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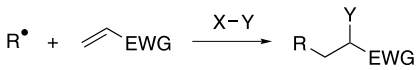
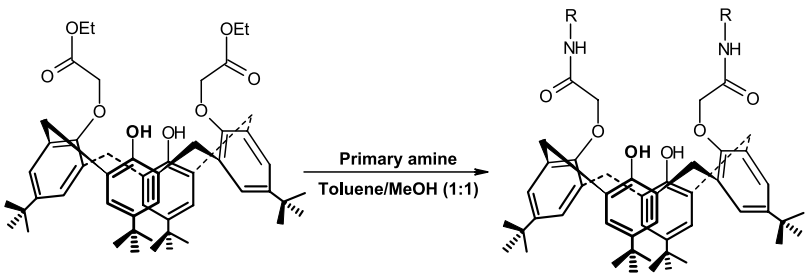
Contents

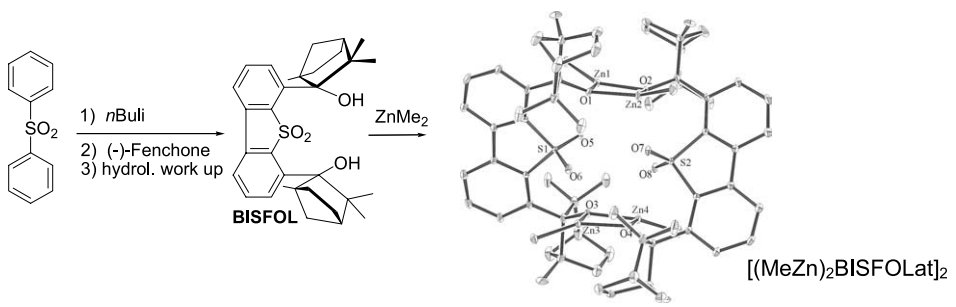
REPORT

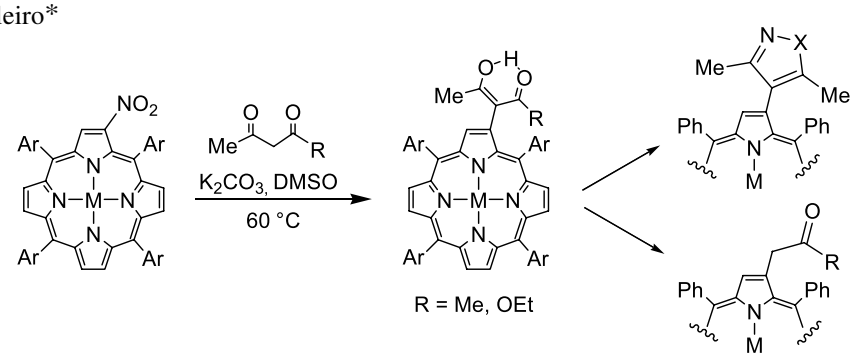


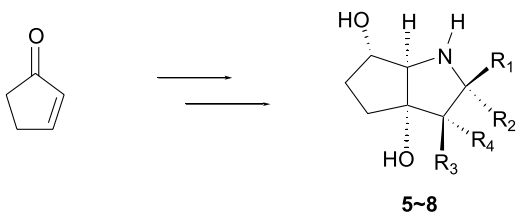
The field of radical conjugate additions, including both intramolecular and intermolecular examples, is reviewed. Stereoselective reactions, tin-free processes, cascade reactions, and applications in total synthesis are highlighted.

ARTICLES

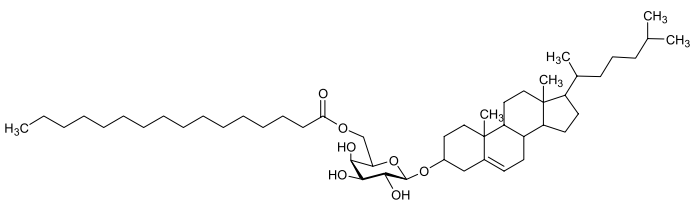


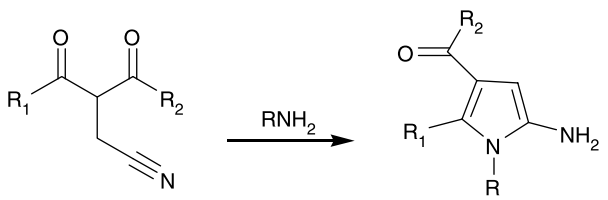


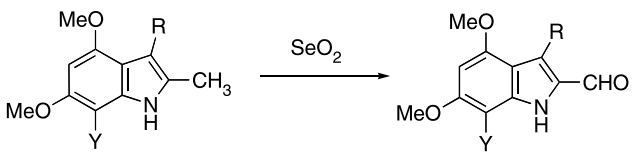


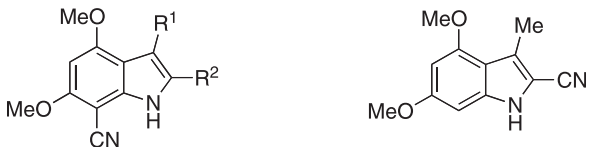


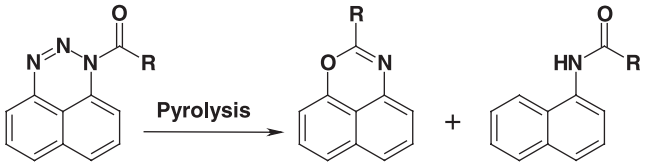
As a prelude to development of a human vaccine against Lyme disease, the first chemical synthesis of glycolipid antigens of *Borrelia burkholderi* is reported. First, cholesteryl β-D-galactopyranoside was synthesized and was converted to partially protected congeners having the HO-6 group of the galactose moiety unprotected. Treatment of these intermediates with palmitic and oleic acid, respectively, under dehydrative conditions followed by removal of the protecting groups afforded cholesteryl 6-*O*-palmitoyl/oleoyl-β-D-galactopyranoside that were identical to the glycolipids isolated from *B. burkholderi*.

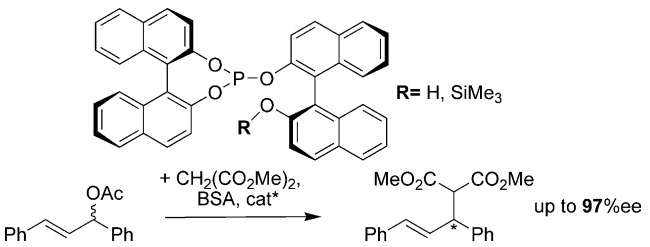


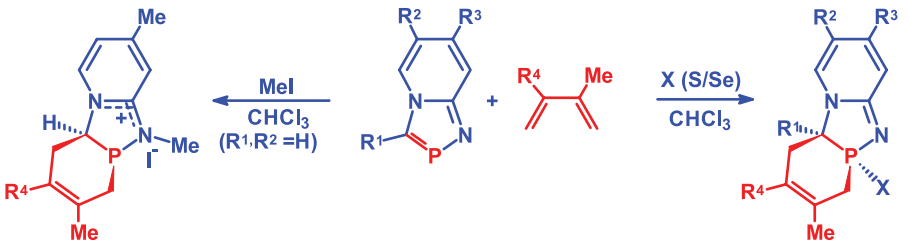


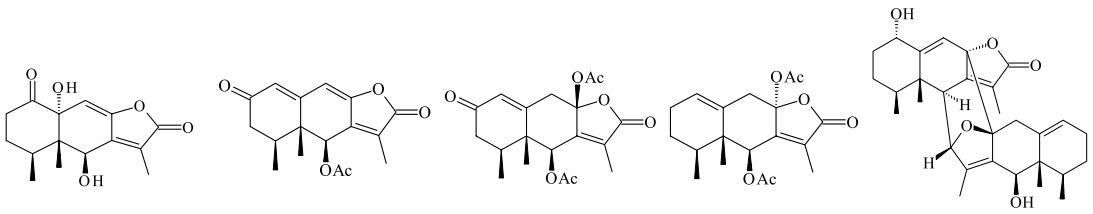


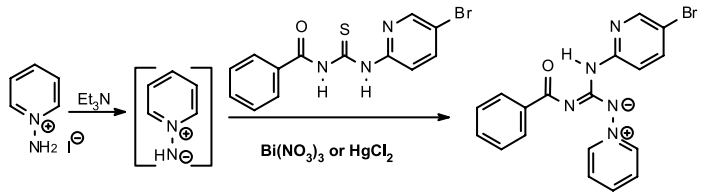


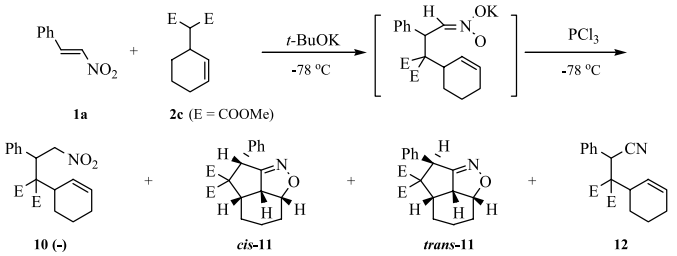


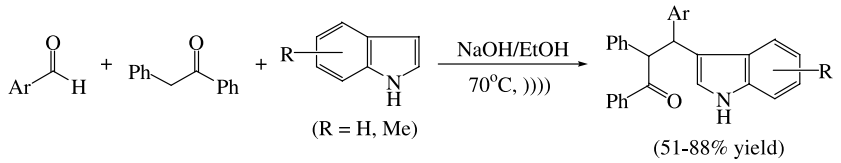


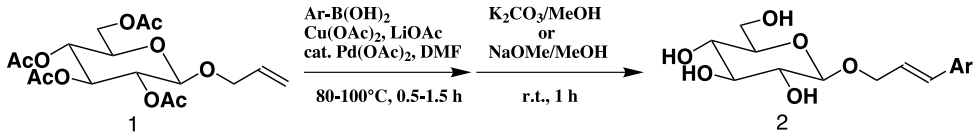


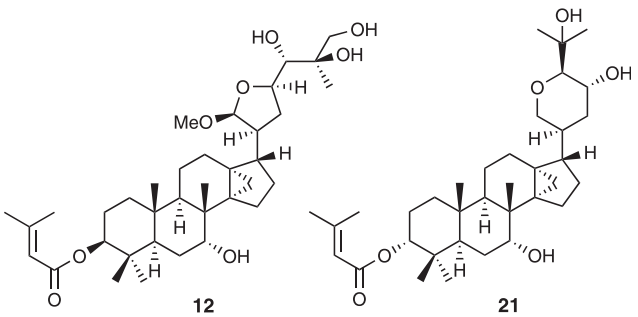


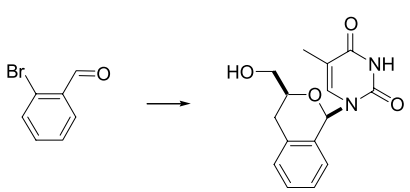












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Advances in radical conjugate additions

G. S. C. Srikanth and Steven L. Castle*

Department of Chemistry, Brigham Young University, Provo, UT 84602, USA

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Keywords: Radical chemistry; Conjugate addition.
* Corresponding author. Tel.: +1 801 422 1780; fax: +1 801 422 0153; e-mail: scastle@chem.byu.edu

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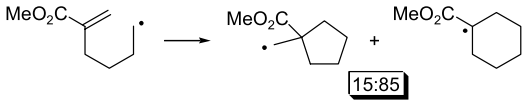
1. Introduction

Although radicals are usually viewed as neutral, relatively nonpolar species, polar effects in radical chemistry are well-known[1] and continue to be exploited in organic synthesis.[2] For example, nucleophilic radicals, or radicals with a singly occupied molecular orbital (SOMO) of relatively high energy, prefer to react with electron-deficient alkenes. In this case, the electron-withdrawing group attached to the alkene lowers the energy of the LUMO, thereby permitting greater overlap between the SOMO of the radical and the LUMO of the alkene. This principle is illustrated by the work of Della (Scheme 1), in which the 5-carbomethoxy-5-hexenyl radical preferred cyclization via the 6-*endo* mode rather than the typically favored 5-*exo* pathway.[3] Consequently, radical conjugate additions (RCAs) constitute a very valuable tool in the arsenal of the synthetic organic chemist. The chief benefit of RCAs over radical additions to unpolarized alkenes is the greater control of regioselectivity. Advantages that RCAs possess over conventional conjugate additions include the ability to leave polar functional groups in the substrate unprotected and the excellent selectivity for 1,4- over 1,2-addition.



Scheme 1.

Several reviews and monographs have been written on the uses of free radicals in organic synthesis;[4] additionally, the topic of conjugate additions has received extensive treatment.[5] However, to the best of our knowledge, Zhang's review of intramolecular radical conjugate additions published in 2001[6] is the only focused treatment of the RCA reaction. Accordingly, the purpose of this Report is to chronicle recent advances in the field of radical conjugate additions. Both intermolecular and intramolecular RCAs will be examined, although coverage of the latter will be limited to recent applications and selected examples presented in the Zhang review. Particular emphasis will be given to stereoselective RCAs as well as the use of RCAs to construct complex organic molecules including natural products. Moreover, coverage of radical additions that can occur with both activated and unactivated olefins as acceptors will be restricted to those processes which benefit substantially from the presence of an electron-withdrawing group on the olefin.

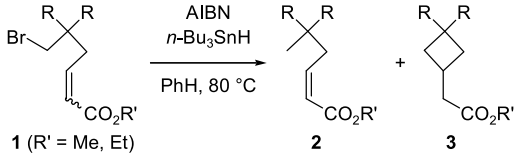
2. Additions to α,β-unsaturated ketones, esters, and amides

Conjugate additions of radicals to α,β-unsaturated ketones, esters, and amides are well-developed and have been widely used in organic synthesis. This section covers the development of methodology for performing RCAs to the aforementioned substrates using traditional methods of radical generation (i.e., AIBN/*n*-Bu_3SnH or RHgX/$NaBH_4$). Applications of this methodology in amino acid or natural product synthesis, its use in cascade reactions, or the performance of these RCAs via tin- and mercury-free methods will be covered in later sections of the review. The reactions in this section are divided into intramolecular and intermolecular RCAs; coverage of the former includes only selected examples cited in the Zhang review[6] and focuses primarily on work disclosed since its publication in 2001.

2.1. Intramolecular radical conjugate additions forming four–seven-membered rings

The synthesis of four-membered rings using 4-*exo-trig* radical cyclizations is rare due to the strain-induced reversibility of the process. Jung found that the presence of geminal disubstitution allowed the construction of cyclobutanes **3** via 4-*exo-trig* cyclizations of 6-bromo-2-hexenoates **1** (Table 1).[7–9] Alkoxy substituents facilitated cyclization to a much greater degree than did alkyl substituents. Interestingly, a substrate containing a six-membered ketal led to nearly exclusive formation of cyclobutane **3** (entry 5), whereas the analogous five-membered ketal afforded reduced compound **2** as the major product (entry 4). However, **3** could be obtained as the major product from all geminal disubstituted substrates by employing slow addition of *n*-Bu_3SnH. Computational studies by Houk and Jung indicated that the activation energies for cyclization of the geminal disubstituted enoates are similar to each other and lower than the activation energy for cyclization of the unsubstituted enoate.[10]

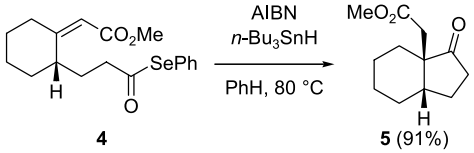
Table 1.



1 (R' = Me, Et) **2** **3**

Entry	R	**2**:**3**
1	H	100:0
2	Me	75:25
3	OEt	0:100
4	$O(CH_2)_2O$	75:25
5	$O(CH_2)_3O$	3:97
6	CO_2Et	30:70

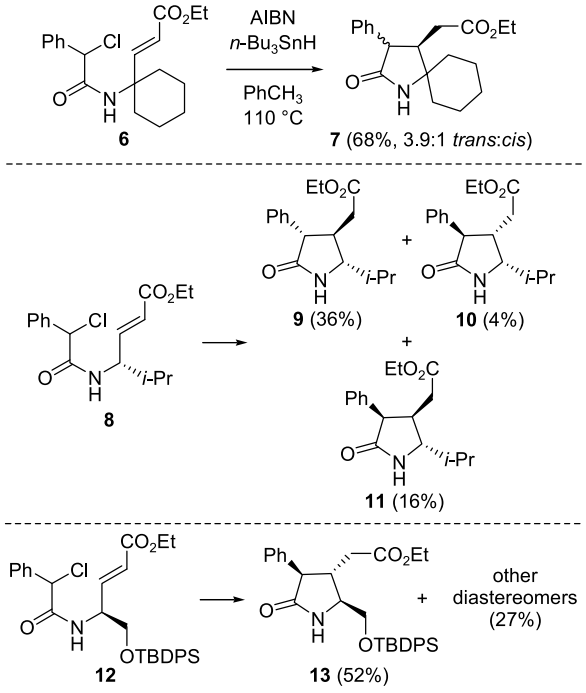
Whiting synthesized *cis*-hydrindane **5** via the 5-*exo-trig* acyl radical cyclization of phenyl selenoester **4** (Scheme 2).[11] The tolerance of β-substitution in the enoate radical acceptor allows construction of a quaternary stereocenter in this reaction. The authors postulate that the *Z*-olefin of **4** forces the adjacent side chain into an axial orientation, thereby delivering *cis*-**5** exclusively.



4 **5** (91%)

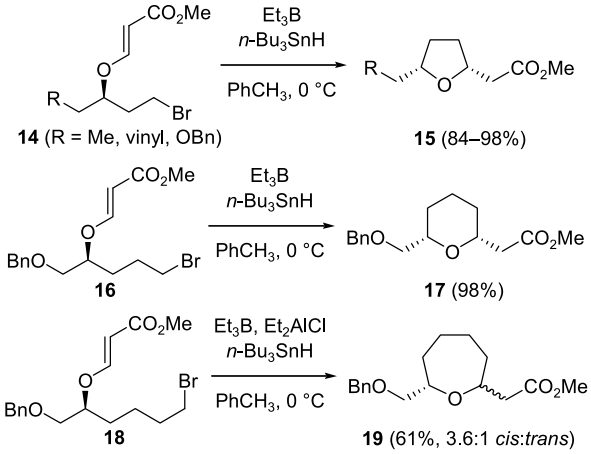
Scheme 2.

Parsons studied the synthesis of substituted pyrrolidinones by means of intramolecular 5-*exo* RCA reactions (Scheme 3). The presence of substituents adjacent to the nitrogen atom was essential to obtaining good yields of cyclized products; presumably, these groups cause an increase in the population of the conformer from which cyclization can occur. Trans (C-3–C-4) diastereoselectivity was observed in the cyclizations of **6** and **8**,[12] and pyrrolidinone **13** was employed in an enantioselective synthesis of phenyl allokainoid.[13,14]



Scheme 3.

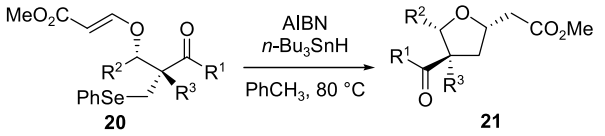
Shibuya studied the synthesis of cyclic ethers via intramolecular RCA reactions of β-alkoxyacrylates (Scheme 4).[15] *Cis*-disubstituted tetrahydrofurans **15** and tetrahydropyran **17** were obtained in high yield as single diastereomers from cyclizations of **14** and **16**, respectively. The preparation of oxepane **19** was marked by a decrease in stereoselectivity, and the addition of a Lewis acid was necessary in order to obtain a good yield.



Scheme 4.

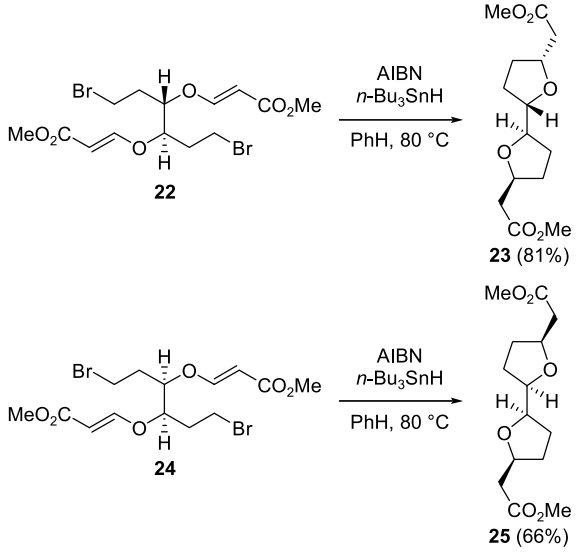
Kamimura constructed tri- and tetrasubstitituted tetrahydrofurans **21** via the intramolecular RCA reactions of β-alkoxyacrylates **20** (Table 2).[16,17] The products were obtained as single isomers, including one case where a quaternary stereocenter was created (entry 5). A transition state in which the substituents all occupy pseudoequatorial positions accounts for the observed stereoselectivity.

Table 2.

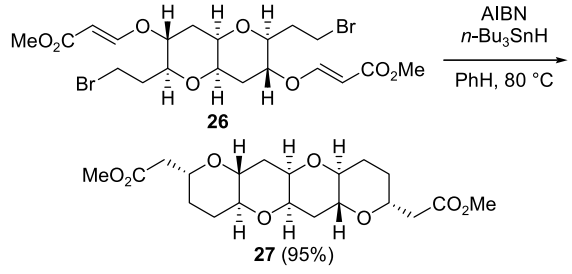


Entry	R^1	R^2	R^3	Yield (%)
1	Me	Me	H	85
2	Me	*i*-Pr	H	59
3	Me	Ph	H	59
4	O*t*-Bu	Ph	H	95
5	O*t*-Bu	Ph	Me	99

Lee investigated the double intramolecular RCA reactions of bis-β-alkoxyacrylates **22** and **24** (Scheme 5).[18] *Meso* bicycle **23** and C_2-symmetric compound **25** were formed in good yields. In both cases the 5-*exo-trig* cyclizations are favored over the 6-*exo-trig* processes leading to fused bicyclic products, although a fused compound was obtained in 6% yield from the cyclization of **24**.



Scheme 5.

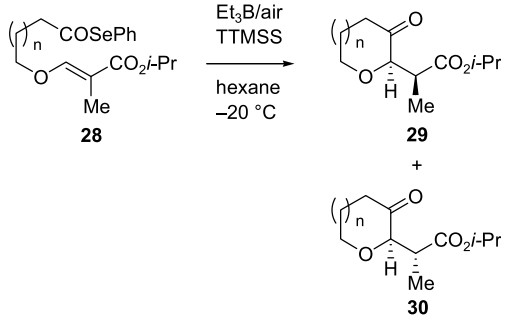


Scheme 6.

Lee subsequently prepared C_2-symmetric fused tetracyclic ether **27** via the double 6-*exo-trig* cyclization of bis-β-alkoxyacrylate **26** (Scheme 6).[19] Substrate **26** was constructed by means of iterative trans-selective *O*-stannyl ketyl radical cyclizations.

Evans studied the diastereoselectivity of intramolecular RCAs of α-substituted β-alkoxyacrylates **28** (Table 3).[20] Although the five- and seven-membered cyclic ethers were furnished with modest selectivity, the six-membered cyclic ether was formed with excellent diastereoselectivity favoring isomer **29**. The authors invoke allylic strain of the ketone carbonyl and the neighboring side chain as the factor controlling the stereoselective hydrogen atom abstraction.

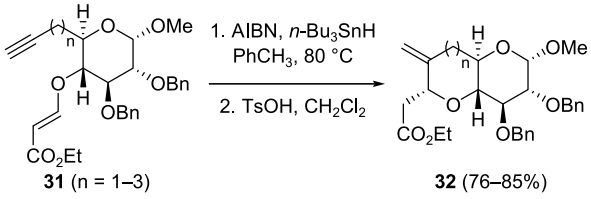
Table 3.



Entry	*n*	Yield (%)	**29**:**30**
1	0	76	4:1
2	1	82	46:1
3[a]	2	81	7:1

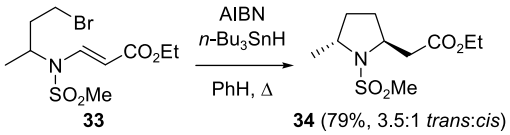
[a] Reaction run at 22 °C.

van Boom disclosed the 5-, 6- and 7-*exo-trig* alkenyl radical cyclizations of carbohydrate-derived β-alkoxy acrylates **31**, affording trans-fused bicyclic ethers **32** in good yields (Scheme 7).[21] This reaction was employed in an iterative fashion to synthesize a tricyclic trans-fused poly(tetrahydropyran) system.



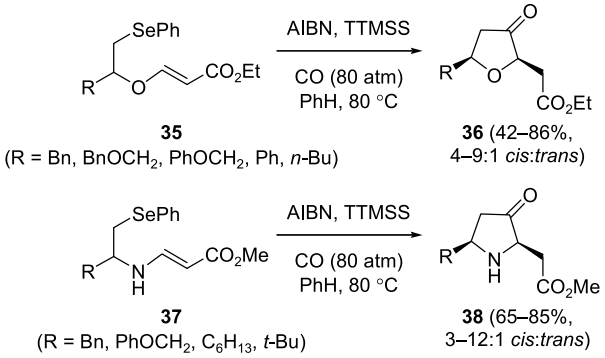
Scheme 7.

Lee found that 5-*exo* intramolecular RCA of sulfonamide-protected β-aminoacrylate **33** yielded 2,5-disubstituted pyrrolidine **34** with trans selectivity (Scheme 8).[22] The corresponding cis-isomers could be obtained by attaching a β-lactam or oxazolidinone template to the cyclization substrate.[23]



Scheme 8.

Engman synthesized *cis*-2,5-disubstituted tetrahydrofuran-3-ones **36** and pyrrolidin-3-ones **38** by the carbonylation/cyclization of phenylselenides **35** and **37** bearing β-alkoxy and β-aminoacrylates as the radical acceptors (Scheme 9).[24,25] The preference for the cis diastereomer was generally greater in the formation of tetrahydrofuran-3-ones **36**. Tris(trimethylsilyl)silane (TTMSS) was found to be a superior hydrogen atom donor than *n*-Bu_3SnH in this reaction.

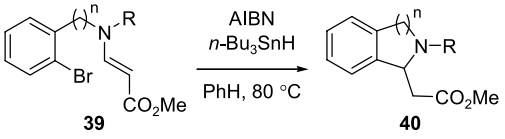


Scheme 9.

Domínguez found that aryl radicals undergo intramolecular RCA to β-amino acrylates, delivering heterocycles **40** (Table 4).[26] The lower yields of *N*-Me derivatives are due to reduction of the aryl radical competing with cyclization.

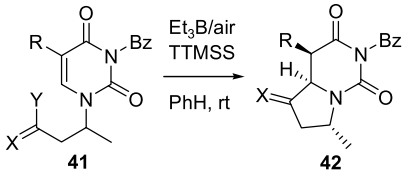
Evans examined the intramolecular RCA of alkyl and acyl radicals to uracil and thymine acceptors (Table 5).[27] In all

Table 4.



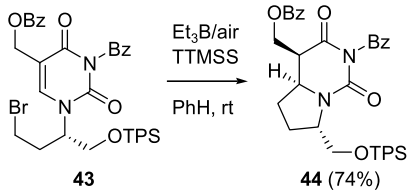
Entry	*n*	R	Yield (%)
1	1	H	71
2	1	Me	56
3	2	H	82
4	2	Me	51

Table 5.



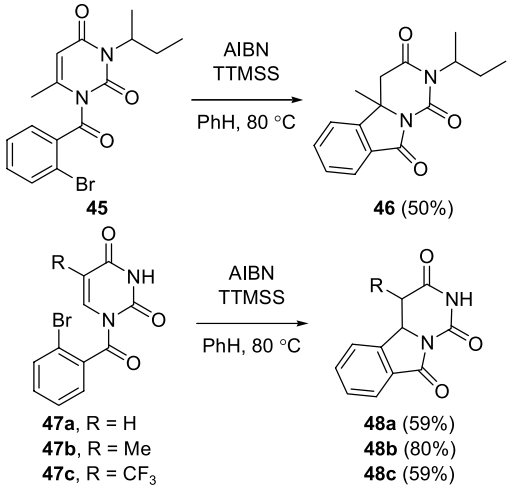
Entry	R	X	Y	Yield (%)
1	H	H_2	Br	78
2	H	O	SePh	70
3	Me	H_2	Br	72
4	Me	O	SePh	81

cases, azabicycles **42** were delivered in good yields and excellent diastereoselectivities. 5-*exo* Cyclization of functionalized substrate **43** afforded a potentially useful intermediate in the synthesis of batzelladine alkaloids (Scheme 10).



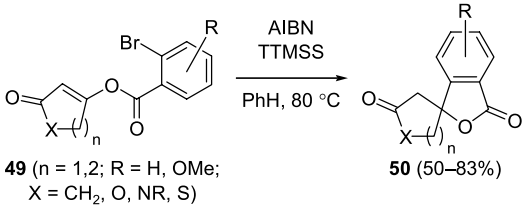
Scheme 10.

Zhang prepared isoindolinones **46** and **48** via 5-*exo-trig* aryl radical cyclizations onto uracil acceptors (Scheme 11).[28,29] Pyridinedione and pyridone moieties could also function as radical acceptors in place of the uracil ring.



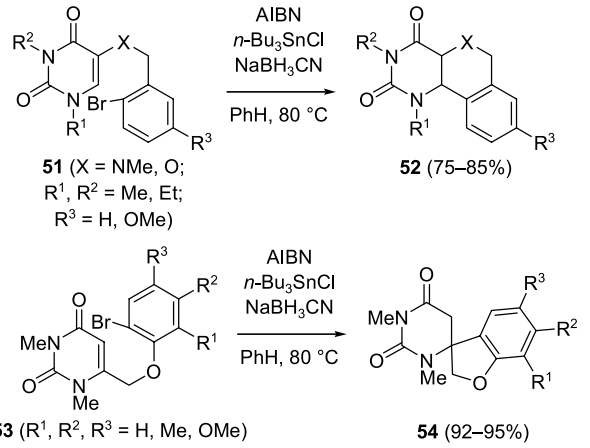
Scheme 11.

Zhang later applied this aryl radical cyclization to the synthesis of spirolactones, spirodilactones, spirolactone–lactams, and spirolactone–thiolactones (Scheme 12).[30–32] Spirolactams were also prepared by cyclizing substrates containing a vinylogous imide in place of the vinylogous anhydride of **49**.[29,30] Additionally, incorporation of a second radical acceptor into **49** allowed the construction of bridged spirolactones via double cyclizations.[32,33]



Scheme 12.

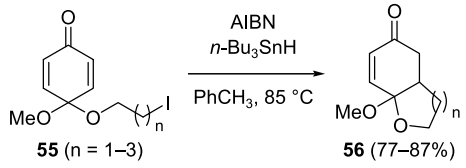
Majumdar has synthesized a variety of heterocyclic systems by RCA of aryl radicals onto uracil acceptors (Scheme 13). Substrates **51** undergo regioselective 6-*endo-trig* cyclization to provide tricycles **52** in good yield.[34,35] However,



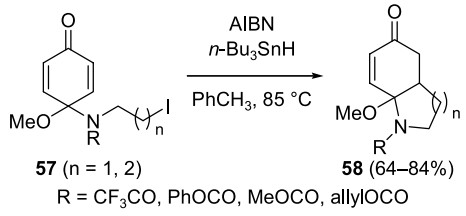
Scheme 13.

changing the attachment point of the side chain to the uracil moiety results in the formation of spiroheterocycles via a 5-*exo-trig* process.[36] Comparison of these two reactions indicates that the regioselectivity is governed by the electron-deficient nature of the uracil C-6 position.

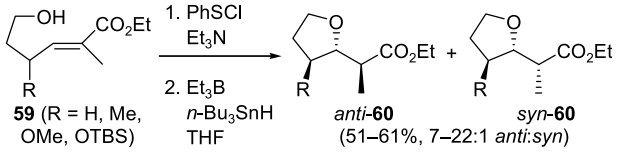
Clive reported that *p*-quinone monoketals **55** could participate in 5-,6-,and 7-*exo-trig* cyclizations, affording bicyclic products **56** in good yields (Scheme 14).[37,38] Treatment of **56** with TsOH delivered aromatized compounds via the elimination of MeOH. Since dienones **55** were prepared from *p*-methoxyphenols via oxidative phenolic coupling with ω-iodo alcohols, the entire process functions as a formal radical cyclization onto a benzene ring. Clive recently extended this method to the preparation of benzo-fused nitrogen heterocycles by employing *p*-aminophenols as the dienone precursors (Scheme 15).[39]



Scheme 14.



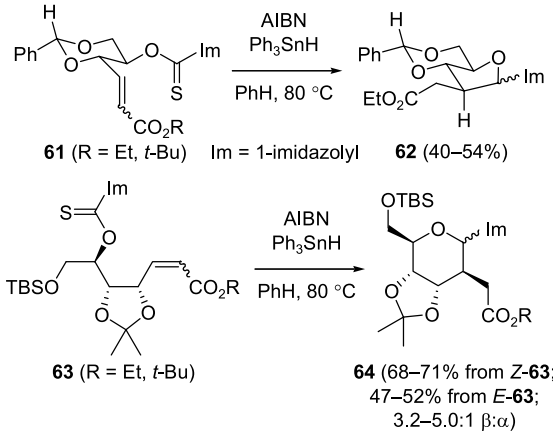
Scheme 15.



Scheme 16.

Guindon studied the stereoselectivity of 5-*exo* cyclizations of oxy radicals onto α-methyl α,β-unsaturated esters (Scheme 16).[40] A strong preference was observed for the *anti* product with 2,3-trans substitution on the tetrahydrofuran ring. 5-*exo* cyclizations of the analogous aminyl radicals proceeded with lower levels of diastereoselectivity, but use of iminyl radicals led to predominant formation of the *anti* heterocycles (7–16:1 dr).[41]

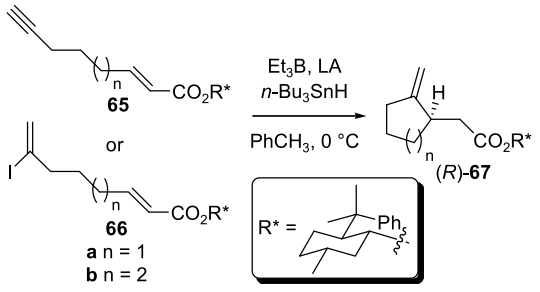
RajanBabu was able to intercept the radicals generated from addition of triphenyltin radical to thiocarbonyl imidazolides **61** and **63** in intramolecular RCA reactions, affording *N*-heterocyclic furanosides **62** and pyranosides **64** (Scheme 17).[42,43] The cyclic acetal in **61** and ketal in **63** were used to control the diastereoselectivity of the cyclization. While furanosides **62** were produced as ca. 1:1 anomeric mixtures, the β-pyranosides **64** predominated. In the latter case, the β-selectivity is attributed to hydrogen atom abstraction by an axial radical that benefits from anomeric stabilization.



Scheme 17.

Nishida and Nishida found that vinyl radicals generated from (−)-8-phenylmenthyl esters **65** and **66** underwent Lewis acid promoted diastereoselective intramolecular RCAs, delivering cyclopentanes and cyclohexanes **67** in good yield (Table 6).[44] The use of a Lewis acid was required for high diastereoselectivity. The authors propose that the Lewis acid facilitates diastereoselective cyclization by fixing the enoate moiety in an *s*-trans conformation.

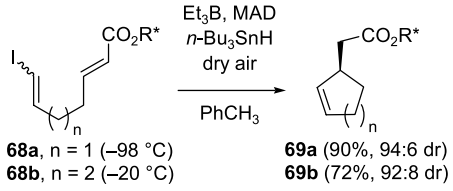
Table 6.



Entry	Substrate	LA	Yield (%)	*R*:*S*
1	**65a**	$BF_3 \cdot OEt_2$	90	76:24
2	**65a**	*i*-Bu_3Al	60	81:19
3	**65b**	$BF_3 \cdot OEt_2$	77	84:16
4	**65b**	*i*-Bu_3Al	72	87:13
5	**66a**	MAD[a]	79	96:4
6	**66b**	$BF_3 \cdot OEt_2$	82	90:10

[a] Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), reaction run at −78 °C.

Nishida and Nishida then performed similar 5- and 6-*exo*-*trig* cyclizations with terminal vinyl radicals (Scheme 18).[45] Cyclopentene **69a** and cyclohexene **69b** were produced in good yield and excellent diastereoselectivity. Additionally, it was discovered that the *i*-Bu_3Al and MAD-mediated reactions depicted in Table 6 and Scheme 18 could be carried out in the absence of Et_3B, albeit with lower yields.[46] Thus, these aluminum reagents are capable of acting as Lewis acids and radical initiators in the same reaction.



Scheme 18.

Nishida developed two new chiral auxiliaries based on *trans*-2-aminocyclohexanol (Fig. 1) and studied the use of substrates bearing these moieties in the reactions described in Scheme 18.[47] In both cases, inferior diastereoselectivities relative to the (−)-8-phenylmenthyl esters were observed.

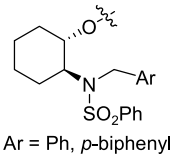
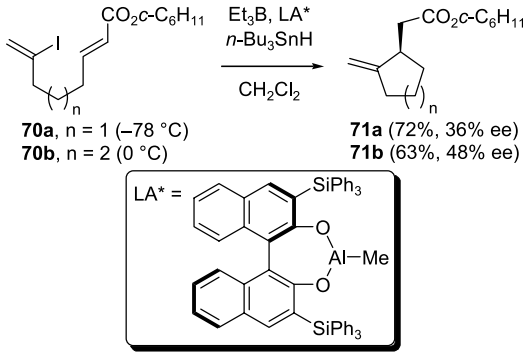


Figure 1.

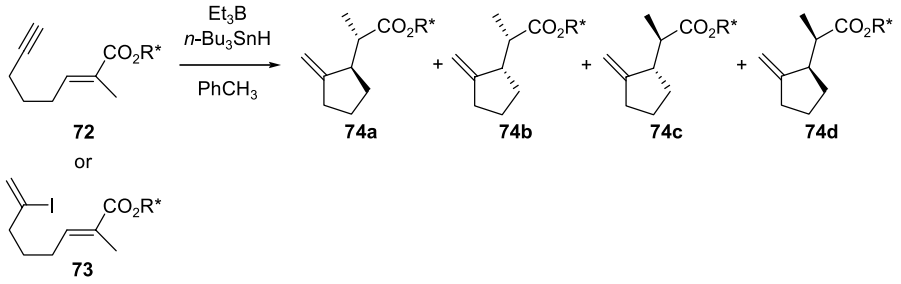
Nishida and Nishida investigated the enantioselective intramolecular RCA of α,β-unsaturated cyclohexyl esters **70** (Scheme 19).[48] A chiral aluminum Lewis acid based on (*R*)-binaphthol delivered carbocycles **71** in modest ee. An excess amount of the chiral Lewis acid (4 equiv) was necessary to achieve these results.

Nishida and Nishida also examined the diastereoselectivity



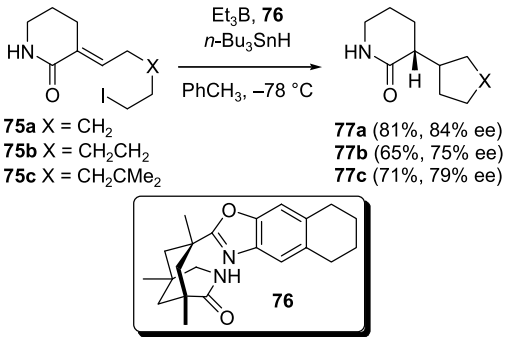
Scheme 19.

Table 7.

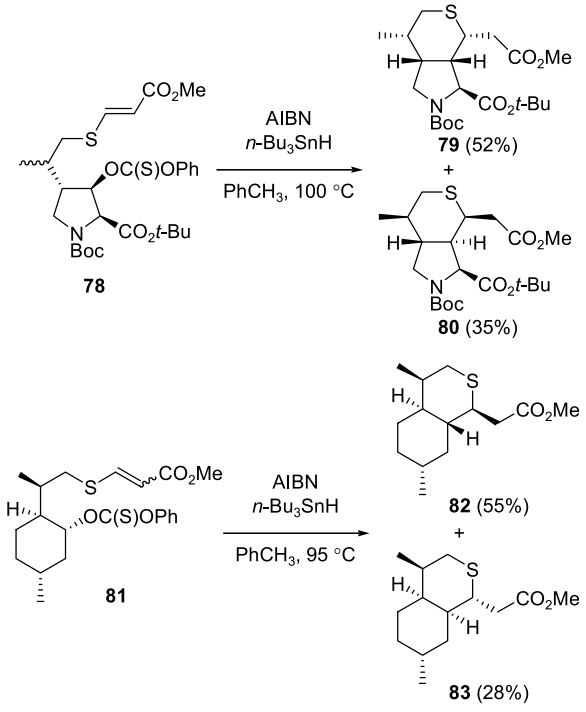


Entry	Substrate	Temperature (°C)	Yield (%)	**74a**:**74b**:**74c**:**74d**
1	**72**	0	77	67:18:9:6
2	**73**	−98	72	78:12:9:1

of 5-*exo-trig* vinyl radical cyclizations of (−)-8-phenylmenthyl α-methyl-α,β-unsaturated esters **72** and **73** (Table 7).[49] In this instance, Lewis acids were not employed and cyclopentane **74a** was obtained as the major diastereomer. The selectivity in formation of the α-stereocenter (5.6–9:1) was greater than the selectivity of β-stereocenter formation (2.7–3.8:1).



Scheme 20.

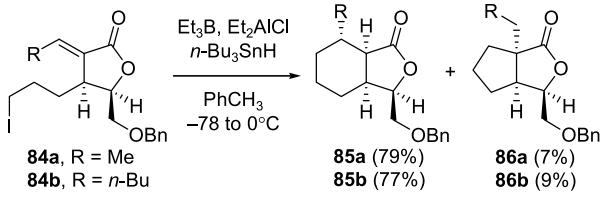


Scheme 21.

Bach employed lactam **76** as a chiral reagent in enantioselective cyclizations of α,β-unsaturated lactams **75** (Scheme 20).[50] It is believed that **76** forms a hydrogen-bond-mediated complex with **75**, allowing the tetrahydronaphthalene moiety to shield the *Re* face of the prochiral radical formed upon cyclization of **75**.

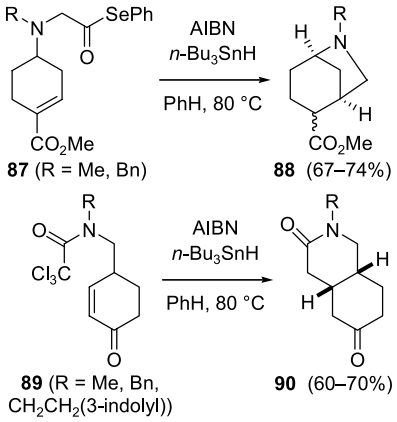
Bachi found that thioacrylates are good acceptors in intramolecular RCA reactions (Scheme 21).[51] The cyclization of **78** is highly stereoselective, as only one product is formed from each epimer of the starting material. Cyclization of **81** was less selective, affording two of the four possible products in a 2:1 ratio.

Sato used a Lewis acid to reverse the regioselectivity of radical cyclizations of α-alkylidenelactones **84** (Scheme 22).[52] In the absence of a Lewis acid, 5-*exo* adducts **86** predominated. However, addition of Et_2AlCl to the reaction mixture redirected the reaction down a 6-*endo* pathway, affording **85** as the major product. Presumably, complexation of the Lewis acid with the carbonyl increases the electrophilicity of the β-carbon, thereby lowering the energy of the RCA process.



Scheme 22.

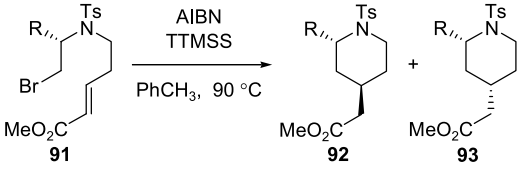
Bonjoch prepared 6-azabicyclo[3.2.1]octanes **88** via the decarbonylative 5-*exo-trig* cyclization of α-amino selenoesters **87** (Scheme 23).[53] Bonjoch subsequently employed carbamoyldichloromethyl radicals in the synthesis of *cis*-perhydroisoquinoline-3,6-diones **90**.[54] The corresponding carbamoylmethyl radical failed to cyclize, affording only reduced compound. The authors attribute the faster cyclization of the carbamoyldichloromethyl radical to the greater degree of pyramidalization at the radical center caused by the presence of the two Cl atoms.



Scheme 23.

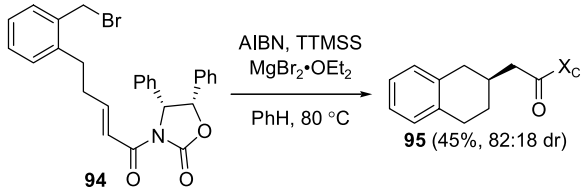
Snaith investigated the stereoselectivity of 6-*exo-trig* intramolecular RCAs of acrylates **91** (Table 8).[55] The trans selectivity increased with the bulk of the 2-substituent; apparently, the transition state leading to **93** is destabilized by pseudo A[1,3] strain between this group and the sulfonamide. Interestingly, the diastereoselectivity of reactions employing TTMSS was slightly enhanced relative to that of reactions mediated by *n*-Bu_3SnH. This is unusual given that the new stereocenter is created prior to the hydrogen atom abstraction step. It is conceivable that the $(Me_3Si)_3SiBr$ or *n*-Bu_3SnBr generated in situ may function as a Lewis acid and affect the cyclization step.

Table 8.



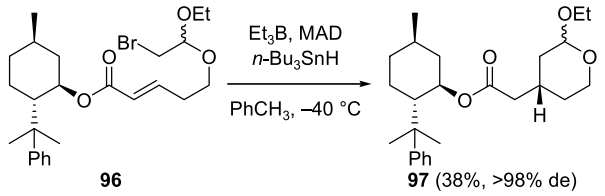
Entry	R	**92**:**93**	Yield (%)
1	Me	72:28	97
2	Bn	92:8	76
3	*i*-Pr	97:3	73

Badone disclosed the diastereoselective 6-*exo-trig* cyclization of α,β-unsaturated *N*-acyloxazolidinone **94** (Scheme 24).[56] The Lewis acid was required for obtaining good diastereoselectivity; it is believed to fix the conformation of **94** via chelation.



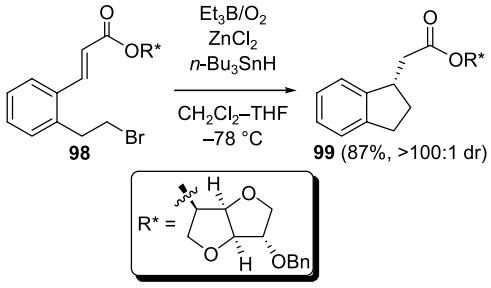
Scheme 24.

Ihara employed 8-phenylmenthol as a chiral auxiliary in the 6-*exo-trig* intramolecular RCA of α-bromo acetal **96** (Scheme 25).[57,58] Cyclic acetal **97** was obtained in modest yield but excellent diastereoselectivity; the bulky Lewis acid is believed to force the enoate to adopt the *s*-trans conformation. Better yields but significantly lower de's were observed in the absence of Lewis acid. Compound **97** was converted into (+)-12b-epidevinylantirhine.



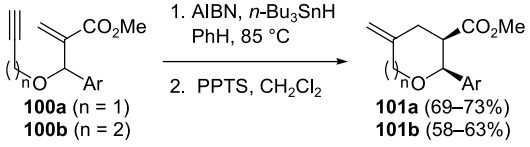
Scheme 25.

Enholm performed highly diastereoselective Lewis acid promoted 5-*exo-trig* cyclizations of cinnamates **98** containing a (+)-isosorbide-derived chiral auxiliary (Scheme 26).[59] Enholm also carried out related diastereoselective 6-*exo-trig* radical cyclizations in which the isosorbide ester was attached to a soluble polymeric support.[60]

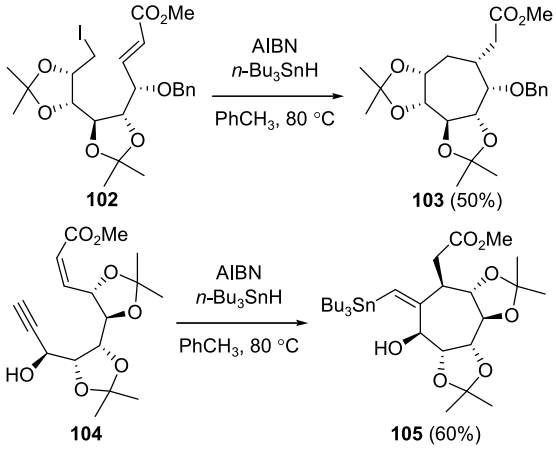


Scheme 26.

Shanmugam prepared *cis*-2,3-substituted tetrahydropyrans **101a** and oxepanes **101b** by means of 6- and 7-*endo* vinyl radical intramolecular conjugate additions (Scheme 27).[61,62] The diastereoselectivity is presumably due to hydrogen



Scheme 27.

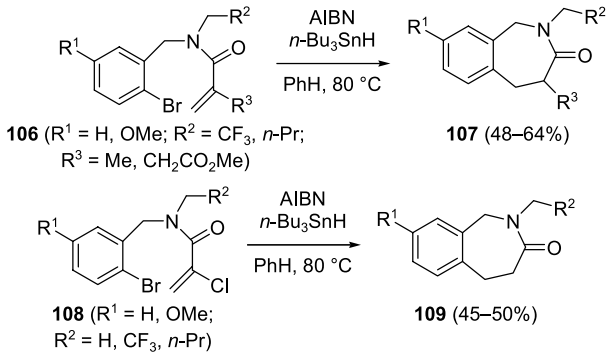


Scheme 28.

atom abstraction occurring on the least hindered face of the cyclic radical intermediates.

Marco-Contelles synthesized seven-membered carbocycles **103** and **105** via intramolecular RCA reactions of carbohydrate-derived substrates **102** and **104** (Scheme 28).[63] The presence of two conformationally constraining isopropylidene groups and the use of an α,β-unsaturated ester as the radical acceptor were necessary for this rare 7-*exo-trig* cyclization to occur in useful yields.

Kamimura employed a 7-*endo-trig* aryl radical cyclization to prepare 2-benzazepines **107** (Scheme 29).[64] The nature of the amide *N*-substituent was critical, as *N*-benzyl amides yielded products generated from 1,5-hydrogen atom abstraction rather than cyclization. α-Substitution on the α,β-unsaturated amide was a requirement for 7-*endo* cyclization; unsubstituted versions of **106** underwent 6-*exo-trig* cyclization instead. Nevertheless, Kamimura was able to prepare unsubstituted benzazepines **109** via incorporation of Cl as a temporary α-substituent in substrate **108**.[65]

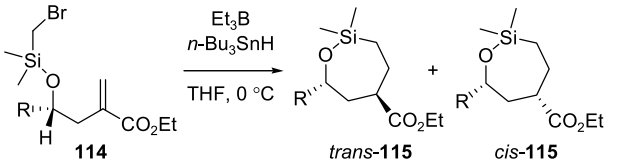


Scheme 29.

Pedrosa performed the diastereoselective 7-*endo-trig* cyclization of optically active α,β-unsaturated amide **110** (Scheme 30).[66] The presence of an α-methyl group was essential to obtaining the observed regiochemistry, as substrates without α-substitution afforded predominantly 6-*exo* adducts. Compound **111** was converted into an enantiomerically pure perhydroazepine after cleavage of the chiral auxiliary.

Nagano constructed cyclic silyl ethers **115** via 7-*endo-trig* cyclizations of α,β-unsaturated esters **114** (Table 9).[67] The trans selectivity increased with the size of the α-oxygen substituent. *trans*-**115** could be transformed into diastereomerically pure triols via reduction and subsequent Tamao–Fleming oxidation.

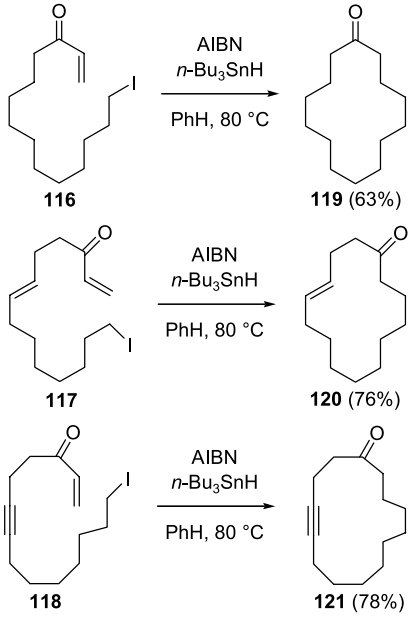
Table 9.



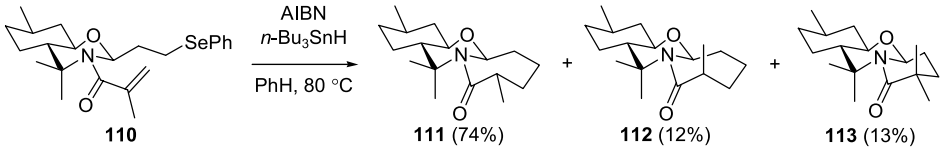
Entry	R	Yield (%)	*trans*/*cis*
1	Ph	97	18:1
2	*i*-Pr	90	34:1
3	*c*-C_6H_{11}	99	39:1
4	*t*-Bu	95	47:1

2.2. Macrocyclization via radical conjugate additions to α,β-unsaturated ketones, esters, and amides

Radical conjugate additions are an important tool in the synthesis of macrocycles. The slower cyclization rates of macrocycles relative to five- and six-membered rings would appear to preclude the use of radical methodology for their construction. However, the synthesis of macrocycles via radical intermediates is possible if the radical acceptor is an electron-deficient alkene. Seminal studies by Porter have established the structural requirements for successful radical macrocyclizations. α,β-Unsaturated ketones **116–118** undergo regioselective radical cyclization to give 14-membered carbocycles **119–121** in good yields at the optimal substrate concentration of 3–6 mM (Scheme 31).[68]



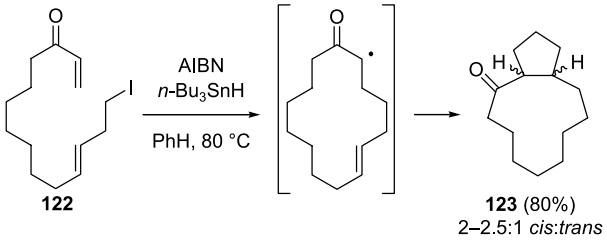
Scheme 31.



Scheme 30.

Enones **117** and **118** containing unsaturated tethers cyclized in greater yields than enone **116** with a fully saturated tether.

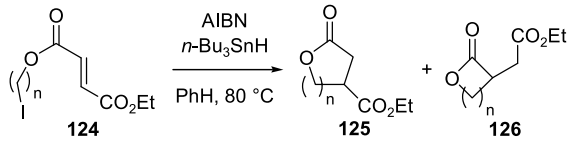
Although the α-carbonyl radical initially formed from 14-*endo* cyclization of **117** could engage the neighboring alkene in a 5-*exo*-*trig* process, this transannular cyclization does not occur. However, Porter discovered that the analogous radical derived from macrocyclization of **122** does undergo a subsequent 5-*exo*-*trig* cyclization, providing bicyclo[9.3.0] system **123** in good yield (Scheme 32).[69] These results indicate that the transannular cyclization can occur if the sp^2-hybridized carbonyl carbon is present in the developing 11-membered ring, but not if it is located in the developing five-membered ring.



Scheme 32.

Porter also found that ω-iodo acrylates analogous to **116** undergo *endo* radical macrocyclizations leading to the formation of 11–20-membered lactones.[70] Interestingly, ω-iodo fumarates **124**, which are sterically and electronically unbiased towards either *endo* or *exo* cyclization, yield predominantly endocyclic lactones **125** (Table 10). This preference for *endo* cyclization is attributed to destabilization of the *exo* transition states by transannular strain. Transannular strain is greatest in medium-sized rings, and decreases with increasing ring size. Thus, *endo*/*exo* ratios are smaller with the 16-*endo*/15-*exo* and 20-*endo*/19-*exo* systems (entries 3 and 4) relative to the 12-*endo*/11-*exo* and 13-*endo*/12-*exo* systems (entries 1 and 2).

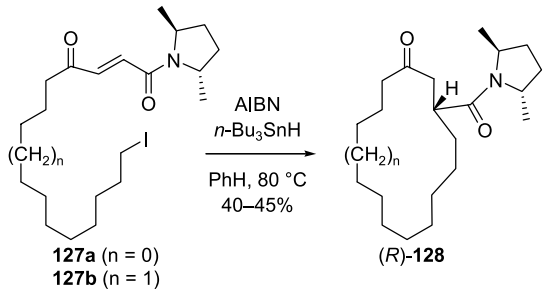
Table 10.



Entry	*n*	*endo*/*exo* ring size	**125**:**126**
1	8	12/11	5:1
2	9	13/12	5:1
3	12	16/15	2.5:1
4	16	20/19	1.1:1

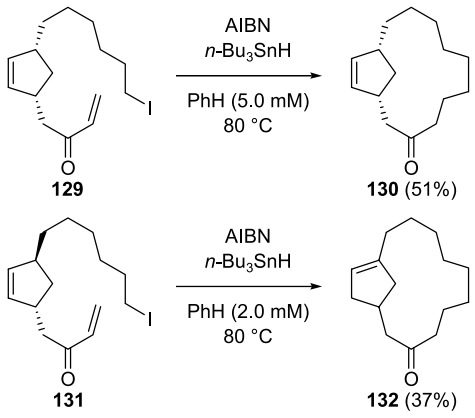
Porter demonstrated that substrates **127** containing a pyrrolidine amide chiral auxiliary deliver macrocyclic ketones (*R*)-**128** in a highly regio- and stereoselective fashion (Table 11).[71] The products of *exo* cyclization were obtained in minor amounts (ca. 4.5:1 *endo*:*exo*) with no diastereoselectivity. This suggests that the diastereoselective formation of **128** is due to approach of the alkyl radical over the pyrrolidine amide in the *endo* transition state.

Table 11.



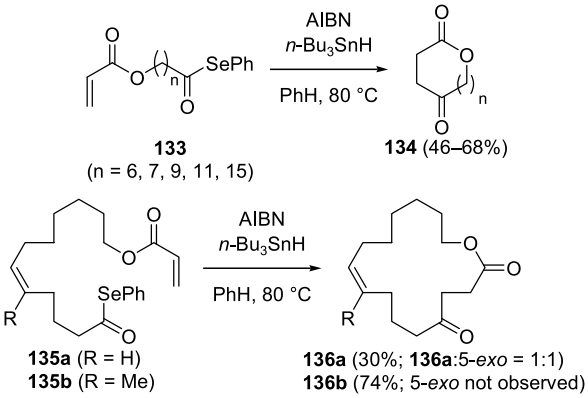
Iodide	(*R*)-**128**:(*S*)-**128**
127a	14:1
127b	13:1

Robertson employed an RCA macrocyclization to prepare bicyclo[10.2.1]pentadecenones **130** and **132** (Scheme 33).[72] In addition to **130**, the product derived from reduction of iodide **129** was also isolated in 31% yield. Trans substrate **131** afforded **132** after silica gel chromatography; presumably, the initially obtained macrocycle isomerizes during purification to afford a less strained product.



Scheme 33.

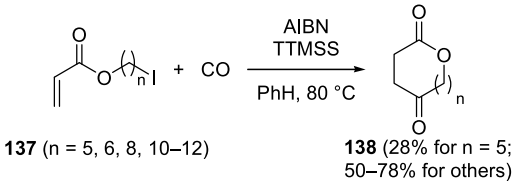
Boger disclosed that acyl radicals can participate in macrocyclizations with acrylate acceptors, forming 11–20-membered rings **134** (Scheme 34) under high-dilution conditions (5–6 mM).[73] Cyclization of substrate **135a** under these conditions demonstrated that the rates of



Scheme 34.

16-*endo-trig* acyl radical cyclization onto an acrylate and 5-*exo-trig* acyl radical cyclization onto an unactivated alkene are competitive. The latter process could be inhibited sterically (cf. **135b→136b**). Cyclizations of substrates isomeric to **135a** revealed that this acyl radical macrocyclization is faster than both 6- and 7-*exo-trig* acyl radical cyclizations.

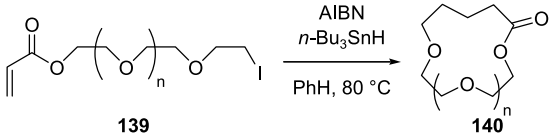
Ryu and Sonoda showed that the acyl radicals utilized by Boger in macrocyclizations could also be generated by carbonylation of alkyl radicals, resulting in the formation of 10–17-membered rings (Scheme 35).[74,75] High-dilution conditions (5–10 mM) and high pressures of CO (30 atm) were necessary to suppress intermolecular RCA reactions as well as macrocyclization of the initially generated alkyl radical. TTMSS was typically used as the radical chain carrier, although use of allyltributyltin provided the α-allylated macrolactones.



Scheme 35.

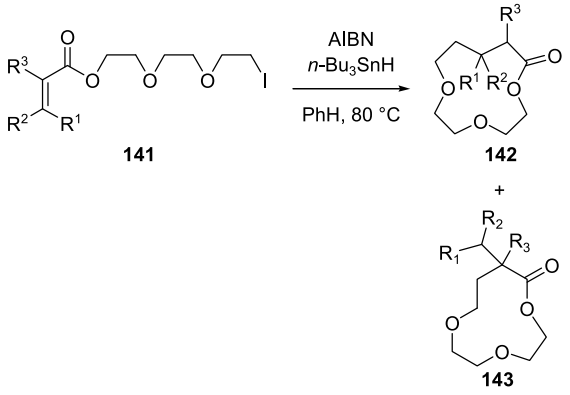
Maillard and Beckwith have prepared macrocyclic polyethers via intramolecular RCA reactions.[76–78] Rings ranging in size from 12 to 21 could be constructed in good yield via this method (Table 12), and high-dilution conditions could be avoided by slowly adding separate solutions of the substrate and *n*-Bu_3SnH to a solution of AIBN. Comparison of rate constants for the cyclization of polyethers **139** with those obtained by Porter for cyclization of the analogous ω-iodo acrylates[70] indicates that the polyether substrates cyclize 10–30 times more rapidly. Maillard and Beckwith attribute this result to a decrease in transition state strain energies caused by replacing methylene groups with oxygen atoms. Interestingly, fumarates **141** cyclized with a considerably lower *endo*/*exo* ratio than did the corresponding fumarates studied by Porter[70] (Table 13, entries 3 and 4 vs Table 10, entry 1). This can be explained by the aforementioned decrease in strain energies resulting in smaller energy differences between the *endo* and *exo* transition states. In addition to macrolactones, polyethers with exocyclic esters could also be synthesized by this method.

Table 12.



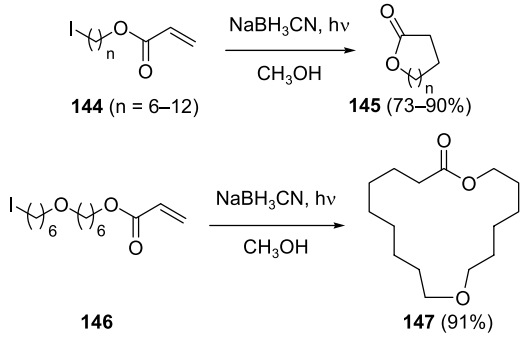
Entry	*n*	Ring size	Yield (%)
1	1	12	78
2	2	15	72
3	3	18	70
4	4	21	63
5	5	24	30

Table 13.



Entry	R^1	R^2	R^3	**142**:**143**
1	H	H	Me	100:0
2	H	Me	H	100:0
3	CO_2Et	H	H	43:57
4	H	CO_2Et	H	58:42
5	H	Ph	H	10:90

Kurata has employed photochemical conditions for the cyclization of ω-iodo acrylates with $NaBH_3CN$ as the radical chain carrier (Scheme 36).[79] The yields of 10–16-membered macrolactones **145** obtained by this method were generally higher than the yields delivered by AIBN–*n*-Bu_3SnH. Oxalactone **147** could also be synthesized using this photochemical, tin-free protocol.[80]

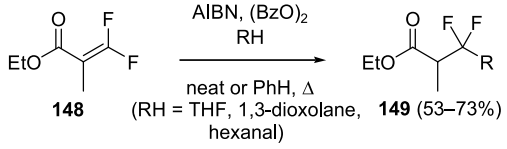


Scheme 36.

2.3. Intermolecular radical conjugate additions to α,β-unsaturated ketones, esters, and amides

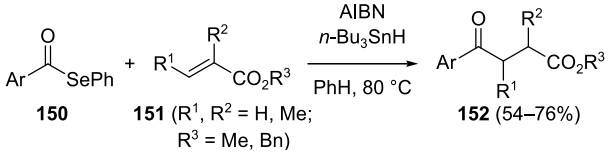
Nucleophilic radicals such as alkyl and acyl radicals can undergo intermolecular conjugate additions to α,β-unsaturated ketones, esters, and amides. A Lewis acid is often needed to activate the acceptor and promote these reactions. In some cases, chiral Lewis acids have been employed for the dual purpose of accelerating the reaction and controlling its stereochemistry. This section is organized according to the stereoselective nature of the reactions. Thus, RCA reactions in which no stereocenter is created are covered first, followed by substrate-controlled diastereoselective RCAs, RCAs employing chiral auxiliaries, and enantioselective RCAs. The bulk of the material presented herein was published since 1991, as earlier work on stereoselective intermolecular RCAs is covered in a review by Porter, Giese, and Curran.[81]

2.3.1. Reactions in which no stereocenter is created. Bumgardner synthesized β-fluorinated carboxylic acid derivatives **149** via intermolecular addition of α-alkoxy and acyl radicals to β,β-difluoroacrylate **148** (Scheme 37).[82] Conventional anionic Michael additions to **148** were plagued by undesired elimination of fluoride from the intermediate enolates.



Scheme 37.

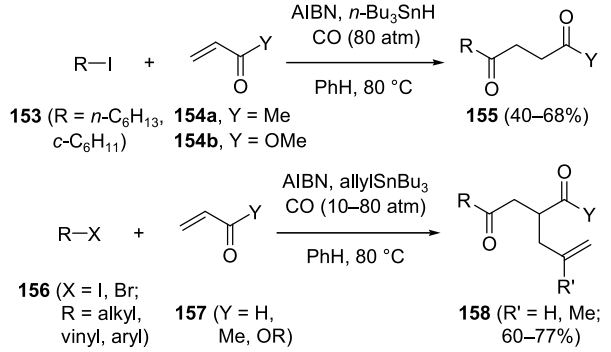
Boger found that acyl radicals generated from aryl phenyl selenoesters **150** participate in intermolecular RCA reactions with acrylates **151**, forming ketones **152** (Scheme 38).[83,84] Primaryl alkyl and vinyl phenyl selenoesters were also good substrates for this process, but secondary alkyl phenyl selenoesters suffered from competitive acyl radical decarbonylation.



Scheme 38.

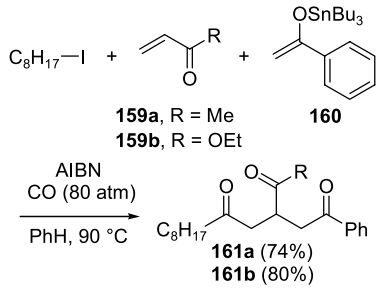
Ryu and Sonoda subsequently disclosed that similar conjugate additions could be performed using acyl radicals derived from radical carbonylation of alkyl iodides **153** (Scheme 39).[85] High pressures of CO were necessary to preclude reduction of the alkyl radical. However, substitution of the poorer hydrogen atom donor TTMSS for *n*-Bu_3SnH allowed these reactions to be carried out at lower CO pressures (20 atm) without competitive reduction.[86] By replacing the hydrogen atom donor with an allylstannane, Ryu and Sonoda were able to effect a four-component coupling that gave rise to β-functionalized δ,ε-unsaturated ketones **158** (Scheme 39).[87] Ryu and Curran used fluorous allyltin reagents in this reaction, which simplified the isolation of **158** from tin byproducts.[88]

Hosomi and Ryu developed a related four-component coupling in which the acyl radical resulting from



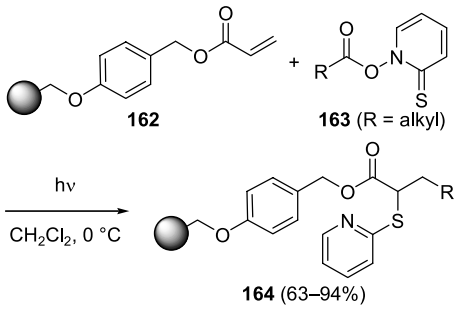
Scheme 39.

carbonylation of octyl iodide underwent intermolecular RCA to α,β-unsaturated ketone **159a** or ester **159b**, and the incipient electrophilic α-acyl radical was trapped with nucleophilic stannyl enolate **160** (Scheme 40).[89]



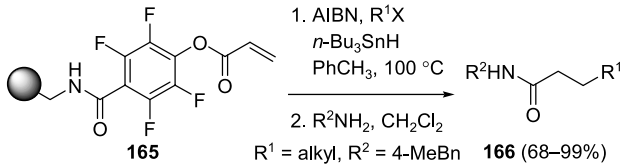
Scheme 40.

Ganesan performed intermolecular RCAs of alkyl radicals to acrylate **162** immobilized on solid phase with the Wang linker (Scheme 41).[90] Use of the Rink amide linker was also tolerated, albeit with a decrease in yield.



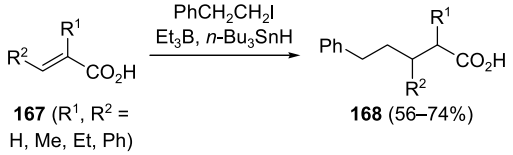
Scheme 41.

Caddick introduced tetrafluorophenol-linked acrylate **165** as a solid-phase acceptor in intermolecular RCA reactions (Scheme 42).[91] Aminolysis of the intermediate adducts led to amides **166** in good yield. When glycosyl halides and amino acid derivatives were employed in this reaction, C-linked glycopeptide mimetics were produced, albeit in modest yield (16–57%).



Scheme 42.

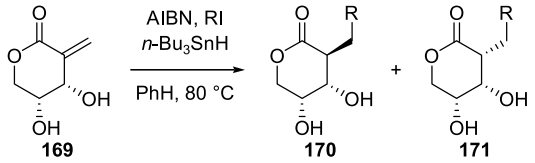
Avery discovered that 2-phenethyl iodide will undergo intermolecular RCA to α,β-unsaturated acids **167** provided Et_3B is employed as the radical initiator (Scheme 43).[92]



Scheme 43.

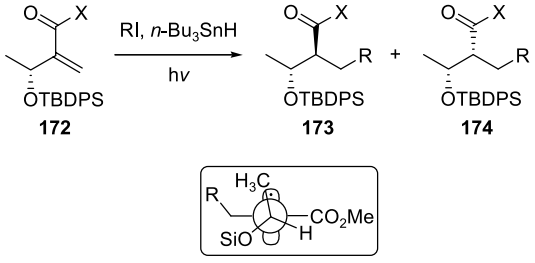
Acids substituted at either the α- or β-positions gave good yields of adducts **168**, but substitution at both positions was not well tolerated. The authors propose that in addition to acting as a radical initiator, Et_3B reacts with **167** to form a borate ester, thereby increasing the alkene electrophilicity and preventing *n*-Bu_3SnH from reacting with the carboxylic acid moiety.

Table 14.



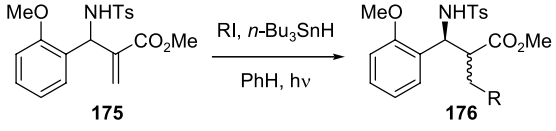
Entry	R	Yield (%)	**170**:**171**
1	*n*-C_6H_{13}	65	40:60
2	*c*-C_6H_{11}	80	60:40
3	*t*-C_4H_9	50	85:15

Table 15.



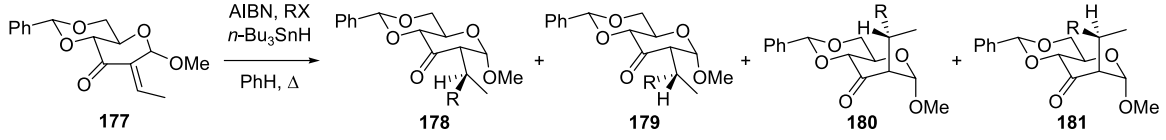
X	Entry	R	Yield (%)	**173**:**174**
Me	1	*t*-Bu	68	>30:1
OMe	2	*t*-Bu	87	19:1
OMe	3	*c*-C_6H_{11}	86	7:1
OMe	4	*n*-C_8H_{17}	75	5:1

Table 16.



Entry	R	Yield (%)	*syn*:*anti*
1	Et	92	5.8:1
2	*c*-C_6H_{11}	95	4.5:1
3	*t*-Bu	89	1.1:1

Table 17.



Entry	R	Yield (%)	(**178**+**179**)/(**180**+**181**)	(**178**+**180**)/(**179**+**181**)
1	*n*-Bu	60	87:13	68:32
2	*s*-Bu	58	69:31	78:22
3	*t*-Bu	35	30:70	81:19

2.3.2. Substrate-controlled diastereoselective reactions. Giese has thoroughly studied the diastereoselectivity of hydrogen atom abstractions by α-carbonyl radicals. Frequently, these species are generated via intramolecular RCA. For example, Giese found that increasing the bulk of the alkyl radical in additions to α,β-unsaturated lactone **169** led to a reversal from a modest tendency for hydrogen atom abstraction to occur trans to the neighboring hydroxyl group to a strong preference for the cis pathway (Table 14). Computational studies of the prochiral α-carbonyl radical indicate that the bulkier alkyl groups prefer to reside *anti* to the hydroxyl group. This causes hydrogen atom abstraction to occur predominantly cis to the alcohol.[93]

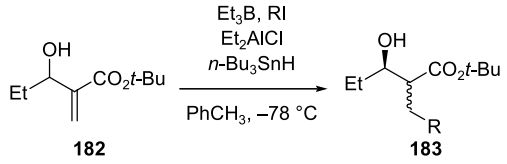
Giese observed significant *anti*-selectivity in RCAs to substrates **172** containing a β-*tert*-butyldiphenylsiloxy group (Table 15).[94] The diastereoselectivity increased along with the size of the alkyl radical. The *anti*-selectivity is consistent with hydrogen atom abstraction occurring opposite the large siloxy group from a conformation in which allylic strain is minimized.

Kündig observed 1,2-asymmetric induction in hydrogen atom abstractions by radicals generated via RCA to acrylates **175** (Table 16).[95] The dr increased with decreasing size of the alkyl radical. The stereoselectivity was attributed to intramolecular hydrogen bonding between the sulfonamide hydrogen and the ester carbonyl.

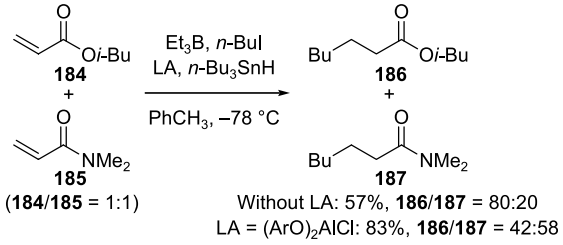
Chapleur studied the diastereoselectivity of intermolecular RCAs to chiral enone **177**.[96] Two stereocenters are formed in this reaction, and the data in Table 17 allow a comparison of the selectivities of the radical addition and hydrogen atom abstraction steps. Whereas the sense of diastereoselectivity in the addition step was consistent and the dr improved with increasing bulk of the alkyl radical, a reversal of stereoselectivity in the hydrogen atom abstraction step occurred with a tertiary radical. The latter phenomenon can be explained by minimization of 1,3-allylic strain in the transition state.

Sato demonstrated that Lewis acids can perform a dual role in intermolecular RCA reactions.[97] The *syn*-stereoselectivity observed in RCAs to hydroxyl-substituted enoate **182** is attributed to a six-membered chelate formed by the substrate and the Lewis acid (Table 18). Competition experiments utilizing enoate **184** and amide **185** revealed that RCA to the latter is favored when a Lewis acid is present (Scheme 44). This suggests that the Lewis acid is binding preferentially to the amide and forming an acceptor that is more reactive than uncomplexed ester **184**. Thus,

Table 18.



Entry	R	Yield (%)	*syn*/*anti*
1	Bu	76	87:13
2	$TBSO(CH_2)_2$	60	75:25
3	*c*-C_6H_{11}	73	60:40

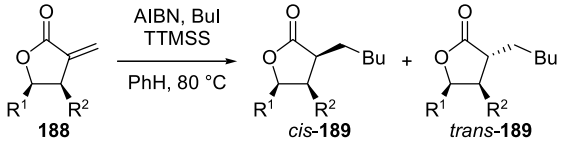


Scheme 44.

Lewis acids can both control stereochemistry and increase acceptor reactivity in RCA reactions.

Sato also showed that a Lewis acid can alter the stereochemical course of an intermolecular RCA.[98] Additions of the butyl radical to α-methylenebutyrolactones **188** afforded primarily *cis* lactones **189** (Table 19). However, use of a bulky aluminum Lewis acid delivered the trans isomers as major products (entry 4).

Table 19.

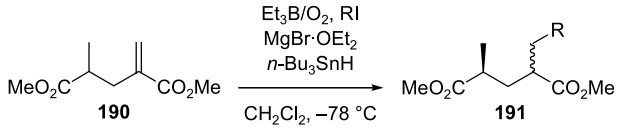


Entry	R^1	R^2	Yield (%)	*cis*:*trans*
1	Ph	H	60	98:2
2	Bu	H	53	78:22
3	H	Ph	60	92:8
4[a]	Ph	H	91	40:60

[a] Conditions: di(2,4,6-trimethylphenoxy)AlCl, Et_3B, *n*-Bu_3SnH, $PhCH_3$, −50 °C.

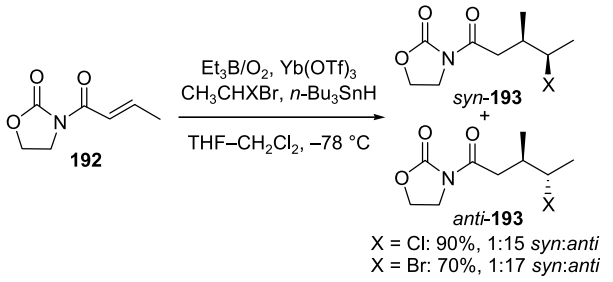
Metzger utilized 2-methyl-4-methyleneglutarate **190** as a substrate for studying 1,3-stereoinduction in RCA reactions (Table 20).[99,100] A Lewis acid was required for diastereoselectivity, suggesting that the reaction was proceeding under chelation control via an eight-membered intermediate. High *syn* selectivity was observed with *tert*-butyl radical, but increasing levels of the *anti* isomer were obtained as the size of the alkyl radical decreased. This trend could be rationalized in terms of the aforementioned chelated radical intermediates. Additionally, raising the reaction temperature often led to increased diastereoselectivity, indicating that entropy has a strong influence on the transition state of hydrogen atom abstraction.

Table 20.



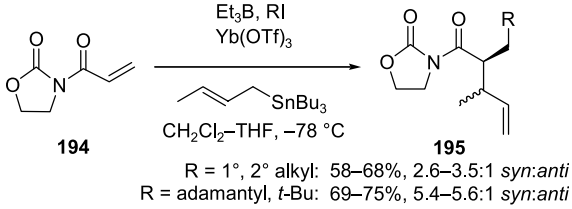
Entry	R	Yield (%)	*anti*:*syn*
1	*t*-Bu	83	2:98
2	*c*-Hex	64	53:47
3	Et	100	85:15

Sibi investigated the diastereoselectivities of prochiral radical additions to prochiral acceptors.[101] Moderate *syn* selectivity (≤6:1) was obtained in additions of alkyl and α-alkoxy radicals to **192**, but excellent *anti* selectivity was observed with less reactive halogenated radicals (Scheme 45). The authors postulate that electronic effects in a late transition state are responsible for these results.

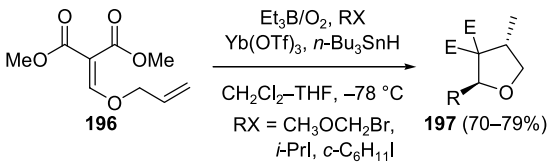


Scheme 45.

Sibi found that crotylstannane trapping of the electrophilic α-carbonyl radicals resulting from Lewis acid promoted RCA to acrylimide **194** delivered adducts **195** with good *syn* selectivity (Scheme 46).[102] Tertiary alkyl radicals gave higher yields and dr's than did primary and secondary alkyl radicals. These results can be explained by an open transition state for crotylation in which *gauche* interactions are minimized. When the alkyl radical contained a suitably positioned olefin, ring-closing metathesis of the adducts provided cyclooctenes.[103]

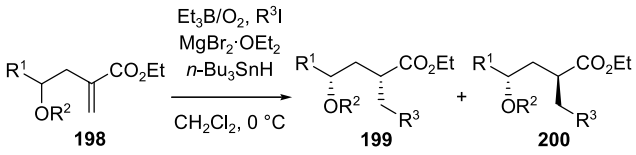


Scheme 46.



Scheme 47.

Table 21.

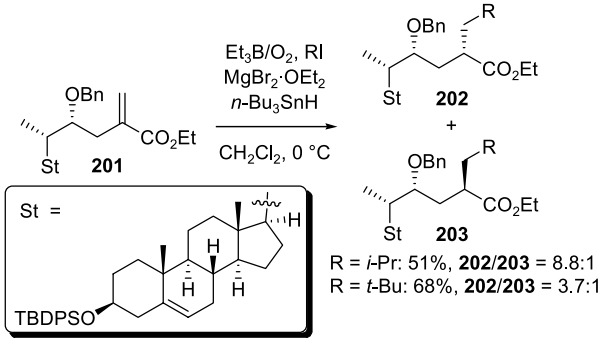


Entry	R^1	R^2	R^3	Yield (%)	**199**:**200**
1	Ph	Me	*i*-Pr	96	4.3:1
2	Ph	Me	*t*-Bu	91	1:3.8
3	Ph	MOM	*i*-Pr	63	2.8:1
4	*t*-Bu	MOM	*i*-Pr	78	10:1

Sibi discovered that β-alkoxy alkylidene malonate **196** was a suitably activated acceptor for intermolecular RCA followed by 5-*exo* cyclization of the incipient radical (Scheme 47).[104] The resultant *trans* tetrahydrofurans **197** were isolated in >50:1 dr. Six-, seven-, and eight-membered cyclic ethers could also be prepared via this method with varying degrees of diastereoselectivity.[105]

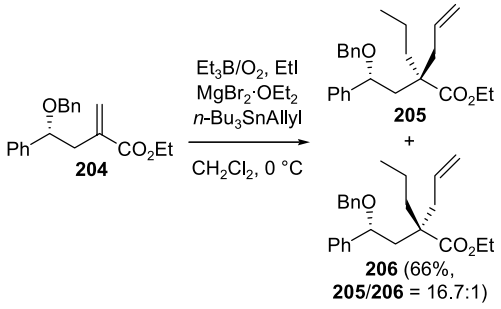
Nagano found that conjugate addition of isopropyl radical to γ-alkoxy-α-methylene esters **198** proceeded with *syn* selectivity in the presence of $MgBr_2 \cdot OEt_2$ or other Lewis acids (Table 21).[106] However, addition of *tert*-butyl radical to **198** gave predominantly *anti* adduct **200** (entry 2). Poor dr's were obtained in the absence of Lewis acids. These results are consistent with the existence of a seven-membered chelated radical intermediate.

Investigations by Nagano of RCAs to steroidal substrates revealed similar trends in diastereoselectivity with the exception of benzyl ether **201**. Thus, while isopropyl radical addition to **201** proceeded with the expected *syn* selectivity, addition of *tert*-butyl radical also gave *syn* isomer **202** as the major product, albeit with a reduced dr (Scheme 48).[107] These results as well as those of the above study were rationalized by a computational study of the chelated radical intermediates.[108] Since the hydrogen atom transfer is exothermic, the structures of these intermediates are expected to approximate the transition states. Subsequent work by Nagano addressed the steric and electronic effects of different substituents on the diastereoselectivity of these reactions.[109,110]



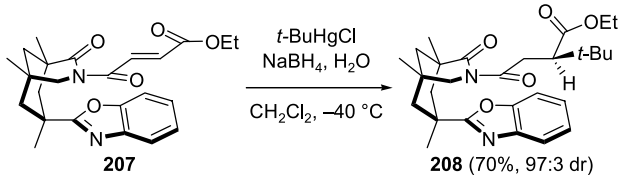
Scheme 48.

By substituting allyltributyltin for *n*-Bu_3SnH, Nagano was able to synthesize esters containing an α-quaternary center in highly diastereoselective fashion (Scheme 49).[111] No reaction occurred in the absence of Lewis acid.



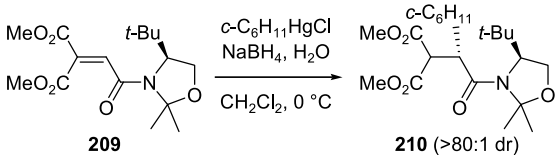
Scheme 49.

2.3.3. Auxiliary-controlled diastereoselective reactions. Curran and Rebek reported that imide **207** bearing a chiral auxiliary derived from Kemp's triacid undergoes *tert*-butyl radical addition with a high level of β-stereocontrol (Scheme 50).[112,113] However, additions of primary and secondary alkyl radicals occurred in slightly less selective fashion. The auxiliary could be cleaved with LiOOH and recovered.



Scheme 50.

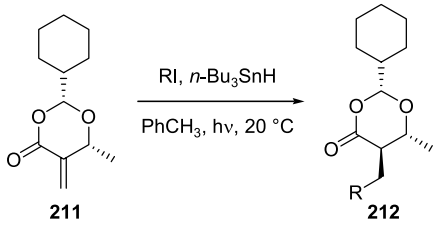
Porter introduced *N*-acyl oxazolidines as useful chiral auxiliaries for intermolecular RCA reactions (Scheme 51).[114,115] The auxiliary was cleaved in HCl/dioxane.



Scheme 51.

Giese found that intermolecular RCA to dioxanone **211** proceeded with excellent trans selectivity irrespective of radical size (Table 22).[116] In contrast, the related substrate containing a methyl ester and TBDPS group in place of the dioxanone exhibited cis selectivity that improved with increasing radical size. Giese subsequently employed a

Table 22.

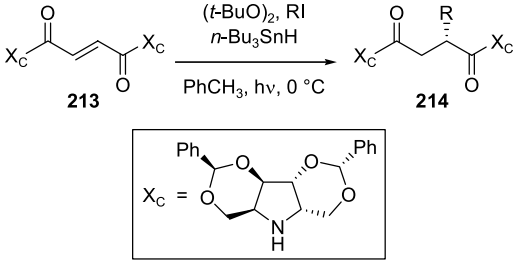


Entry	R	Yield (%)	*trans*:*cis*
1	*t*-Bu	97	>50:1
2	*c*-C_6H_{11}	71	>50:1
3	C_8H_{17}	49	>50:1

dioxanone auxiliary-controlled RCA in the total synthesis of tetrahydrolipostatin.[117]

Giese showed that additions of alkyl radicals to fumaramide **213** bearing C_2-symmetrical pyrrolidine chiral auxiliaries occurred with very high diastereoselectivity (Table 23).[118] Acidic hydrolysis of adducts **214** provided optically pure succinic acids.

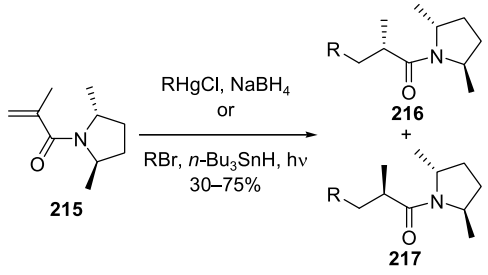
Table 23.



Entry	R	Yield (%)	dr
1	*t*-Bu	24	>200:1
2	*c*-C_6H_{11}	88	>200:1
3	C_6H_{13}	89	>200:1

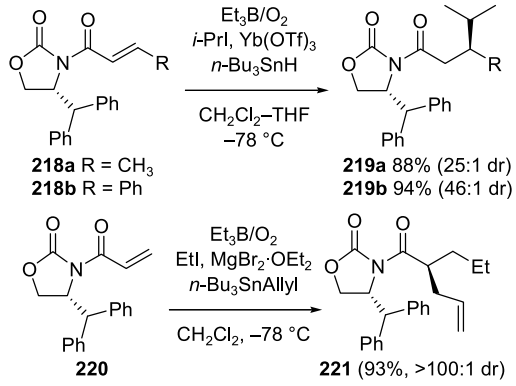
Giese also studied intermolecular RCAs to chiral acrylamide **215**, which involve a diastereoselective hydrogen atom abstraction step. The selectivity of this process was dependent on the alkyl radical size, with larger radicals giving higher dr's (Table 24).[119] These results were interpreted in terms of reaction via a twisted conformation in which the π system is not fully conjugated.

Table 24.



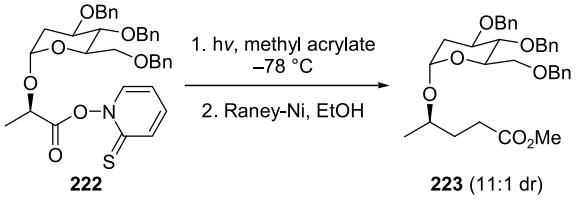
Entry	R	**216**:**217**
1	*t*-Bu	90:10
2	*c*-C_6H_{11}	80:20
3	C_6H_{13}	67:33

Sibi employed $Yb(OTf)_3$ as a Lewis acid to chelate the two carbonyls of chiral *N*-enoyloxazolidinone **218**, thereby controlling the rotamer population and achieving a highly diastereoselective RCA reaction (Scheme 52).[120,121] In addition to isopropyl radical, other alkyl radicals as well as acetyl and methoxymethyl radicals added to **218**, albeit with attenuated diastereoselectivity (7–16:1 for **218a**, 8–26:1 for **218b**). Similar results were obtained from $MgBr_2 \cdot OEt_2$-mediated RCA–allylations of *N*-propenoyloxazolidinone **220**.[122]



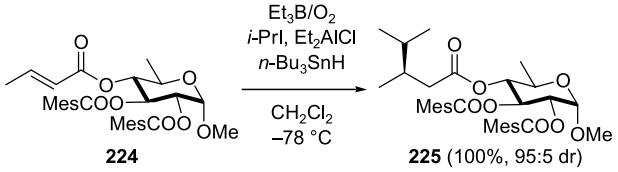
Scheme 52.

Garner demonstrated that the benzylated 2-deoxy-α-glucosyl moiety functions as an effective chiral auxiliary for hydroxyalkyl radicals in additions to methyl acrylate (Scheme 53).[123,124] Other carbohydrate-derived or THP-based chiral auxiliaries were also useful in this reaction.



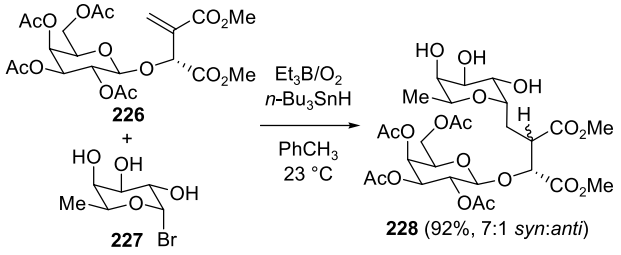
Scheme 53.

Tadano found that crotonate **224** bearing a 6-deoxyglucose-derived auxiliary was an effective acceptor in Lewis acid promoted RCA reactions (Scheme 54).[125] An excess of Et_2AlCl (4 equiv) was necessary for optimal results, presumably due to the abundance of Lewis basic functionality present in **224**.



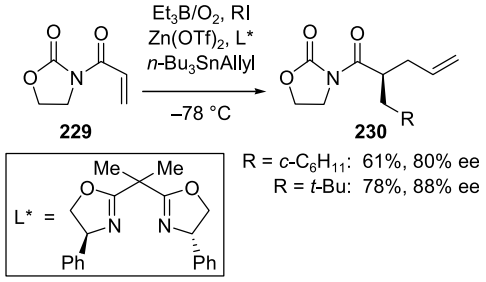
Scheme 54.

Guindon reported that the radical derived from fucosyl bromide **227** added to β-alkoxytaconate **226** via an α-selective *C*-glycosylation followed by a stereoselective hydrogen atom transfer, delivering sLe^X mimic **228** with good *syn*-selectivity (Scheme 55).[126] This process is noteworthy because it controls the formation of two noncontiguous stereocenters.



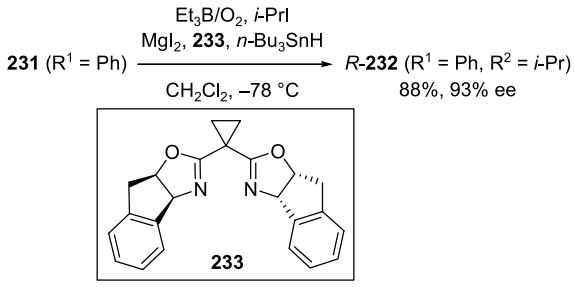
Scheme 55.

2.3.4. Enantioselective reactions. Porter discovered that a bisoxazoline ligand in combination with $Zn(OTf)_2$ could function as a chiral Lewis acid and promote enantioselective RCA–allylations of imide **229** (Scheme 56).[127] In this study, stoichiometric quantities of the chiral Lewis acid were employed. The use of primary alkyl radicals led to lower ee's.[128]



Scheme 56.

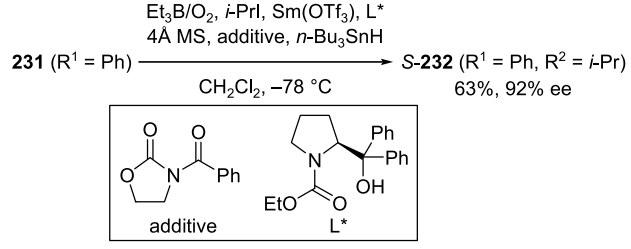
Sibi and Porter found that chiral Lewis acids containing bisoxazoline ligands are able to mediate enantioselective RCAs to acceptor **231** in which a β-stereocenter is created in the addition step (Table 25).[129] Curiously, switching the ligand substituent from alkyl to phenyl resulted in a reversal of enantioselectivity (compare entry 2 with entry 3). Further investigations by Sibi revealed that aminoindanol-derived



Scheme 57.

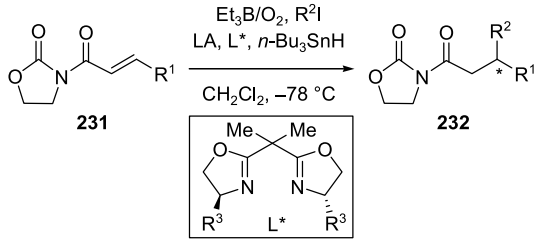
bisoxazoline **233** is the optimal chiral ligand for this process (Scheme 57).[130] Additionally, no drop in yield or ee was observed when substoichiometric quantities of this chiral Lewis acid were used in room temperature reactions. Recently, Sibi established that complexes of metal triflimides with **233** are excellent chiral Lewis acids for this RCA.[131] The triflimide counterion is believed to impart stability, solubility, and higher reactivity to the Lewis acid.

Sibi also introduced a lanthanide triflate–prolinol chiral Lewis acid as a suitable catalyst for this intermolecular RCA reaction (Scheme 58).[132] Several achiral additives were surveyed, and a combination of 4 Å MS with *N*-benzoyl oxazolidinone performed the best. Presumably, these additives coordinate to the metal and affect the geometry of the complex. Lanthanide triflates are useful due to their greater stability to air and moisture relative to most Lewis acids. However, they were less effective than chiral main group Lewis acids in the enantioselective RCA–allylation described by Porter[127] and depicted in Scheme 56.[133] The $Mg(ClO_4)_2$–DBFOX/Ph combination (Fig. 2) is another chiral Lewis acid that has been investigated in RCAs to **231**.



Scheme 58.

Table 25.



Entry	R^1	R^2	R^3	LA	Yield (%)	ee (%)
1	Ph	*i*-Pr	*i*-Bu (*S*,*S*)	MgI_2	88	82 (*R*)
2	CH_3	*t*-Bu	Ph (*R*,*R*)	$Zn(OTf)_2$	90	82 (*R*)
3	CH_3	*t*-Bu	*t*-Bu (*S*,*S*)	$MgBr_2$	78	82 (*R*)

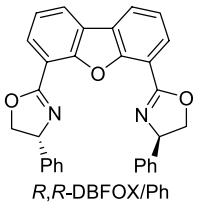
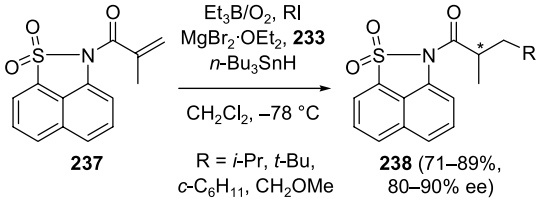


Figure 2.

Curran reported formation of *S*-**232** in 100% yield and 75% ee using stoichiometric amounts of this complex.[134]

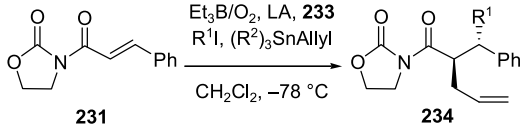
Sibi was able to exert high levels of control over both relative and absolute stereochemistry in the RCA–allylation of **231** promoted by substoichiometric quantities (0.3 equiv) of Lewis acids containing ligand **233** (Table 26).[135] Interestingly, Mg and Cu Lewis acids complexed to the same chiral ligand provided enantiomeric products. Alkyl radicals other than isopropyl and *tert*-butyl could also be employed, albeit with attenuated stereoselectivity.

Sibi has actively investigated the use of achiral templates other than oxazolidinones in enantioselective intermolecular RCAs. A 3,5-dimethylpyrazole template gave inferior ee's relative to those obtained from oxazolidinone-containing substrates.[137] However, in RCAs to methacrylates, which feature an enantioselective hydrogen atom transfer step, Sibi determined that the 1,8-naphthosultam template was optimal (Scheme 59).[138] A catalytic amount of the chiral Lewis acid was sufficient to promote this transformation.



Scheme 59.

Table 26.

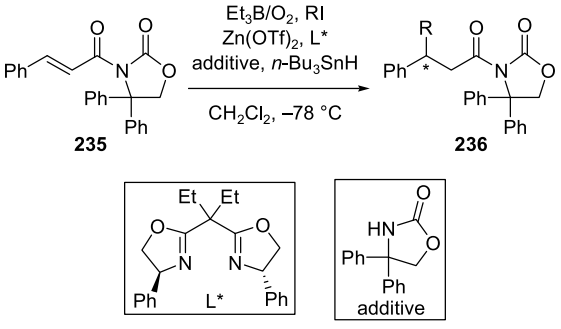


Entry	R^1	R^2	LA	Yield (%)	*anti*:*syn*	ee (%)
1	*i*-Pr	*n*-Bu	MgI_2	93	37:1	93
2	*t*-Bu	*n*-Bu	MgI_2	84	99:1	97
3	*i*-Pr	Ph	$Cu(OTf)_2$	93	30:1	−79
4	*t*-Bu	Ph	$Cu(OTf)_2$	90	99:1	−96

Murakata and Hoshino reported that a catalytic amount (0.25 equiv) of a 1:1:1 complex of $Zn(OTf)_2$, a chiral bisoxazoline ligand, and an achiral oxazolidinone mediates enantioselective RCAs to *N*-cinnamoyloxazolidinone **235** (Table 27).[136] The achiral additive was essential to achieve high ee's; the authors speculate that its role involves displacing a triflate counterion and coordinating to the metal. Significantly, good ee's were obtained in ethyl radical additions to **235**.

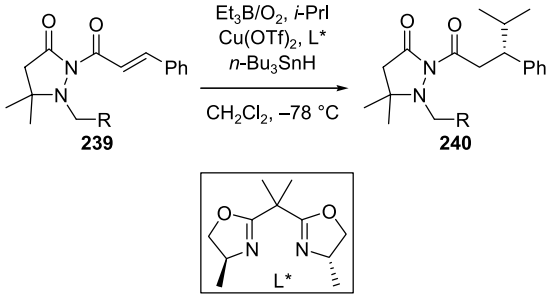
Sibi studied the effect of different *N*-substituents on the ee's of RCAs to cinnamoyl pyrazolidinones **239** (Table 28).[139] The ee's of adduct **240** increased with the size of the fluxional group, demonstrating that the chiral relay principle applies to RCA reactions. It is noteworthy that high ee's can be obtained using a chiral bisoxazoline ligand that possesses very modest steric bias. Moreover, the sense of enantioselectivity was reversed upon switching from $Cu(OTf)_2$ to MgI_2. The authors attribute this phenomenon to the different

Table 27.



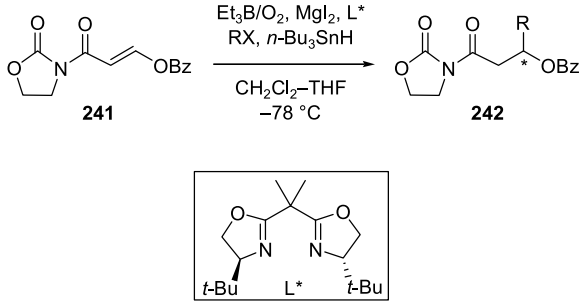
Entry	R	Yield (%)	ee (%)
1	*i*-Pr	92	80
2	*t*-Bu	72	83
3	*c*-C_6H_{11}	86	84
4	Et	91	72

Table 28.



Entry	R	Yield (%)	ee (%)
1	*n*-Pr	95	52
2	*i*-Pr	95	58
3	Ph	92	82
4	1-Naphthyl	91	90

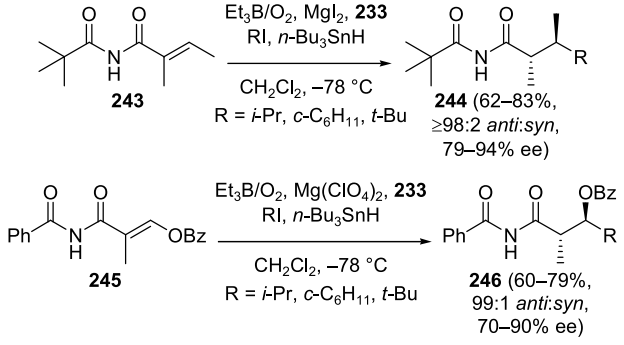
Table 29.



Entry	RX	Yield (%)	ee (%)
1	EtI	90	50
2	CH_3OCH_2Br	70	80
3	*i*-PrI	90	93(*R*)
4	*c*-$C_6H_{11}I$	70	84
5	*t*-BuI	91	89(*R*)

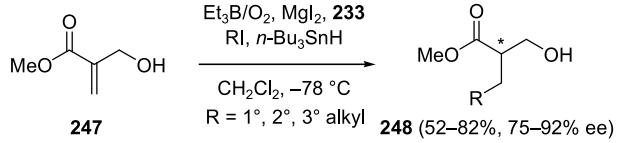
coordination geometries (square planar for Cu vs tetrahedral for Mg) of the two metals.

Sibi has used enantioselective intermolecular RCA reactions as a means of preparing aldol-type products under mild conditions. Alkyl radical additions to β-acyloxy-enoate **241** in the presence of a stoichiometric amount of chiral Lewis acid generated acetate aldol products **242** in moderate to good ee's (Table 29).[140] When additions to α,β-disubstituted imide **243** revealed the ability to control the absolute and relative stereochemistry of both new stereo-centers, Sibi examined RCAs to β-acyloxy-substituted imide **245** mediated by a catalytic amount of the Mg/**233** chiral Lewis acid (Scheme 60).[141] Excellent dr's and good ee's were obtained, and the products **246** are analogous to those produced by *anti*-selective propionate aldol reactions.



Scheme 60.

Recently, Sibi has performed RCA-enantioselective hydrogen atom transfers with enoate **247** (Scheme 61).[142] The products **248** can be considered formaldehyde aldol adducts. Surprisingly, a reversal of enantioselectivity occurred when the methyl ester was replaced with a *tert*-butyl ester.



Scheme 61.

3. Additions to vinyl sulfoxides and sulfones

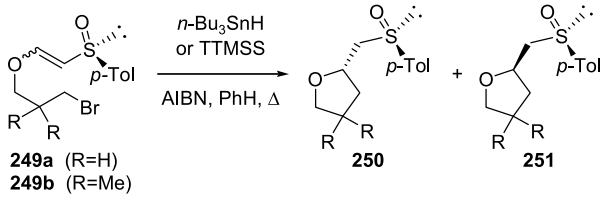
Vinyl sulfoxides and sulfones can serve as acceptors in RCA reactions with a variety of nucleophilic radicals. Optically active sulfoxides are often employed as chiral auxiliaries for controlling stereochemistry at both the α- and β-positions. These chiral sulfur-based auxiliaries are very useful because of their easy introduction into substrates and the many options available for their further functionalization. Lewis acids are known to coordinate with the oxygens attached to the sulfur atom thereby activating the alkene for addition of a nucleophilic radical. Additionally, Lewis acids with appropriate chiral ligands can exert high levels of stereocontrol. In this section, RCA reactions of both vinyl sulfoxides and sulfones will be presented, with an emphasis on stereoselective processes.

3.1. Intramolecular radical conjugate additions to vinyl sulfoxides and sulfones

Vinyl sulfoxides and sulfones undergo facile intramolecular RCAs with alkyl, acyl, and vinyl radicals. In accord with the Beckwith model, many of these cyclizations afford 1,3-cis-substituted products.[143] This mode of cyclization is often used to construct tetrahydrofuran, tetrahydropyran, and oxepane frameworks.

Malacria developed 5-*exo-trig* cyclizations of optically active β-alkoxy vinyl sulfoxides **249** for the construction of tetrahydrofurans (Table 30).[144] Cyclizations of *E*-**249** or *Z*-**249** using *n*-Bu_3SnH or TTMSS resulted in formation of optically active tetrahydrofurans **250** or **251**, respectively, with good dr's obtained from *Z*-**249**. Additionally, vinyl radicals generated by addition of a stannyl radical to an alkyne functioned well in this reaction.

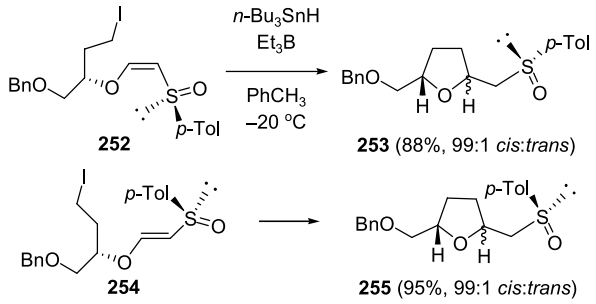
Table 30.



Entry	Substrate	Yield (%) with TTMSS	Yield (%) with *n*-Bu_3SnH	**250**:**251**
1	*E*-**249a**	89	81	70:30
2	*Z*-**249a**	94	87	12:88
3	*E*-**249b**	93	80	82:18
4	*Z*-**249b**	90	79	2:98

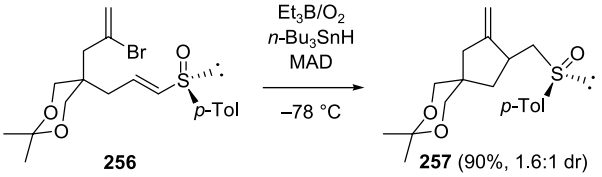
Lee found that β-alkoxyvinyl sulfoxides **252** and **254** prepared from secondary alcohols undergo 5-*exo-trig* cyclizations affording 2,5-disubstituted tetrahydrofurans **253** and **255** with excellent cis selectivity (Scheme 62).[145] The mismatched isomers *E*-**252** and *Z*-**254** provided *cis*-**253** and *cis*-**255** with slightly lower (94:6, 92:8) dr's. The methylenesulfoxide moieties could be transformed into aldehydes via the Pummerer rearrangement.

Malacria investigated the construction of carbocycles via 5-*exo-trig* vinyl radical cyclization of vinyl sulfoxide **256**



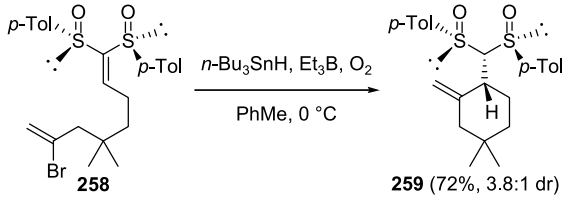
Scheme 62.

(Scheme 63).[146,147] Use of the bulky Lewis acid methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) improved the yield of **257** but had little effect on the diastereoselectivity. The low dr was attributed to lack of control over the vinyl sulfoxide conformation (*s*-cis vs *s*-trans).



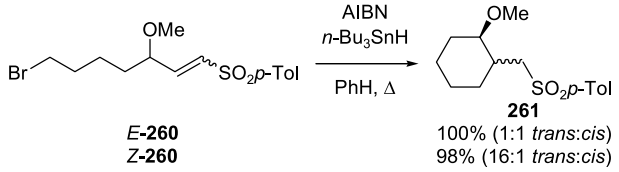
Scheme 63.

In an attempt to increase the diastereoselectivity of carbocycle formation by preventing C–S bond rotation, Malacria examined the intramolecular RCA of 1,1-bis-sulfoxide **258** (Scheme 64).[148] Although the dr was slightly higher than that of the previous reaction, only six-membered rings could be constructed by this method. Efforts to further improve the diastereoselectivity by employing bidentate Lewis acids resulted in low yields.

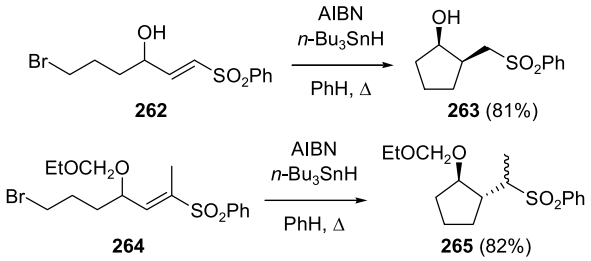


Scheme 64.

Ogura reported that 6-*exo* radical cyclizations of γ-alkoxy α,β-unsaturated sulfones **260** proceed in high yield (Scheme 65).[149] Although no diastereoselectivity was observed with *E*-**260**, *Z*-**260** delivered cyclohexane **261** with a strong preference for the trans isomer.

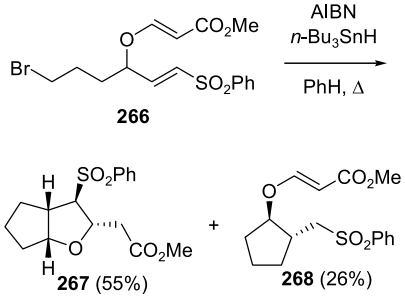


Scheme 65.



Scheme 66.

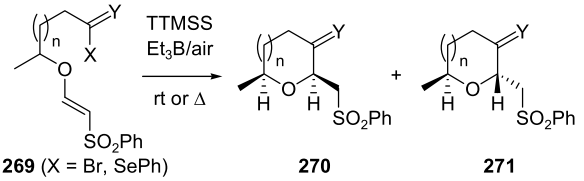
Carretero discovered that γ-oxygenated α,β-unsaturated sulfones undergo highly stereoselective 5-*exo-trig* intramolecular RCAs (Scheme 66).[150,151] Alcohol **262** yielded *cis*-cyclopentane **263** exclusively; the cis selectivity was eroded with substrates containing acetals or silyl ethers. In contrast, α-methylated sulfone **264** afforded *trans*-cyclopentane **265**, with the stereoselectivity attributed to avoidance of 1,3-allylic strain in the transition state. The α-sulfonyl radical resulting from cyclization could be intercepted by a tethered β-alkoxyacrylate moiety, provided a *cis*-cyclopentane was formed in the initial step (Scheme 67).



Scheme 67.

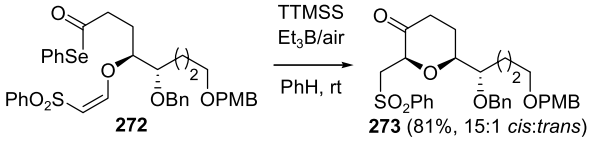
Evans synthesized five-, six-, and seven-membered cyclic ethers by means of intramolecular RCAs of β-alkoxyvinyl sulfones **269** containing alkyl, acyl, or vinyl radical precursors (Table 31).[152,153] *cis*-ethers **270** were the major products as predicted by the Beckwith model. The lowest dr was observed in 6-*exo-trig* acyl radical cyclization (entry 5). Evans hypothesized that switching to a *Z*-vinyl sulfone would improve the stereoselectivity by destabilizing the

Table 31.



Entry	*n*	Y	**270**:**271**	Yield (%)
1	0	H_2	≥19:1	99
2	0	O	17:1	87
3	1	H_2	≥19:1	90
4	1	CH_2	≥19:1	95
5	1	O	6:1	90
6	2	H_2	≥19:1	34
7	2	O	17:1	63

transition state leading to the trans product. This reasoning proved correct, as 6-*exo-trig* cyclization of **272** afforded *cis*-tetrahydropyran **273**, a potential intermediate in the total synthesis of mucocin, in good yield and dr (Scheme 68).[154]



272 **273** (81%, 15:1 *cis*:*trans*)

Scheme 68.

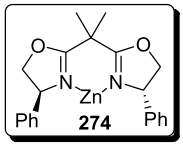
Toru reported that benzimidazolyl ω-iodoalkenyl sulfones **275–277** undergo enantioselective intramolecular RCA reactions upon treatment with chiral Lewis acid **274**, delivering tetrahydropyran **278** and carbocycles **279–280** in good yield and moderate ee (Table 32).[155] In the proposed transition state, the pro-*R* oxygen of the sulfonyl group and the sp^2-nitrogen of the benzimidazolyl moiety coordinate with the tetrahedral zinc atom, avoiding the steric repulsion that would occur if the pro-*S* oxygen were coordinated and facilitating attack of the radical on the *Si*-face of the double bond.

3.2. Intermolecular radical conjugate additions to vinyl sulfoxides and sulfones

Vinyl sulfoxides and sulfones undergo intermolecular conjugate additions with a variety of alkyl radicals. Lewis acids can play an important role in controlling the stereochemistry of the process. The presence of an additional Lewis base such as a hydroxyl, alkoxy, or keto group on the substrate is often essential for stereocontrol via chelation to a Lewis acid or hydrogen bonding.

Toru investigated diastereoselective RCAs of chiral

Table 32.



274

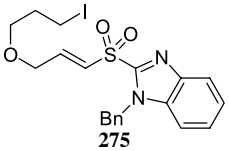
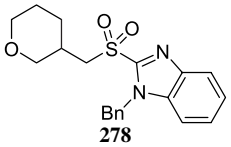
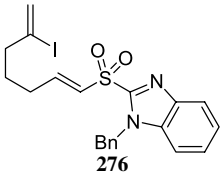
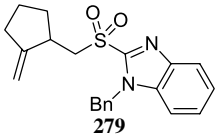
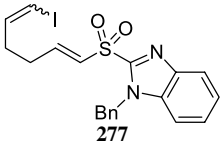
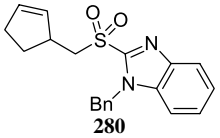
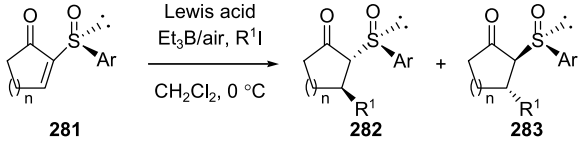
Entry	Vinyl sulfone	H atom donor	Product	Yield (%)	ee (%)
1	 **275**	*n*-Bu_3SnH	 **278**	97	62
2		TTMSS		62	59
3	 **276**	*n*-Bu_3SnH	 **279**	67	60
4		TTMSS		66	66
5	 **277**	*n*-Bu_3SnH	 **280**	93	60
6		TTMSS		96	50

Table 33.

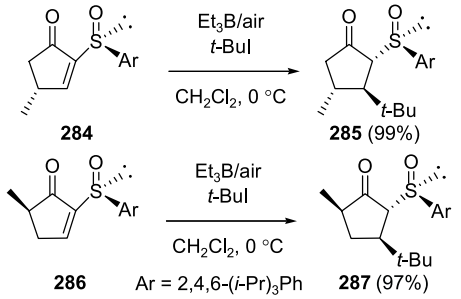


281 **282** **283**

Entry	*n*	Lewis acid	R^1	Ar	Yield (%)	**282**:**283**
1	1	None	*i*-Pr	2,4,6-(*i*-$Pr)_3$Ph	99	98:2
2	1	None	*t*-Bu	2,4,6-Me_3Ph	99	98:2
3	1	$EtAlCl_2$	*t*-Bu	2,4,6-Me_3Ph	99	2:98
4	2	None	*i*-Pr	2,4,6-(*i*-$Pr)_3$Ph	93	98:2

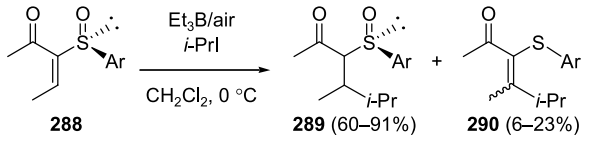
α-sulfoxycyclopentenones and cyclohexenones **281** (Table 33).[156,157] The bulky 2,4,6-triisopropylphenyl-substituted sulfoxide provided **282** in excellent dr without the aid of a Lewis acid (entries 1 and 4). However, the less hindered 2,4,6-trimethylphenyl sulfoxide delivered **282** as the major product in the absence of a Lewis acid and **283** as the major product in the presence of $EtAlCl_2$ (entries 2 and 3). Apparently, the reactions without Lewis acids proceed via a conformation in which the carbonyl and sulfoxide moieties are antiperiplanar. With the smaller sulfoxide substituent, addition of a Lewis acid causes formation of a chelated intermediate, thereby reversing the aryl group orientation and the stereoselectivity.

Toru then studied the effect of substitution at the 4- and 5-positions on the stereoselectivity of RCAs to α-sulfoxycyclopentenones. Compounds **284** and **286** undergo facile addition of *tert*-butyl radical to form **285** and **287**, respectively, as single diastereomers (Scheme 69), whereas the diastereomers of **284** and **286** are inert to these conditions.[158] These results are consistent with the reaction proceeding via a conformation in which the carbonyl and sulfoxide groups are antiperiplanar and the triisopropylphenyl moiety shields the double bond's bottom face.



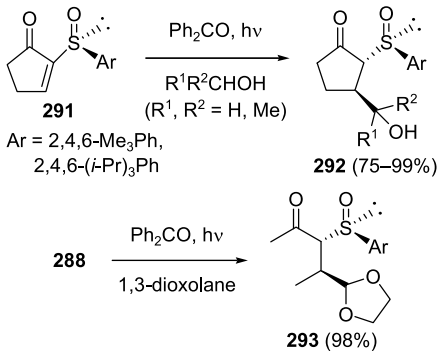
Scheme 69.

Toru attempted to extend this methodology to encompass RCAs of acyclic α-sulfoxyenones. However, isopropyl radical additions to **288** (Ar=2,4,6-triisopropylphenyl) resulted in formation of **289** as a mixture of all possible diastereomers (Scheme 70).[159,160] Additionally, varying amounts of enone **290**, the product of a Pummerer-type reaction of a boron enolate intermediate, were obtained.



Scheme 70.

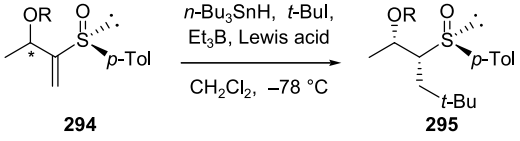
Toru found that chiral α-sulfoxycyclopentenones **291** couple with α-hydroxy alkyl radicals generated by irradiation of MeOH, EtOH, or *i*-PrOH in the presence of benzophenone (Scheme 71).[161] Cyclopentanones **292** were obtained as single diastereomers. Moreover, the formyl radical equivalent derived from photolysis of 1,3-dioxolane added to **291** stereoselectively. This radical also reacted with **288**, providing **293** without the byproducts observed in reactions of **288** with simple alkyl radicals.



Scheme 71.

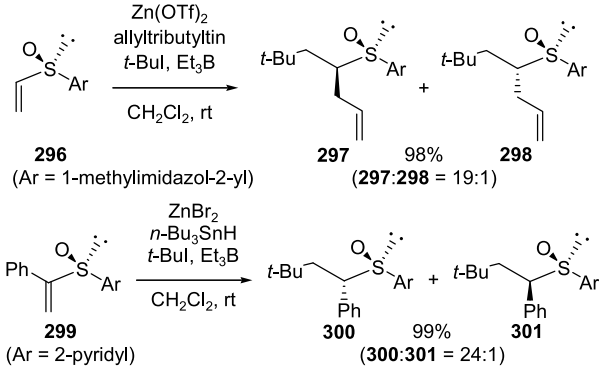
Toru demonstrated that the stereochemistry of intermolecular RCAs to α-(1-hydroxyethyl)vinyl sulfoxides **294** could be controlled by intramolecular hydrogen bonding or Lewis acid chelation (Table 34).[162,163] Adducts **295** were obtained exclusively as the *syn* isomers. Reactions employing *R*-**294** (entry 3) or silylated *S*-**294** (entry 4) led to recovery of starting material. The authors propose that activation by either hydrogen bonding or Lewis acid chelation is necessary for RCAs of **294** to occur. With *R*-**294**, the hydrogen-bonded conformers are destabilized due to steric strain; therefore, RCA does not take place. Alkyl radicals other than *tert*-butyl also added to *S*-**294**; however, the dr decreased with the size of the radicals.

Table 34.



Entry	Substrate	R	Lewis acid	Yield (%)
1	*S*-**294**	H	None	89
2	*S*-**294**	H	$EtAlCl_2$	75
3	*R*-**294**	H	None	No reaction
4	*S*-**294**	$SiPh_3$	None	No reaction

In order to extend the above reaction to include unsubstituted vinyl sulfoxides as substrates, Toru designed vinyl sulfoxide **296** containing an electron-poor heteroaryl group capable of chelating a bidentate Lewis acid (Scheme 72).[164] As predicted, **296** undergoes an RCA–allylation

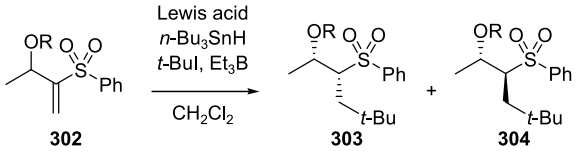


Scheme 72.

process in the presence of $Zn(OTf)_2$ in excellent yield and dr. Additionally, α-phenyl-substituted 2-pyridyl vinyl sulfoxide **299** was a good substrate for $ZnBr_2$-promoted RCAs, affording **300** selectively. In this case, alkyl radicals other than *tert*-butyl added to **299** with similar dr's but diminished yields (42–72%).

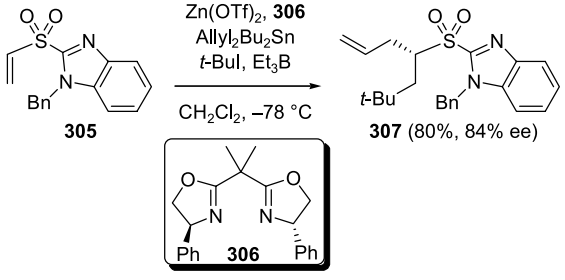
The RCAs of α-(1-hydroxyethyl)vinyl sulfoxides **294** described above (Table 34) led Toru to believe that intramolecular hydrogen bonding between the hydroxyl group and one of the diastereotopic sulfone oxygens in **302** would facilitate a stereoselective RCA (Table 35).[165] This hypothesis was correct, as additions of *tert*-butyl radical to **302** occurred with an excellent dr (entry 1). Use of a chelating Lewis acid also resulted in high *syn* selectivity (entry 2), but the dr was eroded when a bulky monodentate Lewis acid was used (entry 3) or when the hydroxyl group was protected as a silyl ether (entry 4). Other alkyl radicals also added to **302**, but lower dr's (3.2–1.5:1) were observed.

Table 35.



Entry	R	Lewis acid	Yield (%)	**303**:**304**
1	H	None	91	98:2
2	H	$EtAlCl_2$	64	99:1
3	H	MAD	93	88:12
4	$SiPh_3$	None	99	67:33

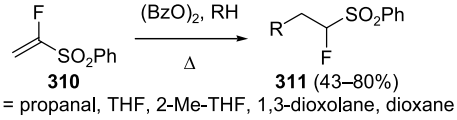
As an extension of the above work, Toru developed the enantioselective RCA–allylation of vinyl sulfone **305** in which the stereochemistry is controlled by selective coordination of a chiral Lewis acid to one of the two enantiotopic sulfonyl oxygens (Scheme 73).[166] The chiral



Scheme 73.

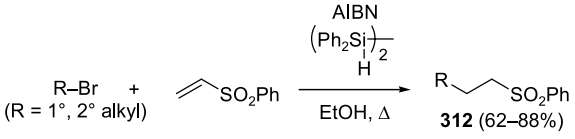
Lewis acid derived from $Zn(OTf)_2$ and bisoxazoline **306** afforded the highest ee's, and use of diallyldibutyltin was necessary to achieve good yields of **307**. This chiral Lewis acid has also been used in enantioselective RCAs to 1-substituted vinyl sulfones **308** (Table 36).[167]

McCarthy showed that phenyl (1-fluorovinyl)sulfone (**310**) could serve as an acceptor in RCAs with several acyl and α-oxy radicals (Scheme 74).[168] Jeong later demonstrated that these types of radicals also add efficiently to α-substituted β,β-difluorovinyl sulfones.[169]



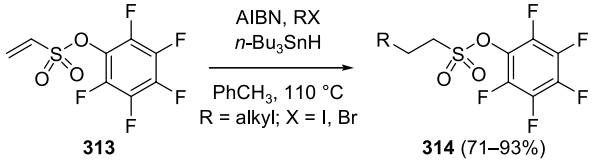
Scheme 74.

Togo and Yokoyama introduced 1,1,2,2-tetraphenyldisilane as a substitute for n-Bu_3SnH in RCAs to phenyl vinyl sulfone (Scheme 75).[170,171] This reagent is crystalline and air-stable, whereas the more commonly used TTMSS is an air-sensitive oil.



Scheme 75.

As part of a route to sulfonamides, Caddick employed pentafluorophenyl vinylsulfonate (**313**) as an acceptor in RCA reactions (Scheme 76).[172] A variety of alkyl radicals were useful in this protocol. The pentafluorophenoxy moiety could be displaced from adducts **314** by amines, generating the desired sulfonamides.

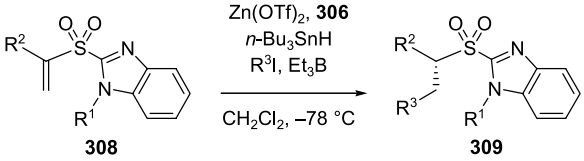


Scheme 76.

4. Radical conjugate additions mediated by SmI_2 or related reagents

Samarium(II) iodide was introduced as a reagent for organic synthesis by Kagan in 1977.[173] It functions as a

Table 36.



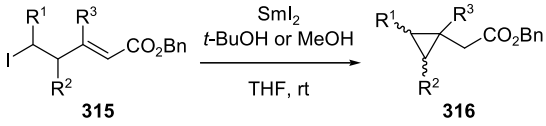
Entry	R^1	R^2	R^3	Yield (%)	ee (%)
1	$(3,5\text{-}Me_2Ph)CH_2$	Me	*t*-Bu	97	82
2	Me	Ph	Et	99	91

single-electron-transfer reagent due to the preference for the more stable Sm(III) oxidation state. Accordingly, it has been used extensively to facilitate radical reactions. SmI_2 reacts readily with alkyl halides, aldehydes, and ketones to afford alkyl radicals in the first case and samarium(III) ketyl radical anions in the latter two instances. A subsequent single-electron transfer from a second equivalent of SmI_2 can reduce radicals to anions; consequently, radical and anionic mechanisms have been proposed for SmI_2-mediated transformations. The ability of a reaction to proceed in the presence of a proton source such as water or an alcohol is usually taken as evidence that a radical process is operative. The use of SmI_2 in organic synthesis has been extensively reviewed;[174] this section focuses on processes employing SmI_2 that are considered to be RCA reactions. Since the bulk of these examples involve ketyl intermediates, RCAs utilizing ketyls generated by other reagents are also presented here.

4.1. Intramolecular conjugate additions of alkyl radicals generated by SmI_2

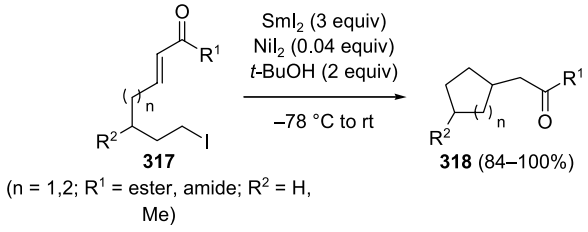
3-*exo-trig* Radical cyclizations are rare due to the fact that the resultant strained cyclopropylcarbinyl radicals are typically less stable than the initially formed acyclic homoallylic radicals.[175] However, Guibé demonstrated that treatment of δ-iodo-α,β-unsaturated esters **315** with SmI_2 in the presence of *t*-BuOH or MeOH as a proton source afforded cyclopropanes **316** in good yields (Table 37), albeit with low diastereoselectivity (1–2:1 dr).[176] Presumably, one-electron reduction of the intermediate cyclopropylcarbinyl radical by SmI_2 to form a Sm(III) enolate competes successfully with reversion of this species to the homoallylic radical; protonation of the enolate then affords **316**. However, subsequent mechanistic investigations by Guibé and Lesot revealed that homochiral substrates **315** underwent extensive racemization at the γ-position. They attributed this to reversible ring opening of the cyclopropylcarbinyl radical intermediate being faster than its reduction by SmI_2.[177]

Table 37.



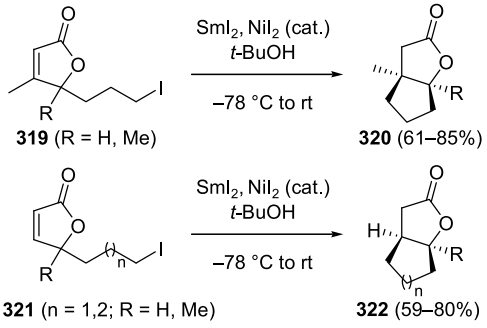
Entry	R^1	R^2	R^3	Yield (%)
1	H	H	H	99
2	Me	H	H	87
3	H	Me	H	82
4	H	*O*-Allyl	H	87
5	Me	Me	H	81
6	H	H	Me	80

Molander reported 5- and 6-*exo-trig* cyclizations of alkyl iodides onto α,β-unsaturated esters and amides mediated by SmI_2 in conjunction with catalytic NiI_2 (Scheme 77).[178] The latter species presumably modulates the reduction potential of SmI_2, preventing conjugate reduction of the substrates. High diastereoselectivity was typically observed, and bridged and fused bicyclic ring systems could be formed by this method.



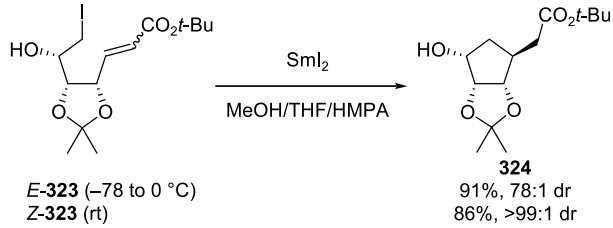
Scheme 77.

Molander later extended the utility of this reaction to include α,β-unsaturated lactones as substrates (Scheme 78).[179] Five-membered rings could be formed easily, whereas the construction of six-membered rings was successful only on substrates without alkyl substitution at the lactone β-position.



Scheme 78.

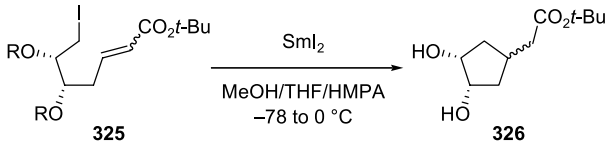
Bennett developed 5-*exo-trig* cyclizations of carbohydrate-derived ω-iodo-α,β-unsaturated ester **323** mediated by SmI_2 and HMPA, affording cylopentane **324** in good yield and dr (Scheme 79).[180,181] HMPA both increases the efficiency and reverses the diastereoselectivity of the RCA, as omission of this cosolvent in the cyclization of *E*-**323** provided a low yield of the cis isomer of **324** as the major product. The authors propose that HMPA increases the bulk around the samarium atom, thereby leading to greater stereoselectivity. Additionally, the *tert*-butyl ester was essential, as use of the corresponding ethyl ester was complicated by competitive reduction of the enoate.



Scheme 79.

Bennett then examined intramolecular RCAs of enoates **325** derived from 2-deoxy-D-ribose (Table 38).[182,183] *E*-enoates underwent cyclization with high cis selectivity, with the dimethyl-ketal-containing substrate as the sole exception (entry 3). In contrast, this substrate as well as *Z*-enoates exhibited a modest preference for *trans*-**326**. The authors attribute the high cis selectivities to the ability of the relevant substrates to react via a chelated transition state.

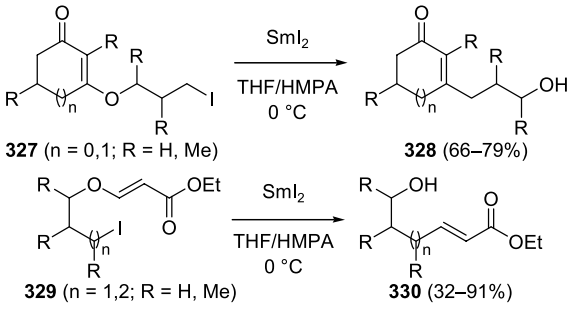
Table 38.



Entry	R	*E*/*Z*	Yield (%)	*cis*:*trans*
1	H	*E*	93	21:1
2	H	*Z*	71	1:2.1
3	CMe_2	*E*	89	1:1.2
4	CMe_2	*Z*	51	1:1.9
5	Ac	*E*	92	16:1
6	5-H, 6-TBS	*E*	92	13:1

Cyclizations of *Z*-**323** and *E*-**325** can also be facilitated by Cp_2TiCl; however, the yields and dr's are poorer than those obtained with SmI_2.[184]

Kang demonstrated that 3-(3-iodopropoxy)-2-cycloalkenones **327** undergo a vinylogous intramolecular nucleophilic acyl substitution reaction when subjected to SmI_2 in the presence of HMPA (Scheme 80).[185] This process could also be applied to β-alkoxyacrylates **329**.[186]

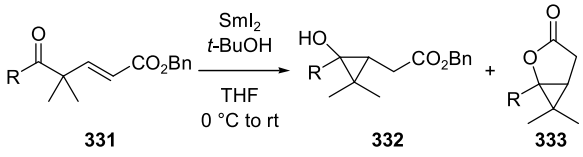


Scheme 80.

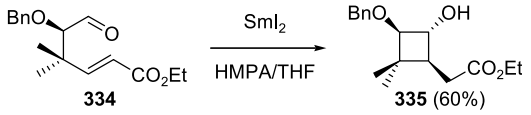
4.2. Intramolecular conjugate additions of ketyls generated by SmI_2

Guibé found that δ-oxo-α,β-unsaturated esters **331** participate in SmI_2-mediated 3-*exo-trig* cyclizations affording *trans*-cyclopropanols **332** and/or lactones **333**, the latter derived from the cis isomers (Table 39).[187] The authors propose that aryl and heteroaryl ketones (entries 1–4) react via initial formation of a ketyl radical species, which undergoes cyclization followed by reduction of the resultant cyclopropylcarbinyl radical and protonation. Stereoelectronic effects are invoked to explain the selectivity in favor of **332** with the exception of the naphthyl ketone (entry 4), which affords **333** as the major product due to sterics. The greater amounts of **333** derived from cyclizations of alkyl ketones and aldehydes (entries 5–8) can be explained by invoking an alternative mechanism involving initial reduction of the enoate.

Table 39.



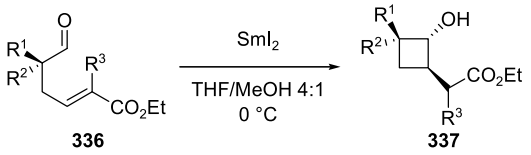
Entry	R	**332** (%)	**333** (%)
1	Ph	85	—
2	2-Furyl	78	14
3	2-Thienyl	60	10
4	1-Naphthyl	25	48
5	CH_3	58	22
6	*i*-Pr	58	32
7	*c*-Pr	—	92
8	H	37	30



Scheme 81.

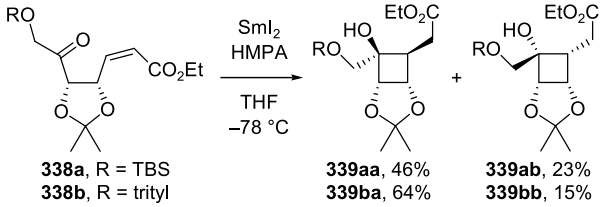
Ketyls generated by SmI_2 can also participate in RCAs to form cyclobutanes. Weinges reported that cyclization of enantiomerically pure **334** affords cyclobutane **335** as a single stereoisomer (Scheme 81).[188] Procter subsequently established that similar 4-*exo-trig* cyclizations occurred without HMPA, provided MeOH was used as the cosolvent (Table 40).[189,190] The authors propose that MeOH increases the reduction potential of SmI_2 in addition to serving as a proton source. A quaternary carbon was required in the tether between the aldehyde and enoate, and cyclobutanes could also be constructed from the vinyl sulfones analogous to **336**, albeit in reduced yield.

Table 40.



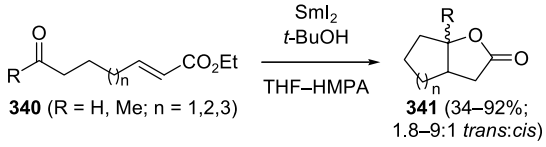
Entry	R^1	R^2	R^3	Yield (%)
1	Me	Me	H	65
2	Me	Me	Me	66 (4:1 dr)
3	OBn	Me	H	57 (4:1 dr)
4	Allyl	Allyl	H	80

Williams showed that carbohydrate-derived substrates **338** form cyclobutanes **339** in moderate dr when treated with SmI_2 (Scheme 82).[191] A fully substituted carbon in the tether is not required; instead, the dimethyl ketal provides the rotational constraints necessary for 4-*exo-trig* cyclization to occur.



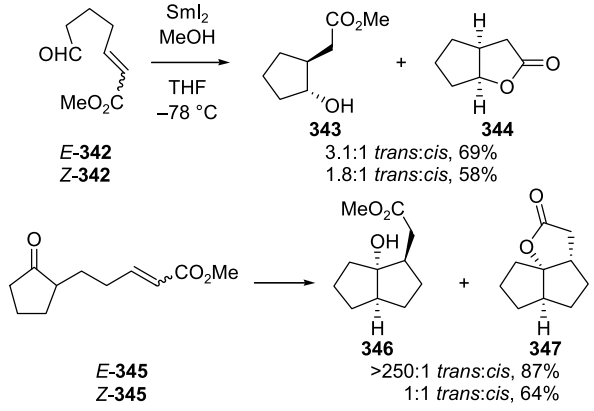
Scheme 82.

Fukuzawa found that bicyclic γ-lactones **341** containing a five-, six-, or seven-membered ring can be prepared by SmI_2-mediated ketyl–olefin cyclizations of enoates **340** (Scheme 83).[192] Both aldehydes and ketones could serve as the ketyl precursor. Yields and dr's varied widely with respect to the nature of the substrate.

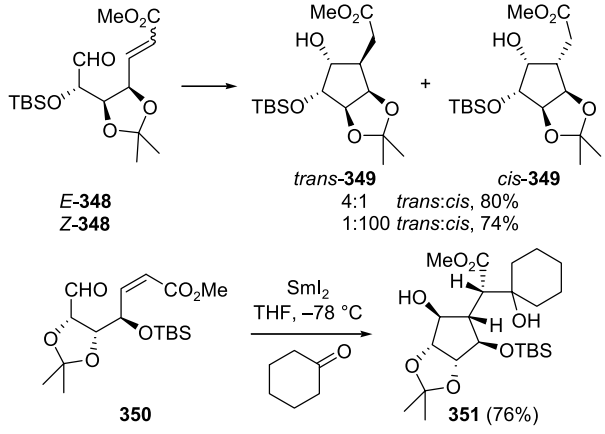


Scheme 83.

Enholm reported the synthesis of five-membered rings via the SmI_2-induced RCA of ketyls to α,β-unsaturated esters (Scheme 84).[193] The alkene geometry was key to the reaction diastereoselectivity, with *E*-isomers affording superior trans selectivity. Enholm extended this method to allow the use of highly functionalized carbohydrate derivatives **348** and **350** as substrates (Scheme 85).[194] In this case *Z*-enoates exhibited excellent selectivity for cis products. When the cyclization of **350** was carried out in the presence of a ketone or aldehyde instead of a proton source, an RCA/aldol sequence occurred, affording diol **351** in good yield and diastereoselectivity.[195] Interestingly, the intramolecular RCA step gave only the trans isomer.

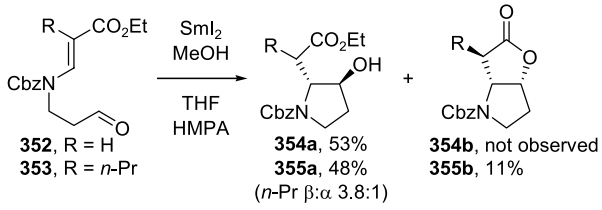


Scheme 84.



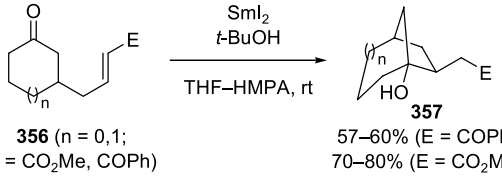
Scheme 85.

MacDonald discovered that β-aminoacrylates **352** and **353** underwent cyclization upon treatment with SmI_2 to form pyrrolidines **354** and **355** with good trans selectivity (Scheme 86).[196] This result can be explained by a minimization of electrostatic repulsions between the ketyl oxygen and the developing α-carbonyl radical in the transition state.



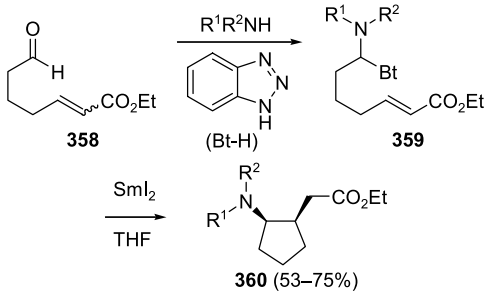
Scheme 86.

Hon converted cyclic ketones **356** with appended enoates or enones into bridgehead alcohols **357** via SmI_2-promoted RCAs (Scheme 87).[197] Enoates gave higher yields than enones.



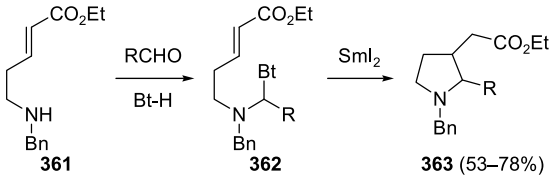
Scheme 87.

Aurrecoechea developed a synthesis of cyclopentylamines that capitalizes on the generation of iminium ions from the condensation of aldehydes and secondary amines in the presence of benzotriazole. This species is reduced by SmI_2 to give an α-amino radical, which then cyclizes onto an enoate (Scheme 88).[198,199] Semiempirical calculations attribute the cis selectivity to a stabilizing secondary orbital interaction between the aminoalkyl radical SOMO and the alkene LUMO. Attempts to extend this method to the preparation of cyclohexylamines were hampered by low dr's.



Scheme 88.

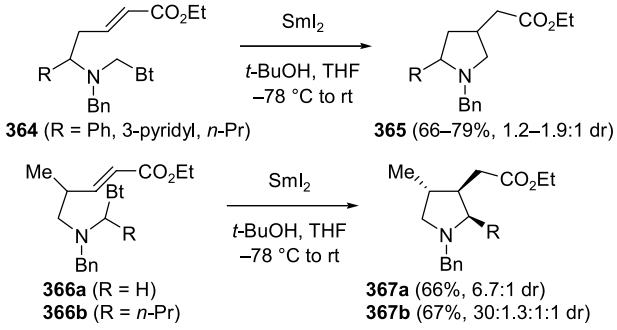
Aurrecoechea subsequently employed this process in the preparation of pyrrolidines **363** by tethering the amine rather than the aldehyde to the enoate (Scheme 89).[200,201] In this case, the aforementioned secondary orbital interaction cannot take place; accordingly, the cis selectivities are attenuated (2.5–10:1) when R is an alkyl group and the trans



Scheme 89.

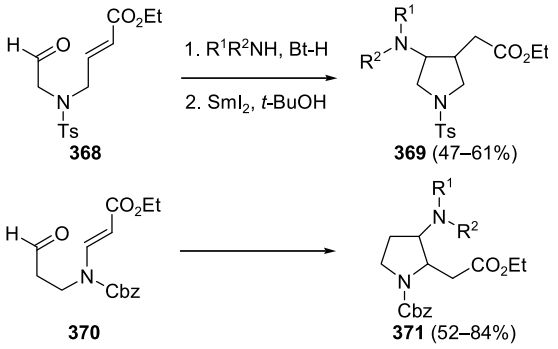
product predominates (5.2–10:1) when R is an aryl group. The trans selectivity with aryl substituents could be a consequence of the reversible nature of the cyclization giving rise to the thermodynamic products.

Aurrecoechea next undertook a study of the effect of substitution patterns on the diastereoselectivity of pyrrolidine formation. 2,4-Disubstituted pyrrolidines **365** were obtained with low dr, whereas 3,4- and 2,3,4-substituted pyrrolidines **367** could be prepared with useful levels of diastereoselectivity (Scheme 90).[202]



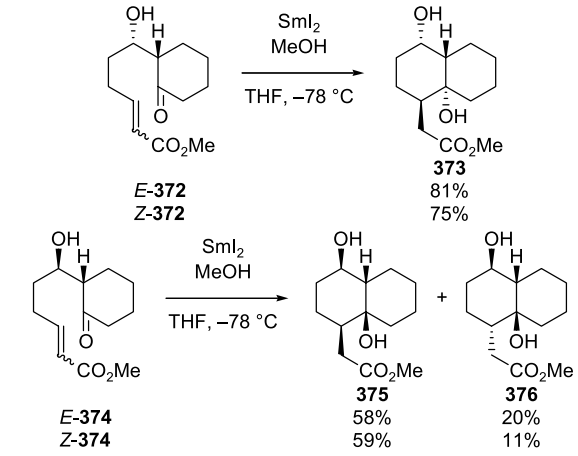
Scheme 90.

Aurrecoechea also demonstrated that 3-aminopyrrolidines **369** and **371** could be constructed via cyclization of the α-aminoalkyl radicals derived from the action of SmI_2 on iminium ions formed from aldehydes **368** and **370** and secondary amines (Scheme 91).[203] Unfortunately, these reactions exhibited low dr's (<2:1).



Scheme 91.

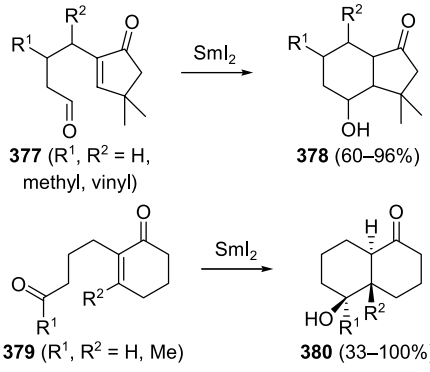
Matsuda and Shirahama examined the stereoselective formation of *trans*- and *cis*-decalins via SmI_2-promoted cyclizations of cyclohexanones **372** and **374** appended with enoates (Scheme 92).[204] *E*-**372** and *Z*-**372** delivered *trans*-decalin **373** exclusively, whereas their epimers *E*-**374** and *Z*-**374** afforded *cis*-decalins **375** and **376**. Chelation of the hydroxyl group and the ketyl by the Sm(III) cation both



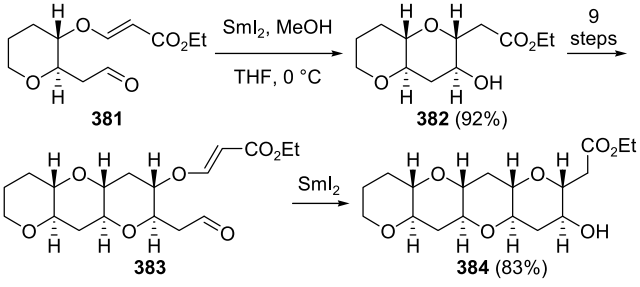
Scheme 92.

controls the stereochemistry and accelerates the reaction, as the TBS ethers of **372** and **374** were unreactive.

Tori prepared 3,3-dimethylhydrindanes **378** by means of the 6-*endo*-*trig* cyclization of enone aldehydes **377** (Scheme 93).[205] Three new stereocenters are formed in this reaction, and the product distribution varied with the nature of the substrates, the use of MeOH or HMPA, and the temperature. The stereochemical picture was clearer in the cyclizations of homologous substrates **379** to form perhydronaphthalenones **380**. The yields varied widely with respect to the additives used (MeOH, HMPA, NiI_2), but the isomer possessing trans ring fusion and a cis relationship between the C-4a and C-5 substituents predominated in most cases.[206]

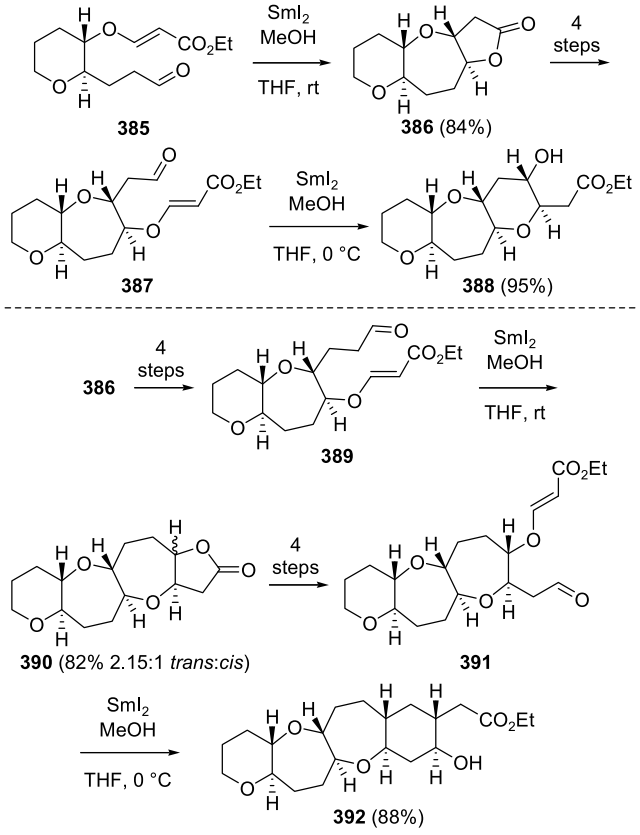


Scheme 93.



Scheme 94.

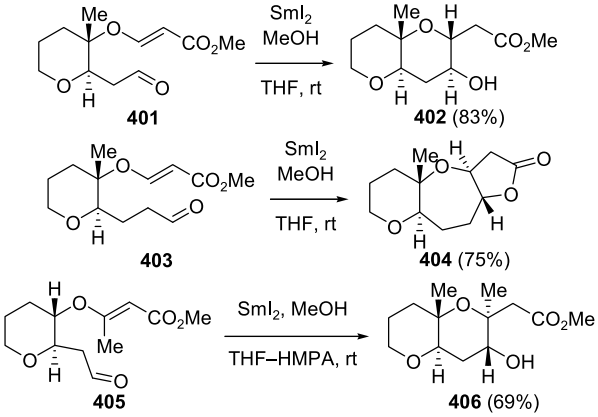
Polycyclic ether systems can be efficiently prepared using SmI_2-mediated intramolecular RCA reactions. Nakata employed an iterative approach for the synthesis of a trans-fused polytetrahydropyran ring system.[207] Treatment of monocyclic β-alkoxyacrylate aldehyde **381** with SmI_2 and MeOH afforded *bis*-tetrahydropyran **382** as a single diastereomer in high yield (Scheme 94). A four-step chain extension sequence followed by a second cyclization afforded a tricycle, and a final iteration delivered trans-fused tetracycle **384**. Chelation of the ketyl and ester moieties by Sm(III) may be responsible for the excellent diastereoselectivity. This method could also be applied to the stereoselective synthesis of trans-fused 6, 7, 6- and 6, 7, 7, 6-membered polycyclic ethers **388** and **392** (Scheme 95).[208] Interestingly, the products of the 7-*exo-trig* cyclization underwent a subsequent lactonization, whereas the 6-*exo-trig* adducts were isolated as hydroxy esters. 6,7,7-Tricycle **390**, the product of a second 7-*exo* cyclization, was obtained as a mixture of isomers; fortunately, the minor *cis*-fused compound could also be converted into **391**. Moreover, the stereoselectivity of the cyclizations **381**→**382** (Scheme 94) and **385**→**386** (Scheme 95) could be inverted to favor cis-fused cyclic ethers if HMPA was included.[209] This bolsters the authors' theory that the trans isomers are formed via chelation control.



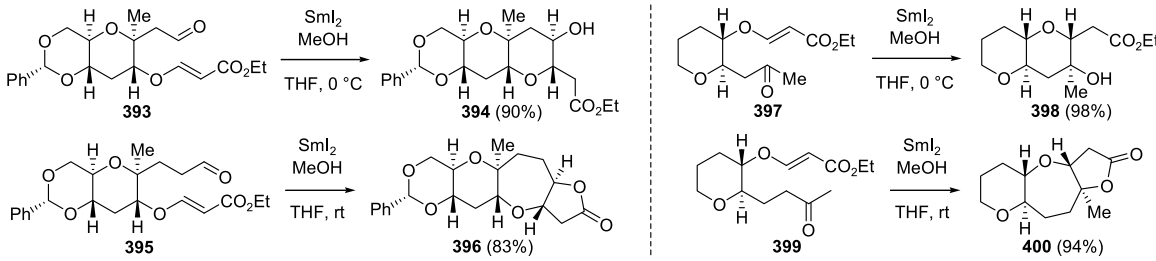
Scheme 95.

Nakata extended this process to the synthesis of trans-fused six, six- and six, seven-membered cyclic ethers containing angular methyl groups. This was accomplished by performing a 6- or 7-*exo-trig* ketyl–olefin cyclization on compounds possessing a methyl substituent at the developing ring junction (i.e., **393**→**394** and **395**→**396**, Scheme 96) and by using ketones as substrates (i.e., **397**→**398** and **399**→**400**).[210] Each product was obtained exclusively as the trans isomer.

Further attempts by Nakata to explore the scope of SmI_2-mediated intramolecular RCAs for the synthesis of cyclic ethers containing angular methyl groups revealed some limitations of this method.[211] Aldehyde–acrylate **401** underwent facile 6-*exo-trig* cyclization, affording bicyclic ether **402** with the expected *syn*,*trans*-stereochemistry (Scheme 97). On the other hand, the homologous aldehyde **403** delivered *anti*,*trans*-tricycle **404** as the sole product. Apparently, steric repulsions between the angular methyl and hydrogen moieties in the transition state leading to the *syn*,*trans*-diastereomer disfavor the route leading to this isomer. Additionally, compound **405** possessing a β-methyl substituent on the acrylate cyclized upon treatment with SmI_2; however, HMPA was required for the reaction to occur. Accordingly, *anti*,*trans*-adduct **406** was formed as the sole product via a nonchelated pathway.

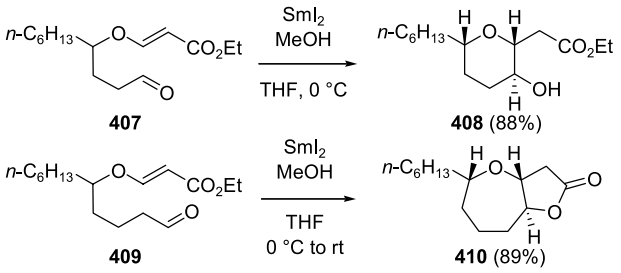


Scheme 97.



Scheme 96.

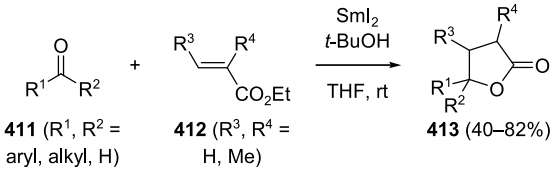
Nakata also demonstrated that a preexisting cyclic ether in the substrate is not necessary for these intramolecular SmI_2-promoted RCAs to occur.[212] Tetrahydropyrans and oxepanes could be constructed in high yield as single isomers (Scheme 98), whereas attempts to form tetrahydrofurans, oxocanes, and oxocenes were plagued by low yields and dr's.



Scheme 98.

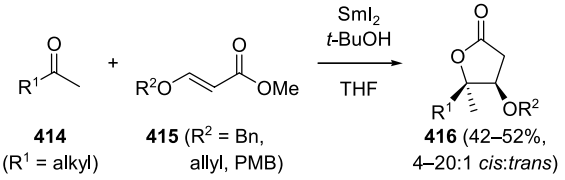
4.3. Intermolecular conjugate additions of ketyls generated by SmI_2

Unlike alkyl radicals generated by SmI_2, ketyls formed by this reagent will undergo intermolecular additions to electron-deficient olefins. This was first demonstrated by Fukuzawa, who in 1986 disclosed that ketones or aldehydes **411** coupled with acrylates **412** to form γ-lactones **413** (Scheme 99).[213,214] Shortly thereafter, Inanaga discovered that HMPA accelerates these intermolecular RCA reactions.[215]



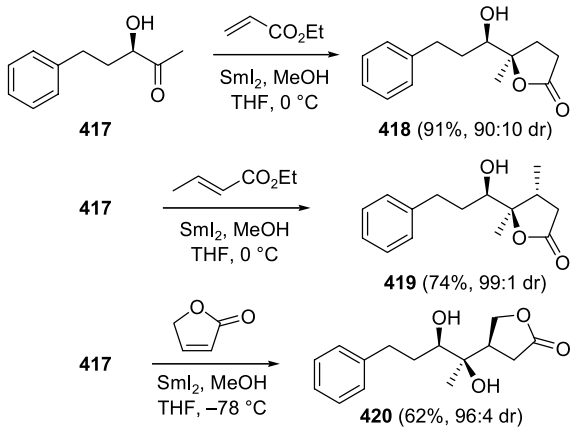
Scheme 99.

Procter recently extended the scope of this reaction to include β-alkoxy acrylates **415** as acceptors (Scheme 100).[216] γ-Lactones **416** were obtained with high cis selectivity but moderate yields due to competing processes such as ketone reduction and pinacol coupling.



Scheme 100.

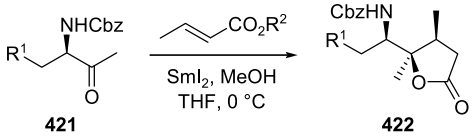
Matsuda examined intermolecular ketyl–olefin couplings of α-hydroxy ketone **417** with enoates and found that γ-lactones **418**–**420** could be constructed with excellent dr's (Scheme 101).[217,218] Chelation of the Sm(III) cation by the hydroxyl group and the ketyl radical is postulated to account for this result, as reactions run with HMPA afforded attenuated selectivity.



Scheme 101.

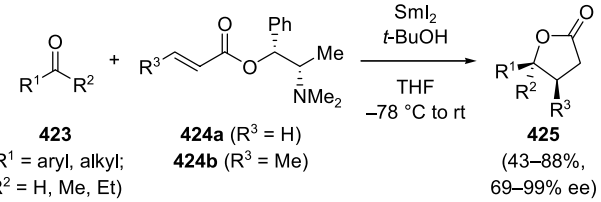
Matsuda discovered that Cbz-protected α-amino-ketones **421** also react with crotonates in the presence of SmI_2, affording γ-lactones **422** in a highly stereoselective fashion (Table 41).[219,220] The dr's increase as the size of the ester increases. Although the *syn* relationship between the amino group and the lactone oxygen is consistent with the *syn*-1,2-diol-type products obtained from hydroxyl ketone substrates (cf. **417**→**419**, Scheme 101), the *anti* relationship between the methyl groups contrasts with the *syn* products observed previously. The authors explain this difference by invoking a seven-membered Sm(III) chelate of the ketyl and carbamate carbonyl as an intermediate. This species exhibits the same facial selectivity as the five-membered chelated intermediate formed from **417**, but it imposes opposite facial selectivity on the crotonate esters.

Table 41.



Entry	R^1	R^2	Yield (%)	dr
1	Ph	Me	87	90:10
2	Ph	Et	85	92:8
3	Ph	*i*-Pr	88	95:5
4	Ph	*t*-Bu	90	98:2
5	*i*-Pr	Me	88	92:8
6	*i*-Pr	Et	87	94:6
7	*i*-Pr	*i*-Pr	91	97:3
8	*i*-Pr	*t*-Bu	86	>99:1

Fukuzawa devised a synthesis of enantiomerically enriched γ-lactones **425** by employing chiral acrylates **424a** and crotonates **424b** derived from *N*-methylephedrine in intermolecular RCAs with ketyls generated by SmI_2

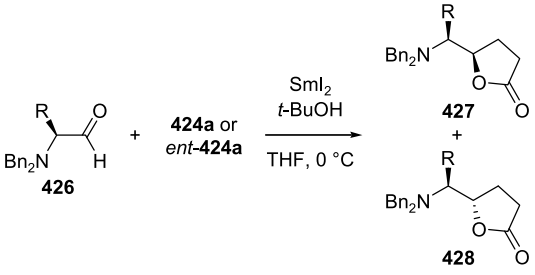


Scheme 102.

(Scheme 102).[221] Additionally, crotonates exhibited very high levels of cis diastereoselectivity (≥97:3) in this reaction. Chelation by the Sm(III) ion likely plays a role in the asymmetric induction, as reactions performed in the presence of HMPA gave racemic products.

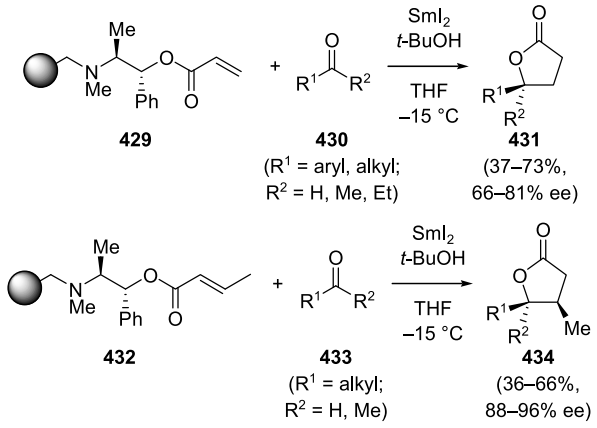
Fukuzawa later used chiral acrylate **424a** in intermolecular ketyl–olefin couplings with chiral α-amino aldehydes (*S*)-**426** to synthesize γ-aminoalkyl γ-lactones **427** and **428** (Table 42).[222] Reactions between matched substrates **426** and *ent*-**424a** afforded **427** in good yields and dr's. The chirality of the aldehyde alone was insufficient to control the reaction stereochemistry, as the use of ethyl acrylate afforded minimal selectivity (2–24% de) for **427**.

Table 42.



Entry	R	Acrylate	Yield (%)	**427**:**428**
1	Bn	**424a**	46	35:65
2	*i*-Bu	**424a**	22	42:58
3	*i*-Pr	**424a**	63	54:46
4	Me	**424a**	22	65:35
5	Bn	*ent*-**424a**	60	92:8
6	*i*-Bu	*ent*-**424a**	40	84:16
7	*i*-Pr	*ent*-**424a**	83	89:11
8	Me	*ent*-**424a**	32	90:10

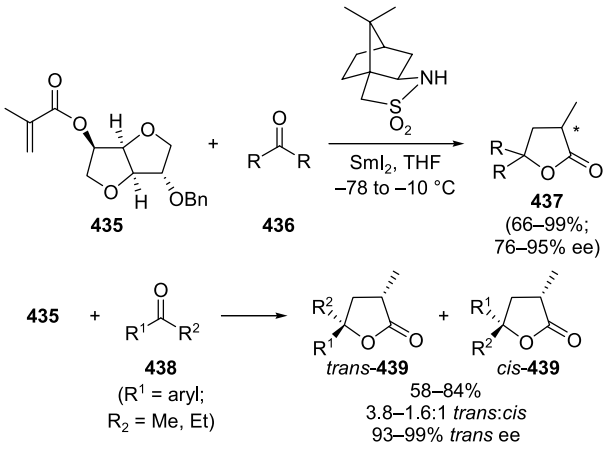
Procter attached the ephedrine-based chiral auxiliary used by Fukuzawa to a resin and synthesized immobilized acrylate **429** and crotonate **432** for use in the construction of optically active γ-lactones **431** and **434** via an 'asymmetric resin capture–release' strategy (Scheme 103).[223,224] The yields obtained with both chiral resins were comparable to those observed by Fukuzawa in the analogous solution phase chemistry, but the ee's of lactones **431** derived from **429** were lower. The authors speculate



Scheme 103.

that the higher reaction temperature may cause this attenuation of ee.

Lin introduced methacrylate **435** containing a chiral auxiliary derived from isosorbide for the synthesis of enantiomerically enriched α,γ-substituted γ-lactones **437** and **439** via intermolecular RCAs of ketyls derived from symmetrical ketones **436** and unsymmetrical ketones **438** (Scheme 104).[225,226] A bulky proton source such as (1*S*)-(−)-2,10-camphorsultam was necessary to achieve high ee's; alternatively, the proton source could be imbedded in the auxiliary by replacing the benzyloxy substituent of **435** with a carbamate or sulfonamide.[227] Although the dr's of reactions with ketones **438** were modest, high ee's were obtained for the trans products. However, ee's of the cis products were considerably lower (4–75%). Thus, Lin searched for auxiliaries, which would afford *cis*-**439** as the major product in high ee and identified D-fructose-derived alcohol **440** as such a compound (Fig. 3).[228] SmI_2-mediated couplings of the methacrylate formed from **440** with unsymmetrical ketones **438** yielded γ-lactones *cis*-**439** in good yields (60–75%), dr's (6.7–49:1), and ee's (77–99%). Additionally, *ent*-**440** could be prepared from L-sorbose, and use of alcohol **441** (prepared from D-fructose) as an auxiliary provided the enantiomer of *trans*-**439** in ≥90% ee. Thus, each of the four stereoisomers of **439** can be prepared in high ee by selection of the proper chiral auxiliary.



Scheme 104.

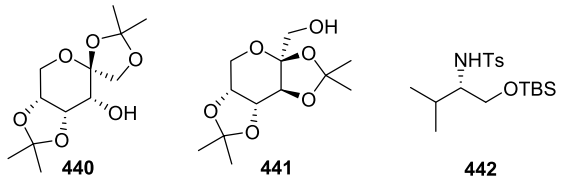


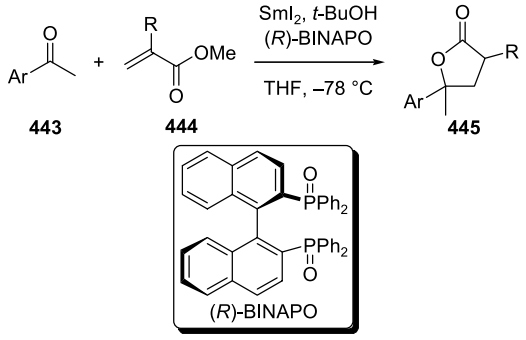
Figure 3.

In principle, a chiral proton source could exert stereocontrol in the reactions depicted in Scheme 104. Indeed, Lin found that when methyl methacrylate was coupled with benzophenone in the presence of SmI_2, HMPA, and chiral sulfonamide **442** (Fig. 3), **437** was obtained in 65% yield and 84% ee.[229] Lower ee's were observed in the absence of

HMPA. Attempts to perform this reaction with unsymmetrical ketones **438** were characterized by low dr's and ee's.

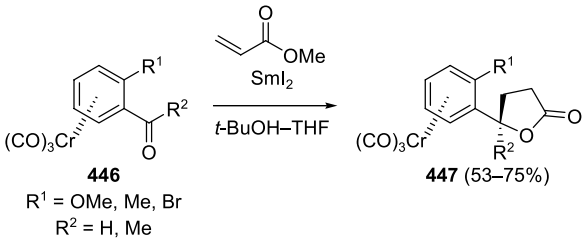
Mikami reported that (*R*)-BINAPO can provide stereocontrol in SmI_2-promoted reductive couplings of aryl ketones **443** and enoates **444** (Table 43).[230] Although dr's were modest with α-substituted esters, reasonable ee's could be obtained.

Table 43.

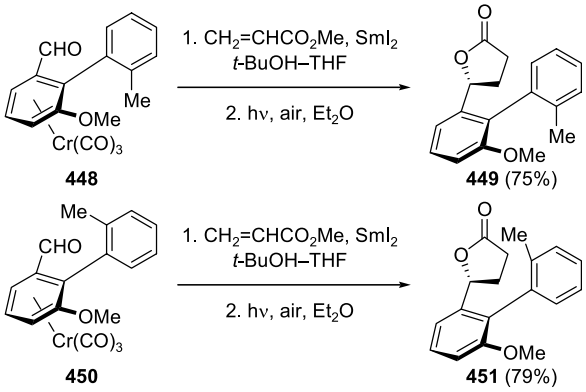


Entry	Ar	R	Yield (%)	*cis*/*trans*	ee (%) (*cis*/*trans*)
1	Ph	H	46	—	67
2	Ph	Me	42	66:34	89/55
3	*p*-MePh	H	58	—	62
4	*p*-MePh	Me	46	51:49	77/nd

Uemura used enantiomerically pure planar chiral chromium tricarbonyl complexes of *o*-substituted benzaldehydes or benzophenones (**446**) in RCAs to methyl acrylate (Scheme 105).[231] γ-Lactones **447** were obtained as single diastereomers, which could be demetallated by treatment with I_2 to afford enantiomerically pure adducts. Axially chiral benzaldehydes **448** and **450** could also be used in this reaction (Scheme 106).[232,233] The planar chirality of the chromium-complexed arene rather than the axial chirality of the biaryl moiety controlled formation of the stereocenter in γ-lactones **449** and **451**, which were each obtained as a single diastereomer.

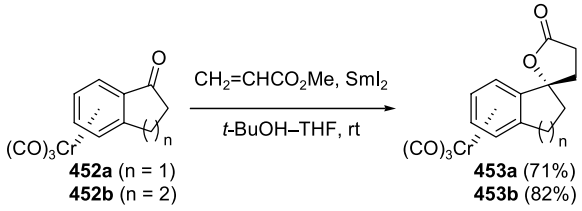


Scheme 105.



Scheme 106.

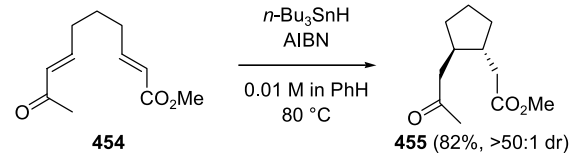
In addition to exploring RCA reactions of ketyls generated from aldehydes **446** to methyl acrylate, Merlic disclosed that ketones containing a chromium tricarbonyl arene complex undergo completely diastereoselective ketyl–olefin couplings upon treatment with SmI_2 (Scheme 107).[234,235] Methyl methacrylate and methyl crotonate could also be used as acceptors for the ketyl radical generated from **452a**, but low levels of selectivity were seen in the formation of the additional stereocenter (1.5–2:1).



Scheme 107.

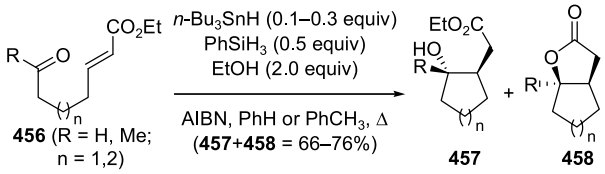
4.4. Conjugate additions of ketyls generated by other reagents

The reaction of *n*-Bu_3SnH with carbonyls in the presence of a radical initiator can generate *O*-stannyl ketyls.[236] Enholm found that treatment of enone **454** with *n*-Bu_3SnH and AIBN afforded an allylic *O*-stannyl ketyl, which underwent 5-*exo*-*trig* cyclization from the β-carbon onto the pendant enoate, delivering cyclopentane **455** as a single diastereomer (Scheme 108).[237,238] High dilution was necessary in order to obtain excellent dr. This is likely due to the reversible nature of the cyclization; the low concentration of *n*-Bu_3SnH allowed the thermodynamically more stable *trans* adduct to predominate.



Scheme 108.

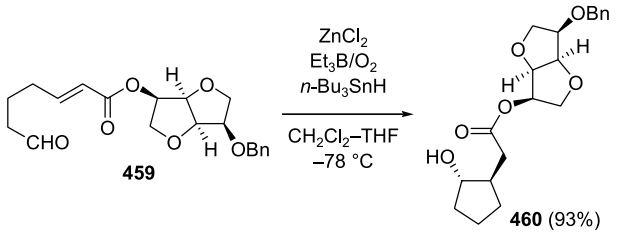
Fu reported that some intramolecular RCAs of *O*-stannyl ketyls introduced by Enholm[239] could be performed with catalytic *n*-Bu_3SnH (Scheme 109).[240,241] EtOH was employed to cleave the tin alkoxide that resulted from



Scheme 109.

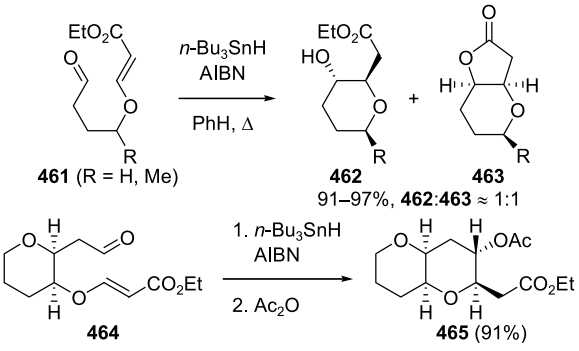
cyclization, and $PhSiH_3$ served to regenerate *n*-Bu_3SnH from *n*-Bu_3Sn–OEt. The dr's of these 5- and 6-*exo* cyclizations were modest (1.0–1.6:1).

Enholm recently used aldehyde–enoate **459** with (+)-isomannide appended as a chiral auxiliary in an intramolecular RCA affording cyclopentane **460** in excellent dr (100:1, Scheme 110).[242] Both the Lewis acid and the low temperature Et_3B/O_2 radical initiation conditions were critical to achieving high diastereoselectivity, although other Lewis acids ($MgBr_2 \cdot OEt_2$, CuOTf) were effective as well.

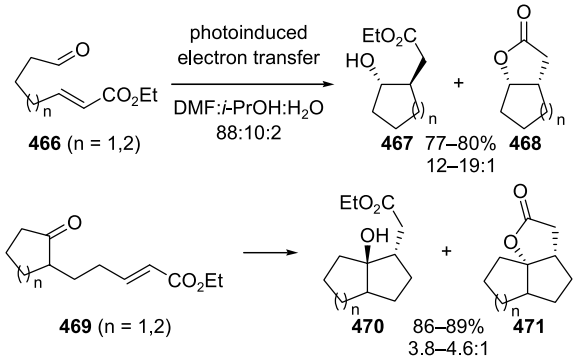


Scheme 110.

Lee disclosed that β-alkoxyacrylates **461** function as efficient acceptors for *O*-stannyl ketyls, yielding tetrahydropyrans **462** and **463** in good yield but negligible dr (Scheme 111).[243] Bicyclic diether **465** could be obtained from **464** as a single diastereomer, but the trans isomer of **464** yielded a mixture of products. Attempts to replace the ethyl ester of **461** with a chiral auxiliary met with modest success (0% de for trans adduct, 42% de for lactone) when (2*R*,3*S*)-3-phenylcholestan-2-ol was employed as the chiral alcohol.[244]



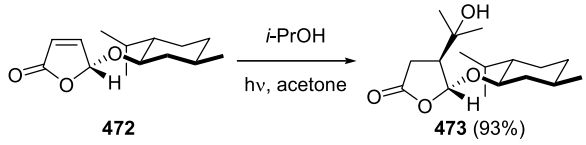
Scheme 111.



Scheme 112.

Pandey demonstrated that light-initiated photosensitized electron transfer can be used to generate ketyls from aldehydes and ketones, which then undergo RCA reactions with a tethered enoate (Scheme 112).[245] High levels of cis selectivity were observed for aldehydes **466**, but with cyclic ketones **469** the dr's were attenuated.

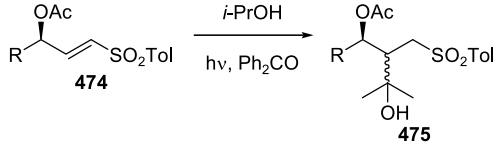
Hoffmann employed menthyloxyfuranone **472** as a chiral acceptor for additions of ketyl radicals formed via photochemically initiated hydrogen atom abstraction from *i*-PrOH and other secondary alcohols (Scheme 113).[246] The ketyl radicals could also be produced from ketones by a photochemical electron transfer/protonation sequence with a tertiary amine partner.[247]



Scheme 113.

Ogura investigated the diastereoselectivity of photochemical ketyl RCAs to γ-acetoxy vinyl sulfone **474** (Table 44).[248] The dr's increased with the size of the γ-alkyl group, but the yields of **475** decreased.

Table 44.



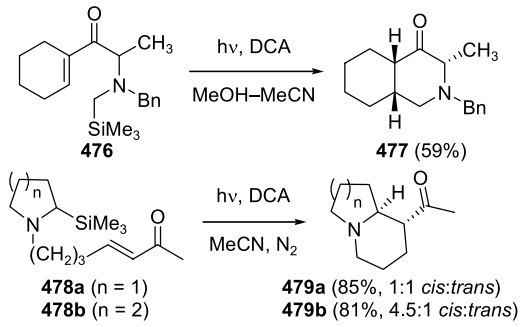
Entry	R	Yield (%)	*anti*:*syn*
1	Me	90	71:29
2	Et	77	79:21
3	*i*-Pr	61	95:5

5. Other tin-free radical conjugate additions

Organotin compounds are frequently used in radical chemistry. Despite their favorable reactivity profiles, these reagents suffer from toxicity and purification problems. Accordingly, there is much interest in developing tin-free radical reactions. Examples of SmI_2-mediated RCAs are numerous and were covered in the previous section. This section covers all other tin-free methods and is organized according to the type of reagents used.

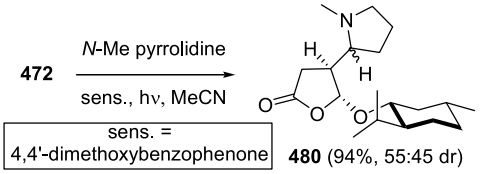
5.1. Photochemical methods

Mariano studied intramolecular RCAs of α-amino radicals generated via single electron transfer processes employing 9,10-dicyanoanthracene (DCA) as sensitizer (Scheme 114).[249–252] Hydroisoquinoline **477** was obtained as a single diastereomer from **476**; however, epimerization of both α-stereocenters occurred upon chromatography. Additionally, DCA-sensitized irradiation of pyrrolidine **478a** and piperidine **478b** provided indolizidines **479a** and quinolizidines **479b**, the latter in good dr.



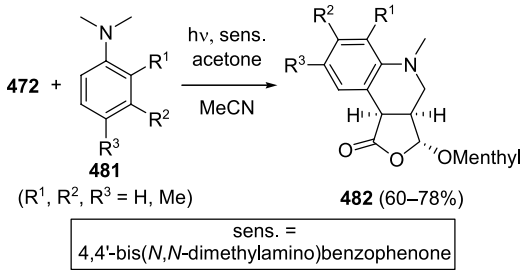
Scheme 114.

Hoffmann found that α-amino radicals generated photochemically undergo intermolecular RCA to menthyloxyfuranone **472** (see Scheme 113) with good yield and excellent facial selectivity at the furanone ring (Scheme 115).[253,254] Unfortunately, the α-amino stereocenter configuration could not be controlled. Adduct **480** and related compounds could be converted into pyrrolizidine alkaloids.[255]



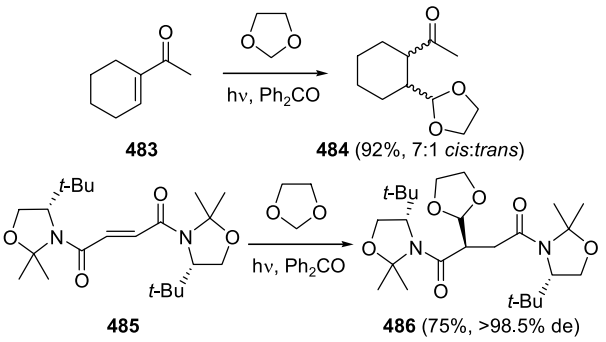
Scheme 115.

When Hoffmann used anilines **481** in photoinduced RCAs to **472**, tricyclic tetrahydroquinolines **482** were obtained as a result of intermediate radical addition to the aromatic ring followed by oxidative rearomatization (Scheme 116).[256,257] A minor amount of the other cis-fused diastereomer (≤3%) was also isolated. Byproducts formed during the rearomatization could be suppressed by inclusion of acetone as a mild oxidant. Studies conducted with the epimer of **472** at the acetal center revealed that both the acetal and menthyl groups contribute to the reaction stereoselectivity.[258]



Scheme 116.

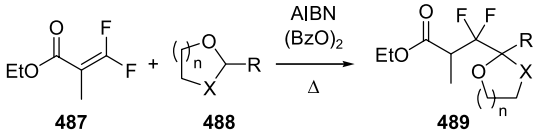
Albini and Fagnoni employed photosensitized hydrogen atom abstraction from 1,3-dioxolane to generate a nucleophilic radical capable of adding to enones (Scheme 117).[259] When 2-alkyl-1,3-dioxolanes were used, monoprotected 1,4-diketones were formed.[260] Dioxolanyl radicals also underwent intermolecular RCA to α,β-unsaturated aldehydes.[261] Additionally, Albini and Fagnoni demonstrated that photochemically produced dioxolanyl radicals add to chiral fumaramide **485** with a high dr.[262]



Scheme 117.

Bumgardner reported that radicals derived from five-membered cyclic ethers and acetals added efficiently to difluoroacrylate **487**, whereas radicals derived from the corresponding six-membered species did not undergo RCA (Table 45).[263] It is believed that the lower bond dissociation energies and higher SOMO levels in the five-membered series are responsible for these results.

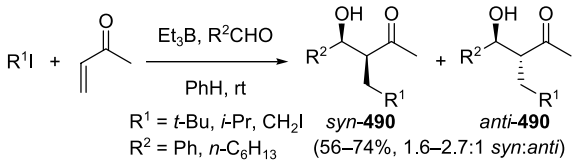
Table 45.



Entry	R	X	*N*	Yield (%)
1	H	CH_2	1	73
2	H	CH_2	2	0
3	H	O	1	71
4	H	O	2	0
5	C_5H_{11}	O	1	73

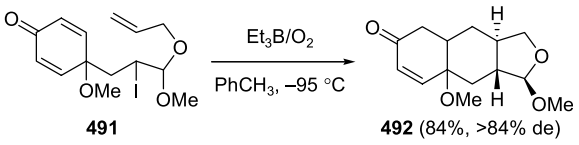
5.2. Additions mediated by organoboranes

The seminal work of Brown and Suzuki established that alkyl radicals derived from organoboranes can participate in RCA reactions.[264–266] Oshima and Utimoto later incorporated this process into a three-component coupling of alkyl radicals, methyl vinyl ketone, and aldehydes (Scheme 118).[267,268] Triethylborane serves as both the initiator and propagator of the radical chain; reaction of the intermediate α-keto radical with Et_3B produces ethyl radical and a boron enolate, the latter of which undergoes an aldol reaction with the aldehyde. The adducts **490** were obtained with modest *syn* selectivity. Subsequent work by Chandrasekhar demonstrated that the *anti* products are favored when electron-rich aryl aldehydes are employed.[269]



Scheme 118.

Renaud found that Et_3B could serve as the initiating and propagating agent in the cascade cyclization of iodide **491**, affording tricycle **492** in good yield (Scheme 119).[270] The

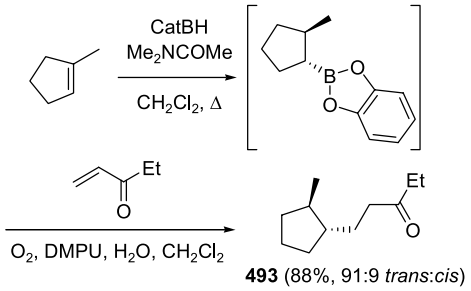


491 **492** (84%, >84% de)

Scheme 119.

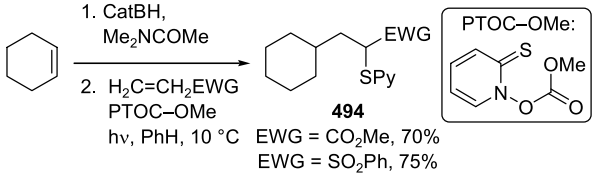
high de is significant given the fact that four stereocenters are created in this reaction.

Renaud has extensively investigated the use of organoboranes in radical reactions. For example, organoboranes generated in situ via hydroboration of alkenes undergo intermolecular RCA to enones and enals in good yield (Scheme 120).[271] However, acrylates do not undergo this reaction, presumably due to inefficient propagation. Renaud solved this problem by employing the Barton carbonate PTOC–OMe as a chain transfer reagent (Scheme 121).[272,273] With this modified protocol, both acrylates and α,β-unsaturated sulfones underwent efficient RCA with *B*-alkylcatecholboranes. Dalko and Cossy independently reported a similar process.[274]



493 (88%, 91:9 *trans*:*cis*)

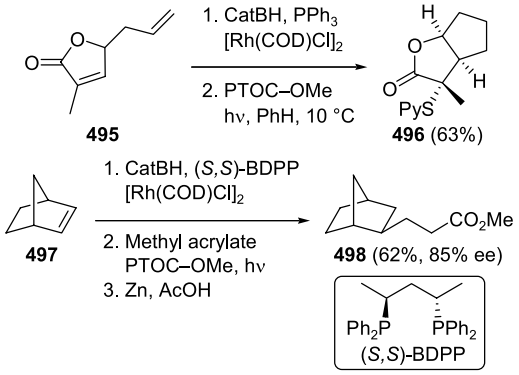
Scheme 120.



494
EWG = CO_2Me, 70%
EWG = SO_2Ph, 75%

Scheme 121.

Renaud then applied this hydroboration–RCA sequence to an intramolecular reaction.[275] In this case, hydroboration of the more electron-rich terminal double bond of **495** was best



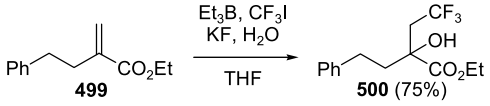
495 **496** (63%)

497 **498** (62%, 85% ee)

Scheme 122.

accomplished under rhodium catalysis. Subsequent intramolecular RCA under the previously reported conditions provided bicyclic lactone **496** as a single diastereomer (Scheme 122). Additionally, enantioselective Rh-catalyzed hydroboration of norbornene (**497**) followed by intermolecular RCA to methyl acrylate and desulfurization delivered ester **498** in 85% ee.[276]

Nagano found that Et_3B could mediate the hydroxytrifluoromethylation of enoates such as **499** (Scheme 123).[277] The hydroxyl group was derived from hydrolysis of the intermediate α-iodide, which was obtained via an atom-transfer process.

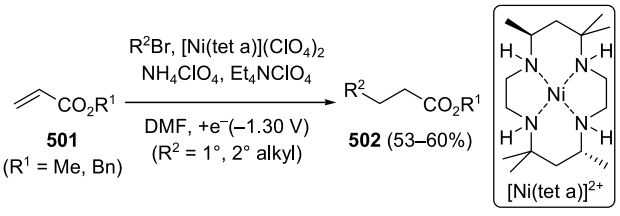


499 **500** (75%)

Scheme 123.

5.3. Additions mediated by Ni, Zn, or other metals

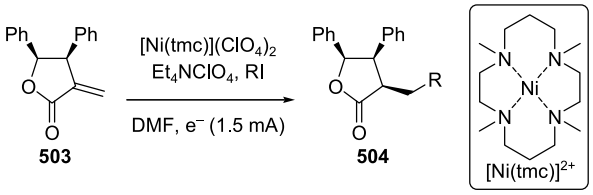
Ozaki generated alkyl radicals via electroreduction of alkyl bromides in the presence of a Ni(II) catalyst.[278] These radicals added to unsubstituted acrylates **501**, forming esters **502** in moderate yield (Scheme 124). A similar reaction with chiral α-methylenebutyrolactone **503** as acceptor occurred with high dr's (Table 46).[279] Mechanistic studies indicated that the intermediate α-carbonyl radical was reduced to an enolate and protonated with adventitious H_2O. The yield and dr both decreased with increasing radical size.



501 (R^1 = Me, Bn) **502** (53–60%)

Scheme 124.

Table 46.

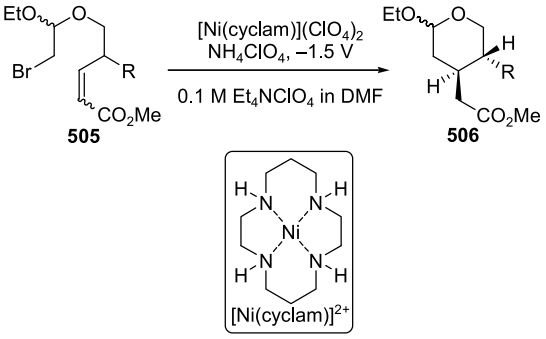


503 **504**

Entry	R	Yield (%)	*cis*:*trans*
1	*n*-Bu	66	>99:1
2	*s*-Bu	56	95:5
3	*t*-Bu	27	89:11

Ihara employed Ni-catalyzed indirect electrolysis of bromo enoates **505** to construct six-membered products **506** with good to excellent trans selectivity (Table 47).[280,281] The greater dr in cyclization of a *Z*-enoate was attributed to minimization of 1,3-allylic strain in the favored transition state. The ethyl-substituted adduct (entries 2 and 3) was an

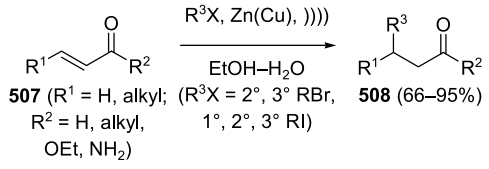
Table 47.



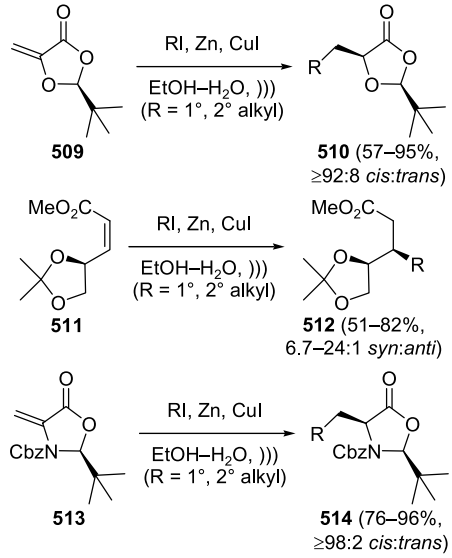
Entry	R	*E*/*Z*	Yield (%)	*trans*:*cis*
1	Ph	*E*	75	>99:1
2	Et	*E*	83	>4:1
3	Et	*Z*	88	>99:1

intermediate in formal total syntheses of (+)-dihydroantirhine and quinine alkaloids.[282]

Luche found that the combination of Zn–Cu couple and sonication mediates the intermolecular addition of alkyl radicals to α,β-unsaturated aldehydes, ketones, esters, and amides in aqueous EtOH (Scheme 125).[283–285] These reactions were typically most efficient with tertiary and secondary radicals. Mechanistic studies suggested that the intermediate α-carbonyl radical is reduced to an enolate and subsequently protonated.[286]



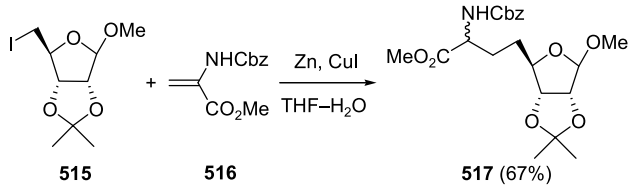
Scheme 125.



Scheme 126.

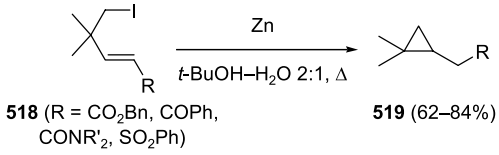
Sarandeses and Pérez Sestelo have employed the Luche protocol in diastereoselective RCA reactions. Methylenedioxolanone **509** and γ,δ-dioxolanyl-α,β-unsaturated ester **511** serve as effective chiral acceptors for the stereoselective synthesis of α- and γ-hydroxy acid derivatives **510** and **512**, respectively, (Scheme 126).[287,288] Similar RCAs conducted with *N*-Cbz methyleneoxazolidinone **513** provided α-amino acid derivatives **514** with very good yields and dr's.[289]

In the course of a synthesis of sinefungin analogues, Fourrey discovered that sonication was not required to promote RCA of ribose derivative **515** to dehydroalanine **516** under modified Luche conditions (Scheme 127).[290–292] Rather, vigorous stirring was sufficient. Similar reactions could also be induced by a Zn–Fe couple.[293]



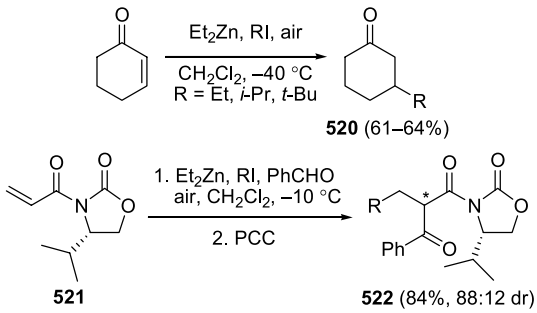
Scheme 127.

Togo reported the Zn-mediated formation of cyclopropanes **519** via rare 3-*exo*-*trig* cyclizations of substrates **518** (Scheme 128).[294] Geminal dialkyl substitution was required. The zinc presumably functions as a single-electron reductant both in forming the initial alkyl radical and in reducing the incipient α-carbonyl or sulfonyl radical faster than the potential fragmentation can occur. This method compares well to similar reactions promoted by SmI_2, as the latter reagent is air-sensitive.



Scheme 128.

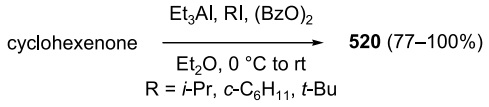
Bertrand disclosed that Et_2Zn can function as a radical initiator and chain transfer agent in intermolecular RCAs to cyclohexenone (Scheme 129).[295] The intermediate zinc enolate was trapped with benzaldehyde in reactions employing chiral *N*-enoyloxazolidinone **521** as the acceptor. Oxidation for analytical purposes delivered β-keto imide



Scheme 129.

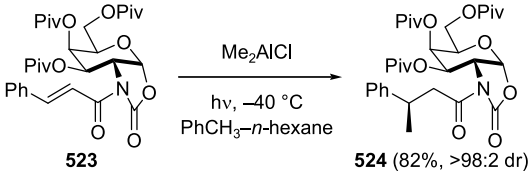
522 in good yield and dr.[296] Trisubstituted γ-lactones were produced from a fumarate-derived oxazolidinone due to cyclization of the intermediate zinc alkoxide.[297]

Yao performed RCAs to cyclohexenone with Et_3Al as the chain transfer agent (Scheme 130).[298] These reactions afforded higher yields than analogous Et_3B-mediated processes, a fact attributed to the greater Lewis acidity of Et_3Al.



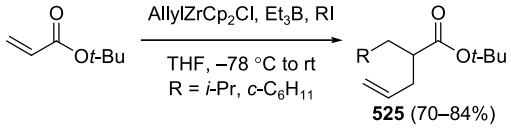
Scheme 130.

Kunz discovered the diastereoselective RCA of dimethylaluminum chloride to bicyclic carbohydrate oxazolidinone **523** (Scheme 131).[299,300] Use of a phenylalaninol-derived oxazolidinone in place of **523** resulted in a lower dr.[301] Interestingly, higher homologues such as diethylaluminum chloride underwent a standard polar conjugate addition rather than the RCA.



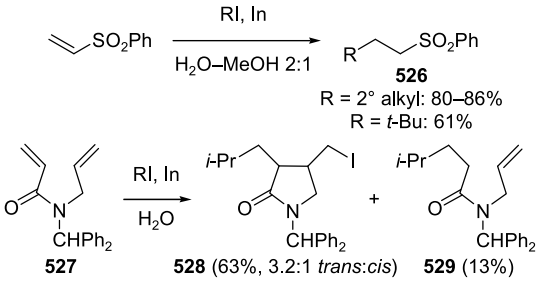
Scheme 131.

Oshima employed an allylzirconium reagent as a substitute for allyltributyltin in RCA–allylations of *tert*-butyl acrylate (Scheme 132).[302]



Scheme 132.

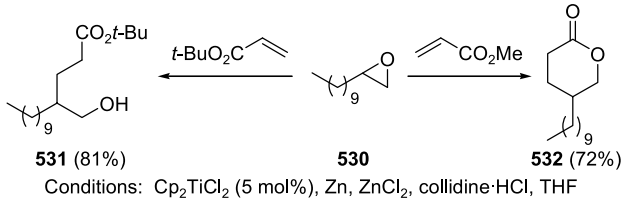
Naito reported the use of indium as a single-electron-transfer agent in intermolecular RCAs to phenyl vinyl sulfone in aqueous media (Scheme 133).[303,304] Additionally, Naito found that similar reactions with amide **527** as acceptor afforded predominantly lactam **528** by means of an addition–cyclization–halide abstraction pathway.[305] Amide



Scheme 133.

529 was formed as a byproduct via reduction of the intermediate α-carbonyl radical.

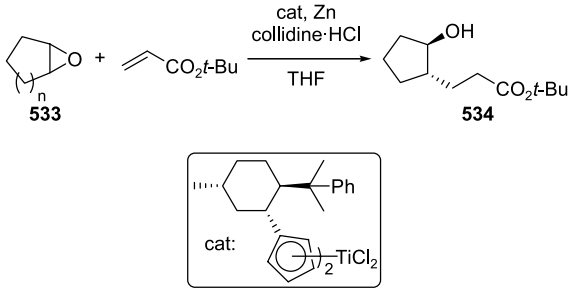
Gansäuer generated β-titanoxy radicals from the reaction of epoxides with catalytic Cp_2TiCl, which was formed in situ by reduction of Cp_2TiCl_2 with Zn. These radicals underwent intermolecular RCA to acrylates, affording ester **531** and lactone **532** (Scheme 134).[306–308] The use of collidine·HCl as a proton source and $ZnCl_2$ as a Lewis acid facilitated catalyst turnover.



Scheme 134.

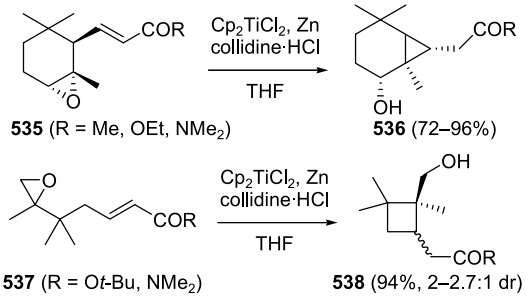
Gansäuer then introduced a chiral titanocene catalyst for enantioselective reductive opening of *meso* epoxides **533** followed by diastereoselective RCA to *tert*-butyl acrylate. Adducts **534** were obtained in good yield, dr, and er (Table 48).[309,310] Further investigations with chiral epoxides determined that the catalyst ligands control the reaction diastereoselectivity.[310,311]

Table 48.



Entry	*n*	Yield (%)	dr	er
1	1	68	>97:3	87:13
2	2	61	81:19	91:9
3	3	65	87:13	91:9

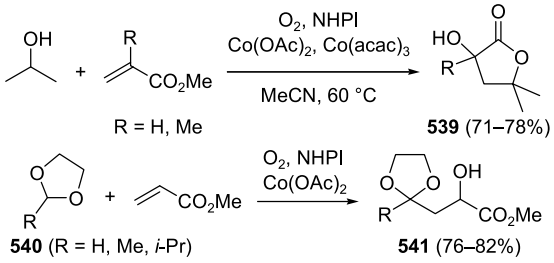
Gansäuer performed 3- and 4-*exo-trig* cyclizations of the β-titanoxy radicals generated from epoxides **535** and **537** (Scheme 135).[312] Rapid reduction of the electrophilic



Scheme 135.

α-carbonyl radical resulting from cyclization is key to the success of this process.

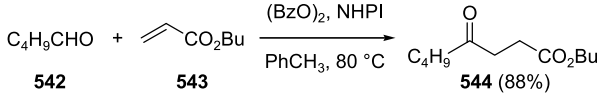
Ishii reported that the oxy radical generated from reaction of *N*-hydroxyphthalimide (NHPI) with a Co(III)–dioxygen complex can abstract hydrogen from alcohols[313] and dioxolanes.[314] The resultant radicals add to acrylates and the adducts are trapped with oxygen, affording α-hydroxy lactones **539** or esters **541** (Scheme 136). Catalytic amounts of NHPI and the Co complexes are sufficient. This process has been extended to include 1,3-dimethyladamantane[315] and cyclic ethers[316] as radical precursors.



Scheme 136.

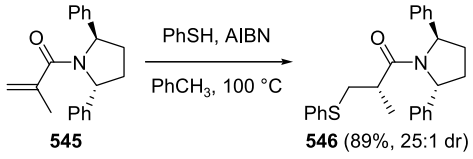
5.4. Other methods

Ishii used a catalytic amount of NHPI as a chain transfer agent in the benzoyl peroxide-initiated addition of acyl radicals to acrylates (Scheme 137).[317] Dioxolanes could also function as the radical sources.



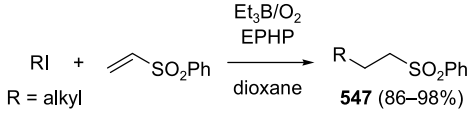
Scheme 137.

Taber found that thiophenol underwent RCA to chiral amide **545** (Scheme 138).[318] The high dr is noteworthy given the elevated reaction temperature.

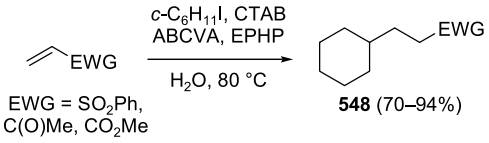


Scheme 138.

Jang reported the use of *N*-ethylpiperidine hypophosphite (EPHP) as a substitute for *n*-Bu_3SnH in RCAs to phenyl vinyl sulfone (Scheme 139).[319] α,β-Unsaturated esters and ketones could also be used as acceptors with reduced yields. Significantly, use of the initiator 4,4′-azobis(4-cyanovaleric acid) (ABCVA) in conjunction with cetyltrimethylammonium bromide (CTAB) allowed performance of the reaction



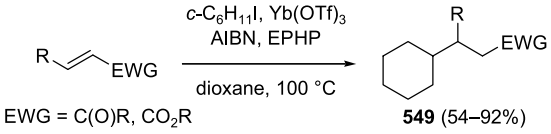
Scheme 139.



Scheme 140.

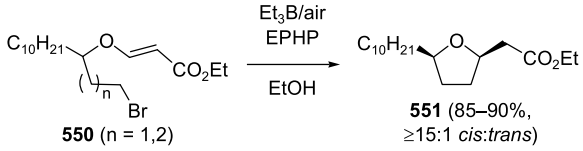
in water (Scheme 140).[320] The surfactant could be omitted if tetraalkylammonium hypophosphites were employed instead of EPHP.[321]

Jang found that Lewis acids were necessary to promote RCAs to β-substituted α,β-unsaturated esters and ketones with EPHP as chain carrier (Scheme 141).[322] In general, yields with ketones were higher than the yields with esters. This process could be carried out under Lewis acid free aqueous conditions if indium was present.[323]



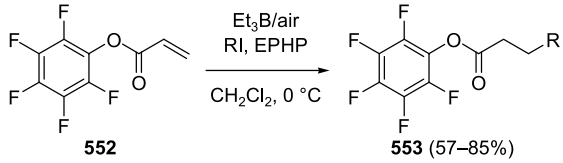
Scheme 141.

Lee performed cyclizations of β-alkoxyacrylates **550** with EPHP as chain carrier and Et_3B as initiator (Scheme 142).[324] These reactions are comparable to the analogous *n*-Bu_3SnH-mediated processes in terms of yield and dr.



Scheme 142.

Caddick employed pentafluorophenyl acrylate **552** as an acceptor in RCAs of primary, secondary, and tertiary alkyl radicals mediated by EPHP (Scheme 143).[325] Adducts **553** could be converted to amides by simple reaction with amines.



Scheme 143.

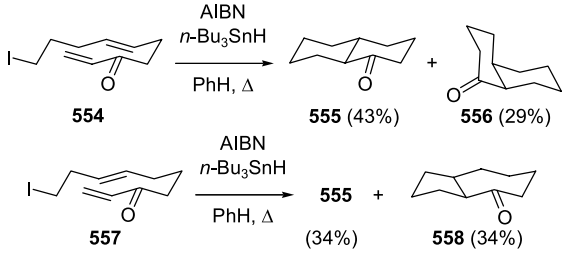
6. Cascade reactions involving radical conjugate additions

Since the product of radical addition to an alkene or alkyne is itself a radical capable of undergoing further transformations, radical reactions are commonly used to create reaction cascades in which the complexity of the product is much greater than that of the starting materials. Radical conjugate additions have been incorporated into several such processes. This section is organized into two parts: the

first covers cascades in which the RCA step is an intramolecular reaction, whereas the second summarizes cascades which feature an intermolecular RCA.

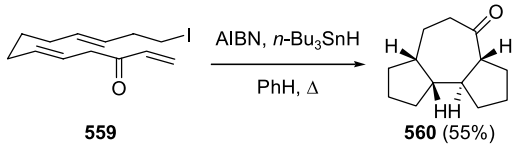
6.1. Cascades incorporating an intramolecular radical conjugate addition

Pattenden studied the synthesis of ring-fused bicycles by a macrocyclization–transannulation process. Iodo dienone **554** delivered a 3:2 mixture of *trans*- and *cis*-decalones **555** and **556** via a 10-*endo*/6-*exo* cyclization cascade (Scheme 144). However, isomeric enone **557** afforded a 1:1 mixture of **555** and *cis*-fused 7,5-bicyclic ketone **558**.[326,327] The differing behaviors of **554** and **557** were rationalized in terms of the preferred conformations of the macrocyclic radical intermediates. Application of this procedure to alkenyl acrylates and acrylamides resulted in stereoselective formation of 5,7-, 6,6-, and 6,8-ring-fused lactones and lactams.[328]



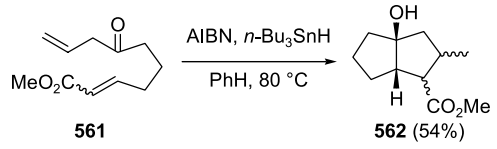
Scheme 144.

Pattenden extended this method to the preparation of tricyclic ketones. Thus, iodo trienone **559** underwent a 13-*endo-trig* macrocyclization followed by two successive 5-*exo-trig* transannulations to give *cis-anti-trans* tricycle **560** as a single isomer (Scheme 145).[329,330]



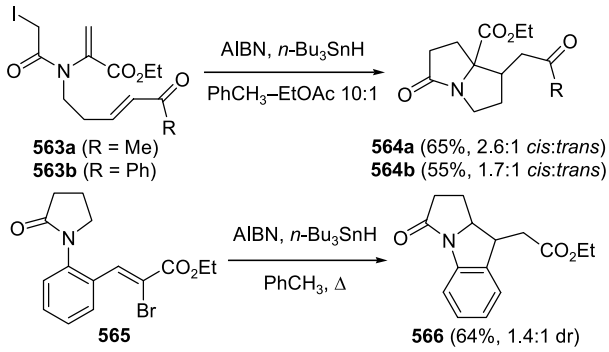
Scheme 145.

Enholm reported that *O*-stannyl ketyl formation from ketone **561** triggered a tandem cyclization providing cis-fused bicyclic ester **562** as a 1:1 mixture of diastereomers (Scheme 146).[331] Replacement of the carbomethoxy group with a phenyl substituent resulted in no cyclization, illustrating the need for an electron-deficient alkene.



Scheme 146.

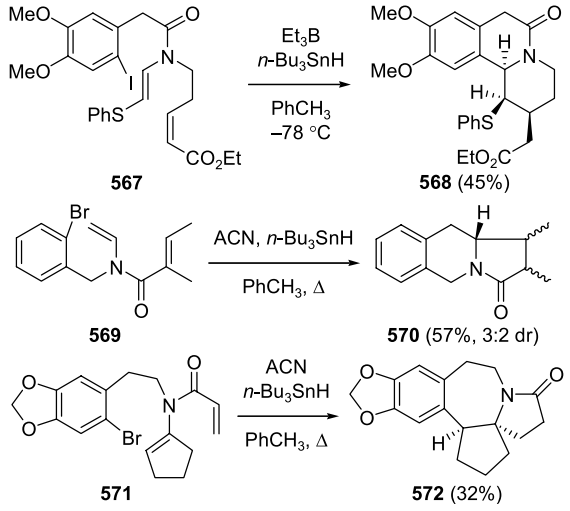
Parsons synthesized pyrrolizidinones **564** from **563** via two consecutive 5-*exo-trig* RCAs (Scheme 147).[332,333] The failure of aryl-tethered substrates to undergo this reaction



Scheme 147.

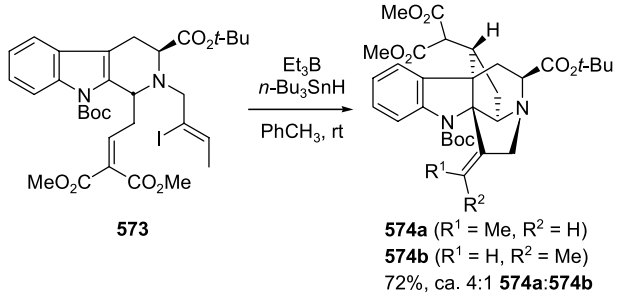
in good yields led to the design of a 1,6-hydrogen atom transfer–5-*exo-trig* sequence for the preparation of tricycle **566** from **565**.[334]

Ishibashi reported a variety of cascades involving cyclization of an aryl radical onto an enamide followed by an intramolecular RCA (Scheme 148, ACN = azobiscyclohexanecarbonitrile).[335–337] The high dr (37:1) in the formation of **568** is noteworthy given that three stereocenters are created in the reaction. Higher reaction temperatures afforded reduced dr's.



Scheme 148.

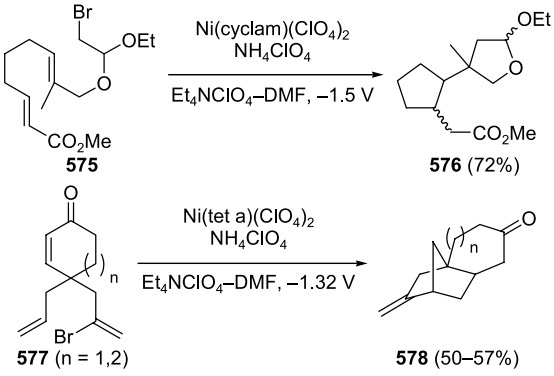
In an attempt to perform a 6-*exo* cyclization of vinyl iodide **573**, Takayama obtained the unusual bridged polycycles **574** as a result of vinyl radical cyclization onto the indole followed by intramolecular RCA (Scheme 149).[338] The



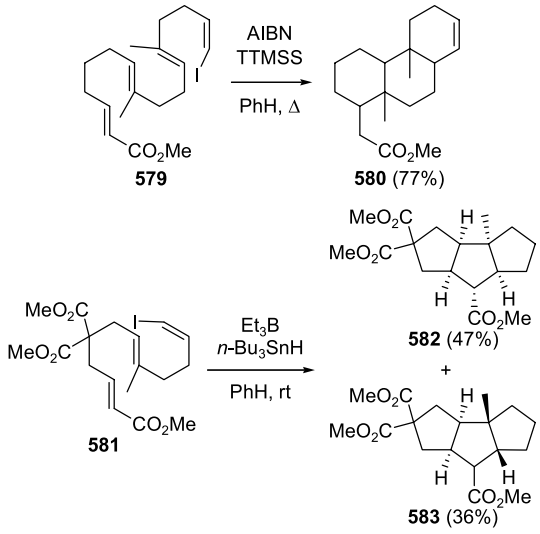
Scheme 149.

authors postulate that the bulk of the *tert*-butyl ester destabilizes the transition state leading to the intended product.

Ihara used Ni-catalyzed electrolysis to generate radicals that engage in 5-*exo*–5-*exo* cascade cyclizations in which the second ring closure is an RCA (Scheme 150).[339,340] In contrast, the 6-*endo*–6-*endo*–6-*exo* cascade of **579** leading to **580** proceeded in poor yield under electrolytic conditions, so TTMSS was employed instead (Scheme 151).[341] Mechanistic investigations revealed that the initial cyclization occurred via a 5-*exo*-*trig* pathway followed by homoallyl–homoallyl radical rearrangement to form the more stable tertiary radical. The synthesis of linear triquinanes **582** and **583** from **581** is an example of a 'round trip' radical reaction in which the intermediate bicyclic α-carbomethoxy radical cyclizes onto the carbon that originally bore the iodine atom.[342]



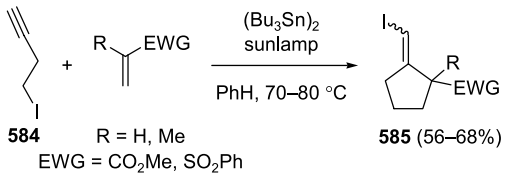
Scheme 150.



Scheme 151.

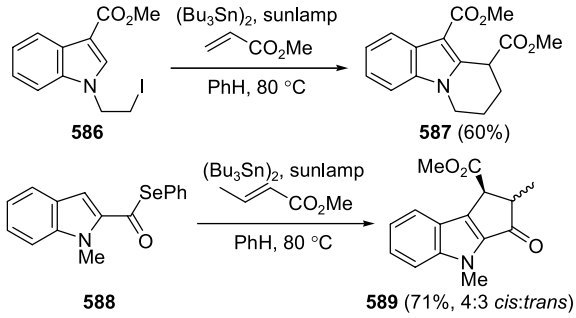
6.2. Cascades incorporating an intermolecular radical conjugate addition

Curran synthesized methylenecyclopentanes **585** via intermolecular RCA of **584** to acrylates and vinyl sulfones followed by 5-*exo*-*dig* cyclization and iodine abstraction (Scheme 152).[343] Conceptually related RCA–cyclization



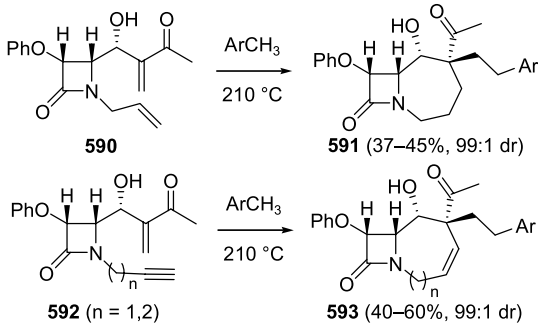
Scheme 152.

cascades involving indoles were reported by Miranda and Cruz-Almanza[344] and Bennasar[345] (Scheme 153). In these reactions, cyclization of the intermediate α-carbonyl radical onto the indole moiety is followed by oxidative rearomatization rather than the atom abstraction that occurs in Curran's work.

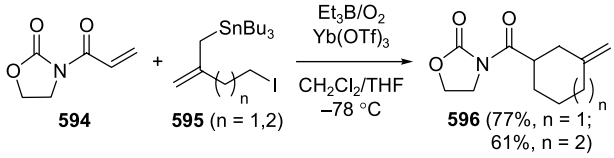


Scheme 153.

Alcaide found that heating Baylis–Hillman adducts **590** and **592** with toluene, xylene, or related compounds produced bicycles **591** and **593** via initial benzylic radical formation, RCA to the enoate acceptor, and 7- or 8-*endo* cyclization of the intermediate α-carbonyl radical (Scheme 154).[346,347] The radical nature of this pathway is indicated by the effect of radical inhibitors on the reaction and the presence of 1,2-diarylethanes as byproducts. Presumably, the steric constraint provided by the β-lactam ring allows the unusual cyclizations to take place.



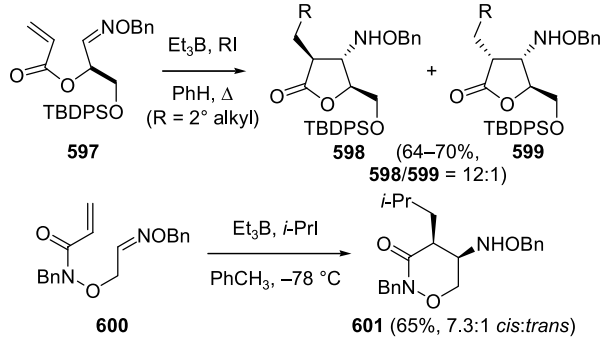
Scheme 154.



Scheme 155.

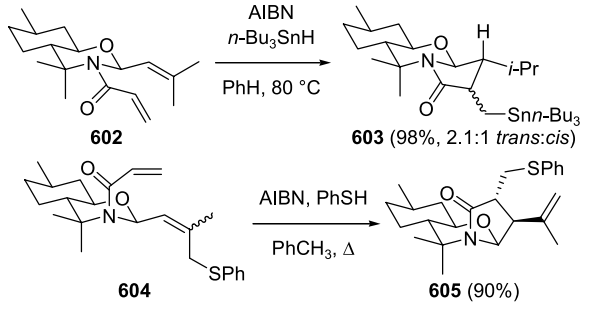
Sibi constructed six- and seven-membered carbocycles via an intermolecular RCA/intramolecular allylation protocol (Scheme 155).[348] β-Substitution on the acrylimide was permitted, and in many cases these reactions were highly diastereoselective. Additionally, the use of an oxazolidinone chiral auxiliary led to excellent levels of diastereoselectivity (>99:1) in the allylation step.

Naito performed tandem intermolecular RCA–cyclizations of oxime ether **597** under tin-free conditions (Scheme 156).[349,350] It is believed that Et_3B acts as initiator, Lewis acid, and chain carrier; the aminoborane adduct is presumably hydrolyzed during workup to afford lactones **598** and **599** in high dr. The diastereoselectivity can be rationalized in terms of minimization of $A^{1,3}$-strain in the transition state. These addition–cyclizations have also been carried out on solid support.[351,352] Recently, Naito has extended this process to include α,β-unsaturated hydroxamates **600** as substrates; in this case, the 6-*exo* cyclization proceeds with cis selectivity in accordance with the Beckwith model.[353]



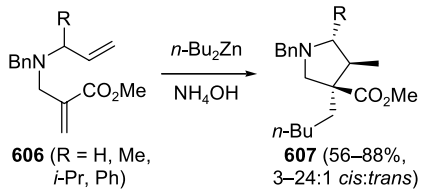
Scheme 156.

Pedrosa studied stereoselective addition–cyclizations of chiral perhydro-1,3-benzoxazines (Scheme 157). Thus, addition of tributylstannyl radical to **602** afforded stannylated lactam **603** with modest dr,[354] whereas the addition–cyclization–elimination cascade of **604** initiated by catalytic amounts of thiophenol delivered **605** as a single diastereomer.[355]



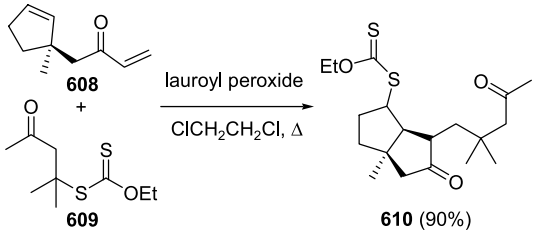
Scheme 157.

Chemla reported the synthesis of pyrrolidines **607** by means of a zinc-mediated RCA–cyclization sequence (Scheme 158).[356] The cyclization proceeded with cis selectivity in accordance with the Beckwith model. Mechanistic studies showed that both the addition and cyclization are radical processes, and that reduction of the pyrrolidinylmethyl radical by *n*-Bu_2Zn regenerates butyl radical, forming an alkylzinc that is subsequently protonated.



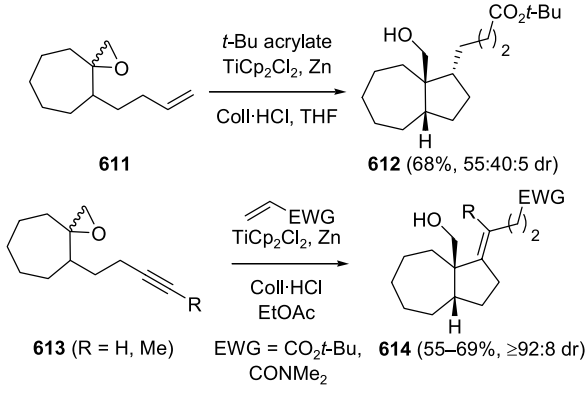
Scheme 158.

Zard found that enones and xanthates such as **608** and **609** undergo an RCA–cyclization cascade that is driven by a xanthate group transfer process (Scheme 159).[357] Adduct **610** could be converted into the linear triquinane framework.



Scheme 159.

Gansäuer performed a cyclization–intermolecular RCA cascade with epoxides **611** and **613** and acrylate or acrylamide acceptors (Scheme 160).[358] The stereoselective formation of tri- and tetrasubstituted olefins **614** by vinyl radical conjugate addition is noteworthy.



Scheme 160.

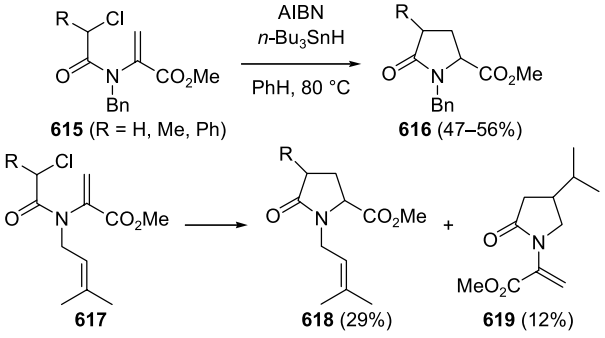
7. Synthesis of amino acids via radical conjugate additions

Radical conjugate additions have been used extensively to prepare amino acids. Many of the methods used to construct α-amino acids entail the addition of nucleophilic radicals to 1,1-disubstituted captodative olefins[359] possessing both an electron-withdrawing group and an electron-donating group. Although it is debatable whether or not these processes are truly RCAs, they are included in this section along with reactions that clearly fall into the RCA category.

A review by Easton gives broad coverage to the synthesis of α-amino acids via radical reactions.[360]

7.1. Intramolecular radical conjugate additions in α-amino acid synthesis

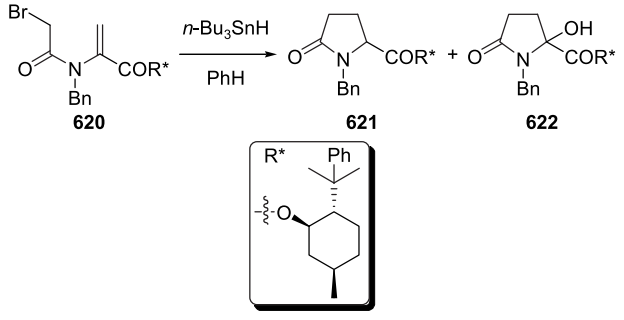
Parsons synthesized pyroglutamates **616** by means of 5-*endo* cyclizations of dehydroalanines **615** (Scheme 161).[361,362] Interestingly, α-chloro amides were better substrates than the corresponding bromides or iodides. Similar effects have been observed in other 5-*endo-trig* cyclizations of α-halo amides.[363,364] The formation of **618** as the major product from **617** demonstrates that in this system 5-*endo* cyclization is faster than the typically favored 5-*exo* pathway. The authors attribute this to the stability of the captodative radical intermediate formed in the 5-*endo* cyclization.



Scheme 161.

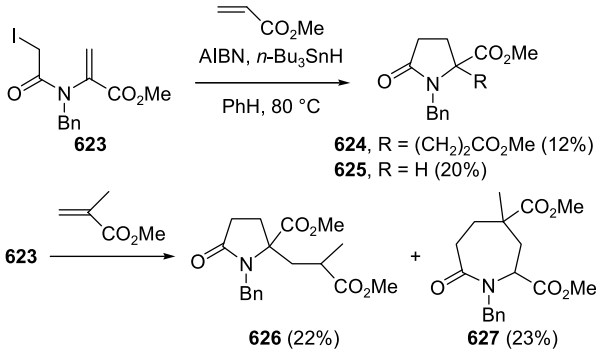
Attempts by Parsons to develop a diastereoselective version of this process met with mixed results. Cyclization of dehydroalanine **620** containing an 8-phenylmenthyl ester delivered pyroglutamate **621** in moderate yield and dr (Table 49).[365] Use of the Et_3B/O_2 initiating system allowed performance of the reaction at a lower temperature and led to slight improvements in the dr. Unfortunately, the yield was low due to competitive formation of hydroxylated pyroglutamate **622**.

Table 49.



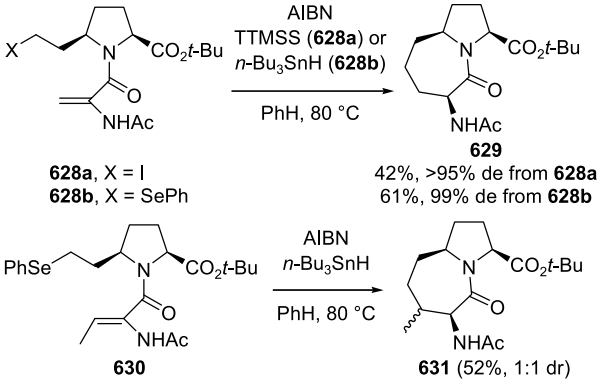
Entry	Conditions	**621** (%)	**622** (%)	dr **621**
1	AIBN, 80 °C	69	—	4:1
2	Et_3B/O_2, 20 °C	22	32	6:1

Parsons next studied trapping with enoates of the captodative radicals generated by cyclization of dehydroalanines (Scheme 162).[366,367] When methyl acrylate was used to trap the radical formed via cyclization of **623**, α-substituted pyroglutamate **624** was obtained in poor yield along with reduction product **625**. However, use of methyl methacrylate afforded the expected pyroglutamate **626** along with seven-membered lactam **627**, the product of intermolecular RCA followed by 7-*endo-trig* cyclization.



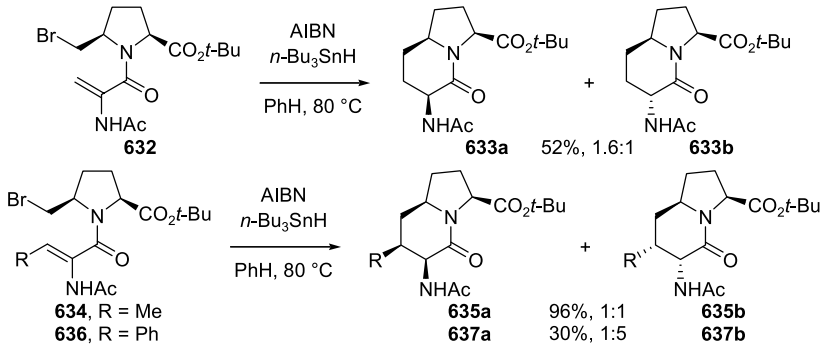
Scheme 162.

Colombo and Scolastico synthesized conformationally constrained dipeptides via 7-*endo* cyclizations of alkyl radicals onto dehydroalanines (Scheme 163).[368–370] The β-unsubstituted dehydroalanine **628** delivered 7,5-fused bicyclic lactam **629** as a single isomer. The greater yield of **629** from phenylselenide **628b** than from iodide **628a** is attributed to the greater thermal stability of the former. Cyclization of β-methyl substituted dehydroalanine **630** was also possible. Lactam **631** was obtained as a 1:1 mixture of epimers at the methyl-bearing carbon, indicating that while the hydrogen abstraction step was diastereoselective, the cyclization step was not.



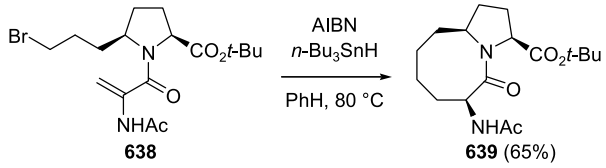
Scheme 163.

Colombo and Scolastico also prepared 6,5-fused bicyclic lactams by this method (Scheme 164).[370] In contrast to the 7,5-systems, lactam **633** was obtained with 1.6:1 dr due to low selectivity in the hydrogen atom abstraction. However, only cis products were obtained from 6-*endo* cyclizations of β-substituted dehydroalanines **634** and **636**, demonstrating that the stereochemistry of hydrogen atom abstraction can be controlled by an adjacent substituent on the six-membered ring.



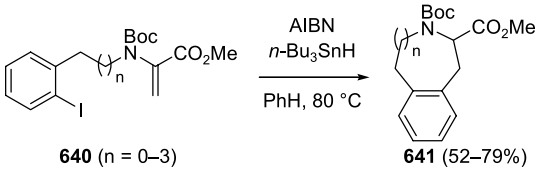
Scheme 164.

Scolastico extended this process to include the synthesis of 8,5-fused bicyclic lactam **639** (Scheme 165).[371] The stereocontrol in the hydrogen atom abstraction is comparable to that observed with the 7,5-systems.



Scheme 165.

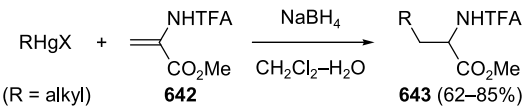
Gibson utilized 6–9-*endo* radical cyclizations of dehydroalanines **640** to prepare conformationally constrained phenylalanine analogues **641** (Scheme 166).[372]



Scheme 166.

7.2. Intermolecular radical conjugate additions in α-amino acid synthesis

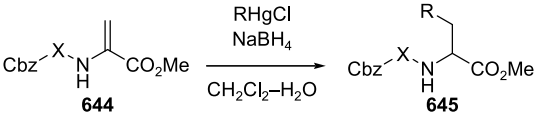
Crich demonstrated that alkyl radicals generated via the reductive mercury method underwent intermolecular conjugate addition to dehydroalanine **642** (Scheme 167).[373] Primary, secondary, and tertiary alkylmercury bromides and chlorides could all be used in this reaction.



Scheme 167.

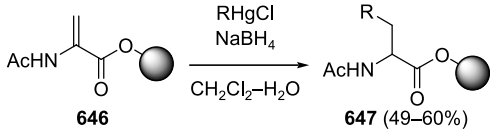
Crich extended this process to the intermolecular RCA of alkyl radicals to dehydroalanine-containing dipeptides **644** (Table 50).[374] The stereocenter present in each substrate exerted little influence over the hydrogen atom abstraction, as the products **645** were obtained in low de. Tripeptides were also viable substrates in this reaction, producing RCA adducts in good yield (87–88%) and poor de (3–15%).

Table 50.



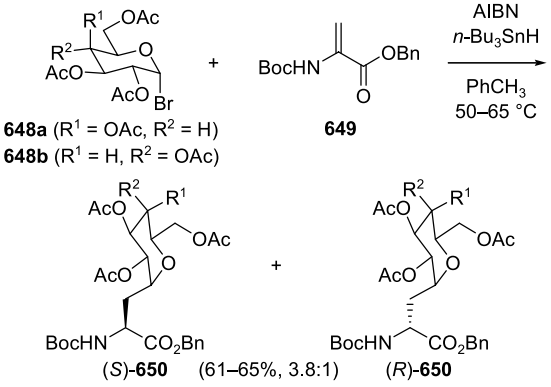
Entry	X	R	Yield (%)	de (%)
1	L-Val	c-C_6H_{11}	71	11
2	L-Phe	c-C_6H_{11}	64	5
3	L-Cys(Z)	c-C_6H_{11}	70	6
4	L-Ser	c-C_6H_{11}	42	1
5	L-Pro	i-Pr	98	1

Yim and Vidal showed that the Crich method could be employed in the solid-phase synthesis of α-amino acids by anchoring the dehydroalanine radical acceptor to Wang resin (Scheme 168).[375] Cleavage of the *N*-acetyl amino acid from the resin was accomplished by acid treatment.



Scheme 168.

As part of a *C*-glycopeptide synthesis, Kessler performed diastereoselective conjugate additions of radicals derived from glycosyl bromides **648** to dehydroalanine **649** (Scheme 169).[376] α-*C*-Glycosides were formed exclusively, and the subsequent hydrogen atom abstraction occurred with moderate (3.8:1) dr.



Scheme 169.

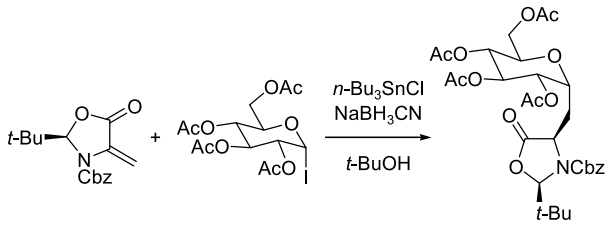
Table 51.

651 652

Entry	R^1	R^2	Method[a]	Yield (%)	*trans*:*cis*
1	Ph	*c*-C_6H_{11}	A	52	91:9
2	Ph	Adamantyl	B	>95	92:8
3	Ph	Me	C	58	78:22
4	Ph	*t*-Bu	A	70	>98:2
5	Bn	*c*-C_6H_{11}	B	86	6:94
6	BnO	*c*-C_6H_{11}	B	60	2:98

[a] A: R^2I, AIBN, *n*-Bu_3SnH; B: R^2HgCl, $NaBH_3CN$; C: R^2I, *n*-Bu_3SnCl, $NaBH_3CN$, hν.

Beckwith disclosed that optically pure methyleneoxazolidinones **651** undergo diastereoselective RCAs, affording amino acid derivatives **652** (Table 51).[377,378] Reactions employing AIBN–*n*-Bu_3SnH (method A) afforded higher dr's than those using organomercury halides and $NaBH_3CN$ (method B), but reactions conducted under the latter conditions gave better yields. Additionally, the dr increased with increasing radical size. Interestingly, the major product varied from trans to cis depending on the nitrogen protecting group; high selectivities for either isomer were possible. α-D-Glucosyl-(*R*)-alanine derivative **654** could be synthesized as a single diastereomer by means of this process (Scheme 170).

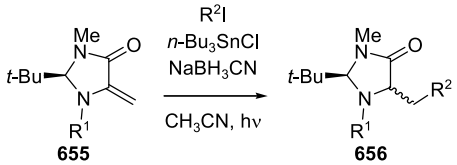


653 654 (88%)

Scheme 170.

Similar results were obtained in Beckwith's investigation of RCAs to chiral methyleneimidazolidinones **655** performed under catalytic tin conditions (Table 52).[379] *N*-Benzoyl substrates provided *trans*-**656** as the major products, whereas phenylcarbamates delivered *cis*-**656** predominantly. Calculated structures of the intermediate radicals reveal that in both cases the phenyl ring is located on the bottom face of the molecule due to the influence of the *tert*-butyl group. However, only in the *N*-benzoyl substrates does the phenyl ring effectively shield the radical, directing hydrogen atom abstraction to the top face and yielding trans products. In the phenylcarbamates, the phenyl ring is too far removed from the radical-bearing carbon atom and the hydrogen atom abstraction occurs *anti* to the *tert*-butyl group, affording cis products. This rationale can also explain the results obtained with methyleneoxazolidinones **651** (Table 51).

Table 52.

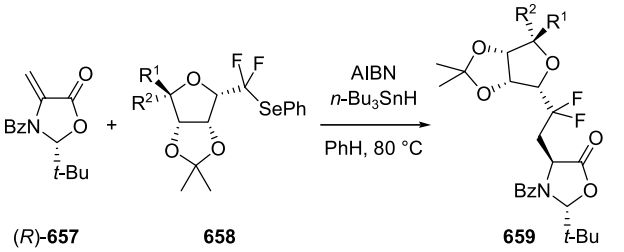


655 656

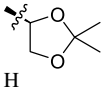
Entry	R^1	R^2	Yield (%)	*trans*:*cis*
1	COPh	*c*-C_6H_{11}	70	21:1
2	COPh	*i*-Pr	73	16:1
3	CO_2Ph	*c*-C_6H_{11}	71	1:6
4	CO_2Ph	*i*-Pr	72	1:6.8

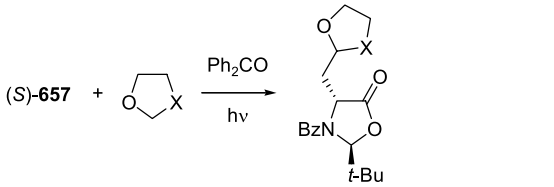
The chiral methyleneoxazolidinones introduced by Beckwith have been applied by others in the synthesis of unusual α-amino acids. Motherwell prepared difluoromethylene-linked serine glycosides **659** via addition of difluoromethyl radicals to *N*-benzoyl methyleneoxazolidinone (*R*)-**657** (Table 53).[380] The trans isomers were the major products, and bulky substituents on the carbohydrate moiety were tolerated.

Table 53.



(*R*)-**657** **658** **659**

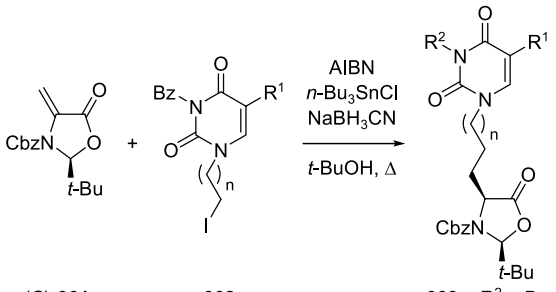
Entry	R^1	R^2	Yield (%)	*trans*:*cis*
1	H		91	4:1
2	H	H	86	5.7:1
3	CH_2OTBS	H	71	6.1:1



660a (X = O, 52%)
660b (X = CH_2, 55%, dr = 57:43)

Scheme 171.

Table 54.



(*S*)-**661** **662** **663a**, R^2 = Bz; **663b**, R^2 = H

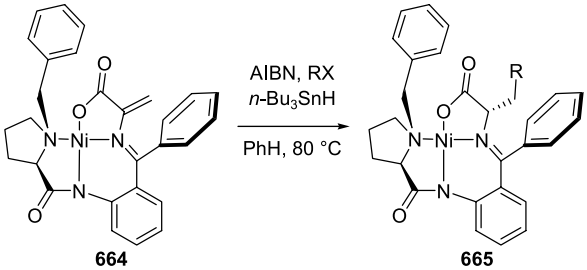
Entry	R^1	*n*	Time (h)	**663a** (%)	**663b** (%)	Reduction products (%)
1	CH_3	1	16	24	30	—
2	CH_3	2	40	—	25	21
3	H	1	7	47	—	46
4	H	2	40	—	44	51

Pyne studied additions of radicals derived from ethers and acetals to (*S*)-**657** (Scheme 171).[381] Photolysis of (*S*)-**657** in 1,3-dioxolane afforded *trans*-**660a** as a single diastereomer. Use of THF as the radical precursor also led exclusively to the trans product as a mixture of diastereomers at C2 of the THF ring.

Jones and Iley synthesized pyrimidine-containing amino acid derivatives **663** by stereoselective RCAs to *N*-Cbz methyleneoxazolidinone (*S*)-**661** (Table 54).[382,383] Debenzoylated adducts **663b** were formed in amounts that increased with reaction time, and products from the reduction of iodides **662** were also obtained. Use of iodoalkylpurines analogous to **662** afforded similar results.

Belokon' introduced nickel(II)–dehydroalanine complex **664** as an effective chiral acceptor in RCAs (Table 55).[384] The (*S*,*S*)-diastereomers of **665** predominated, and the de generally increased with alkyl radical size. In reactions of primary alkyl radicals (entries 1 and 2), epimerization of the product mixture enhanced the de's to >90%.

Table 55.

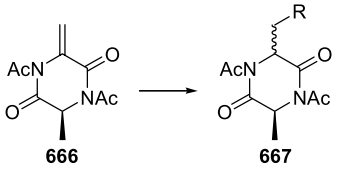


664 **665**

Entry	R	Yield (%)	de (%)
1	Et	90	54
2	Bn	94	40
3	*i*-Pr	90	60
4	*t*-Bu	90	92

Chai demonstrated that alanine-containing methylidenepiperazine-2,5-dione **666** is a useful template for the stereocontrolled synthesis of amino acid derivatives via RCAs (Table 56).[385,386] Despite the small size of the methyl substituent, excellent dr's were obtained, especially with large alkyl radicals. The authors propose that the neighboring *N*-acetyl moiety forces the methyl group into a pseudoaxial orientation, thereby directing hydrogen atom abstraction to the opposite face of the piperazinedione radical.

Table 56.

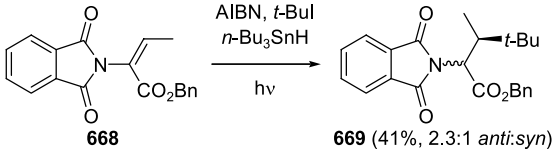


666 **667**

Entry	R	Method[a]	Yield (%)	*cis*:*trans*
1	Me	A	52	4:1
2	Et	A	55	5:1
3	*i*-Pr	B	66	*cis* only
4	*t*-Bu	A	65	*cis* only
5	Bn	A	63	*cis* only

[a] A: RI, AIBN, n-Bu_3SnH; B: RHgCl, $NaBH_4$.

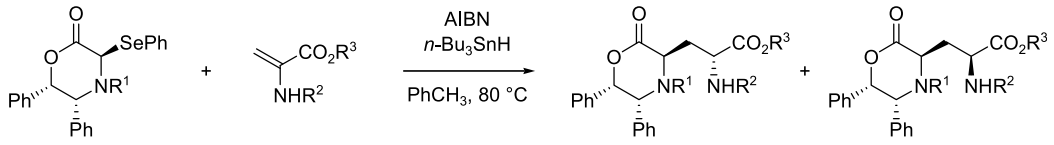
In a rare example of intermolecular RCA to a β-substituted dehydroamino acid, Renaud reported the addition of *tert*-butyl radical to *N*-phthaloyl derivative **668** to give *anti*-**669** as the major diastereomer (Scheme 172).[387] The stereoselectivity is attributed to hydrogen atom abstraction occurring from a conformation that minimizes 1,3-allylic strain.



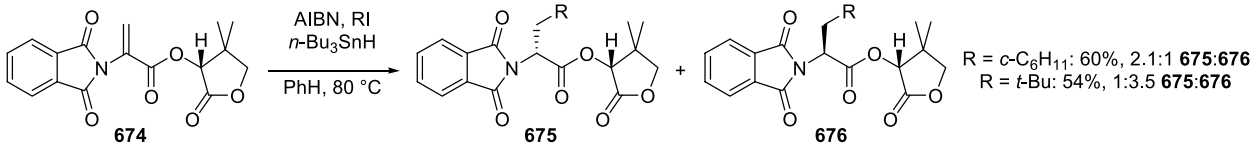
668 **669** (41%, 2.3:1 *anti*:*syn*)

Scheme 172.

Kabat synthesized protected diaminoglutamic acids by employing chiral radical precursors **670** in intermolecular RCAs to dehydroalanines **671** (Scheme 173).[388] This



Scheme 173.



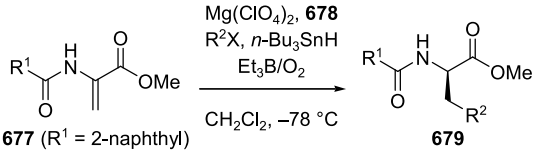
Scheme 174.

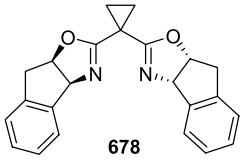
process was tolerant of a variety of protecting groups on both reactants. While the initial radical conjugate addition step was completely stereoselective, the hydrogen atom abstraction proceeded with poor diastereoselectivity. Separable adducts **672** and **673** could be manipulated to afford a variety of diaminoglutamic acid derivatives.

Vidal explored the use of pantolactone derivative **674** in intermolecular RCAs (Scheme 174).[389] The adducts were obtained with modest dr; however, the nature of the selectivity reversed when *tert*-butyl radical was employed in place of cyclohexyl radical. The inclusion of Lewis acids led to minor improvements in yields and dr's.

Sibi used a chiral Lewis acid to effect an enantioselective hydrogen atom transfer to synthesize optically active α-amino acid derivatives **679** from 2-naphthylamide-protected dehydroalanine **677** (Table 57).[390] The 2-naphthoyl moiety afforded significantly better ee's than did other amide or carbamate groups. A variety of alkyl radicals as well as the acetyl radical could be employed in the RCA. A seven-membered chelate between the chiral Lewis acid and the two carbonyls present in **677** is proposed to account for the enantioselectivity.

Table 57.

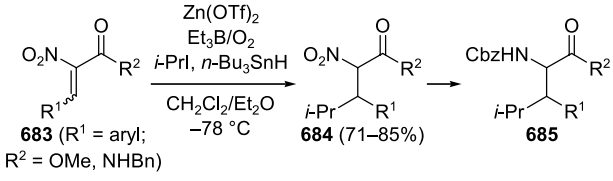




Entry	R^2X	Yield (%)	ee (%)
1	AcBr	76	80
2	$MeOCH_2Br$	71	65
3	EtI	72	85
4	*i*-PrI	62	83
5	*t*-BuI	54	27

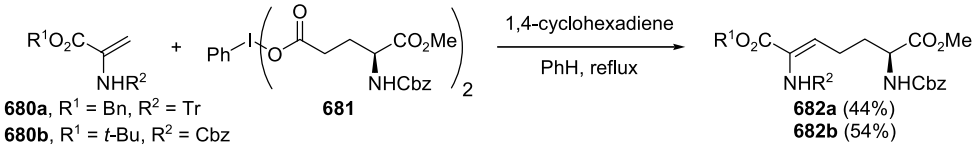
Vederas attempted to synthesize diaminopimelic acid derivatives via RCA of alkyl radicals generated by thermolysis of diacyloxyiodobenzene **681** (Scheme 175).[391] Unexpectedly, unsaturated adducts **682** were formed, indicating that the intermediate radical is unable to abstract a hydrogen atom from 1,4-cyclohexadiene. Alkenes **682** were converted into the target compounds by enantioselective hydrogenation.

Castle found that β-substituted α-amino acids **685** could be prepared via a sequence of Lewis acid promoted intramolecular RCA to β-aryl α,β-unsaturated α-nitro esters and amides **683** followed by nitro reduction and protection (Scheme 176).[392] Use of *n*-Bu_3SnD revealed that both **684** and **685** could be obtained with minimal amounts of D–H exchange, suggesting that racemization of the sensitive α-nitro adducts **684** can be avoided and paving the way for development of a stereoselective variant.



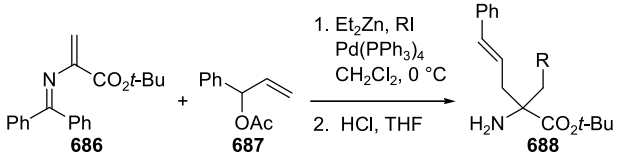
Scheme 176.

Takemoto discovered a tandem RCA–allylic alkylation reaction of dehydroalanine imine **686**, allylic acetate **687**, and alkyl halides mediated by Et_2Zn and $Pd(PPh_3)_4$, resulting in formation of α,α-disubstituted amino acids



Scheme 175.

Table 58.

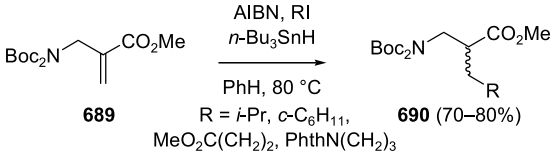


Entry	R	Yield (%)
1	*i*-Pr	56
2	*c*-C_6H_{11}	56
3	*c*-C_5H_9	58

688 (Table 58).[393,394] Presumably, Et_2Zn fills several roles in this process: it initiates the radical reaction, it serves as a Lewis acid to activate **686** towards RCA, and its complex with the initial adduct fragments to generate a zinc enolate and ethyl radical. Allylic phosphates and aryl-substituted allylic acetates other than **687** could also be employed.

7.3. Synthesis of β- and γ-amino acids via radical conjugate additions

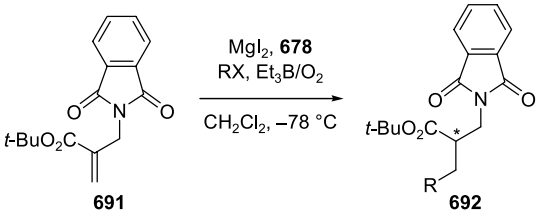
Radical conjugate additions have also been used to synthesize β- and γ-amino acids. In these reactions, the acceptor is a simple α,β-unsaturated ester or amide. Receveur prepared β-amino acids **690** via conjugate addition of alkyl radicals to α-substituted acrylate **689** (Scheme 177).[395]



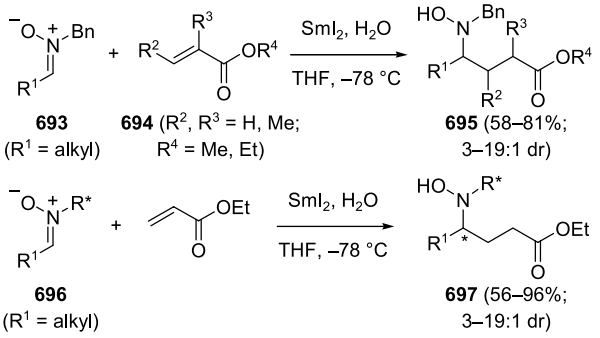
Scheme 177.

Sibi performed a similar reaction in enantioselective fashion by employing the chiral Lewis acid generated from MgI_2 and bisoxazoline **678** (see Table 57) in RCAs to acrylate **691** (Table 59).[396] The ee's of protected β-amino acids **692** increased with the bulk of the alkyl radical. The data in Table 59 were obtained from reactions employing a stoichiometric amount of Lewis acid, but in some cases a catalytic amount was sufficient. The authors propose that the enantioselective hydrogen atom transfer occurs via an eight-membered chelated cyclic radical.

Table 59.

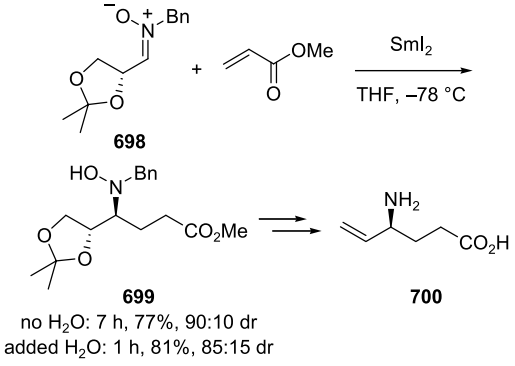


Entry	RX	Yield (%)	ee (%)
1	CH_3OCH_2–Br	85	68
2	Et–I	82	36
3	*i*-Pr–I	91	62
4	*t*-Bu–I	85	92



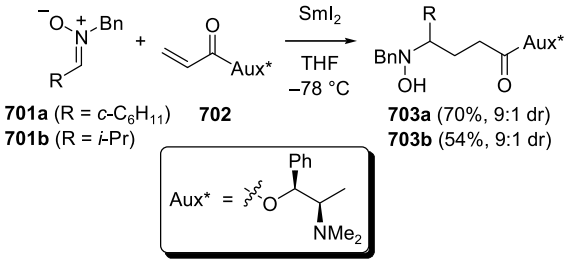
Scheme 178.

Vallée and Py found that radical anions formed by single electron transfer from SmI_2 to nitrones **693** function as nucleophilic radicals in conjugate additions to acrylates **694**, generating γ-amino acids **695** (Scheme 178).[397] The addition of H_2O as a proton source often resulted in increased yields. In cases where two stereocenters were formed or where one stereocenter was formed and a chiral nitrone was employed, good dr's were observed. Additionally, nitrones **696** bearing various chiral auxiliaries could be used in a stereoselective synthesis of γ-amino acids **697**. Vallée and Py employed this methodology in a formal total synthesis of the γ-amino acid (*S*)-vigabatrin (**700**, Scheme 179)[398] and a total synthesis of the pyrrolizidine alkaloid (+)-hyacinthacine A_2.[399]



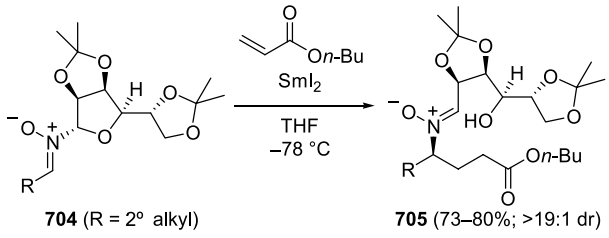
Scheme 179.

In related studies, Skrydstrup found that α,β-unsaturated amides and esters could function as acceptors in RCAs of nitrone-derived radicals and examined the use of chiral auxiliaries appended to the acceptor.[400] Of the auxiliaries tested, (1*R*,2*S*)-*N*-methylephedrine proved to be the most effective, providing γ-amino acid derivatives **703** in high dr (Scheme 180).



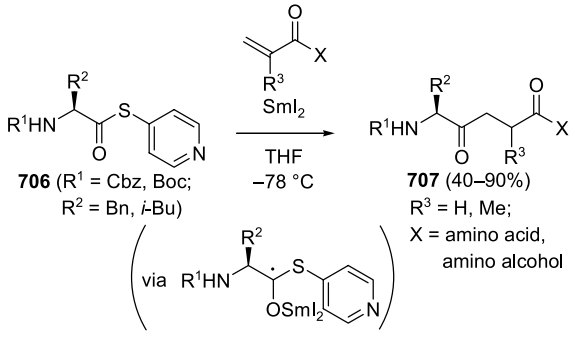
Scheme 180.

Skrydstrup developed an alternative approach to the asymmetric synthesis of γ-amino acids by attaching a D-mannose-based chiral auxiliary to nitrones **704** (Scheme 181).[401] The auxiliary was cleaved from **705** via acidic hydrolysis. Use of a C5-deoxy-D-ribose derivative of **704** led to the enantiomeric γ-amino acids in good yields and ee's.



Scheme 181.

Skrydstrup disclosed that 4-pyridyl thioesters of phenylalanine and leucine (**706**) function as amino acid acyl radical equivalents in SmI_2-promoted conjugate additions to α,β-unsaturated amides (Scheme 182).[402] α-Amino acyl radicals typically decarbonylate to form stabilized α-amino radicals, thereby necessitating the development of a synthon for this species. Mechanistic studies suggested that this reaction proceeds via addition of a ketyl-type radical anion derived from **706**, not an anion generated by further reduction, to the acceptor.[403]



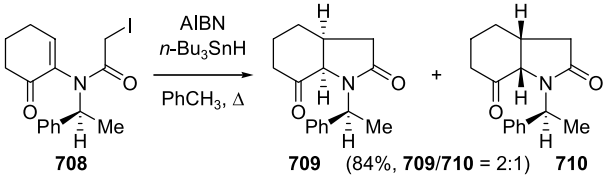
Scheme 182.

8. Radical conjugate additions in natural products synthesis

The ability to use a particular synthetic technique to effect a transformation on a complex starting material containing multiple functional groups and stereocenters is often cited as evidence of the utility of that method. Accordingly, the wide scope of radical conjugate addition has been demonstrated by its application in numerous natural product or complex molecule total syntheses. This section focuses on the use of RCAs in total syntheses from 1991 to the present; earlier examples are covered in the review of Jasperse, Curran, and Fevig.[404] Emphasis is placed on RCAs conducted on complex, late-stage intermediates and stereoselective RCAs. Moreover, coverage of intramolecular RCAs is mostly restricted to reactions not contained in the Zhang review.[6]

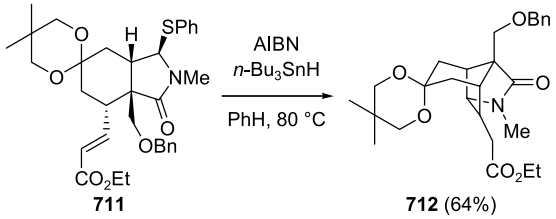
8.1. Additions to α,β-unsaturated ketones, esters, and amides

Ikeda and Ishibashi used a chiral-auxiliary-mediated 5-*endo-trig* cyclization in the total synthesis of (−)-lycorane (Scheme 183).[405] The reaction proceeded with good yield and modest dr; increasing the bulk of the auxiliary led to a greater dr (3.2:1) but significantly lower yield (42%).

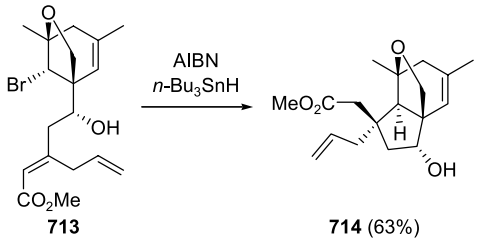


Scheme 183.

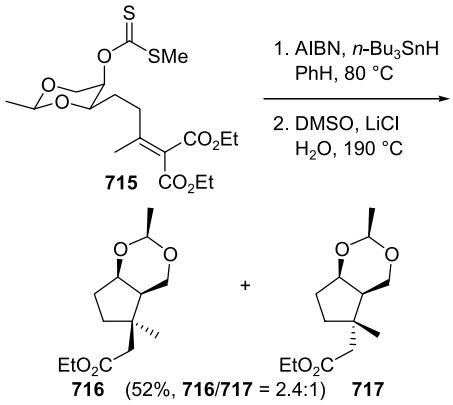
Hart utilized an intramolecular RCA of the α-acylamino radical generated from phenylsulfide **711** in the total synthesis of (±)-21-oxogelsemine (Scheme 184).[406,407] Also noteworthy is the creation of an all-carbon quaternary stereocenter via 5-*exo* RCA in Hart's approach to the C19 quassinoids (Scheme 185).[408]



Scheme 184.



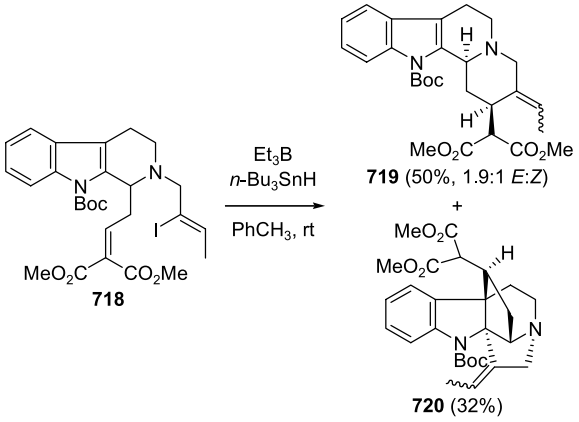
Scheme 185.



Scheme 186.

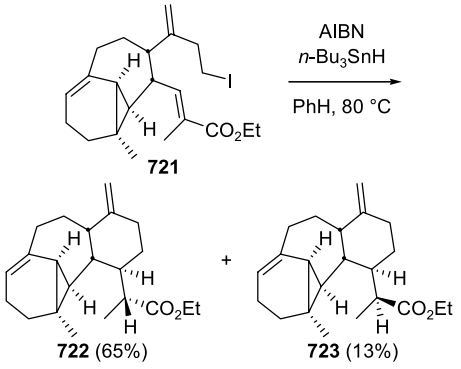
Wu formed the quaternary-stereocenter-bearing cyclopentane portion of clavulactone via 5-*exo* cyclization of diester **715** and subsequent decarboxylation (Scheme 186).[409,410] The extra carboxylate was necessary due to the fact that monoester substrates cyclized to give mainly undesired diastereomers.[411] The major product **716** of the intramolecular RCA of **715** possesses the proper configuration for conversion into clavulactone.

Takayama performed a 6-*exo-trig* vinyl radical cyclization of α,β-unsaturated diester **718** and obtained tetracyclic indole **719**, the *E*-isomer of which was converted into (±)-geissoschizine (Scheme 187).[412] Bridged pentacyle **720**, the product of vinyl radical addition to the indole moiety and subsequent intramolecular RCA, was also produced in moderate yield.



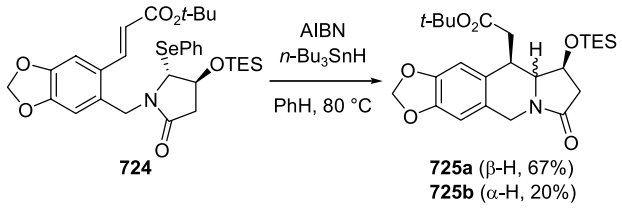
Scheme 187.

In the context of a total synthesis of cerorubenic acid-III methyl ester, Paquette reported the intramolecular RCA of enoate **721** (Scheme 188).[413] This transformation afforded desired product **722** in good yield along with minor amounts of a diastereomer **723**, demonstrating that the RCA step was completely stereoselective and the subsequent hydrogen atom abstraction proceeded with a 4.9:1 dr.



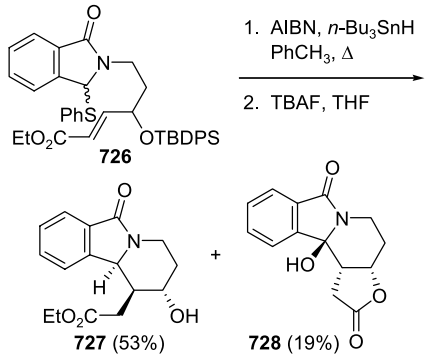
Scheme 188.

Ishizaki and Hoshino performed a diastereoselective 6-*exo-trig* cyclization of the α-acylamino radical derived from phenylselenide **724** in a synthetic approach towards (+)-lycorine (Scheme 189).[414] The nature of the alcohol protecting group was significant, as use of an acetate in place of the triethylsilyl group resulted in lower dr.



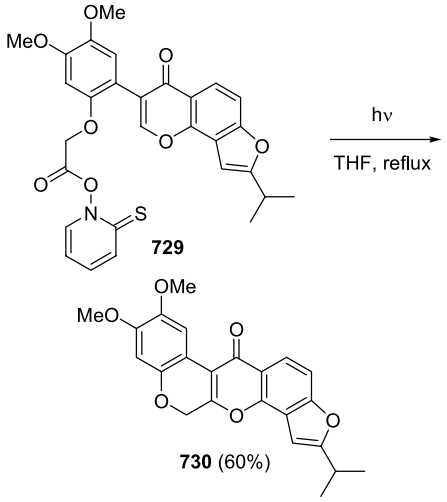
Scheme 189.

As part of an approach towards the Tacaman indole alkaloid D/E ring system, Hunter found that the benzylic α-acylamino radical generated from **726** participated in a 6-*exo* cyclization onto an enoate, affording products **727** and **728** after desilylation (Scheme 190).[415,416] The hydroxylation leading to **728** presumably occurred during the desilylation step. The major product **727** possesses the same configuration as the Tacaman skeleton and is derived from cyclization via a chairlike transition state that places both the enoate and the silyloxy group in axial positions. Such a conformation may serve to minimize steric interactions between these two groups.

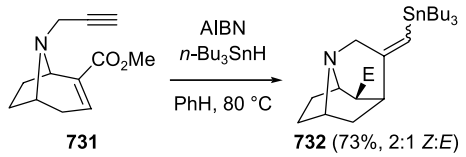


Scheme 190.

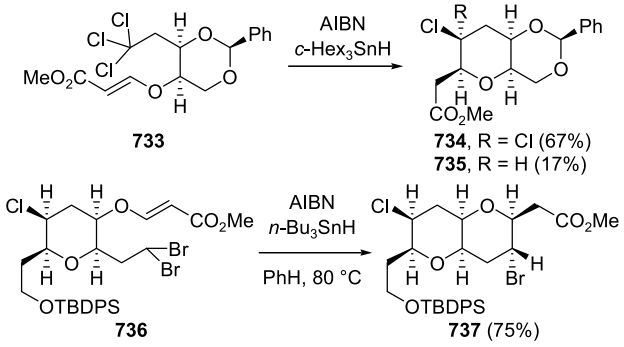
Whiting mimicked a step in the proposed biosynthesis of rotenone by performing a 6-*endo* intramolecular RCA that utilizes the aryloxymethyl radical formed by photolysis of **729** (Scheme 191).[417] Thermal elimination of a putative pyridylthio adduct under the reaction conditions leads to unsaturated product **730**.



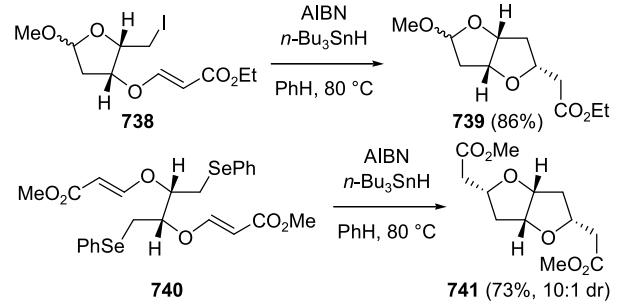
Scheme 191.



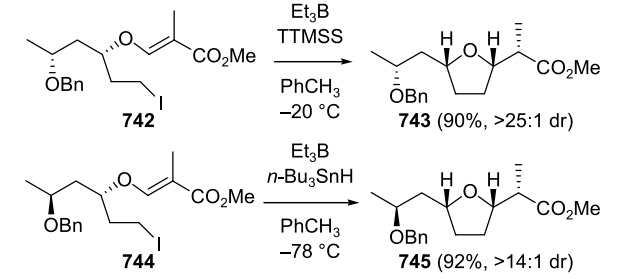
Scheme 192.



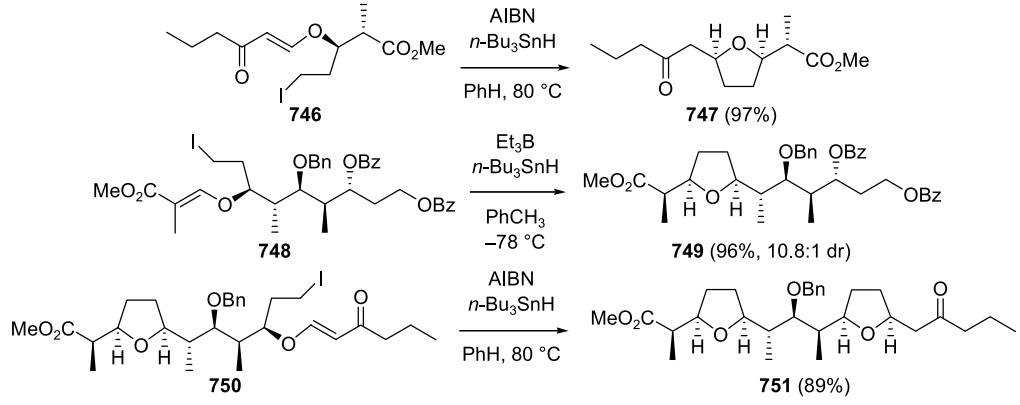
Scheme 193.



Scheme 194.



Scheme 195.



Scheme 196.

Kozikowski reported the 6-*endo-trig* vinyl radical cyclization of cocaine derivative **731** as a key step in the synthesis of constrained tropane analogues (Scheme 192).[418,419] The vinylstannanes could be protodestannylated or used in Stille couplings to prepare a variety of target structures.

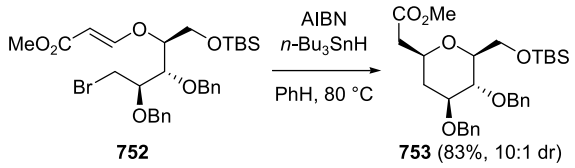
Lee pioneered the use of β-alkoxyacrylates as radical acceptors[15–21] in natural products total synthesis. In the total synthesis of 3*Z*- and 3*E*-dactomelynes, two stereoselective intramolecular β-alkoxyacrylate RCAs were employed to construct the fused bis(tetrahydropyran) motif.[420] Thus, cyclization of tartrate-derived trichloride **733** yielded a mixture of dichloride **734** and monochloride **735** (Scheme 193); this mixture was inconsequential as **734** was converted to **735** via stereoselective dechlorination. Then, exposure of dibromide **736** to AIBN/*n*–Bu_3SnH delivered bicyclic bromide **737** as the sole product.

Lee subsequently prepared the tetrahydrofuran ring of (−)-*trans*-kumausyne and the fused bis(tetrahydrofuran) moiety of (−)-kumausallene via stereoselective 5-*exo-trig* radical cyclizations of β-alkoxyacrylates **738** and **740**, respectively, (Scheme 194).[421,422]

Lee performed intramolecular RCAs to β-alkoxymethacrylates in total syntheses of (+)-methyl nonactate[423] and (+)-methyl-8-*epi*-nonactate[424,425] (Scheme 195). These reactions featured highly stereoselective cyclization and hydrogen atom abstraction steps. The authors propose that hydrogen atom abstraction by the intermediate radical occurs from the least hindered face of a conformation in which both 1,3-allylic strain and electrostatic interactions are minimized.

Lee synthesized all three *cis*-2,5-disubstituted tetrahydrofurans of pamamycin-607 via intramolecular RCAs (Scheme 196).[426,427] Intermediates **747** and **751** were constructed from reactions of β-alkoxyenones, whereas tetrahydrofuran **749** arose from a β-alkoxymethacrylate RCA. A β-alkoxyenone radical cyclization also figured prominently in Lee's total synthesis of (−)-centrolobine.[428]

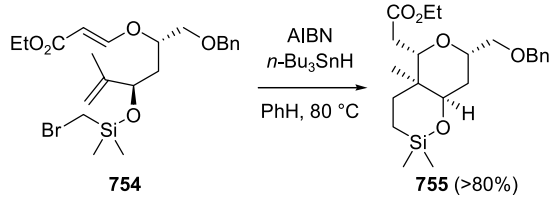
In the context of a total synthesis of ambruticin, Lee prepared β-alkoxyacrylate **752** from L-arabinose and successfully converted it into *cis*-tetrahydropyran **753** by



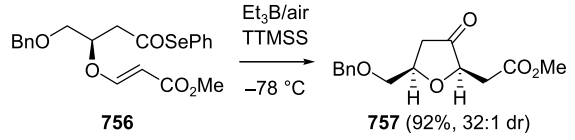
Scheme 197.

means of a stereoselective intramolecular RCA (Scheme 197).[429]

Lee performed two different β-alkoxyacrylate radical cyclizations during the total synthesis of lasonolide A.[430,431] The diastereoselective construction of tetrahydropyran **755** from **754**, in which adjacent quaternary and tertiary stereocenters are formed, is especially noteworthy (Scheme 198). This cyclization is postulated to proceed through a chairlike transition state. Similar reactions were employed by Lee in the preparation of lasonolide A analogues.[432]



Scheme 198.



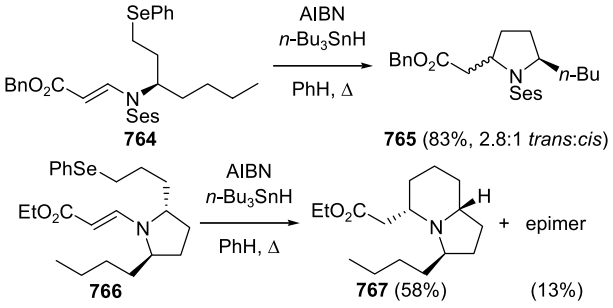
Scheme 199.

Evans carried out the cyclization of an acyl radical onto a β-alkoxyacrylate[20] in the total synthesis of (−)-kumausallene (Scheme 199).[433] The low reaction temperature was necessary to ensure high diastereoselectivity.

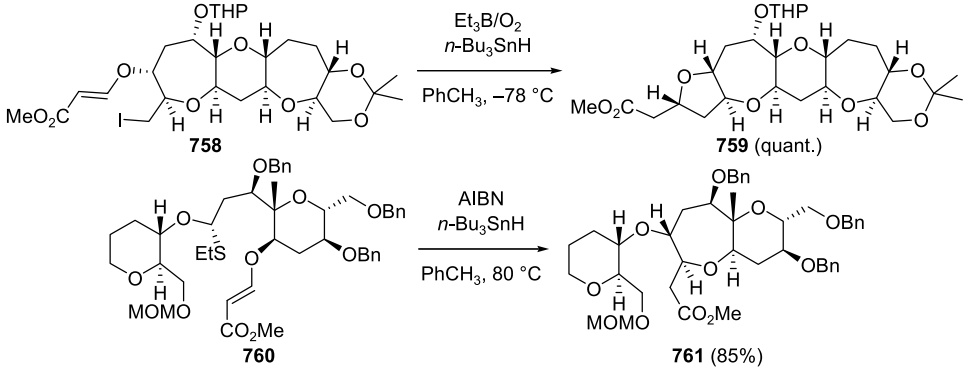
Sasaki and Tachibana utilized a 5-*exo* β-alkoxyacrylate radical cyclization to construct the A-ring of gymnocin A[434,435] and a related 7-*exo* RCA to form the G-ring of ciguatoxin (Scheme 200).[436,437]

Following encouraging results in model systems,[438,439] Hirama and Inoue performed a 7-*exo* β-alkoxyacrylate radical cyclization to form the G ring of ciguatoxin CTX3C (Scheme 201).[440] The product of 6-*exo* cyclization onto the terminal olefin of **762** was isolated in minor amounts; the fact that oxepane **763** predominates in this reaction is a testament to the facility of intramolecular RCAs relative to simple radical cyclizations. Although related substrates that were devoid of the terminal olefin cyclized in higher yields,[441,442] the route proceeding through **762** was the most efficient overall.

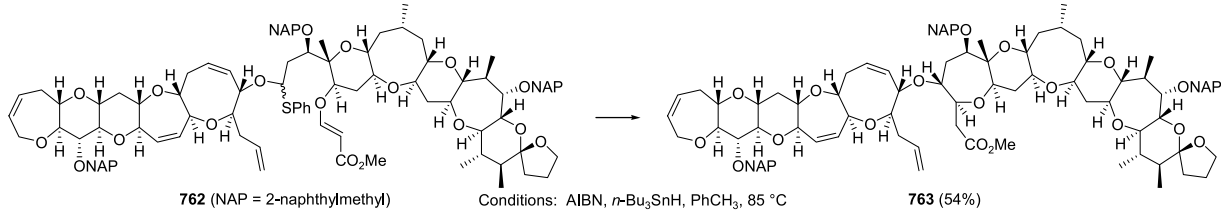
Lee utilized 5- and 6-*exo* β-aminoacrylate RCAs[22–26] in the total synthesis of (−)-indolizidine 223AB (Scheme 202).[443] Both reactions were moderately diastereoselective. Lee



Scheme 202.



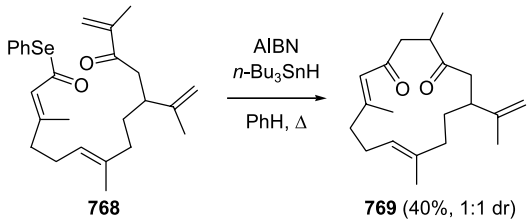
Scheme 200.



Scheme 201.

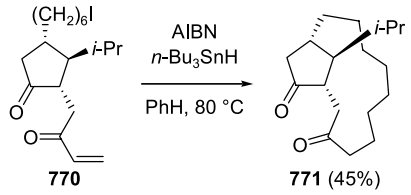
used similar β-aminoacrylate cyclizations in total syntheses of other indolizidines[444] and (+)-monomurine 1.[445]

In an approach to the furanocembranoid lophotoxin, Pattenden performed a 14-*endo* macrocyclization of the acyl radical derived from **768** (Scheme 203).[446,447] Carbocycle **769** was formed as a mixture of diastereomers that was converted into a single racemic furan in the following step.

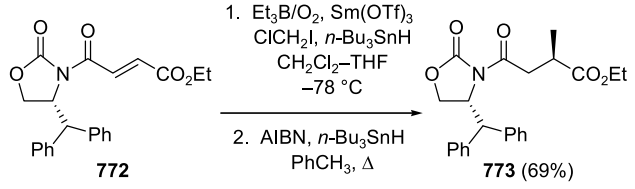


Scheme 203.

Building on previous studies,[72] Robertson constructed bridged macrocycle **771** from the intramolecular RCA of enone **770** (Scheme 204).[448,449] The adduct was employed in a formal total synthesis of roseophilin.

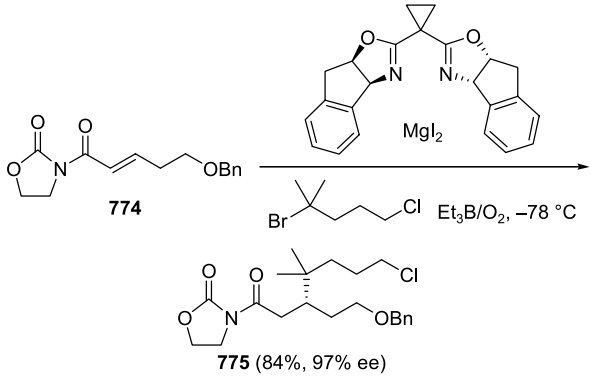


Scheme 204.



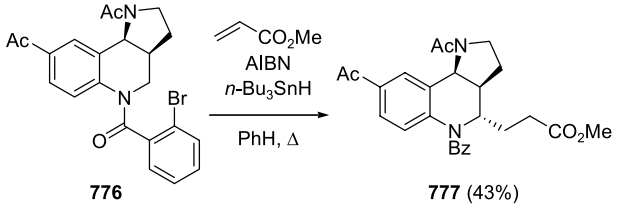
Scheme 205.

Sibi conducted a regio- and diastereoselective intermolecular RCA of chloromethyl radical to desymmetrized fumarate **772** in the course of total syntheses of (−)-nephrosteranic acid and (−)-roccellaric acid (Scheme 205).[450,451] The chloride was subsequently reduced to provide **773**, the product of formal methyl radical addition to **772**. Use of benzylic radicals in this process led to syntheses of a variety of lignans,[451] and an intermolecular RCA–allylstannane trapping sequence with fumarate-type acceptors was employed to generate matrix metalloproteinase inhibitors.[452] Recently, Sibi utilized an enantioselective intermolecular RCA[130] in the total synthesis of (+)-ricciocarpins A and B (Scheme 206).[453]



Scheme 206.

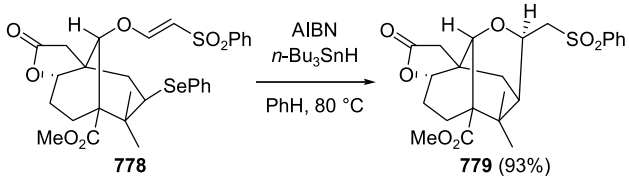
Naito found that aryl bromide **776** reacted with methyl acrylate to provide **777** via a 1,5-hydrogen atom translocation–intermolecular RCA sequence (Scheme 207).[454] A pentacyclic byproduct resulting from oxidative cyclization of the initially formed aryl radical onto the other aromatic ring was isolated in 19% yield. The major product **777** served as an intermediate in a formal total synthesis of martinelline.



Scheme 207.

8.2. Additions to vinyl sulfoxides and sulfones

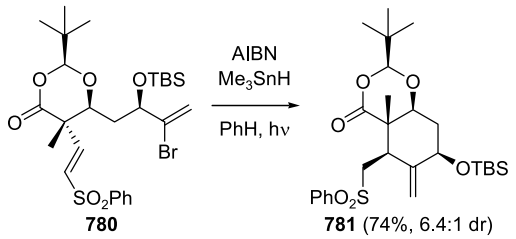
In an approach to garsubellin A, Nicolaou synthesized bridged polycyclic ether **779** by 6-*exo* intramolecular RCA onto a β-alkoxyvinyl sulfone acceptor (Scheme 208).[455] The adduct was isolated in high yield as a single diastereomer.



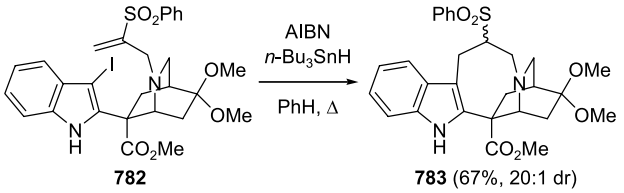
Scheme 208.

Crich prepared the C-ring of taxol by means of 6-*exo* vinyl radical cyclization of vinyl sulfone **780** (Scheme 209).[456] The major diastereomer of **781** is likely formed from a transition state in which the maximum number of substituents occupy equatorial positions.

As part of a study of iboga alkaloid analogues, Sundberg reported the 8-*endo* indolyl radical cyclization of vinyl



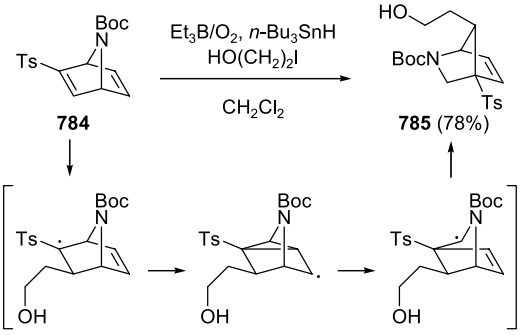
Scheme 209.



Scheme 210.

sulfone **782** (Scheme 210).[457] The analogous vinyl sulfoxide cyclized in lower yield (28%).

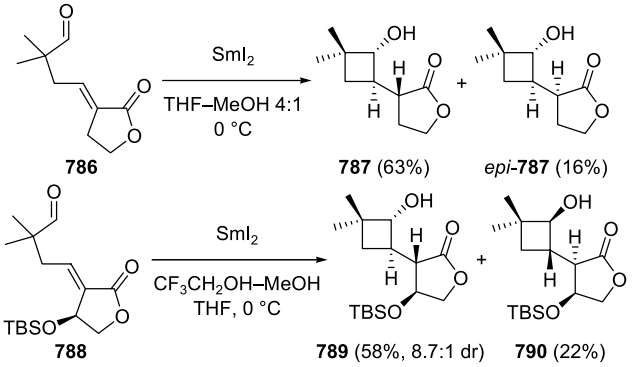
During a synthesis of α-kainic acid, Hodgson constructed 2-azabicyclo[2.2.1]hept-5-ene **785** from reaction of vinyl sulfone **784** with 2-iodoethanol (Scheme 211).[458] This conversion likely proceeds by intermolecular RCA followed by homoallylic radical rearrangement and fragmentation of the resulting cyclopropylcarbinyl radical to form a stabilized α-carbamoyl radical.



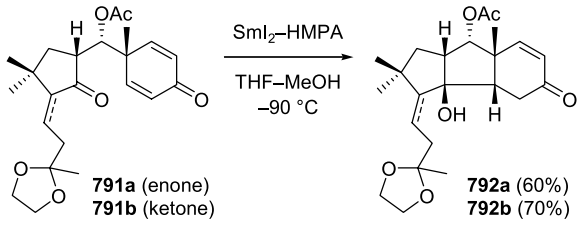
Scheme 211.

8.3. SmI_2-mediated radical conjugate additions

In the course of studies directed towards pestalotiopsin A, Procter examined the 4-*exo-trig* ketyl radical cyclizations[188–190] of lactones **786** and **788**, in which three stereocenters are created (Scheme 212). Lactone **786** cyclized in good yield with reasonable dr, whereas its *Z*-isomer gave a complex mixture of four products.[459,460] Cyclization of OTBS-substituted lactone **788** is noteworthy due to the apparent stereocontrol provided by coordination of Sm(III) to the silyloxy group.[461] 2,2,2-Trifluoroethanol served to protonate the intermediate Sm(III) enolate rapidly, thereby preventing OTBS elimination.



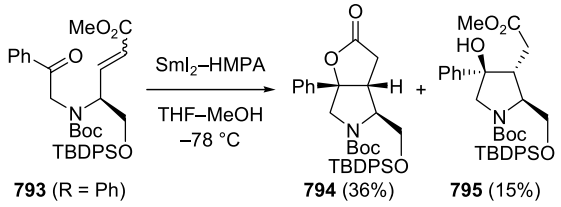
Scheme 212.



Scheme 213.

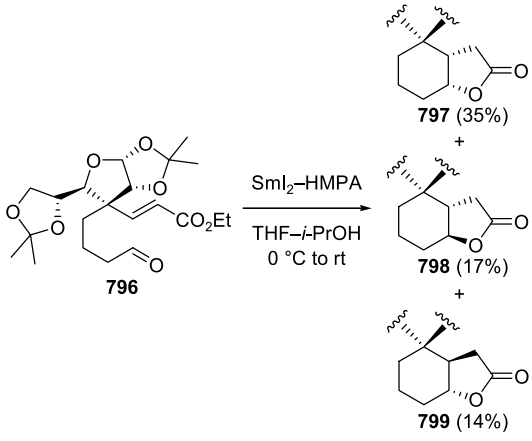
In an approach to taxol, Arseniyadis obtained *cis-syn-cis* tricycles **792** from 5-*exo* ketyl radical cyclizations of enone **791a** and ketone **791b** (Scheme 213).[462,463]

Hashimoto and Shirahama performed the 5-*exo* ketyl radical cyclization of **793** in the context of a formal total synthesis of FPA (Scheme 214).[464] In the presence of MeOH, the desired isomer **794** was produced with modest selectivity; in the absence of MeOH, undesired isomer **795** was obtained exclusively.



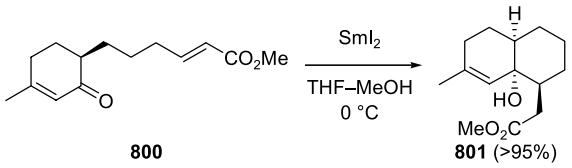
Scheme 214.

Tadano utilized a 6-*exo-trig* ketyl RCA in the total synthesis of (−)-anastrephin (Scheme 215).[465,466] Products **797** and **798** are presumably derived from a chairlike transition state in which the enoate is axially disposed in order to avoid steric interactions with the neighboring isopropylidene ring. The major product **797** was converted into the target molecule.



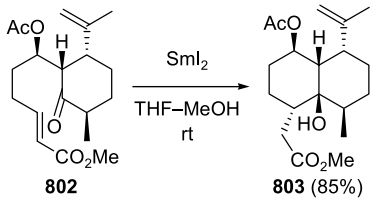
Scheme 215.

In the course of a synthesis of (−)-C_{10}-desmethyl arteannuin B, Little prepared bicyclic γ-hydroxy ester **801** as a single isomer via 6-*exo* ketyl radical cyclization of **800** (Scheme 216).[467] The stereoselectivity is presumably due to chelation by Sm in the transition state.



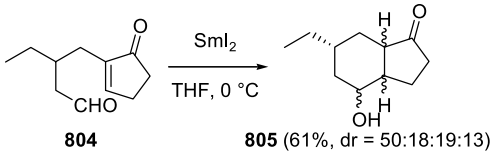
Scheme 216.

Matsuda constructed the *cis*-decalin skeleton of vinigrol by means of stereoselective 6-*exo* ketyl RCA[204] of enoate **802** (Scheme 217).[468] Acetylation of the secondary alcohol was necessary in order to preclude formation of a chelated radical intermediate, which adopted a conformation that prevented cyclization.



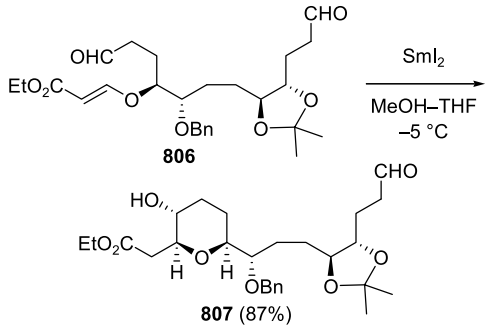
Scheme 217.

Tori applied previously developed methodology[205] to obtain hydrindanone **805** as a mixture of four isomers from the SmI_2-mediated 6-*endo* cyclization of enone **804** (Scheme 218).[469] Each isomer could be used in the total synthesis of coronafacic acid.



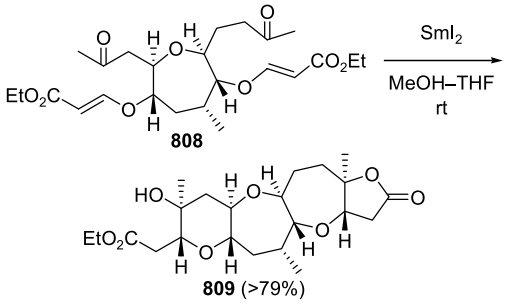
Scheme 218.

Many natural products possessing cyclic ethers have been constructed using Nakata's SmI_2-mediated cyclizations.[207–212] Takahashi and Nakata performed a 6-*exo* β-alkoxyacrylate ketyl radical cyclization in the total synthesis of mucocin (Scheme 219).[470] Pyran **807** was obtained as a single isomer, presumably due to chelation in the transition state. Interestingly, the desired formyl group was selectively reduced, with no reaction of the other formyl group observed under these conditions. A similar transformation was used in the total synthesis of pyranicin.[471]



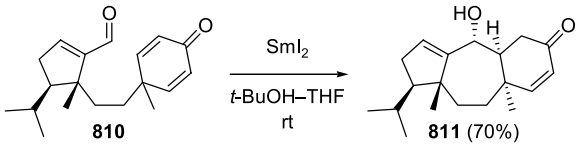
Scheme 219.

Nakata made use of several 6- and 7-*exo* β-alkoxyacrylate ketyl radical cyclizations during the total synthesis of brevetoxin B.[472,473] The conversion of **808** to **809** is noteworthy as it entails simultaneous formation of the tetrahydropyran C ring and oxepane E ring (Scheme 220). Nakata also employed related SmI_2-mediated cyclizations in approaches to maitotoxin, gambierol,[474] yessotoxin, and adriatoxin.[475] Additionally, Yamamoto utilized this reaction in the total synthesis of gambierol to construct the tetrahydropyran C and F rings,[476–479] and Sasaki fashioned both tetrahydropyrans and oxepanes via this method in a total synthesis of gambierol[480] and an approach to ciguatoxin.[481]



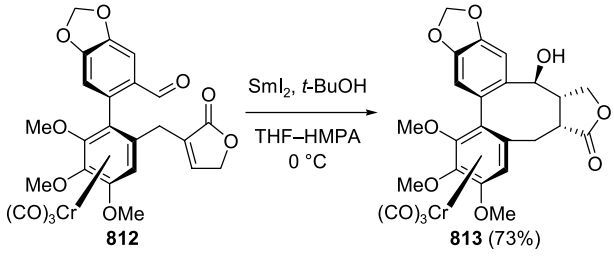
Scheme 220.

In a synthesis of the guanacastepene core, Lee used a 7-*exo* ketyl radical cyclization to desymmetrize the cyclohexadienone moiety of **810**, creating the C8 quaternary stereocenter in the process (Scheme 221).[482] Tricycle **811** was obtained as a single isomer in good yield, which represents an improvement over a previous route.[483]



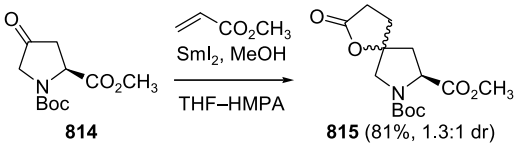
Scheme 221.

The 8-*endo* intramolecular ketyl RCA of **812** was a key step in Molander's total synthesis of (−)-steganone (Scheme 222).[484] Compound **813** was obtained as a single diastereomer from this reaction.



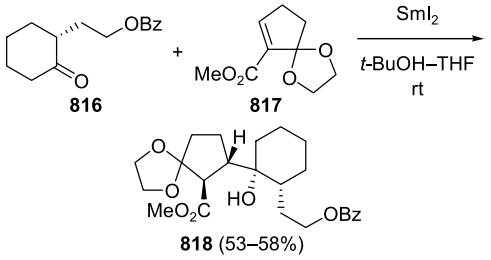
Scheme 222.

Yoshifuji prepared spirocycle **815** by intermolecular addition of the ketyl radical generated from **814** to methyl acrylate and subsequent lactonization (Scheme 223).[485,486] The major diastereomer of **815** was then converted into lycoperdic acid.



Scheme 223.

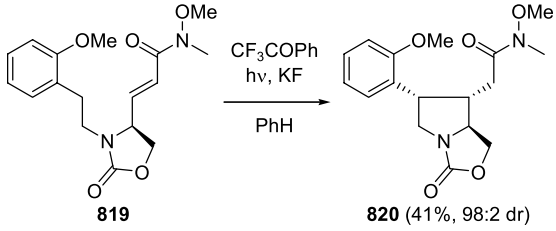
In an approach to the phorbol skeleton, Little performed a SmI_2-mediated intermolecular RCA to join ketone **816** and enoate **817** (Scheme 224).[487] The product was obtained as a single diastereomer, presumably due to reaction via a transition state that maximizes complexation of samarium with the oxygen atoms of the reactants.



Scheme 224.

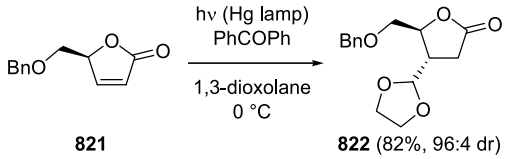
8.4. Other tin-free radical conjugate additions

Hashimoto used photochemistry to generate a benzylic radical from substrate **819**, which subsequently underwent a 5-*exo* RCA onto the α,β-unsaturated Weinreb amide with modest yield but high cis selectivity (Scheme 225).[488] The corresponding enoate gave a slightly higher yield but delivered a 1:1 mixture of diastereomers. Pyrrolidine **820** was converted into MFPA, an acromelic acid analogue.

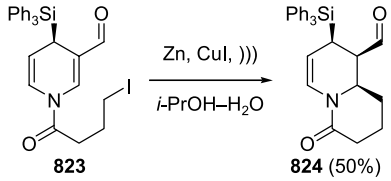


Scheme 225.

In the course of synthesizing the HIV protease inhibitor UIC-94017, Ghosh found that chiral furanone **821** served as an excellent acceptor for diastereoselective intermolecular RCAs. Thus, photochemically generated 1,3-dioxolanyl radicals[259–262] added to **821** to give *trans*-lactone **822** in high yield and dr (Scheme 226).[489]

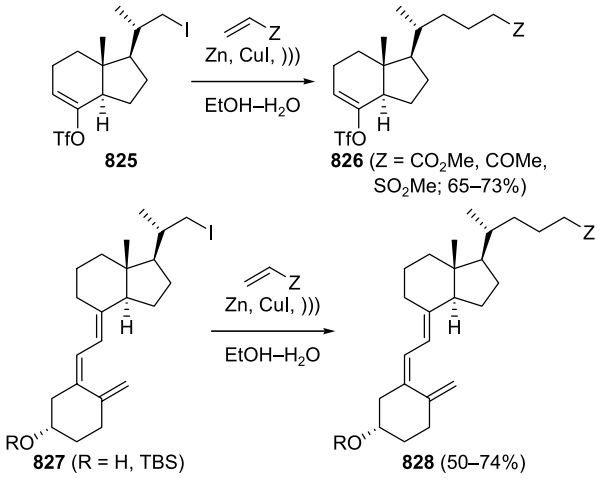


Scheme 226.



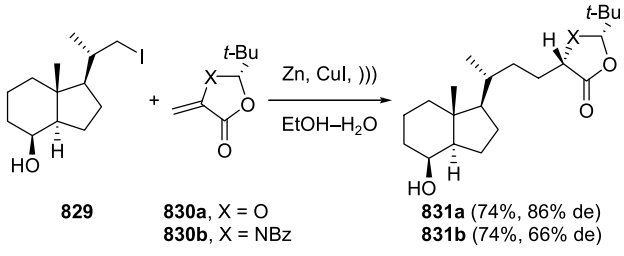
Scheme 227.

Mangeney performed a regio- and stereoselective 6-*exo* intramolecular RCA of 1,4-dihydropyridine **823** under Luche conditions[283–286] (Scheme 227).[490,491] The product was transformed into both (−)-lupinine and (+)-epi-lupinine.

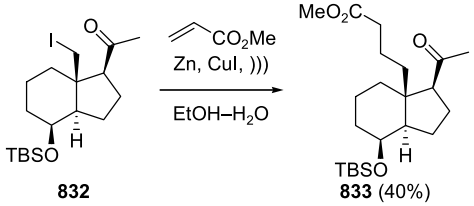


Scheme 228.

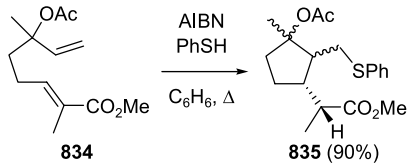
Mouriño used the Luche conditions with acrylate, enoate, and vinyl sulfone acceptors to synthesize vitamin D_3 analogues (Scheme 228).[492–494] In conjunction with studies of stereoselective Luche-type intermolecular RCAs,[287–289] Sarandeses and Pérez Sestelo later employed chiral acceptors **830**, allowing introduction of a stereocenter at C-24 (Scheme 229).[495–497] In a synthesis of C-18-modified vitamin D_3 analogues, Sarandeses performed an intermolecular RCA of hindered neopentylic iodide **832** to methyl acrylate (Scheme 230).[498]



Scheme 229.



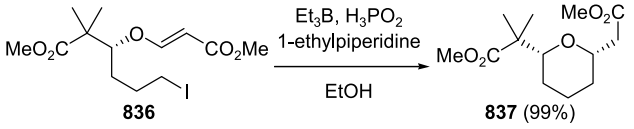
Scheme 230.



Scheme 231.

Barrero reported a sulfanyl radical-triggered 5-*exo* cyclization of enoate **834**, which delivered cyclopentane **835** in high yield as a mixture of diastereomers (Scheme 231).[499] Elimination of acetic acid from **835** yielded the corresponding alkene as a single diastereomer, which was transformed into (±)-dehydroiridomyrmecin.

In the total synthesis of (+)-SCH 351448, Lee used a β-alkoxyacrylate radical cyclization with Et_3B as initiator and EPHP as chain carrier[324] to construct pyran **837** in excellent yield as a single isomer (Scheme 232).[500]

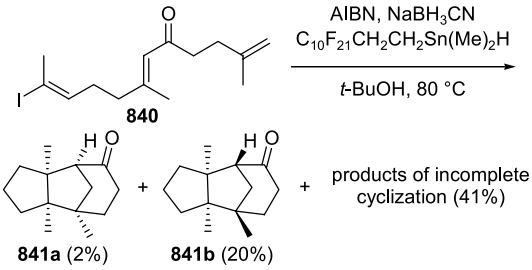


Scheme 232.

8.5. Cascade reactions involving radical conjugate additions

Radical cascade reactions are useful in total syntheses due to their ability to produce complex products from relatively simple starting materials. Feldman disclosed an entry to the brefeldin ring system that entails phenylthio radical addition to the disubstituted alkene of **838**, cyclopropylcarbinyl radical fragmentation, 16-*endo* intramolecular RCA, 5-*exo* transannular cyclization, and β-phenylthio radical fragmentation (Scheme 233).[501] The transannular cyclization provided only cis-fused isomers.

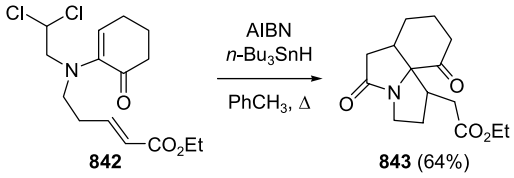
Curran constructed gymnomitrene ketone (**841a**) and isogymnomitrene ketone (**841b**) via 'round trip' radical reaction of **840** (Scheme 234).[502] In addition to activating the neighboring alkene for the initial 5-*exo* vinyl radical cyclization, the ketone also serves to direct the second cyclization down the 6-*endo* pathway. Although the yields are modest, the one-step construction of a bridged tricyclic



Scheme 234.

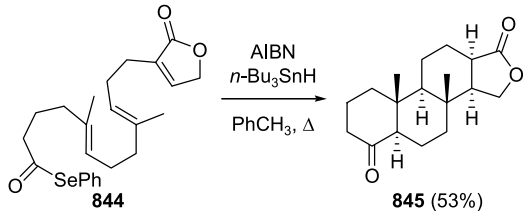
nucleus possessing three quaternary carbon atoms is noteworthy.

Parsons utilized a 5-*endo*/5-*exo* intramolecular RCA cascade to prepare the angularly fused 5,5,6-tricyclic ring system characteristic of the *Erythrina* alkaloids (Scheme 235).[503] The product was obtained as a 1:1 mixture of diastereomers.

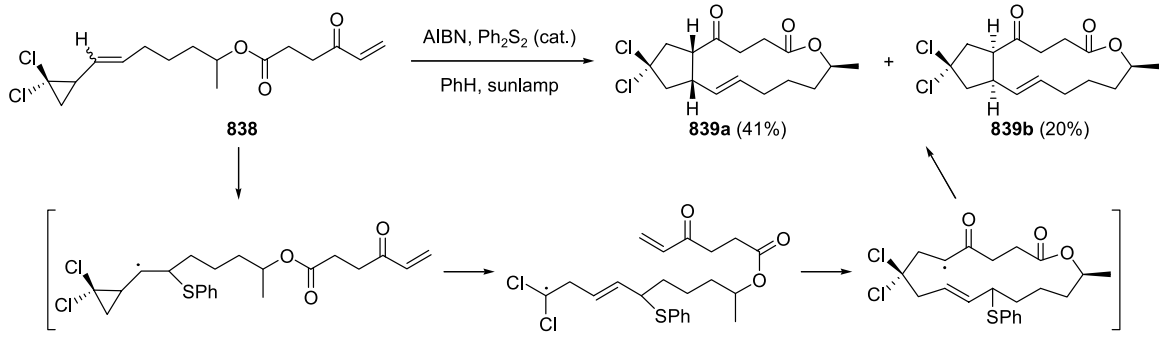


Scheme 235.

Pattenden's studies of radical cascade reactions[326–330] include multiple applications to total synthesis. A key step in the total synthesis of spongian-16-one was the polycyclization of phenyl selenoester **844**, affording *trans*,*anti*,*trans*,*anti*,*cis*-tetracycle **845** as the major product (Scheme 236).[504,505] A small amount (12%) of the *cis*, *anti*, *trans*, *anti*, *cis*-tetracycle was also obtained, which may have been generated by epimerization after cyclization. A similar polycyclization initiated by photoinduced electron transfer



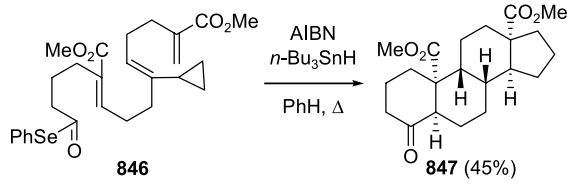
Scheme 236.



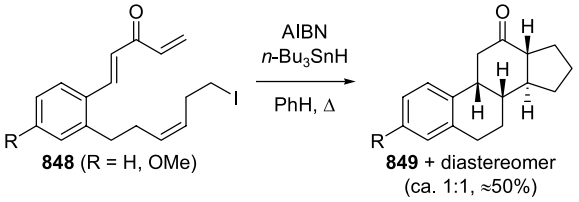
Scheme 233.

was used by Demuth to prepare (±)-3-hydroxyspongian-16-one.[506]

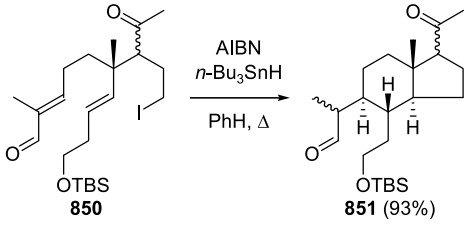
Pattenden has investigated radical cascade approaches to steroids, some of which employ RCAs. For example, the conversion of **846** into **847** features a 6-*endo* RCA followed by another 6-*endo* radical cyclization, cyclopropylcarbinyl radical fragmentation, 9-*endo* RCA, and transannular cyclization (Scheme 237).[507,508] This process yielded the uncommon all-cis stereochemistry in the steroid product. Additionally, Pattenden synthesized the estrone skeleton via the macrocyclization–transannulation cascade reaction of dienone **848** (Scheme 238).[509,510] Also, Takahashi developed a tandem radical cyclization that yields a steroid partial structure (Scheme 239).[511]



Scheme 237.



Scheme 238.



Scheme 239.

9. Conclusions

An impressive array of transformations can be conducted by utilizing RCA methodology. Recent years have seen advances in the ability to conduct these reactions in stereoselective fashion as well as the introduction of tin-free protocols and the development of novel cascade processes. The scope of RCAs has been demonstrated by numerous applications in the synthesis of natural products and other complex molecules. Despite these impressive achievements, many challenges remain. Thus, it is likely that the radical conjugate addition field will remain a ripe area for discovery.

Acknowledgements

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Biographical sketch

Sarat Chandra Srikanth Gorantla was born in Hyderabad, India. He received his MSc Degree in 1996 from the University of Hyderabad. He earned his PhD in 2002 from Indian Institute of Technology, Bombay under the supervision of Professor Girish Kumar Trivedi. He was awarded UGC and GATE fellowships during his PhD. He currently is working as a postdoctoral fellow with Professor Steven L. Castle. His research interests include the design and synthesis of complex natural products.

Steven L. Castle was born in 1971 in Albuquerque, New Mexico. His first exposure to organic chemistry came during summers in high school, when he worked in the laboratory of his grandfather, Professor Raymond N. Castle of the University of South Florida. He received his BS with Honors in chemistry from Brigham Young University in 1995, where he performed undergraduate research with Professor Jerald S. Bradshaw. He earned his PhD in 2000 from The Scripps Research Institute under the direction of Professor Dale L. Boger. After a 2-year stay as a National Institutes of Health postdoctoral fellow in the laboratory of Professor Larry E. Overman at the University of California, Irvine, he began his independent academic career at Brigham Young University in 2002. Professor Castle's research interests encompass the development of new methodology directed towards the total synthesis of complex natural products, with an emphasis on radical chemistry. He is the recipient of a Research Innovation Award from Research Corporation.

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Synthesis of two calix[4]arene diamide derivatives for extraction of chromium(VI)

Selahattin Bozkurt, Aysegul Karakucuk, Abdulkadir Sirit and Mustafa Yilmaz*

Department of Chemistry, Selçuk University, 42031 Konya, Turkey

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Abstract—The synthesis of four diamide derivatives of the *p-tert*-butylcalix[4]arenes from the reaction of 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene **2** with various primary amines were reported. The ^{1}H and ^{13}C NMR, data showed that the synthesized compounds exist in the cone conformation. The complexing properties of these compounds toward $Cr_2O_7^{2-}/HCr_2O_7^{-}$ anions are also studied. It has been observed that receptors **5** and **6** are better extractant than the compounds **3** and **4**. The protonated alkyl ammonium form of **5** and **6** is an effective extractant for transferring $HCr_2O_7^{-}/Cr_2O_7^{2-}$ anions from an aqueous phase into a dichloromethane layer.

1. Introduction

Much attention has been paid in recent years to chemical separation techniques that involve the design and synthesis of new extraction reagents for metal ions. This attention results in part from environmental concerns, efforts to save energy, and recycling at the industrial level. In this respect, supramolecular chemistry has provided solutions in the search for molecular structures that can serve as building blocks for the production of sophisticated molecules by anchoring functional groups oriented in such a way that they delineate a suitable binding site.[1]

Calixarenes are a family of cyclic oligomers prepared from formaldehyde and *para*-substituted phenols via cyclic condensation under alkaline conditions. It was suggested that the calixarenes could be regarded as the third generation of supramolecules, after crowns and cyclodextrins.[1,2] These phenol-based macrocycles have proven to be excellent ligands for the formation of stable complexes with cations, anions, or neutral molecules.[3]

The molecular recognition of anionic guest species by positively charged or electron deficient neutral abiotic receptor molecules is an area of intense current interest. The importance of favorable amine, amide, or imide (–NH_2/OC–NH/OC═N) hydrogen bonding interactions for anion binding has recently been exploited in the design of calix[4]arene anion receptors, although such host molecules are still relatively rare. Several studies on anion coordination have reported using calixarene based chelating units.[4–10] For example, a few excellent approaches emphasized by Beer et al.[5] regarding calixarene based anion receptors, and the work highlighted by Gale[6] for anion and ion-pair receptor chemistry are complimentary studies in the field of anion coordination. Among anions, chromate and dichromate anions are important because of their high toxicity,[9a,b] and also because of their presence in soils and waters.[9c] Chromium(VI) is a carcinogen in humans and animals, with chromates and dichromates being both mutagenic and genotoxic. Chromium(VI) requires intracellular reduction for activation, and this in vivo reduction can produce several reactive intermediates such as chromium(V) and chromium(IV) that can target and damage DNA.[9d] Chromate and dichromate (CrO_4^{2-} and $Cr_2O_7^{2-}$) are dianions with oxide functionalities at their periphery. Nevertheless, since the periphery of the anions has oxide moieties, these are potential sites for hydrogen bonding to the host molecule. Recently we have demonstrated that the amine base derivatives of calix[4]arenes are very effective toward chromate and dichromate anions.[6–10] The main focus of this work is the design of new calixarene-based ionophores that effectively bind anions and can be useful for multiple applications such as laboratory, clinical, environmental, and industrial process analysis. In our previous work,[10] we have extended the field of research of design structures based on a calix[4]arene platform for the extraction of dichromate anions. Herein, we report synthesis and extraction studies of new designed calix[4]arene platform with alkyl amide derivatives on their lower rim.

Keywords: Calix[4]arene; Dichromate anions; Solvent extraction; Diamide.
* Corresponding author. Tel.: +90 332 2232774; fax: +90 332 2410520; e-mail: myilmaz@selcuk.edu.tr

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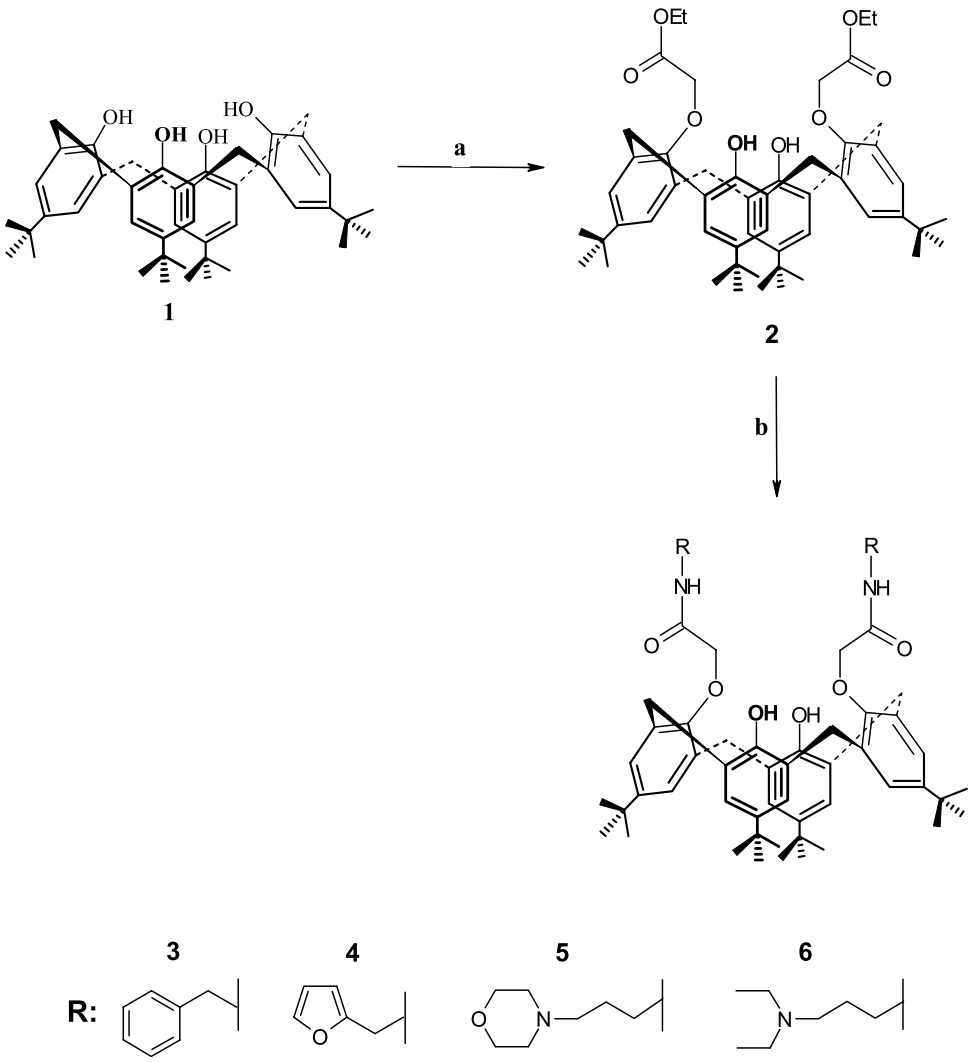
2. Results and discussion

2.1. Design and synthesis of the new hosts

In this work, we extend our previous studies and explore the binding properties of calix[4]arene amide derivatives **3–6** towards anions such as dichromate. To achieve the desired goal, *p-tert*-butylcalix[4]arene **1** was chosen as the precursor.[11] A synthetic scheme was developed to enable its derivatization: the synthetic route is depicted in Scheme 1. The synthesis of compounds **1** and **2** is based on previously published procedures,[12] compounds **4–6** are reported for the first time while compound **3** was previously obtained from the acid chloride derivative of calix[4]-arene.[10d] In the synthesis of calix[4]arene amides, the aminolysis reaction of calix[4]arene esters is a new facile method.[13] Therefore, following the strategy outlined in Scheme 1; 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene **2** was refluxed with, respectively, benzyl amine, furfuryl amine, 3-morpholino propyl amine and 3-ethylamino-1-propyl amine in toluene/MeOH (1:2) mixture to give corresponding amide derivatives of *p-tert*-butyl calix[4]arene **3–6** in 75–80% yield.

The new compounds **3–6** were characterized by a combination of IR, ^{1}H NMR, ^{13}C NMR, FAB-MS, and elemental analysis. The formation of diamide derivatives of calix[4]arene **3–6** was confirmed by the appearance of the characteristic amide bands at about 1684 cm^{-1} in their IR spectra, and by the disappearance of ester carbonyl band at 1755 cm^{-1} in the IR spectra. The conformational characteristics of calix[4]arenes were conveniently estimated by the splitting pattern of the $ArCH_2Ar$ methylene protons in the ^{1}H and ^{13}C NMR spectroscopy.[1]

^{1}H and ^{13}C NMR data showed that compounds **3–6** have a cone conformation. A typical AB pattern was observed for the methylene bridge $ArCH_2Ar$ protons at 3.19 and 3.72 ppm (J=13.4 Hz) for **3**, 3.30 and 3.91 ppm (J=13.3 Hz) for **4**, 3.35 and 4.04 ppm (J=13.3 Hz) for **5** and 3.32 and 4.05 ppm (J=13.2 Hz) for **6** in ^{1}H NMR and two signals covering a range of δ 31.63 and 30.98 ppm in ^{13}C NMR. The high field doublets at 3.19 ppm for **3**, 3.30 ppm for **4**, 3.35 ppm for **5** and 3.32 ppm for **6** were assigned to the equatorial protons of methylene groups, whereas the low field signals at 3.72 ppm for **3**, 3.91 ppm for **4**, 4.04 ppm for **5** and 4.05 ppm for **6** were assigned to the axial protons in the ^{1}H NMR.



Scheme 1. (a) K_2CO_3/acetone, EtBrOAc, reflux, 24 h; (b) Primary amine, MeOH/toluene (1:1), reflux.

2.2. Two-phase solvent extraction

Chromate and dichromate anions are important because of their high toxicity[9b] and their presence in soils and waters.[9a,c] For a molecule to be effective as a host, it is necessary that its structural features are compatible with those of the guest anions. The chromate and dichromate ($Cr_2O_7^{2-}$/$HCr_2O_7^-$) ions are dianions where the periphery of the anions have oxide moeties. It is known that calix[4]arenes with amino functionalities on their lower rim are efficient extractants for oxoanions.[8b,c,10a,b] These oxides alter potential sites for hydrogen bonding to the host molecule.

We were interested in synthesizing new calix[4]arene diamide derivatives in the cone conformation and to examining their extraction properties for dichromate ions. The present work determines the strategic requirements for two-phase extraction measurements. A preliminary evaluation of the extraction efficiencies of **3**–**6** has been carried out by solvent extraction of $Na_2Cr_2O_7$ from water into dichloromethane at different pH values. The results are summarized in Table 1.

Table 1. Percentage extraction of dichromate by extractants **3**, **4**, **5** and **6** at different pH values[a]

	Dichromate anion extracted (%)			
	PH			
Compound	1.5	2.5	3.5	4.5
3	8.2	3.1	3.7	3.6
4	6.1	<0.1	1.0	1.0
5	35.9	23.5	2.1	1.3
6	[b]	87.8	81.6	19.0

[a] Aqueous phase, [metal dichromate]=1×10^{-4} M; organic phase, dichloromethane, [ligand]=1×10^{-3} M or solid phase [ligand]=1×10^{-3} M at 25 °C, for 1 h. The percentage extraction is given by [initial aqueous anion]−[final aqueous anion]/[initial aqueous anion]×100.
[b] Partly soluble at this pH.

From the extraction data (Fig. 1), the percentage of dichromate extracted increased by lowering the pH of the aqueous phase. This pH dependence can be explained by anion hydration. In aqueous solutions having a lower pH the dichromate will be primarily in its protonated form $HCr_2O_7^-$. This monoanion will have a smaller free energy of hydration than does the dianionic form $Cr_2O_7^{2-}$. As a result, there is a smaller loss in hydration energy as $HCr_2O_7^-$ is transferred from the aqueous phase into the dichloromethane phase. An additional advantage of $HCr_2O_7^-$ over $Cr_2O_7^{2-}$ is that for the former only one sodium ion needs to be coextracted to maintain charge balance, whereas for $Cr_2O_7^{2-}$ two sodium ions are extracted, with additional loss of hydration energy. For the calix[4]arene amides **5** and **6** we discount the possibility that increased extraction at lower pH values when compared to **3** and **4**, is due to protonation of the amine nitrogens.

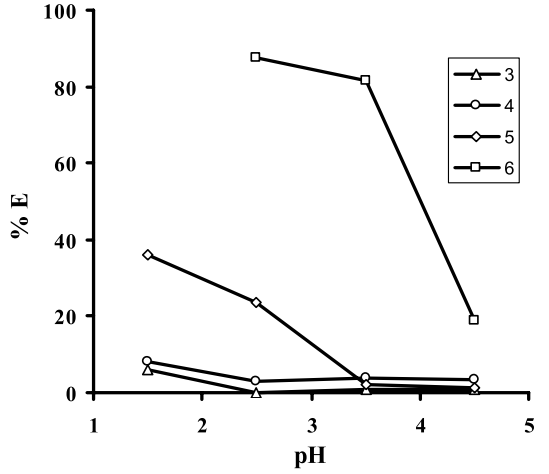


Figure 1. Plots of extraction (*E*%) versus pH following the two phase solvent extraction of dichromate with compounds **3**, **4**, **5** and **6**.

Because the pK_a of protonated amides (R-C(OH^+)NH_2) is approximately −1, the protonated form of calix[4]arene amid derivatives **3** and **4** are not expected to be present in significant concentration in aqueous solutions having pH values in the 1.5–4.5 range.

By contrast, amines **5** and **6** are expected to be protonated in these acidic aqueous solutions (generally the pK_a of protonated amines is around 10–11).

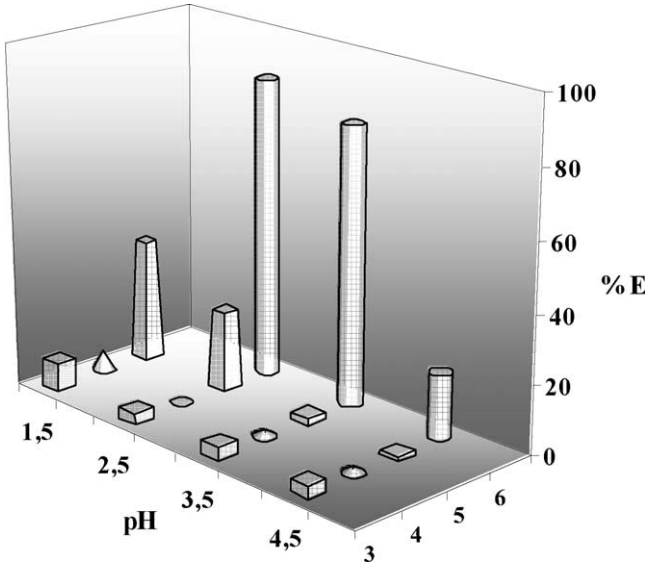
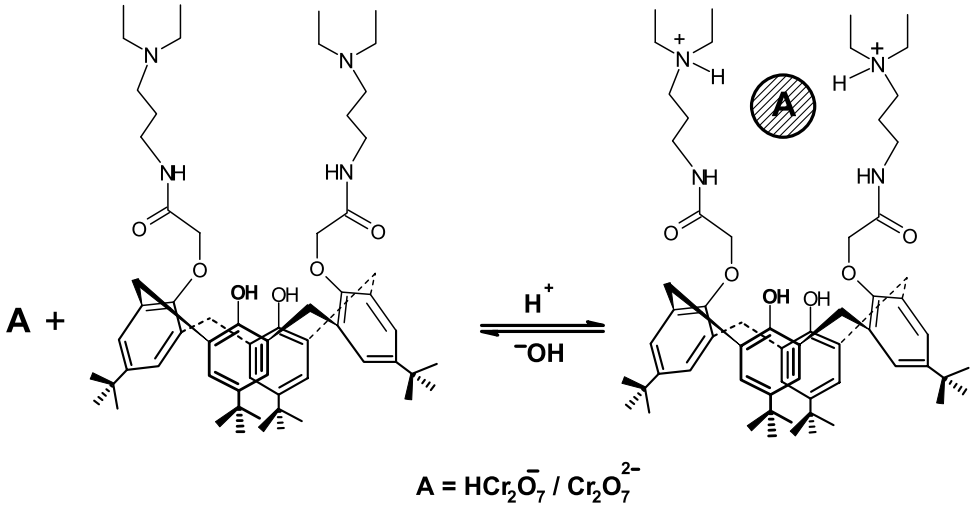


Figure 2. Extraction percentrage of dichromate anions with **3**, **4**, **5** and **6** at pH 1.5–4.5.

The extraction data (Fig. 2) showed that the extractant **6** is more effective for the extraction of dichromate anions at low pH (1.5–4.5) because **5** and **6** contains a protonable amine binding site appropriate for anion binding at low pH. Therefore, it can be demonstrated that because of the proton transfer to the nitrogen atom of the amine unit in **5** and **6**, protonated complex is formed in the two phase extraction system. Upon addition of NaOH to the aqueous layer, the deprotonated calixarene in the CH_2Cl_2 is no longer an effective host molecule for $Cr_2O_7^{2-}$ and the dianion then migrates back into the aqueous layer in a reversible process (Scheme 2).

All data have been analyzed using the classical slope analysis method. Assuming that the extraction of an anion A^{n-} by the receptor LH^{n+} is according to following



Scheme 2. The proposed interactions of compound **6** with $HCr_2O_7^-$ and $Cr_2O_7^{2-}$ ions.

equilibrium:

$$n(LH^{n+})_{org} + nA_{aq}^{n-} \rightleftharpoons ((LH^{n+})_n, A_n^{n-})_{org} \quad (1)$$

The extraction constant K_{ex} is then defined by:

$$K_{ex} = \frac{[((LH^{n+})_n, A_n^{n-})]_{org}}{[A^{n-}]_{aq}^n [LH^{n+}]_{org}^n} \quad (2)$$

Eq. 2 can be re-written as;

$$\log D_A = \log K_{ex} + n \log[LH^{n+}]_{org} \quad (3)$$

where D_A is defined as the ratio of the analytical concentration of the anion A^{n-} in both phases:

$$D_A = [A]_{org}/[A]_{aq}$$

Consequently a plot of the log D_A versus log[*L*] may lead to a straight line with a s[*L*]lope that allows for the determination of the stoichiometry of the extracted species, where is defined as the analytical concentration of the ligand in the organic phase. Figure 3 exhibits the extraction into dichloromethane at different concentrations of **5** and **6** with dichromate, respectively. A linear relationship between log D_A versus log[*L*] is observed with the slope of the line for extraction of dichromate anion by ligands **5** and **6** being approximately equal to 1 (at pH 1.5 for ligand **5** and at pH 2.5 for ligand **6**), suggesting that these ligands **5** and **6** form 1:1 complexes with the dichromate anion.

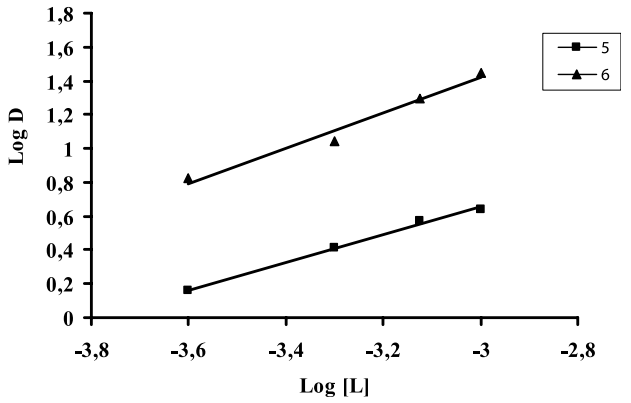


Figure 3. Log *D* versus log[*L*] for the extraction of dichromate by the ligand **5** and **6** from an aqueous phase into dichloromethane at 25 °C.

However, it is well known that at more acidic conditions $Na_2Cr_2O_7$ is converted into $H_2Cr_2O_7$ and after ionization in an aqueous solution it exists in the $HCr_2O_7^-/Cr_2O_7^{2-}$ form. At higher acidic conditions $HCr_2O_7^-$ and $Cr_2O_7^{2-}$ dimers become the dominant Cr^{6+} form and pK_{a_1} and pK_{a_2} values of these equations are 0.74 and 6.49, respectively. It is apparent to us that the ligands **5** and **6** form complex mostly with $HCr_2O_7^-$ ion. This has allowed us to consider that mostly the Eqs. 4 and 5 this simultaneous extraction of 1:1 complexes according to the following equilibria:

$$(LH^+)_{org} + HCr_2O_{7aq}^- \overset{K_{ex}}{\rightleftharpoons} (LH^+, HCr_2O_7^-)_{org} \quad (4)$$

$$(LH_2^{2+})_{org} + Cr_2O_{7aq}^{2-} \overset{K'_{ex}}{\rightleftharpoons} (LH_2^{2+}, Cr_2O_7^{2-})_{org} \quad (5)$$

According to these assumptions, the extraction constant has been calculated from the experimental data with similar K_{ex} and $K_{ex}{}'$ values using Eq. 3. Calculations of these constant values lead to $\log K_{ex} = \log K_{ex}{}' = 3.12 \pm 0.2$ for **5** and $\log K_{ex} = \log K_{ex}{}' = 4.58 \pm 0.2$ for **6**.

3. Conclusion

In conclusion, the synthesis and complexation ability of four calix[4]arene based receptors **3–6** were studied. The spectroscopic data indicated that these compounds (**3–6**) adopt the cone conformation. The complexation studies show that compounds **5** and **6** are better receptors for $Cr_2O_7^{2-}/HCr_2O_7^-$ anions compared with **3** and **4**. Morever, the extraction properties of **5** and **6** are enhanced in the acidic medium for $Cr_2O_7^{2-}/HCr_2O_7^-$ anions due to their protonation from the extraction phenomenon it could be concluded that the complexation of $Cr_2O_7^{2-}/HCr_2O_7^-$ depend on the nature and aggregation of the ions round the receptor. This is a particularly important feature if it is desirable to recover the particular metal in pure form and

reuse the extractant. The calixarene based receptors could be proved to find remarkable applications in the design of chemical sensors, using an electrochemical transduction/as conventional ion selective electrodes (ISE) and solid-state sensors (ISFETs).

4. Experimental

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were obtained on a Perkin Elmer 1605 FTIR spectrometer using KBr pellets. UV–vis spectra were obtained on a Shimadzu 160A UV–vis spectrophotometer. Elemental analyses were performed using a Leco CHNS-932 analyzer. FAB-MS spectra were taken on a Varian MAT 312 spectrometer. A Crison MicropH 2002 digital pH meter was used for the pH measurements.

Analytical TLC was performed using Merck prepared plates (silica gel 60 F_{254} on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 Mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich and used without further purification. Toluene was distilled from CaH_2 and stored over sodium wire. Other commercial grade solvents were distilled, and then stored over molecular sieves. Anions were used as their sodium salts. The drying agent employed was anhydrous $MgSO_4$. All aqueous solutions were prepared with deionized water that had been passed through a Millipore milli-Q Plus water purification system. Compounds **1** and **2** were synthesized according to previously described methods.[12]

4.1. Analytical procedure

The dichromate anion extraction experiments of calix[4] arene daimide derivatives **3**, **4**, **5** and **6** were studied by liquid–liquid extraction experiments following Pedersen's procedure.[14] Into a vial was pipetted an aqueous solution (10 mL) containing sodium dichromate at a concentration of 1×10^{-4} M, a few drops of 0.01 M KOH/HCl solution in order to obtain the desired pH at equilibrium and 10 mL of 1×10^{-3} M calixarene ligand in CH_2Cl_2.The mixture was shaken vigorously in a stoppered glass tube with a mechanical shaker for 2 min and then magnetically stirred in a thermostated water bath at 25 °C for 1 h, and finally left standing for an additional 30 min. The concentration of dichromate ion remaining in the aqueous phase was then determined spectrophotometrically as described previously.[10b] Blank experiments showed that no dichromate extraction occurred in the absence of calix[4]arene. The percent extraction ($E\%$) was calculated from the absorbance A of the aqueous phase measured at 346 nm (for pH 1.5–4.5) using the following expression:

$$(E\%) = \frac{A_0 - A}{A_0} \times 100$$

where A_0 and A are the initial and final concentrations of the dichromate ion before and after the extraction, respectively.

4.2. General procedure for the synthesis of compound 3, 4, 5 and 6

An appropriate primary amine (20.0 mmol) was dissolved in 1:2 toluene/MeOH mixture (60 mL) and added dropwise to a solution of 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxycarbonylmethoxy-26,28-dihydroxycalix[4]arene **2** (4.0 mmol) in 20 mL toluene with continuous stirring at room temperature for about 30 min. Then the reaction mixture was refluxed and the reactions were monitored by TLC. After the substrate had been consumed the solvent was evaporated under reduced pressure and the residue was triturated with MeOH to give a crude product. The crude products were purified by flash chromatography (SiO_2, CH_2Cl_2/Hexane 2:1) and recrystallized from CH_2Cl_2/MeOH.

4.2.1. Compound 3. White crystals; yield 79%; mp 248–250 °C; IR (KBr): 3353 (OH), 1684 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.80 (t, 2H, N*H*), 7.21 (s, 2H, O*H*), 7.18 (m, 10H, Ar*H*), 6.93 (s, 4H, Ar*H*), 6.72 (s, 4H, Ar*H*), 4.45 (d, 4H, NHCH_2), 4.29 (s, 4H, OCH_2CO), 3.72 (d, 4H, $J=13.4$ Hz, ArCH_2Ar), 3.19 (d, 4H, $J=13.4$ Hz, ArCH_2Ar), 1.20 (s, 18H, C(CH_3)$_3$), 0.88 (s, 18H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 167.91 (*C*=O), 149.29, 148.96, 148.12, 142.68, 136.87, 128.94, 128.53, 127.54, 126.79, 126.99, 125.32, 125.00, 123.24 (Ar*C*), 96.20 (*C*(CH$_3$)$_3$), 77.28, 76.96 (O*C*H$_2$), 76.64, 74.65 (NH*C*H$_2$), 31.70, 30.93 (Ar*C*H$_2$Ar); FAB-MS *m/z*: (966.4) $[M+Na]^+$. Anal. Calcd for $C_{62}H_{74}N_2O_6$ (943.3): C, 78.95%; H, 7.91%; N, 2.97%. Found: C, 78.68%; H, 7.76%; N, 2.86%.

4.2.2. Compound 4. White crystals; yield 78%; mp 289–291 °C; IR (KBr): 3326 (OH), 1684 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.01 (t, 2H, N*H*), 7.22 (d, 2H, O*H*), 7.10 (d, 2H, Ar*H*), 7.01 (s, 4H, Ar*H*), 6.82 (s, 4H, Ar*H*, ph), 6.23 (s, 4H, Ar*H*, ph), 4.54 (d, 4H, NHCH_2), 4.45 (s, 4H, OCH_2CO), 3.91 (d, 4H, $J=13.3$ Hz, ArCH_2Ar), 3.30 (d, 4H, $J=13.3$ Hz, ArCH_2Ar), 1.21 (s, 18H, C(CH_3)$_3$), 0.96 (s, 18H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 167.79 (*C*=O), 149.41, 148.83, 148.02, 142.79, 137.05, 132.28, 128.61, 128.23, 127.83, 126.94, 126.10, (Ar*C*), 96.22 (*C*(CH$_3$)$_3$), 77.32, 76.88 (O*C*H$_2$), 76.56, 74.64 (NH*C*H$_2$), 31.74, 30.91 (Ar*C*H$_2$Ar); FAB-MS *m/z*: (946.1) $[M+Na]^+$. Anal. Calcd for $C_{58}H_{70}N_2O_8$ (923.2): C, 75.46%; H, 7.64%; N, 3.03%. Found: C, 75.69; H, 7.27%; N, 3.23%.

4.2.3. Compound 5. White crystals; yield 76%; mp 244–246 °C; IR (KBr): 3351 (OH), 1686 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.87 (t, 2H, N*H*), 7.79 (s, 2H, O*H*), 7.00 (s, 4H, Ar*H*), 6.86 (s, 4H, Ar*H*), 4.50 (s, 4H, OCH_2CO), 4.04 (d, 4H, $J=13.3$ Hz, ArCH_2Ar), 3.54 (b, 8H, OCH_2CH$_2$N), 3.36–3.41 (m, 4H, NHCH_2CH$_2$CH$_2$N), 3.35 (d, 4H, $J=13.3$ Hz, ArCH_2Ar), 2.18 (m, 8H, NCH_2CH$_2$O), 2.30 (m, 4H, NHCH$_2$CH$_2$CH_2N), 1.75 (b, 4H, NHCH$_2$CH_2CH$_2$N), 1.19 (s, 18H, C(CH_3)$_3$), 0.97 (s, 18H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 167.82 (*C*=O), 149.38, 148.65, 148.57, 143.34, 132.22, 127.06, 126.24, 125.62 (Ar*C*), 96.16 (*C*(CH$_3$)$_3$), 77.25 (O*C*H$_2$), 76.93 (NH*C*H$_2$CH$_2$CH$_2$N),

76.62 ($NHCH_2CH_2CH_2N$), 74.83 ($NHCH_2CH_2CH_2N$), 56.27 (OCH_2CH_2N), 53.58 (OCH_2CH_2N), 31.63, 30.97 ($ArCH_2Ar$); FAB-MS *m/z*: (1040.4) $[M+Na]^+$. Anal. Calcd for $C_{62}H_{88}N_2O_8$ (1017.41): C, 73.19%; H, 8.72%; N, 5.51%. Found: C, 73.38%; H, 8.66%; N, 5.40%.

4.2.4. Compound 6. White crystals; yield 78%; mp 179–180 °C; IR (KBr): 3353 (OH), 1684 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.76 (t, 2H, N*H*), 7.62 (s, 2H, O*H*), 7.00 (s, 4H, Ar*H*), 6.83 (s, 4H, Ar*H*), 4.48 (s, 4H, OCH_2CO), 4.05 (d, 4H, $J=13.2$ Hz, $ArCH_2Ar$), 3.42 (q, 4H, $NHCH_2CH_2CH_2N$), 3.32 (d, 4H, $J=13.2$ Hz, $ArCH_2Ar$), 2.35 (t, 4H, $NHCH_2CH_2CH_2N$), 2.28 (q, 8H, NCH_2CH_3), 1.66 (p, 4H, $NHCH_2CH_2CH_2N$), 1.18 (s, 18H, $C(CH_3)_3$), 0.96 (s, 18H, $C(CH_3)_3$), 0.81 (t, 12H, NCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 167.70 (*C*=O), 149.40, 148.77, 148.40, 143.13, 132.30, 127.14, 126.17, 125.57 (Ar*C*), 96.16 ($C(CH_3)_3$), 77.25 (OCH_2), 76.93 ($NHCH_2CH_2CH_2N$), 76.62 ($NHCH_2CH_2CH_2N$), 74.84 ($NHCH_2CH_2CH_2N$), 50.84, 46.70 (CH_3CH_2N), 31.63, 30.98 ($ArCH_2Ar$), 11.65 (CH_3CH_2N); FAB-MS *m/z*: (1012.5) $[M+Na]^+$. Anal. Calcd for $C_{62}H_{92}N_4O_6$ (989.45): C, 75.26%; H, 9.37%; N, 5.66%. Found: C, 75.12%; H, 9.48%; N, 5.72%.

Acknowledgements

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Surprising fenchone induced cyclization: synthesis of the new chiral diol biphenyl-2,2′-sulfone-3,3′-bisfenchol (BISFOL)

Francis Soki, Jörg M. Neudörfl and Bernd Goldfuss*

Institut für Organische Chemie, Universität zu Köln, Greinstrasse 4, D-50939 Köln, Germany

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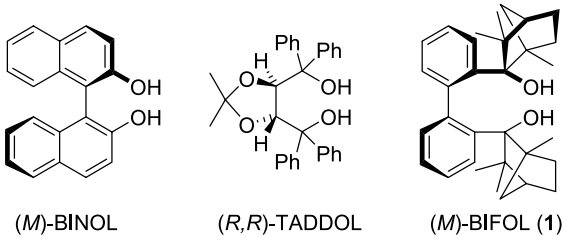
Abstract—The new chiral diol BISFOL (biphenyl-2,2′-sulfone-3,3′-bisfenchol) is surprisingly formed by cyclization of diphenylsulfone after treatment with *n*-buthyllithium at −78 °C and subsequent addition of (−)-fenchone. Formation of fenchyl alcohol as byproduct points to a Meisenheimer intermediate as primary cyclization product, which transfers lithium hydride yielding the cyclic sulfone. As a chiral and chelating ligand, BISFOL catalyzes enantioselective diorganozinc additions to aldehydes and forms with dimethylzinc an unprecedented, macrocyclic, dimeric methylzinc complex.

1. Introduction

Additions of organolithium reagents to chiral ketones are fundamental synthetic methods for syntheses of chiral diols.[1] Chelating diols such as BINOLs[2] and TADDOLs[3] play as chiral ligands an eminent role in enantioselective synthesis. We recently reported the synthesis and the X-ray crystal structure of (*M*)-BIFOL (**1** biphenyl-2,2′-bisfenchol, Scheme 1), which exhibits, as BINOLs, a flexible, chiral biaryl axis with minus (*M*) conformation induced by the hydrogen bonded fenchol moieties, and sterically crowded aliphatic alcohol functions, as TADDOLs.[4]



(*M*)-BINOL (*R,R*)-TADDOL (*M*)-BIFOL (**1**)

Scheme 1. BIFOL (biphenyl-2,2′-bisfenchol) with minus (*M*)-biaryl conformation.

Modular chiral chelating fenchols (Scheme 2), accessible via short synthetic routes, were applied recently as catalysts in enantioselective additions of organozincs to aldehydes,[5] in enantiopure organolithiums reagents,[6] and in fenchyl phosphinites for Pd-catalyzed allylic alkylations.[7] Herein, we present the surprising formation of the new fenchyl alcohol BISFOL (**2**, biphenyl-2,2′-sulfone-3,3′-bisfenchol; Scheme 2) via an unprecedented fenchone induced cyclization.

2. Results and discussion

ortho-Lithiation[8] of diphenylsulfone (**3**) with *n*-butyllithium in diethylether–tetrahydrofuran (1:1) at −78 °C followed by reaction with (−)-fenchone, hydrolytic work up and recrystallization from ethanol/dichloromethane afforded colorless crystals of BISFOL (**2**) in 20% yield. However, the expected open bisfenchol sulfone **4** could not be detected. Besides BISFOL, fenchol, the reduction product of fenchone, was detected (Scheme 3).

The structure of BISFOL (**2**) was confirmed by single-crystal X-ray diffraction (Fig. 1). BISFOL exhibits intramolecular hydrogen bonds between the hydroxy groups of the fenchyl moieties and the oxygen atoms of the sulfone group (O1–H1–O2: 2.17 Å, O1–O2: 2.69 Å, O3–H2–O4: 2.24 Å, O3–O4: 2.72 Å, Fig. 1).

To explore this unexpected fenchone induced cyclization, several carbonyl compounds were employed as electrophiles besides fenchone (Table 1, Scheme 3). Treatment of dilithiodiphenylsulfone with benzophenone or fluorenone gave, after hydrolytic work up, exclusively the non-cyclized, open products (Table 1). Reductions of benzophenone and fluorenone to the corresponding alcohols were not observed,

Keywords: Lithiations; Cyclizations; Diphenylsulfone; Catalysis; Zinc-complexes.
* Corresponding author. Tel.: +49 221 470 5729; fax: +49 221 470 5057; e-mail addresses: goldfuss@uni-koeln.de; URL:http://www.uni-koeln.de/goldfuss

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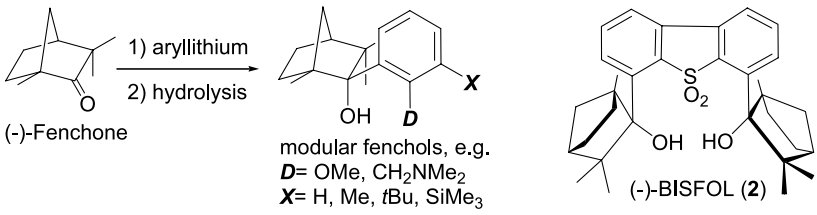
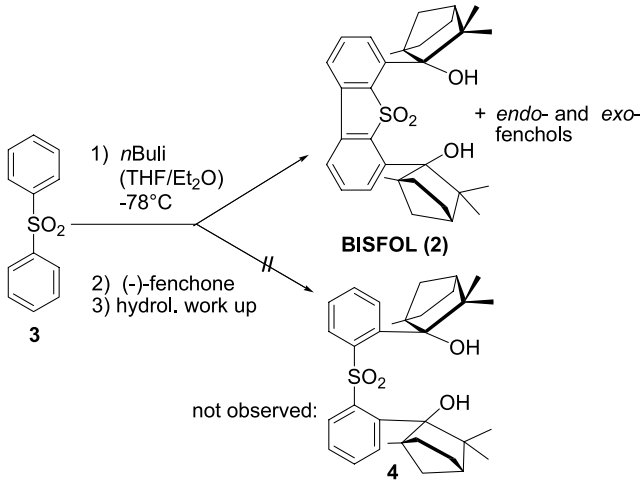


Scheme 2. From fenchone, modular fenchols are efficiently accessible.



Scheme 3. Surprising formation of BISFOL (**2**) via attempted synthesis of the open bisfenchol sulfone **4**.

yet an other difference to the reaction with fenchone. Camphor or benzaldehyde gave under the same reaction conditions neither cyclic nor acyclic products, enolization or reduction were dominating (Table 1). Hence, among the employed carbonyl compounds, only fenchone yields the cyclized diol **2**. The isolation of *endo*- and *exo*-fenchols as byproducts point to the formation of lithium hydride during the reaction. This supports, as a possible mechanistic

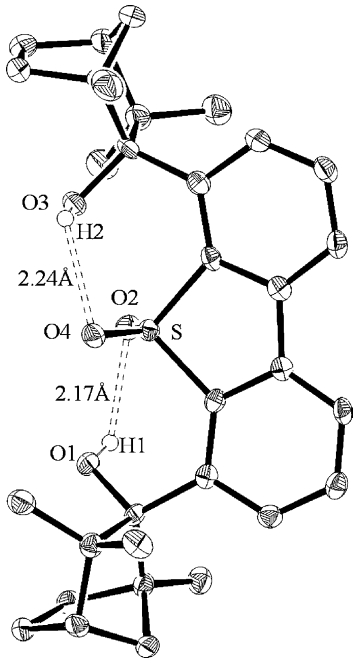
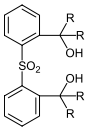
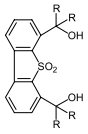
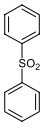


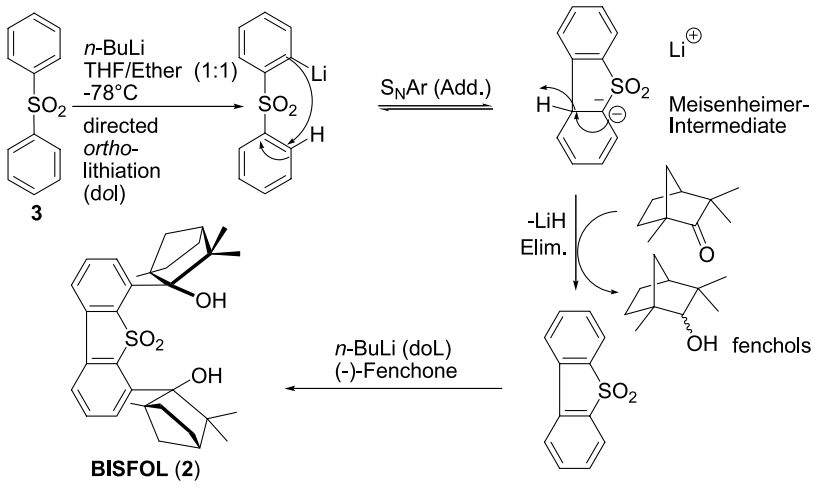
Figure 1. X-ray crystal structure of BISFOL (**2**).

scenario, a cyclization through nucleophilic aromatic substitution of the lithiated diphenylsulfone (**3**) via an addition–elimination sequence (Scheme 4).

Table 1. Treatment of dilithiodiphenylsulfone with different carbonyl compounds (cf. Scheme 3) yielding open or cyclic products

Product[a]					
Carbonyl-compound	Open (%)[b]	Cyclic (%)[c]	Byproduct (%)[d]	Educt (%)[e]	Educt (%)[e]
	27	—	—	70	67
	6	—	—	55	38
	—	—	–	64	30
	—	20	*endo*/*exo* fenchol[f]	60	60
	—	—	23	42	17

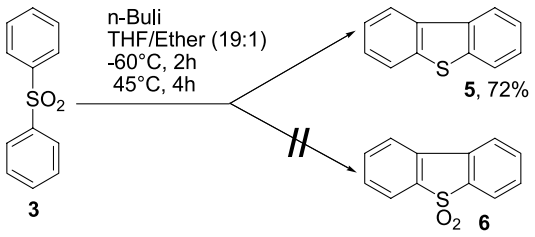
[a] 'R' represents the substituent of the carbonyl group.
[b] No cyclization.
[c] Cyclization.
[d] Reduction product of the employed carbonyl compound during the reaction.
[e] Recovered educt.
[f] The alcohols were identified by gas-chromatography by comparing with the authentic material.



Scheme 4. Proposed reaction mechanism via nucleophilic aromatic substitution.

According to this suggested sequence, *ortho*-lithiation of diphenylsulfone (**3**) yields an aryllithium unit, which adds to the second phenyl group forming a Meisenheimer intermediate being stabilized by the sulfone group. The aryl unit is rearomatized by elimination of lithium hydride, which reduces fenchone to the *endo*- and *exo*- fenchol byproducts (Scheme 4, Table 1). Indeed, Brinon et al. postulated a similar elimination of lithium hydride during an analogue cyclization of diphenylsulfone with *n*-buthyllithium, yielding dibenzothiophene **5**, while no cyclic sulfone **6** was observed (Scheme 5).[9]

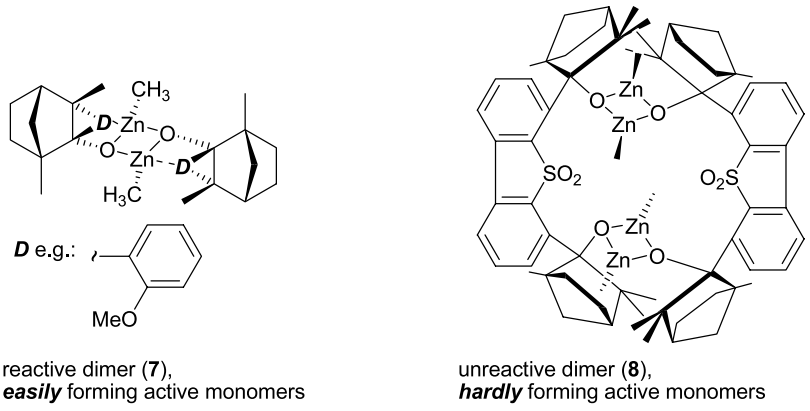
Fenchone seems to be particularly suitable for hydride transfer due to steric reasons, as it was demonstrated by Reetz et al. in the reduction of fenchone with potassium hydride.[10] Hellwinkel et al. have reported unexpected formations of heterocyclic systems from sulfonamides due to rearrangement by the reaction with organolithium compounds.[11] Due to its rigid chiral structure, BISFOL **2** is a promising ligand for enantioselective transformations, for example, catalyzed diorganozinc additions to aldehydes.[12] However, only up to 19% ee were achieved with 3 mol% of **2** in diethylzinc additions to benzaldehyde to give 1-phenylpropanol. The low enantioselectivity and especially the low reactivity of **2** as pre-catalyst in diethylzinc additions might arise from formation of rather stable dimeric and hence passive catalysts.[5] Indeed, reaction of dimethylzinc with a toluene solution of **2** at 0 °C and recrystallization from toluene yields a macrocyclic C_2-symmetrical dimer with two, rather than only one, four-membered, dimer-building Zn_2O_2 rings (Scheme 6, Fig. 2).



Scheme 5. Brinon's cyclization via lithiation of **3** yielding dibenzothiophene **5**.

3. Conclusions

The surprising, fenchone induced cyclization of *ortho*-lithiated bisphenylsulfone can be explained by a nucleophilic aromatic substitution sequence. Besides the new chiral BISFOL fenchole is formed via lithium hydride elimination. The unique propensity of fenchone to support



Scheme 6. Homochiral methylzinc dimers based on fencholes. While reactive dimmers (**7**) easily dissociate into active monomeric catalysts, the macrocycle in **8** inhibits active catalyst formation.

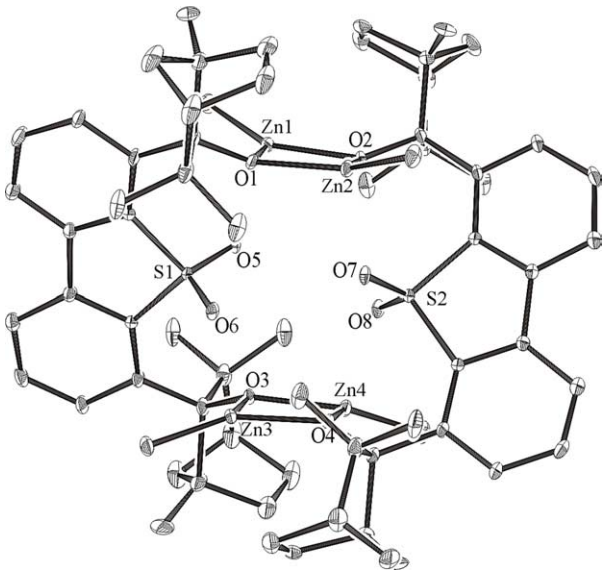


Figure 2. X-ray crystal structure of **8**, the dimeric, macrocyclic zincmethyl complex of BISFOL. Hydrogen atoms are omitted for clarity.

this cyclization is evident from comparisons with other carbonyl compounds. The low reactivity and enantioselectivity of BISFOL in diorganozinc additions to benzaldehyde is explained by the high stability of the macrocyclic alkylzinc complex. Anyhow, as rigid, chelating and C_2-symmetric diol, BISFOL has promising potentials as building block in enantioselective reagents and catalysts.

4. Experimental

All reactions were carried out under argon atmosphere using Schlenk-tube techniques. Solvents were dried by standard methods and distilled under argon prior to use.

4.1. Synthesis of biphenyl-2,2′-sulfone-3,3′-bisfenchol (BISFOL 2)

To a stirred solution of 6.55 g diphenylsulfone (30 mmol) in 45 ml THF and 45 ml Et_2O, which was cooled on a dry ice/alcohol bath (−78 °C), was added 39 ml (1.6 M, 60 mmol) of a solution of *n*-butyllithium in hexane. After the addition was complete, the solution was stirred 10 h by −78 °C. After stirring the solution at room temperature, 9.72 ml (60 mmol) (−)-fenchone were added to the mixture at −78 °C. Hydrolysis was performed with 200 ml H_2O. After separation of the ether layer, the water layer was extracted with 100 ml Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and distillation of the solvents left a yellow oil, to which 100 ml pentane was added. Cooling at −78 °C during 2 h in a dry ice/alcohol bath resulted in the precipitation of a solid, which was isolated by filtration of the mixture. This procedure was repeated, giving a total yield of compound **2** of 1.31 g (20%). After recrystallization from dichloromethane/ethanol the decomposition point was 283 °C.

Analytic and spectroscopic data of **2**. Mp: >283 °C (decomposition); calcd: C 73.81, H 7.74, found C 73.64, H 7.74; ^{1}H NMR ($CDCl_3$, 300 MHz) 0.58 (3H, s), 1.08 (3H, s), 1.26 (3H, s), 1.43–2.38 (6H, m), 3.05 (1H, s), 5.31 (1H, s), 7.52 (1H, t), 7.70 (2H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) 145.87, 137.76, 132.87, 132.38, 131.13, 119.49, 86.42, 54.86, 49.24, 48.12, 43.10, 34.01, 29.94, 24.33, 21.60, 18.01; $[\alpha]_D^{20}$ −253 (*c* 0.3, toluene); EI-MS: 520 (M^+), 504 (M^+-O), 502 (M^+-H_2O); IR KBr, cm^{-1}) 3556 (OH, s), 2989–2800 (C_{alkyl}–H, m), 1300 (C–SO_2, s), 1140 (C–SO_2, s). X-ray crystal data of **2**: $C_{32}H_{40}O_4S$; M=520.70; space group $P2_12_12_1$; a=11.4739(4) Å, b=14.8690(5) Å, c=16.2201(3) Å, V=2767.24(1) Å^3; Z=4; T=100(2) K; μ=0.152 mm^{-1}; reflections total: 22,011, unique: 6037, observed: 4905 ($I>2\sigma$ (I)); parameters refined: 494; $R1$=0.0347, $wR2$=0.0623; GOF=1.026.

4.2. Synthesis and X-ray analysis of Me_2Zn–BISFOL 8

A solution of dimethylzinc (0.5 mmol, 2 M, 0.25 ml) in toluene was added at room temperature to a solution of 0.5 mmol (260 mg) of **2** in 1 ml of toluene. The mixture was stirred for 30 min. After cooling the solution to −78 °C and thawing three times, the precipitate formed was dissolved in hot toluene. Slow cooling to room temperature yielded the homochiral dimer as colorless crystals. X-ray crystal data of **8**: $C_{34}H_{44}O_4SZn_2$; M=679.49; space group $I222$; a=10.848(1) Å, b=17.585(1) Å, c=18.632(1) Å, V=3554.3(4) Å^3; Z=4; T=293(2) K; μ=1.441 mm^{-1}; reflections total: 10,367, unique: 3847, observed: 2359 ($I>2\sigma$ (I)); parameters refined: 189; $R1$=0.0817, $wR2$=0.2013; GOF=1.064.

4.3. Catalytic $ZnEt_2$-additions to benzaldehyde

0.12 mmol (3 mol% with respect to benzaldehyde) of **2** was treated with 4.52 ml (4.07 mmol, 0.9 M) of diethylzinc in hexane at 0 °C for 15 min. Benzaldehyde (0.40 ml, 3.84 mmol) was added and this mixture was kept for 24 h at −30 °C. After quenching with water and hydrolyzing with hydrochloric acid, the organic layer was separated, neutralized ($NaHCO_3$) and dried (Na_2SO_4). The enantiomeric excess was analyzed by GC (Chiraldex G-TA column).

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Synthesis and reactivity of 2-(porphyrin-2-yl)-1,3-dicarbonyl compounds

Francesca Giuntini, Maria A. F. Faustino, Maria G. P. M. S. Neves, Augusto C. Tomé, Artur M. S. Silva and José A. S. Cavaleiro*

Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

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Abstract—A simple and efficient procedure for the synthesis of porphyrins bearing 1,3-dicarbonyl moieties at the β-position is described. The new compounds were further functionalized and new derivatives containing an heterocyclic ring, an ethyl acetate residue or a 2-oxopropyl group at the β-position have been obtained.

1. Introduction

Modification of *meso*-tetraarylporphyrins at the β-pyrrolic positions has been explored as a way to gain access to new derivatives for application in a number of areas, ranging from photosensitizers to molecular devices for electron transfer processes.[1] β-Nitroporphyrins are very useful starting compounds to achieve such modifications, both for their relative synthetic availability and for the peculiar nitroalkene-like reactivity they display. Those porphyrins undergo reactions with a wide range of nucleophiles revealing the Michael acceptor character of such molecules.[2–4]

The reactivity of 'active methylene' compounds toward β-nitroporphyrins have been successfully used to generate highly functionalized porphyrins.[2–5] Classically, the reaction is carried out under mildly basic conditions using malonate derivatives. However, since 1,3-diketones and 3-ketoesters are able to participate in reactions that also involve their deprotonation at the α carbon, we reasoned that they could act as nucleophiles in Michael additions with β-nitroporphyrins. Moreover, the variety of the chemical reactions 1,3-dicarbonyls can participate in (condensation reactions to build heterocycles,[6] complexation of metal ions,[7] multicomponent reactions, such as Biginelli or Hantzch reactions[8]) make them an appealing moiety with a rich synthetic potentiality to be introduced on the periphery of the porphyrin ring.[9] We describe here a simple and efficient procedure for the synthesis of porphyrins bearing 1,3-dicarbonyl moieties at the β-position and their subsequent conversion into other useful derivatives

2. Results and discussion

2,4-Pentanedione (acetylacetone) and ethyl 3-oxobutanoate (ethyl acetoacetate) react with β-nitro-*meso*-tetraaryl-porphyrins **1–3** to afford the corresponding 1,3-dicarbonyl derivatives **4–12** in good yields (Scheme 1, Table 1). The reactions occur in DMSO at 60 °C in the presence of K_2CO_3; usually after 40 min the starting nitroporphyrin is no longer present in the reaction mixture. In all cases the reaction leads to the formation of one compound only. It was not possible to isolate the 2-nitrochlorin intermediate from any of the reactions, although in some cases a sharp and very short-lived peak at about 650 nm was observed in the UV–vis spectrum of the reaction mixture.

1,3-Diketones and 3-ketoesters exist as a solvent-dependent tautomeric mixture:[10] the tautomerism also contributes to stabilize the anions, which may show an ambident reactivity.[11] The structure of the monoanions, and hence their reactivity toward electrophiles, varies according to the different reaction conditions, but it is mainly influenced by the type of counter cation and the solvent. We wanted to verify whether the change of the reaction solvent had any effect upon the reactivity of the system and/or on the product formed. We observed that in aromatic hydrocarbons, such as toluene or xylenes, the reaction does not take place while in DMF it leads to an extensive

Keywords: Porphyrins; 1,3-Dioxo-compounds; Michael addition; Acyl cleavage; Heterocycles.
* Corresponding author. Tel.: +351 234 370 717; fax: +351 234 370 084; e-mail: jcavaleiro@dq.ua.pt

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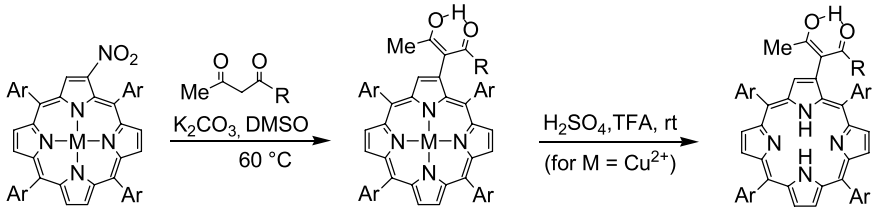


1a: Ar = Ph, M = 2H
1b: Ar = Ph, M = Cu^{2+}
1c: Ar = Ph, M = Ni^{2+}
2: Ar = C_6F_5, M = Zn^{2+}
3: Ar = 4-$MeOC_6H_4$, M = Cu^{2+}

Scheme 1.

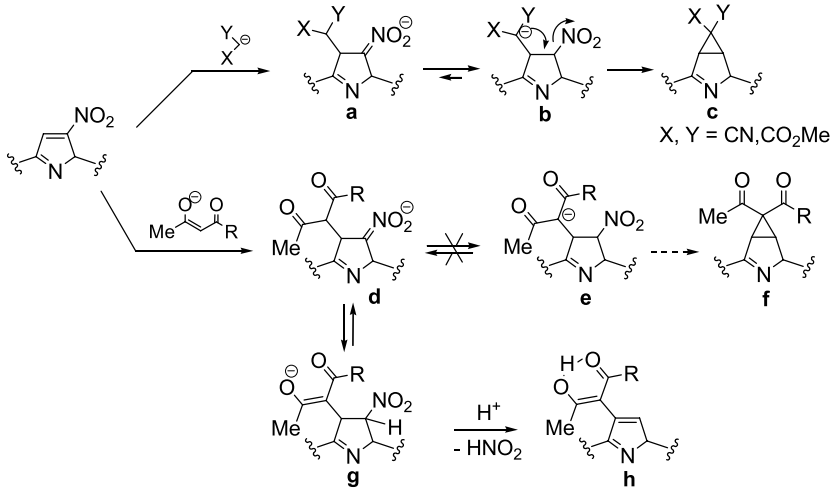
Table 1

Compound	Ar	M	R	Reaction time (min)	Yield (%)
4	Ph	2H	Me	50	72
5	Ph	Cu^{2+}	Me	40	86
6	Ph	Ni^{2+}	Me	40	81
7	C_6F_5	Zn^{2+}	Me	50	85
8	4-$MeOC_6H_4$	Cu^{2+}	Me	40	80
9	Ph	Cu^{2+}	OEt	40	88
10	Ph	Ni^{2+}	OEt	40	83
11	C_6F_5	Zn^{2+}	OEt	50	82
12	4-$MeOC_6H_4$	Cu^{2+}	OEt	50	77
13[a]	4-$MeOC_6H_4$	—	Me	15	94
14[a]	Ph	—	OEt	15	97
15[a]	4-$MeOC_6H_4$	—	OEt	15	93

[a] Compounds obtained by demetallation of the corresponding Cu^{2+} complexes (see below).

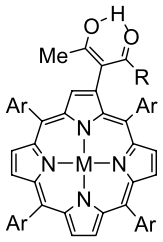
decomposition of the starting nitroporphyrin. In THF the reaction is clean but it is slow and incomplete (35–40% of the starting nitroporphyrin is recovered). The best solvent for these reactions is, indubitably, DMSO. The temperature at which the reaction is carried out also requires some attention: no reaction occurs at room temperature and when it is raised above 90 °C the desired porphyrin undergoes a rapid carbon–carbon bond cleavage (see below). Changing the central metal ion or the *meso*-aryl-substituent does not affect significantly the reactivity of the system, nor in terms of yield nor in terms of the reaction time, as shown in Table 1.

Smith et al.[2] have shown that β-nitroporphyrins react with 'methylene active' compounds (e.g., malonates, malononitrile) to afford cyclopropyl chlorins of the **c** type (Scheme 2). In those reactions, the intermediate nitronate **a** evolves to **b**, which then cyclizes to the cyclopropyl chlorin. Depending on the reaction conditions such chlorins may undergo a ring opening reaction leading to 2,3-disubstituted chlorins. In our reactions, the formation of a similar chlorin derivative (**f**) or a 2,3-disubstituted chlorin was never observed. A plausible explanation for this different behavior relays in the fact that with 1,3-diketones and 3-ketoesters the initial nitronate **d** is in equilibrium with



Scheme 2.

Table 2. Selected data from the ^{1}H NMR spectra of the compounds



Compound	CH_3	OH	OCH_2CH_3	H-3	NH	β-H
4	1.86	15.43	—	8.65	−2.68	8.86–8.65
6	1.83	16.37	—	8.56	—	8.68–8.60
7	1.96	16.62	—	8.82	—	8.99–8.84
10	1.76	12.83	4.08–3.88 (m) 0.96 (t)	8.51	—	8.64–8.54
11	1.92	13.13	4.22–4.16 and 3.92–3.80 (m) 0.79 (t)	8.78	—	9.01–8.74
13	1.92 2.17	16.47	—	8.69	−2.72	8.83–8.73
14	1.79	12.85	4.95–3.96 (m) 0.82 (t)	8.63	−2.71	8.89–8.74
15	2.07–1.99 (1.84)	12.92 (5.08)	4.19–4.16 (m) 0.90–0.82 (t)	8.66	−2–75	8.88–8.79

enolate **g**, rather than with the anion **e**, which leads to compounds **h**.

The free bases of compounds **8**, **9** and **12** (compounds **13**–**15**), prepared for structural elucidation purposes, were obtained by treating the metal complexes with 5% H_2SO_4 in TFA in nearly quantitative yields (Scheme 1). The structures of the new compounds were elucidated from the data of 1D NMR (^{1}H, ^{13}C) and 2D NMR (^{1}H,^{1}H COSY, ^{1}H,^{13}C HSQC and ^{1}H,^{13}C HMBC) spectroscopy. The presence of a sharp peak at δ 12.83–16.47 ppm (Table 2) shows that all new 2-(porphyrin-2-yl)-1,3-dicarbonyl compounds exist in solution predominantly as the enolic tautomer. The ketonic form is only detected in the spectrum of compound **15**; the singlet at δ 5.08 ppm was attributed to the methynic proton of the ketonic tautomer of this porphyrin, on the basis of ^{1}H,^{13}C HMBC and ^{1}H,^{13}C HSQC data. The new compounds show UV–vis spectra typical of etio-type porphyrins;[12] their absorption bands are red-shifted when compared to those of the parent nitroporphyrins.

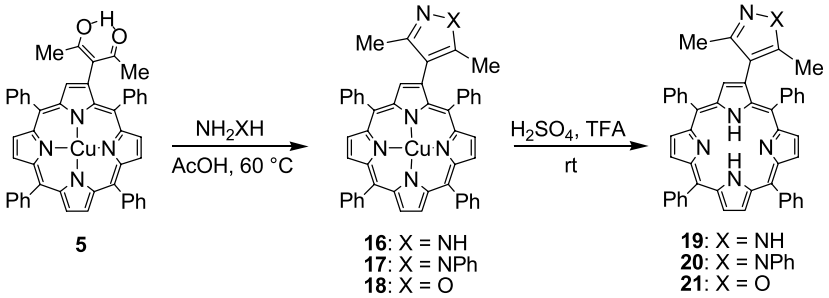
2.1. Synthesis of five-membered heterocycles

1,3-Dioxo-compounds are widely employed as the C3 synthon for the synthesis of heterocycles.[13] We have also used our 1,3-dicarbonyl derivatives as precursors of porphyrins bearing an heteroaromatic group at the β-position. Thus, from the reaction of compound **5** with hydrazine hydrate[14] in acetic acid at 55 °C we obtained pyrazole **16** in 87% yield. Under similar conditions, compound **5** reacted with phenylhydrazine and hydroxylamine hydrate to afford, respectively, pyrazole **17** (67% yield) and isoxazole **18** (81% yield) (Scheme 3).[15] Similarly, ketoester **9** reacted with phenylhydrazine to give the corresponding pyrazolone **22** in 60% yield (Scheme 4).[14]

2.2. Carbon–carbon bond cleavage reactions

3-Ketoesters undergo de-alkoxycarbonylation to afford

The structures of the new heterocyclic compounds were deduced from the NMR spectra (1D and 2D) of the corresponding free bases **19**–**21** and **23**, obtained by treating the metalated compounds with H_2SO_4/TFA. The pyrazolone structure of compound **23** was confirmed by the ^{1}H and ^{13}C NMR spectra, which show, respectively, a broad singlet at δ 3.76 ppm corresponding to the proton in position 4 of the heterocyclic ring, and a signal at δ 208.8 ppm corresponding to the carbonyl group.

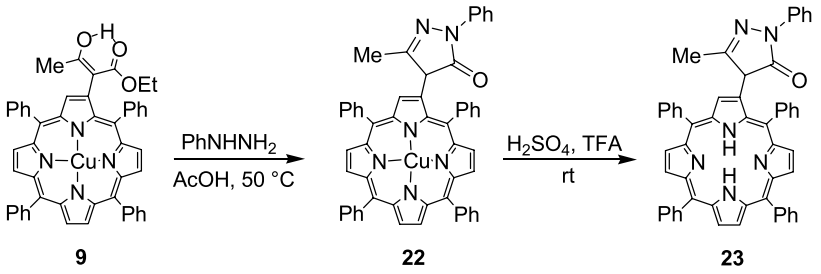


5

16: X = NH
17: X = NPh
18: X = O

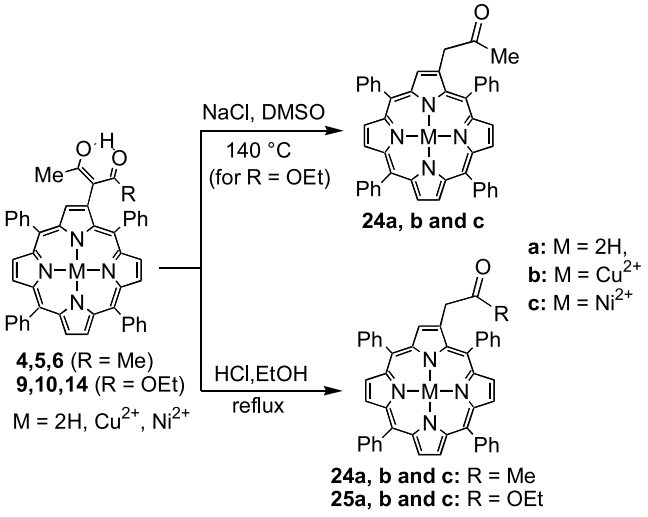
19: X = NH
20: X = NPh
21: X = O

Scheme 3.



Scheme 4.

methylene ketones, a class of compounds with many interesting applications.[16] This reaction, known as Krapcho degradation, was studied with compounds **9**, **10**, and **14**. These compounds, when heated at 140 °C in DMSO, in the presence of NaCl, were converted into ketones **24a**,**b**,**c** (Scheme 5) in high yields (76–83%).



Scheme 5.

1,3-Diketones and 3-ketoesters can also give acyl cleavage degradation reactions.[17] Those reactions normally occur in basic conditions. Surprisingly we found that when compounds **4**–**6** and **9**, **10**, and **14** were heated in ethanol in acidic conditions (10% HCl) such degradation took place almost quantitatively, giving compounds **24a**,**b**,**c** and **25a**,**b**,**c**, respectively. These results show that both Krapcho and acyl cleavage degradations are effective on the free bases and on the metal complexes of the dioxoporphyrins (Scheme 5).

3. Experimental

3.1. General remarks

Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^{1}H and ^{13}C solution NMR spectra were recorded either on a Bruker Avance 300 spectrometer at 300.13 and 75.47 MHz, respectively, or on a Bruker Avance 500 spectrometer at 500.13 and 125.76 MHz, respectively. $CDCl_3$ was used as solvent and TMS as internal reference; the chemical shifts are expressed in δ (ppm) and the coupling constants (J) in Hertz (Hz). Unequivocal ^{1}H assignments were made with aid of 2D COSY ($^{1}H/^{1}H$), while ^{13}C assignments were made on the basis of 2D HSQC ($^{1}H/^{13}C$) and HMBC (delay for long-range J C/H couplings were optimized for 7 Hz) experiments. Mass spectra and HRMS were recorded on VG AutoSpec Q and M mass spectrometers using $CHCl_3$ as solvent and NBA as matrix. Elemental analyses were performed in a Leco 999 CHN analyzer. The UV–vis spectra were recorded on an Uvikon spectrophotometer using CH_2Cl_2 or $CHCl_3$ as solvent. Column chromatography was carried out using silica gel (Merck, 35–70 mesh). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick).

The solvents were purified or dried according to the literature procedures.[18] 2-Nitroporphyrins were synthesized according to literature methods,[19] and all the other chemicals were used as supplied.

3.2. Synthesis of 2-(porphyrin-2-yl)-1,3-dicarbonyl derivatives. Typical procedure: [2-(1-acetyl-2-oxo-propyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 5

To a solution of 2,4-pentanedione (300 μL, 2.8 mmol) and K_2CO_3 (300 mg, 2.2 mmol) in DMSO (5 mL), the appropriate 2-nitroporphyrinato-Cu(II) (200 mg, 0.28 mmol) was added and the mixture was stirred for 40 min at 60 °C under a N_2 atmosphere. The mixture was then allowed to cool to room temperature, diluted with CH_2Cl_2 (50 mL), and the resulting solution was washed twice with brine. The organic layer was separated, dried (Na_2SO_4), and the solvent was evaporated. The desired compound was isolated by flash chromatography (silica gel) using toluene as the eluent. Crystallization from toluene/methanol afforded **5** (182 mg, 86% yield). Mp > 300 °C. FAB-MS: 774 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 417 (4.72), 541 (3.02) nm.

3.2.1. 2-(1-Acetyl-2-oxopropyl)-5,10,15,20-tetraphenylporphyrin 4. (Yield 72%, 16 mg). Mp 285–287 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.43 (s, 1H, OH), 8.86–8.82 (m, 4H, H-β), 8.77 (d, 1H, J=4.8 Hz, H-β), 8.66 (d, 1H, J=4.8 Hz, H-β), 8.65 (s, 1H, H-3), 8.23–8.18 (m, 6H, Ph-H_o), 7.96–7.93 (m, 2H, Ph-H_o), 7.79–7.72 (m, 11H, Ph-$H_{m/p}$), 7.67–7.61 (m, 3H, Ph-H_p), 1.86 (s, 6H, CH_3), −2.68 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 142.3, 142.0, 141.7, 141.2, 135.3, 134.7, 134.6, 134.5, 132.3, 131.6, 131.2, 128.2, 127.8, 127.8, 126.9, 126.8, 126.7, 120.6, 120.4, 119.8, 119.7, 111.2, 24.9. FAB-MS: 713 $(M+H)^+$, 669 $(M-Ac)^+$. UV–vis ($CHCl_3$) (log ε): 420 (5.19), 517 (3.50), 551 (3.05), 591 (2.98), 648 (2.69) nm.

$C_{49}H_{36}N_4O_2 \cdot H_2O$: calcd C: 80.53, H: 5.24, N: 7.67; found C: 80.10, H: 5.37, N: 7.91.

3.2.2. [2-(1-Acetyl-2-oxopropyl)-5,10,15,20-tetraphenylporphyrinato]nickel(II) 6. (Yield 81%, 81 mg). Mp 270–273 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.37 (s, 1H, OH), 8.75–8.70 (m, 4H, H-β), 8.67 (d, 1H, J=5.0 Hz, H-β), 8.61 (d, 1H, J=5.0 Hz, H-β), 8.56 (s, 1H, H-3), 8.01–7.97 (m, 6H, Ph-H$_o$), 7.71–7.67 (m, 10H, Ph-H$_{m/p}$), 7.60–7.49 (m, 4H, Ph-H$_p$), 1.83 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 142.7, 142.3, 140.9, 140.7, 140.6, 140.5, 140.4, 139.9, 136.4, 133.7, 133.6, 132.8, 132.7, 132.4, 131.9, 131.4, 128.1, 127.9, 127.8, 127.7, 126.9, 119.3, 118.9, 118.4, 111.8, 24.9. ESI-HRMS$^+$: $C_{49}H_{34}N_4O_2Ni$: calcd 768.2035, found 768.2031. UV–vis ($CHCl_3$) (log ε): 418 (5.34), 532 (3.57) nm.

3.2.3. [2-(1-Acetyl-2-oxopropyl)-5,10,15,20-tetrakis-(pentafluorophenyl)porphyrinato]zinc(II) 7. (Yield 82%, 86 mg). Mp 255–257 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 16.62 (s, 1H, OH), 9.30–9.11 (m, 7H, H-β), 1.90 (s, 3H, CH_3). ^{13}C NMR (75 MHz, d_6-DMSO): δ 206.6, 190.7, 154.6, 152.3, 150.2, 150.1, 149.9, 147.6, 146.9, 144.4, 143.3, 140.2, 139.0, 136.6, 135.5, 132.8, 132.5, 131.7, 113.9, 109.8, 103.5, 103.3, 103.0, 102.2, 24.3. ESI-HRMS$^+$: $C_{49}H_{14}F_{20}N_4O_2Zn+H$: calcd 1135.0161, found 1135.0196. UV–vis ($CHCl_3$) (log ε): 422 (5.61), 553 (3.25) nm.

3.2.4. [2-(1-Acetyl-2-oxopropyl)-5,10,15,20-tetrakis(3-methoxyphenyl)porphyrinato] copper(II) 8. (Yield 80%, 85 mg). Mp 233–236 °C. FAB-MS: 893 $(M)^+$, 878 $(M-CH_3)^+$. UV–vis ($CHCl_3$) (log ε): 417 (5.50), 540 (4.13) nm.

3.2.5. [2-(1-Acetyl-1-ethoxycarbonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 9. (Yield 88%, 215 mg). Mp 254–257 °C. FAB-MS: 803 $(M+H)^+$, 757 $(M-OEt)^+$. UV–vis ($CHCl_3$) (log ε): 416 (5.45), 539 (4.06) nm.

3.2.6. [2-(1-Acetyl-1-ethoxycarbonylmethyl)-5,10,15,20-tetraphenylporphyrinato]nickel(II) 10. (Yield 83%, 102 mg). Mp 257–260 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.83 (s, 1H, OH), 8.74–8.70 (m, 4H, H-β), 8.65 (d, 1H, J=5.0 Hz, H-β), 8.60 (d, 1H, J=5.0 Hz, H-β), 8.51 (s, 1H, H-3), 8.02–7.98 (m, 6H, Ph-H$_o$), 7.85 (m, 2H, Ph-H$_o$), 7.71–7.47 (m, 12H, Ph-H$_{m/p}$), 4.08–3.88 (m, 2H, OCH_2CH$_3$), 2.17 (s, 3H, CH_3), 0.96 (t, 3H, J=7.1 Hz, OCH$_2$$CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 172.0, 142.4, 142.2, 142.1, 140.8, 140.7, 140.6, 140.1, 136.4, 133.8, 133.6, 132.5, 132.4, 132.3, 132.2, 132.1, 131.7, 127.8, 127.7, 126.9, 126.9, 126.5, 119.1, 118.7, 118.1, 101.3, 60.4, 20.6, 14.1. ESI-HRMS: $C_{50}H_{36}N_4O_3Ni+H$: calcd 799.2213, found 799.2221. UV–vis ($CHCl_3$) (log ε): 418 (5.33), 531 (3.97) nm.

3.2.7. [2-(1-Acetyl-1-ethoxycarbonylmethyl)-5,10,15,20-tetrakis(pentafluorophenyl)porphyrinato]zinc(II) 11. (Yield, 82%, 53 mg). Mp>300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.13 (s, 1H, OH), 9.15–8.97 (m, 4H, H-β), 8.95 (d, 1H, J=4.9 Hz, H-β), 8.85 (d, 1H, J=4.9 Hz, H-β), 8.78 (s, 1H, H-3), 4.22–4.16 and 3.93–3.80 (m, 2H, OCH_2CH$_3$), 1.96 (s, 3H, CH_3), 0.79 (t, 3H, J=7.1 Hz, OCH$_2$$CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 172.1, 150.6, 150.3, 150.2, 150.1, 148.5, 148.2, 144.8, 140.5, 139.2, 136.0, 135.8, 135.4, 132.2, 132.0, 131.9, 131.7, 116.5, 116.3, 104.4, 104.1, 103.9, 103.4, 98.9, 61.2, 20.2, 12.9. ESI-HRMS$^+$: $C_{50}H_{16}F_{20}N_4O_3Zn+H$: calcd 1165.0267, found 1165.0302. UV–vis ($CHCl_3$) (log ε): 422 (5.65), 541 (4.10) nm.

3.2.8. [2-(1-Acetyl-1-ethoxycarbonylmethyl)-5,10,15,20-tetrakis(3-methoxyphenyl)porphyrinato]copper(II) 12. (Yield 77%, 84 mg). Mp 247–250 °C. FAB-MS: 924 $(M+H)^+$, 878 $(M-OEt)^+$. UV–vis ($CHCl_3$) (log ε): 418 (4.70), 541 (3.31) nm.

3.3. Demetallation of Cu^{2+} porphyrin complexes. Typical procedure: 2-(1-acetyl-2-oxopropyl)-5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin 13

Porphyrin **8** (15 mg, 1.7×10^{-2} mmol) was stirred in the minimal amount of a 5% solution of H_2SO_4 in TFA, at room temperature, for 15 min. The solution was then carefully neutralized with an ice-cold saturated Na_2CO_3 solution, and the porphyrin was extracted in CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4) and the solvent was evaporated. The desired product was purified by crystallization from CH_2Cl_2/MeOH (13 mg, 94% yield). Mp 236–239 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 16.47 (s, 1H, OH), 8.89–8.86 (m, 4H, H-β), 8.82 (d, 1H, J=4.8 Hz, H-β), 8.74 (d, 1H, J=4.8 Hz, H-β), 8.69 (s, 1H, H-3), 7.82–7.78 (m, 6H, Ar-H$_o$), 7.67–7.48 (m, 6H, Ar-H$_{o/m}$), 7.35–7.31 (m, 3H, Ar-H$_p$), 7.22–7.18 (m, 1H, Ar-H$_p$), 3.99–3.96 (m, 12H, OCH_3), 1.92 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), −2.72 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 189.9, 158.0, 157.9, 157.8, 143.5, 143.3, 143.0, 142.4, 128.1, 127.8, 127.7, 127.62, 127.60, 127.5, 127.4, 120.9, 120.5, 120.4, 120.3, 120.0, 119.6, 119.5, 119.4, 113.6, 113.5, 113.3, 113.1, 111.0, 25.1, 24.0. FAB-MS: 833 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 421 (5.67), 517 (4.31), 591 (3.78), 647 (3.43) nm. $C_{53}H_{44}N_4O_6 \cdot H_2O$: calcd C: 74.81, H: 5.45, N: 6.58; found C: 74.81, H: 5.51, N: 6.58.

3.3.1. 2-(1-Acetyl-1-ethoxycarbonylmethyl)-5,10,15,20-tetraphenylporphyrin 14. (Yield 97%, 18 mg). Mp> 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.85 (s, 1H, OH), 8.86–8.79 (m, 4H, H-β), 8.75 (d, 1H, J=4.8 Hz, H-β), 8.62–8.63 (m, 2H, H-β), 8.28–8.16 (m, 6H, Ph-H$_o$), 7.99 (d, 1H, J=7.1 Hz, Ph-H$_o$), 7.90 (d, 1H, J=7.1 Hz, Ph-H$_o$), 7.76–7.54 (m, 12H, Ph-H$_{m/p}$), 4.05–3.96 (m, 2H, OCH_2CH$_3$), 1.79 (s, 3H, CH_3), 0.85–0.82 (m, 3H, OCH$_2$$CH_3$), −2.71 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 172.0, 142.5, 142.2, 141.9, 141.2, 134.7, 134.6, 134.5, 132.7, 132.6, 130.9, 127.9, 127.7, 126.7, 126.6, 126.5, 126.4, 126.3, 120.3, 119.9, 119.6, 100.6, 68.1, 60.4, 20.5, 10.9. FAB-MS: 743 $(M+H)^+$, 697 $(M-CH_3)^+$. UV–vis ($CHCl_3$) (log ε): 419 (5.62), 517 (2.97), 559 (3.81), 591 (3.73), 646 (3.48) nm. $C_{50}H_{38}N_4O_3 \cdot 1/2H_2O$: calcd C: 79.87, H: 5.23, N: 7.45; found C: 80.19, H: 5.34, N: 7.35.

3.3.2. 2-(1-Acetyl-1-ethoxycarbonylmethyl)-5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin 15. (Yield 93%, 20 mg). Mp 247–250 °C. The compound exists as a mixture of two tautomers in $CDCl_3$ solution (ketone/enol=75:25). ^{1}H NMR (300 MHz, $CDCl_3$): *Ketone*: δ 5.08 (s, 1H, CH),

2.08 and 1.99 (two s, 3H, CH_3). *Enol*: δ 12.92 (d, 1H, J= 8.2 Hz, OH), 1.84 and 1.74 (2d, 3H, J=8.2 Hz, CH_3). *Common signals*: δ 8.88–8.79 (m, 3H, H-β), 8.72–8.69 (m, 3H, H-β), 8.66 (s, 1H, H-3), 7.82–7.77 (m, 6H, Ph-H_o), 7.67–7.48 (m, 6H, Ar-$H_{o/m}$), 7.34–7.31 (m, 3H, Ar-H_p), 7.22–7.20 (m, 1H, Ar-H_p), 4.19–4.16 (m, 2H, O$CH_2$$CH_3$), 3.99–3.90 (m, 12H, OCH_3), 0.90–0.82 (m, 3H, OCH_2CH_3), −2.75 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 172.2, 169.0, 158.0, 157.9, 157.9, 157.8, 143.7, 143.5, 143.3, 143.2, 142.5, 131.8, 131.5, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 125.9, 120.8, 120.5, 120.4, 120.0, 119.8, 119.6, 119.3, 115.5, 113.2, 113.1, 100.5, 100.4, 60.5, 60.3, 55.5, 29.3, 20.5, 13.9. FAB-MS: 863 $(M+H)^+$, 817 $(M-OEt)^+$. UV–vis ($CHCl_3$) (log ε): 421 (5.53), 526 (4.26), 549 (3.78), 590 (3.73), 646 (3.37) nm. $C_{54}H_{46}N_4O_7\cdot 2H_2O$: calcd C: 72.14, H: 5.61, N: 6.23; found C: 72.56, H: 5.61, N: 6.23.

3.4. Synthesis of five-membered heterocycles. Typical procedure: [2-(3,5-dimethylpyrazol-4-yl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 16

To a solution of porphyrin **5** (20 mg, 0.03 mmol) in acetic acid (5 mL) and toluene (1 mL), hydrazine hydrate (30 μL, 0.56 mmol) was added, and the resulting solution was stirred at 55 °C for 5.5 h. The mixture was then allowed to cool at room temperature, diluted with toluene, and washed three times with a saturated Na_2CO_3 solution and twice with brine. The organic layer was separated, dried (Na_2SO_4) and the solvent was evaporated. The crude mixture was crystallized from toluene/hexane to afford the desired compound (20 mg, 87% yield). Mp > 300 °C. FAB-MS: 770 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 417 (5.57), 541 (3.97) nm.

3.4.1. [2-(3,5-Dimethyl-1-phenylpyrazol-4-yl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 17. (Yield 67%, 17 mg). Mp > 300 °C. FAB-MS: 846 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 417 (5.62), 541 (4.04) nm.

3.4.2. [2-(3,5-Dimethylisoxazol-4-yl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 18. (Yield 81%, 18 mg). Mp > 300 °C. FAB-MS: 771 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 417 (5.47), 541 (3.87) nm.

3.4.3. [2-(3-Methyl-1-phenyl-pyrazol-5-one-4-yl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 22. (Yield 60%, 10 mg). Mp > 300 °C. FAB-MS: 848 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 417 (5.60), 540 (3.97) nm.

3.5. Demetallation of compounds 16–18 and 22

These compounds were demetallated as described above for the other Cu^{2+} porphyrin complexes.

3.5.1. 2-(3,5-Dimethylpyrazol-4-yl)-5,10,15,20-tetraphenylporphyrin 19. (Yield 89%, 12 mg). Mp 298–303 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85–8.82 (m, 4H, H-β), 8.74 (d, 1H, J=4.8 Hz, H-β), 8.66 (s, 1H, H-3), 8.64 (d, 1H, J=4.8 Hz, H-β), 8.25–8.09 (m, 6H, Ph-H_o), 7.95–7.93 (m, 2H, Ph-H_o), 7.77–7.71 (m, 9H, Ph-$H_{m/p}$), 7.42–7.39 (m, 3H, Ph-H_p), 2.03 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 142.2, 141.9, 140.9, 134.6, 134.6, 133.3, 131.9, 131.4, 129.0, 128.2, 127.7, 127.5, 126.8, 126.7, 126.6, 125.7, 125.5, 125.3, 120.6, 120.3, 120.0, 119.7, 11.7. FAB-MS: 709 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 420 (5.61), 517 (3.53), 551 (3.11), 592 (3.00), 648 (2.77) nm. For $C_{49}H_{36}N_6\cdot H_2O$: calcd C: 80.37, H: 5.27, N: 11.56; found C: 80.24, H: 5.28, N: 11.69.

3.5.2. 2-(3,5-Dimethyl-1-phenylpyrazol-4-yl)-5,10,15,20-tetraphenylporphyrin 20. (Yield 88%, 8.2 mg). Mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87–8.84 (m, 4H, H-β), 8.76–8.74 (m, 2H, H-β), 8.66 (d, 1H, J=4.8 Hz, H-β), 8.27–8.22 (m, 6H, Ph-H_o), 8.03–7.96 (m, 2H, Ph-H_o), 7.78–7.72 (m, 8H, Ph-H_m), 7.53–7.35 (m, 9H, Ph-H_p and NPh-H), 2.15 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), −2.64 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 142.4, 142.2, 141.9, 141.0, 136.5, 134.6, 134.6, 133.6, 133.3, 128.9, 128.4, 127.7, 127.4, 127.0, 126.2, 125.3, 124.6, 120.5, 120.4, 120.1, 119.7, 117.9, 12.8, 12.1. FAB-MS: 785 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 420 (6.00), 539 (3.87), 553 (3.49), 591 (3.45), 648 (3.26) nm. For $C_{55}H_{40}N_6\cdot 2H_2O$: calcd C:80.46, H: 5.27, N: 11.56; found C: 80.29, H: 5.28, N: 11.56.

3.5.3. 2-(3,5-Dimethylisoxazol-4-yl)-5,10,15,20-tetraphenylporphyrin 21. (Yield 87%, 8.0 mg). Mp > 300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85–8.81 (m, 4H, H-β), 8.79 (d, 1H, J=4.8 Hz, H-β), 8.69 (d, 1H, J=4.8 Hz, H-β), 8.64 (s, 1H, H-3), 8.24–8.19 (m, 6H, Ph-H_o), 7.96–7.94 (m, 2H, Ph-H_o), 7.78–7.74 (m, 8H, Ph-H_m), 7.55–7.48 (m, 4H, Ph-H_p), 2.17 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), −2.67 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 142.4, 142.2, 141.9, 141.0, 136.5, 134.6, 134.5, 133.6, 133.3, 128.9, 128.4, 127.7, 127.4, 127.0, 126.2, 125.3, 124.6, 120.5, 120.4, 120.1, 119.7, 117.9, 12.8, 12.1. FAB-MS: 710 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 419 (5.52), 516 (3.92), 552 (3.88), 592 (3.44), 648 (3.24) nm. $C_{49}H_{35}N_5O\cdot 2H_2O$: calcd C: 78.90, H: 5.27, N: 9.39; found C: 78.86, H: 5.07, N: 9.50.

3.5.4. 2-(3-Methyl-1-phenylpyrazol-5-one-4-yl)-5,10,15,20-tetraphenylporphyrin 23. (Yield 94%, 8.7 mg) was obtained from porphyrin **16** (10 mg, 1.1×10^{-2} mmol), after crystallization from CH_2Cl_2/hexane. Mp 296–299 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 8.84–8.69 (m, 7H, H-β), 8.26–8.19 (m, 6H, Ph-H_o), 7.98–7.96 (m, 2H, Ph-H_o), 7.79–7.75 (m, 8H, Ph-H_m), 7.62–7.60 (m, 2H, Ph-H_p), 7.48–7.39 (m, 5H, Ph-H_p and NPh-H), 7.27 (dd, 1, J=7.3 Hz, Ph-H_p), 2.19 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.8, 142.3, 142.1, 141.9, 141.3, 134.7, 133.3, 126.6, 128.9, 127.9, 127.6, 126.9, 126.9, 125.8, 122.5, 120.5, 120.3, 120.0, 30.9. FAB-MS: 787 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 417 (5.53), 517 (3.82), 552 (3.76), 592 (3.23), 648 (3.20) nm. $C_{54}H_{38}N_6O\cdot H_2O$: calcd C: 80.58, H: 5.01, N: 10.44; found C: 80.22, H: 5.24, N: 10.21.

3.6. Krapcho decarboxylation. Typical procedure: [2-(2-oxopropyl)-5,10,15,20-tetraphenylporphyrinato]-copper(II) 24b

A solution of the compound **9** (100 mg, 0.12 mmol) in 4 mL of DMSO and brine (1%) was heated at 140 °C during 6 h. The reaction mixture was allowed to cool at room temperature, and then it was partitioned between CH_2Cl_2 and brine. The organic layer was washed once more with brine, separated, dried (Na_2SO_4), and the solvent was

evaporated. The desired compound was isolated by flash chromatography (silica gel) using $CHCl_3$ as eluent. The compound was then crystallized from CH_2Cl_2/hexane (73 mg, 83% yield). Mp 280–283 °C. FAB-MS: 732 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 415 (5.58), 529 (3.92) nm.

3.6.1. [2-(2-Oxopropyl)-5,10,15,20-tetraphenylporphyrinato]nickel(II) 24c. (Yield 76%, 20 mg). Mp 267–270 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71–8.26 (m, 5H, H-β), 8.59 (d, 1H, $J=5.0$ Hz, H-β), 8.51 (s, 1H, H-3), 7.98–7.97 (m, 6H, Ph-H_o), 7.83–7.81 (m, 2H, Ph-H_o), 7.69–7.58 (m, 12H, Ph-$H_{m/p}$), 3.96 (s, 2H, CH_2), 1.91 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 143.2, 140.6, 138.6, 135.9, 133.7, 133.3, 132.9, 132.7, 132.6, 132.4, 132.3, 132.2, 132.1, 131.8, 128.2, 127.7, 127.3, 127.2, 126.9, 126.8, 119.1, 118.7, 117.8, 46.1, 29.6. ESI-HRMS$^+$: $C_{47}H_{32}N_4ONi+H$: calcd 727.2004, found 727.2009. UV–vis ($CHCl_3$) (log ε): 415 (5.34), 530 (3.98) nm.

3.6.2. 2-(2-Oxopropyl)-5,10,15,20-tetraphenylporphyrin 24a. (Yield 80%, 43 mg). Mp 272–275 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85–8.873 (m, 3H, H-β), 8.80 (d, 1H, $J=4.7$ Hz, H-β), 8.77 (d, 1H, $J=4.7$ Hz, H-β), 8.63 (s, 1H, H-3), 8.56 (d, 1H, $J=4.8$ Hz, H-β), 8.23–8.18 (m, 6H, Ph-H_o), 8.06–8.03 (m, 2H, Ph-H_o), 7.80–7.68 (m, 12H, Ph-$H_{m/p}$), 4.11 (s, 2H, CH_2), 1.56 (s, 3H, CH_3), −2.75 (s, 2H, NH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.1, 142.5, 142.2, 141.9, 141.8, 134.6, 134.5, 134.4, 133.6, 128.2, 127.7, 127.1, 126.7, 126.6, 126.5, 120.4, 120.1, 119.4, 119.3, 45.6, 29.7. FAB-MS: 671 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 419 (5.80), 515 (3.91), 550 (3.36), 590 (3.34), 646 (3.20) nm. For $C_{47}H_{34}N_4O\cdot 2H_2O$: calcd C: 79.80, H: 5.42, N: 7.93; found C: 79.36, H: 5.44, N: 7.54.

3.7. Acyl cleavage degradation reactions. Typical procedure: 2-(2-oxopropyl)-5,10,15,20-tetraphenylporphyrin 24a

A solution of porphyrin **4** (18 mg) in EtOH (20% HCl) was heated at reflux for 2 h, then the reaction mixture was allowed to cool at room temperature, diluted with CH_2Cl_2, and the resulting solution was washed with a saturated Na_2CO_3 solution. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The desired compound was purified by flash chromatography (silica gel) using $CHCl_3$ as eluent and then crystallized from $CHCl_3$/hexane (11 mg, 63% yield). (Spectroscopic data above).

3.7.1. [2-(2-Oxopropyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 24b. (Yield 66%, 12 mg). (Spectroscopic data above).

3.7.2. [2-(2-Oxopropyl)-5,10,15,20-tetraphenylporphyrinato]nickel(II) 24c. (Yield 60%, 11 mg). (Spectroscopic data above).

3.7.3. [2-(Ethoxycarbonylmethyl)-5,10,15,20-tetraphenylporphyrinato]copper(II) 25b. (Yield 76%, 14 mg). Mp 276–279 °C. FAB-MS: 761 $(M)^+$. UV–vis ($CHCl_3$) (log ε): 414 (5.35), 540 (4.03) nm.

3.7.4. [2-(Ethoxycarbonylmethyl)-5,10,15,20-tetraphenylporphyrinato]nickel(II) 25c. (Yield 67%, 13 mg). Mp 241–244 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72–8.59 (m, 7H, H-β), 8.00–7.96 (m, 6H, Ph-H_o), 7.86–7.83 (m, 2H, Ph-H_o), 7.69–7.61 (m, 12H, Ph-$H_{m/p}$), 4.06 (q, 2H, $J=$ 7.1 Hz, OCH_2CH$_3$), 3.81 (s, 2H, CH_2), 1.19 (t, 3H, $J=$ 7.1 Hz, OCH$_2$$CH_3$), -2.76 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ171.6, 142.4, 142.3, 142.2, 140.8, 140.7, 140.6, 138.5, 135.2, 133.7, 132.8, 132.6, 132.4, 132.3, 132.2, 132.1, 131.7, 128.2, 127.7, 127.2, 126.9, 126.8, 119.2, 118.7, 117.9, 60.6, 36.8, 14.1. ESI-HRMS$^+$: $C_{48}H_{34}N_4O_2$-Ni+H: calcd 757.2108, found 757.2089. UV–vis ($CHCl_3$) (log ε): 416 (5.34), 539 (3.94) nm.

3.7.5. 2-(Ethoxycarbonylmethyl)-5,10,15,20-tetraphenylporphyrin 25a. (Yield 63%, 11 mg). Mp 263–266 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84–8.74 (m, 5H, H-β), 8.70 (br s, 1H, H-3), 8.60 (d, 1H, $J=4.8$ Hz, H-β), 8.23–8.18 (m, 6H, Ph-H_o), 8.08–8.06 (m, 2H, Ph-H_o), 7.79–7.67 (m, 12H, Ph-$H_{m/p}$), 4.10 (q, 2H, $J=7.1$ Hz, OCH_2CH$_2$), 3.95 (s, 2H, CH_2), 1.19 (t, 3H, $J=7.1$ Hz, OCH$_2$$CH_3$), −2.76 (s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 142.5, 142.2, 141.9, 141.7, 134.6, 134.5, 134.4, 133.4, 131.5, 130.4, 128.3, 127.7, 127.0, 126.4, 126.6, 126.5, 120.4, 120.1, 119.5, 119.4, 60.7, 36.3, 14.1. FAB-MS: 701 $(M+H)^+$. UV–vis ($CHCl_3$) (log ε): 418 (5.99), 515 (3.96), 549 (3.49), 590 (3.44), 646 (3.24) nm. $C_{48}H_{36}N_4O_2$: calcd C: 82.26, H: 5.18, N: 7.99; found C: 82.01, H: 5.46, N: 7.94.

Acknowledgements

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A new route into hexahydro-cyclopenta[*b*]pyrrole-*cis*-3a,6-diols. Synthesis of constrained bicyclic analogues of pyrrolidine azasugars

Hongbin Sun, Khalil A. Abboud and Nicole A. Horenstein*

Department of Chemistry, University of Florida, Gainesville FL 32611-7200, USA

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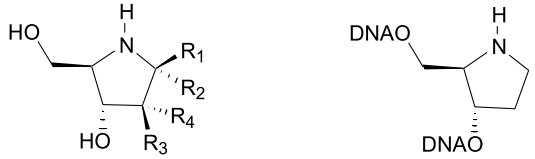
Abstract—Compounds that simultaneously combine charge and conformational features of glycosyltransfer transition states are of interest as transition state analog inhibitors. The synthesis of a central intermediate, *cis*-3a,6-dihydroxy-hexahydro-cyclopenta[*b*]pyrrol-2-one, which yielded a family of substituted *cis*-3a,6-dihydroxy-hexahydro-cyclopenta[*b*]pyrroles that combine conformational biasing and transition state charge mimicry, is described. The key steps in this synthesis involve synthesis of (2-azido-1,3-dihydroxy-cyclopentyl)-acetic acid ethyl ester in four steps from cyclopentenone, followed by an efficient reductive cyclization of the azide to the bicyclic lactam. The lactam was subsequently converted into the corresponding bicyclic pyrrolidine, and analogs having phenyl, hydroxyl, and phosphate substituents.

1. Introduction

Naturally occurring and synthetic polyhydroxylated pyrrolidine and piperidine derivatives, examples of 'azasugars', (Fig. 1) have found application as transition state analog inhibitors of *O*- and *N*-glycosyl hydrolase enzymes. For example, the natural product swainsonine is an effective mannosidase inhibitor.[1] Natural product DAB-1 **1** and its enantiomer LAB-1 are very potent inhibitors of a variety of α-glucosidases.[2] Azasugar **2** is an effective inhibitor for both α-glucosidases and β-glucosidase.[3,4] Pyrrolidine C-nucleosides **3** are a remarkably effective family of transition state analog inhibitors for nucleoside hydrolase and phosphorylase enzymes with inhibition constants ranging into the picomolar range.[5,6] Verdine and co-workers prepared a pyrrolidine-containing oligonucleotide **4** as an abasic transition-state analog to multiple DNA glycosylases.[7,8] The basis for the success of these compounds is often considered to stem from the ability of the basic nitrogen to reside in the ammonium form, providing a charge analogous to that found in the oxocarbenium ion like transition state of the glycohydrolase catalyzed reaction. However, the understanding of the details of inhibitor-enzyme binding may be incomplete and other factors have been discussed.[9] As part of our interest in the utilization of conformational restriction for inhibitor design[10,11] we wished to develop the synthesis of a framework that would allow investigation of the effect of conformational restriction of the hydroxymethyl group in furanoside analog inhibitors. In part this goal stems from the observation that glycohydrolase-bound transition states (TS's) and corresponding TS analogs can have the hydroxymethyl group oriented in a specific conformation.[12] The so-called bicyclonucleosides[13,14] provide a conceptual basis for the design of new compounds that are conformationally biased TS analogs. A 1-aza [3.3.0] bicyclic framework (octahydro cyclopenta[*b*]pyrroles) would provide a means for locking the hydroxymethyl group and the mimic of the furanosyl ring via an ethano bridge between atoms analogous to the 3′ and 5′ carbons of the furanoside, as embodied in compounds **5**-**8**. We thus, sought a synthesis that would provide entry into this group of compounds via a central precursor lactam as illustrated in Figure 2. While the octahydro



1 R_1=R_2=R_4=H, R_3=OH
2 R_1=R_4=H, R_2=CH_2OH, R_3=OH,
3 R_1=Ar, R_2=R_3=H, R_4=OH

4

Figure 1. Pyrrolidine glycosyltransfer inhibitors.

Keywords: Azasugar; Bicyclic; Constrained; Cyclization; C-nucleoside; Transition state analog.
* Corresponding author. Tel.: +1 352 392 9859; Fax: +1 352 846 2095; e-mail: horen@chem.ufl.edu

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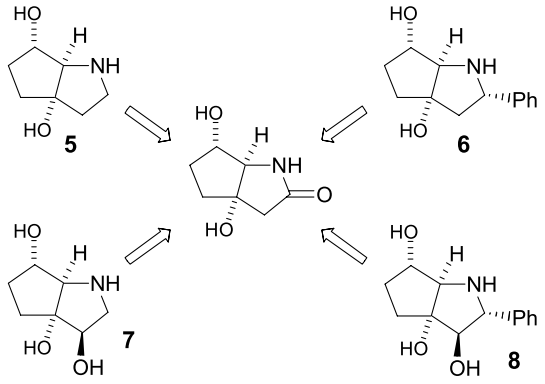
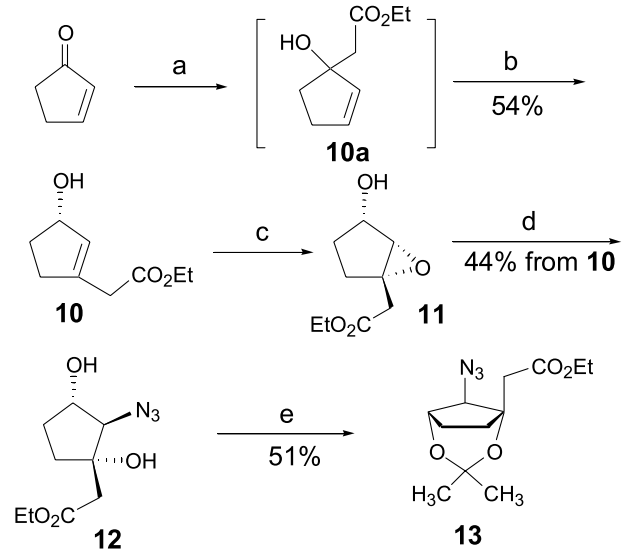


Figure 2. New compounds **5–8** from a central lactam intermediate.

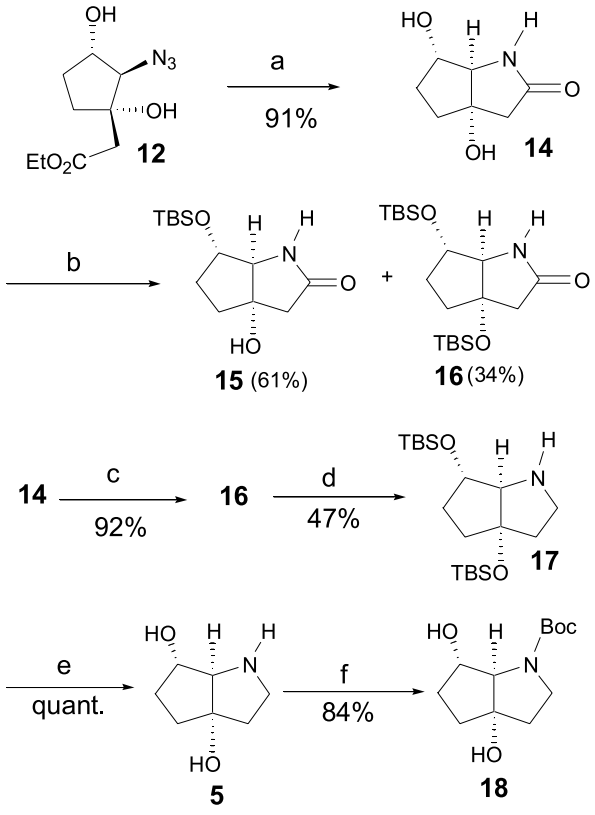
cyclopenta[*b*]pyrrole ring system is known,[15] a synthesis was not available for ready introduction of the minimum hydroxylation pattern found in deoxyribofuranosides and arabinosides. We therefore sought a route that would readily allow creation of a varied oxygenation pattern, provide transition state charge mimicry, and allow for introduction of an aglycon mimic. In this report, we describe the first synthesis of a family of octahydro cyclopenta[*b*]pyrrole *cis*-3a,6-diols via transformations of a central common bicyclic lactam intermediate.

2. Results and discussion

Our synthetic plan began with the key intermediate **10** (Scheme 1). Initial synthesis of **10** was based on reduction of (3-oxo-cyclopent-1-enyl)-acetic acid ethyl ester available in four steps from the sodium salt of cyclopentadiene **6**,[15–17] however, yields were poor for this strategy. An improved synthesis of **10** was devised which featured an allylic rearrangement in an efficient one-pot procedure (Scheme 1). Thus, addition of the lithium enolate of ethyl acetate to 2-cyclopentene-1-one at −78 °C gave 1,2-adduct **10a** as the major product, which was treated with aqueous acid solution to afford the desired allylic alcohol **10**. Several acids (e.g., hydrochloric acid, acetic acid, formic acid, oxalic acid, etc.) were examined as catalysts for the rearrangement reaction of **10a**, and it was found that using saturated aqueous oxalic acid at 0 °C gave the best results, providing allylic alcohol **10** in 54% overall yield. Hydroxyl-directed *syn*-epoxidation of **10** with *m*-chloroperoxybenzoic acid was performed with complete diastereoselectivity to give epoxide **11**. Ring-opening of **11** with sodium azide in the presence of ammonium chloride furnished azide **12** (44% overall from **10**), with azide attacking at the less hindered C-2. Protection of **12** with 2,2-dimethoxypropane in the presence of a catalytic amount of camphorsulfonic acid (CSA) provided bicyclic azide **13** (51%), which is very acid-sensitive. The success in ketalization of **12** demonstrated the *syn*-relationship between the two hydroxyl groups. However, attempted reduction and ring-closure of azide **13** to the desired tricyclic compound was unsuccessful, presumably due to considerable strain in the system. Reduction of azide **12** and subsequent ring closure was accomplished smoothly in a one-pot reaction by treating **12** with triphenylphosphine and then water to give bicyclic lactam **14** in 91% yield (Scheme 2). Silylation of **14** with TBDMSCl and imidazole gave mono-silyl ether **15** (61%) and bis-silyl ether **16** (34%). When TBDMSOTf and 2,6-lutidine were used for silylation of **14**, the bis-silyl ether **16** was obtained in 92% yield. These latter conditions for synthesis of **16** provide a good indication that despite the hindered environment around the tertiary hydroxyl, it can be derivatized with a suitably electrophilic reagent. The relative stereochemistry of the lactam system was confirmed



Scheme 1. Reagents and conditions: (a) $LiCH_2CO_2Et$, THF, −78 °C; (b) saturated oxalic acid, 0 °C; (c) *m*CPBA, CH_2Cl_2, 0 °C; (d) NaN_3, NH_4Cl, EtOH–H_2O, reflux; (e) $(CH_3)_2C(OCH_3)_2$, CSA (cat.), CH_2Cl_2, rt, 20 min.



Scheme 2. Reagents and conditions: (a) (1) PPh_3, THF, rt, (2) H_2O; (b) TBDMSCl, imidazole, DMF; (c) TBDMSOTf, 2,6-lutidine, DMF; (d) BH_3, THF, reflux; (e) 3 N HCl, reflux; (f) $(Boc)_2O$, Et_3N, CH_2Cl_2.

by X-ray crystallographic analysis of silyl ether **15**. When bis-silyl ether **16** was subjected to the borane reduction in refluxing THF, bicyclic amine **17** was obtained in reasonable yield (47%). Desilylation of **17** was best achieved by treating **17** with 3 N HCl at 100 °C to give **5**·HCl in quantitative yield. Other desilylation conditions (TBAF/THF, room temperature; KF/18-crown-6; AcOH, 90 °C; HF/pyridine; formic acid, 90 °C, etc.) failed to give satisfactory results. N-Protection of **5** ($(Boc)_2O$, Et_3N, CH_2Cl_2) gave *N*-Boc iminocyclitol **18** in 84% yield. The structure of **18** was unambiguously determined by single-crystal X-ray analysis (Fig. 3).

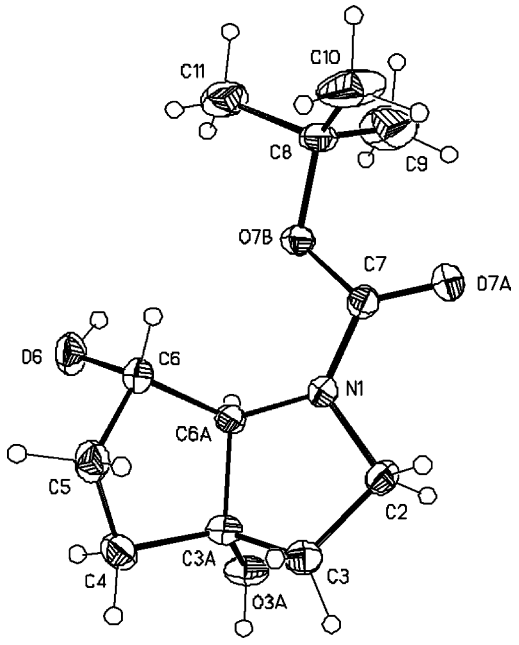
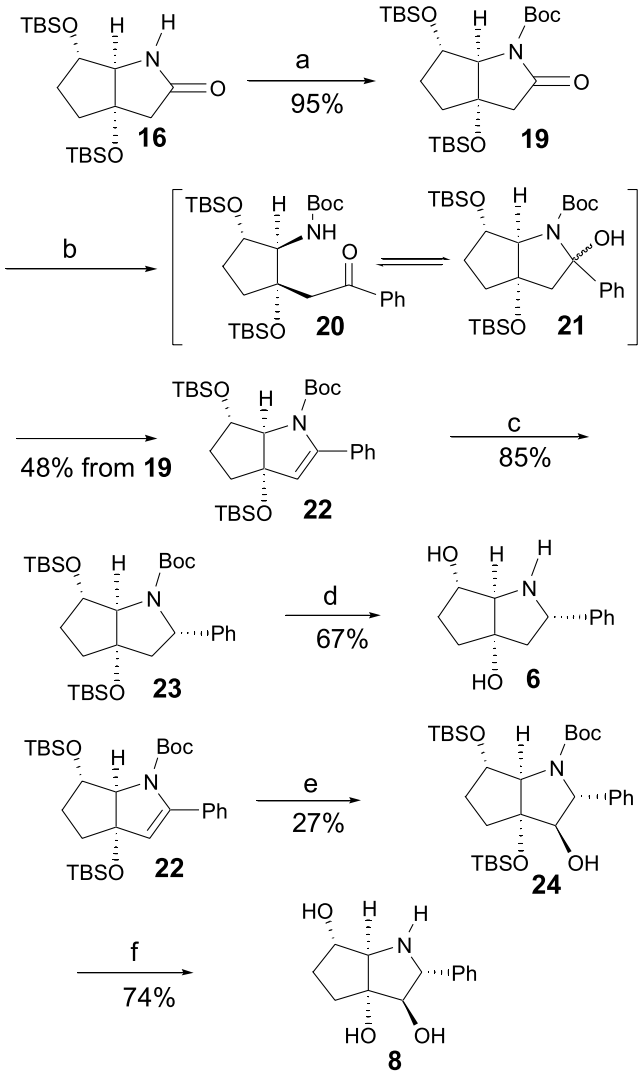


Figure 3. Thermal ellipsoids drawing of **18**.

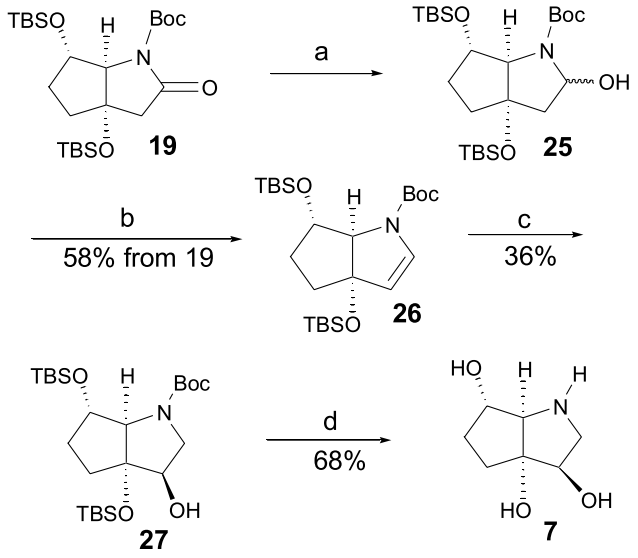
The *N*-Boc lactam **19** was prepared in high yield (95%) by metalation of lactam **16** with BuLi in THF at −78 °C, followed by treatment with $(Boc)_2O$ (Scheme 3). Savoia and co-workers reported that five-membered *N*-Boc lactams underwent ring-opening reactions with Grignard reagents to give *N*-Boc-ω-amino ketones.[18] In the present case, addition of phenylmagnesium bromide to bicyclic *N*-Boc lactam **19** in THF at −78 °C, followed by quenching the reaction with saturated aqueous NH_4Cl, gave lactamol **21** as the major product, and only a trace amount of ketone **20** was detected. On the other hand, when the reaction was quenched with 15% HCl, an equilibrium mixture of ketone **20** and lactamol **21** was obtained, in which neither **20** or **21** was dominant. When the acidic quenched reaction mixture was further stirred at room temperature for some time, the desired enecarbamate **22** was formed with the consumption of both **20**, and **21**. Using this one-pot procedure, enecarbamate **22** was prepared in 48% overall yield from the *N*-Boc lactam **19**. The mechanism for the formation of **22** presumably involves an acid-catalyzed dehydration of lactamol **21**. Palladium-catalyzed reduction of **22** using ammonium formate as the hydrogen donor proceeded smoothly at room temperature to give compound **23** as a sole diastereoisomer in 85% isolated yield. When using hydrogen gas as the hydrogen donor, hydrogenolysis was



Scheme 3. Reagents and conditions: (a) (1) BuLi, THF, −78 °C, (2) $(Boc)_2O$, 95%; (b) (1) PhMgBr, THF, −78 °C→−20 °C, (2) 15% HCl; (c) Pd/C, HCO_2NH_4, MeOH, rt 85%; (d) TFA–H_2O; (e) (1) BH_3, THF, reflux, (2) H_2O_2, NaOH; (f) (1) TFA, CH_2Cl_2, rt, (2) 3 N HCl, reflux.

the major process. Deprotection of **23** (trifluoroacetic acid–water, room temperature) afforded iminocyclitol **6** in 67% yield. Hydroboration of enecarbamate **22** in refluxing THF (no reaction was observed at room temperature), followed by oxidation (H_2O_2, NaOH), furnished alcohol **24** in 27% yield together with some unidentified side products. Deprotection of **24** gave iminocyclitol **8** in 74% yield. The relative stereochemistry of **6**, and **8** was confirmed by NOE difference experiments.

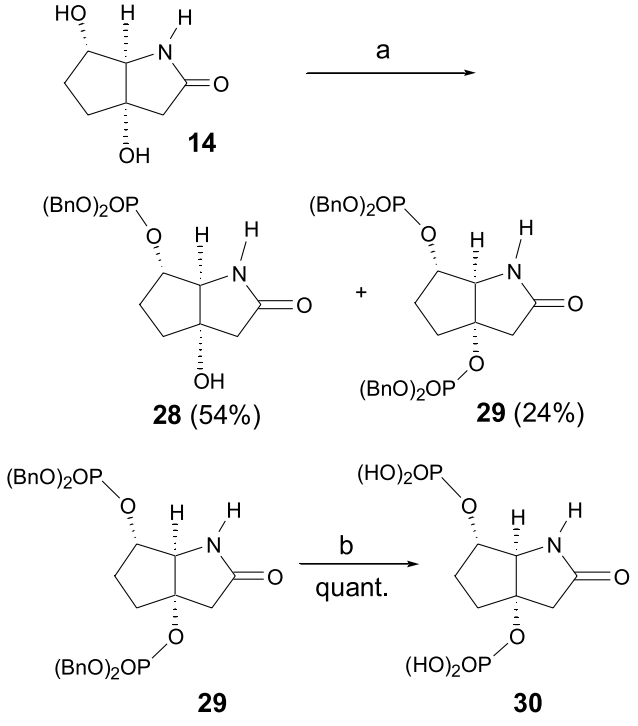
To prepare enecarbamate **26**, we followed a literature procedure (Scheme 4).[19] Thus, reduction of *N*-Boc lactam **19** using diisobutylaluminum hydride (Dibal-H) at −78 °C gave lactamol **25** as a 3:1 mixture of epimers. Treatment of lactamol **25** with trifluoroacetic anhydride (TFAA) in the presence of 2,6-lutidine (−78 °C to room temperature) gave enecarbamate **26** in 58% overall yield. Considering that enecarbamate **22** could be conveniently prepared by acid-catalyzed dehydration of lactamol **21**, we attempted to synthesize **26** in the same fashion. Thus, after the reduction of **19** with Dibal-H, the reaction mixture was immediately



Scheme 4. Reagents and conditions: (a). (1) Dibal-H, THF, −78→0 °C, (2) 10% Na_2CO_3; (b) TFAA, 2,6-lutidine, CH_2Cl_2, −78 °C→rt; (c) (1) BH_3, THF, rt, (2) H_2O_2, NaOH; (d) (1) TFA, CH_2Cl_2, rt, (2) 3 N HCl, reflux.

treated with 15% HCl and kept at room temperature for some time, however, the isolated yield of the desired product **26** was low (28%). Hydroboration–oxidation of **26** at room temperature gave alcohol **27** in 36% yield. Further study on hydroboration–oxidation of **22**, and **26** will be required in order to improve the yields and stereoselectivity. Deprotection of **27** afforded iminocyclitol **7** in 68% yield. The relative stereochemistry of **7** was confirmed by NOE difference experiments.

To demonstrate the potential for phosphorylation of the above bicyclic compounds, we sought to synthesize diphosphate **30**. Accordingly, reaction of lactam **14** with dibenzyl diisopropylphosphoramidite in the presence of 1H-tetrazole in DMF, followed by oxidation with *tert*-butyl hydroperoxide, gave monophosphate **28** (54%) and diphosphate **29** (24%) (Scheme 5). Palladium-catalyzed hydrogenolysis of **29** in MeOH gave diphosphate **30** in quantitative yield. As observed previously for preparation of silyl derivatives, the tertiary hydroxyl group of **14** is hindered, and somewhat unreactive. Further experimentation will be required to optimize introduction of P^{III} species at this position. However, with this modification accessible, the incorporation of the new compounds into oligonucleotides appears to be feasible.



Scheme 5. Reagents and conditions: (a) (1) $(BnO)_2PN(iPr)_2$, 1H-tetrazole, DMF, rt, (2) *t*-BuOOH; (b) Pd/C, H_2, MeOH.

3. Conclusions

In summary, an efficient synthesis of novel bicyclic iminocyclitols **5**-**8**, which were designed as conformationally restricted analogues of pyrrolidine azasugars, has been developed. The key steps involve an allylic rearrangement, a hydroxyl-directed epoxidation, and an acid-catalyzed formation of enecarbamate **22**. The present route allows for the flexible incorporation of functionality into the basic bicyclic structure including hydroxylation and alkylation with mimics of the furanosyl aglycon. Further application of these synthesized iminocyclitols in developing specific inhibitors of glycoprocessing enzymes is in progress.

4. Experimental

4.1. General

Reagents and solvents were purchased from Acros or Aldrich. Melting points were measured on a Fisher-Johns melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were obtained at 300 and 75.4 MHz, respectively, on Varian VXR-300, Gemini-300 or Mercury-300 spectrometers. $CDCl_3$ was used as NMR solvent unless otherwise mentioned. Chemical shifts are in ppm and *J* values are in Hz. Mass spectra were obtained on a Finnegan MAT95 spectrometer operated in the EI mode. Solvents were dried by distillation from the appropriate drying agent under inert atmosphere. Reagents were employed as received unless otherwise noted. Column chromatography employed 200–400 mesh silica. All new compounds displayed satisfactory $^1H/^{13}C$ NMR and mass spectra.

4.1.1. (3-Hydroxy-cyclopent-1-enyl)-acetic acid ethyl ester (10). To a solution of diisopropylamine (25.6 mL,182.7 mmol) in THF (150 mL) was added slowly a 2.5 M solution of *n*-BuLi in hexanes (73.1 mL, 183 mmol) at −78 °C, and the resulting mixture was warmed to 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C, and a solution of EtOAc (17.8 mL, 182 mmol) in THF (20 mL) was added dropwise. After stirring at −78 °C for an additional 1.5 h, a solution of 2-cyclopenten-1-one (10 g, 122 mmol) in THF (20 mL) was added dropwise, and the reaction mixture was kept at −78 °C for 2 h before it was quenched with saturated aqueous NH_4Cl. The mixture

was diluted with ethyl ether, washed with water, and concentrated at aspirator pressure. The residue was dissolved in ethyl ether (250 mL), and saturated oxalic acid (200 mL) was added dropwise at 0 °C over 30 min. After stirring at 0 °C for 4 h (the reaction was monitored by TLC), the organic layer was separated. The aqueous layer was cooled to 0 °C, carefully rendered basic with solid $NaHCO_3$ and extracted with EtOAc (6×50 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel, eluting with petroleum ether–ethyl ether (4/1–1/1), to give **10** as a colorless oil (11.2 g, 54%): ^{1}H NMR: δ 5.66 (m, 1H), 4.84 (broad s, 1H), 4.14 (q, 2H, J=7.2 Hz), 3.15 (m, 2H), 2.52 (m, 1H), 2.31 (m, 2H), 1.89 (s, 1H), 1.75 (m, 1H), 1.26 (t, 3H, J=7.2 Hz); ^{13}C NMR: δ 171.8, 141.5, 130.8, 77.5, 60.8, 37.0, 34.0, 33.5, 14.2; HRMS calcd for $C_9H_{15}O_3$ (M^++H): 153.0916; found: 153.0912.

4.1.2. (1,4-*cis*-4-Hydroxy-6-oxa-bicyclo[3.1.0]hex-1-yl)-acetic acid ethyl ester (11). To a solution of **10** (10.43 g, 61.4 mmol) in CH_2Cl_2 (400 mL) was added *m*CPBA (68%, 18.7 g, 73.6 mmol) in portions at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was filtered. The filtrate was washed with 10% Na_2CO_3 and brine, dried ($MgSO_4$), and concentrated to give **11** as a crude product, which was used for the next reaction without further purification. A pure sample **11** was obtained as a colorless oil by flash chromatography on silica gel (petroleum ether/ethyl ether 1:2): ^{1}H NMR: δ 4.31 (m, 1H), 4.14 (q, 2H, J=7.2 Hz), 3.45 (broad s, 1H), 2.9 (broad, 1H), 2.78 (d, 1H, J=16.0 Hz), 2.67 (d, 1H, J=16.0 Hz), 2.08 (m, 1H,), 1.96 (m, 1H), 1.72 (m, 1H), 1.34 (m, 1H), 1.25 (t, 3H, J=7.2 Hz); ^{13}C NMR: δ 169.7, 73.2, 64.1, 62.8, 60.9, 37.8, 28.6, 28.5, 14.1; HRMS calcd for $C_9H_{15}O_4$ (M^++H): 187.0970; found: 187.0952.

4.1.3. (1,2-*trans*-2-Azido-1,3-*cis*-dihydroxy-cyclopentyl)-acetic acid ethyl ester (12). A mixture of the above crude epoxide **11** (ca. 60 mmol), sodium azide (19.7 g, 300 mmol), NH_4Cl (16 g, 300 mmol), 95% EtOH (200 mL) and H_2O (100 mL) was heated at 90 °C for 9 h. The mixture was then concentrated to ca. 100 mL, and extracted with EtOAc (6×50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with petroleum ether–ethyl ether (4/1), to give **12** as a pale yellow oil (6.17 g, 44% from **10**): ^{1}H NMR: δ 4.21 (m, 3H), 3.83 (broad s, 1H), 2.72 (d, 1H, J=16.9 Hz), 2.58 (d, 1H, J=16.9 Hz), 2.20 (m, 1H), 1.99 (m, 1H), 1.87 (m, 1H,), 1.65 (m, 1H), 1.30 (t, 3H, J=7.2 Hz); ^{13}C NMR: δ 173.2, 81.1, 77.1, 74.4, 61.2, 39.3, 35.4, 31.4, 14.1; HRMS calcd for $C_9H_{16}N_3O_4$ (M^++H): 230.1141; found: 230.1175.

4.1.4. (1,8-*cis*-8-Azido-3,3-dimethyl-2,4-dioxa-bicyclo-[3,2,1]oct-1-yl)-acetic acid ethyl ester (13). A solution of **12** (80 mg, 0.352 mmol), 2,2-dimethoxypropane (2 mL) and camphorsulfonic acid (10 mg, 0.043 mmol) in CH_2Cl_2 was stirred at room temperature for 20 min, then a drop of Et_3N was added to quench the reaction. The mixture was concentrated to dryness, and the residue was purified by flash chromatography on silica gel, eluting with petroleum ether–ethyl ether (4/1, 2% Et_3N), to give **13** as a colorless oil (48 mg, 51%): ^{1}H NMR: δ 4.26–4.18 (m, 3H), 4.07 (m, 1H), 3.81 (d, 1H, J=5.3 Hz), 2.67 (d, 1H, J=16.4 Hz), 2.48 (d, 1H, J=16.4 Hz), 2.05–1.82 (m, 3H), 1.64 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.29 (t, 3H, J=7.2 Hz); ^{13}C NMR: δ 101.2, 79.0, 75.7, 75.5, 61.2, 40.3, 35.9, 31.1, 25.8, 25.2, 14.4; MS calcd for $C_{12}H_{20}N_3O_4$ (M^++H): 270; found: 270.

4.1.5. 3a,6a,6-*cis*-3a,6-Dihydroxy-hexahydro-cyclopenta[*b*]pyrrole-2-one (14). To a solution of **12** (6.17 g, 26.9 mmol) in THF (100 mL) was added triphenylphosphine (7.07 g, 26.9 mmol) in one portion at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was warmed to room temperature and stirred for 48 h. Water (20 mL) was then added. After stirring at room temperature for an additional 12 h, the reaction mixture was concentrated to dryness, and the residue was purified by flash chromatography on silica gel, eluting with CH_2Cl_2–MeOH (10/1–5/1), to give **14** as a white solid (3.86 g, 91%): ^{1}H NMR: (DMSO-d_6) δ 7.80 (s, 1H, NH), 5.25 (s, 1H, OH), 4.82 (d, 1H, OH, J=3.4 Hz), 3.65 (m, 1H), 3.29 (broad s, 1H), 2.32 (d, 1H, J=17.6 Hz), 2.22 (d, 1H, J=17.6 Hz), 1.95 (m, 1H), 1.69–1.58 (m, 3H); ^{13}C NMR: (DMSO-d_6) δ 174.8, 82.0, 76.3, 73.5, 46.0, 37.9, 32.0; HRMS calcd for $C_7H_{12}NO_3$ (M^++H): 158.0817; found:158.0818.

4.1.6. 3a,6a,6-*cis*-6-(*tert*-Butyl-dimethyl-silanyloxy)-3a-hydroxy-hexahydro-cyclopenta[*b*]pyrrole-2-one (15) and 3a,6a,6-*cis*-3a,6-bis-(*tert*-butyl-dimethyl-silanyloxy)-hexahydro-cyclopenta[*b*]pyrrole-2-one (16). A mixture of **14** (0.52 g, 3.31 mmol), TBDMSCl (1.492 g, 9.92 mmol), imidazole (0.674 g, 9.92 mmol) and DMF (3 mL) was stirred at room temperature for 6 h. After removal of the bulk of the DMF in vacuo, the residue was purified by flash chromatography on silica gel, eluting with petroleum ether–ethyl acetate (5/1–1/1), to give **15** as a white solid, mp 136–138 °C, (0.549 g, 61%), together with **16** (a white solid, 105–107 °C, 0.4 g, 34%). 15: ^{1}H NMR: δ 6.15 (s, 1H, NH), 3.97 (broad s, 1H), 3.58 (broad s, 1H), 2.80 (s, 1H, OH), 2.67 (d, 1H, J=17.9 Hz), 2.51 (d, 1H, J=17.7 Hz), 2.2–2.1 (m, 1H), 2.0–1.9 (m, 1H), 1.85–1.76 (m, 1H), 0.88 (s, 9H), 0.073 (s, 3H), 0.069 (s, 3H); ^{13}C NMR: δ 175.9, 83.4, 77.3, 73.7, 45.4, 39.4, 32.8, 25.7, 18.0, −4.7, −4.8; HRMS calcd for $C_{13}H_{26}NO_3Si$ (M^++H): 272.1682; found:272.1688. 16: ^{1}H NMR: δ 6.36 (s, 1H, NH), 3.85 (m, 1H), 3.59 (broad s, 1H), 2.60 (d, 1H, J=17.9 Hz), 2.46 (d, 1H, J=17.9 Hz), 2.24 (m, 1H), 1.83–1.72 (m, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.065 (s, 3H), 0.055 (s, 3H); ^{13}C NMR: δ 175.9, 84.9, 74.8, 46.5, 38.9, 32.9, 25.7, 25.6, 17.95, 17.76, −2.74, −2.83, −4.69, −4.83; HRMS calcd for $C_{19}H_{40}NO_3Si_2$ (M^++H): 386.2547; found:386.2553.

4.1.7. 3a,6a,6-*cis*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyloxy)-octahydro-cyclopenta[*b*]pyrrole (17). To solution of **14** (3.16 g, 20.13 mmol) in DMF (10 mL) was added TBDMSOTf (9.73 mL, 42.3 mmol) at 0 °C, then 2,6-lutidine (9.4 mL, 80.51 mmol) was added. The resulting mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated $NaHCO_3$, extracted with ethyl ether (3×100 mL). The organic layer was washed with 2 N HCl and brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl ether 10:1–1:1) to give **16** as a white solid (7.13 g, 92%). To

a solution of **16** (1.17 g, 3.04 mmol) in THF (20 mL) was added a 1 M solution of BH_3–THF complex in THF (15.2 mL, 15.2 mmol). The resulting mixture was refluxed for 12 h. After cooling to 0 °C, the reaction mixture was carefully quenched with aqueous NaOH, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 40:1) to give **17** as a colorless oil (0.531 g, 47%): ^{1}H NMR: δ 3.77 (broad s, 1H), 3.21 (broad s, 1H), 3.05–2.96 (m, 1H), 2.94–2.88 (m, 1H), 2.1 (m,1H), 2.02 (broad s, 1H), 1.88–1.62 (m, 5H), 0.88 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR: δ 90.9, 79.3, 78.6, 47.1, 42.1, 37.1, 33.6, 25.8, 25.7, 18.0, 17.8, −2.7, −4.7; HRMS calcd for $C_{19}H_{42}NO_2Si_2$ (M^++H): 372.2754; found: 372.2745.

4.1.8. 3a,6a,6-*cis*-Hexahydro-cyclopenta[*b*]pyrrole-3a,6-diol (5). A mixture of **17** (318 mg, 0.857 mmol) and 3 N HCl (10 mL) was heated at 100 °C for 1 h, then cooled to room temperature, diluted with water, and filtered. The filtrate was extracted with ethyl ether. The aqueous layer was then concentrated to dryness to give pure product **5** as the HCl salt (160 mg, ca.100%): ^{1}H NMR (300 MHz, D_2O) δ 4.24 (m, 1H), 3.60 (d, 1H, J=3.91 Hz), 3.52–3.36 (m, 2H), 2.16–1.88 (m, 6H); ^{13}C NMR (75 MHz, D_2O) δ 87.3, 75.6, 74.0, 46.6, 37.8, 35.6, 32.5; HRMS (in D_2O) calcd for C_7H_{12} D_2NO_2: 146.1150; found: 146.1119.

4.1.9. 3a,6a,6-*cis*-3a,6-Dihydroxy-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (18). A mixture of **5** (HCl salt form, 160 mg, 0.89 mmol), $(Boc)_2O$ (584 mg, 2.67 mmol), Et_3N (0.494 mL, 3.56 mmol) and CH_2Cl_2 (7 mL) was stirred at room temperature overnight, and then concentrated to dryness. The residue was purified by flash chromatography on silica gel (EtOAc) to give **18** as a white solid, mp 116–118 °C (176 mg, 84%): ^{1}H NMR: δ 4.09 (m, 0.33H, minor conformational isomer), 4.0 (m, 0.67H, major conformational isomer), 3.65–3.53 (m, 2H), 3.39 (m, 1H), 2.05–1.82 (m, 6H), 1.48 (s, 3H, minor conformational isomer), 1.44 (s, 6H, major conformational isomer); ^{13}C NMR: δ 155.6, 154.1, 88.7, 87.7, 80.2, 78.5, 77.8, 77.5, 47.1, 45.9, 38.5, 37.3, 36.7, 32.5, 28.4; HRMS calcd for $C_{12}H_{22}NO_4$ (M^++H): 244.1549; found: 244.1545.

4.1.10. 3a,6a,6-*cis*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyl-oxy)-2-oxo-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (19). To a solution of **16** (5.92 g, 15.38 mmol) in THF (60 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (6.15 mL, 15.38 mmol) at −78 °C. After stirring at −78 °C for 30 min, a solution of $(Boc)_2O$ (4.02 g, 18.5 mmol) in THF (15 mL) was added dropwise. The resulting reaction mixture was stirred at −78 °C for an additional 4 h, and then quenched with saturated NH_4Cl, and diluted with ethyl ether. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel, eluting with petroleum ether–ethyl ether (50/1–10/1), to give **19** as a white solid, mp 96–97 °C, (7.09 g, 95%): ^{1}H NMR: δ 4.05 (d, 1H, J=2.1 Hz), 4.0 (m, 1H), 2.76 (d, 1H, J=18.8 Hz), 2.62 (d, 1H, J=18.8 Hz), 2.29 (m, 1H), 1.84–1.70 (m, 2H), 1.62–1.49 (m, 1H), 1.54 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR: δ 172.4, 150.0, 83.2, 80.2, 78.0, 76.2, 48.6, 38.3, 32.7, 28.0, 25.7, 25.5, 17.8, 17.7, −2.8 (broad), −4.7, −4.8; HRMS calcd for $C_{24}H_{48}NO_5Si_2$ (M^++H): 486.3071; found: 486.3088.

4.1.11. 3a,6a,6-*cis*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyl-oxy)-2-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (22). To a solution of **19** (1.89 g, 3.89 mmol) in THF (6 mL) was added a 1 M solution of phenylmagnesium bromide in THF (5.84 mL, 5.84 mmol) at −78 °C. The reaction mixture was gradually warmed to −10 °C over 1.5 h, and then quenched with 15% HCl (12 mL). The resulting mixture was stirred at room temperature for an additional 5 h. The organic layer was separated, and the aqueous layer was extracted with ethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with petroleum ether, to give **22** as a white solid (1.025 g, 48%): ^{1}H NMR: δ 7.40 (m, 5H), 5.02 (s, 1H), 4.17 (m,1H), 4.08 (broad s, 1H), 2.32 (m, 1H), 1.84 (m, 1H), 1.67 (m, 1H), 1.44 (m, 1H), 1.21 (s, 9H), 0.93 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR: δ 152.9, 145.2, 134.7, 127.7, 127.6, 126.9, 116.7 88.2, 80.2, 78.1, 38.3, 32.7, 25.8, 18.0, −2.1, −3.0, −4.1; HRMS calcd for $C_{30}H_{52}NO_4Si_2$ (M^++H): 546.3435; found: 546.3433.

4.1.12. 2,3a,6a,6-*cis*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyl-oxy)-2-phenyl-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (23). A mixture of **22** (205 mg), ammonium formate (1 g), 10% Pd/C (50 mg) and MeOH (30 mL) was stirred at room temperature for 48 h. The catalyst was removed by filtration and the filtrate was concentrated. Water was added to the residue, and the mixture was extracted with ethyl ether. The ether layer was dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl ether 50:1) to give **23** as a colorless oil (175 mg, 85%): ^{1}H NMR: δ 7.20 (m, 5H), 5.0–4.8 (m, 1H), 4.2 (broad s, 1H), 4.06 (broad s, 1H), 2.4–2.05 (m, 3H), 1.72 (m, 3H), 1.46 and1.13 (broad s, 9H, two conformational isomers), 0.92 (broad s, 9H), 0.70 (broad s, 9H), 0.22–0.05 (m, 9H), −0.21 (s, 3H); ^{13}C NMR: δ 153.9, 145.5, 127.8, 126.2, 126.0, 125.5, 89.7, 79.9, 79.0, 75.7, 63.4, 48.9, 38.2, 33.6, 28.0, 25.9, 25.5, 17.9, 17.7, −2.6, −3.0, −4.4, −5.2; HRMS calcd for $C_{30}H_{54}NO_4Si_2$ (M^++H): 548.3591; found: 548.3588.

4.1.13. 2,3a,6a,6-*cis*-2-Phenyl-hexahydro-cyclopenta[*b*]pyrrole-3a,6-diol (6). A mixture of **23** (126 mg, 0.23 mmol), trifluoroacetic acid (2 mL) and water (2 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated, and the residue was made alkaline with NH_4OH, and then concentrated again. The residue was purified by flash chromatography on silica gel, eluting with CH_2Cl_2–MeOH (10/1), to give **6** as a colorless oil (50 mg, 67%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.49 (m, 5H), 4.66 (dd, 1H, J=5.8, 12.9 Hz), 4.24 (m, 1H), 3.53 (d, 1H, J=5.8 Hz), 2.48 (dd, 1H, J=5.8, 13.2 Hz), 2.28 (dd, 1H, J=12.9, 13.2 Hz), 2.15–1.92 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 136.2, 130.6, 128.7, 87.3, 77.5, 77.3,

63.7, 46.5, 38.2, 34.0; HRMS calcd for $C_{13}H_{18}NO_2$ (M^+ + H): 220.1338; found: 220.1354.

4.1.14. 2,3a,6a,6-*cis*-2,3-*trans*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-2-phenyl-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (24). To a solution of **22** (510 mg, 0.94 mmol) in THF (30 mL) was added a 1 M solution of BH_3–THF complex in THF (4.68 mL, 4.68 mmol) at room temperature. The reaction mixture was refluxed for 1 h, then cooled to 0 °C. 3 M NaOH (5 mL) was added carefully, then 30% H_2O_2 (5 mL) was added. The resulting mixture was stirred at room temperature overnight. After the removal of THF by evaporation, the residue was extracted with ethyl ether. The ether layer was washed with saturated $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl ether 20:1) to give **24** (141 mg, 27%) as a colorless oil: ^{1}H NMR: δ 7.35 (m, 5H), 4.52 (m, 1H), 4.40 (m, 1H), 4.30 (broad s, 1H), 4.24 (m, 1H), 2.50–2.05 (m, 4H), 1.6–1.03 (m, 27H), 0.38–0.24 (m, 12H); ^{13}C NMR: δ 153.6, 142.8, 128.4, 127.0, 126.3, 89.9, 86.5, 79.4, 77.2, 68.5, 34.8, 32.1, 27.8, 26.0, 25.6, 18.1, 17.9, −2.7, −2.8, −4.5, −5.1; HRMS calcd for $C_{30}H_{54}NO_5Si_2$ (M^+ + H): 564.3541; found: 564.3538.

4.1.15. 2,3a,6a,6-*cis*-2,3-*trans*-2-Phenyl-hexahydro-cyclopenta[*b*]pyrrole-3,3a,6-triol (8). To a solution of **24** (140 mg, 0.249 mmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (1 mL) at room temperature. After stirring at this temperature for 1 h, the reaction mixture was concentrated to dryness. The residue was dissolved in 3 N HCl (4 mL) and heated at 100 °C for 1 h. After cooling to room temperature, the mixture was diluted with water, and filtered. The filtrate was extracted with ethyl acetate, and the aqueous layer was concentrated to dryness to give pure product **8** as a HCl salt, mp 210 °C (dec), (50 mg, 74%): ^{1}H NMR (300 MHz, D_2O) δ 7.58 (m, 5H), 4.57 (d, 1H, J=11.1 Hz), 4.44 (m, 2H), 3.68 (d, 1H, J=5.3 Hz), 2.15 (m, 2H), 1.99 (m, 1H), 1.87 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 130.8, 130.6, 129.8, 128.5, 86.7, 79.0, 75.9, 72.8, 63.8, 32.1, 31.1; HRMS calcd for $C_{13}H_{18}NO_3$ (M^+ + H): 236.1287; found: 236.1277.

4.1.16. 3a,6a,6-*cis*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (25). To a solution of **19** (155 mg, 0.339 mmol) in THF (2 mL) was added dropwise a 1 M solution of Dibal-H in hexanes (0.678 mL, 0.678 mmol) at −78 °C. After the addition, the reaction mixture was slowly warmed to 0 °C over 3 h, quenched carefully with 10% Na_2CO_3 (4 mL), and diluted with ethyl ether. The resulting mixture was stirred at room temperature for an additional 20 min, and then filtered through Celite. The filtrate was dried ($MgSO_4$), and concentrated to give **25** as a 3:1 mixture of epimers, which could be used for the next reaction without further purification. The major isomer of **25** was obtained as a white solid by flash chromatography on silica gel (petroleum ether/ethyl ether 10:1): ^{1}H NMR: δ 5.40 (m, 1H), 4.10 (broad s, 1H), 3.81 (d, 1H, J=1.8 Hz), 2.22 (m, 1H), 2.04–1.96 (m, 2H), 1.76–1.56 (m, 3H), 1.48 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.17 (broad s, 6H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR: δ 155, 90.0, 84.0, 79.9, 77.8, 75.4, 46.5, 37.5, 35.7, 33.6, 28.4, 25.8, 25.7, 17.9, 17.8, −2.7, −2.8, −4.5, −5.3; HRMS calcd for $C_{24}H_{50}NO_5Si_2$ (M^+ + H): 488.3228; found: 488.3243.

4.1.17. 3a,6a,6-*cis*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester(26). To a solution of crude **25** (ca. 0.25 mmol) in CH_2Cl_2 (1 mL) was added successively 2,6-lutidine (584 μL, 5 mmol) and trifluoroacetic anhydride (39 μL, 0.275 mmol) at −78 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL), and extracted with ethyl ether. The combined organic layer was washed with 5% HCl and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl ether 50:1) to give **26** (92 mg, 58% from 19) as a colorless oil: ^{1}H NMR: δ 6.65 (d, 0.6H, J=3.9 Hz, conformational isomer) and 6.48 (d, 0.4H, J=3.9 Hz, conformational isomer), 4.94 (d, 0.6H, J=3.9 Hz, conformational isomer) and 4.85 (d, 0.4H, J=3.7 Hz, conformational isomer), 4.08 (d, 1H, J=2.9 Hz), 3.83 (m, 1H), 2.3 (m, 1H), 1.80 (m, 1H), 1.62 (m, 1H), 1.51 and1.48 (two s, 9H, two conformational isomers), 1.35 (m, 1H), 0.89 (s, 9H), 0.86 (s, 9H), 0.16–0.01 (m, 12H); ^{13}C NMR: δ 186.0, 131.3, 113..2, 112.8, 92.0, 76.1, 75.7, 75.4, 38.4, 38.1, 32.7, 32.5, 28.6, 28.4, 25.7, 17.8, 0.1, −2.5, −3.4; HRMS calcd for $C_{24}H_{48}NO_4Si_2$ (M^+ + H): 470.3122; found: 470.3115.

4.1.18. 3a,6a,6-*cis*-3,3a-*trans*-3a,6-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-hydroxy-hexahydro-cyclopenta[*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (27). To a solution of **26** (201 mg, 0.43 mmol) in THF (5 mL) was added a 1 M solution of BH_3–THF complex in THF (1.07 mL, 1.07 mmol) at room temperature. After stirring overnight at room temperature, the reaction mixture was cooled to 0 °C, 15% NaOH (2 mL) was added carefully, and then 30% H_2O_2 (2 mL) was added. The mixture was warmed to room temperature and stirred for 2 h. After extraction with ethyl ether, the combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl ether 6:1–2:1) to give **27** as a colorless oil (75 mg, 36%): ^{1}H NMR: δ 4.19 (m, 1H), 4.11 (broad s, 1H), 3.97 (m, 1H), 3.83 (broad s, 1H), 2.88 (m, 1H), 2.28 (m, 1H), 1.95 (m, 1H), 1.75 (m, 2H), 1.47 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.13 (s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR: δ 155.0, 92.0, 80.1, 77.6, 77.2, 75.1, 51.0, 34.4, 31.2, 28.5, 25.9, 25.7, 18.1, 17.9, −2.8, −4.5; HRMS calcd for $C_{24}H_{50}NO_5Si_2$ (M^+ + H): 488.3228; found: 488.3200.

4.1.19. 3a,6a,6-*cis*-3,3a-*trans*-Hexahydro-cyclopenta[*b*]pyrrole-3,3a,6-triol (7). To a solution of **27** (73 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (1 mL) at room temperature. After stirring at this temperature for 1 h, the reaction mixture was concentrated to dryness. The residue was dissolved in 3 N HCl (4 mL) and heated at 100 °C for 1 h. After cooling to room temperature, the mixture was diluted with water, and filtered. The filtrate was extracted with ethyl acetate, and the aqueous layer was concentrated to dryness to give pure

product **7** as a HCl salt (20 mg, 68%): ^{1}H NMR (300 MHz, D_2O) δ 4.32 (m, 1H), 4.15 (m, 1H), 3.66–3.59 (m, 2H), 3.38 (m, 1H), 2.24–2.10 (m, 2H), 1.97 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 89.4, 75.9, 75.3, 74.1, 53.2, 33.6, 29.9; HRMS calcd for $C_7H_{14}NO_3$ ($M^+ + H$): 160.0974; found: 160.0971.

4.1.20. Phosphoric acid dibenzyl ester (3a,6a,6-*cis*-3a-hydroxy-2-oxo-octahydro-cyclopenta[*b*]pyrrol-6-yl) ester (28) and Phosphoric acid dibenzyl ester [3a,6a,6-*cis*-6-(bis-benzyloxy-phosphoryloxy)-2-oxo-hexahydro-cyclopenta[*b*]pyrrol-3a-yl] ester (29). To a solution of **14** (28 mg, 0.18 mmol) in DMF (0.5 mL) was added successively dibenzyl diisopropylphosphoramidite (150 μL, 0.45 mmol) and 1H-tetrazole (32 mg, 0.45 mmol) at 0 °C. The mixture was then warmed to room temperature and stirred overnight. A solution of *t*-BuOOH in CH_2Cl_2 (ca. 7.5 M, 0.5 mL) was added, and the mixture was stirred at room temperature for additional 2 h. After evaporation, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 20:1) to give **28** (40 mg, 54%) and **29** (29 mg, 24%) as colorless oils, respectively. **28**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 (broad s, 10H), 5.08 (m, 4H), 4.45 (m, 1H), 3.74 (s, 1H), 2.53 (d, 2H, J=4.1 Hz), 2.13–1.86 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 178.2, 137.8, 129.9, 129.8, 129.4, 84.6, 84.4, 83.7, 74.0, 73.95, 71.1, 71.08, 46.6, 38.8, 32.0, 31.9; ^{31}P NMR (CD_3OD) δ −3.38; HRMS calcd for $C_{21}H_{25}NO_6P$ ($M^+ + H$): 418.1420; found: 418.1366. 29: ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 (m, 20H), 5.05–4.98 (m, 8H), 4.49 (m, 1H), 4.08 (broad s, 1H), 2.97 (d, 1H, J=18.5 Hz), 2.64 (d, 1H, J=18.5 Hz), 2.43 (m, 1H), 2.12 (m, 1H), 1.94 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.3, 136.7, 130.0, 129.9, 129.5, 129.4, 92.5, 92.4, 83.3, 83.2, 72.7, 72.6, 72.5, 71.3, 71.2, 44.7, 38.3, 38.2, 31.7, 31.6; ^{31}P NMR (CD_3OD) δ −3.39, −6.41; HRMS calcd for $C_{35}H_{38}NO_9P_2$ ($M^+ + H$): 678.2022; found: 678.2022.

4.1.21. Phosphoric acid mono-(3a,6a,6-*cis*-2-oxo-6-phosphonooxy-hexahydro-cyclopenta[*b*]pyrrol-3a-yl) ester (30). A mixture of **29** (29 mg, 0.043 mmol) and 10% Pd/C (10 mg) in MeOH (12 mL) was hydrogenated overnight at 1 atm H_2. The mixture was filtered through Celite. The filtrate was concentrated to dryness, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 2:1) to give **30** (13 mg, 100%): ^{1}H NMR (300 MHz, CD_3OD) δ 4.35 (m, 1H), 4.22 (broad s, 1H), 3.21 (d, 1H, J=18.5 Hz), 2.61 (d, 1H, J=18.5 Hz), 2.60 (m, 1H), 2.07 (m, 2H), 1.92 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 178.0, 89.6 (d), 81.9 (d), 73.5, 45.6, 38.3 (d), 32.1 (d); ^{31}P NMR (CD_3OD) δ −1.52, −4.3; HRMS (for the Na salt of **30**) calcd for $C_7H_{10}NO_9Na_4$ ($M^+ + H$): 405.9422; found:405.9409.

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Synthesis of two glycolipid antigens of the causative agent of Lyme disease

Vince Pozsgay,* Joanna Kubler-Kielb, Bruce Coxon and Göran Ekborg

National Institute of Child Health and Human Development, National Institutes of Health, 31 Center Dr. MSC 2423 Bethesda, MD 20892-2423, USA

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Abstract—As a prelude to development of a human vaccine against Lyme disease, the first chemical synthesis of glycolipid antigens of *Borrelia burkholderi* is reported. First, cholesteryl β-D-galactopyranoside was synthesized and was converted to partially protected congeners having the HO-6 group of the galactose moiety unprotected. Treatment of these intermediates with palmitic and oleic acid, respectively, under dehydrative conditions followed by removal of the protecting groups afforded cholesteryl 6-*O*-palmitoyl/oleoyl-β-D-galactopyranosides that were identical to the glycolipids isolated from *B. burkholderi*.
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1. Introduction

Lyme disease, a vector-borne infection caused by the tick-transmitted spirochaete *Borrelia burgdorferi*, frequently occurs in the United States, Europe, and North Asia.[1,2] This disease was identified in 1977 when an unusually large number of children with arthritis-like symptoms in and around the township of Lyme, Connecticut was identified.[3] Since then, the Centers for Disease Control and Prevention has reported a steadily increasing number of cases, reaching more than 23,000 in 2002.[4] Most cases occur in the age-groups 5–14 and 50–59 years[4] in northeastern, mid-Atlantic, and north central states. Borrelia organisms enter the circulatory system of the host via the bite of an infected Ixodes tick and infect various organs, including the brain and joints.[5] Some patients develop chronic Lyme disease that can be disabling[6] when the infection persists for years.

B. burgdorferi belongs to the bacterial order *Spirochaetales*, which is divided into two families, each divided into genera. The first family, *Spirochaetaceae* includes four genera: *Spirochaeta*, *Cristaspira*, *Treponema*, and *Borrelia*, whereas the second family, *Leptospiraceae* encompasses two genera: *Leptospira* and *Leptonema*.[7] The pathogen's helically shaped, motile cells are surrounded by an outer cell membrane, which together with flagella are assumed to play a role in the host–parasite interaction.[8] The bacterium's surface-exposed proteins are immunogenic[9] and a recombinant lipidated outer surface protein, referred to as OspA, was the major component of a licensed vaccine[10] LYMErix (SmithKline Beecham) that was withdrawn from medical use in 2002. Currently, there is no licensed vaccine to prevent Lyme disease.

Borrelia are considered Gram-negative bacteria but there is no evidence for the presence of a characteristic lipopoly- or lipooligosaccharide on their surface. Work in our laboratory[11] has identified two major glycolipids (**1**, **2**) in *B. burgdorferi* that contain cholesteryl β-galactoside in which O-6 of the galactose residue is substituted either by a palmitoyl or an oleoyl group, respectively. Cholesteryl glycosides occur in many plants[12] and fungi[13] but they are rare in animals and bacteria. The bacteria *Acholeplasma* spp.,[14] *Mycoplasma gallinarum*,[15] *Spiroplasma citri*,[16] *Borrelia hermsi*,[17] and *Helicobacter pylori*[18] have been reported to express cholesteryl glucoside but not galactoside. The presence of galactose in cholesteryl glycosides is, therefore, a unique feature of *B. burgdorferi*. The native glycolipids **1** and **2** differing in the fatty acid residue at O-6 of the galactose moiety could not be separated.[11] Therefore, the structural elucidation was performed on their mixture estimated to contain **1** and **2** in an approx. 1:1 ratio. Because of the difficulties in growing *B. burgdorferi*, glycolipids **1** and **2** could be obtained only in small quantities. This fact combined with the difficulty to separate them, prompted us to synthesize **1** and **2** in quantities and purity suitable for immunization experiments. Availability of well-defined compounds was expected to remove uncertainties that

Keywords: *Borrelia burkholderi*; Cholesterol; Glycolipid; Lyme disease; Vaccine.
* Corresponding author. Tel.: +1 301 295 2266; fax: +1 301 295 1435; e-mail: pozsgayv@mail.nih.gov

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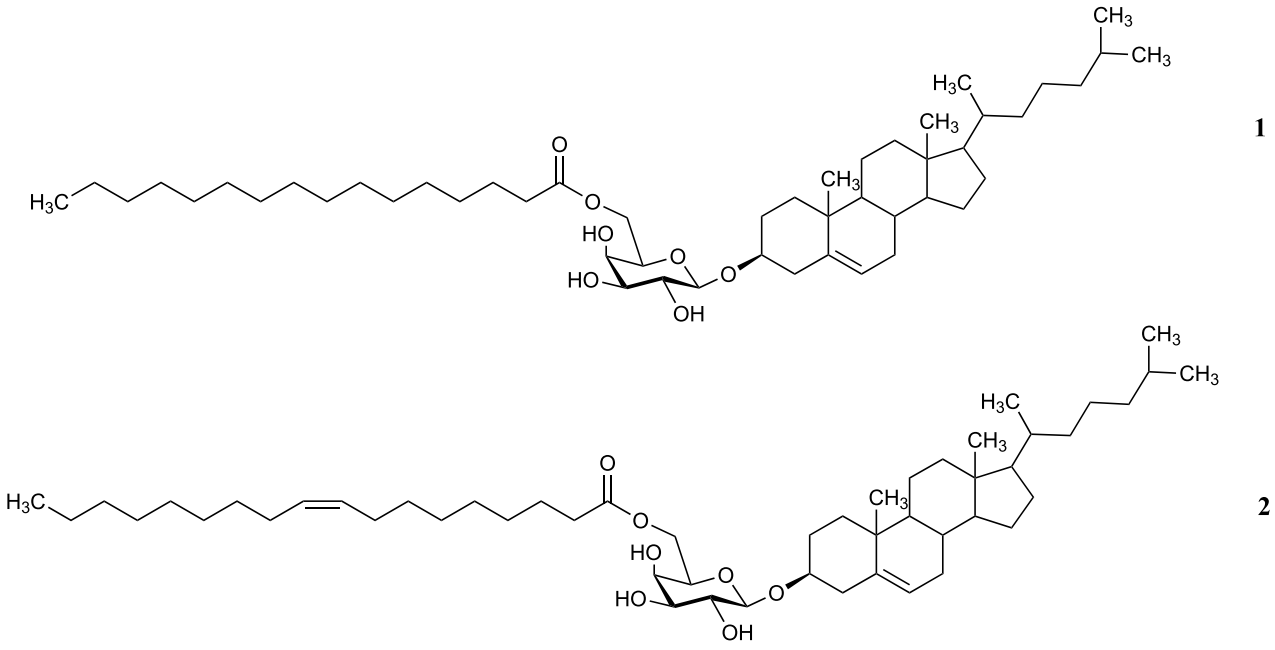
arose from the fact that the structural studies were carried out on a mixture. Here, we report chemical synthetic approaches to glycolipids **1** and **2**, and provide confirmatory evidence for the native structures. We also describe a simple method to eliminate the virtual couplings in the chloroform-*d* ^{1}H NMR spectra of **1** and **2** and their synthetic intermediates.

2. Results and discussion

Two approaches were designed to the synthetic targets **1** and **2**. The first involved the preparation of a 6-*O*-palmitoyl/oleoyl-galactopyranosyl donor that was coupled to HO-3 of cholesterol. Because of the limitations imposed upon the synthetic scheme by the cholesterol's own double bond, as



1

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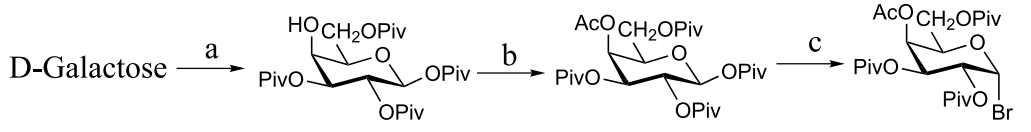
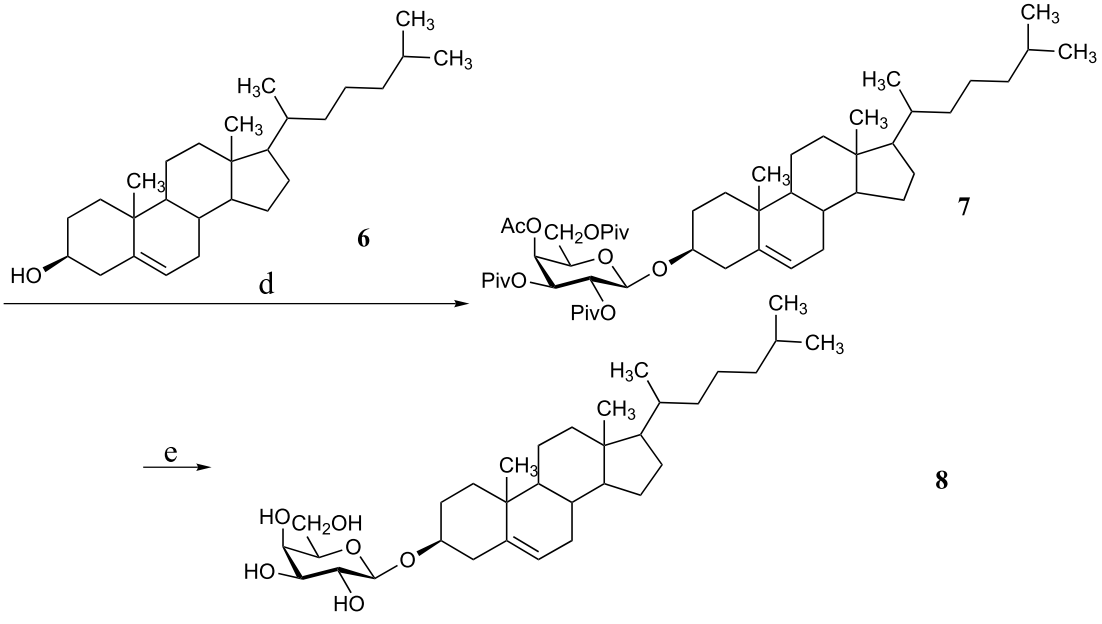


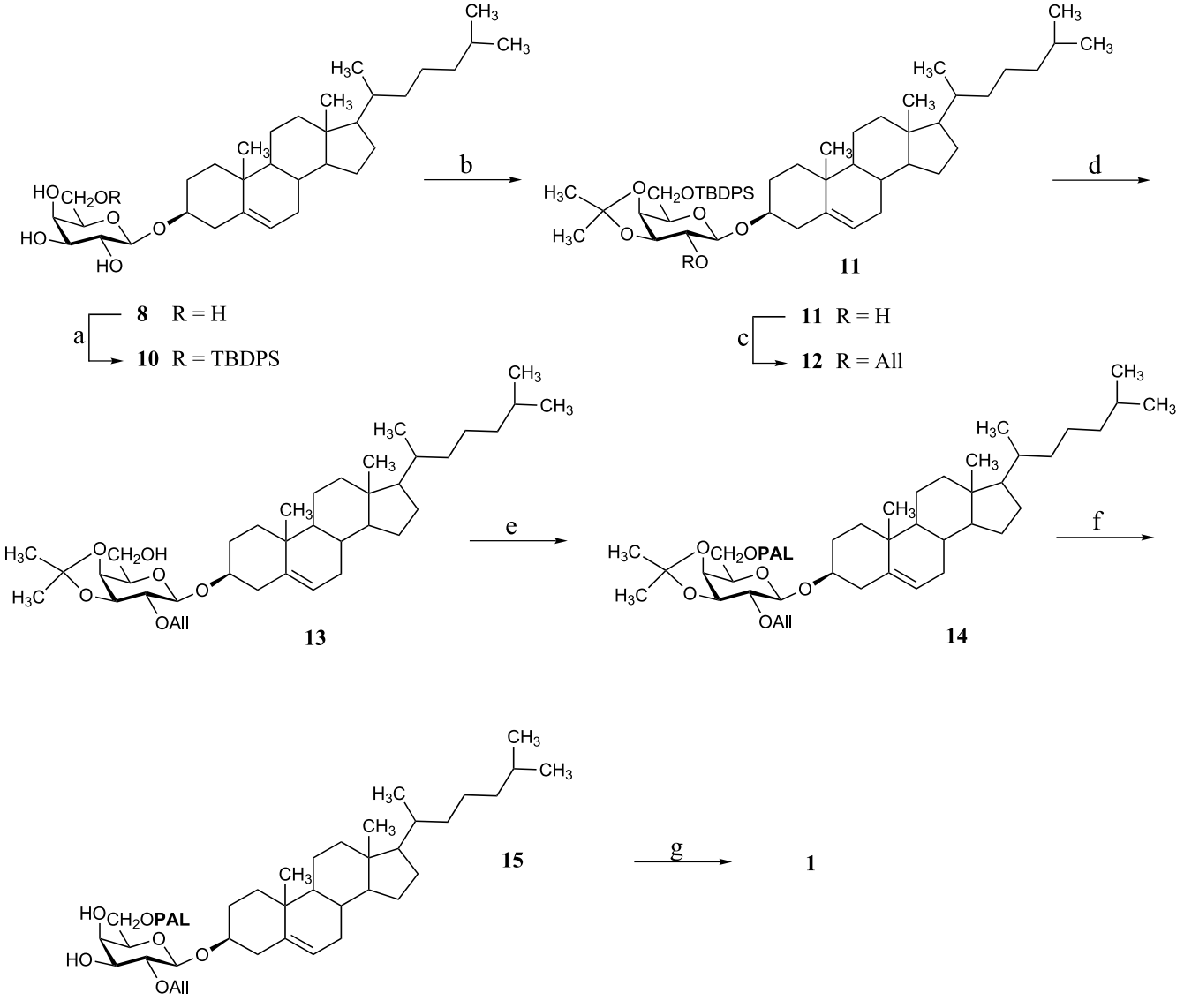
3 **4** **5**



6 **7** **8**

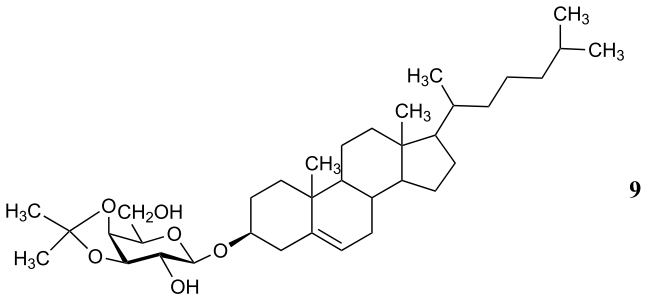
Scheme 1. Reagents and conditions: (a) 1.32 equiv of $(CH_3)_3COCl$, C_5H_5N, $CHCl_3$, 23 °C, 24 h, 30%; (b) Ac_2O, C_5H_5N, 23 °C, 4 h, quant.; (c) HBr/AcOH, CH_2Cl_2, 0→23 °C, (d) 1.44 equiv of **5**, 1.88 equiv of 2,6-di-*tert*-butyl-4-methylpyridine, 1.5 equiv of AgOTf, −40→0 °C, 1 h, 85%; (e) CH_3ONa (excess), CH_3OH, CH_2Cl_2, 23 °C, 24 h, 94%.

well as the need for a 'participating' protecting group at O-2 to lead to the β anomeric stereochemistry, this scheme required a per-*O*-acylated donor where the *O*-acyl groups at HO-2, 3, and 4 were to be chemoselectively cleavable, leaving the palmitoyl/oleoyl group at O-6 intact during deprotection. For this purpose the levulinoyl and the chloroacetyl groups were tested because they can be selectively cleaved in the presence of alkanoyl and aroyl groups. Unfortunately, this approach proved to be abortive because attempted, selective cleavage of the protecting groups at O-2, 3, and 4 caused extensive acyl migrations leading to inseparable product mixtures. In the alternative approach, cholesteryl galactopyranoside **8** was prepared first as shown in Scheme 1, in which the 6-*O*-acyl moieties were installed at a later stage. Thus, galactose was first treated with pivaloyl chloride in pyridine containing 4-dimethylaminopyridine, to afford a mixture of fully and partially pivaloylated galactose derivatives. This protecting group was chosen because it suppresses the formation of unwanted orthoesters.[19] Complete pivaloylation could not be achieved even after extended reaction times at an elevated temperature. Previously, Kunz et al.[20] reported that pivaloylation of galactose with pivaloyl chloride in pyridine for 6 days afforded penta-pivaloyl galactopyranose in 63% yield.[20] Serendipitously, we found that 1,2,3,6-tetra-*O*-pivaloyl-β-D-galactopyranose **3** could be isolated from the pivaloylation reaction mixture in pure form after only 1 day by crystallization, in 30% yield. (Scheme 1) Because of the inexpensive nature of the reagents, no attempt was made for optimization. Compound **3** was converted to the fully acylated derivative **4** by treatment with Ac_2O in pyridine, in a quantitative yield. Next, **4** was transformed into the



Scheme 2. Reagents and conditions: (a) 1.3 equiv of *tert*-butyl-diphenylsilyl chloride, C_5H_5N, 23 °C, 5 h, 96%; (b) $(CH_3O)_2C(CH_3)_2$ (excess), CSA (cat), 23 °C, 20 min, 91%; (c) 2.4 equiv of NaH, DMF, 1.4 equiv of All-Br, 0→23 °C, 92%; (d) Bu_4NF (excess), THF, 23 °C, 2.5 h, 97%; (e) 3 equiv of palmitic acid, 6.4 equiv of DCC, MDAP, 23 °C, 6 h, 99%; (f) AcOH–MeOH–H_2O, 70 °C, 6 h, 70%; (g) $C_{34}H_{38}F_6IrP_3$, THF, 23 °C, 24 h then AcOH/TFA, 23 °C, 24 h, 88%.

galactosyl donor **5** by treatment with hydrogen bromide. Stereoselective glycosylation of cholesterol (**6**) with **5** under promotion by silver triflate afforded the glycoside **7** in 85% yield, without the formation of an orthoester.



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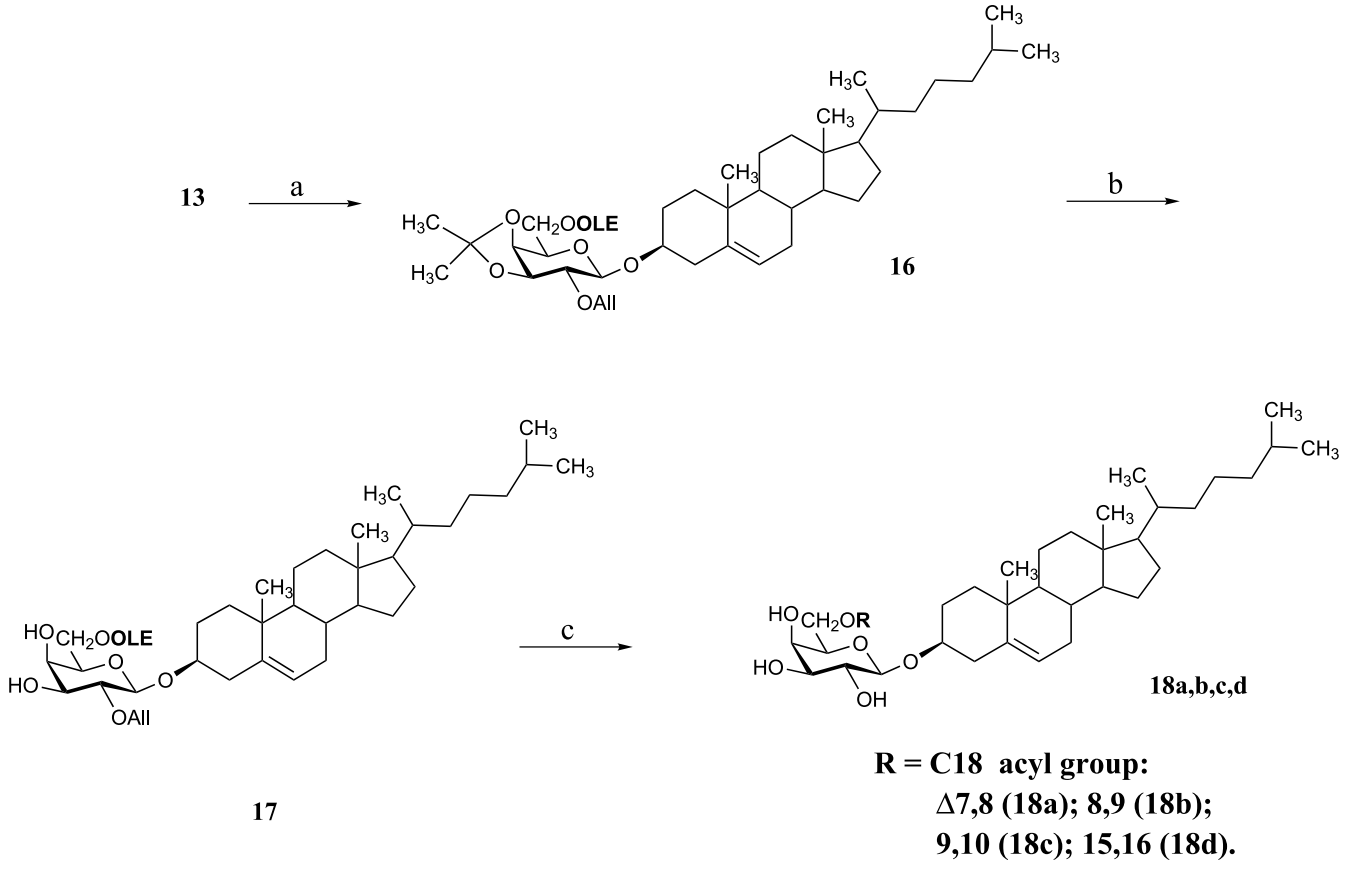
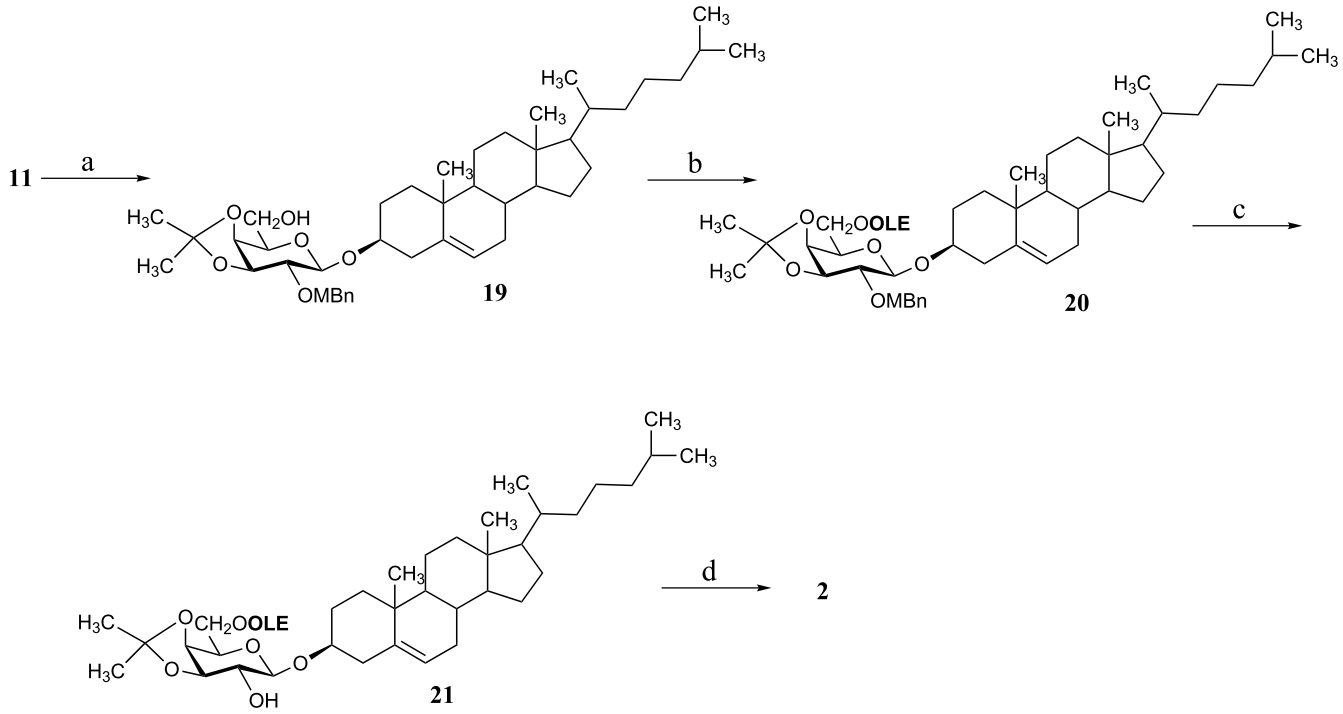
Treatment of the glycoside **7** with sodium methoxide afforded the tetraol **8** in 94% yield. The isolation of **8** in a pure form was facilitated by the fact that **8**, a crystalline material, is insoluble in most organic solvents, whereas all of the impurities are soluble. Next, we envisioned protection schemes for the introduction of the acyl moieties at O-6 of the galactose unit. Initially, we prepared the isopropylidene derivative **9** by treating the tetraol **8** with 2,2-dimethoxypropane in the presence of CSA (→**9**, 34%) in the hope that subsequent *O*-acylations would take place preferentially or exclusively at O-6. Unexpectedly, condensation of **9** with palmitic acid in the presence of DCC afforded at least two products that could not be separated and that are conceivably the 2-*O* and the 6-*O*-acyl derivatives. This led us to synthesize the highly protected intermediate **13** in a series of protective-deprotective steps, as shown in Scheme 2. Thus, compound **8** was first converted to the 6-*O*-silyl derivative **10** using *tert*-butyl-diphenylsilyl chloride in pyridine in 96% yield, followed by acid catalyzed transacetalization with 2,2-dimethoxypropane to afford the alcohol **11** (91%). Treatment of **11** with allyl bromide and NaH afforded the fully protected intermediate **12** (92%) as expected. Next, reaction of compound **12** with tetrabutylammonium fluoride provided the alcohol **13** (97%) from which acylation with palmitic acid/DCC provided the fully protected derivative **14** (99%). Compound **14** was deprotected in a three-step sequence involving acid-catalyzed hydrolysis of the isopropylidene acetal in AcOH–MeOH–H_2O (→**15**, 70%), and allyl isomerization[21,22] with (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate in THF, followed by TFA hydrolysis of the 2-*O*-(1-propylene) derivative (not isolated) affording[23] **1** in 88% yield.



Scheme 3. Reagents and conditions: (a) 2 equiv of oleic acid, 5.9 equiv of DCC, DMAP, EtOAc, 23 °C, 2 h, 75%; (b) AcOH–MeOH–CH_2Cl_2, reflux, 6 h, 70%; (c) $C_{34}H_{38}F_6IrP_3$, THF, 23 °C, 24 h then AcOH/TFA, 23 °C, 24 h.



Scheme 4. Reagents and conditions: (a) 6.6 equiv of NaH, DMF, 0 °C, 10 min, then 6 equiv of MBn–Br, 0 °C, 6 h, then Bu_4NF (excess), THF, 23 °C, 6 h, 78%; (b) 2.2 equiv of oleic acid, 6.8 equiv of DCC, DMAP, EtOAc, 23 °C, 6 h, 81%; (c) 1.3 equiv of CAN, CH_2Cl_2, H_2O, 23 °C, 6 h, 93%; (d) AcOH–H_2O, 65 °C, 4 h, 92%.

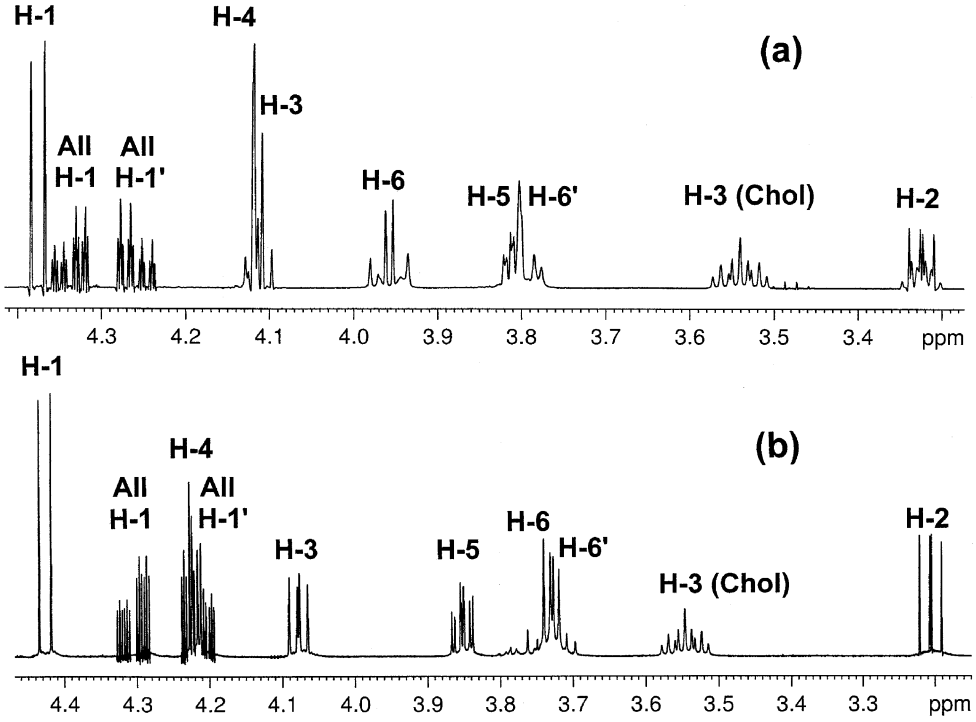


Figure 1. Partial ^1H NMR spectra of cholesteryl 2-*O*-allyl-3,4-di-*O*-isopropylidene-β-D-galactopyranoside **13** at 500 MHz; (a) the spectrum of a solution in $CDCl_3$ shows 'virtual coupling' in the H-2 multiplet because of strong coupling of H-3 and H-4, and in the H-6 multiplet because of strong coupling of H-5 and H-6′; (b) no virtual coupling is observed in the spectrum of a solution of **13** in acetone-d_6.

Table 1. Selected ^{1}H chemical shifts[a] of synthetic glycolipid antigens and their precursors

Compound	Galactose							Allyl					Cholesterol		Others
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	H-1	H-1′	H-2	H-3	H-3′	H-3	H-6	
1[b] (at 300 K)	4.335	3.474	3.535	3.827	3.739	4.388	4.153	—	—	—	—	—	3.500	5.357	HO-2 4.051, HO-3 4.022, HO-4 3.674
2[b]	4.336	3.476	3.536	3.828	3.738	4.382	4.157	—	—	—	—	—	3.502	5.365	Oleoyl H-9,10 5.371, 5.359 HO-2 4.059, HO-3 4.032, HO-4 3.678
3	5.666	5.466	5.014	4.033	3.899	4.336	4.292	—	—	—	—	—	—	—	Piv Me 1.205, 1.194, 1.182, 1.128
4[c]	5.673	5.585	5.059	5.359	3.451	4.077	3.979	—	—	—	—	—	—	—	Piv Me 1.143, 1.126, 1.110, 1.110 Ac Me 1.658
7	4.604	5.240	5.060	5.421	3.932	4.176	4.074	—	—	—	—	—	3.478	5.326	Piv Me 1.180, 1.176, 1.112 Ac Me 2.130
8[d]	4.744	4.036	3.948	4.287	3.898	4.145	4.107	—	—	—	—	—	3.810	5.401	
9[b,e]	4.337	3.378	4.030	4.214	3.863	3.758	3.733	—	—	—	—	—	3.553	5.345	Ip Me 1.416, 1.275
10	4.312	3.610	~3.577	4.049	3.519	3.916	3.876	—	—	—	—	—	3.556	5.344	*t*-Bu Me 1.050
11	4.256	3.529	4.065	4.237	3.851	3.956	3.916	—	—	—	—	—	3.553	5.352	Ip Me 1.507, 1.336, *t*-Bu Me 1.048
12	4.318	3.307	4.068	4.204	3.783	3.928	3.899	4.337	4.249	5.940	5.303	5.160	3.512	5.343	Ip Me 1.491, 1.324, *t*-Bu Me 1.043
13[b]	4.435	3.207	4.078	4.220	3.853	3.745	3.714	4.306	4.216	5.909	5.307	5.100	3.546	5.361	Ip Me 1.441, 1.278
14[b]	4.440	3.228	4.124	4.221	4.078	4.360	4.201	4.304	4.213	5.905	5.307	5.106	3.508	5.373	Ip Me 1.458, 1.296
15	4.395	3.393	3.575	3.895	3.635	4.328	4.295	4.454	4.176	5.935	5.295	5.201	3.524	5.355	
16[b]	4.439	3.228	4.123	4.221	4.076	4.358	4.203	4.304	4.214	5.906	5.307	5.107	3.510	5.366	Oleoyl H-9,10 5.366 Ip Me 1.459, 1.297
19[b]	4.479	3.268	4.117	4.210	3.856	3.740	3.709	—	—	—	—	—	3.578	5.364	Ip Me 1.332, 1.268, MBn CH_2 4.772, 4.694, H-2,6 7.322, H-3,5 6.894, OMe 3.784
20[b]	4.490	3.283	4.158	4.197	4.073	4.351	4.192	—	—	—	—	—	3.539	5.367	Ip Me 1.344, 1.283, MBn CH_2 4.769, 4.692, H-2,6 7.319, H-3,5 6.896, OMe 3.785, Oleoyl H-9, 10 5.367
21[b]	4.351	3.386	4.075	4.216	4.094	4.367	4.210	—	—	—	—	—	3.511	5.366	Ip Me 1.433, 1.291, Oleoyl H-9, 10 5.366

[a] In ppm from internal Me_4Si, in $CDCl_3$ solution unless stated otherwise.
[b] In fresh acetone-d_6.
[c] In 4:1 v/v benzene-d_6/$CDCl_3$.
[d] In 1:1 v/v methylsulfoxide-d_6/pyridine-d_5.
[e] At 318 K.

Table 2. Selected ^{13}C chemical shifts[a] of synthetic glycolipid antigens and their precursors

Compound	Galactose						Allyl			Cholesterol			Others
	C-1	C-2	C-3	C-4	C-5	C-6	C-1	C-2	C-3	C-3	C-5	C-6	
1[b]	102.89	72.16	74.42	69.74	73.40	64.38	—	—	—	79.39	141.82	122.16	C═O 173.49
2[b]	102.85	72.10	74.36	69.69	73.33	64.37	—	—	—	79.33	141.75	122.17	C═O 173.48, Oleoyl C-9,10 130.65, 130.53
3	92.26	67.54	72.94	66.89	72.99	61.71	—	—	—	—	—	—	Piv Me 27.11, 27.11, 27.08, 26.89
4[c]	92.35	68.20	71.02	66.73	71.62	60.69	—	—	—	—	—	—	Piv Me 27.20, 27.09, 27.07, 26.92, Ac Me 20.00 Piv C═O 177.20, 176.77, 176.36, 176.27 Ac C═O 169.68
7	100.19	68.88	70.97	67.08	70.69	61.47	—	—	—	80.13	140.29	122.10	Piv Me 27.20, 27.06, 26.96, Ac Me 20.68 Piv C═O 177.95, 177.27, 176.51, Ac C═O 169.97
8[d]	102.29	71.76	74.43	69.25	75.92	61.50	—	—	—	77.92	140.76	121.69	
9[b,e]	102.07	74.27b	80.65	74.71	74.77	62.38b	—	—	—	78.89	141.77	122.24	Ip Me 28.53, 26.67, Ip OCO 109.87
10	101.25	72.22	73.68	68.83	74.44	62.97	—	—	—	78.82	140.35	122.06	TBDPS Ar 135.63, 135.55, 133.10, 132.94, 129.86, 129.85, 127.80, 127.79, *t*-Bu Me 26.77, *t*-Bu C-1 19.18
11	100.63	73.75	78.62	73.24	73.67	62.71	—	—	—	78.98	140.36	122.06	TBDPS Ar 135.63, 135.60, 133.42, 133.35, 129.69, 127.70, 127.63, Ip OCO 110.04, Ip Me 28.21, 26.31, *t*-Bu Me, 26.72, *t*-Bu C-1 19.20
12	101.64	79.84	79.11	73.38	73.22	62.79	72.88	135.14	117.03	79.47	140.68	121.79	TBDPS Ar 135.64, 135.60, 133.46, 133.38, 129.67, 127.69, 127.62, Ip OCO 109.75, Ip Me 28.03, 26.33, *t*-Bu Me 26.72, *t*-Bu C-1 19.20
13[b]	101.99	81.11	80.09	74.74	74.44	62.17	72.93	136.85	115.93	79.14	141.56	122.35	Ip OCO 109.92, Ip Me 28.42, 26.64
14[b]	102.08	80.84	80.12	74.69	71.50	64.00	72.92	136.74	116.06	79.79	141.57	122.35	C═O 173.39, Ip OCO 110.32, Ip Me 28.32, 26.60
15	102.29	78.67	72.95	68.19	71.89	62.46	73.52	134.70	117.66	79.95	140.55	121.95	C═O 173.77
16[b]	102.06	80.83	80.10	74.68	71.48	63.99	72.91	136.73	116.06	79.78	141.56	122.35	C═O 173.38, Oleoyl C-9,10 130.65, 130.50 Ip OCO, 110.31, Ip Me 28.31, 26.60
19[b]	101.99	80.78	80.13	74.72	74.43	62.18	—	—	—	79.09	141.57	122.37	Ip Me 28.35, 26.66, Ip OCO 109.92 MBn CH_2 73.64, C-1 132.04, C-2,6 130.21, C-3,5 113.23, C-4 160.07, OMe 55.48
20[b]	102.11	80.48	80.13	74.66	71.48	64.00	—	—	—	79.77	141.59	122.38	Ip Me 28.24, 26.63, Ip OCO 110.31, MBn CH_2 73.63, C-1 131.92, C-2,6 130.26, C-3,5 114.25, C-4 160.11, OMe 55.49 Oleoyl C-9,10 130.66, 130.51, C═O 173.39
21[b]	102.02	73.97	80.60	74.54	71.66	64.07	—	—	—	79.40	141.66	122.25	Ip Me 28.44, 26.64, Ip OCO 110.19, Oleoyl C-9,10, C═O 173.41

[a] In ppm from internal Me_4Si, in $CDCl_3$ solution unless stated otherwise.
[b] In acetone-d_6.
[c] In 4:1 v/v benzene-d_6/$CDCl_3$.
[d] In 1:1 v/v methylsulfoxide-d_6/pyridine-d_5.
[e] At 318 K.

An initial approach to the synthesis of the oleoyl glycolipid **2** was based on the method just described for the preparation of **1**. (Scheme 3.) Thus, the alcohol **13** was acylated with oleic acid/DCC to afford compound **16** in a near quantitative yield, from which acid-catalyzed removal of the isopropylidene group provided the diol **17** in an uneventful transformation. Removal of the allyl group by isomerization with the iridium reagent, followed by hydrolysis as described for **1** gave a chromatographically homogeneous material (**18**) that showed the expected C-5 and C-6 ^{13}C NMR resonances for the double bond of the cholesterol unit (140 and 122 ppm, respectively) but lacked the characteristic olefinic carbon resonances of the oleoyl residue (18:1) at ~130 ppm. Instead, a number of low intensity signals appeared at ~130 ppm, hinting at extensive migration of the double bond. In order to gain insight into the extent of isomerization, compound **18** was subjected to transesterification with methanol followed by reaction with 2-amino-2-methylpropanol as described.[24] GC–MS of the resulting oxazoline derivatives revealed unsaturations mainly at C-7, C-8, and C-15. Thus, while the iridium reagent preserved the location of the cholesterol double bond, it caused extensive double bond migration in the oleoyl residue, necessitating an alternative approach depicted in Scheme 4. Alcohol **11** was first treated with 4-methoxybenzyl bromide/NaH followed by removal of the silyl protecting group with tetrabutylammonium fluoride in THF to afford compound **19** in 78% combined yield. Next, treatment of the alcohol **19** with oleic acid/DCC led to the desired oleoyl ester **20**, from which removal of the 4-methoxybenzyl (→**21**) and isopropylidene groups using standard procedures successfully afforded the oleoyl glycolipid **2** in 86% combined yield.

For solutions of members of this series of glycolipids in $CDCl_3$, virtual coupling[25] in their ^1H NMR spectra was extremely common. This was often due to strong coupling (large J/δ) of H-3 and H-4 of the Gal residue, which led to second order effects in the H-2 and H-5 multiplets in the form of additional lines in the multiplets that complicated the first order analysis of the spectra. (Fig. 1) Rather than resorting to iterative spectral simulations, the virtual coupling problem was overcome by the use of solvent shifts in acetone-d_6 to increase the dispersion of the spectra. Selected ^1H and ^{13}C chemical shifts of the synthetic glycolipids **1** and **2** and their precursors are shown in Tables 1 and 2, respectively, and selected ^1H coupling constants in Table 3.

The measured values of the ^1H–^1H coupling constant $^3J_{1,2}$ = 7.5–8.4 Hz and $^1J_{C\text{-}1,H\text{-}1}$ = 155.2–166.3 Hz indicated that except for **5**, all of the galactopyranose precursors, glycolipid intermediates, and target glycolipids had the β anomeric configuration, as required for duplicative synthesis of the natural glycolipids. For the pivaloyl esters **3** and **4**, the observed values $^1J_{C\text{-}1,H\text{-}1}$ = 165.7–166.3 Hz (Table 3) are 5–10 Hz greater than the range for many β-D-galactopyranosides, due to the electronegativity of the acyloxy group at C-1.[26]

As usual, TOCSY experiments did not work well for compounds containing undistorted galactopyranose residues, because of the small $J_{4,5}$ values, which inhibited transfer of magnetization from H-4 through to H-5, H-6, and H-6′. However, in compounds **9**, **11**–**14**, **16**, and **19**–**21** the attachment of the 3,4-*O*-isopropylidene ring flattened the chair form of the galactopyranose ring somewhat, causing $J_{4,5}$ to be larger (~2 Hz, Table 3), with a resulting improvement in TOCSY transfer. Nevertheless, in the end, most of the ^1H assignments could be made by simple COSY experiments, and the ^{13}C assignments by HSQC based on the ^1H assignments. The positions of the various substituents on the Gal ring were indicated by HMBC connectivities.

Table 3. Selected ^1H coupling constants (Hz)[a] of synthetic glycolipid antigens and their precursors

Compound	Galactose								Allyl									
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{C\text{-}1,H\text{-}1}$	$J_{1,1'}$	$J_{1,2}$	$J_{1',2}$	$J_{1,3}$	$J_{1,3'}$	$J_{1',3}$	$J_{1',3'}$	$J_{2,3}$	$J_{2,3'}$	$J_{3,3'}$
1[b] (at 300 K)	7.5	9.5	3.5	1.1	8.3	4.1	11.4	57.4										
2[b]	7.5	9.5	3.5	1.1	8.2	4.2	11.3	56.1										
3	8.3	10.3	3.4	1.1	6.2	6.7	11.5	165.7										
4[c]	8.4	10.2	3.6	1.2	6.9	7.0	11.1	166.3										
7	8.0	10.4	3.6	1.1	7.0	6.6	11.2	158.5										
8[d]	7.6	9.6	3.4	1.1[e]	6.1	6.3	11.0	156.3[e]										
9[b,f]	8.1	7.1	5.6	2.2	6.5	5.8	11.1	156.1										
10	7.5	9.4	~2.0	~0.9	6.2	5.5	10.5	160.8										
11	8.3	7.5	5.4	2.2	7.0	6.3	10.0	155.9										
12	8.2	7.1	5.5	2.1	6.9	6.4	10.0	155.2	12.7	5.5	6.0	1.6	1.4	1.5	1.3	17.2	10.4	1.9
13[b]	8.1	7.1	5.6	2.1	6.5	5.9	11.1	156.8	13.4	5.9	5.5	1.7	1.6	1.6	1.5	17.3	10.5	2.0
14[b]	8.1	7.0	5.6	2.1	8.7	3.5	11.6	157.2	13.4	5.0	5.5	1.8	1.6	1.6	1.5	17.3	10.5	2.0
15	7.7	9.5	3.3	1.2	6.3	6.9	11.4	157.8	12.6	5.5	6.3	1.5	1.3	1.4	1.2	17.2	10.3	1.4
16[b]	8.1	7.0	5.6	2.1	8.6	3.6	11.5	157.0	13.4	5.1	5.5	1.8	1.5	1.7	1.4	17.3	10.5	2.1
19[b,g]	8.1	7.1	5.6	2.1	6.6	5.8	11.1	156.8										
20[b,g]	8.1	6.9	5.6	2.1	8.7	3.6	11.5	157.0										
21[b]	8.1	7.1	5.6	2.2	8.6	3.7	11.5	156.8										

[a] Measured at 500 MHz, for $CDCl_3$ solutions unless stated otherwise.
[b] In fresh acetone-d_6, $J_{2,HO\text{-}2}$ = 3.5, $J_{3,HO\text{-}3}$ = 5.0, $J_{4,HO\text{-}4}$ = 4.0, $J_{5,HO\text{-}4}$ = 0.9.
[c] In 4:1 v/v benzene-d_6/$CDCl_3$.
[d] In 1:1 v/v methylsulfoxide-d_6/pyridine-d_5.
[e] In pyridine-d_5.
[f] At 318 K.
[g] MBn $J(CH_2)$ = 11.5 Hz.

The chemical synthesis of the palmitoyl (**1**) and oleoyl (**2**) glycolipids as separate entities afforded us the opportunity to test a previous interpretation[11] of the ^{13}C NMR spectrum of a mixture of two major and several minor glycolipids termed 'Glycolipid I', isolated from *B. burgdorferi*. It was proposed[11] that the doubling of the C-4, C-5, and C-6 signals of Gal and the C-3 resonance of the cholesteryl moiety that was observed for glycolipid I was due to its isolation as a chromatographically inseparable mixture of mainly **1** and **2**, even though the points of difference in the fatty acid residues of these molecules are quite remote from the nuclei showing the doubling of signals. When, in the current work we recorded the ^{13}C spectrum of a 1:1 mixture of synthetic **1** and **2**, this spectrum was almost identical with that of glycolipid I, thus confirming our previous interpretation.[11] This was true as long as care was taken with concentration, because **1** and **2** showed an unexpected sensitivity to concentration of the galactose C-2 resonance, possibly due to molecular aggregation, amounting to changes in the ^{13}C chemical shifts as large as 1 ppm. Molecular aggregation may produce this effect. Hydroxyl proton coupled ^{1}H NMR spectra were obtained for **1** and **2** by use of freshly opened vials of acetone-d_6 solvent (see OH chemical shifts and coupling constants in Tables 1 and 3, respectively). Otherwise, the use of acetone-d_6 that had been exposed to the atmosphere a number of times yielded ^{1}H NMR spectra in which a major proportion of the hydroxyl proton signals was absent due to decoupling of the OH protons by chemical exchange. In these spectra, the OH proton coupled species appeared only as a minor component amounting to 14% for **1** at 310 K, and 15% for **2** at 300 K.

3. Conclusion

In summary, we have presented successful syntheses of *O*-lipidated galactosyl cholesterols **1** and **2** that can now be used individually for detailed biological studies. Current work is directed towards synthesizing an experimental vaccine against Lyme disease. This vaccine will consist of glycolipid **1** carrying a reactive end group at the alkyl chain through which it will be covalently attached to protein carriers[27] to form immunogenic lipoglycoproteins.

4. Experimental

4.1. General methods

All chemicals were commercial grade and were used without purification. Solvents for chromatography were distilled prior to use. Anhydrous solvents were obtained from Aldrich. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). Melting points were taken on a Meltemp capillary melting point apparatus and are uncorrected. Optical rotations were measured at 23 °C with a Perkin-Elmer Type 341 polarimeter.

NMR spectroscopy. NMR spectra were acquired at 300 K by use of a Bruker DRX-500 NMR spectrometer equipped with a 5 mm TXI HCN cryoprobe with *z*-gradient coil, a Silicon Graphics O2 workstation, and Bruker XWINNMR software, version 3.5, patch level 6. ^{1}H NMR spectra were acquired at 500 MHz by using 32,768 point data sets, a 30° pulse (2.2–2.4 μs), and a pulse recycle time of 6 s. An optimum concentration for obtaining good resolution and sensitivity was 5–6 mg of glycolipid intermediate in 0.5 mL of solvent. The resolution of the spectra was enhanced by Gaussian multiplication of the free induction decay, using a line-broadening of −1 to −3 Hz and a Gaussian truncation fraction of 0.3, together with linear prediction to 65,536 points, or linear prediction to 131,072 points with zero-filling to 262,144 points. ^{13}C NMR spectra were acquired at 126 MHz by using 65,536 point data sets, a 90° pulse (14 μs), and a pulse recycle time of 1.5 s. Resolution was enhanced by exponential multiplication with a line-broadening of −0.2 Hz, together with forward, complex linear prediction to 131,072 points. ^{1}H and ^{13}C chemical shifts were referenced to internal tetramethylsilane (0 ppm). ^{1}H-coupled ^{13}C NMR spectra were acquired with the nuclear Overhauser effect (NOE) by use of gated, WALTZ-16 irradiation at the ^{1}H frequency. These spectra were used to measure $^{1}J_{C\text{-}1,H\text{-}1}$. All 2D NMR spectra were acquired by field gradient-selected methods. Forward linear prediction to larger data sizes was used to improve the resolution of 2D spectra, where necessary. 2D COSY and HMBC NMR spectra were obtained by using 2048 (t_2)×512 (t_1) point data sets, zero-filled to 2048 (F_2)×2048 (F_1) points. For 2D COSY and TOCSY, the spectral width was 5.48 kHz in each dimension, and for COSY, the read pulse was 30° (2.2–2.4 μs). For 2D HSQC and HMBC, the ^{1}H and ^{13}C spectral widths were 5.48 kHz (F_2) and 25.1 kHz (F_1), respectively. 2D TOCSY NMR spectra were acquired by use of 16,384 (t_2)×512 (t_1) point data sets, zero-filled to 32,768 (F_2)×2048 (F_1) points. High-resolution 2D HSQC spectra were acquired in 2048×512 point data sets, linear predicted to 4096 points in both dimensions.

The mass spectra were recorded at the Laboratory of Bioorganic Chemistry, NIDDK, NIH, Bethesda, MD. The fast atom bombardment (FAB) mass spectra were obtained using 6 keV Xe atoms to ionize samples from dithiothreitol/dithioerythritol, 3-nitrobenzyl alcohol, or glycerol as the matrix. The purity of all new compounds was determined to be >95% by ^{1}H NMR spectroscopy. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

4.1.1. 1,2,3,6-Tetra-*O*-trimethylacetyl-β-D-galacto-pyranose (3). To a stirred mixture of anhydrous $CHCl_3$ (80 mL), C_5H_5N (45 mL), and trimethylacetyl chloride (45 mL, 365 mmol) was added D-galactose (10 g, 55 mmol, 0.75 equiv) in portions. After 24 h at room temperature, TLC (3:1 hexane/EtOAc) indicated the formation of several products. Their ratios did not change significantly after the addition of more trimethylacetyl chloride or heating for another 24 h. The mixture was concentrated under reduced pressure and the residue so obtained was triturated with diethyl ether. The solids were isolated by filtration and were discarded. To the filtrate was added isopropyl ether and the mixture was left standing at room temperature for 3 h. Filtration followed by washing with isopropyl ether afforded **3** (8.5 g, 30%) as a crystalline material: $[\alpha]_D$ +15 (*c* 0.8, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{26}H_{44}O_{10}Li$ 523.3105, found 523.3095.

4.1.2. 4-*O*-Acetyl-1,2,3,6-tetra-*O*-(trimethylacetyl)-β-D-galactopyranose (4). Compound **3** was treated with Ac_2O and C_5H_5N at room temperature followed by removal of the volatiles to afford **4** as a crystalline material in a quantitative yield: $[\alpha]_D$ +9 (*c* 1.2, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{28}H_{46}O_{11}Li$ 565.3230, found 565.3200.

4.1.3. 4-*O*-Acetyl-2,3,6-tri-*O*-(trimethylacetyl)-α-D-galactopyranosyl bromide (5). To a solution of compound **4** (8.5 g, 15 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added a 30% solution of hydrogen bromide in acetic acid (15 mL). The solution was allowed to reach room temperature. After 1 h, the solution was extracted with ice-water (5×100 mL) followed by drying (Na_2SO_4), filtration, and concentration to afford a colorless syrup that was used in the next step without further purification.

4.1.4. Cholesteryl 4-*O*-acetyl-2,3,6-tri-*O*-(trimethylacetyl)-β-D-galactopyranoside (7). To a stirred solution of compound **5** (2.0 g, 3.73 mmol), cholesterol (**6**, 1.0 g, 2.58 mmol), and di-*tert*-butyl-4-methylpyridine (1.0 g, 4.87 mmol) in anhydrous CH_2Cl_2 (10 mL) was added at −40 °C CF_3SO_3Ag (2.0 g, 3.89 mmol). The mixture was allowed to reach 0 °C then was treated with Bu_4NBr followed by aq $NaHCO_3$. The solids were removed by filtration and the organic layer was concentrated under vacuum. The residue was stirred in MeOH overnight. The solids were collected by filtration and were washed with cold MeOH to afford pure **7** (1.85 g, 85%) as a crystalline material: $[\alpha]_D$ −18 (*c* 0.5, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{50}H_{82}O_{10}Li$ 849.6071, found 849.6068.

4.1.5. Cholesteryl β-D-galactopyranoside (8). A stirred mixture of compound **7** (1.8 g, 2.1 mmol), CH_2Cl_2 (5 mL), and CH_3OH (5 mL) was treated with an excess of CH_3ONa. After 24 h, the solids were isolated by filtration and were washed with CH_3OH to afford **8** (1.10 g, 94%) as a crystalline material: $[\alpha]_D$ −58 (c 0.4, C_5H_5N). For NMR data, see Tables 1–3. Anal. Calcd for $C_{33}H_{56}O_7$: C, 72.22; H, 10.29. Found: C, 71.83; H, 10.29.

4.1.6. Cholesteryl 3,4-*O*-isopropylidene-β-D-galactopyranoside (9). To a solution of **8** (1.1 g, 2.0 mmol) in DMF (5 mL) was added 2,2-dimethoxypropane (5 mL) and camphorsulfonic acid (100 mg). Thin-layer chromatography (5:1 hexanes/EtOAc) revealed the initial formation of two products. After 48 h, the faster-moving component had almost completely disappeared. Neutralization ($NaHCO_3$) followed by extractive work-up ($CHCl_3/H_2O$) afforded an amorphous residue that was purified by silica gel column chromatography using 8:1 hexanes/EtOAc as the eluant to afford **9** (365 mg, 34%): $[\alpha]_D$ −24 (c 0.8, $CHCl_3$). For NMR data, see Tables 1–3. MS *m/z* Calcd for $C_{36}H_{60}O_6Li$ 593.4533, found 595.4550.

4.1.7. Cholesteryl 6-*O*-(*tert*-butyl-diphenylsilyl)-β-D-galactopyranoside (10). To a stirred solution of tetraol **9** (8.2 g, 14.9 mmol) in C_5H_5N (50 mL) were added at room temperature *tert*-butyl-diphenylsilyl chloride (8.2 mL, 19.2 mmol) and a catalytic amount of 4-dimethylaminopyridine. After 5 h, MeOH was added (2 mL) followed by concentration under reduced pressure. Column chromatographic purification of the residue afforded **10** (11.93 g, 96%) as a syrup: $[\alpha]_D$ −44 (*c* 0.4, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{49}H_{74}O_6LiSi$ 793.5420, found 793.5415.

4.1.8. Cholesteryl 6-*O*-(*tert*-butyl-diphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (11). To a stirred solution of triol **10** (10.4 g (18.9 mmol) in 2,2-dimethoxypropane (100 mL) was added at room temperature camphorsulfonic acid (0.5 g). After 20 min TLC (4:1 hexane/EtOAc) indicated that no starting material remained. To the solution was added triethylamine (2 mL). The solution was concentrated and the residue purified by column chromatography using a gradient of hexane/EtOAc 10:1–5:1 to obtain **11** (10.0 g, 91%) as a syrup: $[\alpha]_D$ −26 (*c* 0.6, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{48}H_{86}O_{11}LiSi$ 873.6071, found 873.6099.

4.1.9. Cholesteryl 2-*O*-allyl-6-*O*-(*tert*-butyl-diphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (12). To a stirred solution of **11** (384 mg, 0.46 mmol) in DMF (2 mL) was added at 0 °C NaH (45 mg of a 60% suspension in oil). After 20 min, allyl bromide (56 μL, 0.65 mmol) was added. The solution was allowed to reach room temperature and was stirred for a further period of 45 min. The mixture was cooled to 0 °C and was treated with CH_3OH (1 mL) followed by CH_3CO_2H (0.5 mL).The mixture was concentrated and the residue was equilibrated between $CHCl_3$ and H_2O. Concentration of the organic layer followed by column chromatographic purification of the residue using 10:1 hexane/EtOAc afforded **12** (370 mg, 92%) as a syrup: $[\alpha]_D$ −18 (*c* 0.4, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{48}H_{86}O_{11}LiSi$ 873.6071, found 873.6099.

4.1.10. Cholesteryl 2-*O*-allyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (13). To a solution of compound **12** (2.9 g, 3.6 mmol) in anhydrous THF (20 mL) was added at room temperature a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.2 mL) under argon. After 2 ½ h, the solution was concentrated. Silica gel column chromatographic purification of the residue using a gradient of 10:1–3:1 hexane/EtOAc afforded **13** (2.05 g, 97%) as a syrup: $[\alpha]_D$ −21 (*c* 1.0, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{39}H_{64}O_6Li$ 635.4866, found 635.4863.

4.1.11. Cholesteryl 2-*O*-allyl-3,4-*O*-isopropylidene-6-*O*-palmitoyl-β-D-galactopyranoside (14). A stirred solution of **13** (300 mg, 0.38 mmol), palmitic acid (300 mg, 1.17 mmol), dicyclohexyl carbodiimide (0.5 g, 2.42 mmol), and 4-dimethylaminopyridine (100 mg) in EtOAc (6 mL) was kept at room temperature for 6 h. MeOH (2 mL) was added and the mixture was filtered. The solids were discarded and the filtrated concentrated. Silica gel column chromatographic purification of the residue (100:2 $CHCl_3$/MeOH) afforded **14** (410 mg, 99%) as a syrup: $[\alpha]_D$ −20 (*c* 0.7, $CHCl_3$). For NMR data, see Tables 1–3. Anal. Calcd for $C_{55}H_{94}O_7$: C, 76.16; H, 10.92. Found: C, 75.95; H, 10.49.

4.1.12. Cholesteryl 2-*O*-allyl-6-*O*-palmitoyl-β-D-galactopyranoside (15). To a solution of **14** (400 mg, 0.46 mmol) in CH_2Cl_2 (2 mL) was added a solution of AcOH in MeOH (80%, 25 mL) followed by H_2O (2 mL). The solution was stirred at 70 °C for 6 h. Removal of the volatiles under reduced pressure afforded a syrup, which was purified by silica gel column chromatography using 10:1 $CHCl_3$/MeOH as the eluant to afford **15** (270 mg, 70%) as a syrup: $[\alpha]_D$ −12 (*c* 0.1, $CHCl_3$). For NMR data, see Tables 1–3. MS *m/z* Calcd for $C_{52}H_{90}O_7Na$ 849.66, found 849.60. Anal. Calcd for $C_{52}H_{90}O_7$: C, 75.50; H, 10.97. Found: C, 74.47; H, 10.91.

4.1.13. Cholesteryl 6-*O*-palmitoyl-β-D-galactopyranoside (1). To a solution of **15** (240 mg, 0.29 mmol) in THF (5 mL) at room temperature was added a solution of (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate[21] (40 mg, 0.28 mmol) in THF (5 mL) through which H_2 was bubbled for 15 min before addition. After 24 h, the solution was concentrated and the residue was dissolved in AcOH (5 mL) followed by addition of TFA (1 mL) at room temperature. After 6 h, the solution was concentrated and the residue was purified by silica gel column chromatography using 20:1 $CHCl_3$/MeOH as the eluant to afford **1** (200 mg, 88%) as an amorphous substance: $[\alpha]_D$ −29 (*c* 0.5, $CHCl_3$). For NMR data, see Tables 1–3. MS *m/z* Calcd for $C_{49}H_{86}O_7Na$ 809.63, found 809.68. Anal. Calcd for $C_{49}H_{86}O_7 \cdot$MeOH: C, 73.30; H, 11.07. Found: C, 73.49; H, 11.00.

4.1.14. Cholesteryl 2-*O*-allyl-3,4-*O*-isopropylidene-6-*O*-oleoyl-β-D-galactopyranoside (16). A stirred solution of **13** (205 mg, 0.33 mmol), oleic acid (200 μL, 180 mg, 0.63 mmol), dicyclohexyl carbodiimide (0.4 g, 1.94 mmol), and 4-dimethylaminopyridine (100 mg) in EtOAc (5 mL) was kept at room temperature for 2 h. MeOH (1 mL) was added and the mixture was filtered. The solids were discarded and the filtrated concentrated. Silica gel column chromatographic purification of the residue (8:1 hexanes/EtOAc) afforded **16** (220 mg, 75%) as a syrup: $[\alpha]_D$ −23 (*c* 0.2, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{57}H_{96}O_7Li$ 899.7297, found 899.7361.

4.1.15. Cholesteryl 2-*O*-allyl-6-*O*-oleoyl-β-D-galactopyranoside (17). To a solution of **16** (200 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added a solution of AcOH in MeOH (80%, 25 mL) followed by H_2O (2 mL). The solution was stirred under reflux for 6 h. Removal of the volatiles under reduced pressure afforded a syrup, which was purified by silica gel column chromatography using 10:1 $CHCl_3$/MeOH as the eluant to afford **17** (133 mg, 70%) as a syrup: $[\alpha]_D$ −10 (*c* 0.3, $CHCl_3$). For NMR data, see Tables 1–3. Anal. Calcd for $C_{54}H_{92}O_7$: C, 76.01; H, 10.87. Found: C, 75.86; H, 11.06.

4.1.16. Cholesteryl 6-*O*-octadecenoyl-β-D-galactopyranosides (18a,b,c,d). Compound **17** was treated as described for the preparation of **1**. The product was purified by silica gel column chromatography using 20:1 EtOAc/MeOH as the eluant to afford **18a–d**, as determined by GC–MS.

4.1.17. Cholesteryl 3,4-*O*-isopropylidene-2-*O*-(4-methoxybenzyl)-β-D-galactopyranoside (19). To a stirred solution of **11** (10.0 g, 12.1 mmol) in dry DMF (50 mL) at 0 °C was added NaH (2.2 g of a 60% suspension in oil). After 10 min, freshly prepared 4-methoxybenzyl bromide (15 mL) was added dropwise and the mixture was stirred for 6 h followed by the usual work-up and silica gel column chromatography using 4:1 hexanes/EtOAc as the eluant to afford a syrup. This was dissolved in dry THF (100 mL) and the solution so obtained was treated with a solution of tetrabutylammonium fluoride (25 mL of a 1 M solution in THF) at 23 °C. After 6 h, the solution was concentrated and the residue purified by silica gel column chromatography using a 4:1→1:1 hexanes/EtOAc gradient as the eluant to afford **19** (6.7 g, 78%) as a solid: $[\alpha]_D$ +22 (*c* 0.6, $CHCl_3$). For NMR data, see Tables 1–3. MS *m/z* Calcd for $C_{44}H_{68}O_7Na$ 731.49, found 732.08.

4.1.18. Cholesteryl 3,4-*O*-isopropylidene-2-*O*-(4-methoxybenzyl)-6-*O*-oleoyl-β-D-galactopyranoside (20). A stirred solution of **19** (1.1 g, 1.41 mmol), oleic acid (890 mg, 3.1 mmol), dicyclohexyl carbodiimide (2.0 g, 9.68 mmol), and 4-dimethylaminopyridine (100 mg) in EtOAc (6 mL) was kept at room temperature for 6 h. MeOH (4 mL) was added and the mixture was filtered. The solids were discarded and the filtrate was concentrated. Silica gel column chromatographic purification of the residue (100:2 $CHCl_3$/MeOH) afforded **20** (1.2 g, 81%) as a waxy solid: $[\alpha]_D$ +17 (*c* 1.0, $CHCl_3$). For NMR data, see Tables 1–3. Anal. Calcd for $C_{49}H_{86}O_7$: C, 76.50; H, 10.35. Found: C, 76.53; H, 10.51.

4.1.19. Cholesteryl 3,4-*O*-isopropylidene-6-*O*-oleoyl-β-D-galactopyranoside (21). To a stirred mixture of **20** (1.1 g, 1.13 mmol), CH_2Cl_2 (10 mL), and H_2O (0.4 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (333 mg, 1.47 mmol). After 6 h, the reaction mixture treated with aq $NaHCO_3$ followed by extractive work-up ($CHCl_3/H_2O$). Silica gel column chromatographic purification of the residue, using 6:1 hexanes/EtOAc as the eluant afforded **21** (1.0 g, 93%) as an amorphous solid: $[\alpha]_D$ −17 (*c* 0.6, $CHCl_3$). For NMR data, see Tables 1–3. HRMS *m/z* Calcd for $C_{54}H_{92}O_7Li$ 859.7032, found 859.7003.

4.1.20. Cholesteryl 6-*O*-oleoyl-β-D-galactopyranoside (2). A solution of **21** (250 mg, 0.29 mmol) in AcOH (15 mL) and H_2O (1.3 mL) was stirred at 65 °C until TLC (1:1 hexanes/EtOAc) indicated disappearance of **21** (approx. 4 h). Removal of the volatiles under reduced pressure afforded a semisolid that was purified by silica gel column chromatography using a 1:1→1:3 hexanes/EtOAc gradient as the eluant to afford glycolipids **2** (220 mg, 92%) as a waxy solid: $[\alpha]_D$ −29 (*c* 0.5, $CHCl_3$). For NMR data, see Tables 1–3. MS *m/z* Calcd for $C_{51}H_{88}O_7Na$ 835.64, found 836.41. Anal. Calcd for $C_{51}H_{88}O_7 \cdot ½$MeOH: C, 74.59; H, 10.91. Found: C, 74.36; H, 10.99.

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An effective new synthesis of 2-aminopyrrole-4-carboxylates

Ayhan S. Demir* and Mustafa Emrullahoglu

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

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Abstract—Efficient syntheses of 2-aminopyrroles are presented starting from β-dicarbonyl compounds, bromoacetonitrile, and amines. Alkylation of β-dicarbonyl compounds with bromoacetonitrile furnished α-cyanomethyl-β-dicarbonyl compounds. The condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by *p*-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond of nitrile furnished 2-aminopyrroles in high yields.

1. Introduction

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry primarily due to the fact that many pyrroles are subunits of natural products, pharmaceutical agents and polymers.[1] The valuable and diverse biological properties of pyrroles make the development of efficient methods for the preparation of these compounds, having a defined substitution pattern, a focus of considerable synthetic effort. β-Dicarbonyl compounds are versatile intermediates for the synthesis of pyrrole derivatives.[2] Pioneering work on the synthesis of pyrroles from β-dicarbonyl compounds was carried out by Hantzsch in 1890. Many studies have been published on the synthesis of pyrroles using the principle of Hantzsch's method starting from β-dicarbonyl compounds.[3] Aminopyrroles have been found to show interesting biological properties[4,5] or have been used as precursors[6] for known drugs, in which they have found use as synthetic precursors for acyclic nucleoside analogues of the pyrrolo[2,3-*d*]pyrimidine ring system.[7]

Aminopyrroles are not readily available through general pyrrole ring-formation methods.[8] Despite the large number of published methods for the elaboration of various pyrroles, relatively few examples have been reported for the preparation of simple 2-amino derivatives.

Most compounds of this type have been obtained by the reaction of a nitrogen-two-carbon compound with an appropriate two-carbon unit, for example, base-promoted condensation of an amino ketone[9] or a conjugated azoalkene[10] with a nitrile containing an active methylene group; 1,3-dipolar cycloaddition of conjugated azoalkenes with 1-propynyldiethylamine;[11] or base-induced 1,3-dipolar cycloaddition of 4,5-diaminothiazolium salts with electrophilic alkynes.[12] Recent access to 2-(alkylamino)- and 2-(arylamino)pyrroles by the addition of isocyanides to protonated 1-azabutadienes is described by Morel et al.[13] Other miscellaneous and limited methods were also described in the review by Trofimov et al.[14]

To continue our investigations that are directed towards the synthesis of substituted pyrroles[15] and related compounds,[16] we were especially interested in obtaining 2-amino-4-carboxyl- derivatives of pyrroles. These compounds are conformationally restricted GABA structure analogous (Fig. 1).

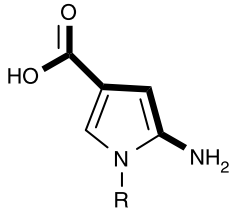

Figure 1.

2. Results and discussion

From a synthetic point of view, 2-aminopyrroles can be synthesized via a reaction sequence involving α-alkylation of β-dicarbonyl compounds with bromoacetonitrile,

Keywords: 2-Aminopyrroles; Amination; Cyclization; 1,3-Dicarbonyls.
* Corresponding author. Tel.: +90 312 2103242; fax: +90 312 2101280; e-mail: asdemir@metu.edu.tr

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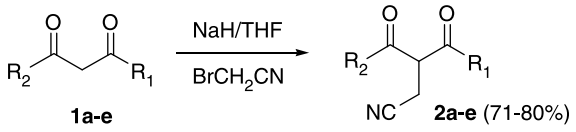
enamine formation, and finally a ring closure reaction. This seems like a very attractive route because a wide variety of substituents (R^1, R^2, and R^3) can be used, originating from readily accessible starting materials.

As shown in Scheme 1, α-cyanomethyl-β-dicarbonyl compounds **2a–e** were synthesized by alkylation of β-dicarbonyl compounds with bromoacetonitrile (NaH/THF and DBU/benzene) according to the literature procedure in 71–80% yields (Scheme 1).[17]



1a: R_1= Me, R_2= Me
1b: R_1= OEt, R_2= Me
1c: R_1= OEt, R_2= Et
1d: R_1= OEt, R_2= Ph
1e: R_1= OEt, R_2= 2-F-Ph

Scheme 1.

As shown in Scheme 2, the enamine derivatives **4a–i** were easily prepared from amines **3a–c** and α-cyanomethyl-β-dicarbonyl compounds **2a–e** in benzene at reflux with the addition of a catalytical amount of *p*-TsOH in 68–75% yields after purification of the crude products by column chromatography (Table 1). The formation of enamines by using ethyl 2-(cyanomethyl)-3-oxo-3-phenylpropanoate (**2d**) was not successful under the above described conditions. There are many general methods for the synthesis of β-amino-α,β-unsaturated carbonyl compounds, but as far as we know no convenient procedure is described in the literature for the formation of enamines starting from 2-alkyl-3-aryl-1,3-dicarbonyl compounds. Various reaction conditions were applied in order to find a convenient procedure for the formation of enamine **4j** (ethyl-3-(benzylamino)-2-cyanomethyl-3-phenylacrylate) with benzylamine as described below:

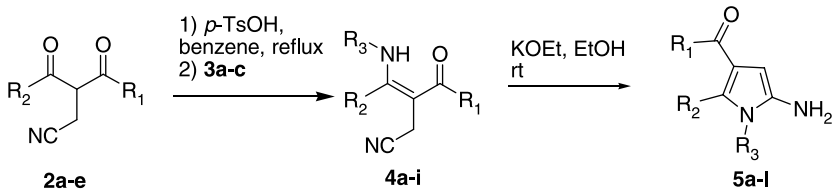
1. *p*-TsOH–Benzene (or Toluene), azeotropic removal of water. (1 equiv **2d**, 2 equiv **3c**, 10 ml solvent, 48 h): product was obtained in very low yield.
2. TFA–Benzene (1 equiv **2d**, 2 equiv diketone, 10 ml solvent, 48 h): trace amount of product formation (GC–MS).
3. BF_3–Et_2O, Toluene (1 equiv **2d**, 2 equiv **3c** 10 ml solvent): no product formation.
4. Al_2O_3 supported reaction[18] (1 equiv **2d**, 1.5 equiv **3c**, Al_2O_3, at 70 °C): no product formation.
5. Al_2O_3 supported microwave reaction (1 equiv **2d**, 1.5 equiv **3c**, Al_2O_3): starting material and unidentified side products.
6. *p*-TsOH, silica gel or K-10 Montmorillonitrite clay supported microwave reaction[19] (1 equiv **2d**, 1.5 equiv **3c**): product was observed, but in low yield (5–7%).
7. Stefani et al.[20] described the preparation of enaminones from β-ketoesters or β-diketones and primary amines in water. Application of this procedure to **2d** (1 equiv **2d**, 2 equiv **3c**, 5 ml H_2O, stirred at room temperature for 3 h) furnished the decarboxylation product **6** in 10% yield (Scheme 3).
8. Five equivalents **3c** was neutralized with 5 equiv acetic acid added to 1 equiv **2d** solution refluxed in ethanol for 24 h:[21] product formed with very low yield, but was not reproducible.
9. Finally the highest yield (46%) was achieved from **2d** and **3c** without a solvent and excess amine. This reaction was carried out at 140 °C for 4 h. Increasing temperature increases the amount of side products, which could not be identified. This reaction was also carried out under microwave conditions without heat and solvent, in which the product was obtained in 40% yield.

After many trials, we found that the latter procedure was the best choice for the conversion of **2d–e** to enamine **4j–l**.

The cyanomethyl substituted enamines **4a–l** were also assumed to be obtained starting from β-dicarbonyl compounds **1a–e** and amines, by the formation of enamine followed by alkylation with bromoacetonitrile. In a representative reaction, **1b** was reacted with aniline in benzene at reflux with the addition of a catalytical amount of *p*-TsOH to give enamine **7** in 79% yield. Deprotonation of the enamine with NaH in THF followed by alkylation with bromoacetonitrile furnished trace amount of the desired product. This method was not suitable for the synthesis of enamines **4a–l**.

Simple and efficient conditions were found for the cyclization of enamines to pyrroles. This condition involved the treatment of enamines **4a–l** with potassium ethoxide in ethanol at room temperature, in which the pyrrole derivatives **5a–l** were obtained in excellent yields in a short reaction time (5–10 min; for aryl substituted enamines 20–30 min) (Scheme 2).

In addition to the above described experiments, many attempts were made for the direct- one pot synthesis of pyrroles starting with; (a) β-dicarbonyl compound, bromoacetonitrile and amine, (b) starting from enamine, bromoacetonitrile, heating in benzene in the presence of catalytical amount of *p*-TsOH or TFA, but none of the reactions were successful.



Scheme 2.

Table 1. Synthesis of substituted 2-aminopyrroles

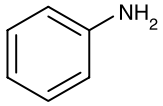
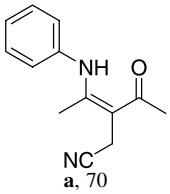
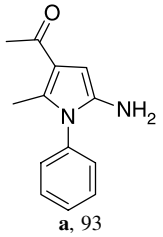
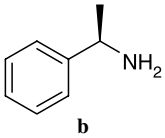
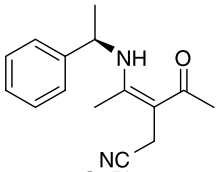
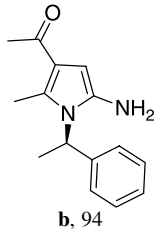
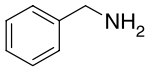
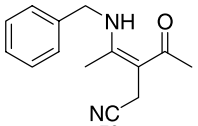
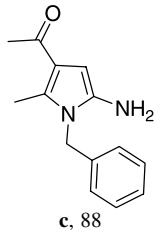
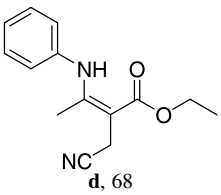
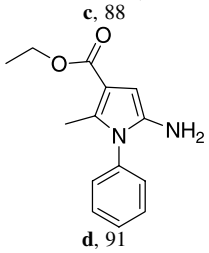
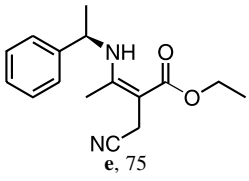
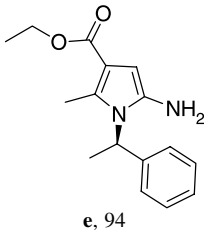
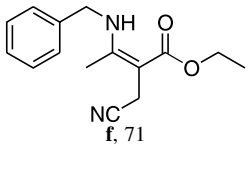
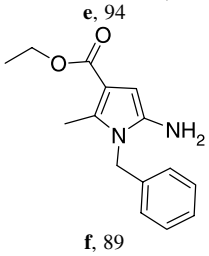
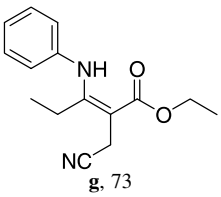
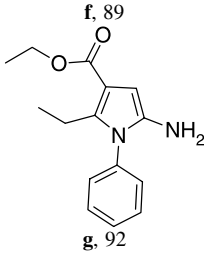
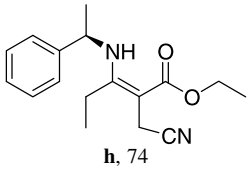
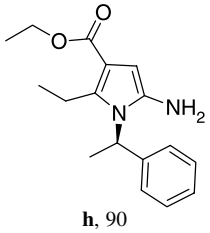
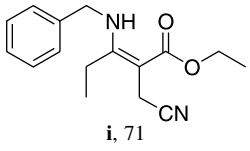
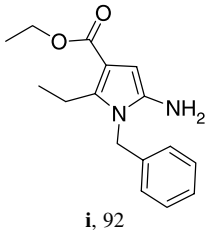
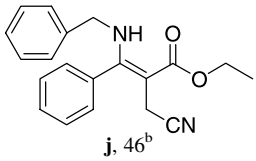
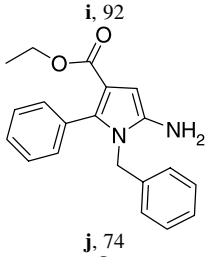
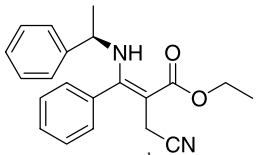
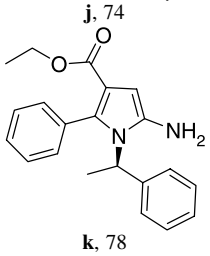
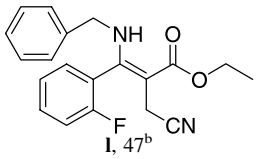
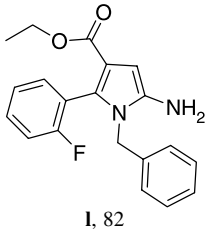
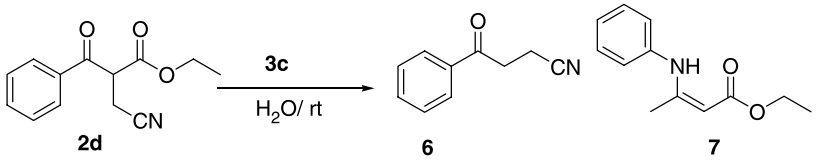
Entry	Dicarbonyl compound **2**	Amine **3**	Enamine **4**, Yield (%)[a]	Pyrrole **5**, Yield (%)[a]
1	**a**	 **a**	 **a**, 70	 **a**, 93
2	**a**	 **b**	 **b**, 71	 **b**, 94
3	**a**	 **c**	 **c**, 73	 **c**, 88
4	**b**	**a**	 **d**, 68	 **d**, 91
5	**b**	**b**	 **e**, 75	 **e**, 94
6	**b**	**c**	 **f**, 71	 **f**, 89
7	**c**	**a**	 **g**, 73	 **g**, 92

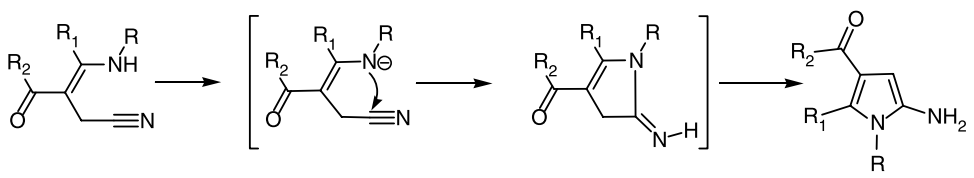
Table 1 (*continued*)

Entry	Dicarbonyl compound **2**	Amine **3**	Enamine **4**, Yield (%)[a]	Pyrrole **5**, Yield (%)[a]
8	**c**	**b**	 **h**, 74	 **h**, 90
9	**c**	**c**	 **i**, 71	 **i**, 92
10	**d**	**c**	 **j**, 46[b]	 **j**, 74
11	**d**	**b**	 **k**, 49[b]	 **k**, 78
12	**e**	**c**	 **l**, 47[b]	 **l**, 82

[a] Isolated yield.
[b] Synthesized by solvent-free heating of α-cyanomethyl-β-dicarbonyl compounds with amines.



Scheme 3.



Scheme 4.

All of the pyrrole derivatives were identified by spectroscopic methods and all spectroscopic data are in agreement with the given structures.

The mechanism is assumed to involve the deprotonation of the enamine, then the addition of the amine moiety to the carbon–nitrogen triple bond to afford the cyclic intermediate (Scheme 4). This is followed by a rearrangement to afford pyrrole **5**. The attack of nitrogen to the carbon–nitrogen triple bond is activated by the potassium ion. This mechanism is consistent with the generally accepted mechanism of the nucleophilic addition to metal-activated carbon–carbon multiple bonds.[22]

3. Conclusions

This investigation has resulted in the elaboration of a convenient procedure for the preparation of 2-aminopyrrole derivatives. The condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by *p*-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond furnished 2-aminopyrroles in high yields.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: $\delta=7.27$), $CDCl_3$ (^{13}C: $\delta=77.0$) and CCl_4 (^{13}C: $\delta=96.4$) as internal standards. IR spectra were recorded on a Perkin Elmer 1600 FTIR series instrument.

Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda=254$ nm). Optical rotations were measured with a Krüss P3002RS automatic polarimeter.

4.2. General procedure for alkylation of β-dicarbonyl compounds

NaH (1.5 mmol) was added slowly to a stirred solution of β-dicarbonyl compound (1 mmol) in THF at room temperature under argon. The reaction mixture was stirred for 1 h and then a solution of bromoacetonitrile (1.2 mmol) in THF (15 ml) was added slowly and stirred for 4 h. The reaction was monitored by TLC. Water was added, the mixture extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$. After the evaporation of the solvent under reduced pressure, the crude product was purified on silica gel to afford **2a–e** (hexane–ethyl acetate (4–1)).

4.2.1. 3-Acetyl-4-oxopentanenitrile (2a). Yield: (105 mg, 76%); yellow oil. IR (neat): 2333, 2976, 1723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.25$ (s, 6H), 2.73 (d, 2H, $J=7.1$ Hz), 4.02 (t, 1H, $J=7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.7$, 23.5, 30.0, 62.9, 117.7, 191.5, 200.1. Anal. Calcd for $C_7H_9NO_2$ (139.15): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.23; H, 6.35; N, 9.83.

4.2.2. Ethyl 2-(cyanomethyl)-3-oxobutanoate (2b). Yield: (181 mg, 71%); yellow oil. IR (neat): 2331, 2978, 1725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.27$ (t, 3H, $J=7.1$ Hz), 2.32 (s, 3H), 2.73–2.79 (m, 2H), 3.75 (t, 1H, $J=7.2$ Hz), 4.23–4.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.4$, 15.8, 29.6, 55.5, 62.6, 117.4, 166.6, 198.6. Anal. Calcd for $C_8H_{11}NO_3$ (169.7): C, 56.80; H, 6.55; N, 8.28. Found: C, 56.66; H, 6.73; N, 7.92.

4.2.3. Ethyl 2-(cyanomethyl)-3-oxopentanoate (2c). Yield: (146 mg, 80%); yellow oil. IR (neat): 2326, 2975, 1720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.05$ (t, 3H, $J=7.2$ Hz), 1.23 (t, 3H, $J=7.1$ Hz), 2.43–2.67 (m, 2H), 2.74 (d, 2H, $J=7.2$ Hz), 3.77 (t, 1H, $J=7.2$ Hz), 4.18 (q, 2H, $J=7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=12.7$, 14.7, 22.4, 30.1, 52.5, 62.2, 116.7, 192.4, 198.1. Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.00; H, 7.15; N, 7.65. Found: C, 58.82; H, 7.33; N, 7.39.

4.2.4. Ethyl 2-(cyanomethyl)-3-oxo-3-phenylpropanoate (2d). Yield: (198 mg, 78%); colorless oil. IR (neat): 2978, 2249, 1736, 1689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.20$ (t, 3H, $J=7.1$ Hz), 3.07 (dd, 1H, $J=5.4$, 17.0 Hz), 3.12 (dd, 1H, $J=6.9$, 17.0 Hz), 4.20 (q, 2H, $J=7.1$ Hz), 4.66 (t, 1H, $J=7.2$ Hz), 7.53–8.05 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.3$, 16.1, 49.7, 62.0, 116.4, 128.3, 128.5, 133.7, 134.5, 166.0, 190.4. Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.38; H, 5.33; N, 5.71.

4.2.5. Ethyl 2-(cyanomethyl)-3-(2-fluorophenyl)-3-oxopropanoate (2e). Yield: (199 mg, 80%); yellow oil. IR (neat): 2954, 2212, 1732, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.17$ (t, 3H, $J=7.0$ Hz), 2.93 (dd, 1H, $J=7.2$, 16.8 Hz,), 3.05 (dd, 1H, $J=6.7$, 16.8 Hz), 4.17 (q, 2H, $J=7.0$ Hz), 4.62 (t, 1H, $J=7.0$ Hz), 7.14–7.94 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.3$, 15.8, 53.2, 61.7, 95.7, 116.1 (d, $J=23$ Hz), 123.6 (d, $J=11$ Hz), 124.3 (d, $J=3$ Hz), 130.8, 135.1 (d, $J=9$ Hz), 161.3 (d, $J=253$ Hz), 166.2, 189.0. Anal. Calcd for $C_{13}H_{12}FNO_3$ (249.24): C, 62.65; H, 4.85; N, 5.62. Found: C, 62.41; H, 4.76; N, 5.31.

4.3. General procedure for enamine formation

Alkylated β-dicarbonyl compound (1 mmol) was dissolved in benzene (10 ml). Corresponding amine (1.2 mmol) together with catalytic amount of PTSA was added to the stirring mixture and heated at 80 °C for 6–10 h using a Dean-Stark trap. Reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude product purified by column chromotography.(hexane–ethyl acetate (4–1)).

4.3.1. (*Z*)-3-acetyl-4-(phenylamino)pent-3-enenitrile (4a). Yield: (149 mg, 70%); brown oil. IR (neat): 2987, 2242, 1592, 1570 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.03$ (s, 3H), 2.22 (s, 3H), 3.29 (s, 2H), 7.09–7.19 (m, 5H), 13.51 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.0$,

20.5, 30.4, 98.3, 120.6, 128.0, 128.8, 131.6, 140.6, 163.0, 196.7. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.62; H, 6.45; N, 12.75.

4.3.2. (*R*)-(*Z*)-4-(1-phenylethylamino)-3-acetylpent-3-enenitrile (4b). Yield: (171 mg, 71%); white solid, mp = 105–106 °C, $[\alpha]_D^{22}$ −586 (1.2, $CHCl_3$). IR (in $CHCl_3$): 3441, 2962, 2921, 2357, 2240, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, 3H, J = 6.7 Hz), 1.84 (s, 3H), 2.14 (s, 3H), 3.11 (d, 1H, J = 18.6 Hz), 3.19 (d, 1H, J = 18.6 Hz), 4.60–4.65 (m, 1H), 7.17–7.44 (m, 5H), 12.56 (d, 1H, J = 7.1 Hz, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 18.4, 25.2, 28.3, 54.1, 94.7, 118.8, 125.8, 127.8, 129.3, 144.2, 163.0, 193.8. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.11; H, 7.22; N, 11.33.

4.3.3. (*Z*)-3-acetyl-4-(benzylamino)pent-3-enenitrile (4c). Yield: (166 mg, 73%); brown oil. IR (neat): 3436, 3028, 2917, 2346, 2240, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 2.10 (s, 3H), 3.17 (s, 2H), 4.37 (d, 2H, J = 5.9 Hz), 7.11–7.21 (m, 5H), 12.32 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 18.5, 28.3, 47.5, 119.0, 127.0, 127.9, 129.2, 137.7, 163.7, 193.8. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.90): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.46; H, 7.24; N, 11.88.

4.3.4. (*Z*)-ethyl 2-(cyanomethyl)-3-(phenylamino)but-2-enoate (4d). Yield: (166 mg, 68%); colorless oil. IR (neat): 3214, 3135, 2981, 2933, 2245, 1606 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, 3H, J = 7.1 Hz), 2.02 (s, 3H), 3.29 (s, 2H), 4.17 (q, 2H, J = 7.1 Hz), 6.96–7.11 (m, 5H), 11.16 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 16.6, 17.9, 31.5, 60.2, 86.1, 118.0, 118.7, 119.0, 125.8, 126.1, 129.5, 130.1, 139.1, 159.0, 168.9. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.57; N, 11.15.

4.3.5. (*R*)-(*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)but-2-enoate (4e). Yield: (203 mg, 75%); yellow oil, $[\alpha]_D^{22}$ −278 (2.1, $CHCl_3$). IR (neat): 3492, 2981, 2363, 2243, 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, 3H, J = 7.1 Hz), 1.46 (d, 3H, J = 6.7 Hz), 1.81 (s, 3H), 3.07 (d, 1H, J = 17.9 Hz), 3.28 (d, 1H, J = 17.9 Hz), 4.01–4.11 (m, 2H), 4.49–4.57 (m, 1H), 7.13–7.22 (m, 5H), 9.88 (d, 1H, J = 5.6 Hz, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 16.0, 16.5, 25.4, 53.8, 59.8, 83.4, 119.4, 125.7, 127.6, 129.3, 144.9, 161.3, 169.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.41; H, 7.32; N, 10.02.

4.3.6. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)but-2-enoate (4f). Yield: (183 mg, 71%); yellow oil. IR (neat): 3254, 2980, 2357, 2242, 1646, 1597 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, 3H, J = 7.0 Hz), 1.90 (s, 3H), 3.20 (s, 2H), 4.07 (q, 2H, J = 7.0 Hz), 4.31 (d, 2H, J = 6.0 Hz), 7.11–7.21 (m, 5H), 9.82 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 15.6, 16.6, 47.5, 59.8, 83.6, 119.5, 125.7, 127.3, 127.9, 128.5, 129.3, 138.5, 161.7, 169.1. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 6.91; N, 10.62.

4.3.7. (*Z*)-ethyl 2-(cyanomethyl)-3-(phenylamino)pent-2-enoate (4g). Yield: (188 mg, 73%); colorless oil. IR (neat): 3489, 2967, 2360, 2253, 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, 3H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.2 Hz), 2.37 (q, 2H, J = 7.6 Hz), 3.27 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 7.01–7.11 (m, 5H), 10.99 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 14.5, 16.0, 22.0, 59.8, 84.7, 119.0, 126.2, 126.3, 129.2, 138.9, 164.2, 169.1. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 7.17; N, 10.61.

4.3.8. (*R*)-(*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)pent-2-enoate (4h). Yield: (211.5 mg, 74%); yellow oil, $[\alpha]_D^{22}$ 365 (1.7, $CHCl_3$). IR (neat): 3321, 3127, 2978, 2142, 1423 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, 3H, J = 7.6 Hz), 1.28 (t, 3H, J = 7.1 Hz), 1.47 (d, 3H, J = 6.8 Hz), 2.13–2.26 (m, 2H), 3.11 (d, 1H, J = 17.8 Hz), 3.21 (d, 1H, J = 17.8 Hz), 4.09–4.21 (m, 2H), 4.48–4.62 (m, 1H), 7.21–7.25 (m, 5H), 9.87 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 14.6, 15.8, 22.2, 25.3, 53.0, 59.5, 82.5, 119.3, 125.3, 127.3, 128.9, 144.9, 165.5, 169.3. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.12; H, 7.71; N, 9.57.

4.3.9. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)pent-2-enoate (4i). Yield: (193 mg, 71%); yellow oil. IR (neat): 3456, 3123, 2903, 2344, 1599 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, 3H, J = 7.7 Hz), 1.25 (t, 3H, J = 7.1 Hz), 2.34 (q, 2H, J = 7.7 Hz), 3.22 (s, 2H), 4.08 (q, 2H, J = 7.1 Hz). 7.19–7.22 (m, 5H), 9.80 (s, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 14.6, 15.9, 21.9, 46.8, 59.5, 82.6, 119.3, 126.2, 127.6, 128.9, 138.2, 165.8 169.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.34; H, 7.32; N, 9.88.

4.3.10. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)-3-phenylacrylate (4j). Yield: (146 mg, 46%) brown oil. IR (neat): 3496, 3321, 2765, 2346, 1587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3H, J = 7.1 Hz), 2.78 (s, 2H), 3.99 (d, 2H, J = 6.3 Hz), 4.12 (q, 2H, J = 7.1 Hz), 7.18–7.22 (m, 10H), 9.63 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 17.8, 30.7, 48.5, 59.7, 84.9, 119.3, 126.7, 127.3, 127.6, 129.1, 129.4, 133.5, 138.5, 163.9, 169.0. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.35; H, 6.58; N, 7.92.

4.3.11. (*R*)-(*Z*)-ethyl 3-(1-phenylethylamino)-2-(cyanomethyl)-3-phenylacrylate (4k). Yield: (168 mg, 49%); brown oil, $[\alpha]_D^{22}$ −420 (2.0, $CHCl_3$). IR (neat): 3436, 3028, 2917, 2240, 1587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, 3H, J = 7.6 Hz), 1.37 (d, 3H, J = 6.8 Hz), 2.69 (d, 1H, J = 17.4 Hz), 2.80 (d, 1H, J = 17.4 Hz), 4.00–4.06 (m, 1H), 4.18–4.23 (m, 2H), 6.65–7.51 (m, 10H), 9.69 (d, 1H, J = 8.8 Hz, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 17.6, 24.6, 29.7, 54.3, 59.8, 84.8, 119.6, 125.5, 127.0, 127.2, 127.8, 128.5, 128.7, 129.0, 129.3, 133.7, 144.5, 163.4, 169.2. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.4): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.38; H, 6.40; N, 8.12.

4.3.12. (*Z*)-ethyl 3-(benzylamino)-2-(cyanomethyl)-3-(2-fluorophenyl)acrylate (4l). Yield: (158 mg, 47%); yellow oil. IR (neat): 3412, 3123, 2923, 2221, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, 3H, J = 7.1 Hz), 2.65 (d, 1H, J = 18.2 Hz), 3.03 (d, 1H, J = 18.2 Hz), 3.92–4.09 (m, 2H),

4.12–4.21 (m, 2H), 7.01–7.31 (m, 9H), 9.61 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.5, 17.6, 48.6, 59.9, 85.5, 116.3 (d, J=20 Hz), 118.8, 120.1, 124.9, 126.9, 127.4, 128.6, 130.0, 131.7, 137.9, 157.8, 161.2 (d, J=252 Hz), 168.7. Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338.38): C, 70.99; H, 5.66; N, 8.28. Found: C, 70.83; H, 5.61; N, 7.92.

4.4. General procedure for base catalyzed cyclization

Enamine (1 mmol) was added to potassium ethoxide in ethanol solution (5 ml, 24 wt%) and stirred for 5–30 min at room temperature. The reaction was monitored by TLC. Then water was added and the mixture extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude pruduct was purified by column chromotography. (hexane–ethyl acetate (4–1)).

4.4.1. 1-(5-Amino-2-methyl-1-phenyl-1*H*-pyrrol-3-yl) ethanone (5a). Yield: (199 mg, 93%); brown oil. IR (neat); 3370, 2989, 1644 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.20 (s, 3H), 2.28 (s, 3H), 2.95 (s, 2H, NH_2), 5.65 (s, 1H), 7.17–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.1, 28.9, 92.3, 128.7, 129.1, 130.0, 130.9, 135.2, 136.2, 194.7. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.76; H, 6.40; N, 12.78.

4.4.2. (*R*)-1-(5-amino-2-methyl-1-(1-phenylethyl)-1*H*-pyrrol-3-yl)ethanone (5b). Yield: (201 mg, 94%); oil, $[\alpha]_D^{22}$ 33 (0.7, $CHCl_3$). IR (neat): 3418, 2901, 2924, 2355, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.80 (d, 3H, J=7.0 Hz), 2.21 (s, 3H), 2.40 (s, 3H), 2.60 (s, 2H, NH_2), 5.53 (q, 1H, J=7.0 Hz), 5.61 (s, 1H), 7.14–7.23 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.1, 18.2, 50.8, 59.5, 110.4, 126.3, 127.4, 129.3, 131.3, 134.7, 141.2, 166.2. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.21; H, 7.23; N, 11.35.

4.4.3. 1-(5-Amino-1-benzyl-2-methyl-1*H*-pyrrol-3-yl) ethanone (5c). Yield: (200 mg, 88%); brown oil. IR (neat): 3388, 3007, 2917, 2849, 1656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.27 (s, 3H), 2.41 (s, 3H), 2.82 (s, 2H, NH_2), 4.99 (s, 2H), 5.76 (s, 1H), 7.15–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.1, 28.9, 30.1, 45.5, 119.4, 126.1, 127.9, 129.3, 131.1, 133.8, 137.4, 194.6. Anal. Calcd for $C_{14}H_{16}N_2O$ (228.18): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.55; H, 7.25; N, 11.88.

4.4.4. Ethyl 5-amino-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (5d). Yield: (222 mg, 91%); yellow oil. IR (neat); 3315, 2982, 2926, 2336, 1687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 2.18 (s, 3H), 2.93 (s, 2H, NH_2), 4.18 (q, 2H, J=7.1 Hz), 5.68 (s, 1H), 7.13–7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 12.59, 15.0, 59.4, 92.2, 96.5, 128.8, 128.9, 129.9, 131.3, 135.2, 136.6, 165.7. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.12): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.76; H, 6.64; N, 11.24.

4.4.5. (*R*)-ethyl 5-amino-2-methyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (5e). Yield (255 mg, 94%); yellow oil, $[\alpha]_D^{22}$ 332 (1.0, $CHCl_3$). IR (neat); 3243, 2923, 2854, 2342, 1688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 1.81 (d, 3H, J=6.7 Hz), 2.40 (s, 3H), 2.67 (s, 2H, NH_2), 4.18 (q, 2H, J=7.1 Hz), 5.51–5.59 (m, 1H), 5.76 (s, 1H), 7.13–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.2, 14.9, 18.3, 51.8, 59.5, 110.5, 126.3, 127.7, 129.1, 131.6, 134.8, 141.3, 166.2. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.52; H, 7.34; N, 9.92.

4.4.6. Ethyl 5-amino-1-benzyl-2-methyl-1*H*-pyrrole-3-carboxylate (5f). Yield: (229 mg, 89%); yellow oil. IR (neat); 3305, 2980, 2933, 2343, 1683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 2.34 (s, 3H), 2.82 (s, 2H, NH_2), 4.13 (q, 2H, J=7.1 Hz), 4.95 (s, 2H), 5.78 (s, 1H), 7.09–7.21 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.6, 15.0, 45.6, 59.3, 96.1, 110.3, 126.2, 127.7, 129.2, 131.4, 134.0, 137.7, 165.8. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 7.05; N, 10.58.

4.4.7. Ethyl 5-amino-2-ethyl-1-phenyl-1*H*-pyrrole-3-carboxylate (5g). Yield: (263 mg, 92%); colorless oil. IR (neat): 3375, 2970, 2913, 2340, 1681 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (t, 3H, J=7.3 Hz), 1.27 (t, 3H, J=7.2 Hz), 2.59 (q, 2H, J=7.3 Hz), 2.86 (br s, 2H, NH_2), 4.20 (q, 2H, J=7.2 Hz), 5.70 (s, 1H), 7.28–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.5, 19.0, 29.7, 58.9, 92.0, 109.9, 114.9, 128.7, 129.4, 134.6, 136.3, 137.3, 165.0. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (286.37): C, 69.74; H, 7.02; N, 10.84; O. Found: C, 69.68; H, 7.01; N, 10.61.

4.4.8. (*R*)-ethyl 5-amino-2-ethyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (5h). Yield: (257 mg, 90%); colorless oil, $[\alpha]_D^{22}$ 197 (1.4, $CHCl_3$). IR (neat): 3298, 2934, 2984, 2323, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.08 (t, 3H, J=7.4 Hz), 1.26 (t, 3H, J=6.9 Hz), 1.86 (d, 3H, J= 7.0 Hz), 2.52 (br s, 2H, NH_2), 2.95 (q, 2H, J=7.4 Hz), 4.17 (q, 2H, J=7.0 Hz), 5.45 (q, 1H, J=7.0 Hz), 5.67 (s, 1H), 7.10–7.19 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6, 15.0, 18.1, 18.7, 51.3, 58.8, 95.4, 109.4, 125.9, 127.3, 128.8, 134.1, 137.0, 141.2. Anal. Calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.68; N, 9.59.

4.4.9. Ethyl 5-amino-1-benzyl-2-ethyl-1*H*-pyrrole-3-carboxylate (5i). Yield: (244 mg, 92%); yellow oil. IR (neat): 3323, 2979, 2934, 2334, 1675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.02 (t, 3H, J=7.4 Hz), 1.27 (t, 3H, J=7.1 Hz), 2.81 (br s, 2H, NH_2), 2.86 (q, 2H, J=7.1 Hz), 4.21 (q, 2H, J=7.4 Hz), 5.12 (s, 2H), 5.72 (s, 1H), 6.81–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.6, 18.7, 29.6, 45.1, 58.8, 96.01, 109.3, 125.6, 127.3, 127.3, 133.3, 137.6, 137.6, 165.0. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (286.37): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.53; H, 7.29; N, 9.95.

4.4.10. Ethyl 5-amino-1-benzyl-2-phenyl-1*H*-pyrrole-3-carboxylate (5j). Yield: (236 mg, 74%); yellow oil. IR (neat): 3312, 2978, 2923, 2332, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (t, 3H, J=7.1 Hz), 2.87 (br s, 2H, NH_2), 4.01 (q, 2H, J=7.1 Hz), 4.84 (s, 2H), 5.93 (s, 1H), 6.84–7.28 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 14.2, 46.4, 58.9, 95.7, 111.7, 125.7, 127.3, 127.9, 127.9,

128.8, 130.8, 132.2, 132.9, 133.9, 135.0, 137.8, 164.5. Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.15): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.80; H, 6.21; N, 8.51.

4.4.11. (*R*)-ethyl 5-amino-2-phenyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carboxylate (5k). Yield: (260 mg, 78%); yellow oil, $[\alpha]_D^{22}$ 413 (3.0, $CHCl_3$). IR (neat): 3298, 2976, 2943, 2321, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.08 (t, 3H, $J=7.1$ Hz), 1.84 (d, 3H, $J=7.0$ Hz), 2.65 (br s, 2H, NH_2), 4.06 (q, 2H, $J=7.1$ Hz), 5.21 (q, 1H, $J=7.0$ Hz), 5.85 (s, 1H), 7.21–7.38 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.2$, 17.8, 52.5, 58.9, 95.3, 111.5, 126.0, 127.3, 127.7, 128.0, 128.8, 130.9, 132.8, 133.8, 135.6, 141.1, 164.5. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.17): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.24; H, 6.55; N, 8.12.

4.4.12. Ethyl 5-amino-1-benzyl-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (5l). Yield: (277 mg, 82%); yellow oil. IR (neat): 3294, 2985, 2934, 2234, 1656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.02$ (t, 3H, $J=7.1$ Hz), 2.93 (br s, 2H, NH_2), 3.98–4.05 (m, 2H), 4.71 (d, 1H, $J=16.3$ Hz), 4.88 (d, 1H, $J=16.3$ Hz), 5.97 (s, 1H), 6.76–7.21 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.7$, 46.6, 50.4, 59.1, 92.6, 113.3, 115.4 (d, $J=22$ Hz), 120.1, 123.4, 126.0, 126.3, 127.2, 127.5, 128.4, 128.8, 130.1 (d, $J=8$ Hz), 133.1, 137.0, 138.9, 139.9, 161.1 (d, $J=253$ Hz), 164.3. Anal. Calcd for $C_{20}H_{19}FN_2O_2$ (338.38): C, 70.99; H, 5.66; N, 8.28. Found: C, 70.91; H, 5.54; N, 8.11.

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New reactivity patterns in activated indoles with 2-methyl substituents

Ashley W. Jones, Tutik Dwi Wahyuningsih, Karin Pchalek, Naresh Kumar and David StC. Black*

School of Chemistry, University of New South Wales, UNSW Sydney NSW 2052, Australia

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Abstract—The synthesis and reactive properties of two new 3-aryl-2-methyl-4,6-dimethoxyindoles are reported. These compounds show typical electrophilic substitution and addition reactions at C7, but not oxidative dimerisation because of the reactivity of the 2-methyl group. This methyl group can be effectively oxidised to a carbaldehyde by selenium dioxide, but formation of 7,7′-diindolylselenides also occurs.

1. Introduction

4,6-Dimethoxy-2,3-diphenylindole and related 2,3-disubstituted indoles have been shown to exhibit considerable reactivity at C7.[1–3] Typical reactions include Vilsmeier formylation, Vilsmeier and Friedel-Crafts acylation, acid catalysed addition of aldehydes, and oxidative dimerisation to form 7,7′-biindolyls. The related 3-substituted-4,6-dimethoxyindoles show similar reactivity towards electrophiles, but reaction can take place either at C7 or C2, or indeed in some cases, at both. For a variety of purposes, we required activated indoles, which were substituted at both C2 and C3, and therefore, regioselectively reactive at C7, but in which the resulting products could be transformed by manipulation of a C2-substituent. We now report the synthesis and some reactions of two 2-methylindoles. While much of the reactivity is similar to that already described for 2,3-diaryl-4,6-dimethoxyindoles, some important differences are evident as a consequence of the 2-methyl group.

2. Results and discussion

2.1. Preparation of 3-aryl-2-methyl-4,6-dimethoxyindoles

The preparation is based on the process already established for the synthesis of a range of 3-aryl-4,6-dimethoxyindoles, by the combination of 3,5-dimethoxyaniline and a bromoacetophenone, followed by protection of the nitrogen of the intermediate amino ketone, and acid catalysed cyclisation to give an indole.[4] Replacement of the bromoacetophenone by a bromopropiophenone leads in the same way to an activated indole bearing a 2-methyl substituent. Thus, α-bromopropiophenone and 4-bromo-α-bromopropiophenone, respectively, led to the aminoketones **1** and **2**, which were acetylated and cyclised to give the *N*-acetylindoles **3** and **4**, and after hydrolysis afforded the indoles **5** and **6**. Protection of the aminoketones requires heating in acetic anhydride at 70 °C for 3 h, because of the steric effect of the adjacent methyl group. Cyclisation is a very clean process under mild conditions but hydrolysis of the *N*-acetyl group requires longer reaction times than for the 2-unsubstituted indoles, again because of the steric influence of the 2-methyl group. The ^{1}H NMR spectra showed resonances for the 2-methyl protons at 2.3 ppm, and the H5 and H7 protons from 6.2–6.4 ppm.

2.2. Formylation and acylation at C7

Treatment of the 2-methylindoles **5**–**6** with 1 equiv of the Vilsmeier reagent at 0 °C gave the corresponding 7-carbaldehydes **7**–**8**, respectively, in 94 and 95% yields. Furthermore, these aldehydes could be reduced readily with excess sodium borohydride in methanol to give the alcohols **9**–**10**, respectively. Vilsmeier acetylation was also effected by treatment of the indoles **5**–**6** with *N*,*N*-dimethylacetamide and phosphoryl chloride, to give the 7-acetylindoles **11**–**12**, respectively, in high yield. The synthetic utility of the Vilsmeier methodology was further illustrated by the reaction of indole **5** with 4-chloro-*N*,*N*-dimethylbenzamide and phosphoryl chloride, to give the 7-aroylindole **13** in 85% yield.

Keywords: Indoles; Oxidation; Selenium dioxide; Aldehydes.
* Corresponding author. Tel.: +61 2 9385 4657; fax: +61 2 9385 6141; e-mail: d.black@unsw.edu.au

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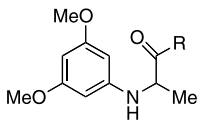
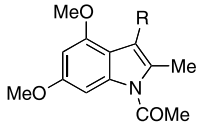
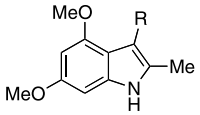


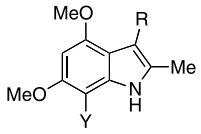
	R
1	Ph
2	4-BrC_6H_4



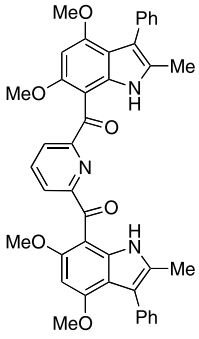
	R
3	Ph
4	4-BrC_6H_4



	R
5	Ph
6	4-BrC_6H_4



	R	Y
7	Ph	CHO
8	4-BrC_6H_4	CHO
9	Ph	CH_2OH
10	4-BrC_6H_4	CH_2OH
11	Ph	COMe
12	4-BrC_6H_4	COMe
13	Ph	COC_6H_4Cl
14	Ph	$COCF_3$
15	4-BrC_6H_4	$COCF_3$
16	Ph	$COCCl_3$
17	4-BrC_6H_4	$COCCl_3$
18	4-BrC_6H_4	$COCO_2Et$
19	4-BrC_6H_4	$COCONMe_2$
20	4-BrC_6H_4	COCONMeOH
22	Ph	NO_2



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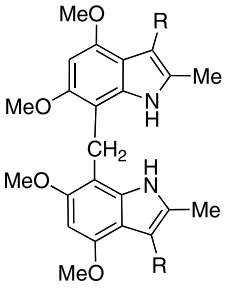
Direct reaction of indoles **5–6** with either trifluoroacetic anhydride or trichloroacetyl chloride gave effectively quantitative yields of the 7-substituted trifluoroacetyl-indoles **14–15** or trichloroacetyl indoles **16–17**. Reaction of indole **6** with oxalyl chloride also gave the 7-chloro-oxalyl derivative, which was easily converted into the ethyl ester **18**, dimethylamide **19** and hydroxamic acid **20**. More conventional Friedel–Crafts conditions were employed, with aluminium chloride as catalyst, in the reaction of indole **5** with pyridine-2,6-dicarbonyl chloride to give in 69% yield the product **21**, which was required for a particular project.

2.3. Nitration at C7

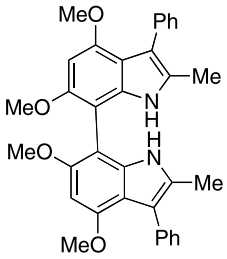
The controlled nitration of suitably activated indoles using nitric acid adsorbed onto silica has been described recently.[5] This reaction is very successful if the activated indole also contains a modifying electron-withdrawing group. Consequently, the *N*-acetylindole **3** was treated with nitric acid on silica to give the corresponding 7-nitro compound, which was rather labile under the reaction conditions, and consequently converted directly into the 7-nitro-indole **22** in good yield.

2.4. Acid-catalysed addition of formaldehyde at C7

Reaction of the indoles **5–6** with formaldehyde in glacial acetic acid gave the 7,7′-diindolylmethanes **23–24** in 86 and 76% yield, respectively. The same compounds can also be obtained by the treatment of the indole methanols **9–10** in tetrahydrofuran with glacial acetic acid. This behaviour is general for 2,3-disubstituted-4,6-dimethoxyindoles and their corresponding 7-methanols.[2] The likely mechanism for the coupling of the methanols is an acid-catalysed *ipso*-substitution at the most nucleophilic 7-position, followed by loss of a proton and formaldehyde to re-establish the aromaticity of the benzene ring.



	R
23	Ph
24	4-BrC_6H_4



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2.5. Oxidative dimerisation at C7

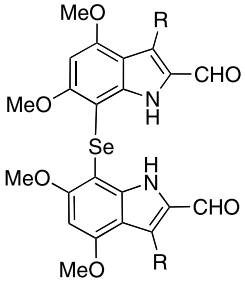
7,7′-Biindolyls have been synthesised previously from 2,3-diaryl-4,6-dimethoxyindoles by oxidation with benzoquinone, chloranil, dichlorodicyanoquinone, copper(II) chloride and iodine monochloride.[2,6] The 2-methyl-3-phenylindole **5** was successfully oxidised to the 7,7′-dimer **25** in 88% yield using benzoquinone. Reaction with dichlorodicyanoquinone gave a lower yield, and the other reagents caused general decomposition of the starting material. It is likely that the 2-methyl group is a source of some instability towards oxidation, as the following section shows.

2.6. Oxidation of the C2-methyl group

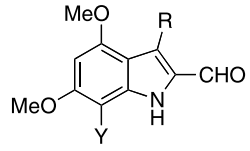
One of the reasons for the interest in 2-methyl indoles relates to the oxidation of the 2-methyl group, with the possibility that further useful functionalisation might be generated at C2, following prior substitution at C7.

It has been reported that 2,3-disubstituted indole derivatives react easily with various oxidants.[7] Oxidations of 2-methyl-3-substituted indoles have been carried out using a wide variety of oxidising reagents, for example, air,[8,9] lead tetraacetate,[10] *t*-butylhypochlorite,[10] activated manganese dioxide,[11] silver acetate,[12] selenium dioxide,[13] or periodic acid.[14] Most oxidising agents act as electrophiles and initially attack the C-3 position of the indole ring, leading to the formation of acyl indoles, oxindole derivatives, dimerized products or products resulting from oxidative cleavage of the C2–C3 double bond. Attempts to oxidise the 2-methylindoles **5–6** to the related 2-formyl indoles with periodate, activated manganese dioxide, ceric ammonium nitrate, or silver acetate proved to be unsuccessful. However, selenium dioxide converted indoles **5–6** into the 2,2′-diformyl-7,7′-diindolylselenides **26–27** in 31 and 30% yield, respectively. The less-activated *N*-acetylindole **3** also gave the selenide **26** in 35% yield. Such selenium insertion reactions have been observed previously for indole and

2-methylindole, with the linkage taking place at C3: however, no 2-methyl oxidation occurred.[15] Similar reaction of simple 2,3-disubstituted indoles with selenium dioxide gives no selenium compounds and the major products are 2-acylindoles in yields of 22–44%.[13] Although indoles **5**–**6** are 2,3-disubstituted, they are also activated at C7, allowing for selenium insertion to occur to form the selenides **26**–**27**.



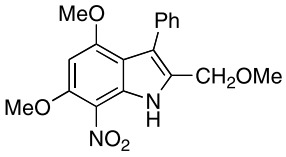
	R
26	Ph
27	4-BrC_6H_4



	R	Y
28	Ph	$COCF_3$
29	4-BrC_6H_4	$COCF_3$
30	Ph	$COCCl_3$
31	4-BrC_6H_4	$COCCl_3$
32	Ph	CO_2H
33	4-BrC_6H_4	CO_2H
34	Ph	NO_2

The ability of selenium dioxide to oxidise the 2-methyl group of indoles **5**–**6** to a 2-formyl group raised the possibility that similar oxidation might occur, but without selenide formation, if C7 was substituted, preferably by an electron-withdrawing group. Reaction of both the 7-trifluoroacetyl indoles **14**–**15** and the 7-trichloroacetyl indoles **16**–**17** with approximately 4 equiv of selenium dioxide in dioxan at reflux overnight, resulted in oxidation of the methyl group to formyl, to give the aldehydes **28**–**29** and **30**–**31**, respectively, in yields of 60–87%. On the other hand, reaction of the 7-acetyl indole **11** gave a complex product mixture. Treatment of the 7-trifluoroacetylindoles **28**–**29** with potassium hydroxide gave the corresponding 2-formyl-7-carboxylic acids **32**–**33** in 95 and 82% yield, respectively.

Furthermore, reaction of the 7-nitro-indole **22** with selenium dioxide proceeds smoothly to produce the 2-formyl-7-nitro-indole **34** in 65% yield. In an alternative reaction, the 7-nitro-indole **22** was converted by sulfuryl chloride to the related 2-chloromethyl compound, which was transformed on chromatography in dichloromethane and methanol into the 2-methoxymethylindole **35**.



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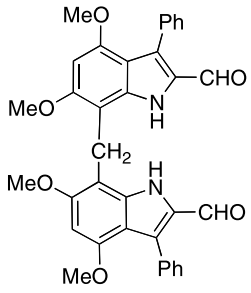

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The 7,7′-diindolylmethane **23** also represents a suitably 7-protected indole, and it underwent reaction with selenium dioxide to give the dialdehyde **36** in 43% yield: significantly there was no oxidation of the methylene link.

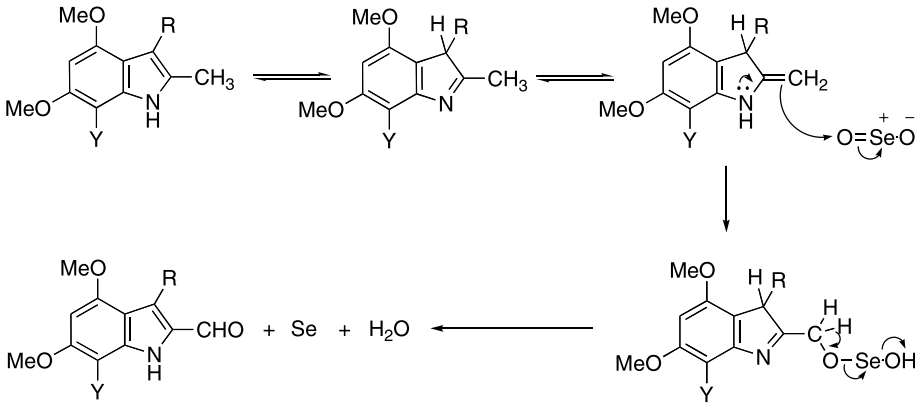
3. Conclusions

In suitable examples, an indole 2-methyl group can be oxidised to a formyl group, in a synthetically useful process that delivers a variety of functionality to the indole ring. The reaction probably proceeds by a mechanism similar to one proposed by Sakai et al.[13] involving direct oxidation at C2 (Scheme 1), rather than the more general initial oxidation at C3 followed by intramolecular oxygen transfer within an intermediate indoline system.

4. Experimental

4.1. General

Mp were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian



Scheme 1.

Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 $60GF_{254}$.

4.2. Preparation of indoles

4.2.1. 2-(3,5-Dimethoxyphenylamino)-1-phenylpropan-1-one (1). A mixture of 3,5-dimethoxyaniline (10.0 g, 65.3 mmol), 2-bromopropiophenone (14.1 g, 66.0 mmol), and sodium hydrogen carbonate 11.0 g, 130.6 mmol in absolute ethanol (100 mL) was heated under reflux for 3 h with stirring. After cooling, the resulting white precipitate was filtered off and washed with water to give the amino ketone **1** (13.00 g, 70%) as a yellow solid, mp 118–119 °C (ethanol). (Found: C, 71.7; H, 6.7; N, 5.0. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.7; N, 4.9%). ν_{max}: 3360, 1670, 1600, 1520, 1220, 1200 cm^{-1}. λ_{max}: 218 nm (ε 15,000 cm^{-1} M^{-1}), 247 (12,200). ^1H NMR spectrum ($CDCl_3$): δ 1.47 (3H, d, $J=7.0$ Hz, Me), 3.74 (6H, s, OMe), 4.77 (1H, br s, NH), 5.09 (1H, q, $J=7.0$ Hz, CH), 5.86–5.90 (3H, m, H2, H4, H6), 7.42–7.52 (4H, m, ArH), 7.58–7.63 (1H, m, ArH). ^{13}C NMR spectrum ($CDCl_3$): δ 19.49 (Me), 53.26 (CH), 55.08 (OMe), 90.07 (C4), 92.29 (C2, C6), 128.39, 128.81, 133.58 (ArCH), 134.58, 148.37, 161.77 (ArC), 200.39 (CO). Mass spectrum (EI): *m/z* 285 (M, 10), 181 (20), 180 (100).

4.2.2. *N*-Acetyl-4,6-dimethoxy-2-methyl-3-phenylindole (3). The anilino ketone **1** (5.00 g, 17.5 mmol) was partially dissolved in acetic anhydride (20 mL) and heated at 70 °C for 3 h. The solution was allowed to cool before water (1 mL) was added and the solution was again warmed to 50–60 °C. Water was then added slowly so that the temperature did not drop below 50 °C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate. The organic phase was washed with water until neutral, saturated sodium hydrogen carbonate solution, brine and dried (sodium sulfate). The solvent was removed under reduced pressure to yield an oil. The crude protected anilino ketone was then dissolved in trifluoroacetic acid (20 mL). The solution was allowed to stir overnight after, which ice/water was added and the resulting solid was filtered off. The precipitate was washed with water until neutral and dried under vacuum. The resulting crude product was purified by recrystallisation from ethanol to yield the *N*-acetyl indole **3** as a white solid (3.52 g, 65%), mp 146–148 °C (ethanol). (Found: C, 73.7; H, 6.1; N, 4.5. $C_{19}H_{19}NO_3$ requires C, 73.4; H, 6.2; N, 4.5%). ν_{max}: 1695, 1590, 1565, 1410, 1360, 1280 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): δ 2.43 (3H, s, Me), 2.72 (3H, s, CO*Me*), 3.61 and 3.89 (6H, 2s, OMe), 6.36 (1H, d, $J=$ 2.0 Hz, H5), 7.33–7.42 (5H, m, ArH), 7.45 (1H, d, $J=$ 2.0 Hz, H7). ^{13}C NMR spectrum ($CDCl_3$): δ 15.0 (Me), 27.4 (CO*Me*), 55.2 and 55.7 (OMe), 92.7 (C5), 95.1 (C7), 126.5, 127.1, 130.9 (ArCH), 113.0, 122.0, 129.7, 135.1, 137.7, 153.5, 158.5 (ArC), 170.8 (CO). Mass spectrum (EI): *m/z* 309 (M, 60), 267 (100), 252 (60), 43 (100).

4.2.3. 4,6-Dimethoxy-2-methyl-3-phenylindole (5). The *N*-acetyl indole **3** (2.00 g, 6.5 mmol) was partially dissolved in ethanol (50 mL). An excess of crushed potassium hydroxide was added to the above mixture and allowed to stir for 2 h. The resulting precipitate was filtered off to yield the indole **5** as a white solid (1.64 g, 95%), mp 130–131 °C (ethanol). (Found: C, 76.4; H, 6.5; N, 5.3. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.3%). ν_{max}: 3380, 3360, 1610, 1595, 1580, 1550, 1500, 1435, 1405, 1330, 1245, 1205, 1185, 1145 cm^{-1}. λ_{max}: 236 nm (ε 23,500 cm^{-1} M^{-1}), 274 (16,600). ^1H NMR spectrum ($CDCl_3$): δ 2.27 (3H, s, Me), 3.74 and 3.81 (6H, 2s, OMe), 6.31 (1H, d, $J=2.0$ Hz, H5), 6.34 (1H, d, $J=2.0$ Hz, H7), 7.31–7.37 (1H, m, ArH), 7.41–7.53 (4H, m, ArH), 7.75 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 11.8 (Me), 55.0 and 55.4 (OMe), 86.8 (C5), 91.9 (C7), 125.4, 127.1, 130.9 (ArCH), 111.6, 113.8, 129.1, 136.7, 154.0, 156.6 (ArC). Mass spectrum (EI): *m/z* 267 (M, 100), 252 (65), 237 (25).

4.2.4. 1-(4-Bromophenyl)-2-[(3,5-dimethoxyphenyl)-amino] propanone (2). 3,5-Dimethoxyaniline (5.00 g, 32.6 mmol), 2,4′-dibromopropiophenone (9.56 g, 32.7 mmol) and sodium hydrogen carbonate (2.72 g, 32.4 mmol) were added to absolute ethanol (100 mL) and heated to reflux for 5 h. The mixture was allowed to cool to room temperature and the resulting yellow precipitate was filtered off, washed with water and dried to yield anilino ketone **2** (10.10 g, 85%) as pale-yellow needles, mp 159–160 °C (from ethyl acetate/light petroleum). (Found: C, 55.8; H, 5.2; N, 3.8. $C_{17}H_{18}BrNO_3$ requires C, 56.0; H, 4.9; N, 3.8%). ν_{max}: 3402, 1687, 1619, 1583, 1479, 1199, 1168, 1070, 958 cm^{-1}. λ_{max}: 228 nm (ε 17,350 cm^{-1} M^{-1}), 263 (16,950). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.46 (3H, d, $J=7.2$ Hz, Me), 3.73 (6H, s, OMe), 5.01 (1H, q, $J=$ 6.8 Hz, C*H*Me), 5.87, 5.90 (3H, 2d, $J=1.9$ Hz, H2, H4, H6), 7.64, 7.85 (4H, 2d, $J=8.7$ Hz, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 19.2 (Me), 53.7 (CH), 55.1 (OMe), 90.7, 92.8, 129.8, 132.1 (ArCH), 128.8, 133.2, 147.6, 161.7 (ArC), 199.1 (CO). Mass spectrum (EI): *m/z* 366 (M+2, ^{81}Br, 1%), 365 (2), 364 (M, ^{79}Br, 1), 363 (2), 180 (100).

4.2.5. *N*-Acetyl-1-(4-bromophenyl)-2-[(3,5-dimethoxyphenyl)amido] propanone. The anilino ketone **2** (0.40 g, 1.10 mmol) was partially dissolved in acetic anhydride (2 mL) and heated at 50 °C overnight. Water was then added slowly so that the temperature did not drop below 50 °C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate and the organic phase was washed with saturated sodium hydrogen carbonate solution and water until neutral, and then dried. The solvent was evaporated off to give the title amido ketone (0.41 g, 92%) as an off white solid, mp 140–14 °C. (Found: C, 56.3; H, 4.8; N, 3.6. $C_{19}H_{20}BrNO_4$ requires C, 56.2; H, 5.0; N, 3.5%). ν_{max}: 1689, 1654, 1592, 1324, 1203, 1162, 1071 cm^{-1}. λ_{max}: 228 nm (ε 14,800 cm^{-1} M^{-1}), 258 (20,900). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.23 (3H, d, $J=7.2$ Hz, Me), 1.85 (3H, s, COMe), 3.72 (6H, s, OMe), 6.06 (1H, q, $J=7.2$ Hz, CH), 6.26 (2H, d, $J=2.3$ Hz, ArH), 6.43 (1H, t, $J=2.3$ Hz, ArH), 7.62, 7.89 (4H, 2d, $J=8.7$ Hz, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.9, 22.5 (Me), 54.9 (CH), 55.4 (OMe), 100.4, 108.1, 129.9, 131.9 (ArCH), 128.2, 134.5, 140.6, 160.9 (ArC), 170.4, 198.0 (CO). Mass spectrum (EI): *m/z* 408 (M+2, ^{81}Br, 100%), 407 (86), 406 (M, ^{79}Br, 92), 405 (51), 383 (40), 236 (47).

4.2.6. 1-Acetyl-3-(4-bromophenyl)-4,6-dimethoxy-2-methylindole (4). *N*-Acetyl-1-(4-bromophenyl)-2-[(3,5-dimethoxyphenyl)amido]propanone (9.40 g, 23.1 mmol) was dissolved in trifluoroacetic acid (32 mL). The solution was stirred overnight after, which ice/water was added and the mixture was extracted with dichloromethane. The combined extract was washed with water until neutral and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed (dichloromethane) to afford the acetyl indole **4** (6.87 g, 77%) as a white solid, mp 172 °C. (Found: C, 58.4; H, 4.6; N, 3.6. $C_{19}H_{18}BrNO_3 \cdot 0.1$ H_2O requires C, 58.5; H, 4.7; N, 3.6%). ν_{max}: 1687, 1595, 1571, 1495, 1418, 1370, 1293, 1216, 1151 cm^{-1}. λ_{max}: 208 nm (ε 39,350 cm^{-1} M^{-1}), 248 (23,600), 319 (4,950). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.40 (3H, s, Me), 2.71 (3H, s, COMe), 3.62, 3.87 (6H, s, OMe), 6.34 (1H, d, $J=2.3$ Hz, H5), 7.38 (1H, d, $J=1.9$ Hz, H7), 7.21, 7.50 (4H, 2d, $J=8.3$ Hz, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.9, 27.4 (Me), 55.1, 55.7 (OMe), 92.6 (C5), 94.9 (C7), 130.3, 132.5 (ArCH), 112.6, 120.7, 120.8, 129.8, 134.0, 137.6, 153.4, 158.6 (ArC), 170.7 (CO). Mass spectrum (EI): *m/z* 390 (M+2, ^{81}Br, 100), 388 (M, ^{79}Br, 100), 348 (56), 346 (60).

4.2.7. 3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindole (6). The *N*-acetyl indole **4** (4.91 g, 12.65 mmol) was partially dissolved in methanol (25 mL). An excess of crushed potassium hydroxide was added and the mixture was allowed to stir overnight. The resulting precipitate was filtered off, washed and dried to yield the indole **6** as a white solid (3.78 g, 86%), mp 162–163 °C. (Found: C, 58.7; H, 4.5; N, 4.1. $C_{17}H_{16}BrNO_2$ requires C, 58.9; H, 4.7; N, 4.1%). ν_{max}: 3338, 1620, 1561, 1487, 1340, 1319, 1217, 1199, 1151, 1129, 814 cm^{-1}. λ_{max}: 232 nm (ε 22,950 cm^{-1} M^{-1}). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.30 (3H, s, Me), 3.70, 3.82 (6H, 2s, OMe), 6.22 (1H, s, H5), 6.42 (1H, s, H7), 7.29, 7.48 (4H, 2d, $J=$ 8.2 Hz, ArH), 7.84 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 54.9, 55.6 (OMe), 86.6 (C5), 91.9 (C7), 130.1, 132.5 (ArCH), 111.4, 112.9, 119.4, 129.0, 134.9, 136.7, 154.0, 156.9 (ArC). Mass spectrum (EI): *m/z* 348 (M+2, ^{81}Br, 12%), 347 (100), 346 (M, ^{79}Br, 12), 345 (98), 332 (29), 330 (29), 266 (8), 251 (86).

4.3. Formylation and acylation of indoles

4.3.1. 4,6-Dimethoxy-2-methyl-3-phenylindole-7-carbaldehyde (7). A solution of phosphoryl chloride (0.04 mL, 0.41 mmol) in anhydrous dimethylformamide (~0.08 mL) was added dropwise to a stirred solution of 3-phenyl indole **5** (0.10 g, 0.37 mmol) in anhydrous dimethylformamide (~1.2 mL) at 0 °C. The mixture was stirred at this temperature for 1 h, then allowed to come to room temperature. Ice water was added and the mixture was made strongly basic with 10% NaOH and stirred for another 15 min. The precipitate was filtered off, washed with water until neutral and dried to give the carbaldehyde **7** (0.10 g, 95%) as a light brown solid, mp 254–256 °C. (Found: C, 72.2; H, 5.8; N, 4.7. $C_{18}H_{17}NO_3 \cdot 0.2$ H_2O requires C, 72.3; H, 5.9; N, 4.7%). ν_{max}: 3314, 1635, 1597, 1449, 1361, 1245, 1161, 1120, 990 cm^{-1}. λ_{max}: 204 nm (ε 30,300 cm^{-1} M^{-1}), 253 (23,050), 328 (10,600). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.36 (3H, s, Me), 3.82, 3.97 (6H, 2s, OMe), 6.13 (1H, s, H5), 7.36–7.39 (5H, m, ArH), 10.26 (1H, br, NH). 10.37 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 55.2, 56.3 (OMe), 86.6 (C5), 125.7, 127.2, 130.8 (ArCH), 104.1, 111.6, 113.9, 130.7, 135.4, 136.2, 160.5, 162.2 (ArC), 188.3 (CO). Mass spectrum (EI): *m/z* 296 (M+1, 100%).

4.3.2. 3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindole 7-carbaldehyde (8). This was prepared as described for the 7-carbaldehyde **7** from a solution of indole **6** (0.50 g, 1.4 mmol) in anhydrous dimethylformamide (~6 mL) and a solution of phosphoryl chloride (0.15 mL, 1.59 mmol) in anhydrous dimethylformamide (~0.4 mL). The resulting precipitate was filtered off, washed with water until neutral and dried to give the carbaldehyde **8** (0.51 g, 94%) as a yellow solid, mp 255–256 °C. (Found: C, 58.1; H, 4.2; N, 3.9. $C_{18}H_{16}BrNO_3$ requires C, 57.8; H, 4.3; N, 3.7%). ν_{max}: 3314, 1637, 1590, 1451, 1390, 1245, 1162, 1118, 991, 813, 742 cm^{-1}. λ_{max}: 204 nm (ε 40,100 cm^{-1} M^{-1}), 229 (23,950), 253 (26,600), 326 (14,150). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.34 (3H, s, Me), 3.83, 3.97 (6H, 2s, OMe), 6.13 (1H, s, H5), 7.25, 7.48 (4H, 2d, $J=8.3$ Hz, ArH), 10.27 (1H, br, NH). 10.36 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 55.2, 56.3 (OMe), 86.6 (C5), 130.3, 132.3 (ArCH), 104.1, 111.3, 112.8, 119.7, 130.8, 134.4, 136.1, 160.4, 162.3 (ArC), 188.3 (CO). Mass spectrum (EI): *m/z* 376 (M+2, ^{81}Br, 19%), 375 (98), 374 (M, ^{79}Br, 21), 373 (100), 360 (20), 358 (21), 279 (27).

4.3.3. 7-Hydroxymethyl-4,6-dimethoxy-2-methyl-3-phenylindole (9). Indole **7** (0.20 g, 0.68 mmol) was dissolved in methanol (30 mL) to which excess sodium borohydride was added. The mixture was then heated to reflux under nitrogen for 1 h. Water was added and the resulting precipitate was filtered, washed with water and dried to yield the methanol **9** (0.19 g, 97%) as a white solid, mp 268 °C (dec). (Found: C, 71.5; H 6.4; N, 4.7. $C_{18}H_{19}NO_3 \cdot 0.3$ H_2O requires C, 71.4; H, 6.5; N, 4.6%). ν_{max}: 3445, 3324, 1620, 1600, 1464, 1325, 1208, 1148, 1101, 997 cm^{-1}. λ_{max}: 203 nm (ε 27,000 cm^{-1} M^{-1}), 230 (38,550), 281 (14,000). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 2.28 (3H, s, Me), 3.64, 3.79 (6H, 2s, OMe), 4.53 (1H, t, $J=5.7$ Hz, OH), 4.71 (2H, d, $J=5.7$ Hz, CH_2), 6.30 (1H, s, H5), 7.16–7.32 (5H, m, ArH), 10.64 (1H, s, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 12.3 (Me), 54.1 (CH_2), 55.4, 57.5 (OMe), 89.5 (C5), 125.3, 127.3, 130.9 (ArCH), 105.6, 111.9, 112.7, 130.8, 136.7, 153.0 (ArC). Mass spectrum (EI): *m/z* 296 (M−1, 25%), 280 (100).

4.3.4. 3-(4-Bromophenyl)-7-hydroxymethyl-4,6-dimethoxy-2-methylindole (10). This was prepared as described for the hydroxymethylindole **9** from indole **75** (0.30 g, 0.80 mmol) in methanol (60 mL) and excess sodium borohydride to yield the methanol **10** (0.28 g, 93%) as a white solid, mp 240 °C (dec). (Found: C, 56.8; H 4.6; N, 3.7. $C_{18}H_{18}BrNO_3 \cdot 0.2$ H_2O requires C, 56.9; H, 4.9; N, 3.7%). ν_{max}: 3580, 3312, 1619, 1595, 1488, 1343, 1150, 1104, 995 cm^{-1}. λ_{max}: 234 nm (ε 27,300 cm^{-1} M^{-1}). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 2.27 (3H, s, Me), 3.66, 3.79 (6H, 2s, OMe), 4.53 (1H, t, $J=5.7$ Hz, OH), 4.69 (2H, d, $J=5.7$ Hz, CH_2), 6.31 (1H, s, H5), 7.25, 7.48 (4H, 2d, $J=8.7$ Hz, ArH), 10.71 (1H, s, NH). ^{13}C NMR spectrum

(75 MHz, d_6-DMSO): 12.2 (Me), 54.1 (CH_2), 55.4, 57.5 (OMe), 89.5 (C5), 130.2, 132.9 (ArCH), 105.6, 111.4, 111.5, 118.4, 131.2, 136.0, 136.7, 152.9, 153.1 (ArC). Mass spectrum (EI): *m/z* 378 (M+2, ^{81}Br, 16%), 377 (93), 376 (M, ^{79}Br, 13), 375 (100), 359 (88), 357 (85), 263 (27), 235 (25).

4.3.5. 7-(4,6-Dimethoxy-2-methyl-3-phenylindolyl)-ethanone (11). Indole **5** (1.0 g, 3.7 mmol) was added to a stirred and ice cooled solution of *N*,*N*-dimethylacetamide (25 mL) and excess phosphoryl chloride (1.2 g, 7.8 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then warmed to 40–60 °C for 6 h. This mixture was then poured into an ice cooled sodium hydroxide solution (10%, 100 mL). The resulting crude product was filtered off, and recrystallised from methanol to afford the 7-acetyl indole **11** (0.94 g, 82%) as an off-white solid, mp 148 °C (from methanol). (Found: C, 73.9; H, 6.1; N, 4.7. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.1; N, 4.5%). ν_{max}: 3370, 1615, 1595, 1575, 1500, 1440, 1350, 1330, 1270, 1235, 1200, 1140 cm^{-1}. λ_{max}: 219 nm (ε 15,500 $cm^{-1}\,M^{-1}$), 251 (19,600), 324 (11,700). ^{1}H NMR spectrum ($CDCl_3$): δ 2.37 (3H, s, Me), 2.69 (3H, s, COMe), 3.80, 3.98 (6H, 2s, OMe), 6.18 (1H, s, H5), 7.24–7.43 (5H, m, ArH), 10.78 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 12.0 (Me), 33.1 (CO*Me*), 55.1, 56.2 (OMe), 87.2 (C5) 125.5, 127.2, 130.9 (ArCH), 104.6, 111.9, 113.6, 130.5, 135.8, 137.5, 158.7, 160.2 (ArC), 198.7 (CO). Mass spectrum (EI): *m/z* 310 (M+1, 45), 309 (M, 100), 294 (55), 266 (75), 251 (20).

4.3.6. 7-(3-(4-Bromophenyl)-4,6-dimethoxy-2-methyl-indolyl)-ethanone (12). To a stirred and ice cooled solution of *N*,*N*-dimethylacetamide (2.4 mL) and excess phosphoryl chloride (0.81 mL, 8.69 mmol) was added indole **6** (0.30 g, 0.87 mmol). The mixture was stirred at room temperature for 30 min and then warmed to 40–60 °C overnight. The mixture was then poured onto crushed ice containing 10% NaOH. The resulting crude product was filtered off, washed till neutral and dried. Column chromatography (dichloromethane) yielded the ketone **12** (0.30 g, 89%) as an off white solid, mp 178–179 °C. (Found: C, 59.0; H, 4.7; N, 3.7. $C_{19}H_{18}BrNO_3$ requires C, 58.8; H, 4.7; N, 3.6%). ν_{max}: 3342, 1620, 1585, 1468, 1347, 1265, 1212, 1134, 1097, 992 cm^{-1}. λ_{max}: 230 nm (Σ 27,150 $cm^{-1}\,M^{-1}$), 255 (26,900), 333 (14,200). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.34 (3H, s, Me), 2.68 (3H, s, COMe), 3.81, 3.98 (6H, 2s, OMe), 6.18 (1H, s, H5), 7.26, 7.48 (4H, 2d, J= 8.3 Hz, ArH), 10.78 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 33.0 (COMe), 55.1, 56.1 (OMe), 87.2 (C5), 130.2, 132.4 (ArCH), 104.5, 111.5, 112.4, 119.5, 130.6, 134.7, 137.5, 158.5, 160.2 (ArC), 198.7 (CO). Mass spectrum (EI): *m/z* 390 (M+2, ^{81}Br, 20%), 389 (96), 388 (M, ^{79}Br, 20), 387 (100), 372 (20), 344 (30), 293 (42), 250 (20).

4.3.7. 7-(4-Chlorobenzoyl)-4,6-dimethoxy-2-methyl-3-phenylindole (13). Phosphoryl chloride (0.2 mL, 2.2 mmol) was added to warm (60 °C) 4-chloro-*N*,*N*′-dimethylbenzamide (0.7 g, 3.8 mmol). After stirring for 5 min, indole **5** (0.5 g, 1.9 mmol) was added and the mixture was heated to 80 °C and stirred for 30 min. The reaction mixture was allowed to cool, then 2 M NaOH (30 mL) was added and the mixture was extracted with dichloromethane. The organic layer was washed with 2 M NaOH, water, dried and concentrated. The residue was chromatographed (dichloromethane) to give the ketone **13** (0.64 g, 85%) as a yellow solid, mp 186–187 °C. (Found: C, 70.9; H, 5.0; N, 3.7. $C_{24}H_{20}ClNO_3$ requires C, 71.0; H, 4.97; N, 3.5%). ν_{max}: 3386, 1589, 1546, 1356, 1287, 1196, 1149, 987 cm^{-1}. λ_{max}: 242 nm (ε 28,450 $cm^{-1}\,M^{-1}$), 258 (28,050), 333 (11,450). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.37 (3H, s, Me), 3.61, 3.81 (6H, 2s, OMe), 6.16 (1H, s, H5), 7.25–7.61 (9H, m, ArH), 10.02 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 55.2, 56.1 (OMe), 87.8 (C5), 125.6, 127.2, 127.7, 129.6, 130.8 (ArCH), 103.5, 112.3, 114.1, 130.6, 135.5, 136.5, 137.6, 140.8, 158.9, 159.0, 173.3 (ArC), 194.5 (CO). Mass spectrum (EI): *m/z* 407 (M+2, ^{37}Cl, 25%), 405 (M, ^{35}Cl, 90), 355 (18), 267 (100), 252 (56).

4.3.8. 4,6-Dimethoxy-2-methyl-3-phenyl-7-trifluoroacetylindole (14). Indole **5** (1.0 g, 3.7 mmol) was dissolved in dry dichloromethane (50 mL) and excess trifluoroacetic anhydride (3.0 mL, 21.3 mmol) was added. The mixture was stirred for 4 h at room temperature before water was added and the organic layer extracted with dichloromethane. The organic layer was washed with water until neutral then dried. The solvent was evaporated off and the residue recrystallised from dichloromethane/light petroleum to give compound **14** (1.1 g, 83%) as a yellow solid, mp 150–151 °C. (Found: C, 62.0; H, 4.5; N, 3.9. $C_{19}H_{16}NO_3F_3 \cdot 0.25\ H_2O$ requires C, 62.0; H, 4.5; N, 3.8%). ν_{max}: 3420, 1630, 1590, 1570, 1550, 1440, 1390, 1360, 1330, 1230, 1200, 1180 cm^{-1}. λ_{max}: 219 nm (ε 20,000 $cm^{-1}\,M^{-1}$), 258 (20,400), 346 (11,000). ^{1}H NMR spectrum ($CDCl_3$): δ 2.36 (3H, s, Me), 3.84, 3.99 (6H, 2s, OMe), 6.16 (1H, s, H5), 7.28–7.41 (5H, m, ArH), 10.36 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 11.8 (Me), 55.3, 56.4 (OMe), 87.4 (C5), 99.7 (CF_3), 125.9, 127.3, 130.8 (ArCH), 112.1, 114.8, 115.5, 119.3, 135.1, 138.0, 161.5, 161.7 (ArC), 178.4 (CO). Mass spectrum (EI): *m/z* 364 (M+1, 15), 363 (M, 100), 294 (85), 147 (20).

4.3.9. 3-(4-Bromophenyl)-4,6-dimethoxy-2-methyl-7-trifluoroacetylindole (15). Indole **6** (0.50 g, 1.4 mmol) was dissolved in dry dichloromethane (25 mL) and excess trifluoroacetic anhydride (1.22 mL, 8.7 mmol) was added. The mixture was stirred for 4 h, water was then added and the organic layer was extracted with dichloromethane. The organic layer was washed with water until neutral then dried. The solvent was evaporated off and the residue was chromatographed (dichloromethane) to give compound **15** (0.63 g, 99%) as a yellow solid, mp 186–187 °C. (Found: C, 51.6; H 3.2; N, 3.3. $C_{19}H_{15}BrF_3NO_3$ requires C, 51.6; H, 3.4; N, 3.2%). ν_{max}: 3371, 1632, 1587, 1327, 1222, 1155, 1128, 988 cm^{-1}. λ_{max}: 237 nm (ε 25,350 $cm^{-1}\,M^{-1}$), 344 (13,600). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.33 (3H, s, Me), 3.85, 3.98 (6H, 2 s, OMe), 6.14 (1H, s, H5), 7.24, 7.49 (4H, 2d, J=8.7 Hz, ArH), 10.35 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.8 (Me), 55.3, 56.5 (OMe), 87.4 (C5), 99.7 (CF_3), 130.4, 132.3 (ArCH), 111.8, 113.6, 115.4, 119.2, 119.9, 130.6, 134.1, 137.9, 161.5 (ArC), 178.8 (CO). Mass spectrum (EI): *m/z* 444 (M+2, ^{81}Br, 20%), 443 (M+1, 100), 442 (M, ^{79}Br, 25), 374 (63), 372 (66).

4.3.10. 4,6-Dimethoxy-2-methyl-3-phenyl-7-trichloroacetylindole (16). Trichloroacetyl chloride (2.0 mL, 17.9 mmol) was added dropwise to a solution of the indole **5** (1.0 g, 3.7 mmol) in chloroform (20 mL). After completion of the addition, the solution was heated to reflux under a nitrogen atmosphere overnight. The solution was allowed to cool to room temperature, then water was added, the organic layer extracted with dichloromethane, dried and concentrated. The residue was recrystallised from dichloromethane/light petroleum to give compound **16**, as an orange solid (1.0 g, 66%), mp 186–187 °C. (Found: C, 55.3; H, 3.9; N, 3.4. $C_{19}H_{16}NO_3Cl_3$ requires C, 55.3; H, 3.9; N, 3.4%). ν_{max}: 3445, 3410, 1640, 1590, 1570, 1560, 1490, 1450, 1410, 1390, 1355, 1320, 1250, 1220, 1200, 1170, 1140 cm^{-1}. λ_{max}: 226 nm (ε 30,100 cm^{-1} M^{-1}), 264 (26,200), 345 (12,700). ^1H NMR spectrum ($CDCl_3$): δ 2.35 (3H, s, Me), 3.83, 3.96 (6H, 2s, OMe), 6.16 (1H, s, H5), 7.27–7.39 (5H, m, ArH), 10.05 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 11.9 (Me), 55.3, 55.5 (OMe), 87.3 (C5), 98.6 (CCl_3), 125.8, 127.2, 130.8 (ArCH), 98.2, 112.2, 114.8, 130.4, 135.2, 138.3, 159.4, 160.7 (ArC), 182.3 (CO). Mass spectrum (EI): *m/z* 415 (M+2, 5), 413 (M, 10), 411 (10), 294 (100).

4.3.11. 3-(4-Bromophenyl)-4,6-dimethoxy-2-methyl-7-trichloroacetylindole (17). Trichloroacetyl chloride (0.4 mL, 3.6 mmol) was added dropwise to a solution of the indole **6** (0.25 g, 0.7 mmol) in chloroform (10 mL), then the solution was heated to reflux under a nitrogen atmosphere overnight, allowed to cool to room temperature, then water was added, the organic layer was extracted with dichloromethane, and concentrated. The residue was chromatographed (dichloromethane) to give compound **17** (0.30 g, 85%) as an orange solid, mp 181–182 °C. (Found: C, 46.7; H, 3.1; N, 2.9. $C_{19}H_{15}BrCl_3NO_3$ requires C, 46.4; H, 3.1; N, 2.8%). ν_{max}: 3407, 1629, 1585, 1560, 1468, 1355, 1247, 993 cm^{-1}. λ_{max}: 237 nm (ε 28,900 cm^{-1} M^{-1}), 347 (7,150). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.33 (3H, s, Me), 3.83, 3.96 (6H, s, OMe), 6.16 (1H, s, H5), 7.24, 7.49 (4H, 2d, J=8.3 Hz, ArH), 10.04 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.8 (Me), 55.2, 55.5 (OMe), 87.4 (C5), 98.5 (CCl_3), 130.3, 132.3 (ArCH), 98.3, 111.9, 113.6, 119.8, 130.4, 134.2, 138.3, 159.5, 160.5 (ArC), 182.3 (CO). Mass spectrum (EI): *m/z* 493 (M+2, 28%), 491 (M, 41), 374 (100), 372 (95), 220 (24).

4.3.12. Ethyl 2-(3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl)glyoxylate (18). Indole **6** (1.50 g, 4.33 mmol) was dissolved in anhydrous dichloromethane (37.5 mL) and the solution cooled to 0 °C. Oxalyl chloride (0.5 mL, 5.2 mmol) was then added rapidly and the solution was allowed to stir for 15 min at this temperature. The solution was then warmed to room temperature and excess ethanol was added. The mixture was refluxed for 1 h, the solvent was then evaporated off, water was added and extracted with dichloromethane. The organic layer was washed with water, dried and concentrated to afford the ester **18** (1.72 g, 89%) as a yellow solid, mp 231–232 °C. (Found: C, 56.7; H, 4.4; N, 3.2. $C_{21}H_{20}BrNO_5$ requires C, 56.5; H, 4.5; N, 3.1%). ν_{max}: 3338, 1735, 1583, 1468, 1210, 1131, 1072, 794 cm^{-1}. λ_{max}: 234 nm (ε 27,350 cm^{-1} M^{-1}), 259 (27,300), 336 (15,400). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.41 (3H, t, J=7.2 Hz, Me), 2.33 (3H, s, Me), 3.82, 3.91 (6H, 2s, OMe), 4.40 (2H, q, J=7.2 Hz, OCH_2), 6.12 (1H, s, H5), 7.24, 7.48 (4H, 2d, J=8.3 Hz, ArH), 10.29 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 14.1 (Me), 55.3, 56.8 (OMe), 61.3 (OCH_2), 87.3 (C5), 130.3, 132.3 (ArCH), 100.5, 111.9, 113.2, 119.8, 130.9, 134.2, 137.0, 161.1, 161.2 (ArC), 166.0, 185.1 (CO). Mass spectrum (EI): *m/z* 448 (M+2, ^{81}Br, 10%), 447 (43), 446 (M, ^{79}Br, 10), 445 (41), 375 (20), 374 (96), 373 (34), 372 (100).

4.3.13. *N*,*N*-Dimethyl-2-(3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl) glyoxylamide (19). Indole **6** (0.80 g, 2.31 mmol) was dissolved in anhydrous dichloromethane (20 mL) and the solution cooled to 0 °C. Oxalyl chloride (0.27 mL, 2.8 mmol) was then added rapidly and the solution was allowed to stir for 15 min at this temperature. The solution was then warmed to room temperature and excess dimethylamine solution (40%) was added. The mixture was stirred for another 1 h, water was added and the mixture extracted with dichloromethane. The organic layer was washed with water, dried and concentrated to afford the amide **19** (0.83 g, 81%) as a yellow solid, mp 249 °C. (Found: C, 56.8; H, 4.7; N, 6.4. $C_{21}H_{21}BrN_2O_4$ requires C, 56.6; H, 4.8; N, 6.3%). ν_{max}: 3354, 1649, 1580, 1451, 1357, 1284, 1228, 1128, 794 cm^{-1}. λ_{max}: 238 nm (Σ 27,700 cm^{-1} M^{-1}), 348 (13,550). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.34 (3H, s, Me), 2.94, 3.07 (6H, 2s, NMe_2), 3.81, 3.91 (6H, 2s, OMe), 6.13 (1H, s, H5), 7.23, 7.48 (4H, 2d, J=8.7 Hz, ArH), 10.45 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.9 (Me), 33.7, 36.6 (NMe_2), 55.3, 57.3 (OMe), 87.5 (C5), 130.3, 132.4 (ArCH), 101.5, 111.9, 113.0, 119.8, 132.4, 134.3, 137.0, 160.7, 161.1 (ArC), 169.2, 190.2 (CO). Mass spectrum (EI): *m/z* 447 (M+2, ^{81}Br, 7%), 446 (34), 445 (M, ^{79}Br, 6), 444 (34), 374 (93), 372 (100).

4.3.14. *N*-Hydroxy-*N*-methyl-[2-(3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl)] glyoxylamide (20). Indole **6** (0.25 g, 0.57 mmol) was dissolved in anhydrous dichloromethane (10 mL) and the solution cooled to 0 °C with an ice bath. Oxalyl chloride (0.06 mL, 0.60 mmol) was then added rapidly and the solution was allowed to stir for 15 min. *N*-methylhydroxylamine hydrochloride (0.25 g, 2.99 mmol) was added, followed by triethylamine (0.4 mL). The mixture was stirred at room temperature for 2 h, water was added and extracted with dichloromethane. The organic layer was acidified with 2 M HCl, washed with water, dried and concentrated to give the hydroxamic acid **20** (0.14 g, 55%) as a yellow solid, mp 242–243 °C (from methanol). (Found: C, 51.9; H, 4.2; N, 6.0. $C_{20}H_{19}BrN_2O_5 \cdot 0.9\ H_2O$ requires C, 51.8; H, 4.5; N, 6.0%). ν_{max}: 3361, 3120, 1646, 1583, 1466, 1368, 1271, 1213, 1121, 985 cm^{-1}. λ_{max}: 234 nm (ε 29,250 cm^{-1} M^{-1}), 348 (12,300). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 2.29 (3H, s, Me), 3.18 (3H, s, NMe), 3.79, 3.88 (6H, 2s, OMe), 6.37 (1H, s, H5), 7.25, 7.51 (4H, 2d, J=8.3 Hz, ArH), 9.94 (1H, s, OH), 11.22 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 12.1 (Me), 35.9 (NMe), 55.9, 57.9 (OMe), 88.8 (C5), 130.4, 133.0 (ArCH), 101.7, 111.5, 112.2, 119.1, 132.4, 135.1, 135.9, 160.1, 161.0 (ArC), 169.3, 189.3 (CO). Mass spectrum (EI): *m/z* 449 (M+2, ^{81}Br, 5%), 448 (24), 447 (M, ^{79}Br, 5), 446 (24), 373 (29), 372 (100).

4.3.15. 2,6-Di-(4,6-dimethoxy-2-methyl-3-phenylindole-7-carbonyl)pyridine (21). To a suspension of aluminium chloride (0.11 g, 0.82 mmol) in anhydrous and ethanol-free chloroform (2 mL) was added pyridine-2,6-dicarbonyl chloride (0.20 g, 0.37 mmol) under an argon atmosphere. The pink mixture was stirred for 2 h, before indole **5** (0.20 g, 0.74 mmol) in chloroform (0.5 mL) was added, and the mixture stirred for another 6 h. Both methanol (5 drops) and water (3 mL) were added and stirring was continued for 30 min. The mixture was extracted with dichloromethane (3×5 mL), dried with magnesium sulfate, and purified by column chromatography on silica gel (dichloromethane/methanol, 98:2) yielding compound **21** (0.34 g, 69%) as a bright yellow powder, mp 260–300 °C (dec). Found: C, 69.8; H, 5.3; N, 5.8. $C_{41}H_{35}N_3O_6\cdot HCl$ requires C, 70.1; H, 5.2; N, 6.0%. ν_{max}: 3383, 3354, 1613, 1586, 1552, 1452, 1368, 1274, 1214, 1160, 990, 702 cm^{-1}. λ_{max}: 232 nm (ε 44,600), 336 (22,700). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.37 (6H, s, Me), 3.53 (6H, s, OMe), 3.77 (6H, s, OMe), 6.07 (2H, m, H5 Ind), 7.33–7.41 (10H, m, Ph), 7.58 (2H, d, *J* 7.9 Hz, Py), 7.93 (1H, t, *J* 7.9 Hz, Py), 10.34 (2H, br s, NH). The compound was too insoluble for measurement of a ^{13}C NMR spectrum. Mass spectrum (EI): *m/z* 1353.6 (100, $[2M+Na]^+$), 666.6 (79, MH^+).

4.3.16. 4,6-Dimethoxy-2-methyl-7-nitro-3-phenylindole (22). To a solution of *N*-acetylindole **3** (2.0 g, 6.5 mmol) in dichloromethane (100 mL) was added concd nitric acid supported on silica gel (2.0 g). The mixture was quickly shaken for 10 s and immediately filtered. The solvent was removed and the residue recrystallised from ethanol to afford 1-acetyl-4,6-dimethoxy-2-methyl-3-phenylindole (0.46 g, 20%) as an orange solid, mp 192–193 °C (from ethanol). ν_{max}: 1720, 1610, 1600, 1585, 1575, 1510, 1435, 1410, 1320, 1260, 1220, 1200, 1180, 1140, 1120 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): δ 2.37 (3H, s, Me), 2.58 (3H, s, COMe), 3.71, 3.98 (6H, 2s, OMe), 6.32 (1H, s, H5), 7.26–7.36 (5H, m, ArH). ^{13}C NMR spectrum ($CDCl_3$): δ 13.3 (Me), 26.7 (CO*Me*), 55.6, 57.7 (OMe), 90.8 (C5) 126.9, 127.4, 130.8 (ArCH), 114.4, 119.1, 127.2, 129.2, 131.3, 134.0, 152.4, 156.7 (ArC), 172.1 (CO). Mass spectrum (EI): *m/z* 354 (M, 10), 312 (100), 236 (20), 220 (25), 192 (20).

The unpurified *N*-acetylindole (0.40 g, 1.1 mmol) was partially dissolved in ethanol (20 mL). An excess of crushed potassium hydroxide was added to the above mixture, which was allowed to stir for 2 h. The resulting precipitate was filtered off to yield the nitro indole **22** (0.32 g, 90%) as a orange solid, mp 229–231 °C (from ethanol). (Found: C, 61.1; H, 4.7; N, 8.3. $C_{17}H_{16}N_2O_4\cdot 0.5\ H_2O$ requires C, 60.9; H, 4.5; N, 8.3%). ν_{max}: 3350, 1610, 1590, 1580, 1560, 1510, 1460, 1440, 1400, 1330, 1285, 1220, 1180, 1120, 980 cm^{-1}. λ_{max}: 220 nm (ε 26,900 $cm^{-1}\,M^{-1}$), 263 (20,000), 362 (8,700). ^1H NMR spectrum ($CDCl_3$): δ 2.37 (3H, s, Me), 3.82, 4.04 (6H, 2s, OMe), 6.19 (1H, s, H5), 7.32–7.39 (5H, m, ArH), 10.05 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 11.9 (Me), 55.5, 57.2 (OMe), 88.2 (C5) 126.1, 127.3, 130.8 (ArCH), 112.5, 115.3, 118.7, 131.1, 132.0, 134.7, 155.9, 159.6 (ArC). Mass spectrum (EI): *m/z* 313 (M+1, 20), 312 (M, 100), 236 (20), 192 (20).

4.3.17. Di-[4,6-dimethoxy-2-methyl-3-phenylindol-7-yl] methane (23). *Method A*. Indole **6** (0.17 g, 0.64 mmol) in glacial acetic acid (5 mL) was warmed at 60 °C and then formaldehyde (40%, 1.5 mL) was added and the mixture stirred overnight. The precipitate was filtered off, washed and dried to give compound **23** (0.13 g, 76%) as a white solid.

Method B. The 7-hydroxymethylindole **9** (0.05 g, 0.17 mmol) in glacial acetic acid (3 mL) and tetrahydrofuran (2 mL) were stirred at room temperature for 30 min. The precipitate was filtered off, washed and dried to produce compound **23** (0.04 g, 79%) as a white solid.

Mp 310 °C (dec). (Found: C, 76.7; H, 6.2; N, 5.1. $C_{35}H_{34}N_2O_4$ requires C, 76.9; H, 6.3; N, 5.1%). ν_{max}: 3338, 1599, 1519, 1435, 1341, 1151, 1115, 1002, 995 cm^{-1}. λ_{max}: 246 nm (Σ 52,250 $cm^{-1}\,M^{-1}$), 310 (17,900). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.38 (6H, s, Me), 3.67, 4.16 (12H, 2s, OMe), 4.28 (2H, s, CH_2), 6.34 (2H, s, H5), 7.22–7.40 (10H, m, ArH), 9.72 (2H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 12.3 (Me), 18.7 (CH_2), 55.6, 57.9 (OMe), 89.9 (C5), 125.1, 126.9, 130.8 (ArCH), 104.4, 112.9, 113.9, 130.2, 136.3, 136.6, 150.6, 152.6 (ArC). Mass spectrum (EI): *m/z* 547 (M, 33%), 280 (72), 268 (100).

4.3.18. Di-[3-(4-bromophenyl)-4,6-dimethoxy-2-methyl-indol-7-yl]methane (24). *Method A*. Indole **6** (0.20 g, 0.58 mmol) in glacial acetic acid (10 mL) was warmed at 60 °C and then formaldehyde (40%, 2 mL) was added and the mixture stirred overnight. The precipitate was filtered off, washed and dried to give compound **24** (0.17 g, 86%) as a white solid.

Method B. The 7-hydroxymethylindole **10** (0.05 g, 0.13 mmol) in glacial acetic acid (2 mL) and tetrahydrofuran (2 mL) were stirred at room temperature for 30 min. The precipitate was filtered off, washed and dried to produce compound **24** (0.03 g, 73%) as a white solid.

Melting point 274 °C (dec). (Found: C, 59.4; H, 4.4; N, 4.0. $C_{35}H_{32}Br_2N_2O_4$ requires C, 59.7; H, 4.6; N, 3.9%). ν_{max}: 3339, 3307, 1625, 1598, 1488, 1460, 1340, 1155, 1119, 999 cm^{-1}. λ_{max}: 244 nm (Σ 52,700 $cm^{-1}\,M^{-1}$). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.35 (6H, s, Me), 3.69, 4.16 (12H, 2s, OMe), 4.25 (2H, s, CH_2), 6.33 (2H, s, H5), 7.23, 7.44 (8H, 2d, $J=8.3$ Hz, ArH), 9.72 (2H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 12.2 (Me), 18.6 (CH_2), 55.4, 57.9 (OMe), 89.7 (C5), 130.1, 132.4 (ArCH), 104.3, 112.6, 112.7, 119.1, 130.3, 135.2, 136.5, 150.7, 152.4 (ArC). Mass spectrum (EI): *m/z* 706 (M+2, ^{81}Br, 20%), 704 (M, ^{79}Br, 35), 360 (88), 358 (100), 346 (60), 345 (68), 330 (23), 251 (59).

4.3.19. 4,6,4′,6′-Tetramethoxy-2,2′-dimethyl-3,3′-diphenyl-7,7′-biindolyl (25). 1,4-Benzoquinone (81 mg, 0.75 mmol) was dissolved in tetrahydrofuran (20 mL), and both concd hydrochloric acid (2 mL) and indole 5 (200 mg, 0.75 mmol) were added. The mixture was stirred vigorously at room temperature for 1 h prior to the addition of water (20 mL) and extraction with dichloromethane (3×20 mL). The combined organic layers were dried with sodium sulfate, the solvent evaporated under reduced pressure and the crude brown residue recrystallised from dichloromethane/light petroleum to yield compound **25** (0.35 g,

88%) as a pale grey powder, mp 220–222 °C. (Found: C, 75.5; H, 6.4; N, 5.2. $C_{34}H_{32}N_2O_4$. $0.5H_2O$ requires: C, 75.4; H, 6.1; N, 5.2%). ν_{max}: 3450, 3167, 2837, 1600, 1511, 1466, 1328, 1212, 1197, 1134, 992, 761 cm^{-1}. λ_{max}: 237 nm (ε 49,300), 290 (19,500). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 2.15 (6H, s, Me), 3.65 (6H, s, OMe), 3.72 (6H, s, OMe), 6.44 (2H, s, H5), 7.15–7.33 (10H, m, Ph), 9.99 (2H, s, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 12.2 (Me), 55.4 (OMe), 56.8 (OMe), 90.0 (C5), 99.4, 111.6, 112.6, 130.8, 137.0, 137.1, 152.9, 153.5 (ArC), 125.1, 127.3, 130.9 (ArCH). Mass spectrum (ES): *m/z* 533.2 (100%, M^+).

4.3.20. 7-7′-Seleno-bis-(4,6-dimethoxy-3-phenylindole)-2,2′-dicarbaldehyde (26). *N*-Acetyl-4,6-dimethoxy-2-methyl-3-phenylindole **3** (1.0 g, 3.2 mmol) was dissolved in dioxane (100 mL) to which selenium dioxide (1.4 g, 12.9 mmol) was added. The mixture was then heated to reflux for 24 h, cooled and filtered. Water was then added to the filtrate and the yellowish precipitate collected and dried. Column chromatography (dichloromethane) yielded the selenide **26** (0.36 g, 35%) as a yellow solid, mp 276–278 °C. (Found: C, 64.2; H, 4.1; N, 4.6. $C_{34}H_{28}N_2O_6Se$ requires C, 63.9; H, 4.4; N, 4.4%). ν_{max}: 3380, 3350, 1645, 1620, 1570, 1540, 1500, 1440, 1340, 1250, 1220, 1210, 1170, 1150 cm^{-1}. λ_{max}: 208 nm (ε 34,400 cm^{-1} M^{-1}), 262 (31,200), 327 (24,800). ^1H NMR spectrum ($CDCl_3$): δ 3.74, 4.26 (12H, 2s, OMe), 6.26 (2H, s, H5), 7.37–7.49 (10H, m, ArH), 9.54 (2H, s, CHO), 10.14 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.3, 57.2 (OMe), 88.4 (C5), 127.4, 127.5, 131.5 (ArCH), 90.9, 111.9, 130.7, 131.5, 132.4, 142.4, 158.6, 160.5 (ArC), 181.7 (CHO). Mass spectrum (EI): *m/z* 641 (M+2, 15), 640 (M+1, 45), 638 (20), 360 (35), 280 (100). This was similarly prepared from the indole **5** in 30% yield.

4.3.21. 7-7′-Seleno-bis-[3-(4-bromophenyl)-4,6-dimethoxyindole]-2,2′-dicarbaldehyde (27). Indole **6** (0.80 g, 2.31 mmol) was dissolved in dioxane (35 mL) to which selenium dioxide (0.66 g, 6.23 mmol) was added. The mixture was then heated to reflux for 9 h and filtered. The filtrate was concentrated and the residue was chromatographed (dichloromethane) to give the selenide **27** (0.17 g, 31%) as a green solid, mp 294 °C (dec). (Found: C, 50.1; H, 3.3; N, 3.3. $C_{34}H_{26}Br_2N_2O_6Se \cdot 0.9\ H_2O$ requires C, 50.2; H, 3.4; N, 3.4%). ν_{max}: 3416, 1639, 1613, 1566, 1527, 1333, 1226, 1215,1139 cm^{-1}. λ_{max}: 229 nm (ε 36,850 cm^{-1} M^{-1}), 265 (55,250), 328 (29,850). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.75, 4.25 (12H, 2s, OMe), 6.26 (2H, s, H5), 7.32, 7.51 (8H, 2d, J=8.4 Hz, ArH), 9.52 (2H, s, CHO), 10.13 (2H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.2, 57.1 (OMe), 88.4 (C5), 130.5, 132.7 (ArCH), 90.9, 111.7, 121.9, 129.1, 131.2, 131.3, 142.3, 158.4, 160.5 (ArC), 181.1 (CO). Mass spectrum (EI): *m/z* 797 (M, ^{81}Br, 10%), 795 (M, ^{79}Br, 7), 438 (50), 362 (100).

4.3.22. 4,6-Dimethoxy-3-phenyl-7-trifluoroacetylindole-2-carbaldehyde (28). 2-Methyl-3-phenyl-4,6-dimethoxy-7-trifluoroacetylindole **14** (0.58 g, 1.6 mmol) was dissolved in dioxane (50 mL) to which selenium dioxide (0.7 g, 6.5 mmol) was added. The mixture was then heated to reflux for 24 h, cooled and filtered. Water was then added to the filtrate and the yellowish precipitate collected and dried. Column chromatography (dichloromethane) yielded the aldehyde **28** (0.36 g, 60%) as a yellow solid, mp 188–190 °C (ethanol). (Found: C, 60.6; H, 3.8; N, 3.9. $C_{19}H_{14}F_3NO_4$ requires C, 60.5; H, 3.7; N, 3.7%). ν_{max}: 3425, 1650, 1620, 1590, 1570, 1540, 1440, 1400, 1340, 1320, 1240, 1210, 1190, 1170, 1130 cm^{-1}. λ_{max}: 208 nm (ε 19,100 cm^{-1} M^{-1}), 249 (27,700), 320 (20,100), 359 (23,600). ^1H NMR spectrum ($CDCl_3$): δ 3.87, 4.02 (6H, 2s, OMe), 6.17 (1H, s, H5), 7.40–7.49 (5H, m, ArH), 9.53 (1H, s, CHO), 10.93 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.8, 56.6 (OMe), 88.2 (C5), 99.6 (CF_3), 27.5, 128.0, 131.1 (ArCH), 112.3, 115.2, 118.8, 130.1, 131.5, 131.8, 139.9, 164.4, 165.3 (ArC), 178.2, 181.2 (CO). Mass spectrum (EI): *m/z* 378 (M+1, 45), 377 (M, 95), 308 (100), 250 (20), 222 (35).

4.3.23. 3-(4-Bromophenyl)-4,6-dimethoxy-7-trifluoroacetylindole-2-carbaldehyde (29). Trifluoroacetylindole **15** (0.15 g, 0.34 mmol) was dissolved in dioxane (15 mL) to which selenium dioxide (0.18 g, 1.7 mmol) was added. The mixture was then heated to reflux for 24 h, cooled and filtered. Water was then added to the filtrate and the precipitate collected and dried. Column chromatography (dichloromethane) yielded the aldehyde **29** (0.13 g, 86%) as a yellow solid, mp 270–271 °C. (Found: C, 49.9; H, 2.7; N, 3.2. $C_{19}H_{13}BrF_3NO_4$ requires C, 50.0; H, 2.9; N, 3.1%). ν_{max}: 3387, 1652, 1581, 1317, 1211, 1158, 1056, 981, 832 cm^{-1}. λ_{max}: 231 nm (ε 22,850 cm^{-1} M^{-1}), 254 (26,700), 348 (9,800), 368 (10,650). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.89, 4.04 (6H, 2s, OMe), 6.19 (1H, s, H5), 7.36, 7.57 (4H, 2d, J=8.3 Hz, ArH), 9.54 (1H, s, CHO), 10.99 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.7, 56.6 (OMe), 88.2 (C5), 99.6 (CF_3), 130.7, 132.6 (ArCH), 112.0, 122.4, 128.5, 130.4, 131.7, 139.8, 164.1, 165.3 (ArC), 180.7 (CO). Mass spectrum (EI): *m/z* 458 (M+2, ^{81}Br, 24%), 457 (90), 456 (M, ^{79}Br, 21), 455 (89), 388 (97), 387 (20), 386 (100).

4.3.24. 4,6-Dimethoxy-3-phenyl-7-trichloroacetylindole-2-carbaldehyde (30). 2-Methyl-3-phenyl-4,6-dimethoxy-7-trichloroacetylindole **16** (0.66 g, 1.6 mmol) was dissolved in dioxane (50 mL) to which selenium dioxide (0.7 g, 6.5 mmol) was added. The mixture was then heated to reflux for 24 h, cooled and filtered. Water was then added to the filtrate and the yellowish precipitate collected and dried. Column chromatography (dichloromethane) yielded the aldehyde **30** (0.41 g, 60%) as a yellow-green solid, mp 200–202 °C. (Found: C, 53.6; H, 3.3; N, 3.5. $C_{19}H_{14}Cl_3NO_4$ requires C, 53.5; H, 3.3; N, 3.3%). ν_{max}: 3440, 1640, 1630, 1590, 1580, 1530, 1450, 1400, 1385, 1350, 1240, 1200 cm^{-1}. λ_{max}: 210 nm (ε 24,100 cm^{-1} M^{-1}), 251 (31,400), 334 (26,300). ^1H NMR spectrum ($CDCl_3$): δ 3.87, 4.02 (6H, 2s, OMe), 6.19 (1H, s, H5), 7.41–7.51 (5H, m, ArH), 9.55 (1H, s, CHO), 10.63 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.6, 55.7 (OMe), 88.1 (C5), 98.5 (CCl_3), 127.5, 127.8, 131.1 (ArCH), 112.5, 130.1, 131.6, 131.7, 140.2, 145.2, 163.2, 163.2 (ArC), 181.3, 182.0 (CO). Mass spectrum (EI): *m/z* 427 (M, 10), 308 (100).

4.3.25. 3-(4-Bromophenyl)-4,6-dimethoxy-7-trichloroacetylindole-2-carbaldehyde (31). Trichloroacetylindole **17** (0.20 g, 0.41 mmol) was dissolved in dioxane (20 mL) to

which selenium dioxide (0.18 g, 1.7 mmol) was added. The mixture was then heated to reflux for 24 h, cooled and filtered. Water was then added to the filtrate and the precipitate collected and dried. Column chromatography (dichloromethane) yielded the aldehyde **31** (0.14 g, 67%) as a pale-yellow solid, mp 234 °C (dec). (Found: C, 44.9; H, 2.2; N, 2.5. $C_{19}H_{13}BrCl_3NO_4$ requires C, 45.1; H, 2.6; N, 2.8%). ν_{max}: 3399, 1652, 1579, 1354, 1238, 1207, 1165, 983 cm^{-1}. λ_{max}: 223 nm (ε 19,600 cm^{-1} M^{-1}), 255 (28,750), 321 (12,450). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.87, 4.02 (6H, 2s, OMe), 6.20 (1H, s, H5), 7.37, 7.57 (4H, 2d, $J=8.3$ Hz, ArH), 9.54 (1H, s, CHO), 10.63 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.6, 55.7 (OMe), 88.3 (C5), 98.4 (CCl_3), 130.7, 132.6 (ArCH), 97.8, 112.3, 122.3, 128.5, 130.6, 131.6, 140.1, 163.0, 163.2 (ArC), 180.7, 182.1 (CO). Mass spectrum (EI): *m/z* 507 (M+2, ^{81}Br, 5%), 505 (M, ^{79}Br, 7), 388 (100), 386 (100).

4.3.26. 2-Formyl-4,6-dimethoxy-3-phenylindole-7-carboxylic acid (32). The mixture of 7-trifluoroacetylindole **28** (2.0 g, 5.3 mmol) and potassium hydroxide (7.5 g, 134 mmol) in ethanol–water (3/1, 400 mL) was heated to reflux for 3 h. After cooling, the mixture was acidified with concd hydrochloric acid to afford the carboxylic acid **32** (1.6 g, 95%) as a white solid, mp 225–226 °C (decarboxylates). (Found: C, 66.3; H, 4.7; N, 4.3. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.6; N, 4.3%). ν_{max}: 3450, 3270, 1700, 1650, 1610, 1590, 1570, 1540, 1520, 1440, 1420, 1340, 1250, 1225, 1200, 1180 cm^{-1}. λ_{max}: 216 nm (ε 19,200 cm^{-1} M^{-1}), 228 (18,800), 248 (20,100), 287 (9,300), 334 (21,200). ^1H NMR spectrum (d_6-DMSO): δ 3.80, 3.97 (6H, 2s, OMe), 6.45 (1H, s, H5), 7.39–7.53 (5H, m, ArH), 9.44 (1H, s, CHO), 10.72 (1H, br s, NH). ^{13}C NMR spectrum (d_6-DMSO): δ 56.1, 57.3 (OMe), 90.3 (C5), 127.8, 131.2, 131.5 (ArCH), 94.8, 135.4, 111.5, 128.0, 129.1, 132.0, 139.9, 160.9, 163.6 (ArC), 167.7, 181.2 (CO). Mass spectrum (EI): *m/z* 326 (M+1, 20%), 325 (M, 95), 307 (100), 306 (55).

4.3.27. 3-(4-Bromophenyl)-2-formyl-4,6-dimethoxyindole-7-carboxylic acid (33). The mixture of indole **29** (0.17 g, 0.37 mmol) and potassium hydroxide (0.51 g, 9.31 mmol) in ethanol–water (3/1, 30 mL) was heated to reflux for 3 h. After cooling, the mixture was acidified with concd hydrochloric acid and the precipitate was filtered off to give the carboxylic acid **33** (0.12 g, 82%) as a yellow solid, mp 232 °C (dec). (Found: C, 53.8; H, 3.4; N, 3.5. $C_{18}H_{14}BrNO_5$ requires C, 53.5; H, 3.5; N, 3.5%). ν_{max}: 3415, 3348, 1702, 1640, 1591, 1469, 1363, 1349, 1233, 1209, 1170, 981 cm^{-1}. λ_{max}: 201 nm (ε 32,000 cm^{-1} M^{-1}), 262 (21,300), 335 (21,000). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 3.83, 3.97 (6H, 2s, OMe), 6.48 (1H, s, H5), 7.48, 7.61 (4H, 2d, $J=8.3$ Hz, ArH), 9.47 (1H, s, CHO), 10.77 (1H, br, NH), 12.48 (1H, br, OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 56.3, 57.3 (OMe), 90.5 (C5), 130.8, 133.5 (ArCH), 94.9, 111.3, 121.7, 127.3, 131.2, 131.3, 139.8, 160.8, 163.6 (ArC), 167.6, 181.3 (CO). Mass spectrum (EI): *m/z* 406 (M+2, ^{81}Br, 7%), 405 (33), 404 (M, ^{79}Br, 7), 403 (34), 387 (65), 386 (31), 361 (94), 359 (100), 265 (48).

4.3.28. 4,6-Dimethoxy-7-nitro-3-phenylindole-2-carbaldehyde (34). 4,6-Dimethoxy-2-methyl-7-nitro-3-phenylindole **22** (100 mg, 0.32 mmol) was dissolved in dioxane (10 mL) to which selenium dioxide (140 mg, 1.3 mmol) was added. The mixture was then heated to reflux for 24 h, cooled and filtered. Water was then added to the filtrate and the yellowish precipitate collected and dried. Column chromatography (dichloromethane) yielded the aldehyde **34** (68 mg, 65%) as a yellow solid, mp 238–240 °C (methanol). (Found: C, 62.3; H, 4.3; N, 8.5. $C_{17}H_{14}N_2O_5$ requires C, 62.6; H, 4.3; N, 8.6%). ν_{max}: 3450, 1650, 1610, 1580, 1560, 1510, 1290, 1130, 1110, 1090 cm^{-1}. λ_{max}: 207 nm (ε 21,000 cm^{-1} M^{-1}), 249 (26,600), 325 (19,500), 366 (16,400). ^1H NMR spectrum ($CDCl_3$): δ 3.87, 4.10 (6H, 2s, OMe), 6.22 (1H, s, H5), 7.43–7.50 (5H, m, ArH), 9.56 (1H, s, CHO), 10.68 (1H, br s, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 55.9, 57.3 (OMe), 88.5 (C5), 127.6, 128.1, 131.0 (ArCH), 112.2, 118.4, 130.3, 131.1, 131.9, 133.9, 159.8, 162.3 (ArC), 181.3 (CO). Mass spectrum (EI): *m/z* 327 (M+1, 20%), 326 (M, 100), 325 (25), 250 (25).

4.3.29. 4,6-Dimethoxy-2-methoxymethyl-7-nitro-3-phenylindole (35). A solution containing the indole **22** (100 mg, 0.32 mmol) in dichloromethane (20 mL) was chilled in an ice bath. To this was added a solution of sulfuryl chloride (43 mg, 0.32 mmol) in dichloromethane (5 mL) slowly over 30 min with stirring. The solvent was then removed under reduced pressure and the residue chromatographed (dichloromethane/methanol 95:5) to produce the methoxymethylindole **35** (46 mg, 42%) as a yellow solid, mp 175–177 °C. (Found: C, 62.0; H, 5.2; N, 8.2. $C_{18}H_{18}N_2O_5 \cdot 0.25\ H_2O$ requires C, 62.3; H, 5.4; N, 8.1%). ν_{max}: 3350, 1610, 1600, 1590, 1570, 1510, 1490, 1440, 1410, 1330, 1300, 1240, 1210, 1190 cm^{-1}. λ_{max}: 224 nm (ε 21,700 cm^{-1} M^{-1}), 257 (19,300), 370 (10,800). ^1H NMR spectrum ($CDCl_3$): δ 3.34, 3.82, 4.05 (9H, 3s, OMe), 4.48 (2H, s, CH_2), 6.21 (1H, s, H5), 7.32–7.48 (5H, m, ArH), 10.30 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 55.5, 57.2, 58.1 (OMe), 65.4 (CH_2), 88.1 (C5) 126.5, 127.3, 130.6 (ArCH), 112.1, 117.4, 127.6, 131.1, 132.4, 133.8, 156.6, 160.2 (ArC). Mass spectrum (EI): *m/z* 343 (M+1, 20%), 342 (M, 100), 326 (40), 311 (50), 292 (25).

4.3.30. Di-(4,6-dimethoxy-3-phenylindol)-7-yl methane-2,2′-dicarbaldehyde (36). This was prepared as described for indole **26** from indole **23** (0.15 g, 0.27 mmol) and selenium dioxide (0.12 g, 1.10 mmol) in dioxane (7.5 mL) under reflux for 4 h to give the dialdehyde **36** (67 mg, 43%) as a white solid, mp 302–304 °C. (Found: C, 73.1; H, 5.3; N, 4.9. $C_{35}H_{30}N_2O_6$ requires C, 73.2; H, 5.3; N, 4.9%). ν_{max}: 3315, 1646, 1618, 1588, 1525, 1446, 1257, 1217, 1157,1120. 991 cm^{-1}. λ_{max}: 229 nm (ε 26,700 cm^{-1} M^{-1}), 266 (56,150), 327 (30,650), 359 (19,900). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.74, 4.34 (12H, 2s, OMe), 4.31 (2H, s, CH_2), 6.35 (2H, s, H5), 7.38–7.51 (10H, m, ArH), 9.55 (2H, s, CHO), 10.55 (2H, br s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 18.1 (CH_2), 55.2, 56.9 (OMe), 88.6 (C5), 127.2, 127.3, 131.3 (ArCH), 102.8, 112.5, 130.1, 131.9, 132.6, 139.2, 155.3, 155.8 (ArC), 181.8 (CO). Mass spectrum (EI): *m/z* 575 (M, 83%), 282 (100), 268 (25).

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Effective synthesis of some indole nitriles from the related carbaldoximes

Tutik Dwi Wahyuningsih, Naresh Kumar, Stephen J. Nugent and David StC. Black*

School of Chemistry, University of New South Wales, UNSW Sydney, NSW 2052, Australia

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Abstract—Four 7-cyano-indoles and one 2-cyano-indole have been synthesized from the related aldoximes, via the intermediate 2,4-dinitrophenyl oxime ethers.

1. Introduction

We have previously shown that the presence of methoxy groups at C4 and C7 in indoles leads to activation at C7 and C2.[1,2] This activation leads readily to carbaldehydes, and we wished to exploit this situation for the generation of indole-7-nitriles in particular. Nitriles are very useful functional groups for their conversion into a range of heterocyclic systems. For example, they can be converted into pyrroles thiazoles, imidazoles, and pyrimidines.[3–6] Examples of indole-7-nitriles have been reported by the reaction of 7-haloindoles with cuprous cyanide in the presence of quinoline, and by the reaction of a 7-indolyloxazoline with phosphoryl chloride.[7–9]

However, there have been many reports of the transformation of aldoximes into the corresponding nitriles.[10–12] In order to synthesise indole-7-nitriles we chose the route via carbaldoxime ether intermediates, which gives high yields of nitriles under mild conditions, and the aldoxime ether intermediates need not necessarily be isolated or purified.[13–18]

2. Results and discussion

2.1. Reactivity of indole-7-aldoximes

Treatment of the 4,6-dimethoxyindole-7-carbaldehydes **1–4** with hydroxylamine hydrochloride and sodium hydroxide gave high yields of the indole-7-aldoximes **5–8**. The structures of the oximes were confirmed by their ^{1}H NMR spectra, which exhibit the characteristic imine resonance at 8.75 ppm in $CDCl_3$ for the respective *anti* isomer.[19]

Treatment of the indole-7-aldoximes **5–8** with sodium ethoxide in absolute ethanol, followed by addition of fluoro-2,4-dinitrobenzene at room temperature yielded the oxime ethers **9–12** in quantitative yield. All of these oxime ethers showed only one isomer, presumed to be the *anti* isomer. This assignment is consistent with ^{1}H NMR evidence showing sharp single peaks at 9.23–9.28 ppm for the resonances of the CH=N protons, and also hydrogen bonding of the indole NH to the oxime N atom. The infrared spectra also showed C=N vibrations in the range of 1592–1603 cm^{-1}, which also correspond to the *anti* isomers.[20] This assignment is also supported by steric reasons as the bulky ether group would probably tend to be away from the NH of the indole ring.

Treatment of indole aldoxime ethers **9–12** with triethylamine in tetrahydrofuran gave almost exclusively the indole-7-nitriles **13–16** (Scheme 1). The reactions were clean and the work-up procedure was relatively simple as all by- products were water-soluble. In addition, the reaction time could be reduced from 6 h to 30 min by the use of a stronger base. For example, treatment of indole **9** with sodium hydride under reflux in dioxan for only 30 min produced the nitrile **13** in 85%. Clear evidence for the indole-7-nitriles was provided by the infrared spectra, which demonstrated the presence of the nitrile frequency in the range 2200–2214 cm^{-1}. The ^{13}C NMR spectra also confirmed the existence of nitrile groups with carbon resonances in the range 116–117 ppm.

Kinetic investigations by Cho[16,17] and Hegarty[18] have proven that the nitrile forming elimination reaction of

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* Corresponding author. Tel.: +61 2 9385 4657; fax: +61 2 9385 6141; e-mail: d.black@unsw.edu.au

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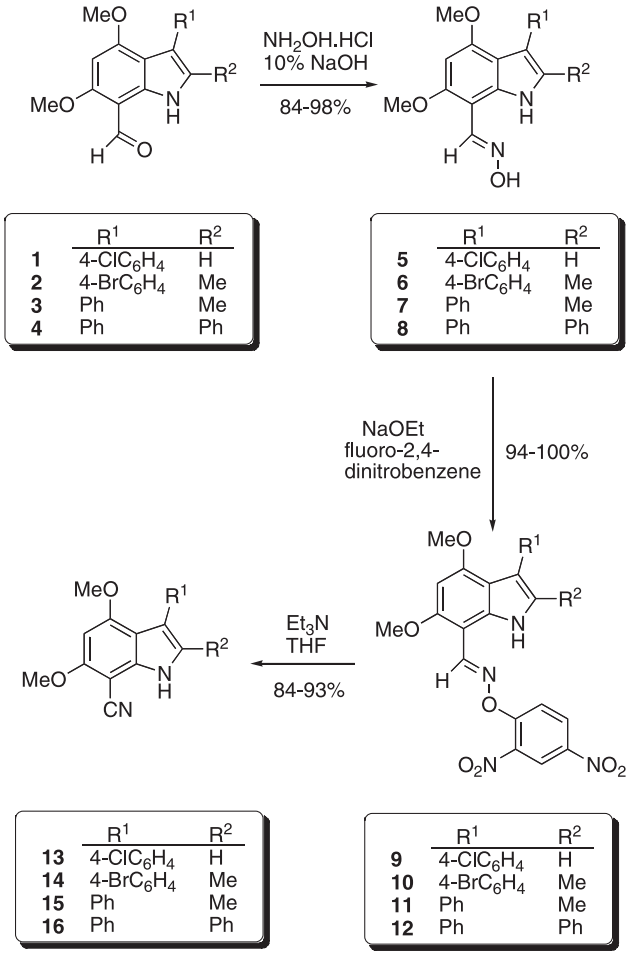


	R^1	R^2
1	4-ClC_6H_4	H
2	4-BrC_6H_4	Me
3	Ph	Me
4	Ph	Ph

	R^1	R^2
5	4-ClC_6H_4	H
6	4-BrC_6H_4	Me
7	Ph	Me
8	Ph	Ph

	R^1	R^2
13	4-ClC_6H_4	H
14	4-BrC_6H_4	Me
15	Ph	Me
16	Ph	Ph

	R^1	R^2
9	4-ClC_6H_4	H
10	4-BrC_6H_4	Me
11	Ph	Me
12	Ph	Ph

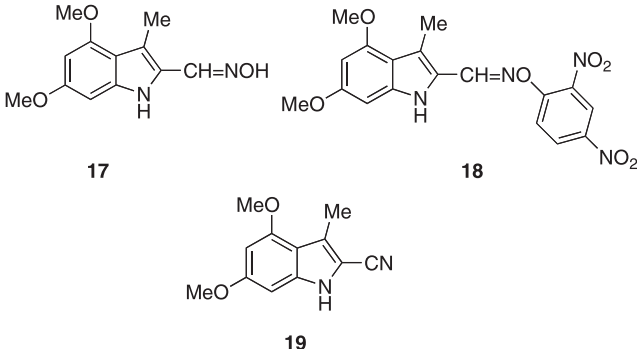
Scheme 1.

anti-aldoxime ethers proceeds via an E2-mechanism, initiated by removal of the acidic proton of the indole aldoxime ether by base.

The two step conversion of aldehydes to nitriles has been performed by Miller[14] utilizing *O*-2,4-dinitrophenylhydroxylamine, while Ho[13] has reported that benzonitrile could be produced directly from the reaction of benzaldoxime in dry acetonitrile with potassium *t*-butoxide and fluoro-2,4-dinitrobenzene. It was decided to shorten the route by reacting the indole-7-aldoxime **8** with fluoro-2,4-dinitrobenzene followed by the addition of base in a one-pot reaction. Lower yields were found when the reaction was carried out with triethylamine as base: however, treatment with sodium hydride produced the indole-7-nitrile **16** in 88%.

2.2. Reactivity of indole-2-aldoximes

It has been reported that treatment of 4,6-dimethoxy-3-methylindole with 1.5 equiv of the Vilsmeier reagent gave the related indole-7- and 2-carbaldehydes in 44 and 46% yield, respectively.[21] The aldoxime **17** was synthesized in 65% by the use of hydroxylamine hydrochloride and sodium acetate in absolute ethanol.[11] It was found that the use of 10% sodium hydroxide gave a higher yield of indole-2-aldoxime: both *syn* and *anti* isomers were indicated by the presence of two imine resonances at 7.46 and 8.10 ppm in the ^{1}H NMR spectrum. Treatment of the aldoxime **17** with fluoro-2,4-dinitrobenzene gave the oxime ether **18**, which was not fully purified but treated directly with sodium hydride under reflux for 30 min to give the indole-2-nitrile **19** in 75% as a colourless solid.



17 **18** **19**

Several indole-2-nitriles have been prepared previously via direct Fischer cyclization of the phenylhydrazone of an acyl cyanide,[22] and by the aldol cyclization of an *N*-cyanomethyl derivative of a 2-aminobenzophenone.[23]

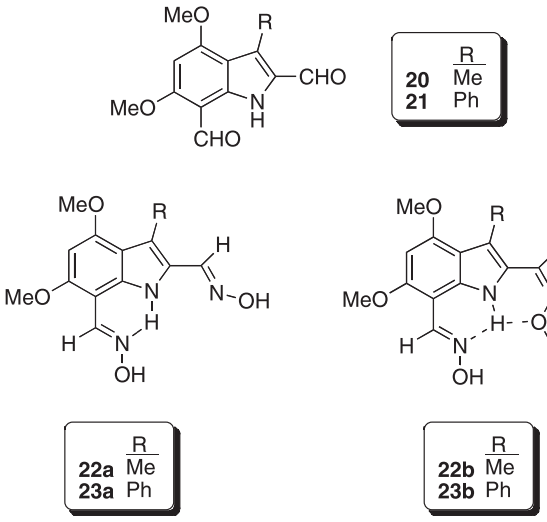
Previous attempts in our laboratory to employ the dehydration of primary amido indoles using phosphoryl chloride[11] led to the formation of indole nitriles contaminated with other products arising from Vilsmeier formylation.

2.3. Reactivity of indole-2,7-dialdoximes

The 2,7-dicarbaldehydes of 3-substituted-4,6-dimethoxyindoles can be readily prepared by reaction with two or more equivalents of Vilsmeier reagent. The indole 2,7-dicarbaldehydes **20**[24] and **21**[21] were treated with hydroxylamine hydrochloride under reflux in ethanol containing sodium hydroxide to give high yields of the indole 2,7-dialdoximes **22** and **23**.

The 2,7-dialdoxime **22** was produced in 73% total yield as a mixture of the *anti*(C7)–*anti*(C2) isomer and the *anti*(C7)–*syn*(C2) isomer in the ratio of 3:1. ^{1}H NMR spectroscopy showed three singlet imine resonance peaks at 7.55, 8.12 and 8.43 ppm indicating the presence of *syn*(C2)- and *anti*(C2 and C7)-isomers, respectively. Furthermore, the indole NH proton for the *anti–anti* isomer **22a** appears at 9.80 ppm showing the effect of hydrogen bonding of the 7-aldoxime on the indole NH, whereas the *anti–syn* isomer **22b** has a downfield resonance at 11.55 ppm consistent with the formation of an additional six-membered ring by hydrogen bonding to the 2-aldoxime.

The 2,7-dialdoxime **23** was produced as a less clearly defined mixture of isomers, the *anti–anti* isomer **23a** and the *anti–syn* isomer **23b**, in 76% yield.



In a variety of attempts to synthesise the related 2,7-dinitriles, the 2,7-dialdoximes **22** and **23** were treated with fluoro-2,4-dinitrobenzene in the presence of sodium, and the unisolated intermediates then treated with sodium hydride and the mixtures refluxed. However, although there were indications of dinitrile formation, pure products could not be separated from complex mixtures.

3. Conclusions

The treatment of 2,4-dinitrophenyl ethers of a range of indole-7- and 2-carbaldoximes with base provides an effective method for the synthesis of indole nitriles. These could serve as useful precursors of biologically interesting tryptamine analogs.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 $60GF_{254}$.

4.1.1. 3-(4-Chlorophenyl)-4,6-dimethoxyindole-7-aldoxime (5). To a solution of 3-(4′-chlorophenyl)-7-formylindole **1**[24] (1.00 g, 3.18 mmol) in 95% ethanol (50 mL), was added hydroxylamine hydrochloride (1.33 g, 19.15 mmol) in water (5.75 mL) and 10% NaOH (5.75 mL). The mixture was heated to reflux for 2 h. After cooling, the solvent was evaporated off under reduced pressure. The residue was dissolved in dichloromethane, washed with water and dried. The solvent was removed and the residue chromatographed (dichloromethane/methanol, 95:5) to yield oxime **5** (0.95 g, 90%) as a cream solid, mp 207–208 °C. (Found: C, 61.9; H, 4.6; N, 8.6. $C_{17}H_{15}ClN_2O_3$ requires C, 61.7; H, 4.6; N, 8.5%). ν_{max}: 3406, 3350, 1622, 1590, 1463, 1344, 1327, 1209, 1110, 1086, 982 cm^{-1}. λ_{max}: 229 nm (ε 23,800 cm^{-1} M^{-1}), 249 (26,200), 310 (13,550). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.87, 3.93 (6H, 2s, OMe), 6.28 (1H, s, H5), 6.91 (1H, s OH), 7.07 (1H, d, J=2.3 Hz, H2), 7.32, 7.52 (4H, 2d, J=8.7 Hz, ArH), 8.74 (1H, s, CH=N) 9.95 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.1, 56.9 (OMe), 88.1 (C5), 121.4 (C2), 127.6, 130.6 (ArCH), 147.3 (C=N), 97.2, 110.2, 117.5, 131.5, 134.3, 135.8, 156.8, 156.9 (ArC). Mass spectrum (EI): m/z 332 (M+2, ^{37}Cl, 33%), 330 (M, ^{35}Cl, 100), 312 (22), 297 (20), 269 (12), 262 (54), 247 (15).

4.1.2. 3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindole-7-aldoxime (6)

This was prepared as described for the indole aldoxime **5** from indole-7-carbaldehyde **2**[25] (0.22 g, 0.59 mmol) in 95% ethanol (12 mL), hydroxylamine hydrochloride (0.25 g, 3.60 mmol) in water (1.25 mL) and 10% NaOH (1.25 mL). After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to yield oxime **6** (0.21 g, 93%) as a white solid, mp 213–214 °C. (Found: C, 55.6; H 4.3; N 7.3. $C_{18}H_{17}BrN_2O_3$ requires C, 55.5; H, 4.4; N, 7.2%). ν_{max}: 3522, 3350, 1623, 1596, 1352, 1254, 1160, 997 cm^{-1}. λ_{max}: 229 nm (Σ 26,000 cm^{-1} M^{-1}), 253 (24,450), 328 (14,450). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.34 (3H, s, Me), 3.77, 3.90 (6H, 2s, OMe), 6.22 (1H, s, H5), 7.02 (1H, br, OH), 7.28, 7.49 (4H, 2d, J=8.7 Hz, ArH), 8.75 (1H, s, CH=N), 9.68 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 12.0 (Me), 55.1, 56.9 (OMe), 88.0 (C5), 130.2, 132.5 (ArCH), 147.5 (C=N), 96.8, 111.5, 112.7, 119.5, 130.3, 134.1, 134.8, 156.0, 156.2 (ArC). Mass spectrum (EI): m/z 391 (M+2, ^{81}Br, 20%), 390 (100), 389 (M, ^{79}Br, 20), 388 (97), 372 (40), 357 (35), 276 (36), 261 (41).

4.1.3. 4,6-Dimethoxy-2-methyl-3-phenylindole-7-aldoxime (7). This was prepared as described for the indole-7-aldoxime **5** from indole-7-carbaldehyde **3**[25] (0.30 g, 1.02 mmol) in 95% ethanol (15 mL), hydroxylamine hydrochloride (0.43 g, 6.19 mmol) in water (1.7 mL) and 10% NaOH (1.7 mL). After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to give oxime **7** (0.26 g, 84%) as a white solid, mp 207–208 °C. (Found: C, 69.6; H, 5.8; N, 9.1. $C_{18}H_{18}N_2O_3$ requires C, 69.7; H, 5.8; N, 9.0%). ν_{max}: 3473, 3366, 1624, 1597, 1462, 1354, 1253, 1216, 1161, 1117, 993 cm^{-1}. λ_{max}: 250 nm (Σ 25,150 cm^{-1} M^{-1}), 328 (14,600). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.37 (3H, s, Me), 3.76, 3.91 (6H, 2s, OMe), 6.21 (1H, s, H5), 7.28–7.41 (6H, m, ArH, OH), 8.76 (1H, s, CH=N), 9.71 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 12.1 (Me), 55.2, 56.9 (OMe), 88.1 (C5), 125.5, 127.1, 130.8 (ArCH), 147.5 (C=N), 96.7, 111.8, 113.9, 130.2, 134.1, 135.8, 156.1, 156.2 (ArC). Mass

spectrum (EI): *m/z* 310 (M, 100%), 292 (19), 278 (31), 277 (49), 262 (24), 249 (12), 234 (18).

4.1.4. 4,6-Dimethoxy-2,3-diphenylindole-7-aldoxime (8). This was prepared as described for the indole-7-aldoxime **5** from 4,6-dimethoxy-2,3-diphenylindole-7-carbaldehyde **4**[26] (1.00 g, 2.80 mmol) in 95% ethanol (50 mL), hydroxylamine hydrochloride (1.31 g, 18.86 mmol) in water (5.6 mL) and 10% NaOH (5.6 mL). After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to yield oxime **8** (1.03 g, 98%) as a white solid, mp 224 °C. (Found: C, 73.8; H, 5.4; N, 7.4. $C_{23}H_{20}N_2O_3 \cdot 0.1\ H_2O$ requires C, 73.8; H, 5.4; N, 7.5%). ν_{max}: 3508, 3401, 1622, 1597, 1463, 1359, 1249, 1217, 1156, 1119, 993 cm^{-1}. λ_{max}: 252 nm (Σ 24,550 $cm^{-1}\,M^{-1}$), 277 (24,700). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.75, 3.93 (6H, 2s, OMe), 6.24 (1H, s, H5), 6.92 (1H, s OH), 7.23–7.38 (10H, m, ArH), 8.77 (1H, s, CH=N), 10.01 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.7, 57.3 (OMe), 89.5 (C5), 126.6, 127.6, 127.7, 127.8, 128.9, 131.4 (ArCH), 144.7 (C=N), 97.4, 112.7, 114.5, 132.3, 132.6, 134.5, 135.9, 156.3, 156.6 (ArC). Mass spectrum (ES): *m/z* 372 (M, ^{35}Cl, 100%).

4.1.5. 3-(4-Chlorophenyl)-4,6-dimethoxy-7-(2,4-dinitrophenoxyiminomethyl)indole (9). The indole-7-aldoxime **5** (0.80 g, 2.42 mmol) was dissolved in absolute ethanol (20 mL) and sodium (0.10 g, 4.35 mmol) was added. The solution became clear and was stirred at room temperature for 30 min, fluoro-2,4-dinitrobenzene (0.35 mL, 2.86 mmol) was then added dropwise. The mixture was stirred for another 2 h and the resulting precipitate was filtered off, washed with absolute ethanol and dried to yield oxime ether **9** (1.06 g, 94%) as a dark-red solid, mp 188–190 °C, which could not be fully purified. ν_{max}: 3454, 1592, 1530, 1468, 1342, 1324, 1267, 1211, 1088 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.92, 3.99 (6H, 2s, OMe), 6.29 (1H, s, H5), 7.16 (1H, d, J=2.3 Hz, H2), 7.35, 7.51 (4H, 2d, J=8.7 Hz, ArH), 7.90 (1H, d, J=9.0 Hz, ArH), 8.49 (1H, dd, J=9.0, 2.6 Hz, ArH), 8.90 (1H, d, J=2.6 Hz, ArH), 9.26 (CH=N), 9.58 (1H, br, OH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 312 (100%), 297 (40), 282 (14), 269 (31), 262 (66).

4.1.6. 3-(4-Bromophenyl)-4,6-dimethoxy-7-(2,4-dinitrophenoxyiminomethyl)-2-methylindole (10). This was prepared as described for the indole oxime ether **9** from indole aldoxime **6** (0.20 g, 0.5 mmol) in absolute ethanol (10 mL) with sodium (10 mg, 0.43 mmol) and fluoro-2,4-dinitrobenzene (0.06 mL, 0.5 mmol). The resulting precipitate was filtered off, washed with absolute ethanol and dried to yield oxime ether **10** (0.27 g, 96%) as an orange solid, mp 180 °C (dec). (Found: C, 51.8; H, 3.3; N, 10.1. $C_{24}H_{19}BrN_4O_7$ requires C, 51.9; H, 3.4; N, 10.1%). ν_{max}: 3428, 1603, 1594, 1526, 1338, 1254, 1165, 991 cm^{-1}. λ_{max}: 234 nm (Σ 35,600 $cm^{-1}\,M^{-1}$), 348 (20,650). ^1H NMR spectrum (300 MHz, d_6-acetone): δ 2.39 (3H, s, CH_3), 3.87, 4.02 (6H, 2s, OMe), 6.54 (1H, s, H5), 7.36, 7.54 (4H, d, J=8.3 Hz, ArH), 8.21 (1H, d, J=9.0 Hz, ArH), 8.56 (1H, dd, J=9.0, 2.6 Hz, ArH), 8.85 (1H, d, J=2.6 Hz, ArH), 9.18 (1H, s, CH=N), 10.07 (1H, br, OH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 373 (21%), 372 (100), 370 (98), 357 (45), 314 (15), 276 (91), 261 (56).

4.1.7. 4,6-Dimethoxy-2-methyl-7-(2,4-dinitrophenoxyiminomethyl)-3-phenylindole (11). This was prepared as described for the indole oxime ether **9** from indole aldoxime **7** (0.15 g, 0.48 mmol) in absolute ethanol (7.5 mL) with sodium (11 mg, 0.48 mmol) and fluoro-2,4-dinitrobenzene (0.06 mL, 0.50 mmol). The resulting precipitate was filtered off, washed with absolute ethanol and dried to yield oxime ether **11** (0.23 g, 100%) as an orange solid, mp 168 °C. (Found: C, 60.3; H, 4.0; N, 11.6. $C_{24}H_{20}N_4O_7$ requires C, 60.5; H, 4.2; N, 11.8%). ν_{max}: 3431, 1600, 1588, 1529, 1465, 1340, 1251, 1164, 1120, 992 cm^{-1}. λ_{max}: 236 nm (Σ 34,100 $cm^{-1}\,M^{-1}$), 348 (19,850). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.42 (3H, s, Me), 3.81, 3.96 (6H, 2s, OMe), 6.23 (1H, s, H5), 7.38–7.41 (5H, m, ArH), 7.86 (1H, d, J=9.4 Hz, ArH), 8.49 (1H, dd, J=6.4, 2.6 Hz, ArH), 8.89 (1H, d, J=2.6 Hz, ArH), 9.24 (1H, s, CH=N), 9.26 (1H, br, NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 476 (M, 6%), 293 (49), 292 (100), 277 (88), 262 (33), 249 (27), 234 (27).

4.1.8. 2,3-Diphenyl-4,6-dimethoxy-7-(2,4-dinitrophenoxyiminomethyl)indole (12). This was prepared as described for the indole oxime ether **9** from indole aldoxime **8** (0.60 g, 1.6 mmol) in absolute ethanol (30 mL) with sodium (0.06 g, 2.61 mmol) and fluoro-2,4-dinitrobenzene (0.2 mL, 1.7 mmol). The resulting precipitate was filtered off, washed with absolute ethanol and dried to yield oxime ether **12** (0.87 g, 100%) as an orange solid, mp 198 °C (dec). (Found: C, 64.6; H, 4.0; N, 10.3. $C_{29}H_{22}N_4O_7$ requires C, 64.7; H, 4.1; N, 10.4%). ν_{max}: 3437, 1598, 1586, 1532, 1464, 1338, 1267, 1258, 1217, 1166, 988 cm^{-1}. λ_{max}: 231 nm (Σ 32,300 $cm^{-1}\,M^{-1}$), 286 (30,350), 334 (28,000). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.80, 3.99 (6H, 2s, OMe), 6.25 (1H, s, H5), 7.32–7.38 (10H, m, ArH), 7.87 (1H, d, J=9.0 Hz, ArH), 8.45 (1H, dd, J=9.0, 2.6 Hz, ArH), 8.91 (1H, d, J=2.6 Hz, ArH), 9.28 (1H, s, CH=N), 9.68 (1H, br, NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 355 (64%), 354 (100), 339 (77), 324 (22), 323 (10), 308 (17), 296 (21).

4.1.9. 3-(4-Chlorophenyl)-4,6-dimethoxyindole-7-nitrile (13). The mixture of indole **9** (0.10 g, 0.20 mmol) and triethylamine (0.5 mL) in tetrahydrofuran (10 mL) was heated under reflux for 6 h and then allowed to cool to room temperature. The solvent was then evaporated off, the residue was dissolved in dichloromethane and the mixture was basified using NaOH (2 M). The organic layer was washed with water and dried. The solvent was evaporated off to give nitrile **13** (56 mg, 89%) as a cream solid, mp 264 °C. (Found: C, 65.1; H, 4.2; N, 9.1. $C_{17}H_{13}ClN_2O_2$ requires C, 65.3; H, 4.2; N, 9.0%). ν_{max}: 3269, 2 214, 1618, 1585, 1464, 1346, 1225, 1109, 978 cm^{-1}. λ_{max}: 241 nm (ε 38,300 $cm^{-1}\,M^{-1}$), 291 (15,150). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 3.87, 3.96 (6H, 2s, OMe), 6.48 (1H, s, H5), 7.27 (1H, d, J=1.9 Hz, H2), 7.35, 7.50 (4H, 2d, J=8.7 Hz, ArH), 11.83 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 56.0, 57.1 (OMe), 88.6 (C5), 117.3 (CN), 123.9 (C2), 127.9, 131.1 (ArCH), 76.0, 110.1, 115.9, 130.8, 134.4, 138.3, 158.9, 161.4 (ArC). Mass spectrum

(EI): *m/z* 314 (M+2, ^{37}Cl, 30%), 312 (M, ^{35}Cl, 100), 297 (15), 262 (37), 254 (15).

4.1.10. 3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindole-7-nitrile (14). This was prepared as described for the indole nitrile **13** from the indole oxime ether **10** (0.13 g, 0.23 mmol) and triethylamine (0.7 mL) in tetrahydrofuran (10 mL). After extraction, the solvent was evaporated off to give nitrile **14** (0.08 g, 93%) as a cream solid, mp 304–306 °C. (Found: C, 57.5; H, 3.9; N, 7.6. 0.3 $C_{18}H_{15}BrN_2O_2 \cdot 0.3\ H_2O$ requires C, 57.4; H, 4.2; N, 7.4%). ν_{max}: 3281, 2214, 1620, 1597, 1569, 1465, 1349, 1220, 1159, 1125, 990 cm^{-1}. λ_{max}: 244 nm (ε 32,800 cm^{-1} M^{-1}), 294 (14,200). ^{1}H NMR spectrum (300 MHz, d_6-DMSO): δ 2.24 (3H, s, Me), 3.77, 3.93 (6H, 2s, OMe), 6.41 (1H, s, H5), 7.24, 7.49 (4H, 2d, J= 8.3 Hz, ArH), 11.62 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 11.9 (Me), 55.9, 57.1 (OMe), 88.4 (C5), 116.2 (CN), 130.4, 132.9 (ArCH), 116.2 (CN), 75.5, 111.2, 112.6, 119.2, 132.6, 134.8, 136.9, 158.0, 160.5 (ArC). Mass spectrum (EI): *m/z* 372 (M+2, ^{81}Br, 95), 370 (M, ^{79}Br, 100), 357 (53), 355 (47), 327 (16), 312 (18), 276 (90), 261 (67).

4.1.11. 4,6-Dimethoxy-2-methyl-3-phenylindole-7-nitrile (15). This was prepared as described for the indole nitrile **13** from the indole oxime ether **11** (0.50 g, 1.05 mmol) and triethylamine (2.5 mL) in tetrahydrofuran (40 mL). After extraction, the solvent was evaporated off to give nitrile **15** (0.26 g, 84%) as a white solid, mp 207–208 °C. (Found: C, 73.1; H, 5.4; N, 9.4. $C_{18}H_{16}N_2O_2 \cdot 0.2\ H_2O$ requires C, 73.1; H, 5.5; N, 9.5%). ν_{max}: 3290, 2210, 1600, 1520, 1465, 1350, 1220, 1160, 1130, 990 cm^{-1}. λ_{max}: 248 nm (ε 33,350 cm^{-1} M^{-1}), 313 (13,450). ^{1}H NMR spectrum (300 MHz, d_6-DMSO): δ 2.24 (3H, s, Me), 3.75, 3.93 (6H, 2s, OMe), 6.4 (1H, s, H5), 7.21–7.33 (5H, m, ArH), 11.54 (1H, s, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 12.0 (Me), 55.8, 57.0 (OMe), 88.3 (C5), 125.9, 127.5, 130.9 (ArCH), 116.3 (CN), 75.4, 88.3, 111.5, 113.9, 132.2, 135.4, 136.9, 158.1, 160.4 (ArC). Mass spectrum (EI): *m/z* 292 (M, 100%), 277 (56), 262 (20), 234 (16).

4.1.12. 4,6-Dimethoxy-2-,3-diphenylindole-7-nitrile (16). *Method A*. This was prepared as described for the indole nitrile **13** from the indole oxime ether **12** (0.80 g, 1.48 mmol) and triethylamine (4 mL) in tetrahydrofuran (60 mL). After extraction, the solvent was evaporated off to give nitrile **16** (0.53 g, 91%) as a cream solid, mp 240–241 °C. (lit.[14] 240–242 °C). ^{1}H NMR spectrum (300 MHz, d_6-DMSO): δ 3.72, 3.96 (6H, 2s, OMe), 6.44 (1H, s, H5), 7.19–7.29 (10H, m, ArH), 11.83 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 56.0, 57.1 (OMe), 88.7 (C5), 115.9 (CN), 126.6, 127.6, 127.7, 128.3, 129.2, 131.5 (ArCH), 75.9, 112.7, 114.9, 131.9, 134.4, 135.6, 137.5, 159.0, 161.6 (ArC).

Method B. The indole aldoxime **8** (0.15 g, 0.40 mmol) was dissolved in absolute ethanol (7.5 mL) and sodium (17 mg, 0.78 mmol) was added. The solution became clear and stirred at room temperature for 10 min, fluoro-2,4-dinitrobenzene (0.35 mL, 2.86 mmol) was then added dropwise. The mixture was stirred for another 15 min, sodium hydride (53 mg (80% dispersion in oil), 1.77 mmol) was added and the mixture was heated at reflux for 1 h. The solvent was then evaporated off, the residue dissolved in dichloromethane and the organic layer washed with water and dried. The solvent was evaporated off to give nitrile **16** (0.13 g, 88%).

4.1.13. 4,6-Dimethoxy-3-methylindole-2-aldoxime (17). This was prepared as described for the indole aldoxime **5** from 4,6-dimethoxy-3-methylindole-2-carbaldehyde[26] (0.15 g, 0.32 mmol) in 95% ethanol (10 mL), hydroxylamine hydrochloride (0.30 g, 4.32 mmol) in water (0.9 mL) and 10% NaOH (0.9 mL). After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to yield oxime **17** (0.14 g, 88%) as a light yellow solid, mp 72–74 °C. (lit.[9] 72–75 °C). ^{1}H NMR spectrum (300 MHz, d_6-DMSO): δ 2.35, 2.42 (6H, 2s, *syn* and *anti* Me), 3.71, 3.77, 3.79 (6H, 3s, *syn* and *anti* OMe), 6.05–6.07 (1H, m, *syn* and *anti* H5), 6.38, 6.63 (1H, d, J= 1.9 Hz, *syn* and *anti* H7), 7.45, 8.09 (1H, 2s, *syn* and *anti* CH=N), 10.67, 10.77, 10.79, 11.36 (2H, 4s, *syn* and *anti* NH, *syn* and *anti* OH).

4.1.14. 4,6-Dimethoxy-3-methylindole-2-nitrile (19). This was prepared using Method B as described for the indole nitrile **16** from the indole oxime **17** (0.14 g, 0.59 mmol) in absolute ethanol (10 mL) with sodium (20 mg, 0.87 mmol), fluoro-2,4-dinitrobenzene (0.1 mL, 0.57 mmol) and sodium hydride (0.14 g (80% dispersion in oil), 4.67 mmol). After extraction and concentration, the residue was chromatographed (dichloromethane) to give nitrile **19** (94 mg, 75%) as a cream solid, mp 192–194 °C. (Found: C, 66.7; H, 5.6; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.6; H, 5.6; N, 12.9%). ν_{max}: 3342, 2207, 1632, 1594, 1526, 1459, 1326, 1258, 1197, 1147, 1068, 795 cm^{-1}. λ_{max}: 240 nm (ε 24,150 cm^{-1} M^{-1}), 294 (17,900). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.56 (3H, s, Me), 3.82, 3.87 (6H, 2s, OMe), 6.15 (1H, d, J=1.9 Hz, H5), 6.32 (1H, d, J= 1.5 Hz, H7), 8.11 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 11.8 (Me), 55.2, 55.5 (OMe), 85.9 (C5), 92.8 (C7), 114.6 (CN), 101.9, 111.9, 126.7, 139.0, 156.1, 160.9 (ArC). Mass spectrum (EI): *m/z* 218 (M+2, 100%), 216 (M, 4).

4.1.15. 4,6-Dimethoxy-3-methylindole-2-7-dialdoxime (22). This was prepared as described for the indole aldoxime **5** from 4,6-dimethoxy-3-methylindole-2,7-dicarbaldehyde **20**[21] (0.20 g, 0.81 mmol) in ethanol 95% (12 mL), hydroxylamine hydrochloride (0.34 g, 4.90 mmol) in water (2.2 mL) and 10% NaOH (2.2 mL). After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to yield dioxime **22** (0.16 g, 73%) as a cream solid, mp 190 °C (dec). (Found: C, 53.4; H, 5.4; N, 13.7. $C_{13}H_{15}N_3O_4 \cdot 0.25\ CH_2Cl_2$ requires C, 53.3; H, 5.2; N, 14.1%). ν_{max}: 3408, 1612, 1597, 1519, 1464, 1364, 1250, 1208, 1139, 992 cm^{-1}. λ_{max}: 235 nm (ε 14,850 cm^{-1} M^{-1}), 332 (11,300). ^{1}H NMR spectrum (300 MHz, d_6-DMSO): δ 2.38, 2.42 (3H, 2s, *syn* and *anti* Me), 3.88–3.92 (6H, 3s, *syn* and *anti* OMe), 6.35, 6.38 (1H, 2s, H_5), 8.18, 8.44 (2H, 2s, *syn* and *anti* CH=N), 9.80, 11.55 (1H, 2s, *syn* and *anti* NH). 10.89, 10.93, 10.97 (2H, 3s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 10.6, 10.9 (*syn* and *anti* Me), 56.0, 57.1, 57.2 (*syn* and *anti* OMe), 88.6 (*syn* and *anti* C5), 135.9, 139.3, 144.8 (*syn* and

anti CH=N), 97.0, 113.1, 114.2, 115.3, 124.9, 126.0, 131.9, 134.2, 135.2, 157.3, 157.3, 157.4 (*syn* and *anti* ArC). Mass spectrum (EI): *m*/*z* 279 (M+2, 100%), 261 (16), 245 (11).

4.1.16. 4,6-Dimethoxy-3-phenylindole-2-7-dialdoxime (23). This was prepared as described for the indole aldoxime **5** from 4,6-dimethoxy-3-phenylindole-2,7-dicarbaldehyde **21** (0.50 g, 1.62 mmol) in 95% ethanol (30 mL), hydroxylamine hydrochloride (0.67 g, 9.72 mmol) in water (4.3 mL) and 10% NaOH (4.3 mL). After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to yield dioxime **23** (0.42 g, 76%) as pale brown solid, mp 230–232 °C. (Found: C, 56.0; H, 4.5; N, 10.8. $C_{18}H_{17}N_3O_4 \cdot 0.7\ CH_2Cl_2$ requires C, 56.3; H, 4.6; N, 10.5%). ν_{max}: 3388, 1627, 1594, 1519, 1466, 1360, 1257, 1213, 1139, 993 cm^{-1}. λ_{max}: 231 nm (ε 20,600 $cm^{-1}\,M^{-1}$), 259 (20,650), 338 (14,950). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 3.74–3.90 (6H, 2s, OMe), 6.42 (1H, s, H5), 7.31–7.38 (5H, m, ArH), 7.79, 8.5 (2H, 2s, CH=N), 10.23 (1H, s, NH). 11.10, 11.18 (2H, 2s, OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 55.8, 57.2 (OMe), 89.4 (C5), 127.1, 127.8, 131.1 (ArC), 139.6, 144.9 (CH=N), 97.1, 111.4, 120.1, 126.6, 133.7, 135.1, 156.8, 157.5 (ArC). Mass spectrum (EI): *m*/*z* 339 (M, 58%), 321 (16), 304 (25), 303 (18), 289 (18), 288 (13), 260 (16), 245 (12), 84 (100).

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Gas-phase thermolysis of 1-acylnaphtho[1,8-*de*][1,2,3]triazines. Interesting direct routes towards condensed naphtho[1,8-*de*] heterocyclic ring systems

Hanan Al-Awadi, Maher R. Ibrahim, Hicham H. Dib, Nouria A. Al-Awadi and Yehia A. Ibrahim*

Chemistry Department, Faculty of Science, Kuwait University, PO Box 5969, Safat 13060, Kuwait

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Abstract—FVP pyrolysis of 1-acylnaphtho[1,8-*de*][1,2,3]triazines at 500 °C and 10^{-2} Torr gave exclusively the corresponding 2-substituted naphtho[1,8-*de*][1,3]oxazines. The latter was also obtained by static pyrolysis but in lower yield along with the corresponding *N*-(naphthalen-1-yl)acylamides. The reaction was studied kinetically and mechanistically.

1. Introduction

In a previous publication[1] we reviewed the flash vacuum pyrolysis (FVP) of cinnolines, 1,2,3-benzotriazines and 1,2,4-benzotriazines, which have been shown to give direct and easy access to many interesting compounds, some of which are otherwise difficult to obtain. The primary step in the pyrolysis of these compounds involves mainly N_2 elimination, yielding the corresponding diradical intermediates. On the other hand, pyrolysis of thieno[3,2-*e*][1,2,4]triazines has been shown to follow in part the same initial step ($-N_2$), in addition to another important pathway leading to N–N cleavage followed by several rearrangements and/or fragmentation leading finally to interesting heterocyclic systems.[1]

In continuation of our recent interest in the pyrolytic behaviour of the above mentioned ring systems, we describe in the present work the pyrolytic behaviour of naphtho[1,8-*de*][1,2,3]triazine derivatives. Little attention has been directed towards such interesting chemistry. Thus, pyrolysis of 1-arylnaphtho[1,8-*de*][1,2,3]triazines **1** has been shown to give the corresponding 7*H*-benzo[*kl*]acridine derivatives **2**.[2] The 8-nitro derivative of **2** has been prepared in a very low yield from the corresponding triazine **1** (Ar=*o*-nitrophenyl) by heating with a large excess of $(EtO)_3P$ along with other products.[3] These two reactions resemble very much the pyrolytic behaviour of the substituted benzotriazoles **3**, which have been extensively used for the preparation of many interesting heterocyclic systems **4**.[4,5] Thus, derivatives of indole,[4,6] carbazole,[7] isomeric pyridoindoles,[7d,8] pyrido[1,2-*a*]benzimidazole,[8] benzimdazo[1,2-*a*]pyrimidine,[9] benzimdazo[1,2-*a*]pyridazine,[9] benzimidazo[2,1-*a*]isoquinoline,[10] benzimidazo[1,2-*b*]cinnoline,[4] benzimidazo[2,1-*b*]benzothiazole,[11] phenanthridine,[12] benzoxazole,[10,13] and quinolines[14] as well as other heterocyclic systems became readily available. Similarity of the pyrolytic behaviour of benzotriazole and naphtho[1,8-*de*][1,2,3]triazine derivatives lies in the fact that they both undergo elimination of N_2 followed by intramolecular cyclization with the appropriate substituent (Scheme 1). Thus, it is expected that pyrolysis of the appropriately substituted naphtho[1,8-*de*][1,2,3]triazine derivatives would open an important synthetic route to many condensed heterocyclic systems, condensed on the *peri* positions of the naphthalene ring. Some diradicals were generated from 1-alkylnaphtho[1,8-*de*][1,2,3]triazine derivatives and 1-acetylnaphtho[1,8-*de*][1,2,3]triazine by photolysis.[15] However, no intramolecular cyclization of these photolytically generated diradicals could be proved.[15]

In order to study the potential application of naphtho[1,8-*de*][1,2,3]triazine in pyrolytic synthesis we describe in the present work, the pyrolytic reactions of 1-acylnaphtho[1,8-*de*][1,2,3]triazines **6** together with kinetic and suggested mechanism for this pyrolytic reaction in comparison with the analogous benzotriazole derivatives.

Keywords: FVP; Naphtho[1,8-*de*][1,2,3]triazines; Naphtho[1,8-*de*][1,3]oxazines; Heterocycles.
* Corresponding author. Tel.: +965 9464215; fax: +965 4836127; e-mail: yehiaai@kuc01.kuniv.edu.kw

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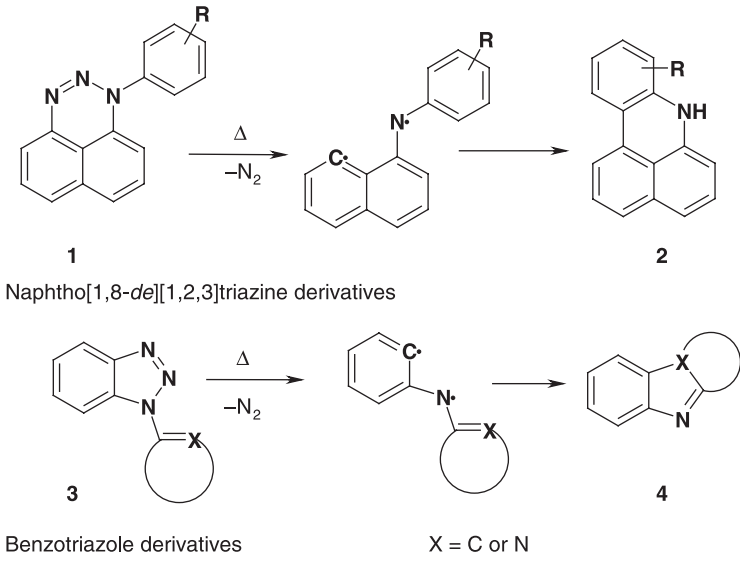


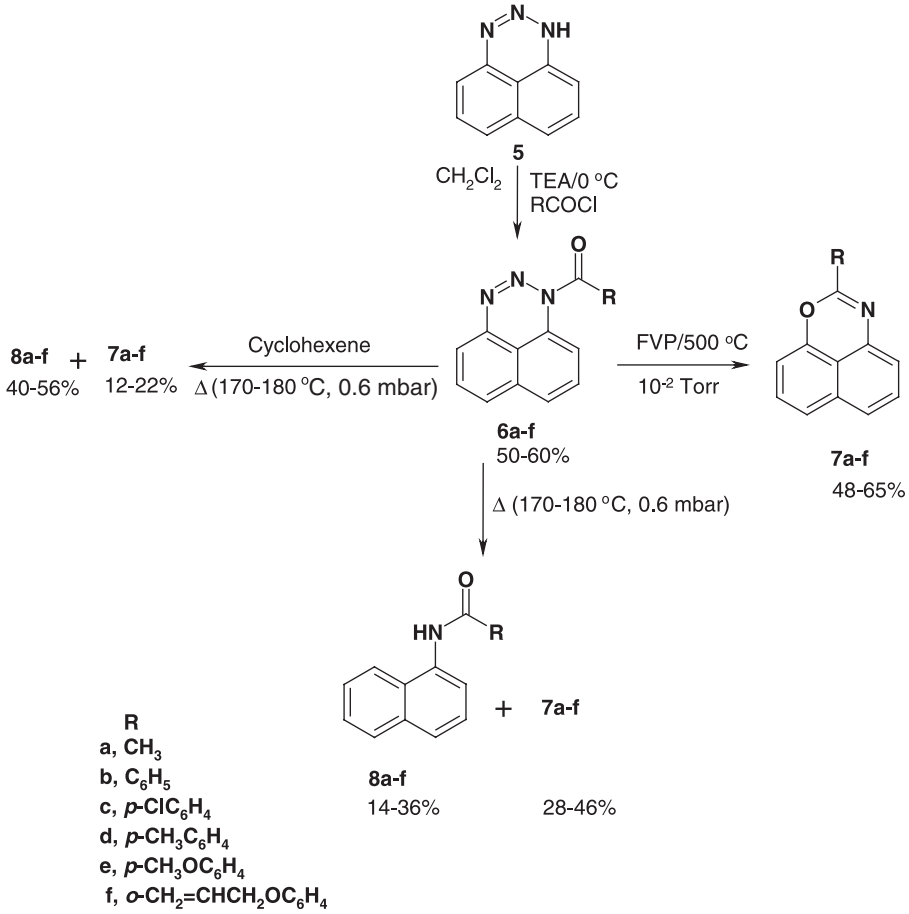
Scheme 1.

2. Results and discussion

2.1. Pyrolysate composition and reaction pathway

Literature shows that only the 1-acetyl derivative **6a** has been prepared in 32% yield by reacting **5** with NaH in dry ether followed by heating at reflux with acetyl chloride.[15] In the present investigation, we have been able to prepare the acyl derivatives **6a–f** (50–60% yields) upon treatment **5** in CH_2Cl_2 and triethylamine at 0 °C with the appropriate acid chloride. This acylation reaction has been found to give a lot of tarry materials and other minor by-products (Scheme 2).

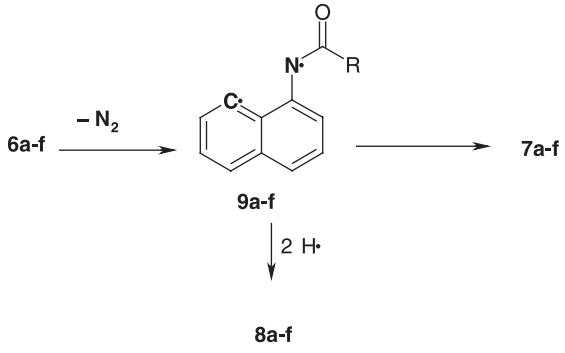
FVP of each of **6a–f** at 500 °C and 0.02 Torr gave the corresponding pure 2-substituted naphtho[1,8-de][1,3]-oxazines **7a–f** in 48–65% yields. On the other hand, gas



Scheme 2.

Table 1. Pyrolysis products of 1-acylnaphtho[1,8-*de*][1,2,3]triazines **6a–d**

Substrate	Pyrolysis products (% yields)	
6a	**7a**	**8a**
FVP	63	0
Static	28	14
Static (cyclohexene)	19	43
6b	**7b**	**8b**
FVP	56	0
Static	40	28
Static (cyclohexene)	12	52
6c	**7c**	**8c**
FVP	65	0
Static	43	29
Static (cyclohexene)	19	54
6d	**7d**	**8d**
FVP	61	0
Static	46	36
Static (cyclohexene)	18	56
6e	**7e**	**8e**
FVP	59	0
Static	39	15
Static (cyclohexene)	22	41
6f	**7f**	**8f**
FVP	48	0
Static	38	17
Static (cyclohexene)	14	40



Scheme 3.

phase pyrolysis of **6a–f** at 170–180 °C and 0.06 mbar gave a mixture of **7a–f** and *N*-(naphthalen-1-yl)acylamides **8a–f** in the percentage yields indicated in Table 1.

The pyrolysates were qualitatively and quantitatively determined by HPLC (Table 1) and by ^{1}H NMR spectroscopy.

Scheme 3 illustrates possible mechanistic routes explaining the formation of the products **7**, **8** obtained in the present pyrolytic study. The reaction starts by extrusion of N_2 to give the diradicals **9a–f**, which then undergo intramolecular cyclization to give the corresponding oxazines **7a–f**. The latter are the only observed product from FVP of **6a–f**. In the present study, attempts to investigate the possible intramolecular cycloaddition of the diradical **9** on C=C by using the *o*-allyloxybenzoyl derivative **6f** did not succeed, and we only obtained the normal reaction observed with the other derivatives **6a–e**. The formation of the acylamide derivatives **8** can be achieved by addition of hydrogen to the diradicals **9**, and this process seems to be appreciable in the static pyrolysis due to the longer reaction times and also as a result of charring of some of the materials, resulting in the availability of hydrogen in the reaction medium. This assumption was substantiated by the fact that repeating all static pyrolysis reaction in the presence of cyclohexene (good hydrogen source)[1] led to an increase in the percent yields of the corresponding derivatives **8**, and a decrease of the corresponding oxazines **7** as shown in Table 1.

2.2. Kinetic data and comparative molecular reactivity

The rates of gas-phase thermolysis of the 1-aroylnaphthotriazines **6b**,**c** and **6e**, were measured over the temperature range 347–428 K with an average range of 55 K per substrate, in order to ensure reliable activation parameters for the first-order gas-phase elimination process of these compounds.[16] The kinetic data is given in Table 2. Each rate constant recorded is an average from at least three independent evaluations of the rate at each reaction temperature, and are in agreement to within ±2% rate spread. The Arrhenius parameters were obtained from strictly linear correlations over >85% reaction. The Arrhenius parameters and rate constants (k/s^{-1}) calculated at 450 K for substrates **6b**,**c** and **6e** are summarized in Table 2. The rate data of related 1-acylbenzotriazoles has been reported in an earlier publication and are tabulated in Table 3.[17] The reaction mechanism (Scheme 3) and the kinetic data allow the following conclusions and structure/reactivity correlations to be made:

Table 2. Rate coeffecients (k/s^{-1}), Arrhenius parameters of 1-acylnaphtho[1,8-*de*][1,2,3]triazines **6b**,**c**,**e**

Compound	*T*/K	10^4 k/s^{-1}	log *A*/s^{-1}	E_a/kJ mol^{-1}	$k_{450\ K}/s^{-1}$
6b	389.25	0.966	7.727±0.69	88.767±5.48	3.508×10^{-3}
	409.25	3.343			
	418.85	4.885			
	428.85	13.01			
	448.55	32.95			
6c	374.15	0.458	8.164±0.28	90.779±2.21	5.641×10^{-3}
	383.85	0.883			
	403.45	3.127			
	413.25	7.564			
	433.15	21.07			
	443.35	40.72			
6e	374.25	0.597	9.143±0.33	96.972±2.50	1.046×10^{-3}
	393.85	2.565			
	413.45	11.70			
	423.40	20.18			

Table 3. k_{rel} of 1-acylnaphtho[1,8-*de*][1,2,3]triazines compared to the corresponding 1-acylbenzotriazoles (ArCOBT)

Ar	(**6b**,**c**,**e**) $k_{N450\ K}/s^{-1}$	ArCOBT $k_{BT450\ K}/s^{-1}$	$K_{rel}=k_N/k_{BT}$
C_6H_5	3.508×10^{-3}	2.543×10^{-3}	1.38
p-ClC_6H_5	5.641×10^{-3}	2.753×10^{-3}	1.94
p-$H_3COC_6H_5$	1.046×10^{-3}	8.243×10^{-4}	4.66

- The aroylbenzotriazoles are less reactive than aroylnapthotriazines. This structural effect could be rathionalized in terms of resonance stabilization extended by conjugation in naphthotriazine more than it does in benzotriazole.
- We have noted earlier[4] that the effect of substituents not conjugated to the benzotriazole radical centre of the benzotriazole biradical intermediate are moderate and that electron-withdrawing groups tend to increase the molecular reactivity of BT compounds while electron-donating groups have an opposite effect. This is also the case with the naphthotriazine substrates **6a–e** under study as evidenced by their rates of pyrolysis (Table 2).

3. Conclusions

The present study offers interesting routes towards many condensed heterocyclic systems condensed on the *peri* positions of the naphthalene ring, of which many derivatives exhibit interesting photo-emission properties. Of the compounds synthesized in the present work some interesting studies on the fluorescence spectra of a series of 1-aminonaphthalene derivatives,[18a] and naphtho[1,8-*de*][1,3]oxazine derivates were reported.[18b]

4. Experimental

All melting points are uncorrected. IR spectra were recorded in KBr disks using Perkin Elmer System 2000 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer. LCMS were measured using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on LECO CHNS-932 Elemental Analyzer.

4.1. Pyrolysis of 6a–f: general procedures

(A) Static pyrolysis of **6a–f**

Each substrate (0.2 g) was introduced in the reaction tube (1.5×12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and placed in the pyrolyser for 15 min at 170–180 °C, a temperature that is required for complete pyrolysis of the substrate as indicated by a preliminary HPLC study. The products were separated by column chromatography using Merck Al-silica gel $60F_{254}$, with EtOAc–petroleum ether (40/60) (1–10% of EtOAc) to give successively **7** followed by **8**.

(B) Static pyrolysis of **6a–f** *with cyclohexene*

Each substrate (0.2 g) and cyclohexene (0.1 g) were introduced in the reaction tube (1.5×12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and placed in the pyrolyser for 15 min at 170–180 °C. The products were separated by column chromatography using Merck Al-silica gel $60F_{254}$, with EtOAC–petroleum ether (40/60) (1–10% of EtOAc) to give successively **7** followed by **8**.

(C) Flash vacuum pyrolysis of **6a–d**

The apparatus used was similar to the one, which has been described in our recent publications.[1,7] The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30×2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to a temperature of 500 °C, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the centre of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≅10 ms. The different zones of the products collected in the U-shaped trap were analyzed by ^1H, ^{13}C NMR, IR and GC–MS. Relative and percent yields were determined from ^1H NMR.

4.2. Pyrolysis products

4.2.1. Naphtho[1,8-*de*][1,3]oxazine 7.

4.2.1.1. 2-Methylnaphtho[1,8-*de*][1,3]oxazine 7a. Colourless crystals from petroleum ether (40–60), mp 68–70 °C (lit.[19] mp 68 °C). LCMS *m*/*z*=184 (M+1). ^1H NMR ($CDCl_3$): δ 7.40 (d, 1H, *J*=8.4 Hz), 7.33 (m, 2H), 7.28 (d, 1H, *J*=8.0 Hz), 6.93 (d, 1H, *J*=7.0 Hz), 6.69 (d, 1H, *J*=7.8 Hz), 2.27 (s, 3H, CH_3).

4.2.1.2. 2-Phenylnaphtho[1,8-*de*][1,3]oxazine 7b. Colourless crystals from ethanol, mp 135–136 °C (lit.[20] mp 134 °C). LCMS *m*/*z*=246 (M+1). IR: 3053, 1638, 1597, 1373, 1315, 1253, 1092, 822, 764, 693. ^1H NMR ($CDCl_3$): δ 8.24 (d, 2H, *J*=7.8 Hz), 7.52 (m, 3H), 7.43 (t, 1H, *J*=8.0 Hz), 7.33 (m, 3H), 7.10 (dd, 1H, *J*=7.8, 1.2 Hz), 6.86 (dd, 1H, *J*=7.8, 1.2 Hz). ^{13}C NMR ($CDCl_3$): δ 155.3 (C), 149.9 (C), 137.9 (C), 134.3 (C), 131.8 (CH), 131.2 (C), 128.8 (CH), 128.4 (2CH), 127.8 (2CH), 122.6 (CH), 123.2 (CH), 120.9 (CH), 119.0 (C), 117.2 (CH), 106.2 (CH). Anal. Calcd for $C_{17}H_{11}NO$ (245.3): C 83.25; H 5.52; N 5.71. Found: C 83.20; H 4.95; N 5.62.

4.2.1.3. 2-(4-Chlorophenyl)naphtho[1,8-*de*][1,3]oxazine 7c. Pale yellow crystals from ethanol, mp 140–142 °C. LCMS *m*/*z*=280 (M+1), 282 (M+3). IR: 3060, 1638, 1590, 1487, 1374, 1252, 1091, 1015, 823, 768, 724.

^{1}H NMR ($CDCl_3$): δ 8.17 (dd, 2H, J=8.4, 1.7 Hz), 7.48 (dd, 2H, J=8.4, 1.7 Hz), 7.44 (d, 1H, J=8 Hz) 7.38 (m, 2H), 7.34 (t, 1H, J=8 Hz), 7.08 (dd, 1H, J=7.6, 1.0 Hz), 6.83 (dd, 1H, J=7.3, 1.0 Hz). ^{13}C NMR ($CDCl_3$): δ 154.4 (C), 149.7 (C), 138.1 (C), 137.6 (C), 134.3 (C), 129.7 (C), 129.1 (2CH), 128.8 (CH), 128.7 (2CH), 127.8 (CH), 123.5 (CH), 121.0 (CH), 118.9 (C), 117.3 (CH), 106.1 (CH). Anal. Calcd for $C_{17}H_{10}ClNO$ (279.7): C 73.00; H 3.60; N, 5.01. Found: C 73.02; H 3.55; N 5.00.

4.2.1.4. 2-(4-Methylphenyl)naphtho[1,8-*de*][1,3]oxazine 7d. Yellow crystals from ethanol, mp 158–160 °C. LCMS m/z=260 (M+1). IR: 3061, 2961, 2923, 2853, 1638, 1594, 1449, 1376, 1251, 1089, 816, 760. ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 2H, J=8.2 Hz), 7.34 (m, 4H), 7.32 (d, 2H, J=8.1 Hz), 7.08 (dd, 1H, J=7.0, 1.0 Hz), 6.84 (dd, 1H, J=7.0, 1.0 Hz), 2.46 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 153.8 (C), 148.3 (C), 140.8 (C), 136.4 (C), 132.7 (C), 127.5 (2CH), 127.1 (CH), 126.8 (C), 126.1 (2CH), 126.0 (CH), 121.4 (CH), 119.2 (CH), 117.4 (C), 115.3 (CH), 104.4 (CH), 20.0 (CH_3). Anal. Calcd for $C_{18}H_{13}NO$ (259.3): C 83.38; H 5.05; N 5.40. Found: C 83.30; H 4.95; N 5.42.

4.2.1.5. 2-(4-Methoxyphenyl)naphtho[1,8-*de*][1,3]oxazine 7e. Yellow crystals from ethanol, mp 142–143 °C. LCMS m/z=276 (M+1). IR: 3060, 1638, 1594, 1499, 1376, 1251, 1089, 816, 760. ^{1}H NMR ($CDCl_3$): δ 8.19 (d, 2H, J=8.8 Hz), 7.42–7.30 (m, 4H), 7.08 (d, 1H, J=6.8 Hz), 7.01 (d, 2H, J=8.8 Hz), 6.83 (dd, 1H, J=7.0, 1.0 Hz), 3.91 (s, 3H). Anal. Calcd for $C_{18}H_{13}NO_2$ (275.3): C 78.53; H 4.72; N 5.09. Found: C 78.50; H 4.55; N 4.92.

4.2.1.6. 2-(2-Allyloxyphenyl)naphtho[1,8-*de*][1,3]oxazine 7f. Colourless crystals from ethanol, mp 98–100 °C. LCMS m/z=302 (M+1). IR: 3060, 2910, 2863, 1691, 1598, 1486, 1450, 1372, 1315, 977, 857, 765. ^{1}H NMR ($CDCl_3$): δ 8.34 (dd, 1H, J=6.8, 1.8 Hz), 7.66 (dd, 1H, J=7.6, 1.4 Hz), 7.53–7.42 (m, 6H), 7.09 (t, 1H, J=8.0 Hz), 6.95 (d, 1H, J=8.4 Hz), 5.90 (m, 1H), 5.29 (dd, 1H, J=17.2, 1.4 Hz), 5.09 (dd, 1H, J=10.4, 1.4 Hz), 4.61 (d, 2H, J=4.8 Hz). ^{13}C NMR ($CDCl_3$): δ 171.4 (C), 155.4 (C), 134.2 (C), 132.7 (C), 132.6 (*CH*=CH_2), 131.7 (CH), 129.0 (CH), 128.9 (C), 128.8 (CH), 128.5 (CH), 127.7 (CH), 126.2 (C), 122.4 (CH), 121.5 (CH), 120.8 (CH), 117.1 (=CH_2), 116.5 (C), 112.2 (CH), 109.9 (CH), 69.4 (CH_2). Anal. Calcd for $C_{20}H_{15}NO_2$ (301): C 79.73; H 4.98; N 4.6. Found: C 79.70; H 4.95; N 4.62.

4.2.2. *N*-[Naphthalen-1-yl]acylamides 8.

4.2.2.1. *N*-[Naphthalen-1-yl]acetamide 8a. Colourless crystals from petroleum ether (40–60), mp 157–158 °C (lit.[21a,b] mp 159–160 °C). LCMS m/z=186 (M+1). ^{1}H NMR (DMSO-d_6): δ 10.01 (br, 1H, NH), 8.00 (m, 2H), 7.74 (d, 1H, J=8 Hz), 7.68 (d, 1H, J=8 Hz, 7.52 (m, 2H), 7.46 (t, 1H, J=8 Hz), 2.17 (s, 3H, CH_3).

4.2.2.2. *N*-(Naphthalen-1-yl)benzamide 8b. Colourless crystals from ethanol, mp 167–168 °C (lit.[22] mp 164–165 °C). LCMS m/z=248 (M+1). ^{1}H NMR ($CDCl_3$): δ 8.22 (br, 1H, NH), 8.10 (d, 1H, J=7 Hz), 8.03 (d, 2H, J=7.2 Hz), 7.94 (m, 2H), 7.78 (d, 1H, J=8.2 Hz), 7.63 (t, 1H, J=7.2 Hz) 7.58 (m, 5H).

4.2.2.3. 4-Chloro-*N*-(naphthalen-1-yl)benzamide 8c. Colourless crystals from petroleum ether (80–100), mp 208–210 °C. LCMS m/z=282 (M+1), 284 (M+3). IR (KBr): 3193 (br), 3047, 1641, 1596, 1483, 1310, 1090, 845, 803, 771, 677. ^{1}H NMR (DMSO): δ 10.54 (br, 1H, NH), 8.11 (d, 2H, J=8.2 Hz), 7.96 (m, 2H), 7.88 (d, 1H, J=7.7 Hz), 7.65 (d, 2H, J=8.1 Hz), 7.57 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 166.3 (CO), 137.6 (C), 134.8 (C), 134.6 (C), 134.2 (C), 130.8 (2CH), 130.2 (C), 129.6 (2CH), 129.1 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.6 (CH), 125.0 (CH), 124.3 (CH). Anal. Calcd for $C_{17}H_{12}ClNO$ (281.7): C 72.47; H 4.29; N 4.97. Found: C 72.40; H 4.21; N 4.86.

4.2.2.4. 4-Methyl-*N*-(naphthalen-1-yl)benzamide 8d. Colourless crystals from ethanol, mp 170–172 °C (lit.[23] mp 171–173 °C). LCMS m/z=262 (M+1). ^{1}H NMR ($CDCl_3$): δ 8.22 (br s, 1H, NH), 8.06 (d, 1H, J=8.0 Hz), 7.91 (m, 4H), 7.77 (d, 1H, J=8.2 Hz), 7.56 (m, 3H), 7.36 (d, 2H, J=8.0 Hz), 2.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 164.6 (C=O), 140.9 (C), 132.5 (C), 130.8 (C), 130.3 (C), 127.9 (2CH), 127.2 (CH), 125.8 (C), 125.6 (2CH), 124.8 (CH), 124.4 (CH), 124.3 (CH), 124.2 (CH), 119.5 (CH), 119.0 (CH), 19.9 (CH_3). Anal. Calcd for $C_{18}H_{15}NO$ (361.3): C 82.73; H 5.79; N 5.36. Found: C 82.59; H 5.77; N 5.44.

4.2.2.5. 4-Methoxy-*N*-(naphthalen-1-yl)benzamide 8e. Colourless crystals from ethanol, mp 205–206 °C (lit.[24] mp 203–205 °C). LCMS m/z=278 (M+1). ^{1}H NMR ($CDCl_3$): δ 8.17 (br, 1H, NH), 8.04 (d, 1H, J=7.8 Hz), 7.98 (d, 2H, J=8.6 Hz), 7.92 (t, 2H, J=7.4 Hz), 7.76 (d, 1H, J=8.2 Hz), 7.55 (m, 3H), 7.03 (d, 2H, J=8.6 Hz), 3.92 (s, 3H, OCH_3).

4.2.2.6. 2-Allyloxy-*N*-(naphthalen-1-yl)benzamide 8f. Colorless crystals from MeOH/H_2O, mp 102–104 °C. LCMS=304 (M+1). IR (KBr): 3356, 3051, 1660, 1598, 1544, 1501, 1483, 1403, 1342, 1297, 1220, 994, 934, 746, 630. ^{1}H NMR ($CDCl_3$): δ 10.44 (br s, 1H, NH), 8.43 (dd, 1H, J=7.8, 1.4 Hz), 8.39 (d, 1H, J=7.6 Hz), 8.04 (d, 1H, J=8.8 Hz), 7.92 (d, 1H, J=6.4 Hz), 7.72 (d 1H, J=8.2 Hz), 7.58–7.52 (m, 4H), 7.21 (t, 1H, J=7.6 Hz), 7.12 (d, 1H, J=8.3 Hz), 6.25 (m, 1H), 5.58 (d, 1H, J=17.2 Hz), 5.46 (d, 1H, J=10.3 Hz), 4.89 (d, 2H, J=5.8 Hz). ^{13}C NMR ($CDCl_3$): δ 163.6 (C), 156.5 (C), 134.1 (C), 133.3 (CH), 132.9 (CH), 131.9 (CH), 128.8 (CH), 126.6 (C), 126.2 (CH), 125.9 (CH), 125.8 (C, CH), 124.9 (CH), 122.3 (C), 122.1 (CH), 121.0 (CH), 120.5 (=CH_2, Dept), 119.8 (CH), 112.7 (CH), 70.6 (CH_2). Anal. Calcd for $C_{20}H_{17}NO_2$ (303.3): C 79.19; H 5.65; N 4.62. Found: C 79.10; H 5.59; N 4.53.

4.2.3. Naphtho[1,8-*de*][1,2,3]triazine 5. To a cold (0 °C) solution of 1,8-diaminonaphthalene (1.58 g, 10 mmol) in aqueous acetic acid (50%, 30 mL) was added portionwise with stirring solid sodium nitrite (0.8 g, 11 mmol). Stirring was then continued for 5 h at 0 °C. The dark brown precipitate was collected and washed with water and then recrystallized from EtOH/H_2O to give reddish brown powder, yield 1.0 g (60%), mp 244–246 °C (dec.) (lit.[25] mp 230 °C, decomp.) LCMS m/z=170 (M+1). IR: 3500–2500 (br), 1642, 1593, 1464, 1356, 1333, 1281, 1184, 1158, 1121, 1086, 887, 815, 758. ^{1}H NMR (DMSO-d_6): δ 13.29 (s,

1H, NH), 7.26 (m, 2H), 7.13 (t, 1H, $J=8.0$ Hz), 7.03 (d, 1H, $J=8.4$ Hz), 6.89 (d, 1H, $J=8.2$ Hz), 6.13 (d, 1H, $J=7.2$ Hz). ^{13}C NMR (DMSO): δ 139.4 (C), 133.9 (C), 133.3 (C), 129.6 (CH), 129.4 (CH), 123.9 (CH), 118.7 (C), 118.6 (CH), 114.4 (CH), 99.0 (CH).

4.3. 1-Acylnaphtho[1,8-*de*][1,2,3]triazines 6a–f: general procedure

To a stirred cold (0 °C) suspension of **5** (1.69 g, 10 mmol) in dichloromethane (25 mL) was added TEA (1 mL) followed by dropwise addition of the appropriate acid chloride (12 mmol). After complete addition the reaction mixture was kept stirring at 0 °C for 2 h and then at room temperature overnight. After washing with sodium bicarbonate solution (10%, 100 mL) the organic layer was separated and dried with anhydrous sodium sulfate. The solvent was then evaporated in vacuo and the residue was crystallized to give the corresponding products **6a–f**.

4.3.1. 1-Acetylnaphtho[1,8-*de*][1,2,3]triazine 6a. Yield 1.3 g (61%.) Yellow crystals from petroleum ether (80–100), mp 98–100 °C (lit.[15] 97–98). LCMS $m/z=212$ (M+1). IR: 3063, 1707, 1628, 1430,1366, 1296, 1033, 944, 828, 771. ^{1}H NMR ($CDCl_3$): δ 8.22 (dd, 1H, $J=7.6$, 1.0 Hz), 7.63 (d, 1H, $J=8.4$ Hz), 7.54 (d, 1H, $J=7.0$ Hz), 7.48–7.38 (m, 3H), 2.72 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.6 (C=O), 134.3 (C), 132.7 (C), 128.8 (CH), 128.7 (C), 128.6 (CH), 127.7 (CH), 122.3 (CH), 121.6 (CH), 116.5 (C), 110.3 (CH), 24.7 (CH_3). Anal. Calcd for $C_{12}H_9N_3O$ (211.2): C 68.24; H 4.29; N 19.65. Found: C 68.31; H 4.21; N 19.55.

4.3.2. 1-Benzoylnaphtho[1,8-*de*][1,2,3]triazine 6b. Yield 1.6 (60%). Yellow crystals from EtOH/$CHCl_3$, mp 145–147 °C. LCMS $m/z=274$ (M+1). IR: 3058, 1689, 1632, 1578, 1524, 1484, 1446, 1410, 1339, 1307, 1255, 1174, 1037, 976, 858, 825, 764, 703. ^{1}H NMR ($CDCl_3$): δ 8.11 (d, 1H, $J=7.4$ Hz), 7.81 (d, 2H, $J=7.3$ Hz), 7.67 (d, 1H, $J=7.6$ Hz), 7.57 (t, 1H, $J=7.6$ Hz), 7.50–7.43 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 171.9 (C=O), 140.4 (C), 134.5 (C), 134.2 (C), 132.9 (C), 131.8 (CH), 139.9 (2CH), 128.8 (CH), 128.7 (CH), 128.1 (2CH), 127.8 (CH), 122.5 (CH), 121.5 (CH), 116.7 (C), 119.8 (CH). Anal. Calcd for $C_{17}H_{11}N_3O$ (273.3): C 74.71; H 4.06; N 15.38. Found: C 74.61; H 4.21; N 14.05.

4.3.3. 1-(4-Chlorobenzoyl)naphtho[1,8-*de*][1,2,3]triazine 6c. Yield 1.8 g (58%). Yellow crystals from petroleum ether (80–100), mp 150–152 °C. LCMS $m/z=308$ (M+1), 310 (M+3). IR: 3051, 1683, 1641, 1593, 1526, 1482, 1277, 1091, 1013, 846, 814, 756. ^{1}H NMR ($CDCl_3$): δ 8.11 (dd, 1H, $J=7.4$, 1.0 Hz), 7.76 (d, 2H, $J=7.8$ Hz), 7.66 (d, 1H, $J=7.2$ Hz), 7.54–7.43 (m, 6H). Anal. Calcd for $C_{17}H_{10}ClN_3O$ (307.7): C 66.35; H 3.28; N 13.65. Found: C 66.34; H 3.63; N 13.43.

4.3.4. 1-(4-Methylbenzoyl)naphtho[1,8-*de*][1,2,3]triazine 6d. Yield 1.6 g (56%). Yellow crystals EtOH, mp 170–172 °C. LCMS $m/z=288$ (M+1). IR: 3052, 2995, 2839, 1687, 1604, 1511, 1371, 1304, 1259, 1176, 1033, 976, 862, 825, 765. ^{1}H NMR ($CDCl_3$): δ 8.05 (dd, 1H, $J=7.2$, 1.2 Hz), 7.74 (d, 2H, $J=8.0$ Hz), 7.63 (dd, 1H, $J=7.2$, 1.0 Hz), 7.50–7.41 (m, 4H), 7.29 (d, 2H, $J=8$ Hz), 2.46 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 171.8 (C=O), 142.7 (C), 134.3 (C), 132.9 (C), 131.4 (C), 130.2 (2CH), 129.3 (C), 128.8 (2CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 122.3 (CH), 121.3 (CH), 116.8 (C), 109.5 (CH), 21.7 (CH_3). Anal. Calcd for $C_{18}H_{13}N_3O$ (287.3): C 75.25; H 4.56; N 14.62. Found: C 74.98; H 4.49; N 14.60.

4.3.5. 1-(4-Methoxybenzoyl)naphtho[1,8-*de*][1,2,3]triazine 6e. Yield 1.8 g (60%). Yellow crystals from EtOH, mp 158–160 °C. LCMS $m/z=304$ (M+1). IR: 3056, 2839, 1686, 1603, 1510, 1373, 1306, 1259, 1176, 1032, 976, 862, 840, 824, 759. ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, 1H, $J=7.0$, 1.5 Hz), 7.86 (d, 2H, $J=8.8$ Hz), 7.62 (dd, 1H, $J=7.6$, 1.6 Hz), 7.49–7.39 (m, 4H), 6.98 (d, 2H, $J=8.8$ Hz), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.0 (C=O), 162.9 (C), 134.5 (C), 133.0 (C), 132.7 (2CH), 129.4 (C), 128.7 (CH), 128.4 (CH), 127.9 (CH), 126.1 (C), 122.1 (CH), 121.0 (CH), 116.9 (C), 113.4 (2CH), 109.1 (CH), 55.5 (OCH_3). Anal. Calcd for $C_{18}H_{13}N_3O_2$ (303.3): C 71.28; H 4.32; N 13.85. Found: C 71.21; H 4.41; N 13.64.

4.3.6. 1-(2-Allyloxybenzoyl)naphtho[1,8-*de*][1,2,3]triazine 6f. Yield 1.6 g (50%). Yellow oil. LCMS $m/z=330$ (M+1). ^{1}H NMR ($CDCl_3$): δ 7.84 (dd, 1H, $J=7.6$, 1.6 Hz), 7.45 (dd, 1H, $J=8.0$, 1.6 Hz), 7.43 (d, 1H, $J=8.0$ Hz), 7.39–7.30 (m, 3H), 7.06 (t, 2H, $J=8.0$ Hz), 7.02 (d, 1H, $J=7.0$ Hz), 6.75 (d, 1H, $J=6.8$ Hz), 6.09 (m, 1H), 5.55 (dd, 1H, $J=15.6$, 1.4 Hz), 5.30 (dd, 1H, $J=10.8$, 1.4 Hz), 4.68 (m, 2H). Anal. Calcd for $C_{20}H_{15}N_3O_2$ (329): C 72.94; H 4.55; N 12.76. Found: C 72.83; H 4.41; N 12.68.

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Facile one-pot synthesis of BINOL- and H_8-BINOL-based aryl phosphites and their use in palladium catalysed asymmetric allylation

Konstantin N. Gavrilov,[a] Sergey E. Lyubimov,[b,*] Pavel V. Petrovskii,[b] Sergey V. Zheglov,[a] Anton S. Safronov,[a] Roman S. Skazov[b] and Vadim A. Davankov[b]

[a]*Department of Chemistry, Ryazan State Pedagogic University, 46 Svoboda Street, Ryazan 390000, Russia*
[b]*Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov Street, 119991 Moscow, Russia*

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Abstract—Novel *P*-monodentate aryl phosphite ligands have been synthesised in one step from (*R*)-BINOL, (*R*)-H_8-BINOL and (*R*)-H_8-3,3′-dibromo-BINOL. With the new aryl phosphites, up to 86% ee was observed in the asymmetric Pd-catalysed amination of 1,3-diphenyl-2-propenyl acetate with sodium diformylamide. In the enantioselective alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, up to 97% enantioselectivity was achieved.

1. Introduction

Enantiomeric atropoisomers of 1,1′-binaphthyl-2,2′-diol (BINOL), 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diol (H_8-BINOL) and their derivatives have been widely used in both stoichiometric and catalytic asymmetric organic reactions.[1–6] Of special interest are compounds containing two BINOL or H_8-BINOL fragments attached to a metal atom or heteroatom (Fig. 1).

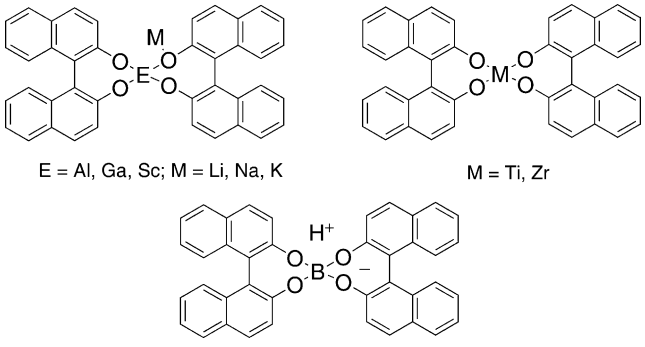

Figure 1. Compounds containing two chiral binaphthyl fragments attached to metal atom or heteroatom.

They proved to be effective stereoselectors in the catalytic asymmetric Michael addition, aza-Diels–Alder and *meso*-epoxide ring opening reactions, synthesis of cyanohydrins, α-hydroxy- and α-aminophosphonates.[1,6] It is also necessary to note that phosphite and phosphoramidite derivatives of BINOL and H_8-BINOL currently represent the most efficient group of P-monodentate ligands for asymmetric metal complex catalysis. They showed excellent results in enantioselective Rh-catalysed hydrogenation, Cu-catalysed addition of organozinc reagents, Ir-catalysed allylic substitution, Pd-catalysed hydrosilylation-oxidation and Ru-catalysed hydrogenation of ketones.[2,3,7–14] Surprisingly, in the literature there are no examples of BINOL- and H_8-BINOL-derived phosphites analogous to the compounds depicted on Figure 1. Previously, we briefly described synthesis and complexation of ligand **1** with rhodium.[15] Developing our project dedicated to application of P-monodentate phosphite and phosphoramidite derivatives of BINOL in the Pd-catalysed asymmetric allylation,[16,17] herein we report synthesis, complexation and catalytic properties of phosphites **1** and **2a**,**b** (Schemes 1 and 2) containing two chiral binaphthyl fragments attached to the phosphorus atom.

2. Results and discussion

The new ligands **1** and **2a**,**b** were readily synthesised from the corresponding binaphthols (Schemes 1 and 2). Notably,

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* Corresponding author. Tel./fax: +7 095 135 6471; e-mail: lssp452@mail.ru

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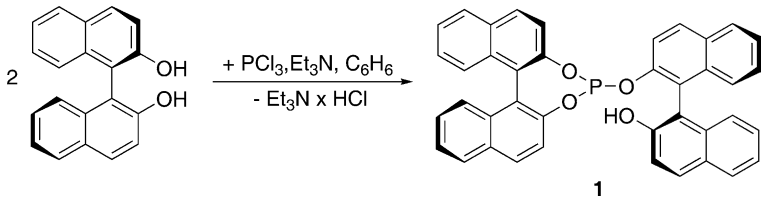
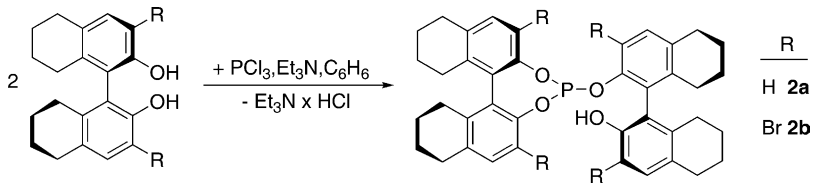


Scheme 1. Synthesis of ligand **1**.



Scheme 2. Synthesis of ligands **2a** and **2b**.

the synthesis does not require obtaining of any intermediate chlorophosphite or phosphoramidite and proceeds in on step.

Compounds **1** and **2a**,**b** are white solids readily soluble in common organic solvents and stable enough to tolerate washing with aqueous $NaHCO_3$. A typical shape of narrow ν(OH) absorption bands for **1** and **2a**,**b** (Table 1) and absence of $\Delta\nu$(OH) in a wide range of concentrations of **1** in CCl_4 solutions indicates intramolecular hydrogen bonding (Fig. 2).

Table 1. ^{31}P NMR chemical shifts (ppm, $CDCl_3$), IR absorption bands (cm^{-1}, $CHCl_3$) and cone angles θ (degree) of ligands **1**–**4**

Ligand	δ_P	ν(OH)	θ
1	145.1	3532	147
2a	138.0 (68%), 138.4 (32%)	3530	154
2b	139.0 (73%), 143.4 (27%)	3520	172
3	−29.3[a]	—	128[b]
4	144.9	—	177

[a] $^1J_{P,H}$=836.5 Hz.
[b] For 'open-chain' form of **3**.

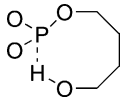
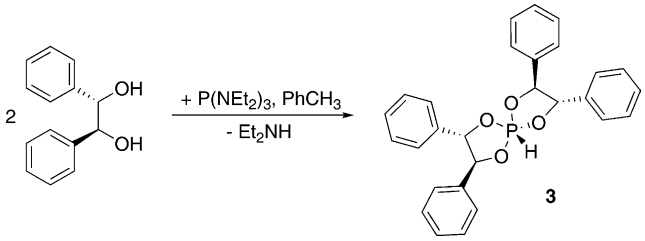


Figure 2. Intramolecular hydrogen bonding in the ligand **1**.

According to the ^{31}P NMR data (Table 1), partially hydrogenated compounds **2a**,**b** are represented by two conformers. A well-known C*-chiral inductor (*S*,*S*)-hydrobenzoin was also directly phosphorylated (Scheme 3).



Scheme 3. Phosphorylation of the (*S*,*S*)-hydrobenzoin.

In this case, hydrospirophosphorane **3** was formed instead of an 'open-chain' form **3′** (Fig. 3). P(III)-tautomer **3′** was detected neither by ^{31}P NMR nor IR spectroscopy, but nevertheless phosphorane **3** is able to coordinate to metal atoms (vide infra).

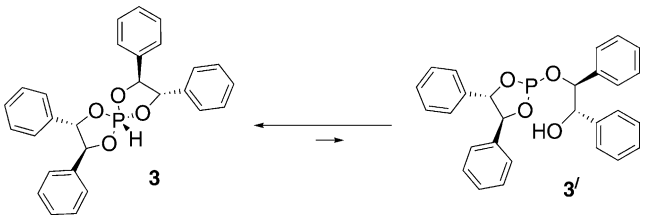


Figure 3. Hydrospirophosphorane and its P(III)-tautomer.

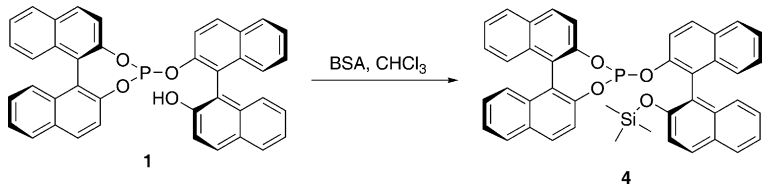
Free OH group provides numerous opportunities for modification of **1** and **2a**,**b**. Thus, trimethylsilylated aryl phosphite **4** was easily obtained by reaction of **1** with *N*,*O*-bis(trimethylsilyl)acetamide at room temperature (Scheme 4).

To estimate steric demands of ligands **1**–**4**, we calculated their Tolman's angles[18] by a reported method, namely semiempirical quantum mechanical AM1 techniques with full optimisation of geometrical parameters.[19] (Table 1). Calculations showed that steric demands increase in the **1**–**2a**–**2b**–**4** row, ligand **4** being the most bulky (θ=177°) thanks to its silyl ether group.

The electronic demands of the novel ligands were determined from the ^{31}P NMR and IR spectroscopic data (Table 2) of their rhodium(I) carbonyl complexes **5**, **6a**,**b** and **7** (Scheme 5).

The $^1J_{P,Rh}$ and ν(CO) data for complexes **5**, **6a**,**b** indicate that **1** and **2a**,**b** represent a novel group of highly π-accepting aryl phosphites. Somewhat lower $^1J_{P,Rh}$ and ν(CO) values of complex **6a** in comparison to those of complex **5** are due to stronger electron donor ability of the H_8-BINOL fragment.[3] Increasing of these values in the case of **6b** is caused by the $-I$ effect of bromine atoms.

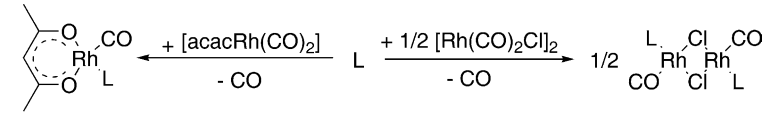
In contrast to **1** and **2a**,**b**, hydrospirophosphorane **3** does not



Scheme 4. Synthesis of the trimethylsilylated aryl phopsphite **4**.

Table 2. Selected spectroscopic data for compounds **5**, **6a**,**b**, **7** and **8** (in $CHCl_3$)

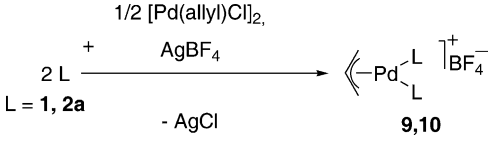
Compound	^{31}P NMR		IR, cm^{-1}		
	δ_P	$^1J_{P,Rh}$ (Hz)	ν(OH)	ν(CO)	ν(acac)
5	143.4	292.5	3532	2020	1580, 1524
6a	137.1	286.1	3530	2016	1584, 1524
6b	137.3	299.5	3526	2022	1581, 1525
7	140.6	265.2	3440	1998	1564, 1524
8	138.3	283.4	3432	2020	—



Scheme 5. Synthesis of rhodium(I) carbonyl complexes.

react with $[acacRh(CO)_2]$ in $CHCl_3$ at room temperature. Only after 1 h of refluxing a mixture **3**/$[acacRh(CO)_2]$ in toluene, product **7** was detected. According to the ^{31}P NMR and IR data (Table 2), complex **7** contains an 'open-chain' form **3′** (Scheme 5). Keeping in mind that $[acacRh(CO)_2]$ reacts with P(III)-ligands immediately and quantitatively, conclusion can be made that coordination of hydrophosphorane **3** is realised by means of oxidative addition.[20] Indeed, reaction of **3** with $[Rh(CO)_2Cl]_2$, that is able to dissociate producing the highly reactive in oxidative addition 14-electron $[Rh(CO)_2Cl]$ particles,[20] readily proceeds in $CHCl_3$ at room temperature to afford the dinuclear rhodium(I) chlorocarbonyl complex **8** (Scheme 5, Table 2).

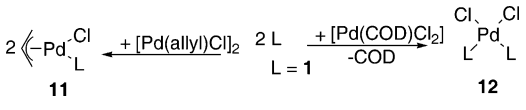
Cationic palladium (II) complexes were obtained for the use in Pd-catalysed allylation (Scheme 6).



Scheme 6. Cationic palladium (II) complexes.

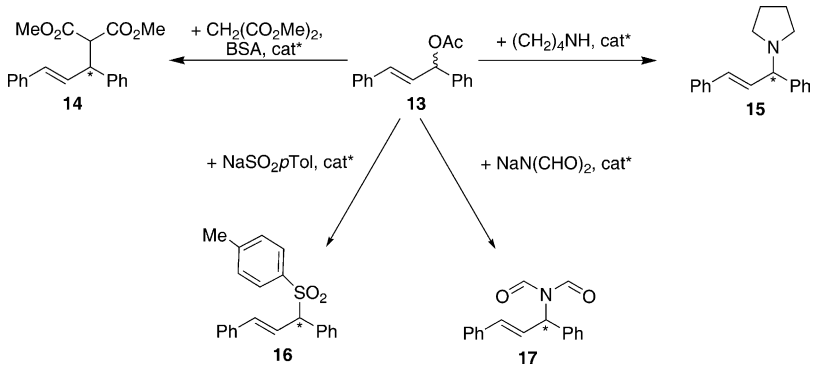
^{31}P NMR, IR and MS spectroscopic data (see Section 4) are in a good agreement with the proposed structures for **9** and **10**. Signals of both *exo* and *endo* isomers of **10** are visible in its ^{31}P NMR spectra. This is not the case for the complex **9**, due either to fast interconversion of its isomers or to the absence of one of them (see Ref. 16 and references cited therein). Unfortunately, an individual $[Pd(allyl)(\mathbf{2b})_2]^+BF_4^-$ complex could not be isolated, for a complicated mixture of products was observed in the ^{31}P NMR spectrum of the corresponding reaction solution in $CHCl_3$ (δ_P 143.5, 143.0, 142.7, 142.5, 127.0, 125.9, 124.9, 10.1 ppm). Pronounced bulkiness of the aryl phosphite **2b** ($\theta = 172°$) is the most probable reason for that. On the contrary, hydrospirophosphorane **3** smoothly formed $[Pd(allyl)(\mathbf{3'})_2]^+BF_4^-$ when reacted with 0.5 equiv $[Pd(allyl)Cl]_2$ and 1 equiv $AgBF_4$ in $CHCl_3$ at room temperature. Immediately after reaction, only a singlet signal δ_P 143.9 ppm corresponding to the $[Pd(allyl)(\mathbf{3'})_2]^+BF_4^-$ complex was visible in the ^{31}P NMR spectrum. But, this product is very unstable, since already a few minutes later precipitation of a black deposit was observed and a series of additional signals occurred in the δ_P 14–5 ppm region.

Besides, some neutral palladium(II) complexes were obtained with the aryl phosphite **1**, where **1** acted as a typical P-monodentate ligand (Scheme 7).



Scheme 7. Neutral palladium (II) complexes.

In particular, the bridge-splitting reaction on the dinuclear compound $[Pd(allyl)Cl]_2$ with 2 equiv of **1** afforded complex **11**, which represents a mixture of *exo* and *endo* isomers (see Section 4). Significant difference in the chemical shifts of two terminal allylic carbons ($\Delta\delta_c = 24.3$ ppm) indicates a strong *trans*-influence of the aryl phosphite **1**.[21] The interaction between 2 equiv of ligand **1** and $[Pd(COD)Cl_2]$ afforded cis palladium complex **12** (Scheme 7). Results of the far-IR spectroscopic studies of



Scheme 8. Application of the ligands in asymmetric Pd-catalysed allylic substitution.

solid **12** or its $CHCl_3$ solution (see Section 4) confirm the cis arrangement of chloride ligands in this complex.[22]

The novel ligands **1**–**4** and their palladium complexes **9** and **10** were tested in the asymmetric Pd-catalysed allylic substitution (Scheme 8, Tables 3 and 4). Trimethylsilylated aryl phosphite **4** demonstrated excellent enantioselectivity in the allylic alkylation of **13** with dimethyl malonate (97% ee, Table 3, entry 20). Ligand **1** showed an almost equal enantioselectivity (up to 95% ee) and good conversion under optimal conditions: L*/Pd=1:1, in CH_2Cl_2 using $[Pd(allyl)Cl]_2$ as a precatalyst (Table 3, entries 1–7). In the case of the partially hydrogenated aryl phosphite **2a**, the highest optical yield was reached with the cationic complex **10** (90%, Table 3, entry 10). Tetrabrominated ligand **2b** afforded only moderate enantioselectivity (up to 63% ee, Table 3, entries 12 and 13), possibly due to the described above unselective complexation with palladium(II). Phosphorane **3** provided moderate enantioselectivity of up to 56% ee, L*/Pd ratio and applied precatalyst having little influence on the outcome (Table 3, entries 16–19). Nevertheless, this is the best result in the asymmetric Pd-catalysed allylic substitution achieved thus far by the use of these unusual hydrospirophosphorane ligands.[23]

In allylic amination (Scheme 8), ligands **1** and **2a** afforded up to 61% and 51% ee, correspondingly (L*/Pd=1:1, Table 4, entries 3 and 6). More bulky aryl phosphites **2b** and **4** gave inferior results (Table 4, entries 9 and 15), while phosphorane **3** provided a nearly racemic product **15**.

Taking into account the above discussed results, we tested the two most efficient aryl phosphites **1** and **2a** in the Pd-catalysed allylic sulfonylation of 1,3-diphenyl-2-propenyl acetate **13** with sodium *para*-toluene sulfinate and in the allylic amination of **13** with sodium diformylamide (Scheme 8). The type of the nucleophile was found to play a key role in these processes. Thus, optical purity of the sulfonylation product **16** obtained by the use of ligand **1** and its complex **9** did not exceed 24% (*R*). Under the same conditions, **2a** demonstrated rather good results in both the $[Pd(allyl)Cl]_2$/4L* (30% yield, 58% ee (*S*)) and **10** (35% yield, 65% ee (*S*)) catalytic systems. On the contrary, in the allylic amination of **13** with $NaN(CHO)_2$ in THF or CH_3CN, ligand **2a** provided no conversion (L*/Pd=1, precatalyst $[Pd(allyl)Cl]_2$), while the catalytic system $[Pd(allyl)Cl]_2$/2L* (L*=**1**) was rather efficient: 53% yield, 60% ee (*R*) in CH_3CN and 47% yield, 86% ee (*R*) in THF.

Table 3. Enantioselective allylic alkylation of **13** with dimethyl malonate

Entry	Catalyst	L*/Pd	Solvent	Conv. (%)	ee (%)
1	$[Pd(allyl)Cl]_2$/**1**	1/1	THF	11	49 (*R*)
2	$[Pd(allyl)Cl]_2$/**1**	2/1	THF	13	18 (*R*)
3	$[Pd(allyl)Cl]_2$/**1**	1/1	CH_2Cl_2	89	95 (*R*)
4	$[Pd(allyl)Cl]_2$/**1**	2/1	CH_2Cl_2	93	78 (*R*)
5	$[Pd_2(dba)_3]\times CHCl_3$/**1**	1/1	CH_2Cl_2	19	39 (*S*)
6	$[Pd_2(dba)_3]\times CHCl_3$/**1**	2/1	CH_2Cl_2	78	43 (*S*)
7	**9**	2/1	CH_2Cl_2	99	86 (*R*)
8	$[Pd(allyl)Cl]_2$/**2a**	1/1	CH_2Cl_2	68	71 (*R*)
9	$[Pd(allyl)Cl]_2$/**2a**	2/1	CH_2Cl_2	69	52 (*R*)
10	**10**	2/1	THF	50	90 (*R*)
11	**10**	2/1	CH_2Cl_2	85	81 (*R*)
12	$[Pd(allyl)Cl]_2$/**2b**	1/1	CH_2Cl_2	5	48 (*R*)
13	$[Pd(allyl)Cl]_2$/**2b**	2/1	CH_2Cl_2	14	63 (*R*)
14	$[Pd(allyl)Cl]_2$/**3**	1/1	THF	—	—
15	$[Pd(allyl)Cl]_2$/**3**	2/1	THF	—	—
16	$[Pd(allyl)Cl]_2$/**3**	1/1	CH_2Cl_2	76	43 (*S*)
17	$[Pd(allyl)Cl]_2$/**3**	2/1	CH_2Cl_2	50	54 (*S*)
18	$[Pd_2(dba)_3]\times CHCl_3$/**3**	1/1	CH_2Cl_2	31	50 (*S*)
19	$[Pd_2(dba)_3]\times CHCl_3$/**3**	2/1	CH_2Cl_2	32	56 (*S*)
20	$[Pd(allyl)Cl]_2$/**4**	1/1	CH_2Cl_2	50	97 (*R*)
21	$[Pd(allyl)Cl]_2$/**4**	2/1	CH_2Cl_2	30	65 (*R*)

Table 4. Enantioselective allylic amination of **13** with pyrrolidine

Entry	Catalyst	L*/Pd	Solvent	Isolated yield (%)	ee (%)
1	$[Pd(allyl)Cl]_2$/**1**	1/1	THF	48	52 (*S*)
2	$[Pd(allyl)Cl]_2$/**1**	2/1	THF	39	48 (*S*)
3	$[Pd(allyl)Cl]_2$/**1**	1/1	CH_2Cl_2	57	61 (*S*)
4	$[Pd(allyl)Cl]_2$/**1**	2/1	CH_2Cl_2	43	14 (*S*)
5	**9**	2/1	THF	65	39 (*S*)
6	$[Pd(allyl)Cl]_2$/**2a**	1/1	THF	68	51 (*S*)
7	$[Pd(allyl)Cl]_2$/**2a**	1/1	CH_2Cl_2	71	50 (*S*)
8	**10**	2/1	THF	65	47 (*S*)
9	$[Pd(allyl)Cl]_2$/**2b**	1/1	THF	56	36 (*S*)
10	$[Pd(allyl)Cl]_2$/**2b**	1/1	CH_2Cl_2	51	23 (*S*)
11	$[Pd(allyl)Cl]_2$/**3**	1/1	THF	15	2 (*R*)
12	$[Pd(allyl)Cl]_2$/**3**	2/1	THF	8	4 (*R*)
13	$[Pd(allyl)Cl]_2$/**3**	1/1	CH_2Cl_2	20	8 (*R*)
14	$[Pd(allyl)Cl]_2$/**3**	2/1	CH_2Cl_2	3	4 (*R*)
15	$[Pd(allyl)Cl]_2$/**4**	1/1	THF	45	45 (*S*)
16	$[Pd(allyl)Cl]_2$/**4**	2/1	THF	80	10 (*S*)

3. Conclusion

To conclude, the one-step phosphorylation of (*R*)-BINOL, (*R*)-H_8-BINOL and (*R*)-H_8-3,3′-dibromo-BINOL with 0.5 equiv of PCl_3 results in stable aryl phosphite ligands bearing two binaphthyl fragments attached to the phosphorus atom. Their high catalytic potentials have been demonstrated by the successful application in asymmetric Pd-catalysed allylic substitution.

4. Experimental

4.1. General

IR spectra were recorded on a Specord M80 or Nicolet 750 instruments. ^{31}P, ^{13}C, ^{1}H and ^{29}Si NMR spectra were recorder with a Bruker AMX 400 instrument (162.0 MHz for ^{31}P, 100.6 MHz for ^{13}C, 400.13 MHz for ^{1}H and 79.46 MHz for ^{29}Si). Complete assignment of all the resonances in ^{13}C NMR spectra was achieved by the use of DEPT techniques. Chemical shifts (ppm) are given relative to Me_4Si (^{1}H, ^{13}C and ^{29}Si NMR) and 85% H_3PO_4 (^{31}P NMR). Mass spectra were recorded with a Varian MAT 311 spectrometer (EI), a Finnigan LCQ Advantage spectrometer (electrospray ionization technique, ESI), an MSVKh TOF spectrometer with ionization by Cf-252 fission fragments (plasma desorption technique, PD), a Varian MAT 731 spectrometer (field desorption technique, FD). Elemental analyses were performed at the Laboratory of Microanalysis (Institute of Organoelement Compounds, Moscow).

Conversion of substrate **13**[24] and optical purity of products **14**[24] and **15**[25] were determined using HPLC (Daicel Chiralcel OD-H column) as described previously. Optical yields of product **16** were determined using HPLC ((*R*,*R*)-WHELK-01 column) according to the literature.[26] Optical yields of product **17** were determined using HPLC (Chiralcel OD column) according to the literature.[27]

All reactions were carried out under a dry argon atmosphere in freshly dried and distilled solvents; Et_3N and pyrrolidine were twice distilled over KOH and then over a small amount of $LiAlH_4$ before use. (*R*)-Br_2-H_8-BINOL and sodium diformylamide were prepared as published.[28,29] The starting substrate **13** was synthesised as published.[30] (*R*)-BINOL, (*S*,*S*)-hydrobenzoin, dimethyl malonate, BSA (*N*,*O*-bis(trimethylsilyl) acetamide) and sodium *para*-toluene sulfinate were commercially available.

$[acacRh(CO)_2]$,[31] $[Rh(CO)_2Cl]_2$,[32] $[Pd(allyl)Cl]_2$,[30] $[Pd(COD)Cl_2]$[33] and $[Pd_2(dba)_3]\cdot CHCl_3$[34] were synthesised using literature procedures. Rhodium(I) complex **8** was synthesised for the ^{31}P NMR and IR experiments in chloroform, analogously to the known procedures.[16] The syntheses of palladium(Ii) complexes **9**, **10** and **11** were performed by techniques similar to that reported.[16]

Catalytic experiments: allylic alkylation of substrate **13** with dimethyl malonate, allylic amination with pyrrolidine, allylic sulfonylation with sodium *para*-toluene sulfinate and allylic amination with $NaN(CHO)_2$ were performed according to the appropriate procedures.[16,17]

4.2. Preparation of ligands 1 and 2a,b. General technique

A solution of PCl_3 (0.44 ml, 0.005 mol) in 50 ml of benzene was added dropwise to a solution of appropriate (*R*)-dihydroxybinaphthyl (0.01 mol) and Et_3N (2.1 ml, 0.015 mol) in 70 ml of benzene on stirring and cooling to 0 °C. The reaction mixture was then heated for a while to the boiling point of the solvent, cooled, and filtered; benzene was removed under reduced pressure (40 Torr), the product was dried in vacuum (1 Torr, 2 h). Crude **1** and **2a** were used without further purification. Crude **2b** was dissolved in CH_2Cl_2 (30 ml) and washed with an aqueous saturated $NaHCO_3$ solution (20 ml). After drying over $MgSO_4$, filtration and evaporation, the product was dried in vacuum (1 Torr, 2 h).

4.2.1. (*R*)-2-((*R*)-1,1′-binaphthyl-2′-hydroxy-2-oxy)-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (1). White solid, 2.76 g, (92% yield). ^{13}C NMR ($CDCl_3$): δ 111.2, 117.6, 120.5, 121.7, 122.4, 123.9, 124.1, 124.3, 124.8, 125.0, 125.7, 126.1, 126.8, 127.0, 127.1, 127.9, 128.0, 128.2, 129.2, 129.6, 130.0, 130.5, 130.6, 131.1, 132.0, 132.5, 133.3, 134.0, 147.0, 147.2, 148.4, 155.8. IR, cm^{-1}: ν(OH) 3538 (CCl_4), 3524 (CH_2Cl_2), 3516 (nujol). MS (PD), *m*/*z* (I, %): 600 (10) $[M]^+$, 585 (21)

$[M-O+H]^+$, 315 (81) $[M-C_{20}H_{13}O_2]^+$, 268 (100) $[C_{20}H_{12}O]^+$. MS (FD), *m/z* (I, %): 600 (100) $[M]^+$, 332 (37) $[C_{20}H_{13}O_3P]^+$. MS (ESI), *m/z* (I, %): 600 (24) $[M]^+$, 585 (20) $[M-O+H]^+$, 315 (16) $[M-C_{20}H_{13}O_2]^+$, 268 (100) $[C_{20}H_{12}O]^+$. Anal. Calcd for $C_{40}H_{25}O_4P$: C, 79.99; H, 4.20; P, 5.16. Found: C, 80.09; H, 4.31; P, 5.04.

4.2.2. (*R*)-2-((*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2′-hydroxy-2-oxy)-5,5′,6,6′,7,7′,8,8′-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (2a). White solid, 2.87 g, (93% yield). ^{13}C NMR (major conformer, $CDCl_3$): δ 22.7, 22.9, 26.6, 27.4, 29.1, 29.3, 112.7, 117.6, 118.3, 118.6, 119.0, 128.4, 128.6, 129.0, 131.2, 133.1, 134.0, 136.5, 137.3, 145.8, 151.3. MS (EI), *m/z* (I, %): 616 (100) $[M]^+$, 340 (80) $[C_{20}H_{21}O_3P]^+$, 294 (82) $[C_{20}H_{22}O_2]^+$. Anal. Calcd for $C_{40}H_{41}O_4P$: C, 77.90; H, 6.70; P, 5.02. Found: C, 78.11; H, 6.82; P, 5.12.

4.2.3. (*R*)-2-((*R*)-3,3′-dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2′-hydroxy-2-oxy)-3,3′-dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (2b). White solid, 3.82 g, (82% yield). ^{13}C NMR (major conformer, $CDCl_3$): δ 22.2, 22.5, 26.7, 27.2, 28.6, 28.8, 107.4, 112.5, 123.9, 129.9, 130.1, 131.2, 132.6, 132.7, 133.0, 134.4, 135.2, 136.7, 137.0, 142.3, 143.0, 147.0. MS (ESI), *m/z* (I, %): 932 (24) $[M]^+$, 852 (49) $[M-Br]^+$, 498 (22) $[C_{20}H_{19}Br_2O_3P]^+$, 481 (40) $[M-C_{20}H_{19}Br_2O_2]^+$, 451 (100) $[C_{20}H_{19}Br_2O_2]^+$. Anal. Calcd for $C_{40}H_{37}Br_4O_4P$: C, 51.53; H, 4.00; P, 3.32. Found: C, 51.31; H, 4.11; P, 3.29.

4.2.4. Preparation of 2*S*,3*S*,7*S*,8*S*-tetraphenyl-1,4,6,9-tetraoxa-5λ⁵-phosphaspiro[4.4]nonane (3). Enantiomerically pure ligand **3**, which was previously reported as a racemic compound,[35] was synthesised according to the following technique: a solution of $P(NEt_2)_3$, (1.37 ml, 0.005 mol) and (*S*,*S*)-hydrobenzoin (2.14 g, 0.01 mol) in 25 ml of toluene was stirred under reflux for 1 h. Then all volatiles were removed in vacuum and the crude product was purified by recrystallisation from toluene/heptane. White solid, 1.85 g, (81% yield). ^{13}C NMR ($CDCl_3$): δ 79.8, 82.7, 126.6, 126.7, 126.8, 127.7, 128.1, 128.2, 128.3, 128.4, 136.3 (d, $^3J_{C,P}=9.5$ Hz), 137.2 (d, $^3J_{C,P}=11.8$ Hz). IR, cm^{-1}: ν(PH) 2416 ($CHCl_3$). MS (ESI), *m/z* (I, %): 456 (4) $[M]^+$, 335 (95) $[M-C_8H_9O]^+$, 260 (100) $[C_{14}H_{13}O_3P]^+$. Anal. Calcd for $C_{28}H_{25}O_4P$: C, 73.67; H, 5.52; P, 6.79. Found: C, 73.61; H, 5.47; P, 6.68.

4.2.5. Preparation of (*R*)-2-((*R*)-1,1′-binaphthyl-2′-trimethylsilanoxy-2-oxy)-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2] dioxaphosphepine (4). Ligand **4** was synthesised according to the known technique:[36] a solution of **1** (0.3 g, 0.5 mmol) and BSA (0.38 ml, 1.5 mmol) in 3 ml of $CHCl_3$ was stirred at room temperature for 1 h. Then the mixture was concentrated under reduced pressure (40 Torr), the residue washed with hexane and dried in vacuum (1 Torr, 3 h) at 60 °C. White solid, 0.3 g, (90% yield). ^1H NMR ($CDCl_3$): δ 0.09 (9H, s), 6.54 (1H, d, $J_{H,H}=8.0$ Hz), 7.23 (10H, m), 7.37 (5H, m), 7.53 (1H, d, $J_{H,H}=9.9$ Hz), 7.73 (1H, d, $J_{H,H}=9.9$ Hz), 7.87 (6H, m). ^{13}C NMR ($CDCl_3$): δ 1.8, 111.4, 117.8, 120.1, 120.7, 122.5, 123.9, 124.6, 124.1, 124.9, 125.3, 125.7, 126.4, 126.6, 127.0, 127.3, 128.1, 128.5, 128.7, 129.2, 129.9, 130.1, 130.5, 130.6, 131.7, 132.2, 132.5, 133.6, 135.0, 146.7, 147.4, 148.3, 152.6. MS (ESI), *m/z* (I, %): 673 (3) $[M]^+$, 585 (11) $[M-OSiMe_3+H]^+$, 332 (100) $[C_{20}H_{13}O_3P]^+$. Anal. Calcd for $C_{43}H_{33}O_4PSi$: C, 76.77; H, 4.94; P, 4.60. Found: C, 76.59; H, 4.79; P, 4.72.

4.3. Preparation of rhodium complexes 5, 6a,b, 7. General technique

Rhodium complexes with ligands **1** and **2a**,**b** were synthesised for the NMR and IR experiments as follows. A solution of the appropriate ligand (0.1 mmol) in 1 ml of $CHCl_3$ was added dropwise to a stirred solution of $[acacRh(CO)_2]$ (0.026 g, 0.1 mmol) in 1 ml of the same solvent. A 1 ml sample of the resulting solution was then transferred to an NMR tube or IR cuvette and spectral experiments were carried out. In the case of **3**, a solution of this ligand (0.046 g, 0.1 mmol) and $[acacRh(CO)_2]$ (0.026 g, 0.1 mmol) in 3 ml of toluene was stirred under reflux for 1 h. Then the solvent was evaporated under reduced pressure (40 Torr), the residue dissolved in 1 ml of $CHCl_3$, transferred to an NMR tube or IR cuvette and spectral experiments were carried out.

4.4. Cationic palladium complexes

4.4.1. $[Pd(allyl)(1)_2]^+ BF_4^-$ (9). White solid, (9 5% yield). ^{31}P NMR ($CDCl_3$): δ 142.6 IR, cm^{-1}: ν(OH) 3526 ($CHCl_3$). MS (ESI), *m/z* (I, %): 1347 (8) $[M-BF_4]^+$, 1062 (100) $[M-BF_4-C_{20}H_{13}O_2]^+$. Anal. Calcd for $C_{83}H_{55}BF_4O_8P_2Pd$: C, 69.45; H, 3.86; P, 4.32. Found: C, 69.67; H, 3.98; P, 4.22.

4.4.2. $[Pd(allyl)(2a)_2]^+ BF_4^-$ (10). White solid, (93% yield). ^{31}P NMR ($CDCl_3$): δ 141.4 (54%), 141.2 (46%). IR, cm^{-1}: ν(OH) 3530 ($CHCl_3$). MS (ESI), *m/z* (I, %): 1381 (46) $[M-BF_4]^+$, 1088 (100) $[M-BF_4-C_{20}H_{21}O_2]^+$. Anal. Calcd for $C_{83}H_{87}BF_4O_8P_2Pd$: C, 67.92; H, 5.97; P, 4.22. Found: C, 67.80; H, 6.11; P, 4.05.

4.5. Neutral palladium complexes

4.5.1. [Pd(allyl)(1)Cl] (11). Light yellow solid, (94% yield). ^{31}P NMR ($CDCl_3$): δ 142.8 (71%), 141.9 (29%). ^{13}C NMR (major isomer, $CDCl_3$): δ 57.3 [s, CH_2(allyl, *trans*-Cl)], 81.6 [d, $J_{C,P}=47.4$ Hz, CH_2(allyl, *trans*-P)], 112.4, 117.8, 118.0 (br s, CH allyl), 120.2, 121.0, 121.8, 122.9, 123.1, 124.5, 124.9, 125.2, 125.9, 126.7, 126.9, 127.1, 127.3, 127.5, 128.8, 129.1, 129.7, 129.9, 130.1, 130.9, 131.0, 131.4, 131.7, 132.8, 133.6, 133.9, 145.6, 146.7, 146.8, 152.5. IR, cm^{-1}: ν(OH) 3531 ($CHCl_3$); ν(Pd–Cl) 282 (nujol). Anal. Calcd for $C_{43}H_{30}ClO_4PPd$: C, 65.92; H, 3.86; P, 3.95. Found: C, 65.99; H, 3.80; P, 4.04.

4.5.2. Preparation of *cis*-$[Pd(1)_2Cl_2]$ (12). A solution of **1** (0.12 g, 0.2 mmol) in 5 ml of $CHCl_3$ was added dropwise to a stirred solution of $[Pd(COD)Cl_2]$ (0.029 g, 0.1 mmol) in 5 ml of the same solvent. The resulting solution was stirred for 1 h and concentrated to 1 ml under reduced pressure (40 Torr). The product was precipitated with hexane–ether (2/1), thoroughly washed three times with ether to remove cycloocta-1,5-diene and dried in vacuum (1 Torr, 1 h). Yellow solid, (91% yield). ^{31}P NMR ($CDCl_3$): δ 105.5. IR, cm^{-1}: ν(OH) 3519 ($CHCl_3$); ν(Pd–Cl) 338, 304 ($CHCl_3$),

335, 304 (nujol). MS (ESI), *m/z* (I, %): 1306 (29) $[M-2Cl]^+$, 1092 (100) $[M-C_{20}H_{13}O_2]^+$. Anal. Calcd for $C_{80}H_{50}Cl_2O_8P_2Pd$: C, 69.70; H, 3.66; P, 4.49. Found: C, 69.92; H, 3.74; P, 4.32.

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Diastereo- and regioselectivity in Diels–Alder reaction of [1,4,2] diazaphospholo[4,5-*a*]pyridines

Raj K. Bansal,[a,*] Konstantin Karaghiosoff,[b] Neelima Gupta,[a] Neelam Gandhi[a] and Surendra K. Kumawat[a]

[a]*Department of Chemistry, University of Rajasthan, Jaipur 302 004, India*
[b]*Department Chemie und Biochemie, Ludwig-Maximilians-Universität, Butenandtstr. 5-13, D-81377 München, Germany*

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Abstract—[1,4,2]Diazaphospholo[4,5-*a*]pyridines undergo diastereoselective Diels–Alder reaction at the >C=P– functionality with 2,3-dimethylbutadiene and isoprene in the presence of sulfur or selenium. The reaction with isoprene occurs regioselectively. On carrying out the reaction with diene in presence of methyl iodide, the initially formed [2+4] cycloadduct is methylated regioselectively at the σ^2,λ^3-nitrogen. The results of the DFT calculations of the Diels–Alder reaction with isoprene are in accord with the observed regioselectivity. The relative stabilities of the two transition structures have been explained on the basis of NBO analysis.

1. Introduction

The Diels–Alder (DA) reaction is perhaps the most widely used synthetic methodology for the construction of six-membered rings.[1] The reaction is accompanied by several striking features such as high regioselectivity and *endo*-stereoselectivity, which have been rationalised on the basis of orbital symmetry[2] and theoretical calculations.[3,4] During the last few years the synthetic utility of the DA reaction has been expanded significantly by the use and the development of a wide variety of dienes and dienophiles.[5] The scope of this reaction has been further extended to the organophosphorus compounds bearing the >C=P– functionality, namely phosphaalkenes,[6–8] heterophospholes including anellated azaphospholes[9–14] and phosphinines.[15] Many of these compounds undergo DA reaction much more readily than across the >C=C< moiety present in the non-phosphorus analogues with high regio- and stereoselectivities. This fact has been rationalised on the basis of theoretical calculations, which indicate that the presence of a two-coordinate phosphorus atom (σ^2,λ^3-P) in a DA reactant lowers the activation energy relative to that of the hydrocarbon system due to the weaker >C=P– π-bond compared to the >C=C< π-bond.[16,17]

In the azaphosphole system, both the phosphorus and the carbon atom of the >C=P– functionality represent prochiral centres and DA reaction on this moiety leads to the generation of two stereogenic centres in one step. The results, however, indicate that these reactions normally proceed with complete diastereoselectivity and regioselectivity. We recently reported the stereo- and regioselective DA reactions of 1,3-azaphospholo[5,1-*a*]-isoquinoline and -[1,5-*a*]pyridine[18–20] and also of thiazolo[3,2-*d*][1,4,2]diazaphospholes and related compounds.[21] All these reactions occurred with complete *endo* stereoselectivity. The reactions with isoprene proceeded with complete regioselectivity as well, the regioisomer having phosphorus and methyl group in 1:3 positions being formed as the sole product, except in one case when the other regioisomer was also produced in minor amount.[21] These results are in conformity with the DA reactions of 1*H*-1,3-benzoxaphosphole[22] and 2-acetyl-1,2,3-diazaphosphole[23,24] reported earlier.

We have reported the synthesis of [1,4,2]diazaphospholo [4,5-*a*]pyridines and their 3-ethoxycarbonyl derivatives through [3+2] cyclocondensation[25] and [4+1] cyclocondensation,[26] respectively. We have now investigated their DA reactions with 2,3-dimethylbutadiene and isoprene. As observed earlier,[21] the presence of a second nitrogen atom (σ^2,λ^3–N) in the azaphosphole ring enhances the reactivity of the >C=P– functionality and it undergoes DA reaction, even in the absence of an oxidizing agent. The resulting phosphinines are, however, very sensitive towards

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* Corresponding author. Tel.: +91 1412701868; fax: +91 1412652730; e-mail: rajbns@yahoo.com

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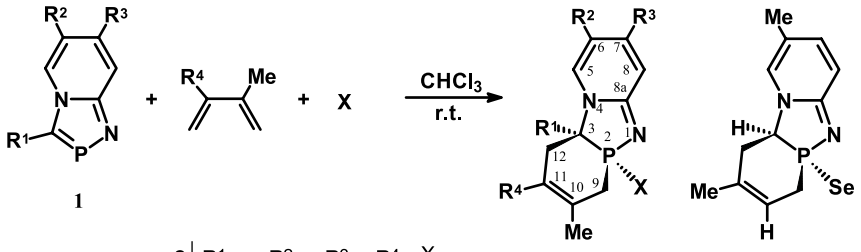


2	R1	R2	R3	R4	X
a	H	H	H	Me	S
b	H	Me	H	Me	S
c	H	H	Me	Me	S
d	H	H	Me	Me	Se
e	CO_2Et	H	H	Me	S
f	CO_2Et	H	H	Me	Se
g	H	Me	H	H	Se

Scheme 1.

air oxidation. In order to simplify workup the cycloadditions are therefore carried out in the presence of sulfur or selenium when clean reactions occur and spectroscopically pure products are obtained. On using methyl iodide in place of sulfur or selenium, the initially formed [2+4] cycloadduct is methylated on σ^2,λ^3-nitrogen instead on phosphorus.[19]

6-Methyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine on reaction with isoprene in presence of selenium affords two regioisomers **2g**, **2g′** (Scheme 1) approximately in 4:1 ratio (as determined by the intensity of the ^{31}P NMR signals of the mixture), which is very close to the ratio calculated from the difference in the activation energies of the transition structures corresponding to the two regioisomers determined at the DFT (b3lyp/6-311++g(d,p)//b3lyp/6-311g(d,p)) level of theory.

2. Results and discussion

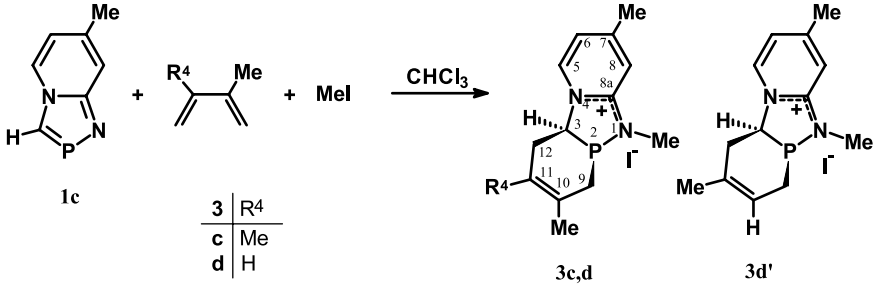
[1,4,2]Diazaphospholo[4,5-*a*]pyridines **1** react with 2,3-dimethylbutadiene in presence of sulfur or selenium in chloroform at room temperature to give [2+4] cycloadducts **2a–f**. The reaction of 6-methyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine **1b** (**1**, $R^1=R^3=H$, $R^2=Me$) with isoprene and selenium under these conditions proceeds regioselectively to give **2g** and **2g′** approximately in 4:1 ratio (Scheme 1).

The reaction of **1b** with 2,3-dimethylbutadiene alone was very slow at room temperature and could be completed only after refluxing in chloroform for 24 days ($\delta\ ^{31}P=66.0$). It is evident that the role of the oxidizing agent, sulfur or selenium, is to oxidize the σ^3-P of the initially formed [2+4] cycloadduct thereby pushing a reversible [2+4] cycloaddition in the forward direction.

7-Methyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine **1c** (**1**, $R^1=R^2=H$, $R^3=Me$) reacts with 2,3-dimethylbutadiene and methyl iodide in chloroform at room temperature to give **3c**, the methylation occurring at the σ^2,λ^3-nitrogen atom of the cycloadduct. The reaction with isoprene under these conditions, however, gave a mixture of both regioisomers **3d** and **3d′**, the former being formed predominantly (70%). It has been reported that [1,4,2]diazaphospholo[4,5-*a*]pyridines **1** do not show any reactivity towards methyl iodide,[27] which indicates that methylation occurs after the [2+4] cycloadduct is formed. Unlike in the [2+4] cycloaddition of 1,3-bis(ethoxycarbonyl)-[1,3]azaphospholo[5,1-*a*]isoquinoline and -[1,5-*a*]pyridine in the presence of methyl iodide,[19] methylation in the present case occurs at σ^2,λ^3-N instead of σ^3-P, due to the +M effect of the bridgehead nitrogen atom (Scheme 2).

The cycloadducts are obtained as pale yellow sharp melting solids, soluble in polar solvents such as chloroform and acetonitrile. ^{31}P, ^1H and ^{13}C NMR data of the cycloadducts **2** and **3** are given in Section 4. Assignment of the ^1H and ^{13}C NMR data is based on $^1H,^1H$ COSY 45, $^1H,^{13}C$ HETCOR and ^1H-coupled ^{13}C NMR experiments performed on selected products.

The Diels–Alder reaction across the >C=P– functionality



3	R4
c	Me
d	H

Scheme 2.

of the azaphosphole ring leads to an increase in the coordination number of the phosphorus atom and is accompanied by an upfield shift in the ^{31}P NMR chemical shifts, which lie in the range $\delta = 75$–96 for **2** characteristic for a four-coordinated phosphorus.[28,29] The ^{31}P NMR chemical shifts for the cycloadducts **3** are found at $\delta \sim 70$, quite close to those of the bicyclic phosphinines having phosphorus at the bridgehead position with C_2N connectivity.[30]

The [2+4] cycloaddition at the >C=P– moiety generates two stereogenic centres in one step. In the ^{1}H NMR spectra of the cycloadducts, the methylene protons at C-9 and C-12 show the expected diastereotopy and display the typical AB pattern of an ABX spin system. The coupling constant to phosphorus (X-nucleus) is generally of the order of 15 Hz, except for H_B at C12. The latter shows a large P,H coupling constant of 22–27 Hz, in accord with its orientation cis to the phosphorus lone pair.[31] In addition, H_B at C12 shows a coupling also to H-3 ($^3J_{HH} = 4.4$ Hz), which results in an overall eight line pattern. A relatively upfield shift of the N_1-*Me* protons at $\delta \sim 3$ indicates delocalisation of the iminium charge over to N-4.

A characteristic feature of the ^{13}C NMR spectra is the one bond coupling of C-3 and C-9 to phosphorus ($^1J_{PC} = 60$–63 Hz). The $^2J_{PC}$ to C-12 in the phosphinine ring is rather weak (3.3–4.6 Hz), while P,C couplings over two bonds to C-10 and C-8a are comparatively stronger (9.2–12.3 Hz). Phosphorus coupling to C-11 over three bonds (12.8–13.8 Hz) is found in the expected range. Delocalisation of the iminium charge results in an upfield shift of the N_1-*Me* ^{13}C NMR signal with a two bond coupling to phosphorus of approximately 17 Hz.

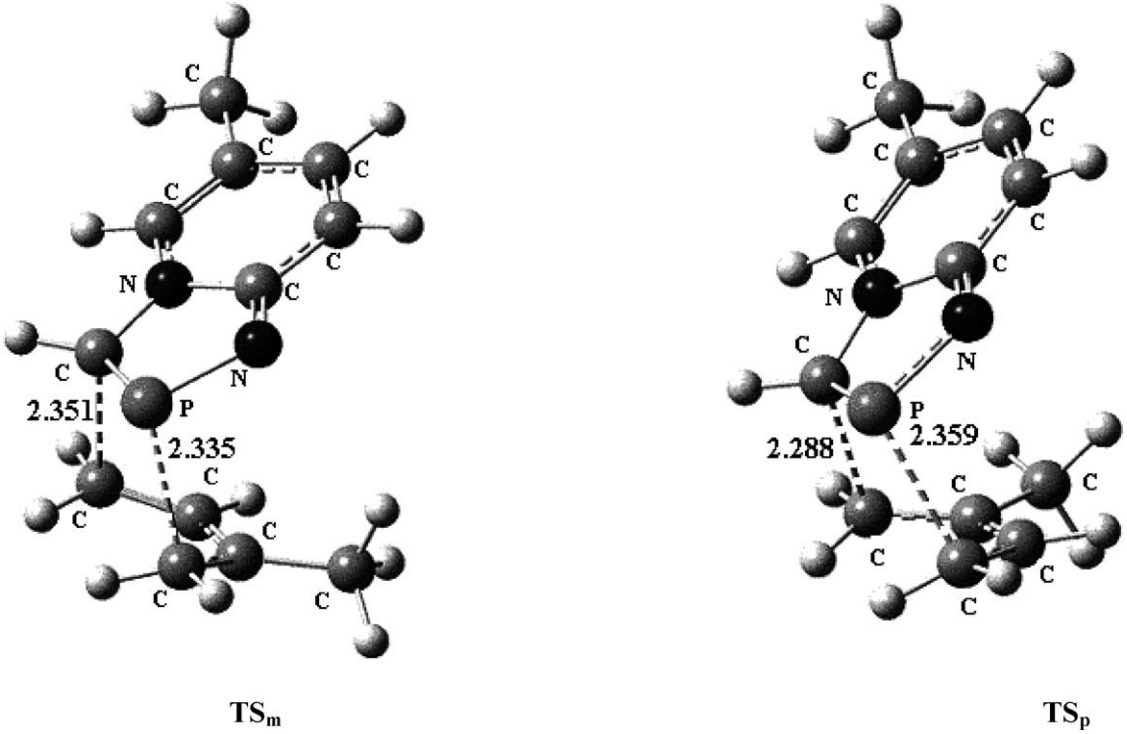
The reaction of **1b** with isoprene in the presence of selenium is regioselective. The product isolated gives two ^{31}P NMR signals at δ 75.6 and δ 75.8 in 4:1 ratio corresponding to **2g** and **2g′**, respectively, (Scheme 1). Satellites of the respective ^{31}P NMR signals are observed due to coupling with selenium ($^1J_{PSe} = 756.8$ Hz). In the ^{1}H NMR spectrum, a singlet at δ 1.76 results due to 10-Me of **2g** while 11-Me of **2g′** gives a singlet at δ 1.82.

In the ^{1}H NMR spectra of the cycloadducts obtained from the reaction of 7-methyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine **1c** with 1,3-dienes, in the presence of methyl iodide, a doublet at $\delta \sim 3$ is observed for the methyl protons. The value of the coupling constant (7.1–7.4 Hz) corresponds to a three bond coupling to phosphorus,[29] which rules out the direct bonding of the methyl group to the phosphorus atom and establishes its position at N_1. The *N*-methylation is further supported by the small P,C coupling constant observed (16.8–17.5 Hz) as well as by the absence of coupling of this carbon with H-3.

In the ^{31}P NMR spectrum of the product obtained from the reaction of **1c** with isoprene and methyl iodide two signals at δ 70.4 and 68.8 are observed, corresponding to **3d** and **3d′**. In the ^{1}H NMR spectrum, a singlet at δ 5.35 is observed for 11-H of **3d** while 10-H of **3d′** appears as a doublet at δ 5.51, due to a three bond coupling with phosphorus.

2.1. DFT calculations and regioselectivity

The stereo- and regioselectivities observed in the Diels–Alder reactions have been recently investigated theoretically by performing DFT calculations and determining the transition structures involved.[3,4,32–38] The ratios of all the products formed in the Diels–Alder reactions of



TS_m TS_p

Figure 1. B3LYP/6-311G** optimized transition structures TS_m and TS_p (bond distances in Å).

Table 1. Calculated energies and regioselectivity in the reaction of **1b** with isoprene

Species	Total energy (a.u.)[a]		Relative energy (kcal mol^{-1})		$\Delta E^{\#}$ (kcal mol^{-1})[b]		Percentage of regioisomers		
							Calcd		exp.
	Gas phase	$CHCl_3$	Gas phase	$CHCl_3$	Gas phase	$CHCl_3$	Gas phase	$CHCl_3$	$CHCl_3$
1b	−721.808722	−721.818008	0.0	0.0					
2	−195.250486	−195.252672	0.0	0.0					
$\mathbf{TS_m}$	−917.027435	−917.037210	19.94	21.00	1.32	0.96			
$\mathbf{TS_p}$	−917.025323	−917.035684	21.26	21.96					
$\mathbf{Pr_m}$	−917.077071	−917.087448	−11.21	−10.52			90	83	80
$\mathbf{Pr_p}$	−917.076146	−917.086977	−10.63	−10.23			10	17	20

[a] Energy at B3LYP/6-311++G(d,p)+ZPE (B3LYP/6-311G(d,p)).
[b] $\Delta E = E^{\#}(TS_p) - E^{\#}(TS_m)$.

vinylboranes with 1,3-dienes were computed from the Boltzmann distribution equation, $k_1/k_2 = e^{-\Delta E^{\#}}/RT$ where $\Delta E^{\#}$ is the difference between the calculated activation energies for two processes (leading to *endo* and *exo* stereoisomers or *o*- and *m*-regioisomers), $T = 298.15$ K and $R = 1.9872$ cal K^{-1} mol^{-1}.[4,39] The calculated values were found to be in very good agreement with the experimental results.

We have investigated the Diels–Alder reaction of 6-methyl-[1,4,2]diazaphospholo[4,5-*a*]pyridine **1b** with isoprene theoretically at the DFT (b3lyp/6-311++g(d,p)//b3lyp/6-311g(d,p)) level. The optimized geometries of the transition structures, $\mathbf{TS_m}$ (P/Me, 1:3) and $\mathbf{TS_p}$ (P/Me, 1:4) are reproduced in Figure 1. As the reactions are actually carried out in chloroform, the solvent effect has also been studied theoretically. Total energies, activation energies, ratios of the two regioisomers, calculated both in gas phase and chloroform and also the experimental values are given in Table 1. It can be noted that the ratios of the two regioisomers obtained by the DFT calculations using solvent effect are in close agreement with the experimental results.

An NBO analysis[40,41] of the two transition structures was done to explain their relative stabilizations leading to regioselectivity. It reveals significant $\pi_{dienophile} \rightarrow \pi^*_{diene}$ and $\pi_{diene} \rightarrow \pi^*_{dienophile}$ interactions (Table 2). It is noteworthy that the two transition structures differ in the stabilization energies associated with the $\pi^*_{C9-C10} \rightarrow \pi^*_{C11-C12}$ interaction significantly, $\mathbf{TS_m}$ being stabilized more effectively.

Table 2. Stabilization energies E_{jj} (kcal mol^{-1}) of major interactions in the transition structures $\mathbf{TS_m}$ and $\mathbf{TS_p}$ obtained from NBO analysis

Interactions	Gas phase		$CHCl_3$	
	$\mathbf{TS_m}$	$\mathbf{TS_p}$	$\mathbf{TS_m}$	$\mathbf{TS_p}$
$\pi_{P2-C3} \rightarrow \pi^*_{C9-C10}$	12.58	13.94	13.29	14.64
$\pi_{P2-C3} \rightarrow \pi^*_{C11-C12}$	12.22	13.68	11.89	13.26
$\pi_{C9-C10} \rightarrow \pi^*_{P2-C3}$	31.00	25.26	30.79	25.47
$\pi_{C11-C12} \rightarrow \pi^*_{P2-C3}$	10.73	15.26	11.08	15.80
$\pi_{C11-C12} \rightarrow \pi^*_{C9-C10}$	20.29	20.84	21.18	21.19
$\pi_{C9-C10} \rightarrow \pi^*_{C11-C12}$	15.43	16.91	15.33	16.79
$n_{P2} \rightarrow \pi^*_{C9-C10}$	12.86	12.15	12.47	11.75
$\pi^*_{P2-C3} \rightarrow \pi^*_{C11-C12}$	14.40	16.53	14.02	16.04
$\pi^*_{P2-C3} \rightarrow \pi^*_{C9-C10}$	45.96	47.08	45.12	45.89
$\pi^*_{C9-C10} \rightarrow \pi^*_{C11-C12}$	246.24	142.21	215.51	129.51

3. Conclusion

[1,4,2]Diazaphospholo[4,5-*a*]pyridines undergo readily Diels–Alder reaction at its >C=P– functionality. The reactions are accompanied by *endo* stereoselectivity and high regioselectivity, the regioisomer having phosphorus and methyl group in 1:3 positions being preferred. The DFT calculations successfully reproduce the experimental regioselectivity results.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of dry argon or nitrogen in flame dried glass apparatus using Schlenk technique. Solvents were freshly dried and distilled. Commercially available 2,3-dimethylbutadiene, isoprene, sulfur and selenium were used without further purification. [1,4,2]Diazaphospholo[4,5-*a*]pyridines **1** were prepared according to the methods reported earlier.[25,26]

Melting points were determined in closed capillaries and are uncorrected. NMR spectra were recorded on a JEOL EX-400 spectrometer at 399.8 MHz (^{1}H) and at 100.5 MHz (^{13}C) or on a JEOL FX-90Q spectrometer at 89.55 MHz (^{1}H), at 22.49 MHz (^{13}C) and at 36.23 MHz (^{31}P). ^{1}H and ^{13}C NMR chemical shifts refer to TMS as internal standard and ^{31}P NMR chemical shifts to 85% H_3PO_4 as external standard. Assignments of the ^{1}H and ^{13}C NMR signals are based on ^{1}H,^{1}H COSY45, ^{1}H,^{13}C HETCOR and ^{1}H coupled ^{13}C NMR spectra for selected compounds.

4.2. Computational methods

All calculations were carried out using Gaussian 03 package.[42] Density functional theory (DFT) with B3LYP hybrid functional has been used due to an increasing number of recent reports showing it to be in good agreement with experimental results of Diels–Alder reactions.[4,38,43] All stationary points corresponding to reactants, cycloadducts and transition structures were optimized at B3LYP/6-311G** level followed by single point energy calculations at B3LYP/6-311++G** level. All optimizations were subjected to frequency calculations at the same level; the transition structures were confirmed by the presence of only one imaginary frequency. Unscaled zero point energy

corrections (ZPE) computed at B3LYP/6-311G** level have been used for calculation of total energies. Solvent effects were investigated by following Tomasi's polarized continuum model using integral equation formalism method (IEFPCM),[44,45] by calculating single point energy of the optimized geometry for the gas-phase species.

4.3. General procedure for the reaction of 1 with 2,3-dimethylbutadiene and sulfur (or selenium) (2a–f)

To a well stirred solution of **1** (2.5 mmol) in chloroform (20 mL) were added 1 equiv of 2,3-dimethylbutadiene (205 mg, 0.28 mL, 2.5 mmol) and equimolar amount of sulfur (80 mg, 2.5 mmol) or selenium (198 mg, 2.5 mmol). After stirring the reaction mixture at ambient temperature (25 °C) for about 7 days the reaction was complete. The solvent was removed under reduced pressure and the residue was recrystallized from methylene chloride to afford spectroscopically pure yellow solid.

4.3.1. Compound 2a. Yellow solid (138 mg, 22%), mp 152–53 °C (CH_2Cl_2); (Found: C, 57.24; H, 5.98; N, 10.93, $C_{12}H_{15}N_2PS$ (250.3) requires C, 57.58; H, 6.04; N, 11.19%); ^{31}P NMR (C_6D_6); δ 87.4; ^{1}H NMR ($CDCl_3$): δ 7.25 (d, 1H, $^3J_{HH}$=7.3 Hz, H-5), 7.12 (ddd, 1H, $^3J_{HH}$=9.3, 6.3 Hz, $^5J_{PH}$=2.4 Hz, H-7), 6.54 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^4J_{HH}$=1.0 Hz, H-8), 6.10 (ddd, 1H, $^3J_{HH}$=6.3, 7.3 Hz, $^4J_{HH}$=1.0 Hz, H-6), 4.17 (broad, 1H, H-3), 2.82 (dd, 1H, $^2J_{HH}$=15.1 Hz, $^3J_{PH}$=14.6 Hz, H_A of 12-CH_2), 2.79 (t, 1H, $^2J_{PH}$=$^2J_{HH}$=15.6 Hz, H_A of 9-CH_2), 2.72 (dd, 1H, $^2J_{HH}$=15.6 Hz, $^2J_{PH}$=15.3 Hz, H_B of 9-CH_2), 2.52 (ddd, 1H, $^3J_{PH}$=27.8 Hz, $^2J_{HH}$=15.1 Hz, $^3J_{HH}$=4.4 Hz, H_B of 12-CH_2), 1.62 (s, 3H, 11-CH_3), 1.46 (d, 3H, $^4J_{PH}$=3.9 Hz, 10-CH_3); ^{13}C NMR ($CDCl_3$): 163.0 (d, $^2J_{PC}$=9.9 Hz, C-8a), 139.4 (d, $^4J_{PC}$=2.8 Hz, C-7), 133.6 (d, $^3J_{PC}$=11.3 Hz, C-5), 126.3 (d, $^2J_{PC}$=11.4 Hz, C-10), 125.2 (d, $^3J_{PC}$=12.8 Hz, C-11), 118.0 (d, $^3J_{PC}$=21.8 Hz, C-8), 107.9 (C-6), 60.8 (d, $^1J_{PC}$=61.1 Hz, C-3), 40.4 (d, $^1J_{PC}$=62.0 Hz, C-9), 36.1 (d, $^2J_{PC}$=3.3 Hz, C-12), 21.0 (d, $^3J_{PC}$=6.2 Hz, 10-CH_3), 20.8 (d, $^4J_{PC}$=3.3 Hz, 11-CH_3).

4.3.2. Compound 2b. Yellow solid (350 mg, 53%), mp 161–62 °C (CH_2Cl_2); (Found: C, 58.97; H, 6.72; N, 11.01, $C_{13}H_{17}N_2PS$ (264.3) requires C, 59.07; H, 6.48; N, 10.59%); ^{31}P NMR ($CDCl_3$); δ 88.5; ^{1}H NMR ($CDCl_3$): δ 7.24 (s, 1H, H-5), 7.17 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^4J_{PH}$=2.0 Hz, H-8), 6.69 (d, 1H, $^3J_{HH}$=9.3 Hz, H-7), 4.33 (ddd, 1H, $^2J_{PH}$=4.9 Hz, $^3J_{HH}$=4.4 Hz, $^3J_{HH}$=4.3 Hz, H-3), 2.97 (ddd, 1H, $^2J_{HH}$=15.6 Hz, $^3J_{PH}$=14.2 Hz, $^3J_{HH}$= unresolved, H_A of 12-CH_2), 2.94 (t, 1H, $^2J_{PH}$=$^2J_{HH}$=16.4 Hz, H_A of 9-CH_2), 2.87 (dd, 1H, $^2J_{HH}$=16.4 Hz, $^2J_{PH}$=13.7 Hz, H_B of 9-CH_2), 2.68 (ddd, 1H, $^3J_{PH}$=27.8 Hz, $^2J_{HH}$=15.6 Hz, $^3J_{HH}$=4.4 Hz, H_B of 12-CH_2), 2.14 (d, 3H, $^4J_{HH}$=1.0 Hz, 6-CH_3), 1.77 (s, 3H, 11-CH_3–), 1.62 (d, 3H, $^4J_{PH}$=4.4 Hz, 10-CH_3); ^{13}C NMR ($CDCl_3$): 161.8 (d, $^2J_{PC}$=9.2 Hz, C-8a), 142.3 (d, $^1J_{CH}$=160.2 Hz, C-7), 131.0 (dddd, $^1J_{CH}$=178.5 Hz, $^3J_{PC}$=10.6 Hz, $^3J_{CH}$=6.1, 4.6 Hz, C-5), 126.3 (d, $^2J_{PC}$=10.7 Hz, C-10), 125.3 (d, $^3J_{PC}$=13.8 Hz, C-11), 117.8 (C-6), 117.5 (dd, $^1J_{CH}$=170.9 Hz, $^3J_{PC}$=21.4 Hz, C-8), 61.1 (dd, $^1J_{CH}$=152.6 Hz, $^1J_{PC}$=61.0 Hz, C-3), 40.5 (tdd, $^1J_{CH}$=132.0 Hz, $^1J_{PC}$=62.6 Hz, $^3J_{CH}$=4.6 Hz, C-9), 36.0 (td, $^1J_{CH}$=129.7 Hz, $^2J_{PC}$=4.6 Hz, C-12), 21.0 (qd, $^1J_{CH}$=125.4 Hz, $^3J_{PC}$=6.1 Hz, 10-CH_3), 20.9 (qd, $^1J_{CH}$=125.8 Hz, $^4J_{PC}$=3.1 Hz, 11-CH_3), 17.1 (qd, $^1J_{CH}$=128.2 Hz, $^3J_{CH}$=4.6 Hz, 6-CH_3).

4.3.3. Compound 2c. Pale yellow solid (469 mg, 71%), mp 163–64 °C (CH_2Cl_2); (Found: C, 58.87; H, 6.35; N, 10.36, $C_{13}H_{17}N_2PS$ (264.3) requires C, 59.07; H, 6.48; N, 10.59%); ^{31}P NMR ($CDCl_3$); δ 96.0; ^{1}H NMR ($CDCl_3$): δ 7.13 (d, 1H, $^3J_{HH}$=7.0 Hz, H-5), 6.34 (dd, 1H, $^4J_{PH}$=0.9 Hz, $^4J_{HH}$=1.9 Hz, H-8), 5.94 (dd, 1H, $^3J_{HH}$=7.0 Hz, $^4J_{HH}$=1.9 Hz, H-6), 4.11 (ddd, 1H, $^2J_{PH}$=4.9 Hz, $^3J_{HH}$=4.4 Hz, $^3J_{HH}$=3.9 Hz, H-3), 2.78 (dd, 1H, $^2J_{HH}$=15.5 Hz, $^3J_{PH}$=15.4 Hz, H_A of 12-CH_2), 2.76 (t, 1H, $^2J_{PH}$=$^2J_{HH}$=16.1 Hz, H_A of 9-CH_2), 2.68 (dd, 1H, $^2J_{PH}$=16.2 Hz, $^2J_{HH}$=16.1 Hz, H_B of 9-CH_2), 2.48 (ddd, 1H, $^3J_{PH}$=27.9 Hz, $^2J_{HH}$=15.5 Hz, $^3J_{HH}$=4.4 Hz, H_B of 12-CH_2), 2.04 (s, 3H, 7-CH_3), 1.59 (s, 3H, 11-CH_3-), 1.44 (d, 3H, $^4J_{PH}$=4.4 Hz, 10-CH_3); ^{13}C NMR ($CDCl_3$): 162.9 (d, $^2J_{PC}$=9.9 Hz, C-8a), 151.5 (d, $^4J_{PC}$=2.6 Hz, C-7), 132.6 (ddd, $^1J_{CH}$=179.3 Hz, $^3J_{PC}$=10.9 Hz, $^3J_{CH}$=4.9 Hz, C-5), 126.3 (d, $^2J_{PC}$=11.6 Hz, C-10), 125.6 (d, $^3J_{PC}$=12.8 Hz, C-11), 116.2 (dddq, $^1J_{CH}$=168.0 Hz, $^3J_{PC}$=21.3 Hz, $^3J_{CH}$=6.2 Hz, C-8), 110.6 (d, $^1J_{CH}$=168.7 Hz, C-6), 60.5 (dd, $^1J_{CH}$=150.8 Hz, $^1J_{PC}$=60.9 Hz, C-3), 40.5 (tdq, $^1J_{CH}$=131.9 Hz, $^1J_{PC}$=62.1 Hz, $^3J_{CH}$=5.0 Hz, C-9), 36.0 (td, $^1J_{CH}$=130.2 Hz, $^2J_{PC}$=3.3 Hz, C-12), 21.6 (qddd, $^1J_{CH}$=128.2 Hz, $^3J_{CH}$=4.4, 3.8 Hz, $^4J_{CH}$=1.0 Hz, 7-CH_3), 21.0 (qd, $^1J_{CH}$=125.6 Hz, $^3J_{PC}$=5.9 Hz, 10-CH_3), 20.9 (qd, $^1J_{CH}$=125.1 Hz, $^4J_{PC}$=3.3 Hz, 11-CH_3).

4.3.4. Compound 2d. Pale yellow solid (358 mg, 46%), mp 186–87 °C (CH_2Cl_2); (Found: C, 50.17; H, 5.56; N, 8.83, $C_{13}H_{17}N_2PSe$ (311.2) requires C, 50.17; H, 5.50; N, 9.00%); ^{31}P NMR ($CDCl_3$); δ 77.2 ($^1J_{SeP}$=756.8 Hz); ^{1}H NMR ($CDCl_3$): δ 7.22 (d, 1H, $^3J_{HH}$=6.8 Hz, H-5), 6.40 (d, 1H, $^4J_{PH}$=1.7 Hz, H-8), 6.03 (dd, 1H, $^3J_{HH}$=6.8 Hz, $^4J_{HH}$=1.7 Hz, H-6), 4.45 (dt, 1H, $^2J_{PH}$=4.4 Hz, $^3J_{HH}$=4.1 Hz, H-3), 2.97 (t, 1H, $^2J_{PH}$=$^2J_{HH}$=16.1 Hz, H_A of 9-CH_2), 2.81–2.89 (m, 2H, H_A of 12-CH_2, H_B of 9-CH_2), 2.56 (ddd, 1H, $^3J_{PH}$=27.6 Hz, $^2J_{HH}$=15.4 Hz, $^3J_{HH}$=4.1 Hz, H_B of 12-CH_2), 2.13 (dd, 3H, $^4J_{HH}$=1.7, 0.8 Hz, 7-CH_3), 1.7 (s, 3H, 11-CH_3), 1.55 (d, 3H, $^4J_{PH}$=4.9 Hz, 10-CH_3); ^{13}C NMR ($CDCl_3$): 163.0 (dd, $^2J_{PC}$=11.9 Hz, $^3J_{CH}$=2.8 Hz, C-8a), 151.5 (dd, $^2J_{CH}$=5.7 Hz, $^4J_{PC}$=2.9 Hz, C-7), 132.3 (ddd, $^1J_{CH}$=179.1 Hz, $^3J_{PC}$=10.9 Hz, $^3J_{CH}$=4.7 Hz, C-5), 126.7 (d, $^2J_{PC}$=12.3 Hz, C-10), 125.4 (d, $^3J_{PC}$=12.3 Hz, C-11), 116.5 (ddd, $^1J_{CH}$=166.8 Hz, $^3J_{PC}$=21.3 Hz, $^3J_{CH}$=7.1 Hz, C-8), 110.7 (dddq, $^1J_{CH}$=168.7 Hz, $^3J_{CH}$=7.5, 4.8 Hz, $^2J_{CH}$=1.9 Hz, C-6), 62.3 (dd, $^1J_{CH}$=152.4 Hz, $^1J_{PC}$=51.6 Hz, C-3), 42.4 (td, $^1J_{CH}$=137.5 Hz, $^1J_{PC}$=51.7 Hz, C-9), 36.0 (td, $^1J_{CH}$=130.1 Hz, $^2J_{PC}$=4.3 Hz, C-12), 21.6 (qt, $^1J_{CH}$=128.4 Hz, $^3J_{CH}$=4.5 Hz, 7-CH_3), 21.0 (qd, $^1J_{CH}$=127.9 Hz, $^3J_{PC}$=4.7 Hz, 10-CH_3), 20.9 (qd, $^1J_{CH}$=128.4 Hz, $^4J_{PC}$=2.3 Hz, 11-CH_3).

4.3.5. Compound 2e. Crystalline pale yellow solid (362 mg, 45%), mp 110–12 °C (CH_2Cl_2); (Found: C, 55.52; H, 5.89; N, 8.60, $C_{15}H_{19}N_2O_2PS$ (322.4) requires C, 55.89; H, 5.94; N, 8.69%); ^{31}P NMR ($CDCl_3$); δ 96.9; ^{1}H NMR ($CDCl_3$): δ 7.38 (t, 1H, $^3J_{HH}$=6.6 Hz, H-7), 7.34 (d, 1H, $^3J_{HH}$=6.8 Hz, H-5), 6.84 (d, 1H, $^3J_{HH}$=6.6 Hz, H-8), 6.34 (t, 1H, $^3J_{HH}$=6.8 Hz, H-6), 4.26 (q, 2H, $^3J_{HH}$=7.1 Hz, OCH_2), 3.39 (t, 1H, $^2J_{HH}$=$^3J_{PH}$=16.8 Hz, H_A of 12-CH_2), 2.86–3.04 (m, 2H, 9-CH_2), 2.70 (dd, 1H, $^3J_{PH}$=22.5 Hz,

$^{2}J_{HH}$=16.8 Hz, H_B of 12-CH_2), 1.68 (s, 3H, 11-CH_3), 1.46 (d, 3H, $^{4}J_{PH}$=5.6 Hz, 10-CH_3), 1.25 (t, 3H, $^{3}J_{HH}$=7.1 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): 167.6 (d, $^{2}J_{PC}$=11.0 Hz, CO), 145.5 (d, $^{2}J_{PC}$=13.9 Hz, C-8a), 141.7 (d, $^{3}J_{PC}$=2.5 Hz, C-5), 135.0 (C-7), 127.0 (d, $^{2}J_{PC}$=13.5 Hz, C-10), 125.9 (d, $^{3}J_{PC}$=12.5 Hz, C-11), 118.1 (d, $^{3}J_{PC}$=13.9 Hz, C-8), 110.1 (C-6), 71.8 (d, $^{1}J_{PC}$=55.6 Hz, C-3), 63.9 (OCH_2), 57.8 (d, $^{1}J_{PC}$=62.0 Hz, C-9), 49.5 (d, $^{2}J_{PC}$=2.4 Hz, C-12), 20.9 (10-CH_3), 19.9 (11-CH_3), 14.8 (OCH_2CH_3).

4.3.7. Compound 2f. Crystalline pale yellow solid (323 mg, 35%), mp 119–21 °C (CH_2Cl_2); (Found: C, 48.49; H, 5.05; N, 7.65, $C_{15}H_{19}N_2O_2PSe$ (369.3) requires C, 48.79; H, 5.19; N, 7.59%); ^{31}P NMR ($CDCl_3$); δ 72.2 ($^{1}J_{SeP}$=797.6 Hz); ^{1}H NMR ($CDCl_3$): δ 7.45 (t, 1H, $^{3}J_{HH}$=7.0 Hz, H-7), 7.28 (d, 1H, $^{3}J_{HH}$=7.0 Hz, H-5), 7.01 (d, 1H, $^{3}J_{HH}$=7.0 Hz, H-8), 6.47 (t, 1H, $^{3}J_{HH}$=7.0 Hz, H-6), 4.24 (q, 2H, $^{3}J_{HH}$=7.0 Hz, OCH_2), 3.58–2.45 (m, 4H, 9-CH_2, 12-CH_2), 1.69 (s, 3H, 11-CH_3), 1.38 (d, 3H, $^{4}J_{PH}$=5.0 Hz, 10-CH_3), 1.24 (q, 3H, $^{3}J_{HH}$=7.0 Hz, OCH_2CH_3).

4.4. Reaction of 1b with isoprene and selenium (2g+2g′)

To a well stirred solution of **1b** (750 mg, 5 mmol) in chloroform (20 mL) were added 1 equiv of isoprene (340 mg, 0.5 mL, 5 mmol) and equimolar amount of selenium (395 mg, 5 mmol). Progress of the reaction was monitored by ^{31}P NMR. After stirring the reaction mixture at ambient temperature (25 °C) for 7 days, the formation of two regioisomers **2g** and **2g′** in 4:1 ratio was indicated. The solvent was removed under reduced pressure and the residue was recrystallized from methylene chloride to afford yellow solid mixture of **2g** and **2g′** (743 mg, 50%); (Found: C, 47.97; H, 5.01; N, 9.51, $C_{12}H_{15}N_2PSe$ (297.2) requires C, 48.49; H, 5.08; N, 9.42%).

4.4.1. Compound 2g. (80%) ^{31}P NMR ($CDCl_3$): δ 75.6 ($^{1}J_{SeP}$=756.8 Hz); ^{1}H NMR ($CDCl_3$): δ 7.10 (d, 1H, $^{3}J_{HH}$=9.3 Hz, H-8), 7.06 (s, 1H, H-5), 6.60 (d, 1H, $^{3}J_{HH}$=9.3 Hz, H-7), 5.41 (m, 1H, H-11), 4.50 (dt, 1H, $^{2}J_{PH}$=4.4 Hz, $^{3}J_{HH}$=4.1 Hz, H-3), 3.25–3.15 (m, 1H, H_A of 12-CH_2), 3.06 (dd, 1H, $^{2}J_{PH}$=16.3 Hz, $^{2}J_{HH}$=15.9 Hz, H_A of 9-CH_2), 4.50 (dd, 1H, $^{2}J_{HH}$=15.9 Hz, $^{2}J_{PH}$=14.1 Hz, H_B of 9-CH_2), 2.76–2.65 (m, 1H, H_B of 12-CH_2), 2.08 (s, 3H, 6-CH_3), 1.76 (s, 3H, 10-CH_3).

4.4.2. Compound 2g′. (20%) ^{31}P NMR ($CDCl_3$): δ 75.8 ($^{1}J_{SeP}$=756.8 Hz); ^{1}H NMR ($CDCl_3$): δ 7.48–6.59 (m, 3H, H-5, H-7, H-8), 5.30 (m, 1H, H-10), 4.60 (m, 1H, H-3), 3.10–2.65 (m, 4H, 12-CH_2 and 9-CH_2), 2.25 (s, 3H, 6-CH_3), 1.82 (s, 3H, 11-CH_3).

4.5. Reaction of 1c with 2,3-dimethylbutadiene and methyl iodide (3c)

To a well stirred solution of **1c** (1.1 g, 7.3 mmol) in chloroform (25 mL) were added 2,3-dimethylbutadiene (600 mg, 0.8 mL, 7.3 mmol) and equimolar amount of methyl iodide (1 g, 0.44 mL, 7.3 mmol). The reaction was completed by heating the reaction mixture at 60 °C for 5 h. The solvent was removed under reduced pressure and the residue was recrystallized from methylene chloride to afford yellow solid (1.690 g, 62%), mp 213–14 °C; (Found: C, 44.64; H, 5.31; N, 7.37, $C_{14}H_{20}N_2PI$ (374.2) requires C, 44.93; H, 5.38; N, 7.48%); ^{31}P NMR ($CDCl_3$); δ 70.4; ^{1}H NMR ($CDCl_3$): δ 8.60 (d, 1H, $^{3}J_{HH}$=6.7 Hz, H-5), 6.83 (d, 1H, $^{4}J_{HH}$=1.7 Hz, H-8), 6.75 (dd, 1H, $^{3}J_{HH}$=6.7 Hz, $^{4}J_{HH}$=1.7 Hz, H-6), 5.93 (dt, 1H, $^{2}J_{PH}$=35.3 Hz, $^{3}J_{HH}$=4.1 Hz, H-3), 3.08 (d, 3H, $^{3}J_{PH}$=7.1 Hz, 1-CH_3), 3.02 (ddd, 1H, $^{2}J_{HH}$=15.8 Hz, $^{3}J_{PH}$=13.0 Hz, $^{3}J_{HH}$=4.1 Hz, H_A of 12-CH_2), 2.66 (dd, 1H, $^{2}J_{HH}$=15.8 Hz, $^{3}J_{HH}$=4.1 Hz, H_B of 12-CH_2), 2.57 (dd, 1H, $^{2}J_{PH}$=18.4 Hz, $^{3}J_{HH}$=16.3 Hz, H_A of 9-CH_2), 2.43 (s, 3H, 7-CH_3), 2.24 (dd, 1H, $^{2}J_{PH}$=16.5 Hz, $^{2}J_{HH}$=16.3 Hz, H_B of 9-CH_2), 1.65 (s, 3H, 11-CH_3), 1.52 (s, 3H, 10-CH_3-); ^{13}C NMR ($CDCl_3$): 158.4 (d, $^{3}J_{CH}$=5.9 Hz, C-7), 155.8 (d, $^{2}J_{PC}$=1.2 Hz, C-8a), 137.6 (dd, $^{1}J_{CH}$=187.7 Hz, $^{3}J_{CH}$=5.0 Hz, C-5), 126.6 (m, $^{2}J_{PC}$=1.2 Hz, $^{2}J_{CH}$ not resolved, C-10), 124.7 (C-11), 116.3 (ddqd, $^{1}J_{CH}$=172.3 Hz, $^{3}J_{CH}$=7.4, 4.7 Hz, $^{2}J_{CH}$=1.9 Hz, C-6), 109.2 (dd, $^{1}J_{CH}$=170.4 Hz, $^{3}J_{CH}$=5.9 Hz, C-8), 60.7 (dd, $^{1}J_{CH}$=154.3 Hz, $^{1}J_{PC}$=25.6 Hz, C-3), 36.1 (td, $^{1}J_{CH}$=130.2 Hz, $^{2}J_{PC}$=1.2 Hz, C-12), 32.7 (qd, $^{1}J_{CH}$=140.6 Hz, $^{2}J_{PC}$=16.8 Hz, 1-CH_3), 31.8 (tdd, $^{1}J_{CH}$=131.7 Hz, $^{1}J_{PC}$=34.8 Hz, $^{3}J_{CH}$=4.5 Hz, C-9), 22.4 (qd, $^{1}J_{CH}$=129.3 Hz, $^{3}J_{CH}$=4.3 Hz, 7-CH_3), 20.7 (qt, $^{1}J_{CH}$=123.1 Hz, $^{3}J_{CH}$ not resolved, 10-CH_3), 20.6 (qt, $^{1}J_{CH}$=120.3 Hz, $^{3}J_{CH}$ not resolved, 11-CH_3).

4.6. Reaction of 1c with isoprene and methyl iodide (3d+3d′)

To a well stirred solution of **1c** (753 mg, 5 mmol) in chloroform (20 mL) were added isoprene (340 mg, 0.5 mL, 5 mmol) and equimolar amount of methyl iodide (685 mg, 0.3 mL, 5 mmol). The reaction was complete after stirring the reaction mixture at ambient temperature (25 °C) for 48 h. Thereafter the solvent was removed under reduced pressure and the residue was recrystallized from methylene chloride to afford yellow solid mixture of **3d** and **3d′**. (936 mg, 72%); (Found: C, 43.63; H, 5.31; N, 7.77, $C_{13}H_{18}N_2PI$ (360.2) requires C, 43.35; H, 5.03; N, 7.77%).

4.6.1. Compound 3d. ^{31}P NMR ($CDCl_3$); δ 70.4; ^{1}H NMR ($CDCl_3$): δ 8.57 (d, 1H, $^{3}J_{HH}$=6.8 Hz, H-5), 6.82 (d, 1H, $^{4}J_{HH}$=1.7 Hz, H-8), 6.78 (dd, 1H, $^{3}J_{HH}$=6.8 Hz, $^{4}J_{HH}$=1.7 Hz, H-6), 5.96 (dt, 1H, $^{2}J_{PH}$=34.7 Hz, $^{3}J_{HH}$=4.0 Hz, H-3), 5.35 (m, 1H, H-11), 3.05 (d, 3H, $^{3}J_{PH}$=7.4 Hz, 1-CH_3), 3.01–3.17 (m, 1H, H_A of 12-CH_2), 2.49–2.67 (m, 1H, H_B of 12-CH_2), 2.49–2.67 (m, 1H, H_A of 9-CH_2), 2.41 (s, 3H, 7-CH_3), 2.29 (t, 1H, $^{2}J_{PH}$=$^{2}J_{HH}$=17.1 Hz, H_B of 9-CH_2), 1.55 (s, 3H, 10-CH_3); ^{13}C NMR ($CDCl_3$): 158.3 (C-7), 155.8 (C-8a), 137.3 (C-5), 135.3 (C-10), 117.7 (C-6), 116.2 (C-11), 109.3 (C-8), 60.2 (d, $^{1}J_{PC}$=29.8 Hz, C-3), 33.7 (C-12), 32.6 (d, $^{2}J_{PC}$=16.8 Hz, 1-CH_3), 25.5 (d, $^{1}J_{PC}$=35.1 Hz, C-9), 24.8 (10-CH_3), 22.3 (7-CH_3).

4.6.2. Compound 3d′. ^{31}P NMR ($CDCl_3$); δ 68.8; ^{1}H NMR ($CDCl_3$): δ 8.45 (d, 1H, $^{3}J_{HH}$=6.9 Hz, H-5), 6.82 (d, 1H, $^{4}J_{HH}$=1.7 Hz, H-8), 6.73 (dd, 1H, $^{3}J_{HH}$=6.9 Hz, $^{4}J_{HH}$=1.7 Hz, H-6), 5.80 (dt, 1H, $^{2}J_{PH}$=35.4 Hz, $^{3}J_{HH}$=3.8 Hz, H-3), 5.51 (m, 1H, H-10), 3.01–3.17 (m, 1H, H_A of 12-CH_2), 3.08 (d, 3H, $^{3}J_{PH}$=7.3 Hz, 1-CH_3), 2.49–2.67 (m, 2H, H_A of 9-CH_2, H_B of 12-CH_2), 2.41 (s, 3H, 7-CH_3), 2.13 (t, 1H, $^{2}J_{PH}$=$^{2}J_{HH}$=16.4 Hz, H_B of 9-CH_2), 1.66 (s, 3H, 11-CH_3); ^{13}C NMR ($CDCl_3$): 158.7 (C-7), 155.6 (C-8a), 137.2 (C-5),

134.5 (C-10), 118.3 (C-6), 116.6 (C-10), 109.2 (C-8), 60.5 (d, $^{1}J_{PC}=30.2$ Hz, C-3), 32.7 (d, $^{2}J_{PC}=17.5$ Hz, 1-CH_3), 30.1 (d, $^{1}J_{PC}=35.9$ Hz, C-9), 29.3 (C-12), 24.7 (11-CH_3), 22.4 (7-CH_3).

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Sesquiterpenoids from *Ligularia virgaurea* spp. *oligocephala*

Quan-Xiang Wu,[a] Ai-Mei Yang[b] and Yan-Ping Shi[a,b,*]

[a]*State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Repubic of China*
[b]*Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Repubic of China*

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Abstract—Four novel eremophilane-type sesquiterpene lactones, 6β,10α-dihydroxy-1-oxoeremophila-7(11),8(9)-dien-12,8-olide (**1**), 6β-acetyl-2-oxoeremophila-1(10),7(11), 8(9)-trien-12,8-olide (**2**), 6β,8β-diacetyl-2-oxoeremophila-1(10),7(11)-dien-12,8-olide (**3**), dimeric eremophilane ligulolide B (**5**), and known sesquiterpenoid, 6β,8α-diacetyleremophila-1(10),7(11)-dien-12,8-olide (**4**), were isolated from an extract of the whole plant of *Ligularia virgaurea* spp. *oligocephala*. The structure of **1** was confirmed by NMR spectra and single crystal X-ray crystallography investigation, as well as **2**, **3**, and **5** were elucidated by spectroscopic methods including 1D and 2D NMR spectra. A discussion of biogenesis of **5** was described. Cytotoxicities of compound **1** were measured in vitro against selected cancer cells human promyelocytic leukemia (HL-60), human ovarian (HO-8910) and human lung epithehial (A-549).

1. Introduction

The investigation of bioactive sesquiterpenoids from the Compositae plant family has been one of the subjects of our studies, in relation to the genera *Artemisia*, *Senecio*, *Carpesium*, *Halenia*, and *Ligularia*.[1] China has more numerous endemic *Ligularia* species than Europe and Japan,[2] therefore, we have focused on the chemical constituents of *Ligularia* species and reported the isolation of a number of new sesquiterpenoids, some compounds possessed novel carbon skeletons and showed interesting biological properties.[3] As part of our ongoing research program on the identification of novel bioactive constitutents from *Ligularia* species, we have investigated the whole plant of *Ligularia virgaurea* spp. *oligocephala*, which has long been used as traditional folk medicine for the treatment of stomachache and nausea.[4] As a result, four novel eremophilane-type sesquiterpene lactones, 6β,10α-dihydroxy-1-oxoeremophila-7(11),8(9)-dien-12,8-olide (**1**), 6β-acetyl-2-oxoeremophila-1(10),7(11),8(9)-trien-12,8-olide (**2**), 6β,8β-diacetyl-2-oxoeremophila-1(10),7(11)-dien-12,8-olide (**3**), dimeric eremophilane ligulolide B (**5**), along with 6β,8α-diacetyleremophila-1(10),7(11)-dien-12,8-olide (**4**),[5] were isolated from the extract of this species. In this study, we report the isolation and structural elucidation of the new compounds, together with the biological test of compound **1** against the HL-60, HO-8910 and A-549 tumor cell lines. As the similarity in the structures of ligulolide B (**5**) and the parent compounds, a brief discussion of their biogenesis was described.

2. Results and discussion

From an extract of the whole plant of *L. virgaurea* spp. *oligocephala* five eremophilanolides, novel eremophilanolides **1**, **2**, **3**, **5**, and known sesquiterpene **4**, were isolated. The known compound **4** was identified by direct comparison of their spectral data (^{1}H, ^{13}C NMR and DEPT 135) with literature values.[5] Compounds **1**, **2**, **3**, and **5** were sesquiterpene lactones, to the best of our knowledge, previously unreported (Fig. 1).

Compound **1** was obtained as colorless needles. The molecular formula of $C_{15}H_{18}O_5$ was deduced from the HR-EI-MS ($[M]^+$ m/z=278.1137). The ^{13}C NMR spectrum (Table 1) displayed 15 carbons including three methyls, two methylenes, three methines, and seven quaternary carbons, assigned by DEPT experiment. Its IR spectrum showed the absorption bands for hydroxyl (3360 cm^{-1}), carbonyl (1755 cm^{-1}) and double bond (1665 cm^{-1}) functions. In the downfield region of the ^{1}H and ^{13}C NMR spectra, there were some characteristic signals at δ_C=207.8 due to a ketone carbonyl group, δ_C=150.1, 125.6, 151.3, 105.3 and

Keywords: *Ligularia virgaurea* spp. *oligocephala*; Sesquiterpenoids; Eremophilane.
* Corresponding author at: State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Repubic of China. Tel.: +86 931 4968208; fax: +86 931 8277088;
e-mail addresses: shiyp@lzb.ac.cn; shiyp@lzu.edu.cn

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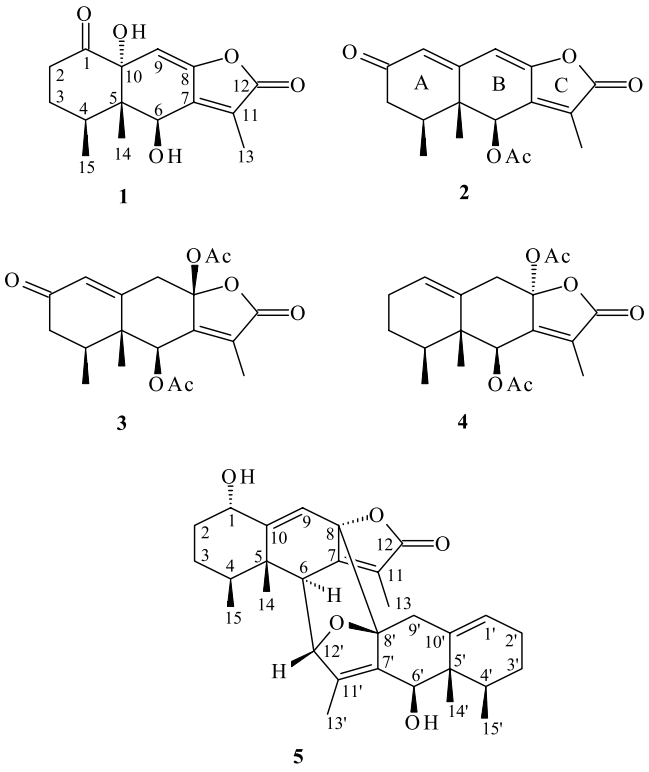

Figure 1. The molecular structures of sesquiterpenes **1**–**5**.

δ_H=6.19 (1H, s) ascribed to two double bond functions, and δ_C=171.4 for a carbonyl group as α,β-unsaturated-γ-lactone, along with δ_C=71.8 and δ_H=5.27 (1H, s) indicating an oxymethine, and δ_C=79.3 an oxygen-bonded quaternary carbon. Based on the above spectral data, compound **1** was considered to be an α,β-unsaturated-γ-lactone sesquiterpene with a ketone and two hydroxyl groups. The ^{1}H and ^{13}C NMR spectra of **1** were close to those of 6α,10α-dihydroxy-1-oxoeremophila-7(11),8(9)-dien-12,8-olide (**6**), which was previously reported[3a] (Table 1). It was revealed that both compounds contained the same molecular carbon skeleton. The intensive inspection of the NMR data of compound **1** and **6** indicated that the only difference between them was OH-6 as β-orientation in **1** and α-orientation in **6**, because of several chemical shift changes at H-6 and C-5, C-6, C-7, CH_3-14, CH_3-15 (Table 1). Consequently, the molecular structure of **1** could be elucidated as 6β,10α-dihydroxy-1-oxoeremophila-7(11), 8(9)-dien-12, 8-olide. The structure and relative stereochemistry of **1** was firmly established by X-ray crystallography (Fig. 2).

Compound **2** was obtained as a yellow gum with a molecular formula of $C_{17}H_{18}O_5$ determined by HR-ESI-MS ($[M+H]^+$ m/z=303.1221). Its IR spectrum showed the absorption bands for ketone carbonyl (1669 cm^{-1}), ester carbonyl (1779 cm^{-1}), α,β-unsaturated-γ-lactone carbonyl (1749 cm^{-1}) and double bond (1640 cm^{-1}) functions. In the downfield region of the ^{1}H and ^{13}C NMR spectra (Table 2), there were some characteristic signals at δ_C= 197.2 due to an α,β-unsaturated-γ-ketone, δ_C=129.1, 158.4, 143.8, 125.8, 151.4, 107.4 and δ_H=6.03 (1H, s) and 6.13 (1H, d, J=2.0 Hz) ascribed to three double bond functions, and δ_C=169.3 for a carbonyl group as α,β-unsaturated-γ-lactone, along with δ_C=73.8 and δ_H=6.14 (1H, d, J=2.0 Hz) indicating an oxymethine, δ_C=170.2, 21.3 and δ_H=2.23 (3H, s) indicating an acetyl group. Based on the above spectral data, compound **2** was considered to be an α,β-unsaturated-γ-lactone sesquiterpene with an α,β-unsaturated-γ-ketone and an acetyl group. The ^{1}H and ^{13}C NMR spectra (Table 2) of **2** were close to those of **1** and **4**. It was revealed that they contained the same molecular carbon skeleton. The position of the α,β-unsaturated-γ-ketone carbonyl group was assembled on the basis of key gHMBC correlations (H-3, 4/C-2 and H-1/C-3, 5, 9), the acetyl was deduced on the basis of strong gHMBC correlations (H-6/acetyl carbonyl carbon). The other substructures assembled into a structure (Fig. 1) were also unambiguously established by gHMBC correlations (Fig. 3). The relative stereochemistry of **2** could be determined on the basis of key NOESY correlations. The strong correlations of H_3-14 to H_3-15 and H-4 to H-6 indicated that CH_3-14, 15 and OAc-6 were in β-orientation

Table 1. NMR spectral data of compound **1** and known **6**

No.	**1**[a]		**6**[b]	
	δ_H (J)	δ_C (DEPT)	δ_H (J)	δ_C (DEPT)
1		207.8s		207.1s
2α	3.16ddd (8.0, 13.6, 13.6)	36.6t	3.15ddd (7.8, 13.6, 13.6)	36.5t
2β	2.09dd (4.4, 13.6)		2.32dd (4.4, 13.6)	
3α	1.72m	31.9t	1.93m	29.2t
3β	1.55dddd (4.4, 13.6, 13.6, 13.6)		1.62dddd (4.4, 13.6, 13.6, 13.6)	
4	2.83dq (6.8, 13.6)	34.2d	3.12dq (6.8, 13.6)	28.2d
5		52.2s		47.4s
6	5.27s	71.8d	4.50s	68.6d
7		150.1s		146.5s
8		151.3s		150.2s
9	6.19s	105.3d	6.18s	104.4d
10		79.3s		80.0s
11		125.6s		127.3s
12		171.4s		170.3s
13	2.00s	8.4q	2.05s	8.8q
14	0.61s	9.4q	0.57s	13.2q
15	1.11d (6.8)	18.2q	1.06d (6.8)	14.1q

[a] ^{1}H NMR (400.16 MHz, δ values, TMS) coupling constants (Hz) are in parentheses and ^{13}C NMR (100.32 MHz, δ values, TMS) multiplication determined by DEPT, measured in acetone-d_6.
[b] Compound **6** is 6α,10α-dihydroxy-1-oxoeremophila-7(11), 8(9)-dien-12, 8-olide, and the data have been reported in Ref. 3a.

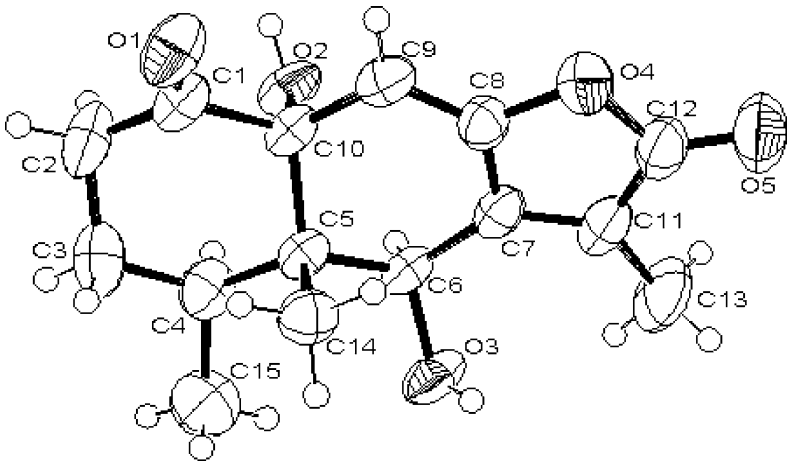

Figure 2. The X-ray crystal structure of **1**.

like compound **1**. Consequently, the molecular structure of **2** could be elucidated as 6β-acetyl-2-oxoeremophila-1(10),7(11),8(9)-trien-12,8-olide.

Compound **3** was obtained as a colorless gum with a molecular formula of $C_{19}H_{22}O_7$ determined by HR-ESI-MS ($[M+NH_4]^+$ m/z=380.1699). Its IR spectrum showed the absorption bands for ketone carbonyl (1753 cm^{-1}), ester carbonyl (1781 cm^{-1}) and double bond (1678 cm^{-1}) functions. In the downfield region of the ^1H and ^{13}C NMR spectra (Table 2), there were some characteristic signals at δ_C=197.4 due to a carbonyl group of an α,β-unsaturated-γ-ketone, δ_C=130.5, 156.3, 151.6, 126.3 and δ_H=5.99 (1H, d, J=2.0 Hz) ascribed to two double bond functions, and δ_C=170.0 for a carbonyl group of an α,β-unsaturated-γ-lactone, along with δ_C=75.6 and δ_H=5.65 (1H, d, J=2.0 Hz) indicating an oxymethine, and δ_C=101.8 a dioxygen-bonded quaternary carbon, δ_C=169.1, 21.5, 167.9, 21.0 and δ_H=2.22 (3H, s) and 2.04 (3H, s) indicating two acetyl groups. Based on the above spectral data, compound **3** was considered to be an α,β-unsaturated-γ-lactone sesquiterpene with an α,β-unsaturated-γ-ketone and two acetyl groups. The ^1H and ^{13}C NMR spectra (Table 2) of **3** were close to those of **2** except the acetyl groups. This was revealed that they contained the same molecular carbon skeleton. Comparing the ^1H and ^{13}C NMR data of **3** to **2** and **4** showed that the A ring was similar to **2** and B, C rings were closed to **4** (Table 2), and the structure of **3** was concluded by gHMBC correlations as shown in Figure 4. Similar to compound **2**, CH_3-14, CH_3-15, and OAc-6 of compound **3** were β-configuration. From the literature[3b,6,7] and the structure of **1**, in the A/B ring trans-series, the methyl singlet was upfield from the methyl doublet, however, the A/B cis-series the methyl doublet (CH_3-15) was upfield, we concluded that OAc-8 was β-orientation. Consequently, the molecular structure of **3** could be elucidated as 6β,8β-diacetyl-2-oxoeremophila-1(10),7(11)-dien-12,8-olide.

Table 2. NMR spectral data of compounds **2**, **3**, **4**[a]

No.	**2**		**3**		**4**	
	δ_H (J)	δ_C (DEPT)	δ_H (J)	δ_C (DEPT)	δ_H (J)	δ_C (DEPT)
1	6.03s	129.1d	5.99d (2.0)	130.5d	5.71 br t (4.0)	130.6d
2		197.2s		197.4s		24.3t
3	2.33dd (12.0, 3.6) 2.41d (12.0)	43.3t	2.28dd (12.0, 3.2) 2.36d (12.0)	42.8t		27.9t
4	2.42m	37.9d	2.31m	37.4d		36.6d
5		44.5s		46.5s		45.2s
6	6.14d (2.0)	73.8d	5.65d (2.0)	75.6d	5.51d (2.0)	77.2d
7		143.8s		151.6s		153.6s
8		151.4s		101.8s		102.9s
9	6.13d (2.0)	107.4d	3.46d (14.8) 2.58dd (14.8, 2.0)	42.8t	3.19d (14.4) 2.34ddd (14.4, 4.0, 2.0)	42.1t
10		158.4s		156.3s		132.5s
11		125.8s		126.3s		124.7s
12		169.3s		170.0s		170.7s
13	1.90d (2.0)	8.7q	1.95d (2.0)	8.5q	1.87d (2.0)	8.3q
14	1.26s	13.9q	1.17s	13.2q	0.93s	13.7q
15	1.03d (6.4)	17.2q	1.07d (6.4)	17.4q	0.95d (6.8)	17.4q
OAc		170.2s		169.1s		169.4s
	2.23s	21.3q	2.22s	21.5q	2.14s	21.4q
OAc′				167.9s		168.1s
			2.04s	21.0q	1.98s	20.9q

[a] ^1H NMR (400.16 MHz, δ values, TMS) coupling constants (Hz) are in parentheses and ^{13}C NMR (100.32 MHz, δ values, TMS) multiplication determined by DEPT, measured in $CDCl_3$.

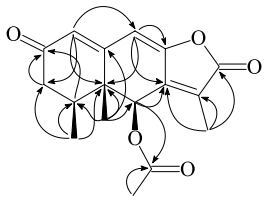

Figure 3. The significant gHMBC correlations (From H to C) of **2**.

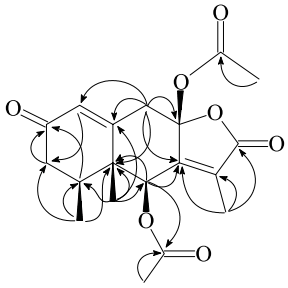

Figure 4. The significant gHMBC correlations (From H to C) of **3**.

Compound **5** was obtained as a colorless gum. Its HR-ESI-MS provided a quasi-molecular ion peak $[M+NH_4]^+$ at $m/z=496.3048$, suggesting the molecular formula as $C_{30}H_{38}O_5$ and 12 degrees of unsaturation. The IR spectrum showed the absorption bands for hydroxyl (3450 cm^{-1}) and α,β-unsaturated-γ-lactone carbonyl (1740 cm^{-1}), as well as double bond (1702 cm^{-1}). The ^{13}C NMR spectrum (Table 3) displayed 30 carbons including six methyls, five methylenes, eight methines and 11 quaternary carbons, assigned by DEPT experiment. In the upfield region of NMR spectrum, there were six methyl signals: $\delta_H=1.70$ (3H, s), 1.80 (3H, d, $J=2.4$ Hz) and $\delta_C=7.7$, 11.2 (olefinic methyl groups); $\delta_H=1.00$ (3H, s), 0.89 (3H, s) and $\delta_C=$ 20.1, 14.9; $\delta_H=0.95$ (3H, d, $J=6.8$ Hz), 0.97 (3H, d, $J=$ 6.8 Hz) and $\delta_C=14.9$, 16.7, which were the typical methyl signals of eremophilane from above compounds. Along with the molecular formula, compound **5** was predicted as a dimeric eremophilane sesquiterpene. In the downfield region of the NMR spectrum, there were some characteristic signals at $\delta_C=153.8$, 114.0, 164.0, 116.6, 127.2, 135.0, 137.7, 135.9 and $\delta_H=5.99$ (1H, d, $J=2.0$ Hz) and 5.70 (1H, t, $J=3.0$ Hz) ascribed to four double bond functions, and $\delta_C=174.7$ to a carbonyl group, indicating an α,β-unsaturated-γ-lactone, along with $\delta_C=69.3$ and $\delta_H=4.15$ (1H, m); $\delta_C=77.2$ and $\delta_H=4.12$ (1H, d, $J=2.4$ Hz) and $\delta_C=83.7$ and $\delta_H=4.60$ (1H, d, $J=2.0$ Hz) due to oxymethines, addition to $\delta_C=85.2$, 88.6 for two oxygen-bonded quaternary carbons. Taking into account the 12 degrees of unsaturation, compound **5** was a seven-cyclic structure with an ester carbonyl carbon, four double bonds and two hydroxyl groups. Extensive analyzes of gHMBC

Table 3. NMR spectral data of compound **5** in $CDCl_3$

No	^1H NMR[a]	^{13}C NMR[b]	gCOSY	gHMBC[c]	NOESY
1	4.15 (m)	69.3d	2, 3	2, 9, 10	14
2	2.05 (m)	35.9t	1, 3		
	2.07 (m)				
3	1.68 (m)	29.0t	1, 2	4	
	1.60 (m)				
4	2.10 (m)	35.5d	15	5, 14, 15	
5		47.6s			
6	2.77 (d, 2.0)	46.3d	12′	5, 7, 8, 10, 11, 14	1, 13, 14, 15, 12′, 13′
7		164.0s			
8		85.2s			
9	5.99 (d, 2.0)	114.0d		1, 5, 7, 10	
10		153.8s			
11		116.6s			
12		174.7s			
13	1.70 (s)	7.7q		7, 11, 12	
14	1.00 (s)	20.1q		4, 5, 6, 10	1, 6, 15
15	0.95 (d, 6.8)	14.9q	4	3, 4, 5	6, 14, 12′
1′	5.70 (t, 3.0)	127.2d	2′	2′, 3′, 5′	
2′	2.02 (m)	22.8t	1′		
	1.99 (m)				
3′	1.23 (m)	27.1t		1′, 2′, 4′, 5′, 15′	
	1.50 (m)				
4′	1.90 (m)	33.4d	15′	2′, 3′, 5′, 15′	6′
5′		44.2s			
6′	4.12 (d, 2.4)	77.2d			4′
7′		137.7s			
8′		88.6s			
9′	2.55 (d, 14.0)	37.1t		8, 1′, 5′, 7′, 8′, 10′	
	2.38 (d, 14.0)				
10′		135.0s			
11′		135.9s			
12′	4.60 (d, 2.0)	83.7d	6, 13′	7, 7′, 8′, 11′	6, 15
13′	1.80 (d, 2.4)	11.2q	12′	7′, 11′, 12′	
14′	0.89 (s)	14.9q		4′, 5′, 6′, 10′	15′
15′	0.97 (d, 6.8)	16.7q	4′	3′, 4′, 5′	14′

[a] Recorded at 400.16 MHz.
[b] Recorded at 100.63 MHz, multiplicity deduced by HMQC.
[c] Protons showing long-range correlation with indicated carbon. δ in ppm and TMS as the intensive standard.

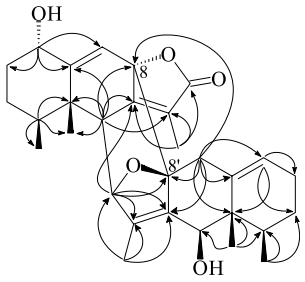

Figure 5. The significant gHMBC correlations (From H to C) of **5**.

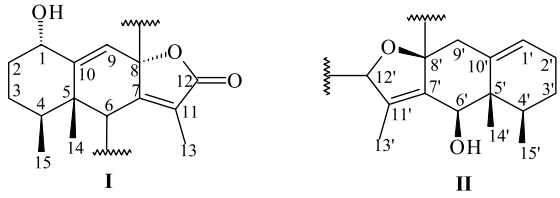

Figure 6. Partial structures from two-dimensional NMR for **5**.

data (Table 3 and Fig. 5) led to two substructures (**I** and **II**, Fig. 6). Substructure **I** was assembled on the basis of gHMBC correlations (H-1/C-2, 9, 10, H-4/C-5, 14, 15, H-6/C-5, 7, 8, 10, 11, 14, H-9/C-1, 5, 7, 10, H-13/C-7, 11, 12, H-14/C-4, 5, 6, 10 and H-15/C-3, 4, 5). Substructure **II** was also deduced on the basis of gHMBC correlations (H-1′/C-2′, 3′, 5′, H-3′/C-1′, 2′, 4′, 5′, 15′, H-4′/C-2′, 3′, 5′, 15′, H-9′/C-1′, 5′, 7′, 8′, 10′, H-12′/C-7′, 8′, 11′, H-13′/C-7′, 11′, 12′, H-14′/C-4′, 5′, 6′, 10′ and H-15′/C-3′, 4′, 5′). The two substructures (**I** and **II**) could be assembled into a structure (Fig. 1) by key gHMBC correlations between H-9′ with C-8 and H-12′ with C-7 as well as gCOSY cross peak between H-6 with H-12′. The relative stereochemistry of the ring system in **5** could be determined on the basis of key NOESY correlations. H_3-14 was correlated with H-1 and H_3-15. If CH_3-14 and CH_3-15 were appointed to β-orientation, the OH-1 was α-configuration. Although H-6 was correlated with H_3-14 and H_3-15, H-6 was an α-orientated equatorial bond in the stereostructure.[8] H-6 correlated with H-12′ and the smaller couple constant of $J_{6,12'}=2.0$ Hz in ^{1}H NMR showed that the dihedral angle between H-6 and H-12′ was almost 90°. From the literature[3b,6,7] and above compounds, it was concluded that OR-8 was α-configuration and OR-8′ was β-configuration. The correlation of H_3-14′ with H_3-15′ and H-4′ with H-6′ indicated the CH_3-14′, CH_3-15′ and OH-6′ had the identical orientation and was β-orientation[3b,6,7] Hence, compound **5** was elucidated as Figure 1 and named ligulolide B after the genus *Ligularia*. A plausible biosynthetic pathway was showed in Figure 7. The routes of which were previously discussed in the case of eremophilanes.[7,9] The naturally occurring 6β,8α-dihydroxy-1-oxoeremophila-7(11),9(10)-dien-12,8-olide (**7**) also obtained from the species by us[3b] and 6β-hydroxyfuroeremophila-1(10)-en (**8**)[10] were perhaps the parent compounds for novel dimeric eremophilane. First the ketone-1 of compound **7** was hydrogenated to obtain compound **7A**, then the two hydroxyls of C-6 and C-8 were oxygenated and eliminated to yield a key intermediate ion **7B**. The furan ring of compound **8** was also oxygenated to produce the endoperoxide **8A**, then eliminated O_2 to bring a central ion **8B**. The coupling reaction was occurred between the ion of **7B** and **8B**.

Sesquiterpene **1** was tested for ability to inhibit human tumor HL-60, HO-8910 and A-549 using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method.[11,12] Compared to Etoposide (VP-16), compound **1** exhibited no significant inhibitory effects with IC_{50} values over 100 μM against HL-60, HO-8910, and A-549 cells.

3. Experimental

3.1. General procedures

Melting points were determined with an X-4 Digital Display Micro-Melting point apparatus, and were uncorrected. Optical rotations were recorded in $CHCl_3$ using a Perkin Elmer 241 polarimeter. UV spectra were measured on a Spect 50-UV/Vis instrument (Analytic Jena AG). IR spectra were measured on an FTS165-IR instrument (Bio-Rad, USA). ^{1}H NMR (400.136 MHz) and ^{13}C NMR (100.62 MHz) were recorded on a Varian INOVA-400 FT-NMR spectrometer (USA) in $CDCl_3$ or acetone-d_6 with TMS as the internal standard. HRMS was recorded on a Bruker APEX II. Silica gel (200–300 mesh) used for column chromatography and silica gel (GF_{254}) for TLC are supplied by the Qingdao Marine Chemical Factory in China. Spots were detected on TLC by visualization under UV light, or by spraying with 98% H_2SO_4–EtOH (v/v=5/95) followed by heating at 110 °C.

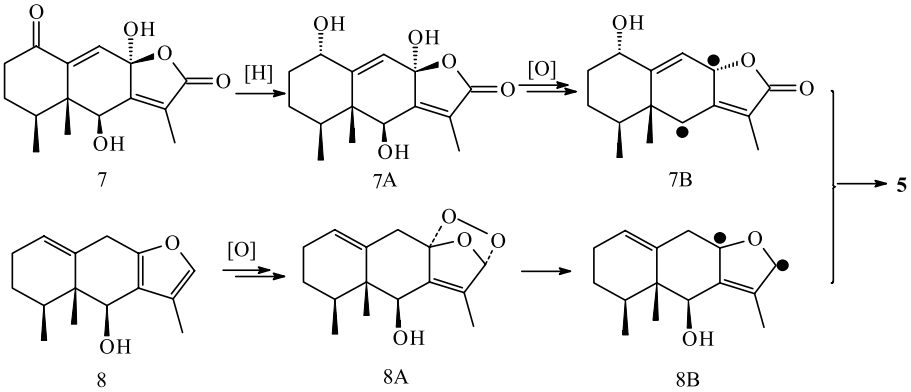

Figure 7. Possible biosynthetic pathway to **5**.

3.2. Plant material

The plant material, *L. virgaurea* spp. *oligocephala* Good (Compositae) was collected in Huzhu County, Qinghai province, P. R. China in August 2002 and was identified by adjunct Prof. Ji MA, Faculty of Pharmacy, First Military Medical University of PLA, Guangzhou, P.R. China. A voucher specimen (no. 2002001) has been deposited at Key Laboratory for Natural Medicine of Gansu province.

3.3. Extraction and isolation

The extraction procedure of the plant material was followed the literature procedure.[3] The EtOAc extract (75 g) was subjected to column chromatography on silica gel (1000 g) using petroleum ether (60–90 °C) with increasing volumes of acetone (V:V=50:1, 30:1, 15:1, 10:1, 7:1, 5:1, 3:1, 1:1, each about 3.0 L) as the eluent. Fractions were examined by TLC and combined to afford eight pooled fractions (1A–1H). Fraction 1E (6.0 g) was further fractionated on a silica gel column (80 g), eluting with petroleum ether–EtOAc (7/1) to give three fractions (fr.1E1, 200 mL; fr.1E2, 500 mL; fr.1E3, 300 mL). Fr.1E1 (2.4 g, 200 mL) was further fractionated on a silica gel column (65 g) using $CHCl_3$–acetone (15/1, 890 mL) to give fractions (fr.1E11, 100 mL; fr.1E12, 700 mL; fr.1E13, 90 mL). Fr.1E12 (1.8 g) was further subjected to column chromatography on silica gel (50 g) eluting with $CHCl_3$–EtOAc (4/1, 610 mL) to give four fractions (fr.1E121, 150 mL; fr.1E122, 170 mL; fr.1E123, 250 mL; fr.1E124, 40 mL). Fr.1E123 (0.25 g) was isolated by column chromatography on silica gel column (20 g) using $CHCl_3$–acetone (15/1, 300 mL) to obtain compound **1** (44 mg, 190 mL). Fraction 1F (0.2 g) was further fractionated on a silica gel column (30 g), eluting with petroleum ether–acetone (5/1, 670 mL) to give two fractions (fr.1F1, 200 mL, fr.1F2, 450 mL). Fr.1F1 (0.03 g, 200 mL) was further fractionated on a silica gel column (15 g) using $CHCl_3$–acetone (10/1, 390 mL) to obtain compound **5** (8 mg, 190 mL). Fr.1F2 (0.15 g) was further subjected to column chromatography on silica gel (50 g) eluting with $CHCl_3$–EtOAc (3/1, 640 mL) to give three fractions (fr.1F21, 150 mL; fr.1F22, 170 mL; fr.1F23, 250 mL). Fr.1F21 (0.05 g) was isolated by column chromatography on silica gel column (10 g) using $CHCl_3$–acetone (15/1, 300 mL) to obtain compound **4** (14 mg, 40 mL). Fr.1F22 (0.03 g) was isolated by column chromatography on silica gel column (8 g) using $CHCl_3$–EtOAc (3/1, 150 mL) to obtain compound **2** (4 mg, 50 mL). Fr.1F23 (0.25 g) was isolated by column chromatography on silica gel column (20 g) using $CHCl_3$–acetone (15/1, 300 mL) to obtain compound **3** (4.6 mg, 30 mL).

3.3.1. Compound 1. Colorless needles from $CHCl_3$–MeOH, mp 183 °C, $[\alpha]_D^{20}$ −109.0 (*c* 0.18, $CHCl_3$). R_f value: 0.62, $CHCl_3$–acetone (15/1). IR (Film): ν_{max}=3360, 2938, 2878, 1755, 1665, 1444, 1383, 1316, 1267, 1254, 1229, 1205, 1179, 1156, 1119, 1065, 1005, 969, 938, 922, 894, 784, 759, 743 cm^{-1}. UV (MeOH): $\lambda(\log\varepsilon)$=208.0 (5.04) nm. HR-EI-MS: revealed *m/z*=278.1137, requires *m/z*=278.1149 for $C_{15}H_{18}O_5$. ^1H and ^{13}C NMR: see Table 1.

3.3.2. Compound 2. Yellow gum, $[\alpha]_D^{18}$ −505.0 (*c* 0.49, $CHCl_3$). IR (Film): ν_{max}=1779, 1749, 1669, 1640, 1582, 1373, 1289, 1225, 1039, 938, 908, 856, 747 cm^{-1}. UV (MeOH): $\lambda(\log\varepsilon)$=318.0 (5.36) nm. HR-ESI-MS: revealed *m/z*=303.1221, requires *m/z*=303.1227 for $C_{17}H_{19}O_5$. ^1H and ^{13}C NMR: see Table 2.

3.3.3. Compound 3. Colorless gum, $[\alpha]_D^{18}$ −29.0 (*c* 1.16, $CHCl_3$). IR (Film): ν_{max}=1781, 1753, 1678, 1371, 1223, 1166, 1055, 1008, 972, 936, 755 cm^{-1}. UV (MeOH): $\lambda(\log\varepsilon)$=215.0 (4.33), 230.0 (4.14) nm. HR-ESI-MS: revealed *m/z*=380.1699, requires *m/z*=380.1704 for $C_{19}H_{26}O_7N$. ^1H and ^{13}C NMR: see Table 2.

3.3.4. Compound 5. Colorless gum, $[\alpha]_D^{17}$ −15.0 (*c* 1.49, CH_2Cl_2). IR (Film): ν_{max}=3450, 2923, 1740, 1702, 1440, 1363, 1225, 1100, 1037, 1003, 976, 756 cm^{-1}. UV (MeOH): $\lambda(\log\varepsilon)$=204.0 (5.15) nm. HR-ESI-MS: revealed *m/z*=496.3048, requires *m/z*=496.3057 for $C_{30}H_{42}O_5N$. ^1H and ^{13}C NMR: see Table 3.

3.4. X-ray crystallographic analysis of compound 1

All measurements were made on a MAC DIP-2030K imaging plate area detector with graphite-monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXL-97) and expanded using Fourier techniques, refined by the program and method NOMCSDP and full-matrix least-squares calculations. Crystals of **1**, a colorless crystal of $C_{15}H_{18}O_5$ having approximate dimensions 0.40×0.30×0.30 mm was mounted on a glass fiber. Crystallized from $CHCl_3$–MeOH, it was belonged to the monoclinic space group $P2_1$. Crystal data: M=278.29, a=6.7970(10), b=14.127(3), c=7.2610(10) Å, β=101.58(3)°, V=683.0(2) $Å^3$, Z=2, D=1.353 g/cm^3. The total number of independent reflections measured was 1250, 989 of which were considered to be observed ($|F|^2 \geq 8\sigma|F|^2$). The final indices were R_f=0.0373, R_w=0.1025 ($w=1/\sigma|F|^2$). Crystallographic data for compound **1** have been deposited at the Cambridge Crystallographic Data Center. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.5. Tests of cytotoxicity against tumor HL-60, HO-8910 and A-549 cells

A MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric assay was performed in 96-well culture plates. The assay was based on reduction of MTT by the mitochondrial dehydrogenase of viable cells to yield a blue formazan product that could be measured spectrophotometrically. In the experiment, the negative controls were isochoric normal saline, 1% DMSO or 0.1% DMSO; positive control was VP-16 at concentrations of 2.5, 5, 10, and 20 μM. HL-60, HO-8910 and A-549 cells at a log phase of their growth cycle (1×10^5 cell/mL) were added to each well (90 μL/well), then treated in four replicates at various concentrations of the drugs with six vacant reference wells set in one plate (100 μL cultured media in each well) and incubated for 44 h at 37 °C in a humidified atmosphere of 5% CO_2. After 44 h, 10 μL of MTT solution (5 mg/mL) was added to each well, which was incubated for another 4 h, after which a solution of 10% sodium dodecyl

sulfate (SDS) was added to each well (100 μL/well). Twelve hours later at room temperature, the optical density (OD) of each well was recorded on an ELISA reader (Bioteck EL-340) at one wavelength of 570 nm.

Acknowledgements

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The first synthesis of pyridinium *N*-benzoylguanidines by bismuth- and mercury-promoted guanylation of *N*-iminopyridinium ylide with thioureas

Silvio Cunha,[a,*] Manoel T. Rodrigues Jr.,[a] Cleuza C. da Silva,[b] Hamilton B. Napolitano,[c] Ivo Vencato[d] and Carlito Lariucci[d]

[a]*Instituto de Química, Universidade Federal da Bahia, Campus de Ondina, Salvador-BA 40170-290, Brazil*
[b]*Departamento de Química, Universidade Estadual de Maringá, Av. Colombo 5720, Maringá-PR 97020-900, Brazil*
[c]*Ciências Exatas e Tecnológicas, Universidade Estadual de Goiás, BR 153, Km 98, 75001-970, Anápolis-GO, Brazil*
[d]*Instituto de Física, Universidade Federal de Goiás, CP 131, 74001-970, Goiânia-GO, Brazil*

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Abstract—This work describes the first successful synthesis of five pyridinium *N*-benzoylguanidines. These new pyridinium ylides were prepared in moderate to good yields through the guanylation reaction of *N*-iminopyridinium ylide with *N*-benzoylthioureas, using both bismuth nitrate and mercury chloride as inorganic thiophiles. X-ray analysis of one pyridinium *N*-benzoylguanidine was investigated and the *E* configuration assigned. Intermolecular interactions of the type C–H···O and C–H···π were observed in the solid state. The results related in this study represent the first description of a ylide as the nucleophilic partner in the guanylation reaction.

1. Introduction

The synthesis of polysubstituted guanidines is a field of intense investigation[1] owing to the presence of guanidinium group in diverse biologically active substances,[2] mainly pharmaceutical compounds with a broad spectrum of activity.[3] To the synthesis of a guanidine-containing compound two general strategies are possible according to Batey and co-workers: a guanidinylation reaction or a guanylation reaction.[4] In the first, a pre-formed guanidine is modified/functionalized (for instance, through *N*-alkylation, *N*-acylation or transamination), and in the latter, typically, a nucleophilic amine is reacted with a electrophilic amidine species (or a carbodiimide equiv). Typical electrophilic reagents employed in guanylation reaction are indicated in Figure 1.[5]

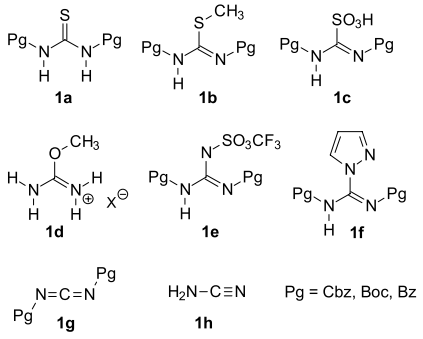

Figure 1. Typical guanylating reagents.

Our research group has continued interest in the area of bismuth- and mercury-promoted guanylation reaction of amines with thioureas in search for new polysubstituted guanidines. Previously, we had described the activation of thioureas by the *N*-benzoyl group in the $HgCl_2$-promoted guanylation.[6] Later, we extended this guanylation reaction to the bismuth approach, whereby $Bi(NO_3)_3$ was employed in the same reaction, being the first description of a bismuth-promoted guanylation of thioureas.[7] While a broad spectrum of amine has been investigated in guanylation methodologies, the use of more functionalized nitrogen nucleophiles is scarce.[8]

The preparation of pyridinium *N*-ylides[9] and their use in the synthesis of nitrogen-containing heterocycles[10] such as 2-aminoazines, 2-aminoazoles, imidazopyridines and tetrahydropyridines has attracted the attention in recent years.[11]

Keywords: Pyridinium; Guanidine; Bismuth.
* Corresponding author. Tel.: +55 71 2375784; fax: +55 71 2374117; e-mail: silviodc@ufba.br

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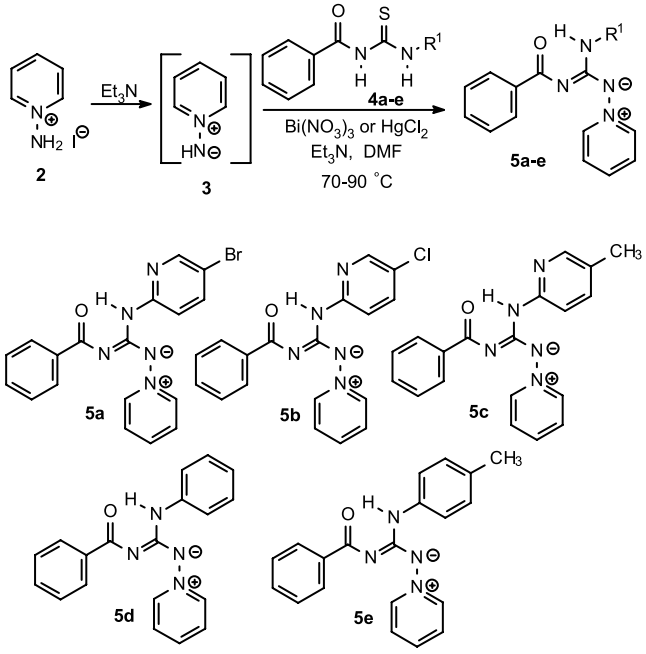
Additionally, pyridinium *N*-ylides are a useful class of compounds in 1,3-dipolar cycloaddition.[12] Thus, these recent developments prompted us to describe here our results in the field of polysubstituted pyridinium *N*-benzoylguanidines synthesis through reaction of thioureas with a pyridinium *N*-ylide. To the best of our knowledge, there is no precedent in the literature of a nitrogen ylide as the nucleophilic component in the guanylation reaction.

2. Results and discussion

To amplify the scope of the nitrogen nucleophile, the *N*-aminopyridinium iodide **2** was submitted to the guanylation reaction conditions, using both $HgCl_2$ and $Bi(NO_3)_3$ as inorganic thiophiles. However, as the active nucleophile from **2** is the in situ formed *N*-iminopyridinium ylide **3**, a small modification of the reaction protocol was necessary, whereby one more equivalent of triethylamine was employed to convert **2** into **3**. Using this modification, **2** was reacted with *N*-benzoylthioureas **4a–e** affording pyridinium *N*-benzoylguanidines **5a–e** in reasonable yields, Scheme 1 and Table 1.



Scheme 1.

Table 1. Isolated pyridinium *N*-benzoylguanidine yields

Compound	Yield, % (time, h)	
	$Bi(NO_3)_3 \cdot 5H_2O$	$HgCl_2$
5a	38 (48)	56 (28)
5b	53 (48)	55 (16)
5c	81 (28)	77 (20)
5d	70 (24)	69 (24)
5e	54 (43)	63 (24)

The electronic nature of the N^2-aryl group in the N^1,N^2-benzoylarylthioureas **4** could vary from electron withdrawing group as in **4a–c** to electron releasing as in **4e**. Hence, potentially, a broad spectrum of pyridinium *N*-benzoylguanidines can be prepared. In addition, both inorganic thiophiles were effective in the guanylation of ylide **3**, but, in general, $HgCl_2$ afforded better yield and shorter reaction time than $Bi(NO_3)_3$.

Despite two configurational isomers (*E* or *Z*) are in principle possible about the C=N double bond of **5a–e**, only one was detected in the ^{1}H NMR spectra. So, a low field chemical shift signal was observed for **5a–e** (~12–13 ppm, D_2O exchangeable) referent to one N–H proton, characteristic of strong internal hydrogen bond. This fact suggests that the *E*-configuration is favored over the *Z*-configuration, because only in the former an intramolecular hydrogen bond is possible, in agreement with the spectral feature. This was further confirmed via an X-ray study (vide infra). Besides, it also suggests that the typical[13] C=N *cis–trans* configurational interconversion should be frozen by this intramolecular hydrogen bond.

From the mechanistic viewpoint, formation of pyridinium *N*-benzoylguanidines **5a–e** can be envisioned as occurring through the reaction of *N*-iminopyridinium ylide **3** with a carbodiimide intermediate, formed from the reaction of thioureas **4a–e** with the inorganic thiophiles, in analogy of previous guanidine synthesis from thioureas.[5] However, an addition–elimination mechanistic pathway involving the

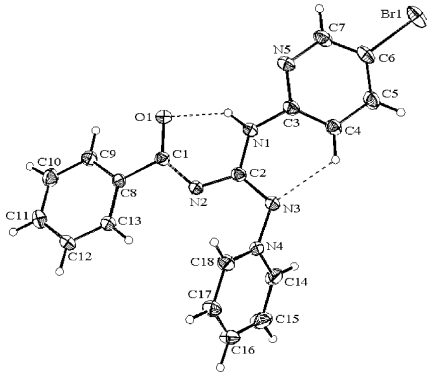


Figure 2. Crystal structure of **5a**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii. The intramolecular H-bonds are shown with dashed lines.

Table 2. Structural parameters for **5a**

Hydrogen bonds				
Atoms	D–H (Å)	H···A (Å)	D···A (Å)	Angle (°)
N1–H1···O1	0.84(4)	1.94(4)	2.630(3)	139(4)
C4–H4···N3	0.99(4)	2.26(4)	2.888(4)	121(3)
C14–H14···O1^{i}	0.91(4)	2.44(4)	3.328(5)	165(3)
C18–H18···Cg01^{ii}	0.94(4)	2.55(4)	3.414(4)	153(3)
C10–H10···N3^{iii}	0.92(4)	2.65(4)	3.483(4)	150(3)
C15–H15···N5^{iv}	0.86(4)	2.74(4)	3.515(5)	150(3)

Selected dihedral angles (°)	
C(3)–N(1)–C(2)–N(3)	5.9(5)
C(3)–N(1)–C(2)–N(2)	172.2(3)
N(3)–C(2)–N(2)–C(1)	178.4(3)
N(1)–C(2)–N(2)–C(1)	−3.6(4)
C(2)–N(2)–C(1)–O(1)	−3.3(5)
N(2)–C(2)–N(3)–N(4)	−2.8(4)
N(1)–C(2)–N(3)–N(4)	179.1(2)
C(2)–N(1)–C(3)–N(5)	174.4(3)
O(1)–C(1)–C(8)–C(9)	25.6(4)

Symmetry operations: i=2−*x*, 1−*y*, −*z*; ii=2−*x*, −*y*, −*z*; iii=2−*x*, *y*, *z*−1 and iv=1+*x*, *y*, *z*

nucleophilic amine and the activated thiourea can not be ruled out at this moment.[14]

The polysubstituted pyridinium *N*-benzoylguanidine **5a** afforded a monocrystal, which structure could be assigned by X-ray analysis, and several structural features emerged and deserve comment. Thus, the *E* configuration of the **5a** was unambiguously confirmed, as can be seen in Figure 2, which shows an ORTEP[15] view. An intramolecular hydrogen bond between atoms N1–H1···O1 [2.629(3) Å, 140.4°] stabilizes the planarity through the conjugation O1–C1–N2–C2–N1 as shown on Figure 2. While the phenyl ring is rotated in relation to the plane involving atoms C1–N2–C2–N1 (see dihedral angles in Table 2), the ring (N5–C3···C7) at N1 is practically coplanar, what can be attributed to the occurrence of the weak C4–H4···N3 intramolecular hydrogen bond.

The crystal packing of **5a** does not show any strong hydrogen bonds. Nevertheless, the *ortho* hydrogens C14–H14 and C18–H18 of the pyridinium moiety of **5a** are involving in two weak intermolecular interactions of the type C–H···O and C–H···π, linking adjacent molecules in two different centrosymmetric dimeric forms, as noted in Figure 3. Additionally two other intermolecular weak interactions make contributions to the molecular packing stabilization, involving atoms C10–H10···N3[iii], responsible for the formation of the infinity chain along the *b* axis, and C15–H15···N5[iv], responsible for the formation of the infinity chain along the *c* axis. Table 2 shows these hydrogen-bonding geometries and related symmetry codes.

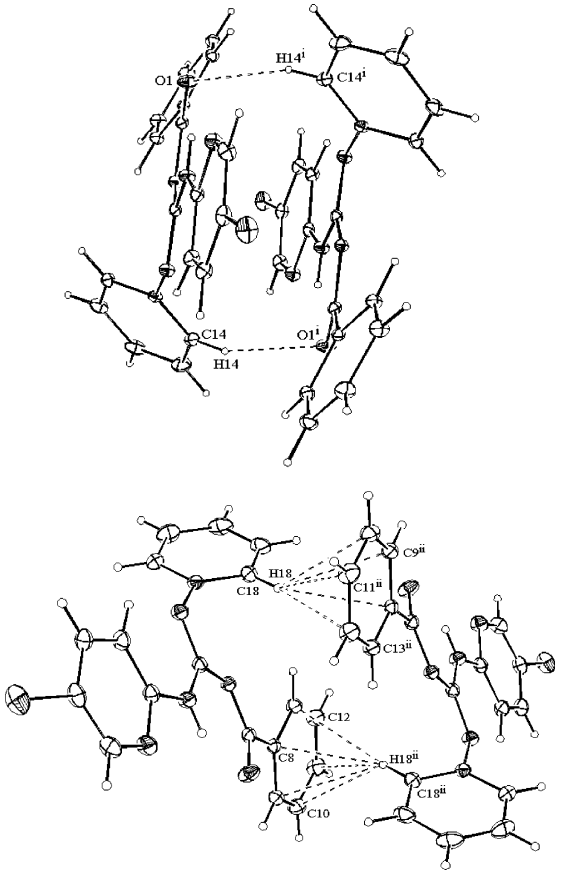


Figure 3. View of **5a** showing solid state dimerizations due to intermolecular interactions C14–H14···.O1[i] (top) and C18–H18···.π[ii] (bottom), indicated with dashed lines (symmetry operations: i = 2−*x*, 1−*y*, −*z*; ii = 2−*x*, −*y*, −*z*).

In conclusion, this work describes the first successful synthesis of pyridinium *N*-benzoylguanidines through the reaction of *N*-iminopyridinium ylide with *N*-benzoylthioureas. The results related in this study represent the first description of a ylide as the nucleophilic partner in the guanylation reaction. The synthetic application of these ylides in the preparation of more complex heterocycles is under investigation in our lab and will be reported opportunely.

3. Experimental

Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a FT-IR BOMEM MB100 instrument. NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm units downfield from reference (internal TMS). Coupling constants (*J*) are in Hertz (Hz). Elemental analyses were performed on a 2400 CHN Perkin Elmer. The single crystal X-ray data collection was carried out on a Nonius CAD-4 diffractometer at Instituto de Física-UFG. *N*-benzoylthioureas[16] and *N*-aminopyridinium iodine[17] were prepared according to known procedures.

3.1. General synthetic procedure

To a solution of 0.5 mmol of thiourea **4a–e** in 4 mL of DMF was added 1 mmol of *N*-aminopyridinium iodide **2** and 1.5 mmol of Et_3N and then 0.5 mmol of $Bi(NO_3)_3 \cdot 5H_2O$ (or $HgCl_2$) was added to the solution with vigorous magnetic stirring and ice-bath cooling. The suspension became black after a few minutes and was left stirring at 70–90 °C, while the progress of the reaction was monitored by TLC. When the thiourea was consumed, 20 mL of CH_2Cl_2 was added and the suspension was filtered through a pad of Celite. The filtrate was extracted with water (4×15 mL) and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated and the crude residue was recrystallized from CH_2Cl_2/petroleum ether.

3.1.1. N^1-Benzoyl-N^2-(5′-bromopyrindin-2′-yl)pyridinium guanidine (5a). Mp 234–236 °C. ν_{max} (KBr) 3236, 1600, 1561 cm^{-1}. ^{1}H (DMSO-d_6) δ 7.24 (2H, t, J= 7.2 Hz); 7.33 (1H, d, J=6.3 Hz); 7.66 (2H, d, J=7.2 Hz); 7.96–8.05 (3H, m); 8.27–8.36 (3H, m); 8.90 (2H, d, J= 6.3 Hz); 12.6 (1H, s). ^{13}C (DMSO-d_6) δ 111.5 (C); 115.9 (CH); 126.8 (CH); 127.5 (CH); 128.3 (CH); 130.3 (CH); 139.3 (C); 140.0 (CH); 140.3 (CH); 144.6 (CH); 148.4 (CH); 151.5 (C); 161.3 (C); 172.8 (C). Anal. Calcd for $C_{18}H_{14}BrN_5O$: C, 54.54%; H, 3.56%; N, 17.67%. Found: C, 54.32%; H, 3.52%; N, 17.58%.

3.1.2. N^1-Benzoyl-N^2-(5′-chloropyrindin-2′-yl)pyridinium guanidine (5b). Mp 212–215 °C. ν_{max} (KBr) 3077, 1596, 1577 cm^{-1}. ^{1}H (DMSO-d_6/$CDCl_3$) δ 7.22 (2H, t, J=6.9 Hz); 7.33 (1H, m); 7.68 (2H, d, J=7.5 Hz);

7.78 (1H, d, J=8.4 Hz); 8.01 (2H, t, J=6.6 Hz); 8.31 (3H, m); 8.87 (2H, d, J=6.0 Hz); 12.60 (1H, s). ^{13}C (DMSO-d_6/$CDCl_3$) δ 115.3 (CH); 123.3 (C); 126.6 (CH); 127.3 (CH); 128.3 (CH); 130.1 (CH); 137.1 (CH); 139.4 (C); 140.0 (CH); 144.6 (CH); 146.0 (CH); 151.2 (C); 161.3 (C); 172.9 (C). Anal. Calcd for $C_{18}H_{14}ClN_5O$: C, 61.46%; H, 4.01%; N, 10.08%. Found: C, 61.40%; H, 3.98%; N, 10.10%.

3.1.3. N^1-Benzoyl-N^2-(5′-methylpyrindin-2′-yl)pyridinium guanidine (5c). Mp 155–157 °C. ν_{max} (KBr) 3103, 1615, 1559 cm^{-1}. ^{1}H (DMSO-d_6) δ 2.3 (3H, s); 7.24 (2H, t, J=7.2 Hz); 7.33 (1H, d, J=6.9 Hz); 7.56 (1H, d, J=8.1 Hz); 7.72 (3H, d, J=7.5 Hz); 7.97 (2H, t, J=6.9 Hz); 8.07 (1H, s); 8.32 (1H, t, J=7.8 Hz); 8.78 (2H, d, J=6.0 Hz); 12.74 (1H, s). ^{13}C (DMSO-d_6) δ 17.2 (CH_3); 113.9 (CH); 126.2 (C); 126.6 (CH); 127.3 (CH); 128.2 (CH); 128.4 (C) 130.1 (CH); 138.2 (CH); 139.9 (CH); 144.7 (CH); 147.6 (CH); 150.1 (C); 161.3 (C); 172.5 (C). Anal. Calcd for $C_{19}H_{17}N_5O$: C, 68.87%; H, 5.17%; N, 21.13%. Found: C, 68.89%; H, 5.17%; N, 21.32%.

3.1.4. N^1-Benzoyl-N^2-(phenyl)pyridinium guanidine (5d). Mp 210–213 °C. ν_{max} (KBr) 3242, 1600, 1568 cm^{-1}. ^{1}H (CD_3OD) δ 7.06 (1H, t, J=7.2 Hz); 7.26 (2H, t, J=9.0 Hz); 7.32–7.38 (3H, m); 7.66 (2H, d, J=7.8 Hz); 7.75–7.80 (4H, m); 8.11 (1H, t, J=7.5 Hz); 8.63 (2H, dd, J=0.9, 6.3 Hz). ^{13}C (DMSO-d_6) δ 119.7 (C); 120.0 (CH); 121.6 (CH); 126.5 (CH); 127.3 (CH); 128.1 (CH); 128.5 (CH); 130.0 (CH); 139.6 (CH); 139.7 (C); 144.6 (CH); 162.1 (C); 172.3 (C). Anal. Calcd for $C_{19}H_{16}N_5O$: C, 69.08%; H, 4.88%; N, 21.20%. Found: C, 68.98%; H, 4.71%; N, 21.32%.

3.1.5. N^1-Benzoyl-N^2-(4′-methylphenyl)pyridinium guanidine (5e). Mp 227–228 °C. ν_{max} (KBr) 3236, 1601, 1558 cm^{-1}. ^{1}H (DMSO-d_6/$CDCl_3$) δ 7.09 (2H, t, J=7.8 Hz); 7.21 (2H, t, J=6.9 Hz); 7.30 (1H, d, J=5.7 Hz); 7.54 (2H, d, J=7.5 Hz); 7.72 (2H, d, J=7.8 Hz); 7.92 (2H, t, J=6.6 Hz); 8.25 (1H, t, J=7.5 Hz); 8.78 (2H, d, J=5.7 Hz); 12.06 (1H, s). ^{13}C (DMSO-d_6/$CDCl_3$) δ 20.3 (CH_3); 120.1 (CH); 126.5 (CH); 127.4 (CH); 128.1 (CH); 129.0 (CH); 130.0 (CH); 130.5 (C); 137.1 (C); 138.9 (CH); 144.6 (CH); 162.2 (C); 172.5 (C). Anal. Calcd for $C_{20}H_{18}N_5O$: C, 69.75%; H, 5.27%; N, 20.34%. Found: C, 69.72%; H, 5.20%; N, 20.21%.

3.2. Crystal structure of 5a

$C_{18}H_{14}BrN_5O$, M_w=396.25, triclinic, space group P-1 [nr 2], Z=2, a=9.274(2), b=9.488(4), c=10.034(2) Å, α=75.44(2), β=78.77(2), γ=82.07(2)°, V=834.5(4) Å^3, D_c=1.577 Mg m^{-3}, λ(Cu Kα)=1.54180 Å, μ=3.498 mm^{-1}, 3081 measured reflections, 2896 unique (R_{int}=0.0204) of which 2700 were considered as observed with $I \geq 2\sigma(I)$. The single crystals were obtained by slow evaporation of a solution of **5a** in CH_3Cl at room temperature. The structures were solved with direct methods using SHELXS97[18] and it were refined anisotropically with full-matrix least-squares on F^2 using SHELXL97.[19] The hydrogen atoms were placed at calculated position except those involved in H-bonds, found on difference maps and refined. Final indices: $R_1(F_o)$=0.0528, wR_2 (F^2)=0.142 for 245 refined parameters. All structural details of the intermolecular contacts for **5a** were interpreted as hydrogen bonds on geometrical grounds.[20] The crystallographic data were deposited at the Cambridge Crystallographic Data Center under the number CCDC 261830. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax +44 1223 336033) or e-mail: deposit@ccdc.camac.uk.

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The study of reaction mechanism for the transformation of nitronate into nitrile by phosphorus trichloride

Zhijay Tu, Yaochung Jang, Chunchi Lin, Ju-Tsung Liu, Jianming Hsu, M. N. V. Sastry and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei, Taiwan 116, ROC

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Abstract—Nitronate was generated using β-nitrostyrene and the anion of dimethyl malonate in THF at 0 °C. Subsequent treatment with PCl_3 in the presence/absence of DMAP either in THF or pyridine afforded nitroalkane, chloroxime, and nitrile. Pyridine, THF, and THF–pyridine co-solvent as solvents were investigated under different conditions. With different anions of malonates containing dipolarphiles, cyclic compounds were obtained as major products indicating nitrile oxides were generated during the reaction. Based on the results, compared to that of the one reported in literature, a plausible mechanism involving nitrile oxide intermediate was proposed.

1. Introduction

Nitrile oxides are the most important intermediates in the synthesis of heterocyclic compounds via 1,3-dipolar cycloaddition.[1] Two widely used methods to produce nitrile oxides are (i) reaction of aldoximes with oxidizing agents or halogenating species[2] and (ii) reaction of primary nitroalkanes with dehydrating agents such as PhNCO and Et_3N,[3] $POCl_3$,[4] diketene and Na,[5] H_2SO_4,[6] Me_3SiCl and Et_3N,[7] Ac_2O and AcONa,[8] AcCl and MeONa,[9] *p*-TsOH,[10] $PhSO_2$-Cl or ClCOOEt and Et_3N,[11] $SOCl_2$ and Et_3N,[12] $(BOC)_2O$ and DMAP,[13] BURGESS and DAST or $(COCl)_2$.[14]

Nitrile is also a valuable synthetic intermediate for organic chemistry including pharmaceuticals, agricultural chemicals, dyes and material science and is also a key constituent in many natural products.[15] Some of the useful methods for the preparation of alkylnitrile includes (i) the direct nucleophilic substitution of alkyl halides with inorganic cyanides;[16a,b] (ii) the exchange of alcohols into cyanides either by using HCN or acetone cyanohydrins under Mitsunobu conditions[16c] and (iii) the use of *n*-Bu_3P/KCN/18-crown-6 for the conversion of only primary alcohols to nitriles.[16d] However, these reactions are frequently accompanied by elimination of hydrogen halides especially when bulky alkyl halides were used and gives lower yields of the products with hindered primary and secondary alcohols. Recently, Iranpoor et al. have reported that alcohols, thiols, and trimethylsilyl ethers can be converted into their corresponding nitriles by using PPh_3/DDQ/*n*-Bu_4NCN in acetonitrile solution at rt.[16e] Usually, α,β-unsaturated nitriles can be obtained through a Wittig reaction of aldehyde with cyanoalkyl phosphonates. However, it always results in an unbiased form of *E*- and *Z*-isomeric nitriles.[17] Preparation of nitrile by means of dehydration of amides or aldoximes with an appropriate nonmetal dehydrating agent is an alternative method, which also suffers from disadvantages, such as inconvenient preparation of the reagents, limited substrate scope or incompatibility of sensitive groups to the reaction condition.[18] Several main or transition metal complexes were also used as dehydrating agents to affect this transformation.[19] The conversion of primary nitro compounds into nitrile were also reported by different electrophilic phosphorus derivatives[20a–c] such as $(EtO)_2PCl$, P_2I_4, and PCl_3, sulfur compounds[21a–d] such as SO_2, $Me_3SiSSSiMe_3$, and CS_2, silyl derivatives[22] such as Me_3SiI, radical chemistry,[23] or isocyanides.[24] Wehrli et al. used PCl_3 in pyridine to generate nitriles from primary nitro compounds in moderate yields and the following reaction mechanism (Scheme 1) has been proposed.[20c]

Our previous studies established that β-nitrostyrenes react with different nucleophiles to generate nitroalkanes, halooximes, nitrile oxides, and polycyclic compounds under different reaction conditions.[25] As part of our incessant research efforts with nitroolefin chemistry, we

Keywords: Reaction mechanism; Nitrile; β-Nitrostyrene; Malonate ester; PCl_3; Nitrile oxide intermediate; Cyclic compounds.
* Corresponding author. Tel.: +886 2 29309092; fax: +886 2 29324249; e-mail: cheyaocf@scc.ntnu.edu.tw

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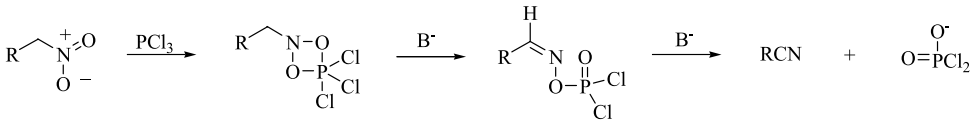


Scheme 1.

wish to report the reaction of *trans*-β-nitrostyrene **1** with different anions of malonate esters to generate nitronates and subsequent treatment with PCl_3 in the absence/presence of DMAP to afford nitroalkane **4** or **7**, chlorooxime **5**, nitrile **6**, **9** or **12**, and cyclic products **8** or **11** under different conditions and also to propose a plausible reaction mechanism.

2. Results and discussion

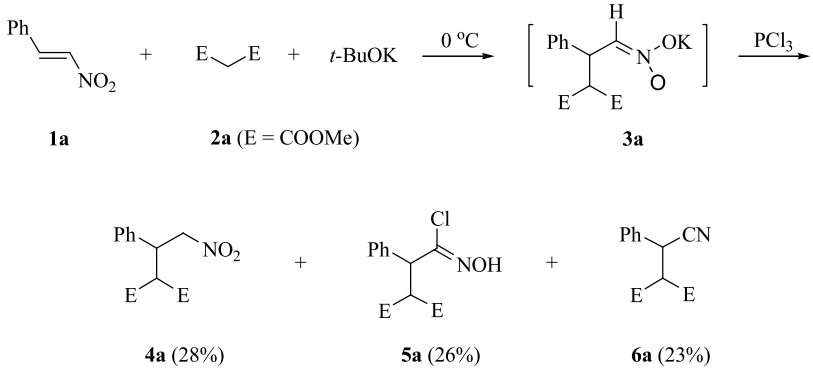
trans-β-Nitrostyrene **1a** reacts with the anion of dimethyl malonate to afford nitronate **3a**, and subsequent treatment with 3 equiv of PCl_3 for 1.5 h at rt afforded nitroalkane **4a** (28%), chlorooxime **5a** (26%), and nitrile **6a** (23%) (Scheme 2).

The compounds **4a**, **5a** and **6a** were characterized thoroughly using ^1H, ^{13}C NMR spectrums and the data is in consistent with the reported literature data.[21] Although parts of the ^1H NMR pattern of **5a** are similar to **6a**, these two products can be distinguished by the following characteristics. For example, the coupling constant of the vicinal proton of chlorooxime **5a** is 12.0 Hz and that of nitrile **6a** is only 9.6 Hz. In addition to this, the D_2O exchangeable proton of ClC═NOH was observed in product **5a**. Besides this, different IR absorptions were also observed for compound **5a** [3410 cm^{-1} (OH, broad) and 1639 cm^{-1} (C═N stretch, weak)] and **6a** [2248 cm^{-1} (CN stretch, weak)]. In the ^{13}C NMR spectrums of these compounds absorption at δ 141.24 ppm corresponds to ClC═NOH in **5a** and at δ 118.40 ppm to CN in **6a** and are also useful to distinguish between the two products.

Similar reactions were also conducted in different solvents with varying amounts of DMAP under different reaction conditions and all the experimental results were shown in Table 1. The result of entry 1 indicates that nitronate **3a** can be converted into **4a**, **5a** and **6a** by reacting with PCl_3 in THF solution. The increase in the amount of PCl_3 from 5 to 10 equiv did not improve the yields of **4a**, **5a** and **6a**. Literature studies revealed that DMAP is one of the most effective reagents to convert the nitronate into the final products.[21] A careful observation has led to identify two different reaction conditions during the addition of DMAP. Addition of 0.5 equiv of DMAP initially to the nitronate solution, followed by PCl_3 resulted in the formation of products **4a** (32%) with increased yield and **5a** (23%) and **6a** (25%) with decreased yield. In another variation, addition of PCl_3 followed by DMAP resulted in the increased yield of nitrile **6a** (38%) with reduced yields of **4a** (13%) and **5a** (15%). The decrease in the yields of **4a** and **5a** and the increase in the yield of **6a** clearly support the assumption that, DMAP plays an important role during reaction. Based on the above observation, increasing the amount of DMAP to 5 equiv afforded the nitrile product **6a** in 49% yield. Similarly, with further increase in the amount of DMAP to 10 equiv the yield of **6a** increased to 62%. These results clearly signify that the increase in the amount of DMAP increases the formation of nitrile product **6a** efficiently.

The effect of solvents and temperature were also investigated by employing different reaction conditions at different reaction times and proved that all the parameters play important roles and may have different effects to the same reaction. After observing the results of entries 1–7 in THF solution, pyridine was used as solvent for similar reactions by modifying the literature procedures and conditions. Only 13% of **4a** and 29% of **6a** were obtained and no product **5a** was observed when the reaction was carried out in pyridine at 95 °C for 2 h (entry 8). However, only 34% of **6a** was isolated when the same solution was stirred at rt for 9 h (entry 9). These results indicate that **4a** can be converted into **6a** slowly in pyridine solution and also consist with literature report.[21c]

Although the use of pyridine as solvent afforded the product **6a** only, the longer reaction times and formation of insoluble materials made the workup very difficult. In addition to this, lower yield of products, tedious workup procedures and longer reaction times limited the use of pyridine as a choice of solvent. In order to attain better yields of the nitrile, a

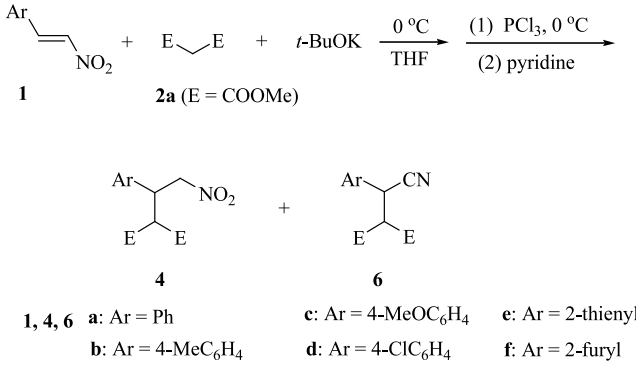


Scheme 2.

Table 1. Reaction of **1a** with anion of **2a** in presence of PCl_3 in different solvents to generate **4a**, **5a**, **6a**

Entry	PCl_3 (equiv)	Solvent	DMAP (equiv)	Condition	Time (h)	**4a** (%)[a]	**5a** (%)[a]	**6a** (%)[a]
1	3	THF	—	rt	1.5	28	26	23
2	5	THF	—	rt	1.5	10	29	24
3	10	THF	—	rt	1.5	12	29	29
4	5	THF	0.5[b]	rt	1.5	32	23	25
5	5	THF	0.5[c]	rt	48	13	15	38
6	5	THF	5[c]	rt	48	10	15	49
7	5	THF	10[c]	rt	48	10	—	62
8	5	Pyridine	—	95 °C	2	13	—	29
9	5	Pyridine	—	rt	9	—	—	34

[a] All compounds were purified by silica gel column chromatography and yields are for pure isolated products, relative to **1a**.
[b] DMAP was initially added to the nitronate solution followed by PCl_3.
[c] PCl_3 was initially added to the nitronate solution followed by DMAP.



Scheme 3.

combination of THF and pyridine were used as solvent. After the generation of nitronate in THF, pyridine was added to form the co-solvent of THF–pyridine solution (Scheme 3).

To our surprise, only 7% of **4a** and 43% of **6a** were isolated and no **5a** was detected by the crude ^1H NMR and GCMS analysis. Increasing the reaction time from 7.5 to 48 h dramatically increased the yield of nitrile **6a** to 60%, without accompanying any other products. To prove the efficiency of the reaction we have subjected various substituted nitroolefins to obtain the products **6b–f** in 17–59% yield under identical reaction conditions (Table 2).

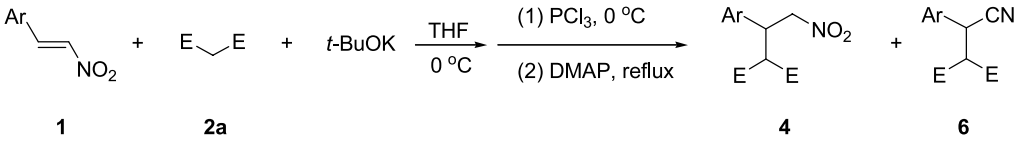
The use of THF–pyridine as co-solvent though yielded **6** only in most cases, similar disadvantages were observed due to formation of insoluble materials. The reaction at higher temperature (95 °C) in the presence of 1 equiv of DMAP under similar conditions resulted the product **6a** in 62% with 27% of **4a** (Scheme 4).

The increase in the amount of DMAP neither improved reaction rate nor the nitrile product formation. In the

Table 2. Reaction of **1** with anion of **2a** PCl_3 in the co-solvent of THF–pyridine solution

Entry	**1**	Solvent[a]	Condition	Time (h)	**4** (%)[b]	**6** (%)[b]
1	**1a**	THF–pyridine	rt	7.5	**4a** (7)	**6a** (43)
2	**1a**	THF–pyridine	rt	48	—	**6a** (60)
3	**1b**	THF–pyridine	rt	48	—	**6b** (59)
4	**1c**	THF–pyridine	rt	48	**4c** (10)	**6c** (31)
5	**1d**	THF–pyridine	rt	48	—	**6d** (51)
6	**1e**	THF–pyridine	rt	48	—	**6e** (34)
7	**1f**	THF–pyridine	rt	48	—	**6f** (17)

[a] After adding PCl_3 to the nitronate in 5 mL THF solution, 10 mL of pyridine was added to form the co-solvent of THF–pyridine solution.
[b] All compounds were purified by using silica gel column chromatography and yields are for pure isolated products, relative to **1**.



Scheme 4.

Table 3. Reaction of **1** with anion of **2a** in presence of PCl_3 and DMAP in THF under refluxing condition

Entry	1	Solvent	DMAP[a]	Time (h)	4 (%)[b]	6 (%)[b]
1	**1a**	THF	—	2	**4a** (7)	**6a** (44)
2	**1a**	THF	1	2	**4a** (27)	**6a** (62)
3	**1a**	THF	2	2	**4a** (10)	**6a** (61)
4	**1a**	THF	10	2	**4a** (11)	**6a** (57)
5	**1a**	THF	10	48	**4a** (11)	**6a** (62)
6	**1b**	THF	1	2	**4b** (31)	**6b** (59)
7	**1c**	THF	1	2	**4c** (19)	**6c** (58)
8	**1d**	THF	1	2	**4d** (27)	**6d** (55)
9	**1e**	THF	1	2	**4e** (35)	**6e** (41)
10	**1f**	THF	1	2	**4f** (26)	**6f** (33)

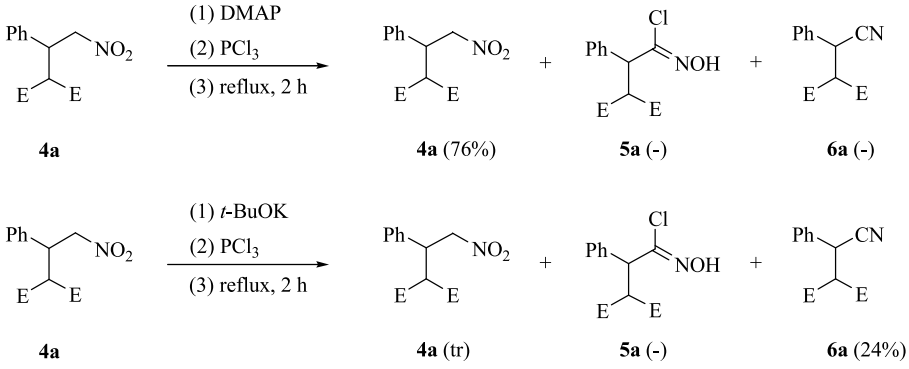
[a] After adding 5 equiv of PCl_3 to the nitronate solution, different amounts of DMAP were added and then the solution was refluxed for 2 h.
[b] All compounds were purified by silica gel column chromatography and yields are for pure isolated products, relative to **1**.

presence of 10 equiv of DMAP under refluxing conditions for 48 h yielded 11% of **4a** and 62% of **6a**. Similarly, substituted nitroolefins afforded products **4b–f** and **6b–f** by subjecting **1b–f** as substrates (Table 3).

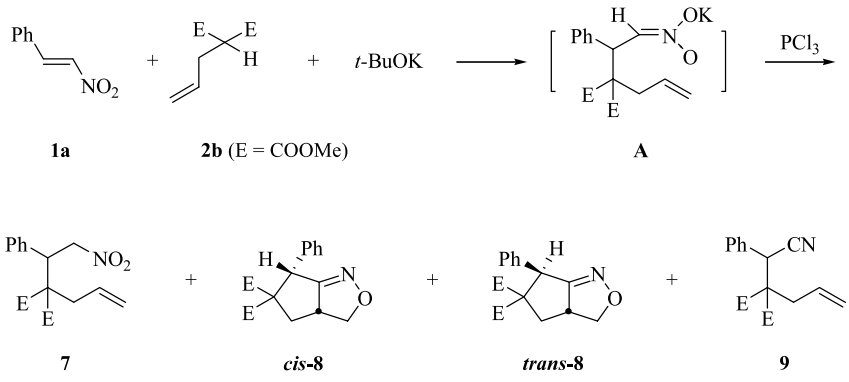
These results clearly indicate that using 1 equiv of DMAP under refluxing conditions for a time period of 2 h not only facilitates the reaction efficiently, but also increased the yield of **6a**. It is also revealed that **4a** is always present in the solution even when excess amounts of DMAP were used under refluxing conditions. To verify this observation, **4a** was first treated with 2 equiv of DMAP and subsequently treated with 5 equiv of PCl_3 in THF solution and the solution was refluxed for 2 h. To our surprise, 76% of unreacted **4a** was recovered and only traces of unidentified products were observed in the crude NMR. On the other hand, traces of **4a** and 24% of **6a** were isolated when **4a** was treated with *t*-BuOK followed by PCl_3 under similar conditions (Scheme 5). These results signify that *t*-BuOK can efficiently acts as a base rather than DMAP to deprotonate **4a** to generate nitronate and to convert it into the final products.

Other than dimethyl malonate **2a**, dimethyl allylmalonate **2b** was also used to react with **1a** and PCl_3 under similar conditions. A trace of nitroalkane **7** along with low to medium yields of bicyclic product **8** and nitrile **9** were obtained (Scheme 6).

It is interesting to find that higher yields (50–58%) of *cis*-**8** and *trans*-**8** (the NMR ratio is from 4.0:1.0 to 4.5:1.0) with better selectivity were observed, when the reaction was



Scheme 5.



Scheme 6.

Table 4. Reaction of **1a** with anion of **2b** in presence of PCl_3 and DMAP to generate **7**, **8**, and **9**

Entry	PCl_3 (equiv)	DMAP (equiv)	Temperature	Time (h)	**7**[a]	**8** (%)[a]	Cis/trans[b]	**9** (%)[a]
1	1.5	—	−78 °C	2	tr	50	4.0:1.0	27
2	2	—	−78 °C	2	tr	56	4.5:1.0	16
3	2	0.5[c]	−78 °C	2	tr	35	3.5:1.0	19
4	5	—	rt	2	3	31	1.0:1.1	16
5	5	—	−0 °C	2	7	32	2.0:1.0	13
6	5	1[c]	−0 °C	2	6	42	1.6:1.0	18
7	5	—	−10 °C	2	8	39	3.2:1.0	25
8	5	—	−78 °C	2	tr	45	4.2:1.0	22
9	5	1[c]	−78 °C	2	tr	53	3.7:1.0	20
10	5	1[d]	−78 °C	2	tr	58	3.8:1.0	26

[a] All compounds were purified by silica gel column chromatography and yields are for pure isolated products relative to **1**.
[b] The cis/trans ratio was measured by ^{1}H NMR.
[c] PCl_3 was added to the nitronate solution followed by DMAP.
[d] DMAP was added initially to the nitronate solution followed by PCl_3.

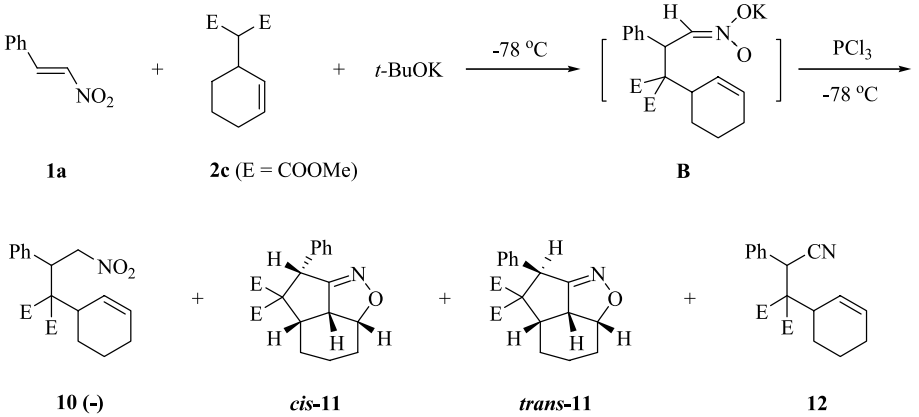
carried out at −78 °C using different equivalents of PCl_3. On the other hand, it was observed that either increase in the amount of PCl_3 or DMAP have no effect on the product yields as well as on the stereoselectivity of **8**. A decrease in the temperature from 25 to 0 °C, and further to −78 °C, reduced the nitroalkane **7** yields and increased the formation of **8** and **9**. A trace of the nitronate was observed at little elevated temperatures (i.e., at 25, 0, −10 °C) and in most cases the nitronate reacts readily with PCl_3 to generate **8** and **9** at −78 °C. Possible explanation is that the presence of the dimethoxycarbonyl group increases the steric hindrance of nitronate (**A**), which facilitates to react with PCl_3 to generate nitrile oxide. This undergoes intramolecular 1,3-dipolar cycloaddition with the vinyl group to produce **8** and little amount of nitrile oxide further reacts with PCl_3 to undergo deoxygenation reaction to yield **9**. Two diastereomers of bicyclic product were isolated and assigned to be *cis*-**8** and *trans*-**8**. Compound *cis*-**8** has been proposed as kinetically controlled product and *trans*-**8** to be thermodynamically controlled product, because the formation of these two products always favors the former at lower temperature and the later at higher temperature (Table 4).

In order to explore further, a different malonate ester such as dimethyl 3-(cyclohexen-1-yl)malonate **2c** also used to react with **1a**, under similar reaction conditions using PCl_3 at −78 °C. As expected, only 49% of tricyclic product **11** (cis/trans =3.8:1) and 9% of nitrile **12** were isolated without a small amount of nitroalkane **10**. The increase in the amount of PCl_3 from 2 to 5 equiv considerably increased the yield of the tricyclic product **11** (cis/trans=3.3:1) to 55%, along with nitrile product **12** (8%). A further increase in the amount of PCl_3 (10 equiv) did not improve the formation of tricyclic product (Table 5). Based on the steric effect in the 1,4-adduct (**B**) one can explain the formation of the products **11** and **12** from **1a** and **2c**. Compared to the results obtained with dimethyl allylmalonate **2b** (Table 4) the complete absence of nitroalkane product **10** implies the role of steric hindrance associated with the intermediate nitronate. The higher steric hindrance of the intermediate nitronate (**B**)

Table 5. Reaction of **1a** with anion of **2c** in presence of PCl_3 to generate **11** and **12**

Entry	PCl_3 (equiv)	Temperature (°C)	Time (h)	**11**[a]	Cis/trans[b]	**12** (%)[a]
1	2	−78	2	49	3.8:1.0	9
2	5	−78	2	55	3.3:1.0	8
3	10	−78	2	45	3.7:1.0	8

[a] All compounds were purified by silica gel column chromatography and yields are for pure isolated products, relative to **1a**.
[b] The cis/trans ratio was measured by ^{1}H NMR.



Scheme 7.

over (**A**) facilitates the formation of **11** and **12** from (**B**) than the formation of **8** and **9** from (**A**) at the same temperature (−78 °C) and the results obtained were also consistent with this assumption (Scheme 7).

The generation of different products can be controlled by changing several parameters such as, use of different solvent systems, conducting the reaction at different temperatures, varying the amounts of reagents and substrates and by using different nucleophiles. Based on these observations, we proposed a stepwise mechanism (Scheme 8) for the formation of different products involving nitronate and nitrile oxide intermediates. The mechanism is different from those reported by Wehrli et al.[20c] in which the generation of nitrile product exclusively proceeds through different steps. The anion generated from malonate ester and *t*-BuOK reacts with nitroolefin to form a nitronate intermediate **C**. The nitronate **C** under mild acidic conditions furnishes the product nitroalkane **4**, from which the nitronate can be regenerated using pyridine as a base. The reaction of PCl_3 on the nitronate generates a nitroso intermediate **E** via **D**. The nitroso compound either rearranges to form chloroxime **5** or to form nitrile oxide intermediate **F**. A clear evidence for the formation of nitrile oxide **F** can be explained on the basis of bicyclic product with dimethyl allylmalonate **2b** and the tricyclic product with 3-(cyclohexen-1-yl)malonate **2c**. We also concluded an important result that either from chloroxime **5** or from nitrile oxide **F**, the nitrile product **6** can be obtained by the reaction of PCl_3.

In conclusion, we have successfully developed a methodology using PCl_3 for the preparation of nitroalkanes, chloroximes, and nitriles using nitronates. We have also tested various parameters such as solvent, temperature and additives to achieve maximum yields of the nitrile compounds. With different anions of malonates containing dipolarphiles, cyclic compounds were obtained as major products indicating, nitrile oxides were generated during the reaction. A plausible reaction mechanism has been proposed involving a nitrile oxide intermediate for the formation of nitrile compounds, which is little different from the one reported in the literature.

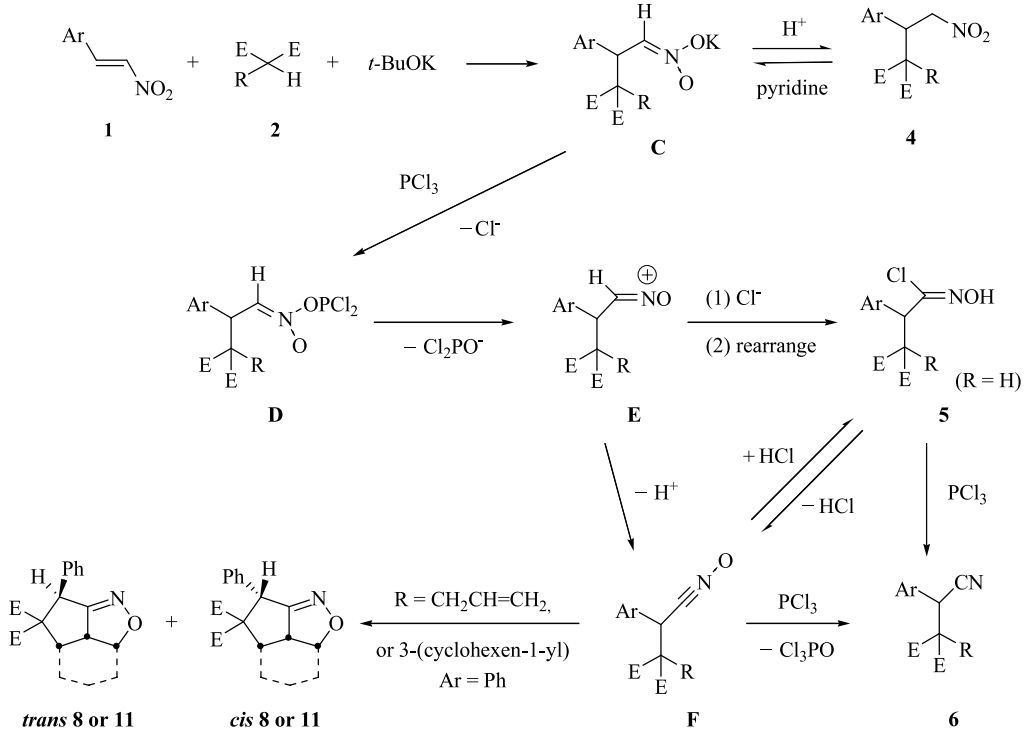
3. Experimental

3.1. General

All reactions were performed in flame or oven-dried glassware under a positive pressure of nitrogen. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by use of E. Merck silica gel 60 (230–400 mesh). THF was distilled over sodium–benzophenone and pyridine was heated under reflux over calcium hydride before use. All melting points were determined on a MEL-TEMP II melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker EX 400 FT NMR. All NMR data were obtained in $CDCl_3$ solution and chemical shift (δ) were given in ppm relative to TMS. MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. Elemental analyses were analyzed by HERAEUS VarioEL-III (for CHN).

3.2. Starting materials

trans-β-Nitrostyrene **1a** and analogues **1b**, **1c**, *trans*-2-(2-nitrovinyl)thiophene **1e**, 2-(2-nitrovinyl)furan **1f**, and other starting materials such as dimethyl malonate **2a**, dimethyl allylmalonate **2b**, *t*-BuOK, DMAP, pyridine, and PCl_3 were



Scheme 8.

purchased from Aldrich Chemical Co., and other commercially available reagents were used with or without further purification. The compounds such as *trans*-4-chloro-β-nitrostyrene **1d**[26] and dimethyl 3-(cyclohexen-1-yl)malonate **2c**[27] were prepared according to literature procedures with slight modifications.

3.3. Typical experimental procedures for the synthesis of nitroalkane 4a, chloroxime 5a, and nitrile 6a using PCl_3 at 0 °C in THF

Typical experimental procedure of entry 1 in Table 1 is representative.

To a 3 mL THF solution of *t*-BuOK (168 mg, 1.5 mmol) added a THF solution of dimethyl malonate **2a** (159 mg, 1.2 mmol) slowly at 0 °C. After stirring the reaction mixture at the same temperature for 30 min, a 5 mL solution of *trans*-β-nitrostyrene **1a** (149 mg, 1.0 mmol) in THF was added dropwise, and stirred for another 30 min. Followed by the addition of PCl_3 (0.26 mL, 3.0 mmol) to the nitronate solution at 0 °C and allowed to stir at rt for 1.5 h. The reaction mixture was poured into the ice cold dil HCl and extracted with CH_2Cl_2 (3×25 mL). The combined CH_2Cl_2 layers were washed with brine, distilled H_2O and dried over $MgSO_4$. Evaporation of the organic solvent, the crude product was purified by flash column chromatography using silica gel (eluent; hexane/ethylacetate; 100:1) to yield nitroalkane **4a** (79 mg, 28% Y), chloroxime **5a** (78 mg, 26% Y), and nitrile **6a** (57 mg, 23% Y).

3.4. Typical experimental procedure for the synthesis of nitrile 6 in a co-solvent of THF–pyridine

Typical experimental procedure of entry 1 in Table 2 is representative.

To a stirred solution of *t*-BuOK (168 mg, 1.5 mmol) in THF (5 mL) added dimethyl malonate **2a** (159 mg, 1.2 mmol) at 0 °C. After stirring the reaction mixture at the same temperature for 30 min, *trans*-β-nitrostyrene **1a** (149 mg, 1.0 mmol) was added to obtain a orange color nitronate **3a** solution. To this, PCl_3 (0.43 mL, 5 mmol) was added and stirred for another 30 min followed by the addition of 10 mL of pyridine to form THF–pyridine co-solvent system. The obtained reaction mixture was further stirred at rt for 7.5 h, and poured the contents into the ice cold dil HCl. The insoluble materials were filtered through a Celite pad and the aq layer was extracted with CH_2Cl_2 (3×25 mL). The combined CH_2Cl_2 layers were washed with ice cold brine solution, distilled water and dried over anhyd $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by flash column chromatography using silica gel (eluent; hexane/ethylacetate; 100:1) to obtain **4a** (20 mg, 7% Y) and **6a** (106 mg, 43% Y).

3.4.1. 3,3-Dimethoxycarbonyl-1-nitro-2-phenylpropane (4a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.93 (dd, J=13.2, 5.3 Hz, 1H), 4.86 (dd, J=13.2, 8.8 Hz, 1H), 4.24 (ddd, J=9.2, 8.8, 5.3 Hz, 1H), 3.86 (d, J=9.2 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.2, 136.1, 129.0, 128.4, 127.8, 77.4, 54.7, 53.0, 52.8, 42.9. IR ($CHCl_3$) ν 3034, 2957 (CH stretch, strong), 1738 (C=O stretch, strong), 1604, 1558 (N=O stretch, strong), 1497, 1456, 1436, 1380, 1292, 1259, 1199, 1158, 1020 cm^{-1}. HRMS (CI) m/z calcd for $C_{13}H_{15}NO_6$ (M^+) 281.0899, found 281.0905. Anal. Calcd for $C_{13}H_{15}NO_6$ C, 55.51; H, 5.38; N, 4.98. Found C, 55.08; H, 5.26; N, 5.26.

3.4.2. 3,3-Dimethoxycarbonyl-1-nitro-2-(4-methylphenyl)propane (4b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 4H), 6.83 (dt, J=8.8, 2.0 Hz, 2H), 4.90 (dd, J=13.0, 5.2 Hz, 1H), 4.84 (dd, J=13.0, 9.0 Hz, 1H), 4.20 (td, J=9.0, 5.2 Hz, 1H), 3.84 (d, J=9.2 Hz, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.2, 138.1, 133.0, 130.0, 127.6, 77.5, 54.7, 52.9, 52.7, 42.5, 21.0. IR ($CHCl_3$) ν 3028, 2956 (CH stretch, strong), 1737 (C=O stretch, strong), 1614, 1556 (N=O stretch, strong), 1516, 1436, 1380, 1291, 1259, 1198, 1159, 1022 cm^{-1}. HRMS (CI) m/z calcd for $C_{14}H_{17}NO_6$ (M^+) 295.1056, found 295.1056. Anal. Calcd for $C_{14}H_{17}NO_6$ C, 56.94; H, 5.80; N, 4.74. Found C, 57.02; H, 5.93; N, 4.69.

3.4.3. 3,3-Dimethoxycarbonyl-1-nitro-2-(4-methoxyphenyl)propane (4c). Mp 100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dt, J=8.8, 2.0 Hz, 2H), 6.83 (dt, J=8.8, 2.0 Hz, 2H), 4.89 (dd, J=13.0, 5.0 Hz, 1H), 4.82 (dd, J=13.0, 9.2 Hz, 1H), 4.19 (td, J=9.2, 5.0 Hz, 1H), 3.83 (d, J=9.2 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.3, 159.5, 129.0, 127.9, 114.4, 77.7, 55.2, 54.9, 53.0, 52.8, 42.3. IR ($CHCl_3$) ν 3006, 2957 (CH stretch, strong), 2841, 1737 (C=O stretch, strong), 1612, 1556 (N=O stretch, strong), 1516, 1436, 1380, 1296, 1255, 1182, 1032 cm^{-1}. HRMS (CI) m/z calcd for $C_{14}H_{17}NO_7$ (M^+) 311.1005, found 311.1000. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 54.02; H, 5.50; N, 4.50. Found C, 53.89; H, 5.44; N, 4.54.

3.4.4. 3,3-Dimethoxycarbonyl-1-nitro-2-(4-chlorophenyl)propane (4d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dt, J=8.4, 2.0 Hz, 2H), 7.17 (dt, J=8.4, 2.0 Hz, 2H), 4.90 (dd, J=13.2, 5.0 Hz, 1H), 4.82 (dd, J=13.2, 9.0 Hz, 1H), 4.23 (td, J=9.0, 5.0 Hz, 1H), 3.82 (d, J=9.0 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.1, 134.7, 134.5, 129.4, 129.3, 77.2, 54.6, 53.1, 53.0, 42.4. IR ($CHCl_3$) ν 3028, 3006, 2957 (CH stretch, strong), 1737 (C=O stretch, strong), 1557 (N=O stretch, strong), 1493, 1436, 1379, 1259, 1199, 1159, 1015 cm^{-1}. HRMS (CI) m/z calcd for $C_{13}H_{14}ClNO_6$ (M^+) 315.0510, found 315.0510. Anal. Calcd for $C_{13}H_{14}ClNO_6$ C, 49.46; H, 4.47; N, 4.44. Found C, 49.35; H, 4.49; N, 4.58.

3.4.5. 3,3-Dimethoxycarbonyl-1-nitro-2-thienylpropane (4e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J=4.8, 1.2 Hz, 1H), 6.95 (dd, J=3.6, 1.2 Hz, 1H), 6.93 (dd, J=4.8, 3.6 Hz, 1H), 4.95 (dd, J=13.6, 5.4 Hz, 1H), 4.90 (dd, J=13.6, 8.0 Hz, 1H), 4.24 (td, J=8.0, 5.4 Hz, 1H), 3.92 (d, J=7.8 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.1, 138.5, 127.1, 126.8, 125.7, 77.9, 55.3, 53.2, 53.1, 38.4. IR ($CHCl_3$) ν 3113, 3010, 2957 (CH stretch, strong), 1732 (C=O stretch, strong), 1604, 1557 (N=O stretch, strong), 1436, 1380, 1265, 1162, 1018 cm^{-1}. HRMS (CI) m/z calcd for $C_{11}H_{13}NO_6S$ (M^+) 287.0464, found 287.0462. Anal. Calcd for $C_{11}H_{13}NO_6S$: C, 45.99; H, 4.56; N, 4.88; S, 11.16. Found C, 45.78; H, 4.29; N, 4.71; S, 10.52.

3.4.6. 3,3-Dimethoxycarbonyl-1-nitro-2-furylpropane (4f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J=1.8, 0.8 Hz, 1H), 6.29 (dd, J=3.2, 1.8 Hz, 1H), 6.22 (dd, J=3.2, 1.8 Hz, 1H), 4.92 (dd, J=13.6, 8.2 Hz, 1H), 4.89 (dd, J=13.6, 5.0 Hz, 1H), 4.39 (td, J=8.0, 5.2 Hz, 1H), 3.94 (d, J=8.0 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.3, 149.4, 142.9, 110.6, 108.5, 75.3, 53.1, 53.0, 52.7, 36.9. IR ($CHCl_3$) ν 3154, 3121, 3011, 2958 (CH stretch, strong), 2852, 1739 (C=O stretch, strong), 1559 (N=O stretch, strong), 1505, 1437, 1379, 1343, 1293, 1264, 1242, 1197, 1163, 1014 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{11}H_{13}NO_7$ (M^+) 271.0692, found 271.0693. Anal. Calcd for $C_{11}H_{13}NO_7$ C, 48.71; H, 4.83; N, 5.16. Found C, 48.92; H, 4.71; N, 5.06.

3.4.7. 3,3-Dimethoxycarbonyl-2-phenylpropanohydroximoyl chloride (5a). Mp 149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (br, 1H, D_2O exchangeable), 7.34–7.27 (m, 5H), 4.50 (d, J=12.0 Hz, 1H), 4.27 (d, J=12.0 Hz, 1H), 3.78 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.2, 141.2, 134.9, 128.8, 128.6, 128.5, 55.7, 53.0, 52.6, 52.5. IR ($CHCl_3$) ν 3410 (OH, broad), 2956 (CH stretch, weak), 1743 (C=O stretch, strong), 1639 (C=N stretch, weak), 1496, 1456, 1436, 1281, 1199, 1156, 1120, 1025 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{13}H_{14}ClNO_5$ (M^+) 299.0561, found 299.0570. Anal. Calcd for $C_{13}H_{14}ClNO_5$ C, 52.10; H, 4.71; N, 4.67. Found C, 52.18; H, 4.67; N, 4.65.

3.4.8. 3,3-Dimethoxycarbonyl-2-(4-methylphenyl)propanohydroximoyl chloride (5b). Mp 144–144.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br, 1H), 7.17 (d, J=8.2 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 4.83 (d, J=12.0 Hz, 1H), 4.32 (d, J=12.0 Hz, 1H), 3.78 (s, 3H), 3.47 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 167.5, 140.9, 138.2, 131.8, 129.5, 128.4, 55.7, 53.1, 52.7, 52.0, 21.1. IR ($CHCl_3$) ν 3410 (OH, broad), 2956 (CH stretch, weak), 1744 (C=O stretch, strong), 1639 (C=N stretch, weak), 1514, 1436, 1280, 1246, 1156, 1120, 1027 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{14}H_{16}^{37}ClNO_5$ ($(M+2)^+$) 315.0682, found 315.0675; (M^+) 313.0712, found 313.0690. Anal. Calcd for $C_{14}H_{16}ClNO_5$ C, 53.60; H, 5.14; N, 4.46. Found C, 53.90; H, 5.17; N, 4.36.

3.4.9. 3,3-Dimethoxycarbonyl-2-(4-methoxyphenyl)propanohydroximoyl chloride (5c). Mp 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (br, 1H), 7.21 (dt, J=8.8, 2.0 Hz, 2H), 6.85 (dt, J=8.8, 2.0 Hz, 2H), 4.44 (d, J=12.0 Hz, 1H), 4.31 (d, J=12.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 167.6, 159.5, 140.9, 129.7, 126.8, 114.2, 55.8, 55.2, 53.0, 52.7, 51.7. IR ($CHCl_3$) ν 3400 (OH, broad), 2957 (CH stretch, weak), 1742 (C=O stretch, strong), 1638 (C=N stretch, weak), 1611, 1513, 1437, 1305, 1256, 1199, 1179, 1119, 1031 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{14}H_{16}^{37}ClNO_6$ ($(M+2)^+$) 331.0631, found 331.0635; (M^+) 329.0661, found 329.0662. Anal. Calcd for $C_{14}H_{16}ClNO_6$ C, 51.00; H, 4.89; N, 4.25. Found C, 51.06; H, 4.84; N, 4.10.

3.4.10. 3,3-Dimethoxycarbonyl-2-(4-chlorophenyl)propanohydroximoyl chloride (5d). Mp 129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br, 1H), 7.31 (dt, J=8.4, 2.0 Hz, 2H), 7.23 (dt, J=8.4, 2.0 Hz, 2H), 4.49 (d, J=11.8 Hz, 1H), 4.26 (d, J=11.8 Hz, 1H), 3.77 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.2, 140.4, 134.5, 133.5, 129.7, 129.1, 55.5, 53.2, 52.9, 51.7. IR ($CHCl_3$) ν 3402 (OH, broad), 2956 (CH stretch, weak), 1743 (C=O stretch, strong), 1639 (C=N stretch, weak), 1595, 1492, 1436, 1361, 1281, 1199, 1156, 1093, 1016 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{13}H_{13}Cl_2NO_5$ (M^+) 333.0171, found 333.0175. Anal. Calcd for $C_{13}H_{13}Cl_2NO_5$ C, 46.73; H, 3.92; N, 4.19. Found C, 47.02; H, 3.89; N, 4.04.

3.4.11. 3,3-Dimethoxycarbonyl-2-thienylpropanohydroximoyl chloride (5e). Mp 157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br, 1H), 7.27 (dd, J=4.8, 1.0 Hz, 1H), 7.01 (dd, J=2.4, 1.0 Hz, 1H), 6.95 (dd, J=4.8, 2.4 Hz, 1H), 4.83 (d, J=12.0 Hz, 1H), 4.30 (d, J=12.0 Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 167.0, 140.6, 137.4, 127.6, 127.0, 126.2, 56.4, 53.10, 52.91, 47.50. IR ($CHCl_3$) ν 3305 (OH, broad), 2956 (CH stretch, weak), 1752 (C=O stretch, strong), 1639 (C=N stretch, weak), 1435, 1315, 1267, 1210, 1177, 1118, 1027 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{11}H_{12}ClNO_5S$ (M^+) 305.0125, found 305.0122. Anal. Calcd for $C_{11}H_{12}ClNO_5S$ C, 43.21; H, 3.96; N, 4.58; S, 10.49. Found C, 43.22; H, 3.76; N, 4.53; S, 9.78.

3.4.12. 3,3-Dimethoxycarbonyl-2-furylpropanohydroximoyl chloride (5f). Mp 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br, 1H), 7.37 (dd, J=1.6, 1.0 Hz, 1H), 6.33 (dd, J=3.2, 1.8 Hz, 1H), 6.22 (dd, J=3.2, 1.8 Hz, 1H), 4.70 (d, J=12.0 Hz, 1H), 4.32 (d, J=12.0 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 148.1, 143.2, 138.5, 110.6, 109.5, 53.6, 53.1, 53.0, 46.1. IR ($CHCl_3$) ν 3410 (OH, broad), 2958 (CH stretch, weak), 1743 (C=O stretch, strong), 1639 (C=N stretch, weak), 1563, 1503, 1437, 1272, 1209, 1151, 1118, 1075, 1014 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{11}H_{12}^{37}ClNO_6$ ($(M+2)^+$) 291.0318, found 291.0309; (M^+) 289.0348, found 289.0344. Anal. Calcd for $C_{11}H_{12}ClNO_6$ C, 45.61; H, 4.18; N, 4.84. Found C, 45.78; H, 4.20; N, 4.70.

3.4.13. 2,2-Dimethoxycarbonyl-1-cyano-1-phenylethane (6a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 5H), 4.53 (d, J=9.6 Hz, 1H), 3.92 (d, J=9.6 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.8, 132.0, 129.2, 129.1, 128.1, 118.4, 56.3, 53.3, 53.1, 36.7. IR ($CHCl_3$) ν 2957 (CH stretch, medium), 2248 (CN stretch, weak), 1740 (C=O stretch, strong), 1497, 1436, 1273, 1199, 1158, 1022 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{13}H_{13}NO_4$ (M^+) 247.0845, found 247.0847. Anal. Calcd for $C_{13}H_{13}NO_4$ C, 63.15; H, 5.30; N, 5.67. Found C, 63.19; H, 5.32; N, 5.60.

3.4.14. 2,2-Dimethoxycarbonyl-1-cyano-1-(4-methylphenyl)ethane (6b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J=8.0 Hz, 2H), 7.17 (d, J=8.0 Hz, 2H), 4.49 (d, J=9.6 Hz, 1H), 3.90 (d, J=9.6 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.9, 139.1, 129.9, 129.0, 128.0, 118.6, 56.4, 53.5, 53.1, 36.4, 21.1. IR ($CHCl_3$) ν 2957 (CH stretch, medium), 2247 (CN stretch, weak), 1739 (C=O stretch, strong), 1436, 1260, 1198, 1159, 1023 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{14}H_{15}NO_4$ (M^+) 261.1001, found 261.1009. Anal. Calcd for $C_{14}H_{15}NO_4$ C, 64.36; H, 5.79; N, 5.36. Found C, 64.27; H, 5.83; N, 5.39.

3.4.15. 2,2-Dimethoxycarbonyl-1-cyano-1-(4-methoxyphenyl)ethane (6c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 4.48 (d, J=9.6 Hz, 1H), 3.89 (d, J=9.6 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.8, 159.9, 129.3, 123.7, 118.6, 114.5, 56.4, 55.3, 53.3, 53.1, 35.9. IR ($CHCl_3$) ν 2958 (CH stretch, medium), 2247 (CN stretch, weak), 1739 (C=O stretch, strong), 1436, 1255, 1200, 1182, 1158, 1032 cm^{-1}. HRMS (CI) m/z calcd for $C_{14}H_{14}NO_5$ (M^+) 277.0945, found 277.0948. Anal. Calcd for $C_{14}H_{14}NO_5$ C, 60.64; H, 5.45; N, 5.05. Found C, 60.82; H, 5.35; N, 5.17.

3.4.16. 2,2-Dimethoxycarbonyl-1-cyano-1-(4-chlorophenyl)ethane (6d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dt, J=8.8, 2.2 Hz, 2H), 7.32 (dt, J=8.8, 2.2 Hz, 2H), 4.52 (d, J=9.6 Hz, 1H), 3.89 (d, J=9.6 Hz, 1H), 3.83 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.6, 135.3, 130.5, 129.6, 129.5, 118.0, 56.1, 53.4, 53.3, 36.1. IR ($CHCl_3$) ν 2957 (CH stretch, medium), 2249 (CN stretch, weak), 1743 (C=O stretch, strong), 1494, 1436, 1271, 1199, 1155, 1094, 1017 cm^{-1}. HRMS (CI) m/z calcd for $C_{13}H_{12}ClNO_4$ (M^+) 281.0455, found 281.0456. Anal. Calcd for $C_{13}H_{12}ClNO_4$ C, 46.73; H, 3.92; N, 4.19. Found C, 46.55; H, 3.98; N, 4.16.

3.4.17. 2,2-Dimethoxycarbonyl-1-cyano-1-thienylethane (6e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J=5.2, 1.2 Hz, 1H), 7.12 (dd, J=3.6, 1.2 Hz, 1H), 6.98 (dd, J=5.2, 3.6 Hz, 1H), 4.84 (d, J=9.2 Hz, 1H), 3.97 (d, J=9.2 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.6, 133.3, 128.2, 127.3, 126.9, 117.5, 56.6, 53.5, 53.4, 31.9. IR ($CHCl_3$) ν 2957 (CH stretch, medium), 2249 (CN stretch, weak), 1741 (C=O stretch, strong), 1436, 1266, 1161, 1021 cm^{-1}. HRMS (CI) m/z calcd for $C_{11}H_{12}ClNO_5S$ (M^+) 305.0125, found 305.0122. Anal. Calcd for $C_{11}H_{12}ClNO_5S$ C, 43.21; H, 3.96; N, 4.58. Found C, 43.43; H, 3.89; N, 4.55.

3.4.18. 2,2-Dimethoxycarbonyl-1-cyano-1-furylethane (6f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J=1.8, 1.0 Hz, 1H), 6.33 (dd, J=3.2, 1.8 Hz, 1H), 6.22 (dd, J=3.2, 1.8 Hz, 1H), 4.70 (d, J=9.0 Hz, 1H), 4.06 (d, J=9.0 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.6, 144.1, 143.7, 116.0, 110.9, 109.7, 53.5, 53.4, 53.3, 30.7. IR ($CHCl_3$) ν 2958 (CH stretch, medium), 2249 (CN stretch, weak), 1742 (C=O stretch, strong), 1503, 1437, 1267, 1208, 1162, 1015 cm^{-1}. HRMS (CI) m/z calcd for $C_{11}H_{11}NO_5$ (M^+) 237.0632, found 237.0641. Anal. Calcd for $C_{11}H_{11}NO_5$ C, 55.70; H, 4.67; N, 5.90. Found C, 55.94; H, 4.56; N, 5.83.

3.5. Typical experimental procedures for the synthesis of nitroalkane 4 and nitrile 6 using PCl_3 and DMAP in THF

Typical experimental procedure of entry 2 in Table 3 is representative.

To a stirred solution of *t*-BuOK (168 mg, 1.5 mmol) in 3 mL THF was added a THF solution of dimethyl malonate **2a** (159 mg, 1.2 mmol) at 0 °C. After stirring the reaction mixture at 0 °C for 30 min, *trans*-β-nitrostyrene **1a** (149 mg, 1.0 mmol) in 5 mL of THF was added dropwise to generate nitronate **3a** solution. To this, PCl_3 (0.43 mL, 5 mmol) followed by DMAP (122 mg, 1.0 mmol) were added sequentially at 0 °C and the resultant solution was refluxed for 30 min. The reaction mixture was then poured into ice cold dil HCl and extracted with CH_2Cl_2 (3×25 mL). The combined CH_2Cl_2 layers were washed with brine, distilled H_2O and dried over anhyd $MgSO_4$. After evaporation of the organic solvent, the crude mixture as purified by flash column chromatography using silica gel (eluent; hexane/ethyl acetate; 100:1) to obtain nitroalkane **4a** (76 mg, 27% Y) and nitrile **6a** (153 mg, 62% Y).

3.5.1. 3,3-Dimethoxycarbonyl-1-nitro-2-phenylhex-5-ene (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 3H), 7.13–7.10 (m, 2H), 5.79–5.70 (m, 1H), 5.15–4.96 (m, 4H), 4.20 (dd, J=10.8, 7.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.58 (dd, J=14.4, 6.7 Hz, 1H), 2.28 (dd, J=14.4, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.9, 134.8, 131.8, 128.8, 128.5, 119.8, 78.3, 60.8, 52.8, 52.7, 46.8, 38.5. IR ($CHCl_3$) ν 3034, 2955 (CH stretch, weak), 1735 (C=O stretch, strong), 1640 (C=C stretch, weak), 1556 (N=O stretch, strong), 1497, 1456, 1436, 1379, 1297, 1285, 1222, 1140, 1088 cm^{-1}. HRMS (CI) m/z calcd for $C_{16}H_{19}NO_6$ (M^+) 321.1212, found 321.1205. Anal. Calcd for $C_{16}H_{17}NO_5$ C, 59.81; H, 5.96; N, 4.36. Found C, 59.70; H, 5.86; N, 4.46.

3.5.2. *cis*-5,5-Dimethoxycarbonyl-6-phenyl-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*cis*-8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 5H), 5.02 (d, J=1.2 Hz, 1H), 4.64 (dd, J=9.7, 8.2 Hz, 1H), 4.10 (dd, J=12.3, 8.2 Hz, 1H), 3.81 (s, 3H), 2.70 (dd, J=13.6, 11.2 Hz, 1H), 2.56 (dd, J=13.6, 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 170.5, 168.4, 135.4, 129.8, 128.1, 127.9, 75.1, 70.2, 53.4, 52.2, 51.9, 46.7, 35.1. IR ($CHCl_3$) ν 3033, 2954 (CH stretch, medium), 2873, 1732 (C=O stretch, strong), 1648 (C=N stretch, weak), 1603, 1497, 1456, 1435, 1274, 1212, 1167, 1100, 1080, 1010 cm^{-1}. HRMS (CI) m/z calcd for $C_{16}H_{17}NO_5$ (M^+) 303.1107, found 303.1109. Anal. Calcd for $C_{16}H_{17}NO_5$ C, 63.36; H, 5.65; N, 4.62. Found C, 63.16; H, 5.49; N, 4.22.

3.5.3. *trans*-5,5-Dimethoxycarbonyl-6-phenyl-3a,4-dihydro-3*H*,6*H*-cyclopenta[*c*]isoxazole (*trans*-8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 5.01 (d, J=1.4 Hz, 1H), 4.68 (dd, J=9.6, 7.7 Hz, 1H), 4.62–4.56 (m, 1H), 3.91 (dd, J=12.0, 7.7 Hz, 1H), 3.81 (s, 3H), 3.04 (s, 3H), 2.87 (dd, J=12.8, 7.6 Hz, 1H), 1.80 (dd, J=12.8, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 169.6, 135.6, 128.7, 128.2, 127.6, 75.7, 71.4, 55.3, 53.1, 52.1, 45.9, 36.5. IR ($CHCl_3$) ν 3004, 2954 (CH stretch, medium), 2870, 1732 (C=O stretch, strong), 1649 (C=N stretch, weak), 1604, 1497, 1455, 1435, 1280, 1259, 1208, 1176, 1102, 1078, 1009 cm^{-1}. HRMS (CI) m/z calcd for $C_{16}H_{17}NO_5$ (M^+) 303.1107, found 303.1111. Anal. Calcd for $C_{16}H_{17}NO_5$ C, 63.36; H, 5.65; N, 4.62. Found C, 63.16; H, 5.14; N, 4.06.

3.5.4. 2,2-Dimethoxycarbonyl-1-cyano-1-phenylpent-4-ene (9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 3H), 7.31–7.28 (m, 2H), 5.82–5.71 (m, 1H), 5.23–5.19 (m, 2H), 4.49 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.78 (dd, J=14.8, 6.9 Hz, 1H), 2.57 (dd, J=14.8, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.3, 131.1, 131.0, 129.2,

129.1, 128.9, 120.6, 118.8, 61.1, 52.9, 52.8, 40.5, 36.9. IR ($CHCl_3$) ν 3034, 2955 (CH stretch, medium), 2246 (CN stretch, weak), 1739 (C=O stretch, strong), 1640 (C=C stretch, weak), 1602, 1495, 1456, 1436, 1300, 1255, 1218, 1141, 1083 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{16}H_{17}NO_4$ (M^+) 287.1158, found 287.1162. Anal. Calcd for $C_{16}H_{17}NO_4$ C, 66.89; H, 5.96; N, 4.88. Found C, 66.81; H, 5.79; N, 4.76.

3.5.5. *cis*-4,4-Dimethoxycarbonyl-3-phenyl-4a,5,6,7,7a,7b-hexahydro-3*H*-indeno[1,7-*cd*]isoxazole (*cis*-11). Mp 189–190 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.23 (m, 5H), 5.02 (s, 1H), 4.81 (dd, $J=17.2$, 8.8 Hz, 1H), 3.84 (s, 3H), 3.77 (dd, $J=9.2$, 8.2 Hz, 1H), 3.26 (s, 3H), 2.99–2.92 (m, 1H), 2.27–2.24 (m, 1H), 2.18–2.13 (m, 1H), 1.74–1.70 (m, 1H), 1.61–1.41 (m, 2H), 1.02–0.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.8, 166.7, 135.7, 129.9, 128.0, 127.6, 78.7, 74.2, 54.2, 53.5, 51.5, 46.6, 41.9, 29.0, 25.4, 19.8. IR ($CHCl_3$) ν 3032, 2952 (CH stretch, medium), 2864, 1729 (C=O stretch, strong), 1645 (C=N stretch, weak), 1497, 1455, 1435, 1355, 1313, 1280, 1254, 1205, 1180, 1079, 1044 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{19}H_{21}NO_5$ (M^+) 343.1420, found 343.1429. Anal. Calcd for $C_{19}H_{21}NO_5$ C, 66.46; H, 6.16; N, 4.08. Found C, 66.40; H, 6.15; N, 3.93.

3.5.6. *trans*-4,4-Dimethoxycarbonyl-3-phenyl-4a,5,6,7,7a,7b-hexahydro-3*H*-indeno[1,7-*cd*]isoxazole (*trans*-11). Mp 154 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.21 (m, 5H), 5.05 (d, $J=2.0$ Hz, 1H), 4.85 (dd, $J=17.2$, 8.8 Hz, 1H), 4.60 (dd, $J=8.6$, 8.2 Hz, 1H), 3.79 (s, 3H), 3.00 (s, 3H), 2.95–2.90 (m, 1H), 2.11–2.06 (m, 1H), 1.69–1.63 (m, 2H), 1.39–1.29 (m, 1H), 1.08–0.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.8, 169.4, 135.6, 128.8, 128.3, 127.6, 77.0, 57.0, 52.6, 52.0, 44.7, 40.5, 28.5, 24.3, 20.3. IR ($CHCl_3$) ν 3032, 2954 (CH stretch, medium), 1730 (C=O stretch, strong), 1644 (C=N stretch, weak), 1601, 1497, 1456, 1435, 1280, 1254, 1207, 1078 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{19}H_{21}NO_5$ (M^+) 343.1420, found 343.1428. Anal. Calcd for $C_{19}H_{21}NO_5$ C, 66.46; H, 6.16; N, 4.08. Found C, 66.41; H, 6.15; N, 3.93.

3.5.7. 2,2-Dimethoxycarbonyl-2-(cyclohex-2-enyl)-1-cyano-1-phenylethane (12). Mp 132 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 3H), 7.34–7.32 (m, 2H), 5.78–5.75 (m, 1H), 5.60–5.56 (m, 1H), 4.93 (s, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 3.38–3.30 (m, 1H), 2.08–1.92 (m, 2H), 1.87–1.18 (m, 1H), 1.68–1.55 (m, 1H), 1.36–1.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 131.8, 129.3, 129.1, 128.8, 128.5, 126.5, 118.5, 65.6, 52.4, 40.9, 40.1, 24.7, 24.3, 22.0. IR ($CHCl_3$) ν 3030, 2952 (CH stretch, strong), 2240 (CN stretch, weak), 1736 (C=O stretch, strong), 1638 (C=C stretch, weak), 1435, 1326, 1293, 1246, 1230, 1152, 1092, 1047, 1022 cm^{-1}. HRMS (CI) *m/z* calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1471, found 327.1479. Anal. Calcd for $C_{19}H_{21}NO_4$ C, 69.71; H, 6.47; N, 4.28. Found C, 69.04; H, 6.33; N, 3.98.

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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.2005.08.041. The spectrums including ^1H, ^{13}C NMR and IR for all important compounds and for some compounds XRD information are available.

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A novel base-promoted synthesis of β-indolylketones via a three-component condensation under ultrasonic irradiation

Zhi-Liang Shen, Shun-Jun Ji,* Shun-Yi Wang and Xiao-Fei Zeng

Key Lab. of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering of Suzhou University, Suzhou, 215006 China

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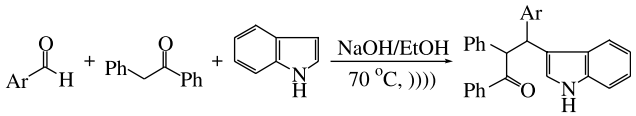
Abstract—A convenient, efficient, and practical method for the synthesis of β-indolylketones via a condensation of indole, aromatic aldehydes, and deoxybenzoin under ultrasonic irradiation was described. It provided a novel base-promoted approach for the one-pot synthesis of β-indolylketones.

1. Introduction

In recent years, a wide variety of organic compounds bearing indole motif have attracted much attention of organic chemists due to the fact that many of them are pharmacologically and biologically active compounds.[1] The β-indolylketones are one of the most significant intermediates for the synthesis of many natural products and biologically active compounds.[2] Therefore, much effort has been directed towards the synthesis of this class of compounds. One of the most useful methods for the synthesis of β-indolylketones is achieved via the protic or Lewis acid-catalyzed Michael addition of indoles with α,β-unsaturated ketones at the 3-position.[2,3] In our previous reports, we have described the synthesis of β-indolylketones by means of the conjugate addition of indole with α,β-unsaturated ketones catalyzed by Lewis (or protic) acid CAN,[3k] I_2,[3l] and PTSA.[3m]

Recently, the utilization of multi-component condensations (MCCs) to generate novel, drug-like scaffolds are replete in current organic reactions due to the fact that products can be prepared directly in a single step and the diversity can be achieved simply by varying the reaction substrates.[4] To our knowledge, one typical MCCs example for the synthesis of β-indolylketones was reported by Yonemitsu etc.[5] via trimolecular condensation of indole with various aldehydes and Meldrum's acid.[6] This one-pot synthetic method provided a very simple, convenient, and efficient approach for the preparation of β-indolylketones. One thing should be noted that, since the acidity of Meldrum's acid is similar to acetic acid, the above reaction is also an acid-promoted, one-pot procedure for the synthesis of β-indolylketones, just the same as the catalytic system of the Michael reaction of indole with α,β-unsaturated ketones (the paper also indicated that proline could accelerate the progress of the reaction). More recently, Yamamoto etc.[7] reported acetic acid-promoted one-pot procedure for the preparation of β-indolylketones, SF2809-V, as a new class of chymase inhibitor.

In continuation of our work aiming at the synthesis of β-indolylketone, herein, we would like to report a novel base-induced method for the synthesis of β-indolylketones via a three-component condensation procedure. Deoxybenzoin as the carbonyl compound was introduced into the reaction (Scheme 1). In addition, all the reactions were carried out under ultrasonic irradiation since the utilization of this technique could accelerate the progress of various organic transformations with mild reaction conditions, short reaction time and high yields.[8,9]



1(a-h) **2** **3** **4(a-h)**

Scheme 1. One-pot synthesis of β-indolylketones.

Keywords: Indole; β-Indolylketone; One-pot synthesis; Ultrasound.
* Corresponding author. Tel.: +86 512 65880086; fax: +86 512 65880089; e-mail: shunjun@suda.edu.cn

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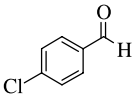
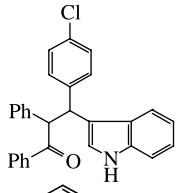
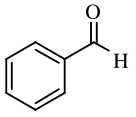
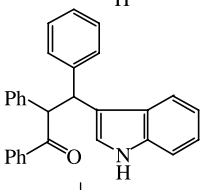
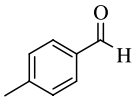
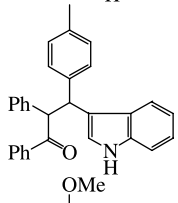
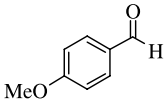
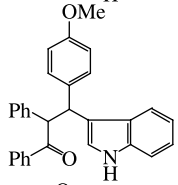
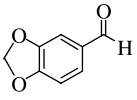
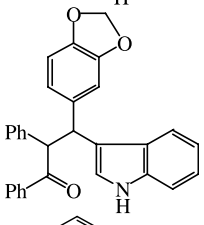
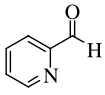
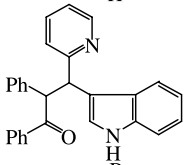
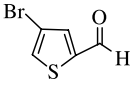
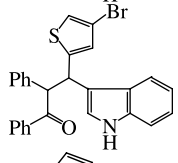
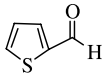
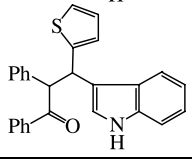
2. Results and discussion

In our initial research, we were surprised to find that when irradiating the mixture of *p*-chlorobenzaldehyde **1a** (1 mmol), deoxybenzoin **2** (1 mmol), and indole **3** (1 mmol) in ethanol (5 mL) employing sodium hydroxide (2 mmol) instead of protic or Lewis acid as the promoter, after ultrasonic irradiation for 2 h at 70 °C, a large quantity of white solid was precipitated from the reaction system. After routine work-up, a pure product was obtained and its structure was confirmed to be **4a** by ^{1}H NMR, IR, HRMS, and elemental analysis. However, the above MCCs reaction proceeded sluggishly under similar conditions in the presence of Lewis (or protic) acids such as $InCl_3$, CAN, I_2, and PTSA, no desired product **4a** was formed according to TLC analysis of the final reaction mixture. It was interesting to find that such kind of one-pot reaction can proceed well under basic conditions.

To test the generality of this reaction, a series of new

Table 1. Base-promoted, one-pot synthesis of β-indolylketones[a]

Entry		Aldehyde	Time (h)		Product	Yield (%)[b]
1	**1a**		2	**4a**		70
2	**1b**		2	**4b**		73
3	**1c**		2	**4c**		71
4	**1d**		3	**4d**		77
5	**1e**		2	**4e**		69
6	**1f**		3	**4f**		88
7	**1g**		2	**4g**		78
8	**1h**		2	**4h**		73

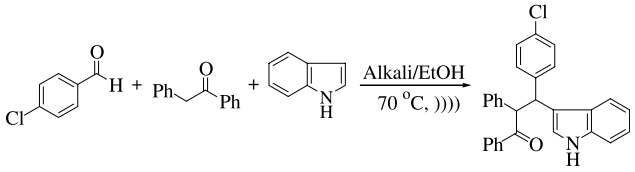
[a] The reactions were operated at 70 °C promoted by sodium hydroxide under ultrasound irradiation.
[b] Isolated yield.

β-indolylketones were prepared by varying aromatic aldehyde using above reaction system, all the results were summarized in Table 1. The corresponding products **4a–h** were obtained in modest to good yields, respectively, after reacting for 2–3 h.

Compared with general methods for the synthesis of β-indolylketones, which utilizing Michael addition of indoles with α,β-unsaturated ketones in the presence of Lewis (or protic) acid, especially expensive reagents such as $InCl_3$, $Bi(OTf)_3$, current base-mediated one-pot synthetic method provided an original, simple, convenient, efficient and cheap route to synthesize β-indolylketones and avoided the complexity of two-step synthetic routes, which needed to prepare α,β-unsaturated ketones first.

In order to study the influence of different alkalies on the reaction, other alkalies were also investigated. The results were listed in Table 2. It was found that when the reaction was carried out without any additives or in the presence of weak alkali sodium carbonate, no desired product was obtained (Table 2, entries 1–2). However, when the reaction was subjected to the inducement of lithium hydroxide, sodium hydroxide, potassium hydroxide, and sodium ethoxide, the desired product was obtained in 68, 74, 85, and 75% yields, respectively, (entries 3–6). Therefore, these four bases could promote the reaction effectively, and sodium hydroxide was commonly used as it was the cheapest.

Table 2. The effect of different alkalies on the reaction

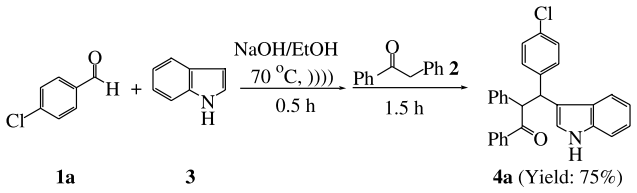


Entry	Alkali	Time (h)	Yield (%)[a]
1	—	2	0
2	Na_2CO_3	2	0
3	LiOH	2	68
4	NaOH	2	74
5	KOH	2	85
6	EtONa	2	75

[a] The yield is tested by HPLC.

Further investigation was revealed that ultrasonic irradiation also played an important role for promoting the progress of the reaction. Without ultrasonic irradiation, the same reaction as outlined in Table 2, entry 4 by conventional heating method only gave the corresponding product **4a** in 51% yield, lower than the yield (74%) obtained under ultrasonic conditions.

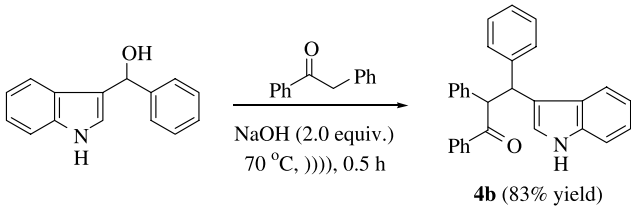
Following effort was focused on the investigation of the reaction mechanism. As shown in Scheme 2, if the equimolar amount of *p*-chlorobenzaldehyde **1a** and indole **3** were reacted together for 0.5 h beforehand in the presence of sodium hydroxide under ultrasonic irradiation, then another equimolar amount of deoxybenzoin **2** was added and reacted continuously for 1.5 h under the same conditions, product **4a** was afforded in 75% yield



Scheme 2. Two-step experiments for mechanism study.

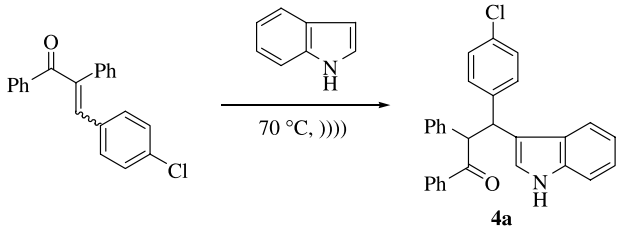
eventually. According to previous literature report,[10] the possible formation of intermediate 3-indolyl-arylmethanol via condensation of aldehyde and indole under basic conditions might be the key step. In fact, we really observed the partial formation of intermediate 3-indolyl-(4-chlorophenyl)methanol in the first step. However, we failed to isolate it by chromatography since it was decomposed slowly in organic solvents.

To further demonstrate the possibility of above hypothesis, 3-indoly-phenylmethanol was prepared via Grignard reaction of indole-3-carboxaldehyde with phenylmagnesium bromide. As expected, the reaction of 3-indolyphenylmethanol with deoxybenzoin was proceeded efficiently at 70 °C in the presence of sodium hydroxide (2.0 equiv) under ultrasound irradiation, and afforded the desired product **4b** in 83% yield within 0.5 h (Scheme 3). Gong[11] and Medebielle[12] also have reported similar reactions under basic conditions before.

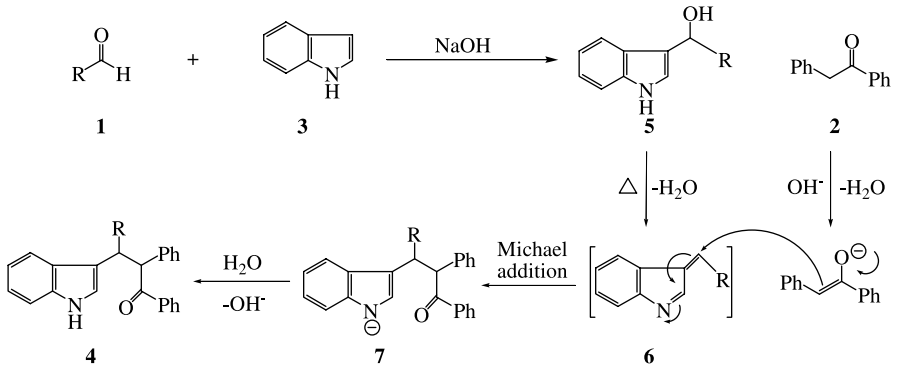


Scheme 3. The reaction of 3-indolyphenylmethanol with deoxybenzoin under basic conditions.

According to previous reports,[2,3] the reaction might proceed via the conjugate addition of indole with enone (derived from the condensation of compound **1** and **2**). In our research it was observed that the reaction of enone (3-(4-chlorophenyl)-1,2-diphenyl-propenone) with indole did occur at 70 °C in the presence of sodium hydroxide (2 equiv) under ultrasonic irradiation, however, the reaction proceeded slowly to give the product only in 32% yield even reacted for 6 h (Scheme 4). In contrast with the results obtained above (entry 1 of Table 1 and Scheme 3), the three-component condensation reaction was more inclined to

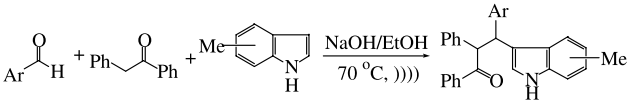


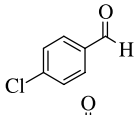
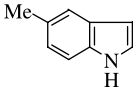
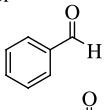
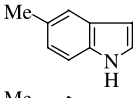
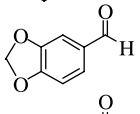
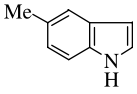
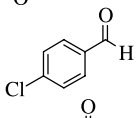
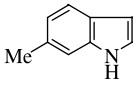
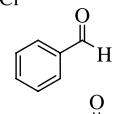
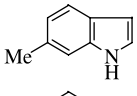
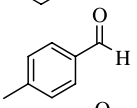
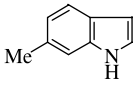
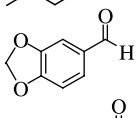
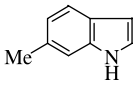
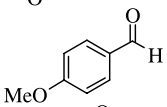
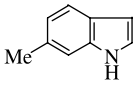
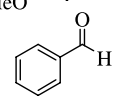
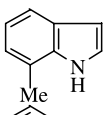
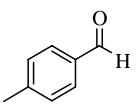
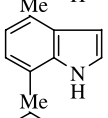
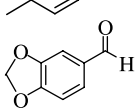
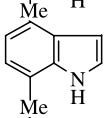
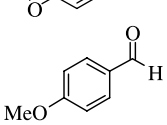
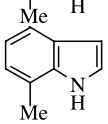
Scheme 4. The reaction of 3-(4-cholorophenyl)-1,2-diphenyl-propenone with indole. Conditions: NaOH (2.0 equiv), 6 h: 32% yield; CAN or $InCl_3$ (0.1 equiv), 2 h: 0% yield.



Scheme 5. The probable mechanism for the one-pot reaction of aldehyde, deoxybenzoin, and indole.

Table 3. Base-promoted, one-pot synthesis of new β-indolylketones[a]



Entry	Aldehyde	Indole	Time (h)	Product	Yield (%)[b]
1			1	**4i**	82
2			1	**4j**	81
3			1	**4k**	63
4			1	**4l**	69
5			1	**4m**	71
6			2	**4n**	81
7			2	**4o**	65
8			2	**4p**	67
9			1	**4q**	69
10			2	**4r**	67
11			2	**4s**	59
12			2	**4t**	51

[a] The reactions were operated at 70 °C promoted by sodium hydroxide under ultrasound irradiation.
[b] Isolated yield.

proceed through the formation of intermediate 3-indolylarylmethanol instead of enone. Furthermore, it was unexpectedly found that the above conjugate addition did not take place in the presence of Lewis acids such as $InCl_3$ and CAN (Scheme 4). It was the first time to know that conjugate addition of indole and enone could take place under basic conditions, even though the yield was relatively low.

Based on the results obtained above, a plausible mechanism was proposed here (Scheme 5). The reaction might occur via an initial condensation of aldehyde **1** and indole **3** to afford 3-indolyl-arylmethanol **5**. The formed intermediate **5** was tended to dehydrate to generate intermediate **6**, which further underwent in situ Michael addition with deoxybenzoin anion to give intermediate **7**. Finally, the anion **7** was protonated by water to form the desired product **4**.

To further demonstrate the efficiency and scope of the reaction, we also applied the three-component reaction to other methyl substituted indole compounds, all the results were summarized in Table 3. It was shown that the reaction involving different methyl substituted indoles could also proceed smoothly under basic condition to give the desired products in 51–82% yields. the position of the methyl group on the indolyl ring also had influence on the reaction time and final yields (Table 3, entries 2, 5, and 9, entries 3, 7, and 11).

3. Conclusion

In conclusion, we have demonstrated the first base-promoted, one-pot protocol for the synthesis of β-indolylketones via a three-component condensation of aldehydes, deoxybenzoin, and indoles under ultrasonic irradiation. The method provides a very efficient, convenient and feasible method for the preparation of β-indolylketones under basic conditions in comparision with current available methodologies. Attempt to extend the reaction system to other active methylene compounds are currently in progress.

4. Experimental

4.1. General

Melting points were recorded on an Electrothermal digital melting point apparatus and uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury 400 MHz spectrometer in $CDCl_3$. IR Spectra were obtained on a Nicolet FT-IR 500 spectrophotometer using KBr pellets. Elemental analysis was performed by a Carlo-Erba EA1110 CNNO-S analyzer. High resolution mass spectra were obtained using GCT-TOF instrument. Ultrasound irradiation was performed in a KQ-250E ultrasonic cleaner with a frequency of 40 KHz and a normal power of 250 W. The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the water bath was controlled by inherently heating. 3-Indolylphenylmethanol[13] and 3-(4-chlorophenyl)-1,2-diphenyl-propenone[14] were prepared according to literature methods.

4.2. Typical experimental procedure

A mixture of aromatic aldehyde **1** (1 mmol), deoxybenzoin **2** (1 mmol), indole **3** (1 mmol), sodium hydroxide (2 mmol) and absolute ethanol (5 mL) were irradiated at 70 °C in the presence of ultrasonic wave for a certain time as shown in Tables 1 and 3. The progress of the reaction was monitored by TLC until the disappearance of aromatic aldehyde. After the completion of the reaction, 10 mL aqueous ethanol (50%) was added to the reaction system. A few minutes later, the desired products **4** could be collected by filtration under reduced pressure. Further purification can be conducted by recrystallization with 95% ethanol.

4.2.1. 3-(3-Indolyl)-3-(4-chlorophenyl)-1,2-diphenylpropan-1-one 4a. White solid; mp 238–240 °C; IR (KBr): ν 3407 (NH), 1669 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (d, J=12 Hz, 1H), 5.56 (d, J=11.2 Hz, 1H), 6.85 (s, 1H), 6.95–7.51 (m, 16H), 7.83 (s, 1H), 7.90 (d, J=6.8 Hz, 2H) ppm; HRMS [found: m/z, 437.1377 (M^+); calcd for $C_{29}H_{22}^{37}ClNO$: M, 437.1360]. Anal. Calcd for $C_{29}H_{22}ClNO$: C, 79.90; H, 5.09; N, 3.21. Found: C, 79.50; H, 5.21; N, 2.78.

4.2.2. 3-(3-Indolyl)-1,2,3-triphenylpropan-1-one 4b. White solid; mp 249–251 °C; IR (KBr): ν 3417, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (d, J=11.2 Hz, 1H), 5.61 (d, J=11.6 Hz, 1H), 6.85 (s, 1H), 6.93–7.48 (m, 17H), 7.80 (s, 1H), 7.88 (d, J=7.2 Hz, 2H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 46.2, 58.1, 110.8, 117.7, 119.2, 119.4, 121.8, 122.37, 126.1, 127.0, 127.1, 128.2, 128.3, 128.4, 128.5, 128.5, 128.9, 132.8, 136.1, 137.5, 137.9, 143.6, 199.6 ppm; HRMS [found: m/z, 401.1750 (M^+); calcd for $C_{29}H_{23}NO$: M, 401.1780].

4.2.3. 3-(3-Indolyl)-3-(4-methylphenyl)-1,2-diphenylpropan-1-one 4c. White solid; mp 247–249 °C; IR (KBr): ν 3409, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 5.27 (d, J=11.2 Hz, 1H), 5.60 (d, J=11.6 Hz, 1H), 6.84 (s, 1H), 6.93–7.48 (m, 16H), 7.78 (s, 1H), 7.90 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 415.1939 (M^+); calcd for $C_{30}H_{25}NO$: M, 415.1936].

4.2.4. 3-(3-Indolyl)-3-(4-methoxyphenyl)-1,2-diphenylpropan-1-one 4d. White solid; mp 227–229 °C; IR (KBr): ν 3417, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 5.27 (d, J=10.4 Hz, 1H), 5.56 (d, J=10 Hz, 1H), 6.69 (d, J=8 Hz, 2H), 6.83 (s, 1H), 6.93–7.46 (m, 14H), 7.78 (s, 1H), 7.88 (d, J=6 Hz, 2H) ppm; HRMS [found: m/z, 431.1866 (M^+); calcd for $C_{30}H_{25}NO_2$: M, 431.1885].

4.2.5. 3-(3-Indolyl)-3-(3,4-methylenedioxyphenyl)-1,2-diphenylpropan-1-one 4e. White solid; mp 241–243 °C; IR (KBr): ν 3415, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (d, J=11.2 Hz, 1H), 5.54 (d, J=11.6 Hz, 1H), 5.81 (s, 2H), 6.61 (d, J=7.6 Hz, 1H), 6.85–7.48 (m, 15H), 7.81 (s, 1H), 7.91 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 445.1691 (M^+); calcd for $C_{30}H_{23}NO_3$ M, 445.1678].

4.2.6. 3-(3-Indolyl)-3-(2-pyridyl)-1,2-diphenylpropan-1-one 4f. White solid; mp 245–247 °C; IR (KBr): ν 3409, 1661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (d, J=11.6 Hz, 1H), 6.04 (s, 1H), 6.93–7.51 (m, 16H), 7.86 (s, 1H),

8.03 (d, J=7.2 Hz, 2H), 8.37 (s, 1H) ppm; HRMS [found: m/z, 402.1740 (M^+); calcd for $C_{28}H_{22}N_2O$: M, 402.1732].

4.2.7. 3-(3-Indolyl)-3-(4-bromo-2-thienyl)-1,2-diphenylpropan-1-one 4g. White solid; mp 226–228 °C; IR (KBr): ν 3419, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.54 (s, 2H), 6.84–7.54 (m, 15H), 7.85 (s, 1H), 7.99 (d, J=7.2 Hz, 2H) ppm; HRMS [found: m/z, 485.0414 (M^+); calcd for $C_{27}H_{20}BrNOS$: M, 485.0449].

4.2.8. 3-(3-Indolyl)-3-(2-thienyl)-1,2-diphenylpropan-1-one 4h. White solid; mp 213–215 °C; IR (KBr): ν 3412, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 2H), 6.77 (s, 1H), 6.86 (s, 1H), 6.93 (s, 1H), 7.01–7.53 (m, 12H), 7.80 (s, 1H), 7.98 (d, J=8.4 Hz, 2H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 41.46, 59.32, 111.01, 117.17, 119.29, 119.54, 121.80, 122.58, 123.46, 124.65, 126.35, 126.67, 127.02, 128.42, 128.56, 128.76, 132.92, 136.13, 137.27, 137.36, 148.12, 199.27 ppm; HRMS [found: m/z, 407.1315 (M^+); calcd for $C_{27}H_{21}NOS$: M, 407.1344]. Anal. Calcd for $C_{27}H_{21}NOS$: C, 79.57; H, 5.19; N, 3.44. Found: C, 79.61; H, 5.09; N, 3.55.

4.2.9. 3-(3-(5-Methyl)-indolyl)-3-(4-chlorophenyl)-1,2-diphenylpropan-1-one 4i. White solid; mp 232–234 °C; IR (KBr): ν 3403, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 5.27 (d, J=12.4 Hz, 1H), 5.53 (d, J=12.8 Hz, 1H), 6.82 (s, 1H), 6.92 (d, J=7.6 Hz, 1H), 6.97–7.52 (m, 14H), 7.76 (s, 1H), 7.95 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 449.1589 (M^+); calcd for $C_{30}H_{24}ClNO$: M, 449.1546].

4.2.10. 3-(3-(5-Methyl)-indolyl)-1,2,3-triphenylpropan-1-one 4j. White solid; mp 236–238 °C; IR (KBr): ν 3434, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 5.28 (d, J=12.8 Hz, 1H), 5.56 (d, J=12.8 Hz, 1H), 6.82 (s, 1H), 6.88 (d, J=8 Hz, 1H), 7.05–7.48 (m, 15H), 7.72 (s, 1H), 7.87 (d, J=8 Hz, 2H) ppm; HRMS [found: m/z, 415.1932 (M^+); calcd for $C_{30}H_{25}NO$: M, 415.1936].

4.2.11. 3-(3-(5-Methyl)-indolyl)-3-(3,4-methylenedioxyphenyl)-1,2-diphenylpropan-1-one 4k. White solid; mp 218–220 °C; IR (KBr): ν 3403, 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 5.09 (d, J=10.4 Hz, 1H), 5.28 (d, J=10.4 Hz, 1H), 5.76 (s, 1H), 5.83 (s, 1H), 6.47 (s, 2H), 6.57 (s, 1H), 6.93 (s, 2H), 7.14–7.53 (m, 10H), 7.75 (s, 1H), 7.99 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 459.1814 (M^+); calcd for $C_{31}H_{25}NO_3$: M, 459.1834].

4.2.12. 3-(3-(6-Methyl)-indolyl)-3-(4-chlorophenyl)-1,2-diphenylpropan-1-one 4l. White solid; mp 213–215 °C; IR (KBr): ν 3458, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.26 (d, J=11.6 Hz, 1H), 5.56 (d, J=11.6 Hz, 1H), 6.81 (d, J=7.6 Hz, 1H), 7.01–7.51 (m, 14H), 7.69 (s, 1H), 7.89 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 449.1516 (M^+); calcd for $C_{30}H_{24}ClNO$: M, 449.1546].

4.2.13. 3-(3-(6-Methyl)-indolyl)-1,2,3-triphenylpropan-1-one 4m. White solid; mp 206–208 °C; IR (KBr): ν 3468, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.28 (d, J=10 Hz, 1H), 5.61 (d, J=10.4 Hz,1H), 6.77–7.49 (m, 17H), 7.67 (s, 1H), 7.89 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 415.1928 (M^+); calcd for $C_{30}H_{25}NO$: M, 415.1936].

4.2.14. 3-(3-(6-Methyl)-indolyl)-3-(4-methylphenyl)-1,2-diphenylpropan-1-one 4n. White solid; mp 217–219 °C; IR (KBr): ν 3454, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.37 (s, 3H), 5.24 (d, J=11.6 Hz, 1H), 5.60 (d, J=12 Hz, 1H), 6.75 (s, 1H), 6.79 (d, J=8.8 Hz, 1H), 6.90–7.49 (m, 14H), 7.64 (s, 1H), 7.90 (d, J=7.2 Hz, 2H) ppm; HRMS [found: m/z, 429.2077 (M^+); calcd for $C_{31}H_{27}NO$: M, 429.2093].

4.2.15. 3-(3-(6-Methyl)-indolyl)-3-(3,4-methylenedioxyphenyl)-1,2-diphenylpropan-1-one 4o. White solid; mp 243–245 °C; IR (KBr): ν 3404, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.22 (d, J=11.6 Hz, 1H), 5.54 (d, J=11.6 Hz, 1H), 5.80 (s, 2H), 6.60 (d, J=7.6 Hz, 1H), 6.76 (s, 1H), 6.81–7.48 (m, 13H), 7.67 (s, 1H), 7.91 (d, J=8.8 Hz, 2H) ppm; HRMS [found: m/z, 459.1831 (M^+); calcd for $C_{31}H_{25}NO_3$: M, 459.1834].

4.2.16. 3-(3-(6-Methyl)-indolyl)-3-(4-methoxyphenyl)-1,2-diphenylpropan-1-one 4p. White solid; mp 226–229 °C; IR (KBr): ν 3426, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.68 (s, 3H), 5.25 (d, J=11.6 Hz, 1H), 5.56 (d, J=12 Hz, 1H), 6.68–7.49 (m, 16H), 7.65 (s, 1H), 7.89 (d, J=7.2 Hz, 2H) ppm; HRMS [found: m/z, 445.2037 (M^+); calcd for $C_{31}H_{27}NO_2$: M, 445.2042].

4.2.17. 3-(3-(7-Methyl)-indolyl)-1,2,3-triphenylpropan-1-one 4q. White solid; mp 218–220 °C; IR (KBr): ν 3376, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.33 (d, J=11.2 Hz, 1H), 5.64 (d, J=11.2 Hz, 1H), 6.87–7.49 (m, 17H), 7.74 (s, 1H), 7.89 (d, J=6.8 Hz, 2H) ppm; HRMS [found: m/z, 415.1918 (M^+); calcd for $C_{30}H_{25}NO$: M, 415.1936].

4.2.18. 3-(3-(7-Methyl)-indolyl)-3-(4-methylphenyl)-1,2-diphenylpropan-1-one 4r. White solid; mp 225–227 °C; IR (KBr): ν 3435, 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.37 (s, 3H), 5.27 (d, J=11.6 Hz, 1H), 5.62 (d, J=11.6 Hz, 1H), 6.86–7.47 (m, 16H), 7.71 (s, 1H), 7.90 (d, J=7.2 Hz, 2H) ppm; HRMS [found: m/z, 429.2103 (M^+); calcd for $C_{31}H_{27}NO$: M, 429.2093].

4.2.19. 3-(3-(7-Methyl)-indolyl)-3-(3,4-methylenedioxyphenyl)-1,2-diphenylpropan-1-one 4s. White solid; mp 231–233 °C; IR (KBr): ν 3392, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.26 (d, J=12 Hz, 1H), 5.56 (d, J=12 Hz, 1H), 5.80 (s, 2H), 6.60 (d, J=8 Hz, 1H), 6.86–7.48 (m, 14H), 7.74 (s, 1H), 7.91 (d, J=6.8 Hz, 2H) ppm; HRMS [found: m/z, 459.1866 (M^+); calcd for $C_{31}H_{25}NO_3$: M, 459.1834].

4.2.20. 3-(3-(7-Methyl)-indolyl)-3-(4-methoxyphenyl)-1,2-diphenylpropan-1-one 4t. White solid; mp 216–218 °C; IR (KBr): ν 3438, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.67 (s, 3H), 5.30 (d, 1H), 5.57 (d, 1H), 6.69 (d, J=8.8 Hz, 2H), 6.86–7.38 (m, 14H), 7.72 (s, 1H), 7.88 (d, J=7.6 Hz, 2H) ppm; HRMS [found: m/z, 445.2023 (M^+); calcd for $C_{31}H_{27}NO_2$: M, 445.2042].

Acknowledgements

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Simple preparation of phenylpropenoid β-D-glucopyranoside congeners by Mizoroki–Heck type reaction using organoboron reagents

Masashi Kishida[a,b] and Hiroyuki Akita[a,*]

[a]*School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274, Japan*
[b]*Tsukuba Research Institute, Novartis Phrma. K.K., 8, Ohkubo, Tsukuba-shi, Ibaraki 300-2611, Japan*

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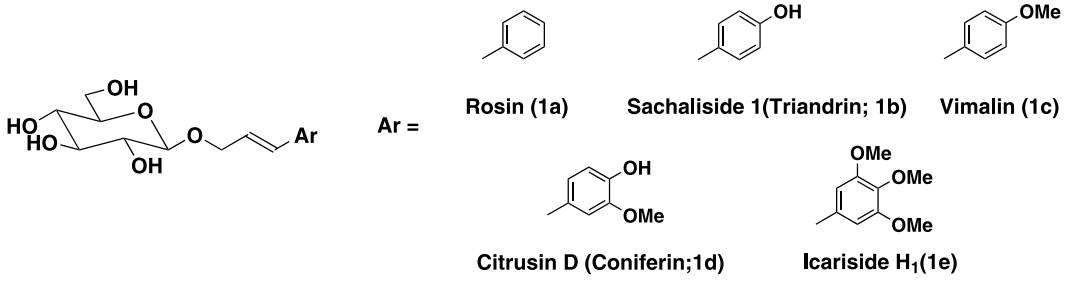
Abstract—Palladium(II)-catalyzed carbon–carbon bond formation between allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) and arylboronic acid congeners gave the corresponding cinnamyl 2,3,4,6-tetra-*O*-acetyl- β-D-glucopyranosides (**4a**–**m**) in good yield. Among them, coupling products **4a**–**m** were converted to not only the naturally occurring phenylpropenoid β-D-glucopyranoside analogues (**1a**–**e**) but also the unnaturally ones (**1f**–**m**).

1. Introduction

Golden root (Roseroot, *Rhodiola rosea* L., Crassulaceae) has been used for a long time as a resource in Chinese traditional medicine.[2] Phenylpropenoid Glucoside, such as Rosin[3] (cinnamyl *O*-β-D-glucopyranoside; **1a**), was isolated from *R. rosea*[3ab] as one of the major active ingredients and reported to be pharmacologically active as antioxidants and neurostimulants.[3d] Moreover, some other phenylpropenoid glucoside analogues have been isolated as bioactive substances. For instance, Sachaliside 1[4] (Triandrin; 4-hydroxycinnamyl *O*-β-D-glucopyranoside; **1b**) and Vimalin[4c,d] (4-methoxycinnamyl *O*-β-D-glucopyranoside; **1c**) have been isolated from the callus cultures of the plant.[4c] In addition, Citrusin D[3c,5] (Coniferin; 4-hydroxy-3-methoxycinnamyl *O*-β-D-glucopyranoside; **1d**) have been isolated from *Citrus unshiu* as an antihypertensive ingredient,[5a,d] and Icariside H_1 (3,4,5-trimethoxycinnamyl *O*-β-D-glucopyranoside; **1e**),[6] from *Epimedium Sagittatuma*[6a] (Scheme 1).

Meanwhile, some syntheses of phenylpropenoid glycoside derivatives have been reported. Matsui et al. reported the synthesis of Citrusin D (**1d**) using silica gel-catalyzed β-*O*-glucosilation of the 3-methoxy-4-(tetrahydropyra-2-yloxy)-cinnamylalcohol and the 1,2-anhydro-3,4,6-tri-*O*-pivaloyl-β-D-glucopyranose as a key reaction.[7] Recently, we have reported that the coupling of cinnamyl alcohol derivatives and 4-nitrophenyl-β-D-glucopyranoside using β-glucosidase (EC 3.2.1.21) in a phosphate buffer (pH 5) gave Rosin (**1a**)



Scheme 1.

Keywords: Mizoroki–Heck type reaction; *Rhodiola rosea*; Cinnamyl ethers.
* Corresponding author. Tel.: +81 474 72 1805; fax: +81 474 76 6195; e-mail: akita@phar.toho-u.ac.jp

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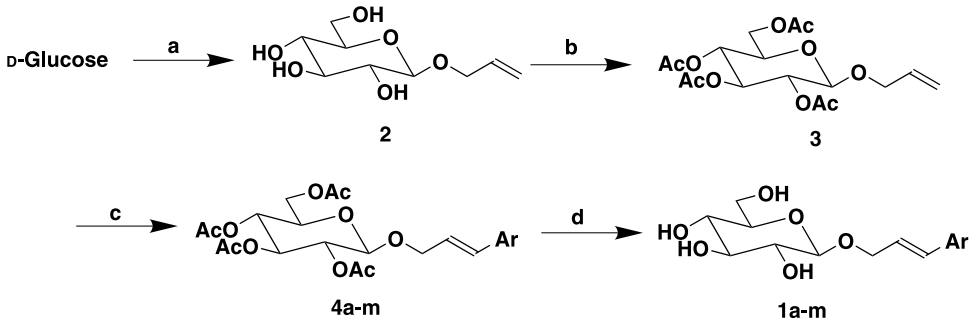


Scheme 2. Regents and conditions: (a) allyl alcohol, H_2O, immobilized β-glucosidase with ENTP-4000, 50 °C, 72 h, 68%; (b) Ac_2O, cat. DMAP, pyridine, rt, overnight, quant.; (c) organoboron reagents, cat. $Pd(OAc)_2$, $Cu(OAc)_2$, LiOAc, DMF, 80–100 °C, 0.5–1.5 h, 42–86%; (d) K_2CO_3, MeOH, rt, 1 h or NaOMe, MeOH, rt, 1 h 63–99%.

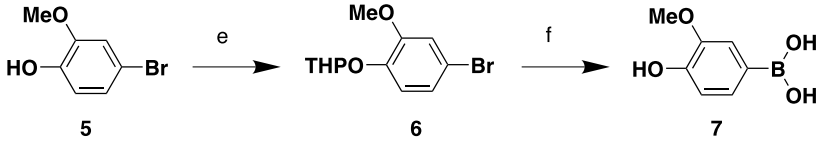
and Vimalin (**1c**).[8] However, to synthesize the diverse phenylpropenoid glucoside analogues using existing glucosilation methods, many kinds of substituted cinnamyl-alcohols should be synthesized. On the other hand, cross-metathesis could be a useful method to prepare phenyl-propenoid glucoside analogues. In fact, Chi-Huey et al. reported the synthesis of some phenylpropenoid galactoside analogues from tetra-*O*-acetyl-α-D-allyl-galactoside and substituted styrene via cross-methathesis.[9] It was an effective method to synthesize a structurally diverse phenylpropenoid library; however, an excess amount of styrenes was required to avoid the production of self-metathesis of tetra-*O*-acetyl-α-D-allyl-galactoside as a by-product. Therefore, other methods to prepare diverse phenylpropenoid analogues including natural ones were expected for investigation of their biological activities. We herein report a simple total synthesis of Rosin (**1a**), Sachaliside 1 (Triandrin; **1b**), Vimalin (**1c**), Citrusin D (Coniferin; **1d**), and Icariside H_1 (**1e**) using the Mizoroki–Heck (MH) type reaction between the substituted arylboronic acid congeners and allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) under Pd(II) condition as the key reaction (Scheme 2, step c).

The synthesis of cinnamyl ethers using the MH-type arylation of allyl ethers with aryl iodides was reported by Tamaru et al.[10] However, the isolated yield was moderate (22–57%) and substantial quantities of benzyl vinyl ethers and 2-phenyl allyl ether (8–43%) were provided as by-products. The MH-type reaction of phenylboronic acids and conjugated olefins, such as butyl acrylate, acrylnitrile, and methyl vinyl ketone under Pd(0)-catalyzed condition was shown by Cho and Uemura.[11a] Moreover, they reported that phenylantimonyl chlorides react smoothly with alkenes in the presence of Pd(II) acetate[11b] and Hiyama et al. also reported arylsilanols or aryltin reagents undergo the MH type reaction under Pd(II) condition.[12] On the other hand, organoboron-mediated MH type reaction via a Pd(II)-species had been also reported by Mori et al.[13] They disclosed that the phenylboronic acid reacted with several olefins other than enones and enals, such as allyl phenyl ether, to give the corresponding coupling products via the Pd(II)-catalyzed MH type reaction. However, only one example of the reaction of allyl ether with phenylboronic acid was examined in this literature and no other examples have been reported in the field of carbohydrate chemistry. Furthermore, we synthesized not only naturally occurring but also unnaturally occurring phenylpropenoid analogues to investigate the limitation of this strategy.

2. Results

2.1. Synthesis of substrate for MH type reaction and 4-hydroxy-3-methoxyphenylboronic acid

Some syntheses of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**)[14] and the direct glucosidation of D-glucose using β-glucosidase (EC 3.2.1.21) from almonds have been reported.[15] Meanwhile, we had reported direct β-glucosidation between D-glucose and primary alcohol using the immobilized β-glucosidase (EC 3.2.1.21) from almonds with the synthetic prepolymer ENTP-4000 gave mono-β-glucopyranoside in moderate yield.[16] As in the previous method, the allyl β-D-glucopyranoside (**2**) was prepared from D-glucose and allyl alcohol using the immobilized β-glucosidase in 68% yield. The immobilized β-glucosidase was reusable and the yield of **2** was 55% in the case of using recovered immobilized β-glucosidase. Acetylation of **2** with acetic anhydride in pyridine afforded allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) as a key substrate for MH type reaction. In the meantime, 4-hydroxy-3-methoxy-phenylboronic acid (**7**) was prepared as shown in Scheme 3. Tetrahydro-pyranyl (THP) protection of the 4-bromoguaicol using dihydropyran (DHP) and 4 M HCl in EtOAc gave 3-methoxy-4-(tetrahydropyra-2-yloxy)-1-bromobenzene (**6**) in 75% yield. To a solution of *n*-BuLi in THF/*n*-hexane at −78 °C was slowly added a THF solution of **6**, then the



Scheme 3. Reagents and conditions: (e) DHP, 4 M HCl in EtOAc, EtOAc, rt, 12 h, 75%; (f) (i) *n*-BuLi, THF, −78 °C; (ii) $B(O\text{-}i\text{-}Pr)_3$; (iii) 1 M HCl aqueous, 91%.

Table 1. Reaction of arylboronic acid with 2,3,4,6-tetra-*O*-accetyl-β-D-glucopyranoside (**3**)[a]

Entry	Ar-B(OH)$_2$ (Ar=)	Product (% yield)
1	Phenyl	**4a** (71)
2	4-Hydroxyphenyl[b]	**4b** (62)
3	4-Methoxyphenyl	**4c** (72)
4	4-Hydroxy-3-methoxyphenyl[c]	**4d** (52)
5	3,4,5-Trimepthoxyphenyl	**4e** (67)
6	3-Methoxyphenyl	**4f** (86)
7	2-Methoxyphenyl	**4g** (74)
8	3,4-Dimethoxyphenyl	**4h** (42)
9	4-Chlorophenyl	**4i** (74)
10	4-Cyanophenyl	**4j** (75)
11	4-Trifluoromethylphenyl	**4k** (45)
12	3-Nitorphenyl	**4l** (63)
13	β-Naphtyl	**4m** (53)

[a] Unless otherwise noted, all coupling reactions were carried out in DMF (4 mL), using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**; 1.0 mmol), Ar-B(OH)$_2$ (1.2 mmol), Pd(OAc)$_2$ (0.1 mmol), Cu(OAc)$_2$ (2 mmol), and LiOAc (3 mmol) at 100 °C for 1.5 h.

[b] Coupling reaction was carried out in DMF (8 mL), using 2,3,4,6-tetra-*O*-β-D-glucopyranoside (**3**; 2.0 mmol), Ar-B(OH)$_2$ (6.0 mmol), Pd(OAc)$_2$ (0.2 mmol), Cu(OAc)$_2$ (10 mmol), and LiOAc (10 mmol) at 80 °C for 0.5 h.

[c] Coupling reaction was carried out in DMF (4 mL), using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**; 1.0 mmol), Ar-B(OH)$_2$ (3.0 mmol), Pd(OAc)$_2$ (0.1 mmol), Cu(OAc)$_2$ (5 mmol), and LiOAc (5 mmol) at 80 °C for 0.5 h.

mixture was treated with a triisopropyl borate to provide the desired **7** in 91% yield.

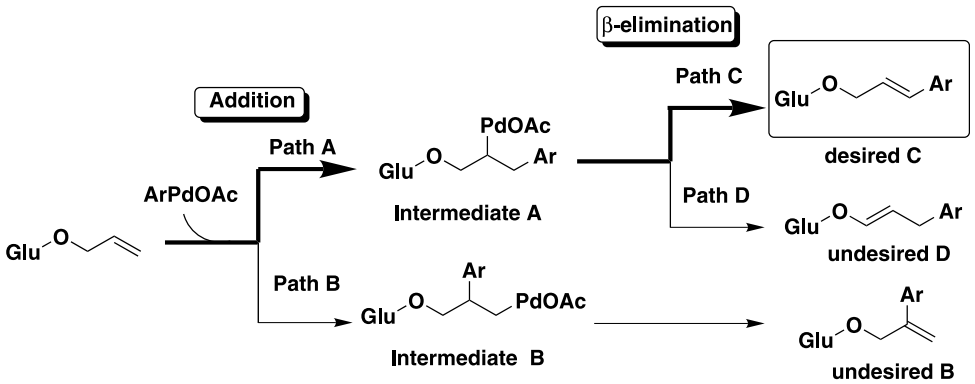
2.2. Synthesis of phenylpropenoid β-D-glucopyranoside using MH-type reaction

As summarized in Table 1, we examined the coupling reaction of various phenylboronic acids with **3**. The MH-type reaction was carried out using the substrate **3** (1 mmol), substituted phenylboronic acids (1.2 mmol), Cu(OAc)$_2$ (2.0 mmol), LiOAc (3.0 mmol) in the presence of 10 mol% Pd(OAc)$_2$ in DMF (4.0 mL) at 100 °C for 1.5 h. All phenylboronic acids having an electron-donating group (entry 3, 5–8) and an electron-withdrawing group (entry 9–12) underwent MH-type reactions smoothly in reasonable yield. However, 3.0 equiv of phenylboronic acid having a non-protected hydroxyl (entry 2, 4) group at the 4-position with 5.0 equiv of Cu(OAc)$_2$ and LiOAc were needed to proceed the coupling reaction. Because the deborilation of phenylboronic acids was occurred in this coupling condition and phenols were obtained as by-products. Moreover, the reaction of **3** and 4-hydroxy-3-methoxyphenyl boronic acid was carried out at 80 °C due to the thermolability of the coupling product **4d** (entry 4). In fact, **4d** was decomposed rapidly at 100 °C under the coupling condition.

After deprotection of substituted cinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides (**4a**–**4n**) using NaOMe/MeOH or K_2CO_3/MeOH, many kinds of the desired phenylpropenoid glycoside analogues (**1a**–**1m**) were provided rapidly. It should be noted that Citrusin D (Coniferin; **1d**) was unstable, therefore, evaporation of **1d** was required to be performed at under 5 °C. The spectral data (^{1}H and ^{13}C NMR) and specific rotation {$[\alpha]_D$} of synthetic natural-type phenylpropenoid glycoside analogues (**1a**, **1b**, **1c**, **1d**, and **1e**) were identical with those of natural products.

3. Discussion

The MH-type reaction of silanols and organotin compounds with olefins via a Pd(II)-mediated pathway has been reported by Hiyama and co-workers.[12] Based on this pathway, a plausible MH type reaction mechanism with arylboronic acids had been presented by us.[1] According to this mechanism, the aryl unit migrated to the palladium center from arylboronic acid to furnish an aryl palladium species first, and this reactive aryl palladium species was added to an olefin of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) to afford an intermediate A. After reductive β-elimination of the intermediate A, the desired product was obtained along with the release of palladium(0). Finally, the palladium(0) species was oxidized by a combination of copper(II) acetate and lithium acetate to regenerate palladium(II) as the key species of this catalytic reaction. The MH type arylation of allyl ethers with aryl halides was reported to give some regioisomers as by-products.[10] Taking into account for this reference in the present case, undesired products B and D via path B and path D, respectively, as shown in Scheme 4 are considered as by-products. Indeed, the ^{1}H NMR analysis of crude products indicated that a little amount of regioisomers (less than 5%) might be provided as by-products. However, these by-products could be easily removed by the following purifications. Moreover, the treatment of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**3**) and phenylboronic acid in the presence of tetrakistriphenylphosphine palladium(0)



Scheme 4. The plausible MH type reaction pathway with arylboronic acid.

effected removal of the allyl group instead of the desired MH-type reaction. In addition, non-protected allyl β-D-glucopyranoside (**2**) could be reacted with arylboronic acid under the same conditions. However, the chemical yield was poor due to low conversion. For instance, when allyl β-D-glucopyranoside (**2**) was treated with phenylboronic acid in the presence of LiOAc, $Cu(OAc)_2$, and a catalytic amount of $Pd(OAc)_2$ in DMF at 100 °C for 5 h, the desired cinnamyl β-D-glucopyranoside (**1a**) could be obtained in only 11% yield along with a large amount of the starting material. This phenomenon might be explained by the deactivation of arylboronic acid due to the formation of arylboronic ester from arylboronic acid and allyl β-D-glucopyranoside (**2**). In fact, the 4-hydroxyphenylboronic acid could be reacted with **3** in 62%; however, 4,4,5,5-tetramethyl-2- (4-hydroxyphenyl)-1,3-dioxaborane failed to react under the same conditions. This result suggested that an arylboronic ester was less reactive than an arylboronic acid with the allyl ether **3** in this case.

4. Conclusion

In conclusion, natural phenylpropenoid glucopyranosides, such as Rosin (**1a**), Sachaliside 1 (Triandrin; **1b**), Vimalin (**1c**), Citrusin D (Coniferin; **1d**), and Icariside H_1 (**1e**), have been prepared based on the MH type reaction using the substituted arylboronic acid congeners. Moreover, structurally diverse unnatural phenylpropenoid glucopyranoside analogues (**1f–1m**) were also obtained. Therefore, this strategy is effective to prepare a variety of phenylpropenoid glucopyranoside congeners using a number of commercially available substituted arylboronic acids.

5. Experimental

5.1. 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 or Bruker 400 spectrometer in $CDCl_3$, methanol-d_4, DMSO-d_6, D_2O and pyridine-d_5 with Me_4Si as an internal reference. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) 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 reagents were purchased from commercial sources and were used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed and for flash column chromatography, silica gel (Silica Gel 60N, spherical, neutral, 40–50 μm) was employed.

5.2. Immobilization of β-D-glucosidase using a prepolymer

β-D-Glucosidase (EC 3.2.1.21) from almonds was purchased from Sigma Chemical Co. (G-0395, 2.5–3.6 units/mg). The preparation of the immobilized β-D-glucosidase from almonds on the photocross-linkable resin prepolymer (ENTP-4000) was carried out using the following procedure. One gram of ENTP-4000 was mixed with 10 mg of photosensitizer, benzoin ethyl ether, and 74 mg of β-D-glucosidase from almonds (3.4 units/mg). The mixture was layered on a sheet of transparent polyester film (thickness, ca. 0.5 mm). The layer was covered with transparent thin film and then illuminated with chemical lamps (wavelength range, 300–400 nm) for 3 min. The gel film thus obtained was cut into small pieces ($0.5\times0.5\times5$ mm) and used for the bioconversion reaction.

5.2.1. Allyl β-D-glucopyranoside (2). A mixture of D-glucose (1.1 g, 6.1 mmol), water (2 mL), allyl alcohol (18 mL), and the immobilized β-D-glucosidase (250 units) was incubated for 3 days at 50 °C. The reaction mixture was filtered off and the recovered immobilized β-D-glucosidase was washed with water (4 mL) and AcOEt (7 mL). The combined filtrate was directly chromatographed on silica gel (35 g) to give **2** (0.91 g, 68%) as a colorless crystal from the $CHCl_3$/MeOH=9:1 eluent. Mp: 101–103 °C; $[\alpha]_D^{28}$ −41.4 (*c* 0.43, MeOH); IR (KBr) 3385, 1645, 1415, 1074 cm^{-1}; ^1H NMR (D_2O-acetone-d_6, 400 MHz) δ: 5.90–5.80 (m, 1H), 5.25 (d, J=17.6 Hz, 1H), 5.16 (d, J=10.3 Hz, 1H), 4.37 (d, J=7.8 Hz, 1H), 4.26 (dd, J=6.6, 12.7 Hz, 1H), 4.10 (dd, J=6.6, 12.7 Hz, 1H), 3.78 (dd, J=5.9, 12.2 Hz, 1H), 3.58 (dd, J=5.9, 12.2 Hz, 1H), 3.36 (t, J=9.3 Hz, 1H), 3.31 (m, 1H), 3.25 (m, 1H), 3.15 (m, 1H); ^{13}C NMR (D_2O-acetone-d_6, 100 MHz) δ: 134.2, 119.5, 102.0, 76.7, 76.6, 74.0, 71.4, 70.5, 61.6. Anal. Found: C, 49.01; H, 7.36%. Calcd for $C_9H_{16}O_6$: C, 49.08; H, 7.32%.

5.2.2. Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (3). A mixture of **2** (0.50 g, 2.3 mmol), Ac_2O (1.85 g, 18.1 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP; 10 mg, 0.08 mmol) in pyridine (2 mL) was stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with 10% aqueous HCl and brine. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (20 g) to afford **3** (0.88 g, quantitative yield) as colorless needles from the *n*-hexane/AcOEt=3:1 eluent. Mp: 83–88 °C; $[\alpha]_D^{25}$ −26.1 (*c* 0.96, $CHCl_3$); IR (KBr) 3379, 2945, 1751, 1228, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.90–5.80 (m, 1H), 5.27 (dd, J=1.6, 17.2 Hz, 1H), 5.21 (t, J=9.5 Hz, 1H), 5.21 (dd, J=1.6, 10.8 Hz, 1H), 5.10 (d, J=9.5 Hz, 1H), 4.03 (dd, J=8.0, 9.5 Hz, 1H), 4.56 (d, J=8.0 Hz, 1H), 4.34 (dd, J=5.0, 13.1 Hz, 1H), 4.27 (dd, J=4.7, 12.2 Hz, 1H), 4.15 (dd, J=2.4, 12.2 Hz, 1H), 4.10 (dd, J=6.4, 13.1 Hz, 1H), 3.69 (ddd, J=2.4, 4.7, 9.5 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7, 170.3, 169.4, 169.3, 133.3, 117.7, 99.6, 72.9, 71.8, 71.3, 70.0, 68.5, 62.0, 20.7, 20.7, 20.6. Anal. Found: C, 52.49; H, 6.29%. Calcd for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23%.

5.2.3. 2-(4-Bromo-2-methoxyphenoxy)tetrahydropyran (6). A mixture of 4-bromoguaicol (4.06 g, 0.020 mmol) and dihydropyrane (DHP; 16.80 g, 0.20 mmol) in AcOEt (40 mL) was treated with 4 M HCl in AcOEt (3 mL) and stirred at room temperature for 24 h. The mixture was

poured into saturated $NaHCO_3$ aqueous solution and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography to afford **6** (4.31 g, 75%) as colorless syrup. IR (KBr) 2944, 1469, 1253, 1221, 1030, 958, 916, 856 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.00 (s, 3H), 5.35 (t, $J=3.3$ Hz, 1H), 3.99–3.92 (m, 1H), 3.84 (s, 3H), 3.62–3.55 (m, 1H), 2.05–1.83 (m, 3H), 1.71–1.60 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.1, 145.6, 123.6, 119.2, 115.7, 114.5, 97.7, 62.1, 56.2, 30.3, 25.2, 18.7. Anal. Found: C, 50.03; H, 5.12%. Calcd for $C_{12}H_{15}BrO_3$: C, 50.19; H, 5.27%.

5.2.4. 4-Hydroxy-3-methoxyphenylboronic acid (7). A solution of *n*-buthyllithium in hexane (1.5 M, 9.7 mL, 14.6 mmol) was added to THF (30 mL), keeping the temperature below −60 °C. 2-(4-Bromo-2-methoxyphenoxy)tetrahydropyran **6** (3.80 g, 13.2 mmol) dissolved in THF (8.0 mL) was added, keeping the temperature below −65 °C during the addition. After 10 min at this temperature triisopropyl borate (6.10 mL, 26.5 mmol) was added neat at −65 °C. The mixture was stirred at the same temperature for 10 min, quenched by addition of 1 N HCl aqueous solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The product was collected by filtration and washed with CH_2Cl_2/hexane (1:1), and dried in vacuo to give **7** (2.02 g, 91%) as a white solid, which was used for the next reaction without further purification. IR (KBr) 3285, 1599, 1520, 1421, 1341, 1264, 1232, 1162, 1096, 1033, 881, 819, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.81 (dd, $J=1.0$, 8.0 Hz, 1H), 7.26 (d, $J=1.0$ Hz, 1H), 7.06 (d, $J=8.0$ Hz, 1H), 6.00 (s, 1H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.6, 145.7, 121.5, 120.1, 114.5, 110.7, 55.9.

5.3. General procedure for MH-type reaction of arylboronic acids with allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (3)

A mixture of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **3** (0.39 g, 1.0 mmol), arylboronic acids (1.2 mmol), copper(II) acetate (0.36 g, 2.0 mmol), lithium acetate (0.20 g, 3.0 mmol) and palladium(II) acetate (0.022 g, 0.10 mmol) in DMF (4 mL) was stirred for 1.5 h at 100 °C. Allowed to cool to room temperature, the reaction mixture was diluted with AcOEt and washed with 1 M HCl and brine. The organic layer was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt as an eluent) to afford the corresponding product.

5.3.1. Cinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4a). Obtained in 71% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4a** in 36% yield, a pure white powder to be analyzed by microanalyses. Mp: 72.4–73.2 °C; $[\alpha]_D^{27}$ −32.1 (*c* 0.40, MeOH); IR (KBr) 1746, 1443, 1371, 1228, 1169, 1134, 1042, 984, 914, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.40–7.23 (m, 5H), 6.59 (d, $J=15.6$ Hz, 1H), 6.22 (dt, $J=15.6$, 5.5 Hz, 1H), 5.22 (t, $J=9.6$ Hz, 1H), 5.11 (t, $J=9.6$ Hz, 1H), 5.05 (dd, $J=8.0$, 9.6 Hz, 1H), 4.62 (d, $J=8.0$ Hz, 1H), 4.50 (ddd, $J=1.5$, 5.5, 13.1 Hz, 1H), 4.32–4.25 (m, 2H), 4.16 (dd, $J=2.0$, 12.1 Hz, 1H), 3.71 (ddd, $J=2.0$, 5.0, 10.1 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7, 170.3, 169.4, 169.3, 136.3, 133.1, 128.6, 127.9, 126.5, 124.5, 99.5, 72.9, 71.8, 71.3, 69.8, 68.4, 62.0, 20.7, 20.59, 20.57. Anal. Found: C, 59.40; H, 6.05%. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08%.

5.3.2. 4-Hydroxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4b). A mixture of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (0.78 g, 2.0 mmol), 4-hydroxyphenylboric acid (0.82 g, 6.0 mmol), copper(II) acetate (1.81 g, 10 mmol), lithium acetate (0.66 g, 10 mmol) and palladium(II) acetate (0.044 g, 0.20 mmol) in DMF (8.0 mL) was stirred for 0.5 h at 80 °C. Allowed to cool to room temperature, the reaction mixture was diluted with EtOAc and washed with 1 M HCl and brine. The organic layer was evaporated to dryness and the residue was purified by flash column chromatography to afford **4b** (0.60 g, 62%) as a white solid. The white solid was recrystallized from ether/*n*-hexane to give **4b** (0.50 g, 52%), a pure colorless needle to be analyzed by microanalyses. Mp: 146.0–147.0 °C; $[\alpha]_D^{29}$ −31.5 (*c* 0.47, MeOH); IR (KBr) 3370, 1754, 1713, 1609, 1514, 1442, 1371, 1227, 1170, 1043, 972, 913, 843, 625 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.25 (d, $J=8.6$ Hz, 2H), 6.79 (d, $J=8.6$ Hz, 2H), 6.50 (d, $J=16.1$ Hz, 1H), 6.05 (ddd, $J=5.5$, 6.6, 15.6 Hz, 1H), 5.45 (s, 1H), 5.22 (t, $J=9.6$ Hz, 1H), 5.09 (t, $J=9.6$ Hz, 1H), 5.05 (dd, $J=8.1$, 9.6 Hz, 1H), 4.62 (d, $J=8.1$ Hz, 1H), 4.46 (dd, $J=5.5$, 12.6 Hz, 1H), 4.29–4.22 (m, 2H), 4.17 (dd, $J=2.0$, 12.1 Hz, 1H), 3.70 (ddd, $J=2.5$, 4.5, 9.6 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.9, 170.4, 169.5, 169.4, 155.7, 133.0, 129.1, 127.9, 122.0, 115.5, 99.4, 72.9, 71.8, 71.4, 70.1, 68.4, 62.0, 20.72, 20.71, 20.60, 20.57. Anal. Found: C, 57.29; H, 5.97%. Calcd for $C_{23}H_{28}O_{11}$: C, 57.50; H, 5.87%.

5.3.3. 4-Methoxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4c). Obtained in 72% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4c** in 35% yield, a pure white solid to be analyzed by microanalyses. Mp: 81.5–83.0 °C; $[\alpha]_D^{27}$ −28.4 (*c* 0.18, MeOH); IR (KBr) 1744, 1514, 1370, 1228, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.31 (d, $J=8.6$ Hz, 2H), 6.86 (d, $J=8.6$ Hz, 2H), 6.53 (d, $J=15.6$ Hz, 1H), 6.07 (ddd, $J=5.5$, 6.6, 15.6 Hz, 1H), 5.21 (t, $J=9.6$ Hz, 1H), 5.11 (t, $J=9.6$ Hz, 1H), 5.04 (dd, $J=7.6$, 9.6 Hz, 1H), 4.62 (d, $J=7.6$ Hz, 1H), 4.47 (ddd, $J=1.5$, 5.5, 13.1 Hz, 1H), 4.30 (ddd, $J=1.0$, 6.6, 13.1 Hz, 1H), 4.26 (dd, $J=5.0$, 12.1 Hz, 1H), 4.25 (dd, $J=2.5$, 12.1 Hz, 1H), 3.81 (s, 3H), 3.70 (ddd, $J=2.5$, 5.0, 9.6 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7, 170.3, 169.4, 169.3, 159.5, 133.0, 129.1, 127.7, 122.1, 114.0, 99.4, 72.9, 71.8, 71.3, 70.1, 68.4, 62.0, 55.3, 20.7, 20.59, 20.57. Anal. Found: C, 57.85; H, 5.99%. Calcd for $C_{24}H_{30}O_{11}$: C, 58.29; H, 6.12%.

5.3.4. 4-Hydroxy-3-methoxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4d). A mixture of allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **3** (0.39 g, 1.0 mmol), 4-hydroxy-3-(methoxy)phenylboric acid **7** (0.51 g, 3.0 mmol), copper(II) acetate (0.91 g, 5.0 mmol), lithium acetate (0.33 g, 5.0 mmol) and palladium(II) acetate (0.022 g, 0.10 mmol) in DMF (4 mL) was stirred for 0.5 h at

80 °C. Allowed to cool to room temperature, the reaction mixture was diluted with EtOAc and washed with 1 M HCl and brine. The organic layer was evaporated to dryness and the residue was purified by flash chromatography to afford **4d** (0.27 g, 52%) as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4d** (0.22 g, 42%), a pure white powder. Mp: 185.0–187.0 °C; $[\alpha]_D^{29}$ −32.6 (*c* 0.24, $CDCl_3$); IR (KBr) 3399, 1753, 1517, 1370, 1228, 1129, 1040, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 6.91–6.85 (m, 3H), 6.51 (d, *J*=15.6 Hz, 1H), 6.06 (ddd, *J*=5.5, 6.5, 15.6 Hz, 1H), 5.63 (s, 1H), 5.22 (t, *J*=9.6 Hz, 1H), 5.11 (t, *J*=9.6 Hz, 1H), 5.04 (dd, *J*=8.0, 9.6 Hz, 1H), 4.62 (d, *J*=8.0 Hz, 1H), 4.47 (ddd, *J*=1.5, 5.6, 12.6 Hz, 1H), 4.30–4.23 (m, 2H), 4.17 (dd, *J*=2.0, 12.1 Hz, 1H), 3.92 (s, 3H), 3.70 (ddd, *J*=2.0, 4.5, 9.6 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.7, 170.3, 169.40, 169.35, 146.6, 145.8, 133.3, 128.9, 122.1, 120.4, 114.4, 108.3, 99.5, 72.9, 71.8, 71.4, 70.1, 68.4, 62.0, 55.9, 20.72, 20.60, 20.59; HR-MS (FAB-MS) *m/z*: 511.1840 $(M+1)^+$; Calcd for $C_{24}H_{30}O_{12}$ *m/z*: 511.1815 $(M+1)^+$.

5.3.5. 3,4,5-Trimethoxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4e). Obtained in 67% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4e** in 46% yield, pure colorless needles to be analyzed by microanalyses. Mp: 131.0–132.0 °C; $[\alpha]_D^{29}$ −30.3 (*c* 0.29, MeOH); IR (KBr) 1752, 1583, 1506, 1422, 1371, 1335, 1228, 1128, 1043, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 6.61 (s, 2H), 6.52 (d, *J*=16.1 Hz, 1H), 6.14 (ddd, *J*=5.5, 6.5, 16.1 Hz, 1H), 5.22 (t, *J*=9.6 Hz, 1H), 5.12 (t, *J*=9.6 Hz, 1H), 5.05 (dd, *J*=8.1, 9.6 Hz, 1H), 4.63 (d, *J*=8.1 Hz, 1H), 4.49 (ddd, *J*=1.5, 5.5, 12.6 Hz, 1H), 4.30–4.23 (m, 2H), 4.17 (dd, *J*=2.5, 12.6 Hz, 1H), 3.88 (s, 6H), 3.85 (s, 3H), 3.71 (ddd, *J*=2.5, 4.5, 9.6 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.6, 170.3, 169.4, 169.3, 153.3, 138.1, 133.0, 132.1, 124.0, 103.7, 99.6, 72.9, 71.8, 71.3, 69.8, 68.4, 61.9, 60.9, 56.2, 20.70, 20.59, 20.57. Anal. Found: C, 56.01; H, 6.10%. Calcd for $C_{26}H_{35}O_{13}$: C, 56.31; H, 6.18%.

5.3.6. 3-Methoxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4f). Obtained in 86% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4f** in 54% yield, a pure white powder to be analyzed by microanalyses. Mp: 102.0–103.5 °C; $[\alpha]_D^{27}$ −31.1 (*c* 0.50, MeOH); IR (KBr) 1743, 1600, 1439, 1369, 1325, 1227, 1169, 1040, 986, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.22 (dd, *J*=7.6, 8.1 Hz, 1H), 6.96 (d, *J*=7.6 Hz, 1H), 6.92 (d, *J*=2.5 Hz, 1H), 6.81 (dd, *J*=2.5, 8.1 Hz, 1H), 6.56 (d, *J*=15.6 Hz, 1H), 6.21 (td, *J*=6.5, 15.6 Hz, 1H), 5.21 (t, *J*=9.6 Hz, 1H), 5.11 (t, *J*=9.6 Hz, 1H), 5.05 (dd, *J*=7.6, 9.6 Hz, 1H), 4.62 (d, *J*=7.6 Hz, 1H), 4.49 (ddd, *J*=1.5, 5.6, 13.1 Hz, 1H), 4.31–4.24 (m, 2H), 4.16 (dd, *J*=2.5, 12.1 Hz, 1H), 3.82 (s, 3H), 3.71 (ddd, *J*=2.5, 5.0, 9.6 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.7, 170.2, 169.4, 169.3, 159.8, 137.8, 132.9, 129.6, 124.8, 119.1, 113.5, 111.9, 99.6, 72.9, 71.8, 71.3, 69.8, 68.4, 61.9, 55.2, 20.69, 20.58, 20.56. Anal. Found: C, 58.23; H, 6.09%. Calcd for $C_{24}H_{30}O_{11}$: C, 58.29; H, 6.12%.

5.3.7. 2-Methoxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4g). Obtained in 74% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4g** in 42% yield, pure colorless needles to be analyzed by microanalyses. Mp: 88.9–89.5 °C; $[\alpha]_D^{27}$ −25.1 (*c* 0.33, MeOH); IR (KBr) 1745, 1372, 1224, 1046, 984 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.42 (dd, *J*=1.5, 7.6 Hz, 1H), 7.25–7.22 (m, 1H), 6.95–6.86 (m, 3H), 6.21 (ddd, *J*=5.7, 7.0, 16.1 Hz, 1H), 5.21 (t, *J*=9.6 Hz, 1H), 5.11 (t, *J*=9.6 Hz, 1H), 5.05 (dd, *J*=8.1, 9.6 Hz, 1H), 4.63 (d, *J*=8.1 Hz, 1H), 4.49 (ddd, *J*=1.5, 5.6, 13.1 Hz, 1H), 4.30 (ddd, *J*=1.0, 6.5, 13.1 Hz, 1H), 4.27 (dd, *J*=5.0, 12.6 Hz, 1H), 4.16 (dd, *J*=2.5, 12.1 Hz, 1H), 3.85 (s, 3H), 3.70 (dd, *J*=2.5, 5.0, 9.6 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.7, 170.3, 169.39, 169.38, 156.7, 129.0, 128.4, 127.0, 125.4, 124.9, 120.7, 110.8, 99.2, 72.9, 71.8, 71.3, 70.2, 68.4, 62.0, 55.4, 20.69, 20.65, 20.60, 20.57. Anal. Found: C, 58.25; H, 6.08%. Calcd for $C_{24}H_{30}O_{11}$: C, 58.29; H, 6.12%.

5.3.8. 3,4-Dimethoxycinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4h). Obtained in 42% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4h** in 32% yield, pure colorless needles to be analyzed by microanalyses. Mp: 78.0–79.5 °C; $[\alpha]_D^{27}$ −30.3 (*c* 0.29, MeOH); IR (KBr) 1747, 1516, 1444, 1369, 1225, 1166, 1038, 981, 609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 6.95–6.90 (m, 2H), 6.82 (d, *J*=8.0 Hz, 1H), 6.53 (d, *J*=16.1 Hz, 1H), 6.09 (td, *J*=6.4, 16.1 Hz, 1H), 5.22 (t, *J*=9.6 Hz, 1H), 5.09 (t, *J*=9.6 Hz, 1H), 5.05 (dd, *J*=8.1, 9.6 Hz, 1H), 4.63 (d, *J*=8.1 Hz, 1H), 4.47 (dd, *J*=5.5, 12.6 Hz, 1H), 4.29–4.23 (m, 2H), 4.17 (dd, *J*=2.0, 12.6 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.71 (ddd, *J*=2.5, 4.5, 9.6 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.6, 170.3, 169.4, 169.3, 149.12, 149.05, 133.1, 129.4, 122.4, 119.8, 111.1, 108.9, 99.5, 72.9, 71.8, 71.4, 70.0, 61.9, 55.9, 55.8, 20.71, 20.59, 20.57. Anal. Found: C, 57.05; H, 6.09%. Calcd for $C_{25}H_{32}O_{12}$: C, 57.25; H, 6.15%.

5.3.9. 4-Chlorocinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4i). Obtained in 74% yield as a white solid. The white solid was recrystallized from ether/*n*-hexane to give **4i** in 51% yield, a pure white powder to be analyzed by microanalyses. Mp: 92.3–94.0 °C; $[\alpha]_D^{29}$ −31.4 (*c* 0.44, $CHCl_3$); IR (KBr) 1748, 1369, 1229, 1169, 1041, 987, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.29 (s, 4H), 6.54 (d, *J*=16.1 Hz, 1H), 6.19 (ddd, *J*=5.5, 6.5, 16.1 Hz, 1H), 5.22 (t, *J*=9.6 Hz, 1H), 5.11 (t, *J*=9.6 Hz, 1H), 5.05 (dd, *J*=8.1, 9.6 Hz, 1H), 4.61 (d, *J*=8.1 Hz, 1H), 4.49 (ddd, *J*=1.5, 5.5, 13.1 Hz, 1H), 4.29–4.23 (m, 2H), 4.16 (dd, *J*=2.0, 12.6 Hz, 1H), 3.71 (ddd, *J*=2.0, 4.6, 9.6 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.6, 170.3, 169.4, 169.3, 134.9, 133.1, 131.6, 128.8, 127.7, 125.2, 99.7, 72.8, 71.8, 71.3, 69.7, 68.4, 61.9, 20.70, 20.59, 20.57. Anal. Found: C, 55.08; H, 5.43%. Calcd for $C_{23}H_{27}ClO_{10}$: C, 55.37; H, 5.25%, Cl, 7.11%.

5.3.10. 4-Cyanocinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4j). Obtained in 75% yield as a white solid. The white solid was recrystallized from ether/*n*-hexane to get **4j** in 51% yield, a pure white solid. Mp:

135.5–137.0 °C; $[\alpha]_D^{30}$ −29.3 (*c* 0.29, $CHCl_3$); IR (KBr) 2226, 1745, 1604, 1381, 1227, 1038, 977, 906, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.61 (d, *J*=8.6 Hz, 2H), 7.45 (d, *J*=8.6 Hz, 2H), 6.61 (d, *J*=16.1 Hz, 1H), 6.35 (ddd, *J*=5.0, 6.0, 16.1 Hz, 1H), 5.23 (t, *J*=9.6 Hz, 1H), 5.12 (t, *J*=9.6 Hz, 1H), 5.06 (dd, *J*=8.3, 9.6 Hz, 1H), 4.61 (d, *J*=8.3 Hz, 1H), 4.54 (ddd, *J*=1.5, 5.0, 13.6 Hz, 1H), 4.30 (ddd, *J*=1.5, 6.0, 13.6 Hz, 1H), 4.27 (dd, *J*=4.6, 12.1 Hz, 1H), 4.17 (dd, *J*=2.5, 12.1 Hz, 1H), 3.72 (ddd, *J*=2.5, 4.6, 9.6 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.6, 170.2, 169.4, 169.3, 140.9, 132.4, 130.4, 129.7, 126.9, 118.8, 111.1, 100.0, 72.7, 71.9, 71.3, 69.2, 68.3, 61.8, 20.7, 20.56, 20.54; HR-MS (FAB-MS) *m/z*: 490.1718 $(M+1)^+$; Calcd for $C_{24}H_{27}NO_{10}$ *m/z*: 490.1713 $(M+1)^+$.

5.3.11. 4-(Trifluoromethyl)cinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4k). Obtained in 45% yield as a colorless prism. Mp: 98.0–98.6 °C; $[\alpha]_D^{30}$ −26.7 (*c* 0.29, $CHCl_3$); IR (KBr) 1753, 1374, 1330, 1222, 1165, 1120, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.58 (d, *J*=8.1 Hz, 2H), 7.46 (d, *J*=8.1 Hz, 2H), 6.63 (d, *J*=16.1 Hz, 1H), 6.32 (td, *J*=5.6, 15.6 Hz, 1H), 5.23 (t, *J*=9.6 Hz, 1H), 5.12 (t, *J*=9.6 Hz, 1H), 5.06 (dd, *J*=7.6, 9.6 Hz, 1H), 4.62 (d, *J*=7.6 Hz, 1H), 4.53 (ddd, *J*=1.5, 5.6, 13.6 Hz, 1H), 4.33–4.25 (m, 2H), 4.17 (dd, *J*=2.5, 12.1 Hz, 1H), 3.72 (ddd, *J*=2.5, 4.5, 9.6 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.6, 170.2, 169.34, 169.26, 139.9, 131.0, 129.6 (q, J_{C-F}=32 Hz), 127.4, 126.6, 125.5 (q, J_{C-F}=3.7 Hz), 124.1 (q, J_{C-F}=270 Hz), 99.9, 72.8, 71.9, 71.3, 69.4, 68.3, 61.9, 20.7, 20.54, 20.52. Anal. Found: C, 54.04; H, 5.26%. Calcd for $C_{24}H_{27}F_3O_{10}$: C, 54.14; H, 5.11%.

5.3.12. 3-Nitrocinnamyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4l). Obtained in 63% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4l** in 55% yield, a pure white powder to be analyzed by microanalyses. Mp: 150.7–151.3 °C; $[\alpha]_D^{30}$ −28.6 (*c* 0.39, $CHCl_3$); IR (KBr) 1755, 1530, 1349, 1216, 1163, 1038, 815, 736, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.23–8.22 (m, 1H), 8.12–8.09 (m, 1H), 7.67 (d, *J*=8.1 Hz, 1H), 7.50 (t, *J*=8.1 Hz, 1H), 6.66 (d, *J*=16.1 Hz, 1H), 6.37 (td, *J*=5.6, 15.6 Hz, 1H), 5.23 (t, *J*=9.6 Hz, 1H), 5.12 (t, *J*=9.6 Hz, 1H), 5.07 (dd, *J*=7.6, 9.6 Hz, 1H), 4.63 (d, *J*=7.6 Hz, 1H), 4.55 (ddd, *J*=1.5, 5.6, 13.6 Hz, 1H), 4.31 (ddd, *J*=1.5, 6.0, 13.6 Hz, 1H), 4.28 (dd, *J*=4.5, 12.1 Hz, 1H), 4.17 (dd, *J*=2.5, 12.1 Hz, 1H), 3.72 (ddd, *J*=2.5, 4.5, 9.6 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.6, 170.2, 169.33, 169.25, 148.6, 138.2, 132.3, 129.9, 129.5, 128.0, 122.3, 121.0, 99.9, 72.7, 71.9, 71.2, 69.2, 68.3, 61.8, 20.7, 20.54, 20.52. Anal. Found: C, 54.24; H, 5.32; N, 2.75%. Calcd for $C_{24}H_{27}F_3O_{10}$: C, 54.14; H, 5.11; N, 2.79%.

5.3.13. Naphthalene-2-ylalloxy 2,3,4,6-tetra-*O*-acethyl-β-D-glucopyranoside (4m). Obtained in 53% yield as a white solid. The white solid was recrystallized from AcOEt/*n*-hexane to give **4m** in 43% yield, a pure white solid to be analyzed by microanalyses. Mp: 147.5–149.2 °C; $[\alpha]_D^{31}$ −29.4 (*c* 0.38, $CHCl_3$); IR (KBr) 1748, 1369, 1225, 1167, 1128, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 00 MHz) *δ*: 7.80–7.78 (m, 3H), 7.73 (1H, s), 7.58 (dd, *J*=1.5, 8.6 Hz, 1H), 7.49–7.42 (m, 2H), 6.76 (d, *J*=16.1 Hz, 1H), 6.34 (ddd, *J*=5.6, 6.6, 15.6 Hz, 1H), 5.23 (t, *J*=9.6 Hz, 1H), 5.12 (t, *J*=9.6 Hz, 1H), 5.07 (dd, *J*=8.1, 9.6 Hz, 1H), 4.66 (d, *J*=8.1 Hz, 1H), 4.55 (ddd, *J*=1.5, 5.6, 13.1 Hz, 1H), 4.34 (ddd, *J*=1.5, 6.5, 13.1 Hz, 1H), 4.28 (dd, *J*=4.5, 12.1 Hz, 1H), 4.17 (dd, *J*=2.5, 12.1 Hz, 1H), 3.72 (ddd, *J*=2.5, 4.5, 9.6 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 170.7, 170.3, 169.38, 169.35, 133.8, 133.5, 133.14, 133.11, 128.3, 128.0, 127.7, 126.6, 126.3, 126.0, 124.8, 123.4, 99.7, 72.9, 71.8, 71.4, 70.0, 68.4, 61.9, 20.7, 20.60, 20.57; HR-MS (FAB-MS) *m/z*: 515.1920 $(M+1)^+$; Calcd for $C_{27}H_{30}O_{10}$ *m/z*: 515.1918 $(M+1)^+$.

5.3.14. Cinnamyl β-D-glucopyranoside (Rosin) (1a). Compound **4a** (0.10 g, 0.22 mmol) was dissolved in 2 mL of methanol and 25% NaOMe in MeOH (0.14 g, 0.66 mmol) was added. The solution was stirred for 30 min. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness to give **1a** (0.061 g, 95%) as a colorless amorphous. $[\alpha]_D^{27}$ −52.4 (*c* 0.49, MeOH) {lit.[3a,b] $[\alpha]_D^{20}$ −44.8 (*c* 2.8, $CHCl_3$–MeOH [1/1])}; IR (KBr) 3398, 1652, 1564, 1075 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) *δ*: 7.43–7.40 (m, 2H), 7.32–7.27 (m, 2H), 7.23–7.19 (m, 1H), 6.68 (d, *J*=15.6 Hz, 1H), 6.37 (dt, *J*=15.6, 6.0 Hz, 1H), 4.53 (ddd, *J*=1.5, 6.0, 12.6 Hz, 1H), 4.36 (d, *J*=7.6 Hz, 1H), 4.32 (ddd, *J*=1.5, 6.5, 12.6 Hz, 1H), 3.88 (dd, *J*=5.0, 11.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.38–3.20 (m, 4H); ^1H NMR (acetone-d_6, 400 MHz) *δ*: 7.34–7.31 (m, 2H), 7.22–7.18 (m, 2H), 7.13–7.09 (m, 1H), 6.57 (d, *J*=15.9 Hz, 1H), 6.24 (dt, *J*=6.1, 15.9 Hz, 1H), 4.36 (ddd, *J*=1.5, 5.6, 13.1 Hz, 1H), 4.26 (d, *J*=7.8 Hz, 1H), 4.13 (ddd, *J*=1.5, 6.3, 13.1 Hz, 1H), 3.72 (dd, *J*=2.5, 11.6 Hz, 1H), 3.54 (dd, *J*=5.6, 11.6 Hz, 1H), 3.33–3.10 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) *δ*: 138.0, 133.5, 129.3, 128.4, 127.3, 126.5, 103.1, 77.9, 77.8, 74.9, 71.5, 70.6, 62.6; HR-MS (FAB-MS) *m/z*: 297.1333; Calcd for $C_{15}H_{20}O_6$ *m/z*: 297.1338 $(M+1)^+$.

5.3.15. 4-Hydroxycinnamyl β-D-glucopyranoside (Sachaliside 1, Triandirin) (1b). Compound **4b** (0.10 g, 0.21 mmol) was dissolved in 2 mL of methanol and 25% NaOMe in MeOH (0.14 g, 0.66 mmol) was added. The solution was stirred for 30 min. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness to give **1b** (0.062 g, 95%) as a colorless amorphous. $[\alpha]_D^{22}$ −62.2 (*c* 0.60, MeOH) {lit.[4e] $[\alpha]_D^{20}$ −62.3 (H_2O)}; IR (KBr) 3299, 2929, 1609, 1515, 1443, 1375, 1249, 1170, 1083, 841 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) *δ*: 7.40 (d, *J*=8.6 Hz, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 6.73 (d, *J*=15.6 Hz, 1H), 6.36 (dt, *J*=6.0, 15.6 Hz, 1H), 4.99 (d, *J*=7.6 Hz, 2H), 4.75 (dd, *J*=6.0, 12.6 Hz, 1H), 4.58 (dd, *J*=1.5, 11.6 Hz, 1H), 4.47 (dd, *J*=6.0, 12.6 Hz, 1H), 4.41 (dd, *J*=5.0, 11.6 Hz, 1H), 4.32–4.24 (m, 2H), 4.14–4.08 (m, 1H), 4.00–3.94 (m, 1H); ^{13}C NMR (pyridine-d_5, 100 MHz) *δ*: 158.9, 132.6, 128.6, 128.4, 116.5, 103.9, 78.59, 78.55, 75.3, 71.7, 70.1, 62.8; ^{13}C NMR (DMSO-d_6, 100 MHz) *δ*: 157.1, 131.7, 127.6, 127.5, 122.6,

115.4, 102.0, 76.9, 76.8, 73.5, 70.1, 68.8, 61.1; HR-MS (FAB-MS) *m/z*: 313.1288 $(M+1)^+$; Calcd for $C_{15}H_{20}O_7$ *m/z*: 313.1287 $(M+1)^+$.

5.3.16. 4-Methoxycinnamyl β-D-glucopyranoside (Vimalin) (1c). A mixture of **4c** (0.055 g, 0.11 mmol) and K_2CO_3 (0.15 g, 1.1 mmol) in MeOH (1.1 mL) was stirred for 30 min at room temperature. The reaction mixture was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH as an eluent) to afford **1c** (0.025 g, 69%) as a white solid. Mp: 111.0–112.5 °C; $[\alpha]_D^{22}$ −54.7 (*c* 1.40, MeOH){lit.[4b,c] $[\alpha]_D^{20}$ −60.6 (MeOH)}; IR (KBr) 3350, 2938, 1605, 1514, 1368, 1245, 1169, 1083, 1022, 968, 781 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ: 7.38 (d, *J*=8.6 Hz, 1H), 6.95 (d, *J*=8.6 Hz, 1H), 6.74 (d, *J*=16.1 Hz, 1H), 6.38 (dt, *J*=16.1, 6.0 Hz, 1H), 4.99 (d, *J*=8.0 Hz, 1H), 4.76 (ddd, *J*=1.5, 5.6, 12.6 Hz, 1H), 4.59 (dd, *J*=2.0, 11.6 Hz, 1H), 4.50–4.41 (m, 2H), 4.32–4.25 (m, 2H), 4.15–4.11 (m, 1H), 4.02–3.95 (m, 1H), 3.66 (s, 3H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ: 159.9, 132.1, 130.2, 128.2, 124.6, 114.6, 104.1, 78.8, 78.7, 75.4, 71.8, 70.1, 62.9, 55.3; HR-MS (FAB-MS) *m/z*: 327.1417 $(M+1)^+$; Calcd for $C_{16}H_{22}O_7$ *m/z*: 327.1444 $(M+1)^+$.

5.3.17. 4-Hydroxy-3-methoxycinnamyl β-D-glucopyranoside (Citrusin D, Coniferin) (1d). Compound **4d** (0.051 g, 0.10 mmol) was dissolved in 1 mL of methanol and 25% NaOMe in MeOH (0.020 g, 0.10 mmol) was added. The solution was stirred for 1 h. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness under 5 °C to give **1e** (0.034 g, 99%) as a pale yellow amorphous. $[\alpha]_D^{23}$ −36.0 (*c* 0.54, MeOH); IR (KBr) 3382, 2862, 1515, 1278, 1032 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.01 (d, *J*=2.0 Hz, 1H), 6.85 (dd, *J*=2.0, 8.1 Hz, 1H), 6.73 (d, *J*=8.1 Hz, 1H), 6.57 (d, *J*=16.1 Hz, 1H), 6.19 (td, *J*=6.0, 16.1 Hz, 1H), 4.49 (ddd, *J*=1.5, 5.6, 12.6 Hz, 1H), 4.36 (d, *J*=8.0 Hz, 1H), 4.29 (ddd, *J*=2.0, 6.5, 12.6 Hz, 1H), 3.90–3.82 (m, 1H), 3.86 (s, 3H), 3.68 (dd, *J*=5.0, 12.1 Hz, 1H), 3.38–3.20 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 149.1, 147.7, 134.3, 130.4, 123.7, 121.2, 116.2, 110.6, 103.2, 78.1, 78.0, 75.1, 71.7, 71.0, 62.8, 56.4; HR-MS (FAB-MS) *m/z*: 343.1365 $(M+1)^+$; Calcd for $C_{18}H_{26}O_9$ *m/z*: 343.1393 $(M+1)^+$.

5.3.18. 3,4,5-Trimethoxycinnamyl β-D-glucopyranoside (Icariside H_1) (1e). Compound **4e** (0.055 g, 0.10 mmol) was dissolved in 1 mL of methanol and 25% NaOMe in MeOH (0.020 g, 0.10 mmol) was added. The solution was stirred for 1 h. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness to give **1e** (0.038 g, 99%) as a colorless amorphous. $[\alpha]_D^{26}$ −42.2 (*c* 0.24, MeOH){lit.[6a] $[\alpha]_D^{23}$ −47.6 (*c* 0.62, MeOH)}; IR (KBr) 3398, 1583, 1507, 1460, 1419, 1336, 1243, 1125 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 6.63 (s, 2H), 6.52 (d, *J*=16.1 Hz, 1H), 6.21 (dt, *J*=6.0, 16.1 Hz, 1H), 4.41 (ddd, *J*=1.5, 5.6, 12.6 Hz, 1H), 4.27 (d, *J*=7.5 Hz, 1H), 4.22 (ddd, *J*=2.0, 6.5, 12.6 Hz, 1H), 3.78 (dd, *J*=2.0, 12.1 Hz, 1H), 3.74 (s, 6H), 3.62 (s, 3H), 3.68 (dd, *J*=5.0, 12.1 Hz, 1H), 3.28–3.12 (m, 4H); ^1H NMR (pyridine-d_5, 400 MHz) δ: 6.76 (s, 2H), 6.75 (d, *J*=15.6 Hz, 1H), 6.46 (dt, *J*=6.0, 15.6 Hz, 1H), 4.99 (d, *J*=8.0 Hz, 1H), 4.78 (ddd, *J*=1.5, 5.6, 12.6 Hz, 1H), 4.57 (dd, *J*=2.5, 12.1 Hz, 1H), 4.51 (dd, *J*=6.0, 12.6 Hz, 1H), 4.39 (dd, *J*=5.5, 11.6 Hz, 1H), 4.29–4.23 (m, 2H), 4.14–4.10 (m, 1H), 4.00–3.95 (m, 1H), 3.87 (s, 3H), 3.74 (s, 6H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 154.4, 138.7, 134.2, 133.4, 126.1, 104.7, 103.2, 77.9, 77.8, 74.9, 71.5, 70.5, 62.6, 60.9, 56.4; ^{13}C NMR (pyridine-d_5, 100 MHz) δ: 154.0, 138.7, 133.2, 132.2, 126.2, 104.4, 104.0, 78.6, 75.3, 71.7, 69.7, 62.8, 60.6, 56.0; HR-MS (FAB-MS) *m/z*: 387.1620 $(M+1)^+$; Calcd for $C_{18}H_{26}O_9$ *m/z*: 387.1655 $(M+1)^+$.

5.3.19. 3-Methoxycinnamyl β-D-glucopyranoside (1f). A mixture of **4f** (0.23 g, 0.46 mmol) and K_2CO_3 (0.64 g, 4.6 mmol) in MeOH (4.6 mL) was stirred for 30 min at room temperature. The reaction mixture was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH as an eluent) to afford **1f** (0.12 g, 79%) as a colorless solid. Mp: 85.0–86.0 °C; $[\alpha]_D^{22}$ −40.9 (*c* 0.77, MeOH); IR (KBr) 3370, 2925, 1603, 1581, 1489, 1432, 1366, 1255, 1159, 1078, 1046, 765, 685, 632 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.21 (t, *J*=8.1 Hz, 1H), 6.99 (d, *J*=8.1 Hz, 1H), 6.96 (d, *J*=2.0 Hz, 1H), 6.80 (dd, *J*=2.0, 8.1 Hz, 1H), 6.65 (d, *J*=16.1 Hz, 1H), 6.36 (dt, *J*=16.1, 6.0 Hz, 1H), 4.52 (ddd, *J*=1.5, 6.0, 12.6 Hz, 1H), 4.37 (d, *J*=7.6 Hz, 1H), 4.32 (ddd, *J*=1.0, 6.5, 12.6 Hz, 1H), 3.89 (dd, *J*=1.5, 12.1 Hz, 1H), 3.78 (s, 3H), 3.69 (dd, *J*=5.6, 12.1 Hz, 1H), 3.38–3.20 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 161.3, 139.6, 133.6, 130.5, 127.0, 120.1, 114.3, 112.8, 103.3, 78.1, 77.9, 75.1, 71.6, 70.7, 62.8, 55.6; HR-MS (FAB-MS) *m/z*: 349.1270 $(M+Na)^+$; Calcd for $C_{16}H_{22}O_7$ *m/z*: 349.1263 $(M+Na)^+$.

5.3.20. 2-Methoxycinnamyl β-D-glucopyranoside (1g). Compound **4g** (0.20 g, 0.40 mmol) was dissolved in 4 mL of methanol and 25% NaOMe in MeOH (0.26 g, 1.2 mmol) was added. The solution was stirred for 30 min. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness to give **1g** (0.11 g, 82%) as a colorless amorphous. $[\alpha]_D^{27}$ −36.7 (*c* 1.03, MeOH); IR (KBr) 3386, 2926, 1575, 1490, 1462, 1245, 1024, 754 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.45 (dd, *J*=1.5, 7.6 Hz, 1H), 7.21 (ddd, *J*=1.5, 7.6, 7.6 Hz, 1H), 6.97–6.87 (m, 3H), 6.35 (dt, *J*=16.1, 6.0 Hz, 1H), 4.52 (ddd, *J*=1.5, 6.0, 12.6 Hz, 1H), 4.37 (d, *J*=7.6 Hz, 1H), 4.31 (ddd, *J*=1.5, 6.5, 12.6 Hz, 1H), 3.87 (dd, *J*=2.0, 12.1 Hz, 1H), 3.83 (s, 3H), 3.68 (dd, *J*=5.0, 12.1 Hz, 1H), 3.38–3.20 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 158.0, 129.8, 128.8, 127.7, 126.8, 126.7, 121.5, 111.8, 103.1, 77.9, 77.8, 74.9, 71.4, 70.2, 62.6, 55.4; HR-MS (FAB-MS) *m/z*: 327.1447 $(M+1)^+$; Calcd for $C_{16}H_{22}O_7$ *m/z*: 327.1444 $(M+1)^+$.

5.3.21. 3,4-Dimethoxycinnamyl β-D-glucopyranoside (1h). A mixture of **4h** (0.059 g, 0.11 mmol) and K_2CO_3 (0.15 g, 1.1 mmol) in MeOH (1.1 mL) was stirred for 30 min at room temperature. The reaction mixture was

evaporated to dryness and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH as an eluent) to afford **1h** (0.024 g, 60%) as a colorless amorphous. $[\alpha]_D^{27}$ −30.2 (*c* 1.08, MeOH); IR (KBr) 3391, 1515, 1461, 1264, 1024, 621 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 6.95 (d, J=1.5 Hz, 1H), 6.85 (dd, J=1.5, 8.6 Hz, 1H), 6.79 (d, J=8.6 Hz, 1H), 6.50 (d, J=16.1 Hz, 1H), 6.15 (dt, J=16.1, 6.0 Hz, 1H), 4.40 (ddd, J=1.5, 5.6, 12.6 Hz, 1H), 4.27 (d, J=7.5 Hz, 1H), 4.21 (dd, J=7.0, 12.6 Hz, 1H), 3.78 (dd, J=2.0, 12.1 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.58 (dd, J=5.0, 12.1 Hz, 1H), 3.28–3.10 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 150.3, 150.2, 133.6, 131.4, 124.5, 120.8, 112.6, 110.5, 103.0, 77.9, 77.8, 74.9, 71.5, 70.7, 62.6, 56.3, 56.2; HR-MS (FAB-MS) *m/z*: 357.1519 $(M+1)^+$; Calcd for $C_{17}H_{24}O_8$ *m/z*: 357.1549 $(M+1)^+$.

5.3.22. 4-Chlorocinnamyl β-D-glucopyranoside (1i). Compound **4i** (0.20 g, 0.40 mmol) was dissolved in 4 mL of methanol and 25% NaOMe in MeOH (0.26 g, 1.2 mmol) was added. The solution was stirred for 30 min. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness to give **1i** (0.13 g, 85%) as a white solid. Mp: 160.2–161.5 °C; $[\alpha]_D^{27}$ −48.5 (*c* 0.55, MeOH); IR (KBr) 3314, 2870, 2371, 1746, 1491, 1363, 1229, 1170, 1091, 1041, 976 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.40 (d, J=8.6 Hz, 2H), 7.30 (d, J=8.6 Hz, 2H), 6.67 (d, J=15.6 Hz, 1H), 6.38 (dt, J=15.6, 6.0 Hz, 1H), 4.52 (ddd, J=1.5, 6.0, 12.6 Hz, 1H), 4.35 (d, J=7.6 Hz, 1H), 4.32 (ddd, J=1.5, 6.5, 12.6 Hz, 1H), 3.90–3.86 (m, 1H), 3.70–3.65 (m, 1H), 3.38–3.20 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 136.8, 134.0, 131.9, 129.4, 128.7, 127.6, 103.2, 77.9, 77.8, 74.9, 71.5, 70.3, 62.6; HR-MS (FAB-MS) *m/z*: 331.0944 $(M+1)^+$; Calcd for $C_{15}H_{19}ClO_6$ *m/z*: 331.0948 $(M+1)^+$.

5.3.23. 4-Cyanocinnamyl β-D-glucopyranoside (1j). Compound **4j** (0.50 g, 0.10 mmol) was dissolved in 2 mL of methanol and 25% NaOMe in MeOH (0.024 g, 0.11 mmol) was added. The solution was stirred for 30 min. A small amount of ion exchange resin (Amberlyst 15, H^+-form) was added to remove sodium ions. The reaction mixture was diluted with methanol and resin was filtered off and washed thoroughly. The filtrate was evaporated to dryness to give **1j** (0.033 g, 100%) as a white solid. Mp: 131.0–133.0 °C; $[\alpha]_D^{27}$ −35.1 (*c* 0.70, MeOH); IR (KBr) 3398, 2927, 2225, 1723, 1604, 1367, 1285, 1170, 1076, 850, 550 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.66 (d, J=7.6 Hz, 2H), 7.58 (d, J=7.6 Hz, 2H), 6.77 (d, J=16.1 Hz, 1H), 6.56 (dt, J=16.1, 6.0 Hz, 1H), 4.57 (dd, J=5.0, 12.6 Hz, 1H), 4.38–4.33 (m, 2H), 3.88 (d, J=11.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.39–3.22 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 142.9, 133.3, 131.2, 131.0, 128.0, 119.6, 111.5, 103.4, 77.9, 77.8, 74.9, 71.5, 70.0, 62.6; HR-MS (FAB-MS) *m/z*: 322.1283 $(M+1)^+$; Calcd for $C_{16}H_{19}NO_6$ *m/z*: 322.1291 $(M+1)^+$.

5.3.24. 4-(Trifluoromethyl)cinnamyl β-D-glucopyranoside (1k). A mixture of **4k** (0.18 g, 0.34 mmol) and K_2CO_3 (0.47 g, 3.4 mmol) in MeOH (1.7 mL) was stirred for 2 h at room temperature. The reaction mixture was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH as an eluent) to afford **1k** (0.077 g, 63%) as a white solid. Mp: 142.5–144.5 °C; $[\alpha]_D^{27}$ −39.8 (*c* 0.41, MeOH); IR (KBr) 3362, 2931, 1418, 1328, 1171, 1110, 1070, 1041, 849, 639 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.60 (s, 4H), 6.78 (d, J=16.1 Hz, 1H), 6.56 (dt, J=16.1, 6.0 Hz, 1H), 4.56 (ddd, J=1.5, 5.5, 13.6 Hz, 1H), 4.39–4.33 (m, 2H), 3.88 (dd, J=2.0, 11.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.39–3.22 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 142.2, 131.8, 130.3 (q, J_{C-F}=27 Hz), 130.1, 127.9, 126.5, 125.7 (q, J_{C-F}=269 Hz), 103.6, 78.1, 78.0, 75.1, 71.7, 70.3, 62.8; HR-MS (FAB-MS) *m/z*: 365.1216 $(M+1)^+$; Calcd for $C_{16}H_{19}NO_6$ *m/z*: 365.1212 $(M+1)^+$.

5.3.25. 3-Nitrocinnamyl β-D-glucopyranoside (1l). A mixture of **4l** (0.14 g, 0.27 mmol) and K_2CO_3 (0.38 g, 2.7 mmol) in MeOH–THF (4 mL, 1/1, v/v) was stirred for 30 min at room temperature. The reaction mixture was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH as an eluent) to afford **1l** (0.082 g, 87%) as a white solid. Mp: 139.2–140.7 °C; $[\alpha]_D^{22}$ −40.3 (*c* 0.52, MeOH); IR (KBr) 3370, 2926, 2500, 1527, 1347, 1169, 1077, 1041, 729, 668, 630 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 8.28 (t, J=2.0 Hz, 1H), 8.12–8.07 (m, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.56 (t, J=8.0 Hz, 1H), 7.83 (d, J=15.6 Hz, 1H), 6.57 (dt, J=15.6, 5.6 Hz, 1H), 4.57 (ddd, J=1.5, 5.0, 13.6 Hz, 1H), 4.40–4.33 (m, 2H), 3.88 (d, J=11.6 Hz, 1H), 3.70–3.65 (m, 1H), 3.39–3.22 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 150.0, 140.3, 133.4, 130.8, 130.6, 130.5, 123.0, 121.9, 103.6, 78.1, 78.0, 75.1, 71.7, 70.2, 62.8; HR-MS (FAB-MS) *m/z*: 342.1176 $(M+1)^+$; Calcd for $C_{15}H_{19}NO_8$ *m/z*: 342.1189 $(M+1)^+$.

5.3.26. 3-Naphthalene-2-ylalloxy β-D-glucopyranoside (1m). A mixture of **4m** (0.18 g, 0.35 mmol) and K_2CO_3 (0.49 g, 3.5 mmol) in MeOH–THF (4 mL, 1/1, v/v) was stirred for 30 min at room temperature. The reaction mixture was evaporated to dryness and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH as an eluent) to afford **1m** (0.090 g, 73%) as a white solid. Mp: 161.0–163.0 °C; $[\alpha]_D^{22}$ −46.8 (*c* 0.36, MeOH); IR (KBr) 3518, 3339, 2931, 2871, 1153, 1037, 967, 896, 798, 744, 618, 480 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) δ: 7.60–7.55 (m, 4H), 7.44 (dd, J=2.0, 8.5 Hz, 1H), 7.24–7.20 (m, 2H), 6.64 (d, J=16.1 Hz, 1H), 6.29 (dt, J=6.0, 16.1 Hz, 1H), 4.37 (ddd, J=1.5, 6.0, 12.6 Hz, 1H), 4.18 (d, J=7.6 Hz, 1H), 4.17 (ddd, J=1.5, 6.6, 12.6 Hz, 1H), 3.67 (dd, J=2.0, 11.6 Hz, 1H), 3.50–3.44 (m, 1H), 3.39–3.22 (m, 4H); ^{13}C NMR (methanol-d_4, 100 MHz) δ: 135.7, 135.1, 134.5, 133.7, 129.2, 129.0, 128.6, 127.5, 127.2, 126.8, 124.6, 124.5, 103.4, 78.1, 78.0, 75.1, 71.7, 70.8, 62.8.; HR-MS (FAB-MS) *m/z*: 369.1318 $(M+Na)^+$; Calcd for $C_{19}H_{22}O_6$ *m/z*: 369.1314 $(M+Na)^+$.

References and notes

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Triterpenoids from *Cedrela sinensis*

Kumiko Mitsui, Masato Maejima, Hiroaki Saito, Haruhiko Fukaya, Yukio Hitotsuyanagi and Koichi Takeya*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo, 192-0392 Japan

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Abstract—Twenty-three new triterpenoids (**1**–**23**), all having an apotirucallane skeleton, were isolated from the seeds, leaves, and stems of *Cedrela sinensis* (Meliaceae). Their structures were determined by 2D NMR experiments, X-ray crystallographic analysis, and chemical methods. These triterpenoids showed a moderate cytotoxic activity against P-388 murine leukemia cells (IC_{50} 0.26–9.9 μg/mL).

1. Introduction

Cedrela sinensis Juss. (Meliaceae) is a tall tree growing in China and Korea, and the leaves of this plant have been used for treatment of enteritis, dysentery, and itch. This plant is known to contain limonoids, along with phytol derivatives, flavonoids, and phenolic compounds.[1,2] In the present study, we isolated twenty-three new triterpenoids (**1**–**23**), all having an apotirucallane skeleton, from the seeds, leaves, and stems of *C. sinensis*.

2. Results and discussion

2.1. Separation of triterpenoids

By a series of column chromatography including Diaion HP-20, activated charcoal, and silica gel column chromatographies and subsequent purification by preparative HPLC, a MeOH extract of the seeds of *C. sinensis* gave compounds **1** and **4**, that from the leaves gave compounds **1**–**3**, **7**, **8**, **10**–**12**, **14**–**16**, **18**, and **21**–**23**, and that from the stems of the plant gave compounds **1**–**7**, **9**, **13**, **17**, and **18**–**20**. Thus, twenty-three new triterpenoids **1**–**23** were separated from *C. sinensis* (Fig. 1).

2.2. Characterization of triterpenoids 1–23

Compound **1** was isolated as an amorphous solid. Its molecular formula was determined to be $C_{36}H_{58}O_7$ by the $[M+Na]^+$ ion peak at *m/z* 625.4056 (calcd for $C_{36}H_{58}O_7Na$, 625.4080) in the HRESIMS. Its ^1H NMR spectrum displayed signals due to eight tertiary methyl groups (δ 0.85, 0.89, 0.90, 1.02, 1.26, 1.30, 1.90, and 2.17), a cyclopropyl methylene group (δ 0.49 and 0.76, both d, $J=$ 4.7 Hz), a methoxyl group (δ 3.35, s), an acetal methine proton (δ 4.86, d, $J=3.7$ Hz), and an olefinic proton (δ 5.76, s-like) (Table 1). The ^{13}C NMR spectrum indicated the presence of nine methyls, nine methylenes, ten methines, and eight quaternary carbons, one of the quaternary carbons at δ 166.5 being assigned to an ester carbonyl carbon (Table 2). The molecular formula and the ^1H and ^{13}C NMR spectra suggested that **1** was a triterpenoid having an apotirucallane skeleton with a senecioyl ester side chain. The location of the methoxyl group was shown to be at C-21 by the HMBC cross-signal between C-21 (δ_C 109.2) and the *O*-methyl protons (δ_H 3.35), and that of the ester group to be at C-3 by the cross-signal between C-1′ (δ_C 166.5) and H-3 (δ_H 4.68). Further analysis of the ^{13}C NMR and HMBC spectra demonstrated the presence of three hydroxyl groups at C-7, C-24, and C-25, and a cyclopropane ring at C-13, C-14, and C-18 (Fig. 2), which demonstrated that **1** was a triterpenoid of the 14,18-cycloapotirucallane-type. As regards the stereochemistry of **1**, the NOE correlations between H-3/H_3-29, H-5/H-6α, H-5/H-9, H-5/H_3-28, H-6β/H-7, H-6β/H_3-19, H-6β/H_3-29, H-6β/H_3-30, H-7/H_3-30, H-9/H-18a, H-17/H_3-30, H_3-19/H_3-29, and H_3-19/H_3-30 (Fig. 3) showed that H-5, OH-7, H-9, and 14,18-cyclopropane ring were of α-orientation, whereas H-3, H-17, Me-19, and Me-30 were of β-orientation. The correlations among H-20/H_3CO-21/H-23 revealed that these protons and methoxyl group occupy the same face of the tetrahydrofuran ring. When compound **1** was treated with boron trifluoride diethyl etherate in $CHCl_3$, compound **1a** was produced via an oxonium intermediate (Scheme 1).[3] In its ^1H NMR

Keywords: *Cedrela sinensis*; Meliaceae; Triterpenoid; Apotirucallane; Cytotoxicity.
* Corresponding author. Tel.: +81 426 76 3007; fax: +81 426 77 1436; e-mail: takeyak@ps.toyaku.ac.jp

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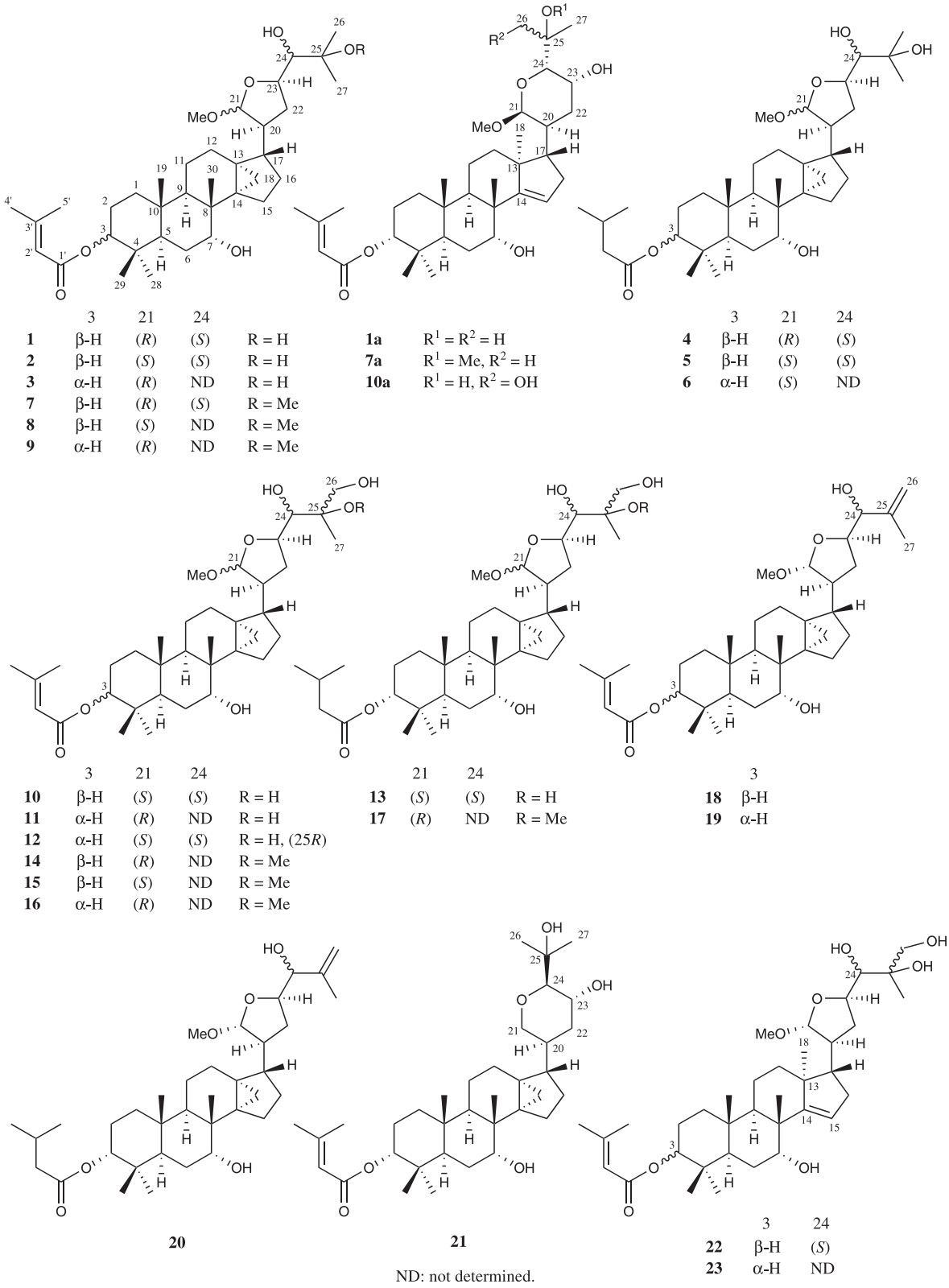


Figure 1.

spectrum were observed an olefinic proton at δ 5.46 (d, J= 2.4 Hz, H-15) and a methyl proton signal at δ 1.08 (s, H_3-18), which were absent in the spectrum of **1**. In the HMBC spectrum of **1a**, correlations were observed between the methine carbon at δ 72.3 (C-24) and the methine proton at δ 4.78 (d, J=2.8 Hz, H-21), and between the methine carbon at δ 100.4 (C-21) and the methoxyl protons at δ 3.33, suggesting that C-21 carrying the OMe was linked to C-24 via an ether bridge. In the NOESY spectrum of **1a** in pyridine-d_5, the correlations detected between the relevant signals were between H-17/H-21, H-17/H_3CO-21, H_3-18/H-20, and H_3-18/H-21 (Fig. 4). These correlations are

Table 1. ^{1}H NMR (500 MHz) spectral data for **1–23** in $CDCl_3$ at 300 K

Position	**1**[a]	**2**	**3**[a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
1α	1.18 (m)	1.18 (m)	1.04 (m)	1.18 (m)	1.18 (m)	1.04 (m)	1.18 (m)	1.18 (m)	1.04 (m)	1.18 (m)	1.04 (m)	1.04 (m)
1β	1.38 (m)	1.38 (m)	1.60 (m)	1.38 (m)	1.38 (m)	1.61 (m)	1.38 (m)	1.38 (m)	1.60 (m)	1.36 (m)	1.60 (m)	1.60 (m)
2α	1.60 (m)	1.60 (m)	1.60 (m)	1.58 (m)	1.58 (m)	1.60 (m)	1.60 (m)	1.60 (m)	1.60 (m)	1.60 (m)	1.60 (m)	1.60 (m)
2β	1.90 (m)	1.90 (m)	1.70 (m)	1.89 (m)	1.89 (m)	1.70 (m)	1.90 (m)	1.90 (m)	1.70 (m)	1.90 (m)	1.70 (m)	1.70 (m)
3	4.68 (t-like, 2.6)	4.68 (br s)	4.54 (dd, 4.7, 11.6)	4.65 (br s)	4.66 (br s)	4.53 (dd, 4.9, 11.3)	4.68 (br s)	4.68 (br s)	4.55 (dd, 4.8, 11.5)	4.68 (br s)	4.54 (dd, 4.7, 11.5)	4.54 (dd, 4.7, 11.4)
5	2.00 (m)	2.00 (m)	1.60 (m)	1.98 (m)	1.98 (m)	1.60 (m)	2.00 (m)	2.00 (m)	1.60 (m)	2.00 (m)	1.60 (m)	1.60 (m)
6α	1.63 (m)	1.63 (m)	1.74 (m)	1.63 (m)	1.63 (m)	1.74 (m)	1.63 (m)	1.63 (m)	1.74 (m)	1.63 (m)	1.74 (m)	1.74 (m)
6β	1.57 (m)	1.57 (m)	1.60 (m)	1.57 (m)	1.57 (m)	1.60 (m)	1.57 (m)	1.57 (m)	1.60 (m)	1.57 (m)	1.60 (m)	1.60 (m)
7	3.74 (br s)	3.75 (br s)	3.75 (br s)	3.74 (br s)	3.75 (br s)	3.76 (br s)	3.74 (br s)	3.74 (br s)	3.74 (br s)	3.75 (br s)	3.74 (br s)	3.76 (br s)
9	1.32 (m)	1.32 (m)	1.25 (m)	1.32 (m)	1.32 (m)	1.25 (m)	1.32 (m)	1.32 (m)	1.25 (m)	1.32 (m)	1.25 (m)	1.25 (m)
11α	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)
11β	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)
12α	1.84 (m)	1.67 (m)	1.84 (m)	1.84 (m)	1.67 (m)	1.67 (m)	1.85 (m)	1.67 (m)	1.85 (m)	1.67 (m)	1.84 (m)	1.67 (m)
12β	1.84 (m)	1.94 (m)	1.84 (m)	1.84 (m)	1.94 (m)	1.94 (m)	1.85 (m)	1.94 (m)	1.85 (m)	1.94 (m)	1.84 (m)	1.93 (m)
15 (α)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)
15 (β)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)
16α	1.66 (m)	1.66 (m)	1.66 (m)	1.67 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)
16β	1.66 (m)	1.66 (m)	1.66 (m)	1.67 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)
17	2.00 (m)	2.16 (m)	2.00 (m)	2.00 (m)	2.17 (m)	2.16 (m)	2.00 (m)	2.16 (m)	2.00 (m)	2.17 (m)	2.00 (m)	2.16 (m)
18 (a)	0.76 (d, 4.7)	0.71 (d, 4.7)	0.71 (d, 4.9)	0.77 (d, 4.8)	0.71 (d, 4.7)	0.67 (d, 5.0)	0.75 (d, 4.7)	0.71 (d, 4.6)	0.71 (d, 4.7)	0.71 (d, 4.5)	0.71 (d, 4.9)	0.67 (d, 4.7)
18 (b)	0.49 (d, 4.7)	0.46 (d, 4.7)	0.49 (d, 4.9)	0.50 (d, 4.8)	0.46 (d, 4.7)	0.45 (d, 5.0)	0.48 (d, 4.7)	0.45 (d, 4.6)	0.48 (d, 4.7)	0.45 (d, 4.5)	0.47 (d, 4.9)	0.44 (d, 4.7)
19	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.89 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.89 (s, 3H)	0.90 (s, 3H)
20	2.07 (m)	1.84 (m)	2.07 (m)	2.07 (m)	1.84 (m)	1.84 (m)	2.07 (m)	1.84 (m)	2.07 (m)	1.85 (m)	2.07 (m)	1.85 (m)
21α		4.80 (d, 3.8)			4.81 (d, 3.7)	4.81 (d, 3.6)		4.78 (d, 3.9)		4.82 (d, 3.2)		4.83 (d, 3.1)
21β	4.86 (d, 3.7)		4.86 (d, 3.6)	4.87 (d, 3.7)			4.86 (d, 3.6)		4.86 (d, 3.1)		4.87 (d, 3.8)	
22α	1.90 (m)	1.86 (m)	1.90 (m)	1.90 (m)	1.84 (m)	1.84 (m)	1.92 (m)	1.90 (m)	1.92 (m)	1.95 (m)	1.95 (m)	1.95 (m)
22β	1.82 (m)	1.86 (m)	1.82 (m)	1.82 (m)	1.84 (m)	1.84 (m)	1.60 (m)	1.76 (m)	1.60 (m)	1.85 (m)	1.74 (m)	1.85 (m)
23	4.25 (ddd, 1.5, 5.1, 10.2)	4.41 (m)	4.25 (dd, 5.2, 10.1)	4.25 (m)	4.41 (m)	4.41 (m)	4.20 (m)	4.43 (m)	4.20 (m)	4.48 (m)	4.23 (m)	4.48 (m)
24	3.23 (dd, 1.5, 10.2)	3.16 (m)	3.23 (d, 10.1)	3.22 (m)	3.15 (m)	3.15 (m)	3.37 (m)	3.23 (m)	3.37 (m)	3.33 (br s)	3.43 (br s)	3.32 (br s)
26 (a)	1.26 (s, 3H)	1.26 (s, 3H)	1.26 (s, 3H)	1.27 (s, 3H)	1.26 (s, 3H)	1.27 (s, 3H)	1.15 (s, 3H)	1.18 (s, 3H)	1.15 (s, 3H)	3.57 (s, 2H)	3.69 (d, 11.3)	3.56 (s, 2H)
26 (b)											3.52 (d, 11.3)	
27	1.30 (s, 3H)	1.27 (s, 3H)	1.30 (s, 3H)	1.30 (s, 3H)	1.27 (s, 3H)	1.27 (s, 3H)	1.24 (s, 3H)	1.24 (s, 3H)	1.24 (s, 3H)	1.22 (s, 3H)	1.19 (s, 3H)	1.22 (s, 3H)
28	0.85 (s, 3H)	0.85 (s, 3H)	0.87 (s, 3H)	0.85 (s, 3H)	0.85 (s, 3H)	0.87 (s, 3H)	0.85 (s, 3H)	0.85 (s, 3H)	0.87 (s, 3H)	0.85 (s, 3H)	0.86 (s, 3H)	0.86 (s, 3H)
29	0.89 (s, 3H)	0.89 (s, 3H)	0.86 (s, 3H)	0.88 (s, 3H)	0.88 (s, 3H)	0.85 (s, 3H)	0.89 (s, 3H)	0.89 (s, 3H)	0.86 (s, 3H)	0.89 (s, 3H)	0.85 (s, 3H)	0.86 (s, 3H)
30	1.02 (s, 3H)	1.04 (s, 3H)	1.01 (s, 3H)	1.03 (s, 3H)	1.04 (s, 3H)	1.03 (s, 3H)	1.02 (s, 3H)	1.03 (s, 3H)	1.01 (s, 3H)	1.04 (s, 3H)	1.00 (s, 3H)	1.03 (s, 3H)
2′	5.76 (s-like)	5.76 (s)	5.67 (s-like)	2.21 (d, 6.6, 2H)	2.21 (d, 6.6, 2H)	2.21 (d, 6.4, 2H)	5.76 (s)	5.76 (s)	5.67 (s)	5.77 (s)	5.66 (s)	5.66 (s)
3′				2.10 (m)	2.10 (m)	2.12 (m)						
4′	1.90 (s, 3H)	1.90 (s, 3H)	1.88 (s, 3H)	0.97 (d, 6.6, 3H)	0.96 (d, 6.6, 3H)	0.95 (d, 6.4, 3H)	1.90 (s, 3H)	1.90 (s, 3H)	1.88 (s, 3H)	1.90 (s, 3H)	1.87 (s, 3H)	1.88 (s, 3H)
5′	2.17 (s, 3H)	2.18 (s, 3H)	2.16 (s, 3H)	0.97 (d, 6.6, 3H)	0.97 (d, 6.6, 3H)	0.96 (d, 6.4, 3H)	2.17 (s, 3H)	2.18 (s, 3H)	2.16 (s, 3H)	2.18 (s, 3H)	2.15 (s, 3H)	2.15 (s, 3H)
OMe-21	3.35 (s, 3H)	3.39 (s, 3H)	3.35 (s, 3H)	3.35 (s, 3H)	3.39 (s, 3H)	3.39 (s, 3H)	3.35 (s, 3H)	3.38 (s, 3H)	3.35 (s, 3H)	3.42 (s, 3H)	3.35 (s, 3H)	3.41 (s, 3H)
OMe-25							3.23 (s, 3H)	3.24 (s, 3H)	3.23 (s, 3H)			

Position	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
1α	1.18 (m)	1.18 (m)	1.18 (m)	1.04 (m)	1.18 (m)	1.18 (m)	1.04 (m)	1.18 (m)	1.18 (m)	1.18 (m)	1.04 (m)
1β	1.37 (m)	1.37 (m)	1.36 (m)	1.60 (m)	1.37 (m)	1.37 (m)	1.60 (m)	1.37 (m)	1.37 (m)	1.37 (m)	1.60 (m)
2α	1.60 (m)	1.60 (m)	1.60 (m)	1.60 (m)	1.58 (m)	1.60 (m)	1.60 (m)	1.58 (m)	1.60 (m)	1.60 (m)	1.61 (m)
2β	1.90 (m)	1.90 (m)	1.90 (m)	1.70 (m)	1.88 (m)	1.90 (m)	1.70 (m)	1.89 (m)	1.90 (m)	1.90 (m)	1.70 (m)
3	4.66 (br s)	4.68 (br s)	4.68 (br s)	4.55 (dd, 4.7, 11.5)	4.65 (br s)	4.68 (br s)	4.55 (dd, 4.8, 11.5)	4.66 (br s)	4.68 (br s)	4.70 (br s)	4.55 (dd, 4.8, 11.5)
5	1.99 (m)	2.00 (m)	2.00 (m)	1.60 (m)	1.99 (m)	2.00 (m)	1.60 (m)	2.00 (m)	2.00 (m)	2.00 (m)	1.60 (m)
6α	1.63 (m)	1.63 (m)	1.63 (m)	1.73 (m)	1.63 (m)	1.63 (m)	1.73 (m)	1.63 (m)	1.63 (m)	1.72 (m)	1.81 (m)
6β	1.57 (m)	1.57 (m)	1.57 (m)	1.60 (m)	1.57 (m)	1.57 (m)	1.60 (m)	1.58 (m)	1.57 (m)	1.68 (m)	1.71 (m)
7	3.75 (br s)	3.75 (br s)	3.75 (br s)	3.74 (br s)	3.74 (br s)	3.74 (br s)	3.74 (br s)	3.74 (br s)	3.75 (br s)	3.91 (br s)	3.91 (br s)
9	1.32 (m)	1.32 (m)	1.32 (m)	1.25 (m)	1.32 (m)	1.32 (m)	1.24 (m)	1.32 (m)	1.30 (m)	2.00 (m)	1.99 (m)
11α	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.50 (m)	1.48 (m)
11β	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.33 (m)	1.75 (m)	1.75 (m)
12α	1.67 (m)	1.84 (m)	1.67 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.46 (m)	1.44 (m)
12β	1.93 (m)	1.84 (m)	1.93 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.84 (m)	1.80 (m)	1.80 (m)
15 (α)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.55 (m)	1.99 (m)	5.45 (br s)	5.44 (br s)
15 (β)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)	1.99 (m)		
16α	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.56 (m)	1.74 (m)	1.73 (m)

(*continued on next page*)

Table 1 (*continued*)

Position	13	14	15	16	17	18	19	20	21	22	23
16β	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.66 (m)	1.90 (m)	2.12 (m)	2.11 (m)
17	2.17 (m)	2.01 (m)	2.17 (m)	2.01 (m)	2.00 (m)	2.00 (m)	2.00 (m)	2.00 (m)	1.53 (m)	1.72 (m)	1.72 (m)
18 (a)	0.72 (d, 4.5)	0.76 (d, 5.2)	0.71 (d, 4.7)	0.71 (d, 4.8)	0.76 (d, 4.7)	0.76 (d, 4.9)	0.72 (d, 4.9)	0.77 (d, 4.9)	0.73 (d, 4.6)	1.08 (s, 3H)	1.05 (s, 3H)
18 (b)	0.46 (d, 4.5)	0.48 (d, 5.2)	0.45 (d, 4.7)	0.47 (d, 4.8)	0.49 (d, 4.7)	0.47 (d, 4.9)	0.47 (d, 4.9)	0.48 (d, 4.9)	0.45 (d, 4.6)		
19	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.89 (s, 3H)	0.89 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.90 (s, 3H)	0.89 (s, 3H)	0.91 (s, 3H)	0.91 (s, 3H)
20	1.86 (m)	2.07 (m)	1.83 (m)	2.07 (m)	2.07 (m)	2.10 (m)	2.11 (m)	2.11 (m)	2.19 (m)	2.37 (m)	2.37 (m)
21α	4.84 (d, 2.9)		4.82 (d, 3.3)						3.40 (dd, 2.4, 11.6)		
21β		4.88 (d, 4.0)		4.89 (d, 3.9)	4.90 (d, 3.8)	4.88 (d, 3.8)	4.88 (d, 3.5)	4.89 (d, 3.2)	4.10 (d, 11.6)	4.83 (d, 3.5)	4.82 (d, 3.8)
22α	1.95 (m)	1.95 (m)	1.95 (m)	1.95 (m)	1.95 (m)	1.90 (m)	1.90 (m)	1.90 (m)	1.50 (m)	2.20 (m)	2.20 (m)
22β	1.85 (m)	1.74 (m)	1.83 (m)	1.74 (m)	1.74 (m)	1.38 (m)	1.38 (m)	1.38 (m)	2.00 (m)	2.00 (m)	2.00 (m)
23	4.48 (m)	4.18 (m)	4.44 (m)	4.18 (m)	4.18 (m)	4.06 (m)	4.06 (m)	4.06 (m)	3.86 (m)	4.23 (m)	4.23 (m)
24	3.33 (br s)	3.60 (br s)	3.50 (br s)	3.60 (br s)	3.60 (br s)	3.92 (m)	3.91 (m)	3.92 (m)	2.91 (d, 9.1)	3.46 (br s)	3.45 (br s)
26 (a)	3.57 (s, 2H)	3.67 (s, 2H)	3.65 (s, 2H)	3.67 (s, 2H)	3.67 (s, 2H)	5.00 (br s)	5.00 (br s)	5.00 (br s)	1.29 (s, 3H)	3.70 (d, 11.3)	3.70 (d, 11.3)
26 (b)						4.91 (br s)	4.91 (br s)	4.91 (br s)		3.52 (d, 11.3)	3.52 (d, 11.3)
27	1.25 (s, 3H)	1.13 (s, 3H)	1.17 (s, 3H)	1.12 (s, 3H)	1.13 (s, 3H)	1.77 (s, 3H)	1.77 (s, 3H)	1.78 (s, 3H)	1.32 (s, 3H)	1.21 (s, 3H)	1.20 (s, 3H)
28	0.85 (s, 3H)	0.84 (s, 3H)	0.85 (s, 3H)	0.86 (s, 3H)	0.84 (s, 3H)	0.85 (s, 3H)	0.87 (s, 3H)	0.85 (s, 3H)	0.85 (s, 3H)	0.86 (s, 3H)	0.88 (s, 3H)
29	0.88 (s, 3H)	0.88 (s, 3H)	0.89 (s, 3H)	0.85 (s, 3H)	0.88 (s, 3H)	0.89 (s, 3H)	0.86 (s, 3H)	0.88 (s, 3H)	0.89 (s, 3H)	0.88 (s, 3H)	0.88 (s, 3H)
30	1.04 (s, 3H)	1.02 (s, 3H)	1.03 (s, 3H)	1.01 (s, 3H)	1.02 (s, 3H)	1.02 (s, 3H)	1.01 (s, 3H)	1.03 (s, 3H)	1.07 (s, 3H)	1.06 (s, 3H)	1.05 (s, 3H)
2′	2.21 (d, 6.5, 2H)	5.76 (s)	5.77 (s)	5.66 (s)	2.22 (d, 6.4, 2H)	5.76 (s)	5.67 (s)	2.22 (d, 6.6, 2H)	5.76 (s)	5.77 (s)	5.67 (s)
3′	2.10 (m)				2.10 (m)			2.10 (m)			
4′	0.96 (d, 6.5, 3H)	1.89 (s, 3H)	1.90 (s, 3H)	1.88 (s, 3H)	0.96 (d, 6.4, 3H)	1.90 (s, 3H)	1.90 (s, 3H)	0.96 (d, 6.6, 3H)	1.89 (s, 3H)	1.89 (s, 3H)	1.88 (s, 3H)
5′	0.97 (d, 6.5, 3H)	2.17 (s, 3H)	2.17 (s, 3H)	2.15 (s, 3H)	0.96 (d, 6.4, 3H)	2.17 (s, 3H)	2.16 (s, 3H)	0.97 (d, 6.6, 3H)	2.17 (s, 3H)	2.17 (s, 3H)	2.16 (s, 3H)
OMe-21	3.42 (s, 3H)	3.36 (s, 3H)	3.39 (s, 3H)	3.36 (s, 3H)	3.36 (s, 3H)	3.37 (s, 3H)	3.37 (s, 3H)	3.37 (s, 3H)		3.37 (s, 3H)	3.36 (s, 3H)
OMe-25		3.29 (s, 3H)	3.28 (s, 3H)	3.28 (s, 3H)	3.28 (s, 3H)						

[a] Run at 600 MHz.

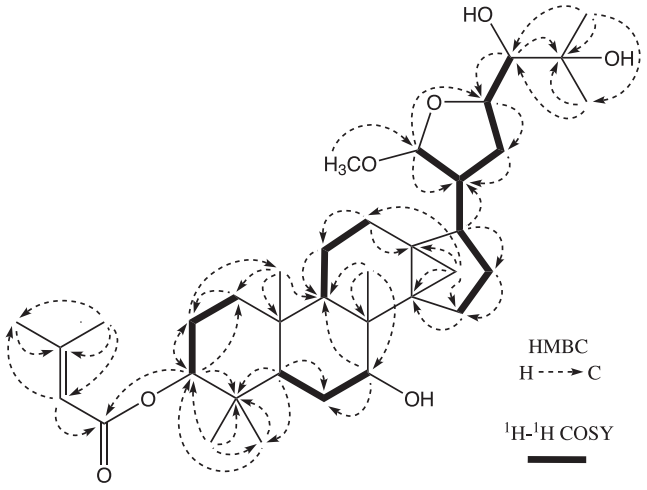


Figure 2. Selected COSY and HMBC correlations for **1**.

possible when **1a** has the 20*S* configuration (apotirucallane skeleton). The NOE correlations between H_3CO-21/H-22β, H_3CO-21/H-24, H-22β/H-23, H-22β/H-24, and H-23/H-24, and a small coupling constant (<1 Hz) between H-23 and H-24 showed that the configurations at C-21 and C-24 were both *S*, and that at C-23 was *R*. Thus, the structure of **1** was determined to be as shown in Figure 1.

Compound **2** was obtained as an amorphous solid. Its molecular formula, $C_{36}H_{58}O_7$, was determined by the $[M+Na]^+$ ion peak in the HRESIMS at *m/z* 625.4056 (calcd for $C_{36}H_{58}O_7Na$, 625.4080). Analysis and comparison of the HMBC and COSY spectra demonstrated that **1** and **2** had the same gross structure. The differences observed between them were that **2** gave an NOE correlation between H-21/H-23 (Fig. 5), which was not seen in **1**, and that the ^{13}C NMR signals of C-17 and C-21 in **1** (δ 48.4 and 109.2, respectively) were considerably upfield shifted in **2** (δ 44.6 and 105.3, respectively), whereas that of C-23 in **1** (δ

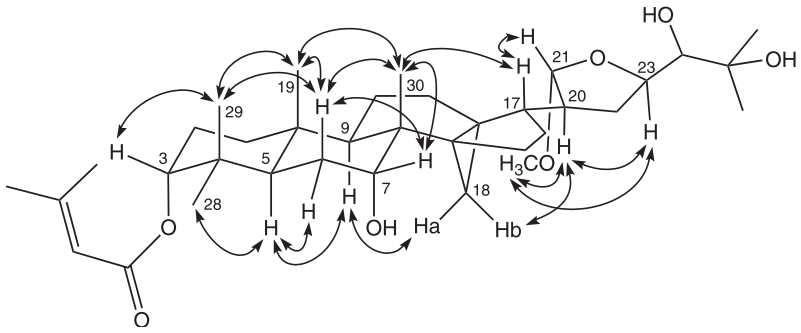
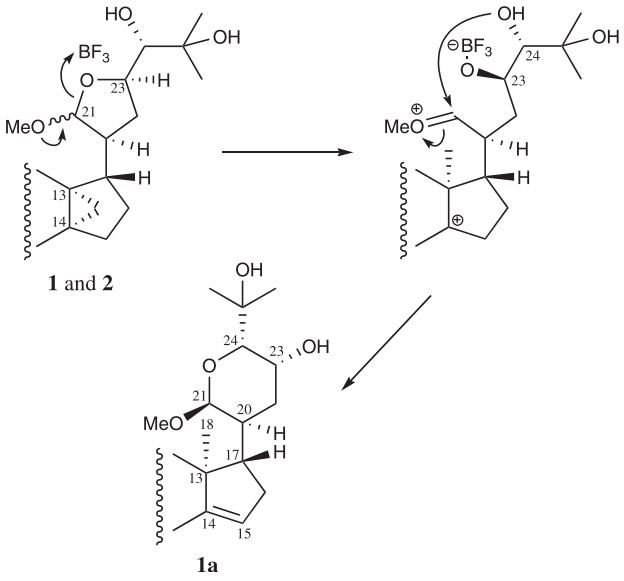


Figure 3. Selected NOE correlations for **1**.



Scheme 1. Acid-catalyzed formation of **1a** from **1** and **2**.

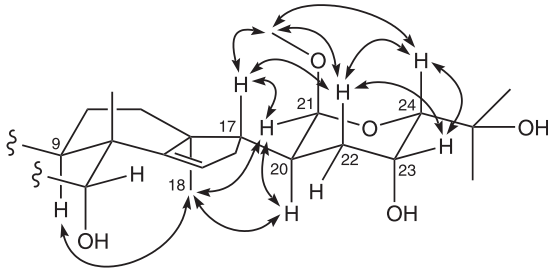


Figure 4. Selected NOE correlations for **1a**.

77.0) was slightly downfield shifted in **2** (δ 78.9) (Table 2).[4,5] The fact implied that **2** was the 21*S* epimer of **1**, as shown in Figure 1. It was verified by the production of **1a** by the treatment of **2** with boron trifluoride diethyl etherate in $CHCl_3$.

Compound **3** was obtained as an amorphous solid. By the $[M+Na]^+$ ion peak at *m*/*z* 625.4082 (calcd for $C_{36}H_{58}O_7Na$, 625.4080) in the HRESIMS, its molecular formula was determined to be $C_{36}H_{58}O_7$. The ^1H and ^{13}C NMR spectra of **3** showed close resemblance to those of **1**, implying that **1** and **3** were of the same gross structure. The difference noted between the NMR spectra of **1** and **3** was that the C-3 signal of **3** (δ 79.7) was in a lower field than the corresponding C-3 signal of **1** (δ 77.1). The chemical shift of the H-3 signal (δ 4.54) and its coupling constants (dd, $J=$ 4.7, 11.6 Hz) and the NOE correlations detected between H-3/H-5, H-3/H_3-28, and H-5/H_3-28 (Fig. 6) demonstrated that in **3**, the senecioyl ester side chain at C-3 was of β-orientation. From these observations, **3** was determined to have the structure shown in Figure 1.

Compound **4** was obtained as an amorphous solid. Its molecular formula was determined to be $C_{36}H_{60}O_7$ by the $[M+Na]^+$ ion peak at *m*/*z* 627.4286 (calcd for $C_{36}H_{60}O_7Na$, 627.4237) in the HRESIMS. The NMR spectra of **4** were generally similar to those of **1**, suggesting that **4** was also a triterpenoid of the same series. However, the C-2′ and C-3′ carbon signals in **4** were considerably in an upper field than the corresponding C-2′ and C-3′ signals in **1** (Table 2), and the H-4′ and H-5′ proton signals in **4** were both doublets, demonstrating that the C-2′/C-3′ olefinic bond in **1** was saturated in **4**. Hydrogenation of **1** with Pd–C afforded a product, whose spectral data were identical to those of natural **4**, proving that the structure of **4** was as shown in Figure 1.

Compound **5** was isolated as an amorphous solid. Its molecular formula of $C_{36}H_{60}O_7$ was determined by the $[M+Na]^+$ ion peak at *m*/*z* 627.4255 (calcd for $C_{36}H_{60}O_7Na$, 627.4237) in the HRESIMS. The NMR spectra of **5** were quite similar to those of **2**, suggesting that they had the same basic structure with the difference as observed between **1** and **4**. Thus, **5** was considered to have an isovaleryl ester side chain of α-orientation at C-3. Hydrogenation of **2** with Pd–C afforded a product whose spectral data were identical to those of natural **5**, to prove that **5** had the structure shown in Figure 1.

Compound **6** was isolated as an amorphous solid. Its molecular formula was determined to be $C_{36}H_{60}O_7$ by the $[M+Na]^+$ ion peak at *m*/*z* 627.4239 (calcd for $C_{36}H_{60}O_7Na$, 627.4237) in the HRESIMS. Its HMBC and COSY spectra generally resembled those of **5**, suggesting that **6** had the same gross structure. The difference observed between the spectra of **5** and **6** was the chemical shifts and the coupling pattern of the C-3 carbon and the H-3 proton signals, implying that H-3 of **6** was of α-orientation. Thus, **6** was determined to have the structure shown in Figure 1.

Compound **7** was obtained as an amorphous solid. The $[M+Na]^+$ ion peak at *m*/*z* 639.4194 (calcd for $C_{37}H_{60}O_7Na$, 639.4237) in the HRESIMS determined its

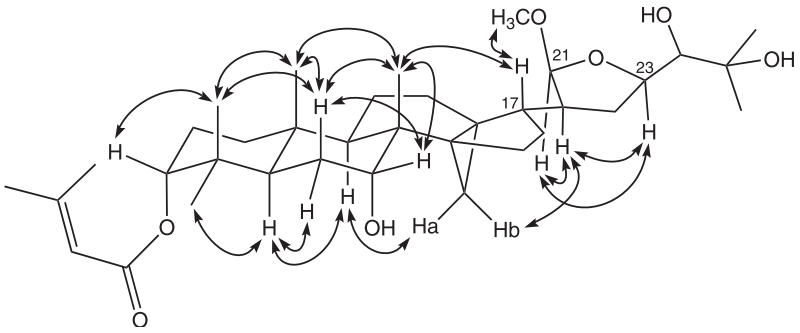


Figure 5. Selected NOE correlations for **2**.

Table 2. ^{13}C NMR (125 MHz) spectral data for **1–23** in $CDCl_3$ at 300 K

Position	**1**[a]	**2**	**3**[a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
1	33.9 (t)	34.0 (t)	38.2 (t)	33.8 (t)	33.9 (t)	38.3 (t)	34.0 (t)	34.0 (t)	38.3 (t)	34.0 (t)	38.2 (t)	38.8 (t)
2	22.8 (t)	22.9 (t)	23.7 (t)	22.9 (t)	22.9 (t)	23.6 (t)	22.8 (t)	22.9 (t)	23.7 (t)	22.9 (t)	23.7 (t)	23.6 (t)
3	77.1 (d)	77.0 (d)	79.7 (d)	77.8 (d)	77.8 (d)	80.5 (d)	77.0 (d)	77.0 (d)	79.8 (d)	77.0 (d)	79.7 (d)	79.7 (d)
4	36.3 (s)	36.3 (s)	37.2 (s)	36.2 (s)	36.2 (s)	37.0 (s)	36.3 (s)	36.3 (s)	37.3 (s)	36.3 (s)	37.3 (s)	37.3 (s)
5	41.3 (d)	41.3 (d)	46.2 (d)	41.4 (d)	41.3 (d)	46.1 (d)	41.3 (d)	41.3 (d)	46.2 (d)	41.3 (d)	46.1 (d)	46.1 (d)
6	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)
7	74.2 (d)	74.3 (d)	74.2 (d)	74.2 (d)	74.2 (d)	74.3 (d)	74.3 (d)	74.3 (d)	74.2 (d)	74.3 (d)	74.2 (d)	74.3 (d)
8	39.1 (s)	39.1 (s)	38.9 (s)	39.1 (s)	39.0 (s)	38.9 (s)	39.1 (s)	39.0 (s)	38.9 (s)	39.0 (s)	38.9 (s)	38.3 (s)
9	43.9 (d)	44.0 (d)	43.9 (d)	43.9 (d)	44.0 (d)	44.1 (d)	43.9 (d)	44.0 (d)	44.0 (d)	44.0 (d)	43.9 (d)	44.0 (d)
10	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.2 (s)	37.2 (s)
11	16.1 (t)	16.3 (t)	16.3 (t)	16.1 (t)	16.3 (t)	16.5 (t)	16.1 (t)	16.3 (t)	16.3 (t)	16.3 (t)	16.3 (t)	16.4 (t)
12	25.6 (t)	25.4 (t)	25.6 (t)	25.6 (t)	25.4 (t)	25.4 (t)	25.5 (t)	25.4 (t)	25.5 (t)	25.4 (t)	25.5 (t)	25.3 (t)
13	28.5 (s)	28.9 (s)	28.5 (s)	28.6 (s)	28.9 (s)	28.9 (s)	28.6 (s)	29.0 (s)	28.6 (s)	28.9 (s)	28.4 (s)	28.8 (s)
14	36.3 (s)	37.1 (s)	36.2 (s)	36.4 (s)	37.1 (s)	37.2 (s)	36.3 (s)	37.1 (s)	36.1 (s)	37.1 (s)	36.2 (s)	37.0 (s)
15	25.9 (t)	26.3 (t)	25.8 (t)	25.9 (t)	26.3 (t)	26.3 (t)	25.9 (t)	26.3 (t)	25.9 (t)	26.3 (t)	25.8 (t)	26.2 (t)
16	26.3 (t)	27.6 (t)	26.3 (t)	26.3 (t)	27.6 (t)	27.6 (t)	26.3 (t)	27.6 (t)	26.2 (t)	27.6 (t)	26.2 (t)	27.5 (t)
17	48.4 (d)	44.6 (d)	48.4 (d)	48.5 (d)	44.6 (d)	44.7 (d)	48.5 (d)	44.7 (d)	48.5 (d)	44.7 (d)	48.4 (d)	44.6 (d)
18	13.6 (t)	13.6 (t)	13.6 (t)	13.6 (t)	13.6 (t)	13.6 (t)	13.6 (t)	13.6 (t)	13.5 (t)	13.6 (t)	13.6 (t)	13.6 (t)
19	15.7 (q)	15.7 (q)	15.9 (q)	15.6 (q)	15.7 (q)	16.0 (q)	15.7 (q)	15.7 (q)	15.9 (q)	15.7 (q)	15.9 (q)	15.9 (q)
20	49.1 (d)	48.6 (d)	49.0 (d)	49.1 (d)	48.6 (d)	48.6 (d)	49.4 (d)	48.8 (d)	49.3 (d)	48.6 (d)	49.1 (d)	48.5 (d)
21	109.2 (d)	105.3 (d)	109.2 (d)	109.3 (d)	105.3 (d)	105.3 (d)	108.9 (d)	105.2 (d)	109.0 (d)	105.5 (d)	109.4 (d)	105.5 (d)
22	32.2 (t)	31.0 (t)	32.2 (t)	32.3 (t)	31.0 (t)	31.0 (t)	33.9 (t)	31.9 (t)	34.0 (t)	31.2 (t)	33.1 (t)	31.2 (t)
23	77.0 (d)	78.9 (d)	77.0 (d)	77.3 (d)	78.9 (d)	79.0 (d)	75.2 (d)	77.9 (d)	75.2 (d)	78.1 (d)	75.7 (d)	78.0 (d)
24	75.5 (d)	76.6 (d)	75.5 (d)	75.6 (d)	76.7 (d)	76.6 (d)	76.4 (d)	76.9 (d)	76.5 (d)	75.8 (d)	75.4 (d)	75.6 (d)
25	73.1 (s)	72.9 (s)	73.1 (s)	73.1 (s)	72.9 (s)	72.9 (s)	77.3 (s)	77.1 (s)	77.0 (s)	74.5 (s)	74.3 (s)	74.5 (s)
26	26.4 (q)	26.4 (q)	26.4 (q)	26.4 (q)	26.4 (q)	26.4 (q)	20.1 (q)	20.0 (q)	20.1 (q)	67.3 (t)	67.9 (t)	67.3 (t)
27	26.5 (q)	26.4 (q)	26.5 (q)	26.5 (q)	26.4 (q)	26.4 (q)	21.6 (q)	22.4 (q)	21.6 (q)	20.6 (q)	20.7 (q)	20.4 (q)
28	27.8 (q)	27.8 (q)	27.7 (q)	27.8 (q)	27.8 (q)	27.8 (q)	27.7 (q)	27.8 (q)	27.7 (q)	27.8 (q)	27.7 (q)	27.7 (q)
29	21.9 (q)	21.9 (q)	16.9 (q)	21.9 (q)	21.9 (q)	16.8 (q)	21.9 (q)	21.9 (q)	16.9 (q)	21.9 (q)	16.8 (q)	16.8 (q)
30	19.5 (q)	19.5 (q)	19.4 (q)	19.5 (q)	19.5 (q)	19.5 (q)	19.4 (q)	19.5 (q)	19.4 (q)	19.5 (q)	19.4 (q)	19.5 (q)
1′	166.5 (s)	166.5 (s)	166.6 (s)	173.0 (s)	172.9 (s)	172.9 (s)	166.5 (s)	166.5 (s)	166.6 (s)	166.5 (s)	166.6 (s)	166.6 (s)
2′	117.0 (d)	117.0 (d)	116.7 (d)	43.9 (t)	43.9 (t)	44.0 (t)	117.0 (d)	117.0 (d)	116.7 (d)	117.0 (d)	116.7 (d)	116.6 (d)
3′	155.8 (s)	155.8 (s)	155.9 (s)	25.8 (d)	25.8 (d)	25.8 (d)	155.8 (s)	155.8 (s)	155.8 (s)	155.8 (s)	155.8 (s)	155.8 (s)
4′	27.4 (q)	27.4 (q)	27.4 (q)	22.5 (q)	22.5 (q)	22.4 (q)	27.4 (q)	27.4 (q)	27.4 (q)	27.4 (q)	27.4 (q)	27.4 (q)
5′	20.3 (q)	20.3 (q)	20.2 (q)	22.5 (q)	22.5 (q)	22.5 (q)	20.3 (q)	20.3 (q)	20.2 (q)	20.3 (q)	20.2 (q)	20.2 (q)
OMe-21	55.7 (q)	55.2 (q)	55.7 (q)	55.7 (q)	55.2 (q)	55.2 (q)	55.5 (q)	54.9 (q)	55.5 (q)	55.4 (q)	55.9 (q)	55.3 (q)
OMe-25							49.2 (q)	49.3 (q)	49.2 (q)			

Position	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
1	33.9 (t)	33.9 (t)	33.9 (t)	38.9 (t)	33.8 (t)	33.9 (t)	38.3 (t)	33.8 (t)	34.0 (t)	33.4 (t)	37.7 (t)
2	22.9 (t)	22.8 (t)	22.8 (t)	23.7 (t)	22.9 (t)	22.8 (t)	23.7 (t)	22.9 (t)	22.9 (t)	22.8 (t)	23.7 (t)
3	77.8 (d)	77.0 (d)	77.0 (d)	79.7 (d)	77.8 (d)	77.0 (d)	79.7 (d)	77.8 (d)	77.0 (d)	77.1 (d)	79.7 (d)
4	36.2 (s)	36.3 (s)	36.3 (s)	37.3 (s)	36.2 (s)	36.3 (s)	37.2 (s)	36.2 (s)	36.3 (s)	36.3 (s)	37.3 (s)
5	41.3 (d)	41.3 (d)	41.3 (d)	46.1 (d)	41.3 (d)	41.3 (d)	46.2 (d)	41.3 (d)	41.2 (d)	41.7 (d)	46.7 (d)
6	24.3 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	24.2 (t)	23.6 (t)	23.7 (t)
7	74.2 (d)	74.3 (d)	74.3 (d)	74.2 (d)	74.2 (d)	74.2 (d)	74.2 (d)	74.2 (d)	74.4 (d)	72.2 (d)	72.2 (d)
8	39.1 (s)	39.1 (s)	39.0 (s)	38.2 (s)	39.1 (s)	39.1 (s)	38.9 (s)	39.1 (s)	39.0 (s)	44.5 (s)	44.3 (s)
9	44.0 (d)	44.0 (d)	44.0 (d)	43.9 (d)	43.9 (d)	43.9 (d)	44.0 (d)	43.9 (d)	44.0 (d)	41.8 (d)	41.7 (d)
10	37.3 (s)	37.3 (s)	37.3 (s)	37.2 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.3 (s)	37.4 (s)	37.6 (s)	37.5 (s)
11	16.3 (t)	16.1 (t)	16.2 (t)	16.3 (t)	16.1 (t)	16.1 (t)	16.3 (t)	16.1 (t)	16.6 (t)	16.3 (t)	16.4 (t)
12	25.4 (t)	25.6 (t)	25.4 (t)	25.5 (t)	25.5 (t)	25.7 (t)	25.6 (t)	25.6 (t)	28.2 (t)	32.8 (t)	32.7 (t)
13	28.9 (s)	28.6 (s)	28.9 (s)	28.5 (s)	28.6 (s)	28.6 (s)	28.6 (s)	28.6 (s)	28.8 (s)	47.0 (s)	47.0 (s)
14	37.1 (s)	36.4 (s)	37.1 (s)	36.2 (s)	36.3 (s)	36.4 (s)	36.2 (s)	36.3 (s)	37.2 (s)	162.5 (s)	162.3 (s)
15	26.3 (t)	25.9 (t)	26.2 (t)	25.8 (t)	25.9 (t)	25.9 (t)	25.9 (t)	25.9 (t)	28.0 (t)	119.2 (d)	119.3 (d)
16	27.6 (t)	26.3 (t)	27.6 (t)	26.2 (t)	26.3 (t)	26.4 (t)	26.2 (t)	26.2 (t)	26.2 (t)	34.7 (t)	34.6 (t)
17	44.7 (d)	48.4 (d)	44.6 (d)	48.4 (d)	48.4 (d)	48.6 (d)	48.5 (d)	48.6 (d)	40.4 (d)	57.6 (d)	57.6 (d)
18	13.6 (t)	13.7 (t)	13.6 (t)	13.6 (t)	13.6 (t)	13.7 (t)	13.6 (t)	13.6 (t)	14.2 (t)	19.4 (q)	19.3 (q)
19	15.7 (q)	15.7 (q)	15.7 (q)	15.9 (q)	15.6 (q)	15.7 (q)	15.9 (q)	15.6 (q)	15.9 (q)	15.3 (q)	15.5 (q)
20	48.6 (d)	49.4 (d)	48.6 (d)	49.4 (d)	49.4 (d)	49.8 (d)	49.7 (d)	49.8 (d)	45.9 (d)	46.0 (d)	46.0 (d)
21	105.5 (d)	109.4 (d)	105.4 (d)	109.3 (d)	109.4 (d)	109.0 (d)	109.0 (d)	109.0 (d)	70.7 (t)	109.8 (d)	109.8 (d)
22	31.2 (t)	33.5 (t)	31.5 (t)	33.4 (t)	33.5 (t)	32.6 (t)	32.5 (t)	32.6 (t)	36.5 (t)	34.7 (t)	34.7 (t)
23	78.1 (d)	75.3 (d)	77.8 (d)	75.3 (d)	75.3 (d)	79.0 (d)	79.0 (d)	79.0 (d)	64.9 (d)	75.6 (d)	75.6 (d)
24	75.8 (d)	73.7 (d)	73.4 (d)	73.7 (d)	73.7 (d)	78.2 (d)	78.3 (d)	78.3 (d)	86.6 (d)	75.4 (d)	75.4 (d)
25	74.5 (s)	78.5 (s)	78.6 (s)	78.5 (s)	78.5 (s)	144.5 (s)	144.5 (s)	144.5 (s)	74.2 (s)	74.3 (s)	74.3 (s)
26	67.3 (t)	64.4 (t)	64.3 (t)	64.4 (t)	64.4 (t)	113.3 (t)	113.3 (t)	113.3 (t)	24.1 (q)	67.9 (t)	67.9 (t)
27	20.6 (q)	15.5 (q)	15.2 (q)	15.5 (q)	15.5 (q)	18.2 (q)	18.2 (q)	18.2 (q)	28.6 (q)	20.7 (q)	20.8 (q)
28	27.8 (q)	27.8 (q)	27.7 (q)	27.7 (q)	27.8 (q)	27.8 (q)	27.7 (q)	27.8 (q)	27.7 (q)	27.8 (q)	27.7 (q)
29	21.9 (q)	21.9 (q)	21.9 (q)	16.8 (q)	21.9 (q)	21.9 (q)	16.9 (q)	21.9 (q)	21.9 (q)	21.8 (q)	16.8 (q)
30	19.5 (q)	19.5 (q)	19.5 (q)	19.4 (q)	19.4 (q)	19.5 (q)	19.4 (q)	19.4 (q)	19.9 (q)	27.7 (q)	27.6 (q)
1′	172.9 (s)	166.5 (s)	166.5 (s)	166.5 (s)	172.9 (s)	166.5 (s)	166.6 (s)	172.9 (s)	166.5 (s)	166.5 (s)	166.6 (s)
2′	43.9 (t)	117.0 (d)	116.9 (d)	116.7 (d)	43.9 (t)	117.0 (d)	116.7 (d)	43.9 (t)	117.0 (d)	117.0 (d)	116.7 (d)
3′	25.8 (d)	155.7 (s)	155.8 (s)	155.7 (s)	25.8 (d)	155.8 (s)	155.8 (s)	25.8 (d)	155.8 (s)	155.7 (s)	155.8 (s)

Table 2 (*continued*)

Position	13	14	15	16	17	18	19	20	21	22	23
4′	22.5 (q)	27.4 (q)	27.4 (q)	27.4 (q)	22.5 (q)	27.4 (q)	27.4 (q)	22.5 (q)	27.4 (q)	27.4 (q)	27.4 (q)
5′	22.5 (q)	20.3 (q)	20.3 (q)	20.2 (q)	22.5 (q)	20.3 (q)	20.2 (q)	22.5 (q)	20.3 (q)	20.3 (q)	20.3 (q)
OMe-21	55.4 (q)	55.9 (q)	55.1 (q)	55.8 (q)	55.8 (q)	55.5 (q)	55.5 (q)	55.5 (q)		55.8 (q)	55.8 (q)
OMe-25		49.3 (q)	49.5 (q)	49.2 (q)	49.3 (q)						

[a] Run at 150 MHz.

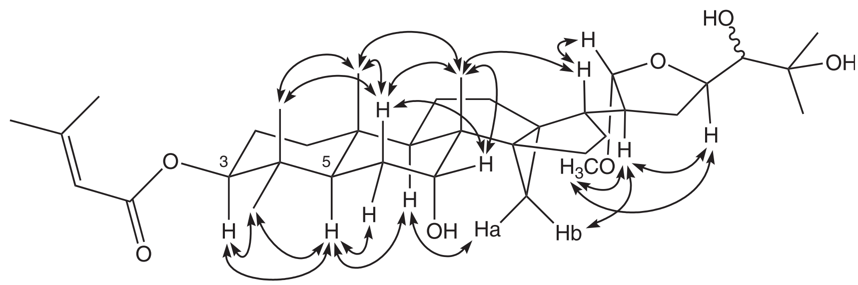


Figure 6. Selected NOE correlations for **3**.

molecular formula to be $C_{37}H_{60}O_7$. The ^{1}H and ^{13}C NMR spectra of **7** were almost superimposable to those of **1**, except for the presence of an extra methoxy signal (δ_C 49.2, δ_H 3.23). The molecular formula and analysis of the HMBC spectra revealed that **7** was an analogue of **1** with a methoxyl group at C-25, instead of a hydroxyl group in **1**. The configurations at C-23 and C-24 were determined to be *R* and *S*, respectively, by acid-catalyzed formation of **7a** from **7**. Thus, the structure of **7** was determined to be as shown in Figure 1.

Compound **8** was obtained as an amorphous solid. The $[M+Na]^+$ ion peak at *m*/*z* 639.4212 (calcd for $C_{37}H_{60}O_7Na$, 639.4237) in the HRESIMS determined its molecular formula to be $C_{37}H_{60}O_7$. The molecular formula of **8** was the same as that of **7**, and the NMR spectra of **8** closely resembled those of **7**, except for the minor difference as observed between the spectra of **1** and **2**, which suggested that **8** and **7** were the epimers at C-21. The NOE correlations and the chemical shifts of the C-17, C-21, C-23, and H-3 signals revealed that in **8**, H-3 was of β-orientation and C-21 of *S* configuration. Thus, the structure of **8** was determined to be as shown in Figure 1.

Compound **9** was obtained as an amorphous solid. Its molecular formula was determined to be $C_{37}H_{60}O_7$ by the $[M+Na]^+$ ion peak at *m*/*z* 639.4275 (calcd for $C_{37}H_{60}O_7Na$, 639.4237) in the HRESIMS, which was the same as that of **7** and **8**. The NMR spectra of **9** were quite similar to those of **7** with the minor difference analogous to that observed between **1** and **3**, suggesting that **9** was the epimer of **7** at C-3. The NOE correlations and the chemical shifts of the C-17, C-21, and C-23 signals and the coupling constants of the H-3 signal showed that in **9**, H-3 was of α-orientation and C-21 of *R* configuration. Thus, the structure of **9** was determined to be as shown in Figure 1.

Compound **10** was isolated as an amorphous solid. Its molecular formula of $C_{36}H_{58}O_8$ was determined by the $[M+Na]^+$ ion peak at *m*/*z* 641.4073 (calcd for $C_{36}H_{58}O_8Na$, 641.4029) in the HRESIMS. The NMR spectra of **10** were generally similar to those of **1**, suggesting that they had the same basic structure. The major difference between them was that C-26 of **10** was a hydroxymethylene group (δ_C 67.3 (t)) and not a methyl group as in **1**. The NOE correlations and the chemical shifts of the C-17, C-21, C-23, and H-3 signals suggested that H-3 was of β-orientation and C-21 of *S* configuration. When compound **10** was treated with boron trifluoride diethyl etherate in $CHCl_3$, compounds **10a** and **22** were produced. Thus, the structure of **10** was determined to be as shown in Figure 1.

The structures of compounds **11** and **14–16** were determined to be as shown in Figure 1 on the basis of their spectral data and their comparison in an analogous manner as used for the structural elucidation of **2**, **3**, and **7–9**.

Compound **12** was obtained as colorless prisms. Its molecular formula was determined to be $C_{36}H_{58}O_8$ by the $[M+Na]^+$ ion peak at *m*/*z* 641.4077 (calcd for $C_{36}H_{58}O_8Na$, 641.4029) in the HRESIMS. The NMR data suggested that **12** was a stereoisomer of **10** at C-3. The X-ray crystallographic analysis (Fig. 7) determined the relative configuration of **12** to be as shown in Figure 1.

Compound **13** was isolated as an amorphous solid. Its molecular formula of $C_{36}H_{60}O_8$ was determined by the HRESIMS ion peak at *m*/*z* 643.4227 (calcd for $C_{36}H_{60}O_8Na$, 643.4186). The NMR spectra of **13** were very similar to those of **10**, suggesting that they had the same basic structure. The difference observed between **10** and **13** was analogous to that observed between **2** and **5**, implying that **13** had an isovaleryl ester side chain of α-orientation at C-3. Hydrogenation of **10** with Pd–C afforded a product, whose spectral data were identical to those of **13**. Thus, **13** had the structure shown in Figure 1.

Compound **17** was isolated as an amorphous solid. Its molecular formula of $C_{37}H_{62}O_8$ was determined by the $[M+Na]^+$ ion peak at *m*/*z* 657.4379 (calcd for $C_{37}H_{62}O_8Na$, 657.4342) in the HRESIMS. The NMR spectra of **17** were very similar to those of **14**, suggesting that they had the same basic structure. The difference observed between **14** and **17** was analogous to that observed

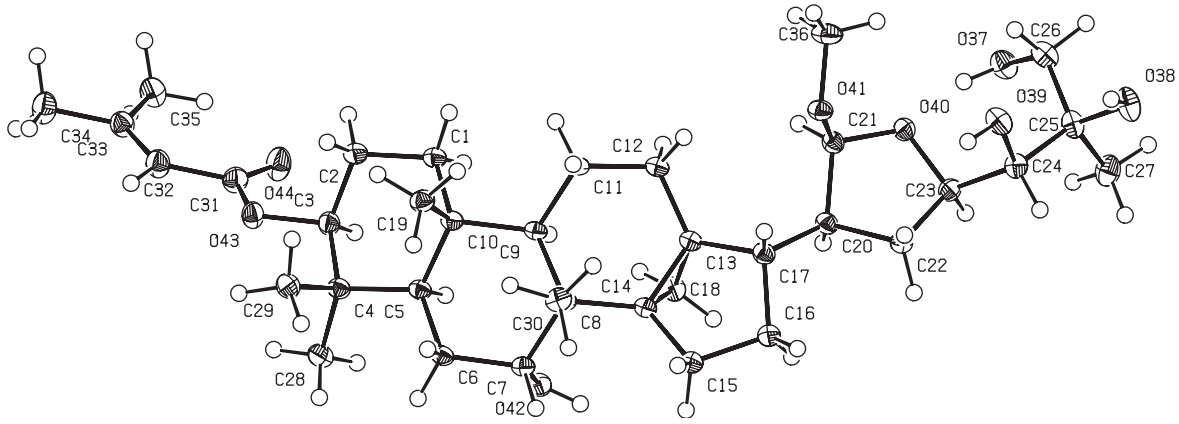


Figure 7. Crystal structure of compound **12**.

between **10** and **13**, showing that **17** had an isovaleryloxy group of α-orientation at C-3. The hydrogenation product of **14** with Pd–C was shown to be identical to natural **17** by comparison of the spectral data. Thus, **17** was shown to have the structure given in Figure 1.

Compound **18** was isolated as an amorphous solid. Its molecular formula was determined to be $C_{36}H_{56}O_6$ by the $[M+Na]^+$ ion peak at *m*/*z* 607.4012 (calcd for $C_{36}H_{56}O_6Na$, 607.3975) in the HRESIMS. The NMR spectra of **18** were generally similar to those of **1**, implying that **18** was also an apotirucallane triterpenoid of the same series. Analysis of the ^{13}C NMR and HMBC spectra revealed a double bond between the C-25 quaternary carbon and the C-26 methylene carbon. The NOE correlations and the chemical shift values of the key C-17, C-21, and H-3 signals were in good agreement with those of the compounds of this series having H-3 of β-orientation and C-21 of *R* configuration. Thus, the structure of **18** was determined to be as shown in Figure 1.

Compound **19** was isolated as an amorphous solid. Its molecular formula of $C_{36}H_{56}O_6$ was determined by the HRESIMS ion peak at *m*/*z* 585.4200 $[M+H]^+$ (calcd for $C_{36}H_{57}O_6$, 585.4155). The HMBC and COSY spectra of **19** were very similar to those of **18**, implying that they had the same gross structure. The difference observed between **18** and **19** was analogous to that observed between **1** and **3**, suggesting that they were stereoisomers at C-3. Its NOESY spectrum, chemical shifts of C-17, C-21, and C-23 resonances, and the coupling constants of the H-3 signal demonstrated that **19** had the structure shown in Figure 1.

Compound **20** was isolated as an amorphous solid. Its

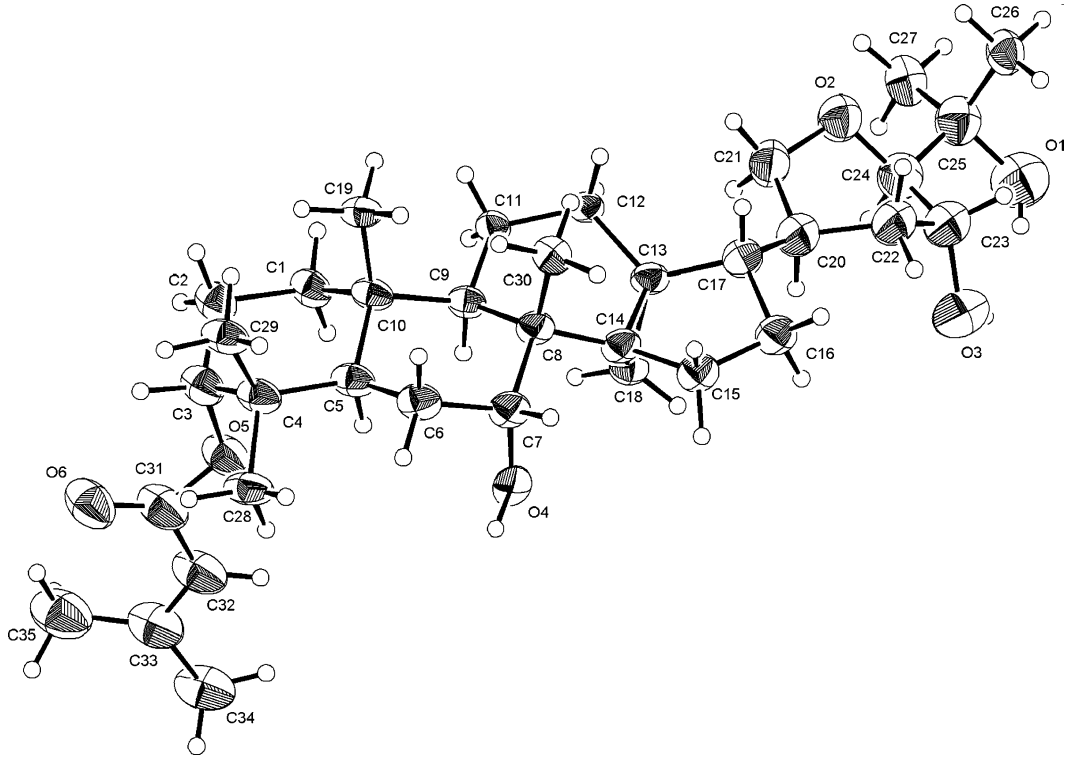


Figure 8. Crystal structure of compound **21**.

Table 3. Cytotoxicity of compounds **1–23** against P-388 leukemia cells

Compound	IC_{50} (μg/mL)	Compound	IC_{50} (μg/mL)	Compound	IC_{50} (μg/mL)
1	6.5	**9**	5.8	**17**	6.7
2	6.2	**10**	6.4	**18**	5.3
3	6.3	**11**	6.9	**19**	5.8
4	7.7	**12**	6.0	**20**	5.9
5	7.8	**13**	6.1	**21**	6.2
6	7.8	**14**	6.7	**22**	0.26
7	6.2	**15**	6.6	**23**	9.9
8	6.4	**16**	6.8	Mitomycin C	0.029

molecular formula was determined to be $C_{36}H_{58}O_6$ by the $[M+H]^+$ ion peak at *m/z* 587.4296 (calcd for $C_{36}H_{59}O_6$, 587.4312) in the HRESIMS. The NMR spectra of **20** were very similar to those of **18**. The only difference between them was analogous to that observed between **1** and **4** and was ascribed to the difference in the side chain at C-3: the signals due to an isovaleryl ester side chain were observed in **20**. Thus, the structure of **20** was determined to be as shown in Figure 1.

Compound **21** was isolated as colorless prisms. Its molecular formula was determined to be $C_{35}H_{56}O_6$ by the $[M+Na]^+$ ion peak at *m/z* 595.4011 (calcd for $C_{35}H_{56}O_6Na$, 595.3975) in the HRESIMS. The NMR spectra of **21** were similar to those of **1**, demonstrating that **21** had the same apotirucallane skeleton as **1**. The NMR spectra of **1** and **21** revealed that the difference between **1** and **21** was only in the side chain at C-17. Compound **1** had an acetal methine group at C-21, whereas **21** had a methylene group (δ_C 70.7) at C-21. In the HMBC spectrum of **21**, the correlations between the methine carbon at δ 86.6 (C-24) and the methylene protons at δ 3.40 (dd, $J=2.4$, 11.6 Hz, H-21α) and δ 4.10 (d, $J=11.6$ Hz, H-21β) suggested that C-21 was linked to C-24 via an oxygen bridge to form a cyclic ether. The coupling constant ($J=$ 9.1 Hz) between H-23 and H-24 suggested their anti-periplanar relation. The NOESY spectra and the X-ray analysis revealed that the configuration at C-23 and that at C-24 were both *R* (Fig. 8). Thus, the structure of **21** was determined to be as shown in Figure 1.

Compound **22** was obtained as an amorphous solid. By the $[M+Na]^+$ ion peak at *m/z* 641.4037 (calcd for $C_{36}H_{58}O_8Na$, 641.4029) in the HRESIMS, its molecular formula was determined to be $C_{36}H_{58}O_8$. The NMR spectra of **22** were generally similar to those of **10**, though they showed no resonances ascribable to the 14,18-cyclopropane ring, and instead, had an olefinic proton signal at δ 5.45 (br s, H-15) and a methyl signal at δ 1.08 (s, H_3-18). Analysis of the HMBC spectrum revealed the presence of a tertiary methyl group at C-13 and a double bond between C-14 and C-15. The NOESY spectrum of **22** showed correlations between H-9/H_3-18 and between H_3-18/H-20, indicating that the C-18 methyl group was of α-orientation. The NOE correlations between H-17/H-21, H_3-18/H-20, H_3-18/H-21, and H_3-18/H_3CO-21 indicated its 20*S* configuration. Since compound **22** was obtained by acid treatment of **10**, the configuration at C-24 was assigned to be *S*. Thus, the structure of **22** was determined to be as shown in Figure 1.

Compound **23** was obtained as an amorphous solid. Its molecular formula was determined to be $C_{36}H_{58}O_8$ by the $[M+Na]^+$ ion peak at *m/z* 641.4061 (calcd for $C_{36}H_{58}O_8Na$, 641.4029) in the HRESIMS. The difference in the spectral data between **22** and **23** revealed that **23** had the structure shown in Figure 1.

Apotirucallane-triterpenoids have been found in plants of the families Simaroubaceae,[6–8] Rutaceae,[9,10] and Meliaceae.[11–17] Previous studies revealed that many triterpene glucosides with a 14,18-cycloapotirucallane skeleton exhibited cytotoxicity against human cancer cell lines.[16,17] In the present study, compounds **1–23** were evaluated for their cytotoxic activity by using P-388 murine leukemia cells. The results are shown in Table 3. Mitomycin C was used as a control. All the compounds exhibited moderate activities, and of them, compound **22** was the most active with an IC_{50} value of 0.26 μg/mL.

3. Experimental

3.1. General

Optical rotations were measured on a JASCO DIP-360 digital polarimeter, UV spectra on a Hitachi 557 spectrophotometer, IR spectra on a Perkin-Elmer 1710 spectrophotometer, mass spectra on a Micromass LCT spectrometer, and NMR spectra on Bruker DRX-500 and AV-600 spectrometers at 300 K. ^1H chemical shifts in $CDCl_3$ or pyridine-d_5 were referenced to the residual $CHCl_3$ (7.26 ppm) or pyridine-d_4 (7.21 ppm); ^{13}C chemical shifts were referenced to the solvent ($CDCl_3$, 77.03 ppm; pyridine-d_5, 135.5 ppm). Preparative HPLC was performed on a Shimadzu LC-6AD system equipped with a SPD-10A UV detector (at 205 nm) and a reverse-phase column, Wakosil-II 5C18HG prep (5 μm, 20×250 mm), by using a mixed solvent system of MeOH–H_2O or MeCN–H_2O, at a flow rate of 10 mL/min. X-ray single crystal analysis was carried out on Mac Science DIP and Bruker AXS SMART APEX diffractometers with Mo Kα radiation ($\lambda=$ 0.71073 Å).

3.2. Plant material

The seeds, leaves, and stems of *C. sinensis* were collected in Jilin Province, China, in September 2000, and the botanical origin was identified by Professor Soo-Cheol Kim of the Agricultural College of Yanbian University, China. A voucher specimen (00CHI002-004) has been deposited in the Herbarium of Tokyo University of Pharmacy and Life Science.

3.3. Extraction and isolation

Dried and powdered seeds of *C. sinensis* (530 g) were extracted with hot MeOH (4×500 mL). The combined MeOH extracts were concentrated under reduced pressure to give a residue (108 g), which was placed on a column of Diaion HP-20 (325 g), and fractionated into five fractions by eluting with H_2O, H_2O–MeOH (1/1), H_2O–MeOH (1/4), MeOH, and acetone (each 3.2 L). The residue of the MeOH fraction (10.7 g) was subjected to silica gel (107 g) column chromatography eluting with $CHCl_3$–hexane (1/1), $CHCl_3$–MeOH (20/1), and MeOH (each 500 mL). The $CHCl_3$–MeOH (20/1) eluate (1.6 g) was then subjected to activated charcoal (5.0 g) column chromatography eluting with $CHCl_3$–MeOH (1/9), $CHCl_3$–MeOH (1/1), and $CHCl_3$ (each 250 mL). The $CHCl_3$–MeOH (1/9) eluate (690 mg) was further subjected to ODS HPLC eluted with MeOH–H_2O (80/20) to afford two fractions. After evaporation of the solvent, those two fractions were each purified by repeated ODS HPLC using MeCN–H_2O (55/45) and then using MeOH–H_2O (75/25) to give **1** (4.2 mg) and **4** (7.9 mg), respectively. By the same procedure, the $CHCl_3$–MeOH (1/1) eluate from the silica gel column chromatography (467 mg) yielded **4** (1.6 mg).

Dried and powdered leaves of *C. sinensis* (10.3 kg) were extracted with hot MeOH (3×230 L). The residue of the MeOH extract (900 g) was placed on a column of Diaion HP-20 (3.0 kg), and fractionated into five fractions by eluting sequentially with H_2O, H_2O–MeOH (1/1), H_2O–MeOH (1/4), MeOH, and acetone (each 28 L). The fraction eluted with H_2O–MeOH (1/4) (150 g) was subjected to activated charcoal (400 g) column chromatography eluting sequentially with MeOH, $CHCl_3$–MeOH (1/9), and $CHCl_3$–MeOH (1/1) (each 22 L). The $CHCl_3$–MeOH (1/1) eluate (27 g) was further subjected to silica gel (265 g) column chromatography eluting sequentially with $CHCl_3$–EtOAc (5/1), $CHCl_3$–MeOH (20/1), and $CHCl_3$–MeOH (10/1) (each 1.3 L). The $CHCl_3$–EtOAc (5/1) eluate (8.5 g) was further subjected to ODS HPLC eluting with MeOH–H_2O (80/20) to afford nine fractions. After evaporation of the solvent, those nine fractions were each purified by repeated ODS HPLC using MeCN–H_2O (60/40) and MeOH–H_2O (75/25) to give **15** (68.9 mg), **2** (135.9 mg), **3** (18.6 mg), **18** (76.9 mg), **7** (149.4 mg), **10** (28.0 mg), **14** (25.2 mg), **1** (32.5 mg), and **8** (9.8 mg), respectively. The $CHCl_3$–MeOH (20/1) eluate from the silica gel column chromatography (4.7 g) was further subjected to ODS HPLC eluted with MeOH–H_2O (80/20) to afford five fractions. After evaporation of the solvent, those five fractions were each purified by ODS HPLC using MeCN–H_2O (60/40) and MeOH–H_2O (75/25) to give **1** (10.2 mg), **10** (68.0 mg), **23** (2.2 mg), **22** (3.3 mg), and **11** (28.7 mg), respectively. The MeOH eluate (329 g) from the Diaion HP-20 column chromatography was subjected to silica gel (3.3 kg) column chromatography eluting sequentially with $CHCl_3$–hexane (1/1), $CHCl_3$–EtOAc (5/1), $CHCl_3$–MeOH (20/1), and MeOH (each 16 L). The $CHCl_3$–MeOH (20/1) eluate (71 g) was then passed though an activated charcoal column (210 g) and the column was eluted with $CHCl_3$–MeOH (1/9), $CHCl_3$–MeOH (1/1), and $CHCl_3$ (each 11 L), sequentially. The $CHCl_3$–MeOH (1/9) eluate (30 g) was further subjected to ODS HPLC eluting with MeOH–H_2O (80/20) to afford eleven fractions. After evaporation of the solvent, those eleven fractions were each purified by repeated ODS HPLC using MeCN–H_2O (60/40) and MeOH–H_2O (75/25) to give **10** (181.0 mg), **14** (24.5 mg), **1** (66.3 mg), **12** (43.0 mg), **15** (17.2 mg), **16** (14.1 mg), **21** (17.4 mg), **2** (3.3 mg), **3** (4.2 mg), **18** (6.8 mg), and **7** (19.7 mg), respectively. The $CHCl_3$–MeOH (1/1) eluate (24 g) was further subjected to ODS HPLC eluted with MeOH–H_2O (80/20) to afford four fractions. After evaporation of the solvent, those four fractions were each purified by repeated ODS HPLC using MeCN–H_2O (55/45) and MeOH–H_2O (75/25) to give **10** (7.8 mg), **14** (8.1 mg), **1** (3.0 mg), and **7** (8.2 mg), respectively.

Dried and powdered stems of *C. sinensis* (3.3 kg) were extracted with hot MeOH (3×80 L). The residue of the MeOH extract (304 g) was placed on a column of Diaion HP-20 (1.0 kg), and fractionated into five fractions by eluting sequentially with H_2O, H_2O–MeOH (1/1), H_2O–MeOH (1/4), MeOH, and acetone (each 9 L). The MeOH fraction (61 g) was passed through an activated charcoal (180 g) column and eluted sequentially with MeOH, $CHCl_3$–MeOH (1/9), and $CHCl_3$–MeOH (1/1) (each 9 L). The $CHCl_3$–MeOH (1/9) eluate (6.2 g) was then subjected to silica gel (62 g) column chromatography eluting sequentially with $CHCl_3$–EtOAc (5/1), $CHCl_3$–MeOH (20/1), and MeOH (each 300 mL). The $CHCl_3$–MeOH (20/1) eluate (1.6 g) was further subjected to ODS HPLC eluted with MeOH–H_2O (80/20) to afford five fractions. After evaporation of the solvent, those five fractions were each purified by repeated ODS HPLC using MeCN–H_2O (60/40) and MeOH–H_2O (75/25) to give **7** (1.3 mg), **1** (22.6 mg), **4** (13.8 mg), **2** (25.0 mg), and **5** (2.2 mg), respectively. The $CHCl_3$–MeOH (1/1) eluate (9.0 g) from the charcoal column was subjected to silica gel (90 g) column chromatography eluting with $CHCl_3$–EtOAc (5/1), $CHCl_3$–MeOH (20/1), and MeOH (each 450 mL). The $CHCl_3$–MeOH (20/1) eluate (1.9 g) was further subjected to ODS HPLC eluting with MeOH–H_2O (80/20) to afford eight fractions. After evaporation of the solvent, those eight fractions were each purified by repeated ODS HPLC using MeCN–H_2O (60/40) and MeOH–H_2O (75/25) to give **13** (2.9 mg), **17** (3.0 mg), **3** (3.3 mg), **18** (3.3 mg), **20** (0.8 mg), **6** (1.1 mg), **9** (2.6 mg), and **19** (2.0 mg), respectively.

The yields of the twenty-three new triterpenoids **1**–**23** separated from *C. sinensis* are summarized below. The seeds of *C. sinensis* gave compounds **1** (4.2 mg, 0.00079%) and **4** (9.5 mg, 0.0018%), the leaves gave compounds **1** (112.0 mg, 0.0011%), **2** (139.2 mg, 0.0014%), **3** (22.8 mg, 0.00022%), **7** (177.3 mg, 0.0017%), **8** (9.8 mg, 0.000095%), **10** (284.8 mg, 0.0028%), **11** (28.7 mg, 0.00028%), **12** (43.0 mg, 0.00042%), **14** (57.8 mg, 0.00056%), **15** (86.1 mg, 0.00084%), **16** (14.1 mg, 0.00014%), **18** (83.7 mg, 0.00081%), **21** (17.4 mg, 0.00017%), **22** (3.3 mg, 0.000032%), and **23** (2.2 mg, 0.000021%), and the stems gave compounds **1** (22.6 mg, 0.00068%), **2** (25.0 mg, 0.00076%), **3** (3.3 mg, 0.00010%), **4** (13.8 mg, 0.00042%), **5** (2.2 mg, 0.000067%), **6** (1.1 mg, 0.000033%), **7** (1.3 mg, 0.000039%), **9** (2.6 mg, 0.000079%), **13** (2.9 mg, 0.000088%), **17** (3.0 mg, 0.000091%), **18** (3.3 mg, 0.00010%), **19** (2.0 mg, 0.000061%), and **20** (0.8 mg, 0.000024%).

3.4. Characteristics of each triterpenoid

3.4.1. Compound 1. Amorphous solid; $[\alpha]_D^{20}$ −52.7 (*c* 0.21, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 218 (4.11); IR (film) ν_{max} cm^{-1}: 3486, 2944, 2871, 1711, 1651, 1566, 1446, 1387, 1282, 1231, 1147, 1098, 1073, 1035, 990, 949, 917, 890, 853, 755, 665; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 625.4056 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_7Na$, 625.4080).

3.4.2. Compound 2. Amorphous solid; $[\alpha]_D^{28}$ −5.8 (*c* 0.12, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 217 (4.06); IR (film) ν_{max} cm^{-1}: 3492, 2942, 2871, 1712, 1651, 1537, 1463, 1445, 1386, 1282, 1231, 1204, 1147, 1072, 1027, 990, 910, 887, 854, 755; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 625.4056 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_7Na$, 625.4080).

3.4.3. Compound 3. Amorphous solid; $[\alpha]_D^{28}$ −7.8 (*c* 0.21, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 218 (4.16); IR (film) ν_{max} cm^{-1}: 3583, 3348, 2922, 2852, 1712, 1642, 1444, 1384, 1261, 1230, 1151, 801; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 625.4082 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_7Na$, 625.4080).

3.4.4. Compound 4. Amorphous solid; $[\alpha]_D^{20}$ −47.0 (*c* 0.38, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3486, 2955, 2871, 1725, 1466, 1389, 1372, 1295, 1258, 1202, 1168, 1120, 1098, 1068, 1034, 989, 950, 910, 873, 756; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 627.4286 ($[M+Na]^+$, calcd for $C_{36}H_{60}O_7Na$, 627.4237).

3.4.5. Compound 5. Amorphous solid; $[\alpha]_D^{24}$ −3.8 (*c* 0.35, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3455, 2951, 2871, 1726, 1587, 1535, 1467, 1388, 1295, 1257, 1201, 1167, 1121, 1094, 1069, 1026, 990; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 627.4255 ($[M+Na]^+$, calcd for $C_{36}H_{60}O_7Na$, 627.4237).

3.4.6. Compound 6. Amorphous solid; $[\alpha]_D^{24}$ −3.1 (*c* 0.06, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3583, 3408, 2925, 2854, 1728, 1587, 1536, 1467, 1389, 1260, 1095, 1028; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 627.4239 ($[M+Na]^+$, calcd for $C_{36}H_{60}O_7Na$, 627.4237).

3.4.7. Compound 7. Amorphous solid; $[\alpha]_D^{20}$ −51.0 (*c* 0.41, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 218 (4.18); IR (film) ν_{max} cm^{-1}: 3583, 3499, 2945, 2871, 1712, 1652, 1446, 1386, 1365, 1348, 1309, 1281, 1231, 1147, 1099, 1074, 1035, 990, 951, 914, 894, 853, 755, 665; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 639.4194 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_7Na$, 639.4237).

3.4.8. Compound 8. Amorphous solid; $[\alpha]_D^{23}$ −7.5 (*c* 0.11, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 217 (4.05); IR (film) ν_{max} cm^{-1}: 3583, 3499, 2941, 2871, 2830, 1712, 1651, 1712, 1651, 1514, 1463, 1447, 1386, 1363, 1280, 1255, 1230, 1204, 1146, 1105, 1072, 1027, 1005, 990, 888, 855, 808, 756, 665; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 639.4212 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_7Na$, 639.4237).

3.4.9. Compound 9. Amorphous solid; $[\alpha]_D^{24}$ −1.8 (*c* 0.13, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 216 (4.09); IR (film) ν_{max} cm^{-1}: 3583, 3347, 2925, 1725, 1712, 1692, 1659, 1643, 1589, 1550, 1537, 1514, 1469, 1443, 1383, 1229, 1149; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 639.4275 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_7Na$, 639.4237).

3.4.10. Compound 10. Amorphous solid; $[\alpha]_D^{20}$ +2.2 (*c* 0.39, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 219 (4.20); IR (film) ν_{max} cm^{-1}: 3442, 2943, 2871, 1705, 1652, 1446, 1387, 1348, 1289, 1232, 1147, 1092, 1072, 1027, 991, 972, 755; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 641.4073 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_8Na$, 641.4029).

3.4.11. Compound 11. Amorphous solid; $[\alpha]_D^{28}$ −4.6 (*c* 0.29, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 221 (4.20); IR (film) ν_{max} cm^{-1}: 3417, 2942, 2872, 1697, 1650, 1513, 1446, 1389, 1354, 1315, 1262, 1230, 1152, 1100, 1067, 1037, 998, 949, 915, 896, 853, 756, 665; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 641.4077 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_8Na$, 641.4029).

3.4.12. Compound 12. Colorless prisms (hexane–EtOAc); mp 241–243 °C; $[\alpha]_D^{28}$ +35.6 (*c* 0.43, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 219 (4.18); IR (film) ν_{max} cm^{-1}: 3584, 3418, 2938, 2871, 1697, 1651, 1556, 1539, 1454, 1387, 1316, 1229, 1151, 1064, 1040, 995, 905, 853, 755; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 641.4077 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_8Na$, 641.4029).

3.4.13. Compound 13. Amorphous solid; $[\alpha]_D^{24}$ −4.0 (*c* 0.14, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3583, 3416, 2928, 2871, 1727, 1659, 1642, 1550, 1536, 1465, 1452, 1388, 1294, 1258, 1201, 1167, 1093, 1028, 991, 905; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 643.4227 ($[M+Na]^+$, calcd for $C_{36}H_{60}O_8Na$, 643.4186).

3.4.14. Compound 14. Amorphous solid; $[\alpha]_D^{20}$ −54.4 (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 218 (4.23); IR (film) ν_{max} cm^{-1}: 3443, 2940, 2871, 1712, 1652, 1567, 1446, 1387, 1348, 1281, 1231, 1147, 1102, 1070, 1034, 990, 950, 914, 895, 873, 854, 805, 755, 665; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 655.4220 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_8Na$, 655.4186).

3.4.15. Compound 15. Amorphous solid; $[\alpha]_D^{28}$ +1.9 (*c* 0.17, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 216 (4.12); IR (film) ν_{max} cm^{-1}: 3408, 2925, 2854, 1714, 1651, 1574, 1454, 1387, 1316, 1261, 1229, 1203, 1150, 1065, 996, 905, 887, 852, 829, 802, 757, 721; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 655.4214 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_8Na$, 655.4186).

3.4.16. Compound 16. Amorphous solid; $[\alpha]_D^{28}$ −4.4 (*c* 0.14, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 221 (4.25); IR (film) ν_{max} cm^{-1}: 3453, 2942, 2872, 1712, 1650, 1513, 1464, 1446, 1388, 1354, 1315, 1261, 1230, 1151, 1102, 1069, 1048, 1030, 998, 949, 895, 866, 852, 803, 756, 666; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 655.4214 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_8Na$, 655.4186).

3.4.17. Compound 17. Amorphous solid; $[\alpha]_D^{24}$ −31.8 (*c*

0.10, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3357, 2928, 1718, 1653, 1641, 1549, 1386, 1172, 1073, 1042; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 657.4379 ($[M+Na]^+$, calcd for $C_{37}H_{62}O_8Na$, 657.4342).

3.4.18. Compound 18. Amorphous solid; $[\alpha]_D^{28}$ −58.9 (*c* 0.36, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 221 (4.19); IR (film) ν_{max} cm^{-1}: 3583, 3441, 2926, 2870, 1712, 1651, 1555, 1537, 1445, 1386, 1260, 1230, 1147, 1098, 1072, 1028, 991, 910, 876, 803, 755; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 607.4012 ($[M+Na]^+$, calcd for $C_{36}H_{56}O_6Na$, 607.3975).

3.4.19. Compound 19. Amorphous solid; $[\alpha]_D^{24}$ −5.1 (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 215 (4.03); IR (film) ν_{max} cm^{-1}: 3583, 3409, 2926, 2855, 1725, 1712, 1693, 1659, 1643, 1632, 1588, 1550, 1537, 1514, 1464, 1444, 1384, 1229, 1150, 1069, 1029; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 585.4200 ($[M+H]^+$, calcd for $C_{36}H_{57}O_6$, 585.4155).

3.4.20. Compound 20. Amorphous solid; $[\alpha]_D^{24}$ −71.8 (*c* 0.04, $CHCl_3$); IR (film) ν_{max} cm^{-1}: 3583, 3416, 2957, 2926, 2869, 1726, 1659, 1643, 1584, 1554, 1537, 1469, 1444, 1389, 1294, 1029; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 587.4296 ($[M+H]^+$, calcd for $C_{36}H_{59}O_6$, 587.4312).

3.4.21. Compound 21. Colorless prisms (hexane–EtOAc); mp 180–185 °C; $[\alpha]_D^{28}$ −8.1 (*c* 0.37, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 220 (4.16); IR (film) ν_{max} cm^{-1}: 3583, 3387, 2960, 2921, 2851, 1694, 1651, 1463, 1445, 1384, 1260, 1232, 1148, 1070, 1024, 934, 859, 800, 758; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 595.4011 ($[M+Na]^+$, calcd for $C_{35}H_{56}O_6Na$, 595.3975).

3.4.22. Compound 22. Amorphous solid; $[\alpha]_D^{24}$ −111 (*c* 0.17, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 213 (4.12); IR (film) ν_{max} cm^{-1}: 3583, 3408, 2936, 1711, 1693, 1659, 1643, 1631, 1587, 1550, 1537, 1514, 1463, 1443, 1384, 1231, 1147, 1034, 998; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 641.4037 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_8Na$, 641.4029).

3.4.23. Compound 23. Amorphous solid; $[\alpha]_D^{23}$ −53.1 (*c* 0.09, $CHCl_3$); UV (MeOH) λ_{max} nm (log ε): 221 (4.20); IR (film) ν_{max} cm^{-1}: 3417, 2929, 2871, 2856, 1712, 1651, 1567, 1463, 1445, 1386, 1259, 1230, 1147, 1119, 1099, 1069, 1036, 998, 967, 853, 803, 756; ^1H and ^{13}C NMR: refer to Tables 1 and 2; HRESIMS *m/z* 641.4061 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_8Na$, 641.4029).

3.5. Identification of structural relations between the triterpenoids by chemical transformations

3.5.1. Treatment of 1 with boron trifluoride diethyl etherate. To a solution of compound **1** (10 mg) in $CHCl_3$ (2 mL) was added boron trifluoride diethyl etherate (1 μL), and the mixture was stirred at room temperature for 30 min. The mixture was diluted with $CHCl_3$, washed successively with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by ODS HPLC using MeCN–H_2O (85/15) to give **1a** (1.4 mg).

Compound **1a**. Amorphous solid; $[\alpha]_D^{25}$ −77.4 (*c* 0.07, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 5.78 (t-like, 1H, *J*=1.3 Hz, H-2′), 5.46 (d, 1H, *J*=2.4 Hz, H-15), 4.78 (d, 1H, *J*=2.8 Hz, H-21), 4.69 (t-like, 1H, *J*=2.7 Hz, H-3), 4.12 (br s, 1H, H-23), 3.90 (br s, 1H, H-7), 3.34 (d, 1H, *J*=0.9 Hz, H-24), 3.33 (s, 3H, OCH_3-21), 2.34 (m, 1H, H-20), 2.18 (m, 1H, H-16β), 2.17 (s, 3H, H-5′), 2.08 (m, 1H, H-16α), 2.01 (m, 1H, H-5), 2.00 (m, 1H, H-9), 1.91 (m, 1H, H-2β), 1.90 (s, 3H, H-4′), 1.78 (dt, 1H, *J*=7.5, 10.8 Hz, H-17), 1.75 (m, 1H, H-12β), 1.73 (m, 1H, H-11β), 1.72 (m, 2H, H-6α, H-22α), 1.68 (m, 1H, H-6β), 1.61 (m, 1H, H-2α), 1.60 (m, 1H, H-22β), 1.51 (m, 1H, H-12α), 1.50 (m, 1H, H-11α), 1.37 (m, 1H, H-1β), 1.34 (s, 3H, H-27), 1.26 (s, 3H, H-26), 1.18 (m, 1H, H-1α), 1.08 (s, 3H, H-18), 1.06 (s, 3H, H-30), 0.91 (s, 6H, H-19, H-29), 0.86 (s, 3H, H-28); ^1H NMR (500 MHz, pyridine-d_5) δ 5.63 (br s, 1H, H-2′), 5.44 (d, 1H, *J*=2.2 Hz, H-15), 4.97 (m, 2H, H-3, H-21), 4.41 (br s, 1H, H-23), 4.09 (br s, 1H, H-7), 3.55 (br s, 1H, H-24), 3.44 (s, 3H, OCH_3-21), 2.71 (br t, 1H, *J*=11.0 Hz, H-20), 2.49 (m, 1H, H-5), 2.34 (m, 1H, H-9), 2.22 (s, 3H, H-5′), 2.18 (m, 1H, H-16β), 2.00 (m, 1H, H-17), 1.99 (m, 1H, H-2β), 1.96 (m, 1H, H-16α), 1.88 (m, 2H, H-22α, H-22β), 1.87 (m, 1H, H-6α), 1.83 (m, 2H, H-12α, H-12β), 1.79 (m, 1H, H-6β), 1.78 (m, 1H, H-1β), 1.76 (m, 1H, H-2α), 1.73 (m, 1H, H-11β), 1.61 (s, 3H, H-4′), 1.59 (s, 3H, H-27), 1.51 (s, 3H, H-26), 1.50 (m, 1H, H-11α), 1.40 (m, 1H, H-1α), 1.15 (s, 3H, H-18), 1.12 (s, 3H, H-30), 1.02 (s, 3H, H-28), 0.92 (s, 3H, H-19), 0.90 (s, 3H, H-29); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6 (s, C-1′), 162.1 (s, C-14), 155.9 (s, C-3′), 119.6 (d, C-15), 117.0 (d, C-2′), 100.4 (d, C-21), 77.5 (d, C-3), 73.9 (s, C-25), 72.3 (d, C-24), 72.2 (d, C-7), 65.6 (d, C-23), 54.4 (q, OCH_3-21), 54.1 (d, C-17), 46.7 (s, C-13), 44.4 (s, C-8), 41.9 (d, C-5), 41.6 (d, C-9), 37.6 (s, C-10), 36.3 (s, C-4), 33.8 (t, C-16), 33.4 (t, C-1), 33.4 (d, C-20), 33.3 (t, C-12), 31.2 (t, C-22), 28.1 (q, C-27), 27.8 (q, C-28), 27.8 (q, C-30), 27.4 (q, C-4′), 24.8 (q, C-26), 23.6 (t, C-6), 22.8 (t, C-2), 21.8 (q, C-29), 20.3 (q, C-5′), 19.5 (q, C-18), 16.5 (t, C-11), 15.3 (q, C-19); ^{13}C NMR (125 MHz, pyridine-d_5) δ 166.3 (s, C-1′), 162.7 (s, C-14), 156.0 (s, C-3′), 119.3 (d, C-15), 117.2 (d, C-2′), 100.5 (d, C-21), 77.2 (d, C-3), 73.4 (d, C-24), 73.2 (s, C-25), 72.5 (d, C-7), 65.9 (d, C-23), 54.7 (d, C-17), 54.1 (q, OCH_3-21), 46.9 (s, C-13), 44.5 (s, C-8), 42.3 (d, C-9), 42.3 (d, C-5), 37.9 (s, C-10), 36.6 (s, C-4), 34.3 (t, C-16), 34.2 (d, C-20), 34.0 (t, C-1), 32.6 (t, C-12), 29.9 (t, C-22), 28.2 (q, C-30), 28.0 (q, C-28), 27.7 (q, C-27), 27.0 (q, C-26), 26.9 (q, C-4′), 25.2 (t, C-6), 23.3 (t, C-2), 22.0 (q, C-29), 20.2 (q, C-5′), 19.5 (q, C-18), 16.9 (t, C-11), 15.5 (q, C-19); HRESIMS *m/z* 625.4035 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_7Na$, 625.4080).

3.5.2. Treatment of 2 with boron trifluoride diethyl etherate. Compound **2** (10 mg) was treated with boron trifluoride diethyl etherate (1 μL) in the same manner as described for **1** to give a product (1.2 mg); $[\alpha]_D^{25}$ −75.7 (*c* 0.06, $CHCl_3$). By comparison of the ^1H and ^{13}C NMR spectra, HRESIMS, and optical rotations, this product was shown to be identical to **1a** from **1**.

3.5.3. Treatment of 7 with boron trifluoride diethyl etherate. Compound **7** (25 mg) was treated with boron trifluoride diethyl etherate (1 μL) in the same manner as described for **1** to give **7a** (3.5 mg).

Compound **7a**. Amorphous solid; $[\alpha]_D^{25}$ −64.4 (*c* 0.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (br s, 1H, H-2′), 5.45 (d, 1H, J=1.8 Hz, H-15), 4.82 (d, 1H, J=2.5 Hz, H-21), 4.69 (br s, 1H, H-3), 4.15 (br s, 1H, H-23), 3.89 (br s, 1H, H-7), 3.36 (br s, 1H, H-24), 3.34 (s, 3H, OCH_3-21), 3.33 (s, 3H, OCH_3-25), 2.34 (m, 1H, H-20), 2.18 (m, 1H, H-16β), 2.17 (s, 3H, H-5′), 2.08 (m, 1H, H-16α), 2.01 (m, 1H, H-5), 2.00 (m, 1H, H-9), 1.91 (m, 1H, H-2β), 1.89 (s, 3H, H-4′), 1.78 (m, 1H, H-17), 1.73 (m, 3H, H-11β, H-12β, H-22α), 1.72 (m, 1H, H-6α), 1.68 (m, 1H, H-6β), 1.61 (m, 1H, H-2α), 1.58 (m, 1H, H-22β), 1.51 (m, 1H, H-12α), 1.50 (m, 1H, H-11α), 1.38 (m, 1H, H-1β), 1.35 (s, 3H, H-27), 1.31 (s, 3H, H-26), 1.18 (m, 1H, H-1α), 1.06 (s, 3H, H-18), 1.05 (s, 3H, H-30), 0.90 (s, 6H, H-19, H-29), 0.85 (s, 3H, H-28); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6 (s, C-1′), 162.2 (s, C-14), 155.8 (s, C-3′), 119.6 (d, C-15), 117.0 (d, C-2′), 100.7 (d, C-21), 78.7 (s, C-25), 77.1 (d, C-3), 74.0 (d, C-24), 72.2 (d, C-7), 65.1 (d, C-23), 54.4 (d, C-17), 54.4 (q, OCH_3-21), 49.8 (q, OCH_3-25), 46.7 (s, C-13), 44.4 (s, C-8), 41.8 (d, C-5), 41.7 (d, C-9), 37.6 (s, C-10), 36.3 (s, C-4), 33.8 (t, C-16), 33.4 (t, C-1), 33.4 (t, C-12), 33.2 (d, C-20), 31.6 (t, C-22), 27.8 (q, C-28), 27.8 (q, C-30), 27.4 (q, C-4′), 23.6 (t, C-6), 22.8 (t, C-2), 22.2 (q, C-26), 21.8 (q, C-29), 21.6 (q, C-27), 20.3 (q, C-5′), 19.5 (q, C-18), 16.5 (t, C-11), 15.3 (q, C-19); HRESIMS *m/z* 639.4218 ($[M+Na]^+$, calcd for $C_{37}H_{60}O_7Na$, 639.4237).

3.5.4. Treatment of 10 with boron trifluoride diethyl etherate. Compound **10** (15 mg) was treated with boron trifluoride diethyl etherate (1 μL) in the same manner as described for **1** to give **10a** (2.2 mg) and **22** (2.0 mg, $[\alpha]_D^{25}$ −108 (*c* 0.10, $CHCl_3$)), which was identical to natural **22** by comparison of their ^1H and ^{13}C NMR spectra, HRESIMS, and optical rotations.

Compound **10a**. Amorphous solid; $[\alpha]_D^{25}$ −77.1 (*c* 0.11, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (br s, 1H, H-2′), 5.45 (br s, 1H, H-15), 4.80 (d, 1H, J=2.8 Hz, H-21), 4.70 (br s, 1H, H-3), 4.12 (br s, 1H, H-23), 3.90 (br s, 1H, H-7), 3.72 (d, 1H, J=11.1 Hz, H-26a), 3.62 (d, 1H, J=11.1 Hz, H-26b), 3.54 (br s, 1H, H-24), 3.35 (s, 3H, OCH_3-21), 2.34 (m, 1H, H-20), 2.18 (m, 1H, H-16β), 2.17 (s, 3H, H-5′), 2.08 (m, 1H, H-16α), 2.01 (m, 1H, H-5), 2.00 (m, 1H, H-9), 1.91 (m, 1H, H-2β), 1.90 (s, 3H, H-4′), 1.78 (m, 1H, H-17), 1.73 (m, 3H, H-11β, H-12β, H-22α), 1.72 (m, 1H, H-6α), 1.68 (m, 1H, H-6β), 1.62 (m, 1H, H-22β), 1.61 (m, 1H, H-2α), 1.52 (m, 1H, H-12α), 1.50 (m, 1H, H-11α), 1.38 (m, 1H, H-1β), 1.32 (s, 3H, H-27), 1.18 (m, 1H, H-1α), 1.08 (s, 3H, H-18), 1.06 (s, 3H, H-30), 0.91 (s, 6H, H-19, H-29), 0.86 (s, 3H, H-28); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5 (s, C-1′), 162.2 (s, C-14), 155.8 (s, C-3′), 119.5 (d, C-15), 117.0 (d, C-2′), 100.4 (d, C-21), 77.3 (d, C-3), 75.1 (s, C-25), 72.3 (d, C-7), 71.9 (d, C-24), 67.2 (t, C-26), 65.8 (d, C-23), 54.6 (q, OCH_3-21), 54.1 (d, C-17), 46.7 (s, C-13), 44.4 (s, C-8), 41.9 (d, C-5), 41.7 (d, C-9), 37.6 (s, C-10), 36.3 (s, C-4), 33.9 (t, C-16), 33.7 (d, C-20), 33.4 (t, C-1), 33.3 (t, C-12), 31.6 (t, C-22), 27.8 (q, C-30), 27.7 (q, C-28), 27.4 (q, C-4′), 23.6 (t, C-6), 22.8 (t, C-2), 22.5 (q, C-27), 21.8 (q, C-29), 20.3 (q, C-5′), 19.5 (q, C-18), 16.5 (t, C-11), 15.3 (q, C-19); HRESIMS *m/z* 641.4085 ($[M+Na]^+$, calcd for $C_{36}H_{58}O_8Na$, 641.4029).

3.5.5. Hydrogenation of 1, 2, 10, and 14. Compounds **1**, **2**, **10**, and **14** (5.0 mg) were each dissolved in MeOH (2 mL) and hydrogenated over 10% Pd–C (10 mg) in a flask equipped with a hydrogen-filled balloon for 7 h. After removal of the catalyst by filtration, each filtrate was concentrated to give products (each 5.0 mg), which were identified as **4**, **5**, **13**, and **17**, respectively, by comparison of the ^1H and ^{13}C NMR spectra, and HRESIMS.

3.6. X-ray crystallographic studies of 12 and 21

Crystal data for **12**: $C_{36}H_{58}O_8$, M=618.82, 0.50×0.50×0.50 mm^3, orthorhombic, $P2_12_12_1$, a=10.62500(10) Å, b=14.34700(10) Å, c=22.1910(2) Å, V=3382.73(5) $Å^3$, Z=4, D_x=1.215 Mg m^{-3}, μ(Mo Kα)=0.084 mm^{-1}, 4166 reflection measured, 4162 unique reflections, R=0.0352, R_w=0.0936.

Crystal data for **21**: $C_{35}H_{56}O_6$, M=572.80, 0.34×0.24×0.19 mm^3, tetragonal, $P4_12_12$, a=22.8180(9) Å, b=22.8180(9) Å, c=31.7048(17) Å, V=16507.5(13) $Å^3$, Z=20, D_x=1.152 Mg m^{-3}, μ(Mo Kα)=0.077 mm^{-1}, 114761 reflection measured, 19773 unique reflections, R=0.0880, R_w=0.2599.

The structure was determined by the direct method using the maXus crystallographic software package[18] and the refinement was carried out by the program SHELXL-97.[19]

CCDC 248094-248095 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

3.7. Cytotoxicity assays

Evaluation of cytotoxicity against P-388 murine leukemia cells were assessed as described previously.[20]

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Synthesis of diastereoisomeric pairs of novel analogues of d4T having an isochroman glycon moiety; their enzymatic kinetic resolution, their enantiopure synthesis, molecular modeling and NMR structural study

Christophe Len,[a,b,*] Serge Pilard,[c] Emmanuelle Lipka,[d] Claude Vaccher,[d] Marie-Pierre Dubois,[e] Yana Shrinska,[e] Vinh Tran[e] and Claude Rabiller[e]

[a]*Synthèse et Réactivité des Substances Naturelles, UMR 6514 CNRS, FR 2703, Université de Poitiers, 40, avenue du Recteur Pineau, F-86022 Poitiers cedex, France*
[b]*Laboratoire des Glucides, FRE 2779 CNRS, Université de Picardie, 33, rue Saint Leu, F-80039 Amiens, France*
[c]*Plate-Forme Analytique, Université de Picardie, 33, rue Saint Leu, F-80039 Amiens, France*
[d]*Laboratoire de Chimie Analytique, EA 1043, Université de Lille 2, BP 83-3, rue du Pr. Laguesse, F-59006 Lille, France*
[e]*Biotechnologie, Biocatalyse et Biorégulation, UMR 6204 CNRS, Université de Nantes, 2, rue de la Houssinière, F-44322 Nantes cedex 03, France*

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Abstract—An efficient route, starting from 2-bromobenzaldehyde, is described to synthesize racemic diastereoisomeric thymine derivatives of isochroman, which are aromatic analogues of Stavudine, an approved anti-HIV drug. The relative configurations were determined by NOE proton NMR experiments in connection with molecular modeling. Following the separation of the latter diastereoisomers, kinetic resolution was achieved via a transesterification reaction catalyzed by lipases. Using this method, moderate ee's were obtained (0.74–0.98). Thus, an alternative strategy starting from D-mannitol was proposed to provide pure enantiomers. The attribution of absolute configurations was made by chemical filiation on the basis of the configurations obtained from D-mannitol. The structural attributions were confirmed by studying the behavior of proton NMR shifts of the corresponding isochroman Mosher's esters.

1. Introduction

Natural nucleosides are of great biological importance in metabolic pathways.[1] For many years, the typical structure of nucleosides was described by scientists as two molecular fragments: D-ribose or D-deoxyribose as the sugar moiety connected by a β-glycosyl linkage to different heterocyclic bases such as thymine, uracil, cytosine, adenine and guanine. This dogma disappeared when different groups reported the isolation of natural nucleosides having D-arabinose or 2′,3′-didehydro-2′,3′-dideoxy-D-glucose instead of the D-ribose part (Fig. 1). In 1950, Bergmann et al. reported the isolation of spongouridine (**1**) and spongothymidine (**2**) from marine Caribbean sponges *Cryptotheca crypta*, which had D-arabinose as the sugar

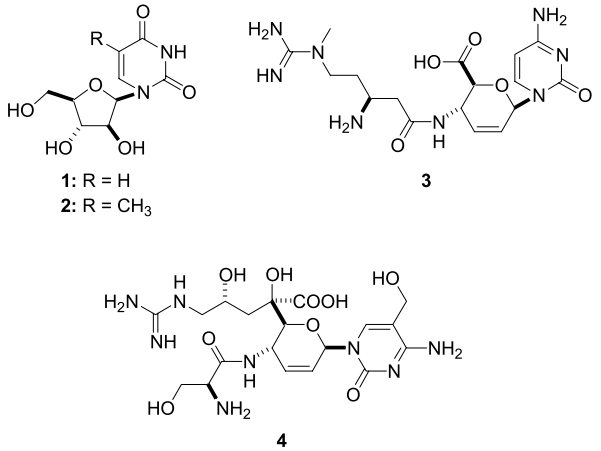

Figure 1. Natural compounds having a nucleoside moiety.

Keywords: d4T Analogue synthesis; Lipase resolution; Enantiopure synthesis; NMR configuration attribution; Molecular modeling.
* Corresponding author. Tel.: +33 549366389; fax: +33 549453501; e-mail: christophe.len@univ-poitiers.fr

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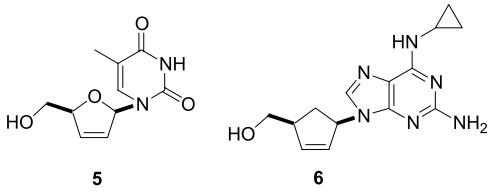


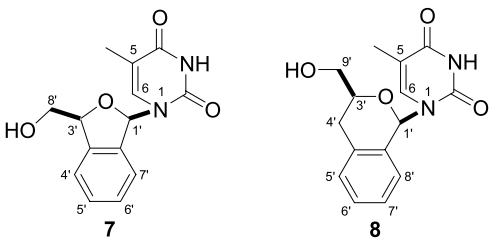
5 6

Figure 2. Stavudine **5** and abacavir **6**.

moiety.[2] In 1958, Y. Yonehara et al. reported the discovery of a metabolite of *Streptomyces griseochromogenes*, Blasticidin S (**3**),[3] which controls rice blast *Pyricularia oryzae*.[4] In 1978, K. Suetomi et al. reported the isolation of antifungal mildiomycin (**4**) from a culture of *Streptoverticillium rimofaciens*.[5]

These discoveries led to a large number of nucleoside analogues that were tested for the treatment of viral diseases.[6] Among the US FDA approved compounds used in the treatment of acquired immunodeficiency syndrome (AIDS), the 2′,3′-didehydro-3′-deoxythymidine d4T (**5**)[7–9] and the carbocyclic 2-amino-6-cyclopropylaminopurine analogue abacavir (**6**)[10,11] showed potent anti-human immunodeficiency virus (HIV) activity (Fig. 2).

However, side effects and drug-resistant variants remained a problem with these antiviral agents.[12–14] Moreover, the introduction of the 2′,3′-double bond in compound **5** resulted in an increased lipophilicity compared to the corresponding natural and saturated 2′,3′-dideoxynucleoside series but decreased the chemical stability in acidic medium. In the course of the search for new antiviral agents with a higher therapeutic index, the obvious emphasis was on the design of drugs with potent activity, high stability, low cytotoxicity, minimal side effects. In our previous studies, we reported the synthesis of pyrimidine nucleoside analogues of d4T based on the 1,3-dihydrobenzo[*c*]furan core **7** (Fig. 3).[15,16] This class of nucleoside with a modified glycon part was attractive because: (i) it retained the phosphorylation site; (ii) the presence of the benzene ring as electron-withdrawing group stabilized the glycosidic bond compared to the olefinic analogue: 2′,3′-didehydro-2′,3′-dideoxynucleoside; (iii) the introduction of the aromatic residue increased the lipophilicity compared to d4T.[17] In an attempt to expand the variety of nucleoside antiviral drugs, a novel range of unsaturated nucleoside analogues of d4T **8** were synthesized to explore their potential as antiviral drugs.



7 8

Figure 3. Isobenzofuran and isochroman derivatives **7** and **8**.

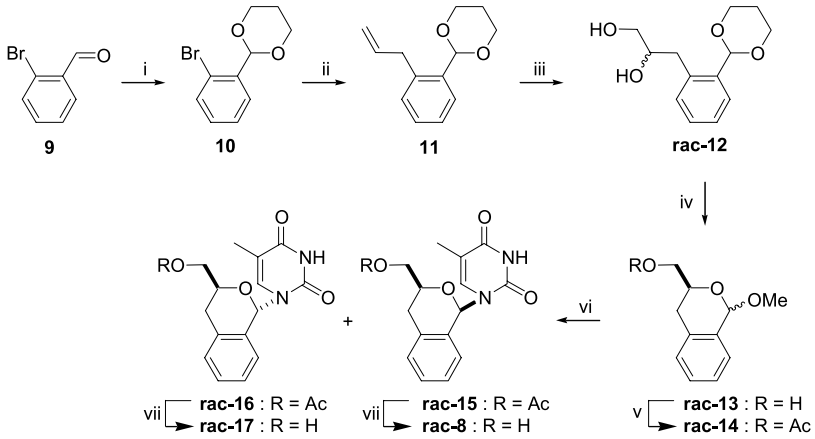
2. Results and discussion

2.1. Synthesis of racemic unsaturated nucleosides and determination of their relative configuration

A retrosynthetic analysis suggested that the starting material for the synthesis of nucleoside analogue **8** was the 2-bromobenzaldehyde (**9**). This compound had the advantage of being stable, inexpensive and easily available.

The aldehyde **9** was converted into the protected compound **10** by acetonide formation in the presence of propan-1,3-diol and catalytic amounts of PTSA in 84% yield (Scheme 1). The aromatic ring of **10** was metalated and allylated to the olefin **11** in 87% yield. Based on the Sharpless mnemonic device,[18–20] asymmetric dihydroxylation (AD) of the terminal olefin **11** using AD-mix α was expected to afford the *S* configuration that was required for the synthesis of the nucleoside analogue **8**. Thus, the alkene **11** was reacted with AD-mix α in a mixture of *tert*-butyl alcohol and water using classical Sharpless dihydroxylation methodology. Unfortunately, this oxidation furnished the diol as a mixture of the expected Sharpless diol having the *S* configuration and the unexpected Sharpless diol having the *R* configuration (ee = 0.2). On the contrary, the catalytic AD system displayed very high enantioselectivity in the preparation of the diol **19** (ee = 0.98) starting from the styrene derivative **18** (Scheme 2).[16] The presence of a methylene group in **11** between the vinyl and the phenyl groups probably decreased the selectivity (ee = 0.98 for **19** vs 0.2 for **12*S***) due to the loss of rigidity.

Considering this low enantiofacial discrimination, the allyl derivative **11** afforded the diol **rac-12** as a racemic mixture, using OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide (NMO) as co-oxidant, in 75% yield. The subsequent removal of the acetal group using HCl 10% in methanol for 2 h resulted in spontaneous cyclization to afford the isochroman derivatives **rac-13** as the major stereoisomers. It was notable that the cyclization between the primary hydroxyl and formyl groups giving 1,3,4,5-tetrahydrobenzo[*c*]oxepine derivative was not observed during this rearrangement. The alcohol **rac-13** was converted into the corresponding acetate **rac-14**, which was used as a glycosyl donor in a Vorbruggen condensation reaction.[21] Thus, treatment of the acetylated derivative **rac-14** with silylated thymine in the presence of $SnCl_4$ afforded a mixture of diastereoisomeric nucleoside analogues **rac-15** and **rac-16** that were readily separated by chromatography. The condensation reaction gave the two isomers **rac-15** and **rac-16** due to the lack of a participating effect by neighboring groups. Classical removal of the acetyl group of **rac-15** and **rac-16** by treatment with saturated methanolic ammonia produced the desired free nucleosides **rac-8** and **rac-17**, respectively, in quantitative yield. The nucleoside analogues **rac-8** and **rac-17** obtained by the method shown in Scheme 1 were of course a pair of enantiomers. Unfortunately, the heterocyclic compounds **rac-8** and **rac-17** gave poor quality crystals thus, precluding the determination of their configurations by X-ray crystallography. Thus, the absolute configurations of the two asymmetric carbons $C_{1'}$ and $C_{3'}$ included in the isochroman core were determined by NMR experiments and



Scheme 1. Reagents and conditions: (i) propan-1,2-diol, PTSA, toluene reflux; (ii) BuLi, THF then CH_2CHCH_2Br; (iii) OsO_4, H_2O, NMO, pyridine, *tert*-BuOH; (iv) HCl, MeOH; (v) Ac_2O, pyridine; (vi) silylated thymine, $C_2H_4Cl_2$, $SnCl_4$; (vii) NH_3, MeOH.

independent chemical correlation. The relative configurations for the nucleoside analogues **rac-8** and **rac-17** were assigned as $1'R$, $3'S$ ($1'S$,$3'R$) and $1'S$,$3'S$ ($1'R$,$3'R$), respectively, on the basis of proton NMR NOE experiments. Thus, in the racemic mixture **rac-8**, irradiation of $H_{1'}$ proton gave enhanced signals for $H_{3'}$ proton. The same was true for $H_{1'}$ proton when $H_{3'}$ proton was irradiated. Conversely, no NOE effect was observed for the same protons of **rac-17** while the irradiation of $H_{3'}$ proton showed an interaction with H_6 proton and vice-versa. The study of the conformational analysis made by means of molecular modeling confirmed these attributions. Thus, for the lowest energy conformer found for **rac-8**, (Fig. 4 and Table 1), the proximity of $H_{3'}$ and $H_{1'}$ explained the NOE interaction observed. Similarly, the lowest energy conformer of **rac-17** (Fig. 4), which presented a closer disposition for $H_{3'}$ and H_6 protons than that of **rac-8**, accounted for the proton dipolar interaction observed for these protons in the former compound.

The comparison of the chemical shifts and coupling constants of $H_{4'}$ protons for the two diastereoisomers was also very interesting. For **rac-8**, the following NMR parameters were measured for $H_{4'a}$ and $H_{4'b}$ protons (subscripts a and b refer, respectively, to the lower cis and to the higher trans $^3J_{3',4'}$ values): $\delta_{H\text{-}4'a}=2.86$ ppm, $J_{3',4'a}=3.2$ Hz and $\delta_{H\text{-}4'b}=2.70$ ppm, $J_{3',4'b}=10.7$ Hz, while for **rac-17**: $\delta_{H\text{-}4'a}=2.72$ ppm, $J_{3',4'a}=2.8$ Hz and $\delta_{H\text{-}4'b}=2.86$ ppm, $J_{3',4'b}=11.5$ Hz. Thus, for the latter, the $H_{4'b}$ proton (high coupling constant) resonated at a lower field than the $H_{4'a}$ proton while in the former the reverse situation was observed. This difference was very probably due to different anisotropic contributions on these proton chemical shifts exerted by $C_{1'}$–$O_{2'}$ and $C_{9'}$–$O_{9'}$ bonds, aromatic and thymine rings. The contribution of the $C_{1'}$–$O_{2'}$ bond could not explain this effect since molecular modeling (Fig. 4 and Table 1) indicated that the positions of $H_{4'a}$ and $H_{4'b}$ protons toward the oxygen atom $O_{2'}$ of the pyran cycle remained the same whichever diastereoisomer was considered.

The effect of the aromatic ring was also unable to explain the chemical shift differences since, for each diastereoisomer, the same orientations of $H_{4'a}$ and $H_{4'b}$ protons toward the plane of the cycle were observed on the molecular

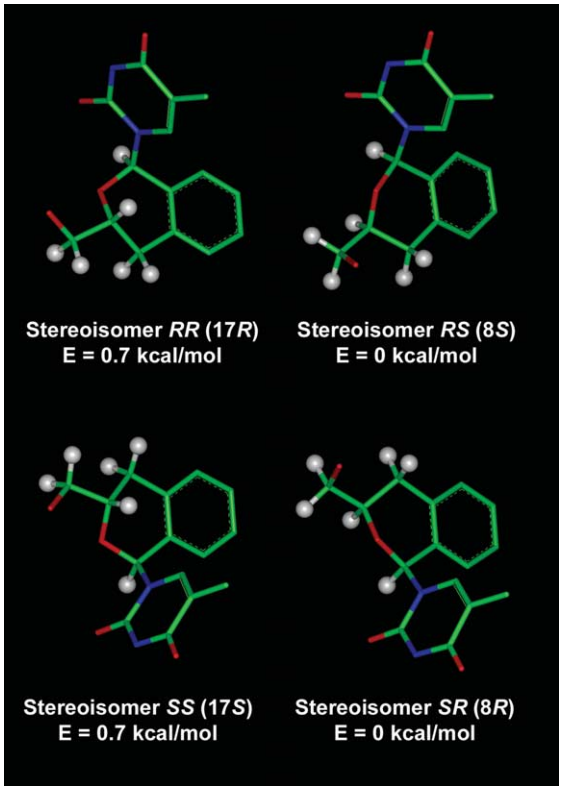
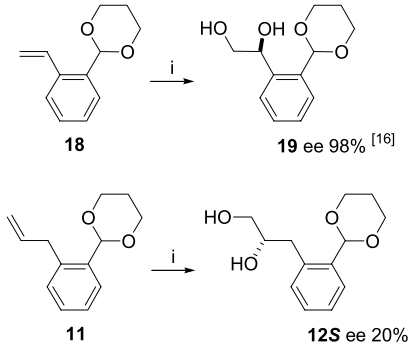


Figure 4. Lowest energy conformers obtained by molecular modeling for **rac-8** and **rac-17**.

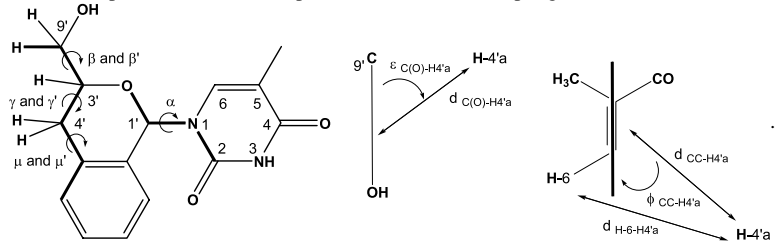


Scheme 2. Reagents and conditions: (i) AD-mix α, *tert*-BuOH, H_2O.

Table 1. Angles (deg) and interatomic distances (Å) for the lowest energy conformer of **rac-8** and **rac-17**

Angles (deg)	**rac-8** 1′*S*,3′*R* (1′*R*,3′*S*)	**rac-17** 1′*S*,3′*S* (1′*R*,3′*R*)	Distances (Å)	**rac-8** 1′*S*,3′*R* (1′*R*,3′*S*)	**rac-17** 1′*S*,3′*S* (1′*R*,3′*R*)
α	92	74	d_{H6-OH}	4.6	5.1
β	−57	+66	$d_{H6-H4'a}$[a]	5.1	4.2
β'	+59	−177	$d_{H6-H4'b}$[a]	3.8	4.9
γ_a[a]	+56	−53	$d_{H6-H3'}$	4.9	2.7
γ_b[a]	+173	−170	$d_{C(O)-H4'a}$[a]	3.1	3.5
μ_a[a]	+37	−37	$d_{C(O)-H4'b}$[a]	2.7	3.4
μ_b[a]	−81	+81	$d_{CC-H4'a}$[a]	6.3	5.4
$\varepsilon_{C(O)-H4'a}$[a]	66	26	$d_{CC-H4'b}$[a]	5.1	5.9
$\varepsilon_{C(O)-H4'b}$[a]	94	15			
$\phi_{CC-H4'a}$[a]	12	30			
$\phi_{CC-H4'b}$[a]	25	19			

[a] The subscripts 'a' and 'b' for 4′ protons refer to their coupling constant with $H_{3'}$; $H_{4'a}$ has the lower *cis J* value while $H_{4'b}$ has the higher *trans J* value



model. Similarly, the influence exerted by the thymine ring looked non-determinant because, in each of the lowest energy conformers of **rac-8** and **rac-17**, the H_6 proton pointed out in the direction of $H_{4'}$ protons (the values for $\phi_{CC-H4'a}$ and $\phi_{CC-H4'b}$ angles were ,respectively, 12 and 25° for **rac-8**, 30 and 19° for **rac-17**). Conversely, the different anisotropic contributions of the $C_{9'}$–$O_{9'}$ bond in the chemical shifts of $H_{4'}$ protons for each diastereoisomer seemed able to explain the effect. Thus, molecular modeling indicated that, for diastereoisomer **rac-8**, the values for angles $\varepsilon_{C(O)-H4'a}$ and $\varepsilon_{C(O)-H4'b}$ were, respectively, 66 and 94°. According to the Mc Connell and Pople relationship[22] giving the anisotropic contribution of an axial symmetry bond (like the $C_{9'}$–$O_{9'}$ bond):

$$\Delta\sigma = \left(\frac{\Delta\chi}{3\,N_0 d_{C(O)-H4'a}}\right)(1-3\cos^2\varepsilon_{C(O)-H4'})$$

where $\Delta\chi$ and N_0 are, respectively, the difference between the susceptibility parallel to the axis and the transverse susceptibility and the Avogadro number, the contribution $\Delta\sigma$ is positive (diamagnetic effect) for $\varepsilon_{C(O)-H4'} > 54°45'$. Thus, both $H_{4'a}$ and $H_{4'b}$ protons of **rac-8** should receive an upfield shielding, a high one for $H_{4'b}$ ($\varepsilon_{C(O)-H4'b} \approx 90°$) and a very low one for $H_{4'a}$ ($\varepsilon_{C(O)-H4'b} \approx 54°45'$). Conversely, both $H_{4'a}$ and $H_{4'b}$ protons of **rac-17**, for which $\varepsilon_{C(O)-H4'a} = 26°$ and $\varepsilon_{C(O)-H4'b} = 15°$, would receive a negative downfield shielding with a more intense effect for $H_{4'b}$ since $\varepsilon_{C(O)-H4'b}$ is lower than $\varepsilon_{C(O)-H4'a}$. These remarks, made on the basis of the most stable conformers obtained from a molecular modeling study, which are in agreement with measured chemical shifts of $H_{4'}$ protons, gave confirmation of the diastereoisomer structural attribution.

2.2. Lipase-catalyzed kinetic resolution of rac-8 and rac-17

The synthesis of enantiomerically pure nucleoside analogues was undertaken. For this purpose, several methods have been described in the literature, for example, enantioselective reaction using Jacobsen epoxidation,[23] enzymatic resolution[24] or formation of diastereoisomeric esters.[25] Considering the practical aspects, the kinetic enzymatic resolution was chosen although enzyme-catalyzed reactions have not been fully exploited in nucleoside chemistry.[26] Thus, compounds **rac-8** and **rac-17** were subjected to enzymatic transesterification using vinyl acetate as an acyl donor and organic solvent in the presence of different lipases. The behavior of six different enzymes (*Candida rugosa* lipase, novozym 435 lipase, pork liver esterase, porcine pancreatic lipase, *Geotricum candida* lipase and *Pseudomas* sp. lipase) was screened. Porcine pancreatic lipase presented the best selectivity and enzymatic activity (Table 2).

Table 2. Lipase screening for the resolution of alcohols **rac-8** and **rac-17** (conditions: 0.2 mg of **rac-8** (or **rac-17**) in 200 μL of vinyl acetate and 3 mg of enzyme powder, +++ means that the conversion reached 50% at the time indicated)

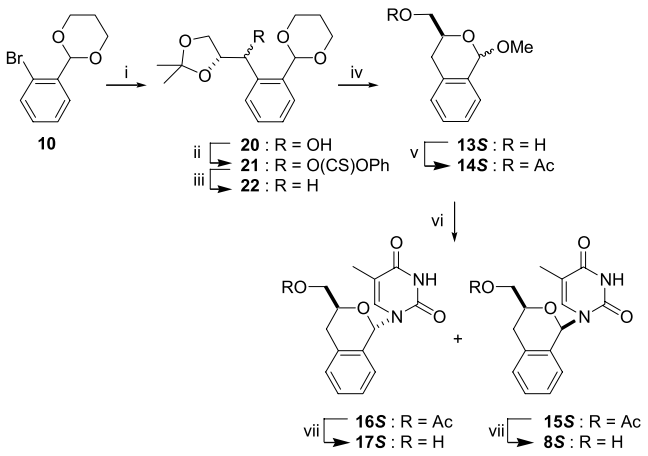
Enzyme	$t=2$ h **rac-17**	**rac-8**	$t=18$ h **rac-17**	**rac-8**	$t=24$ h **rac-17**	**rac-8**	$t=30$ h **rac-17**	**rac-8**	$t=72$ h **rac-17**	**rac-8**
C. rugosa lipase	+	−+	++	+	++	++	++	++	++	+++
Novozym 435 lipase	+++	++	+++	+++	+++	+++				
Pork liver esterase	−	−	−	−	−	−	−	−	−	−
Porcine pancreatic lipase	−	+	+	++	+	++	+	++	++	+++
G. candida lipase	−	−	+	+	+	++	+	++	++	+++
Pseudomas sp. lipase	−	−+	−	+	−	++	−	++	−	+++

Among the enzymes used, novozym 435 lipase gave the highest reaction rates with both **rac-8** and **rac-17**, but did not seem to present a high enantiomeric discrimination factor since the transesterification took place to a great extent beyond 50% conversion. We discarded *Pseudomonas* sp. lipase because it induced very low reaction rates, particularly with **rac-17**. Thus, two enzymes were selected: *C. rugosa* lipase (AY 30 Amano) and porcine pancreatic lipase (PPL). The results, determined by means of chiral HPLC, showed that a better enantiomeric discrimination was obtained when using PPL.

Thus, starting from **rac-8**, the ee's of ester and of remaining substrate were 0.98 (the major being 1′*R*, 3′*S*) and 0.74 (the major being 1′*S*, 3′*R*), respectively, after 33% of conversion (reaction time, 7 h). Starting from **rac-17**, the ee's of ester and residual substrate were 0.74 (the major being 1′*R*, 3′*R*) and 0.78 (the major being 1′*S*, 3′*S*), respectively, after 51% of conversion (reaction time, 48 h), (Fig. 5). The absolute configurations were determined as described later in this paper. Considering these results, enzyme-catalyzed transesterification was not adopted as a method for the separation of the racemic nucleosides **rac-8** and **rac-17**.

2.3. Single enantiomer synthesis using 2,3-*O*-isopropylidene-D-glyceraldehyde

A selective synthetic strategy avoiding the need for resolution procedures was shown to afford the enantiomerically pure target nucleosides **8*S*** and **17*S***. The strategy used for this purpose is shown in Scheme 3. The starting material was enantiomerically pure 2,3-*O*-isopropylidene-D-glyceraldehyde, prepared from the oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol. The chiral glyceraldehyde derivative was reacted with the metalated aromatic ring of **10** to give the diastereoisomeric mixture of the alcohols **20** (ratio 1:1) in 51% yield. Esterification of the secondary hydroxyl of compound **20** as phenylthionocarbonate esters **21** followed by standard Barton deoxygenation[27] yielded the desired enantiomerically pure compound **22** in 69% yield. The intermediate **22** was then converted to epimeric methoxide **13*S*** as major anomer by treatment with HCl 10% in methanol, followed by acetylation of the primary hydroxyl group to afford acetate **14*S*** in 72% yield. As described in the racemic synthesis, the formation of the thymine derivatives by standard Vorbruggen chemistry[21] resulted in a mixture of anomers **15*S*** and **16*S*** was formed due to the lack of anchimeric assistance. Removal of the acetyl group by treatment with saturated methanolic ammonia produced the desired free nucleosides **8*S*** and **17*S*** in quantitative yield.



Scheme 3. Reagents and conditions: (i) BuLi, THF then 2,3-*O*-isopropylidene-D-glyceraldehyde; (ii) PhO(CS)Cl, DMAP, EtOAc; (iii) Bu_3SnH, AIBN, toluene, 100 °C; (iv) HCl, MeOH; (v) Ac_2O, pyridine; (vi) silylated thymine, $C_2H_4Cl_2$, $SnCl_4$; (vii) NH_3, MeOH.

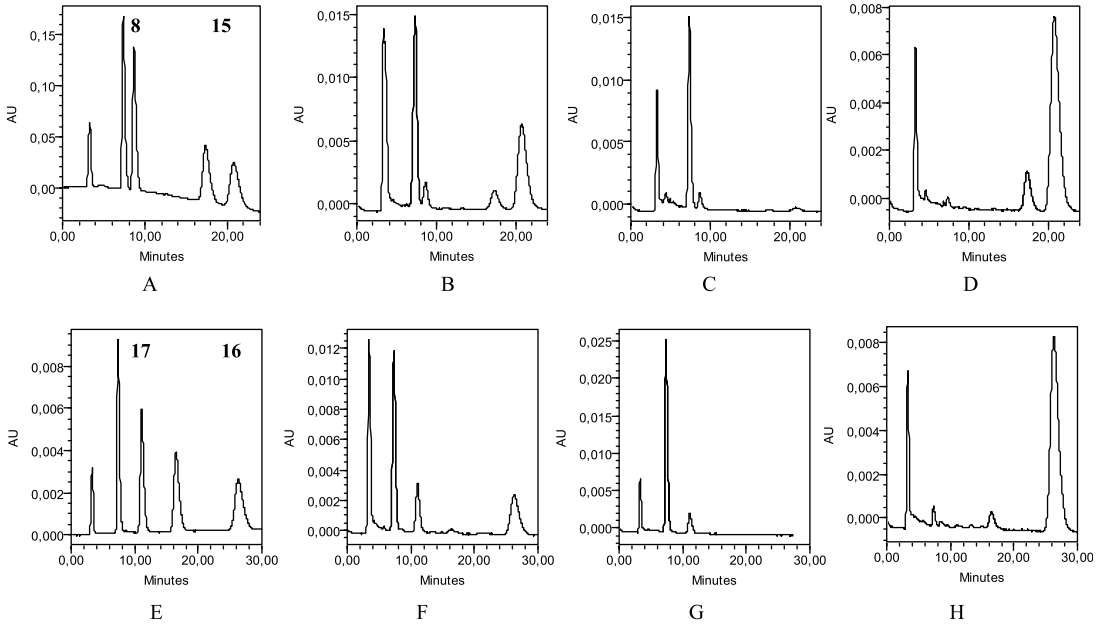


Figure 5. Chiral HPLC chromatograms. A: **rac-15** and **rac-8** (50/50). B: **15** and **8** from the enzymatic reaction without purification. C: **8** from the enzymatic reaction after purification. D: **15** from the enzymatic reaction after purification. E: **rac-16** and **rac-17** (50/50). F: **16** and **17** from the enzymatic reaction without purification. G: **17** from the enzymatic reaction after purification. H: **16** from the enzymatic reaction after purification. Conditions: Chiralcel OJ (250×46 mm), 1 mL/min, 30 °C, EtOH–hexane (30/70), λ=200 nm.

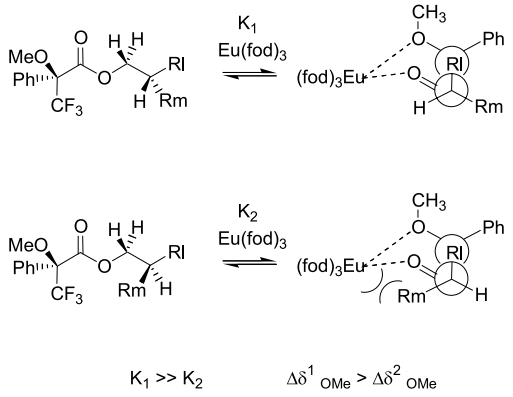
The positive ion ESI mass spectra of nucleosides **8*S*** and **17*S*** indicated a high level of purity (Fig. 6). Indeed, the target molecules **8*S*** and **17*S*** showed abundant cationic monocharged ions: $[M+Na]^+$ *m/z* 311.08 and $[M+K]^+$ *m/z* 327.06. The other ions observed at *m/z* 163.07, 149.03 and 117.07 were attributed to fragments of the sodium adduct by an MS/MS experiment.

Comparison of the proton NMR spectra of **8*S*** and **17*S*** with those of **rac-8** and **rac-17** allowed the respective trans and cis relative configurations to be ascribed. Moreover, due to the 3′-*S* carbon configuration afforded by D-mannitol, the absolute configuration of **8*S*** and **17*S*** were 1′*R*, 3′*S* and 1′*S*, 3′*S*, respectively. As a consequence, it was possible to ascribe by comparison the absolute configurations of the stereoisomers obtained via lipase kinetic resolution.

2.4. Confirmation of the absolute configuration determination of 8*S*, 8*R* and 17*S* and 17*R* isochromans by means of NMR study of their Mosher's esters 23–26

A review about the determination of the absolute configuration of chiral alcohols and amines by means of NMR spectroscopy has recently been published.[28] Thus, the derivatization of the titled enantiomers into diastereoisomeric esters or amides by means of enantiopure acid derivatives (like Mosher's esters, for example) and the study of their chemical shifts induced by an aromatic group of the chiral center of the auxiliary compound was shown to be particularly efficient in the case of secondary alcohols (or amines). The application of this technique to primary alcohols having the chiral center beside the hydroxymethyl group was not so powerful. The reasons were: (i) lower substituent effects due to the greater distance between the perturbing groups of the auxiliary chiral center and the methylene protons; (ii) the presence of supplementary C–C bonds reduces the conformational preference and thus, can make difficult the interpretation of the chemical shift variations usually induced by phenyl substituents. In order to avoid these drawbacks and to enhance the intensity of the perturbing magnetic fields, larger aromatic substituents, like anthryl groups, have been proposed.[29,30] Thus, a number of rules concerning the configuration of aliphatic chiral primary alcohols were drawn from a molecular modeling study that had shown a conservation of the conformational preference in this series.[31] Unfortunately, these rules could not be applied to primary alcohols whose vicinal chiral centres were included in a cycle, which is the case for isochromans **8** and **7**. Meanwhile, it was shown that for Mosher's esters [α-methoxy-α-(trifluoromethyl)phenylacetyl or MTPA esters], the absolute configuration of the vicinal carbon can be deduced from the relative magnitude of the lanthanide-induced chemical shift (LIS) of the methoxy group for each diastereoisomer.[32] In that case, it was assumed that complexation of europium salts with both oxygens of the ester and of methoxy groups induced the existence of the conformers indicated in Scheme 4.

Thus, starting from the isochroman derivatives **8*R***, **8*S***, **17*R*** and **17*S***, the corresponding (*S*)-MTPA esters **23*S***, **23*R***, **24*R*** and **24*S*** (Fig. 7) were prepared using classical methodology



Scheme 4. Application of the lanthanide-induced shifts (LIS) for OCH_3 groups of (*S*)-MTPA esters for the determination of the absolute configuration of alcohols (K_1 and K_2 are the equilibrium constants between the complexed and the free forms of diastereoisomeric Mosher's esters; $\Delta\delta_{OMe}$ = difference between the chemical shift for the methoxy group of the esters with and without the Europium salt).

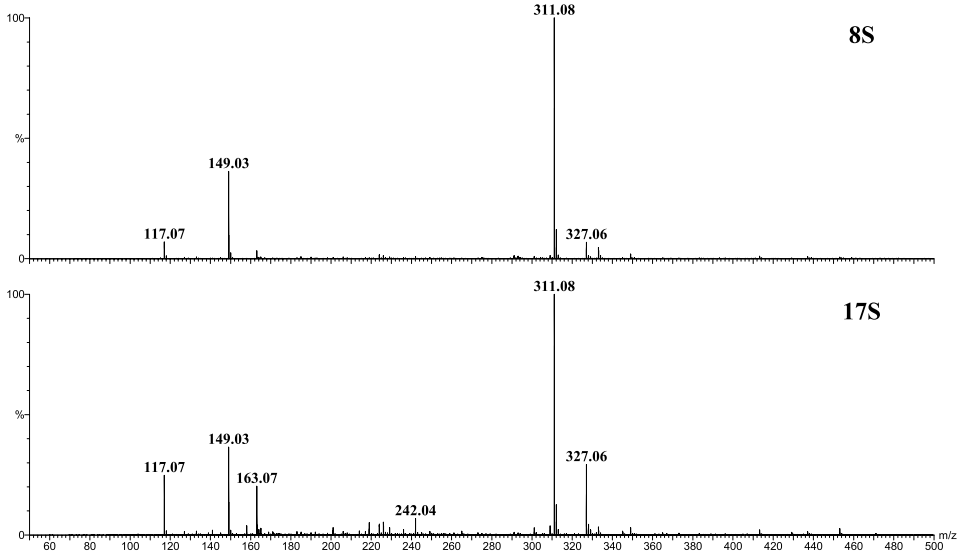


Figure 6. Positive ion ESI mass spectra of compounds **8*S*** (top) and **17*S*** (bottom).

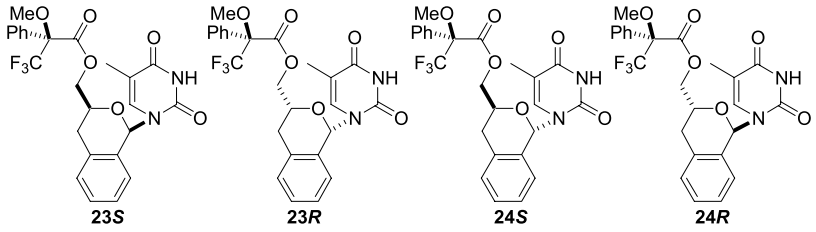


Figure 7. (*S*)-MTPA esters **23*S***, **23*R***, **24*R*** and **24*S***.

and the classical shifts induced by Eu(fod)$_3$ on the methoxy group were studied.

Thus, the lanthanide induced shifts on the methoxy groups of (*S*)-MTPA esters **23** and **24** of the remaining alcohol obtained after lipase resolution (Table 3) gave a clear confirmation of the absolute configurations already determined by the use of 2,3-*O*-isopropylidene-D-glyceraldehyde as an optically pure precursor.

Table 3. Lanthanide-induced shifts on the proton chemical shifts of (*S*)-MTPA esters **23** and **24** and absolute configuration of the major remaining alcohol obtained after lipase resolution

(*S*)-MTPA esters	Remaining	$\Delta\delta_{OCH3}$*	$\Delta\delta_{OCH3}$**	Configuration
23	major	+0.31	+0.52	1′*S*,3′*R*
	minor	+0.24	+0.44	1′*R*,3′*S*
24	major	+0.11	+0.29	1′*S*,3′*S*
	minor	+0.15	+0.36	1′*R*,3′*R*

$\Delta\delta_{OCH3}$ (ppm)=δ_{OCH3} [with Eu(fod)$_3$/$CDCl_3$]−δ_{OCH3} ($CDCl_3$). * And **: molar ratio between MTPA esters and Eu(fod)$_3$ were, respectively, 0.5 and 1.

Previous NMR studies of MTPA esters of primary alcohols showed that there was a correlation between the shape of the signals due to the methylenic protons of the CH_2O group of (*R*)- and (*S*)-MTPA esters and the absolute configuration of the vicinal asymmetric carbon. Thus, in a series of 24-methyl-26-hydroxy steroids, the chemical shift difference between the two OCH_2 protons of (*S*)-MTPA esters was larger when the configuration of C-26 was *S* than when this carbon presented the *R* spatial arrangement.[33] Obviously, this simple rule, established in a series of steroids for which conformational features remained constant throughout the series, could not be applied in our case. Moreover, the low and similar $\Delta\delta_{H9'}$ values measured for each (*S*)-MTPA esters **23*S***, **23*R***, **24*S***, and **24*R*** (ca. 0.04 ppm) (Figs. 8 and 9) have precluded any reliable interpretation.

3. Conclusion

In this work, we have described an efficient route, starting from 2-bromobenzaldehyde, to synthesize racemic diastereoisomeric thymine derivatives of isochroman. The relative configurations were determined by NOE proton NMR experiments in connection with molecular modeling. Following the separation of the latter diastereoisomers, kinetic resolution was achieved via a transesterification reaction catalyzed by lipases. Using this method, moderate ee's were obtained (0.75–0.98). Thus, an alternative strategy starting from D-mannitol was proposed to provide pure enantiomers. The attribution of absolute configurations was made by chemical filiation on the basis of the configurations obtained from D-mannitol. The structural attributions were confirmed by studying the proton NMR LIS of the methoxy group of the corresponding isochroman Mosher's esters **23** and **24**. An attempt to correlate the chemical shifts of $O_{9'}$–$C_{9'}H_2$ protons of the Mosher's esters **23** and **24** with the absolute configuration was unsuccessful because the diastereoisomeric esters exhibited a too small $\Delta\delta_{H9'}$ value. The isochroman derivatives were evaluated for their inhibitory effect on the replication of HIV-1 in human

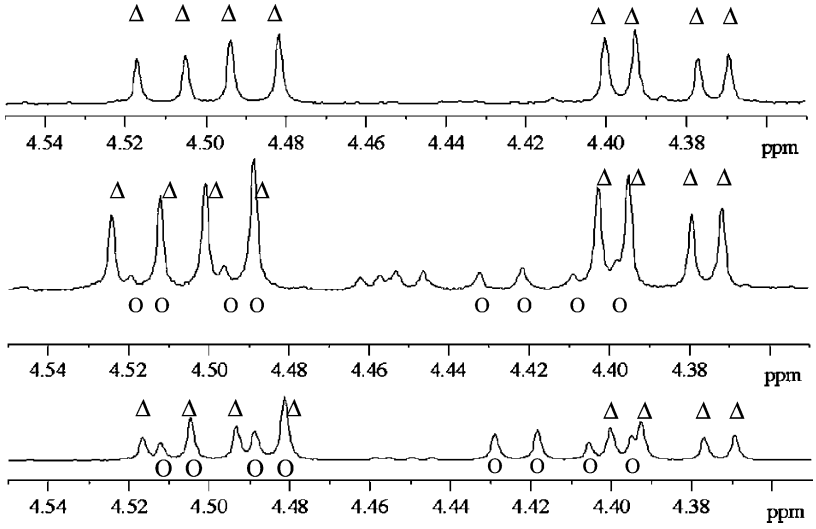


Figure 8. Proton NMR spectra ($CDCl_3$) of $H_{9'}$ protons of Mosher's esters **23*S*** (△) and **23*R*** (○). (a) spectra of pure enantiomers prepared from D-mannitol, (b) spectra of enantiomerically enriched enantiomers obtained via lipase resolution, (c) spectra of racemic mixture.

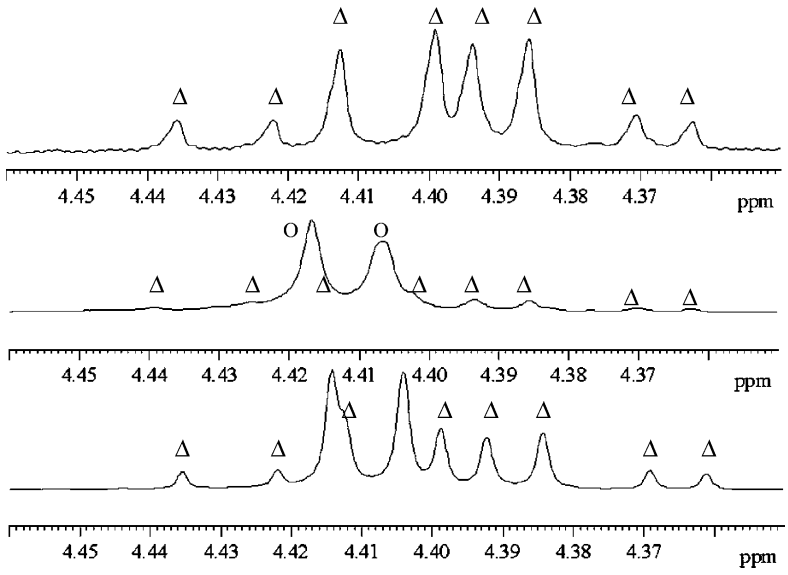


Figure 9. Proton NMR spectra ($CDCl_3$) of $H_{9'}$ protons of Mosher's esters **24*S*** (△) and **24*R*** (○). (a) spectra of pure enantiomers prepared from D-mannitol, (b) spectra of enantiomerically enriched enantiomers obtained via lipase resolution, (c) spectra of racemic mixture.

T4-lymphoblastoid cells, CEM-SS and MT-4. Unfortunately, these compounds were found inactive against HIV-1 replication at concentrations up to 10 μM.

4. Experimental

4.1. General

Melting points were determined on a digital melting-point apparatus (Electrothermal) and were uncorrected. Optical rotations were recorded in $CHCl_3$ or MeOH solutions with a digital polarimeter DIP-370 (JASCO) using a 1 dm cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6 (internal Me_4Si), respectively, at 300.13 MHz (Bruker Avance-300) and at 500 MHz (Bruker AX500). TLC was performed on Silica F254 (Merck) and detection was by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was carried out on Silica Gel 60 (Merck, 230 mesh). EtOAc, diethyl ether and petroleum ether were distilled before use. Bases and solvents were used as supplied. MeOH–NH_3 was methanol saturated with ammonia gas at rt.

Electron impact analysis (EI) was performed on a Waters-Micromass AUTOSPEC *Ultima* (EBE geometry) high-resolution mass spectrometer (HRMS). Electron energy, emission current and accelerating voltage values were 70 eV, 200 μA and 8 kV, respectively. Accurate mass measurements of molecular and fragment ions were performed using perfluoro kerosene (PFK) as the internal reference. High-resolution electrospray experiments (ESI-HRMS) were performed on a Waters-Micromass Q-TOF *Ultima Global* hybrid quadrupole time-of-flight instrument, equipped with a *Z*-spray ion source. The source and desolvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 2.5 kV, the cone voltage 100 V and the RF lens1 energy 50 V. For accurate mass measurements, a single internal lock mass correction, using characteristic ions of reference components, was applied. For both EI-HRMS and ESI-HRMS measurements, data acquisition and processing were performed with MassLynx 4.0 software.

Chromatographic analysis was performed on a Waters 600 HPLC system equipped with a Waters 996 photodiode array spectrophotometer. The sample loop was 20 μL (Rheodyne 7125 injector). Chromatographic data were collected and processed on a computer running with Millennium 2010 (Waters). The stainless steel column Chiralcel OJ (cellulose tris-methylbenzoate; 250×4.6 mm i.d.; 10 μm) was purchased from Daicel Chemical Industries. Lyophilized enzymes were kindly donated by Amano Enzyme Inc. (Nagoya, Japan), apart from porcine pancreatic lipase, which was supplied by Sigma (PPL type II). The enantiomeric excesses (ee) of the substrates and of the acetates were determined using chiral high performance liquid chromatography (HPLC, Chiralcel OJ) with the following experimental conditions: sample concentration 0.21 mM; eluent: *n*-hexane/ethanol, 70:30; flow-rate: 1 mL/min; temperature: 30 °C; wavelengths: 200, 226 nm.

Molecular modeling calculations were made on a silicon graphics (SGI) computer. Molecular building and energy calculations were produced by means of InsightII, Biopolymer, Discover and CFF91 (force fields) software from Accelrys (San Diego, CA, USA)

4.2. Synthesis of racemic nucleosides rac-8 and rac-17

4.2.1. 2-(2-Bromophenyl)-1,3-dioxane (10). A stirred mixture of 2-bromobenzaldehyde (10.0 g, 53.9 mmol), propan-1,3-diol (4.9 g, 53.9 mmol), toluene-4-sulfonic acid (0.4 g) and toluene (15 mL) was refluxed for 4 h using a Dean-Stark condenser. Et_3N (2 mL) was added and the reaction mixture cooled and extracted with diethyl ether (8 mL). The extract was worked up and the crude product was purified by flash chromatography (diethyl ether/petroleum ether, 5:95) to yield compound **10** (11.2 g,

84%) as a white solid: mp 54–55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (m, 1H, H aromatic), 7.36 (m, 3H, H aromatic), 5.97 (s, 1H, H-2), 4.29, 4.05 (m, 4H, H-4, H-6), 2.09, 1.47 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8 (C), 133.0 (CH), 130.7 (CH), 128.5 (CH), 128.0 (CH), 122.7 (*C*Br), 101.3 (C-2), 68.0 (2C, C-4, C-6), 26.1 (C-5); EI-HRMS: $M^{+\cdot}$ *m/z* 242, found 241.9931, $C_{10}H_{11}O_2Br$ requires 241.9942 and $[M-H^{\cdot}]^+$ *m/z* 241, found 240.9863, $C_{10}H_{10}O_2Br$ requires 240.9864. Anal. Calcd for $C_{10}H_{11}BrO_2$ (241.99 g/mol): C, 49.41; H, 4.56. Found: C, 49.39; H, 4.58.

4.2.2. 2-(2-Allylphenyl)-1,3-dioxane (11). To a solution of bromide **10** (2.0 g, 8.3 mmol) in THF (32 mL) was added *n*-BuLi (10 mL, 1.6 M solution) in THF at −10 °C under argon. After 1 h, a solution of allyl bromide (2.15 mL, 12.3 mmol) was added dropwise to the mixture at the same temperature and the mixture was stirred overnight at rt. The solution was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc (100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:95) to yield compound **11** (1.47 g, 87%) as an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (m, 1H, H aromatic), 7.34 (m, 3H, H aromatic), 6.03 (m, CH allyl), 5.73 (s, 1H, H-2), 5.18 (m, CH allyl), 4.29, 4.01 (m, 4H, H-4, H-6), 3.64 (m, 2H, CH_2 allyl), 2.26, 1.41 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.9 (CH allyl), 137.8 (C), 136.8 (C), 130.1 (CH), 129.3 (CH), 126.6 (CH), 126.5 (CH), 116.1 (CH_2 allyl), 10.3 (C-2), 68.0 (2C, C-4, C-6), 37.1 (CH_2 allyl), 26.1 (C-5); EI-HRMS: $[M-H^{\cdot}]^+$ *m/z* 203, found 203.1072, $C_{13}H_{15}O_2$ requires 203.1072. Anal. Calcd for $C_{13}H_{16}O_2$ (204.12 g/mol): C, 76.44; H, 7.90. Found: C, 76.51; H, 7.86.

4.2.3. 3-(2-(1,3)-Dioxan-2-ylphenyl)-propan-1,2-diol (rac-12). *N*-Methylmorpholine-*N*-oxide (6.9 g, 58.8 mmol), pyridine (0.5 mL), H_2O (0.7 mL) and OsO_4 (32 μL of a 2.5% solution in *tert*-BuOH, 0.1 mmol) were added to a solution of alkene **11** (2.0, 9.80 mmol) in *tert*-BuOH (10 mL). The mixture was stirred at rt overnight then treated with 20% aqueous sodium bisulfite solution (4 mL) and evaporated to dryness. Saturated aqueous NaCl (5 mL) was added and the mixture was extracted twice with EtOAc. The combined extracts were worked up and the crude product was purified by flash chromatography (EtOAc/petroleum ether, 50:50) to yield compound **rac-12** (1.75 g, 75%) as an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 1H, H aromatic), 6.99 (m, 3H, H aromatic), 5.44 (s, 1H, H-2), 3.94 (m, 5H, H-4, H-6, C*H*OH, 2OH), 3.67 (m, 2H, H-4, H-6), 3.32 (dd, J=11.3, 3.5 Hz, 1H, CH_2OH), 3.22 (dd, J=6.1 Hz, 1H, CH_2OH), 2.68 (d, J=6.6 Hz, CH_2 allyl), 1.87, 1.13 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.0 (C), 136.8 (C), 131.0 (CH), 129.0 (CH), 126.9 (CH), 126.5 (CH), 100.6 (C-2), 73.4 (CHOH), 67.6 (2C, C-4, C-6), 66.1 (CH_2OH), 30.0 (CH_2 allyl), 25.8 (C-5). Anal. Calcd for $C_{13}H_{18}O_4$ (238.12 g/mol): C, 65.53; H, 7.61. Found: C, 65.60; H, 7.62.

4.2.4. (1*R*,3*S*)- and (1*S*,3*R*)-3-Acetyloxymethyl-1-methoxyisochroman (rac-14). Compound **rac-12** (2.4 g, 10.0 mmol) was dissolved in methanol HCl (1%, 60 mL) and the resulting mixture was stirred for 2 h at rt. Et_3N (4 mL) was added, the mixture was stirred for 30 min at rt and then extracted with EtOAc (100 mL). The extract was worked up and the crude product was co-evaporated successively with toluene (3×10 mL) and pyridine (10 mL). The residue was dissolved in anhydrous pyridine (8.5 mL) and Ac_2O (1.2 mL, 13.0 mmol) was added. The resulting mixture was stirred overnight at rt. MeOH (10 mL) was added and the mixture was evaporated to dryness. The residue was co-evaporated with toluene and purified by flash chromatography (EtOAc/petroleum ether, 30:70) to yield **rac-14** (1.78 g, 75%) as an oil. The major isomer **rac-14** had the (1′*R*,3′*S*) and (1′*S*,3′*R*) configuration; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (m, 3H, H aromatic), 6.91 (m, 1H, H aromatic), 5.36 (s, 1H, H-1), 4.16 (m, 1H, H3), 4.08 (m, 2H, H9a, H-9b), 3.39 (s, 3H, OCH_3), 2.57 (dd, 1H, $J_{4'a,4'b}$= 16.5 Hz, $J_{3',4'b'}$=11.3 Hz, H4′b), 2.39 (dd, 1H, $J_{3',4'a}$= 2.6 Hz, H4′a), 1.94 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7 (*C*OCH_3), 134.8, 134.1 (2C, C-10, C-11), 128.8 (CH), 128.5 (CH), 127.8 (CH), 126.6 (CH), 98.5 (C-1′), 66.4 (C-3), 65.4 (C-9), 55.2 (O*C*H_3), 29.9 (C-4), 20.9 (*C*H_3CO). Anal. Calcd for $C_{13}H_{16}O_4$ (236.10 g/mol): C, 66.09; H, 6.83. Found: C, 66.10; H, 6.90.

4.2.5. (1′*R*,3′*S*)- and (1′*S*,3′*R*)-1-(3-Acetyloxymethyl-isochroman-1-yl)thymine (rac-15) and (1′*S*,3′*S*)- and (1′*R*,3′*R*)-1-(3-acetyloxymethyl-isochroman-1-yl(thymine) (rac-16). A mixture of thymine (534 mg, 4.23 mmol), anhydrous HMDS (50 mL) and $(NH_4)_2SO_4$ (10 mg) was refluxed under N_2 until a clear solution was obtained (ca. 12 h). Then the solvent was removed under reduced pressure to give a colorless syrup that was dissolved in anhydrous dichloroethane (10 mL). To the solution of silylated thymine in anhydrous dichloroethane were added acetate **rac-14** (500 mg, 2.12 mmol) in anhydrous dichloroethane and $SnCl_4$ (578 mL, 4.24 mmol) at −10 °C. After stirring the mixture for 3 h at rt, saturated $NaHCO_3$ (50 mL) was added, the mixture was stirred for 30 min and then extracted with CH_2Cl_2. This extract was worked up and the crude product was purified by flash chromatography (EtOAc/petroleum ether, 40:60) to give compound **rac-15** (276 mg, 39%) as a foam as first eluting compound and compound **rac-16** (259 mg, 37%) as a foam as second eluting compound. **rac-15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H, NH), 6.62 (d, J=1.3 Hz, 1H, H-6), 7.30, 7.23, 7.20, 6.97 (4H, H aromatic), 7.00 (s, 1H, H-1′), 4.22 (m, $J_{3',9'b}$=6.1 Hz, $J_{9'a,9'b}$=11.7 Hz, 1H, H-9′b), 4.14 (m, $J_{3',9'a}$=4.1 Hz, 1H, H-9′a), 4.09 (m, $J_{3',4'a}$=5.0 Hz, $J_{3',4'b}$=8.7 Hz, 1H, H-3′), 2.85 (m, $J_{4'a,4'b}$=16.3 Hz, 1H, H-4′a), 2.80 (m, 1H, H-4′b), 2.00 (s, 1H, CH_3CO), 1.73 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8 (*C*OCH3), 163.6 (C-4), 151.1 (C-2), 137.0 (C-6), 134.5, 130.8 (2C, C-10′, C-11′), 110.4 (C-5), 79.8 (C-1′), 68.0 (C-3′), 65.6 (C-9′), 29.8 (C-4′), 20.8 (CH_3CO), 12.5 (CH_3 thymine). Anal. Calcd for $C_{17}H_{18}N_2O_5$ (330.12 g/mol): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.79; H, 5.53; N, 8.45. **rac-16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (s, 1H, NH), 6.68 (d, J=1.3 Hz, 1H, H-6), 7.25, 7.18, 7.14, 6.91 (4H, H aromatic), 7.04 (s, 1H, H-1′), 4.14-4.23 (m, $J_{3',9'b}$=6.7 Hz, $J_{9'a,9'b}$=11.5 Hz, 1H, $J_{3',9'a}$=3.5 Hz, $J_{3',4'a}$=2.4 Hz, $J_{3',4'b}$=11.5 Hz, 3H, H-3′, H-9′a, H-9′b), 2.89 (m, $J_{4'a,4'b}$=16.3 Hz, 1H, H-4′b), 2.70 (m, 1H, H-4′a), 2.05 (s, 1H, CH_3CO), 1.75 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 170.9 (*C*OCH3), 163.7 (C-4), 151.2 (C-2), 136.7 (C-6), 134.5, 132.0 (2C, C-10′, C-11′), 111.9 (C-5), 81.1 (C-1′), 72.9 (C-3′), 65.9 (C-9′), 29.7 (C-4′), 20.9 (CH_3CO), 12.4 (CH_3 thymine). Anal. Calcd for $C_{17}H_{18}N_2O_5$ (330.12 g/mol): C, 61.81; H, 5.49; N, 8.48. Found: C, 61.81; H, 5.51; N, 8.47.

4.2.6. (1′*R*,3′*S*)- and (1′*S*,3′*R*)-1-(3-Hydroxymethyl-isochroman-1-yl)thymine (rac-8). The protected compound **rac-15** (500 mg, 1.51 mmol) was dissolved in methanolic ammonia (5 mL) and the mixture stirred for 24 h. After evaporation of the solvent the crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 2:98) to yield compound **rac-8** (414 mg, 95%) as a foam, ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 11.39 (s, 1H, NH), 6.98 (d, *J*=1.1 Hz, 1H, H-6), 7.34, 7.30, 7.25, 7.07 (4H, H aromatic), 6.89 (s, 1H, H-1′), 4.82 (d, *J*=5.8 Hz, 1H, OH), 3.96 (m, 1H, H-3′), 3.52 (dd, $J_{9'a,9'b}$=11.3 Hz, $J_{3',9'a}$=4.8 Hz, 1H, H-9′a), 3.47 (dd, $J_{3',9'b}$=5.4 Hz, 1H, H-9′a), 2.86 (dd, $J_{4'a,4'b}$=16.6 Hz, $J_{3',4'a}$=3.2 Hz, $J_{3',4'b}$=10.7 Hz, 1H, H-4′a), 2.70 (dd, 1H, H-4′b), 1.64 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8 (C-4), 151.1 (C-2), 137.6 (C-6), 135.5, 130.2 (2C, C-10′, C-11′), 108.8 (C-5), 78.6 (C-1′), 70.2 (C-3′), 63.5 (C-9′), 29.5 (C-4′), 11.9 (CH_3 thymine). Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.11 g/mol): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.53; H, 5.65; N, 9.70.

4.2.7. (1′*S*,3′*S*)- and (1′*R*,3′*R*)-1-(3-Hydroxymethyl-isochroman-1-yl)thymine (rac-17). The protected compound **rac-16** (500 mg, 1.51 mmol) was dissolved in methanolic ammonia (5 mL) and the mixture stirred for 24 h. After evaporation of the solvent, the crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 2:98) to give compound **rac-17** (410 mg, 94%) as a foam, ^{1}H NMR (Me_2SO-d_6, 300 MHz) δ 11.45 (s, 1H, NH), 6.96 (d, *J*=1.2 Hz, 1H, H-6), 7.29, 7.24, 7.22, 6.95 (4H, H aromatic), 6.93 (s, 1H, H-1′), 4.87 (d, *J*=5.8 Hz, 1H, OH), 4.03 (m, 1H, H-3′), 3.56 (dd, $J_{3',9'b}$=5.8 Hz, 1H, H-9′a), 3.52 (dd, $J_{9'a,9'b}$=11.6 Hz, $J_{3',9'a}$=4.5 Hz, 1H, H-9′a), 2.86 (dd, 1H, H-4′b), 2.72 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=2.8 Hz, $J_{3',4'b}$=11.57 Hz, 1H, H-4′a), 1.68 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7 (C-4), 151.1 (C-2), 136.8 (C-6), 135.7, 132.7 (2C, C-10′, C-11′), 110.3 (C-5), 80.3 (C-1′), 75.5 (C-3′), 63.7 (C-9′), 29.5 (C-4′), 11.9 (CH_3 thymine). Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.11 g/mol): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.55; H, 5.57; N, 9.75.

4.3. Selective synthesis of nucleosides 8*S* and 17*S*

4.3.1. ((*S*)-2,2-Dimethyl-(1,3)-dioxolan-4-yl)-(2-(1,3)-dioxan-2-ylphenyl)-methanol (20). *n*-Butyl lithium (1.6 M in hexane, 23.8 mL, 38 mmol) was added dropwise to a solution of bromide **10** (4.6 g, 19.0 mmol) in dry THF (50 mL) at −15 °C under argon. After 1 h, a solution of 1,2-*O*-isopropylidene-D-glyceraldehyde[28] (500 mg, 3.84 mmol) in THF (10 mL) was added dropwise at −15 °C under argon. After being stirred overnight at rt, the reaction mixture was treated with aqueous NH_4Cl and extracted with ethylacetate. The extract was worked up and the crude product was purified by flash chromatography (ethylacetate/petroleum ether, 20:80) to yield compound **20** (577 mg, 51%) as an oil; ESI-HRMS: $[M+Na]^+$ *m*/*z* 317, found 317.1361, $C_{16}H_{22}O_5Na$ requires 317.1365. Anal. Calcd for $C_{16}H_{22}O_5$ (294.15 g/mol): C, 65.29; H, 7.53. Found: C, 65.32; H, 7.50. First stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (m, 2H, H aromatic), 7.31 (m, 2H, H aromatic), 5.73 (s, 1H, H-2), 5.22 (dd, *J*=2.0, 5.6 Hz, CHOH), 4.49 (q, *J*=6.1 Hz, CHO), 4.28, 4.00 (m, 4H, H-4, H-6), 4.13 (dd, *J*=6.5, 8.4 Hz, CHO), 3.96 (dd, *J*=6.8 Hz, CHO), 3.24 (d, OH), 2.26, 1.41 (m, 2H, H-5), 1.49 (s, CH_3), 1.39 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6 (C), 136.9 (C), 129.7 (CH), 128.3 (CH), 217.1 (CH), 126.9 (CH), 109.7 (C*iso*), 100.8 (C-2), 78.4 (CH), 69.8 (CHOH), 67.9 (2C, C-4, C-6), 66.0 (CH_2O), 27.0 (CH_3), 26.0 (C-5), 25.7 (CH_3). Second stereoisomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (m, 1H, H aromatic), 7.45 (m, 1H, H aromatic), 7.26 (m, 2H, H aromatic), 5.72 (s, 1H, H-2), 5.10 (dd, *J*=3.0, 7.3 Hz, CHOH), 4.44 (q, *J*=6.7 Hz, CHO), 4.22, 3.95 (m, 4H, H-4, H-6), 3.74 (d, *J*=6.6 Hz, CHO), 3.39 (d, OH), 2.20, 1.41 (m, 2H, H-5), 1.50 (s, CH_3), 1.40 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6 (C), 136.7 (C), 129.7 (CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 110.2 (C*iso*), 101.2 (C-2), 80.2 (CH), 71.5 (CHOH), 67.8 (2C, C-4, C-6), 66.4 (CH_2O), 27.2 (CH_3), 26.1 (2C, C-5, CH_3).

4.3.2. ((*S*)-2,2-Dimethyl-(1,3)-dioxolan-4-yl)-(2-(1,3)-dioxan-2-ylphenyl)-methane (22). Phenoxythiocarbonyl chloride (282 μg, 2.04 mmol) was added to a solution of alcohol **20** (400 mg, 1.36 mmol) and DMAP (498 mg, 4.08 mmol) in dry AcOEt (20 mL) at rt under argon. The mixture was stirred for 12 h at rt and then diluted with AcOEt (30 mL). The whole was washed with H_2O (3× 20 mL) and the extract was worked up. The residue was co-evaporated twice with toluene then dissolved in toluene (3 mL). Bu_3SnH (3.28 mL, 12.2 mmol) was added to the above solution containing AIBN (44.7 mg, 0.27 mmol) at 100 °C under argon atmosphere. After being heated for 45 min, the solvent was removed in vacuo and the crude product was purified by flash chromatography (ethylacetate/petroleum ether, 10:90) to yield compound **22** (261 mg, 69%) as an oil; $[\alpha]_D^{22}$ +8 (*c* 0.05 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (m, 1H, H aromatic), 7.25 (m, 3H, H aromatic), 5.70 (s, 1H, H-2), 4.39 (m, CHO), 4.26, 3.99 (m, 4H, H-4, H-6), 3.96 (dd, *J*=5.9, 8.2 Hz, CHO), 3.70 (dd, *J*=6.9 Hz, CHO), 3.18 (dd, *J*=6.0, 3.9 Hz, CH), 2.95 (dd, *J*=3.2, 13.9 Hz, CH), 2.26, 1.41 (m, 2H, H-5), 1.48 (s, CH_3), 1.37 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.3 (C), 135.7.9 (C), 130.7 (CH), 129.3 (CH), 127.2 (CH), 127.1 (CH), 109.3 (C*iso*), 100.6 (C-2), 77.0 (CHO), 69.3 (CH_2O), 67.9 (2C, C-4, C-6), 36.7 (CH_2), 27.5 (CH_3), 26.2 (CH_3), 26.1 (C-5); ESI-HRMS: $[M+Na]^+$ *m*/*z* 301, found 301.1418, $C_{16}H_{22}O_4Na$ requires 301.1416. Anal. Calcd for $C_{16}H_{22}O_4$ (278.15 g/mol): C, 69.04; H, 7.97. Found: C, 69.15; H, 8.02.

4.3.3. (1*R*,3*S*)-Acetyloxymethyl-1-methoxyisochroman (14*S*). Compound **22** (500 mg, 1.80 mmol) was dissolved in methanol HCl (1%, 10 mL) and the resulting mixture was stirred for 2 h at rt. Et_3N (2 mL) was added, the mixture was stirred for 30 min at rt and then extracted with EtOAc (10 mL). The extract was worked up and the crude product was co-evaporated successively with toluene (3×5 mL) and pyridine (5 mL). The residue was dissolved in anhydrous pyridine (3 mL) and Ac_2O (235 μL, 2.5 mmol) was added. The resulting mixture was stirred overnight at rt. MeOH (3 mL) was added and the mixture was evaporated to

dryness. The residue was co-evaporated with toluene and was purified by flash chromatography (EtOAc/petroleum ether, 30:70) to yield the (1*R*,3*S*) isomer **14*S*** as the major isomer; enantiomer **14*S*** had NMR data identical to those for the racemic compound **rac-14**; ESI-HRMS: $[M+Na]^+$ *m/z* 259, found 259.0950, $C_{13}H_{16}O_4Na$ requires 259.0946.

4.3.4. (1′*R*,3′*S*)-1-(3-Acetyloxymethyl-isochroman-1-yl) thymine (15*S*) and (1′*S*,3′*S*)-1-(3-acetyloxymethyl-1-isochroman-1-yl)thymine (16*S*). Compound **14*S*** was converted to the thymine nucleoside analogue by the procedure employed above for the racemate. The mixture of stereoisomers was separated by chromatography as above to give the (1*R*,3*S*) isomer **15*S*** $[\alpha]_D^{22}$ +16 (*c* 0.05 in $CHCl_3$); enantiomer **15*S*** had NMR data identical to those for the racemic compound **rac-15**; ESI-HRMS: $[M+Na]^+$ *m/z* 353, found 353.1118, $C_{17}H_{18}N_2O_5Na$ requires 353.1113 and the (1*S*,3*S*) isomer **16*S*** $[\alpha]_D^{22}$ −4 (*c* 0.05 in $CHCl_3$); ESI-HRMS: $[M+Na]^+$ *m/z* 353, found 353.1098, $C_{17}H_{18}N_2O_5Na$ requires 353.1113.

4.3.5. (1′*R*,3′*S*)-1-(3-Hydroxymethyl-isochroman-1-yl) thymine (8*S*). Compound **15*S*** was converted to the thymine nucleoside analogue by the procedure employed above for the racemate to give the nucleoside **8*S***; enantiomer **8*S*** had NMR data identical to those for the racemic compound **rac-8**; $[\alpha]_D^{22}$ +18 (*c* 0.06 in $CHCl_3$); ESI-HRMS: $[M+Na]^+$ *m/z* 311, found 311.1017, $C_{15}H_{16}N_2O_4Na$ requires 311.1008.

4.3.6. (1′*S*,3′*S*)-1-(3-Hydroxymethyl-isochroman-1-yl) thymine (17*S*). Compound **16*S*** was converted to the thymine nucleoside analogue by the procedure employed above for the racemate to give the nucleoside **17*S***; enantiomer **17*S*** had NMR data identical to those for the racemic compound **rac-17**; $[\alpha]_D^{22}$ +3 (*c* 0.06 in $CHCl_3$); ESI-HRMS: $[M+Na]^+$ *m/z* 311, found 311.0995, $C_{15}H_{16}N_2O_4Na$ requires 311.1008.

4.4. Lipase-catalyzed kinetic resolution of rac-8 and rac-17

4.4.1. Lipase screening for the resolution of isochromans 8 and 17. Ten milligrams of each isochroman of was dissolved in 100 mL of vinyl acetate. Then, 0.2 mL of this solution was incubated at rt in the presence of 3 mg of each lyophilized enzymatic preparation. The course of the transesterification was followed by means of TLC (silica gel plates, eluent petroleum ether/acetone 1:1, R_f 0.35 and 0.73 for 17 and corresponding acetate, 0.29 and 0.69 for 8 and corresponding acetate). Spots were revealed by UV at 254 nm.

4.4.2. Enzymatic resolution of isochroman rac-17. rac-17 31.8 mg (0.11 mmol) in 200 mL of vinyl acetate and 500 mg of freeze-dried PPL lipase were incubated at rt for 48 h with magnetic stirring. Then, the lipase was filtered and vinyl acetate was eliminated under vacuum. NMR analysis of the mixture indicated a conversion of 51%. The reaction products were separated by silica gel flash chromatography (eluent petroleum ether/acetone 1:1), which afforded 16 mg of ester (96% yield, ee=0.74, determined by means of chiral HPLC t_{r1}=16.8 min and t_{r2}=26.8 min) and 14 mg of remaining alcohol (84% yield, ee=0.78, determined by means of chiral HPLC t_{r1}=7.5 min and t_{r2}=11.2 min).

4.4.3. Enzymatic resolution of isochroman rac-8. rac-8 30 mg (0.10 mmol) in 200 mL of vinyl acetate and 300 mg of freeze-dried PPL lipase were incubated at rt for 7 h with magnetic stirring. Then, the lipase was filtered and vinyl acetate was eliminated under vacuum. NMR analysis of the mixture indicated a conversion of 33%. The reaction products were separated by silica gel flash chromatography (eluent petroleum ether/acetone 1:1), which afforded 9 mg of ester (90% yield, ee=0.98, determined by means of chiral HPLC t_{r1}=17.2 min and t_{r2}=20.7 min) and 16 mg of remaining alcohol (80% yield, ee=0.74, determined by means of chiral HPLC t_{r1}=7.5 min and t_{r2}=8.8 min).

4.5. Synthesis of the Mosher's esters 23*S*, 23*R*, 24*S* and 24*R*

4.5.1. General procedure for the preparation of Mosher's esters of isochromans. Purified acetates obtained by lipase transesterification were hydrolyzed in the presence of ammoniac methanol solution. Corresponding alcohols as well as remaining alcohols were derivatized as follows. In an NMR tube, isochroman **8** or **17** (5 mg, 17 μmol) was dissolved in 0.7 mL of pyridine d_5 and 25 μL of a solution of (*R*)-Mosher's chloride (50 mg, 198 mmol in 0.25 mL of CCl_4) was added. The course of the reaction was followed by means of ^1H NMR spectroscopy. When the alcohol had completely disappeared, the solvents were removed under reduced pressure. Then, the residue was dissolved in 20 mL of ether and the solution was washed twice with Na_2CO_3 saturated solution, then twice with water. After elimination of ether, the corresponding (S)-Mosher's esters were obtained with sufficient purity for their further analysis by NMR spectroscopy.

4.5.2. Compound 23*S*. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.22 (s, 1H, NH), 7.25, 7.19, 7.18, 6.97 (9H, H aromatic), 7.00 (s, 1H, H-1′), 6.60 (q, J=1.2 Hz, 1H, H-6), 4.17 (m, 1H, H-3′), 4.41 (dd, $J_{9'a,9'b}$=11.7 Hz, $J_{3',9'a}$=5.1 Hz, 1H, H-9′a), 4.41 (dd, $J_{3',9'b}$=5.1 Hz, 1H, H-9′b), 3.44 (s, 3H, CH_3O), 2.77 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=5.3 Hz, 1H, H-4′a), 2.77 (dd, $J_{3',4'b}$=8.4 Hz, 1H, H-4′b), 1.71 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (COO), 163.4 (C-4), 151.0 (C-2), 136.9 (C-6), 123.2 (CF_3), 110.6 (C-5), 79.7 (C-1′), 67.9 (C-3′), 67.1 (C-9′), 29.8 (C-4′), 12.5 (CH_3 thymine).

4.5.3. Compound 23*R*. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.18 (s, 1H, NH), 7.25, 7.19, 7.18, 6.97 (9H, H aromatic), 6.99 (s, 1H, H-1′), 6.57 (q, J=1.2 Hz, 1H, H-6), 4.12 (m, 1H, H-3′), 4.42 (dd, $J_{9'a,9'b}$=11.7 Hz, $J_{3',9'b}$=6.8 Hz, 1H, H-9′b), 4.38 (dd, $J_{3',9'a}$=4.0 Hz, 1H, H-9′a), 3.45 (s, 3H, CH_3O), 2.77 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=6.8 Hz, 1H, H-4′a), 2.77 (dd, $J_{3',4'b}$=6.8 Hz, 1H, H-4′b), 1.69 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5 (COO), 163.4 (C-4), 151.0 (C-2), 136.9 (C-6), 123.3 (CF_3), 110.4 (C-5), 79.7 (C-1′), 67.8 (C-3′), 67.2 (C-9′), 29.8 (C-4′), 12.4 (CH_3 thymine).

4.5.4. Compound 24*S*. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 1H, NH), 7.25, 7.19, 7.12, 6.91 (9H, H aromatic), 7.02 (s, 1H, H-1′), 6.62 (q, J=1.2 Hz, 1H, H-6), 4.25 (m, 1H, H-3′), 4.50 (dd, $J_{9'a,9'b}$=11.7 Hz, $J_{3',9'b}$=6.1 Hz, 1H, H-9′b), 4.38

(dd, $J_{3',9'a}$=3.9 Hz, 1H, H-9′a), 3.48 (s, 3H, CH_3O), 2.67 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=2.8 Hz, 1H, H-4′a), 2.96 (dd, $J_{3',4'b}$=11.6 Hz, 1H, H-4′b), 1.74 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (COO), 163.3 (C-4), 151.0 (C-2), 136.5 (C-6), 123.2 (CF_3), 111.8 (C-5), 81.0 (C-1′), 72.2 (C-3′), 67.0 (C-9′), 29.8 (C-4′), 12.4 (CH_3 thymine).

4.5.5. Compound 24*R*. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 1H, NH), 7.25, 7.19, 7.12, 6.92 (9H, H aromatic), 7.04 (s, 1H, H-1′), 6.61 (q, J=1.2 Hz, 1H, H-6), 4.25 (m, 1H, H-3′), 4.49 (dd, $J_{9'a,9'b}$=11.8 Hz, $J_{3',9'b}$=3.8 Hz, 1H, H-9′b), 4.41 (dd, $J_{3',9'a}$=5.3 Hz, 1H, H-9′a), 3.49 (s, 3H, CH_3O), 2.67 (dd, $J_{4'a,4'b}$=16.3 Hz, $J_{3',4'a}$=2.8 Hz, 1H, H-4′a), 2.93 (dd, $J_{3',4'b}$=11.7 Hz, 1H, H-4′b), 1.69 (d, 1H, CH_3 thymine); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (COO), 163.3 (C-4), 149.9 (C-2), 136.5 (C-6), 123.2 (CF_3), 111.8 (C-5), 81.0 (C-1′), 72.1 (C-3′), 67.0 (C-9′), 29.8 (C-4′), 12.3 (CH_3 thymine).

4.6. Molecular modeling

4.6.1. Force fields and energy minimization. The conformational analysis was studied considering molecules without the presence of solvent and with the hypothesis that the energies of the conformations were qualitatively correlated to their existence probability via the Boltzmann relationship. Considering molecular mechanics calculations, only the relative energies of identical configurations were comparable and the lowest energies correspond to the most stable conformations. Since the molecular weights of the molecules studied were relatively low, it was possible to undertake a systematic study of the conformations via a screening of dihedral angles. In connection with this systematic conformational research, the different molecular geometries studied were not obtained from experimental data but were produced from a builder module ('Builder').

4.6.2. Initial molecular building. Enantiomers of isochromans **8** and **17** were first studied. The central bicyclic nucleus presented a low conformational flexibility since the aromatic ring considerably limited the pseudo-rotation of the pyran ring. Thus, this bicyclic system adopted a quasi-planar geometry and the only conformational duality was revealed by the shift of the pyran oxygen atom above or below the plane. The energy barrier between the two resulting conformations was sufficient to divide further energy calculations into two individual classes, unable to interconvert when energy minimizations were applied. In the initial molecular building, two dihedral angles were systematically screened with 10° steps: $C_2N_1C_{1'}O_{2'}$ (α angle already defined in text, see Table 1) and $O_{2'}C_{3'}C_{9'}O_{9'}$.

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