_{23}H_{26}N_2O_2Si$: 390.1764. Found: 390.1752.

3.2.13. *tert*-Butyl 2-[(1*E*)-1-(2-methyl-1-oxo-2,3-dihydroisoquinolin-4(1*H*)-ylidene)ethyl]-1*H*-indole-1-carboxylate (7e). Colorless crystals. Mp 166–167 °C (hexane–AcOEt). IR ($CHCl_3$): 1722, 1636 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.59 (s, 9H), 2.16 (s, 3H), 3.24 (s, 3H), 4.27 (d, 2H, *J*=4.0 Hz), 6.13 (s, 1H), 6.79 (d, 1H, *J*=8.0 Hz), 7.03 (t, 1H, *J*=7.5 Hz), 7.18 (t, 1H, *J*=7.5 Hz), 7.20 (t, 1H, *J*=7.5 Hz), 7.29 (t, 1H, *J*=7.5 Hz), 7.37 (d, 1H, *J*=7.5 Hz), 8.05 (d, 1H, *J*=7.5 Hz), 8.18 (d, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.6, 28.1, 35.1, 50.9, 84.1, 108.8, 115.5, 120.9, 123.0, 124.3, 125.8, 126.7, 127.5, 127.8, 128.6, 128.9, 129.4, 130.8, 136.5, 136.7, 140.5, 149.8, 164.4. MS *m/z*: 402 (M^+). Anal. Calcd for $C_{25}H_{26}N_2O_3\cdot 2/3H_2O$: C, 72.44; H, 6.65; N, 6.76. Found: C, 72.65; H, 6.43; N, 6.72.

3.2.14. (4*E*)-2-Methyl-4-(1-methylpropylidene)-3,4-dihydroisoquinolin-1(2*H*)-one (8a). Colorless crystals. Mp 100–101 °C (hexane–AcOEt). IR ($CHCl_3$): 1632, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, 3H, *J*=7.5 Hz), 1.92 (s, 3H), 2.35 (q, 2H, *J*=7.5 Hz), 3.17 (s, 3H), 4.09 (s, 2H), 7.26–7.38 (m, 2H), 7.43 (dt, 1H, *J*=1.1, 7.5 Hz), 8.07 (dd, 1H, *J*=1.5, 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.0, 18.5, 27.7, 34.9, 51.1, 122.7, 126.7, 127.0, 127.9, 129.5, 130.5, 137.3, 137.7, 164.6. MS *m/z*: 215 (M^+). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.21; H, 8.08; N, 6.43.

3.2.15. (4*Z*)-2-Methyl-4-[1-(trimethylsilyl)propylidene]-3,4-dihydroisoquinolin-1(2*H*)-one (8b). Viscous oil. IR (neat): 1642, 1598 cm^{-1}. ^{1}H NMR (acetone-d_6) δ: 0.06 (s, 9H), 0.84 (t, 3H, *J*=7.5 Hz), 2.17 (q, 2H, *J*=7.5 Hz), 2.86 (s, 3H), 3.90 (s, 2H), 7.11–7.30 (m, 3H), 7.73 (dd, 1H, *J*=1.5, 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 1.2, 15.9, 25.8, 34.3, 55.6, 127.5, 128.5, 128.6, 131.0, 131.3, 138.3, 138.5, 145.3, 164.5. HRMS *m/z* Calcd for $C_{16}H_{23}NOSi$: 273.1549. Found: 273.1547.

3.2.16. Diethyl (4*Z*)-4-[1-(1-methyl-1*H*-indol-2-yl)ethylidene]-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (10a). Viscous oil. IR (neat): 1732 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.10–1.35 (m, 6H), 2.26 (s, 3H), 3.00 (s, 3H), 3.15–3.45 (m, 2H), 4.10–4.30 (m, 4H), 6.39 (s, 1H), 6.42 (d, 1H, *J*=8.0 Hz), 6.64 (t, 1H, *J*=7.5 Hz), 6.97 (dt, 1H, *J*=1.0, 7.3 Hz), 7.05–7.16 (m, 4H), 7.57 (d, 1H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.8, 29.8, 34.7, 35.6, 54.8, 61.5, 100.4, 109.4, 119.4, 120.1, 121.0, 124.5, 125.9, 126.8, 127.7, 128.0, 128.1, 131.7, 134.3, 135.7, 136.9, 142.8, 170.9. HRMS *m/z* Calcd for $C_{27}H_{29}NO_4$: 431.2097. Found: 431.2112.

3.2.17. Diethyl (4*E*)-4-[(1-methyl-1*H*-indol-2-yl)(trimethylsilyl)methylene]-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (10b). Viscous oil. IR (neat): 1732 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.18 (s, 9H), 1.18 (t, 3H, *J*=7.3 Hz), 1.24 (t, 3H, *J*=7.3 Hz), 3.22 (s, 3H), 3.26 (s, 2H), 3.34 (d, 1H, *J*=15.0 Hz), 3.49 (d, 1H, *J*=15.0 Hz), 3.91–4.09 (m, 4H), 6.10 (s, 1H), 6.60–6.75 (m, 2H), 6.97 (dt, 1H, *J*=2.0, 7.5 Hz), 7.04–7.10 (m, 1H), 7.10 (dt, 1H, *J*=1.0, 7.5 Hz), 7.14 (d, 1H, *J*=7.5 Hz), 7.51 (d, 1H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 0.49, 14.0, 29.5, 34.0, 37.7, 54.6, 61.6, 99.5, 108.9, 119.1, 119.8, 120.0, 126.4, 127.6, 128.1, 128.4, 131.8, 134.9, 136.0, 136.7, 141.7, 150.0, 170.0, 171.0. HRMS *m/z* Calcd for $C_{27}H_{29}NO_4$: 489.2336. Found: 489.2342.

3.2.18. 3-Ethyl-1-methyl-1,3-dihydro-2*H*-indol-2-one (12). Viscous oil. IR ($CHCl_3$): 1696 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 3H, *J*=7.5 Hz), 1.95–2.08 (m, 2H), 3.19 (s, 3H), 3.40 (t, 1H, *J*=5.7 Hz), 6.82 (d, 1H, *J*=7.5 Hz), 7.05 (t, 1H, *J*=7.5 Hz), 7.24–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.2, 23.8, 26.2, 46.7, 107.9, 122.3, 123.9, 127.9, 129.1, 140.2, 178.1. HRMS *m/z* Calcd for $C_{11}H_{13}NO$: 175.0997. Found: 175.0981.

3.2.19. 3-[1-(2-Ethyl-1-methyl-1*H*-indol-3-yl)ethyl]-1-methyl-1,3-dihydro-2*H*-indol-2-one (13). Colorless crystals. Mp 198–199 °C (hexane–AcOEt). IR ($CHCl_3$): 1692 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.82 (t, 3H, *J*=7.5 Hz), 1.86 (d, 3H, *J*=6.9 Hz), 2.49 (q, 2H, *J*=7.5 Hz), 3.16 (s, 3H), 3.17–3.22 (m, 1H), 3.66 (s, 3H), 3.88 (d, 1H, *J*=10.4 Hz), 6.03 (d, 1H, *J*=6.9 Hz), 6.65 (t, 1H, *J*=7.5 Hz), 6.69 (d, 1H, *J*=7.5 Hz), 7.02 (t, 1H, *J*=7.5 Hz), 7.12 (t, 1H, *J*=7.5 Hz), 7.16 (t, 1H, *J*=7.5 Hz), 7.30 (d, 1H, *J*=8.0 Hz), 7.61 (d, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.1, 17.6, 19.2, 26.1, 29.6, 34.9, 50.0, 107.4, 109.0, 112.9, 118.9, 119.9, 120.6, 121.6, 125.6, 126.2, 127.6, 128.8, 137.1, 139.2, 144.2, 177.6. MS *m/z*: 332 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O\cdot 1/5H_2O$: C, 78.63; H, 7.32; N, 8.34. Found: C, 78.64; H, 7.38; N, 8.33.

3.2.20. 1,3-Dimethyl-3-[(1-methyl-1*H*-indol-2-yl)-methyl]-1,3-dihydro-2*H*-indol-2-one (15a). Colorless crystals. Mp 106–107 °C (hexane–AcOEt). IR ($CHCl_3$): 1708 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 3H), 3.09 (s, 3H), 3.14 (d, 1H, *J*=14.6 Hz), 3.22 (d, 1H, *J*=14.6 Hz), 3.36 (s, 3H), 6.02 (s, 1H), 6.72 (d, 1H, *J*=7.5 Hz), 6.90 (d, 1H, *J*=7.3 Hz), 6.95 (t, 1H, *J*=7.3 Hz), 7.02 (t, 1H, *J*=7.3 Hz), 7.11 (t, 1H, *J*=7.8 Hz), 7.16 (d, 1H, *J*=8.0 Hz), 7.21 (t, 1H, *J*=7.8 Hz), 7.44 (d, 1H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.9, 26.0, 29.6, 33.9, 48.6, 101.7, 108.0, 109.1, 119.1, 119.9, 120.7, 122.2, 123.1, 127.5, 128.0, 132.8, 135.2, 136.9, 143.1, 179.9. MS *m/z*: 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.89; H, 6.73; N, 9.08.

3.2.21. 3-[(1-Methoxy-1*H*-indol-2-yl)methyl]-1,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (15b). Colorless crystals. Mp 121–122 °C (hexane–AcOEt). IR ($CHCl_3$): 1702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.55 (s, 3H), 3.17 (s, 3H), 3.32 (s, 2H), 3.92 (s, 3H), 5.73 (s, 1H), 6.78 (d, 1H, J=7.5 Hz), 6.99–7.06 (m, 2H), 7.11 (d, 1H, J=7.5 Hz), 7.16 (t, 1H, J=7.5 Hz), 7.25 (t, 1H, J=8.0 Hz), 7.33 (d, 1H, J=8.0 Hz), 7.41 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.9, 26.4, 32.5, 48.5, 65.0, 97.4, 108.2, 108.3, 120.0, 120.5, 121.6, 122.5, 123.4, 123.9, 128.2, 131.6, 132.4, 133.2, 143.3, 180.1. MS *m/z*: 320 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.89; H, 6.37; N, 8.65.

3.2.22. *tert*-Butyl 2-[(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl]-1*H*-indole-1-carboxylate (15c). Viscous oil. IR (neat): 1708 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (s, 3H), 1.55 (s, 9H), 3.16 (s, 3H), 3.62 (d, 1H, J=14.9 Hz), 3.82 (d, 1H, J=14.9 Hz), 6.22 (s, 1H), 6.74 (d, 1H, J=8.0 Hz), 6.92–6.96 (m, 2H), 7.11–7.21 (m, 3H), 7.38 (d, 1H, J=7.5 Hz), 7.93 (d, 1H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.6, 26.3, 28.2, 35.8, 48.8, 83.9, 108.0, 109.9, 115.8, 120.0, 122.4, 122.6, 123.4, 123.6, 127.9, 128.9, 133.4, 136.5, 136.9, 143.1, 150.6, 180.4. HRMS *m/z* Calcd for $C_{24}H_{26}N_2O_3$: 390.1943. Found: 390.1951.

3.2.23. 2-[(1-Acetyl-3-methyl-2,3-dihydro-1*H*-indol-3-yl)methyl]-1-methyl-1*H*-indole (18a). Colorless crystals. Mp 151–152 °C (hexane–AcOEt). IR ($CHCl_3$): 1652 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.51 (s, 3H), 2.23 (s, 3H), 3.01 (d, 1H, J=18.0 Hz), 3.06 (d, 1H, J=18.0 Hz), 3.15 (s, 3H), 3.76 (d, 1H, J=10.3 Hz), 4.07 (d, 1H, J=10.3 Hz), 6.31 (s, 1H), 6.73 (d, 1H, J=7.5 Hz), 6.94 (t, 1H, J=7.5 Hz), 7.10 (t, 1H, J=7.5 Hz), 7.16–7.24 (m, 3H), 7.56 (d, 1H, J=7.5 Hz), 8.21 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.3, 25.1, 29.3, 37.8, 44.4, 62.0, 101.9, 109.4, 117.1, 119.7, 120.0, 121.1, 122.8, 123.9, 127.6, 128.5, 136.2, 137.3, 138.0, 142.1, 168.9. MS *m/z*: 318 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.48; H, 7.07; N, 8.73.

3.2.24. *tert*-Butyl 2-[(1-acetyl-3-methyl-2,3-dihydro-1*H*-indol-3-yl)methyl]-1*H*-indole-1-carboxylate (18b). Colorless crystals. Mp 167–168 °C (hexane–AcOEt). IR ($CHCl_3$): 1724, 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (s, 3H), 1.65 (s, 9H), 2.17 (s, 3H), 3.35 (d, 1H, J=14.9 Hz), 3.67 (d, 1H, J=10.3 Hz), 3.75 (d, 1H, J=14.9 Hz), 4.09 (d, 1H, J= 10.3 Hz), 6.14 (s, 1H), 7.00–7.08 (m, 2H), 7.16–7.28 (m, 3H), 7.42 (d, 1H, J=8.0 Hz), 7.99 (d, 1H, J=8.0 Hz), 8.18 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.3, 26.8, 28.3, 38.7, 44.7, 61.2, 84.3, 110.4, 115.8, 117.1, 120.1, 122.6, 122.9, 123.8, 128.1, 128.9, 136.4, 137.6, 138.8, 142.1, 150.9, 168.7. MS *m/z*: 404 (M^+). Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.23; H, 6.98; N, 6.93.

3.2.25. *N*-[2-(1-Methyl-1*H*-indol-2-yl)phenyl]-*N*-(2-methylprop-2-en-1-yl)acetamide (19a). Colorless crystals. Mp 120–121 °C (hexane–AcOEt). IR ($CHCl_3$): 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.61 (s, 3H), 2.00 (s, 3H), 3.07 (d, 1H, J=15.0 Hz), 3.61 (s, 3H), 4.54 (s, 1H), 4.64 (d, 1H, J=15.0 Hz), 4.71 (s, 1H), 6.44 (s, 1H), 7.15 (t, 1H, J= 7.5 Hz), 7.24–7.30 (m, 2H), 7.35–7.45 (m, 4H), 7.62 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.5, 23.0, 31.1, 54.0, 102.7, 109.6, 113.4, 120.2, 121.0, 122.2, 127.9, 128.0, 129.3, 130.5, 132.8, 136.2, 137.9, 140.9, 141.9, 170.5. MS *m/z*: 318 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.48; H, 7.07; N, 8.73.

3.2.26. *N*-[2-(1-Methoxy-1*H*-indol-2-yl)phenyl]-*N*-(2-methylprop-2-en-1-yl)acetamide (19b). Colorless crystals. Mp 168–169 °C (hexane–AcOEt). IR (neat): 1644 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.67 (s, 3H), 2.01 (s, 3H), 3.05 (d, 1H, J=14.9 Hz), 3.70 (s, 3H), 4.56 (s, 1H), 4.72 (s, 1H), 4.81 (d, 1H, J=14.9 Hz), 6.41 (s, 1H), 7.15 (t, 1H, J=7.5 Hz), 7.24–7.30 (m, 2H), 7.40–7.49 (m, 3H), 7.60 (d, 1H, J=8.0 Hz), 7.80 (dd, 1H, J=1.7, 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.7, 22.9, 53.2, 64.5, 100.4, 109.1, 113.3, 120.9, 121.3, 123.2, 124.3, 128.1, 128.2, 129.1, 130.7, 131.9, 132.7, 133.3, 140.8, 141.0, 170.9. MS *m/z*: 334 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O_2 \cdot 1/10H_2O$: C, 75.02; H, 6.66; N, 8.33. Found: C, 74.98; H, 6.61; N, 8.36.

3.2.27. 2,4-Dimethyl-4-[(1-methyl-1*H*-indol-2-yl)-methyl]-3,4-dihydroisoquinolin-1(2*H*)-one (21a). Colorless crystals. Mp 118–119 °C (hexane–AcOEt). IR ($CHCl_3$): 1638 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.43 (s, 3H), 2.95 (d, 1H, J=14.5 Hz), 3.01 (s, 3H), 3.23 (s, 3H), 3.24 (d, 1H, J=14.5 Hz), 3.27 (d, 1H, J=12.6 Hz), 3.62 (d, 1H, J=12.6 Hz), 6.29 (s, 1H), 6.86 (d, 1H, J=8.0 Hz), 7.07–7.12 (m, 1H), 7.13–7.17 (m, 2H), 7.29 (dt, 1H, J=1.8, 8.0 Hz), 7.36 (dt, 1H, J=1.2, 7.5 Hz), 7.56 (d, 1H, J=8.0 Hz), 8.18 (dd, 1H, J=1.2, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.7, 29.1, 35.6, 36.0, 38.3, 59.0, 102.9, 109.4, 119.6, 119.9, 121.1, 124.7, 127.4, 127.6, 128.4, 128.7, 132.0, 135.8, 137.3, 144.4, 164.7. MS *m/z*: 318 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O \cdot 3/10H_2O$: C, 77.89; H, 7.03; N, 8.65. Found: C, 77.99; H, 6.92; N, 8.54.

3.2.28. 4-[(1-Methoxy-1*H*-indol-2-yl)methyl]-2,4-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-one (21b). Viscous oil. IR (neat): 1648, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.38 (s, 1H), 2.99 (d, 1H, J=14.5 Hz), 3.15 (d, 1H, J=14.5 Hz), 3.21 (s, 3H), 3.31 (d, 1H, J=12.6 Hz), 3.40 (d, 1H, J=12.6 Hz), 3.85 (s, 3H), 6.02 (s, 1H), 7.11 (t, 1H, J=7.5 Hz), 7.22 (t, 1H, J=7.5 Hz), 7.28 (d, 1H, J=7.5 Hz), 7.38 (t, 2H, J=7.5 Hz), 7.47 (dt, 1H, J=1.7, 7.5 Hz), 7.54 (d, 1H, J=8.0 Hz), 8.19 (dd, 1H, J=1.7, 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.7, 34.9, 35.4, 38.3, 57.3, 64.6, 99.1, 108.4, 120.4, 120.5, 121.9, 123.9, 124.2, 127.3, 128.3, 128.7, 131.8, 132.0, 132.5, 145.5, 164.7. HRMS *m/z* Calcd for $C_{21}H_{22}N_2O_2$: 334.1681. Found: 334.1678.

3.2.29. *tert*-Butyl 2-[(2,4-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl]-1*H*-indole-1-carboxylate (21c). Colorless crystals. Mp 141–142 °C (hexane–AcOEt). IR ($CHCl_3$): 1728, 1646 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.32 (s, 3H), 1.69 (s, 9H), 3.18 (s, 3H), 3.37 (d, 1H, J=12.6 Hz), 3.38 (d, 1H, J=14.8 Hz), 3.42 (d, 1H, J=12.6 Hz), 3.80 (d, 1H, J=14.8 Hz), 6.01 (s, 1H), 7.10 (d, 1H, J=7.4 Hz), 7.18 (t, 1H, J=7.4 Hz), 7.23 (d, 1H, J=7.4 Hz), 7.34 (t, 1H, J=7.4 Hz), 7.38 (dt, 1H, J=1.1, 7.4 Hz), 7.42 (d, 1H, J=7.4 Hz), 7.97 (d, 1H, J=8.5 Hz), 8.14 (dd, 1H, J=1.1, 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.5, 28.4, 35.5, 36.8, 38.7, 58.2, 84.3, 111.3, 115.7, 120.1, 122.8, 123.7, 124.6, 127.0, 128.3, 128.6, 128.8, 131.7, 136.6, 137.5, 145.2, 150.9, 164.8. MS *m/z*: 404 (M^+). Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.16; H, 7.07; N, 6.81.

3.2.30. *N*-Methyl-2-(1-methyl-1*H*-indol-2-yl)-*N*-(2-methylprop-2-en-1-yl)benzamide (22a). Viscous oil. IR (neat): 1638 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 and 1.47 (two s, 3H), 2.55 and 2.75 (two s, 3H), 2.88–3.04 (two br s, 1H), 3.63 (s, 3H), 4.44 and 4.56 (two s, 1H), 4.60 and 4.74 (two s, 1H), 4.85–4.98 (m, 1H), 6.51 and 6.55 (two s, 1H), 7.07–7.15 (m, 1H), 7.20–7.27 (m, 1H), 7.30–7.50 (m, 4H), 7.55–7.64 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 19.4, 19.7, 28.1, 28.2, 31.2, 32.1, 35.6, 52.3, 56.6, 102.2, 103.0, 109.7, 112.5, 113.0, 119.8, 120.6, 120.8, 121.8, 126.8, 127.3, 127.9, 128.4, 128.5, 128.6, 128.7, 128.9, 129.6, 130.9, 131.3, 137.6, 138.0, 138.3, 138.5, 139.9, 140.0, 170.1, 171.2. HRMS *m/z* Calcd for $C_{21}H_{22}N_2O$: 318.1732. Found: 318.1728.

3.2.31. 2-(1-Methoxy-1*H*-indol-2-yl)-*N*-methyl-*N*-(2-methylprop-2-en-1-yl)benzamide (22b). Viscous oil. IR (neat): 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.51 and 1.60 (two s, 3H), 2.66 and 2.93 (two s, 3H), 3.18–3.25 (m, 1H), 3.78 (s, 3H), 3.95–4.15 (m, 1H), 4.70 and 4.74 (two s, 1H), 4.82 (s, 1H), 6.51 and 6.52 (two s, 1H), 7.09–7.15 (m, 1H), 7.22–7.29 (m, 1H), 7.38–7.51 (m, 4H), 7.56 and 7.57 (two d, 1H, J=8.0 Hz), 7.75 (d, 1H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.8, 20.0, 32.3, 35.8, 52.5, 56.7, 64.7, 100.3, 100.6, 108.8, 113.1, 120.6, 120.7, 121.2, 121.3, 122.8, 122.9, 124.1, 127.2, 127.3, 127.4, 127.5, 128.3, 128.5, 128.9, 129.0, 130.2, 130.4, 133.4, 134.0, 134.1, 136.4, 137.1, 140.1, 140.3, 170.9, 171.5. HRMS *m/z* Calcd for $C_{21}H_{22}N_2O_2$: 334.1681. Found: 334.1680.

3.3. General procedure for the tandem cyclization–carbonylation-cross-coupling reaction of 2 with 14, 17, and 20

To a THF solution of indolylborate (**2**) generated from indole (**1**) (2 mmol) in situ under an argon atmosphere, **3**, **6**, **9**, **11**, **14**, **17**, or **20** (1 mmol) was added, and the apparatus was filled with carbon monoxide. Palladium complex (0.05 mmol) was placed in a flask, and then carbon monoxide was introduced up to 10 atm. The whole was heated at 60 °C overnight. The mixture was ice-cooled, and 10% NaOH (10 mL) and 30% H_2O_2 (2 mL) were added. After stirring for 10 min, the mixture was diluted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane–AcOEt.

3.3.1. 1,3-Dimethyl-3-[2-(1-methyl-1*H*-indol-2-yl)-2-oxoethyl]-1,3-dihydro-2*H*-indol-2-one (23a). Colorless crystals. Mp 145–146 °C (hexane–AcOEt). IR ($CHCl_3$): 1702, 1662, 1612 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (s, 3H), 3.30 (s, 3H), 3.62 (d, 1H, J=17.2 Hz), 3.73 (d, 1H, J=17.2 Hz), 3.81 (s, 3H), 6.87 (d, 1H, J=8.0 Hz), 6.96 (t, 1H, J=7.5 Hz), 7.13 (t, 1H, J=8.0 Hz), 7.17 (d, 1H, J=7.5 Hz), 7.24 (t, 1H, J=7.5 Hz), 7.26–7.31 (m, 2H), 7.37 (t, 1H, J=7.5 Hz), 7.67 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 25.1, 26.5, 32.0, 45.7, 46.9, 108.2, 110.3, 111.3, 120.8, 122.1, 122.2, 122.9, 125.7, 126.0, 127.9, 133.6, 134.4, 140.0, 143.8, 180.7, 189.9. MS *m/z*: 332 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.80; H, 6.08; N, 8.29.

3.3.2. *tert*-Butyl 2-[(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]-1*H*-indole-1-carboxylate (23b). Colorless crystals. Mp 154–155 °C (hexane–AcOEt). IR ($CHCl_3$): 1706, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.42 (s, 3H), 1.47 (s, 9H), 3.19 (s, 3H), 3.54 (s, 2H), 6.82 (d, 1H, J=8.0 Hz), 6.89 (s, 1H), 6.96 (t, 1H, J=7.5 Hz), 7.18–7.25 (m, 3H), 7.38 (t, 1H, J=8.0 Hz), 7.55 (d, 1H, J=8.0 Hz), 7.97 (d, 1H, J=8.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.7, 26.4, 27.7, 45.6, 48.0, 84.8, 108.1, 114.7, 114.9, 122.3, 122.4, 122.5, 123.3, 127.2, 127.4, 128.0, 133.2, 137.7, 138.4, 143.9, 149.5, 180.1, 189.4. MS *m/z*: 418 (M^+). Anal. Calcd for $C_{25}H_{26}N_2O_4 \cdot 3/10H_2O$: C, 70.84; H, 6.33; N, 6.61. Found: C, 70.94; H, 6.20; N, 6.44.

3.3.3. 2-(1-Acetyl-3-methyl-2,3-dihydro-1*H*-indol-3-yl)-1-(1-methyl-1*H*-indol-2-yl)ethanone (24). Colorless crystals. Mp 91–92 °C (hexane–AcOEt). IR ($CHCl_3$): 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.50 (s, 3H), 2.21 (s, 3H), 3.17 (d, 1H, J=15.8 Hz), 3.46 (d, 1H, J=15.8 Hz), 3.96 (d, 1H, J=11.0 Hz), 4.03 (s, 3H), 4.34 (d, 1H, J=11.0 Hz), 7.05 (t, 1H, J=7.5 Hz), 7.15 (t, 1H, J=6.9 Hz), 7.18–7.27 (m, 3H), 7.34–7.42 (m, 2H), 7.66 (d, 1H, J=8.0 Hz), 8.20 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.3, 26.4, 32.3, 42.8, 49.2, 61.3, 110.5, 112.1, 117.2, 121.0, 122.2, 123.0, 123.9, 125.7, 126.4, 128.3, 135.2, 139.0, 140.3, 141.7, 168.9, 192.1. MS *m/z*: 346 (M^+). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.30; H, 6.48; N, 7.98.

3.3.4. 2,4-Dimethyl-4-[2-(1-methyl-1*H*-indol-2-yl)-2-oxoethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (25). Viscous oil. IR ($CHCl_3$): 1642 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.53 (s, 3H), 3.09 (s, 3H), 3.12 (d, 1H, J=14.3 Hz), 3.20 (d, 1H, J=14.3 Hz), 3.52 (d, 1H, J=12.6 Hz), 3.68 (d, 1H, J=12.6 Hz), 4.04 (s, 3H), 7.10 (s, 1H), 7.13 (dt, 1H, J=1.8, 8.0 Hz), 7.31–7.41 (m, 4H), 7.46 (t, 1H, J=7.5 Hz), 7.63 (d, 1H, J=8.0 Hz), 8.12 (d, 1H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.1, 32.4, 35.1, 37.7, 47.5, 57.2, 110.4, 112.5, 120.9, 123.1, 123.8, 125.6, 126.3, 127.3, 128.3, 128.7, 132.1, 135.6, 140.4, 145.2, 164.6, 192.0. HRMS *m/z* Calcd for $C_{22}H_{22}N_2O_2$: 346.1681. Found: 346.1673.

3.3.5. *N*-Methyl-2-[(1-methyl-1*H*-indol-2-yl)carbonyl]-*N*-(2-methylprop-2-en-1-yl)benzamide (26). Viscous oil. IR (neat): 1632 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.63 and 1.67 (two s, 3H), 2.86 and 2.92 (two s, 3H), 3.76 (s, 1H), 4.03 (s, 1H), 4.10 (s, 3H), 4.87 (s, 1H), 4.90 and 4.94 (two s, 1H), 6.95 (d, 1H, J=4.6 Hz), 7.10–7.16 (m, 1H), 7.35–7.58 (m, 5H), 7.60–7.64 (m, 1H), 7.73 (d, 1H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.9, 20.1, 32.0, 32.6, 36.3, 52.7, 53.5, 57.3, 110.3, 112.5, 112.9, 115.7, 115.8, 120.8, 123.2, 125.9, 126.2, 126.3, 126.7, 127.2, 128.2, 128.3, 129.9, 130.1, 130.8, 135.1, 137.6, 137.9, 138.2, 138.5, 140.5, 140.6, 170.6, 171.3, 188.4, 188.5. HRMS *m/z* Calcd for $C_{22}H_{22}N_2O_2$: 346.1681. Found: 346.1677.

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References and notes

1. (a) Diederich, F.; Stang, P. J. *Metal-catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, 1998; (b) Prim, D.; Campage, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075; (c) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722.
2. (a) Grigg, R. *J. Heterocycl. Chem.* **1994**, *31*, 631–639; (b) Grigg, R.; Sridharan, V. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 299–321.
3. Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes*; Aldrich Chemical: Milwaukee, WI, 2003; Vol. 3.
4. (a) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511–2514; (b) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972–6975; (c) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741–3744.
5. (a) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135–1138; (b) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393–4396; (c) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429–4432; (d) Grigg, R.; Sandano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thompton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803–11826.
6. Ishikura, M. *Curr. Org. Chem.* **2002**, *6*, 507–521.
7. Ishikura, M.; Terashima, M. *J. Chem. Soc., Chem. Commun.* **1989**, 135–136.
8. Ishikura, M. *J. Chem. Soc., Chem. Commun.* **1995**, 409–410.
9. Ishikura, M.; Agata, I.; Katagiri, N. *J. Heterocycl. Chem.* **1999**, *36*, 873–879.
10. (a) Ozawa, F.; Sugimoto, T.; Yuasa, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 683–692; (b) Huang, L.; Ozawa, F.; Yamamoto, A. *Organometallics* **1990**, *9*, 2603–2611.
11. Wang, R. T.; Chou, F. L.; Luo, F. T. *J. Org. Chem.* **1990**, *55*, 4846–4849.
12. (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; (b) Cornils, B.; Hermann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley: Weinheim, 1999; (c) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, UK, 2000.
13. Canty, A. J. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 9, pp 225–290.
14. Ishikura, M.; Matsuzaki, Y.; Agata, I.; Katagiri, N. *Tetrahedron* **1998**, *54*, 13929–13942.
15. Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553.
16. Ishikura, M.; Terashima, M. *J. Org. Chem.* **1994**, *59*, 2634–2637.

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Alternative synthesis of cystothiazole A

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Abstract—Palladium-catalyzed methoxycarbonylation of (−)-(2*R*,3*S*)-1-*tert*-butyldimethylsiloxy-3-methyl-2-methoxypenta-4-yne **9** derived from (2*R*,3*S*)-epoxy butanoate **5** gave the acetylenic ester **10**, which was treated with MeOH in the presence of Bu_3P to afford selectively (*Z*)-β-methoxy acrylate congener **11** in 86% yield. Treatment of (*Z*)-**11** with 99.8% enrichment of $CDCl_3$ followed by consecutive desilylation and oxidation afforded the left-half aldehyde (+)-**2**. The overall yield (10 steps from **5**; 23%) of (+)-**2** via the present route was improved in comparison to that (10 steps from **5**; 10%) of the previously reported route. By applying the modified Julia's coupling method, selectivity (*E*/*Z*=14:1) of the (*E*)-form (cystothiazole A **1**) against the (*Z*)-form was improved in comparison to the Wittig method (*E*/*Z*=4:1 to 6.9:1).

1. Introduction

Antifungal substances, myxothiazole A[1] and cystothiazole A **1**,[2] were isolated from different strains of myxobacterium *Myxococcus fulvus* and *Cystobacter fuscus*, respectively. These antibiotics possessing a bis-thiazole skeleton as well as a β-methoxy acrylate moiety and cystothiazole A **1** have indicated potent antifungal activity against the phytopathogenic fungus, *Phytophthora capsici* (2 μg/disk), and have shown activity against a broad range of additional fungi with no effect on bacterial growth.[2] Furthermore, cystothiazole A **1** was examined for in vitro cytotoxicity using human colon carcinoma HCT-116 and human leukemia K562 cells. The IC_{50} values of cystothiazole A **1** were 110–130 ng/ml, which were significantly higher than those of myxothiazole A. The fungicidal activity of these β-methoxy acrylate (MOA) inhibitors has been shown to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome *b* and cytochrome *c*.[3] The absolute structure of cystothiazole A **1** was established by a combination of spectroscopic analysis and chemical degradation of the natural product.[2] The left-half structure of cystothiazole A **1** has been reported to be responsible for antifungal activity.[4] In future, for the purpose of structure–biological activity relationship study of cystothiazole A congeners, efficient synthesis of the left-half aldehyde **2** is considered to be highly important.

The first enantiocontrolled synthesis of cystothiazole A **1** was achieved based on the preparation of a bis-thiazole core for the application of the asymmetric Evans aldol methodology for the development of the C(4)/C(5) vicinal stereochemistry.[5] After our synthesis of cystothiazoles A **1**[6a,b] and B[6c] was reported, syntheses of cystothiazoles A **1**,[4,7–9] B,[9] C,[5,7] and E[10] were reported. In this paper, we describe a new chiral synthesis of cystothiazole A **1** for the purpose of improvement of the overall yield and the (*E*)-selectivity of the C(6)/C(7) double bond. Our retrosynthetic strategy of cystothiazole A **1** is illustrated in Scheme 1. Retrosynthetically, the synthesis of **1** can be achieved by the modified Julia's coupling[11] of the left-half aldehyde **2** and the right-half sulfone **3** or **4**. The synthesis of the left-half aldehyde **2** is shown in Scheme 2.

By applying the previously reported procedure,[6b] the reaction of (2*R*,3*S*)-epoxy butanoate **5**[12] and lithium silyl-acetylide in the presence of Et_2AlCl gave **6** in 71% yield. Methylation of **6** followed by consecutive reduction and silylation afforded the silyl ether **9** possessing the terminal acetylene group in 52% overall yield from **6**. By applying Tsuji's procedure,[13] the acetylenic compound **9** was converted to acetylenecarboxylate **10** in 87% yield under atmospheric pressure (balloon) of carbon monoxide at room temperature using 5 mol % of $PdCl_2$ and a stoichiometric amount of $CuCl_2$ in MeOH. By applying the reported procedures,[14] conjugate addition of MeOH to acetylenecarboxylate **10** in the presence of a catalytic amount of Bu_3P afforded the corresponding (*Z*)-β-methoxy-α,β-unsaturated ester **11** in 86% yield. The (*Z*)-geometry of **11** was confirmed by the NOE enhancement for the olefinic proton and the methine proton (8.6%). Isomerization of (*Z*)-**11** to (*E*)-**12** was carried out by the following procedure. When a solution of (*Z*)-**11** in $CDCl_3$ (chloroform-*d*+1% v/v TMS (D, 99.8%)+silver foil) from Cambridge Isotope Laboratories, Inc.) was stood for 3 days at room temperature, (*E*)-**12** was

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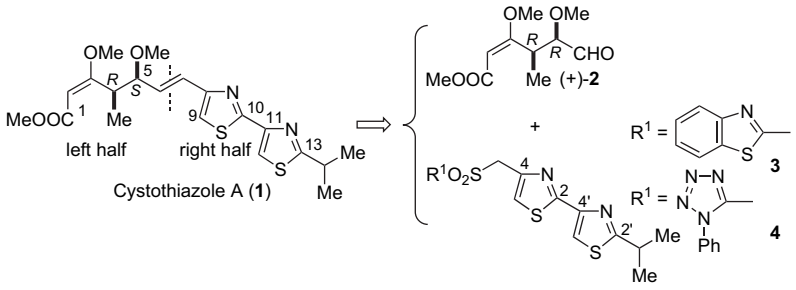
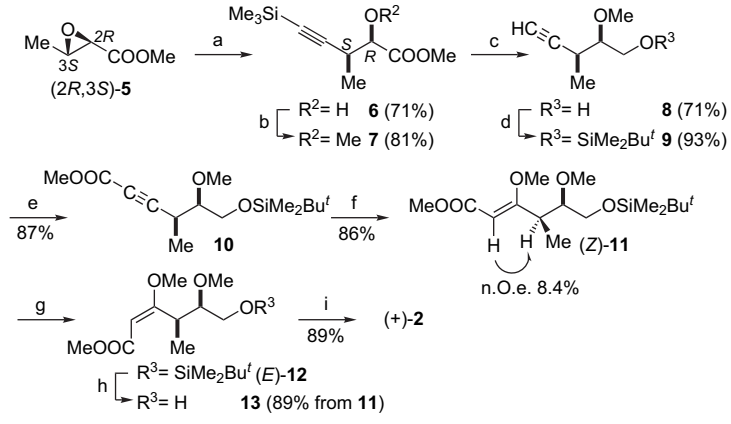


Scheme 1.

exclusively obtained. The crude (*E*)-**12** was treated with $Et_3N\cdot(HF)_3$ in CH_2Cl_2 to give the primary alcohol (+)-**13** ($[\alpha]_D$ +91.4 (*c* 0.64, $CHCl_3$)) in 85% overall yield from (*Z*)-**11**, which was identical with the reported (+)-**13** ($[\alpha]_D$ +76.1 (*c* 0.7, $CHCl_3$)).[6b] Another $CDCl_3$ (99.8% atom % D from Aldrich) was also effective for this selective isomerization. On the other hand, the distillated $CHCl_3$, CH_2Cl_2, $(CF_3SO_3)Yb/CH_2Cl_2$, and silica gel/MeOH were inactive for this selective isomerization. Treatment of (*Z*)-**11** with pyridinium *p*-toluenesulfonate (PPTS)/MeOH/PhH or $(CF_3SO_3)Sc/CH_2Cl_2$ or $InCl_3/CH_2Cl_2$ gave a complex mixture including a mixture of (*Z*)-**12** and (*E*)-**12**. The same type of isomerization as conversion of (*Z*)-**11** to (*E*)-**12** in 99.8% $CDCl_3$ was observed in our previous case.[15] In the case of β-methoxy acrylate, it was reported that a trace amount of acidic impurities often was sufficient to bring about rapid equilibration toward the (*E*)-form from the (*Z*)-form at ordinary temperatures.[16] The thus-obtained (+)-**13** was subjected to Dess–Martin periodinane oxidation to provide the desired aldehyde (+)-**2** ($[\alpha]_D$ +104.7 (*c* 0.55, $CHCl_3$)) in 89% yield. Then, the synthesis of the right-half sulfone **3** or **4** is carried out as shown in Scheme 3.

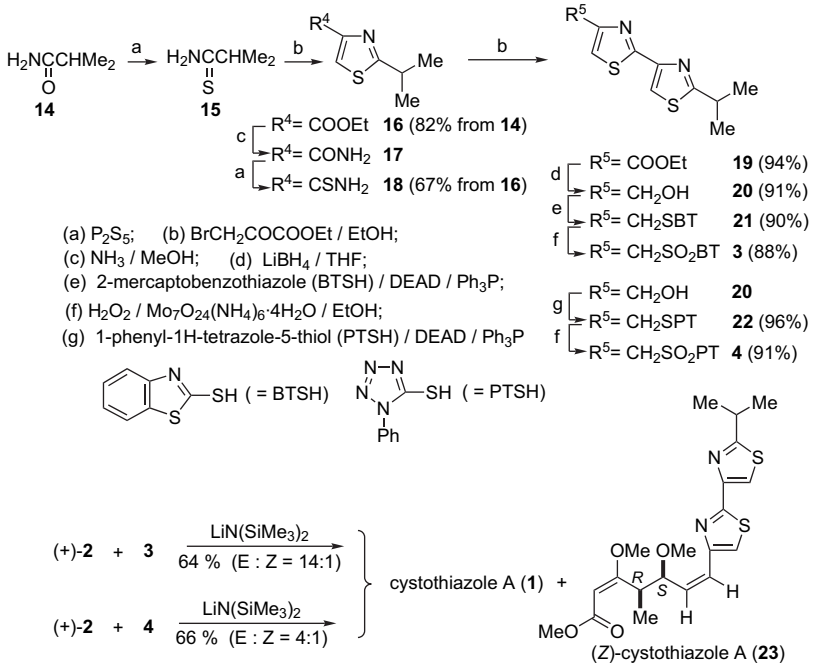
Treatment of isopropylamide **14** with P_4S_{10} gave an isopropylthioamide **15**, which was reacted with α-bromopyruvate to afford a mono-thiazole ester **16** in 82% overall yield from **14**. Treatment of **16** with NH_3/MeOH followed by thioamidation with P_4S_{10} yielded a thioamide **18** in 67% overall yield from **16**. The reaction of **18** with α-bromopyruvate afforded a bithiazole ester **19** in 94% yield. $LiBH_4$ reduction (**20**, 91% yield) of **19** followed by treatment with 2-mercaptobenzothiazole (BTSH)/Ph_3P/diethylazodicarboxylate (DEAD) provided a sulfide **21** in 90% yield. The sulfide **21** was subjected to oxidation with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ to give the corresponding sulfone **3** in 88% yield. Moreover, an alcohol **20** was treated with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH)/Ph_3P/diethylazodicarboxylate (DEAD) to provide a sulfide **22** in 96% yield. The sulfide **22** was subjected to oxidation with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ to give the corresponding sulfone **4** in 91% yield. Then, the modified Julia's coupling of the aldehyde **2** with sulfones (**3** or **4**) was carried out. The reaction of **2** and **3** in the presence of lithium bis(trimethylsilyl)amide in THF gave a mixture (*E*/*Z*=14:1) of cystothiazole A **1** and (*Z*)-cystothiazole A **23** in 64% yield. A part of this mixture was again subjected to chromatography to provide (*E*)-**1**, whose spectral data (^1H and ^{13}C NMR) were identical with those of the reported data.[6b] The reaction of **2** and **4** in the presence of lithium bis(trimethylsilyl)amide in THF gave a mixture (*E*/*Z*=4:1) of cystothiazole A **1** and (*Z*)-cystothiazole A **23** in 66% yield.

In conclusion, palladium-catalyzed methoxycarbonylation of (–)-(2*R*,3*S*)-1-*tert*-butyldimethylsiloxy-3-methyl-2-methoxypenta-4-yne **9** derived from (2*R*,3*S*)-epoxy butanoate **5** gave the acetylenic ester **10**, which was treated with MeOH in the presence of Bu_3P to afford selectively



(a) $Li^+ {}^-C{\equiv}C{-}SiMe_3$ / Et_2AlCl; (b) MeI / Ag_2O; (c) (1) $Bu_4N^+F^-$, (2) $LiBH_4$;
(d) $^tBuMe_2SiCl$ / imidazole / DMF; (e) $PdCl_2$ (5 mol %) / $CuCl_2$ / NaOAc / CO (balloon) / CH_2Cl_2;
(f) Bu_3P/MeOH; (g) $CDCl_3$ (D; 99.8%); (h) $Et_3N\cdot(HF)_3$ / CH_2Cl_2; (i) Dess-Martin periodinane

Scheme 2.



Scheme 3.

(*Z*)-β-methoxy acrylate congener **11** in 86% yield. Treatment of (*Z*)-**11** with 99.8% enrichment of $CDCl_3$ followed by consecutive desilylation and oxidation gave the left-half aldehyde (+)-**2**. The overall yield (10 steps from **5**, 23%) of (+)-**2** via the present route was improved in comparison to that (10 steps from **5**, 10%) of the previously reported route.[6a,b] By applying the modified Julia's coupling method, selectivity (*E*/*Z*=14:1) of the (*E*)-form (cystothiazole A **1**) against the (*Z*)-form was improved in comparison to the Wittig method (*E*/*Z*=4:1[6b] to 6.9:1[8]).

2. Experimental

2.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FABMS) were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

2.2. (−)-(2*R*,3*S*)-1-*tert*-Butyldimethylsiloxy-3-methyl-2-methoxypenta-4-yne (9)

n-Butyllithium (*n*-BuLi, 1.6 M in hexane, 24.5 ml, 39.2 mmol) was added to a stirred solution of trimethylsilylacetylene (3.8 g, 38.7 mmol) in toluene (50 ml) at −40 °C under an argon atmosphere and the mixture was stirred for 1 h at 0 °C. A solution of (2*R*,3*S*)-**5** (3.0 g, 25.8 mmol) in toluene (10 ml) was added to the above reaction mixture and the whole mixture was stirred for 3 h at 5–10 °C. The reaction mixture was diluted with H_2O (20 ml) at 0 °C and the generated white precipitate was filtered off with the aid of Celite. The precipitate was washed with AcOEt and the washing and filtrate were combined. The extracted organic layer was dried over $MgSO_4$ and evaporated to give an oily product, which was chromatographed on silica gel (60 g, *n*-hexane–AcOEt 30:1) to afford methyl (2*R*,3*S*)-2-hydroxy-3-methyl-5-trimethylsilyl-4-pentynoate **6** (3.91 g, 71% yield) as a colorless oil. Compound (−)-**6**: $[\alpha]_D^{25}$ −24.1 (*c* 1.07, $CHCl_3$); IR (neat): 3482, 2168, 1741 cm^{-1}; ^1H NMR: δ 0.15 (9H, s), 1.21 (3H, d, *J*=7.2 Hz), 2.86–2.93 (1H, m), 3.81 (3H, s), 4.21 (1H, d, *J*=4.4 Hz); ^{13}C NMR: δ −0.07, 15.8, 32.3, 52.4, 73.5, 86.9, 106.1, 173.1; HRMS (FAB) calcd for $C_{10}H_{19}O_3Si$ (M^++1): 215.1104. Found: *m*/*z*: 215.1106.

A mixture of **6** (2.105 g, 9.8 mmol), methyl iodide (18 g, 127 mmol), and Ag_2O (3.2 g, 13.8 mmol) in DMF (6 ml) was stirred for 48 h at room temperature. The reaction mixture was diluted with AcOEt (30 ml) and filtered off with the aid of Celite. The filtrate was diluted with H_2O and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (50 g, *n*-hexane–AcOEt 60:1) to provide methyl (2*R*,3*S*)-2-methoxy-3-methyl-5-trimethylsilyl-4-pentynoate **7** (1.819 g, 81% yield) as a colorless oil. Compound (−)-**7**: $[\alpha]_D^{23}$ −0.32 (*c* 1.225, $CHCl_3$); IR (neat): 1752, 2170 cm^{-1}; ^1H NMR: δ 0.14 (9H, s), 1.23 (3H, d, *J*=6.8 Hz), 2.89 (1H, dq, *J*=6.4, 6.8 Hz), 3.43 (3H, s), 3.71 (1H, d, *J*=6.4 Hz), 3.77 (3H, s); ^{13}C NMR: δ −0.02, 16.4, 30.5, 51.8, 58.9, 84.0, 86.6, 106.3, 171.4; HRMS (FAB) calcd for $C_{11}H_{21}O_3Si$ (M^++1): 229.1260. Found: 229.1289.

To a solution of (2*R*,3*S*)-**7** (1.66 g, 7.3 mmol) in THF (20 ml) was added 1 M tetrabutylammonium fluoride (TBAF) in THF solution (3.7 ml, 3.7 mmol) at 0 °C and the whole mixture was stirred for 10 min at 0 °C. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was used for the next reaction without further purification. To a solution of the above 2-methoxy ester in THF (20 ml) was added $LiBH_4$ (0.641 g, 29.4 mmol) at 0 °C and the whole mixture was stirred for 60 min at room temperature. The reaction mixture was diluted with MeOH (2 ml), H_2O (100 ml), and Et_2O (100 ml), and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of Celite to afford the filtrate. The filtrate was extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the filtrate gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt 5:1) to provide (–)-**8** as a colorless oil (0.66 g, 71%). Compound (–)-**8**: $[\alpha]_D^{27}$ −27.6 (*c* 1.05, $CHCl_3$); IR (neat): 3429, 3296, 2113 cm^{-1}; ^1H NMR: δ 1.25 (3H, d, *J*=6.8 Hz), 2.11 (1H, d, *J*=2.4 Hz), 2.38 (1H, br s), 2.76 (1H, ddq, *J*=2.4, 6.8, 6.8 Hz), 3.16 (1H, ddd, *J*=3.2, 5.6, 6.8 Hz), 3.80 (2H, dq, *J*=12, 5.6 Hz); ^{13}C NMR: δ 17.1, 27.3, 58.4, 61.9, 70.3, 84.5, 85.5; HRMS (FAB) calcd for $C_7H_{13}O_2$ (M^++1): 129.0916. Found: 129.0919.

A solution of (–)-**8** (0.452 g, 3.5 mmol), imidazole (0.492 g, 7.1 mmol), and *tert*-butyldimethylsilyl chloride (TBDMSCl, 0.797 g, 5.3 mmol) in DMF (2 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with brine and extracted with AcOEt/*n*-hexane (1:1). The organic layer was dried over $MgSO_4$ and evaporated to give a crude **9**, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt 30:1) to afford **9** (0.801 g, 93%) as a colorless oil. Compound (–)-**9**: $[\alpha]_D^{25}$ −4.74 (*c* 1.06, $CHCl_3$); IR (neat): 2115 cm^{-1}; ^1H NMR: δ 0.06 (6H, s), 0.89 (9H, s), 1.21 (3H, d, *J*=7.2 Hz), 2.05 (1H, d, *J*=2.4 Hz), 2.68 (1H, ddq, *J*=2.4, 7.2, 6.4 Hz), 3.16 (1H, ddq, *J*=4.4, 5.6, 6.4 Hz), 3.71 (1H, dd, *J*=5.6, 10.8 Hz), 3.82 (1H, dd, *J*=4.4, 10.8 Hz); ^{13}C NMR: δ −5.46, −5.41, 16.4, 18.3, 25.9 (3C), 27.4, 59.0, 63.3, 69.4, 84.6, 86.5; HRMS (FAB) calcd for $C_{13}H_{27}O_2Si$ (M^++1): 243.1781. Found: 243.1785.

2.3. (–)-Methyl (4*S*,5*R*)-6-*tert*-butyldimethylsiloxy-4-methyl-5-methoxy-2-hexynoate (10)

A 100-ml two-necked round-bottomed flask, containing a magnetic stirring bar, $PdCl_2$ (47 mg, 0.27 mmol), anhydrous $CuCl_2$ (1.79 g, 13.2 mmol), and anhydrous NaOAc (1.09 g, 13.3 mmol) in MeOH (25 ml), was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping–filling via the three-way stopcock. A solution of (–)-**9** (1.289 g, 5.33 mmol) in MeOH (3.5 ml) was added to the above stirred mixture via a syringe at 0 °C. After being stirred for 4 h, the reaction mixture was diluted with AcOEt (100 ml)/H_2O (100 ml). The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt 50:1) to provide (–)-**10** as a homogeneous oil (1.399 g, 87%). $[\alpha]_D^{24}$ −15.1 (*c* 0.86, $CHCl_3$); IR (neat): 2236, 1717 cm^{-1}; ^1H NMR: δ 0.06 (6H, s), 0.89 (9H, s), 1.25 (3H, d, *J*=7.2 Hz), 2.86 (1H, dq, *J*=7.2, 6.8 Hz), 3.23–3.27 (1H, m), 3.47 (3H, s), 3.68–3.77 (2H, m), 3.74 (3H, s); ^{13}C NMR: δ −5.52, −5.47, 15.0, 18.2, 25.8 (3C), 27.5, 52.5, 59.0, 62.7, 73.7, 83.6, 91.3, 154.1; HRMS (FAB) calcd for $C_{15}H_{29}O_4Si$ (M^++1): 301.1836. Found: 301.1837.

2.4. (–)-Methyl (4*R*,5*R*)-6-*tert*-butyldimethylsiloxy-3,5-dimethoxy-4-methyl-2(*Z*)-hexenoate (11)

A mixture of (–)-**10** (1.25 g, 4.2 mmol), Bu_3P (0.254 g, 1.25 mmol), and MeOH (0.335 g, 10.5 mmol) in CH_2Cl_2 (25 ml) was stirred for 4 h at room temperature. The reaction mixture was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt 50:1) to afford (–)-**11** (1.90 g, 86%) as a colorless oil. Compound (–)-**11**: $[\alpha]_D^{24}$ −15.6 (*c* 0.96, $CHCl_3$); IR (neat): 1717, 1630 cm^{-1}; ^1H NMR: δ 0.05 (6H, s), 0.89 (9H, s), 1.11 (3H, d, *J*=7.2 Hz), 2.59 (1H, dq, *J*=6.8, 6.8 Hz), 3.30 (1H, dd, *J*=5.6, 6.8 Hz), 3.41 (3H, s), 3.61 (2H, d, *J*=5.6 Hz), 3.66 (3H, s), 3.91 (3H, s), 5.07 (1H, s); ^{13}C NMR: δ −5.45, −5.38, 13.4, 18.3, 25.9 (3C), 40.5, 50.9, 59.3, 60.2, 62.9, 83.1, 95.8, 165.9, 174.7; HRMS (FAB) calcd for $C_{16}H_{33}O_5Si$ (M^++1): 333.2097. Found: 332.2120.

2.5. (+)-Methyl (4*R*,5*R*)-6-hydroxy-3,5-dimethoxy-4-methyl-2(*E*)-hexenoate (13)

A solution of (–)-**11** (0.103 g, 0.45 mmol) in $CDCl_3$ (2 ml; D, 99.8% including 1% v/v TMS, silver foil, available from Cambridge Isotope Laboratories Inc.) was stood for 2 weeks at room temperature. Evaporation of the solvent gave **12** as a colorless oil, which was used for the next reaction without further purification. Compound **12**: ^1H NMR: δ 0.03 (6H, s), 0.87 (9H, s), 1.15 (3H, d, *J*=7.2 Hz), 3.33 (1H, dq, *J*=3.0, 7.2 Hz), 3.46 (3H, s), 3.54 (1H, dd, *J*=7.2, 11.2 Hz), 3.61 (3H, s), 3.61–3.65 (1H, m), 3.65 (3H, s), 3.97–4.04 (1H, m), 4.96 (1H, s).

A mixture of **12** and $Et_3N\cdot(HF)_3$ (0.6 g, 3.7 mmol) in CH_2Cl_2 (4 ml) was stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt 3:1) to afford (+)-**13** (0.06 g, 89% from (–)-**11**) as a colorless oil. Compound (+)-**13**: $[\alpha]_D^{23}$ +91.4 (*c* 0.64, $CHCl_3$); IR (KBr): 3450, 1711, 1623, 1150 cm^{-1}; ^1H NMR: δ 1.19 (3H, d, *J*=6.8 Hz), 3.24–3.32 (1H, m), 3.44–3.48 (1H, m), 3.45 (3H, s), 3.63 (3H, s), 3.67–3.73 (1H, m), 3.69 (3H, s), 4.07–4.15 (1H, m), 5.05 (1H, s); ^{13}C NMR: δ 14.5, 36.0, 51.2, 55.6, 58.1, 61.4, 83.6, 91.4, 168.6, 176.6; HRMS (FAB) calcd for $C_{10}H_{17}O_5$ (M^++1): 217.1076. Found: 217.1079.

2.6. (+)-Methyl (4*R*,5*R*)-3,5-dimethoxy-4-methyl-2(*E*)-hexenoate (2)

A mixture of (+)-**14** (0.142 g, 0.65 mmol) and Dess–Martin reagent (0.708 g, 1.67 mmol) in CH_2Cl_2 (6 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with ether. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of

the organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt 9:1) to provide (+)-**2** as a colorless oil (0.125 g, 89%). Compound (+)-**2**: $[\alpha]_D^{23}$ +104.7 (*c* 0.55, $CHCl_3$); IR (KBr): 1712, 1628, 1441, 1149, 1095 cm^{-1}; ^1H NMR: δ 1.20 (3H, d, *J*=7.2 Hz), 3.43 (3H, s), 3.56 (1H, dd, *J*=2.4, 6.8 Hz), 3.64 (3H, s), 3.68 (3H, s), 4.48 (1H, dq, *J*=6.8, 7.2 Hz), 5.07 (1H, s), 9.59 (1H, q, *J*=2.4 Hz); ^{13}C NMR: δ 13.9, 36.5, 51.0, 55.7, 58.6, 87.4, 91.9, 167.6, 174.4, 202.1; HRMS (FAB) calcd for $C_{10}H_{17}O_5$ (M^++1): 217.1076. Found: 217.1079.

2.7. Ethyl 2-isopropylthiazole-4-carboxylate (16)

To a solution of phosphorus pentasulfide (P_4S_{10}; 5.1 g, 11.47 mmol) in ether (40 ml) was added isobutylamide **14** (10 g, 114.7 mmol) and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a crude **15**. A mixture of the crude **15** and ethyl α-bromopyruvate (22.39 g, 114.5 mmol) in EtOH (100 ml) was stirred at reflux for 15 min. The reaction mixture was evaporated, diluted with AcOEt, and washed with 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (200 g, *n*-hexane/AcOEt 20:1) to afford **16** as a colorless compound (18.92 g, 82% overall yield from **14**). Compound **16**: IR (neat): 1726 cm^{-1}; ^1H NMR: δ 1.40 (3H, t, *J*=7.2 Hz), 1.42 (6H, t, *J*=7.0 Hz), 3.43 (1H, sept, *J*=7.0 Hz), 4.42 (2H, q, *J*=7.2 Hz), 8.06 (1H, s); ^{13}C NMR: δ 14.4, 23.3 (C2), 33.6, 61.4, 126.4, 146.6, 161.6, 179.0; MS (FAB) *m/z*: 200 (M^++1).

2.8. 2-Isopropylthiazole-4-thioamide (18)

The thiazole ester **16** (20.01 g, 100.1 mmol) was treated with saturated NH_3 in MeOH (10 ml) in a sealed tube and the whole mixture was left to stand for 3 days at room temperature. After cooling, the reaction mixture was concentrated to afford a crude amide **17**. To a solution of crude **17** in benzene (300 ml) was added phosphorus pentasulfide (P_4S_{10}; 36.5 g, 82.1 mmol) and the whole mixture was stirred for 2 h at reflux. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (300 g, *n*-hexane/AcOEt 10:1) to afford **18** as a pale yellow compound (12.53 g, 67% from **16**). Recrystallization of **18** from *n*-hexane afforded **18** as pale yellow needles. Compound **18**: mp 83–85 °C; IR (KBr): 3290, 3155, 1634 cm^{-1}; ^1H NMR: δ 1.40 (6H, d, *J*=6.9 Hz), 3.28 (1H, sept, *J*=6.9 Hz), 7.79 (1H, br s), 8.32 (1H, s), 8.70 (1H, br s); ^{13}C NMR: δ 22.9, 33.3, 85.1, 126.4, 152.5, 177.7, 190.9. Anal. Calcd for $C_7H_{10}N_2S_2$: C, 45.13; H, 5.41; N, 15.04%. Found: C, 45.13; H, 5.36; N, 15.01. FABMS *m/z*: 187 (M^++1).

2.9. Ethyl 2′-isopropyl[2,4′]bithiazolyl-4-carboxylate (19)

A solution of **19** (0.99 g, 5.3 mmol) and ethyl bromopyruvate (1.14 g, 5.8 mmol) in absolute EtOH (30 ml) was stirred for 1 h at reflux. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt 30:1) to afford **19** (1.41 g, 94%). Recrystallization of **19** from *n*-hexane provided **19** as colorless needles. Compound **19**: mp 76–77 °C; IR (KBr): 1729 cm^{-1}; ^1H NMR: δ 1.43 (3H, d, *J*=7.1 Hz), 1.44 (6H, d, *J*=6.9 Hz), 3.36 (1H, sept, *J*=6.9 Hz), 4.44 (2H, q, *J*=7.1 Hz), 8.02 (1H, s), 8.16 (1H, s); ^{13}C NMR: δ 14.4, 23.1, 33.4, 61.5, 116.1, 127.4, 147.5, 147.6, 161.3, 163.5, 178.4. Anal. Calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.02; H, 5.00; N, 9.92%. Found: C, 50.89; H, 5.02; N, 9.96. FABMS *m/z*: 283 (M^++1).

2.10. 2′-Isopropyl[2,4′]bithiazolyl-4-methyl alcohol (20)

A mixture of **19** (1.787 g, 6.3 mmol) and $LiBH_4$ (0.69 g, 31.6 mmol) in THF (20 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O (10 ml) and the whole was stirred for 5 h at the same temperature. The reaction mixture was extracted with AcOEt and washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt 5:1) to afford **20** (1.506 g, 91%). Recrystallization of **20** from *n*-hexane provided **20** as colorless needles. Compound **20**: mp 56–58 °C; IR (KBr): 3247, 1536, 1447 cm^{-1}; ^1H NMR: δ 1.44 (6H, d, *J*=7.2 Hz), 3.25–3.40 (1H, br s), 3.37 (1H, sept, *J*=7.2 Hz), 4.81 (2H, s), 7.19 (1H, t, *J*=0.8 Hz), 7.84 (1H, s); ^{13}C NMR: δ 23.1, 23.1, 33.4, 60.9, 115.0, 115.2, 148.4, 157.2, 163.7, 178.8. Anal. Calcd for $C_{10}H_{12}N_2OS_2$: C, 49.97; H, 5.03; N, 11.66%. Found: C, 50.27; H, 5.19; N, 11.43. FABMS *m/z*: 241 (M^++1).

2.11. 2′-Isopropyl[2,4′]bithiazolyl-4-methylenethio-2-benzothiazole (21) and 2′-isopropyl[2,4′]bithiazolyl-4-methylenesulfonyl-2-benzothiazole (3)

To a mixture of **20** (0.1 g, 0.42 mmol), triphenylphosphine (0.218 g, 0.83 mmol), and diethylazocarboxylate (0.27 g, 0.62 mmol) in THF (5 ml) was added 2-mercaptobenzothiazole (0.14 g, 0.84 mmol) under argon atmosphere and the whole mixture was stirred for 60 min at room temperature. The reaction mixture was diluted with 2 M aqueous NaOH and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt 30:1) to afford **22** (0.146 g, 90%). Recrystallization of **21** from *n*-hexane provided **21** as colorless needles. Compound **21**: mp 74–75 °C; IR (KBr): 3119, 2962, 1430, 997 cm^{-1}; ^1H NMR: δ 1.42 (6H, d, *J*=7.0 Hz), 3.36 (1H, sept, *J*=7.0 Hz), 4.76 (2H, s), 7.27–7.31 (1H, m), 7.33 (1H, s), 7.40–7.44 (1H, m), 7.73–7.75 (1H, m), 7.82 (1H, s), 7.89–7.91 (1H, m); ^{13}C NMR: δ 23.1, 23.1, 33.0, 33.3, 115.0, 117.5, 121.0, 121.6, 124.3, 126.0, 135.4, 148.4, 152.1, 153.1, 163.2, 166.0, 178.7. Anal. Calcd for $C_{17}H_{15}N_3S_4$: C, 52.41; H, 3.88; N, 10.79%. Found: C, 52.44; H, 3.96; N, 10.33. FABMS *m/z*: 390 (M^++1).

To a solution of **21** (0.094 g, 0.24 mmol) in EtOH (2 ml) were added $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$ (0.03 g, 0.024 mmol) and 30% H_2O_2 (0.5 ml) at 0 °C, and the whole mixture was stirred for 60 min at room temperature. The reaction mixture

was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (15 g, *n*-hexane/AcOEt 3:1) to afford **3** (0.089 g, 88%). Recrystallization of **3** from *n*-hexane/AcOEt provided **3** as colorless needles. Compound **3**: mp 129–130 °C; IR (KBr): 1332, 1150 cm^{-1}; ^1H NMR: δ 1.38 (6H, d, J=6.8 Hz), 3.31 (1H, sept, J=6.8 Hz), 5.15 (2H, s), 7.19 (1H, s), 7.68 (1H, s), 7.67–7.71 (1H, m), 7.74–7.78 (1H, m), 8.21–8.23 (1H, m), 8.29–8.31 (1H, m); ^{13}C NMR (acetone-d_6): δ 23.1, 23.1, 33.8, 57.4, 115.7, 122.9, 123.8, 126.1, 128.7, 128.9, 138.2, 144.7, 148.9, 153.8, 163.6, 167.1, 179.4. Anal. Calcd for $C_{17}H_{15}N_3O_2S_4$: C, 48.43; H, 3.59; N, 9.97%. Found: C, 48.30; H, 3.61; N, 9.80. FABMS *m/z*: 422 (M^++1).

2.12. 2′-Isopropyl[2,4′]bithiazolyl-4-methylenethio-5-(1-phenyl-1*H*)-tetrazole (22) and 2′-isopropyl[2,4′]-bithiazolyl-4-methylenesulfonyl-5-(1-phenyl-1*H*)-tetrazole (4)

To a mixture of **20** (0.1 g, 0.42 mmol), triphenylphosphine (0.218 g, 0.83 mmol), and diethylazocarboxylate (0.27 g, 0.62 mmol) in THF (5 ml) was added 1-phenyl-1*H*-tetrazole-5-thiol (0.148 g, 0.83 mmol) under argon atmosphere and the whole mixture was stirred for 60 min at room temperature. The reaction mixture was diluted with 2 M aqueous NaOH and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt 6:1) to afford **22** (0.16 g, 96%). Recrystallization of **22** from *n*-hexane provided **22** as colorless needles. Compound **22**: mp 102–104 °C; IR (KBr): 3114, 2957, 1498, 1393 cm^{-1}; ^1H NMR: δ 1.43 (6H, d, J=6.8 Hz), 3.36 (1H, sept, J=6.8 Hz), 4.77 (2H, s), 7.43 (1H, s), 7.51–7.55 (5H, m), 7.79 (1H, s); ^{13}C NMR: δ 23.1, 23.1, 33.0, 33.3, 115.1, 118.4, 123.9, 123.9, 129.8, 129.8, 130.1, 133.6, 148.3, 150.9, 153.8, 163.5, 178.8. Anal. Calcd for $C_{17}H_{16}N_6S_3$: C, 50.98; H, 4.03; N, 20.98%. Found: C, 51.00; H, 4.00; N, 20.89. FABMS *m/z*: 401 (M^++1).

To a solution of **22** (0.34 g, 0.85 mmol) in EtOH (1 ml) were added $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ (0.105 g, 0.085 mmol) and 30% H_2O_2 (1 ml) at 0 °C, and the whole mixture was stirred for 60 min at room temperature. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt 8:1) to afford **4** (0.333 g, 91%). Recrystallization of **4** from *n*-hexane/AcOEt provided **4** as colorless needles. Compound **4**: mp 121–122 °C; IR (KBr): 1338, 1160 cm^{-1}; ^1H NMR: δ 1.43 (6H, d, J=6.8 Hz), 3.35 (1H, sept, J=6.8 Hz), 5.02 (2H, s), 7.44 (1H, s), 7.50–7.60 (5H, m), 7.66 (1H, s); ^{13}C NMR: δ 23.1, 23.1, 33.3, 58.1, 115.7, 122.4, 125.6, 125.6, 129.5, 129.5, 131.5, 132.9, 141.3, 147.7, 153.2, 164.2, 179.1. Anal. Calcd for $C_{17}H_{16}N_6O_2S_3$: C, 47.21; H, 3.73; N, 19.43%. Found: C, 47.24; H, 3.77; N, 19.17. FABMS *m/z*: 433 (M^++1).

2.13. Modified Julia's coupling of (+)-2 and 3 (synthesis of cystothiazole A (*E*)-1)

To a solution of **3** (0.17 g, 0.40 mmol) in THF (3 ml) was added lithium bis(trimethylsilyl)amide (1 M solution in THF, 0.4 ml, 0.4 mmol) at 0 °C under argon atmosphere and the whole mixture was stirred for 20 min at the same temperature. A solution of (+)-**2** (0.073 g, 0.34 mmol) in THF (2 ml) was added to the above reaction mixture at 0 °C and the whole mixture was stirred for 20 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product, which was chromatographed on silica gel (12 g, *n*-hexane/AcOEt 20:1) to give a 14:1 mixture (0.091 g, 64%) of (*E*)-**1** and (*Z*)-cystothiazole **23**. A part of this mixture was again subjected to chromatography on silica gel (5 g, *n*-hexane/AcOEt 20:1) to afford (*E*)-**1** (0.005 g). ^1H and ^{13}C NMR data of the present (*E*)-**1** were identical with those of the reported data.[2,5]

2.14. Modified Julia's coupling of (+)-2 and 4 (synthesis of cystothiazole A (*E*)-1)

To a solution of **4** (0.216 g, 0.50 mmol) in THF (5 ml) was added lithium bis(trimethylsilyl)amide (1 M solution in THF, 0.5 ml, 0.5 mmol) at 0 °C under argon atmosphere and the whole mixture was stirred for 20 min at the same temperature. A solution of (+)-**2** (0.09 g, 0.42 mmol) in THF (2 ml) was added to the above reaction mixture at 0 °C and the whole mixture was stirred for 20 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product, which was chromatographed on silica gel (15 g, *n*-hexane/AcOEt 20:1) to give a 4:1 mixture (0.116 g, 66%) of (*E*)-**1** and (*Z*)-cystothiazole **23**.

References and notes

1. (a) Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W. *J. Antibiot.* **1980**, *33*, 1474–1479; (b) Trowitzsch, W.; Reifenstahl, G.; Wray, V.; Gerth, K. *J. Antibiot.* **1980**, *33*, 1480–1490; (c) Trowitzsch, W.; Höfle, G.; Sheldrick, W. S. *Tetrahedron Lett.* **1981**, *22*, 3829–3832.
2. Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998**, *51*, 275–281.
3. Thierbach, G.; Reichenbach, H. *Biochim. Biophys. Acta* **1981**, *638*, 282–289.
4. Ojika, M.; Watanabe, T.; Qi, J.; Tanino, T.; Sakagami, Y. *Tetrahedron* **2004**, *60*, 187–194.
5. Williams, D. R.; Patnaik, S.; Clark, M. C. *J. Org. Chem.* **2001**, *66*, 8463–8469.
6. (a) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 643–645; (b) Kato, K.; Sasaki, T.; Takayama, H.; Akita, H. *Tetrahedron* **2003**, *59*, 2679–2685; (c) Sasaki, T.; Kato, K.; Akita, H. *Chem. Pharm. Bull.* **2004**, *52*, 770–771.
7. Bach, T.; Heuser, S. *Chem.—Eur. J.* **2002**, *8*, 5585–5592.
8. DeRoy, P. L.; Charette, A. B. *Org. Lett.* **2003**, *5*, 4163–4165.
9. Shao, J.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3083–3085.
10. Bach, T.; Heuser, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3184–3185.
11. Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

12. (a) Akita, H.; Kawaguchi, T.; Enoki, Y.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 323–328; (b) Akita, H.; Todoroki, R.; Endo, H.; Ikari, Y.; Oishi, T. *Synthesis* **1993**, 513–516; (c) Kato, K.; Ono, M.; Akita, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2295–2298. Now, *n*-butyl (2*R*,3*S*)-epoxy butyrate corresponding to (2*R*,3*S*)-**5** is commercially available from Osaka Yuki Kagaku Kogyo Co., Ltd (Japan). Japan Kokai Tokkyo Koho JP 3095539.
13. Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849–850.
14. Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244.
15. Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203–4205.
16. Rhoads, S. J.; Chattopadhyay, J. K.; Waali, E. E. *J. Org. Chem.* **1970**, *35*, 3352–3358.

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A novel *tert*-butoxycarbonylation reagent: 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI)

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Abstract—The use of 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as a *tert*-butoxycarbonylation reagent for acidic proton-containing substrates such as phenols, aromatic and aliphatic amines hydrochlorides, and aromatic carboxylic acids in the absence of a base is described. The reactions proceed chemoselectively in high yield under mild conditions.

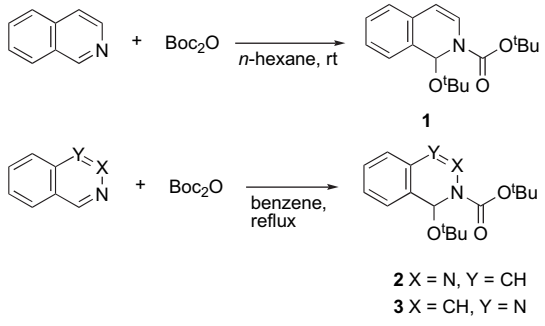
1. Introduction

The development of mild and selective methods for the protection and deprotection of functional groups continues to be an important tool in the synthetic chemistry of functional molecules.[1] Among the various protection groups available, the *tert*-butoxycarbonyl (Boc) group is resistant to nucleophilic reagents, because of the electron donating and sterically bulky *tert*-butyl group.[1] It is noteworthy that the Boc group for protecting amino functionalities is most frequently used in organic synthesis due to its chemical stability to nucleophiles and strong basic conditions and its ease of removal under specific conditions.[2] In addition, the Boc group can also act as a useful protecting group for alcohols and phenols, since it is more stable than the corresponding ester under basic conditions.[3] Various reagents and methods for introducing this group using Boc_2O have been developed. Most reactions are carried out in the presence of a base such as DMAP[4] or organic/inorganic bases.[3a,5] In addition, the *tert*-butoxycarbonylation of acidic substrates such as phenol and thiophenol also require a base.[6] On the other hand, the use of a Lewis acid catalyst to perform this protection has not been extensively studied.[7] In these contexts, we discovered that the Reissert like reaction of Boc_2O with isoquinoline afforded 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) **1**, which appears to be a promising *tert*-butoxycarbonylating agent.[8] Our efforts toward the use of BBDI **1** as a de novo *tert*-butoxycarbonylation reagent for acidic proton-containing substrates such as amine hydrochlorides, phenols, and carboxylic acids have been described in detail.[9]

2. Results and discussion

2.1. The reaction of Boc_2O with nitrogen-containing aromatic compounds

We, first, found that the exposure of isoquinoline to Boc_2O in *n*-hexane at room temperature resulted in the loss of carbon dioxide to give **1** in 86% yield, which is stable and can be stored at room temperature for periods of over 1 year without any decomposition. Similarly, when a solution of phthalazine and quinazoline is refluxed with Boc_2O in benzene, the adducts **2** and **3** are produced, in 86% and 68% yields, respectively (Scheme 1). Surprisingly, the addition of Boc_2O to pyridine, pyrimidine, quinoline, and quinoxaline gave no adducts, resulting in the recovery of starting materials. Only heterocycles bearing a nitrogen at the β-position in the naphthalene ring such as isoquinoline, phthalazine, and quinazoline were amenable to reaction with Boc_2O to give the corresponding adducts **1**–**3**, although the reasons for this remain unclear.



Scheme 1. Synthesis of **1**–**3**.

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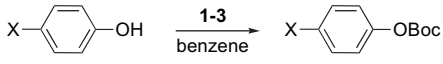
2.2. *tert*-Butoxycarbonylation of phenols with BBDI

A variety of natural polyphenols that have attracted the interest of scientists and synthetic research into this class of compounds has been vigorously carried out in recent years.[10] The phenolic hydroxyl group(s) on those compounds often play an important role in their biological activities.[11] The protection of the hydroxyl group(s) is necessary in order to maintain these activities and to avoid expected side reactions. A variety of protecting groups for phenols have been developed and have been utilized in synthetic studies.[1] Recent studies have highlighted the utility of the *tert*-butoxycarbonyl (Boc) group for phenols.[4] Based on these properties, we embarked on an investigation of the *tert*-butoxycarbonylation of phenol (**4a**) using **1**. A solution of **4a** and **1** in benzene was heated under reflux for 1 h to give phenyl *tert*-butyl carbonate (**5a**) in quantitative yield. The *tert*-butoxycarbonylation of **4a** using **2** and **3**, however, resulted in low yields (Table 1, entries 2 and 3). The reaction of *p*-methoxy- and *p*-nitorophenol (**4b** and **4c**), respectively, with **1** afforded the corresponding carbonates **5b** and **5c** in high yields, respectively (Table 1, entries 4 and 5). In the case of **4c**, however, the reaction proceeded easily at room temperature. Unfortunately, the exposure of **2** and **3** to **4c** also resulted in low yields (Table 1, entries 6 and 7). It is noteworthy that the *tert*-butoxycarbonylation of *p*-hydroxymethylphenol (**4d**) took place chemoselectively to give **5d** without any substitution of the hydroxymethyl group. Surprisingly, although the *tert*-butoxycarbonylation of phenols in alkaline media has been reported,[4,6] this is the first example of such a reaction in the absence of base.

2.3. *tert*-Butoxycarbonylation of amine hydrochlorides with BBDI

The Boc group is extensively used for amino protection because of its chemical inertness to nucleophilic reagents including base and deprotection using acid reagents.[12] The *tert*-butoxycarbonylation of aniline with **1** was examined first. However, no reaction occurred and **1** was recovered. As described above, it was found that the *tert*-butoxycarbonylation at **4c** (pK_a=10.8)[13] proceeds under more mild conditions compared with those of **4a** (pK_a=18.0).[13] With these results in hand, we concluded that reactivity is proportional to the acidity of the substrates. Because the conjugate acid **6a** (pK_a=3.6)[13] of aniline (pK_a=30.6)[13] is stronger acid than **4a**, we tried the *tert*-butoxycarbonylation of aniline hydrochloride (**6a**). Treatment of **6a** with **1** in benzene at room temperature afforded *N*-Boc aniline **7a**, as expected, in 81% yield (Table 2, entry 1). The use of dimethoxyethane (DME) instead of benzene as solvent dramatically increased the yield of **7a** (entry 2). A similar treatment of *p*-methoxyaniline hydrochloride (**6b**) with **1** afforded *N*-Boc aniline **7b** in high yield (entry 3). On the other hand, the reaction of *p*-nitroaniline hydrochloride (**6c**) with **1** resulted in low yields. Although this reason remains unclear, a decomposition of **1** may occur due to a stronger acidity of **6c** compared with that (pK_a=3.6)[13] of **6a**. Actually, an evolution of gas presumed to be isobutylene was observed in a reaction flask. A high degree of chemoselectivity was also demonstrated by using **6d** of the coexistence of an aliphatic hydroxyl group, as shown in entry 4.

Table 1. *tert*-Butoxycarbonylation of **4a–d** with **1–3**



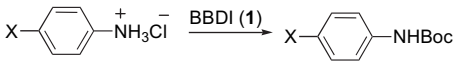
4a-d
a, X = H
b, X = OMe
c, X = NO_2
d, X = CH_2OH

5a-d
a, X = H
b, X = OMe
c, X = NO_2
d, X = CH_2OH

Entry	Reagent	Substrate (X)	Temp	Time (h)	Prod.	Yield (%)[a]
1	**1**	**4a** (H)	Reflux	1	**5a**	99
2	**2**	**4a** (H)	Reflux	2	**5a**	21
3	**3**	**4a** (H)	Reflux	5	**5a**	2
4	**1**	**4b** (OMe)	Reflux	1	**5b**	92
5	**1**	**4c** (NO_2)	rt	3	**5c**	96
6	**2**	**4c** (NO_2)	rt	3	**5c**	21
7	**3**	**4c** (NO_2)	rt	3	**5c**	17
8	**1**	**4d** (CH_2OH)	Reflux	3	**5d**	91

[a] Isolated yields.

Table 2. *tert*-Butoxycarbonylation of **6** with **1**



6a-e
a, X = H
b, X = OMe
c, X = NO_2
d, X = CN
e, X = CH_2CH_2OH

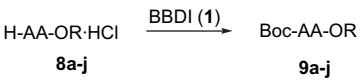
7a-e
a, X = H
b, X = OMe
c, X = NO_2
d, X = CN
e, X = CH_2CH_2OH

Entry	Substrate (X)	Temp	Solvent	Prod.	Yield (%)[a]
1	**6a** (H)	rt	Benzene	**7a**	81
2	**6a** (H)	rt	DME	**7a**	97
3	**6b** (OMe)	rt	DME	**7b**	98
4	**6c** (NO_2)	rt	DME	**7c**	19
5	**6c** (NO_2)	−10 °C	DME	**7c**	38
6	**6d** (CN)	rt	DME	**7d**	75
7	**6e** (CH_2CH_2OH)	rt	DME	**7e**	97

[a] Isolated yields.

The *tert*-butoxycarbonylation of α-amino acids ester hydrochlorides (pK_a=7.6–8.7)[14] as the weaker conjugate acid was next examined. Screening experiments were conducted with L-Met–OMe·HCl **8a** as a model compound using **1** in DME. The use of 3 equiv of **1** gave the best yield (93%, Table 3, entry 1), whereas the use of 2 and 1.2 equiv of **1** resulted in 82% and 33% yields, respectively. The use of diethyl ether (reflux) and chloroform as solvents provided similar results (95% and 92%), respectively, whereas dioxane resulted in a low yield (53%). Moreover, the decrease of the amounts of **1** was examined. Consequently, the treatment of **8a** with **1** (2 equiv) in acetonitrile at 0 °C provided **9a** in 97% yield (entry 3). On the basis of these results, the standard condition for the *tert*-butoxycarbonylation of several α-amino acid ester hydrochlorides **8** with **1** (3 equiv) was in DME at room temperature (A) or in diethyl ether under reflux (B). Thirdly, the use of 2 equiv of **1** in acetonitrile at 0 °C was carried out (C). Thus the *tert*-butoxycarbonylation of various α-amino acids occurs, and the corresponding *N*-Boc L-amino acid esters were obtained in high yields as shown in Table 3. The identification of *N*-Boc L-amino acid esters was confirmed by comparison of ^{1}H NMR and IR data and $[\alpha]_D$

Table 3. *tert*-Butoxycarbonylation of **8** with **1**



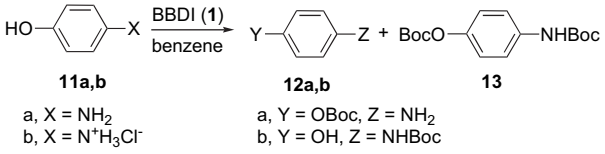
Entry	H–AA–OR·HCl **8**	Method[a]	Boc–AA–OR **9**	Yield (%)[b]
1	Met–OMe·HCl **8a**	A	Boc–Met–OMe **9a**[15]	93
2	Met–OMe·HCl **8a**	B	Boc–Met–OMe **9a**[15]	95
3	Met–OMe·HCl **8a**	C	Boc–Met–OMe **9a**[15]	97
4	Ala–OEt·HCl **8b**	B	Boc–Ala–OEt **9b**[16]	87
5	Leu–OEt·HCl **8c**	B	Boc–Leu–OEt **9c**[16]	91
6	Leu–OEt·HCl **8c**	C	Boc–Leu–OEt **9c**[16]	90
7	Val–OMe·HCl **8d**	A	Boc–Val–OMe **9d**[15]	86
8	Phe–OMe·HCl **8e**	A	Boc–Phe–OMe **9e**[17]	97
9	Pro–OMe·HCl **8f**	A	Boc–Pro–OMe **9f**[18]	98
10	Pro–OMe·HCl **8f**	C	Boc–Pro–OMe **9f**[18]	92
11	Glu(OEt)–OEt·HCl **8g**	B	Boc–Glu(OEt)–OEt **9g**[19]	98
12	Ser–OMe·HCl **8h**	A	Boc–Ser–OMe **9h**[20]	92
13	Cys–OMe·HCl **8i**	A	Boc–Cys–OMe **9i**[21]	87
14	Tyr–OMe·HCl **8j**	A	Boc–Tyr–OMe **9j**[22]	76[c]

[a] Method A: in 1,2-dimethoxyethane at room temperature overnight with 3 equiv of BBDI. Method B: in diethyl ether under reflux overnight with 3 equiv of BBDI. Method C: in acetonitrile at 0 °C for 2 days with 2 equiv of BBDI.
[b] Isolated yield.
[c] A small amount of Boc–Tyr(Boc)–OMe (**10**) was also obtained.

values with the reported data.[15–22] In general, α-amino acid esters are commercially available in the form of hydrochloride salts. Therefore, this procedure without any additive such as a base is a convenient procedure for *N*-*tert*-butoxycarbonylation.

2.4. The chemoselectivity of *tert*-butoxycarbonylation

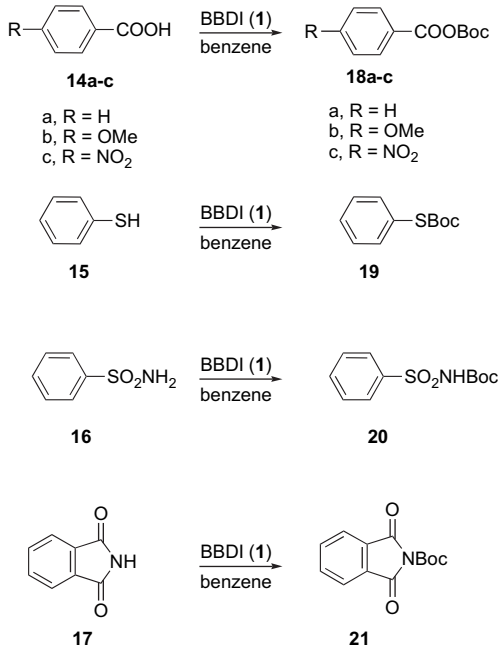
As an application, the chemoselectivity of *tert*-butoxycarbonylation for amino and hydroxyl groups on a benzene ring was investigated using 4-aminophenol (**11a**) and 4-aminophenol hydrochloride (**11b**). When **11a** was reacted with 2 equiv of **1** in benzene under reflux, the *O*-Boc derivative **12a** was obtained in 94% yield together with small amounts of *N*,*O*-(Boc)$_2$ derivative **13**. In contrast, when **11b** was subjected to a reaction with 2 equiv of **1**, the *N*-Boc derivative **12b** was isolated in 93% yield together with small amounts of **13** (Scheme 2). It was found that a higher acidity-containing functional group is preferentially *tert*-butoxycarbonylated.



Scheme 2.

2.5. *tert*-Butoxycarbonylation of various acidic substrates

Further, the *tert*-butoxycarbonylation of several acidic substrates, such as benzoic acid derivatives **14a** (pK_a=11.0),[13] **14b**, **14c**, benzenethiol (**15**) (pK_a=10.2),[13] benzenesulfonamide (**16**) (pK_a=16.1),[13] and phthalimide (**17**) (pK_a=14.6)[23] with **1** without any base was examined. The reaction of **1** (1.2 equiv) with the above substrates in benzene gave the corresponding Boc-derivatives, as shown in Scheme 3 and Table 4. In particular, the *tert*-butoxycarbonylation of **14** was performed under mild conditions for a short time (Table 1, entries 1–3). The Boc-products **18** were somewhat unstable. Therefore, the yield of **18c** was low presumably due to the decomposition of **18c** during silica gel chromatography.



Scheme 3. *tert*-Butoxycarbonylation of various acidic substrates with BBDI.

Although we attempted the *tert*-butoxycarbonylation of *N*-protected amino acids **22**, Boc-compounds **23** were not isolated because of their labilities. However, the Boc anhydrides **23** were regarded to be a promising active intermediate for esterification. In practice, a simple and mild esterification of *N*-protected amino acids via Boc-anhydride **23** using BBDI as a novel condensing reagent in a one-pot method was developed (Table 5).[24] This protocol has several advantages including the use of nearly equimolar amounts of alcohols, no requirement for additives, and no racemization occurs.

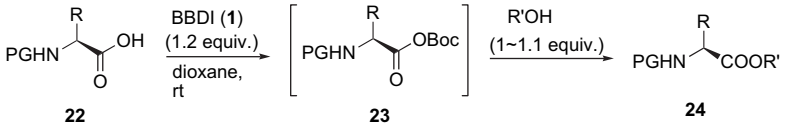
On the other hand, neutral substrates such as alcohols, thiol, and pyrrolidone, when subjected to *tert*-butoxycarbonylation with **1**, gave no Boc-products. Treatment of 1 equiv of methanol (pK_a=29.0)[13] with **1** in benzene under reflux

Table 4. *tert*-Butoxycarbonylation of various acidic substrates with **1**

Entry	Substrate	Condition	Prod.	Yield (%)[a]
1	**14a**	rt/10 min	**18a**	86
2	**14b**	rt/10 min	**18b**	87
3	**14c**	rt/3 min	**18c**	58
4	**15**	Reflux/5 h	**19**	89
5	**16**	Reflux/3 days	**20**	65
6	**17**	Reflux/overnight	**21**	49

[a] Isolated yield.

Table 5. Esterification of *N*-protected amino acids **22** with **1**

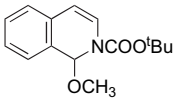


22 **23** **24**

Entry	Substrate	PG	R	R′	Prod.	Yield (%)[a]
1	**22a**	Cbz	Me	Me	**24a**	86
2	**22b**	Cbz	Me	Et	**24b**	95
3	**22c**	Cbz	Ph	Allyl	**24c**	91
4	**22d**	Cbz	$MeSCH_2CH_2$	$PhCH_2$	**24d**	91
5	**22e**	Boc	Me	*p*-MeOPh	**24e**	95
6	**22f**	Fmoc	Ph	Allyl	**24f**	90

[a] Isolated yield.

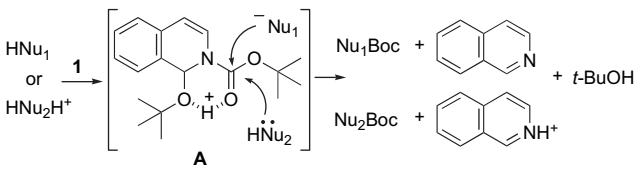
gave a 5/2 mixture of **25** and **1**. The use of a large excess of methanol (15 equiv) in benzene at room temperature provided **25** in 92% yield. Unfortunately, the reactions of propanethiol (pK_a=17.0)[13] and pyrrolidone (pK_a=24.2)[13] gave complex mixtures, which were not identified. Thus, no *tert*-butoxycarbonylation was observed for non-acidic proton-containing substrates.



25

2.6. A mechanism of *tert*-butoxycarbonylation with BBDI

On the basis of these results, a proposed mechanism for this reaction is as follows: Presumably **1** would be first protonated to form a cyclic six-membered intermediate **A**. A subsequent attack of its resulting conjugated base (Nu anion or HNu_2) to the activated carbonyl of **A** followed by cleavage could produce the *tert*-butoxycarbonylation product, isoquinoline or its salt, and *tert*-butyl alcohol. Namely, **1** would act as a weak Lewis base (pseudo base) (Scheme 4).[25] Accordingly, this *tert*-butoxycarbonylation would depend on the strength of the acidity. For the reason that protons of neutral substrates such as alcohols, thiol, and pyrrolidone cannot be captured by **1**, their *tert*-butoxycarbonylation would not take place. It would be difficult to form an **A**-like intermediate in *tert*-butoxycarbonylation using reagents **2** and **3** due to protonation of the more basic nitrogen atoms of **2** and **3**.



Scheme 4. A plausible mechanism of *tert*-butoxycarbonylation with BBDI.

3. Conclusion

In summary, a novel and chemoselective *tert*-butoxycarbonylation reagent, BBDI **1** is reported. This reagent is easily prepared in quantitative yield by the reaction of isoquinoline with Boc_2O. In general, the *tert*-butoxycarbonylation of acidic compounds such as phenols and carboxylic acids using Boc_2O require a base. Interestingly, BBDI easily caused the *tert*-butoxycarbonylation of acidic substrates in the absence of bases. The strength of the acidity of substrates appears to influence the reaction rate, in fact, a higher acidic substrate hastened the reaction compared to a low acidic one. Furthermore, *tert*-butoxycarbonylation of *N*-protected amino acids with BBDI is applicable to their simple and mild esterification using nearly equimolar amounts of alcohols in a one-pot procedure.

4. Experimental

4.1. General information

Melting points were determined on a Mel-Temp melting point apparatus using an open-capillary tube. All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin–Elmer CHN 2400 Elemental Analyzer. Optical rotations were measured with a JASCO DIP-360 or JASCO P-1020 digital polarimeter. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-EX 270 (270 MHz) or JEOL JNM-AL 400 (400 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Column chromatography was carried out on Merck Silica gel 60 (230–400 mesh) or KANTO Silica Gel 60N (40–50 μm) for flash chromatography.

4.1.1. 1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (1). A mixture of isoquinoline (3.87 g, 30 mmol) and di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) in hexane (30 mL) was stirred at room temperature for 8 h. After concentration in vacuo, the residue was purified by recrystallization from Et_2O–hexane to give **1** (7.87 g, 86%) as colorless prisms. Mp 114–115 °C (Et_2O–hexane). IR (neat) cm^{-1}: 1712. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.52 (s, 9H), 6.10 (d, J=7.5 Hz, 1H), 6.66 (s, 1H), 6.88 (d, J=7.3 Hz, 1H), 7.17–7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 28.7, 74.3, 75.3, 81.8, 109.3, 124.1, 125.0, 126.4, 126.8, 128.0, 130.0, 131.3, 152.1. MS

(EI) *m/z* 303 (M^+). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.38; H, 8.02; N, 4.54.

4.1.2. 1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydrophthalazine (2). A mixture of phthalazine (3.90 g, 30 mmol) and di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) in benzene (30 mL) was heated under reflux for 6 h. After concentration in vacuo, the residue was purified by recrystallization from hexane or distilled under reduced pressure to give **3** (7.8 g, 86%) as colorless needles. Bp 146–149 °C (1 mmHg), mp 117–118 °C (hexane). IR (neat) cm^{-1}: 1695. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.60 (s, 9H), 6.82 (br s, 1H), 7.28–7.32, (m, 1H), 7.39–7.47 (m, 2H), 7.46–7.54 (m, 1H), 7.99 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.7, 72.2, 74.8, 82.6, 124.0, 125.6, 125.7, 128.6, 131.3, 131.5, 132.4, 143.9. MS (EI) *m/z* 304 (M^+). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 68.08; H, 7.95; N, 9.20. Found: C, 67.79; H, 7.97; N, 9.30.

4.1.3. 3-*tert*-Butoxy-4-*tert*-butoxycarbonyl-3,4-dihydroquinazoline (3). A mixture of quinazoline (3.90 g, 30 mmol) and di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) in benzene (30 mL) was heated under reflux for 30 h. After concentration in vacuo, the residue was purified by recrystallization from hexane to give **3** (5.9 g, 65%) as colorless prisms. Mp 134–135 °C (hexane). IR (neat) cm^{-1}: 1716. ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.57, (s, 9H), 6.49 (br s, 1H), 7.20–7.30, (m, 2H), 7.36–7.47 (m, 2H), 8.12 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 28.2, 73.1, 74.9, 83.8, 126.0, 126.1, 126.2, 126.8, 129.0, 140.0, 141.5, 151.1. MS (EI) *m/z* 304 (M^+). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 68.08; H, 7.95; N, 9.20. Found: C, 68.08; H, 8.04; N, 9.26.

4.2. General procedure for *tert*-butoxycarbonylation of phenols 4 by BBDI 1 (Table 1)

A mixture of **1** (1.52 g, 5 mmol) and phenol **4a** (5 mmol) in benzene (10 mL) was heated under reflux or stirred at room temperature for reaction times as indicated in Table 1. The reaction mixture was washed with 5% HCl solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **5a–d** in yields as shown in Table 1.

4.2.1. *tert*-Butyl phenyl carbonate (5a). A colorless liquid. Bp 88–90 °C (1 mmHg) [lit.[26] bp 74–78 °C (0.5 mmHg)]. IR (neat) cm^{-1}: 1758. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 6.97–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 83.5, 121.3, 125.7, 129.4, 151.1, 151.9. MS (EI) *m/z* 194 (M^+).

4.2.2. *tert*-Butyl 4-methoxyphenyl carbonate (5b). A colorless plates. Mp 66–67 °C (hexane). IR (KBr) cm^{-1}: 1752. ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 9H), 3.79 (s, 3H), 6.86–6.89 (d, *J*=9.2 Hz, 2H), 7.07–7.09 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 55.6, 83.3, 114.3, 122.1, 144.7, 152.3, 157.2. MS (EI) *m/z* 224 (M^+). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.24.

4.2.3. *tert*-Butyl 4-nitrophenyl carbonate (5c). A white powder. Mp 78–79 °C (hexane) [lit.[27] mp 78.5–79.5 °C]. IR (KBr) cm^{-1}: 1346, 1757. ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 7.37 (d, *J*=9.2 Hz, 2H), 8.27 (d, *J*=9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 84.8, 121.9, 125.2, 145.1, 150.5, 155.7. MS (EI) *m/z* 240 (M^++1).

4.2.4. *tert*-Butyl 4-(hydroxymethyl)phenyl carbonate (5d).[28] A white powder. Mp 39–40 °C (pentane). IR (KBr) cm^{-1}: 1762, 3270. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 2.01 (br s, 1H), 4.64 (s, 2H), 7.14 (d, *J*=8.7 Hz, 2H), 7.35 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 64.0, 83.6, 121.3, 128.0, 138.4, 150.4, 151.9. MS (EI) *m/z* 224 (M^+).

4.3. General procedure for the *tert*-butoxycarbonylation of aniline hydrochlorides 6 by 1 (Table 2)

A solution of **1** (6 mmol) in DME (10 mL) was added to a stirred suspension of aniline hydrochloride **6** (5 mmol) in DME (10 mL), with stirring at room temperature for 16 h. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5% HCl solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **7** in yields as shown in Table 2.

4.3.1. *tert*-Butyl *N*-phenylcarbamate (7a). A colorless needles. Mp 137–138 °C (Et_2O–hexane) [lit.[29] mp 135–136 °C]. IR (KBr) cm^{-1}: 1687, 3313. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 6.49 (br s, 1H), 6.99–7.06 (m, 1H), 7.25–7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 80.5, 118.5, 123.0, 128.9, 138.3, 152.7. MS (EI) *m/z* 193 (M^+).

4.3.2. *tert*-Butyl *N*-(4-methoxyphenyl)carbamate (7b). A colorless needles. Mp 96–97 °C (hexane) [lit.[30] 91.5–92.5 °C]. IR (KBr) cm^{-1}: 1695, 3366. ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.78 (s, 3H), 6.36 (br s, 1H), 6.83 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 55.5, 80.2, 114.2, 120.6, 131.4, 153.2, 155.7. MS (EI) *m/z* 223 (M^+).

4.3.3. *tert*-Butyl *N*-(4-nitrophenyl)carbamate (7c). A yellow needless. Mp 111–112 °C. [lit.[31] 108–109 °C]. IR (KBr) cm^{-1}: 1543, 1600, 1735, 1746, 3397. ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 6.90 (br s, 1H), 7.53 (d, *J*=9.2 Hz, 2H), 8.18 (d, *J*=9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.9, 117.5, 125.2, 142.7, 144.5, 151.8. MS (EI) *m/z* 238 (M^+). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.49; H, 5.92; N, 11.75.

4.3.4. *tert*-Butyl *N*-(4-cyanophenyl)carbamate (7d). A colorless needles. Mp 118–119 °C [lit.[32] 113–114 °C]. IR (KBr) cm^{-1}: 1500, 1522, 1694, 2227, 2996, 3370. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 6.86 (br s, 1H), 7.49 (d, *J*=8.7 Hz, 2H), 7.57 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.6, 105.6, 118.0, 119.0, 133.2, 142.6, 152.0.

4.3.5. *tert*-Butyl *N*-[4-(2-hydroxyethyl)phenyl]carbamate (7e). A white powder. Mp 109–110 °C (hexane). IR (KBr) cm^{-1}: 1699, 3364, 3413. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J*=5.6 Hz, 1H), 1.51 (s, 9H), 2.82 (t, *J*=6.5 Hz,

2H), 3.82 (q, J=6.3 Hz, 2H), 6.45 (br s, 1H), 7.14 (d, J=8.7 Hz, 2H), 7.30 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 38.4, 63.7, 80.5, 118.9, 130.0, 133.1, 136.8, 152.9. MS (EI) m/z 237 (M^+). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.01; H, 8.03; N, 5.88.

4.4. General procedure for the *N*-*tert*-butoxycarbonylation of amino acid esters 8 by 1

Method A: A solution of **1** (15 mmol) in DME (20 mL) was added to a stirred suspension of amino acid ester hydrochloride **8** (5 mmol) in DME (10 mL), with stirring at room temperature for overnight. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5% HCl solution (10 mL×2) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **9**. Method B: A stirred mixture of **1** (15 mmol) and amino acid alkyl ester hydrochloride (5 mmol) in Et_2O (30 mL) was refluxed for overnight. The reaction mixture was washed with 5% HCl solution (10 mL×2) and brine (10 mL), dried over $MgSO_4$ and then evaporated. The residue was purified by flash column chromatography on silica gel to give **9**. Method C: A stirred mixture of **1** (10 mmol) and amino acid alkyl ester hydrochloride (5 mmol) in acetonitrile (30 mL) was stirred for 48 h. The reaction mixture was washed with 5% HCl solution (10 mL×2) and brine (10 mL), dried over $MgSO_4$ and then evaporated. The residue was purified by flash column chromatography on silica gel to give **9**. Yields are shown in Table 3.

4.4.1. Boc–Met–OMe (9a). A colorless liquid. $[\alpha]_D^{26}$ −34.0 (c 2.6, MeOH) [lit.[15] $[\alpha]_D^{amb}$ −34.0 (c 1.0, MeOH)]. IR (neat) cm^{-1}: 1715, 1745, 3359. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.84–1.99 (m, 1H), 2.08–2.18 (m, 1H), 2.10 (s, 3H), 2.54 (t, J=7.6 Hz, 2H), 3.76 (s, 3H), 4.34–4.46 (br, 1H), 5.08–5.20 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 28.3, 30.0, 32.2, 52.4, 52.7, 80.0, 155.3, 172.8. MS (EI) m/z 263 (M^+).

4.4.2. Boc–Ala–OEt (9b). A colorless liquid. $[\alpha]_D^{26}$ −39.8 (c 2.5, MeOH) [lit.[16] $[\alpha]_D$ −42.5 (c 1.0, MeOH)]. IR (neat) cm^{-1}: 1715, 1738, 3367. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J=7.0 Hz, 3H), 1.38 (d, J=7.2 Hz, 3H), 1.45 (s, 9H), 4.20 (q, J=7.1 Hz, 2H), 4.23–4.36 (m, 1H), 5.10 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.6, 28.3, 31.1, 49.2, 61.2, 79.7, 155.1, 173.3. MS (EI) m/z 217 (M^+).

4.4.3. Boc–Leu–OEt (9c). A colorless liquid. $[\alpha]_D^{25}$ −34.6 (c 2.3, MeOH) [lit.[17] $[\alpha]_D$ −37.0 (c 1.0, MeOH)]. IR (neat) cm^{-1}: 1716, 1740, 3365. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (dd, J=6.5, 3.1 Hz, 6H), 1.28 (t, J=7.1 Hz, 3H), 1.44 (s, 9H), 1.48–1.78 (m, 3H), 4.18 0 (q, J=7.2 Hz, 2H), 4.24–4.33 (m, 1H), 4.90 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.9, 22.8, 24.8, 28.3, 41.9, 52.1, 61.1, 79.7, 155.4, 173.5. MS (EI) m/z 260 (M^++1).

4.4.4. Boc–Val–OMe (9d). A colorless liquid. $[\alpha]_D^{25}$ −21.9 (c 2.2, MeOH) [lit.[15] $[\alpha]_D^{amb}$ −22.7 (c 2.0, MeOH)]. IR (neat) cm^{-1}: 1715, 1746, 3369. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (dd, J=25.8, 7.0 Hz, 6H), 1.45 (s, 9H), 2.06–2.16 (m, 1H), 3.74 (s, 3H), 4.22 (dd, J=9.2, 4.8 Hz, 1H), 5.03 (br d, J=8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 18.9, 28.3, 31.3, 52.0, 58.5, 79.8, 155.7, 172.9. MS (EI) m/z 231 (M^+).

4.4.5. Boc–Phe–OMe (9e). A colorless liquid. $[\alpha]_D^{25}$ −6.0 (c 2.5, MeOH) [lit.[17] $[\alpha]_D^{20}$ −3.0 (c 2.0, MeOH)]. IR (neat) cm^{-1}: 1716, 1746, 3368. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.97–3.16 (m, 2H), 3.70 (s, 3H), 4.52–4.65 (m, 1H), 5.03 (br d, J=7.6 Hz, 1H), 7.11–7.24 (m, 2H), 7.27–7.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 38.3, 52.2, 54.4, 79.9, 127.0, 128.5, 129.3, 136.0, 155.1, 172.3. MS (EI) m/z 279 (M^+).

4.4.6. Boc–Pro–OMe (9f). A colorless liquid. $[\alpha]_D^{27}$ −54.5 (c 1.1, CH_2Cl_2) [lit.[18] $[\alpha]_D^{25}$ −52.47 (c 0.99, CH_2Cl_2)]. IR (neat) cm^{-1}: 1702, 1752. ^{1}H NMR (400 MHz, $CDCl_3$, major/minor) δ 1.41/1.47 (2×s, 9H), 1.85–2.03 (m, 3H), 2.14–2.30 (m, 1H), 3.36–3.60 (m, 2H), 3.72 (s, 3H), 4.22/4.33 (dd, J=8.5, 4.1 Hz, 0.6H/J=8.7, 3.4 Hz, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$, major/minor) δ 23.6/24.2, 28.2/28.3, 30.8/29.8, 46.2/46.5, 51.8/52.0, 59.0/58.6, 79.7, 153.7/154.3, 173.7/173.4. MS (EI) m/z 229 (M^+).

4.4.7. Boc–Glu(OEt)–OEt (9g). A colorless needles. Mp 46–47 °C (pentane). $[\alpha]_D^{27}$ −18.2 (c 1.3, Acetone) [lit.[19] mp 46–47 °C, $[\alpha]_D$ −16.4 (c 1.0, Acetone)]. IR (KBr) cm^{-1}: 1682, 1694, 1732, 3352. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.44 (s, 9H), 1.88–2.01 (m, 1H), 2.12–2.24 (m, 1H), 2.30–2.44 (m, 2H), 4.14 (q, J=7.1 Hz, 2H), 4.20 (q, J=7.1 Hz, 2H), 4.23–4.37 (m, 1H), 5.12 (br d, J=7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.1, 27.7, 28.2, 30.3, 52.9, 60.6, 61.4, 79.9, 155.5, 172.2, 172.7. MS (EI) m/z 304 (M^++1).

4.4.8. Boc–Ser–OMe (9h). A colorless liquid. $[\alpha]_D^{26}$ +9.1 (c 1.3, $CHCl_3$) [lit.[20] $[\alpha]_D^{20}$ +9.0 (c 1.0, $CHCl_3$)]. IR (neat) cm^{-1}: 1717, 1747, 3399. ^{1}H NMR (400 MHz, $CDCl_3$) 1.45 (s, 9H), 3.08 (br s, 1H), 3.78 (s, 3H), 3.87–3.90 (m, 1H), 3.95–3.97 (m, 1H), 4.38 (br s, 1H), 5.59 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 52.5, 55.6, 63.2, 80.2, 155.8, 171.4. MS (EI) m/z 220 (M^++1).

4.4.9. Boc–Cys–OMe (9i). A colorless liquid. $[\alpha]_D^{26}$ +27.5 (c 1.0, $CHCl_3$) [lit.[21] $[\alpha]_D^{21}$ +28.5 (c 318 mM, $CHCl_3$)]. IR (neat) cm^{-1}: 1712, 1747, 3368. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.84 (br s, 1H), 2.95–2.99 (m, 2H), 3.79 (s, 3H), 4.61–4.80 (br s, 1H), 5.45 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.2, 52.6, 54.8, 80.3, 155.1, 170.8. MS (EI) m/z 235 (M^+).

4.4.10. Boc–Tyr–OMe (9j). Colorless prisms. Mp 102–104 °C (Et_2O–hexane), $[\alpha]_D^{27}$ +12.0 (c 2.2, EtOH) [lit.[31] mp 101–103 °C, $[\alpha]_D^{25}$ +10.6 (c 2, EtOH)]. IR (KBr) cm^{-1}: 1690, 1716, 1761, 3389. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.91–3.07 (m, 2H), 3.71 (s, 3H), 4.47–4.60 (m, 1H), 5.04 (br d, J=8.1 Hz, 1H), 6.55 (br s, 1H), 6.72 (d, J=8.1 Hz, 2H), 6.95 (d, J=8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 37.5, 52.3, 54.6, 80.3, 115.5, 127.3, 130.3, 155.2, 155.4, 172.7. MS (EI) m/z 295 (M^+).

4.4.11. Boc–Tyr(Boc)–OMe (10). Colorless needles. Mp 90–91 °C (hexane). $[\alpha]_D^{20}$ −0.6 (c 2.3, MeOH). IR (KBr)

cm^{-1}: 1716, 1758, 3455. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.55 (s, 9H), 3.02–3.14 (m, 2H), 3.71 (s, 3H), 4.51–4.62 (m, 1H), 4.98 (br d, J=8.1 Hz, 1H), 7.06–7.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.2, 37.6, 52.2, 54.3, 80.0, 83.5, 121.3, 130.2, 133.5, 150.1, 151.8, 155.0, 172.1. MS (EI) m/z 395 (M^+). Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.64; H, 7.24; N, 3.63.

4.5. *tert*-Butyl 4-aminophenyl carbonate (12a)

A mixture of **1** (3.03 g, 10 mmol) and 4-aminophenol (**11a**) (0.55 g, 5 mmol) in benzene (15 mL) was heated under reflux for 8 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **12a** (0.98 g, 94%) as colorless needles, *tert*-butyl 4-*tert*-butoxycarbonylaminophenyl carbonate (**13**) (0.08 g, 5%) as a brown powder.

12a: Mp 113–114 °C (Et_2O–hexane) [lit.[6] mp 113.5–114.5 °C]. IR (KBr) cm^{-1}: 1744, 3384, 3475. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 3.63 (br s, 2H), 6.64 (d, J=8.7 Hz, 2H), 6.94 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 83.1, 115.5, 121.9, 143.3, 144.1, 152.5. MS (EI) m/z 209 (M^+).

13: Mp 137–138 °C (hexane) [lit.[6] mp 135–137 °C]. IR (KBr) cm^{-1}: 1704, 1754. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.55 (s, 9H), 6.53 (br s, 1H), 7.08 (d, J=8.7 Hz, 2H), 7.34 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.3, 80.6, 83.4, 119.3, 121.6, 135.9, 146.4, 152.0, 152.7. MS (EI) m/z 309 (M^+).

4.6. *tert*-Butyl *N*-(4-hydroxyphenyl)carbamate (12b)

A solution of **1** (3.03 g, 10 mmol) in DME (15 mL) was added to a stirred suspension of 4-aminophenol hydrochloride (**11b**) (0.73 g, 5 mmol) in DME (10 mL), with stirring at room temperature for 16 h. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5% HCl solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **12b** (0.97 g, 93%) as colorless needles and **13** (0.08 g, 5%) as a brown powder.

12b: Mp 142–143 °C (Et_2O–hexane) [lit.[33] mp 144–145 °C]. IR (KBr) cm^{-1}: 1698, 3362. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 5.59 (br s, 1H), 6.35 (br s, 1H), 6.73 (d, J=8.7 Hz, 2H), 7.16 (d, J=8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 80.4, 115.7, 121.4, 130.9, 152.1, 153.6. MS (EI) m/z 209 (M^+).

4.7. General procedure for the *tert*-butoxycarbonylation of acidic substrates by 1 (Table 4)

To a solution of **1** (5 mmol) in benzene (15 mL) were added acidic substrates (5 mmol) at room temperature, and the resulting mixture was stirred at room temperature for **14a–c** or refluxed for **15–17**. The reaction times were shown in Table 4. The reaction mixture was washed with 5% HCl solution (10 mL), dried, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the products **18–21**. The yields are shown in Table 4.

4.7.1. Benzoic *tert*-butylcarbonic anhydride (18a).

A colorless liquid. IR (neat) cm^{-1}: 1742, 1800. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 7.45–7.49 (m, 2H), 7.61–7.64 (m, 1H), 8.05–8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 85.6, 128.0, 128.6, 130.4, 134.2, 147.2, 161.8. MS (EI) m/z 222 (M^+). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.39.

4.7.2. 4-Methoxybenzoic *tert*-butylcarbonic anhydride (18b).

A colorless liquid. IR (neat) cm^{-1}: 1736, 1795. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 3.87 (s, 3H), 6.94 (d, J=8.9 Hz, 2H), 8.01 (d, J=9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 55.5, 85.3, 113.9, 120.2, 132.6, 147.4, 161.4, 164.4. MS (EI) m/z 252 (M^+). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.71; H, 6.40.

4.7.3. 4-Nitrobenzoic *tert*-butylcarbonic anhydride (18c).

A pale yellow needles. Mp 94–96 °C. IR (neat) cm^{-1}: 1747, 1799. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 8.25 (d, J=9.2 Hz, 2H), 8.33 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 86.8, 123.8, 131.5, 133.5, 146.2, 151.2, 160.1. MS (EI) m/z 268 (M^++1). Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.12; H, 4.89; N, 5.13.

4.7.4. *O*-*tert*-Butyl *S*-phenyl thiocarbonate (19).[34]

A colorless liquid. IR (neat) cm^{-1}: 1728, 1698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 7.36–7.42 (m, 3H), 7.51–7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 85.4, 128.6, 129.0, 129.2, 134.8, 167.7. MS (EI) m/z 210 (M^+). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 62.80; H, 6.84.

4.7.5. *tert*-Butyl (benzenesulfonyl)carbamate (20).

A colorless needles. Mp 128–130 °C (Et_2O–hexane). IR (KBr) cm^{-1}: 1722, 1732, 3241. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, s), 7.45 (1H, br), 7.53–7.65 (3H, m), 8.00–8.04 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 84.2, 128.1, 128.9, 133.7, 138.9, 149.1. MS (EI) m/z 256 (M^++1). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.47; H, 5.64; N, 5.29.

4.7.6. *tert*-Butoxycarbonyl phthalimide (21).

A colorless needles. Mp 91–93 °C (Et_2O–hexane) [lit.[35] 97.4 °C]. IR (KBr) cm^{-1}: 1721, 1768, 1802. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.64 (9H, s), 7.74–7.86 (2H, m), 7.93–7.99 (2H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 27.9, 85.4, 124.3, 131.2, 135.1, 146.7, 164.2. MS (EI) (m/z) 247 (M^+). Anal. Calcd $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.32; H, 5.20; N, 5.78.

4.8. General procedure for esterification of *N*-protected amino acids 22 with BBDI 1

BBDI **1** (1.2 mmol) was added to a solution of *N*-protected amino acid **22** (1 mmol) in dioxane (5 mL) with sitirring at room temperature. The reaction mixture was stirred for 30 min. To the reaction mixture was alcohol (1 or 1.1 mmol) (amounts of alcohol of entries 2, 4, and 6 in Table 5 were used 1 mmol and others were used 1.1 mmol), and after the addition, the reaction mixture was stirred for 5 h, and then

concentrated. After the addition of ethyl acetate, the organic phase was washed twice with 5% HCl and brine. The organic layers were dried ($MgSO_4$) and the solvent evaporated to give the crude compound, which was purified by chromatography on a short column using a mixture of *n*-hexane and ethyl acetate as eluant to yield *N*-protected amino acid ester **24**. Yields and reaction times are shown in Table 5.

4.8.1. *N*-Cbz–Ala methyl ester (24a). Colorless needles. Mp 47–48.5 °C [lit.[15] 45–46 °C]. $[\alpha]_D^{23}$ −33.0 (*c* 1.2, MeOH) [lit.[36] $[\alpha]_D^{25}$ −32.7 (*c* 1.3, MeOH)]. IR (KBr) cm^{-1}: 1685, 1755, 3340. ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (3H, d, *J*=7.1 Hz), 3.74 (3H, s), 4.30–4.46 (1H, m), 5.11 (2H, s), 5.24–5.38 (1H, m), 7.22–7.46 (5H, m). MS (EI) *m/z* 237 (M^+).

4.8.2. *N*-Cbz–Ala ethyl ester (24b). Colorless liquid. $[\alpha]_D^{27}$ −32.6 (*c* 1.5, MeOH) [lit.[36] $[\alpha]_D^{25}$ −32.2 (*c* 1.0, MeOH)]. IR (neat) cm^{-1}: 1723, 3341. ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (3H, t, *J*=7.1 Hz), 1.40 (3H, d, *J*=7.3 Hz), 4.18 (2H, q, *J*=7.0 Hz), 4.27–4.38 (1H, m), 5.10 (2H, s), 5.32–5.49 (1H, m), 7.19–7.43 (5H, m). MS (EI) *m/z* 251 (M^+). HRMS *m/z* Calcd for $C_{13}H_{17}NO_4$ (M^+) 251.1158. Found: 251.1142.

4.8.3. *N*-Cbz–Phe allyl ester (24c). Colorless liquid. $[\alpha]_D^{21}$ −14.8 (*c* 1.3, MeOH) [lit.[37] $[\alpha]_D^{25}$ −15.6 (*c* 2.03, MeOH)]. IR (KBr) cm^{-1}: 1714, 1728, 3340. ^1H NMR (270 MHz, $CDCl_3$) δ 3.04–3.19 (2H, m), 4.59 (2H, d, *J*=5.8 Hz), 4.60–4.71 (1H, m), 5.08 (2H, s), 5.21–5.35 (3H, m), 5.77–5.91 (1H, m), 7.07–7.19 (2H, m), 7.24–7.38 (8H, m). MS (EI) *m/z* 339 (M^+). HRMS *m/z* Calcd for $C_{20}H_{21}NO_4$ (M^+) 339.1471. Found: 339.1458.

4.8.4. *N*-Cbz–Met benzyl ester (24d). Colorless needles. Mp 37–38 °C. $[\alpha]_D^{21}$ −30.6 (*c* 1.0, MeOH). IR (KBr) cm^{-1}: 1689, 1738, 3312. ^1H NMR (270 MHz, $CDCl_3$) δ 1.84–2.20 (5H, m), 2.40–2.52 (2H, m), 4.37–4.58 (1H, m), 5.09 (2H, s), 5.10–5.21 (2H, m), 5.47–5.60 (1H, m), 7.28–7.51 (10H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.1, 29.5, 31.5, 53.0, 66.8, 67.0, 127.8, 127.9, 128.1, 128.3, 128.4, 134.9, 135.0, 136.0, 155.7, 171.6. MS (EI) *m/z* 373 (M^+). HRMS *m/z* Calcd for $C_{20}H_{23}NO_4S$ (M^+) 373.1348. Found: 373.1328.

4.8.5. *N*-Boc–Ala *p*-methoxyphenyl ester (24e). Colorless needles. Mp 82–83 °C. $[\alpha]_D^{30}$ −63.4 (*c* 1.1, MeOH). IR (KBr) cm^{-1}: 1687, 1774, 3386. ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.54 (3H, d, *J*=7.0 Hz), 3.80 (3H, s), 4.47–4.60 (1H, m), 5.05–5.11 (1H, m), 6.86–6.91 (2H, m), 6.98–7.04 (2H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.2, 28.2, 49.3, 55.4, 79.8, 114.3, 121.9, 143.9, 155.0, 157.2, 172.2. MS (EI) *m/z* 295 (M^+). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.09; H, 7.16; N, 4.70.

4.8.6. *N*-Fmoc–Phe allyl ester (24f). Colorless needles. Mp 105–106 °C [lit.[38] mp 92–95 °C]. $[\alpha]_D^{27}$ +15.2 (*c* 0.9, $CHCl_3$) [lit.[38] $[\alpha]_D^{20}$ +15.9 (*c* 0.8, $CHCl_3$)]. IR (KBr) cm^{-1}: 1690, 1735, 3343. ^1H NMR (270 MHz, $CDCl_3$) δ 3.05–3.19 (2H, m), 4.19 (1H, t, *J*=6.8 Hz), 4.29–4.46 (2H, m), 4.60 (2H, d, *J*=5.6 Hz), 4.65–4.73 (1H, m), 5.22–5.32 (3H, m), 5.78–5.93 (1H, m), 6.92–7.11 (2H, m), 7.20–7.43 (7H, m), 7.49–7.59 (2H, m), 7.74 (2H, d, *J*=7.2 Hz). MS (EI) *m/z* 427 (M^+). Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.75; H, 5.92; N, 3.18.

4.8.7. 2-*tert*-Butoxycarbonyl-1-methoxy-1,2-dihydroisoquinoline (25). To a solution of **1** (3.03 g, 10 mmol) in benzene (15 mL) was added absolute methanol (6 mL, 148 mmol) with stirring for 6 h at room temperature. After concentration in vacuo, the residue was purified by distilled under reduced pressure to give **25** (2.40 g, 92%) as a colorless prism. Mp 61–62 °C (pentane). IR (KBr) cm^{-1}: 1718. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (9H, s), 3.30 (3H, s), 6.01 (1H, br s), 6.44 (1H, br), 7.00 (1H, br s), 7.19–7.35 (4H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.1, 54.5, 81.6, 82.3, 107.3, 124.2, 124.9, 126.6, 127.5, 128.2, 129.0, 130.4, 152.5. MS (EI) (*m/z*) 261 (M^+). Anal. Calcd $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.92; H, 7.51; N, 5.28.

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References and notes

1. (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, NY, 1999; (b) Kocienski, P. J. *Protecting Groups*; George Thieme: Stuttgart, 2000.
2. (a) Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron* **1998**, *54*, 6385–6402; (b) Gunnarsson, K.; Grehn, L.; Ragnarsson, U. *Angew. Chem.* **1988**, *100*, 411–412.
3. (a) Hansen, M. M.; Riggis, J. R. *Tetrahedron Lett.* **1998**, *39*, 2705–2706; (b) Jarowicki, K.; Koci'nski, P. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1589–1615; (c) Water, R. W. V. D.; Magdzisk, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502–6503.
4. (a) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368–6380; (b) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510–511; (c) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5681–5684.
5. (a) Bailey, S. W.; Chandrasekaran, R. Y.; Ayling, J. E. *J. Org. Chem.* **1992**, *57*, 4470–4477; (b) Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003–9006.
6. Houlihan, F.; Bouchard, F.; Frechet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153–162.
7. Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 1794–1798.
8. (a) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Chem. Pharm. Bull.* **1984**, *32*, 2174–2181; (b) Grapsas, I.; Cho, Y. G.; Mobashery, S. *J. Org. Chem.* **1994**, *59*, 1918–1922.
9. Ouchi, H.; Saito, Y.; Yamamoto, Y.; Takahata, H. *Org. Lett.* **2002**, *4*, 585–587.
10. (a) Konieczny, M. T.; Horowska, B.; Kunikowski, A.; Konopa, J.; Wierzba, K.; Yamada, Y.; Asao, T. *J. Org. Chem.* **1999**, *64*, 359–364; (b) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176–5190; (c) Al-Maharik,

N. I.; Kaltia, S. A. A.; Mutikainen, I.; Wähälä, K. *J. Org. Chem.* **2000**, *65*, 2305–2308; (d) Kozikowski, A.; Tückmantel, W.; George, C. *J. Org. Chem.* **2000**, *65*, 5371–5381; (e) Speranza, G.; Morelli, C. F.; Manitto, P. *Synthesis* **2000**, 123–126; (f) Al-Maharik, N. I.; Mutikainen, I.; Wähälä, K. *Synthesis* **2000**, 411–416; (g) Taniguchi, H.; Hosoda, A.; Tuno, T.; Maruta, Y.; Nomura, E. *Anticancer Res.* **1999**, *19*, 3557–3562; (h) Horiuchi, H.; Shirase, H.; Okutsu, T.; Matsushima, R.; Hiratsuka, H. *Chem. Lett.* **2000**, 96–97.

11. (a) Onyeneho, S. N.; Hettiarachchy, N. S. *J. Agric. Food Chem.* **1992**, *40*, 1496–1500; (b) Shahidi, F.; Wanasundara, P. K. J. P. D. *Crit. Rev. Food Sci. Nutr.* **1992**, *32*, 67–103; (c) Bravo, L. *Nutr. Rev.* **1998**, *56*, 317–333.
12. (a) Yajima, H.; Fujii, N. *The Peptides: Analysis, Synthesis, Biology*; Gross, E., Meienhofer, J., Eds.; Academic: New York, NY, 1983; Vol. 5, pp 65–109; (b) Bodanszky, M. *Principles of Peptide Chemistry*; Springer: New York, NY, 1984; p 99.
13. pK_a values were measured in dimethyl sulfoxide. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
14. pK_a values were measured in dimethyl sulfoxide. David, L. H.; James, J. B.; Edward, J. J. G. *J. Org. Chem.* **1986**, *51*, 2579–2585.
15. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.
16. Cantacuzène, D.; Pascal, F.; Guerreiro, C. *Tetrahedron* **1987**, *43*, 1823–1826.
17. Bajgrowicz, J. A.; Hallaoui, A. E.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843.
18. Keith, J.; King, -C. W. *Tetrahedron* **1991**, *47*, 7179–7184.
19. Santiago, C.; Paloma, L.-S.; Marta, F.; María, I. B.; Ana, M.; María, I. R.-F. *Tetrahedron* **1997**, *53*, 11745–11752.
20. Torrini, I.; Zecchini, P. Z.; Agrosi, F.; Paradisi, M. P. *J. Heterocycl. Chem.* **1986**, *23*, 1459–1463.
21. Threadgill, M. D.; Gledhill, A. P. *J. Org. Chem.* **1989**, *54*, 2940–2949.
22. Pozdnev, V. F. *Int. J. Pept. Protein Res.* **1992**, *40*, 407–414.
23. The pK_a[13] of succinimide is described in place of phthalimide (**17**).
24. Saito, Y.; Yamaki, T.; Kohashi, F.; Watanabe, T.; Ouchi, H.; Takahata, H. *Tetrahedron Lett.* **2005**, *46*, 1277–1279.
25. Cremin, D. J.; Hegarty, A. F.; Begley, M. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 412–420.
26. Carpino, L. A.; Carpino, B. A.; Giza, C. A.; Murray, R. W.; Santilli, A. A.; Terry, P. H. *Org. Synth. Coll. Vol.* **1973**, *V*, 168–171.
27. Anderson, J. W.; McGregor, A. C. *J. Am. Chem. Soc.* **1957**, *79*, 6180–6183.
28. Ito, H.; Ichimura, K. *Macromol. Chem. Phys.* **2000**, *201*, 132–138.
29. Bailey, W. J.; Griffith, J. R. *J. Org. Chem.* **1978**, *43*, 2690–2692.
30. Cho, I.-S.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288–7291.
31. Leardini, R.; Zanardi, G. *Synthesis* **1982**, *3*, 225–227.
32. Chankeshwara, S. V.; Chakraborti, A. K. *Tetrahedron Lett.* **2006**, *47*, 1087–1091.
33. Vigroux, A.; Bergon, M.; Zedde, C. *J. Med. Chem.* **1995**, *38*, 3983–3994.
34. Kolodziejczyk, A. M.; Manning, M. *J. Org. Chem.* **1981**, *46*, 1944–1946.
35. Tavecchis, P.; Marazzi, A.; Dallanoce, C.; Trani, A.; Ciciliato, I.; Ferrari, P.; Selva, E.; Ciabatti, R. *J. Antibiot.* **1996**, *49*, 1249–1257.
36. Gibson, F. S.; Park, M. S.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 7503–7507.
37. Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063–1066.
38. Oppolzer, W.; Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572–2582.

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Correlation of calculated halonium ion structures with product distributions from fluorine substituted terminal alkenes

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Abstract—Calculated equilibrium geometries, bond lengths, and charge densities were performed on halonium ions derived by the addition of halogen electrophiles to fluoro-substituted terminal alkenes. The calculated structures correlate with regiochemical product distributions from ring-opening of halonium ions by anions or by the solvent methanol. Calculated halonium ion structures and the Hammond postulate are utilized to predict the regiochemical product distributions for reactions of halogens with fluoroalkenes that are not investigated experimentally.

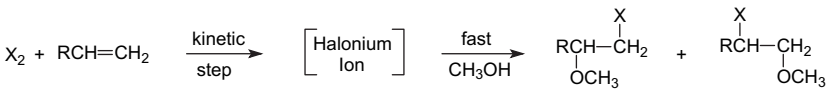
1. Introduction

Recently, we reported on the symmetry of halonium ions from ionic reaction of chlorine (Cl_2), bromine (Br_2), and the interhalogens iodine monochloride (ICl) and chlorine monofluoride (ClF) with terminal alkenes.[1–5] The product regiochemistry, Markovnikov **M** or anti-Markovnikov **aM**, is determined by the fast-step. Our study reported that the **M/aM** product distribution was greatly influenced by the symmetry of the halonium ions; and that the halonium ion symmetry was changed dramatically by fluorine substitution.[1] Regioisomers from Cl_2 and Br_2 were obtained from their solvent incorporated products in methanol as shown below. All ClF reactions with terminal alkenes were carried out in methylene chloride as solvent.

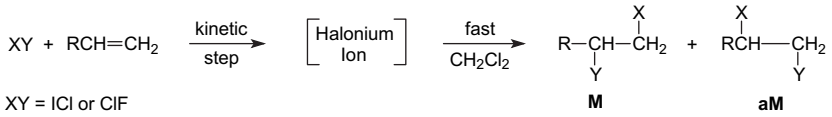
Substituting a vinyl hydrogen with a fluorine presents an interesting situation for electrophilic reactions. The π-bond is less reactive toward electrophiles due to the electron-withdrawing effect of the vinyl fluorine. Therefore, carbocations or radical cations are destabilized by fluorine and the intermediates are difficult to generate. When the ionic intermediate is formed, it can be stabilized by back-bonding from the lone-pair (2p) electrons on the fluorine.

(3)

A vinyl fluorine alters the shape of the halonium ion intermediate and the **M** to **aM** product distribution.[6] The **M** to **aM** product ratio was also greatly influenced by the alkyl



(1)



(2)

Keywords: Halonium ions; Symmetry; Fluorine substituents; Computations.
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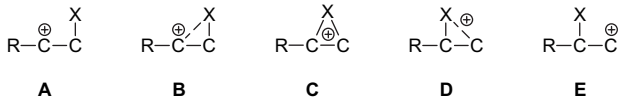
substituent on the terminal alkene. A structure for the halonium ion intermediate was assigned on the basis of the **M/aM** ratio as either **A**, **B**, **C**, **D**, or **E**.[1]



In this paper, we utilize quantum chemical calculations to probe the bond distance, bond angles, and charges on substituted terminal halonium ions. The calculated data are correlated with our assigned structures (**A**→**E**) of halonium ions from regiochemical product distributions (**M/aM** product ratio[1]) formed under kinetically controlled reaction conditions. These calculated halonium ion structures and the Hammond postulate are also utilized to predict the regiochemical kinetic product distributions for reaction of halogens with terminal fluoroalkenes that are not investigated experimentally. Geometry calculations have been performed by others[7–12] but little has been done to investigate the asymmetrical bridged structures. While Sordo et al.[11] propose that a tightly bridged structure is energetically unfavorable, others[8,9] show they are the preferred structures.

2. Methods

Geometry optimizations were performed at the second-order perturbation theory level (MP2, also known as MBPT(2)),[13] using the Spartan02 program and also at the density functional theory level, using the GAMESS[14] quantum chemistry code with the B3LYP hybrid functional,[15] which included the VWN5 correlation functional.[15] In addition, a separate set of B3LYP calculations incorporating the Polarizable Continuum Model (PCM)[16] were performed to probe the methanol solvent effects. The 6-311++G(d,p) basis set[17] was used for all calculations. Other work has shown the necessity for diffuse and polarization basis functions,[12,18] which we have used in our study. There was no attempt made to quantify the sensitivity of predicted geometries to the choice of basis set. Harmonic vibrational frequencies were calculated at the B3LYP and B3LYP+PCM levels for each structure to ensure that the optimized structure is indeed a local minimum on the ground state potential energy surface. Unless otherwise noted, R=CH_3 and R_f=CF_3.

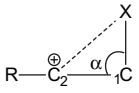
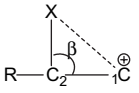
The product ratios were determined experimentally under conditions of kinetic control and reported previously.[1,2] For experimental reactions, side chains are generally longer than those used for calculations (CH_3– and CF_3–) reported in Table 1.

3. Results and discussion

Table 1 contains the X–C_1–C_2 and X–C_2–C_1 bond angles from calculations obtained using the B3LYP/6-311++G(d,p) PCM method, which includes corrections for the solvent methanol. The X–C_2–C_1 bond angles from the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) calculations, which do not include corrections for solvent, are also included in Table 1. The MP2 and B3LYP calculations are similar and are confirmed by our gas phase data in Table 1. Halonium ion structures of **A** through **E**, assigned from the calculated structures and also independently assigned from our experimental data[1,2] are in Table 1. These calculated data provide a more refined structure for the halonium ion than we were able to predict based on experimental data.[1,2] Where experimental data are lacking, we give the calculated halonium ion structure in Table 1. Regiochemical product distributions can be estimated for reactions that are not done experimentally using the Hammond postulate and the calculated halonium ion structure.

3.1. Refined structures defined

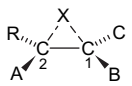
The X–C_1–C_2 bond angle is best suited for assigning structures **A** and **B** while the X–C_2–C_1 bond angle is used for structures **D** and **E**. For example, a X–C_1–C_2 bond angle of 90° or more is assigned as structure **A** while a X–C_1–C_2 bond angle (α) of 75–80° represents structure **B**. Bond angles of 85–90° describe halonium ions as resembling **A** but approaching structure **B**, and 80–85° like structure **B** but becoming like structure **A**; this is denoted as **A**⇒**B** and **B**⇒**A**, respectively. A bond angle α of 75–80° represents structure **B**; 70–75° as **B**⇒**C**, and 65–70° as **C**⇒**B**. Symmetrical structure **C** is represented by 55–65° for either the X–C_1–C_2 or X–C_2–C_1 bond angle. Similarly, a X–C_2–C_1 bond angle of 90° or more represents structure **E**, 85–90 **E**⇒**D**, 80–85 **D**⇒**E**, 75–80 **D**, 70–75 **D**⇒**C**, 65–70 **C**⇒**D**, and 55–65 as the symmetrical structure **C**. These refined structures could not be gleaned from our experimental data.[1,2]

Bond angles	
	
α>90° **A**	β>90° **E**
α>85–90° **A**⇒**B**	β>85–90° **E**⇒**D**
α>80–85° **B**⇒**A**	β>80–85° **D**⇒**E**
α>75–80° **B**	β>75–80° **D**
α>70–75° **B**⇒**C**	β>70–75° **D**⇒**C**
α>65–70° **C**⇒**B**	β>65–70° **C**⇒**D**
α or β 55–65° **C**	

3.2. Comparing the models

Table 2 contains bond lengths from the B3LYP calculations, both with and without corrections for solvent, and Table 3 summarizes the MP2 bond lengths. Table 4 lists the atomic charges from the B3LYP+PCM and MP2 calculations. The MP2 and B3LYP C_1–C_2 computed bond lengths are in excellent agreement, with differences of at most 0.02 Å. Inclusion of solvent effects via the B3LYP+PCM method has a small effect on the C_1–C_2 bond lengths, which differ from the B3LYP values by at most 0.01 Å. However, the predicted C_1–X and C_2–X bond lengths are more sensitive to the theoretical method than the C_1–C_2 bond distances. In general, the incorporation of solvent effects using the PCM method has minor effects on the halonium ion bond angles (Table 1), bond lengths (Table 2), and charge densities (Table 4) relative to the corresponding predictions in the gas phase. Experimentally predicted structures and calculated geometries are consistent where carbocations with monocoordinated halonium ions (i.e., having structure **A** or **E**) are anticipated (Table 1, structure **A**, runs 3 and 13; structure

Table 1. Bond angle (degrees)/halonium ion structure

						B3LYP/6-311++G(d,p)+PCM(CH_3OH)				B3LYP/6-311++G(d,p)		MP2/6-311++G(d,p)		**M/aM** Experimental product ratio[b]	Predicted structure from experimental[b] data (CH_3OH)
						Bond angle		Structure[a] based on angles		Bond angle	Structure[a]	Bond angle	Structure[a]		
Run	R	A	B	C	X	X–C_2–C_1	X–C_1–C_2	X–C_2–C_1	X–C_1–C_2	X–C_2–C_1	X–C_2–C_1	X–C_2–C_1			
1	CH_3	H	H	H	Cl	61.2	75.7	**C**	***B***	61.7	**C**	64.7	**C**	2.6/1	**B**
					Br	64.3	75.8	**C**	**B**	64.3	**C**	62.9	**C**	3.1/1	**B**
2	CH_3	H	F	H	Cl	67.1	69.6	**C⇒D**	**C⇒D**	68.2	**C⇒D**	68.6	**C⇒D**	**aM** only	**D**
					Br	69.9	70.0	**C⇒D**	**D⇒C**	70.5	**D⇒C**	71.6	**D⇒C**	1/9.0	**D**
3	CH_3	F	H	H	Cl	46.3	97.9		**A**	49.8		55.9	**C**	**M** only	**A**
					Br	51.3	93.8		**A**	54.2		48.7		**M** only	**A**
4	CH_3	H	F	F	Cl	93.3	49.5	**E**		87.1	**E⇒D**	88.0	**E⇒D**	—	—
					Br	88.3	55.4	**E⇒D**		83.2	**D⇒E**	95.3	**E**	—	—
5	CH_3	F	H	F	Cl	44.8	93.3		**A**	48.9		58.2	**C**	—	—
					Br	51.4	93.0		**A**	55.4		47.1		—	—
6	CH_3	F	F	F	Cl	43.3	100.8		**A**	46.2		46.2		—	—
					Br	49.0	95.6		**A**	54.0		89.3	**E⇒D**	—	—
7	CF_3	H	H	H	Cl	68.6	66.1	**C⇒D**	**C⇒B**	67.9	**C⇒D**	67.4	**C⇒D**	**aM** only	**D**
					Br	70.2	68.0	**D⇒C**	**C⇒B**	69.6	**C⇒D**	69.4	**C⇒D**	**aM** only	**D**
8	CF_3	H	F	H	Cl	80.0	57.8	**D**	**C**	77.8	**D**	73.0	**D**	—	—
					Br	78.3	61.8	**D**	**C**	77.5	**D**	75.3	**D**	—	—
9	CF_3	F	H	H	Cl	63.9	72.3	**C**	**B⇒C**	61.8	**C**	64.9	**C**	**aM** only	**D**
					Br	65.9	73.5	**C⇒D**	**B⇒C**	64.4	**C**	66.2	**C⇒D**	—	—
10	CF_3	H	F	F	Cl	99.3	45.1	**E**		95.4	**E**	97.8	**E**	—	—
					Br	95.6	49.8	**E**		91.6	**E**	93.8	**E**	—	—
11	CF_3	F	H	F	Cl	75.6	60.9	**D**	**C**	71.5	**D⇒C**	70.0	**D⇒C**	1.8/1[c]	**C**
					Br	73.2	65.8	**D⇒C**	**C⇒B**	71.8	**D⇒C**	71.5	**D⇒C**	—	—
12	CF_3	F	F	F	Cl	99.4	44.2	**E**		95.4	**E**	98.8	**E**	**aM** only	**E**
					Br	94.4	49.9	**E**		89.3	**D⇒E**	92.4	**E**	—	—
13	CH_3O	H	H	H	Cl	41.9	105.0		**A**	46.0		45.5		**M** only[d]	**A**[d]
					Br	46.5	100.9		**A**	49.8		45.6		**M** only[d]	**A**[d]
14	CF_3O	F	F	F	Cl	40.3	105.4		**A**	41.0		40.6		2.4/1	**B**
					Br	43.6	103.4		**A**	44.6		43.8		1/4.7	**C**
15	$Br(CH_2)_2$	F	F	F	Cl	43.1	101.0		**A**	45.2		44.9		1/2.1	**C**
					Br	50.5	93.4		**A**	52.4		92.5	**E**	1/1.3[e]	**C**[e]

[a] The symbol ⇒ means becomes like. For example, **C⇒B** means the structure resembles **C** but contains some of the symmetrical structure **B**. It resembles **C** more than **B**. The structure was not assigned when the angle is around 55° or less.

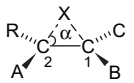
[b] Structures were assigned using experimental data in Ref. 1 unless noted.

[c] Experimental data from Ref. 2.

[d] Unpublished data.

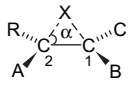
[e] The product ratios in Ref. 1 were influenced by the 1,2,4-tribromo-1,1,2-trifluorobutane product overlapping the **aM** product in the gas chromatograph. A more accurate **M/aM** product ratio of 1:1.3 was obtained by ^{19}F NMR.

Table 2. Bond lengths (angstroms)



Run	R	A	B	C	X	B3LYP/6-311++G(d, p)+PCM(CH_3OH) C_1–C_2	C_1–X	C_2–X	C_1–F_B	C_1–F_C	C_2–F_A	Predicted structures PCM	B3LYP/6-311++G(d, p) (Gas phase) C_1–C_2	C_1–X	C_2–X	C_1–F_B	C_1–F_C	C_2–F_A
1	CH_3	H	H	H	Cl	1.456	1.867	2.065	—	—	—	**C⇒B**	1.460	1.865	2.043	—	—	—
					Br	1.448	2.021	2.114				**C⇒B**	1.454	2.020	2.169			
2	CH_3	H	F	H	Cl	1.453	1.952	1.985	1.306	—	—	**C⇒D**	1.458	1.967	1.968	1.298	—	—
					Br	1.445	2.112	2.114	1.308			**D⇒C**	1.452	2.122	2.107	1.302		
3	CH_3	F	H	H	Cl	1.473	1.820	2.495	—	—	1.277	**A**	1.469	1.824	2.386	—	—	1.282
					Br	1.457	1.984	2.538			1.286	**A**	1.456	1.989	2.454			1.290
4	CH_3	H	F	F	Cl	1.471	2.425	1.846	1.254	1.255	—	**E**	1.466	2.312	1.862	1.263	1.263	—
					Br	1.454	2.455	2.022	1.264	1.264		**E⇒D**	1.453	2.360	2.040	1.273	1.272	
5	CH_3	F	H	F	Cl	1.498	1.800	2.522	—	1.347	1.269	**A**	1.491	1.813	2.402	—	1.335	1.278
					Br	1.478	1.980	2.531		1.340	1.279	**A**	1.474	1.999	2.421		1.329	1.289
6	CH_3	F	F	F	Cl	1.526	1.783	2.555	1.325	1.329	1.262	**A**	1.519	1.794	2.472	1.316	1.324	1.269
					Br	1.506	1.965	2.590	1.322	1.325	1.270	**A**	1.495	1.993	2.463	1.310	1.317	1.280
7	CF_3	H	H	H	Cl	1.454	1.905	1.871	—	—	—	**C⇒D**	1.458	1.902	1.889	—	—	—
					Br	1.451	2.047	2.018				**D⇒C**	1.453	2.047	2.035			
8	CF_3	H	F	H	Cl	1.457	2.133	1.832	1.271	—	—	**D**	1.459	2.097	1.847	1.277	—	—
					Br	1.452	2.213	1.991	1.283			**D**	1.453	2.205	2.004	1.286		
9	CF_3	F	H	H	Cl	1.450	1.879	1.994	—	—	1.290	**B⇒C**	1.455	1.869	2.047	—	—	1.285
					Br	1.445	2.026	2.129			1.297	**B⇒C**	1.450	2.023	2.170			1.293
10	CF_3	H	F	F	Cl	1.482	2.507	1.798	1.245	1.246	—	**E**	1.476	2.438	1.807	1.255	1.252	—
					Br	1.464	2.563	1.966	1.252	1.253		**E**	1.460	2.491	1.978	1.263	1.259	
11	CF_3	F	H	F	Cl	1.472	2.068	1.865	—	1.274	1.311	**D**	1.474	2.011	1.915	—	1.282	1.303
					Br	1.467	2.143	2.043		1.289	1.310	**D⇒C**	1.469	2.135	2.074		1.291	1.307
12	CF_3	F	F	F	Cl	1.517	2.520	1.781	1.239	1.241	1.334	**E**	1.511	2.453	1.795	1.249	1.249	1.329
					Br	1.495	2.554	1.959	1.246	1.248	1.332	**E**	1.488	2.463	1.982	1.258	1.259	1.326
13	CH_3O	H	H	H	Cl	1.477	1.808	2.615	—	—	—	**A**	1.475	1.813	2.496	—	—	—
					Br	1.467	1.973	2.671				**A**	1.464	1.977	2.575			
14	CF_3O	F	F	F	Cl	1.543	1.768	2.637	1.329	1.326	1.265	**A**	1.548	1.768	2.616	1.327	1.323	1.275
					Br	1.532	1.941	2.738	1.329	1.327	1.267	**A**	1.533	1.942	2.707	1.326	1.323	1.276
15	$Br(CH_2)_2$	F	F	F	Cl	1.527	1.781	2.558	1.325	1.328	1.262	**A**	1.521	1.793	2.504	1.318	1.325	1.273
					Br	1.503	1.972	2.549	1.319	1.322	1.271	**A**	1.499	1.986	2.506	1.313	1.319	1.281

Table 3. Bond lengths (angstroms)



						MP2/6-311++G(d,p) (Gas phase)					
Run	R	A	B	C	X	C_1–C_2	C_1–X	C_2–X	C_1–F_B	C_1–F_C	C_2–F_A
1	CH_3	H	H	H	Cl	1.462	1.842	1.909	—	—	—
					Br	1.441	2.012	2.205			
2	CH_3	H	F	H	Cl	1.457	1.920	1.890	1.298	—	—
					Br	1.436	2.129	2.089	1.273		
3	CH_3	F	H	H	Cl	1.458	1.815	2.174	—	—	1.284
					Br	1.463	1.958	2.587			1.249
4	CH_3	H	F	F	Cl	1.461	2.294	1.821	1.257	1.257	—
					Br	1.464	2.564	1.973	1.229	1.229	
5	CH_3	F	H	F	Cl	1.470	1.831	2.112	—	1.317	1.288
					Br	1.486	1.939	2.615		1.317	1.243
6	CH_3	F	F	F	Cl	1.513	1.762	2.429	1.315	1.322	1.260
					Br	1.473	2.151	2.104	1.279	1.284	1.311
7	CF_3	H	H	H	Cl	1.461	1.858	1.839	—	—	—
					Br	1.458	2.020	2.002			
8	CF_3	H	F	H	Cl	1.456	1.975	1.826	1.284	—	—
					Br	1.454	2.144	1.988	1.288		
9	CF_3	F	H	H	Cl	1.455	1.853	1.921	—	—	1.294
					Br	1.453	2.011	2.095			1.297
10	CF_3	H	F	F	Cl	1.476	2.459	1.776	1.248	1.245	—
					Br	1.460	2.519	1.958	1.254	1.251	
11	CF_3	F	H	F	Cl	1.469	1.948	1.878	—	1.285	1.298
					Br	1.467	2.108	2.048		1.289	1.301
12	CF_3	F	F	F	Cl	1.512	2.486	1.756	1.240	1.241	1.333
					Br	1.488	2.502	1.951	1.249	1.250	1.329
13	CH_3O	H	H	H	Cl	1.476	1.784	2.474	—	—	—
					Br	1.475	1.946	2.669			
14	CF_3O	F	F	F	Cl	1.540	1.740	2.590	1.325	1.322	1.269
					Br	1.531	1.921	2.707	1.325	1.322	1.270
15	$Br(CH_2)_2$	F	F	F	Cl	1.514	1.756	2.465	1.319	1.327	1.266
					Br	1.473	2.140	2.112	1.281	1.286	1.312

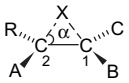
E, run 12 for chlorine, the perfluoroalkene in run 12 did not react ionically with bromine). The calculated structures, including those corrected for solvent, are generally more symmetrical than structures **B** and **D** predicted from experimental data[1,2] (Table 1, runs 1, 2, 7, and 9 for chlorine). Halonium ions formed from alkenes with fluorine on both carbon-1 and carbon-2 (Table 1, runs 11 for chlorine, and runs 14 and 15) gave calculated structures less symmetrical than what we predicted based on experimental data.[1,2]

The MP2, B3LYP, and B3LYP+PCM data in Table 1 overall are in good agreement. In those instances where they disagree (runs 3 and 5, and the bromonium ions from runs 4 and 9), the B3LYP and B3LYP+PCM results are generally similar to each other but distinct from MP2. An exception is the bromonium ion case from run 12, in which case the MP2 and B3LYP+PCM predictions are similar but in slight disagreement with B3LYP. However, these differences are typically small and the overall level of consistency between the three theoretical methods lends confidence to their reliability.

3.3. Trends

Structures for the halonium ions **A** through **E** were assigned from X–C_1–C_2 and X–C_2–C_1 bond angles. These assignments are generally supported by bond lengths (Tables 2 and 3) and charge densities (Table 4). Halonium ions assigned unsymmetrical structure **A** (runs 3, 5, 6, 13, 14, and 15) have shorter C_1–X than C_2–X bond lengths (see Tables 2 and 3), except for the MP2 predicted geometries of the bromonium ions in runs 6 and 15, in which the C_1–Br bond lengths are slightly longer than C_2–Br. Furthermore, the positive charges are greater on carbon-2 than on carbon-1 (Table 4), with the sole exception of the bromonium ion in run 5, for which the B3LYP+PCM Löwdin atomic charge of C_1 exceeds that of C_2. In runs 1, 2, and 9, in which the assigned halonium ion structure is nearly symmetrical like **C**, the predicted C_1–X bond lengths are smaller than C_2–X (except for X=Br in run 2). In contrast, the C_1–X bond lengths are larger than C_2–X in the nearly symmetrical halonium ions in run 7. The PCM Löwdin atomic charges on carbon-1 and carbon-2 of the symmetrical ions (runs 1, 2, 7, and 9) differ by less than 0.1 electron (although in the instance of the chloronium cation in run 1, the difference in charges on C_1 and C_2 is 0.39 electron). In contrast, the MP2 natural population analysis of the charges on C_1 and C_2 in the nearly symmetrical halonium ions shows considerable more variation than the corresponding B3LYP+PCM Löwdin atomic charges. Unsymmetrical structure like **D** or **E** (runs 4, 8, 10, 11, and 12) has the positive charge primarily

Table 4. Charge densities



						Atomic charges–PCM[a]				Predicted structures PCM	Atomic charges–MP2[b]					
Run	R (Rc)	A	B	C	Halogen	C_1	C_2	C_3	X		C_1	C_2	X	F_C	F_B	F_A
1	CH_3	H	H	H	X=Cl	0.24	−0.15	0.09	0.35	**C⇒B**	0.258	−0.043	0.406			
					X=Br	−0.04	0.03	−0.20	0.38	**C⇒B**	0.313	0.134	0.307			
2	CH_3	H	F	H	X=Cl	0.07	−0.02	−0.19	0.41	**C⇒D**	0.373	−0.124	0.363	−0.256		
					X=Br	0.10	0.00	−0.19	0.40	**D⇒C**	0.482	−0.098	0.294	0.315		
3	CH_3	F	H	H	X=Cl	−0.16	0.20	−0.15	0.23	**A**	−0.394	0.700	0.251			−0.240
					X=Br	−0.09	0.17	−0.16	0.24	**A**	−0.524	0.978	0.191			−0.303
4	CH_3	H	F	F	X=Cl	0.21	−0.13	−0.19	0.27	**E**	1.072	−0.296	0.188	−0.194	−0.190	
					X=Br	0.18	−0.07	−0.19	0.30	**E⇒D**	1.294	−0.381	0.194	−0.262	−0.260	
5	CH_3	F	H	F	X=Cl	−0.06	0.21	−0.15	0.28	**A**	0.217	0.623	−0.275	−0.278		−0.241
					X=Br	0.30	0.17	−0.16	0.29	**A**	0.111	0.964	−0.187	−0.355		−0.291
6	CH_3	F	F	F	X=Cl	−0.06	0.22	−0.13	0.34	**A**	0.624	0.775	0.175	−0.293	−0.284	−0.186
					X=Br	0.02	0.19	−0.14	0.34	**A**	0.623	0.696	0.270	−0.240	−0.230	−0.269
7	CF_3	H	H	H	X=Cl	0.00	−0.04	0.09	0.57	**C⇒D**	−0.224	−0.196	0.489			
					X=Br	0.02	0.00	0.09	0.54	**D⇒C**	−0.281	−0.251	0.604			
8	CF_3	H	F	H	X=Cl	0.19	−0.11	0.09	0.47	**D**	0.431	−0.281	0.410		−0.230	
					X=Br	0.16	−0.04	0.09	0.48	**D**	0.398	−0.348	0.517		−0.234	
9	CF_3	F	H	H	X=Cl	−0.03	0.05	0.10	0.52	**B⇒C**	−0.295	0.425	0.436			−0.245
					X=Br	0.00	0.07	0.10	0.52	**B⇒C**	−0.367	0.395	0.543			−0.249
10	CF_3	H	F	F	X=Cl	0.24	−0.15	0.09	0.35	**E**	1.134	−0.436	0.198	−0.158	−0.163	
					X=Br	0.21	−0.07	0.09	0.36	**E**	1.089	−0.495	0.325	−0.172	−0.179	
11	CF_3	F	H	F	X=Cl	0.16	−0.04	0.09	0.53	**D**	0.361	0.335	0.393	−0.227		−0.245
					X=Br	0.14	0.03	0.09	0.53	**D⇒C**	0.312	0.294	0.497	−0.232		−0.249
12	CF_3	F	F	F	X=Cl	0.24	−0.10	0.08	0.41	**E**	1.106	0.143	0.204	−0.150	−0.145	−0.286
					X=Br	0.20	−0.01	0.08	0.40	**E**	1.045	0.106	0.331	−0.167	−0.164	−0.281
13	CH_3O	H	H	H	X=Cl	−0.19	0.17	0.04	0.15	***A***	−0.446	0.499	0.101			
					X=Br	−0.11	0.14	0.03	0.14	***A***	−0.502	0.666	0.134			
14	CF_3O	F	F	F	X=Cl	−0.05	0.18	0.07	0.33	**A**	0.610	0.937	0.139	−0.292	−0.294	−0.202
					X=Br	0.04	0.17	0.07	0.29	**A**	0.560	0.926	0.216	−0.293	−0.294	−0.203
15	$Br(CH_2)_2$	F	F	F	X=Cl	−0.06	0.22	−0.15	0.35	**A**	0.620	0.756	0.170	−0.301	−0.289	−0.196
					X=Br	0.04	0.17	−0.16	0.35	**A**	0.637	0.664	0.298	−0.243	−0.233	−0.270

[a] Löwdin atomic charges from the B3LYP/6-311++G(d,p)+PCM calculations.
[b] Natural population analysis charges from the MP2/6-311++G(d,p) calculations.

on carbon-1 (Table 4) and C_1–X bond lengths, which are shorter than C_2–X. The chlorine and bromine atoms in all of the halonium ions have positive charges, except in the case of the MP2 natural population analysis of the charges for run 5 (see Table 4). Atomic charges and the C_1–X, C_2–X relative bond lengths are generally consistent with the structural assignments based upon the X–C_1–C_2 and X–C_2–C_1 bond angles, which provide the most reliable correlation with experimental data.

3.4. Structures

3.4.1. Hydrocarbon substituents (R=alkyl).

3.4.1.1. No vinyl fluorines on carbon-1 or carbon-2. The halonium ion geometries from the PCM calculations on the hydrocarbon alkene propene (Table 1, run 1) have an X–C_2–C_1 bond angle consistent with structure **C** and an X–C_1–C_2 bond angle more like **B**. The X–C_2 bond is longer than the bond at all computational levels (Tables 2 and 3, run 1), which indicates some asymmetry toward **B**. In run 1, carbon-1 is more positively charged than carbon-2, except for the B3LYP+PCM bromonium ion. Our calculations indicate a slightly more symmetrical intermediate (**C** from X–C_2–C_1 bond angle and **B** from X–C_1–C_2 bond angle, Table 1) than that predicted by experimental product ratios (**B**, Table 1). Throughout this study, we find that calculated structures tend to be slightly more symmetrical than those inferred by experimental data in solution.

The hydrocarbon vinyl ether halonium ions have X–C_1–C_2 bond angles of 100° and X–C_2–C_1 around 40°, consistent with an open-ion **A** (Table 1, run 13). Bond lengths (X–C_2>X–C_1) and the positive charge on carbon-2 support the open-ion structures (Tables 2–4).

3.4.1.2. With one vinyl fluorine on either carbon-1 or carbon-2. Halonium ions from a terminal alkene with a single fluorine on the number-2 carbon have a small X–C_2–C_1 angle (β<56°), where the halogen (X) is more closely associated with the terminal carbon (Table 1, run 3). Therefore, the X–C_1–C_2 (α) bond angle is a better model than the X–C_2–C_1 (β) angle to predict the intermediate, and the open-ion **A** is indicated, although the MP2 geometry is more consistent with the symmetrical structure **C**. The open-ion is supported by bond length and charge distributions (Tables 2–4, run 3). Experimentally, exclusive formation of Markovnikov products in methanol as solvent also support an open-ion intermediate[1] **A** (Table 1, run 3). We suggest that halonium ions from terminal alkenes with a single fluorine on the number-2 carbon are unsymmetrical and open-ion intermediates.

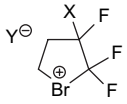
A single fluorine on the terminal carbon (Table 1, run 2) makes the halonium ion more symmetrical as the X–C_1–C_2 and X–C_2–C_1 bond angles are ca. 70°, which suggest structure **C**⇒**D**. Charge distribution (Table 4, run 2) data show that more positive charge is concentrated on carbon-1 than on carbon-2. Our experimental data were best described by the unsymmetrical halonium ion **D** (Table 1, run 2). The calculated geometry is more symmetrical than intermediate **D** and is best described as **C** with some asymmetry associated with **D** (Table 1, run 2). The positive charge density on carbon-1 (Table 4, run 2) supports the formation of anti-Markovnikov products predominately or exclusively in methanol as solvent.[1] We suggest that gas phase reactions of 1-fluoro terminal alkenes with interhalogens will give predominately **aM** products primarily due to the positive charge density on carbon-1 (Table 4, run 2). The bond length data of C_1–X and C_2–X are similar and suggest a rather symmetrical intermediate, while slightly asymmetric structures (**C**⇒**D**) are indicated and supported by charge densities and bond angles (Tables 1 and 4, run 2).

3.4.1.3. With two vinyl fluorines: 1,1- or 1,2-difluoro-terminal alkenes. Two fluorines on the terminal carbon give X–C_2–C_1 bond angles of 83–95° (Table 1, run 4), which place the halogen almost directly above carbon-2. The X–C_2 bond is shorter than the X–C_1 bond (Tables 2 and 3, run 4), and the positive charge on carbon-1 is high (Table 4, run 4), which supports intermediate **E** for the chloronium ion and **E**⇒**D** for the bromonium ion. It is well known that bromine bridges better than chlorine[1,19] and that is confirmed by both B3LYP and B3LYP+PCM calculations, but not by MP2. The positive charge on carbon-1 may induce the lone-pair electrons on both fluorines to back-bond as indicated by the shorter C_1–F bond length and decrease in negative charge on the fluorines (compare the C–F bond lengths in Table 2, run 4 with run 3, and the charges on fluorine Table 4, run 4 with run 3). We did not treat any 1,1-difluoro terminal alkenes with halogens in our earlier paper[1] but it is clear from these calculations that only anti-Markovnikov products would be expected from an open-ion **E**.

Placing a fluorine on carbon-1 and on carbon-2 (Table 1, run 5) moves the halogen closer to the terminal carbon as indicated by the B3LYP+PCM X–C_1–C_2 bond angles of 93°. The larger X–C_2 bond length compared to X–C_1, also supports a structure like **A** (Table 2, run 5). The positive charge is greater on carbon-2 than on carbon-1 and the negative charge of the fluorine on carbon-2 is less than carbon-1 (Table 4, run 5). We did not react a 1,2-difluoro-alkene with halogens in our earlier study[1] but these data suggest that Markovnikov products would be expected from an intermediate like **A** (Table 1, run 5).

3.4.1.4. With three vinyl fluorines: 1,1,2-trifluoro terminal alkenes. The structure of the halonium ions is best represented by **A** when all the vinyl hydrogens are substituted for fluorines (Table 1, run 6). The halogens are above carbon-1 as evidence by the 95–100° bond angles, and structures like **A** are also supported by the longer bond length of the X–C_2 compared to X–C_1 bond (Table 2, run 6). Note, however, that the MP2 bromonium ion geometry is more symmetrical (**E**⇒**D**). Although, we did not experimentally carry out halogenation of an exact model for run 6, we did reactions with the alkene in run 15 and we have experimental data for that compound. The calculated data for runs 6 and 15 (Tables 1–4) are similar and support an open-ion **A** (except for the MP2 prediction for the bromonium ion, as previously noted). Our experimental data (Table 1, run 15) for chlorination and bromination show that significant anti-Markovnikov products are formed and that the **M/aM** product ratios are more consistent for a symmetrical structure like **C**. We explained the large amount of **aM** products as evidence for neighboring group participation of the

number-4 bromine to form five-membered ring tetramethylene bromonium ion intermediates (**F**).[1]



F

The ability to predict the regiochemical product distributions from a calculated three-membered halonium ion is apparent. However, experimental data for the bromination of 4-bromo-1,1,2-trifluorobutene-1 in methanol was not consistent with these calculations.[1] We looked back at our experimental data and noticed that the amount of **aM** product we reported[1] was overstated since 1,3,4-tribromo-3,4,4-trifluorobutane, the major product, trailed into the **aM** peak. These two products, the dibromo addition product and the **aM** bromomethoxy product, could not be resolved by capillary gas chromatography. The **M/aM** ratio of 1/1.3 in Table 1 (run 15 for bromination) was obtained by ^{19}F NMR integration. Our earlier reported value of 1/6.5 suggested structure **C**.[1] Our calculated data support structure **A** for runs 6 and 15 and we speculate that the five-membered tetramethylene halonium ion in run 15 plays a lesser role in this sequence than we described earlier.[1] Thus, a hydrocarbon substituent and a fluorine on the number-2 carbon (Table 1, runs 3, 5, and 6) support open-ion intermediates like **G**. Halonium ions from 4-halo-1,1,2-trifluoro-1-butenes are special cases, which we are continuing to study.

3.4.2. Perfluorocarbon substituents (R=perfluoroalkyl). Changing the hydrocarbon alkyl group of a terminal alkene to a perfluorocarbon destabilizes the positive charge on carbon-2. In fact carbon-2 is generally negative (Table 4, runs 7, 8, 10, and B3LYP+PCM for run 12) unless the carbon-2 contains a fluorine (Table 4, runs 9 and 11), a hydrocarbon (run 15), or a perfluoroether moiety (run 14). The positive charge on the chlorine and bromine is increased (Table 4, runs 7 through 12) when a perfluoroalkyl group replaces a hydrocarbon alkyl group of a terminal alkene.

3.4.2.1. No vinyl fluorines on carbon-1 or carbon-2. Calculations on a terminal alkene with a fluorocarbon alkyl and no vinyl fluorines (Table 1, run 7) show that the halonium ions are somewhat symmetrical by the X–C_2–C_1 and X–C_1–C_2 bond angles. The similar X–C_2 and X–C_1 bond lengths are also consistent with a symmetrical halonium ion (Tables 2 and 3, run 7). The positive charge now resides primarily on the chlorine or bromine (Table 4, run 7). Experimentally 1*H*,1*H*,2*H*-perfluoroalkenes react slowly,[3] and the inability of carbons 1 and 2 to support positive charge is consistent with the sluggish nature of these alkenes toward electrophiles (Table 4, run 7). Our earlier experimental data[1] support the unsymmetrical halonium ion **D** for this reaction (Table 1, run 7). We now believe that more symmetrical intermediates are indicated (**C**⇒**D** or **D**⇒**C**). The anti-Markovnikov products are best accounted for by an S_N2-like ring-opening of the halonium ion at the sterically least hindered carbon-1. Ring-opening of normal halonium ions in the fast product-determining step by a nucleophile or solvent represents an S_N2 reaction with much S_N1 character because of the positive charge localized on the carbon atoms. In alkenes with electron-withdrawing substituents like the model in run 7, the positive charge is on the chlorine or bromine and ring-opening is primarily S_N2.

3.4.2.2. With one vinyl fluorine on carbon-1 or carbon-2. Halonium ions with a perfluoroalkyl group and a single fluorine on the number-2 carbon (Table 1, run 9) appear to be nearly symmetrical (X–C_2–C_1, ca. 65° and X–C_1–C_2, ca. 73°) with the X–C_2 bond length slightly longer than X–C_1 (Tables 2 and 3, run 9). The positive charge is greater on carbon-2 where it can be stabilized by the lone-pair of the fluorine (Table 4, run 9). These data indicate that some Markovnikov product should be formed. Experimentally, however, only anti-Markovnikov product was found for chlorination of 1*H*,1*H*,7*H*-perfluoro-heptene-1 in *tert*-butanol; only a small amount of Markovnikov product resulted from the reaction of chlorine monofluoride in methylene chloride.[2] The experimental product distribution for Cl_2 or ClF in solution was consistent with structure **D**.[1] We now believe that a more symmetrical intermediate like **C** is indicated and that the ring-opening of the halonium ion occurs via an S_N2 reaction at the less sterically hindered carbon-1. Bromine did not react with this electron-deficient alkene[2] by a way of an ionic process, but we predict that the products would be similar to those we found for chlorination.

A single fluorine (Table 1, run 8) on the terminal carbon gives a less symmetrical intermediate (X–C_2–C_1 angle 73–80°), and the X–C_1 bond length is greater than X–C_2 (Tables 2 and 3, run 8), the charge is positive on carbon-1 and negative on carbon-2 (Table 4, run 8). These data suggest an unsymmetrical structure **D** (Table 1, run 8). Experimentally, we did not run a model similar to run 8, but we anticipate substantial amounts of anti-Markovnikov product based on our past experimental data[1–4] and this study. This prediction is based on the intermediate's slight asymmetry and the substantial positive charge on the number-1 carbon, which make the nucleophilic attack on carbon-1 more like an S_N2-like process with some S_N1 character.

3.4.2.3. With two vinyl fluorines: 1,1- or 1,2-difluoro-terminal alkenes. Our compound modeled in run 10 has two vinyl fluorines on the terminal carbon. The halogens are above carbon-2 (X–C_2–C_1; β>90°), (Table 1, run 10), and the X–C_2 bond is considerably shorter than X–C_1 bond (Tables 2 and 3, run 10). Geometrical data and the large positive charge on carbon-1 (Table 4, run 10) support an open-ion structure **E** for 2*H*-perfluoroalkenes (Table 1, run 10). Our data predict that only anti-Markovnikov products would be formed by the capture of the open-ions **E**.

The model in run 11 has a fluorine on carbon-1 and on carbon-2. The bond angle (X–C_2–C_1 ca. 70°, Table 1) and bond length (X–C_1>X–C_2) data (Tables 2 and 3, run 11) point to a structure close to **D**. The positive charges are also larger on carbon-1 than on carbon-2 (Table 4, run 11). This is in contrast to the halonium ions with one fluorine on each carbon when the alkyl group is a hydrocarbon (run 5) where the positive charge is greater on carbon-2. Comparison of these

two structures indicates that the trifluoromethyl reduces the amount of positive charge on carbon-2, and it forces the halonium to become more symmetrical (CH_3=**A**; CF_3= more like **D**). Thus we would predict less **M** products from alkenes like the model in run 11 compared to the model in run 5. Chlorination of (*E*)-1*H*-perfluoroheptene-1 in methanol gave a substantial amount of **M** product[2] (Table 1, run 11; **M/aM**, 1.8/1.0). The amount of **M** product is greater than we would predict based on the symmetry and charge distribution on carbons 1 and 2. Reaction of (*E*)-1*H*-perfluoroheptene-1 was very slow and only 35% of the alkene reacted with chlorine after 2 days.[2] (*E*)-1*H*-Perfluoroheptene-1 was too unreactive for bromine electrophiles, but we anticipate a similar product distribution from bromine since our calculations show that the halonium ions are similar.

3.4.2.4. With three vinyl fluorines: perfluoroalkyl terminal alkenes. The trifluoromethyl group (Table 1, run 12) tightens the bridging in the halonium ion from the perfluoroalkene and places the halogen above carbon-2. The X–C_2 bond is considerably shorter than the X–C_1 bond, and the positive charge is greatly concentrated on carbon-1 (Tables 2–4, run 12). These data clearly predict the nucleophilic attacks on the terminal carbon to give anti-Markovnikov products via intermediate **E** (Table 1, run 12). This structure was confirmed experimentally since only anti-Markovnikov products were found for ionic reaction of perfluoroheptene-1 with chlorine in a protic solvent, and for the ionic reaction of chlorine monofluoride in aprotic solvent.[2] Again bromine did not react by an ionic pathway.

Experimentally, perfluorovinyl ether was most interesting. In this case, we experimentally assigned the intermediate structure **D** for the iodonium ion, structure **C** for the bromonium ion, and **B** for the chloronium ion.[1] Our calculations for the perfluorovinyl ether (Table 1, run 14) are quite similar for both chloronium and bromonium ions, and indicate a structure like **A** (Table 1, run 14). The chloronium ion has slightly more positive charge on carbon-2 than the bromonium ion, and the X–C_1–C_2 bond angle is 2° larger for the chloronium ion. We suggest that these calculated values are too small to account for the large change in product regioisomers for this reaction[1,3] (Table 1, run 14). Based on these calculations and our experimental data, we predict structure **A** for the chloronium ion and probably structure **B** for the bromonium ion since bromine bridges better than chlorine.[1,19]

4. Conclusion

In conclusion, we have shown that the calculated equilibrium geometries best describe the halonium ion intermediates from ionic halogenation of terminal fluoroalkenes. These calculated data support experimental product distributions and can predict product regiochemistry from interhalogen electrophiles (XF; X=I, Br, Cl; BrCl; IBr, ICl, etc.), or by the capture of the halonium ion by solvent. Halonium ion bond angles provide the best correlation with experimental data and are generally supported by bond length and charge densities. Electron-withdrawing alkyl groups tend to decrease the S_N1 character of the product determining the ring-opening transition state and an S_N2-like process occurs, which is more susceptible to steric effects.

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References and notes

1. Shellhamer, D. F.; Allen, J. L.; Allen, R. D.; Gleason, D. C.; O'Neil Schlosser, C.; Powers, B. J.; Probst, J. W.; Rhodes, M. C.; Ryan, A. J.; Titterington, P. K.; Vaughan, G. G.; Heasley, V. L. *J. Org. Chem.* **2003**, *68*, 3932–3937.
2. Shellhamer, D. F.; Titterington, P. K.; Heasley, V. L. *J. Fluorine Chem.* **2003**, *124*, 17–20.
3. Shellhamer, D. F.; Allen, J. L.; Allen, R. D.; Bostic, M. J.; Miller, E. A.; O'Neil, C. M.; Powers, B. J.; Price, E. A.; Probst, J. W.; Heasley, V. L. *J. Fluorine Chem.* **2000**, *106*, 103–112.
4. Shellhamer, D. F.; Horney, M. J.; Pettus, B. J.; Pettus, T. L.; Stringer, J. M.; Heasley, V. L.; Syvret, R. G.; Dobrolsky, J. M., Jr. *J. Org. Chem.* **1999**, *64*, 1094–1098.
5. Shellhamer, D. F.; Gleason, D. C.; Vaughan, G. G.; Ryan, A. J.; Titterington, P. K.; Heasley, V. L.; Lehman, J. J. *J. Fluorine Chem.* **2003**, *123*, 171–176.
6. The contribution of resonance by chlorine was reported for the structure of the chloronium ion from ethylene, see: Amovilli, C.; Floris, F. M.; Mennucci, B. *Int. J. Quantum Chem.* **1999**, *74*, 59–67.
7. Haubenstock, H.; Sauers, R. R. *Tetrahedron* **2004**, *60*, 1191–1196; Teberekidis, V. I.; Sigalas, M. P. *Tetrahedron* **2002**, *58*, 6171–6178.
8. Hamilton, T. P.; Schaefer, H. F. *J. Am. Chem. Soc.* **1990**, *112*, 8260–8265.
9. Rodriquez, C. F.; Bohme, D. K.; Hopkinson, A. C. *J. Am. Chem. Soc.* **1993**, *115*, 3263–3269.
10. Yamabe, S.; Minato, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3339–3344.
11. Brana, P.; Mendez, B.; Fernandez, T.; Sordo, J. A. *Chem. Phys. Lett.* **2000**, *325*, 693–696.
12. Reynolds, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 8676–8682.
13. Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618–622; Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem.* **1976**, *S10*, 1–13; Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 275–280; Bartlett, R. J.; Silver, D. M. *Int. J. Quantum Chem. Symp.* **1975**, *9*, 183–198.
14. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
15. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; Stephens, P. J.; Devlin, F. J.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627; Hertwig, R. H.; Koch, W. *Chem. Phys. Lett.* **1997**, *268*, 345–351; (b) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200–1211.

16. Li, H.; Pomelli, C. S.; Jensen, J. H. *Theor. Chim. Acta* **2003**, *109*, 71–84; Li, H.; Jensen, J. H. *J. Comput. Chem.* **2004**, *25*, 1449–1462; Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117–129; Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094; Cammi, R.; Tomasi, J. *J. Comput. Chem.* **1995**, *16*, 1449–1458.
17. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654; Curtiss, L. A.; McGarth, M. P.; Blandeau, J. P.; Davis, N. E.; Binning, R. C., Jr.; Radom, L. *J. Chem. Phys.* **1995**, *103*, 6104–6113; Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. *J. Comput. Chem.* **1983**, *4*, 294–301.
18. Karpfen, A. *J. Phys. Chem. A* **1999**, *103*, 2821–2827.
19. Peterson, P. E.; Bopp, R. J.; Chevli, D. E.; Curran, E. L.; Dillard, D. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 5902–5911.

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Reaction of (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile with *N*-arylisoindolines

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Dedicated to Professor Howard E. Zimmerman for four decades of friendship

Abstract—In a multistep reaction, 3,3′-(2-aryl-2*H*-isoindol-1,3-ylene)-di-(1,4-naphthoquinone-2-carbonitriles) **13a–f** have been formed in 25–61% yield from a series of *N*-arylisoindolines **8a–f** with (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (**1**) in aerated pyridine. The structure of one of these products (**13f**) has been unambiguously confirmed by a single crystal X-ray structure analysis. Under otherwise the same conditions, 2-(3-methoxyphenyl)-isoindoline (**8g**) and **1** gave 38% of [4-(2,3-dihydro-1*H*-isoindol-2-yl)-2-methoxyphenyl]-1,3-dioxoindan-2-ylidene)acetonitrile (**15**). Rationales for these conversions involving the known rearrangement of the radical anion of **1** into the radical anion of 1,4-naphthoquinone-2,3-dicarbonitrile (**3**) are presented.

1. Introduction

(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (**1**, also referred to as 2-(dicyanomethylene)-1,3-indanedione, see Chart 1) may be considered to be analogous to ethenetetracarbonitrile (**2**) in its reactions. Like the latter it readily adds *N*-nucleophiles such as secondary aliphatic[1] and primary aromatic amines[2] at the dicyanomethylene carbon atom with release of hydrogen cyanide analogously to the corresponding reactions of **2**.[3] Tertiary aromatic amines (like *N*,*N*-dimethylaniline) are prone to attack with their *p*-carbon atom, followed by release of HCN.[2b,4]

Like **2**, acceptor **1** is also able to generate iminium ions **6** from the tertiary cyclic amines **4a** and **4b** in ethanol or acetonitrile solution.[5] Cyanide ion released from the anion **5** in turn intercepts **6** to generate the α-cyanated amines **7** (Scheme 1).[5]

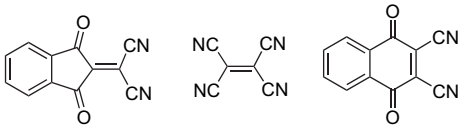
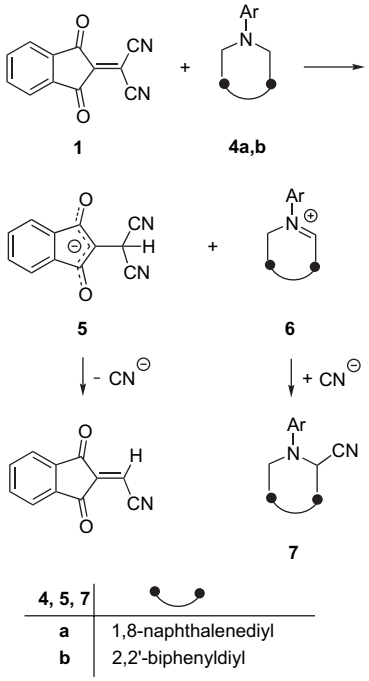


Chart 1.



Ar = R-C_6H_4 with R = H, 4-Me, 4-OMe, 4-Cl

Scheme 1.

Keywords: Donor–acceptor interactions; 2*H*-Isoindoles; Merocyanines; Rearrangement; Radical ions; X-ray crystal structure analysis.
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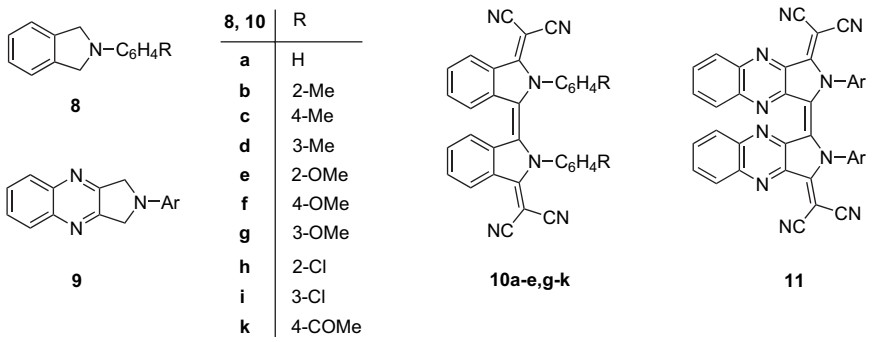


8, 10	R
a	H
b	2-Me
c	4-Me
d	3-Me
e	2-OMe
f	4-OMe
g	3-OMe
h	2-Cl
i	3-Cl
k	4-COMe

Chart 2.

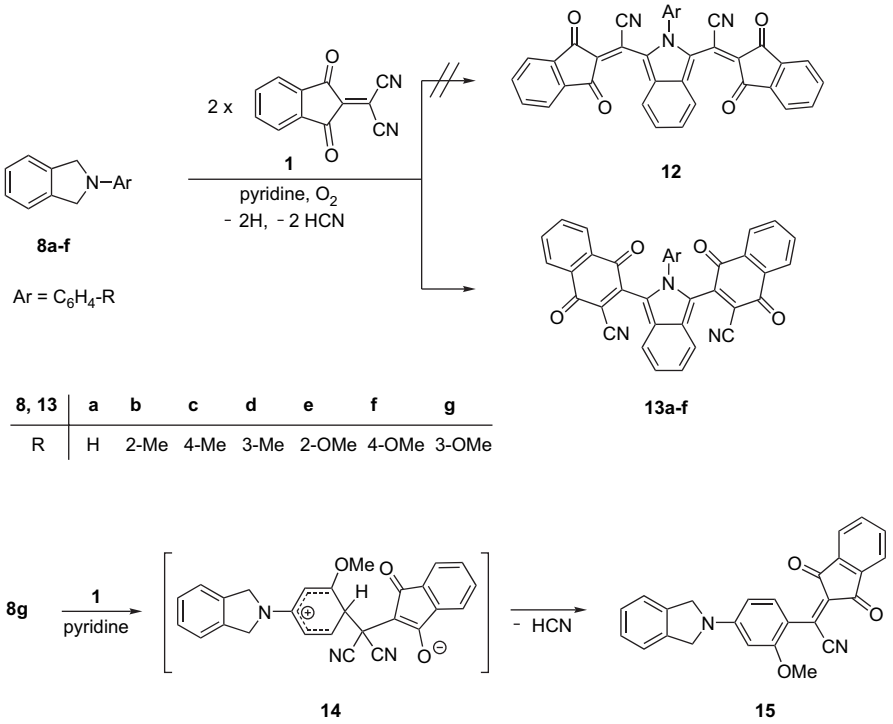
Recently we have reported an efficient transformation of 2-arylisoindolines (2-aryl-1,3-dihydro-2*H*-isoindoles) **8a–e**,**g–k** with **2** into the *cis*-isoindigo like compounds **10**[6] (Chart 2). Closely analogous compounds **11** had been obtained from dihydropyrrolo[3,4-*b*]quinoxalines **9** and **2**.[7] Also (2,4,7-trinitro-9*H*-fluoren-9-ylidene)propanedinitrile has acted as an dicyanomethylenating agent on isoindolines **8**.[8]

This paper is focused on the reactions of the acceptor **1** with isoindolines **8**. The latter compounds and the aforementioned amines **4a** and **4b** (Scheme 1) have in common the methylene groups α to nitrogen that do enjoy benzylic activation, and **4b** may be looked at as a phenylene homologue of **8**.[5] We therefore were interested in clarifying how **1**, which needs to be treated in context with its isomeric quinone **3**[9] (see chart 1), reacts with isoindolines **8**.

2. Results

Solutions of **8a–g** (1 mmol each) in 10 mL of dry pyridine were added dropwise to solutions of **1** (2 mmol) in 20 mL of the same solvent. The mixtures were gently warmed to 50–60 °C and kept at this temperature for 3 h with stirring and admission of air and were finally warmed to 100 °C for 3 min. The residue obtained from concentration at 50 °C consisted of a complex mixture containing a deep blue main component and numerous coloured byproducts each in small quantities. From their gross composition and spectroscopic evidence the main products from **8a–f** were found to be formed from two molecules of **1** and one molecule of **8a–f** by loss of 2H and two molecules of HCN. Thus, both a net didehydrogenation and a twofold reaction analogous to a tricyanovinylation[3] were suspected to have taken place at C-1 and C-3 of **8**.

Therefore, structure **12** (Scheme 2) was assigned to the main products first but later, mainly on the basis of a single crystal X-ray structure determination of **13f**, replaced by **13**. Thus the skeletal rearrangement of reactant **1** to the connectivity of the quinone **3** had taken place under the reaction conditions, a phenomenon observed earlier in a different context by Bryce et al.[9]



8, 13	a	b	c	d	e	f	g
R	H	2-Me	4-Me	3-Me	2-OMe	4-OMe	3-OMe

Scheme 2.

Table 1. Visible absorptions of compounds **13a–f** in acetonitrile

13	a	b	c	d	e	f
λ_{max} [nm]	648	660	650	648	668	654
log ε	3.9	4.0	4.1	3.9	4.0	4.2

The visible absorptions in acetonitrile solution are around 650 nm for **13a**,**c**,**d** and **f** and somewhat higher for **13b** and **13e** bearing *o*-substituted phenyl groups on the isoindole nitrogen (Table 1). The IR spectra are characterized by weak CN-absorptions (2220–2230 cm^{-1}) characteristical for CN groups in systems heavily substituted with polar electron attracting groups[10] and two carbonyl absorptions (1675–1665 and 1660–1645 cm^{-1}) as expected.

NMR spectroscopy was hampered by insufficient solubility in $CDCl_3$, so CD_3NO_2 and DMF-d_7 had to be used. Raising the temperature to 70 °C (in the cases of **13b** and **13f**) did improve the solubility but was insufficient to accelerate internal rotations to a suitable extent to simplify spectra. In general, partial decomposition and/or precipitation had been observed when long measuring times had to be applied. Still, both the ^1H and ^{13}C NMR spectra (we restrict the presentation to the two examples **13b** and **13f**) are in accord with the proposed structures.

Unambiguous support for these came from the X-ray structure analysis of **13f** (see Fig. 1 and Table 2, note that the crystallographic numbering does not reflect the systematic numbering). Since the molecule **13f** from its connectivity may be divided in two symmetrical halves, the emphasis in Table 2 has been laid on grouping corresponding bonds and angles within or close to the main chromophore. The sum of the angles around the isoindole N atom (C1–N1–C9, C8–N1–C9 and C1–N1–C8) is close to 360° suggesting planarity around N1. Due to steric encumbering there is a substantial twisting of the anisyl and naphthoquinonyl groups out of the plane of the isoindolylene moiety. Least squares planes for these groups have been defined as follows: Plane 1 (pyrrol ring) by N1–C1–C2–C7–C8, plane 2 (anisyl group) by C9–C10–C11–C12–C13–C14, plane 3 (C1-naphthoquinonyl) by C16–C17–C18–C23–C24–C25 and plane 4 (C8-naphthoquinonyl) by C36–C37–C38–C43–C44–C45. The twist angles with respect to plane 1 are 53.99(3)° for the anisyl group (plane 2), 41.07(2)° and 48.84(2)° for the C1- and C8-naphthoquinonyl groups (planes 3 and 4), respectively.

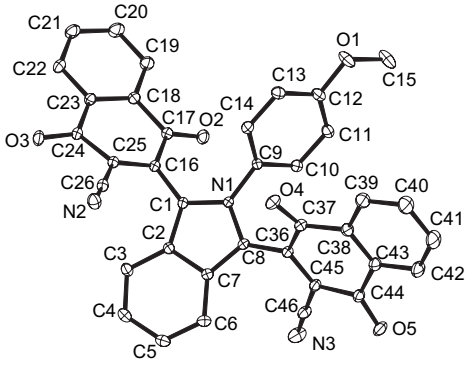


Figure 1. Molecular structure of compound **13f** in the crystal. The crystallographic numbering does not reflect the systematic numbering. Anisotropic displacement parameter ellipsoid is drawn at 50% probability.

Table 2. Selected bond lengths and bond angles of compound **13f**

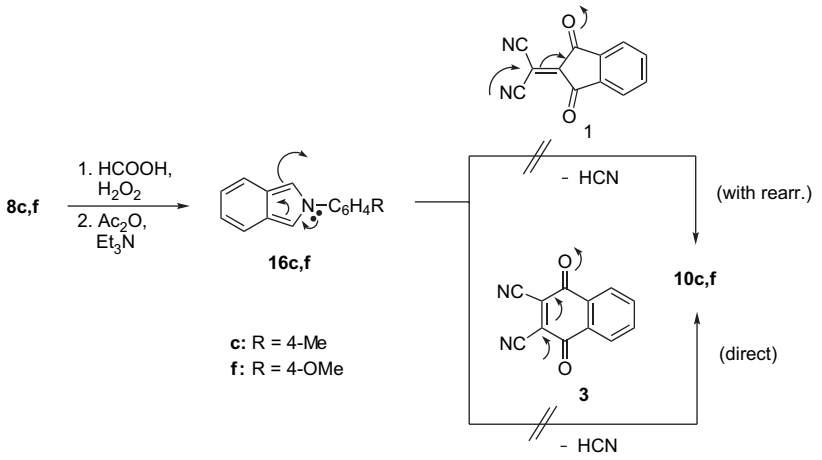
Bond lengths (Å):			
C4–C5	1.4166(15)	C2–C7	1.4247(13)
Bond lengths listed in pairs of corresponding bonds (Å)			
C1–C2	1.4212(13)	C7–C8	1.4115(13)
C2–C3	1.4120(14)	C6–C7	1.4132(13)
C3–C4	1.3754(14)	C5–C6	1.3733(15)
C1–N1	1.3797(12)	C8–N1	1.3692(12)
C1–C16	1.4359(13)	C8–C36	1.4514(13)
C16–C17	1.5060(13)	C36–C37	1.5111(14)
C17–O2	1.2174(12)	C37–O4	1.2172(12)
C16–C25	1.3719(25)	C36–C45	1.3570(13)
C25–C26	1.4349(14)	C45–C46	1.4375(14)
C26–N2	1.1529(14)	C46–N3	1.1486(14)
C24–C25	1.4753(13)	C44–C45	1.4853(13)
C24–O3	1.2270(12)	C44–O5	1.2210(12)
Bond angles (°), listed in pairs of corresponding angles			
C1–N1–C8	110.36(8)		
C1–N1–C9	127.66(8)	C8–N1–C9	121.93(8)
N1–C1–C16	127.09(9)	N1–C8–C36	128.29(9)
C2–C1–C16	125.79(9)	C7–C8–C36	128.29(9)
C2–C1–N1	107.12(8)	C7–C8–N1	108.32(8)
C1–C16–C17	122.19(8)	C8–C36–C37	117.72(8)
C1–C16–C25	118.99(9)	C8–C36–C45	122.94(9)
C17–C16–C25	118.56(8)	C37–C36–C45	118.91(9)

In contrast to the results with **8a–f**, a different product (**15**) was obtained from **8g** (Scheme 2, bottom). The gross formula $C_{26}H_{18}N_2O_3$ is confirmed by its mass spectrum (M^+ at m/z=406), which also shows fragments for loss of CN and CO. The ^1H NMR clearly demonstrates the isoindoline structure by the presence of a 4H singlet at 4.81 ppm (in $CDCl_3$) for the methylene protons and a negative signal in the ^{13}C DEPT 135 spectrum at 55.2 ppm. Also, the ^{13}C carbonyl resonances (in CD_3NO_2) are found at 188.1 and 189.0 ppm compared to 160 ppm (in DMF-d_7) for **13f**. It should be pointed out that from this spectral information the indanedione moiety had not been rearranged to a quinonyl residue as in **13a–f**. In addition, it was corroborated in a separate test experiment that **8g** and the quinone **3** in pyridine did not form **15**, which therefore is the product of an electrophilic attack of the exocyclic methylene C of **1** on the phenyl p-C of **8g** with release of HCN analogous to a tricyanovinylation.[4]

3. Discussion

Clearly, the transformation of **8a–f** with **1** to **13a–f** must involve a multitude of steps and is necessarily complex. Moderate yields as found and based throughout on the amount of starting material **8** used are therefore acceptable, and it will not be possible—except when unduly large efforts are made—to identify every byproduct and to clarify all details. Therefore, we will concentrate on the interplay between formation of the main products and the necessary skeletal rearrangement **1**→**3** in the light of the findings reported by Bryce et al.[9] who had demonstrated that **1** is isomerized to **3** when brought in contact with electron donors, e.g., tetrathiafulvalene.[9c]

It had been reported earlier[11] that isoindolines **8a**, **8c** and **8f** as well as other *p*-substituted 2-phenylisoindolines of type **8**



Scheme 3.

react with quinone **3** in ethyl acetate under admission of air to form *N*,*N*-diarylisoindigo structures and *not* compounds of type **13**. On the other hand, it has been known for more than half a century that quinones tend to abstract hydride ions from suitable donors giving eventually didehydrogenated products thereof,[12] and that this initial hydride abstraction may in fact be a two-step process involving radicals.[13] It was therefore felt necessary to rule out that a dehydrogenation of **8** to the corresponding 2*H*-isoindoles (like **16b** and **16c**) occurred and that these isoindoles react with either **1** or its isomer **3** (if formed under our reaction conditions). To test this possibility, 2-(4-methylphenyl) (**16c**) and 2-(4-methoxyphenyl)-2*H*-isoindole (**16f**) have been prepared according to the procedures published by Kreher.[14] Isoindole **16f** was chosen in spite of the low yield to be expected[14] in its preparation. To our surprise, neither **16c** nor **16f** gave the corresponding products **13c** and **13f**, respectively, upon reaction with doubled molar amounts of either **1** or **3** in aerated pyridine at 50–60 °C (Scheme 3). At this occasion, quinone **3** was found to be less stable than **1** in pyridine. These findings rendered the isoindoles **16** unlikely as intermediates.

Another point of concern is the fact that in **13** *two* quinonyl residues are attached to the isoindole skeleton with release of two molecules of HCN and thus these two consecutive introductions of the quinonyl residues have to be of equal (or almost equal) probability. It is hard to see how either **1** or **3** could react with isoindoles **16** in this way, since the introduction of the first quinonyl residue by whatever mechanism would decrease the electron richness of the isoindole unit due to conjugation with an acceptor and thus hamper the introduction of the second. Thus, 2*H*-isoindoles as **16a** and **16f** had to be ruled out as intermediates.

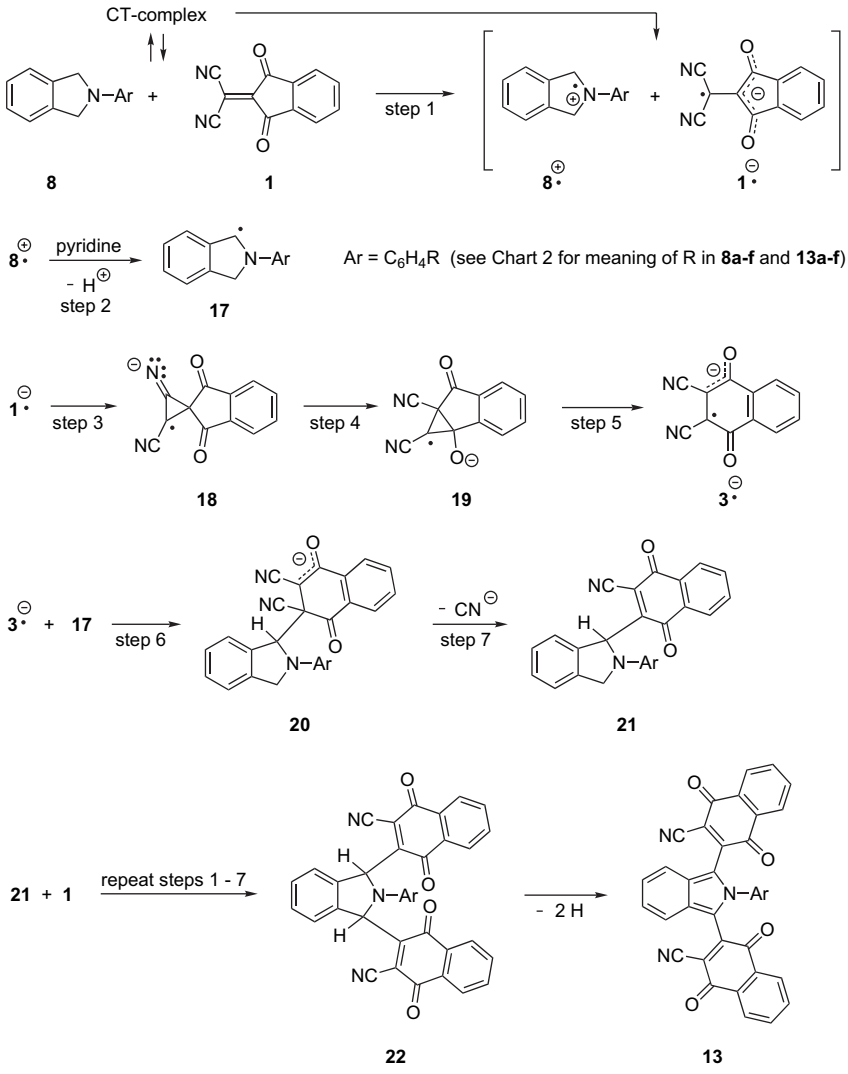
A rationale in accord with all findings and considerations is presented in Scheme 4. Charge transfer complexation of **8a–g** with **1** in dichloromethane has been observed[15] and may as well be operating in pyridine. Formation of a radical ion pair [$\mathbf{1}^{\bullet-}$/$\mathbf{8}^{\bullet+}$] may be envisaged (analogous to such ion pair formation from **2** and *N*,*N*-diethylaniline[16]) as the first chemical event, which is made likely by the observation of a green colouration attributed to the radical anion $\mathbf{1}^{\bullet-}$.[9] Next, the solvent pyridine abstracts a proton from the radical cation $\mathbf{8}^{\bullet+}$ to generate the α-amino radical **17**. In this way, back electron transfer with regeneration of the starting materials **1** and **8** is retarded. The anion radical $\mathbf{1}^{\bullet-}$ undergoes rearrangement[9] via intermediates **18** and **19** (steps 3–5) to form the anion radical $\mathbf{3}^{\bullet-}$, which combines with **17** to form **20**, which in turn by release of cyanide ion generates **21** (steps 6 and 7). In the latter compound, 3-CH_2 has a similar reactivity as 1-CH_2 had before, so steps 1–7 may well be repeated using the second molecule of **1**. At the end, the dihydroproduct **22** is didehydrogenated to **13** by air or any residual **1** or **3**.

In this treatment so far the introduction of the quinonyl groups into the products **13** is linked to the isomerization of **1** to the quinone structure. It could be argued, though, that the rearrangement of **1**→**3** could well take place independently and that isoindolines **8** would be attacked later by the quinone **3**. To test this possibility, **8f** was reacted with twofold molar amounts of **1** and **3** at otherwise the same conditions as in the preparative runs but in parallel semi-micro experiments. Whereas the preparative reaction between **8f** and **1** (see above) was perfectly matched, no **13f** was ever formed in the reactions of **8f** with **3**.

The question remains why **8g** does not follow the reaction pattern shown by **8a–f**. No formation of a product of type **13** is ever observed, also in semi-micro trials to react **8g** with **3**. Since **15** cannot be obtained from **8g** and the quinone **3**, its structure must be that of an indanedione and not that of a quinone derivative. Indeed, **8g** is the most suitable starting material (among **8a–g**) for electrophilic attack by **1** at the phenyl C-4 since the isoindoline nitrogen and the 3-methoxy group do combine their +M effects to stabilize intermediate **14** (Scheme 2) and thus the electron transfer process typical for **8a–f** and required for the formation of **13a–f** is no longer competitive.

4. Conclusion

Novel and interesting diquinone structures have been obtained from the interaction of electron rich 2-arylisoindolines **8** with the TCNE-analogous acceptor 2-(dicyanomethylene)-indane-1,3-dione (**1**). The skeletal rearrangement of **1** into a structure derived from **3**[9] is connected with the introduction of the



Scheme 4.

quinonyl residues at C-1 and C-3 of the starting materials. An independent isomerization of **1**→**3** prior to reaction of the acceptor with either the starting materials **8** or their dehydrogenation products **16** is not required. While in the work of Bryce[9] the radical anion of **3** functions as the counterion to a cation derived from an organic donor within a salt, it has in this work been covalently bonded to an α-amino radical followed by loss of cyanide. It is also noteworthy that **1** does not, to a measurable extent, act as a cyanating agent on C-1/C-3 of **8** analogously as it does in the cyanation of the cyclic amines **4a** and **4b**[5] (Scheme 1).

The cyanine-like character of compounds **15** has been pointed out earlier,[4a–c] thus **15** and as well **13** may be classified as merocyanines.[17] Two isoindole based merocyanines with *N*-phenylrhodanine as acceptor moiety have been described.[18]

5. Experimental

5.1. General

Mp's were determined with a Reichert Thermovar hot stage microscope and are uncorrected. The UV–vis spectra were recorded on a Perkin–Elmer 554 spectrometer and the IR spectra on Perkin–Elmer 397 and Bruker Vector 22 spectrometers using potassium bromide pellets; band intensities, s strong, w weak. ^{1}H 300 MHz and ^{13}C NMR 75 MHz spectra were recorded on a Bruker WM 300 instrument, 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra on a Bruker DRX 500 spectrometer. Chemical shifts are expressed as δ [ppm] with reference to tetramethylsilane as an internal standard, s=singlet, d=doublet, dd=doublet of doublets and m=multiplet. ^{13}C assignments (qC=sp^2 quaternary carbon atoms) were made with the aid of DEPT 135/90 spectra. For EI (70 eV) mass spectra Varian MAT 311 and AMD 605 instruments were used. Elemental analyses were run on a Carlo Erba 1106 CHNS analyzer. For preparative layer chromatography (plc) 1.0 mm thick air-dried layers of slurry applied silica gel Merck PF_{254} on 48 cm wide and 20 cm high glass plates were used, zones were detected by their colour and indicator fluorescence quenching upon exposure to 254 nm light and extracted with acetone.

5.2. Starting materials

2-Aryl-2,3-dihydro-1*H*-isoindoles (=2-arylisoindolines) **8a–g** and two 2*H*-isoindoles (**16c** and **16f**) were prepared

Table 3. ^{1}H chemical shifts (δ_H) of compounds **8a**,**c**,**d**,**f** and **g** (300 MHz)

8	Solvent	Isoindoline protons			*N*-Phenyl protons					Other protons	
		1-H/3-H	4-,5-,6-,7-H		2′-H	3′-H	4′-H	5′-H	6′-H		
			AA′	BB′							
a	$CDCl_3$	4.63	7.30		6.70	7.30	6.75	7.30	6.70	—	
	DMSO-d_6	4.58	7.39	7.30	6.67	7.23	6.64	7.23	6.67		
c	$CDCl_3$	4.61	7.30		6.60	7.11	—	7.11	6.60	4′-Me	2.28
	DMSO-d_6	4.54	7.38	7.30	5.75	7.05	—	7.05	5.75		2.20
d	$CDCl_3$	4.64	7.31		6.51	—	6.58	7.20	6.49	3′-Me	2.36
	DMSO-d_6	4.56	7.38	7.30	6.48s[a]	—	6.48m[a]	7.11dd	6.48m[a]		2.27
f	$CDCl_3$	4.61	7.31		6.64	6.78	—	6.78	6.64	4′-MeO	3.78
	DMSO-d_6	4.52	7.38	7.29	6.62	6.87	—	6.87	6.62		3.67
g	$CDCl_3$	4.63	7.31		6.22	—	6.32	7.21	6.32	3′-MeO	3.83

[a] Accidentally superimposed.

according to the procedures published by Kreher.[14] The ^{1}H spectral data ($CDCl_3$ as solvent) of **8a–g** were in full accord with the published data,[14] in addition, the ^{1}H NMR spectra of **8a–f** have been recorded in DMSO-d_6 (Table 3). In this solvent the AA′BB′ systems of 4-H–7-H appear as baseline separated AA′ and BB′ parts instead of narrow multiplets. ^{13}C NMR 75 MHz spectra have also been recorded (Table 4).

Compound **8a**: 2-phenyl-, mp 170–171 °C (lit.[14] 172–173 °C); *Compound* **8b**: 2-(2-methylphenyl)-, bp 118–120 °C/1.33×10^{-2} mbar (lit.[14] 117 °C/1.33×10^{-2} mbar); *Compound* **8c**: 2-(4-methylphenyl)-, mp 190–192 °C (lit.[14] 193 °C); *Compound* **8d**: 2-(3-methylphenyl)-, mp 105–106 °C (lit.[14] 111 °C); *Compound* **8e**: 2-(2-methoxyphenyl)-, bp 136–138 °C/1.33×10^{-2} mbar (lit.[14] 133–135 °C/1.33×10^{-2} mbar); *Compound* **8f**: 2-(4-methoxyphenyl)-, mp 218–220 °C (lit.[14] 219 °C); *Compound* **8g**: 2-(3-methoxyphenyl)-, mp 121–122 °C (sublimed, lit.[14] 120 °C, lit.[19] 115–117 °C).

2-(4-Methylphenyl)-2*H*-isoindole (**16c**) greyish crystals, mp 172–173 °C (lit.[14] 171 °C); 2-(4-methoxyphenyl)-2*H*-isoindole (**16f**), cream-coloured crystals, mp 174–176 °C (lit.[14] 176 °C) with rapid sublimation. Upon ice/salt cooling, the mother liquor of **16f** gave another precipitate of mp 116–123 °C (lit.[14] 114 °C), which is probably 2-(2-acetoxy-4-methoxyphenyl)-2,3-dihydro-1*H*-isoindole. Compounds **16c** and **16f** were stored at −18 °C under nitrogen.

2-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile ('dicyanomethyleneindane-1,3-dione', **1**) was prepared according to Chatterjee,[20] yellow crystals, mp 282–284 °C (with decomposition, block preheated to 260 °C, lit.[20] 280–285 °C with decomp.). IR (KBr): $\tilde{\nu}$ = 2220w(CN), 1705s (C═O) cm^{-1}. ^{1}H NMR (CD_3NO_2) 300 MHz: δ= 8.16 (AA′BB′, aryl H); ^{13}C NMR (CD_3NO_2) 75 MHz: δ=91.4 (C-2), 111.8 (CN), 126.1 (C-5′, C-6′), 139.8 (C-4′, C-7′), 143.3 (C-3a′, C-7a′), 153.5 (C-2′), 184.3 (C-1′, C-3′).

1,4-Naphthoquinone-2,3-dicarbonitrile (**3**) was prepared according to Chatterjee,[21] yellow crystals, mp 278–279 °C (with rapid sublimation and slight decomp., lit.[21] 270–271 °C, from di-chloromethane). IR (KBr): $\tilde{\nu}$ = 2235w(CN), 1676s (C═O), 1603 and 1584 cm^{-1} (aryl and C═C). ^{1}H NMR (CD_3NO_2) 300 MHz: δ=8.21 (m, AA′, 5-H, 8-H), 8.04 (m, BB′, 6-H, 7-H). ^{13}C NMR (CD_3NO_2) 75 MHz: δ=112.6 (CN), 129.0 (C-5, C-8), 131.4 (C-4a, C-8a), 132.1 (C-2, C-3), 137.6 (C-6, C-7), 178.4 (C-1, C-4).

5.3. Reactions of 2-arylisoindolines 8a–g with 1

5.3.1. General procedure. To a solution of **1** (416 mg, 2.0 mmol) in dry pyridine (15 mL) a solution of **8a–g** (1.0 mmol each) in 5 mL of pyridine was added dropwise over 5 min at room temperature with stirring and admission of air. The mixture was warmed gently to 50–60 °C and kept at this temperature with stirring and admission of air for 3 h, then warmed to max. 100 °C for few minutes and concentrated to dryness at 50 °C. The residue was taken up several times with cold ethanol (10 mL) and the slurry was concentrated again to remove any residual pyridine. The solid was then taken up in hot methanol, and the solution was filtered.

Table 4. ^{13}C chemical shifts (δ_C) of compounds **8a**,**c**,**d**,**f** and **g** (75 MHz)

8	Solvent	Isoindoline carbon atoms				*N*-Phenyl carbon atoms						Other C-signals	
		1,3	4,7	5,6	3a,7a	1′	2′	3′	4′	5′	6′		
a	$CDCl_3$	53.7	122.6	127.1	137.9	147.1	111.6	129.4	116.1	129.4	116.1	—	
	DMSO-d_6	53.5	122.8	127.3	137.8	147.2	111.9	129.3	116.1	129.3	111.9	—	
c	$CDCl_3$	53.7	122.6	127.1	138.0	145.2	111.6	129.9	125.2	129.9	111.6	4′-Me	20.3
	DMSO-d_6	53.5	122.8	127.2	138.0	145.3	111.9	129.8	124.5	129.8	111.9		20.2
d	$CDCl_3$	53.8	122.6	127.1	138.0	147.2	112.3	139.1	117.2	129.2	108.8	3′-Me	21.9
	DMSO-d_6	53.5	122.8	127.2	137.9	147.2	112.5	138.3	117.0	129.2	109.2		21.7
f	$CDCl_3$	54.3	122.5	127.1	138.3	142.2	112.4[a]	115.3	151.3	115.3	112.4	4′-OMe	56.0
	DMSO-d_6	54.0	122.8	127.2	138.2	142.1	112.7	115.1	151.1	115.1	112.7		55.6
g	$CDCl_3$	53.8	122.6	127.2	137.9	148.5	104.8	160.9	98.0	130.1	101.3	3′-OMe	55.1

[a] Broadened.

This operation was repeated four times. Filtrates and extracts were combined and concentrated to dryness and the residue was dissolved in acetone (5 mL). This solution in each case was applied to 5 plc-plates and developed with cyclohexane/ethyl acetate (4:1) for the run with **8a**, toluene/ethyl acetate (5:1) for the run with **8f**, and toluene/ethyl acetate (10:1) for all other runs. Intense blue main zones (from **8a–f**) and the purple main zone from **8g** were extracted and the residue subjected to repeated plc with the same solvents. Crystallization from acetonitrile afforded pure samples of **13a–f**, all appearing black (but tinted to some extent) with a metallic shine in incident light, but giving blue solutions in acetonitrile, ethyl acetate, chloroform or methanol. Numerous other mostly coloured zones were observed but it always contained too little material to allow for isolation of significant amounts and had to be discarded as well as the tarry materials remaining at the start line.

5.3.2. 3,3′-(2-Phenyl-2*H*-isoindol-1,3-ylene)-di-(1,4-naphthoquinone-2-carbonitrile) (13a). Black crystals, mp 331–332 °C, 139 mg (25%). IR: $\tilde{\nu}$ = 2210w (CN), 1670 and 1655 (C═O), 1585 and 1550 (aryl and C═C), 1273 cm^{-1}. ^1H NMR (CD_3NO_2) 300 MHz δ=7.22–7.36 (m, 3H, isoindolylene 6-H, 7-H and phenyl 4-H), 7.44–7.52 (m, 4H, phenyl 2-, 3-, 5-, 6-H), 7.70–7.91 (partially broadened m, 8H, isoindolylene 4-H, 7-H and 6 naphtho H), 8.12–8.19 (m, 2H, naphtho H). MS: *m/z* (%)=555 (M^+, 100), 528 (37), 502 (20), 373 (6), 347 (9), 104 (23). Anal. Calcd for $C_{36}H_{17}N_3O_4$: C, 77.83; H, 3.08; N, 7.56. Found: C, 77.84; H, 3.00; N, 7.63.

5.3.3. 3,3′-[2-(2-Methylphenyl)-2*H*-isoindol-1,3-ylene]-di-(1,4-naphthoquinone-3-carbonitrile) (13b). Black-red crystals, mp 314–315 °C, 308 mg (54%). IR: $\tilde{\nu}$ = 2210 (CN), 1675 and 1660 (C═O), 1585 and 1540 (aryl, C═C), 1270 cm^{-1}. ^1H NMR (CD_3NO_2, 297 K) 300 MHz δ=2.20 (s, 3H, CH_3), 7.05–7.20 (m, 2H, isoindolylene 5-H, 6-H), 7.35–7.65 (m, 4H, phenyl 3-, 4-, 5-, 6-H), 7.70–7.95 (m, 8H, isoindolylene 4-H, 7-H and 6 naphtho-H), 8.00–8.25 (m, 2H, naphtho H). (DMF-d_7, 343 K): δ=2.26 (broadened, 3H, CH_3), 7.15 (m, 3H, isoindolylene 5-H, 6-H and 1 phenyl H), 7.45 (m, 2H, phenyl H), 7.51 (m, 1H, phenyl H), 7.74 (broadened, 2H, isoindolylene 4-H, 7-H), 7.79–8.05 (m, 6H, naphtho H) and 8.12 (m, 2H, naphtho H). ^{13}C NMR (DMF-d_7, 343 K) 75 MHz δ=18.02 (CH_3); signals for sp^2 *C*H (for 2C each) at 121.9, 126.0, 127.0, 127.3, 135.4, 135.5 and for 1C each at 126.8, 129.9, 131.0 and 131.9 (all phenyl); signals for qC (all broadened, 2 qC each) at 132.2 (C-3a, C-7a), 132.7, 136.7, 137.9, weak and broadened signals at 179 and 181 (C═O), two signals for 2qC each and two signals for 1qC each could not be determined, also CN resonances were not detected. MS: *m/z* (%)=569 (M^+, 100), 554 (8), 543 (16), 517 (4), 399 (7), 387 (55), 361 (7), 284 (7), 104 (23), 76 (31). Anal.: See below.

5.3.4. 3,3′-[2-(4-Methylphenyl)-2*H*-isoindol-1,3-ylene]-di-(1,4-naphthoquinone-2-carbonitrile) (13c). Black-red crystals, mp 321–323 °C, 239 mg (42%). IR: $\tilde{\nu}$ = 2210w (CN), 1670–1650 (C═O), 1590 and 1540 (aryl and C═C), 1270 cm^{-1}; ^1H NMR (CD_3NO_2) 300 MHz δ=2.20 (s, 3H, CH_3), 7.05–7.18 (m, 2H, isoindolylene 5-H, 6-H), 7.28–7.55 (m, 4H, 2-, 3-, 5-, 6-H), 7.70–8.00 (partly broadened m, 8H, isoindolylene 5-H and 6-H and 6 naphtho H), 8.10–8.20 (m, 2H, naphtho H). MS: *m/z* (%)=569 (100, M^+), 554 (4), 543 (22), 517 (13), 486 (8), 361 (21), 284 (10), 104 (14), 76 (42). Anal.: See below.

5.3.5. 3,3′-[2-(3-Methylphenyl)-2*H*-isoindol-1,3-ylene]-di-(1,4-naphthoquinone-2-carbonitrile) (13d). Black crystals, mp 282–283 °C, 182 mg (32%). IR: $\tilde{\nu}$ = 2210w (CN), 1680–1665 and 1650 (C═O), 1580 and 1530 (aryl and C═C), 1270 cm^{-1}. ^1H NMR (CD_3NO_2) 300 MHz δ=2.15 (s, 3H, CH_3), 7.08–7.55 (series of 5 mostly broadened m, 8H, isoindolylene 4-, 5-, 6-, 7-H and phenyl 2-, 4-, 5-, 6-H), 7.66–7.92 (partially broadened m, 6H, naphtho H), 8.16–8.20 (m, 2H, naphtho H). MS: *m/z* (%)=569 (100, M^+), 554 (5), 543 (29), 517 (13), 387 (8), 361 (24), 104 (83), 76 (44). Anal. Calcd for $C_{37}H_{19}N_3O_4$: C, 78.02; H, 3.36; N, 7.37. Found: **13b**: C, 77.94; H, 3.33; N, 7.50. **13c**: C, 77.83; H, 3.22; N, 7.48. **13d**: C, 77.88; H, 3.35; N, 7.29.

5.3.6. 3,3′-[2-(2-Methoxyphenyl)-2*H*-isoindol-1,3-ylene]-di-(1,4-naphthoquinone-2-carbonitrile) (13e). Purple-black crystals, mp 327–328 °C, 357 mg (61%). IR: $\tilde{\nu}$ = 2210w (CN), 1665–1650 (C═O), 1585–1545 (aryl and C═O), 1270 cm^{-1}. ^1H NMR (CD_3NO_2) 300 MHz δ=3.75 (s, 3H, OCH_3), series of 4 sharp lined m at 6.75–7.30 (3H, isoindolylene 5-H, 6-H and 1 phenyl H), 7.31–7.55 (3H, phenyl H), 7.65–8.00 (8H, isoindolylene 4-H, 7-H and 6 naphtho H), 8.05–8.25 (2H, naphtho H). MS: *m/z* (%)=585 (100, M^+), 570 (7), 554(9), 528 (9), 502 (4), 403 (22), 389 (13), 76 (33). Anal.: See below.

5.3.7. 3,3′-[2-(4-Methoxyphenyl)-2*H*-isoindol-1,3-ylene]-di-(1,4-naphthoquinone-2-carbonitrile) (13f). Black-red crystals, mp 337–338 °C, 275 mg (47%). IR: $\tilde{\nu}$ = 2210w (CN), 1670–1660 and 1645 (C═O), 1590, 1530 and 1503 (aryl and C═C), 1272 cm^{-1}. ^1H NMR (CD_3NO_2) 300 MHz δ=3.68 (s, 3H, OCH_3), 6.74–6.95 (m, 2H isoindolylene 5-H, 6-H), 7.30–7.58 (m, 4H, phenyl H), 7.70–8.00 (m, 8H, isoindolylene 4-H, 7-H and 6 naphtho H), 8.10–8.28 (m, 2H, naphtho H). ^1H NMR (DMF-d_7, 297 K) 500 MHz δ=3.68 (s, 3H, OCH_3), 6.89 (m, 2H, isoindolylene 5-H, 6-H), 7.47 (m, 2H, phenyl 3-, 5-H); the following low-field signals for isoindolylene and naphtho H were all structureless and broadened: 7.66 (3H), 7.80–8.10 (7H), 8.17 (2H). ^1H NMR (DMF-d_7, 343 K) 500 MHz δ=3.68 (s, 3H, OCH_3), 6.88 (m, 2H, isoindolylene 5-H, 6-H), 7.41 (dd, *J*=9.0 and 2.5 Hz, 2H, phenyl 3-H, 5-H), all other signals were broadened and structureless: 7.51 (2H, phenyl 2-H, 6-H), 7.70 (2H, isoindolylene 4-H, 7-H); the naphthoquinonyl H gave multiplets at 7.82 (2H), 7.92 (4H) and 8.13 (2H). ^{13}C NMR (DMF-d_7, 297 K) 125 MHz δ=55.9 (OCH_3); sharp sp^2 *C*H resonances (for 2C each) at 115.5, 121.9, 125.7 and as broadened signals for 2C each: 126.9, 127.2, 129.1, 135.3, 135.6; several unresolved resonances for qC at 132.1–133.5, 160.0 (C═O, only one signal observed), no CN signals. (DMF-d_7, 343 K): δ=55.9 (OCH_3), sp^2 *C*H signals (for 2C each) at 115.6, 121.8, 125.8, 127.0, 127.3, 129.5 (broadened), 135.4, 135.5; several broad unresolved signals for qC at 132.0–133.5, 160.4 (C═O, only one signal observed), no CN signals. MS: *m/z* (%)=585 (100, M^+), 570 (5), 543 (20), 528 (13), 502 (3), 403 (8), 104 (38), 76 (35). Anal. Calcd for $C_{37}H_{19}N_3O_5$: C, 75.89; H, 3.27; N, 7.17. Found: **13e**: C, 75.70; H, 3.00, N, 713. **13f**: C, 75.91; H, 3.22; N, 7.19.

5.3.8. [4-(2,3-Dihydro-1*H*-isoindol-2-yl)-2-methoxyphenyl]-(1,3-dioxoindan-2-ylidene)-acetonitrile (15). This substance is characterized on the solvent moist plc-plate by a purple zone, which changes to grey-violet on drying. Black to blue-violet crystals (from ethanol), mp 224–226 °C, 154 mg (38%). Vis (methanol): λ_{max}=560 nm, log ε=4.1. IR: $\tilde{\nu}$ = 2230−2220 (CN), 1675s (C═O), 1616, 1590, 1530 and 1505 cm^{-1} (aryl, C═C). ^1H NMR ($CDCl_3$, ambient temp) 300 MHz δ=3.91 (s, 3H, OCH_3), 4.81 (s, 4H, CH_2), 6.14 (d, J=2.2 Hz, 1H, phenyl 2-H), 6.37 (dd, J=8.8 and 2.2 Hz, 1H, phenyl 6-H), 7.30 (m, 4H, isoindolinyl aryl H), 7.54 (d, J=8.8 Hz, 1H, phenyl 5-H), 7.63–8.08 (m, 4H, dione aryl H). ^1H NMR (CD_3NO_2, 297 K) 500 MHz δ=3.97 (s, 3H, OCH_3), 4.88 (s, 4H, CH_2), 6.36 (d, J=2.3 Hz, 1H, phenyl-2H), 6.49 (dd, J=8.8 and 2.3 Hz, 1H, phenyl 6-H), 7.38 (m, 2H) and 7.46 (m, 2H, isoindoline aryl H), 7.52 (d, J=8.9 Hz, 1H, phenyl 5-H), 7.89–8.12 (broadened, several m, 4H, dione aryl H). ^{13}C NMR (CD_3NO_2, 297 K) 125 MHz δ=55.2 ($2CH_2$), 56.5 (OCH_3), sp^2 *C*H signals at 95.7 (phenyl C-2), 106.3 (phenyl C-6), 111.6 (CN), 124.1 (isoindolinyl C-5, C-6), 129.0 (isoindolinyl C-4, C-7), 137.0 and 137.1; qC at 138.4 (isoindolinyl C-3a, C-7a), 117.7, 123.3, 133.4, 142.1, 143.0, 154.6, 163.2, 188.1 (C═O), 189.0 (C═O). MS: *m*/*z* (%)=406 (11, M^+), 380 (70), 349 (2), 224 (100), 209 (24), 193 (11), 179 (43). Anal. Calcd for $C_{26}H_{18}N_2O_3$: C, 76.83; H, 4.46; N, 6.89. Found: C, 76.68; H, 4.53; N, 7.19.

5.3.9. Semi-micro-scale conversions.

5.3.9.1. With isoindolines 8f and 8g. Samples (11 mg, 0.05 mmol) each of **8f** and **8g**, respectively, in 0.5 mL of pyridine were added to solutions (1 mL) of 31 mg (0.15 mmol) of **1** and **3**, respectively, in the same solvent (runs A–D). The mixtures were kept under otherwise the same conditions as used in the preparative scale runs (gentle warming up to 50 °C, 3 h at this temperature with admission of air). After concentration to dryness the residues were examined by tlc. Significant spots were identified by comparison with and admixing of authentical samples. A (**8f+1**): First light green, than deep green colouration, later greyish blue, compound **13f** definitively present. B (**8f+3**): Deep red-brown colouration, later brown. Compound **13f** definitively absent (3 repetitions). C (**8g+1**): Dark olive green colouration, spot of **15** dominating. D (**8g+1**): Dark brown, compound **15** definitively absent, some minor coloured zones detectable.

5.3.9.2. With 2*H*-isoindoles 16c and 16f. Samples 0.05 mmol each of **16c** and **16f**, respectively, in 0.5 mL of pyridine were treated as described above with solutions of **1** and **3** (0.1 mmol each) in pyridine, and the reaction residues were examined by tlc. The definite absence of products **13c** and **13f**, respectively, in the reaction both with **1** and **3** was corroborated by parallel chromatography and addition of authentic samples.

5.4. Single crystal X-ray structure determination of 13f

Suitable crystals were obtained by recrystallization from acetonitrile. Data were recorded using an Enraf–Nonius Kappa CCD diffractometer with graphite-monochromated Mo K_α-radiation (λ=0.71073 Å). The crystal was mounted in a stream of cold nitrogen gas. The structure was solved by direct methods (*SHELXS-97*[22]) and refined by full matrix least squares techniques against F^2 (*SHELXL-97*[23]). Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program.

Crystal data. $C_{37}H_{19}N_3O_5$, M_r=585.55 g mol^{-1}, dark red, crystal size 0.43×0.34×0.12 mm^3, monoclinic, $P2_1/n$, [no. 14], a=15.83020(10) Å, b=10.91510(10) Å, c=16.62470(10) Å, β=103.65(3)°, V=2791.38(4) $Å^3$, D_{calc}=1.393 Mg m^{-3}, μ=0.094 mm^{-1}, T=100 K, λ=0.71073 Å, θ range for data collection 2.25–33.22°, 94943 reflections collected, 10676 independent reflections, 9362 reflections with $I>2\sigma(I)$; Gaussian absorption correction, max. 0.99/min. 0.95, 482 parameters, S=1.439, R_1=0.0504, wR^2=0.1803, largest difference max. and min. 0.9/−0.9 e$Å^{-3}$.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 615812. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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References and notes

1. (a) Aigner, H.; Junek, H.; Sterk, H. *Monatsh. Chem.* **1970**, *101*, 1145–1148; (b) Fischer-Colbrie, H.; Aigner, H.; Junek, H. *Monatsh. Chem.* **1975**, *106*, 743–753.
2. (a) Junek, H.; Aigner, H.; Fischer-Colbrie, H. *Monatsh. Chem.* **1972**, *103*, 639–648; (b) Rappoport, Z.; Ladkani, D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1045–1052; (c) Boila-Göckel, A.; Fabian, W. M. F.; Junek, H. *Liebigs Ann. Chem.* **1996**, 397–402.
3. Fatiadi, A. J. *Synthesis* **1986**, 249–284 and refs. cited therein.
4. (a) Junek, H.; Hermetter, A.; Fischer-Colbrie, H.; Aigner, H. *Tetrahedron Lett.* **1973**, 2995–2996; (b) Junek, H.; Fischer-Colbrie, H.; Hermetter, A. *Z. Naturforsch. B* **1977**, *32b*, 898–903; (c) Nesterov, V. N.; Aitov, I. A.; Sharanin, Yu. A.; Struchkov, Yu. T. *Russ. Chem. Bull.* **1996**, *45*, 164–167; (d) Bespalov, B. P.; Getmanova, E. V.; Abolin, A. G. *J. Org. Chem. (USSR)* **1981**, 1612–1617; *Zh. Org. Khim.* **1980**, *16A*, 1896–1901; (e) Junek, H.; Klade, M.; Biza, P.; Geringer, M.; Sterk, H. *Liebigs Ann. Chem.* **1990**, 741–744.
5. Döpp, D.; Jüschke, S.; Henkel, G. *Z. Naturforsch. B* **2002**, *57b*, 460–470.
6. Döpp, D.; Hassan, A. A.; Mourad, A.-F. E.; Nour El-Din, A. M.; Angermund, K.; Krüger, C.; Lehmann, C. W.; Rust, J. *Tetrahedron* **2003**, *59*, 5073–5081.
7. Hassan, A. A.; El-Shaieb, K. M.; Döpp, D. *ARKIVOC* **2005**, *x*, 139–149; http://www.arkat-usa.org/journal/2005/I10_Balaban/1343/1343.pdf.
8. Hassan, A. A.; Döpp, D.; Henkel, G. *J. Heterocycl. Chem.* **1998**, *35*, 121–128.
9. (a) Ashwell, G. J.; Bryce, M. R.; Davies, S. R.; Hasan, M. *J. Org. Chem.* **1988**, *53*, 4585–4587; (b) Bryce, M. R.;

Davies, S. R.; Hasan, M.; Ashwell, G. J.; Szablewski, M.; Short, R.; Hursthouse, M. B. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1285–1292; (c) Batsanov, A. S.; Bryce, M. R.; Davies, S. R.; Howard, J. A. K.; Whitehead, R.; Tanner, B. K. *J. Chem. Soc., Perkin Trans. 2* **1993**, 313–319.
10. Nakanishi, K.; Solomon, P. H. *Infrared Absorption Spectroscopy*, 2nd ed.; Holden-Day: San Francisco, 1977; p 64.
11. Hassan, A. A. *Bull. Soc. Chim. Fr.* **1991**, *128*, 544–549.
12. Braude, E. A.; Jackman, L. M.; Linstead, R. P. *J. Chem. Soc.* **1954**, 3548–3563 and following papers.
13. Reid, D. H.; Fraser, M.; Molloy, B. B.; Payne, H. A. S.; Sutherland, R. G. *Tetrahedron Lett.* **1961**, 530–535.
14. Kreher, R. P.; Feldhoff, U.; Seubert, J.; Schmitt, D. *Chem.-Ztg.* **1987**, *111*, 155–169.
15. Nour El-Din, A. M.; Mourad, A.-F. E.; Hassan, A. A.; Döpp, D. *Z. Phys. Chem. [Leipzig]* **1988**, *269*, 832–838.
16. Farrell, P. G.; Ngo, P. N. *J. Chem. Soc., Perkin Trans. 2* **1974**, 552–556.
17. Zollinger, H. *Color Chemistry*, 3rd revised ed.; Wiley-VCH: Weinheim, 2003; p 45.
18. Kovtunenko, V. A.; Tyltin, A. K.; Turov, A. V.; Babichev, F. S. *Russ. J. Org. Chem.* **1989**, 972–977; *Zh. Org. Khim.* **1989**, *25*, 1080–1085.
19. Watanabe, Y.; Shim, S. C.; Uchida, H.; Mitsudo, T.; Takagami, Y. *Tetrahedron* **1979**, *35*, 1433–1436.
20. Chatterjee, S. *J. Chem. Soc. (B)* **1969**, 725–729.
21. Chatterjee, S. *J. Chem. Soc. (B)* **1971**, 2194–2197.
22. Sheldrick, G. M. *SHELXS-97: Program for the Determination of Crystal Structures*; University of Göttingen: Germany, 1997.
23. Sheldrick, G. M. *SHELXL-97: Program for Least Squares Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.

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A facile access to bridged 1,2,4-trioxanes

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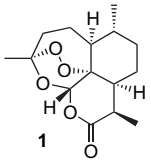
Abstract—Bicyclo[3.2.1] type 1,2,4-trioxanes are readily synthesized from precursors that may form intramolecular hemiketals using UHP (H_2O_2–urea complex) as the source of the peroxy bond and *p*-TsOH or CSA as the catalyst. The ring closure through an intramolecular Michael addition occurred in a highly stereoselective way, giving only one diasteromer as shown by the NMR spectra.

1. Introduction

Organic peroxides are currently of great interest because of the excellent antimalarial activity observed with qinghaosu[1] (artemisinin, **1**) and closely related organic peroxide. The peroxy bond in **1** constitutes a part of 1,2,4-trioxane ring system. Therefore, the 1,2,4-trioxane class of peroxides are considered to be particularly interesting among various organic peroxides over the last decades. Considerable efforts in synthesizing this class of compounds have been documented in the literature.



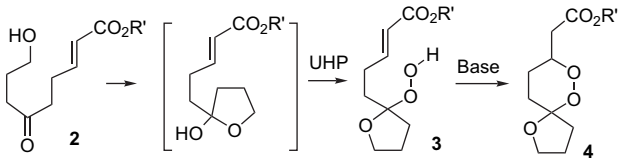
1

Organic peroxides are difficult to synthesize partly because formation of an O–O bond between two alkoxyl-related species is practically impossible unless using radical coupling strategy. As a consequence, the peroxy bonds in organic peroxides are all essentially acquired through making a C–O bond on each end of an inorganic species that contains an O–O bond. It is therefore not surprising that the existing methodologies for incorporating/introducing peroxy bonds into organic molecules are rather few. In fact those of synthetic significance are: (1) photosensitized oxygenation,[2] (2) trapping ozonides of enolates or vinylsilanes,[3] (3) ring opening of epoxides with H_2O_2,[4] and (4) transition metal ion-mediated radical trapping of O_2.[5]

Apart from the extremely limited number of means for introducing peroxy bonds, another factor also contributes to the difficulty of synthesizing organic peroxides—the peroxy bonds themselves are much more fragile than most other covalent bonds in organic compounds, with an average bond energy of only 34 kcal/mol[1e] (less than half of that for a C–C single bond). Hence, the timing of incorporating the peroxy bond into the substrate must be carefully planned to avoid involvement of reagents and conditions that would cleave the peroxy bond after their introduction. This of course adds additional difficulties to the synthesis. Consequently, cautious design of a precursor for incorporating the peroxy bond in combination of a proper choice of the peroxy bond source is of critical importance in the synthesis of novel organic peroxides. Here in this paper we wish to report an experimentally feasible entry to a bridged 1,2,4-trioxane system.

2. Results and discussions

Using Kobayashi's[6] methodology, we previously synthesized[7] some spiro 1,2-dioxanes, where the key step of incorporating a hydroperoxyl group was realized by exploiting facile formation of intramolecular hemiketals as illustrated in Scheme 1 through converting precursor **2** into hydroperoxy compound **3**. Encouraged by those results, we set out to explore the possibility of extending this methodology from the spiro systems to bridged ones.



Scheme 1.

Keywords: Antimalarials; Hemiketals; Peroxides; Cyclization; Heterocycles.
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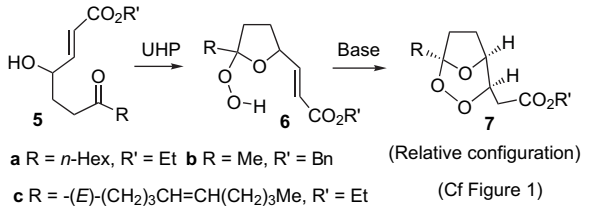
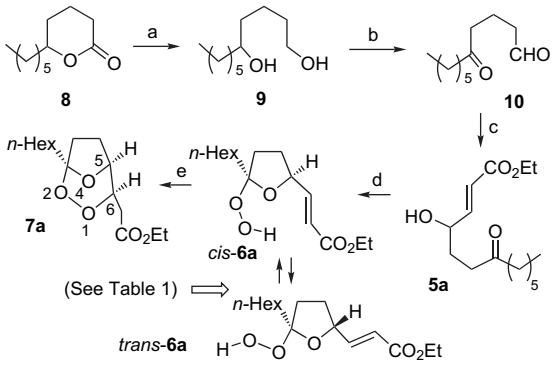
In the present work we designed (Scheme 2) a new type of substrates **5**, which were expected to form hydroperoxy intermediates **6** and eventually led to bridged 1,2,4-trioxanes **7**. Compared with the previous mono cyclic[6] or the spiro[7] systems, such a trioxane system is much closer to the core structure of qinghaosu **1** and therefore deserves investigation.



Scheme 2.

Synthesis of the first target **7a** started from the commercially available lactone **8** (Scheme 3). Reduction with $LiAlH_4$ gave diol **9**[8] in 95% yield. Both hydroxyl groups were then oxidized to the intermediate aldehyde–ketone **10** by Swern oxidation. The resulting **10** when treated with the sulfoxide reagent **11**[9] in the presence of piperidine afforded the desired hydroperoxidation precursor **5a**.

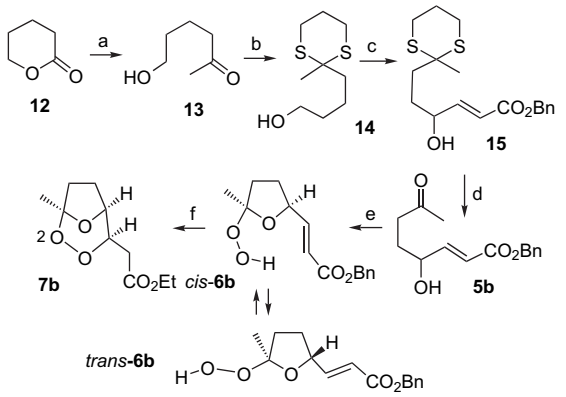


Scheme 3. (a) $LiAlH_4$/THF, 95%; (b) Swern oxidation; (c) $PhS(O)CH_2$–CO_2Et (**11**)/piperidine/rt/15 h, 41% from **10**; (d) UHP (ca. 7.5 equiv)/*p*-TsOH/DME/rt/overnight, 89% (*trans*-**6a**/*cis*-**6a**=1.6:1); and (e) cat. $HNEt_2/F_3CCH_2OH$/rt/12 h, 35%.

The hydroperoxyl group was then introduced by treatment with UHP (urea–H_2O_2 complex, a commercially available solid reagent) in the presence of *p*-TsOH in DME ($MeO(CH_2)_2OMe$) in 89% yield. It should be noted that if MeOH is used as solvent as in Kobayashi's original recipe, the yield of the hydroperoxy hemiketals *trans*-**6a** and *cis*-**6a** was <50%.

The *cis*-**6a**, which was readily separated from *trans*-**6a** on silica gel, was treated with Et_2NH/F_3CCH_2OH, giving the end product **7a** in 35% yield.

When the *n*-hexyl group was replaced by a methyl group, which is much smaller in size, the selective reaction of $PhSOCH_2CO_2Bn$ (**16**) with the aldehyde group in the presence of a ketone functionality was not possible, presumably due to the interference of the intramolecular aldol reaction. For this reason, we next turned to a slightly longer route (Scheme 4), where the ketone carbonyl group could be masked during the reaction of the aldehyde with the sulfoxide reagent **16**.



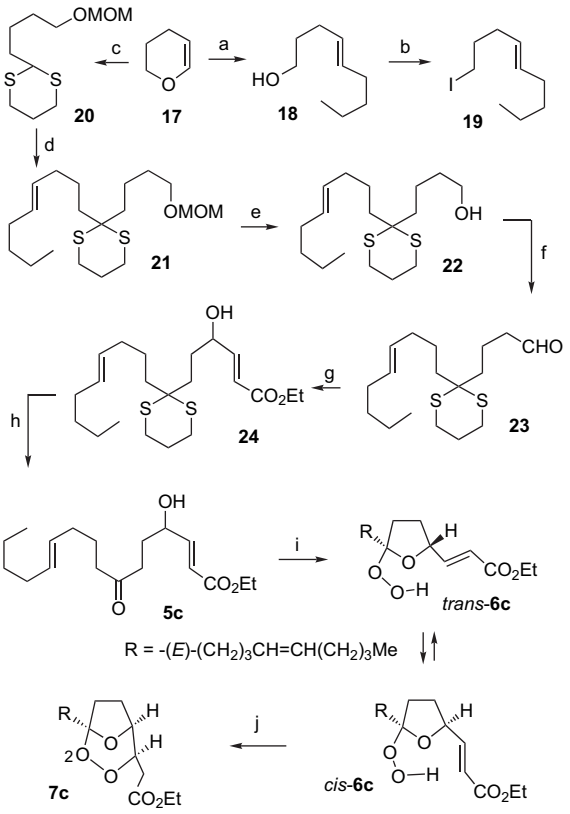
Scheme 4. (a) MeLi/Et_2O/−78 °C, 80%; (b) $HS(CH_2)_3SH/F_3B\cdot OEt_2/CH_2Cl_2$, 98%; (c) (i) $SO_3\cdot Py$/DMSO/NEt_3, 92%; (ii) $PhS(O)CH_2CO_2Bn$ (**16**)/piperidine/rt/15 h, 60%; (d) $I_2/NaHCO_3$/acetone–H_2O, 95%; (e) UHP (ca. 7.5 equiv)/*p*-TsOH/DME/rt/12 h, 88% (*trans*-**6b**/*cis*-**6b**=1.8:1); and (f) cat. $HNEt_2/F_3CCH_2OH$/rt/12 h, 29%.

The starting material in this case was, again, a lactone (**12**). Addition of methyllithium to **12** under carefully controlled conditions resulted in the methyl ketone **13**. The carbonyl group was then protected with $HS(CH_2)_2SH$ in the presence of borontrifluoride etherate and the alcohol was oxidized with $SO_3\cdot Py$ to afford the intermediate aldehyde, which on treatment with the sulfoxide reagent **16** gave the α,β-unsaturated ester **15**.

The sulfur protecting group was then removed with $I_2/NaHCO_3$ in 5:1 acetone–H_2O to give the hydroperoxidation precursor **5b** in 95% yield. The subsequent introduction of the hydroperoxyl group was performed under the same conditions as described above for the synthesis of **6a**, giving **6b** in 88% yield as a 1.8:1 mixture of *trans*-**6b** and *cis*-**6b**. The desired isomer *cis*-**6b** was separated from *trans*-**6b** by chromatography on silica gel and treated with $HNEt_2$ in F_3CCH_2OH to yield the end product **7b**.

The long-chain substrate **7c** was synthesized from dihydropyran **17** using the sequence outlined in Scheme 5. The iodide **19** was obtained by reaction of **17** with 2 equiv of *n*-BuLi to afford the alcohol **18**,[10] followed by treatment with Ph_3P/I_2/imidazole in MeCN–Et_2O. The dithiane moiety **20** was constructed by reaction of $HS(CH_2)_2SH$ with **17** and subsequent protection of the newly formed terminal hydroxyl group as a MOM ether.

The coupling of **19**[11] with **20** (prepared from the corresponding alcohol following the literature[12]) was then realized under action of *n*-BuLi. The MOM protecting group was then cleaved with MeOH and the resulting alcohol was oxidized with $SO_3\cdot Py$ to afford the aldehyde **23**. Further treatment of the aldehyde with sulfoxide reagent **11** led to α,β-unsaturated ester **24**, which on deprotection of the thioketal gave the hydroperoxidation precursor **5c**. Conversion of **5c** to **7c** was performed in a similar fashion as described above for **7a** and **7b**.



Scheme 5. (a) *n*-BuLi (2 equiv)/reflux/3 h, 80%; (b) I_2/imidazole/Ph_3P/MeCN–Et_2O (1:4)/15 min, 82%; (c) (i) $HS(CH_2)_3SH/BF_3\cdot Et_2O$, 90%; (ii) MOMCl/*i*-$Pr_2NEt/CH_2Cl_2$/rt, 85%; (d) (i) *n*-BuLi/THF/−78 to −20 °C/4 h, (ii) HMPA/**19**/0 °C/12 h, 68% from **20**; (e) *p*-TsOH/MeOH/40–50 °C/3 h, 90%; (f) $SO_3\cdot Py$/DMSO/NEt_3, 86%; (g) $PhS(O)CH_2CO_2Et$ (**11**)/piperidine/rt/15 h, 63%; (h) $I_2/NaHCO_3$/acetone–H_2O, 87%; (i) UHP (ca. 7.5 equiv)/*p*-TsOH/DME/rt/12 h, 86% (*trans*-**6c**/*cis*-**6c**=2.3:1); and (j) cat. $HNEt_2/F_3CCH_2OH$/rt/12 h, 32%.

The *trans*-**6**a–c isomers, which were unable to undergo the Michael addition, could be partially transformed into the corresponding cis ones by acid catalyzed equilibration. The conversion ratio varied depending on the catalyst (exemplified with the re-equilibrium of **6a** in Table 1). In DME with CSA ((±)-camphor-10-sulfonic acid) as the catalyst (entry 1), the trans/cis ratio at the end of the equilibration was 2.3:1 (calculated from the isolated yields). Using TFA (trifluoroacetic acid) as the catalyst, however, did not result in any conversion at all under the otherwise same conditions (entry 2).

p-TsOH gave more or less the same conversion ratio as CSA. The recovery rate was usually excellent in DME, but not so good in MeOH (entry 5). Presence of a small amount of MeOH apparently facilitated the conversion. Thus, in 9:1 DME–MeOH, the trans/cis ratio could reach 1.8:1.

It is noteworthy that unlike in the monocyclic or spirocyclic cases encountered in our previous work, where both diastereomers were formed in rather close amounts, in the present system the Michael addition proceeded in a highly stereoselective manner, leading to only one diastereomer.

With assistance of 2D NMR experiments including COSY, NOESY, and HMQC, the structure of the bridged product was firmly established. The relative configuration at C-6 was assigned as follows: As the coupling between H-5 and H-6 was essentially 0 Hz (Fig. 1), the dihedral angle between these two hydrogens must be near 90°. From molecular model it can be seen that only the relative configuration as depicted in Figure 1 could satisfy this requirement.

Table 1. Acid catalyzed re-equilibrium between *trans*-**6a** and *cis*-**6a**[a]

Entry	Acid	Solvent[b]	*trans*/*cis*	Recovery[c] (%)
1	CSA	DME	2.3:1	100
2	F_3CCO_2H	DME	NC[d]	100
3	$BF_3\cdot OEt_2$	DME	5.6:1	96
4	*p*-TsOH	DME	2.1:1	94
5	*p*-TsOH	MeOH	2.1:1	84
6	*p*-TsOH	PEG 400	7.8:1	76
7	*p*-TsOH	9:1 DME–MeOH	1.8:1	100
8	CSA	9:1 DME–MeOH	1.8:1	100

[a] The re-equilibrium of the *trans*-**6a** was performed by stirring a 0.025 M solution of *trans*-**6a** in the indicated solvent in the presence of 7.5 equiv of UHP and 1.2 equiv of the indicated acid at ambient temperature overnight.
[b] PEG 400=polyethylene glycol (molecular weight=400).
[c] The total yield of *trans*-**6a** and *cis*-**6a**.
[d] No changes were observed.

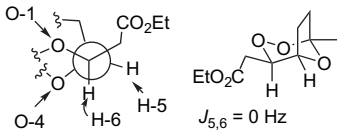


Figure 1. The dihedral angle between H-5 and H-6 is close to 90°.

3. Conclusions

A convenient approach to a 1,2,4-trioxane system has been developed, which utilized the commercially available and easy-handling solid UHP as the source of the peroxy bond and complements the existing protocols that do not involve excited state chemistry.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruke Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FT-IR. EIMS and EIHRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and a APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. Elemental analyses were performed on an Elementar VarioEL III instrument. The melting point was uncorrected. Dry THF was distilled from Na/Ph_2CO under N_2. Dry CH_2Cl_2 was distilled over CaH_2 and kept over 4 Å molecular sieves. UHP was purchased from Acros. All other solvents and reagents were commercially available and used as received without any further purification.

4.2. Reduction of lactone 8 (9)

$LiAlH_4$ (1.143 g, 30.08 mmol) was added in portions to a solution of **8** (3.738 g, 20.30 mmol) in anhydrous THF (95 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 40 min before the excess hydride was destroyed by addition of 2 N HCl with cooling in an ice-water bath. The mixture was extracted with EtOAc (4×100 mL). The combined organic layers were washed with water, satd aq $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvent and drying agent was chromatographed (3:2 *n*-hexane/EtOAc) on silica gel to give diol **9**[8] as a colorless wax (3.625 g, 95% yield). ^{1}H NMR δ 3.67–3.63 (m, 3H), 1.97 (s, 2H), 1.60–1.25 (m, 16H), 0.89 (t, J=7.2 Hz, 3H).

4.3. Synthesis of 5a

DMSO (5.16 mL, 72.27 mmol) was added dropwise to a solution of $(COCl)_2$ (2.84 mL, 32.85 mmol) in dry CH_2Cl_2 (36 mL) stirred at −60 °C under N_2. After completion of the addition, the mixture was stirred at the same temperature for 30 min. A solution of **9** (1.235 g, 6.57 mmol) in dry CH_2Cl_2 (14 mL) was added slowly. After another 30 min stirring at −60 °C, NEt_3 (8.20 mL, 59.13 mmol) was introduced dropwise. The stirring was continued at −60 °C. When TLC showed completion of the oxidation, HCl (2.4 N, 11 mL) was added. The mixture was extracted with Et_2O (3×50 mL). The combined ethereal phases were washed with diluted HCl until pH 7, then with water and brine before being dried over anhydrous Na_2SO_4. The residue (**10**) after removing drying agent and the solvent was added slowly to a solution of $PhSOCH_2CO_2Et$ (1.393 g, 6.57 mmol) and piperidine (0.67 mL, 6.57 mmol) in MeCN (11 mL) stirred at rt. The stirring was continued at rt until TLC showed completion of the reaction. The mixture was partitioned between water (25 mL) and Et_2O (25 mL). The phases were separated and the aqueous layer was back extracted with Et_2O (3×50 mL). The combined ethereal phases were washed with diluted HCl until *p*H 7, then with water and brine before being dried over anhydrous Na_2SO_4. The residue after removal of solvent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **5a** as a yellowish oil (727 mg, 41% from **9**). FTIR (film) 3447, 1720, 1661, 1466, 1272, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.91 (dd, J=15.7, 4.5 Hz, 1H), 6.06 (d, J=15.4 Hz, 1H), 4.37 (s, 1H), 4.20 (q, J=6.8 Hz, 2H), 3.02 (d, J=5.2 Hz, 1H), 2.60 (t, J=5.9 Hz, 2H), 2.43 (t, J=7.5 Hz, 2H), 1.96–1.80 (m, 2H), 1.58–1.54 (m, 2H), 1.35–1.28 (m, 9H), 0.88 (t, J=6.7 Hz, 3H); ESIMS *m*/*z* 271.2 ([M+H]$^+$); ESIHRMS calcd for $C_{15}H_{26}O_4Na$ ([M+Na]$^+$) 293.1729; found 293.1720.

4.4. Hydroperoxidation of 5a (*cis*-6a and *trans*-6a)

A mixture of **5a** (285 mg, 1.05 mmol), UHP (748 mg, 8.0 mmol), and *p*-TsOH·H_2O (248 mg, 1.30 mmol) in DME (42 mL) was stirred at rt overnight. The solvent was removed by rotary evaporation and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to afford *cis*-**6a** (103 mg, 0.360 mmol, 34% yield) and *trans*-**6a** (165 mg, 0.576 mmol, 55% yield) as colorless oils. Data for compound *cis*-**6a** (the less polar component): FTIR (film): 3386, 1718, 1659, 1463, 1304, 1271, 1179, 1041 cm^{-1}; ^{1}H NMR δ 7.99 (s, 1H), 6.78 (dd, J=6.1, 15.3 Hz, 1H), 6.05 (d, J=15.4 Hz, 1H), 4.69–4.66 (m, 1H), 4.21 (q, J=6.9 Hz, 2H), 2.15–2.11 (m, 4H), 1.70–1.25 (m, 13H), 0.86 (t, J=9.3 Hz, 3H). Data for compound *trans*-**6a** (the more polar component): FTIR (film) 3390, 1722, 1660, 1465, 1304, 1267, 1041 cm^{-1}; ^{1}H NMR δ 8.07 (s, 1H), 6.91 (dd, J=5.2, 15.8 Hz, 1H), 6.05 (d, J=15.8 Hz, 1H), 4.80–4.78 (m, 1H), 4.21 (q, J=7.0 Hz, 2H), 2.33–1.96 (m, 4H), 1.75–1.22 (m, 13H), 0.87 (t, J=10.5 Hz, 3H). Because these hydroperoxides are not very stable, they should be used as soon as possible.

4.5. Synthesis of 7a

A mixture of *cis*-**6a** (83 mg, 0.29 mmol) and $HNEt_2$ (4 μL) in CF_3CH_2OH (1.5 mL) was stirred at rt for ca. 14 h, when TLC showed disappearance of the starting material. The solvent was removed by rotary evaporation and the residue was chromatographed (20:1 *n*-hexane/EtOAc) on silica gel to yield **7a** as a colorless oil (29 mg, 0.101 mmol, 35% yield). FTIR (film) 2956, 2925, 2854, 1741, 1426, 1185, 1026 cm^{-1}; ^{1}H NMR δ 4.89 (t, J=7.2 Hz, 1H), 4.34 (d, J=4.3 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.33–2.27 (m, 3H), 1.99–1.87 (m, 3H), 1.77–1.68 (m, 2H), 1.16–1.09 (m, 2H), 1.04–0.98 (m, 9H), 0.70 (t, J=7.0 Hz, 3H); MALDIHRMS *m*/*z* calcd for $C_{15}H_{26}O_5Na$ ([M+Na]$^+$) 309.16725; found 309.1679.

4.6. Addition of methyllithium to lactone 12 (13)

MeLi (2.2 M in Et_2O, 2.35 mL, 5.16 mmol) was added to a solution of **12** (516 mg, 5.16 mmol) in anhydrous Et_2O (13 mL) stirred at −78 °C under N_2. The mixture was stirred at the same temperature for 15 min and aq satd NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O (3×30 mL) and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (2:1 *n*-hexane/EtOAc) on silica gel to give **13**[13] as a colorless oil (479 mg, 4.12 mmol, 80% yield). ^{1}H NMR δ 3.62 (t, J=6.0 Hz, 2H), 2.49 (t, J=6.9 Hz, 2H), 2.19 (s, 1H), 2.18 (s, 3H), 1.72–1.51 (m, 4H).

4.7. Protection of 13 with propane-1,3-dithiol (14)

A solution of **13** (479 mg, 4.12 mmol), $HS(CH_2)_2SH$ (0.42 mL, 4.12 mmol), and $BF_3\cdot Et_2O$ (0.22 mL) in CH_2Cl_2 (20 mL) was stirred at rt for 3 h, when TLC showed completion of the reaction. Acetone was added (to remove excess thiol) and the stirring was continued for 1 h and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed in turn with aq $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to give **14**[14] as a colorless oil (832 mg, 4.04 mmol, 98% yield). ^{1}H NMR δ 3.68 (t, J=6.0 Hz, 2H), 2.87–2.83 (m, 4H), 1.98–1.92 (m, 4H), 1.63 (s, 3H), 1.60–1.58 (m, 4H).

4.8. Synthesis of 15

A solution of $SO_3\cdot Py$ (446 mg, 2.81 mmol) in DMSO (4 mL) was added slowly to a solution of **14** (165 mg,

0.80 mmol) and NEt_3 (0.55 mL, 4.0 mmol) in dry CH_2Cl_2 (2 mL) and stirred at 0 °C. After completion of the addition, the bath was removed and the mixture was stirred at rt until TLC showed (ca. 3 h) full disappearance of the starting alcohol. Water (10 mL) was added to quench the reaction and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed with aq satd $CuSO_4$ (until no more floccule formed), water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (40:1 *n*-hexane/EtOAc) on silica gel to give the known intermediate aldehyde[15] as a colorless oil (150 mg, 0.74 mmol, 92% yield). ^{1}H NMR δ 9.80 (s, 1H), 2.88–2.82 (m, 4H), 2.51 (t, J=6.7 Hz, 2H), 1.99–1.80 (m, 6H), 1.61 (s, 3H).

A solution of the above prepared aldehyde (3.046 g, 14.93 mmol) in MeCN (25 mL) was added dropwise to a solution of $PhSOCH_2CO_2Bn$ (**16**, 4.091 g, 14.93 mmol) and piperidine (1.48 mL, 14.93 mmol) in MeCN (50 mL) and stirred at rt. The stirring was continued at rt until TLC showed completion of the reaction. Water was added to quench the reaction and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed first with diluted HCl until pH 7 and then with water and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to give **15** as a yellowish oil (3.144 g, 8.93 mmol, 60% yield). FTIR (film) 3447, 2923, 1717, 1655, 1455, 1274, 1162, 979, 908, 738, 697 cm^{-1}; ^{1}H NMR δ 7.39–7.33 (m, 5H), 7.00 (dd, J=4.7, 15.5 Hz, 1H), 6.12 (d, J=15.6 Hz, 1H), 5.20 (s, 2H), 4.39–4.35 (m, 1H), 2.86–2.76 (m, 4H), 2.13–1.73 (m, 7H), 1.58 (s, 3H); ESIMS *m*/*z* 370.2 ([M+NH_4]$^+$); ESIHRMS calcd. for $C_{18}H_{24}O_3S_2Na$ ([M+Na]$^+$) 375.1065; found 375.1060.

4.9. Deprotection of 15 (5b)

Powdered $NaHCO_3$ (300 mg, 3.57 mmol) and I_2 (369 mg, 1.44 mmol) were added in turn to a solution of **15** (146 mg, 0.41 mmol) in acetone (4 mL) and water (1 mL) and stirred in an ice-water bath. The mixture was stirred for 15 min when TLC showed disappearance of the starting material. Aq satd $Na_2S_2O_3$ (2 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed in turn with aq satd $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **5b** as a yellowish oil (103 mg, 0.39 mmol, 96% yield). FTIR (film) 3448, 1716, 1658, 1455, 1271, 1164, 1112, 984, 699 cm^{-1}; ^{1}H NMR δ 7.38–7.32 (m, 5H), 6.95 (dd, J=15.5, 4.3 Hz, 1H), 6.12 (d, J=15.7 Hz, 1H), 5.19 (s, 2H), 4.38–4.35 (m, 1H), 2.70 (d, J=4.8 Hz, 1H), 2.61 (t, J=6.5 Hz, 2H), 2.17 (s, 3H), 2.02–1.92 (m, 1H), 1.81–1.74 (m, 1H); ESIMS *m*/*z* 263 ([M+H]$^+$); ESIHRMS calcd for $C_{15}H_{18}O_4Na$ ([M+Na]$^+$) 285.1103; found 285.1098.

4.10. Synthesis of 7b

A mixture of **5b** (43 mg, 0.16 mmol), UHP (100 mg, 1.06 mmol), and *p*-TsOH·H_2O (37 mg, 0.19 mmol) in DME (4.6 mL) was stirred at rt overnight. The solvent was removed by rotary evaporation and the residue was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to afford *cis*-**6b** (14 mg, 0.050 mmol, 32%) and *trans*-**6b** (25 mg, 0.090 mmol, 56%) as colorless oils. Data for compound *cis*-**6b** (the less polar component): FTIR (film) 3389, 1719, 1659, 1456, 1379, 1301, 1227, 1171, 1030 cm^{-1}; ^{1}H NMR δ 8.18 (s, 1H), 7.36–7.32 (m, 5H), 7.02 (dd, J=6.0, 15.6 Hz, 1H), 6.11 (d, J=15.5 Hz, 1H), 5.19 (s, 2H), 4.74–4.76 (m, 1H), 2.26–1.60 (m, 4H), 1.55 (s, 3H). Data for compound *trans*-**6a** (the more polar component): FTIR (film): 3394, 1720, 1659, 1456, 1380, 1300, 1270, 1170, 1028 cm^{-1}; ^{1}H NMR δ 8.14 (s, 1H), 7.37–7.35 (m, 5H), 6.96 (dd, J=4.8, 15.7 Hz, 1H), 6.10 (d, J=15.7 Hz, 1H), 5.19 (s, 2H), 4.80–4.78 (m, 1H), 2.33–2.26 (m, 1H), 2.17–2.08 (m, 1H), 1.98–1.88 (m, 1H), 1.75–1.71 (m, 1H), 1.57 (s, 3H). Because these hydroperoxides are not very stable, they should be used as soon as possible.

A mixture of *cis*-**6b** (175 mg, 0.63 mmol) and $HNEt_2$ (6 μL) in CF_3CH_2OH (37 mL) was stirred at rt until TLC showed disappearance of the starting material. The solvent was removed by rotary evaporation and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to yield **7b** as a colorless oil (51 mg, 0.18 mmol, 29% yield). FTIR (film) 2993, 2956, 1736, 1457, 1170, 1032, 983, 877, 752, 699 cm^{-1}; ^{1}H NMR δ 7.38–7.36 (m, 5H), 5.14 (s, 2H), 4.91 (t, J=7.1 Hz, 1H), 4.91 (br s, 1H), 2.44–2.26 (m, 3H), 2.00–1.82 (m, 3H), 1.46 (s, 3H); EIHRMS *m*/*z* calcd for $C_{15}H_{18}O_5$ (M^+) 278.1267; found 278.1142.

4.11. Synthesis of the benzyl ester sulfoxide reagent 16

PhSH (3.46 mL, 33.78 mmol) was added dropwise to EtONa solution (freshly prepared by dissolving 388 mg of Na metal in 12.5 mL of anhydrous EtOH). The mixture was stirred at rt for 1 h before a solution of $BrCH_2CO_2Bn$ (3.867 g, 16.89 mmol) in anhydrous EtOH (5 mL) was introduced. The mixture was heated to reflux with stirring for 2 h and re-cooled to rt. Water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3×30 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the residue (the sulfide) was used directly in the next step.

$NaIO_4$ (9.037 g, 42.22 mmol) was added to a solution of the above prepared sulfide (4.358 g, 16.89 mmol) in MeOH (32 mL) and water (17 mL). The mixture was stirred at rt overnight before being diluted with Et_2O (40 mL). The solids were filtered off (washed with Et_2O) and the filtrate was washed with water. The aqueous layer was back extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The residue after removal of solvent was chromatographed (3:1 *n*-hexane/EtOAc) on silica gel to give **16** as a colorless oil (4.078 g, 14.88 mmol, 88% yield). FTIR (film) 1732, 1658, 1444, 1270, 1050 cm^{-1}; ^{1}H NMR δ 7.65–7.25 (m, 10H), 5.12 (s, 2H), 3.91 (d, J=13.5 Hz, 1H), 3.71 (d, J=13.8 Hz, 1H); ESIMS *m*/z 275 ([M+H]$^+$); EIHRMS calcd for $C_{15}H_{14}O_3S$ (M^+) 274.0664; found 274.0673.

4.12. Synthesis of iodide 19

Solid I_2 (2.54 g, 10 mmol) was added in portions to a solution of alcohol **18**[10] (1.42 g, 10 mmol), Ph_3P (2.62 g, 10 mmol),

and imidazole (680 mg, 10 mmol) in 4:1 (v/v) Et_2O–CH_3CN (50 mL) stirred in an ice-water bath. After completion of the addition, the stirring was continued for 30 min. *n*-Hexane (100 mL) was added. The solids were filtered off and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed (*n*-hexane) on silica gel to give iodide **19** as a colorless oil (2.06 g, 8.17 mmol, 82% yield). FTIR (film) 2956, 2925, 1459, 1219, 1167 cm^{-1}; ^1H NMR δ 5.51–5.29 (m, 2H), 3.18 (t, J=6.5 Hz, 2H), 2.12–1.84 (m, 6H), 1.32–1.25 (m, 4H), 0.89 (t, J=6.1 Hz, 3H); EIMS *m*/*z* (%) 252 (M, 15.8), 210 (M−$CH_3CH{=}CH_2$, 0.8); EIHRMS calcd for $C_9H_{17}I$ (M^+) 252.0375; found 252.0386.

4.13. Synthesis of 20

Dihydropyran **17** (2.42 mL, 26 mmol) was added dropwise to a solution of $HS(CH_2)_2SH$ (2.6 mL, 25.8 mmol) and $BF_3{\cdot}Et_2O$ (0.5 mL) in CH_2Cl_2 (25 mL) and stirred at −78 °C. After completion of the addition, the cooling bath was removed and the mixture was stirred at rt for 5 h, when TLC showed completion of the reaction. Water (5 mL) was added to quench the reaction. Et_2O (50 mL) was added and the phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with aq satd $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed (3:1 *n*-hexane/EtOAc) on silica gel to give the intermediate alcohol[12] as a colorless oil (4.50 g, 23.4 mmol, 90% yield).

A solution of the above prepared alcohol (480 mg, 2.5 mmol), *i*-Pr_2NEt (0.87 mL, 5 mmol), and MOMCl (0.38 mL, 5 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 15 h. Water (10 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous phases were extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to afford **20** as a yellowish oil (502 mg, 2.13 mmol, 85% yield). FTIR (film) 1413, 1269, 1146, 1111, 1043, 916 cm^{-1}; ^1H NMR δ 4.62 (s, 2H), 4.05 (t, J=6.9 Hz, 1H), 3.53 (t, J=5.5 Hz, 2H), 3.36 (s, 3H), 2.93–2.80 (m, 4H), 2.16–2.04 (m, 1H), 1.92–1.75 (m, 3H), 1.66–1.59 (m, 4H); ESRMS *m*/*z* 236 ([M+Na]$^+$); MALDIHRMS calcd for $C_{10}H_{20}O_2S_2Na$ ([M+Na]$^+$) 259.0797; found 259.0802.

4.14. Coupling of 19 with 20 (21)

n-BuLi (1.6 M, 4.0 mL, 6.54 mmol) was added to a solution of **20** (1.14 g, 5.94 mmol) in dry THF (20 mL) stirred at −78 °C under N_2. After completion of the addition, the stirring was continued at −25 °C for 4 h. Dry HMPA (1.04 mL, 5.94 mmol) was introduced, followed by iodide **19** (1.496 g, 5.94 mmol, dissolved in 5 mL of dry THF). The mixture was then stirred at 0 °C for 17 h. The reaction was quenched by addition of aq satd NH_4Cl (10 mL). The mixture was diluted with Et_2O (50 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed first with 1 N HCl and then with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (12:1 *n*-hexane/EtOAc) on silica gel to give **21** as a colorless oil (1.454 g, 4.04 mmol, 68% yield). FTIR (film) 1456, 1274, 1151, 1111, 1044, 968, 919 cm^{-1}; ^1H NMR δ 5.47–5.35 (m, 2H), 4.63 (s, 2H), 3.54 (t, J=6.6 Hz, 2H), 3.37 (s, 3H), 2.82–2.78 (m, 4H), 2.04–1.84 (m, 9H), 1.64–1.30 (m, 11H), 0.89 (t, J=7.1 Hz, 3H); ESRMS *m*/*z* 383 ([M+Na]$^+$); MALDIHRMS calcd for $C_{19}H_{36}O_2S_2Na$ ([M+Na]$^+$) 383.2049; found 383.2060.

4.15. Removal of the MOM protecting group in 21 (22)

A solution of **21** (2.02 g, 5.6 mmol) and *p*-$TsOH{\cdot}H_2O$ (106 mg, 0.56 mmol) in THF (40 mL) was stirred at 40 °C for 3 h. Water (10 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed first with aq satd $NaHCO_3$ to neutral and then with water and brine before being dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **22** as a yellowish oil (1.59 g, 5.03 mmol, 90% yield). FTIR (film) 3392, 2930, 2860, 1456, 1274, 1070, 967 cm^{-1}; ^1H NMR δ 5.47–5.35 (m, 2H), 3.68 (t, J=6.0 Hz, 2H), 2.83–2.79 (m, 4H), 2.04–1.85 (m, 9H), 1.65–1.26 (m, 11H), 0.89 (t, J=6.6 Hz, 3H); ESRMS *m*/*z* 355 ([M+K]$^+$); MALDIHRMS calcd for $C_{17}H_{32}OS_2Na$ ([M+Na]$^+$) 339.1787; found 339.1797.

4.16. Oxidation of 22 (23)

A solution of $SO_3{\cdot}Py$ (1.040 g, 6.54 mmol) in DMSO (9.2 mL) was added dropwise to a solution of **22** (690 mg, 2.18 mmol) in CH_2Cl_2 (7.3 mL) and stirred in an ice-water bath. The stirring was continued for 30 min. Water (5 mL) and Et_2O (200 mL) were added and the phases were separated. The organic layer was washed in turn with aq satd $CuSO_4$ (3×5 mL), water (3×5 mL), and brine (10 mL) before being dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (15:1 *n*-hexane/EtOAc) on silica gel to afford the aldehyde **23** as a colorless oil (589 mg, 1.87 mmol, 86% yield). FTIR (film) 1724, 1455, 1238, 1083, 968 cm^{-1}; ^1H NMR δ 9.79 (s, 1H), 5.49–5.33 (m, 2H), 2.83–2.78 (m, 4H), 2.48 (t, J=7.6 Hz, 2H), 2.04–1.75 (m, 12H), 1.52–1.44 (m, 2H), 1.37–1.25 (m, 4H), 0.89 (t, J=7.3 Hz, 3H); ESRMS *m*/*z* 315 ([M+H]$^+$); MALDIHRMS calcd for $C_{17}H_{31}OS_2$ ([M+H]$^+$) 315.1811; found 315.1815.

4.17. Synthesis of 24

A solution of aldehyde **23** (288 mg, 0.91 mmol) in CH_3CN (5 mL) was added to a solution of the sulfoxide reagent **11** (193 mg, 0.91 mmol) in CH_3CN (5 mL). The stirring was continued at rt overnight. Water (5 mL) and Et_2O (30 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to afford the aldehyde **24** as a colorless oil (229 mg, 0.57 mmol, 63% yield). FTIR (film) 3465,

2930, 2860, 1719, 1656, 1454, 1271, 1173, 1039, 970 cm^{-1}; ^1H NMR δ 6.95 (dd, J=16.0, 4.1 Hz, 1H), 6.06 (d, J=16.0 Hz, 1H), 5.47–5.35 (m, 2H), 4.35 (s, 1H), 4.21 (q, J=6.8 Hz, 2H), 2.81–2.79 (m, 4H), 2.09–1.27 (m, 22H), 0.89 (t, J=6.6 Hz, 3H); ESRMS m/z 423 ($[M+Na]^+$); MALDIHRMS calcd for $C_{21}H_{36}O_3S_2Na$ ($[M+Na]^+$) 423.1998; found 423.2003.

4.18. Deprotection of 24 (5c)

Powdered $NaHCO_3$ (548 mg, 6.53 mmol) and I_2 (666 mg, 2.63 mmol) were added in turn to a solution of **24** (300 mg, 0.75 mmol) in 5:1 (v/v) acetone–water (7.5 mL) stirred in an ice-water bath. The mixture was stirred for 15 min when TLC showed disappearance of the starting material. Aq satd $Na_2S_2O_3$ (10 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed in turn with aq satd $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **5c** as a yellowish oil (285 mg, 0.92 mmol, 87% yield). FTIR (film) 3463, 1716, 1658, 1464, 1368, 1304, 1270, 1176, 1039, 970 cm^{-1}; ^1H NMR δ 6.90 (dd, J=15.8, 4.5 Hz, 1H), 6.06 (d, J=15.6 Hz, 1H), 5.41–5.33 (m, 2H), 4.38–4.34 (m, 1H), 4.20 (q, J=7.8 Hz, 2H), 2.66 (d, J=4.8 Hz, 1H), 2.58 (t, J=8.1 Hz, 2H), 2.42 (t, J=7.6 Hz, 2H) 2.01–1.97 (m, 5H), 2.02–1.95 (m, 1H), 1.67–1.26 (m, 2H), 1.39–1.27 (m, 7H), 0.89 (t, J=7.1 Hz, 3H); ESRMS m/z 333 ($[M+Na]^+$); MALDIHRMS calcd for $C_{18}H_{30}O_4Na$ ($[M+Na]^+$) 333.2036; found 333.2040.

4.19. Synthesis of 7c

A mixture of **5c** (233 mg, 0.75 mmol), UHP (529 mg, 5.63 mmol), and *p*-TsOH·H_2O (171 mg, 0.90 mmol) in DME (15 mL) was stirred at rt overnight. The solvent was removed by rotary evaporation and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to afford *cis*-**6c** (63 mg, 0.19 mmol, 26% yield) and *trans*-**6c** (146 mg, 0.45 mmol, 60% yield) as colorless oils. Data for compound *cis*-**6c** (the less polar component): FTIR (film) 3387, 1722, 1660, 1447, 1304, 1268, 1177, 1039 cm^{-1}; ^1H NMR δ 8.21 (s, 1H), 6.97 (dd, J=16.0, 6.0 Hz, 1H), 6.04 (d, J=16.0 Hz, 1H), 5.47–5.38 (m, 2H), 4.82–4.75 (m, 1H), 4.21 (q, J=7.1 Hz, 2H), 2.17–1.96 (m, 9H), 1.71–1.23 (m, 10H), 0.88 (t, J=6.4 Hz, 3H). Data for compound *trans*-**6c** (the more polar component): FTIR (film) 3393, 1722, 1660, 1460, 1370, 1304, 1268, 1178, 1042 cm^{-1}; ^1H NMR δ 8.16 (s, 1H), 6.91 (dd J=15.6, 5.0 Hz, 1H), 6.04 (d, J=15.5 Hz, 1H), 5.47–5.32 (m, 2H), 4.70–4.65 (m, 1H), 4.20 (q, J=7.2 Hz, 2H), 2.32–2.23 (m, 1H), 2.09–2.02 (m, 7H), 1.75–1.26 (m, 11H), 0.89 (t, J=7.1 Hz, 3H). Because these hydroperoxides are not very stable, they should be used as soon as possible.

A mixture of *cis*-**6c** (51 mg, 0.156 mmol) and $HNEt_2$ (1 μL, 0.00975 mmoL) in CF_3CH_2OH (10 mL) was stirred at rt for one day until TLC showed disappearance of the starting material. The solvent was removed by rotary evaporation and the residue was chromatographed (20:1 *n*-hexane/EtOAc) on silica gel to yield **7c** as a colorless oil (16 mg, 0.0491 mmol, 32% yield). FTIR (film) 2956, 2925, 2850, 1739, 1462, 1377, 1278, 971, 911 cm^{-1}; ^1H NMR δ 5.46–5.29 (m, 2H), 4.88 (t, J=6.6 Hz, 1H), 4.33 (d, J=4.6 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 2.38–2.21 (m, 3H), 2.02–1.82 (m, 7H), 1.79–1.64 (m, 2H), 1.53–1.43 (m, 2H), 1.33–1.24 (m, 7H), 0.88 (t, J=6.5 Hz, 3H); MALDIHRMS m/z calcd for $C_{18}H_{30}O_5Na$ ($[M+Na]^+$) 349.1986; found 349.1985.

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References and notes

1. See: e.g., (a) Li, Y.; Wu, Y.-L. *Curr. Med. Chem.* **2003**, *10*, 2197–2230; (b) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73–79; (c) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945–2964; (d) Robert, A.; Dechy-Cabaret, O.; Cazalles, J. M.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167–174; (e) Cremer, D. *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, UK, 1983; Chapter 1, p 3.
2. See: e.g., (a) Griesbeck, A. G.; El-Idreesy, T. T.; Fiege, M.; Brun, R. *Org. Lett.* **2002**, *4*, 4193–4195; (b) McCullough, K. J.; Nonami, Y.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett.* **1999**, *40*, 9151–9155; (c) Dussault, P. H.; Eary, C. T.; Lee, R.; Zope, U. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2188–2204.
3. See: e.g., (a) Ushigoe, Y.; Kano, Y.; Nojima, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 5–10; (b) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *J. Org. Chem.* **1989**, *54*, 1792–1795.
4. (a) Kerr, B.; McCullough, K. J. *J. Chem. Soc., Chem. Commun.* **1985**, 590–591; (b) Subramanyam, V.; Brizulela, C. L.; Soloway, A. H. *J. Chem. Soc., Chem. Commun.* **1976**, 508–509.
5. (a) O'Nill, P. M.; Pugh, M.; Davies, J.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569–4571; (b) O'Nill, P. M.; Hindley, S.; Pugh, M.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, S. A.; Stocks, P. A. *Tetrahedron Lett.* **2003**, *44*, 8135–8138; (c) Tokuyasu, T.; Kunikawa, S.; Abe, M.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Begum, K.; Wataya, Y. *J. Org. Chem.* **2003**, *68*, 7361–7367; (d) Tokuyasu, T.; Kunikawa, S.; McCullough, K. J.; Masuyama, A.; Nojima, M. *J. Org. Chem.* **2005**, *70*, 251–260.
6. (a) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Tetrahedron Lett.* **2001**, *42*, 7281–7285; (b) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 69–72.
7. Jin, H.-X.; Liu, H.-H.; Zhang, Q.; Wu, Y.-K. *Tetrahedron Lett.* **2005**, *46*, 5767–5769.
8. Morimoto, T.; Hirano, M.; Iwasaki, K.; Ishikawa, T. *Chem. Lett.* **1994**, 53–54.
9. (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887–4902; (b) Tanikaga, R.; Nishida, M.; Ono, N.; Kaji, A. *Chem. Lett.* **1980**, 781–782; (c) Tanikaga, R.;

Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134–135; (d) Tanikaga, R.; Nozaki, Y.; Nishida, M.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 729–733.
10. Pattison, F. L. M.; Dear, R. E. A. *Can. J. Chem.* **1963**, *41*, 2600–2606.
11. Amouroux, R.; Ejjiyar, S. *Tetrahedron Lett.* **1991**, *26*, 3059–3062.
12. Winkler, J. D.; Hollardl, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8215–8230.
13. Fleming, I.; Maiti, P.; Ramarao, C. *Org. Biomol. Chem.* **2003**, *1*, 3989–4004.
14. Imai, T.; Muramoto, T.; Tsuji, T. *Chem. Lett.* **1995**, 355–356.
15. Schultz, M.; Waldmann, H.; Kunz, H.; Vogt, W. *Liebigs Ann. Chem.* **1990**, *10*, 1019–1024.

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Oligomers of β-amino acid bearing non-planar amides form ordered structures

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Abstract—In this report, we explore the feasibility of using bicyclic chiral β-amino acids, (1*R*,2*R*,4*S*)- and (1*S*,2*S*,4*R*)-7-azabicyclo[2.2.1]-heptane-2-carboxylic acid (*R*-**Ah2c** and *S*-**Ah2c**, respectively), to prepare novel peptides with unique properties. Facile *cis–trans* isomerization of the non-planar amide bonds of these β-amino acids should result in great flexibility of the backbone structure of β-peptides containing them. Indeed, oligomers of these amino acids showed thermostability and characteristic CD absorptions, which were not concentration-dependent, suggesting that the oligomers remained monomeric. The results indicated the formation of self-organized monomeric structures with chain-length-dependent stabilization. Energy calculations suggested that the peptides can take helical structures in which the energy barriers to cis–trans isomerization are greater for the central amide bonds than for the terminal amides.

1. Introduction

Recently, design of β-peptides, i.e., peptides containing β-amino acids, has been attracting attention because of the feasibility of derivatization with various side chains at either or both of the α- and β-positions.[1,2] This extends the range of peptide scaffolds potentially available for the creation of novel functional molecules and materials. Since β-peptides are not readily susceptible to proteolysis, they are also promising platforms for the design of new pharmaceuticals, including enzyme inhibitors, receptor agonists, and antagonists.[3]

β-Peptides, comprised of β-amino acids, have an extra methylene group along the backbone, compared with natural proteins. This extra methylene group provides more scope for the introduction of functional side chains on the peptide backbone, but simultaneously results in greater flexibility of the peptide backbone. Therefore, in order to create a spatially ordered structure, methods to reduce the flexibility of the peptide backbone, such as introduction of 2-aminocyclohexanecarboxylic acid,[2c] β-prolines[2d] or bulky substituents,[1a] have been employed. Such structures would diminish the loss of entropy of the protein when an ordered structure is formed by enthalpy-driven intramolecular interaction.[4] Amide bonds in a peptide backbone usually take a planar structure, and this structural feature can be considered to compensate, in some respects, for the entropic loss upon the formation of higher-order structures.[1,2] On the other hand, the planar amide structure also restricts the structural design of peptides, because if we could employ a non-planar amide backbone structure, novel high-order structures might be designable.

Bicyclic 7-azabicyclo[2.2.1]heptane amides (Fig. 1a) take intrinsically non-planar structures, i.e., they exhibit nitrogen-pyramidalization and twisting with respect to the N–C(=O) bond, in the solid,[5a] solution,[5c] and gas (computation) phases.[5b,c] The tilt angles (α) of *N*-aroyl-7-azabicyclo[2.2.1]-heptanes range from 26 to 31° in the X-ray crystal structures.[5] Non-planarity of these amides in solution has also been suggested on the basis of the reduction of rotational barriers to the cis–trans isomerization of the amide bonds (see Fig. 4a). These dynamic features of this skeleton have been proposed to stem from: (i) angle strain of the bicyclic ring structure and (ii) 1,3-allylic type strain induced by the repulsion between the bridgehead protons and the amide moiety. The rigid bicyclic ring structure should also be beneficial to diminish the entropic loss if oligomers of these amino acids form higher-order structures. Although employment of

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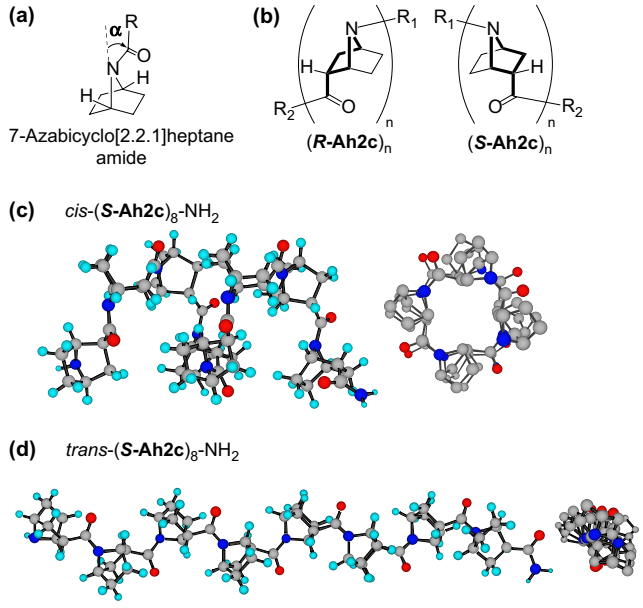


Figure 1. (a) 7-Azabicyclo[2.2.1]heptane amide and (b) **Ah2c** peptides. n=1, 2, 3, 4, 5; R_1=H·HCl, R_2=OH; HCl·H-(*S*-**Ah2c**)$_n$-OH. n=4, 5, 8; R_1=H, R_2=NH_2; H-(*S*-**Ah2c**)$_n$-NH_2. n=8; R_1=H, R_2=NH_2; H-(*R*-**Ah2c**)$_n$-NH_2. Side view and top views of (c) *cis*- and (d) *trans*-H-(*S*-**Ah2c**)$_8$-NH_2 obtained by B3LYP/6-31G* calculations.

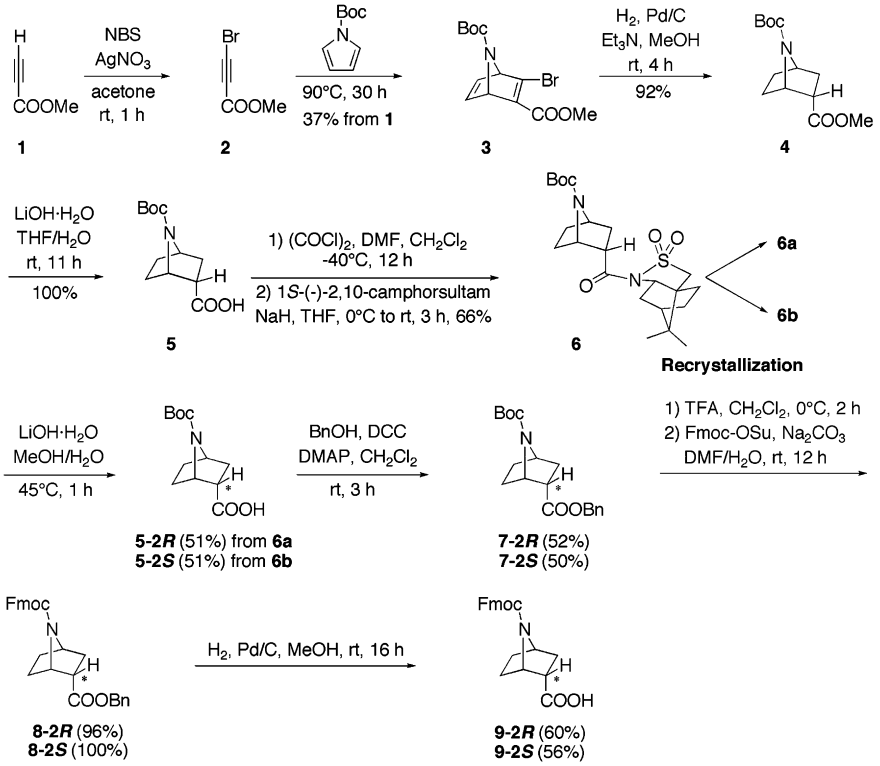
such non-planar-amide amino acids is expected to broaden the scope for design of novel peptide-based scaffolds, few studies have been reported on the structures of homo-oligomers with enforced non-planar amides.[6] Thus, in order to obtain basic information about the influence of amide non-planarity on the formation of high-order structures as a step toward the design of functional molecules composed of such amino acids,[7] we have investigated in this study the properties of oligomers of chiral β-amino acids based on the 7-azabicyclo[2.2.1]heptane skeleton, i.e., (1*R*,2*R*,4*S*)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (*R*-**Ah2c**) and (1*S*,2*S*,4*R*)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (*S*-**Ah2c**) (Fig. 1b). We show that oligopeptides of our β-amino acids, having enhanced nitrogen inversion and facile *cis–trans* amide isomerization, do form ordered monomeric structures, suggesting the feasibility of employing peptides composed of amino acids bearing non-planar amide bonds as novel peptide scaffolds.

2. Results and discussion

2.1. Synthesis of bicyclic β-amino acids and their homopeptides

Racemic amino acid **5** was synthesized by modifications of the method of Zhang and Trudell,[8] and the enantiomers **6a** and **6b** were each obtained in enantiopure form by repeated recrystallization after introducing Oppolzer's camphorsultam on the carboxylic acid moiety as a chiral auxiliary (Scheme 1).[9]

For the synthesis of the oligomers of this amino acid, the Boc derivatives (**5**-2*R* and 2*S*) and the Fmoc derivatives (**9**-2*R* and 2*S*) were prepared. Since these amino acids have highly hindered and strained structures, we first examined whether construction of oligomers was possible by using solution- and solid-phase methods. Solution-phase synthesis was employed for the preparation of the dimer to pentamer of *S*-**Ah2c**. The benzyl ester of *S*-**Ah2c** was obtained by removing the Boc group from **7**-2*S*, and this was condensed with Boc derivatives of *S*-**Ah2c** (**5**-2*S*) using the hydrochloride



Scheme 1. Synthesis of bicyclic amino acids.

salt of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI·HCl) in DMF (n=2, 3, 4, 5, R_1=*tert*-butoxycarbonyl, R_2=OCH_2Ph). The repetitive removal of the N-terminus of the oligomer and introduction of the Boc derivative of *S*-**Ah2c**, followed by the final deprotection of the N-terminal *tert*-butoxycarbonyl and C-terminal benzyl groups (n=1, 2, 3, 4, 5, R_1=H·HCl, R_2=OH) with catalytic hydrogenation and 4 N HCl treatment, yielded the desired oligomers of *S*-**Ah2c**. Alternatively, solid-phase synthesis using the Rink amide resin and the benzotriazolyloxotris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP)–*N*-hydroxybenzotriazole (HOBt) coupling procedure was employed for the preparation of the 4-, 5-, and 8-mers of *S*-**Ah2c** (n=4, 5, 8, R_1=H, R_2=NH_2).[9] After construction of the peptide chains, the peptide-resin was treated with trifluoroacetic acid in the presence of ethanedithiol, followed by HPLC purification to give highly pure peptides. The octamer of *R*-**Ah2c** was similarly prepared by the solid-phase procedure (n=8, R_1=H, R_2=NH_2). All syntheses proceeded without difficulty. This suggested that the conventional solution- and solid-phase methods are applicable to this amino acid, in spite of the steric hindrance due to the rigid side chain.

2.2. CD and UV spectroscopic studies of oligomers: chain-length dependence of spectra

In order to study whether the oligomers of *R*-**Ah2c** can generate structure in solution, the circular dichroism (CD) spectra in methanol (100 μM) were recorded. A characteristic and intense CD spectrum of the octamer H-(*R*-**Ah2c**)$_8$-NH_2 was obtained in the far-UV region (190–260 nm) (Fig. 2a). The mean residue ellipticity of H-(*R*-**Ah2c**)$_8$-NH_2 shows a maximum at 198 nm and a minimum at 217 nm. This spectrum does not coincide with those of typical structures of natural peptides (composed of α-amino acids), but resembles those observed for helical β-peptide oligomers based on β-proline[2d] and those of helical β-peptide oligomers with amide protons based on *trans*-2-aminocyclopentanecarboxylic acid[2c] or β^{2,3}-peptide (compound **7c** in Ref. 1a), reported previously.

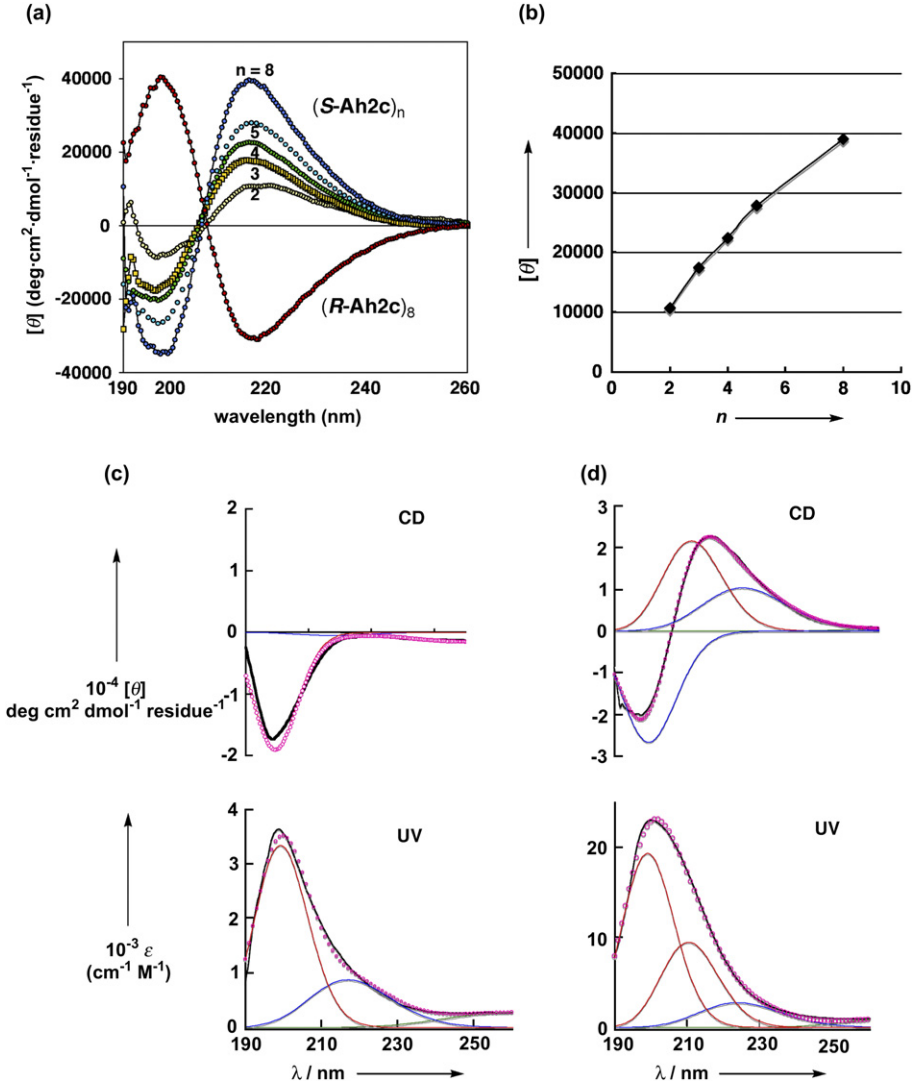


Figure 2. (a) CD spectra of H-(*R*-**Ah2c**)$_8$-NH_2, HCl·H-(*S*-**Ah2c**)$_{1-5}$-OH, and H-(*S*-**Ah2c**)$_8$-NH_2 measured at 100 μM in MeOH at 20 °C. (b) Dependence of CD intensity at 217 nm on the number of oligomers of (*S*-**Ah2c**)$_n$, derived from (a). Band deconvolution of the UV and CD spectra of (c) HCl·H-(*S*-**Ah2c**)-OH (monomer) measured at 100 μM in MeOH and (d) HCl·H-(*S*-**Ah2c**)$_4$-OH (tetramer) measured at 100 μM in MeOH. Sample cells of 1-mm path length were used for CD measurement. Black line: experimental spectra of **Ah2c** monomer or tetramer measured at 100 μM in MeOH at 20 °C (CD) and at rt (UV), red line: π–π* transition, blue line: n–π* transition, pink circles: simulated spectra.

The octamer peptide of the enantiomeric configuration, H-(*S*-**Ah2c**)$_8$-NH$_2$, showed a symmetric spectrum with respect to that of H-(*R*-**Ah2c**)$_8$-NH$_2$ in terms of the Cotton effects. This suggests that, even though these enantiomeric amino acids have flexibility in the amide structure, their oligomers converge in terms of higher-order structures; this suggests the induction of thermodynamically stable conformations. Of particular interest is the observation of an apparent length-dependent trend in the CD spectra of the *S*-**Ah2c** oligomers: in the CD spectra of the trimer, tetramer, pentamer, and octamer of *S*-**Ah2c**, the positions of the minimum (198 nm) and the maximum (217 nm) are similar, and the intensity per residue (values normalized for concentration and the number of residues) at both the minimum and the maximum increase as the number of monomer units increases (Fig. 2b).[10] These oligomers also showed an isodichroic point (see below). This observation strongly suggests that CD-active regular secondary structures are induced and are increasingly favored as the peptide chain is elongated. Note that H-(*S*-**Ah2c**)$_n$-NH$_2$ and H-(*S*-**Ah2c**)$_n$-OH (n=4 and 5) showed practically identical CD spectra in methanol, indicating that the difference in C-terminal structure does not significantly affect the higher-order structure formation. Similar chain-length-dependent increase in CD intensities has also been observed in other ordered systems.[3,10] In the case of water-soluble amphiphilic peptides, aggregation stimulated by hydrophobic interaction would be a cause of such stabilization. However, this is not so in the present case; essentially identical CD spectra were obtained at peptide concentrations in the range of 50–1000 μM for H-(*S*-**Ah2c**)$_5$-NH$_2$ and HCl·H-(*S*-**Ah2c**)$_4$-OH with no significant change in molecular ellipticity at 217 nm ($[\theta]_{217}$) (Fig. 3). Since methanol is effective to reduce hydrophobic interactions, inhibiting possible aggregation of peptides,[11] these results are suggestive of monomeric structures of the oligomers.

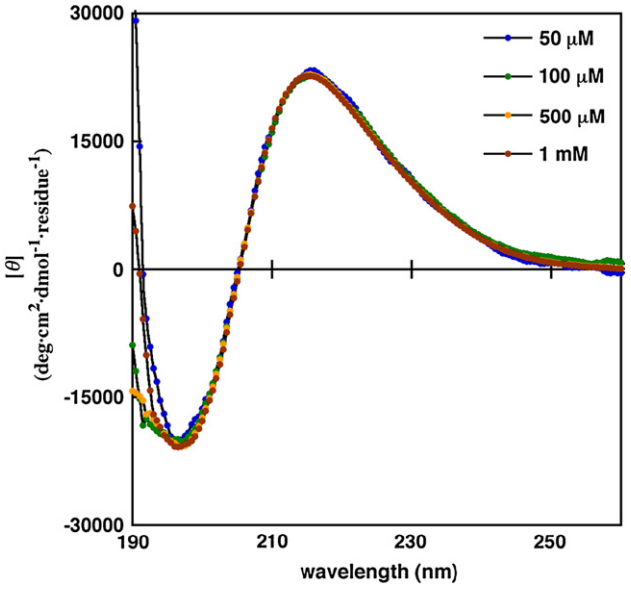


Figure 3. Concentration dependence study. CD spectra of HCl·H-(*S*-**Ah2c**)$_4$-OH at 50, 100, 500, and 1000 μM (1 mM) in MeOH at 20 °C. There is a normal concentration dependency in the intensity of the CD spectra between 50 and 1000 μM in methanol; that is, after concentration normalization, the CD spectra are consistent.

Therefore, the **Ah2c** peptides are considered to adopt a *self-organized* monomeric structure. The question arises, what is the major driving force for the structure formation? In a hydrophobic environment, intramolecular hydrogen bonding or ion-pair interaction is effective. However, this is not the case here, since there is no amide proton or charged group in these peptides; thus, presumably the increase of the inter-residue van der Waals attraction[3,12] is a factor in this structural organization. Support for this interpretation comes from the results of the study of the thermal stability of these peptides. A gradual decrease in $[\theta]_{217}$ in the CD spectra of the octamer, pentamer, and tetramer peptides was observed when the temperature was raised to 60 °C: decreases of 11, 20, and 31% compared with the $[\theta]_{217}$ values at 20 °C were obtained, respectively, and no significant thermal transition of these peptides was observed. The degree of the reduction of $[\theta]_{217}$ is smaller in longer peptides, which suggests stabilization of the secondary structures in longer peptides.

2.3. Structure of the oligomers

The above results suggested that, even when a peptide lacks a planar amide structure and has flexibility in the amide bonds, it can show a preference for ordered structures, presumably with the contribution of conformationally strained side chains to reduce entropic loss upon the thermodynamically driven formation of the high-order structures. NMR study of the tetramer only gave broad signals for all the protons (see Supplementary data, Fig. S3), which is consistent with the presence of a mixture of isomers with respect to the *cis–trans* amides in the oligomers. This possible cis–trans isomerization was confirmed by NMR measurement of the terminal-protected dimer of **Ah2c**; in the ^{1}H NMR spectrum ($CDCl_3$) of the *N*-Boc-*S*-dimer-benzyl ester, a mixture of *cis*- and *trans*-amide (*cis:trans*=47:53) structures with respect to the central amide bond was observed (see Supplementary data, Fig. S2) (the *trans*-amide crystal structure was obtained for *t*-Boc-(*R*-**Ah2c**)$_2$-OBn; Fig. 4 (CCDC 621064), see Supplementary data for a summary of the data). This observed non-biased mixture of the isomers is compatible with the calculated small energy difference (Fig. 5). Thus, there is an equilibrium mixture of *cis*- and *trans*-amide structures in solution. Since the oligomers have several amide bonds, overlapping of the signals from various *cis–trans* isomerization states of the peptide would give broad and complex signals, making structural characterization difficult. However, it is plausible that oligomerization of **Ah2c** may increase the preference for the ultimate, thermodynamically stable ordered structures. This would be consistent with the observed chain-length dependency and thermostability of the peptides.

The possible formation of helical structure was next examined. Firstly, the UV and CD spectra of the oligopeptides were compared with those of the corresponding monomeric amino acid. As shown in Figure 2c, the monomer exhibited an intense absorption band at ca. 200 nm and a shoulder at longer wavelength. As is usual for naturally occurring peptides, these bands can be assigned, respectively, to the electric dipole allowed π–π* transition and the forbidden n–π* transition of the peptide chromophore.[13] The UV absorption bands of the oligomers broadened systematically toward

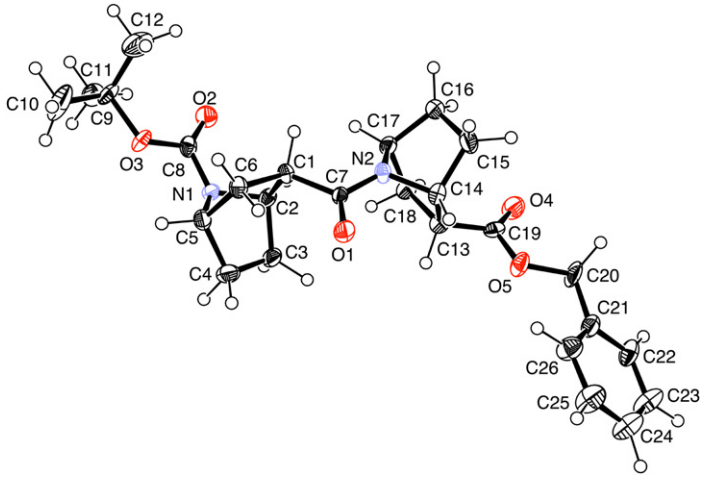


Figure 4. ORTEP diagram of *trans*-amide structure of dimer, *t*-Boc-(*R*-**Ah2c**)$_2$-OBn (at 150 K).

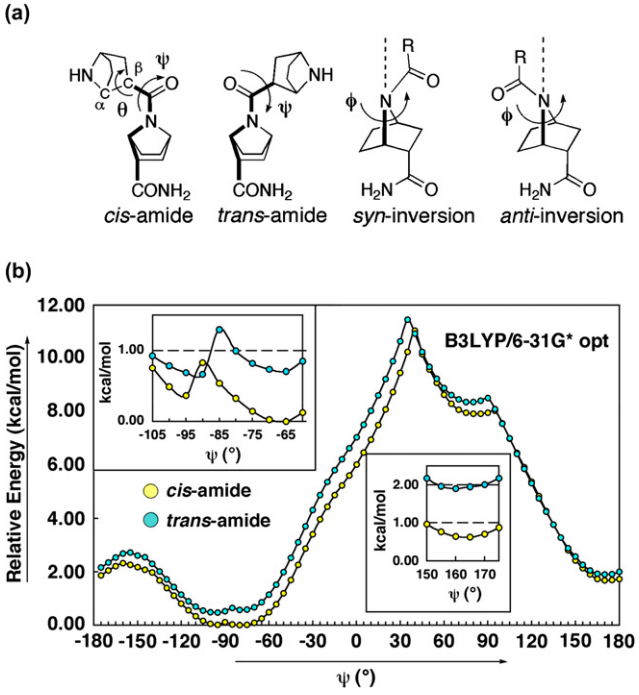


Figure 5. (a) *cis*- and *trans*-Amide dimers, H-(*S*-**Ah2c**)$_2$-OH, of 7-azabicyclo[2.2.1]heptane amide and their *syn*- and *anti*-inversions. (b) Scans of the potential surface at the B3LYP/6-31G* level for the cis- (yellow) and trans-conformers (green). The potential surface was scanned with respect to the ψ torsion for *cis*-H-(*S*-**Ah2c**)$_2$-OH (yellow) and *trans*-H-(*S*-**Ah2c**)$_2$-OH (green). Inset: energies (MP2/6-31G* level) are relative to the global minimum, *cis* (−65°). Two additional minima for *cis*-(*S*-**Ah2c**)$_2$ are located at ψ values of −95° and 165°. Three minima for *trans*-H-(*S*-**Ah2c**)$_2$-OH are located at −90°, −65°, and 160°.

the longer-wavelength region, with increasing number of monomeric units. While the CD signals of the oligopeptides appear to be dispersion-type signals, an absorption-shaped CD signal was observed for the monomeric amino acid.

In order to estimate the number of transitions in the UV region, a band deconvolution analysis of the experimental data was carried out (Fig. 2c and d). This approach rests on the fact that a single set of Gaussian components can be used for fitting of both the UV and CD spectra (Table 1).[14] In the case of the monomer, three Gaussian bands were used, two of which can be associated with the π–π* (red line, λ_{max}=200 nm, f=0.063) (red line) and n–π* (blue line, λ_{max}=218 nm, f=0.022) (blue line) transitions (Fig. 2c). In contrast, at least four Gaussian bands were required to fit the spectra of the tetramer. The two higher-energy bands (λ_{max}=199 nm, f=0.374 and λ_{max}=211 nm, f=0.182) should be associated with the splitting of the π–π* transitions (red line) as a result of the strong exciton interactions, while the lower-energy band (λ_{max}=225 nm, f=0.066) was assigned to the n–π* band (blue line) (Fig. 2d). As a result, the intense CD signals observed for the oligomers are considered to arise from couplings between the n–π* transition and the π–π* transitions on nearby amides,[15] as well as couplings between the π–π* transitions of the amide units,[16] similar to those of α-helical polypeptides. Since these CD signals would depend strongly on the transition moment directions, it can be concluded that the oligomers adopt well-defined structures, plausibly helical structures, under the experimental conditions.

Table 1. Results of the Gaussian fit analysis of the monomer and tetramer

Compound	Band no.	Assignment	Wavelength (nm)	Energy (cm^{-1})	Intensity (dm^3/mol cm)	Bandwidth (cm^{-1})	Oscillator strength (f)	μ (D)
Monomer	1		262	38,140	274	6666	0.008	0.09
	2	n–π*	218	45,970	874	5390	0.022	0.19
	3	π–π*	200	50,121	3332	4103	0.063	0.51
Tetramer	1		271	36,908	1373	5258	0.033	0.37
	2	n–π*	225	44,529	2721	5282	0.066	0.61
	3	π–π*	211	47,454	9475	4169	0.182	1.57
	4	π–π*	199	50,157	19,299	4209	0.374	3.05

2.4. Model study

Assuming that the oligomers prefer helical structures, then what kind of structure is probable? To address this question, quantum chemical calculations were carried out first for the dimer, H-(*S*-**Ah2c**)$_2$-OH, at the B3LYP/6-31G* level. In the case of β-amino acids such as those in this study, there are three valuable parameters.[17] The ϕ, θ, and ψ torsions are defined as [$C_{(i-1)}$–N_i–$C_{\alpha i}$–$C_{\beta i}$], [N_i–$C_{\alpha i}$–$C_{\beta i}$–C_i], and [$C_{\alpha i}$–$C_{\beta i}$–C_i–$N_{(i+1)}$], respectively. In the present case, $\phi=-91^\circ$ (in the case of *syn*) or -151° (in the case of *anti*) and $\theta=-162^\circ$ due to the rigid bicyclic 7-azabicyclo[2.2.1]-heptane structure, so that the most stable structure(s) can be obtained only by changing ψ. We have considered two types of isomerism of amide (*cis* and *trans*) and two directions of inversion (*syn* and *anti*) (Fig. 5a). The ψ value was changed stepwise every five degrees and the obtained structures were optimized. For each ψ, both *syn*- and *anti*-inversion cases were calculated for the *cis*-amide and *trans*-amide structures and the energetically more stable cases with respect to the inversion were chosen (Fig. 5b). A calculated inversion barrier was small (2.5 kcal/mol).[5c] Three energetically minimum structures were obtained for both the *cis*- and *trans*-amide structures. The results indicate that the amide bonds are not planar and that they take *cis*- or *trans*-conformation. Further calculations at the MP2/6-31G* level in the vicinity of the above three minima revealed that the most stable structure is the *cis*-amide at $\psi=-65^\circ$ attained via *syn*-inversion (the most stable *trans*-amide was obtained at $\psi=-90^\circ$ via *syn*-inversion, but the energy is higher than that of the most stable *cis*-amide by 0.69 kcal/mol). The same result was obtained when the solvent (water) was taken into account. The ϕ, θ, and ψ values in the most stable structure, after full optimization, were -86°, -162°, and -65°, respectively.

A single crystal structure of the *trans*-amide of the enantiotropic dimer, *t*-Boc-(*R*-**Ah2c**)$_2$-OBn was obtained (Fig. 4). The central amide bond is pyramidalized ($\alpha=21.5^\circ$), and the nitrogen atom is *syn*-inverted. The observed torsion angles, ψ, ϕ and θ were +82.9 (3)°, +98.3 (3)°, and +153.2 (2)°, respectively. The absolute magnitudes of these values were consistent with the computationally estimated values (-90°, -91°, and -162°, respectively) of the most stable *trans*-amide structure of the *S*-dimers (that is, *syn*-inverted). This supports the validity of the present computational structural analysis.

In the next step, a Monte-Carlo conformation search was performed for the all *cis*- or *trans*-amide forms of the octamer (H-(*S*-**Ah2c**)$_8$-NH_2) by means of MMFF94s force-field calculations, and the resultant most stable structure was further optimized at the B3LYP/6-31G* level. It was found that the *cis*-amide conformer takes a left-handed helical structure with four residues per turn (Fig. 1c), while the *trans*-amide conformer takes an elongated helical structure with roughly two residues per turn (Fig. 1d). The average values of the torsion angle ψ ($C_{\alpha i}$–$C_{\beta i}$–C_i–$N_{(i+1)}$) of the optimized structures of the octamer are -68° for the *cis*-amide helix, and -90° for the *trans*-amide helix. These ψ values are consistent with those for the energy minimum structures of the *cis*- and *trans*-dimers, respectively (Fig. 5). The *cis*-amide helix structure was estimated to be more stable than the *trans*-amide helical structure by 7.8 kcal/mol by means of MP2/6-31G* calculations. This result, together with the presence of an isodichroic point for oligomers with $n=3$–8 (Fig. 2a), allows us to propose a possible ultimate structure of the oligomers of bicyclic β-amino acids with 7-azabicyclo[2.2.1]heptane, i.e., a helical structure with *cis*-amide and with four residues per turn, in the presence of the *trans* conformer to some extent. It was also shown that the energy barriers with respect to the *cis–trans* isomerization increase in the center of the oligomers as compared with the terminal amides in the hexamer (H-(*S*-**Ah2c**)$_6$-NH_2): in the model cis-helix structure of the hexamer (H-(*S*-**Ah2c**)$_6$-NH_2) obtained similarly, the *cis*-to-*trans* rotational barriers were as follows: with respect to the first amide bond from the N-terminal: HF/6-31G*, 10.65 kcal/mol (HF/3-21G*, 9.28 kcal/mol); the second amide bond: HF/6-31G*, 11.32 kcal/mol (HF/3-21G*, 9.08 kcal/mol); the third amide bond: HF/6-31G*: 12.29 kcal/mol (HF/3-21G*:11.52 kcal/mol). The rotational barrier increased toward the center along the helix. This is consistent with the length-dependent increase of the robustness of the ordered structures deduced from the CD spectra.

3. Conclusions

In this study, we have shown that homooligomers of bicyclic β-amino acids containing 7-azabicyclo[2.2.1]heptane **Ah2c**, which lacks amino hydrogen and has a spatially hindered structure, can be synthesized without difficulty. Although coexistence of the *cis* and *trans* isomers with respect to the non-planar amide bonds has been suggested, oligomerization of **Ah2c** significantly promoted the formation of higher-order structures, yielding characteristic CD spectra. Deconvolution and modeling studies suggest the formation of unique helical structures without intramolecular hydrogen bonds. These results support the idea that β-amino acids bearing non-planar amide bonds can be used to generate novel protein scaffolds. The ordered structure may be attained owing to the spatially strained structure of the side chain, which would compensate for the loss of entropy and simultaneously gain enthalpy to form the ordered structures in the presence of cis–trans isomerizable amide bonds. On the other hand, the non-planarity of the amide bond should endow the resulting scaffolds with unique features, which may yield properties different from those of scaffolds composed of units with typical planar amide bonds. The results obtained in this study suggest that it may also be feasible to construct protein scaffolds comprised of other *N*-substituted β-amino acids. Because of the interest in chemical features of amino acid derivatives based on the 7-azabicyclo[2.2.1]-heptanes, the possibility of derivatization at amide nitrogen, in addition to α- and β-carbon atoms, should offer great scope to design novel functional molecules and materials showing unique chemical and physical properties. Thus, we believe our results make feasible a novel approach to protein scaffold design.

4. Experimental

4.1. General methods

All the melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Proton

(400 MHz) NMR spectra were measured on a JEOL Caliber-GX400 NMR spectrometer with TMS as an internal reference in $CDCl_3$ as the solvent, unless otherwise specified. Chemical shifts δ are shown in parts per million. Coupling constants are given in hertz. Low-resolution EI mass spectra (MS, EI^+) and high-resolution EI mass spectra (HRMS, EI^+) were recorded on a JEOL JMS-O1SG-2 spectrometer. Low-resolution FAB mass spectra (MS, FAB^+) and high-resolution FAB mass spectra (HRMS, FAB^+) were recorded on a JEOL MStation JMS-700 spectrometer. Matrix-assisted laser desorption ionization time-of-flight mass spectra (MALDI-TOF MS) were recorded on an Applied Biosystems Voyager-DE STR instrument. ESI-TOF MS (ESI^+) were recorded on a Bruker Daltonics, micro-TOF-LC, and Micromass, micromass-LCT instruments. Column chromatography was carried out on silica gel (silica gel 60 N (100–210 μm), Merck). The combustion analyses were carried out in the microanalytical laboratory of this faculty.

4.2. Materials

Racemic bicyclic amino acid (**5**) was synthesized by modifications of the method of Zhang and Trudell and Singh et al.,[8,18–20] and each optically pure enantiomer was obtained by repeated recrystallization after introducing Oppolzer's camphorsultam on the carboxylic acid moiety as a chiral auxiliary.

4.3. Synthesis of chiral bicyclic amino acids

4.3.1. Methyl 3-bromopropiolate (2). To a magnetically stirred solution of methyl propionate **1** (25 mL, 281 mmol) in acetone (300 mL) at rt, silver nitrate (4.71 g, 27.7 mmol) was added, followed by the addition of *N*-bromosuccinimide (58.26 g, 327.3 mmol) in one portion. The homogeneous solution turned cloudy within 5 min, then a grayish solid was precipitated and the whole was stirred for 1 h. Acetone was removed carefully under reduced pressure at rt and the residue was distilled at rt to afford **2** as a pale yellow oil (45.2 g as a mixture of acetone, 67% NMR yield).

^{1}H NMR: 3.79 (s, 3H).

4.3.2. Methyl 2-bromo-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (3). A solution of **2** (188 mmol) and *tert*-butyl 1-pyrrolecarboxylate (100 mL, 598 mmol) in acetone was heated at 90 °C for 30 h with stirring under Ar atmosphere. The resulting mixture was subjected to column chromatography (*n*-hexane/AcOEt 9:1). Compound **3** (33.92 g, 37% yield) was obtained as a yellow oil.

^{1}H NMR: 7.13 (br s, 2H), 5.50 (br s, 1H), 5.15 (br s, 1H), 3.79 (s, 3H), 1.41 (s, 9H).

4.3.3. Methyl 7-(*tert*-butoxycarbonyl)-7-azabicyclo-[2.2.1]heptane-2-carboxylate (4). A solution of **3** (367 mg, 1.11 mmol) in MeOH was hydrogenated catalytically (10% Pd/C) in the presence of triethylamine (218 mg, 2.15 mmol). The mixture was filtrated, the solvent was evaporated, and the residue was subjected to column chromatography (*n*-hexane/$CHCl_3$=1/6, then $CHCl_3$ only). Hydrogenated compound **4** (262 mg, 92% yield) was obtained as a yellow oil.

^{1}H NMR: 4.39 (br s, 1H), 4.21 (br s, 1H), 3.70 (s, 3H), 3.04 (m, 1H), 2.00–1.50 (m, 6H), 1.47 (s, 9H).

4.3.4. 7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (5). To a solution of **4** (7.90 g, 30.95 mmol) in THF (80 mL), a solution of lithium hydroxide monohydrate (1.60 g, 38.13 mmol) in 20 mL of water was added, and the mixture was stirred at rt for 11 h. The organic solvent was evaporated and the residue was acidified to pH=2. Then the whole was extracted with AcOEt, the organic phase was washed with brine, and the solvent was evaporated to afford **5** (7.25 g, quant.) as a brown oil.

MS (*m*/*z*): 241 ($M+H^+$). HRMS (EI^+, $M+H^+$) calcd for $C_{12}H_{19}NO_4$: 241.1313; obsd: 241.1308. ^{1}H NMR: 4.45 (br s, 1H), 4.23 (br s, 1H), 3.13–3.10 (m, 1H), 2.00–1.46 (m, 6H), 1.46 (s, 9H).

4.3.5. 7-(*tert*-Butoxycarbonyl)-2-*endo*-bornane-2,10-sultam-7-azabicyclo[2.2.1]heptane (6). To a stirred solution of **5** (936 mg, 3.79 mmol) in dry CH_2Cl_2 was added dropwise a solution of oxalyl chloride (0.8 mL, 9.1 mmol) in dry CH_2Cl_2 at −70 °C. When the addition was finished, a catalytic amount of dry DMF (two drops) was added, and the reaction mixture was stirred for 24 h at −40 °C. The solvent and unreacted oxalyl chloride were removed in vacuum to afford the acid chloride. Under Ar atmosphere, a solution of 1*S*-(−)-2,10-camphorsultam (1000 mg, 4.64 mmol) in THF was added to a solution of NaH (65% in oil, washed with *n*-hexane, 383 mg, 10.37 mmol) in THF at 0 °C and the reaction mixture was stirred for 20 min at 0 °C. Then to the mixture was added dropwise a solution of the acid chloride in THF at 0 °C and the whole was stirred for 12 h at rt. Addition of water, followed by 2 N aqueous HCl, quenched the reaction, and the whole was extracted with AcOEt, and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated to give a pale yellow solid, which was chromatographed (*n*-hexane/AcOEt=4/1) to give a mixture of **6a** and **6b** (1.13 g, 66% yield). The mixture was stirred in *n*-hexane/Et_2O/AcOEt to give a suspension and the precipitate was filtered to afford **6b** as a colorless solid. Pure **6a** was obtained as colorless needles by recrystallization of the residue from *n*-hexane/CH_3CN/$^i Pr_2O$.

4.3.5.1. 6a + 6b. Anal. Calcd for $C_{22}H_{34}N_2O_5S$: C, 60.25; H, 7.81; N, 6.39. Found: C, 59.95; H, 7.58; N, 6.32.

Compound **6a**: mp 182.9–183.1 °C (colorless needles). Anal. Calcd for $C_{22}H_{34}N_2O_5S$: C, 60.25; H, 7.81; N, 6.39. Found: C, 60.55; H, 7.86; N, 6.40. ^{1}H NMR: 4.71–4.69 (1H, m), 4.25–4.21 (1H, m), 3.91–3.87 (1H, m), 3.58–3.53 (1H, m), 3.51 (1H, d, *J*=14.0 Hz), 3.46 (1H, d, *J*=14.0 Hz), 2.10–1.63 (13H, m), 1.47 (9H, s), 1.15 (3H, s), 0.98 (3H, s).

Compound **6b**: mp 208.0–208.5 °C (colorless solid). Anal. Calcd for $C_{22}H_{34}N_2O_5S$: C, 60.25; H, 7.81; N, 6.39. Found: C,

60.10; H, 7.76; N, 6.40. ^{1}H NMR: 4.66–4.64 (1H, m), 4.24–4.22 (1H, m), 3.91–3.89 (1H, m), 3.62–3.55 (1H, m), 3.52 (1H, d, J=14.0 Hz), 3.44 (1H, d, J=13.6 Hz), 2.10–1.80 (7H, m), 1.80–1.65 (2H, m), 1.60–1.40 (4H, m), 1.47 (9H, s), 1.15 (3H, s), 0.99 (3H, s).

4.3.6. (1*R*,2*R*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (5-2*R*). A solution of **6a** (2.29 g, 5.21 mmol) in 40 mL of MeOH/H_2O (3:1) mixture containing $LiOH\cdot H_2O$ (220 mg, 5.24 mmol) was warmed to 45 °C with stirring. After 1 h, the mixture was cooled and the resulting solution was extracted with AcOEt to remove the chiral auxiliary sultam. The aqueous layer was acidified to pH=3 with 1 N aqueous HCl under an ice-cold condition, and the whole was extracted with $CHCl_3$. The crude acid **5**-2*R* (641 mg, yield 51%) was obtained as a pale yellow oil after evaporation of the organic solvent.

4.3.7. (1*S*,2*S*,4*R*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (5-2*S*). Compound **5**-2*S* was obtained in a similar manner to **5**-2*R*, described above.

4.3.8. Determination of the absolute stereochemistry of 5-2*R*. The absolute configuration of the resolved material was established by the optical rotation, and crystallographically.

Carboxylic acid **5**-2*R* (8 mg, 0.033 mmol) was converted to methyl ester by using TMS–diazomethane in benzene. Then the reaction mixture was evaporated to give quantitatively 10 mg of white solid (**4**-2*R*).

$[\alpha]_D^{23}$ −20.80 (*c* 0.50, $CHCl_3$), lit.[20] $[\alpha]_D^{23}$ −22.6 (*c* 1.01, $CHCl_3$).

4.3.9. (1*R*,2*R*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid 2-benzyl ester (7-2*R*). To a solution of **5**-2*R* (713 mg, 2.95 mmol), benzyl alcohol (0.95 mL, 9.11 mmol), and dimethylaminopyridine (290 mg, 2.37 mmol) in 5 mL of CH_2Cl_2 was added dicyclohexylcarbodiimide (671 mg, 3.25 mmol) at 0 °C. The whole was warmed to rt and stirred for 3 h. The precipitate was filtered and washed with ether. The combined organic layer was washed with 0.5 N aqueous HCl, saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and the solvent was evaporated. The residue was chromatographed (*n*-hexane/AcOEt=2/1) to give **7**-2*R* as a yellow oil (513 mg, 52% yield).

MS (*m*/*z*): 331 ($M+H^+$). HRMS (EI^+, $M+H^+$) calcd for $C_{19}H_{25}NO_4$: 331.1782; obsd: 331.1797. ^{1}H NMR: 7.40–7.33 (5H, m), 5.14 (2H, s), 4.42–4.40 (1H, m), 4.21–4.19 (1H, m), 3.13–3.06 (1H, m), 1.97–1.91 (1H, m), 1.90–1.85 (1H, m), 1.85–1.80 (1H, m), 1.73–1.67 (1H, m), 1.45 (9H, s), 1.45 (2H, m, overlap).

4.3.10. (1*S*,2*S*,4*R*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid 2-benzyl ester (7-2*S*). Compound **7**-2*S* was obtained in a similar manner to **7**-2*R*, described above.

4.3.11. (1*R*,2*R*,4*S*)-7-(Fluorenylmethyl)-7-azabicyclo[2.2.1]heptane-2,7-dicarboxylic acid 2-benzyl ester (8-2*R*). To a solution of **7**-2*R* (351 mg, 1.06 mmol) in 2 mL of dry CH_2Cl_2 was added 2 mL of trifluoroacetic acid at 0 °C and the mixture was stirred for 1.5 h at 0 °C. Then the solvent was evaporated to give a crude oil. This residue was dissolved in 7 mL of water, and to this solution Na_2CO_3 (320 mg, 3.01 mmol) was added, followed by the addition of a solution of 9-fluorenylmethyl succinimidyl carbonate (471 mg, 1.40 mmol) in 7 mL of dry DMF at 0 °C. The resultant viscous solution was stirred vigorously for 12 h at rt. The aqueous layer was acidified to pH=3 with 1 N aqueous HCl and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give a crude oil, which was chromatographed (*n*-hexane/AcOEt=2/1) to give **8**-2*R* as a red-brown oil (461 mg, 96% yield). MS (*m*/*z*): 453 ($M+H^+$). HRMS (EI^+, $M+H^+$) calcd for $C_{29}H_{27}NO_4$: 453.1939; obsd: 453.1931. ^{1}H NMR: 7.71–7.69 (2H, m), 7.58–7.55 (2H, m), 7.38–7.26 (9H, m), 5.13 (2H, s), 4.49–4.30 (2H, m), 4.38 (1H, br s), 4.19 (2H, t, J=6.2 Hz), 3.00–2.80 (1H, br s), 1.84–1.82 (2H, m), 1.70–1.67 (1H, m), 1.63–1.58 (1H, m), 1.46–1.37 (2H, m).

4.3.12. (1*S*,2*S*,4*R*)-7-(Fluorenylmethyl)-7-azabicyclo[2.2.1]heptane-2,7-dicarboxylic acid 2-benzyl ester (8-2*S*). Compound **8**-2*S* was obtained in a similar manner to **8**-2*R*, described above.

4.3.13. (1*R*,2*R*,4*S*)-7-(Fluorenylmethyl)-7-azabicyclo[2.2.1]heptane-2,7-dicarboxylic acid (9-2*R*). Debenzylation of **8**-2*R* (400.0 mg, 0.88 mmol) was carried out by hydrogenation over Pd/C (94.7 mg) in MeOH (10 mL) at rt for 24 h. The reaction mixture was filtered and the filtrate was evaporated to give a crude oil, which was chromatographed (*n*-hexane/$CHCl_3$=1/6, then a small amount of acetic acid was added to the eluent) to give **9**-2*R* as a pale yellow oil (190 mg, 60% yield). Pale yellow amorphous solid. MS (*m*/*z*): 363 ($M+H^+$). HRMS (EI^+, $M+H^+$) calcd for $C_{22}H_{21}NO_4$: 363.1471; obsd: 363.1496. ^{1}H NMR: 7.78–7.76 (2H, m), 7.60–7.57 (2H, m), 7.42–7.38 (2H, m), 7.34–7.30 (2H, m), 4.49 (2H, d, J=6.2 Hz), 4.45 (1H, br s), 4.23 (1H, br s, overlap), 4.22 (1H, t, J=6.2 Hz), 2.93 (1H, br s), 1.95–1.45 (6H, m). $[\alpha]_D^{21}$ −14.4 (*c* 0.46, $CHCl_3$).

4.3.14. (1*S*,2*S*,4*R*)-7-(Fluorenylmethyl)-7-azabicyclo[2.2.1]heptane-2,7-dicarboxylic acid (9-2*S*). Compound **9**-2*S* was obtained in a similar manner to **9**-2*R*, described above. $[\alpha]_D^{21}$ +14.6 (*c* 0.48, $CHCl_3$).

4.3.15. Boc-(*S*-Ah2c)$_2$-OBn. Compound **7**-2*S* (252 mg, 0.76 mmol) was dissolved in 4 N HCl in dioxane (1.7 mL) and stirred for 1 h. The solvent was then removed in vacuum, and the residue was dried in vacuum. Compound **5**-2*S* (171 mg, 0.74 mmol) and DMAP (129.0 mg, 1.06 mmol) were added to the flask, followed by the addition of DMF (3 mL). Then EDCI·HCl (284 mg, 1.48 mmol) was added, and the whole was stirred for 48 h under Ar. DMF was removed in vacuum and the residue was washed with 1 N aqueous HCl, the whole was extracted with $CHCl_3$, then the solvent was evaporated to give a white sticky solid, which was chromatographed (*n*-hexane/AcOEt=1/1) to give a colorless amorphous solid (270 mg, 78% yield). MS (*m*/*z*): 455 ($M+H^+$). HRMS (FAB^+, $M+H^+$) calcd for $C_{26}H_{35}N_2O_5$: 455.2541; obsd: 455.2548. ^{1}H NMR: 7.38–7.35 (5H, m), 5.17–5.15 (2H, a mixture of conformers), (amide *cis*–*trans* mixture) 4.88 (0.5H, m), 4.67 (0.5H, m),

4.52 (0.5H, m), 4.35 (0.5H, m), 3.10–3.03 (2H, m), 2.08–1.50 (12H, m), 1.48 (9H, m).

4.3.16. HCl·H-(*S*-Ah2c)$_2$-OH. Debenzylation of Boc-(*S*-**Ah2c**)$_2$-OBn (77 mg, 0.17 mmol) was carried out by hydrogenation over Pd/C (60.1 mg) in MeOH (1.5 mL) at rt for 1.5 h. The reaction mixture was filtered and the filtrate was evaporated to give a crude oil. The residue was dissolved in 4 N HCl in dioxane (0.4 mL) and the resultant solution was stirred for 1 h. The solvent was then removed by a stream of Ar, and the residue was dried in vacuum to afford HCl·H-(*S*-**Ah2c**)$_2$-OH (63 mg, quant.). HRMS (FAB$^+$, M+H$^+$) calcd for $C_{14}H_{21}N_2O_3$: 265.1552; obsd: 265.1587.

4.3.17. HCl·H-(*S*-Ah2c)$_3$-OH. The preparation of HCl·H-(*S*-**Ah2c**)$_3$-OH was carried out in a similar manner to the dimer HCl·H-(*S*-**Ah2c**)$_2$-OH. HRMS (FAB$^+$, M+H$^+$) calcd for $C_{21}H_{30}N_3O_4$: 388.2236; obsd: 388.2207.

4.3.18. HCl·H-(*S*-Ah2c)$_4$-OH. The preparation of HCl·H-(*S*-**Ah2c**)$_4$-OH was carried out in a similar manner to the dimer HCl·H-(*S*-**Ah2c**)$_2$-OH. HRMS (FAB$^+$, M+H$^+$) calcd for $C_{28}H_{39}N_4O_5$: 511.2921; obsd: 511.2830.

4.3.19. HCl·H-(*S*-Ah2c)$_5$-OH. The preparation of HCl·H-(*S*-**Ah2c**)$_5$-OH was carried out in a similar manner to the dimer HCl·H-(*S*-**Ah2c**)$_2$-OH. HRMS (FAB$^+$, M+H$^+$) calcd for $C_{28}H_{39}N_4O_5$: 634.3605; obsd: 634.3559.

4.4. Solid-phase synthesis of Ah2c oligomers

4.4.1. Reversed-phase (RP) HPLC analysis and purification. RP-HPLC purification was performed on a Cosmosil 5C18-AR-II column (10×250 mm, Nacalai Tesque) with a linear gradient of A (0.1% TFA in H_2O) and B (0.1% TFA in MeCN) at a flow rate of 1 mL min^{-1} (Hitachi HPLC system); UV detection at 215 nm.

4.4.2. Peptide synthesis.

4.4.2.1. H-(*R*-Ah2c)$_8$-NH$_2$. The Rink amide resin (200 mg, 0.04 mmol; loading 0.21 mmol g^{-1}) was swelled in DMF (5 mL) for 90 min and Fmoc was deprotected using 20% piperidine in DMF (2 mL, 15 min). The resin was filtered and washed with DMF (5×4 mL). A solution of Fmoc-*R*-**Ah2c**-OH (**9**-2*R*) (43 mg, 3 equiv), PyBOP (3 equiv) and HOBt (3 equiv) in DMF (0.9 mL), and *N*-methylmorpholine (6 equiv) were added successively to the resin and the suspension was mixed for 1.5 h at rt. The resin was then filtered and washed with DMF (5×4 mL) prior to the following Fmoc deprotection step. The Fmoc group was removed using 20% piperidine in DMF (2 mL, 15 min). The resin was filtered and washed with DMF (5×4 mL). For each coupling, a solution of the Fmoc-amino acid (3 equiv), PyBOP (3 equiv) and HOBt (3 equiv) in DMF (0.9 mL), and *N*-methylmorpholine (6 equiv) were added successively to the resin and the suspension was mixed for 1.5 h at rt. The resin was then filtered and washed with DMF (5×4 mL). After coupling the last amino acid, the Fmoc group was cleaved and the resin was washed with DMF (5×4 mL), MeOH (5×4 mL), Et_2O (5×4 mL). Drying overnight under vacuum afforded the Fmoc-deprotected peptide-resin (209 mg). The dry Fmoc-deprotected peptide-resin was treated with a mixture of TFA (10 mL) and ethanedithiol (0.5 mL) for 2 h at rt. The resin was filtered and the reaction mixture was evaporated. The precipitate formed upon addition of cold Et_2O (15 mL) to the oily residue was separated by decanting the solvent. The precipitate was lyophilized to yield 25 mg of the crude peptide. Purification of the crude peptide by RP-HPLC (15–40% B in 25 min) afforded the TFA salt of H-(*R*-**Ah2c**)$_8$-NH$_2$, 4.91 mg (4.1%) as a white fluffy powder. MS (*m*/*z*): 1003.75 (M+H$^+$). MS (*m*/*z*) (ESI$^+$, [M+H]$^+$) calcd for $C_{56}H_{76}N_9O_8$: 1002.5811; obsd: 1002.5804.

4.4.2.2. H-(*S*-Ah2c)$_4$-NH$_2$. The preparation of H-(*S*-**Ah2c**)$_4$-NH$_2$ was carried out in a similar manner to (*R*-**Ah2c**)$_8$-NH$_2$. Colorless oil. MS (*m*/*z*): 511 (MALDI-TOF MS, [M+H]$^+$).

4.4.2.3. H-(*S*-Ah2c)$_5$-NH$_2$. The preparation of H-(*S*-**Ah2c**)$_5$-NH$_2$ was carried out in a similar manner to H-(*R*-**Ah2c**)$_8$-NH$_2$. Colorless oil. MS (*m*/*z*): 633 (MALDI-TOF MS, [M+H]$^+$).

4.4.2.4. H-(*S*-Ah2c)$_8$-NH$_2$. The preparation of H-(*S*-**Ah2c**)$_8$-NH$_2$ was carried out in a similar manner to H-(*R*-**Ah2c**)$_8$-NH$_2$. White fluffy powder. MS (*m*/*z*) (ESI-TOF, [M+H]$^+$) calcd for $C_{56}H_{76}N_9O_8$: 1002.5811; obsd: 1002.5770.

4.5. CD measurements

Dry peptide samples were weighed and dissolved in an appropriate amount of spectroscopic grade methanol. Sample cells of 1-mm path length were used. Data were collected on a JASCO J-820 spectrometer at 20 °C. Data are represented in terms of mean residue ellipticity, [θ] (deg cm^2 decimol^{-1} residue^{-1}).

The mean residue ellipticities for H-(*S*-**Ah2c**)$_8$-NH$_2$ are ca. -3.5×10^4 deg cm^2 decimol^{-1} residue^{-1} at 198 nm (a minimum) and 4.0×10^4 at 217 nm (a maximum), while those for H-(*R*-**Ah2c**)$_8$-NH$_2$ are 4.0×10^4 at 198 nm and -3.1×10^4 at 217 nm. The two oligomers have the crossover point at about 206 nm.

The positions and intensities of the minimum and maximum peaks of H-(*S*-**Ah2c**)$_4$-NH$_2$ and HCl·H-(*S*-**Ah2c**)$_4$-OH in the CD spectra are practically identical, H-(*S*-**Ah2c**)$_4$-NH$_2$: ca. -1.9×10^4 deg cm^2 decimol^{-1} residue^{-1} at 197 nm (minimum) and 2.4×10^4 at 216 nm (maximum); HCl·H-(*S*-**Ah2c**)$_4$-OH: ca. -2.0×10^4 deg cm^2 decimol^{-1} residue^{-1} at 197 nm (minimum) and 2.4×10^4 at 216 nm (maximum).

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Supplementary data

Supporting information, additional structural data, and ^{1}H NMR spectra are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.062.

References and notes

1. (a) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932–982; (b) Review: Seebach, D.; Matthews, J. *Chem. Commun.* **1997**, 2015–2022; (c) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers.* **2004**, *1*, 1111–1239.
2. Review: (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J., Jr.; Gellman, S. H. *Nature* **1997**, *387*, 381–384; (c) Appella, D. H.; Barchi, J. J.; Durell, S. R.; Gellman, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 2309–2310; (d) While β-proline oligomers form helices without intramolecular hydrogen bonding, their amide bonds are planar; the sum of the bond angles around the amide nitrogen is 359.95° in the crystal structure of the dimers of β-proline derivatives: Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 9035–9037; (e) Schmitt, M. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2004**, *126*, 6848–6849.
3. (a) Seebach, D.; Albert, M.; Arvidsson, P. I.; Rueping, M.; Schreiber, J. V. *Chimia* **2001**, *55*, 345–353; (b) Hamuro, Y.; Schneider, J. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200–12201; (c) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblumand, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
4. For a review of foldamers: Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011.
5. (a) Ohwada, T.; Achiwa, T.; Okamoto, I.; Shudo, K. *Tetrahedron Lett.* **1998**, *39*, 865–868; (b) Review: Ohwada, T. *Yakugaku Zasshi* **2001**, *121*, 65–77; (c) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191–15199.
6. Non-planarity of peptide bonds has been discussed: (a) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169–182; (b) Buck, M.; Karplus, M. *J. Am. Chem. Soc.* **1999**, *121*, 9645–9658; (c) Mannfors, B. E.; Mirkin, N. G.; Palmo, K.; Krimm, S. *J. Phys. Chem. A* **2003**, *107*, 1825–1832; (d) Fischer, S.; Dunbrack, R. L.; Karplus, M. *J. Am. Chem. Soc.* **1994**, *116*, 11931–11937; (e) Head-Gordon, T.; Head-Gordon, M.; Frisch, M. J.; Brooks, C. L., III; Pople, J. *J. Am. Chem. Soc.* **1991**, *113*, 5989–5997; (f) Guo, H.; Karplus, M. *J. Phys. Chem.* **1992**, *96*, 7273–7287; (g) Sulzbach, H. M.; Schleyer, P. v. R.; Schefer, H. F., III. *J. Am. Chem. Soc.* **1995**, *117*, 2632–2637; (h) MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1996**, *264*, 1180–1195; (i) Hu, J.-S.; Bax, A. *J. Am. Chem. Soc.* **1997**, *119*, 6360–6368.
7. An example of the use of the present bicyclic structure as a peptidomimetic was presented by Avenoza, A.; Busto, J. H.; Peregrina, J. M.; Rodriguez, F. *J. Org. Chem.* **2002**, *67*, 4241–4249.
8. Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189–7191.
9. The structure of 7-(*tert*-butoxycarbonyl)-2-*endo*-bornane-2,10-sultam-7-azabicyclo[2.2.1]heptane (**6b**) was determined by X-ray crystallographic analysis.
10. This kind of molecular weight dependence of the CD spectra is one of the criteria for judging the helical nature of polymers (Gu, H.; Nakamura, Y.; Sato, T.; Teramoto, A.; Green, M. M.; Andreola, C.; Peterson, N. C.; Lifson, S. *Macromolecules* **1995**, *28*, 1016–1024); and oligomers (Stone, M. T.; Heemstra, J. M.; Moore, J. S. *Acc. Chem. Res.* **2006**, *39*, 11–20).
11. (a) Mitaku, S.; Suzuki, K.; Odashima, S.; Ikuta, K.; Suwa, M.; Kukita, F.; Ishikawa, M.; Itoh, H. *Proteins* **1995**, *22*, 350–362; (b) Bhakuni, V. *Arch. Biochem. Biophys.* **1998**, *357*, 274–284.
12. A similar intra-residue attraction was discussed in Tanatani, A.; Yokoyama, A.; Azumaya, I.; Takakura, Y.; Mitsui, C.; Shiro, M.; Uchiyama, M.; Muranaka, A.; Kobayashi, N.; Yokozawa, T. *J. Am. Chem. Soc.* **2005**, *127*, 8553–8561.
13. Berova, N.; Nakanishi, K.; Woody, R. W. *Circular Dichroism: Principles and Applications*, 2nd ed.; Wiley-VCH: New York, NY, 2000.
14. (a) Browett, W. R.; Stillman, M. J. *Comput. Chem.* **1987**, *11*, 241–250; (b) Gasyna, Z.; Browett, W. R.; Nyokong, T.; Kitchenham, R.; Stillman, M. J. *Chemom. Intell. Lab. Syst.* **1989**, *5*, 233–246; (c) Mack, J.; Stillman, M. J. *Handbook of Porphyrins and Related Macrocycles*; Kadish, K., Smith, K., Guilard, R., Eds.; Academic: New York, NY, 2003; Vol. 16, Chapter 103, pp 43–116.
15. Schellman, J. A.; Oriel, P. J. *J. Chem. Phys.* **1962**, *37*, 2114–2124.
16. Moffitt, W.; Fitts, D. D.; Kirkwood, J. G. *Proc. Natl. Acad. Sci. U.S.A.* **1957**, *43*, 723–730.
17. Sandvoss, L. M.; Carlson, H. A. *J. Am. Chem. Soc.* **2003**, *125*, 15855–15862.
18. Leroy, J. *Synth. Commun.* **1992**, *22*, 567–572.
19. Singh, S.; Basmadjian, G. P. *Tetrahedron Lett.* **1997**, *38*, 6829–6830.
20. Hern′andez, A.; Macros, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683–2691.

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Phenol-containing bis(oxazolines): synthesis and fluorescence sensing of amines

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Abstract—The fluorescence sensing of primary amines as their neutral forms has been studied with bis(oxazolinyl)phenols (Me-BOP, Ph-BOP), which are efficiently synthesized starting from mesitylene in six steps and in overall 12–22% yields. The BOP sensors showed fluorescence enhancement toward butylamine and several arylethylamines, whereas they showed fluorescence quenching toward secondary and branched amines. The opposite fluorescence behavior is explained by an increased conformational restriction at the excited state, at which a proton transfer complex between the host and guest forms that is stabilized in a tripodal hydrogen bonding mode. This is the first example in which fluorescence enhancement is observed in amine sensing with phenolic fluorophores. Enantiomeric α-chiral organoamines were also sensed with different fluorescent intensity changes by Ph-BOP, complementing the previous tris(oxazolines) that sense enantiomeric α-chiral organoammonium ions.

1. Introduction

Among various sensing techniques available for clinical, biological, and environmental analyses, fluorescence sensing has advantages of high sensitivity and compatibility for the online and real-time analyses.[1] Amines are an important class of biologically active compounds among those to be sensed by fluorescence analysis. Amines as their neutral forms are generally sensed with fluorescence sensors based on binol or other phenolic fluorophores, mostly in the fluorescence quenching mode.[1f,2] In some cases, amines are sensed as their ammonium salts, which results in the fluorescence enhancement through the photo-induced electron-transfer mechanism.[3] Recently, we have introduced novel tris(oxazoline) receptors **1**, which selectively recognize certain organoammonium ions and also show unusual chiral discrimination toward α-, β-, and α,β-chiral organoammonium ions (Fig. 1).[4] Interestingly, the receptors also sense organoammonium ions with fluorescence enhancement.[4d] The enhancement was attributed to the conformational restriction of the tripodal ligands upon guest binding. As an extension of this novel sensing mechanism, we were interested in an analogous tripodal system that may recognize organoamines in their neutral forms. Thus, we designed a phenol-containing bis(oxazoline) system such as **2** (Fig. 1), in which the acidic hydroxyl group is expected to act as a hydrogen bond donor toward amine guests. With this hydrogen bond donor together with the two oxazoline hydrogen bond

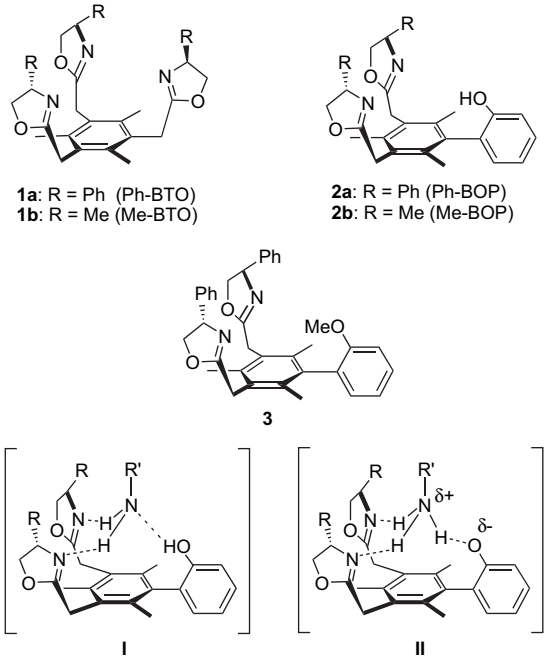

Figure 1. Structures of tripodal oxazolines **1**, phenol-containing bis(oxazolines) **2**, their amine inclusion complexes **I** (at the ground state) and **II** (at the excited state), and a reference compound **3**.

Keywords: Amine sensing; Fluorescence sensors; Hydrogen bonding; Chiral sensing.
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acceptors, the new receptors may recognize an amine guest in a tripodal hydrogen bonding mode, which is reminiscent of the tripodal hydrogen bonding between tris(oxazolines) **1** and organoammonium ions. The recognition of amines by the phenol-containing receptors **2** in the tripodal fashion is expected to generate a proton transfer complex such as **II** at the excited state, because the phenol at the excited state becomes much more acidic than its ground state (phenol: pK_a^*=4.1 vs pK_a=9.0).[5] Thus, the proton transfer complex is supposed to be conformationally more rigid compared to its ground state complex **I**. Therefore, the receptor's fluorescence property is expected to change upon guest binding, hopefully to a fluorescence enhancement mode. Described herein are an efficient synthesis of bis(oxazolinyl)phenols (BOPs) **2** and an investigation of their fluorescence behavior toward various organoamines.

2. Results and discussion

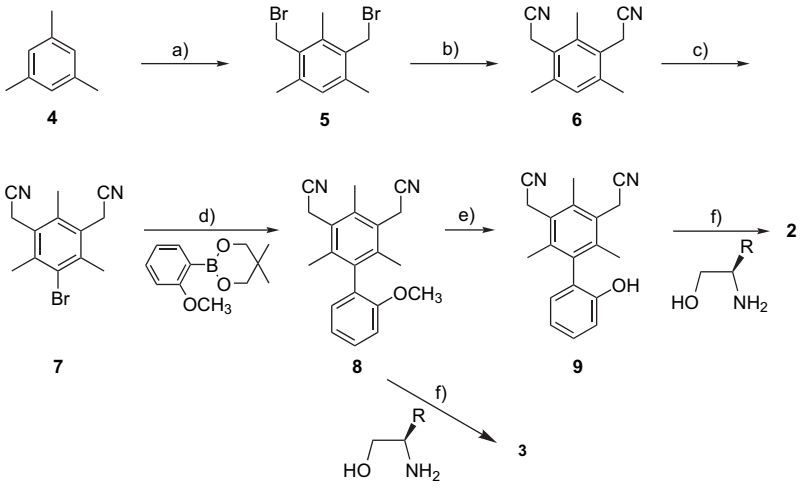
2.1. Synthesis

Our synthetic efforts started from commercially available mesitylene. A controlled bromomethylation of mesitylene with paraformaldehyde and HBr in acetic acid[6] and subsequent nucleophilic substitution of the resulting bis(bromomethyl) compound **5** by cyanide afforded the bis(nitrile) compound **6**. Bromination of this compound with $Me_3(PhCH_2)NBr_3/ZnCl_2$[7] gave the bromo compound **7**. It is worth mentioning that attempts to prepare **7** directly from 2-bromomesitylene via the above sequence, namely bromomethylation and substitution, failed as the bromomethylation of 2-bromomesitylene stopped at the mono-bromomethylated stage even under severe reaction conditions. This could be probably owing to the deactivating effects of the bromine and bromomethyl group toward the electrophilic substitution on the benzene ring. Next, the Suzuki coupling[8] was employed to construct the carbon–carbon bond of the biphenyl core. Thus, the coupling of **7** with 5,5-dimethyl-2-(2-methoxyphenyl)-1,3,2-dioxaborinane[9] yielded methyl ether **8**, which on subsequent deprotection with BBr_3 afforded **9**. Finally, the oxazoline ring was constructed by double condensation of amino alcohols with nitrile group of **9** in the presence of cadmium acetate as a mild Lewis acid catalyst[10] to afford the BOP sensors **2** (Scheme 1).

2.2. Fluorescence studies

The UV–vis spectra of Ph-BOP **2a** in acetonitrile showed absorption maxima at 196 and 276 nm at 0.1 mM concentration. The fluorescence emission spectra displayed emission of the biphenyl nucleus at λ_{max}=300 nm when excited at 276 nm. Similarly, Me-BOP **2b** showed absorption maxima at 276 nm and the fluorescence emission at λ_{max}=305 nm when excited at 275 nm in acetonitrile (at 0.1 mM concentration). The emission wavelengths observed were shorter than that of *o*-phenylphenol[11] because little conjugation is expected between the two phenyl rings.

When Ph-BOP **2a** (0.1 mM in CH_3CN) was titrated with increasing amount of 2-(3,4-dimethoxy)phenylethylamine (**Am4**) as a guest at 25 °C, about 2-fold increase in the fluorescence intensity of the sensor was observed (Fig. 2a). This is an interesting result because so far fluorescence sensing of amines with phenol- or binaphthol-derived sensors resulted in fluorescence quenching rather than enhancement.[1f] Also, amines are efficient fluorescence quenchers of most unsubstituted aromatic hydrocarbon fluorophores such as anthracene, perylene, and carbazole.[1b] The fluorescence enhancement was further confirmed by titrating Ph-BOP **2a** with a non-fluorescent guest such as butylamine (Fig. 2b). Similarly, Me-BOP **2b** also gave a fluorescence enhancement upon titrating with butylamine (Fig. 2c). Although the enhancement is not large, as far as we know, this is the first example of neutral amine sensing with phenol-containing sensors in the fluorescent enhancement mode. We evaluated other amine guests that have different structural features, which are listed in Figure 3. The guests such as 2-phenylethylamine (**Am1**), 4-methoxyphenylethylamine (**Am3**), and tryptamine (**Am5**) also exhibited fluorescence enhancement. It should be noted that in the case of the guests containing aromatic fluorophores such as **Am1** and **Am3**–**Am5**, the fluorescence from the guest itself overlapped



Scheme 1. Synthesis of compounds **2** and **3**. Reagents and conditions: (a) paraformaldehyde, 30% HBr in AcOH, AcOH, 80 °C, 5 h, 95%; (b) NaCN, MeOH/H_2O (5:2), reflux, 5 h, 76%; (c) $Me_3(PhCH_2)NBr_3$, $ZnCl_2$, AcOH, 70 °C, 6 h, 75%; (d) 5 mol % $Pd(PPh_3)_4$, K_3PO_4, DMF, 100 °C, 24 h, 86%; (e) BBr_3, CH_2Cl_2, 25 °C, 48 h, 76%; (f) $Cd(OAc)_2$, PhCl, reflux, 96 h, 58% (R=Ph, **2a**), 32% (R=Me, **2b**), 55% (R=Ph, **3**).

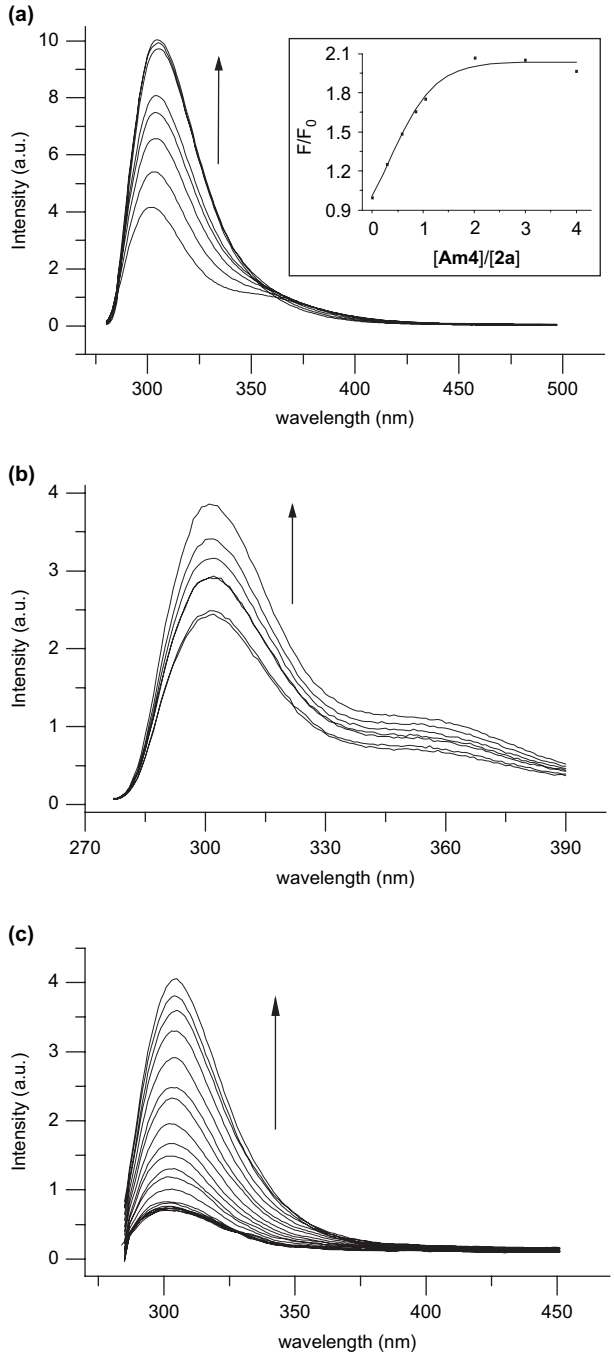


Figure 2. Fluorescence changes measured in CH_3CN at λ_{ex}=276 nm: (a) titration of Ph-BOP **2a** (0.1 mM) with **Am4** (0.0–4.0 equiv from the bottom) (inset: dependence of fluorescence intensity (F/F_0) depending on the ratio [**Am4**]/[**2a**]); (b) titration of Ph-BOP **2a** (0.1 mM) with **Am2** (0.0–6.2 equiv from the bottom); (c) titration of Me-BOP **2b** (0.1 mM) with **Am2** (0.0–10 equiv from the bottom) with λ_{ex}=275 nm.

with that of the host–guest complex. However, the fluorescence enhancement due to the complexation was apparent, as inferred from a non-linear increase of the fluorescence intensity in the plot of F/F_0 versus $[G]_0/[H]_0$ (Fig. 4). The fluorescence intensity increases rather rapidly up to the equivalent point and then slows down upon titration of **2a** with **Am1**, which can be interpreted in this way: at the initial stage, the fluorescence increase results from both the host–guest complex and guest, while in the later stage, the increase is mainly due to the guest added.

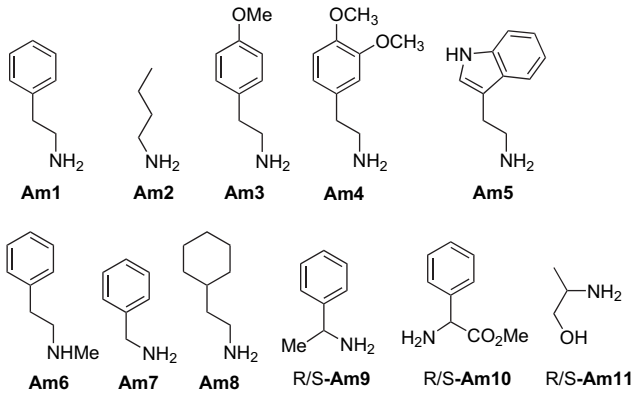


Figure 3. Chemical structures of the amine guests studied.

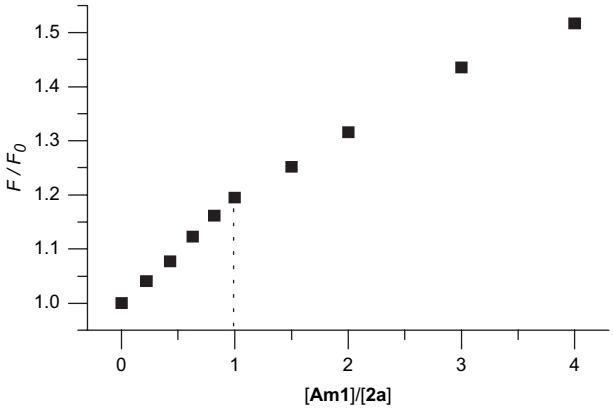


Figure 4. A plot of F/F_0 versus [**Am1**]/[**2a**].

In contrast to the β-arylethylamine or butylamine guests (**Am1**–**Am5**), interestingly, fluorescence quenching was observed for other types of guests such as **Am6**–**Am11**. For example, titrations of Ph-BOP **2a** with **Am6** resulted in fluorescence quenching (Fig. 5), and a similar level of quenching was observed in the case of other guests. How can we rationalize such an opposite result depending on the guests? We suppose that the fluorescence enhancement or quenching observed is dependent on the guest's binding affinity, which is related to the fluorescence enhancement mechanism. Previously we have shown that the ammonium

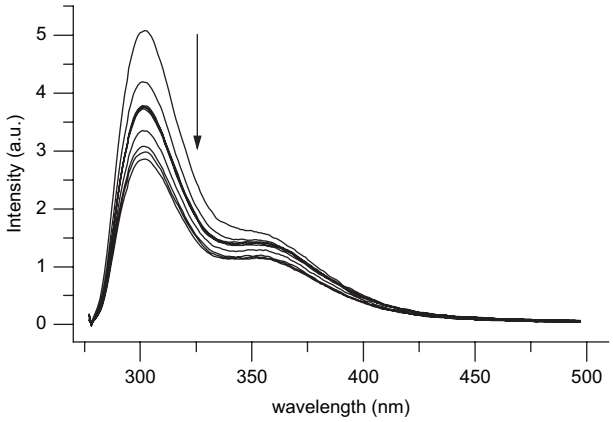


Figure 5. Fluorescence changes upon titration of Ph-BOP **2a** (0.1 mM) with **Am6** (0.0–6.0 equiv from the top) in acetonitrile at λ_{ex}=276 nm.

ions of linear primary amines **Am1**–**Am5** are bound more strongly to the tris(oxazoline) receptors **1** than those of branched or secondary amines **Am6**–**Am11**, because the former guests experience less steric strain from the host's 4-oxazolinyl substituents (Ph or Me in the case of Ph-BTO and Me-BTO, respectively) in the inclusion complexes than the latter guests.[4] Similarly, the steric strain between BOPs **2** and the guests can be expected under the tripodal hydrogen bonding mode (Fig. 6), and under this reasoning, we can expect that BOPs **2** would experience less steric strain in binding the linear organoamines than the others such as the branched guests. In the case of the secondary amines such as **Am6**, BOPs **2** cannot form the tripodal hydrogen bonding suggested. The molecular interactions between Ph-BOP **2a** and amines have been studied by ^{1}H NMR titrations. Although the binding induced chemical shifts were small, certain proton peaks (particularly, the oxazoline ring protons) shifted to downfield upon guest binding ($\Delta\delta$=0.025 ppm when 2 equiv of **Am1** were added).

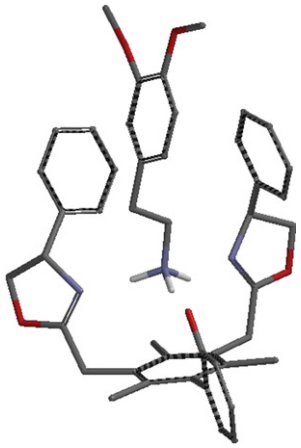


Figure 6. An energy minimized structure of the inclusion complex between Ph-BOP **2a** and **Am4**.

As noted above, the acidity of the phenolic ligand would increase at the excited state and thus proton transfer complexes would form when the receptors bind amines. The proton transfer complexes should be tighter and thus conformationally more rigid than the host–guest complexes at the ground state. This enhanced conformational restriction is believed to contribute to the fluorescence enhancement observed. Such an explanation is based on the tripodal hydrogen bonding mode between the host and guest. When the tripodal hydrogen bonding is not strong enough, we may not expect the enforced conformational restriction and thus little fluorescence enhancement would result. Instead, we may observe fluorescence quenching because generally amines are fluorescence quenchers toward the phenol-based fluorophores. In this way, the observed fluorescence behavior of BOPs toward the amines can be explained.

To get a better understanding for the structural factors that are responsible for the fluorescence enhancement observed, we further examined the fluorescence behavior with reference compounds. We performed the fluorescence titration of **Am1** with the reference compound **3**, in which the phenolic hydroxyl group is protected as its methyl ether, under otherwise identical conditions. As expected, fluorescence quenching was observed in this case upon increasing the amount of **Am1** (Fig. 7a), which indicates that the hydroxyl group in BOPs **2** is essential for the fluorescence enhancement. As discussed above, the hydroxyl group of Ph-BOP **2a** and an amine guest form a proton transfer complex at the excited state, which is stabilized through the hydrogen bonding by the oxazoline ligands. When the hydroxyl group is blocked, no such proton transfer complex would form, and thus no fluorescence enhancement is expected, as observed in the case of **3**.

A direct and straightforward consequence of our presumption should be that phenol **9**, in which two oxazoline ligands are replaced by nitrile groups, should show fluorescence quenching toward amines, as the nitrile groups cannot act as hydrogen bond acceptors to stabilize the host–guest complex. Indeed, fluorescence quenching was observed when phenol **9** was titrated with **Am1** under otherwise identical conditions (Fig. 7b).

These observations clearly augment our presumption to be true and also highlight the key role of the oxazoline ligands in the fluorescence enhancement observed for amines **Am1**–**Am5**. Moreover, the absorption spectra measured during the titration of Ph-BOP **2a** with **Am1** showed no appreciable change, which indicates that the enhanced fluorescence is not due to an increased absorption.

The fluorescence enhancement resulting from the conformational restriction alone, however, seems to be moderate, such as a few times enhancement as observed previously by us.[4d] In this conformational restriction model, the hydrogen bonding interactions are also believed to reduce the charge

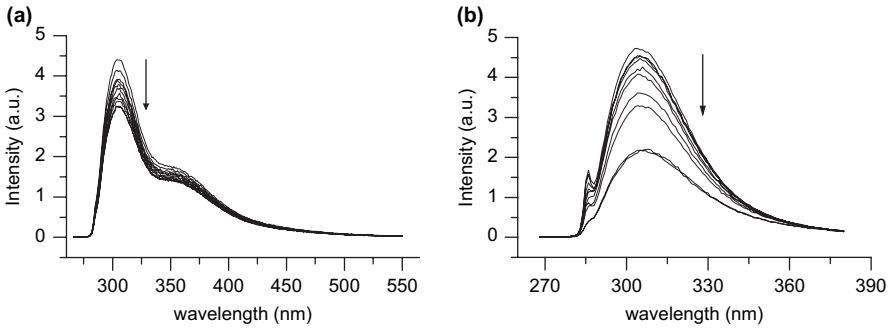


Figure 7. Fluorescence changes measured in CH_3CN: (a) titration of reference compound **3** (0.1 mM) with **Am1** (0.0–4.2 equiv from the top) at λ_{ex}=284 nm; (b) titration of phenol **9** (1.0 mM) with **Am1** (0–10 equiv from the top) at λ_{ex}=287 nm.

separation of the excited state host–guest complex, thereby suppressing some possible quenching processes.[12] At this point, it is premature to speculate on the nature of the host–guest complex at the excited state, but it is certain that the degree of the proton transfer between the phenolic host and an amine is reduced by the 'backside' hydrogen bonding provided by the two oxazoline ligands, which results in the fluorescence modulation of the phenolic fluorophore toward amines, from quenching to enhancement, as observed for the amines **Am1**–**Am5**.

The association constants for the complex formation of Ph-BOP **2a** with some amine guests can be obtained from the observed fluorescence data. On the assumption that host **2a** (H) and a guest amine (G) interact in a 1:1 fashion, the non-linear least squares fit[13] by the following equation[14] gives the association constants K_{11},

$$F/F_0 - (k_G/k_H)[G] = 1 + (k_{11}/k_H)K_{11}[G]/\{1 + K_{11}[G]\}$$

where F_0 is the fluorescence intensity of free host and F is the observed fluorescence intensity during titration, which can be expressed as $F=k_G[G]+k_H[H]+k_{11}[HG]$. The k_G/k_H value can be obtained by measuring concentration-dependent fluorescence changes for the guest and host separately under the same conditions. Association constants thus obtained were in the range of 10^2–10^3 M^{-1} (Table 1), which are much less than that obtained with tris(oxazoline) receptors **1** ($\log K_{11}=6.65$ M^{-1} for *n*-$BuNH_3^+$, determined by UV–vis titration).[4a] This is not an unexpected result because

Table 1. Association constants K_{11} and Stern–Volmer constants K_{SV} determined from the fluorescence titration of Ph-BOP **2a** with the amines in acetonitrile at 25 °C

	Am1	**Am2**	**Am3**	**Am4**	**Am5**
K_{11} (M^{-1})	2100	330	2440	3200	7490
	Am6	**Am7**	**Am8**	(*R*)-**Am9**	(*S*)-**Am9**
K_{SV} (M^{-1})	1290	930	1080	1290	770

neutral hydrogen bonding in the case of BOPs **2** should be much weaker than the charged hydrogen bonding between an ammonium ion and BTOs **1**. The association data indicate that the fluorescence enhancement is related to the association constant: as in the case of the tris(oxazoline) receptor Ph-BTO **1**, the β-aryl-substituted linear amine guests (**Am1** and **Am3**–**Am5**), which show larger fluorescence enhancement compared to an aliphatic guest **Am2**, also gave larger association constants. In the case of amine guests **Am6**–**Am10**, which are believed to have poor binding affinities, we were not able to determine meaningful association constants due to large errors in the non-linear regression process. Instead, the Stern–Volmer constants were obtained for these weakly binding amine guests, which showed linear relationships for the equation: $F_0/F=1+K_{SV}[G]$.[1b]

2.3. Enantio-discrimination

We reasoned that Ph-BOP **2a** might discriminate α-chiral amines because the two phenyl-substituted oxazolines could provide a pseudo-C_2-symmetric chiral environment toward α-substituents of α-chiral amines. The steric interactions between the oxazolinyl phenyl substituents and the guest's α-substituents would be different between the enantiomers, which would lead to different fluorescence properties, as we pointed out above in the cases of different achiral amines. Indeed, we were able to observe substantial differences in the fluorescence behavior between the enantiomeric α-chiral amines examined. For example, when Ph-BOP **2a** was titrated with each of the enantiomeric α-methylbenzylamines (**Am9**), fluorescence quenching resulted in both cases but with different magnitude. Plots of F/F_0 depending on [**Am9**]/[**2a**] values for each of the enantiomeric guests show significant differences in the F/F_0 values between the enantiomers (Fig. 8). Similarly, the other two guests also showed different fluorescence quenching behaviors depending on enantiomeric guests.

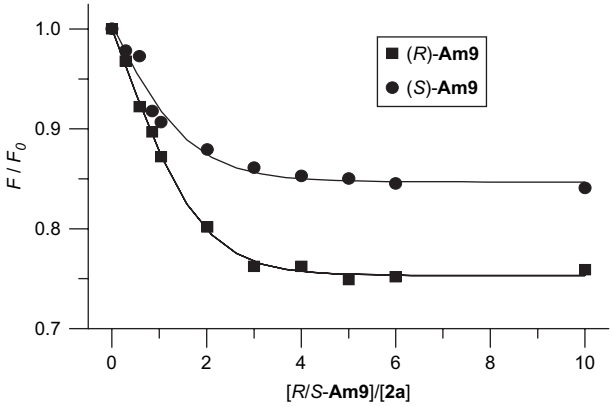


Figure 8. A plot of F/F_0 versus [**Am9**]/[**2a**] depending on the enantiomeric guest.

Therefore, Ph-BOP **2a** can be used as a fluorescence sensor for the monitoring of enantiomeric purity of certain amines in their neutral forms, which complements the enantiomeric sensing of α-chiral organoammonium ions by its tris(oxazoline) analogue **1a**.

3. Conclusion

In conclusion, we have synthesized the phenol-containing bis(oxazolines) as novel fluorescence sensors toward primary amines. The sensors showed fluorescence enhancement toward some linear primary amines and fluorescence quenching toward branched and secondary amines. The observed fluorescence enhancement is ascribed to the conformational restriction and modulation of charge separation of the excited state host–guest complex through hydrogen bonding by the well-directed oxazoline ligands. Although the observed fluorescence enhancement is moderate, it should be noted that this is the first example of amine sensing by phenolic fluorophores in the fluorescence enhancement mode. We have also shown that Ph-BOP **2a** is capable of enantio-discriminating α-chiral amines and thus may be useful for the determination of their enantiomeric purities. A further study on the structure modification of the present system toward a colorimetric sensor of amines is underway.

4. Experimental

4.1. General

2,4-Bis(bromomethyl)-1,3,5-trimethylbenzene,[6] 5,5-dimethyl-2-(2-methoxyphenyl)-1,3,2-dioxaborinane,[9] and benzyl(trimethyl)ammonium tribromide[7] were prepared according to the literature procedures. All other chemicals were commercially available and used without further purification. The solvents for dry reactions were dried with appropriate desiccants and distilled prior to use. Unless otherwise mentioned, all NMR spectra were recorded in $CDCl_3$ solution containing tetramethylsilane as internal standard. Chemical shifts are reported in δ unit. For column chromatography silica gel of 230–400 mesh was used. Fluorescence spectra were recorded on Photon Technical International Fluorescence system. Fluorescence experiments were carried out in 10-mm quartz cuvette at room temperature. Fluorescence titrations were performed at 0.1 mM concentration and the required guest solutions (10–30 mM) are prepared from appropriate amount of amines in 0.1 mM host solution. Both excitation and emission slit widths were 2 nm.

4.1.1. [(3-Cyanomethyl-2,4,6-trimethyl)phenyl]acetonitrile (6). A mixture of 2,4-bis-(bromomethyl)-1,3,5-trimethylbenzene (**5**) (3.06 g, 10 mmol), sodium cyanide (1.47 g, 30 mmol) in water (20 mL) and methanol (50 mL) was refluxed for 5 h. The solvent was evaporated and diluted with cold water (100 mL) to give the product as a precipitate, which was filtered and washed with water (1.5 g, 76%). An analytically pure sample was obtained by recrystallization from dichloromethane/hexane: R_f=0.3 (dichloromethane/hexane=4/1); mp 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.3 (s, 6H), 2.4 (s, 3H), 3.7 (s, 4H), 7.0 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 16.5, 18.4, 117.3, 126.5, 131.1, 135.6, 136.9; MS (EI) *m/z* 198.10 (M^+); HRMS calcd for $C_{13}H_{14}N_2$ (M^+) required 198.1157, found 198.1155. Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.84; H, 7.20; N, 13.89.

4.1.2. [(3-Bromo-5-cyanomethyl-2,4,6-trimethyl)phenyl]acetonitrile (7). To a suspension of bis(nitrile) **6** (0.99 g, 5.0 mmol) in AcOH (1.7 mL) were charged benzyl(trimethyl)ammonium tribromide (1.47 g, 5 mmol) and zinc chloride (0.75 g, 5.5 mmol). The resulting mixture was stirred at 70 °C for 5 h, and then cooled and poured into crushed ice containing 5% sodium hydrogen sulfate. The precipitate was filtered, washed with excess water, and recrystallized from ethyl acetate/hexane to yield **7** (1.05 g, 76%) as white needles: R_f=0.3 (dichloromethane); mp 185 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.4 (s, 6H), 2.6 (s, 3H), 3.8 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.5, 20.5, 22.3, 117.3, 128.4, 128.7, 135.0, 138.0; MS (EI) *m/z* 276.13 (M^+), 278.12 (M^++2); HRMS calcd for $C_{13}H_{13}BrN_2$ (M^+) required 276.0262, found 276.0262. Anal. Calcd for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 55.84; H, 4.68; N, 10.05.

4.1.3. [(5-Cyanomethyl-2′-methoxy-2,4,6-trimethyl)biphenyl-3-yl]acetonitrile (8). A mixture of bromide **7** (0.28 g, 1.0 mmol), 5,5-dimethyl-2-(2-methoxyphenyl)-1,3,2-dioxaborinane (0.60 g, 2.75 mmol), $Pd(PPh_3)_4$ (0.05 g, 5 mol %), and K_3PO_4 (1.16 g, 5.5 mmol) in DMF (5 mL) was stirred at 100 °C for 24 h. The resulting mixture was filtered through Celite, washed with hot ethyl acetate, and then the filtrate was concentrated to yield a black residue. Purification by column chromatography gave **8** (0.26 g, 86%): mp 134 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.0 (s, 6H), 2.1 (s, 3H), 3.7 (s, 7H), 7.0–7.1 (m, 3H), 7.3–7.4 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.5, 18.7, 19.6, 56.1, 111.6, 118.2, 121.6, 126.9, 129.7, 130.0, 131.4, 135.0, 136.6, 139.0, 157.1; MS (EI) *m/z* 304.21 (M^+); HRMS calcd for $C_{20}H_{20}N_2O$ (M^+) required 304.1576, found 304.1580. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.48; H, 6.61; N, 9.30.

4.1.4. [(5-Cyanomethyl-2′-hydroxy-2,4,6-trimethyl)biphenyl-3-yl]acetonitrile (9). To a solution of **8** (0.3 g, 1.0 mmol) in dichloromethane was charged $BF_3\cdot OEt_2$ (8.0 mL, 8.0 mmol) (1.0 M in dichloromethane) at 0 °C, and the mixture was allowed to stir at room temperature for 48 h. An aqueous workup and subsequent purification by column chromatography gave **9** (0.22 g, 76%); mp 202 °C. ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.1 (s, 6H), 2.5 (s, 3H), 3.8 (s, 4H), 6.9–7.0 (m, 3H), 7.28–7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.5, 18.5, 19.7, 116.4, 117.7, 121.9, 127.3, 128.1, 130.2, 130.8, 136.3, 136.4, 137.7; MS (EI) *m/z* 290.19 (M^+); HRMS calcd for $C_{19}H_{18}N_2O$ (M^+) required 290.1419, found 290.1420. Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 76.75; H, 6.19; N, 9.68.

4.1.5. [2′,4′,6′-Trimethyl-3′,5′-bis(4-phenyl-4,5-dihydrooxazol-2-yl)methyl]biphenyl-2-ol (Ph-BOP, 2a). A mixture of bis(nitrile) **9** (0.29 g, 1.0 mmol), (*S*)-(+)-2-phenylglycinol (0.54 g, 4.0 mmol), and $Cd(OAc)_2$ (0.013 g, 0.25 mmol) in chlorobenzene was refluxed for 4 days while a mild stream of nitrogen was bubbled through the reaction mixture. Evaporation of the solvent gave a black residue, which was purified by column chromatography (gradient elution: 10%→60% ethyl acetate in hexane) to give **2a** (0.3 g, 58%): mp 90 °C; $[\alpha]_D^{25}$ +87.3 (*c* 0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.05 (s, 3H), 2.08 (s, 3H), 2.4 (s, 3H), 3.8 (s, 4H), 4.0–4.1 (m, 2H), 4.6–4.7 (m, 2H), 5.0–5.1 (m, 2H), 6.9–7.0 (m, 4H), 7.1–7.3 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.1, 18.0, 19.0, 29.9, 69.3, 69.4, 75.2, 75.5, 116.2, 120.1, 126.5, 127.6, 127.7, 128.1, 128.8, 128.89, 128.93, 130.2, 131.1, 135.3, 136.5, 142.3, 142.5, 154.1, 167.7; MS (EI) *m/z* 530.39 (M^+); HRMS calcd for $C_{35}H_{34}N_2O_3$ (M^+) required 530.2569, found 530.2560. Anal. Calcd for $C_{35}H_{34}N_2O_3$: C, 79.22; H, 6.46; N, 5.28. Found: C, 77.07; H, 6.69; N, 5.18.

4.1.6. [2′,4′,6′-Trimethyl-3′,5′-bis(4-methyl-4,5-dihydrooxazol-2-yl)methyl]biphenyl-2-ol (Me-BOP, 2b). Prepared from **9** as above in 32% yield: mp 133 °C; $[\alpha]_D^{25}$ +11.2 (*c* 0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 1.2 (q, 6H), 2.0 (s, 6H), 2.3 (s, 3H), 3.7 (s, 4H), 3.78–3.83 (m, 2H), 4.07–4.12 (m, 2H), 4.3–4.4 (m, 2H), 6.9–7.0 (m, 3H), 7.2–7.4 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.2, 18.3, 18.4, 22.17, 22.2, 30.3, 61.7, 61.8, 75.0, 116.7, 120.5, 128.7, 129.4, 130.7, 131.69, 131.73, 136.8, 154.7, 166.6; MS (EI) *m/z* 406.27 (M^+); HRMS calcd for $C_{25}H_{30}N_2O_3$ (M^+) required 406.2256, found 406.2253. Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 69.94; H, 7.67; N, 6.77.

4.1.7. {[3,5-Bis(4-phenyl-4,5-dihydrooxazol-2-yl)-methyl]-2′-methoxy-2,4,6-trimethyl}biphenyl (3). Prepared from **8** similarly as above in 55% yield: mp 93 °C; $[\alpha]_D^{25}$ +74.37 (*c* 0.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 2.06 (s, 3H), 2.07 (s, 3H), 2.6 (s, 3H), 3.7 (s, 3H), 3.9 (s, 4H), 4.0–4.1 (m, 2H), 4.56–4.62 (m, 2H), 5.1–5.2 (m, 2H), 7.0–7.1 (m, 4H), 7.0–7.3 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 17.4, 18.3, 30.3, 55.6, 69.7, 75.0, 110.9, 120.8, 126.8, 126.9, 127.3, 127.6, 128.1, 128.5, 128.8, 129.1, 130.3, 131.1, 131.3, 135.4, 136.1, 137.1, 142.8, 156.9, 167.4; MS (EI) *m*/*z* 545.25 (M^++1); HRMS calcd for $C_{36}H_{36}N_2O_3$ (M^+) required 544.2726, found 544.2729. Anal. Calcd for $C_{36}H_{36}N_2O_3$: C, 79.38; H, 6.66; N, 5.14. Found: C, 79.23; H, 6.57; N, 5.13.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.060.

References and notes

1. (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515; (b) Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*; Kluwer Academic, Plenum: New York, NY, 1999; (c) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3; (d) Prodi, L.; Bolletta, F.; Montalti, M.; Zaccheroni, N. *Coord. Chem. Rev.* **2000**, *205*, 59; (e) Fabbrizzi, L.; Licchelli, M.; Rabaioli, G.; Taglietti, A. *Coord. Chem. Rev.* **2000**, *205*, 85; (f) Pu, L. *Chem. Rev.* **2004**, *104*, 1687.
2. (a) Yorozu, T.; Hayashi, K.; Irie, M. *J. Am. Chem. Soc.* **1981**, *103*, 5480; (b) Grady, T.; Harris, S. J.; Smyth, M. R.; Diamond, D. *Anal. Chem.* **1996**, *68*, 3775; (c) Pugh, V. J.; Hu, Q.-S.; Pu, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3638; (d) Beer, G.; Rurack, K.; Daub, J. *Chem. Commun.* **2001**, 1138; (e) Jennings, K.; Diamond, D. *Analyst* **2001**, *126*, 1063; (f) Reetz, M. T.; Sostmann, S. *Tetrahedron* **2001**, *57*, 1515.
3. (a) de Silva, A. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1173; (b) Ballardini, R.; Balzani, V.; Credi, A.; Gandolfi, M. T.; Hibert, F. K.; Lehn, J.-M.; Pordi, L. *J. Am. Chem. Soc.* **1994**, *116*, 5741.
4. (a) Kim, S.-G.; Ahn, K. H. *Chem.—Eur. J.* **2000**, *6*, 3399; (b) Kim, S.-G.; Kim, K.-H.; Jung, J.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2002**, *124*, 591; (c) Ahn, K. H.; Ku, H.-Y.; Kim, Y.-S.; Kim, S.-G.; Kim, Y. K.; Son, H. S.; Ku, J. K. *Org. Lett.* **2003**, *5*, 1419; (d) Ahn, K. H.; Kim, S.-G.; Kim, K.-H.; Kim, Y. K.; Shin, S. K. *J. Am. Chem. Soc.* **2003**, *125*, 13819; (e) Kim, Y. K.; Lee, Y.-H.; Lee, H.-Y.; Kim, K. M.; Cha, G. S.; Ahn, K. H. *Org. Lett.* **2003**, *5*, 4003; (f) Kim, J.; Kim, S.-G.; Seong, H. R.; Ahn, K. H. *J. Org. Chem.* **2005**, *70*, 7227; (g) Kim, J.; Raman, B.; Ahn, K. H. *J. Org. Chem.* **2006**, *71*, 38.
5. Iwanek, W.; Mattay, J. *J. Photochem. Photobiol. A: Chem.* **1992**, *67*, 209.
6. van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262.
7. Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Tanaka, T.; Fujusaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 439.
8. Watanabe, T.; Miyura, N.; Suzuki, A. *Synlett* **1992**, 207.
9. Chaumeil, H.; Signorella, S.; Le Derian, C. *Tetrahedron* **2000**, *56*, 9655.
10. Witte, H.; Seeliger, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 287; Gerisch, M.; Krumper, J. R.; Bergman, R. G.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 5818.
11. Garcia Reyes, I. F.; Llorent Martínez, E. J.; Ortega Barrales, P.; Molina Díaz, A. *Anal. Bioanal. Chem.* **2004**, *378*, 429. The maxima excitation/emission wavelengths of an aqueous solution of *o*-phenylphenol are 243/350 nm.
12. It is well known that the proton transfer complex between a phenolic host and an amine guest results in fluorescence quenching. The hydrogen bonding stabilization of the complex **II** by the oxazoline ligands certainly reduces its charge separation and thereby modulates its quenching processes.
13. Computer software program Origin 7.0 was used.
14. (a) Eric, J.; Davies, D.; Ripmeester, J. A. *Comprehensive Supramolecular Chemistry*; Pergamon: Oxford, UK, 1996; (b) Conners, K. A. *Binding Constants*; Wiley: New York, NY, 1987.

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Fast and efficient preparation of Baylis–Hillman-derived (*E*)-allylic azides and related compounds in aqueous medium

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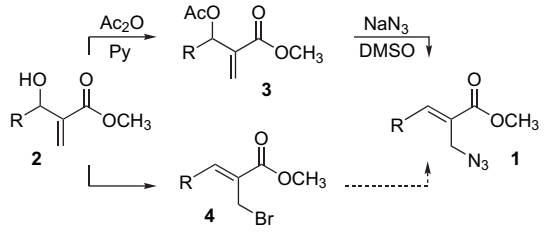
Abstract—A practical access to alkyl- and aryl-substituted (*E*)-2-(azidomethyl)alkenoates and related azido compounds from the corresponding allylic bromides in aqueous acetone is described. An alternative method to obtain the starting bromides based on heterogeneous catalysis under mild conditions was also investigated.

1. Introduction

While the enormous interest in the chemistry of azides and azido-related compounds[1] dates from the 19th century, only recently have the synthesis and reactivity of multifunctional allylic azides become an area of active research.[2] Allylic azides are versatile building blocks for the synthesis of natural products and nitrogen-containing heterocycles of pharmacological relevance.[3] However, the propensity of allylic azides to undergo dynamic [3,3]-sigmatropic rearrangement[4] at ambient temperature must be taken into account, because the thermodynamic ratio of the two equilibrating regioisomeric azides is normally substrate-dependent.[5] Therefore, the development of simple and efficient methods to selectively access allylic azides of structural complexity is highly desirable. 3-Aryl-2-(azidomethyl)alkenoates **1** are a class of stable allylic azides,[6] which are not prone to rearrangement, making them attractive intermediates for synthesis. Multifunctional allylic azides of structure **1** have been prepared by a two-step sequence involving acetylation of α-methylene-β-hydroxy esters **2** (Baylis–Hillman[7] adducts) followed by reaction of acetate **3** with NaN_3 in a S_N2'-type mechanism (Scheme 1).[8] However, nucleophilic displacements of this type involve long reaction times and the use of a toxic and high-boiling solvent such as DMSO. These shortcomings could be partially circumvented by the introduction of 1 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) in aqueous THF to accelerate the substitution reaction,[9] although the required presence of an additive creates further environmental and economic concerns. Indeed, water or aqueous solutions[10] can be viewed as very attractive mediums for these transformations.[11]



Scheme 1.

In continuation of our studies on synthetic methodologies involving allylic azides and Baylis–Hillman adducts,[6,12,13] we envisaged that allylic bromides **4**, readily obtained[13,14] by direct bromination of Baylis–Hillman adducts **2**, would be the useful substrates[15] for an easy introduction of azide, as well as for other nucleophilic groups, onto the allylic framework. In this paper we describe a practical and efficient preparation of alkyl- and aryl-substituted (*E*)-2-(azidomethyl)alkenoates and related azido compounds from the corresponding allylic bromides in aqueous medium. We also investigate an alternative method to obtain the starting bromides based on heterogeneous catalysis under mild conditions.

2. Results and discussion

Allylic bromides such as **4** have been routinely prepared by treatment of Baylis–Hillman adducts **2** with a combination of HBr and H_2SO_4 in CH_2Cl_2 at low temperature.[13a,14a] In spite of the good yields commonly associated with this transformation, the utilization of large quantities of strong

Keywords: Baylis–Hillman reaction; Allylic azides; Allylic bromides; [3,3]-Sigmatropic rearrangement; Aqueous solvents; Heterogeneous catalysis.
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mineral acids is a major drawback due to the safety procedures required for the manipulation of hazardous reagents and wastes. Also, substrates carrying acid-labile groups such as electron-rich olefins and aromatics are incompatible with the strongly acidic conditions, thus limiting the scope of the method. Heterogeneous catalysis is amongst the most efficient and environmentally friendly processes in chemical synthesis, allowing the performance of operationally-simple reactions without the use of toxic or corrosive reagents.[16] Alternative methods to access allylic bromides **4** employing inexpensive solid catalysts include the use of montmorillonite KSF clay and silica-supported $NaHSO_4$[17] in combination with a bromide source.[14b,d] In our hands, however, attempts to react substrates **2a** and **2b** under these conditions led to modest conversions to **4a** and **4b** (up to 40%). Montmorillonite K10, zeolite ZSM-5, and 5 Å molecular sieves were also ineffective catalysts under similar experimental procedure.

A smooth conversion of Baylis–Hillman adducts **2** to the corresponding bromides **4** was achieved with Amberlist-15®/LiBr (or NaBr) in acetonitrile at ambient temperature (Table 1). High yields were obtained with alcohols bearing alkyl or electron-rich aryl groups (entries 1–6 and 9). Accordingly, piperonyl-substituted alcohol **2b** reacted almost instantaneously under the stated conditions to give bromide **4b** in excellent yield (entries 2 and 3). Even reused Amberlist-15® (which was readily recovered by filtration of the reaction mixture and successive washings with 1 M HCl and H_2O) was suitable for another cycle, in spite of the partially decreased catalytic activity (entry 4). Styryl-derived substrate **2d** is also very reactive toward Amberlist-15®/LiBr, but the formation of the expected (*E*,*E*)-diene **4d** was accompanied by small amounts of an unstable by-product, possibly a geometrical isomer, that could not be isolated. Gratifyingly, a fractional crystallization of the crude reaction mixture in ethanol gave bromide **4d** in higher purity and better yield than those obtained with the HBr–H_2SO_4 method (entry 6). However, the relative reactivity of alcohols **2** was remarkably dependent upon the substitution pattern. Very slow conversions were observed for electron-deficient substrates, even after a prolonged time under reflux (entries 7 and 8). The anticipated[13,14] *Z*-stereochemistry assigned to 2-(bromomethyl)-2-alkenoates **4** was based on the characteristic NMR shift of the β-olefinic hydrogen *cis* to the carboxyl group and also on the X-ray crystallography of **4b**.[18]

Next, the preparation of allylic azides **1** from bromides **4** was investigated. Bromide **4a** was selected as a model substrate for reactions with NaN_3 under different reaction parameters in order to achieve optimal conversions to azide **1a** (Table 2). Reaction rates were strongly influenced by the nature of the solvent (or solvent combination) used, slow conversions being a consequence of the low solubility of sodium azide (entries 1–3) or **4a** (entry 4) in the medium. DMSO (entry 5) and DMF (entry 6), typically employed for azide displacement of bromide,[2c,19] enabled quantitative conversion to allylic azide **1a** in 10 min. However, both solvents are toxic, expensive, and difficult to separate from the crude product by simple aqueous workup. In contrast, a combination of acetone/water proved to be the best solvent system for the reaction (entries 7–9). Allylic azide **1a** was quantitatively obtained with either 1.5 equiv of NaN_3 in 10 min (entry 8) or 2.0 equiv in 5 min (entry 9). It is also noteworthy that acceptable conversions to **1a** could be performed using a nearly equimolar amount of NaN_3 in 5 min (entry 10).

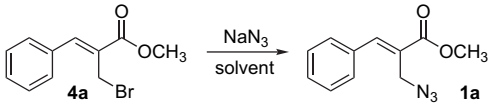
Encouraged by the excellent results achieved with the NaN_3/acetone/water system, we further extended this procedure to the azidation of representative allylic bromides **4** (Table 3). The corresponding aromatic-substituted (*E*)-allylic azides **1a–f** were cleanly obtained in nearly quantitative yields after purification in a short plug of silica gel. On the other hand, when aliphatic-substituted allylic bromides **4g–i** were subjected to the present protocol, NMR analysis of the crude reaction indicated the formation of the expected allylic azides **1g–i** accompanied by a minor product (5–30%), which was assigned as the rearranged regioisomers **5g–i** (Scheme 2).

Table 1. Synthesis of (*E*)-allylic bromides **4** from alcohols **2**[a]

Entry	Product	R	Yield (%) with HBr/H_2SO_4[b]	Yield (%)[c] with LiBr/Amberlist-15®	Time (h)
1	**4a**	C_6H_5	85	64	6
2	**4b**	3,4-$(OCH_2O)C_6H_3$	60	91	1
3	**4b**	3,4-$(OCH_2O)C_6H_3$		90[d]	1
4	**4b**	3,4-$(OCH_2O)C_6H_3$		77[e]	1
5	**4c**	2-$C_{10}H_7$	85	85	2
6	**4d**	(*E*)-C_6H_5CH═CH	64	75	0.5
7	**4e**	2-ClC_6H_4	80	45[f]	4
8	**4f**	4-$NO_2C_6H_4$	65	0	50
9	**4g**	CH_3	70	75	6

[a] Isolated yields.
[b] Data from Ref. 13a.
[c] Conditions: 1.0 mmol **2**, 1.0 g Amberlist-15®, 2.0 mmol LiBr, acetonitrile or acetone (3 mL) at 25 °C.
[d] Amberlist-15® (0.5 g/mmol **2b**) was used.
[e] The reaction was carried out with recycled Amberlist-15®.
[f] The reaction was carried out at reflux temperature for 4 h.

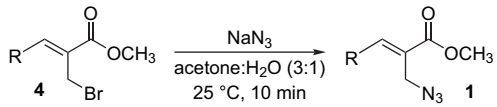
Table 2. Conversion of bromide **4a** to azide **1a** under different reaction conditions[a]



	Solvent system	NaN_3 (equiv)	Conversion to **1a** (%)[b]
1	THF	2.0	5
2	CH_3CN	2.0	18
3	Me_2CO	2.0	31
4	H_2O	2.0	0
5	DMSO[c]	2.0	100
6	DMF[c]	2.0	100
7	Me_2CO/H_2O 3:1	2.0	100
8	Me_2CO/H_2O 3:1	1.5	100
9	Me_2CO/H_2O 3:1[d]	2.0	100
10	Me_2CO/H_2O 3:1[d]	1.2	78

[a] Allylic bromide **4a** (1 mmol) and NaN_3 (1.2–2.0 mmol) in 4 mL of a given solvent were stirred at 25 °C for 10 min (unless otherwise stated), followed by quenching the reaction mixture with CH_2Cl_2 and H_2O.
[b] Determined by ^1H NMR spectrum (400 MHz, $CDCl_3$).
[c] Solvent residue (10–20%) present in the crude reaction product after aqueous workup.
[d] Reaction was quenched (CH_2Cl_2/H_2O) after 5 min.

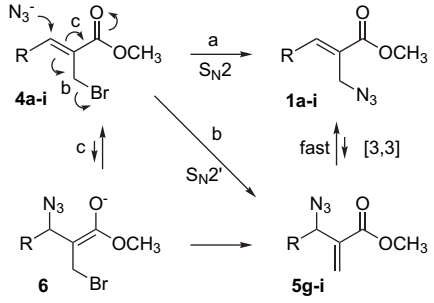
Table 3. Synthesis of (*E*)-allylic azides **1** from bromides **4** in acetone/water (3:1)



Product	R	Yield (%)[a]
1a	C_6H_5	97
1b	3,4-$(OCH_2O)C_6H_3$	93
1c	2-$C_{10}H_7$	95
1d	(*E*)-$C_6H_5CH{=}CH$	96
1e	2-ClC_6H_4	96
1f	4-$NO_2C_6H_4$[b]	97
1g	CH_3[c]	92
1h	$CH_3CH_2CH_2$[c]	95
1i	$CH_3CH_2(CH_3)CH$[c]	93

[a] Isolated yields.
[b] A higher acetone/water ratio (6:1) was used due to the low solubility of nitro-derivative **4f** in aqueous acetone.
[c] Obtained as inseparable mixture of regioisomers **1** and **5**.

Unfortunately, all attempts to isolate any compound by chromatography led to extensive decomposition to an intractable mixture of products.



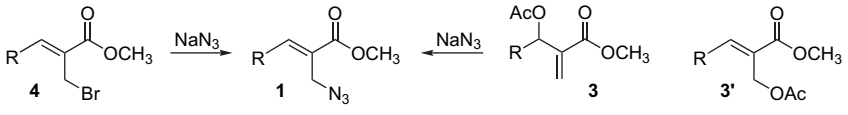
Scheme 2.

In order to monitor these transformations by ^1H NMR (400 MHz), reactions of phenyl- (**4a**) and methyl- (**4g**) substituted bromides were also performed in standard NMR tubes, using $(CD_3)_2CO/D_2O$ as the solvent system under the present conditions. For phenyl-substituted allylic bromide **4a**, products arising from rearrangement were not detected and a quantitative conversion to allylic azide **1a** reached completion after 2 min. In the case of methyl-substituted allylic bromide **4g**, however, conversion to both the allylic azide **1g** and the corresponding rearranged isomer **5g** (ratio **1g**:**5g** ~3:1) was observed in the early stages, with the isomeric ratio being unaltered throughout the entire course of the reaction (conversion higher than 95% was accomplished after 2 min).

These results indicate that alkyl-substituted azides **1g–i** might co-exist with their rearranged isomers **5g–i** in a fast equilibrium shifted to the thermodynamically more stable olefins[20] **1g–i**. The absence of rearranged products for the aryl series **1a–f** might have been due to a stronger stabilization of the double bond by an extensive conjugation through the carboxyl and the aromatic ring, precluding isomerization to the less stable **5a–f**. From a mechanistic view, nucleophilic attack of azide anion on an allylic bromide system would lead to the formation[21] of either S_N2- or S_N2'-type products **1** or **5**, respectively (Scheme 2). While the direct S_N2 attack leading to the more stable **1** (path a) seems to be the exclusive (or at least preferential) pathway for aryl-substituted bromides **4a–f**, the S_N2' mechanism (path b) or even an addition-elimination process via intermediate **6** (path c) could not be excluded at this moment to account for the formation of alkyl-substituted azides **1g–i**. The DABCO salt concept has been successfully applied for the introduction of nucleophiles at the secondary position of Baylis–Hillman adducts by S_N2'-type process.[22] In order to tentatively obtain the elusive azide **5a**, we treated bromide **4a** with DABCO followed by the addition of NaN_3, but the only product formed in the reaction was, again, the S_N2-type **1a**. Whether the mechanism is a direct S_N2 (path a) or S_N2' (path b) still remains to be determined, because in both the cases the product distribution (**1**:**5**) must be regarded as a thermodynamic rather than a kinetic control due to the fast equilibration between the regioisomeric allylic azides.

The superior reactivity of allylic bromides **4** over the acetates **3** was demonstrated by control experiments performed in acetone/water and in DMSO under equivalent conditions. The results summarized in Table 4 clearly show that allylic bromides **4** are much more reactive than acetates **3** (and

Table 4. Conversion (%)[a] of allylic acetates **3** and bromides **4** to allylic azides **1**



Entry	Compound	R	Solvent system	Conversion (%)	
				10 min	2 h
1	**4a**	C_6H_5	DMSO	100	
	3a	C_6H_5	DMSO	65	100
2	**4a**	C_6H_5	Acetone/H_2O (3:1)	100	
	3a	C_6H_5	Acetone/H_2O (3:1)	18	59
3	**4g**	CH_3	DMSO	100	
	3g[b]	CH_3	DMSO	47	78
4	**4g**	CH_3	Acetone/H_2O (3:1)	100	
	3g[b]	CH_3	Acetone/H_2O (3:1)	5	58

[a] Conversions to azide **1** were performed by adding NaN_3 (2 mmol) to a stirring solution of acetate **3** or bromide **4** (1 mmol) in 4 mL of acetone/H_2O (3:1) or DMSO, then quenching the reaction with CH_2Cl_2/H_2O after 10 min or 2 h. After aqueous workup the conversion (%) was determined by ^1H NMR integration (400 MHz, $CDCl_3$) of the crude mixture (~95% purity).
[b] Pure **3** or a mixture of **3**:**3**′ (3:1) was employed, leading to similar results.

3′) toward azide anion under any given conditions and this difference in reactivity is remarkably enhanced in acetone/water medium (entries 2 and 4).

Finally, simple azido compounds **7**–**10** (Fig. 1) were also prepared in high yields and short reaction times (10–30 min) from the corresponding bromides and NaN_3 under aqueous acetone as outlined here.

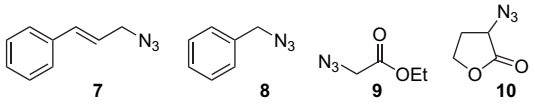


Figure 1.

3. Conclusion

The alternative access to 2-(bromomethyl)-2-alkenoates **4** by Amberlist-15®-mediated bromination of Baylis–Hillman adducts **2** is a synthetically useful transformation, particularly for substrates bearing electron-rich groups. The simple protocol for conversion of allylic bromides **4** to the corresponding azides **1** in acetone/H_2O is straightforward and superior to conventional methods, leading to fast reactions, reproducible conditions, easy workup, and excellent yields, avoiding the use of potential contaminants such as high-boiling solvents or organic additives. The mechanistic aspects involved in these nucleophilic displacements and the application of this simple methodology to more complex systems are currently being investigated.

4. Experimental

4.1. General

All chemicals were of reagent grade and were used as received. Melting points were determined using a Microquímica MQPF301 apparatus and are uncorrected. Infrared spectra were acquired with a Perkin–Elmer FTIR 1600 spectrometer using KBr for solids and film for liquid samples (range 4000–400 cm^{-1}). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz, fully decoupled) spectra were recorded with a Varian AS-400 spectrometer. Samples were prepared in $CDCl_3$ solution containing 1–2% tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in parts per million (δ) relative to TMS. Coupling constants (J) are measured in hertz (Hz). Elemental analyses were conducted in a Carlo Erba CHN equipment by UFSC-Central Analítica, Departamento de Química, Florianópolis, SC, Brazil. Purifications by column chromatography were performed with silica gel (Aldrich, 100–200 mesh particle size). Compounds **1a**,**b**[6,8a] and **4a–c**,**e–i**[13,14] were fully characterized spectroscopically (IR, ^1H NMR, CHN) and showed physical and spectral data in accordance with their expected structure and by comparison with spectral data in literature.

4.2. Typical procedure for the synthesis of 2-(bromomethyl)-2-alkenoates (4)

To a stirred solution of a Baylis–Hillman adduct **2** (1.0 mmol) in 3.0 mL of acetonitrile at 25 °C were added 2.0 mmol of LiBr and 1.0 g of Amberlist-15® (Merck) and stirring was continued for the time presented in Table 1. The final mixture was filtered, the catalyst was rinsed with CH_2Cl_2, and the filtrate was washed with H_2O, satd $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on a short plug of silica gel (hexane/ethyl acetate 9:1) to give the corresponding methyl 2-(bromomethyl)-2-alkenoates **4** in the yields presented in Table 1 (not optimized). Solid products were purified by recrystallization with ethanol.

4.2.1. Methyl (2*E*,4*E*)-2-(bromomethyl)-5-phenyl-2,4-pentadienoate (4d). Yellow solid; mp 86.1–86.6 °C; IR (KBr): ν_{max} 3017, 2942, 1711, 1604, 1236, 742 cm^{-1}; ^1H NMR: δ 3.85 (s, 3H), 4.47 (s, 2H), 7.03 (d, J=15.5 Hz, 1H), 7.13 (dd, J=15.5, 11.0 Hz, 1H), 7.36–7.41 (m, 3H), 7.51 (d, J=11.0 Hz, 1H), 7.53–7.56 (m, 2H); ^{13}C NMR: δ 24.7, 52.2, 122.4, 126.8, 127.5 (2×C_{Ar}), 128.9 (2×C_{Ar}), 129.6, 135.8, 142.7, 142.8, 166.3. Anal. Calcd for $C_{13}H_{13}BrO_2$ (%): C, 55.54; H, 4.66. Found: C, 55.93; H, 5.01.

4.3. Typical procedure for the synthesis of 2-(azidomethyl)-2-alkenoates (1)

To a stirred solution of the allylic bromides **4** (1.0 mmol) in 4.0 mL of acetone/H_2O (3:1) at 25 °C was added 2.0 mmol of NaN_3 and stirring was continued for a further 10 min. The final mixture was diluted with CH_2Cl_2, washed with H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on a short plug of silica gel (hexane/ethyl acetate 9:1) to give the corresponding methyl 2-(azidomethyl)-2-alkenoates **1** quantitatively.

4.3.1. Methyl (*E*)-2-(azidomethyl)-3-(2-naphthyl)-2-propenoate (1c). Clear yellow oil; IR (neat): ν_{max} 3065, 2998, 2951, 2926, 2850, 2109, 1709, 1626 cm^{-1}; ^1H NMR: δ 3.90 (s, 3H), 4.24 (s, 2H), 7.46–7.50 (m, 3H), 7.80–7.91 (m, 4H), 8.09 (s, 1H); ^{13}C NMR: δ 47.1, 52.4, 126.3, 126.6, 127.3, 127.6, 127.8, 128.4, 128.6, 129.8, 131.5, 133.0, 133.5, 144.5, 167.4. Anal. Calcd for $C_{15}H_{13}N_3O_2$ (%): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.11; H, 4.88; N, 15.80.

4.3.2. Methyl (2*E*,4*E*)-2-(azidomethyl)-5-phenyl-2,4-pentadienoate (1d). White solid; mp 59.2–59.6 °C; IR (KBr): ν_{max} 2946, 2105, 1705, 1615, 1283 cm^{-1}; ^1H NMR: δ 3.84 (s, 3H), 4.24 (s, 2H), 7.00 (d, J=15.0 Hz, 1H), 7.07 (dd, J=15.0, 10.5 Hz, 1H), 7.33–7.39 (m, 3H), 7.49–7.51 (m, 2H), 7.61 (d, J=10.5 Hz, 1H); ^{13}C NMR: δ 46.2, 52.5, 122.4, 124.7, 127.8 (2×C_{Ar}), 129.1 (2×C_{Ar}), 129.8, 135.9, 143.2, 143.8, 167.5. Anal. Calcd for $C_{13}H_{13}N_3O_2$ (%): C, 64.19; H, 5.39; N, 17.27. Found: C, 64.53; H, 5.74; N, 16.91.

4.3.3. Methyl (*E*)-2-(azidomethyl)-3-(2-chlorophenyl)-2-propenoate (1e). Clear yellow oil; IR (neat): ν_{max} 3063, 2999, 2952, 2847, 2099, 1716, 1638 cm^{-1}; ^1H NMR: δ 3.90 (s, 3H), 4.09 (s, 2H), 7.32–7.45 (m, 4H), 8.04 (s, 1H); ^{13}C NMR: δ 46.9, 52.3, 126.7, 128.4, 129.5, 130.2, 130.4, 132.5, 134.1, 140.9, 166.7. Anal. Calcd for $C_{11}H_{10}ClN_3O_2$ (%): C, 52.50; H, 4.01; N, 16.70. Found: C, 52.34; H, 3.81; N, 16.58.

4.3.4. Methyl (*E*)-2-(azidomethyl)-3-(4-nitrophenyl)-2-propenoate (1f). Yellow solid; mp 102.5–103.5 °C; IR (KBr): ν_{max} 3107, 3082, 3006, 2955, 2110, 1722, 1633, 1514, 1263 cm^{-1}; ^1H NMR: δ 3.92 (s, 3H), 4.14 (s, 2H), 7.59 (d, J=8.0 Hz, 2H), 7.96 (s, 1H), 8.29 (d, J=8.0 Hz, 2H); ^{13}C NMR: δ 46.5, 52.6, 123.7 (2×C_{Ar}), 129.8, 130.1 (2×C_{Ar}), 140.2, 141.3, 147.8, 166.5. Anal. Calcd for $C_{11}H_{10}N_4O_4$ (%): C, 50.38; H, 3.84; N, 21.36. Found: C, 50.43; H, 4.04; N, 21.31.

4.3.5. Methyl (*E*)-2-(azidomethyl)-2-butenoate (1g) and methyl 3-azido-2-methylenebutanoate (5g). Unstable oil, obtained as a mixture with the corresponding isomer **5g** in 90–95% purity (ratio **1g/5g** ~4:1); IR (neat): ν_{max} 2993, 2954, 2853, 2107, 1717, 1652 cm^{-1}; major isomer (**1g**) exhibited the following spectral properties: ^1H NMR: δ 1.93 (d, J=7.0 Hz, 3H), 3.79 (s, 3H), 4.08 (s, 2H), 7.19 (q, J=7.0 Hz, 1H); ^{13}C NMR: δ 14.9, 45.6, 52.0, 127.4, 143.9, 166.6. Data for minor isomer (**5g**): ^1H NMR: δ 1.36 (d, J=6.5 Hz, 3H), 3.74 (s, 3H), 4.44 (q, J=6.5 Hz, 1H), 5.81 (s, 1H), 6.30 (s, 1H); ^{13}C NMR: δ 19.3, 51.7, 56.6, 125.5, 139.8, 165.7.

4.3.6. Methyl (*E*)-2-(azidomethyl)-4-methyl-2-hexenoate (1i). Unstable oil, obtained as a mixture with the corresponding isomer **5i** in 90–95% purity (ratio **1g/5g** ~9:1); IR (neat): ν_{max} 2962, 2930, 2875, 2105, 1719, 1646 cm^{-1}; ^1H NMR: δ 0.96 (t, J=7.5 Hz, 3H), 1.06 (d, J=3.5 Hz, 3H); 1.35–1.52 (m, 2H), 2.41–2.51 (m, 1H), 3.83 (s, 3H), 4.05 (s, 2H), 6.85 (d, J=10.5 Hz, 1H); ^{13}C NMR: δ 11.7, 20.0, 29.4, 35.2, 45.9, 52.4, 125.3, 154.0, 167.5.

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References and notes

1. (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240; (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (c) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368; (d) Hassner, A. *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic: New York, NY, 1984.
2. (a) Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 13444–13445; (b) Mangelinckx, S.; Boeykens, M.; Vliegen, M.; Van der Eycken, J.; De Kimpe, N. *Tetrahedron Lett.* **2005**, *46*, 525–529; (c) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Piccinelli, F.; Tolomelli, A. *Org. Lett.* **2005**, *7*, 533–536; (d) Takasu, H.; Tsuji, Y.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 11027–11031; (e) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884–892; (f) Papeo, G.; Posteri, H.; Vianello, P.; Varasi, M. *Synthesis* **2004**, 2886–2892.
3. (a) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737–8740; (b) Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485–7488; (c) Capaccio, C. A. I.; Varela, O. *Tetrahedron: Asymmetry* **2000**, *11*, 4945–4954; (d) Cleophax, J.; Olesker, A.; Rolland, A.; Gero, S. D.; Forchioni, A. *Tetrahedron* **1977**, *33*, 1303–1308; (e) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11368–11378; (f) Askin, D.; Angst, C.; Danishefsky, S. J. *J. Org. Chem.* **1985**, *50*, 5005–5007.
4. Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956–5958.
5. (a) Fava, C.; Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2731–2741; (b) Kawabata, H.; Kubo, S.; Hayashi, M. *Carbohydr. Res.* **2001**, *333*, 153–158; (c) Göksu, S.; Ozalp, C.; Seçen, H.; Sütbeyaz, Y.; Saripinar, E. *Synthesis* **2004**, 2849–2854; (d) Gagnon, D.; Lauzon, S.; Godbout, C.; Spino, C. *Org. Lett.* **2005**, *7*, 4769–4771.
6. Sá, M. M. *J. Braz. Chem. Soc.* **2003**, *14*, 1005–1010.
7. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Ciganek, E. *Organic Reactions*; Wiley: New York, NY, 1997; Vol. 51, pp 201–350.
8. (a) Foucaud, A.; Guemmout, F. E. *Bull. Soc. Chim. Fr.* **1989**, 403–408; (b) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981–984; (c) Ko, S. H.; Lee, K.-J. *J. Heterocycl. Chem.* **2004**, *41*, 613–616; (d) Sreedhar, B.; Reddy, P. S.; Kumar, N. S. *Tetrahedron Lett.* **2006**, *47*, 3055–3058; (e) Chandrasekhar, S.; Basu, D.; Rambabu, Ch. *Tetrahedron Lett.* **2006**, *47*, 3059–3063.
9. Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2002**, 1819–1822.
10. Lubineau, A.; Augé, J. *Topics in Current Chemistry*; Springer: Berlin, 1999; Vol. 206, pp 2–40.
11. Yadav, J. S.; Gupta, M. K.; Pandey, S. K.; Reddy, B. V. S.; Sarma, A. V. S. *Tetrahedron Lett.* **2005**, *46*, 2761–2763.
12. (a) Padwa, A.; Sá, M. M. *Tetrahedron Lett.* **1997**, *38*, 5087–5090; (b) Padwa, A.; Sá, M. M. *J. Braz. Chem. Soc.* **1999**, *10*, 231–236.
13. (a) Fernandes, L.; Bortoluzzi, A. J.; Sá, M. M. *Tetrahedron* **2004**, *60*, 9983–9989; (b) Nascimento, M. G.; Zanotto, S. P.; Melegari, S. P.; Fernandes, L.; Sá, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3111–3115.
14. (a) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213–1221; (b) Das, B.; Banerjee, J.; Ravindranath, N. *Tetrahedron* **2004**, *60*, 8357–8361; (c) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849–3859; (d) Yadav, J. S.; Reddy, B. V. S.; Madan, C. *New J. Chem.* **2001**, *25*, 1114–1117; (e) Foucaud, A.; Gruiec, A. *New J. Chem.* **1991**, *15*, 943–947; (f) Chen, H.-Y.; Patkar, L. N.; Ueng, S.-H.; Lin, C.-C.; Lee, A. S.-Y. *Synlett* **2005**, 2035–2038.
15. Zvak, V.; Kovac, J.; Dandarova, M.; Gracza, T.; Kriz, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 1764–1773.
16. (a) Clark, J. H. *Green Chem.* **2006**, *8*, 17–21; (b) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199–250.
17. Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952–8954.
18. Bortoluzzi, A. J.; Fernandes, L.; Sá, M. M. *Acta Crystallogr., Sect. E* **2006**, *62*, o3391–o3392.
19. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413–414.
20. Cunha, S. *Quim. Nova* **2003**, *26*, 948–951.
21. Eagen, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 3863–3866.
22. (a) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron* **2006**, *62*, 8798–8804; (b) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett.* **2001**, *42*, 477–479.

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A new one-pot synthesis of Gb_3 and $isoGb_3$ trisaccharide analogues

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Abstract—Gb_3 and $isoGb_3$ are both biologically important oligosaccharides. A new efficient synthesis of Gb_3 and $isoGb_3$ trisaccharide analogues has been achieved by one-pot sequential glycosylation strategy starting from simple monosaccharide building blocks promoted by *N*-(phenylthio)-ε-caprolactam at room temperature.

1. Introduction

Glycosphingolipids[1] are a class of naturally occurring bioactive compounds usually embedded in the membrane of all animal cells and some plant cells. The clinically important blood group antigens and the immunologically relevant tumor-associated antigens are examples of glycosphingolipids. Gb_3 glycolipid [α-D-Gal-(1→4)-β-D-Gal(1→4)-β-D-Glc-1→*O*-ceramide] (Fig. 1) is highly enriched in Burkitt lymphoma cell-lines, human teratocarcinoma, human embryonal carcinoma, and other types of tumor cells, and Gb_3 glycolipid is also closely related to Fabry's disease, a lysosomal storage disorder caused by a deficiency of human lysosomal α-galactosidase A.[2]

Gb_3 also serves as a cell-surface receptor for *Shiga*-like toxins (SLTs).[3] *Shiga*-like toxins belong to a small but clinically significant family of AB_5 bacterial toxins. They consist of a cytotoxic enzyme A subunit noncovalently linked to a homopentameric cell-adhesion carrier, B_5. The entry of the enzymatic A subunit into the host cell relies on adhesion of the B_5 subunit to the cell membrane, a recognition that is highly specific and mediated by multiple terminal trisaccharide of Gb_3, known as P^k-trisaccharide. Inhibition of interactions between toxin B pentamer and its cell-surface receptors hold a potential treatment for bacterial infections.

Another glycosphingolipid, $isoGb_3$, also plays an important role in many events.[4] It was found to be associated with

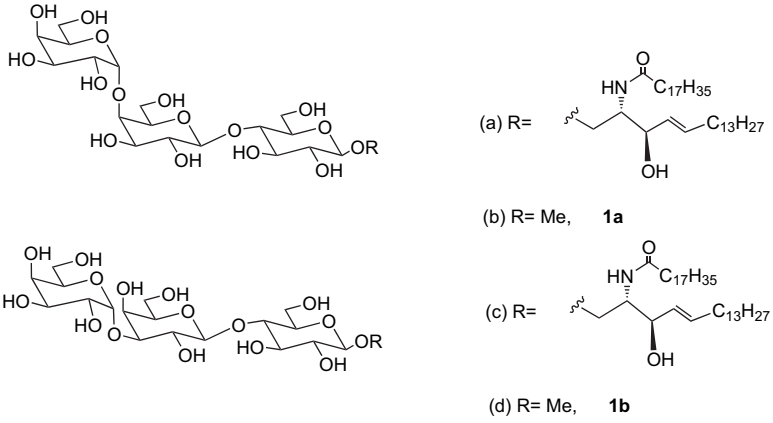

Figure 1. The structures of Gb_3, $isoGb_3$, and their methyl glycoside analogues **1a** and **1b**.

Keywords: Gb_3; $isoGb_3$; Thioglycoside; One-pot synthesis; Glycosylation.
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malignant neoplasms[4a,b] and shown that the Gal(αl-3)Gal segment of many glycosphingolipids can act as an attachment site for bacteria, bacterial toxins, and viruses.[4c,d] Recently, isoGb$_3$ was disclosed as an endogenous ligand for human NKT cells.[4f,g]

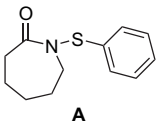
Because of their biological significance as well as common structures shared by various *globo*-series glycosphingolipids, a number of Gb$_3$/isoGb$_3$ tri- and di-saccharide analogues have been synthesized.[5] However, in the reported chemical syntheses of Gb$_3$ and isoGb$_3$, the trisaccharide donors are normally prepared in 17–19 steps due to the tedious functional group manipulations and glycosylations, more efficient synthetic routes to the trisaccharide analogues are still needed. Herein we wish to report a new synthesis of the methyl glycosides **1a** and **1b** (Fig. 1), using one-pot sequential glycosylation strategy.

2. Results and discussion

Oligosaccharide synthesis by one-pot sequential glycosylation strategy[6] is one of the efficient routes for saccharide assembly. Recently many important oligosaccharides such as fucosyl GM$_1$,[7] Globo-H,[8] Lewis Y,[9] antigen N3 minor glycoside,[10] and α-Gal epitopes[11] have been synthesized using one-pot method. Promoters play an important role in the one-pot synthesis. There are many promoters available including dimethyl-(thiomethyl)sulfonium triflate (DMTST),[12] *N*-iodosuccinimide/triflic acid (NIS/TfOH),[13] phenylsulfenyl chloride and silver triflate (PhSCl/AgOTf),[14] and 1-benzenesulfinylpiperidine and triflic anhydride (BSP/Tf$_2$O),[15] but all of them have to be employed under low temperature (−78 °C to 0 °C) conditions. Very recently, a new promoter, *N*-(phenylthio)-ε-caprolactam (Fig. 2), has been reported by Wong's group.[16] This reagent can be used at room temperature to promote the glycosyl coupling reactions. We decided to make the trisaccharides **1a** and **1b** with this new promoter by one-pot glycosylation procedure.

For the synthesis of the target trisaccharides, we chose thioglycosides as glycosyl donors because they are stable enough in storage and can be activated by a variety of promoters including *N*-(phenylthio)-ε-caprolactam. The retrosynthetic analysis of **1a** and **1b** is shown in Figure 3. For the synthesis of **1a**, the perbenzylated thiogalactoside **2** and 2,3-*O*-benzoylated-6-*O*-benzylated thiogalactoside **3** are chosen as the first and second components, and the methyl glucoside **4** is selected as the third component. For the synthesis of **1b**, thiogalactoside **5** is used as the second building block instead of **3**. All the designed building blocks are very simple with the widely used benzyl/benzylidene and benzoyl functionalities as the hydroxyl protecting groups.

The galactosyl donor **2**[6a] was prepared from galactose pentaacetate in a three-step process as shown in Scheme 1.



A

Figure 2. The structure of *N*-(phenylthio)-ε-caprolactam.

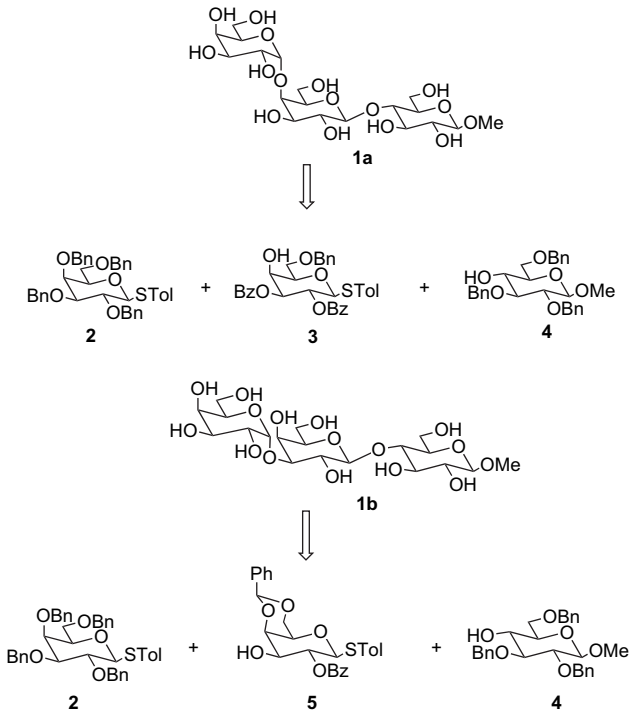
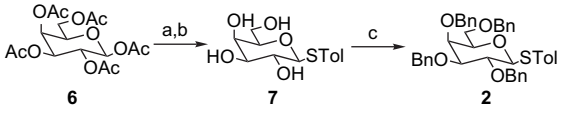


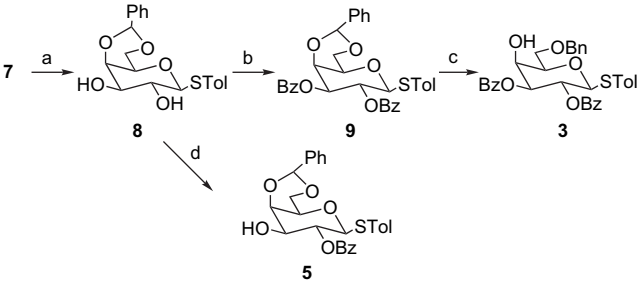
Figure 3. The retrosynthesis of trisaccharides **1a** and **1b**.

Treatment of the peracetylated galactose **6** with thiocresol in the presence of BF$_3$·Et$_2$O followed by O-deacetylation with NaOMe afforded compound **7**.[17] O-Benzylation of **7** provided the desired galactosyl donor **2** in 84% isolated yield.

The synthesis of galactosyl building block **3**[6a] began from compound **7** in three steps as shown in Scheme 2. Treatment of **7** with benzaldehyde dimethyl acetal and a catalytic amount of DL-10-camphorsulfonic acid (CSA) in acetonitrile yielded the 4,6-*O*-benzylidene derivative **8**.[18] The remaining free hydroxyl groups of **8** were benzoylated to afford fully protected saccharide **9**,[18] which was subjected



Scheme 1. Synthesis of galactosyl donor **2**. Reagents and conditions: (a) MePhSH, BF$_3$·Et$_2$O, CH$_2$Cl$_2$, 80%; (b) NaOMe, MeOH, 99%; (c) BnBr, NaH, DMF, 84%.



Scheme 2. Synthesis of galactosyl donor–acceptors **3** and **5**. Reagents and conditions: (a) benzaldehyde dimethyl acetal, CSA, MeCN, 81%; (b) BzCl, pyridine, 74%; (c) NaCNBH$_3$, HCl·Et$_2$O, THF, 93%; (d) BzCl, Ag$_2$O, KI, DCM, 50%.

to regioselective reductive cleavage by treatment with $NaCNBH_3$ in the presence of etheral hydrochloride, providing the acceptor–donor **3** with the 4-OH exposed. On the other hand, diol **8** was regioselectively benzoylated to obtain the desired building block **5**[19,6a] with the 3-OH free in 50% isolated yield.

The synthesis of acceptor **4** (Scheme 3) started from methyl glucoside **10**. After 4,6-*O*-benzylidenation of **10**, the remaining two OH groups of **11**[20] were benzylated to provide **12**.[21] Compound **12** was then transformed into the 4-OH free derivative **4**[22] with $NaCNBH_3/HCl\cdot Et_2O$ in 90% isolated yield.

With all these building blocks in hand, glycosylations between the donors and acceptors were explored. The coupling reaction of donor **2** and acceptor **3** at room temperature with *N*-(phenylthio)-ε-caprolactam/Tf_2O as the promoter was firstly tried. Although it was often thought that the 4-OH of galactose moiety is not easy to couple with glycosyl donors, we successfully obtained the desired disaccharide **13** in 87% isolated yield (Scheme 4). It is also noteworthy that only the desired α-anomer was obtained in the glycosylation of **2** with **3**. The configuration of the newly formed glycosidic linkage was confirmed by the ^1H NMR coupling constant of the anomeric proton H-1 (3.5 Hz). The successful preparation of disaccharide **13** indicated that *N*-(phenylthio)-ε-caprolactam/Tf_2O can serve as the promoter for stereoselective glycosylation. We next focused on applying this promoter to the one-pot synthesis of trisaccharide **14**. Consecutive coupling of *p*-tolyl thiogalactosides **2** and **3**, and methyl glucoside **4** in dichloromethane at room temperature produced trisaccharide **14** smoothly in 47% isolated yield (Scheme 4). Finally, global deprotection of **14** was performed in two steps: the benzoyl group was removed with NaOMe in methanol, and the benzyl functionality was cleaved with Pd/C catalyzed hydrogenolysis. The target trisaccharide **1a** was obtained in 80% yield from **14**.

Similarly, for the synthesis of $isoGb_3$ trisaccharide **1b**, we also checked the two-component coupling reaction of **2** and **5**, and we obtained disaccharide **15** in 90% isolated yield (Scheme 5). After successful preparation of disaccharide **15**, the one-pot sequential glycosylations of building blocks **2** and **5**, and methyl glucoside **4** were performed at room temperature, leading to trisaccharide **16** in 50% isolated yield (Scheme 5). Global deprotection of **16** was carried out in the same way as above-mentioned to provide the target trisaccharide **1b** in 90% yield.

The structures of **1a** and **1b**, as well as the correct anomeric configuration of each glycosidic linkage were confirmed by their ^1H NMR, ^{13}C NMR, and HRMS analyses.

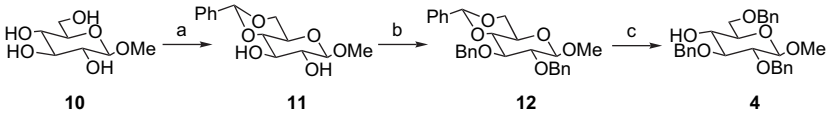
3. Conclusion

In conclusion, the trisaccharide analogues of Gb_3 and $isoGb_3$ were synthesized in an efficient way with high stereoselectivity by one-pot sequential glycosylation strategy using very common building blocks. Importantly, all the glycosyl coupling reactions were carried out at room temperature in the presence of *N*-(phenylthio)-ε-caprolactam/Tf_2O.

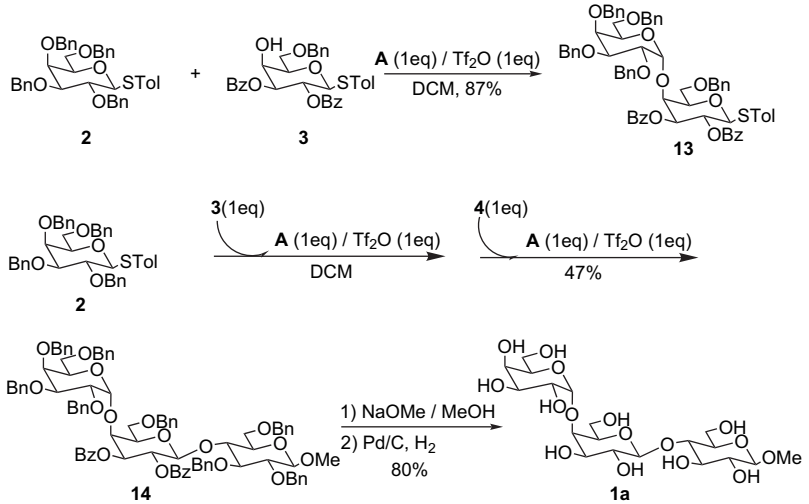
4. Experimental

4.1. General methods

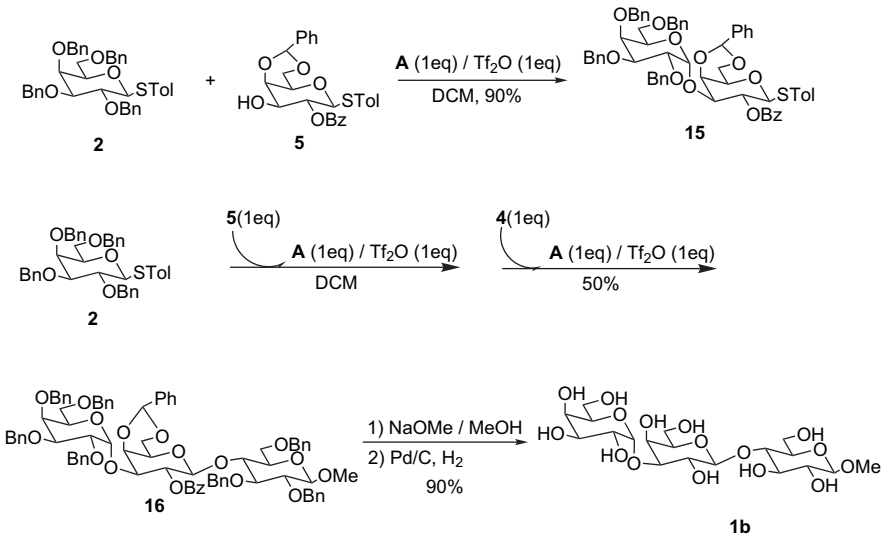
All reactions were carried out under an atmosphere of nitrogen unless noted otherwise. All solvents were dried and distilled by standard techniques. Analytical thin-layer



Scheme 3. Synthesis of glucosyl acceptor **4**. Reagents and conditions: (a) benzaldehyde dimethyl acetal, CSA, MeCN, 80%; (b) BnBr, NaH, DMF, 74%; (c) $NaCNBH_3$, $HCl\cdot Et_2O$, THF, 90%.



Scheme 4. Synthesis of Gb_3 trisaccharide **1a**.



Scheme 5. Synthesis of isoGb$_3$ trisaccharide **1b**.

chromatography (TLC) was performed on silica gel 60 F_{254} (E. Merck Co.). Compounds spots were visualized by UV light and/or by staining with an ethanol solution of phosphomolybdic acid and cerium sulfate. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Chemical Industry). NMR spectra were recorded with Varian INOVA-500 spectrometer. Chemical shifts were referenced to the internal TMS. Mass spectra were recorded on a PE SCLEX QSTAR spectrometer.

Optical rotations were measured with an AA-10R automatic polarimeter.

4.2. Synthesis

4.2.1. *p*-Methylphenyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-1-thio-β-D-galactopyranoside (13). To a solution of **2** (100.0 mg, 0.155 mmol), **3** (90.5 mg, 0.155 mmol), and *N*-(phenylthio)-ε-caprolactam (34.0 mg, 0.155 mmol) in CH_2Cl_2 (45 mL) was added 4 Å molecular sieves (600.0 mg). The mixture was stirred for 2 h at room temperature, and then Tf_2O (43.7 mg, 0.155 mmol) was added. The resulting mixture was stirred at room temperature for 0.5 h. The course of the reaction was monitored by TLC. Et_3N (0.5 mL) was then added to the mixture. The precipitate was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give **13** (137.1 mg, 87%) as a thick oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.92–2.95 (m, 1H), 3.33 (t, 1H, J=9.0 Hz), 3.71–3.74 (m, 1H), 3.87–3.95 (m, 2H), 3.98–4.09 (m, 6H), 4.25–4.30 (m, 2H), 4.39 (d, 1H, J=2.5 Hz), 4.46 (d, 1H, J=11.0 Hz), 4.66 (d, 1H, J=12.0 Hz), 4.75 (d, 1H, J=11.5 Hz), 4.79 (d, 1H, J=11.5 Hz), 4.83 (d, 1H, J=11.0 Hz), 4.88 (d, 1H, J=3.5 Hz, H-1′), 4.90 (d, 1H, J=11.5 Hz), 5.23 (dd, 1H, J=2.5 Hz, 10.0 Hz), 5.69 (t, 1H, J=10.0 Hz), 6.96 (d, 2H, J=8.0 Hz), 7.18–7.45 (m, 32H, Ar-H), 7.48–7.51 (m, 1H), 7.88–7.90 (m, 2H), 7.94–7.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.38, 67.66, 68.18, 69.53, 69.63, 72.64, 73.15, 73.33, 74.28, 74.95, 75.18, 75.70, 76.91, 78.54, 78.96, 86.15, 100.21, 127.31, 127.36, 127.45, 127.54, 127.63, 127.94, 128.07, 128.19, 128.34, 128.08, 129.50, 129.68, 129.91, 130.07, 133.16, 133.67, 133.98, 138.30, 138.69, 138.87, 165.10, 166.28. HRMS (ESI) Anal. Calcd for $C_{68}H_{66}NaO_{12}S$ $[M+Na]^+$: 1129.4167; found: 1129.4168.

4.2.2. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[2′,3′-di-*O*-benzoyl-6′-*O*-benzyl-4′-*O*-(2″,3″,4″,6″-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranoside (14). After a mixture of donor **2** (100.0 mg, 0.155 mmol), acceptor **3** (90.5 mg, 0.155 mmol), *N*-(phenylthio)-ε-caprolactam (34.0 mg, 0.155 mmol) and 4 Å molecular sieves (600.0 mg) in CH_2Cl_2 (45 mL) was stirred for 2 h at room temperature, Tf_2O (43.7 mg, 0.155 mmol) was added via a syringe. After 0.5 h, TLC indicated that both the donor and acceptor were consumed completely, **4** (72.0 mg, 0.155 mmol) and *N*-(phenylthio)-ε-caprolactam (34.0 mg, 0.155 mmol) were then added into the flask. The reaction mixture was stirred for another 10 min, and Tf_2O (43.7 mg, 0.155 mmol) was added. After stirring for 1 h, the reaction was quenched with Et_3N (0.5 mL) and all insoluble materials were removed by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1 to 2:1) to provide **14** (104.9 mg, 47%) as a thick oil. $[\alpha]_D^{20}$ 8.0 (c 0.0025, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.93–2.96 (m, 1H), 3.26–3.29 (m, 1H), 3.33–3.37 (m, 2H), 3.48 (s, 3H), 3.52–3.62 (m, 4H), 3.68–3.70 (m, 1H), 3.93–4.01 (m, 3H), 4.05–4.07 (m, 3H), 4.10–4.12 (m, 1H), 4.19 (d, 1H, J=8.0 Hz, H-1), 4.20–4.43 (m, 7H), 4.51–4.59 (m, 3H), 4.62–4.65 (m, 2H), 4.73 (d, 1H, J=11.5 Hz), 4.78–4.85 (m, 3H), 4.91 (d, 1H, J=3.5 Hz, H-1″), 4.94 (d, 1H, J=8.0 Hz, H-1′), 5.03–5.07 (m, 2H), 5.74 (dd, 1H, J=7.5 Hz, 10.5 Hz), 7.14–7.38 (m, 46H), 7.46–7.49 (m, 1H), 7.86–7.89 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.94, 67.40, 67.80, 68.18, 69.48, 70.68, 72.33, 72.87, 73.00, 73.35, 73.74, 74.09, 74.34, 74.72, 74.88, 75.64, 76.24, 79.10, 81.86, 82.33, 100.66, 100.84, 104.44, 127.22, 127.35, 127.44, 127.50, 127.76, 127.89, 127.96, 128.02, 128.12, 128.19, 128.30, 128.42, 129.30, 129.56, 129.83, 133.06, 133.15, 138.19, 138.40, 138.61, 138.76, 138.92, 139.18, 165.15, 166.44. HRMS (ESI) Anal. Calcd for $C_{89}H_{90}NaO_{18}$ $[M+Na]^+$: 1469.6019; found: 1469.6013.

4.2.3. Methyl 4-*O*-[4′-*O*-(α-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranoside (1a). To a solution of compound **14** (45.0 mg, 0.03 mmol) in MeOH (10 mL) was added NaOMe/MeOH (30 wt %, 0.4 mL), and the reaction mixture was stirred for 8 h at room temperature. The mixture was neutralized (H^+ resin, weak acid). The resin was filtered off and the filtrate was concentrated. The resulting residue was dissolved in THF/AcOH/H_2O (v/v 2:2:1, 10 mL) and then Pd/C (10.0 mg) was added. The reaction mixture was stirred under H_2 atmosphere for 24 h. The Pd/C was filtered off and the filtrate was concentrated. The product was purified by C-18 reverse-phase column chromatography to give **1a** (12.9 mg, 80%) as an oil. $[\alpha]_D^{20}$ 17.7 (*c* 0.00338, H_2O/CH_3OH 1:2); ^1H NMR (500 MHz, D_2O): δ 3.27–3.31 (m, 1H), 3.56 (s, 3H), 3.57–3.60 (m, 2H), 3.60–3.64 (m, 2H), 3.67–3.73 (m, 3H), 3.75 (d, 1H, *J*=3.0 Hz), 3.77–3.79 (m, 1H), 3.79–3.87 (m, 4H), 3.87–3.94 (m, 2H), 4.00 (d, 1H, *J*=7.5 Hz), 4.02–4.04 (m, 2H), 4.35 (t, 1H, *J*=6.0 Hz), 4.40 (d, 1H, *J*=8.0 Hz, H-1′), 4.50 (d, 1H, *J*=7.5 Hz, H-1), 4.94 (d, 1H, *J*=4.0 Hz, H-1″); ^{13}C NMR (125 MHz, D_2O): δ 57.95, 60.76, 61.12, 61.27, 69.31, 69.70, 69.86, 71.57, 71.66, 72.91, 73.62, 75.19, 75.55, 76.17, 78.10, 79.40, 101.05, 103.77, 104.10. HRMS (ESI) Anal. Calcd for $C_{19}H_{34}NaO_{16}$ $[M+Na]^+$: 541.1739; found: 541.1728.

4.2.4. *p*-Methylphenyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-galactopyranosyl)-1-thio-β-D-galactopyranoside (15). To a solution of **2** (100.0 mg, 0.155 mmol), **5** (74.1 mg, 0.155 mmol), and *N*-(phenylthio)-ε-caprolactam (34.0 mg, 0.155 mmol) in CH_2Cl_2 (45 mL) was added 4 Å molecular sieves (600.0 mg), and the mixture was stirred for 2 h at room temperature. Tf_2O (43.7 mg, 0.155 mmol) was then added, and the reaction mixture was stirred at room temperature for 0.5 h. The course of the reaction was monitored by TLC. Et_3N (0.5 mL) was then added to the mixture. The precipitate was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to give **15** (134.9 mg, 90%) as an oil. ^1H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.17–3.25 (m, 2H), 3.41 (s, 2H), 3.63 (dd, 1H, *J*=3.0 Hz, 10.0 Hz), 3.82 (t, 1H, *J*=6.5 Hz), 3.92–3.96 (m, 2H), 4.00 (dd, 1H, *J*=3.0 Hz, 10.0 Hz), 4.25 (d, 1H, *J*=10.5 Hz), 4.31–4.47 (m, 6H), 4.56 (d, 1H, *J*=11.5 Hz), 4.62 (d, 1H, *J*=12.0 Hz), 4.72 (d, 1H, *J*=10.0 Hz, H-1), 4.77 (d, 1H, *J*=11.5 Hz), 5.05 (d, 1H, *J*=3.5 Hz, H-1′), 5.38 (s, 1H), 5.60 (t, 1H, *J*=9.5 Hz), 6.96–7.42 (m, 32H, Ar-H), 8.02 (d, 2H, *J*=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.25, 68.66, 68.98, 69.34, 69.84, 69.91, 71.80, 72.17, 73.11, 73.23, 74.57, 74.94, 75.53, 75.80, 78.59, 85.44, 94.64, 101.04, 126.55, 127.25, 127.30, 127.38, 127.46, 127.55, 127.66, 127.80, 128.06, 128.10, 128.14, 128.22, 128.29, 128.89, 129.46, 129.81, 130.07, 132.92, 134.16, 137.66, 138.08, 138.28, 138.54, 138.66, 138.80, 164.63. MS (ESI) Anal. Calcd for $C_{61}H_{64}NO_{11}S$ $[M+NH_4]^+$: 1018.4; found: 1018.7.

4.2.5. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[2′-*O*-benzoyl-4′,6′-*O*-benzylidene-3′-*O*-(2″,3″,4″,6″-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranoside (16). After a mixture of donor **2** (100.0 mg, 0.155 mmol), acceptor **5** (74.1 mg, 0.155 mmol), *N*-(phenylthio)-ε-caprolactam (34.0 mg, 0.155 mmol) and 4 Å molecular sieves (600.0 mg) in CH_2Cl_2 (45 mL) was stirred for 2 h at room temperature, Tf_2O (43.7 mg, 0.155 mmol) was added via a syringe. After 0.5 h, TLC indicated that both the donor and acceptor were consumed completely, **4** (72.0 mg, 0.155 mmol) and *N*-(phenylthio)-ε-caprolactam (34.0 mg, 0.155 mmol) were then added. After stirring for another 10 min, Tf_2O (43.7 mg, 0.155 mmol) was added. After stirring for 1 h, the reaction was quenched with Et_3N (0.5 mL) and all insoluble materials were removed by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 3:1) to give **16** (103.9 mg, 50%) as a thick oil. $[\alpha]_D^{20}$ 6.2 (*c* 0.0030, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 2.97 (s, 1H), 3.16 (dd, 1H, *J*=6.0 Hz, 9.0 Hz), 3.22–3.28 (m, 2H), 3.39 (t, 1H, *J*=7.5 Hz), 3.46–3.48 (m, 5H), 3.60–3.68 (m, 4H), 3.73 (d, 1H, *J*=11.0 Hz), 3.79 (dd, 1H, *J*=3.5 Hz, 10.0 Hz), 3.84 (t, 1H, *J*=6.5 Hz), 3.88–3.91 (m, 1H), 3.94–3.97 (m, 1H), 4.11–4.26 (m, 6H), 4.35 (t, 2H, *J*=12.0 Hz), 4.42–4.53 (m, 4H), 4.58–4.63 (m, 2H), 4.69 (d, 1H, *J*=6.0 Hz), 4.77–4.86 (m, 4H), 5.04 (d, 1H, *J*=3.5 Hz, H-1″), 5.10 (d, 1H, *J*=11.0 Hz), 5.32 (s, 1H), 5.61 (dd, 1H, *J*=8.5 Hz, 10.0 Hz), 7.06–7.38 (m, 40H), 7.48–7.50 (m, 3H), 7.97–7.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.95, 66.60, 68.36, 68.73, 68.80, 69.84, 71.37, 72.13, 72.26, 73.09, 73.14, 73.22, 74.41, 74.64, 74.68, 74.92, 75.26, 75.48, 75.84, 77.64, 78.58, 81.96, 83.03, 95.55, 100.95, 101.20, 104.48, 126.39, 127.09, 127.29, 127.37, 127.45, 127.49, 127.58, 127.65, 127.81, 127.91, 127.99, 128.09, 128.15, 128.23, 128.34, 128.41, 128.70, 129.76, 129.85, 133.01, 137.77, 138.16, 138.46, 138.60, 138.65, 138.78, 139.07, 164.69. HRMS (ESI) Anal. Calcd for $C_{82}H_{88}NO_{17}$ $[M+NH_4]^+$: 1358.6047; found: 1358.6053.

4.2.6. Methyl 4-*O*-[3′-*O*-(α-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranoside (1b). To a solution of compound **16** (40.2 mg, 0.03 mmol) in MeOH (10 mL) was added NaOMe/MeOH (30 wt %, 0.4 mL), and the reaction mixture was stirred for 8 h at room temperature. The mixture was neutralized (H^+ resin, weak acid). The resin was filtered off and the filtrate was evaporated in vacuum. The resulting residue was dissolved in THF/AcOH/H_2O (v/v 2:2:1, 10 mL) and then Pd/C (10.0 mg) was added. The reaction mixture was stirred under H_2 atmosphere for 24 h. The Pd/C was filtered off and the filtrate was concentrated. The product was purified by C-18 reverse-phase column chromatography to give **1b** (13.9 mg, 90%) as an oil. $[\alpha]_D^{20}$ 20.1 (*c* 0.00579, H_2O/CH_3OH 1:2); ^1H NMR (500 MHz, D_2O): δ 3.29–3.30 (m, 1H), 3.58 (s, 3H), 3.61–3.63 (m, 1H), 3.65–3.68 (m, 3H), 3.71–3.87 (m, 8H), 3.94–4.02 (m, 3H), 4.18–4.21 (m, 2H), 4.41 (d, 1H, *J*=8.0 Hz, H-1), 4.52 (d, 1H, *J*=7.5 Hz, H-1′), 5.14 (d, 1H, *J*=4.0 Hz, H-1″); ^{13}C NMR (125 MHz, D_2O): δ 57.98, 60.88, 61.68, 61.74, 65.56, 68.95, 69.89, 70.03, 70.33, 71.59, 73.52, 75.21, 75.49, 75.80, 77.96, 79.38, 96.19, 103.60, 103.83. HRMS (ESI) Anal. Calcd for $C_{19}H_{34}O_{16}Na$ $[M+Na]^+$: 541.1739; found: 541.1748.

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References and notes

1. (a) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500–507; (b) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532–1568; (c) Cremeti, E. A.; Fischl, S. A. *Lipids* **2000**, *35*, 937–945; (d) Harouse, J. M.; Bhat, S.; Spitalnik, S. L. *Science* **1991**, *253*, 320–323; (e) Lourenco, A.; Lobo, A. M.; Rodriguez, B.; Jimeno, M. L. *Phytochemistry* **1996**, *43*, 617–619.
2. (a) Naika, M.; Marcus, D. M. *Biochem. Biophys. Res. Commun.* **1974**, *60*, 1105–1111; (b) Wiels, J.; Holmes, E. H.; Cochran, N.; Tursz, T.; Hakomori, S. *J. Biol. Chem.* **1984**, *259*, 14783–14787; (c) Kannagi, R.; Levery, S. B.; Ishigami, F.; Hakomori, S.; Shevinsky, L. H.; Knowles, B. B.; Solter, D. *J. Biol. Chem.* **1983**, *258*, 8934–8942; (d) Fukuda, M. N.; Bothner, B.; Lloyd, K. O.; Rettig, W. J.; Tiller, P. R.; Dell, A. *J. Biol. Chem.* **1986**, *261*, 5145–5153; (e) Kniep, B.; Monner, D. A.; Schwulera, U.; Muhlradt, P. F. *Eur. J. Biochem.* **1985**, *149*, 187–191; (f) Kint, J. A. *Science* **1970**, *167*, 1268–1273; (g) Li, Y.-T.; Li, S.-C. *J. Biol. Chem.* **1971**, *246*, 3769–3771.
3. (a) Keusch, G. T.; Jacewicz, M.; Acheson, D. W. K.; Donohue-Rolfe, A.; Kane, A. V.; McCluer, R. H. *Infect. Immun.* **1995**, *63*, 1138–1141; (b) Nyholm, P.-G.; Magnusson, G.; Zheng, Z.; Norel, R.; Binnington-Boyd, B.; Lingwood, C. A. *Chem. Biol.* **1996**, *4*, 263–275; (c) Fan, E.; Merritt, E. A.; Verlinde, C. L. M. J.; Hol, W. G. J. *Curr. Opin. Struct. Biol.* **2000**, *10*, 680–686; (d) Ling, H.; Boodhoo, A.; Hazes, B.; Cummings, M. D.; Armstrong, G. D.; Brunton, J. L.; Read, R. J. *Biochemistry* **1998**, *37*, 1777–1788; (e) Shimizu, H.; Field, R. A.; Homans, S. W.; Donohue-Rolfe, A. *Biochemistry* **1998**, *37*, 11078–11082; (f) Stein, P. E.; Boodhoo, A.; Tyrrell, G. J.; Brunton, J. L.; Read, R. J. *Nature* **1992**, *355*, 748–750; (g) Lindberg, A. A.; Brown, J. E.; Stromberg, N.; Westling-Ryd, M.; Schultz, J. E.; Karlsson, K.-A. *J. Biol. Chem.* **1987**, *262*, 1779–1785.
4. (a) Makita, A.; Taniguchi, N. *Glycolipids*; Wiegand, H., Ed.; Elsevier: Amsterdam, 1985; pp 1–82; (b) Adga, T.; Yu, R. K.; Scarsdale, J. N.; Suzuki, M.; Kuroda, Y.; Kitagawa, H.; Miyatake, T. *Biochemistry* **1988**, *27*, 5335–5340; (c) Bock, K.; Breimer, M. E.; Bdgnole, A.; Hansson, G. C.; Karlsson, K. A.; Larson, G.; Leffler, H.; Samuelsson, B. E.; Stromberg, N.; Svanborg-Eden, K.; Thurin, J. *J. Biol. Chem.* **1985**, *260*, 8545–8551; (d) Karlsson, K. A. *Pure Appl. Chem.* **1987**, *59*, 1447–1448; (e) Ashline, S.; Singh, A.; Hanneman, V. R. *Anal. Chem.* **2005**, *77*, 6250–6262; (f) Zhou, D.; Mattner, J.; Schrantz, C. N.; Yin, N.; Gao, Y.; Sagiv, Y.; Hudspeth, K.; Wu, Y.-P.; Yamashita, T.; Teneberg, S.; Wang, D.; Proia, R. L.; Levery, S. B.; Savage, P. B.; Teyton, L.; Bendelac, A. *Science* **2004**, *306*, 1786–1789; (g) Dale, I. G.; Daniel, G. P.; Smyth, M. J. *Science* **2004**, *306*, 1687–1689; (h) Wuhrer, M.; Grimm, C.; Dennis, R. D.; Idris, M. A.; Geyer, R. *Glycobiology* **2004**, *14*, 115–126; (i) Teneberg, S.; Alsen, B.; Angstrom, J.; Winter, H. C.; Goldstein, I. J. *Glycobiology* **2003**, *13*, 479–486; (j) Hynes, S. O.; Teneberg, S.; Roche, N.; Wadstrom, T. *Infect. Immun.* **2003**, *71*, 2976–2980.
5. (a) Shapiro, D.; Acher, A. J. *Chem. Phys. Lipids* **1978**, *22*, 197–206; (b) Koike, K.; Sugimoto, M.; Sato, S.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1987**, *163*, 189–208; (c) Nicolaou, K. C.; Caulfield, T. J.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910–7912; (d) Nicolaou, K. C.; Caulfield, T. J.; Kataoka, H. *Carbohydr. Res.* **1990**, *202*, 177–191; (e) Qiu, D.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 217–224; (f) Hashimoto, S.-I.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S.-I.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969–8972; (g) Bosse, F.; Marcaurelle, L. A.; Seeberger, P. H. *J. Org. Chem.* **2002**, *67*, 6659–6670; (h) Hsieh, S. Y.; Jan, M. D.; Patkar, L. N.; Chen, C. T.; Lin, C. C. *Carbohydr. Res.* **2005**, *340*, 49–57; (i) Yao, Q.; Song, J.; Xia, C.; Zhang, W.; Wang, P. G. *Org. Lett.* **2006**, *8*, 911–914.
6. (a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753; (b) Ye, X.-S.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2410–2431; (c) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465–4493; (d) Ley, S. V.; Priepke, H. W. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2292–2294; (e) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51–65; (f) Raghaven, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580–1581; (g) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919–7920; (h) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221–5224; (i) Wang, Y.; Zhang, L.-H.; Ye, X.-S. *Comb. Chem. High Throughput Screen.* **2006**, *9*, 63–75.
7. Mong, T. K.-K.; Lee, H.-K.; Duron, S. G.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797–802.
8. Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1274–1277.
9. Mong, K.-K. T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4087–4090.
10. Lee, J.-C.; Wu, C.-Y.; Apon, J. V.; Siuzdak, G.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2753–2757.
11. (a) Wang, Y.; Huang, X.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2004**, *6*, 4415–4417; (b) Wang, Y.; Yan, Q.; Wu, J.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron* **2005**, *61*, 4313–4321.
12. Fugedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, c9–c12.
13. Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313–4316.
14. (a) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702–1706; (b) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348.
15. Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.
16. Duron, S. G.; Polat, T.; Wong, C.-H. *Org. Lett.* **2004**, *6*, 839–841.
17. Magnusson, G. *J. Org. Chem.* **1977**, *42*, 913–914.
18. Vargas-berenguel, A.; Meldal, M.; Paulsen, H.; Jensen, K. J.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3287–3294.
19. Wang, H.; She, J.; Zhang, L.-H.; Ye, X.-S. *J. Org. Chem.* **2004**, *69*, 5774–5777.
20. Evans, M. E. *Carbohydr. Res.* **1972**, *21*, 473–475.
21. Pennison, J. C.; McGilary, O. I. *J. Chem. Soc.* **1951**, 1616–1617.
22. Garegg, J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97–101.

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The crucial role of the nitrogen substituent in the desymmetrisation of cyclic *meso*-imides using *B*-Me and *B*-OMe oxazaborolidine catalysts

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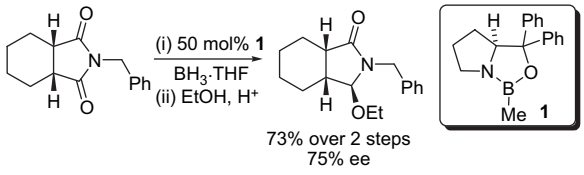
Abstract—Various cyclic *meso*-imides have been desymmetrised via enantioselective reduction using two chiral oxazaborolidine catalysts derived from (1*R*,2*S*)-*cis*-1-amino-indan-2-ol followed by the reduction of the hydroxylactam product to give the γ-lactam. The enantiomeric excesses were shown to be 27–99% by chiral HPLC and chiral GC of the γ-lactam products with the nitrogen substituent playing a pivotal role in determining yield and selectivity.

1. Introduction

Desymmetrisation of *meso*-compounds is a powerful and versatile strategy in asymmetric synthesis as the differentiation of two enantiotopic groups facilitates the formation of multiple stereocentres in a single transformation.[1] There have been several previous reports of the catalytic desymmetrisation of *meso*-imides using oxazaborolidines derived from α,α-diphenylprolinol (CBS catalyst, Scheme 1).[2]



Scheme 1. Desymmetrisation of *meso*-imides using a CBS catalyst.

Loadings of catalyst **1** of 50 mol % were required to maintain high yields and selectivities although lower loadings could be used but this was sensitive to the nature of the nitrogen substituent, *N*-phenyl substrates requiring 10 mol % catalyst to achieve an ee of 68%. The role played by the nitrogen substituent on the ee was also noted by Kang et al. who used catalytic thiazazincolidine complexes to reduce related systems.[3] In this case, *N*-aryl groups gave better selectivities than *N*-benzyl at catalyst loading of 20 mol %, with *N*-phenyl providing the better ee over the more sterically demanding *N*-2,6-dichlorophenyl (86% ee vs 50% ee).

Previous work from this group has described the use of various *B*-substituted oxazaborolidines **2** and **3** derived from (1*R*,2*S*)-*cis*-1-amino-indan-2-ol as catalysts for the asymmetric reduction of prochiral ketones (Fig. 1).[4] Following from this work, various *N*-substituted oxazaborolidines **4** (R=Me, Et and Bn) were probed as possible catalysts for the catalytic desymmetrisation of *meso*-imides. The results showed that the unsubstituted oxazaborolidine **2** proved to be the most efficient.[5]

Although *B*-OMe oxazaborolidines such as catalyst **3** have been shown to be successful in the asymmetric reduction of various prochiral ketones,[6] their use in imide reduction has not yet been explored. Herein we describe their application in the desymmetrisation of various cyclic *meso*-imides and further investigate the effect that the changing

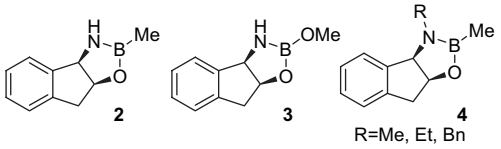


Figure 1. *cis*-1-Amino-indan-2-ol derived oxazaborolidines.

Keywords: Asymmetric reduction; Oxazaborolidine; Catalysis; Imides.
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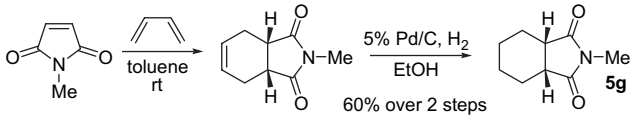
N-substituent has on the enantioselectivity of this type of asymmetric reduction.

2. Results and discussion

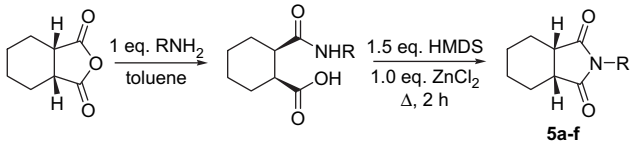
2.1. Substrate synthesis

Various *N*-substituted hexahydroisolidine-1,3-diones **5a–f** were prepared via two different methods starting from either the corresponding dicarboxylic acid or the carboxylic acid anhydride. This methodology, however, could not be applied to the *N*-methyl **5g** derivative, which was prepared from the corresponding *N*-methylmaleimide by Diels–Alder reaction with 1,3-butadiene followed by hydrogenation (Scheme 2).



Scheme 2.

The first method involved application of a previously reported procedure for the Lewis acid and hexamethyldisilazane (HMDS) promoted condensation between a primary amine and cyclohexane-1,2-dicarboxylic acid anhydride (Scheme 3, Table 1).[7] This method proved to be useful in the synthesis of all the required substrates, however, with bulky and highly electron deficient amines the yield was reduced considerably. However, this method accessed the required products in good yields.



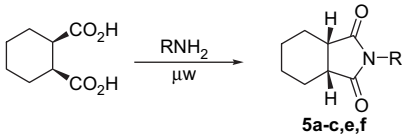
Scheme 3.

Table 1. *meso*-Imide preparation using $ZnCl_2$/HMDS promoted conditions

Entry	Amine	Product	Yield (%)
1	$BnNH_2$	**5a**	55
2	$PhNH_2$	**5b**	81
3	(*p*-OMe)$PhNH_2$	**5c**	88
4	(*p*-NO_2)$PhNH_2$[a]	**5d**	15
5	CH_2=$CHCH_2NH_2$	**5e**	69
6	*t*-$BuNH_2$	**5f**	33

[a] Reflux overnight instead of 2 h.

The second method employed for the synthesis of the *meso*-imides **5** used a microwave promoted condensation between various primary amines and *cis*-cyclohexane-1,2-dicarboxylic acid (Scheme 4).[8] For this a mixture of both the amine and dicarboxylic acid were subjected to microwave radiation in a domestic microwave oven for various periods of time (Table 2).



Scheme 4.

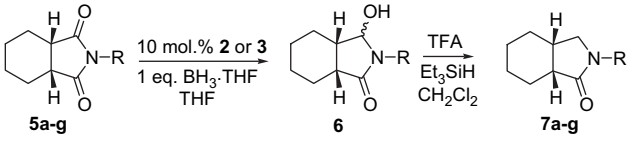
Table 2. *meso*-Imide synthesis via microwave promoted conditions

Entry	Amine	Time (min)	Product	Yield (%)
1	$BnNH_2$	15	**5a**	50
2	$PhNH_2$	25	**5b**	60
3	(*p*-OMe)$PhNH_2$	25	**5c**	33
4	CH_2=$CHCH_2NH_2$	10	**5e**	48
5	*t*-$BuNH_2$	20	**5f**	17

Imide **5d** could not be prepared in this manner, since microwave irradiation caused rapid heating and volatilisation of the aniline, presumably due to the ability of this dipolar molecule to efficiently absorb this radiation. Use of the microwave procedure enabled large amounts of the desired starting materials to be prepared quickly and efficiently in comparison to the $ZnCl_2$/HMDS promoted conditions, which took considerably longer due to prolonged purification procedures to remove impurities. However, the yield of the microwave reactions was considerably reduced, providing a trade-off between yield of product and speed of synthesis.

2.2. Desymmetrisation

Both oxazaborolidine catalysts vary in the method of preparation prior to their use in the reaction. Catalyst **2** is made separately prior to use from trimethylboroxine and *cis*-1-amino-indan-2-ol but is only stable for approximately 48 h under a nitrogen atmosphere. Conversely catalyst **3** can be made in situ from trimethyl borate and *cis*-1-amino-indan-2-ol. Hexahydroisolidinediones **5a–g** were firstly treated with 10 mol % of either catalyst **2** or **3** and 1 equiv of $BH_3\cdot THF$ at 25 °C for 18 h to yield a mixture of the optically active 5-hydroxy-2-pyrrolidinones **6** (Scheme 5). In order to simplify analysis, the crude mixture was immediately treated with TFA and Et_3SiH to give the γ-lactam **7**, which was isolated after silica gel chromatography. The enantiomeric excess was then established via either chiral HPLC or chiral GC.



Scheme 5.

Results indicated that both catalysts were as equally effective in terms of enantioselectivity of the lactam obtained (Table 3), but in all cases there was a marked difference in the yield of the reaction with the *B*-OMe catalyst **3** in comparison to the *B*-Me catalyst **2**. This is probably due to the reduced Lewis acidity of the boron centre by the additional oxygen substituent, therefore, retarding the rate of reduction. As previously observed, no background reaction was observed with $BH_3\cdot THF$, although this was not the case with $BH_3\cdot DMS$.[5]

Several important points were observed in terms of the yield of product. For alkyl substituents **5a**,**e–g** low yields were obtained for both allyl **5e** and *tert*-butyl **5f** groups, probably resulting in competitive hydroboration of the alkene for the former. In the case of the large *tert*-butyl group **5f**, poor

Table 3. Reductions of *meso*-imides **5a–g** using catalysts **2** and **3**

Entry	Imide	Catalyst **2**		Catalyst **3**	
		Yield of **7** (%)[a]	ee	Yield of **7** (%)[a]	ee
1	**5a**	57	84[b]	53	82[b]
2	**5b**	49	99[b]	23	99[b]
3	**5c**	41	99[b]	28	99[b]
4	**5d**	24	99[b]	9	99[b]
5	**5e**	24	33[c]	24	32[c]
6	**5f**	19	0[c]	21	0[c]
7	**5g**	52	75[c]	30	70[c]

[a] Refers to yield after two-step procedure.
[b] ee Determined by HPLC.
[c] ee Determined by GC.

binding to the catalyst due to the steric bulk may be responsible for the low yield, which is also reflected in the poor enantioselectivity observed for this substrate. Both benzyl **5a** and methyl **5g** gave comparable yields, which is not surprising since the benzyl group can adopt a conformation which places the phenyl group away from the catalyst, effectively mimicking a methyl group.

Those substrates with *N*-Ph and *N*-*p*-MeOPh groups gave slightly reduced yields, while *N*-*p*-NO_2Ph was very disappointing. With all of these substrates a significant amount of a doubly reduced product **8** (Fig. 2) was obtained, with more being isolated from the reaction with *N*-*p*-NO_2Ph imide **5d** (Table 4). The lower yield for all of these *N*-aryl substrates is probably a reflection of the ability of the aromatic ring to engage the lone pair of the nitrogen atom, reducing the amide character of the imide, making these more 'ketone-like' and more prone to reduction. In the case of the *p*-NO_2Ph substituent, the additional electron withdrawing group further accentuates this effect. This was confirmed from the ^{1}H NMR spectrum of the crude hydroxylactam **6d**, where approximately 10% of double reduction product was observed, demonstrating the susceptibility of this system to reduction.

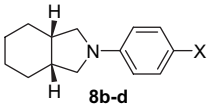


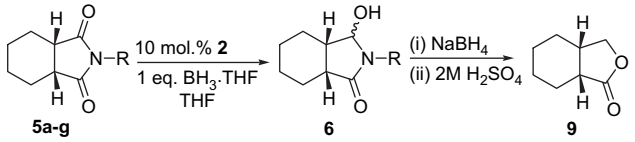
Figure 2.

Table 4. Yield of double reduction product with catalysts **2** and **3**[a]

Entry	Substrate	Product	Catalyst **2**
1	**5b**	**8b**	16
2	**5c**	**8c**	18
3	**5d**	**8d**	52

[a] Refers to yield of **8b–d** after the two-step procedure depicted in Scheme 5.

The identity of the major enantiomer formed in each case was determined by comparison of the specific rotation with those in the literature and by conversion of the intermediate hydroxylactam **6** to the lactone **9** via an established protocol (Scheme 6, Table 5). This additionally allowed the ee of the asymmetric reduction to be confirmed by a second independent method. In all these cases the major enantiomer formed was found to be the (3a*S*,7a*R*).



Scheme 6.

Table 5. Formation of lactone **9** using catalyst **2**

Entry	Imide	Yield of **9** (%)[a]	ee[b]
1	**5a**	62	88
2	**5b**	40	99
3	**5e**	25	31
4	**5f**	23	0
5	**5g**	37	75

[a] Refers to yield after two-step procedure.
[b] ee Determined by GC.

Although the enantioselectivities observed with either catalyst are nearly identical, a significant variation in ee was observed with different nitrogen substituents. In general, little variation of ee was observed with alkyl substituents **5a** and **5e**, since each of these groups appear identical when bound to the catalyst, the selectivity with the benzyl imide **5a** again resulting from this substrate adopting a conformation that locates the aromatic ring away from the catalyst.

The lower ee with the allyl group **5e** probably results from hydroboration of the alkene, which can then act as a competitive reagent and/or hydride source for reduction. Somewhat surprisingly, the more bulky *tert*-butyl group **5f** gave racemic material. As previously noted, the large steric bulk of this substrate probably inhibits tight binding to the catalyst thus resulting in a looser transition state and hence non-selective reduction. More pleasingly though, all of the *N*-phenyl substrates **5b–d** gave a single enantiomer of product irrespective of the electronic nature of the phenyl group.

The selectivities at first appear to support the previously proposed model with the prolinol derived catalyst (Fig. 3).[2] In this model, the fused ring system is considered as the small substituent (R_s) with the nitrogen moiety considered the large group (R_L). The *N*-phenyl substrates have sufficient free rotation to allow them to adopt a conformation orthogonal to the carbonyl groups similar to that proposed by Kang,[3] thus allowing optimum binding to the catalyst. It is important to note that the previously proposed model should not be blindly adopted, since making the nitrogen substituent as big as possible should result in excellent selectivity, while

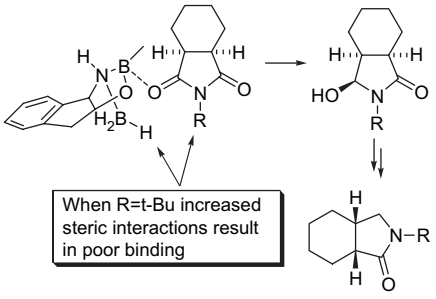


Figure 3. Model for the proposed selectivity.

in reality the *tert*-butyl substrate gives by far the worst selectivity and yield.

3. Conclusion

We have shown oxazaborolidines **2** and **3** to be effective catalysts for the enantioselective reduction of a series of *meso*-imides, with the *B*-methyl catalyst **2** providing better yields of product. More importantly we have also demonstrated that varying the nitrogen substituent on the imide greatly affects the level of enantioselectivity observed with *N*-aryl groups providing single enantiomers of product, the selectivities far exceeding those ever previously obtained with similar catalysts and conditions.

4. Experimental

4.1. General

All solvents were obtained dry from a Grubbs dry solvent system and glassware was flame dried and cooled under vacuum before use. All reactions were carried out under nitrogen. TLC was carried out using Merck aluminium TLC sheets (silica gel 60 F_{254}), visualisation of TLC plates was performed using a UV lamp or by dipping in $KMnO_4$ then exposure to heat. Flash column chromatography was carried out with Silica Gel 40–63u 60A (Fluorochem Ltd.). ^{1}H and ^{13}C NMR spectra were measured using $CDCl_3$ as a solvent unless otherwise stated, on a Bruker AC250 machine with an automated sample changer. Chemical shifts for carbon and hydrogen are given on the δ scale relative to TMS (tetramethylsilane, δ=0 ppm). Coupling constants were measured in hertz. ^{13}C NMR spectra were recorded using the JMOD method. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-Line) and measured at 20 °C unless otherwise stated. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR machine using 0.5 mm NaCl cells and mass spectra were recorded on a Kratos instrument. HPLC was carried out on a Gilson analytical system using a Chiralcel OD (4.8 mm×250 mm) column with 8% IPA in heptane as the solvent (unless otherwise stated). The flow rate was 1.00 cm^3 per minute and the detector was set at 254 nm. GC analysis was carried out using a Perkin–Elmer Autosystem XL gas chromatograph fitted with a Supleco fused silica capillary column (ALPHA DEX™ 120) (30 m×0.25 mm×0.25 μm film thickness) using nitrogen as the carrier gas and detection by standard FID. All chemicals were used as received without further purification except (1*R*,2*S*)-*cis*-1-amino-2-indanol, which was recrystallised from hot toluene prior to use.

4.1.1. *cis*-2-Methyl-hexahydro-isoindole-1,3-dione 5g.[9]

1,3-Butadiene was bubbled through a solution of *N*-methylmaleimide (1.38 g, 12 mmol) in toluene (30 cm^3) and the reaction stirred for 2 h. The solution was then cooled to −5 °C and the resulting white precipitate collected. This was dissolved in ethanol (5 cm^3) and 5% Pd/C was added. The suspension was left to stir for 24 h under a balloon pressure of H_2, the solution filtered through Celite and the solvent removed under vacuum to give a crude oil. Flash column chromatography eluting with 30% EtOAc/petroleum ether (40:60) gave the title compound as colourless crystals (1.2 g, 60% yield); mp 44–46 °C (lit.[9] 47–48 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.32–1.49 (4H, m, CH_2), 1.65–1.83 (4H, m, CH_2), 2.76–2.84 (2H, m, C*H*C=O), 2.91 (3H, s, CH_3); ^{13}C NMR (250 MHz; $CDCl_3$) δ_C 21.9 (*C*H$_2$), 24.0 (CH$_2$), 25.0 (CH$_3$), 40.1 (CHC=O), 180.3 (C=O). NMR data was broadly in accordance with the literature (literature multiplicities appear to have been misinterpreted).

4.2. General procedure A for the preparation of *N*-substituted *cis*-hexahydro-isoindole-1,3-diones 5a–f

A solution of cyclohexane-1,2-carboxylic acid anhydride (25 mmol) in toluene (70 cm^3) was treated with amine (25 mmol) and allowed to stir at room temperature for 1 h. Dry zinc (II) chloride (25 mmol) was added, the reaction warmed to 80 °C and hexamethyldisilazane (37 mmol) was added over a 40 min period. The reaction was heated to reflux for a further 2 h, allowed to cool to room temperature and added to 1 M HCl (30 cm^3). The product was extracted with EtOAc (3×15 cm^3) and the combined organic extracts were washed with saturated $NaHCO_3$ (3×15 cm^3), brine (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed by rotary evaporation under vacuum and the imide recrystallised from EtOAc/petroleum ether (60:80).

4.3. General procedure B for the preparation of *N*-substituted *cis*-hexahydro-isoindole-1,3-diones 5a–c, e and f

A mixture of *cis*-cyclohexane-1,2-dicarboxylic acid (25 mmol) and amine (25 mmol) were heated in a domestic microwave oven (750 W 70% of total power) until no starting materials were observed by TLC. The imide was purified via flash column chromatography eluting with 20% EtOAc/petroleum ether (40:60).

4.3.1. *cis*-2-Benzyl-hexahydro-isoindole-1,3-dione 5a.[2b]

The title compound was obtained as colourless needles either using general procedure A (55%) or B (50%); mp 58–60 °C (lit.[2b] 71–72 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.31–1.51 (4H, m), 1.60–1.91 (4H, m), 2.77–2.89 (2H, m, 2×C*H*C=O), 4.65 (2H, s, NCH_2), 7.26–7.39 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.0 (*C*H$_2$), 24.1 (*C*H$_2$), 40.2 (*C*HC=O), 42.5 (*C*H$_2$Ph), 128.2 (Ar*C*H), 129.0 (Ar*C*H), 136.5 (Ar*C*), 179.8 (*C*=O). All NMR data was in accordance with the literature.

4.3.2. *cis*-2-Phenyl-hexahydro-isoindole-1,3-dione 5b.[2b]

The title compound was obtained as white crystals either using general procedure A (81%) or B (60%); mp 134–135 °C (lit.[2b] 70.5–72.5 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.48–1.56 (4H, m), 1.82–2.02 (4H, m), 2.98–3.11 (2H, m, 2×C*H*C=O), 7.25–7.51 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.3 (*C*H$_2$), 24.4 (*C*H$_2$), 40.5 (*C*HC=O), 126.7 (Ar*C*H), 128.7 (ArC*H*), 129.5 (ArC*H*), 132.5 (Ar*C*), 179.0 (*C*=O). All NMR data was in accordance with the literature.

4.3.3. *cis*-2-(*p*-Methoxyphenyl)-hexahydro-isoindole-1,3-dione 5c.[10]

The title compound was obtained as white crystals either using general procedure A (88%) or B (33%);

mp 154–157 °C (lit.[10] 161.5–162.5 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.46–1.55 (4H, m), 1.79–2.00 (4H, m), 2.97–3.07 (2H, m, 2×C*H*C=O), 3.81 (3H, s, OCH_3), 6.96 (2H, AA′BB′, ArC*H*), 7.19 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.9 (*C*H_2), 24.0 (*C*H_2), 40.1 (*C*HC=O), 55.5 (*C*H_3), 114.6 (Ar*C*H), 124.7 (Ar*C*), 127.5 (Ar*C*H), 159.3 (Ar*C*), 178.9 (*C*=O). ^{1}H NMR data reported previously was recorded in DMSO-d_6.

4.3.4. *cis*-2-(*p*-Nitrophenyl)-hexahydro-isoindole-1,3-dione 5d. The title compound was obtained as white crystals using only general procedure A (15%); mp 186–189 °C (EtOH); (Found: C, 61.46; H, 5.05; N, 9.85. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.14; N, 10.21%); ν_{max} (KBr disc)/cm^{-1} 1781, 1610, 1494; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.51–1.54 (4H, m), 1.83–2.03 (4H, m), 3.05–3.13 (2H, m, 2×C*H*C=O), 7.61 (2H, AA′BB′, ArC*H*), 8.34 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.3 (*C*H_2), 24.4 (*C*H_2), 40.6 (*C*HC=O), 124.7 (Ar*C*H), 126.9 (Ar*C*H), 138.1 (Ar*C*), 147.1 (Ar*C*), 178.1 (*C*=O); *m*/*z* (EI) 274.0948 (100% M$^+$ $C_{14}H_{14}N_2O_4$ requires 274.0954), 109 (6, $C_7H_9O^+$), 82 (37), 67 (35), 54 (18).

4.3.5. *cis*-2-Allyl-hexahydro-isoindole-1,3-dione 5e.[11] The title compound was obtained a colourless oil either using general procedure A (69%) or B (48%); ν_{max} (film)/cm^{-1} 1785, 1703; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.33–1.51 (4H, m), 1.65–1.93 (4H, m), 2.79–2.89 (2H, m, 2×C*H*C=O), 4.05 (2H, dt, *J* 5.9, 1.4, NCH_2), 5.07–5.16 (2H, m, CH=CH_2), 5.64 (1H, ddt, *J* 17.3, 9.8 and 5.9, C*H*=CH$_2$); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.6 (*C*H_2), 23.7 (*C*H_2), 39.7 (*C*HC=O), 40.4 (N*C*H$_2$), 118.0 (CH=*C*H$_2$), 130.9 (*C*H=CH$_2$), 179.2 (*C*=O); *m*/*z* (EI) 193 (100% M$^+$), 82 (46), 67 (55), 54 (30). No NMR data were reported in the literature.

4.3.6. *cis*-2-*tert*-Butyl-hexahydro-isoindole-1,3-dione 5f.[12] The title compound was obtained as a white powder either using general procedure A (33%) or B (17%); mp 58–61 °C (lit.[12] 54–55 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.41–1.86 (4H, m), 1.55 (9H, s, 3×CH_3), 1.62–1.83 (4H, m), 2.65 (2H, m, 2×C*H*C=O); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.9 (CH_2), 24.0 (CH_2), 27.4 (CH_3), 40.2 (C*H*C=O), 58.2 [N*C*(CH$_3$)$_3$], 180.7 (*C*=O). All NMR data were in accordance with the literature.

4.4. General procedure C for the reduction of imides using catalyst 3

(1*R*,2*S*)-*cis*-1-Aminoindan-2-ol (0.25 mmol) was suspended in dry toluene (2 cm^3 mmol^{-1}) and treated with trimethylboroxine (0.08 mmol). After stirring at room temperature for 30 min, toluene (5 cm^3) was added and the resulting solution was concentrated to approximately 2 cm^3 by distillation. This process was repeated twice after which the toluene was removed under reduced pressure to give the catalyst as a white solid. THF (5 cm^3) was added and the active catalyst **2** was used immediately. Thus no analytical data was obtained for this species. BH_3·THF (1 M, 2.5 mmol) was added and the solution allowed to stir at rt for 30 min. A solution of *meso*-imide **5a**–**g** (2.5 mmol) in THF (5 cm^3) was added and the solution was allowed to stir at rt for 18 h. The crude reaction mixture was extracted with CH_2Cl_2 (3×15 cm^3), the combined organic extracts were washed with 1 M HCl (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude hydroxylactam that was immediately redissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This was allowed to stir at rt for 1 h and the solution was added to an ice–water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3×15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum and purified via flash column chromatography eluting with 20% EtOAc/petroleum ether (40:60).

4.5. General procedure D for the reduction of imides using catalyst 3

A solution of (1*R*,2*S*)-*cis*-1-aminoindan-2-ol (0.25 mmol) in dry THF (20 cm^3) was treated with trimethyl borate (0.25 mmol) and the resulting solution allowed to stir at room temperature for 30 min. BH_3·THF (1 M, 2.5 mmol) was added, followed by a solution of *meso*-imides **5a**–**g** (2.5 mmol) in THF (5 cm^3) and the solution was allowed to stir at rt for 18 h. The crude reaction mixture was extracted with CH_2Cl_2 (3×15 cm^3), the combined organic extracts were washed with 1 M HCl (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude hydroxylactam that was immediately redissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This was allowed to stir at rt for 1 h and the solution was added to an ice–water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3×15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum and purified via flash column chromatography eluting with 20% EtOAc/petroleum ether (40:60).

4.5.1. (3a*S*,7a*R*)-2-Benzyl-octahydro-isoindol-1-one 7a.[5] The title compound was obtained as a colourless oil with imide **5a** either using general procedure C (57%, ee 84%) or D (53%, ee 82%); $[\alpha]_D$ +15.0 (*c* 1, $CHCl_3$; ee 84%), lit.[5] +19.6 (*c* 0.5, $CHCl_3$; ee 91%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 0.97–1.26 (3H, m), 1.32–1.62 (4H, m), 1.92–2.05 (1H, m), 2.15–2.27 (1H, m), 2.37–2.46 (1H, m, C*H*C=O), 2.66 (1H, dd, *J* 9.5, 2.5, 1×CH_2N), 3.16 (1H, dd, *J* 9.5, 6.0, 1×CH_2N), 4.29 (1H, d, *J* 14.5, 1×CH_2Ph), 4.45 (1H, d, *J* 14.5, 1×CH_2Ph), 7.12–7.27 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.0 (*C*H_2), 23.5 (2×*C*H_2), 27.9 (*C*H_2), 32.3 (CH), 41.9 (*C*HC=O), 46.8 (N*C*H$_2$), 50.7 (N*C*H$_2$Ph), 127.1 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 136.8 (Ar*C*), 175.9 (*C*=O); Chiral HPLC: CHIRALCEL OD, 10% *i*-PrOH in hexane, t_R 8.06 min and 10.09 min. All NMR data were in accordance with the literature.

4.5.2. (3a*S*,7a*R*)-2-Phenyl-octahydro-isoindol-1-one 7b.[10] The title compound was obtained as a white powder with imide **5b** either using general procedure C (49%, ee 99%) or D (23%, ee 99%); mp 88–90 °C (lit.[10] 87.5–89 °C); $[\alpha]_D$ +4.0 (*c* 0.5, $CHCl_3$; ee 99%), lit.[10] −4.8 (*c* 0.5, $CHCl_3$; (3a*R*,7a*S*) ee 93%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.17–1.34 (3H, m), 1.51–1.63 (3H, m), 1.69–1.77 (1H, m), 2.07–2.25 (1H, m), 2.37–2.45 (1H, m), 2.59–2.65 (1H,

m, C*H*C=O), 3.29 (1H, dd, *J* 9.4, 2.2, 1×CH_2N), 3.52 (1H, dd, *J* 9.4, 5.8, 1×CH_2N), 7.23–7.54 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.1 (*C*H_2), 23.9 (*C*H_2), 24.1 (*C*H_2), 28.4 (*C*H_2), 32.3 (*C*H), 43.8 (*C*HC=O), 53.0 (*C*H_2N), 119.9 (Ar*C*H), 124.5 (Ar*C*H), 129.5 (Ar*C*H), 129.2 (Ar*C*H), 140.5 (Ar*C*), 175.5 (*C*=O); Chiral HPLC: CHIRALCEL OD, 8% *i*-PrOH in hexane, t_R 10.94 min and 12.22 min. ^{1}H NMR data were in accordance with the literature (no ^{13}C NMR data were reported).

4.5.3. (3a*S*,7a*R*)-2-(*p*-Methoxyphenyl)-octahydro-isoindol-1-one 7c.[10] The title compound was obtained as a white powder with imide **7c** either using general procedure C (41%, ee 99%) or D (28%, ee 99%); mp 76–77 °C (lit.[10] 77–78 °C); $[\alpha]_D$ +6.6 (*c* 0.6, $CHCl_3$; ee 99%), lit.[10] +4.4 (*c* 0.5, $CHCl_3$; ee 87%); ν_{max} (film)/cm^{-1} 1705, 1509; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.23–1.39 (3H, m), 1.50–1.68 (3H, m), 1.73–1.85 (1H, m), 2.09–2.23 (1H, m), 2.39–2.51 (1H, m), 2.64–2.75 (1H, m, C*H*C=O), 3.36 (1H, dd, *J* 9.4, 2.2, 1×CH_2N), 3.80–3.84 (4H, m, CH_3 and 1×CH_2N), 6.93 (2H, d, *J* 6.9, ArC*H*), 7.56 (2H, d, *J* 6.9, ArC*H*); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 23.1 (*C*H_2), 23.8 (*C*H_2), 23.9 (*C*H_2), 28.2 (*C*H_2), 32.4 (*C*H), 43.4 (*C*HC=O), 53.3 (*C*H_2N), 55.7 (O*C*H_3), 114.2 (Ar*C*H), 121.5 (Ar*C*H), 133.7 (Ar*C*), 156.5 (Ar*C*), 175.0 (*C*=O); Chiral HPLC: CHIRALCEL OD, 8% *i*-PrOH in hexane, t_R 9.81 min and 10.73 min. ^{1}H NMR data were in accordance with the literature (no ^{13}C NMR data were reported).

4.5.4. (3a*S*,7a*R*)-2-(*p*-Nitrophenyl)-octahydro-isoindol-1-one 7d. The title compound was obtained as a yellow powder with imide **7d** either using general procedure C (24%, ee 99%) or D (9%, ee 99%); mp 189–191 °C; $[\alpha]_D$ −15.0 (*c* 0.4, $CHCl_3$; ee 99%), ν_{max} (KBr disc)/cm^{-1} 2935, 1707, 1593, 1500, 1469, 1387, 1291; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.14–1.27 (3H, m), 1.45–1.64 (3H, m), 1.78–1.89 (1H, m), 2.10–2.22 (1H, m), 2.45–2.57 (1H, m), 2.69–2.80 (1H, m, C*H*C=O), 3.39 (1H, dd, *J* 9.4, 2.2, 1×CH_2N), 3.80 (1H, dd, *J* 9.4, 5.8, 1×CH_2N), 7.80 (2H, d, *J* 7.2, ArC*H*), 8.20 (2H, d, *J* 7.2, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.0 (*C*H_2), 23.7 (*C*H_2), 23.9 (*C*H_2), 28.4 (*C*H_2), 32.1 (*C*H), 44.0 (*C*HC=O), 52.9 (*C*H_2N), 118.7 (Ar*C*H), 125.1 (Ar*C*H), 143.5 (Ar*C*), 146.1 (Ar*C*), 176.4 (*C*=O); *m*/*z* (EI) 260.1150 (100%, M$^+$ $C_{14}H_{16}N_2O_3$ requires 260.1161), 217 (6), 206 (6), 151 (28), 135 (8), 120 (10), 105 (9), 95 (14), 67 (22); Chiral HPLC: CHIRALCEL OD, 8% *i*-PrOH in hexane, t_R 9.70 min and 12.40 min.

4.5.5. (3a*S*,7a*R*)-2-Allyl-octahydro-isoindol-1-one 7e. The title compound was obtained as a colourless oil with imide **7e** either using general procedure C (24%, ee 33%) or D (24%, ee 32%); $[\alpha]_D$ −0.14 (*c* 1, $CHCl_3$; ee 32%), ν_{max} (film)/cm^{-1} 2929, 2843, 1640; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.10–1.20 (3H, m), 1.38–1.68 (4H, m), 1.89–1.99 (1H, m), 2.22–2.30 (1H, m), 2.37–2.44 (1H, m, C*H*C=O), 2.81 (1H, dd, *J* 9.5, 2.1, 1×NCH_2), 3.24 (1H, dd, *J* 9.5, 5.8, 1×NCH_2), 3.76 (1H, dd, *J* 15.2, 6.1, 1×CH_2CH=CH_2), 3.88 (1H, ddt, *J* 15.2, 6.1, 1.3, 1×CH_2CH=CH_2), 5.14 (1H, dq, *J* 10.1, 1.3, 1×CH$_2$CH=CH_2), 5.17 (1H, dq, *J* 17.3, 1.3, 1×CH$_2$CH=CH_2), 5.76 (1H, ddt, *J* 17.3, 10.2, 5.8, CH$_2$C*H*=CH$_2$); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.8 (*C*H_2), 23.5 (*C*H_2), 23.6 (*C*H_2), 27.9 (*C*H_2), 32.3 (*C*H), 41.9 (*C*HC=O), 41.9 (NCH_2CH=CH$_2$), 50.8 (NCH_2CH), 117.9 (=*C*H), 132.7 (=*C*H$_2$), 175.7 (*C*=O); *m*/*z* (EI) 179.1309 (100%, M$^+$ $C_{11}H_{17}NO$ requires 179.1310), 164 (30), 152 (15), 136 (18), 124 (22), 95 (24), 70 (38), 67 (30); Chiral GC: β-DEX, 135 °C, t_R 43.52 min and 43.78 min.

4.5.6. *cis-tert*-Butyl-octahydro-isoindol-1-one 7f. The title compound was obtained as a colourless oil with imide **7f** either using general procedure C (19%, ee 0%) or D (17%, ee 0%); ν_{max} (film)/cm^{-1} 2925, 2852, 1638, 1559; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.16–1.22 (4H, m), 1.35 (9H, s, 3×CH_3), 1.48–1.53 (2H, m), 1.59–1.67 (1H, m), 1.91–1.99 (1H, m), 2.14–2.19 (1H, m, C*H*), 2.33–2.39 (1H, m, C*H*C=O), 2.96 (1H, dd, *J* 9.5, 2.1, 1×NCH_2), 3.34 (1H, dd, *J* 9.5, 5.8, 1×NCH_2); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.8 (*C*H_2), 23.3 (*C*H_2), 23.6 (*C*H_2), 27.6 (*C*H_3), 27.7 (*C*H_2), 31.7 (*C*H), 43.2 (*C*HC=O), 49.6 (N*C*H_2), 53.4 [N*C*$(CH_3)_3$], 175.9 (*C*=O); *m*/*z* (EI) 195.1631 (12%, M$^+$ $C_{12}H_{21}NO$ requires 195.1623), 180 (100), 178 (15), 152 (25), 140 (10), 124 (12), 95 (15); Chiral GC: α-DEX, 105 °C, t_R 67.28 min and 68.59 min.

4.5.7. (3a*S*,7a*R*)-2-Methyl-octahydro-isoindol-1-one 7g.[13] The title compound was obtained as a colourless oil with imide **7g** either using general procedure C (52%, ee 75%) or D (30%, ee 70%); $[\alpha]_D$ −17.0 (*c* 1, $CHCl_3$; ee 75%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.05–1.25 (3H, m) 1.31–1.55 (3H, m), 1.59–1.70 (1H, m), 1.86–1.99 (1H, m), 2.16–2.28 (1H, m), 2.32–2.40 (1H, m, C*H*C=O), 2.84 (3H, s, CH_3), 2.74 (1H, dd, *J* 9.4, 2.2, 1×NCH_2), 3.30 (1H, dd, *J* 9.4, 5.8, 1×NCH_2); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.1 (*C*H_2), 23.8 (*C*H_2), 23.9 (*C*H_2), 28.3 (*C*H_2), 30.2 (*C*H), 32.6 (*C*H_3), 41.9 (C*H*C=O), 54.0 (*C*H_2N), 176.2 (C=O); Chiral GC: α-DEX, 100 °C, t_R 58.85 min and 59.60 min. Only racemic material was reported in the literature. ^{1}H NMR data were in accordance with the literature (no ^{13}C NMR data were reported).

4.5.8. *cis*-2-Phenyl-octahydro-isoindole 8b.[14] The title compound was obtained as a by-product using general procedure C (30%) or D (29%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.23–1.66 (8H, m) 2.20–2.31 (2H, m), 3.09 (1H, dd, *J* 8.9, 5.2, 1×CH_2N), 3.21 (1H, dd, *J* 8.9, 6.7, 1×CH_2N), 6.43 (2H, d, *J* 7.5, ArC*H*), 6.55 (1H, t, *J* 7.5, ArC*H*), 7.10–7.18 (2H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.2 (*C*H_2), 26.5 (*C*H_2), 37.4 (*C*H), 51.7 (*C*H_2), 111.1 (Ar*C*H), 114.9 (Ar*C*H), 129.1 (Ar*C*H), 148.2 (Ar*C*). No NMR data were reported in the literature.

4.5.9. *cis*-2-(4-Methoxyphenyl)-octahydro-isoindole 8c. The title compound was obtained as a by-product using general procedure C (33%) or D (33%); ν_{max} (film)/cm^{-1} 2922, 2851, 1599, 1511, 1482; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.34–1.64 (8H, m), 2.18–2.30 (2H, m), 3.06 (1H, dd, *J* 8.9, 5.2, 1×CH_2N), 3.14–3.23 (1H, m, 1×CH_2N), 3.68 (3H, s, OCH_3), 6.38 (2H, br d, *J* 8.8, ArC*H*), 6.74–6.81 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.2 (*C*H_2), 26.5 (*C*H_2), 37.5 (*C*H), 52.2 (*C*H_2), 56.1 (*C*H_3O), 111.6 (Ar*C*H), 115.2 (Ar*C*H), 126.2 (Ar*C*), 143.4 (Ar*C*); *m*/*z* (EI) 231.1625 (100%, M$^+$ $C_{15}H_{21}NO$ requires 231.1623), 216 (50), 149 (10), 134 (12), 121 (21).

4.5.10. *cis*-2-(4-Nitrophenyl)-octahydro-isoindole 8d. The title compound was obtained as a by-product using general procedure C (30%) or D (30%); mp 110–111 °C; ν_{max} (film)/cm^{-1} 2925, 2852, 1603, 1462; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.33–1.68 (8H, m), 2.26–2.39 (2H, m), 3.20 (1H, dd, *J* 10.1, 5.5, 1×C*H*$_2$N), 3.34 (1H, dd, *J* 10.1, 7.0, 1×C*H*$_2$N), 6.37 (2H, AA′BB′, ArC*H*), 8.05 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.8 (*C*H$_2$), 26.0 (*C*H$_2$), 37.1 (*C*H), 52.1 (*C*H$_2$), 110.2 (Ar*C*H), 126.3 (Ar*C*H), 132.2 (Ar*C*), 152.4 (Ar*C*); *m*/*z* (EI) 246.1363 (100%, M$^+$ $C_{14}H_{18}N_2O_2$ requires 246.1368), 164 (27), 151 (5), 136 (30).

4.5.11. (3a*S*,7a*R*)-Hexahydroisobenzofuran-1-one 9.[10] A solution of hydroxylactam (1.25 mmol) in 60% ethanol (10 cm^3) was treated with sodium borohydride (2.5 mmol) and the resulting solution was stirred at 50 °C for 4 h. Once cooled EtOAc (10 cm^3) was added followed by 5% HCl (5 cm^3), upper organic layer was extracted and solvent was removed under vacuum to give crude amide. Crude product was suspended in 2 M H_2SO_4 and heated at 80 °C for 2 h. Product was extracted with CH_2Cl_2 (3×15 cm^3). Combined organic extracts were dried over $MgSO_4$. Solvent was removed under vacuum and purified via flash column chromatography eluting with 30% EtOAc/petroleum ether (40:60). Title compound was obtained as a clear oil (62%); $[\alpha]_D$ −63.0 (*c* 0.4, $CHCl_3$; ee 99%), lit.[10] −43.2 (*c* 1, $CHCl_3$; ee 89%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.09–1.27 (3H, m), 1.41–1.63 (3H, m), 1.71–1.80 (1H, m), 1.98–2.10 (1H, m), 2.33–2.46 (1H, m), 2.50–2.61 (1H, m, C*H*C=O), 3.88 (1H, dd, *J* 8.9, 1.2, 1×C*H*$_2$O), 4.13 (1H, dd, *J* 8.9, 4.9, 1×C*H*$_2$O); Chiral GC: α-DEX, 100 °C, t_R 39.893 min and 40.658 min. ^{1}H NMR data were in accordance with the literature.

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References and notes

1. Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765–1784.
2. (a) Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 1087–1090; (b) Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773–1789.
3. Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett.* **1995**, *36*, 4265–4268.
4. (a) Jones, S.; Atherton, J. C. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4543–4548; (b) Glimore, N. J.; Jones, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2115–2118; (c) Gilmore, N. J.; Jones, S.; Muldowney, M. P. *Org. Lett.* **2004**, *6*, 2805–2808.
5. Jones, S.; Dixon, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1115–1119.
6. (a) Masui, M.; Takayuki, S. *Synlett* **1997**, 273–274; (b) Ponzo, V. L.; Kaufman, T. S. *Molecules* **2000**, *5*, 495–496; (c) Lagasse, F.; Tsukamoto, M.; Welch, C. J.; Kagan, H. B. *J. Am. Chem. Soc.* **2003**, *125*, 7490–7491; (d) Xu, J.; Su, X.; Zhang, Q. *Tetrahedron: Asymmetry* **2003**, *14*, 1781–1786; (e) Duquette, J.; Zhang, M.; Lei, Z.; Reeves, R. S. *Org. Process Res. Dev.* **2003**, *7*, 285–288.
7. Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652–2654.
8. Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M.; Núñez-Corredoira, G. *J. Chem. Res.* **1999**, 420–421.
9. Bailey, B.; Haworth, R. D.; McKenna, J. E. *J. Chem. Soc.* **1954**, 967–976.
10. Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1994**, *42*, 9–18.
11. Newman, S. S.; Magerlein, B. J.; Wheatley, W. B. *J. Am. Chem. Soc.* **1946**, *68*, 2112, 2114–2115.
12. Bilyard, K. G.; Garratt, P. J.; Hunter, R.; Lete, E. *J. Org. Chem.* **1982**, *47*, 4731–4736.
13. Milewska, M. J.; Bytner, T.; Polonski, T. *Synthesis* **1996**, 1485–1488.
14. Khandewal, G. D.; Swan, G. A.; Roy, R. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 891–896.

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Fully symmetrical functionalization of multivalent scaffold molecules on solid support

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Abstract—A new methodology for the functionalization of scaffold molecules on solid support is described, which does not require (partial) protection of the scaffold or a special functional group arrangement on it, while maintaining scaffold symmetry in the final product. As an illustration of the versatility of this approach, three scaffold molecules (1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene, tris(2-aminoethyl)-amine, and triazacyclononane) were functionalized with different functional groups in a moderate to high yield and purity. The developed protocol is a valuable tool for an easy access to multivalent molecules.

1. Introduction

Multivalent molecules, i.e., molecules containing multiple copies of a chemical function, are of increasing interest, because of their ability to efficiently interfere in biological processes.[1–4] Most recognition and catalytic processes in nature are governed by cooperative interactions between chemical functions present on the surface or in the active site of proteins. Approaches toward analogous artificial structures very frequently involve a scaffold molecule containing multiple sites for the introduction of functionalities.[5] In this way numerous artificial receptors,[6–10] catalysts,[11–13] and other biomimetic structures[14,15] have been prepared. Importantly, the activity of this kind of biomimetic structure depends critically on the scaffold, as it controls the spatial orientation of the functional groups.[16,17] Remarkably however, in virtually all reported studies the scaffold molecule is never taken as a variable; structural variations normally occur in the attached functionalities.[18] To our opinion, this limitation arises from the absence of a synthetic methodology that permits an easy variation of the scaffold molecule. Currently, scaffold functionalization occurs both in solution and, more frequently, on solid support. Intrinsically, solution-based strategies are less amendable to combinatorial chemistry, and, specifically for these kinds of structures, are often hampered by a difficult purification. The synthesis on solid phase relies on the use of AB_3-type scaffolds, in which functionality A is used for attachment to the resin and functionalities B for chemical diversification.[19–24] Although this permits the combinatorial synthesis of large libraries of biomimetic structures, the low commercial and synthetic accessibility of scaffold molecules with the required AB_3 functionalization pattern is a general limitation. Furthermore, the presence of chemical functionality A generally disrupts the symmetry of the scaffold, with the consequence that the functionalities B are not totally identical. Here, we describe a new synthetic protocol for the solid-phase functionalization of A_3-type scaffold molecules, maintaining C_3-symmetry in the final products. This approach is a valuable tool for an easy synthetic access to multivalent molecules.

2. Results and discussion

The synthetic scheme relies on conventional Fmoc-based peptide chemistry and uses, as starting material, Fmoc-Asp(OH)-OAll connected to Wang resin via the aspartic acid side chain, either commercially available or easily synthesizable following conditions reported in the literature.[25] The crucial steps are outlined in Scheme 1. Initially, the Fmoc-protecting group is replaced by Mmt (4-methoxytrityl), because of its higher stability against the nucleophilic/basic properties of the amino groups present in scaffold **1** added in the next steps. Subsequently, the allyl-group is removed under reported reductive conditions[26] and the resulting free acid activated with PyBOP (step i, Scheme 1). At this point, addition of a scaffold molecule **1** with three amino groups results in the linkage of the scaffold to the resin via 1, 2 or 3 amino groups.[27] For example, addition of 1,3,5-tris-(aminomethyl)-2,4,6-triethylbenzene **1a**, a frequently used scaffold molecule,[28] results in the formation of three products

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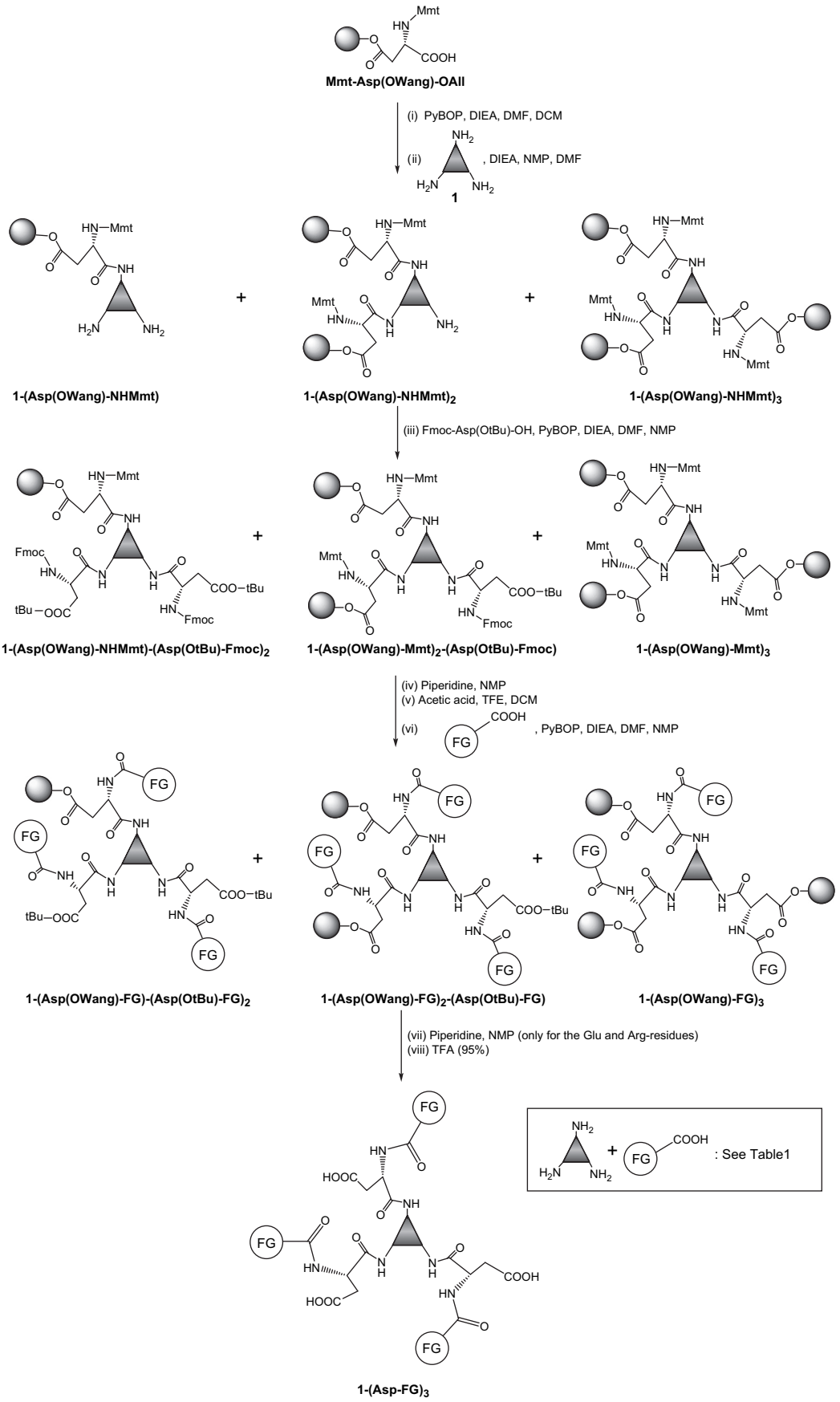


Scheme 1. Synthetic procedure for the synthesis of C_3-symmetrically functionalized scaffold molecules on solid support.

(step ii, Scheme 1, **1a**-(Asp(OWang)-NHMmt), **1a**-(Asp(OWang)-NHMmt)$_2$, and **1a**-(Asp(OWang)-NHMmt)$_3$). This is evidenced by the presence of three peaks in the HPLC spectrum after cleavage (Fig. 1a) corresponding to compounds **1a**-(Asp-NH$_2$), **1a**-(Asp-NH$_2$)$_2$, and **1a**-(Asp-NH$_2$)$_3$, as confirmed by ESI-MS. The mono-, di-, and tri-adducts are formed in a ratio of 48:35:17 based on integration of the HPLC signals. In the next step, *pseudo*-C_3-symmetry is restored by the addition of an excess of Fmoc-Asp(OtBu)-OH (activated with PyBOP) to the resin, which reacts with the remaining free amino groups of **1a** (step iii, Scheme 1). At this point, all three amino groups of **1a** are substituted with an Asp-residue, with an Mmt- or Fmoc-protected terminal amino group and with the side chains either connected to the Wang resin or protected as a *tert*-butyl ester. Next, removal of both the Mmt- and Fmoc-protecting groups renders scaffold molecule, **1a**-(Asp-NH$_2$)$_3$, accessible for further functionalization (steps iv and v, Scheme 1) with any carboxylic acid-containing moiety (FG). As an example, Fmoc-Glu(O*t*-Bu)-OH was added as the next residue, giving compound **1a**-(Asp-Glu-NH$_2$)$_3$ with a very high purity (>95%) after cleavage from the resin (Fig. 1b and step vi, Scheme 1). Upon cleavage from the resin (95% TFA) C_3-symmetry is completely restored since the Asp-side chains are obtained as the free carboxylic acid, regardless whether they were connected to the resin or protected as a *tert*-butyl ester. The product was fully characterized by ^{1}H NMR, HR ESI-MS, and HPLC. In a similar way, other functionalities, i.e., a basic amino acid residue (arginine) and an azacrown derivative for metal-binding ((1,4,7-triazacyclonon-1-yl)-acetic acid, AA$_{TACN}$), were connected to the scaffold molecule giving compounds **1a**-(Asp-Arg-NH$_2$)$_3$ and **1a**-(Asp-AA$_{TACN}$)$_3$ with purities of 88 and 83%, respectively (Table 1).

From the synthetic scheme just described it is evident that this approach is not restricted to the use of AB$_3$-type scaffold molecules, neither does it require the (partial) protection of the scaffold molecule. To illustrate its versatility, the synthetic procedure was repeated using two other scaffold molecules, **1b** and **1c** that are very frequently used in the literature, and which, in addition, have different characteristics with respect to scaffold **1a**. Tris(2-aminoethyl)amine (**1b**, Tren) has a much higher conformational freedom compared to **1a**, whereas the macrocycle triazacyclononane (**1c**, Tacn) has secondary amines as attachment points. Both scaffolds **1b** and **1c** were used in the same manner as discussed for **1a** and functionalized with the same functional groups

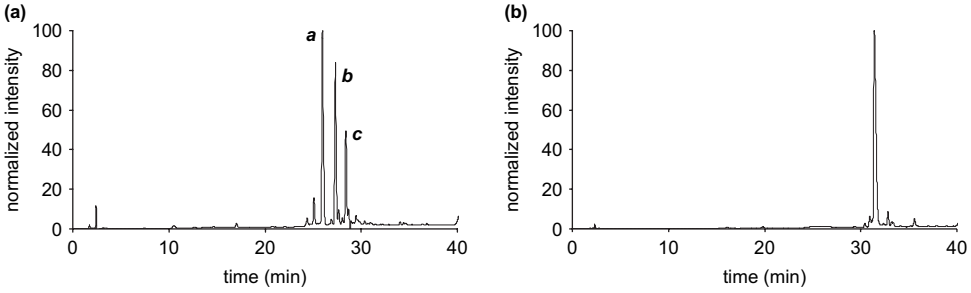
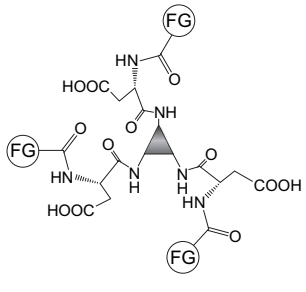


Figure 1. HPLC chromatograms of (a) the products: compounds **1a**-(Asp-NH$_2$) (peak a, 48%), **1a**-(Asp-NH$_2$)$_2$ (peak b, 35%), and **1a**-(Asp-NH$_2$)$_3$ (peak c, 17%) obtained after cleavage from resin after the addition of scaffold **1a** to the resin (step ii, Scheme 1) and (b) the final product **1a**-(Asp-Glu-NH$_2$)$_3$ after cleavage from resin (step viii, Scheme 1).

Table 1. Summary of the nine compounds synthesized using the described synthetic protocol with purities[a] and yields[b]



1-(Asp-FG)$_3$

scaffold / FG	**1a**	**1b**	**1c**
H$_2$N-Glu-OH	**1a-(Asp-Glu)$_3$** *Purity:>95%* *Yield: 91%*	**1b-(Asp-Glu)$_3$** *Purity:61%* *Yield: 57%*	**1c-(Asp-Glu)$_3$** *Purity:73%* *Yield: 66%*
H$_2$N-Arg-OH	**1a-(Asp-Arg)$_3$** *Purity: 88%* *Yield: 80%*	**1b-(Asp-Arg)$_3$** *Purity:48%* *Yield: 45%*	**1c-(Asp-Arg)$_3$** *Purity:78%* *Yield: 70%*
AA$_{TACN}$	**1a-(Asp-AA$_{TACN}$)$_3$** *Purity:83%* *Yield: 75%*	**1b-(Asp-AA$_{TACN}$)$_3$** *Purity:50%* *Yield: 45%*	**1c-(Asp-AA$_{TACN}$)$_3$** *Purity:80%* *Yield: 72%*

[a] Purities based on the ratio between peaks present in the HPLC spectra after cleavage from resin.
[b] Yields based on the initial loading of Fmoc-Asp(OH)-OAll to the resin (for **1a** compounds after precipitation from diethyl ether and for **1b/1c** compounds after purification with RP-HPLC).

i.e., Glu, Arg, and AA_{TACN}, obtaining a total of six additional products (Table 1). Purities of the crude mixtures were typically in the order of 50–80%, somewhat lower when compared to the analogous compounds based on scaffold **1a** but still very satisfactory. Especially the use of Tren as a scaffold causes the formation of one major side-product (30–40%) with a mass difference of −18 amu with respect to the desired product. We hypothesize that this side-product forms via an intramolecular cyclization between a terminal amine and one of the ester linkages between the scaffold and the resin. The occurrence of this reaction seems to be related to the conformational flexibility of the scaffold, because the formation of this side-product for the more rigid scaffolds **1a** and **1c** typically does not exceed 5%. However, even in cases where this side-product is present, all compounds could be easily purified using preparative RP-HPLC.

3. Conclusion

In conclusion, we have described a new methodology that permits an easy functionalization of scaffold molecules on solid support. No special requirements in terms of (partial) protecting groups on the scaffold molecule or functional group arrangements (for instance AB_3-type) are necessary, while the symmetry of the scaffold is maintained in the final products. The versatility of this approach was illustrated by the functionalization of three diverse scaffolds with a variety of functions. This methodology offers a valuable tool for an easy synthetic access to multivalent molecules.

4. Experimental

4.1. General

All starting materials, solvents, and resins were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Bruker AC-300 (300, 13 MHz) spectrometer at 301 K. HPLC spectra were measured using a Shimadzu LC-10AT dual pump system and a Shimadzu SPD-10A UV–vis detector. HR ESI-mass spectra were obtained using a Perspective Biosystem Mariner spectrometer, equipped with a TOF-analyzer.

4.2. General procedure for the synthesis of compounds 1-(Asp-AA-NH_2)$_3$

Following a literature procedure,[25] Fmoc-Asp(OH)-OAll (6 equiv) was attached to Wang resin (100 mg, 0.093 mmol endgroups) using DIC (*N*,*N*-diisopropylcarbodiimide, 6 equiv) and DMAP (*N*,*N*-dimethylaminopyridine, 0.2 equiv) activation in DMF with subsequent acetylation of the non-reacted hydroxyl-moieties. The Fmoc-group was replaced by Mmt using 20% piperidine in NMP and subsequent capping with Mmt-Cl (4-methoxytriphenylchloromethane, 6 equiv) in the presence of DIEA (*N*,*N*-diisopropylethylamine, 15 equiv) in dichloromethane. Next, the allyl-group was removed under reported reductive conditions[26] (0.2 equiv tetrakis(triphenylphosphine)palladium(0) and 10 equiv phenylsilane in DCM, 1.5 h at rt under an inert N_2 atmosphere) and the resulting free acid activated with PyBOP (6 equiv) in NMP/DCM in the presence of DIEA (15 equiv). At this point, the scaffold molecule (3 equiv) was added to NMP/DMF containing DIEA (15 equiv), after which the resin was treated with Fmoc-Asp(O*t*-Bu)-OH activated prior with PyBOP under basic conditions. Finally, the Fmoc and Mmt functional groups were removed in two subsequent deprotection steps (first, 20% piperidine in NMP, and second, a mixture of acetic acid/TFE/DCM (1:2:6)). At this point, conventional peptide chemistry (PyBOP activation in the presence of DIPEA) was used to further functionalize the scaffold molecules. After the syntheses, the final compounds were cleaved from the resin with simultaneous side-chain deprotection using 95% TFA in DCM. After evaporation of volatiles, the crude products were precipitated from cold ether and purified by RP-HPLC when necessary. All compounds were characterized by RP-HPLC, high resolution ESI-MS, and ^{1}H NMR spectroscopy.

4.2.1. 1a-(Asp-Glu-NH_2)$_3$. Isolated yield: 20 mg, 91% after precipitation with diethyl ether, colorless solid. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 3 to 30% in 30 min, UV-detection 226 nm): 31.4 min (>95%). ^{1}H NMR (CD_3OD, 250 MHz) δ 4.71 (t, J=5.8 Hz, 3H), 4.45 (s, 6H), 3.95 (t, J=6.4 Hz, 3H), 2.75 (q, J=7.3 Hz, 6H,), 2.51 (t, J=8.0 Hz, 6H), 2.2–2.0 (m, 12H), 1.15 (t, J=7.3 Hz, 9H); ESI-MS $[M+H]^+$ requires 982.4291; found 982.4308.

4.2.2. 1a-(Asp-Arg-NH_2)$_3$. Isolated yield: 19 mg, 80% after precipitation with diethyl ether, yellowish solid. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 3 to 30% in 30 min, UV-detection 226 nm): 19.9 min (88%). ^{1}H NMR (CD_3OD, 250 MHz) δ 4.71 (t, J=5.8 Hz, 3H), 4.43 (s, 6H), 4.00 (t, J=6.4 Hz, 3H), 3.25 (t, J=6.4 Hz, 6H), 2.8–2.6 (m, 12H), 2.1–1.9 (m, 6H), 1.8–1.6 (m, 6H), 1.15 (t, J=7.3 Hz, 9H); ESI-MS $[M+H]^+$ requires 1063.6047; found 1063.6095.

4.2.3. 1a-(Asp-AA_{TACN})$_3$. Isolated yield: 18 mg, 75% after precipitation with diethyl ether, pale yellow solid. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 3 to 30% in 30 min, UV-detection 226 nm): 19.8 min (83%). ^{1}H NMR (CD_3OD, 300 MHz) δ 4.74 (t, J=6.0 Hz, 3H), 4.47 (m, 6H), 3.66 (br s, 12H), 3.53 (d, J=3.7 Hz, 6H), 3.34 (br s, 12H), 3.05 (br s, 12H), 2.8–2.6 (m, 12H), 1.14 (t, J=7.3 Hz, 9H); ESI-MS $[M+H]^+$ requires 1102.6659; found 1102.6691.

4.2.4. 1b-(Asp-Glu-NH_2)$_3$. Isolated yield: 12 mg, 57% after purification with RP-HPLC, yellowish thick oil. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 3 to 30% in 30 min, UV-detection 226 nm): 13.8 min (100%). ^{1}H NMR (CD_3OD, 300 MHz) δ 4.72 (t, J=6.0 Hz, 3H), 4.01 (t, J=6.3 Hz, 3H), 3.61 (br s, 6H), 3.46 (br s, 6H), 3.0–2.8 (m, 6H), 2.54 (t, J=6.6 Hz, 6H), 2.2–2.1 (m, 6H); ESI-MS $[M+H]^+$ requires 879.3618; found 879.3598.

4.2.5. 1b-(Asp-Arg-NH_2)$_3$. Isolated yield: 10 mg, 45% after purification with RP-HPLC, colorless thick oil. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 8 to 30% in 25 min, UV-detection 226 nm): 24.2 min (100%). ^{1}H NMR (CD_3OD, 250 MHz) δ 4.78 (t, J=5.8 Hz, 3H), 4.00 (t, J=6.4 Hz, 3H), 3.6–3.4

(m, 12H), 3.25 (t, J=6.4 Hz, 6H), 2.9–2.7 (m, 6H), 2.0–1.9 (m, 6H), 1.8–1.7 (m, 6H); ESI-MS $[M+H]^+$ requires 960.5373; found 960.5401.

4.2.6. 1b-(Asp-AA$_{TACN}$)$_3$. Isolated yield: 10 mg, 45% after purification with RP-HPLC, colorless oil that solidifies on standing. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 8 to 30% in 30 min, UV-detection 226 nm): 21.6 min (100%). ^{1}H NMR (CD_3OD, 250 MHz) δ 4.81 (t, J=5.8 Hz, 3H), 3.67 (br s, 12H), 3.6–3.4 (m, 18H), 3.3 (br s, 12H), 3.1 (br s, 12H), 2.9–2.8 (m, 6H); ESI-MS $[M+H]^+$ requires 999.5985; found 999.6009.

4.2.7. 1c-(Asp-Glu-NH$_2$)$_3$. Isolated yield: 13 mg, 66% after purification with RP-HPLC, colorless solid. HPLC (Agilent Eclipse XDB-C18; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 3 to 30% in 30 min, UV-detection 226 nm): 10.9 min (100%). ^{1}H NMR (CD_3OD, 250 MHz) δ 4.72 (t, J=5.8 Hz, 3H), 4.01 (t, J=6.4 Hz, 3H), 3.8–3.4 (m, 12H), 2.9–2.8 (m, 6H), 2.54 (t, J=7.0 Hz, 6H), 2.2–2.0 (m, 6H); ESI-MS $[M+H]^+$ requires 862.3352; found 862.3398.

4.2.8. 1c-(Asp-Arg-NH$_2$)$_3$. Isolated yield: 18 mg, 70% after purification with RP-HPLC, pale yellow solid. HPLC (Jupiter Proteo 90 Å, 4 μ; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 5 to 25% in 30 min, UV-detection 226 nm): 13.1 min (100%). ^{1}H NMR (CD_3OD, 250 MHz) δ 5.01 (t, J=5.8 Hz, 3H), 3.95 (t, J=6.4 Hz, 3H), 3.8–3.4 (m, 12H), 3.25 (t, J=6.4 Hz, 6H), 3.0–2.8 (m, 6H), 2.1–2.0 (m, 6H), 1.8–1.7 (m, 6H); ESI-MS $[M+H]^+$ requires 942.5108; found 942.5196.

4.2.9. 1c-(Asp-AA$_{TACN}$)$_3$. Isolated yield: 16 mg, 72% after purification with RP-HPLC, colorless solid. HPLC (Jupiter Proteo 90 Å, 4 μ; gradient: H_2O/TFA (0.1%)–CH_3CN/TFA (0.1%) from 10 to 30% in 30 min, UV-detection 226 nm): 9.3 min (100%). ^{1}H NMR (CD_3OD, 250 MHz) δ 5.09 (t, J=5.8 Hz, 3H), 3.8–3.5 (m, 30H), 3.3 (br s, 12H), 3.1 (br s, 12H), 2.7–2.6 (m, 6H); ESI-MS $[M+H]^+$ requires 982.5720, found 982.5801.

Acknowledgements

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References and notes

1. Mammen, M.; Choi, S. K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2755–2794.
2. Sacchettini, J. C.; Baum, L. G.; Brewer, C. F. *Biochemistry* **2001**, *40*, 3009–3015.
3. Handl, H. L.; Vagner, J.; Han, H. Y.; Mash, E.; Hruby, V. J.; Gillies, R. J. *Expert Opin. Ther. Targets* **2004**, *8*, 565–586.
4. Kiessling, L. L.; Gestwicki, J. E.; Strong, L. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2348–2368.
5. Badjic, J. D.; Nelson, A.; Cantrill, S. J.; Turnbull, W. B.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 723–732.
6. Puerta, D. T.; Botta, M.; Jocher, C. J.; Werner, E. J.; Avedano, S.; Raymond, K. N.; Cohen, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 2222–2223.
7. Tajc, S. G.; Miller, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 2532–2533.
8. Tobey, S. L.; Jones, B. D.; Anslyn, E. V. *J. Am. Chem. Soc.* **2003**, *125*, 4026–4027.
9. Yun, S.; Ihm, H.; Kim, H. G.; Lee, C. W.; Indrajit, B.; Oh, K. S.; Gong, Y. J.; Lee, J. W.; Yoon, J.; Lee, H. C.; Kim, K. S. *J. Org. Chem.* **2003**, *68*, 2467–2470.
10. Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem.—Eur. J.* **2005**, *11*, 5648–5660.
11. Molenveld, P.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 3189–3192.
12. Scarso, A.; Scheffer, U.; Gobel, M.; Broxterman, Q. B.; Kaptein, B.; Formaggio, F.; Toniolo, C.; Scrimin, P. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5144–5149.
13. Komiyama, M.; Kina, S.; Matsumura, K.; Sumaoka, J.; Tobey, S.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2002**, *124*, 13731–13736.
14. Cai, W. B.; Kwok, S. W.; Taulane, J. P.; Goodman, M. *J. Am. Chem. Soc.* **2004**, *126*, 15030–15031.
15. Guo, Y. M.; Oike, H.; Aida, T. *J. Am. Chem. Soc.* **2004**, *126*, 716–717.
16. Fan, E. K.; Zhang, Z. S.; Minke, W. E.; Hou, Z.; Verlinde, C.; Hol, W. G. J. *J. Am. Chem. Soc.* **2000**, *122*, 2663–2664.
17. Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 14922–14933.
18. For exceptions: (a) Hay, B. P.; Dixon, D. A.; Vargas, R.; Garza, J.; Raymond, K. N. *Inorg. Chem.* **2001**, *40*, 3922–3935; (b) Mahajan, S. S.; Hou, L.; Doneanu, C.; Paranji, R.; Maeda, D.; Zebala, J.; Atkins, W. M. *J. Am. Chem. Soc.* **2006**, *128*, 8615–8625.
19. (a) Siracusa, L.; Hurley, F. M.; Dresen, S.; Lawless, J. L.; Pérez-Payán, M. N.; Davis, A. P. *Org. Lett.* **2002**, *4*, 4639–4642; (b) Del Amo, V.; Siracusa, L.; Markidis, T.; Baragaña, B.; Bhattarai, K. M.; Galobardes, M.; Naredo, G.; Pérez-Payán, M. N.; Davis, A. P. *Org. Biomol. Chem.* **2004**, *2*, 3320–3328.
20. Li, C. H.; Atiqur, R.; Dalley, N. K.; Savage, P. B. *Tetrahedron Lett.* **1999**, *40*, 1861–1864.
21. Kinberger, G. A.; Cai, W. B.; Goodman, M. *J. Am. Chem. Soc.* **2002**, *124*, 15162–15163.
22. Li, H. G.; Wang, L. X. *Org. Biomol. Chem.* **2003**, *1*, 3507–3513.
23. Lebreton, S.; How, S. E.; Buchholz, M.; Yingyongnarongkul, B. E.; Bradley, M. *Tetrahedron* **2003**, *59*, 3945–3953.
24. Chamorro, C.; Hofman, J. W.; Liskamp, R. M. J. *Tetrahedron* **2004**, *60*, 8691–8697.
25. Alcaro, M. C.; Sabatino, G.; Uziel, J.; Chelli, M.; Ginanneschi, M.; Rovero, P.; Papini, A. M. *J. Pept. Sci.* **2004**, *10*, 218–228.
26. Dessolin, M.; Guillerez, M. G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741–5744.
27. A similar experiment reported by Anslyn and co-workers resulted exclusively in the formation of the mono-adduct. Presumably, the difference is related to the length of the spacer: Schneider, S. E.; O'Neill, S. N.; Anslyn, E. V. *J. Am. Chem. Soc.* **2000**, *122*, 542–543; For a related approach see: Ashraf, M. A.; Notta, J. K.; Snaith, J. S. *Tetrahedron Lett.* **2003**, *44*, 9115–9119.
28. Hennrich, G.; Anslyn, E. V. *Chem.—Eur. J.* **2002**, *8*, 2219–2224.

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Microwave-promoted cross-coupling of acid chlorides with arylboronic acids: a convenient method for preparing aromatic ketones

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Abstract—Simple catalytic systems for cross-coupling reactions of acyl chlorides with arylboronic acids under microwave conditions were tested. Microwave irradiation facilitated the reaction course. Mild reaction conditions afford the symmetrical and unsymmetrical aryl ketones in reasonable to high yields within a short time. A wide range of substrates bearing an electron-donating or an electron-withdrawing substituent on aryl ring of acid chloride as well as on boronic acid were examined and high yields of ketones were produced.

1. Introduction

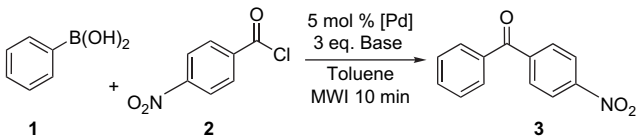
Aromatic ketones are important building blocks for a large number of natural products and are most frequently prepared by a Friedel–Crafts type reaction.[1] Suzuki cross-coupling reaction[2] is a very attractive method for the formation of carbon–carbon single bonds between boronic acids and alkenyl or arylhalides, which is demonstrated in several review articles devoted to this field of chemistry.[3–5] The cross-coupling reaction between arylboronic acids, carbon monoxide (1 atm), and aryl iodides in the presence of palladium catalyst and base also provided biaryl ketones in high yields.[6]

On the other hand in the recent review[7] are just three papers,[8–10] describing Pd-catalyzed reaction of different acyl chlorides with boronic acids. To get good yields of the product it is necessary to heat the reaction mixture for several hours up to 100 °C, or to prolong the reaction time up to several days. This was also the case when aliphatic acid chlorides as well as unsaturated acyl chlorides were used as the substrates.[11,12] Coupling of substituted benzoyl chlorides with phenylboronic acid proceeded at room temperature in a short time in the case when equivalent amount of copper(I) thiophene-2-carboxylate was used as a co-catalyst.[13] Several non-traditional methods have been developed for the Suzuki–Miyaura synthesis of unsymmetrical biaryls such as high intensity ultrasound,[14,15] which accelerates the reactions of aryl iodides and aryl bromides, and especially microwave irradiation,[16–18] which also promotes the reaction of aryl chlorides.

The main goal of our work was to examine if Suzuki–Miyaura coupling of arylboronic acids with acyl chlorides can be promoted by microwave irradiation. The second aim was also to find out if this reaction can be used also for the preparation of unusually substituted aryl ketones.

2. Results and discussion

At the beginning of our work we decided to examine the effect of the catalytic system (Pd source and base) on the course of Suzuki cross-coupling of phenylboronic acid with 4-nitrobenzoyl chloride (Scheme 1, Table 1). While our work was in progress an interesting paper appeared, describing a very rapid reaction of arylboronic acids with different acyl chlorides by grinding reactants with $PdCl_2$ and Na_2CO_3.[19] We decided to test this catalytic system in toluene under MWI too. Catalytic systems $PdCl_2$ and Na_2CO_3 (entry 1) and $Pd(OAc)_2$ and K_2CO_3 (entry 2) was not effective under MWI.



Scheme 1.

Keywords: Palladium; Cross-coupling reaction; Boronic acid; Acyl chlorides; Ketones; Microwave irradiation.
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Table 1. Effect of catalyst systems on the Suzuki–Miyaura coupling of phenylboronic acid with 4-nitrobenzoyl chloride in toluene, under MWI, reaction time 10 min

Entry	[Pd]	Base	Yield **3** (%)
1	$PdCl_2$	Na_2CO_3	n.d.
2	$Pd(OAc)_2$	K_2CO_3	n.d.
3	$Pd[PPh_3]_4$	Cs_2CO_3	93 (13)[a]
4	$PdCl_2(PPh_3)_2$	$K_3PO_4 \cdot 1.5H_2O$	91 (79)[a]
5	$PdCl_2(PPh_3)_2$	$K_3PO_4 \cdot 1H_2O$	35 (25)[a]
6	$PdCl_2(PPh_3)_2$	K_3PO_4	8

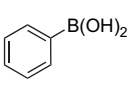
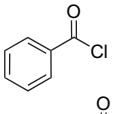
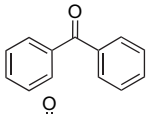
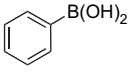
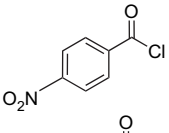
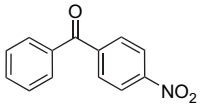
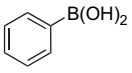
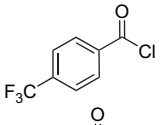
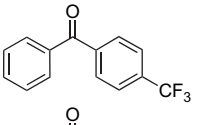
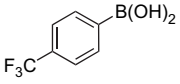
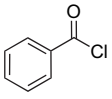
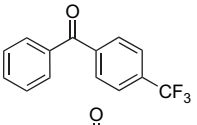
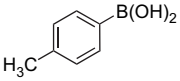
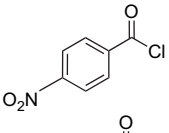
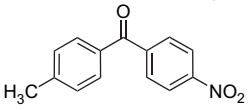
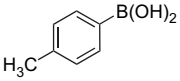
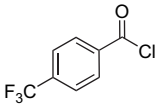
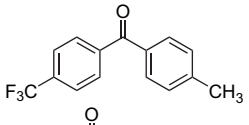
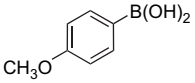
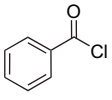
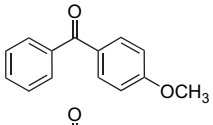
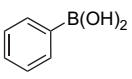
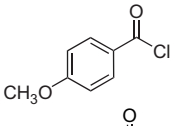
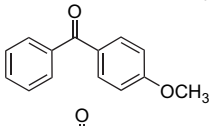
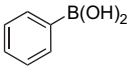
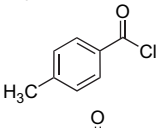
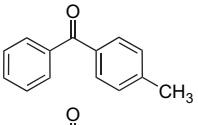
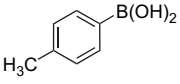
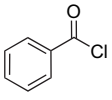
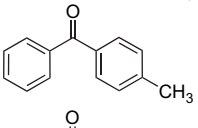
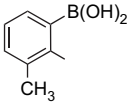
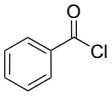
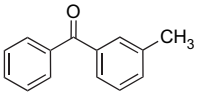
[a] On oil bath for 10 min.

On the other hand $Pd(PPh_3)_4$ and Cs_2CO_3 (entry 3) was found to be the best catalyst system because the cross-coupling product **3** was isolated in 93% yield. Control experiment, without microwave irradiation gave only 13% yield of product **3**. We decided to test also $PdCl_2(PPh_3)_2$ and K_3PO_4 as catalyst system (entries 4–6), and we found that results are very dependent on the quality of potassium phosphate, which is in accord with Ref. 11.

Our next aim was to test the applicability of the catalytic system $Pd(PPh_3)_4$ and Cs_2CO_3 for Suzuki coupling of different arylboronic acids with various acid chlorides. Results are summarized in Table 2.

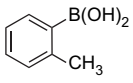
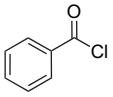
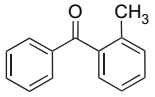
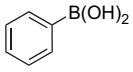
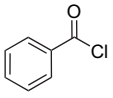
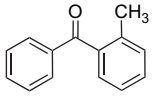
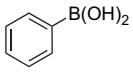
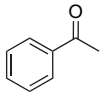
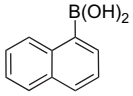
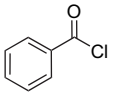
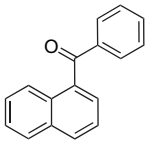
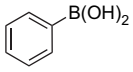
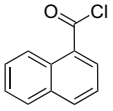
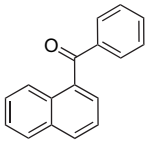
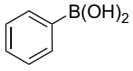
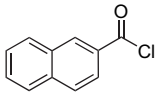
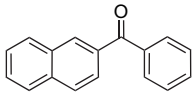
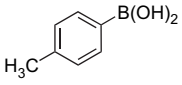
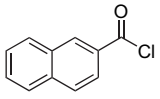
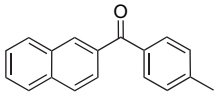
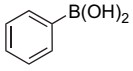
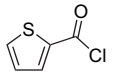
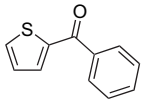
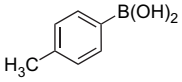
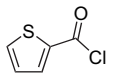
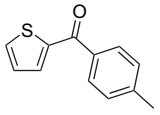
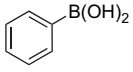
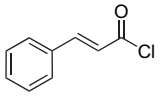
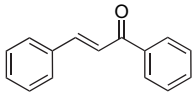
The present methodology is important because it provided the ketones in high yields within a short reaction time (10 min). The reactions of acid chlorides bearing electron-withdrawing (entries 2, 3) and electron-donating (entries 8, 9) groups proceed in good to high yields. Heteroaromatic acid chloride such as 2-furyl (entries 19, 20) afforded the corresponding ketones in 72 and 74% isolated yields. Alkyl- and alkenyl-acid chlorides (entries 14, 21) gave no desired product. The reactions with arylboronic acids bearing electron-donating groups (entries 5–7, 10–12) gave reasonable

Table 2. Effect of the substituent on acid chlorides and of arylboronic acids on the microwave-promoted Suzuki-type coupling catalyzed by $Pd(PPh_3)_4$ in toluene with Cs_2CO_3 as the base, rt, 10 min

Entry	Arylboronic acid	Acid chloride	Ketone	Product	Yield (%)
1				**4**	68[21]
2				**3**	93[20]
3				**5**	90[22]
4				**5**	18[22]
5				**6**	60[23]
6				**7**	57[24]
7				**8**	49[21]
8				**8**	73[21]
9				**9**	60[21]
10				**9**	80[21]
11				**10**	74[22]

(*continued*)

Table 2. (*continued*)

Entry	Arylboronic acid	Acid chloride	Ketone	Product	Yield (%)
12				**11**	61[22]
13				**11**	41[22]
14				**12**	0
15				**13**	77[25]
16				**13**	74[25]
17				**14**	80[22]
18				**15**	50[26]
19				**16**	74[27]
20				**17**	72[28]
21				**18**	0

to high yield of the cross-coupling products. A sterically hindered 2-methylphenylboronic acid (entry 12) gave 61% yield of the product **11**. On the other hand, the reaction of benzoyl chloride with arylboronic acid bearing electron-withdrawing CF_3-group (entry 4) gave only 18% yield of 4-(trifluoromethyl)benzophenone **5**, but this product **5** was obtained in 90% yield when phenylboronic acid with 4-(trifluoromethyl)benzoyl chloride was used (entry 3).

3. Conclusion

In summary we found that microwave irradiation had positive effect on the Suzuki reaction of acid chlorides with arylboronic acids. Catalytic system ($Pd(PPh_3)_4$ and Cs_2CO_3) under microwave irradiation gave ketones in good to high yields in moist toluene (water content in toluene was not controlled). The present methodology is important because it provides a new convenient method for the synthesis of diaryl ketones.

4. Experimental

4.1. General

All microwave experiments were carried out in the Initiator-Biotage reactor (power setting 260 W, 10 min at 98 °C). The reactions were performed in an argon atmosphere. All the products were analyzed by ^{1}H NMR and GC–MS and compared with the authentic samples of the products. The ^{1}H NMR spectra were measured at 300 MHz on a Varian Gemini spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. GC–MS measurements were performed on a gas chromatograph Trace GC 2000 Series Thermoquest CE Instruments with a flame ionization detector and a Voyager GC–MS Thermoquest Finnigan in SCAN-mode. Mass spectral data were obtained by cyclic scanning from 15 to 350 mass units with a cyclic time of 0.2 s. Transfer line temperature was 200 °C. Quadrupole conditions were as follows: electron energy 70 eV, emission current 150 μA, and ion source temperature 150 °C. Each GC

peak was inspected for constancy of MS pattern in order to detect possible overlapping compounds and to measure their retention time. Melting points were determined on a Kofler hot stage.

4.2. Reactions under thermal heating

Base Cs_2CO_3 (1.5 mmol, 0.488 g) and $Pd(PPh_3)_4$ (5 mol %, 0.029 g) catalyst were added to the solution of phenylboronic acid (0.5 mmol, 0.061 g) and 4-nitrobenzoyl chloride (1 mmol 0.186 g) in 7 mL solvent of toluene. The reaction mixture was heated on the oil bath at 98 °C for 10 min. The solution was washed with sodium bicarbonate, water, and brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent, product **3** was separated by column chromatography (silica gel, 1:9 ethyl acetate–hexanes) and identified by spectroscopic analyses. Compound **3**: 13%; Mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (2H, t, J=8.0 Hz), 7.64 (1H, d, J=7.6 Hz), 7.81 (2H, d, J=7.9 Hz), 7.94 (2H, d, J=8.4 Hz), 8.35 (2H, d, J=8.4 Hz). ^{1}H NMR spectroscopy and melting point were compared with the authentic samples of the product.[20]

4.3. Reactions under microwave irradiation

Base Cs_2CO_3 (1.5 mmol, 0.488 g) and $Pd(PPh_3)_4$ (5 mol %, 0.029 g) catalyst were added to the solution of phenylboronic acid (0.5 mmol, 0.061 g) and 4-nitrobenzoyl chloride (1 mmol, 0.186 g) in 7 mL solvent of toluene. The reaction mixture was microwave-irradiated for 10 min. The solution was washed with sodium bicarbonate, water, and brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent, product **3** was separated by column chromatography (silica gel, 1:9 ethyl acetate–hexanes) and identified by spectroscopic analyses. Compound **3**: 93%; Mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (2H, t, J=8.0 Hz), 7.64 (1H, d, J=7.6 Hz), 7.81 (2H, d, J=7.9 Hz), 7.94 (2H, d, J=8.4 Hz), 8.35 (2H, d, J=8.4 Hz). ^{1}H NMR spectroscopy and melting point were compared with the authentic samples of the product.[20]

The same procedure was used for preparation of product **4**–**18**. All products were found to be identical (^{1}H NMR data) with the data described in literature.[20–28]

Acknowledgements

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References and notes

1. *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, NY, 1964; Vol. 3.
2. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.
3. Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419–422.
4. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
5. Miyaura, N. *Advances in Metal–organic Chemistry*; Liebeskind, L. S., Ed.; Jai: London, 1999; Vol. 6, pp 187–243.
6. Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595–7598.
7. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
8. Cho, C. S.; Itotani, K.; Uemura, S. *J. Organomet. Chem.* **1993**, *443*, 253–259.
9. Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057–3060.
10. Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109–3112.
11. Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271–273.
12. Urawa, Y.; Nishiura, K.; Souda, S.; Ogura, K. *Synthesis* **2003**, 2882–2885.
13. Nishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K. *Synlett* **2005**, 2309–2312.
14. Poláčková, V.; Huťka, M.; Toma, Š. *Ultrason. Sonochem.* **2005**, *12*, 99–102.
15. Cravotto, G.; Beggiato, M.; Penoni, A.; Palmisano, G.; Tollari, S.; Leveque, J. M.; Bonrath, W. *Tetrahedron Lett.* **2005**, *46*, 2267–2271.
16. Bedford, R. B.; Butts, C. P.; Hurst, T. E.; Lindstrőm, P. *Adv. Synth. Catal.* **2004**, *346*, 1627–1630.
17. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
18. Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892.
19. Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2005**, *46*, 7627–7630.
20. Suzuki, H.; Murashima, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 903–908.
21. Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199–7203.
22. Wang, D.; Zhang, Zh. *Org. Lett.* **2003**, *24*, 4645–4648.
23. Findeis, M. A.; Kaiser, E. T. *J. Org. Chem.* **1989**, *54*, 3478–3482.
24. Leigh, W. J.; Arnold, D. R.; Humphreys, R. W. R.; Wong, Ch. P. *Can. J. Chem.* **1980**, *58*, 2537–2549.
25. Asao, N.; Aikawa, H.; Yamamato, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458–7459.
26. Utley, J. H. P.; Rozenberg, G. G. *Tetrahedron* **2002**, *58*, 5251–5265.
27. Goossen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, *19*, 3254–3267.
28. Jeon, K. O.; Jun, J. H.; Yn, J. S.; Lee, Ch. K. *J. Heterocycl. Chem.* **2003**, *40*, 763–772.

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Regio- and diastereoselective functionalization of (−)-cytisine

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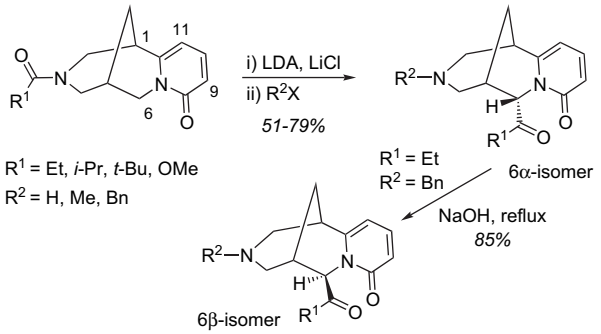
Abstract—(−)-*N*-Benzyl cytisine has been stereoselectively substituted in moderate to high yields on its carbon 6 (Csp^3 α to the pyridone nitrogen). The reaction involved the in situ trapping of the carbanion formed by reaction of lithium diisopropyl amide (LDA) and its reaction with electrophiles (alkyl, allyl, benzyl halides, non-enolizable aldehydes, and Weinreb amide). In the absence of an electrophile or with its addition after the formation of the carbanion, a dimeric structure was isolated (yield: 42%) resulting from the 1,4-addition of the carbanion on the pyridone ring of another cytisine molecule. Deprotection of the benzyl group (Olofson's reagent) allowed the formation of 6-substituted derivatives of the natural product, cytisine, a potent agonist of nicotinic receptors of subtype $\alpha_4\beta_2$.

1. Introduction

Cytisine was recognized as a nicotinic agonist as far back as 1912.[1] With an affinity for neuronal nicotinic acetyl choline receptors (AChRs) greater than that of nicotine,[2] and a high specificity for the $\alpha_4\beta_2$ subtype, it is marketed as Tabex, for use as a smoking cessation aid. Its structure has only been exploited very recently as a template for the synthesis of new compounds with pharmaceutical interest,[3–7] as medical imaging agents[8–10] or as chiral sources for asymmetric synthesis.[11–13]

Analogs have been limited to those easily obtained from the natural material. Substitution of the secondary amine was easily achieved by alkylation or acylation and has led to compounds of various biological activities.[7,14,15] Particularly, *N*-methyl cytisine had reduced potency and affinities for the *n*AChRs[16] and its biodistribution in vivo was not consistent with that expected for $\alpha_4\beta_2$ nicotinic receptors.[8] Introduction of a substituent on the pyridone ring of cytisine usually started with an electrophilic substitution (nitration, halogenation). A mixture of C-9 and C-11 regioisomers was obtained, the affinity toward *n*AChRs of these C-11-substituted derivatives being usually lower than cytisine.[17] Halogen substitution at C-9 and particularly bromo-substitution led to increased affinity and functional potency.[18,19] Cross coupling reactions from these analogs allowed the introduction of alkyl or (hetero)aryl groups.[9,3a] Recently, functionalization of the C-10 position of cytisine substituted was described.[4] It was not achieved directly from cytisine but by using a recently described total synthesis,[20] introducing the substituent early in the synthesis.

A few years ago, we reported a stereoselective functionalization of the C-6 position of cytisine.[21] This was the result of an N→C acyl migration. When *N*-acyl cytisines were treated with LDA in the presence of an excess of LiCl, 6α-acylcytisines were obtained in 51–79% yield. The efficiency of the N–C acyl transfer was shown to be dependent on the nature of the *N*-acyl group. Complete epimerization 6α→6β of the newly created stereocenter was observed under basic conditions (Scheme 1). We report here the direct synthesis of new 6β-substituted cytisines. The strategy is based on the intermolecular reaction of the carbanion formed on the position adjacent to the pyridone ring with different electrophiles.



Scheme 1. Intramolecular functionalization of cytisine via an N→C transfer of an acyl group.

2. Results and discussion

In order to study the alkylation of the 6-position of cytisine while avoiding the N→C transfer observed previously with acyl groups, we protected the secondary amine with a benzyl

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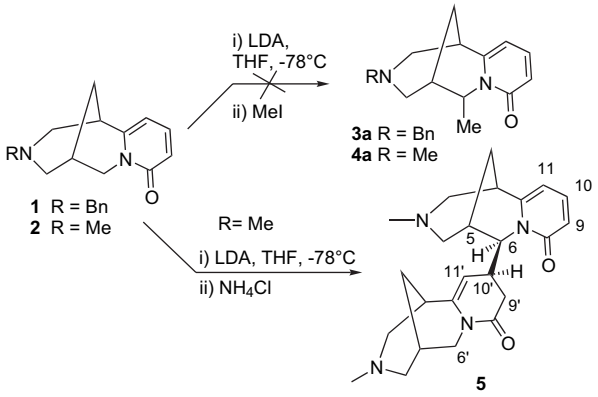
group. In our first attempts, *N*-benzyl cytisine **1** was treated by LDA (5 equiv) in THF at −78 °C. To the mixture was added methyl iodide (2.6 equiv). No expected 6-methyl cytisine **3a** was obtained but a complex mixture was formed from which we could detect, by mass spectrometry, a dimeric product. To simplify NMR spectra of such a compound, *N*-methyl cytisine **2** was submitted to the same reaction conditions but quenched with NH_4Cl to give the adduct **5** (Scheme 2).



Scheme 2. Reaction of LDA with *N*-substituted-cytisines.

Several conditions were tried to optimize the reaction (Table 1). Under the best ones, product **5** was isolated with a 42% yield along with unreacted starting material. Attempts to reduce the temperature (entry 2), to use lithium chelating agent such as TMEDA (entry 3) or to use alkyllithium as bases (entries 4 and 5) did not improve the yield of the reaction.

Such a type of dimerization was previously observed when 1-alkyl-4,6-diphenyl-2-pyridones were treated with LDA.[22] The mechanism postulated was a carbonyl directed lithiation on carbon adjacent to nitrogen (equivalent to C-6 of cytisine) then a Michael addition on a second molecule of alkyl pyridone (addition equivalent to C-10 of cytisine), and finally a migration of the first subunit to the carbon adjacent of the carbonyl of the second pyridone. This should lead, in our case to a connection of the cytisine molecules, C-6 to C-9′. However, we did not observe the subsequent rearrangement described in this paper. Based on this publication and a series of NMR experiments (^1H, ^{13}C, JMOD, COSY, HMQC, and HMBC) the structure of **5**, among the two possible (Fig. 1), was assigned unambiguously.

Table 1. Optimization of the dimerization of **2**[a]

Entry	Base	*T* (°C)	Ratio **2**/**5** (yield, %)[c]
1	LDA	−78	17/83 (42)
2	LDA	−120	23/77
3	LDA	−78[b]	13/87[d]
4	BuLi	−78	40/60
5	MeLi	−78	32/68

[a] Reaction conditions: **2** (1 mmol), base (5 equiv), THF, 4 h at −78 °C then NH_4Cl, −78 °C → room temperature, 3 h.
[b] Addition of TMEDA (5 equiv), quench with MeI.
[c] Ratio of starting material **2**/dimer **5** from ^1H NMR of the crude product. Isolated yield of **5** are in parentheses.
[d] Complex mixture.

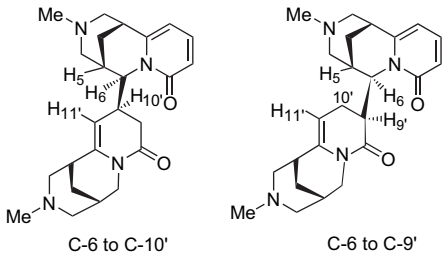
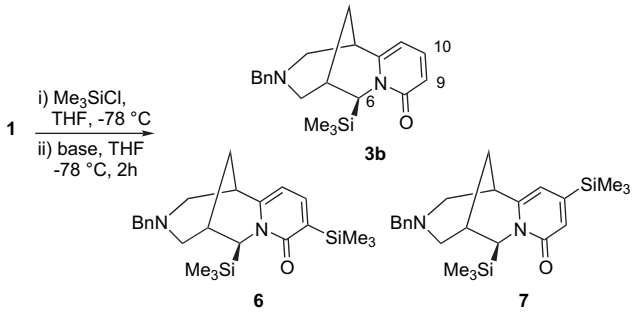


Figure 1. Possible connections for dimer **5**.

On the ^1H NMR spectrum, only one pyridone subunit remained (protons H_9–H_{11} with characteristic chemical shifts at 5.95, 6.40, and 7.23 ppm). On signals in the range 3–5 ppm: first, a doublet at 4.61 ppm ($J_{H6–H10'}$=5.6 Hz) attributed to H_6 (a common chemical shift for this type of proton) connected to sp^3 carbon (HMQC), and a doublet ($J_{H11'–H10'}$=5.1 Hz) at 4.33 ppm attributed to $H_{11'}$ connected to sp^2 carbon (HMQC), both coupling with the same proton, $H_{10'}$, at 3.6–3.7 ppm showing as a multiplet (COSY). Also in the same ^1H NMR range at 3.66 and 3.58 ppm, one might recognize two characteristic signals for the $H_{6'}$ of the second cytisine subunit showing as a doublet (mixed with $H_{10'}$ multiplet) and a doublet of doublet. The absolute configuration of C-6 was clearly assigned based on our previous work.[21] Indeed, the observed coupling constant for H_6 is due to $H_{10'}$ and not H_5. Therefore, since no coupling is occurring between H_6 and H_5, the configuration of C-6 is *S* (H_6 in α position). We were not able to define the absolute configuration of C-10′. However, based on the known stereochemical outcome of the pyridone hydrogenation of cytisine,[11a] we assumed that the addition has occurred on the less hindered *exo* face at the C-10′ position. Next we needed to assert the position of the connection between both cytisine units, i.e., between C-6 and C-10′, mainly because of the rearrangement described in Katritzky's paper.[22] Beside coupling with H_6 and $H_{11'}$, the COSY experiment revealed for $H_{10'}$ two correlations with signals at 2.53 ppm (dd, *J*=7, 16 Hz, 1H) and at 2.66 ppm (part of a multiplet). These two protons were connected to the same carbon (HMQC), which was a CH_2 type of carbon (JMOD). This carbon was therefore assigned to C-9′. All attributions (protons and carbons) were confirmed by an HMBC experiment. In the other hypothesis connecting C-6 with C-9′ (involving a migration following the Michael addition) the coupling patterns would be notably different.

We used *N*-benzyl cytisine **1** for the following part of the study in order to remove easily the nitrogen protecting group. Because of the high reactivity of the carbanion generated at C-6, we attempted to trap it by an electrophile immediately after its formation using the inverse addition procedure.[23] Under these conditions, the treatment of a mixture of **1** and methyl iodide in THF by LDA (2 equiv) afforded 6β-methyl cytisine **3a** in 75% yield (not optimized). A quick search of the most appropriate base to carry out this selective deprotonation using chlorotrimethylsilane as the electrophile was undertaken (Scheme 3). Some relevant results are presented in Table 2. Three bases of increasing pK_a were tested. Lithium hexamethyldisilylamide (LHMDS) gave no reaction, while lithium tetramethylpiperidinamide (LTMP) afforded a mixture of products arising

from mono or disilylation (**3b**, **6**, **7**). LDA appeared as the most selective base as previously shown.[24]



Scheme 3. Selectivity of the deprotonation of *N*-benzyl cytisine **1**.

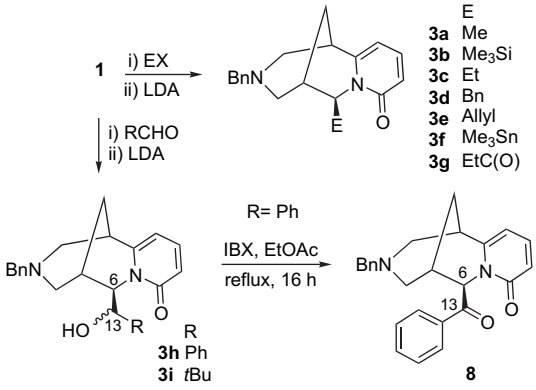
Table 2. Choice of base for the deprotonation of **1**

Entry	Base[a]	pK_a[25]	Yield (%)[b]	Ratio (%)[c]		
				3b	**6**	**7**
1	LHMDS	29.5	[d]	0	0	0
2	LDA	35.7	78	100	0	0
3	LTMP	37.3	56	32	64	4

[a] Reaction conditions: **1** (1 mmol), Me_3SiCl (2.6 equiv), THF, −78 °C then base (2.6 equiv), 2 h, −78 °C.
[b] Isolated yields.
[c] Determined from ^{1}H NMR of the crude product.
[d] Starting material was recovered quantitatively.

The reaction with LDA was regio- and diastereoselective at C-6. Only product **3b** resulting from the silylation of **1** in the position 6β was observed, the absolute configuration of the product being determined by ^{1}H NMR as described in our previous report.[21] Alkyl, allyl, benzyl, and trimethylstannyl halides were successfully used as electrophiles (Table 3, entries 1–6). Weinreb amide[26] and non-enolizable aldehydes can be employed in the inverse addition conditions affording ketone **3g** or alcohols **3h** and **3i**, respectively (entries 7–9).

Alkylation of *N*-benzyl cytisine carbanion with aldehydes generated a second stereogenic center, carbon 13 in **3h** or **3i**. Only two diastereoisomers were produced showing a very high asymmetric induction at one carbon and a poor selectivity for the other (Table 3, entries 8 and 9). The stereochemistry at C-6 of compounds **3h** was deduced from that of the ketone **8** obtained by a mild oxidation of alcohols **3h** using IBX[27] (Scheme 4). Only one ketone **8** was formed and the coupling constant J_{H5-H6}=0 Hz showed unambiguously that H6 proton was in the alpha position. A low asymmetric induction was occurring at C-13 since alcohols **3h** and **3i** were isolated as mixture of diastereoisomers, in 61/39 and 54/46 ratios, respectively. The absolute configuration of C_{13} for each diastereoisomer was assigned by comparing the observed vicinal coupling constants between protons H_6 and H_{13} and those calculated from molecular modeling simulations (AM1, Spartan®). After minimization of the structures of both isomers of **3h**, a dihedral angle of 50° was measured for the (*R*) isomer and 96° for the (*S*) isomer corresponding to coupling constants J_{H6-H13} of 5 Hz and 0 Hz (Fig. 2). In the ^{1}H NMR spectrum of compounds **3h**, we found J_{H6-H13}=7.4 Hz for the major diastereoisomer (61%), therefore assigned as the (*R*)-C_{13} and J_{H6-H13}=2.0 Hz for the (*S*)-C_{13} minor product. The same calculations were carried out with diastereoisomers of **3i**. Dihedral angles of the calculated structures were 40° and 92° for (*R*) and (*S*) diastereoisomers, respectively, corresponding to J_{H6-H13} of 6.9 Hz and 0.0 Hz. The (*R*)-C_{13} major isomer (54%) had a coupling constant J_{H6-H13} of 7.8 Hz and the (*S*) minor isomer of 0 Hz.



Scheme 4. Regio- and diastereoselective alkylation of *N*-Bn-cytisine **1**.

Next, we tried to introduce a second alkyl group on the 6-position of compound **3a**. The reaction was carried out under the same conditions as for the first alkylation. No product **9** was obtained and the starting material was recovered quantitatively. The second deprotonation did not seem to occur (Scheme 5).

Finally, in order to test the new compounds towards *n*AChRs, debenzylation of the tertiary amine was carried out (Scheme 6). Hydrogenolytic removal of *N*-benzyl groups is traditional but is clearly inapplicable to residues such as allyl groups. Therefore we turned our attention towards Olofson's reagent, α-chloroethyl chloroformate (ACE-Cl).[28]

Table 3. Diastereoselective alkylation of *N*-Bn-cytisine **1**[a]

Entry	EX	Product	Yield (%)[b]
1	MeI	**3a**	98
2	Me_3SiCl	**3b**	78
3	EtBr	**3c**	70
4	BnBr	**3d**	62
5	Allyl-Br	**3e**	69
6	Me_3SnCl	**3f**	44
7	EtC(O)N(Me)OMe	**3g**	42
8	PhCHO	**3h**	76[c]
9	*t*-BuCHO	**3i**	78[d]

[a] Reaction conditions: **1** (1 mmol) and electrophile (2.6 equiv), THF, −78 °C then LDA (3 equiv), −78 °C, 2 h then room temperature for 16 h.
[b] Isolated yields.
[c] As a 61/39 ratio of diastereoisomers.
[d] As a 54/46 ratio of diastereoisomers.

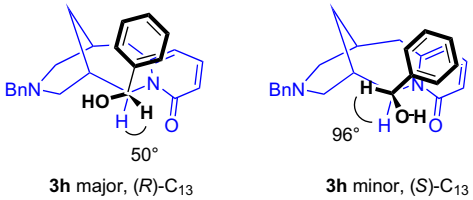
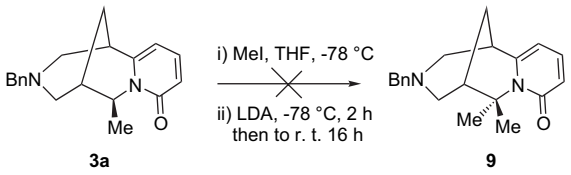
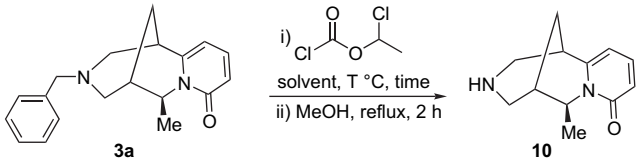


Figure 2. Molecular modeling simulations for C-13 epimer **3h**.



Scheme 5.



Scheme 6. Debenzylation of **3a**.

Debenzylation was tried on *N*-benzyl-6β-methyl-cytisine **3a**. Several attempts were needed to determine the optimal conditions (Table 4). In dichloromethane, reaction was not reproducible and starting material was mainly recovered (entries 1–4). Debenzylation took place in refluxing dichloroethane for 24 h with an excess of ACE-Cl to afford 6β-methyl-cytisine **10** in 72% isolated yield (Table 4, entry 8).

Table 4. Debenzylation of *N*-benzyl-6β-methyl-cytisine **3a**

Entry	ACE-Cl[a] (equiv)	Solvent	Temp	Time (h)	Yield[b] (%)
1	1.3	CH_2Cl_2	rt	1.5	[c]
2	1.5	CH_2Cl_2	rt	0.5	(25)[d]
3	1.5	CH_2Cl_2	rt	16	[c]
4	4	CH_2Cl_2	rt	16	[c]
5	1.5	$ClCH_2CH_2Cl$	Reflux	2	(30)[d]
6	4	$ClCH_2CH_2Cl$	Reflux	6	49
7	4	$ClCH_2CH_2Cl$	Reflux	16	53
8	4	$ClCH_2CH_2Cl$	Reflux	24	72

[a] α-Chloroethyl chloroformate (number of equivalent).
[b] Isolated yields.
[c] Starting material was recovered quantitatively.
[d] Conversion determined by ^{1}H NMR.

3. Conclusion

This work demonstrated the possibility of intermolecular functionalization of cytisine on carbon 6 via an original lithiation reaction. The key step was the regiospecific carbonyl directed deprotonation of cytisine by LDA followed by in situ trapping of the anion by various electrophiles (inverse addition procedure). With alkyl halides the alkylation was totally stereoselective at C-6 (position 6β) and opposite to the acyl migration previously observed (position 6α), but poorly diastereoselective on the second stereogenic center created when using aldehydes. To avoid the described carbonyl migration following the deprotonation when cytisine was *N*-substituted by an acyl residue, a benzyl group was used to protect cytisine, which allowed for its easy and selective removal by α-chloroethyl chloroformate. A dimer of cytisine was isolated while using the normal addition conditions for the deprotonation–alkylation sequence or in the absence of electrophile. Finally, the reaction developed here offers the potential for the synthesis of a wide variety of new ligands for receptors of the central nervous system or of new chiral sources for asymmetric synthesis.

4. Experimental

4.1. General methods and starting materials

The reactions were carried out under nitrogen or argon in flasks dried in an oven at 110 °C. THF and CH_2Cl_2 were dried with a PURESOLV™ apparatus (Innovative Technology Inc.). Diisopropylamine was distilled from calcium hydride. Methyl iodide, ethyl bromide, benzyl bromide, allyl bromide, trimethylsilyl chloride, benzaldehyde, and pivalaldehyde were distilled before use. A commercial solution of trimethyltin chloride (1 M in THF, Aldrich) was used. Thin layer chromatography (TLC) was performed using aluminum sheets precoated with silica gel 60 F_{254} (Merck). Flash chromatography was carried out on silica gel SI 60 (0.040–0.063 mm, Merck). Melting points were obtained using a Köfler bench apparatus (uncorrected). Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Infrared spectra (IR) were recorded with a FT-IR Perkin–Elmer 684 spectrometer. Mass and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. NMR spectra were recorded on a Brucker Avance DPX-250 (^{1}H at 250.1 MHz; ^{13}C at 62.9 MHz; TMS as internal standard). Elementary analyses were performed on a Thermoquest apparatus by the microanalytical service of the Laboratory of Molecular and Thioorganic Chemistry of ENSICaen, Caen. Cytisine [(−)-(1*R*,5*S*)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*]-[1,5]diazocin-8-one] was extracted from commercially available seeds of *Cytisus laburnum anagyroïdes* (Vilmorin Company, France). The procedure was reported in the supporting information (free of charge via the Internet at http://pubs.acs.org) of a previous publication.[9]

4.1.1. Synthesis of (−)-(1*R*,5*S*)-*N*-benzyl cytisine 1.[29,11d] To a solution of cytisine (1.0 g, 5.26 mmol) in 20 mL of CH_2Cl_2 was added Na_2CO_3 (1.1 g, 10.5 mmol, 2 equiv) in 10 mL of H_2O followed by benzyl bromide (6.31 mmol, 1.2 equiv) at room temperature. After stirring 4 h at reflux temperature, the reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. Purification of the crude product by flash chromatography (CH_2Cl_2/MeOH, 95:5) afforded **1** as a white solid (1.13 g, 77%): mp 142–144 °C; $[\alpha]_D^{22}$ −219 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.8–1.9 (m, 2H), 2.3–2.5 (m, 3H), 2.8–3.0 (m, 3H), 3.37 and 3.46 (AB, J_{AB}=13.6 Hz, 2H, CH_2Bn), 3.91 (dd, *J*=15.4, 6.5 Hz, 1H, H-6β), 4.10 (d, *J*=15.4 Hz, 1H, H-6α), 5.90 (dd, *J*=6.9, 1.3 Hz, 1H, H-11), 6.48 (dd, *J*=9.0, 1.3 Hz, 1H, H-9), 6.9–7.0 (m, 2H), 7.1–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 26.3, 28.5, 35.9, 50.3, 60.3, 60.4, 62.3, 105.0, 116.8, 127.2, 128.5, 138.4, 138.9, 151.8, 164.0; IR (NaCl, cm^{-1}) 2926, 2794, 1652, 1546, 1140, 800, 736, 698; HRMS (EI) calcd for $C_{18}H_{20}N_2O_2$ 280.1576, found 280.1578.

4.1.2. Dimerization of *N*-methyl-cytisine 2. To a solution of *N*-methyl-cytisine **2** (250 mg, 1.22 mmol, 1 equiv) in

10 mL of THF was added dropwise an LDA solution [prepared in situ from diisopropylamine (0.52 mL, 3.68 mmol, 3 equiv) and *n*-butyllithium (1.6 M solution in hexanes, 2.30 mL, 3.68 mmol, 3 equiv) in 5 mL of THF at −20 °C] at −78 °C under nitrogen. After stirring 4 h at −78 °C, the reaction was quenched with a saturated aqueous ammonium chloride solution. Ammonia was then added until basic pH. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 92:8) to afford dimer **5** as a yellow oil (0.105 g, 42%); $[\alpha]_D^{22}$ +259 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.41 (d, *J*=11.0 Hz, 1H), 1.47 (d, *J*=13.0 Hz, 1H), 1.65 (d, *J*=13.0 Hz, 1H), 2.02 (s, 3H), 2.0–2.1 (m, 2H), 2.11 (s, 3H), 2.1–2.2 (m, 3H), 2.24 (br s, 1H), 2.3–2.4 (m, 2H), 2.53 (dd, *J*=7.0, 16.0 Hz, 1H, H-9′), 2.59–2.70 (m, 3H), 2.73 (d, *J*=10.0 Hz, 1H), 2.8–2.9 (m, 2H), 3.58 (dd, *J*=7.0, 13.2 Hz, 1H, H-6′β), 3.6–3.7 (m, 2H, H-6′α and H-10′), 4.33 (d, *J*=5.1 Hz, 1H, H-11′), 4.61 (d, *J*=5.6 Hz, 1H, H-6α), 5.95 (dd, *J*=1.4, 6.8 Hz, 1H, H-11), 6.40 (dd, *J*=1.4, 9.0 Hz, 1H, H-9), 7.23 (dd, *J*=6.8, 9.0 Hz, 1H, H-10). ^{13}C NMR ($CDCl_3$) δ 23.8, 26.4, 27.6, 29.5, 31.2, 34.5, 35.4, 36.5, 46.1, 46.5, 47.5, 61.6, 62.1, 63.0, 63.6, 101.5, 104.6, 117.8, 138.6, 142.4, 151.6, 163.4, 169.5; IR (NaCl, cm^{-1}) 3419, 2937, 2780, 1645, 1544, 907, 723; HRMS (ESI) calcd for $C_{24}H_{33}N_4O_2$ 409.2604, found 409.2593.

4.2. General procedure for alkylation at C-6 position

To a solution of *N*-benzyl-cytisine **1** (250 mg, 0.89 mmol, 1 equiv) in 7 mL of THF was added the electrophile (2.32 mmol, 2.6 equiv) at −78 °C under nitrogen. An LDA solution [prepared in situ from diisopropylamine (0.37 mL, 2.67 mmol, 3 equiv) and *n*-butyllithium (1.6 M solution in hexanes, 1.67 mL, 2.67 mmol, 3 equiv) in 5 mL of THF at −20 °C] was then added dropwise. After stirring 2 h at −78 °C, the reaction was stirred overnight at room temperature. The mixture was quenched with a saturated aqueous ammonium chloride solution and then ammonia was added until basic pH. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum.

4.2.1. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-methyl-cytisine 3a. The electrophile added was methyl iodide. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford **3a** as a white solid (0.257 g, 98%): mp 152 °C; $[\alpha]_D^{22}$ −51 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (d, *J*=6.4 Hz, 3H), 1.6–1.8 (m, 2H), 2.02 (s, 1H), 2.22 (d, *J*=1.3 Hz, 1H), 2.26 (d, *J*=1.3 Hz, 1H), 2.43 (dd, *J*=2.5, 11.0 Hz, 1H), 2.67 (dd, *J*=1.6, 10.4 Hz, 1H), 2.91 (br s, 1H), 3.03 (d, *J*=11.0 Hz, 1H), 3.27 and 3.45 (AB, J_{AB}=13.6 Hz, 2H, CH_2Bn), 4.78 (q, *J*=6.4 Hz, 1H, H-6α), 5.86 (dd, *J*=1.2, 6.7 Hz, 1H, H-11), 6.48 (dd, *J*=1.2, 9.0 Hz, 1H, H-9), 6.9–7.1 (m, 5H), 7.2–7.3 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 23.5, 34.9, 36.1, 54.7, 59.9, 60.8, 61.8, 104.8, 117.5, 126.8, 128.1, 138.1, 150.9, 163.2; IR (KBr, cm^{-1}) 3423, 2918, 2809, 1648, 1569, 1542, 801, 735, 698; HRMS (ESI) calcd for $C_{19}H_{23}N_2O$ 295.1810, found 295.1809.

4.2.2. (+)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-trimethylsilyl-cytisine 3b. The electrophile added was chlorotrimethylsilane. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford **3b** as a yellow oil (0.245 g, 78%); $[\alpha]_D^{22}$ +16 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 9H, Si(CH_3)$_3$), 1.7–1.8 (m, 2H), 1.82 (dd, *J*=1.7, 10.5 Hz, 1H), 2.39 (br s, 1H), 2.50 (dd, *J*=2.6, 11.0 Hz, 1H), 2.91 (s, 1H), 2.94 (dt, *J*=1.8, 8.8 Hz, 1H), 2.98 (d, *J*=11.0 Hz, 1H), 3.26 and 3.49 (AB, J_{AB}=13.7 Hz, 2H, CH_2Bn), 4.26 (s, 1H, H-6α), 5.87 (dd, *J*=1.3, 6.9 Hz, 1H, H-11), 6.47 (dd, *J*=1.4, 9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −0.9, 25.8, 30.7, 35.4, 53.2, 60.2, 61.7, 62.4, 104.4, 115.5, 126.6, 126.7, 127.9, 128.0, 137.4, 138.1, 150.9, 163.3; IR (NaCl, cm^{-1}) 3421, 2938, 2793, 1647, 1546, 1247, 840, 732, 698; HRMS (EI) calcd for $C_{21}H_{29}N_2OSi$ 353.2049, found 353.2032.

4.2.3. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-ethyl-cytisine 3c. The electrophile added was ethyl bromide. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford **3c** as a white solid (0.192 g, 70%): mp 161 °C; $[\alpha]_D^{22}$ −13 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J*=7.4 Hz, 3H), 1.3–1.4 (m, 1H), 1.6–1.7 (m, 1H), 1.7–2.0 (m, 1H), 2.1–2.3 (m, 3H), 2.49 (dd, *J*=11.0, 2.6 Hz, 1H), 2.65 (d, *J*=10.4 Hz, 1H), 2.90 (s, 1H), 2.96 (d, *J*=11.0 Hz, 1H), 3.27 and 3.46 (AB, J_{AB}=13.7 Hz, 2H, CH_2Bn), 4.42 (d, *J*=8.3 Hz, 1H, H-6α), 5.82 (d, *J*=6.8 Hz, 1H, H-11), 6.48 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.0, 23.9, 27.5, 30.7, 36.4, 60.6, 61.0, 61.1, 62.2, 104.9, 117.8, 127.1, 128.4, 138.4, 138.6, 151.2, 163.5; IR (KBr, cm^{-1}) 3421, 2935, 2801, 1649, 1569, 1544, 735, 699; HRMS (EI) calcd for $C_{20}H_{24}N_2O$ 309.1967, found 309.1962.

4.2.4. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-benzyl-cytisine 3d. The electrophile added was benzyl bromide. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford **3d** as a yellow oil (0.204 g, 62%); $[\alpha]_D^{22}$ −101 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.6–1.7 (m, 2H), 2.0–2.5 (m, 4H), 2.54 (d, *J*=10.9 Hz, 1H), 2.66 (d, *J*=10.9 Hz, 1H), 2.66 (br s, 1H), 3.22 and 3.42 (AB, J_{AB}=13.7 Hz, 2H, NCH_2Bn), 3.45 (d, *J*=12.9 Hz, 1H), 4.79 (d, *J*=10.3 Hz, 1H, H-6α), 5.89 (d, *J*=6.8 Hz, 1H, H-11), 6.57 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.4 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 23.6, 29.9, 36.4, 39.9, 53.7, 60.5, 60.9, 61.1, 62.1, 105.2, 117.9, 126.8, 127.1, 128.4, 128.4, 128.8, 129.9, 138.5, 138.8, 138.9, 139.4, 151.3, 163.4; IR (NaCl, cm^{-1}) 3416, 2939, 2794, 1648, 1567, 1546, 910, 800, 733, 699; HRMS (ESI) calcd for $C_{25}H_{27}N_2O$ 371.2123, found 371.2105.

4.2.5. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-allyl-cytisine 3e. The electrophile added was allyl bromide. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford **3e** as a yellow oil (0.197 g, 69%); $[\alpha]_D^{22}$ −26 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.1–2.2 (m, 5H), 2.4–2.5 (m, 1H), 2.6–2.7 (m, 1H), 2.7–3.0 (m, 3H), 3.27 and 3.46 (AB, J_{AB}=13.6 Hz, 2H, CH_2Bn), 4.56 (t, *J*=7.7 Hz, 1H, H-6α), 5.0–5.1 (m, 2H), 5.8–5.9 (m, 2H), 6.50 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.6, 30.7, 36.4, 38.7, 53.8, 58.6, 60.4, 61.0, 62.1, 105.1, 117.8, 117.9, 127.1, 128.4,

128.5, 135.9, 138.6, 138.6, 151.2, 163.4; IR (NaCl, cm^{-1}) 3397, 2938, 2794, 1648, 1546, 912, 800, 732, 698; HRMS (EI) calcd for $C_{21}H_{24}N_2O$ 321.1967, found 321.1952.

4.2.6. (+)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-trimethylstannyl-cytisine 3f. The electrophile added was trimethyltin chloride. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford **3f** as a colorless oil (0.174 g, 44%); $[\alpha]_D^{22}$ +114 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.03 (s, J^2_{Sn-H}=51.3 Hz, 9H, $Sn(CH_3)_3$), 1.7–1.8 (m, 2H), 2.26 (dd, *J*=1.7, 10.5 Hz, 1H), 2.4–2.5 (m, 2H), 2.80 (dt, *J*=1.7, 10.5 Hz, 1H), 2.9–3.0 (m, 2H), 3.33 and 3.46 (AB, J_{AB}=13.6 Hz, 2H, CH_2Bn), 4.14 (s, J^2_{Sn-H}= 51.3 Hz, 1H, H-6α), 5.95 (dd, *J*=1.3, 6.9 Hz, 1H, H-11), 6.48 (dd, *J*=1.4, 8.9 Hz, 1H, H-9), 6.9–7.0 (m, 2H), 7.1–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −8.1, 26.3, 32.6, 36.1, 54.0, 56.1, 61.0, 62.5, 63.0, 106.1, 115.3, 127.3, 128.7, 128.7, 137.7, 138.8, 151.1, 162.9; IR (NaCl, cm^{-1}) 2925, 2795, 1638, 1543, 1142, 769, 731, 698; HRMS (EI) calcd for $C_{21}H_{29}N_2OSn$ 445.1302, found 445.1317.

4.2.7. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-propionyl-cytisine 3g.[21] The electrophile added was *N*-methoxy-*N*-methylpropionamide. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to afford **3g** as a viscous colorless oil (0.125 g, 42%).

4.2.8. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-[(hydroxy,phenyl)-methyl]-cytisine 3h. The electrophile added was benzaldehyde. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford **3h** as a 61/39 mixture of diastereoisomers (0.261 g, 76%). Analytical samples of each diastereoisomer were obtained from a second tedious chromatography of the mixture using the same eluting system.

Major diastereoisomer at C-13, (*R*): $[\alpha]_D^{22}$ −99 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (d, *J*=13.1 Hz, 1H), 1.49 (d, *J*=13.1 Hz, 1H), 2.0–2.1 (m, 2H), 2.19 (dd, *J*= 2.5, 11.1 Hz, 1H), 2.4–2.5 (m, 1H), 2.6–2.7 (m, 2H), 3.09 and 3.29 (AB, J_{AB}=13.7 Hz, 2H, CH_2Bn), 4.89 (d, *J*= 7.3 Hz, 1H, H-6α), 5.04 (d, *J*=7.4 Hz, 1H), 5.31 (br s, 1H), 5.86 (d, *J*=6.9 Hz, 1H, H-11), 6.53 (d, *J*=8.9 Hz, 1H, H-9), 6.7–6.8 (m, 2H), 7.0–7.1 (m, 3H), 7.1–7.2 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 23.4, 28.9, 36.1, 60.3, 60.9, 61.6, 63.6, 75.9, 106.6, 117.1, 127.2, 127.8, 128.1, 128.4, 128.5, 138.1, 139.6, 142.4, 151.7, 166.0; IR (NaCl, cm^{-1}) 3279, 2939, 2794, 1642, 1542, 1136, 908, 726, 698; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_2$ 387.2073, found 387.2081.

Minor diastereoisomer at C-13, (*S*): $[\alpha]_D^{22}$ −139 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48 (d, *J*=12.3 Hz, 1H), 2.1–2.2 (m, 3H), 2.5–2.7 (m, 2H), 2.8–2.9 (m, 1H), 2.94 (br s, 1H), 3.20 and 3.40 (AB, J_{AB}=13.7 Hz, 2H, CH_2Bn), 3.6–3.7 (m, 1H), 4.85 (d, *J*=2.0 Hz, 1H, H-6α), 5.74 (br s, 1H), 5.96 (d, *J*=6.9 Hz, 1H, H-11), 6.45 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 3H), 7.2–7.3 (m, 4H), 7.52 (d, *J*=7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.9, 28.1, 36.5, 60.8, 61.5, 63.9, 73.3, 105.5, 117.2, 126.9, 127.0, 127.1, 128.2, 128.3, 128.7, 138.4, 139.0, 142.5, 152.7, 164.1; IR (NaCl, cm^{-1}) 3282, 2931, 2794, 2758, 1643, 1542, 1134, 908, 803, 734, 699; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_2$ 387.2073, found 387.2068.

4.2.9. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-[(hydroxy,*tert*-butyl)-methyl]-cytisine 3i. The electrophile added was pivalaldehyde. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to afford **3i** as a 54/46 mixture of diastereoisomers (0.254 g, 78%). Analytical samples of each diastereoisomer were obtained from a second tedious chromatography of the mixture using the same eluting system.

Major diastereoisomer at C-13, (*R*): $[\alpha]_D^{22}$ −24 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.6–1.7 (m, 2H), 2.1–2.2 (m, 2H), 2.26 (br s, 1H), 2.45 (dd, *J*=2.6, 11.1 Hz, 1H), 2.66 (d, *J*=10.3 Hz, 1H), 2.95 (s, 1H), 3.01 (d, *J*=11.1 Hz, 1H), 3.2–3.3 (m, 2H), 3.25 and 3.52 (AB, J_{AB}=13.7 Hz, 2H, CH_2Bn), 4.76 (d, *J*=7.8 Hz, 1H, H-6α), 5.94 (d, *J*=6.9 Hz, 1H, H-11), 6.51 (d, *J*=8.9 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 3H), 7.2–7.3 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.0, 27.5, 33.2, 35.8, 37.1, 59.2, 60.4, 60.8, 61.8, 81.6, 106.5, 117.0, 126.9, 128.1, 128.2, 138.1, 139.3, 152.0, 166.4; IR (NaCl, cm^{-1}) 2949, 2794, 1644, 1542, 1134, 912, 800, 731, 698; HRMS (ESI) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2368.

Minor diastereoisomer at C-13, (*S*) isolated as an enriched mixture with its epimer. ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.4–1.5 (m, 1H), 2.1–2.2 (m, 1H), 2.2–2.4 (m, 2H), 2.6–2.7 (m, 2H), 2.7–2.8 (m, 1H), 2.8–2.9 (m, 2H), 3.26 and 3.50 (AB, J_{AB}=13.4 Hz, 2H, CH_2Bn), 3.4–3.5 (m, 1H), 4.08 (s, 1H), 4.88 (s, 1H, H-6α), 5.88 (d, *J*=7.5 Hz, 1H, H-11), 6.46 (d, *J*=8.9 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.3, 27.5, 29.5, 36.0, 36.1, 60.2, 60.7, 61.0, 61.8, 78.8, 104.9, 117.1, 126.7, 128.0, 128.1, 138.2, 138.3, 152.9, 163.5; HRMS (ESI) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2400.

4.2.10. (+)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6,9-bistrimethylsilyl-cytisine 6. Same procedure as for compound **3b** with LTMP as base. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to afford **6** as a yellow oil (186 mg, 36%); $[\alpha]_D^{22}$ +46 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.29 (s, 9H), 1.7–1.8 (m, 2H), 2.23 (dd, *J*=1.6, 10.4 Hz, 1H), 2.34 (br s, 1H), 2.50 (dd, *J*=2.4, 10.9 Hz, 1H), 2.72 (dt, *J*=1.7, 10.4 Hz, 1H), 2.87 (br s, 1H), 2.99 (d, *J*=10.9 Hz, 1H), 2.80 and 3.46 (AB, J_{AB}=13.9 Hz, 2H, CH_2Bn), 4.33 (s, 1H, H-6α), 5.85 (d, *J*=6.7 Hz, 1H, H-11), 6.8–6.9 (m, 2H), 7.0–7.1 (m, 3H), 7.30 (d, *J*=6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.5, −0.7, 26.0, 31.2, 35.9, 53.1, 60.7, 61.7, 62.5, 105.1, 125.3, 126.8, 128.1, 128.2, 138.7, 143.5, 151.9, 165.6; IR (NaCl, cm^{-1}) 2942, 2802, 2760, 1624, 1544, 1242; MS (EI) *m/z* (%) 424 (M^+, 25), 409 (42), 290 (47), 202 (38), 91 (100), 73 (77), 57 (46).

4.3. Oxidation of epimeric alcohols 3h

4.3.1. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-benzoyl-cytisine 8. To a solution of a mixture of diastereoisomers **3h** (70 mg, 0.181 mmol, 1 equiv) in 5 mL of ethyl acetate was added IBX (301 mg, 1.08 mmol, 6 equiv). The mixture was heated at 80 °C for 16 h. The reaction was filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 99.5:0.5) to afford **8** as a colorless oil (0.054 g, 76%); $[\alpha]_D^{22}$ −123 (*c* 0.6,

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.62 (dt, J=3.0, 13.0 Hz, 1H), 2.13 (d, J=13.0 Hz, 1H), 2.3–2.4 (m, 2H), 2.46 (dd, J=3.0, 11.0 Hz, 1H), 2.88 (d, J=11.0 Hz, 1H), 3.02 (s, 1H), 3.14 (d, J=10.0 Hz, 1H), 3.45 and 3.55 (AB, J_{AB}=14.0 Hz, 2H, CH_2Bn), 5.90 (s, 1H, H-6α), 6.03 (d, J=8.0 Hz, 1H, H-11), 6.49 (d, J=9.0 Hz, 1H, H-9), 7.0–7.1 (m, 2H), 7.2–7.3 (m, 3H), 7.3–7.4 (m, 1H), 7.4–7.5 (m, 2H), 7.5–7.6 (m, 1H), 8.06 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.0, 30.7, 35.2, 59.7, 59.9, 62.0, 62.6, 104.9, 116.8, 127.2, 128.3, 128.4, 128.6, 128.9, 133.3, 135.0, 137.9, 139.5, 151.7, 162.9; IR (NaCl, cm^{-1}) 2939, 2800, 1691, 1650, 1544, 1219, 1142, 908, 798, 723, 693; HRMS (ESI) calcd for $C_{25}H_{25}N_2O_2$ 385.1916, found 385.1923.

4.4. Debenzylation of 3a

4.4.1. (+)-(1*R*,5*S*,6*S*)-6-Methyl-cytisine 10. To a solution of *N*-benzyl-6-methyl-cytisine **3a** (50 mg, 0.17 mmol, 1 equiv) in 1 mL of anhydrous dichloroethane was slowly added α-chloroethyl chloroformate (75 μL, 0.68 mmol, 4 equiv) under nitrogen. The reaction was heated to 80 °C during 24 h. After evaporation of the solvent, the residue was dissolved in 2 mL of methanol and the solution was refluxed for 2 h. Methanol was evaporated and ammonia was added until basic pH. After extraction four times with CH_2Cl_2 and evaporation of the solvent, the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1+1% NH_3 28%) affording **10** as a colorless oil (25 mg, 72%); $[\alpha]_D^{22}$ +107 (*c* 0.96, $CHCl_3$); ^1H ($CDCl_3$) δ 1.38 (d, J=6.3 Hz, 3H), 1.60 (br s, 1H), 1.91 (d, J=6.1 Hz, 2H), 2.24 (d, J=12.7 Hz, 1H), 2.8–2.9 (m, 2H), 3.1–3.2 (m, 2H), 4.79 (q, J=6.1 Hz, 1H, H-6α), 5.99 (dd, J=1.0, 6.8 Hz, 1H, H-11), 6.4 (dd, J=1.0, 9.0 Hz, 1H, H-9), 7.26 (dd, J=6.8, 9.0 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$) δ 20.7, 22.9, 33.6, 35.1, 51.1, 54.3, 58.5, 106.0, 118.2, 138.9, 149.0, 163; IR (NaCl, cm^{-1}) 2944, 2800, 1650, 1548; MS (EI) *m*/*z* (%) 204 (M^+, 29), 46 (15), 109 (16), 44 (100).

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References and notes

1. Dale, H. H.; Laidlaw, P. P. *J. Pharmacol. Exp. Ther.* **1912**, *3*, 205–221.
2. (a) Pabreza, L. A.; Dhawan, S.; Kellar, K. J. *Mol. Pharmacol.* **1991**, *39*, 9–12; (b) Heinemann, S. F.; Papke, R. L. *Mol. Pharmacol.* **1994**, *45*, 142–149; (c) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, *6*, 465–486; (d) Ferger, B.; Spratt, C.; Teismann, P.; Seitz, G.; Kuschinsky, K. *Eur. J. Pharmacol.* **1998**, *360*, 155–163.
3. (a) O'Neill, B. T. PCT Int. Appl. WO98 18,798, 1998; *Chem. Abstr.* **1998**, *119*, 4774k; (b) Canu Boido, C.; Sparatore, F. *Farmaco* **1999**, *54*, 438–451; (c) Imming, P.; Klaperski, P.; Stubbs, M. T.; Seitz, G.; Gündisch, D. *Eur. J. Med. Chem.* **2001**, *36*, 375–388.
4. Chellappan, S. K.; Xiao, Y.; Tueckmantel, W.; Kellar, K. J.; Kozikowski, A. P. *J. Med. Chem.* **2006**, *49*, 2673–2676.
5. Khisamutdinova, R. Y.; Yarmukhamedov, N. N.; Gabdrakhmanova, S. F.; Karachurina, L. T.; Sapozhnikova, T. A.; Baibulatova, N. Z.; Baschenko, N. Zh.; Zarudii, F. S. *Pharm. Chem. J.* (*Translation of Khimiko-Farmatsevticheskii Zhurnal*) **2004**, *38*, 311–313; *Chem. Abstr.* **2004**, *142*, 411207.
6. Bakbardina, O. V.; Rakhimzhanova, N. Z.; Gazalieva, M. A.; Fazyov, S. D.; Baimagambetov, E. Z. *Russ. J. Appl. Chem.* **2006**, *79*, 504–505.
7. (a) Nicolotti, O.; Canu Boido, C.; Sparatore, F.; Carotti, A. *Farmaco* **2002**, *57*, 469–478; (b) Canu Boido, C.; Tasso, B.; Boido, V.; Sparatore, F. *Farmaco* **2003**, *58*, 265–277.
8. Valette, H.; Bottlaender, M.; Dollé, F.; Dolci, L.; Syrota, A.; Crouzel, C. *Nucl. Med. Commun.* **1997**, *18*, 164.
9. Marrière, E.; Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121–1124.
10. Roger, G.; Lagnel, B.; Rouden, J.; Besret, L.; Valette, H.; Demphel, S.; Gopisetti, J.; Coulon, C.; Ottaviani, M.; Wrenn, L. A.; Letchworth, S. R.; Bohme, G. A.; Benavides, J.; Lasne, M.-C.; Bottlaender, A.; Dollé, F. *Bioorg. Med. Chem.* **2003**, *11*, 5333–5343.
11. (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871; (b) Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977–3988; (c) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789–5792; (d) Genet, C.; McGrath, M. J.; O'Brien, P. *Org. Biomol. Chem.* **2006**, *4*, 1376–1382; (e) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480–15489.
12. Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833–1844.
13. (a) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. C. *Tetrahedron: Asymmetry* **2004**, *15*, 3531–3538; (b) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 894–1896.
14. Turdybekov, D. M.; Fazylov, S. D.; Turdybekov, K. M.; Gazaliev, A. M.; Zhivotova, T. S. *Russ. J. Org. Chem.* **2004**, *40*, 719–722.
15. Kozikowski, Alan P.; Musachio, John L.; Kellar, Kenneth J.; Xiao, Yingxian; Wei, Zhi-Liang. PCT Int. Appl. WO 2004-US18340 20040609, 2005; *Chem. Abstr.* **2004**, *142*, 114316.
16. Barlow, R. B.; McLeod, L. J. *J. Pharmacol.* **1969**, *35*, 161–174.
17. Slater, Y. E.; Houlihan, L. M.; Maskell, P. D.; Exley, R.; Bermudez, I.; Lukas, R. J.; Valdivia, A. C.; Cassels, B. K. *Neuropharmacology* **2003**, *44*, 503–515.
18. Fitch, R. W.; Kaneko, Y.; Klaperski, P.; Daly, J. W.; Seitz, G.; Gündisch, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1221–1224.
19. Abin-Carriquiry, J. A.; Voutilainen, M. H.; Barik, J.; Cassels, B. K.; Iturriaga-Vasquez, P.; Bermudez, I.; Durand, C.; Dajas, F.; Wonnacott, S. *Eur. J. Pharmacol.* **2006**, *536*, 1–11.
20. O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201–4204.
21. Rouden, J.; Ragot, A.; Gouault, S.; Cahard, D.; Plaquevent, J.-C.; Lasne, M.-C. *Tetrahedron: Asymmetry* **2002**, *13*, 1299–1305.

22. Katritzky, A. R.; Arrowsmith, J.; Grzeskowiak, N. E.; Salgado, H. J.; Bahari, Z. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 143–151.
23. (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157; (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495–498.
24. Katritzky, A. R.; Grzeskowiak, N. E.; Salgado, H. J.; Bin Bahari, Z. *Tetrahedron Lett.* **1980**, *21*, 4451–4454.
25. Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196.
26. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
27. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.
28. Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082.
29. Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499–504.

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Cholic acid-based high sensitivity fluorescent sensor for α,ω-dicarboxylate: an intramolecular excimer emission quenched by complexation

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Abstract—Fluorescent receptors (**1** and **2**) bearing two binding units on C3 and C24 and two signal display units on C7 and C12 of cholic acid, respectively, were designed and synthesized. Both **1** and **2** emit a much weaker fluorescence than that of the control compound **3** lacking of the binding units reflecting that a PET process originated from the C-3 thiourea group to the plural pyrenyl pendant groups is operative. Addition of terminal dicarboxylate anions to the CH_3CN solution of **1** or **2** enhances the PET process, which leads to a significant and highly sensitive fluorescence response, resulting in an almost complete quenching of the excimer emission of the signal units. To maximize the interaction of the host and the guest, carboxylates of more than five carbon chains could penetrate through the space between the two pyrenyl pendants of the host, triggering a considerable conformational change of the fluorophores. As a result, an enhancement of the monomer emission at the expense of the excimer emission will take place. The binding properties and mechanism of **1** and **2** to dicarboxylates in CH_3CN were manifested by the combined fluorescence, UV–vis, and ^1H NMR spectroscopic method.

1. Introduction

Anions play an important role in a wide range of chemical, environmental, and biological processes.[1] The quest for chemosensors capable of effecting the selective and sensitive binding and sensing of negatively charged species through visible, electrochemical, and optical responses has continued to attract considerable attention in scientific community.[2] Dicarboxylates are among the most attractive targets for the study of anion recognition and sensing because of their biological importance,[3] such as their critical roles in numerous metabolic processes.[4] Therefore, their sensitive detection is of great interest in a variety of areas in bioanalytical and biomedical researches.[4b,5] The optical methods, owing to their simplification of manipulation and sensitivity of transduction of binding behaviors, are extensively adopted in the investigation of molecular/ion recognition.[6] Numerous endeavors have been particularly devoted to the design and synthesis of ditopic anion receptors bearing optical signal display subunits (i.e., chromophore or fluorophore) as sensing probes for dicarboxylates.[7]

The structural complementary between receptors and terminal dicarboxylates ($^-OOC(CH_2)_nCOO^-$) plays a crucial role in the selective recognition processes.[8] To assemble selective artificial ditopic receptors for terminal dicarboxylates, based on cyclopolyammonium,[9] sapphyrin,[10] and calix[4]-arene,[11] some classical molecular skeletons were rationally designed and exquisitely synthesized. Charge neutral chemosensors, which are immune from cross pH interference are particularly attractive. Gunnlaugsson and Davis[12] reported a neutral fluorescent PET sensor for glutarate while He's group developed two fluorescent sensors for adipate.[13] Mei and Wu reported a sensor containing a naphthalene group as the signal unit for pimelate.[14] However, most of these chemosensors exhibit good selectivity only for dicarboxylates of a relatively short chain length ($n \leq 3$) and with moderate binding constants of $10^5\ M^{-1}$. It is very difficult to construct a suitable receptor for a long-chain terminal dicarboxylate using the classical molecular scaffolds such as polyazamacrocycles and calixarenes. To our best knowledge, there is no example of chemosensor, which can bind strongly with a long-chain terminal dicarboxylate ($n>5$). In this paper, we report the design and synthesis of two cholic acid-based fluorescent sensors, which are amenable to the sensitive detection of long-chain terminal dicarboxylates ($n=6$ and 8).

Pioneered by the seminal works of Davis and others, cholic acid has recently emerged as a promising natural material to

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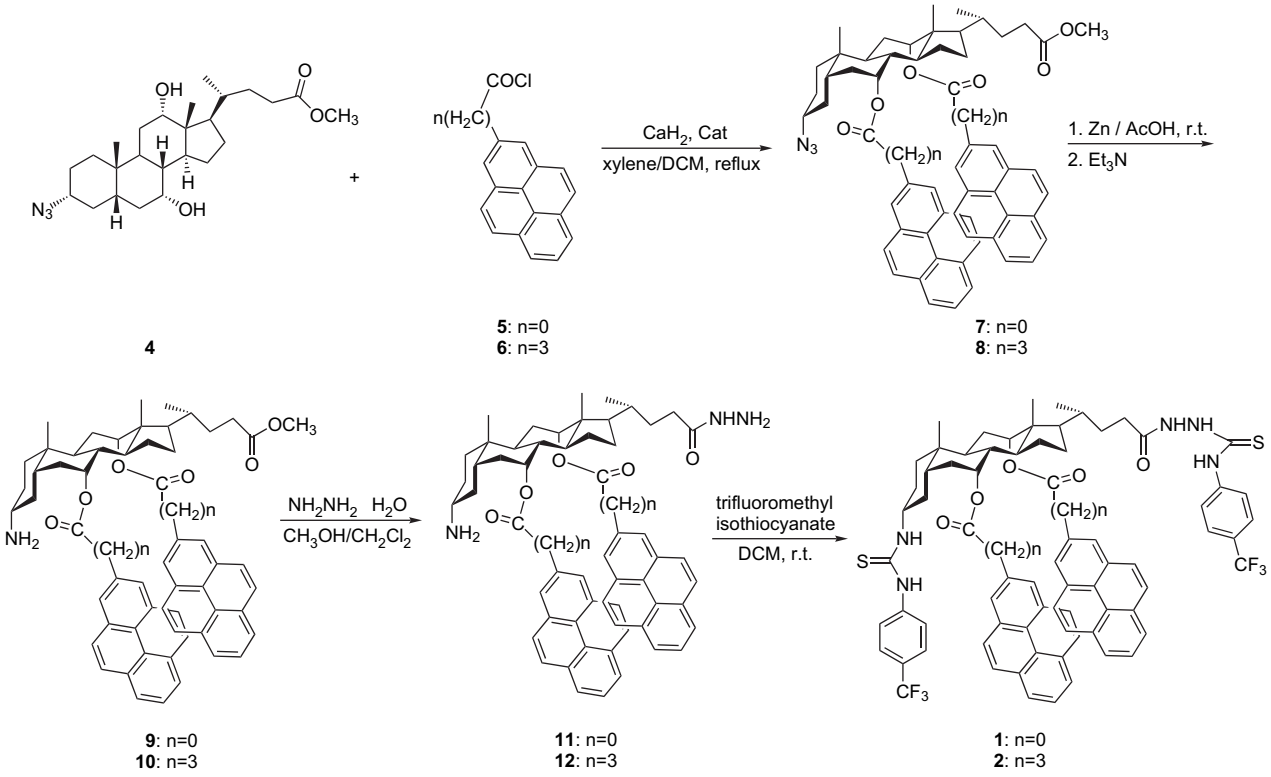
construct supramolecular systems for molecular recognition.[15] To achieve high affinity and selectivity to the 'host', the three axially oriented functionalities at the C3, C7, and C12 of cholic acid could be modified and assembled in such a way to confer cooperative binding interactions to a specific guest anion. Recently, by incorporation of two thiourea groups connected to an anthracene moiety at the C3 and C24 as the signal subunit, we have created a fluorescent ditopic receptor possessing binding capability to dicarboxylates even in aqueous media.[16] Our findings represent the first charge neutral chemosensor, which can be exploited for binding dicarboxylates in aqueous conditions. However, the fluorescent signal change of the sensor over a wide concentration range of the guest is only moderate. To further improve the sensitivity and selectivity of the sensor, we envisage that, if two pyrene moieties are introduced onto the C7 and C12 as signal display units and two thiourea receptive subunits were appended onto C3 and C24 of cholic acid, upon association with dicarboxylates, a distinct fluorescent response indicative of binding will be observed. The two pendent proximate pyrenyl groups can display not only a well-defined monomer emission at 370~430 nm but also an efficient excimer emission at around 480 nm.[17] To effectively interact with the host, the terminal dicarboxylates may penetrate through the space between the plural pyrenyl pendants reaching the two receptive sites at the two ends of the host. The binding event can trigger conformational changes of the pyrene-appended signal display units, which could upset the equilibrium between the monomer and the excimer emissions. Besides, the fluorescence of the system will be quenched by the formation of the complex via a PET (photo-induced electron transfer) mechanism. In addition, appending bulky pyrenyl groups to the C7 and C12 of cholic acid can also create a bigger steric hindrance and sharpen the selectivity of the sensor favoring the binding between the host and long-chain terminal dicarboxylates.

Herein, we report the synthesis and structural characterization of two new charge neutral fluorescent sensors **1** and **2** bearing two signal subunits at C7 and C12 and two binding subunits at C3 and C24 of cholic acid, respectively. The binding abilities of **1** and **2** to dicarboxylates were demonstrated by fluorescence emission spectra, UV–vis spectra, and ^{1}H NMR method.

2. Results and discussion

2.1. Synthesis

Treatment of 1-pyrenyl acid or 1-pyrenebutyric acid with sulfuryl dichloride in benzene afforded the corresponding acid chlorides **5** and **6** in 100% yield, which could be directly used for the subsequent condensation reaction (Scheme 1). To overcome the high steric hindrance of introducing the plural pyrenyl moieties on the C7 and C12 of the cholic acid scaffold, we adopted the Maitra's protocol by reacting excess **5** or **6** with methyl 3-azidocholate (**4**)[15c] in a mixed solvent of dichloromethane and xylene (1:10) using CaH_2 as a base with a catalytic amount of benzyltriethylammonium chloride, giving rise to **7** and **8** in ca. 40% yield, respectively.[18] Reduction of **7** (or **8**) by zinc dust in acetic acid followed by hydrazidation with hydrazine yielded amine **11** (or **12**). Condensation reactions were performed between **11** (or **12**) and 4-trifluoromethylphenylisothiocyanate in dichloromethane and the target compounds **1** and **2** were



Scheme 1. Synthetic routes for receptors **1** and **2**.

obtained in ca. 30~50% over two steps. In order to investigate the effect of binding behaviors on the fluorescence of **1** and **2**, control compound **3** was synthesized from methyl 3α-acetyl-7α,12α-dihydroxy-5β-cholan-24-oate.[19]

2.2. Binding properties

As expected, when excited at 352 nm in CH_3CN, receptor **1** (1×10^{-5} M) displayed a monomer emission at 388 nm and an excimer emission at 488 nm, with an intensity ratio of monomer to excimer emission (I_M/I_E) as 2.42. Compared to sensor **1**, **2** (1×10^{-5} M) was excited in CH_3CN at a shorter wavelength (342 nm) and gave a monomer and an excimer emission at 375 and 475 nm, respectively, the ratio of I_M/I_E was found to be 0.21, which is substantially smaller than that of **1**. This indicated that, in comparison with **1**, the presence of the more flexible three carbon spacer in **2** between the pyrenyl groups and the C-7 and C-12 ester functionalities enables a tighter excimer formation arising from a stronger π–π stacking in receptor **2**. In both **1** and **2**, the intensity of ratio of monomer to excimer is barely changed in the concentration range of 10^{-7}–10^{-4} M, implicating that their excimer emissions result from an intramolecular excimer but not from an intermolecular excimer (Supplementary data).

To unravel the details of the interaction between the host and the guest, compound **3** lacking the thiourea groups on the C3 and C24 served as the control was synthesized. Compared with **1** and **2**, **3** can emit relatively stronger emissions and give a monomer emission at 388 nm and an excimer at 488 nm when excited at 352 nm. On this basis a higher I_M/I_E ratio of 0.84 was obtained for **3** compared with the value of 0.21 for **1**, it is quite likely that the quenching effect by the thiourea group is more pronounced to the excimer than that to the monomer (Fig. 1). Apparently, the thiourea groups not only affect the ratio of monomer to excimer emission but also quench the fluorescence of receptors **1** and **2**. This is conceivably attributable to the fact that the thiourea groups take part in the PET process in which an electron is transferred from a lone-pair electron of the sulfur atom to two excited pyrenyl units of **1** and **2**.[20] The quantum yield of **1**, **2** and **3** were assessed using pyrene as the standard and the results are tabulated in Table 1. The quantum yield of **3** was much higher than that of **1** and **2** with the order of $\Phi_3>\Phi_2>\Phi_1$. Due to the more proximal thiourea groups at the two pyrenyl units in receptor **1** than in receptor **2**, a more effective PET process was effectuated for **1**.

To obtain insight into the binding properties of **1** and **2** toward dicarboxylate anions, we first investigated the fluorescence change of the sensors upon addition of dicarboxylates in CH_3CN. With a gradual increase in the concentration of dicarboxylate anions, malonate, succinate, glutarate, adipate, suberate, and sebacate (all as tetrabutylammonium salts), the monomer emission of **1** (1×10^{-5} M) can be quenched ca. 50% and the excimer can be quenched as much as >90%. Comparing with our previously reported anthracene based carboxylate sensors,[16] the extent of quenching of the present systems caused by the guests is significantly enhanced. Potentially, sensors **1** and **2** would be more sensitive optical probes toward dicarboxylates. Typical fluorescence change of **1** and **2** modulated with different amounts of suberate in CH_3CN is showed in Figures 2 and 3, respectively. The inset of the graph shows the change of the fluorescence intensity of the monomer and excimer upon addition of suberate. Several interesting features of the plots are noteworthy. Firstly, both sensors are ratiometric, which are more superior systems in sensor design due to their ability to eliminate the sample matrix effect in the recognition process. Both sensors operate complementarily to each other. As the concentration of the guest increases, the I_M/I_E of **1** and **2** responds differently (i.e., the ratio of **1** decreases while that of **2** increases, Supplementary data). It is noteworthy that, when treated with different amounts of dicarboxylate anions, the excimer of receptor **2** at 475 nm (1×10^{-5} M in CH_3CN) had shown a more sensitive fluorescence response than that of receptor **1** and the excimer was almost completely quenched. The guest induced conformational change of sensor **2** was implicated at the moderate concentration of suberate as a slightly increase in the monomer peak was observed. Expansion of Figure 3 in the range of 400–450 nm allows the manifestation of an iso-emission point at around 421 nm (Supplementary data).

Regarding the nature of the guest–host interaction in the sensor systems, the key question was: how do dicarboxylates preorganize themselves in reaching the two binding sites of the host? Could they penetrate through or just move around the space between the pyrenyl pendent groups in the

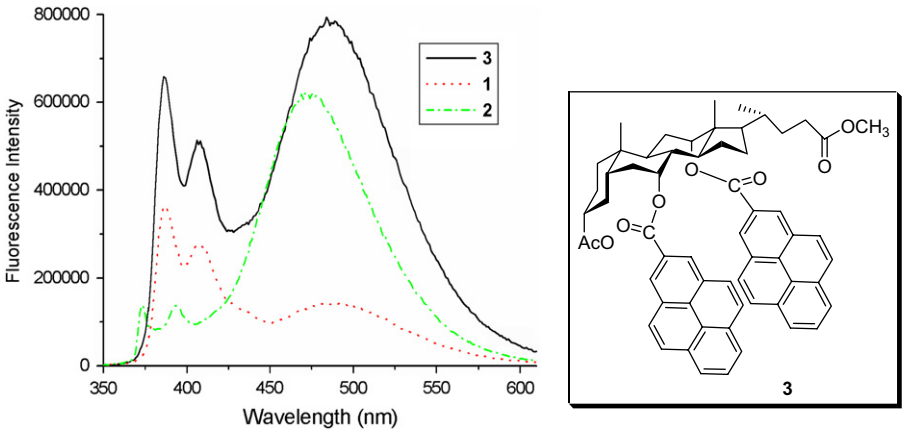


Figure 1. The fluorescence emission spectra of **1**, **2**, and **3** in CH_3CN (1×10^{-6} M) (**1** and **3** were excited at 352 nm, and **2** at 342 nm).

Table 1. Absorption and fluorescence spectral data of **1**, **2**, and **3** in CH_3CN

Sample	λ_{abs} (nm)	ε (10^4 M^{-1} cm^{-1})[a]	$\Phi_{313\ nm}$
Pyrene	231/240/262/272/306/319/334	3.83/6.95/2.15/4.05/1.02/2.53/4.15	0.530[b,d]
3	282/352/385	7.49/6.95/2.18	0.877[c,d]
2	235/242/265/276/313/327/343	11.1/14.9/7.09/10.3/3.09/5.49/6.97	0.699[c,d]
1	280/348/383	7.44/4.96/1.33	0.592[c,d]

[a] The concentration is 1×10^{-5} M.
[b] Quantum yield was detected in EtOH and used as the standard.
[c] Quantum yield was detected in CH_3CN.
[d] Quantum yield was determined with λ_{ex}=303 nm.

respective complexes? Treated with ca. 60 equiv of malonate and succinate anions (i.e., short chain dicarboxylates), the fluorescence response of **1** or **2** attained equilibrium, while with only ca. 15 equiv of other longer chain dicarboxylate anions an equilibrium could be observed. The excimer emission is more sensitive to the dicarboxylates than the monomer emission both in **1** and **2**. With the increase of the length of the dicarboxylate anion, the sensitivity of both **1** and **2** toward dicarboxylate increases. For long chain dicarboxylates, there is a significant fluorescence response even at the concentration at around 10^{-8} M (Supplementary data). Sensor **2** has a more sensitive response to the same dicarboxylate than **1** because of its two pyrenyl groups linked with flexible spacers, which lead to a stronger excimer emission. Introducing dicarboxylates and other anions such as AcO^-, Cl^-, Br^-, and I^- to the CH_3CN solution of **3**, there is no change observed in the fluorescence spectra. This indicated that the anions quenched the fluorescence intensity of pyrenyl groups only by coordinating with thiourea groups present in **1** and **2**.

After binding the dicarboxylate anion, the electron-donating power of either the aminothiourea or amidothiourea group in the hosts can be enhanced, which leads to a stronger PET process from the thiourea to the pyrenyl units (vide supra). This possibly contributes to the quenching of the monomer and excimer. At the same time, when the binding events occurred, the dicarboxylate anion would go through the C-7 and C-12 pendent groups of the cholic acid derivatives. Such type of interaction could destroy the π–π stack of the two pyrenyl units leading to the enhancement of the monomer emission at the expense of the excimer peak (vide supra). The observation appears to be consistent with this interaction model. When treated with 100 equiv of AcO^-, the monomer emission of **1** and **2** could be quenched ca. 50% as the extent of quench caused by dicarboxylates (except malonate and succinate) while both the excimer of **1** and **2** only could be quenched at about 50% (Supplementary data). Apparently, acetate due to its small size could not go through the space of the two pendent groups. This observation strongly supported that the long-chain dicarboxylates (n=3, 4, 6, 8) went through rather than passed around the two pyrenyl units, which also contributed to a great quenching of the excimer of **1** and **2** (i.e., from 50 to 90%). In response to the combined electronic and conformational change effects triggered by complex formation, an enhancing PET process from thiourea groups to the pyrenyl groups and a decrease of the π–π stack between the two pyrenyl groups take place. Accordingly, the excimer emission can be quenched significantly, which creates a highly sensitive fluorescence responsive system to dicarboxylates. While treated with 100 equiv of other anions, spherical anions such as Cl^-, Br^-, and I^-, only less than 10% quenching was observed in the fluorescence spectra of **1** and **2**.

Job plot[21] showed that both **1** and **2** formed 1:2 complexes with malonate and succinate (Fig. 4) and 1:1 complexes with other dicarboxylate anions (Supplementary data). This result is consistent with the phenomena observed in the fluorescence spectra (vide supra) and suggest that pyrenyl groups on C7 and C12 not only act as signal units but also play

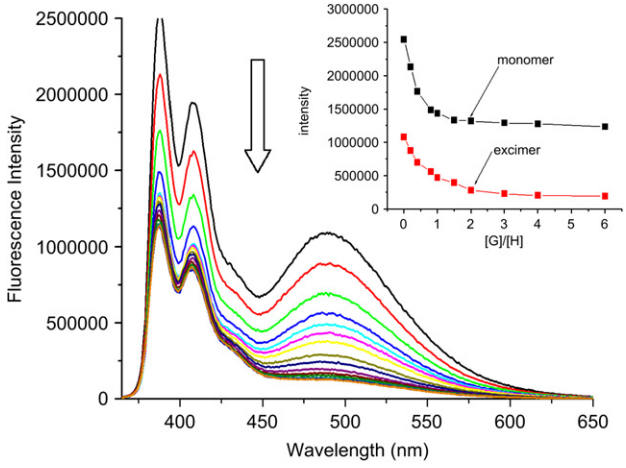


Figure 2. The fluorescence emission spectra of **1** (1×10^{-5} M) with suberate in CH_3CN, λ_{ex}=352 nm. Inset: the fluorescence intensity of **1** at 388 nm (monomer) and 488 nm (excimer) with different amounts of suberate.

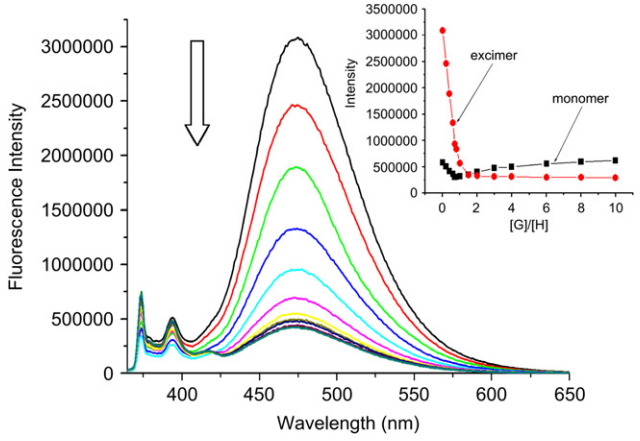


Figure 3. The fluorescence emission spectra of **2** (1×10^{-5} M) with suberate in CH_3CN, λ_{ex}=342 nm. Inset: the fluorescence intensity of **1** at 475 nm with different amounts of suberate.

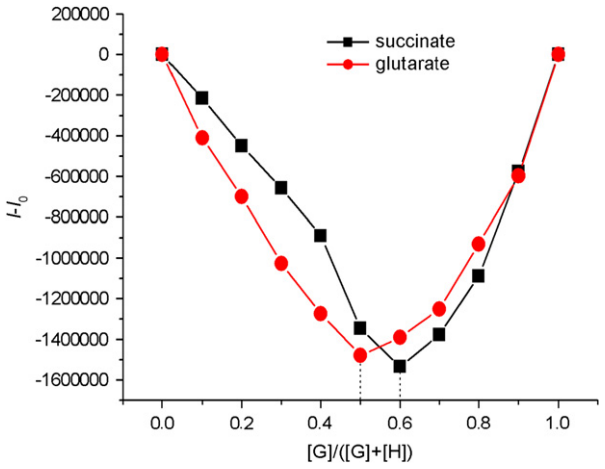


Figure 4. Job plot for the complexation of **2** with succinate and glutarate in CH_3CN (the total concentration is 1×10^{-5} M).

important roles in complexing with terminal dicarboxylate anions. Specifically, non-bonding repulsion between the host and malonate (or succinate) precludes the formation of a 1:1 complex by passing through the bulky pyrenyl pendants. We have reported for the first time that the flexible C17 side chain of cholic acid derivatives can be exploited to provide a binding unit onto the C24[22] and the resulting fluorescent sensor had demonstrated a fairly selective binding toward adipate,[16] which possesses a carbon chain of suitable length. With the help of the flexible binding arm on C17 and the steric constraint of the pendent groups on C7 and C12, **1** and **2** can show a selective recognition to some long-chain terminal dicarboxylate anions.

On the basis of the change in fluorescent intensity associated with the stepwise addition of guest dicarboxylates, the complex association constants (K_a) for 1:1 binding model were calculated using non-linear least-squares curve fitting[23] and are compiled in Table 2. Excellent relative coefficients (R>0.99) were obtained and demonstrated that **1** and **2** formed 1:1 complexes with long-chain terminal dicarboxylate anions (n=3, 4, 6, 8).[24] The association constants of **1** and **2** to sebacate are much larger than those of other dicarboxylates, suggesting that both **1** and **2** exhibit selective recognition to sebacate. For all 1:1 binding models, **1** presumably due to its more rigid structure has a slightly weaker binding ability to dicarboxylates than **2**.

For short chain dicarboxylates, the complex association constants (log K_a) and the stoichiometry for 1:2 binding model are calculated using the Benesi–Hildebrand equation[25] and are listed in Table 3. Both **1** and **2** gave the values of stoichiometry (n) with malonate and succinate close to 2, which corroborated well with the results obtained from the Job plot (vide supra).

To investigate the chiral discriminative power of the sensors, L-, D-glutamate, and *N*-acetyl-L-glutamate (used as tetrabutylammonium salts) were chosen to introduce into the CH_3CN solution of **1** and **2** (1×10^{-5} M). The corresponding association constants are determined and are given in Table 2. Within the experimental errors, the binding strength of the hosts and glutamate was found to be slightly greater than that of the hosts and glutarate. The possible H-bonding between the α-amino group of glutamate and the oxygen of the C-7/C-12 ester group of the host may contribute to the additional binding interaction. Interestingly, comparing the binding constants of the two antipodal forms of glutamate to the hosts, enantioselective factors exhibited by **1** and **2** to the guests were found to be 1.53 and 1.79, respectively. The ^{1}H NMR also showed that, under the chiral influence of the host **1**, the splitting of the two β-proton signals of glutamate centered at δ 2.08 and 2.18 was evident. Reciprocally, the C-7 and C-12 protons of **1** at δ 5.40 and 5.60 were split by the racemic glutamate (Supplementary data).

To substantiate the binding interaction between the dicarboxylates and the hosts, all titration experiments were performed in CH_3CN with UV–vis spectroscopic method. The typical spectra of **1** and **2** (1×10^{-5} M) with different amounts of suberate in CH_3CN are shown in Figures 5 and 6, respectively. Sensor **1** has two characteristic peaks at 280 and 348 nm, with addition of suberate, the intensity of both peaks was increased with a slight blue shift and a new absorption band appeared at around 308 nm. At the same time, in the first derivative of the UV titration curves, an isosbestic peak at 269 nm could be easily identified.

The free **2** gives a similar absorption with pyrene in CH_3CN. Adding suberate anion into the solution of **2**, the characteristic peak at 265 nm ascribed to the absorption of trifluoromethylphenyl ring was increased discernibly. A new absorption band appeared at the range of 283~323 nm and an isosbestic point at 276 nm could be observed in the first derivative of the corresponding UV-titration curves

Table 2. The association constants of **1** and **2** with dicarboxylates (1:1 binding model) in CH_3CN

Anion	**1**		**2**	
	K_a[a]	K_a[b]	K_a[a]	K_a[b]
Glutarate[c]	$(8.22\pm1.51)\times10^5$	$(1.08\pm0.09)\times10^6$	$(1.68\pm0.17)\times10^6$	$(1.60\pm0.11)\times10^5$
Adipate[c]	$(1.27\pm0.12)\times10^6$	$(1.29\pm0.14)\times10^6$	$(5.56\pm0.42)\times10^6$	$(1.87\pm0.14)\times10^7$
Suberate[c]	$(1.64\pm0.14)\times10^6$	$(1.03\pm0.06)\times10^6$	$(2.10\pm0.19)\times10^7$	$(3.19\pm0.10)\times10^7$
Sebacate[c]	$(2.27\pm0.23)\times10^7$	$(2.30\pm0.23)\times10^7$	$>10^{8d}$	$>10^{8d}$
L-Glutamate[c]	$(1.18\pm0.13)\times10^6$	$(2.21\pm0.13)\times10^6$	$(2.35\pm0.11)\times10^6$	$(2.03\pm0.22)\times10^6$
D-Glutamate[c]	$(1.81\pm0.11)\times10^6$	$(1.81\pm0.19)\times10^6$	$(4.21\pm0.23)\times10^6$	$(5.23\pm0.11)\times10^6$
N-Acetyl-L-glutamate[c]	$(1.29\pm0.19)\times10^6$	$(1.09\pm0.10)\times10^6$	$(1.63\pm0.21)\times10^6$	$(8.35\pm1.30)\times10^5$

[a] The values were calculated from the change of the fluorescence spectra.
[b] The values were calculated from the change of the UV–vis spectra.
[c] Anions were used as their tetrabutylammonium salts.
[d] The value is too large to calculate.

Table 3. The association constants of **1** and **2** with dicarboxylates (1:2 binding model) in CH_3CN

Anion	1				2			
	n[a]	log K_a[a]	n[b]	log K_a[b]	n[a]	log K_a[a]	n[b]	log K_a[b]
Manolate[c]	1.84	8.07±0.59	1.75	7.93±0.14	2.02	9.01±0.15	2.2	8.85±0.09
Succinate[c]	1.96	8.76±0.61	2.13	8.87±0.26	2.11	9.47±0.13	2.09	8.67±0.12

[a] The values were calculated from the change of the fluorescence spectra.
[b] The values were calculated from the change of the UV–vis spectra.
[c] Anions were used as their tetrabutylammonium salts.

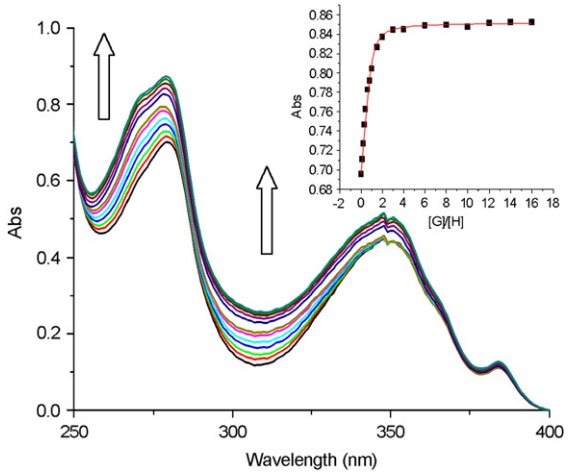


Figure 5. The absorption of **1** with different amounts of suberate in CH_3CN. Inset: the change of the absorption of **1** at 280 nm.

(Supplementary data). In contrast, the characteristic peaks at 326 and 343 nm ascribed to the pyrenyl group seem to be intact. This strongly suggested that the pyrenyl groups in the ground state had not been involved in the interaction with dicarboxylates. According to the change of absorption during the titrations, the complex association constants are calculated and are listed in Tables 2 and 3. The values of the association constants are comparable with those obtained from the fluorescence titration experiments.

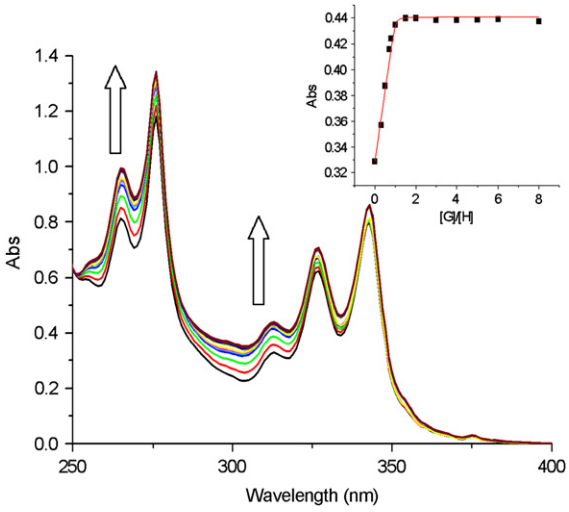


Figure 6. The absorption of **2** with different amounts of suberate in CH_3CN. Inset: the change of the absorption of **2** at 313 nm.

^{1}H NMR spectra also had been used to study the binding properties of **1** and **2** toward dicarboxylates. When **1** was treated with 1 equiv of adipate anion in DMSO-d_6, the intensity of the proton signals ascribed to the thiourea hydrogens diminished significantly and at least one of these protons recorded a downfield shift of 0.07 ppm, which is indicative of H-bonding interaction between the host and the guest (Supplementary data). The aromatic protons of the trifluoromethylphenyl ring of **1** underwent a clear upfield shift from 7.63 to 7.34 ppm after the thiourea groups were bound with the anion.

3. Conclusion

Charge neutral fluorescent chemosensors **1** and **2** for dicarboxylates have been rationally designed and synthesized. Both **1** and **2**, functionalized adequately at the C3, C7, C12, and C24 of cholic acid, showed high affinities to dicarboxylates resulting from multiple hydrogen bonding interactions. A significant fluorescence response of the sensors took place through an intramolecular excimer emission quenched by complexation. The preorganization of **1** and **2** permits two points binding with the guests on C3 and C24 receptive sites under the cooperation of bulky signal groups on C7 and C12 to produce highly selective affinities to long-chain terminal dicarboxylates. Sensors **1** and **2** exhibit high sensitive response to long-chain dicarboxylates (n=6 and 8) and the strong binding between the host and the guest rendered the detection of dicarboxylates possible even at the concentration of 10^{-8} M. Sensors **1** and **2** are promising fluorescent sensors for suberate and sebacate. The recognition characteristics of the novel hosts developed in this work are established unambiguously by the combined UV, fluorescence, and ^{1}H NMR spectroscopic methods. In addition, the moderate chiral recognition ability of the host was also demonstrated.

4. Experimental

4.1. General methods

Melting point was determined with a MEL-TEMPII melting-point apparatus (uncorrected). IR spectra were obtained on a Nicolet MAGNA-IR 550 spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, with Me_4Si as the internal standard, on a JEOL EX270 spectrometer and ^{13}C NMR spectra on a Varian INOVA-400 FT NMR spectrometer. High-resolution mass spectra were recorded on a Bruker Autoflex mass spectrometer (MALDI-TOF) or Electrospray ionization high-resolution mass spectra on an API

Qstar Pulsari mass spectrometer (ESI-TOF). Infrared spectra were recorded on MAGNA-IR 550 spectrometer. Absorption spectra were recorded on a Hewlett Packard 8453 UV–vis spectrophotometer. Fluorescent emission spectra were collected on a Photon Technology International (PTI) at 293 K. CH_2Cl_2 and xylene were dried and distilled from CaH_2, and benzene was dried and distilled from Na freshly. THF was distilled under nitrogen in the presence of sodium chips using benzophenone ketyl as the indicator. All other commercially available reagents were used as received.

4.2. General procedure for the synthesis of 7 and 8

To a mixture solution of **4** (0.45 g, 1 mmol) in xylene/CH_2Cl_2 (10:1, 5 mL) were added calcium hydride (0.63 g, 15 mmol) and benzyltriethylammonium chloride (0.01 g, 0.04 mmol), and the mixture was refluxed for 10 min under a nitrogen atmosphere. To the refluxing solution was added a solution of freshly prepared 1-pyrenoyl chloride or 1-pyrenebutanoyl chloride (3 mmol) in xylene (10 mL) and refluxed for 24 h. The reaction mixture was filtered under reduced pressure, diluted with ethyl acetate, and washed with aq $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed.

4.3. Methyl 3α-azide-7α,12α-dipyrenylcarbonyl-5β-cholan-24-oate (7)

The crude product was chromatographed on silica gel (230–400 mesh) eluting first with 25% ethyl acetate/petroleum ether (60–80 °C) and then with pure dichloromethane to give the pure product (0.33 g, 37%): mp 130 °C; IR (KBr, cm^{-1}): 3438, 2948, 2871, 2089, 1736, 1705, 1596, 1446, 1389, 1255, 1229, 1145, 1133, 849, 710; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (s, 3H), 0.96 (d, J=8.91 Hz, 3H), 1.11 (s, 3H), 3.03 (m, 1H), 3.52 (s, 3H), 5.48 (br, 1H), 5.70 (br, 1H), 7.58–8.61 (m, 16H), 9.16–9.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.2, 167.5, 167.0, 134.0, 133.9, 131.1, 131.0, 130.3, 130.2, 129.6, 129.4, 127.6, 127.4, 126.9, 126.1, 124.8, 124.6, 124.4, 124.1, 76.2, 71.5, 60.5, 51.4, 47.8, 45.6, 44.0, 41.5, 40.0, 38.7, 37.3, 35.4, 35.1, 34.8, 34.7, 31.7, 31.0, 30.7, 29.6, 29.0, 28.5, 27.4, 26.9, 25.9, 25.6, 24.5, 23.3, 22.8, 21.6, 17.9, 17.8, 17.2, 12.5; MALDI TOF HRMS: calcd for $C_{59}H_{57}N_3O_6$ $(M+H)^+$, 903.4247; found, 903.4218.

4.4. Methyl 3α-azide-7α,12α-di(1-pyrenebutanoyl)-5β-cholan-24-oate (8)

The crude product was chromatographed on silica gel (230–400 mesh) eluting first with 20% ethyl acetate/petroleum ether (60–80 °C) and then for the second time with pure dichloromethane to give the pure product (0.34 g, 35%): mp 90 °C; IR (KBr, cm^{-1}): 3442, 2953, 2865, 2089, 1727, 1638, 1456, 1384, 1251, 1182, 1094, 844, 716; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.75 (s, 3H), 0.81 (d, 3H), 0.94 (s, 3H), 3.10–3.28 (m, 4H), 3.57 (s, 3H), 5.02 (br, 1H), 5.17 (br, 1H), 7.68–8.19 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.7, 173.1, 173.0, 135.8, 135.7, 131.6, 131.1, 130.2, 130.1, 129.0, 128.9, 128.6, 127.7, 127.6, 127.4, 127.0, 126.1, 125.3, 125.2, 125.1, 125.0, 124.9, 123.5, 123.4, 75.6, 71.0, 60.9, 51.7, 47.8, 45.4, 43.7, 41.5, 38.2, 35.4, 35.0, 34.7, 34.6, 34.5, 33.0, 32.8, 31.6, 31.2, 31.0, 29.0, 27.5, 27.1, 27.0, 26.8, 25.6, 23.3, 22.8, 17.9, 12.5; MALDI TOF HRMS: calcd for $C_{65}H_{69}N_3O_6$, 987.5186; found, 987.5204.

4.5. General procedure for the synthesis of 9 and 10

Activated zinc powder (0.65 mg, 10 mmol) was added to a solution of **7** or **8** (0.5 mmol) in glacial acetic acid (10 mL). The mixture was stirred vigorously for 24 h. Acetic acid was then completely removed under reduced pressure by adding toluene for several times. The residue, acetate ammonium salt of **9** or **10**, was dissolved by saturated sodium chloride solution (10 mL). Basification of the solution by excessive triethylamine and extraction of it by ethyl acetate gave amine **9** or **10** as the pure product. After drying by sodium sulfate and removal of organic solvent, compound **9** or **10** was obtained.

4.6. Methyl 3α-amino-7α,12α-dipyrenylcarbonyl-5β-cholan-24-oate (9)

Compound **9** was obtained as yellow foam (0.44 g, 99%): mp 122–124 °C; IR (KBr, cm^{-1}): 3437, 2949, 2912, 2876, 1735, 1704, 1632, 1607, 1456, 1446, 1389, 1255, 1231, 1193, 1145, 1133, 1086, 849, 721; ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.54 (s, 3H), 5.47 (br, 1H), 5.68 (br, 1H), 7.26–8.56 (m, 16H), 9.24–9.30 (m, 2H); MALDI TOF HRMS: calcd for $C_{59}H_{59}NO_6$ $(M+H)^+$, 878.4420; found, 878.4405.

4.7. Methyl 3α-amino-7α,12α-di(1-pyrenebutanoyl)-5β-cholan-24-oate (10)

Compound **10** was obtained as yellow foam (0.43 g, 90%): mp 100–104 °C; IR (KBr, cm^{-1}): 3436, 2948, 2914, 2876, 1735, 1705, 1632, 1607, 1457, 1448, 1389, 1255, 1231, 1197, 1140, 1132, 1086, 846, 725; ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.12–3.30 (m, 4H), 3.48 (s, 3H), 4.86 (br, 1H), 5.05 (br, 1H), 7.61–8.08 (m, 18H); MALDI TOF HRMS: calcd for $C_{65}H_{71}NO_6$ $(M+H)^+$, 962.5359; found, 962.5392.

4.8. General procedure for the synthesis of 11 and 12

The mixture of **9** or **10** (0.5 mmol) and hydrazine (1.0 mL, large excess) monohydrate in a mixture solution of methanol/CH_2Cl_2 (10 mL, 2:1) was stirred under nitrogen at ambient temperature for 48 h. Then organic solvent and the excess of hydrazine were removed under reduced pressure. The residue was poured into 30 mL cold water and stirred for 10 min. After filtration, the solid was washed with large amount of cold water and dried in vacuum at 60 °C. The product was obtained as a yellow solid.

4.9. 1-Hydrazide 3α-amino-7α,12α-dipyrenylcarbonyl-5β-cholan-24-oate (11)

Compound **11** was obtained as a yellow solid in a 76% yield (0.33 g) and need no further purification for the next reaction: mp>166 °C (decomposed); IR (KBr, cm^{-1}): 3430, 2921, 2876, 1702, 1625, 1389, 1250, 1231, 1194, 1145, 1133, 1086, 849, 705; ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.72 (br, 4H), 5.46 (br, 1H), 5.67 (br, 1H), 6.55 (br, 1H), 7.60–8.55 (m, 16H), 9.24–9.30 (m, 2H); MALDI TOF

HRMS: calcd for $C_{58}H_{59}N_3O_5$ $(M+H)^+$, 878.4532; found, 878.4519.

4.10. 1-Hydrazide 3α-amino-7α,12α-di(1′-pyrenebutanoyl)-5β-cholan-24-oate (12)

Compound **12** was obtained as a yellow solid in a 80% yield (0.38 g) and need no further purification for the next reaction: mp>140 °C (decomposed); IR (KBr, cm^{-1}): 3418, 2933, 2864, 1722, 1645, 1622, 1456, 1379, 1249, 1183, 1143, 1016, 844, 705; ^1H NMR (270 MHz, $CDCl_3$): δ 3.26 (m, 4H), 3.70 (br, 4H), 4.97 (br, 1H), 5.14 (br, 1H), 6.35 (br, 1H), 7.72–8.19 (m, 18H); MALDI TOF HRMS: calcd for $C_{64}H_{71}N_3O_5$ $(M+H)^+$, 962.5471; found, 962.5495.

4.11. 1-[(4′-Trifluoromethylphenyl)thioureido]hydrazide 3α-[(4′-trifluoromethylphenyl)thioureido]-7α,12α-dipyrenylcarbonyl-5β-cholan-24-oate (1)

To a solution of **11** (0.26 g, 0.3 mmol) in dried CH_2Cl_2 (10 mL), 4-trifluoromethylphenylisocyanate (0.15 g, 0.7 mmol) was added and stirred at room temperature for 36 h under nitrogen. The reaction mixture was diluted with CH_2Cl_2. The organic solution was first washed by saturated brine and then dried by anhydrous sodium sulfate. Purification of the crude by preparative TLC plate (SiO_2) eluted by the solvent of ethyl acetate/dichloromethane (20:100) gave the pure product **1** as a yellow solid (0.20 g, 52%): mp 164–166 °C; IR (KBr, cm^{-1}): 3394, 2938, 2865, 1706, 1622, 1520, 1324, 1257, 1232, 1166, 1125, 1066, 850, 705; ^1H NMR (270 MHz, DMSO-d_6): δ 0.81 (d, J=8.1 Hz, 3H), 3.86 (m, 1H), 5.39 (br, 1H), 5.57 (br, H), 7.33–8.49 (m, 26H), 9.04–9.25 (m, 4H), 9.70 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 179.0, 170.1, 170.0, 148.5, 134.1, 133.6, 133.4, 133.2, 130.9, 130.5, 130.1, 130.0, 129.8, 129.7, 129.6, 128.3, 127.6, 127.3, 127.1, 1265.8, 126.7, 126.4, 125.2, 124.6, 124.0, 123.3, 123.0, 121.1, 116.6, 76.3, 72.2, 53.9, 47.9, 45.2, 43.6, 41.1, 40.1, 37.7, 35.4, 34.5, 34.1, 31.3, 30.1, 28.8, 26.8, 26.3, 25.3, 23.6, 22.8, 22.5, 20.3, 17.7, 17.0, 12.1; ESI TOF HRMS: calcd for $C_{74}H_{67}F_6N_5O_5S_2Na$ $(M+Na)^+$, 1306.4385; found, 1306.4436.

4.12. 1-[(4′-Trifluoromethylphenyl)thioureido]hydrazide 3α-[(4′-trifluoromethylphenyl)thioureido]-7α,12α-di(1′-pyrenebutanoyl)-5β-cholan-24-oate (2)

To a solution of **12** (0.29 g, 0.3 mmol) in dried CH_2Cl_2 (10 mL), 4-trifluoromethylphenylisocyanate (0.15 g, 0.7 mmol) was added and stirred at room temperature for 36 h under nitrogen. The reaction mixture was diluted with CH_2Cl_2. The organic solution was first washed by saturated brine and then dried by anhydrous sodium sulfate. Purification of the crude by preparative TLC plate (SiO_2) eluted by the solvent of ethyl acetate/dichloromethane (10:100) gave the pure product **2** as a yellow solid (0.20 g, 29%): mp 138–140 °C; IR (KBr, cm^{-1}): 3430, 3274, 2953, 2865, 1720, 1617, 1549, 1524, 1324, 1249, 1165, 1122, 1067, 850, 724; ^1H NMR (400 MHz, $CDCl_3$): δ 0.69 (s, 3H), 0.78 (d, J=4.1 Hz, 3H), 0.96 (s, 3H), 3.0–3.26 (m, 4H), 4.00 (br, 1H), 5.06 (br, 1H), 5.19 (br, 1H), 6.49 (br, 1H), 6.61 (br, 1H), 7.00 (br, 1H), 7.48–8.24 (m, 18H), 8.87 (br, 1H), 9.82 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 182.9, 178.9, 172.6, 172.3, 170.5, 140.9, 139.6, 136.5, 135.0, 134.8, 133.0, 131.2, 131.1, 131.0, 129.9, 129.8, 128.5, 127.7, 127.6, 127.3, 127.2, 127.0, 126.8, 126.7, 126.5, 126.1, 126.0, 125.2, 125.0, 124.9, 124.8, 124.7, 124.5, 124.3, 122.8, 116.9, 76.7, 75.4, 55.1, 47.3, 45.2, 43.4, 41.2, 37.9, 35.6, 35.2, 34.6, 34.5, 34.1, 32.3, 31.5, 31.1, 29.7, 29.0, 27.5, 27.2, 26.4, 25.4, 22.9, 22.6, 17.6, 12.2; MALDI TOF HRMS: calcd for $C_{80}H_{79}F_6N_5O_5S_2$ $(M+H)^+$, 1368.5505; found, 1368.5400.

4.13. Methyl 3α-acetyl-7α,12α-dipyrenylcarbonyl-5β-cholan-24-oate (3)

To a mixture solution of methyl 3α-acetyl-7α,12α-dihydroxy-5β-cholan-24-oate (0.46 g, 1 mmol) in xylene/CH_2Cl_2 (10:1, 5 mL) were added calcium hydride (0.63 g, 15 mmol) and benzyltriethylammonium chloride (0.01 g, 0.04 mmol), and the mixture was refluxed for 10 min under a nitrogen atmosphere. To the refluxing solution was added a solution of freshly prepared 1-pyrenoyl chloride (0.79 g, 3 mmol) in xylene (10 mL) and refluxed for 24 h. The reaction mixture was filtered under reduced pressure, diluted with ethyl acetate, and washed with aq $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed. The crude product was chromatographed on silica gel (230–400 mesh) eluting first with 10% ethyl acetate/petroleum ether (60–80 °C) and then for the second time with pure dichloromethane to give the pure product (0.25 g, 26%): mp 114–116 °C; IR (KBr, cm^{-1}): 3446, 3042, 2932, 2873, 1735, 1705, 1559, 1449, 1393, 1254, 1231, 1145, 1133, 1087, 1045, 848, 712; ^1H NMR (270 MHz, $CDCl_3$): δ 0.85 (s, 3H), 1.01 (d, J=6.48 Hz, 3H), 1.11 (s, 3H), 3.54 (s, 3H), 4.55 (m, 1H), 5.47 (br, 1H), 5.72 (br, 1H), 7.26–8.53 (m, 16H), 9.20–9.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.4, 170.4, 168.2, 168.0, 167.5, 133.9, 133.7, 133.5, 130.9, 130.8, 130.7, 130.2, 130.0, 129.5, 129.4, 129.2, 129.1, 128.9, 128.7, 127.6, 127.4, 127.2, 127.1, 127.0, 126.9, 126.8, 126.4, 126.3, 126.2, 126.0, 125.9, 125.4, 125.0, 124.8, 124.6, 124.4, 124.1, 123.7, 74.8, 74.3, 73.5, 72.0, 71.8, 68.2, 51.4, 47.9, 47.8, 46.7, 45.6, 44.0, 41.2, 41.0, 38.7, 34.8, 34.7, 34.6, 31.6, 31.5, 31.0, 30.7, 29.7, 28.2, 27.2, 26.9, 26.7, 25.9, 25.8, 23.2, 22.5, 22.4, 21.1, 17.8, 12.4; MALDI TOF HRMS: calcd for $C_{61}H_{60}O_8Na$ $(M+Na)^+$, 943.418; found, 943.4147.

4.14. Binding experiments

All dicarboxylate anions were obtained from the respective dicarboxylic acid treated with 2.0 equiv of tetrabutylammonium hydroxide in CH_3OH and dried in vacuum at 60 °C for over night. The structures of these guest anions were verified by ^1H NMR.

All the host compounds **1**, **2**, and **3** were prepared as $2\sim5\times10^{-4}$ mol/L stock solutions in acetonitrile. All anions used in this report were in the form of tetrabutylammonium salt. They were prepared to approximate 0.01 mol/L and $2\sim5\times10^{-3}$ mol/L of stock solutions in acetonitrile. The work solutions were prepared by adding different volumes of anion stock solution to a series of test tubes followed by dilution to 5 mL by acetonitrile. Then, the same amount of stock solution of the host compound was added into each of the test tube. After shaking for several minutes, the work solutions could be measured immediately.

Association constants (1:1) of **1** and **2** with anions are calculated by non-linear least square curve fitting using the following equation in origin 7.0:

$$X = X_0 + 0.5\Delta\varepsilon\left\{c_H + c_G + 1/K_{ass} - \left[(c_H + c_G + 1/K_{ass})^2 - 4c_H c_G\right]^{1/2}\right\}$$

Association constants (1:2) of **1** and **2** with anions are calculated by Benesi–Hildebrand equation and linearly fitted in origin 7.0:

$$\log[(X - X_0)/(X_\infty - X)] = n\log[G] + \log K_a$$

X_0: fluorescent intensity or absorption of host without anions; X: fluorescent intensity or absorption reaching a limitation by adding excessive anions; c_H: concentration of host molecule; c_G: concentration of anions added.

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Supplementary data

Synthesis and characterization spectra of **1** and **2**, the fluorometric titration experiment and the ^{1}H NMR study, the fluorescence intensity of **1** and **2** with different concentration in CH_3CN, Job plot of **1** and **2** with dicarboxylates. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.042.

References and notes

1. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646; (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (c) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev.* **2003**, *240*, 3–15; (d) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, NY, 1997.
2. (a) Shin-ichi, S.; Masaaki, M.; Koichiro, N.; Yoshito, T. *J. Org. Chem.* **2000**, *65*, 275–289; (b) Sessler, J. L.; Davis, J. M. *Acc. Chem. Res.* **2001**, *34*, 989–997; (c) Amendola, V.; Fabbrizzi, L.; Monzani, E. *Chem.—Eur. J.* **2004**, *10*, 76–82; (d) Kristln, B. J. *Acc. Chem. Res.* **2005**, *38*, 671–678; (e) Myiaji, H.; Kim, K. H.; Sim, E. K.; Lee, C. K.; Cho, W. S.; Sessler, J. L.; Lee, C. H. *J. Am. Chem. Soc.* **2005**, *127*, 12510–12512; (f) Sessler, J. L.; Cho, W.-S.; Gross, D. E.; Shriver, D. E.; Lynch, V. M.; Marquez, M. *J. Org. Chem.* **2005**, *70*, 5982–5986; (g) Chmielewski, M. J.; Jurczak, J. *Chem.—Eur. J.* **2005**, *11*, 6080–6094; (h) Juewen, L.; Yi, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 90–94; (i) Massimiliano, T.; Salvatore, S.; Andrew, P. W.; Francisco, M. R. *J. Org. Chem.* **2006**, *71*, 744–753; (j) Nieto, S.; Pérez, J.; Riera, L.; Riera, V.; Miguel, D. *Chem.—Eur. J.* **2006**, *12*, 2244–2251.
3. Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; Wiley: New York, NY, 1995.
4. (a) Nohta, H.; Sonoda, J.; Yoshida, H.; Satozono, H.; Ishida, J.; Yamaguchi, M. *J. Chromatogr., A* **2003**, *1010*, 37–44; (b) Miao, H.; Rubakhin, S. S.; Sweedler, J. V. *Anal. Chem.* **2005**, *77*, 7190–7194.
5. (a) Cordek, J.; Wang, X.; Tan, W. *Anal. Chem.* **1999**, *71*, 1529–1533; (b) Rossi, S.; Kyne, G. M.; Turner, D. L.; Wells, N. J.; Kilburn, J. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4233–4236.
6. (a) Fabbrizzi, L.; Licchelli, M.; Rabaioli, M. G.; Taglietai, A. *Coord. Chem. Rev.* **2000**, *205*, 85–108; (b) Amendola, V.; Boiocchi, M.; Fabbrizzi, L.; Palchetti, A. *Chem.—Eur. J.* **2005**, *11*, 5648–5660; (c) Qing, G.-Y.; He, Y.-B.; Zhao, Y.; Hu, C.-G.; Liu, S.-Y.; Yang, X. *Eur. J. Org. Chem.* **2006**, 1574–1580.
7. (a) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419–4476; (b) Pu, L. *Chem. Rev.* **2004**, *104*, 1687–1716; (c) Vázquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; González-Noya, A. M.; Bermejo, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1962–1965; (d) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Tierney, J. *J. Org. Chem.* **2005**, *70*, 10875–10878; (e) Peng, X.; Wu, Y.; Tian, M.; Han, K. *J. Org. Chem.* **2005**, *70*, 10524–10531; (f) Ragusa, A.; Rossi, S.; Hayes, J. M.; Stein, M.; Kilburn, J. D. *Chem.–Eur. J.* **2005**, *11*, 5674–5688.
8. Hosseini, M. W.; Lehn, J.-M. *Helv. Chim. Acta* **1986**, *69*, 587–603.
9. (a) Lara, K. O.; Godoy-Alcántar, C.; Rivera, I. L.; Eliseev, A. V.; Yatsimirsky, A. K. *J. Phys. Org. Chem.* **2001**, *14*, 453–462; (b) Boiocchi, M.; Bonizzoni, M.; Fabbrizzi, L.; Piovani, G.; Taglietti, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3847–3852; (c) Bonizzoni, M.; Fabbrizzi, L.; Piovani, G.; Taglietti, A. *Tetrahedron* **2004**, *60*, 11159–11162.
10. Král, V.; Andrievsky, A.; Sessler, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 2953–2954.
11. Liu, S.-Y.; He, Y.-B.; Wu, J.-L.; Wei, L.-H.; Qin, H.-J.; Meng, L.-Z.; Hu, L. *Org. Biomol. Chem.* **2004**, *2*, 1582–1586.
12. Gunnlaugsson, T.; Davis, A. P. *Org. Lett.* **2002**, *4*, 2449–2452.
13. (a) Zeng, Z.-Y.; He, Y.-B.; Wu, J.-L.; Wei, L.-H.; Liu, X.; Meng, L.-Z.; Yang, X. *Eur. J. Org. Chem.* **2004**, 2888–2893; (b) Wu, J.-L.; He, Y.-B.; Zeng, Z.-Y.; Wei, L.-H.; Meng, Z.; Yang, T.-X. *Tetrahedron* **2004**, *60*, 4309–4314.
14. Mei, M.; Wu, S. *New J. Chem.* **2001**, *25*, 471–475.
15. (a) Davis, A. P.; Joos, J. B. *Coord. Chem. Rev.* **2003**, *240*, 143–156; (b) Lawless, L. J.; Blackburn, A. G.; Ayling, A. J.; Pérez-Payán, M.; Davis, A. P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1329–1341; (c) Vijayalakshmi, N.; Maitra, U. *Org. Lett.* **2005**, *7*, 2727–2730; (d) Sisson, A. L.; Clare, J. P.; Davis, A. P. *Chem. Commun.* **2005**, 5263–5265.
16. Liu, S.-Y.; Fang, L.; He, Y.-B.; Chan, W.-H.; Yeung, K.-T.; Cheng, Y.-K.; Yang, R.-H. *Org. Lett.* **2005**, *7*, 5825–5828.
17. (a) Birks, J. B. *Photophysics of Aromatic Molecules*; Wiley-Interscience: London, 1970; (b) Winnik, F. M. *Chem. Rev.* **1993**, *93*, 587–614; (c) Seiichi, N.; Yuichi, K.; Norio, T. *J. Am. Chem. Soc.* **1999**, *121*, 9463–9464; (d) Akimitsu, O.; Keiichiro, K.; Isao, S. *J. Am. Chem. Soc.* **2004**, *126*, 4820–4827; (e) Vyacheslav, V. F.; Erik, B. P. *J. Am. Chem. Soc.* **2005**, *127*, 14849–14858.
18. Potluri, V. K.; Maitra, U. *J. Org. Chem.* **2000**, *65*, 7764–7769.
19. Davis, A. P.; Pérez, P. M. N. *Synlett* **1999**, 991–993.
20. Lee, S. H.; Kim, S. H.; Kim, S. K.; Jung, J. H.; Kim, J. S. *J. Org. Chem.* **2005**, *70*, 9288–9295.

21. (a) Job, A. *Ann. De Chim. (Paris)* **1928**, *9*, 133–157; (b) Nishizawa, S.; Kato, R.; Hayashita, T.; Teramae, N. *Anal. Sci.* **1998**, *14*, 595–597.
22. Fang, L.; Chan, W.-H.; He, Y.-B.; Kwong, D. W. J.; Lee, A. W. M. *J. Org. Chem.* **2005**, *70*, 7640–7646.
23. Valeur, B.; Pouget, J.; Bourson, J. *J. Phys. Chem.* **1992**, *96*, 6545–6549.
24. (a) Bernard, V. *Molecular Fluorescence: Principles and Applications*; Wiley-VCH: Weinheim, Germany, 2002; (b) Wu, F. Y.; Li, Z.; Wen, Z. C.; Zhou, N.; Zhao, Y. F.; Jiang, Y. B. *Org. Lett.* **2002**, *4*, 3203–3205.
25. (a) Pocker, Y.; Ciula, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4728–4753; (b) Bourson, J.; Pouget, J.; Valeur, B. *J. Phys. Chem.* **1993**, *97*, 4552–4557.

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Hydrotalcites as catalysts for the Baeyer–Villiger oxidation of cyclic ketones with hydrogen peroxide/benzonitrile

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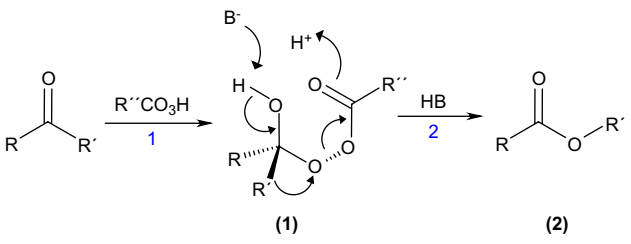
Abstract—Hydrotalcites (HTs) in variable Mg/Al ratios were used as catalysts for the Baeyer–Villiger (BV) oxidation of cyclic ketones with hydrogen peroxide. All HTs studied were found to be active in the BV oxidation of cyclohexanone, their activity increases with increasing Mg/Al ratio. The reaction, which was conducted under very mild conditions (viz. atmospheric pressure and a temperature of 70 °C), provided conversions above 70% with 100% selectivity only after 6 h. This outcome was found to require the presence of a nitrile in the reaction medium, so a mechanism involving adsorption of the nitrile and cyclohexanone onto the catalyst is proposed that is consistent with the experimental results. Based on the proposed mechanism, the presence of a surfactant should result in improved conversion and catalytic activity, as was indeed observed with sodium dodecylsulfate in the reaction medium. The best catalyst among those tested was used with other cyclic ketones and found to provide excellent conversion and selectivity results in most cases.

1. Introduction

Hydrotalcite-like compounds, also known as layered double hydroxides, have aroused much interest by virtue of their potential uses in various scientific fields such as organic synthesis.[1–3] The structure of these compounds is based on that of a natural mineral called hydrotalcite,[4] which is a magnesium-aluminum hydroxycarbonate of formula $Mg_6Al_2(OH)_{16}CO_3\cdot 4H_2O$ structurally similar to brucite except for the fact that some Mg^{2+} ions have been replaced with Al^{3+}; this results in the presence of layers bearing positive charge that is countered by carbonate ions in the interlayer spacing. Replacing the magnesium, aluminum or both cations with another metal, or the carbonate with another anion, allows a large family of compounds known as hydrotalcite-like compounds (HTs) or layered double hydroxides (LDHs) of formula $[M(II)_{1-x}M(III)_x(OH)_2]^{x+}(A^{n-})_{x/n}\cdot mH_2O$ to be obtained. In the formula, M(II) is a divalent cation such as Mg, Cu, Ni, Co, or Zn;[3] M(III) is a trivalent cation such as Al, Fe, Cr, V, Mn, Ga, or In;[3,5,6] A^{n-} is the charge-balancing anion, which can be organic or inorganic and widely variable in nature; and x=M(III)/[M(II)+M(III)].

In this work, we synthesized HTs in variable Mg/Al ratios for use as catalysts in the Baeyer–Villiger oxidation of cyclohexanone. This reaction was first employed in 1899 by Baeyer and Villiger to convert ketones into esters.[7] Since then, it has become a very important tool for organic synthesis, and been the subject of a number of books and of both dedicated[8–12] and general organic oxidation reviews.[13,14] Currently, the Baeyer–Villiger reaction involves the oxidation of ketones with organic peroxyacids or alkyl hydroperoxides to obtain esters (or lactones) or, alternatively, alcohol or acid derivatives. The reaction also includes the oxidation of aldehydes to the corresponding esters of formic acid or their hydrolysis products. The accepted mechanism for this process involves two steps (see Scheme 1), namely: addition of the peroxyacid to the carbonyl compound to form a Criegee adduct (**1**) and rearrangement of the adduct to the reaction end-product (**2**). The migration of group R' occurs in a concerted manner with the cleavage of the O–O bond. The rearrangement step is facilitated by the presence of bases, which helps to remove the hydroxyl proton from the Criegee



Scheme 1. General mechanism for the Baeyer–Villiger oxidation of ketones with organic peracids.

Keywords: Hydrotalcite; Baeyer–Villiger oxidation; Cyclic ketones; Hydrogen peroxide.
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intermediate. The Baeyer–Villiger oxidation of ketones provides a number of advantages such as: (a) a high tolerance to the presence of a variety of functional groups in the substrate (thus, peracids usually attack the carbonyl group in an unsaturated ketone as long as the double bond is not conjugated), (b) regiochemical selectivity control via the migration ability of various groups (with some compounds such as bicyclic systems, the oxygen insertion regioselectivity can be influenced by specific stereoelectronic factors, however), and (c) the ability to use a wide variety of oxidants.

Ti-silicalite (TS-1) was one of the catalysts that revolutionized the field of organic oxidations. This solid consists of a zeolite structure (silicalite) into which titanium is incorporated.[15] Its high oxidizing power lies in the ability of titanium metal sites to form Ti-peroxy species that can activate hydrogen peroxide in various oxidation reactions including epoxidations, ammonoxidations, and CH oxidations.[16,17] These catalysts have been further developed by inserting new oxidizing metals into zeolite structures, albeit with poorer results than those originally obtained with titanium. However, Corma et al. developed a catalyst consisting of Sn incorporated into a beta zeolite that has provided results comparable to those of TS-1 in processes involving the activation of hydrogen peroxide in some step.[18] In subsequent work,[19–24] Corma et al. conducted extensive research into Baeyer–Villiger oxidation reactions using their Sn-beta zeolite catalysts. Recently, they proposed a mechanism for the underlying process from a combination of theoretical and experimental data;[25] according to it, tin, which acts as an oxygen transfer agent, activates the carbonyl group in cyclohexanone.

As noted earlier, in this work we tested various HT-based heterogeneous catalysts in combination with hydrogen peroxide as oxidant in the Baeyer–Villiger oxidation reaction. In previous work, our group found HTs to be effective catalysts for reactions requiring the presence of a base (e.g., the epoxidation of limonene with hydrogen peroxide[26,27] or the Meerwein–Ponndorf–Verley reaction).[28–32] Other authors have also previously used HTs as catalysts for the BV reaction, albeit with a mixture of molecular oxygen and benzaldehyde[33,34] or a peroxyacid[35] as oxidant. Also, a hydrotalcite-supported SnO_2 catalyst was found to effect the BV reaction with hydrogen peroxide as oxidant in the presence of a nitrile as oxygen transfer agent.[36]

2. Results and discussion

2.1. Characterization of catalysts

2.1.1. Elemental analysis. Table 1 shows the chemical composition and empirical formula of each HT used as determined by ICP-MS. The experimentally determined values were quite consistent with their theoretical counterparts, the differences falling within the experimental error range.

2.1.2. XRD results. Figure 1 shows the XRD patterns of the studied HTs. As can be seen, they exhibit the typical signals for hydrotalcite,[37] with tall, sharp, symmetric peaks for the planes (003), (006), (110), and (113), and broad, somewhat less symmetric peaks for the planes (009), (015), and (016), all of which are typical of the layered clay minerals.

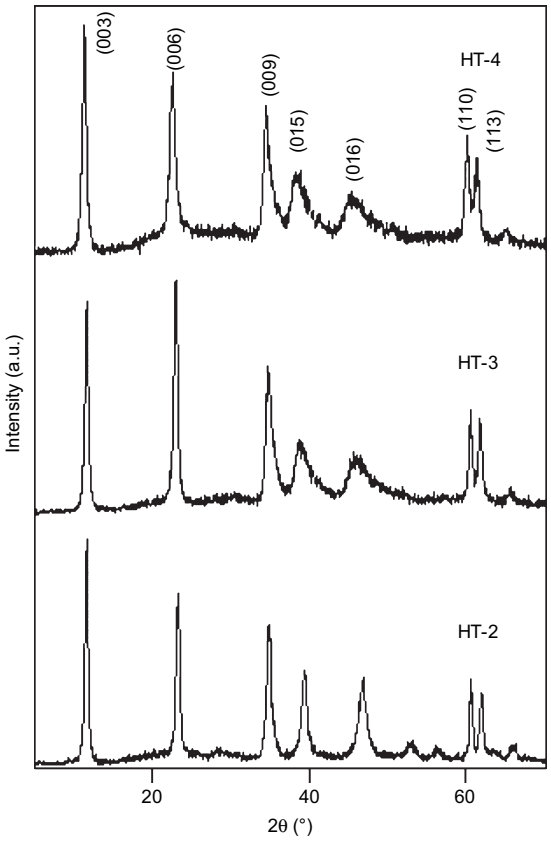


Figure 1. XRD patterns for the HTs synthesized.

Table 1 gives the lattice parameters a and c as determined from the XRD patterns [$a=2\times d_{(110)}$ and $c=3\times d_{(003)}$]. Parameter a can be likened to the distance between two adjacent ions in a brucite-like layer; based on Table 1, a increased with decreasing metal ratio x [x=Al/(Mg+Al)] or increasing Mg/Al ratio. These results are consistent with an increase in the proportion of trivalent cation (aluminum)

Table 1. Metal ratios, chemical formulae, and lattice parameters for the HTs

Catalyst	x_{ther}[a]	x_{exp}[b]	Chemical formulae[c]	a[d] (Å)	c[d] (Å)
HT-2	0.33	0.37	$Mg_{0.631}Al_{0.369}(OH)_2(CO_3)_{0.185}\cdot 0.65H_2O$	3.046	22.860
HT-3	0.25	0.29	$Mg_{0.710}Al_{0.290}(OH)_2(CO_3)_{0.145}\cdot 0.61H_2O$	3.052	22.878
HT-4	0.20	0.22	$Mg_{0.779}Al_{0.211}(OH)_2(CO_3)_{0.110}\cdot 0.60H_2O$	3.068	23.421

[a] Theoretical metal ratio [x=Al/(Mg+Al)].
[b] Experimental metal ratio as determined by ICP-MS.
[c] Crystallization water was quantified by thermogravimetric analysis.
[d] Lattice parameters.

increasing in the distance between cations in the brucite-like layers.[38] In addition, parameter c increased with decreasing metal ratio x; although its relationship to such a ratio is unclear, it usually exhibits the observed trend.[38]

2.1.3. Textural properties. Table 2 lists the specific surface area, average pore diameter, and pore volume of the HTs, all of which fall within the usual ranges for this type of solid.

Table 2. Specific surface area, pore volume, and average pore diameter of the synthesized solids and their calcination products

Catalyst	S_{BET} (m^2/g)[a]	V_p (mL/g)[b]	d_p (Å)[c]
HT-2	65.2	166.9	0.59
HT-3	72.4	169.8	0.62
HT-4	75.8	158.8	0.74

[a] Specific surface area.
[b] Pore volume.
[c] Average pore diameter.

The nitrogen adsorption–desorption isotherms were similar for the three HTs. By way of example, Figure 2 shows that for solid HT-4. All isotherms were of type II in the IUPAC classification[39] and exhibited a hysteresis cycle closing at ca. 0.8 (P/P_0) of type H3 in the de Boer classification;[40] therefore, the samples were mesoporous or macroporous and contained no micropores. The fact that the adsorption and desorption branches of the isotherms are nearly parallel suggests the presence of pores of regular geometry; also, the high slopes of the desorption branch suggest that the pore dimensions span a narrow range.[41]

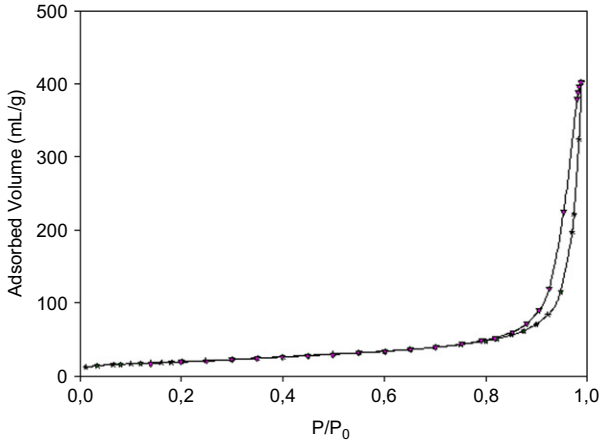


Figure 2. Nitrogen adsorption–desorption for sample HT-4.

2.2. Baeyer–Villiger oxidation

2.2.1. Catalytic activity. The Baeyer–Villiger oxidation under the reaction conditions used is a complex process as regards both the reactants, the catalysts and the resulting products. It is thus crucial to determine the role played by each reactant as a function of its nature and concentration. This entails conducting a series of kinetic tests ensuring a constant behavior in the reactants with time. The overall process can be fitted to a general kinetic equation such as

$$v = k[\text{cyclohexanone}][H_2O_2][\text{benzonitrile}]$$

which contains a concentration term for each reactant. This involves the unsurmountable difficulty of mixing arising from the low aqueous solubility of the organic products over some concentration ranges. We thus chose to conduct our experiments under reaction conditions where the orders with respect to H_2O_2 and the benzonitrile used would be zero, so the overall kinetic equation could simplify to

$$v = k'[\text{cyclohexanone}]$$

and the results obtained would only be a consequence of changes in the cyclohexanone conversion. Consequently, the experiments described below were carried out in excess H_2O_2 and benzonitrile relative to the stoichiometric amounts.

Catalytic activity experiments were preceded by blank tests intended to ascertain that the reaction developed to no appreciable extent in the absence of the catalyst and that the presence of a nitrile was essential. As can be seen from Table 3 (entries 7 and 8) the reaction did not develop in the absence of catalyst or benzonitrile.

Table 3. Conversion to ε-caprolactone in the Baeyer–Villiger oxidation of cyclohexanone

Entry	Catalyst	Conversion (%)[a]	t (h)[b]	r_a (mmol/h)[c]
1	HT-2	71	6	6.6
2	HT-3	74	6	7.1
3	HT-4	88	6	8.0
4	HT-4-reused-1	89	6	7.8
5	HT-4-reused-2	87	6	8.0
6	HT-4-reused-3	88	6	7.9
7	Without catalyst	0	24	0
8	Without benzonitrile	0	24	0

[a] Conversion to ε-caprolactone.
[b] Reaction time.
[c] Initial catalytic activity (mmol of ε-caprolactone/h).

Table 3 lists the conversion values obtained at different reaction times and the initial catalytic activity. The latter was determined from the slope of the temporal variation of the conversion to ε-caprolactone, which was linear at low conversion levels. Based on the results, the initial catalytic activity of the studied solids increased with increasing Mg/Al ratio.

2.2.2. Catalyst reuse. Calcining a hydrotalcite above 350 °C destroys the layered structure by conversion into a mixed oxide $Mg(Al)O_x$.[5] However, the hydrotalcite structure can be recovered from solids calcined at 400–800 °C. We thus exploited this memory effect to reuse the catalyst. For this purpose, the solid was calcined at 450 °C and treated with a sodium carbonate solution to recover the layered structure

following filtration of the reaction mixture. Based on the catalytic activity and conversion results obtained (Table 3), the catalyst exhibited no appreciable loss of activity after three reuses.

2.2.3. Mechanism of the process. Scheme 2 shows the proposed mechanism for the Baeyer–Villiger oxidation of ketones over HT catalysts. The process takes place in two steps. In the first, hydrogen peroxide attacks a Brönsted basic site on the catalyst surface to form a hydroperoxide species that subsequently attacks benzonitrile to give a peroxycarboximidic acid intermediate. This step is similar to that generally accepted for the epoxidation of alkenes with hydrogen peroxide over basic catalysts in the presence of nitriles or amides.[28,42] In the second step, the intermediate attacks the ketone, adsorbed at a Lewis acid site in the catalyst, to form an intermediate equivalent to the Criegee adduct in homogeneous catalysis processes that subsequently undergoes rearrangement to the final lactone. Corma et al.[18] reported a similar mechanism for the Baeyer–Villiger reaction with hydrogen peroxide over Sn-beta zeolite catalysts, where the carbonyl compound was adsorbed at Sn acid sites. These authors confirmed their mechanism via tests involving ^{18}O isotopic labeling, IR spectroscopy, and GC–MS and theoretical studies.[25]

If the proposed mechanism is accepted then the Baeyer–Villiger oxidation occurs at the interface between the organic and aqueous phases in the reaction medium, cyclohexanone and benzonitrile being in the organic phase, and hydrogen peroxide and the catalyst in the aqueous phase. Accordingly, the presence of a surfactant should expedite the reaction by both increasing the contact surface area between the two phases, and favoring the transfer of a lipophilic ketone from the organic phase to the interface. In order to confirm these assumptions, we conducted the reaction under the same conditions except for the presence of an amount of 0.6 mmol of surfactant in the medium. Both sodium dodecylsulfate (DS) and dodecylbenzenesulfonate (DBS) resulted in improved conversion and catalytic activity while preserving 100% selectivity. Figure 3 illustrates the favorable effect of the addition of a surfactant on the reaction rate; as can be seen, DS provided better results than DBS.

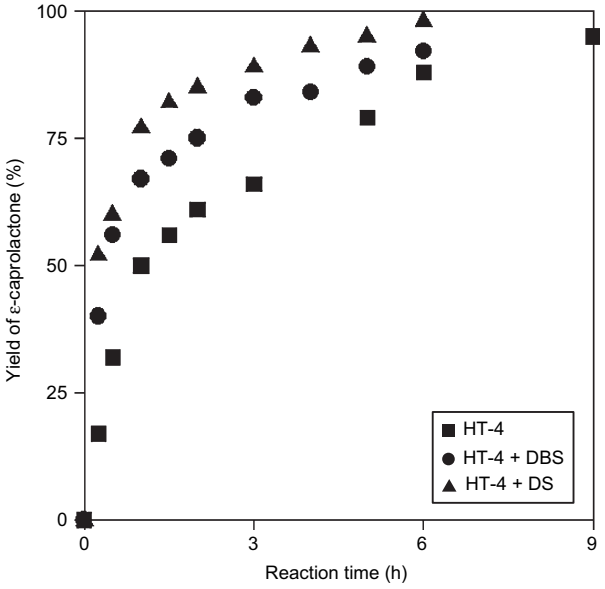
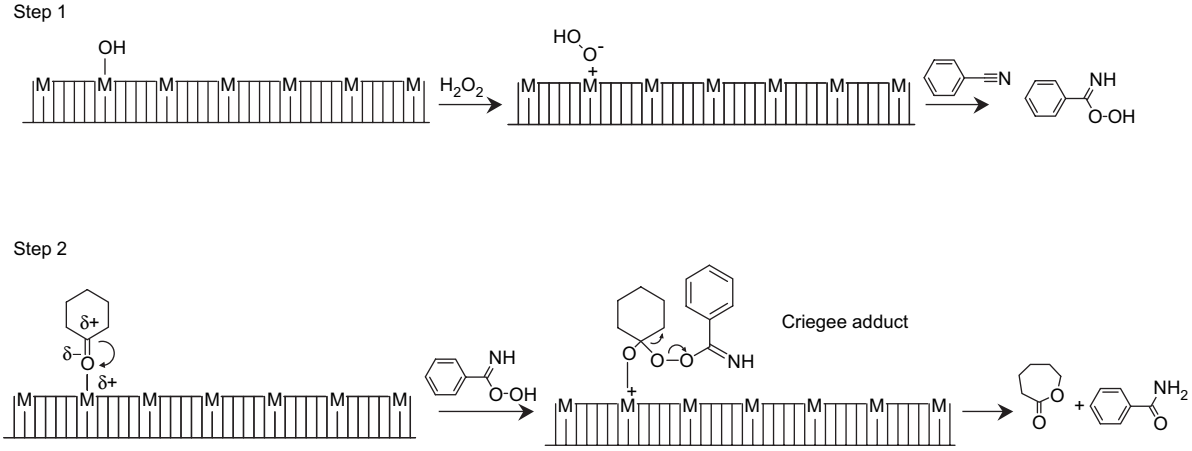


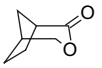
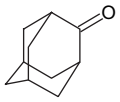
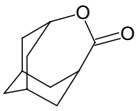
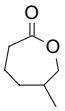
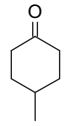
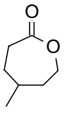
Figure 3. Reaction profile of the Baeyer–Villiger oxidation of cyclohexanone catalyzed with HT-4 with and without surfactants. Reaction conditions: cyclohexanone (12 mmol), benzonitrile (98 mmol), catalyst HT-4 (250 mg), 30% H_2O_2 (4 mequiv), surfactant (0.6 mmol), T=70 °C.

2.2.4. Oxidation of other cyclic ketones. The best catalyst among those studied was tested on other cyclic ketones in order to assess its efficiency. As can be seen in Table 4, the conversion after 6 h of reaction was always equal or close to 100%. With substituted methylcyclohexanones, the initial catalytic activity decreased in the sequence from that with the methyl group at position 4 to that with the group at position 2. These results are consistent with the proposed mechanism. In fact, the presence of a methyl substituent in cyclohexanone must hinder the adsorption of the catalyst and hence the formation of the Criegee adduct; because position 2 was the most sterically hindered, the corresponding methylcyclohexanone was the one that exhibits the lowest catalytic activity values among the three. Similar arguments can be used with adamantanone and norcamphor. Also, the fact that 2- and 3-methylcyclohexanones exhibited less than 100% selectivity can be ascribed to their asymmetry



Scheme 2. Proposed mechanism for the Baeyer–Villiger oxidation of cyclohexanone over HTs.

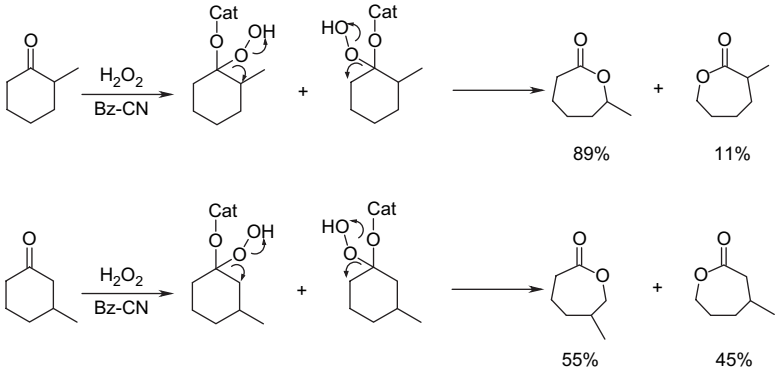
Table 4. Conversion obtained in the Baeyer–Villiger oxidation of various saturated cyclic ketones with hydrogen peroxide over solid HT-4 as catalyst

Entry	Substrate	Product	Conversion (%)[a]	Selectivity (%)[b]	t (h)[c]	r_a (mmol/h)[d]
1			100	100	6	25.1
2			100	100	6	16.1
3			89	100	6	11.8
4			90	89	6	12.8
5			96	55	6	16.7
6			95	100	6	17.8

[a] Conversion to lactone.
[b] Selectivity to lactone.
[c] Reaction time.
[d] Initial catalytic activity (mmol of ε-caprolactone/h).

allowing the formation of two different lactones. With 2-methylcyclohexanone, the selectivity for the desired product (entry 4 in Table 4) was close to 90% by virtue of the migrating ability being more favorable in a tertiary carbon than in a secondary one. With 3-methylcyclohexanone (entry 5 in Table 4), however, the selectivity was close to 50% by effect of the migrating ability of the two methylene groups in α with respect to the carbonyl carbon being similar. Scheme 3 is consistent with the previous reasoning.

ε-caprolactone. Their catalytic activity was found to increase with increasing magnesium content in the solid. These results are consistent with a mechanism involving the adsorption of hydrogen peroxide at a Brönsted basic site in the catalyst to form a peroxycarboximidic acid intermediate with benzonitrile that effects the transfer of oxygen to cyclohexanone adsorbed at a Lewis acid site in the catalyst. The solids were found to retain their catalytic activity after three reuses. Based on the proposed mechanism, the



Scheme 3. Criegee adducts proposed as intermediates in the Baeyer–Villiger oxidation of 2- and 3-methylcyclohexanones.

3. Conclusions

We synthesized hydrotalcite-like compounds in variable Mg/Al ratios and used them in the Baeyer–Villiger oxidation of cyclohexanone with hydrogen peroxide, where they exhibited good catalytic activity and selectivity toward presence of a surfactant in the reaction medium should increase the conversion. This was indeed the case with sodium dodecylbenzenesulfonate and, especially, sodium dodecylsulfate. Finally, the best catalyst among those studied also proved effective in the oxidation of other cyclic ketones, with excellent conversion and selectivity results.

4. Experimental

4.1. General

$Mg(NO_3)_2 \cdot 6H_2O$, $Al(NO_3)_3 \cdot 9H_2O$, and H_2O_2 (about 30%) were purchased from Panreac. Cyclic ketones, nitriles, and surfactants were purchased from Aldrich and used without further purification. All of the oxidation products were identified by mass spectrometry.

4.1.1. General procedure for the preparation of hydrotalcite-like compounds. The HTs were prepared from solutions of $Mg(NO_3)_2 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$ in Mg(II)/Al(III) ratio=2, 3, and 4 using a coprecipitation method described elsewhere.[5] In a typical synthetic run, a solution containing 0.3 mol of $Mg(NO_3)_2 \cdot 6H_2O$ and 0.15 mol of $Al(NO_3)_3 \cdot 9H_2O$ in 250 mL of de-ionized water was used. This solution was slowly dropped over 500 mL of Na_2CO_3 solution at pH 10 at 60 °C under vigorous stirring. The pH was kept constant by adding appropriate volumes of 1 M NaOH during precipitation. The suspension thus obtained was kept at 80 °C for 24 h, after which the solid was filtered and washed with 2 L of de-ionized water. The HTs with Mg(II)/Al(III) ratios=3 and 4 were obtained by following the same procedure, using appropriate amounts of the Mg(II) and Al(III) nitrates.

The HTs thus prepared were ion-exchanged with carbonate to remove ions intercalated between layers. The procedure involved suspending the solids in a solution containing 0.345 g of Na_2CO_3 in 50 mL of bidistilled, de-ionized water per gram of HT at 100 °C for 2 h. Then, each solid was filtered off in vacuo and washed with 200 mL of bidistilled, de-ionized water. The HTs thus obtained were subjected to a second ion-exchange operation under the same conditions. The exchanged HT solids were named HT-2, HT-3, and HT-4, indicating a Mg/Al ratio=2, 3, and 4, respectively.

4.1.2. Experimental techniques. The HTs obtained were characterized by using various instrumental techniques.

The metal contents in the catalysts were determined by inductively coupled plasma-mass spectrometry on a Perkin–Elmer ICP-MS instrument under standard conditions.

X-ray diffraction (XRD) analysis was performed in all catalysts in order to check for crystallinity. Powder patterns were recorded on a Siemens D-5000 diffractometer using Cu Kα radiation. Scans were performed over the 2θ range from 5 to 70°, using a resolution of 0.02° and a count time of 2 s at each point.

Thermogravimetric analysis was performed on a Setaram Setsys 12 instrument by heating in an argon atmosphere from 25 to 800 °C at a 10 °C/min rate.

BET surface areas, pore diameter, and pore volumes were calculated from nitrogen adsorption–desorption isotherms that were obtained at −196 °C using a Micromeritics ASAP 2010 instrument. Samples were outgassed in vacuo at 100 °C for 12 h prior to use.

4.1.3. General procedure for the Baeyer–Villiger oxidation with hydrotalcites. Baeyer–Villiger oxidations runs were performed at 70 °C in a two-mouthed flask containing 12 mmol of cyclohexanone, 98 mmol of benzonitrile, 4 mequiv of hydrogen peroxide and 250 mg of catalyst. One of the flasks' mouth was fitted with a reflux condenser and the other was used for sampling at regular intervals. The system was shaken throughout the process. Products were identified from their retention times as measured by GC–MS analysis on an HP 5890 GC instrument furnished with a Supelcowax 30 m×0.32 mm column and an HP 5971 MSD instrument.

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References and notes

1. Vaccari, A. *Appl. Clay Sci.* **1999**, *14*, 161–198.
2. Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *Catal. Rev.—Sci. Eng.* **2001**, *43*, 443–488.
3. Cavanni, F.; Trifiro, F.; Vaccari, A. *Catal. Today* **1991**, *2*, 173–301.
4. Miyata, S. *Clays Clay Miner.* **1975**, *23*, 369–375.
5. Aramendia, M. A.; Avilés, Y.; Borau, V.; Luque, J. M.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *J. Mater. Chem.* **1999**, *9*, 1603–1607.
6. Aramendia, M. A.; Borau, V.; Jimenez, C.; Luque, J. M.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Mater. Lett.* **2000**, *43*, 118–121.
7. Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625–3627.
8. Hassal, C. H. *Org. React.* **1957**, *9*, 73–74.
9. Krow, G. R. *Org. React.* **1993**, *42*, 251–252.
10. Krow, G. R. *Tetrahedron* **1981**, *37*, 2697–2702.
11. Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198–1209.
12. Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737–750.
13. Plesnicar, B. *Oxidation in Organic Chemistry*; Trahanosky, W. S., Ed.; Academic: New York, NY, 1978; p 254.
14. Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990; p 186.
15. Taramasso, M.; Perego, G.; Notari, B. U.S. Patent 4,410,501, 1983.
16. Corma, A.; García, H. *Chem. Rev.* **2002**, *102*, 3837–3892.
17. Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307–4365.
18. Corma, A.; Nemeth, L. T.; Renz, M.; Valencia, S. *Nature* **2001**, *412*, 423–425.
19. Renz, M.; Blasco, T.; Corma, A.; Fornés, V.; Jensen, R.; Nemeth, L. *Chem.—Eur. J.* **2002**, *8*, 4708–4717.
20. Corma, A.; Navarro, M. T.; Renz, M. *J. Catal.* **2003**, *219*, 242–246.
21. Corma, A.; Fornés, V.; Iborra, S.; Mifsud, M.; Renz, M. *J. Catal.* **2004**, *221*, 67–76.
22. Corma, A.; Iborra, S.; Mifsud, M.; Renz, M.; Susarte, M. *Adv. Synth. Catal.* **2004**, *346*, 257–262.
23. Boronat, M.; Concepción, P.; Corma, A.; Renz, M.; Valencia, S. *J. Catal.* **2005**, *234*, 111–118.

24. Corma, A.; Iborra, S.; Mifsud, M.; Renz, M. *J. Catal.* **2005**, *234*, 96–100.
25. Boronat, M.; Corma, A.; Renz, M.; Sastre, G.; Viruela, P. M. *Chem.—Eur. J.* **2005**, *11*, 6905–6915.
26. Aramendia, M. A.; Borau, V.; Jiménez, C.; Luque, J. M.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Appl. Catal., A: Gen.* **2001**, *216*, 257–265.
27. Aramendia, M. A.; Borau, V.; Jiménez, C.; Luque, J. M.; Marinas, J. M.; Romero, F. J.; Ruiz, J. R.; Urbano, F. J. *Stud. Surf. Sci. Catal.* **2000**, *130*, 1667–1672.
28. Aramendia, M. A.; Borau, V.; Jiménez, C.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Appl. Catal., A: Gen.* **2001**, *206*, 95–101.
29. Aramendia, M. A.; Borau, V.; Jiménez, C.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *J. Mol. Catal., A: Chem.* **2001**, *171*, 153–158.
30. Aramendia, M. A.; Borau, V.; Jiménez, C.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Appl. Catal., A: Gen.* **2003**, *255*, 301–308.
31. Ruiz, J. R.; Jiménez-Sanchidrián, C.; Hidalgo, J. M.; Marinas, J. M. *J. Mol. Catal., A: Chem.* **2006**, *246*, 190–195.
32. Jiménez-Sanchidrián, C.; Hidalgo, J. M.; Ruiz, J. R. *Appl. Catal., A: Gen.* **2006**, *303*, 23–28.
33. Kaneda, K.; Ueno, S. *ACS Symp. Ser.* **1996**, *638*, 300–318.
34. Ueno, S.; Ebitani, K.; Ookubo, A.; Kaneda, K. *Appl. Surf. Sci.* **1997**, *121–122*, 366–371.
35. Kaneda, K.; Yamashita, T. *Tetrahedron Lett.* **1996**, *37*, 4555–4558.
36. Pillai, U. R.; Sahle-Demessie, E. *J. Mol. Catal., A: Chem.* **2003**, *191*, 93–98.
37. JCPDS X-ray Powder Diffraction File no. 22-700, 1986.
38. Brindley, G. W.; Kikkawa, K. *Neues Jahrb. Miner. Monatsh.* **1967**, 137–141.
39. Sing, K. S. W.; Everett, D. H.; Haul, R. A. W.; Moscou, L.; Pierotti, R.; Rouquerol, J.; Sieminiewska, J. *Pure Appl. Chem.* **1985**, *57*, 69–74.
40. Greegs, S. J.; Sing, K. S. W. *Adsorption Surface Area and Porosity*; Academic: New York, NY, 1967.
41. Malherbe, F.; Forano, C.; Besse, J. P. *Microporous Mater.* **1997**, *10*, 67–84.
42. Yamaguchi, K.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **1999**, *64*, 2966–2968.

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Synthesis and structural study of tetrahydroindazolones

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Abstract—Multinuclear magnetic resonance spectroscopy allowed us to characterize four 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one derivatives (**1**–**4**) and establish the most stable tautomer in each case. The crystal structure of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) (orthorhombic space group *P*2(1)2(1)2(1), *a*=10.1243(8), *b*=21.526(2), *c*=24.992(2) Å, *Z*=4, 293 K) presents two different trimers, bonded through N–H···N hydrogen bonds involving tautomers 1*H* and 2*H*. In crystalline 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) (monoclinic space group *P*2(1)/*c*, *a*=5.9827(7), *b*=16.494(2), *c*=11.012(1) Å, *β*=93.464(2)°, *Z*=4, 293 K) only tautomer 2*H* exists forming a hydrogen-bonded network through the 4-oxo group and a water molecule.

1. Introduction

The main difference between pyrazoles **I** and their benzo derivatives, indazoles **II** (Fig. 1) is related to their annular tautomerism.[1] In pyrazoles **I**, although the tautomeric equilibrium constant depends on the nature of R^3 and R^5, it is always not very different from 1. Substituent R^4 (symmetric with regard to N1 and N2) exerts its effect through interactions with R^3 and R^5. In the case of indazoles **II**, the aromaticity of the benzene ring strongly favors the N(H)1 tautomer and only in very special cases tautomer N(H)2 becomes stable.[2]

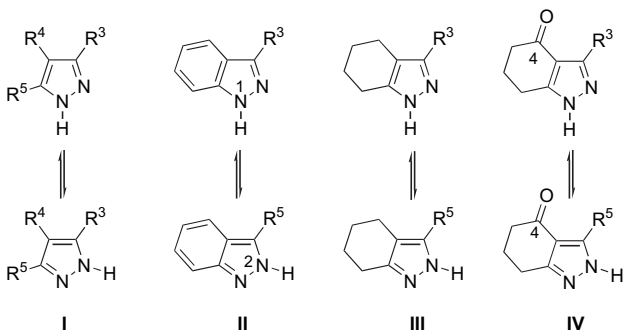

Figure 1. Structural relationships between derivatives **I**–**IV**.

If the six-membered ring is saturated, the resulting 4,5,6,7-tetrahydroindazoles **III** become again like pyrazoles [3(5),4-tetramethylenepyrazoles], both tautomers being again of similar energy.[3] The compounds that interest us now are 4-oxo derivatives **IV** of tetrahydroindazoles and therefore it is expected that, in what annular tautomerism is concerned, both tautomers would be of comparable stability.

Both pyrazoles[4,5] and indazoles[6,7] are frequently found in medicinal chemistry. Compounds **IV** have a structure intermediate between **II** and **III** because, even if the 4-hydroxy tautomer is energetically disfavored, the sp^2 hybridization at position 4 should modify the conformation of the six-membered ring.

The purpose of the present paper is twofold: (i) study the structure and tautomerism of compounds **1**–**4** belonging to the **IV** series; (ii) prepare new compounds related to indazoles for future studies as NOS inhibitors.[8–11] With these objectives, we have synthesized and characterized four 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one derivatives shown in Figure 2, where the two main tautomeric forms are represented.

To approach the study of the interaction between new inhibitors and the heme catalytic domain of the endothelial isoform of NOS (eNOS),[12] it is crucial to elucidate in which tautomeric form the entitled compounds will exist. Thus, we have performed a structural study of compounds **1**–**4** to know the predominant, or the unique tautomer, by

Keywords: Tetrahydroindazolones; Indazoles; Tautomerism; X-ray; NMR.
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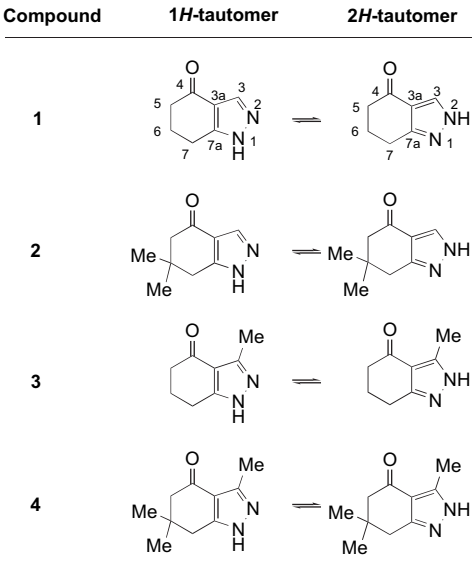


Figure 2. The four tetrahydroindazolones.

multinuclear NMR spectroscopy in solution and in solid state. Besides, in the cases of tetrahydroindazolones **2** and **4** the X-ray crystal structure was determined.

2. Results and discussion

2.1. Chemistry

4,5,6,7-Tetrahydroindazoles [3(5),4-tetramethylenepyrazoles] are usually prepared from cyclohexanone and its derivatives.[13,14] If instead of cyclohexanones, 1,3-cyclohexanediones are used, 1(2),5,6,7-tetrahydro-4*H*-indazol-4-ones are obtained.[15,16] These compounds (Fig. 3) have a rich reactivity with not less than four reactive positions that make them interesting scaffolds in medicinal chemistry.[17]

Known from a long time,[17–22] their chemistry was extensively studied by Sucrow et al. in 1970s and 1980s (see Ref. 24 for their reactivity)[23–29] with other significant contributions by Strakova and Gudriniece,[30] Akhrem (or Achrem),[31,32] Nunn and Rowell,[33] Schenone et al.,[34] Dalla Croce and La Rosa,[35] Le Tourneau and Peet,[36] Anderson-McKay et al.,[37] and Molteni et al.[38]

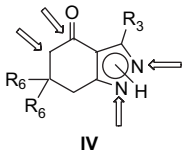
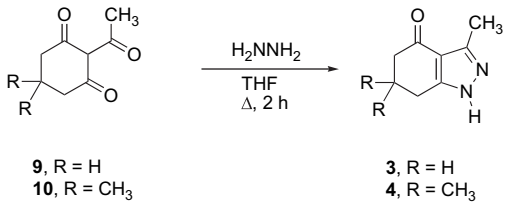


Figure 3. Reactivity of 6,6-disubstituted tetrahydroindazolones.

1(2),5,6,7-Tetrahydro-4*H*-indazol-4-one (**1**) and 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) (Scheme 1) were prepared according to the literature[38] starting from 1,3-cyclohexanedione (**5**) and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**6**), respectively, through the corresponding dimethylaminomethylene derivatives **7** and **8**.[34] Yields were moderate and their purification was achieved by column chromatography.

Similarly, 3-methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**3**) and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) (Scheme 2) were synthesized[37] from 2-acetyl-1,3-cyclohexanedione (**9**) and 2-acetyldimedone (**10**) with satisfactory yields and their purification was straightforward (see Section 4).

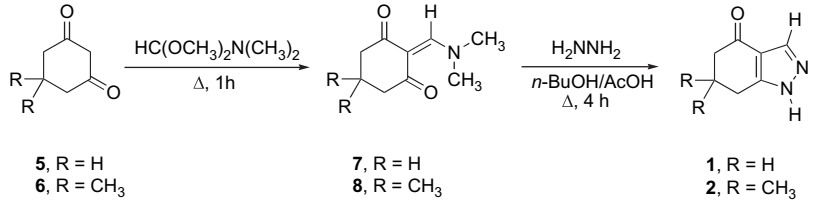


Scheme 2. Synthesis of compounds **3** and **4**.

Of the four compounds, only **2** was not previously reported. Since there are some discrepancies amongst the melting points (ours being measured by DSC) it is worth to recapitulate them here: compound **1** 163.8 °C (DSC), lit. 164–165 °C;[38] compound **2** 132.1 °C (DSC, new); compound **3** 160.3 °C (DSC), lit. 155 °C,[32] 152–154 °C;[35] compound **4** 101.4 °C (DSC), lit. 101–103 °C,[30] 101–102 °C,[31] 100.3–102.4 °C.[37]

2.2. Computational studies

On excluding OH-tautomers that are much less stable than the oxo forms,[39] the tautomerism of tetrahydroindazolones reduces, as in pyrazoles, to 1*H*- and 2*H*-tautomers. We already carried out computational studies (ab initio HF/6-31G*, HF/6-31G**, and DFT B3LYP/6-31G**)[39] establishing that in the gas phase tautomer 2*H* is the most stable one in all the four cases (B3LYP/6-31G**). On the other hand, according to HF/6-31G* and HF/6-31G** calculations, for derivatives **1** and **2**, tautomer 1*H* is more stable than 2*H* by about 0.65 kJ mol^{-1}, but for compounds **3** and **4** (with a methyl group at the 3-position) the 2*H* tautomer will be stabilized with respect to 1*H* by about 2 kJ mol^{-1}. The calculated dipole moments, by all methods, show that 1*H* tautomers have dipole moments nearly 2.5 times higher than 2*H* tautomers. Thus polar solvents will favor the 1*H* tautomer. In Table 1 we have summarized the results of



Scheme 1. Synthesis of compounds **1** and **2**.

Table 1. Energy differences in kJ mol^{-1} and dipole moments in brackets [Debye]

Compound	Methods	1*H*	2*H*
1	HF/6-31G**	0.0 [5.66]	0.45 [2.13]
	B3LYP/6-31G** (+ZPE)	1.18 [5.27]	0.0 [2.18]
2	HF/6-31G**	0.0 [5.65]	0.68 [2.12]
	B3LYP/6-31G** (+ZPE)	0.91 [5.26]	0.0 [2.17]
3	HF/6-31G**	2.03 [5.25]	0.0 [1.94]
	B3LYP/6-31G** (+ZPE)	3.64 [4.80]	0.0 [2.0]
4	HF/6-31G**	1.89 [5.24]	0.0 [1.94]
	B3LYP/6-31G** (+ZPE)	3.14 [4.79]	0.0 [2.0]

the calculations at the ab initio HF/6-31G** and density functional B3LYP/6-31G** levels for tautomers 1*H* and 2*H*.

2.3. NMR spectroscopy

In the following tables we report the NMR results concerning compounds **1**–**4**: Table 2 (^{1}H NMR), Table 3 (^{13}C NMR), and Table 4 (^{15}N NMR). Figure 4 illustrates the observation of the NH signals in ^{1}H NMR for compound **4**. Such clear observation of pyrazole tautomers is not at all usual,[40–42] in the present case it allows to determine the tautomeric equilibrium constants by simple integration of the ^{1}H NMR signals. The K_{eq} defined as [1*H*]/[2*H*] of 1.04 obtained for compound **3**, can be compared with that of 1.44 determined in 3-methyl-1(2),5,6,7-tetrahydroindazole,[43] allowing us to point out that a carbonyl group in position 4 favors the 2*H* tautomer.

The assignment of the signals has been achieved taking into account the chemical shift values, their multiplicity and, when necessary, 2D homonuclear and heteronuclear correlations were undertaken. Literature data concerning the ^{13}C NMR and ^{15}N NMR of pyrazoles have been of much use to assign the signals to each tautomer 1*H* and 2*H*.[44,45]

Table 2. Solution ^{1}H NMR chemical shifts (δ in ppm) of 1*H* and 2*H* tautomers with the indication of the equilibrium constants K_{eq} defined as [1*H*]/[2*H*]

Compound	%	K_{eq}	NH	H-3	H-5	H-6	H-7	CH_3(3)	CH_3(6)
1 (1*H*)[a]	65		13.15	7.74	2.35	2.01	2.82	—	—
1 (2*H*)[a]	35		13.24	8.19	2.35	2.01	2.74	—	—
1[a]		1.86							
1 (1*H*)[b]	63		12.61	7.73	2.37	2.06	2.87	—	—
1 (2*H*)[b]	37		12.69	8.16	2.37	2.06	2.77	—	—
1[b]		1.70							
2 (1*H*)[a]	57		13.14	7.75	2.27	—	2.68	—	1.00
2 (2*H*)[a]	43		13.14	8.19	2.27	—	2.68	—	1.00
2[a]		1.33							
2 (1*H*)[b]	55		12.75	7.76	2.28	—	2.77	—	1.06
2 (2*H*)[b]	45		12.83	8.21	2.28	—	2.67	—	1.06
2[b]		1.22							
3 (1*H*)[c]	51		14.32	—	2.40	2.05	2.87	2.45	—
3 (2*H*)[c]	49		14.34	—	2.40	2.05	2.82	2.53	—
3[c]		1.04							
4 (1*H*)[a]	44		12.72	—	2.22	—	2.65	2.28	1.00
4 (2*H*)[a]	56		12.86	—	2.22	—	2.56	2.39	0.98
4[a]		0.79							
4 (1*H*)[b]	42		12.56	—	2.24	—	2.71	2.32	1.03
4 (2*H*)[b]	58		12.75	—	2.24	—	2.60	2.45	1.03
4[b]		0.72							

[a] DMSO-d_6 at 300 K.
[b] THF-d_8 at 207 K.
[c] CD_2Cl_2 at 175 K.

Table 3. Solution ^{13}C NMR chemical shifts (δ in ppm) of 1*H* and 2*H* tautomers

Compound	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	CH_3(3)	CH_3(6)
1 (1*H*)[a]	136.7	117.9	192.4	37.8	23.2	20.4	150.3	—	—
1 (2*H*)[a]	128.7	117.9	193.8	38.6	23.5	22.4	155.8	—	—
2 (1*H*)[b]	137.7	118.1	193.5	52.8	36.5	34.8	149.9	—	28.5
2 (2*H*)[b]	129.4	118.1	191.9	53.3	36.0	37.2	156.0	—	28.5
3 (1*H*)[c]	148.0	114.9	194.8	37.9	22.5	20.9	151.2	13.4	—
3 (2*H*)[c]	141.9	114.5	196.0	38.5	23.1	23.3	156.7	11.1	—
4 (1*H*)[a]	146.8	113.9	192.4	52.3	35.4	34.2	150.0	13.2	27.9
4 (2*H*)[a]	140.8	113.5	193.8	52.7	34.9	36.5	155.3	10.5	27.9

[a] DMSO-d_6 at 300 K.
[b] THF-d_8 at 207 K.
[c] CD_2Cl_2 at 175 K.

In what concerns the ^{13}C NMR chemical shifts for each pair of tautomers the main conclusions from Table 4 are that in 1*H* tautomers δC-3 is downfield by about 7 ppm with respect to δC-3 of 2*H* tautomers, but on the contrary the δC-7a values for the 1*H* forms are upfield in approximately 5.5 ppm comparatively to those of tautomers 2*H*. The remaining signals have similar δ values and are not of use to distinguish between them.

In Table 4 are reported the chemical shifts of ^{15}N NMR of both tautomers for each compound, obtained by ^{1}H–^{15}N 2D inverse proton detection heteronuclear shift correlation experiments. The pyrrole N*H* was detected in all cases, but not so in the pyridine nitrogen, as no correlations could be observed in the experimental conditions tested.

The equilibrium constants in Table 2 should depend on the substituent at position 3 (0 if H and 1 if CH_3), the substituents at position 6 (0 if H and 1 if $(CH_3)_2$) and the solvent. For the solvent we have selected the SPP^N parameter.[46,47] A multiregression on the seven values leads to the following equation:

$$Ln\,K_{eq} = (0.109 \pm 0.018) - (0.519 \pm 0.003)\,\text{Pos 3} - (0.338 \pm 0.003)\,\text{Pos 6} + (0.510 \pm 0.020)\,SPP^N \qquad r^2 = 0.99994 \qquad (1)$$

The coefficients of Eq. 1 mean: the intercept corresponds to the unsubstituted compound **1** in the gas phase (SPP^N=0.00), i.e., in the gas phase there should be a slight excess of 1*H*-tautomer (53%). A methyl group at position 3 decreases

Table 4. Solution ^{15}N NMR chemical shifts (δ in ppm) of 1*H* and 2*H* tautomers

Compound	Solvent	N-1	N-2
1 (1*H*)	THF-d_8 at 207 K	−178.8	[a]
1 (2*H*)	THF-d_8 at 207 K	[a]	−175.1
2 (1*H*)	THF-d_8 at 207 K	−177.6	−79.2
2 (2*H*)	THF-d_8 at 207 K	[a]	−174.1
3 (1*H*)	CD_2Cl_2 at 175 K	−180.7	−102.6
3 (2*H*)	CD_2Cl_2 at 175 K	−110.1	−172.0
4 (1*H*)	THF-d_8 at 207 K	−183.2	[a]
4 (2*H*)	THF-d_8 at 207 K	[a]	−173.5

[a] No correlations were detected using gs-HMQC and gs-HMBC with various delays.

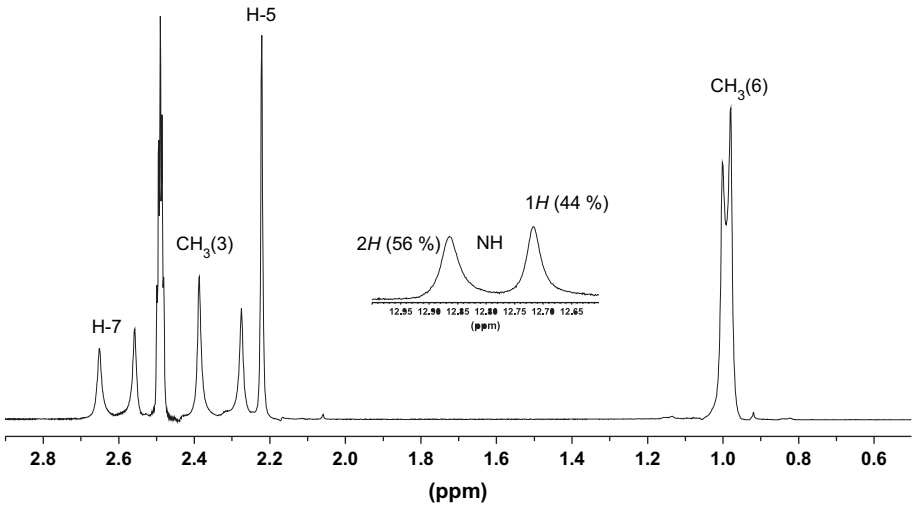


Figure 4. ^{1}H NMR spectrum of 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) in DMSO-d_6 at 300 K.

the population of the 1*H*-tautomer probably due to a destabilizing interaction with the carbonyl oxygen (this will have consequences on the crystal structures of **2** and **4**). Although weaker, the same happens with a *gem*-dimethyl substitution at position 6 probably mediated by a conformational change of the six-membered ring. An increase of the solvent polarity favors the 1*H*-tautomer in agreement with the calculated dipole moments of Table 1.

Table 5 presents the NMR data, ^{13}C and ^{15}N chemical shifts, obtained for all compounds **1**–**4** in solid state. As the X-ray structures of derivatives **2** and **4** described in the next section of the present paper clearly show that 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) exists as a mixture of 2/3 of 1*H* and 1/3 of 2*H* tautomers (see Figs. 5 and 6 for the corresponding ^{13}C and ^{15}N CPMAS spectra) and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one

Table 5. ^{13}C NMR and ^{15}N NMR chemical shifts (δ in ppm) in solid state of compounds **1**–**4**

Compound	N-1	N-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	Others
1	−172.1	−75.6	*138.1*	118.8	195.6	36.9	23.5	21.2	*151.5*	—
2	−111.7[a]		*132.2*	117.8	191.0	50.7	35.1	30.6	*150.1*	Me (6)
	−123.0[a]		*133.3*	118.6	192.0	51.8	36.0	32.2	*151.3*	25.6
	−139.7[a]		*135.0*	119.2	193.2				*151.9*	26.3
	−151.1[a]		*137.2*						*152.7*	27.7
	−165.0[a]									28.5
3	−178.5	−79.7	*146.2*	114.9	196.1	38.9	23.1	20.9	*152.3*	Me (3)
						40.1				14.8
4	−100.1	−163.2	*141.3*	113.3	196.9	53.2	36.0	36.0	*155.9*	Me (3)
										11.6
										Me (6)
										25.8, 30.9

[a] No assignment of the signals was made.

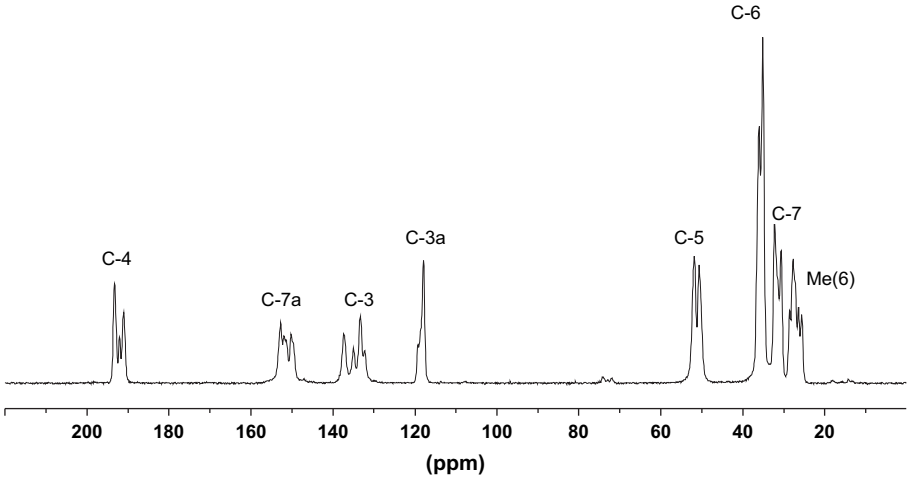


Figure 5. ^{13}C CPMAS NMR spectrum of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) from dichloromethane/petroleum ether.

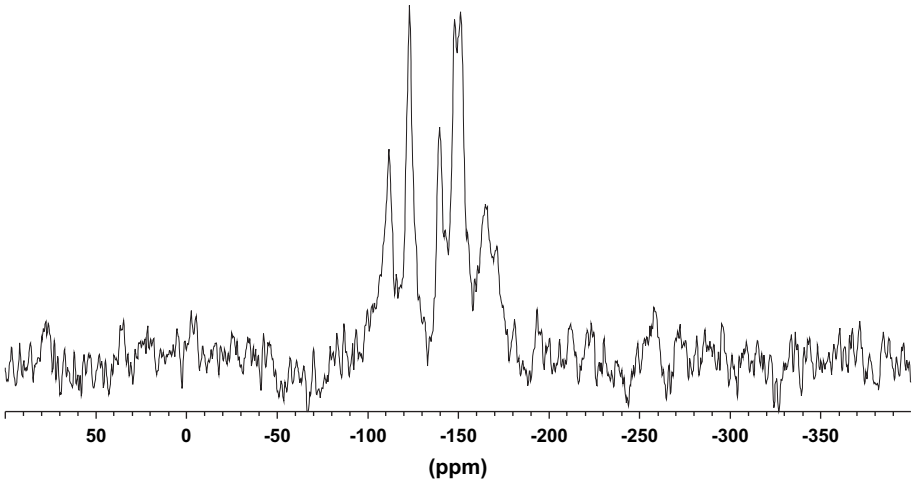


Figure 6. ^{15}N CPMAS NMR spectrum of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) from dichloromethane/petroleum ether.

(**4**) only in the 2*H* form, in view of the CPMAS NMR data analysis we can conclude that derivatives **1** and **3** are 1*H* tautomers in solid state, confirming again that the predominating tautomer in solution is in most of the cases the one existing in solid state.[48]

2.4. X-ray crystal and molecular structures

Crystals of enough quality to be analyzed by X-ray diffraction were obtained only for compound **2** from dichloromethane/petroleum ether and for compound **4** from water.

Six crystallographic independent molecules bonded by strong hydrogen bonds were identified in the structural determination of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**). All pyrazole rings are planar with distances and angles within the normal ranges.[49] Hydrogen bonds lead to trimers as shown in Figure 7 (Table 6).[50]

Table 6. Hydrogen bonds for compounds **2** and **4**, distances in Å, angles in °

Compound	D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	<(DHA)
2	N(11)–H(11)···N(12)	1.05	1.94	2.877(6)	147.3
	N(22)–H(22)···N(23)	1.06	1.76	2.802(6)	169.0
	N(13)–H(13)···N(21)	1.00	2.01	2.826(6)	137.5
	N(14)–H(14)···N(26)	0.99	1.92	2.891(7)	166.2
	N(16)–H(16)···N(15)	1.04	2.00	2.976(5)	154.5
	N(25)–H(25)···N(24)	0.94	1.83	2.765(7)	179.7
4	O(2)–H(2B)···O(1)	0.93	1.90	2.830(2)	172.5
	N(2)–H(2)···O(2)[a]	0.92	1.86	2.772(2)	170.4
	O(2)–H(2A)···N(1)[b]	0.94	1.89	2.822(2)	172.1

Symmetry transformations used to generate equivalent atoms.
[a] $-x+1, y-1/2, -z+1/2$.
[b] $x-1, -y+3/2, z-1/2$.

Additionally, weak hydrogen bonds (C33–H33···O11′ ($-x+2$, $y-1/2$, $-z+1/2$), *d*(C33···O11′)=3.234(7) Å <C33H33O11′=142°) and (C34–H34···O16″ ($-x+1$, $y-1/2$, $-z+1/2$), *d*(C34···O16″)=3.250(7) Å, <C34H34O16″=163.5°) form chains along the *b* axis. These chains exhibit weak

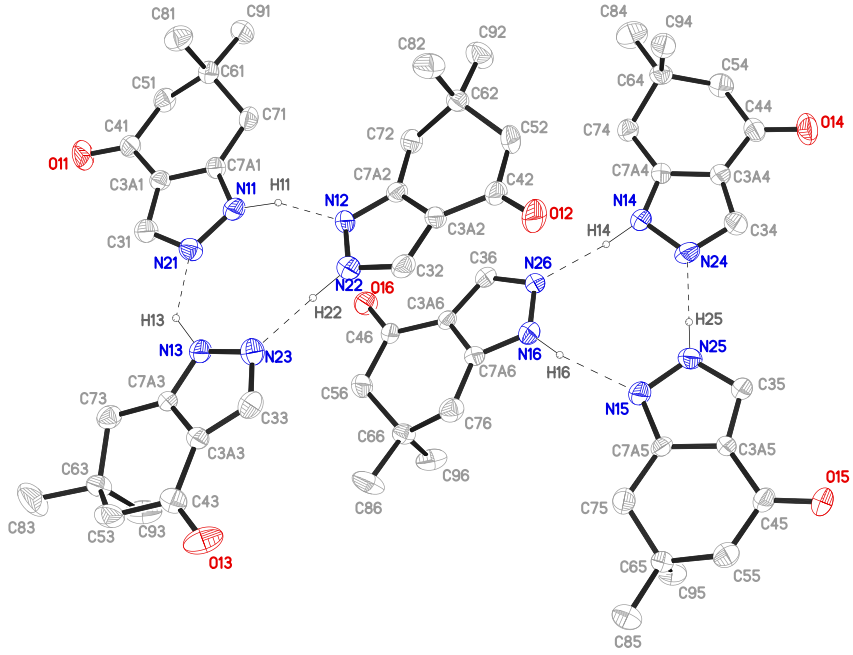


Figure 7. ORTEP view (35% probability) of the two trimers of **2**.

interactions (C96–H96···O13‴(−*x*+1, *y*, *z*), *d*(C96···O13‴)=3.306(7) Å, <C96H96AO16″=130°) piling up along the *a* axis (Fig. 8).

Figure 9 shows the asymmetric unit of 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**), the crystal consists of molecules held together by water molecules involving three hydrogen bonds (Table 6 and Fig. 10). These features lead to a layer parallel to [10−2] plane and these layers are within van der Waals distances. As in previous compound **2**, distances and angles lie in the normal ranges.

Compound **2** crystallizes forming trimers, one of the secondary structures that pyrazoles and indazoles can adopt in the crystal.[50,51] Which is not common at all is that the trimer is formed by two different tautomers, two of them being 2*H* and the third one being 1*H*. The only precedent is the recently described example of a tetramer formed by two

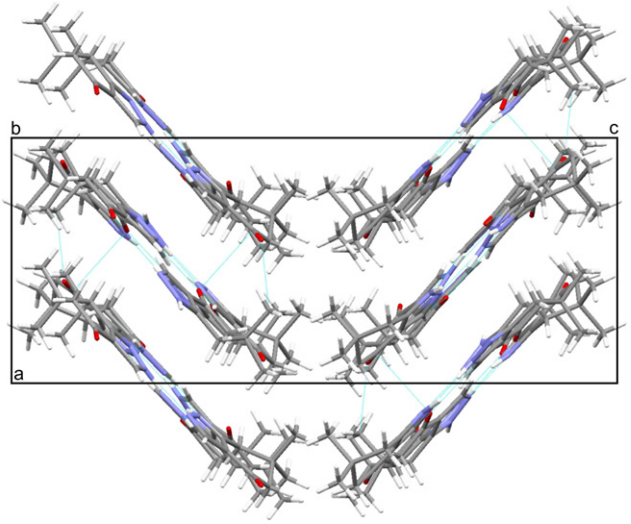


Figure 8. 2D network along the *b* axis in **2**.

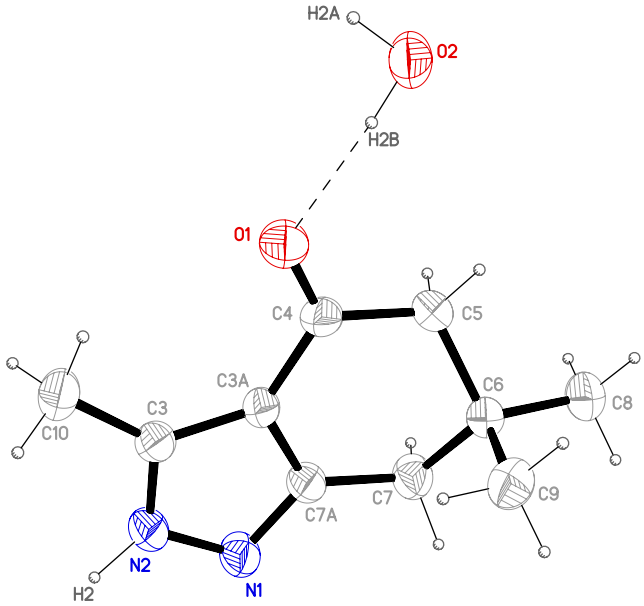


Figure 9. ORTEP view (40% probability) of the molecular structure of **4** plus one water molecule.

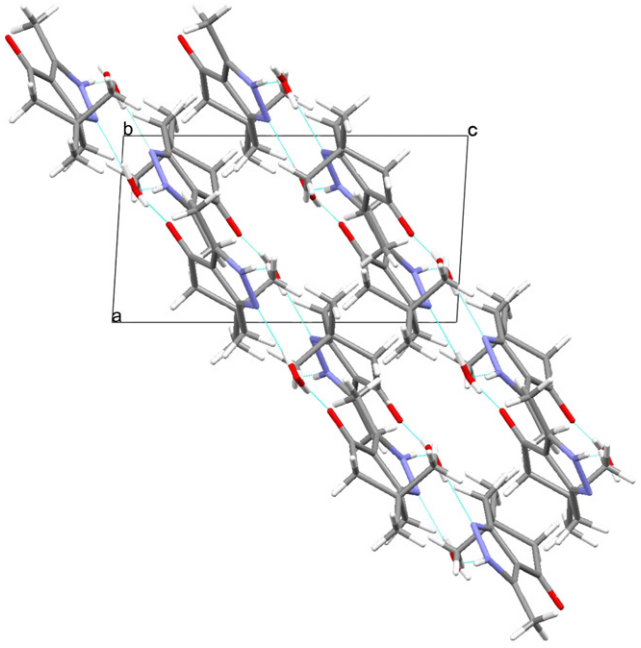


Figure 10. 2D network along the *b* axis in **4**.

tautomers in a 3:1 ratio (older examples were known but for balanced 2:2 tetramers).[42] This corresponds to two tautomers of almost the same energy (Table 2, compound **2**). The other unexpected result is that the hydrogen-acceptor (HBA) ability of the carbonyl oxygen is not used and thus Desiraju's principle of maximum saturation of HBs is not followed.[52–54]

On the other hand, compound **4** has a 2*H*-tautomer clearly more stable than the 1*H* (Table 2 and Eq. 1) and only this tautomer is present in the crystal forming chains, catemers, but using water molecules to saturate the HBA properties of the carbonyl group.

3. Conclusions

Computational calculations of 1(2),5,6,7-tetrahydro-4*H*-indazol-4-ones (**1**–**4**) conclude that the two main tautomeric forms 1*H* and 2*H* are very close in energy in the gas phase. Moreover, as tautomers 1*H* have dipole moments nearly 2.5 times higher than the 2*H* ones, polar solvents will favor the 1*H* forms.

In solution, tetrahydroindazolones **1**–**4** exist as mixtures of both tautomers with equilibrium constants K_{eq} defined as [1*H*]/[2*H*] varying in the following order **1** (1.70, THF-d_8 at 207 K)>**2** (1.22, THF-d_8 at 207 K)>**3** (1.04, CD_2Cl_2 at 175 K)>**4** (0.72, THF-d_8 at 207 K).

In the solid state 6,6,-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) forms trimers composed by 2/3 of 1*H* and 1/3 of 2*H* tautomers and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) gives rise to chains containing only 2*H* forms and water molecules, as X-ray diffraction analysis demonstrates. The CPMAS NMR data of 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**1**) and 3-methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**3**) are in agreement with the presence of 1*H* tautomers.

The four compounds will be tested as NOS inhibitors within the framework of a collaborative project with Professor C. S. Raman, Dr. Pierre Nioche (University of Texas Houston) and Professor Dario Acuña-Castroviejo (Universidad de Granada).

4. Experimental

4.1. Chemistry

The starting materials 1,3-cyclohexanedione 97% (**5**), dimedone 95% (**6**), and 2-acetyl-1,3-cyclohexanedione 98% (**9**) were commercially available from Aldrich and 2-acetyldimedone 98% (**10**) from Fluka and were used without further purification. Melting points for tetrahydroindazolones were determined by DSC on a Seiko DSC 220C connected to a Model SSC5200H Disk Station and for the other compounds a ThermoGalen hot stage microscope was used. Thermograms (sample size 0.003–0.0010 g) were recorded at a scanning rate of 2.0 °C min^{-1}. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh) and the R_f values were measured on aluminum baked TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. Elemental analyses for carbon, hydrogen, and nitrogen were carried out by the Microanalytical Service of the Universidad Complutense of Madrid on a Perkin–Elmer 240 analyzer.

4.1.1. 2-(Dimethylaminomethylene)-1,3-cyclohexanedione (7). A solution of 1,3-cyclohexanedione (**5**) (0.50 g, 4.5 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2 mL) was refluxed for 1 h. The excess acetal was distilled off under reduced pressure to obtain the pure product **7** as a dark solid (0.76 g, 100%). Mp: 117–119 °C (lit. mp:[34] 118 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.93 (2H, dt, ^3J=6.4 Hz, $CH_2CH_2CH_2$), 2.45 (4H, t, ^3J=6.4 Hz, CH_2CO), 3.16 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 8.04 (1H, s, =C*H*N).

4.1.2. 2-(Dimethylaminomethylene)-5,5-dimethyl-1,3-cyclohexanedione (8). A solution of 5,5-dimethyl-1,3-cyclohexanedione (**6**) (0.50 g, 3.6 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2 mL) was refluxed for 1 h. The excess acetal was distilled off under reduced pressure to obtain the pure product **8** as a yellowish solid (0.70 g, 100%). Mp: 92–94 °C (lit. mp:[34] 93 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.05 (3H, s, $(CH_3)_2$), 2.35 (4H, s, CH_2), 3.18 (3H, s, NCH_3), 3.37 (3H, s, NCH_3), 7.99 (1H, s, =C*H*N).

4.1.3. 1(2),5,6,7-Tetrahydro-4*H*-indazol-4-one (1). A solution of 1 g of 2-(dimethylaminomethylene)-1,3-cyclohexanedione (**7**, 6.0 mmol), 0.35 g of 55% hydrazine hydrate (6.0 mmol), and 0.6 mL of acetic acid, in 15 mL of 1-butanol was heated under reflux in a round bottom flask for 4 h. The mixture is allowed to cool to room temperature and the solvent evaporated under reduced pressure to leave a dark solid. After column chromatography on silica using ethyl acetate/hexane 2:1 as eluent, pure product **1** was obtained as a white solid (0.24 g, 30%). Mp: 163.8 °C (DSC) (lit. mp:[38] 164–165 °C). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.4 (br s, C4), 153.2 (br s, C7a), 134.5 (vbr s, C3), 118.8 (s, C3a), 38.4 (t, ^1J=128.0 Hz, C5), 23.5 (t, ^1J=130.3 Hz, C6), 21.8 (t, ^1J=129.4 Hz, C7).

4.1.4. 6,6-Dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (2). One gram of 55% hydrazine hydrate (16.5 mmol) was added dropwise under stirring to a solution of 2-(dimethylamino-methylene)dimedone (**8**) (3 g, 15 mmol) and acetic acid (0.5 mL) in 45 mL of 1-butanol in a three necked round bottom flask. The resulting mixture was heated under reflux for 4 h and then allowed to cool to room temperature. After evaporation of the solvent, the residue was redissolved in dichloromethane and filtered (a yellowish solid was discarded). Evaporation of dichloromethane gave a yellowish solid that was purified by column chromatography (silica gel) with ethyl acetate/hexane 1:1 as eluent. Product **2** thus obtained, was crystallized from water (1 g, 41%). Mp: 132.1 °C (DSC). Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.61; H, 7.29; N, 16.79. ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.8 (t, ^2J=6.3 Hz, C4), 152.4 (m, C7a), 133.9 (d, ^1J=190.4 Hz, C3), 117.6 (s, C3a), 52.6 (tt, ^1J=127.3 Hz, ^3J=4.1 Hz, C5), 35.7 (m, ^2J=3.8 Hz, C6), 35.7 (tt, ^1J=129.6 Hz, ^3J=4.5 Hz, C7), 28.4 [q, ^1J=125.8 Hz, Me (6)].

4.1.5. 3-Methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (3). To a solution of 0.5 g (3.2 mmol) of 2-acetyl-1,3-cyclohexanedione (**9**) in 20 mL of tetrahydrofuran, in a three necked round bottom flask, were added dropwise under stirring 0.21 g of 55% hydrazine hydrate (3.6 mmol). The mixture was refluxed for 2 h, allowed to cool to room temperature and filtered through Celite. The solution was evaporated under reduced pressure to leave a yellowish solid that was purified by column chromatography (silica gel) with diethyl ether/hexane 2:1 as eluent. This way pure product **3** was obtained (0.41 g, 85%). Mp: 160.3 °C (DSC) (lit. mp: 155 °C,[32] 152–154 °C.[35] Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.90; H, 6.58; N, 18.26. ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.2 (t, ^2J=6.1 Hz, C4), 154.7 (br s, C7a), 145.3 (br s, C3), 115.7 (s, C3a), 38.9 (tt, ^1J=127.6 Hz, ^2J=4.1 Hz, C5), 23.7 (tt, ^1J=130.3 Hz, H, ^2J=4.1 Hz, C6), 22.4 (t, ^1J=130.4 Hz, C7), 12.1 [q, ^1J=129.7 Hz, Me (3)].

4.1.6. 3,6,6-Trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (4). In a three necked round bottom flask a solution of 0.72 g of 2-acetyldimedone (**10**) (4.0 mmol) in 20 mL of tetrahydrofuran was prepared to which 0.26 g of 55% hydrazine hydrate (4.5 mmol) were added dropwise and under stirring. The mixture was heated under reflux for 2 h and allowed to cool to room temperature. After evaporation of the solvent a yellowish solid was obtained, which was crystallized from ether and recrystallized from water to give product **4** (0.45 g, 63%). Mp: 101.4 °C (DSC) (lit. mp:[37] 100.3–102.4 °C). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.5 (t, ^2J=6.1 Hz, C4), 154.0 (t, ^2J=7.0 Hz, C7a), 145.0 (q, ^3J=6.8 Hz, C3), 114.6 (s, C3a), 53.0 (t, ^1J=127.3 Hz, C5), 36.2 (t, ^1J=129.8 Hz, C7), 35.5 (m, C6), 28.4 [q, ^1J=123.7 Hz, Me (6)], 11.9 [q, ^1J=129.8 Hz, Me (3)].

4.2. NMR parameters

Solution spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and

40.56 MHz for ^{15}N) spectrometer with a 5-mm inverse-detection H–X probe equipped with a *z*-gradient coil for ^{1}H, ^{13}C, and ^{15}N. Chemical shifts (δ in ppm) are given from internal solvents, $CDCl_3$ (7.26), CD_2Cl_2 (5.32), THF-d_8 (3.58), DMSO-d_6 (2.49) for ^{1}H and $CDCl_3$ (77.0), THF-d_8 (67.4), CD_2Cl_2 (54.0), DMSO-d_6 (39.5) for ^{13}C and nitromethane (0.00) for ^{15}N NMR was used as external reference. Typical parameters for ^{1}H NMR spectra were spectral width 6400 Hz, pulse width 7.5 μs at an attenuation level of 0 dB and resolution 0.39 Hz per point. Typical parameters for ^{13}C NMR spectra were spectral width 20,500 Hz, pulse width 10.6 μs at an attenuation level of −6 dB and resolution 0.63 Hz per point; WALTZ-16 was used for broadband proton decoupling; the FIDs were multiplied by an exponential weighting (lb=1 Hz) before Fourier transformation. 2D (^{1}H–^{1}H) gs-COSY and inverse proton detected heteronuclear shift correlation spectra, (^{1}H–^{13}C) gs-HMQC, (^{1}H–^{13}C) gs-HMBC, (^{1}H–^{15}N) gs-HMQC, and (^{1}H–^{15}N) gs-HMBC, were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode.[55] Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms. Variable temperature experiments were recorded on the same spectrometer. A Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures. Solid state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra were obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probe head. Samples were carefully packed in a 4-mm diameter cylindrical zirconia rotor with Kel-F end-caps. Operating conditions involved 3.2 μs 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. The NQS (non-quaternary suppression) technique[55] to observe only the quaternary C-atoms was employed. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me_4Si (for the carbonyl atom δ (glycine)=176.1 ppm) and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ ^{15}N(nitromethane)=δ ^{15}N(ammonium chloride) −338.1 ppm. The typical acquisition parameters for ^{13}C CPMAS were spectral width 40 kHz, recycle delay 5 s, acquisition time 30 ms, contact time 2 ms, and spin rate 12 kHz. And for ^{15}N CPMAS spectral width 40 kHz, recycle delay 5 s, acquisition time 35 ms, contact time 6 ms, and spin rate 6 kHz.

4.3. X-ray data collection and structure refinement

Suitable crystals for X-ray diffraction experiments were obtained by crystallization from dichloromethane/petroleum ether (**2**) or water (**4**). Data collection were carried out at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo Kα radiation (λ= 0.71073 Å) operating at 50 kV and 30 mA. In both cases, data were collected over a hemisphere of the reciprocal space by combination of three exposure sets, each exposure was of 20 s covering 0.3° in ω. The first 50 frames were recollected at the end of the data collection to monitor crystal decay. A summary of the fundamental crystal and refinement data are given in Table 7. The structures were solved by direct methods and refined by full-matrix least-square procedures on F^2 (SHELXL-97).[56] All non-hydrogen atoms were refined anisotropically. In both cases, all hydrogen atoms were included in their calculated positions and refined riding on the respective carbon atoms with the exceptions listed below. In the structure of **4** the hydrogen atoms bonded to N2 atom and the hydrogen atoms bonded to O2 (water) were located in a Fourier synthesis and refined riding on the respective bonded atoms. The same treatment was followed with the hydrogen atoms bonded to N11, N13, N14, N16, N22 and N25 in the structure of **2**. Largest peaks and holes in the final difference map were 0.194 and −0.204 e Å^{-3} for **2** and 0.196 and −0.147 e Å^{-3} for **4**. Final *R* (*Rw*) values were 4.83 (13.91) for **2** and 4.97 (15.26) for **4**. The flack parameter is 0.00, an indication of the correct determination of the crystalline absolute structure. Further crystallographic details for the structures reported in this paper may be obtained from the Cambridge Crystallographic Data Center, on quoting the depository numbers CCDC-608789 and CCDC-608790.

Table 7. Crystal data and structure refinement for 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) and 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**)

Crystal data	**2**	**4**
Identification code	CCDC-608790	CCDC-608789
Empirical formula	$C_9H_{12}N_2O$	$C_{10}H_{16}N_2O_2$
Formula weight	164.21	196.25
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	*P*2(1)2(1)2(1)	*P*2(1)/*c*
Unit cell dimensions		
a (Å)	10.1243(8)	5.9827(7)
b (Å)	21.526(2)	16.494(2)
c (Å)	24.992(2)	11.012(1)
β (°)	—	93.464(2)
Volume (Å^3)	5446.6(7)	1084.7(2)
Z	24	4
Density (calculated) (Mg/m^3)	1.202	1.202
Absorption coefficient	0.081 (mm^{-1})	0.085 (mm^{-1})
F(000)	2112	424
Theta range (°) for data collection	1.25–25.0	2.23–28.72
Index ranges	$-12\le h\le 12$ $-20\le k\le 25$ $-29\le l\le 29$	$-8\le h\le 7$ $-20\le k\le 21$ $-14\le l\le 11$
Reflections collected	42,257	6842
Independent reflections	9572 [*R* (int)=0.1342]	2582 [*R* (int)=0.0712]
Data/restraints/ parameters	9572/0/688	2582/0/133
Goodness-of-fit on F^2	0.801	0.909
R[a] [$I>2\sigma$ (I)]	0.0484 (3204 obs. reflect.)	0.0497 (1374 obs. reflect.)
Rw_F[b] (all data)	0.1391	0.1526

[a] $\sum \|\|F_o\|-\|F_c\|\| / \sum |F_o|$.
[b] $\{\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]\}^{1/2}$.

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References and notes

1. (a) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic: New York, NY, 1976; 655 p; (b) Minkin, V. I.; Garnosvskii, A. D.; Elguero, J.;

Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 157–323.
2. Alkorta, I.; Elguero, J. *J. Phys. Org. Chem.* **2005**, *18*, 719–724.
3. (a) Ramos, M.; Alkorta, I.; Elguero, J. *Tetrahedron* **1997**, *53*, 1403–1410; (b) Alkorta, I.; Elguero, J. *Struct. Chem.* **1997**, *8*, 189–195.
4. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Pyrazoles as Drugs: Facts and Fantasies in Targets in Heterocyclic Systems*; Italian Society of Chemistry: Roma, 2002; Vol. 6; pp 52–98.
5. (a) Southan, G. J.; Gauld, D.; Lubeskie, A.; Zingarelli, B.; Cuzzocrea, S.; Salzman, A. L.; Szabo, C.; Wolff, D. J. *Biochem. Pharmacol.* **1997**, *54*, 409–417; (b) Kim, S. H.; Won, S. J.; Mao, X. O.; Jin, K.; Greenberg, D. A. *Mol. Pharmacol.* **2006**, *69*, 691–696.
6. Cerecetto, H.; Gerpe, A.; González, M.; Arán, V. J.; Ochoa de Ocáriz, C. *Mini-Rev. Med. Chem.* **2006**, *6*, 869–878.
7. (a) Murineddu, G.; Ruiu, S.; Mussinu, J.-M.; Loriga, G.; Grella, G. E.; Carai, M. A. M.; Lazzari, P.; Pani, L.; Pinna, G. A. *Bioorg. Med. Chem.* **2005**, *13*, 3309–3320; (b) Foloppe, N.; Fisher, L. M.; Francis, G.; Howes, R.; Kierstan, P.; Potter, A. *Bioorg. Med. Chem.* **2006**, *14*, 1792–1804.
8. Lee, Y.; Martàsek, P.; Roman, L. J.; Silverman, R. B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2771–2774.
9. Claramunt, R. M.; Sanz del Castillo, D.; Elguero, J.; Nioche, P.; Raman, C. S.; Martasek, P.; Masters, B. S. S. *Drugs Future* **2002**, *27*, 177.
10. Camacho, M. E.; León, J.; Entrena, A.; Velasco, G.; Carrión, M. D.; Escames, G.; Vivó, A.; Acuña-Castroviejo, D.; Gallo, M. A.; Espinosa, A. *J. Med. Chem.* **2004**, *47*, 5641–5650.
11. Pérez-Medina, C.; Pérez-Torralba, M.; López, C.; Claramunt, R. M.; Nioche, P.; Raman, C. S. XIV Congreso Nacional de la Sociedad Española de Química Terapeútica; Sociedad Española de Química Terapeútica: Bilbao, September, 2005.
12. Raman, C. S.; Li, H.; Martasek, P.; Southan, G.; Masters, B. S.; Poulos, T. L. *Biochemistry* **2001**, *40*, 13448–13455.
13. Behr, L. C.; Fusco, R.; Jarboe, C. H. *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Interscience, Wiley: New York, NY, 1967; p 364.
14. (a) Elguero, J. *Pyrazoles and their Benzo Derivatives*. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; pp 167–343; (b) Elguero, J. Pyrazoles. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; pp 1–75.
15. Strakov, A. Ya.; Gudrinietse, E. Yu.; Zicane, D. R. *Khim. Geterotsikl. Soedin.* **1974**, 1011–1030; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1974**, 881–897; Strakov, A. Ya.; Gudrinietse, E. Yu.; Strakova, I. A. *Khim. Geterotsikl. Soedin.* **1988**, 723–738; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1988**, 585–599.
16. Marko, M.; Milata, V.; Kada, R.; Ilavsky, D. *Curr. Org. Chem.* **2004**, *8*, 695–714.
17. D'Alessio, R.; Bargiotti, A.; Metz, S.; Brasca, M. G.; Cameron, A.; Ermoli, A.; Marsiglio, A.; Polucci, P.; Roletto, F.; Tibolla, M.; Vazquez, M. L.; Vulpetti, A.; Pevarello, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1315–1319.
18. Dieckmann, W.; Stern, R. *Chem. Ber.* **1904**, *37*, 3370–3384.
19. Crossley, A. W.; Renouf, N. *J. Chem. Soc.* **1912**, *101*, 1524–1538.
20. Wichterle, O.; Prochazka, J.; Hofman, J. *Collect. Czech. Chem. Commun.* **1948**, *13*, 300–315.
21. Smith, H. *J. Chem. Soc.* **1953**, 803–810.
22. Strakova, I. A.; Gudrinietse, E. Yu.; Linaberg, Ya. Ya.; Strakov, A. Ya.; Kreitsberga, D. R. *Chem. Heterocycl. Compd.* **1970**, *6*, 481–485.
23. Sucrow, W.; Slopianka, M. *Chem. Ber.* **1972**, *105*, 3807–3813.
24. Sucrow, W.; Mentzel, C.; Slopianka, M. *Chem. Ber.* **1973**, *106*, 450–459.
25. Sucrow, W.; Slopianka, M.; Mentzel, C. *Chem. Ber.* **1973**, *106*, 745–750.
26. Sucrow, W.; Slopianka, M.; Flessas, E. *Chem. Ber.* **1973**, *106*, 3432–3437.
27. Bardakos, V.; Sucrow, W. *Chem. Ber.* **1976**, *109*, 1898–1910.
28. Sucrow, W.; Brockmann, R. *Liebigs Ann. Chem.* **1982**, 1891–1896.
29. Sutthivaiyakit, S.; Sucrow, W.; Wonnemann, H.; Krüger, C. *Liebigs Ann. Chem.* **1985**, 794–801.
30. Strakova, I. A.; Gudriniece, E. *Latv. PSR Zinat. Akad. Vestis. Khim. Ser* **1966**, 680–683; *Chem. Abstr.* **1967**, *67*, 116848v.
31. Achrem, A. A.; Moiseenkov, A. M.; Andaburskaya, M. B.; Strakov, A. J. *J. Prakt. Chem.* **1972**, *314*, 31–35.
32. Akhrem, A. A.; Lakhvich, F. A., Khim. Dikalbonil′nykh Soedin. Tezisy Dokl. Vses Konf. 4th ed.; 1975 (publ. 1976); pp 11–12; *Chem. Abstr.* **1977**, *87*, 68119.
33. Nunn, A. J.; Rowell, F. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2697–2703.
34. Schenone, P.; Mosti, L.; Menozzi, G. *J. Heterocycl. Chem.* **1982**, *19*, 1355–1361.
35. Dalla Croce, P.; La Rosa, C. *Synthesis* **1984**, 982–983.
36. Le Tourneau, M. E.; Peet, N. P. *J. Org. Chem.* **1987**, *52*, 4384–4387.
37. Anderson-McKay, J.; Savage, G. P.; Simpson, G. W. *Aust. J. Chem.* **1996**, *49*, 163–166.
38. Molteni, V.; Hamilton, M. H.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, 1669–1674.
39. Pérez-Medina, C.; López, C.; Claramunt, R. M. *Molecules* **2006**, *11*, 415–420.
40. Claramunt, R. M.; Elguero, J.; Marzin, C.; Seita, J. *An. Quim.* **1979**, *75*, 701–706.
41. García, M. A.; López, C.; Claramunt, R. M.; Kenz, A.; Pierrot, M.; Elguero, J. *Helv. Chim. Acta* **2002**, *85*, 2763–2776.
42. Claramunt, R. M.; Cornago, P.; Santa María, M. D.; Torres, V.; Pinilla, E.; Torres, M. R.; Elguero, J. *Supramol. Chem.* **2006**, *18*, 349–356.
43. Martinez, A.; Jimeno, M. L.; Elguero, J.; Fruchier, A. *New J. Chem.* **1994**, *18*, 269–277.
44. Claramunt, R. M.; Sanz, D.; López, C.; Jiménez, J. A.; Jimeno, M. L.; Elguero, J.; Fruchier, A. *Magn. Reson. Chem.* **1997**, *35*, 35–75.
45. Begtrup, M.; Boyer, G.; Cabildo, P.; Cativiela, C.; Claramunt, R. M.; Elguero, J.; García, J. I.; Toiron, C.; Vedsø, P. *Magn. Reson. Chem.* **1993**, *31*, 107–168.
46. Catalán, J.; López, V.; Pérez, P.; Martín-Villamil, R.; Rodríguez, G. *Liebigs Ann. Chem.* **1995**, 241–253.
47. Paéz, J. A.; Campillo, N.; Elguero, J. *Gazz. Chim. Ital.* **1996**, *126*, 307–311.
48. Claramunt, R. M.; López, C.; Santa María, M. D.; Sanz, D.; Elguero, *J. Prog. Nucl. Magn. Reson. Spectrosc.*, in press.
49. Llamas-Saiz, A. L.; Foces-Foces, C.; Elguero, J. *J. Mol. Struct.* **1994**, *319*, 231–260.
50. Foces-Foces, C.; Alkorta, I.; Elguero, J. *Acta Crystallogr., Sect. B* **2000**, *B56*, 1018–1028.
51. Foces-Foces, C. *Acta Crystallogr., Sect. E* **2005**, *E61*, o337–o339.
52. Allen, F. H.; Lommerse, J. P. M.; Hoy, V. J.; Howard, J. A. K.; Desiraju, G. R. *Acta Crystallogr., Sect. B* **1996**, *B52*, 734–745.

53. Infantes, L.; Chisholm, J.; Motherwell, S. *Crystallogr. Eng. Commun.* **2003**, *5*, 480–486.
54. Infantes, L.; Motherwell, S. *Chem. Commun.* **2004**, 1166–1167.
55. Berger, S.; Braun, S. *200 and more NMR Experiments*; Wiley-VCH: Weinheim, 2004.
56. Sheldrick, G. M. *SHELX97, Program for Refinement of Crystal Structure*; University of Göttingen: Göttingen, Germany, 1997.

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An efficient one-pot construction of substituted pyrimidinones

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Abstract—A concise, scaleable synthesis of building block **10** for p38 kinase inhibitor **B** is described. The key step is the one-pot construction of 5-aryl-3-methyl-2-methylsulfanyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one **4** from arylacetic acid ethyl ester **1**. Subsequent hydrolysis of the thiomethyl group to the hydroxy group and chlorination provided the key intermediate, 2-chloro-3-methyl-6-pyridin-4-yl-5-aryl-3*H*-pyrimidin-4-one **10**. This class of reactive building blocks enabled the rapid evaluation of a variety of side chains at the 2-position of the pyrimidinone in SAR studies of inhibitors of p38 MAP kinase.

1. Introduction

Inhibition of p38 MAP kinase (p38α) has been proposed as a disease-modifying approach toward the treatment of inflammatory disorders.[1–8] The vicinal aryl/pyridinyl heterocycles **A** are the most widely studied early p38 inhibitors.[2,3] Drug discovery efforts at Amgen have identified a variety of aryl/pyridyl pyrimidinones **B** (Fig. 1) as potent and selective inhibitors of p38α kinase. They can be generated via nucleophilic displacement of a leaving group at the 2-position by amines (Scheme 1). In order to facilitate the exploration of a broad array of substituents at the 2-position of this heterocycle, a concise, scaleable process leading to a suitably reactive intermediate was desired. The resulting process was ultimately used to prepare large quantities of particular leads for preclinical studies.

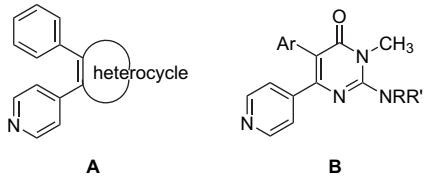
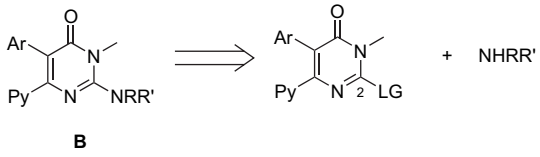


Figure 1.



Scheme 1.

Early exploratory efforts involving ring formation of 5,6-disubstituted-2-thiomethyl-pyrimidin-4-one **4** via condensation of a β-keto-ester and thiourea are summarized in Scheme 2. In this process, commercially available ethyl 2-(3-methylphenyl) acetate **1** was reacted with ethyl isonicotinate using NaH as a base to yield ethyl α-phenyl-β-oxo-4-pyridinepropanoate **2** after column chromatography.[9] When the β-ketoester **2** was treated with thiourea at 140 °C (melt) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate, thiouracil **3** was isolated, but only in low yield (<20%). The crude product also required repeated recrystallization. Subsequent bis-methylation resulted in 2-thiomethyl-pyrimidin-4-one **4** along with a variety of by-products, including *S*-monomethyl and *O*,*S*-dimethyl derivatives, which were removed by column chromatography. Due

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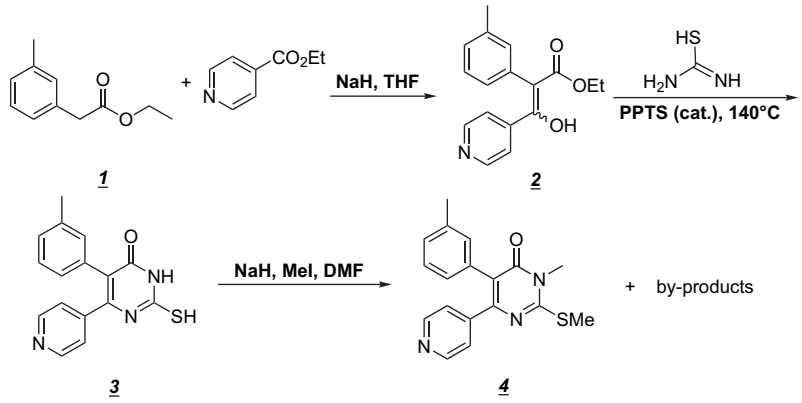
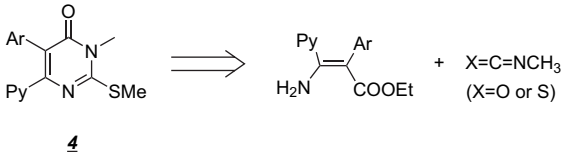


Scheme 2. Early route to 2-thiomethyl-pyrimidin-4-one.

to these issues, an alternative approach for construction of the pyrimidinethione ring was investigated.

The preparation of 4-pyrimidinethiones and related compounds from enamines and acryl/aryl isothiocyanates has been extensively investigated.[10–14] Of particular relevance to our target is the report of Hassan and co-workers[14] describing the synthesis of a 2-thiouracil from 2-amino-nicotinate and phenyl isothiocyanate. This encouraged us to utilize the reactivity of 3-amino-2-alkenoates toward methyl isothiocyanate (Scheme 3).



Scheme 3. Alternative approach to 2-thiomethyl-pyrimidin-4-one.

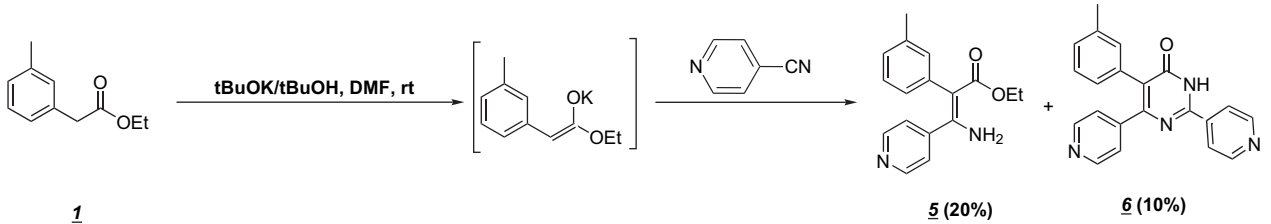
2. Results and discussion

2.1. Addition of alkanoate potassium enolates to nitriles

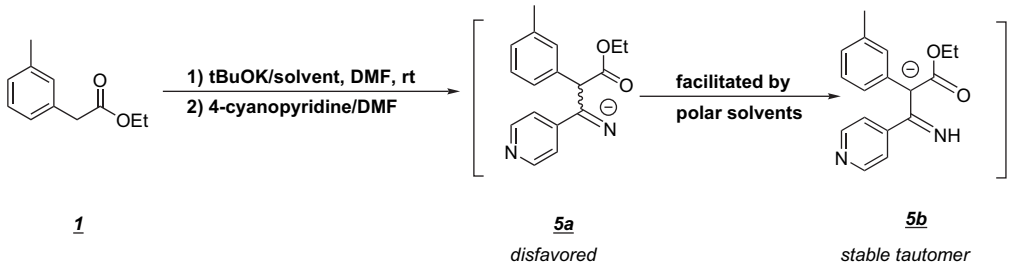
It has been reported that magnesium ester enolates can react with nitriles to provide (*Z*)-3-amino-2-alkenolates in moderate to good yields.[15] Although nitriles are usually considered to be inert to enolates, some pyridyl-derived analogs were found to be reactive. Our first attempt to generate the magnesium enolate of ethyl 2-(3-methylphenyl) acetate **1** with magnesium amide, as reported by Hiyama,[15] in the presence of 4-cyanopyridine was unsuccessful. Presumably, $Mg(NH_2)_2$ is not of sufficient basicity to deprotonate the α-position of **1**. In accordance with Hiyama's results,[15] the use of a lithium or sodium counterion also failed to provide any carbon–carbon bond formation. We envisaged that the use of a potassium counterion might render the enolate more reactive.[16] Indeed, it was found that the potassium enolate of *m*-tolyl-acetic acid ethyl ester **1**, prepared with potassium *tert*-butoxide, reacted with 4-cyanopyridine in DMF at room temperature to provide the corresponding 3-amino-2-alkenolate **5** along with a by-product, characterized as bis-pyridyl pyrimidinone **6** (Scheme 4). Although **6** was isolated in only 10% yield, this served to demonstrate the potential of this reaction sequence to construct the desired heterocyclic ring system in a stepwise, one-pot fashion.

Subsequent experiments produced some interesting observations: (i) the nitrile addition appeared to be faster and cleaner when *t*-BuOK in *t*-BuOH was used as opposed to *t*-BuOK in THF and (ii) use of KH in DMF or THF did not result in any of the desired alkenoate **5**, even though the dark purple color of the KH–ester mixture was indicative of enolate anion formation. It is likely that *t*-BuOH serves to either directly protonate the incipient, nitrogen-centered anion generated during attack of enolate **1** upon the nitrile substrate, or to facilitate subsequent tautomerization to the more stable **5b**. B3LYP/6-31G* calculations fail to locate a non-tautomerized minimum corresponding to **5a** in the gas phase; its existence in solution is likely to be disfavored as well. In the presence of protic solvents, formation of **5b** is facilitated, whereas in non-protic media, addition of **1** to the nitrile is disfavored (Scheme 5).

A loose correlation is observed between nitrile electrophilicity (as gauged by LUMO energy at the RHF/6-31G* level) and both the calculated exothermicity of the model enolate addition, as well as final yield of 'one pot' cyclization/quenching product **4** (Table 1).

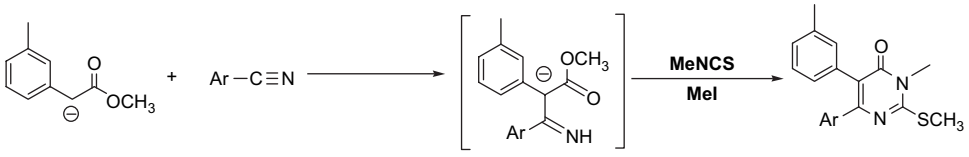


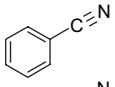
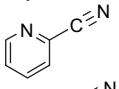
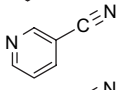
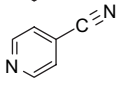
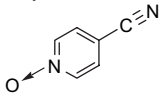
Scheme 4. Formation of 3-amino-2-alkenoate.



Scheme 5. Addition of potassium ester enolates to nitriles.

Table 1. Computed electrophilicities and relative reactivities of aryl nitrile substrates



2	E_{rxn} (**1**+**2**→**5**)[a,b]	E(LUMO), **2**[c]	% Yield, **4**[d]
	−9.9 (**0.0**)	+0.08353	0
	−11.8 (**−1.9**)	+0.06960	0
	−14.6 (**−4.7**)	+0.07126	30
	−16.6 (**−6.7**)	+0.05903	50−60
	−19.1 (**−9.2**)	+0.03844	40

[a] Absolute (relative in bold) energies of reaction (kcal/mol) at the B3LYP/6-31G*+ZPE level.
[b] All calculations performed with the Gaussian 98[17] program system.
[c] a.u., RHF/6-31G*//B3LYP/6-31G*.
[d] From Table 2.

2.2. Quenching of the amino alkenoate anion by electrophiles

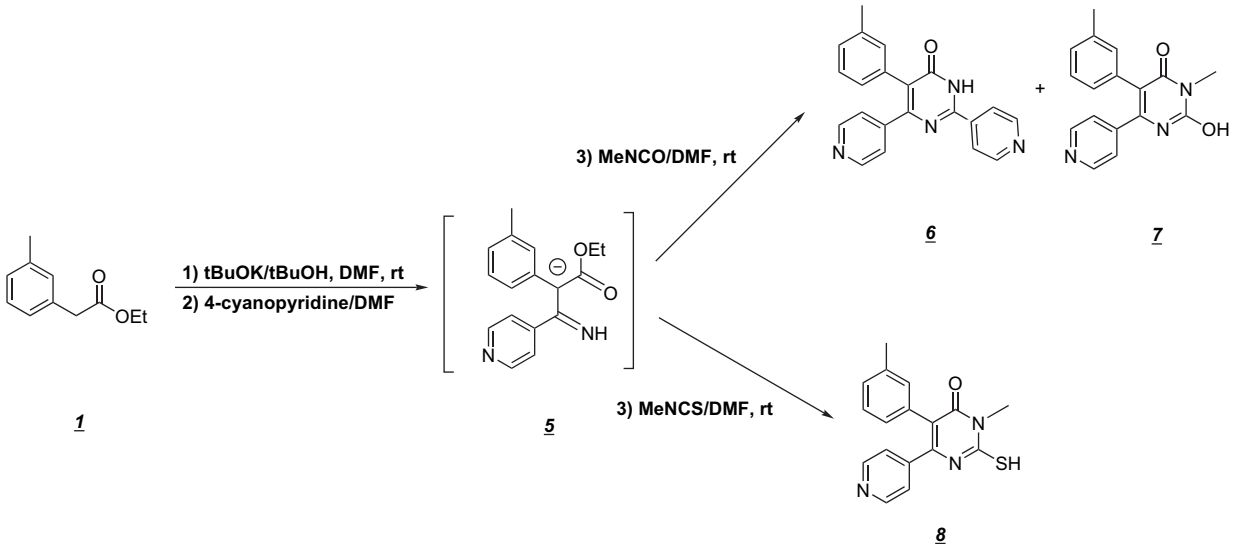
With the chemistry leading to amino alkenoate anion **5** established, efforts were undertaken to trap and cyclize this intermediate into the uracil- or thiouracil-like pyrimidinone in a single step. Early attempts to quench **5** with methyl isocyanate resulted in the formation of uracil **7** and bis-pyridyl pyrimidinone **6** as 1:1 mixture based on HPLC area ratio (Scheme 6).

In contrast, quenching **5** with methyl isothiocyanate in DMF at room temperature afforded the corresponding thiouracil **8** in good conversion (~95%) (Scheme 6). Furthermore, sequential addition of methyl isothiocyanate to **5**, followed by iodomethane, provided the desired 2-thiomethyl-pyrimidin-4-one **4** in 50% overall yield. Conveniently, the product **4** could be precipitated as an off-white solid by simple addition of an equal volume of water to the DMF and stirring at −5 to 0 °C for 48 h (Scheme 7).

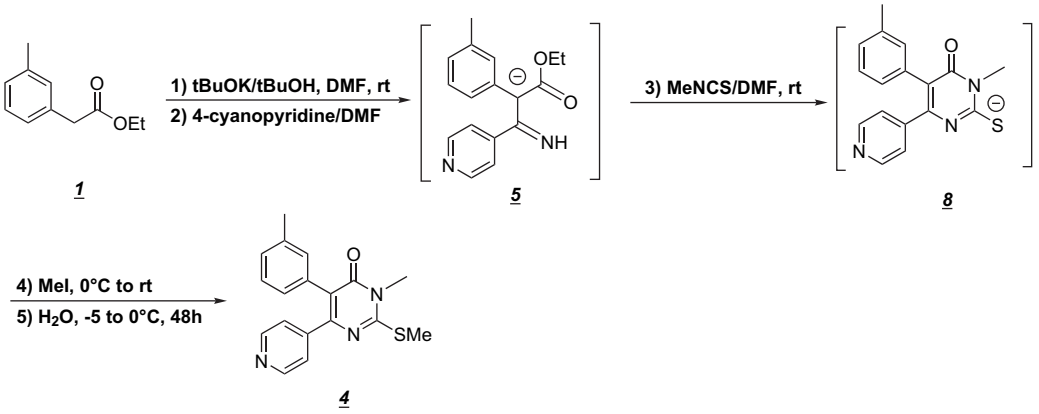
This one-pot process, consisting of enolate/nitrile addition, isothiocyanate addition/cyclization, and S-methylation, produced the desired 2-thiomethyl-pyrimidin-4-one **4**, for which an early medicinal chemistry route had required in three steps (Scheme 2). In addition to the simplification of the procedure, the overall yield increased by more than 10-fold. These conditions require only 1 equiv each of *t*-BuOK, the nitrile, methyl isothiocyanate, and iodomethane in relation to the starting ester. The convenient temperature range of this reaction (−5 to 25 °C) is another attractive feature, enabling successful scale-up to a multi-kilogram quantity.

2.3. The scope and limitation of the one-pot construction

When ethyl 2-(4-fluorophenyl) acetate was used as starting material, a complex mixture along with 4-cyanopyridine was obtained instead of the corresponding sulfide, possibly arising from defluorination of the aryl ring upon generation of the enolate. Therefore, the one-pot process was modified to avoid potential decomposition or self-condensation of the



Scheme 6. Quenching of 3-amino-2-alkenoate.



Scheme 7. The one-pot reaction.

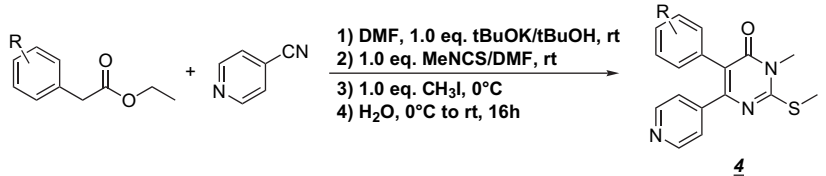
alkenoate anion. In the improved procedure, *t*-BuOK/*t*-BuOH was added to the premixed DMF solution of the ester and 4-cyanopyridine, allowing for immediate addition with the nitrile substrate upon enolate generation. The rest of reaction sequence remains same (Scheme 8).

This one-pot reaction has been used to generate the 2-thiomethyl-pyrimidin-4-ones **4** as reported in Table 2.

Contrary to when generated in situ, aminoalkenoate **5**, isolated after work-up, reacted poorly with alkyl nitriles in the presence of base or acid over a wide temperature range (rt–120 °C).[18] Neutral enamine **5** could potentially exist as either (*E*) or (*Z*)-isomers; B3LYP/6-31G* calculations predict (*Z*)-**5** (Fig. 2) to be 6.1 kcal/mol lower in energy than (*E*)-**5** due in part to intramolecular hydrogen bonding and π-stacking of the aromatic rings and 7.5 kcal/mol lower in energy than its imine tautomer. The prediction of (*Z*)-**5** as the exclusive neutral species present upon protonation of the anion of **5** was subsequently confirmed on the basis of NOE experiments (see Section 3.6).

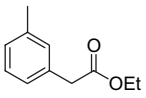
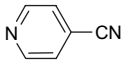
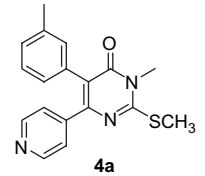
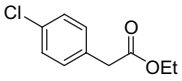
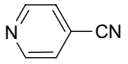
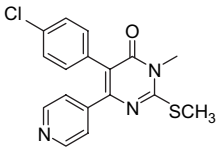
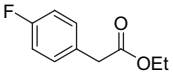
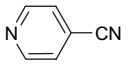
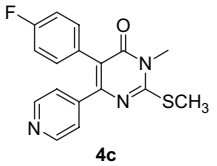
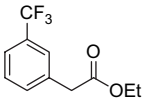
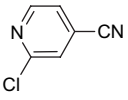
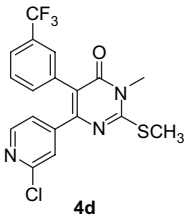
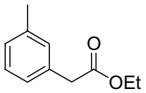
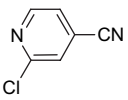
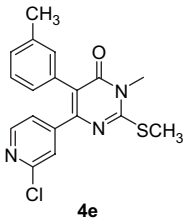
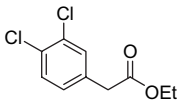
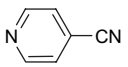
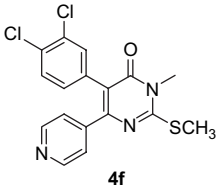
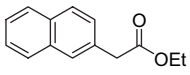
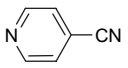
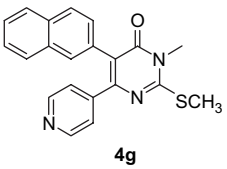
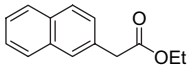
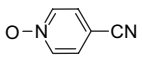
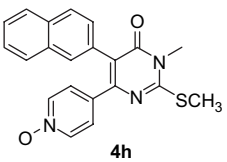
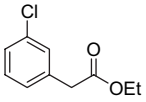
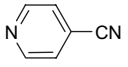
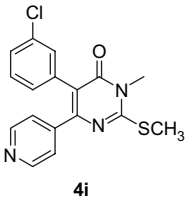
2.4. Conversion of the sulfide-pyrimidinones to the more reactive chloro-pyrimidinones

The thiomethyl moiety could, in principle, be used as a leaving group to introduce amines at the 2-position. However, we found that this displacement required harsh conditions (neat, high temperature, and sealed vessel), which were not practical for scale-up. As the displacement of



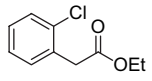
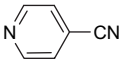
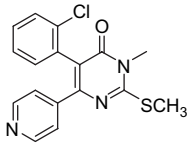
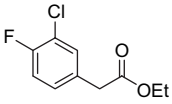
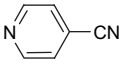
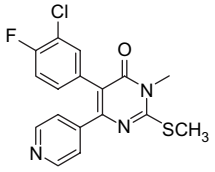
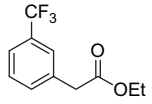
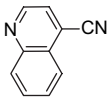
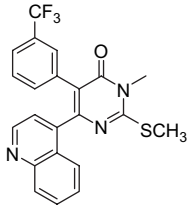
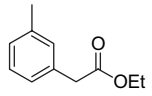
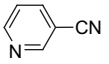
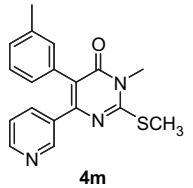
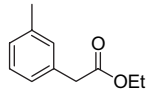
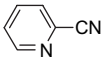
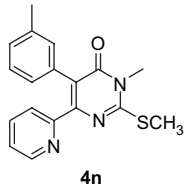
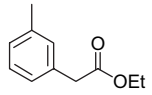
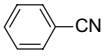
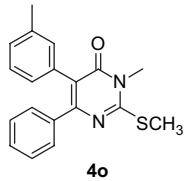
Scheme 8. The modified one-pot process.

Table 2. Syntheses of 2-thiomethyl-pyrimidin-4-ones **4** via Scheme 8

Entry	Ester	Nitrile	Product	Yield (%)
1			 **4a**	51
2			 **4b**	51
3			 **4c**	50
4			 **4d**	50
5			 **4e**	50
6			 **4f**	65
7			 **4g**	63
8			 **4h**	40
9			 **4i**	60

(*continued*)

Table 2. (*continued*)

Entry	Ester	Nitrile	Product	Yield (%)
10			 **4j**	60
11			 **4k**	66
12			 **4l**	25
13			 **4m**	30
14			 **4n**	0
15			 **4o**	0

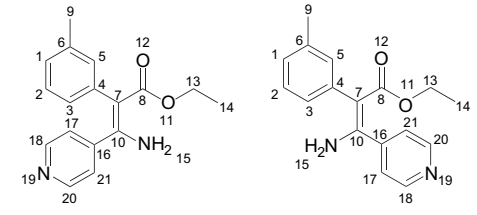
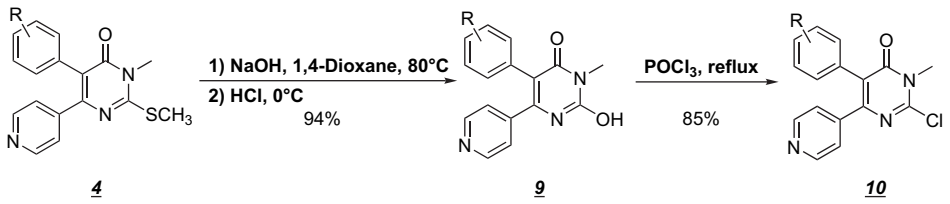


Figure 2.

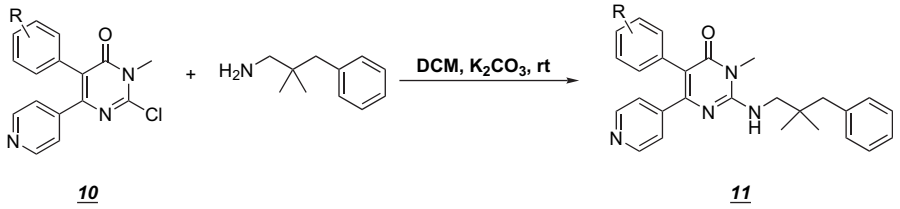
chloro-pyrimidines with amino nucleophiles has been reported to proceed under mild conditions,[19] the 2-thiomethyl moiety was converted to the more reactive corresponding 2-chloro derivative. First, hydrolysis of the sulfide was readily accomplished with aqueous sodium hydroxide in an organic solvent system (e.g., dioxane or THF/MeOH). Adjustment of the pH of the reaction solution to 6–7 precipitated the desired hydroxypyrimidinones **9** (Scheme 9).

Standard procedures were applied for the conversion of uracil **9** into the chloropyrimidinone **10**, utilizing either PCl_5, $SOCl_2$, or $POCl_3$.[20] The use of neat $POCl_3$ as solvent under reflux conditions afforded the best results (Scheme 9). After chromatographic purification, the chloride **10** was used as a reactive intermediate to introduce a variety of amines via nucleophilic displacement under mild conditions. An example is shown in Scheme 10.

In summary, a concise, scaleable synthesis of **10**, a building block for p38 kinase inhibitors, has been realized. This new route represents a significant improvement over the initial medicinal chemistry route. The key step is the one-pot construction of 5-aryl-3-methyl-2-methylsulfanyl-6-pyridin-4-



Scheme 9. Conversion of the sulfide-pyrimidinone **4** to chloro-pyrimidinone **10**.



Scheme 10. Nucleophilic displacement of chloro-pyrimidinone **10** with amine.

yl-3*H*-pyrimidin-4-one **4** from aryl acetic acid ethyl ester **1** and 4-cyanopyridine via enolate/nitrile nucleophilic condensation, isothiocyanate additon/cyclization, and subsequent S-methylation using equimolar amounts of all reactants. The convenient temperature range of this process (−5 °C to rt) and ease of isolation offer additional advantages. Subsequent hydrolysis of the thiomethyl group to the hydroxyl group, followed by chlorination provided the key intermediate, 2-chloro-3-methyl-6-pyridin-4-yl-5-aryl-3*H*-pyrimidin-4-one **10**. This class of reactive building blocks enabled the exploration of a variety of side chains at the 2-position of the pyrimidinone in an effort to optimize potency and in vivo efficacy.

3. Experimental

3.1. General

Solvents and reagents were obtained from commercial sources and used as received. Proton and carbon NMR spectra were obtained using a Bruker Avance II 400 MHz spectrometer. The signals are reported in parts per million relative to TMS using $CDCl_3$ as a solvent (unless otherwise indicated). The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in Hertz (Hz) using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. High-resolution mass spectra (HRMS) were acquired on a 7 Tesla Bruker Apex IV Fourier-Transform Mass Spectrometer (FTMS) using ESI ionization modes. FTIR spectra were obtained using a Nicolet 410 FT-IR spectrophotometer. Mercaptan safety studies were performed by the Wisconsin Occupational Health Lab of Madison, Wisconsin. Column chromatography was performed using silica gel 60-200 from EM Science. High-pressure liquid chromatography (HPLC) was performed with an Agilent 1100 series.

3.2. General procedure for the preparation of 5-aryl-3-methyl-2-methylsulfanyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (4)

To a solution of the ester (6.9 mol) and 4-cyanopyridine (7.0 mol) in DMF (15 L) was slowly added *t*-BuOK (1.0 M in *t*-BuOH, 7 L, 7.0 mol). The resultant dark-red solution was stirred at room temperature for 1.5 h. A DMF solution of methyl isothiocyanate (8.4 mol dissolved in 614 mL DMF) was added to the dark-red solution at such a rate that the internal temperature was maintained below 25 °C. After the addition was complete, the mixture was stirred at room temperature for 1 h. The solution was cooled to 0 °C, and methyl iodide (7.0 mol) was added at such a rate that temperature remained below 5 °C. The reaction mixture was stirred for 1 h at room temperature, and then cooled to 0 °C. Deionized water (21.5 L) was added at such a rate that internal temperature was maintained below 10 °C. The resulting suspension was stirred at room temperature for 16 h. The solid was filtered off via an Aurora filter. The wet cake was washed with water (3×3 L) and dried in an oven under vacuum at 70 °C to provide the desired pyrimidinones.

4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.66 (s, 3H), 3.61 (s, 3H), 6.9 (d, J=7.5 Hz, 1H), 7.03 (s, 1H), 7.08 (d, J=7.5 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.23 (d, J=6 Hz, 2H), 8.46 (d, J=6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 21.3, 30.8, 120.8, 123.8, 127.7, 128.2, 128.7, 131.1, 133.1, 137.8, 145.9, 149.4, 154.0, 161.0, 162.3. FTIR (KBr) ν_{max} 1659, 1596, 1571, 1540, 1525, 1409, 1367, 1347, 1310, 1188, 1165, 1099, 1088, and 1068 cm^{-1}. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{17}N_3OS$ 323.1092, found 323.1079.

4b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 7.12 (d, J=5.33 Hz, 2H), 7.22 (d, J=3.82 Hz, 2H), 7.26 (d, J=5.33 Hz, 2H), 8.50 (d, J=3.82 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.9, 119.4, 123.9, 128.6, 131.8, 132.2, 134.0, 145.7, 149.7, 154.6, 161.8, 162.1. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}ClN_3OS$ 344.0624, found 344.0618.

4c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 6.98 (d, J=8.61 Hz, 2H), 7.15 (d, J=8.61 Hz, 2H), 7.22 (d, J=5.87 Hz, 2H), 8.49 (d, J=5.87 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 30.9, 115.6, 119.6, 123.9, 129.2, 132.6, 145.8, 149.6, 154.5, 161.2, 162.3, 163.6. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}FN_3OS$ 328.09144, found 328.09166.

4d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.63 (s, 3H), 6.96 (dd, J=5.28, 1.37 Hz, 1H), 7.33 (d, J=8.22 Hz, 1H), 7.35 (s, 1H), 7.43 (t, J=8.22 Hz, 1H), 7.49 (s, 1H), 7.57 (d, J=7.63 Hz, 1H), 8.21 (d, J=5.28 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 31.0, 119.5, 122.5, 124.5, 125.2, 127.7, 129.0, 130.8, 131.1, 133.8, 134.2, 148.5, 149.3, 151.7, 153.7, 161.7, 162.7. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{13}ClF_3N_3OS$ 412.01927, found 412.04932.

4e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.66 (s, 3H), 3.61 (s, 3H), 6.90 (d, J=7.43 Hz, 1H), 7.01 (m, 2H), 7.12 (d, J=7.63 Hz, 1H), 7.19 (t, J=7.63 Hz, 1H), 7.41 (s, 1H), 8.18 (d, J=5.09 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.4, 29.9, 120.3, 121.8, 123.5, 126.7, 127.5, 128.1, 130.1, 131.7, 137.2, 148.0, 148.1, 150.4, 151.7, 160.5, 161.2. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{16}ClN_3OS$ 358.0781, found 358.0785.

4f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 6.95 (dd, J=5.2, 1.24 Hz, 1H), 7.23 (dd, J=6.06, 1.57 Hz, 2H), 7.33 (d, J=8.41 Hz, 1H), 7.37 (d, J=1.76 Hz, 1H), 8.54 (dd, J=6.26, 1.57 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 31.0, 118.2, 123.8, 130.2, 130.3, 132.2, 132.5, 132.7, 133.4, 145.3, 149.8, 155.0, 161.8, 162.4. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{13}Cl_2N_3OS$ 378.02291, found 378.02324.

4g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.67 (s, 3H), 7.25 (m, 3H), 7.48 (m, 2H), 7.77 (m, 4H), 8.45 (d, J=7.24 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 31.4, 120.9, 124.4, 126.5, 126.8, 127.9, 128.1, 128.2, 128.3, 128.6, 128.8, 130.6, 131.2, 133.2, 133.6, 146.4, 149.9, 154.9, 161.8, 162.8. HRMS (ESI) *m/e* (M+H) calcd for $C_{21}H_{17}N_3OS$ 360.11651, found 360.11635.

4h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.64 (s, 3H), 7.25 (m, 5H), 7.48 (m, 2H), 7.75 (m, 2H), 7.83 (m, 2H), 7.93 (d, J=7.24 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 31.0, 120.1, 126.4, 126.7, 126.8, 127.7, 128.0, 128.2, 128.5, 130.1, 130.6, 132.9, 133.3, 135.7, 138.6, 152.1, 161.6, 162.3. HRMS (ESI) *m/e* (M+H) calcd for $C_{21}H_{17}N_3O_2S$ 376.1119, found 376.1116.

4i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 7.00 (d, J=8.02 Hz, 1H), 7.17–7.19 (m, 1H), 7.22 (dd, J=6.26, 1.57 Hz, 2H), 7.25–7.27 (m, 2H), 8.50 (d, J=6.06 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.9, 119.3, 123.8, 129.1, 130.8, 134.2, 135.2, 145.5, 149.7, 154.8, 161.9, 162.0. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}ClN_3OS$ 344.0624, found 344.0622.

4j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 3.63 (s, 3H), 7.08 (dd, J=7.63, 1.57 Hz, 1H), 7.17–7.29 (m, 4H), 7.41 (d, J=7.24 Hz, 1H), 8.48 (d, J=5.87 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.9, 118.8, 123.1, 127.1, 129.7, 129.8, 132.2, 133.0, 134.7, 145.5, 149.6, 155.3, 161.4, 162.4. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}ClN_3OS$ 344.0624, found 344.0615.

4k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.62 (s, 3H), 6.95 (m, 1H), 7.03 (t, J=8.60 Hz, 1H), 7.23 (dd, J=6.06, 1.57 Hz, 2H), 7.32 (dd, J=7.04, 2.15 Hz, 1H), 8.53 (d, J=6.06 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 31.0, 116.7, 118.4, 121.2, 123.8, 130.4, 130.8, 133.0, 145.5, 149.8, 154.9, 156.5, 159.0, 162.2. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{13}ClFN_3OS$ 362.0530, found 362.0522.

4l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.62 (s, 3H), 6.95 (dd, J=5.2, 1.24 Hz, 1H), 7.23 (dd, J=3.8, 1.88 Hz, 2H), 7.33 (d, J=5.17 Hz, 1H), 7.37 (d, J=1.22 Hz, 1H), 8.53 (d, J=3.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 31.0, 120.7, 121.4, 122.4, 124.4, 125.4, 126.9, 127.3, 128.3, 130.0, 130.4, 133.4, 133.9, 144.2, 148.4, 149.6, 154.9, 156.5, 161.7, 162.2. HRMS (ESI) *m/e* (M+H) calcd for $C_{22}H_{16}F_3N_3OS$ 428.1044, found 428.1047.

4m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.66 (s, 3H), 3.61 (s, 3H), 6.9 (d, J=7.5 Hz, 2H), 6.92 (d, J=4.70 Hz, 1H), 7.06–7.15 (m, 4H), 7.55 (t, J=4.70 Hz, 1H), 8.45 (d, J=3 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 21.4, 30.8, 120.4, 122.4, 127.9, 128.3, 128.7, 131.4, 133.5, 134.1, 137.0, 138.0, 149.4, 150.8, 154.0, 161.0, 162.4. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{17}N_3OS$ 324.1170, found 324.1171.

3.3. General procedure for the preparation of 5-aryl-2-hydroxy-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (9)

To a solution of the sulfide (1.32 mol) in 1,4-dioxane (1.05 L) was added 2 N NaOH (6.6 mol, 5 equiv). The solution was heated to 80 °C and allowed to stir overnight under N_2. Upon complete conversion, the reaction mixture was cooled to 0 °C. HCl 1 N (6.1 L) was added slowly until the pH reached 7. The product was then collected on a fritted glass funnel, and washed three times with copious amount of water. The solid was then dried at 80 °C in vacuo to provide the product as a white solid (94%). This product is of suitable purity to be taken directly to the next step; however, a cleaner reaction profile was obtained if the crude product was further dried via azeotropic distillation with toluene.

9a (R=*m*-CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.23 (s, 3H), 6.76 (d, J=7.5 Hz, 1H), 6.9 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 7.04 (t, J=7.5 Hz, 1H), 7.2 (d, J=6.0 Hz, 2H), 8.48 (d, J=6.0 Hz, 2H), 11.5 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 27.2, 111.8, 120.7, 123.7, 127.6, 128.5, 132.0, 132.7, 136.6, 140.3, 146.0, 149.5, 150.8, 162.8. FTIR (KBr) ν_{max} 3056, 3041, 2917, 2776, 1720, 1652, 1602, 1450, 1420, 1297, 1228, 1072, and 1004 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.50; H, 5.18; N, 14.45.

3.4. General procedure for the preparation of 5-aryl-2-chloro-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (10)

A three-necked, 2-L round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, temperature probe, and gas inlet/exit was charged with the hydroxide (2 mol) and then $POCl_3$ (70 mol, 35 equiv). The suspension was heated to reflux and a solution was obtained within 10 min. The reaction was allowed to proceed for 16 h at reflux, and the excess $POCl_3$ was distilled under low pressure. The resulting dark residue was allowed to cool to −5 to 0 °C

and a mixture of dichloromethane/ice water was added. Saturated aqueous $NaHCO_3$ was added dropwise into the cooled DCM/water solution with aggressive agitation. The basic quenching was completed once the pH reached 6–7. The phases were separated and the organic layer was washed with a 10% aq solution of $NaHCO_3$ followed by water, and allowed to dry over Na_2SO_4. The crude chloride was isolated after removal of solvent and purified by chromatography with ethyl acetate/hexanes to give the pure chloride (85%).

10a (R=*m*-CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.76 (s, 3H), 6.91 (d, J=7.5 Hz, 1H), 7.02 (s, 1H), 7.16 (m, 4H), 8.48 (d, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 33.9, 123.5, 124.4, 127.4, 128.4, 129.2, 129.3, 130.8, 132.1, 138.1, 144.4, 147.8, 149.6, 154.6, 162.3. FTIR (KBr) ν_{max} 1662, 1582, 1551, 1532, 1414, 1350, 1167, and 1094 cm^{-1}. Anal. Calcd for $C_{17}H_{14}Cl\ N_3O_2$: C, 65.49; H, 4.53; N, 13.45. Found: C, 65.41; H, 4.54; N, 13.26.

3.5. General procedure for the preparation of 2-alkylamino-5-aryl-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (11)

A three-necked, 2-L round-bottomed flask equipped with a mechanical stirrer, reflux condenser, temperature probe, and gas inlet/exit were charged with 5-aryl-2-chloro-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (0.15 mol), the alkylamine (0.165 mol), dichloromethane (1 L, 0.15 M), and potassium carbonate (0.165 mol). The reaction mixture was stirred for 16 h at ambient temperature under nitrogen. Water was then added into the reaction solution. The phases were separated, and the organic layer was washed with a 10% aq solution of $NaHCO_3$, followed by water, and allowed to dry over Na_2SO_4. The crude product was isolated after removal of solvent and purified by chromatography with ethyl acetate/hexanes to give the pure product (90%).

11 (R=*o*-F): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H), 2.67 (s, 2H), 3.11 (s, 3H), 3.56 (d, J=5.7 Hz, 2H), 5.30 (s, 1H), 6.90–6.94 (m, 2H), 7.05–7.09 (m, 2H), 7.12–7.14 (m, 2H), 7.23–7.25 (m, 2H), 7.29–7.36 (m, 3H), 8.40 (d, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.8, 36.1, 47.8, 51.4, 113.5, 115.1, 115.3, 124.0, 126.8, 128.6, 130.3, 132.8, 138.7, 146.9, 149.4, 152.5, 156.5, 162.6, 163.6. HRMS (ESI) *m/e* (M+H) calcd for $C_{27}H_{27}FN_4O$ 443.2242, found 443.2246.

3.6. Structural elucidation of 5

^{1}H and ^{13}C NMR spectra were recorded in 0.15 mL DMSO-d_6 at 30 °C (303 K) in 3 mm NMR tube (3 mm Bruker DCH Dual CryoProbe) and run at 600.13 and 150.92 MHz on a Bruker Avance 600 MHz spectrometer. Chemical shifts are reported in parts per million by assigning the residual solvent peak to 2.50 and 39.51 ppm for DMSO for ^{1}H and ^{13}C, respectively. The nuclear overhauser effect (NOE) experiments were determined with an 800 ms mixing time for the one-dimensional (1D) selective NOE and the two-dimensional (2D) nuclear overhauser effect spectroscopy (NOESY). Both the ^{1}H–^{13}C heteronuclear single quantum correlation (HSQC) and the ^{1}H–^{13}C heteronuclear multiple bond correlation (HMBC) spectra were determined using gradient pulses for coherence selection. The HSQC spectrum was determined with decoupling during acquisition. Delays corresponding to one bond ^{13}C–^{1}H coupling (ca. 145 Hz) for the low-pass filter and the 2–3 bond ^{13}C–^{1}H long-range coupling (7.7 Hz) were used for the HMBC.

3.6.1. (*Z*)-3-Amino-3-pyridin-4-yl-2-*m*-tolyl-acrylic acid ethyl ester ((*Z*)-5). ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.09 (t, J=7.1 Hz, 3H, H-14), 2.09 (s, 3H, H-9), 4.04 (q, J=7.1 Hz, 2H, H-13), 6.71 (d, J=7.6 Hz, 1H, H-3), 6.74 (s, 1H, H-5), 6.79 (d, J=7.6 Hz, 1H, H-1), 6.91 (t, J=7.6 Hz, 1H, H-2), 7.07 (d, J=6.1 Hz, 2H, H-17, 21), 7.77 (d, J=6.1 Hz, 1H, H-15), 8.38 (d, J=6.1 Hz, 2H, H-18, 20), 8.71 (d, J=6.1 Hz, 1H, H-15); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.5 (C-14), 20.9 (C-9), 58.7 (C-13), 97.1 (C-7), 123.5 (C-17, 21), 126.2 (C-1), 127.0 (C-2), 129.8 (C-3), 133.4 (C-5), 135.9 (C-4), 137.0 (C-6), 145.5 (C-16), 149.1 (C-18, 20), 150.3 (C-10), 169.0 (C-8).

1D ^{1}H NOE experiments using selective excitation with a shaped pulse (gradient version) were used to determine the stereochemistry of **5** (Fig. 2). Irradiation of the aromatic protons at C-17, 21 elicited NOE signals from H-3 (weak), H-5 (weak), and H-18, 20 (strong), confirming further that the disposition of tolyl and the pyridine rings are such as those for the (*Z*) isomer and suggestive of a stacking interaction. Irradiation of the methyl protons at C-9 elicited NOE signals from H-1 (weak), H-3 (strong), H-5 (strong), H-13 (weak), H-14 (weak), H-17, 21 (weak), and H-18, 20 (weak), indicating once again that compound **5** exists as the (*Z*) isomer, with evidence of stacking of the aromatic rings and a disposition of the ethyl group *syn* to the tolyl ring. The distinct proton chemical shifts corresponding to the primary amino group (δ, 7.77 and 8.71 ppm) suggest restricted rotation about the C–N bond.

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References and notes

1. Lee, J. C.; Laydon, J. T.; McDonnell, P. C. *Nature* **1994**, *372*, 739–746.
2. Hanson, G. J. *Exp. Opin. Ther. Patents* **1997**, *15*, 729–733.
3. Boehem, J. C.; Adams, J. L. *Exp. Opin. Ther. Patents* **2000**, *10*, 25–37.
4. Lee, J. C.; Kumar, S.; Griswold, D. C.; Underwood, D. C.; Votta, B. J.; Adams, J. L. *Immunopharmacology* **2000**, *47*, 185–201.
5. Adams, J. L.; Gallagher, T. F.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Gum, R. J.; Webb, E. F.; Sorenson, M. E.; Smietana, J. M.; Garigipati, R. S.; Hall, R. F. *Spec. Publ. R. Soc. Chem.* **2001**, *264*, 162–173.
6. Adams, J. L.; Badger, A. M.; Kumar, S.; Lee, J. C. *Prog. Med. Chem.* **2001**, *38*, 1–60.

7. Dominguez, C.; Tamayo, N. *Exp. Opin. Ther. Patents* **2005**, *15*, 801–816.
8. Dominguez, C.; Powers, D.; Tamayo, N. *Curr. Opin. Drug Discov. Devel.* **2005**, *8*, 421–430.
9. Carabateas, P. M.; Brundage, R. P.; Gelotte, K. O.; Gruett, M. D.; Lorenz, R. R.; Opalka, C. J., Jr.; Singh, B.; Thielking, W. H.; Williams, G. J.; Lesher, G. Y. *J. Heterocycl. Chem.* **1984**, *21*, 1849–1856.
10. DeStevens, G.; Blatter, H. M.; Carney, R. W. J. *Angew. Chem.* **1966**, *5*, 35–39.
11. Goerdeler, J.; Pohland, H. W. *Chem. Ber.* **1963**, *96*, 526–533.
12. Goerdeler, J.; Gnad, J. *Chem. Ber.* **1965**, *98*, 1531–1543.
13. Lamon, R. W. *J. Heterocycl. Chem.* **1986**, *5*, 837–842.
14. Hassan, K. M.; Youssef, M. S. K.; El-Zohry, M. F.; El-Wafa, R. A. *Phosphorus and Sulfur* **1988**, *40*, 237–241.
15. (a) Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2127–2137; (b) Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 1597–1600.
16. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, B*; Plenum: New York, NY, 2001; Chapter 1.
17. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, B.; Mennuci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowki, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, M.; Head-Gordon, M.; Repogle, E. S.; Pople, J. A. *Gaussian 98 (Revision A.11)*; Gaussian: Pittsburgh, PA, 2001.
18. Cai, G. Unpublished results.
19. Imbach, J. L.; Jacquier, R.; Romane, A. F. S.; Montpellier, F. *J. Heterocycl. Chem.* **1967**, *4*, 451–452.
20. Chesterfield, J. H.; McOmie, J. F. W.; Tute, M. S. *J. Chem. Soc.* **1960**, 4590–4596.

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Synthesis and anticancer activity studies of novel 1-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)uracil and (6′-substituted)-7- or 9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*- or 9*H*-purines

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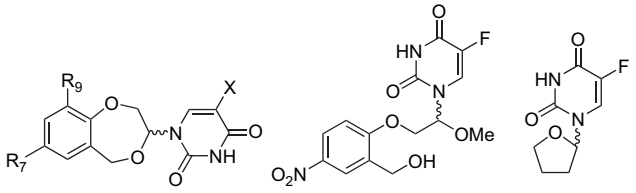
Abstract—On the basis of a molecular variation on an isosteric replacement (F→H) from the prototype (*RS*)-1-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracil, the derivative (*RS*)-1-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)uracil **4** was prepared. Later on, the pyrimidine base was substituted by the purine moiety with the objective of increasing both the lipophilicity and the structural diversity of the target molecules. The 6′-halogen substituent of the (*RS*)-9- or 7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*- or 7*H*-purines shows an interesting reactivity, which is presented and discussed. The anticarcinogenic potential of the target molecules is reported against the MCF-7 cancer cell line.

1. Introduction

The development of new drugs against cancer remains among the priorities of the development of science and fundamental research. The importance of 5-fluorouracil (5-FU) as first choice drug in carcinomas of the gastrointestinal tract is well known, but its toxicity limits its use as a practical antitumour agent for human beings. With the aim of diminishing the toxicity and obtaining biologically active derivatives of 5-FU suitable for oral administration great effort has been made in the preparation of 5-FU prodrug derivatives. Prodrugs have been described as the chemical modification of a biologically active compound to form a new compound, which by either in vivo enzymatic or non-enzymatic attack will liberate the parent drug.[1] A review of the literature on the various prodrugs of 5-FU has been recently published.[2] 1-(2,3-Dihydro-5*H*-1,4-benzodioxepin-3-yl)-5-fluorouracils (**1**–**3**) have proved to be good antiproliferative agents against the MCF-7 human breast cancer cell line (Fig. 1).[3] Such compounds accumulate the cancerous cells in the G_0/G_1 phase. It



1 $R_7 = R_9 = H$; X = F
2 $R_7 = OMe$; $R_9 = H$; X = F
3 $R_7 = H$; $R_9 = OMe$; X = F
4 $R_7 = R_9 = H$; X = H

5

Figure 1.

is important to emphasize that in recent years, the agents targeting the cell cycle are being increasingly appreciated as being ideal for the management of cancer.[4,5] Compound **5**[6] acts similar to Ftorafur, a known prodrug of 5-FU (Fig. 1), because both gather together the cancerous cells in the synthesis phase (S). In contrast to 5-FU,[7] the benzannelated 5-FU derivatives[3] and corresponding open analogues[6] have proved to be non-toxic.

With all this background it seems that compounds **1**–**3** are drugs per se, whilst **5** is a prodrug of 5-FU. In the first phase, we decided to substitute the synthetic pyrimidine base 5-FU

Keywords: Amination; Antitumour compounds; Benzodioxepins; Suzuki reaction; Trifluoromethylation reaction.
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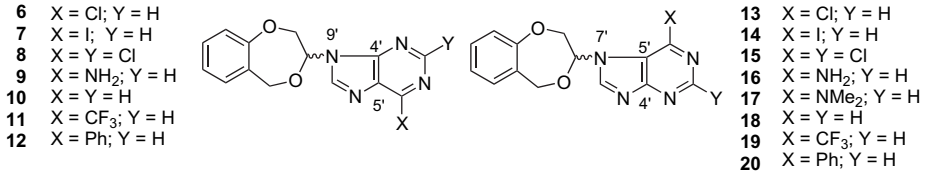


Figure 2.

in derivatives **1–3** for the naturally occurring one, uracil, to produce **4** and to assay its biological properties. Later on, we substituted the pyrimidine base for the purine one, with the objective of increasing both the lipophilicity and the structural diversity of the target molecules. In this case, two isomers were obtained: the *N*-9′-purines **6–12**,[8] and the *N*-7′-purines **13–20** (Fig. 2). Should these compounds show antiproliferative activities, new avenues in anticancer research would be opened based on the non-toxic natural base uracil and purines and with a mechanism of action different from that of 5-FU.

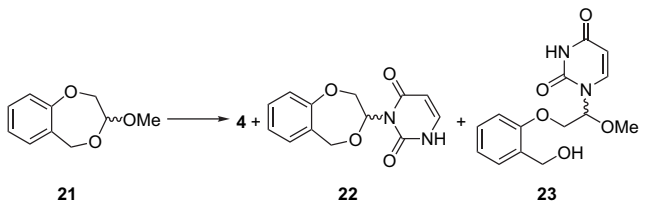
2. Results and discussion

2.1. Synthesis

The preparation of **4** was first achieved by the one-pot condensation of the cyclic acetal **21**[3] and uracil, using trimethylchlorosilane (TCS), 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and tin(IV) chloride as the Lewis acid in anhydrous acetonitrile at room temperature (Table 1): apart from the desired product **4** (3%), the acyclic hemiaminal **23** (5%) was obtained (Table 1, entry 1). As the reaction proceeded with a very low yield, we repeated the process, but varying the reaction time and the Lewis acid. No further improvement in the yield of the target molecule **4** was obtained when the reaction temperature was increased up to 50 °C and with the same Lewis acid. In this case, the disappearance of **21** and the appearance of the *N*-3′ uracil hemiaminal[9] **22** were observed (Table 1, entry 2).

Since TMSOTf is a weaker Lewis acid than $SnCl_4$, less σ complex between uracil and the Lewis acid is formed in the equilibrium,[10] and more free base is present and consequently more *N*-1′ derivatives should have been obtained. Compound **22** was not formed, and the *N*-1′ acyclic derivative **23** was formed in a 29% yield. Trivalent rare earth compounds such as $Sc(OTf)_3$ exhibit characteristic Lewis acid properties, and they activate oxygen and nitrogen functionalities to promote synthetically useful organic transformations.[11] For this reason, certain rare earth(III) compounds, such as $Sc(OTf)_3$ are frequently employed as highly efficient reagents or catalysts in modern organic synthesis. However, the origin of the characteristic chemical properties of rare earth(III) compounds is not yet well understood, although they are generally explained in terms of moderate to strong oxophilicity, long ionic radius and high coordination ability. In addition, when $Sc(OTf)_3$ is used no rigorous anhydrous conditions are required, the workup is simpler and the Lewis acid can be recovered and reused. In this case, the total yield of the alkylated uracils was 44% [23% (**4**), 2% (**22**) and 19% (**23**), Table 1, entry 4].

Table 1. Reaction between **21** and uracil

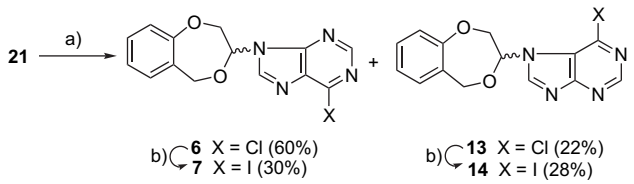


21 **22** **23**

Entry	Lewis acid	Reaction time (h)	Temperature (°C)	**4** (%)[a]	**22** (%)[a]	**23** (%)[a]
1	$SnCl_4$	24	rt	3	—	5
2	$SnCl_4$	20	50	4	9	—
3	TMSOTf	20	50	4	—	29
4	$Sc(OTf)_3$	21	50	23	2	19

All reactions were carried out with HMDS, TCS, Lewis acid in anhydrous acetonitrile under argon.
[a] Isolated yields.

In order to obtain the (*RS*)-(2,3-dihydro-5*H*-benzo-1,4-dioxepin-3-yl)adenine derivatives **9** (*N*-9′) and **16** (*N*-7′) (see Fig. 2) the direct condensation reaction between **21**[3] and adenine was tried under our simple standard one-step/one-pot conditions.[3,6] However, an inseparable mixture of compounds was obtained and this inconvenience compelled us to change the synthetic strategy, i.e., starting from 6-chloropurine derivatives **6** and **13**, we decided to change the chlorine atom for the amino group. The condensation reaction between **21** and 6-chloropurine was accomplished using tin(IV) chloride as a 1.0 M solution in dichloromethane, TCS and HMDS in dry acetonitrile for 18 h at 45 °C (Scheme 1). The *N*-9′ (**6**, 60%) and *N*-7′ (**13**, 24%) regioisomers produced were separated by flash chromatography. Nucleophilic displacement of halogen atoms in halopurines, especially the readily available chloropurines, has provided the major route to a wide variety of substituted purines including nucleosides.[12] The purine 6-position is the most reactive towards nucleophilic substitution, and moderately elevated temperatures (25–80 °C) are usually applied in order to introduce aliphatic or aromatic amines.[13] Several conditions were used, such as treating **6** and **13** with a saturated solution of ammonia in ethanol at 80 °C during 4 and 27 h in a sealed tube. As the starting materials were



Scheme 1. Reagents and conditions: (a) 6-chloropurine, HMDS, TCS, $SnCl_4/CH_2Cl_2$, MeCN, 18 h, 45 °C; (b) NaI/TFA/butanone at −50 to −40 °C.

recovered unaltered we decided to force the experimental conditions, changing the solvent (ethanol by DMF) thus allowing us to increase the heating temperature in a sealed tube (120 °C). Under such conditions, **6** yielded the *N*-9′ adenine derivative **9** and the *N*-7′ adenine one **16**, which were separated by flash chromatography (Table 2, entry 1). Reversibility of such a process is the more plausible interpretation for the course of this reaction. The *N*-9′-tetrahydropyranyl-2,6-dichloropurine fragment, which is a similar compound to **6**, loaded in the Merrifield resin, has been reported in combinatorial chemistry.[14,15] The ligand contained two differentially reactive Cl substituents at C-6′ and C-2′ that could be sequentially reacted with a variety of amines. In the first relatively mild reaction, the chlorine atom at C-6′ was replaced (5 equiv of amine, 80 °C, 3 h). The *N*-9′-tetrahydropyranyl-2,6-dichloropurine moiety and compounds **6** and **13** are very similar but the latter are more stable and consequently, their chlorine atoms at C-6′ were displaced under harsher conditions.

When the *N*-7′-alkylated-6′-chloropurine **13** was treated under the conditions used for **6**, the *N*-7′-(dimethylamino)purine **17** was obtained, together with the *N*-7-adenine **16**. Trying to extend the scope of the unreported reversibility from the *N*-9′-(6-halopurine) we used two cross-coupling reactions. To undertake these reactions we previously changed the *N*-9′-(6-chloropurine) **6** to the 6-iodo analogue **7** (Finkelstein reaction, Scheme 1), under conditions successfully used to perform the same process in nucleosides.[16] Such a process carried out on the *N*-7′-(6-chloropurine) **13** gave the *N*-7′-(6-iodopurine) **14** (Scheme 1). Compounds **7** and **14** were also obtained by the direct condensation between **21**[3] and 6-iodopurine[17] but were produced with poorer yields (9% of **7** and 15% of **14**).

The copper(I) iodide/potassium fluoride-mediated trifluoromethylation reaction on **7** was tried next under conditions previously used for a 9-(THP-protected) 6-iodopurine.[18] In this way 6-trifluoromethyl isomers **11** and **19** were isolated (Table 2, entry 2), proving the reversibility of the process, in contrast to what was reported by Hocek and Holý.[18] The same reaction carried out on the *N*-7′-protected 6-iodopurine **14** produced only the *N*-7′ isomer **19** (Table 3, entry 2). Finally the Suzuki cross-coupling reaction was carried out on **7** using the conditions described by Mederski et al.,[19] and the two 6-phenyl isomers **12** and **20** (Table 2, entry 3) were produced. When the same reaction was carried out on **14**, compound **20** was the only product obtained (Table 3, entry 3).

Table 3. Amination, copper(I) iodide/potassium fluoride-mediated trifluoromethylation and Suzuki cross-coupling reactions carried out on the *N*-7′-alkylated-6′-halopurines **13** and **14**

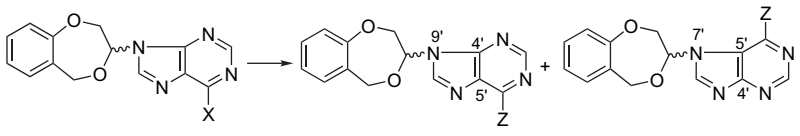
Entry	Starting material	Conditions	*N*-7-(6-Substituted)purine, yield (%)
1	**13** (X=Cl)	DMF, saturated solution of NH_3, 120 °C, sealed tube	**17** (Z=NMe_2), 70 + **16** (Z=NH_2), 12
2	**14** (X=I)	CF_3SiMe_3, KF and CuI in a mixture of DMF and NMP, 60 °C, sealed tube	**19** (Z=CF_3), 14
3	**14** (X=I)	$PhB(OH)_2$, $PdCl_2(dppf)$,[a] 85 °C, Na_2CO_3 in dimethoxyethane	**20** (Z=Ph), 13

[a] [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).

2.2. Mechanistic aspects on the synthesis of the *N*-9′ and *N*-7′ alkylated purine

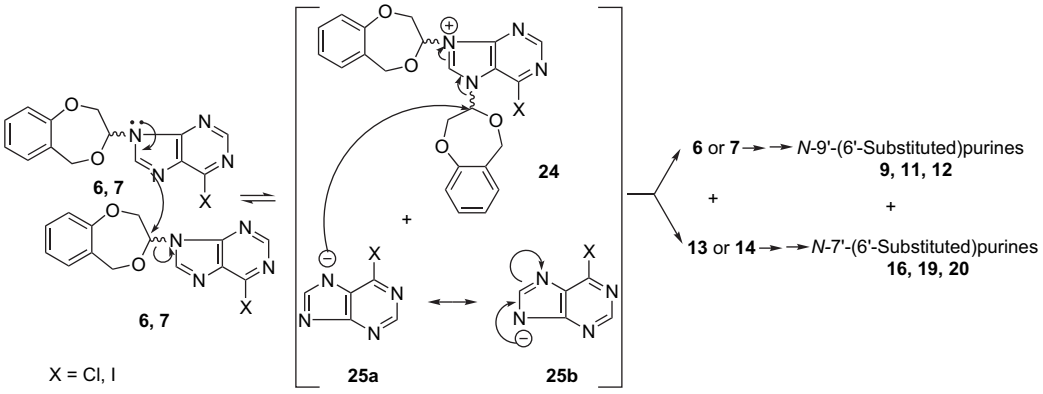
Little attention has been paid to the fact that preformed purine *N*-7′- or *N*-9′-nucleosides can isomerize at elevated temperatures. It was observed that *N*-9′-ribosylated 6-oxopurines or their corresponding acyclic derivatives, which are fully acylated, undergo thermal isomerization to *N*-7′/*N*-9′-mixtures.[20,21] The reaction takes place even in the absence of a catalyst when the starting material is melted for 5–10 min at a temperature exceeding 190 °C. Golankiewicz et al.[22] have reported the isomerization of protected 2′-deoxyguanosine derivatives, melted and in solution. It has been postulated in relation to the mechanism of the *N*-9′→*N*-7′ isomerization reactions of 6-oxopurine ribonucleosides[23] and acyclonucleosides,[24] that a bis-riboside is the intermediate of such transformations. We used this background and a tentative explanation is depicted in Scheme 2, through the intermediate (*RS*)-6′-halo-7,9-bis(2,3-dihydro-5*H*-benzo-1,4-dioxepin-3-yl)purine **24**.

Table 2. Amination, copper(I) iodide/potassium fluoride-mediated trifluoromethylation and Suzuki cross-coupling reactions carried out on the *N*-9′-alkylated-6′-halopurines **6** and **7**



Entry	Starting material	Conditions	*N*-9′-Alkylated-(6′-substituted)purine, yield (%)	*N*-7′-Alkylated-(6′-substituted)purine, yield (%)
1	**6** (X=Cl)	DMF, saturated solution of NH_3, 120 °C, sealed tube	**9** (Z=NH_2), 60	**16** (Z=NH_2), 22
2	**7** (X=I)	CF_3SiMe_3, KF and CuI (DMF and NMP), 60 °C, sealed tube	**11** (Z=CF_3), 49	**19** (Z=CF_3), 20
3	**7** (X=I)	$PhB(OH)_2$, $PdCl_2(dppf)$,[a] 85 °C, Na_2CO_3 in dimethoxyethane	**12** (Z=Ph), 52	**20** (Z=Ph), 26

[a] [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).



Scheme 2. Mechanism of the transformation of the *N*-9′-alkylated-6′-halopurines **6**, **7** into the *N*-9′-(6′-substituted)purines **9**, **11** and **12**, and the *N*-7′-(6′-substituted)purines **16**, **19** and **20**.

The electronic pair of *N*-9′ assisted the nucleophilic attack of the $N_{7'}$=$C_{8'}$ double bond of compounds **6** and **7** to the hemiaminalic carbon atom (C-3) of the benzo-1,4-dioxepin-3-yl moiety of other molecules **6** and **7**, consequently producing the leaving 6-halopurine in its anionic forms **25a** and **25b**. Nevertheless, it has to be pointed out that the resonance hybrid **25a** is favoured over **25b** due to the stabilization of its negative charge on *N*-7′ by the −I effect caused by the halogen atom at position 6′. Anion derived from the 7*H*-purine **25a** is responsible for the formation of compounds **13** and **14**, the electron deficient character of *N*-9′ atom of the intermediate **24** being the driving force of such a process. The whole transformation is reversible, the major products being the *N*-9′-purines **9**, **11** and **12**, over their corresponding regioisomers **16**, **19** and **20**. Compounds **9**, **11** and 1**2** are more stable than their regioisomers **16**, **19** and **20**. The most stable conformation of **9** is thermodynamically favoured over the most stable one of its *N*-7′ isomer **16**, the difference in the heats of formation being ≈5 kcal/mol. Conformational analysis of **9** and **16** was performed as previously reported.[6] Therefore, it can be concluded that the isomerization *N*-9′→*N*-7′ is thermodynamically controlled (the *N*-9′/*N*-7′ ratios are always >1:**9**/**16**=60/22=2.7; **11**/**19**=49/20=2.4; **12**/**20**=52/26=2, Table 2). Once the isomerization *N*-9′→*N*-7′ had taken place, the subsequent irreversible process occurred (S_NAr by the amino group, and cross-coupling reactions) to produce the target compounds **16**, **19** and **20**. In order to cast some light on the mechanism, we heated compound **9** at 130 °C for 27 h in a sealed tube that contained a saturated solution of NH_3 gas in DMF and no transformation was observed. This experimental feature may be accounted for if we assume that the *N*-9′-alkylated-6′-halopurine→*N*-7′-alkylated-6′-halopurine isomerizations (**6**→**13** and **7**→**14**) took place *before* the substitution process (Scheme 2).

When we tried to systematize the transformation shown in Table 3, entry 1 there was one distinctive fact: the chlorine atom at position 6′ of the purine base was substituted by the NMe_2 group when, in the case of **6** (*N*-9′), the only nucleophile was ammonia. The irreversible interchange reaction between the chlorine atom of **13** and the two nucleophilic species (NH_3 and $HNMe_2$) produced **17** and **16** (Table 3, entry 1). It has been reported that the synthesis of 4-(dimethylamino)quinoline is accomplished by the treatment of 4-chloroquinoline with DMF and KOH at reflux for 20 h.[25] Moreover, a convenient dimethylamination of various heterocyclic, including 6-chloropurine, and aromatic compounds having the activated chlorine atom has recently been published.[26] By means of this procedure the dimethylamino compound **17** is obtained, together with the amino one **16**.

It can be hypothesized that a reversible process took place when the *N*-7′-alkylated-6′-halopurines **13** or **14** was the starting reactants through the intermediate **26** (Fig. 4). In this case, the target molecules **16**, **17**, **19** and **20** could be formed directly from the starting materials **13** or **14**, or from the resonance hybrid **25a**. It is worth pointing out that the nucleophilic attack of **25a** over C-3 of the intermediate **26** (similar to the attack of **25a** on **24**, depicted in Scheme 2) would give rise to two molecules of **13** or **14**. Moreover, the *N*-9′-alkylated-6′-halopurines **6** or **7**, or the substitution products at their 6′-positions were not detected, in accordance with the experimental results. On comparing both intermediates (**24** and **26**), it seems that **26** is less stable than **24**, owing to the −I effect of the 6′-halogen. Accordingly,

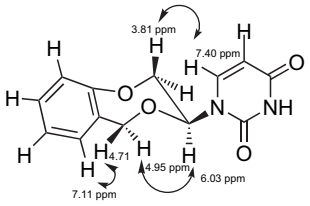


Figure 3. Conformation of **4**, showing the NOE effects by the double arrows, found in the NOESY experiment.

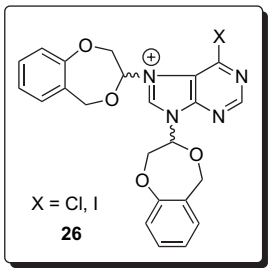


Figure 4. Intermediate **26** is hypothesized when the *N*-7′-alkylated-6′-halopurines **13**, **14** are the starting materials for their transformations into the *N*-7′-(6′-substituted)purines **16**, **19** and **20**.

the yields of compounds **16**, **19** and **20** obtained from the *N*-9′-alkylated-6′-halopurines **6** and **7** were higher than those of the same compounds prepared from the *N*-7′-alkylated-6′-halopurines **13** and **14** (compare entries 1, 2 and 3 of Tables 2 and 3). Entries 2 and 3 of Table 3 show the yields of the 6′-trifluoromethyl-*N*′-7-alkylated purine (**19**, 14%) and the 6′-phenyl-*N*′-7-alkylated purine (**20**, 13%) derivatives.

2.3. Spectroscopic analysis of 4, and of the *N*-9′ and the *N*-7′ alkylated purines

Hydrogens of the seven-membered framework of **4** appear between $\delta \approx 6$ ppm and 3.80 ppm. The chemical shift found for the hemiaminalic hydrogen H-3 is δ 6.03 ppm with a dd multiplicity, and the respective couplings to the vicinal hydrogens (H-2) are 2.2 and 6.5 Hz. In fact, the two H-2 atoms appear as two dd's with a J_{gem}=12.9 Hz and the two coupling constants observed at δ 6.03 ppm (2.2 and 6.5 Hz). Finally, each of the two benzylic H-5 atoms resonates as two doublets at δ 4.95 and 4.71 ppm with a J_{gem}=14.1 Hz, showing a diastereotopic character. At δ 5.65 ppm one hydrogen resonates as a dd (J=1.6 and 8.1 Hz), the latter coupling constant being typical of an aromatic hydrogen atom, and this resonance could be assigned to H-5′ of the uracil base. If this is so, H-6′ should also appear as a doublet downfield in relation to H-5′ (δ 7.40 ppm, d, J=8.2 Hz). Should that really be the case, the chemical shift of H-5′ would be confirmed through the connectivity to H-6′ by a ^{1}H–^{1}H-COSY experiment, and the experimental data support these assignments. Similarly, H-3 is related with the more deshielded H-5 atom (δ 4.95 ppm) and this fact strongly supports a chair conformation of the seven-membered moiety in which the hemiaminalic hydrogen atom adopts an axial disposition and hence, the uracil moiety occupies an equatorial position (Fig. 3)

The unequivocal assignment of the benzene hydrogens is the following step. The coupling pattern for H-6 and H-9 is the same (doublets), whilst the same holds true for H-7 and H-8 (double doublets). Nevertheless, the cross-peak in the ^{1}H–^{1}H NMR experiment between the doublet at δ 4.71 ppm (one H-5) and the doublet at δ 7.11 ppm (J=6.3 Hz), allows us to assign the latter to H-6, and the doublet at δ 7.00 ppm (J=7.7 Hz) is indirectly assigned to H-9. The chemical shifts attributed to C-2′, C-9a and C-4′ were distinguished on the basis of their HMBC connectivities. Cross correlations are observed between H-6′ (δ 7.40 ppm), C-2′ (δ 149.91 ppm) and C-4′ (δ 162.90 ppm), between H-8 (δ 7.22 ppm) and C-9a (δ 158.46 ppm), between H-6 (δ 7.11 ppm) and C-9a (δ 158.46 ppm). Additionally, H-9 (δ 7.00 ppm) exhibits a two-bond correlation to C-9a (δ 158.46 ppm), whilst both H-5 and H-2 atoms exhibit a three-bond connectivity to C-9a.

The most important consequence of the ^{1}H NMR study is that it unequivocally proves that the linkage between the seven-membered moiety and uracil is through *N*-1′: (a) on the one hand, the coupling pattern is a double doublet (dd) for H-5′ due to its coupling with H-6′ and a small one ($J_{H5'-H'3}$) through a 1–3 bond relationship, and a doublet for H-6′. Nevertheless, had the hemiaminalic bond been established with *N*-3′ the coupling pattern would have been more complicated due to the simultaneous coupling of H-6′ with H-5′ and H-3′; (b) on the other, the NOESY experiment (correlation through space) between H-6′ and H-2β justifies the conformational preference of the uracil moiety in which H-6′ is near in space to H-2β and accordingly, the carbonyl group C-2′ is far from the referred hydrogen atom and this obviously implies the linkage through *N*-1′.

^{1}H–^{13}C HMBC experiments enabled the complete regiochemical assignment of **6** and **13**. The discrimination between *N*-9′-substituted derivatives on one hand and *N*-7′-substituted derivatives on the other relies on the correlation between H-3 of the seven-membered moiety and C-4′ and C-5′. Very important is the correlation between H-3 (δ 6.32 ppm) and the quaternary carbon at δ 151.58 ppm of **6**, which has the following two consequences: (a) this signal can be assigned to C-4′ and (b) this correlation proves unequivocally that the linkage between the seven-membered moiety and the purine base takes place through *N*-9′ in compound **6**. On the other hand, a cross-peak was found in the HMBC spectrum between H-3 (δ 6.55 ppm) and C-5′ (δ 143.26) of **13**; this experimental fact is unequivocal evidence that the 2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl fragment and the 6-chloropurine system are linked through *N*-7′ in **13**.

Assignments of *N*-9′ versus *N*-7′ isomers can be readily made from the ^{13}C NMR signal of the C-4′ peaks ($CDCl_3$); for the *N*-9′ isomers: δ 151.58 ppm (**6**), δ 152.28 ppm (**8**), δ 150.00 ppm (**9**) and δ 153.07 ppm (**10**); for the *N*-7′ isomers: δ 162.07 ppm (**13**), δ 163.78 ppm (**15**), δ 162.84 ppm (**16**), δ 160.85 ppm (**17**), δ 161.00 ppm (**18**) and δ 161.40 ppm (**20**). These values agree with previous findings on acyclic adenine derivatives.[27]

The most pronounced differences in *N*-9′ (**6**) and *N*-7′ (**13**) regioisomers were found for the proton signals H-2′ and H-8′ of the purine skeleton. Thus, the protons H-2′ and H-8′ in the *N*-7′ isomer (**13**) were shifted downfield (δ 8.90 and 8.70 ppm, respectively) relative to the corresponding ones (δ 8.78 and 8.44 ppm) in the *N*-9′-substituted molecule (**6**). This principle applies for the remaining of the *N*-9′ and *N*-7′ purine isomers, except in two cases: (a) the CF_3-6-substituted purine compounds (**11** and **19**) in which the ^{1}H chemical shifts of both H-2′ and H-8′ atoms are identical and (b) the adenine-containing compounds (**9** and **16**) in which chemical shifts of H-2′ are almost identical (δ 8.35 ppm for **9** and δ 8.36 ppm for **16**).

2.4. Antiproliferative activity against the MCF-7 human breast cancer cell line

Table 4 shows the antiproliferative activities against the MCF-7 human breast cancer cell line for the target compounds, including 5-FU. As a rule the following could be stated: (a) compound **4** shows a similar antiproliferative activity as the 5-FU-containing derivatives **1** and **2** and a better one than **3**; (b) in general, the *N*-7′ purine derivatives present a better activity than the their *N*-9′ regioisomers, except in the case of the CF_3-6′-substituted compounds (**11** and **19**); (c) the adenine-containing derivatives (**9** and **16**) and the *N*,*N*-dimethyladenine structure (**17**) do not show any interesting antiproliferative activities, in contrast to the natural base-containing (uracil) derivative **4**; (d) the presence of at least one halogen atom on the purine skeleton (or in a 6′-methyl group, such as **11**) is necessary to improve the

Table 4. Antiproliferative activities against the MCF-7 cell line for uracil (5-FU and **1**–**4**), *N*-9′ (**6**–**12**) and *N*-7′ (**13**–**20**) purine compounds

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
5-FU	4.32±0.02	**8**	4.40±0.88	**15**	1.28±0.61
1	7.00±0.61[a]	**9**	18.4±3.16	**16**	27.1±4.93
2	4.50±0.33[a]	**10**	44.9±9.83	**17**	22.2±3.80
3	22.0±0.93[a]	**11**	3.21±0.40	**18**	40.4±7.85
4	5.00±0.05	**12**	16.4±0.26	**19**	24.9±1.83
6	4.63±0.01	**13**	2.74±0.31	**20**	22.8±0.19
7	6.75±0.23	**14**	4.01±0.33		

[a] Data taken from Ref. 3.

antiproliferative activity; (e) the most active compound is the *N*-7′-2′,6′-dichlorosubstituted purine (**15**), which is 3.4-fold more potent than 5-FU; its *N*-9′ isomer is equipotent to 5-FU; (f) to the best of our knowledge, the hemiaminals **4**, **13**, **14** and **15** represent a new kind of compounds with a novel structure and a significant anticancer activity against the MCF-7 cell line.

3. Conclusion

In summary, we have synthesized 16 compounds and tested their in vitro anticancer activities against the MCF-7 cancer cell line.[28] These results provide promising information for further development of potent antiproliferative agents. At present, studies are being carried out to determine the mechanism of action at the molecular level of the most active compounds. From a chemical point of view the following aspects have to be pointed out: (a) the NOEDIFF data for **4** are compatible with a chair conformation for the seven-membered ring and an equatorial orientation of the uracil moiety on the C-3 position; (b) the course of the formation of the target molecules **9**, **11** and **12** is the first example of S_NAr and cross-coupling reactions of 6-halopurine through a reversible process, when starting from *N*-9′-alkylated 6′-halopurine isomers. The process is also reversible when the starting materials are the *N*-7′-alkylated 6′-halopurine derivatives (**13** and **14**), but produced only the *N*-7′ products (**16**, **19** and **20**). In both cases, (*RS*)-6′-halo-7,9-bis(2,3-dihydro-5*H*-benzo-1,4-dioxepin-3-yl)purines (**24** and **26**) have been hypothesized as intermediates; (c) in the amination that occurs from the *N*-7′-alkylated 6′-chloropurine **13**, together with ammonia, a second nucleophile arises (dimethylamine) as a consequence of the decomposition of DMF under the high temperature and basic conditions in the sealed tube; (d) in relation to the ^{13}C NMR data, the most pronounced differences affect the C-4′ and C-5′ atoms of both compounds. The signal at ca. δ 162 ppm, corresponding to C-4′ of the purine base, is unequivocal proof of an *N*-7′ isomer against the one at ca. δ 151 ppm, corresponding to the same carbon atom of the other regioisomer (*N*-9′).

4. Experimental

4.1. Chemistry

The general methods were the same as those previously described.[3,6] One-dimensional NOE-difference experiments were performed by irradiation for 4 s in series of eight scans with altering on- and off-resonance. The irradiating power was set low to achieve selectivity. The HMBC spectra[29] were measured using a pulse sequence optimized for 10 Hz (inter-pulse delay for the evolution of long-range couplings: 50 ms) and a 5:3:4 gradient combination. In this way, direct responses (^1J couplings) were not completely removed.

4.2. General procedure for the reaction between (*RS*)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepine 21 and uracil

4.2.1. Method A. Synthesis of (*RS*)-1-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)uracil (4) and (*RS*)-1-[2-(2-hydroxymethylphenoxy)-1-methoxyethyl]uracil (23). A 1.0 M solution of $SnCl_4/CH_2Cl_2$ (1.2 equiv) was added dropwise with stirring under argon at room temperature to a suspension of **21**[3] (1 equiv), uracil (1 equiv), which contains trimethylchlorosilane (TCS, 0.8 equiv) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 0.8 equiv) in dry acetonitrile (4 mL/mmol of **21**). After 24 h of stirring, the reaction was quenched by the addition of a concentrated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 (3×20 mL). The organic layers were pooled, dried (Na_2SO_4), filtered and the solvent removed under vacuum. The residue was purified by flash chromatography under gradient elution conditions using mixtures of CH_2Cl_2/MeOH (100/1→100/5), and **4** (3%) and **23** (5%) were obtained.

*Compound **4***: mp 153–154 °C (decomp.). R_f (EtOAc): 0.69; R_f (EtOAc/hexane, 2/1): 0.42. ^1H–^1H-COSY and NOESY experiments were carried out on **4**. ^1H NMR (300 MHz, $CDCl_3$): δ 8.83 (s, 1H, NH); 7.40 (d, 1H, H-6′, J=8.2 Hz); 7.22 (dd, 1H, H-8, J=1.7, 6.3 Hz); 7.11 (d, 1H, H-6, J=6.3 Hz); 7.02 (dd, 1H, H-7, J=6.4 Hz and indet.); 7.00 (d, 1H, H-9, J=7.7 Hz); 6.03 (dd, 1H, H-3α, J=2.2, 6.5 Hz); 5.65 (d, 1H, H-5′, J=8.2 Hz); 4.95 (d, 1H, H-5α, J_{gem}=14.1 Hz); 4.71 (d, 1H, H-5β, J_{gem}=14.1 Hz); 4.45 (dd, 1H, H-2α, J=2.2, 12.9 Hz); 3.81 (dd, 1H, H-2β, J=6.5, 12.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.90 (C-4′); 158.46 (C-9a); 149.91 (C-2′); 140.51 (C-6′); 129.91 (C-8); 129.83 (C-5a); 129.05 (C-6); 123.97 (C-7); 120.70 (C-9); 102.69 (C-5′); 84.30 (C-3); 73.43 (C-2); 69.86 (C-5). HR (EI) calcd for $C_{13}H_{12}N_2O_4$ 260.0797, found 260.0797. Anal. for $C_{13}H_{12}N_2O_4$: calcd: C 60.00; H 4.65; N 10.76. Found: C 59.88; H 4.35; N 10.38.

*Compound **23***: mp 153–155 °C. R_f (EtOAc): 0.38; R_f (EtOAc/hexane, 2/1): 0.10. ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H, NH); 7.47 (d, 1H, J=8.1 Hz); 7.28 (dd, 1H, J=1.4, 7.5 Hz); 7.26 (dt, 1H, J=1.4, 8.0 Hz); 6.97 (t, 1H, J=7.5 Hz); 6.81 (d, 1H, J=8.0 Hz); 5.99 (t, 1H, J=4.9 Hz); 5.83 (d, 1H, J=8.0 Hz); 4.60 (s, 2H); 4.24 (dd,

1H, J=4.3, 10.1 Hz); 4.12 (dd, 1H, J=5.6, 10.1 Hz); 3.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.11; 155.78; 151.60; 138.86; 129.71; 129.38; 129.06; 121.89; 111.33; 103.50; 84.50 (C-3); 68.00; 61.57; 57.41; one carbon missing. HR LSIMS calcd for $C_{14}H_{16}N_2O_5Na$ $(M+Na)^+$ 315.0956, found 315.0956. Anal. for $C_{14}H_{16}N_2O_5$: calcd: C 57.53; H 5.52; N 9.58. Found: C 57.34; H 5.45; N 9.71.

4.2.2. Method B. Synthesis of 4 and (*RS*)-3-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)uracil (22). The differences in relation to Method A are the following: temperature of addition of the reagents was 0 °C, the reaction temperature was 50 °C and the reaction time 20 h. After the usual workup, **4** (4%) and **22** (9%) were obtained. *Compound 22*: mp 226–228 °C. R_f (EtOAc): 0.49; R_f (EtOAc/hexane, 2/1): 0.21. ^{1}H NMR (DMSO-d_6; 300 MHz): δ 11.20 (s, 1H, NH); 7.45 (d, J=7.6 Hz, 1H); 7.25 (m, 2H); 7.05 (m, 2H); 6.15 (dd, J=1.7, 8.9 Hz, 1H); 5.55 (d, J=7.6 Hz, 1H); 4.90 (d, J_{gem}=13.9 Hz, 1H); 4.75 (dd, J_{gem}=8.9, 12.5 Hz, 1H); 4.65 (d, J_{gem}=13.9 Hz, 1H); 4.35 (dd, J_{gem}=1.6, 12.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 163.35; 159.54; 151.54; 142.28; 131.82; 130.00; 123.87; 120.85; 100.51; 84.44 (C-3); 74.05 (C-2); 70.63 (C-5); one carbon missing. Anal. for $C_{13}H_{12}N_2O_4$: calcd: C 60.00; H 4.65; N 10.76. Found: C 59.77; H 4.58; N 10.42.

4.2.3. Method C. The difference in relation to Method B is the following: the Lewis acid is trimethylsilyl triflate (TMSOTf), and after the usual workup, **4** (4%), and **23** (29%) were obtained.

4.2.4. Method D. The differences in relation to Method B are the following: The reaction time is 21 h, and the Lewis acid is scandium triflate. After the usual workup, **4** (23%), **22** (2%) and **23** (19%) were obtained.

4.2.5. Synthesis of (*RS*)-6-chloro-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purine (6) and (*RS*)-6-chloro-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-purine (13). Starting from **21**[3] and 6-chloropurine, and following Method B the residue obtained was purified by flash chromatography using a mixture of EtOAc/hexane: 6/4 as eluent to give the first fraction as an amorphous white powder identified as **6** (60%); mp 133–134 °C. R_f (EtOAc): 0.42. HMBC experiments were carried out on **6**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H, H-2′); 8.44 (s, 1H, H-8′); 7.31 (dt, 1H, J=1.4, 7.5 Hz, H-8); 7.22 (d, 1H, J=7.5 Hz, H-6); 7.12 (d, 1H, J=8.6 Hz, H-9); 7.11 (t, 1H, J=7.5 Hz, H-7); 6.32 (dt, 1H, J=2.2, 6.2 Hz, H-3); 4.89 (s, 2H, H-5); 4.62 (dd, 1H, J=2.2, 13.0 Hz, H-2); 4.43 (dd, 1H, J=6.2, 13.0 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.79 (C-9a); 152.44 (C-2′); 151.58 (C-4′); 143.88 (C-8′); 137.41 (C-5′); 132.75 (C-5a); 129.36 (C-6); 130.13 (C-8); 124.38 (C-7); 115.12 (C-9); 84.17 (C-3); 73.57 (C-2); 69.10 (C-5); one quaternary carbon missing. HR LSIMS (NOBA matrix) calcd for $C_{14}H_{11}ClN_4O_2Na$ $(M+Na)^+$: 325.0468; found: 325.0468. Anal. for $C_{14}H_{11}ClN_4O_2$: calcd: C 55.55; H 3.66; N 18.51. Found: C 55.63; H 3.80; N 18.46.

The second fraction, as an amorphous white powder was identified as **13** (22%); mp 138–139 °C. R_f (EtOAc): 0.17. HMBC experiments were carried out on **13**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H, H-2′); 8.70 (s, 1H, H-8′); 7.31 (dt, 1H, J=1.6, 7.7 Hz, H-8); 7.22 (d, 1H, J=7.2 Hz, H-6); 7.13 (d, 1H, J=8.1 Hz, H-9); 7.10 (t, 1H, J=7.5 Hz, H-7); 6.55 (dd, 1H, J=2.2, 5.2 Hz, H-3); 4.80 (dd, 2H, J=9.0, 14.0 Hz, H-5); 4.66 (dd, 1H, J=2.2, 13.1 Hz, H-2); 4.40 (dd, 1H, J=5.3, 13.0 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.07 (C-4′); 158.72 (C-9a); 152.98 (C-2′); 147.61 (C-8′); 143.26 (C-5′); 130.32 (C-5a); 130.26 (C-8); 129.45 (C-6); 124.66 (C-7); 120.80 (C-9); 85.08 (C-3); 74.09 (C-2); 68.42 (C-5); C-6′ missing. HR LSIMS (NOBA matrix) calcd for $C_{14}H_{11}ClN_4O_2Na$ $(M+Na)^+$: 325.0468; found: 325.0468. Anal. for $C_{14}H_{11}ClN_4O_2$: calcd: C 55.55; H 3.66; N 18.51. Found: C 55.43; H 3.90; N 18.86.

4.2.6. Synthesis of (*RS*)-6-iodo-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purine (7) and (*RS*)-6-iodo-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-purine (14). Starting from **21**[3] and 6-iodopurine,[17] and following Method B the residue obtained was purified by flash chromatography using a gradient mixture of EtOAc/hexane (2/8 → 4/6 → 6/4) as eluent to give the first fraction as an amorphous white powder identified as **7** (9%); mp 137–138 °C. R_f (EtOAc/hexane, 6/4): 0.41. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H, H-2′); 8.44 (s, 1H, H-8′); 7.30 (dt, 1H, J=1.8, 7.0 Hz, $H_{benzene}$); 7.21 (d, 1H, J=7.0 Hz, $H_{benzene}$); 7.12 (d, 1H, J=7.5 Hz, $H_{benzene}$); 7.10 (dt, 1H, J=1.1, 8.3 Hz, $H_{benzene}$); 6.28 (dd, 1H, J=2.3, 6.3 Hz, H-3); 4.88 (s, 2H, H-5); 4.61 (dd, 1H, J=2.3, 13.0 Hz, H-2); 4.41 (dd, 1H, J=6.3, 13.0 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.72; 152.33; 147.39; 143.14; 138.56; 130.11; 130.06; 129.31; 124.30; 122.47; 120.72; 84.11 (C-3); 73.49 (C-2); 69.06 (C-5). Anal. for $C_{14}H_{11}IN_4O_2$: calcd: C 42.66; H 2.81; N 14.21. Found: C 42.63; H 2.80; N 14.48.

The second fraction, as an amorphous white powder was identified as **14** (15%); mp 133–134 °C. R_f (EtOAc/hexane, 6/4): 0.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H, H-2′); 8.70 (s, 1H, H-8′); 7.30 (m, 1H, $H_{benzene}$); 7.20 (d, 1H, J=7.2 Hz, $H_{benzene}$); 7.10 (m, 2H, $H_{benzene}$); 6.54 (dd, 1H, J=2.3, 5.3 Hz, H-3); 4.82 (d, J=14.0 Hz, 1H, H-5); 4.77 (d, J=14.0 Hz, 1H, H-5); 4.66 (dd, 1H, J=2.2, 13.2 Hz, H-2); 4.42 (dd, 1H, J=5.3, 13.2 Hz, H-2). Anal. for $C_{14}H_{11}IN_4O_2$: calcd: C 42.66; H 2.81; N 14.21. Found: C 42.55; H 2.69; N 14.03.

4.2.7. Method E. Synthesis of 7. Compound **6** (0.25 g, 0.88 mmol), trifluoroacetic acid (TFA, 0.34 mL, 4.4 mmol) and NaI (2.64 g, 17.6 mmol) in butanone (20 mL) were stirred at −40 to −50 °C for 5 h. The reaction mixture was poured into saturated $NaHCO_3/H_2O$ solution and extracted (CH_2Cl_2, 50 mL). The organic layer was washed ($NaHSO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was purified by flash chromatography (gradient elution with EtOAc/hexane, 1/9 → 2/8 → 3/7 → → 7/3). Finally, **7** was recrystallized from EtOH (0.104 g, 30% yield).

4.2.8. Synthesis of 14. Following Method E compound **14** (0.117 g, 28% yield) was obtained.

4.2.9. Synthesis of (*RS*)-2,6-dichloro-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purine (8) and (*RS*)-2,6-dichloro-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-purine (15). Starting from **21**[3] and 2,6-dichloropurine, and

following Method B the residue obtained was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH: 9.8/0.2 as eluent to give the first fraction as an amorphous white powder identified as **8** (14%); mp 154–156 °C. R_f (CH_2Cl_2/MeOH, 9.8/0.2): 0.42. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H, H-8′); 7.31 (m, 1H, $H_{benzene}$); 7.23 (m, 1H, $H_{benzene}$); 7.12 (m, 2H, $H_{benzene}$); 6.29 (dd, 1H, J=2.3, 6.1 Hz, H-3); 4.95 (d, 1H, J=14.1 Hz, H-5); 4.95 (d, 1H, J=14.1 Hz, H-5); 4.86 (d, 1H, J=14.1 Hz, H-5); 4.63 (dd, 1H, J=2.3, 13.1 Hz, H-2); 4.34 (dd, 1H, J=6.1, 13.1 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.67; 153.51; 152.28 (C-4′); 144.42; 130.78; 130.15; 129.87; 129.32; 124.39; 120.76; 84.11 (C-3); 73.46 (C-2); 69.21 (C-5); one carbon missing. Anal. for $C_{14}H_{10}Cl_2N_4O_2$: calcd: C 49.87; H 2.99; N 16.62. Found: C 49.93; H 3.11; N 16.67.

The second fraction, as an amorphous white powder was identified as **15** (7%); mp 178–180 °C. R_f (CH_2Cl_2/MeOH, 9.8/0.2): 0.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (s, 1H, H-8′); 7.33 (m, 1H, $H_{benzene}$); 7.23 (m, 1H, $H_{benzene}$); 7.13 (m, 2H, $H_{benzene}$); 6.50 (dd, 1H, J=2.2, 5.0 Hz, H-3); 4.81 (d, 1H, J=14.1 Hz, H-5); 4.76 (d, 1H, J=14.1 Hz, H-5); 4.65 (dd, 1H, J=2.2, 13.2 Hz, H-2); 4.44 (dd, 1H, J=5.0, 13.2 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.78 (C-4′); 158.68; 153.83; 149.09; 144.04; 130.34; 130.12; 129.48; 124.75; 120.79; 84.98 (C-3); 73.85 (C-2); 68.26 (C-5); one carbon missing. Anal. for $C_{14}H_{10}Cl_2N_4O_2$: calcd: C 49.87; H 2.99; N 16.62. Found: C 50.03; H 2.89; N 16.72.

4.2.10. Method F. Synthesis of (*RS*)-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-adenine (9) and (*RS*)-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-adenine (16). Compound **6**[3] (0.142 mg, 0.470 mmol) was dissolved in a saturated solution of NH_3 in dry DMF (20 mL) and the corresponding solution was heated at 120 °C in a sealed tube for 27 h. After cooling, the solvent was removed under vacuum and the residue was dissolved in $CHCl_3$ (20 mL), washed with H_2O (2×10 mL) and the organic layer dried (Na_2SO_4). After filtration, the solvent was removed and the residue was purified by flash chromatography using a mixture of $CHCl_3$/MeOH: 9.5/0.5 as eluent to give the first fraction as an amorphous white powder identified as **9** (78 mg, 60%); mp: 136–137 °C. R_f (EtOAc): 0.36. HMBC experiments were carried out on **9**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H, H-2′); 7.98 (s, 1H, H-8′); 7.28 (dt, 1H, J=1.6, 7.7 Hz, H-8); 7.20 (dd, 1H, J=1.2, 7.4 Hz, H-6); 7.10 (d, 1H, J=7.5 Hz, H-9); 7.08 (t, 1H, J=7.4 Hz, H-7); 6.22 (dd, 1H, J=2.3, 6.7 Hz, H-3); 4.86 (s, 2H, H-5); 4.53 (dd, 1H, J=2.3, 12.9 Hz, H-2); 4.35 (dd, 1H, J=6.7, 12.9 Hz, H-2); 3.50 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.93 (C-9a); 155.02 (C-6′); 152.82 (C-2′); 150.00 (C-4′); 136.64 (C-8′); 130.86 (C-5a); 129.85 (C-8); 129.32 (C-6); 124.11 (C-7); 120.77 (C-9); 119.30 (C-5′); 83.50 (C-3); 74.01 (C-2); 69.03 (C-5). HR LSIMS (NOBA matrix) calcd for $C_{14}H_{13}N_5O_2Na$ $(M+Na)^+$: 306.0967; found: 306.0968. Anal. for $C_{14}H_{13}N_5O_2$: calcd: C 59.36; H 4.63; N 24.72. Found: C 59.45; H 4.30; N 24.96.

The second fraction, as an amorphous white powder was identified as **16** (32 mg, 22%); mp: 190–191 °C. R_f (EtOAc): 0.19. HMBC experiments were carried out on **16**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H, H-2′); 8.10 (s, 1H, H-8′); 7.29 (dt, 1H, J=1.6, 7.7 Hz, H-8); 7.19 (dd, 1H, J=1.2, 7.4 Hz, H-6); 7.10 (d, 1H, J=6.0 Hz, H-9); 7.08 (t, 1H, J=7.4 Hz, H-7); 6.23 (dd, 1H, J=2.3, 6.4 Hz, H-3); 5.98 (br s, 2H, NH_2); 4.86 (s, 2H, H-5); 4.56 (dd, 1H, J=2.4, 13.0 Hz, H-2); 4.41 (dd, 1H, J=6.4, 13.0 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.84 (C-4′); 158.84 (C-9a); 155.70 (C-6′); 153.47 (C-2′); 139.15 (C-8′); 130.56 (C-5a); 129.90 (C-8); 129.32 (C-6); 124.16 (C-7); 120.72 (C-9); 111.00 (C-5′); 83.60 (C-3); 73.79 (C-2); 68.90 (C-5). HR LSIMS (NOBA matrix) calcd for $C_{14}H_{13}N_5O_2Na$ $(M+Na)^+$: 306.0969; found: 306.0967. Anal. for $C_{14}H_{13}N_5O_2$: calcd: C 59.36; H 4.63; N 24.72. Found: C 59.15; H 4.78; N 24.46.

4.2.11. Synthesis of (*RS*)-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-*N*,*N*-dimethyladenine (17) and 16. According to Method F and starting with **13** the residue was purified by flash chromatography using a mixture of $CHCl_3$/MeOH: 9/1 as eluent to give an amorphous white powder identified as **17** (70%); mp: 160–161 °C. R_f (EtOAc): 0.10. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H, H-2′); 8.28 (s, 1H, H-8′); 7.30 (dt, 1H, J=1.6, 7.7 Hz, H-8); 7.23 (d, 1H, J=6.7 Hz, H-6); 7.13 (d, 1H, J=6.7 Hz, H-9); 7.12 (t, 1H, J=7.7 Hz, H-7); 6.21 (dd, 1H, J=2.2, 7.1 Hz, H-3); 4.92 (d, J=13.8 Hz, 1H, H-5); 4.85 (d, J=13.8 Hz, 1H, H-5); 4.38 (dd, 1H, J=2.2, 12.7 Hz, H-2); 4.14 (dd, 1H, J=7.1, 12.7 Hz, H-2); 3.09 (s, 6H, N*Me*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.85 (C-4′); 158.66 (C-9a); 155.93 (C-6′); 152.68 (C-2′); 144.54 (C-8′); 130.48 (C-5a); 130.21 (C-8); 129.36 (C-6); 124.53 (C-7); 120.84 (C-9); 113.81 (C-5′); 85.09 (C-3); 74.79 (C-2); 69.17 (C-5); 41.28 (N*Me*$_2$). HR LSIMS (NOBA matrix) calcd for $C_{16}H_{17}N_5O_2Na$ $(M+Na)^+$: 334.1283; found: 334.1282. Anal. for $C_{16}H_{17}N_5O_2$: calcd: C 61.72; H 5.50; N 22.49. Found: C 62.00; H 5.20; N 22.71.

The second fraction, as an amorphous white powder was identified as **16** (12%).

4.2.12. Synthesis of (*RS*)-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purine (10) and (*RS*)-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-purine (18). Starting from **21**[3] and purine, and following Method B the residue obtained was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH: 9.8/0.2 as eluent to give the first fraction as a syrup identified as **10** (11%). R_f (CH_2Cl_2/MeOH, 9.5/0.5): 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H, H-6′); 9.01 (s, 1H, H-2′); 8.41 (s, 1H, H-8′); 7.31 (m, 1H, $H_{benzene}$); 7.21 (m, 1H, $H_{benzene}$); 7.11 (m, 2H, $H_{benzene}$); 6.35 (dd, 1H, J=2.4, 6.3 Hz, H-3); 4.90 (s, 2H, H-5); 4.65 (dd, 1H, J=2.4, 13 Hz, H-2); 4.47 (dd, 1H, J=6.3, 13 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.83; 153.07 (C-4′); 150.88; 149.06; 143.88; 134.01; 130.29; 130.03; 129.32; 124.26; 120.74; 83.71 (C-3); 73.63 (C-2); 69.06 (C-5). Anal. for $C_{14}H_{12}N_4O_2$: calcd: C 62.68; H 4.51; N 20.88. Found: C 62.60; H 4.17; N 20.99.

The second fraction, as a syrup was identified as **18** (5%). R_f (CH_2Cl_2/MeOH, 9.5/0.5): 0.20. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H, H-6′); 9.10 (s, 1H, H-2′); 8.60 (s, 1H, H-8′); 7.34 (m, 1H, $H_{benzene}$); 7.24 (m, 1H, $H_{benzene}$); 7.14 (m, 2H, $H_{benzene}$); 5.98 (dd, 1H, J=2.4, 4.4 Hz, H-3); 4.72 (d, 2H, H-5); 4.64 (dd, 1H, J=4.55, 13.4 Hz, H-2); 4.54 (dd, 1H, J=2.4, 13.4 Hz, H-2). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 161.00 (C-2′); 158.93; 154.06; 146.95; 141.49; 130.38; 130.33; 129.56; 124.78; 120.81; 85.19 (C-3); 73.39 (C-2); 67.72 (C-5); one carbon missing. Anal. for $C_{14}H_{12}N_4O_2$: calcd: C 62.68; H 4.51; N 20.88. Found: C 63.01; H 4.34; N 20.89.

4.2.13. Method G. Synthesis of (*RS*)-6-trifluoromethyl-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purine 11 and (*RS*)-6-trifluoromethyl-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-purine 19, obtained from 7. A mixture of the iodopurine derivative **7** (0.188 g, 0.5 mmol), CF_3SiMe_3 (0.1 mL, 0.7 mmol), KF (0.041 g, 0.7 mmol), CuI (0.152 g, 0.8 mmol), DMF (0.5 mL) and *N*-methylpyrrolidone (NMP, 0.5 mL) was stirred in a 5 mL glass vial at 60 °C for 24 h. After cooling to room temperature the solvents were evaporated under low pressure (ca. 100 Pa, bath temperature ca. 40 °C) and the residue was purified by flash chromatography (gradient elution with a mixture of EtOAc/hexane: 2/8→3/7) to give the first fraction as an amorphous white solid identified as **11** (80 mg, 49%); mp 70–71 °C. R_f (EtOAc/hexane, 6/4): 0.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.10 (s, 1H, H-2′); 8.60 (s, 1H, H-8′); 7.31 (m, 1H, $H_{benzene}$); 7.23 (m, 1H, $H_{benzene}$); 7.12 (m, 2H, $H_{benzene}$); 6.39 (dd, 1H, J=2.3, 6.2 Hz, H-3); 4.90 (s, 2H, H-5); 4.66 (dd, 1H, J=2.4, 13.0 Hz, H-2); 4.44 (dd, 1H, J=6.2, 13.0 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.74; 153.20; 152.36; 145.97; 145.50; 130.14; 130.02; 129.34; 124.39; 122.53; 120.75; 84.09; 73.48; 69.17. Anal. for $C_{15}H_{11}F_3N_4O_2$: calcd: C 53.58; H 3.30; N 16.66. Found: C 53.42; H 3.59; N 16.42.

The second fraction, as an amorphous white powder was identified as **19** (33 mg, 20%); mp 126–127 °C. R_f (EtOAc/hexane, 6/4): 0.34. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.10 (s, 1H, H-2′); 8.60 (s, 1H, H-8′); 7.33 (m, 1H, $H_{benzene}$); 7.23 (m, 1H, $H_{benzene}$); 7.13 (m, 2H, $H_{benzene}$); 6.40 (dd, 1H, J=2.3, 6.2 Hz, H-3); 4.91 (dd, 1H, J=3.7, 14.1 Hz, H-5); 4.66 (dd, 1H, J=2.3, 13.0 Hz, H-2); 4.44 (dd, 1H, J=6.2, 13.0 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.78; 153.22; 152.39; 145.95; 145.46; 130.18; 130.06; 129.37; 124.43; 122.55; 120.79; 84.12; 73.54; 69.22; one carbon missing. Anal. for $C_{15}H_{11}F_3N_4O_2$: calcd: C 53.58; H 3.30; N 16.66. Found: C 53.31; H 3.71; N 16.68.

4.2.14. Synthesis of 11 and 19, obtained from 14. Following Method G, with the same amount of reactants and starting from **14** a fraction identified as **19** (24 mg, 14%) was obtained.

4.2.15. Method H. Synthesis of (*RS*)-6-phenyl-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purine 12 and (*RS*)-6-phenyl-7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*-purine 20, obtained from 7. To a 2 N solution of Na_2CO_3 (1.7 mL), phenylboronic acid (0.1 g, 0.83 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [Pd(II)Cl_2dppf, 4.15 mg] was added the solution of **7** (0.311 g, 0.83 mmol) in dimethoxyethane (8.3 mL) under argon. The resulting solution was stirred at 85 °C for 24 h. After adding H_2O, the product was extracted (EtOAc), the organic layer dried (Na_2SO_4), filtered and concentrated in vacuo to give a residue, which was purified by flash chromatography (gradient elution with a mixture of EtOAc/hexane: 2/8→3/7) to give the first fraction as a syrup identified as **12** (149 mg, 52%). R_f (EtOAc/hexane, 6/4): 0.59. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H, H-2′); 8.78 (m, 2H, H_{phenyl}); 8.42 (s, 1H, H-8′); 7.56 (m, 3H, H_{phenyl}); 7.31 (dt, 1H, J=1.8, 7.6 Hz, $H_{benzene}$); 7.22 (dd, 1H, J=1.7 Hz, indet., $H_{benzene}$); 7.13 (dd, 1H, $J\approx$1 Hz, indet., $H_{benzene}$); 7.11 (dt, 1H, J=1.2, 7.3 Hz, $H_{benzene}$); 6.37 (dd, 1H, J=2.4, 6.5 Hz, H-3); 4.92 (s, 2H, H-5); 4.64 (dd, 1H, J=2.4, 12.9 Hz, H-2); 4.46 (dd, 1H, J=6.5, 12.9 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.88; 155.18; 152.67; 151.96; 142.89; 135.38; 131.38; 130.93; 130.45; 129.96; 129.33; 128.78; 124.23; 120.76; 83.86 (C-3); 73.76 (C-2); 69.13 (C-5); one carbon missing. Anal. for $C_{20}H_{16}N_4O_2$: calcd: C 69.76; H 4.68; N 16.27. Found: C 69.93; H 4.39; N 15.99.

The second fraction was identified as **20** (74.4 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H, H-2′); 8.55 (s, 1H, H-8′); 7.72 (m, 2H, H_{phenyl}); 7.58 (m, 3H, H_{phenyl}); 7.27 (dt, 1H, J=1.8, 7.7 Hz, $H_{benzene}$); 7.15 (dd, 1H, J=1.8, 7.4 Hz, $H_{benzene}$); 7.06 (dt, 1H, J=1.8 Hz, indet., $H_{benzene}$); 7.05 (dd, 1H, J=1.8, 7.9 Hz, $H_{benzene}$); 5.70 (m, 1H, H-3); 4.61 (d, 1H, J=14 Hz, H-5); 4.39 (d, 1H, J=14 Hz, H-5); 4.36 (m, 1H, H-2); 4.21 (dd, 1H, J=6.1, 12.7 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.40 (C-4′); 158.50; 153.39; 152.49; 146.97; 136.03; 130.49; 130.10; 129.25; 128.95; 128.79; 124.52; 120.77; 84.51 (C-3); 73.86 (C-2); 68.72 (C-5); one carbon missing. Anal. for $C_{20}H_{16}N_4O_2$: calcd: C 69.76; H 4.68; N 16.27. Found: C 69.99; H 4.55; N 16.03.

4.2.16. Synthesis of 20, obtained from 14. Following Method H, with the same amount of reactants and starting from **14** a fraction identified as **20** (37 mg, 13%) was obtained.

4.3. Biological activity

The biological methods were the same as those previously described.[30]

Acknowledgements

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References and notes

1. Friis, G. J.; Bundgaard, H. *A Textbook of Drug Design and Development*; Krogsgaard-Larsen, P., Liljefors, T., Madsen, U., Eds.; Harwood Academic: Amsterdam, 1996; pp 351–385.
2. Malet-Martino, M.; Jolimaitre, P.; Martino, R. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 267.
3. Saniger, E.; Campos, J.; Entrena, A.; Marchal, J. A.; Súarez, I.; Aránega, A.; Choquesillo, D.; Niclós, J.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **2003**, *59*, 5457.
4. Schwartz, G. K.; Shah, M. A. *J. Clin. Oncol.* **2005**, *23*, 9408.
5. Shapiro, G. I. *J. Clin. Oncol.* **2006**, *24*, 1770.
6. Saniger, E.; Campos, J.; Entrena, A.; Marchal, J. A.; Boulaiz, H.; Aránega, A.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **2003**, *59*, 8017.
7. Campos, J.; Domínguez, J. F.; Gallo, M. A.; Espinosa, A. *Curr. Pharm. Des.* **2000**, *6*, 1797.

8. For the numbering of the compounds, the atoms of the benzodioxepin ring are tagged with numbers without primes, while those of the pyrimidine and purine bases are numbered with primes (′).
9. Functional groups possessing an sp^3 hybridized carbon bonded to oxygen and to nitrogen are known as *O*,*N*-acetals or hemiaminals.
10. Vorbrüggen, H.; Ruh-Pohlenz, C. *Organic reactions*; Paquette, L. A., Ed.; Wiley: New York, NY, 2000; Vol. 55, p 1.
11. *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Kirby, G. W., Volume Ed.; Pergamon: Oxford, 1995; Vol. 4.
12. Hall, R. H. *The Modified Nucleosides in Nucleic Acids*; Columbia University Press: New York, NY, 1971.
13. Rodenko, B.; Wanner, M. J.; Koomen, G.-J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1247.
14. Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201.
15. Chang, J.; Dong, C.; Guo, X.; Hu, W.; Cheng, S.; Wang, Q.; Chen, R. *Bioorg. Med. Chem.* **2005**, *13*, 4760.
16. Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917.
17. Elion, G. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 3508.
18. Hocek, M.; Holý, A. *Collect. Czech. Chem. C* **1999**, *64*, 229.
19. Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757.
20. Boryski, J.; Golankiewicz, B. *Nucleic Acids Res.* **1987**, *18*, 45.
21. Boryski, J.; Golankiewicz, B. *Nucleosides Nucleotides* **1989**, *8*, 529.
22. Golankiewicz, B.; Ostrowski, T.; Leonard, P.; Seela, F. *Helv. Chim. Acta* **2002**, *85*, 388.
23. Dudycz, L. W.; Wright, G. E. *Nucleosides Nucleotides* **1984**, *3*, 33.
24. Boryski, J.; Manikowski, A. *Nucleosides Nucleotides* **1999**, *18*, 1057.
25. McCurdy, A.; Jiménez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314.
26. Agarwal, A.; Chauhan, P. M. S. *Synth. Commun.* **2004**, *34*, 2925.
27. Gómez, J. A.; Campos, J.; Marchal, J. A.; Trujillo, M. A.; Melguizo, C.; Prados, J.; Gallo, M. A.; Aránega, A.; Espinosa, A. *Tetrahedron* **1997**, *53*, 7319.
28. Campos, J. M.; Espinosa, A.; Gallo, M. A.; Gómez-Vidal, J. A.; Núñez, M. C.; Aránega, A.; Marchal, J. A.; Rodríguez-Serrano, F. Spanish Patent, Application No. P200601538, 2006.
29. Wilker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem.* **1993**, *31*, 287.
30. Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547.

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Novel oxybispyridylboronic acids: synthesis and study of their reactivity in Suzuki-type cross-coupling reactions

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Abstract—This paper sets forth the synthesis of novel oxybispyridylboronic acids, which are prepared from the corresponding halo-oxybispyridines via halogen–metal exchange using *n*-butyllithium and treatment with triisopropylborate. A range of efficient cross-coupling reactions of these novel boronic acids with selected aryl halides is described. This strategy produces novel pyridylethers of interest in cholinergic medicinal chemistry.

1. Introduction

Ligands of neuronal nicotinic cholinergic receptors (nAChRs) have been widely investigated[1] and several strategies applied in nAChR ligand design have been considered. But, the vast majority of nAChR ligands published to date suffer from a lack of selectivity for neuronal nAChR subtypes and design of novel nAChR ligands still remains to be studied.

We were particularly interested in 3-pyridylethers since these compounds have been previously identified to be potent ligands of the α4β2 nAChR subtype.[2]

In this study, we chose to develop the synthesis of novel pyridylethers taking RWJ-314313[2] and ABT-594[3] as examples (Fig. 1). RWJ-314313 is a neuronal nAChR ligand with nanomolar affinity for the α4β2 subtype ([^{3}H]cytisine binding, rat brain (α4β2), IC_{50}=22 nM), and ABT-594 is a potent agonist of α4β2 nAChRs ([^{3}H]cytisine binding, rat brain (α4β2), K_i=0.03 nM).

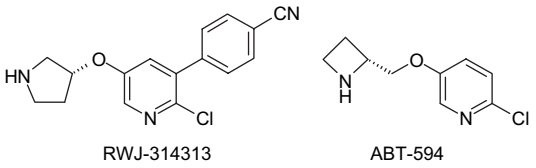
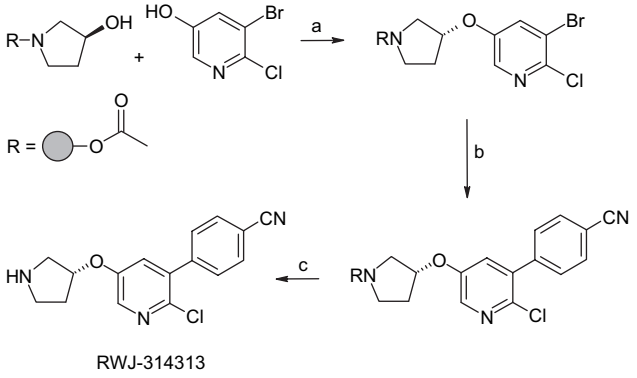


Figure 1. Nicotinic cholinergic agonists (α4β2).

These two ligands were prepared using a Mitsunobu coupling between 2-chloro-5-hydroxypyridine derivatives and appropriate *N*-protected azacycles. In the case of RWJ-314313, a Suzuki cross-coupling between pyridylether and 4-cyanophenylboronic acid provided the desired compound (Scheme 1). This synthetic strategy is limited by the availability of aryl boronic acids.



Scheme 1. Synthesis of RWJ-314313. Reagents and conditions: (a) PPh_3, DEAD, THF; (b) 4-cyanophenylboronic acid, LiCl, $Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH; (c) 95% TFA/H_2O.

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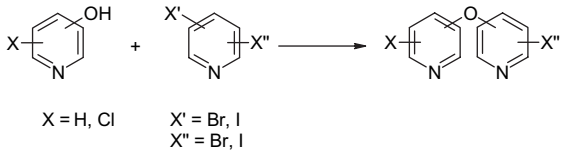
In this work, we suggested to develop an opposite strategy and to prepare boronic acid of pyridylethers in order to produce new potent pyridylethers. Moreover, this methodology seems to be more attractive insofar as numerous aryl halides are easily available.

2. Results and discussion

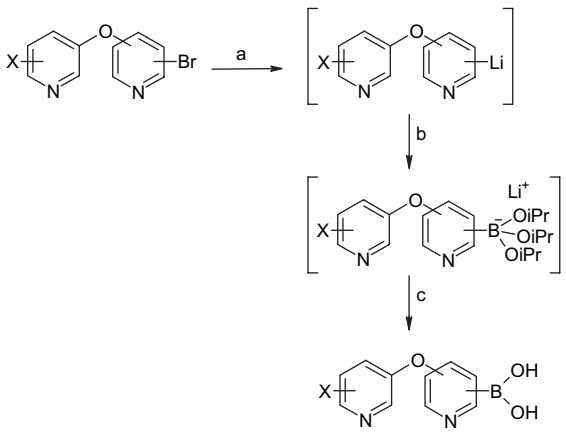
On the one hand, we recently prepared novel halo-oxybispyridines[4] from hydroxypyridines we previously published[5] (Scheme 2).



Scheme 2. Synthesis of halo-oxybispyridines. Reagents and conditions: NaH 60% (1.25 equiv), DMF, reflux, 48 h.

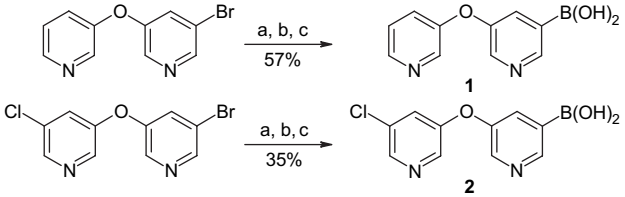
On the other hand, we described the synthesis and the isolation of halopyridylboronic acids and esters prepared taking into account a regioselective halogen–metal exchange using *n*-BuLi or a directed *ortho*-metalation using LDA.[6–9]

We report in this study the synthesis and the isolation of novel oxybispyridylboronic acids prepared via a regioselective halogen–metal exchange from the corresponding halo-oxybispyridines (Scheme 3). Bromine–lithium exchange was carried out in ether at −78 °C with *n*-BuLi, followed by the reaction with triisopropylborate B(O*i*-Pr)$_3$, then by a controlled hydrolysis.



Scheme 3. Synthesis of novel oxybispyridylboronic acids. Reagents and conditions: (a) *n*-BuLi 1.25 equiv, ether, −78 °C; (b) B(O*i*-Pr)$_3$ 1.25 equiv, −78 °C; (c) hydrolysis.

Our first attempts used 3-bromo-5-(pyridin-3-yloxy)pyridine as starting material with 1.25 equiv of *n*-BuLi. Bromine–lithium exchange was characterized by a yellow precipitate corresponding to the lithiopyridine, which then reacted with 1.25 equiv of B(O*i*-Pr)$_3$. The mixture was quenched by slow addition of 1 M aqueous NaOH solution at room temperature and the resulting aqueous layer neutralized by careful addition of HCl 6 N to prevent protodeboronation. These first conditions allowed us to obtain 5-(pyridin-3-yloxy)pyridin-3-yl boronic acid **1** with 57% yield (Scheme 4).



Scheme 4. Synthesis of novel oxybispyridylboronic acids **1** and **2**. Reagents and conditions: (a) *n*-BuLi 1.25 equiv, ether, −78 °C; (b) B(O*i*-Pr)$_3$ 1.25 equiv, −78 °C; (c) hydrolysis.

The same conditions applied to 3-bromo-5-(5-chloropyridin-3-yloxy)pyridine afforded 5-(5-chloropyridin-3-yloxy)-pyridin-3-yl boronic acid **2** (35%) (Scheme 4).

In order to generalize these conditions, we decided to prepare boronic acids of the other halo-oxybispyridines we previously synthesized, which contain pyridylether pattern in 2-position of the pyridine (Fig. 2).

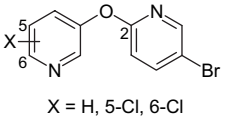


Figure 2. Halo-oxybispyridines containing pyridylether pattern in 2-position of the pyridine.

However, when using the same conditions, we did not manage to obtain the expected products. Indeed, 1 equiv of *n*-BuLi could be involved in an internal cooperating lithium complexation by both the pyridine nitrogen and pyridyloxy group as shown in Figure 3. This kind of chelation effect was already described in pyridino-directed lithiation of 2-(2-methoxyphenyl)pyridines,[10] where the cooperative internal chelation occurs with the pyridine nitrogen and methoxy group. Then, a second equivalent of *n*-BuLi could afford the corresponding boronic acids.

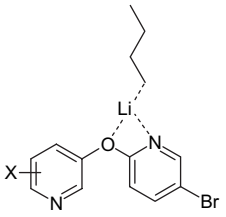
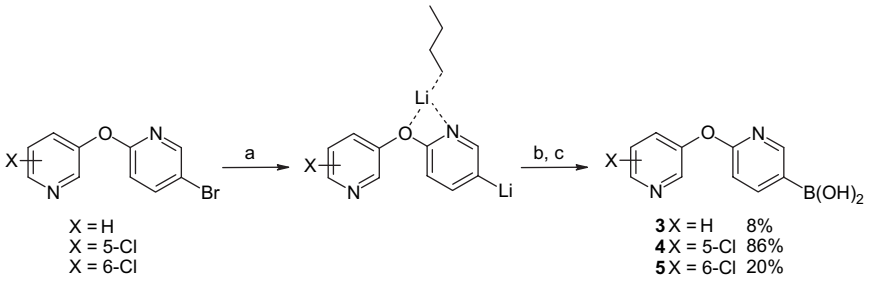


Figure 3. Proposed model for cooperative internal chelation.

Therefore, we used 2.2 equiv of *n*-BuLi and 2.2 equiv of B(O*i*-Pr)$_3$. These conditions allowed us to prepare 6-(pyridin-3-yloxy)pyridin-3-yl boronic acid **3**, 6-(5-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **4** and 6-(6-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **5** from the corresponding halo-oxybispyridines in 8%, 86% and 20% yields, respectively (Scheme 5).

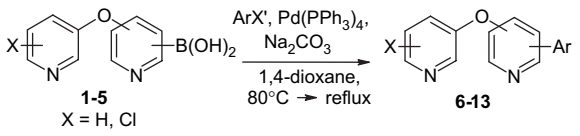
Such heterogeneous yields were surprising. Indeed, in the case of compounds **3** and **5**, boronic acids were obtained



Scheme 5. Synthesis of novel oxybispyridylboronic acids **3**–**5**. Reagents and conditions: (a) *n*-BuLi 2.2 equiv, ether, −78 °C; (b) B(O*i*-Pr)$_3$ 2.2 equiv, −78 °C; (c) hydrolysis.

with degradation products and without starting materials. So, these results could be explained not by a lack of reactivity of halo-oxybispyridines but by a lack of stability of the resulting boronic acids.

A range of efficient cross-coupling reactions of alkoxypyridyl boronic acids with selected aryl/heteroaryl halides have been described.[11] As illustrated in Scheme 6, the boronic acids **1**–**5** were efficiently coupled with aryl halides under standard Suzuki-type conditions,[12] furnishing a range of unknown pyridylethers **6**–**13** (Fig. 4) fully characterized and isolated.



Scheme 6. Suzuki cross-coupling of oxybispyridylboronic acids **1**–**5**.

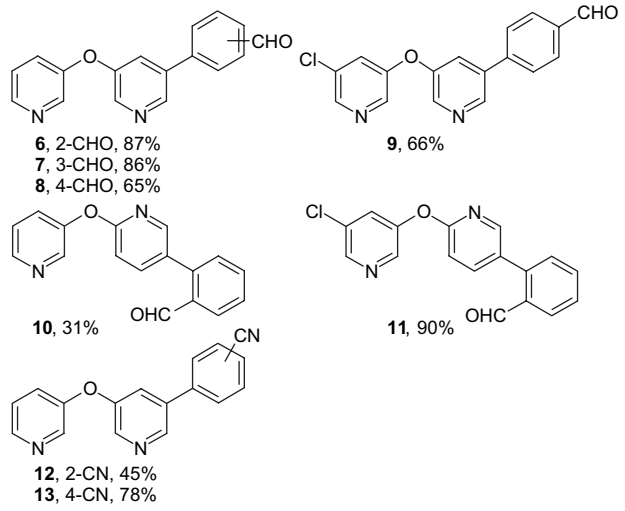


Figure 4. Pyridylethers **6**–**13**.

These pyridylethers were obtained with good yields except for compound **10**. This could be related to the relative instability of the corresponding boronic acid.

Pyridylethers **8**, **9** and **13**, which involve *p*-aryl halides, look like our model, RWJ-314313, so we have considered these compounds as potential ligands bound to the α4β2 nAChR subtype. Therefore, pharmacological studies are currently under investigation.

In conclusion, novel oxybispyridylboronic acids, which afford many potentialities particularly in metal-catalyzed cross-coupling reactions like Suzuki cross-coupling have been synthesized. Further experiments concerning the reactivity of these new compounds are currently under investigation. These new starting materials are used in the production of original libraries of oligopyridines. A detailed study of the Suzuki cross-coupling reaction will be published as soon as possible.

3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler heating bench and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX FT-IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants in Hertz. Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck) and spots were visualized using an ultraviolet-light lamp. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

Starting materials were purchased from Aldrich, Acros Organics and Alfa Aesar and used without purification.

3.2. General procedure 1 for the synthesis of oxybispyridylboronic acids 1–5

To a slurry of 2.5 M solution of *n*-BuLi (1.25 equiv) in anhydrous ether cooled to −78 °C was added dropwise a solution of halo-oxybispyridine (1 equiv) in anhydrous ether. The resulting mixture was allowed to react at this temperature for over 1.5 h. A solution of triisopropylborate (1.25 equiv) in anhydrous ether was then added dropwise, keeping the internal temperature at −78 °C. The mixture was allowed to warm to room temperature and left to react for an additional hour. The resulting mixture was quenched by slow addition of 1 M aqueous NaOH solution. The resulting aqueous layer was collected and acidified to pH 4 by dropwise addition of 6 N HCl, keeping the internal temperature below 5 °C. Extraction with ethyl acetate, evaporation of the organic layer

and crystallization from diethylether afford oxybispyridylboronic acids **1–5**.

3.2.1. 5-(Pyridin-3-yloxy)pyridin-3-yl boronic acid (1). 5-(Pyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a white solid (57%) using 3-bromo-5-(pyridin-3-yloxy)-pyridine according to general procedure 1. Mp 180 °C. IR (KBr): 3391, 1571, 1476, 1422, 1353, 1220, 1148, 1100, 1023, 947, 854, 706 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ=8.56 (s, 1H), 8.41–8.38 (m, 3H), 7.82–7.81 (m, 1H), 7.58–7.55 (m, 1H), 7.51–7.48 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ=154.4, 142.7, 142.5, 140.4, 139.3, 127.8, 127.1, 126.7, 103.3, C-3 not observed. Anal. Calcd for $C_{10}H_9BN_2O_3$: C, 55.61; H, 4.20; N, 12.97. Found: C, 55.28; H, 4.04; N, 12.59.

3.2.2. 5-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid (2). 5-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a yellow solid (35%) using 3-bromo-5-(5-chloropyridin-3-yloxy)pyridine according to general procedure 1. Mp 210 °C. IR (KBr): 3313, 1568, 1425, 1421, 1267, 1139, 1091, 956, 866, 720, 687 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ=8.58 (d, J=2.0, 1H), 8.42 (d, J=1.8, 1H), 8.40 (d, J=1.8, 1H), 8.37 (d, J=2.0, 1H), 7.86 (t, J=2.0, 1H), 7.59 (t, J=1.8, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ=151.6, 144.7, 142.5, 140.9, 140.1, 137.8, 127.1, 126.7, 103.9, C-3 not observed. Anal. Calcd for $C_{10}H_8BClN_2O_3$: C, 47.96; H, 3.22; N, 11.19. Found: C, 47.73; H, 3.09; N, 11.24.

3.2.3. 6-(Pyridin-3-yloxy)pyridin-3-yl boronic acid (3). 6-(Pyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a white solid (8%) using 3-bromo-6-(pyridin-3-yloxy)-pyridine according to general procedure 1 with 2.2 equiv of *n*-BuLi and 2.2 equiv of triisopropylborate. Mp 186 °C. IR (KBr): 3300, 1699, 1576, 1474, 1425, 1262, 1117, 1042, 887, 778 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.92 (d, J=2.4, 1H), 8.71 (dd, J=4.6, 1.4, 1H), 8.70 (s, 2H), 8.66 (d, J=2.4, 1H), 8.37 (dd, J=8.5, 2.4, 1H), 8.29 (part A of systAB, $^3J_{AB}$=8.3, J=2.4, 1.4, 1H), 7.98 (part B of systAB, $^3J_{AB}$=8.3, J=4.6, 1H), 7.32 (d, J=8.5, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=153.1, 150.1, 149.2, 146.1, 145.6, 143.3, 129.1, 124.4, 110.5, C-3 not observed. Anal. Calcd for $C_{10}H_9BN_2O_3$: C, 55.31; H, 4.20; N, 12.97. Found: C, 55.08; H, 4.06; N, 12.83.

3.2.4. 6-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid (4). 6-(5-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as a white solid (86%) using 3-bromo-6-(5-chloropyridin-3-yloxy)pyridine with 2.2 equiv of *n*-BuLi and 2.2 equiv of triisopropylborate. Mp 164 °C. IR (KBr): 3366, 3079, 1598, 1579, 1430, 1364, 1269, 1136, 1095, 938, 885, 660 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.51 (d, J=1.9, 1H), 8.45–8.44 (m, 2H), 8.28 (s, 2H), 8.19 (dd, J=8.3, 1.9, 1H), 7.93 (t, J=2.2, 1H), 7.12 (d, J=8.3, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=163.4, 153.1, 150.2, 146.0, 144.2, 141.8, 130.8, 129.3, 110.5, C-3 not observed. Anal. Calcd for $C_{10}H_8BClN_2O_3$: C, 47.96; H, 3.22; N, 11.19. Found: C, 47.71; H, 2.99; N, 10.84.

3.2.5. 6-(6-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid (5). 6-(6-Chloropyridin-3-yloxy)pyridin-3-yl boronic acid was prepared as an orange solid (20%) using 3-bromo-6-(6-chloropyridin-3-yloxy)pyridine with 2.2 equiv of *n*-BuLi and 2.2 equiv of triisopropylborate according to general procedure 1. Mp 192 °C. IR (KBr): 3360, 3079, 1598, 1576, 1430, 1389, 1364, 1269, 1226, 1101, 938, 885, 757 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.50 (d, J=1.9, 1H), 8.32 (d, J=2.4, 1H), 8.29 (s, 2H), 8.18 (d, J=8.2, 1H), 7.75 (dd, J=8.6, 2.4, 1H), 7.58 (d, J=8.6, 1H), 7.11 (d, J=8.2, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=163.5, 153.1, 149.5, 145.9, 145.3, 143.3, 133.2, 124.9, 110.6, C-3 not observed. Anal. Calcd for $C_{10}H_8BClN_2O_3$: C, 47.96; H, 3.22; N, 11.19. Found: C, 47.29; H, 3.19; N, 10.98.

3.3. General procedure 2 for the synthesis of pyridylethers 6–13

A mixture of oxybispyridylboronic acid (1.1 equiv), aryl halide (1 equiv), tetrakis-(triphenylphosphine) palladium(0) (5 mol %) and aqueous Na_2CO_3 (2.5 equiv) in 1,4-dioxane was heated at 80 °C for 1 h then refluxed for 14 h (total consumption of aryl halide seen on TLC). Ethyl acetate and water were then added to the mixture. The organic layer was separated, dried over $MgSO_4$ and concentrated to dryness. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate: 80/20) to afford pyridylethers **6–13**.

3.3.1. 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (6). 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange solid (87%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 2-bromobenzaldehyde according to general procedure 2. Mp 88 °C. IR (KBr): 3042, 2762, 1686, 1591, 1572, 1474, 1436, 1416, 1305, 1227, 1194, 1019, 886, 800, 705, 643 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=9.93 (s, 1H), 8.51–8.47 (m, 3H), 8.40 (d, J=2.0, 1H), 7.96 (d, J=7.6, 1H), 7.77 (t, J=7.0, 1H), 7.68–7.59 (m, 3H), 7.54 (d, J=7.6, 1H), 7.46–7.43 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=191.6, 152.8, 152.2, 145.3, 145.1, 140.9, 140.4, 139.8, 134.9, 133.9, 133.5, 131.4, 128.9, 128.7, 127.1, 125.8, 124.8. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.69; H, 4.24; N, 10.25.

3.3.2. 3-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (7). 3-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange oil (86%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 3-bromobenzaldehyde according to general procedure 2. IR (KBr): 3055, 2730, 1698, 1578, 1475, 1423, 1377, 1303, 1238, 1188, 1022, 886, 800, 705, 649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H), 8.59 (m, 1H), 8.40–8.33 (m, 3H), 7.97 (d, J=1.2, 1H), 7.83 (dd, J=7.8, 1.2, 1H), 7.74 (dd, J=7.8, 1.2, 1H), 7.54 (t, J=7.8, 1H), 7.47–7.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.6, 153.2, 152.6, 145.3, 143.3, 141.3, 140.2, 137.5, 136.9, 136.4, 132.8, 131.3, 129.8, 128.4, 127.7, 125.7, 123.7. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.83; H, 4.02; N, 10.10.

3.3.3. 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (8). 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange solid (65%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 4-bromobenzaldehyde according to general procedure 2. Mp 80 °C. IR (KBr): 3051, 2733, 1702, 1604, 1567, 1474, 1443, 1423, 1298, 1229, 1184,

1019, 898, 803, 698, 647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H), 8.61 (d, J=2.3, 1H), 8.41 (d, J=2.3, 1H), 8.38–8.33 (m, 2H), 7.90 (part A of systAB, $^3J_{AB}$=8.3, 2H), 7.64 (part B of systAB, $^3J_{AB}$=8.3, 2H), 7.48 (t, J=2.3, 1H), 7.33 (part A of systAB, $^3J_{AB}$=8.3, J=2.7, 1.4, 1H), 7.27 (part B of systAB, $^3J_{AB}$=8.3, J=4.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.4, 153.2, 152.6, 145.4, 143.5, 142.4, 141.4, 140.6, 136.4, 134.5, 130.3 (2C), 127.7 (2C), 125.9, 124.3, 123.8. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.66; H, 4.35; N, 10.07.

3.3.4. 4-[5-(5-Chloropyridin-3-yloxy)pyridin-3-yl]benzaldehyde (9). 4-[5-(5-Chloropyridin-3-yloxy)pyridin-3-yl]-benzaldehyde was prepared as an orange solid (66%) using 5-(5-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **2** and 4-bromobenzaldehyde according to general procedure 2. Mp 110 °C. IR (KBr): 1694, 1606, 1572, 1440, 1421, 1296, 1246, 1219, 1094, 935, 823, 698, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.98 (s, 1H), 8.66 (d, J=1.8, 1H), 8.39 (d, J=1.8, 1H), 8.31 (d, J=2.4, 1H), 8.28 (d, J=2.4, 1H), 7.91 (part A of systAB, $^3J_{AB}$=8.1, 2H), 7.66 (part B of systAB, $^3J_{AB}$=8.1, 2H), 7.52 (t, J=1.8, 1H), 7.31 (t, J=2.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.3, 153.0, 152.4, 144.1, 143.9, 142.0, 140.8, 138.7, 136.6, 135.9, 131.9, 130.3 (2C), 127.7 (2C), 125.3, 124.5. Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; N, 9.01. Found: C, 65.56; H, 3.35; N, 8.92.

3.3.5. 2-[6-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde (10). 2-[6-(Pyridin-3-yloxy)pyridin-3-yl]benzaldehyde was prepared as an orange solid (31%) using 6-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **3** and 2-bromobenzaldehyde according to general procedure 2. Mp 82 °C. IR (KBr): 1692, 1591, 1571, 1447, 1426, 1418, 1306, 1221, 1154, 1029, 926, 849, 725, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=9.94 (s, 1H), 8.50 (d, J=2.4, 1H), 8.42 (d, J=4.6, 1H), 8.08 (d, J=2.7, 1H), 7.97 (dd, J=8.3, 2.4, 1H), 7.70 (dd, J=8.3, 2.7, 1H), 7.67 (part A of systAB, $^3J_{AB}$=7.5, J=7.8, 1.5, 1H), 7.54 (part A of systAB, $^3J_{AB}$=8.3, J=2.7, 1.2, 1H), 7.47–7.50 (m, 2H), 7.35 (dd, J=7.8, 2.1, 1H), 7.05 (d, J=8.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.3, 162.8, 150.3, 147.6, 145.2, 143.6, 141.1, 138.2, 134.3, 133.8, 131.0, 129.3, 129.0, 128.8, 128.6, 124.1, 111.3. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.73; H, 4.10; N, 10.07.

3.3.6. 2-[6-(5-Chloropyridin-3-yloxy)pyridin-3-yl]benzaldehyde (11). 2-[6-(5-Chloropyridin-3-yloxy)pyridin-3-yl]-benzaldehyde was prepared as a yellow solid (90%) using 6-(5-chloropyridin-3-yloxy)pyridin-3-yl boronic acid **4** and 2-bromobenzaldehyde according to general procedure 2. Mp 130 °C. IR (KBr): 1695, 1599, 1573, 1469, 1427, 1304, 1272, 1249, 1020, 921, 848, 762, 685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=10.02 (s, 1H), 8.47 (d, J=2.2, 1H), 8.46 (d, J=2.2, 1H), 8.18 (d, J=2.2, 1H), 8.06 (dd, J=7.8, 2.2, 1H), 7.79 (dd, J=7.8, 1.9, 1H), 7.66 (t, J=2.2, 1H), 7.62 (part B of systAB, $^3J_{AB}$=7.3, J=7.8, 1.0, 1H), 7.64 (part A of systAB, $^3J_{AB}$=7.3, J=7.9, 1.9, 1H), 7.41 (dd, J=7.9, 1.0, 1H), 7.14 (d, J=7.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.2, 162.1, 147.4, 144.8, 144.6, 141.4, 141.3, 140.8, 138.4, 134.0, 133.7, 131.8, 129.8, 129.1, 128.9, 128.6, 111.4. Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; N, 9.01. Found: C, 65.49; H, 3.35; N, 8.89.

3.3.7. 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile (12). 2-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile was prepared as a white solid (45%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 2-bromobenzonitrile according to general procedure 2. Mp 124 °C. IR (KBr): 3026, 2218, 1591, 1574, 1476, 1416, 1229, 1096, 1021, 893, 790, 703 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ=8.69 (s, 1H), 8.64 (d, J=1.9, 1H), 8.58 (d, J=1.9, 1H), 8.50 (d, J=4.4, 1H), 8.06 (d, J=7.8, 1H), 7.91–7.87 (m, 2H), 7.79 (d, J=7.8, 1H), 7.73–7.66 (m, 2H), 7.55–7.51 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=152.5, 152.4, 145.4, 144.5, 141.1, 140.1, 139.2, 134.7, 133.8, 133.7, 130.4, 129.2, 126.0, 125.9, 124.8, 118.1, 110.7. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.66; H, 4.09; N, 15.13.

3.3.8. 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile (13). 4-[5-(Pyridin-3-yloxy)pyridin-3-yl]benzonitrile was prepared as an orange solid (78%) using 5-(pyridin-3-yloxy)-pyridin-3-yl boronic acid **1** and 4-bromobenzonitrile according to general procedure 2. Mp 128 °C. IR (KBr): 3052, 2222, 1604, 1569, 1473, 1425, 1217, 1105, 1016, 893, 802, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.51 (d, J=1.7, 1H), 8.34–8.29 (m, 3H), 7.62 (part A of systAB, $^3J_{AB}$=6.6, J=1.7, 1.7, 2H), 7.53 (part B of systAB, $^3J_{AB}$=6.6, J=1.7, 1.7, 2H), 7.48 (d, J=1.7, 1H), 7.28 (part A of systAB, $^3J_{AB}$=8.4, J=2.7, 1.4, 1H), 7.22 (part B of systAB, $^3J_{AB}$=8.4, J=4.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.2, 152.5, 145.3, 143.1, 141.2, 140.9, 140.6, 135.8, 132.7 (2C), 127.7 (2C), 125.9, 124.3, 123.6, 118.1, 112.1. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.18. Found: C, 74.55; H, 3.99; N, 14.89.

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References and notes

1. For recent reviews on nAChR ligands, see: (a) Romanelli, M. N.; Gualtieri, F. *Med. Res. Rev.* **2003**, *23*, 393–426; (b) Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. *Curr. Top. Med. Chem.* **2004**, *4*, 299–334; (c) Jensen, A. A.; Frölund, B.; Liljefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2005**, *48*, 4705–4745.
2. (a) Lee, J. WO0010997, 2000; (b) Lee, J.; Davis, C. B.; Rivero, R. A.; Reitz, A. B.; Shank, R. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1063–1066.
3. (a) Holladay, M. W.; Wasicak, J. T.; Lin, N. H.; He, Y.; Ryther, K. B.; Bannon, A. W.; Buckley, M. J.; Kim, D. J.; Decker, M. W.; Anderson, D. J.; Campbell, J. E.; Kuntzweiler, T. A.; Donnelly-Roberts, D.; Piattoni-Kaplan, M.; Briggs, C. A.; Williams, S.; Arneric, S. P. *J. Med. Chem.* **1998**, *41*, 407–412; (b) Donnelly-Roberts, D. L.; Puttfarcken, P. S.; Kuntzweiler, T. A.; Briggs, C. A.; Anderson, D. J.; Campbell, J. E.; Piattoni-Kaplan, M.; McKenna, D. G.; Wasicak, J. T.; Holladay, M. W.; Williams, M.; Arneric, S. P. *J. Pharmacol. Exp. Ther.* **1998**, *285*, 777–786.
4. Voisin, A. S.; Bouillon, A.; Lancelot, J.-C.; Lesnard, A.; Rault, R. *Tetrahedron* **2006**, *62*, 6000–6005.

5. Voisin, A. S.; Bouillon, A.; Lancelot, J.-C.; Rault, S. *Tetrahedron* **2005**, *61*, 1417–1421.
6. (a) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885–2890; (b) Sopkova-de Oliveira Santos, J.; Bouillon, A.; Lancelot, J.-C.; Rault, S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2003**, *C58*, o111–o113.
7. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323–3328.
8. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369–4373.
9. (a) Bouillon, A.; Lancelot, J.-C.; Sopkova-de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049; (b) Sopkova-de Oliveira Santos, J.; Bouillon, A.; Lancelot, J.-C.; Rault, S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2003**, *C59*, o596–o597.
10. (a) Parmentier, M.; Gros, P.; Fort, Y. *Tetrahedron* **2005**, *61*, 3261–3269; (b) Gros, P.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 4918–4922.
11. (a) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388–390; (b) Thompson, A. E.; Batsanov, A. S.; Bryce, M. R.; Saygili, N.; Parry, P. R.; Tarbit, B. *Tetrahedron* **2005**, *61*, 5131–5135.
12. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

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1,4-Carbonylative addition of arylboronic acids to methyl vinyl ketone: a new synthetic tool for rapid furan and pyrrole synthesis

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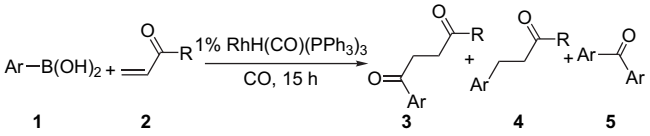
Abstract—The rhodium catalysed 1,4-carbonylative addition of arylboronic acids to methyl vinyl ketone under carbon monoxide pressure was studied. High yields of 1,4-diketones were obtained using a catalytic system formed from $Rh(COD)_2BF_4$ (COD=1,5-cyclooctadiene) and triphenylphosphine even at very low catalyst loading (0.02 mol %). A short synthetic procedure combining this carbonylation reaction with a subsequent cyclisation step affords pyrroles or furans.

1. Introduction

Five membered heterocyclic compounds such as pyrroles, furans or thiophenes and their derivatives are important products in organic chemistry since their structures can be found in many natural or therapeutic compounds.[1] Classical methods to access this class of compounds involve cyclisation reactions of 1,4-dicarbonyl reagents.[2] In this context a straightforward synthesis of 1,4-diketones is a significant objective in synthetic chemistry.

The Stetter reaction of substituted benzaldehydes with enones catalysed by thiazolium salts leads to 1,4-diketones and has already been applied for synthetic purposes but has the disadvantage of requiring high catalytic loadings.[3] Alternatively, several stoichiometric acyl–metal reagents such as acyl cobaltate,[4] ferrate,[5] cuprate,[6] nickelate,[7] molybdate[8] or chromate[9] were also used efficiently. The acyl moiety stabilised by the metal formally acts as a nucleophile with the enones playing the role of Michael acceptors. Unfortunately, the toxicity of the metal salt as well as the cost of their stoichiometric use is a strong limitation to their further development. Further improvements in the use of acyl–transition metal intermediates were dedicated to their production in the course of a catalytic cycle. Oxidative addition of aldehydes at a rhodium centre usually at high reaction temperatures,[10] or transmetallation of the acyl moiety from a acylzirconocene[11] or acylstannyl[12] derivative to a palladium metal centre allowed the use of catalytic amounts of noble metal but needed again the stoichiometric amounts of acyl reagent. In view of the wide availability and low cost of carbon monoxide, another interesting approach would be the development of a catalysed acylating reaction through in situ generation of the metal–acyl reagent via an environmentally clean carbonylation step and using simple reagents. Despite important developments of carbonylation reactions, acylation reactions of enones involving carbon monoxide source are rare.[13]

In this context, the reaction of 1,4-addition of arylboronic acids to α,β-enones attracted our attention.[14] Actually this reaction is catalysed by rhodium salts and involves a rhodium–carbon bond containing intermediate.[15] Since rhodium complexes are suitable for carbonylation reactions, it was anticipated that a molecule of CO would readily insert into the metal–carbon bond to afford a metal–acyl derivative suitable for a subsequent acylation reaction (see Scheme 1). This hypothesis was confirmed experimentally and we recently reported the rhodium catalysed carbonylative 1,4-addition of arylboronic acids to methyl vinyl ketone.[16]



Scheme 1. Rhodium catalysed aroylation of enones with arylboronic acids and carbon monoxide.

Under CO pressure, the reaction allows the conversion of an arylboronic acid **1** and an unsubstituted enone **2** to a 1,4-diketone **3** (Scheme 1). The product **4**, which is selectively obtained when the reaction was carried out in the absence

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of CO and diarylketone **5** are usually obtained as side products in low quantities depending on the reaction conditions. We now wish to report complementary catalytic data to our preliminary communication as well as the direct application of this new reaction in a carbonylation–cyclisation short synthetic procedure for furan or pyrrole heterocycle synthesis.

2. Results and discussion

2.1. Catalytic carbonylation reactions

Reactions performed with phenylboronic acid **1a** and 2 equiv of methyl vinyl ketone **2a** at 80 °C under 20 bar CO showed strongly differing results depending on the nature of the solvent (Table 1). The reaction is completely ineffective in dioxane (entry 3) and only partially occurring in dry THF or in THF/water solvents (entries 1 and 2). Best results were indeed obtained with MeOH as a polar and protic solvent. Dried methanol led to very similar results to those obtained if methanol is combined with 10% H_2O (entries 4 and 8). This observation is rather unexpected since in the parent reaction of rhodium catalysed 1,4-addition of arylboronic acids to enones without CO, it is commonly observed that organic solvent/water solutions are preferred to water free solvents. Water is thought to be involved in a protonolysis step of a rhodium–carbon bond containing intermediate leading to ketone liberation (see Scheme 2). In the case of the carbonylation reaction, water is not necessary for high conversion and it is likely that the proton comes from the boronic acid itself. Actually, the reaction worked in dry THF in which the only source of proton was the boronic acid. The possible role of MeOH as a proton donor cannot be completely discarded. However, the high efficiency observed with this solvent could also arise from its high polarity. Less polar alcoholic solvents gave lower yield of **3** without noticeable changes in the selectivity of the reaction. Moreover, the reaction was completely ineffective in isopropanol.

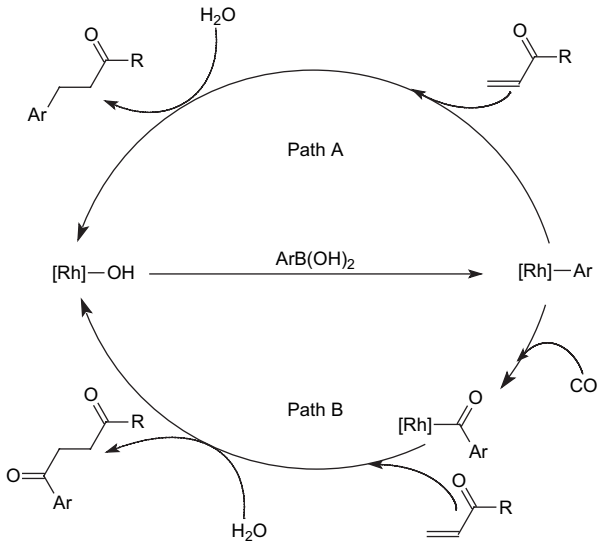
As expected with carbonylation reactions, the CO pressure has a strong effect on the selectivity of the process.[17] For example, when the CO pressure dropped from 20 bar to 1 bar, the yield of by-product **4** increased from 9 to 21% and in the mean time, the yield of carbonylated derivative **3** decreased from 78 to 52%. On the other hand, above 20 bar, the effect of the pressure on the selectivity of the reaction was rather limited (compare entries 4 and 10).

Table 1. Rhodium catalysed aroylation reaction of methyl vinyl ketone **2** with phenylboronic acid **1** under CO pressure[a]

Entry	Solvent	*P* (CO) (atm)	*T* (°C)	**3** (%)[b]	**4** (%)[b]	**5** (%)[b]
1	THF	20	80	42	<2	7
2	THF/H_2O (9/1)	20	80	46	3	9
3	1,4-Dioxane	20	80	0	0	0
4	MeOH	20	80	78	9	7
5	*n*-PrOH	20	80	60	8	6
6	*n*-BuOH	20	80	59	8	6
7	*i*-PrOH	20	80	0	0	0
8	MeOH/H_2O (9/1)	20	80	75	8	6
9	MeOH	1	80	52	21	7
10	MeOH	40	80	76	5	4
11	MeOH	20	100	44	7	18

[a] The reaction was carried out using phenylboronic acid (1.5 mmol), methyl vinyl ketone (3.2 mmol), 1% $RhH(CO)(PPh_3)_3$ and 10 mL solvent for 18 h.

[b] Yields determined by GC based on the arylboronic acid.



Scheme 2. Mechanism proposed for the 1,4-addition of arylboronic acids to α,β-unsaturated ketones.

The selectivity in benzophenone **5** was strongly dependent on the temperature of the reaction. If reaction temperatures higher than 80 °C were used, the quantities of **5** increased at the cost of the yields of ketones **3** and **4**. At 100 °C, the yield of **5** reached 18% and the yield of diketone **3** dropped from 78% at 80 °C to 44% at 100 °C.

In order to get better insight into the reaction, the evolution over time of the quantities of products **3–5** was checked. The reaction was carried out with a methyl vinyl ketone to phenylboronic acid ratio of 2, using $RhH(CO)(PPh_3)_3$ (0.5% vs phenylboronic acid) as a well defined catalyst precursor, at 80 °C and under 20 bar CO. Aliquot samples were taken at regular time intervals and analysed by GC with the help of an internal standard. In order to allow the analysis of enough samples the reaction medium was five times diluted compared to a typical run.

First of all, it should be noticed that the reaction performed under diluted conditions (50 mL MeOH) did not reach such high yields as in a normal catalytic run (10 mL MeOH). The yield of **3** is only 63% compared to the 78% obtained with the more concentrated catalytic run. The yields of **4** and **5** remained, on the other hand, practically unchanged. Nevertheless, Figure 1 shows that after a short activation period of approximately 30 min, the three products **3, 4** and **5** are simultaneously formed with a diketone to ketone ratio or a diketone to diphenylketone ratio that remains unchanged during the course of the reaction. This strongly supports the hypothesis of closely related catalytic cycles explaining the formation of these three products. Based on the catalytic cycle proposed by Hayashi[15] for the direct 1,4-addition of arylboronic acids to α,β-enones, we suggested a related catalytic cycle combining the non-carbonylative and the carbonylative processes and using common catalytic intermediates (Scheme 2).

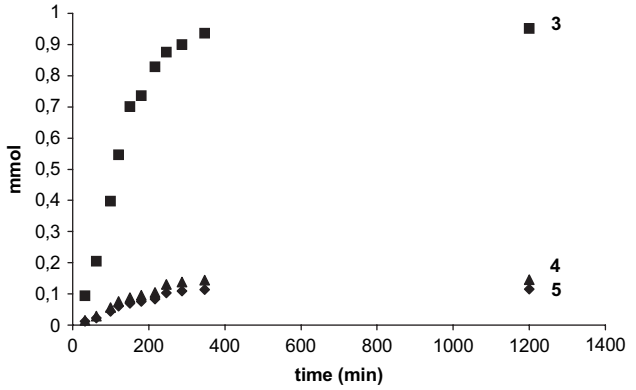


Figure 1. Formation profiles of the products **3**–**5** in the catalytic reaction (Scheme 1) versus time. The reaction was run at 70 °C with methyl vinyl ketone (3 mmol), $PhB(OH)_2$ (1.5 mmol), $RhH(CO)(PPh_3)_3$ (0.015 mmol) and CO (20 bar) in MeOH (50 mL).

The arylrhodium catalytic species is obtained in both cases by a transmetallation step of the phenyl from the boron to the rhodium centre. This intermediate can readily insert the olefin leading to the ketone formation. Alternatively, arylrhodium complexes are known to easily insert a CO molecule to give an aroylrhodium intermediate.[18] Insertion of the olefin into the aroylrhodium bond followed by a hydrolysis step gives the 1,4-diketone. It is noteworthy that under CO pressure, very low amounts of benzene are obtained by hydrololytic B–C bond cleavage of phenylboronic acid. Catalytic experiments with *p*-tolylboronic acid and *m*-chlorophenylboronic acid showed similar results. This is in marked contrast to the usually large excesses of organoboronic acids required for the direct 1,4-addition of arylboronic acids to α,β-enones. Such starting material degradation can be explained by a competitive Rh–C bond protonolysis. Low protonolysis of the arylboronic acid under our conditions can be explained by a fast insertion of the olefin into the arylrhodium or aroylrhodium bond compared to the hydrolysis step. Another explanation can arise from the higher stability of the aroylrhodium complex compared to the arylrhodium complex towards protonolysis. This is supported by the fact that proton NMR and GC analysis of the crude reaction mixture did not show the presence of significant amounts of benzoic acid or methylbenzoic ester as the respective products of hydrolysis and methanolysis of an aroylrhodium intermediate.

As a high loading of expensive rhodium is usually used in the corresponding non-carbonylative reaction, it was important to determine the extent to which it was possible to decrease the amount of catalyst without a dramatic loss of the yields of **3**.

Table 2 shows that as little as 0.01% of the rhodium precursor is enough to complete the reaction within one night at 80 °C using Rh(COD)Cl as the catalyst precursor combined with triphenylphosphine. Phosphine free catalytic systems showed much lower reactivity although they remained efficient if used with a higher amount of rhodium (0.5%). Using the same reaction conditions, experiments carried out with 0.005% of rhodium afforded much lower yields of 1,4-diketone **3**. The combination of different phosphorous based ligands with $Rh(COD)_2BF_4$ did not further improve the yields of **3** and the selectivity of the reaction for **3** versus the non-carbonylated derivative **4** remained rather unchanged. On the other hand, it is noteworthy that the use of low catalyst amounts afforded a better selectivity into the 1,4-diketone product **3**. Experiments carried out with less than 0.02% of rhodium showed the formation of much lower quantities of diphenylketone compared to the standard experiments made with 0.5% catalyst. Actually the use of higher reaction temperatures with high catalyst concentration induced the formation of much higher quantities of the undesired diphenylketone. This drawback can be partially avoided with a lower amount of Rh.

Table 2. Influence of the catalyst precursor on the aroylation reaction of methyl vinyl ketone **2** with phenylboronic acid **1**[a]

Entry	Rhodium catalyst	Catalyst (%)	**3** (%)	**4** (%)	**5** (%)
1	$Rh(COD)_2BF_4+3PPh_3$	0.5	74	9	5
2	$Rh(COD)_2BF_4+3PPh_3$	0.02	80	7	1
3	$Rh(COD)_2BF_4$	0.01	35	3	<1
4	Rh(COD)Cl	0.01	60	5	<1
5	$Rh(COD)_2BF_4+3PPh_3$	0.01	74	7	1
6	$Rh(COD)Cl+3PPh_3$	0.01	70	8	<1
7	$Rh(COD)_2BF_4+3PPh_3$	0.005	42	5	<1
8	$Rh(COD)_2BF_4+6PPh_3$	0.005	39	5	<1
9	$Rh(COD)_2BF_4$+1dppb	0.005	33	4	<1
10	$Rh(COD)_2BF_4$+2dppb	0.005	45	5	<1

[a] Reactions were carried out using phenylboronic acid (1.5 mmol) and methyl vinyl ketone (3.2 mmol) in 10 mL MeOH under 20 bar CO at 80 °C for 18 h.

Using optimised reactions conditions, high yields of diketones that can be easily isolated by column chromatography and fully characterised before further use, are obtained from variously substituted arylboronic acids (Table 3, entries 1 and 5–9).

Additional experiments made with some other well-known transmetalling reagents using the same reaction conditions showed low efficiencies. No reaction was observed with $ArSi(OEt)_3$[19] or another boron derivative such as $NaB(Ar)_4$[20] and only moderate yields was obtained with $ArSn(Bu)_3$ (Table 3, entries 2–4). Boronic acids are thus the best reactant for this carbonylation reaction. Unfortunately, attempts to change the Michael acceptor, using the same reaction conditions and catalyst, have been up until

Table 3. Rhodium catalysed aroylation reaction of methyl vinyl ketone under CO pressure with various boronic acids and transmetallation reagents[a]

Entry	Transmetallation reagent	Ar	**3** (%)[b]
1	$ArB(OH)_2$	C_6H_5	76
2	$ArSn(Bu)_3$	C_6H_5	53
3	$NaB(Ar)_4$	C_6H_5	0[c]
4	$ArSi(OEt)_3$	C_6H_5	0
5	$ArB(OH)_2$	4-MeC_6H_4	78
6	$ArB(OH)_2$	4-$MeOC_6H_4$	72
7	$ArB(OH)_2$	3-ClC_6H_4	65
8	$ArB(OH)_2$	4-ClC_6H_4	68
9	$ArB(OH)_2$	4-FC_6H_4	65

[a] Reactions were carried out using the corresponding transmetallation reagent (1.5 mmol), methyl vinyl ketone (3.2 mmol) and 0.5% $RhH(CO)(PPh_3)_3$ in 10 mL MeOH with 40 bar CO pressure at 80 °C for 18 h.
[b] Isolated yields.
[c] PhCOPh is the only formed product.

now unsuccessful. In particular, substituted enones such as cyclohexenone failed to react even at higher reaction temperatures. The reaction does not proceed with non-activated olefins either, for example, no product was detected with 1-hexene except the diphenylketone.

2.2. Procedure for pyrroles and furans synthesis

For economical and environmental reasons, it is of interest to use the diketones without any previous purification for a further organic transformation. We thus evaluated the possibility to combine, in a short procedure, the diketone formation through carbonylation with a cyclisation step giving pyrrole or furan derivatives (Scheme 3). This procedure would allow simple and fast access to the pyrrole and furan heterocycles in a short catalytic multicomponent synthetic procedure.[21] The Paal–Knorr cyclisation with an amine is a common synthetic pathway to access pyrroles.[22] The procedure commonly requires high temperature reactions and an acidic media. In our case, starting from our crude catalytic mixtures the reaction remained only partially successful. Indeed, pyrroles formation proceeded more efficiently via the iodine catalysed Paal–Knorr cyclisation even though the yield for this step was not quantitative. Better results were obtained when the amount of iodine used was increased compared to the literature procedure from 3 to 40% and the reaction time at 40 °C (instead of room temperature) from 4 h to 16 h.[23]

Under these conditions, GC analysis at the end of the reaction indicated the complete disappearance of the starting diketone along with pyrrole formation. The side products, i.e., ketones **4** and **5** remained unaffected. The analytically pure pyrroles were finally isolated by alumina gel column chromatography with overall 45–60% yields from the starting boronic acid.

The 1,4-diketones can also be reacted without previous purification to form furans. After a carbonylation reaction, the solvent was evaporated. The cyclisation was promoted by *p*-toluenesulfonic acid monohydrate in refluxing toluene for one night.[24] The complete conversion of the reaction product was then confirmed by GC analysis. The furans were finally purified by alumina gel column chromatography and isolated with similar yields to the corresponding pyrroles. Following those procedures, it was possible to synthesise a series of furan and pyrrole heterocycles with good overall yields (Table 4).

To avoid any change of solvent between the catalytic and cyclisation step for furan synthesis, it is noteworthy that the carbonylation reaction could be directly performed in a toluene/water (1/1) mixture with similar yields. The water layer was then extracted and the organic layer dried with magnesium sulfate. After filtration, the toluene solution was refluxed in the presence of *p*-toluenesulfonic acid to generate the furan. This procedure performed with *p*-tolylboronic acid allowed the isolation of the corresponding furan in a similar yield. It has the main advantage of shortening the procedure by avoiding the tedious methanol evaporation step.

Table 4. Carbonylation–cyclisation sequences for pyrroles and furans synthesis[a]

Entry	Ar	X=NPh[b] (%)	X=O[c] (%)
1	C_6H_5	56	49
2	4-MeC_6H_4	51	50 (54)[d]
3	4-$MeOC_6H_4$	45	66
4	4-ClC_6H_4	53	49
5	3-ClC_6H_4	59	44
6	4-FC_6H_4	44	42

[a] The carbonylation reactions were carried out using the corresponding arylboronic reagent (1.5 mmol) and 0.5% $RhH(CO)(PPh_3)_3$ in 10 mL MeOH for 18 h, 20 bar CO and 80 °C.
[b] The crude mixture obtained after carbonylation was stirred overnight with aniline and iodine in dichloromethane.
[c] The crude mixture obtained after carbonylation was refluxed overnight in toluene with 1 equiv *p*-toluenesulfonic acid.
[d] The carbonylation reaction was run in a biphasic toluene (5 mL)/water (5 mL) system and the cyclisation step was run with the organic phase dried with $MgSO_4$.

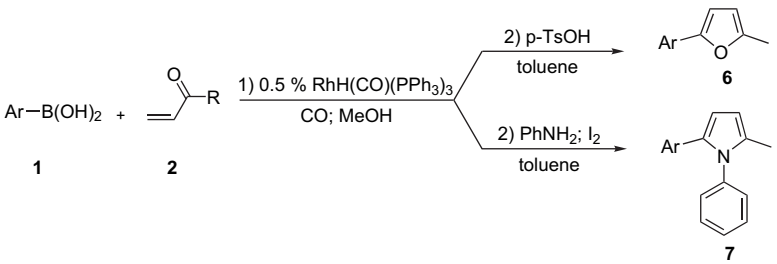
3. Conclusion

We have shown that the carbonylative 1,4-addition of arylboronic acids to enones affords the corresponding diketones with high selectivity even at low catalyst loadings. The reaction allows an efficient access to 1,4-diketones. Interestingly, this reaction can be coupled with a cyclisation without previous purification giving pyrrole or furan derivatives. Thus, the whole process constitutes an efficient way to access these last classes of compounds.

4. Experimental

4.1. General

All experiments were carried out with solvents, rhodium complexes, phosphines, arylboronic acids, amines, APTS and methyl vinyl ketone purchased from Aldrich or Acros and used as received.



Scheme 3. Pyrrole and furan synthesis via a rhodium catalysed aroylation of enones with arylboronic acids and carbon monoxide followed by a cyclisation step.

GLC analyses were performed on a Chrompack CP 9001 apparatus equipped with a flame ionisation detector and a CPSil 5CB (25 m×0.32 mm, Chrompack) column. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a AC-300 Bruker spectrometer at 23 °C; chemical shifts are reported in parts per million downfield from TMS.

4.1.1. General procedure for carbonylation reactions and enones isolation. A 100 mL stainless steel autoclave equipped with a magnetic stirrer was charged with arylboronic acid (1.5 mmol) and the required amount of rhodium catalyst. MeOH (10 mL) was thus added followed by methyl vinyl ketone (0.25 mL, 3 mmol). The autoclave was pressurised to 20 bar and the mixture was warmed at 80 °C for 18 h. After cooling to room temperature, the reactor was vented and the orange-yellow methanol solution was evaporated to dryness. The diketones were finally purified by silica gel column chromatography using petroleum/ether (9/1) as eluent.

1-*p*-Tolylpentane-1,4-dione: white solid, 78% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.85 (d, 2H, $^{3}J_{H-H}$=8 Hz, C*H* aromatic); 7.21 (d, 2H, $^{3}J_{H-H}$=8 Hz, C*H* aromatic); 3.21 (t, 2H, $^{3}J_{H-H}$=6.3 Hz, CH_2); 2.83 (t, 2H, $^{3}J_{H-H}$=6.3 Hz, CH_2); 2.36 (s, 3H, ArCH_3); 2.21 (s, 3H, COCH_3). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=207.41 (s, 1C, CH_3*C*O); 198.10 (s, 1C, Ar*C*O); 143.90 (s, 1C, CH_3*C*); 134.13 (s, 1C, *C*CO); 129.22 (s, 2C, *C*H aromatic); 128.13 (s, 2C, *C*H aromatic); 37.05 (s, 1C, *C*H_2); 32.29 (s, 1C, *C*H_2); 30.09 (s, 1C, *C*H_3); 21.61 (s, 1C, Ar*C*H_3).

1-(4-Methoxyphenyl)pentane-1,4-dione: white solid, 72% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.92 (d, 2H, $^{3}J_{H-H}$=9 Hz, C*H* aromatic); 6.89 (d, 2H, $^{3}J_{H-H}$=9 Hz, C*H* aromatic); 3.83 (s, 3H, OCH_3); 3.19 (t, 2H, $^{3}J_{H-H}$=6.5 Hz, CH_2); 2.85 (t, 2H, $^{3}J_{H-H}$=6.5 Hz, CH_2); 2.23 (s, 3H, COCH_3). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=207.54 (s, 1C, CH_3*C*O); 197.01 (s, 1C, Ar*C*O); 163.51 (s, 1C, CH_3O*C*); 130.29 (s, 2C, *C*H aromatic); 129.12 (s, 1C, *C*CO); 113.69 (s, 2C, *C*H aromatic); 55.45 (s, 1C, O*C*H_3); 37.13 (s, 1C, *C*H_2); 32.05 (s, 1C, *C*H_2); 30.12 (s, 1C, *C*H_3).

1-(4-Chlorophenyl)pentane-1,4-dione: white solid, 68% yield. ^{1}H NMR: (200 MHz, $CDCl_3$) δ=7.83 (d, 2H, $^{3}J_{H-H}$=8 Hz, C*H* aromatic); 7.36 (d, 2H, $^{3}J_{H-H}$=8 Hz, C*H* aromatic); 3.20 (t, 2H, $^{3}J_{H-H}$=6.3 Hz, CH_2); 2.80 (t, 2H, $^{3}J_{H-H}$=6.3 Hz, CH_2); 2.20 (s, 3H, COCH_3). ^{13}C NMR: ($CDCl_3$, 50 MHz) δ=206.65 (s, 1C, CH_3*C*O); 196.78 (s, 1C, Ar*C*O); 138.94 (s, 1C, Cl*C* or *C*CO); 134.13 (s, 1C, Cl*C* or *C*CO); 128.94 (s, 2C, *C*H aromatic); 128.33 (s, 2C, *C*H aromatic); 36.44 (s, 1C, *C*H_2); 31.81 (s, 1C, *C*H_2); 29.46 (s, 1C, *C*H_3).

1-(3-Chlorophenyl)pentane-1,4-dione: yellow liquid, 65% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.89 (s, 1H, C*H* aromatic); 7.80 (d, 1H, $^{3}J_{H-H}$=7.7 Hz, C*H* aromatic); 7.47 (d, 1H, $^{3}J_{H-H}$=7.7 Hz, C*H* aromatic); 7.36 (t, 1H, $^{3}J_{H-H}$= 7.7 Hz, C*H* aromatic); 3.19 (t, 2H, $^{3}J_{H-H}$=5.8 Hz, CH_2); 2.85 (t, 2H, $^{3}J_{H-H}$=5.8 Hz, CH_2); 2.21 (s, 3H, COCH_3). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=207.01 (s, 1C, CH_3*C*O); 197.24 (s, 1C, Ar*C*O); 138.12 (s, 1C, Cl*C* or *C*CO); 134.85 (s, 1C, Cl*C* or *C*CO); 133.03 (s, 1C, *C*H aromatic); 129.93 (s, 1C, *C*H aromatic); 128.12 (s, 1C, *C*H aromatic); 126.71 (s, 1C, *C*H aromatic); 36.93 (s, 1C, *C*H_2); 32.44 (s, 1C, *C*H_2); 29.99 (s, 1C, *C*H_3).

1-(4-Fluorophenyl)pentane-1,4-dione: yellow liquid, 62% yield. ^{1}H NMR: (200 MHz, $CDCl_3$) δ=7.94 (m, 2H, C*H* aromatic); 7.36 (m, 2H, C*H* aromatic); 3.21 (t, 2H, $^{3}J_{H-H}$=5.9 Hz, CH_2); 2.84 (t, 2H, $^{3}J_{H-H}$=5.9 Hz, CH_2); 2.20 (s, 3H, COCH_3). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=206.65 (s, 1C, CH_3*C*O); 196.38 (s, 1C, Ar*C*O); 165.24 (d, 1C, $^{1}J_{F-C}$=254.4 Hz, F*C*); 132.62 (s, 1C, *C*CO); 131.42 (d, 2C, $^{2}J_{F-C}$=117.1 Hz, *C*H aromatic); 115.1 (s, 2C, $^{3}J_{F-C}$=21.6 Hz, *C*H aromatic); 36.48 (s, 1C, *C*H_2); 31.75 (s, 1C, *C*H_2); 29.48 (s, 1C, *C*H_3).

4.1.2. General procedure for pyrroles synthesis. In the first part of the synthesis, the carbonylation reaction was run according to the procedure used for the enones synthesis (vide supra). The mixture obtained was evaporated and the residue dissolved in a solution of iodine (0.183 g, 0.72 mmol) and aniline (0.194 mL, 2.1 mmol) in THF (10 mL). The resulting solution was then heated at 40 °C for one night. The reaction was monitored by GC and ended once the GC peak corresponding to the starting enone has disappeared. The solvent was evaporated and the pyrrole purified by alumina gel column chromatography using petroleum/ether (9/1) as eluent.

2-*p*-Tolyl-5-methyl-1-phenyl-1*H*-pyrrole: yellow-orange solid, 51% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.2–7.3 (m, 3H, C*H* aromatic); 7.06 (m, 2H, C*H* aromatic); 6.86 (m, 4H, C*H* aromatic); 6.45 (d, 1H, $^{3}J_{H-H}$=1.9 Hz, CH_{Pyrr}); 6.21 (d, 1H, $^{3}J_{H-H}$=1.9 Hz, CH_{Pyrr}); 2.35 (s, 3H, CH_3); 2.25 (s, 3H, CH_3). ^{13}C NMR: ($CDCl_3$, 50 MHz) δ=139.15 (s, 1C, NC_{ipso}); 134.83 (s, 1C, *C*q); 133.84 (s, 1C, *C*q); 130.88 (s, 1C, *C*q); 130.36 (s, 1C, *C*q); 128.54 (s, 2C, *C*H aromatic); 128.31 (s, 2C, *C*H aromatic); 128.12 (s, 2C, *C*H aromatic); 127.32 (s, 2C, *C*H aromatic); 126.92 (s, 1C, *C*H aromatic); 107.87 (s, 1C, *C*H$_{Pyrr}$); 107.09 (s, 1C, *C*H$_{Pyrr}$); 20.65 (s, 1C, *C*H_3); 12.95 (s, 1C, *C*H_3).

2-(4-Methoxyphenyl)-5-methyl-1-phenyl-1*H*-pyrrole: red-orange solid, 45% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.42 (m, 3H, C*H* aromatic); 7.22 (d, 2H, $^{3}J_{H-H}$=6.4 Hz, C*H* aromatic); 7.06 (d, 2H, $^{3}J_{H-H}$=8.8 Hz, C*H* aromatic); 6.75 (d, 2H, $^{3}J_{H-H}$=8.8 Hz, C*H* aromatic); 6.36 (d, 1H, $^{3}J_{H-H}$=2.9 Hz, CH_{Pyrr}); 6.15 (d, 1H, $^{3}J_{H-H}$=2.9 Hz, CH_{Pyrr}); 3.77 (s, 3H, OCH_3); 2.21 (s, 3H, CH_3). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=157.84 (s, 1C, O*C*q); 139.53 (s, 1C, NC_{ipso}); 134.05 (s, 1C, *C*q); 130.99 (s, 1C, *C*q); 129.18 (s, 2C, *C*H aromatic); 128.99 (s, 2C, *C*H aromatic); 128.60 (s, 2C, *C*H aromatic); 127.37 (s, 1C, *C*H aromatic); 126.42 (s, 1C, *C*q); 113.52 (s, 2C, *C*H aromatic); 107.81 (s, 1C, *C*H$_{Pyrr}$); 107.38 (s, 1C, *C*H$_{Pyrr}$); 55.15 (s, 1C, O*C*H_3); 13.42 (s, 1C, *C*H_3).

2-(4-Chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrrole: orange solid, 53% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.8–6.8 (m, 9H, C*H* aromatic); 6.41 (br s, 1H, CH_{Pyrr}); 6.15 (br s, 1H, CH_{Pyrr}); 2.18 (s, 3H, CH_3). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=138.71 (s, 1C, NC_{ipso}); 132.45 (s, 1C, *C*q); 131.69 (s, 1C, *C*q); 131.57 (s, 1C, *C*q); 130.95 (s, 1C, *C*q); 128.65 (s, 2C, *C*H aromatic); 128.34 (s, 2C, *C*H aromatic); 127.96 (s, 2C, *C*H aromatic); 127.69 (s, 2C, *C*H aromatic);

127.16 (s, 1C, *C*H aromatic); 108.61 (s, 1C, *C*H$_{Pyrr}$); 107.29 (s, 1C, *C*H$_{Pyrr}$); 13.91 (s, 1C, *C*H$_3$).

2-(3-Chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrrole: orange solid, 59% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.40–7.30 (m, 3H, C*H* aromatic); 7.00–7.23 (m, 5H, C*H* aromatic); 6.88 (m, 1H, C*H* aromatic); 6.41 (d, 1H, $^3J_{H-H}$=2.9 Hz, C*H*$_{Pyrr}$); 6.13 (d, 1H, $^3J_{H-H}$=2.9 Hz, C*H*$_{Pyrr}$); 2.16 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=139.07 (s, 1C, N*C*$_{ipso}$); 135.27 (s, 1C, *C*q); 133.81 (s, 1C, *C*q); 132.63 (s, 1C, *C*q); 132.49 (s, 1C, *C*q); 129.16 (s, 2C, *C*H aromatic); 129.12 (s, 1C, *C*H aromatic); 128.41 (s, 2C, *C*H aromatic); 127.73 (s, 1C, *C*H aromatic); 127.50 (s, 1C, *C*H aromatic); 125.57 (s, 2C, *C*H aromatic); 109.51 (s, 1C, *C*H$_{Pyrr}$); 107.81 (s, 1C, *C*H$_{Pyrr}$); 13.32 (s, 1C, *C*H$_3$).

2-(4-Fluorophenyl)-5-methyl-1-phenyl-1*H*-pyrrole: red-orange solid, 44% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.37 (m, 3H, C*H* aromatic); 7.16 (m, 2H, C*H* aromatic); 7.02 (m, 2H, C*H* aromatic); 6.84 (m, 2H, C*H* aromatic); 6.31 (d, 1H, $^3J_{H-H}$=3.42 Hz, C*H*$_{Pyrr}$); 6.10 (d, 1H, $^3J_{H-H}$=3.42 Hz, C*H*$_{Pyrr}$); 2.16 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=161.92 (d, 1C, $^1J_{F-C}$=245.1 Hz, F*C*); 139.20 (s, 1C, N*C*$_{ipso}$); 138.15 (s, 1C, *C*q); 132.77 (s, 1C, *C*q); 131.13 (s, 1C, *C*q); 128.90 (d, 2C, $^3J_{F-C}$=7.9 Hz, *C*H aromatic); 128.59 (s, 2C, *C*H aromatic); 128.09 (s, 2C, *C*H aromatic); 127.08 (s, 1C, *C*H aromatic); 114.31 (d, 2C, $^2J_{F-C}$=21.6 Hz, *C*H aromatic); 108.22 (s, 1C, *C*H$_{Pyrr}$); 107.17 (s, 1C, *C*H$_{Pyrr}$); 13.13 (s, 1C, *C*H$_3$).

4.1.3. General procedure for furans synthesis. In the first part of the synthesis, the carbonylation reaction is run according to the procedure used for the enones synthesis (vide supra). The mixture obtained is evaporated and the residue dissolved in a solution of *p*-toluenesulfonic acid monohydrate (60 mg, 1.5 mmol) in toluene (10 mL). The resulting solution is then refluxed overnight. After evaporation of the solvent, the furan is purified by alumina gel column chromatography using petroleum/ether (9/1) as eluent. Alternatively, the carbonylation reaction can be run in a toluene/H_2O biphasic system. After one night of reaction with 20 bar of CO at 80 °C, the organic layer is then separated from the aqueous phase, dried over $MgSO_4$ and filtered. Addition of *p*-toluenesulfonic acid monohydrate to the toluene solution followed by overnight refluxing allows the complete transformation of the diketone in the corresponding furan heterocycle.

2-*p*-Tolyl-5-methylfuran: orange oil, 50% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.48 (m, 2H, C*H* aromatic); 7.09 (m, 2H, C*H* aromatic); 6.41 (d, 1H, $^3J_{H-H}$=3.3 Hz, C*H*$_{Fur}$); 5.97 (dq, 1H, $^4J_{H-H}$=1.1 Hz, $^3J_{H-H}$=3.3 Hz, C*H*$_{Fur}$); 2.29 (s, 3H, OC*H*$_3$); 2.28 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=152.73 (s, 1C, *C*q); 151.62 (s, 1C, *C*q); 136.58 (s, 1C, *C*q); 129.51 (s, 2C, *C*H aromatic); 128.81 (s, 1C, *C*q); 107.78 (s, 2C, *C*H aromatic); 105.28 (s, 1C, *C*H$_{Fur}$); 21.33 (s, 1C, O*C*H$_3$); 13.79 (s, 1C, *C*H$_3$).

2-(4-Methoxyphenyl)-5-methylfuran: orange oil, 66% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.60 (d, 2H, $^3J_{H-H}$=6.8 Hz, C*H* aromatic); 6.94 (d, 2H, $^3J_{H-H}$=6.8 Hz, C*H* aromatic); 6.45 (d, 1H, $^3J_{H-H}$=2.9 Hz, C*H*$_{Fur}$); 6.08 (br s, 1H, C*H*$_{Fur}$); 3.83 (s, 3H, OC*H*$_3$); 2.40 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=158.69 (s, 1C, *C*q); 152.40 (s, 1C, *C*q); 151.18 (s, 1C, *C*q); 124.78 (s, 2C, *C*H aromatic); 124.70 (s, 1C, *C*q); 114.11 (s, 2C, *C*H aromatic); 107.60 (s, 1C, *C*H$_{Fur}$); 104.28 (s, 1C, *C*H$_{Fur}$); 55.23 (s, 1C, O*C*H$_3$); 13.68 (s, 1C, *C*H$_3$).

2-(4-Chlorophenyl)-5-methylfuran: orange solid, 53% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.55 (d, 2H, $^3J_{H-H}$=8.6 Hz, C*H* aromatic); 7.32 (d, 2H, $^3J_{H-H}$=8.6 Hz, C*H* aromatic); 6.53 (br s, 1H, C*H*$_{Fur}$); 6.07 (br s, 1H, C*H*$_{Fur}$); 2.38 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=151.80 (s, 1C, *C*q); 150.76 (s, 1C, *C*q); 131.78 (s, 1C, *C*q); 129.21 (s, 1C, *C*q); 128.51 (s, 2C, *C*H aromatic); 124.01 (s, 2C, *C*H aromatic); 107.41 (s, 1C, *C*H$_{Fur}$); 105.90 (s, 1C, *C*H$_{Fur}$); 13.19 (s, 1C, *C*H$_3$).

2-(3-Chlorophenyl)-5-methylfuran: orange solid, 44% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.64 (s, 1H, C*H* aromatic); 7.50 (d, 1H, $^3J_{H-H}$=7.8 Hz, C*H* aromatic); 7.28 (dd, 1H, $^3J_{H-H}$=7.8 Hz, C*H* aromatic); 7.18 (d, 1H, $^3J_{H-H}$=7.8 Hz, C*H* aromatic); 6.57 (d, 1H, $^3J_{H-H}$=3.0 Hz, C*H* aromatic); 6.08 (d, 1H, $^3J_{H-H}$=2.8 Hz, C*H* aromatic); 2.38 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=152.63 (s, 1C, *C*q); 150.84 (s, 1C, *C*q); 134.66 (s, 1C, *C*q); 132.85 (s, 1C, *C*q); 129.89 (s, 1C, *C*H aromatic); 126.59 (s, 1C, *C*H aromatic); 123.26 (s, 1C, *C*H aromatic); 121.13 (s, 1C, *C*H aromatic); 107.98 (s, 1C, *C*H$_{Fur}$); 107.09 (s, 1C, *C*H$_{Fur}$); 13.70 (s, 1C, *C*H$_3$).

2-(4-Fluorophenyl)-5-methylfuran: orange solid, 42% yield. ^{1}H NMR: (300 MHz, $CDCl_3$) δ=7.55 (dd, 2H, $^3J_{H-H}$=8.6 Hz, C*H* aromatic); 7.32 (d, 2H, $^3J_{H-H}$=8.6 Hz, C*H* aromatic); 6.53 (br s, 1H, C*H*$_{Fur}$); 6.07 (br s, 1H, C*H*$_{Fur}$); 2.38 (s, 3H, C*H*$_3$). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ=151.80 (s, 1C, *C*q); 150.76 (s, 1C, *C*q); 131.78 (s, 1C, *C*q); 129.21 (s, 1C, *C*q); 128.51 (s, 2C, *C*H aromatic); 124.01 (s, 2C, *C*H aromatic); 107.41 (s, 1C, *C*H$_{Fur}$); 105.90 (s, 1C, *C*H$_{Fur}$); 13.19 (s, 1C, *C*H$_3$).

References and notes

1. (a) Hall, A.; Bit, R. A.; Brown, S. H.; Chaignot, H. M.; Chessel, I. P.; Coleman, T.; Giblin, G. M. P.; Hurst, D. N.; Kilford, I. R.; Lewell, X. Q.; Michel, A. D.; Mohamed, S.; Naylor, A.; Novelli, R.; Skinner, L.; Spalding, D. J.; Tang, S. P.; Wilson, R. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2666; (b) Lansiaux, A.; Dassonneville, L.; Facompré, M.; Kumar, A.; Stephens, C. E.; Bajic, M.; Tanious, F.; Wilson, W. D.; Boykin, D. W.; Bailly, C. *J. Med. Chem.* **2002**, *45*, 1994; (c) Kikuchi, K.; Tagami, K.; Hibi, S.; Yoshimura, H.; Tokuhara, N.; Tai, K.; Hida, T.; Yamauchi, T.; Nagai, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1215; (d) Biava, M.; Poreta, G. C.; Deidda, D.; Pompei, R.; Tafi, A.; Marinetti, F. *Bioorg. Med. Chem.* **2003**, *11*, 515.
2. (a) Christopfel, W. C.; Miller, L. *J. Org. Chem.* **1986**, *51*, 4169; (b) Freeman, F.; Kim, D. S. H. L. *J. Org. Chem.* **1992**, *57*, 172.
3. (a) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326; (b) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. M.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 4161.
4. Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1985**, *50*, 4955.
5. Cooke, M. P.; Parlman, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 5222.

6. Seyferth, D.; Hui, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4551.
7. (a) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 4926; (b) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4382; (c) Sawa, Y.; Hashimoto, I.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* **1968**, *33*, 2159.
8. Barluenga, J.; Rodriguez, F.; Fañanas, F. J. *Chem.—Eur. J.* **2000**, *6*, 1930.
9. (a) Söderberg, B. C.; York, D. C.; Harriston, E. A.; Caprara, H. J.; Flurry, A. H. *Organometallics* **1995**, *14*, 3712; (b) Yamane, M.; Ishibashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **2000**, *2*, 174.
10. (a) Willis, M. C.; Sapmaz, S. *Chem. Commun.* **2001**, 2558; (b) Jun, C.-H.; Chung, J.-H.; Lee, D.-Y.; Loupy, A.; Chatti, S. *Tetrahedron Lett.* **2001**, *42*, 4803; (c) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem.—Eur. J.* **2002**, *8*, 2423.
11. (a) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 8141; (b) Hanzawa, Y.; Kakuuchi, A.; Yabe, M.; Narita, K.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **2001**, *42*, 1737; (c) Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron Lett.* **2002**, *58*, 7559.
12. Shirakawa, E.; Yamamoto, Y.; Nakao, Y.; Tsuchimoto, T.; Hiyama, T. *Chem. Commun.* **2001**, 1926.
13. Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2004**, *69*, 908.
14. (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829; (b) Hayashi, T. *Synlett* **2001**, 879; (c) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229; (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.
15. Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.
16. Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem. Commun.* **2004**, 1520.
17. See for example: Couve-Bonnaire, S.; Carpentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron* **2003**, *59*, 2793.
18. (a) Stang, P. J.; Song, L.; Lu, Q.; Haltn, B. *Organometallics* **1990**, *9*, 2149; (b) Vicente, J.; Martin, J. *Organometallics* **1989**, *8*, 357; (c) García, M. P.; Martínez, A. P.; Jiménez, M. V.; Siurana, C.; Oro, L. A.; Lahoz, F. J.; Tiripicchio, A. *Inorg. Chim. Acta* **2000**, *308*, 51; (d) Corkey, B. K.; Taw, F. L.; Bergman, R. G.; Brookhart, M. *Polyhedron* **2004**, *23*, 2943.
19. Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667.
20. Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Organomet. Chem.* **2002**, *648*, 297.
21. (a) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465; (b) Dhawan, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468; (c) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238.
22. (a) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389; (b) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. *Tetrahedron Lett.* **2005**, *46*, 2643; (c) Alongi, M.; Mineto, G.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 7069; (d) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277.
23. Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213.
24. Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 3838.

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New cytotoxic cembranolides: isolation, biogenetic studies, and synthesis of analogues

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Abstract—Three new diterpene cembranes (**1**–**3**) along with eunilode (**4**) were isolated from the organic extracts of *Eunicea mammosa*. Biogenetic studies using a cell-free extract demonstrated that hydroxy cembrane **3** is the precursor to the ether-bridged **1**. In order to deduce further structure–activity relationships a series of analogues were synthesized and their cytotoxicity against several cancer cell lines was evaluated.

1. Introduction

Specimens belonging to the genus *Eunicea* have been subjected to numerous chemical investigations yielding a wide variety of diterpenoids, most of them belonging to the oxygenated 14-membered ring cembranoid family.[1]

In our continuing investigations on the study of cytotoxic metabolites from gorgonians[2] and the biosynthetic origin of marine terpenes,[3] particularly on cembranes, we have focused our attention on the Caribbean gorgonian octocoral *Eunicea mammosa*, collected in Bahamas, as it is one of the richest sources of marine cembranoid diterpenoids. Both naturally occurring *Eunicea* cembranoids and some of their synthetic analogues have showed remarkable biological activity as cytotoxic agents.[4] In this paper, we wish to report the structural elucidation of three new cembranoid-diterpenes from *E. mammosa*, some biogenetic studies using its cell-free extract, and chemical transformations to obtain some analogues. Furthermore, the cytotoxic evaluation of both natural and synthetic cembranoids allowed us to enlarge the structure–activity relationships of this type of compounds.

2. Results and discussion

2.1. Isolation

Specimens of *E. mammosa* were collected by hand using SCUBA on Sweetings Cay in the Bahamas during the 1999 FAU expedition. Freshly collected animals were frozen on site and transported back to Florida. Cold specimens were thawed and exhaustively extracted with MeOH to obtain an extract that was fractionated using our standard partitioning procedure. The richest cembrane portion was chromatographed on a silica gel flash column using hexanes/acetone mixtures to yield an enriched diterpene fraction, which was then submitted repeatedly to reverse-phase HPLC (H_2O/MeOH mixtures) to give pure compounds **1**–**3** (Fig. 1).

The molecular formula of $C_{20}H_{30}O_4$ for **1** was obtained from the combination of the ^{13}C NMR data and the HRFABMS of the pseudomolecular ion $[M+Na]^+$ at *m/z* 357.2044, thus indicating six degrees of unsaturation in the molecule. Characteristic features of this new diterpene were defined by ^1H NMR, ^{13}C NMR, DEPT, gradient edited HSQC, HMBC, and DQCOSY experiments. Structural elucidation of **1** begun

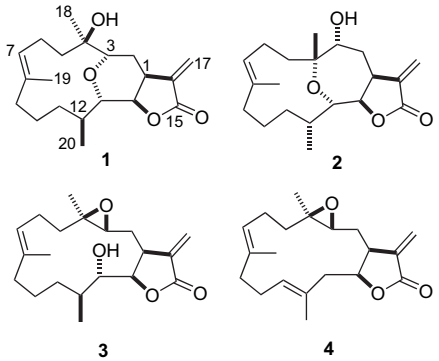

Figure 1. Structures of the cembranoid-diterpenes isolated from *E. mammosa*.

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with the identification of an α-methylene-γ-lactone group in **1**, which was suggested by the proton resonances at δ_H 6.38 (1H, d, J=3.4 Hz) and 5.60 (1H, d, J=3.4 Hz) due, respectively, to H-17α and H-17β, an allylic methine proton at δ_H 3.37 (1H, m), a lactone methine proton at δ_H 4.38 (1H, dd, J=8.0, 8.9 Hz), and a carbon resonance at δ_C 169.9 for a carbonyl lactone. Two ^{13}C NMR sp^2 signals at δ_C 130.9 (s, C-8) and 128.3 (d, C-7) and the methyl group at δ_C 15.9 (q, C-19) suggested the presence of a trisubstituted double bond, which was confirmed by the presence of an olefinic proton at δ_H 5.10 (1H, dd, J=5.9, 9.3 Hz) and an additional vinyl methyl group at δ_H 1.58 (3H, s, H-19). These functionalities accounted for four degrees of unsaturation.

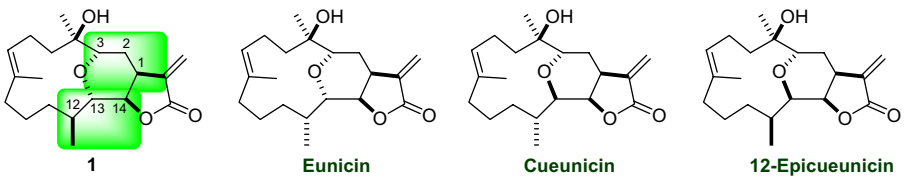
Three additional oxygenated carbons were deduced from the quaternary carbon signal at δ_C 73.4 (s) and the methine carbon signals at δ_C 76.7 (d) and 79.6 (d), which correlated the gradient edited HSQC responses to the oxygenated methines at δ_H 3.20 (1H, dd, J=3.7, 10.0 Hz) and 2.79 (1H, t, J=8.9 Hz). More direct proton–carbon correlations also showed the existence of two other methyl groups from the two quartet signals at δ_c 24.6 and 14.8 attached to the corresponding proton signals at δ_H 1.15 (s) and at δ_H 0.99 (d, J=6.8 Hz). The remaining unsaturations were assigned to a 14-membered ring, which bears an ether bridge between C-3 and C-13 positions. This connectivity was deduced by key HMBC correlations observed between the pairs H3–C13 and/or H13–C3. In this way the isolated H1–H2–H3/H1–H14–H13 spin-systems deduced by the DQCOSY experiment were assigned in a six-membered ring.

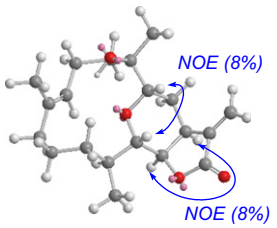
The comparison of these data to those of other cembranoids reported in the literature, indicated that **1** has the same planar structure as eunicin,[5] also isolated from *E. mammosa*, cueunicin isolated from *Eunicea succinea*,[6] and 12-*epi*cueunicin, a synthetic compound obtained from eupalmerin.[4]

To find out the relative stereochemistry of **1** proton–proton coupling constants, NOE differences, NOESY, GMMX calculations, and comparison with the above mentioned cembranes (see Fig. 2) were used. The presence of an observed NOE (8%) between H-1 and H-14 protons, and the coupling constant of 8.0 Hz, which was similar to that found in eunicin ($J_{1,14}$=7.8 Hz) and 12-*epi*cueunicin ($J_{1,14}$=8.7 Hz), clearly suggested a cis configuration for these protons. Also the presence of a NOE difference of 8% between H-13 and H-3 indicated that these protons are on the same face of the molecule assigned arbitrarily as β. This disposition ruled out the relative stereochemistry present in cueunicin and 12-*epi*cueunicin, where those protons are on the opposite faces of the molecule. Further comparison of the NMR data of compound **1** to those of eunicin suggested the same stereostructure, but epimeric at C-12. The proposed stereochemical assignment at this carbon was based on the observation of the different multiplicity of H-13. Thus, while the chemical shift of H-13 in **1** appears as a triplet (J=8.9 Hz), the same proton was observed in the ^{1}H NMR spectrum of eunicin as doublet with coupling constants of 9.5 Hz (J_{13-14}) and 0 Hz (J_{12-13}). This fact suggests an *anti* relative configuration between H-13 with H-12 in **1** instead of *syn* in eunicin. Besides, GMMX energy search minimization showed a low-energy conformer with similar values for the involved proton–proton coupling constants corresponding to the six-membered ring and H-12, and therefore confirmed the relative stereochemistry for all chiral centers (see Fig. 2). As a result of all these data, we have deduced the three dimensional arrangement of this compound, which has been named as 12-*epi*eunicin.

For the new cembranolide **2**, the molecular formula $C_{20}H_{30}O_4$ was obtained from its HRFABMS, which showed the pseudomolecular ion $[M+Na]^+$ at m/z 357.2040. The ^{1}H and ^{13}C NMR spectra of **2** had many features in common with those of **1**. Indeed, ^{1}H NMR, DQCOSY, edited HSQC, and HMBC experiments confirmed the presence of the α-methylene-γ-butyrolactone ring and the *E*-trisubstituted double bond Δ^7.

However, 2D NMR experiments suggested that the oxa-bridge was located between C-4 and C-13 instead of C-3 and C-13 as in **1**, forming now a seven-membered ring. Consequently, the hydroxyl group in **2** was located at C-3 rather than at C-4 as in **1**. This was also shown from an HSQC–TOCSY experiments where correlations from H-13 to H-3 can be found clearly from the TOCSY responses of every proton–carbon pair of this spin system. Also, comparison of the NMR data of compound **2** with those of other cembranes, showed the same planar structure but different relative stereochemistry to jeunicin,[7] its isomers 13αH,14βH-jeunicin[8] and 12,13-bis*epi*jeunicin.[4] The *E* geometry of the Δ^7 double





	1	Calculated by GMMX
^3J(H1-H2α)	3.7	2.1
^3J(H1-H2β)	10.0	11.6
^3J(H12-H13)	8.8	10.4
^3J(H13-H14)	8.8	8.4
^3J(H14-H1)	8.0	7.5

Figure 2. Conformation and key NOE's in the GMMX low-energy conformer of **1** and reported cembranoids with the same planar structure as **1**.

bond was confirmed by the high field position found for the ^{13}C NMR C-19 signal at δ_C 16.3.

In order to deduce the relative stereochemistry at C-1/C-3 and C-12/C-14 fragments, proton–proton coupling constant analysis revealed the same stereochemistry as in jeunicin. This was confirmed from the NOESY correlation between Me-20 and H-14. However, overlapping of the signals corresponding to the H-1 and H-3 protons in the ^1H NMR spectrum of **2** preclude us from determining the relative stereochemistry at C-3 and C-4 by NOE correlations on this compound. For that reason, compound **2** was acetylated to give **5**, whose ^1H NMR spectrum showed clearly H-1 and H-3 protons at different chemical shifts, allowing us to elucidate the relative stereochemistry by an NOESY experiment (Fig. 3).

Indeed, the NOE correlations between H-13 at 3.42 ppm and H-3 at 4.83 ppm and this in turn to Me-18 at 1.14 ppm, proved that those protons are on the same face of the molecule. On the other hand, NOE correlations between H-1 at 3.39 ppm and H-14 at 4.63 ppm and this in turn to Me-20 at 1.01 ppm in the NOESY of **5**, confirmed the relative configurations of these positions. With those last assignments and with the final structure in hand, we have named compound **2** as 4-*epi*jeunicin.

The molecular formula $C_{20}H_{30}O_4$ was established for compound **3** from its HRFABMS corresponding to the pseudomolecular ion $[M+Na]^+$ at *m/z* 357.2030. The ^1H and

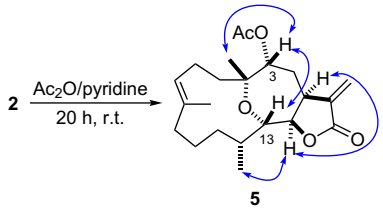


Figure 3. Acetylation of **2** and selected NOESY correlations in compound **5**.

^{13}C NMR spectra of **3** confirmed the presence of an α-methylene-γ-lactone group and a trisubstitued double bond as in **1**. The ^{13}C NMR signals at δ_c 58.4 (s) and 59.7 (d) suggested the presence of an epoxide group, which also was confirmed by the proton chemical shift at δ_H 3.07. Comparison of the NMR data of compound **3** with those of other epoxy-containing cembranes, showed a similar planar structure to eupalmerin,[9] its isomers 12-*epi*eupalmerin acetate[10] and 12,13-bis*epi*eupalmerin.[11] The high field resonance of the Me-19 signal in the ^{13}C NMR spectra of **3** (δ 15.1 ppm) indicated the *E* geometry of the double bond Δ^7. The relative stereochemistries of the epoxide group at C-3 and C-4 and the cis ring fusion at C-1 and C-14 in compound **3** were deduced by comparison of its spectroscopic data to those of cembranoid analogues. Nevertheless, the major differences between these compounds in the ^1H and ^{13}C NMR spectra were observed at the C-12 and C-13 positions and Me-20. The coupling constant of 6.8 Hz between H-13 and H-14 was indicative of an *anti* configuration between these protons as that occurring in 12,13-bis*epi*eupalmerin, which shows a *J* value of 10.0 Hz. However, eupalmerin and 12-*epi*eupalmerin acetate having a *syn* configuration between these protons showed very small coupling constants ($J<1$ Hz). Finally, the relative configuration of the remaining chiral center at C-12 was deduced by comparison of the NMR data of compound **3** to those of 12,13-bis*epi*eupalmerin showing that they have the same relative stereochemistry at all centers except at C-12 (Table 1).

This was confirmed when compound **3** was transformed to compound **1** under acidic conditions (TsOH, benzene) via transannular back-side attack of the C-13 hydroxyl group at C-3 of the epoxide. Thus, we named this as 13-*epi*eupalmerin with the structure as shown in **3**.

2.2. Biogenetic studies

To elucidate the metabolic origin of the terpenes isolated in this study, several incubations with ^3H-labeled metabolites

Table 1. ^{13}C NMR and DEPT data for **1–3** and **5–9** ($CDCl_3$)

Position	1	2	3	5	6	7	8	9
1	38.3 d	38.3 d	40.3 d	38.2 d	37.9 d	38.9 d	38.9 d	39.4 d
2	25.3 t	36.5 t	29.2 t	—	25.6 t	27.4 t	27.1 t	31.0 t
3	76.7 d	74.2 d	59.7 d	78.8 d	79.0 d	80.3 d	77.5 d	60.4 d
4	73.4 s	80.0 s	58.4 s	75.2 s	73.8 s	84.1 s	86.6 s	57.4 s
5	39.0 t	32.1 t	38.7 t	28.9 t	37.5 t	29.7 t	28.9 t	35.7 t
6	20.1 t	23.7 t	23.3 d	23.5 d	35.9 t	26.0 t[a]	36.3 t	24.7 t
7	128.3 d	126.4 d	124.2 d	126.6 d	65.2 d	85.3 d	91.5 s	62.3 d
8	130.9 s	134.7 s	135.7 s	138.6 s	61.1 s	35.2 d	213.2 s	62.6 s
9	36.7 t	40.3 t	36.7 t	40.4 t	36.7 t	25.9 t[a]	32.8 t	36.0 t
10	29.4 t	33.6 t	29.6 t	29.7 t	20.2 t	32.0 t	19.4 t	23.6 t
11	21.6 d	21.5 d	23.3 t	21.4 t	29.8 t	38.9 t	35.4 t	31.2 t
12	36.1 d	35.5 d	36.7 d	36.8 d	36.1 d	33.9 d	34.7 d	36.5 d
13	79.6 d	75.0 d	79.4 d	74.7 d	81.7 d	84.6 d	82.1 d	67.1 d
14	76.7 d	79.2 d	79.4 d	79.2 d	76.7 d	75.6 d	76.2 d	77.9 d
15	169.9 s	169.9 s	170.4 s	169.8 s	170.3 s	170.0 s	169.9 s	170.3 s
16	137.0 s	139.6 s	137.6 s	134.8 s	136.9 s	137.0 s	136.6 s	137.3 s
17	121.2 t	121.9 t	122.3 t	122.6 t	121.8 t	120.9 t	121.1 t	124.7 t
18	24.6 q	21.5 q	16.4 q	21.1 q	16.1 q	25.9 q[a]	24.2 q	15.7 q[a]
19	15.9 q	16.3 q	15.1 q	16.3 q	23.0 q	20.1 q	26.1 q	15.6 q[a]
20	14.8 q	14.2 q	14.6 q	14.2 q	14.7 q	17.1 q	16.6 q	14.0 q
$OCOCH_3$				170.4 s				
$OCOCH_3$				23.3 q				

[a] Interchangeable signals.

were performed using a cell-free extract of the gorgonian *E. mammosa*. We postulated that compound **3** would be the precursor of the ether-bridged terpene **1**. To test this hypothesis, the cell-free extract was incubated with ^{3}H-GGPP and the specific activity of the recovered terpenes (**1–3**) was measured. Biosynthetic intermediates early in a pathway have higher specific activity than those produced in subsequent steps. Thus, following an incubation of the cell-free extract for 24 h the quenched mixture was lyophilized and extracted with methanol. Partitioning of the methanol extract by our standard procedure gave a methylene chloride fraction. Purification of this fraction by RP-HPLC using 20% H_2O/MeOH yielded three radioactive compounds, which were identified as cembranes **1–3** by comparison of HPLC retention times with those of authentic samples. In order to assure that the observed radioactivity was due to these cembranes rather than unknown contaminants, compounds **1–3** were re-injected on HPLC, and a 25% aliquot of each of these cembranes was analyzed by a scintillation counter. Fractions collected prior to and following each of the cembrane peaks were at approximately background levels, indicating that the observed radioactivity was due to the cembranes. The recovered radioactivities and specific activities are summarized in Table 2.

Cembrane **3** has a significantly higher specific activity than **1** providing support for the proposed role of **3** as a precursor to the ether-bridged **1** as described in Figure 4. In addition to compounds **1–3**, euniolide (**4**) was also isolated from our extract of *E. mammosa* suggesting that cembrane **3** is derived from euniolide. The ether bridge of **1** is then derived from **3** by the attack of the hydroxyl substituent at the tertiary epoxide carbon. This biosynthetic proposal is further supported by the biomimetic transformation of **3** to **1**. Specifically, as it was mentioned before, compound **1** was generated from **3** by treatment with *p*-toluenesulfonic acid.

Table 2. Radioactivity recovered from incubation with 1 μCi [C_1–^{3}H]-GGPP

Compound	Recovered radioactivity (dpm)	Specific activity (dpm/mg)
1	11,280	9400
2	14,880	14,880
3	12,400	68,900

2.3. Chemical transformations

With the aim of identifying structure–cytotoxicity activity relationships of this class of terpene, we synthesized new analogues of cembranolides **1–3** using simple functional group interconversions in a concise fashion. The complete structural assignment of all the synthetic cembranoid analogues was accomplished on the basis of comprehensive 1D and 2D NMR and MS experiments.

2.3.1. Transformations of 12-*epi*eunicin (1). Several attempts of structural modification on the major compound isolated from this gorgonian, 12-*epi*eunicin (**1**), were performed (Fig. 5). Epoxidation of the Δ^7 double bond of **1** was achieved with *m*-CPBA in benzene at room temperature to afford, after reversed-phase HPLC separation, the new epoxide cembrane **6**. The (+)-HRESIMS data of the $[M+Na]^+$ pseudomolecular ion at *m*/*z* 373.1991 of **6** allowed us to determine its molecular formula as $C_{20}H_{30}O_5$. The difference of its atom composition in relation to that of **1** by one oxygen along with the carbon signals at 65.2 ppm (C-7) and 61.1 ppm (C-8) in the ^{13}C NMR spectrum, established the presence of an additional epoxide group in compound **6** instead of the Δ^7 double bond of **1**. Furthermore, the occurrence of a proton signal at 2.94 ppm in the ^{1}H NMR spectrum confirmed the trisubstituted epoxide function. The C-7*S**, C-8*S** (α) relative stereochemistry of this epoxide group was recognized by comparison of the ^{13}C NMR chemical shift values for C-7 and C-8 in **6** to those of α-(7*S*,8*S*)-epoxyeunicin (66.8 and 61.2 ppm, respectively) versus β-(7*R*,8*R*)-epoxyeunicin (60.5 and 59.8 ppm, respectively), obtained from epoxidation of euinicin.[12]

Treatment of compound **1** with iodine in CH_2Cl_2 at room temperature for 3 h, led to a complex product mixture from which could be isolated compounds **7** and **8** using a HPLC reversed-phase column. The (+)-HRESIMS data

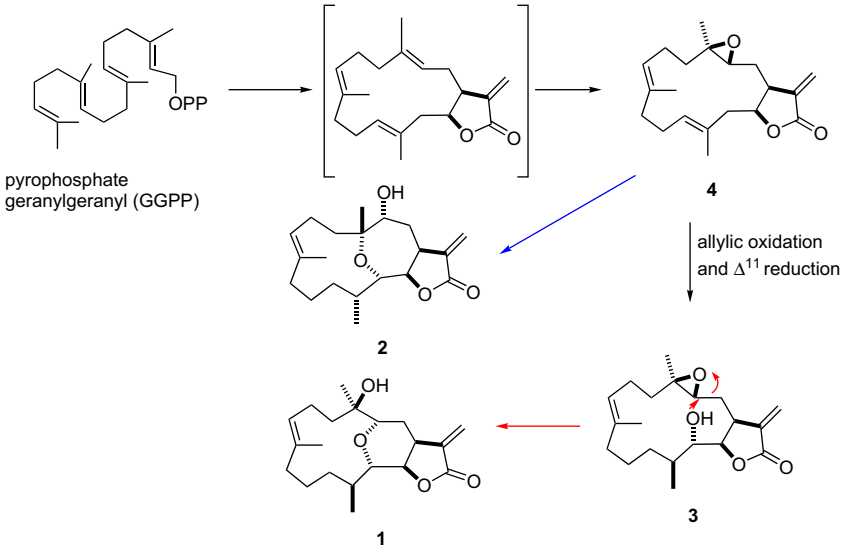


Figure 4. Biogenesis proposal.

of the $[M+Na]^+$ pseudomolecular ion at 377.2045 of compound **7** suggested the molecular formula of $C_{20}H_{30}O_4$ and six degrees of unsaturation. The structure of **7** presented an oxa-bridge function at the C-4/C-7 position, which was deduced from a standard gHMBC experiment. This new furanether **7** showed the same planar structure as inolides-A and B, obtained by others from the reaction of 12,13-bis-*epi*eupalmerin with iodine.[12] A combination of NOESY spectra and comparison of the NMR data of **7** to those of the synthetic analogues inolides-A and B, allowed us to establish the relative configuration of compound **7**. Thus, the NOE correlation between the Me-18 and H-7 indicated that they are on the same face of the molecule, assigned arbitrarily as β. Comparison of the ^{13}C and ^{1}H NMR spectral data of the C-3 to C-10 fragment of compound **7** to those of inolides-A and B allowed us to established the α disposition of the Me-20, which was very close to those of inolide-B.[12] Consequently, compound **7** was named as 12-*epi*inolide-B.

The structure of compound **8** was deduced from its 1D/2D NMR spectra and MS. Comparison of the ^{13}C NMR data of compound **8** to those of **1** indicated the major differences in the C-4/C-11 fragment. The carbon signal in the ^{13}C NMR of **8** at 213.2 ppm indicated the presence of a ketone functionality, which showed HMBC correlations to the H-6 proton at 1.96 ppm, to the H-9 protons at 1.83 ppm, and to the Me-19 at 2.20 ppm. On the other hand, HMBC correlations were observed from the H-5 proton at 1.52 ppm, the H_2-6 protons at 1.96/1.85 ppm, and H-9 protons at 1.83 ppm to the quaternary carbon at 91.5 ppm (C-7). Furthermore, the H_2-5 protons at 2.37 and 1.52 ppm also showed correlations to C-4 at 86.6 ppm and to Me-18 carbon at 24.2 ppm whose protons at 1.26 ppm were in turn HMBC correlated to C-3 carbon at 77.5 ppm. Finally, the H-6 proton at 1.85 ppm displayed a HMBC correlation to the C-9 carbon at 32.8 ppm (see Fig. 5). All of these correlations were in agreement with the presence of a five-membered cyclic ether bearing a methyl ketone group linked to the quaternary carbon at 91.5 ppm. The (+)-HRESIMS data for **8**, which showed the $[M+H]^+$ pseudomolecular ion at 349.2011 corresponding to the molecular formula $C_{20}H_{28}O_5$, confirmed the seven degrees of unsaturation present in the molecule. The lack of NOE correlations for the Me-19 precluded the determination of the relative stereochemistry of the chiral center at C-7.

2.3.2. Transformations of 13-*epi*eupalmerin (3). Conversion of **3** to diepoxide **9** was performed with *m*-CPBA in benzene at room temperature in 36% yield after separation by HPLC. The molecular formula $C_{20}H_{30}O_5$ of **9** was obtained by the (+)-HRESIMS data of the $[M+Na]^+$ pseudomolecular ion at 373.1994. In a similar way as that occurs with the epoxidation of 12,13-bis*epi*eupalmerin,[4] only one diastereoisomer was detected. The relative configuration of the additional epoxide group at C-7/C-8 position was determined by comparison of the NMR data of compound **9** with those reported for 12,13-bis*epi*eupalmerin epoxide, isolated from *E. succinea*,[13] which is epimeric at C-12. Finally, **3** was also transformed to compound **1** by treatment with *p*-toluenesulfonic acid in benzene (Fig. 6).

2.4. Biological studies

All these novel cembranes were studied in vitro with A549 (human lung carcinoma), H116 (human colon carcinoma), PSN1 (human pancreatic adrenocarcinoma), and T98G (human caucasian glioblastoma) tumor cells. The results, expressed as IC_{50} values in μg/mL, are displayed in Table 3. Most of the compounds showed moderate to strong cytotoxicity with the diepoxide **9** the most active and selective

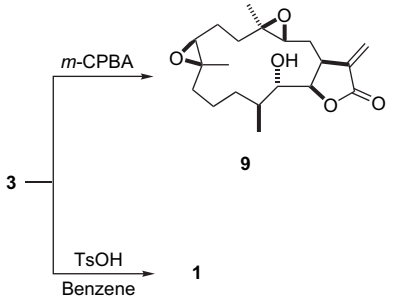


Figure 6. Chemical transformations of **3**.

Table 3. In vitro antitumor activities (IC_{50} in μg/mL) of the natural cembranes and their synthetic analogues

Compound	A-549	H116	PSN1	T98G
1	10	10	10	10
2	10	10	10	>10
3	1	5	5	0.5
5	5	5	5	>10
6	>10	10	>10	>10
7	5	1	1	5
8	10	5	5	>10
9	0.5	0.5	0.5	5

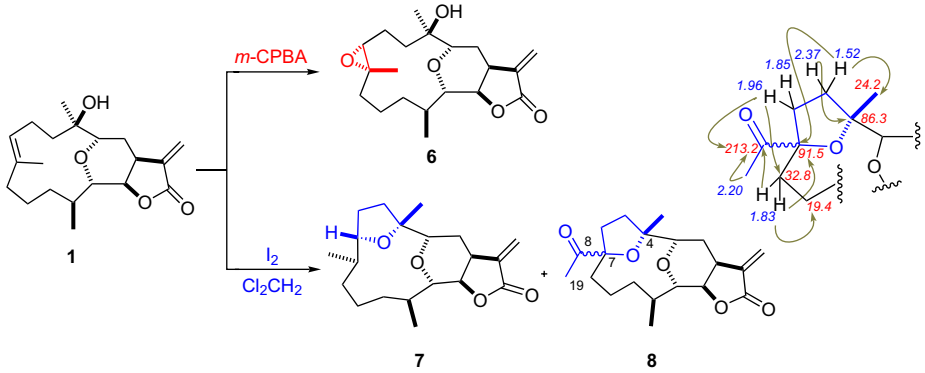


Figure 5. Chemical transformations of **1** and key HMBC correlations found in **8**.

against A-549, H116, and PSN1. It is noteworthy that the synthetic analogues (e.g., **7** and **9**) displayed greater potency than the parent natural products. The introduction of cyclic ether linkages across the cembrane skeleton results in an enhancement of cytotoxic activity. Thus, compound **7** is 10 times more active against H116 and PSN1 tumor cells than **1** (IC_{50}=10 μg/mL in **1** to IC_{50}=1 μg/mL in **7**). Furthermore, the cytotoxic activity present in compound **3** was significantly enhanced by the introduction of an extra epoxide functionality in compound **9** against H116 and PSN1 (IC_{50}=5 μg/mL in **3** to IC_{50}=0.5 μg/mL in **9**). These results corroborated the assessment that analogues of this series appear to be attractive targets for the development of antitumor agents.

3. Experimental

3.1. General methods

NMR spectra were recorded at 500/125 MHz ($^1H/^{13}C$), Bruker AVANCE 500; 200/50 MHz ($^1H/^{13}C$), Bruker AC-200 NMR spectrometer in $CDCl_3$. Carbon multiplicities were determined using DEPT-135 and DEPT-90 sequences. Atom connectivities were determined using gradient edited HSQC, HMBC, and DQCOSY experiments. Gradient NOESY experiments were carried out using a mixing time of 0.8 s and HSQC–TOCSY was run using a mixing time of 60 ms. (+)-LRAPCIMS and (+)-LRESIMS were measured on ThermoQuest Navigator spectrometer while (+)-HRESIMS were measured on VG Autospec and Bruker spectrometers. Optical rotations were determined on a JASCO DIP-1000 with an Hg lamp at 590 nm. Semipreparative HPLC was performed using Sharlau Nucleosil C18 column (300×8 mm) with RI detection.

3.2. Biological material

Specimens of *E. mammosa* were collected using SCUBA on Sweetings Cay in the Bahamas during the 1999 and 2000 FAU expeditions. Voucher samples are deposited at the Departamento de Química Fundamental, Universidade de A Coruña, under reference UDC 9951 and UDC 00EM.

3.3. Extraction and isolation

Specimens of the gorgonian collected in 1999 (337 g) were homogenized in MeOH (3×2.5 L), and the solvent was evaporated under reduced pressure. The crude extract was partitioned between CH_2Cl_2 and H_2O (1/1). The fraction soluble in CH_2Cl_2 was evaporated under pressure and partitioned between 10% aqueous MeOH (400 mL) and hexane (2×400 mL). Water was added to the polar fraction until the mixture became 50% in aqueous MeOH and then was extracted with CH_2Cl_2 (3×400 mL). The viscous oil (8.3 g) obtained from the CH_2Cl_2 fraction was submitted repeatedly to flash column chromatography (eluting with hexane/acetone mixtures of increasing polarity) to give several fractions. Fraction eluted with 15% acetone/hexane gave 505 mg of compound **1**. A second fraction eluted with 15–20% acetone/hexane (3 g) was separated by reversed-phase HPLC eluting with MeOH/H_2O (8/2) to obtain 22.4 mg of compound **3**, 11.3 mg of **2**, and 26.2 mg of **1**.

Specimens of the gorgonian collected in 2000 (350 g) were homogenized in MeOH (3×2.5 L), and the solvent was evaporated under reduced pressure. The crude extract was partitioned between 10% aqueous MeOH (400 mL) and hexane (2×400 mL) to give, after evaporation under pressure, 12.2 g of the hexane fraction. A portion of this fraction (500 mg) was submitted to flash column chromatography (eluting with hexane/acetone mixtures of increasing polarity) to give 2.8 mg of eunolide (**4**).

3.3.1. 12-*epi*Eunicin (1). Amorphous white solid. $[\alpha]_D$ −11.5 (*c* 1.20, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, δ_H ppm): 6.38 (1H, d, *J*=3.4 Hz, H-17α); 5.60 (1H, d, *J*=3.4 Hz, H-17β); 5.10 (1H, dd, *J*=5.9 and 9.3 Hz, H-7); 4.38 (1H, dd, *J*=8.0 and 8.9 Hz, H-14); 3.37 (1H, m, H-1); 3.20 (1H, dd, *J*=3.7 and 10.0 Hz, H-3); 2.79 (1H, t, *J*=8.9 Hz, H-13); 2.11 (2H, m, H-2); 1.58 (3H, s, H-19); 1.15 (3H, s, H-18); 0.99 (3H, d, *J*=6.8 Hz, H-20). ^{13}C NMR see Table 1. (+)-HR-ESIMS: *m/z* 357.2044 $[M+Na]^+$ (calcd for $C_{20}H_{30}O_4Na$, 357.2036). (+)-LR-APCIMS *m/z*: 335 $[M+H]^+$, 357 $[M+Na]^+$.

3.3.2. 4-*epi*Jeunicin (2). Amorphous colorless oil. $[\alpha]_D$ −50.3 (*c* 0.53, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, δ_H ppm): 6.30 (1H, d, *J*=2.9 Hz, H-17); 5.61 (1H, d, *J*=2.9 Hz, H-17′); 5.23 (1H, dd, *J*=5.6 and 7.5 Hz, H-7); 4.59 (1H, dd, *J*=8.8 and 10.0 Hz, H-14); 3.57 (2H, m, H-1 and H-3); 3.38 (1H, dd, *J*=1.2 and 10.0 Hz, H-13); 1.68 (1H, m, H-12); 1.64 (3H, br s, H-19); 1.21 (3H, s, H-18); 0.97 (3H, d, *J*=7.3 Hz, H-20). ^{13}C NMR see Table 1. (+)-HR-ESIMS: *m/z* 357.2040 $[M+Na]^+$ (calcd for $C_{20}H_{30}O_4Na$, 357.2036). (+)-LR-APCIMS *m/z*: 335 $[M+H]^+$, 357 $[M+Na]^+$, 317 $[M+H-H_2O]^+$.

3.3.3. 13-*epi*Eupalmerin (3). Amorphous colorless oil. $[\alpha]_D$ +15.8 (*c* 0.12, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, δ_H ppm): 6.33 (1H, d, *J*=2.4 Hz, H-17α); 5.82 (1H, d, *J*=2.4 Hz, H-17β); 5.18 (1H, dd, *J*=5.9 and 8.3 Hz, H-7); 4.56 (1H, t, *J*=6.8 Hz, H-14); 3.80 (1H, br t, *J*=5.2 Hz, H-13); 3.46 (1H, m, H-1); 3.07 (1H, br d, *J*=7.8 Hz, H-3); 1.58 (3H, s, H-19); 1.31 (3H, s, H-18); 1.02 (3H, d, *J*=6.8 Hz, H-20). ^{13}C NMR see Table 1. (+)-HR-ESIMS: *m/z* 357.2030 $[M+Na]^+$ (calcd for $C_{20}H_{30}O_4Na$, 357.2036). (+)-LR-APCIMS *m/z*: 335 $[M+H]^+$, 357 $[M+Na]^+$.

3.4. Biogenetic studies

A cell-free extract was prepared from flash frozen *E. mammosa* (stored at −80 °C) by homogenizing in a phosphate buffer (pH 7.7 with EDTA and β-mercaptoethanol) with liquid nitrogen in a Waring blender. To remove cellular debris, the homogenate was centrifuged for 15 min at 9000×*g*. The supernatant was centrifuged at 18,000×*g* for 3 h and then passed through 0.45 μm nylon membrane filters. The cell-free extract (37 mL) was incubated with 1 μCi of ^3H-GGPP and $MgCl_2$ (7.3 mg, 1 mM) at room temperature for 24 h at 200 rpm. The incubation was lyophilized and extracted with methanol. The methanol extract was partitioned as before and the methylene chloride fraction was purified by reversed-phase HPLC eluting with 20% H_2O/MeOH. Compounds **1**–**3** were identified in the HPLC by comparison of retention times with those of an authentics samples. The radioactivity of these compounds was

determined using a scintillation counter. Compounds **1**–**3** were reinjected, and a small portion of each of these cembranes was analyzed by a scintillation counter. Fractions collected prior to and following each of the cembrane peaks were at approximately background levels, indicating that the observed radioactivity was due to the cembranes.

3.5. Acetylation of 4-*epi*jeunicin (2)

A solution of 4-*epi*jeunicin (**2**) (5 mg, 0.015 mmol) in Ac_2O (1 mL) and Py (1 mL) was stirred vigorously at room temperature overnight and concentrated to leave a residue identified as compound **5** (6 mg, quantitative yield).

3.5.1. Compound 5. Amorphous colorless oil. $[\alpha]_D$ +34.0 (*c* 0.09, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, δ_H ppm): 6.36 (1H, d, *J*=2.5, H-17α); 5.68 (1H, d, *J*=2.5 Hz, H-17β); 5.24 (1H, dd, *J*=5.7 and 7.1 Hz, H-7); 4.83 (1H, d, *J*=7.4 Hz, H-3); 4.63 (1H, dd, *J*=8.6 and 10.1 Hz, H-14); 3.42 (1H, d, *J*=10.1 Hz, H-13); 3.39 (1H, m, H-1); 2.17 (3H, s, OAc); 1.65 (3H, br s, H-19); 1.14 (3H, s, H-18); 1.01 (3H, d, *J*=7.1 Hz, H-20). ^{13}C NMR see Table 1. (+)-LR-ESIMS *m/z* (rel int.): 415 $[M+K]^+$ (35), 399 $[M+Na]^+$ (100).

3.6. Reaction of 12-*epi*eunicin (1) with *m*-chloroperbenzoic acid

A solution of 12-*epi*eunicin (**1**) (100 mg, 0.299 mmol) in dry benzene (15 mL) was stirred vigorously with *m*-CPBA (67 mg, 0.39 mmol) at room temperature for 4 h and concentrated to afford a residue (112 mg) that was purified by reverse-phase HPLC (Sharlau C18, elution with MeOH/H_2O 65/35) to give compound **6** (11 mg, 11%).

3.6.1. Compound 6. Amorphous colorless oil. $[\alpha]_D$ +141 (*c* 0.08, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, δ_H ppm): 6.40 (1H, d, *J*=2.9 Hz, H-17); 5.64 (1H, d, *J*=2.9 Hz, H-17′); 4.41 (1H, t, *J*=8.3 Hz, H-14); 3.38 (1H, m, H-1); 3.30 (1H, dd, *J*=4.5 and 9.1 Hz, H-3); 2.94 (1H, dd, *J*=1.2 and 9.3 Hz, H-7); 2.83 (1H, t, *J*=9.2 Hz, H-13); 2.05 (2H, m, H-2); 1.26 (3H, s, H-18); 1.26 (3H, s, H-19); 1.02 (3H, d, *J*=7.0 Hz, H-20). ^{13}C NMR see Table 1. (+)-HR-ESIMS *m/z* 373.1991 $[M+Na]^+$ (calcd for $C_{20}H_{30}O_5Na$, 373.1990).

3.7. Reaction of 12-*epi*eunicin (1) with iodine

A solution of iodine (49.2 mg, 0.196 mmol, 1.07 equiv) in Cl_2CH_2 (4 mL) was added drop wise over 3 min to a magnetically stirred solution of **1** (60 mg, 0.18 mmol) in Cl_2CH_2 (10 mL) and was stirred at room temperature for 3 h, concentrated and the resulting oil (108 mg) was purified by means of reverse-phase HPLC (Sharlau C18, elution with MeOH/H_2O 75/25) to give **7** (8 mg, 13%) and **8** (4 mg, 6%).

3.7.1. Compound 7. Amorphous colorless oil. $[\alpha]_D$ +91 (*c* 0.11, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, δ_H ppm): 6.39 (1H, d, *J*=3.5 Hz, H-17α); 5.54 (1H, d, *J*=3.5 Hz, H-17β); 4.52 (1H, dd, *J*=7.9 and 9.6 Hz, H-14); 4.17 (1H, m, H-7); 3.41 (1H, m, H-1); 3.22 (1H, dd, *J*=2.4 and 11.8 Hz, H-3); 2.68 (1H, dd, *J*=8.3 and 9.5 Hz, H-13); 1.18 (3H, s, H-18); 1.00 (3H, d, *J*=7.2 Hz, H-20); 0.78 (3H, d, *J*=7.3 Hz, H-19). ^{13}C NMR see Table 1. (+)-HR-ESIMS *m/z* 357.2045 $[M+Na]^+$ (calcd for $C_{20}H_{30}O_4Na$, 357.2036).

3.7.2. Compound 8. Amorphous colorless oil. $[\alpha]_D$ +34 (*c* 0.13, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, δ_H ppm): 6.43 (1H, d, *J*=3.6 Hz, H-17α); 5.58 (1H, d, *J*=3.6 Hz, H-17β); 4.46 (1H, t, *J*=8.5 Hz, H-14); 3.43 (1H, m, H-1); 3.29 (1H, dd, *J*=2.0 and 12.3 Hz, H-3); 2.88 (1H, t, *J*=9.1 Hz, H-13); 2.37 (1H, ddd, *J*=8.4, 11.9 and 11.9 Hz, H-5); 2.20 (3H, s, H-19); 2.00 (1H, m, H-2); 1.96 (1H, m, H-6); 1.89 (1H, m, H-12); 1.85 (1H, m, H-6′); 1.83 (2H, m, H-9); 1.80 (1H, m, H-2′); 1.60 (2H, m, H-10 and H-11); 1.52 (1H, dd, *J*=8.4 and 11.9 Hz, H-5′); 1.26 (3H, s, H-18); 1.22 (1H, m, H-10′); 0.99 (3H, d, *J*=7.0 Hz, H-20). ^{13}C NMR see Table 1. (+)-HR-ESIMS: 349.2011 $[M+H]^+$ (calcd for $C_{20}H_{29}O_5$, 349.2010).

3.8. Reaction of 13-*epi*eupalmerin (3) with *m*-chloroperbenzoic acid

A solution of **3** (20 mg, 0.05 mmol) in dry benzene (3 mL) was stirred vigorously with *m*-CPBA (17 mg, 0.099 mmol, 1.3 mequiv) at room temperature for 4.5 h. Following it was concentrated to leave a residue that was purified by means of reverse-phase HPLC (Sharlau C18, elution MeOH/H_2O 65/35) to give **9** (6.3 mg, 36%).

3.8.1. Compound 9. Amorphous colorless oil. $[\alpha]_D$ +21 (*c* 0.03, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, δ_H ppm): 6.47 (1H, d, *J*=1.4 Hz, H-17α); 5.84 (1H, d, *J*=1.4 Hz, H-17β); 4.41 (1H, m, H-14); 3.98 (1H, d, *J*=9.3 Hz, H-13); 3.45 (1H, ddd, *J*=1.9, 12.2 and 12.2 Hz, H-1); 2.76 (1H, dd, *J*=3.3 and 10.9 Hz, H-7); 2.73 (1H, m, H-2); 2.71 (1H, br s, H-3); 1.99 (1H, m, H-12); 1.67 (1H, m, H-2′); 1.33 (1H, s, H-18); 1.27 (1H, s, H-19); 1.09 (1H, d, *J*=6.8 Hz, H-20). ^{13}C see Tables 1 and 2. (+)-HR-ESIMS *m/z* 373.1994 $[M+H]^+$ (calcd for $C_{20}H_{30}O_5Na$, 373.1985).

3.9. Reaction of 13-*epi*eupalmerin (3) with *p*-toluenesulfonic acid hydrate

A solution of compound **3** (1.3 mg, 0.003 mmol) in dry benzene (0.3 mL) was stirred vigorously with *p*-toluenesulfonic acid hydrate (0.022 mg, 0.0001 mmol, 0.03 mequiv) at room temperature for 24 h. Then, the reaction product was concentrated. The identification of compound **1** in the reaction products was carried out with analytical Hypersil® Elite C18, 150×4.6 mm 5μ, reverse-phase HPLC using MeOH/H_2O 75/25 as the mobile phase with a flow of 0.7 mL/min by comparison of the retention time (10.5 min) and co-injection with compound **1**.

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References and notes

1. Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571–4618.
2. (a) Rodríguez, J.; Nieto, R. M.; Jiménez, C. *J. Nat. Prod.* **1998**, *61*, 313–317; (b) García, M.; Rodríguez, J.; Jiménez, C. *J. Nat. Prod.* **1999**, *62*, 257–260; (c) González, N.; Barral, M. A.; Rodríguez, J.; Jiménez, C. *Tetrahedron* **2001**, *57*, 3487–3497.
3. Ferns, T.; Kerr, R. G. *Tetrahedron* **2005**, *61*, 12358–12365.
4. Rodríguez, A. D.; Piña, I. C.; Acosta, A. L.; Barnes, C. L. *Tetrahedron* **2001**, *57*, 93–107.
5. Gampe, R. T.; Alam, M.; Weinheimer, A. J.; Martin, G. E.; Matson, J. A.; Willcott, M. R.; Inners, R. R.; Hurd, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 1823–1826.
6. Sen Gupta, P. K.; Hossain, M. B.; Van der Helm, D. *Acta Crystallogr.* **1986**, *C42*, 434–436.
7. Sanduja, R.; Linz, G. S.; Alam, M.; Weinheimer, A. J.; Martin, G. E.; Ezell, E. L. *J. Heterocycl. Chem.* **1986**, *23*, 529–535.
8. Weinheimer, A. J.; Matson, J. A.; Poling, M.; Van der Helm, D. *Acta Crystallogr.* **1982**, *B38*, 580–583.
9. Fontán, L. A.; Rodríguez, A. D. *J. Nat. Prod.* **1991**, *54*, 298–301.
10. Rodríguez, A. D.; Dhasmana, H. *J. Nat. Prod.* **1993**, *56*, 564–570.
11. Gopichand, Y.; Ciereszko, L. S.; Schmitz, F. J.; Switzner, D.; Rahman, A.; Hossain, M. B.; van der Helm, D. *J. Nat. Prod.* **1984**, *47*, 607–614.
12. Rodríguez, A. D.; Piña, I. C. *J. Org. Chem.* **1995**, *60*, 8096–8100.
13. Rodríguez, A. D.; Acosta, A. L. *J. Nat. Prod.* **1998**, *61*, 40–45.

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Synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones by sequential application of domino reactions of 1,3-bis(silyl enol ethers) with benzopyrylium triflates

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Abstract—The domino, Michael–retro-Michael–aldol, reaction of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-formylchromones afforded 4-(2-hydroxybenzoyl)-2-acetylphenols, which were transformed into 6-(2-hydroxybenzoyl)chromones. The Me_3SiOTf-mediated condensation of the latter with 1,3-bis(silyl enol ethers) and subsequent domino 'retro-Michael–aldol–lactonization' reaction afforded 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones.

1. Introduction

Functionalized 6*H*-benzo[*c*]chromen-6-ones (dibenzo[*b*,*d*]-pyran-6-ones) occur in a number of pharmacologically active natural products, such as autumnariol,[1a] autumnariniol,[1b] alternariol[1c] or altenuisol,[1d] and are specific inhibitors of the growth of endothelic cells[2a] and oestrogen receptors.[2b] Dibenzo[*c*,*d*]chromen-6-ones are present in various natural antibiotics and antitumour agents, such as the gilvocarcins, chrysomycins and ravidomycins.[3] The related ellagic and coruleoellagic acids are found in plants.[4] Functionalized benzophenones also occur in a variety of natural products and represent important core structures for the development of pharmaceuticals.[5] For example, the benzophenone phenstatin was discovered as an antitubulin agent (microtubules represent an important target for anticancer therapy).[6] Recently, Hsieh and co-workers reported that cytotoxic 2-hydroxy- and 2-aminobenzophenones represent potent antitubulin agents.[7]

1,3-Bis(silyl enol ethers) represent d^4 synthons and can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions.[8] In recent years, we have developed a number of domino reactions of 1,3-bis(silyl enol ethers) with pyrylium salts. For example, the Me_3SiOTf-mediated reaction of 3-formylchromones with 1,3-bis(silyl enol ethers) allows the synthesis of 4-(2-hydroxybenzoyl)phenols.[9] The Me_3SiOTf-mediated reaction of 1,3-bis(silyl enol ethers) with chromones provides a facile access to 6*H*-benzo[*c*]-chromen-6-ones.[10] Herein, we report the combination of these two domino reactions based on sequential use of 1,3-bis(silyl enol ethers) at two stages of the synthesis. This strategy allows a convenient synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones, which combine the structural features of 6*H*-benzo[*c*]chromen-6-ones and 4-(2-hydroxybenzoyl)phenols.

2. Results and discussion

The reaction of 1,3-bis(silyl enol ether) **2** with 3-formylchromones **1a–c** afforded the 4-(2-hydroxybenzoyl)phenols **3a–c** (Scheme 1, Table 1). The syntheses of **3a**[9b] and **3b**,**c**[11] have been previously reported. The formation of the products can be explained by a domino 'Michael–retro-Michael–Aldol' reaction. Compounds **3a–c** were transformed into the novel chromones **4a–c** by treatment with triethyl orthoformate and perchloric acid.[12] The Me_3SiOTf-mediated condensation of **4a–c** with 1,3-bis(silyl enol ethers) **5a–d** gave the 2,3-dihydrobenzopyrans **6a–e**, which were transformed—by treatment with NEt_3—into the novel 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones **7a–e**. The formation of these products proceeds by a domino 'retro-Michael–aldol–lactonization' reaction.[10] Notably, the reaction of **4** with **5** generally afforded the 2,3-dihydropyrans **6** together with a small amount of **7**. Therefore, a mixture of these two compounds was separated from polar

Keywords: Chromones; Cyclizations; Domino reactions; Oxygen heterocycles; Silyl enol ethers.
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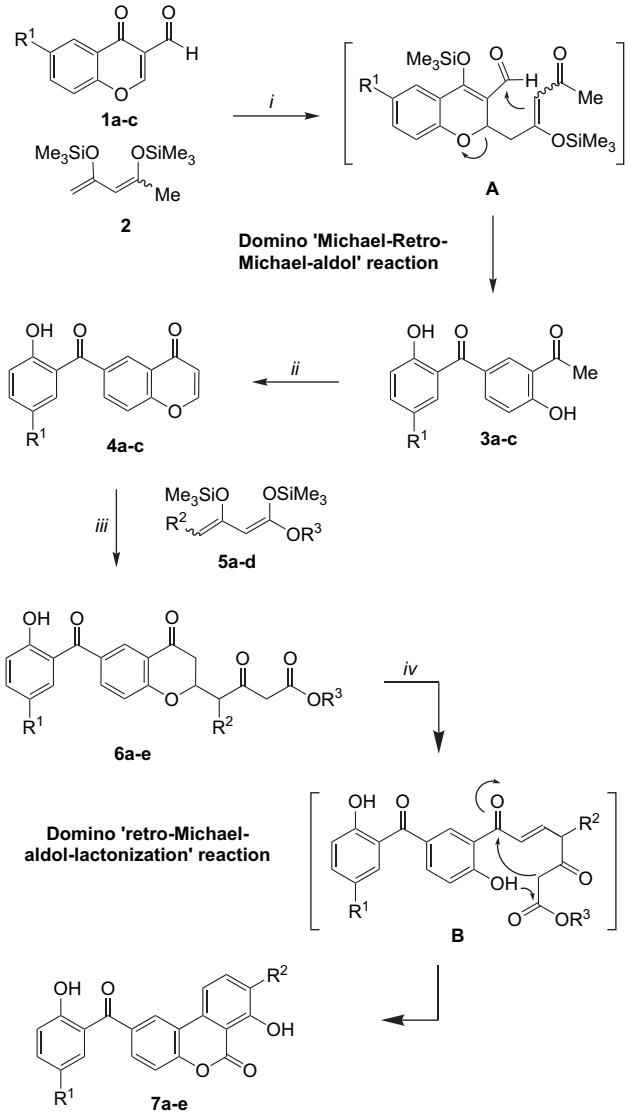
side-products by chromatography and subsequently treated with NEt_3. Notably, the use of hydroxyl protective groups was not required for the transformation of **4a–c** into **7a–e**.



Scheme 1. Synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones **7a–e**: (i) (1) Me_3SiOTf (0.3 equiv), 0 °C; (2) CH_2Cl_2, then **2**, 0→20 °C, 12 h; (ii) $HC(OEt)_3$, $HClO_4$ (70%), 0→20 °C, 12–20 h; (iii) (1) Me_3SiOTf (1.3 equiv), 0 °C, 1 h; (2) CH_2Cl_2, then **5a–d** (1.3 equiv), 12 h; (3) HCl (10%); (iv) NEt_3, EtOH, 12 h, 20 °C.

Table 1. Products and yields

	R^1	R^2	R^3	**3** (%)[a]	**4** (%)[a]	**7** (%)[a]
a	H	H	Et	43	52	48
b	Cl	H	Me	25	65	70
c	Me	H	Me	29	58	51
d	H	Me	Et	43	52	41
e	H	Et	Me	43	52	23

[a] Yields of isolated products.

The core structure of the products **7** contains 20 carbon atoms out of which 9 carbons are derived from the two 1,3-bis(silyl enol ethers), 10 carbons from the 3-formylchromone and 1 carbon from the orthoformate.

In conclusion, the combination of the Me_3SiOTf-mediated domino Michael–retro-Michael–aldol reaction of 1,3-bis(silyl enol ethers) with 3-formylchromones with the domino 'retro-Michael–aldol–lactonization' reaction of 1,3-bis(silyl enol ethers) with chromones allowed an efficient synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones. These products combine the structural features of 6*H*-benzo[*c*]chromen-6-ones and 4-(2-hydroxybenzoyl)phenols.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. The melting points are corrected.

3.2. General procedure for the synthesis of 4-(2-hydroxybenzoyl)phenols 3a–c

To the 3-formylchromone **1** (1.0 equiv) was added Me_3SiOTf (0.3 equiv) at 20 °C. After stirring for 10 min CH_2Cl_2 (8 mL) was added, the solution was cooled to 0 °C and the 1,3-bis(silyl enol ether) (1.3 equiv) was added. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3×80 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc=10:1→3:1).

3.2.1. 1-[2-Hydroxy-5-(2-hydroxybenzoyl)phenyl]ethanone (3a). The synthesis of **3a** has been previously reported.[9a] Starting with **1a** (200 mg, 1.15 mmol), Me_3SiOTf (77 mg, 0.34 mmol) and 1,3-bis(silyl enol ether) **2a** (365 mg, 1.49 mmol), **3a** was isolated as a colourless solid (127 mg, 43%), mp 129 °C.

3.2.2. 1-[5-Chloro-2-hydroxybenzoyl)-2-hydroxyphenyl]-ethanone (3b). The synthesis of **3b** has been previously reported.[11] Starting with **1b** (202 mg, 1.10 mmol), Me_3SiOTf (75 mg, 0.33 mmol) and 1,3-bis(silyl enol ether) **2a** (350 mg, 1.43 mmol), **3b** was isolated as a colourless solid (80 mg, 25%), mp 145–146 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=12.71 (s, 1H, OH), 11.64 (s, 1H, OH), 8.19 (d, ^4J=2.1 Hz, 1H, Ar), 7.85 (dd, ^3J=8.9 Hz, ^4J=2.1 Hz, 1H, Ar), 7.54 (d, ^4J=2.4 Hz, 1H, Ar), 7.47 (dd, ^3J=8.9 Hz, ^4J=2.4 Hz, 1H, Ar), 7.11 (d, ^3J=8.9 Hz, 1H, Ar), 7.05 (d, ^3J=8.9 Hz, 1H, Ar), 7.05 (d, ^3J=8.9 Hz, 1H, Ar), 2.70 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=204.3 (C=O), 197.7, 165.8 (C–OH), 161.4 (C_{Ar}), 137.2, 136.1, 133.3, 131.6 (CH), 128.0, 123.5 (C), 120.3 (CH), 119.6, 119.3 (C_{Ar}), 118.8 (CH), 26.7 (CH_3).

3.2.3. 1-[(2-Hydroxy-5-methylbenzoyl)-2-hydroxyphenyl]ethanone (3c). The synthesis of **3c** has been previously reported.[11] Starting with **1c** (433 mg, 2.64 mmol), Me_3SiOTf (179 mg, 0.79 mmol) and 1,3-bis(silyl enol ether) **2a** (840 mg, 3.43 mmol), **3c** was isolated as a colourless solid (207 mg, 29%), mp 140–141 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=12.66 (s, 1H, OH), 11.58 (s, 1H, OH), 8.19 (d, ^4J=2.1 Hz, 1H, Ar), 2.28 (s, 3H, CH_3), 7.84 (dd, ^3J=8.9 Hz, ^4J=2.1 Hz, 1H, Ar), 7.31–7.37 (m, 2H, Ar), 7.08 (d, ^3J=8.9 Hz, 1H, Ar), 6.99 (d, ^3J=8.9 Hz, 1H, Ar), 2.68 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=204.4 (C=O), 198.7, 165.4 (C–OH), 160.9, 137.3, 133.1, 132.4 (CH), 128.9, 127.9, 119.2 (C), 118.6, 118.4, 118.3 (CH), 26.7, 20.5 (CH_3).

3.3. General procedure for the synthesis of chromones 4a–c

To a solution of 4-(2-hydroxybenzoyl)-2-acetylphenols **3** (1.0 equiv) in triethyl orthoformate (10.0 equiv) was added perchloric acid (60%, 1.3 equiv) at 0 °C. The temperature was allowed to rise slowly to 20 °C and the solution was stirred for additional 12 h. The product was separated from the solution by filtration and purified by column chromatography (silica gel, *n*-heptane/EtOAc=9:1).

3.3.1. 6-(2-Hydroxybenzoyl)chromone (4a). Starting with **3a** (292 mg, 1.14 mmol), triethyl orthoformate (1.35 g, 1.49 mL, 9.08 mmol) and perchloric acid (60%, 240 mg, 0.24 mL, 1.47 mmol), **4a** was isolated (158 mg, 52%) by chromatography (silica gel, hexanes/EtOAc=5:1) as a yellow solid, mp 172 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ=10.27 (s, 1H, OH), 8.36 (d, ^3J=6.2 Hz, 1H, CH), 8.27 (d, ^4J=2.2 Hz, 1H, Ar), 8.16 (dd, ^3J=8.8 Hz, ^4J=2.3 Hz, 1H, Ar), 7.78 (d, ^3J=8.6 Hz, 1H, Ar), 7.47 (m, 1H, Ar), 7.38 (dd, ^3J=7.6 Hz, ^4J=1.6 Hz, 1H, Ar), 6.98 (m, 2H, Ar), 6.42 (d, ^3J=6.2 Hz, 1H, CH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=195.3, 176.1 (C=O), 158.3 (C_{Ar}), 157.4 (CH_{Ar}), 156.4, 134.3 (C_{Ar}), 133.9, 133.3, 130.2, 127.3 (CH_{Ar}), 124.8, 123.7 (C_{Ar}), 119.3, 119.2, 116.7, 112.6 (CH_{Ar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3426 (m), 3258 (w), 3175 (w), 3086 (m), 2928 (m), 1656 (s), 1616 (s), 1481 (s), 1443 (s), 1340 (s), 1300 (s), 1247 (s), 1175 (m), 1137 (m), 1027 (w), 959 (w), 846 (m), 800 (w), 762 (m), 724 (w), 624 (w), 545 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε): 338 (3.73), 305 (3.88), 242 (4.35), 216 (4.38). MS (EI, 70 eV): *m*/*z* (%)=266 (M^+, 100), 237 (56), 221 (10), 173 (17), 145 (14), 121 (40), 93 (11), 90 (16), 66 (18). Anal. $C_{16}H_{10}O_4$ (266.3) calcd: C, 72.18; H, 3.79; found: C, 71.92; H, 3.65.

3.3.2. 6-(5-Chloro-2-hydroxybenzoyl)chromone (4b). Starting with **3b** (80 mg, 0.28 mmol), triethyl orthoformate (332 mg, 2.24 mmol) and perchloric acid (70%, 0.05 mL), **4b** was isolated (54 mg, 65%) as a yellow solid; R_f 0.33 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=11.69 (s, 1H, OH), 8.50 (d, ^4J=2.4 Hz, 1H, Ar), 8.00 (dd, ^3J=8.5 Hz, ^4J=2.4 Hz, 1H, Ar), 7.92 (d, ^3J=6.1 Hz, 1H, =CH), 7.63 (d, ^3J=8.5 Hz, 1H, Ar), 7.51–7.46 (m, 2H, Ar), 7.06 (d, ^3J=8.5 Hz, 1H, Ar), 6.42 (d, ^3J=6.1 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=198.6, 176.6 (C=O), 161.7, 158.4 (C_{Ar}–O), 155.5, 136.7 (CH_{Ar}), 134.1 (C_{Ar}), 133.8, 131.9, 127.6 (CH_{Ar}), 124.4 (C_{Ar}), 123.7 (C_{Ar}), 120.3 (CH_{Ar}), 119.5 (C_{Ar}), 119.3 (CH_{Ar}), 113.6 (CH_{Ar}). MS (EI, 70 eV): *m*/*z* (%)=302 (M^+, ^{37}Cl, 32), 300 (M^+, ^{35}Cl, 100), 271 (71), 222 (10), 173 (28), 154 (23). HRMS (EI, 70 eV): calcd for $C_{16}H_9ClO_4$ (M^+): 300.01705; found: 300.01839.

3.3.3. 6-(2-Hydroxy-5-methylbenzoyl)chromone (4c). Starting with **3c** (207 mg, 0.81 mmol), triethyl orthoformate (960 mg, 6.48 mmol) and perchloric acid (70%, 0.15 mL), **4c** was isolated (132 mg, 58%) by chromatography (silica gel, *n*-heptane/EtOAc) as a colourless solid; R_f 0.38 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=11.64 (s, 1H, OH), 8.50 (d, ^4J=2.1 Hz, 1H, Ar), 8.02 (dd, ^3J=8.5 Hz, ^4J=2.1 Hz, 1H, Ar), 7.91 (d, ^3J=6.1 Hz, 1H, =CH), 7.61 (d, ^3J=8.5 Hz, 1H, Ar), 7.38–7.29 (m, 2H, Ar), 7.00 (d, ^3J=8.5 Hz, 1H, Ar), 6.42 (d, ^3J=6.1 Hz, 1H, =CH), 2.25 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=199.4, 176.8 (C=O), 161.2, 158.1 (C_{Ar}–O), 155.5, 137.9 (CH_{Ar}), 134.9 (C_{Ar}), 134.0, 132.7 (CH_{Ar}), 128.2 (C_{Ar}), 127.5 (CH_{Ar}), 124.2 (C_{Ar}), 119.0 (CH_{Ar}), 118.5 (C_{Ar}), 118.4, 113.5 (CH_{Ar}), 20.5 (CH_3). MS (EI, 70 eV): *m*/*z* (%)=280.0 (M^+, 100), 279.0 (83), 251.0 (45), 235.1 (12), 173.0 (14), 135.0 (28). HRMS (EI, 70 eV): calcd for $C_{17}H_{12}O_4$ (M^+): 280.07301; found: 280.07231.

3.4. General procedure for the synthesis of 7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-ones 7a–e

To chromone **4** (1.0 equiv) was added Me_3SiOTf (1.3 equiv) at 20 °C and the mixture was stirred for 1 h at 20 °C. Subsequently, dichloromethane (8 mL/mmol) was added and the solution was cooled to 0 °C. The 1,3-bis(silyl enol ether) **3** (1.3 equiv) was added, the temperature was allowed to warm slowly to 20 °C and the solution was stirred for 12 h. To the mixture was added hydrochloric acid (10%), the organic and the aqueous layers were separated and the latter was extracted with dichloromethane (3×50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by a rapid flash chromatography (silica gel, *n*-heptane/EtOAc=5:1) to remove polar side-products. The 2,3-dihydrobenzopyran **6** (together with some amount of **7**) was dissolved in dry ethanol (10 mL/mmol), triethylamine (3.0 equiv) was added and the solution was stirred for 12 h at 20 °C. To the solution was added hydrochloric acid (10%) and diethyl ether. After stirring for 30 min, the organic and the aqueous layers were separated and the latter was extracted with diethyl ether (3×80 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc=20:1) to give the product **7**.

3.4.1. 7-Hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]chromen-6-one (7a). Starting with **4a** (252 mg, 0.95 mmol), Me_3SiOTf (274 mg, 0.22 mL, 1.24 mmol) and **5a** (340 mg, 1.24 mmol) (first step), and triethylamine (435 mg, 4.3 mmol) and ethanol (10 mL) (second step), **7a** was isolated (151 mg, 48%) as a colourless solid, mp 220 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ=11.85 (s, 1H, OH), 11.24 (s, 1H, OH), 8.41 (d, ^4J=1.9 Hz, 1H, Ar), 7.83 (dd, ^3J=8.5 Hz, ^4J=2.0 Hz, 1H, Ar), 7.77 (t, ^3J=8.1 Hz, 1H, Ar), 7.59 (m, 3H, Ar), 7.51 (d, ^3J=8.5 Hz, 1H, Ar), 7.15 (m, 2H, Ar), 6.93 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz):

δ=199.7 (C=O), 164.8, 163.3, 162.6, 152.7 (C_{Ar}–O), 137.7, 136.8 (CH_{Ar}), 134.9, 134.3 (C_{Ar}), 133.1, 131.4, 125.1, 119.0 (CH_{Ar}), 118.9 (C_{Ar}), 118.8 (CH_{Ar}), 118.6 (C_{Ar}), 117.9, 117.5, 112.6 (CH_{Ar}), 106.1 (C_{Ar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3122 (m), 3052 (m), 1683 (s), 1626 (s), 1593 (s), 1484 (m), 1447 (s), 1347 (m), 1302 (m), 1276 (s), 1243 (s), 1206 (s), 1139 (m), 1072 (m), 994 (w), 840 (w), 760 (m), 710 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε): 349 (4.09), 338 (4.10), 261 (4.37), 231 (4.42), 217 (4.39). Fluorescence (CH_3CN, nm): Fλ_{max} (λ_{Ex}): 485 (340). MS (EI, 70 eV): *m*/*z* (%)=332 (M^+, 8), 256 (71), 241 (10), 212 (18), 163 (24), 148 (21), 121 (100), 105 (22), 66 (31).

3.4.2. 7-Hydroxy-2-(5-chloro-2-hydroxybenzoyl)-[*c*]chromen-6-one (7b). Starting with **4b** (54 mg, 0.18 mmol), Me_3SiOTf (51 mg, 0.23 mmol) and **5b** (60 mg, 0.23 mmol) in CH_2Cl_2 (1.8 mL) (first step), and triethylamine (85 mg, 0.85 mmol) in ethanol (1.5 mL) (second step), **7b** was isolated (46 mg, 70%) as a slightly yellow solid; R_f 0.66 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.72 (s, 1H, OH), 11.22 (s, 1H, OH), 8.40 (d, ^4J=2.1 Hz, 1H, Ar), 7.84–7.75 (m, 2H, Ar), 7.64 (d, ^3J=8.2 Hz, 1H, Ar), 7.57–7.49 (m, 3H, Ar), 7.17 (d, ^3J=8.2 Hz, 1H, Ar), 7.09 (d, ^3J=8.2 Hz, 1H, Ar). ^{13}C NMR (DMSO, 63 MHz): δ=193.7 (C=O) 163.6, 161.1, 154.7, 152.9 (C_{Ar}–O), 137.8 (CH_{Ar}), 134.2, 133.9, 133.7 (C_{Ar}), 132.4, 131.8, 129.1 (CH_{Ar}), 126.8 (C_{Ar}), 125.0 (CH_{Ar}), 122.8 (C_{Ar}), 118.4 (CH_{Ar}), 118.0 (C_{Ar}), 117.6, 116.8, 113.1 (CH_{Ar}). MS (EI, 70 eV): *m*/*z* (%)=368 (M^+, ^{37}Cl, 15), 366 (M^+, ^{35}Cl, 46), 239 (13), 212 (100), 155 (17). HRMS (EI, 70 eV): calcd for $C_{20}H_{11}CO_5$ (M^+): 366.02895; found: 366.02788.

3.4.3. 7-Hydroxy-2-(2-hydroxy-5-methylbenzoyl)benzo-[*c*]chromen-6-one (7c). Starting with **4c** (130 mg, 0.46 mmol), Me_3SiOTf (133 mg, 0.60 mmol), **5b** (156 mg, 0.60 mmol) in CH_2Cl_2 (8 mL) (first step), and triethylamine (218 mg, 2.15 mmol) in ethanol (5 mL) (second step), **7c** was isolated (80 mg, 51%) as a colourless solid, mp 213–214 °C; R_f 0.70 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.67 (s, 1H, OH), 11.25 (s, 1H, OH), 8.39 (d, ^4J=2.1 Hz, 1H, Ar), 7.83–7.79 (m, 1H, Ar), 7.75 (d, ^3J=8.5 Hz, 1H, Ar), 7.63 (d, ^3J=8.9 Hz, 1H, Ar), 7.51 (d, ^3J=8.9 Hz, 1H, Ar), 7.40–7.34 (m, 2H, Ar), 7.15 (dd, ^4J=2.1 Hz, ^3J=8.5 Hz, 1H, Ar), 7.03 (d, ^3J=8.5 Hz, 1H, Ar), 2.27 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 199.6 (C=O), 164.8, 162.6, 161.2, 152.5 (C_{Ar}–O), 137.8, 137.7 (CH_{Ar}), 135.0, 134.3, 133.2 (C_{Ar}), 132.7, 131.3 (CH_{Ar}), 128.2 (C_{Ar}), 124.9, 118.6, 118.5, 117.7 (CH_{Ar}), 117.4 (C_{Ar}), 112.5 (CH_{Ar}), 106.1 (C_{Ar}), 20.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3441 (s, br), 3079 (w), 3058 (w), 2925 (m), 2855 (m), 1691 (s), 1629 (s), 1592 (s). MS (EI, 70 eV): *m*/*z* (%)=346.0 (M^+, 15), 311.0 (10), 265.0 (37), 251.0 (24), 221.0 (27), 178.0 (25), 134.0 (21). HRMS (EI, 70 eV): calcd for $C_{21}H_{14}O_5$ (M^+): 346.0836; found: 346.0842.

3.4.4. 7-Hydroxy-2-(2-hydroxybenzoyl)-8-(methyl)benzo-[*c*]chromen-6-one (7d). Starting with **4a** (360 mg, 1.35 mmol), Me_3SiOTf (391 mg, 1.76 mmol) and **5c** (385 mg, 1.76 mmol) in CH_2Cl_2 (7 mL) (first step), and triethylamine (545 mg, 5.4 mmol) in ethanol (20 mL) (second step), **7d** was isolated (192 mg, 41%) as a slightly yellow solid, mp 190–191 °C; R_f 0.51 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.87 (s, 1H, OH), 11.47 (s, 1H, OH), 8.38 (d, ^4J=2.1 Hz, 1H, Ar), 7.79 (dd, ^3J=8.5 Hz, ^4J=2.1 Hz, 1H, Ar), 7.65–7.46 (m, 5H, Ar), 7.13 (d, ^3J=8.5 Hz, 1H, Ar), 6.93 (t, ^3J=8.5 Hz, 1H, Ar), 2.38 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=199.8 (C=O), 165.2, 163.3, 160.6, 152.4 (C_{Ar}–O), 138.6, 136.7 (CH_{Ar}), 134.7, 134.1 (C_{Ar}), 133.1 (CH_{Ar}), 131.7 (C_{Ar}), 130.7 (CH_{Ar}), 127.2 (C_{Ar}), 124.7 (CH_{Ar}), 118.9 (C_{Ar}), 118.9 (CH_{Ar}), 118.7, 117.7, 111.9 (CH_{Ar}), 105.3 (C_{Ar}), 15.8 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ = 1685 (s), 1623 (s), 1603 (s). MS (EI, 70 eV): *m*/*z* (%)=346 (M^+, 100), 345 (35), 266 (27), 265 (25), 226 (82), 121 (44). HRMS (EI, 70 eV): calcd for $C_{21}H_{14}O_5$ (M^+): 346.08358; found: 346.08421.

3.4.5. 8-Ethyl-7-hydroxy-2-(2-hydroxybenzoyl)benzo[*c*]-chromen-6-one (7e). Starting with **4a** (267 mg, 0.5 mmol), Me_3SiOTf (145 mg, 0.65 mmol) and **5d** (144 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) (first step), and triethylamine (202 mg, 2.0 mmol) and ethanol (5 mL) (second step), **7e** was isolated (40 mg, 23%) as a colourless solid, mp 160–161 °C; R_f 0.28 (*n*-heptane/EtOAc=9:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=11.86 (s, 1H, OH), 11.47 (s, 1H, OH), 8.34 (s, 1H, Ar), 8.36 (d, ^4J=2.1 Hz, 1H, Ar), 7.78 (dd, ^3J=8.5 Hz, ^4J=2.1 Hz, 1H, Ar), 7.65–7.48 (m, 4H, Ar), 7.12 (d, ^3J=8.5 Hz, 1H, Ar), 6.92 (m, 1H, Ar), 2.78 (q, ^3J=7.3 Hz, 2H, CH_2CH_3), 1.28 (t, ^3J=7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=199.8 (C=O), 165.2, 163.3, 160.3, 152.4 (C_{Ar}–O), 137.0, 136.7 (CH_{Ar}), 134.7 (C_{Ar}), 133.1 (CH_{Ar}), 133.0 (C_{Ar}), 131.6 (C_{Ar}), 130.8, 124.7 (CH_{Ar}), 118.9 (C_{Ar}), 118.9, 118.7, 117.7, 112.1 (CH_{Ar}), 105.4 (C_{Ar}), 2.9 (CH_2CH_3), 13.5 (CH_2CH_3). MS (EI, 70 eV): *m*/*z* (%)=360 (M^+, 100), 345 (98), 240 (49), 225 (56), 121 (38). HRMS (EI, 70 eV): calcd for $C_{22}H_{16}O_5$ (M^+): 360.0980; found: 360.0992.

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References and notes

1. (a) Sidwell, W. T. L.; Fritz, H.; Tamm, C. *Helv. Chim. Acta* **1971**, *54*, 207; (b) Tamm, C. *Arzneim.-Forsch.* **1972**, *22*, 1776; (c) Raistrick, H.; Stilkings, C. E.; Thomas, R. *Biochemistry* **1953**, *55*, 421; (d) Pero, R. W.; Harvan, D.; Blois, M. C. *Tetrahedron Lett.* **1973**, *14*, 945.
2. (a) Schmidt, J. M.; Tremblay, G. B.; Page, M.; Mercure, J.; Feher, M.; Dunn-Dufault, R.; Peter, M. G.; Redden, P. R. *J. Med. Chem.* **2003**, *46*, 1289; (b) Pandey, J.; Jha, A. K.; Hajela, K. *Bioorg. Med. Chem.* **2004**, *12*, 2239.
3. (a) McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695; (b) Hart, D. J.; Mannino, A. *Tetrahedron* **1996**, *52*, 3841; (c) Fischer, C.; Lipata, F.; Rohr, J. *J. Am. Chem. Soc.* **2003**, *125*, 7818 and references cited therein.
4. (a) Sayer, J. M.; Haruhiko, Y.; Wood, A. W.; Conney, A. H.; Jerina, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5562; (b) Geevanada, Y. A.; Gunawardana, P.; Kumar, N. S.; Sultanbawa, M. U. S. *Phytochemistry* **1979**, *18*, 1017.

5. For salicylic esters and salicylic glycosides (e.g., salicortin), see for example: *Römpp Lexikon Naturstoffe*; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, 1997.
6. Pettit, G. R.; Toki, B.; Herald, D. L.; Verdier-Pinard, P.; Boyd, M. R.; Hamel, E.; Pettit, R. K. *J. Med. Chem.* **1998**, *41*, 1688.
7. (a) Liou, J.-P.; Chang, J.-Y.; Chang, C.-W.; Chang, C.-Y.; Mahindroo, N.; Kuo, F.-M.; Hsieh, H.-P. *J. Med. Chem.* **2004**, *47*, 2897; (b) Liou, J.-P.; Chang, C.-W.; Song, J. S.; Yang, Y. S.; Yeh, C. F.; Tseng, H. Y.; Lo, Y. K.; Chang, C.-L.; Chang, C.-M.; Hsieh, H.-P. *J. Med. Chem.* **2002**, *45*, 2556.
8. For a review of 1,3-bis(silyl enol ethers), see: Langer, P. *Synthesis* **2002**, 441.
9. (a) Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, *44*, 7921; (b) Nguyen, V. T. H.; Appel, B.; Langer, P. *Tetrahedron* **2006**, *62*, 7674; (c) Appel, B.; Rotzoll, S.; Kranich, R.; Reinke, H.; Langer, P. *Eur. J. Org. Chem.* **2006**, 3638.
10. (a) Langer, P.; Saleh, N. N. R.; Freifeld, I. *Chem. Commun.* **2002**, 168; (b) Appel, B.; Saleh, N. N. R.; Langer, P. *Chem.—Eur. J.* **2006**, *12*, 1221; (c) Ullah, E.; Appel, B.; Fischer, C.; Langer, P. *Tetrahedron* **2006**, *62*, 9694.
11. Banyopadhyay, C.; Sur, K. R.; Patra, R. *J. Chem. Res., Synop.* **1998**, *12*, 802.
12. Jean, J. C.; Wise, L. D.; Heffner, T. G.; Pugsley, T. A.; Meltzer, L. T. *J. Med. Chem.* **1991**, *34*, 248.

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Transition metal-catalyzed formation of CF_3-substituted α,β-unsaturated alkene and the synthesis of α-trifluoromethyl substituted β-amino ester

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Abstract—A new transition metal-catalyzed formation of CF_3-substituted α,β-unsaturated alkenes through the ylide intermediate from the reaction between methyl 3,3,3-trifluoro-2-diazopropionate **1** and aryl aldehydes has been developed. Further transformation of the alkene affords the α-trifluoromethyl substituted β-amino ester, a valuable intermediate in the synthesis of fluorine-containing amino acids with potential biological application.

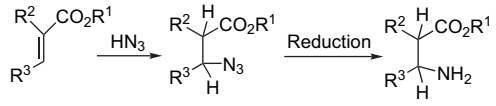
1. Introduction

It is well documented that the replacement of hydrogen with fluorine in organic molecules can make a profound and unexpected influence on the physical and biological properties of organic compounds.[1] Much attention has been directed toward the fluoro substitution during the last decade.[2] What is more, due to the unique physical and biological properties impacted by the CF_3 group, trifluoromethylation is an ongoing area of research. Thus, the preparation of trifluoromethyl containing molecules has been of great interest not only to biochemists and medicinal chemists, but also to the synthetic organic fluorine chemists.[3]

Amino acids are the basic units of proteins. More than 200 different amino acids are found in living organisms.[4] Hence, synthesis of novel amino acids has always been one of the research focuses of organic chemists. Among them, fluorine-containing amino acids have attracted considerable attention and enjoyed widespread bioorganic applications.[5] The strong carbon–fluorine bond is particularly resistant to metabolic transformations, and the electronegativity of fluorine can have a significant effect on the basicity or acidity of neighboring groups and on the electron distribution, and can change the overall reactivity and stability of the molecules.[6]

Fluorinated amino acids also play an important role in the field of biological tracers, mechanistic probes, enzyme inhibitors, and medical applications including control of blood pressure, treatment of allergies, and inhibition of tumor growth.[7] Additionally, fluorinated β-amino acids are now recognized as potentially exciting building blocks for the synthesis of β-peptides, antibiotics, and enzyme inhibitors.[8]

Usually, β-amino acid can be synthesized from the α,β-unsaturated carboxylic ester. Michael addition of hydrazoic acid (HN_3) produces the azide compound, which can be easily converted to the corresponding β-amino ester using well established chemistry (Scheme 1).[9] In this paper, in order to avoid the explosive hydrazoic acid, we chose the readily available and relatively stable sodium azide as the direct azide source. Advantages of the protocol include high-yielding reaction and mild reaction condition.



Scheme 1.

In our previous work, we have developed several methods to synthesize fluorinated alkene from fluorinated diazo compounds and aldehydes through the ylide intermediate.[10a] Therefore, we wondered whether methyl 3,3,3-trifluoro-2-diazopropionate **1** could react with aldehydes to give the

Keywords: Catalysis; CF_3-substituted; Ylide; α,β-Unsaturated alkenes; β-Amino ester.
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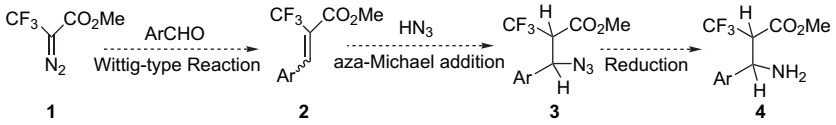


Scheme 2.

corresponding CF_3-containing α,β-unsaturated alkenes **2** through the ylide intermediate, which could be easily transformed into the corresponding trifluoromethyl containing β-amino esters (Scheme 2).

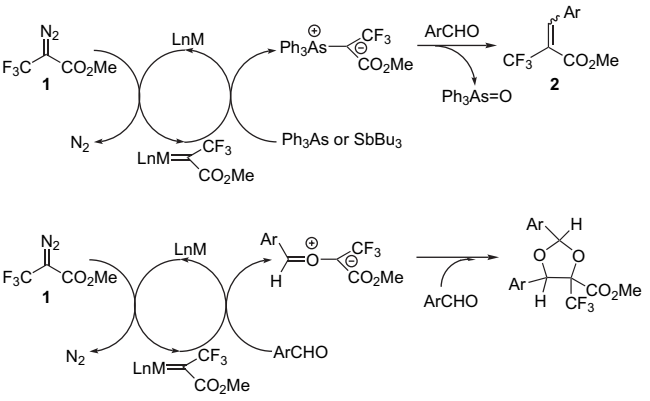
Herein, we wish to report a successful synthesis of trifluoromethylated β-amino esters from diazo compound **1**.

2. Results and discussion

Initially, arsonium ylide intermediate was used to prepare alkene **2**. 4-Nitrobenzaldehyde was used as the substrate, 1 mol % $Rh_2(OAc)_4$ was used as the catalyst, and refluxing THF as the solvent. The expected alkene **2b** was isolated in only 9% yield. In the meantime, trace amount of 1,3-dioxolane **5** (3%) was isolated (Table 1, entry1). It should come from the 1,3-dipolar addition of the carbonyl ylide intermediate and the aldehyde (Scheme 3).[3a]

The proposed reaction mechanism is depicted in Scheme 4. Due to the electron-withdrawing properties of the flanking trifluoromethyl and methoxyl carbonyl groups, the ylide intermediate could be too stable to react with the aldehyde to give alkene **2**. To improve the yield, more severe reaction conditions were employed. Increasing the reaction temperature to 80 °C (refluxing in benzene), improved the yields of alkene **2b** and 1,3-dioxolane **5** to 19 and 14%, respectively (Table 1, entry 2). Further increasing the reaction temperature to 110 °C (refluxing in toluene), improved the yield of **2b** to 36%. But the yield of **5** fell to 7% (Table 1, entry 3).

As indicated in Table 1, the reaction yields, through arsonium ylide intermediate, are unsatisfied even using refluxing toluene. It is known that antimony ylide is more reactive than the arsonium ylide. We envisioned that antimony ylide could give better reaction results. When $SbBu_3$ was used instead of Ph_3As, under the same reaction conditions, however, no alkene product was detected (Table 1, entries 4 and 5). It may be explained that the rhodium catalyst was poisoned by the strong reductive $SbBu_3$. When cuprous bromide (CuBr) was used as the catalyst, alkene **2c** was isolated in moderate yield in refluxing benzene (Table 1, entry 6). The yield of product **2c** was not improved at higher temperature (refluxing in toluene) (Table 1, entry 7). Inorganic or organic copper catalyst such as CuBr, $Cu(acac)_2$, and $Cu(hfacac)_2$

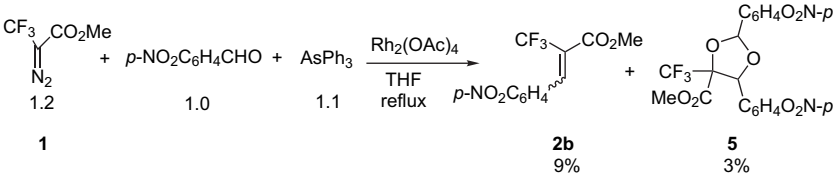


Scheme 4.

Table 1. The optimization of reaction condition

Entry	ArCHO (Ar=)	Lewis base	Catalyst	Solvent	Product yield (%)[a]	
					2	**5**
1	*p*-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	THF	9 (**2b**)	3
2	*p*-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	Benzene	19 (**2b**)	14
3	*p*-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	Toluene	36 (**2b**)	7
4	*p*-BrC_6H_4-	$SbBu_3$	$Rh_2(OAc)_4$	Benzene	—	—
5	*p*-BrC_6H_4-	$SbBu_3$	$Rh_2(OAc)_4$	Toluene	—	—
6	*p*-BrC_6H_4-	$SbBu_3$	CuBr	Benzene	55 (**2c**)	—
7	*p*-BrC_6H_4-	$SbBu_3$	CuBr	Toluene	59 (**2c**)	—
8	*p*-BrC_6H_4-	$SbBu_3$	$Cu(acac)_2$	Benzene	57 (**2c**)	—
9	*p*-BrC_6H_4-	$SbBu_3$	$Cu(hfacac)_2$	Toluene	54 (**2c**)	—

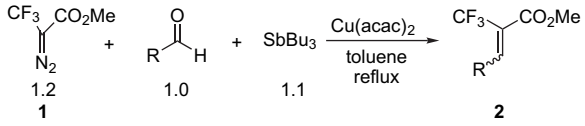
[a] Isolated yields based on aldehyde.



Scheme 3.

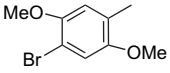
gave the corresponding alkenes in similar yields (Table 1, entries 6–9).

Then under the optimized reaction conditions (Table 1, entry 8), (Scheme 5), a series of aromatic aldehydes were used to prepare various alkene **2**. The results are summarized in Table 2.



Scheme 5.

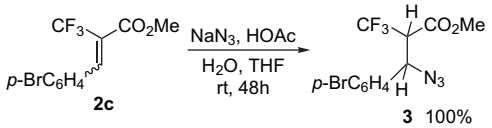
Table 2. Reaction results of **1** with aryl aldehydes and $SbBu_3$[a]

Entry	ArCHO (Ar=)	Product	Yield (%)[b]
1	Ph-	**2a**	46
2	*p*-$NO_2C_6H_4$-	**2b**[c]	36
3	*p*-BrC_6H_4-	**2c**	57
4	*o*-ClC_6H_4-	**2d**	69
5	*p*-$CH_3OC_6H_4$-	**2e**	62
6		**2f**	62
7	*trans*-PhCH=CH-	**2g**	85
8		**2h**	77

[a] $Cu(acac)_2$ (10 mol %), diazo compound:aldehyde:$SbBu_3$=1.2:1.0:1.1 are used for all reactions.
[b] Isolated yields based on aldehyde.
[c] $Rh_2(OAc)_4$ and Ph_3As system was used.

It shows that all of the aromatic aldehydes employed afford the corresponding alkene **2** in satisfying yields.

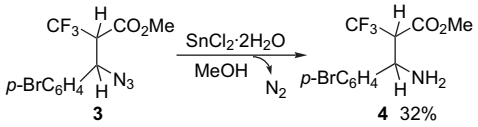
With the α,β-unsaturated alkenes in hand, we then explored its reaction with the hydrazoic acid (HN_3) to produce the azide compound. It is necessary to generate the HN_3 in situ, because it is explosive and poisonous. Based on the literature,[12] methyl 3-(4-bromophenyl)-2-(trifluoromethyl)-acrylate **2c** was chosen as the substrate. In aqueous THF, **2c** reacted with the hydrazoic acid, which was generated in situ from NaN_3 and HOAc, for 48 h at room temperature to give the corresponding azide **3** in quantitative yield. The product was essentially pure after general work-up and could be used directly in the next step (Scheme 6).



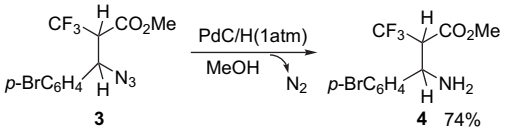
Scheme 6.

It is well known that azide can be easily reduced to give the corresponding amine product.[11] Initially, $SnCl_2 \cdot 2H_2O$ was used to reduce the azide **3** to give only 32% of the desired α-trifluoromethyl substituted β-amino ester **4** (Scheme 7).

Pd–C/H_2 is the most popular catalytic system for the reduction of the azide. Furthermore, it is an atom economical and environmental benign reaction. The reaction results showed that the azide can be easily transformed into the desired amino ester **4** in 74% yield using Pd–C/H_2 (1 atm) (Scheme 8).



Scheme 7.



Scheme 8.

The structure of **4** was further confirmed by the X-ray crystal diffraction (Fig. 1).

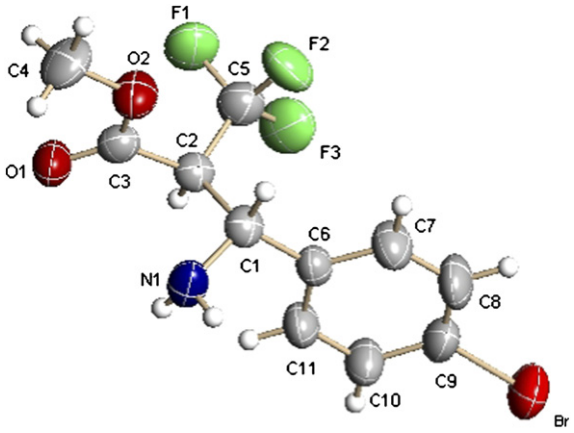


Figure 1. Crystal structure of **4**.

3. Conclusion

In summary, we successfully synthesize a series of CF_3-substituted α,β-unsaturated alkenes from the transition metal-catalyzed reaction between methyl 3,3,3-trifluoro-2-diazopropionate **1** and aryl aldehydes. CF_3-Substituted α,β-unsaturated alkenes can be further transferred into β-amino ester through a two-step procedure. This paper provides a good choice for the synthesis of CF_3-substituted β-amino acid.

4. Experimental

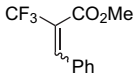
4.1. General

Melting points were measured in a SGW® X-4 micro-melting point apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded on a Bruker AM-300 spectrometer with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low-resolution mass spectra or high-resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAR-8430 instrument using the electron impact ionization technique (70 eV), respectively. The X-ray structural analysis was performed with a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by this institute.

4.2. General method for the reaction of methyl 3,3,3-trifluoro-2-diazopropionate 1 with aldehydes

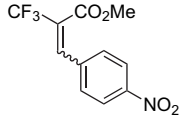
A mixture of **2** (1 mmol), $AsPh_3$ or $SbBu_3$ (1.5 mmol), and $Rh_2(OAc)_4$ (5 mg, 1 mol %) or $Cu(acac)_2$ (78.6 mg, 20 mmol %) in anhydrous toluene (1.5 ml) in a schrock tube was heated to reflux and a solution of **1a** (252 mg, 1.5 mmol) in toluene (2 ml) was added dropwise. The resulting mixture was stirred for 15 h under N_2 atmosphere. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the crude product was filtered. The residue was purified by column chromatography on silica gel using ethyl ester–hexane as eluent to give **3a** (106 mg, 46%).

4.2.1. Methyl 3-phenyl-2-(trifluoromethyl)acrylate (3a).



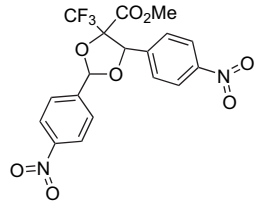
Colorless liquid, *Z*/*E*=1:3.6. IR (KBr), cm^{-1}: 2956, 2929, 1958, 1736, 1638, 1578, 1496, 1450, 1438, 1391, 1280, 1167, 1136, 1043. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.10 (1H, s), 7.42–7.37 (5H, m, Ar), 3.90 (3H, s, *Z*), 3.78 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.0 (CF_3, s, *Z*), −63.8 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.8, 140.4 (t, J_{CF}=5.8 Hz), 132.2, 130.4, 130.2, 129.3, 128.8, 128.3, 52.3 ppm. MS (70 eV, EI): 230 (M^+, 54), 229 (M^+−1, 52), 211 (M^+−F, 1.6), 199 (57), 151 (40), 109 (100), 77 (25), 69 (8.0). HRMS for $C_{11}H_9O_2F_3$ calcd: 230.0555. Found: 230.0556.

4.2.2. Methyl 3-(4-nitrophenyl)-2-(trifluoromethyl)acrylate (3b).



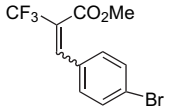
Colorless solid with mp: 54–56 °C. IR (KBr), cm^{-1}: 2998, 2964, 1941, 1733, 1655, 1602, 1523, 1443, 1384, 1354, 1312, 1237, 1217, 1164, 1143, 1019. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, 2H, *J*=9.0 Hz), 7.54 (d, 2H, *J*=9.0 Hz), 3.79 (s, 3H) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.7 (s, *E*) ppm. MS (70 eV, EI): 275 (M^+, 90), 274 (70), 258 (58), 244 (100), 243 (52), 228 (27), 206 (M^+−F, 13), 198 (67), 169 (55). Anal. Calcd for $C_{11}H_8F_3O_4N$: C, 48.01; H, 2.93; N, 5.09%. Found: C, 48.26; H, 3.06; N, 5.00%.

4.2.3. Methyl 2,5-bis(4-nitrophenyl)-4-(trifluoromethyl)-1,3-dioxolane-4-carboxylate (5).



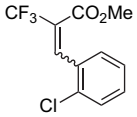
Colorless solid with mp: 171–173 °C. IR (KBr), cm^{-1}: 3089, 2958, 1752, 1608, 1521, 1351, 1302, 1200, 1117. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.33 (2H, d, *J*=9.0 Hz), 8.28 (2H, d, *J*=9.0 Hz), 7.78 (2H, d, *J*=9.0 Hz), 7.60 (2H, d, *J*=9.0 Hz), 6.87 (1H, s), 5.65 (1H, s), 3.43 (3H, s) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.8 (CF_3, s) ppm. MS (70 eV, EI): 443 ($[M+1]^+$, 1), 291 (13), 275 (42), 258 (16), 166 (100), 150 (19), 89 (30), 59 (30). Anal. Calcd for $C_{18}H_{13}F_3O_8N_2$: C, 48.88; H, 2.96; N, 6.33%. Found: C, 49.01; H, 3.01; N, 6.23%.

4.2.4. Methyl 3-(4-bromophenyl)-2-(trifluoromethyl)-acrylate (3c).



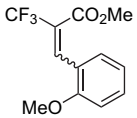
Colorless solid with mp: 43–45 °C, *Z*/*E*=1:3.3. IR (KBr), cm^{-1}: 2996, 2959, 1917, 1724, 1649, 1490, 1440, 1384, 1312, 1278, 1133, 1021. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.51 (2H, m), 7.27–7.24 (2H, m), 379 (3H, s) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.5 (CF_3, s, Z), −64.4 (CF_3, s, E) ppm. MS (70 eV, EI): 310 (M^+, 100), 308 (95), 291 (M^+−F, 2.7), 279 (63), 277 (67), 250 (40), 248 (40), 198 (48), 189 (25), 187 (23), 170 (50), 169 (49), 151 (37), 101 (29), 75 (47), 69 (39). Anal. Calcd for $C_{11}H_8BrF_3O_2$: C, 42.75; H, 2.61%. Found: C, 42.86; H, 2.65%.

4.2.5. Methyl 3-(2-chlorophenyl)-2-(trifluoromethyl)-acrylate (3d).



Colorless liquid, *Z*/*E*=1:5.3. IR (KBr), cm^{-1}: 2957, 1739, 1647, 1471, 1439, 1387, 1290, 1269, 1171, 1141, 1045. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (1H, s), 7.44–7.25 (4H, m, Ar), 3.91 (3H, s, *Z*), 3.70 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.5 (CF_3, s, *Z*), −64.1 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.0, 145.5 (t, J_{CF}=3.0 Hz), 133.3, 131.8, 131.0, 130.9, 129.3, 129.2, 126.5, 126.4, 53.0 ppm. MS (70 eV, EI): 264 (M^+, 1.4), 245 (M^+−F, 1.0), 233 (12), 230 (13), 229 (100), 195 (14), 161 (17), 101 (12), 75 (20), 69 (6.6). HRMS for $C_{11}H_8O_2F_2Cl$ calcd: 245.0181. Found 245.0182 (M^+−F).

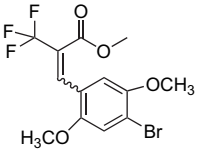
4.2.6. Methyl 3-(2-methyloxyphenyl)-2-(trifluoromethyl)-acrylate (3e).



Colorless liquid, *Z*/*E*=1:1.4. IR (KBr), cm^{-1}: 2957, 2843, 1732, 1634, 1514, 1463, 1439, 1393, 1264, 1175, 1129, 1032. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.00 (1H, s, *Z*), 7.40 (2H, m, Ar), 6.93–6.88 (2H, m, Ar), 3.87 (3H, s, *Z*), 3.84 (3H, s) 3.82 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.0 (CF_3, s, *Z*), −63.3 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 164.2, 148.3 (t, J_{CF}=2.8 Hz, *Z*),

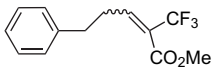
140.1 (t, J_{CF}=5.6 Hz, *E*), 132.3, 131.6, 124.6, 124.5, 114.1, 113.9, 55.3, 52.3 ppm. MS (70 eV, EI): 260 (M^+, 100), 241 (M^+−F, 3.9), 229 (55), 200 (52), 139 (83), 75 (8.5), 69 (7.9). HRMS for $C_{12}H_{11}O_3F_3$ calcd: 260.0660. Found: 260.0660.

4.2.7. Methyl 3-(2,5-dimethyloxy-4-bromophenyl)-2-(trifluoromethyl)acrylate (3f).



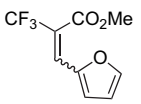
Colorless solid with mp: 127–129 °C, *Z*/*E*=3.2:1. IR (KBr), cm^{-1}: 2969, 2857, 1732, 1632, 1603, 1488, 1465, 1441, 1432, 1394, 1296, 1258, 1214, 1179, 1127, 1054, 1040, 1025. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (1H, s), 7.12 (1H, s, Ar), 6086 (1H, s, Ar), 3.90 (3H, s, *Z*), 3.85 (3H, s), 3.83 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.6 (CF_3, s, *Z*), −63.7 (CF_3, s, *E*) ppm. MS (70 eV, EI): 370 (M^++1, 56), 369 (M^+, 9.3), 368 (55), 339 (54), 337 (61), 246 (23), 231 (44), 69 (14), 59 (100). Anal. Calcd for $C_{13}H_{12}BrF_3O_4$: C, 42.30; H, 3.28%. Found: C, 42.41; H, 3.36%.

4.2.8. Methyl 3-phenylvinyl-2-(trifluoromethyl)acrylate (3g).



Colorless liquid, *Z*/*E*=1:1.8. IR (KBr), cm^{-1}: 3027, 2956, 1724, 1624, 1595, 1438, 1384, 1293, 1245, 1129. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.96 (1H, dd, *J*=15, 11 Hz), 7.57–7.54 (2H, m, Ar), 7.40–7.37 (3H, m, Ar), 7.31 (1H, d, *J*=11 Hz), 7.08 (1H, d, *J*=15 Hz), 3.86 (3H, s, *Z*), 3.89 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −57.9 (CF_3, s, *Z*), −63.0 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.1, 146.0 (t, J_{CF}=5.3 Hz), 147.2, 135.5, 130.4, 129.0, 128.1, 124.6, 123.0, 121.0, 52.1 ppm. MS (70 eV, EI): 256 (M^+, 38), 237 (M^+−F, 2.9), 177 (100), 128 (52), 102 (32), 77 (47), 69 (23), 51 (49). HRMS for $C_{13}H_{11}O_2F_3$ calcd: 256.0711. Found: 256.0711.

4.2.9. Methyl 3-furan-2-(trifluoromethyl)acrylate (3h).

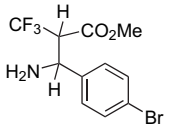


Colorless liquid, *Z*/*E*=1:4.5. IR (KBr), cm^{-1}: 2959, 2928, 2856, 1731, 1633, 1468, 1438, 1377, 1285, 1224, 1134, 1044, 1025. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (1H, s, *Z*), 7.58 (1H, s, *E*), 7.67 (1H, d, *J*=1 Hz, *Z*), 7.30 (1H, d, *J*=3 Hz, *E*), 7.08 (1H, d, *J*=3 Hz, *Z*), 7.24 (1H, d, *J*=1 Hz, *E*), 6.59 (1H, dd, *J*=1, 3 Hz, *Z*), 6.56 (1H, dd, *J*=1, 3 Hz, *E*), 3.92 (3H, s, *Z*), 3.88 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −59.5 (CF_3, s, *Z*), −63.0 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.3, 152.2, 146.3, 128.0 (t, J_{CF}=3.0 Hz), 119.6, 119.5, 113.0, 112.9, 52.4 ppm. MS (70 eV, EI): 220 (M^+, 34), 201 (M^+−F, 3.9), 189 (48), 160 (18), 113 (32), 99 (100), 83 (23), 69 (9.1), 68 (2.9), 63 (52), 59 (43). HRMS for $C_9H_7O_3F_3$ calcd: 220.0347. Found: 220.0351.

4.3. General method for the synthesis of α-trifluoromethyl substituted β-amino ester (4)

In a 25 ml flask containing alkene **2c** (352 mg, 1 mmol) was added 5 ml of THF and cooled in an ice-water bath, then a solution of NaN_3 (260 mg, 4 mmol) in H_2O (1 ml) was added. The temperature of the mixture is adjusted to 0 °C, and a solution of HOAc (240 mg, 4 mmol) was added dropwise with vigorous stirring over 20–30 min. The yellow reaction mixture was allowed to stir for 48 h at room temperature. After the reaction was completed (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2, which was washed with saturated $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. The yield was almost quantitative. The product was essentially pure after general work-up and could be used directly in the next step. A mixture of the crude azide and 10% palladium-on-carbon (20 mg) in absolute ethanol (6 ml) was stirred at 25 °C under 1 atm of hydrogen for 24 h. The catalyst was filtered and washed with CH_2Cl_2. The filtrates were concentrated under reduced pressure using a rotary evaporator, and the crude reaction product was purified by column chromatography on silica gel using ethyl acetate–hexane as eluent to give **4** (243 mg, 74%).

4.3.1. Methyl 2-(amino(4-bromophenyl)methyl)-3,3,3-trifluoropropanoate (4).



Colorless solid with mp: 72–74 °C. IR (KBr), cm^{-1}: 2957, 2930, 1908, 1751, 1641, 1489, 1438, 1409, 1354, 1163, 1119, 1074, 1012. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.43 (2H, m), 7.23–7.19 (2H, m), 4.51–4.47 (1H, m), 3.76 (3H, s), 3.44 (1H, s), 1.73 (2H, s) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (d, *J*=7.9 Hz), −64.32 (d, *J*=8.4 Hz) ppm. EIMS (*m*/*z*, %): 327/325 (M+2/M^+, 3/3), 186 (98), 184 (100), 159 (9), 157 (9), 77 (27), 59 (16). Anal. Calcd for $C_{11}H_{11}F_3BrO_2N$: C, 40.51; H, 3.40; N, 4.30%. Found: C, 40.69; H, 3.52; N, 4.19%.

4.3.1.1. X-ray data of 4. $C_{11}H_{11}BrF_3NO_2$: MW=326.12, CCDC no. 614315, monoclinic, space group: *C*2/*c*, *a*=21.606(3) Å, *b*=5.4235(7) Å, *c*=24.378(3) Å; α=90.00°, β=2599.4(6)°, γ=90.00°; *V*=2599.4(6) $Å^3$, *Z*=8, Dc=1.667 g/cm^3, *F*(000)=1296. Radiation, Mo Kα (λ=0.71073 Å). Crystal dimension, 0.467×0.89×0.329 mm.

Intensity data were collected at 293(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). A total of 2815 independent reflection was measured in the range $1.84<\theta<27.00°$.

The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically; hydrogen atoms were included but not refined. The final cycle of full matrix least-square refinement was based on F^2. The final R and wR value were 0.0457 and 0.0889, respectively. All calculations were performed using the SHELX-97 program.

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References and notes

1. (a) Goldman, P. *Science* **1969**, *164*, 1123–1130; (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197.
2. (a) *Asymmetric Fluoroorganic Chemistry*; Ramachandran, P. V., Ed.; ACS symposium Series 746; American Chemical Society: Washington, DC, 1999; (b) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Gordon and Breach Science: Amsterdam, 1998; (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996; (d) *Synthesis and Chemistry of Agrochemical III*; Baker, D. R., Fenyes, J. G., Steffens, J. J., Eds.; ACS Symposium Series 504; American Chemical Society: Washington, DC, 1992; (e) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symposium Series; American Chemical Society: Washington, DC, 1991.
3. (a) Jiang, B.; Zhang, X. B.; Luo, Z. H. *Org. Lett.* **2002**, *4*, 2453–2455; (b) Shi, G. Q.; Xu, Y. Y. *J. Chem. Soc., Chem. Commun.* **1987**, 607–608; (c) Shi, G. Q.; Xu, Y. Y. *Tetrahedron* **1991**, *47*, 1629–1648; (d) Shi, G. Q.; Xu, Y. Y.; Xu, M. *J. Fluorine Chem.* **1991**, *52*, 149–157; (e) Shi, G. Q.; Xu, Y. Y. *J. Org. Chem.* **1990**, *55*, 3383–3386; (f) Shi, G. Q.; Cao, Z. Y.; Cai, W. L. *Tetrahedron* **1995**, *51*, 5011–5018; (g) Mloston, G. *Helv. Chim. Acta* **1996**, *79*, 1537–1545; (h) Hoffmann, M. G.; Wenkert, E. *Tetrahedron* **1993**, *49*, 1057–1067; (i) Guillaume, M.; Janousek, Z.; Viehe, H. G.; Wynants, C.; Declercq, J.-P.; Tinant, B. *J. Fluorine Chem.* **1994**, *69*, 253–256; (j) Guillaume, M.; Janousek, Z.; Viehe, H. G. *Synthesis* **1995**, 921–923.
4. Horton, H. R.; Moran, L. A.; Ochs, R. S.; Rawn, J. D.; Scrimgeous, K. G. *Principle of Biochemistry*, 3rd ed.; 2003; p 59.
5. (a) Osipov, S. N.; Sewald, N.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *Tetrahedron Lett.* **1996**, *37*, 615–618; (b) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914; (c) Yoder, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335–341; (d) Katagiri, T.; Uneyama, K. *Chirality* **2003**, *15*, 4–9; (e) Dave, R.; Badet, B.; Meffre, P. *Amino Acids* **2003**, *24*, 245–261.
6. Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621–631.
7. (a) Qiu, X. L.; Meng, W. D.; Qing, F. L. *Tetrahedron* **2004**, *60*, 6711–6745; (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035; (c) Schirlin, D.; Baltzer, S.; Altenburger, J. M.; Tarnus, C.; Remy, J. M. *Tetrahedron* **1996**, *52*, 305–318; (d) Nakayama, K.; Kawato, H. C.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 977–980.
8. (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447–1465; (b) van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503–7524; (c) Soloshonok, V. A.; Soloshonok, I. V.; Kukhar, V. P.; Svedas, V. D. *J. Org. Chem.* **1998**, *63*, 1878–1884; (d) Uneyama, K.; Hao, J.; Amii, H. *Tetrahedron Lett.* **1998**, *39*, 4079–4082; (e) Abouabdellah, A.; Bégué, J.-P.; Binnet-Delpon, D.; Thanh Nga, T. T. *J. Org. Chem.* **1997**, *62*, 8826–8833.
9. (a) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319–1322; (b) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141–2144; (c) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891–3894; (d) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114; (e) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406–3418; (f) Lakshmipathi, P.; Rao, A. V. R. *Tetrahedron Lett.* **1997**, *38*, 2551–2552; (g) Cuerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107–1109; (h) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960; (i) Horstmann, T. E.; Cuerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635–3638.
10. (a) Zhu, S. F.; Liao, Y. X.; Zhu, S. Z. *Org. Lett.* **2004**, *6*, 377–380; (b) Zhu, S. F.; Liao, Y. X.; Zhu, S. Z. *Synlett* **2005**, 1429–1432; (c) Zhu, S. F.; Xing, C. H.; Zhu, S. Z. *Tetrahedron* **2006**, *62*, 829–832; (d) Zhu, S. Z.; Zhu, S. F.; Liao, Y. X. *J. Fluorine Chem.* **2004**, *125*, 1071–1076; (e) Zhu, S. F.; Xing, C. H.; Pang, W.; Zhu, S. Z. *Tetrahedron Lett.* **2006**, *47*, 5897–5900.
11. (a) Xu, L. W.; Xia, C. G.; Li, J. W.; Zhou, S. L. *Synlett* **2003**, 2246–2248; (b) Xu, L. W.; Xia, C. G.; Zhou, S. L.; Li, J. W. *Tetrahedron Lett.* **2004**, *45*, 1219–1221.
12. (a) Zou, Y.; Fahmi, N. E.; Vialas, C.; Miller, G. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 9476–9488; (b) Belleau, B.; Cooper, P. *J. Med. Chem.* **1963**, *6*, 579–583; (c) Walborsky, H. M.; Baum, M. E. *J. Org. Chem.* **1956**, *21*, 538–539.

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1-Aryltetralin privileged structure-based libraries: parallel synthesis of *N*-aryl and *N*-biaryl γ-lactam lignans

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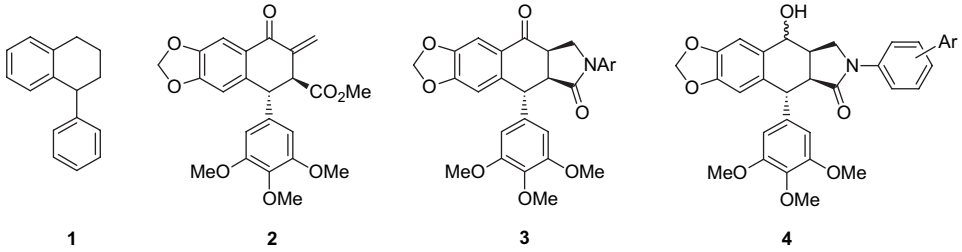
Abstract—The parallel solution-phase synthesis of two libraries of product-like compounds derived from a 1-aryltetralin privileged structure is described. The *N*-aryl picropodophyllone γ-lactams were synthesized from methyl ester thuriferic acid via $InCl_3$-tandem aza-Michael addition–cyclization reaction of anilines. Bromo-aryl compounds from this library were subjected to a ligandless palladium Suzuki cross-coupling to give the expected *N*-biaryl picropodophyllin γ-lactams.

1. Introduction

There is growing current interest in using specific structures, generally found within a class of natural products, as starting points for library design.[1] The core scaffold of a natural product can provide a biologically validated framework with diverse functional groups. The resulting libraries can then be used to address a variety of biological targets.[2] Within this context, we initiated the synthesis of γ-lactam lignans based on the 1-aryltetralin skeleton **1** as a privileged structure[3–9] (Fig. 1). Lignans of 1-aryltetralin type possess a diverse range of biological activities[10–13] including inhibition of the tubulin polymerization, inhibition of DNA topoisomerase II, and immunosuppressive, anti-HIV, and antidepressant activities. Recently, cyclolignans as inhibitors of the phosphorylation of the insuline-like growth factor receptor (IGF-1R) have been reported.[14–20] γ-Lactam motif as well as the biaryl subunit[21] are also valuable pharmacophoric groups found in a variety of molecules presenting biological properties. The combination of such fragments may qualitatively enrich the compounds collection. In the field of podophyllotoxin chemistry, it is worth noting that only two syntheses exemplifying the combination of **1** with γ-lactam rings have been reported so far, i.e., the semi-synthesis of etoposide-lactam derivatives[22] and the total synthesis of (±)-demethoxy epiisopicropodophyllin *N*-benzyl lactam.[23]

Our first approach involved a synthesis of *N*-aryl picropodophyllone γ-lactams[24] via aza-Michael addition from thuriferic acid methyl ester **2** under basic conditions. In this paper, we describe the extension of our work with the parallel solution-phase synthesis of *N*-aryl γ-lactam lignans **3** via a tandem aza-Michael addition–cyclization from **2**[25–31] using a catalytic amount of $InCl_3$, and then the parallel



1 2 3 4

Figure 1.

Keywords: Biaryls; Lactam lignans; Privileged structure; Tandem reaction; $InCl_3$; Ligandless Suzuki reaction; Parallel solution-phase synthesis.
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solution-phase synthesis of *N*-biaryl γ-lactam lignans **4** from the corresponding bromo adducts via a ligandless palladium Suzuki cross-coupling (Fig. 1).

2. Results and discussion

2.1. Parallel solution-phase synthesis of *N*-aryl γ-lactam lignans

Michael addition of amines to α,β-unsaturated ketones usually require basic conditions or acid catalysis. In the past few years, a number of alternative procedures have been developed and in particular, various Lewis acid-induced and transition metal salts catalyzed reactions have been reported.[32–42] Recently, indium salts have emerged as powerful catalysts in many chemical processes both in aqueous and organic media.[43–50] Loh and co-workers have reported indium trichloride as an excellent catalyst in the Mukaiyama aldol reactions,[51–53] Diels–Alder reactions,[54] aldol-type Mannich reactions,[55] and Michael reaction[56,57] under mild conditions. As indium trichloride has these unique properties compared to other Lewis acids—which include stability and recoverability from water[56]—and since indium salts allowed tandem reactions[49,50] and one-pot multistep transformation,[47] we decided to exploit this catalyst to construct our small γ-lactam lignans libraries from methyl ester thuriferic acid **2** with the aim to develop a one-pot protocol, which would be an improvement over our previous synthesis.[24]

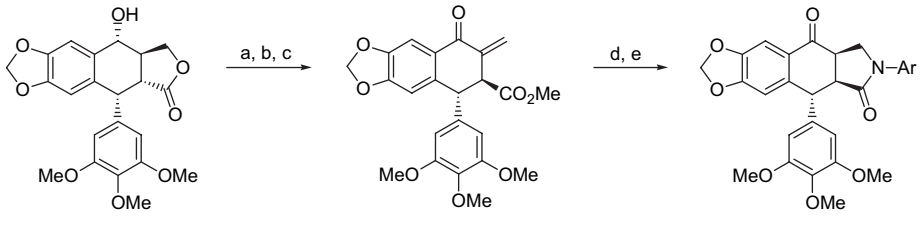
Methyl ester thuriferic acid **2** was obtained in a three-step sequence[24] from podophyllotoxin **5**, as outlined in Scheme 1. To our delight, the *N*-aryl picropodophyllone γ-lactams **3** were synthesized from **2** via $InCl_3$-catalyzed tandem aza-Michael addition–cyclization reaction of substituted anilines. γ-Lactams **3** were obtained as a single isomer and their stereochemistry were determined to be cis by NOESY experiment.[24] The parallel solution-phase synthesis of *N*-aryl picropodophyllone lactams was conducted on the Quest 210® (Argonaut Technologies) using 10 mL Teflon reaction vessels (Table 1). We used sulfonyl chloride resin as a polymer-supported scavenger[58] for anilines in order to facilitate the purification of products.

For monohalogenated anilines (Table 1, entries 1–6) and activated anilines (Table 1, entries 7–13), the tandem reaction with **2** catalyzed by $InCl_3$ (0.5 equiv) afforded exclusively *cis*-γ-lactams **3a–f** and **3g–m** after 48 h at 80 °C in DCE in 61–94% yields. Surprisingly, one activated aniline (entry 14) required addition of a base for the synthesis of **3n** under these catalytic conditions. Indeed, for 2-aminofluorene, a mixture of the *cis*-γ-lactam **3n** as a major product together with the *cis*- and *trans*-β-amino ketones **6n** was obtained under $InCl_3$ catalysis[59] (^{1}H NMR analysis). Addition of DBU to the reaction mixture favored the cyclization step providing the *cis*-γ-lactam **3n** in 66% yield. The scope of this tandem reaction found to be limited. Deactivated anilines 4-nitroaniline and 4-trifluoroaniline behave differently during the necessary one-pot process since no cyclization products were obtained by using only $InCl_3$: following addition of DBU, while the formation of the desired *cis*-γ-lactam **3o** was observed (50%), demonstrating the reactivity of the aza-Michael adduct **6o** obtained from 4-nitro-aniline (Fig. 2), no cyclization occurred from the *cis*- and *trans*-β-amino ketones **6p**.[59] Furthermore, reaction of deactivated 5-aminoanthraquinone resulted only in recovered starting material **2**. Reaction of *ortho*-substituted anilines such as 2-bromoaniline, 2,4-dibromoaniline, 5-chloro-2-methylaniline, 1-amino-5,6,7,8-tetrahydronaphthalene, and 2,3-dimethylaniline furnished the corresponding aza-Michael adduct **6** in the presence of the starting material **2** (^{1}H NMR analysis of the crude product). For example, for 1-amino-5,6,7,8-tetrahydronaphthalene and 2,3-dimethylaniline we obtained a mixture of starting material **2** and aza-Michael adduct **6** in 33 and 66% yields, respectively. Finally, in the case of 4-iodoaniline, the expected products (**6** and/or **3**) could not be observed in the NMR spectra, only an unidentified mixture of products being obtained.

2.2. Parallel solution-phase synthesis of *N*-biaryl γ-lactam lignans

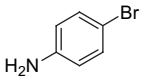
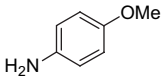
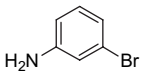
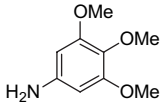
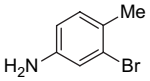
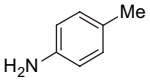
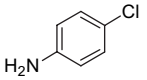
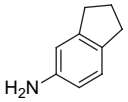
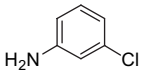
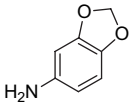
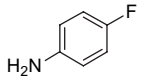
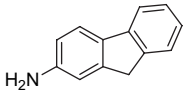
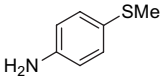
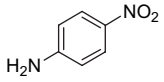
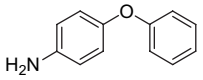
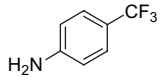
The synthesis of libraries of biaryl small molecules is vitally important to the pharmaceutical industry in the search for biologically active compounds. Consequently, we turned out our attention to the parallel solution-phase synthesis of *N*-biaryl γ-lactam lignans **4** from the bromo adducts **3a** and **3b**. We used 'ligandless' palladium catalytic conditions, which have demonstrated many advantages over classical coupling methodologies.[60–68]

We therefore decided to apply this methodology from compounds **3a** and **3b** for the parallel solution-phase synthesis of *N*-biaryl γ-lactam lignans on the Quest 210®. The Suzuki–Miyaura coupling of **3a** with substituted phenylboronic acids (i.e., phenylboronic acid, 4-chlorophenylboronic acid, and 4-methoxyphenylboronic acid) was examined under a variety of conditions. Unfortunately, the reaction afforded partial conversion of **3a** into the desired biaryl derivative and/or degradation products. In the latter case, ^{1}H NMR analysis of the crude product revealed the disappearance of the signals of the H_1, H_2, and H_3 protons and appearance of other aromatic protons. Given the acidity of the H_3 proton, this result is likely due to aromatization reaction

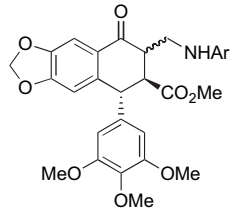


Scheme 1. (a) PCC, DCM, rt; (b) *t*-BuOK, *t*-BuOH, reflux; (c) MeI, $NaHCO_3$, DMF, rt; (d) $ArNH_2$, $InCl_3$, DCE, 80 °C; (e)  $ArSO_2Cl$, Et_3N.

Table 1

Entry	Aniline	Product[a] (%)	Yield[b] (%)	Purity[c] (%)	Entry	Aniline	Product[a] (%)	Yield[b] (%)	Purity[c] (%)
1[d]		**3a**	94	87	9[d]		**3i**	90	91
2[d]		**3b**	91	89	10[d]		**3j**	90	77
3[d]		**3c**	85	92	11[d]		**3k**	92	79
4[d]		**3d**	91	94	12[d]		**3l**	81	81
5[d]		**3e**	76	79	13[d]		**3m**	61	87
6[d]		**3f**	85	92	14[e]		**3n**	66[59]	86
7[d]		**3g**	82	88	15[e]		**3o**	50[59]	80
8[d]		**3h**	71	79	16[f]		**3p**	0[59]	

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[b] Isolated yields.
[c] ^{1}H NMR estimation after scavenging with sulfonyl chloride resin and filtration on silica pad.
[d] $InCl_3$ (0.5 equiv), 48 h.
[e] $InCl_3$ (0.5 equiv), 48 h, then DBU (5 equiv), 24 h.
[f] Obtention of β-aminoketone **6p** and recovered starting material **2**.

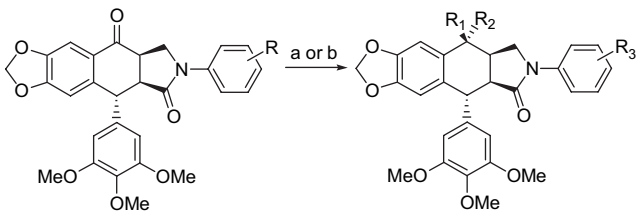


6n (aniline = 2-aminofluorene)
6o (aniline = 4-nitroaniline)
6p (aniline = 4-trifluoroaniline)

Figure 2.

occurring during cross-coupling. To circumvent this problem, we opted for a reduction of the carbonyl function at C-4 on the picropodophyllone derivatives **3a** and **3b**.

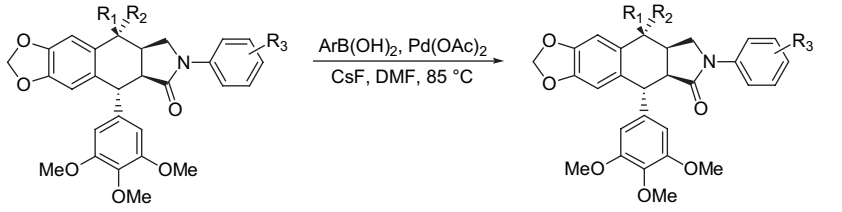
Accordingly, we examined the reduction of the carbonyl function at C-4 of the picropodophyllone *N*-4-bromophenyl γ-lactam **3a** and the picropodophyllone *N*-3-bromophenyl γ-lactam **3b** under different reducing conditions (i.e., $NaBH_4$, $NaBH_4/CeCl_3$, $NaHB(OAc)_3$, L-Selectride, catecholboranehydride). It was found that $NaBH_4$ at −78 °C gave the best results to obtain the 4-OH group in the α-configuration, thereby leading to **7a** (75%, dr=87%) and **8a** (67%, dr=87%) from **3a** and **3b**, respectively (Scheme 2). In contrast, the use of L-Selectride at −78 °C allowed the opposite selectivity, **7b** (86%) and **8b** (80%) were thus prepared with an excellent diastereoisomeric excess (dr>95%). The relative stereochemistry of these compounds was deduced from the $J_{3,4}$ coupling constants (8.2 Hz for **7a**, 5.0 Hz for



3a: R = 4-Br
3b: R = 3-Br

7a: R_1 = H, R_2 = OH, R_3 = 4-Br
7b: R_1 = OH, R_2 = H, R_3 = 4-Br
8a: R_1 = H, R_2 = OH, R_3 = 3-Br
8b: R_1 = OH, R_2 = H, R_3 = 3-Br

Scheme 2. (a) $NaBH_4$, THF, MeOH, −78 °C; (b) L-Selectride, THF, −78 °C.



7a: R_1 = H, R_2 = OH, R_3 = 4-Br
7b: R_1 = OH, R_2 = H, R_3 = 4-Br
8a: R_1 = H, R_2 = OH, R_3 = 3-Br
8b: R_1 = OH, R_2 = H, R_3 = 3-Br

4aa-ai: R_1 = H, R_2 = OH, R_3 = 4-aryl
4ba-bd: R_1 = OH, R_2 = H, R_3 = 4-aryl
4ca,cb: R_1 = H, R_2 = OH, R_3 = 3-aryl
4da,db: R_1 = OH, R_2 = H, R_3 = 3-aryl

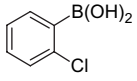
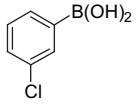
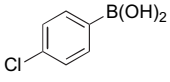
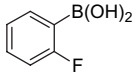
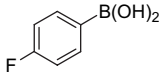
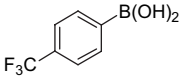
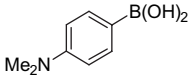
Scheme 3. Suzuki–Miyaura cross-coupling reaction.

7b, 7.5 Hz for **8a**, and 4.5 Hz for **8b**) and was confirmed from NOESY correlations (H_3/H_2, H_1/H_4, $H_{2'}$–$H_{6'}/H_2$ for **7a**).

Since the Suzuki–Miyaura reaction is tolerant of a broad range of functional groups including hydroxyl group,[68–71] the biphenyl synthesis from **7** or **8** was realized without the protection of the benzyl alcohol.

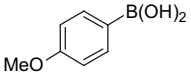
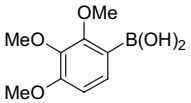
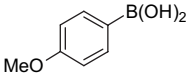
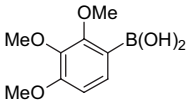
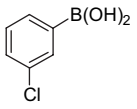
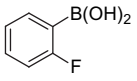
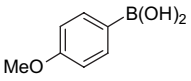
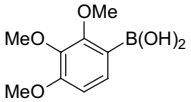
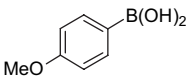
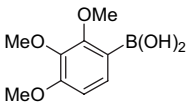
The optimized reaction conditions have been determined by coupling **7a** with 2-chlorophenylboronic acid, 4-fluorophenylboronic acid, and the sterically hindered 2,3,4-trimethoxyphenylboronic acid. The best results were obtained with 2.5 equiv of boronic acid in the presence of CsF (7.5 equiv) and $Pd(OAc)_2$ (10%) in DMF at 85 °C for 20 h (Scheme 3). DMF was chosen since the substrates **7** and **8** exhibit poor solubility in other solvent systems. The results of the parallel Suzuki–Miyaura coupling (Quest 210®) from **7a** with a variety of phenylboronic acids are summarized in Table 2.

Table 2

Entry[a]	Substrate	$ArB(OH)_2$	Time (h)	Product	Yield[b] (%)
1	**7a**		20	**4aa**	59[c]
2	**7a**		20	**4ab**	67[d]
3	**7a**		20	**4ac**	67[e]
4	**7a**		20	**4ad**	82
5	**7a**		20	**4ae**	81
6	**7a**		20	**4af**	85
7	**7a**		20	**4ag**	18

(*continued*)

Table 2. (*continued*)

Entry[a]	Substrate	$ArB(OH)_2$	Time (h)	Product	Yield[b] (%)
8	**7a**		20	**4ah**	95
9	**7a**		20	**4ai**	66
10	**8a**		20	**4ca**	72
11	**8a**		20	**4cb**	63
12	**7b**		5	**4ba**	70[f]
13	**7b**		5	**4bb**	79
14	**7b**		5	**4bc**	81
15	**7b**		5	**4bd**	67
16	**8b**		5	**4da**	75
17	**8b**		5	**4db**	59

[a] $ArB(OH)_2$ (2.5 equiv), $Pd(OAc)_2$ (10%), CsF (10 equiv), DMF, 85 °C.
[b] Isolated yields with purity>95% after workup (i.e., extraction and silica pad filtration).
[c] Triphenyl (11%), starting material (15%) (HPLC/LC–MS analysis).
[d] Triphenyl (15%), tetraphenyl (2%), starting material (11%) (HPLC/LC–MS analysis).
[e] Triphenyl (25%), tetraphenyl (4%) (HPLC/LC–MS analysis).
[f] Polyphenyls (e), starting material (10%).

Cross-coupling of **7a** with halogenated phenylboronic acids provided biaryls **4aa–ae** in 59–82% yields (entries 1–5). In addition, triphenyl and tetraphenyl derivatives resulting from successive Suzuki coupling of **4aa** and **4ab** with the corresponding chlorophenylboronic acid were formed in low yields. The electron-deficient 4-(trifluoromethyl)phenylboronic acid afforded biaryl **4af** in 85% yield (entry 6). Surprisingly, the reaction of the electron-rich 4-(dimethylamino)phenylboronic acid gave low conversion of **7a** (entry 7). In contrast, 4-methoxyphenylboronic acid furnished the biaryl **4ah** in 95% yield (entry 8). Sterically hindered 2,3,4-trimethoxyphenylboronic acid was also reactive and the desired product **4ai** was isolated in 66% (entry 9). An attempt to couple this boronic acid with **7a** failed using K_2CO_3 as base and a shorter reaction time, this is likely due to the formation of the deprotoboranation product under these conditions.[72] Suzuki reaction of **8a** with 4-methoxyphenylboronic and 2,3,4-trimethoxyphenylboronic acids gave the corresponding biaryls **4ca** (72%) and **4cb** (63%). The Suzuki coupling proceeds faster from the substrates **7b** and **8b** with some representative boronic acids. Indeed, the biaryls **4ba–bd** (67–81%) and **4da** and **4db** (59 and 75%) were obtained in good yields after 5 h. This observation suggests that the stereochemistry of the alcohol at C-4 may exert an influence on the kinetic of the coupling reaction.

3. Conclusion

We have synthesized two small libraries of *N*-aryl γ-lactam lignans and *N*-biaryl γ-lactam lignans based on the 1-aryltetralin privileged structure with parallel solution-phase methodologies. In particular, the above-descripted procedure catalyzed by indium(III) chloride represents an efficient synthesis of *N*-aryl picropodophyllone γ-lactams from the methyl ester of thuriferic acid via tandem aza-Michael addition–cyclization reaction of anilines. We are currently examining the biological activity of these compounds as well as the preparation of larger and more diverse 1-aryltetralin-based libraries.

4. Experimental

4.1. General

Reactions were carried out in dried glassware under an argon atmosphere and parallel synthesis with the Quest 210® (Argonaut Technologies) in dried Teflon reactors. All commercial reagents were used without purification, and all solvents were reaction grade and dried over molecular sieves. THF was freshly distilled from sodium/benzophenone under argon and dichloromethane from phosphorus pentoxide. All reaction mixtures were stirred magnetically and monitored by thin-layer chromatography using Merck silica gel 60 F_{256}, visualized with UV light, and then developed by using Merck silica gel 60 (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra (1D and 2D) were recorded on a Bruker AM 300 spectrometer. Deuteriated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Melting points were determined with Electrothermal (Digital Melting Point Apparatus). Infrared spectra were recorded on a Perkin–Elmer 1710 spectrometer. Optical rotations were measured with Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a Nermag R10-10C.

4.2. Preparation of the methyl ester of thuriferic acid 3

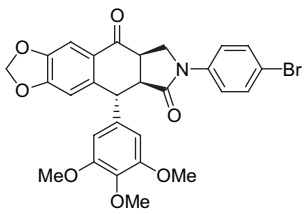
4.2.1. Podophyllotoxone. To a solution of podophyllotoxin (**5**, 8.05 g, 19.4 mmol) in anhydrous dichloromethane was added pyridinium chlorochromate (6.55 g, 30.4 mmol). The mixture was stirred at room temperature for 2 h, then filtered on Celite and washed with distilled water. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column (cyclohexane/ethyl acetate 3/2) to give podophyllotoxone (80%) as a white solid. Spectral and physical properties were identical to those described in Ref. 29.

4.2.2. Methyl ester of thuriferic acid 2. To a solution of podophyllotoxone (7.74 g, 18.8 mmol) in *t*-BuOH (280 mL) was added *t*-BuOK (19 mmol). The mixture was stirred at reflux for 2.5 h under nitrogen atmosphere. The solvent was then removed in vacuo and the residue was dissolved in DMF. Iodomethane (6.60 mL, 0.1 mol) and $NaHCO_3$ were added to the mixture, which was stirred at room temperature for 24 h. The reaction mixture was quenched with water (250 mL). The aqueous layer was extracted with ethyl acetate (3×300 mL) and the combined organic layers were washed with water and brine (300 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column (cyclohexane/ethyl acetate 1/1) to yield **2** (95%) as a off-white solid. Spectral and physical properties of **2** were identical to those described in Refs. 25 and 73.

4.3. Representative experimental procedure for tandem addition–cyclization catalyzed by $InCl_3$

To a 10 mL Quest 210 Teflon reaction vessel was added a solution of the methyl ester of thuriferic acid **2** (50 mg, 0.117 mmol) in DCE (3 mL) followed by $InCl_3$ (13 mg, 0.058 mmol) and 4-bromoaniline (101 mg, 0.585 mmol, 5 equiv). The solution was stirred for 48 h at 80 °C. Chlorosulfonyl resin (560 mg, 12 equiv) and Et_3N (0.25 mL, 15 equiv) were added and the reaction mixture was stirred for 24 h at 60 °C in order to scavenge excess of aniline. Filtration and evaporation of the solvent under reduced pressure afforded a residue, which was purified by filtration on silica pad (H 3.5 cm, Ø 1.7 cm) with cyclohexane then cyclohexane/EtOAc gradient [9/1 to 2/8] to give 62 mg (94%) of **3a**.

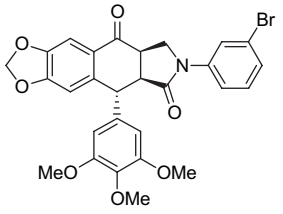
4.3.1. (1*R*,2*S*,3*R*)-*N*-(4-Bromophenyl)-picropodophyllone-*cis*-γ-lactam 3a.



White solid; 62 mg; yield: 94%; mp: 143–145 °C; $[\alpha]_D^{20}$ −252 (*c* 0.25, $CHCl_3$); IR 3014, 2980–2900, 1702, 1668,

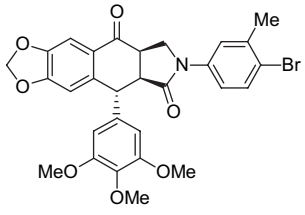
1591, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (m, 5H, H_5, $H_{2''}$, $H_{3''}$, $H_{5''}$, $H_{6''}$), 6.72 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.03 (m, 2H, OCH_2O), 4.79 (d, J=1.6 Hz, 1H, H_1), 4.24 (d, J=9.7 Hz, 1H, H_{11a}), 3.95 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7 (C_4), 171.7 (C_{13}), 153.7 ($C_{3'}$, $C_{5'}$), 153.6 (C_7), 148.2 (C_6), 139.9 (C_9), 138.6 ($C_{1'}$), 137.9 ($C_{1''}$), 137.1 ($C_{4'}$), 131.8 ($C_{3''}$, $C_{5''}$), 127.2 (C_{10}), 121.0 ($C_{2''}$, $C_{6''}$), 117.8 ($C_{4''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}BrNO_7$ 566.0814 and 568.0799, found 566.0809 and 568.0798.

4.3.2. (1*R*,2*S*,3*R*)-*N*-(3-Bromophenyl)-picropodophyllone-*cis*-γ-lactam 3b.



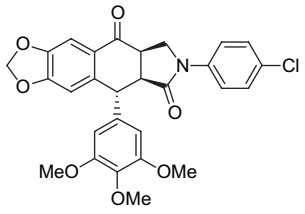
White solid; 60 mg; yield: 91%; mp: 128–130 °C; $[\alpha]_D^{20}$ −187 (c 0.17, $CHCl_3$); IR ($CHCl_3$) 3028, 3012, 2970–2900, 1704, 1669, 1592, 1506, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J=1.7 Hz, 1H, $H_{2''}$), 7.46 (dd, J=8.0, 1.7 Hz, 1H, $H_{6''}$), 7.45 (s, 1H, H_5), 7.24 (m, 1H, $H_{4''}$), 7.16 (t, J=8 Hz, 1H, $H_{5''}$), 6.70 (s, 1H, H_8), 6.26 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.79 (d, J=1.6 Hz, 1H, H_1), 4.26 (d, J=9.7 Hz, 1H, H_{11a}), 3.96 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6 (C_4), 171.8 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 140.1 ($C_{1''}$), 139.9 (C_9), 138.5 ($C_{1'}$), 137.1 ($C_{4'}$), 130.1 ($C_{5''}$), 127.8 ($C_{4''}$), 127.2 (C_{10}), 122.6 ($C_{3''}$), 122.5 ($C_{2''}$), 117.8 ($C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{5'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}BrNO_7$ 566.0814 and 568.0799, found 566.0803 and 568.0794.

4.3.3. (1*R*,2*S*,3*R*)-*N*-(3-Bromo-4-methyl-phenyl)-picropodophyllone-*cis*-γ-lactam 3c.



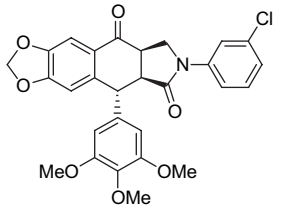
White solid; 58 mg; yield: 85%; mp: 121–123 °C; $[\alpha]_D^{20}$ −230 (c 0.18, $CHCl_3$); IR ($CHCl_3$) 2940, 1699, 1669, 1592, 1506, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 1H, H_5), 7.44 (m, 2H, $H_{2''}$, $H_{5''}$), 7.24 (dd, J=8.3, 2.5 Hz, 1H, $H_{6''}$), 6.72 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.03 (m, 2H, OCH_2O), 4.79 (d, J=1.7 Hz, 1H, H_1), 4.24 (d, J=9.7 Hz, 1H, H_{11a}), 3.96 (m, J=9.8, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.33 (dd, J=7.5, 1.7 Hz, 1H, H_2), 3.21 (m, 1H, H_3), 2.36 (s, 3H, Ph-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8 (C_4), 171.7 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 138.6 ($C_{1'}$), 138.5 ($C_{1''}$), 138.0 ($C_{3''}$), 137.0 ($C_{4'}$), 132.5 ($C_{5''}$), 127.2 (C_{10}), 121.8 ($C_{2''}$), 120.4 ($C_{4''}$), 118.4 ($C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 51.0 (C_{11}), 50.5 (C_2), 43.1 (C_1), 40.0 (C_3), 23.1 (Ph-*Me*); HRMS (DCI/NH_3): calcd for $C_{29}H_{27}NO_7Br$ 580.0971 and 582.0956, found 580.0970 and 582.0954.

4.3.4. (1*R*,2*S*,3*R*)-*N*-(4-Chlorophenyl)-picropodophyllone-*cis*-γ-lactam 3d.



White solid; 56 mg; yield: 91%; mp: 138–140 °C; $[\alpha]_D^{20}$ −211 (c 0.22, $CHCl_3$); IR 3012, 2960–2900, 1702, 1671, 1592, 1495, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=9 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.45 (s, 1H, H_5), 7.27 (d, J=9 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.70 (s, 1H, H_8), 6.26 (s, 2H, $H_{2'}$, $H_{6'}$), 6.00 (m, 2H, OCH_2O), 4.79 (d, J=1.7 Hz, 1H, H_1), 4.23 (d, J=9.7 Hz, 1H, H_{11a}), 3.95 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.79 (s, 3H, $OMe_{(4')}$), 3.74 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.7 Hz, 1H, H_2), 3.21 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8 (C_4), 171.7 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 138.6 ($C_{1'}$), 137.4 ($C_{1''}$), 137.0 ($C_{4'}$), 130.0 ($C_{4''}$), 128.9 ($C_{3''}$, $C_{5''}$), 127.2 (C_{10}), 120.7 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}ClNO_7$ 522.1320 and 524.1305, found 522.1318 and 524.1311.

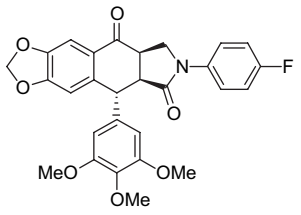
4.3.5. (1*R*,2*S*,3*R*)-*N*-(3-Chlorophenyl)-picropodophyllone-*cis*-γ-lactam 3e.



White solid; 46 mg; yield: 76%; mp: 124–126 °C; $[\alpha]_D^{20}$ −124 (c 0.32, $CHCl_3$); IR ($CHCl_3$) 3036, 2978–2900, 1706, 1671, 1594, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (t, J=1.8 Hz, 1H, $H_{2''}$), 7.47 (s, 1H, H_5), 7.43 (dd, J=8.2, 1.0 Hz, 1H, $H_{6''}$), 7.25 (t, J=8.2 Hz, 1H, $H_{5''}$), 7.11 (dd, J=8.2, 1.0 Hz, 1H, $H_{4''}$), 6.72 (s, 1H, H_8), 6.30 (s, 2H, $H_{2'}$, $H_{6'}$), 6.02 (m, 2H, OCH_2O), 4.80 (d, J=1.7 Hz, 1H, H_1), 4.27 (d, J=9.7 Hz, 1H, H_{11a}), 3.97 (dd, J=9.7, 6.4 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76

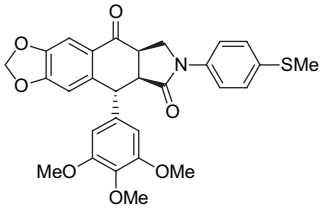
(s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=7.5, 1.7 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7 (C_4), 171.9 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 139.8 ($C_{1''}$), 138.5 ($C_{1'}$), 137.0 ($C_{4'}$), 134.6 ($C_{3''}$), 129.8 ($C_{5''}$), 127.2 (C_{10}), 124.9 ($C_{4''}$), 119.7 ($C_{2''}$), 117.3 ($C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}ClNO_7$ 522.1320 and 524.1305, found 522.1312 and 524.1312.

4.3.6. (1*R*,2*S*,3*R*)-*N*-(4-Fluorophenyl)-picropodophyllone-*cis*-γ-lactam 3f.



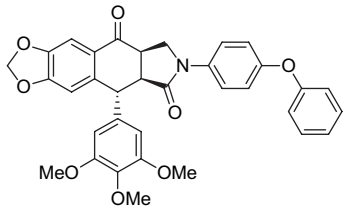
White solid; 50 mg; yield: 85%; mp: 127–129 °C; $[\alpha]_D^{20}$ −202 (*c* 0.23, $CHCl_3$); IR 3022, 3011, 2970–2900, 1699, 1668, 1592, 1510, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (m, 2H, $H_{2''}$, $H_{6''}$), 7.46 (s, 1H, H_5), 7.00 (t, J=8.6 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.71 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.79 (d, 1.6 Hz, 1H, H_1), 4.23 (d, J=9.7 Hz, 1H, H_{11a}), 3.96 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.21 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.9 (C_4), 171.6 (C_{13}), 161.4 (d, J=249 Hz, $C_{4''}$), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 137.0 ($C_{4'}$), 135.0 ($C_{1''}$), 127.3 (C_{10}), 121.5 (d, J=7.5 Hz, $C_{2''}$, $C_{6''}$), 115.6 (d, J=22.5 Hz, $C_{3''}$, $C_{5''}$), 109.6 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 51.3 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.1 (C_3); MS (DCI/NH_3): 506 $[M+H]^+$, 523 $[M+NH_4]^+$.

4.3.7. (1*R*,2*S*,3*R*)-*N*-(4-Thiomethylphenyl)-picropodophyllone-*cis*-γ-lactam 3g.



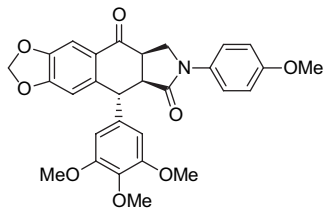
Off-white solid; 51 mg; yield: 82%; mp: 120–122 °C; $[\alpha]_D^{20}$ −306 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 3021, 3012, 2971–2900, 1697, 1669, 1592, 1498, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J=8.8 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.46 (s, 1H, H_5), 7.21 (d, J=8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 6.71 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.79 (d, J=1.6 Hz, 1H, H_1), 4.23 (d, J=9.8 Hz, 1H, H_{11a}), 3.96 (dd, J=9.8, 6.4 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.20 (m, 1H, H_3), 2.43 (s, 3H, *S*-Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0 (C_4), 171.6 (C_{13}), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 137.1 ($C_{4'}$), 136.4 ($C_{1''}$), 134.6 ($C_{4''}$), 127.5 ($C_{3''}$, $C_{5''}$), 127.3 (C_{10}), 120.1 ($C_{2''}$, $C_{6''}$), 109.6 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2($OMe_{(3',5')}$), 51.0 (C_{11}), 50.5 (C_2), 43.2 (C_1), 40.1 (C_3), 16.4 (*S*-Me); HRMS (DCI/NH_3): calcd for $C_{29}H_{28}NO_7S$ 534.1586, found 534.1591.

4.3.8. (1*R*,2*S*,3*R*)-*N*-(4-Phenoxyphenyl)-picropodophyllone-*cis*-γ-lactam 3h.



Off-white solid; 48 mg; yield: 71%; mp: 218–220 °C; $[\alpha]_D^{20}$ −113 (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 3025, 2970–2900, 1696, 1670, 1591, 1507, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=9 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.48 (s, 1H, H_5), 7.29 (m, 2H, $H_{3''}$, $H_{5''}$), 7.07 (t, J=7.5 Hz, 1H, $H_{4''}$), 6.97 (m, 4H, $H_{3''}$, $H_{5''}$, $H_{2'''}$, $H_{6'''}$), 6.72 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.81 (d, J =1.6 Hz, 1H, H_1), 4.25 (d, J=9.7 Hz, 1H, H_{11a}), 3.97 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=7.4, 1.6 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0 (C_4), 171.5 (C_{13}), 157.3 ($C_{1'''}$), 154.0 ($C_{4''}$), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 136.9 ($C_{4'}$), 134.3 ($C_{1''}$), 129.7 ($C_{3'''}$, $C_{5'''}$), 127.3 (C_{10}), 123.2 ($C_{4'''}$), 121.3 ($C_{2''}$, $C_{6''}$), 119.3 ($C_{2'''}$, $C_{6'''}$), 118.5 ($C_{3''}$, $C_{5''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.3 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.1 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{30}NO_8$ 580.1971, found 580.1968.

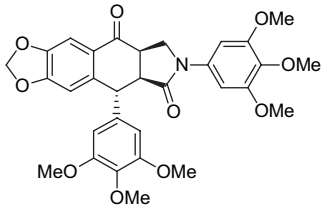
4.3.9. (1*R*,2*S*,3*R*)-*N*-(4-Methoxyphenyl)-picropodophyllone-*cis*-γ-lactam 3i.



Off-white solid; 54 mg; yield: 90%; mp: 124–126 °C; $[\alpha]_D^{20}$ −246 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3022, 3016, 2965–2900, 1694, 1670, 1592, 1512, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H, H_5), 7.42 (d, J=9 Hz, 2H, $H_{2''}$, $H_{6''}$), 6.84 (d, J=9 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.71 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.80 (d, J=1.7 Hz, 1H, H_1), 4.21 (d, J=9.8 Hz, 1H, H_{11a}), 3.96 (dd, J=9.8, 6.4 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.75 (s, 3H, $OMe_{(4'')}$), 3.33 (dd, J=7.4, 1.7 Hz, 1H, H_2), 3.20 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (C_4), 171.3 (C_{13}), 156.8 ($C_{4''}$), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.1 (C_6), 139.9 (C_9), 138.8 ($C_{1'}$), 136.9 ($C_{4'}$), 132.1 ($C_{1''}$), 127.3 (C_{10}), 121.4 ($C_{2''}$, $C_{6''}$), 114.0 ($C_{3''}$, $C_{5''}$), 109.5 (C_8), 105.8 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.0

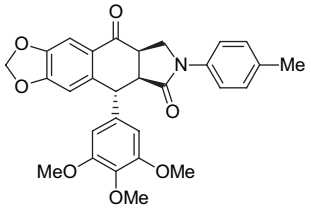
(OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 55.4 ($OMe_{(4'')}$), 51.5 (C_{11}), 50.3 (C_2), 43.2 (C_1), 40.2 (C_3); HRMS (DCI/NH_3): calcd for $C_{29}H_{28}NO_8$ 518.1815, found 518.1807.

4.3.10. (1*R*,2*S*,3*R*)-*N*-(3,4,5-Trimethoxyphenyl)-picropodophyllone-*cis*-γ-lactam 3j.



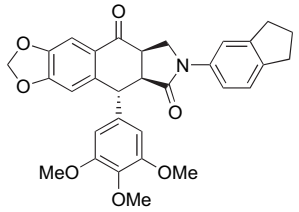
Pale yellow solid; 61 mg; yield: 90%; mp: 125–127 °C; $[\alpha]_D^{20}$ −244 (*c* 0.16, $CHCl_3$); IR 3023, 3010, 2970–2900, 1698, 1668, 1593, 1508, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1H, H_5), 6.87 (s, 2H, $H_{2''}$, $H_{6''}$), 6.71 (s, 1H, H_8), 6.26 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.78 (d, *J*=1.3 Hz, 1H, H_1), 4.28 (d, *J*=9.7 Hz, 1H, H_{11a}), 3.95 (dd, *J*=9.7, 6.4 Hz, 1H, H_{11b}), 3.84 (s, 6H, $OMe_{(3'',5'')}$), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(4'')}$), 3.74 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, *J*=7.4, 1.3 Hz, 1H, H_2), 3.20 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8 (C_4), 171.7 (C_{13}), 153.7 ($C_{3'}$, $C_{5'}$, C_7), 153.2 ($C_{3''}$, $C_{5''}$), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 137.1 ($C_{4'}$), 135.6 ($C_{4''}$), 135.0 ($C_{1''}$), 127.2 (C_{10}), 109.6 (C_8), 105.9 (C_5), 104.9 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 97.6 ($C_{2''}$, $C_{6''}$), 60.9 (OMe), 60.8 (OMe), 56.2 ($OMe_{(3',5',3'',5'')}$), 51.3 (C_{11}), 50.7 (C_2), 43.2 (C_1), 39.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{31}H_{32}NO_{10}$ 578.2026, found 578.2021.

4.3.11. (1*R*,2*S*,3*R*)-*N*-(4-Methylphenyl)-picropodophyllone-*cis*-γ-lactam 3k.



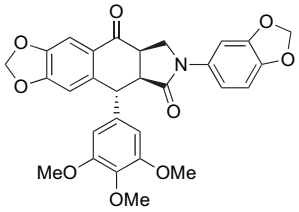
White solid; 54 mg; yield: 92%; mp: 129–130 °C; $[\alpha]_D^{20}$ −259 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3012, 2975–2900, 1693, 1669, 1592, 1506, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1H, H_5), 7.41 (d, *J*=8.4 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.13 (d, *J*=8.4 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.72 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.02 (m, 2H, OCH_2O), 4.81 (d, *J*=1.8 Hz, 1H, H_1), 4.24 (d, *J*=9.9 Hz, 1H, H_{11a}), 3.95 (dd, *J*=9.9, 6.2 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, *J*=7.5, 1.8 Hz, 1H, H_2), 3.21 (m, 1H, H_3), 2.30 (s, 3H, Ph-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (C_4), 171.5 (C_{13}), 153.7 (C_7, $C_{3'}$, $C_{5'}$), 148.1 (C_6), 139.9 (C_9), 138.8 ($C_{1'}$), 136.9 ($C_{4'}$), 136.4 ($C_{1''}$), 134.6 ($C_{4''}$), 129.4 ($C_{3''}$, $C_{5''}$), 127.3 (C_{10}), 119.7 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.2 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.1 (C_3), 20.8 (Ph-*Me*); HRMS (DCI/NH_3): calcd for $C_{29}H_{28}NO_7$ 502.1866, found 502.1865.

4.3.12. (1*R*,2*S*,3*R*)-*N*-Indan-5-yl-picropodophyllone-*cis*-γ-lactam 3l.



Off-white solid; 50 mg; yield: 81%; mp: 114–116 °C; $[\alpha]_D^{20}$ −258 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3029, 3012, 2973–2900, 1695, 1669, 1592, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H, H_5), 7.40 (d, *J*=1.5 Hz, 1H, $H_{4''}$), 7.21 (dd, *J*=8.2, 1.5 Hz, 1H, $H_{6''}$), 7.15 (d, *J*=8.2 Hz, 1H, $H_{7''}$), 6.72 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.81 (d, *J*=1.6 Hz, 1H, H_1), 4.22 (d, *J*=9.8 Hz, 1H, H_{11a}), 3.97 (dd, *J*=9.8, 6.4 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.33 (dd, *J*=7.4, 1.6 Hz, 1H, H_2), 3.19 (m, 1H, H_3), 2.84 (m, 4H, $H_{1''}$, $H_{3''}$), 2.04 (m, 2H, $H_{2''}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (C_4), 171.4 (C_{13}), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.1 (C_6), 145.1 ($C_{3a''}$), 141.1 ($C_{7a''}$), 140.0 (C_9), 138.8 ($C_{1'}$), 137.1 ($C_{5''}$), 137.0 ($C_{4'}$), 127.4 (C_{10}), 124.4 ($C_{7''}$), 118.0 ($C_{6''}$), 116.5 ($C_{4''}$), 109.5 (C_8), 105.8 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.7 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.2 (C_3), 33.0 ($C_{3''}$), 32.3 ($C_{1''}$), 25.6 ($C_{2''}$); HRMS (DCI/NH_3): calcd for $C_{31}H_{30}NO_7$ 528.2022, found 528.2028.

4.3.13. (1*R*,2*S*,3*R*)-*N*-(3,4-Methylenedioxyphenyl)-picropodophyllone-*cis*-γ-lactam 3m.

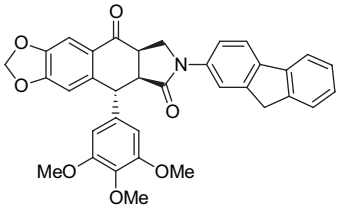


Off-white solid; 38 mg; yield: 61%; yellow powder; mp 187–190 °C; $[\alpha]_D^{20}$ −91 (*c* 0.15, $CHCl_3$); IR 3023, 2970–2900, 1714, 1672, 1597, 1505, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H, H_5), 7.22 (d, *J*=1.8 Hz, 1H, $H_{2''}$), 6.78 (dd, *J*=10.4, 1.8 Hz, 1H, $H_{6''}$), 6.73 (d, *J*=10.4 Hz, 1H, $H_{5''}$), 6.71 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.02 (m, 2H, $OCH_2O_{(6,7)}$), 5.92 (d, *J*=1.0 Hz, 2H, $OCH_2O_{(3'',4'')}$), 4.79 (d, *J*=1.7 Hz, 1H, H_1), 4.18 (d, *J*=9.7 Hz, 1H, H_{11a}), 3.93 (dd, *J*=9.7, 6.3 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.32 (dd, *J*=7.4, 1.7 Hz, 1H, H_2), 3.19 (dd, *J*=7.4, 6.3 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1 (C_4), 171.4 (C_{13}), 153.6 (C_7), 153.5 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 147.8 ($C_{3''}$), 144.8 ($C_{4''}$), 139.2 ($C_{1'}$), 138.8 ($C_{1''}$), 136.9 ($C_{4'}$), 133.2 (C_9), 127.3 (C_{10}), 112.9 ($C_{6''}$), 109.5 (C_8), 107.9 ($C_{5''}$), 105.8 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.6 ($C_{2''}$), 102.1 ($OCH_2O_{(6,7)}$), 101.3 ($OCH_2O_{(3'',4'')}$), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.8 (C_{11}), 50.3 (C_2), 43.2 (C_1), 40.1 (C_3); MS (ES+): 532 $[M+H]^+$, 554 $[M+Na]^+$.

4.4. Representative experimental procedure for sequential one-pot addition–cyclization catalyzed by $InCl_3$

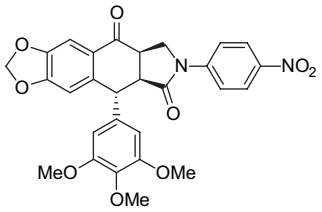
To a 10 mL Quest 210 Teflon reaction vessel was added a solution of the methyl ester of thuriferic acid **2** (50 mg, 0.117 mmol) in DCE (3 mL) followed by $InCl_3$ (13 mg, 0.058 mmol) and 2-aminofluorene (106 mg, 0.585 mmol, 5 equiv). The solution was stirred for 48 h at 80 °C and then DBU (88 μL, 0.585 mmol) was added and the solution was stirred for 24 h at 80 °C. Chlorosulfonyl resin (560 mg, 12 equiv) and Et_3N (0.25 mL, 15 equiv) were added and the reaction mixture was stirred for 24 h at 60 °C in order to scavenge excess of aniline. Filtration and evaporation of the solvent under reduced pressure gave a residue, which was purified by filtration on silica pad with cyclohexane then cyclohexane/EtOAc gradient [9/1 to 2/8] to furnish 44 mg (66%) of **3n**.

4.4.1. (1*R*,2*S*,3*R*)-*N*-Fluoren-2-yl-picropodophyllone-*cis*-γ-lactam 3n.



Yellow solid; 44 mg; yield: 66%; mp: 139–141 °C; $[\alpha]_D^{20}$ −227 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3026, 3014, 2974–2900, 1696, 1668, 1592, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J*=2.0 Hz, 1H, $H_{1''}$), 7.72 (m, 2H, $H_{4''}$, $H_{5''}$), 7.51 (m, 1H, $H_{8''}$), 7.49 (s, 1H, H_5), 7.48 (m, 1H, $H_{3''}$), 7.35 (t, *J*=7.2 Hz, 1H, $H_{6''}$), 7.27 (dt, *J*=7.2, 1.2 Hz, 1H, $H_{7''}$), 6.74 (s, 1H, H_8), 6.30 (s, 2H, $H_{2'}$, $H_{6'}$), 6.03 (m, 2H, OCH_2O), 4.84 (d, *J*=1.8 Hz, 1H, H_1), 4.34 (d, *J*=9.8 Hz, 1H, H_{11a}), 4.06 (dd, *J*=9.8, 6.3 Hz, 1H, H_{11b}), 3.87 (s, 2H, $H_{9''}$), 3.82 (s, 3H, $OMe_{(4')}$), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.39 (dd, *J*=7.5, 1.8 Hz, 1H, H_2), 3.25 (dd, *J*=7.5, 6.3 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1 (C_4), 171.7 (C_{13}), 153.6 (C_7, $C_{3'}$, $C_{5'}$), 148.2 (C_6), 144.0 ($C_{9a'}$), 143.2 ($C_{8a'}$), 141.2 ($C_{4b''}$), 139.9 ($C_{1'}$), 138.8 (C_9), 138.6 ($C_{2''}$), 137.7 ($C_{4a''}$), 136.9 ($C_{4'}$), 127.3 (C_{10}), 126.8 ($C_{7''}$), 126.6 ($C_{6''}$), 125.0 ($C_{8''}$), 120.0 ($C_{4''}$), 119.7 ($C_{5''}$), 118.4 ($C_{3''}$), 116.9 ($C_{1''}$), 109.6 (C_8), 105.9 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 51.5 (C_{11}), 50.6 (C_2), 43.2 (C_1), 40.2 (C_3), 37.0 ($C_{9''}$); HRMS (DCI/NH_3): calcd for $C_{35}H_{29}NO_7S$ 576.2056, found 576.2013.

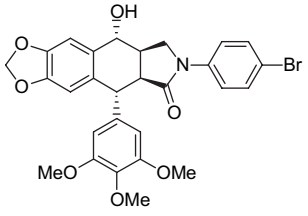
4.4.2. (1*R*,2*S*,3*R*)-*N*-(4-Nitrophenyl)-picropodophyllone-*cis*-γ-lactam 3o.



Yellow solid; 31 mg; yield: 50%; yellow powder; mp 235–240 °C; $[\alpha]_D^{20}$ −110 (*c* 0.34, $CHCl_3$); IR 3020, 2970–2900, 1713, 1670, 1596, 1504, 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J*=9.3 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.79 (d, *J*=9.3 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.48 (s, 1H, H_5), 6.73 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.04 (m, 2H, OCH_2O), 4.81 (d, *J*=1.7 Hz, 1H, H_1), 4.38 (d, *J*=9.7 Hz, 1H, H_{11a}), 4.01 (m, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.40 (dd, *J*=7.6, 1.7 Hz, 1H, H_2), 3.29 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9 (C_4), 172.3 (C_{13}), 153.7 (C_7), 153.5 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 144.1 ($C_{1''}$), 143.6 ($C_{4''}$), 139.6 (C_9), 138.1 ($C_{1'}$), 137.0 ($C_{4'}$), 126.9 (C_{10}), 124.5 ($C_{2''}$, $C_{6''}$), 118.6 ($C_{3''}$, $C_{5''}$), 109.3 (C_8), 105.8 (C_5), 104.6 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.6 ($OMe_{(4')}$), 56.0 ($OMe_{(3',5')}$), 50.5 (C_2), 43.3 (C_{11}), 42.9 (C_1), 39.5 (C_3); MS (DCI/NH_3): 533 $[M+H]^+$, 550 $[M+NH_4]^+$.

4.5. Reduction procedures of bromo *N*-aryl lactam lignans

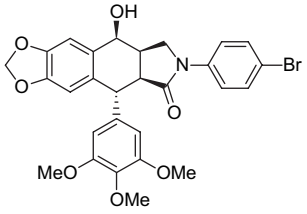
4.5.1. (1*R*,2*S*,3*R*,4*R*)-*N*-(4-Bromophenyl)-picropodophyllin-*cis*-γ-lactam 7a.



To a mixture of **3a** (247 mg, 0.436 mmol) in THF (4 mL) was added MeOH (4 mL). The solution was cooled to −78 °C and $NaBH_4$ (25 mg, 0.654 mmol) was added. The reaction mixture was removed from the cold bath and was stirred for 3 h, water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) and recrystallized from cyclohexane and EtOAc to yield 186 mg (75%) of **7a** as a white solid.

Compound **7a**: 186 mg; yield: 75%; mp: 228–230 °C; $[\alpha]_D^{20}$ −69 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3008, 2960–2900, 1695, 1592, 1504, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J*=8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.45 (d, *J*=8.6 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.03 (s, 1H, H_5), 6.47 (s, 2H, $H_{2'}$, $H_{6'}$), 6.37 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.51 (t, *J*=8.0 Hz, 1H, H_4), 4.20 (d, *J*=4.9 Hz, 1H, H_1), 3.95 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, *J*=9.2, 4.9 Hz, 1H, H_2), 2.69 (m, 1H, H_3), 2.15 (d, *J*=8.0 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.1 ($C_{1'}$), 138.2 ($C_{1''}$), 136.7 ($C_{4'}$), 132.2 (C_9), 131.8 ($C_{2''}$, $C_{6''}$), 131.1 (C_{10}), 121.0 ($C_{3''}$, $C_{5''}$), 117.5 ($C_{4''}$), 109.3 (C_8), 105.5 ($C_{2'}$, $C_{6'}$), 105.3 (C_5), 101.1 (OCH_2O), 70.2 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 50.2 (C_{11}), 48.9 (C_2), 44.2 (C_1), 38.7 (C_3); HRMS (FAB+): calcd for $C_{28}H_{26}NO_7Br$ 567.0893 and 569.0877, found 567.0886 and 569.0887; HRMS (DIC/NH_3): calcd for $C_{28}H_{27}NO_7Br$ 568.0971 and 570.0955, found 568.0956 and 570.0966.

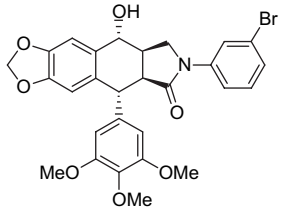
4.5.2. (1*R*,2*S*,3*R*,4*S*)-*N*-(4-Bromophenyl)-epipicropodophyllin-*cis*-γ-lactam 7b.



To a mixture of **3a** (199 mg, 0.351 mmol) in anhydrous THF (5 mL) at −78 °C was added 1 M L-Selectride solution in THF (422 μL, 0.422 mmol) dropwise. The reaction mixture was removed from the cold bath and was stirred for 2 h. A saturated solution of NH_4Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) to yield 172 mg (86%) of **7b** as a white solid.

Compound **7b**: 172 mg; yield: 86%; mp: 149–152 °C; $[\alpha]_D^{20}$ +51 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3013, 2970–2900, 1692, 1591, 1505, 1491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J*=10.4 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.41 (d, *J*=10.4 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.07 (s, 1H, H_5), 6.66 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.95 (m, 2H, OCH_2O), 4.89 (t, *J*=4.7 Hz, 1H, H_4), 4.55 (d, *J*=2.2 Hz, 1H, H_1), 3.82 (s, 3H, $OMe_{(4')}$), 3.80 (m, 1H, H_{11a}), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.67 (m, 1H, H_{11b}), 3.61 (dd, *J*=10.6, 2.2 Hz, 1H, H_2), 3.20 (m, 1H, H_3), 2.08 (d, *J*=4.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_6, C_7), 138.2 ($C_{1'}$ or $C_{1''}$), 138.0 ($C_{1''}$ or $C_{1'}$), 136.6 ($C_{4'}$), 131.7 ($C_{3''}$, $C_{5''}$), 131.6 (C_9), 129.7 (C_{10}), 121.4 ($C_{2''}$, $C_{6''}$), 117.5 ($C_{4''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.6 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 48.7 (C_2), 48.2 (C_{11}), 45.7 (C_1), 35.4 (C_3); HRMS (FAB+): calcd for $C_{28}H_{27}NO_7Br$ 568.0971 and 570.0955, found 568.0980 and 570.0940.

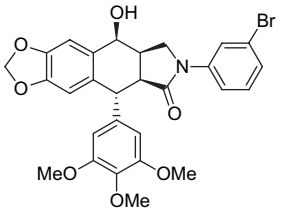
4.5.3. (1*R*,2*S*,3*R*,4*R*)-*N*-(3-Bromophenyl)-picropodophyllin-*cis*-γ-lactam 8a.



To a mixture of **3b** (218 mg, 0.385 mmol) in THF (4 mL) was added MeOH (4 mL). The solution was cooled to −78 °C and $NaBH_4$ (29 mg, 0.770 mmol) was added. The reaction mixture was removed from the cold bath and was stirred for 3 h, water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) and then recrystallized from hexane and benzene to yield 147 mg (67%) of **8a** as a white solid.

Compound **8a**: 147 mg; yield: 67%; mp: 216–218 °C; $[\alpha]_D^{20}$ −59 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3012, 2970–2900, 1702, 1592, 1504, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J*=1.8 Hz, 1H, $H_{2''}$), 7.59 (m, 1H, $H_{6''}$), 7.27 (m, 1H, $H_{4''}$), 7.22 (m, 1H, $H_{5''}$), 7.04 (s, 1H, H_5), 6.48 (s, 2H, $H_{2'}$, $H_{6'}$), 6.35 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.48 (t, *J*=7.5 Hz, 1H, H_4), 4.19 (d, *J*=5.1 Hz, 1H, H_1), 3.97 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.36 (dd, *J*=9.3, 5.1 Hz, 1H, H_2), 2.69 (m, 1H, H_3), 2.31 (d, *J*=7.5 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (C_{13}), 153.4 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.4 ($C_{1''}$), 140.1 ($C_{1'}$), 136.7 ($C_{4'}$), 132.2 (C_9), 131.1 (C_{10}), 130.1 ($C_{5''}$), 127.6 ($C_{4''}$), 122.6 ($C_{3''}$), 122.5 ($C_{2''}$), 117.9 ($C_{6''}$), 109.3 (C_8), 105.5 ($C_{2'}$, $C_{6'}$), 105.3 (C_5), 101.1 (OCH_2O), 70.1 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 50.2 (C_{11}), 48.9 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): *m*/*z*=568, 570 $[M+H]^+$, 590, 592 $[M+Na]^+$.

4.5.4. (1*R*,2*S*,3*R*,4*S*)-*N*-(3-Bromophenyl)-epipicropodophyllin-*cis*-γ-lactam 8b.



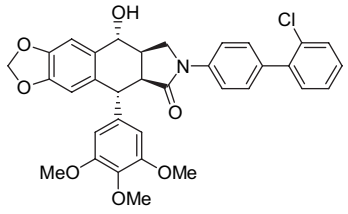
To a mixture of **3b** (196 mg, 0.346 mmol) in anhydrous THF (5 mL) at −78 °C was added 1 M L-Selectride solution in THF (415 μL, 0.415 mmol) dropwise. The reaction mixture was removed from the cold bath and was stirred for 2 h. A saturated solution of NH_4Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) to yield 157 mg (80%) of **8b** as a white solid.

Compound **8b**: 157 mg; yield: 80%; mp: 149–153 °C; $[\alpha]_D^{20}$ +46 (*c* 2.30, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3011, 2980–2900, 1694, 1591, 1505, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J*=1.7 Hz, 1H, $H_{2''}$), 7.53 (m, 1H, $H_{6''}$), 7.23 (m, 1H, $H_{4''}$), 7.13 (m, 1H, $H_{5''}$), 7.08 (s, 1H, H_5), 6.65 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.95 (m, 2H, OCH_2O), 4.89 (t, *J*=4.5 Hz, 1H, H_4), 4.55 (d, *J*=2.0 Hz, 1H, H_1), 3.82 (s, 3H, $OMe_{(4')}$), 3.80 (m, 1H, H_{11a}), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.67 (m, 1H, H_{11b}), 3.61 (dd, *J*=10.7, 2.0 Hz, 1H, H_2), 3.20 (m, 1H, H_3), 2.16 (d, *J*=4.5 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 153.3 ($C_{3'}$, $C_{5'}$), 147.2 (C_6, C_7), 140.3 ($C_{1'}$), 138.1 ($C_{1''}$), 136.7 ($C_{4'}$), 131.4 (C_9), 130.0 ($C_{5''}$), 129.8 (C_{10}), 127.5 ($C_{4''}$), 122.6 ($C_{2''}$), 122.5 ($C_{3''}$), 118.1 ($C_{6''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.7 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 48.7 (C_2), 48.1 (C_{11}), 45.7 (C_1), 35.4 (C_3); MS (ES+): *m*/*z*=568, 570 $[M+H]^+$, 590, 592 $[M+Na]^+$.

4.6. Representative experimental procedure for Suzuki cross-coupling

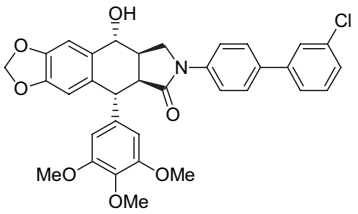
To a 10 mL Quest 210 Teflon reaction vessel was added a solution of *N*-4-bromophenyl γ-lactam lignan **7b** (30 mg, 0.053 mM) and $Pd(OAc)_2$ (1.2 mg, 10 mol %) in DMF (3 mL) followed by substituted phenylboronic acid (0.132 mM, 2.5 equiv) and CsF (Table 2). The reaction mixture was stirred at 85 °C, filtered, and poured into water. After extraction with EtOAc (3×7 mL), the combined organic phases were washed with brine and evaporated under reduced pressure. The residue was purified on silica pad with cyclohexane then cyclohexane/EtOAc gradient [9/1 to 2/8] to give the desired biaryl product.

4.6.1. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′-Chlorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4aa.



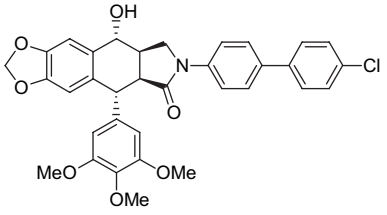
White solid; 18.8 mg; yield: 59%; mp: 151–155 °C; $[\alpha]_D^{20}$ −72 (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3019, 2960–2900, 1696, 1593, 1505, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.45 (m, 3H, $H_{3''}$, $H_{5''}$, $H_{6'''}$), 7.24 (m, 3H, $H_{3'''}$, $H_{4'''}$, $H_{5'''}$), 7.04 (s, 1H, H_5), 6.50 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.93 (m, 2H, OCH_2O), 4.51 (dd, *J*=8.0, 7.1 Hz, 1H, H_4), 4.25 (d, *J*=4.7 Hz, 1H, H_1), 4.02 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.38 (dd, *J*=9.2, 4.7 Hz, 1H, H_2), 2.73 (m, 1H, H_3), 2.08 (d, *J*=7.1 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.4 (C_7), 146.8 (C_6), 139.7 ($C_{1'}$), 138.5 ($C_{4''}$), 137.6 ($C_{1'''}$), 136.6 ($C_{4'}$), 135.8 ($C_{1''}$), 132.5 ($C_{2'''}$), 132.1 (C_9), 131.3 (C_{10}, $C_{3'''}$), 130.0 ($C_{3''}$, $C_{5''}$, $C_{6'''}$), 128.6 ($C_{4'''}$), 126.9 ($C_{5'''}$), 119.1 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.5 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 70.5 (C_4), 60.9 (OMe), 56.1 ($OMe_{(3',5')}$), 50.4 (C_{11}), 49.0 (C_2), 44.3 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}NO_7Cl$ 600.1789 and 602.1779, found 600.1774 and 602.1768.

4.6.2. (1*R*,2*S*,3*R*,4*R*)-*N*-(3′-Chlorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ab.



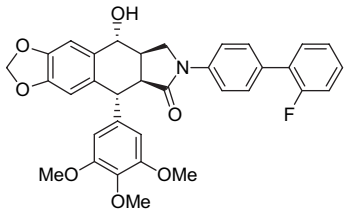
White solid; 21.3 mg; yield: 67%; $[\alpha]_D^{20}$ −90 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3600–3300, 3020, 2970–2900, 1697, 1593, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J*=8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.53 (m, 3H, $H_{3''}$, $H_{5''}$, $H_{2'''}$), 7.36 (m, 3H, $H_{4'''}$, $H_{5'''}$, $H_{6'''}$), 7.05 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.37 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.49 (t, *J*=7.0 Hz, 1H, H_4), 4.22 (d, *J*=4.8 Hz, 1H, H_1), 4.01 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.37 (dd, *J*=9.2, 4.8 Hz, 1H, H_2), 2.69 (m, 1H, H_3), 2.42 (d, *J*=7.0 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 142.1 ($C_{3'''}$), 140.3 ($C_{1'}$), 138.9 ($C_{1''}$), 136.7 ($C_{4'}$), 135.9 ($C_{1'''}$), 134.7 ($C_{4''}$), 132.3 (C_9), 131.1 (C_{10}), 130.0 ($C_{5'''}$), 127.4 ($C_{3''}$, $C_{5''}$), 127.2 ($C_{4'''}$), 126.9 ($C_{2'''}$), 125.0 ($C_{6'''}$), 119.9 ($C_{2''}$, $C_{6''}$), 109.3 (C_8), 105.6 ($C_{2'}$, $C_{6'}$), 105.3 (C_5), 101.1 (OCH_2O), 70.1 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.3 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}NO_7Cl$ 600.1789 and 602.1779, found 600.1787 and 602.1752.

4.6.3. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Chlorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ac.



White solid; 21.3 mg; yield: 67%; mp: 125–130 °C; $[\alpha]_D^{20}$ −29 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) 3500–3200, 3022, 3014, 2975–2900, 1702, 1592, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.55 (d, *J*=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.49 (d, *J*=8.6 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 7.39 (d, 2H, *J*=8.6 Hz, $H_{2'''}$, $H_{6'''}$), 7.04 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.94 (m, 2H, OCH_2O), 4.56 (t, *J*=7.4 Hz, 1H, H_4), 4.26 (d, *J*=4.6 Hz, 1H, H_1), 4.03 (m, 2H, H_{11}), 3.86 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.40 (dd, *J*=9.4, 4.6 Hz, 1H, H_2), 2.74 (m, 1H, H_3), 2.06 (d, *J*=7.4 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (C_{13}), 153.7 ($C_{3'}$, $C_{5'}$), 147.1 (C_7), 146.7 (C_6), 140.2 ($C_{1'}$), 138.9 ($C_{1'''}$), 138.7 ($C_{4''}$), 136.8 ($C_{4'}$, $C_{1''}$), 134.6 ($C_{4'''}$), 132.3 (C_9), 131.2 (C_{10}), 128.8 ($C_{3'''}$, $C_{5'''}$), 127.7 ($C_{3''}$, $C_{5''}$, $C_{2'''}$, $C_{6'''}$), 120.0 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.5 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 70.4 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.4 (C_{11}), 49.0 (C_2), 44.3 (C_1), 38.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}NO_7Cl$ 600.1789 and 602.1779, found 600.1774 and 602.1768.

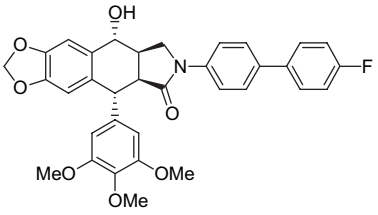
4.6.4. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′-Fluorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ad.



White solid; 25.4 mg; yield: 82%; mp: 82 °C; $[\alpha]_D^{20}$ −44 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) 3550–3300, 3031, 3011, 2974–2900, 1693, 1591, 1504, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.53 (d, *J*=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.40 (dt, *J*=7.8, 1.6 Hz, 1H, $H_{6'''}$), 7.29 (m, 1H, $H_{4'''}$), 7.20 (m, 1H, $H_{5'''}$), 7.13 (m, 1H, $H_{3'''}$),

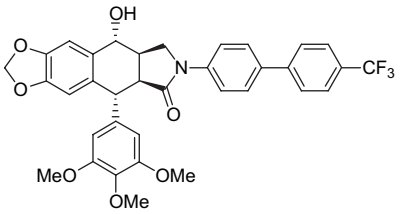
7.05 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.38 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.50 (dd, J=7.0, 4.1 Hz, 1H, H_4), 4.24 (d, J=4.8 Hz, 1H, H_1), 4.01 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.37 (dd, J=9.2, 4.8 Hz, 1H, H_2), 2.71 (m, 1H, H_3), 2.35 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (C_{13}), 158.3 (d, J=247.4 Hz, $C_{2''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_6, C_7), 140.3 ($C_{1'}$), 138.5 ($C_{1''}$), 136.6 ($C_{4'}$), 132.3 (C_9), 131.0 (C_{10}), 130.5 ($C_{4''}$, $C_{6'''}$), 129.3 ($C_{3''}$, $C_{5''}$), 129.1 (d, J=8.1 Hz, $C_{4'''}$), 128.5 (d, J=13.3 Hz, $C_{1'''}$), 124.4 ($C_{5'''}$), 119.7 ($C_{2''}$, $C_{6''}$), 116.3 (d, J=22.6 Hz, $C_{3'''}$), 109.3 (C_8), 105.6 ($C_{2'}$, $C_{6'}$, C_5), 101.1 (OCH_2O), 70.1 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.3 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): m/z=584 $[M+H]^+$.

4.6.5. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Fluorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ae.



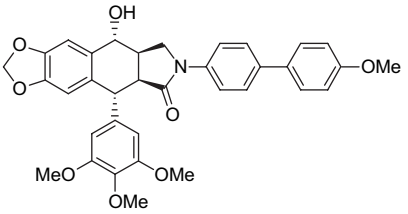
White solid; 28.4 mg; yield: 92%; mp: 209–212 °C; $[\alpha]_D^{20}$ −77 (c 0.35, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3005, 2960–2900, 1695, 1593, 1500, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.52 (d, J=8.7 Hz, 2H, $H_{2'''}$, $H_{6'''}$), 7.50 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.11 (t, 2H, J=8.7 Hz, $H_{3'''}$, $H_{5'''}$), 7.05 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.93 (m, 2H, OCH_2O), 4.53 (t, J=7.7 Hz, 1H, H_4), 4.25 (d, J=4.8 Hz, 1H, H_1), 4.04 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.38 (dd, J=9.2, 4.8 Hz, 1H, H_2), 2.72 (m, 1H, H_3), 2.17 (d, J=7.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 162.5 (d, J=226.4 Hz, $C_{4'''}$), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.3 ($C_{1'}$), 138.4 ($C_{1''}$), 136.7 ($C_{4'}$), 136.5 ($C_{4''}$, $C_{1'''}$), 132.2 (C_9), 131.2 (C_{10}), 128.4 (d, J=7.9 Hz, $C_{2'''}$, $C_{6'''}$), 127.3 ($C_{3''}$, $C_{5''}$), 120.0 ($C_{2''}$, $C_{6''}$), 115.6 (d, J=21.3 Hz, $C_{3'''}$, $C_{5'''}$), 109.4 (C_8), 105.5 ($C_{2'}$, $C_{6'}$), 105.4 (C_5), 101.1 (OCH_2O), 70.4 (C_4), 60.9 (OMe), 56.1 ($OMe_{(3',5')}$), 50.4 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}FNO_7$ 584.2085, found 584.2075.

4.6.6. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Trifluoromethylbiphenyl)-picropodophyllin-*cis*-γ-lactam 4af.



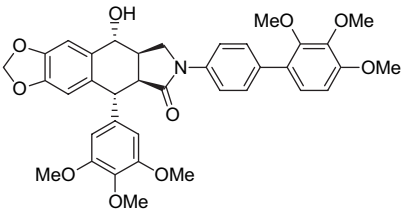
White gum; 28.5 mg; yield: 85%; $[\alpha]_D^{20}$ −26 (c 0.13, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3029, 3012, 2975–2900, 1697, 1592, 1504, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.67 (m, 4H, $H_{2'''}$, $H_{3'''}$, $H_{5'''}$, $H_{6'''}$), 7.60 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.05 (s, 1H, H_5), 6.50 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.93 (m, 2H, OCH_2O), 4.55 (d, J=8.0 Hz, 1H, H_4), 4.27 (d, J=4.8 Hz, 1H, H_1), 4.05 (m, 2H, H_{11}), 3.86 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.41 (dd, J=9.2, 4.8 Hz, 1H, H_2), 2.75 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.3 (C_7), 146.8 (C_6), 143.5 ($C_{1'''}$), 140.2 ($C_{1'}$), 139.4 ($C_{1''}$), 136.6 ($C_{4'}$), 135.9 ($C_{4''}$), 132.1 (C_9), 131.1 (C_{10}), 130.1 (m, $C_{4'''}$), 127.7 ($C_{3''}$, $C_{5''}$), 127.1 ($C_{2'''}$, $C_{6'''}$), 125.7 (m, $C_{3'''}$, $C_{5'''}$), 122.4 (q, J=251 Hz, CF_3), 120.0 ($C_{2''}$, $C_{6''}$), 109.4 (C_8), 105.5 ($C_{2'}$, $C_{6'}$, C_5), 101.1 (OCH_2O), 70.4 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 50.3 (C_{11}), 49.0 (C_2), 44.3 (C_1), 38.9 (C_3); MS (ES+): m/z=558 $[M+H]^+$.

4.6.7. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Methoxybiphenyl)-picropodophyllin-*cis*-γ-lactam 4ah.



White solid; 30.0 mg, yield: 95%; mp: 227 °C; $[\alpha]_D^{20}$ −91 (c 0.42, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3021, 3008, 2960, 1697, 1592, 1502, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J=8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.51 (d, J=8.6 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.49 (d, J=8.6 Hz, 2H, $H_{2'''}$, $H_{6'''}$), 7.06 (s, 1H, H_5), 6.95 (d, J=8.6 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.36 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.48 (t, J=7.1 Hz, 1H, H_4), 4.21 (d, J=4.9 Hz, 1H, H_1), 4.00 (m, 2H, H_{11}), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.36 (dd, J=9.0, 4.9 Hz, 1H, H_2), 2.68 (m, 1H, H_3), 2.54 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 159.1 ($C_{4'''}$), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.4 ($C_{1'}$), 137.8 ($C_{1''}$), 137.2 ($C_{4''}$), 136.7 ($C_{4'}$), 132.8 ($C_{1'''}$), 132.3 (C_9), 131.2 (C_{10}), 129.9 ($C_{2'''}$, $C_{6'''}$), 127.0 ($C_{3''}$, $C_{5''}$), 120.0 ($C_{2''}$, $C_{6''}$), 114.2 ($C_{3'''}$, $C_{5'''}$), 109.4 (C_8), 105.6 ($C_{2'}$, $C_{6'}$), 105.4 (C_5), 101.1 (OCH_2O), 70.2 (C_4), 60.9 (OMe), 56.1 ($OMe_{(3',5')}$), 55.3 (OMe), 50.4 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{35}H_{34}NO_8$ 596.2284, found 596.2272.

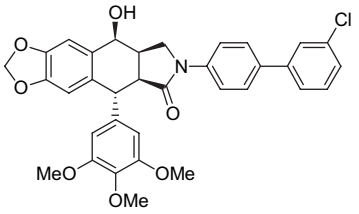
4.6.8. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′,3′,4′-Trimethoxybiphenyl)-picropodophyllin-*cis*-γ-lactam 4ai.



Off-white solid; 22.9 mg; yield: 66%; mp: 148–153 °C; $[\alpha]_D^{20}$ −56 (c 0.17, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 2970–2900, 1693, 1594, 1504, 1488 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.51 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.04 (s, 1H, H_5), 7.00 (d, J=8.6 Hz, 1H, $H_{6'''}$), 6.72 (d, J=8.6 Hz, 1H, $H_{5'''}$), 6.50 (s, 2H, $H_{2'}$, $H_{6'}$), 6.41 (s, 1H, H_8), 5.93 (m, 2H, OCH2O), 4.54 (t,

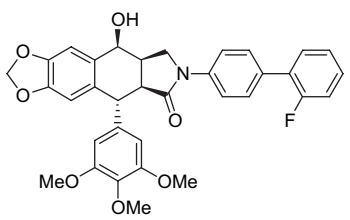
J=8.5 Hz, 1H, H_4), 4.27 (d, J=4.7 Hz, 1H, H_1), 4.03 (m, 2H, H_{11}), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.83 (s, 6H, OMe), 3.65 (s, 3H, OMe), 3.38 (dd, J=9.2, 4.7 Hz, 1H, H_2), 2.73 (m, 1H, H_3), 2.17 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 153.2 ($C_{4''}$), 151.5 ($C_{2''}$), 147.2 (C_7), 146.8 (C_6), 142.1 ($C_{3''}$), 140.4 ($C_{1'}$), 137.8 ($C_{1''}$), 136.8 ($C_{4'}$), 134.8 ($C_{4''}$), 132.2 (C_9), 131.2 (C_{10}), 129.5 ($C_{3''}$, $C_{5''}$), 128.0 ($C_{1''}$), 124.6 ($C_{6''}$), 119.4 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 107.5 ($C_{5''}$), 105.5 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (O–CH_2–O), 70.4 (C_4), 60.9 (OMe), 56.2 (OMe), 50.4 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{37}H_{38}NO_{10}$ 656.2496, found 656.2493.

4.6.9. (1*R*,2*S*,3*R*,4*S*)-*N*-(3′-Chlorobiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4ba.



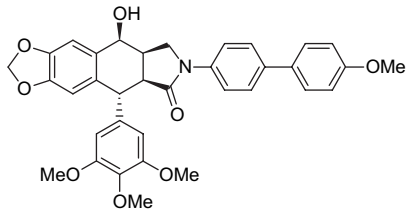
White solid; 22.3 mg; yield: 70%; mp: 168–173 °C; $[\alpha]_D^{20}$ +35 (c 0.48, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3010, 2970–2900, 1690, 1591, 1505, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.49 (m, 3H, $H_{3''}$, $H_{5''}$, $H_{2'''}$), 7.33 (m, 3H, $H_{4'''}$, $H_{5'''}$, $H_{6'''}$), 7.10 (s, 1H, H_5), 6.67 (s, 1H, H_8), 6.35 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91 (t, J=4.1 Hz, 1H, H_4), 4.59 (d, 1H, J=2.4 Hz, H_1), 3.84 (m, 1H, H_{11a}), 3.82 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.63 (dd, J=10.7, 2.4 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.44 (d, J=4.1 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_7, C_6), 142.2 ($C_{3'''}$), 138.8 ($C_{1''}$), 138.2 ($C_{1'}$), 136.6 ($C_{4'}$), 135.9 ($C_{1'''}$), 134.7 ($C_{4''}$), 131.7 (C_9), 130.0 ($C_{5'''}$), 129.8 (C_{10}), 127.4 ($C_{3''}$, $C_{5''}$), 127.3 ($C_{4'''}$), 127.2 ($C_{2'''}$), 125.4 ($C_{6'''}$), 121.4 ($C_{2''}$, $C_{6''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.6 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 48.8 (C_2), 48.2 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=600, 602 $[M+H]^+$, 622, 624 $[M+Na]^+$.

4.6.10. (1*R*,2*S*,3*R*,4*S*)-*N*-(2′-Fluorobiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4bb.



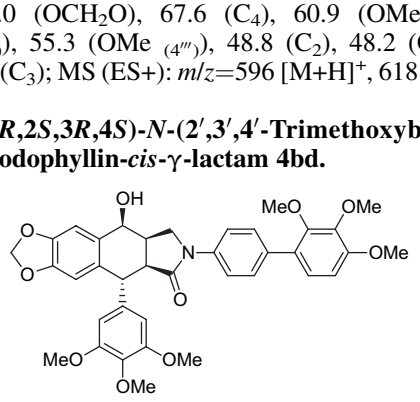
White solid; 24.2 mg; yield: 79%; mp: 146–148 °C; $[\alpha]_D^{20}$ +49 (c 0.61, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3025, 3018, 2960–2900, 1686, 1590, 1506, 1485 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J=8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.49 (dd, J=8.8, 1.3 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.37 (dt, J=7.7, 1.8 Hz, 1H, $H_{6'''}$), 7.28 (m, 1H, $H_{4'''}$), 7.17 (dt, J=7.7, 1.2 Hz, 1H, $H_{5'''}$), 7.10 (m, 2H, H_5, $H_{3'''}$), 6.68 (s, 1H, H_8), 6.36 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91 (t, J=4.5 Hz, 1H, H_4), 4.59 (d, J=2.3 Hz, 1H, H_1), 3.84 (m, 1H, H_{11a}), 3.82 (s, 3H, $OMe_{(4')}$), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.64 (dd, J=10.7, 2.3 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.36 (d, J=4.5 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (C_{13}), 159.7 (d, J=246.1 Hz, $C_{2'''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.2 (C_6, C_7), 138.5 ($C_{1''}$), 138.2 ($C_{1'}$), 136.6 ($C_{4'}$), 131.9 (C_9), 131.6 ($C_{6'''}$), 130.5 ($C_{4''}$), 129.7 (C_{10}), 129.3 ($C_{3''}$, $C_{5''}$), 128.9 (d, J=8.2 Hz, $C_{4'''}$), 128.3 (d, J=13.3 Hz, $C_{1'''}$), 124.4 (d, J=3.5 Hz, $C_{5'''}$), 119.7 ($C_{2''}$, $C_{6''}$), 116.1 (d, J=22.6 Hz, $C_{3''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.7 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 48.8 (C_2), 48.2 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=584 $[M+H]^+$, 606 $[M+Na]^+$.

4.6.11. (1*R*,2*S*,3*R*,4*S*)-*N*-(4′-Methoxybiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4bc.



White solid; 25.6 mg; yield: 81%; mp: 148–150 °C; $[\alpha]_D^{20}$ +43 (c 0.48, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3008, 2960–2900, 1688, 1590, 1502, 1484 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.48 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.43 (d, J=8.8 Hz, 2H, $H_{2'''}$, $H_{6'''}$), 7.10 (s, 1H, H_5), 6.94 (d, J=8.8 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 6.69 (s, 1H, H_8), 6.36 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91 (t, J=4.3 Hz, 1H, H_4), 4.59 (d, J=2.2 Hz, 1H, H_1), 3.84 (m, 1H, H_{11a}), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.63 (dd, J=10.7, 2.2 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.29 (d, J=4.3 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3 (C_{13}), 159.1 ($C_{4'''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_6, C_7), 138.2 ($C_{1'}$), 137.7 ($C_{1''}$), 137.1 ($C_{4''}$), 136.7 ($C_{4'}$), 132.9 ($C_{1'''}$), 131.6 (C_9), 129.8 (C_{10}), 127.9 ($C_{2'''}$, $C_{6'''}$), 126.9 ($C_{3''}$, $C_{5''}$), 120.2 ($C_{2''}$, $C_{6''}$), 114.2 ($C_{3'''}$, $C_{5'''}$), 110.0 (C_8), 105.6 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.6 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 55.3 ($OMe_{(4''')}$), 48.8 (C_2), 48.2 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=596 $[M+H]^+$, 618 $[M+Na]^+$.

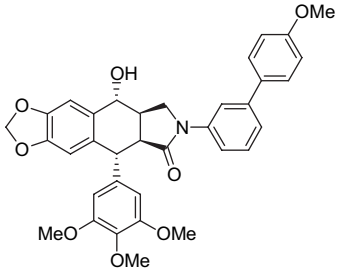
4.6.12. (1*R*,2*S*,3*R*,4*S*)-*N*-(2′,3′,4′-Trimethoxybiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4bd.



Off-white solid; 23.3 mg; yield: 67%; mp: 136–139 °C; $[\alpha]_D^{20}$ +42 (c 0.59, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3018, 2980–2900, 1690, 1591, 1504, 1485 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J=8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.43 (d, J=8.8 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.12 (s, 1H, H_5), 6.97 (d, J=8.6 Hz, 2H, $H_{6'''}$), 6.70 (d, J=8.6 Hz, 2H, $H_{5'''}$), 6.69 (s, 1H, H_8), 6.35 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91

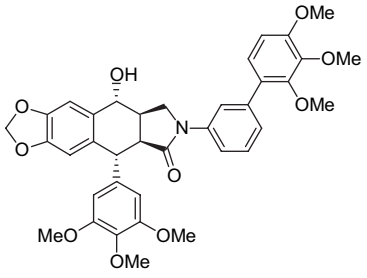
(t, J=4.5 Hz, 1H, H_4), 4.59 (d, J=2.1 Hz, 1H, H_1), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.86 (m, 1H, H_{11a}), 3.81 (s, 3H, OMe), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.75 (m, 1H, H_{11b}), 3.65 (s, 3H, OMe), 3.62 (m, 1H, H_2), 3.22 (m, 1H, H_3), 2.55 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$), 153.1 ($C_{4'''}$), 151.3 ($C_{2'''}$), 147.2 (C_7), 147.0 (C_6), 142.5 ($C_{3'''}$), 138.3 ($C_{1'}$), 137.7 ($C_{1''}$), 136.6 ($C_{4'}$), 134.5 ($C_{4''}$), 131.8 (C_9), 129.7 (C_{10}), 129.4 ($C_{3''}$, $C_{5''}$), 127.8 ($C_{1'''}$), 124.6 ($C_{6'''}$), 119.6 ($C_{2''}$, $C_{6''}$), 109.9 (C_8), 107.5 ($C_{5'''}$), 105.7 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.5 (C_4), 61.0 (OMe), 60.9 (OMe), 56.2 (OMe), 56.0 (OMe), 48.9 (C_2), 48.2 (C_{11}), 45.9 (C_1), 35.5 (C_3); MS (ES+): m/z=656 $[M+H]^+$, 678 $[M+Na]^+$.

4.6.13. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Methoxybiphen-2-yl)-picropodophyllin-*cis*-γ-lactam 4ca.



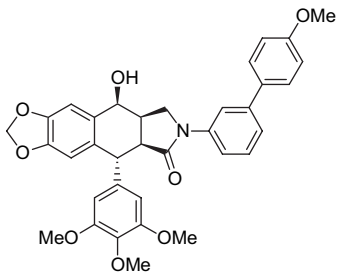
White solid; 22.7 mg; yield: 72%; mp: 220–223 °C; $[\alpha]_D^{20}$ −73 (c 0.34, $CHCl_3$); IR ($CHCl_3$) 3500–3200, 2980–2900, 1697, 1591, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H, $H_{2''}$), 7.49 (m, 3H, $H_{6''}$, $H_{2'''}$, $H_{6'''}$),7.35 (m, 2H, $H_{4''}$, $H_{5''}$), 7.04 (s, 1H, H_5), 6.94 (d, J=8.4 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.37 (s, 1H, H_8), 5.91 (m, 2H, OCH_2O), 4.50 (t, J=7.7 Hz, 1H, H_4), 4.23 (d, J=5.0 Hz, 1H, H_1), 4.03 (m, 2H, H_{11}), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=9.2, 5.0 Hz, 1H, H_2), 2.68 (m, 1H, H_3), 2.26 (d, J=7.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 159.3 ($C_{4'''}$), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.7 (C_6), 141.7 ($C_{3''}$), 140.5 ($C_{1'}$), 139.6 ($C_{1''}$), 136.7 ($C_{4'}$), 133.2 ($C_{1'''}$), 132.3 (C_9), 131.1 (C_{10}), 129.2 ($C_{5''}$), 128.3 ($C_{2'''}$, $C_{6'''}$), 123.1 ($C_{4''}$), 118.3 ($C_{2''}$), 118.0 ($C_{6''}$), 114.2 ($C_{3'''}$, $C_{5'''}$), 109.4 (C_8), 105.6 ($C_{2'}$, $C_{6'}$), 105.4 (C_5), 101.1 (OCH_2O), 70.2 (C_4), 60.8 (OMe), 56.2 ($OMe_{(3',5')}$), 55.3 (OMe), 50.5 (C_{11}), 49.1 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): m/z=618 $[M+Na]^+$.

4.6.14. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′,3′,4′-Trimethoxybiphen-2-yl)-picropodophyllin-*cis*-γ-lactam 4cb.



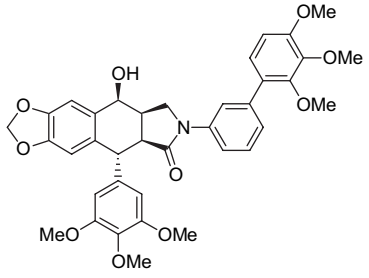
White solid; 10 mg; yield: 29%; mp: 203–208 °C; $[\alpha]_D^{20}$ −69 (c 0.33, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3009, 2980–2900, 1695, 1592, 1504, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H, $H_{2''}$), 7.66 (d, J=7.8 Hz, 1H, $H_{6''}$), 7.37 (t, J=7.8 Hz, 1H, $H_{5''}$), 7.28 (m, 1H, $H_{4''}$), 7.03 (s, 1H, H_5), 7.02 (d, J=9.4 Hz, 1H, $H_{6'''}$), 6.71 (d, J=9.4 Hz, 1H, $H_{5'''}$), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.39 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.52 (d, J=8.0 Hz, 1H, H_4), 4.26 (d, J=4.8 Hz, 1H, H_1), 4.01 (m, 2H, H_{11}), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.84 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.67 (s, 3H, OMe), 3.36 (dd, J=9.0, 4.8 Hz, 1H, H_2), 2.71 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (C_{13}), 153.4 ($C_{3'}$, $C_{5'}$), 153.3 ($C_{4'''}$), 151.3 ($C_{2'''}$), 147.2 (C_7), 146.8 (C_6), 142.5 ($C_{3''}$), 140.5 ($C_{1'}$), 139.0 ($C_{1''}$, $C_{3''}$), 136.7 ($C_{4'}$), 132.2 (C_9), 131.2 (C_{10}), 128.5 ($C_{5''}$), 128.1 ($C_{1'''}$), 125.6 ($C_{4''}$), 124.9 ($C_{6'''}$), 120.5 ($C_{2''}$), 118.4 ($C_{6''}$), 109.4 (C_8), 107.5 ($C_{5'''}$), 105.7 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 70.3 (C_4), 61.1 (OMe), 61.0 (OMe), 60.9 (OMe), 56.2 ($OMe_{(3',5')}$), 56.1 (OMe), 50.6 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): m/z=656 $[M+H]^+$, 678 $[M+Na]^+$.

4.6.15. (1*R*,2*S*,3*R*,4*S*)-*N*-(4′-Methoxybiphen-2-yl)-epipicropodophyllin-*cis*-γ-lactam 4da.



White solid; 23.7 mg; yield: 75%; mp: 147–152 °C; $[\alpha]_D^{20}$ +28 (c 0.49, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3010, 2960–2900, 1689, 1590, 1504, 1484 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H, $H_{2''}$), 7.46 (m, 3H, $H_{6''}$, $H_{2'''}$, $H_{6'''}$),7.31 (m, 2H, $H_{4''}$, $H_{5''}$), 7.11 (s, 1H, H_5), 6.93 (d, 2H, J=8.4 Hz, $H_{3'''}$, $H_{5'''}$), 6.68 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.93 (m, 2H, OCH_2O), 4.90 (m, 1H, H_4), 4.59 (d, J=2.1 Hz, 1H, H_1), 3.85 (m, 1H, H_{11a}), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.74 (m, 1H, H_{11b}), 3.62 (dd, 1H, J=10.7, 2.1 Hz, H_2), 3.21 (m, 1H, H_3), 2.54 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 159.3 ($C_{4'''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 147.0 (C_6), 141.5 ($C_{3'''}$), 139.4 ($C_{1'}$), 138.3 ($C_{1''}$), 136.5 ($C_{4'}$), 133.2 ($C_{1'''}$), 131.7 (C_9), 129.7 (C_{10}), 129.1 ($C_{5''}$), 128.3 ($C_{2'''}$, $C_{6'''}$), 123.1 ($C_{4''}$), 118.5 ($C_{2''}$), 118.2 ($C_{6''}$), 114.1 ($C_{3'''}$, $C_{5'''}$), 109.9 (C_8), 105.7 (C_5), 104.6 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.5 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 55.3 ($OMe_{(4''')}$), 49.0 (C_2), 48.4 (C_{11}), 45.9 (C_1), 35.5 (C_3); MS (ES+): m/z=596 $[M+H]^+$, 618 $[M+Na]^+$.

4.6.16. (1*R*,2*S*,3*R*,4*S*)-*N*-(2′,3′,4′-Trimethoxybiphen-2-yl)-epipicropodophyllin-*cis*-γ-lactam 4db.



Off-white solid; 20.5 mg; yield: 59%; mp: 147–150 °C; $[\alpha]_D^{20}$ +24 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3023, 3007, 2974–2900, 1689, 1590, 1504, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H, $H_{2''}$), 7.54 (d, J=8.0 Hz, 1H, $H_{6''}$), 7.32 (t, J=8.0 Hz, 1H, $H_{5''}$), 7.24 (m, 1H, $H_{4''}$), 7.01 (s, 1H, H_5), 6.99 (d, J=8.6 Hz, 1H, $H_{6'''}$), 6.70 (d, J=8.6 Hz, 1H, $H_{5'''}$), 6.67 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.93 (m, 2H, OCH_2O), 4.90 (t, J=4.1 Hz, 1H, H_4), 4.58 (d, J=2.0 Hz, 1H, H_1), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.84 (m, 1H, H_{11a}), 3.81 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.67 (s, 3H, OMe), 3.62 (dd, J=10.5, 2.0 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.57 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$, $C_{4'''}$), 151.3 ($C_{2'''}$), 147.2 (C_7), 147.0 (C_6), 142.4 ($C_{3'''}$), 138.9 ($C_{1'}$), 138.8 ($C_{1''}$), 138.3 ($C_{3''}$), 136.6 ($C_{4'}$), 131.8 (C_9), 129.7 (C_{10}), 128.4 ($C_{5''}$), 128.1 ($C_{1'''}$), 125.6 ($C_{4''}$), 124.9 ($C_{6'''}$), 120.8 ($C_{2''}$), 118.6 ($C_{6''}$), 110.0 (C_8), 107.4 ($C_{5'''}$), 105.6 (C_5), 104.6 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.5 (C_4), 61.1 (OMe), 61.0 (OMe), 60.9 (OMe), 56.2 ($OMe_{(3',5')}$), 56.0 (OMe), 48.9 (C_2), 48.4 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=656 $[M+H]^+$, 678 $[M+Na]^+$.

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References and notes

1. Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284–289.
2. Shang, S.; Tan, D. S. *Curr. Opin. Chem. Biol.* **2005**, *9*, 248–258.
3. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S., et al. *J. Med. Chem.* **1988**, *31*, 2235–2246.
4. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.
5. Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954–9967.
6. Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968–9976.
7. Müller, G. *Drug Discov. Today* **2003**, *8*, 681–691.
8. Patchett, A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289–298.
9. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
10. Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183–205.
11. Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43–74.
12. Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96.
13. Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967–8976.
14. Girnita, A.; Girnita, L.; del Prete, F.; Bartolazzi, A.; Larsson, O.; Axelson, M. *Cancer Res.* **2004**, *64*, 236–242.
15. Vasilcanu, D.; Girnita, A.; Girnita, L.; Vasilcanu, R.; Axelson, M.; Larsson, O. *Oncogene* **2004**, *23*, 7854–7862.
16. Menu, E.; Jernberg-Wiklund, H.; Stromberg, T.; De Raeve, H.; Girnita, L.; Larsson, O.; Axelson, M.; Asosingh, K.; Nilsson, K.; Van Camp, B.; Vanderkerken, K. *Blood* **2006**, *107*, 655–660.
17. Stromberg, T.; Ekman, S.; Girnita, L.; Dimberg, L. Y.; Larsson, O.; Axelson, M.; Lennartsson, J.; Hellman, U.; Carlson, K.; Osterborg, A.; Vanderkerken, K.; Nilsson, K.; Jernberg-Wiklund, H. *Blood* **2006**, *107*, 669–678.
18. Axelson, M.; Larsson, O. PCT WO 2004093781 (04.11.2004).
19. Axelson, M.; Larsson, O. PCT WO 2004054996 (01.07.2004).
20. Axelson, M.; Larsson, O. PCT WO 02102805 (27.12.2002).
21. Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.
22. Kadow, J. F.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1989**, *30*, 3299–3302.
23. Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456–9459.
24. Dorbec, M.; Florent, J.-C.; Monneret, C.; Rager, M.-N.; Bertounesque, E. *Synlett* **2006**, 591–594.
25. Lopez-Perez, J.; del Olmo, E.; de Pascual-Teresa, B.; Merino, M.; Martin, S.; San Feliciano, A. *Tetrahedron* **1995**, *51*, 6343–6348.
26. Lopez-Perez, J.; del Olmo, E.; de Pascual-Teresa, B.; Merino, M.; San Feliciano, A. *Tetrahedron* **1996**, *52*, 4903–4910.
27. Madrigal, B.; Puebla, P.; Ramos, A.; Pelaez, R.; Gravalos, D.; Caballero, E.; Medarde, M. *Bioorg. Med. Chem.* **2002**, *10*, 303–312.
28. Pohmakotr, M.; Komutkul, T.; Tuchinda, P.; Prabpai, S.; Kongsaeree, P.; Reutrakul, V. *Tetrahedron* **2005**, *61*, 5311–5321.
29. Höfert, P. H.; Matusch, R. *Helv. Chim. Acta* **1994**, *77*, 771–777.
30. Wagh, A. P.; Kulkarni, A. B. *Indian J. Chem.* **1974**, *12*, 923–925.
31. López-Pérez, J. L.; Abad, A.; del Olmo, E.; San Feliciano, A. *Tetrahedron* **2006**, *62*, 2370–2379.
32. Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319–1322.
33. Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891–3894.
34. Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484–493.
35. Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383–387.
36. Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, *2005*, 633–639.
37. Gandelman, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2393–2397.
38. Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045–9048.
39. Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052–9055.
40. Li, K.; Phua, P. H.; Hii, K. K. M. *Tetrahedron* **2005**, *61*, 6237–6242.
41. Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 720–722.
42. Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114.
43. Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1–7.
44. Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149–11176.
45. Li, Z.; Zhang, J.; Li, C.-J. *Tetrahedron Lett.* **2003**, *44*, 153–156.
46. Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171–4174.
47. Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704.
48. Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627–1638.

49. Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813–819.
50. Yadav, J. S.; Reddy, B. V.; Padmavani, B. *Synthesis* **2004**, 405–408.
51. Loh, T. P.; Pei, J.; Cao, G. Q. *Chem. Commun.* **1996**, 1819–1820.
52. Loh, T. P.; Pei, J.; Koh, S. V.; Cao, G. Q.; Li, X. R. *Tetrahedron Lett.* **1997**, *38*, 3465–3468.
53. Loh, T. P.; Chua, G. L.; Vittal, J. J.; Wong, M. W. *Chem. Commun.* **1998**, 861–871.
54. Loh, T. P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315–2316.
55. Loh, T. P.; Wei, L. L. *Tetrahedron Lett.* **1998**, *39*, 323–326.
56. Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975–976.
57. Loh, T. P.; Wei, L. L. *Tetrahedron* **1998**, *54*, 7615–7624.
58. For a review on scavenger resins, see: Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679.
59. The aza-Michael adducts **6n**–**p** are given in Figure 2.
60. Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
61. Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034–5037.
62. Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–168.
63. Tsvetkov, A. V.; Latyshev, G. V.; Lukashev, N. V.; Beletskaya, I. P. *Tetrahedron Lett.* **2002**, *43*, 7267–7270.
64. Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199–8202.
65. Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170–7173.
66. Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885–3890.
67. Lepine, R.; Zhu, J. *Org. Lett.* **2005**, *7*, 2981–2984.
68. Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.
69. Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75–78.
70. Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362–2366.
71. Monovich, L. G.; Le Huerou, Y.; Ronn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52–57.
72. Smith, K.; Campi, E.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. M.; Deacon, G. *Synlett* **1997**, 131–132.
73. Jackson, D. E.; Dewick, P. M. *Phytochemistry* **1981**, *20*, 2277–2280.

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An approach to triquinane synthesis using the Pauson–Khand reaction

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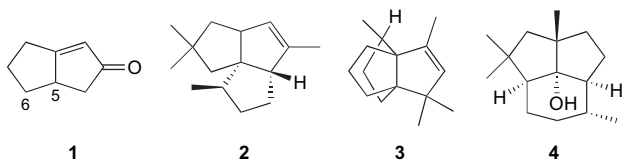
Abstract—Tricyclic skeletons have been generated from acyclic enyne precursors by using an intramolecular Pauson–Khand reaction in combination with aldol, Michael and alkylation reactions.

1. Introduction

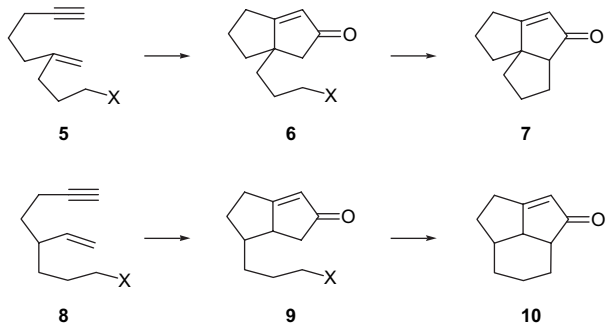
The Pauson–Khand reaction (PKR) is widely regarded as one of the most efficient and versatile methods for cyclopentenone synthesis.[1] The reaction is a cobalt mediated [2+2+1] cycloaddition and has been shown to be a powerful method for the generation of the bicyclo[3.3.0]oct-1-ene-3-one system **1** (Fig. 1).[2] It has been used as a key step in the synthesis of a number of natural products including hirsutene,[3] kainic acid,[4] pentalenene,[5] brefeldin-A,[6] asteriscanolide,[7] and epoxydictymene.[8] Pauson–Khand reactions have been used in tandem[9] with other processes to make tricycles, for example, Clive's synthesis of angularly fused triquinanes via the PKR, leaving a chain in the allylic position, followed by a radical cyclization.[10] Triquinanes continue to be a focus of interest, in part due to their inherently interesting structures but also since some possess biological activity.[11,12]

The goal of this study was a one-pot synthesis of tricycles using Pauson–Khand reactions followed by aldol or alkylation processes.[9] Unexpectedly, the enone moiety of the bicyclooctenones formed in the PKR was quite reactive and became the unanticipated focal point of subsequent cyclizations. Incorporation of a side chain bearing reactive functionality at either C-5 or C-6 of bicyclooctenone **1** was found to be useful in key transformations providing access to the ring systems found in tricyclic natural products such as pentalenene (**2**),[5,13] modhephene (**3**),[14,15,16] and presilphiperfolanol (**4**).[17] Intramolecular Pauson–Khand reactions with enynes such as **5** and **8** (Scheme 1) should provide bicyclooctenones **6** and **9**, which after a second appropriate carbon–carbon bond forming reaction, would be expected to generate tricycles **7** and **10**, respectively.



1 2 3 4

Figure 1.



Scheme 1.

2. Results and discussion

Our first goal was synthesis of the tricyclo[6.3.0.0]undecane ring system. Toward this end, bromide **11**[18] was transformed into the corresponding Grignard reagent and then treated with aldehyde **18**[19] generating alcohol **12** in 58% yield

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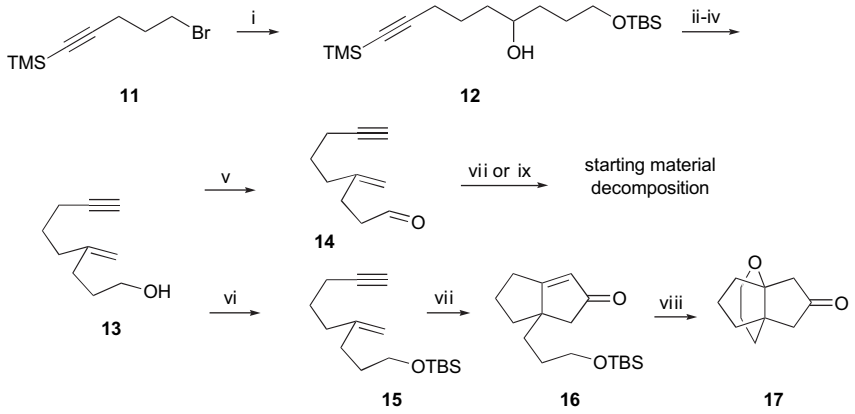
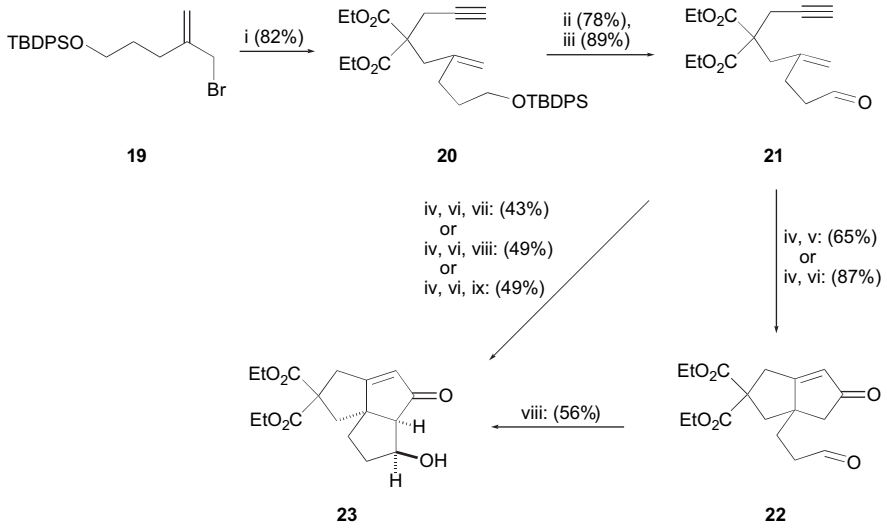


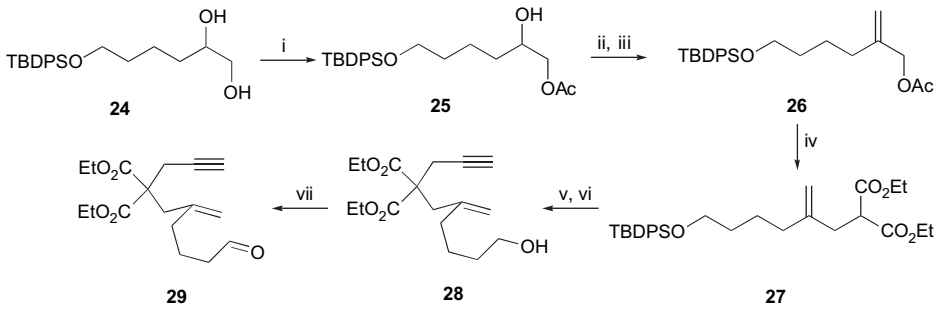
Scheme 2. Reagents and conditions: (i) a, Mg, Et_2O, rt; b, $TBSOCH_2CH_2CH_2CHO$ **18**[19] Et_2O, rt 58%; (ii) $(COCl)_2$, DMSO, NEt_3, THF, −78 °C, 94%; (iii) Tebbe reagent, THF, −40 °C, 78%; (iv) TBAF, THF, rt, 49%; (v) PCC, CH_2Cl_2, rt, 73%; (vi) TBSCI, imidazole, CH_2Cl_2, rt, 88%; (vii) $CO_2(CO)_8$, toluene, 110 °C, 32%; (viii) TBAF, THF, rt, 44%; and (ix) a, $Co_2(CO)_8$, CH_2Cl_2, rt; b, $NMO{\cdot}H_2O$, CH_2Cl_2, rt.

(Scheme 2). Swern oxidation of alcohol **12**, followed by Tebbe olefination and deprotection (TBAF) of both the silyl ether and acetylene moieties gave enyne **13** in 36% overall yield. PCC oxidation of alcohol **13** gave aldehyde **14**, which when subjected to either thermal or trialkylamine *N*-oxide promoted Pauson–Khand reaction conditions, resulted in only decomposition of the starting material. Alcohol **13** was subsequently protected as the TBS ether **15**. Subjection of enyne **15** to *N*-methylmorpholine *N*-oxide (NMO)-promoted Pauson–Khand reaction conditions led only to alkyne decomplexation, whereas, thermal conditions gave a modest yield of bicyclooctenone **16**. No other identifiable compounds were isolable. Interestingly and unexpectedly, attempted desilylation of enone **16** under a variety of conditions gave [4.3.3]propellane **17** resulting from conjugate addition of the alcohol to the cyclopentenone moiety.

Due to the low yield in the Pauson–Khand reaction of enyne **16**, a diester moiety was incorporated into the enyne to provide Thorpe–Ingold assistance[20] in the Pauson–Khand reaction. Thus, our attention was next turned to the synthesis and reactions of enynal **21** (Scheme 3). The synthesis of **21** was achieved via palladium-catalyzed alkylation[21] of allylic bromide **19**[22] using the sodium salt of propargyl diethyl malonate, which gave enyne **20** in 82% yield. Deprotection of the silyl protected alcohol using TBAF followed by Swern oxidation gave aldehyde **21** in 69% overall yield. Pauson–Khand reaction of enynal **21**, under thermal conditions, led to decomposition of the starting material. In contrast, the NMO-promoted Pauson–Khand reaction gave bicyclooctenone **22** in 65% yield, however, when anhydrous Me_3NO (TMANO) was used,[23] bicyclooctenone **22** was obtained in 85% yield. Aldol cyclization of **22** was investigated next. Use of potassium carbonate, cesium carbonate, zirconium(IV)*tert*-butoxide, and potassium methoxide all led to decomposition of the starting material. However, when DBU was used in the aldol cyclization of **22**, tricyclo[6.3.0.0]-undecane **23** was obtained in 56% yield. Having established that the stepwise Pauson–Khand sequence from enynal **21** to triquinane **23**, was successful, we then considered the possibility of performing a one-pot transformation. Use of the optimal Me_3NO-promoted conditions for the Pauson–Khand



Scheme 3. Reagents and conditions: (i) Na-propargyl diethyl malonate, $Pd(OAc)_2$, PPh_3, THF, Δ; (ii) TBAF, THF, rt; (iii) $(COCl)_2$, DMSO, NEt_3, THF, -78 °C; (iv) $Co_2(CO)_8$, CH_2Cl_2, rt; (v) $NMO{\cdot}H_2O$, CH_2Cl_2, rt; (vi) Me_3NO, CH_2Cl_2, rt; (vii) DBU, CH_2Cl_2, rt; (viii) DBN, CH_2Cl_2, rt; and (ix) 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine, CH_2Cl_2, rt.



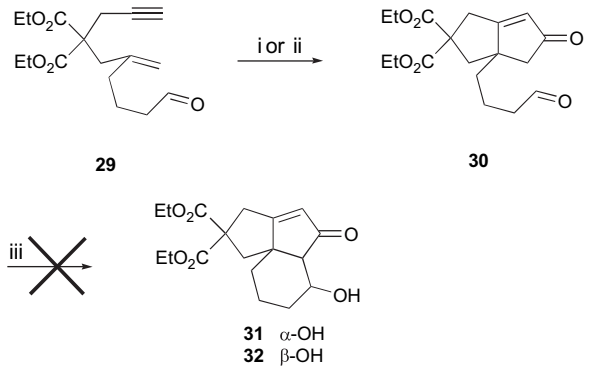
Scheme 4. Reagents and conditions: (i) AcCl, 2,4,6-collidine, CH_2Cl_2, −78 °C, 100%; (ii) Jones reagent, benzene, rt, 80%; (iii) Ph_3PCH_2, THF, −78 °C, 65%; (iv) Na-diethyl malonate, PdCl(allyl)PPh_3, THF, Δ, 68%; (v) a, NaH, THF, 0 °C; b, propargyl bromide, rt, 82%; (vi) TBAF, THF, rt, 88%; and (vii) PCC, CH_2Cl_2, rt, 90%.

reaction with DBU as base gave triquinane **23** in 43% yield as a single diastereomer. Changing the base to DBN or 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine resulted in the formation of triquinane **23** in 49% yield for both of the one-pot processes. It was therefore possible to prepare tricycle **23** in four synthetic operations from allylic bromide **19**. As anticipated, geminal substitution on the tether between the alkene and alkyne greatly facilitated the PKR with the substituted alkene.

Having gained access to the tricyclo[6.3.0.0]undecane ring system found in pentalenene **2**, the length of the side chain at the ring fusion of PK bicyclooctenone **22** was increased by one carbon in an attempt to prepare a homolog of **23**. The synthesis of enynal **29** started from the known diol **24**[24] (Scheme 4), which was selectively acetylated[25] to give alcohol **25**. Jones oxidation to the corresponding ketone followed by Wittig olefination using methyltriphenylphosphonium bromide gave allylic acetate **26** in 55% overall yield. Palladium-catalyzed alkylation[21] using the sodium salt of diethyl malonate provided malonate **27** in 68% yield. Alkylation of malonate **27** using propargyl bromide followed by deprotection of the silyl ether gave alcohol **28** in 72% overall yield. Oxidation of alcohol **28** using PCC provided enyne aldehyde **29** in 90% yield.

Pauson–Khand reaction of enynal **29** under thermal conditions again led to decomposition of the starting material. However, the NMO-promoted Pauson–Khand reaction gave enone **30** in 63% yield and the Me_3NO-promoted[23] reaction cleanly provided enone **30** in 82% yield (Scheme 5). Unfortunately, treatment of enone **30** with DBU or piperidine did not generate the desired tricyclic alcohols **31** or **32**.

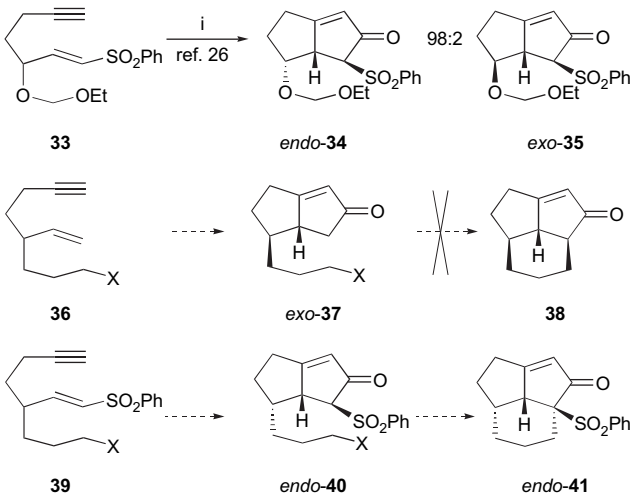
Another ring system examined was the tricyclo[6.2.1.$0^{4,11}$]-undecane motif found in presilphiperfolanol **4**. In order to follow a PKR with an enolate alkylation to generate the bridging ring (Scheme 1), *endo* selectivity in the PKR is required. Carretero has reported that incorporation of an α,β-unsaturated phenylsulfone moiety as the alkene component in intramolecular Pauson–Khand reactions results in high levels of *endo* selectivity with certain enynes.[26] When enyne **33** was subjected to Me_3NO-promoted Pauson–Khand[23] reaction conditions bicyclooctenones **34** and **35** were obtained in 76% yields (>98:<2, *endo*:*exo*, Scheme 6).[26] Pauson–Khand reaction of enyne **36** might be expected to give *exo*-bicyclooctenone **37**, which would place the side chain bearing reactive functionality at C-6 of the bicyclooctenone



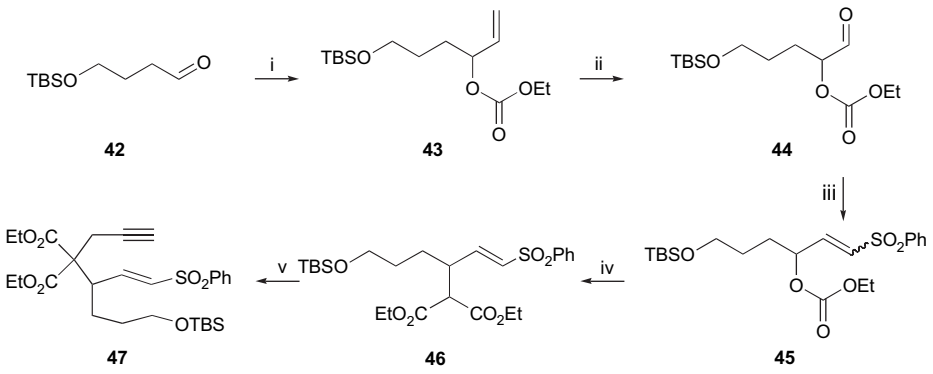
Scheme 5. Reagents and conditions: (i) a, $Co_2(CO)_8$, hexane, rt; b, $NMO\cdot H_2O$, CH_2Cl_2, rt, 63%; (ii) a, $Co_2(CO)_8$, hexane; b, Me_3NO, CH_2Cl_2, O_2(g), rt, 82%; and (iii) DBU, CH_2Cl_2, rt, or piperidine, rt, CH_2Cl_2.

ring on the *exo* face. The subsequent base promoted cyclization to triquinane **38** would therefore not occur due to steric constraints. In contrast, based on Carretero's results, incorporation of an α,β-unsaturated phenylsulfone moiety into enyne **39** should give *endo*-bicyclooctenone **40**, allowing for a facile six-membered ring closure to tricyclo-[6.2.1.$0^{4,11}$]undecane **41**.

Enyne **47** was identified as a potential target to test the PKR/alkylation sequence. Treatment of aldehyde **42**[27] with



Scheme 6. Reagents and conditions: (i) a, $Co_2(CO)_8$, CH_2Cl_2, rt; b, $Me_3NO\cdot 2H_2O$, rt, 76%, *endo* **34**:*exo* **35**, 98:2.

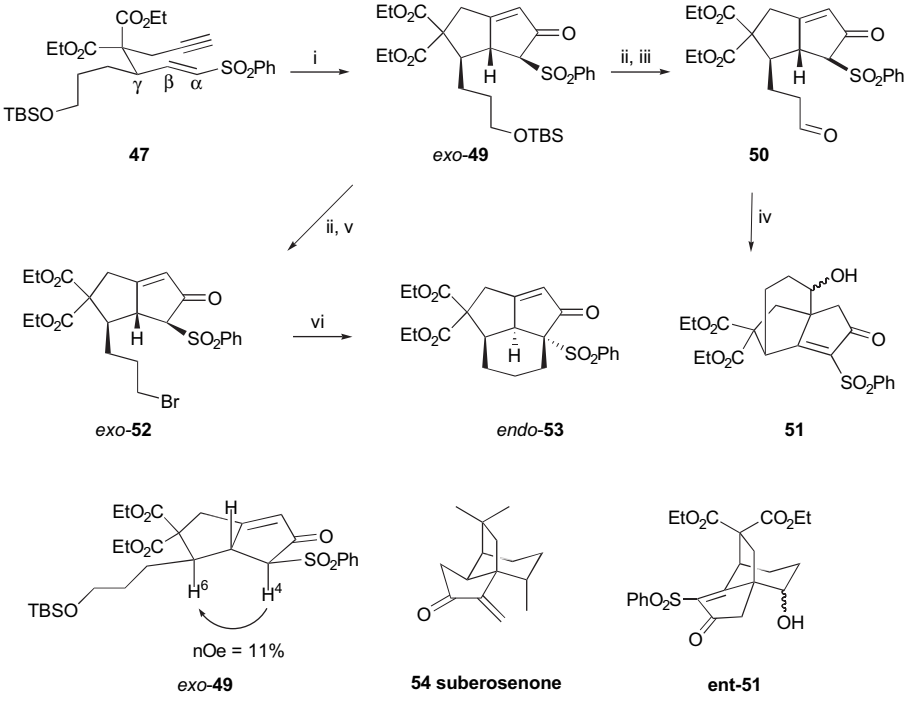


Scheme 7. Reagents and conditions: (i) a, vinylmagnesium bromide, THF, rt; b, $ClCO_2Et$, NEt_3, THF, rt, 66%; (ii) a, O_3, CH_2Cl_2, −78 °C; b, NEt_3, CH_2Cl_2, −78 °C, 86%; (iii) $(EtO)_2P(O)CHLiSO_2Ph$ **48**,[28] THF, −78 °C to rt, 73%; (iv) diethyl malonate, Pd_2dba_3, dppe, 4 Å MS, THF, Δ, 81%; and (v) a, NaH, THF, rt; (b) propargyl bromide, THF, rt, 99%.

vinylmagnesium bromide followed by quenching of the resultant alkoxide with ethyl chloroformate gave allylic carbonate **43** in 66% yield (Scheme 7). Ozonolysis of **43** gave aldehyde **44** in 86% yield, which upon treatment with $(EtO)_2P(O)CHLiSO_2Ph$ **48**,[28] provided α,β-unsaturated sulfone **45** in 73% yield (*E*/*Z*, 2.5:1). Palladium-catalyzed alkylation[29] of carbonate **45** using the sodium salt of diethyl malonate gave exclusively the thermodynamically preferred (*E*)-α,β-unsaturated sulfone **46** in 81% yield, presumably via a π–σ–π isomerization with a corresponding bond rotation.[30] Alkylation of **46** using sodium hydride followed by propargyl bromide gave enyne **47** in 99% yield.

When enyne **47** was subjected to Me_3NO-promoted Pauson–Khand reaction conditions *exo*-bicyclooctenone **49** was formed exclusively in 82% yield (Scheme 8). The stereoselectivity was confirmed by the presence of a NOE enhancement between H_4 and H_6 and X-ray crystallography (Fig. 2). The observed *exo* selectivity can be explained by considering the precyclization conformation of enyne **47** (Scheme 8). Carretero's study showed that there was a qualitative correlation between the value of $J_{\beta,\gamma}$ and the *endo*/*exo* ratios of the bicyclooctenone products. Enynes with the lowest $J_{\beta,\gamma}$ values gave rise to predominantly *endo* selective Pauson–Khand reactions, whereas higher $J_{\beta,\gamma}$ values gave *exo* selectivity. For enyne **47**, $J_{\beta,\gamma}$=10.3 Hz, which was higher than any of the $J_{\beta,\gamma}$ values found in substrates was examined in Carretero's study. A high $J_{\beta,\gamma}$ value places H_β and H_γ in an *anti* configuration, with the substituent at C_γ in a sterically more favored pseudoequatorial position in the precyclization conformation.

Despite the fact that the side chain bearing reactive functionality of bicyclooctenone **49** was on the *exo* face, it seemed



Scheme 8. Reagents and conditions: (i) a, $Co_2(CO)_8$, hexane, rt; (b) Me_3NO, CH_2Cl_2, rt, 82%; (ii) $B_{10}H_{14}$, MeOH, 94%; (iii) PCC, CH_2Cl_2, 81%; (iv) DBU, CH_2Cl_2, 47%; (v) Br_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 86%; and (vi) DBU, CH_2Cl_2, Δ, 70%.

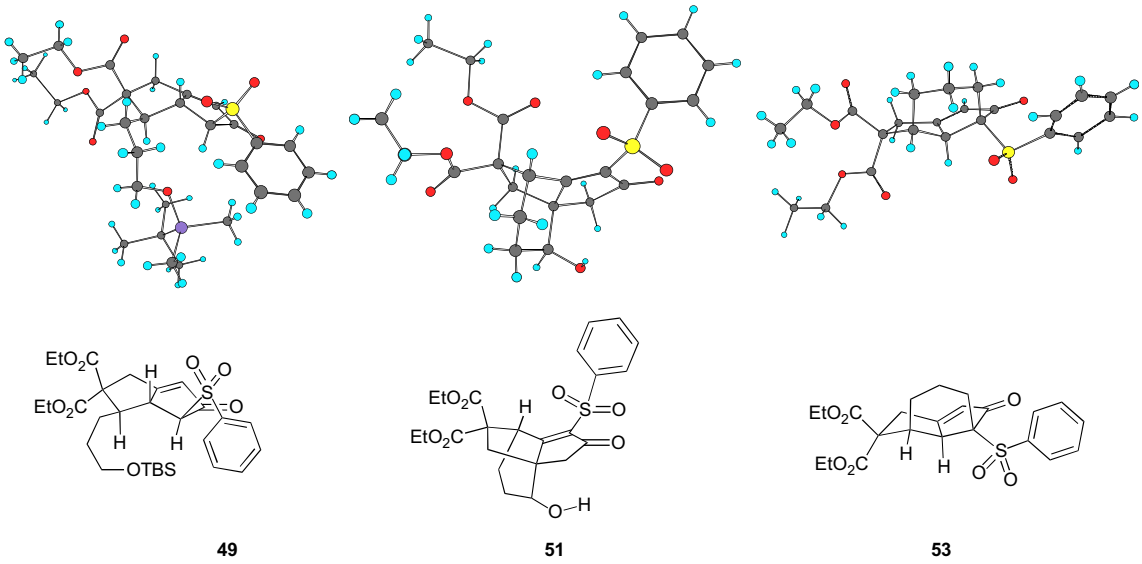


Figure 2. X-ray crystal structures of **49**, **51**, and **53**.

likely that a set of conditions for the formation of the tricyclo[6.2.1.0^{4,11}]undecane ring system could be found. The acidic H-5 proton might be expected to epimerize with the correct choice of base. Deprotection of silyl ether **49** using decaborane[31] followed by PCC oxidation gave aldehyde **50** in 76% overall yield. Surprisingly, reaction of aldehyde **50** with DBU gave rise to the unexpected tricyclo[4.3.2.0^{1,5}]undecane **51** in 47% yield as a 3:2 mixture of carbinol isomers via an isomerization and aldol cyclization (X-ray structure of one isomer, Fig. 2). The tricyclo[4.3.2.0^{1,5}]undecane motif is present in the cytotoxic sesquiterpene suberosenone **54**.[32] This result is particularly surprising in light of the failure of a related Michael addition to generate an analogous tricyclic ring system.[33] Our attention next turned to bromide **52**, which was prepared by silyl ether deprotection followed by bromination using bromine and triphenylphosphine. Treatment of bromide **52** with DBU in CH_2Cl_2 gave no reaction at rt however, after refluxing it overnight *endo*-tricyclo[6.2.1.0^{4,11}]undecane **53** was obtained in 70% yield. The structure was again confirmed by X-ray crystallography (Fig. 2). Formation of the six-membered ring in *endo*-**53** was presumably made possible by epimerization of the ring fusion proton of *exo*-**52** to *endo*-**52**, via the dienolate, under the basic reaction conditions.

In conclusion, we have used an intramolecular Pauson–Khand reaction in combination with, aldol, Michael, and alkylation reactions to gain rapid access to tricyclo[6.3.0.0]undecane, tricyclo[6.2.1.0^{4,11}]undecane, and tricyclo[4.3.2.0^{1,5}]undecane ring systems. We are currently using the methodology developed herein in the total synthesis of tricyclic natural products.

3. Experimental

3.1. General

Solvents for reactions were reagent grade and distilled from the indicated drying agents: tetrahydrofuran (THF) was distilled from lithium aluminum hydride and diethyl ether (Et_2O) was distilled from potassium. Methylene chloride (CH_2Cl_2), triethylamine (NEt_3), and pyridine were distilled from calcium hydride. Hexane, chloroform, methanol, and ethyl acetate (EtOAc) were distilled prior to use. All reactions were performed under an atmosphere of nitrogen unless otherwise specified. Melting points were obtained in an open capillary and are uncorrected. ^{1}H NMR spectra were obtained at 500 MHz on a Varian Gemini spectrometer and ^{13}C NMR spectra were obtained at 75 MHz on a Bruker AC 300 spectrometer in $CDCl_3$ solutions unless otherwise stated. Infrared spectra (IR) were obtained on a Perkin–Elmer Paragon 1000 FT-IR neat as thin films. Low-resolution mass spectra were obtained on a Finnigan 4510 GC/MS instrument and high-resolution mass spectra were obtained on a AEI MS 902 instrument. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Flash column chromatography was performed with silica gel 60 particle size 40–63 μm.

3.1.1. Malonate (20). Propargyl diethyl malonate (1.23 g, 5.80 mmol) in THF (10 mL) was added dropwise to an ice cold suspension of hexane washed 60% sodium hydride (0.28 g, 6.96 mmol) in THF (20 mL). After stirring for 15 min the mixture was allowed to warm to rt. This solution was added to a mixture of bromide **19**[22] (2.42 g, 5.80 mmol) in THF (20 mL) followed by $Pd(OAc)_2$ (26 mg, 0.12 mmol) and triphenylphosphine (122 mg, 0.46 mmol) and the resulting mixture was refluxed overnight. After allowing the solution to cool to rt the reaction mixture was washed with water, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was passed through a plug of silica (EtOAc). After evaporation of solvent the resultant yellow oil was further purified by flash column chromatography (hexane/EtOAc, 9:1) to give malonate **20** (2.53 g, 82%) as a clear oil: IR 2932, 2360, 1729, 1428 cm^{-1}; ^{1}H NMR δ 7.65 (4H, dd, J=7.5, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.90 (1H, d, J=1.5 Hz, $(CH_2)_2CCHH$), 4.87 (1H, br s, CCH_2CCH_2CCH, CCH_2CCH), 4.21 (2H, ABq, J_{AB}=10.8,

J=7.3 Hz, CH_3CH_2), 4.14 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 3.64 (2H, t, J=6.4 Hz, TBDPSOCH_2), 2.83 (4H, br s, $(CH_2)_2CCH_2$), 2.03 (2H, t, J=7.8 Hz, TBSPSOCH$_2$CH$_2$CH_2), 2.00 (1H, t, J=2.4 Hz, CH_2CCH), 1.72–1.67 (2H, m, TBDPSOCH$_2$CH_2), 1.24 (6H, t, J=7.3 Hz, CH_2CH_3), 1.04 (9H, s, $C(CH_3)_3$); ^{13}C NMR δ 170.1, 143.6, 135.5, 133.9, 129.5, 127.6, 114.9, 79.3, 71.7, 63.3, 61.6, 56.5, 37.2, 32.8, 30.8, 26.8, 22.5, 19.2, 14.0; Anal. Calcd for $C_{32}H_{42}O_5Si$: C, 71.87; H, 7.92. Found: C, 72.01; H 7.99.

3.1.2. 2-[2-(3-Oxo-propyl)-allyl]-2-prop-2-ynyl-malonic acid diethylester (21). Tetrabutylammonium fluoride 1.0 M (7.1 mL, 7.1 mmol) was added to silyl ether **20** (2.53 g, 4.73 mmol) in THF (15 mL). After stirring for 3 h, water (200 mL) was added and the mixture extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 4:1) to give the corresponding alcohol (1.09 g, 78%) as a colorless oil: IR 3282, 2942, 2360, 1716 cm^{-1}; ^{1}H NMR δ 4.95 (1H, d, J=1.5 Hz, $(CH_2)_2CCHH$), 4.92 (1H, br s, $(CH_2)_2CCHH$), 4.23 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.18 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 3.63 (2H, dt, J=6.0, 6.0 Hz, $HOCH_2$), 2.85 (2H, br s, $(CO_2Et)_2CCH_2CCH_2$), 2.84 (2H, d, J=2.9 Hz, $HCCCH_2$), 2.03 (1H, t, J=2.4 Hz, CH_2CCH), 2.02 (2H, t, J=7.8 Hz, $HOCH_2CH_2CH_2$), 1.71 (2H, tt, J=6.9, 6.9 Hz, $HOCH_2CH_2$), 1.29 (1H, t, J=5.8 Hz, OH), 1.26 (6H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 170.1, 143.3, 115.2, 79.1, 71.7, 62.1, 61.7, 56.4, 37.0, 32.5, 30.7, 22.5, 13.9; HRESIMS calcd for $C_{16}H_{24}O_5Na$ ([M+Na]$^+$): 319.1521; found: 319.1517.

Pyridinium chlorochromate (457 mg, 2.12 mmol) was added to the alcohol (315 mg, 1.06 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h the mixture was filtered through a plug of silica gel and the solvent was evaporated. The resultant oil was purified by flash column chromatography (hexane/EtOAc, 9:1) to give aldehyde **21** (254 mg, 81%) as a colorless oil: IR 2285, 2984, 2726, 2360, 1758 cm^{-1}; ^{1}H NMR δ 9.75 (1H, t, J=1.5 Hz, CHO), 4.95 (1H, br s, $(EtO_2C)_2CCH_2CCHH$), 4.92 (1H, d, J=1.0 Hz, $(EtO_2C)_2CCH_2CCHH$), 4.23 (2H, ABq, J_{AB}=10.8, J=7.2 Hz, CH_3CH_2), 4.18 (2H, ABq, J_{AB}=10.8, J=7.2 Hz, CH_3CH_2), 2.86 (2H, br s, $(EtO_2C)_2CCH_2CCHH$), 2.84 (2H, d, J=2.7 Hz, $(EtO_2C)_2CCH_2CCH$), 2.58 (2H, td, J=7.3, 1.5 Hz, $CHOCH_2$), 2.27 (2H, t, J=7.3 Hz, $CHOCH_2CH_2$), 2.04 (1H, t, J=2.9 Hz, CH_2CCH), 1.26 (6H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 201.5, 169.8, 142.1, 115.6, 79.0, 71.9, 61.7, 56.3, 41.9, 37.4, 28.5, 22.5, 13.9; HRESIMS calcd for $C_{16}H_{22}O_5Na$ ([M+Na]$^+$): 317.1365; found: 317.1376.

3.1.3. Enone (22). Dicobaltoctacarbonyl (309 mg, 0.93 mmol) was added to aldehyde **21** (254 mg, 0.86 mmol) in hexane (3 mL). After the enyne was consumed according to TLC, the solvent was evaporated and CH_2Cl_2 (17 mL) was added. Anhydrous trimethylamine *N*-oxide (59 mg, 0.86 mmol) was added every 30 min (four times) and the mixture was stirred for an additional 1 h under an oxygen atmosphere. The mixture was passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 3:1) to give bicyclooctenone **22** (236 mg, 85%) as a colorless oil: IR 3460, 2982, 2728, 1724, 1636 cm^{-1}; ^{1}H NMR δ 9.73 (1H, br s, CHO), 5.93 (1H, d, J=1.5 Hz, $(CH_2)_2CCH$), 4.27 (2H, q, J=7.3 Hz, CH_3CH_2), 4.19 (2H, q, J=7.3 Hz, CH_3CH_2), 3.39 (1H, dd, J=17.6, 1.5 Hz, $CHOCH_2CH_2CCH_2CCHH$), 3.28 (1H, d, J=17.6 Hz, $CHOCH_2CH_2CCH_2CCHH$), 2.71 (1H, d, J=13.9 Hz, $(EtO_2C)_2CCHHCCH_2$), 2.44 (1H, ddd, J=15.1, 10.3, 5.9 Hz, $CHOCHH$), 2.38 (1H, d, J=17.6 Hz, $HCCOCHHC$), 2.32 (1H, dddd, J=15.1, 10.3, 5.9, 1.0 Hz, $CHOCHH$), 2.29 (1H, d, J=17.6 Hz, $HCCOCHHC$), 2.15 (1H, d, J=13.9 Hz, $(EtO_2C)_2CCHHCCH_2$), 1.82 (1H, ddd, J=14.7, 9.8, 5.4 Hz, $CHOCH_2CHH$), 1.68 (1H, ddd, J=14.7, 9.8, 5.4 Hz, $CHOCH_2CHH$), 1.29 (3H, t, J=7.3 Hz, CH_2CH_3), 1.24 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 207.3, 200.2, 186.0, 171.9, 171.5, 126.2, 62.5, 62.3, 53.1, 49.2, 43.2, 39.8, 34.7, 29.7, 14.3, 14.2; HRESIMS calcd for $C_{17}H_{23}O_6$ ([M+H]$^+$): 323.1495; found: 323.1492.

3.1.4. Tricyclic enone (23). 1,3,4,6,7,8-Hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (96 μL, 0.67 mmol) was added to aldehyde **22** (216 mg, 0.67 mmol) in CH_2Cl_2 (6.7 mL) containing 4 Å powdered molecular sieves (5 g) and the reaction mixture was stirred overnight. The solution was filtered then washed with saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil filtered through a plug of silica gel (EtOAc). After evaporation of the solvent the resultant oil was purified by flash column chromatography (hexane/EtOAc, 3:2) to give tricycle **23** (106 mg, 49%) as a colorless oil (stereochemistry determined by ^{1}H NOE NMR spectroscopy): ^{1}H NMR δ 5.98 (1H, s, $(EtO_2C)_2CCH_2CCH$), 4.29 (1H, partly obscured ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.24 (1H, partly obscured ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.17 (1H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.10 (1H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.24 (1H, obscured m, HOCH), 3.87 (1H, d, J=3.9 Hz, CH_2CCHCO), 2.95 (1H, d, J=14.7 Hz, $HOCHCH_2CH_2CCHH$), 2.35 (1H, AB, J_{AB}=18.1 Hz, $HOCHCHCOCHCCHH$), 2.30 (1H, AB, J_{AB}=18.1 Hz, $HOCHCHCOCHCCHH$), 1.98 (1H, dd, J=5.8, 5.8 Hz, $HOCHCH_2CHHC$), 1.92 (1H, dd, J=14.7, 1.0 Hz, $HOCHCH_2CH_2CCHH$), 1.87 (1H, m, $HOCHCHHCH_2C$), 1.71 (1H, ddd, J=12.7, 12.7, 5.4 Hz, $HOCHCH_2CHHC$), 1.62 (1H, dd, J=12.7, 5.4 Hz, $HOCHCHHCH_2C$), 1.29 (3H, t, J=7.3 Hz, CH_2CH_3), 1.20 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 208.5, 187.4, 171.1, 169.3, 124.6, 70.4, 62.2, 51.8, 49.4, 49.2, 39.8, 37.4, 27.1, 14.3, 14.1; HRESIMS calcd for $C_{17}H_{22}O_6Na$ ([M+Na]$^+$): 345.1303; found: 345.1314.

3.1.4.1. Procedure for the one-pot synthesis of tricyclic enone (23). Dicobaltoctacarbonyl (60 mg, 0.18 mmol) was added to a solution of aldehyde **21** (47 mg, 0.16 mmol) in CH_2Cl_2 (7 mL). After the enyne was consumed according to TLC, trimethylamine *N*-oxide (60 mg, 0.80 mmol) was added to the solution. The mixture was stirred for 12 h at rt then 4 Å powdered molecular sieves (1 g) were added. After 1 h, DBN (20 μL, 0.16 mmol) was added and the reaction mixture was stirred overnight. The solution was filtered then washed with saturated aqueous ammonium chloride. The

organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil filtered through a plug of silica gel (EtOAc). After evaporation of the solvent the resultant oil was purified by flash column chromatography (hexane/EtOAc, 3:2) to give tricycle **23** (27 mg, 49%) as a colorless oil.

3.1.5. Acetic acid 6-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-hexylester (25). 2,4,6-Collidine (10.6 mL, 80.5 mmol) was added dropwise to a solution of diol **24**[24] (10.0 mL, 40.3 mmol) in CH_2Cl_2 (200 mL) at −78 °C. After stirring for 30 min acetyl chloride (3.43 mL, 48.3 mmol) in CH_2Cl_2 (25 mL) was added dropwise and the mixture was stirred for an additional 3 h. The reaction mixture was allowed to warm to rt and the organic layer was washed with 2 M HCl (200 mL), water (200 mL), dried over $MgSO_4$, filtered, and evaporated, and the resultant oil purified by flash column chromatography (hexane/EtOAc, 9:1) to give alcohol **25** (11.3 g, 100%) as a colorless oil: IR 3458, 2930, 1736, 1589 cm^{-1}; ^1H NMR δ 7.66 (4H, d, J=6.8 Hz, Ar*H*), 7.44–7.36 (6H, m, Ar*H*), 4.12 (1H, dd, J=11.2, 3.0 Hz, AcOC*H*HCH), 3.92 (1H, dd, J=11.2, 7.3 Hz, AcOCH*H*CH), 3.79–3.84 (1H, m, C*H*OH), 3.66 (2H, t, J=5.9 Hz, CH_2OTBDPS), 2.10 (3H, s, $COCH_3$), 1.97 (1H, d, J=4.4 Hz, O*H*), 1.61–1.42 (6H, m, TBDPSOCH$_2$CH_2CH_2CH_2), 1.04 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 171.2, 135.5, 134.0, 129.5, 127.6, 69.8, 68.7, 63.6, 33.0, 32.3, 26.8, 21.7, 20.9, 19.2; MS (ESI^+) *m*/*z* 437 (M+Na); Anal. Calcd for $C_{24}H_{34}O_4Si$: C, 69.53; H, 8.27. Found: C, 69.24; H, 8.24.

3.1.6. Acetic acid 2-[4-(*tert*-butyldiphenylsilanyloxy)-butyl]-allylester (26). Jones reagent (2.67 M) was added to a solution of alcohol **25** (44.0 g, 0.106 mol) in benzene (200 mL) until there was a persistent orange color. The excess Jones reagent was quenched by addition of isopropyl alcohol and the solution was washed with water. The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil purified by flash column chromatography (hexane/EtOAc, 99:1) to give the requisite ketone (35.0 g, 80%) as a colorless oil: IR 3070, 2931, 2858, 1753, 1736, 1589 cm^{-1}; ^1H NMR δ 7.65 (4H, dd, J=7.8, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.61 (2H, s, AcOCH_2), 3.66 (2H, t, J=5.9 Hz, TBDPSOCH_2), 2.40 (2H, t, J=7.3 Hz, CH_2COCH$_2$OAc), 2.16 (3H, s, $COCH_3$), 1.71 (2H, tt, J=7.3, 7.3 Hz, CH_2CH$_2$COCH$_2$OAc), 1.59–1.54 (2H, m, TBDPSOCH$_2$CH_2), 1.05 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 203.7, 170.2, 135.5, 133.8, 129.6, 127.6, 67.9, 63.3, 38.4, 31.7, 26.8, 20.5, 19.7, 19.2; MS (ESI^+) *m*/*z* 435 (M+Na); Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.86; H, 7.82. Found: C, 69.88; H, 7.86.

Butyllithium (9.6 mL, 1.44 M, 13.8 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (5.28 g, 14.8 mmol) in THF (100 mL) at −78 °C. After stirring for 30 min the reaction mixture was warmed to 0 °C and above ketone (4.07 g, 9.9 mmol) in THF (20 mL) was added dropwise. The reaction mixture was allowed to warm to rt and was stirred for 1 h. Water (100 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 98:2) to give alkene **26** (2.65 g, 65%) as a colorless oil: IR 3071, 3050, 2932, 2858, 1744, 1654, 1589 cm^{-1}; ^1H NMR δ 7.66 (4H, m, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 5.02 (1H, br s, (CH$_2$)$_2$CC*H*H), 4.92 (1H, br s, (CH$_2$)$_2$CCH*H*), 4.50 (2H, s, AcOCH_2), 3.67 (2H, t, J=5.9 Hz, TBDPSOCH_2), 2.08 (3H, s, $COCH_3$), 2.05 (2H, t, J=7.8 Hz, $CH_2CH_2CCH_2OAc$), 1.59–1.51 (4H, m, TBDPSOCH$_2$CH_2CH_2), 1.05 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 170.7, 143.8, 135.6, 134.0, 129.5, 127.6, 112.2, 66.9, 63.6, 33.9, 32.1, 26.9, 23.7, 20.9, 19.2; Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.08; H, 8.28.

3.1.7. Malonate (27). Diethyl malonate (3.3 mL, 21.9 mmol) was added dropwise to an ice cold suspension of hexane washed 60% sodium hydride (0.90 g, 22.5 mmol) in THF (30 mL). After stirring for 15 min the mixture was allowed to warm to rt. This solution was added to a mixture of allyl acetate **26** (5.00 g, 12.2 mmol) in THF (60 mL) followed by Pd(allyl)PPh_3Cl (0.55 g, 1.22 mmol) and the resulting mixture was refluxed for 48 h. After cooling to rt the reaction mixture was washed with water, and then extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was passed through a plug of silica (EtOAc). After evaporation of solvent the resultant yellow oil was further purified by flash column chromatography (hexane/EtOAc, 99:1) to give malonate **27** (4.20 g, 68%) as a colorless oil: IR 3071, 2933, 2858, 1735, 1648, 1589 cm^{-1}; ^1H NMR δ 7.66 (4H, dd, J=7.8, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.77 (1H, s, (CH$_2$)$_2$CC*H*H), 4.75 (1H, s, (CH$_2$)$_2$CCH*H*), 4.18 (4H, q, J=7.2 Hz, CH_3CH_2), 3.66 (2H, t, J=5.9 Hz, TBDPSOCH_2), 3.56 (1H, t, J=7.8 Hz, (EtO$_2$C)$_2$C*H*), 2.60 (2H, d, J=7.8 Hz, (EtO$_2$C)$_2$CHCH_2), 2.01 (2H, t, J=7.3 Hz, TBDPSO(CH$_2$)$_3$CH_2), 1.58–1.48 (4H, m, TBDPSOCH$_2$CH_2CH_2), 1.25 (6H, t, J=7.3 Hz, CH_2CH_3), 1.04 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 169.1, 145.5, 135.5, 134.0, 129.5, 127.6, 111.0, 63.7, 61.4, 50.6, 35.6, 34.7, 32.1, 26.8, 23.7, 19.2, 14.1; Anal. Calcd for $C_{30}H_{42}O_5Si$: C, 70.55; H, 8.29. Found: C, 70.68; H, 8.24.

3.1.8. 2-[2-(4-Hydroxy-butyl)-allyl]-2-prop-2-ynyl-malonic acid diethylester (28). Malonate **27** (9.15 g, 17.9 mmol) in THF (70 mL) was added to a suspension of hexane washed 60% sodium hydride (1.43 g, 35.8 mmol) in THF (70 mL) at 0 °C. After stirring for 15 min the mixture was allowed to warm to rt and was stirred for 30 min. A solution of 80% propargyl bromide in toluene (39.9 mL, 0.358 mol) was added and the mixture was stirred overnight. Water (100 mL) was added and the mixture extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 98:2) to give the enyne (8.10 g, 82%) as a colorless oil: IR 3290, 3071, 2934, 2859, 1736, 1641, 1589 cm^{-1}; ^1H NMR δ 7.65 (4H, dd, J=7.8, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.88 (1H, s, (CH$_2$)$_2$CC*H*H), 4.87 (1H, s, (CH$_2$)$_2$CCH*H*), 4.21 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.14 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 3.63 (2H, t, J=6.4 Hz, TBDPSOCH_2), 2.81 (4H, br s, CCH_2CCHH, CCH_2CCH), 2.00 (1H, t, J=2.4 Hz, CH_2CCH), 1.89 (2H, t, J=7.8 Hz, TBDPSO(CH$_2$)$_3$CH_2), 1.53–1.46 (4H, m, TBDPSOCH$_2$CH_2CH_2), 1.24 (6H, t, J=6.8 Hz, CH_2CH_3), 1.04 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 170.0, 143.7, 135.4, 133.9, 129.4, 127.5, 114.9, 79.2,

71.6, 63.6, 61.5, 56.4, 36.9, 36.1, 32.0, 23.9, 22.4, 19.1, 13.9; MS (ESI$^+$) *m/z* 571 (M+Na); Anal. Calcd for $C_{33}H_{44}O_5Si$: C, 72.22; H, 8.08. Found: C, 72.02; H, 8.07.

Tetrabutylammonium fluoride (120 mL, 1.0 M, 120 mmol) was added to the silyl ether enyne (6.70 g, 12.2 mmol) in THF (20 mL). After stirring for 3 h, water (200 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 4:1) to give alcohol **28** (3.32 g, 88%) as a colorless oil: IR 3289, 2938, 2122, 1732, 1642 cm^{-1}; ^{1}H NMR δ 4.92 (1H, d, J=1.5 Hz, $(EtO_2C)_2CCH_2CHH$), 4.89 (1H, br s, $(EtO_2C)_2CCH_2CHH$), 4.23 (2H, ABq, J_{AB}=11.0, J=7.3 Hz, CH_3CH_2), 4.17 (2H, ABq, J_{AB}=11.0, J=7.3 Hz, CH_3CH_2), 3.64 (2H, t, J=5.9 Hz, $HOCH_2$), 2.84 (2H, s, $(EtO_2C)_2CCH_2CCHH$), 2.83 (2H, d, J=2.9 Hz, $(EtO_2C)_2CCH_2CCH$), 2.03 (1H, t, J=2.9 Hz, CH_2CCH), 1.95 (2H, t, J=7.3 Hz, $HO(CH_2)_3CH_2$), 1.57–1.47 (4H, m, $HOCH_2CH_2CH_2$), 1.26 (6H, t, J=6.8 Hz, CH_2CH_3); ^{13}C NMR δ 170.0, 143.6, 115.0, 79.2, 71.7, 62.5, 61.6, 56.4, 36.9, 36.1, 32.1, 23.9, 22.5, 13.9; HRESIMS calcd for $C_{17}H_{26}O_5Na$ ([M+Na]$^+$): 333.1678; found: 333.1677.

3.1.9. Aldehyde (29). Pyridinium chlorochromate (420 mg, 1.94 mmol) was added to alcohol **28** (300 mg, 0.97 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h the mixture was filtered through a plug of silica gel and the solvent was evaporated. The resultant oil was purified by flash column chromatography (hexane/EtOAc, 9:1) to give aldehyde **29** (270 mg, 90%) as a colorless oil: IR 3279, 2982, 2939, 2723, 1733, 1642 cm^{-1}; ^{1}H NMR δ 9.76 (1H, t, J=1.5 Hz, CHO), 4.93 (2H, s, $(EtO_2C)_2CCH_2CCH_2$), 4.23 (2H, ABq, J_{AB}=10.6, J=7.2 Hz, CH_3CH_2), 4.17 (2H, ABq, J_{AB}=10.6, J=7.2 Hz, CH_3CH_2), 2.83 (4H, br s, $(EtO_2C)_2CCH_2CCH$ and $(EtO_2C)_2CCH_2CCH_2$), 2.41 (2H, td, J=7.3, 1.5 Hz, $CHOCH_2$), 2.03 (1H, t, J=2.4 Hz, CH_2CCH), 1.98 (2H, t, J=7.3 Hz, $(EtO_2C)_2CCH_2CCH_2(CH_2)_2$), 1.78 (2H, tt, J=7.3, 7.3 Hz, $CHOCH_2CH_2$), 1.25 (6H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 201.1, 170.3, 144.1, 116.0, 79.9, 72.8, 62.0, 57.1, 43.4, 37.8, 36.3, 23.4, 20.7, 14.3; HRESIMS calcd for $C_{17}H_{24}O_5Na$ ([M+Na]$^+$): 331.1521; found: 331.1533.

3.1.10. Bicyclooctenone (30). Dicobaltoctacarbonyl (200 mg, 0.58 mmol) was added to aldehyde **29** (180 mg, 0.58 mmol) in hexane (12 mL). After the enyne was consumed according to TLC, the solvent was evaporated and CH_2Cl_2 (12 mL) was added. Anhydrous trimethylamine *N*-oxide (40 mg, 0.58 mmol) was added every 30 min (four times) and the mixture was stirred for an additional 1 h under an oxygen atmosphere. The mixture was passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 3:1) to give bicyclooctenone **30** (160 mg, 82%) as a colorless oil: IR 3459, 2982, 1728, 1636 cm^{-1}; ^{1}H NMR δ 9.72 (1H, br s, CHO), 5.90 (1H, d, J=1.5 Hz, $(EtO_2C)_2CCH_2CCH$), 4.26 (2H, q, J=7.3 Hz, CH_3CH_2), 4.18 (2H, q, J=7.3 Hz, CH_3CH_2), 3.37 (1H, dd, J=17.6, 2.4 Hz, $CHO(CH_2)_3CCCHH$), 3.24 (1H, d, J=17.6 Hz, $CHO(CH_2)_3CCCHH$), 2.71 (1H, d, J=14.0 Hz, $CHO(CH_2)_3CCHHC(CO_2Et)_2$), 2.49 (1H, d, J=17.6 Hz, $CCHHCO$), 2.41 (2H, t, J=6.8 Hz, $CHOCH_2$), 2.27 (1H, d, J=17.6 Hz, $CCHHCO$), 2.13 (1H, d, J=14.0 Hz, $CHO(CH_2)_3CCHHC(CO_2Et)_2$), 1.64–1.40 (4H, m, $CHOCH_2(CH_2)_2$), 1.28 (3H, t, J=7.3 Hz, CH_2CH_3), 1.24 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 208.0, 207.8, 200.7, 186.3, 186.1, 172.0, 171.6, 125.9, 62.4, 62.3, 60.4, 53.9, 49.4, 43.7, 42.9, 37.3, 34.7, 18.9, 18.0, 14.3, 14.2; HRESIMS calcd for $C_{18}H_{24}O_6Na$ ([M+Na]$^+$): 359.1471; found: 359.1472.

3.1.11. Carbonate (43). Vinylmagnesium bromide (28.6 mL, 28.6 mmol) was added to a solution of 4-(*tert*-butyl-dimethylsilanyloxy)-butyraldehyde **42**[27] (5.73 g, 28.3 mmol) in THF (280 mL) and the mixture was stirred for 10 min. Ethyl chloroformate (5.4 mL, 56.6 mmol) followed by triethylamine (11.8 mL, 84.9 mmol) were added and the mixture was stirred for 30 min. Ether (200 mL) was added and the reaction mixture was washed with 2 M HCl (300 mL) then brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 97:3) to give carbonate **43** (5.7 g, 66%) as a colorless oil: IR 2955, 2858, 1747, 1648 cm^{-1}; ^{1}H NMR δ 5.79 (1H, ddd, J=17.1, 10.3, 6.8 Hz, $CH(OCO_2Et)CHCH_2$), 5.30 (1H, d, J=17.1 Hz, $CH(OCO_2Et)CHCHH$), 5.21 (1H, d, J=10.3 Hz, $CH(OCO_2Et)CHCHH$), 5.07 (1H, td, J=6.8, 6.8 Hz, $CH_2CH(OCO_2Et)$), 4.18 (2H, q, J=7.3 Hz, CH_3CH_2), 3.63 (1H, ABt, J_{AB}=10.1, J=6.8 Hz, $TBSOCHH$), 3.61 (1H, ABt, J_{AB}=10.1, J=6.8 Hz, $TBSOCHH$), 1.76–1.66 (2H, m, $TBSOCH_2CH_2CH_2$), 1.63–1.51 (2H, m, $TBSOCH_2CH_2$), 1.30 (3H, t, J=7.3 Hz, CH_2CH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 154.6, 136.0, 117.4, 78.6, 63.8, 62.6, 30.6, 28.2, 25.9, 18.3, 14.2, −5.4; Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.77; H, 9.96.

3.1.12. Aldehyde (44). Ozone was bubbled through a solution of alkene **43** (7.34 g, 24.3 mmol) at −78 °C in CH_2Cl_2 (240 mL) until there was a persistent blue color. The excess ozone was removed by bubbling nitrogen through the reaction mixture until the solution was clear. Triethylamine (3.4 mL, 24.3 mmol) was added dropwise at −78 °C and a stream of nitrogen was bubbled through the reaction mixture for 30 min. After warming to rt the solvent was evaporated and the resultant oily residue was purified by passing through a plug of silica gel (hexane/EtOAc, 85:15) to give aldehyde **44** (6.34 g, 86%) as a colorless oil: IR 3479, 2929, 1746, 1470 cm^{-1}; ^{1}H NMR δ 9.58 (1H, d, J=1.0 Hz, CHO), 4.92 (1H, dd, J=8.3, 4.9 Hz, $CHOCH$), 4.26 (1H, ABq, J=10.3, 7.3 Hz, $CHHCH_3$), 4.24 (1H, ABq, J=10.3, 7.3 Hz, $CHHCH_3$), 3.65 (1H, ABt, J_{AB}=10.2, J=5.7 Hz, $TBSOCH_2$), 3.63 (1H, ABt, J_{AB}=10.2, J=5.7 Hz, $TBSOCH_2$), 1.98 (1H, ABddd, J_{AB}=14.3, J=8.8, 7.3, 4.8 Hz, $CHOCHCHH$), 1.82 (1H, ABtd, J_{AB}=14.3, J=8.2, 5.9 Hz, $CHOCHCHH$), 1.69–1.63 (2H, m, $TBSOCH_2CH_2$), 1.35 (3H, t, J=7.3 Hz, CH_3CH_2), 0.89 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 198.0, 154.7, 80.9, 64.7, 62.1, 27.8, 25.9, 25.5, 18.3, 14.1, −5.4; HRESIMS calcd for $C_{14}H_{28}O_5SiNa$ ([M+Na]$^+$): 327.1604; found: 327.1606.

3.1.13. Vinyl sulfone (45). Butyllithium (32.3 mL, 1.42 M, 45.8 mmol) was added dropwise to methylphenylsulfone (3.60 g, 22.9 mmol) in THF (150 mL) at 0 °C and the solution was stirred for 30 min. Diethylchlorophosphate (3.6 mL, 22.9 mmol) in THF (30 mL) was added dropwise and the mixture was stirred for 30 min. After cooling to −78 °C, aldehyde **44** (6.34 g, 20.8 mmol) in THF (30 mL) was added and the mixture was stirred for 3 h. Upon warming to rt the mixture was stirred for an additional 2 h. Brine (200 mL) was added and the mixture extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of the solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 95:5) to give vinylsulfone **45** as a 2.5:1 mixture of *E*/*Z* isomers (6.76 g, 73%) as a colorless oil: IR 3063, 2953, 1748, 1634, 1585 cm^{-1}; MS (ESI^+) *m*/*z* 465 (M+Na); Anal. Calcd for $C_{21}H_{34}O_6SSi$: C, 56.98; H, 7.74. Found: C, 57.07; H, 7.80.

3.1.14. Malonate (46). A solution of diethyl malonate (1.6 mL, 10.6 mmol) and allylcarbonate **45** (1.18 g, 2.66 mmol) in degassed THF (26 mL) was added to a suspension of tris(dibenzylideneacetone)dipalladium(0)-chloroform (140 mg, 0.13 mmol), 1,2-bis(diphenylphosphino)ethane (210 mg, 0.53 mmol), and 4 Å powdered molecular sieves (0.6 g, half by weight of allylcarbonate (**45**) in degassed THF (10 mL). After heating to reflux for 12 h the mixture was cooled to rt, passed through Celite and the solvent was evaporated. The resultant oil was purified by flash column chromatography (hexane/EtOAc, 95:5) to give malonate **46** (1.1 g, 81%) as a white solid, mp 62–64 °C: IR 3059, 2931, 2857, 1733, 1625 cm^{-1}; ^1H NMR δ 7.87–7.85 (2H, m Ar*H*), 7.60 (1H, tt, *J*=7.3, 1.0 Hz, Ar*H*), 7.52 (2H, t, *J*=7.3 Hz, Ar*H*), 6.88 (1H, dd, *J*=15.1, 9.3 Hz, PhO_2SCHCH), 6.39 (1H, d, *J*=15.1 Hz, PhO_2SCHCH), 4.12 (2H, q, *J*=6.8 Hz, CH_3CH_2), 4.06 (1H, ABq, J_{AB}=10.0, *J*=6.8 Hz, CH_3CH*H*), 4.03 (1H, ABq, J_{AB}=10.0, *J*=6.8 Hz, CH_3CH*H*), 3.55 (2H, t, *J*=5.9 Hz, $TBSOCH_2$), 3.43 (1H, d, *J*=8.3 Hz, $(EtO_2C)_2CH$), 2.99 (1H, ddt, *J*=9.3, 8.3, 5.0 Hz, $(EtO_2C)_2CHCH$), 1.65 (1H, m, $TBSOCH_2CH_2CH$H), 1.55–1.37 (3H, m, $TBSOCH_2CH_2CH$H), 1.21 (3H, t, *J*=6.8 Hz, CH_2CH_3), 1.18 (3H, t, *J*=6.8 Hz, CH_2CH_3), 0.86 (9H, s, $C(CH_3)_3$), 0.01 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 167.3, 167.1, 145.7, 140.3, 133.3, 132.7, 129.1, 127.5, 62.3, 61.6, 61.5, 55.7, 41.2, 30.0, 28.3, 25.8, 18.2, 13.9, −5.5; Anal. Calcd for $C_{25}H_{40}O_7SSi$: C, 58.56; H, 7.86. Found: C, 58.87; H, 7.87.

3.1.15. Enyne (47). Malonate **46** (0.81 g, 1.57 mmol) was added to an ice cold suspension of hexane washed 60% sodium hydride (69 mg, 1.73 mmol) in THF (16 mL) and the mixture was stirred for 3 h. Propargyl bromide (3.5 mL, 31.4 mmol) was added and the mixture was stirred overnight. Water (30 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated and the resultant oil purified by flash column chromatography (hexane/EtOAc, 9:1) to give enyne **47** (0.86 g, 99%) as a colorless oil: IR 3276, 2930, 2857, 1732 cm^{-1}; ^1H NMR δ 7.89–7.87 (2H, m, Ar*H*), 7.60 (1H, tt, *J*=7.8, 1.5 Hz, Ar*H*), 7.53 (2H, br t, *J*=7.8 Hz, Ar*H*), 6.87 (1H, dd, *J*=15.1, 10.3 Hz, $PhSO_2CHCH$), 6.47 (1H, d, *J*=15.1 Hz, $PhSO_2CH$), 4.22–4.11 (4H, m, CH_3CH_2), 3.55 (2H, t, *J*=5.9 Hz, $TBSOCH_2$), 3.09 (1H, ddd, *J*=10.3, 10.3, 2.4 Hz, $PhSO_2CHCHCH$), 2.84 (1H, dd, *J*=17.1, 2.4 Hz, HCCCHH), 2.70 (1H, dd, *J*=17.1, 2.4 Hz, HCCCHH), 1.98 (1H, t, *J*=2.4 Hz, CH_2CCH), 1.87–1.81 (1H, m, $TBSOCH_2CH_2CH$H), 1.49–1.40 (1H, m, $TBSOCH_2CH$H), 1.4–1.3 (2H, m, $TBSOCH_2CH$HCHH), 1.24 (3H, t, *J*=7.3 Hz, CH_2CH_3), 1.22 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.87 (9H, s, $C(CH_3)_3$), 0.01 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 168.6, 168.5, 145.0, 140.6, 133.6, 133.3, 129.2, 127.5, 78.4, 72.2, 62.4, 61.9, 59.7, 44.3, 30.9, 25.9, 23.6, 18.2, 13.9, −5.4; HRESIMS calcd for $C_{28}H_{42}O_7SiSNa$ ($[M+Na]^+$): 573.2318; found: 573.2320.

3.1.16. Bicyclooctenone (49). Dicobaltoctacarbonyl (1.31 g, 3.83 mmol) was added to enyne **47** (2.01 g, 3.65 mmol) in hexane (18 mL). After the enyne was consumed according to TLC the solvent was evaporated and CH_2Cl_2 (73 mL) was added. Anhydrous trimethylamine *N*-oxide (250 mg, 3.65 mmol) was added every 30 min four times under an oxygen atmosphere and the mixture was stirred until the alkyne cobalt complex was consumed according to TLC. The mixture was passed through a plug of silica gel (EtOAc). After evaporation of solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 4:1) to give bicyclooctenone **49** (1.73 g, 82%) as a white solid: mp 109–111 °C; IR 3066, 2929, 1713, 1644, 1586 cm^{-1}; ^1H NMR δ 7.94–7.92 (2H, m, Ar*H*), 7.67 (1H, t, *J*=7.3 Hz, Ar*H*), 7.57 (2 H, br t, *J*=7.3 Hz, Ar*H*), 5.86 (1H, d, *J*=1.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.32 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 4.26 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 4.22 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 4.19 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 3.97 (1H, d, *J*=2.9 Hz, PhO_2SCH), 3.73–3.61 (3H, m, $TBSOCH_2$ and $PhSO_2CHCH$), 3.60 (1H, partly obscured d, *J*=18.4 Hz, $(EtO_2C)_2CCH$H), 3.03 (1H, d, *J*=18.4 Hz, $(EtO_2C)_2CCH$H), 2.40 (1H, ddd, *J*=12.2, 7.3, 6.3 Hz, $TBSO(CH_2)_3CH$), 1.88–1.68 (4H, m, $TBSOCH_2CH_2CH_2$), 1.32 (3H, t, *J*=7.3 Hz, CH_2CH_3), 1.27 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.05 (3H, s, $(H_3C)_3CSi(CH_3)_2$), 0.04 (3H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 196.8, 183.3, 170.5, 138.1, 134.1, 129.3, 128.9, 124.9, 72.5, 63.2, 63.0, 62.1, 61.8, 50.8, 49.1, 36.6, 31.1, 27.3, 25.9, 18.2, 14.0, 13.9, −5.4; Anal. Calcd for $C_{29}H_{42}O_8SSi$: C, 60.18; H, 7.31. Found: C, 59.93; H, 7.40.

3.1.17. Aldehyde (50). Decaborane (15 mg, 0.12 μmol) was added to a solution of enone **49** (1.34 g, 2.32 mmol) in methanol (18 mL) and THF (5 mL). After stirring at rt for 2 h the solvent was evaporated. The resultant oily residue was purified by flash column chromatography (hexane/EtOAc, 3.2) to give alcohol (1.01 g, 94%) as a colorless oil: IR 3548, 2937, 1720, 1639 cm^{-1}; ^1H NMR δ 7.93 (2H, d, *J*=7.3 Hz, Ar*H*), 7.68 (1H, t, *J*=7.3 Hz, Ar*H*), 7.58 (2H, t, *J*=7.3 Hz, Ar*H*), 5.87 (1H, s, $(EtO_2C)_2CCH_2CCH$), 4.33 (1H, ABq, J_{AB}=10.8, *J*=6.9 Hz, CH_3CH*H*), 4.28 (1H, ABq, J_{AB}=11.2, *J*=7.3 Hz, CH_3CH*H*), 4.27 (1H, ABq, J_{AB}=11.2, *J*=7.3 Hz, CH_3CH*H*), 4.18 (1H, ABq, J_{AB}=10.8, *J*=7.3 Hz, CH_3CH*H*), 3.92 (1H, d, *J*=3.4 Hz, PhO_2SCH), 3.73–3.64 (3H, m, $HOCH_2$ and $PhSO_2CHCH$), 3.59 (1H, d, *J*=18.6 Hz, $(EtO_2C)_2CCH$H), 3.01 (1H, d, *J*=18.6 Hz, $(EtO_2C)_2CCH$H), 2.40 (1H, ddd, *J*=12.2, 7.3, 4.9 Hz, $HO(CH_2)_3CH$), 1.92–1.73 (4H, m, $HOCH_2CH_2CH_2$), 1.33

(3H, t, J=7.3 Hz, CH_2CH_3), 1.27 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 196.6, 183.1, 170.6, 170.3, 137.7, 134.1, 129.3, 128.9, 124.8, 72.5, 62.8, 62.2, 62.1, 61.9, 51.0, 48.5, 36.4, 30.7, 26.5, 14.0, 13.8; HRESIMS calcd for $C_{23}H_{28}O_8SNa$ ([M+Na]$^+$): 487.1402; found: 487.1406. PCC (370 mg, 1.71 mmol) was added to a solution of alcohol (400 mg, 0.86 mmol) in CH_2Cl_2 (9 mL) and the mixture was stirred for 1 h at rt. The reaction mixture was then passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of the solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 3:2) to give aldehyde **50** (320 mg, 81%) as a colorless oil: IR 2982, 1721, 1641 cm^{-1}; ^{1}H NMR δ 9.81 (1H, s, C*H*O), 7.96–7.94 (2H, m, Ar*H*), 7.69 (1H, t, J=7.3 Hz, Ar*H*), 7.59 (2H, br t, J=7.3 Hz, Ar*H*), 5.87 (1H, d, J=1.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.34 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 4.30 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 4.25 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 4.18 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 3.97 (1H, d, J=3.4 Hz, $PhSO_2CH$), 3.66 (1H, br d, J=19.0, $(EtO_2C)_2$-CC*H*H), 3.64 (1H, partly obscured dm, J=12.0 Hz, $PhSO_2CHCH$), 3.01 (1H, d, J=19.0 Hz, $(EtO_2C)_2CCH$*H*), 2.92 (1H, br dt, J=18.1, 7.3 Hz, CHOC*H*H), 2.61 (1H, ddt, J=18.1, 1.0, 7.3 Hz, CHOCH*H*), 2.42 (1H, ddd, J=12.7, 6.8, 6.8 Hz, $CHO(CH_2)_2CH$), 2.28 (1H, ABdt, J_{AB}=14.8, J=7.2, 6.8 Hz, $CHOCH_2CHH$), 1.80 (1H, ABdt, J_{AB}=14.8, J=6.8, 6.8 Hz, $CHOCH_2CHH$), 1.34 (3H, t, J=7.3 Hz, CH_2CH_3), 1.27 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 201.1, 196.5, 181.6, 170.9, 170.6, 139.4, 133.9, 130.0, 129.1, 125.5, 73.3, 63.6, 62.4, 62.0, 51.3, 48.5, 42.2, 36.6, 23.3, 14.4, 14.1; HRESIMS calcd for $C_{23}H_{26}O_8SNa$ ([M+Na]$^+$): 485.1246; found: 485.1236.

3.1.18. Tricycle (51). Diazabicycloundecane (54 μL, 0.60 mmol) was added to aldehyde **50** (280 mg, 0.60 mmol) in CH_2Cl_2 (12 mmol) and the mixture was stirred for 4 h at rt. The reaction mixture was washed with 1 M HCl (10 mL) and water (10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil purified by flash column chromatography (hexane/EtOAc, 3:2) to give tricycle **51** as a 3:2 mixture of carbinol isomers (130 mg, 47%, white solid: mp 134–138 °C); HRESIMS calcd for $C_{23}H_{26}O_8SNa$ ([M+Na]$^+$): 485.1246; found: 485.1250; Anal. Calcd for $C_{23}H_{26}O_8SSi$: C, 59.73; H, 5.67. Found: C, 59.84; H, 5.60.

3.1.19. Keto-bromide (52). Triphenylphosphine (120 mg, 0.46 mmol) was added to a solution of bromine (23 μL, 0.46 mmol) in CH_2Cl_2 (4 mL) followed by imidazole (31 mg, 0.46 mmol) then alcohol (190 mg, 0.42 mmol). After stirring at rt for 15 min, 1 M HCl (5 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water (5 mL), dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 4:1) to give bromide **52** (190 mg, 86%) as a colorless oil: IR 3036, 2982, 2937, 1714, 1644, 1585 cm^{-1}; ^{1}H NMR δ 7.96–7.94 (2H, m, Ar*H*), 7.69 (1H, t, J=7.3 Hz, Ar*H*), 7.59 (2H, t, J=7.3 Hz, Ar*H*), 5.89 (1H, d, J=1.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.37–4.16 (4H, m, CH_3CH_2), 3.83 (1H, d, J=2.9 Hz, PhO_2SCH), 3.64 (1H, br dd, J=19.0, 1.9 Hz, $(EtO_2C)_2$-CC*H*H), 3.63 (1H, obscured m, $PhSO_2CHCH$), 3.51 (1H, ABt, J_{AB}=10.0, J=5.8 Hz, $BrCH_2$), 3.44 (1H, ABdd, J_{AB}=10.0, J=8.3, 6.3 Hz, $BrCH_2$), 3.02 (1H, d, J=19.0 Hz, $(EtO_2C)_2CCH$*H*), 2.34 (1H, dt, J=12.7, 6.8 Hz, $Br(CH_2)_3CH$), 2.24–2.16 (1H, m, $BrCH_2CHH$), 2.03 (1H, m, $BrCH_2CH$*H*), 1.90–1.79 (2H, m, $BrCH_2CH_2CH_2$), 1.34 (3H, t, J=7.3 Hz, CH_2CH_3), 1.28 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 196.3, 182.6, 170.4, 170.2, 137.8, 134.1, 129.2, 129.0, 124.9, 72.5, 62.8, 62.2, 61.9, 50.9, 48.2, 36.6, 33.5, 30.8, 28.8, 14.0, 13.8; HRESIMS calcd for $C_{23}H_{27}O_7BrSNa$ ([M+Na]$^+$): 549.0558; found: 549.0558.

3.1.20. Tricycle (53). Diazabicycloundecane (37 μL, 0.25 mmol) was added to bromide **52** (132 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) and the mixture was refluxed overnight. Cooling to rt the reaction mixture was washed with 1 M HCl (5 mL) and water (5 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 3:1) to give tricycle **53** (78 mg, 70%) as a white solid: mp 163–165 °C; IR 2940, 2360, 1729, 1638, 1584 cm^{-1}; ^{1}H NMR δ 8.00–7.99 (2H, m, Ar*H*), 7.66 (1H, t, J=7.3 Hz, Ar*H*), 7.57 (2H, t, J=7.3 Hz, Ar*H*), 5.83 (1H, d, J=2.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.32–4.13 (4H, m, CH_3CH_2), 4.03 (1H, d, J=6.8 Hz, $PhSO_2CCHCH$), 3.59 (1H, d, J=21.0 Hz, $(EtO_2C)_2CCH$*H*), 3.11 (1H, d, J=21.0 Hz, $(EtO_2C)_2CCH$*H*), 3.03 (1H, td, J=6.8, 6.8 Hz, $PhSO_2CCHCH$), 2.59 (1H, br d, J=15.6 Hz, $PhSO_2CCHHCH_2$), 1.60–1.59 (1H, m, $PhSO_2CCHHCH_2$), 1.53–1.36 (3H, m, $PhSO_2CCH_2CH_2$ and $PhSO_2CCH_2CH_2CHH$), 1.29 (3H, t, J=6.8 Hz, CH_2CH_3), 1.26 (3H, t, J=6.8 Hz, CH_2CH_3), 0.68 (1H, dtd, J=13.2, 13.2, 2.5 Hz, $PhSO_2CCH_2CH_2CH$*H*); ^{13}C NMR, δ 182.3, 170.6, 168.4, 159.1, 136.4, 134.1, 130.6, 128.9, 122.4, 73.1, 65.0, 62.1, 61.9, 60.3, 50.8, 40.5, 33.7, 26.3, 22.0, 21.0, 14.0; MS (ESI$^+$) m/z 469.2 (M+Na); Anal. Calcd for $C_{23}H_{26}O_7S$: C, 61.87; H, 5.87. Found: C, 61.92; H, 5.90.

3.2. Crystallographic information

X-ray crystal data tables for compounds **49**, **51**, and **53**. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229389–229391. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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References and notes

1. Selected reviews: Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263; Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022; Gibson, S. E.; Stevanazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800; Laschat, S.; Becheanu, A.;

Bell, T.; Baro, A. *Synlett* **2005**, 2547; Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795; Park, K. H.; Chung, Y. K. *Synlett* **2005**, 545.
2. For representative examples for utilization of the Pauson–Khand reaction in triquinane synthesis, see: (a) Mukai, C.; Kobayashi, M.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225; (b) Iura, Y.; Sughara, T.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 291; (c) Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* **2001**, *57*, 2729; (d) Renaud, K. L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113; Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477; Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025.
3. Castro, J.; Sörensen, H.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388.
4. Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169.
5. Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853.
6. Bernardes, V.; Kann, N.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 6670.
7. Krafft, M. E.; Cheung, Y. Y.; Juliano-Capucao, C. A. *Synthesis* **2000**, 1020.
8. Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.
9. Tandem reactions: Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289; de Meijere, A.; von Zezschwitz, P.; Nüske, H.; Stulgies, B. *J. Organomet. Chem.* **2002**, *653*, 129; Malacria, M. *Chem. Rev.* **1996**, *96*, 289.
10. Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396.
11. For a recent review of polyquinane synthesis see: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671.
12. For a review of linear triquinane synthesis see: Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647.
13. Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92.
14. Zakow, L. H.; Harris, R. N., III; Van Derveers, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 420; (b) Jasperse, C. R.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601.
15. For a general discussion of propellane chemistry, see: Ginsburg, D. *Propellanes, Structure and Reactions*; Chemie: Weinheim, 1975.
16. Clive attempted a tandem Pauson–Khand/radical cyclization approach to the propellanes, however, the initial PKR failed. See Ref. 10.
17. (a) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 2239; (b) Marco, J. A.; Sanz-Cervera, J. F.; Morante, M. D.; Garcia-Lliso, V.; Valles-Xirau; Kakupovic, J. *Phytochemistry* **1996**, *41*, 837; (c) Weyerstahl, P.; Marschall, H.; Schulze, M.; Schwope, I. *Liebigs Ann. Chem.* **1996**, 799.
18. Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611.
19. Bonini, C.; Checconi, M.; Righi, G.; Rossi, L. *Tetrahedron* **1995**, *51*, 4111.
20. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1992**, *113*, 224; Jung, M. E. *Synlett* **1999**, 843.
21. For leading references on the Tsuji–Trost reaction, see: (a) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: Chichester, UK, 2000; (b) Trost, B. M.; Lee, C. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, NY, 2000; Chapter 8E.
22. Hitchcock, S.; Houldsworth, S.; Pattenden, G.; Pryde, D.; Thomson, N.; Blake, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3181.
23. Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204.
24. Vries, E.; Brussee, J.; Gen, A. *J. Org. Chem.* **1994**, *59*, 7133.
25. Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.
26. (a) Adrio, J.; Rodriguez, R.; Carretero, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906; (b) Adrio, J.; Rodriguez, R.; Carretero, J. *Chem.—Eur. J.* **2001**, *7*, 2435; For examples of mechanics calculations to predict *endo*/*exo* ratios, see: Breczinski, P. M.; Stumpf, A.; Hope, H.; Krafft, M. E.; Casalnuovo, J. A.; Schore, N. E. *Tetrahedron* **1999**, *55*, 6797.
27. Barrett, A. G.; Flygare, J. A.; Spilling, C. D. *J. Org. Chem.* **1989**, *54*, 4723.
28. Lee, J. W.; Dong, Y. O. *Synth. Commun.* **1989**, *19*, 2209.
29. (a) Alonso, I.; Carretero, J.; Garrido, J.; Magro, V.; Pedregal, C. *J. Org. Chem.* **1997**, *62*, 5682; (b) Garrido, J.; Alonso, I.; Carretero, J. *J. Org. Chem.* **1998**, *63*, 9406.
30. Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464.
31. Jeong, Y. J.; Lee, J. J.; Park, E. S.; Yoon, C. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1223. Typical methods for desilylation (tetrabutylammonium fluoride, HF/pyridine) did not give clean results.
32. (a) Sheu, J. H.; Hung, K. C.; Wang, G. H.; Duh, C. Y. *J. Nat. Prod.* **2000**, *63*, 1603; (b) Lee, H. Y.; Kim, B. G. *Org. Lett.* **2000**, *2*, 1951.
33. Cooper, K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 799; Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K.; Springer, J. P. *Tetrahedron Lett.* **1980**, 2625.

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Synthesis of novel spiro-cyclohexene bicyclo[2.2.2]octane derivatives

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Abstract—A methodology for the synthesis of novel spiro-cyclohexene bicyclo[2.2.2]octane derivatives, including Claisen rearrangement and ring-closing metathesis (RCM) as key synthetic steps, is described.

1. Introduction

Spiro-cyclohexane bicyclo[2.2.2]octanes are rarely occurring molecular frameworks, and only a few examples of the synthesis of such systems have been reported so far.[1] The base catalyzed dimerization of substituted cyclohexenones, leading to structurally simple spiro-bicyclics, is one of the earliest reported procedures.[2–4] The Diels–Alder reaction between spirodi-*o*-xylylene and maleic anhydride resulted in a spiro-bicycle, as reported by Errede.[5] More structurally advanced spiro-cyclohexane bicyclo[2.2.2]-octanes were synthesized by Holton et al.[6] In the late 1990s Kuwajima et al. reported, in a number of papers, their studies towards the synthesis of taxane diterpenoidic skeletons.[7–9] These were based on a general cyclization procedure for the construction of the eight-membered B-ring of the tricyclic taxane skeleton. As reported, under certain conditions the cyclization-reaction resulted in the formation of spiro-bicyclic by-products, and in one particular study, they were able to optimize the formation of these spiro-bicycles.[10] Notably, compound **1** (Fig. 1) was found to exhibit multi-drug resistance (MDR) reversing activity with the same potency as verapamil. As far as we know there are only two reports concerning natural products containing the substructure of a spiro-bicyclo[2.2.2]octane unit (isolation from *Daphniphyllum* species).[11,12]

Since the early 1990s our group has been involved in the synthesis of bicyclo[2.2.2]octane compounds, mostly in connection with ligand design and also for other synthetic purposes.[13,14] Recently, we reported the synthesis of spiro-bicycle **3** as a mimetic of paclitaxel.[15] Since this compound was inactive it motivated the incorporation of additional pharmacophores. Thus, we decided to develop a method

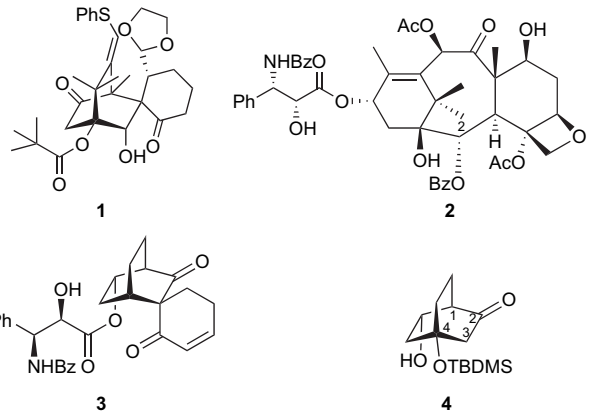

Figure 1.

for the synthesis of bridgehead oxy-functionalized spiro-bicyclo[2.2.2]octanes. As a first step in this direction we developed a synthesis of compound **4**.[16] The initial plan for the spiro-annulation of compound **4** at position 3, was to utilize the same route as employed for the synthesis of compound **3**.[15] However, in the case of the bridgehead silyl-oxy-functionalized derivatives this route was unproductive, and therefore a different methodology had to be developed. Herein, we wish to report our synthetic strategy towards novel bridgehead methoxy substituted spiro-cyclohexene bicyclo[2.2.2]octane derivatives, which includes Claisen rearrangement and ring-closing metathesis (RCM) as key synthetic transformations.

2. Results and discussion

As a first step we decided to protect the 6-OH in **4** as its benzyl ether. For practical reasons we used an 85:15 mixture

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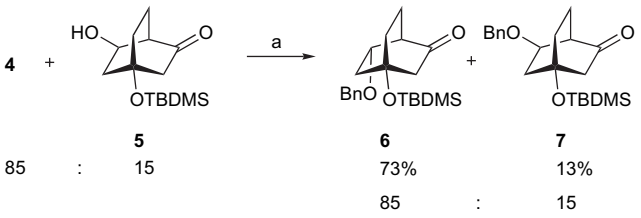
of **4** and **5**, respectively, as starting materials since **4** and **5** were equilibrating under various conditions (Scheme 1).

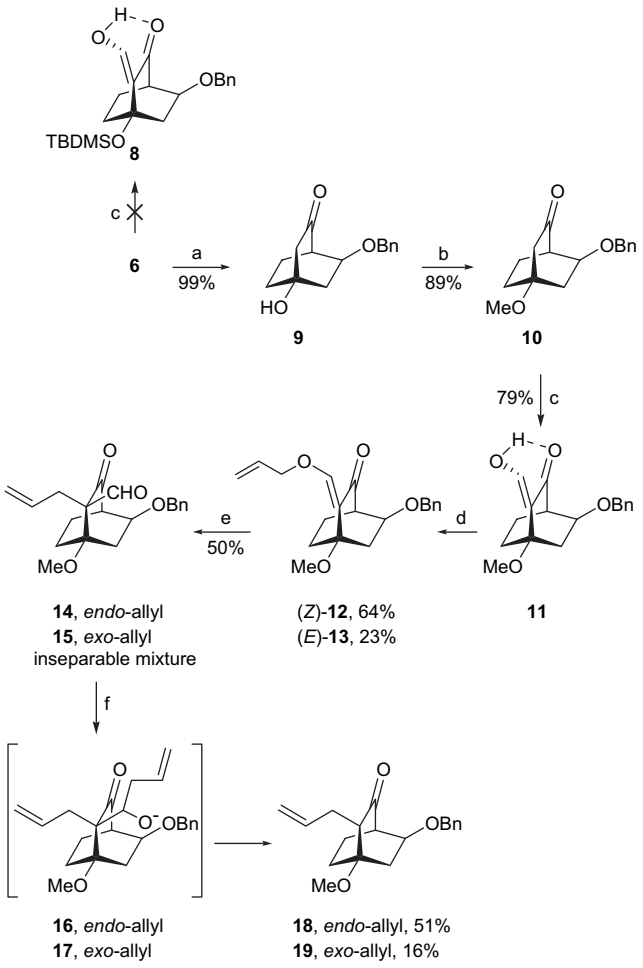


Scheme 1. Benzyl protection of diastereomers **4** and **5**. Reaction conditions: (a) NaH (2.5 equiv), BnBr (2.7 equiv), TBAI (0.5 equiv), THF, 0 °C–rt, 1.5 h.

Endo-alcohol **4** and *exo*-alcohol **5**, were obtained via a ring-closing aldolization reaction as a diastereomeric mixture in a ratio of 85:15, respectively.[16] Compounds **4** and **5** could easily be separated by column chromatography. However, when treated with NaH, a fast ring-opening and -closing occurred, yielding the same ratio of 85:15 diastereomers **6** and **7**, respectively, after the addition of BnBr/TBAI. Diastereomers **6** and **7**, obtained in 86% combined yields, were then separated by column chromatography.

Initial attempts to formylate **6** with ethyl formate, in the presence of NaH, to produce **8**, were unproductive (Scheme 2). This is probably due to the steric hindrance imposed by the large TBDMS protective group positioned at the bridgehead oxygen. We therefore decided to replace the bulky TBDMS group with the much smaller methyl group despite the bad prospect of removing it later. Thus, the TBDMS–ether was cleaved by use of $BF_3 \cdot OEt_2$ in MeCN at 0 °C,[17] which gave bridgehead hydroxyl compound **9** in 99% yield. Methylation of compound **9** was performed by the use of Ag_2O and methyl iodide, which gave methyl ether **10** (89%). Subsequent condensation of compound **10** with ethyl formate produced hydroxymethylenated product **11** in 79% yield.

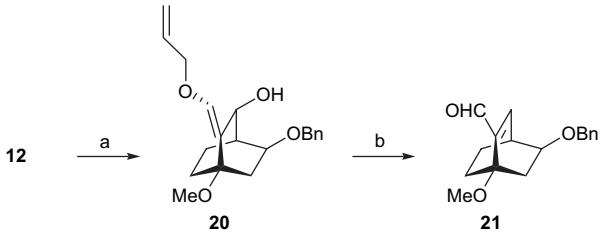
For the attachment of an allyl group at the α-carbon, we planned to employ the Tsuji–Trost reaction,[18] which was reported to give *C*-allylation exclusively.[19] However, when subjecting compound **11** to $Pd(dba)_2/PPh_3$/allyl acetate with NaH as the base, it led to complex reaction mixtures, from which only a small amount of the *O*-allylated derivative **12** was obtained after column chromatography (Scheme 2). This observation made us change strategy, and instead of optimizing the Tsuji–Trost reaction, we decided to perform a Claisen rearrangement[20] of the *O*-allylated product, which ultimately would lead to the same product as expected from the Tsuji–Trost reaction. Thus, compound **11** was subjected to NaH and allyl bromide in THF, which yielded the *O*-allylated products **12** and **13** (75:25) in 87% combined yields (Scheme 2). The mixture of **12** and **13** was then heated at 165 °C in toluene for 12 h and the Claisen rearrangement products **14** and **15** (70:30 as determined by ^1H NMR analysis) were obtained as an inseparable mixture in 50% yield together with 47% combined yield of recovered starting materials **12** and **13**. Even though products **14** and **15** were impossible to be separated by column chromatography, we decided to continue with this mixture of isomers, with the hope to be able to achieve separation at a later stage. Reaction of the aldehyde functionalities of compounds **14** and **15** with allyl Grignard reagent apparently gave the desired allyl-



Scheme 2. Reaction conditions: (a) $BF_3 \cdot OEt_2$ (1 equiv), MeCN, −10 °C, 2 h; (b) MeI (35 equiv), Ag_2O (3.8 equiv), MeCN, 40 °C, 48 h; (c) NaH (3.0 equiv), ethyl formate (10 equiv), THF, 0 °C–rt, 48 h; (d) NaH (2.5 equiv), allyl bromide (2.0 equiv), THF, 50 °C, 4 h; (e) toluene, 165 °C, 12 h (sealed tube); (f) allyl magnesium bromide (1 equiv), THF, −78 °C to rt.

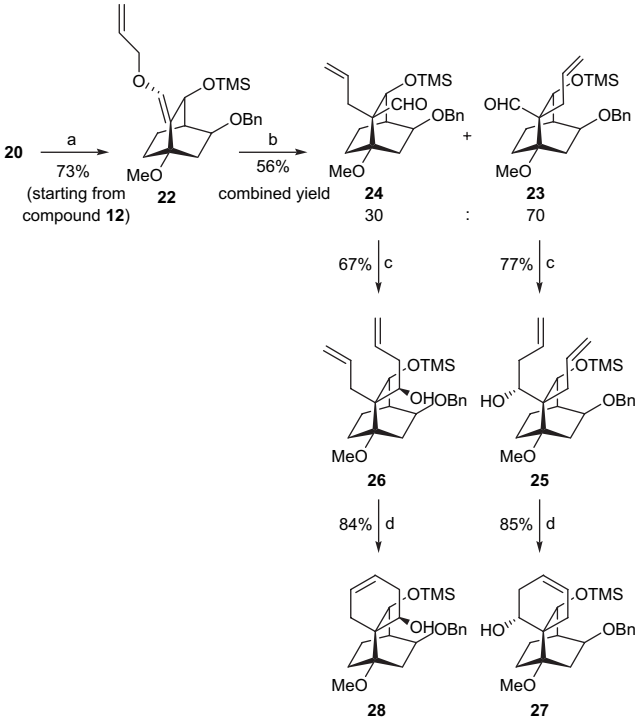
addition products. However, the intermediate homo allylic alcoholates **16** and **17** (shown in brackets in Scheme 2) were unstable. The compounds obtained from this reaction were the mono-allylic derivatives **18** and **19** (67% combined yields, **18/19** 75:25, respectively). Thus, elimination of the homoallylic part had occurred. Attempts were made to try and capture the intermediate alkoxide in situ by addition of TMS–Cl to the allyl Grignard reaction mixture. However, the elimination was too fast at 0 °C, and at lower temperatures (−78 °C) no reaction took place at all. Apparently, the elimination of the homoallylic part of intermediates **16** and **17** involves assistance from the ketone functionality by enolate formation. Accordingly, reduction of the ketocarbonyl group of compound **12** would render the elimination impossible in the following allyl-addition reaction. The same reasoning would, of course, also apply for ketone **13**. However, since this isomer was obtained in minor amounts, we decided to continue the synthesis using only compound **12**. Thus, the ketone functionality of compound **12** was reduced by employing a modified Luche reagent ($NaBH_4/CeCl_3$/2,6-lutidine), which had been applied before by Banwell et al.[21] in a similar situation. The reduction

exclusively afforded *endo*-alcohol **20** (Scheme 3), but when this compound was tested in the Claisen rearrangement reaction, it resulted in the isolation of α,β-unsaturated aldehyde **21**, which was formed together with minor amounts of an unidentified product.



Scheme 3. Reaction conditions: (a) $NaBH_4$ (2.0 equiv), $CeCl_3$ (2.0 equiv), 2,6-lutidine, EtOH (95%), 0 °C, 1 h and (b) toluene, 165 °C, 12 h (sealed tube).

Apparently, formation of **21** from **20** (Scheme 3) involved some kind of elimination of allylic alcohol, which may occur via proton induced removal of water followed by hydrolysis. To circumvent the formation of unwanted product **21**, crude alcohol **20** was TMS protected to give compound **22** (73% yield, starting from **12**) (Scheme 4), which in turn was subjected to Claisen rearrangement conditions (165 °C in toluene). This resulted in the formation of the desired allyl-aldehydes **23** and **24** (56% combined yields). In this case, the starting material, compound **22**, was fully consumed after 20 h, in contrast to the reaction when performed with ketones **12** and **13**, as mentioned. The modest yield obtained of compounds **23** and **24** (56%) can be ascribed to the formation of several unidentified by-products.



Scheme 4. Synthesis of spiro-bicycles **27** and **28**. Reaction conditions: (a) TMSCl (2.5 equiv), Et_3N (2.5 equiv), DMAP (cat.), CH_2Cl_2, 0 °C, 0.5 h; (b) toluene, 165 °C, 20 h (sealed tube); (c) allyl magnesium bromide (2 equiv), THF, 0 °C, 1.5 h and (d) [$RuCl_2$(=CHPh)(PCy_3)$_2$] (10 mol %), CH_2Cl_2, 40 °C, 10 h.

After separation by column chromatography, compounds **23** and **24** (ratio: 70:30, respectively) were reacted separately in subsequent transformations. Thus, by subjecting **23** and **24** to allyl Grignard reagent in THF at 0 °C, homoallylic alcohols **25** and **26** were obtained in 77% and 67% yields, respectively. The diastereoselectivity of this reaction turned out to be high, as only one diastereomer was isolated in each case, as indicated by ^{1}H NMR analysis. The last step in the reaction sequence consisted of a ring-closing metathesis reaction,[22,23] which progressed nicely, affording spirocyclohexene bicyclo[2.2.2]octanes **27** and **28** in 85% and 84% yields, respectively.

The structure of target molecule **27** was confirmed by single-crystal X-ray analysis (Fig. 2 and Supplementary data), which revealed the hydroxyl group, positioned at the spiro-ring, to have an *endo*-configuration (in relation to the bicyclic framework).

The structure of product **27** could also be established on the basis of 2D-NMR experiments (COSY and NOESY). Specifically, the absence of a W-coupling between protons Ha-6′ and H-2′ in the COSY spectrum of compound **27** (Fig. 3a) again established the spiro-hydroxyl to have an *endo*-configuration.

Unfortunately, we were unable to find a suitable solvent-system for the crystallization of compound **28**, and therefore single-crystal X-ray diffraction could not be carried out in order to confirm its structure. Instead, COSY and NOESY spectroscopies were used for this purpose. Thus, in the case of compound **28**, the characteristic correlation between protons Ha-6′ and H-2′ in the COSY spectrum (W-coupling shown in red in Fig. 3b), indicated the spiro-hydroxyl to have an *exo*-configuration.

It should be pointed out that compound **4** can be obtained in an optically pure state, but that method must be optimized in order to be adaptable to a larger scale.[25] Thus, it is in principle possible to install two adjacent quarternary stereogenic carbon centres in **27** and **28**, although at present not in

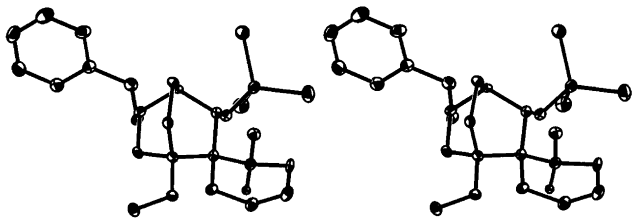


Figure 2. DIAMOND[24] drawing of compound **27**, shown in stereo view. For clarity, all hydrogen atoms, except for the one on C-2′ (see Fig. 3), have been omitted. Thermal ellipsoids are shown at the 30% probability level.

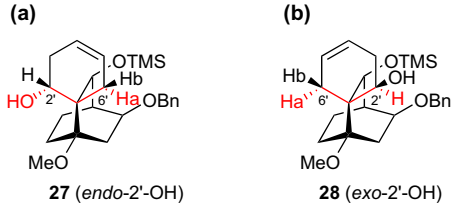


Figure 3.

a highly diastereoselective manner. This demands further investigations and optimizations.

3. Conclusions

We have shown that spirocyclization starting from **4** is a non-selective but yet viable route to spiro-bicyclic compounds **27** and **28**. These compounds contain four hydroxyl groups of which three are protected with orthogonal protective groups, which make them attractive for further transformations. Furthermore, another quarternary carbon centre was installed next to the one already present in **4**.

4. Experimental

4.1. (±)-6-*endo*-Benzyloxy-4-(*tert*-butyl-dimethyl-silyloxy)-bicyclo[2.2.2]octan-2-one (6) and (±)-6-*exo*-benzyloxy-4-(*tert*-butyl-dimethyl-silyloxy)-bicyclo[2.2.2]octan-2-one (7)

NaH (60% in mineral oil, 1.74 g, 43.5 mmol) was added to a solution of **4** and **5** (85:15, respectively)[16] (4.70 g, 17.4 mmol) in dry THF (30 mL) at 0 °C. After 20 min of stirring, TBAI (3.20 g, 8.70 mmol) and BnBr (2.70 mL, 47.0 mmol) were added. Stirring was continued at 0 °C for 5 min and then at rt for 1.5 h. The reaction mixture was again cooled to 0 °C, and water (5 mL) was added dropwise. The water phase was then extracted with EtOAc (3×10 mL), and the combined organic phases were washed with brine and dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, pentane/ether 9:1) to give **6** (4.60 g, 12.7 mmol, 73%) and **7** (810 mg, 2.25 mmol, 13%) as colourless oils. Compound **6** crystallized upon standing at 4 °C. For compound **6**: mp: 45.7–48.2 °C; IR (KBr) 2938, 2872, 1720 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.36–7.26 (m, 2H) 7.13–7.06 (m, 3H) 4.40 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.16 (dAB, J_{AB}=11.9 Hz, 1H) 3.40–3.36 (m, 1H) 2.60–2.53 (m, 2H) 2.29–2.24 (m, 1H) 1.88–1.79 (m, 2H) 1.31–1.24 (m, 3H) 0.98–0.92 (m, 1H) 0.91 (s, 9H) –0.03 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 208.4, 128.6, 128.1, 127.9, 127.5, 74.4, 72.2, 70.0, 52.5, 46.2, 43.01, 33.0, 25.9, 18.3, 18.0, −2.0; HRMS (FAB+) calcd for $C_{21}H_{33}O_3Si$ (M+H): 361.2199. Found: 361.2195. Anal. calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 70.11; H, 8.87. For compound **7**: IR (NaCl) 2955, 2855, 1722 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.21–7.18 (m, 2H) 7.15–7.06 (m, 3H) 4.12 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.02 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.51–3.47 (m, 1H) 2.57–2.54 (m, 1H) 2.23 (br d_{AB}, J_{AB}=18.1 Hz, 1H) 2.09 (dd_{AB}, J=3.1 Hz, J_{AB}=18.2 Hz, 1H) 2.04–2.01 (m, 1H) 1.77–1.75 (m, 2H) 1.73–1.70 (m, 1H) 1.41–1.35 (m, 1H) 1.27–1.19 (m, 1H) 0.92 (s, 9H) –0.03 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 209.1, 138.7, 128.6, 127.9, 127.7, 72.5, 72.1, 70.3, 52.1, 47.0, 43.8, 33.2, 25.8, 18.0, 16.9, −2.0; HRMS (FAB+) calcd for $C_{21}H_{33}O_3Si$ (M+H): 361.2199. Found: 361.2207. Anal. calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 70.05; H, 8.92.

4.2. (±)-6-*endo*-Benzyloxy-4-hydroxy-bicyclo[2.2.2]-octan-2-one (9)

$BF_3 \cdot OEt_2$ (1.60 mL, 12.7 mmol) was added to a solution of **6** (4.60 g, 12.7 mmol) in MeCN (200 mL) at −10 °C. Stirring was continued at −10 °C for approximately 2 h; where after 0.4 M aq $NaHCO_3$ solution (20 mL) was added. The water phase was extracted with EtOAc (3×100 mL) and the combined organic phases were dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 1:1) to give **9** (3.10 g, 12.6 mmol, 99%) as a colourless oil. IR (NaCl) 3408, 2953, 2874, 1720 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.24–7.17 (m, 2H) 7.14–7.06 (m, 3H) 4.35 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.12 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.35–3.31 (m, 1H) 2.50–2.47 (m, 1H) 2.36 (br d_{AB}, J_{AB}=17.9 Hz, 1H) 2.07 (dd_{AB}, J=3.3 Hz, J_{AB}=17.9 Hz, 1H) 1.74–1.70 (m, 1H) 1.59–1.56 (m, 1H) 1.28–1.20 (m, 1H) 1.17–1.12 (m, 2H) 0.93–0.90 (m, 1H) 0.87 (s, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 208.6, 138.6, 128.6, 128.1, 127.9, 127.5, 74.3, 69.8, 69.3, 51.9, 46.3, 42.2, 32.2, 18.2; HRMS (FAB+) calcd for $C_{15}H_{19}O_3$ (M+H): 247.1334. Found: 247.1328. Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.21; H, 7.34.

4.3. (±)-6-*endo*-Benzyloxy-4-methoxy-bicyclo[2.2.2]-octan-2-one (10)

For the methyl protection, it was important to use commercial Ag_2O, since the yield was low (40%) when we used a home-made quality. MeI (28.0 mL, 445 mmol) and Ag_2O (11.0 g, 47.3 mmol) were added to a solution of **9** (3.10 g, 12.6 mmol) in MeCN (60 mL). The resulting mixture was stirred at 40 °C for 48 h. The reaction mixture was then allowed to cool to rt, and filtered through a pad of Celite, which was rinsed with EtOAc. After concentration at reduced pressure, the resulting residue was purified by column chromatography (SiO_2, heptane/EtOAc 75:25) to give **10** (2.91 g, 11.2 mmol, 89%) as a slightly yellow oil. IR (NaCl) 2953, 2876, 1732 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.25–7.24 (m, 2H) 7.14–7.06 (m, 3H) 4.38 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.14 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.39–3.35 (m, 1H) 2.83 (s, 3H) 2.52–2.47 (m, 2H) 2.21–2.15 (m, 1H) 1.82–1.79 (m, 1H) 1.75–1.68 (m, 1H) 1.29–1.22 (m, 3H) 0.97–0.91 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 208.3, 138.6, 128.6, 128.1, 127.9, 127.5, 74.2, 74.0, 69.9, 49.2, 47.5, 46.3, 38.1, 28.7, 18.0; HRMS (FAB+) calcd for $C_{16}H_{21}O_3$ (M+H): 261.1491. Found: 261.1490. Anal. calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.74; H, 7.67.

4.4. (±)-6-*endo*-Benzyloxy-3-hydroxymethylene-4-methoxy-bicyclo[2.2.2]octan-2-one (11)

Compound **10** (2.31 g, 8.89 mmol), dissolved in THF (15 mL), was added drop wise to a solution of NaH (60% in mineral oil, 1.10 g, 26.7 mmol) in dry THF (70 mL) at 0 °C. Stirring was continued for 20 min at 0 °C and then ethyl formate (7.20 mL, 88.9 mmol) was added drop wise. Stirring was continued for 5 min at 0 °C and then at rt for 48 h. After cooling to 0 °C, the reaction mixture was quenched by slow addition of 2 M aq H_2SO_4 (80 mL). The organic phase was separated and the water phase extracted with EtOAc (3×80 mL). The combined organic phases were then washed with brine and dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 85:15) to give **11**

(2.03 g, 7.04 mmol, 79 %) as a colourless oil. IR (NaCl) 2955, 2874, 1666, 1597 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.37 (s, 1H) 7.25–7.23 (m, 2H) 7.13–7.06 (m, 3H) 4.39 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.17 (d_{AB}, J_{AB}=12.1 Hz, 1H) 3.37 (dt, J=9.3, 3.1 Hz, 1H) 2.87 (s, 3H) 2.65–2.63 (m, 1H) 1.80 (dd_{AB}, J=9.1 Hz, J_{AB}=12.8 Hz, 1H) 1.64 (td_{AB}, J=2.9 Hz, J_{AB}=12.8 Hz, 1H) 1.30–1.22 (m, 2H) 1.19–1.14 (m, 1H) 0.97–0.88 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 203.3, 158.9, 138.6, 128.6, 128.1, 127.9, 127.8, 127.5, 117.1, 74.7, 74.5, 69.8, 50.2, 45.1, 39.2, 28.9, 18.6; HRMS (FAB+) calcd for $C_{17}H_{21}O_4$ (M+H): 289.1440. Found: 289.1452. Anal. calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.94; H, 6.91.

4.5. (±)-(*Z*)-3-Allyloxymethylene-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (12) and (±)-(*E*)-3-allyloxymethylene-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (13)

Compound **11** (1.74 g, 6.04 mmol), dissolved in THF (10 mL), was added drop wise to a solution of NaH (60% in mineral oil, 605 mg, 15.1 mmol) in THF (10 mL) at 0 °C. Stirring was continued for 20 min at 0 °C before ally bromide (1.10 mL, 12.1 mmol) was added. The reaction mixture was then kept at 50 °C for 4 h, after which the reaction mixture was allowed to cool to rt, before being quenched with water (10 mL) at 0 °C. The organic phase was separated, and the water phase saturated with NaCl before being extracted with EtOAc (5×10 mL). The combined organic phases were then washed with brine and dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 7:3) to give compound **12** (1.26 g, 3.84 mmol, 64%) as a yellow solid and compound **13** (456 mg, 1.39 mmol, 23%) as a yellow oil. For compound **12**: mp 61.1–65.2 °C; IR (KBr) 2941, 2876, 1693, 1618 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.35 (s, 1H) 7.31–7.29 (m, 2H) 7.13–7.05 (m, 3H) 5.47–5.40 (m, 1H) 5.01–4.95 (m, 1H) 4.87–4.84 (m, 1H) 4.51 (d_{AB}, J_{AB}=12.0 Hz, 1H) 4.24 (d_{AB}, J_{AB}=12.0 Hz, 1H) 3.74–3.71 (m, 2H) 3.53–3.49 (m, 1H) 3.27 (s, 3H) 2.76–2.75 (m, 1H) 2.24 (td_{AB}, J=2.9 Hz, J_{AB}=13.1 Hz, 1H) 1.95 (dd_{AB}, J=9.4 Hz, J_{AB}=13.1 Hz, 1H) 1.85–1.77 (m, 1H) 1.53–1.44 (m, 1H) 1.40–1.33 (m, 1H) 1.14–1.06 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 199.1, 151.6, 138.9, 132.8, 128.5, 128.1, 127.9, 119.1, 118.0, 77.2, 75.1, 74.6, 69.9, 52.5, 46.3, 41.0, 30.6, 18.5; HRMS (FAB+) calcd for $C_{20}H_{24}NaO_4$ (M+Na): 351.1572. Found: 351.1573. Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.06; H, 7.32. For compound **13**: IR (NaCl) 2951, 2870, 1701, 1616 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.30–7.28 (m, 2H) 7.15–7.06 (m, 3H) 6.63 (s, 1H) 5.58–5.50 (m, 1H) 5.17–5.12 (m, 1H) 4.90–4.87 (m, 1H) 4.53 (d_{AB}, J_{AB}=12.0 Hz, 1H) 4.24 (d_{AB}, J_{AB}=12.0 Hz, 1H) 3.90–3.88 (m, 2H) 3.47 (dt, J=9.4, 3.1 Hz, 1H) 3.00 (s, 3H) 2.76–2.74 (m, 1H) 2.00 (dd_{AB}, J=9.3 Hz, J_{AB}=12.8 Hz, 1H) 1.80 (td_{AB}, J=2.8 Hz, J_{AB}=12.9 Hz, 1H) 1.51–1.34 (m, 3H) 1.07–0.99 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 194.6, 150.9, 139.0, 133.3, 128.5, 128.1, 127.9, 118.6, 117.7, 75.7, 75.1, 74.4, 69.8, 50.0, 47.0, 39.5, 29.0, 18.4; HRMS (FAB+) calcd for $C_{20}H_{24}NaO_4$ (M+Na): 351.1572. Found: 351.1574. Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.08; H, 7.26.

4.6. (±)-2-*endo*-Allyl-5-*endo*-benzyloxy-1-methoxy-3-oxo-bicyclo[2.2.2]octane-2-carbaldehyde (14) and (±)-2-*exo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-oxo-bicyclo[2.2.2]octane-2-carbaldehyde (15)

Compounds **12** and **13** (276 mg, 0.84 mmol, **12/13** 75:25, respectively) dissolved in toluene (5 mL) were placed in a sealed pressurized vessel and heated at 165 °C for 12 h. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 7:3) to give an inseparable diastereomeric mixture of compounds **14** and **15** (138 mg, 0.42 mmol, 50%) as a colourless oil, together with starting materials **12** and **13** (130 mg, 0.40 mmol, 47%). Analysis for the mixture of **14** and **15**: IR (NaCl) 2957, 2878, 2833, 1738, 1705 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{24}NaO_4$ (M+Na): 351.1572. Found: 351.1575. Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.21; H, 7.32. Selected ^1H NMR signals for compound **14** (400 MHz, benzene-d_6): δ 6.43–6.33 (m, 1H) 4.33 (d_{AB}, J_{AB}=12.0 Hz, 1H) 4.07 (d_{AB}, J_{AB}=12.0 Hz, 1H) 3.26–3.22 (m, 1H) 3.14–3.08 (m, 1H) 3.00–2.94 (m, 1H) 2.74 (s, 3H). Selected ^1H NMR signals for compound **15** (400 MHz, benzene-d_6): δ 6.23–6.12 (m, 1H) 4.25 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.13 (d_{AB}, J_{AB}=12.1 Hz, 1H) 3.35–3.31 (m, 1H).

4.7. Attempted allyl Grignard addition to aldehydes 14 and 15, leading to (±)-3-*endo*-allyl-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (18) and (±)-3-*exo*-allyl-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (19)

Allyl magnesium bromide (150 μL, 1.0 M in Et_2O) was added to a solution of **14** and **15** (70:30, respectively, 50.0 mg, 150 μmol) in THF (1 mL) at −78 °C. The temperature was then slowly allowed to reach rt, where after H_2O (1 mL) was added the organic phase was separated; the water phase extracted with CH_2Cl_2 (3×2 mL), and the combined organic phases were dried. After concentration at reduced pressure the residue was purified by column chromatography (SiO_2, pentane/ether 8:2) to yield compound **18** (23.0 mg, 76.6 μmol, 51%) and compound **19** (7.0 mg, 23.3 μmol, 16%) as colourless oils. For compound **18**: ^1H NMR (400 MHz, benzene-d_6) δ 7.24–7.22 (m, 2H) 7.14–7.05 (m, 3H) 6.46–6.35 (m, 1H) 5.18–5.13 (m, 1H) 5.08–5.05 (m, 1H) 4.35 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.12 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.34–3.31 (m, 1H) 2.84 (s, 3H) 2.76–2.69 (m, 1H) 2.63–2.56 (m, 1H) 2.52–2.46 (m, 1H) 2.28–2.24 (m, 1H) 1.91 (br d_{AB}, J_{AB}=14.2 Hz, 1H) 1.74 (br ddd_{AB}, J=2.1, 9.4 Hz, J_{AB}=14.2 Hz, 1H) 1.31–1.10 (m, 3H) 0.97–0.89 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 211.2, 138.8, 138.6, 128.6, 127.9, 127.8, 115.1, 75.6, 74.5, 69.8, 55.0, 48.9, 46.6, 35.4, 30.9, 28.0, 17.5; HRMS (FAB+) calcd for $C_{19}H_{25}O_3$ (M+H): 301.1804. Found: 301.1803. For compound **19**: ^1H NMR (400 MHz, benzene-d_6) δ 7.26–7.24 (m, 2H) 7.14–7.06 (m, 3H) 6.34–6.27 (m, 1H) 5.17–5.13 (m, 1H) 5.04–5.01 (m, 1H) 4.38 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.14 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.38 (dt, J=9.3, 3.1 Hz, 1H) 2.83 (s, 3H) 2.56–2.38 (m, 4H) 1.78 (td_{AB}, J=2.9 Hz, J_{AB}=13.4 Hz, 1H) 1.71 (dd_{AB}, J=9.2 Hz, J_{AB}=13.3 Hz, 1H) 1.55–1.47 (m, 1H) 1.32–1.13 (m, 2H) 1.01–0.93 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 211.5, 138.6, 138.5, 128.6, 128.1, 127.9, 115.4, 76.0, 73.9, 70.0, 54.2,

49.2, 46.6, 38.3, 30.1, 25.6, 18.5; HRMS (FAB+) calcd for $C_{19}H_{25}O_3$ (M+H): 301.1804. Found: 301.1818.

4.8. (±)-(3-Allyloxymethylene-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]oct-2-*endo*-yloxy)-trimethylsilane (22)

$NaBH_4$ (220 mg, 5.78 mmol) was added to a solution of dry-$CeCl_3$ (1.42 g, 5.78 mmol) in EtOH (99.5%, 60 mL) at 0 °C. After 0.5 h a solution of compound **12** (950 mg, 2.89 mmol) in EtOH (99.5%, 30 mL) and 2,6-lutidine (5.72 mL, 49.1 mmol) was added drop wise, and after 1 h of additional stirring at 0 °C, H_2O (260 μL) was added. The reaction mixture was then directly filtered through a pad of SiO_2 and Celite, and the product was eluted (heptane/EtOAc 1:1). After concentration at reduced pressure, crude alcohol **20** was collected as a slightly yellow oil, and was used directly in the following step. A small sample was purified for analytical purposes (SiO_2, heptane/EtOAc 85:15+10% Et_3N). IR (NaCl) 3512, 2947, 2872 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.20–7.18 (m, 2H) 7.14–7.04 (m, 3H) 6.43 (s, 1H) 5.75–5.65 (m, 1H) 5.24–5.18 (m, 1H) 5.00–4.96 (m, 1H) 4.37–4.33 (m, 1H) 4.23 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.14 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.94–3.90 (m, 2H) 3.89 (s, 1H) 3.59–3.56 (m, 1H) 3.40 (s, 3H) 2.29 (td_{AB}, J=3.1 Hz, J_{AB}=13.0 Hz, 1H) 2.12–2.09 (m, 1H) 1.87 (dd_{AB}, J=9.2 Hz, J_{AB}=13.0 Hz, 1H) 1.80–1.72 (m, 1H) 1.25–1.18 (m, 2H) 1.06–0.97 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 142.8, 134.5, 128.7, 128.1, 128.0, 127.9, 120.4, 116.6, 78.8, 76.6, 73.6, 73.4, 70.3, 52.0, 40.9, 36.9, 29.3, 20.1; HRMS (FAB+) calcd for $C_{20}H_{26}O_4$ (M): 330.1831. Found: 330.1821. Et_3N (1.0 mL, 7.23 mmol), DMAP (cat.) and TMSCl (925 μL, 7.23 mmol) were added to a solution of crude alcohol **20** in CH_2Cl_2 (23 mL) at 0 °C. Stirring was continued for 0.5 h, and then the solvent was removed at reduced pressure and replaced with cold pentane. The resulting mixture was filtered through Hyflo-Supercel. After concentration at reduced pressure the residue was purified by column chromatography (SiO_2, heptane/EtOAc 9:1) to give TMS/ether **22** (849 mg, 2.11 mmol, 73% starting from compound **12**) as a colourless oil. IR (NaCl) 2949, 2868 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.45–7.43 (m, 2H) 7.26–7.22 (m, 2H) 7.12–7.11 (m, 1H) 6.09 (d, J=1.2 Hz, 1H) 5.76–5.66 (m, 1H) 5.27–5.21 (m, 1H) 5.03–4.99 (m, 1H) 4.46 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.34 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.29–4.28 (m, 1H) 3.94 (dt, J=5.1, 1.6 Hz, 2H) 3.69–3.64 (m, 1H) 3.42 (s, 3H) 2.53 (ddd_{AB}, J_d=2.9, 5.7 Hz, J_{AB}=12.0 Hz, 1H) 2.06–2.04 (m, 1H) 2.02 (dd_{AB}, J=9.4 Hz, J_{AB}=11.9 Hz, 1H) 1.86–1.78 (m, 1H) 1.50–1.41 (m, 1H) 1.27–1.12 (m, 2H) 0.18 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 142.9, 140.1, 134.5, 127.9, 127.6, 127.3, 119.2, 116.8, 77.8, 77.1, 73.7, 73.3, 70.1, 51.9, 39.8, 37.0, 30.8, 21.3, 0.6; HRMS (FAB+) calcd for $C_{23}H_{34}O_4Si$ (M): 402.2226. Found: 402.2223. Anal. calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.56; H, 8.49.

4.9. (±)-2-*endo*-Allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]octane-2-carbaldehyde (23) and (±)-2-*exo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]-octane-2-carbaldehyde (24)

Compound **22** (849 mg, 2.11 mmol) dissolved in toluene (14 mL) was placed in a sealed pressurized vessel and was heated at 165 °C for 20 h, where the reaction mixture was allowed to cool to rt. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 95:5) to give compound **23** (325 mg, 808 μmol, 38%) and **24** (149 mg, 370 μmol, 18%) as colourless oils. For compound **23**: IR (NaCl) 2953, 2876, 1717 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 10.07 (s, 1H) 7.42 (br d, J=7.6 Hz, 2H) 7.23 (br t, J=7.6 Hz, 2H) 7.13–7.09 (m, 1H) 6.14–6.04 (m, 1H) 5.18–5.14 (m, 1H) 5.05–5.02 (m, 1H) 4.92 (br t, J=1.9 Hz, 1H) 4.60 (d_{AB}, J_{AB}=11.7 Hz, 1H) 4.20 (d_{AB}, J_{AB}=11.7 Hz, 1H) 3.60–3.54 (m, 1H) 3.43–3.38 (m, 1H) 3.27–3.21 (m, 1H) 2.77 (s, 3H) 1.98 (br s, 1H) 1.88 (td_{AB}, J=2.9 Hz, J_{AB}=13.6 Hz, 1H) 1.66 (dd_{AB}, J=9.9 Hz, J_{AB}=13.6 Hz, 1H) 1.44–1.36 (m, 1H) 1.20–1.06 (m, 2H) 0.83–0.75 (m, 1H) 0.16 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 206.4, 139.7, 137.3, 128.5, 127.9, 127.5, 117.3, 78.7, 76.5, 70.0, 69.1, 59.0, 49.1, 35.5, 32.6, 31.5, 23.1, 20.2, 0.2; HRMS (FAB+) calcd for $C_{23}H_{35}O_4Si$ (M+H): 403.2305. Found: 403.2296. Anal. calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.73; H, 8.46. For compound **24**: IR (NaCl) 2955, 2882, 1717 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 10.60 (br d, J=1.1 Hz, 1H) 7.37–7.35 (m, 2H) 7.25–7.22 (m, 2H) 7.13–7.11 (m, 1H) 6.37–6.27 (m, 1H) 5.09–5.04 (m, 2H) 4.37 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.29 (d_{AB}, J_{AB}=12.1 Hz, 1H) 3.88–3.86 (m, 1H) 3.56–3.52 (m, 1H) 3.11–3.06 (m, 1H) 2.81 (s, 3H) 2.29–2.21 (m, 2H) 1.92–1.90 (m, 1H) 1.87–1.81 (m, 1H) 1.38–1.26 (m, 1H) 1.17–0.92 (m, 3H) 0.08 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 203.9, 139.7, 137.8, 127.9, 127.6, 127.4, 116.6, 77.7, 77.6, 77.2, 70.2, 57.7, 49.2, 36.7, 36.4, 34.0, 23.9, 20.7, 0.5; HRMS (FAB+) calcd for $C_{23}H_{35}O_4Si$ (M+H): 403.2305. Found: 403.2301. Anal. calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.43; H, 8.44.

4.10. General procedure for the allyl Grignard addition reaction, leading to compounds (±)-1-(2-*endo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]oct-2-yl)-but-3-en-1-ol (25) and (±)-1-(2-*exo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]oct-2-yl)-but-3-en-1-ol (26)

Allyl magnesium bromide (2 equiv, 1.0 M in Et_2O) was added to a solution of **23** (325 mg, 808 μmol) or **24** (149 mg, 370 μmol) in THF (0.5 mL/0.1 mmol) at 0 °C. The temperature was then slowly allowed to reach rt, where after satd aq NH_4Cl was added. The organic phase was separated, the water phase extracted with EtOAc (×3), and the combined organic phases were dried. After concentration at reduced pressure the residue was purified by column chromatography (SiO_2, heptane/EtOAc 95:5) to yield compound **25** (275 mg, 619 μmol, 77%) or **26** (110 mg, 247 μmol, 67%) as colourless oil. For compound **25**: IR (NaCl) 3566, 2949, 2878 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.43 (br d, J=7.6 Hz, 2H) 7.23 (br t, J=7.6 Hz, 2H) 7.14–7.10 (m, 1H) 6.63–6.53 (m, 1H) 6.06–5.96 (m, 1H) 5.19–5.13 (m, 2H) 5.10–5.03 (m, 2H) 4.48 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.46 (s, 1H) 4.33 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.06–4.01 (m, 1H) 3.51–3.48 (m, 1H) 3.30–3.24 (m, 1H) 3.01–2.94 (m, 2H) 2.84 (s, 3H) 2.51–2.43 (m, 1H) 2.07 (td_{AB}, J=3.7 Hz, J_{AB}=13.4 Hz, 1H) 1.98–1.95 (m, 1H) 1.92 (d, J=6.4 Hz, 1H) 1.88–1.79 (m, 1H) 1.73 (dd_{AB}, J=10.1 Hz,

J_{AB}=13.4 Hz, 1H) 1.48–1.38 (m, 1H) 1.21–1.14 (m, 1H) 1.06–0.96 (m, 1H) 0.21 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 141.0, 137.9, 128.5, 128.1, 127.9, 127.4, 116.8, 115.1, 78.8, 77.3, 75.0, 74.4, 70.1, 52.1, 48.4, 39.2, 37.1, 34.1, 33.2, 24.1, 21.3, 0.8; HRMS (FAB+) calcd for $C_{26}H_{41}O_4Si$ (M+H): 445.2775. Found: 445.2786. Anal. calcd for $C_{26}H_{40}O_4Si$: C, 70.23; H, 9.07. Found: C, 70.29; H, 9.02. For compound **26**: ^{1}H NMR (400 MHz, benzene-d_6) δ 7.39 (br d, J=7.4 Hz, 2H) 7.21 (br t, J=7.5 Hz, 2H) 7.13–7.09 (m, 1H) 6.59–6.48 (m, 1H) 6.15–6.05 (m, 1H) 5.35–5.30 (m, 1H) 5.18–5.15 (m, 1H) 5.11–5.07 (m, 2H) 4.53–4.52 (m, 1H) 4.48 (d_{AB}, J_{AB}=11.6 Hz, 1H) 4.46 (s, 1H) 4.22 (d_{AB}, J_{AB}=11.6 Hz, 1H) 3.92–3.91 (m, 1H) 3.57–3.54 (m, 1H) 3.37–3.32 (m, 1H) 3.04–2.96 (m, 1H) 2.89 (s, 3H) 2.86–2.82 (m, 1H) 2.80–2.74 (m, 1H) 2.03–1.98 (m, 1H) 1.84–1.83 (m, 1H) 1.78–1.72 (m, 1H) 1.34–1.28 (m, 1H) 1.18–1.00 (m, 3H) 0.07 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 140.3, 139.4, 135.9, 128.5, 127.8, 127.5, 117.5, 114.5, 80.3, 78.8, 77.4, 75.6, 70.1, 50.4, 48.3, 40.4, 39.0, 37.6, 32.6, 24.7, 20.7, 0.6; HRMS (FAB+) calcd for $C_{26}H_{41}O_4Si$ (M+H): 445.2775. Found: 445.2769.

4.11. General procedure for the ring-closing metathesis reaction, leading to compounds (1*R**,2,1′*R**,3*S**,5*S**,2′*R**)-(±)-spiro[5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilyloxybicyclo[2.2.2]-octane-2,1′-cyclohex-4′-en]-2′-ol (27) and (1*R**,2,1′*S**,3*S**,5*S**,2′*R**)-(±)-spiro[5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilyloxybicyclo[2.2.2]-octane-2,1′-cyclohex-4′-en]-2′-ol (28)

Grubb's phosphorylidine catalyst [$RuCl_2$(=CHPh)(PCy_3)$_2$] (10 mol %) was added to a solution of **25** (275 mg, 619 μmol) or **26** (103 mg, 232 μmol) in degassed CH_2Cl_2 (1.6 mL/100 μmol). The reaction mixture was heated in a sealed pressurized vessel at 40 °C for 10 h. After concentration at reduced pressure the residue was purified by column chromatography to give compound **27** (219 mg, 526 μmol, 85%) or **28** (81.5 mg, 196 μmol, 84%) as off-white solids. Compound **27** was crystallized from pentane, which resulted in off-white needles. For compound **27** (SiO_2, heptane/EtOAc 9:1): mp: 79.8–82.8 °C; IR (KBr) 3439, 3022, 2936 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.44 (br d, J=7.6 Hz, 2H) 7.25 (br t, J=7.6 Hz, 2H) 7.12–7.11 (m, 1H) 5.82–5.78 (m, 1H) 5.44–5.39 (m, 1H) 4.47 (d_{AB}, J_{AB}=12.3 Hz, 1H) 4.36 (d_{AB}, J_{AB}=12.3 Hz, 1H) 4.37–4.31 (m, 2H) 3.58–3.53 (m, 1H) 3.19–3.14 (m, 1H) 3.02 (s, 3H) 2.52–2.47 (m, 1H) 2.33–2.26 (m, 1H) 2.18–2.10 (m, 1H) 2.03–1.93 (m, 3H) 1.75–1.63 (m, 2H) 1.31–1.23 (m, 1H) 1.18–1.11 (m, 1H) 0.78 (br d, J=3.7 Hz, 1H) 0.18 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 140.1, 130.2, 128.4, 127.9, 127.3, 121.2, 77.4, 77.3, 72.2, 70.0, 69.0, 49.5, 49.1, 37.4, 34.6, 33.7, 28.2, 25.2, 21.3, 0.9; HRMS (FAB+) calcd for $C_{24}H_{37}O_4Si$ (M+H): 417.2462. Found: 417.2466. Anal. calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 69.26; H, 8.65. For compound **28** (SiO_2, heptane/EtOAc 85:15): mp: 110.4–113.0 °C; IR (KBr) 3422, 3018, 2959 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.38 (br d, J=7.6 Hz, 2H) 7.24 (br t, J=7.6 Hz, 2H) 7.13–7.11 (m, 1H) 5.86–5.84 (m, 1H) 5.73–5.69 (m, 1H) 5.11 (br s, 1H) 4.97 (br s, 1H) 4.35 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.28 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.72–3.71 (m, 1H) 3.43–3.38 (m, 1H) 3.01–2.96 (m, 1H) 2.91–2.87 (m, 1H) 2.63 (s, 3H) 2.61–2.56 (m, 1H) 2.20–2.15 (m, 1H) 1.97–1.91 (m, 1H) 1.89 (br s, 1H) 1.52–1.46 (m, 1H) 1.16–0.91 (m, 4H) 0.13 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 139.7, 128.5, 127.9, 127.6, 127.2, 122.9, 81.2, 78.8, 77.9, 70.5, 66.6, 48.4, 46.5, 38.0, 35.3, 31.1, 28.9, 22.6, 20.4, 0.7; HRMS (FAB+) calcd for $C_{24}H_{37}O_4Si$ (M+H): 417.2462. Found: 417.2465. Anal. calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 68.80; H, 8.54.

4.12. (±)-5-*endo*-Benzyloxy-1-methoxy-bicyclo-[2.2.2]oct-2-ene-2-carbaldehyde (21)

Compound **20** (17 mg, 51.5 μmol) dissolved in toluene (1 mL) was placed in a sealed pressurized vessel and heated at 165 °C for 12 h. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 85:15) to give **21** (8.0 mg, 24.2 μmol, 47%) as a yellow oil. ^{1}H NMR (400 MHz, benzene-d_6) δ 9.73 (s, 1H) 7.22–7.18 (m, 4H) 7.11–7.08 (m, 1H) 6.75 (d, J=6.4 Hz, 1H) 4.16 (s, 2H) 3.40–3.36 (m, 1H) 3.20 (s, 3H) 2.60–2.56 (m, 1H) 1.73 (dd_{AB}, J=8.4 Hz, J_{AB}=12.6 Hz, 1H) 1.62 (td_{AB}, J=3.1 Hz, J_{AB}=12.6 Hz, 1H) 1.25–1.13 (m, 2H) 0.98–0.90 (m, 1H) 0.88–0.79 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 187.5, 146.4, 146.2, 139.0, 128.6, 127.9, 127.6, 78.2, 77.3, 69.9, 52.3, 39.8, 35.6, 28.7, 20.9; HRMS (FAB+) calcd for $C_{17}H_{21}O_3$ (M+H): 273.1491. Found: 273.1496.

4.13. X-ray crystallographic analysis of compound 27

Crystallization from pentane gave needles of compound **27** suitable for X-ray diffraction. Intensity data were collected at 150 K with an Oxford Diffraction Xcalibur 3 system using ω-scans and Mo Kα (λ=0.71073 Å).[26] CCD data were extracted and integrated using Crysalis RED.[27] The structure was solved by direct methods and refined by full-matrix least-squares calculations on F^2 using SHELXTL 5.1.[28] Non-H atoms were refined with anisotropic displacement parameters. All hydrogen atoms, except for those on the hydroxy group, were constrained to parent sites, using a riding model. The high residuals in the final difference map are situated around 2.9 Å from Si20. Attempts to refine them as partially occupied solvent molecules failed. Full crystallographic data in CIF-format has been deposited (CCDC 617804). Crystal data: $C_{24}H_{35}O_4Si$, M=415.61, triclinic, a=6.608(4), b=8.91(2), c=19.75(2) Å, α=84.39(14), β=81.38(7), γ=77.90(13)°, V=1521.1(4) Å^3, space group $P1$, Z=2, D_{calcd}=1.231 g cm^{-3}, μ=0.132 mm^{-1} θ range=2.34–28.98°, 12957 reflections measured, 5017 unique (R_{int}=0.0948), which were used in all calculations. The final $wR(F^2)$ was 0.3086 (all data) and the $R(F)$ was 0.1222 ($I>2\sigma(I)$) using 264 parameters. S=1.493.

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Supplementary data

General experimental procedures. ^{1}H and ^{13}C NMR spectra for compounds **14** and **15** (isomeric mixture), **18**, **19**, **21** and **26**. COSY and NOESY spectra for the isomeric mixture of **14** and **15** and for compounds **27** and **28**. A figure giving atomic numbering of the DIAMOND drawing of compound **27**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.015.

References and notes

1. For a recent review on spiro-cyclizations in general see: Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779.
2. Ruzicka, L. *Helv. Chim. Acta* **1920**, *3*, 781.
3. Buchi, G.; Hansen, J. H.; Knutson, D.; Koller, E. *J. Am. Chem. Soc.* **1958**, *80*, 5517.
4. Gurst, J. E.; Miller, R. W.; McPhail, A. T. *Tetrahedron Lett.* **1980**, *21*, 3223.
5. Errede, L. A. *J. Org. Chem.* **1961**, *26*, 2606.
6. Holton, R. A.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1986**, *51*, 5480.
7. Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186.
8. Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072.
9. Seto, M.; Sakurai, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 993.
10. Kusama, H.; Morihira, K.; Nishimori, T.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1999**, *40*, 4235.
11. Kobayashi, J. i.; Ueno, S.; Morita, H. *J. Org. Chem.* **2002**, *67*, 6546.
12. Kubota, T.; Matsuno, Y.; Morita, H.; Shinzato, T.; Sekiguchi, M.; Kobayashi, J. i. *Tetrahedron* **2006**, *62*, 4743.
13. Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, *23*, 1499.
14. Sarvary, I.; Norrby, P.-O.; Frejd, T. *Chem.—Eur. J.* **2004**, *10*, 182.
15. Almqvist, F.; Manner, S.; Thornqvist, V.; Berg, U.; Wallin, M.; Frejd, T. *Org. Biomol. Chem.* **2004**, *2*, 3085.
16. Thornqvist, V.; Manner, S.; Wingstrand, M.; Frejd, T. *J. Org. Chem.* **2005**, *70*, 8609.
17. King, S. A.; Pipik, B.; Thompson, A. S.; DeCamp, A.; Verhoeven, T. R. *Tetrahedron Lett.* **1995**, *36*, 4563.
18. Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, NY, 1995; 297 pp.
19. Bates, R. W.; Kongsaeree, P.; Nontapattamadul, N. *ARKIVOC* [online] **2001**, 269.
20. Martin Castro Ana, M. *Chem. Rev.* **2004**, *104*, 2939.
21. Banwell, M. G.; McRae, K. J.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2194.
22. Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.
23. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
24. Brandenburg, K. *DIAMOND, Program for Molecular Graphics*; Crystal Impact: Bonn, Germany, 1996–1998.
25. Thornqvist, V.; Manner, S.; Frejd, T. *Tetrahedron: Asymmetry* **2006**, *17*, 410.
26. *Crystal CCD*; Oxford Diffraction: Abingdon, Oxfordshire, UK, 2005.
27. *Crysalis RED*; Oxford Diffraction: Abingdon, Oxfordshire, UK, 2005.
28. Sheldrick, G. M. *SHELXTL5.1, Program for Structure Solution and Least Squares Refinement*; University of Göttingen: Göttingen, Germany, 1998.

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First-principle predictions of basicity of organic amines and phosphines in acetonitrile

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Abstract—Amines and phosphines are widely utilized as bases and basic organocatalysts in organic chemistry. Thus it is highly valuable to develop a coherent theoretical method that can accurately predict the basicity of structurally unrelated amines and phosphines in organic solvents from the first principles. Herein we developed the first ab initio protocol that could predict the pK_a value of any protonated amine or phosphine in acetonitrile through systematic benchmarking. By comparing to a variety of available experimental data (total number=98), it was determined that the precision of the optimized method in basicity prediction was as low as 1.1 pK_a unit. With the powerful new method in hand, we subsequently conducted some systematic studies about the basicity of organic amines and in particular phosphines, for which very few experimental data were available. It was found that the solvent exerted profound effects on the basicity of amines and phosphines. Accordingly we concluded that it was not valid to use gas-phase data to interpret the solution-phase basicity of amines and phosphines. Next we reported the basicity of a number of synthetically important aliphatic and aromatic amines and phosphines in acetonitrile. We also compared, for the first time, the α-substituent effects on the basicity of aliphatic amines and phosphines and the remote substituent effects on the basicity of aromatic amines and phosphines. Finally, we studied for the first time the basicity of cyclic amines and phosphines. It was found that the ring strain exerted some interesting effects on the basicity of amines and phosphines.

1. Introduction

Proton transfer is one of the most important processes in the transformations of organic molecules.[1] Consequently a precise knowledge about the acidity and basicity of organic compounds in various solvents is fundamental for the study of mechanistic organic chemistry. In this connection, considerable efforts have been made in the past several decades to develop experimental methods for the determination of acidity and basicity of diverse types of organic compounds.[2] However, not all organic molecules (such as reaction intermediates, very strong acids/bases, and very weak acids/bases) are readily amenable to experimental characterization. Besides, there is often a need to estimate the acidity or basicity of a particular compound before it is synthesized. To solve these problems, there has been widespread interest in developing theoretical approaches to calculate acidity or basicity in an ab initio fashion.

Thanks to the remarkable development of computational chemistry, the acidity and basicity of organic molecules in the gas phase can now be calculated with equivalent or greater accuracy than that obtained experimentally.[3] In spite of this accomplishment, there remains a significant challenge that has to be overcome before one can successfully predict acidity and basicity in the solution phase. This challenge is how to accurately describe the solvation effect that has been known to exert profound influence on the proton transfer thermodynamics. To meet this challenge, a few different theoretical approaches have been investigated recently to deal with the solvation effects. These include molecular simulations,[4] integral equation techniques,[5] and dielectric continuum methods.[6] Among them, the dielectric continuum methods are the most popular because they are easier to handle and more broadly applicable.[7]

Using the dielectric continuum methods, a number of groups have recently developed theoretical protocols to calculate the acidity and basicity of various organic compounds in water.[8] The root-of-mean square (rms) errors in these calculations were usually found to be as low as about 0.5–2.0 pK_a units as compared to the experimental data. This appears to indicate that it is no longer a problem to calculate pK_a's in aqueous solution. Nonetheless, it must be stressed that the success of a protocol in predicting pK_a's in water does not automatically validate its use to predict pK_a's in organic solvents. The reason is that the parameters utilized by a dielectric continuum method to describe the solvation cavity may change considerably from water to organic solvents.[7] As a result, a careful calibration against available experimental pK_a's has to be done before one can calculate the pK_a's in a particular organic solvent.

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Up to now dimethyl sulfoxide (DMSO) is the only organic solvent for which clear-cut calibrations have been performed in the pK_a calculations. In the calibration by Pliego et al., the pK_a values of 41 organic acids in DMSO were calculated and the rms error was determined to be 2.2 pK_a units.[9] At almost the same time, we also developed a first-principle procedure to calculate the pK_a's of organic acids in DMSO.[10] Over 250 structurally unrelated organic compounds were examined in our calibration and the rms error was determined to be 1.4 pK_a units. On the basis of these results we concluded that the problem of predicting pK_a's in DMSO has been largely solved. Consequently we have turned our attention to the acidity/basicity of organic acids in other commonly used organic solvents such as acetonitrile. Compared to DMSO, acetonitrile has a lower dielectric constant (ε=37.5 as opposed to 46.7 for DMSO). As a result, in acetonitrile all the pK_a values are significantly higher than the DMSO values. Since acetonitrile is widely used as a polar, aprotic solvent in organic reactions,[11] there has been a strong need to accurately determine the pK_a values of various organic acids in acetonitrile even if the corresponding DMSO values have been measured.

In the present study we attempt to develop a first-principle theoretical method that can reliably predict the basicity of diverse organic amines and phosphines in acetonitrile (or, the pK_a values of the corresponding protonated amines and phosphines in acetonitrile). We consider this study to be important because amines and phosphines are widely used as bases to mediate or catalyze organic transformations. Evidently basicity is one of the important factors to tune the reactivity of such transformations. As a result, considerable experimental studies have been done in the past to measure the basicity of organic amines and phosphines in polar solvents, in particular in acetonitrile.[12] Meanwhile, some theoretical studies have also been performed to interpret certain experimental observations.[13] However, in most of these theoretical studies only the gas-phase calculations were conducted. Thus, before the present study there was not any ab initio method that could reliably predict the basicity of diverse amines and phosphines in acetonitrile.

2. Gas-phase calculations

Before we try to calculate the solution-phase pK_a value of a protonated amine or phosphine A-H$^+$, it is important to ascertain that we can reliably calculate its gas-phase acidity defined as the free energy change of the following reaction in the gas phase at 298 K, 1 atm.

$$\text{A-H}^+(\text{g}) \rightarrow \text{A}(\text{g}) + \text{H}^+(\text{g}) \quad (1)$$

Thus, we selected 20 representative protonated amines (see Table 1), and we utilized a variety of popular ab initio and density functional theory (DFT) methods to calculate their gas-phase acidities (see Table 2).[14] The standard 6-31G(d) basis set was used in the geometry optimization, and the 6-311++G(2df,2p) basis set was used to calculate the single-point electronic energy.[15] After this was completed, the zero-point vibrational energy, thermal corrections (0–298 K), and the entropy term were added to the single-point electronic energy to provide the free energy. It is worth noting that we did not try more demanding methods such as MP2 or MP4 for the energy calculation, because we needed to develop a method that could be used for relatively large amines and phosphines that may contain more than 10 non-hydrogen atoms.

Table 1. Experimental and theoretical (PBEPBE/6-311++G(2df,2p)// PBEPBE/6-31G(d)) gas-phase acidities for 20 protonated amines and phosphines (kcal/mol)

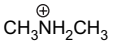
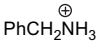
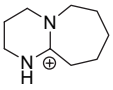
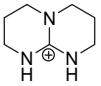
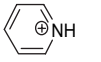
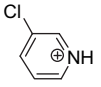
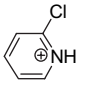
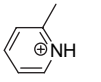
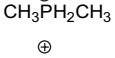
Compound	ΔG (exp)	ΔG (theor)
	206.0	206.6
	212.5	214.3
	216.2	219.4
	225.1	227.0
	201.9	203.3
	213.2	210.2
	218.4	218.8
	219.7	220.0
	243.5	242.7
	244.9	244.3
	214.9	214.7
	209.9	208.3
	208.6	208.0
	219.3	219.2
	195.0	195.4
	209.0	209.8
	219.8	221.4
	225.9	227.5
	225.0	224.6
	189.9	187.7

Table 2. The performances of different theoretical methods in the gas-phase calculations

Method	*r*	Mean error	rms error
HF//HF	0.995	6.5	6.8
BH&HLYP//BH&HLYP	0.995	3.3	3.6
B3LYP//B3LYP	0.996	1.7	2.3
B3P86//B3P86	0.995	2.4	2.7
MPWPW91//MPWPW91	0.994	1.2	1.9
PBEPBE//PBEPBE	0.994	0.0	1.3

As shown in Table 2, it was found that the HF method could not reliably predict the gas-phase acidities because the corresponding mean error and root-of-mean-square (rms) error were as large as 6.5 and 6.8 kcal/mol. In comparison, all the DFT methods provided much better predictions than the HF method. Among all the density functionals, it was found that the BH&HLYP method gave the worst predictions (mean error=3.3 kcal/mol, rms error=3.6 kcal/mol). The more popular B3LYP and B3P86 methods showed slightly improved performances (rms error=2.3 and 2.7 kcal/mol). More encouraging results were then obtained with the MPWPW91 method where the rms error was lower than 2.0 kcal/mol. Finally, it was found that the PBEPBE functional recently developed by Perdew et al. exhibited the best performance, where the mean error and rms error were 0.0 and 1.3 kcal/mol, respectively (see Fig. 1). It is worth noting that the experimental errors of the gas-phase acidities are about 1.0–2.0 kcal/mol. As a result we concluded that the theoretical predictions at the PBEPBE/6-311++G(2df,2p)//PBEPBE/6-31G(d) level were sufficiently accurate for the gas-phase acidities of protonated amines and phosphines.

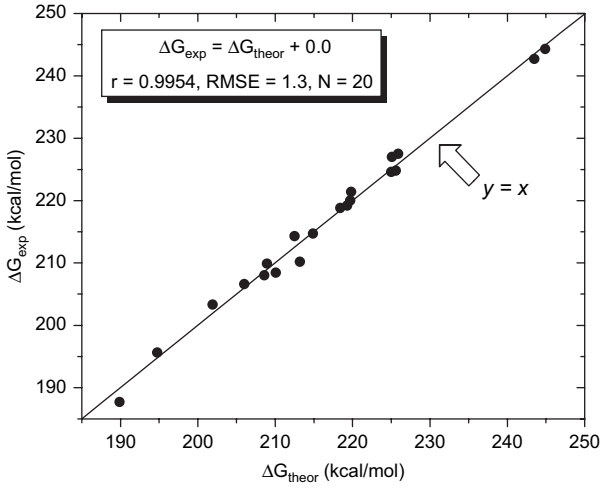


Figure 1. The correlation between the experimental and theoretical gas-phase acidities for protonated amines and phosphines.

3. Solution-phase calculations

With a reliable method to calculate the gas-phase acidities in hand, we next needed to derive the equations for the pK_a calculation. Thus, we considered the following proton-exchange reaction between a protonated amine or phosphine, A-H$^+$, and a reference compound whose pK_a has been well characterized experimentally, i.e., pyridine

$$\text{A-H}^+ + \text{C}_5\text{H}_4\text{N} \rightarrow \text{A} + \text{C}_5\text{H}_4\text{NH}^+ \quad (2)$$

If the free energy change of the above reaction in the acetonitrile solution was defined as $\Delta G_{\text{exchange}}$, the p$K_a$ of the protonated amine or phosphine, A-H$^+$, could be calculated by Eq. 3.

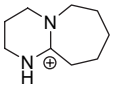
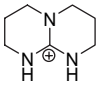
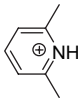
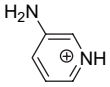
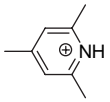
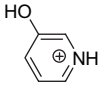
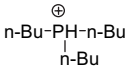
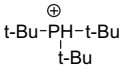
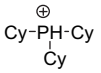
$$pK_a\left(\text{A-H}^+\right) = pK_a\left(\text{C}_5\text{H}_4\text{NH}^+\right) + \frac{\Delta G_{\text{exchange}}}{2.303RT} \quad (3)$$

The experimental pK_a value for pyridine is 12.53 in acetonitrile. It is also known from the Section 2 that the gas-phase free energy change can be reliably calculated. Thus, whether Eq. 3 can successfully predict pK_a's mainly relies on the quality of the solvation energy calculations. Herein we decided to utilize the polarized continuum model (PCM) to calculate the solvation free energies. The central idea of this solvation model is the construction of a solvent-inaccessible cavity in which the solute molecule resides.[7] In practice, this solvent-inaccessible cavity is built as a union of overlapping spheres centered on the nuclei of atoms or chemical groups. The sphere radii are usually proportional to the atomic radii with a scale factor (*f*). It is worth noting that currently there are a few versions of PCM methods such as IEFPCM (integral equation formalism model), CPCM (polarizable conductor calculation model), and IPCM (static isodensity surface polarized continuum model). There are also a few scales of atomic radii that can be used in the PCM methods including Bondi, Pauling, UAHF, UAKS, and UA0. Furthermore, for each combination of solvation model and atomic radius scale, the *f* value has to be specifically optimized. Although considerable optimization work has been done previously for the aqueous solution, very little has been known about the optimal parameters for the acetonitrile solution.

In order to identify the optimal method to calculate the solvation energies in acetonitrile, herein we systematically examined a variety of combinations of the solvation model, radius scale, and *f* value (see Table 4). After comparing the correlation coefficients (*r*), mean errors, and rms errors for calculating the pK_a values listed in Table 3, we were able to make the following conclusions: (1) the HF method performed equally well as, if not better than, the DFT methods in the solvation energy calculations; (2) increase of the basis set from 6-31G(d) to 6-311++G(2df,2p) did not improve the solvation energy calculations; (3) Bondi radii provided better results than other scales of radii including Pauling, UA0, UAHF, and UAKS; (4) the IEFPCM model performed equally well as, if not better than, the CPCM and IPCM models; and (5) for the IEFPCM/Bondi method, the optimal *f* value was determined to be 1.10. On the basis of the above findings, we concluded that the optimal compromise between the accuracy and cost for calculating the solvation energies in acetonitrile was HF/6-31G(d)-IEFPCM method, in which radii=Bondi and *f*=1.10.

Using the above solvation model and Eq. 3, we found that the pK_a's of the 20 protonated amines and phosphines listed in Table 3 could be calculated with fairly high accuracy (see Fig. 2). The correlation coefficient between the theoretical and experimental pK_a values was as high as 0.9800. The

Table 3. Experimental and theoretical pK_a's for 20 protonated amines and phosphines (kcal/mol)

Compound	pK_a (exp)	pK_a (theor)
	19.6[16a]	18.0
	18.9[16b]	18.2
	24.1[16c]	24.5
	26.0[16a]	24.8
	13.3[16a]	13.5
	14.1[16a]	14.4
	14.2[16a]	12.2
	14.5[16a]	13.6
	15.0[16a]	15.8
	12.5[16a]	12.5
	10.0[16a]	10.8
	6.8[16a]	7.1
	7.0[16d]	7.1
	9.5[16d]	10.6
	8.3[16d]	9.3
	12.6[16d]	12.8
	15.1[16e]	16.2
	17.0[16e]	17.8
	17.2[16e]	16.9

(*continued*)

Table 3. (*continued*)

Compound	pK_a (exp)	pK_a (theor)
	10.0[16a]	10.7
	12.7[16e]	13.9
	11.5[16e]	10.2

The solvation energies were calculated by the HF/6-31G(d)-IEFPCM method, radii=Bondi, f=1.10.

mean error was −0.2 pK_a unit and the rms error was 1.0 pK_a unit.

4. Comparing more theoretical and experimental data

As described in the previous sections, by using 20 representative amines and phosphines we optimized a first-principle method for calculating the pK_a's of protonated amines and phosphines in acetonitrile. Next we wished to know whether the same method could successfully predict the basicity of more diverse amines and phosphines in acetonitrile. Thus we collected the experimental pK_a values for a huge variety of protonated amines and phosphines (see Table 5). Using the methods described in the previous sections, we calculated the gas-phase acidities and solution-phase pK_a values. It was found that the rms error for the gas-phase acidity calculation was 1.6 kcal/mol for a sample containing 63 species (see Fig. 3). The rms error for the solution-phase pK_a calculations were 1.1 pK_a units for a sample containing 98 species (see Fig. 4). These results confirmed that the method we developed could be used to predict the basicity of structurally unrelated amines and phosphines in acetonitrile.

5. Discussion

In the above sections we developed a first-principle method that could predict the pK_a's of a variety of structurally unrelated protonated amines and phosphines in acetonitrile. The error bar of the prediction was determined to be around 1.1 pK_a units through comparison with a large number of experimental data. Thus the new method would enable us, for the first time, to estimate the pK_a of any protonated amine or phosphine in acetonitrile with a relatively small error bar. It is worth pointing out that the basicity of many important amines and phosphines (in particular) still remain unknown due to many complicated reasons (such as: (1) phosphines are highly unstable in air; (2) reliable measurement requires special expertise).[17] Therefore, the method developed here should be practically valuable for organic chemists studying the use of amines or phosphines in organic synthesis (for example, in the cases of base catalysis and organocatalysis). Furthermore, the method developed here also allowed us to generate some systematic data about the basicity of amines and phosphines in acetonitrile. On the basis of these data we could discuss, for the first time, some important yet

Table 4. The performances of different theoretical methods in the solution-phase calculations

Method	Solvation model	Cavity	*f*	*r*	Mean error	rms error
HF/6-31G(d)	IEFPCM	UA0	1.00	0.973	0.5	1.2
B3LYP/6-31G(d)	IEFPCM	UA0	1.00	0.970	0.8	1.4
B3P86/6-31G(d)	IEFPCM	UA0	1.00	0.969	0.8	1.4
PBEPBE/6-31G(d)	IEFPCM	UA0	1.00	0.960	1.1	1.7
BHANDHLYP/6-31G(d)	IEFPCM	UA0	1.00	0.971	0.6	1.3
MPWPW91/6-31G(d)	IEFPCM	UA0	1.00	0.963	1.0	1.6
HF/6-31+G(d)	IEFPCM	UA0	1.00	0.972	0.4	1.3
HF/6-31G(d,p)	IEFPCM	UA0	1.00	0.973	0.5	1.3
HF/6-31++G(d,p)	IEFPCM	UA0	1.00	0.972	0.5	1.3
HF/6-311G(2df,2p)	IEFPCM	UA0	1.00	0.972	0.6	1.3
HF/6-311++G(2df,2p)	IEFPCM	UA0	1.00	0.972	0.6	1.3
HF/6-31G(d)	IEFPCM	Bondi	1.00	0.981	0.2	1.1
HF/6-31G(d)	IEFPCM	Pauling	1.00	0.972	0.8	1.7
HF/6-31G(d)	IEFPCM	UAHF	1.00	0.966	−1.7	2.4
HF/6-31G(d)	IEFPCM	UAKS	1.00	0.968	−1.5	2.1
HF/6-31G(d)	CPCM	UA0	1.00	0.974	0.5	1.2
HF/6-31G(d)	CPCM	Bondi	1.00	0.980	0.2	1.1
HF/6-31G(d)	CPCM	Pauling	1.00	0.970	0.7	1.7
HF/6-31G(d)	CPCM	UAHF	1.00	0.964	−1.7	2.4
HF/6-31G(d)	CPCM	UAKS	1.00	0.968	−1.5	2.2
HF/6-31G(d)	COSMOS-RS	KLAMT	1.00	0.973	−0.8	1.4
HF/6-31G(d)	IPCM	—	1.00	0.971	−0.2	1.2
HF/6-31G(d)	IEFPCM	Bondi	0.90	0.964	0.7	1.8
HF/6-31G(d)	IEFPCM	Bondi	0.95	0.974	0.4	1.4
HF/6-31G(d)	IEFPCM	Bondi	1.05	0.978	0.2	1.0
HF/6-31G(d)	IEFPCM	Bondi	1.10	0.980	−0.2	1.0
HF/6-31G(d)	IEFPCM	Bondi	1.15	0.979	−0.3	1.0
HF/6-31G(d)	IEFPCM	Bondi	1.20	0.975	−0.3	1.0
HF/6-31G(d)	IEFPCM	Bondi	1.25	0.974	−0.3	1.0
HF/6-31G(d)	IEFPCM	Bondi	1.30	0.971	−0.4	1.1

unanswered questions concerning the similarity and difference between the basicity of amines and phosphines.

5.1. Solvent effects on basicity

The first question concerning the basicity of amines and phosphines in organic solvents is whether or not the solvent can produce strong effects on basicity. If this is not the case, the basicity of amines and phosphines in solvents can be easily predicted from their gas-phase protonation free energies. Unfortunately this important question has not been answered previously, presumably because of the lack of systematic data. Herein we plotted the theoretical gas-phase acidities (error bar=1.6 kcal/mol) against the theoretical pK_a values (error bar=1.1 pK_a units) for 98 protonated amines and phosphines in Figure 5. It was obvious from Figure 5 that the gas-phase acidities had a very loose correlation with the solution-phase pK_a values. Accordingly, we concluded that the solvent (=acetonitrile) exerted fairly strong effects on the basicity of amines and phosphines. It is not valid to use gas-phase acidities to interpret the solution-phase behaviors of amine and phosphine bases.

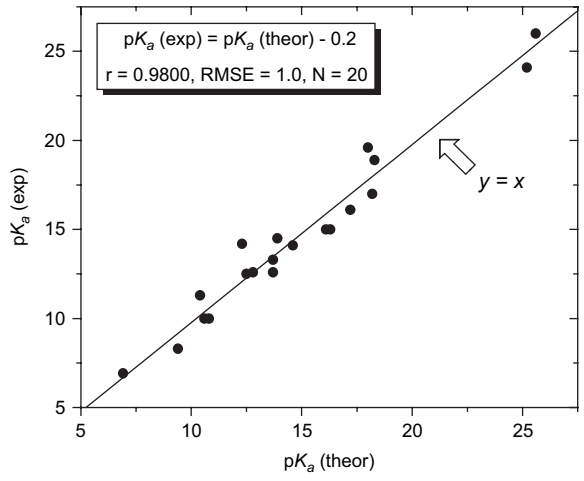


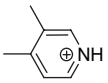
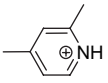
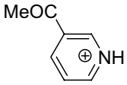
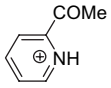
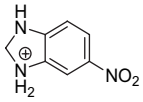
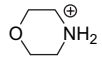
Figure 2. The correlation between the experimental and theoretical pK_a values for 20 protonated amines and phosphines.

5.2. Basicity of aliphatic and aromatic amines and phosphines

The relative basicity of primary, secondary, and tertiary amines has been discussed previously by several authors.[18] What remains unknown is the relative basicity of these amines compared to that of the phosphines. Since we now can reliably predict these data (see Table 6), we should fulfill the gap in our existing knowledge.

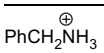
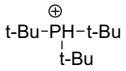
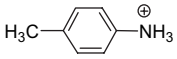
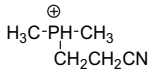
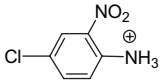
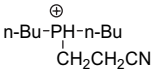
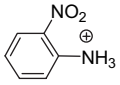
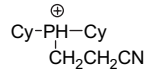
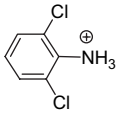
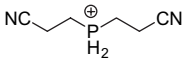
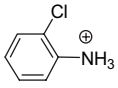
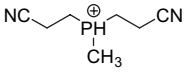
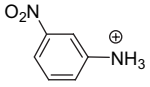
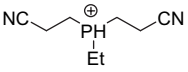
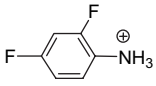
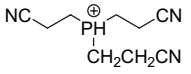
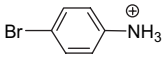
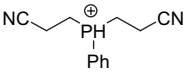
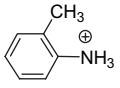
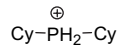
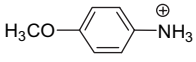
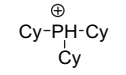
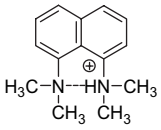
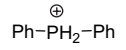
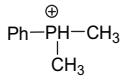
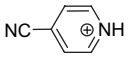
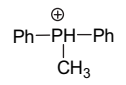
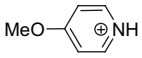
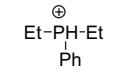
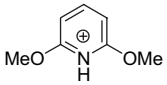
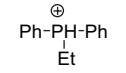
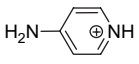
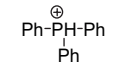
As shown in Figure 6, comparing the pK_a's of protonated aliphatic amines and phosphines in acetonitrile we found that common aliphatic amines were always more basic than the corresponding phosphines. NH_3 was more basic than PH_3 by about 10 pK_a units. Primary aliphatic amines were more basic than primary aliphatic phosphines by about 8 pK_a units. Secondary aliphatic amines were more basic than secondary aliphatic phosphines by about 4 pK_a units. Tertiary aliphatic amines were more basic than tertiary aliphatic phosphines by about 2 pK_a units. Furthermore, considering the error bar of the pK_a prediction (~1.1 pK_a units), we concluded that the basicities of primary, secondary, and tertiary aliphatic amines were very close to each other

Table 5. Collection of gas-phase acidities (ΔG, kcal/mol) and solution-phase pK_a's in acetonitrile for protonated amines and phosphines

Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)	Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)
NH_4^+	195.7	194.7	16.5[16b]	14.4		221.6	223.0	14.8[16d]	14.9
$H_3C-NH_3^+$	206.0	206.6	18.4[16b]	17.0		221.2	223.1	14.7[16d]	15.0
$H_3C-NH^+-CH_3$	212.4	214.3	18.7[16b]	17.3		222.5	224.5	15.0[16d]	15.4
$H_3C-NH^+(CH_3)-CH_3$	216.2	219.4	17.6[16b]	16.5		211.4	215.3	10.8[16d]	11.8
$Et-NH_3^+$	210.0	209.8	18.4[16b]	17.3		—	212.4	9.6[16d]	11.4
$Et-NH_2^+-Et$	219.7	219.0	18.8[16b]	17.9		—	209.0	10.4[16a]	10.8
$Et-NH^+(Et)-Et$	225.2	227.0	18.5[16b]	18.5		213.0	212.5	16.6[16b]	16.0
$HOCH_2CH_2NH_3^+$	214.3	211.3	17.5[16b]	16.2		227.7	225.5	19.5[16g]	18.6
$n\text{-}Pr-NH_3^+$	211.3	211.1	18.2[16b]	17.1		223.4	221.6	18.3[16g]	16.6
$n\text{-}Pr-NH^+(n\text{-}Pr)-n\text{-}Pr$	229.5	227.6	18.1[16b]	18.1	$H_3C-PH^+(CH_3)-CH_3$	221.4	219.9	16.6[12d]	17.0
$n\text{-}Bu-NH_3^+$	211.9	212.0	18.3[16f]	17.3	$Et-PH^+-Et$ (Et)	227.5	225.9	16.6[12d]	16.2
$n\text{-}Bu-NH_2^+-n\text{-}Bu$	223.5	222.9	18.3[16b]	18.1	$H_3C-PH^+(Et)-CH_3$	—	222.0	16.5[12d]	16.7
$n\text{-}Bu-NH^+(n\text{-}Bu)-n\text{-}Bu$	231.3	229.4	18.1[16b]	18.2	$Et-PH^+(CH_3)-Et$	—	224.1	16.5[12d]	16.5
$i\text{-}Bu-NH_3^+$	212.9	212.3	17.9[16b]	17.0	$n\text{-}Pr-PH^+-n\text{-}Pr$ (n-Pr)	—	228.7	16.5[12d]	16.4
$i\text{-}Bu-NH_2^+-i\text{-}Bu$	221.1	223.4	17.9[16b]	18.0	$n\text{-}Bu-PH_2^+-n\text{-}Bu$	—	217.7	11.1[12d]	14.2
$i\text{-}Bu-NH^+(i\text{-}Bu)-i\text{-}Bu$	231.3	228.4	18.0[16b]	16.2	$n\text{-}Bu-PH^+(n\text{-}Bu)-n\text{-}Bu$	—	229.7	16.3[12d]	16.2
$t\text{-}Bu-NH_3^+$	215.1	215.7	18.1[16f]	17.2	$i\text{-}Bu-PH_3^+$	—	201.0	5.2[12d]	9.6
$t\text{-}Bu-NH^+(t\text{-}Bu)-t\text{-}Bu$	—	238.0	18.1[16b]	22.2	$i\text{-}Bu-PH_2^+-i\text{-}Bu$	—	217.7	10.6[12d]	12.2
$Ph-NH_3^+$	203.3	201.9	10.6[16b]	7.8	$i\text{-}Bu-PH^+(i\text{-}Bu)-i\text{-}Bu$	—	228.9	15.7[12d]	13.7

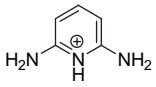
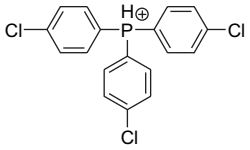
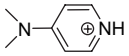
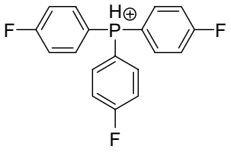
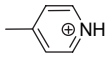
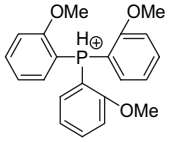
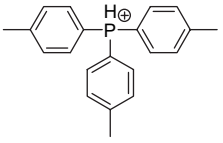
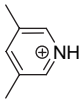
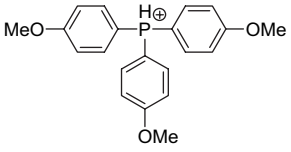
(*continued*)

Table 5. (*continued*)

Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)	Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)
	210.2	213.2	16.7[16b]	16.2		—	237.0	17.0[16e]	17.8
	206.7	205.6	11.3[16b]	9.5		—	210.8	13.5[12d]	13.9
	—	194.5	3.8[16a]	5.4		—	217.9	13.7[12d]	13.1
	—	193.9	4.8[16a]	3.2		—	225.1	14.6[12e]	14.5
	—	196.7	5.1[16a]	3.1		—	190.9	5.7[12d]	7.6
	—	199.3	7.9[16a]	5.5		—	202.3	9.9[12d]	10.7
	—	190.9	7.7[16a]	6.4		—	204.6	10.2[12e]	10.2
	—	195.9	8.4[16a]	5.7		—	194.3	7.0[12d]	7.1
	—	198.8	9.4[16a]	7.8		—	206.6	9.4[12e]	7.5
	205.3	203.7	10.5[16a]	7.8		—	223.1	11.2[12d]	13.2
	207.6	207.8	11.9[16a]	10.6		—	237.5	16.1[16e]	16.9
	—	236.6	19.6[16a]	18.7		—	215.2	5.2[12d]	6.7
	202.0	201.9	8.0[16d]	8.6		223.9	223.4	13.7[12e]	14.2
	202.9	203.8	8.5[16d]	9.5		224.6	225.0	10.0[16a]	10.7
	222.2	223.5	14.2[16a]	15.2		—	226.9	13.4[16e]	13.9
	—	217.8	7.6[16a]	8.7		—	226.4	11.5[16e]	10.2
	226.5	228.6	17.0[16a]	17.5		224.8	225.6	8.8[12d]	6.5

(*continued*)

Table 5. (*continued*)

Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)	Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)
	—	223.8	14.6[16d]	14.5		—	220.7	6.6[16h]	7.5
	232.1	233.0	18.2[16d]	18.4		—	221.5	7.8[16h]	7.9
	218.8	219.8	14.5[16d]	14.0		—	229.5	9.2[16h]	8.0
	217.9	218.5	13.7[16d]	13.4		—	232.4	10.2[16h]	9.7
	220.7	222.2	13.9[16d]	14.5		—	237.8	11.2[16h]	13.2

(within 1 pK_a unit). On the other hand, as to aliphatic phosphines the order of basicity evidently followed the rule: primary<secondary<tertiary.

Compared to aliphatic amines and phosphines, aromatic amines and phosphines showed very different trends in basicity. As shown in Figure 7, incremental substitution of the phenyl group to ammonia dramatically decreased the basicity by about 8 ($PhNH_2$), 12 (Ph_2NH), and 17 (Ph_3N) pK_a units. On the other hand, $PhPH_2$, Ph_2PH, and Ph_3P exhibited similar basicity and they were more basic than PH_3 by about 2 pK_a units.

5.3. α-Substituent effects on the basicity of aliphatic amines and phosphines

As previously studied, a substituent at the α-position often exerts strong effects on the acidity of a carbon-centered acid.[19] Herein, we were interested in whether similar effects could be observed for the basicity of aliphatic amines and

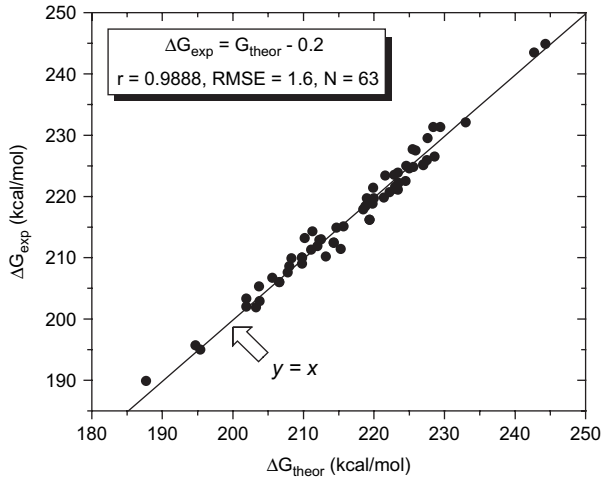


Figure 3. The correlation between the experimental and theoretical gas-phase acidities for 63 protonated amines and phosphines.

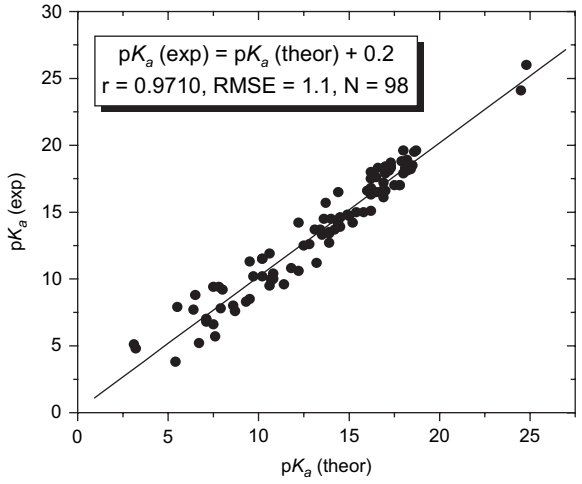


Figure 4. The correlation between the experimental and theoretical pK_a values for 98 protonated amines and phosphines.

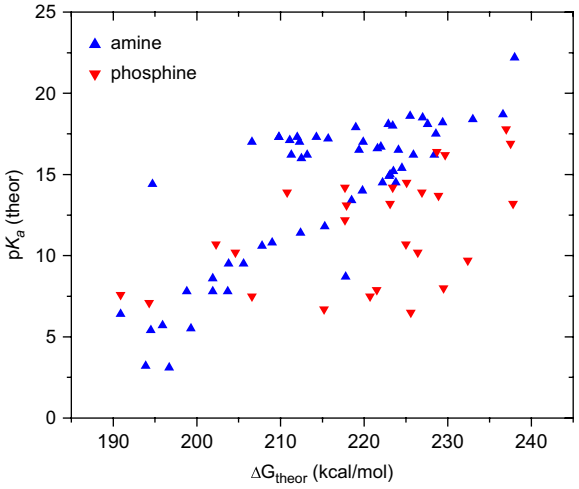


Figure 5. Comparing the theoretical gas-phase acidities with the theoretical pK_a values.

phosphines. As a result, we calculated the basicity for a number of representative α-substituted amines and phosphines as shown in Table 7. It was found that an α-methyl group did not exhibit any significant effect on the basicity of an amine (pK_a change=0.3 pK_a unit). On the other hand an α-phenyl group decreased the basicity by about 1 pK_a unit. Being a σ-acceptor, an α-methoxyl group decreased the basicity by about 4 pK_a units. Finally, strong electron-withdrawing groups at the α-position such as CN and CF_3 dramatically decreased the basicity of an amine by about 7 pK_a units.

Compared to amines, phosphines showed slightly different α-substituent effects. Here the α-Ph, α-OMe, α-CN, and α-CF_3 groups decreased the basicity of a phosphine by about 2, 3, 7, and 4 pK_a units, respectively.

5.4. Remote substituent effects on the basicity of aromatic amines and phosphines

Other important effects on basicity were exerted by the remote substituents in the aromatic systems. Although some studies have been performed in the past about the remote substituent effects on the gas-phase basicity of amines,[20] no work has been done about the solution-phase basicity of aromatic amines. Herein we calculated the basicity of a number of aromatic amines and phosphines containing some representative *para*-substituents (see Table 8). Plotting the basicity against the Hammett substituent constants we obtained a straight line for aromatic amines (Fig. 8a). The slope of the regression (i.e., the reaction constant) was −7.9. In comparison, the Hammett plot for aromatic phosphines showed significant deviations from a straight line (Fig. 8b). The reaction constant (−2.8) for aromatic phosphines was also much lower than that for aromatic amines (−7.9). From these results we concluded that the remote substituents exerted much stronger effects on the basicity of amines than phosphines.

5.5. Basicity of cyclic amines and phosphines

Besides the α-substituent effects and the remote substituent effects, an additional structural factor that can affect the activity is the ring strain. Previously it was shown that carbon acidities could be dramatically changed due to the ring strain.[21] Herein we tried to find out whether a similar strain effect could be observed for the basicity of amines and phosphines. Accordingly we calculated the basicity of cyclic amines and phosphines of different ring sizes (see Table 9). For amines, it was found that the three-membered cyclic amine exhibited significantly lower basicity than all the other cyclic amines by about 3 pK_a units, whereas the basicity of the four-, five-, six-, and seven-membered cyclic amines showed similar basicity.

In comparison, the phosphines showed more pronounced ring strain effect. Thus from the three-membered cyclic phosphine to the seven-membered cyclic phosphine the basicity increased dramatically by 13 pK_a units. It appeared that the difference between the cyclic amines and phosphines stemmed from the size of the phosphorus atom versus the nitrogen atom. Because the phosphorus atom is much larger than nitrogen, phosphines should exhibit stronger strain effects.

6. Summary

Amines and phosphines are widely utilized as bases and basic catalysts in organic chemistry. Thus it is highly valuable to develop a coherent theoretical method that can accurately predict the basicity of structurally unrelated amines and phosphines in organic solvents from the first principles. Herein we developed the first ab initio protocol that could predict the pK_a value of any protonated amine or phosphine in acetonitrile through systematic benchmarking. By comparing to a variety of available experimental data (total number=98), it was determined that the precision of the optimized method in basicity prediction was as low as 1.1 pK_a unit.

With the powerful new method in hand, we subsequently conducted some systematic studies about the basicity of organic amines and in particular phosphines, for which very few experimental data have been available. It was found that the solvent exerted profound effects on the basicity of amines and phosphines. Accordingly we concluded that it was not valid to use gas-phase data to interpret the solution-phase basicity of amines and phosphines. Next we reported the basicity of a number of synthetically important aliphatic and aromatic amines and phosphines in acetonitrile. We also compared, for the first time, the α-substituent effects on the basicity of aliphatic amines and phosphines and the remote substituent effects on the basicity of aromatic amines and phosphines. Finally, we studied for the first time the basicity of cyclic amines and phosphines. It was found that the ring strain exerted some interesting effects on the basicity of amines and phosphines.

Thus, by developing practical theoretical methods and utilizing them to solve realistic problems that remain difficult to settle by experiments, we hope to demonstrate that ab initio methods can now be developed to make not only reliable, but also *useful*, predictions for solution-phase organic chemistry.

Table 6. Gas-phase acidities (ΔG, kcal/mol) and solution-phase pK_a's in acetonitrile for protonated aliphatic and aromatic amines and phosphines

Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)	Compound	ΔG (exp)	ΔG (theor)	pK_a (exp)	pK_a (theor)
NH_4^+	195.7	194.7	16.5[16b]	14.4	PH_4^+	179.5	176.4		4.2
n-Bu$-NH_3^+$	211.9	212.0	18.3[16f]	17.3	n-Bu$-PH_3^+$		200.2		9.6
i-Bu$-NH_3^+$	212.9	212.3	17.9[16b]	17.0	i-Bu$-PH_3^+$		201.0	5.2[16g]	9.6
s-Bu$-NH_3^+$	214.1	214.4		17.1	s-Bu$-PH_3^+$		202.4		8.6
t-Bu$-NH_3^+$	215.1	215.7	18.1[16f]	17.2	t-Bu$-PH_3^+$		202.9		8.0
n-Bu$-NH_2^+$-n-Bu	223.5	222.9	18.3[16b]	18.1	n-Bu$-PH_2^+$-n-Bu		218.3		14.3
i-Bu$-NH_2^+$-i-Bu	221.1	223.4	17.9[16b]	18.0	i-Bu$-PH_2^+$-i-Bu		217.3		12.0
s-Bu$-NH_2^+$-s-Bu	226.5	226.4		18.4	s-Bu$-PH_2^+$-s-Bu		219.3		11.4
t-Bu$-NH_2^+$-t-Bu	228.2	227.8		18.9	t-Bu$-PH_2^+$-t-Bu		222.5		12.1
n-Bu-NH^+(n-Bu)-n-Bu	231.3	229.4	18.1[16b]	18.2	n-Bu-PH^+(n-Bu)-n-Bu		229.7	16.3[16g]	16.2
i-Bu-NH^+(i-Bu)-i-Bu	231.3	229.3	18.0[16b]	16.4	i-Bu-PH^+(i-Bu)-i-Bu		228.5	15.7[16g]	13.8
s-Bu-NH^+(s-Bu)-s-Bu		231.7		18.6	s-Bu-PH^+(s-Bu)-s-Bu		233.4		15.9
t-Bu-NH^+(t-Bu)-t-Bu		229.3		19.0	t-Bu-PH^+(t-Bu)-t-Bu		237.0	17.0[16e]	17.8
Ph$-NH_3^+$	203.3	201.9		7.8	Ph$-PH_3^+$		199.8		6.2
Ph$-NH_2^+$-CH_3		207.8		7.9	Ph$-PH_2^+$-CH_3		212.5		10.2
Ph$-NH^+$(CH_3)-CH_3	217.3	213.0		8.6	Ph$-PH^+$(CH_3)-CH_3	223.9	223.4	13.7[12e]	14.2
Ph$-NH_2^+$-Ph		206.5		2.4	Ph$-PH_2^+$-Ph		215.2	5.2[12d]	6.7
Ph$-NH^+$(Ph)-CH_3		211.6		3.7	Ph$-PH^+$(Ph)-CH_3	224.6	225.0	10.0[16a]	10.7
Ph-NH^+(Ph)-Ph	209.5	208.7		−2.4	Ph-PH^+(Ph)-Ph	224.8	225.6	8.8[12d]	6.5

7. Computational methodology

All the theoretical calculations were conducted using the Macromodel programs[22] and Gaussian 03 programs.[15] The conformation search for each compound was performed using the Macromodel (version 9.1) and its graphical user interface (GUI) Maestro (version 7.5), which used torsional sampling MCMM (Monte Carlo Multiple Minimum) method to generate multiple conformations under the OPLS_2005 force field. These conformations were then used as initial structures for the quantum mechanics geometry optimization. The conformation with the lowest energy was used for all the following calculations. A number of theoretical methods including HF, B3LYP, B3P86, BH&LYP, PBEPBE, MPWPW91 with varying basis sets (i.e., 6-31G(d), 6-31+G(d), 6-31G(d,p), 6-31++G(d,p), 6-311G(2df,2p), 6-31++G(2df,2p)), varying solvation models (i.e., IEFPCM, CPCM, IPCM, COSMOS-RS), and varying cavity models (i.e., UA0, BONDI, PAULING, UAHF, UAKS) and electrostatic scaling factors (0.90–1.30)

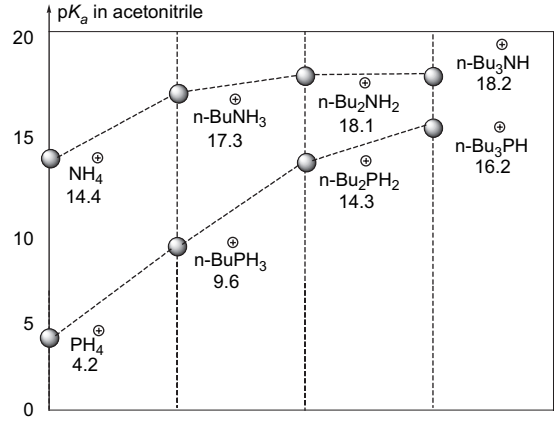


Figure 6. Comparing the pK_a's of protonated aliphatic amines and phosphines in acetonitrile.

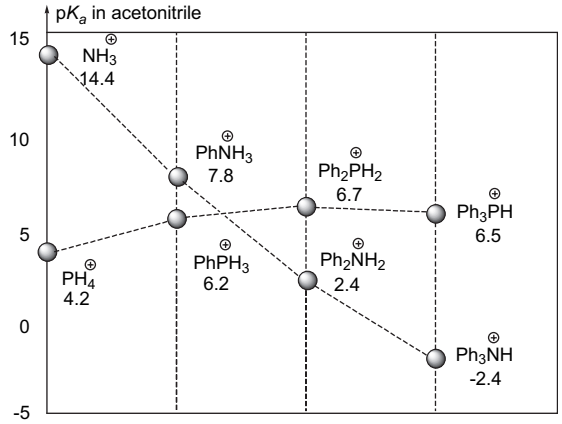
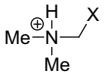
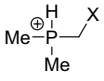


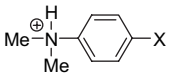
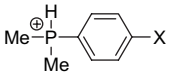
Figure 7. Comparing the pK_a's of protonated aromatic amines and phosphines in acetonitrile.

Table 7. α-Substituent effects on the basicity of aliphatic amines and phosphines[a]

	ΔG (theor) kcal/mol	pK_a (theor)
		
X=H	219.4 (216.2)	16.5 (17.6[16b])
X=CH_3	219.2 (222.1)	16.8
X=Ph	221.5	15.6
X=OCH_3	215.7	12.9
X=CN	201.4 (204.0)	9.3
X=CF_3	204.0	9.7
		
X=H	219.9 (221.4)	17.0 (16.6[16g])
X=CH_3	221.8	16.7
X=Ph	223.0	14.5
X=OCH_3	219.1	13.9
X=CN	204.7	9.5
X=CF_3	210.6	11.5

[a] Values in the parentheses are the available experimental data.

Table 8. Remote substituent effects on the basicity of aromatic amines and phosphines[a]

	σ_p	ΔG (theor) kcal/mol	pK_a (theor)
			
X=H	0.00	213.0	8.6
X=CH_3	−0.17	216.2	9.5
X=F	0.06	211.1	8.5
X=OCH_3	−0.27	218.2	11.4
X=CN	0.66	200.4	3.5
X=$COCH_3$	0.50	206.2	4.7
X=NO_2	0.78	198.5	2.7
			
X=H	0.00	223.4 (223.9)	14.2 (13.7)
X=CH_3	−0.17	227.2	15.9
X=F	0.06	221.2	14.3
X=OCH_3	−0.27	227.8	15.8
X=CN	0.66	214.7	12.7
X=$COCH_3$	0.50	220.2	13.5
X=NO_2	0.78	213.8	13.0

[a] Values in the parentheses are the available experimental data.

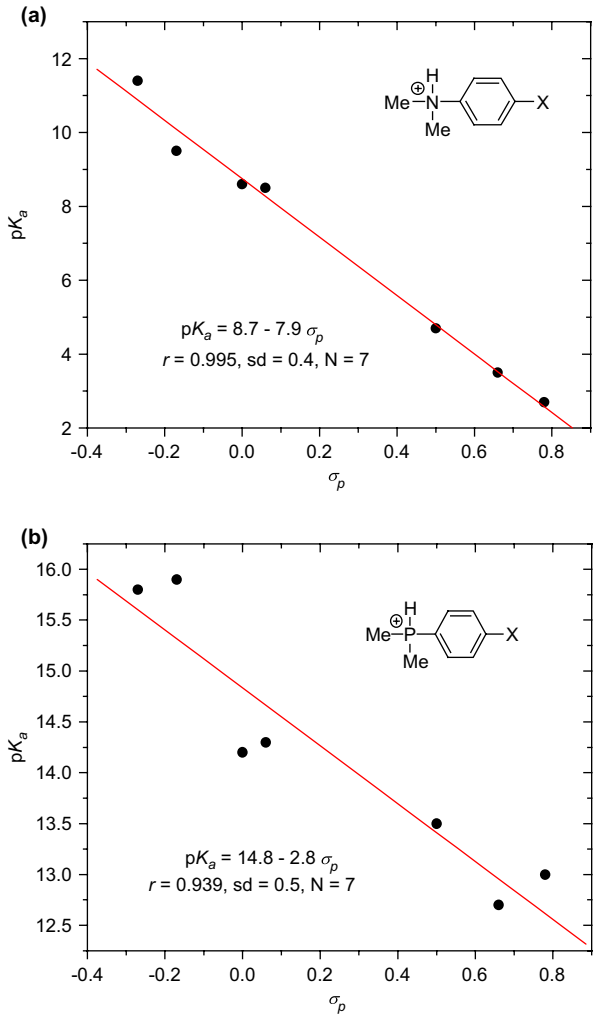


Figure 8. Hammett plots for the basicity of aromatic amines (a) and phosphines (b).

Table 9. Basicity of cyclic amines and phosphines[a]

Compound	ΔG (theor) kcal/mol	pK_a (theor)
	213.2 (216.1)	13.9
	218.7	16.9
	221.1 (223.4)	17.5
	222.0 (224.7)	17.2
	224.2	18.1
	199.5	4.6
	214.9	13.3
	220.6	15.4
	224.3 (223.9)	16.8
	226.7	17.5

[a] Values in the parentheses are the available experimental data.

were systematically utilized and compared. It is worth noting that geometry optimizations were re-performed in the acetonitrile solution in order to calculate the solvation free energies.

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Supplementary data

The Cartesian coordinates of the optimized molecules, the calculated electronic energies, thermal corrections to Gibbs free energies, and solvation free energies. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.018.

References and notes

1. Bell, R. P. *The Proton in Chemistry*; Chapman and Hall: London, 1973.
2. Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: New York, NY, 1984.
3. (a) Smith, B. J.; Radom, L. *J. Am. Chem. Soc.* **1993**, *115*, 4885–4888; (b) Ochterski, J.; Petersson, G. A.; Wiberg, K. B. *J. Am. Chem. Soc.* **1995**, *117*, 11299–11308; (c) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764–7776; (d) Peterson, K. A.; Xantheas, S. S.; Dixon, D. A.; Dunning, T. H., Jr. *J. Phys. Chem. A* **1998**, *102*, 2449–2454; (e) Pokon, E. K.; Liptak, M. D.; Feldgus, S.; Shields, G. C. *J. Phys. Chem. A* **2001**, *105*, 10483–10487; (f) Wiberg, K. B. *J. Org. Chem.* **2002**, *67*, 4787–4794; (g) Remko, M. *J. Phys. Chem. A* **2002**, *106*, 5005–5010.
4. (a) Jorgensen, W. L.; Briggs, J. M.; Gao, J. *J. Am. Chem. Soc.* **1987**, *109*, 6857–6858; (b) Guissani, Y.; Guillot, B.; Bratos, S. *J. Chem. Phys.* **1988**, *88*, 5850–5856; (c) Jorgensen, W. L.; Briggs, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 4190–4197; (d) Gao, J.; Li, N.; Freinforf, M. *J. Am. Chem. Soc.* **1996**, *118*, 4912–4913; (e) Figueirido, F.; Del Buono, G. S.; Levy, R. M. *J. Phys. Chem.* **1996**, *100*, 6389–6392; (f) Byun, K.; Mo, Y.; Gao, J. *J. Am. Chem. Soc.* **2001**, *123*, 3974–3979.
5. (a) Lim, C.; Bashford, D.; Karplus, M. *J. Phys. Chem.* **1991**, *95*, 5610–5620; (b) Kawata, M.; Ten-no, S.; Kato, S.; Hirata, F. *Chem. Phys.* **1996**, *203*, 53–67; (c) Kawata, M.; Ten-no, S.; Kato, S.; Hirata, F. *J. Phys. Chem.* **1996**, *100*, 1111–1117; (d) Sato, H.; Hirata, F. *J. Phys. Chem. A* **1998**, *102*, 2603–2608; (e) Sato, H.; Hirata, F. *J. Phys. Chem. B* **1999**, *103*, 6596–6604.
6. (a) Topol, I. A.; Tawa, G. J.; Caldwell, R. A.; Eissenstat, M. A.; Burt, S. K. *J. Phys. Chem. A* **2000**, *104*, 9619–9624; (b) Jang, Y. H.; Sowers, L. C.; Cagin, T.; Goddard, W. A., III. *J. Phys. Chem. A* **2001**, *105*, 274–280; (c) Klicic, J. J.; Friesner, R. A.; Liu, S.-Y.; Guida, W. C. *J. Phys. Chem. A* **2002**, *106*, 1327–1335; (d) Lopez, X.; Schaefer, M.; Dejaegere, A.; Karplus, M. *J. Am. Chem. Soc.* **2002**, *124*, 5010–5018; (e) Adam, K. R. *J. Phys. Chem. A* **2002**, *106*, 11963–11972.
7. Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161–2200.
8. For other pK_a calculation methods, see: (a) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **1999**, *103*, 11194–11199; (b) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **2000**, *104*, 2402–2409; (c) Liptak, M. D.; Shields, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 7314–7319; (d) Toth, A. M.; Liptak, M. D.; Phillips, D. L.; Shields, G. C. *J. Chem. Phys.* **2001**, *114*, 4595–4606; (e) Liptak, M.; Shields, G. C. *Int. J. Quantum Chem.* **2001**, *85*, 727–741; (f) Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421–6427; (g) Namazian, M.; Heidary, H. *Theochem* **2003**, *620*, 257–263; (h) Saracino, G. A. A.; Improta, R.; Barone, V. *Chem. Phys. Lett.* **2003**, *373*, 411–415; (i) Klamt, A.; Eckert, F.; Diedenhofen, M.; Beck, M. E. *J. Phys. Chem. A* **2003**, *107*, 9380–9386; (j) Namazian, M.; Halvani, S.; Noorbala, M. R. *Theochem* **2004**, *711*, 13–18; (k) Magill, A. M.; Yates, B. F. *Aust. J. Chem.* **2004**, *57*, 1205–1210; (l) am Busch, M. S.; Kanpp, E.-W. *ChemPhysChem* **2004**, *5*, 1513–1522; (m) Soriano, E.; Cerdan, S.; Ballesteros, P. *Theochem* **2004**, *684*, 121–128; (n) Barone, V.; Improta, R.; Rega, N. *Theor. Chem. Acc.* **2004**, *111*, 237–245; (o) Qi, Y.-H.; Zhang, Q.-Y.; Luo, C.-C.; Wang, J.; Xu, L. *Chem. J. Chin. Univ.* **2004**, *25*, 1100–1103; (p) De Abreu, H. A.; De Almeida, W. B.; Duarte, H. A. *Chem. Phys. Lett.* **2004**, *383*, 47–52; (q) Nakamura, S.; Hirao, H.; Ohwada, T. *J. Org. Chem.* **2004**, *69*, 4309–4316; (r) Murlowska, K.; Sadlej-Sosnowska, N. *J. Phys. Chem. A* **2005**, *109*, 5590–5595; (s) Han, J.; Deming, R. L.; Tao, F.-M. *J. Phys. Chem. A* **2005**, *109*, 1159–1167; (t) Gao, D.; Svoronos, P.; Wong, P. K.; Maddalena, D.; Hwang, J.; Walker, H. *J. Phys. Chem. A* **2005**, *109*, 10776–10785; (u) Wang, X.; Li, S.-H.; Jiang, Y.-S. *J. Phys. Chem. A* **2005**, *109*, 10770–10775; (v) Philips, D. L.; Zhao, C.; Wang, D. *J. Phys. Chem. A* **2005**, *109*, 9653–9673; (w) Eckert, F.; Klamt, A. *J. Comput. Chem.* **2006**, *27*, 11–19.

9. (a) Pliego, J. R. *Chem. Phys. Lett.* **2003**, *367*, 145–149; (b) Almerindo, G. I.; Tondo, D. W.; Pliego, J. R., Jr. *J. Phys. Chem. A* **2004**, *108*, 166–171.
10. (a) Fu, Y.; Liu, L.; Li, R.-Q.; Liu, R.; Guo, Q.-X. *J. Am. Chem. Soc.* **2004**, *126*, 814–822; (b) Fu, Y.; Liu, L.; Wang, Y.-M.; Li, J.-N.; Yu, T.-Q.; Guo, Q.-X. *J. Phys. Chem. A* **2006**, *110*, 5874–5886.
11. (a) Sun, S.-G.; Peng, X.-J.; Fan, M.-W.; Xu, Y.-Q. *Chin. J. Org. Chem.* **2004**, *24*, 953–956; (b) Chen, W.-Y.; Lu, J. *Chin. J. Org. Chem.* **2004**, *24*, 1111–1113; (c) Yuan, Y.-B.; Nie, J.; Wang, S.-J.; Zhang, Z.-B. *Chin. J. Org. Chem.* **2005**, *25*, 394–398; (d) Shi, Y.; Yao, G.-W.; Ma, M. *Chin. J. Org. Chem.* **2005**, *25*, 730–733; (e) Li, Q.-R.; Gu, C.-Z.; Yin, H.; Zhang, Y. *Chin. J. Org. Chem.* **2005**, *25*, 1416–1419; (f) Wang, X.-M.; Zhu, T.; Zheng, L.-Y.; Li, Y.-Z.; Zhang, S.-Q.; Bai, J. *Chin. J. Org. Chem.* **2006**, *26*, 660–666; (g) Zhang, X.; Qing, Z.-L. *Chin. J. Org. Chem.* **2006**, *26*, 870–873.
12. (a) Kolthoff, I. M.; Chantooni, J. M. K.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23–28; (b) Bokanov, A. I.; Korolev, B. A.; Stepanov, B. I. *Zh. Obshch. Khim.* **1965**, *35*, 1879–1880; (c) Bush, R. C.; Angelici, R. J. *Inorg. Chem.* **1988**, *27*, 681–686; (d) Henderson, W. A., Jr.; Streuli, C. A. *J. Am. Chem. Soc.* **1960**, *82*, 5791–5794; (e) Streuli, C. A. *Anal. Chem.* **1960**, *32*, 985–987; (f) Allman, T.; Goel, R. G. *Can. J. Chem.* **1982**, *60*, 716–722; (g) Heemstra, J. M.; Moore, J. S. *Tetrahedron* **2004**, *60*, 7287–7292; (h) Streitwieser, A.; McKeown, A. E.; Hasanayn, F.; Davis, N. R. *Org. Lett.* **2005**, *7*, 1259–1262; (i) Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, 147–149; (l) Soovali, L.; Kaljurand, I.; Kutt, A.; Leito, I. *Anal. Chim. Acta* **2006**, *566*, 290–303.
13. Some recent examples: (a) Koppel, I. A.; Schwesinger, R.; Breuer, T.; Burk, P.; Herodes, K.; Koppel, I.; Leito, I.; Mishima, M. *J. Phys. Chem. A* **2001**, *105*, 9575–9586; (b) Kovacevic, B.; Maksic, Z. B. *Chem.—Eur. J.* **2002**, *8*, 1694–1702; (c) Ohwada, T.; Hirao, H.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 7486–7494; (d) Pham-Tran, N.-N.; Bouchoux, G.; Delaere, D.; Nguyen, M. T. *J. Phys. Chem. A* **2005**, *109*, 2957–2963; (e) Alder, R. W. *J. Am. Chem. Soc.* **2005**, *127*, 7924–7931; (f) An interesting method was reported very recently where the basicity of organic bases in aqeuous solution was successfully predicted by an ab initio method: see Ref. 8w. (g) For an earlier study on the similar problem, see: Kallies, B.; Mitzner, R. *J. Phys. Chem. B* **1997**, *101*, 2959–2967.
14. Gas-phase acidities are taken from NIST Standard Reference Database 69, March 1998 release: NIST Chemistry WebBook (data compiled by J. E. Bartmess).
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C. 02*; Gaussian: Pittsburgh, PA, 2003.
16. (a) Kaljurand, I.; Kutt, A.; Soovali, L.; Rodima, T.; Maemets, V.; Leito, I.; Koppel, I. *J. Org. Chem.* **2005**, *70*, 1019–1028; (b) Coetzeel, J. F.; Padmanabhan, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 5005–5010; (c) Kaljurand, I.; Rodima, T.; Leito, I.; Koppel, I.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 6202–6208; (d) Augustin-Nowacka, D.; Chmurzynski, L. *Anal. Chim. Acta* **1999**, *381*, 215–220; (e) Abdur-Rashid, K.; Fong, T. P.; Greaves, B.; Gusev, D. G.; Hinman, J. G.; Landau, S. E.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 9155–9171; (f) Nachtigall, F. F.; Lazzarottoa, M.; Nome, F. *J. Braz. Chem. Soc.* **2002**, *13*, 295–299; (g) Streitwieser, A.; Kim, Y. J. *J. Am. Chem. Soc.* **2000**, *122*, 11783–11786; (h) Angelici, R. A. *Acc. Chem. Res.* **1995**, *28*, 51–60.
17. Some recent computational studies to address the related problems: (a) Kovacevic, B.; Maksic, Z. B. *Chem. Commun.* **2006**, 1524–1526; (b) Kovacevic, B.; Maksic, Z. B. *Tetrahedron Lett.* **2006**, *47*, 2553–2555; (c) Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453–4462.
18. (a) Brown, H. C.; Taylor, M. D. *J. Am. Chem. Soc.* **1944**, *66*, 846–847; (b) Brown, H. C.; Pearsall, H. *J. Am. Chem. Soc.* **1945**, *67*, 1765–1767; (c) Taft, R. W.; Levitt, L. S. *J. Org. Chem.* **1977**, *42*, 916–918; (d) Mo, O.; Yanez, M.; Michele, D.; Jean-Francois, G.; Pierre-Charles, M.; Jean-Claude, G. *J. Am. Chem. Soc.* **1999**, *121*, 4653–4663; (e) Cao, C.-Z. *Chin. J. Org. Chem.* **2000**, *20*, 258–262; (f) Nie, C.-M.; Wang, H.-Q.; Fan, M.-F.; Xia, L.-S. *Chin. J. Org. Chem.* **2001**, *21*, 305–309; (g) Caskey, D. C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* **2002**, *67*, 5098–5105; (h) Zhang, X.-L.; Wang, Y.-X.; Li, J.-L. *Chin. J. Org. Chem.* **2003**, *23*, 198–202; (i) Korzheneyskaya, N. G.; Rybachenko, V. I.; Kovalenko, V. V. *Russ. Chem. Bull.* **2003**, *52*, 893–899; (j) Graton, J.; Berthelot, M.; Besseau, F.; Laurence, C. *J. Org. Chem.* **2005**, *70*, 7892–7901.
19. (a) Beale, R. N. *J. Chem. Soc.* **1954**, 4494–4499; (b) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 318–329; (c) Cherkasov, A. R.; Jonsson, M.; Galkin, V. *J. Mol. Graph. Mod.* **1999**, *17*, 28–42; (d) Graton, J.; Berthelot, M.; Laurence, C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2130–2135.
20. (a) Stewart, R.; O'Donnell, J. P. *Can. J. Chem.* **1964**, *42*, 1694–1698; (b) Ikuta, S.; Kebarle, P. *Can. J. Chem.* **1983**, *61*, 97–102; (c) Marquis, E.; Graton, J.; Berthelot, M.; Planchat, A.; Laurence, C. *Can. J. Chem.* **2004**, *82*, 1413–1422.
21. Alkorta, I.; Elguero, J. *Tetrahedron* **1997**, *53*, 9741–9748.
22. *MacroModel, Version 9.1*; Schrödinger: New York, NY, 2005.

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Synthesis of oligonucleoside phosphorodithioates on a solid support by the *H*-phosphonothioate method

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Abstract—Phosphorodithioate-type short oligonucleotides were efficiently synthesized using bis(2,6-dimethylphenyl) phosphorochloridate as a coupling agent on a solid support by application of the *H*-phosphonothioate method, where oxidation was facilitated using elemental sulfur following completion of *H*-phosphonothioate oligomer assembly, as with the standard *H*-phosphonate method.

1. Introduction

Oligonucleotide analogues bearing modified phosphodiester linkages are generating increasing interest as potential therapeutic or diagnostic reagent[1] and as novel tools for studying various biochemical processes.[2] Phosphorothioate DNA is the most extensively studied variation to date. Substitution of a single nonbridging oxygen atom with a sulfur atom renders the internucleotide linkage nuclease resistant[2b] and the modified phosphorus center, which is chiral, results in a mixture of unresolvable diastereomeric oligomers possessing variable properties. One especially attractive analogue is the phosphorodithioate internucleotide linkage since, like natural DNA, it is achiral at phosphorous. This linkage has been found to be highly stable toward enzymatic hydrolysis and oligonucleotides have proven useful as antisense probes.[3] Several synthetic approaches for these analogues involving the use of phosphorodithioate,[3a,b,d,4,5] thiophosphoroamidite,[3d,g,i,5–7] *H*-phosphonothioate,[3d,5,8–13] *H*-phosphonodithioate,[3j,14] phosphorodithioate,[3h,15] or dithiophospholane[16] monomers have been developed. The *H*-phosphonothioate method has advantages in that the *H*-phosphonothioate monomers are stable to hydrolysis and oxidation, the cycle time is short, and there is the possibility of oxidation without using elemental sulfur in every cycle but only at the end of the synthesis, just as in the standard *H*-phosphonate method (Scheme 1). The central issue for phosphorodithioate oligomer synthesis by the *H*-phosphonothioate method involves selective O-activation (**4**) of the *H*-phosphonothioate **3** by a coupling agent. In a study pertaining to the synthesis of dinucleoside *H*-phosphonothioates Stawinski et al. reported ^{31}P NMR studies on the coupling reactions using deoxynucleoside *H*-phosphonothioates **3** (R=DMTr) with a variety of activators.[8,9,17] When diphenyl phosphorochloridate (DPCP) or diethyl phosphorochloridate (DECP) was used as a coupling agent, the *H*-phosphonothioate monomers could be selectively activated at the oxygen and coupled in less than 5 min without side products that may have been generated from the subsequent reaction of dinucleoside *H*-phosphonothioate with the coupling agent (phosphite triester or hypophosphates). In reactions when more than an equimolar amount of a hydroxylic component was used, some 5′-phosphorylation of the nucleoside by DPCP was observed. Caruthers et al. developed a synthetic cycle for the solid-phase synthesis of oligonucleoside phosphonothioates using *H*-phosphonothioates **3** (R=DMTr).[12,13] They reported that oxidation with elemental sulfur following completion of *H*-phosphonothioate oligomer assembly, as with the standard *H*-phosphonate method, gave rise to the formation of significant amounts of desulfurized products. The synthesis of oligodeoxynucleoside phosphorodithioates was accomplished using DPCP as a coupling agent and incorporating an oxidation step using 2,4-dichlorobenzyl thiosuccinimide in each coupling cycle.

On the other hand, we reported the synthesis of oligonucleoside phosphorodithioates using nucleoside 3′-*H*-phosphonothioates **3** (R=LMNBz) by the standard *H*-phosphonate method, where oxidation was achieved using elemental sulfur following completion of *H*-phosphonothioate oligomer assembly.[18–20] The phosphorodithioate trimer ($T_{PS2}T_{PS2}T$) was efficiently synthesized using DECP as a coupling agent.[20] The successful synthesis of $T_{PS2}T_{PS2}T$ prompted us to further investigate the utility of this method. We performed further investigations on the synthesis of

Keywords: Antisense oligonucleotide; Oligonucleoside phosphorodithioates; *H*-Phosphonothioate method.
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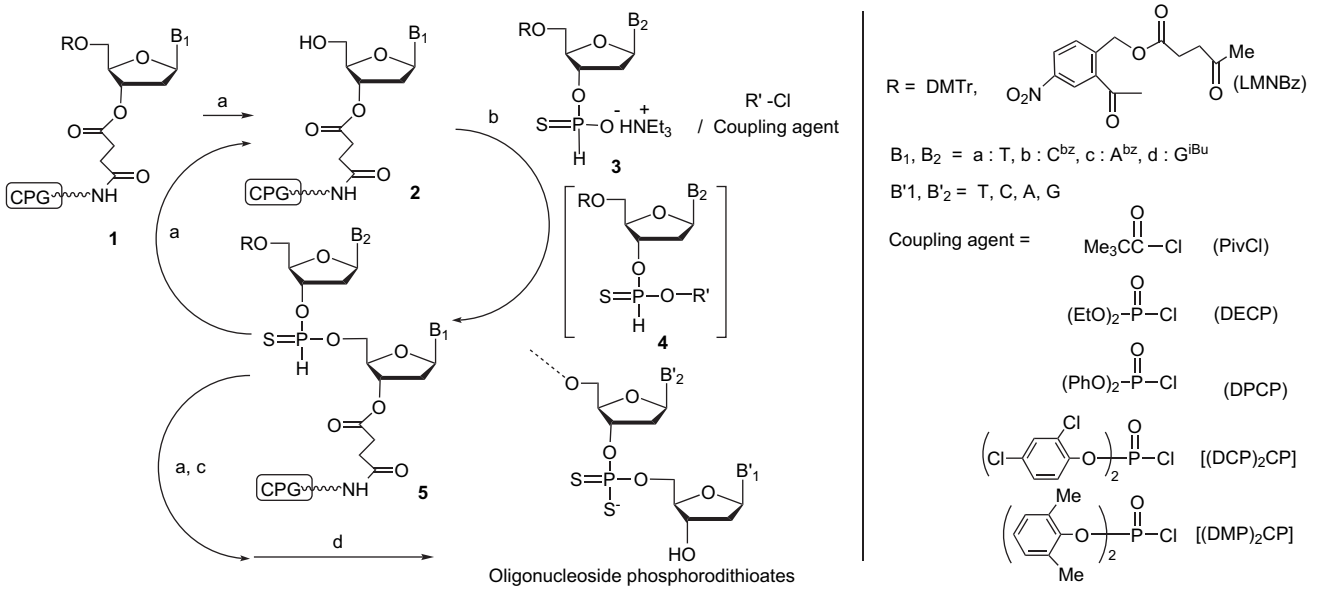

Scheme 1. Reaction cycle for assembly of oligonucleoside phosphorodithioates. Conditions: (a) 3% CCl_3COOH/CH_2Cl_2, 1 min (for deprotection of the DMTr group) or (i) 0.5 M $NH_2NH_2\cdot H_2O$, 1:4 CH_3COOH/pyridine, 15 min, (ii) 0.5 M imidazole, CH_3CN, 5 min (for deprotection of the LMNBz group); (b) 0.05 M **3**, 0.15–0.25 M coupling agent, 1:4 pyridine/CH_3CN, 10 min; (c) 0.3 M S_8, 1:9 2,6-lutidine/CH_2Cl_2, 1 h; (d) 1:1 concd NH_4OH/EtOH, rt, 3 h, −55 °C, 5 h.

oligonucleoside phosphorodithioates by the *H*-phosphonothioate method through oxidation using elemental sulfur at the end of the synthesis.

We recently reported[21] that the phosphorodithioate-type short thymidine oligomers were efficiently synthesized using bis(2,6-dimethylphenyl) phosphorochloridate [$(DMP)_2CP$] as a coupling agent using the *H*-phosphonothioate method, where the oxidation was facilitated using elemental sulfur following completion of *H*-phosphonothioate oligomer assembly. In order to further assess the potential of this synthetic approach, we performed a study involving the synthesis of heterosequences containing all four nucleotides. The results of these studies will be described in full herein.

2. Results and discussion

2.1. Comparative study of various coupling agents in the synthesis of oligonucleoside phosphorodithioates

Based on the aforementioned reports,[8,9,12,13,17,20,22] the reaction of *H*-phosphonothioate **3** with hydroxylic component **2** using the bulky phosphorochloridate derivative as a coupling agent could be expected to be selectively activated at oxygen and coupled without side reactions, i.e., the generation of phosphorothioate oligomers and the 5′-phosphorylation of nucleotide by a coupling agent. Additionally, using diphenyl phosphorochloridate derivatives having substituents on the phenyl groups as a bulky coupling agent, it was expected that the selectivity relating to O-activation (**4**) of the phosphonothioate **3** by a coupling agent could be improved by changing the reactivity of the coupling agent through electronic effects of the substituents. The commercially available bis(2,4-dichlorophenyl) phosphorochloridate [$(DCP)_2CP$] and $(DMP)_2CP$ were considered as candidates for effective coupling. We performed a comparative study of various coupling agents, which included pivaloyl chloride (PivCl), DPCP, DECP, $(DCP)_2CP$, and $(DMP)_2CP$.[21] These were employed in the synthesis of oligonucleoside phosphorodithioates as exemplified by the synthesis of the dimer $T_{PS2}T$ using 5′-*O*-DMTr-thymidine 3′-*H*-phosphonothioate **3a**[17] on T-CPG support **1a** (R=DMTr) through oxidation using elemental sulfur as shown in Scheme 1 by manual synthesis.[23] The effectiveness of $(DMP)_2CP$ can clearly be seen from the HPLC profiles shown in Figure 1 (I–V). The decrease in reactivity of the diphenyl phosphorochloridate derivative resulting from the effect of the electron-donating substituents on the phenyl groups is likely to have enhanced the selectivity of O-activation (**4**) of *H*-phosphonothioate **3**. DECP, which possesses electron-donating substituents in the ester moiety, also showed highly selective O-activation (**4**).

Based on these results, the phosphorodithioate dimers $dC_{PS2}T$, $dA_{PS2}T$, and $dG_{PS2}T$ were synthesized using $(DMP)_2CP$ as a coupling agent. Following deprotection of the DMTr group of 5′-*O*-DMTr-thymidine linked to CPG support **1a**, *H*-phosphonothioate **3**(**b**, **c** or **d**) (R=DMTr) was coupled to thymidine (**2a**) in the presence of $(DMP)_2CP$. Following *H*-phosphonothioate dimer **5** (B_1=T, B_2=C^{Bz}, A^{Bz}, or G^{iBu}, R=DMTr) assembly and subsequent removal of the DMTr group, oxidation was performed using a 0.3 M solution of elemental sulfur in 1:9 2,6-lutidine/dichloromethane for 1 h to yield the desired phosphonodithioate dimer. The phosphorodithioate dimer was cleaved from the support[24] and then analyzed by reversed-phase HPLC. $(DMP)_2CP$ also showed highly selective O-activation (**4**) of the *H*-phosphonothioates (**3b**, **3c**, and **3d**) [Fig. 1 (VI–VIII)].

2.2. Synthesis of oligonucleoside phosphorodithioates

In the synthesis of oligonucleoside phosphonodithioates using *H*-phosphonothioates **3** (R=DMTr), significant amounts of desulfurized products were formed during oxidation using elemental sulfur following completion of *H*-phosphonothioate oligomer assembly as reported by Caruthers and

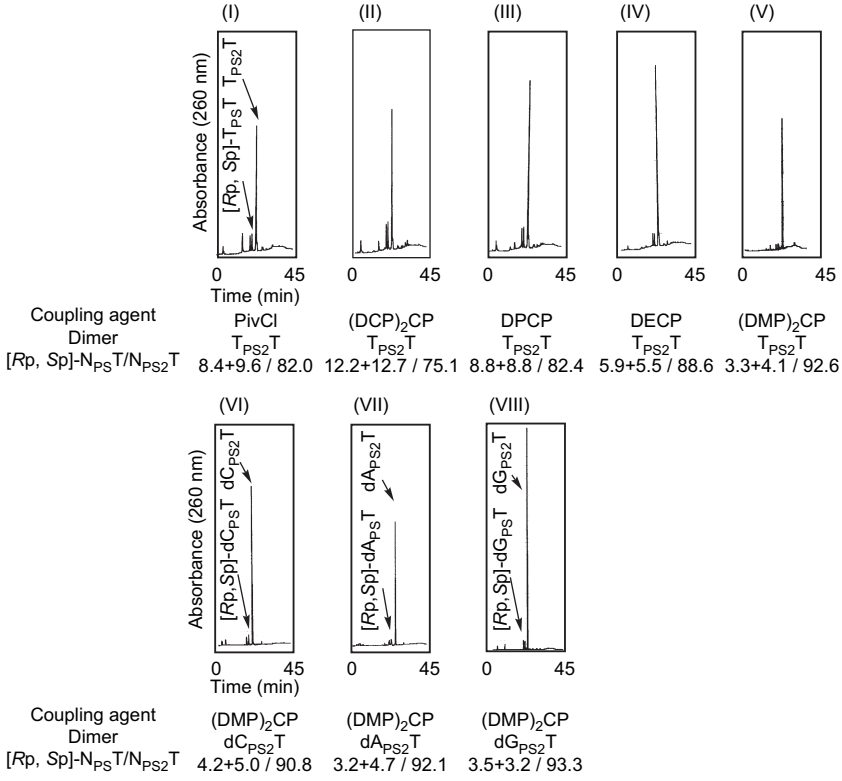

Figure 1. Reversed-phase HPLC profiles of crude products of phosphorodithioate dimer [$N_{PS2}T$(N=T, dC, dA, and dG)] preparations using the 5′-*O*-DMTr-2′-deoxynucleoside *H*-phosphonothioate **3** (B=T, C^{Bz}, A^{Bz}, and G^{iBu}) on T-CPG **1a** (R=DMTr) in the presence of PivCl (I), $(DCP)_2CP$ (II), DPCP (III), DECP (IV), and $(DMP)_2CP$ (V–VIII) as a coupling agent.

Seeberger, although detailed data were not shown.[13] We investigated the stability of $T_{PS2}T$ as a model oligomer under oxidation conditions prior to long-chain oligomer synthesis.[24] Following *H*-phosphonothioate dimer **5** (B_1=B_2=T, R=DMTr) assembly using $(DMP)_2CP$ as a coupling agent and subsequent removal of the DMTr group, oxidation with elemental sulfur was performed for either 15 min, 1 h, 4 h or 8 h. $T_{PS2}T$ was cleaved from the support and subjected to analysis by reversed-phase HPLC. It was determined that sulfurization was complete within 15 min and that the amount of desulfurized products ([*R*p]- and [*S*p]-phosphorothioate thymidine dimers=[*R*p, *S*p]−$T_{PS}T$) increased slightly with increased time (Fig. 2).

Based on the studies described above, we extended our studies to the synthesis of long-chain oligonucleoside phosphonodithioates. Using the same procedure employed with $(DMP)_2CP$ as a coupling agent through oxidation using elemental sulfur for 1 h at the end of the synthesis, oligomers [$(T_{PS2})_nT$: trimer, tetramer, hexamer, and octamer] were assembled and HPLC tracings of each of the resulting mixtures are shown in Figure 3 (I–IV). The desired oligomers were obtained as a main peak.[21]

Finally, in order to further assess the potential of this synthetic approach, investigations involving the synthesis of heterosequences containing all four nucleotides were

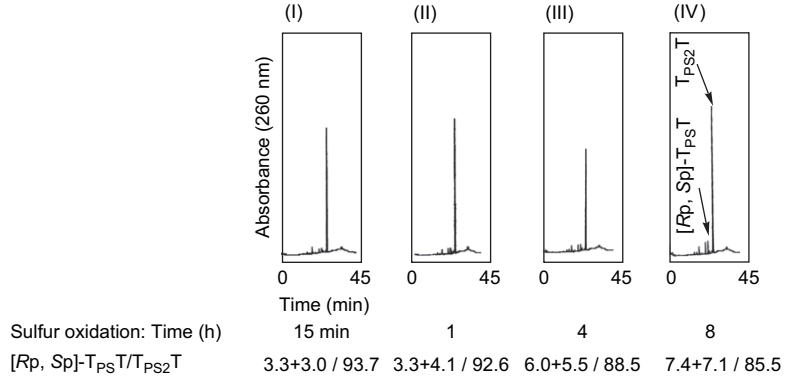

Figure 2. Reversed-phase HPLC profiles of crude products of phosphorodithioate dimer [$T_{PS2}T$] preparations using the 5′-*O*-DMTr-thymidine *H*-phosphonothioate **3a** on T-CPG **1a** (R=DMTr) in the presence of $(DMP)_2CP$ as a coupling agent through treatment with 0.3 M solution of S_8 in 1:9 2,6-lutidine/pyridine for 15 min (I), 1 h (II), 4 h (III), and 8 h (IV).

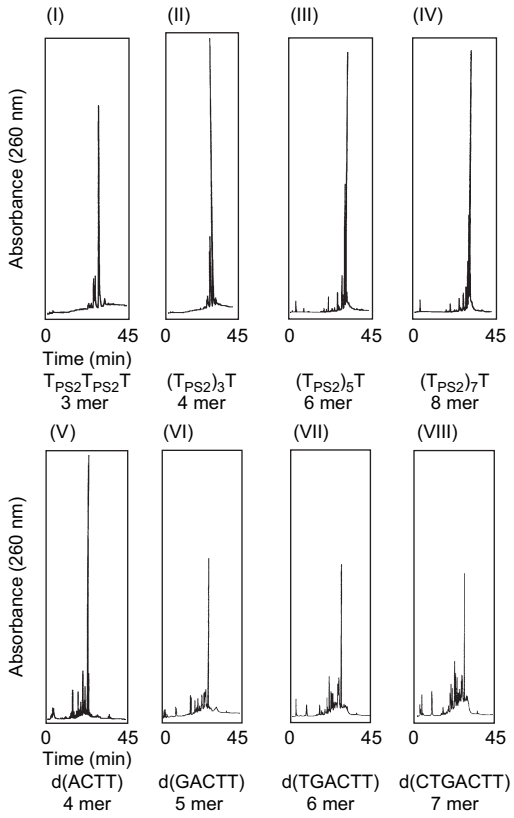

Figure 3. Reversed-phase HPLC profiles of crude products of phosphorodithioate oligomer preparations using the 5′-*O*-DMTr-2′-deoxynucleoside 3′-*H*-phosphonothioate **3** (B=T, C^{Bz}, A^{Bz}, and G^{iBu}) on T-CPG **1a** (R=DMTr) in the presence of $(DMP)_2CP$, though oxidation with S_8 for 1 h at the end of the synthesis. Conditions of reversed-phase HPLCs: column μBONDASPHERE 5 μ C18 (3.9 mm ID × 150 mm L); elution buffer 7.25–50% CH_3CN/0.1 M TEAA (pH 7); flow rate 1 mL/min; detection UV at 260 nm.

carried out. Using the same procedure, oligomers [tetramer $d(A_{PS2}C_{PS2}T_{PS2}T)$, pentamer $d(G_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$, hexamer $d(T_{PS2}G_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$, and heptamer $d(C_{PS2}T_{PS2}G_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$] were assembled and HPLC tracings of each of the resulting mixtures are shown in Figure 3 (V–VIII). The desired oligomers were easily purified by reversed-phase HPLC, and the electrophoretic profiles gave clear single bands (Fig. 4 for the heptamer). The structure of the products was consistent with the data derived from ^{31}P NMR (Fig. 5 for the heptamer) and ESI-TOF MS analyses.

In conclusion, the synthesis of phosphorodithioate-type oligomers was accomplished by employing $(DMP)_2CP$ as

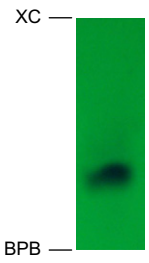

Figure 4. Electrophoresis of the heptamer [$d(C_{PS2}T_{PS2}C_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$] on a 20% polyacrylamide gel containing 7 M urea, visualized by UV-shadowing.

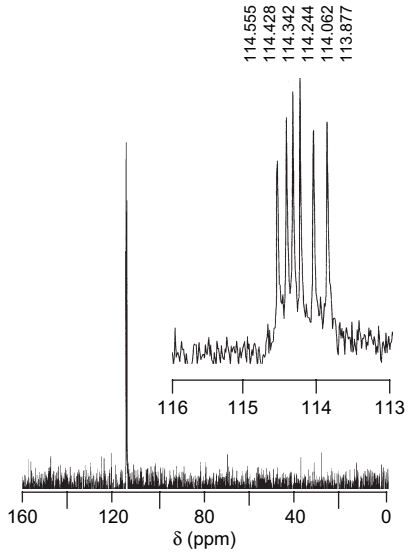

Figure 5. ^{31}P NMR of the heptamer [$d(C_{PS2}T_{PS2}C_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$] in D_2O.

a coupling agent in the synthetic cycles using the *H*-phosphonothioate method, and oxidation using elemental sulfur was achieved following completion of *H*-phosphonothioate oligomer assembly. Application of the approach detailed in this investigation will be useful in the synthesis of phosphorodithioate-type short oligonucleotides.

3. Experimental

3.1. General

HPLC was performed on a Waters liquid chromatograph (600E system) equipped with UV–vis detector (2487 Dual λ), data module (741 type), and fraction collector. A μBONDASPHARE 5μ C18 (3.9 mm ID×150 mm L) column with gradients of CH_3CN in water (0.01 M TEAA, pH 7) was used. ^{31}P NMR spectra were recorded on a Bruker DRX 400 apparatus with D_2O as an internal standard. Mass spectra were recorded on a Micromass Q-Tof Ultima API apparatus. Compounds **3a**, **3b**, **3c**, and **3d** (R=DMTr) were prepared according to the procedure described by Stawinski et al.[17]

3.2. Comparative study of the synthesis of phosphorodithioate dimer $T_{PS2}T$ using PivCl, DPCP, DECP, $(DCP)_2CP$, and $(DMP)_2CP$ as coupling agents

The dimer $T_{PS2}T$ was synthesized on a 1 μmol scale on a CPG support with a syringe-based system.[23] The T-CPG **1a** (R=DMTr, purchased from Applied Biosystems Pty Ltd) was treated with 3% w/v Cl_3CCOOH in CH_2Cl_2 solution (1 mL×2) for 1 min, followed by washing with CH_3CN (2 mL×2). A 0.1 M solution of **3a** (R=DMTr, 22 mg, 0.03 mmol) in CH_3CN (0.3 mL) and a solution of the coupling agent, 0.5 M PivCl (19 μL, 0.15 mmol), 0.3 M DPCP (19 μL, 0.09 mmol), 0.3 M DECP (13 μL, 0.09 mmol), 0.3 M $(DCP)_2CP$ (37 mg, 0.09 mmol), or 0.3 M $(DMP)_2CP$ (29 mg, 0.09 mmol) in 3:2 CH_3CN/pyridine (0.3 mL) were delivered to the synthesis column. Following 10 min, the

coupling agents were ejected from the synthesis column, and the CPG support was washed with CH_3CN (2 mL×2) to give *H*-phosphonothioate dimer **5** (B_1=B_2=T, R=DMTr). The terminal DMTr protecting group was removed following treatment with 3% w/v Cl_3CCOOH in CH_2Cl_2 solution (1 mL×2) for 1 min. The CPG support was washed with CH_3CN (2 mL×2). The internucleotidic *H*-phosphonate linkages were sulfurized using a mixture of 0.3 M solution of S_8 (19 mg) in 1:9 2,6-lutidine/CH_2Cl_2 (2 mL) for 1 h. Washings were performed using CH_3CN (2 mL×2). The resulting dimer $T_{PS2}T$ was then cleaved from the CPG support by treatment with 1:1 concd NH_4OH/ethanol[24] (2 mL×2) for 3 h at room temperature. Following evaporation of the resulting solution, the dimer $T_{PS2}T$ was purified by reversed-phase HPLC [Fig. 1 (I–V)].

The $T_{PS2}T$ dimers isolated yielded 8.8 (PivCl), 8.3 [$(DCP)_2CP$], 10.1 (DPCP), 11.9 (DECP), and 12.2 [$(DMP)_2CP$] A_{260} units: HPLC t_R 23.36 min; ^{31}P NMR (D_2O) δ 114.55 (s, PS_2, 1P); ESI-TOF MS calcd for $C_{20}H_{27}N_4O_{10}PS_2Na$ $(M+Na)^+$ 601.0804, found 601.1043.

3.3. Synthesis of phosphorodithioate dimers ($dC_{PS2}T$, $dA_{PS2}T$, and $dG_{PS2}T$) using $(DMP)_2CP$ as a coupling agent

Following chain elongation with a syringe-based reaction system using a column of T-CPG **1a** (R=DMTr, 1 μmol scale), *H*-phosphonothioate monomer [**3b** (R=DMTr, 24 mg, 0.03 mmol), **3c** (R=DMTr, 25 mg, 0.03 mmol), or **3d** (R=DMTr, 25 mg, 0.03 mmol)], and $(DMP)_2CP$ (29 mg, 0.09 mmol) as a coupling agent as described above, the terminal DMTr protecting group of *H*-phosphonothioate dimer **5** was removed following treatment with 3% w/v Cl_3CCOOH in CH_2Cl_2 solution (1 mL×2) for 1 min. The CPG support was washed with CH_3CN (2 mL×2). The internucleotidic *H*-phosphonate linkages were sulfurized using a mixture of 0.3 M solution of S_8 (19 mg) in 1:9 2,6-lutidine/CH_2Cl_2 (2 mL) for 1 h. Washings were performed using CH_3CN (2 mL×2). The resulting oligomer was then cleaved from the CPG support following treatment with 1:1 concd NH_4OH/ethanol (2 mL×2) for 3 h at room temperature. The resulting solution was heated in a sealed vial at 55 °C for 5 h. Following evaporation, the residue was dissolved in water (5 mL), washed with ethyl acetate (5 mL×3), and then the aqueous layer was evaporated. The phosphorodithioate dimer was purified by reversed-phase HPLC [Fig. 1 (VI–VIII)].

The dimer $dC_{PS2}T$ isolated yielded 11.4 A_{260} units: HPLC t_R 21.31 min [Fig. 1 (VI)]; ^{31}P NMR (D_2O) δ 114.67 (s, PS_2, 1P); ESI-TOF MS calcd for $C_{19}H_{26}N_5O_9PS_2$ $(M+H)^+$ 564.0988, found 564.0963.

The dimer $dA_{PS2}T$ isolated yielded 10.5 A_{260} units: HPLC t_R 26.18 min [Fig. 1 (VII)]; ^{31}P NMR (D_2O) δ 114.43 (s, PS_2, 1P); ESI-TOF MS calcd for $C_{20}H_{26}N_7O_9PS_2$ $(M+H)^+$ 588.1100, found 588.1116.

The dimer $dG_{PS2}T$ isolated yielded 10.4 A_{260} units: HPLC t_R 26.23 min [Fig. 1 (VIII)]; ^{31}P NMR (D_2O) δ 114.33 (s, PS_2, 1P); ESI-TOF MS calcd for $C_{20}H_{26}N_7O_9PS_2$ $(M+H)^+$ 604.1049, found 604.1068.

3.4. Phosphorothioate dimers ($T_{PS}T$, $dC_{PS}T$, $dA_{PS}T$, and $dG_{PS}T$)

The phosphorothioate dimer byproducts [Fig. 1 (I–VIII) and Fig. 2 (I–IV)] were identified and compared with authentic samples, which were synthesized by the phosphoramidite method.[25]

The phosphorothioate dimer was synthesized by assembling the phosphite dimer on the CPG support using T-CPG **2a** and 5′-*O*-DMTr-2′-deoxyribonucleoside 3′-(2-cyanoethyl) *N*,*N*-diisopropylphosphite (2′-deoxyribonucleoside=thymidine, N^4-benzoylcytidine, N^6-benzoyladenosine, or N^2-isobutyrylguanosine, purchased from Applied Biosystems Pty Ltd), subsequent removal of the DMTr group, oxidation with S_8, and treatment with concd NH_4OH as described for the synthesis of phosphorodithioate dimers.

[*R*p,*S*p]-$T_{PS}T$: HPLC t_R 19.84 and 20.96 min; ^{31}P NMR (D_2O) δ 56.61 (s, PS) and 56.21 (s, PS).[26]

[*R*p,*S*p]-$dC_{PS}T$: HPLC t_R 17.56 and 18.99 min; ^{31}P NMR (D_2O) δ 57.17 (s, PS) and 56.92 (s, PS).

[*R*p,*S*p]-$dA_{PS}T$: HPLC t_R 22.39 and 23.53 min; ^{31}P NMR (D_2O) δ 56.88 (s, PS) and 56.03 (s, PS).

[*R*p,*S*p]-$dG_{PS}T$: HPLC t_R 22.19 and 23.54 min; ^{31}P NMR (D_2O) δ 56.68 (s, PS) and 56.05 (s, PS).

3.5. Synthesis of oligonucleoside phosphorodithioates

3.5.1. Stability of phosphorodithioate dimer $T_{PS2}T$ under oxidation conditions. Following *H*-phosphonothioate dimer **5** (B_1=B_2=T, R=DMTr, 1 μmol scale) assembly using $(DMP)_2CP$ as a coupling agent and subsequent removal of the DMTr group as described above, oxidation was performed using 0.3 M solution of S_8 (19 mg) in 1:9 2,6-lutidine/CH_2Cl_2 (2 mL) for either 15 min, 1 h, 4 h or 8 h. $T_{PS2}T$ was cleaved from the support and subjected to analysis by reversed-phase HPLC (Fig. 2).

3.5.2. Synthesis of phosphorodithioate thymidine oligomers [$(T_{PS2})_nT$]. Following chain elongation with a syringe-based reaction system using a column of T-CPG **1a** (R=DMTr, 1 μmol scale), **3a** (R=DMTr, 22 mg, 0.03 mmol), and $(DMP)_2CP$ (29 mg, 0.09 mmol) as a coupling agent as described above (average coupling yield of greater than 99% as measured by trityl cation release[27]) (Scheme 1), the terminal DMTr protecting group of the *H*-phosphonothioate oligomer was removed following treatment with 3% w/v Cl_3CCOOH in CH_2Cl_2 solution (1 mL×2) for 1 min. The CPG support was washed with CH_3CN (2 mL×2). The internucleotidic *H*-phosphonate linkages were sulfurized using a mixture of 0.3 M solution of S_8 (19 mg) in 1:9 2,6-lutidine/CH_2Cl_2 (2 mL) for 1 h. Washings were performed using CH_3CN (2 mL×2). The resulting oligomer was then cleaved from the CPG support following treatment with 1:1 concd NH_4OH/ethanol (2 mL×2) for 3 h at room temperature. Following evaporation of the resulting solution, the oligomer was purified by reversed-phase HPLC [Fig. 3 (I–IV)].

The trimer $(T_{PS2})_2T$ isolated yielded 13.7 A_{260} units [Fig. 3 (I)]: ^{31}P NMR (D_2O) δ 114.39 and 114.77 (2s, PS_2, 2P); ESI-TOF MS calcd for $C_{30}H_{40}N_6O_{15}P_2S_4Na$ $(M+Na)^+$ 937.0807, found 937.1310.

The tetramer $(T_{PS2})_3T$ isolated yielded 13.4 A_{260} units [Fig. 3 (II)]: ^{31}P NMR (D_2O) δ 114.38 (s, PS_2, 1P) and 114.59 (s, PS_2, 2P); ESI-TOF MS calcd for $C_{40}H_{53}N_8O_{20}P_3S_6Na$ $(M+Na)^+$ 1273.0811, found 1273.0354.

The hexamer $(T_{PS2})_5T$ isolated yielded 11.6 A_{260} units [Fig. 3 (III)]: ^{31}P NMR (D_2O) δ 114.29, 114.32, 114.38, 114.40, and 114.46 (5s, PS_2, 5P); ESI-TOF MS calcd for $C_{60}H_{79}N_{12}O_{30}P_5S_{10}Na$ $(M+Na)^+$ 1945.0818, found 1944.8640.

The octamer $(T_{PS2})_7T$ isolated yielded 17.5 A_{260} units [Fig. 3 (IV)]: ^{31}P NMR (D_2O) δ 114.26–114.44 (m, PS_2, 7P); ESI-TOF MS calcd for $C_{80}H_{105}N_{16}O_{40}P_7S_{14}Na$ $(M+Na)^+$ 2617.0825, found 2617.0222.

3.5.3. Synthesis of phosphorodithioate oligomers (hetero-sequences). Following chain elongation with a syringe-based reaction system using a column of T-CPG **1a** (R=DMTr, 1 μmol scale), **3a** (R=DMTr, 22 mg, 0.03 mmol), **3b** (R=DMTr, 24 mg, 0.03 mmol), **3c** (R=DMTr, 25 mg, 0.03 mmol), **3d** (R=DMTr, 25 mg, 0.03 mmol), and $(DMP)_2CP$ (29 mg, 0.09 mmol) as a coupling agent as described above (average coupling yield of greater than 94% as measured by trityl cation release[27]) (Scheme 1), the terminal DMTr protecting group was removed following treatment with 3% w/v Cl_3CCOOH in CH_2Cl_2 solution (1 mL×2) for 1 min. The CPG support was washed with CH_3CN (2 mL×2). The internucleotidic *H*-phosphonate linkages were sulfurized using a mixture of 0.3 M solution of S_8 (19 mg) in 1:9 2,6-lutidine/CH_2Cl_2 (2 mL) for 1 h. Washings were performed using CH_3CN (2 mL×2). The resulting oligomer was then cleaved from the CPG support following treatment with 1:1 concd NH_4OH/ethanol (2 mL×2) for 3 h at room temperature. The resulting solution was heated in a sealed vial at 55 °C for 5 h. Following evaporation, the residue was dissolved in water (5 mL), washed with ethyl acetate (5 mL×3), and the aqueous layer was evaporated. The oligomer was purified by reversed-phase HPLC [Fig. 3 (V–VIII)].

The tetramer $d(A_{PS2}C_{PS2}T_{PS2}T)$ isolated yielded 6.7 A_{260} units from [Fig. 3 (V)]: ^{31}P NMR (D_2O) δ 114.24, 114.31, and 114.34 (3s, PS_2, 3P); ESI-TOF MS calcd for $C_{39}H_{51}N_{12}O_{17}P_3S_6$ $(M+H)^+$ 1245.1110, found 1245.0988.

The pentamer $d(G_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$ isolated yielded 6.6 A_{260} units [Fig. 3 (VI)]: ^{31}P NMR (D_2O) δ 113.80, 114.29, 114.37, and 114.46 (4s, PS_2, 4P); ESI-TOF MS calcd for $C_{49}H_{63}N_{17}O_{21}P_4S_8$ $(M+H)^+$ 1606.1179, found 1606.1173.

The hexamer $d(T_{PS2}G_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$ isolated yielded 5.4 A_{260} units [Fig. 3 (VII)]: ^{31}P NMR (D_2O) δ 113.79, 113.90, 114.27, 114.37, and 114.47 (5s, PS_2, 5P); ESI-TOF MS calcd for $C_{59}H_{76}N_{19}O_{26}P_5S_{10}$ $(M+H)^+$ 1942.0082, found 1942.1296.

The heptamer $d(C_{PS2}T_{PS2}G_{PS2}A_{PS2}C_{PS2}T_{PS2}T)$ isolated yielded 4.2 A_{260} units [Fig. 3 (VIII)]: ^{31}P NMR (D_2O) δ 113.88, 114.06, 114.24, 114.34, 114.43, and 114.46 (6s, PS_2, 6P) (Fig. 5); ESI-TOF MS calcd for $C_{68}H_{88}N_{22}O_{30}P_6S_{12}$ $(M+H)^+$ 2263.1189, found 2263.1184.

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References and notes

1. (a) Goodchild, J.; Agrawal, S.; Civeira, M. P.; Sarin, P. S.; Sun, D.; Zamecnik, P. C. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 5507; (b) Smith, C. C.; Aurelian, L.; Reddy, M. P.; Miller, P. S.; Ts'o, P. O. P. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 2787; (c) Matsukura, M.; Shinozuka, K.; Zon, G.; Mitsuya, H.; Reitz, M.; Cohen, J. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7706; (d) Lemaitre, M.; Bayard, B.; Leblue, B. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 648.
2. (a) Noble, S. A.; Fisher, E. F.; Caruthers, M. H. *Nucleic Acids Res.* **1984**, *12*, 3387; (b) Eckstein, F. *Annu. Rev. Biochem.* **1985**, *54*, 367; (c) Letsinger, R. L.; Singman, C. N.; Histand, G.; Salunkhe, M. *J. Am. Chem. Soc.* **1988**, *110*, 4470.
3. (a) Nielsen, J.; Brill, W. K.-D.; Caruthers, M. H. *Tetrahedron Lett.* **1988**, *29*, 2911; (b) Grandas, A.; Marshall, W. S.; Nielsen, J.; Caruthers, M. H. *Tetrahedron Lett.* **1989**, *30*, 543; (c) Caruthers, M. H.; Beaton, G.; Cummins, L.; Dellinger, D.; Graff, D.; Ma, Y.-X.; Marshall, W. S.; Sasmor, H.; Shankland, P.; Wu, J. V.; Yan, E. K. *Nucleosides Nucleotides* **1991**, *10*, 47; (d) Beaton, G.; Brill, W. K.-D.; Grandas, A.; Ma, Y.-X.; Nielsen, J.; Yan, E.; Caruthers, M. H. *Tetrahedron* **1991**, *47*, 2377; (e) Marshall, W. S.; Beaton, G.; Stein, C. A.; Matsukura, M.; Caruthers, M. H. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 6265; (f) Marshall, W. S.; Caruthers, M. H. *Science* **1993**, *259*, 1564; (g) Dahl, B. H.; Bjergarde, K.; Sommer, V. B.; Dahl, O. *Acta Chem. Scand.* **1989**, *43*, 896; (h) Dahl, B. H.; Bjergarde, K.; Nielsen, J.; Dahl, O. *Tetrahedron Lett.* **1990**, *31*, 3489; (i) Bjergarde, K.; Dahl, O. *Nucleic Acids Res.* **1991**, *19*, 5843; (j) Porritt, G. M.; Reese, C. B. *Tetrahedron Lett.* **1989**, *30*, 4713; (k) Okruszek, A.; Sierzchala, A.; Feason, K. L.; Stec, W. J. *J. Org. Chem.* **1995**, *60*, 6998.
4. Dahl, B. H.; Bjergarde, K.; Sommer, V. B.; Dahl, O. *Nucleosides Nucleotides* **1989**, *8*, 1023.
5. Brill, W. K.-D.; Nielsen, J.; Caruthers, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 3972.
6. (a) Brill, W. K.-D.; Nielsen, J.; Caruthers, M. H. *Tetrahedron Lett.* **1988**, *29*, 5517; (b) Farschtschi, N.; Gorenstein, D. G. *Tetrahedron Lett.* **1988**, *29*, 6843.
7. Piotto, M. E.; Granger, J. N.; Cho, Y.; Fraschtschi, N.; Gorenstein, D. G. *Tetrahedron* **1991**, *47*, 2449.
8. Stawinski, J.; Thelin, M.; Zain, R. *Tetrahedron Lett.* **1989**, *30*, 2157.
9. Zain, R.; Stawinski, J. *J. Org. Chem.* **1996**, *61*, 6617.
10. Dreef, C. E.; Dreef-Tromp, C. M.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1990**, 481.
11. Wada, T.; Hata, T. *Tetrahedron Lett.* **1990**, *31*, 7461.

12. Greef, C. H.; Seeberger, P. H.; Caruthers, M. H. *Tetrahedron Lett.* **1996**, *26*, 4451.
13. Seeberger, P. H.; Caruthers, M. H. *Tetrahedron* **1999**, *55*, 5759.
14. (a) Brill, W. K.-D.; Yan, E. K.; Caruthers, M. H. *Tetrahedron Lett.* **1989**, *30*, 6621; (b) Porritt, G. M.; Reese, C. B. *Tetrahedron Lett.* **1990**, *31*, 1319; (c) Murata, T.; Iwai, S.; Ohtsuka, E. *Nucleic Acids Res.* **1990**, *18*, 7279.
15. Yau, E. K.; Ma, Y.-X.; Caruthers, M. H. *Tetrahedron Lett.* **1990**, *31*, 1953.
16. Okruszek, A.; Sierzchala, A.; Sochacki, M.; Stec, W. J. *Tetrahedron Lett.* **1992**, *33*, 7585.
17. Stawinski, J.; Thelin, M.; Westman, E.; Zain, R. *J. Org. Chem.* **1990**, *55*, 3503.
18. Kamaike, K.; Takahashi, H.; Kakinuma, T.; Morohoshi, K.; Ishido, Y. *Tetrahedron Lett.* **1997**, *38*, 6857.
19. Kamaike, K.; Takahashi, H.; Morohoshi, K.; Kataoka, N.; Kakinuma, T.; Ishido, Y. *Acta Biochim. Pol.* **1998**, *45*, 949.
20. Kamaike, K.; Hirose, K.; Kawashima, E. *Nucleic Acids Symp. Ser.* **2000**, *44*, 33.
21. Kamaike, K.; Hirose, K.; Kayama, Y.; Kawashima, E. *Tetrahedron Lett.* **2004**, *45*, 5803.
22. Matsuzaki, J.; Hotoda, H.; Sekine, M.; Hata, T. *Tetrahedron Lett.* **1984**, *25*, 4019.
23. Seliger, H.; Scalfi, C.; Eisenbeiss, F. *Tetrahedron Lett.* **1983**, *24*, 4963.
24. Wiesler, W. T.; Caruthers, M. H. *J. Org. Chem.* **1996**, *61*, 4272.
25. Stec, W. J.; Zon, G.; Egan, W.; Stec, B. *J. Am. Chem. Soc.* **1984**, *106*, 6077.
26. Stec, W. J.; Grajikowski, A.; Koziolkiewcz, M.; Uznanski, B. *Nucleic Acids Res.* **1991**, *19*, 5883.
27. Gait, M. J.; Matthes, H. W. D.; Singh, M.; Sproat, B. S.; Titmas, R. *Cold Spring Harbor Symp. Quant. Biol.* **1982**, *47*, 393.

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Highly efficient stereoselective synthesis of D-*erythro*-sphingosine and D-*lyxo*-phytosphingosine

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Abstract—Starting from a single suitable functionalised epoxide, a highly efficient stereoselective synthesis of D-*erythro*-sphingosine and D-*lyxo*-phytosphingosine is described. The approach allows the formal preparation of all stereoisomers of these sphingoid structures.

1. Introduction

Sphingolipids such as ceramides, cerebrosides and gangliosides are ubiquitous components of cell membranes, where they are involved in various processes based on recognition phenomena.[1] Common to this diverse group of natural products is a sphingoid base scaffold with a polar 2-amino alcohol head and a long aliphatic chain with a 4,5-trans double bond as in sphingosines (Fig. 1) or an 2-amino-1,3,4 triol head group without unsaturation as in phytosphingosines (Fig. 2).[2] The hydrophilic moiety, located on the external surface of the membrane, determines the specificity of interactions, whereas the lipophilic portion, anchored on the outer-leaflet, contributes primarily to the structural rigidity of the membrane.[3]

The wide spectrum of the biological activity of these molecules justifies the efforts towards the synthesis of them as well as of their stereoisomers and various analogues. Although the most commonly employed strategies are those which make use of carbohydrates[4] and serine[5] as source of chirality, many approaches are also based on asymmetric reactions, such as aldol condensation[6] as well as Sharpless asymmetric dihydroxylation[7] and asymmetric epoxidation (using Shi's catalyst[8] or Sharpless protocol[9]).

However, using the above-mentioned asymmetric reactions, the required introduction of the amino group often suffered from low regio- and stereoselectivity and therefore these approaches were scarcely utilised compared to those of natural products from the chiral pool. Furthermore, rarely a single

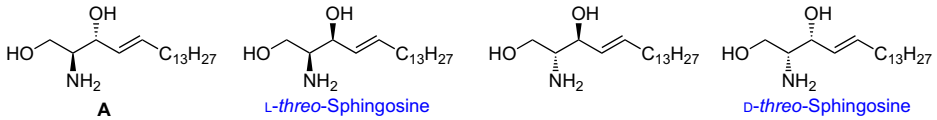

Figure 1.

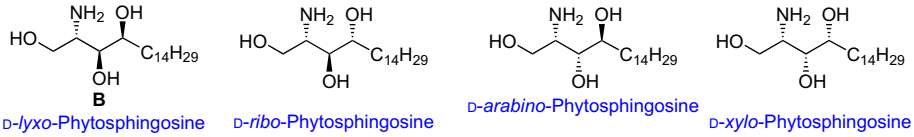

Figure 2.

Keywords: Functionalised epoxides; Amino alcohols; Sphingosines; Phytosphingosines.
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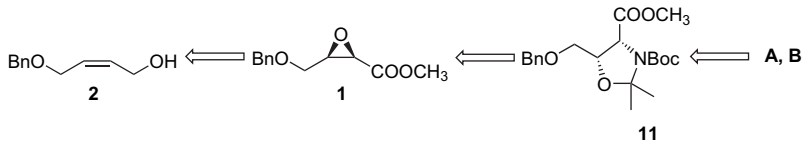


Scheme 1.

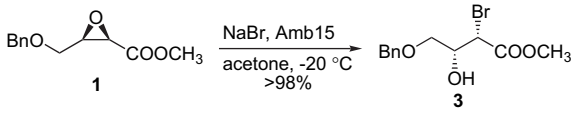
strategic approach has been designed to both sphingosines and phytosphingosines classes, due to the differences in their structure.

2. Results and discussion

In this regard, our approach to both classes of sphingoid structures is based on a stereoselective route from an easily prepared chiral epoxide **1**, obtained by the Sharpless AE of commercial allylic alcohol **2** (Scheme 1).

The introduction of the amino group to the common key oxazolidine **11** could be easily achieved based on the results obtained in the regio- and stereoselective opening of bifunctionalised epoxides with metal halides,[10] a route which can be considered very attractive for its generality.

Our synthesis started with known α,β-epoxy ester **1**, derived from the commercially available *Z*-4-benzyloxy-2-buten-1-ol **2**. Treatment with the NaBr/Amberlyst 15 system, already utilised for the regioselective opening of differently substituted α,β-epoxy esters,[11] furnished, with excellent stereoselectivity and chemical yield, the bromohydrin **3** (Scheme 2).



Scheme 2.

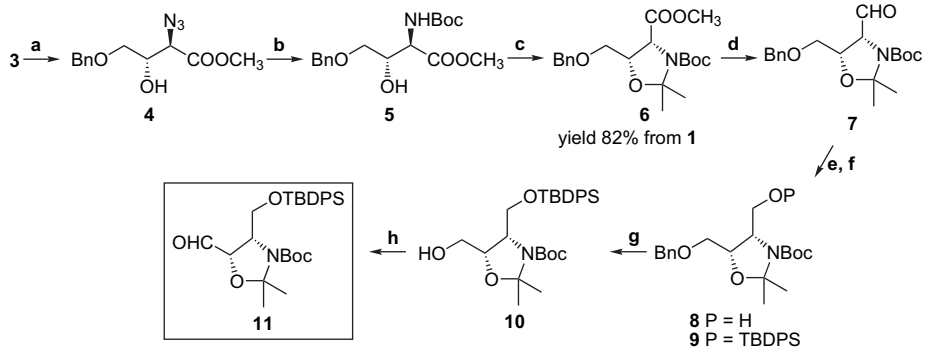
The polar 2-amino alcohol head was then easily obtained by subsequent transformation of the halide into an amino group: thus stereoselective azide nucleophilic substitution furnished the corresponding azido alcohol **4** in nearly quantitative yield (Scheme 3). The subsequent hydrogenation of **4** afforded the vicinal *anti* amino alcohol **5**, which was easily transformed into **6**. Worthy of note is that the key oxazolidine **6** was obtained from **1** with an overall yield of 82% without any purification of the previous intermediates.

Successively, **6** was converted into **11**, a suitable common precursor for the synthesis of sphingosine and phytosphingosine, through a few high-yielding steps. As shown in Scheme 3, the transformation of **6** into the alcohol **8** was performed by first reducing **6** with DIBAL to the aldehyde **7** and then with $NaBH_4$ to **8**.[12] After protection of the hydroxyl function of **8** as silyl ether, **9** was debenzylated and then the free alcohol group of **10** was oxidised to the aldehyde with the Py/SO_3 complex in a high-yielding sequence.

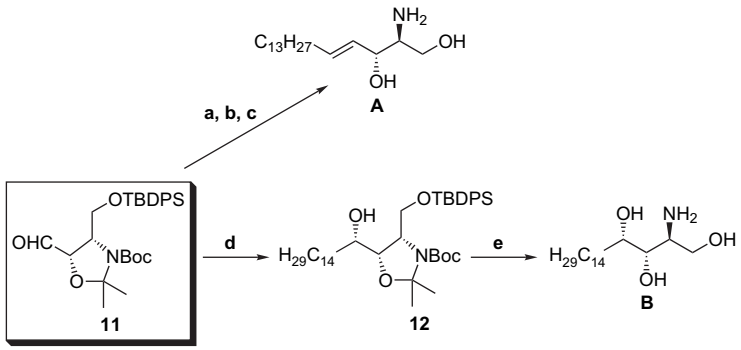
Multifunctional aldehyde **11** represents the key intermediate for the final transformation into different sphingoid structures, such as the D-*erythro*-sphingosine **A** and D-*lyxo*-phytosphingosine **B**. Although its preparation was already known starting from isoascorbic acid, our route is shorter (11 steps) and with higher overall yield. Furthermore, starting from *ent*-epoxy ester **2** the opposite enantiomer of **11** can be prepared.

Finally, aldehyde **11** was transformed into the D-*erythro*-sphingosine **A** following the already reported synthetic sequence[13] (Scheme 4). On the other hand, the D-*lyxo*-phytosphingosine **B** was finally prepared through the stereoselective addition of the required lithium cuprate, obtained from tetradecyl bromide, as clearly demonstrated by the value of the coupling constant of the diol system of **12** (J~4 Hz), which confirms its *syn* stereochemistry.[14] Subsequent deprotection afforded the phytosphingosine **B**, with its tetraacetate derivative resulting identical to the data reported in literature.[5a,c,7b]

In summary, through stereocontrolled, facile and high-yield reactions, we have developed a general highly efficient route, starting from the easily accessible *Z*-4-benzyloxy-2-buten-1-ol, to the preparation of both enantiomers D- and L-*erythro*-sphingosines. Starting from the known *E*-4-benzyloxy-2-buten-1-ol and following the same synthetic scheme it would be possible to have access to the D- and



Scheme 3. (a) NaN_3, DMF, rt; (b) H_2/Pd, Boc_2O, EtOAc, rt; (c) 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt; (d) DIBAL, toluene, −78 °C, >95%; (e) $NaBH_4$, *i*-PrOH/THF, rt, >95%; (f) TBDPSCl, Et_3N, DMAP, rt, 93%; (g) H_2/Pd, MeOH, rt, 93%; (h) Py/SO_3, DMSO, 0 °C, 85%.



Scheme 4. (a) nC$_{14}$H$_{29}$PPh$_3$Br, nBuLi, THF, −78 °C to rt, 95%; (b) hν, PhSSPh cat., c-hexane, 91% (*Z*/*E*, 30/70); (c) TFA/H$_2$O 1:1, rt, 75%; (d) (nC$_{14}$H$_{29}$)$_2$CuLi, Et$_2$O, −20 °C, 65%; (e) TFA/H$_2$O 1:1, rt, 75%.

L-*threo*-diastereoisomers of sphingosine. Preliminary studies have shown in fact for this substrate the same aptitude for the formation of the corresponding oxazolidine (Scheme 5).

On the other hand, we have also prepared the D-*lyxo* phytosphingosine as well as, formally, the L-*lyxo*-phytosphingosine, throughout the *syn* diastereoselective addition of tetradecyl lithium cuprate to the aldehyde **11**.[14] Starting from the *E*-4-benzyloxy-2-buten-1-ol, the same diastereoselective reaction would give access to the D- or L-*xylo*-phytosphingosine. Moreover, the use of a diastereoselective organometallic *anti* addition to the aldehyde **11**[14] could be, in principle, adaptable even for the synthesis of D-*ribo*-phytosphingosine starting from the *Z*-4-benzyloxy-2-buten-1-ol and of D-*arabino*-phytosphingosine starting from the *E*-4-benzyloxy-2-buten-1-ol (Scheme 6).

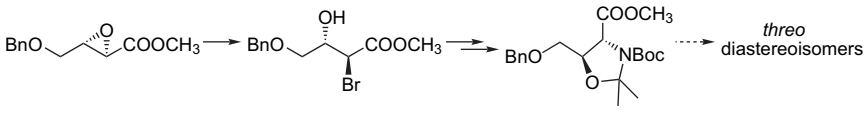
3. Experimental

3.1. General

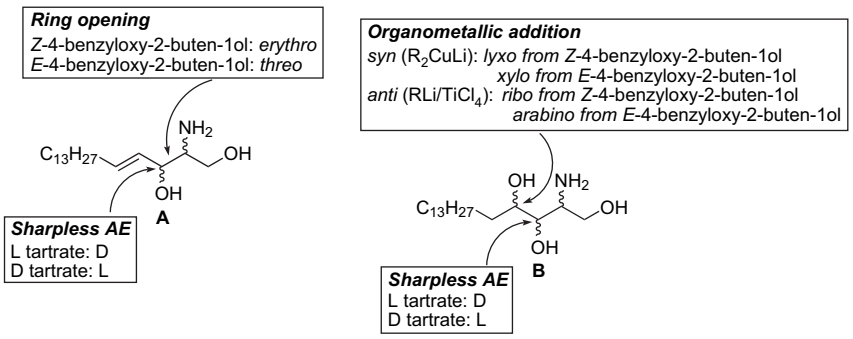
^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively. Reactions were monitored by TLC using Merck silica gel 60 F$_{254}$ plates with UV indicator or/and visualised with phosphomolybdic acid (10% solution in EtOH). Flash column chromatography on silica gel was normally used for purification of the reaction mixtures. All solvents were purified before use with standard drying procedures, unless otherwise specified. Elemental analyses for C and H were performed by the Servizio Microanalisi of the Dip. Chimica of the Università of Roma 'La Sapienza'.

Compounds **A** and **B** and its tetraacetyl derivative are known.[5a,c,13]

3.1.1. (2*R*,3*R*)-*Z*-4-Benzyloxy-2,3-epoxybutanoic acid methyl ester 1. To 2 mL of a 0.5 M solution of the (2*R*,3*R*)-*Z*-4-benzyloxy-2,3-epoxybutanal[15](192 mg, 1 mmol) in alcohol/water (9:1) buffered with NaHCO$_3$ (1682 mg, 20 mmol) was added 2 M solution of bromine (3 mmol) in MeOH/water (9:1 by volume). After stirring for 5 h, solid sodium thiosulfate was added to quench excess bromine and dilution with water (2 mL) was followed by extraction with 8 mL of diethylether (three times). Combined organic layers were dried (Na$_2$SO$_4$), filtered and the solvent was evaporated in vacuo, giving **1** as yellow pale oil (210 mg, 95%). No chromatographic purification was necessary. R_f (20% EtOAc/petroleum ether) 0.82. $[\alpha]_D^{20}$ −12.7 (*c* 5.0, CHCl$_3$); ν_{max} (liquid film) 3010, 1735, 1060, 830 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 7.39–7.27 (5H, m, Ph), 4.85 (1H, d, *J* 11.5 Hz, C*H*$_a$Ph), 4.74 (1H, d, *J* 11.5 Hz, C*H*$_b$Ph), 3.73 (3H, s, O*Me*), 3.82–3.65 (2H, m, OC*H*$_2$), 3.56



Scheme 5.



Scheme 6.

(1H, d, *J* 4.4 Hz, OC*H*), 3.43 (1H, dd, *J* 4.4, 9.9 Hz, OC*H*); δ_C (50 MHz, $CDCl_3$) 167.9, 137.5, 128.3, 127.6, 73.2, 66.9, 55.5, 52.2, 51.2. Anal. Calcd for $C_{12}H_{14}O_4$ (222.09): C 64.85; H 6.35. Found: C 65.1; H 6.5.

3.1.2. (2*S*,3*R*)-4-Benzyloxy-2-bromo-3-hydroxybutanoic acid methyl ester 3. To a solution of **1** (222 mg, 1 mmol) in acetone (10 mL) was added NaBr (416 mg, 4 mmol) and Amberlyst 15 (240 mg). The solution was stirred at −20 °C for 6 h (TLC monitoring), then was filtered through a Celite pad and the solvent evaporated in vacuo affording **3** as yellow oil in almost quantitative yield (300 mg, >98%). R_f (20% EtOAc/petroleum ether) 0.23. $[\alpha]_D^{20}$ −23.7 (*c* 3.5, $CHCl_3$); ν_{max} (liquid film) 3200, 3010, 1740, 1260, 1060, 550 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.43–7.27 (5H, m, Ph), 4.59 (1H, d, *J* 3.7 Hz, C*H*Br), 4.55 (2H, s, CH_2Bn), 4.21–4.09 (1H, m, C*H*OH), 3.71 (3H, s, O*Me*), 3.70–3.49 (2H, m, CH_2OBn), 2.89 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 169.1, 137.2, 128.2, 127.6, 73.3, 70.2, 69.7, 53.2, 48.8. Anal. Calcd for $C_{12}H_{15}BrO_4$ (303.02): C 47.54; H 4.99. Found: C 47.8; H 5.1.

3.1.3. (2*R*,3*S*)-2-Azido-4-benzyloxy-3-hydroxybutanoic acid methyl ester 4. To a solution of **3** (303 mg, 1 mmol) in 4 mL of DMF (or DMSO, 4 mL), NaN_3 (260 mg, 4 mmol) was added and the mixture was stirred at room temperature for 24 h. Then the reaction was diluted with EtOAc (8 mL) and washed several times with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo affording quantitatively **4** as yellow pale oil (265 mg, >98%). R_f (20% EtOAc/petroleum ether) 0.20. $[\alpha]_D^{20}$ +10.7 (*c* 3.5, $CHCl_3$); ν_{max} (liquid film) 3200, 3010, 2235, 1740, 1250, 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.41–7.26 (5H, m, Ph), 4.53 (2H, s, CH_2Ph), 4.20–4.02 (1H, m, C*H*OH), 3.85–3.65 (2H, m, CH_2OBn), 3.74 (3H, s, O*Me*), 3.61 (1H, d, *J* 4.4 Hz, C*H*N_3), 3.13 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 168.9, 137.3, 128.2, 127.6, 73.3, 70.6, 69.8, 63.2, 52.4. Anal. Calcd for $C_{12}H_{15}N_3O_4$ (265.11): C 54.33; H 5.70; N 15.84. Found: C 54.7; H 5.3; N 16.1.

3.1.4. (2*R*,3*S*)-4-Benzyloxy-2-*tert*-butoxycarbonylamino-3-hydroxybutanoic acid methyl ester 5. A solution of **4** (281 mg, 1 mmol) in EtOAc (2 mL) was hydrogenated at atmospheric pressure over 10% Pd/C (51 mg) in the presence of Boc_2O (231 mg, 1.2 mmol) for 1.5 h at room temperature. The solution was then filtered on a Celite pad and concentrated in vacuo affording **5** in almost quantitative yield as yellow pale oil (335 mg, >98%). R_f (30% EtOAc/petroleum ether) 0.25. $[\alpha]_D^{20}$ −14.3 (*c* 2.5, $CHCl_3$); ν_{max} (liquid film) 3250, 3010, 2950, 1740, 1630, 1200, 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.44–7.27 (5H, m, Ph), 5.5 (1H, br d, *J* 7.3 Hz, CHN*H*), 4.69–4.41 (1H, m, C*H*OH), 4.50 (2H, s, CH_2Ph), 4.17 (1H, dd, *J* 7.3, 4.5 Hz, C*H*NH), 3.67 (3H, s, O*Me*), 3.55 (1H, d, *J* 5.9 Hz, CH_2OBn), 3.24 (1H, br s, O*H*), 1.44 (s, 9H, C(CH_3)$_3$); δ_C (50 MHz, $CDCl_3$) 170.5, 146.6, 137.5, 128.2, 127.6, 80.2, 73.4, 71.0, 70.5, 56.5, 52.2, 24.2. Anal. Calcd for $C_{17}H_{25}NO_6$ (339.17): C 60.16; H 7.42; N 4.13. Found: C 60.5; H 7.6; N 4.3.

3.1.5. (4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidine-4-carboxylic acid methyl ester 6. A solution of **5** (338 mg, 1 mmol), DMP (1.3 mL, 10 mmol) and *p*-TsOH (cat.) in CH_2Cl_2 (1 mL) was stirred at room temperature; after 3 h (TLC monitoring) the mixture was diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (15 mL, satd aq). The organic extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/Et_2OAc, 8:2) affording **6** (348 mg, 0.91 mmol) (yield 82% from **1**). ν_{max} (liquid film) 3010, 2950, 1730, 1310 (br), 1200, 1060 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.39–7.23 (5H, m, Ph), 4.58–4.34 (3H, m, C*H*OH+CH_2Ph), 3.75–3.47 (3H, m, CHN+CH_2OBn), 3.65 (3H, s, O*Me*), 1.72 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.43 (9H, s, C(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 169.3, 150.9, 137.4, 127.5, 126.9, 126.8, 93.4, 78.9, 74.3, 72.3, 67.5, 60.1, 51.1, 27.5, 25.0, 23.8. Anal. Calcd for $C_{20}H_{29}NO_6$ (379.20): C 63.31; H 7.70; N 3.69. Found: C 63.7; H 7.9; N 3.9.

3.1.6. (4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-formyl-2,2-dimethyl-1,3-oxazolidine 7. To a stirred solution of **6** (379 mg, 1 mmol) in toluene (2 mL) at −78 °C was added DIBAL (0.8 mL of a solution of 1.5 M in toluene, 1.2 mmol) dropwise. The reaction mixture was stirred for 2 h (TLC monitoring) and then was quenched by slowly adding, at −78 °C, cold MeOH (0.38 mL). The resulting white emulsion was slowly poured into 6.5 mL of HCl 1 N with stirring over 15 min and the aqueous mixture was then extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo without further purification, affording **7** (340 mg, 97%) as colourless oil. ν_{max} (liquid film) 3010, 2950, 1720, 1390, 1200, 1060 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 9.60 (1H, d, *J* 2.9 Hz, C*H*O), 7.51–7.29 (5H, m, Ph), 4.73–4.49 (1H, m, C*H*OCH_2OBn), 4.59 (2H, s, CH_2Ph), 4.46 (1H, dd, *J* 7.3, 2.9 Hz, C*H*N), 3.78 (1H, dd, *J* 10.9, 4.4 Hz, CH_aOBn), 3.66 (1H, dd, *J* 10.9, 3.6 Hz, CH_bOBn), 1.8 (3H, s, CH_3), 1.6 (3H, s, CH_3), 1.5 (9H, s, C(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 198.7, 151.3, 137.3, 128.4, 128.3, 127.7, 94.9, 80.8, 75.7, 73.5, 67.0, 66.2, 28.1, 26.3, 23.8. Anal. Calcd for $C_{19}H_{27}NO_5$ (349.19): C 65.31; H 7.79; N 4.01. Found: C 65.7; H 7.9; N 4.3.

3.1.7. (4*S*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-2,2-dimethyl-4-hydroxymethyl-1,3-oxazolidine 8. To an ice-cold solution of **7** (336 mg, 1 mmol) in 12 mL of isopropyl alcohol/THF (1:1) was added $NaBH_4$ (110 mg, 3 mmol). After the mixture was stirred for 2 h (TLC monitoring) and then was portioned between HCl 1 N and EtOAc until neutrality. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo without further purification, affording **8** (446 mg, 96%) as colourless oil. ν_{max} (liquid film) 3200, 3010, 2950, 1260, 1200, 1060 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.49–7.28 (5H, m, Ph), 4.59 (2H, s, CH_2Ph), 4.34 (1H, ddd, *J* 5.8, 5.1 Hz, C*H*OCH_2OBn), 4.15–4.02 (1H, m, C*H*N), 3.89–3.05 (5H, m, CH_2OBn+CH_2OH+OH), 1.59 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.47 (9H, s, C(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 151.5, 137.3, 128.4, 127.9, 127.6, 93.2, 80.8, 74.4, 73.8, 67.4, 61.6, 60.4, 28.3, 27.4, 24.6. Anal. Calcd for $C_{19}H_{29}NO_5$ (351.2): C 64.93; H 8.32; N 3.99. Found: C 65.2; H 8.5; N 3.6.

3.1.8. (4*S*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-2,2-dimethyl-1,3-oxazolidine 9. To a solution of **8** (338 mg,

1 mmol) dissolved in 5 mL of CH_2Cl_2 at 0 °C, Et_3N (0.27 mL, 1.1 mmol) and cat. DMAP were added. After 5 min TBDPSCl (180 mg, 1.5 mmol) was added; the mixture was stirred at room temperature for 24 h. After TLC monitoring, the mixture was quenched with $NaHCO_3$ (10 mL, satd aq). Aqueous layer was extracted with CH_2Cl_2 and organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 9:1) affording **9** (547 mg, yield 93%). ν_{max} (liquid film) 3010, 2950, 1200, 1090, 1060, 970 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.85–7.55 (5H, m, Ph), 7.51–7.24 (10H, m, 2Ph), 4.71–4.33 (3H, m, C*H*OCH_2OBn+CH_2Ph), 4.11–3.49 (5H, m, C*H*N+CH_2OBn+CH_2OTBDPS), 1.52 (6H, s, C(CH_3)$_2$), 1.11 (9H, s, OC(CH_3)$_3$), 1.03 (9H, s, SiC(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 150.8, 137.4, 135.0, 134.9, 134.7, 134.1, 129.1, 128.9, 127.7, 92.8, 79.1, 75.2, 72.8, 68.2, 60.8, 58.8, 26.0, 24.5, 22.8, 18.4. Anal. Calcd for $C_{35}H_{47}NO_5Si$ (589.32): C 71.27; H 8.03; N 2.37. Found: C 71.4; H 8.2; N 2.4.

3.1.9. (4*S*,5*S*)-3-*N*-*tert*-Butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-2,2-dimethyl-5-hydroxymethyl-1,3-oxazolidine 10. A solution of **9** (589 mg, 1 mmol) in MeOH (2 mL) was hydrogenated at atmospheric pressure over 10% Pd/C (51 mg) for 3 h at room temperature; then the solution was filtered on a Celite pad and concentrated in vacuo affording **10** (474 mg, 95%) as colourless oil. ν_{max} (liquid film) 3200, 3010, 2950, 1260, 1090, 1060, 970 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.81–7.61 (5H, m, Ph), 7.55–7.31 (5H, m, Ph), 4.42–4.21 (1H, m, C*H*OCH_2OH), 4.19–3.82 (3H, m, C*H*N+CH_2OH), 3.80–3.51 (2H, m, CH_2OTBDPS), 2.97 (1H, br t, OH), 1.53 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.25 (9H, s, OC(CH_3)$_3$), 1.07 (9H, s, SiC(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 151.4, 135.6, 135.3, 134.8, 127.8, 127.6, 93.4, 80.0, 75.8, 61.5, 60.8, 59.4, 26.9, 24.6, 23.3, 19.1. Anal. Calcd for $C_{28}H_{41}NO_5Si$ (499.28): C 67.30; H 8.27; N 2.80. Found: C 67.7; H 8.4; N 3.0.

3.1.10. (4*S*,5*S*)-3-*N*-*tert*-Butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-5-formyl-2,2-dimethyl-1,3-oxazolidine 11. To a solution of **10** (499 mg, 1 mmol) in 7.5 mL of CH_2Cl_2, Et_3N (0.56 mL, 4 mmol) was added and then the mixture was stirred at 0 °C. After 10 min, a solution of pyridine/SO_3 (477 mg, 3 mmol) in 3 mL of DMSO was poured into the reaction mixture. After 2 h TLC monitoring, the mixture was diluted with 20 mL of Et_2O and 41 mL of hexane and washed with 19 mL of aq $NaHCO_3$. The combined organic layers were washed with 39 mL of NaH_2PO_4 1 M and then with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/Et_2O, 8:2) afforded **11** as colourless oil (462 mg, yield 93%). ν_{max} (liquid film) 3010, 2950, 1720, 1090, 1060, 980 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 9.93 (1H, d, *J* 2.1 Hz, C*H*O), 7.79–7.54 (5H, m, Ph), 7.52–7.30 (5H, m, Ph), 4.64–4.51 (1H, m, C*H*O), 4.49–4.25 (1H, m, C*H*N), 3.76 (1H, dd, *J* 10.4, 7.4 Hz, CH_aOTBDPS), 3.64 (1H, dd, *J* 10.4, 3.7 Hz, CH_bOTBDPS), 1.81 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.32 (9H, s, OC(CH_3)$_3$), 1.12 (9H, s, SiC(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 197.1, 149.3, 136.2, 134.8, 129.4, 127.7, 127.6, 94.8, 79.7, 79.1, 60.8, 60.3, 28.2, 26.5, 24.7, 23.5, 19.0. Anal. Calcd for $C_{28}H_{39}NO_5Si$ (497.26): C 67.57; H 7.90; N 2.81. Found: C 67.8; H 8.1; N 3.1.

3.1.11. (4*S*,5*S*,1′*S*)-3-*N*-*tert*-Butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-5-(1′-hydroxypentadecyl)-2,2-dimethyl-1,3-oxazolidine 12. To a solution of ($nC_{14}H_{29}$)$_2$CuLi freshly prepared in Et_2O (10 mL) at −20 °C, **11** (497 mg, 1 mmol) was added. The resulting solution was stirred for 5 h and after TLC monitoring, the reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O; the combined organic extracts were dried over Na_2SO_4 and then evaporated to dryness in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 6:4) affording **12** (323 mg, yield 63%). ν_{max} (liquid film) 3200, 3010, 2950, 1260, 1090, 1060, 990 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.84–7.58 (5H, m, Ph), 7.53–7.32 (5H, m, Ph), 4.26–4.07 (1H, m, C*H*OH), 3.83 (1H, dd, *J* 4.8, 4 Hz, C*H*O), 3.87–3.41 (3H, m, C*H*N+CH_2OTBDPS), 2.73 (1H, br d, *J* 7.3 Hz, OH), 1.52 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.48–1.19 (m, 26H), 1.25 (9H, s, OC(CH_3)$_3$), 1.06 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, t, *J* 6.0 Hz); δ_C (50 MHz, $CDCl_3$) 147.3, 135.2, 134.6, 129.2, 127.7, 126.7, 93.7, 79.5, 76.3, 72.4, 61.3, 60.9, 32.5, 32.0, 30.6, 30.3, 30.1, 28.5, 26.5, 24.7, 24.2, 23.5, 22.5, 19.0, 13.5. Anal. Calcd for $C_{42}H_{69}NO_5Si$ (695.49): C 72.47; H 9.99; N 2.01. Found: C 72.7; H 10.1; N 3.3.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.049.

References and notes

1. For reviews, see: (a) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715; (b) Koshinen, P. M.; Koshinen, A. M. P. *Synthesis* **1998**, 1075.
2. Karlsson, K. A. *Lipids* **1970**, *5*, 878.
3. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354.
4. (a) Kiso, M.; Nakamura, A.; Tomita, Y.; Hasegawa, A. *Carbohydr. Res.* **1986**, *158*, 101; (b) Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 663; (c) Hirata, N.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkin Trans 1* **1991**, 2279; (d) Bettelli, E.; Chinzari, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G.; Topai, A. *Korean J. Med. Chem.* **1996**, *6*, 339; (e) Lu, X.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2004**, *69*, 5433; (f) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805.
5. (a) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643; (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439 and reference therein; (c) Sugiyama, S.; Honda, M.; Komora, T. *Liebigs Ann. Chem.* **1990**, 1069.
6. Enders, D.; Whitehouse, D. L.; Runsink, J. *Chem.—Eur. J.* **1995**, *1*, 382.
7. (a) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309; (b) Martin, C.; Prunk, W.; Bortolussi, M.; Bloch, R. *Tetrahedron: Asymmetry* **2000**, *11*, 1585.
8. Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514.

9. (a) Li, S.; Pang, J.; Wilson, W. K.; Schroepfer, G. J., Jr. *Tetrahedron: Asymmetry* **1999**, *10*, 1697; (b) Lin, G.; Shi, Z. *Tetrahedron* **2001**, *57*, 5649; (c) Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368.
10. Righi, G.; Pescatore, G.; Bonadies, F.; Bonini, C. *Tetrahedron* **2001**, *57*, 5649.
11. (a) Bonini, C.; Righi, G.; Rumboldt, G. *Tetrahedron* **1995**, *51*, 13401; (b) Bonini, C.; Righi, G.; Rumboldt, G. *J. Org. Chem.* **1996**, *61*, 3557; (c) Righi, G.; D'Achille, C.; Pescatore, G.; Bonini, C. *Tetrahedron Lett.* **2003**, *44*, 6999.
12. The overall yield of these two steps (>95%) is better than the yield of the direct reduction with $NaBH_4$/THF or diossane. (Bianco, A.; Passacantilli, P.; Righi, G. *Synth. Commun.* **1988**, *18*, 1765).
13. Tuch, A.; Saniere, M.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron: Asymmetry* **1996**, *7*, 897.
14. Ginesta, X.; Pastò, M.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2003**, *5*, 3001.
15. Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1991**, *39*, 5345.