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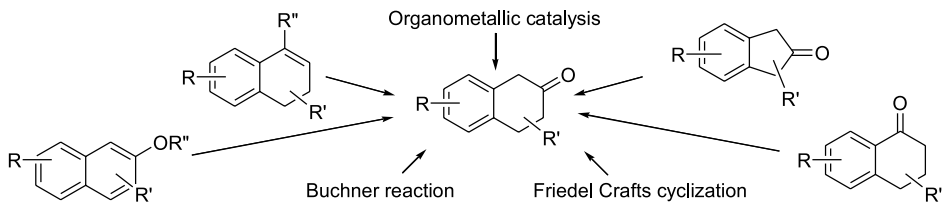
Contents

REPORT



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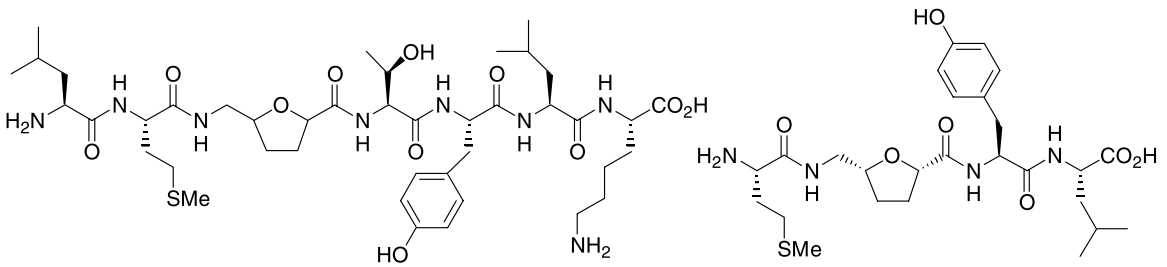

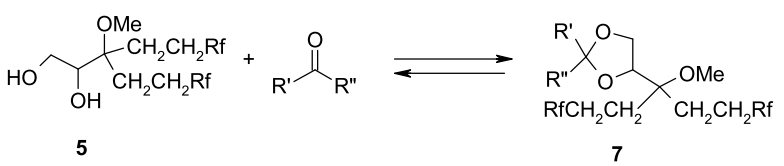

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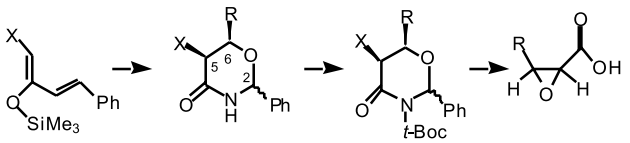
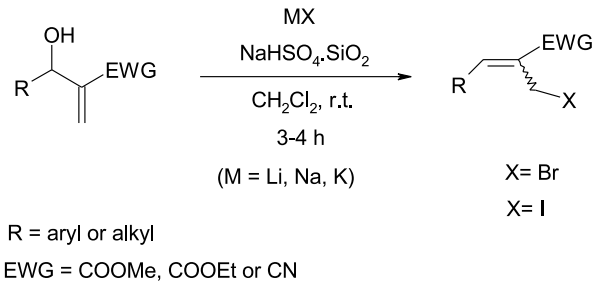
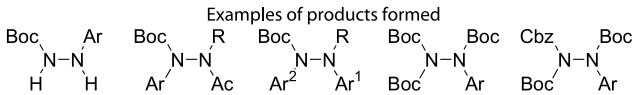
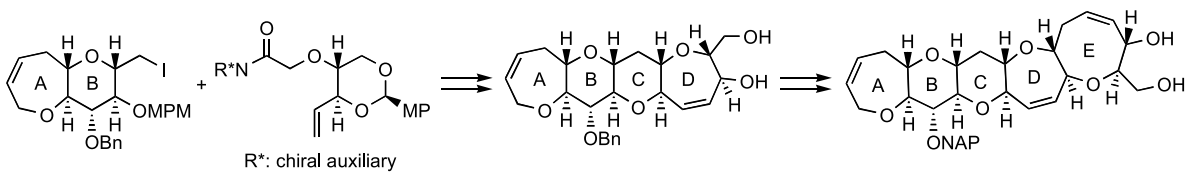
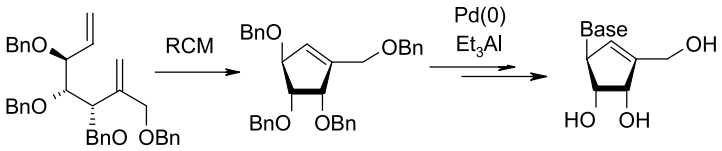


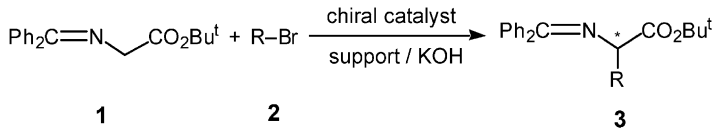


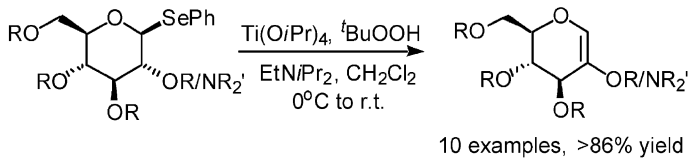


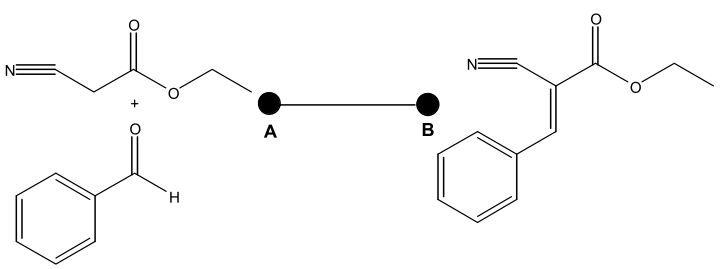




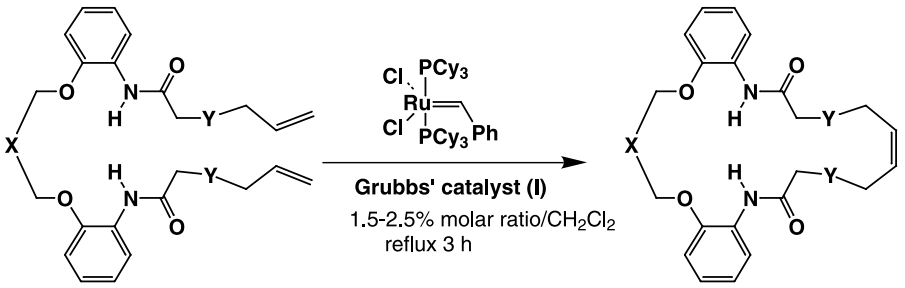
The enantiomeric synthesis of L-cyclopentenyl nucleosides is described using a ring closing metathesis reaction and the coupling of purine and pyrimidine bases under Pd(0)-catalyzed Tsuji–Trost allylic alkylation's. The Pd catalyzed reaction was found to require the use of $AlEt_3$.



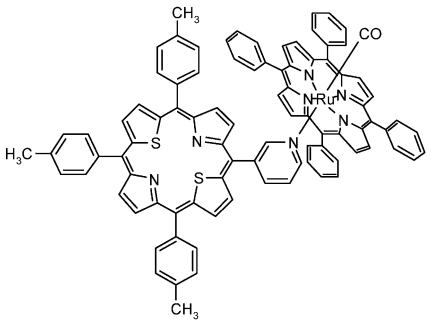


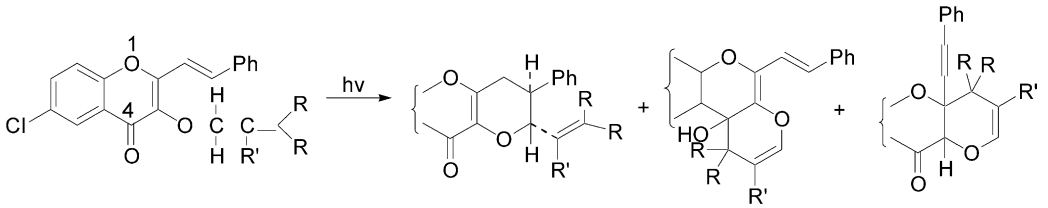


By incorporating a series of silica-supported bases into an EOF-based flow reactor, we demonstrate the synthesis of eight condensation products in excellent yields, without the need for additional purification steps.

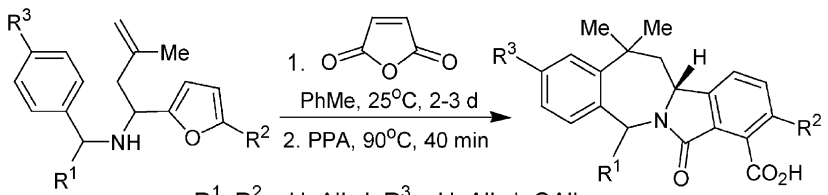


X = -, CH_2, (CH_2OCH_2), $(CH_2OCH_2)_2$, *o*-C_6H_4; Y = O, *o*-OC_6H_4O

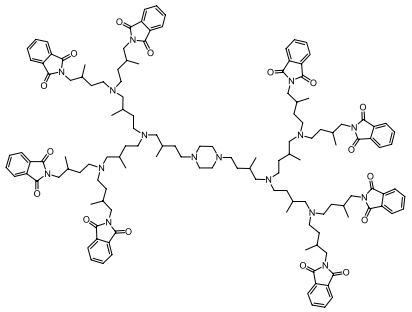


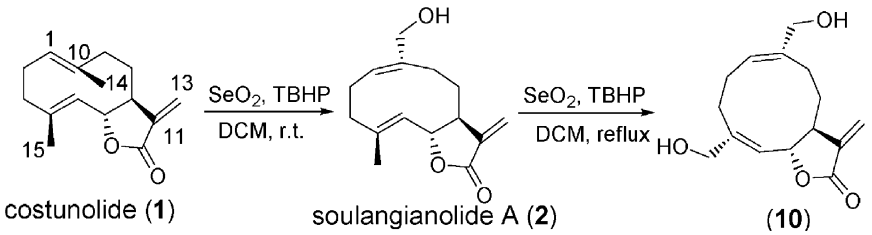


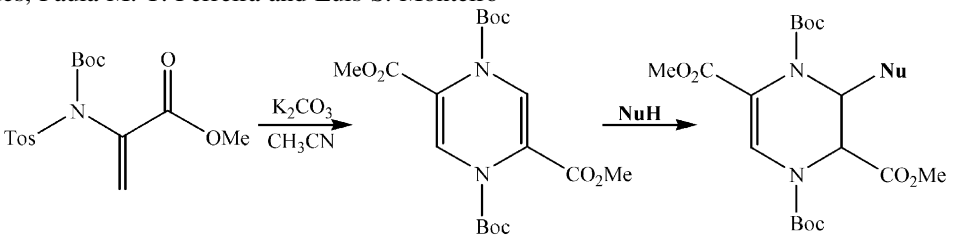
R = R' = H; R = H, R' = CH_3; R = CH_3, R' = H



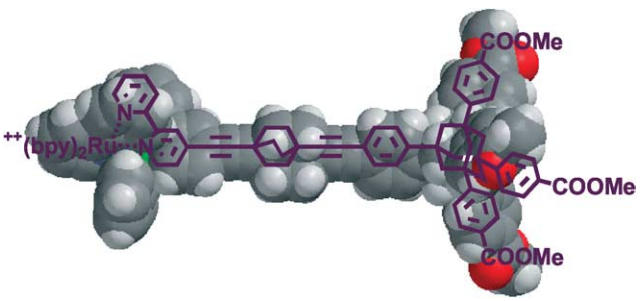
R^1, R^2 = H, Alkyl; R^3 = H, Alkyl, OAlk

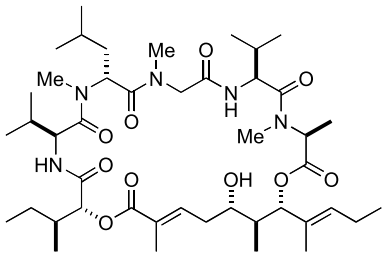


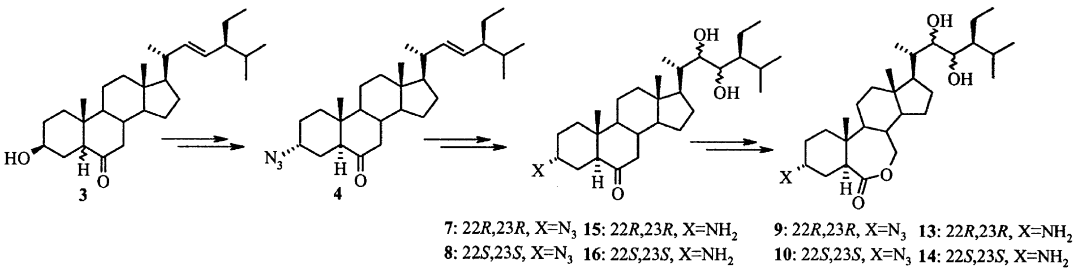


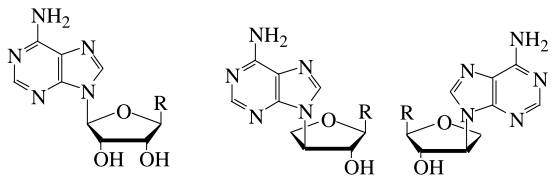


N,*N*-Bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine can be obtained in high yield by treatment of the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine with dimethylaminopyridine and potassium carbonate. This compound was used as substrate in Michael addition reactions with several nucleophiles. The electrochemical behaviour of this dehydropyrazine was studied by cyclic voltammetry and by controlled potential electrolysis.



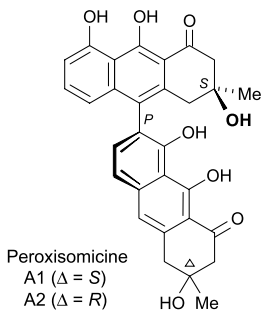


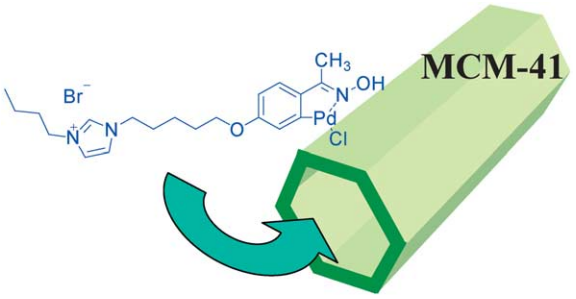


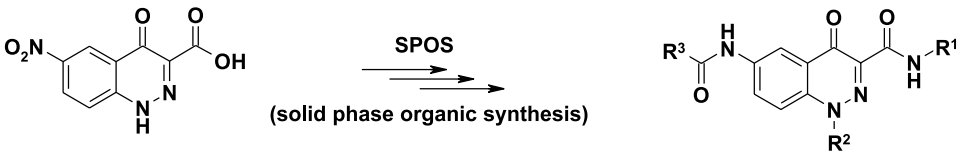


R=Ethylenic and Acetylenic groups

Two series of 6′-halovinyl-adenosine stereoisomers were synthesized. Some isomers show the inhibition of SAH hydrolase and inhibition effects on the growth of HeLa cells or Bel-7420 cells.







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*Corresponding author
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Synthetic approaches to 2-tetralones

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1. Introduction

The 2-tetralones, also known as 3,4-dihydro-1*H*-naphthalen-2-ones and β-tetralones (Fig. 1), are aromatic bicyclic ketones derived from tetraline (**1**). 2-Tetralone (**2**) is the simplest member of this family of useful ketones. The 2-tetralones are of great interest in organic synthesis, specially because of their high reactivity[1] and suitability as precursors of several natural products and their derivatives.[2,3] The 2-tetralones are also very useful as starting materials for synthetic compounds with biological activities and other useful properties, including steroids (specially estrogens and antiandrogens), prostaglandin analogs, dyes, heterocycles and pharmaceuticals.[4–7]

1 **2**

Figure 1. Chemical structures of tetraline (**1**) and 2-tetralone (**2**).

However, unlike their congeners the 1-tetralones, which are inexpensive substances, the 2-tetralones are usually more difficult to synthesize and some of them are highly unstable, requiring proper storage conditions, such as freezing, for their long-time preservation. In addition, preparation of 2-tetralones has long been hampered either by poor yields or difficulty accessible starting materials.

Chemists have been interested in 2-tetralones since the beginnings of the 20th century and even before.[8] However, after the Robinson's paper describing the use of 2-tetralones as starting materials for the preparation of steroids,[9] the increasing interest and application of 2-tetraline derivatives have stimulated the publication of a large number of articles describing aspects related to the preparation and reactivity of these valuable ketones.

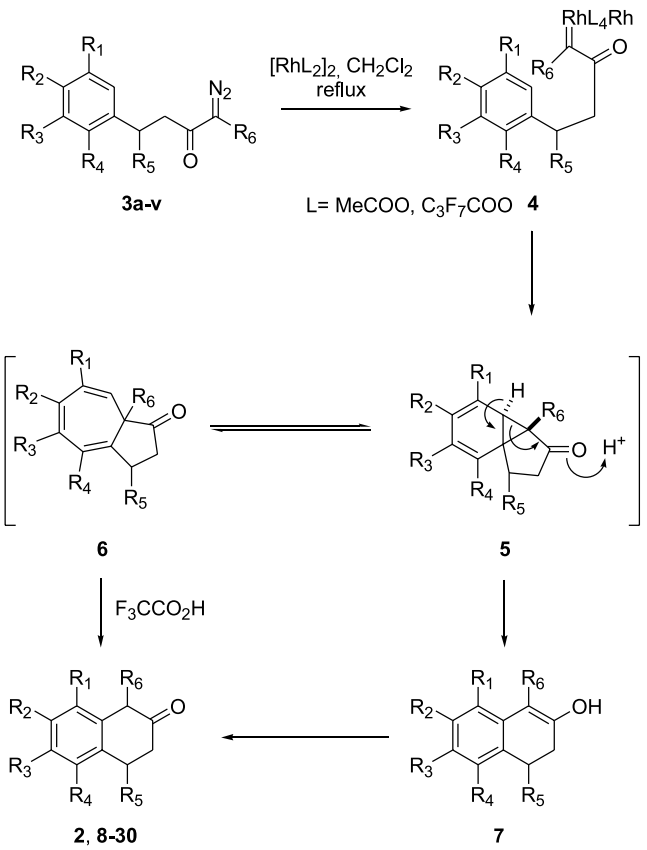
This allowed the synthesis of terpenes, novel aminoacids, benzomorphan derivatives, and bioactive compounds of interest in medicinal chemistry[10,11] and other fields. A simple chemical test has been designed for their detection, and 2-tetralones unsubstituted on C-1 give a characteristic reaction in the 'tetralone blue' test, first described by Cornforth.[12]

The only review article covering the preparation, chemical properties and some applications of 2-tetralones dates from 1966,[13] and since then several important improvements, as well as new, more general and powerful methodologies aiming towards the synthesis of 2-tetralones, have been described. In this review, we will provide an update on the different methods available for the synthesis of 2-tetralones. Aspects regarding the reactivity and use of 2-tetralones for the elaboration of more complex targets will not be covered, except for some specific examples.

For a better discussion, the arsenal of synthetic methodologies for the preparation of 2-tetralones has been divided here into three major groups: (a) methods involving the direct building of tetralines, generally from monocyclic aromatic precursors; (b) methods involving transformations within a pre-formed tetraline ring or a naphthalene type precursor, and (c) methods based on the ring-expansion of 1-indanones.

2. Methods involving the direct building of tetralines

Until the middle of the 1960s, the most frequently employed methods for the synthesis of 2-tetralones were those related to transformations of preformed precursors, specially those with a naphthalene framework (2-naphthol and/or 2-methoxynaphtalene, and their derivatives).[8,10,14,15] The main reason behind this preference was that this approach



Scheme 1. Rhodium(II)-catalyzed cyclization of α-diazoketones employing the Buchner reaction.

furnished the desired products either in pure form or with their isomeric composition unequivocally known in advance. At that time, this was an important synthetic aspect, considering the severe limitations of the methods available for characterization of the products.

However, with the advent of modern analytical techniques, specially high field NMR, together with the development of more selective methodologies for the direct building of polysubstituted tetralines, the de novo synthesis of tetraline derivatives, comprising the construction of the tetraline ring system from appropriately substituted benzenoid precursors, became one of the most widely employed approaches to 2-tetralones, specially for those carrying activating substituents on the aromatic ring.

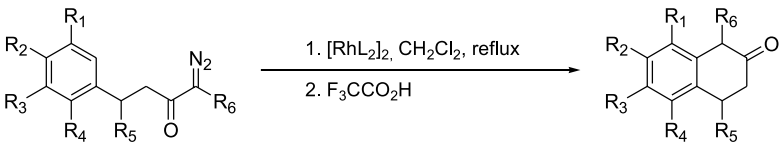
2.1. Intramolecular cyclization of α-diazo carbonyl compounds

The rhodium(II)-catalyzed decomposition of α-diazoketones **3** with concomitant rearrangement (Scheme 1), known as the Buchner reaction,[16] was first described as a convenient and general entry to polysubstituted 2-tetralones by McKervey and co-workers, in 1984.[17]

This was disclosed following the discovery of Teyssié that rhodium(II) carboxylates strongly facilitate nitrogen loss from diazo compounds, presumably by forming carbenoid species, such as **4**.[18] These authors synthesized several 2-tetralones (**2**, **8**–**30**) in very good yields (Table 1). It was observed that rhodium(II) acetate, as well as the corresponding heptafluorobutyrate can be used in this transformation, the latter forming more reactive, highly electrophilic carbenoids, compared with the former.

Several other groups employed this method to prepare 2-tetralones, as intermediates for their projected syntheses of natural alkaloids,[19] tetraline analogues of amphetamine[20a] topoisomerase I inhibitors,[21] melatonin analogues,[22] and a new series of α-adrenergic agonists.[23] The mechanistic aspects of the reaction have been exhaustively studied, as a consequence of the observation

Table 1. Synthesis of 2-tetralones employing the Buchner reaction



3a-v **2, 8-30**

Entry no.	Diazoketone	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	Reference
1	**3a**	**2**	H	H	H	H	H	H	87	17a
									86	17b
2	**3b**	**8**	H	H	H	OMe	H	H	63	25d
									—[a]	25a
									13	25c
3	**3c**	**9**	H	H	OMe	H	H	H	65	25a
									86	17a
									—[a]	17b
4	**3d**	**10**	H	H	H	OMe	Me	H	60	24a
5	**3e**	**11**	H	Me	H	H	H	H	84	17a
									85	17b
6	**3f**	**12**	H	OMe	H	H	H	H	88	17a,b
7	**3g**	**13**	H	Oac	H	H	H	H	90	17a,b
8	**3h**	**14**	H	H	H	Me	H	H	86	17a,b
9	**3i**	**15**	OMe	H	H	H	H	H	84	17a,b
									20	22a
10	**3j**	**16**	H	H	OAc	H	H	H	77	17a
									80	17b
11	**3k**	**17**	H	H	OMe	H	H	Me	80	25a
12	**3l**	**18**	Me	H	H	H	H	H	87 (7:3)	17b
		19	H	H	Me	H	H	H		
13	**3m**	**20**	H	OMe	OMe	H	H	H	96 (8:2)	17a,b
		21	OMe	OMe	H	H	H	H		
14	**3n**	**22**	H	–OCH$_2$O–			H	H	97	17a,b
									35.5	20a
15	**3o**	**23**	–OCH$_2$O–		H	H	H	H	21	20a
16	**3p**	**24**	OMe	OMe	OMe	H	H	H	89	17a
									90	17b
17	**3q**	**25**	H	OMe	OAc	H	H	H	65	17a
18	**3r**	**26**	H	Oac	OAc	H	H	H	95	17a
19	**3s**	**27**	H	CF_3	H	H	H	H	61	23a
20	**3t**	**28**	H	Me	H	Me	H	H	—[a]	23a
21	**3u**	**29**	H	Me	H	OMe	H	H	—[a]	23a
22	**3v**	**30**	Cl	H	H	OMe	H	H	—[a]	23a

[a] Chemical yields were not informed.

of conflicting results regarding the nature of the intermediates and the products formed, when the starting diazoketone carried methoxy groups capable of participating in the reaction.[24,25]

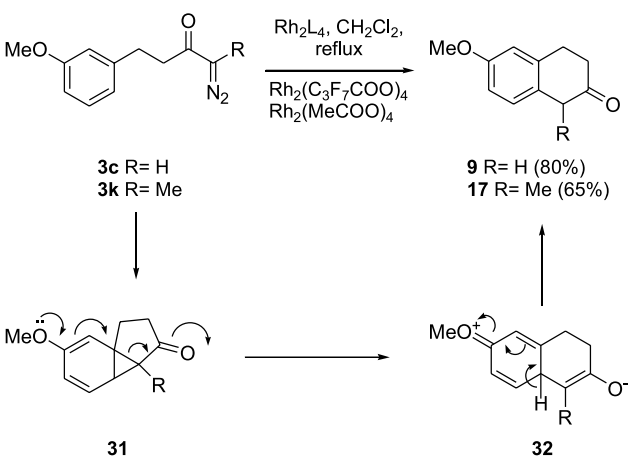
A salient feature of this transformation is the proposed equilibrium between the norcaradienone (**5**) and the cycloheptatrienone [3,8a-dihydroazulen-1(2*H*)-one, **6**] intermediates (Scheme 1).[17a,23a]

Under acidic conditions, the tricyclic intermediate **5** which is the kinetic product, can be protonated leading to a formal cyclopropyl carbenium ion. In turn, this rearranges[26] by the opening of a C–C bond to allow rearomatization, leading to the enolic form **7** of the product.

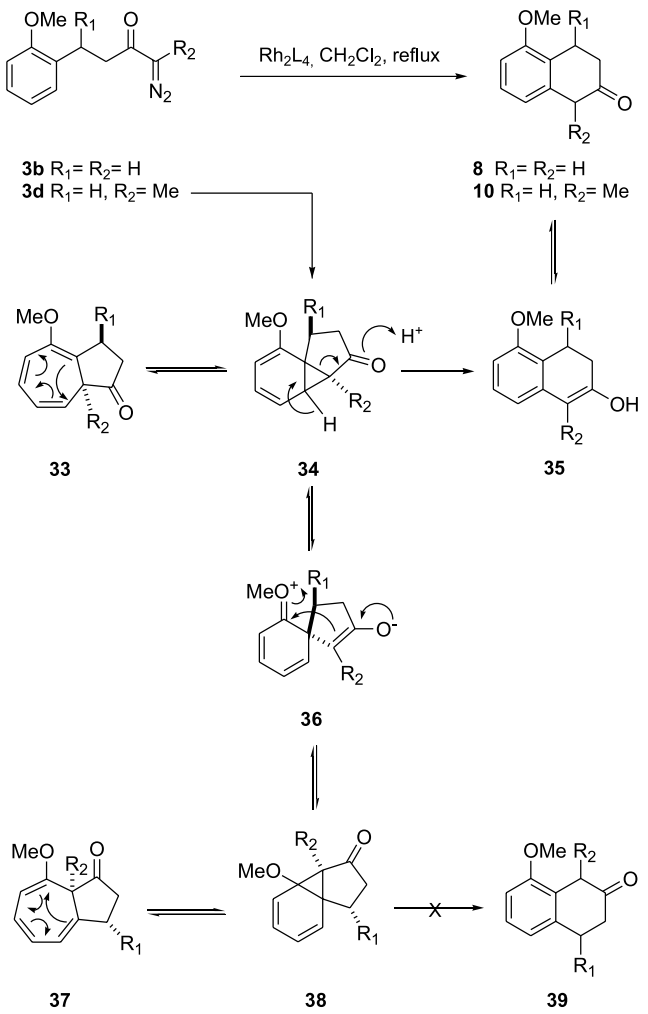
A similar mechanism was proposed to explain the rearrangement and the occurrence of 6-oxo-isopropylcyclohexene from a cyclopropyl ketone derivative.[27]

Interestingly, the methoxy substituent can affect the efficiency of the cyclization, and its regio- and stereoselectivity, having also some effect on the position of the equilibrium between the norcaradiene and the cycloheptatriene tautomers, by affecting their relative stabilities.[24]

Schemes 2 and 3 illustrate about the participation of the methoxy groups in the course of the reaction. In the first case, access to 2-tetralones **9** and **17** was carried out from the corresponding diazoderivatives **3c** and **3k** (Scheme 2). Presumably, in this reaction caradiene **31** is an intermediate which, aided by the methoxy group, provides enolate **32**. In the second case, 2-tetralones such as **8** and **10** can be obtained through the intermediacy of caradienone **34** and enol **35**, being cycloheptatriene derivative **33** one of the species in equilibrium with the caradienone. Other equilibria and products can be postulated for this reaction. Intermediate **34** can be in equilibrium with caradienone **38**, through spiro derivative **36**. The methoxy group plays here an important role, allowing the potential rearrangement of **36** to **38** and vice versa. In turn, **38** can be in equilibrium with cycloheptatrienone **37**; however, because of structural factors, it seems that **37** cannot rearrange to tetralone **39**, which is not observed in the reaction medium.



Scheme 2. Mechanism of the rhodium(II)-catalyzed cyclization of α-diazoketones. Participation of the *m*-methoxy group.



Scheme 3. Mechanism of the rhodium(II)-catalyzed cyclization of α-diazoketones. Participation of the *o*-methoxy group.

The starting α-diazoketones **3** can be conveniently accessed from the related phenylpropionic acids, by the reaction of their corresponding acid chlorides with diazomethane (R_6=H) or other diazo derivatives.[23a] The introduction of the R_5 substituent has been conveniently carried out in 45–73% yield, by conjugate addition of aryl Grignard reagents to buten-2-oic acid or aliphatic Grignards to cinnamic acid derivatives.[24a] It has been observed that sometimes, the Buchner reaction method is not selective, delivering more than one product; this is the case of some substituents and substitution patterns, (cf. Table 1, entries 12 and 13). Noteworthy, 5-methoxy-2-tetralone (**8**) and 6-methoxy-2-tetralone (**9**) accessed by this method, have been employed as starting materials for the synthesis of homosteroids.[23b]

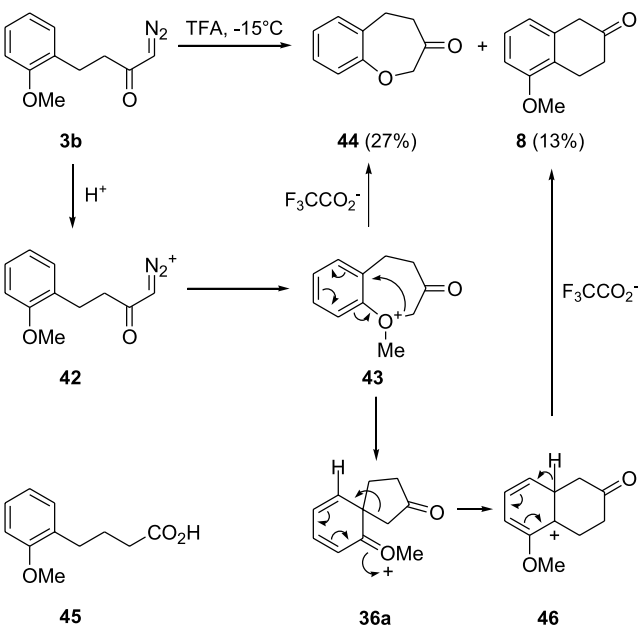
In an extension of the same transformation, 5,6a-dihydrocyclohepta[*a*]naphthalen-6-one **41** was prepared by rhodium catalyzed decomposition of biphenyl derivative **40** carrying a suitably placed α-diazoketone side chain, as shown in Scheme 4,[28] and the solid-phase synthesis of 7-hydroxy-2-tetralone in 60% overall yield, by the diazoketone cyclization methodology and employing the Wang resin, has been recently reported.[29]

Scheme 4. Synthesis of 5,6a-dihydro-cyclohepta[*a*]naphthalen-6-one **41**.

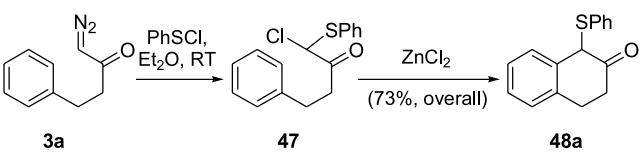
Interestingly, Ghosh and co-workers published the synthesis of 5-methoxy-2-tetralone (**8**) in 13% yield, by the trifluoroacetic acid-catalyzed cyclization of the corresponding α-diazoketone **3b**; in this process, however, the related benzo[*b*]-1-oxepan-3-one **44** was obtained as the main product, in 27% yield.

The postulated reaction mechanism, different from the rhodium-catalyzed decomposition of α-diazoketones, is shown in Scheme 5. It involves the participation of the methoxy group and the aromatic ring in the ketocarbocations **36a** and **46** successively produced from **43** by TFA-mediated (thermodynamic control) protonation of **3b** and attack of the resulting **42** to the methyl ether.[30] Interestingly, attempts to photochemically (254 nm or 365 nm) cyclize diazoketone **3b** met with failure, providing butyric acid derivative **45**.[31]

A somehow related transformation starting with α-diazoketones was disclosed by McKervey and Ratananukul (Scheme 6).[32] Employing phenylsulfenyl chloride, diazoketone **3a** was converted into the α-chloro-α-phenylsulfenyl ketone **47**. This adduct is a powerful electrophile for intramolecular cyclization, leading to tetralone **48a** upon reaction with a Lewis acid such as zinc chloride, as promoter.[33] The transformation **47→48a** bears some resemblance with the cyclization of β-ketosulfoxides, discussed in Section 2.5.



Scheme 5. Acid-catalyzed decomposition of α-diazocarbonyls. Proposed mechanism.

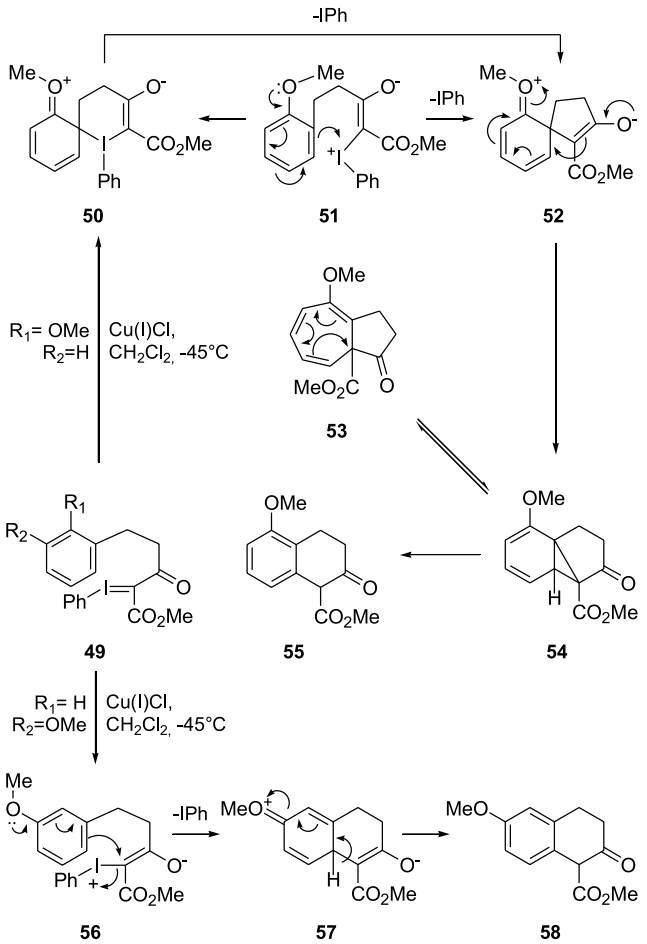


Scheme 6. Cyclization of α-halo-α-phenylthio ketones to 2-tetralone **48a**.

2.2. Intramolecular cyclization of aryl substituted iodonium ylides with copper(I) chloride

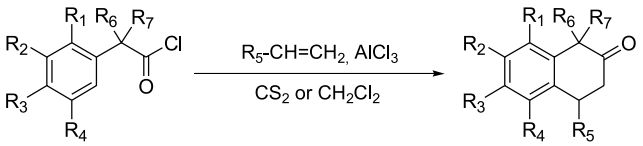
Iodonium ylides derived from β-dicarbonyl compounds are synthetically equivalent to the corresponding diazo β-dicarbonyl compounds in certain reactions. For example, the hypervalent iodine derivatives formed from β-ketoesters participate in the copper(I) chloride promoted intramolecular cyclopropanation of alkenes if the double bonds are appropriately positioned within the molecule.[34] Iodonium ylides of β-ketoesters also effect intramolecular C–H insertion upon decomposition by $Rh_2(OAc)_4$[35] and the group of Padwa has used iodonium ylides as diazo equivalents in intramolecular cycloadditions of carbonyl ylides.[36]

This analogy was exploited by Moriarty and co-workers in the design of a cyclization strategy, which is very similar to the Buchner reaction, where a C=N unit was substituted by



Scheme 7. Synthesis of 2-tetralones by intramolecular cyclization of aryl substituted iodonium ylides.

Table 2. Preparation of 2-tetralones by cyclization of phenyl acetyl chlorides with different alkenes, under Friedel–Crafts reaction conditions



59

Entry no.	Phenylacetyl chloride	Product (2-tetralone)	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield (%)	References
1	**59a**	**60**	H	H	H	H	Bn	H	H	26	48a
2	**59a**	**61**	H	H	H	H	Ph	H	H	56	50c
3	**59b**	**62**	H	H	Cl	H	H	H	H	70	46a
										84	49e
4	**59c**	**63**	Cl	H	H	H	H	H	H	69	49b
5	**59d**	**64**	H	Cl	H	H	H	H	H	47	46a
										61	49e
6	**59d**	**63**	H	Cl	H	H	H	H	H	—[a]	49b
		65	H	H	H	Cl	H	H	H	**63**+**65** (7:3)	
7	**59e**	**66**	H	Cl	H	Cl	H	H	H	58	46a
8	**59f**	**67**	H	Cl	Cl	H	H	H	H	58	46a
9	**59g**	**11**+**14** (2:1)								95	46b
		11	H	Me	H	H	H	H	H	—[a]	46c
		14	H	H	H	Me	H	H	H	52	38b
10	**59h**	**18**	Me	H	H	H	H	H	H	80	46b
		14	H	H	H	Me	H	H	H	**18**+**14** (1:2)	
11	**59i**	**19**	H	H	Me	H	H	H	H	86	46b
12	**59j**	**68**	H	Me	Me	H	H	H	H	—[a]	46c
		69	H	H	Me	Me	H	H	H	**68**+**69** (4:1)	
13	**59k**	**70**	Br	H	H	H	H	H	H	68	46d
										64	49b
14	**59k**	**71**	H	Br	H	H	H	H	H	68	46c
15	**59l**	**72**	H	H	Br	H	H	H	H	—[a]	48c
16	**59m**	**9**	H	H	OMe	H	H	H	H	68	49a
										85	49b
17	**59n**	**20**	H	OMe	OMe	H	H	H	H	50	49d
										—[a]	49e
18	**59o**	**73**	H	H	OEt	H	H	H	H	—[a]	49e
19	**59p**	**74**	H	H	O^{n}Pr	H	H	H	H	—[a]	49e
20	**59q**	**75**	H	H	I	H	H	H	H	37	50b
21	**59r**	**76**	–N(Ts)CH=CH–							62	48d
22	**59s**	**77**	H	H	H	H	H	Me	1-Phthalimide	14	48e

[a] Product yield was not informed.

a C=IPh group.[37] The advantages of this substitution are important, since it avoids potential carcinogenicity hazards associated with diazo compounds, allows the multigram preparation of the starting materials under safe conditions and synthesis of the iodonium ylides is simply done by treatment of the β-dicarbonyl compounds with $PhI(OAc)_2$ and KOH.

The proposed cyclization mechanism is somehow reminiscent to that of the α-diazoketones and is depicted in Scheme 7. Attack to **49** may be at the iodonium center with subsequent loss of iodobenzene from **51**, or from the tricoordinated iodane intermediate **50**, forming spirocyclic compound **52**. In the case of 5-MeO and 7-MeO derivatives, the reaction mechanism involves intramolecular cyclopropanation of the arene ring, furnishing intermediate **54**. In turn, this can eventually be in equilibrium with the corresponding Buchner type cycloheptatriene ketone **53** or be transformed into 2-tetralone **55**.

Only the *meta*-methoxy derivative **56** can directly aromatize to 2-tetralone **58** by simple deprotonation of the intermediate **57**. Employing this approach, three different 2-tetralones were synthesized in 75–82% yield; curiously, however, the role of Cu(I)Cl in the generation of the dipolar intermediates **51** and **56** is unknown. 5-Methoxy derivative **55** has been employed as precursor for the synthesis of a benzidine analog of prostacyclin.[38]

2.3. Synthesis of 2-tetralones using a Friedel–Crafts acylation–cycloalkylation sequence with simple alkenes

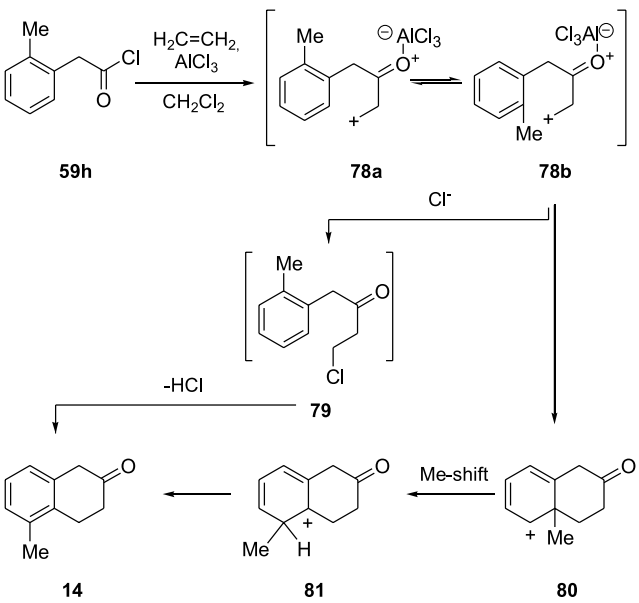
Carboannulation processes are among the most important reactions in organic synthesis.[39] The Friedel–Crafts type electrophilic substitution reactions are one of the most common carboannulation strategies available to the synthetic chemist.[40,41] The Friedel–Crafts acylation followed by cycloalkylation, through the reaction of aryl acetyl chlorides with olefins in the presence of $AlCl_3$, was initially reported by Cologne and Chambion in 1947.[42] Burckhalter and Campbell were the first in using ethylene for this kind of transformation, in 1961,[43] following the observations made in 1958 by Matsumoto, Hata and Nishida, that benzoyl chloride and ethylene formed 3-chloro-3-methyl butyrophenone in the presence of aluminum chloride as catalyst.[44] The reaction of acyl chlorides with ethylene to give ketones

is also known as the Darzens reaction.[45] Nowadays, this is one of the preferred methods for the preparation of 2-tetralones and since the original description, several publications have focused on the scope of the reaction (Table 2), reporting improvements and limitations.[23,46–50]

The best performance of the transformation was obtained with the use of an excess of $AlCl_3$ (3 equiv.) and the in situ generation of the acyl chloride. Sometimes, CH_2Cl_2 was found to be a better solvent than CS_2,[46b] being this attributed to the ability of the solvent to dissolve the acyl chloride–aluminum chloride complex.[46f] It was also demonstrated that the reaction can be carried out at room temperature and even at lower temperatures, depending on the activation degree of the aromatic ring.

Analogously to the Buchner cyclization, and despite the ready availability of the starting chlorides and the moderate to good yields obtained, this method suffers from low selectivity for some substrates, such as 3-chloro-phenylacetyl chloride (**59d**), 2- and 3-methylphenylacetyl chloride (**59g** and **59h**) and 3,4-dimethylphenylacetyl chloride (**59j**). The reaction mechanism, depicted in Scheme 8, provides the basis for rationalizing some interesting observations, such as the fact that 2-methyl phenylacetyl chloride **59h** gave rise to two isomeric 2-tetralones, **14** and **18**. Formation of unexpected 2-tetralone **14** occurs through a methyl migration (**80**→**81**).[46b] In this type of transformation, β-chloroethyl ketones like **79**, related to **78a** and **78b** have been isolated as intermediates.[49e,51]

It is accepted that the aluminum catalyst forms an acylium intermediate, which losses halide ion to form a carbocation which may react with a suitably placed π-system, such as ethylene, to furnish cationic intermediates (**78a**, **78b**); in turn, the latter may add chloride ion, to provide β-chloro-ketones such as **79**,[48a] or cyclize intramolecularly to yield the 2-tetralone products.

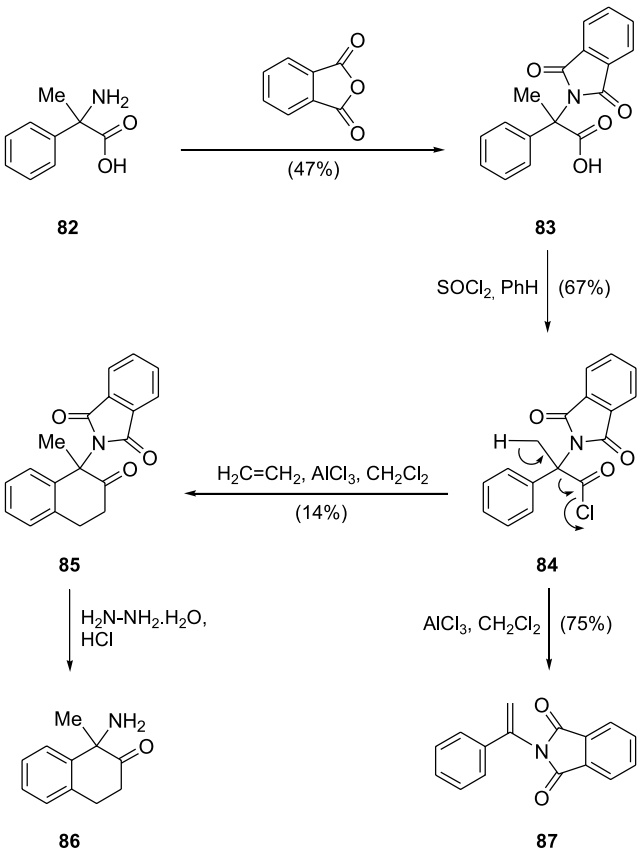


Scheme 8. Proposed mechanism for the formation of 5-methyl-2-tetralone **14** from 2-methyl-phenylacetyl chloride **59h**.[35b]

Chlorinated tetralone **62** and the related 1-methyl-6-chloro-2-tetralone[47a] were employed for the syntheses of the benzoquinolinones LY191704 and LY266111, which act as human type 1 steroid 5-α-reductase inhibitors,[47b] as well as for the elaboration of other benzoquinolinones with similar activity.[47c] Interestingly, however, the related 6-bromo-2-tetralone **72** was employed for the evaluation of an electrochemical reactor system in the biotransformation to the corresponding 2-tetralol,[47d] and in the synthesis of conformationally constrained phosphotyrosyl mimetics.[47e]

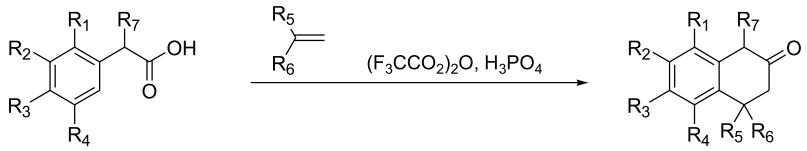
The intermediacy of **80** and a methyl shift explain the formation of rearranged 2-tetralone **14**. As expected, the reaction fails with some substrates carrying electron-withdrawing groups such as nitro on the aromatic moiety; nevertheless, some chlorinated derivatives have been obtained in fairly good yields following this method. It appears that the halogens retard the reaction rate to some extent, without affecting the preparative usefulness of the process.[52] The 6-nitro and 7-nitro 2-tetralones were simultaneously obtained by nitration of a preformed 2-tetralone.[50a] Similarly, nitration of 6-chloro-2-tetralone furnished the 7-nitro derivative.[50b] On the other hand, in case of *ortho* disubstituted ethers next to the acetyl side chain, an unusual reaction takes place, furnishing 2[3*H*]-benzofuranone derivatives, due to ether cleavage and intramolecular cyclization, instead of reaction with ethylene.[43]

When compared with older but not less effective methods, resorting to the reduction of naphthalene derivatives, the



Scheme 9. Friedel–Crafts type synthesis of 1-amino-2-tetralone **86**.

Table 3. Synthesis of 2-tetralones employing an environmentally friendly Friedel–Crafts reaction



85 **86**

Entry no.	Arylacetic acid	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield (%)
1	**88a**	**89a**	H	H	H	H	*n*-Bu	H	H	55
2	**88b**	**89b**	H	H	F	H	*n*-Bu	H	H	37
3	**88c**	**89c**	H	H	Me	H	*n*-Bu	H	H	74
4	**88d**	**89d**	H	H	OMe	H	*n*-Bu	H	H	62
5	**88e**	**89e**	H	OMe	OMe	H	*n*-Bu	H	H	76
6	**88f**	**89f**	H	H	H	H	*n*-Bu	H	Me	51
7	**88a**	**89g**	H	H	H	H	$CH_2CH_2CH_2Br$	H	H	55
8	**88c**	**89h**	H	H	Me	H	Me	Me	H	70

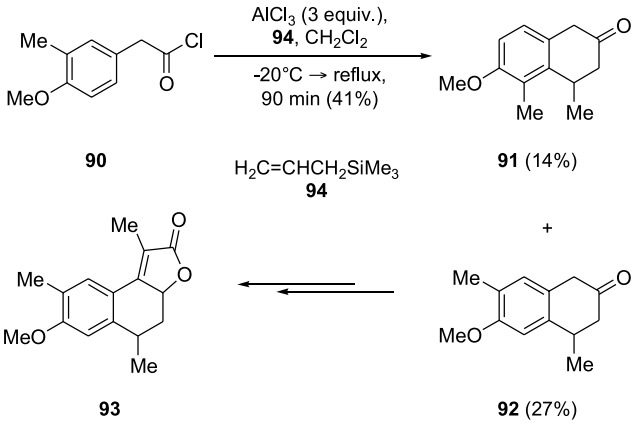
most attractive advantages of the Friedel–Crafts approach to 2-tetralones are that halogenated tetralones can be conveniently prepared, and that the starting acyl chlorides are readily available, against the relative inaccessibility of polysubstituted 2-methoxy naphthalene derivatives.

The Burckhalter and Campbell protocol was also employed for the synthesis of 1,1-disubstituted 2-tetralones. As part of a study on hypnotic and locomotive properties of ketamine analogs, Yang and Davisson[48e] prepared 1-methyl-1-amino-2-tetralone **86** from α-methyl phenylglycine **82**. Their synthesis is depicted in Scheme 9. The acyl chloride **84**, obtained by reacting the phthalimido derivative **83** with either thionyl chloride or phosphorus pentachloride, was treated with ethylene in the presence of aluminum chloride to give the expected *N*-protected aminotetralone **85** in good overall yield. Cyclization of the latter, however, proceeded in no more than 15% yield, constituting α-phthalimido styrene **87** more than 75% of the recovered products. Unfortunately, no improvement was recorded when reaction time, temperature and the sequence of addition of the reagents were changed. Conventional hydrazinolysis of the phthalimide **85** provided the required aminotetralone **86**.

An eco-friendly version of the Burckhalter and Campbell reaction was developed recently by Gray and Smith.[53] In this cleaner approach, the trifluoroacetic anhydride/H_3PO_4 system was used instead of the more contaminating metal-based ($AlCl_3$) methodology. In this way, 2-tetralones **89a–h** were prepared from starting phenylacetic acid derivatives **88a–f**.

Additional advantages of this green methodology are the use of an arylacetic acid as starting material instead of the related acyl chloride, which is very unpleasant to work with, and the avoidance of dichlorometane, employed as solvent in the former procedure. The reaction involves the in situ formation of a mixed anhydride of the arylacetic acid, a process that takes place near to room temperature, furnishing the 2-tetralones in good yields, as shown in Table 3.

An interesting modification of the Friedel–Crafts acylation–cycloalkylation approach with simple alkenes consists in the use of an allylsilane as the alkene moiety. Recently, Silveira and co-workers performed this type of study involving the use of allyltrimethylsilane (**94**) as the olefinic component of the cyclization. This allowed the preparation of several aryl-substituted (Cl, Br, OMe, Me)-4-methyl-2-tetralones. A mixture of 2-tetralones **91** and **92** was obtained in 41% combined yield from acid chloride **90**.[42] The 6-methoxy-4,7-dimethyl-2-tetralone **92**, prepared by this new allylsilane methodology, was employed as a key intermediate in a total synthesis of heritonin **93**, a tricyclic lactone isolated from *Heritiera littoralis*, which acts as a powerful natural piscicide (Scheme 10).[54]

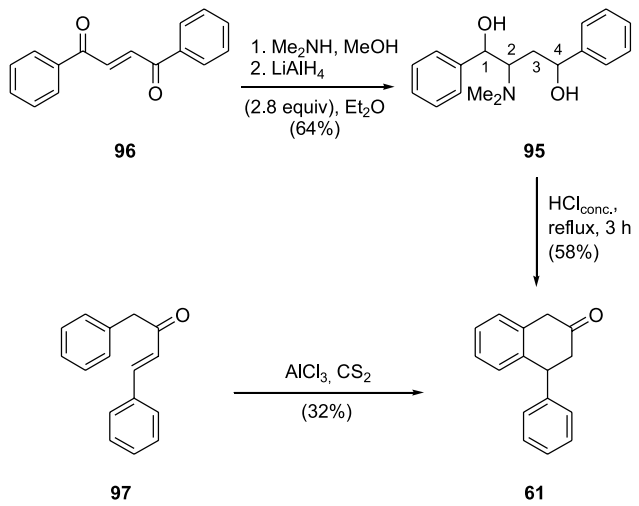


Scheme 10. Synthesis of 6-methoxy-4,7-dimethyl-2-tetralone **92**, through an allylsilane mediated Friedel–Crafts type cyclization.

2.4. Friedel–Crafts intramolecular alkylation

There are scattered examples reported about this approach, which provides 4-phenyl-substituted 2-tetralones. Exposure of 2-(*N*,*N*-dimethylamino)-1,4-diphenyl-1,4-butanediol (**95**) to refluxing concentrated HCl was used to prepare 4-phenyl-2-tetralone **61**, in up to 58% yield (Scheme 11).[55]

The starting diol **95** was easily obtained by reduction of 2-(*N*,*N*-dimethylamino)-1,4-diphenyl-1,4-butanedione **96** with excess of $LiAlH_4$. On the other hand, other aqueous mineral acids such as HBr, or H_2SO_4 can be employed in place of HCl.[56] This transformation probably proceeds through a Friedel–Crafts-type intramolecular alkylation

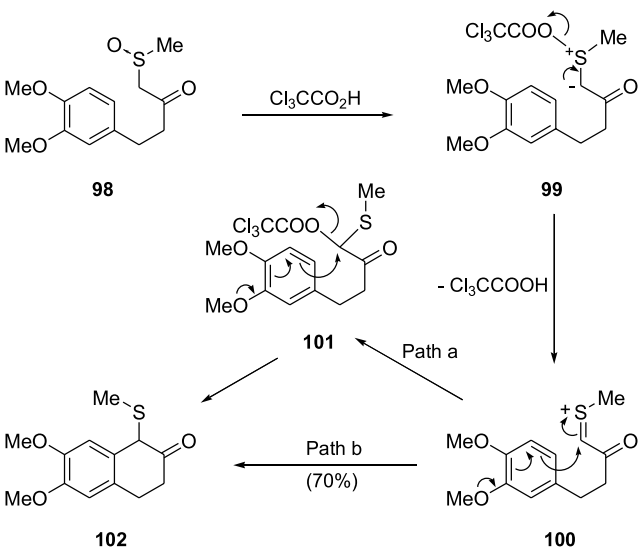


Scheme 11. Intramolecular Friedel–Crafts cyclization for the synthesis of 4-phenyl-2-tetralone (**61**).

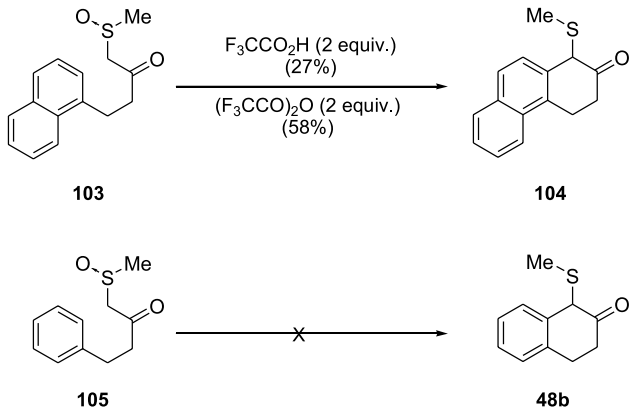
with C-4. In a second stage, dehydration of the benzyl alcohol on C-1, next to the amine moiety, yields an enamine, which readily hydrolyzes in the reaction medium, furnishing the product. In one alternative approach, the synthetically equivalent α,β-unsaturated ketone **97**[57] was converted into the same 2-tetralone (**61**) by Friedel–Crafts reaction with $AlCl_3$ in CS_2, albeit in only 32% yield; 2-tetralone **61** was also prepared in 45% overall yield from benzaldehyde, by reaction of trimethyl-styrylsilane with phenylacetyl chloride, under $AlCl_3$ catalysis (Table 2, entry 2).[50c]

2.5. Cyclization of β-ketosulfoxides

β-Ketosulfoxides are easily available by the well-known reaction of methylsulfinyl carbanion with the corresponding lower homologous esters.[58] The β-ketosulfoxides can undergo cyclization under acid catalysis to yield 2-tetralones, as illustrated in Scheme 12. The transformation takes place by protonation of the sulfinyl oxygen of the starting material (**98**) to form ylide **99**, which in turn can readily form the ylene intermediate **100** and rearrange to the α-acyl-α-thio acetal **101** upon attack by an appropriate nucleophile. This transformation is known as the Pummerer rearrangement. A nucleophile existing at a suitable position may attack intramolecularly the mixed acetal resulting from the rearrangement. Employing aromatic rings as internal nucleophiles (path a), 1-methylthio-2-tetralones **102** and **104** were prepared by cyclization of β-ketosulfoxides **98** and **103**, respectively (Schemes 12 and 13). An alternative route (path b) can be devised, by which the ylene intermediate **100** suffers intramolecular nucleophilic attack to furnish the product. Interestingly, while the cyclization is a first order process, the rearrangement is a second order reaction. Experimental evidence pointed to an acid catalyzed cyclization of the ylene (**100**), without rearrangement taking place, when trichloroacetic acid was employed.



Scheme 12. Mechanism of the synthesis of 2-tetralone derivatives employing the Pummerer rearrangement of β-ketosulfoxides.



Scheme 13. Synthesis of 2-tetralones by acid-catalyzed cyclization of β-ketosulfoxides.

In fact, cyclized products could be obtained in the presence of relatively weak acids, such as dichloroacetic acid and although rearranged products (mixed acetals) were isolated under certain conditions, they could not be converted into cyclized products following the cyclization protocol. However, the mechanism changed to a Pummerer rearrangement mediated cyclization when trifluoroacetic anhydride was employed as cyclization agent.[59a]

In the case of **98**, use of tricloroacetic acid furnished the product in 70% yield, while the same amount of trifluoroacetic acid provided 64% of the 2-tetralone **102**.[60] For the cyclization of **103**, trifluoroacetic acid yielded only 27% of the product **104**, while trifluoroacetic anhydride raised the yield to 58%.[59a] These reactions proceed in the presence of 2 equiv. of a trihalo-acid or trihalo-anhydride, under reflux during 1–2 h. The 1-methylthio-6,7-dimethoxy-2-tetralone **102** thus produced was desulfurized with hydrogen and Pd/C to give the expected 6,7-dimethoxy-2-tetralone **20** in 60% yield.[61] The cyclization of β-ketosulfoxides to 2-teralone derivatives was used for the preparation of starting materials for the elaboration of benzacridines as mammalian topoisomerase poisons. The method, however, is not suitable for the elaboration of 2-tetralones containing unsubstituted or deactivated aromatic rings, such as **48b**, by cyclization of the corresponding sulfoxide **105** (Scheme 13).

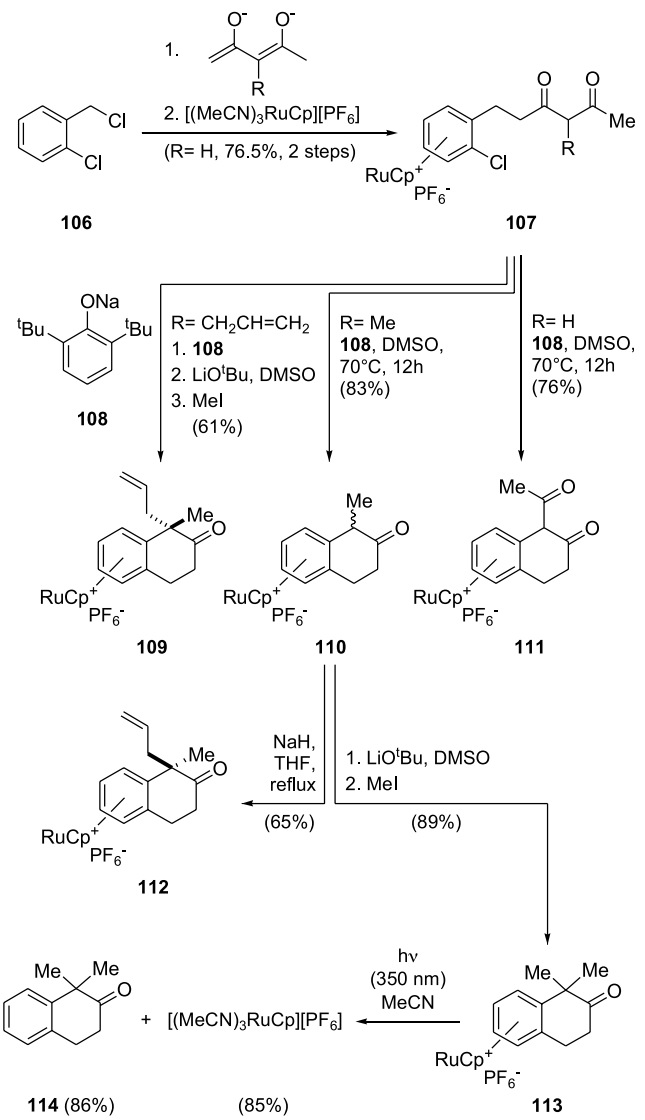
2.6. Intramolecular S_NAr reaction of (η^6-arene) ruthenium complexes

Cationic (η^6-arene)ruthenium(II) complexes are easily prepared and behave as useful air and moisture stable materials. The coordinated arene ring in this organometallic species exhibits a unique and potentially useful reactivity pattern, due to the activating effect exerted by the CpRu(II) fragment.[62]

(Chloroarene)Ru–Cp (Cp=cyclopentadienyl) moieties have been shown to be excellent electrophilic partners for nucleophilic aromatic substitution reactions. Despite the high cost of the transformations requiring stoichiometric amounts of ruthenium, this expense is somewhat mitigated by the availability of methods to recover the CpRu(II) fragment in forms suitable for reuse after removal of the arene ligand.[63]

Stabilized enolates generated from δ-aryl-β-dicarbonyl compounds **107** were induced to participate in a series of intramolecular S_NAr reactions assisted by the (arene)Ru moiety attached to it. The β-dicarbonyl compounds were prepared by first reacting the dianion of acetylacetone with 2-chlorobenzyl chloride **106**,[64] being this followed by introduction of the CpRu(II) fragment, using [$(MeCN)_3$-RuCp][PF_6] as a ruthenium transfer reagent.[63] Despite the possibility of coordinating to the acac moiety, it was found that the ruthenium coordinates solely with the arene ring.[65] Using hindered sodium phenoxide derivative **108** as base, acetyl tetralone **111** was conveniently isolated. Employing δ-aryl-β-dicarbonyl compounds functionalized between the carbonyls, different 1-substituted- (**110**) and 1,1-disubstituted-2-tetralones (**109** and **113**) were obtained in good yields (Scheme 14).[66] Monosubstituted 2-tetralones were regioselectively alkylated and the bulk of the CpRu(II) fragment allowed the stereocontrolled synthesis of 1,1-disubstituted 2-tetralones (compare **112** with **109**).[67]

The CpRu(II) moiety was easily removed under mild photochemical conditions, by irradiation at 350 nm in acetonitrile, and recovered in a reusable form in excellent yield, such as in **113→114**. The scope and limitations of the reaction have not been fully explored, since this methodology was employed only for the preparation of 2-tetralones functionalized at C-1 and unsubstituted on the aromatic ring. Interestingly, however, it is expected that the use of planar chiral (arene)Ru complexes may lead to useful chiral 1,1-disubstituted tetralones.



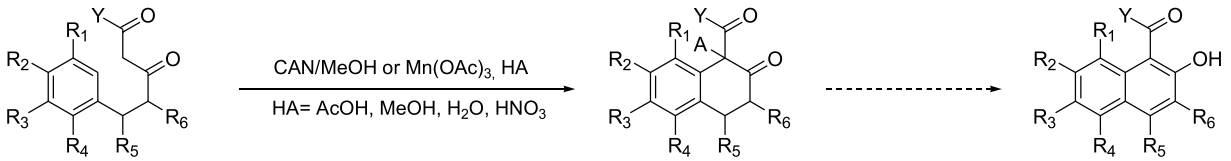
Scheme 14. Synthesis of 2-tetralones employing an intramolecular S_NAr reaction of (η^6-arene) ruthenium complexes.

2.7. Radical-mediated oxidative cyclization of δ-aryl-β-dicarbonyl compounds with Mn(III) and Ce(IV) salts

2-Tetralone derivatives were also prepared from δ-aryl-β-dicarbonyl compounds[64] by reaction with Mn(III) and with Ce(IV) salts. This entailed an intramolecular homolytic aromatic substitution reaction, with the α-dicarbonyl radicals generated by inner-sphere electron transfer from high-valent metal complex to the β-dicarbonyl compounds.[68] The transformation, which yielded tetralones **116a–116j** as examples, was initially developed with the aim of synthesizing 2-hydroxy-1-naphthoic acids, being the reaction conducing to the latter a four electron oxidation process. The cyclization proceeded only when the aromatic ring was sufficiently electron-rich. Cerium ammonic nitrate (CAN) performed better that Mn(III) acetate, not requiring, as the latter, electron releasing groups on the aromatic ring, *meta* to the dicarbonyl substituent.[69] The β-acyl-2-tetralones **116a–116c** were prepared with the aid of CAN, while their congeners **116d–116j** were synthesized employing Mn(III) acetate (Table 4).

In many cases, the 1-substituted 2-tetralones thus prepared, could not be isolated as such, being readily oxidized in situ by excess of reagent to the related 1-acetoxy (also hydroxy or methoxy) derivatives **116**, through the corresponding enolic form of the 2-tetralone.[70] They furnished the expected naphthoic acids **117** upon dehydration with silica gel in hot benzene or prolonged chromatography. It has been shown that the reaction can be stopped at the tetralone stage when the enol content of the latter is low.

Table 4. Synthesis of 2-tetralones employing the Ce(IV) or Mn(III)-mediated oxidative cyclization of δ-aryl-β-dicarbonyl compounds



115 **116** **117**

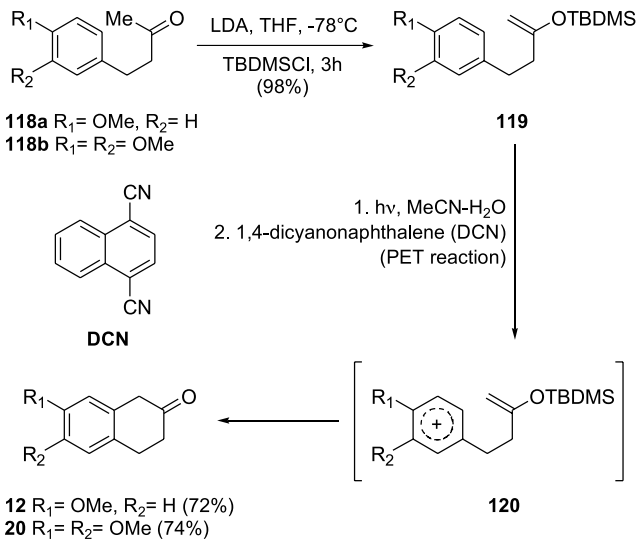
Entry no.	β-Dicarbonyl	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	A	Y	Yield (%)	Reference
1	**115a**	**116a**	H	H	H	H	H	H	OMe	OEt	22	69
2	**115a**	**116b**	H	H	H	H	H	H	ONO_2	OEt	26	69
3	**115b**	**116c**	H	H	OMe	H	H	Me	OAc	OMe	29	69
4	**115c**	**116d**	H	H	H	H	H	Me	OAc	Et	9	70
5	**115d**	**116e**	H	H	OMe	OBn	H	Me	OAc	Et	56	70
6	**115e**	**116f**	OBn	H	Obn	H	H	Me	OAc	Et	93	70
7	**115f**	**116g**	OBn	H	NHAc	H	H	Me	OAc	Et	93	70
8	**115g**	**116h**	OMe	H	OMe	H	H	H	OAc	Me	71	70
9	**115h**	**116i**	OMe	H	OMe	H	OH	H	OAc	Me	95	70
10	**115i**	**116j**	H	H	OMe	OBn	H	H	OAc	OEt	81	70

2.8. Intramolecular addition of silylenol ethers to PET-generated arene radical cations

The carboannulation reaction involving the intramolecular nucleophilic addition of silyl enol ethers to photochemically generated arene radical cations, was employed to synthesize two different 2-tetralones in good yields.[71] The intermediate radical cations were obtained by a 1,4-dicyanonaphthalene photosensitized electron transfer (PET) reaction. Starting ketones **118** were converted into the corresponding kinetic silyl enol ethers **119** by treatment with LDA and capture of the enolates with TBDMS chloride.[72]

After irradiation of the enol ether in a 4:1 MeCN–H_2O mixture for 3 h, through a Pyrex filter (>280 nm), without removing dissolved oxygen, 7-methoxy- (**12**, 72% yield) and 6,7-dimethoxy-2-tetralone (**20**, 74% yield) were prepared through the intermediacy of cations **120** (Scheme 15).

The 1,4-dicyanonaphthalene sensitizer was recovered almost quantitatively.[73] The synthesis seems to be flexible enough to incorporate other functionalities. In case of **118b** two products are possible; however, the regioselectivity observed is in accordance with the calculated electron densities (Huckel or MNDO) at the carbons of the HOMO of the arene radical cation.

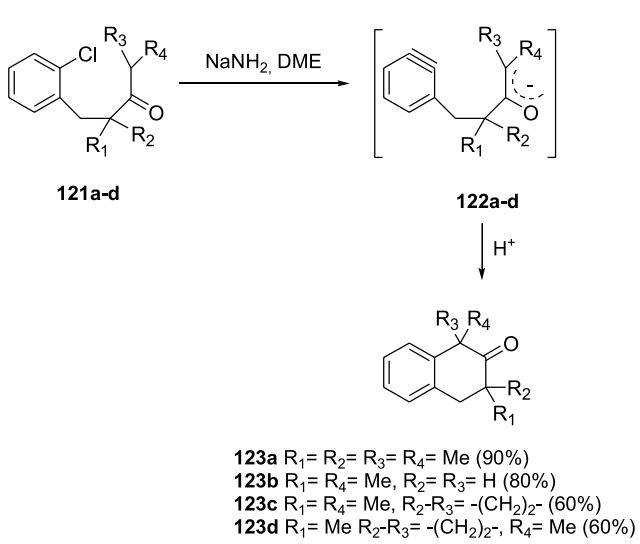


Scheme 15. Preparation of 2-tetralones **12** and **20** via intramolecular addition of silylenol ethers to PET-generated arene radical cations.

2.9. Intramolecular cyclization via benzyne intermediates

Several 1- and 3-substituted 2-tetralones were prepared by means of the intramolecular condensation of 2-chloro-benzyl acetone enolates.[74,75]

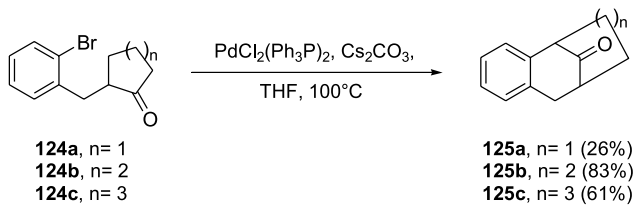
The reaction proceeded via the benzyne intermediates **122a–d**, generated by treatment of 2-chlorobenzyl acetone derivatives, **121a–d**, with a strong base in THF/HMPA or DME. The transformation was completed after ca. 12 h at 40–45 °C, and four different 1- and 3-substituted 2-tetralones (**123a–d**), were prepared in 60–90% yield (Scheme 16).



Scheme 16. Synthesis of 2-tetralones by intramolecular cyclization through benzyne intermediates.

2.10. Palladium-catalyzed intramolecular α-arylation of aliphatic ketones

The cyclization of 2-(2′-halobenzyl)-substituted cycloalkanones to bridged 2-tetralones was effected under promotion of palladium complexes. This is an intramolecular version of the widely studied α-arylation reaction of aliphatic ketones.[71,76,77] As examples, the 2-bromo cycloketones **124a–c** were submitted to intramolecular cyclization to afford bridged tricyclic 2-tetralones **125a–c** in 26–83% yield.[78] The reaction takes place in the presence of catalytic amounts of $PdCl_2(Ph_3P)_2$, with Cs_2CO_3 (3 equiv.) as base, and requires heating at 100 °C during 13–16 h (Scheme 17). While enones, formed by palladium-catalyzed dehydrogenation of the ketones (cyclized and uncyclized), have occasionally been found in the reaction mixture, the debrominated starting ketones are the main side products of this transformation. In another application of palladium reagents, Lipshutz described the synthesis of 1-aryl 2-tetralone derivatives by palladium(II) catalyzed hydrolysis of dioxolane acetals/ketals of 2-tetralones in moist acetonitrile.[79]

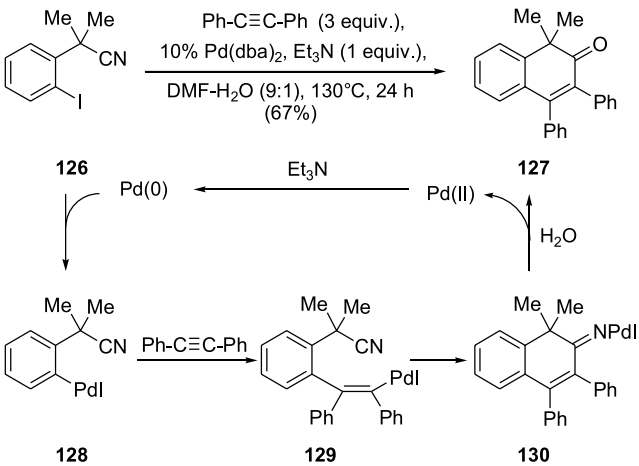


Scheme 17. Synthesis of 2-tetralones employing a palladium-catalyzed intramolecular α-arylation of aliphatic ketones.

2.11. Carbopalladation of aromatic nitriles in the presence of acetylenes

The carboannulation of 2′-iodophenyl-2-methyl-propanenitrile **126** with diphenylacetylene was effected under palladium catalysis, affording the unsaturated 1,1-dimethyl-3,4-diphenyl-2-tetralone **127** in 67% yield.[80]

For the only example available, 10% $Pd(dba)_2$ was employed as catalyst (Scheme 18). The process appears to involve formation of arylpalladium **128** and subsequent alkyne insertion (**129**) to produce a vinylic palladium imine intermediate (**130**), which hydrolyzes to the corresponding ketone. This is a catalytic process that requires reduction of the palladium(II) salt produced. This is probably carried out by the triethylamine added to the reaction. The protocol can afford only 1,1-disubstituted 2-tetralones; when it was applied to 2-iodophenyl acetonitrile, the intermediate imine aromatized and β-naphthylamines were obtained instead.

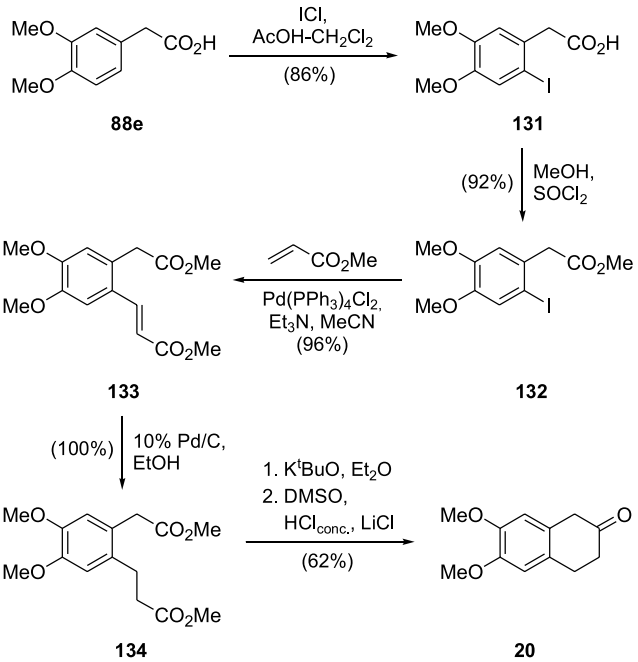


Scheme 18. Palladium catalysis for the preparation of 1,1-dimethyl-3,4-diphenyl-2-tetralone **127**.

2.12. Dieckmann condensation followed by decarboxylation

The highly useful 6,7-dimetoxy-2-tetralone **20** was synthesized in reasonable overall yield by a Dieckmann condensation protocol, employing 3,4-dimethoxy-phenylacetic acid **88e** as starting material.[81]

This 2-tetralone has been employed as starting material for the elaboration of the known dopamine agonist dihydrexidine and some of its derivatives,[82] as well as various aminotetralines,[49d,83,84] isoquinoline derived dopaminergic agents,[85] catecholamine mimicking agents,[86] naturally occurring alkaloids[19] and cyclic aminoacids.[87] The method involved the preparation of iodide **131** by selective iodination of the starting acid. This was esterified in over 70% overall yield to iodoester **132**[88] and then submitted to a Heck cross-coupling reaction[89] with methyl acrylate and 1 mol% of dichlorobis (triphenylphosphine) palladium(II) as catalyst, furnishing 96% of cinnamate **133**. Dichlorobis (triphenylphosphine) palladium(II) is a highly stable and low-cost form of palladium.[90] The so obtained cinnamate **133** was converted quantitatively to the dihydrocinnamate derivative intermediate **134**, by catalytic hydrogenation with Pd/C, which in turn was submitted to a Dieckmann condensation with potassium *tert*-butoxide, followed by decarboxylation of the resulting potassium salt under mild conditions,[91] to afford the desired 2-tetralone **20** in 62%

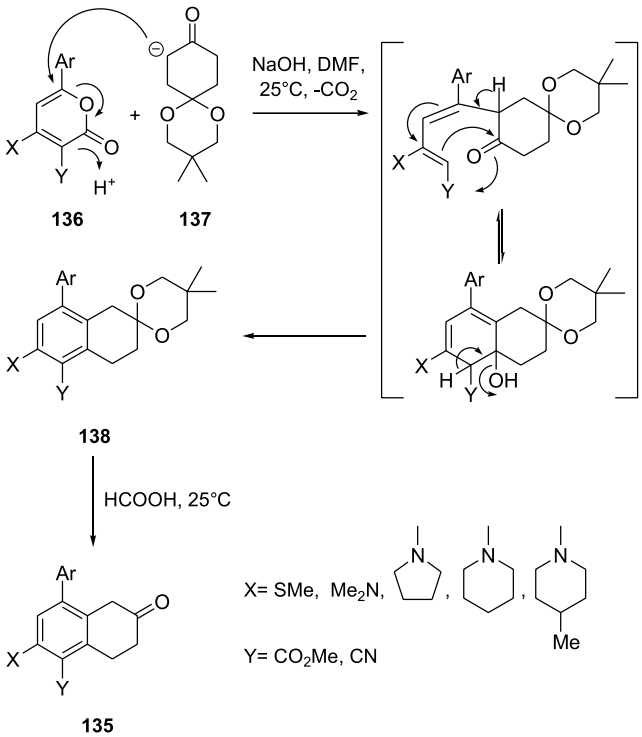


Scheme 19. 6,7-Dimetoxy-2-tetralone **20** prepared by a Dieckmann condensation strategy.

yield (Scheme 19). The tetralone was conveniently purified through its bisulfite adduct.

2.13. Carbanion-induced condensation of 2*H*-pyran-2-ones with 1,4-cyclohexanedione monoketal

Recently, the preparation of several functionalized 2-tetralones (**135a–o**) by means of the carbanion induced reaction of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl- and 6-aryl-3-cyano-4-*sec*-amino-2*H*-pyran-2-ones **136** with 1,4-cyclohexanedione mono-(2,2-dimethyl trimethylene) ketal **137**, was described (Scheme 20, Table 5).[92]



Scheme 20. Synthesis of 2-tetralones by condensation of 2*H*-pyran-2-ones **136** with 1,4-cyclohexanedione monoketal **137**.

The reaction yielded 8-aryl-5-methoxycarbonyl-6-methylsulfanyl-3,4-dihydro-2(1*H*)-naphthalenone (2,2-dimethyltrimethylene) ketals **138** and the related nitriles. Mild acid hydrolysis of the ketals yielded exclusively the expected 2-tetralones **135**. The method is highly suitable for the introduction of diverse functionalities at positions 5, 6 and 8. The mechanism of the reaction can be rationalized by assuming an initial attack of the carbanion generated from **137** by the base in DMF at position 6 of the pyran ring of the pyrone **136**. The reaction then proceeds with ring opening followed by decarboxylation and condensation–cyclization involving the carbonyl functionality and C-3 of the pyran ring, leading to **138**. The latter compounds may also arise through an inverse electron-demand Diels–Alder cycloaddition of the enolate to the 2*H*-pyran-2-one **136**, but this mechanism is not very likely, taking into account previous precedents[93] and the mildness of the reaction conditions (Scheme 20). This is a very useful method for the preparation of 2-tetralones with electron-withdrawing groups in the aromatic ring (CN, CO_2Me).

2.14. One-pot annulation through an alkylation–acylation and decarboxylation sequence

A regioselective one-pot annulation process involving the bifunctional (nucleophilic and electrophilic centers within the same molecule) bromosulfone **139** and deprotonated malonate esters was reported by Ghera and Ben-David.[94]

The protocol is advantageous for the synthesis of 3-susbtituted 2-tetralones, because the starting materials are readily available.

In this transformation, the bromosulfone **139** acted as a 1,4-dipole, and the reaction took place by an alkylation–acylation sequence, providing the 1-phenylsulfonyl-2-tetralones **140a–e**. During the transformation, self-reactivity was avoided. When submitted to an in situ hydrolysis and decarboxylation, **140b** allowed access to 1-phenylsufonyl-3-alkyl-2-tetralone **141** in good yield (Scheme 21).

It has been demonstrated that, alternatively, deprotonated lactones (**142**)[95] can be used in the ring closure process instead malonate anions. In this case, γ- and δ-hydroxy-2-tetralones **143a**,**b** were obtained in good yields from bromosulfones **139** (Scheme 22).[94]

A more sophisticated version of this cyclization entailed the use of bromosulfone **145**, prepared from **139** through the intermediacy of olefin **144**. Carrying phenylsulfonyl and diester groups within the same molecule, bromosulfone **145** furnished the tricyclic 2-tetralone derivative **146** in 71% yield and 90% d.e. In this case, generation of the malonate and α-sulfonyl carbanions produced a double cyclization, leading to the product (Scheme 23).

2.15. Miscellaneous syntheses of 2-tetralones

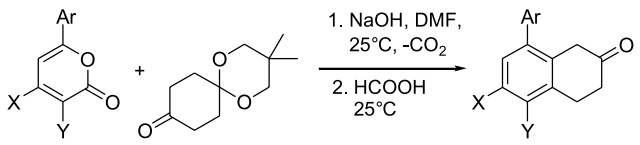
The preparation of 1,1,4,4-tetramethyl 2-tetralone **148** by the intermolecular Friedel–Crafts-type reaction of 2,2,5,5-tetramethyl tetrahydro-3-ketofuran (**147**) with benzene, as reactant and solvent in the presence of $AlCl_3$ as catalyst, was described (Scheme 24).[75b]

The compound was employed, as part of a series of photochemical studies of 2-tetralones in which it gave aldehyde **149** as the only photoproduct.[75a] The scope of the reaction remains unexplored.

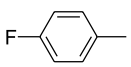
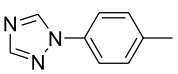
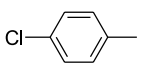
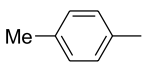
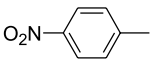
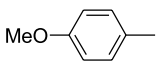
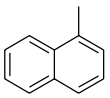
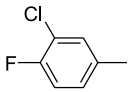
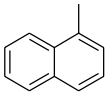
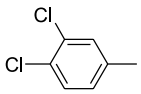
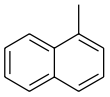
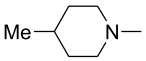
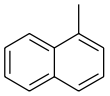
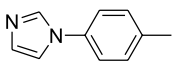
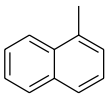
3. Methods involving transformations in a pre-formed tetralinic ring or a naphthalene precursor

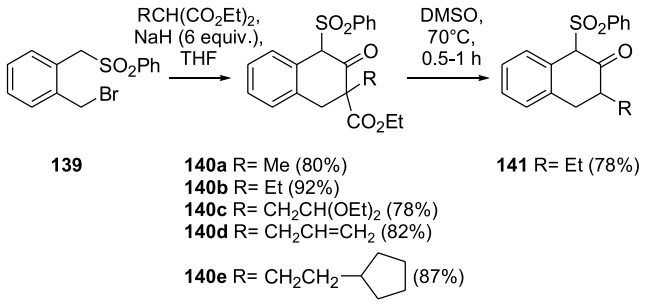
One of the most frequently used methods for the preparation of functionalized 2-tetralones involves chemical transformations of a pre-formed tetraline derivative. Despite the requirement of preparing the appropriate tetraline or naphthalene precursor before obtaining the 2-tetralone, this approach is very useful for accessing substituted 2-tetralones with their structure unequivocally known in advance. Mixtures of isomers, which are a serious problem when ring-closing methods are employed for some

Table 5. Polysubstituted 2-tetralones **135a**–**o** obtained by carbanion induced condensation of 2*H*-pyran-2-ones **136** with 1,4-cyclohexanedione monoketal (**137**)



136 **137** **135**

2-Tetralone	X	Y	Ar	Yield (%)	2-Tetralone	X	Y	Ar	Yield (%)
135a	SMe	CO_2Me		31	**135i**	SMe	CO_2Me		38
135b	SMe	CO_2Me		39	**135j**		CN		42
135c	SMe	CO_2Me		43	**135k**		CN		40
135d	SMe	CO_2Me		41	**135l**	Me_2N	CN		51
135e	SMe	CO_2Me		34	**135m**		CN		49
135f	SMe	CO_2Me		30	**135n**		CN		51
135g	SMe	CO_2Me		46	**135o**		CN		47
135h	SMe	CO_2Me		38	**135p**		CN		52

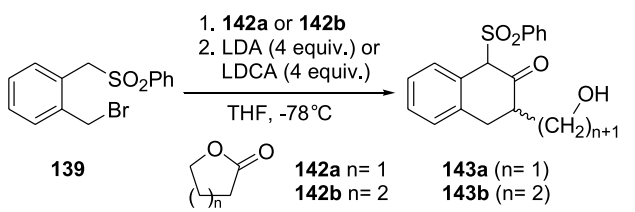


139

140a R= Me (80%)
140b R= Et (92%)
140c R= $CH_2CH(OEt)_2$ (78%)
140d R= $CH_2CH{=}CH_2$ (82%)
140e R= CH_2CH_2 (87%)

141 R= Et (78%)

Scheme 21. Synthesis of 2-tetralones by annulation of bromosulfone **139** and malonate anion derivatives.

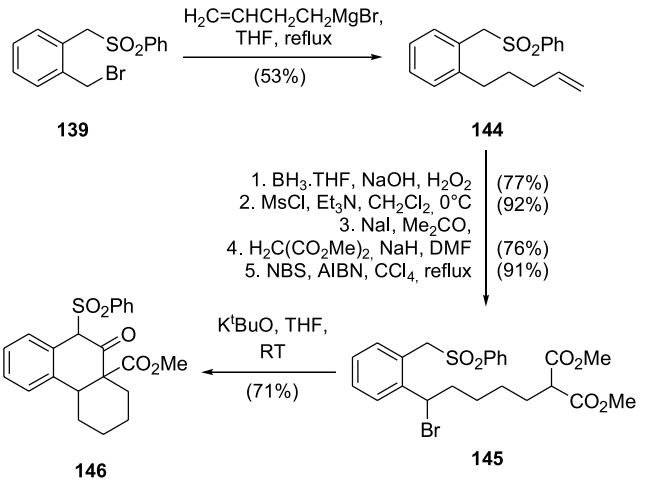


139

142a n= 1
142b n= 2

143a (n= 1)
143b (n= 2)

Scheme 22. Synthesis of 2-tetralones **143a**,**b** by annulation of bromosulfone **139** with deprotonated lactones **142a**,**b**.



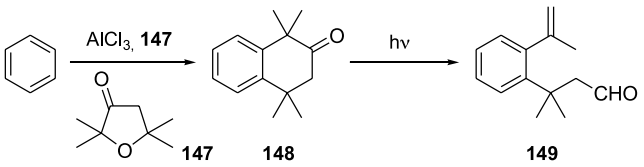
139 **144**

145

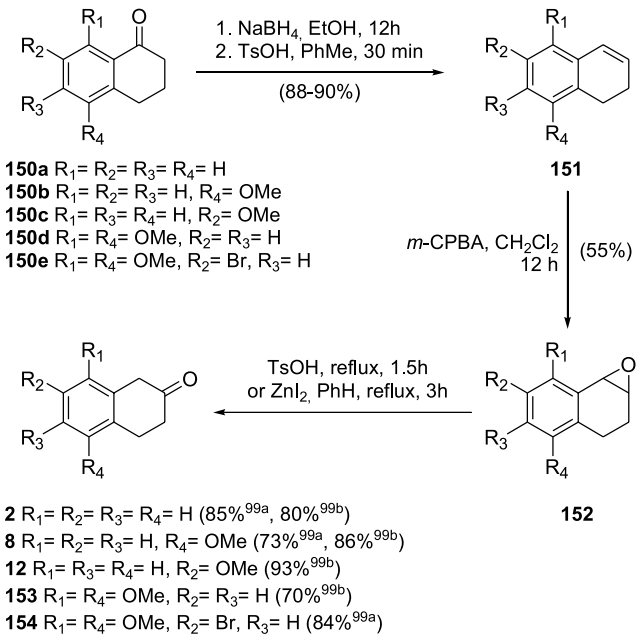
146

Scheme 23. Preparation of 2-tetralone **146** from bromosulfone **139** by a double annulation reaction.

substrates, are thus avoided. Another aspect that turns more useful this approach, is the possibility to synthesize 2-tetralones with electron-withdrawing groups attached to the aromatic ring.



Scheme 24. Synthesis and photodegradation of 2-tetralone **148**.



Scheme 25. Synthesis of 2-tetralones employing $NaBH_4$-generated 1-tetralols as intermediates.

3.1. 1,2-Carbonyl transposition of 1-tetralones

Being a key function in organic synthesis, a number of methods exist for the transposition of a carbonyl group in sequences ranging from 3 to 10 steps.[96] The 1,2-carbonyl transposition of 1-tetralones is one of the two most frequently employed methods for the elaboration of 2-tetralones from precursors having an already preformed tetraline ring system.[97] This strategy takes advantage of the ready availability of polysubstituted 1-tetralones. Several techniques to achieve the 1,2-transposition have been developed during the last decades; the most successfully employed ones and those with a more general scope, will be covered here.

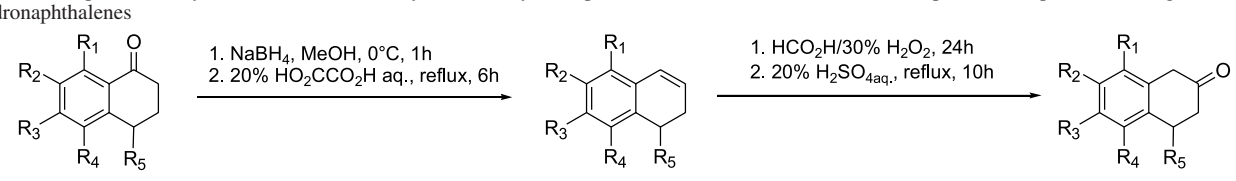
3.1.1. Carbonyl transposition by rearrangement of epoxides. The rearrangement of epoxides to ketones has been repeatedly used in organic synthesis.[98] The first reports on the use of epoxide rearrangements in the synthesis of 2-tetralones date from the 1940s,[13] where simple oxiranes derived from the inexpensive 1-tetralones were rearranged in good yields to 2-tetralones. However, several improvements were achieved during the last decades and the scope of the reaction was widened, making this a very useful and efficient methodology, especially for the selective preparation of 1- and 3-substituted 2-tetralones.

There are several ways to convert 1-tetralones into the respective epoxides and the most frequently used method is the epoxidation of an olefin, generated by dehydration of the corresponding 1-tetralol. The requisite alcohol, in turn, can be easily obtained by direct hydride reduction or by addition of an alkyl- or aryl Grignard (or organolithium) reagent to the carbonyl group of the starting 1-tetralone. The reaction sequence exploits the enhanced propensity of benzylic alcohols, compared to their aliphatic counterparts, to undergo acid-catalyzed dehydration.

Several 2-tetralones unsubstituted on C-1 were prepared from 1-tetralones **150a–e** through the intermediacy of the corresponding 1-tetralols, conveniently synthesized by $NaBH_4$ reduction of the 1-tetralones. After dehydration of the 1-tetralols with *p*-TsOH,[48a] the resulting olefins **151** were transformed into the corresponding epoxides **152** and then isomerized to the respective 2-tetralones **2**, **8**, **12**, **153** and **154** in good yields under acid catalysis of TsOH or ZnI_2 (Scheme 25).[99]

A slightly different procedure, involving oxalic acid for the

Table 6. Examples of the synthesis of 2-tetralones by 1,2-carbonyl transposition of the related 1-tetralones via epoxidation-apoxide rearrangement of 3,4-dihydronaphthalenes

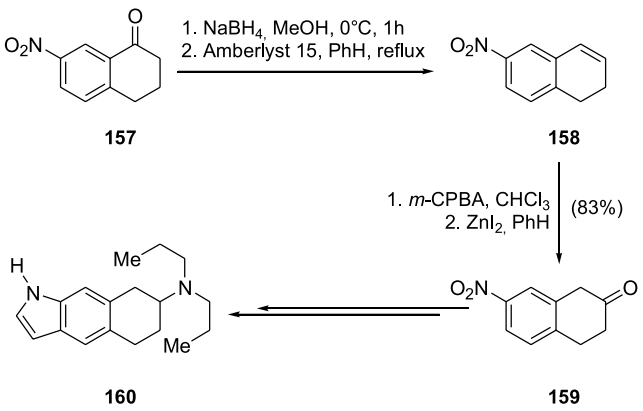


Entry no.	1-Tetralone	2-Tetralone	R_1	R_2	R_3	R_4	R_5	Yield (%)	Reference
1	**150c**	**12**	H	OMe	H	H	H	76	100
2	**150f**	**15**	OMe	H	H	H	H	93	100
3	**150g**	**156a**	H	H	H	H	Me	75	100
4	**150h**	**61**	H	H	H	H	Ph	71	100
5	**150i**	**14**	H	H	H	Me	H	74	100
								—[a]	46c
6	**150j**	**156b**	H	H	H	Ph	H	78	100
7	**150k**	**156c**	H	H	H	Me	Me	73	100
								74	46c
8	**150l**	**156d**	Me	H	Me	H	H	—[a]	46c

[a] Product yields were not informed.

dehydration of the 1-tetralol intermediate to **155** and the use of HCO_2H/H_2O_2 reagent as oxidant for the preparation of several 2-tetralones in good yields (Table 6) was also reported.[100]

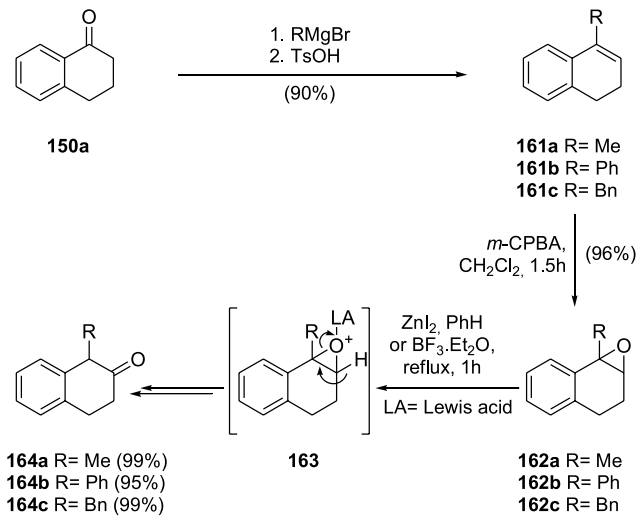
Several other acids were employed to catalyze the dehydration of the 1-tetralol precursors.[101] Thus, Amberlyst 15 was used for dehydration of the 1-tetralol derivative of 7-nitro-1-tetralone **157**, in the synthesis of 7-nitro-2-tetralone **159**, which occurred in 74% yield via dihydronaphthalene **158** (Scheme 26).[101a] Compound **159** was employed as key intermediate during the synthesis of *N*,*N*-di-*n*-propyl- 5,6,7,8- tetrahydro-benz[*f*]indol-7-amine **160**, an interesting dopaminergic agonist.[101a]



Scheme 26. Synthesis of 7-nitro-2-tetralone by 1,2-carbonyl transposition of the related 1-tetralone **157**.

Three different 1-substituted 2-tetralones (**164a**–**c**) were obtained by selective acid-catalyzed isomerization of 1-organyl-1,2-epoxytetralines **162a**–**c**.[102]

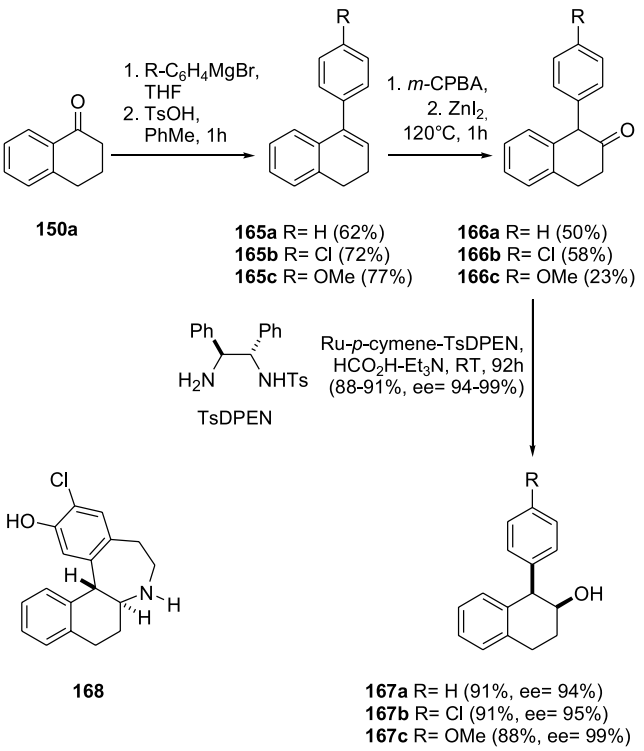
Coordination of the oxygen atom of the oxirane with the Lewis acid (**163**) is necessary for the reaction to take place. The olefinic precursors **161a**–**c** were obtained by dehydration of the tertiary alcohols generated by the attack of Grignard reagents to the 1-tetralone **150a** (Scheme 27).



Scheme 27. Synthesis of 2-tetralones employing epoxytetralines as intermediates.

The authors used $BF_3{\cdot}Et_2O$ and ZnI_2[101a] to perform the isomerization, with no relevant difference in yields.

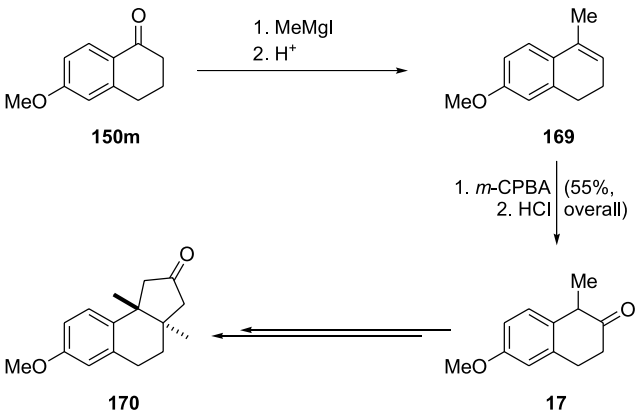
1-Aryl-2-tetralones **166a**–**c**, prepared by ZnI_2-assisted epoxide isomerization, have been employed for the dynamic kinetic resolution-asymmetric transfer hydrogenation to yield chiral 1-aryl-2-tetralols **167a**–**c**. The oxiranes were prepared by epoxidation of 3,4-dihydronaphthalene derivatives **165a**–**c** and the methodology was considered relevant for the synthesis of the benzodiazepine type dopamine D_1 agonist Sch-39166, **168** (Scheme 28).[103] The use of 1,2-diols and their monoester derivatives instead of the related epoxide were explored, with somewhat better results for substituted tetralones.[102] This variant of 1,2-carbonyl transposition will be discussed below (Section 3.1.6).



Scheme 28.

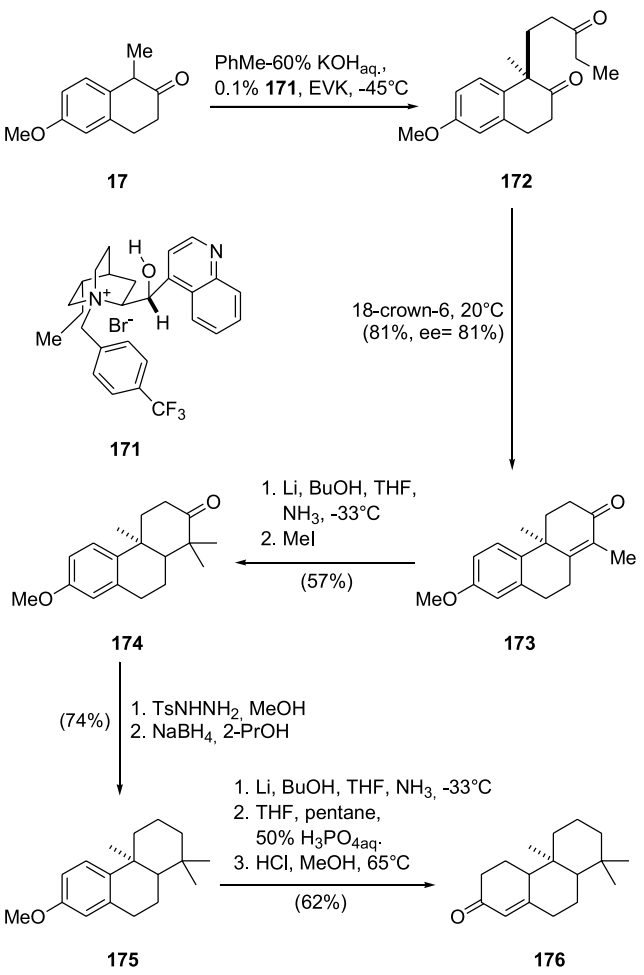
Alternatively, indium(III) chloride catalysis[104] and the ion exchange resin Dowex-50W[105] were used to promote the rearrangement of epoxides. For example, when the epoxide **162a** was stirred with a suspension of $InCl_3$ in THF at room temperature for 45 min, 1-methyl-2-tetralone **164a** was obtained in 87% yield.[104]

During a study of the synthesis of tetracyclic triterpenes, 6-methoxy-1-methyl-2-tetralone **17** was accessed in 55% yield using a similar alkylative transposition procedure from 1-tetralone **150m**. This was done through the intermediacy of **169**, employing HCl to effect the epoxide rearrangement (Scheme 29).[106] Tetralone **17** was recently employed for a study of the asymmetric alkylation of α-aryl substituted carbonyl compounds employing chiral phase transfer catalysts.[107] When mono perphthalic acid was used instead of *m*-CPBA for the epoxidation step, the yield was unsatisfactory (16%). In this sequence, the epoxide intermediate was not isolated and the 2-tetralone **17** was



Scheme 29. Synthesis of 6-methoxy-1-methyl-2-tetralone **17** employing the *m*-CPBA-mediated 1,2-carbonyl transposition of **169**.

used directly for the preparation of the B–C–*trans*-D benzindanone **170**, a potential intermediate for the synthesis of triterpenes of the lanostane–cycloartane group. The 2-tetralone **17** also served as starting material for the synthesis of podocarpenone **176**, as shown in Scheme 30. Robinson annulation of **17** with ethyl vinyl ketone (EVK) under phase transfer catalysis of the dihydrocinchoninium derivative **171** gave tricyclic compound **173** through the intermediacy of 1,5-diketone **172**. Reductive alkylation of **173**, followed by carbonyl desoxygenation of **174** through

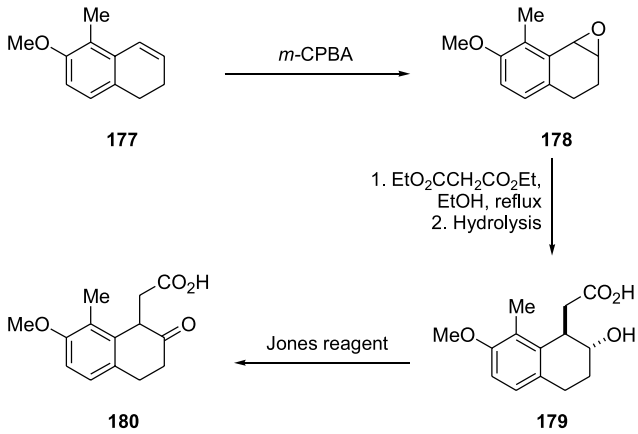


Scheme 30. Enantioselective synthesis of podocarpenone **176** from 2-tetralone **17**.

the corresponding tosylhydrazone furnished aromatic intermediate **175**; in turn, this was subjected to Birch reduction with lithium in liquid ammonia, and final conjugation of the double bond with the carbonyl.

The oxidation described in Scheme 27 was also performed using peroxyacetamidic acid (PAA) instead of *m*-CPBA, during 24 h,[108] furnishing 6-methoxy-1-methyl-2-tetralone **17** in 68% yield. PAA was prepared in situ by reacting acetonitrile, 30% H_2O_2, and $KHCO_3$ (pH 7.5).

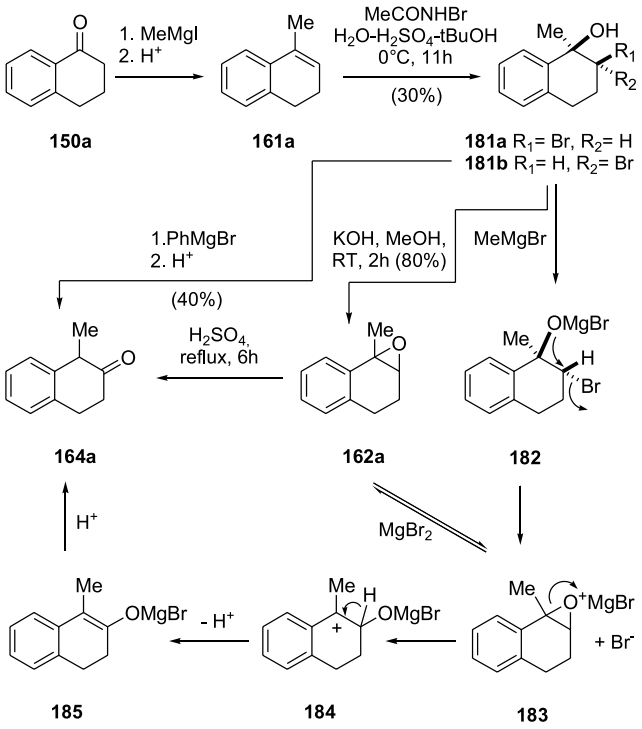
A variation on the epoxide strategy leading to 1-substituted 2-tetralones from the related 1-tetralones was disclosed by Chatterjee and co-workers.[108b] Analogous to other syntheses, their protocol involved reduction of the 1-tetralone, dehydration of the resulting 1-tetralol to the corresponding 3,4-dihydronaphthalene **177** and epoxidation of the latter to **178**. However, instead of epoxide rearrangement, the epoxidation stage was followed by nucleophilic ring opening of the oxirane ring with malonate derivatives in refluxing anhydrous ethanol. This furnished *cis* or *trans* lactones (or hydroxyacids such as **179**) or mixtures of both. Finally, Jones oxidation of the hydroxyacids/lactones provided 1-substituted 2-tetralone derivatives such as **180**, as shown in Scheme 31.



Scheme 31. Synthesis of 1-substituted 2-tetralones by ring opening of epoxides.

The epoxide **162a**, was also prepared by KOH treatment of *trans*-2-bromo-1-methyl-1-tetralol **181b**, that was obtained by hydrobromination of 1-methyl-3,4-dihydronaphthalene **161a**.[109] This procedure was used to convert 1-tetralone **150a** into 1-methyl-2-tetralone **164a**.[110]

When the bromohydrin **181b** was treated with PhMgBr as base, a rearrangement took place, converting directly the 1-methyl-1-tetralol **181b** into 1-methyl-2-tetralone **164a**, in 40% yield (Scheme 32). This was explained as being a consequence of the formation of an oxonium ion (**183**) upon nucleophilic attack of the halomagnesium derivative (**184**) to the carbon atom supporting the bromine atom, followed by its rearrangement through internal displacement to **184** and the related enolate **185**. This reaction mechanism also explains why between **181b** and the related *cis* bromohydrin **181a**, only the *trans* bromohydrin **181b**, which is the only diastereomer capable of furnishing the oxonium



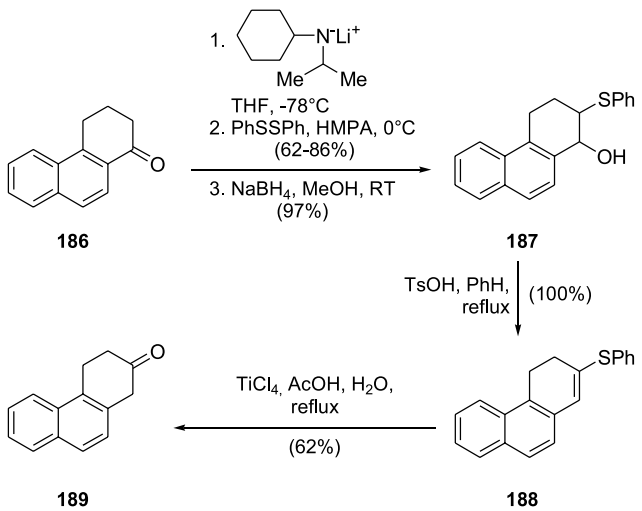
Scheme 32. Bromohydrins as epoxide precursors. Synthesis of 2-tetralone **164a** from 2-bromo-1-tetralol **181b**.

intermediate **183**, is capable of undergoing rearrangement to the 2-tetralone **164a**.

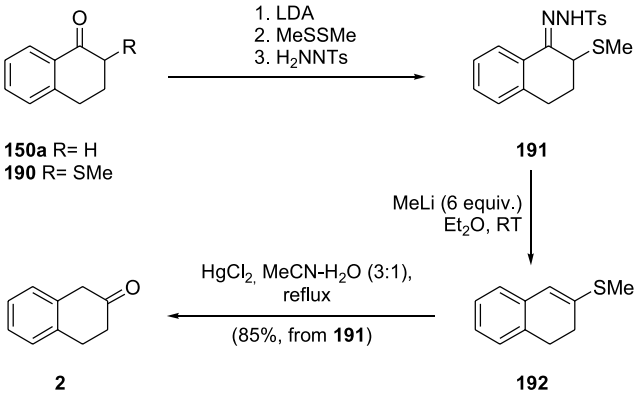
3.1.2. Carbonyl transposition via vinyl sulfides. An interesting and general procedure for carbonyl transposition has been provided by Trost and co-workers in 1975.[111]

The 1,2-carbonyl transposition was accomplished by monosulfenylation of a starting ketone, like **186**[112] followed by reduction of the resulting α-thio ketone to the corresponding β-hydroxy thioether **187** and dehydration of the alcohol so produced to give the vinyl sulfide **188**.

A final step consisting in the hydrolysis of the vinyl



Scheme 33. Synthesis of 2-tetralones employing a 1,2-carbonyl transposition with vinyl sulfides as intermediates.



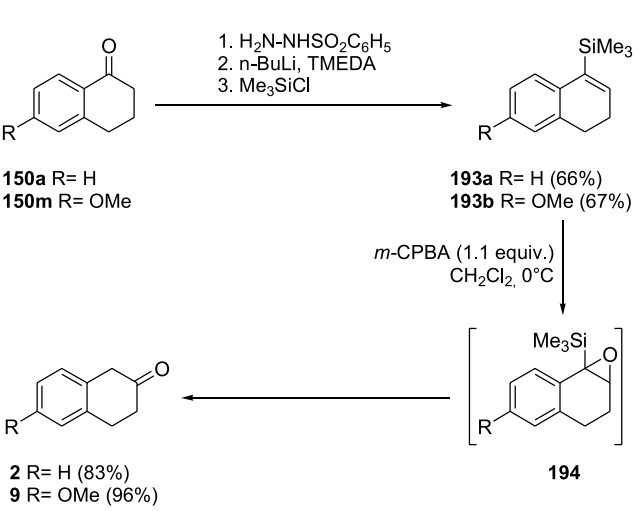
Scheme 34. Synthesis of 2-tetralone **2** by intermediacy of *p*-toluenesulfonylhydrazone **191**.

sulfide,[113] yielded the expected transposed ketone **189** in good yield (Scheme 33). A slightly different sequence for carrying out the carbonyl transposition was employed by Kano and co-workers.[114]

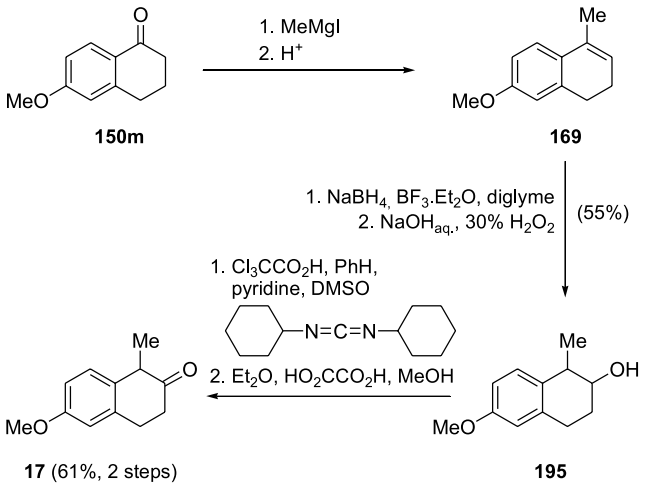
The α-thioketone **190**, derived from α-tetralone **150a**, on treatment with *p*-toluene-sulfonylhydrazide furnished *p*-toluenesulfony-lhydrazone **191**. Further reaction of **191** with methyllithium produced the vinyl sulfide **192**, which upon hydrolysis gave the β-tetralone **2** (Scheme 34).

3.1.3. Carbonyl transposition via vinylsilanes. The use of a vinylsilane as relay intermediate for the 1,2-carbonyl transposition was developed by Fristad and co-workers.[115] Vinylsilanes **193a**,**b** derived from α-tetralones **150a** and **150m**, were generated through reaction of ketone arene-sulfonyl-hydrazones with alkyllithium reagents and condensation of the resulting vinyl carbanions with chlorotrimethylsilane.[116]

They were next submitted to epoxidation, furnishing the non-isolated epoxysilanes **194**, when exposed to buffered ($NaHCO_3$) *m*-chloroperbenzoic acid in dichloromethane.[117] Contrary to other systems where carbonyl transposition requires $LiAlH_4$ reduction of the epoxide and chromic acid



Scheme 35. Synthesis of 2-tetralones by epoxidation–epoxide rearrangement of vinylsilanes.



Scheme 36. Synthesis of 6-methoxy-1-methyl-2-tetralone (**17**) by direct oxidation of 6-methoxy-1-methyl-2-tetralol **195**.

oxidation of the resulting alcohol, with concomitant desilylation, in these cases the corresponding β-tetralones **2** and **9** were accessed directly and in high yields (Scheme 35).[115] This result was attributed to the high activation of the system. The precise mechanistic details of this one-pot reaction have not been elucidated, but it is assumed that the procedure takes advantage of the properties associated with covalently bonded silicon.

3.1.4. Hydroboration–oxidation of dihydronaphthalene derivatives. Hydroboration–oxidation of trisubstituted alkenes (formed by Grignard addition to 1-tetralones and subsequent dehydration of the so produced tertiary alcohols), followed by oxidation of the resulting secondary alcohol constitutes an alternative to the epoxidation–epoxide rearrangement sequence for effecting the (alkylative)-1,2-carbonyl transposition.

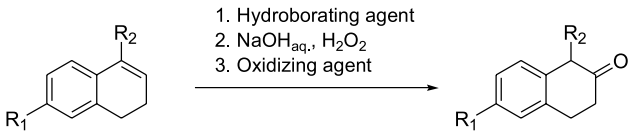
Thus, hydroboration–oxidation of 7-methoxy-4-methyl-1,2-dihydronaphthalene **169** with diborane, generated in situ from sodium borohydride and boron trifluoride and a Pfitzner–Moffatt oxidation, were employed to convert this trisubstituted olefin into **17** (61% yield from 1-tetralone **169**).[106] The reaction took place through the 6-methoxy-1-methyl-tetralin-2-ol intermediate **195** (Scheme 36). A similar approach to 2-tetralols was used by Parker during the synthesis of an inhibitor of the β-amiloid$_{1-42}$ aggregation,[118] and by Reddy and co-workers, the latter employing the chiral monoisopinocamphenyl borane for the hydroboration step.[119] Several other hydroborating reagents, such as 9-BBN and BH_3, have been reported for a similar reaction sequence,[120] and different oxidation systems have been tested for the oxidation of selected 2-tetralols. Unfortunately, CrO_3/H_2O/acetone, CrO_3/H_2O/pyridine, pyridine–chlorine complex, and the standard Oppenauer conditions, all met with failure. However, oxidation with the *N*-chlorosuccinimide–dimethyl sulfide complex provided **17**, albeit in modest yield (30%)[115] and the $Na_2Cr_2O_7/H_2SO_4$ reagent allowed the preparation of 1-organyl-2-tetralones in 53–73% yield,[120] as shown in Table 7.

A synthesis of **205**, an advanced intermediate towards triptoquinone employing the strategy of hydroboration–oxidation of dihydronaphthalene derivatives, was recently described by Shishido and co-workers. This natural product inhibits interleukin I release. As shown in Scheme 37, Claisen rearrangement of the allyl ether derivative **197** of bromophenol **196**, furnished allyl phenol **198**, which was conveniently manipulated to produce 1-tetralone **202** by a Friedel–Crafts type ring closure of intermediate **201**. The latter was produced by oxidative fission of the allyl moiety of **199** and oxidation of the resulting aldehyde **200**. Alkylation and dehydration of the tetralone furnished 1-methyl dihydronaphthalene **203**, which was hydroborated and oxidized, furnishing the expected 2-tetralol **204**. Finally, Swern oxidation of the 2-tetralol gave access to the natural product.

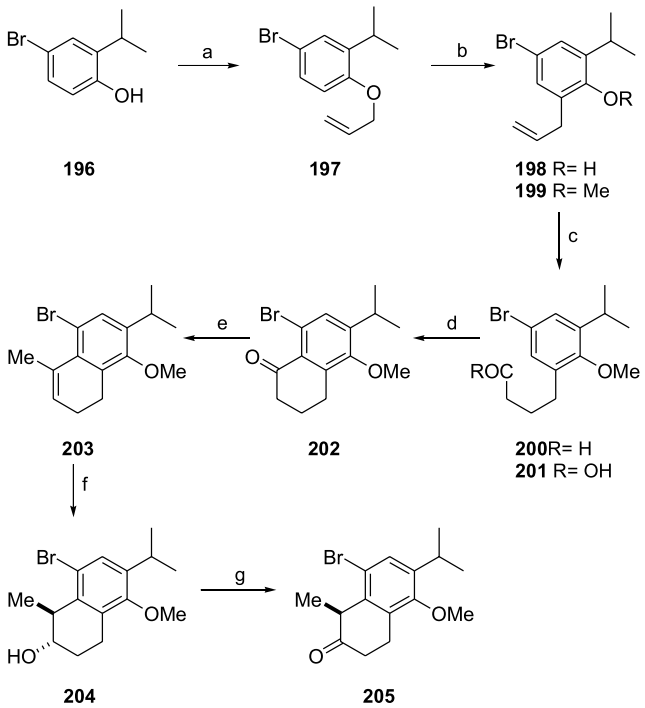
Miller and Shi reported the use of an hydroboration–oxidation strategy for the conversion of a 1,1-disubstituted 2-tetralone into a 4,4-disubstituted 2-tetralone, as depicted in Scheme 38. To this end, the starting 2-tetralone **206** was converted into dihydronaphthalene **207** by intermediacy of the related tosylhydrazone; in turn, this was submitted to an hydroboration–oxidation protocol, employing the bulky disiamyl borane reagent. Chromic oxidation of the resulting 2-tetralol **208** afforded the transposed 2-tetralone **209**.

Exposure of the 2-tetralone **209** to phosphorus pentabromide transformed the latter into 2-hydroxy-naphthalene derivative **213** by the bromoketone–phenol rearrangement. In this rearrangement, the tetralone was first α-brominated at the C-1 position, leading to compound **210**. Compound **211**, the enolic form of **210**, then favored migration of the

Table 7. Synthesis of 2-tetralones by hydroboration-oxidation of 1-organyl-3,4-dihydronaphthalenes and further oxidation of the resulting 2-tetralols



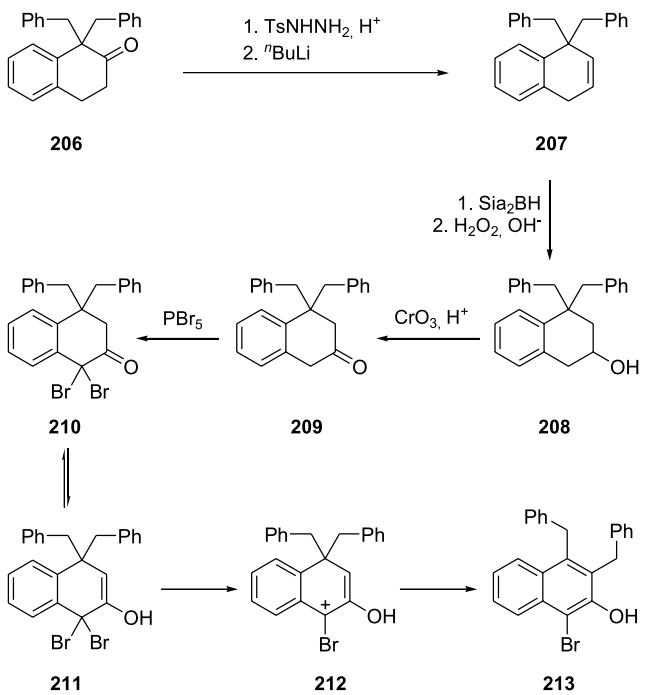
Entry no.	Hydro-borating agent	Oxidizing agent	Product	R_1	R_2	Yield (%)
1	$NaBH_4$, BF_3·Et_2O diglyme	Cl_3CCO_2H, DCC	**17**	OMe	Me	61
2	9-BBN, 0 °C→rt overnight	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**17**	OMe	Me	69
3	BH_3·THF	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164a**	H	Me	73
4	9-BBN, 0 °C→rt overnight	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164b**	H	Ph	53
5	BH_3·THF	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164d**	H	Et	55
6	9-BBN, 0 °C→rt overnight	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164e**	OMe	Ph	59



Scheme 37. (a) 1. $H_2C{=}CHCH_2Br$, K_2CO_3, DMF (78%); 2. NaOMe, CuI, MeOH, DMF (92%); (b) 1. 200 °C (91%); 2. Me_2SO_4, K_2CO_3, Me_2CO (99%); (c) 1. 9-BBN, CO, $LiAlH(t\text{-}BuO)_3$, HOO^- (58%); 2. H_2NSO_3H, $NaClO_2$, dioxane–H_2O (97%); (d) PPA (78%); (e) 1. MeMgI, PhH, Et_2O; 2. TsOH, PhH (88%); (f) $BH_3{\cdot}SMe_2$, HOO^- (87%); (g) $(COCl)_2$, DMSO, Et_3N (90%).

benzyl group through the carbocationic intermediate **212**. The rearrangement is spontaneous, since isolated dibromo tetralone **210** gives the bromonaphthol **213** on standing.[121a]

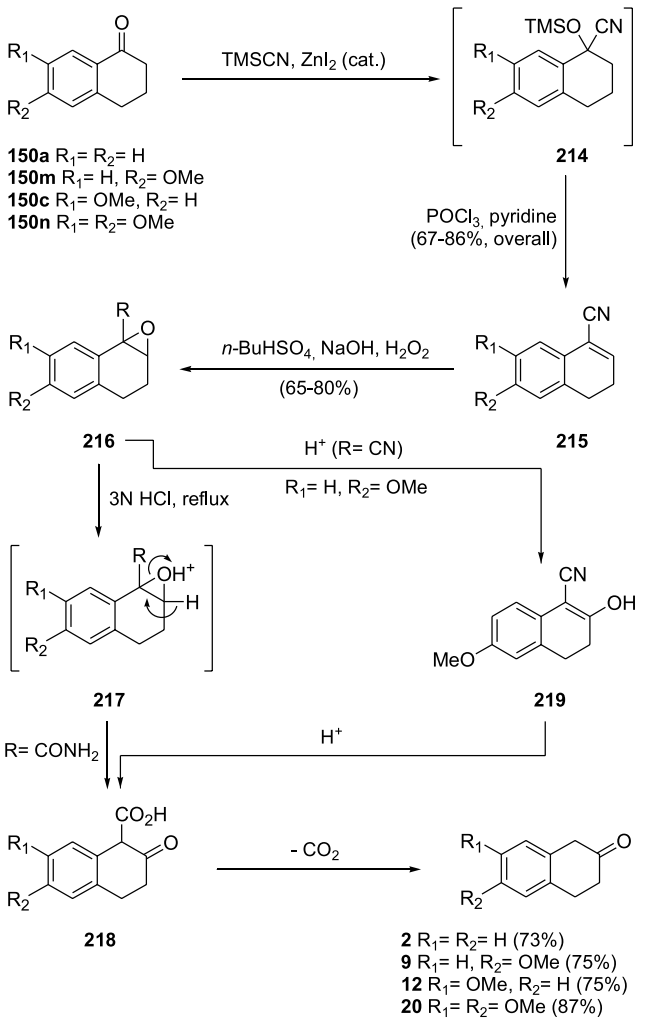
Unlike the known dienone–phenol rearrangement[121b] in which the migrating group is initially located *ortho* or *para* to the carbonyl, in this rearrangement the migrating group is originally located *meta* to the carbonyl function.



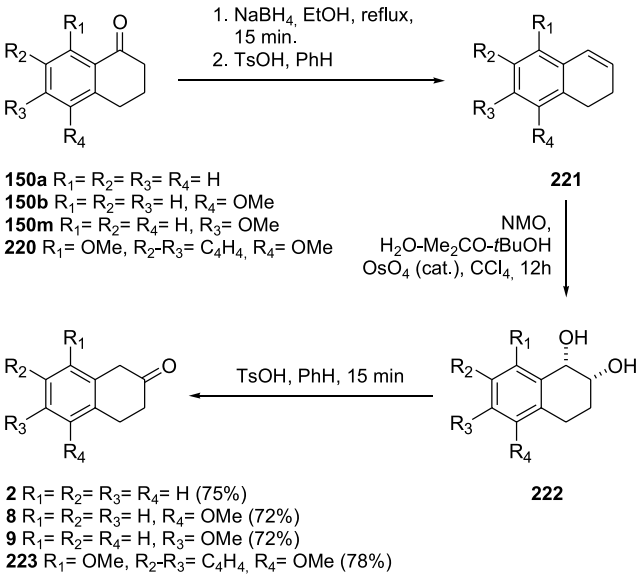
Scheme 38.

3.1.5. Carbonyl transposition via acid-catalyzed rearrangement of epoxyamides and epoxynitriles. Epoxynitriles **216** (R=CN), have been accessed by the Strecker silylcyanation of 1-tetralones **150a**, **150c**, **150m**, and **150n**,[122] followed by elimination of the resulting tertiary silyl ethers (**214**) and phase-transfer epoxidation[123] of the thus formed α,β-unsaturated nitriles **215**.

By refluxing with 3 N HCl, rearrangement of the epoxides took place, with concomitant partial hydrolysis of the nitrile moiety to the amide, furnishing the corresponding 2-tetralones in good yields, through the corresponding epoxyamides **217** (R=$CONH_2$) as intermediates. Four different congeners (**2**, **9**, **12** and **20**) were prepared by this procedure (Scheme 39).[124] It was observed that the epoxynitriles **216** (R=CN) themselves, prepared under non-hydrolytic conditions,[125] also rearranged to the 2-tetralones, albeit in very low yields (8%), being the enol **219** the major product (25%). The overall sequence is shown in Scheme 39. Apparently, epoxidation occurs before nitrile hydrolysis, being both relatively rapid processes. In acidic media, protonation of the epoxide **217**, was followed by ring opening and proton loss; final hydrolysis leads to the



Scheme 39. Synthesis of 2-tetralones by hydrolysis of epoxyamides.



Scheme 40. Preparation of 2-tetralones by selective partial dehydration of 1,2-diols **222**.

β-ketoacid **218**, which readily decarboxylates in situ to the corresponding tetralone. The protocol requires the development of a positive charge at the benzylic carbon which bears the nitrile or amide group (**217**);[126] this probably explains why the sequence does not seem to be effective with compounds carrying electron withdrawing groups on C-6, located *para* to C-1.

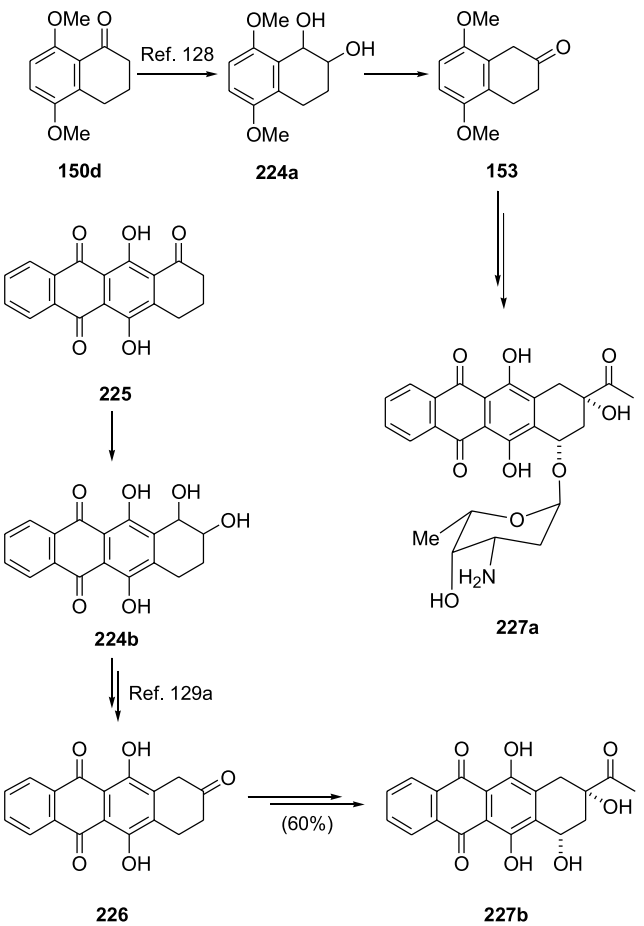
3.1.6. Carbonyl transposition by selective dehydration of 1,2-diols derived from 1-tetralones. This strategy takes advantage of the relative ease of benzylic alcohols to dehydrate under acid catalysis. Several 3,4-dihydronaphthalenes **221** were synthesized in a sequence starting with 1-tetralones **150a**, **150b**, **150m** and **220** and involving dehydration of the benzylic alcohol moiety of their corresponding 1-tetralols.

This was followed by dihydroxylation with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine–*N*-oxide[127] or trimethylamine *N*-oxide as stoichiometric co-oxidants, furnishing diols **222**.[111] The diols were rearranged with *p*-toluenesulfonic acid in benzene to the transposed ketones in overall yields of approximately 70% (Scheme 40).

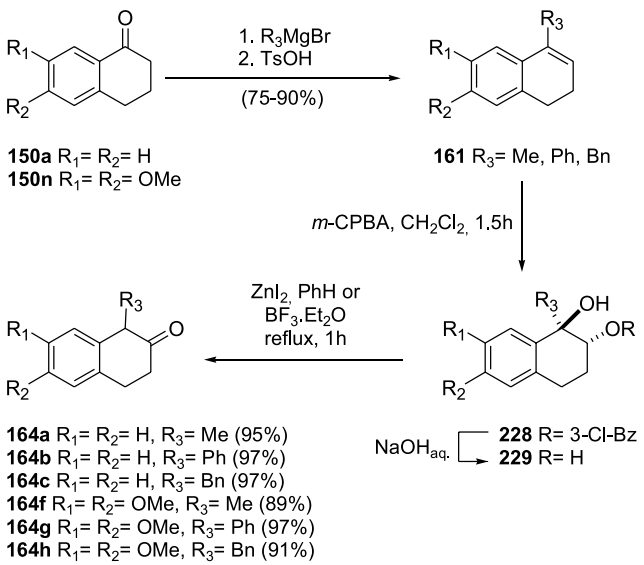
The strategy described in Scheme 40 was used during the total synthesis of idarubicine **227a**,[128] an antileukemic glycoside, and (±)-daunomycinone **227b**,[129] a potent antibiotic with anticancer activity.

In these syntheses, the 2-tetralone intermediates **153** and **226**, generated from the respective 1-tetralones **150d** and **225** through diols **224a** and **224b**, were involved (Scheme 41).

Despite previous reports indicating that the hydroxylation of dihydronaphthalenes with peracids often gives complex product mixtures as well as overoxidation products,[130] the sequence described in Scheme 40 was performed by several other reagents, such as the *m*-CPBA/NaOH reagent combination, for the generation of 1,2-diols **229** from their glycol monobenzoate intermediates **228**, and with ZnI_2 or BF_3 for their dehydration to 2-tetralones (Scheme 42).[102]



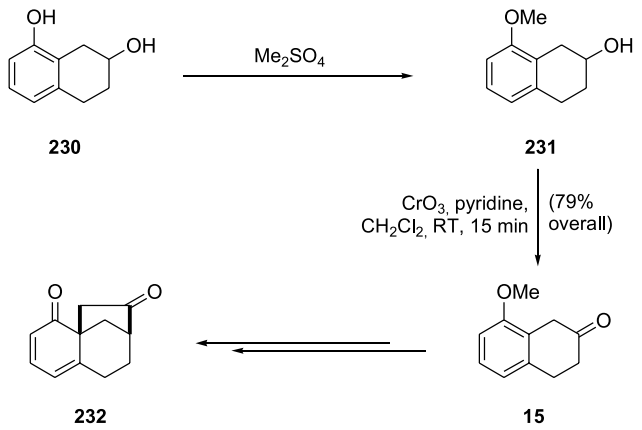
Scheme 41. Examples of the synthesis and use of 2-tetralones **153** and **226** employing the strategy of dehydration of 1,2-diols **224a** and **224b**.



Scheme 42. Synthesis of 1-organyl-2-tetralones **164a–c** and **164f–h** by 1,2-carbonyl transposition, through the intermediacy of 1,2-diols **229**.

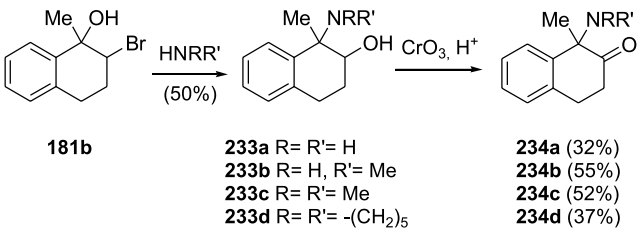
3.2. Direct oxidation of 2-tetralols

The CrO_3/pyridine/CH_2Cl_2 system was employed for the preparation of 8-methoxy-2-tetralone **15** from 8-methoxy-2-tetralol (**231**), in 85% yield.[131] The 2-tetralone **15** so obtained was used in the synthesis of the tricyclic dione **232**, a suitable intermediate for the preparation of tetracyclic terpenoids following the BC+D+A approach (Scheme 43). The partially methylated tetralol **231** is easily accessed by selective Williamson etherification of **230**.



Scheme 43. Synthesis of 8-methoxy-2-tetralone **15** by direct oxidation of the corresponding 8-methoxy-2-tetralol **231**.

1,1-Disubstituted 2-tetralols **233a–d**, accessed by regioselective ring opening of the epoxide formed by base treatment of bromohydrin **181b**, were converted to the respective 1,1-diorganyl-2-tetralones **234a–d** in modest yields, with Jones reagent (Scheme 44).[48e]

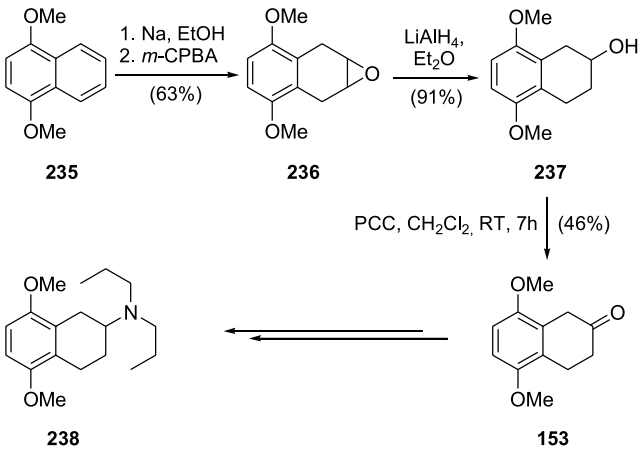


Scheme 44. Synthesis of 1-methyl-1-amino-2-tetralones **234a–d** from bromohydrin **181b** by epoxide formation, nucleophilic epoxide ring opening and direct oxidation of 1,1-disubstituted 2-tetralols **233a–d**.

The 1-methyl-1-amino-2-tetralones were synthesized to evaluate their hypnotic and locomotive properties in mice. They proved to be devoid of hypnotic activity, but showed to depress spontaneous locomotive activity.

The synthesis of 5,8-dimethoxy-2-(di-*n*-propylamino) tetralin **238**, a dopamine agonist (Scheme 45) demanded the preparation of 5,8-dimethoxy-2-tetralone **153**. This was effected in 46% yield through the oxidation of 5,8-dimethoxy-2-tetralol **237** with PCC in dichloromethane.[132]

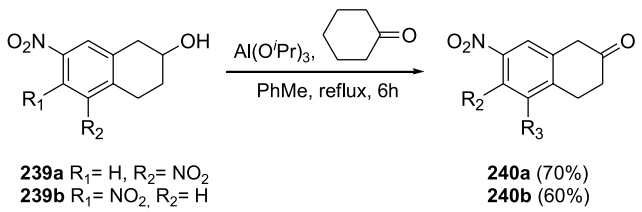
The intermediate 2-tetralol **237** was conveniently accessed by a three-step sequence involving partial reduction of 5,8-dimethoxynaphthalene **235**, followed by epoxidation of the resulting alkene and reduction of the oxirane group (**236**) with lithium aluminum hydride in ether. The 2-tetralone **153**



Scheme 45. 5,8-Dimethoxy-2-tetralone **153** via direct oxidation of 5,8-dimethoxy-2-tetralol.

was also employed for a study on anthracyclinone derivatives.[133]

The Oppenauer oxidation was employed for the preparation of 6,7- and 5,7-dinitro-2-tetralones (**240a**,**b**) from the respective 2-tetralols **239a**,**b**.[134] The 2-tetralones were obtained in good yields after refluxing the 2-tetralols with $Al(O^iPr)_3$ in the presence of a large excess of cyclohexanone during 6 h (Scheme 46). The oxidation of 2-tetralols was also discussed in Section 3.1.4.

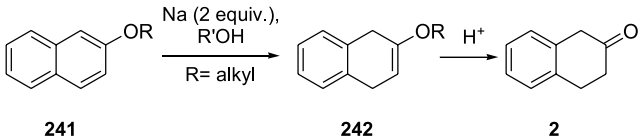


Scheme 46. Synthesis of 2-tetralones **240** by Oppenauer oxidation of 2-tetralols **239**.

3.3. Reduction of 2-alkoxynaphthalenes and 2-naphthols

3.3.1. Reduction of naphthalene derivatives with sodium in alcohol (Na/ROH). The Na/ROH reduction of 2-alkoxynaphthalenes, first described 60 years ago by Cornforth and co-workers,[12,15c] remains as one of the most important methodologies used for the syntheses of 2-tetralones. Several minor changes in the original reaction conditions have been made in order to optimize the transformation and adjust conditions to specific substrates.[20,21,46b,49d,135–137]

Basically, the procedure consists in reacting an alcoholic (ethanol, 2-propanol, isoamyl alcohol, etc.) solution of 2-alkoxynaphthalene (**241**) with 2 equiv. of sodium metal; submission of the resulting enol-ether **242** to acid hydrolysis yields the 2-tetralone product (Scheme 47).

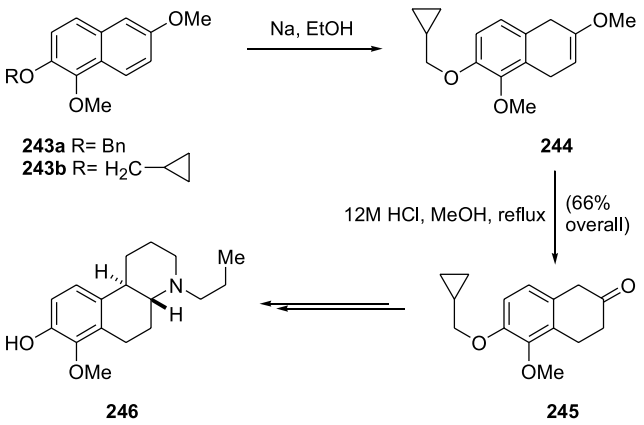


Scheme 47. Synthesis of 2-tetralone by Na/ROH reduction of 2-alkoxynaphthalenes.

The required alkoxynaphthalenes are not always easily available. Sometimes, they have been accessed from the related bromonaphthalenes employing an Ullman type coupling reaction with sodium methoxide, from sulfonic acids, and even from other 2-tetralones. It has been observed that the presence of a methoxy group in the α-position of one ring enhanced the reduction of the other ring, while the presence of the same substituent on the β-position enhanced the reduction of the ring the substituent was attached to. Amino and hydroxy groups display the same effects.

The Na/ROH reduction of alkoxynaphthalenes was employed for the preparation of a large number of 2-tetralones, precursors of compounds with biological and pharmacological activities,[22,38,49d,138–141] including dopaminergic agonists,[49d] benzoquinolines,[138] antiulcer agents,[38] radiolabelled compounds[140] and (−)-morphine.[141]

The 2-tetralone **245**, a key intermediate in the synthesis of *trans*-8-hydroxy-7-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[*f*]quinoline **246**, was also prepared by this method.[138] Attempts to effect the reduction of 2,5-dimethoxy-6-(benzyloxy)naphthalene (**243a**) to 5-methoxy-6-(benzyloxy)-2-tetralone, resulted in concomitant cleavage of the benzyl ether moiety. However, when the benzyl protecting group was replaced by a cyclopropylmethyl moiety, as in **243b**, the 2-tetralone enol ether derivative **244** was obtained, furnishing **245** in 66% overall yield after acid hydrolysis (Scheme 48).

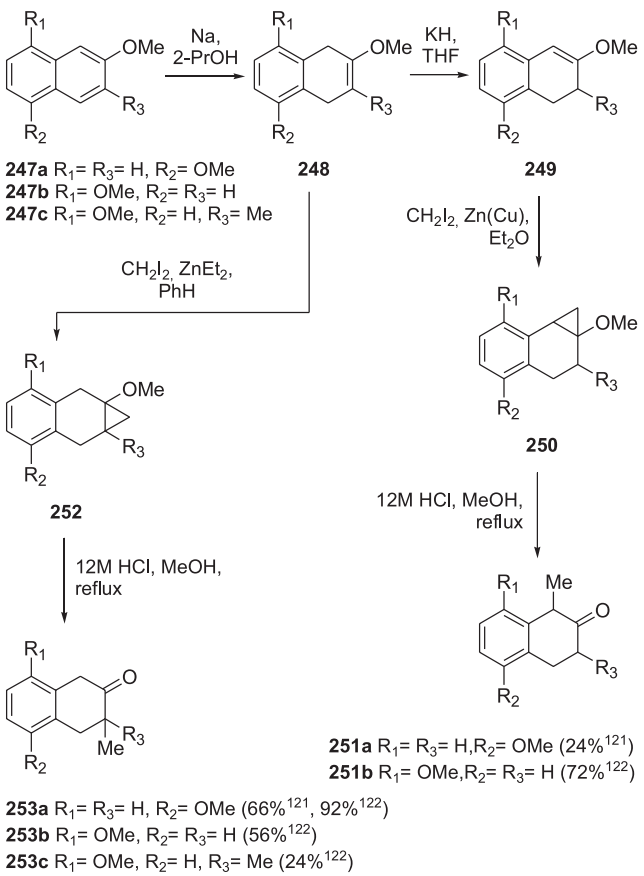


Scheme 48. Synthesis of 2-tetralone **245** by the Na/EtOH reduction of dimethoxynaphthalene **244**.

The naphthol ether reduction strategy was also considered very important to solve the problem of poor selectivity of the methods involving alkylation of 2-tetralones, for the preparation of 1- and 3-substituted 2-tetralones.[75]

While it is easy to prepare C-1[142] substituted 2-tetralones, C-3 substituted 2-tetralones are more difficult to access. The main synthetic route towards C-3-alkyl-substituted 2-tetralones involve specific carboxylation on C-3 with magnesium methyl carbonate, followed by alkylation of the resulting ketoester and final hydrolysis and decarboxylation;[143] however, this sequence is only moderately efficient. An alternative consists in protecting the more reactive C-1, alkylating the less acidic C-3 position and finally removing the protecting group. Unfortunately, introduction and removal of the protecting group add two steps to the route and reduces its efficiency in approximately 50%.[144] The formation of the dianion of 1-carboxymethyl-2-tetralones has been disclosed as another alternative that permits the efficient alkylation of C-3,[38] and condensation of 2-(phenylsulfonylmethyl)benzyl bromide **139** with the anion of monosubstituted malonates regioselectively provided C-3 substituted 2-tetralones, as discussed in Section 2.7,[145] offering additional possibilities.

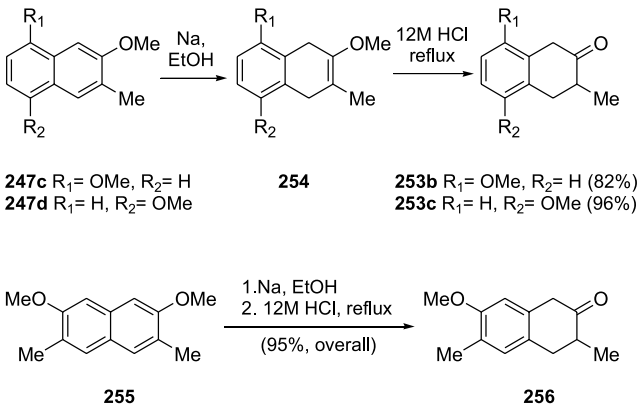
On the other hand, when the enol ether intermediate **248** was isomerized with strong base to **249** before the cyclopropanation step to **250**, it was possible to obtain 1-methyl-5-methoxy-2-tetralones **251a** selectively and in good yield (Scheme 49).



Scheme 49. Selective preparation of 1-methyl- and 3-methyl-2-tetralones **251a**,**b** and **253a**–**c** by the Na/ROH reduction of naphthalene derivatives **247a**–**c**.

When the solvent was changed to ethanol, and 3-methyl dimethoxynaphthalenes **247c** and **247d** were submitted to the dissolving-metal reduction, 3-methyl-2-tetralones **253b** and **253c** were prepared in good yields. Enol ethers **254** were intermediates of this transformation (Scheme 50).[146] By using the sodium in alcohol reduction of the symmetrical naphthalene **255**, the 7-methoxy-3,6-dimethyl-2-tetralone **256** was also successfully prepared, in 95% yield (Scheme 50).[148]

Exhaustive studies on the regioselective preparation of C-3 substituted 2-tetralones through the reduction of dimethoxynaphthalenes **247a**–**c** with Na/ROH have been

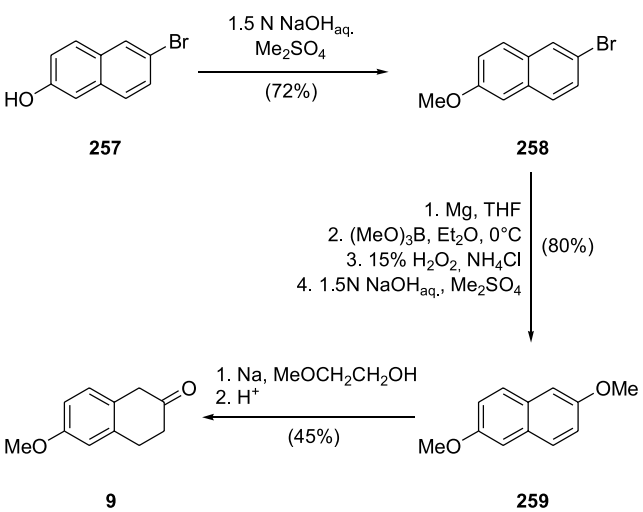


Scheme 50. Synthesis of 3-methyl-2-tetralones by reduction of naphthalene derivatives with Na/EtOH.

described.[145,146] Several experimental conditions were tested and the authors concluded that it was possible to control the regiochemistry of the reaction with the appropriate choice of the solvent system, which avoids the simultaneous formation of **248** and **249**.

Thus, 3-methyl-5-methoxy-2-tetralone (**253a**) was successfully obtained when the easily available 1,6-dimethoxy naphthalene **247a** was submitted to reduction with the Na/2-PrOH reagent system to give almost exclusively **248**. This was followed by a Simmons–Smith cyclopropanation to **252** with $CH_2I_2/Zn(Et)_2$ and an acid-catalyzed cyclopropane ring opening with MeOH/HCl.[147]

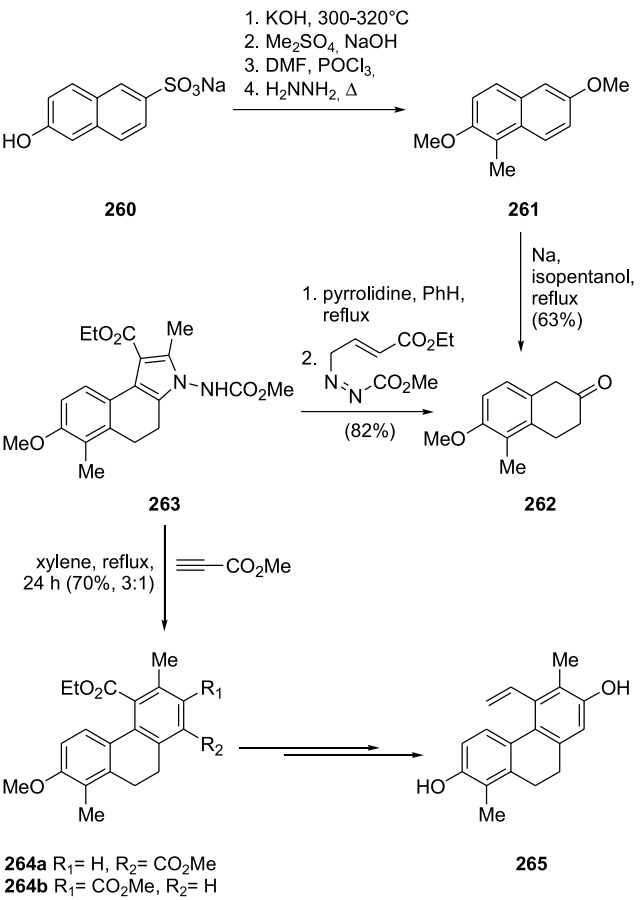
The Na/2-methoxyethanol system served to synthesize 6-methoxy-2-tetralone **9** in 70% yield from **259**. The starting symmetrical dimethoxynaphthalene was prepared in several steps from bromonaphthol **257**, being Williamson etherification to **258** the first of them (Scheme 51).[149] The same approach was employed for the preparation of a tyrosine analog of pharmacological interest.[150]



Scheme 51. Preparation of dimethoxynaphthalene **259** and its reduction with Na/2-methoxyethanol to 2-tetralone **9**.

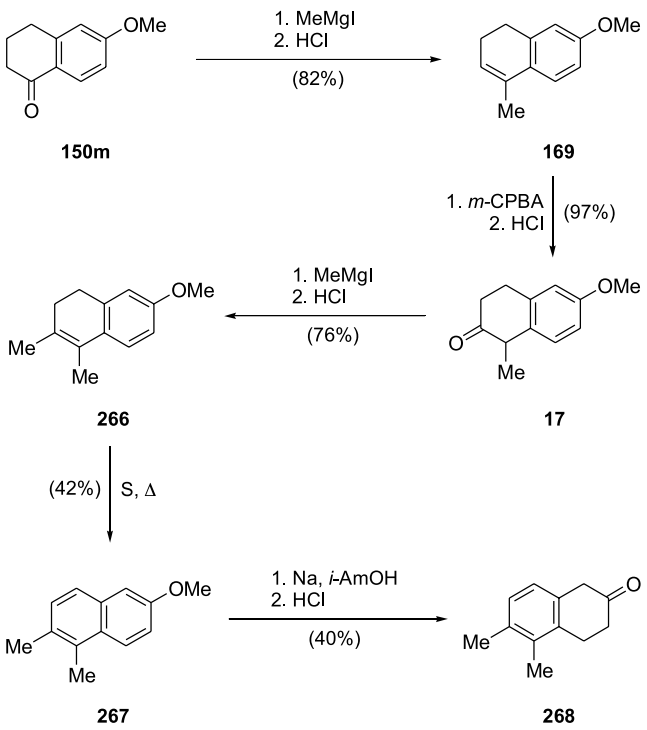
During their studies on the bio-reduction of 2-tetralones with Baker's yeast, Speranza and co-workers[151] synthesized several 2-tetralones employing the Na/EtOH system for the reduction of 2-methoxy-naphthalenes. Interestingly, recent publications disclosed the reverse path, reporting on the use of 2-tetralones as starting materials for the preparation of 1-substituted 2-naphthol derivatives.[152]

A further refinement of this reverse path is seen in the recent formal total synthesis of Emmotin G methyl ether from 5,8-dimethyl 2-tetralone (**153**), through its conversion into 6-methoxy-7-acetyl-1,4-dimethylnaphthalene.[153] The 2-tetralone derivative **262** was prepared in five steps and 72% overall yield from commercially available 2,6-dihydroxynaphthalene (**259**), in turn available from sodium 6-hydroxynaphthalene-2-sulfonate **260**. This compound was employed in a formal total synthesis of the cytotoxic phytoalexin juncusol (**265**), a natural product active against human nasopharynx carcinoma (Scheme 52).[154]



Scheme 52. Synthesis and use of the 2-tetralone **262** in the formal total synthesis of juncusol.

Condensation of **262** with pyrrolidine in benzene under reflux conditions, followed by reaction of the resulting enamine with ethyl 3-carbomethoxyazo-2-butenoate in THF gave pyrrole **263** in 82% yield. A Diels–Alder reaction with butyn-2-one in xylene at reflux temperature gave 70% of a 3:1 mixture of **264a** and **264b**. Functional group transformations lead to a previously synthesized juncusol precursor.[155] On the other hand, Rosowsky[46c] reported the joint use of the carbonyl transposition of a 1-tetralone (**150m**) to access a 2-tetralone intermediate (**17**) which, in turn was converted into a different 2-tetralone (**268**) by way of functionalization (**266**), aromatization (**267**) and sodium in isoamyl alcohol reduction, as shown in Scheme 53.

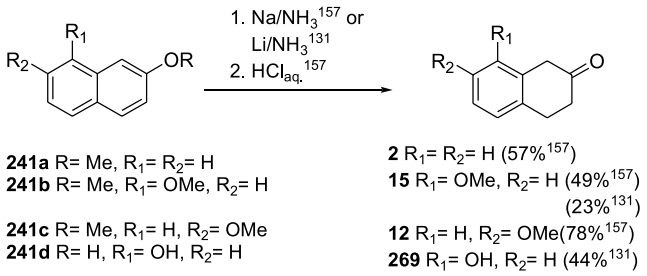


Scheme 53.

3.3.2. Reduction of naphthalene derivatives with dissolving metals in liquid ammonia (M/NH_3).

The dissolving metal reduction in liquid ammonia (Birch–Dryden reaction) has been reported as an efficient methodology for the synthesis of 2-tetralones. Similarly to the Na/ROH reduction methodology previously described, the M/NH_3 reduction of 2-naphthols and 2-methoxynaphthalenes is not new.[13,156,157]

Thus, lithium[131] and sodium[158] dissolved in NH_3 were employed for the conversion of 2-hydroxy-[131] and 2-methoxynaphtalenes (**241a–d**)[131,158a,b] into 2-tetralones **2**, **12**, **15** and **269** in reasonable to good yields (Scheme 54).



Scheme 54. Synthesis of 2-tetralones employing the M/NH_3 reduction of 2-methoxynaphthalenes and 2-naphthols.

By using the procedure described in Scheme 54, key 2-tetralones were produced and several 3-amino-2-tetralones were synthesized and biologically evaluated for their ability to selectively inhibit the membrane-bound zinc-dependent aminopeptidase-M, isolated from porcine kidney. The 1-phenethyl-3-amino-2-tetralone hydrochloride **270** and the tricyclic tetralone **271** were the most active among the tested 2-tetralones-based inhibitors (Fig. 2).[131,158]

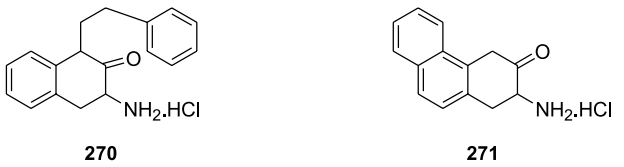
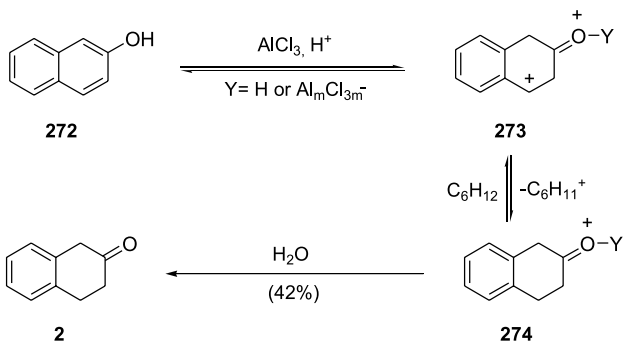


Figure 2. Structures of 3-amino-2-tetralones with potent and selective activity as inhibitors of aminopeptidase-M.

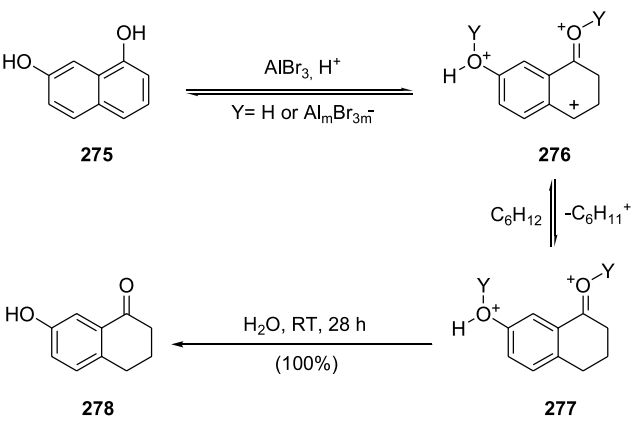
3.4. Ionic hydrogenation of 2-naphthols

2-Naphthol (**272**) was transformed into 2-tetralone **2** in 42% yield by means of an ionic hydrogenation with cyclohexane in the presence of $AlCl_3$ and HCl, as shown in Scheme 55.[158b] Compounds **273** and **274** have been postulated as reaction intermediates of this process.



Scheme 55. Ionic hydrogenation of 2-naphthol **272** with cyclohexane–$AlCl_3$. Synthesis of 2-tetralone (**2**).

The method, however, has some known limitations. For example and not unexpectedly, when 1,7-dihydroxynaphthalene **275** was submitted to the same conditions, replacing $AlCl_3$ with $AlBr_3$, 7-hydroxy-1-tetralone **278** was the only isolated product and none of **269** was observed. The tetralone **278** was formed through the intermediacy of **276** and **277** (Scheme 56). Interestingly, the thermolysis of 2-naphthol is known to produce 2-tetralone (**2**) as the major product.[159]



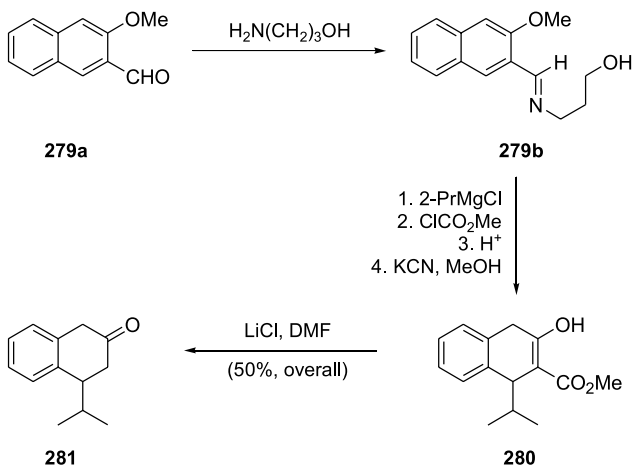
Scheme 56. Ionic hydrogenation of 7-hydroxy-1-naphthol **275** with cyclohexane/$AlBr_3$, yielding 1-tetralone **278**.

3.5. Tandem Grignard addition to 2-methoxynaphthyl imines. Synthesis of chiral 2-tetralones

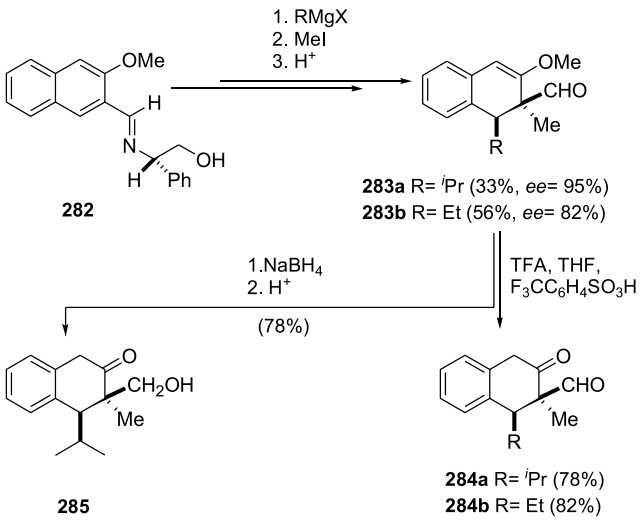
Recently, an elegant methodology that allows the preparation of 4-alkyl-, 3,4-dialkyl-, 3,4-disubstituted and 3,3,4-trisubstituted 2-tetralones with different substitution patterns, was described.[160]

The strategy involves the tandem addition of Grignard reagents to naphthalene derived imine **279** and it is suitable for the preparation of chiral 2-tetralones.

By this procedure, 4-isopropyl-2-tetralone **281** was obtained in 50% yield from **279b** (which is easily available from **279a**), being **280** the enolic form of a β-ketoester, an intermediate of this synthetic protocol (Scheme 57). When 2-PrMgCl and EtMgBr where added to the (*R*)-phenylglycinol imine **282**, chiral 3,3,4-trisubstituted 2-tetralones **284a**, **284b** and **285**, were obtained in good yields (Scheme 58).



Scheme 57. Synthesis of 2-tetralones employing the tandem addition of Grignard reagents to 2-methoxynaphthyl imines and acid hydrolysis.



Scheme 58. Synthesis of chiral 2-tetralones **284a**,**b** and **285** by tandem addition of Grignard reagents to 2-methoxynaphthyl imine **282** and subsequent α-carbonyl alkylation.

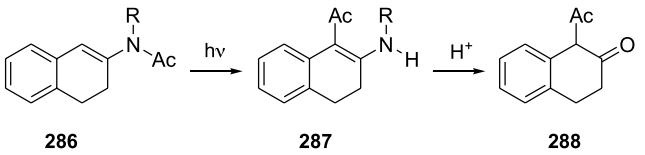
Reduction of the aldehyde moiety of intermediate **283a** prior to acid hydrolysis allowed differentiation of the carbonyl functions, as in **285**.

3.6. Photochemical reactions leading to polysubstituted 2-tetralones

Besides the intramolecular addition of silylenol ethers to PET-generated arene radical cations as a strategy for the synthesis of 2-tetralones, discussed in Section 2.8, other photochemical processes have been disclosed, the products of which are substituted 2-tetralones.

For example, Ninomiya and co-workers[161] reported that the photochemical reaction of *N*-acylenamines of aromatic systems **286** affords acyl migrated products. Thus, irradiation of *N*-acetyl enamines **286a**–**d** furnished 1-acyl-2-tetralone **288**, after acid hydrolysis of the *C*-acyl enamine intermediates **287a**–**d**. Table 8 shows the yields of the transformation employing different enamines.

Table 8. Photochemical reactions of *N*-acylenamines **286a**–**d**. Synthesis of 1-acetyl-2-tetralone **288**



Entry no.	Enamine	R	**287**, Yield (%)	**288**, Yield (%)
1	**286a**	$CH_2CH{=}CH_2$	60	70
2	**286b**	Me	67	65
3	**286c**	Bn	46	55
4	**286d**	n-C_4H_9	50	60

In another research work, a photocycloaddition reaction has been reported, by which in the presence of Lewis acids, 2-naphthols **290** add ethylene, furnishing [2+2] cycloadducts **292**, when irradiated with a high pressure mercury lamp through a Pyrex filter, at −78 °C.

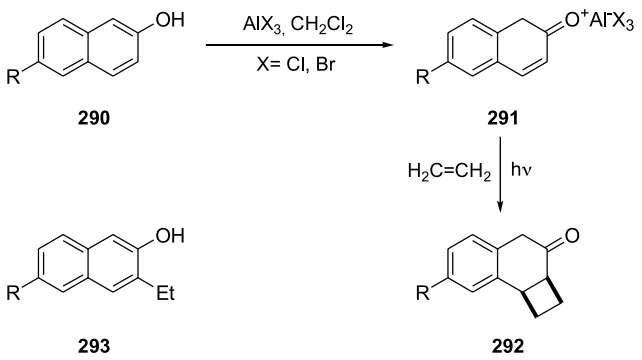
The reaction formally proceeds through the keto tautomer form (**291**) of the naphthol, formed under the assistance of the Lewis acid. Table 9 displays the results of the cycloaddition, employing different starting naphthols.[162] Interestingly, only $AlCl_3$ (5 equiv.) and $AlBr_3$ proved to be effective, and minor amounts of the ethyl substituted 2-naphthol **293** as well as 3-ethyl-2-tetralone, were isolated as side products.

4. Thallium(III)-promoted ring-expansion of 1-indanone exo-methylene derivatives

There are many publications[23,138,146] describing the preparation of several 2-tetralones from 1-indanones **294**. The reaction, originally developed by Taylor and co-workers[163] involves an initial Wittig reaction with $Ph_3PCH_3^+Br^-$ on the indanones, which yields the exocyclic methylene derivatives **295**.

The subsequent ring expansion/oxidation with $Tl(NO_3)_3$ in

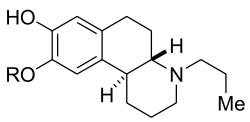
Table 9. Photoreaction of 2-naphthols with ethylene under the assistance of Lewis acids



Entry no.	R	Lewis acid	Yield (%)
1	H	$AlCl_3$	70
2	OH	$AlCl_3$	49
3	OMe	$AlCl_3$	66
4	Br	$AlCl_3$	68
5	CO_2Me	$AlCl_3$	68
6	H	$AlBr_3$	63

MeOH/$CHCl_3$ furnishes the corresponding 2-tetralones (**298**) in reasonable to good yields (Table 10). The use of a mixture of methanol and trimethyl orthoformate as solvent leads to the formation of the dimethylketal of the 2-tetralone product, from which the ketone can be obtained by acid hydrolysis, while the use of methanol alone as solvent conduces directly to the 2-tetralone. The starting indanones are easily available in high yield by means of short synthetic sequences.[164]

The protocol has been employed for the preparation of a differentially protected 2-tetralone, which served as an intermediate for the synthesis of aminotetraline derivative **300a**, a catechol *O*-methyltransferase metabolite (Fig. 3). This compound when evaluated in the cat cardioaccelerator nerve assay showed 50% inhibition at a dose of 300 μg/kg, 1000 times less potent than the related catechol **300b**.[118a]



300a R= Me
300b R= H

Figure 3.

The overall transformation, depicted in Scheme 59, is initiated by an oxythallation of the double bond of the exo-methylene derivative **295**, followed by a 1,2-rearrangement of the aryl group, as shown in the conversion of **296** to **297**; the carbon atom to which the aryl group was originally attached emerges in the final product as a carbonyl (**298**) or protected carbonyl (**299**), depending on the reaction conditions.

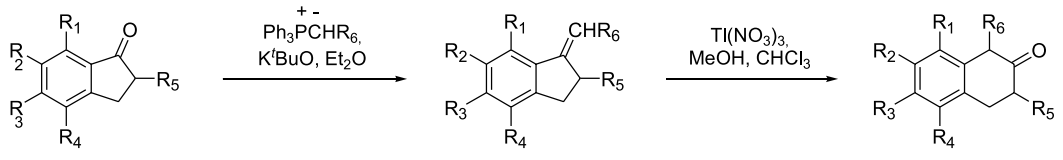
In an interesting example of carbonyl functionalization, compound 2**98i** was recently used as starting material for the synthesis of Wy-16225 (**306**),[118] a potent analgesic drug, as shown in Scheme 60.

Enantioselective alkylation of **298i** with 1,5-dibromo-pentane, under phase transfer catalysis of cinchoninium derivative **301** furnished bromide **302**, which was subjected to intramolecular cyclization, yielding **303**. Elaboration of the amine intermediate **305** through oximation (**304**) was followed by boron tribromide-assisted demethylation, efficiently providing the final product.

5. Conclusions

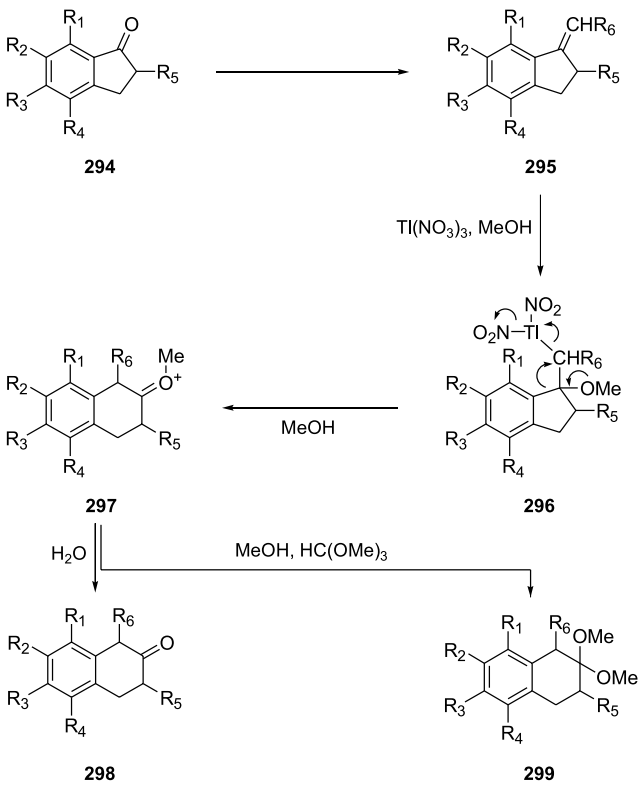
Known to chemists for over a century, 2-tetralones have become increasingly useful intermediates for the synthesis of natural products and their derivatives, as well as for the elaboration of novel, interesting and structurally accessible pharmacologically active compounds.

Table 10. The synthesis of 2-tetralones **253a** and **298a–j** employing the thallium(III)-promoted ring expansion of 1-indanones **294a–k**

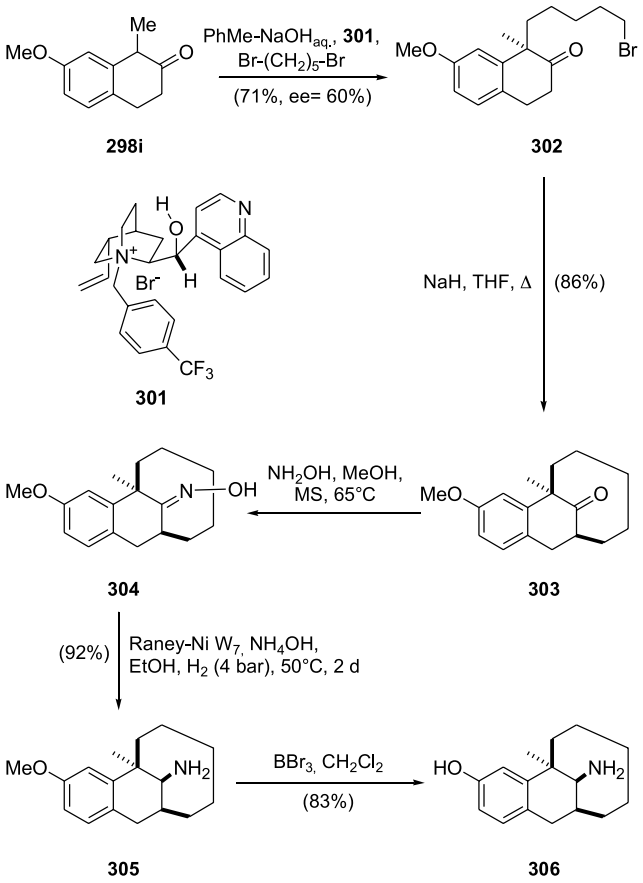


Entry no.	1-Indanone	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	Reference
1	**294a**	**253a**	H	H	H	OMe	Me	H	46	122
2	**294b**	**298a**	H	OMe	H	H	Me	H	45	122
3	**294c**	**298b**	H	Et	H	H	H	H	36	16
4	**294d**	**298c**	H	^{i}Pr	H	H	H	H	—[a]	16
5	**294e**	**298d**	H	^{t}Bu	H	H	H	H	—[a]	16
6	**294f**	**298e**	OMe	H	H	OEt	H	H	—[a]	16
7	**294g**	**298f**	Oet	H	H	OEt	H	H	—[a]	16
8	**294h**	**298g**	H	OMe	Obn	H	H	H	27	118a
9	**294i**	**298h**	H	OBn	OMe	H	H	H	13	118a
10	**294j**	**298i**	H	OMe	H	H	H	Me	93	132
11	**294k**	**298j**	H	H	Me	H	H	H	96[b]	132

[a] Yields were not reported.
[b] Obtained as the dimethylketal derivative.



Scheme 59.



Scheme 60. Synthesis of analgesic agent Wy-16225 (**306**).

Many strategies were designed during the first half of the 20th century for the preparation of 2-tetralones; however, during the last 40 years, a number of new, cleaner and atom-efficient methods for the synthesis of 2-tetralones have been devised and a series of important improvements to previously existing methodology have been disclosed. In addition, methods for the regio- and enantioselective synthesis of polysubstituted 2-tetralones have been reported, especially in recent times and chiral 2-tetralone derivatives have been used as key intermediates of complex enantioselective syntheses.

Although a few strategies seem to be rather narrow in scope or their scope has not been exhaustively studied to date, others are general and of broad application and some of them have been thoroughly studied even from the mechanistic point of view, being their advantages and limitations known in good detail.

These advances have made readily available many members of this class of compounds, some of which were difficult to prepare not long ago and discouraged chemists from using them as starting materials of devising syntheses carrying 2-tetralones as key intermediates.

It is beyond doubt that the current arsenal of synthetic approaches to the elaboration of 2-tetralones will continue to increase and diversify, and methods will improve, as more demanding synthetic targets will continue to capture organic chemists' imagination.

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Conformational studies of 3,4-dideoxy furanoid sugar amino acid containing analogs of the receptor binding inhibitor of vasoactive intestinal peptide

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Abstract—Conformational analysis of vasoactive intestinal peptide (VIP) receptor binding inhibitor Leu[1]-Met[2]-Tyr[3]-Pro[4]-Thr[5]-Tyr[6]-Leu[7]-Lys[8] **1** by various NMR techniques and constrained molecular dynamics (MD) simulation studies revealed that the molecule had a turn structure involving its Tyr[3]-Pro[4]-Thr[5]-Tyr[6] moiety with intramolecular hydrogen bond between Tyr[6]NH→Tyr[3]CO. In order to mimic the structure of **1**, peptidomimetic analogs **2–4** were synthesized using conformationally constrained scaffolds of 3,4-dideoxy furanoid sugar amino acids (2*S*,5*R*)-ddSaa1 **5** and its enantiomer (2*R*,5*S*)-ddSaa2 **6**. All these analogs displayed well defined three-dimensional structures akin to that found in **1**. Peptides **2** and **3**, which differed only in the sugar amino acid stereochemistry, show propensity of structures with identical intramolecular hydrogen bonds between ThrNH→MetCO. A similar structure with a hydrogen bond between TyrNH→MetCO was observed in **4**.

1. Introduction

Vasoactive intestinal peptide (VIP) is a widely distributed naturally occurring neuropeptide containing 28 amino acids with wide ranging biological activities.[1] It has been found that VIP receptors are over-expressed on a variety of malignant tumor cells that are also associated with the synthesis and secretion of detectable levels of the VIP by the malignant cells themselves.[2] The in vitro studies suggest that VIP acts as a growth factor and plays a dominant role in the sustained or indefinite proliferation of cancer cells. Focus is on the development of VIP receptor binding inhibitors that will have the potential to arrest the growth of malignant cells.[3] The peptide sequence Leu[1]-Met[2]-Tyr[3]-Pro[4]-Thr[5]-Tyr[6]-Leu[7]-Lys[8] **1** is known to be one such VIP receptor binding inhibitor.[4] The role of this octapeptide as a VIP receptor binding inhibitor[5] and its anti cancer activities in combination with other neuropeptide analogs[6] ha1ve been well established. Several novel analogs of this peptide containing α,α-dialkylated amino acids and its lipoconjugates have been synthesized and tested for their anti cancer activities.[7] This prompted us to undertake the development of new peptidomimetic analogs of **1** based on conformationally constrained nonproteinogenic scaffolds in order to increase their physiological stabilities.

It was envisaged that the design of the peptidomimetic analogs of **1** could be greatly facilitated by the knowledge of its three-dimensional structure. This prompted us to undertake first the structural studies of the octapeptide **1**. In this paper, we describe the detailed conformational analysis of **1** using various NMR techniques that established a well-defined turn structure involving Tyr[3]-Pro[4]-Thr[5]-Tyr[6] residues. Based on these structural studies, novel peptidomimetic analogs **2–4** were subsequently developed using 3,4-dideoxy furanoid sugar amino acids **5** (ddSaa1) and **6** (ddSaa2) as building blocks. In recent years, sugar amino acids have emerged as a class of versatile templates that have been used extensively as conformationally constrained scaffolds in many peptidomimetic studies.[8] Insertion of sugar amino acids (2*S*,5*R*)-ddSaa1 **5** and its enantiomer (2*R*,5*S*)-ddSaa2 **6** as dipeptide isosteres in place of the Tyr[3]-Pro[4] segment of **1** led to the formation of analogs **2** and **3**, respectively.

Keywords: 3,4-Dideoxy furanoid sugar amino acids; VIP receptor; Conformation; NMR.
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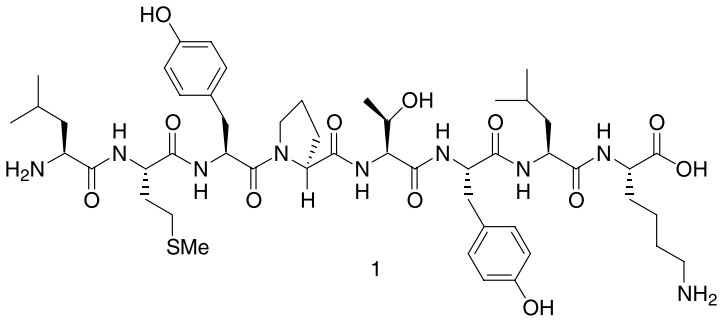

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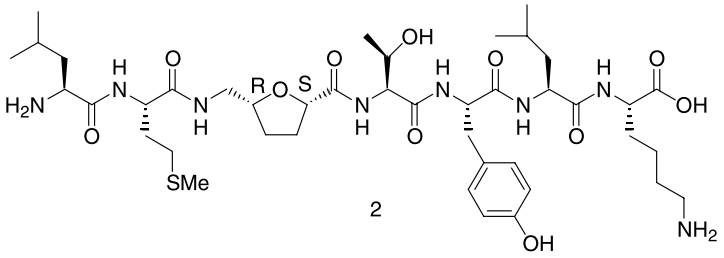

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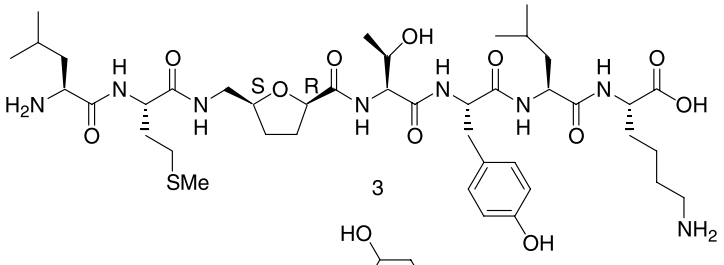

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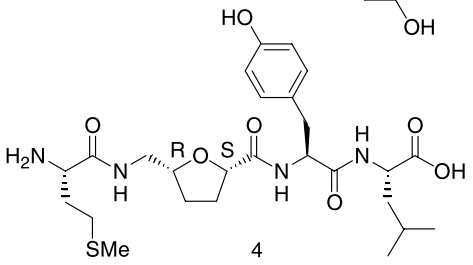

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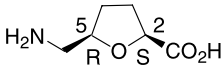

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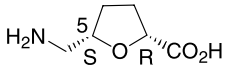

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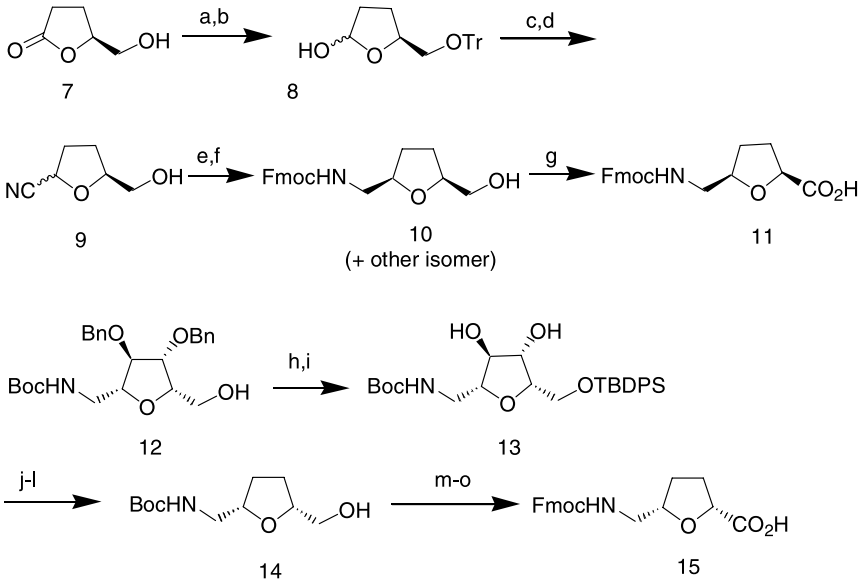
Compounds **2** and **3** displayed nucleation of well-defined turn structures, similar to the one found in **1**, with an intramolecular hydrogen bond between ThrNH→MetCO. Further truncation of **1**, replacing three of its amino acids Tyr[3]-Pro[4]-Thr[5] with ddSaa1 and deleting one residue each from both the termini, still retained the essential 10-membered β-turn like structure in the resulting analog **4** with a TyrNH→MetCO hydrogen bond, underlying the turn-inducing effect of 2,5-*syn* furanoid sugar amino acids. The details of the synthesis and structural studies of peptide **1** and its analogs **2**–**4** are described here.

2. Results and discussions

2.1. Synthesis of sugar amino acids 5 and 6 with Fmoc-protection

Scheme 1 describes the synthesis of Fmoc-protected 3,4-dideoxy furanoid sugar amino acids ddSaa1 and ddSaa2.[9] The starting material for the synthesis of Fmoc-ddSaa1 was (5*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one **7**, which was prepared from L-glutamic acid in two steps using known methods.[10] Protection of the primary hydroxyl of **7** as the trityl ether, and subsequent reduction of the lactone using DIBAL-H furnished the lactol **8** as a mixture of isomers. Acylation of the lactol hydroxyl group led to the formation of a glycosyl acetate intermediate that was treated with trimethylsilyl cyanide in the presence of BF_3–Et_2O to get a diastereomeric mixture of the glycosyl cyanides **9**.[11] Reduction of the cyanide group of **9** with $LiAlH_4$ gave a primary amine intermediate that was protected in situ using FmocOSu to furnish the intermediate **10**. The faster moving spot on the TLC was the desired (2*S*,5*R*)-isomer that could be separated easily at this stage using standard silica gel column chromatography. The relative stereochemistries of the separated isomers were further confirmed by ^{1}H NOE difference spectroscopic studies. Irradiation of the C2–*H*



Scheme 1. Reagents and conditions: (a) pyridine, TrCl, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 12 h; (b) DIBAL-H, CH_2Cl_2, −78 °C, 10 min; (c) Et_3N, Ac_2O, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 30 min; (d) TMSCN, BF_3–Et_2O, CH_3CN, rt, 4 h; (e) $LiAlH_4$, Et_2O, 0 °C, 5 min, reflux, 3 h; (f) FmocOsu, CH_2Cl_2, 0 °C to rt, 1 h; (g) Jones reagent, acetone, 0 °C to rt, 3 h; (h) H_2, 10% $Pd(OH)_2$–C, MeOH, rt, 8 h; (i) TBDPSCl, Et_3N, DMAP (cat.), DMF, 0 °C to rt, 3 h; (j) Ph_3P, imidazole, I_2, toluene, reflux, 3 h; (k) H_2, 10% $Pd(OH)_2$–C, MeOH, rt, 1 h; (l) TBAF, THF, 0 °C to rt, 3 h; (m) $NaIO_4$, $RuCl_3 \cdot 3H_2O$ (cat.), CH_3CN:CCl_4:H_2O (1:1:1.5), 0 °C, 2 h; (n) TFA, CH_2Cl_2, 0 °C, 2 h; (o) FmocOSu, 10% aqueous Na_2CO_3, dioxane, 0 °C to rt, 12 h.

signal of the (2*S*,5*R*)-isomer **10** enhanced the peak of C5–*H* confirming their *syn*-relationship. Oxidation of the primary hydroxyl of **10** to carboxylic acid using Jones' reagent furnished the target molecule Fmoc-ddSaa1 **11**.

Synthesis of the other enantiomer of **11**, Fmoc-ddSaa2, was started with the known compound **12**, which was prepared by us earlier from D-glucose.[12] Debenzylation of **12** was followed by selective protection of the primary hydroxyl group as the TBDPS ether to get the intermediate diol **13**. Next, the diol **13** was transformed into the 3,4-dideoxy intermediate **14** in three steps—reductive elimination of the 3,4-diol moiety using Ph_3P/I_2/imidazole,[13] hydrogenation of the resulting 3,4-olefin function and finally, desilylation of the C1-hydroxyl group using TBAF. Compound **14** was transformed into the required Fmoc-protected product **15** following a three-step process—oxidation of the primary hydroxyl to get the carboxylic acid, Boc-deprotection using trifluoroacetic acid in dichloromethane, followed by Fmoc protection using FmocOSu to furnish the required product **15**.

2.2. Synthesis of peptides 2–4

Peptides **2**–**4** were synthesized by solid phase method on Wang resin using the Fmoc strategy.[14] Substitution levels for automated synthesis were preferably between 0.9 and 1.2 mmol amino acid per gram resin. Preferably, DIPC/HOBt or HBTU/DIPEA and PyBOP/DIPEA were used as activating reagents in the coupling reactions.[15] The coupling reactions were carried out in DMF, CH_2Cl_2 or NMP[15] or a mixture of these solvents. The Fmoc group was cleaved by using 20% piperidine in DMF for 30 min. Usually, 3–4 equiv of activating agents and 3–4 equiv of Fmoc protected amino acid per resin nitrogen equivalent were used per coupling step. The side chain protecting groups were deprotected and the peptide was simultaneously cleaved from the resin by treatment with trifluoroacetic acid, crystalline phenol, ethanedithiol, thioanisole and deionized water for 2–3 h at room temperature. The crude peptides obtained by precipitation with cold dry ether were purified by preparative HPLC and used for conformational analysis by NMR.

2.3. Conformational analysis. NMR studies

NMR studies of **1**–**4** were carried out in DMSO-d_6. The spectra were well resolved and most of the spectral parameters could be obtained easily and are reported in the Tables 1–4. While the assignments were carried out with the help of total correlation spectroscopy (TOCSY),[16] rotating frame nuclear Overhauser effect spectroscopy (ROESY)[17] experiments provided the information on the proximity of protons, the details of which are provided in Section 4. Variable temperature studies were carried out to measure the temperature coefficients of the amide proton chemical shifts ($\Delta\delta(\Delta($, which provided information about their involvements in intramolecular hydrogen bonds.[18] The cross-peak intensities in the ROESY spectra, shown schematically in Figures 1–4, were used for obtaining the restraints in the simulated molecular dynamics (MD) calculations,[19] the detailed protocol of which is included in Section 4.

2.4. Conformational analysis of 1

Proline, the unique cyclic natural amino acid, can undergo *cis–trans* rotamerisation with preceding amino acid, because of the presence of imide bond. Invariably the *trans* rotamer predominates the *cis* rotamer in solution. Peptide **1** shows two sets of resonances with 6:1 ratio, because of the existence of *cis*/*trans* isomers about Tyr^3-Pro^4 amide linkage. The observation of strong rOe cross-peaks, as shown in **A** in Figure 1, between

Table 1. ^{1}H chemical shifts (δ in ppm), coupling constants (J in Hz) and temperature coefficients ($\Delta\delta/\Delta T$ in ppb/deg K) of **1** in DMSO-d_6 at 500 MHz

Amino acid	NH	CαH	CβH	CγH	CδH	Others	$\Delta\delta/\Delta T$
Leu[1]	—	3.71 (m)	1.45–1.49 (m)	1.59 (m)	0.86 (d, J=6.7 Hz), 0.84 (d, J=6.8 Hz)		
Met[2]	8.49 (d) (J=8.5 Hz)	4.39 (m)	1.86, 1.74 (m)	2.41 (m)		2.02 (SCH_3)	−5.5
Tyr[3]	8.20 (d) (J=7.8)	4.55 (ddd) (J=4.5, 8.2 Hz)	2.86 (dd, J=4.5, 14.3), 2.67 (dd, J=8.9, 14.3 Hz)			7.04, 6.61 (Ph), 9.15 (OH)	−7.8
Pro[4]	—	4.43 (m)	1.96, 1.88 (m)	1.82 (m), 1.81 (m)	3.59 (m), 3.43 (m)		
Thr[5]	7.78 (d) (J=8.1 Hz)	4.18 (dd) (J=4.2 Hz)	3.96 (m)	1.01 (d, J=6.4 Hz)		4.91 (OH)	−6.0
Tyr[6]	7.68 (d) (J=8.1 Hz)	4.44 (m)	2.93 (dd, J=4.4, 14.3 Hz), 2.71 (dd, J=9.1, 14.3 Hz)			6.99, 6.60 (Ph)	−3.6
Leu[7]	7.94 (d) (J=8.2 Hz)	4.30 (q) (J=8.2 Hz)	1.45–1.47 (m)	1.58 (m)	0.87, 0.83		−6.9
Lys[8]	7.99 (d) (J=7.9 Hz)	4.13 (dt) (J=5.0 Hz)	1.72 (m)	1.60 (m), 1.54 (m)	1.36 (m)	2.76	−6.9

Table 2. ^{1}H chemical shifts (δ in ppm), coupling constants (J in Hz) and temperature coefficients ($\Delta\delta/\Delta T$ in ppb/deg K) of **2** in DMSO-d_6 at 500 MHz

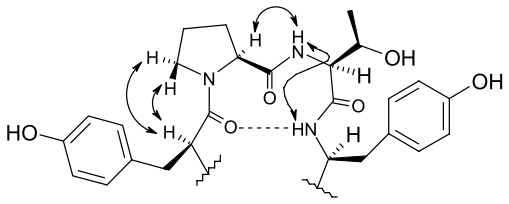
Amino acid	NH	CαH	CβH	CγH	CδH	Others	$\Delta\delta/\Delta T$
Leu	8.08 (bs)	3.80 (m)	1.52–1.61 (m)			0.87 (d), 0.88 (d)	
Met	8.61 (d) (J=8.1 Hz)	4.41 (dt) (J=5.2 Hz)	1.91 (m), 1.80 (m)	2.48 (m), 2.43 (m)		2.03 (SCH_3)	−5.5
ddSaa1	8.33 (d) (J=5.8 Hz)	4.30 (m)	1.87 (m), 2.11 (m)	1.46 (m)	3.96	3.34, 3.16	−7.3
Thr	7.60 (d) (J=8.4 Hz)	4.19 (dd) (J=4.6 Hz)	3.98 (m)	0.99 (m)		4.94 (OH)	−2.8
Tyr	7.87 (d) (J=8.2 Hz)	4.49 (dt) (J=4.4 Hz)	2.90 (dd, J=4.5, 14.2 Hz), 2.67 (dd, J=8.7, 14.2 Hz)			6.98 (d, J=8.4 Hz), 6.59 (d, J=8.4 Hz)	−4.7
Leu	7.96 (d) (J=8.1 Hz)	4.31 (m)	1.45–1.47	1.60 (m)	0.87 (d), 0.84 (d)		−6.5
Lys	8.08 (d) (J=7.7 Hz)	4.15 (dt) (J=5.0 Hz)	1.72	1.60 (m), 1.54 (m)	1.36 (m)	2.76	−7.8

Table 3. ^{1}H chemical shifts (δ in ppm), coupling constants (J in Hz) and temperature coefficients ($\Delta\delta/\Delta T$ in ppb/deg K) of **3** in DMSO-d_6 at 500 MHz

Amino acid	NH	CαH	CβH	CγH	CδH	Others	$\Delta\delta/\Delta T$
Leu	8.07 (bs)	3.80 (m)	1.50 (m)	1.59 (m)	0.87 (d, J=6.5 Hz), 0.87 (d, J=6.5 Hz)		—
Met	8.61 (d) (J=8.1 Hz)	4.39 (ddd) (J=5.0, 8.4 Hz)	1.90 (m), 1.80 (m)	2.47 (m), 2.42 (m)		2.03 (SCH_3)	−5.0
ddSaa2	8.25 (d) (J=5.8 Hz)	4.28 (dd) (J=5.2, 8.3 Hz)	1.88 (m)	1.51 (m)	3.97 (m)	3.24 (m), 3.12 (m)	−6.7
Thr	7.53 (d) (J=8.2 Hz)	4.17 (d) (J=4.6 Hz)	3.95 (m)	0.95 (d, J=6.3 Hz)		5.00 (d, J=5.5 Hz, OH)	−2.2
Tyr	7.93 (d) (J=8.3 Hz)	4.46 (dt) (J=4.3 Hz)	2.92 (dd, J=4.4, 14.1 Hz), 2.67 (dd, J=8.9, 14.1 Hz)			6.98 (d, J=8.5 Hz), 6.60 (d, J=8.5 Hz)	−4.9
Leu	7.94 (d) (J=8.1 Hz)	4.31 (dt) (J=6.1, 8. 1 Hz)	1.45–1.47 (m)	1.60 (m)	0.87 (d, J=6.5 Hz), 0.83 (d, J=6.5 Hz)		−6.1
Lys	8.07 (d) (J=7.5 Hz)	4.14 (m)	1.72 (m)	1.60 (m), 1.54 (m)	1.35	2.75 (m), 7.65 (bs)	−7.4

Table 4. ^{1}H chemical shifts (δ in ppm), coupling constants (J in Hz) and temperature coefficients ($\Delta\delta/\Delta T$ in ppb/deg K) of **4** in DMSO-d_6 at 500 MHz

Amino acid	NH	CαH	CβH	CγH	CδH	Others	$\Delta\delta/\Delta T$
Met	8.16 (bs)	3.84 (m)	2.48 (m), 1.98 (m)	3.30 (m), 3.30 (m)		2.05 (s, SCH_3)	—
ddSaa1	8.69 (t) (J=5.8 Hz)	4.18 (dd) (J=5.4, 8.0 Hz)	1.29 (m), 1.84 (m)	1.66 (m), 2.05 (m)	3.94 (m)	3.12 (m), 3.22 (m)	−4.7
Tyr	7.56 (d) (J=8.8 Hz)	4.58 (ddd) (J=4.1, 9.3 Hz)	2.96 (dd, J=4.4, 14.0 Hz), 2.67 (dd, J=9.8, 14.0 Hz)			6.63 (d, J=8.5 Hz), 7.07 (d, J=8.5 Hz), 9.15 (OH)	−2.8
Leu	8.38 (d) (J=8.0 Hz)	4.23 (ddd) (J=6.0, 8.5 Hz)	1.63–1.52 (m)		0.90 (d, J=6.7 Hz), 0.84 (d, J=6.7 Hz)		−6.9



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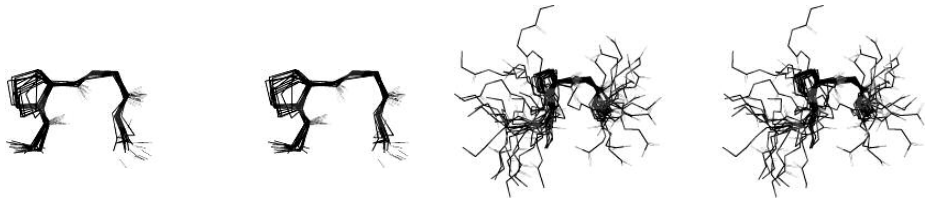
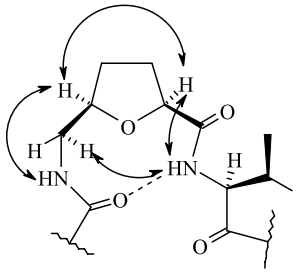


B

Figure 1. (A) Schematic representation of the proposed β-turn involving Tyr^3-Pro^4-Thr^5-Tyr^6 residues in **1** with some of the prominent long-range rOes seen in its ROESY spectrum. (B) Stereo view of the 25 superimposed energy-minimized structures of **1** sampled during 50 cycles of the 300 ps constrained MD simulations following the simulated annealing protocol: H-bonded region (left), full structure (right).

$Tyr^3C\alpha H \leftrightarrow Pro^4C\delta H$ and $Tyr^3C\alpha H \leftrightarrow Pro^4C\delta' H$ in the ROESY spectrum show that the major isomer has a *trans* imide bond preceding Pro^4. Moderate magnitude of $\Delta\delta/\Delta T = -3.6$ ppb/deg K for Tyr^6NH indicates the propensity of a structure, with its participation in intramolecular hydrogen bonding. Observation of rOe cross-peaks between $Thr^5NH \leftrightarrow Tyr^6NH$ and $Tyr^6NH \leftrightarrow Leu^7NH$ as well as the participation of Tyr^6NH in hydrogen bonding shows the existence of a 10-membered β-turn around Pro^4-Thr^5 residues. The presence of similar intensities of rOe cross-peaks of $Thr^5NH \leftrightarrow Pro^4C\alpha H$ and $Thr^5NH \leftrightarrow Thr^5C\alpha H$ imply that the observed turn is a type-II β-turn.

The molecular dynamics calculations on **1** clearly show structures with a type-II β-turn about Pro^4-Thr^5 residues. Figure 1 depicts the assembly **B** of the backbone superimposed turn structures of the 25 samples collected during 300 ps simulated annealing protocol (detailed protocol has been given in the Supporting Information). It clearly shows a type-II β-turn about Pro^4-Thr^5 residues, where as the other



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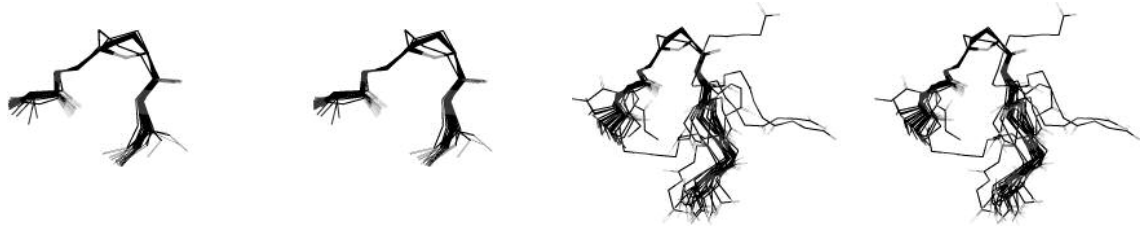

B

Figure 2. (A) Schematic representation of the proposed β-turn like structures involving Met-ddSaa1-Thr residues in **2** with some of the prominent long-range rOes seen in its ROESY spectrum. (B) Stereo view of the 25 superimposed energy-minimized structures of **2** sampled during 50 cycles of the 300 ps constrained MD simulations following the simulated annealing protocol: H-bonded region (left), full structure (right).

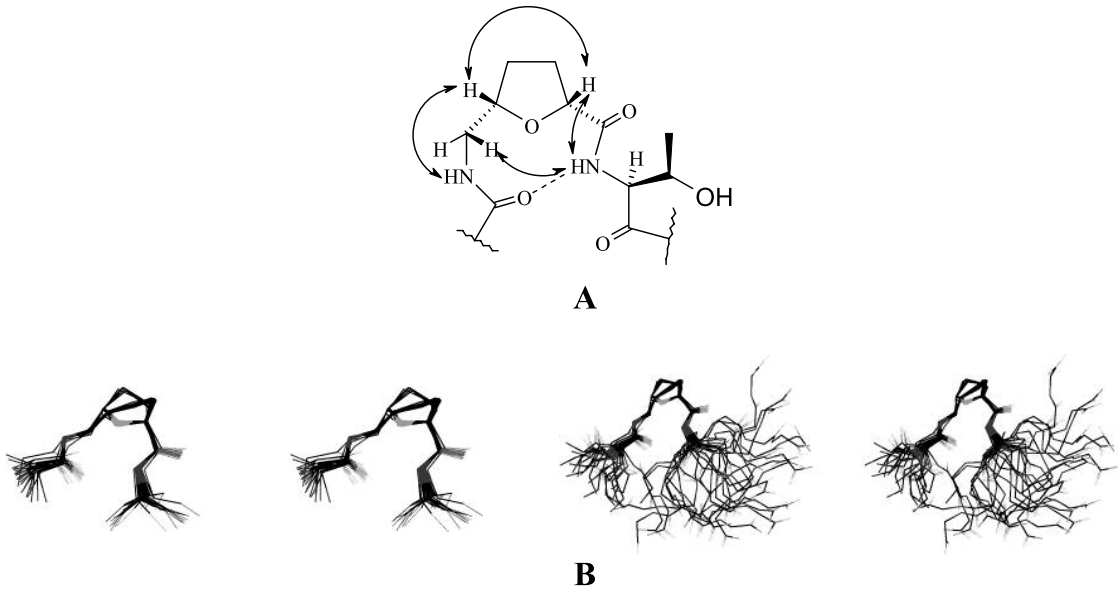

Figure 3. (A) Schematic representation of the proposed β-turn like structures involving Met-ddSaa2-Thr residues in **3** with some of the prominent long-range rOes seen in its ROESY spectrum. (B) Stereo view of the 25 superimposed energy-minimized structures of **3** sampled during 50 cycles of the 300 ps constrained MD simulations following the simulated annealing protocol: H-bonded region (left), full structure (right).

part of the peptide backbone shows an irregular (extended) conformation. The average pair wise backbone RMSD for the structures is 0.47 ± 0.16 Å.

2.5. Conformational analysis of 2

As compared to **1**, in peptide **2**, the dipeptide isostere (2*S*,5*R*)-ddSaa1 **5**, has been inserted in place of the Tyr^3-Pro^4 residues. The relative configuration of the ddSaa1 at the C2 and C5 carbons was confirmed by the observation of the rOe cross-peak between ddSaa1C2–H↔C5–H, which imply that these protons are on the same side of the five-membered sugar ring. Temperature coefficient, $\Delta\delta/\Delta T = -2.8$ ppb/deg K, for Thr^5NH showed that it participates in intramolecular hydrogen bonding. Appearances of the sequential $NH_i \leftrightarrow NH_{i+1}$ rOe cross-peaks (MetNH↔ddSaa1NH, ddSaa1NH↔ThrNH, ThrNH↔TyrNH, TyrNH↔LeuNH and LeuNH↔LysNH) in the ROESY spectrum show that there is a propensity towards a helical structure. The presence of rOes between ddSaa1NH↔ThrNH, ThrNH↔TyrNH, ThrNH↔ddSaa1C6–$H_{2(\alpha,\alpha')}$ (**A** in Fig. 2) coupled with the intramolecular hydrogen bonding of ThrNH imply that the molecule has a β-turn like structure around Met-ddSaa1-Thr residues,

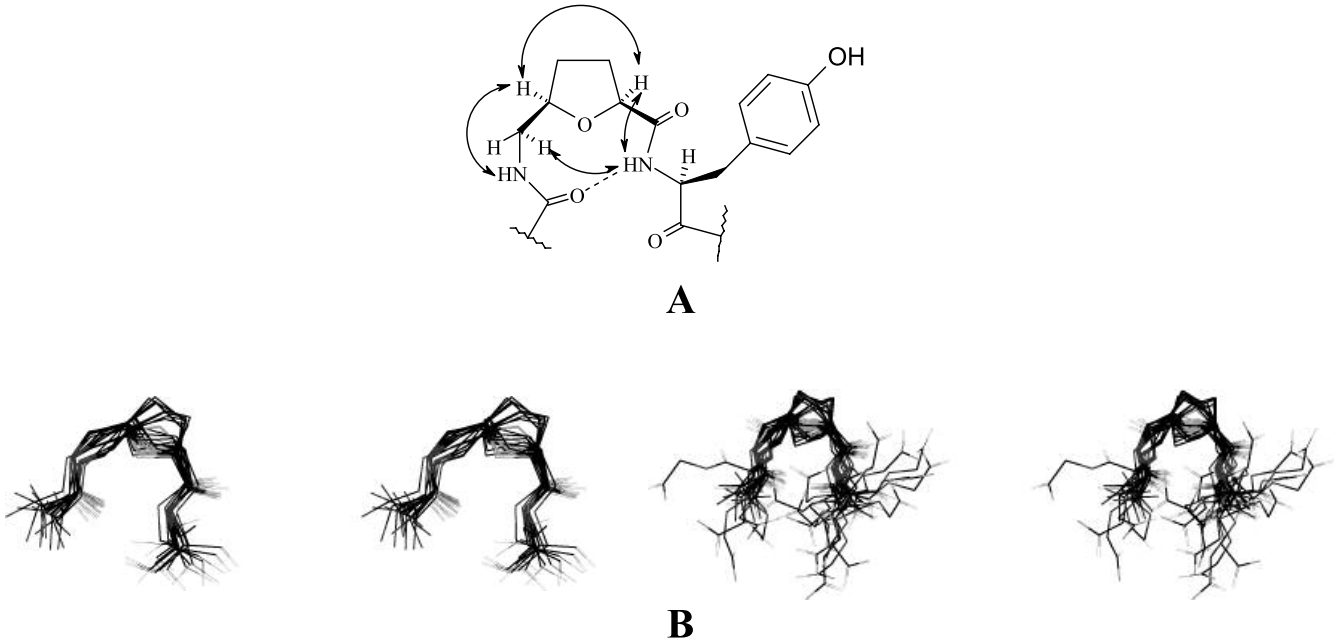

Figure 4. (A) Schematic representation of the proposed β-turn like structures involving Met-ddSaa1-Tyr residues in **4** with some of the prominent long-range rOes seen in its ROESY spectrum. (B) Stereo view of the 25 superimposed energy-minimized structures of **4** sampled during 50 cycles of the 300 ps constrained MD simulations following the simulated annealing protocol: H-bonded region (left), full structure (right).

which is stabilized by the ThrNH→MetCO H-bond. The observed β-turn is similar to that observed earlier by us[20] and others[21] for oligomers containing furanoid sugar amino acids. The MD calculations on **2** show the existence of a 10-membered hydrogen bonded turn structure between ThrNH→MetCO, which mimics a regular β-turn structure, where as the rest of the peptide backbone seem to take an extended conformation. Figure 2 shows an ensemble **B** of 25 conformations superimposed at the turn structure during 50 cycles of 300 ps simulated annealing MD run. The average pair wise backbone RMSD is 0.87±0.39 Å.

2.6. Conformational analysis of 3

In compound **3**, containing the dipeptide isostere (2*R*,5*S*)-ddSaa2 **6**, the observed conformation of the peptide is similar to that of **2**, which had the isomeric sugar amino acid. The small magnitude of $\Delta\delta/\Delta T = -2.2$ ppb/deg K for Thr^5NH confirms its participation in hydrogen bonding probably with $Met^2C{=}O$. Similar to **2**, all the sequential $NH_i \leftrightarrow NH_{i+1}$ rOe cross-peaks (MetNH↔ddSaa2NH, ddSaa2NH↔ThrNH, ThrNH↔TyrNH, TyrNH↔LeuNH and LeuNH↔LysNH) in the ROESY spectrum were observed. It supports the presence of an incipient helix. Participation of the ThrNH in hydrogen bonding, as well as the observation of rOe cross-peaks between ddSaa2NH↔ThrNH, ThrNH↔TyrNH and ThrNH↔ddSaa2C6–$H_{2(\alpha,\alpha')}$ (**A** in Fig. 3) indicate that the molecule has a β-turn like structure involving Met-ddSaa2-Thr residues. The observed β-turn is similar to that found in **2** and in various oligomers containing furanoid sugar amino acids.[20,21]

Molecular mechanics calculations clearly show the existence of a 10-membered H-bond between ThrNH→MetCO. Figure 3 shows an ensemble **B** of 25 conformations superimposed at the turn structure during 50 cycles of 300 ps simulated annealing MD run. The average pair wise backbone RMSD is 0.41±0.23 Å.

2.7. Conformational analysis of 4

In compound **4**, TyrNH shows small magnitude of $\Delta\delta/\Delta T$ (−2.8 ppb/deg K), indicating its participation in intramolecular hydrogen bonding. The presence of ROESY cross-peaks between TyrNH↔ddSaa1C2–H and TyrNH↔ddSaa1C6–H coupled with the participation of TyrNH in hydrogen bonding suggests that a 10-membered β-turn like structure, similar to the one observed earlier by us and others,[20,21] is stabilized by a hydrogen bond between TyrNH→MetCO. Appearance of a rOe cross-peak between the ddSaa1C2–H↔ddSaa1C5–H indicates that the two protons are on the same side of the five-membered ring. The $^3J_{NH-C\alpha H}$ of 8.8 and 8.0 Hz for Tyr and Leu residues, respectively, indicate that there is propensity of structures with backbone ϕ angles in the β-region of the Ramachandran plot. The cross-peak intensities in the ROESY spectrum of **4** (**A** in Fig. 4) were used for obtaining the restraints in the MD calculations. The molecular dynamics calculations showed the existence of a β-turn like structure as shown in **B** in Figure 4 having a 10-membered intramolecular hydrogen bond. The average pair wise backbone RMSD is 1.20±0.33 Å.

3. Conclusion

3,4-Dideoxy furanoid sugar amino acids **5** and **6**, having a *syn* relationship between C2–H and C5–H, belong to the growing family of very useful molecular building blocks of sugar amino acids and display remarkable propensities to induce well defined turn structures in small peptides. The β-turn structure found in VIP anatagonist **1** was successfully reproduced by introducing the nonproteinogenic dipeptide isostere **5** and **6** in the molecule, resulting in the development of novel peptidomimetic analogs **2**–**4**. Although both ddSaa1 **5** and ddSaa2 **6** gave rise to the similar 10-membered hydrogen bonded structures, the turn induced by the latter with (2*R*,5*S*) stereochemistry was more pronounced than those derived from the former having the (2*S*,5*R*) stereochemistry. These studies may help in designing mimics of the bioactive peptide conformations of small peptides, where proline residue participates in well-defined β-turn structures.

4. Experimental

4.1. General experimental procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under a nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat or 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)—heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Melting points are uncorrected. IR spectra were recorded as neat liquids or KBr pellets on FT-IR Nicolet-740. Mass spectra were obtained on Micromass Autospec and Quattro spectrometers under liquid secondary ion mass spectrometric (LSIMS) and electron spray ionisation (ESI) techniques, respectively. Optical rotations were measured with a Jasco Dip-370 and Horiba Sepa-300 digital polarimeters.

4.2. NMR spectroscopy

NMR spectra of the peptides **1**–**4** were recorded on Varian Unity-Inova 500 MHz spectrometer at 30 °C with 2–10 mM solutions in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded on Bruker Avance-300 spectrometer at 75 MHz with complete proton decoupling. The chemical shift assignments were carried out with the help of two-dimensional total correlation spectroscopy (TOCSY)[16] and rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments,[17] the later also provided the information on the proximity of protons. All the experiments were carried out in the phase sensitive mode.[22] The spectra were acquired

with 2×256 or 2×192 free induction decays (FID) containing 8–16 transients with relaxation delays of 1.0–1.5 s. The ROESY experiments were performed with mixing time of 0.3 s. For ROESY experiments a spin-locking field of about 2 kHz was used. The TOCSY experiments were performed with the spin locking fields of about 10 kHz and a mixing time of 0.08 s. The two-dimensional data were processed with Gaussian apodization in both the dimensions. To obtain the temperature coefficients of NH-chemical shifts, the spectra were recorded between 30 and 70 °C (at 30, 40, 50, 60, and 70 °C) in DMSO-d_6. The temperature coefficients $\Delta\delta/\Delta T$ were determined from the slopes of the linear regression lines obtained from the chemical shift versus temperature plots (see Supplementary Information).[18]

4.3. Molecular dynamics

Molecular mechanics/dynamics calculations were carried out using the Sybyl 6.8 program on a Silicon Graphics O2 workstation. The Tripos force field, with default parameters, was used throughout the simulations.

A dielectric constant of 47 Debye was used in all minimizations as well as in MD runs. Minimizations were done first with steepest decent, followed by conjugate gradient methods for a maximum of 2000 iterations each or RMS deviation of 0.005 kcal/mol, whichever was earlier. The energy-minimized structures were then subjected to MD studies. A number of inter atomic distance constraints (more than three bond away) were used in the MD studies that were derived from the rOe cross-peaks (see Supplementary Information) on the basis of two-spin approximation by taking the TyrCβH protons distance (1.8 Å) as an internal standard. For all the amide bonds, the torsional angle 180° was used as a constraint. No H-bonding constraint was used. For distance constraints, a force constant of 15 kcal/Å was applied in the form of flat bottom potential well and a force constant of 5 kcal/Å was employed for the dihedral angle constraints.[19] The energy-minimized structures were subjected to constrained MD simulations for duration of 300 ps using 50 cycles, each of 6 ps period, of the Simulated Annealing protocol. The atomic velocities were applied following Boltzmann distribution about the center of mass, to obtain a starting temperature of 700 deg K.[23]

After simulating for 1 ps at high temperature, the system temperature was reduced exponentially over a 5 ps period to reach a final temperature of 300 °K. Structures were sampled after every two cycle, leading to an ensemble of total 25 structures. The sampled structures were energy-minimized using the above-mentioned protocol and the superimposed structures obtained by backbone alignment are shown in Figures 1–4. To determine the backbone and the average pair-wise heavy atom RMSD, the structures were analyzed using the MOLMOL program.[24]

4.3.1. (5*S*)-Tetrahydro-5-[(triphenylmethoxy)methyl]-2-furanol (8). To a solution of **7** (46 g, 396 mmol) in dry CH_2Cl_2 (800 mL), Et_3N (82.8 mL, 594 mmol), trityl chloride (121.4 g, 435.6 mmol) and DMAP (9.68 g, 79.2 mmol) were sequentially added at 0 °C and stirred at room temperature for 12 h. The reaction was then quenched with saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography afforded (5*S*)-5-[(triphenylmethoxy)methyl]dihydrofuran-2(3*H*)-one (110.6 g) in 77% yield.

The product (110 g, 307 mmol) was dissolved in CH_2Cl_2 (600 mL) and the solution was cooled to −78 °C. DIBAL-H (1.2 M in toluene, 281 mL, 337.7 mmol) was added dropwise and stirred for 15 min at this temperature. The reaction mixture was then quenched with MeOH followed by saturated sodium potassium tartrate solution and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography afforded the title compound **8** (95 g, 86%) as a mixture of diastereomers at the anomeric position. Data for **8**: R_f=0.35 (silica gel, 40% EtOAc in petroleum ether); IR (neat) ν_{max} 3448, 3350, 1479, 1433, 1219, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, mixture of isomers 1:1) δ 7.48–7.22 (m, 15H, Ar*H*), 5.62 and 5.48 (two m, 1H, anomeric *H*), 4.45 (dq, J=7.5, 5.3 Hz) and 4.27 (m) (total 1H), 3.30 and 3.22 (two dd, J=9.8, 3.7, 9.8, 4.5 Hz) and 3.10 (d, J=5.3 Hz) (total 2H), 2.83 (d, J=6.0 Hz) and 2.50 (m) (total 1H), 2.08–1.82 (m, 3H), 1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of isomers) δ 144.00, 143.78, 128.74, 128.68, 127.77, 127.71, 127.02, 126.89, 98.91, 98.68, 79.31, 77.57, 66.84, 66.10, 34.03, 32.74, 25.93, 25.25; MS (ESI): m/z (%): 383 (100) $[M+Na]^+$, 399 (55) $[M+K]^+$; HRMS (ESI): Calcd for $C_{24}H_{24}O_3Na$ $[M+Na]^+$ 383.1623, found 383.1606.

4.3.2. (5*S*)-Tetrahydro-5-(hydroxymethyl)-2-furancarbonitrile (9). The lactol **8** (95 g, 264 mmol) was dissolved in CH_2Cl_2 (500 mL) and the solution was cooled to 0 °C. Et_3N (55.2 mL, 396 mmol) was added drop wise. After 10 min, Ac_2O (30 mL, 317 mmol) was added followed by DMAP (6.48 g, 53 mmol) and stirred for 30 min. The reaction was then quenched with saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography afforded the expected acetate intermediate (102 g) in 96% yield as a mixture of diastereomers at the anomeric position.

The acetate (100 g, 249 mmol) was dissolved in acetonitrile (500 mL) and to it trimethylsilyl cyanide (50 mL, 375 mmol) was added at room temperature. This was followed by the addition of $BF_3.Et_2O$ (25.2 mL, 199 mmol) and the reaction mixture was stirred for 4 h. The solution was then concentrated and purified by column chromatography to afford the title compound **9** (20.2 g) as a mixture of diastereomers in 64% yield. Data for **9**: R_f=0.39 (silica gel, 70% EtOAc in petroleum ether); IR (neat) ν_{max} 3410 (br), 2896, 1752, 1704, 1432, 1204, 1166, 1120, 1040, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, mixture of isomers 1:1) δ 4.79 and 4.71 (two dd, J=4.2, 7.8, 3.62, 7.8 Hz, total 1H), 4.33–4.28 and 4.21–4.15 (two m, total 1H), 3.78 (m,

1H), 3.66 and 3.56 (two dd, J=6.03, 12.0, 4.83, 12.0 Hz, 2H), 2.38–2.25 and 2.13–2.00 (two m, 2H), 2.21–2.14 and 1.94–1.86 (two m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of isomers) δ 119.40, 119.00, 82.19, 80.82, 66.72, 66.40, 64.27, 63.90, 31.99, 31.61, 26.52, 26.03; MS (ESI): m/z (%): 150 (12) $[M+Na]^+$; HRMS (ESI): Calcd for $C_6H_9NO_2Na$ $[M+Na]^+$ 150.0531, found 150.0531.

4.3.3. (2*S*,5*R*)-5-[*N*-(9-Fluorenylmethoxycarbonyl)-aminomethyl]tetrahydro-2-furanmethanol (10). To the solution of **9** (20 g, 157.48 mmol) in dry ether (350 mL) at 0 °C, $LiAlH_4$ (14.94 g, 393.7 mmol) was added portion wise. After the addition was over the solution was refluxed for 3 h. It was then cooled to 0 °C and quenched by the sequential addition of water (15 mL), 3 M NaOH (15 mL) and water (45 mL). Stirring was continued till free flowing solids were formed. Then the mixture was filtered through a sintered funnel, and washed thoroughly with EtOAc. The combined organic filtrate and washings were concentrated in vacuo to dryness. The resulting crude amine was dissolved in CH_2Cl_2 (250 mL), FmocOSu (58.4 g, 173.23 mmol) was added at 0 °C and stirred for 1 h at rt. Then the solution was concentrated in vacuo and directly subjected to purification by column chromatography to separate the isomers furnishing the title compound **10** (15.1 g, 57% yield) as colorless oil. Data for **10**: R_f=0.33 (silica gel, 70% EtOAc in petroleum ether); $[\alpha]^{26}_D$=−4.47 (c 1.9, $CHCl_3$); IR (neat) ν_{max} 3426 (br), 2924, 2850, 2337, 1704, 1538, 1436, 1220, 1085, 772, 656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (d, J=7.84 Hz, 2H, Ar*H*), 7.60 (d, J=7.24 Hz, 2H, Ar*H*), 7.39 (t, J=7.24 Hz, 2H, Ar*H*), 7.31 (t, J=7.24, Hz, 2H, Ar*H*), 5.22 (bs, 1H, N*H*), 4.45–4.39 (m, 2H, OCH_2 of Fmoc), 4.22 (t, J=6.64 Hz, 1H, OCH_2CH of Fmoc), 4.08–4.01 (m, 2H), 3.75 (dd, J=11.5, 1.8 Hz, 1H), 3.48 (dd, J=11.5, 4.83 Hz, 1H), 3.36–3.22 (m, 2H), 2.45 (bs, 1H, O*H*), 2.02–1.95 (m, 1H), 1.93–1.86 (m, 1H), 1.84–1.78 (m, 1H), 1.68–1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.07, 144.53, 143.90, 141.25, 128.48, 127.97, 127.61, 127.00, 125.03, 119.89, 80.30, 78.88, 66.58, 64.37, 47.16, 45.29, 28.44, 26.47, 22.65; MS (ESI): m/z (%): 376 (95) $[M+Na]^+$; HRMS (ESI): Calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ 376.1525, found 376.1491.

4.3.4. (2*S*,5*R*)-5-[*N*-(9-Fluorenylmethoxycarbonyl)-aminomethyl]tetrahydro-2-furancarboxylic acid (11). To a solution of **10** (14 g, 39.62 mmol) in acetone (100 mL) at 0 °C, was added freshly prepared Jones reagent carefully and drop by drop till the orange color persisted. The reaction mixture was stirred for 0.5 h at 0 °C, then warmed to rt, and stirred for an additional 3 h. Then the reaction mixture was quenched with isopropanol (80 mL) and diluted with EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by colomun chromatography afforded the title compound **11** (9.72 g) in 67% yield. Data for **11**: R_f=0.4 (10% MeOH in $CHCl_3$); $[\alpha]^{26}_D$=−6.4 (c 0.74, MeOH); IR (neat) ν_{max} 3418 (br), 2898, 2841, 2363, 1628, 1436, 1372, 1256, 1134, 1070, 762, 651 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.87 (d, J=7.81 Hz, 2H, Ar*H*), 7.68 (d, J=7.21 Hz, 2H, Ar*H*), 7.64 (br s, 1H, N*H*), 7.40 (t, J=7.2 Hz, 2H, Ar*H*), 7.32 (t, J=7.2 Hz, 2H, Ar*H*), 4.34–4.19 (m, 4H), 4.01 (t, J=6.01 Hz, 1H), 3.22–3.10 (m, 2H), 2.16 (td, J=8.4, 20.4 Hz, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.58 (td, J=8.4, 19.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 174.97, 156.53, 144.00, 140.86, 127.79, 127.23, 125.37, 120.25, 79.22, 76.51, 65.66, 46.84, 44.34, 29.98, 27.80; MS (ESI): m/z (%): 390 (100) $[M+Na]^+$, 406 (10) $[M+K]^+$; HRMS (ESI): Calcd for $C_{21}H_{21}NO_5Na$ $[M+Na]^+$ 390.1317, found 390.1310.

4.3.5. *N*-(9-Fluorenylmethoxycarbonyl)-6-amino-2,5-anhydro-1-*O*-(*tert*-butyldiphenyl)silyl-6-deoxy-D-glucitol (13). To a solution of compound **12** (9.56 g, 21.55 mmol) in MeOH was added 10% $Pd(OH)_2$ on C (1.08 g). It was hydrogenated for 8 h under atmospheric pressure using a H_2 balloon. The reaction mixture was then filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. The residue was azeotroped with dry toluene and used directly in the next step without further purification.

The above-prepared intermediate triol was dissolved in dry DMF (65 mL) and treated at 0 °C under a nitrogen atmosphere with Et_3N (4.5 mL, 32.33 mmol). After 10 min, TBDPSCl (6.08 mL, 23.71 mmol) followed by DMAP (264 mg, 2.16 mmol) were added. After stirring for 3 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl and brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 30–35% EtOAc in petroleum ether eluant) afforded the title compound **13** (9.84 g, 91% in two steps). Data for **13**: R_f=0.6 (silica gel 60% EtOAc in petroleum ether); $[\alpha]^{26}_D$=−22.83 (c 2.37, $CHCl_3$); IR (neat) ν_{max} 3418 (br), 3214, 2970, 2932, 2360, 1695, 1513, 1428, 1391, 1366, 1252, 1221, 1167, 1111, 824, 770, 704, 613, 505 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J=7.7 Hz, 2H, Ar*H*), 7.65 (d, J=7.7 Hz, 2H, Ar*H*), 7.44–7.37 (m, 6H, Ar*H*), 4.89 (br s, 1H, N*H*), 4.24 (m, 1H), 4.01 (dd, J=3.6, 8.3 Hz, 2H), 3.99 (dd, J=4.7, 8.9 Hz, 1H), 3.94 (dd, J=4.7, 8.3 Hz, 1H), 3.73 (q, J=4.7 Hz, 1H), 3.63 (br s, 1H, O*H*), 3.41 (m, 1H), 3.37 (m, 1H), 2.58 (br s, 1H, O*H*), 1.43 (s, 9H, Boc), 1.06 (s, 9H, Si^{t}Bu); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.58, 135.58, 135.49, 132.51, 132.30, 129.94, 127.80, 83.01, 79.63, 79.43, 79.08, 63.35, 42.41, 28.33, 26.73, 18.98; MS (LSIMS): m/z (%): 402 (95) $[M+H-C_5H_8O_2]^+$; HRMS (LSIMS): Calcd for $C_{22}H_{32}NO_4Si$ $[M+H-C_5H_8O_2]^+$ 402.2101, found 402.2108.

4.3.6. (2*R*,5*S*)-5-[*N*-(*tert*-Butoxycarbonyl)-aminomethyl]tetrahydro-2-furanmethanol (14). To a solution of compound **13** (9.84 g, 19.61 mmol), Ph_3P (20.58 g, 78.45 mmol) and imidazole (5.34 g, 78.45 mmol) at reflux in toluene (200 mL), I_2 (14.93 g, 58.84 mmol) was added in small portions with stirring. The white finely dispersed complex initially formed was transformed into a clear yellow solution that darkened as iodine was liberated at the bottom of the reaction vessel, a dark tarry complex was formed from which the product was gradually dissolved. After 3 h, the reaction mixture was cooled and iodine (4.98 g, 19.6 mmol) was added, followed by aqueous sodium hydroxide (6.28 g, 156.88 mmol, 120 mL water). The mixture was stirred until virtually all of the tarry red deposits were dissolved. The mixture was transferred into a separating funnel. The aqueous layer was separated and the organic layer was washed successively with water, saturated aqueous sodium thiosulphate, saturated aqueous $NaHCO_3$

and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 15–18% EtOAc in petroleum ether eluant) afforded the olefin intermediate (7.79 g, 85%).

To a solution of the olefin intermediate (6.52 g, 13.94 mmol) in MeOH (100 mL) was added 10% $Pd(OH)_2$ on C (700 mg). It was hydrogenated for 1 h under atmospheric pressure using a H_2 balloon. The reaction mixture was then filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. The residue was azeotroped with dry toluene to afford the 3,4-dideoxy intermediate, which was used directly in the next step without further purification.

A solution of the above-prepared dideoxy compound in THF (42 mL) was treated at 0 °C with TBAF (1 M in THF, 15.33 mL, 15.33 mmol). The reaction mixture was stirred at room temperature for 3H, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 65–70% EtOAc in petroleum ether eluant) afforded the title compound **14** (2.09 g, 65% in two steps). Data for **14**: R_f=0.4 (silica gel, 70% EtOAc in petroleum ether); $[\alpha]_D^{26}$=(55.59 (*c* 1.6, $CHCl_3$); IR (neat) ν_{max} 3322 (br), 3014, 2976, 1692, 1516, 1393, 1366, 1251, 1218, 1169, 1080, 978, 941, 771, 697, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.89 (t, *J*=5.6 Hz, 1H, N*H*), 4.05 and 4.01 (two m, 2H), 3.74 (dd, *J*=2.7, 11.7 Hz, 1H), 3.49 (dd, *J*=4.9, 11.7 Hz, 1H), 3.24 (ddd, *J*=3.7, 5.5, 13.5 Hz, 1H), 3.18 (dd, *J*=6.7, 13.5 Hz, 1H), 2.66 (br s, 1H), 1.99 (m, 1H), 1.88 (m, 1H), 1.69 (m, 1H), 1.64 (m, 1H), 1.45 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.58, 80.35, 79.36, 78.99, 64.33, 44.94, 28.47, 28.31, 26.41; MS (LSIMS): *m*/*z* (%): 132 (95) $[M+H-C_5H_8O_2]^+$, 232 (35) $[M+H]^+$; HRMS (ESI): Calcd for $C_{11}H_{21}NO_4Na$ $[M+Na]^+$ 254.1368, found 254.1369.

4.3.7. (2*R*,5*S*)-5-[*N*-(9-Fluorenylmethoxycarbonyl)-aminomethyl]tetrahydro-2-furancarboxylic acid (15). A mixture of $NaIO_4$ (5.58 g, 26.07 mmol) and $RuCl_3 \cdot 3H_2O$ (22.5 mg, 0.087 mmol) in $CH_3CN/CCl_4/H_2O$ (1:1:1.5, 53 mL) was stirred at rt for 45 min and then added to a solution of the alcohol (2.01 g, 8.69 mmol) in CH_3CN (25 mL) at 0 °C. After stirring for 5 min, an additional amount of $NaIO_4$ (1.86 g, 8.69 mmol) was added to the reaction mixture. After 2 h, it was diluted with EtOAc, washed with saturated aqueous NH_4Cl, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography afforded the acid (1.71 g, 80%).

To a solution of the acid in dry CH_2Cl_2 (16 mL) at 0 °C, trifluoroacetic acid (5 mL) was added and stirred for 2 h at rt. The excess trifluoroacetic acid was then evaporated off on rotary evaporator and dried thoroughly under high vacuum. The resulting TFA salt was dissolved in dioxane and cooled to 0 °C. Then 10% aqueous Na_2CO_3 (17.4 mL) followed by FmocOSu (2.35 g, 6.97 mmol) were added and stirred for 12 h at rt. The dioxane was then evaporated in vacuo and the residual aqueous layer was washed with EtOAc. The aqueous layer was acidified with 1 M HCl pH≈2, extracted with EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 12–15% MeOH in chloroform eluant) afforded the title compound **15** (2.17 g, 85% yield). Data for **15**: R_f=0.4 (10% MeOH in $CHCl_3$); $[\alpha]_D^{26}$=+8.13 (*c* 1.01, MeOH); IR (neat) ν_{max} 3304 (br), 3019, 1698, 1622, 1449, 1331, 1216, 1099, 977, 943, 753, 696 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.25 (br s, 1H, N*H*), 7.87 (d, *J*=7.2 Hz, 2H, Ar*H*), 7.71 (d, *J*=7.2 Hz, 2H, Ar*H*), 7.40 (t, *J*=7.2 Hz, 2H, Ar*H*), 7.31 (t, *J*=7.2 Hz, 2H, Ar*H*), 4.34–4.19 (m, 4H), 4.05 (t, *J*=6.01 Hz, 1H), 3.25–3.15 (m, 2H), 2.08 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H), 1.61 (td, *J*=8.4, 19.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 176.24, 156.64, 143.93, 140.69, 127.62, 127.12, 125.38, 120.10, 78.55, 78.08, 65.57, 46.70, 43.97, 30.28, 27.28; MS (LSIMS): *m*/*z* (%): 390 (65) $[M+Na]^+$; HRMS (LSIMS): Calcd for $C_{21}H_{21}NO_5Na$ $[M+Na]^+$ 390.1317, found 390.1304.

4.3.8. Data for 1. ^1H NMR (DMSO-d_6, 500 MHz): see Table 1; quant. HPLC profile: RP-18 column, 50×300 mm, mobile phase: A=water (0.1% TFA), B=acetonitrile (0.1% TFA), gradient: 20–40% B in 20 min, detection at 220 nm, retention time=7.71 min; MS (LSIMS): *m*/*z* (%): 1029 (4.6) $[M+H]^+$.

4.3.9. Data for 2. ^1H NMR (DMSO-d_6, 500 MHz): see Table 2; quant. HPLC profile: RP-18 column, 50×300 mm, mobile phase: A=water (0.1% TFA), B=acetonitrile (0.1% TFA), gradient: 20–40% B in 20 min, detection at 220 nm, retention time=6.96 min; MS (LSIMS): *m*/*z* (%): 895 (70) $[M+H]^+$, 917 (20) $[M+Na]^+$; HRMS (LSIMS): Calcd for $C_{42}H_{71}N_8O_{11}S$ $[M+H]^+$ 895.4963, found 895.4970.

4.3.10. Data for 3. ^1H NMR (DMSO-d_6, 500 MHz): see Table 3; quant. HPLC profile: RP-18 column, 50×300 mm, mobile phase: A=water (0.1% TFA), B=acetonitrile (0.1% TFA), gradient: 20–40% B in 20 min, detection at 220 nm, retention time=6.60 min; MS (LSIMS): *m*/*z* (%): 895 (100) $[M+H]^+$, 917 (11) $[M+Na]^+$; HRMS (LSIMS): Calcd for $C_{42}H_{71}N_8O_{11}S$ $[M+H]^+$ 895.4963, found 895.4982.

4.3.11. Data for 4. ^1H NMR (DMSO-d_6, 500 MHz): see Table 4; quant. HPLC profile: RP-18 column, 50×300 mm, mobile phase: A=water (0.1% TFA), B=acetonitrile (0.1% TFA), gradient: 20–40% B in 20 min, detection at 220 nm, retention time=7.33 min; MS (LSIMS): *m*/*z* (%): 553 (98) $[M+H]^+$, 575 (9) $[M+Na]^+$; HRMS (LSIMS): Calcd for $C_{26}H_{41}N_4O_7S$ $[M+H]^+$ 553.2695, found 553.2686.

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Supplementary data

Supplementary data associated with this article can be found at doi:10.1016/j.tet.2004.07.032.

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14. DCC = 1,3-dicyclohexylcarbodiimide; DIPC = 1,3-diisopropylcarbodiimide; HOBt = 1-hydroxybenzotriazole; HBTU = O-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; DIPEA = *N*,*N*-diisopropylethylamine; PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; NMP = *N*-methyl-2-pyrrolidinone
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Fluorous glycol derivatives: novel carbonyl protective groups

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Abstract—Fluorous glycol derivatives **5** were prepared and evaluated as reagents for the protection of carbonyl groups for use in fluorous synthesis. The acetals formed from fluorous diol **5b** (Rf=*n*-C_8F_{17}) with carbonyl compounds can be separated and purified by simple fluorous-organic extraction.

1. Introduction

Fluorous tagging methods for small molecule synthesis are rapidly developing into a strategic alternative to traditionally solid phase synthesis.[1] Fluorous tags are often fashioned after standard protecting groups for organic functionalities. Ideally, fluorous protective groups must not only fulfill the general requirement of standard protecting groups but also make it possible to separate the protected substrate from reaction mixtures by standard fluorous techniques through liquid–liquid extraction with fluorous solvents or solid–liquid extraction with fluorous reverse phase silica gel. In addition, the fluorous protective groups should be recyclable after detachment from the products. Recently, a variety of fluorous alcohol and amine protective groups have been developed.[2]

Acetals are widely used in synthesis for the temporary protection of aldehydes and ketones,[3] and as acetonides, for the masking of diol functionality.[4] Most recently, Read and co-workers have reported the synthesis of fluorous acetal derivatives from fluorous 1,3-alkanediols and aldehydes (ketones),[5] which could be purified by combinations of chromatography, distillation and recrystallization. In this context we present the synthesis of new fluorous glycol derivatives **5** and their application as protective groups for aldehydes and ketones. We found that both installation and cleavage of fluorous diols **5** could be achieved under mildly acidic conditions, and the fluorous protected acetals **7** could be separated by simple fluorous-organic extraction.

Keywords: Fluorous synthesis; Carbonyl protective groups.
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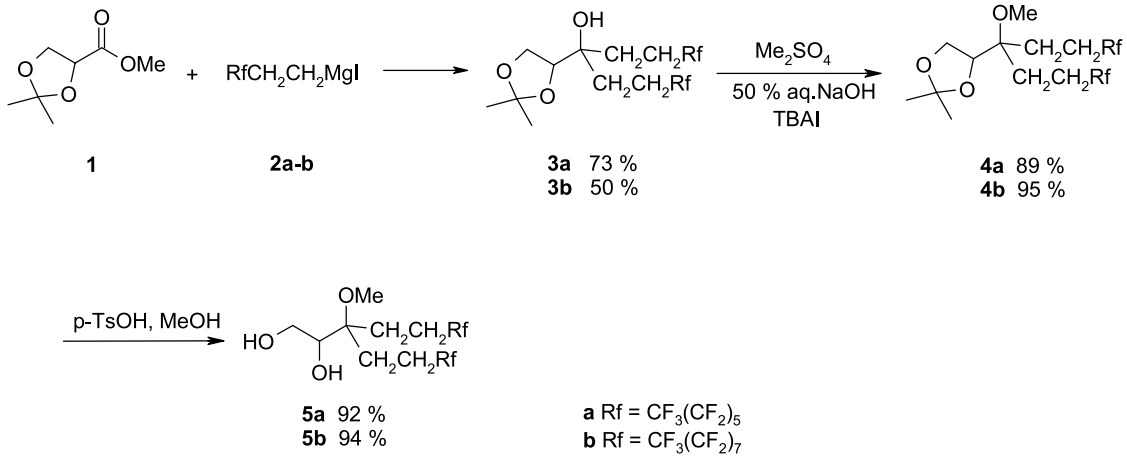
2. Results and discussion

The new fluorous glycol derivatives (terminal 1,2-diols) **5** were readily prepared as shown in Scheme 1. Treatment of Grignard reagent **2** with 2,3-*O*-isopropylidene-glyceric acid methyl ester **1** afforded alcohols **3** in moderate yields. Methylation[6] of **3** with Me_2SO_4 in 1:1 solution of 50% aqueous NaOH and THF at 0 °C for 5 h gave methyl ether **4** in excellent yields, and then deprotection of **4** under acidic condition afforded fluorous terminal 1,2-diols **5** in high yields.

With diols **5** in hand, we firstly chose trifluoro-*p*-tolualdehyde **6a** as a substrate to test the formation of acetals. Reaction of **6a** with **5a** and **5b** in CF_3Ph in the presence of 4 Å MS and catalytic amount of *p*-toluenesulfonic acid gave the corresponding acetals **7aa** and **7ba** in 95 and 96% yields respectively (Table 2, entries 1 and 2) after fluorous liquid–liquid extraction (FC-77/CH_3CN).[7]

These results showed that the diols **5** could be used as carbonyl protective groups. Then we turned to examine which diol (**5a** or **5b**) had better immobilization capability in a fluorous phase. The approximate partition coefficient of **7aa** and **7ba** were determined by a simple method[2i] as shown in Table 1. As expected, acetal **7ba** showed higher affinities for the fluorous phase than **7aa**. The length of the perfluorinated chain showed a distinct effect on the partition coefficients. In most cases efficient extraction of **7ba** could be achieved whether the organic solvents were highly polar (acetonitrile, methanol) or less polar (toluene, chloroform). However, **7aa** showed an effective extraction only when highly polar organic solvents (acetonitrile, methanol) were used.

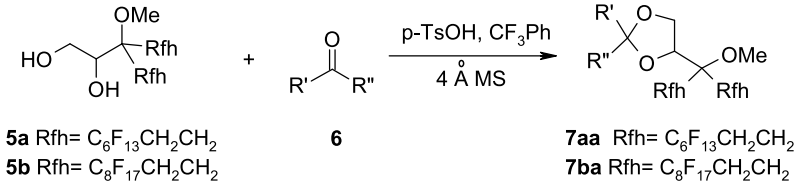


Scheme 1. Synthesis of fluorous terminal 1,2-diols.

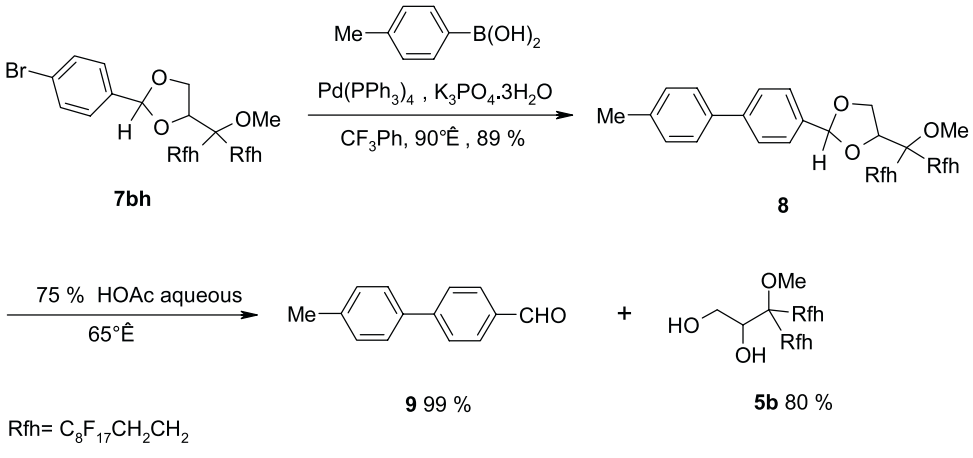
Table 1. Partition coefficients of fluorous acetals **7aa** and **7ba** in organic solvent and FC-77 ($K_D = C_{FC\text{-}77}/C_{organic\ phase}$)

Organic solvents	K_D		Organic solvents	K_D	
	7aa	**7ba**		**7aa**	**7ba**
Acetonitrile	9.17	16.25	Chloroform	0.93	9.0
CH_2Cl_2	1.94	10.17	Ethyl acetate	0.39	1.61
Methanol	9.20	18.0	Acetone	0.38	1.72
Toluene	2.40	9.0	Hexane	2.77	4.0
THF	0.37	1.95			

Once we verified that **5b** was a more effective protective group to achieve fluorous liquid–liquid extraction than **5a**, the scope of this acetal formation was examined. A range of aldehydes and ketones were readily coupled with **5b** under standard reaction condition. The aliphatic and aromatic fluorous acetals **7ba**–**7bl** can be isolated and purified in high yields by fluorous liquid–liquid extraction (FC-77/CH_2Cl_2 or FC-77/CH_3CN) (Scheme 2 and Table 2). In the case of aldehydes and asymmetric ketones both diastereomeric products were obtained during the reaction. In view of that the chiral center would disappear after deprotection, and it was not necessary to separate the two diastereomeric products.

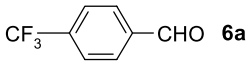
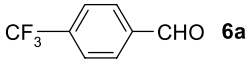
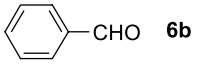
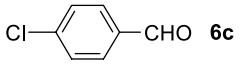
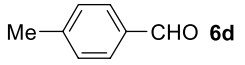
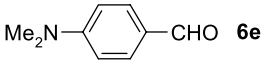
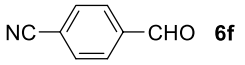
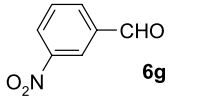
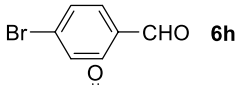
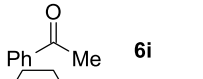
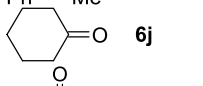
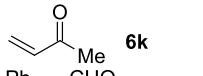
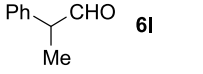


Scheme 2. Preparation of fluorous acetals.



Scheme 3.

Table 2. Preparation of fluorous diols protected acetals[a]

Entry	Reactants	Acetals	Yield (%)[b]
1	 **6a**	**7aa**	99
2	 **6a**	**7ba**	92
3	 **6b**	**7bb**	98
4	 **6c**	**7bc**	93
5	 **6d**	**7bd**	98
6	 **6e**	**7be**	96
7	 **6f**	**7bf**	91
8	 **6g**	**7bg**	91
9	 **6h**	**7bh**	91
10	 **6i**	**7bi**	90
11	 **6j**	**7bj**	99
12	 **6k**	**7bk**	97
13	 **6l**	**7bl**	95

[a] All reaction were carried out using *p*-TsOH (10 mol%) and 4 Å MS in CF_3Ph, reflux for 18 h.
[b] Isolated yield by fluorous liquid–liquid extraction (FC-77/CH_2Cl_2 or FC-77/CH_3CN).

To demonstrate the utility of **5b** as a protective group for fluorous organic synthesis, we performed a Suzuki cross-coupling reaction on the fluorous protected aromatic halide **7bh** (Scheme 3). Suzuki coupling of **7bh** with *p*-methylphenylboronic acid in CF_3Ph in the presence of K_3PO_4 and catalytic amount of $Pd(PPh_3)_4$ afforded coupling product **8** in 89% yield, which was then deprotected in 75% aqueous HOAc to afford aldehyde **9** and diol **5b** in high yields.

In summary, we have synthesized two new fluorous terminal 1,2-diols and demonstrated their application of them as the carbonyl protective groups. The acetals formed with **5b** and carbonyl compounds can be separated and purified by simple fluorous-organic extraction. By using highly polar organic solvents as partition partner or fluorous solid–liquid extraction with fluorous reverse silica gel,[8] the less fluorinated diol **5a** is also useful for fluorous organic synthesis.

3. Experimental

3.1. General

All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out using standard Schlenk techniques under a dry nitrogen atmosphere. NMR spectra were determined at 300 MHz for ^1H NMR and 282 MHz for ^{19}F NMR. Chemical shifts (δ) were in ppm relative to TMS for ^1H NMR and to $CFCl_3$ for ^{19}F NMR (high field was negative).

3.1.1. Preparation of 9-(2,2-dimethyl-[1,3]dioxolan-4-yl)-1,1,1,2,2,3,3,4,4,5,5,6,6,12,12,13,13,14,14,15,15,16,16,17,17,17-hexacosafluoro-heptadecan-9-ol (3a). 2,3-*O*-Isopropylidene glyceric acid methyl ester **1** (3.52 g, 22 mmol) was added dropwise to the Grignard reagent **2a** (2.4 equiv) prepared from perfluorinated alkyl iodide and magnesium turnings in ether. After refluxing for 12 h, the reaction mixture was cooled to 0 °C, quenched with saturated ammonium chloride solution and the aqueous phase was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified on a silica gel column (hexane/EtOAc = 10:1) to afford a colorless liquid (13.2 g, 73%). ^1H NMR ($CDCl_3$) δ 4.06–4.02 (m, 2H), 3.93–3.86 (m, 1H), 2.32–2.05 (m, 5H), 1.88–1.59 (m, 4H), 1.46 (s, 3H), 1.39 (s, 3H); ^{19}F NMR δ −81.16 (t, J = 10.4 Hz, 6F), −114.81 to −115.08 (m, 4F), −122.26 (s, 4F), −123.21 (s, 4F), −123.66 (s, 4F), −126.50 (s, 4F); IR (thin film) 3484, 2994, 1459, 1239, 1207, 1145, 1066 cm^{-1}. Anal. Calcd for $C_{22}H_{18}F_{26}O_3$: C, 32.05; H, 2.20. Found: C, 32.07; H, 2.43.

3.1.2. 11-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,14,14,15,15,16,16,17,17,18,18,19,19,20,20,21,21,21-tetratriacontafluoro-henicosan-11-ol (3b). ^1H NMR ($CDCl_3$) δ 4.05–4.02 (m, 2H), 3.88 (t, J = 9.9 Hz, 1H), 2.30–2.04 (m, 5H), 1.88–1.58 (m, 4H), 1.46 (s, 3H), 1.39 (s, 3H); ^{19}F NMR δ −81.16 (t, J = 10.7 Hz, 6F), −114.78 to −115.07 (m, 4F), −122.09 (s, 4F), −122.28 (s, 8F), −123.09 (s, 4F), −123.70 (s, 4F), −126.52 (s, 4F); IR (neat) 3483, 1459, 1375, 1243, 1207, 1151, 1064 cm^{-1}. Anal. Calcd for $C_{26}H_{18}F_{34}O_3$: C, 30.49; H, 1.77. Found: C, 30.54; H, 1.92.

3.1.3. Preparation of 2,2-dimethyl-4-[4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-1-methoxy-1-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)-nonyl]-[1,3]dioxolane (4a). The reaction system consisting of a solution of the alcohol **3** (1.24 g, 1.5 mmol) and TBAI (0.1 equiv) in THF (8 mL) and 50% aqueous NaOH (2.7 equiv) was equilibrated by vigorous stirring for 15–30 min at 10 °C, which caused slight evolution of heat, Me_2SO_4 (378 mg, 3.0 mmol) was then added dropwise with cooling. The reaction mixture was then stirred for 10 h at room temperature. After addition of saturated NaOH solution (10 mL) for further 30 min at room temperature, the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified on a silica gel column (hexane/EtOAc = 20:1) to afford a waxy solid (1.11 g, 89%). ^1H NMR ($CDCl_3$) δ 4.16 (t, J = 7.2 Hz, 1H), 4.01 (t, J = 7.1 Hz, 1H), 3.89 (t, J = 8.1 Hz, 1H), 3.28 (s, 1H), 2.29–2.15 (m, 4H), 1.96–1.81 (m, 4H), 1.45 (s, 3H), 1.35 (s, 3H); ^{19}F NMR δ −81.12 (t, J = 9.8 Hz, 6F), −115.06 to −115.37 (m, 4F), −122.21 (s, 4F), −123.17 (s, 4F), −123.69 (s, 4F), −126.45 (s, 4F); IR (neat) 2996, 1463, 1375, 1240, 1203, 1146 cm^{-1}. Anal. Calcd for $C_{23}H_{20}F_{26}O_3$: C, 32.95; H, 2.40. Found: C, 33.03; H, 2.46.

3.1.4. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2,2-dimethyl-[1,3]-dioxolane (4b). ^{1}H NMR ($CDCl_3$) δ 4.16 (t, J=6.9 Hz, 1H), 4.02 (dd, J_1=7.2 Hz, J_2=8.4 Hz, 1H), 3.88 (dd, J_1=7.2 Hz, J_2=8.4 Hz, 1H), 3.27 (s, 1H), 2.32–2.11 (m, 4H), 2.00–1.78 (m, 4H), 1.45 (s, 3H), 1.35 (s, 3H); ^{19}F NMR δ −81.15 (t, J=10.1 Hz, 6F), −115.10 to −115.41 (m, 4F), −122.05 (s, 4F), −122.25 (s, 8F), −123.08 (s, 4F), −123.71 (s, 4F), −126.48 (s, 4F); IR (neat) 3000, 1463, 1375, 1203, 1149, 657 cm^{-1}. Anal. Calcd for $C_{27}H_{20}F_{34}O_3$: C, 31.23; H, 1.94. Found: C, 30.18; H, 1.96.

3.1.5. Preparation of 6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-3-methoxy-3-(3,3,4,4,5,5,6, 6,7,7,8,8,8-tridecafluoro-octyl)-undecane-1,2-diol (5a). A mixture of **4a** and catalytic amount of *p*-TsOH (0.1 equiv) in methanol and CF_3Ph (v/v, 2:1) was stirred at room temperature for 36 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel, eluting with petroleum ether/EtOAc (5:1 to 3:1) to afford the desired terminal 1,2-diols **5a** as a white solid. ^{1}H NMR ($CDCl_3$) δ 3.81–3.76 (m, 2H), 3.69–3.64 (m, 1H), 3.25 (s, 3H), 2.43–2.07 (m, 6H), 1.96–1.78 (m, 4H); ^{19}F NMR δ −71.29 (t, J=10.2 Hz, 6F), −115.49 to −115.79 (m, 4F), −122.41 (s, 4F), −123.40 (s, 4F), −123.82 (s, 4F), −126.61 to −126.70 (m, 4F); IR (neat) 3376, 2970, 1475, 1369, 1241, 1191, 1145, 1066 cm^{-1}. Anal. Calcd for $C_{20}H_{16}F_{26}O_3$: C, 30.09; H, 2.02. Found: C, 30.20; H, 2.04.

3.1.6. 6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-3-methoxy-tridecane-1,2-diol (5b). ^{1}H NMR (Methanol-d_4) δ 3.78 (dd, J_1=3.0 Hz, J_2=10.8 Hz, 1H), 3.70 (dd, J_1=2.7 Hz, J_2=7.5 Hz, 1H), 3.55 (dd, J_1=7.8 Hz, J_2=10.5 Hz, 1H), 3.36 (br, 2H), 3.27 (s, 3H), 2.39–2.13 (m, 4H), 1.84–1.97 (m, 4H); ^{19}F NMR (Methanol-d_4) δ −77.77 (t, J=9.9 Hz, 6F), −111.77 to −111.98 (m, 4F), −118.62 (s, 4F), −118.77 (s, 8F), −119.61 (s, 4F), −120.25 (s, 4F), −123.04 (s, 4F); IR (neat) 3391, 2960, 1373, 1204, 1148, 1066 cm^{-1}. Anal. Calcd for $C_{24}H_{16}F_{34}O_3$: C, 28.87; H, 1.62. Found: C, 28.88; H, 1.74.

3.2. General procedure for the formation of acetals 7

To a solution of trifluoro-*p*-tolualdehyde **6a** (52 mg, 0.3 mmol, 1.5 equiv) and **5b** (200 mg 0.2 mmol, 1.0 equiv) in 4 mL CF_3Ph was added *p*-toluenesulfonic acid (5 mg, 0.02 mmol) and 4 Å MS (200 mg). The solution was stirred at 85 °C for 18 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and extracted twice with FC-77. The combined FC-77 layers were concentrated to afford the acetal **7ba** as a waxy solid in 92% yield.

3.2.1. 4-[4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-1-methoxy-1-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)-nonyl]-2-(4-trifluoromethyl-phenyl)-[1,3]dioxolane (7aa). ^{1}H NMR ($CDCl_3$) δ 7.67–7.54 (m, 4H), 6.10, 5.80 (2s, 1H), 4.32–4.02 (m, 3H), 3.32, 3.27 (2s, 3H), 2.25–2.12 (m, 4H), 2.07–1.81 (m, 4H); ^{19}F NMR δ −62.91 (t, J=62.0 Hz, 3F), −80.80 (s, 6F), −114.92 to −115.29 (m, 4F), −122.00 (s, 4F), −122.97 (s, 4F), −123.48 (s, 4F), −126.23 (s, 4F); IR (neat) 2964, 1610, 1262, 1203, 1147, 1018 cm^{-1}. Anal. Calcd for $C_{28}H_{19}F_{29}O_3$: C, 35.24; H, 2.01. Found: C, 35.22; H, 2.23.

3.2.2. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-(4-trifluoromethyl-phenyl)-[1,3]dioxolane (7ba). ^{1}H NMR ($CDCl_3$) δ 7.66–7.54 (m, 4H), 6.10, 5.80 (2s, 1H), 4.32–4.02 (m, 3H), 3.32, 3.27 (2s, 3H), 2.25–2.06 (m, 4H), 2.00–1.85 (m, 4H); ^{19}F NMR δ −63.54 (t, J=70.5 Hz, 3F), −80.84 (t, J=10.7 Hz, 6F), −114.93 to −115.28 (m, 4F), −121.86 (s, 4F), −122.07 (s, 8F), −122.85 (s, 4F), −123.52 (s, 4F), −126.27 (t, J=14.1 Hz, 4F); IR (neat) 2962, 1710, 1331, 1245, 1207, 1147, 1020 cm^{-1}. Anal. Calcd for $C_{32}H_{19}F_{37}O_3$: C, 33.29; H, 1.66. Found: C, 33.24; H, 1.70.

3.2.3. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-phenyl-[1,3]dioxolane (7bb). ^{1}H NMR ($CDCl_3$) δ 7.49–7.38 (m, 5H), 6.07, 5.76 (2s, 1H), 4.98–4.30 (m, 3H), 3.33, 3.30 (2s, 3H), 2.26–2.09 (m, 4H), 2.07–1.80 (m, 4H); ^{19}F NMR δ −81.10 (t, J=8.7 Hz, 6F), −115.02 to −115.36 (m, 4F), −122.03 (s, 4F), −122.23 (s, 8F), −123.04 (s, 4F), −123.65 (s, 4F), −126.44 (s, 4F); IR (neat) 2990, 1246, 1204, 1149, 1070 cm^{-1}. Anal. Calcd for $C_{31}H_{20}F_{34}O_3$: C, 34.27; H, 1.86. Found: C, 34.17; H, 1.85.

3.2.4. 2-(4-Chloro-phenyl)-4-[4,4,5,5,6,6,7,7,8,8,9,9,10, 10,11,11,11-heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9, 9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-[1,3]dioxolane (7bc). ^{1}H NMR ($CDCl_3$) δ 7.43–7.35 (m, 4H), 6.03, 5.73 (2s, 1H), 4.29–4.03 (m, 3H), 3.33, 3.29 (2s, 3H), 2.27–2.12 (m, 4H), 2.03–1.87 (m, 4H); ^{19}F NMR δ −81.14 (s, 6F), −114.99 to −115.26 (m, 4F), −122.06 (s, 4F), −122.24 (s, 8F), −123.06 (s, 4F), −123.67 (s, 4F), −126.46 (t, J=14.1 Hz, 4F); IR (neat) 2992, 1606, 1244, 1206, 1149, 1017 cm^{-1}. Anal. Calcd for $C_{31}H_{19}F_{34}O_3Cl$: C, 33.22; H, 1.71. Found: C, 32.94; H, 1.69.

3.2.5. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-*p*-tolyl-[1,3]dioxolane (7bd). ^{1}H NMR ($CDCl_3$) δ 7.34 (t, J=6.9 Hz, 2H), 7.20 (d, J=8.1 Hz, 2H), 6.04, 5.72 (2s, 1H), 4.28–3.96 (m, 3H), 3.33, 3.30 (2s, 3H), 2.37 (s, 3H), 2.30–2.07 (m, 4H), 2.03–1.85 (m, 4H); ^{19}F NMR δ −81.13 (t, J=8.5 Hz, 6F), −115.03 to −115.27 (m, 4F), −122.00 (s, 4F), −122.22 (s, 8F), −123.05 (s, 4F), −123.63 (s, 4F), −126.44 (s, 4F); IR (neat) 2990, 1610, 1206, 1148, 1085, 981 cm^{-1}. Anal. Calcd for $C_{32}H_{22}F_{34}O_3$: C, 34.93; H, 2.02. Found: C, 35.12; H, 2.19.

3.2.6. (4-{4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-[1,3]dioxolan-2-yl}-phenyl)-dimethyl-amine (7be). ^{1}H NMR ($CDCl_3$) δ 7.30 (t, J=8.9 Hz, 2H), 6.71 (d, J=8.7 Hz, 2H), 5.96, 5.66 (2s, 1H), 4.24–3.92 (m, 3H), 3.32, 3.29 (2s, 3H), 2.96 (s, 6H), 2.35–2.06 (m, 4H), 2.03–1.77 (m, 4H); ^{19}F NMR δ −81.28 (t, J=9.8 Hz, 6F), −115.19 to −115.52 (m, 4F), −122.24 (s, 4F), −122.44 (s, 8F), −123.26 (s, 4F),

−123.82 (s, 4F), −126.66 (s, 4F); IR (neat) 2958, 2896, 1619, 1531, 1354, 1242, 1209, 1088, 977 cm^{-1}. Anal. Calcd for $C_{33}H_{25}F_{34}NO_3$: C, 35.09; H, 2.23; N, 1.24. Found: C, 34.91; H, 2.33; N, 1.26.

3.2.7. 4-{4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-[1,3]dioxolan-2-yl}-benzonitrile (7bf). ^1H NMR ($CDCl_3$) δ 7.69 (d, J=8.4 Hz, 2H), 7.57 (d, J=8.4 Hz, 2H), 5.78 (s, 1H), 4.30 (dd, J_1=6.0 Hz, J_2=6.9 Hz, 1H), 4.19–4.07 (m, 2H), 3.27 (s, 3H), 2.24–2.09 (m, 4H), 1.99–1.85 (m, 4H); ^{19}F NMR δ −81.21 (t, J=9.0 Hz, 6F), −115.24 to −115.60 (m, 4F), −122.23 (s, 4F), −122.40 (s, 8F), −123.21 (s, 4F), −123.85 (s, 4F), −126.59 (s, 4F); IR (neat) 2833, 2231, 1463, 1204, 1148, 997 cm^{-1}. Anal. Calcd for $C_{32}H_{19}F_{34}NO_3$: C, 34.58; H, 1.72; N, 1.26. Found: C, 34.65; H, 1.82; N, 1.25.

3.2.8. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-(3-nitro-phenyl)-[1,3]dioxolane (7bg). ^1H NMR ($CDCl_3$) δ 8.34 (d, J=8.4 Hz, 1H), 8.28–8.24 (m, 1H), 7.79 (dd, J_1=8.1 Hz, J_2=9.6 Hz, 1H), 7.58 (t, J=8.1 Hz, 1H), 6.11, 5.84 (2s, 1H), 4.35–4.05 (m, 3H), 3.33, 3.29 (2s, 3H), 2.24–2.10 (m, 4H), 2.05–1.81 (m, 4H); ^{19}F NMR δ −81.32 (t, J=9.9 Hz, 6F), −115.37 to −115.69 (m, 4F), −122.27 (s, 4F), −122.47 (s, 8F), −123.29 (s, 4F), −123.88 (s, 4F), −126.68 (s, 4F); IR (neat) 2962, 1610, 1541, 1467, 1352, 1205, 1114, 976 cm^{-1}. Anal. Calcd for $C_{31}H_{19}F_{34}NO_5$: C, 32.91; H, 1.69; N, 1.24. Found: C, 32.83; H, 1.81; N, 1.19.

3.2.9. 2-(4-Bromo-phenyl)-4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-[1,3]dioxolane (7bh). ^1H NMR ($CDCl_3$) δ 7.52 (d, J=8.7 Hz, 2H), 7.31 (dd, J_1=6.9 Hz, J_2=8.4 Hz, 2H), 6.01, 5.70 (2s, 1H), 4.28–3.96 (m, 3H), 3.31, 3.25 (2s, 3H), 2.27–2.11 (m, 4H), 2.05–1.78 (m, 4H); ^{19}F NMR δ −81.30 (t, J=9.9 Hz, 6F), −115.29 to −115.63 (m, 4F), −122.27 (s, 4F), −122.46 (s, 8F), −123.28 (s, 4F), −123.87 (s, 4F), −126.68 (s, 4F); IR (neat) 2962, 1599, 1206, 1147, 1014 cm^{-1}. Anal. Calcd for $C_{31}H_{19}F_{34}O_3Br$: C, 31.95; H, 1.64. Found: C, 31.89; H, 1.68.

3.2.10. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-methyl-2-phenyl-[1,3]dioxolane (7bi). ^1H NMR ($CDCl_3$) δ 7.48–7.30 (m, 5H), 4.31 (t, J=7.5 Hz) and 3.98 (dd, J_1=6.0 Hz, J_2=7.8 Hz, 1H), 4.16 (dd, J_1=6.6 Hz, J_2=8.1 Hz) and 3.75 (t, J=7.5 Hz, 1H), 3.93–3.84 (m,1H), 3.28, 3.23 (2s, 3H), 2.34–2.16 (m, 4H), 2.08–1.75 (m, 4H), 1.66 (s, 2.58H), 1.63 (s, 1.42H); ^{19}F NMR δ −81.14 (t, J=10.7 Hz, 6F), −115.03 to −115.46 (m, 4F), −122.04 (s, 4F), −122.26 (s, 8F), −123.08 (s, 4F), −123.70 (s, 4F), −126.50 (s, 4F); IR (neat) 2995, 1463, 1250, 1205, 1147, 1089 cm^{-1}. Anal. Calcd for $C_{32}H_{22}F_{34}O_3$: C, 34.93; H, 2.01. Found: C, 34.81; H, 2.00.

3.2.11. 2-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-1,4-dioxa-spiro[4.5]decane (7bj). ^1H NMR ($CDCl_3$) δ 4.16 (t, J=6.9 Hz, 1H), 4.01 (t, J=7.5 Hz, 1H), 3.86 (t, J=7.8 Hz, 1H), 3.28 (s, 3H), 2.31–2.17 (m, 4H), 2.03–1.75 (m, 4H), 1.64–1.58 (m, 8H), 1.43–1.41 (m, 2H); ^{19}F NMR δ −81.14 (t, J=8.5 Hz, 6F), −115.11 to −115.40 (m, 4F), −122.06 (s, 4F), −122.26 (s, 8F), −123.08 (s, 4F), −123.76 (s, 4F), −126.48 (s, 4F); IR (neat) 2949, 2868, 1465, 1203, 1148, 1089 cm^{-1}. Anal. Calcd for $C_{30}H_{24}F_{34}O_3$: C, 33.41; H, 2.24. Found: C, 33.19; H, 2.28.

3.2.12. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-methyl-2-vinyl-[1,3]dioxolane (7bk). ^1H NMR ($CDCl_3$) δ 5.90 (dd, J_1=10.5 Hz, J_2=17.4 Hz, 0.22H), 5.76 (dd, J_1=10.5 Hz, J_2=17.4 Hz, 0.78H), 5.41 (d, J=17.1 Hz, 0.22H), 5.35 (d, J=17.4 Hz, 0.78H), 5.18 (d, J=10.5 Hz, 0.22H), 5.15 (d, J=10.5 Hz, 0.78H), 4.18 (t, J=7.5 Hz, 0.25H), 4.06 (t, J=6.6 Hz, 1H), 3.95–3.83 (m, 1.75H), 3.26 (s, 3H), 2.24–2.10 (m, 4H), 1.98–1.78 (m, 4H), 1.48, 1.42 (2 s, 3H); ^{19}F NMR δ −81.36 (t, J=10.1 Hz, 6F), −115.35 to −115.68 (m, 4F), −122.30 (s, 4F), −122.49 (s, 8F), −123.32 (s, 4F), −123.94 (s, 4F), −126.73 (s, 4F); IR (neat) 2998, 1464, 1205, 1148, 1089, 991 cm^{-1}. Anal. Calcd for $C_{28}H_{20}F_{34}O_3$: C, 32.02; H, 1.92. Found: C, 32.09; H, 1.94.

3.2.13. 4-[4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10, 10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-(1-phenyl-ethyl)-[1,3]dioxolane (7bl). ^1H NMR ($CDCl_3$) δ 7.33–7.21 (m, 5H), 5.12–5.13, 4.89–4.85 (2m, 1H), 4.10–3.98 (m, 1H), 3.96–3.73 (m, 2H), 3.24–3.18 (m, 3H), 3.05–2.96 (m, 1H), 2.23–2.06 (m, 4H), 1.89–1.56 (m, 4H), 1.37–1.26 (m, 3H); ^{19}F NMR δ −81.28 (t, J=9.6 Hz, 6F), −115.40 (s, 4F), −122.24 (s, 4F), −122.44 (s, 8F), −123.26 (s, 4F), −123.87 (s, 4F), −126.66 (s, 4F); IR (neat) 2996, 1480, 1204, 1088 cm^{-1}. Anal. Calcd for $C_{33}H_{24}F_{34}O_3$: C, 35.56; H, 2.17. Found: C, 35.56; H, 2.14.

3.2.14. Preparation of 4-[4,4,5,5,6,6,7,7,8,8,9,9,10, 10,11,11,11-Heptadecafluoro-1-(3,3,4,4,5,5,6,6,7,7,8,8, 9,9,10,10,10-heptadecafluoro-decyl)-1-methoxy-undecyl]-2-(4′-methyl-biphenyl-4-yl)-[1,3]dioxolane (8). $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and $K_3PO_4\cdot 3H_2O$ (266 mg, 1.0 mmol) were added to a solution of **7bh** (582 mg, 0.5 mmol) and *p*-methyl-phenylboronic acid (82 mg, 0.6 mmol) in CF_3Ph (4 mL). The reaction mixture was heated to reflux for 18 h and then cooled to room temperature, filtered and concentrated. CH_3CN (5 mL) was added to the residue and extracted four times with FC-77 (4 mL). The combined FC-77 layers were evaporated to dryness to afford the product **8** in 89% yield as a waxy solid. ^1H NMR ($CDCl_3$) δ 7.55–7.41 (m, 5H), 7.20–7.17 (m, 3H), 6.04, 5.72 (2s, 1H), 4.24–3.94 (m, 3H), 3.27, 3.24 (2s, 3H), 2.33 (s, 3H), 2.27–2.10 (m, 4H), 2.06–1.77 (m, 4H); ^{19}F NMR δ −81.22 (t, J=9.9 Hz, 6F), −115.203 to −115.53 (m, 4F), −122.21 (s, 4F), −122.40 (s, 8F), −123.21 (s, 4F), −123.78 (s, 4F), −126.61 (s, 4F); IR (neat) 2964, 1617, 1262, 1203, 1147, 1018, 809 cm^{-1}. Anal. Calcd for $C_{38}H_{26}F_{34}O_3$: C, 38.79; H, 2.23. Found: C, 38.78; H, 2.58.

3.2.15. Preparation of 4′-methyl-biphenyl-4-carbaldehyde (9). Compound **8** was added to 75% aqueous HOAc and refluxed for 24 h. After cooled to room temperature the reaction mixture was concentrated and purified by flash chromatography (silica gel, hexane/EtOAc 20:1; 10:1; 3:1) to afford **9** and **7b** in 99 and 80% yields, respectively. The data of **9** were identical with those in references.[9]

3.3. Partition coefficients

The partition coefficients were determined by dissolving the fluorous compound (100 mg) in the biphasic system (4 mL, 1:1 v/v). The resulting mixture was vigorously stirred for 10 min in a 10 mL vial at 10 °C. After two clear layers were obtained, a 1 mL aliquot was removed from each layer with a syringe. This was evaporated to dryness, and the weight of each residue was determined. The partition coefficients were calculated as the ratio of the amount of residue from each layer.

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Convergent synthesis of *cis*-α,β-epoxy-carboxylic acids from 1-halo-2-trimethylsilyloxy-3-aza-4-phenyl-1,3-butadiene

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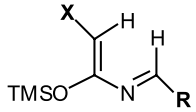
Abstract—Reaction of a wide variety of aldehydes with the easily prepared 2-azadienes, in the presence of BF_3 etherate, furnishes the corresponding hetero Diels–Alder adducts which have been converted, mainly, to cis epoxides via *N*-Boc protection followed by one-pot two-step ring opening and nucleophilic displacement of the halogen atom, resulting in final formation of an oxirane ring.

1. Introduction

The application of hetero Diels–Alder (HDA) strategy to heterocycles and natural products synthesis has been well known for long time.[1–5] An important part of this strategy takes into account the use of imino Diels Alder reaction which provides a rapid stream to the construction of functionalized six-membered nitrogen-containing heterocyclic structures,[6] with control of regio-, diastereo- and enantioselectivity.[7] The HDA adducts thus obtained, in turn, have been used as such for the synthesis of more complex cyclic structures, or have been easily converted into new heterocycles or into open-chain compounds. Recent years have witnessed the usefulness of azadienes of type **A** (Fig. 1) in the preparation of important intermediates in organic synthesis.[8–11] After the pioneering work by the Ghosez group,[12,13] azadienes of type **A** have been proved to be useful starting compounds in hetero Diels–Alder reaction, with carbonyl compounds as dienophiles, by the Barluenga group,[14,15] ourselves[16–21] and the same Ghosez group.[22,23] We now describe the results of our study on the synthesis of α,β-epoxy-carboxylic acids by the above reported HDA strategy. Carboxylic acids bearing in α,β-position an oxirane ring functionality are, in fact, useful intermediates in the synthesis of biologically active compounds. They have recently found application in the synthesis of Taxol and Taxotere derivatives and the carboxy-acid functionality presents several advantages over the corresponding carboxy-ester in the coupling reaction of Bacchatin 10 and side chains,[24] adding extra value to their synthesis.



A

X= NR^1R^2, ArO, Halogen, ArS, H
R= Alkyl, Aryl.

Figure 1.

2. Results and discussions

2.1. Synthesis of perhydrooxazinones

The starting azadienes **3** were prepared from the corresponding acid halides **2** and *N*-trimethylsilyl imines[25] **1** following the general procedure described in literature.[13,19,26] Scheme 1 and Table 1 summarize the results of the cycloaddition reactions of **3** with aldehydes **4** to give the six-membered ring adducts **5** and **6**. The relative configurations of C_2–H, C_5–H and C_6–H in the products **5**, **6** were established on the basis of ^{1}H NMR chemical shifts, coupling constants (C_5–H/C_6–H) and NOE values. All the products reported in Table 1 present a (H_5–H_6)-*cis* relationship as it is shown by the values of coupling

Keywords: Hetero Diels–Alder; Azadiene; Epoxy-acids.
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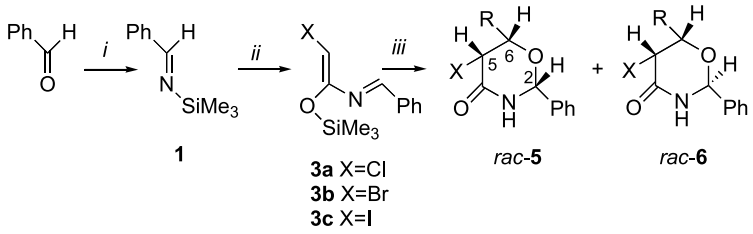


Scheme 1. Reagents and conditions. (i) LiHMDS, TMSCl; (ii) XCH_2COX^1 (**2a**: X=X^1=Cl; **2b**: X=X^1=Br; **2c**: X=I, X^1=Cl), TEA; (iii) BF_3, RCHO (**4a**: R=Me; **4d**: R=propyl; **4e**: R=heptyl; **4g**: R=*i*-propyl; **4h**: R=*t*-butyl; **4i**:R=Ph: **4j**: R=*p*-NO_2Ph), −78 to rt.

Table 1. Cycloaddition of 3-azadienes **3** with RCHO **4**

Ex	X	R^1	Products	Ratio[a]	Yield (%)[b,c]
1	Cl	Me	**5a/6a**	>98	40
2	Br	Me	**5b/6b**	>98	45
3	Br	Me	**5b/6b**	>98	45[d]
4	I	Me	**5c/6c**	92/8	48
5	Br	Propyl	**5d/6d**	94/6	56
6	Br	*n*-Heptyl	**5e/6e**	>98	50
7	Br	*n*-Heptyl	—	—	0[e]
8	Br	*i*-Propyl	**5g/6g**	9/91	52
9	Br	*i*-Propyl	**5g/6g**	9/91	45[f]
10	Br	*t*-Butyl	**5h/6h**	30/70	40
11	Br	Ph	**5i/6i**	61/39	40
12	Br	*p*-NO_2-Ph	**5j/6j**	80/20	41

[a] Diastereomeric ratio was evaluated by ^{1}H NMR analysis of the crude reaction mixture. No changes were observed after silica gel column purification.
[b] Yields were calculated on the basis of mmol of benzaldehyde used for the preparation of azadienes **3** and refer to chromatographically isolated products.
[c] All products were identified by their IR, ^{1}H and ^{13}C NMR, Mass spectroscopic data and gave satisfactory EA.
[d] The experiment was performed reversing the order of reactant addition (first the BF_3 to the diene and after 15 min at −78 °C the aldehyde).
[e] The reaction was performed in absence of BF_3 in acetonitrile at reflux for 18 h. No traces of the perhydrooxazinones **5e** and **6e** were detected by ^{1}H NMR analysis on the crude reaction mixture.
[f] The reaction was performed at −78 °C and quenched after 1.5 h at the same temperature.

constant, being between 1.4–2.6 Hz, and by a positive NOE effect between them. The basket configuration of the protons (H_2–H_5–H_6), in the series of compounds **5**, has been demonstrated by a positive NOE effect between the H_2 and H_6. The absence of this effect for the compounds **6** allow the configurations to be assigned.

Final confirmation of the conformation arises from the X-ray analysis of compound **6g** which shows a *trans* relationship between the substituents in positions 2 and 5 (Fig. 2). It is interesting to note that in the solid state the molecules form dimers via one pair of N–H…O hydrogen bonds.[27]

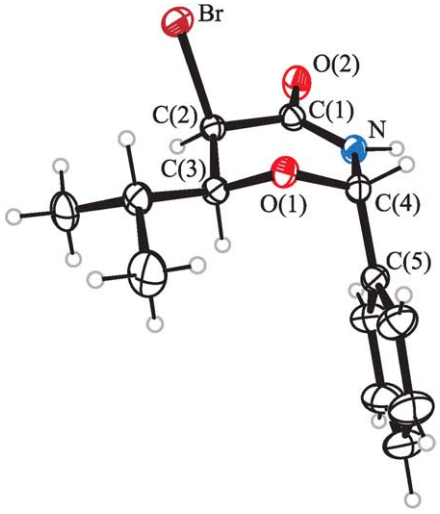


Figure 2. ORTEP drawing of compound **6g**.

Examination of Table 1 leads to the following remarks: (1) Irrespective of the nature of R in the dienophilic aldehyde, the cycloaddition takes place with a complete (H_5–H_6)-*cis* diastereoselectivity. (2) The HDA cycloaddition works well with linear aliphatic aldehydes with an almost complete (H_2–H_5–H_6) relative diastereoselectivity (entries 1–6, Table 1). Accordingly, the final cycloaddition adducts resulted from an *endo* approach of the reactants.[19] (3) No change in yields and diastereoselectivity is observed reversing the addition of the reactants (entry 3, Table 1). (4) The reaction takes place at low/ambient temperature under BF_3 mediated cycloaddition, whereas no cycloadduct products were obtained under Ghosez conditions[22,23] (acetonitrile/reflux/no LA added, see entry 7, Table 1).

(5) Using aliphatic aldehydes with branched side chains (entries 8–10) or aromatic aldehydes (entries 11–13) gives mixtures of cycloadducts **5** and **6** in variable ratio. The products of series **6** show, once again, a complete *cis*-diastereoselectivity between C_5–H and C_6–H but a *trans*-relationship between C_2–H and C_5–H. Whereas the formation of cycloadduct **5** is well explained by an HDA mechanism via an *endo* attack, the *trans* relationship between the C_2–H and C_5–H, observed for compounds of series **6**, is unlikely to come from a concerted [4+2] mechanism. In the reactions of carbonyl compounds with silyloxy-dienes, such as Danishefsky's diene, catalyzed by Lewis acids, besides the classical HDA mechanism a

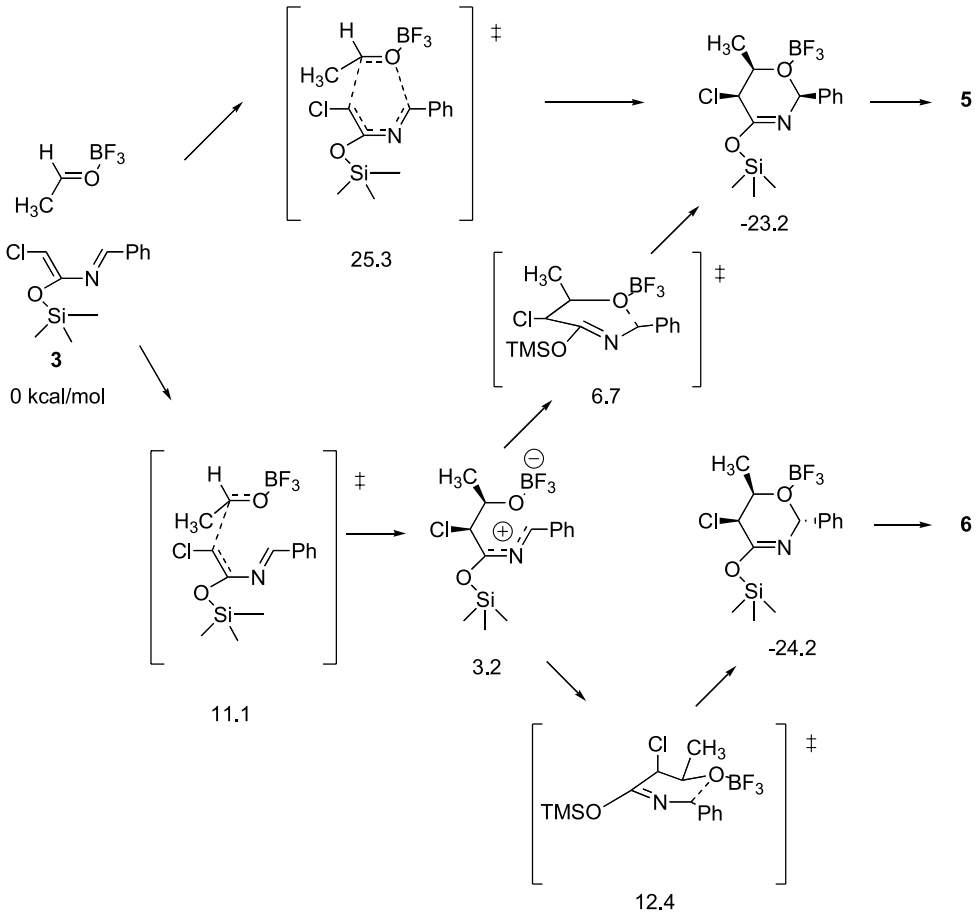
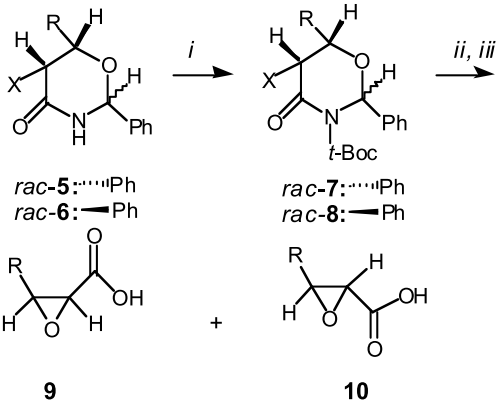


Figure 3. AM1 Semiempirical calculations of the possible pathways from **3** to **5** and **6**.

competitive open-chain pathway has to be considered. Several authors,[28,29] including Danishefsky himself,[30] reported that the reaction of 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-pentadiene with benzaldehyde, in the presence of BF_3, proceeds via a stepwise mechanism.[31] In analogy, two possible mechanisms may be taken into account for our case: a concerted hetero Diels–Alder mechanism and a Mukaiyama type addition of silylenol ether to aldehyde and final ring closure to perhydroxazin-4-one (Fig. 3). The strict control of the diastereoselectivity on the C_5–C_6 stereocenters formation demonstrates that, as for the concerted HDA mechanism and as for the Mukaiyama type mechanism, the first attack takes place with an *endo* pathway. This fact is easily explained, taking into account that the Lewis acid (BF_3) must assume an *anti* conformation with the R group of the dienophile. A careful inspection of the molecular structure of the complex shows that severe steric hindrance occurs between the Lewis acid and the diene skeleton when an *exo* attack of the aldehyde occurs. This fact favors an *endo* attack. Preliminary AM1 semiempirical calculations[32] are in agreement with this mechanism (see Fig. 3). (6) The formation of the two diastereoisomers in the Mukaiyama type mechanism may be explained by a different attack of the nucleophilic alcoholate on the imine double bond. As a matter of fact this attack may take place via a *supra* or *antara* pathway. In the first case we will observe the formation of the diastereoisomer of series **5** whereas the *antara* attack will give rise to the formation of the diastereoisomer of series **6**. However, the formation of isomer **6**, due to the epimerization of the stereocenter 2 in the product **5**, cannot be, in principle, ruled out. The lack of variability in the ratio of **5** and **6**, quenching the reaction mixture, after 90 min, at low temperature (−78 °C), (entry 9 Table 1) makes this hypothesis unlikely.



Scheme 2. Reagents and Conditions. (i) TEA, di-*tert*-butyl-dicarbonate, DMAP, DCM, 20 °C. (ii) Method A: LiOH, THF, rt, Method B: LiOH, H_2O_2, EtOH/H_2O, rt (iii) HCl (1 N), 0 °C.

Table 2. *t*-Boc Derivatives **7** and **8**

Ex	Subs	X	R^1	Products[a]	Yield (%)[b]
1	**5b**	Br	Me	**7b**	80
2	**5d**	Br	Propyl	**7d**	90
3	**5e**	Br	*n*-Heptyl	**7e**	98
4	**5g**	Br	*i*-Propyl	**7g**	98
5	**6g**	Br	*i*-Propyl	**8g**	97
6	**5h**	Br	*t*-Butyl	**7h**	80
7	**6h**	Br	*t*-Butyl	**8h**	85
8	**5i**	Br	Ph	**7i**	67
9	**6i**	Br	Ph	**8i**	69
10	**5j**	Br	*p*-NO_2-Ph	**7j**	35
11	**6j**	Br	*p*-NO_2-Ph	**8j**	40

[a] For the sake of clarity the products are labelled with the same alphabetical letter of the parent compounds.
[b] Yields refer to chromatographically isolated products, which were characterized by standard analytical methodologies.

2.2. Synthesis of α,β-epoxy-carboxylic acids

Perhydrooxazinones **5** and **6** were processed to the final oxirane derivatives **9** and **10** by the sequential reactions depicted in Scheme 2. In order to facilitate the lactamic ring opening the corresponding *t*-Boc-derivatives **7** and **8** were prepared (Table 2).

It is well known that a facile opening of lactamic ring takes place when a *t*-Boc group is directly linked to the lactamic nitrogen.[33] Final ring closure to the expected oxirane was studied in detail (Scheme 2). Among the methods tested, in order to achieve one-pot two-step perhydrooxazinone ring opening and nucleophilic substitution of halogen atom with the formation of the final oxirane ring, the best conditions have been proved to be those reported in the Scheme 2 as Method A and Method B. The two methods differ each other in the presence of hydrogen peroxide (Method B). The basis for the use of method B is to allow the use oxygen nucleophiles that have positive deviation from the Bronsted-type nucleophilicity plot. These molecules are said to exhibit an α-effect, a term describing a nucleophile alpha to an atom having a lone pair of electrons.[34,35] The most extensive class of α-nucleophiles are peroxy anions, which include hydrogen peroxide salts. Our objective was to take advantage of this increased nucleophilicity for a faster ring opening of the perhydrooxazinones, in the hope of lowering the rate of isomerization and side product formation. Unfortunately (see entry 1 and 2, Table 3) a better yield corresponds with a decreasing diastereomeric ratio. In fact, partial isomerization at the C-5 stereocenter, presumibly due to the basic condition used, is observed with both methods. This side reaction takes place at the perhydrooxazinone stage because of the high lability of the C_5–H proton under the basic conditions used. A direct isomerization of the epoxy acid lithium salts is unreasonable. Indeed, such isomerizations are known to require drastic conditions on the corresponding epoxy esters.[36] Most important are the results reported in entries 5, 6 and 7 (Table 3). Using as starting perhydrooxazinones the compounds of series **7** and **8**, the expected oxiranes were obtained in almost the same diastereomeric ratio compared to that obtained starting from the single pure isomer. For this reason a mixture of the diastereomeric perhydrooxazinones has been used as starting material for the final step of our strategic plane.

3. Conclusion

The above results must be considered a further advance in adding variants to the use of azadienes and the HDA strategy in the synthesis of valuable intermediates. The synthetic protocol, for the synthesis of *cis* α,β-epoxy oxiranes, here described, may be considered a convergent synthesis of *cis*-epoxydes in good to high stereochemical fashion, due to the strict control of the stereoselectivity during the formation of the C_5–C_6 stereocenters. The lack of high stereocontrol in the formation of the C_2 stereocenter is not crucial for our strategy, since this stereocenter is destroyed during the final step of the oxirane formation.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian VXR-200 or on Varian

Table 3. Selected epoxides **9** and **10** from *t*-Boc *rac*-**7** and *rac*-**8**

Ex	Compound	X	R^1	Yield (%)	Method	Products	(Ratio)	Hrs	References
1	**7b**	Br	Me	55	**A**	**9b/10b**	(90/10)	8	37
2	**7b**	Br	Me	90	**B**	**9b/10b**	(70/30)	3	
3	**7d**	Br	Propyl	60	**A**	**9d/10d**	(75/25)	3	38–40
4	**7e**	Br	*n*-Heptyl	80	**A**	**9e/10e**	(80/20)	3	41
5	**7g**	Br	*i*-Propyl	60	**A**	**9g/10g**	(95/5)	3	38,42
6	**8g**	Br	*i*-Propyl	80	**A**	**9g/10g**	(80/20)	3	
7	**7g**+**8g** (10/90)	Br	*i*-Propyl	78	**A**	**9g/10g**	(88/12)	3	
8	**7h**+**8h** (30/70)	Br	*t*-Butyl	70	**B**	**9h/10h**	(48/52)	48	43
9	**7i**+**8i** (61/39)	Br	Ph	85	**A**	**9i/10i**	(>98/2)	8	38
10	**7j**+**8j** (47/53)	Br	*p*-NO_2-Ph	75	**B**	**9j/10j**	(45/55)	3	44–46

For Method A and Method B see Scheme 2 and typical procedure. Diastereomeric ratio was evaluated by ^1H NMR of the crude reaction mixture.

Mercury 400 MHz spectrometers. Chemical shifts are reported in δ scale and coupling constants (J) are reported in Hertz. Infrared spectra were recorded on a Perkin–Elmer Spectrum BX spectrophotometer in $CHCl_3$. Mass spectra were recorded on Finnigan MAT GCQ instrument. Solvents were distilled according to standard procedures before use.

4.2. General procedure for the preparation of azadiene (3)

1 mL of benzaldehyde (1 mmol) was added to a solution of LiHMDS (1.1 mL of 1 M sol in THF) and heptane (5 mL) at 0 °C under inert atmosphere. The reaction mixture was stirred at 0 °C for 1 h. IR analysis confirmed the formation of silylimine **1** ($\nu_{CN}=1655\ cm^{-1}$). TMSCl (0.14 mL, 1 mmol) was added in one portion and after stirring for 10 min at 0 °C the mixture was allowed to stir for 1 h at rt. A white precipitate formed. The mixture was cooled at 0 °C, triethylamine (0.3 mL, 2 mmol) was added in one portion and after 5 min a solution of acid halide **2** (1 mmol) in 5 mL of heptane was added. Stirring was maintained for 2 h and precipitate appeared. The mixture was filtered through Celite® under argon and the solvent was removed in vacuo to afford an oil, which was analyzed by ^1H NMR spectroscopy.

4.2.1. 1-Chloro-2-trimethylsilyloxy-3-aza-4-phenyl-butan-1,3-diene (3a). Prepared according the general procedure above described starting from chloro acetyl chloride **2a**.

^1H NMR (400 MHz, $CDCl_3$): 8.39 (s, 1H), 7.81 (m, 2H), 7.45 (m, 3H), 6.00 (s, 1H), 0.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 155.1, 153.5, 135.7, 131.3, 128.7, 101.3, 0.6.

4.2.2. 1-Bromo-2-trimethylsilyloxy-3-aza-4-phenyl-butan-1,3-diene (3b). Prepared according the general procedure above described starting from bromo acetyl bromide **2b**.

^1H NMR (400 MHz, $CDCl_3$): 8.40 (s, 1H), 7.80 (m, 2H), 7.44 (m, 3H), 5.93 (s, 1H), 0.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.4, 155.6, 135.5, 131.3, 128.8, 128.6, 88.0, 0.9.

4.2.3. 1-Iodo-2-trimethylsilyloxy-3-aza-4-phenyl-butan-1,3-diene (3c). Prepared according the general procedure above described starting from iodo acetyl chloride **2c**.[47]

^1H NMR (400 MHz, $CDCl_3$): 8.37 (s, 1H), 7.78 (m, 2H), 7.44 (m, 3H), 5.56 (s, 1H), 0.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.2, 156.8, 135.1, 131.6, 128.9, 128.7, 92.6, 1.1.

4.3. General procedure for the preparation of perhydrooxazin-4-ones (5, 6)

Azadiene **3**, prepared as reported above, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at −78 °C. Aldehyde **4** (1 mmol) dissolved in methylene chloride (2 mL) was added followed by a very slow addition of BF_3 etherate (0.12 mL, 1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight while the temperature was allowed to reach rt. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 70/30.

4.3.1. (2*R,5*R**,6*S**)-5-Chloro-6-methyl-2-phenyl-[1,3]-oxazinan-4-one (5a).** ^1H NMR (400 MHz, $CDCl_3$): 7.48 (m, 2H), 7.41 (m, 3H), 6.67 (bs, 1H), 5.77 (s, 1H), 5.27 (dq, 1H, $J=6.0$, 2.4 Hz), 4.16 (d, 1H, $J=2.4$ Hz), 1.45 (d, 3H, $J=6.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 137.0, 130.1, 128.8, 126.9, 85.9, 72.9, 57.1, 17.8; IR (cm^{-1}): 3395, 1686; MS *m/z*: 226, 224, 148, 146, 105, 83. Anal. calcd for $C_{11}H_{12}ClNO_2$: C 58.54; H 5.36. Found: C 58.44; H 5.37.

4.3.2. (2*R,5*R**,6*S**)-5-Bromo-6-methyl-2-phenyl-[1,3]-oxazinan-4-one (5b).** Mp = 156–157 °C; ^1H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.43 (m, 3H), 6.29 (bs, 1H), 5.84 (s, 1H), 4.29 (d, 1H, $J=2.0$ Hz), 4.04 (dq, 1H, $J=$ 2.0, 6.0 Hz), 1.43 (d, 3H, $J=6.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 166.4, 137.2, 130.3, 129.0, 127.1, 86.0, 72.4, 48.8, 19.6; IR (cm^{-1}) 3395, 1685; MS *m/z*: 270, 268, 149, 122, 105, 77. Anal. calcd for $C_{11}H_{12}BrNO_2$: C 48.91; H 4.48. Found: C 48.98; H 4.50.

4.3.3. (2*R,5*R**,6*S**)-5-Iodo-6-methyl-2-phenyl-[1,3]oxazinan-4-one (5c).** ^1H NMR (400 MHz, $CDCl_3$): 7.51 (m, 2H), 7.40 (m, 3H), 6.54 (bs, 1H), 5.93 (s, 1H), 4.49 (d, 1H, $J=2.4$ Hz), 3.12 (dq, 1H, $J=6.0$, 2.4 Hz), 1.35 (d, 3H, $J=$ 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.1, 137.3, 129.9, 128.7, 126.9, 85.9, 71.9, 30.1, 23.5; IR (cm^{-1}): 3395, 1677; MS *m/z*: 316, 189, 174, 168, 147, 105, 77. Anal. calcd for $C_{11}H_{12}INO_2$: C 41.66; H 3.81. Found: C 41.75; H 3.84.

4.3.4. (2*S,5*R**,6*S**)-5-Iodo-6-methyl-2-phenyl-[1,3]oxazinan-4-one (6c).** ^1H NMR (400 MHz, $CDCl_3$): 7.43 (m, 6H), 6.10 (s, 1H), 4.51 (d, 1H, $J=2.4$ Hz), 3.09 (dq, 1H, $J=$ 6.0, 2.4 Hz), 1.23 (d, 3H, $J=6.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.5, 138.5, 129.2, 128.7, 126.4, 82.2, 65.7, 30.1, 22.9; IR (cm^{-1}): 3395, 1677; MS *m/z*: 316, 189, 174, 168, 147, 105, 77. Anal. calcd for $C_{11}H_{12}INO_2$: C 41.66; H 3.81. Found: C 41.80; H 3.84.

4.3.5. (2*R,5*R**,6*S**)-5-Bromo-6-propyl-2-phenyl-[1,3]-oxazinan-4-one (5d).** ^1H NMR (400 MHz, $CDCl_3$): 7.70 (bs, 1H), 7.48 (m, 2H), 7.38 (m, 3H), 5.77 (s, 1H), 4.19 (d, 1H, $J=2.0$ Hz), 3.74 (m, 1H), 1.42 (m, 1H), 1.29 (m, 1H), 1.20 (m, 2H), 0.95 (t, 3H, $J=7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.0, 137.4, 129.8, 128.7, 126.9, 85.7, 75.8, 47.4, 35.2, 17.9, 13.7; IR (cm^{-1}) 3395, 1682; MS *m/z*: 298, 296, 254, 252, 218, 175, 146, 122, 105, 77. Anal. calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41. Found: C 52.48; H 5.44.

4.3.6. (2*S,5*R**,6*S**)-5-Bromo-6-propyl-2-phenyl-[1,3]-oxazinan-4-one (6d).** ^1H NMR (400 MHz, $CDCl_3$): 8.15 (bs, 1H), 7.42 (m, 5H), 6.12 (s, 1H), 4.23 (d, 1H, $J=2.4$ Hz), 3.65 (m, 1H), 1.75 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H), 1.19 (m, 1H), 0.78 (t, 3H, $J=7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.2, 138.0, 129.1, 128.6, 126.4, 82.2, 69.1, 50.0, 35.1, 18.0, 13.7; IR (cm^{-1}) 3399, 1682; MS *m/z*: 298, 296, 254, 252, 146, 105, 77. Anal. calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41. Found: C 52.56; H 5.44

4.3.7. (2*R,5*R**,6*S**)-5-Bromo-6-heptyl-2-phenyl-[1,3]-oxazinan-4-one (5e).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.40 (m, 3H), 7.11 (bs, 1H), 5.79 (s, 1H), 4.22 (d, 1H, J=1.6 Hz), 3.74 (m, 1H), 1.83 (m, 1H), 1.63 (m, 1H), 1.28 (m, 10H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 166.8, 137.4, 129.9, 128.8, 127.0, 85.9, 76.2, 47.5, 33.2, 31.6, 29.2, 29.0, 24.6, 22.5, 14.0; IR (cm^{-1}); 3396, 1682; MS *m*/*z*: 355, 353, 293, 291, 273. Anal. calcd for $C_{17}H_{24}BrNO_2$: C 57.63; H 6.83. Found: C 57.73; H 6.88.

4.3.8. (2*R,5*R**,6*S**)-5-Bromo-6-isopropyl-2-phenyl-[1,3]oxazinan-4-one (5g).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.43 (m, 3H), 6.58 (bs, 1H), 5.79 (s, 1H), 4.37 (d, 1H, J=2.0 Hz), 3.27 (dd, 1H, J=2.0, 9.2 Hz), 2.06 (m, 1H), 1.07 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 137.4, 130.1, 128.9, 127.0, 86.2, 82.2, 46.0, 30.9, 18.9, 17.1; IR (cm^{-1}): 3401, 1681; MS *m*/*z*: 299, 298, 297, 296, 256, 254, 228, 226, 216, 146, 132, 107. Anal. calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41. Found: C 52.18; H 5.43.

4.3.9. (2*S,5*R**,6*S**)-5-Bromo-6-isopropyl-2-phenyl-[1,3]oxazinan-4-one (6g).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (m, 6H), 6.14 (s, 1H), 4.28 (d, 1H, J=2.0 Hz), 3.05 (dd, 1H, J=2.0, 9.2 Hz), 1.99 (m, 1H), 0.85 (d, 3H, J=6.4 Hz), 0.76 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.4, 137.9, 129.0, 128.4, 126.6, 82.3, 74.6, 46.7, 31.0, 19.0, 17.1; IR (cm^{-1}): 3401, 1681; MS *m*/*z*: 299, 298, 297, 296, 256, 254, 228, 226, 216, 146, 132, 107. Anal. calcd for $C_{13}H_{16}BrNO_2$: C 52.36; H 5.41. Found: C 52.46; H 5.45.

4.4. X-ray crystallography for 6g

The diffraction experiments were carried out for **6g** at rt on a Bruker AXS SMART 2000 CCD based diffractometer using graphite monochromated Mo-Kα radiation (λ=0.71073 Å). Intensity data were measured over full diffraction spheres using 0.3° wide ω scans, crystal-to-detector distance 5.0 cm. The software SMART[48] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by software SAINT[48] and an empirical absorption correction was applied with SADABS.[49] The structures were solved by direct methods (SIR 97)[50] and subsequent Fourier syntheses, and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[51] attributing anisotropic thermal parameters to the non-hydrogen atoms. The aromatic hydrogen atoms were placed in calculated positions and refined with idealized geometry ($C(sp^2)$–H=0.93 Å) whereas the other H atoms were located in the Fourier map and refined isotropically.

Crystallographic data for **6g**:[52] $C_{13}H_{16}BrNO_2$, M=298.18, monoclinic, space group $P2_1/c$ (No. 14), a=10.5542(4) Å, b=8.9243(4) Å, c=14.3655(6) Å, β=91.218(1)°, Z=4, V=1352.8(1) Å^3, d_{calc}=1.464 Mg m^{-3}, μ=3.029 mm^{-1}. 9340 reflections were collected, 3768 unique, observed for $I>2\sigma(I)$ which were used in all calculations. Final R factors: R_1=0.0411 [$I>2\sigma(I)$], wR_2=0.1108 (all data).

4.4.1. (2*R,5*R**,6*S**)-5-Bromo-6-*tert*-butyl-2-phenyl-[1,3]oxazinan-4-one (5h).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (m, 2H), 7.42 (m, 3H), 6.69 (bs, 1H), 5.77 (s, 1H), 4.37 (d, 1H, J=0.8 Hz), 3.53 (d, 1H, J=0.8 Hz), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.1, 137.7, 129.9, 128.8, 126.9, 86.3, 82.5, 43.9, 34.9, 26.4; IR (cm^{-1}): 3401, 1686; MS *m*/*z*: 313, 311, 257, 255, 177. Anal. calcd for $C_{14}H_{18}BrNO_2$: C 53.86; H 5.81. Found: C 53.98; H 5.85.

4.4.2. (2*S,5*R**,6*S**)-5-Bromo-6-*tert*-butyl-2-phenyl-[1,3]oxazinan-4-one (6h).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (m, 5H), 7.16 (bs, 1H), 6.23 (s, 1H), 4.34 (d, 1H, J=1.6 Hz), 3.45 (d, 1H, J=1.6 Hz), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.7, 137.6, 129.4, 128.6, 126.9, 82.4, 75.4, 44.3, 34.6, 26.3; IR (cm^{-1}): 3401, 1686; MS *m*/*z*: 313, 311, 257, 255, 177. Anal. calcd for $C_{14}H_{18}BrNO_2$: C 53.86; H 5.81. Found: C 53.98; H 5.87.

4.4.3. (2*R,5*R**,6*S**)-5-Bromo-2,6-diphenyl-[1,3]oxazinan-4-one (5i).** Mp: 173–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.62–7.34 (m, 10H), 6.65 (bs, 1H), 6.02 (s, 1H), 5.17 (d, 1H, J=2.0 Hz), 4.54 (d, 1H, J=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 166.4, 137.2, 136.5, 130.3, 128.9, 128.3, 127.2, 125.5, 86.1, 77.1, 47.9; IR (cm^{-1}): 3396, 1682; MS *m*/*z*: 332, 330, 252, 227, 225, 211, 109, 184, 182, 146, 118, 77. Anal. calcd for $C_{16}H_{14}BrNO_2$: C 57.85; H 4.25. Found: C 57.71; H 4.23.

4.4.4. (2*S,5*R**,6*S**)-5-Bromo-2,6-diphenyl-[1,3]oxazinan-4-one (6i).** Mp: 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (bs, 1H), 7.52–7.33 (m, 10H), 6.33 (s, 1H), 5.07 (d, 1H, J=2.0 Hz), 4.56 (d, 1H, J=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.1, 137.7, 136.5, 129.5, 128.9, 128.3, 128.2, 126.6, 125.7, 82.4, 71.3, 47.7; IR (cm^{-1}) 3396, 1682; MS *m*/*z*: 332, 330, 252, 227, 225, 211, 209, 146, 131, 118, 77. Anal. calcd for $C_{16}H_{14}BrNO_2$: C 57.85; H 4.25. Found: C 57.98; H 4.27.

4.4.5. (2*R,5*R**,6*S**)-5-Bromo-6-*p*-nitrophenyl-2-phenyl-[1,3]oxazinan-4-one (5j).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (d, 2H, J=6.7 Hz), 7.59 (m, 2H), 7.52 (d, 2H, J=6.7 Hz), 7.48 (m, 3H), 6.83 (bs, 1H), 6.04 (s, 1H), 5.28 (d, 1H, J=2.0 Hz), 4.57 (d, 1H, J=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 147.8, 143.5, 136.7, 130.5, 129.0, 127.2, 126.6, 123.6, 86.2, 76.5, 46.6; IR (cm^{-1}): 3395, 1682; MS *m*/*z*: 377, 375, 297, 256, 254, 176, 146, 105, 78. Anal. calcd for $C_{16}H_{13}BrN_2O_4$: C 50.95; H 3.47. Found: C 51.15; H 3.50.

4.4.6. (2*S,5*R**,6*S**)-5-Bromo-6-*p*-nitrophenyl-2-phenyl-[1,3]oxazinan-4-one (6j).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.24 (d, 2H, J=6.6 Hz), 7.50 (d, 2H, J=6.6 Hz), 7.43 (m, 5H), 7.22 (bs, 1H), 6.37 (s, 1H), 5.17 (d, 1H, J=2.4 Hz), 4.54 (d, 1H, J=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 165.9, 147.8, 143.7, 137.2, 129.8, 129.1, 126.7, 126.5, 123.6, 82.6, 70.9, 46.5; IR (cm^{-1}): 3395, 1682; MS *m*/*z*: 377, 375, 297, 256, 254, 176, 146, 105, 78. Anal. calcd for $C_{16}H_{13}BrN_2O_4$: C 50.95; H 3.47. Found: C 51.08; H 3.49.

4.5. General procedure for the preparation of N-*t*-Boc-perhydroxazin-4-ones (7, 8)

Perhydroxazinones **5** and **6** prepared as reported above (1 mmol), were dissolved in CH_2Cl_2 (10 mL); Et_3N

(1.2 mmol), DMAP (cat) and di-*tert*-butyldicarbonate (2 mmol) were added. The mixture was stirred at rt until the starting material disappeared (3 h) then it was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 90/10. The yields are reported in Table 2.

4.5.1. (2*R,5*R**,6*S**)-5-Bromo-6-methyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (7b).** Mp=174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.40 (m, 3H), 6.13 (s, 1H), 4.37 (d, 1H, J=2.0 Hz), 4.03 (dq, 1H, J=6.0, 2.0 Hz), 1.40 (d, 3H, J=6.0 Hz), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 149.9, 137.6, 129.8, 128.6, 127.5, 90.2, 84.4, 71.3, 49.7, 27.2, 19.1; IR (cm^{-1}): 1776, 1735; MS *m*/*z*: 370, 368, 316, 314, 298, 296, 270, 268, 190, 122, 105, 77. Anal. calcd for $C_{16}H_{20}BrNO_4$: C 51.90; H 5.44. Found: C 52.07; H 5.46.

4.5.2. (2*R,5*R**,6*S**)-5-Bromo-6-propyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (7d).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.48 (m, 2H), 7.37 (m, 3H), 6.09 (s, 1H), 4.38 (d, 1H, J=1.2 Hz), 3.80 (m, 1H), 1.83–1.32 (m, 4H), 1.11 (s, 9H), 0.92 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 149.8, 137.6, 129.7, 128.5, 127.4, 90.3, 85.1, 75.0, 48.3, 34.8, 27.4, 17.8, 13.7; IR (cm^{-1}): 1776, 1734; MS *m*/*z*: 344, 342, 326, 324, 298, 296, 218, 122, 105, 77. Anal. calcd for $C_{18}H_{24}BrNO_4$: C 54.28; H 6.07. Found: C 54.48; H 6.10.

4.5.3. (2*R,5*R**,6*S**)-5-Bromo-6-hepthyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (7e).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (m, 2H), 7.39 (m, 3H), 6.11 (s, 1H), 4.40 (d, 1H, J=1.6 Hz), 3.79 (m, 1H), 1.81 (m, 1H), 1.61 (m, 1H), 1.26 (m, 10H), 1.13 (s, 9H), 0.86 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 164.5, 149.7, 137.7, 129.5, 128.6, 127.4, 90.3, 84.3, 75.3, 48.3, 32.7, 31.6, 29.1, 28.9, 27.1, 24.5, 22.5, 14.0; IR (cm^{-1}): 1777, 1738; MS *m*/*z*: 400, 398, 382, 380, 354, 352, 274, 105. Anal. calcd for $C_{22}H_{32}BrNO_4$: C 58.15; H 7.10. Found: C 58.10; H 7.08.

4.5.4. (2*R,5*R**,6*S**)-5-Bromo-6-isopropyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (7g).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (m, 2H), 7.40 (m, 3H), 6.09 (s, 1H), 4.49 (d, 1H, J=1.6 Hz), 3.29 (dd, 1H, J=1.6, 9.2 Hz), 2.03 (m, 1H), 1.14 (s, 9H), 1.05 (d, 3H, J=6.8 Hz), 0.90 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 164.6, 149.7, 137.8, 129.8, 128.6, 127.4, 90.5, 84.3, 81.1, 46.9, 30.6, 27.2, 18.7, 17.1; IR (cm^{-1}): 1776, 1726; MS *m*/*z*: 326, 324, 298, 296, 218, 176, 132, 122, 105. Anal. calcd for $C_{18}H_{24}BrNO_4$: C 54.28; H 6.07. Found: C 54.48; H 6.09.

4.5.5. (2*S,5*R**,6*S**)-5-Bromo-6-isopropyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (8g).** Mp: 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (m, 3H), 7.30 (m, 2H), 6.68 (s, 1H), 4.31 (d, 1H, J=2.0 Hz), 3.02 (dd, 1H, J=2.0, 9.2 Hz), 1.97 (m, 1H), 1.40 (s, 9H), 0.82 (d, 3H, J=6.4 Hz), 0.74 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 165.5, 150.1, 137.6, 129.1, 128.6, 126.5, 86.1, 84.2, 74.9, 48.6, 30.9, 27.7, 18.6, 16.7; IR (cm^{-1}): 1776, 1726; MS *m*/*z*: 398, 344, 342, 326, 324, 298, 296, 218, 176, 132, 122, 105. Anal. calcd for $C_{18}H_{24}BrNO_4$: C 54.28; H 6.07. Found: C 54.39; H 6.09.

4.5.6. (2*R,5*R**,6*S**)-5-Bromo-6-*tert*-butyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (7h).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (m, 2H), 7.40 (m, 3H), 6.06 (s, 1H), 4.50 (d, 1H, J=2.0 Hz), 3.52 (d, 1H, J=2.0 Hz), 1.14 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.8, 149.9, 137.8, 129.6, 128.4, 127.7, 90.8, 84.2, 81.4, 44.8, 34.9, 27.2, 26.5; IR (cm^{-1}): 1774, 1726; MS *m*/*z*: 413, 411, 358, 356, 340, 338, 314, 312, 311, 310, 256, 254, 232, 146, 132,106. Anal. calcd for $C_{19}H_{26}BrNO_4$: C 55.35; H 6.36. Found: C 55.55; H 6.38.

4.5.7. (2*S,5*R**,6*S**)-5-Bromo-6-*tert*-butyl-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (8h).** Mp: 162–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (m, 3H), 7.32 (m, 2H), 6.69 (s, 1H), 4.36 (d, 1H, J=2.0 Hz), 3.32 (d, 1H, J=2.0 Hz), 1.37 (s, 9H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 150.0, 137.3, 129.1, 128.5, 126.6, 86.2, 83.1, 74.8, 46.6, 34.6, 27.7, 26.3; IR (cm^{-1}): 1774, 1726; MS *m*/*z*: 413, 411, 358, 356, 340, 338, 314, 312, 311, 310, 256, 254, 232, 146, 132, 106. Anal. calcd for $C_{19}H_{26}BrNO_4$: C 55.35; H 6.36. Found: C 55.45; H 6.39.

4.5.8. (2*R,5*R**,6*S**)-5-Bromo-4-oxo-2,6-diphenyl-[1,3]-oxazinane-3-carboxylic acid *tert*-butyl ester (7i).** Mp: 167–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (m, 2H), 7.44 (m, 3H), 7.32 (m, 5H), 6.30 (s, 1H), 5.15 (d, 1H, J=2.0 Hz), 4.62 (d, 1H, J=2.0 Hz), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 149.9, 137.5, 135.8, 129.9, 128.5, 128.4, 128.3, 127.7, 125.5, 90.3, 84.5, 76.0, 48.9, 27.2; IR (cm^{-1}): 1777, 1735; MS *m*/*z*: 332, 330, 252, 146, 131, 105, 77. Anal. calcd for $C_{21}H_{22}BrNO_4$: C 58.34; H 5.13. Found: C 58.44; H 5.15.

4.5.9. (2*S,5*R**,6*S**)-5-Bromo-4-oxo-2,6-diphenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (8i).** Mp: 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.25 (m, 10H), 6.89 (s, 1H), 4.92 (d, 1H, J=2.0 Hz), 4.53 (d, 1H, J=2.0 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.3, 150.1, 137.2, 136.3, 129.3, 128.9, 128.3, 128.2, 126.5, 125.4, 86.1, 84.5, 70.7, 49.9, 27.7; IR (cm^{-1}): 1777, 1735; MS *m*/*z*: 332, 330, 252, 227, 225, 146, 131, 105, 77. Anal. calcd for $C_{21}H_{22}BrNO_4$: C 58.34; H 5.13. Found: C 58.45; H 5.15.

4.5.10. (2*R,5*R**,6*S**)-5-Bromo-6-(4-nitro-phenyl)-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (7j).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.22 (d, 2H, J=6.7 Hz), 7.69 (m, 3H), 7.47 (m, 4H), 6.33 (s, 1H), 5.29 (d, 1H, J=2.0 Hz), 4.65 (d, 1H, J=2.0 Hz), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.6, 149.6, 147.9, 142.7, 137.0, 130.2, 128.7, 127.7, 126.5, 123.6, 90.3, 84.9, 75.4, 47.7, 27.2; IR (cm^{-1}): 1778, 1735; MS *m*/*z*: 477, 475, 377, 375, 297, 256, 254. Anal. calcd for $C_{21}H_{21}BrN_2O_6$: C 52.84; H 4.43. Found: C 52.80; H 4.41

4.5.11. (2*S,5*R**,6*S**)-5-Bromo-6-(4-nitro-phenyl)-4-oxo-2-phenyl-[1,3]oxazinane-3-carboxylic acid *tert*-butyl ester (8j).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (d, 2H, J=6.6 Hz), 7.71 (d, 2H, J=6.6 Hz), 7.53–7.40 (m, 5H), 6.91 (s, 1H), 5.12 (d, 1H, J=2.0 Hz), 4.58 (d, 1H, J=2.0 Hz), 1.43

(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.7, 149.9, 147.6, 142.8, 136.5, 130.0, 128.7, 127.6, 126.4, 123.5, 86.4, 84.78, 69.9, 48.6, 27.7; IR (cm^{-1}): 1778, 1735; MS *m*/*z*: 477, 475, 377, 375, 297, 256, 254. Anal. calcd for $C_{21}H_{21}BrN_2O_6$: C 52.84; H 4.43. Found: C 52.94; H 4.44.

4.6. General procedure for the preparation of epoxide (9, 10)

Method A. *N*-*t*-Boc-perhydroxazinone **7** and/or **8** (1 mmol) were dissolved in THF (10 mL) and LiOH 1 M (3 mmol) was added. The mixture was stirred at rt until TLC showed the disappearance of the starting material. The crude mixture was concentrated to half of the starting volume, water (5 mL) was added and the mixture was extracted with ether. The aqueous layers were made acidic by HCl 1 N at 0 °C. Extraction with ethyl acetate and removal of the solvent, purification of the crude mixture by short path flash chromatography (eluted with toluene/CH_3COOH 4/1) yielded the epoxy acids **9** and **10**. The yields are reported in Table 3.

Method B. *N*-*t*-Boc-perhydroxazinone **7** or **8** (1 mmol) were dissolved in a solution of ethanol/water 5/1 (10 mL). LiOH (5 mmol) and H_2O_2 30% (5 mmol) were added. The mixture was stirred at rt until TLC showed the disappearance of the starting material. The crude mixture was concentrated to half of the starting volume, water (5 mL) was added and the mixture was extracted with ether. The aqueous layers were made acidic by HCl 1 N at 0 °C. Extraction with ethyl acetate and removal of the solvent, followed by purification of the crude mixture by short path flash chromatography (eluted with toluene/CH_3COOH 4/1) yielded the epoxy acids **9** and **10**. The yields are reported in Table 3.

Analytical data for known compounds are in ageement with those reported in literature (for the interested readers see the references reported in Table 3).

4.6.1. (2*S,3*S**)-3-Methyl-oxirane-2-carboxylic acid (9b).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (bs, 1H), 3.56 (d, 1H, J= 4.8 Hz), 3.36 (dq, 1H, J=4.8, 5.2 Hz), 1.43 (d, 3H, J= 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.30, 54.02, 52.67, 12.89; IR (cm^{-1}): 3580, 1736.

4.6.2. (2*S,3*R**)-3-Methyl-oxirane-2-carboxylic acid (10b).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (bs, 1H), 3.28 (dq, 1H, J=2.0, 5.2 Hz), 3.22 (d, 1H, J=2.0 Hz), 1.42 (d, 3H, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 174.34, 55.08, 53.43, 17.12; IR (cm^{-1}): 3580, 1736.

4.6.3. (2*S,3*S**)-3-Propyl-oxirane-2-carboxylic acid (9d).** ^{1}H NMR (400 MHz, $CDCl_3$): 3.57 (d, 1H, J=4.4 Hz), 3.24 (m, 1H,), 1.74–1.42 (m, 4H) 0.97 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 172.78, 58.06, 52.88, 29.28, 19.46, 13.74.

4.6.4. (2*S,3*R**)-3-Propyl-oxirane-2-carboxylic acid (10d).** ^{1}H NMR (400 MHz, $CDCl_3$): 6.65 (bs, 1H), 3.26 (d, 1H, J=1.6 Hz), 3.18 (m, 1H), 1.65–1.20 (m, 4H), 0.98 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 174.06, 58.80, 52.95, 29.69, 18.99, 13.73.

4.6.5. (2*S,3*S**)-3-Heptyl-oxirane-2-carboxylic acid (9e).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.05 (bs, 1H), 3.57 (d, 1H, J= 4.8 Hz), 3.23 (m, 1H), 1.62 (m, 2H), 1.26 (m, 10H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.57, 58.25, 52.66, 31.41, 29.16, 28.19, 27.28, 26.11, 22.57, 14.05.

4.6.6. (2*S,3*R**)-3-Heptyl-oxirane-2-carboxylic acid (10e).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (bs, 1H), 3.25 (d, 1H, J=2.0 Hz), 3.19 (m, 1H), 1.65 (m, 2H), 1.31 (m, 10H), 0.87 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 174.62, 59.05, 52.66, 31.66, 29.07, 28.16, 27.26, 25.62, 22.58, 14.05.

4.6.7. (2*S,3*S**)-3-Isopropyl-oxirane-2-carboxylic acid (9g).** ^{1}H NMR (400 MHz, $CDCl_3$): 3.57 (d, 1H, J= 4.4 Hz), 2.90 (dd, 1H, J=4.4, 9.2 Hz), 1.64 (m, 1H), 1.13 (d, 3H, J=6.8 Hz), 0.95 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 172.58, 63.39, 53.14, 27.10, 20.09, 18.30.

4.6.8. (2*S,3*R**)-3-Isopropyl-oxirane-2-carboxylic acid (10g).** ^{1}H NMR (400 MHz, $CDCl_3$): 3.28 (d, 1H, J= 2.0 Hz), 2.30 (dd, 1H, J=2.0, 6.8 Hz), 1.45 (m, 1H), 1.03 (d, 3H, J=6.8 Hz), 0.99 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.90, 63.75, 51.79, 30.06, 18.67, 18.01.

4.6.9. (2*S,3*S**)-3-*tert*-Butyl-oxirane-2-carboxylic acid (9h).** ^{1}H NMR (400 MHz, $CDCl_3$): 3.51 (d, 1H, J= 4.8 Hz), 3.00 (d, 1H, J=4.8 Hz), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 172.10, 66.55, 53.69, 31.86, 25.72.

4.6.10. (2*S,3*R**)-3-*tert*-Butyl-oxirane-2-carboxylic acid (10h).** ^{1}H NMR (400 MHz, $CDCl_3$): 3.35 (d, 1H, J= 2.0 Hz), 3.02 (d, 1H, J=2.0 Hz), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.56, 66.53, 49.98, 31.04, 25.52.

4.6.11. (2*S,3*S**)-3-Phenyl-oxirane-2-carboxylic acid (9i).** ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (m, 5H), 4.32 (d, 1H, J= 4.8 Hz), 3.87 (d, 1H, J=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.51, 132.02, 128.47, 128.12, 126.64, 57.87, 55.38.

4.6.12. (2*S,3*S**)-3-*p*-nitrophenyl-oxirane-2 carboxylic acid (9j).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.30 (d, 2H, J= 6.7 Hz), 7.62 (d, 2H, J=6.7 Hz), 4.50 (bs, 1H), 4.39 (d, 1H, J=4.8 Hz), 3.94 (d, 1H, J=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 141.6, 131.1, 128.4, 123.5, 56.9, 55.4.

4.6.13. (2*S,3*S**)-3-p-nitrophenyl-oxirane-2 carboxylic acid methyl ester (9j′).**[46] ^{1}H NMR (400 MHz, $CDCl_3$): 8.22 (d, 2H, J=6.7 Hz), 7.60 (d, 2H, J=6.7 Hz), 4.34 (d, 1H, J=4.8 Hz), 3.91 (d, 1H, J=4.8 Hz), 3.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 141.9, 130.6, 127.6, 123.8, 56.7, 55.7, 52.4; MS *m*/*z*: 223, 207, 192, 166.

4.6.14. (2*S,3*R**)-3-*p*-Nitrophenyl-oxirane-2-carboxylic acid (10j).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (d, 2H, J= 6.6 Hz), 7.48 (d, 2H, J=6.6 Hz), 4.60 (bs, 1H), 4.24 (d, 1H, J=1.6 Hz), 3.52 (d, 1H, J=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.7, 139.4, 127.7, 123.9, 123.2, 57.0, 56.5.

4.6.15. ($2S^*$,$3R^*$)-3-*p*-Nitrophenyl-oxirane-2-carboxylic acid methyl ester (10j′).[46] ^{1}H NMR (400 MHz, $CDCl_3$): 8.19 (d, 2H, J=6.6 Hz), 7.47 (d, 2H, J=6.6 Hz), 4.21 (d, 1H, J=2.0 Hz), 3.85 (s, 3H), 3.50 (d, 1H, J=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 166.0, 139.7, 126.5, 123.4, 123.2, 56.9, 56.8, 52.9; MS *m/z*: 223, 207, 192, 166.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.07.019

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A simple and facile stereoselective synthesis of (*Z*)- and (*E*)-allyl halides catalyzed by silica supported sodium hydrogen sulfate: factors influencing the yields and stereochemistry of allyl halides☆

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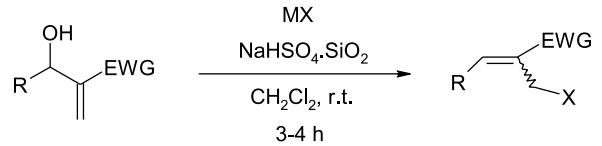
Abstract—A simple, mild and efficient stereoselective synthesis of (*Z*)- and (*E*)-allyl bromides and iodides has been developed by treatment of the Baylis–Hillman adducts with lithium bromide and iodide, respectively, in methylene chloride catalyzed by silica supported sodium hydrogen sulfate at room temperature. The role of various solvents, different reacting metallic halides, nature of the adducts and activity of several heterogeneous catalysts on the yields and stereochemistry of the products have been thoroughly studied.

1. Introduction

The reaction involving the coupling of activated vinylic systems with electrophiles under the catalytic influence of a tertiary amine (usually DABCO), known as the Baylis–Hillman reaction, is a useful carbon carbon bond forming method in synthetic organic chemistry.[1] The Baylis–Hillman adducts, 3-hydroxy-2-methylene-alkanoates (derived from acrylate esters) or 3-hydroxy-2-methylene-alkanenitriles (derived from acrylonitrile) are important precursors for stereoselective synthesis of various functionalized molecules.[1b,2] The allyl halides prepared from these adducts have been utilized for the synthesis of different natural bioactive molecules and their analogues such as α-methylene-γ-butyrolactones,[2a] α-alkylidene-β-lactams[2b] and flavonoids.[2c] The direct conversion of the Baylis–Hillman adducts to the corresponding halides has earlier been carried out using hydrogen halides along with strong acids (HBr–H_2SO_4, HI–H_3PO_4),[2a,3a–c] organic acid halides (oxalyl chloride, MsCl),[3d,e] HCA–PPh_3 complex,[3e] NCS/NBS–Me_2S,[3f–h] Lewis acids ($FeCl_3$, $InCl_3$)[3i] and KSF clay under microwaves.[3j] However, most of these methods are associated with different drawbacks including the use of concentrated acids, low stereoselectivity, unsatisfactory yields, long reaction times, incompatibility with other functional groups and special or complex experimental procedures. The methods for the conversion of the Baylis–Hillman adducts into the corresponding allyl iodides are also limited. Here we describe a convenient and efficient synthesis of (*Z*)- and (*E*)-allyl bromides and iodides from the Baylis–Hillman adducts in a single step.

2. Results and discussion

The Baylis–Hillman adduct, **1** (3-hydroxy-2-methylene alkanoates or 3-hydroxy-2-methylene alkanenitriles) was treated with metal halides (MX: M = Li, Na or K and X = Br or I) in the presence of silica supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) as a heterogeneous catalyst to directly produce the corresponding allyl halides **2** and **3**. The reaction occurred smoothly at room temperature within 3–4 h. Allyl halides containing both aryl and alkyl groups were prepared by this method (Scheme 1).



1 **2** X= Br **3** X= I

R = aryl or alkyl

EWG = COOMe, COOEt or CN

Scheme 1.

☆ Part 37 in the series, 'Studies on Novel Synthetic Methodologies'.

Keywords: Baylis–Hillman adducts; (*Z*)- and (*E*)-Allyl bromides and iodides; Metallic halides; $NaHSO_4 \cdot SiO_2$; Stereochemistry.
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Table 1. Reaction of **1a** (R=Ph, EWG=COOMe) with Li-halides using $NaHSO_4 \cdot SiO_2$ at room temperature in different solvents

Product	Time (h)	Yield (%) with solvents			
		CH_2Cl_2	1,4-Dioxane	MeCN	MeOH
2a	3	97	46	34	15
3a	3	98	48	35	18

The role of solvents, metallic halides, electron withdrawing groups present in the adducts and catalysts (which have been found to be the guiding factors for the yields and stereochemistry of the products) have been thoroughly studied. CH_2Cl_2 was found to be the most suitable solvent for the conversion with excellent yields. We have tried the reaction with different solvents such as 1,4-dioxane, MeCN and MeOH (Table 1). However, as the polarity of the solvents increased the yields of the products decreased. The solubility of metallic halides increases in a more polar solvent but the activity of the catalyst decreases due to its better dissociation to the corresponding ions. $NaHSO_4 \cdot SiO_2$ has been found to work less efficiently when its ionization increases possibly due to the disturbance of the solid surface reaction.[4] Thus, the bromide **2a** (Table 1) was formed with yields of 97 and 15%, when the reaction was carried out with LiBr in CH_2Cl_2 and MeOH, respectively, under otherwise identical experimental conditions. Similarly, LiI produced the iodide **3a** in 98 and 18% in these two solvents. The yields of the products thus depend highly on the solvent used in the reaction.

The yields of the products also depended on the reacting metallic halides (Table 2). The yields of the halides were maximum with LiBr and LiI but lower with NaBr (or NaI) and KBr (or KI). Thus, the separate reactions of **1A** with LiBr, NaBr and KBr catalyzed by $NaHSO_4 \cdot SiO_2$ produced **2A** in yields of 97, 72 and 68%, respectively. Similarly, when the reaction was carried out with LiI, NaI and KI the yields of **3A** was 98, 73 and 67%, respectively. Thus, as the ionic property of the metallic halides increases the yields of the allyl halides decreases as the concentration of halide ions decreases in CH_2Cl_2 with gradual lowering of solubility of the metallic halides. However, the actual reactivities of bromide and iodide for the reaction was similar in terms of yields and reaction times.

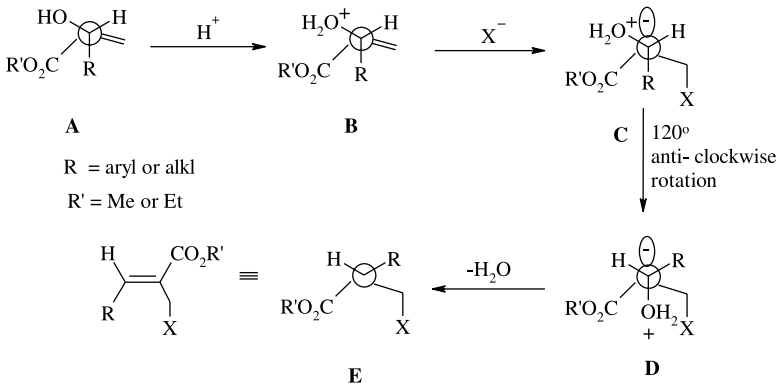
Table 2. Synthesis of allyl halides (**2** and **3**) with different metallic halides using $NaHSO_4 \cdot SiO_2$ in CH_2Cl_2 at room temperature

Entry	R	EWG	Time (h)	MX	Isolated yield (%)
A	C_6H_5	COOMe	3	LiBr	97
				NaBr	72
				KBr	68
				LiI	98
				NaI	73
				KI	67
B	4-ClC_6H_4	COOMe	3	LiBr	96
				NaBr	70
				KBr	64
				LiI	95
				NaI	72
				KI	68
C	4-$O_2NC_6H_4$	COOMe	4	LiBr	94
				NaBr	73
				KBr	68
				LiI	96
				NaI	75
				KI	70

Table 3. Synthesis of (*Z*)- and (*E*)-allyl halides using Li-halides in the presence of $NaHSO_4 \cdot SiO_2$ in CH_2Cl_2 at room temperature[a]

Entry	R	EWG	Time (h)	Isolated yield (%)[b] of		*Z*/*E*
				2	**3**	
a	C_6H_5	COOMe	3	97	98	100:0
b	2-ClC_6H_4	COOMe	3	95	96	100:0
c	4-ClC_6H_4	COOMe	3	96	95	100:0
d	4-$O_2NC_6H_4$	COOMe	4	94	94	100:0
e	$CH_3(CH_2)_7CH_2$	COOMe	4	83	83	100:0
f	$C_6H_4CH_2CH_2$	COOMe	4	80	81	100:0
g	4-ClC_6H_4	COOEt	3	95	96	100:0
h	4-$MeOC_6H_4$	COOEt	3	98	98	100:0
i	C_6H_5	CN	4	82	83	94:6
j	3-$O_2NC_6H_4$	CN	4	80	80	97:3
k	3,4-$Cl_2C_6H_3$	CN	4	81	83	95:5

[a] The structures of the products were settled from their spectral (IR, ^1H NMR and MS) and analytical data.
[b] The total yields of the products (*Z*+*E* isomers) are given; for **2** and **3** (entries a–h) the products are only (*Z*)-isomer while for entries i–k the major products are (*E*)-isomer along with minor (<10%) (*Z*)-isomer.



Scheme 2.

The electron withdrawing groups present in the Baylis–Hillman adducts as well as the metallic halides direct the stereochemistry of the products (Table 3). When –COOMe or –COOEt groups are present in **1** the conversion afforded the allyl halides with (*Z*)-stereochemistry as the major products. However, if –CN is present as the electron withdrawing group the major products have (*E*) stereochemistry. The stereoselective formation of allyl halide can be explained with the suggestion of Buchholz and Hoffmann (Scheme 2).[5]

As –COOR′ group is sterically more demanding than CH_2X group counter clock-wise rotation of 120° around the central C–C bond in **C** is favoured than a clock-wise rotation of 60° to achieve **D** for departure of the leaving group (H_2O). This suggestion explains the (*Z*) selectivity of the generated allyl halides and also the loss of (*Z*) selectivity with the replacement of –COOR′ group with –CN.

The role of metallic halides is also very important in this connection. The reaction of **1** (having –COOMe or –COOEt group) with NaBr (or NaI) and KBr (or KI) produced the (*E*)-allyl halides in the range of 16–22% and 28–35%, respectively, while with LiBr (or LiI) the allyl halides were produced solely with (*Z*)-stereochemistry. The stereoselectivity was also lower when NaBr (or NaI) and KBr (or KI) reacted with **1** containing –CN group. Thus the yields of (*Z*)- isomers were in the range of 18–26 and 32–38%, respectively.

Stereoselectivity was higher with lithium halides forming predominantly the (*E*)-isomers. Thus, it was observed as the used halides became more ionic the stereoselectivity of the produced allyl halides also decreased. This is because the concentration of the halide ions decreases in CH_2Cl_2 and the rate of the reaction becomes slow. The reaction could tolerate various functional groups like alkyl, ether, halogen and nitro groups. The structures and stereochemistry of the products were established from their spectral (^{1}H NMR and MS) and analytical data. The (*Z*)- and (*E*) stereochemistry of the allyl halides could easily be settled from the assignment of the chemical shift values of the vinyl and allylic protons in their ^{1}H NMR spectra. In ^{1}H NMR spectrum β-vinylic proton *cis* and *trans* to the ester group resonates at δ 7.5 and 6.5, respectively, when R is aryl.[6,7] The same proton *cis* and *trans* to the ester group appears at δ 6.8 and 5.7, respectively, when R is alkyl.[8,9] Similarly the β-vinylic proton *cis* and *trans* to the nitrile group appears at δ 6.3 and 6.1, respectively, when R is alkyl[10,11] while the same proton *cis*and *trans*to the nitrile group resonates at δ 7.6 and 6.8 when R is aryl.[12,13] Moreover, the allylic proton of (*Z*)-isomer appears downfield compare to that of (*E*)-isomer in the ^{1}H NMR spectra.[3j] The products, (*Z*)- and (*E*)-allyl bromides and iodides can be utilized as useful precursors for stereoselective synthesis of useful allyl amines and azetidines.[14]

The catalyst, $NaHSO_4 \cdot SiO_2$ was found to be highly efficient for the preparation of allyl halides from the corresponding Baylis–Hillman adducts. The catalyst works under heterogeneous conditions. In recent years, heterogeneous catalysts have attracted a great attention due to efficiency, economic and environmental considerations. We have tried the conversion with different other heterogeneous catalysts such as montmorillonite K10 clay, KSF clay, HY-Zeolite and Amberlyst-15 under the similar experimental conditions (Table 4). However, the catalytic activity of $NaHSO_4 \cdot SiO_2$ is much more higher than that of the other catalysts. This catalyst can easily be prepared[15] from the readily available inexpensive ingredients, $NaHSO_4$ and silica gel (finer than 200 mesh). The catalyst can conveniently be handled and removed from the reaction mixture. Thus the remarkable catalytic activity together with operational simplicity have made it as the most suitable catalyst for the target conversion.

Table 4. Reaction of **1a** (R=Ph, EWG=COOMe) with Li-halides in CH_2Cl_2 at room temperature in the presence of various heterogeneous catalysts

Catalyst	Time (h)	Isolated yield (%) of	
		2a	**3a**
$NaHSO_4 \cdot SiO_2$	3	98	97
K-10 clay	3	70	74
KSF Clay	3	68	71
HY-Zeolite	3	63	65
Amberlyst-15	3	0	0

3. Conclusion

In conclusion, we have converted the Baylis–Hillman adducts into the (*Z*)- and (*E*)-allyl bromides and iodides by treatment with lithium halides in CH_2Cl_2 using $NaHSO_4 \cdot SiO_2$ as a heterogeneous catalyst. The role of

different possible factors such as solvents, reacting metallic halides, nature of the adducts and various catalysts have been studied well. The conversion of the adducts with LiBr or LiI in CH_2Cl_2 catalyzed by $NaHSO_4 \cdot SiO_2$ at room temperature was found to be highly efficient for the preparation of (*Z*)- and (*E*)-allyl halides in high yields and stereoselectivity. The mild reaction condition, shorter reaction times, convenient experimental procedure and inexpensive catalyst are the great advantages associated with this method. We feel the present process will find important applications for the stereoselective synthesis of allyl halides.

4. Experimental

4.1. General methods

Baylis–Hillman adducts were prepared following the standard methods.[1b] The metallic halides and the heterogeneous catalysts, clays, HY-Zeolite and Amberlyst-15 were obtained commercially. The ^{1}H NMR spectra were run on varian Gemini 200 MHz and EIMS on VG Micromass 7070 H (70 eV).

4.2. Typical experimental procedure

To a solution of Baylis–Hillman adduct (3 mmol) in CH_2Cl_2 (10 mL) metallic halide (4 mmol) and $NaHSO_4 \cdot SiO_2$ (300 mg) were added. The mixture was stirred at room temperature and the reaction was monitored by TLC. On completion the mixture was filtered. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel. The products were eluted with EtOAc (5–10%) in hexane.

4.3. Characterization data

The prepared compounds, methyl-(2*Z*)-2-(bromomethyl)-3-(phenyl)-propenoate (**2a**), methyl-(2*Z*)-2-(iodomethyl)-3-(phenyl)-propenoate (**3a**), methyl-(2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)-propenoate (**2c**), methyl-(2*Z*)-2-bromomethyl)-3-(4-nitrophenyl)-propenoate (**2d**), methyl-(2*Z*)-2-(bromomethyl)-3-(nonyl)-propenoate (**2e**), (2*E*)-2-(bromomethyl)-3-(phenyl)-propenenitrile (**2i**), (2*E*)-2-(iodomethyl)-3-(phenyl)-propenenitrile (**3i**), (2*E*)-2-(bromomethyl)-3-(3,4-dichlorophenyl)-propenenitrile (**2k**) and (2*E*)-3-(3,4-dichlorophenyl)-2-(iodophenyl)-poropenenitrile (**3k**) are known compounds.[3j,16]

The spectral and analytical data of the unknown compounds are given below.

4.3.1. Methyl-(2*Z*)-2-(bromomethyl)-3-(2-chlorophenyl)-propenoate (2b). Yellow oil; ν_{max} (KBr) 2952, 2363, 1722, 1630, 1437, 1266, 766 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.80 (1H, s), 7.66 (1H, d, J=8.0 Hz), 7.62 (1H, d, J=8.0 Hz), 7.40 (1H, t, J=8.0 Hz), 7.22 (1H, t, J=8.0 Hz), 4.14 (2H, s), 3.82 (3H, s); *m/z* (%) 292 ($M^{+\cdot}$, 1), 290 ($M^{+\cdot}$, 4)$^{\cdot}$ 288 ($M^{+\cdot}$, 3), 254 (M^+−Cl, 27), 253 (38), 252 (23), 209 (M^+−Br, 10), 174 (42), 115 (100). Anal. Calcd for $C_{11}H_{10}O_2ClBr$: C, 45.67%; H, 3.46%. Found: C, 45.49%; H, 3.41%.

4.3.2. Methyl-(2*Z*)-3-(2-chlorophenyl)-2-(iodomethyl)-propenoate (3b). Yellow oil; ν_{max} (KBr) 2926, 1720, 1466, 1436, 1290, 1237, 770 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.75 (1H, s), 7.68 (1H, d, J=8.0 Hz), 7.62 (1H, d, J=8.0 Hz), 7.42 (1H, t, J=8.0 Hz), 7.20 (1H, t, J=8.0 Hz), 4.12 (2H, s), 3.90 (3H, s); *m/z* (%) 211 ($M^{+\cdot}$−I, 2), 209 ($M^{+\cdot}$−I, 7), 191 (100), 174 (4), 159 (18). Anal. Calcd for $C_{11}H_{10}O_2ClI$: C, 39.28%; H, 2.97%. Found: C, 39.09%; H, 2.93%.

4.3.3. Methyl-(2*Z*)-3-(4-chlorophenyl)-2-(iodomethyl) propenoate (3c). Brown oil; ν_{max} (KBr) 2982, 1713, 1491, 1268, 839, 771 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.82 (1H, s), 7.52 (2H, d, J=8.0 Hz), 7.34 (2H, d, J=8.0 Hz), 4.20 (2H, s), 3.81 (3H, s); δ_C ($CDCl_3$, 300 MHz) 165.8, 141.6, 135.9, 133.4, 131.2, 130.2, 129.3, 59.9, 29.6; *m/z* (%) 211 ($M^{+\cdot}$−I, 15), 209 ($M^{+\cdot}$−I, 44), 174 (13), 111 (100). Anal. Calcd for $C_{11}H_{10}O_2ClI$: C, 39.28%; H, 2.97%. Found: C, 39.12%; H, 2.94%.

4.3.4. Methyl-(2*Z*)-2-(iodomethyl)-3-(4-nitrophenyl) propenoate (3d). Yellow solid, mp 91–92 °C; ν_{max} (KBr) 2998, 1736, 1562, 1473, 1254, 736 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.34 (2H, d, J=8.0 Hz), 7.76 (2H, d, J=8.0 Hz), 7.66 (1H, s), 4.20 (2H, s), 3.84 (3H, s); *m/z* (%) 220 ($M^{+\cdot}$-I, 29), 205 (26), 174 (73), 150 (67), 121 (100). Anal. Calcd for $C_{11}H_{10}NO_4I$: C, 38.04%; H, 2.88%. Found: C, 37.79%; H, 2.82%.

4.3.5. Methyl-(2*Z*)-2-(iodomethyl)-3-(nonyl)-propenoate (3e). Brown oil; ν_{max} (KBr) 2927, 2856, 1722, 1442, 1281, 771 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 6.82 (1H, t, J=7.0 Hz), 4.08 (2H, s), 3.78 (3H, s), 2.22–2.16 (2H, m), 1.60–1.42 (2H, m), 1.40–1.18 (br, 12H), 0.84 (3H, t, J=7.0 Hz); *m/z* (%) 352 (M^+, 4), 225 (M^+−I, 12), 165 (14), 127 (10), 98 (17), 81 (23). Anal. Calcd for $C_{14}H_{25}O_2I$: C, 47.72%; H, 7.10%. Found: C, 47.53%; H, 6.98%.

4.3.6. Methyl-(2*Z*)-2-(bromomethyl)-3-(2-phenethyl)-propenoate (2f). Yellow oil; ν_{max} (KBr) 3027, 2927, 2857, 1716, 1439, 1287, 749, 701 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.42–7.08 (5H, m), 6.68 (1H, t, J=7.0 Hz), 4.07 (2H, s), 3.82 (3H, s), 2.80 (2H, t, J=7.0 Hz), 2.55–2.47 (2H, m); *m/z* (%) 284 ($M^{+\cdot}$, 7) 282 ($M^{+\cdot}$, 7), 203 (M^+−Br, 13), 171 (20), 143 (16), 91 (100). Anal. Calcd for $C_{13}H_{15}O_2Br$: C, 55.12%; H, 5.30%. Found: C, 54.91%; H, 5.26%.

4.3.7. Methyl-(2*Z*)-2-(iodomethyl)-3-(2-phenethyl)-propenoate (3f). Brown oil; ν_{max} (KBr) 3024, 2926, 2852, 1717, 1437, 1280, 744, 704 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.40–7.02 (5H, m), 6.88 (1H, t, J=7.0 Hz), 4.03 (2H, s), 3.78 (3H, s), 2.82 (2H, t, J=7.0 Hz), 2.58–2.49 (2H, m); *m/z* (%) 203 (M^+−I, 18), 171 (23), 143 (19), 91 (100). Anal. Calcd for $C_{13}H_{15}O_2I$: C, 47.27%; H, 4.54%. Found: C, 47.22%; H, 4.51%.

4.3.8. Ethyl-(2*Z*)-2-(bromomethyl)-3-(4-chlorophenyl)-propenoate (2g). Yellow oil; ν_{max} (KBr) 2980, 1714, 1628, 1489, 1270, 770 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.80 (1H, s), 7.51 (2H, d, J=8.0 Hz), 7.42 (2H, d, J=8.0 Hz), 4.24 (2H, s), 4.21 (2H, q, J=7.0 Hz), 1.30 (3H, t, J=7.0 Hz); δ_C ($CDCl_3$, 300 MHz) 166.2, 141.4, 136.0, 133.1,

131.2, 130.1, 129.5, 61.8, 30.0, 14.5; *m/z* (%) 306 ($M^{+\cdot}$, 1), 304 ($M^{+\cdot}$,4), 302 ($M^{+\cdot}$, 3), 223 ($M^{+}-Br$, 37), 151 (50), 149 (38), 115 (100). Anal. Calcd for $C_{12}H_{12}O_2ClBr$: C, 63.55%; H, 3.96%. Found: C, 63.27%; H, 3.85%.

4.3.9. Ethyl-(2*Z*)-3-(4-chlorophenyl)-2-(iodomethyl)-propenoate (3g). Brown oil; ν_{max} (KBr) 2975, 1717, 1634, 1445, 1274, 837, 767 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.84 (1H, s), 7.54 (2H, d, J=8.0 Hz), 7.38 (2H, d, J=8.0 Hz), 4.22 (2H, s), 4.20 (2H, q, J=7.0 Hz), 1.25 (3H, t, J=7.0 Hz); *m/z* (%) 225 ($M^{+\cdot}-I$, 48), 223 ($M^{+\cdot}-I$, 48), 151 (46), 149 (29), 115 (100). Anal. Calcd for $C_{12}H_{12}O_2ClI$: C, 41.14%; H, 3.42%. Found: C, 40.88%; H, 3.39%.

4.3.10. Ethyl-(2*Z*)-2-(bromomethyl)-3-(4-methoxyphenyl)-propenoate (2h). Yellow oil; ν_{max} (KBr) 2932, 1704, 1623, 1457, 1236, 745 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.66 (1H, s), 7.42 (2H, d, J=8.0 Hz), 6.83 (2H, d, J=8.0 Hz), 4.28 (2H, s), 4.22 (2H, q, J=7.0 Hz), 3.80 (3H, s), 1.23 (3H, t, J=7.0 Hz); *m/z* (%) 300 ($M^{+\cdot}$, 6) 298 ($M^{+\cdot}$, 6), 219 ($M^{+}-Br$, 14), 189 (17), 160 (24), 135 (21), 91 (38). Anal. Calcd for $C_{13}H_{15}O_3Br$: C, 52.17%; H, 5.01%. Found: C, 51.82%; H, 4.95%.

4.3.11. Ethyl-(2*Z*)-2-(iodomethyl)-3-(4-methoxyphenyl)-propenoate (3h). Brown oil; ν_{max} (KBr) 2937, 1705, 1630, 1448, 1242, 750 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.68 (1H, s), 7.50 (2H, d, J=8.0 Hz), 6.98 (2H, d, J=8.0 Hz), 4.28 (2H, q, J=7.0 Hz), 4.24 (2H, s), 3.82 (3H, s), 1.22 (3H, s); *m/z* (%) 219 ($M^{+}-I$, 9), 189 (13), 160 (20), 135 (23), 91 (31). Anal. Calcd for $C_{13}H_{15}O_3I$: C, 45.08%; H, 4.33%. Found: C, 44.84%; H, 4.29%.

4.3.12. (2*E*)-2-(Bromomethyl)-3-(3-nitrophenyl)-propenenitrile (2j). White solid, mp 54–55 °C; ν_{max} (KBr) 2923, 2352, 1686, 1530, 1348, 1218, 772 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.45 (1H, s), 8.32 (1H, d, J=8.0 Hz), 8.28 (1H, d, J=8.0 Hz), 7.67 (1H, t, J=8.0 Hz), 7.22 (1H, s), 4.18 (2H,s); *m/z* (%) 268 ($M^{+\cdot}$, 3) 266 ($M^{+\cdot}$, 3), 187 ($M^{+}-Br$, 49), 149 (27), 141 (100), 115 (18). Anal. Calcd for $C_{10}H_7N_2O_2Br$: C, 44.94%; H, 2.62%. Found: C, 44.68%; H, 2.58%.

4.3.13. (2*E*)-2-(Iodomethyl)-3-(3-nitrophenyl)-propenenitrile (3j). Yellow solid, mp 120–121 °C; ν_{max} (KBr) 2925, 2354, 1686, 1534, 1348, 1218, 771 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.43 (1H, s), 8.28 (1H, d, J=8.0 Hz), 8.24 (1H, d, J=8.0 Hz), 7.66 (1H, t, J=8.0 Hz), 7.22 (1H, s), 4.21 (2H,s); δ_C ($CDCl_3$, 300 MHz) 143.3, 134.0, 133.7, 130.2, 125.4, 124.4, 121.5, 116.0, 115.1, 29.6; *m/z* (%) 187 ($M^{+}-I$, 56), 149 (24), 141 (100), 115 (17). Anal. Calcd for $C_{10}H_7N_2O_2I$: C, 38.21%; H, 2.22%. Found: C, 38.01%; H, 2.19%.

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Arylation of diversely substituted hydrazines by tri- and pentavalent organobismuth reagents

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Abstract—Various hydrazine derivatives were studied with respect to arylation by triarylbismuthane and triarylbismuth diacetate reagents with emphasis on scope and limitations. Among these reagents, a few contained bulky substituents in their aromatic rings. The applied substrates spanned a range from simple hydrazides to triply protected hydrazines and included a large number of intermediates of principal synthetic interest. In the case of mono- and disubstituted hydrazines the results demonstrate apparent advantages of pentavalent over trivalent reagents, exemplified by fast, highly chemoselective monoarylation of acylhydrazines at the terminal nitrogen. In contrast, trisubstituted hydrazines are more efficiently substituted by trivalent reagents. With these substrates, a strong influence of steric factors was occasionally observed, as reflected in lower yields and even complete reaction inhibition. The introduction of two different aromatic substituents into disubstituted hydrazines using step-by-step or one-pot procedures was accomplished.

1. Introduction

The problems associated with arylation of organic compounds have for a long time attracted many synthetic chemists and continue to do so. Along with such modification at carbon and oxygen, NH arylation is particularly challenging because it reveals new pathways to compounds of pharmaceutical and technical importance and has the potential to simplify their selective synthesis.

From the earlier days of copper catalysis, initiated by Ullmann,[1] great progress on NH arylation has been made. During the last decade, these efforts were crowned by prominent work by Buchwald and Hartwig based on application of palladium catalysis.[2] Even earlier, around 1980, another approach was developed by Barton and Finet,[3] who applied tri- and pentavalent organobismuth compounds, in the presence of Cu salts as catalysts, for this purpose. Trivalent bismuth reagents Ar_3Bi, triarylbismuthanes, are synthesized from the corresponding arylmagnesium halides and $BiCl_3$.[4] Triarylbismuth diacetates are the most common pentavalent bismuth reagents and are readily obtained from Ar_3Bi by oxidation using $NaBO_3$/AcOH.[4] Chan introduced a useful modification of Barton's method, involving employment of a promoter (Et_3N or pyridine) in work with amides.[5]

Hydrazine derivatives play important roles in the agrochemical and dye-stuff industries, as well as in a number of pharmaceuticals. Thus an increasing interest in arylsubstituted hydrazines can presently be recognized.[6]

For the synthesis of hydrazine derivatives a large number of specialized procedures have been developed.[7] More recently, a number of protected reagents have emerged and been applied to make such derivatives in a stepwise fashion.[8–11] After initial substitution, by alternating cleavages and substitutions, an ideal reagent of this type with three orthogonal protecting groups would allow any required hydrazine derivative to be formed. Protecting groups such as alkoxycarbonyl, arylsulfonyl, phthaloyl and triphenylphosphonium were exploited in these reagents, by use of which alkylation and acylation have been

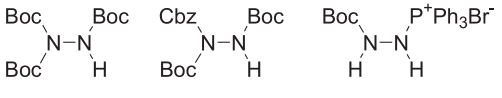

Figure 1. Protected precursors for substituted hydrazines employed in this work.

Keywords: Hydrazines; Arylation; Organobismuth reagents; Protecting groups; Chemoselectivity.
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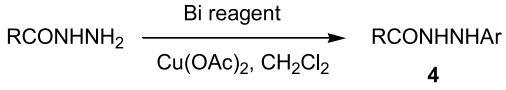
accomplished and optimized, resulting in hydrazine derivatives with up to four different substituents.

To insert aryl groups into hydrazines by the organobismuth approach is attractive because of its practical convenience and mild reaction conditions. Recently we used simple triarylbismuthanes to arylate precursors **1** and **2** (Fig. 1) in essentially quantitative yields.[12] Due to the oxidation of BocNHNHR by stoichiometric amount of Cu(II), these reagents were unsuitable but could be replaced by triarylbismuth diacetates. A number of model compounds BocNHNArR were isolated in 74–95% yields.[13] In view of the fact that pentavalent organobismuth reagents are themselves oxidizing agents,[14] these results might at first seem contradictory but can be understood in the light of the fact that only a catalytic amount (5%) of Cu(II) was required in these experiments. Obviously a more scrupulous study of the scope of these two types of bismuth reagents with respect to arylation of different kinds of substituted hydrazines is required.

As exemplified by Finet et al., steric hindrance occasionally plays an important role in arylation by organobismuth reagents.[15] Therefore, we decided to include a few bulky reagents in this study.

Whereas on one hand the idea behind the design of triprotected precursors like **1** and **2** was to provide a uniform site, at which substitution could be driven to completion under tolerable conditions, **3** on the other hand requires a high degree of regioselectivity to be practically useful. This has also been demonstrated in several instances, furnishing a considerable number of di- and trisubstituted hydrazines.[13] These compounds, together with **1** and **2** and a few simple monoacylhydrazines have been used as substrates in the present work.



Scheme 1. Selective arylation of monoacylhydrazines.

2. Results and discussion

2.1. Arylation of monoacylhydrazines

Successful arylation of monoacylhydrazines by arylhalides under Cu or Pd catalysis has been reported recently.[6a–c] Steric factors were found to determine the outcome of the reactions. The presence of a substituent in the *ortho*-position of the arylhalide resulted in the predominant formation of RCONHNHAr, while otherwise $RCOArNNH_2$ was obtained.[6a,b] All these procedures require heating and the reactions require hours to go to completion.

Sorenson recently succeeded in arylating difunctional substrates, containing amide and primary amine functions, using triarylbismuthanes.[16] Analogously, it should be possible and desirable to substitute $RCONHNH_2$ chemoselectively (Scheme 1). Up to now there are no examples of using organobismuth reagents for the substitution of monoacylhydrazines in the literature.

When we tried to arylate compounds $RCONHNH_2$ (RCO = Boc, Troc, Cbz, Ph) using the standard Chan procedure[5] (rt, $Ph_3Bi/Cu(OAc)_2/Et_3N/CH_2Cl_2$), our first efforts failed. The starting material decomposed with violent gas evolution. Considering the facile oxidation of hydrazides by copper compounds, known to take place under quantitative expulsion of nitrogen,[17] an alternative procedure was sought which required only a substoichiometric amount of copper salt.

Pentavalent organobismuth reagents $Ar_3Bi(OAc)_2$ are usually considered to be more reactive than trivalent ones and require only a catalytic amount of Cu salt. Their reactivity was explored as shown above in Table 1, in most cases with tri(*p*-tolyl)bismuth diacetate and $BocNHNH_2$ as model compounds. The reactions occur extremely rapidly at rt, producing a considerable amount of by-product, detected by TLC. As disubstituted hydrazines can readily be oxidized to the corresponding azo compounds and the ^1H NMR spectrum of crude **4a** revealed two singlets at 1.64 and 2.41 ppm, the by-product was identified as *p*-TolN=NBoc. When pure **4a** was exposed to $Cu(OAc)_2$ the same compound was formed as detected by TLC. An analogous

Table 1. Optimizing experiments with monoacylhydrazine and $Ar_3Bi(OAc)_2$[a]

Entry	Compound	RCO	Ar	$Cu(OAc)_2$, mol%	*t*, °C	Yield, %
1[b]	**4a**	Boc	*p*-Tol	5	rt	45
2	**4a**	Boc	*p*-Tol	5	−84	51
3	**4a**	Boc	*p*-Tol	2	−10	61
4	**4a**	Boc	*p*-Tol	2	−50	75
5	**4a**	Boc	*p*-Tol	20	−50	27
6	**4a**	Boc	*p*-Tol	2	−91	74
7[c]	**4a**	Boc	*p*-Tol	2	−60	91
8[c]	**4a**	Boc	*p*-Tol	2	rt	56
9[c]	**4b**	Boc	*o*-Tol	2	−60	80
10[c]	**4e**	Troc	*o*-Tol	2	−60	91
11[c]	**4c**	Ac	1-Np[d]	2	−60	72
12[c]	**4d**	Cbz	An[e]	2	−60	72

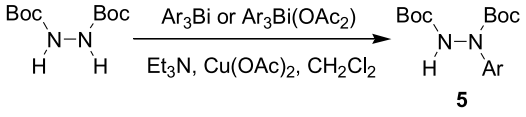
[a] Acylhydrazine (carbazate)/$Ar_3Bi(OAc)_2$ (1 equiv)/$Cu(OAc)_2$ (as indicated)/CH_2Cl_2.
[b] All $(p\text{-Tol})_3Bi(OAc)_2$ was added in one batch. In the other experiments, the solution of organobismuth reagent was added dropwise during 20–50 min. Experiments 5 and 7–12 were carried out under argon.
[c] 3% of BHT (2,6-di-*tert*-butyl-4-methyl-phenol; butylated hydroxytoluene) was added.
[d] Np = 1-Naphthyl.
[e] An = 4-Anisyl.

by-product was also isolated in the synthesis of **4d**, for which the structure *p*-$CH_3OC_6H_4N{=}NCOOCH_2Ph$ was confirmed by ^1H and ^{13}C NMR spectroscopy and elemental analysis. Reducing the temperature and amount of Cu gave somewhat better results (entries 2 and 4), but **4a** isolated by column chromatography still contained ~10% of azo compound. The situation changed drastically, when we added the antioxidant BHT (entry 7). Still, in entry 12, 14% of azo compound was isolated together with **4d**. All remaining arylation experiments went smoothly and only traces of azo compounds could be detected by TLC. The reactions were complete immediately after addition of the reagents and column chromatography furnished products in good to high yields, completely pure by TLC and NMR spectroscopy.

This is the first demonstration of mild, fast and highly selective monoarylation of $RCONHNH_2$ at the terminal nitrogen. Although the reasons are not understood, it seems that the combined effect of low temperature and addition of an antioxidant results in a useful decrease in substrate oxidation, allowing the intended reaction to take place. No difference in selectivity was noticed with the more bulky *o*-tolyl and 1-naphthyl bismuth reagents, in contrast to earlier findings involving methods quoted below.[6a,b]

2.2. Arylation of disubstituted hydrazines

Hydrazines with two electron-withdrawing groups can be smoothly arylated by organobismuth reagents in the presence of promoter Et_3N and $Cu(OAc)_2$. Symmetrical substrates, such as BocNHNHBoc, give monoarylated products (Scheme 2). Phenyl (**5a**) was introduced more efficiently when Ar_3Bi was used (2 h, 100%) instead of $Ar_3Bi(OAc)_2$ (4 h, 86%)[13] and we experienced no difficulties with the more bulky 1-naphthyl (**5b**) using Np_3Bi (3 h, 93%). Unsymmetrically substituted hydrazines (CbzNHNHBoc, CbzNHNHTs, CbzNHNHTroc) and Ar_3Bi yield mixtures of both possible monoaryl derivatives, as determined by NMR spectra. Reactions are complete in 0.5–4 h.



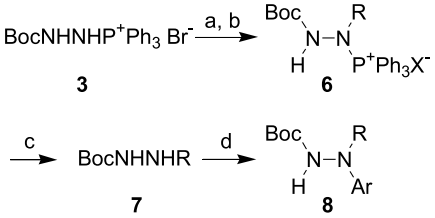
Scheme 2. Arylation of 1,2-di-Boc-hydrazine.

Substituted substrates with one electron-withdrawing and one electron-donating group are more challenging, due to regioselective arylation. Indeed such a reaction could be realized recently for a small set of substrates,[13] but this has now been expanded with further examples (**8f**, **8g**, **8h**, **8i**) as seen in Table 2. Compounds **7**, generated in situ from the phosphonium salts **6**, were obtained as illustrated in Scheme 3. Like acylhydrazines they cannot be arylated by Chan's method,[5] because of rapid oxidation. With only 1 equiv of $Ar_3Bi(OAc)_2$ and 5% of $Cu(OAc)_2$, however, clean transformation could be carried out in 5–10 min, furnishing products in good to high yields,[13] calculated over two steps from **6**. Table 2 also includes **9** and **10**, with Cbz and Ac instead of Boc groups. It should be noted that some more bulky substituents were successfully introduced in these experiments (**8c**, **8f**, **8i**), although the yield was significantly lower for the last compound, in which case the formation of a considerable amount of by-product, probably hydrazone, was also detected by TLC.

Table 2. Arylation of 1-acyl-2-alkylhydrazines **7**, prepared in situ from **6**, by $Ar_3Bi(OAc)_2$

Compound	Product	Yield,[a] %
8a	BocNHNBzlPh	95
8b	BocNHNBuPh	86
8c	BocNHNMeNp	87
8d	BocNHN($CH_2C{\equiv}CH$)(*p*-Tol)	93
8e	BocNHN(CH_2COOEt)(*p*-Tol)	74
8f	BocNHNMe(*o*-Tol)	86
8g	BocNHNBu(*p*-Tol)	89
8h	BocNHNBuAn	92
8i	BocNHNBu(2-MeO-4-MeC_6H_3)	48
9	CbzNHNMe(*p*-Tol)	82
10	AcNHNMe(Np)	80

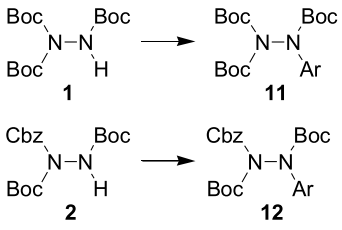
[a] Yield over two steps from **6**.



Scheme 3. Synthesis of compounds **8**. (a) BuLi, THF; (b) RX; (c) 1 M $NaOH/CH_2Cl_2$; (d) arylation with organobismuth compounds.

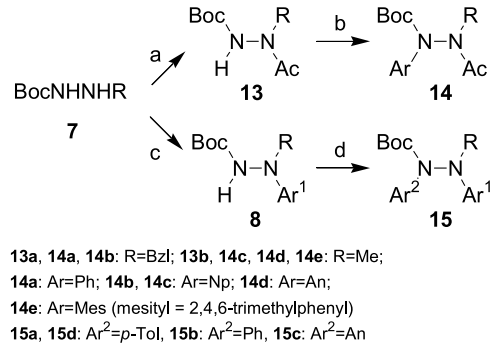
2.3. Arylation of trisubstituted hydrazines

This section deals with the arylation of the triprotected precursors **1** and **2** (Scheme 4) and the trisubstituted hydrazines **8** and **13** (Scheme 5) by organobismuth reagents. Since all substrates are BocNH-acids and electronic effects of substituents on the second nitrogen are expected to be of minor importance, their acidity should be quite similar. In related work with less reactive NH compounds an effect of their basicity has been invoked.[5]



11a, **12a**: Ar=Ph; **11b**, **12b**: Ar=*o*-Tol;
11c, **12c**: Ar=Np;
11d, **12d**: Ar=2-OMe-4-MeC_6H_3

Scheme 4. Arylation of precursors **1** and **2**.



Scheme 5. Aryl derivatives originating from precursor **3**. (a) Ac_2O; (b, d) arylation; (c) $Ar_3Bi(OAc)_2$, $Cu(OAc)_2$, CH_2Cl_2.

2.3.1. Precursors 1 and 2. Quantitative arylation of **1** and **2** by a few trivalent bismuth reagents was previously reported,[12] but in that context no examples involving sterically hindered aryl groups were presented and are therefore included in this work. *ortho*-Substituted arylating reagents have been observed occasionally to react poorly[15] and this tendency might be reinforced with these substrates, as they are quite bulky. Initially, we also wanted to find out whether pentavalent bismuth reagents offer some advantage over trivalent ones in these cases. Hence, **1** and **2** were reacted with $Ph_3Bi(OAc)_2$ to afford products **11a** and **12a** in 74 and 86% yields, respectively. The high reactivity of this reagent toward amino functions, that could be exploited above with mono- and disubstituted hydrazines, was not verified in these experiments, when much longer reaction times were required. Longer reaction times and lower yields provide evidence in favour of Ar_3Bi.

All new results related to the arylation of **1** and **2** are presented in Table 3. First we tried to introduce *o*-tolyl and 1-naphthyl substituents by the standard protocol at rt but only very little **11b** was obtained and neither **1** nor **2** reacted with Np_3Bi. Instead, naphthyl acetate was isolated by column chromatography from the reaction mixture (structure confirmed by NMR spectroscopy), indicating a gradual decomposition of the bismuth reagent.[15] By carrying out the experiments in refluxing CH_2Cl_2, however, both **1** and **2** could be brought to react and as shown the corresponding products (**11b**, **11c**, **12b** and **12c**) isolated in high yields, provided the decomposition of Ar_3Bi was compensated for by additional amounts of fresh reagents. Precursor **2** showed somewhat better reactivity than **1** in this context. Also, the bulky (2-MeO-4-$MeC_6H_3)_3Bi$ reagent reacted correspondingly and only the highly hindered Mes_3Bi failed to react completely, even at reflux.

Cleavage of one Boc group from **11c** by magnesium perchlorate in acetonitrile furnished **5b** in quantitative yield[18] with NMR spectra identical with those measured earlier in the direct synthesis of **5b** from BocNHNHBoc (Section 2.2).

2.3.2. Trisubstituted hydrazines with the general formula BocNHNAcR. With reference to the results in the preceding paragraph, the next step was to study two less hindered substrates, derived from precursor **3**. These compounds, **13a** (R=Bzl) and **13b** (R=Me) described previously, were obtained as outlined in Scheme 5[11] and the corresponding results are shown below in Table 4.

All transformations in this table were conducted at rt, in most cases without supplying additional amounts of reagents during the reaction. With compound **13a** as a substrate, using the corresponding tri- and pentavalent reagents, firstly phenylation was compared and again Ph_3Bi was found to be more efficient than $Ph_3Bi(OAc)_2$ as judged by reaction time and especially the yield.

Secondly, the compounds **13a** and **13b** were compared as substrates by reacting them with Np_3Bi. Although they only differ by one of the substituents on the not directly involved

Table 3. Arylation of trisubstituted reagents **1** and **2** by sterically hindered bismuth reagents

Compound	Arylating agent[a]	*t*, °C	Reaction time	Yield, %
11a	$Ph_3Bi(OAc)_2$	rt	5 days	74
12a	$Ph_3Bi(OAc)_2$	rt	32 h	86
11b	*o*-Tol_3Bi	rt	96 h	26
11b	*o*-Tol_3Bi	Reflux	72 h	100
12b	*o*-Tol_3Bi	Reflux	54 h	98
11c	Np_3Bi	rt	5 days	—
11c	Np_3Bi	Reflux	96 h	83
12c	Np_3Bi	Reflux	96 h	73
11d	(2-OMe-4-$MeC_6H_3)_3Bi$	Reflux	40 h	85
12d	(2-OMe-4-$MeC_6H_3)_3Bi$	Reflux	40 h	97
11e	Mes_3Bi	Reflux	3 days	—

[a] $Ar_3Bi(OAc)_2 \geq 1.2$ equiv/$Cu(OAc)_2 \geq 1.2$ equiv/$Et_3N \geq 1.2$ equiv/CH_2Cl_2; $Ar_3Bi \geq 1.5$ equiv/$Cu(OAc)_2 \geq 1.5$ equiv/$Et_3N \geq 1.5$ equiv/CH_2Cl_2.

Table 4. Arylation of trisubstituted hydrazines **13**

Starting material[a]	Arylating agent	Product	Reaction time, h	Yield, %
13a	Ph_3Bi	**14a**	9	93
13a	$Ph_3Bi(OAc)_2$	**14a**	12	73
13a	Np_3Bi	**14b**	46	51
13b	Np_3Bi	**14c**	14	100
13b	An_3Bi	**14d**	6	100
13b	Mes_3Bi	**14e**	20	56

[a] See Scheme 5.

Table 5. Arylation of trisubstituted hydrazines **8**

Starting material[a]	Arylating agent	Product	Reaction time, h	Yield, %
8a	$(p\text{-Tol})_3Bi$	**15a**	26	92
8e	Ph_3Bi	**15b**	44	80
8g	$(p\text{-An})_3Bi$	**15c**	45	96
8h	$(p\text{-Tol})_3Bi$	**15d**	46	100

[a] See Table 2.

nitrogens, the results indicate that the latter substrate provides significantly less hindrance for the approaching reagent. When **13b** was arylated by three different Ar_3Bi reagents with gradually increasing bulkiness from *p*-anisyl to mesityl, the experiments demonstrated a clear dependence of bismuthane reactivity upon steric factors. It is noteworthy that **14e** could be made in this way as Mes_3Bi did not react with **1** which underlines the effect of the substituents on the neighbouring nitrogen.

2.3.3. Trisubstituted hydrazines with the general formula BocNHNAr[1]R. The trisubstituted hydrazines **8**, described in Section 2.2, could be used as substrates in order to explore the synthesis of derivatives with two different aryl substituents by means of triarylbismuthanes. Considering the fact that such substituents on the second nitrogen can be quite bulky, it follows from above that they could impede the further reaction. A set of four compounds **8** was examined with respect to arylation by simple triarylbismuthanes and the related data is shown in Table 5. The reactions were monitored by TLC and they occasionally required small amounts of bismuthane in excess of 1.5 equiv to go to completion within one to two days, whereupon the products were purified by column chromatography to afford pure products in satisfactory yields. It should again be pointed out that argon had a negative effect on the reaction rates in these experiments. As a comparison, when **8a** was reacted with $p\text{-Tol}_3Bi$ under argon, the reaction was not complete after three days and several by-products were formed and the same observations were made in the case of **8e**.

Based on the data in Table 5 it is concluded that a phenyl ring as such on the neighbouring nitrogen does not block access of a simple triarylbismuthane to the reactive site but in a fifth experiment $(p\text{-Tol})_3Bi$ failed to react with **8i**. AM1 quantum chemical calculations on this compound (using Spartan Pro 1.08 software) afforded a Boc-*N*-*o*-Me*O* distance of 2.273 Å, which indicates that a strong hydrogen bonding is present. As a result the molecule is presumably locked in a rigid conformation that no longer allows reaction to take place.

Compound **15a** together with **15e** (R=*n*-Bu, Ar^1=Ph, Ar^2=*p*-Tol) was also obtained by a three-stage one-pot procedure **6**→**7**→**8**→**15** (Schemes 3 and 5). After cleavage of the phosphonium protecting group, exploiting the high reactivity of $Ar^1{}_3Bi(OAc)_2$ the substituent Ar^1 could be inserted in 10 min as described previously (monitored by TLC).[13] This was directly followed by reaction with $Ar^2{}_3Bi$ and auxiliary reagents ($Ar^2{}_3Bi/Et_3N/Cu(OAc)_2$ 1.5:1.5:1.5 equiv).[12] Compound **15a** was obtained in 85 and 69% overall yields, after final reaction for nearly 2 days at rt, alternatively 1.5 days in boiling dichloromethane. The analogous preparation, detailed in Section 4, furnished **15e** in 83% yield. The Ph_3PO initially formed was readily removed in the final chromatographic purification of the products.

3. Conclusions

Based on experiments with a large number of model hydrazine substrates, it appears that tri- and pentavalent organobismuth reagents complement each other with respect to arylation on nitrogen. As pentavalent reagents exhibit high chemoselectivity for amino over amide functions and require only a catalytic amount of copper, they are especially useful for monoacylated free and 2-alkyl substituted substrates which are sensitive, the former indeed hypersensitive, to oxidation. Arylation of carbazates is further improved by cooling and addition of antioxidant. Arylation of amidic NH in disubstituted RCONHNHCOR[1] or BocNH in trisubstituted hydrazines can be performed by both types of reagents. In most cases, trivalent reagents in the presence of a stoichiometric amount of Cu salt faster afforded the products. More bulky substituents, such as *o*-tolyl, 1-naphthyl and 2-methoxy-4-methylphenyl, were introduced into trisubstituted precursors **1** and **2** under standard conditions ($Ar_3Bi/Cu(OAc)_2/Et_3N$) except that refluxing dichloromethane was required. For another trisubstituted substrate, 1-acetyl-1-methyl-2-Boc-hydrazine, a dependence of the reactivity on the bulkiness of the reagent was demonstrated. A bulky substituent on the non-reacting nitrogen can also influence arylation reactivity. A few tetrasubstituted hydrazines with two different aryl groups were also obtained.

4. Experimental

4.1. General methods

All melting points were measured on a Gallenkamp melting point apparatus. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}). TLC spots were visualized under UV light or by alcoholic phosphomolybdic acid with subsequent heating (blue spots). Column chromatography was carried out on Merck Kieselgel (70–230 mesh). ^1H NMR were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz on a Bruker AC 200P spectrometer in $CDCl_3$ solution. Chemical shifts are given in ppm using TMS as reference and coupling constants in Hz. Chemical shifts of conformers are given in decreasing order of intensity and separated by slashes. Positive-ion mass spectra were recorded on an Ettan ESI-ToF electrospray time-of-flight mass spectrometer (Amersham Biosciences, Uppsala, Sweden) at capillary

exit voltages 80–150 V and capillary temperature 170 °C. Electrospray tuning mix (Agilent, USA) was used for calibration of the instrument. Samples were dissolved in HPLC grade acetonitrile or methanol (Sigma-Aldrich, Germany) and infused at 10–50 μL/min via ESI source using a syringe pump. $Cu(OAc)_2$ was dried at 90 °C in vacuo (1 mm Hg). All remaining reagents and solvents were used as supplied without prior purification.

4.2. Synthesis of organobismuth reagents

Typical preparations of Ar_3Bi and $Ar_3Bi(OAc)_2$ were described elsewhere.[4,15] Similar procedures were used for the synthesis tris(2-methoxy-4-methylphenyl)bismuthane and tris(2-methoxy-4-methylphenyl)bismuth diacetate.

4.2.1. Tris(2-methoxy-4-methylphenyl)bismuthane. 2.951 g were obtained in 93% crude yield (essentially pure by TLC and NMR), further crystallized from $CHCl_3$/EtOH in 54% yield (1.740 g). White shiny plates, which tend to darken on storage. mp 145–147 °C. IR (KBr): 1226 cm^{-1}; ^1H NMR: $\delta=2.13$ (s, 3H, CH_3), 3.71 (s, 3H, CH_3O), 6.9–7.3 (m, 3H, Ar); ^{13}C NMR: $\delta=20.6$ (CH_3), 55.8 (CH_3O), 109.8, 129.5, 132.9, 139.6, 142.9, 160.4 (Ar). Anal. calcd for $C_{24}H_{27}BiO_3$: C, 50.46; H, 4.75; found C, 50.34; H, 4.62.

4.2.2. Tris(2-methoxy-4-methylphenyl)bismuth diacetate. A crude product was obtained by evaporating most of acetic acid (reaction medium) and chloroform (extractive agent) in vacuo. It was then recrystallized from Et_2O–hexane in 52% yield, furnishing 863 mg of the acetic acid solvate, pure by TLC and NMR. Yellow crystals, mp 148–150 °C. The unsolvated product was obtained by dissolving in chloroform–ethanol mixture and evaporating the solvents in vacuo. IR (KBr): 1756, 1719, 1253 cm^{-1}; ^1H NMR: $\delta=$ 1.79 (s, 12H, CH_3CO and CH_3COOH), 2.37 (s, 9H, $CH_3C_6H_3$), 3.85 (s, 9H, CH_3O), 7.0–7.3 (m, 6H, Ar), 8.0–8.1 (m, 3H, Ar); ^{13}C NMR: $\delta=21.0$ ($CH_3C_6H_3$), 21.8 (CH_3CO), 56.3 (CH_3O), 112.8, 132.3, 132.6, 133.9, 150.9, 156.3, 175.9. Anal. calcd for $C_{28}H_{33}BiO_7\times2AcOH$ ($C_{32}H_{41}BiO_{11}$): C, 47.41; H, 5.10; found C, 46.87; H, 4.79.

4.3. Synthesis of 1-acyl-2-arylhydrazines (compounds 4)

4.3.1. 1-*tert*-Butoxycarbonyl-2-(*p*-tolyl)-hydrazine (4a). *tert*-Butyl carbazate (77 mg, 0.583 mmol) was dissolved in dichloromethane (2 mL) and BHT (3 mg, 0.03 equiv) was added to the solution. The mixture was cooled to −60 °C and $Cu(OAc)_2$ (2 mg, 0.02 equiv) was added. Under stirring, a solution of $(p\text{-Tol})_3Bi(OAc)_2$ (350 mg, 1 equiv) in dichloromethane (2 mL) was added dropwise during 30 min. The reaction was monitored by TLC (EtOAc–hexane 1:1 and 1:4) and the starting material was consumed just after the reagent was added. The reaction mixture was let to warm to the rt. 0.8 g of silica was added and the solvent evaporated in vacuo. The remaining material was placed on top of a short silica column and eluted first with EtOAc–hexane 1:20 to remove unpolar components, then with EtOAc–light petroleum 1:4 to isolate yellow solid **4a** in 91% yield, pure by TLC and NMR. Analytical sample was prepared by crystallization from hexane. White needles, mp 89.5–91 °C (lit. 85.5–86.5 °C), spectroscopic data identical to literature.[19]

4.3.2. 1-*tert*-Butoxycarbonyl-2-(*o*-tolyl)-hydrazine (4b). The mixtures EtOAc–hexane 1:20 and 1:3 were used for chromatography, furnishing the yellow solid (80%), pure by TLC and NMR. Analytical sample was prepared by crystallization from hexane/$CHCl_3$. Yellowish needles, mp 89–91 °C (lit. 77 °C), spectroscopic data identical to literature.[6b]

4.3.3. 1-Acetyl-2-(1-naphthyl)-hydrazine (4c). The mixture EtOH–$CHCl_3$ 1:7 was used to monitor the arylation. 0.8 g of silica was added to the reaction mixture and the solvent was evaporated in vacuo. The remaining material was placed on the top of a chromatography column (18× 1.5 cm) and eluted with EtOH–$CHCl_3$ 1:9. Product was obtained in 72% yield, pure by TLC and NMR. Analytical sample was prepared by crystallization from hexane/$CHCl_3$. Yellow solid, mp 137.5–139.5 °C, lit. 143 °C from ethanol.[20] IR (KBr): 3283, 3241, 1646 cm^{-1}; ^1H NMR: $\delta=$ 2.04/2.06 (s, 3H, CH_3), 6.4–6.9 (m, 2H, 2×NH), 7.2–7.9 (m, 7H, 1-Np); ^{13}C NMR: $\delta=20.9/19.0$ (CH_3), 106.2, 107.8, 119.4, 120.4, 121.5, 121.8, 125.5, 125.7, 125.9, 126.1, 126.3, 128.6, 128.9, 134.3, 142.6 (1-Np), 169.8 (CO, Boc).

4.3.4. 1-Benzyloxycarbonyl-2-(*p*-anisyl)-hydrazine (4d). $CbzNHNH_2$ was dissolved in 3 mL of CH_2Cl_2. Eluent mixtures EtOAc–hexane 1:5 and EtOAc–hexane 1:1 was used to elute azo compound (14%) and the bright yellow solid product (72%), both pure by TLC and NMR. Analytical samples of azo-compound was prepared by crystallization from hexane and very pure **4d** was obtained from hexane/$CHCl_3$.

$p\text{-}CH_3OC_6H_4N{=}NCOOCH_2Ph$, orange-red crystals, mp 47–48 °C. IR (KBr): 1730, 1232, 1137 cm^{-1}; ^1H NMR: $\delta=3.90$ (s, 3H, CH_3O), 5.46 (s, 2H, CH_2), 6.99 (d, $J_{HH}=$ 9 Hz, 2H, C_6H_4), 7.3–7.5 (m, 5H, Ph), 7.96 (d, $J_{HH}=9$ Hz, 2H, C_6H_4); ^{13}C NMR: $\delta=55.8$ (CH_3O), 69.7 (CH_2), 114.6, 126.5, 128.7, 128.8, 134.9, 146.3, 162.2 (Ar), 164.8 (CO, Cbz). Anal. calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36; found C, 66.82; H, 5.26; N, 10.03.

Compound **4d**, slightly yellowish plates, mp 110–111 °C. IR (KBr): 3325, 3225, 1703, 1232, 1163 cm^{-1}; ^1H NMR: $\delta=$ 3.73 (s, 3H, CH_3O), 5.13 (s, 2H, CH_2), 5.66 (br s, 1H, ArNH), 6.7–7.3 (m, together 10H, Ar and BocNH); ^{13}C NMR: $\delta=55.7$ (CH_3O), 67.5 (CH_2), 114.8, 114.9, 128.2, 128.4, 128.6, 136.0, 141.8, 154.7 (Ar), 157.2 (CO, Cbz). Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; found C, 66.18; H, 5.87; N, 10.25.

4.3.5. 1-(2,2,2-Trichloroethoxycarbonyl)-2-(*o*-tolyl)-hydrazine (4e). The mixtures EtOAc–hexane 1:20 and 1:3 were used for chromatography, furnishing the yellow solid (91%), pure by TLC and NMR. Analytical sample was prepared by crystallization from hexane/$CHCl_3$. White needles, mp 104.5–106 °C. IR (KBr): 3356, 3277, 1719, 1237, 1169 cm^{-1}; ^1H NMR: $\delta=2.16$ (s, 3H, $CH_3C_6H_4$), 4.77 (s, 2H, CH_2), 5.74 (s, 1H, ArNH), 6.8–6.9 (m, 2H, C_6H_4), 6.95 (br s, 1H, BocNH), 7.0–7.2 (s, 2H, C_6H_4); ^{13}C

NMR: δ=16.8 ($CH_3C_6H_4$), 74.9 (CH_2), 95.1 (CCl_3), 111.8, 121.1, 122.7, 127.0, 130.6, 145.1 (Ar), 155.3 (CO, Troc). Anal. calcd for $C_{10}H_{11}Cl_3N_2O_2$: C, 40.36; H, 3.73; N, 9.41; found C, 40.56; H, 3.65; N, 9.34.

4.4. Synthesis of compounds 5 RCONArNHCOR

4.4.1. 1,2-Bis(*tert*-butoxycarbonyl)-1-phenylhydrazine (5a).[13] To the solution of BocNHNHBoc (69.7 mg, 0.300 mmol) in CH_2Cl_2 (2 mL) Et_3N (84 μL, 2 equiv), $Cu(OAc)_2$ (14 mg, 0.25 equiv) were added, followed by $Ph_3Bi(OAc)_2$ (335 mg, 2 equiv). The reaction was monitored by TLC, using EtOAc–light petroleum 1:5 as eluent. After 30 min 0.5 equiv $Ph_3Bi(OAc)_2$ and 1 equiv of Et_3N were added to accelerate the process. Most of the starting material reacted in 3 h and some minimal traces were detected even after 4 h. Then 0.8 g of silica was added to the reaction mixture and the solvent was evaporated in vacuo. The remaining product was placed on the top of chromatography column (18×1.5 cm). For purification the mixture EtOAc–light petroleum 1:5 was used as eluent, yielding 79.2 mg (86%) of **5a** as yellowish solid, pure by TLC and NMR. The ^1H and ^{13}C NMR spectra were identical with previously published data.[12]

4.4.2. 1,2-Bis(*tert*-butoxycarbonyl)-1-(1-naphthyl)hydrazine (5b). To the solution of BocNHNHBoc (80 mg, 0.344 mmol) in CH_2Cl_2 (1 mL) Et_3N (72 μL, 1.5 equiv), $Cu(OAc)_2$ (94 mg, 1.5 equiv) were added, followed by Np_3Bi (305 mg, 1.5 equiv). The reaction was monitored by TLC, using EtOAc–light petroleum 1:3 as eluent. Most of the starting material reacted in 2 h and the reaction was complete in 3 h. Then 0.8 g of silica was added to the reaction mixture and the solvent was evaporated in vacuo. The remaining product was placed on the top of short chromatography column. At first EtOAc–light petroleum 1:20 was used to elute most of unpolar components. The elution was continued using mixture EtOAc–light petroleum 1:4, yielding 114 mg (93%) of 1,2-bis(*tert*-butoxycarbonyl)-1-(1-naphthyl)hydrazine, pure by TLC and NMR. Analytical sample was obtained by crystallization from hexane–$CHCl_3$, mp 142.5–143.5 °C. IR (KBr): 3288, 1746, 1688, 1247, 1153 cm^{-1}; ^1H NMR: δ=1.33, 1.46 (two s overlapped, 18H, 2×Boc), 7.2–8.0 (m, 7H, 1-Np); ^{13}C NMR: δ=28.1, 28.3 (two s overlapped, 2×Boc), 81.4, 81.9 (C_q), 123.0, 125.5, 126.0, 126.4, 128.2, 130.3, 134.4, 138.8 (1-Np), 154.8, 155.5 (CO, Boc). Anal. calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82; found C, 66.97; H, 7.34; N, 7.71.

4.5. Synthesis of 1-*tert*-butoxycarbonyl-2-alkyl-2-arylhydrazines (compounds 8)

Substances **8a**–**8e**, **9** and **10** were synthesized before.[13] Compounds **8f**–**8i** were prepared using the same procedure, pure by TLC and NMR.

4.5.1. 1-(*tert*-Butoxycarbonyl)-2-methyl-2-(*o*-tolyl)-hydrazine (8f). Slightly yellowish crystals, mp 49.5–50.5 °C (from hexane). IR (KBr): 3225, 1709, 1274, 1179 cm^{-1}; ^1H NMR: δ=1.42 (s, 9H, Boc), 2.32 (s, 3H, $CH_3C_6H_4$), 3.04 (CH_3N), 6.17 (s, 1H, NH), 6.9–7.2 (m, 4H, C_6H_4); ^{13}C NMR: δ=18.7 ($CH_3C_6H_4$), 28.4 (CH_3, Boc), 43.0 (CH_3N), 80.4 (C_q), 117.8, 123.7, 126.1, 131.4, 131.8, 149.1 (C_6H_4), 154.7 (CO, Boc). Anal. calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; found C, 66.10; H, 8.55; N, 11.80.

4.5.2. 1-(*tert*-Butoxycarbonyl)-2-(*n*-butyl)-2-(*p*-tolyl)-hydrazine (8g). Slightly yellowish crystals, mp 41–42 °C (from hexane). IR (film): 3298, 1704, 1247, 1163 cm^{-1}; ^1H NMR: δ=0.95 (t, 3H, J_{HH}=7 Hz, CH_3 of *n*-Bu), 1.2–1.7 (overlapped s and m, together 14H, $CH_2CH_2CH_2CH_3$ and Boc), 2.25 (s, 3H, $CH_3C_6H_4$), 3.40 (br m, 2H, $CH_2CH_2CH_2CH_3$), 6.32/6.09 (br s, 1H, NH), 6.73 (d, J_{HH}=8.4 Hz, 2H, C_6H_4), 7.04 (d, J_{HH}=8.4 Hz, 2H, C_6H_4); ^{13}C NMR: δ=14.0 (CH_3 of *n*-Bu), 20.3 (overlapped $CH_3CH_2CH_2CH_2$ and $CH_3C_6H_4$), 28.4 (CH_3, Boc), 28.9 ($CH_3CH_2CH_2CH_2$), 52.7 (CH_2N), 80.7 (C_q), 113.2, 128.4, 129.6, 147.4 (C_6H_4), 155.1 (CO, Boc). Anal. calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06; found C, 69.00; H, 9.45; N, 9.95.

4.5.3. 1-(*tert*-Butoxycarbonyl)-2-(*n*-butyl)-2-(*p*-anisyl)-hydrazine (8h). Colourless viscous oil. IR (film): 3298, 1714, 1242, 1163 cm^{-1}; ^1H NMR: δ=0.94 (t, J_{HH}=7.2 Hz, 3H, CH_3 of *n*-Bu), 1.3–1.6 (overlapped s and m, together 14H, $CH_2CH_2CH_2CH_3$ and Boc), 3.34 (m, 2H, CH_2N), 3.72 (s, 3H, CH_3O), 6.50/6.36 (br s, 1H, NH), 6.79 (s, 4H, C_6H_4); ^{13}C NMR: δ=14.0 (CH_3 of *n*-Bu), 20.3 ($CH_3CH_2CH_2CH_2$), 28.4 (CH_3, Boc), 29.0 ($CH_3CH_2CH_2CH_2$), 53.1 (CH_2N), 55.7 (CH_3O), 80.5 (C_q), 114.6, 115.0, 144.1, 153.5 (C_6H_4), 155.2 (CO, Boc). Anal. calcd for $C_{16}H_{26}N_2O_3$: C, 66.20; H, 9.15; N, 9.08; found C, 62.00; H, 9.18; N, 8.98.

4.5.4. 1-(*tert*-Butoxycarbonyl)-2-(*n*-butyl)-2-(2-methoxy-4-methyl)-hydrazine (8i). Colourless viscous oil. IR (film): 3293, 1698, 1242, 1163 cm^{-1}; ^1H NMR: δ=0.95 (t, 3H, J_{HH}=6.8 Hz, CH_3 of *n*-Bu), 1.3–1.6 (overlapped s and m, together 14H, $CH_2CH_2CH_2CH_3$ and Boc), 2.29 (s, 3H, $CH_3C_6H_3$), 3.28 (t, J_{HH}=7.2 Hz, 2H, CH_2N), 3.84 (s, 3H, CH_3O), 6.7–7.2 (overlapped br s and m, together 4H, NH and C_6H_3); ^{13}C NMR: δ=14.0 (CH_3 of *n*-Bu), 20.2 ($CH_3C_6H_3$), 20.6 ($CH_3CH_2CH_2CH_2$), 28.4 (CH_3, Boc), 29.8 ($CH_3CH_2CH_2CH_2$), 55.6 (CH_2N), 55.8 (CH_3O), 79.8 (C_q), 112.3, 123.8, 125.1, 130.1, 139.0, 151.5 (C_6H_3), 155.8 (CO, Boc). Anal. calcd for $C_{17}H_{28}N_2O_3$: C, 65.28; H, 8.90; N, 9.52; found C, 65.29; H, 8.94; N, 9.30.

4.6. Synthesis of 1,1,2-tris(*tert*-butoxycarbonyl)-2-arylhydrazines (11) and 1,2-bis(*tert*-butoxycarbonyl)-1-benzyloxycarbonyl-2-arylhydrazines (12)

4.6.1. 1,1,2-Tris(*tert*-butoxycarbonyl)-2-phenylhydrazine (11a) and 1,2-bis(*tert*-butoxycarbonyl)-1-(benzoxycarbonyl)-2-phenylhydrazine (12a). Compounds **11a** and **12a** were synthesized analogously with preparation of 1,2-bis(*tert*-butoxycarbonyl)-1-phenylhydrazine (**5a**) as described above (Section 4.4.1). Products were pure by TLC and NMR spectra were fully consistent with experimental data published previously.[12]

In the synthesis of **11a**, 0.7 equiv of each reagent ($Ph_3Bi(OAc)_2$, Et_3N and $Cu(OAc)_2$) were added after 24 h in order to bring the reaction to completion (48 h).

4.6.2. 1,1,2-Tris(*tert*-Butoxycarbonyl)-2-(*o*-tolyl)hydrazine (11b). To the solution of BocNHNHBoc (116 mg, 0.349 mmol) in CH_2Cl_2 (1.5 mL) Et_3N (73 μL, 1.5 equiv), $Cu(OAc)_2$ (95 mg, 1.5 equiv) were added, followed by $(o\text{-Tol})_3Bi$ (252 mg, 1.5 equiv). The resulting mixture was heated under reflux (~45 °C). The reaction was monitored by TLC, using EtOAc–light petroleum 1:5 as eluent and EtOAc–light petroleum 1:30 was used to monitor the consumption of $(o\text{-Tol})_3Bi$. In order to accelerate the reaction and due to the disappearance of bismuth compound, during the 72 h additional amounts of reagents were added (in all 4.5 equiv of Et_3N, 1.5 equiv of $(o\text{-Tol})_3Bi$ and 1.7 equiv of $Cu(OAc)_2$). Then 0.8 g of silica was added to the reaction mixture and the solvent was evaporated in vacuo. The remaining product was placed on the top of short chromatography column. At first EtOAc–light petroleum 1:20 was used to elute most of non-polar components. The elution was continued using mixture EtOAc–light petroleum 1:7, yielding 150 mg (100%) of 1,1,2-tris(*tert*-butoxycarbonyl)-1-(*o*-tolyl)hydrazine as colourless viscous oil, pure by TLC. IR (film): 1798, 1761, 1730, 1253, 1142 cm^{-1}; ^1H NMR: δ=1.54/1.52/1.44 (s, 27H, Boc), 2.35/2.40 (s, 3H, $CH_3C_6H_4$), 7.1–7.5 (m, 4H, C_6H_4); ^{13}C NMR: δ=18.8 ($CH_3C_6H_4$), 28.1/28.2 (Boc), 81.7/82.0, 83.9/83.8 (C_q), 124.6, 125.2, 126.2, 127.1, 130.7, 130.9, 135.7, 135.8, 139.5, 140.2 (C_6H_4), 151.2/151.3, 152.0/152.5 (CO, Boc). Anal. calcd for $C_{23}H_{32}N_2O_3$: C, 62.54; H, 8.11; N, 6.63; found C, 62.29; H, 8.15; N, 6.21.

4.6.3. 1,2-Bis(*tert*-butoxycarbonyl)-1-(benzyloxycarbonyl)-2-(*o*-tolyl)hydrazine (12b). Compound **12b** was prepared analogous to **11b**. During the 54 h of reaction, additional amounts of reagents were added (in all 2.5 equiv of Et_3N, 0.2 equiv of $(o\text{-Tol})_3Bi$ and 0.2 equiv of $Cu(OAc)_2$). The chromatography was carried out the same way as above, only using EtOAc–light petroleum 1:5 to elute the product in 98% as colourless viscous oil, pure by TLC. IR (film): 1803, 1767, 1730, 1253, 1153 cm^{-1}; ^1H NMR: δ=1.28/1.27, 1.40/1.38 (s, 18H, Boc), 2.12/2.13 (s, 3H, $CH_3C_6H_4$), 5.2–5.3 (m, 2H, CH_2), 7.0–7.3 (m, 9H, Ph and C_6H_4); ^{13}C NMR: δ=18.5 ($CH_3C_6H_4$), 27.98/28.03/28.10 (Boc), 69.1/69.2 (CH_2), 82.0/82.3 (C_q), 84.5/84.4 (C_q), 124.6, 125.1, 126.2, 126.3, 127.3, 128.28, 128.34, 128.5, 130.8, 131.0, 135.1, 135.9, 136.1, 139.2, 139.9 (Ar), 150.7, 151.6, 152.5/152.7 (CO, Boc and Cbz). Anal. calcd for $C_{26}H_{34}N_2O_7$: C, 65.77; H, 7.07; N, 6.14; found C, 65.79; H, 7.19; N, 5.87.

4.6.4. 1,1,2-Tris(*tert*-butoxycarbonyl)-2-(1-naphthyl)-hydrazine (11c). Compound **11c** was prepared analogous to **11b**. During the 96 h of reaction, additional amounts of reagents were added (in all 3.5 equiv of Et_3N, 1.4 equiv of Np_3Bi and 0.4 equiv of $Cu(OAc)_2$). The product was obtained in 83% as slightly yellow viscous oil, pure by TLC. IR (film): 1798, 1761, 1730, 1247, 1153 cm^{-1}; ^1H NMR: δ=1.27, 1.54/1.57 (s, 27H, Boc), 7.4–7.9 (m, 7H, 1-Np); ^{13}C NMR: δ=28.1/27.9/28.2 (Boc), 82.1, 84.1 (C_q), 122.5, 123.3, 125.1, 125.3, 125.5, 125.8, 125.9, 127.7, 127.90, 127.95, 128.4, 130.1, 130.4, 134.1, 134.3, 138.1, 138.6 (1-Np), 151.43/151.39, 152.9/153.0 (CO, Boc); HRESIMS *m/z* 481.2332 $[M+Na]^+$; calcd for $C_{25}H_{34}N_2NaO_6$ 481.2315.

4.6.5. 1,2-Bis(*tert*-butoxycarbonyl)-1-(benzyloxycarbonyl)-2-(1-naphthyl)hydrazine (12c). Compound **12c** was prepared analogously with **11b**. During the 96 h of reaction, additional amounts of reagents were added (in all 2.5 equiv of Et_3N, 1.5 equiv of Np_3Bi and 0.9 equiv of $Cu(OAc)_2$). The product was obtained in 73% as slightly yellow viscous oil, pure by TLC. IR (film): 1803, 1767, 1730, 1247, 1153 cm^{-1}; ^1H NMR: δ=1.24, 1.46/1.54 (s, 18H, Boc), 5.1–5.3 (m, 2H, CH_2), 7.2–7.8 (m, 12H, 1-Np and Ph); ^{13}C NMR: δ=28.0/27.8/28.1 (Boc), 69.2/69.3 (CH_2), 82.4, 84.6/84.7 (C_q), 122.6, 123.4, 124.8, 125.2, 125.3, 125.4, 125.8, 125.9, 126.0, 127.7, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7, 130.1, 130.3, 134.1, 134.3, 135.0, 137.8, 138.2 (1-Np and Ph), 151.0/150.9, 152.8/152.7 (CO, Boc and Cbz). Anal. calcd for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69; found C, 68.57; H, 6.44; N, 5.40.

4.6.6. 1,1,2-Tris(*tert*-butoxycarbonyl)-2-(2-methoxy-4-methylphenyl)hydrazine (11d). Compound **11d** was prepared analogously with **11b**. The reaction was monitored by TLC, using toluene–EtOAc 4:1 as eluent. For the isolation of product, at first hexane–$CHCl_3$ 1:2 was used to elute most of non-polar components. The elution was continued using mixture EtOAc–light petroleum 1:4, yielding 118 mg (85%) of **11d** as colourless viscous oil, pure by TLC. The chromatography also afforded 27 mg of **11d**, slightly contaminated by another component probably due to the partial Boc group removal. ^1H NMR: δ=1.52/1.48 (br s, 27H, Boc), 2.25/2.29/2.27 (s, 3H, $CH_3C_6H_3$), 3.76/3.78 (s, 3H, CH_3O), 6.7–7.2 (m, 3H, C_6H_3). ^{13}C NMR: δ=20.4 ($CH_3C_6H_4$), 28.0/28.2 (Boc), 55.8 (br s, CH_3O), 81.4, 83.1 (C_q), 111.4, 112.6, 123.4, 127.1, 127.9, 128.2, 129.3 (C_6H_3), 151.0, 152.5 (CO, Boc). HRESIMS *m/z* 475.2454 $[M+Na]^+$; calcd for $C_{23}H_{36}N_2NaO_7$ 475.2420.

4.6.7. 1,2-Bis(*tert*-butoxycarbonyl)-1-(benzyloxycarbonyl)-2-(2-methoxy-4-methylphenyl)hydrazine (12d). Compound **12d** was prepared analogously with **11b**. The reaction was monitored by TLC, using EtOAc–hexane 1:4 as eluent. For the isolation of product, at first hexane–$CHCl_3$ 1:2 was used to elute most of non-polar components. The elution was continued using mixture EtOAc–light petroleum 1:3, yielding 97% of **12d** as colourless viscous oil, pure by TLC. IR (film): 1798, 1767, 1724, 1253, 1158 cm^{-1}; ^1H NMR: δ=1.40, 1.51 (s, 18H, Boc), 2.21/2.29/2.27 (s, 3H, $CH_3C_6H_3$), 3.63/3.57/3.78/3.81 (s, 3H, CH_3O), 5.1–5.4 (m, 2H, CH_2), 6.6–7.4 (m, 8H, Ph and C_6H_3); ^{13}C NMR: δ=20.4 ($CH_3C_6H_4$), 27.97, 28.04 (overlapped s, Boc), 55.7/55.2 (CH_2), 68.7 (CH_3O), 81.7, 83.7 (C_q), 112.4, 127.1, 128.4, 129.3, 135.4 (C_6H_3), 150.5, 152.5 (CO, Boc, Cbz); HRESIMS *m/z* 509.2243 $[M+Na]^+$; calcd for $C_{26}H_{34}N_2NaO_7$ 509.2264.

4.6.8. Selective Boc-cleavage from 1,1,2-tris(*tert*-butoxycarbonyl)-2-(1-naphthyl)hydrazine (11c).[18] Compound **11c** (77 mg, 0.168 mmol) was dissolved in acetonitrile (1 mL) and the solution was rapidly heated to 50 °C under argon and stirring. $Mg(ClO_4)_2$ (13 mg, 0.35 equiv) was added and the reaction was monitored by TLC (EtOAc–hexane 1:8). Almost all starting material was consumed within 10 min when 0.2 equiv of $Mg(ClO_4)_2$ were added to complete the reaction. After 30 min the reaction was quenched with 0.2 M citric acid (3 mL), brine (2 mL) and

ethyl ether (15 mL). The aq. phase was extracted with ethyl ether (3×10 mL), the combined extracts washed with brine to neutral (4×3 mL) and dried (Na_2SO_4). After evaporation in vacuo, a product was obtained in quantitative yield with data in agreement with those of **5b** from 1,2-bis(*tert*-butoxycarbonyl)hydrazine.

4.7. Synthesis of 1-(*tert*-butoxycarbonyl)-1-aryl-2-acetyl-2-alkylhydrazines (14)

1-(*tert*-Butoxycarbonyl)-2-acetyl-2-benzylhydrazine (**13a**) and 1-(*tert*-butoxycarbonyl)-2-acetyl-2-methylhydrazine (**13b**) were prepared as described elsewhere.[11]

4.7.1. 1-(*tert*-Butoxycarbonyl)-1-phenyl-2-acetyl-2-benzylhydrazine (14a). The synthesis was carried out using 1.5 equiv of Ph_3Bi or 1.2 equiv of $Ph_3Bi(OAc)_2$ as arylating reagent (in analogy with procedures detailed in Sections 4.4.2 or 4.4.1). The reaction was monitored by TLC, using EtOAc–hexane 1:4 as eluent. Mixtures 1:20 and 1:4 were used to isolate product by short column chromatography, furnishing 93% and 73% of **14a** depending on use of either Ph_3Bi or $Ph_3Bi(OAc)_2$. Product was obtained as colourless viscous oil, pure by TLC. IR (film): 1719, 1678, 1253, 1153 cm^{-1}; ^1H NMR: $\delta=1.25$ (s, 9H, Boc), 2.16 (s, 3H, CH_3CO), 4.09 (d, 1H, CH_2, $J=14$ Hz), 5.14 (d, 1H, CH_2, $J=14$ Hz), 7.2–7.4 (m, 10H, Ph); ^{13}C NMR: $\delta=20.5$ (CH_3CO), 27.9 (Boc), 49.9 (CH_2), 82.9 (C_q), 121.8, 125.3, 127.8, 128.3, 128.9, 130.4, 135.6, 139.6 (Ph), 152.3 (CO, Boc), 173.2 (CH_3CO). Anal. calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23; found C, 70.60; H, 7.17; N, 8.27.

4.7.2. 1-(*tert*-Butoxycarbonyl)-1-(1-naphthyl)-2-acetyl-2-benzylhydrazine (14b). Compound **14b** was synthesized analogously with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:4 as eluent. During the process, 0.2 equiv of each reagent was added to accelerate the reaction. Mixtures EtOAc–hexane 1:20 and 1:3 were used to isolate product by short column chromatography, furnishing **14b** as yellowish viscous oil in 51% yield, pure by TLC. IR (film): 1719, 1678, 1258, 1158 cm^{-1}; ^1H NMR: $\delta=1.28$/1.20/1.26/1.46/1.22 (overlapped s, 9H, Boc), 2.44/2.00/2.19/2.22 (s, 3H, CH_3CO), 4.6–5.3 (m, 2H, CH_2), 7.0–7.9 (m, 12H, Ph and 1-Np). ^{13}C NMR: $\delta=20.8$/22.0 (CH_3CO), 27.9/28.2/29.7 (Boc), 50.9 (CH_2), 82.8/81.8 (C_q), 122.4, 123.6, 125.3, 125.9, 126.2, 127.2, 127.8, 128.3, 128.5, 128.7, 129.3, 129.8, 134.4, 136.4 (Ph and 1-naphthyl), 153.0 (CO, Boc), 173.0 (CH_3CO). Anal. calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17; found C, 73.62; H, 6.66; N, 6.86.

4.7.3. 1-(*tert*-Butoxycarbonyl)-1-(1-naphthyl)-2-acetyl-2-methylhydrazine (14c). Compound **14c** was synthesized analogously with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:1 and 1:4 as eluent. Mixtures EtOAc–hexane 1:20 and 1:1 were used to isolate product by short column chromatography, furnishing **14c** as light-brown viscous oil in quantitative yield, pure by TLC. It solidified while standing in refrigerator and was recrystallized from hexane, giving yellowish microcrystalline product, mp 107–108.5 °C. IR (KBr): 1719, 1672, 1237, 1158 cm^{-1}; ^1H NMR: $\delta=1.27$/1.54 (br s, 9H, Boc), 2.36/2.06/2.16 (s, 3H, CH_3CO), 3.19/3.33/3.30 (s, 3H, CH_3N), 7.4–8.0 (m, 7H, 1-Np); ^{13}C NMR: $\delta=20.7$/21.9 (CH_3CO), 28.1/28.3 (Boc), 82.9/81.8 (C_q), 122.9, 123.0, 124.8, 125.5, 125.9, 126.2, 126.5, 128.3, 128.7, 128.8, 129.8, 134.4, 137.0 (1-Np). HRESIMS *m/z* 315.1726 $[M+H]^+$; calcd for $C_{18}H_{23}N_2O_3$ 315.1709.

4.7.4. 1-(*tert*-Butoxycarbonyl)-1-(*p*-anisyl)-2-acetyl-2-methylhydrazine (14d). Compound **14d** was synthesized analogously with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:2 as eluent. Mixtures EtOAc–hexane 1:20 and 1:2 were used to isolate product by short column chromatography, furnishing **14d** as slightly yellow viscous oil in quantitative yield, pure by TLC. It solidified on standing for several months in the refrigerator, mp 67.5–69.5 °C, but resisted further crystallization. IR (KBr): 1709, 1672, 1252, 1163 cm^{-1}; ^1H NMR: $\delta=1.53$ (s, 9H, Boc), 2.10 (s, 3H, CH_3CO), 3.13 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 6.89 (perturbed d, $J_{HH}=9$ Hz, 2H, C_6H_4), 7.32 (perturbed d, $J_{HH}=9$ Hz, 2H, C_6H_4); ^{13}C NMR: $\delta=20.2$ (CH_3CO), 28.3 (Boc), 34.0 (CH_3N), 55.5 (CH_3O), 82.9 (C_q), 114.3, 123.2, 133.2, 152.5 (C_6H_4), 157.5 (CO, Boc), 173.4 (CH_3CO). HRESIMS *m/z* 317.1497 $[M+Na]^+$; calcd for $C_{15}H_{22}N_2NaO_4$ 317.1477.

4.7.5. 1-(*tert*-Butoxycarbonyl)-1-(2,4,6-trimethylphenyl)-2-acetyl-2-methylhydrazine (14e). Compound **14e** was synthesized analogously with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:1 as eluent. Mixtures EtOAc–hexane 1:8 and 1:1 were used to isolate product by short column chromatography, furnishing **14d** as colourless oil in 56% yield, pure by TLC. It solidified on standing in refrigerator and was recrystallized from hexane, giving white crystals, mp 88–90.5 °C. IR (KBr): 1719, 1672, 1247, 1163 cm^{-1}; ^1H NMR: $\delta=1.54$/1.42/1.40/1.50 (s, 9H, Boc), 2.1–2.3 (overlapped m, together 12H, CH_3CO and $(CH_3)_3C_6H_2$), 2.92/2.91/3.05/3.08 (s, 3H, CH_3N), 6.9 (br s, 2H, C_6H_2); ^{13}C NMR: $\delta=18.7$, 18.8, 18.9, 19.0, 19.2, 19.9, 20.0, 20.70, 20.75, 20.79, 20.85, 22.1, 22.3 (CH_3CO and $(CH_3)_3C_6H_2$), 28.3/28.2/30.9/30.7/29.7 (Boc), 36.1/36.0 (CH_3N), 82.6/82.3/81.1/81.4 (C_q), 128.9, 129.3, 129.7, 130.2, 130.3, 130.5, 130.7, 133.1, 133.6, 135.87, 135.94, 136.26, 136.29, 137.3, 137.7, 137.8, 138.0 (C_6H_2), 153.6/154.7/152.5 (CO, Boc), 172.8/168.1/173.2 (CH_3CO). Anal. calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 9.14; N, 8.55; found C, 66.83; H, 9.06; N, 8.68.

4.8. Synthesis of 1-(*tert*-butoxycarbonyl)-1,2-diaryl-2-alkylhydrazines (15)

4.8.1. 1-(*tert*-Butoxycarbonyl)-1-(*p*-tolyl)-2-phenyl-2-benzylhydrazine (15a). Compound **15a** was synthesized analogously with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:10 as eluent. During the process, 0.2 equiv of each reagent was added to the mixture in order to accelerate the reaction. Mixtures $CHCl_3$–hexane 1:2 and CH_2Cl_2–hexane 1:1 were used to isolate product by column chromatography, furnishing **15a** as slightly yellow viscous oil in 92% yield, pure by TLC. It solidified while standing in refrigerator and was recrystallized from hexane, giving yellowish solid, mp 75.5–76.5 °C. IR (KBr): 1709, 1253, 1158 cm^{-1}; ^1H NMR: $\delta=1.32$ (s, 9H, Boc), 2.29/2.27/2.33 (s, 3H, $CH_3C_6H_4$), 4.59, 4.67, 4.79, 4.87 (AB_q, 2H, CH_2), 6.8–7.3 (m, 14H, 2×Ph and C_6H_4); ^{13}C NMR: $\delta=20.8$ ($CH_3C_6H_4$), 28.2 (Boc), 58.2 (CH_2N), 81.7 (C_q), 113.0,

119.6, 122.4, 127.2, 128.2, 128.3, 128.9, 129.1, 134.3, 137.2, 139.9, 149.7 (Ph and C_6H_4), 153.9 (CO, Boc). Anal. calcd for $C_{20}H_{26}N_2O_4$: C, 77.29; H, 7.21; N, 7.26; found C, 77.18; H, 7.35; N, 7.04.

4.8.2. 1-(*tert*-Butoxycarbonyl)-1-(phenyl)-2-(*p*-tolyl)-2-(ethoxycarbonylmethyl)hydrazine (15b). Compound **15b** was synthesized analogously with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:1 and 1:4 as eluent. During the process, 0.1 equiv of $Cu(OAc)_2$ and 0.2 equiv of Ph_3Bi were added to accelerate the reaction. Mixtures EtOAc–hexane 1:30 and EtOAc–hexane 1:10 were used to isolate product by column chromatography, furnishing **15b** as colourless viscous oil in 80% yield, pure by TLC. IR (film): 1756, 1719, 1253, 1153 cm^{-1}; ^1H NMR: $\delta=1.18$ (t, 3H, $J_{HH}=7.2$ Hz, CH_3CH_2), 1.32 (s, 9H, Boc), 2.26 (s, 3H, $CH_3C_6H_4$), 4.0–4.5 (overlapped q and AB_q, together 4H, CH_3CH_2), 6.6–7.7 (9H, Ph, C_6H_4); ^{13}C NMR: $\delta=14.0$ (CH_3CH_2), 20.3 ($CH_3C_6H_4$), 28.2 (Boc), 56.8 (CH_2N), 61.1 (CH_3CH_2O), 82.2 (C_q), 112.2, 121.0, 124.3, 128.5, 129.2, 129.7, 142.0, 146.1 (Ph and C_6H_4), 153.9 (CO, Boc), 169.6 (*COO*Et). Anal. calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29; found C, 68.92; H, 7.35; N, 6.72.

4.8.3. 1-(*tert*-Butoxycarbonyl)-1-(*p*-anisyl)-2-(*p*-tolyl)-2-(*n*-butyl)hydrazine (15c). Compound **15c** was synthesized similarly with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:10 as eluent. Mixtures $CHCl_3$–hexane 1.5:1 and EtOAc–hexane 1:5 were used to isolate product by column chromatography, furnishing **15c** as colourless viscous oil in 92% yield, pure by TLC. IR (film): 1714, 1247, 1158 cm^{-1}; ^1H NMR: $\delta=0.85$ (t, $J_{HH}=7.4$ Hz, 3H, $CH_3CH_2CH_2CH_2$), 1.2–1.6 (overlapped s and m, together 13H, Boc and $CH_3CH_2CH_2CH_2$), 2.26 (s, 3H, $CH_3C_6H_4$), 3.3–3.6 (m, 2H, $CH_3CH_2CH_2CH_2$), 3.75 (s, 3H, CH_3O), 6.6–7.4 (m, 8H, $2\times C_6H_4$); ^{13}C NMR: $\delta=13.9$ ($CH_3CH_2CH_2CH_2$), 20.3, 20.5 ($CH_3C_6H_4$ and $CH_3CH_2CH_2CH_2$), 28.2 (Boc), 29.6 ($CH_3CH_2CH_2CH_2$), 52.3 (CH_2N), 55.4 (CH_3O), 81.3 (C_q), 112.3, 113.7, 123.0, 128.0, 129.6, 136.1, 147.3, 154.1 ($2\times C_6H_4$), 156.6 (CO, Boc). Anal. calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29; found C, 71.75; H, 8.43; N, 6.85.

4.8.4. 1-(*tert*-Butoxycarbonyl)-1-(*p*-tolyl)-2-(*p*-anisyl)-2-(*n*-butyl)hydrazine (15d). Compound **15d** was synthesized similarly with **5b**. The reaction was monitored by TLC using EtOAc–hexane 1:10 as eluent. Mixtures $CHCl_3$–hexane 1:1 and EtOAc–hexane 1:5 were used to isolate product by column chromatography, furnishing **15d** as colourless viscous oil in quantitative yield, pure by TLC. It solidified on standing for several months in the refrigerator and was recrystallized from hexane/$CHCl_3$, mp 67–69 °C. IR (film): 1704, 1242, 1153 cm^{-1}; ^1H NMR: $\delta=0.85$ (t, $J_{HH}=7.2$ Hz, 3H, $CH_3CH_2CH_2CH_2$), 1.2–1.6 (overlapped s and m, together 13H, Boc and $CH_3CH_2CH_2CH_2$), 2.29 (s, 3H, $CH_3C_6H_4$), 3.3–3.6 (m, 2H, $CH_3CH_2CH_2CH_2$), 3.74 (s, 3H, CH_3O), 6.7–7.5 (m, 8H, $2\times C_6H_4$). ^{13}C NMR: $\delta=13.8$ ($CH_3CH_2CH_2CH_2$), 20.5, 20.7 ($CH_3C_6H_4$ and $CH_3CH_2CH_2CH_2$), 28.2 (Boc), 29.6 ($CH_3CH_2CH_2CH_2$), 52.6 (CH_2N), 55.7 (CH_3O), 81.4 (C_q), 113.6, 114.7, 121.3, 129.0, 133.6, 140.6, 143.8, 153.2 ($2\times C_6H_4$), 154.0 (CO, Boc). Anal. calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29; found C, 72.08; H, 8.47; N, 7.20.

4.8.5. 1-(*tert*-Butoxycarbonyl)-1-(*p*-tolyl)-2-phenyl-2-(*n*-butyl)hydrazine (15e) by a one pot reaction. 1-(*tert*-Butoxycarbonyl)-2-(*n*-butyl)hydrazine (0.441 mmol) as equimolar mixture with Ph_3PO was prepared as described previously.[11] It was dissolved in dichloromethane (2 mL) and $Cu(OAc)_2$ (4 mg, 0.05 equiv) was added, followed by $Ph_3Bi(OAc)_2$ (246 mg, 1 equiv). The reaction was monitored by TLC, using EtOAc–hexane 1:5 as eluent. It was complete in 10 min and then Et_3N (92 μL, 1.5 equiv), $Cu(OAc)_2$ (120 mg, 1.5 equiv) and $(p\text{-Tol})_3Bi$ (319 mg, 1.5 equiv) were added. The reaction mixture was heated under reflux. After 22 h, the transformation was complete (EtOAc–hexane 1:10). Then 0.8 g of silica was added to the reaction mixture and the solvent was evaporated in vacuo. The remaining product was placed on the top of chromatography column and eluted with $CHCl_3$-hexane 1:2. It was obtained 129 mg (83%) of **15e** as colourless oil, pure by TLC. IR (film): 1714, 1253, 1163 cm^{-1}; ^1H NMR: $\delta=0.86$ (t, $J_{HH}=7$ Hz, 3H, $CH_3CH_2CH_2CH_2$), 1.2–1.7 (overlapped s and m, together 13H, Boc and $CH_3CH_2CH_2CH_2$), 2.30 (s, 3H, $CH_3C_6H_4$), 3.3–3.6 (m, 2H, $CH_3CH_2CH_2CH_2$), 6.7–7.6 (m, 10H, Ph and C_6H_4); ^{13}C NMR: $\delta=13.8$ ($CH_3CH_2CH_2CH_2$), 20.5, 20.7 ($CH_3C_6H_4$ and $CH_3CH_2CH_2CH_2$), 28.1 (Boc), 29.5 ($CH_3CH_2CH_2CH_2$), 52.3 (CH_2N), 81.5, 81.7 (C_q), 112.1, 118.8, 119.0, 121.1, 124.2, 128.4, 129.0, 129.1, 133.7, 140.2, 149.4 (Ph and C_6H_4), 153.9 (CO, Boc). Anal. calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90; found C, 74.56; H, 8.55; N, 7.71.

4.8.6. 1-(*tert*-Butoxycarbonyl)-1-(*p*-tolyl)-2-phenyl-2-benzylhydrazine (15a). This synthesis was carried out in a manner similar to that described in Section 4.8.2. Mixtures $CHCl_3$–hexane 1:3 and $CHCl_3$–hexane 1:1 were used to isolate product by column chromatography, furnishing **15a** as slightly yellow viscous oil in 85% yield, pure by TLC. The ^1H and ^{13}C NMR spectra were identical with data obtained in the procedure 4.8.1.

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Stereocontrolled synthesis of the ABCDE ring moiety of ciguatoxin CTX3C

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Abstract—The ABCDE ring moiety of ciguatoxin CTX3C, a major causative agent of ciguatera poisoning, was stereoselectively synthesized. The key transformations are a chiral auxiliary-based asymmetric alkylation and an asymmetric aldol condensation, which controlled the formation of the C11 and C21-stereocenters, respectively. A highly practical and efficient route to the ABCD ring fragment, a common precursor for the divergent synthesis of the left wings of ciguatoxins, was also established.

1. Introduction

Ciguatoxins (CTXs) produced by a marine dinoflagellate (*Gambierdiscus toxicus*) living on macroalgae, are transferred to and accumulated in a number of fish through the food chain, causing ciguatera seafood poisoning primarily in tropical and subtropical areas.[1] The complex structures of more than 20 CTX congeners such as CTX3C (**1**),[2] 51-hydroxyCTX3C (**2**),[3] CTX4B (**3**),[4] and CTX (**4**)[4] were elucidated on the basis of NMR and MS analyses. Biological studies have revealed that CTXs exert their toxicity through the activation of voltage-sensitive sodium channels (VSSCs).[5] To elucidate the interaction with VSSCs in more detail at the molecular level[5d] as well as to develop reliable immunochemical methods for detecting CTXs,[6] a practical supply of CTXs and their structural analogs has been required. However, the extremely low content of CTXs in fish has limited their supply from natural sources. Therefore, a number of synthetic efforts have been undertaken,[7] culminating in the first total synthesis of CTX3C (**1**) in our laboratory.[8] Our convergent strategy to synthesize **1** relied on the coupling of the left (ABCDE) wing and the right (HIJKLM) wing with the concomitant construction of the central FG ring system.[8,9] This strategy is expected to be applicable to all CTXs due to the common FG ring structure. Our recent research greatly improved the synthesis of the HIJKLM ring[10] in terms of number of synthetic steps, stereoselectivity, and overall yield.[11] On the other hand, preparation of the ABCDE ring moiety **5**[12] was yet to be optimized, especially with regard to stereocontrol. In the original synthesis of **5**, the stereoselectivity of the coupling between AB ring **9** and E ring **8** was unsatisfactory. Furthermore, E ring **8** was prepared from D-glucose via a non-stereocontrolled aldol condensation. Therefore, separation of undesired stereoisomers was required, followed by repeated epimerization processes, to supply a sufficient quantity of ring fragments for total synthesis. To overcome these stereochemical disadvantages, an alternative approach featuring chiral auxiliary-based stereoselective alkylation of **12** with **9** was developed to afford the ABCD ring fragment **11**.[13] The intermediate **11** was expected to be a common precursor for the divergent synthesis of the left wings of **1**, **2**, **3** and **4**. In our previous report,[14] the fully functionalized ABCDE ring moiety (**10**) of **4** was synthesized from **11** through installation of the dihydroxybutenyl substituent at C5 in the A ring and the tetrahydrooxepin E ring. In this publication, we have developed a stereocontrolled route to **5** from **11** using an asymmetric aldol condensation to regulate the C21-stereochemistry as a key transformation. A practical synthesis of the key intermediate **11** is also described herein. These developments are depicted in Scheme 1.

2. Results and discussion

2.1. Practical synthesis of the ABCD ring moiety

The AB ring unit **9** was synthesized from commercially

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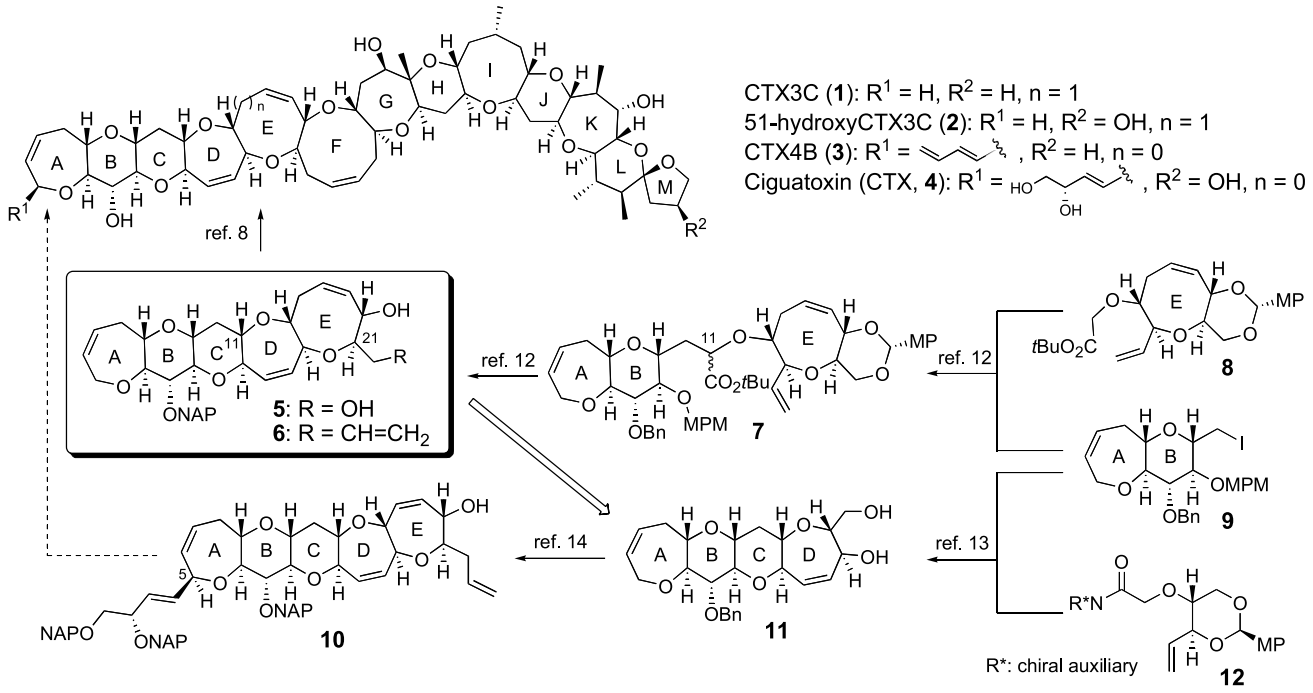
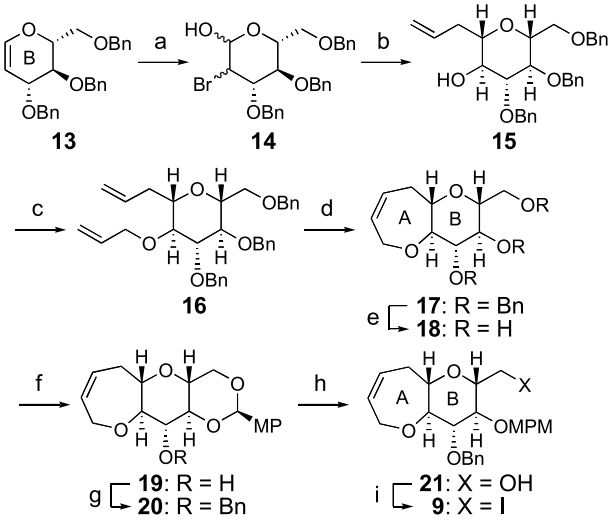


Scheme 1. Structures of ciguatoxins (CTXs) and synthetic strategy for the total synthesis of CTXs. Bn=benzyl; MP=*p*-methoxyphenyl; MPM=*p*-methoxybenzyl; NAP=2-naphthylmethyl.

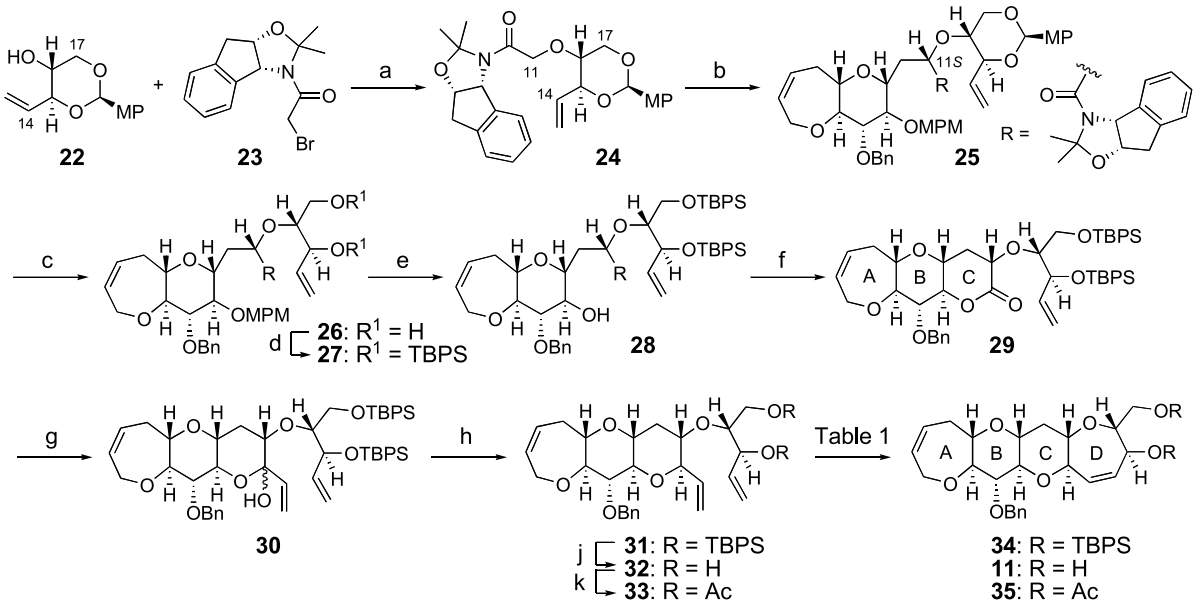
available tri-*O*-benzyl-D-glucal (**13**) using a slight modification of a previously reported procedure (Scheme 2),[12,15] as follows. Treatment of **13** with NBS in aqueous THF gave a diastereomeric mixture of bromohydrins **14**, which was converted to **15** using the Spilling method.[16] To obtain **15** with high stereoselectivity, it was critical to maintain strict temperature control at −78 °C during the treatment of **14**



Scheme 2. Reagents and conditions: (a) NBS, THF–H_2O (10:1), 0 °C, 1 h; (b) $KN(SiMe_3)_2$, 18-crown-6, toluene, −78 °C, 6 h, then allylmagnesium bromide, toluene–Et_2O, −68 °C to rt, 24 h, 45% (2 steps); (c) allyl bromide, NaH, THF–DMF (4:1), 0 °C to rt, 13 h, 99%; (d) $(PCy_3)_2Cl_2Ru$=CHPh (2 mol%), CH_2Cl_2, 4.5 h, 84%; (e) $TiCl_4$ (1.9 equiv.), $MeNO_2$, −5 °C, 30 min; (f) *p*$MeOC_6H_4CH(OMe)_2$, TsOH·H_2O, DMF, 0 °C to rt, 18 h, 91% (2 steps); (g) BnBr, NaH, THF–DMF (4:1), 0 °C to rt, 18 h; (h) DIBAL, CH_2Cl_2, −78 to −33 °C, 12 h, 97% (2 steps); (i) PPh_3, I_2, imidazole, toluene, 6 h, 96%. NBS=*N*-bromosuccinimide; Cy=cyclohexyl; DIBAL=diisobutylaluminum hydride; Ts=*p*-toluenesulfonyl.

with $KN(TMS)_2$. Alcohol **15** was then reacted with allyl bromide to give diene **16**, which was subjected to ring-closing metathesis (RCM)[17] to yield the AB ring **17**. Removal of the benzyl group of **17** under Birch conditions or with the use of lithium 4,4′-di-*tert*-butylbiphenyl resulted in the partial cleavage of the allylic ether linkage in the A ring.[8a,12] After considerable investigation, Lewis acid-mediated debenzylation using $TiCl_4$[18] was found to be optimal and selectively yielded triol **18**, which was easily converted to acetal **19** (91%, 2 steps). The secondary alcohol of **19** was protected as a benzyl ether, and the *p*-methoxybenzylidene acetal of **20** was selectively cleaved to give primary alcohol **21**. Finally, iodination of **21** afforded the AB ring moiety **9**.

The C14–C17 unit[19] was then assembled onto **9** (Scheme 3). After considerable experimentation,[20] we found that the protected (1*R*,2*S*)-1-amino-2-indanol derivative **24**[21] was suitable for diastereoselective alkylation. Amide **24** was readily prepared from alcohol **22**[12b] and bromide **23**. The key coupling reaction between iodide **9** and **24** (3.3 equiv.) was successfully performed using BuLi (3.3 equiv.) in the presence of DMPU (4.5 equiv.). The reaction reproducibly afforded the desired isomer **25** almost exclusively, even at the reaction scale of 17 g (33 mmol) of **9**, possibly through the transition state as shown in Figure 1, which shows attack of electrophile **9** from the less hindered C11-*si* face of the kinetically and thermodynamically favored *Z*-enolate of **24**.[21a,22] Selective removal of *p*-methoxybenzylidene acetal of **25** with PPTS and subsequent TBPS protection with TBPSOTf[23] in the presence of 2,6-lutidine afforded **27** in 74% overall yield from **9**. Oxidative MPM deprotection was then carefully performed at −5 °C to avoid Bn deprotection, yielding secondary alcohol **28**. Subsequent lactonization was not trivial. After extensive experimentation, it was found that addition of a catalytic amount of *p*-anisaldehyde



Scheme 3. Reagents and conditions: (a) NaH, THF–DMF (4:1), 13 h, 79%; (b) **9**, BuLi, DMPU, THF, −78 °C to rt, 19 h; (c) PPTS, PrOH, 16 h, 81% (2 steps); (d) TBPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 91%; (e) DDQ, CH_2Cl_2-H_2O (20:1), −5 °C, 2.5 h (three cycles), 86%; (f) CSA (3 equiv.), *p*-anisaldehyde (0.4 equiv.), toluene, 90 °C, 3 h; (g) tetravinyltin, MeLi, THF, −100 to −90 °C, 45 min, 77% (2 steps); (h) Et_3SiH, TMSOTf, CH_3CN, −40 to −20 °C, 40 min; (i) TBAF, THF, 44 h, 82% (2 steps); (j) Ac_2O, pyridine, DMAP, CH_2Cl_2, 3 h, 89%. DMPU=*N*,*N*′-dimethylpropyleneurea; PPTS=pyridinium *p*-toluenesulfonate; TBPS=*t*-butyldiphenylsilyl; DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone; CSA=(*1S*)-(+)-10-camphorsulfonic acid; TMS=trimethylsilyl; Tf=trifluoromethanesulfonyl; TBAF=tetrabutylammonium fluoride; Ac=acetyl; DMAP=4-(dimethylamino)pyridine.

to the reaction mixture of **28** and CSA (3 equiv.) in toluene at 90 °C reproducibly produced lactone **29** in good yield. This can be explained as follows: acid-catalyzed cleavage of the acetonide group on the chiral auxiliary can be expected to compete with the direct lactonization of tertiary amide **28**. The resultant secondary amide is likely to be less susceptible to lactonization. However, once it is converted in the presence of *p*-anisaldehyde to the corresponding *p*-methoxybenzylidene acetal, this tertiary amide would become reactive enough to form **29**. A vinyl group was then added to **29** at a temperature less than −90 °C to yield hemiacetal **30** as a mixture of diastereomers. Direct reduction of **30** was achieved with triethylsilane in the presence of TMSOTf in acetonitrile to afford a mixture of bis-TBPS ether **31**, diol **32**, and mono-TBPS ethers. The remaining TBPS groups were wholly removed by TBAF to yield **32** from **28** with an overall yield of 63%.

Subsequent RCM of the diene was highly dependent on the protective group and catalyst used, as shown in Table 1. The reaction of bis-TBPS ether **31** using catalyst **36**[17] or **37**[24] was very sluggish, presumably due to steric hindrance of the TBPS groups (entries 1 and 2). Although the reaction with the less hindered acetate **33** did proceed, more than 1 equiv. of catalyst and a long reaction time were required (entries 3 and 4). On the contrary, diol **32** smoothly underwent RCM (entries 5–7), and a catalytic amount of **37** was sufficient to yield **11** in 99% yield (entry 7). Thus, a reliable and stereoselective protocol for preparing the ABCD ring moiety **11** on a several-gram scale was developed.

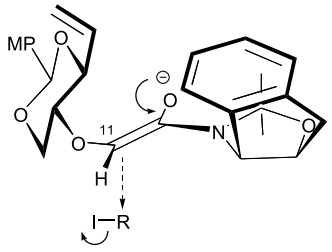


Figure 1. Proposed transition state of the alkylation of **24** with **9**. The energy-minimized structure of the *Z*-enolate of **24** was obtained using Macro Model ver. 6.0 with the MM2* force field.

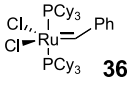
2.2. Attempts to construct the tetrahydrooxocin E ring using a chlorosulfide synthon

The tetrahydrooxocin E ring of **1** and **2** was constructed by adoption of the recently developed *O*,*S*-acetal forming reaction[9b,c,25] using the chlorosulfide synthon **41**[14] (Scheme 4). Since the 2-naphthylmethyl (NAP) group proved to be optimal for the global deprotection step in the last stage of the total synthesis of **1**,[8b] the benzyl group of **11** was replaced by the NAP group. Debenzylation was successfully performed under Lewis acidic conditions.[26] After sequential manipulation of the protective groups, primary alcohol **38** was converted to nitrile **39**. Reduction of the nitrile (**39**) with DIBAL and subsequent Wittig olefination followed by removal of the TBS group yielded alcohol **40**. This alcohol was successfully coupled with α-chlorosulfide **41** in the presence of AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine to yield *O*,*S*-acetal **42** as a major diastereomer (6:1) in 84% yield.[27] RCM of the corresponding C20-alcohol **43** proceeded smoothly to afford **44** in 88% yield. After TBS protection, sulfide **45** was carefully oxidized to sulfone **46** by use of *m*CPBA at −15 °C. The stereochemistry of **46** was established by NOE experiments.

To insert the allyl group at C21, which is necessary for the construction of the nine-membered F ring via RCM in the

Table 1. RCM of the D ring

Entry	Substrate	Catalyst	mol% of Catalyst	Temperature	Time (h)	Yield (%)
1	**31**	**36**	Excess	Reflux	42	<10
2	**31**	**37**	50	Reflux	21	No reaction
3	**33**	**36**	120	Reflux	39	83
4	**33**	**37**	8	Reflux	3	No reaction
5	**32**	**36**	20	Reflux	5	Complex mixture
6	**32**	**37**	20	Reflux	0.5	48
7	**32**	**37**	2	rt	2.5	99



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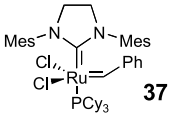

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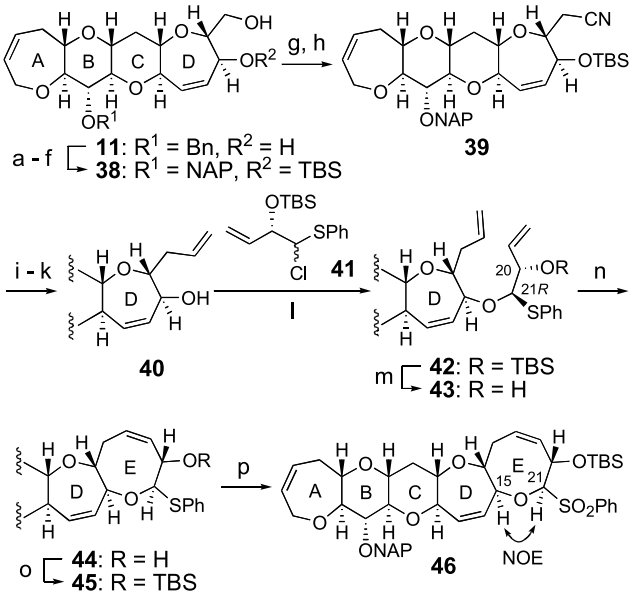
total synthesis of **1** and **2**,[8,9a,b] Lewis acid-mediated coupling of anomeric sulfone **46** with allyltrimethylsilane was attempted in the presence of $AlCl_3$ (Scheme 5).[14,28] However, ring-contraction products **51** and **52** were obtained in 50 and 20% yield, respectively, instead of the desired alkene **47**.[29] This can be explained as shown in Scheme 5. The rearrangement would be initiated via oxonium cation **48**. The resultant allylic cation **49** might form the less strained oxepin ring **50**, to which allylation could occur to produce **51** and **52**. To prevent this ring contraction, we planned insertion of the C22 carbon unit before the formation of the eight-membered ring. Acyclic sulfone **53**, which was prepared by the selective oxidation of **42** (*m*CPBA, CH_2Cl_2, −20 °C, 1 h, 31% yield), was treated with TMSCN and $EtAlCl_2$ (Scheme 6). In this case, the intramolecular cyclization product **56**[30] was mainly obtained instead of the desired **54**. Therefore, we abandoned the Lewis acid-mediated coupling strategy using anomeric sulfones, and investigated an alternative route, as described below.

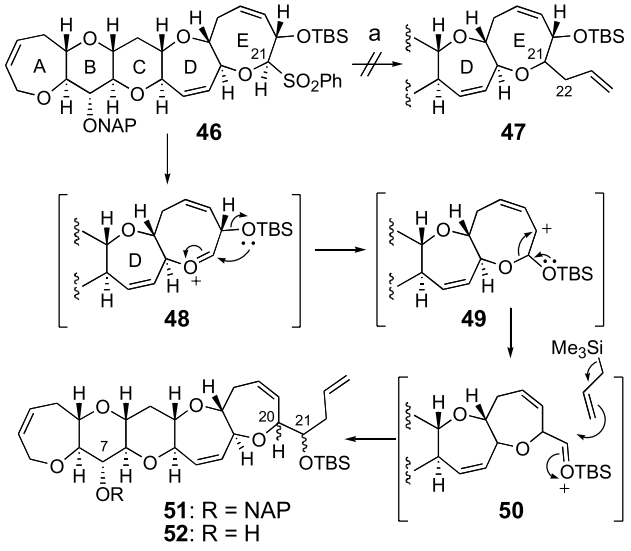


Scheme 4. Reagents and conditions: (a) $AlCl_3$ (3 equiv.), CH_2Cl_2–CH_3NO_2 (3:1), 0 °C, 20 min, 97%; (b) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2–DMF (1:1), 13 h, 84%; (c) NAPBr, NaH, TBAI, THF–DMF (3:1), 40 °C, 30 min, 88%; (d) TsOH·H_2O, MeOH–THF (2:1), 27 h; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 1 h, 98% (2 steps); (f) CSA, MeOH–THF (1:1), −15 °C, 14 h, 85%; (g) TsCl, pyridine, MS4A, 24 h, 96%; (h) NaCN, DMSO, 50 °C, 20 h, 94%; (i) DIBAL, CH_2Cl_2, −70 °C, 3 h; (j) Ph_3PCH_3Br, $NaN(SiMe_3)_2$, 0 °C, 1 h, 82% (2 steps); (k) TBAF, THF, 18 h, 91%; (l) **41** (3 equiv.), AgOTf (3.5 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (4.2 equiv.), MS4A, CH_2Cl_2, −40 to −20 °C, 1 h, 84% (21*R*/21*S*=6:1); (m) TBAF, THF, 1 h, 98%; (n) **37** (0.05 equiv.), CH_2Cl_2, 1 h, 88%; (o) TBSCl, imidazole, DMF, 24 h, 95%; (p) *m*CPBA, CH_2Cl_2, −15 °C, 4 h (three cycles), 98%. TBS=*tert*-butyldimethylsilyl; TBAI=tetrabutylammonium iodide; MS4A=molecular sieve 4 Å; *m*CPBA=*m*-chloroperbenzoic acid.

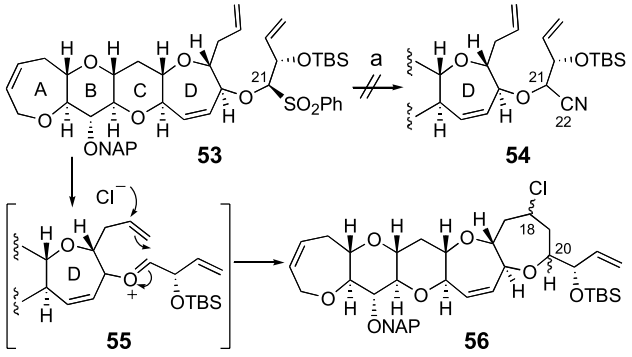
2.3. Stereocontrolled synthesis of the ABCDE ring moiety featuring an asymmetric aldol reaction and RCM

An alternative synthesis plan for the ABCDE ring moiety is outlined in Scheme 7. The key transformation is a chiral auxiliary-based asymmetric aldol reaction[31,32] of *O*-alkylated glycolic amide **57**. Since Crimmins and co-workers have recently succeeded in carrying out a 1,2-*anti*-selective aldol reaction by use of titanium enolates of *N*-glycolyloxazolidinethiones,[33,34] model experiments were first performed using chiral amides **59**–**61** (Table 2).

Under the Crimmins conditions,[33a] however, 20,21-*syn* aldol products (**63**, **64**) predominated (entry 1),[35] which implied that the 20,21-*syn*/*anti* selectivity is highly dependent on the structure of the *O*-alkyl group. Further investigation revealed that this selectivity was greatly



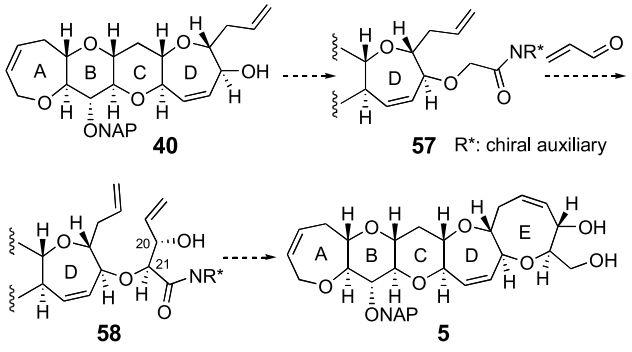
Scheme 5. Reagents and conditions: (a) allyltrimethylsilane, $AlCl_3$, CH_2Cl_2, −60 °C, 30 min, **51** (50%, 2:1 stereoisomers), **52** (20%, 2:1 stereoisomers).



Scheme 6. Reagents and conditions: (a) TMSCN, $EtAlCl_2$, CH_2Cl_2, −50 to −30 °C, 1 h, **56** (35%, 2:1 stereoisomers).

affected by the amines used. A remarkable preference of 20,21-*syn* isomer **64** with the undesired C21-configuration (21*R*) was observed when *i*Pr_2NEt or Et_3N was used (entries 3 and 4). Since the stereochemistry at C20 can be readily inverted through the Mitsunobu reaction,[36,37] we decided to change the chiral auxiliary from (*R*)-4-benzyl-2-oxazolidinethione to its enantiomer to reverse the C21-stereochemistry. As expected, the titanium enolate of **60** produced by $TiCl_4$ and *i*Pr_2NEt afforded a 5:95 mixture of 20,21-*anti* **62** and 20,21-*syn* isomer **63**, both of which possessed the desired C21-configuration (21*S*) (entry 5). The use of Et_3N accelerated the reaction and increased the proportion of 20,21-*anti* isomer **62** (entry 6). A similar result was obtained with (*S*)-4-benzyl-2-oxazolidinone **61**, although the undesired 15,21-*anti* isomer **64** was also produced (entry 7). The observed 20,21-*syn* selectivity can be explained by the Evans-type six-membered chair-like transition state as shown in Figure 2.[32–34]

Based on these model experiments, either the (*S*)-4-benzyl-2-oxazolidinethione or the (*S*)-4-benzyl-2-oxazolidinone auxiliary was introduced into the ABCD ring moiety **40** (Scheme 8). Since the direct *O*-alkylation of **40** with *N*-bromoacetyl-(*S*)-4-benzyl-2-oxazolidinone[38] in the presence of NaH was unsuccessful, the auxiliary was installed onto **40** in a stepwise manner. First, alkylation of **40** with *t*-butyl bromoacetate gave ester **65**, which was hydrolyzed by 10 M HCl. The resulting carboxylic acid **66** was converted to amide **70** or **71** via pivaloyl anhydride **67**, in preparation for the key asymmetric aldol reaction. When oxazolidinethione **70** was used, the desired 20,21-*anti*-15,21-*syn* isomer **72** and 20,21-*syn*-15,21-*syn* isomer **73**[39] were



Scheme 7. Synthesis plan of the ABCDE ring moiety featuring an asymmetric aldol reaction and RCM.

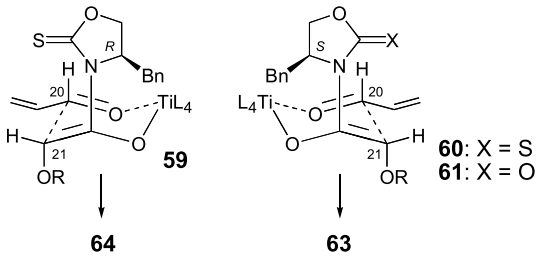


Figure 2. Proposed transition states involved in the formation of 20,21-*syn* products **64** and **63**.

obtained in 15 and 61% yield, respectively. Importantly, the use of Et_3N was essential and no reaction proceeded with *i*Pr_2NEt. The minor isomer **72** was directly converted to the ABCDE ring moiety **5**[12] by removal of the chiral auxiliary and constructing the tetrahydrooxocin E ring. On the other hand, the aldol reaction using oxazolidinone **71** gave rise to 20,21-*syn*-15,21-*syn* isomer **74** selectively in 72% yield along with a small amount of the corresponding 20,21-*syn*-15,21-*anti* product (12%). Chiral auxiliaries of the major products **73** and **74** were removed and the resulting diol **75** was subjected to RCM, yielding the C20-epimer **76** of **5**. Exposure of the mono-TBS ether **77** to standard Mitsunobu conditions[36,37] afforded benzoate **78** with complete inversion of the C20-stereochemistry. Finally, removal of the protective groups of **78** except NAP afforded **5** from **78** with an overall yield of 85%.

3. Conclusion

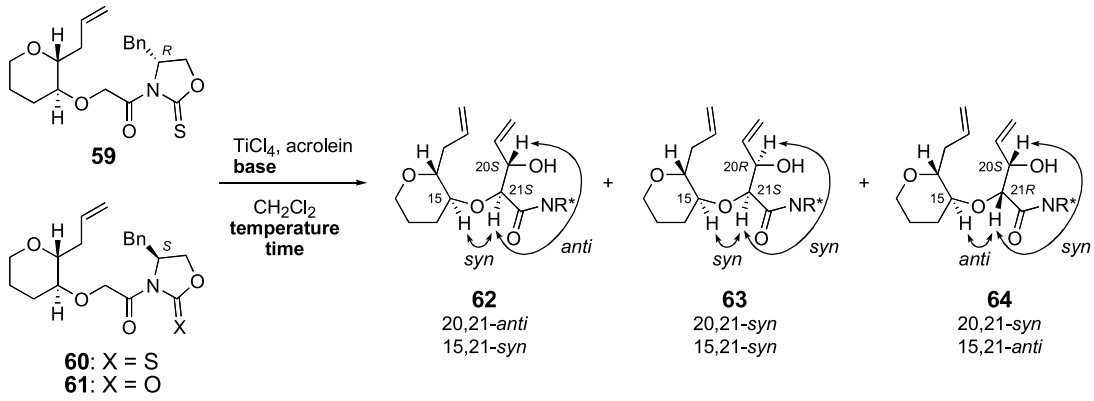
The left wing (**5**) of CTX3C (**1**) and 51-hydroxyCTX3C (**2**) was synthesized in a stereocontrolled manner from commercially available tri-*O*-benzyl-D-glucal (**13**). The key features of the present synthesis involve the highly practical and stereoselective preparation of the valuable ABCD ring intermediate **11**, as well as asymmetric construction of the tetrahydrooxocin E ring system. This synthesis avoids the repeated separation of undesired isomers and subsequent epimerization processes. The high reliability of the synthesis established here will enable a practical supply of the left wing not only for the total syntheses of CTXs but also for biomedical applications. Further investigations along this line are currently underway in our laboratory.

4. Experimental

4.1. General methods

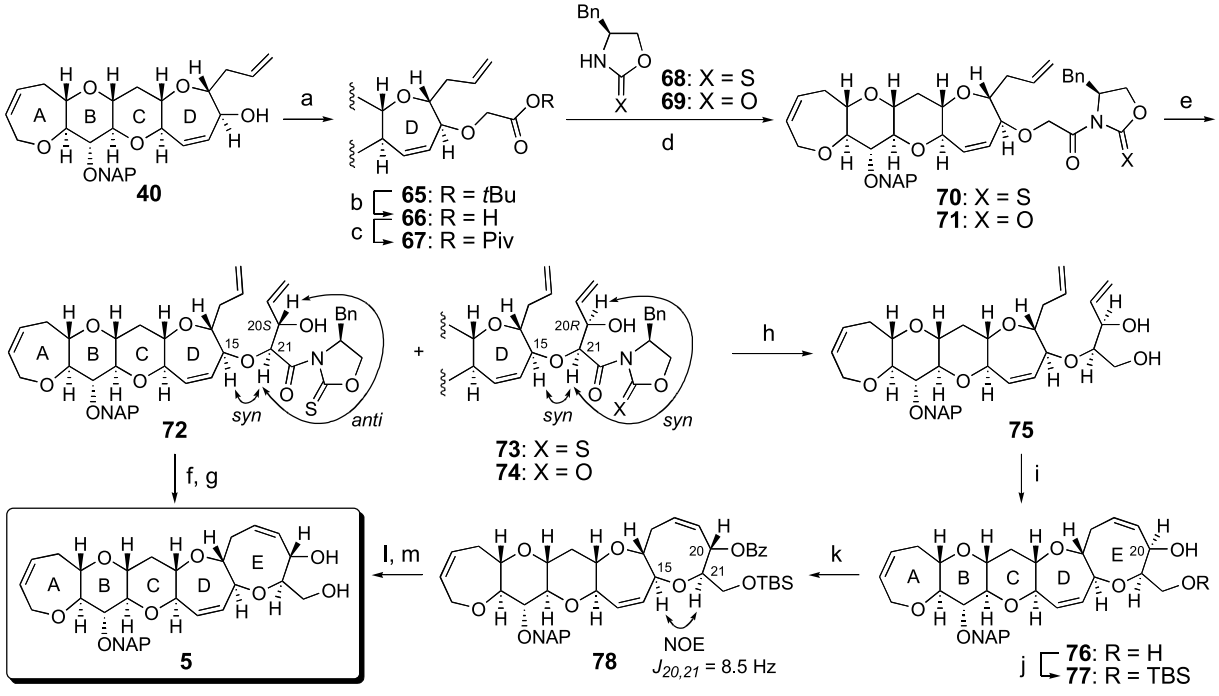
^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (200 MHz) or a Varian INOVA-500 (500 MHz) spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Matrix assisted laser desorption ionization time-of-flight mass spectra (MALDI-TOF MS) were recorded on an Applied Biosystems Voyager DE STR SI-3 instrument using α-cyano-4-hydroxy cinnamic acid as a matrix. Electron spray ionization time-of flight mass spectra (ESI-TOF MS) were recorded on an Applied Biosystems Mariner instrument. Optical rotations were recorded on a JASCO DIP-370

Table 2. Asymmetric aldol condensations in a model system[a]



Entry	Substrate	Amine	Temperature (°C)	Time (h)	Yield (%)[b]	Ratio (**62**:**63**:**64**)[c,d]	Recovery of s.m. (%)[b]
1[e]	**59**	(−)-Sparteine	−78	1	55	13:63:24	<10
2	**59**	TMEDA	−78 to −40	5	34	25:50:25	44
3	**59**	*i*Pt$_2$NEt	−78 to −50	4	58	2:5:93	20
4	**59**	Et$_3$N	−70	0.5	69	6:13:81	9
5	**60**	*i*Pt$_2$NEt	−78 to −50	4	67	5:95:0	23
6	**60**	Et$_3$N	−78	1	71	25:75:0	6
7	**61**	Et$_3$N	−78	0.5	72	3:72:25	2

[a] Performed with 4–6 equiv. of $TiCl_4$, 10 equiv. of amine, and 10 equiv. of acrolein except entry 1.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Corresponding *anti*,*anti* isomer was not detected in each case.
[e] Since Crimmins' original method using 1.2 equiv. of (−)-sparteine and 1.2+4 equiv. of $TiCl_4$[33a] gave aldol products in low yield, excess (−)-sparteine (3 equiv.) and *N*-methyl-2-pyrrolidinone (3 equiv.)[33] were used along with 1.5+4 equiv. of $TiCl_4$.



Scheme 8. Reagents and conditions: (a) $BrCH_2CO_2tBu$, NaH, THF–DMF (4:1), 0 °C to rt, 10 h, 92%; (b) 10M HCl–THF (1:2), 30 °C, 23 h, 81%; (c) PivCl, Et_3N, CH_2Cl_2, −78 °C to rt, 40 min; (d) **68** or **69**, *n*BuLi, THF, −78 to 0 °C, 0.5–1 h, 51% for **70**, 96% for **71** (2 steps); (e) $TiCl_4$ (10 equiv.), Et_3N (20 equiv.), acrolein (20 equiv.), CH_2Cl_2, −78 °C, 20 min, **72** (15% from **70**), **73** (58% from **70**), **74** (72% from **71**); (f) $NaBH_4$, THF–H_2O (4:1), 10 min, 85%; (g) **37**, (0.1 equiv.), CH_2Cl_2, 30 min, 82%; (h) $NaBH_4$, THF–H_2O (4:1), 10–20 min, 79% from **73**, 99% from **74**; (i) **37**, (0.1 equiv.), CH_2Cl_2, 1 h, 92%; (j) TBSCl, imidazole, CH_2Cl_2, 0.5 h, 83%; (k) PPh_3, DEAD, BzOH, toluene, 20 min, 100%; (l) TBAF, THF, 3 h, 92%; (m) K_2CO_3, MeOH–THF (2:1), 1.5 h, 92%. Piv = pivaloyl; Bz = benzoyl; DEAD = diethyl azodicarboxylate.

digital polarimeter. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Open column chromatography was performed using 100–210 μm Silica Gel 60 N (Kanto Chemical Co., Inc.), and for flash column chromatography 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions. Dry solvents purchased from Kanto Chem. Co. were also used.

4.2. Synthesis of the ABCD ring fragment

4.2.1. Alcohol 15. To a solution of benzyl ether **13** (30.0 g, 72.0 mmol) in THF (160 ml) and H_2O (16 ml) was added NBS (14.1 g, 79.2 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with water. Aqueous phase was extracted with Et_2O, and the combined organic phase was washed with saturated $Na_2S_2O_3$ solution, brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave bromide **14** (45.3 g) as a diastereomeric mixture.

To a 2 l three-necked round-bottom flask equipped with mechanical stirrer and dropping funnel was added a solution of **14** (45.3 g) and 18-crown-6 (32.0 g, 121 mmol) in toluene (180 ml). The solution was cooled to −78 °C, and $KN(TMS)_2$ (1.2 M solution in toluene, 120 ml, 144 mmol) was slowly added over 1 h. The resulting mixture was stirred for 6 h at −78 °C and then warmed to −68 °C. Allylmagnesium bromide (0.8 M solution in ether, 180 ml, 144 mmol) was added over 1 h, and the resulting mixture was gradually warmed to room temperature over 24 h with stirring. The mixture was quenched with saturated NH_4Cl solution and neutralized with conc. HCl. Aqueous phase was extracted with hexane–EtOAc, and the organic phase was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10–5) to give alcohol **15** (15.5 g, 32.6 mmol, 45%) as yellow oil. All spectroscopic data are identical to those reported in the literature.[12]

4.2.2. Diene 16. To a solution of alcohol **15** (12.6 g, 26.6 mmol) in THF (64 ml) and DMF (16 ml) was added NaH (60% dispersion in mineral oil, 2.55 g, 63.8 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C followed by the addition of allyl bromide (3.45 ml, 39.9 mmol). The resulting mixture was further stirred for 13 h at room temperature. The mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with hexane–EtOAc. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8) to give diene **16** (13.6 g, 26.5 mmol, 99%) as yellow oil. All spectroscopic data are identical to those reported in the literature.[12]

4.2.3. AB ring 17. To a solution of diene **16** (13.6 g, 26.5 mmol) in CH_2Cl_2 (530 ml) was added Grubbs catalyst **36** (536 mg, 0.650 mmol). The mixture was stirred for 4.5 h at ambient temperature and quenched with Et_3N (900 μl, 6.50 mmol). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7.5) to give AB ring **17** (10.9 g, 22.4 mmol, 84%). All spectroscopic data are identical to those reported in the literature.[12]

4.2.4. Alcohol 19. To a solution of AB ring **17** (10.1 g, 20.7 mmol) in CH_3NO_2 (103 ml) was slowly added a solution of $TiCl_4$ (5.47 ml, 39.4 mmol) in CH_3NO_2 (103 ml) at −5 °C. The mixture was stirred for 30 min at −5 °C and quenched by the slow addition of MeOH. The resulting dark purple suspension was concentrated, and the residue was diluted with MeOH and filtered through a pad of Celite. The filter cake was washed with MeOH sufficiently and the combined filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc/MeOH = 10) to give triol **18** (5.59 g).

To a solution of triol **18** (5.59 g) in DMF (120 ml) were added anisaldehyde dimethyl acetal (9.58 ml, 51.7 mmol) and $TsOH \cdot H_2O$ (418 mg, 2.20 mmol) at 0 °C. The mixture was stirred for 18 h at ambient temperature and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc and the organic phase was concentrated at 70 °C (to remove DMF). Et_2O was added to the residue, and the resulting precipitate was collected by filtration to yield acetal **19** (6.27 g, 18.8 mmol, 91% in 2 steps) as colorless powder. All spectroscopic data are identical to those reported in the literature.[12]

4.2.5. Alcohol 21. To a solution of alcohol **19** (13.0 g, 38.9 mmol) in THF (160 ml) and DMF (40 ml) was added NaH (60% dispersion in mineral oil, 1.70 g, 42.8 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C. BnBr (5.09 ml, 42.8 mmol) was added and the resulting mixture was stirred for 18 h at room temperature. The mixture was quenched with H_2O at 0 °C and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave benzyl ether **20**.

A 1 l three-necked round-bottom flask equipped with mechanical stirrer and dropping funnel was charged with DIBAL (0.93 M in hexane, 335 ml, 311 mmol). The solution was cooled to −78 °C and a solution of **20** in CH_2Cl_2 (78 ml) was slowly added over 1.5 h. The mixture was gradually warmed to −33 °C over 12 h with stirring and re-cooled to −78 °C. EtOAc (100 ml) and Rochelle salt solution (60 ml) were added at −78 °C and the resulting mixture was vigorously stirred for 6 h at room temperature. The mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2) to give alcohol **21** (16.1 g, 37.7 mmol, 97% in 2 steps). All spectroscopic data are identical to those reported in the literature.[12]

4.2.6. Iodide 9. To a solution of alcohol **21** (12.1 g, 28.3 mmol) in toluene (142 ml) were added PPh_3 (14.9 g, 56.7 mmol), imidazole (5.79 g, 75.1 mmol) and iodide (10.8 g, 42.6 mmol) in this order. The mixture was stirred for 6 h and quenched with saturated $Na_2S_2O_3$ solution. Organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After

concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 50–7.9–3.0) to give iodide **9** (14.6 g, 27.2 mmol, 96%). All spectroscopic data are identical to those reported in the literature.[12]

4.2.7. Amide 23. To a solution of (1*R*,2*S*)-1-amino-2-indanol (20.0 g, 134 mmol) in THF (500 ml) were added Et_3N (20.6 ml, 148 mmol) and bromoacetyl bromide (12.9 ml, 148 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature and cooled to 0 °C. CSA (12.5 g, 53.8 mmol) and 2-methoxypropene (25.7 ml, 268 mmol) were added and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C, diluted with hexane (250 ml) and quenched with saturated $NaHCO_3$ solution (250 ml). Aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was recrystallized from AcOEt to give amide **23** (14.2 g, 45.9 mmol, 34%). The filtrate was concentrated and the residue was purified by flash column chromatography to give **23** (17.6 g, 56.7 mmol, 42%). **23**: colorless plate; mp 134–136 °C (hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, auxiliary), 1.62 (s, 3H, auxiliary), 3.15 (d, 1H, J=1.0 Hz, auxiliary), 3.16 (d, 1H, J=4.0 Hz, auxiliary), 4.03 (d, 1H, J=10.0 Hz, H11), 4.23 (d, 1H, J=10.0 Hz, H11), 4.95 (dt, 1H, J=4.0, 1.0 Hz, auxiliary), 5.39 (d, 1H, J=4.0 Hz, auxiliary), 7.24–7.34 (m, 4H, auxiliary); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.95, 26.32, 29.23, 36.16, 66.16, 78.89, 96.84, 123.68, 125.97, 127.21, 128.65, 139.83, 140.74, 163.04; FT-IR (KBr) ν 3038, 2984, 2933, 1654, 1458, 1373, 1312, 1221, 1168, 1116, 1049, 1024, 983, 952, 907, 823 cm^{-1}; ESI-TOF MS $[M+H]^+$ calcd for $C_{14}H_{17}BrNO_2$ 310.0443, found 310.0424; $[\alpha]_D^{28.0}$ −165° (*c* 1.00, $CHCl_3$).

4.2.8. Amide 24. To a solution of alcohol **22**[12] (26.6 g, 113 mmol) and bromide **23** (42.0 g, 135 mmol) in THF (320 ml) and DMF (80 ml) was added NaH (60% dispersion in mineral oil, 5.4 g, 135 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature and quenched with water at 0 °C. Aqueous phase was extracted with hexane, and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography to give amide **24** (51.6 g, 110 mmol, 98%). **24**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H, auxiliary), 1.64 (s, 3H, auxiliary), 3.13 (s, 2H, auxiliary), 3.54 (dt, 1H, J=10.0, 5.0 Hz, H16), 3.76 (t, 1H, J=10.0 Hz, H17), 3.80 (s, 3H, OMe), 4.18 (dd, 1H, J=10.0, 6.0 Hz, H15), 4.45 (d, 1H, J=14.0 Hz, H11), 4.57 (d, 1H, J=14.0 Hz, H11), 4.60 (dd, 1H, J=10.0, 5.0 Hz, H17), 4.87 (dt, 1H, J=4.5, 2.5 Hz, auxiliary), 5.31 (d, 1H, J=4.5 Hz, auxiliary), 5.33 (d, 1H, J=11.0 Hz, *CH*$_2$=CH–), 5.51 (d, 1H, J=17.0 Hz, *CH*$_2$=CH–), 5.51 (s, 1H, *CH*MP), 6.09 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H14), 6.88 (d, 2H, J=8.0 Hz, MP), 7.23–7.33 (m, 4H, auxiliary), 7.43 (d, 2H, J=8.0 Hz, MP); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.10, 26.44, 36.25, 55.19, 64.65, 69.14, 70.65, 74.37, 79.30, 81.12, 96.98, 100.69, 113.51, 118.48, 124.19, 125.94, 127.20, 127.42, 128.61, 130.02, 135.01, 140.32, 140.76, 159.96, 165.14; FT-IR (film) ν 2935, 1661, 1615, 1518, 1426, 1376, 1249, 1172, 1142, 1103, 1032, 933, 904, 830 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_6$ 488.2049, found 488.2003; $[\alpha]_D^{29.0}$ −121° (*c* 1.00, $CHCl_3$).

4.2.9. Diol 26. To a solution of amide **24** (51.2 g, 110 mmol) in THF (170 ml) was slowly added *n*BuLi (1.56 M solution in hexane, 70.5 ml, 110 mmol) over 30 min at −78 °C. The mixture was stirred for 20 min at −78 °C, and a solution of iodide **9** (17.9 g, 33.3 mmol) and DMPU (18.1 ml, 150 mmol) in THF (50 ml) was slowly added over 20 min at −78 °C. The resulting mixture was gradually warmed to room temperature over 3 h and the stirring was continued for an additional 15 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc. The combined organic phase was concentrated and the residue was roughly purified by open column chromatography (silica gel, hexane/EtOAc = 6–3–2) to give amide **25** (47.4 g).

To a solution of **25** (47.4 g) in *n*PrOH (362 ml) was added PPTS (3.64 g, 14.5 mmol). The mixture was stirred for 16 h at room temperature and quenched with Et_3N (35 ml). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8–3–1) to give diol **26** (21.0 g, 27.8 mmol, 76% in 2 steps) and recovery of **25** (8.47 g). The recovered **25** (8.47 g) was subjected to the same reaction and purification conditions to yield **26** (1.08 g, 1.43 mmol, 5% in 2 steps). **26**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, auxiliary), 1.59 (s, 3H, auxiliary), 1.72 (brs, 2H, OH), 2.08–2.18 (m, 2H, H4, H10), 2.25 (ddd, 1H, J=15.5, 8.5, 4.5 Hz, H10), 2.44 (ddd, 1H, J=16.0, 8.5, 4.0 Hz, H4), 2.99 (dd, 1H, J=17.0, 4.0 Hz, auxiliary), 3.09 (d, 1H, J=17.0 Hz, auxiliary), 3.24 (dt, 1H, J=9.5, 4.0 Hz, H5), 3.36 (t, 1H, J=9.5 Hz, H6), 3.50 (dt, 1H, J=9.5, 4.5 Hz, H9), 3.54–3.61 (m, 2H, H7, H8), 3.74 (d, 1H, J=9.0 Hz, H17), 3.78–3.87 (m, 2H, H16, H17), 3.80 (s, 3H, OMe), 3.98 (dq, 1H, J=16.0, 3.0 Hz, H1), 4.12 (brs, 1H, H15), 4.25 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.61 (t, 1H, J=4.0 Hz, auxiliary), 4.68 (d, 1H, J=10.0 Hz, *CH*$_2$Ph), 4.81 (d, 1H, J=11.0 Hz, *CH*$_2$Ph), 4.86 (d, 1H, J=10.0 Hz, *CH*$_2$Ph), 4.94 (d, 1H, J=11.0 Hz, *CH*$_2$Ph), 5.00 (dd, 1H, J=8.5, 2.0 Hz, H11), 5.16 (d, 1H, J=10.5 Hz, *CH*$_2$=CH–), 5.27 (d, 1H, J=4.0 Hz, auxiliary), 5.32 (d, 1H, J=17.0 Hz, *CH*$_2$=CH–), 5.66 (ddt, 1H, J=11.5, 8.5, 3.0 Hz, H3), 5.83 (ddt, 1H, J=11.5, 6.0, 3.0 Hz, H2), 5.96 (ddd, 1H, J=17.0, 10.5, 6.0 Hz, H14), 6.85 (d, 2H, J=8.5 Hz, MPM), 7.21 (d, 2H, J=8.5 Hz, MPM), 7.24–7.39 (m, 8H, auxiliary, Bn), 7.51 (d, 1H, J=7.5 Hz, auxiliary); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.67, 26.54, 33.92, 34.63, 36.17, 55.21, 63.04, 64.22, 67.78, 72.09, 74.74, 75.58, 75.90, 76.07, 76.67, 79.15, 79.84, 83.74, 85.52, 87.52, 97.15, 113.81, 116.57, 124.13, 125.89, 126.58, 127.39, 127.55, 127.85, 128.29, 128.64, 129.47, 130.40, 131.37, 136.34, 138.71, 139.69, 140.62, 159.25, 171.01; FT-IR (KBr) ν 3379, 2933, 1638, 1513, 1431, 1363, 1247, 1192, 927, 822 cm^{-1}; ESI-TOF MS $[M+H]^+$ calcd for $C_{44}H_{54}NO_{10}$ 756.3748, found 756.3651; $[\alpha]_D^{28.0}$ −109° (*c* 1.00, $CHCl_3$).

4.2.10. TBPS ether 27. To a solution of diol **26** (30.5 g, 40.4 mmol) and 2,6-lutidine (37.6 ml, 323 mmol) in CH_2Cl_2 (202 ml) was added TBPSOTf (46.0 g, 118 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C and quenched with

saturated $NaHCO_3$ solution. Aqueous phase was extracted with hexane–EtOAc, and the combined organic phase was washed with 1M HCl and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=10–5–4) to give bis-TBPS ether **27** (45.2 g, 36.7 mmol, 91%). **27**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H, *t*-Bu), 1.00 (s, 9H, *t*-Bu), 1.24 (s, 3H, auxiliary), 1.58 (s, 3H, auxiliary), 1.98 (ddd, 1H, J=13.0, 9.5, 5.0 Hz, H10), 2.08 (ddq, 1H, J=16.0, 9.0, 3.0 Hz, H4), 2.16 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.35 (ddd, 1H, J=13.0, 9.0, 2.5 Hz, H10), 2.97 (dd, 1H, J=17.0, 4.0 Hz, auxiliary), 3.09 (dt, 1H, J=9.0, 4.0 Hz, H8), 3.09 (d, 1H, J=17.0 Hz, auxiliary), 3.16 (t, 1H, J=9.0 Hz, H8), 3.28 (t, 1H, J=9.0 Hz, H6), 3.31 (ddd, 1H, J=9.5, 9.0, 2.5 Hz, H9), 3.52 (t, 1H, J=9.0 Hz, H7), 3.70–3.76 (m, 2H, H17, H17), 3.74 (s, 3H, OMe), 3.94 (dq, 1H, J=15.0, 3.0 Hz, H1), 3.97 (td, 1H, J=7.0, 2.0 Hz, H16), 4.24 (dq, 1H, J=15.0, 6.0 Hz, H1), 4.45 (d, 1H, J=10.5 Hz, CH_2Ph), 4.64–4.69 (m, 1H, H15), 4.65 (d, 1H, J=10.5 Hz, CH_2Ph), 4.66 (dd, 1H, J=4.5, 4.0 Hz, auxiliary), 4.74 (d, 1H, J=11.0 Hz, CH_2Ph), 4.83 (d, 1H, J=17.5 Hz, CH_2=CH–), 4.88 (d, 1H, J=11.0 Hz, CH_2Ph), 4.90 (d, 1H, J=10.0 Hz, CH_2=CH–), 4.99 (dd, 1H, J=9.0, 5.0 Hz, H11), 5.59 (ddd, 1H, J=12.0, 8.0, 3.0 Hz, H3), 5.63 (d, 1H, J=4.5 Hz, auxiliary), 5.84 (ddt, 1H, J=12.0, 6.0, 3.0 Hz, H2), 5.90 (ddd, 1H, J=17.5, 10.0, 7.0 Hz, H14), 6.75 (d, 2H, J=8.5 Hz, MPM), 7.10 (d, 2H, J=8.5 Hz, MPM), 7.16–7.38 (m, 21H, Ph), 7.52–7.58 (m, 4H, Ph), 7.60–7.65 (m, 4H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.08, 19.42, 24.50, 26.71, 26.90, 27.08, 34.55, 35.58, 36.45, 55.20, 63.55, 65.06, 67.86, 74.64, 75.63, 75.80, 75.85, 76.05, 76.38, 76.62, 79.41, 81.40, 85.31, 87.96, 97.09, 113.67, 116.51, 125.42, 126.63, 127.26, 127.33, 127.46, 127.62, 127.83, 128.28, 129.40, 129.53, 129.59, 130.43, 131.60, 133.18, 133.25, 133.94, 134.03, 135.53, 136.17, 137.06, 139.12, 140.18, 141.01, 159.07, 168.48; FT-IR (film) ν 2930, 2856, 1654, 1513, 1459, 1427, 1361, 1247, 1111, 923, 823 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{76}H_{89}NaNO_{10}Si_2$ 1254.5917, found 1254.5856; $[\alpha]_D^{29.0}$ −26.0° (*c* 1.00, $CHCl_3$).

4.2.11. Alcohol 28. To a solution of MPM ether **27** (46.2 g, 37.5 mmol) in CH_2Cl_2 (357 ml) and water (17.8 ml) was added 2.41 g (10.7 mmol) each of DDQ in four portions at intervals of 30 min at −5 °C. The mixture was totally stirred for 2.5 h at −5 °C, and quenched with saturated $Na_2S_2O_3$ solution and then saturated $NaHCO_3$ solution. The resulting suspension was filtered though a pad of Celite and the filtrate was extracted with hexane–EtOAc. The combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=10–8–6–2.9, twice) to give alcohol **28** (29.0 g, 26.1 mmol, 70%) and recovery of **27** (13.2 g, 10.7 mmol, 29%). The recovered **27** (13.2 g) was subjected to the same reaction and purification conditions another twice to give **28** (6.85 g, 6.16 mmol, 16%). **28**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 9H, *t*-Bu), 1.03 (s, 9H, *t*-Bu), 1.24 (s, 3H, auxiliary), 1.59 (s, 3H, auxiliary), 2.03 (dt, 1H, J=12.5, 7.0 Hz, H10), 2.14 (ddq, 1H, J=15.0, 9.0, 3.0 Hz, H4), 2.24–2.32 (m, 2H, H4, H10), 2.41 (d, 1H, J=1.5 Hz, OH), 3.03 (dd, 1H, J=17.0, 3.0 Hz, auxiliary), 3.10 (d, 1H, J=17.0 Hz, auxiliary), 3.12 (td, 1H, J=9.0, 4.0 Hz, H5), 3.26–3.30 (m, 4H, H6, H7, H8, H9), 3.71 (dd, 1H, J=10.5, 7.0 Hz, H17), 3.76 (dd, 1H, J=10.5, 6.0 Hz, H17), 3.89–3.97 (m, 1H, H1), 3.93 (dd, 1H, J=7.0, 6.0 Hz, H16), 4.24 (dq, 1H, J=15.5, 6.0 Hz, H1), 4.71 (d, 1H, J=11.0 Hz, CH_2Ph), 4.72 (t, 1H, J=4.0 Hz, auxiliary), 4.75 (d, 1H, J=7.0 Hz, H15), 4.85 (d, 1H, J=17.5 Hz, CH_2=CH–), 4.90 (d, 1H, J=10.5 Hz, CH_2=CH–), 4.92 (d, 1H, J=11.0 Hz, CH_2Ph), 5.03 (dd, 1H, J=7.0 Hz, H11), 5.63 (d, 1H, J=4.0 Hz, auxiliary), 5.61–5.68 (m, 1H, H3), 5.80–5.89 (m, 1H, H2), 5.84 (ddd, 1H, J=17.5, 10.0, 7.0 Hz, H14), 7.04 (t, 1H, J=7.5 Hz, Ph), 7.20–7.39 (m, 19H, Ph), 7.53–7.58 (m, 5H, Ph), 7.62–7.66 (m, 4H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.14, 19.43, 24.34, 26.72, 26.94, 27.11, 34.57, 35.99, 36.46, 63.44, 65.06, 67.87, 73.94, 75.22, 75.80, 75.95, 76.09, 76.34, 76.59, 79.38, 81.54, 84.84, 87.48, 97.10, 116.59, 125.31, 125.43, 126.81, 127.27, 127.37, 127.61, 127.74, 128.19, 128.42, 129.44, 129.53, 131.51, 133.24, 133.31, 133.94, 134.06, 135.56, 136.18, 136.93, 139.11, 140.16, 140.93, 168.61; FT-IR (KBr) ν 3427, 3069, 3045, 2930, 2890, 2856, 1660, 1650, 1471, 1461, 1427, 1330, 1241, 1111, 1090, 934, 822 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{68}H_{81}NNaO_9Si_2$ 1134.5342, found 1134.5345; $[\alpha]_D^{29.0}$ −28.9° (*c* 1.00, $CHCl_3$).

4.2.12. Hemiacetal 30. A solution of alcohol **28** (2.00 g, 1.80 mmol) and *p*-anisaldehyde (43.8 µl, 0.360 mmol) in toluene (18 ml) was warmed to 90 °C. CSA (836 mg, 3.60 mmol) was added and the mixture was stirred for 1 h at 90 °C. *p*-Anisaldehyde (43.8 µl, 0.360 mmol) and CSA (418 mg, 1.80 mmol) were further added to the mixture, and the stirring was continued for an additional 1 h at 90 °C. The reaction mixture was cooled to 0 °C, and diluted with hexane (35 ml) and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc, and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was roughly purified by open column chromatography (FLORISIL® =10 g, hexane/EtOAc=5) to give lactone **29** (1.58 g). Analytical sample was obtained by further purification using silica gel column chromatography. **29**: colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H, *t*-Bu), 1.01 (s, 9H, *t*-Bu), 1.86 (ddd, 1H, J=14.0, 9.5, 5.0 Hz, H10), 2.26–2.36 (m, 1H, H4), 2.46 (dt, 1H, J=14.0, 7.0 Hz, H10), 2.63 (ddd, 1H, J=17.0, 8.0, 4.0 Hz, H4), 3.25 (td, 1H, J=9.0, 4.0 Hz, H5), 3.28 (t, 1H, J=9.0 Hz, H6), 3.34 (td, 1H, J=9.5, 7.0 Hz, H9), 3.52 (dd, 1H, J=9.5, 9.0 Hz, H7), 3.68 (dd, 1H, J=12.0, 9.0 Hz, H17), 3.89 (dt, 1H, J=9.0, 4.5 Hz, H16), 3.89 (dd, 1H, J=12.0, 4.5 Hz, H17), 3.98 (dd, 1H, J=16.0, 3.0 Hz, H1), 4.21 (dd, 1H, J=7.0, 4.5 Hz, H15), 4.24 (dd, 1H, J=16.0, 10.0 Hz, H1), 4.26 (t, 1H, J=9.5 Hz, H8), 4.46 (dd, 1H, J=7.0, 5.0 Hz, H11), 4.79 (d, 1H, J=11.5 Hz, CH_2Ph), 4.80 (d, 1H, J=18.0 Hz, CH_2=CH–), 4.88 (d, 1H, J=11.5 Hz, CH_2Ph), 4.89 (d, 1H, J=10.5 Hz, CH_2=CH–), 5.72 (ddd, 1H, J=18.0, 10.5, 7.0 Hz, H14), 5.72–5.77 (m, 1H, H3), 5.85 (ddt, 1H, J=12.0, 6.0, 3.0 Hz, H2), 7.22–7.45 (m, 17H, Ph), 7.53 (d, 2H, J=7.5 Hz, Ph), 7.56 (d, 2H, J=7.5 Hz, Ph), 7.61 (d, 4H, J=8.0 Hz, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.29, 26.84, 26.97, 33.30, 34.36, 64.96, 68.38, 71.07, 74.31, 75.19, 75.84, 76.84, 79.44, 81.90, 83.56, 86.65, 117.95, 126.31, 127.22, 127.37, 127.43, 127.74, 128.16, 129.40, 129.49, 129.65, 129.72, 131.30, 133.07, 133.24, 133.55, 133.75, 135.53, 136.03, 136.08, 136.91, 138.79, 169.01; FT-IR (film) ν 3071, 2931, 2890, 2858,

1757, 1471, 1427, 1361, 1113, 935, 823 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{56}H_{66}NaO_8Si_2$ 945.4188, found 945.4189; $[\alpha]_D^{29.0}$ −47.8° (*c* 1.00, $CHCl_3$).

To a solution of tetravinyltin (249 μl, 1.37 mmol) in THF (13 ml) was added MeLi (0.92 M solution in Et_2O, 5.58 ml, 5.13 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C and then cooled to −100 °C. A solution of lactone **29** (1.58 g) in THF (16 ml) was slowly added over 30 min and the resulting mixture was stirred for 15 min at −100 °C to −90 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with hexane–EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=5) to give hemiacetal **30** (1.31 g, 1.38 mmol, 77% in 2 steps). **30**: colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.02 (s, 9H), 1.56 (ketoalcohol, q, 1H, J=12.0 Hz), 1.81 (ketoalcohol, ddt, 1H, J=16.0, 9.0, 4.5 Hz), 2.05–2.19 (m), 2.28–2.42 (m), 2.38 (ketoalcohol, ddd, 1H, J=16.0, 8.0, 4.0 Hz), 2.51 (hemiacetal, brs, 1H), 2.64 (hemiacetal, ddd, 1H, J=16.0, 8.0, 3.0 Hz), 2.96 (hemiacetal, ddd, 1H, J=12.0, 10.0, 4.0 Hz), 3.02 (ketoalcohol, td, 1H, J=9.5, 4.0 Hz), 3.18–3.29 (m), 3.32 (hemiacetal, t, 1H, J=9.0 Hz), 3.37 (hemiacetal, s, 1H), 3.45 (hemiacetal, t, 1H, J=9.0 Hz), 3.49–3.80 (m), 3.91 (ketoalcohol, dq, 1H, J=15.0, 3.0 Hz), 3.98 (hemiacetal, t, 1H, J=9.5 Hz), 4.00 (hemiacetal, dq, 1H, J=15.5, 3.0 Hz), 4.22 (ketoalcohol, dd, 1H, J=15.0, 6.0 Hz), 4.28 (hemiacetal, dd, 1H, J=15.5, 6.0 Hz), 4.40 (hemiacetal, d, 1H, J=8.0 Hz), 4.46 (ketoalcohol, d, 1H, J=7.0 Hz), 4.47 (hemiacetal, m, 1H), 4.53 (ketoalcohol, dd, 1H, J=8.0, 4.0 Hz), 4.58–4.99 (m), 5.20 (hemiacetal, dd, 1H, J=10.5, 1.5 Hz), 5.46 (hemiacetal, dd, 1H, J=17.0, 1.5 Hz), 5.56 (ketoalcohol, dd, 1H, J=11.0, 2.0 Hz), 5.69 (ddt, 1H, J=12.0, 8.0, 3.0 Hz), 5.76 (ddd, 1H, J=18.0, 10.5, 7.0 Hz), 5.81–5.89 (m), 5.84 (ketoalcohol, ddt, 1H, J=12.0, 6.0, 3.0 Hz), 6.08 (hemiacetal, dd, 1H, J=17.0, 10.5 Hz), 6.28 (ketoalcohol, dd, 1H, J=17.5, 2.0 Hz), 6.81 (ketoalcohol, dd, 1H, J=17.5, 11.0 Hz), 7.22–7.44 (m, 17H), 7.50–7.66 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.05, 19.30, 26.77, 27.08, 31.11, 34.02, 34.69, 34.86, 63.46, 63.92, 67.70, 68.40, 72.96, 73.00, 73.37, 74.32, 74.55, 75.04, 75.71, 75.83, 76.49, 76.71, 77.19, 81.24, 81.44, 81.66, 83.03, 84.94, 87.30, 87.86, 94.71, 115.97, 117.12, 126.60, 127.27, 127.45, 127.55, 127.64, 127.77, 127.86, 128.06, 128.33, 128.49, 129.47, 129.57, 129.63, 131.28, 131.39, 132.42, 133.15, 133.21, 133.67, 133.84, 135.51, 136.03, 136.29, 139.04, 139.10, 139.40, 200.32; FT-IR (film) ν 3470, 3071, 2931, 2857, 2360, 1702, 1611, 1589, 1471, 1427, 1361, 1112, 998, 935, 823 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{58}H_{70}NaO_7Si_2$ 973.4501, found 973.4455; $[\alpha]_D^{28.0}$ −13.1° (*c* 1.50, $CHCl_3$).

4.2.13. Diol 32. To a solution of hemiacetal **30** (3.02 g, 3.17 mmol) and Et_3SiH (5.06 ml, 31.7 mmol) in CH_3CN (14 ml) was added TMSOTf (500 μl, 2.76 mmol) at −40 °C. The mixture was gradually warmed to −20 °C over 40 min with stirring and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc, and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=50–20–15–7–5–2–0.5) to give bis-TBPS ether **31** (789 mg, 0.844 mmol, 27%), C15-mono-TBPS ether (378 mg, 0.542 mmol, 17%), C17-mono-TBPS ether (277 mg, 0.397 mmol, 13%), and diol **32** (370 mg, 0.810 mmol, 24%).

To a mixture of bis-TBPS ether **31** (789 mg, 0.844 mmol, 27%), C15-mono-TBPS ether (378 mg, 0.542 mmol, 17%), and C17-mono-TBPS ether (277 mg, 0.397 mmol, 13%) in THF (18 ml) was added TBAF (1.0 M solution in THF, 4.46 ml, 4.46 mmol). The mixture was stirred for 44 h at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=3–0.5, then hexane/EtOAc/MeOH=5:10:1) to give diol **32** (818 mg, 1.78 mmol, 58% in 2 steps). **32**: colorless powder; mp 159–160 °C (hexane–CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (q, 1H, J=11.5 Hz, H10), 1.90 (brs, 1H, OH), 2.33 (ddq, 1H, J=16.0, 9.0, 3.0 Hz, H4), 2.39 (brs, 1H, OH), 2.56 (dt, 1H, J=11.5, 4.5 Hz, H10), 2.63 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.14 (ddd, 1H, J=11.5, 9.0, 4.5 Hz, H9), 3.20 (t, 1H, J=9.0 Hz, H8), 3.29 (td, 1H, J=9.0, 4.0 Hz, H5), 3.31–3.38 (m, 1H, H11), 3.34 (t, 1H, J=9.0 Hz, H6), 3.46–3.50 (m, 1H, H16), 3.49 (t, 1H, J=9.0 Hz, H7), 3.65 (brd, 1H, J=12.0 Hz, H17), 3.68–3.73 (m, 1H, H17), 3.73 (dd, 1H, J=9.5, 5.5 Hz, H12), 4.02 (dq, 1H, J=15.0, 3.0 Hz, H1), 4.29 (dd, 1H, J=15.0, 6.0 Hz, H1), 4.33 (brs, 1H, H15), 4.81 (d, 1H, J=11.0 Hz, CH_2Ph), 4.88 (d, 1H, J=11.0 Hz, CH_2Ph), 5.24 (dt, 1H, J=11.0, 1.5 Hz, CH_2=CH–), 5.35 (dq, 1H, J=10.0, 1.5 Hz, CH_2=CH–), 5.37 (dt, 1H, J=17.0, 1.5 Hz, CH_2=CH–), 5.46 (dt, 1H, J=17.0, 1.5 Hz, CH_2=CH–), 5.76 (ddt, 1H, J=11.0, 8.0, 3.0 Hz, H3), 5.84 (ddd, 1H, J=17.0, 11.0, 5.5 Hz, H14), 5.86 (ddt, 1H, J=11.0, 6.0, 3.0 Hz, H2), 6.00 (ddd, 1H, J=17.0, 10.0, 5.5 Hz, H13), 7.23–7.28 (m, 1H, Ph), 7.32 (t, 2H, J=8.0 Hz, Ph), 7.40 (d, 2H, J=8.0 Hz, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.58, 36.21, 61.55, 68.34, 72.84, 75.03, 76.04, 76.34, 76.79, 80.75, 81.01, 81.80, 87.18, 116.68, 118.25, 126.52, 127.33, 127.80, 128.10, 131.82, 135.78, 135.91, 138.99; FT-IR (film) ν 3446, 3028, 2930, 2874, 1455, 1361, 1263, 1096, 926, 738 cm^{-1}; ESI-TOF MS $[M+NH_4]^+$ calcd for $C_{26}H_{38}NO_7$ 476.2648, found 476.2623; $[\alpha]_D^{28.0}$ +23.1° (*c* 1.30, $CHCl_3$).

4.2.14. ABCD ring 11. A solution of diol **32** (500 mg, 1.09 mmol) and Grubbs catalyst **37** (18.5 mg, 0.0218 mmol) in CH_2Cl_2 (55 ml) was stirred for 2.5 h at room temperature. Et_3N (400 μl) was added and the mixture was concentrated. The residue was washed with hexane by decantation and the remaining precipitate was recrystallized from hexane–EtOAc to give ABCD ring **11** (463 mg, 1.08 mmol, 99%). **11**: colorless solid; mp 190 °C (hexane–AcOEt); ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (q, 1H, J=11.0 Hz, H10), 2.15 (t, 1H, J=6.5 Hz, OH), 2.19 (d, 1H, J=6.0 Hz, OH), 2.30–2.36 (m, 1H, H4, H10), 2.64 (ddd, 1H, J=16.5, 7.5, 4.0 Hz, H4), 3.08–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, J=9.5, 4.0 Hz, H5), 3.32–3.37 (m, 1H, H11), 3.34 (t, 1H, J=8.5 Hz, H6), 3.44 (ddd, 1H, J=9.5, 6.0, 4.0 Hz, H16), 3.48 (t, 1H, J=8.5 Hz, H7), 3.73 (dt, 1H, J=12.0, 6.0 Hz, H17), 3.84–3.88 (m, 2H, H12, H17), 4.01 (brdt, 1H, J=15.5, 3.0 Hz, H1), 4.29 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.29–4.38 (m, 1H, H15), 4.83 (d, 1H, J=11.5 Hz, CH_2Ph), 4.87 (d, 1H, J=11.5 Hz, CH_2Ph), 5.66–5.74 (m, 2H, H13, H14),

5.74–5.80 (m, 1H, H3), 5.84–5.89 (m, 1H, H2), 7.24–7.29 (m, 1H, Ph), 7.33 (t, 2H, J=8.0 Hz, Ph), 7.41 (d, 2H, J=8.0 Hz, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.75, 36.89, 64.35, 68.53, 71.76, 73.23, 75.33, 77.00, 78.51, 80.45, 81.12, 82.20, 84.01, 87.54, 126.85, 127.59, 127.90, 128.36, 131.30, 131.53, 134.37, 139.29; FT-IR (film) ν 3331, 3208, 3032, 2935, 2873, 2824, 1488, 1453, 1363, 1326, 1289, 1261, 1105, 1066, 1040, 978, 957 cm^{-1}; ESI-TOF MS $[M+NH_4]^+$ calcd for $C_{24}H_{34}NO_7$ 448.2335, found 448.2314; $[\alpha]_D^{19.2}$ −7.3° (c 0.670, $CHCl_3$).

4.3. Attempts to construct the tetrahydrooxocin E ring using a chlorosulfide synthon

4.3.1. Alcohol 38. To a solution of diol **11** (500 mg, 1.16 mmol) in CH_2Cl_2 (17 ml) was added a solution of $AlCl_3$ (465 mg, 3.48 mmol) in CH_3NO_2 (5 ml) at 0 °C. The mixture was stirred for 20 min at 0 °C and quenched by the slow addition of MeOH (8 ml). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=5–3.5–0.5, then EtOAc/MeOH=20–10) to give a corresponding triol (384 mg, 1.13 mmol, 97%).

To a solution of the triol (384 mg, 1.13 mmol) in DMF (6 ml) and CH_2Cl_2 (6 ml) were added 2,2-dimethoxypropane (1.38 ml, 11.3 mmol) and PPTS (85.0 mg, 0.338 mmol). The mixture was stirred for 13 h at room temperature and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with Et_2O, and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was recrystallized from hexane–EtOAc to give a corresponding acetonide (360 mg, 0.946 mmol, 84%). colorless powder; mp 245–245 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H, Me), 1.47 (s, 3H, Me), 1.52 (q, 1H, J=11.5 Hz, H10), 2.29 (dt, 1H, J=11.8, 4.4 Hz, H10), 2.34–2.40 (m, 1H, H4), 2.61 (brddd, 1H, J=16.0, 8.5, 2.8 Hz, H4), 3.04 (t, 1H, J=9.3 Hz, H8), 3.13 (ddd, 1H, J=11.8, 9.3, 4.5 Hz, H9), 3.21–3.28 (m, 2H, H5, H6), 3.30–3.38 (m, 2H, H11, H16), 3.60 (d, 1H, J=11.0 Hz, H17), 3.62–3.66 (m, 1H, H7), 3.82 (dd, 1H, J=11.5, 5.5 Hz, H17), 3.92 (brdq, 1H, J=9.3, 2.2 Hz, H12), 4.02 (brdq, 1H, J=15.0, 3.0 Hz, H1), 4.33 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.35 (brdd, 1H, J=9.0, 2.0 Hz, H15), 5.64 (brdt, 1H, J=12.7, 2.4 Hz, H13), 5.74 (brdt, 1H, J=12.5, 2.1 Hz, H14), 5.80–5.86 (m, 1H, H3), 5.90–5.95 (m, 1H, H2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.68, 28.75, 34.25, 36.47, 62.51, 68.16, 72.75, 72.96, 74.01, 75.21, 75.94, 76.79, 80.14, 80.59, 87.61, 98.33, 127.54, 131.29, 131.60, 132.46; FT-IR (film) ν 3446, 3028, 2930, 2874, 1455, 1361, 1263, 1096, 926, 738 cm^{-1}; $[\alpha]_D^{19.3}$ −9.3° (c 1.03, $CHCl_3$).

To a solution of the acetonide (2.75 g, 7.24 mmol) in THF (120 ml) and DMF (40 ml) were added NAPBr (4.80 g, 21.7 mmol) and NaH (60% dispersion in mineral oil, 1.45 g, 36.2 mmol) at room temperature. After stirring for 5 min, TBAI (2.67 g, 7.24 mmol) was added and the resulting mixture was stirred for 30 min at 40 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=30–1.5) to give a corresponding NAP–ether (3.31 g, 6.36 mmol, 88%). All spectroscopic data are identical to those reported in the literature.[14]

To a solution of the NAP–ether (1.14 g, 2.18 mmol) in MeOH (32 ml) and THF (16 ml) was added $TsOH\cdot H_2O$ (57.0 mg, 0.218 mmol). The mixture was stirred for 27 h at room temperature and quenched with Et_3N (1 ml). Concentration of the solution gave a corresponding diol (1.11 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (q, 1H, J=11.5 Hz, H10), 2.31–2.37 (m, 2H, H4, H10), 2.64 (1H, ddd, J=16.0, 8.0, 4.0 Hz, H4), 3.10–3.16 (m, 2H, H8, H9), 3.29 (ddd, 1H, J=10.5, 10.5, 4.0 Hz, H5), 3.35 (ddd, 1H, J=11.5, 9.5, 5.0 Hz, H11), 3.38 (dd, 1H, J=9.0, 9.0 Hz, H6), 3.45 (ddd, 1H, J=9.0, 6.0, 4.0 Hz, H16), 3.53 (t, 1H, J=9.0 Hz, H7), 3.74 (dt, 1H, J=11.5, 5.5 Hz, H17), 3.86 (dd, 1H, J=7.0, 4.0 Hz, H17), 3.89 (brd, 1H, J=9.5 Hz, H12), 4.04 (ddd, 1H, J=15.5, 5.5, 2.5 Hz, H1), 4.31 (dd, 1H, J=15.5, 5.5 Hz, H1), 4.37 (brdd, 1H, J=9.0, 5.5 Hz, H15), 5.00 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.72 (s, 2H, H13, H14), 5.78 (ddt, 1H, J=11.5, 8.5, 3.0 Hz, H3), 5.88 (ddt, 1H, J=11.5, 6.0, 3.5 Hz, H2), 7.44–7.47 (m, 2H, NAP) 7.55 (dd, 1H, J=9.0, 2.0 Hz, NAP) 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.79, 34.74, 36.87, 44.93, 49.95, 64.34, 68.53, 71.75, 73.21, 75.35, 78.47, 80.44, 81.09, 82.10, 83.98, 87.62, 125.81, 126.05, 126.22, 126.48, 126.91, 127.82, 128.02, 131.55, 134.36, 146.88; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{28}H_{32}NaO_7$ 503.2046, found 503.2215.

To a solution of the diol (1.11 g) and 2,6-lutidine (763 μl, 6.55 mmol) in CH_2Cl_2 (44 ml) was added TBSOTf (1.5 ml, 6.55 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc and the combined organic phase was washed with 1M HCl, brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10) to give a corresponding bis-TBS ether (1.52 g, 2.15 mmol, 98% in 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04–0.10 (m, 12H, TBS), 0.88–0.92 (m, 18H, TBS) 1.56 (q, 1H, J=11.0 Hz, H10), 2.32–2.37 (m, 2H, H4, H10), 2.65 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.11–3.18 (m, 2H, H8, H9), 3.27–3.34 (m, 2H, H5, H11), 3.36–3.40 (m, 2H, H6, H16), 3.53 (t, 1H, J=8.5 Hz, H7), 3.64 (dd, 1H, J=11.0, 6.0 Hz, H17), 3.82 (dd, 1H, J=10.5, 1.5 Hz, H17), 3.87 (d, 1H, J=8.5 Hz, H12), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.26 (d, 1H, J=9.0 Hz, H15), 4.31 (dd, 1H, J=15.5, 5.5 Hz, H1), 4.99 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=11.5 Hz, NAP), 5.65 (s, 2H, H13, H14), 5.78 (ddt, 1H, J=11.0, 7.5, 3.0 Hz, H3), 5.88 (ddd, 1H, J=12.5, 6.5, 3.5 Hz, H2), 7.43–7.48 (m, 2H, NAP), 7.55 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.96, −4.87, −4.33, −3.43, 18.11, 18.66, 25.79, 25.85, 25.93, 26.14, 34.78, 36.95, 64.21, 68.51, 71.27, 73.42, 75.29, 78.27, 80.75. 81.12, 82.15, 85.74, 87.57, 104.90, 125.76, 126.00, 126.24, 126.44, 126.91, 127.80, 128.00, 128.04, 130.42, 131.58, 136.26, 136.84; FT-IR (film) ν 2953, 2930, 2857, 1469, 1362, 1254, 1091, 1007, 940, 869, 836 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{40}H_{60}NaO_7Si_2$ 731.3775, found 731.3781.

To a solution of the bis-TBS ether (1.52 g, 2.15 mmol) in MeOH (22 ml) and THF (22 ml) was added CSA (50.0 mg, 0.215 mmol) at −15 °C. The mixture was stirred for 14 h at −15 °C, and quenched with Et_3N (218 μl) and then saturated $NaHCO_3$ solution. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1) to give alcohol **38** (1.09 g, 1.83 mmol, 85%), recovery of bis-TBS ether (130 mg, 0.183 mmol, 9%) and a corresponding diol (38.2 mg, 0.0795 mmol, 4%). **38**: colorless solid; mp: 160–161 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, $SiMe_3$), 0.10 (s, 3H, $SiMe_3$), 0.90 (s, 9H, *t*Bu), 1.55 (dd, 1H, *J*=11.5 Hz, H10), 2.14–2.16 (m, 1H, H17), 2.32–2.37 (m, 2H, H4, H10), 2.65 (ddd, 1H, *J*=16.0, 8.0, 4.0 Hz, H4), 3.10–3.16 (m, 2H, H8, H9), 3.29 (td, 1H, *J*=9.0, 4.0 Hz, H5), 3.34 (ddd, 1H, *J*=13.5, 5.0, 2.5 Hz, H11), 3.38 (t, 1H, *J*=9.0 Hz, H6), 3.46–3.55 (m, 2H, H7, H16), 3.77–3.82 (m, 1H, H17), 3.90 (d, 1H, *J*=8.5 Hz, H12), 4.04 (brdd, 1H, *J*=12.5, 2.5 Hz, H1), 4.22 (brd, 1H, *J*=8.5 Hz, H15), 4.32 (dd, 1H, *J*=15.0, 5.5 Hz, H1), 4.99 (d, 1H, *J*=12.5 Hz, NAP), 5.04 (d, 1H, *J*=12.0 Hz, NAP), 5.68 (s, 2H, H13, H14), 5.78 (ddt, 1H, *J*=11.0, 8.5, 2.5 Hz, H3), 5.88 (ddd, 1H, *J*=12.0, 6.0, 3.0 Hz, H2), 7.43–7.48 (m, 2H, NAP), 7.55 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.90, −4.32, 18.06, 25.87, 34.73, 36.82, 63.79, 68.51, 72.45, 73.14, 75.30, 78.07, 80.44. 81.01, 82.03, 84.42, 87.58, 125.78, 126.01, 126.23, 126.46, 126.92, 127.80, 128.01, 128.02, 130.77, 131.54, 133.11, 133.41, 136.13, 136.77; FT-IR (film) ν 2931, 2859, 2070, 1254, 1087, 864, 838 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{34}H_{46}NaO_7Si$ 617.2910, found 617.2963; $[\alpha]_D^{22.0}$ +25.7°(*c* 0.780, $CHCl_3$).

4.3.2. Nitrile 39. To a suspension of alcohol **38** (1.05 g, 1.76 mmol) and MS4A (powder, activated) in pyridine (22 ml) was added TsCl (1.34 g, 7.03 mmol). The mixture was stirred for 24 h at room temperature, and diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–5) to give a corresponding tosylate (1.26 g, 1.68 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3H, $SiMe_3$), 0.09 (s, 3H, $SiMe_3$), 0.88 (s, 9H, *t*Bu), 1.39 (dd, 1H, *J*=11.5 Hz, H10), 2.18 (dt, 1H, *J*=11.5, 4.5 Hz, H10), 2.33–2.39 (m, 1H, H4), 2.44 (s, 3H, Ts), 2.66 (ddd, 1H, *J*=16.0, 8.0, 4.0 Hz, H4), 3.04–3.12 (m, 2H, H8, H9), 3.20 (ddd, 1H, *J*=13.5, 5.0, 1.5 Hz, H11), 3.28 (td, 1H, *J*=9.5, 4.0 Hz, H5), 3.38 (t, 1H, *J*=9.0 Hz, H6), 3.53 (t, 1H, *J*=8.0 Hz, H7), 3.58 (ddd, 1H, *J*=8.5, 6.5, 2.0 Hz, H16), 3.83 (brdd, 1H, *J*=9.0, 2.0 Hz, H12), 4.02 (dd, 1H, *J*=10.5, 7.0 Hz, H17), 4.05 (brdd, 1H, *J*=15.5, 2.5 Hz, H1), 4.19 (brdd, 1H, *J*=9.5, 2.0 Hz, H15), 4.24 (dd, 1H, *J*=10.5, 2.5 Hz, H17), 4.32 (dd, 1H, *J*=15.5, 6.0 Hz, H1), 5.00 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=12.5 Hz, NAP), 5.62 (dt, 1H, *J*=13.5, 2.0 Hz, H13), 5.67 (dt, 1H, *J*=13.0, 2.0 Hz, H14), 5.79 (ddt, 1H, *J*=11.0, 8.0, 2.5 Hz, H3), 5.88 (ddd, 1H, *J*=12.5, 6.5, 3.5 Hz, H2), 7.33 (d, 2H, J=8.0 Hz, Ts), 7.46 (dt, 2H, *J*=5.5, 2.0 Hz, NAP), 7.56 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.79–7.84 (m, 6H, NAP, Ts); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.95, −4.28, 17.95, 21.73, 25.81, 25.90, 34.75, 36.56, 68.51, 70.85, 71.36, 73.11, 75.25, 78.18, 80.33, 81.10, 82.07, 82.18, 87.58, 125.76, 126.00, 126.19, 126.40, 126.88, 127.78, 127.97, 128.00, 128.13, 129.86, 129.97, 131.31, 131.50, 133.10, 133.29, 133.41, 135.25, 136.81, 144.77; FT-IR (film) ν 3026, 2928, 1919, 1733, 1654, 1599, 1509, 1495, 1462, 1368, 1258, 1258, 1098, 838 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{41}H_{52}NaO_9SSi$ 771.2999, found 771.2968; $[\alpha]_D^{18.0}$ +13.2° (*c* 0.874, $CHCl_3$).

To a solution of the tosylate (582 mg, 0.778 mmol) in DMSO (11 ml) was added NaCN (78.9 mg, 1.61 mmol). The mixture was stirred for 20 h at 50 °C and diluted with AcOEt. The organic phase was washed with water and brine, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10) to give nitrile **39** (443 mg, 0.733 mmol, 94%). **39**: colorless solid; mp 121–122 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H, $SiMe_3$), 0.12 (s, 3H, $SiMe_3$), 0.91 (s, 9H, *t*Bu), 1.58 (q, 1H, *J*=11.0 Hz, H10), 2.32–2.43 (m, 2H, H4, H10), 2.49 (dd, 1H, *J*=16.5, 8.0 Hz, H17), 2.64 (ddd, 1H, *J*=16.5, 8.5, 4.5 Hz, H4), 2.75 (dd, 1H, *J*=16.5, 3.5 Hz, H17), 3.09–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, *J*=9.5, 4.0 Hz, H5), 3.34 (ddd, 1H, *J*=13.5, 4.0, 2.5 Hz, H11), 3.39 (t, 1H, *J*=9.5 Hz, H6), 3.53 (t, 1H, *J*=8.5 Hz, H7), 3.63 (td, 1H, *J*=7.5, 3.0 Hz, H16), 3.91 (brdd, 1H, *J*=9.0, 2.5 Hz, H17), 4.04 (brdd, 1H, *J*=15.5, 2.5 Hz, H1), 4.17 (brdd, 1H, *J*=9.0, 2.0 Hz, H15), 4.32 (dd, 1H, *J*=15.5, 5.5 Hz, H1), 5.00 (d, 1H, *J*=11.5 Hz, NAP), 5.03 (d, 1H, *J*=12.5 Hz, NAP), 5.66 (dt, 1H, *J*=13.5, 2.5 Hz, H13), 5.72 (dt, 1H, *J*=12.5, 2.5 Hz, H14), 5.78 (ddt, 1H, *J*=11.0, 8.0, 2.0 Hz, H3), 5.87 (ddd, 1H, *J*=12.0, 6.0, 3.0 Hz, H2), 7.44–7.48 (m, 2H, NAP), 7.55 (dd, 1H, *J*=9.0, 1.5 Hz, NAP), 7.82–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.83, −4.16, 17.99, 22.80, 25.84, 34.71, 36.55, 68.50, 73.07, 73.56, 75.25, 78.49, 80.06, 80.27, 81.04, 82.04, 87.59, 117.84, 125.77, 126.00, 126.19, 126.42, 126.96, 127.78, 127.98, 128.00, 131.47, 131.97, 133.09, 133.39, 134.83, 136.78; FT-IR (film) ν 3023, 2954, 2858, 2359, 2252, 1509, 1467, 1365, 1302, 1258, 1094, 1009, 910, 861 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{35}H_{45}NaNO_6Si$ 626.2914, found 626.2835; $[\alpha]_D^{26.8}$ +24.4° (*c* 1.01, $CHCl_3$).

4.3.3. Alcohol 40. To a solution of nitrile **39** (854 mg, 1.41 mmol) in CH_2Cl_2 (60 ml) was added DIBAL (0.93 M solution in hexane, 3.00 ml, 2.83 mmol) at −70 °C. The mixture was stirred for 3 h at −70 °C and quenched with saturated Rochelle salt solution. The resulting mixture was stirred for 2 h at room temperature and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave a corresponding aldehyde, which was subjected to the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (3.03 g, 8.49 mmol) in THF (100 ml) was added $NaN(SiMe_3)_2$ (2.0 M solution in THF, 3.50 ml, 7.07 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C followed by the addition of the crude aldehyde in THF (40 ml). The resulting mixture was stirred for 1 h at 0 °C and quenched with saturated NH_4Cl solution. Aqueous phase

was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 10) to give a corresponding alkene (246 mg, 0.407 mmol, 29% in 2 steps) and recovery of aldehyde (457 mg, 0.753 mmol, 53%). The recovered aldehyde (457 mg, 0.753 mmol) was subjected to the same reaction and purification conditions to give the alkene (481 mg, 0.795 mmol, 56% in 2 steps).

To a solution of the alkene (1.02 g, 1.68 mmol) in THF (60 ml) was added TBAF (1.0 M solution in THF, 3.80 ml, 3.80 mmol). The mixture was stirred for 18 h at room temperature and quenched with water. Aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 30–10–3) to give alcohol **40** (749 mg, 1.53 mmol, 91%). **40**: colorless solid; mp 178–179 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (dd, 1H, J = 11.0 Hz, H10), 1.79 (brs, 1H, OH), 2.26 (dt, 1H, J = 15.0, 7.5 Hz, H17), 2.31–2.37 (m, 2H, H4, H10), 2.53–2.58 (m, 1H, H17), 2.63 (ddd, 1H, J = 16.0, 8.0, 4.0 Hz, H4), 3.09–3.17 (m, 2H, H8, H9), 3.26–3.31 (m, 2H, H5, H11), 3.35–3.40 (m, 2H, H6, H16), 3.53 (t, 1H, J = 8.0 Hz, H7), 3.87 (d, 1H, J = 9.0 Hz, H12), 4.04 (brdd, 1H, J = 15.5, 2.5 Hz, H1), 4.15 (brd, 1H, J = 10.0 Hz, H15), 4.31 (dd, 1H, J = 16.0, 6.0 Hz, H1), 4.99 (d, 1H, J = 12.0 Hz, NAP), 5.04 (d, 1H, J = 12.0 Hz, NAP), 5.08 (d, 1H, J = 10.5 Hz, CH_2=CH–), 5.12 (d, 1H, J = 17.0 Hz, CH_2=CH–), 5.70 (dd, 2H, J = 16.5, 13.0 Hz, H13, H14), 5.77 (ddt, 1H, J = 11.5, 8.5, 2.5 Hz, H3), 5.85–5.97 (m, 2H, H2, H18), 7.43–7.47 (m, 2H, NAP), 7.55 (d, 1H, J = 8.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.76, 36.79, 37.71, 68.53, 73.36, 73.81, 75.34, 78.78, 80.54, 81.13, 82.21, 84.50, 87.60, 117.22, 125.78, 126.02, 126.21, 126.43, 126.91, 127.80, 128.00, 128.02, 131.35, 131.51, 133.11, 133.42, 134.29, 135.03, 136.80; FT-IR (KBr) ν 3327, 3021, 2881, 2351, 1842, 1638, 1505, 1438, 1353, 1099, 1008, 916, 854 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{30}H_{34}NaO_6Si$ 513.2253, found 513.2307; $[\alpha]_D^{28.0}$ −5.93° (c 1.01, $CHCl_3$).

4.3.4. Alcohol 43. To a solution of (2*S*)-1-phenylthio-2-*tert*-butyldimethylsilyloxy-3-butene[14] (187 mg, 0.636 mmol) in CCl_4 (6 ml) was added NCS (98.0 mg, 0.734 mmol). The mixture was stirred for 2 h at room temperature and filtered. The filter cake was washed with CCl_4 and the filtrate was concentrated to give the α-chlorosulfide **41**. To a suspension of alcohol **40** (95.7 mg, 0.195 mmol) and MS4A (50 mg, powdered, activated) in CH_2Cl_2 (5 ml) were added AgOTf (151 mg, 0.683 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (168 mg, 0.819 mmol) at −40 °C. After stirring for 15 min at −40 °C, a solution of **41** in CH_2Cl_2 (5 ml) was added and the resulting mixture was gradually warmed to 0 °C over 1 h with stirring. The mixture was eluted through a short plug of silica gel (silica gel = 2.5 g, hexane/AcOEt = 0.5) to give yellow oil, which was further purified by flash column chromatography (silica gel, hexane/AcOEt = 10–5–2–1) to give TBS ether **42** (129 mg, 0.165 mmol, 84%) as a 6:1 diastereomeric mixture, and recovery of **40** (7.1 mg, 0.0145 mmol, 7%).

To a solution of the TBS ether **42** (129 mg, 0.165 mmol) in THF (3 ml) was added TBAF (1.0 M in THF solution, 329 μl, 0.329 mmol). The mixture was stirred for 1 h at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 10–5–3) to give alcohol **43** (92.3 mg, 0.138 mmol, 84%) and a C21-epimer of **43** (15.4 mg, 0.0230 mmol, 14%). **43**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (q, 1H, J = 11.5 Hz, H10), 2.09 (dt, 1H, J = 15.0, 7.5 Hz, H17), 2.23–2.37 (m, 2H, H4, H10), 2.47–2.53 (m, 1H, H17), 2.57 (d, 1H, J = 4.5 Hz, OH), 2.63 (ddd, 1H, J = 14.0, 7.5, 3.5 Hz, H4), 3.07–3.15 (m, 2H, H8, H9), 3.25–3.31 (m, 2H, H5, H11), 3.38 (t, 1H, J = 9.0 Hz, H6), 3.49 (td, 1H, J = 9.0, 3.0 Hz, H16), 3.53 (t, 1H, J = 8.5 Hz, H7), 3.83 (brdd, 1H, J = 8.5, 2.0 Hz, H12), 4.04 (brdd, 1H, J = 15.5, 2.5 Hz, H1), 4.08 (brdd, 1H, J = 8.5, 2.0 Hz, H15), 4.27–4.33 (m, 2H, H1, H20), 4.80 (d, 1H, J = 5.5 Hz, H21), 4.99–5.06 (m, 4H, CH_2=CH-, NAP), 5.34 (brd, 1H, J = 10.0 Hz, CH_2=CH–), 5.47 (dt, 1H, J = 15.5, 1.5 Hz, CH_2=CH–), 5.73 (dt, 1H, J = 13.0, 2.5 Hz, H14), 5.76–5.83 (m, 2H, H3, H18), 5.87 (ddd, 1H, J = 12.0, 6.0, 3.0 Hz, H2), 5.98 (dt, 1H, J = 13.0, 2.5 Hz, H13), 6.04 (ddd, 1H, J = 17.0, 10.5, 5.5 Hz, H19), 7.31–7.34 (m, 3H, Ph), 7.45–7.48 (m, 2H, NAP), 7.50–7.52 (m, 2H, Ph), 7.56(dd, 1H, J = 8.5, 1.5 Hz, NAP), 7.82–7.86 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.73, 36.65, 37.12, 68.49, 73.27, 74.17, 75.31, 78.61, 80.40, 81.05, 81.13, 82.15, 83.43, 87.60, 96.67, 117.23, 118.19, 125.77, 126.01, 126.18, 126.41, 126.86, 127.79, 127.99, 128.00, 128.30, 129.39, 131.46, 131.48, 132.79, 132.91, 133.09, 133.20, 133.41, 133.58, 134.83, 135.87, 136.79; FT-IR (film) ν 3466, 2877, 1737, 1439, 1368, 1260, 1098, 922, 855, 817 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd. for $C_{40}H_{44}NaO_7S$ 691.2705, found 691.2722.

4.3.5. TBS ether 45. A solution of alcohol **43** (106 mg, 0.158 mmol) and Grubbs catalyst **37** (4.0 mg, 4.7 μmol) in CH_2Cl_2 (16 ml) was stirred for 6 h at room temperature. Et_3N (100 μl) was added and the mixture was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 5–3–1–AcOEt only) to give alcohol **44** (91.2 mg, 0.142 mmol, 90%).

To a solution of the alcohol **44** (91.2 mg, 0.142 mmol) in DMF (7 ml) were added imidazole (194 mg, 2.85 mmol) and TBSCl (215 mg, 1.42 mmol). The mixture was stirred for 25 h at room temperature and diluted with AcOEt and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 20–5) to give TBS ether **45** (103 mg, 0.136 mmol, 95%). **45**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H, $SiMe_3$), 0.16 (s, 3H, $SiMe_3$), 0.94 (s, 9H, *t*Bu), 1.47 (q, 1H, J = 12.5 Hz, H10), 2.22–2.25 (m, 2H, H10, H17), 2.29–2.34 (m, 1H, H4), 2.62 (ddd, 1H, J = 16.0, 7.5, 4.0 Hz, H4), 2.76 (ddd, 1H, J = 13.0, 9.0, 4.0 Hz, H17), 3.02–3.08 (m, 2H, H8, H9), 3.10–3.15 (m, 1H, H11), 3.25 (td, 1H, J = 9.0, 4.0 Hz, H5), 3.33 (t, 1H, J = 8.0 Hz, H6), 3.46 (t, 1H, J = 8.0 Hz, H7), 3.54 (dt, 1H, J = 8.5, 3.5 Hz, H16), 3.68 (brdd, 1H, J = 9.0, 2.0 Hz, H12), 3.90 (brdd, 1H, J = 9.0, 2.0 Hz, H15), 4.01 (brdd, 1H, J = 16.0, 3.0 Hz, H1), 4.29 (dd, 1H, J = 15.5,

6.5 Hz, H1), 4.46 (dd, 1H, J=8.5, 3.0 Hz, H20), 4.65 (dt, 1H, J=13.0, 3.0 Hz, H13), 4.93 (d, 1H, J=8.5 Hz, H21), 4.94 (d, 1H, J=12.5 Hz, NAP), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.29 (dt, 1H, J=12.5, 2.0 Hz, H14), 5.73 (d, 2H, J=3.0 Hz, H18, H19), 5.73–5.78 (m, 1H, H3), 5.83–5.88 (m, 1H, H2), 7.29–7.54 (m, 8H, Ph, NAP), 7.79–7.83 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.73, −4.24, 18.41, 25.78, 25.99, 32.61, 34.74, 36.90, 68.50, 72.94, 73.24, 75.22, 77.93, 80.51, 80.99, 82.13, 82.25, 84.22, 87.48, 97.05, 125.77, 126.00, 126.16, 126.38, 126.80, 126.88, 127.80, 127.86, 127.93, 127.99, 129.05, 129.13, 130.29, 130.64, 131.49, 133.08, 133.41, 133.70, 133.93, 134.13, 136.82, 137.21; FT-IR (film) ν 3009, 2931, 2858, 1735, 1648, 1602, 1584, 1509, 1472, 1440, 1391, 1363, 1302, 1256, 1216, 1087, 837 cm^{-1}; MALDI-TOF MS [M+Na]$^+$ calcd for $C_{44}H_{54}NaO_7SSi$ 777.3257, found 777.3306; $[\alpha]_D^{22.0}$ −27.5° (c 0.412, $CHCl_3$).

4.3.6. Sulfone 46. To a solution of sulfide **45** (103 mg, 0.136 mmol) in CH_2Cl_2 (30 ml) was added *m*-CPBA (180 mg, 0.679 mmol) at −15 °C. The mixture was stirred for 4 h at −15 °C and quenched with Et_3N and then saturated $NaHCO_3$ solution. Aqueous phase was extracted with AcOEt, and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–5–3–1) to give sulfone **46** (79.1 mg, 0.101 mmol, 74%) and a corresponding sulfoxide (29.8 mg). The sulfoxide (29.8 mg) was subjected to the same reaction and purification conditions another twice to give **46** (25.9 mg, 0.033 mmol, 24%). **46**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3H, $SiMe_3$), 0.22 (s, 3H, $SiMe_3$), 0.96 (s, 9H, *t*Bu), 1.43 (q, 1H, J=12.0 Hz, H10), 2.20–2.33 (m, 3H, H4, H10, H17), 2.61 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.67 (ddd, 1H, J=12.5, 8.5, 3.5 Hz, H17), 3.00–3.03 (m, 2H, H8, H9), 3.07 (ddd, 1H, J=11.0, 9.0, 5.0 Hz, H11), 3.24 (td, 1H, J=9.5, 4.0 Hz, H5), 3.32 (t, 1H, J=9.0 Hz, H6), 3.44 (t, 1H, J=8.5 Hz, H7), 3.48 (dt, 1H, J=9.0, 2.5 Hz, H16), 3.62 (brdd, 1H, J=8.5, 2.0 Hz, H12), 3.83 (brdd, 1H, J=8.5, 2.5 Hz, H15), 3.87 (brd, 1H, J=12.5 Hz, H14), 4.00 (brdd, 1H, J=15.0, 3.0 Hz, H1), 4.28 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.31 (d, 1H, J=8.5 Hz, H21), 4.92 (d, 1H, J=12.0 Hz, NAP), 4.93 (d, 1H, J=8.5 Hz, H20), 4.96 (d, 1H, J=12.0 Hz, NAP), 5.18 (dt, 1H, J=12.5, 2.5 Hz, H13), 5.71–5.77 (m, 3H, H3, H18, H19), 5.85 (ddd, 1H, J=7.5, 6.0, 3.0 Hz, H2), 7.42–8.08 (m, 12H, Ph, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.77, −4.36, 14.27, 18.33, 22.80, 25.96, 31.74, 32.59, 34.72, 36.79, 68.51, 69.92, 73.12, 75.22, 77.90, 80.31, 80.96, 82.14, 83.62, 84.10, 87.47, 97.59, 125.82, 126.03, 126.12, 126.34, 126.86, 127.82, 127.94, 127.96, 129.09, 129.60, 129.96, 131.24, 131.48, 131.55, 133.07, 133.40, 133.65, 133.81, 136.79, 138.79; FT-IR (film) ν 3026, 2931, 2858, 1726, 1446, 1328, 1257, 1153, 1089, 1006, 857, 839 cm^{-1}; MALDI-TOF MS [M+Na]$^+$ calcd for $C_{44}H_{54}NaO_9SSi$ 809.3155, found 809.2830; $[\alpha]_D^{20.0}$ −54.2° (c 1.12, $CHCl_3$).

4.3.7. Attempted allylation of 46 with allyltrimethylsilane in the presence of $AlCl_3$. Allyltrimethylsilane (95.3 μl, 0.600 mmol) was added to a suspention of $AlCl_3$ (40.0 mg, 0.300 mmol) in CH_2Cl_2 (3 ml) at −70 °C. The mixture was stirred for 30 min at −70 °C, followed by the addition of sulfone **46** (47.2 mg, 0.0600 mmol) in CH_2Cl_2 (3 ml), and the resulting mixture was stirred for 30 min at −60 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=7–3–1) to give NAP ether **51** (20.8 mg, 30.3 μmol, 50%, 2:1 stereoisomers) and a corresponding C7-alcohol **52** (6.7 mg, 12.3 μmol, 20%, 2:1 stereoisomers).

To a solution of TBS ether **51** (29.2 mg, 0.0430 mmol, 2:1 stereoisomers) in THF (2 ml) was added TBAF (1.0 M solution in THF, 85 μl, 0.085 mmol). The mixture was stirred for 24 h at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt=5–3–1) to give a corresponding C21-alcohol (24.7 mg, 0.043 mmol, 100%) as a 2:1 stereoisomers. The stereoisomers were separated by HPLC for spectral analyses. Major stereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.58 (m, 1H, H10), 2.26–2.31 (m, 3H, H4, H17, H22), 2.34–2.39 (m, 2H, H10, H22), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.77 (brdd, 1H, J=15.5, 6.5 Hz, H17), 3.09–3.15 (m, 2H, H8, H9), 3.28 (td, 2H, J=9.5, 4.0 Hz, H5, H11), 3.38 (t, 1H, J=9.0 Hz, H6), 3.51–3.56 (m, 2H, H7, H16), 3.67 (brs, 1H, H21), 3.89 (ddd, 1H, J=9.0, 4.5, 2.5 Hz, H12), 4.04 (brdd, 1H, J=15.0, 2.5 Hz, H1), 4.08 (td, 1H, J=4.0, 2.0 Hz, H20), 4.25 (brdd, 1H, J=8.0, 2.5 Hz, H15), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.11–5.16 (m, 2H, H24, H24), 5.66 (dd, 1H, J=12.5, 4.0 Hz, H19), 5.68 (dt, 1H, J=12.0, 2.5 Hz, H14), 5.79 (ddt, 1H, J=10.5, 8.5, 2.5 Hz, H3), 5.79–5.92 (m, 4H, H2, H13, H18, H23), 7.44–7.47 (m, 2H, NAP), 7.55 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.24, 34.76, 37.02, 37.42, 68.52, 72.82, 73.33, 75.32, 78.06, 80.61, 81.05, 82.16, 82.33, 82.71, 82.74, 87.62, 117.82, 125.79, 126.03, 126.24, 126.47, 126.94, 127.82, 128.01, 128.04, 128.33, 128.38, 129.19, 130.85, 130.98, 131.54, 133.12, 133.44, 134.13, 134.55, 136.82; FT-IR (film) ν 3468, 3027, 2931, 2875, 1640, 1509, 1438, 1367, 1270, 1087, 1011, 915, 855, 817 cm^{-1}; MALDI-TOF MS [M+Na]$^+$ calcd for $C_{35}H_{40}NaO_7$ 595.2672, found 595.2608; $[\alpha]_D^{23.0}$ −34.3° (c 0.150, $CHCl_3$). Minor stereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.56 (m, 1H, H10), 2.00 (d, 1H, J=6.0 Hz, OH), 2.26–2.31 (m, 3H, H10, H17, H22), 2.33–2.39 (m, 2H, H4, H22), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.76–2.81 (m, 1H, H17), 3.08–3.14 (m, 2H, H8, H9), 3.28 (td, 2H, J=10.0, 4.0 Hz, H5, H11), 3.38 (t, 1H, J=9.0 Hz, H6), 3.52 (t, 1H, J=8.5 Hz, H7), 3.56 (dt, 1H, J=8.5, 5.0 Hz, H16), 3.78 (dtd, 1H, J=9.0, 8.5, 4.5 Hz, H21), 3.89 (ddd, 1H, J=9.0, 4.0, 2.0 Hz, H12), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.18 (brs, 1H, H20), 4.24 (ddd, 1H, J=8.5, 5.0, 3.0 Hz, H15), 4.31 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.12–5.17 (m, 2H, H24, H24), 5.67 (dt, 1H, J=12.5, 2.5 Hz, H14), 5.70 (brdd, 1H, J=11.5, 3.0 Hz, H19), 5.77 (ddt, 1H, J=11.5, 8.5, 3.0 Hz, H3), 5.83 (dt, 1H, J=13.0, 3.0 Hz, H13), 5.85–5.89 (m, 2H, H2, H23), 5.88–5.93 (m, 1H, H18), 7.44–7.47 (m, 2H, NAP), 7.55 (dd, 1H, J=9.0, 1.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ

33.24, 34.78, 37.02, 37.12, 68.53, 73.17, 73.35, 75.32, 77.11, 78.02, 80.67, 81.06, 82.18, 83.13, 83.32, 87.62, 118.07, 125.78, 126.02, 126.24, 126.46, 126.94, 127.82, 128.00, 128.04, 128.16, 130.12, 130.73, 131.53, 133.14, 133.46, 134.41, 134.84, 136.85; FT-IR (film) ν 3481, 3025, 2875, 1734, 1643, 1508, 1454, 1367, 1261, 1087, 1011, 914, 855, 817 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{35}H_{40}NaO_7$ 595.2672, found 595.2677.

4.3.8. Attempted cyanization of 53 with TMSCN in the presence of $EtAlCl_2$. To a solution of sulfide **42** (129 mg, 0.165 mmol) in CH_2Cl_2 (8 ml) was added *m*-CPBA (131 mg, 0.495 mmol) at −20 °C. After stirring for 1 h at −20 °C to −10 °C, the reaction mixture was quenched with saturated $NaHSO_3$ solution and then saturated $NaHCO_3$ solution. Aqueous phase was extracted with AcOEt, and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10–5–2) to give sulfone **53** (41.7 mg, 0.0512 mmol, 31%).

Trimethylsilyl cyanide (29.9 μl, 0.238 mmol) was added to a suspension of $EtAlCl_2$ (132 μl, 0.119 mmol) in CH_2Cl_2 (1 ml) at −50 °C. The mixture was stirred for 10 min at −50 °C followed by the addition of the sulfone **53** (9.7 mg, 0.0119 mmol) in CH_2Cl_2 (1 ml). The resulting mixture was stirred for 2 h at −50 °C to −30 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution and then saturated Rochelle salt solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=7–3–1) to give chloride **56** (3.6 mg, 5.08 μmol, 35%) as a 2:1 stereoisomers. **56** (2:1 stereoisomers): ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H, TBS major), 0.05 (s, 3H, TBS minor), 0.08 (s, 3H, TBS minor), 0.08 (s, 3H, TBS major), 0.90 (s, 9H, TBS major), 0.90 (s, 9H, TBS minor), 1.48–1.53 (m, 1H, H10), 1.82–1.89 (m, 1H, H19 minor), 1.91 (ddd, 1H, J=14.0, 9.5, 5.5 Hz, H19 major), 2.23–2.40 (m, 4H, H4, H10, H17, H19), 2.44 (dd, 1H, J=13.5, 4.0 Hz, H17), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.08–3.14 (m, 2H, H8, H9), 3.21–3.31 (m, 2H, H5, H11), 3.38 (t, 1H, J=9.0 Hz, H6), 3.44 (td, 1H, J=9.5, 4.5 Hz, H16), 3.52 (t, 1H, J=8.5 Hz, H7), 3.60 (ddd, 1H, J=10.0, 5.5, 5.0 Hz, H20), 3.85 (brdd, 1H, J=9.0, 2.0 Hz, H12), 3.95 (brdd, 1H, J=9.0, 2.0 Hz, H15), 4.02–4.08 (m, 2H, H1, H21), 4.11–4.20 (m, 1H, H18 major), 4.30 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.41 (brdd, 1H, J=10.0, 7.5 Hz, H18 minor), 4.98 (d, 1H, J=12.0 Hz, NAP minor), 4.99 (d, 1H, J=12.0 Hz, NAP major), 5.03 (d, 1H, J=12.0 Hz, NAP minor), 5.04 (d, 1H, J=12.0 Hz, NAP major), 5.17–5.20 (m, 1H, H23), 5.27 (dt, 1H, J=17.0, 2.0 Hz, H23 minor), 5.29 (dt, 1H, J=17.0, 2.0 Hz, H23 major), 5.64 (ddd, 1H, J=12.0, 2.5 Hz, H14 minor), 5.67 (dt, 1H, J=12.5, 2.5 Hz, H14 major), 5.74–5.90 (m, 4H, H2, H3, H13, H22), 7.43–7.47 (m, 2H, NAP), 7.54 (dd, 1H, J=9.0, 2.0 Hz, NAP), 7.81–7.85 (m, 4H, NAP); FT-IR (film) ν 3024, 2955, 2929, 2857, 1645, 1603, 1509, 1471, 1462, 1455, 1361, 1338, 1257, 1091, 1032, 1007 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{40}H_{53}NaClO_7Si$ 731.3147, found 731.3147.

4.4. General procedure of asymmetric aldol reaction in a model system

To a solution of amine (10 equiv.) in CH_2Cl_2 was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 4–6 equiv.) at −78 °C. The mixture was stirred for 30 min at −78 °C followed by the addition of amide **59**, **60**, or **61** (1 equiv.) and the stirring was continued for an additional 30 min at −78 °C. Freshly distilled acrolein (10 equiv.) was added and the resulting mixture was stirred for indicated times at indicated temperature as shown in Table 2. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography to give a mixture of aldol products **62**, **63**, **64**, and recovery of amide **59**, **60**, or **61**. The aldol products were separated by HPLC for spectral analysis.

4.4.1. 20,21-*anti*-15,21-*syn* Aldol product of 59. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$); δ 1.43 (ddd, 1H, J=23.0, 12.0, 5.5 Hz, H3) 1.58–1.64 (m, 2H, H2, H2) 1.99 (brdd, 1H, J=12.0, 3.0 Hz, H3), 2.29 (dt, 1H, J=15.0, 7.5 Hz, H6), 2.66–2.71 (m, 1H, H6), 2.72 (dd, 1H, J=13.5, 10.0 Hz, H13), 2.85 (d, 1H, J=9.0 Hz, OH), 3.21 (ddd, 1H, J=10.0, 8.5, 4.0 Hz, H4), 3.28–3.33 (m, 3H, H1, H5, H13), 3.87 (dt, 1H, J=11.0, 2.0 Hz, H1), 4.35–4.41 (m, 2H, H15, H15), 4.48 (dt, 1H, J=9.5, 6.0 Hz, H11), 5.01 (ddd, 1H, J=14.0, 7.0, 3.5 Hz, H14), 5.09 (d, 1H, J=9.5 Hz, H8), 5.14 (dd, 1H, J=17.0, 1.5 Hz, H8), 5.32 (dt, 1H, J=10.5, 1.0 Hz, H9), 5.42 (dt, 1H, J=17.5, 1.5 Hz, H9), 5.90 (dddd, 1H, J=17.5, 10.0, 8.0, 7.0 Hz, H7), 6.10 (ddd, 1H, J=17.5, 10.5, 6.0 Hz, H10), 6.30 (d, 1H, J=6.5 Hz, H12), 7.23–7.35 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.45, 30.26, 36.70, 37.74, 60.63, 67.67, 71.28, 74.52, 78.11, 79.23, 79.86, 117.07, 117.81, 127.69, 129.23, 129.53, 135.09, 135.15, 136.29, 173.32, 186.21; FT-IR (film) ν 3481, 3073, 3028, 2930, 2855, 1711, 1642, 1497, 1454, 1369, 1326, 1285, 1197, 1161, 1098 1028, 963 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1661; $[\alpha]_D^{21.0}$ −112° (*c* 0.500, $CHCl_3$).

4.4.2. 20,21-*syn*-15,21-*syn* Aldol product of 59. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (tdd, 1H, J=13.0, 10.5, 5.0 Hz, H3), 1.66 (ddt, 1H, J=26.0, 13.5, 4.5 Hz, H2), 1.71–1.74 (m, 1H, H2), 2.27 (dt, 1H, J=15.0, 7.5 Hz, H6), 2.40 (brdd, 1H, J=12.0, 3.0 Hz, H3), 2.45 (d, 1H, J=7.0 Hz, OH), 2.82 (dd, 1H, J=13.0, 10.5 Hz, H13), 2.82–2.87 (m, 1H, H6), 3.21 (td, 1H, J=8.5, 4.0 Hz, H4), 3.25 (ddd, 1H, J=8.5, 3.0 Hz, H5), 3.35 (td, 1H, J=11.5, 2.5 Hz, H1), 3.37 (dd, 1H, J=13.0, 3.5 Hz, H13), 3.92 (ddt, 1H, J=11.0, 4.5, 1.5 Hz, H1), 4.26 (dd, 1H, J=9.0, 7.5 Hz, H15), 4.35 (dd, 1H, J=9.5, 2.0 Hz, H15), 4.44 (ddt, 1H, J=12.5, 5.5, 1.0 Hz, H11), 4.83 (dddd, 1H, J=10.0, 7.5, 4.0, 2.0 Hz, H14), 5.07 (ddt, 1H, J=10.5, 2.0, 1.0 Hz, H8), 5.16 (ddd, 1H, J=17.0, 4.0, 2.0 Hz, H8), 5.22 (dt, 1H, J=10.5, 1.5 Hz, H9), 5.36 (dt, 1H, J=17.5, 1.5 Hz, H9), 5.93 (ddt, 1H, J=17.5, 10.5, 7.5 Hz, H7), 6.01 (ddd, 1H, J=17.0, 11.0, 5.5 Hz, H10), 6.64 (d, 1H, J=5.5 Hz, H12), 7.22–7.36 (m, 5H, Bn); MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1767.

4.4.3. 20,21-*syn*-15,21-*anti* Aldol product of 59. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (tdd, 1H, J=12.5, 10.5, 4.5 Hz, H3), 1.64 (ddt, 1H, J=26.0, 12.5, 4.5 Hz, H2), 1.72 (brd, 1H, J=12.5 Hz, H2), 2.31 (dt, 2H, J=16.0, 8.0 Hz, H3, H6), 2.46 (d, 1H, J=8.5 Hz, OH), 2.84 (dd, 1H, J=13.0, 10.0 Hz, H13), 2.88 (dddt, 1H, J=14.5, 6.5, 2.5, 1.5 Hz, H6), 3.21 (td, 1H, J=8.5, 4.5 Hz, H4), 3.26 (td, 1H, J=8.5, 3.0 Hz, H5), 3.34 (td, 1H, J=11.5, 2.5 Hz, H1), 3.36 (dd, 1H, J=13.0, 3.5 Hz, H13), 3.91 (brdd, 1H, J=11.5, 5.0 Hz, H1), 4.30 (dd, 1H, J=9.5, 7.5 Hz, H15), 4.37 (dd, 1H, J=9.0, 2.0 Hz, H15) 4.50 (brs, 1H, H11), 4.87 (dddd, 1H, J=10.0, 7.5, 3.5, 2.0 Hz, H14), 5.08 (dd, 1H, J=10.5, 1.5 Hz, H8), 5.17 (dd, 1H, J=17.0, 1.5 Hz, H8), 5.24 (d, 1H, J=10.5 Hz, H9), 5.36 (d, 1H, J=17.0 Hz, H9), 5.90–5.99 (m, 2H, H7, H10), 6.43 (d, 1H, J=3.5 Hz, H12), 7.23–7.36 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.22, 29.08, 36.71, 37.70, 61.02, 67.68, 71.13, 73.83, 76.03, 76.31, 80.15, 116.64, 117.24, 127.65, 129.16, 129.49, 135.07, 135.65, 136.51, 171.54, 185.60; FT-IR (film) ν 3431, 3073, 3028, 2938, 2854, 1714, 1641, 1604, 1497, 1454, 1364, 1327, 1285, 1196, 1098, 960 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1735; $[\alpha]_D^{22.0}$ +21.1° (c 2.04, $CHCl_3$).

4.4.4. 20,21-*anti*-15,21-*syn* Aldol product of 60. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41–1.51 (m, 1H, H3), 1.64–1.69 (m, 2H, H2, H2), 2.16 (brd, 1H, J=12.5 Hz, H3), 2.32 (dt, 1H, J=14.5, 7.5 Hz, H6), 2.39 (d, 1H, J=7.0 Hz, OH), 2.68 (ddt, 1H, J=14.5, 6.5, 1.0 Hz, H6), 2.77 (dd, 1H, J=13.0, 10.5 Hz, H15), 3.30–3.39 (m, 4H, H1, H4, H5, H15), 3.89 (brdt, 1H, J=11.5, 2.0 Hz, H1), 4.27 (dd, 1H, J=9.5, 7.5 Hz, H13), 4.36 (dd, 1H, J=9.5, 2.0 Hz, H13), 4.44 (dd, 1H, J=13.0, 6.0 Hz, H11), 4.85 (dddd, 1H, J=11.0, 7.5, 3.5, 2.0 Hz, H14), 5.10 (dd, 1H, J=10.0, 1.0 Hz, H8), 5.14 (dd, 1H, J=17.5, 1.5 Hz, H8), 5.27 (d, 1H, J=10.5 Hz, H9), 5.39 (brd, 1H, J=17.0 Hz, H9), 5.92 (dddd, 1H, J=17.0, 10.0, 7.0, 6.0 Hz, H7), 6.02 (ddd, 1H, J=17.5, 11.0, 5.5 Hz, H10), 6.52 (d, 1H, J=5.5 Hz, H12), 7.23–7.36 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.50, 30.47, 36.83, 37.76, 60.95, 67.73, 71.13, 74.09, 77.85, 79.16, 79.79, 116.99, 117.54, 127.71, 129.24, 129.56, 135.12, 135.22, 135.96, 173.19, 186.22; FT-IR (film) ν 3400, 3073, 3028, 2933, 2855, 1705, 1641, 1497, 1454, 1364, 1327, 1285, 1196, 1098, 961 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1757; $[\alpha]_D^{22.2}$ +37.7° (c 0.395, $CHCl_3$).

4.4.5. 20,21-*syn*-15,21-*syn* Aldol product of 60. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (ddd, 1H, J=23.0, 12.0, 5.5 Hz, H3), 1.60–1.70 (m, 2H, H2, H2), 2.16 (brdd, 1H, J=12.5, 3.0 Hz, H3), 2.29 (dt, 1H, J=14.5, 7.0 Hz, H6), 2.50 (brd, 1H, J=8.0 Hz, OH), 2.66 (dddt, 1H, J=14.5, 6.5, 3.5, 1.5 Hz, H6), 2.81 (dd, 1H, J=13.5, 10.0 Hz, H15), 3.26–3.31 (m, 1H, H4), 3.33–3.37 (m, 3H, H1, H5, H15), 3.89 (ddt, 1H, J=11.5, 4.0, 2.0 Hz, H1), 4.30 (dd, 1H, J=8.5, 7.5 Hz, H13), 4.37 (dd, 1H, J=9.0, 1.0 Hz, H13), 4.50 (brs, 1H, H11), 4.86 (dddd, 1H, J=10.5, 7.0, 3.0, 2.0 Hz, H14), 5.10 (d, 1H, J=10.5 Hz, H8), 5.14 (dd, 1H, J=17.5, 1.5 Hz, H8), 5.27 (d, 1H, J=11.0 Hz, H9), 5.39 (d, 1H, J=17.5 Hz, H9), 5.91 (ddt, 1H, J=17.0, 10.0, 7.0 Hz, H7), 6.00 (ddd, 1H, J=17.0, 10.0, 5.5 Hz, H10), 6.37 (d, 1H, J=3.5 Hz, H12), 7.23–7.36 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.48, 30.25, 36.86, 37.62, 61.00, 67.67, 71.09, 74.13, 78.50, 79.59, 79.93, 116.99, 117.56, 127.70, 129.22, 129.55, 135.09, 135.15, 136.35, 172.38, 185.54; FT-IR (film) ν 3468, 3074, 3028, 2931, 2855, 1714, 1642, 1497, 1454, 1366, 1327, 1286, 1196, 1098, 958 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaO_5S$ 454.1664, found 454.1793; $[\alpha]_D^{23.0}$ +51.8° (c 1.10, $CHCl_3$).

4.4.6. 20,21-*anti*-15,21-*syn* Aldol product of 61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (brddd, 1H, J=23.0, 13.0, 5.0 Hz, H3), 1.57–1.72 (m, 2H, H2, H2), 2.11 (brdt, 1H, J=12.5, 3.0 Hz, H3), 2.30 (dt, 1H, J=14.5, 7.0 Hz, H6), 2.56 (d, 1H, J=7.5 Hz, OH), 2.65–2.70 (m, 1H, H6), 2.80 (dd, 1H, J=13.0, 10.0 Hz, H13), 3.25 (ddd, 1H, J=10.0, 8.5, 4.0 Hz, H4), 3.32–3.40 (m, 3H, H1, H5, H15), 3.89–3.92 (m, 1H, H1), 4.23–4.27 (m, 2H, H13), 4.37–4.40 (m, 1H, H11), 4.66–4.71 (m, 1H, H14), 5.11 (brd, 1H, J=10.5 Hz, H8), 5.15 (dt, 1H, J=17.0, 1.5 Hz, H8), 5.28 (dt, 1H, J=11.0, 1.5 Hz, H9), 5.30 (d, 1H, J=3.5 Hz, H12), 5.39 (dt, 1H, J=17.0, 1.5 Hz, H9), 5.88–5.94 (m, 1H, H7), 5.98 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H10), 7.24–7.38 (m, 5H, Bn); MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6$ 438.1893, found 438.1861.

4.4.7. 20,21-*syn*-15,21-*syn* Aldol product of 61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (brddd, 1H, J=23.0, 12.0, 5.0 Hz, H3), 1.60–1.71 (m, 2H, H2, H2), 2.11 (brdt, 1H, J=12.5, 3.0 Hz, H3), 2.30 (dt, 1H, J=14.5, 7.0 Hz, H6), 2.56 (d, 1H, J=7.5 Hz, OH), 2.65–2.70 (m, 1H, H6), 2.80 (dd, 1H, J=13.0, 10.0 Hz, H13), 3.25 (ddd, 1H, J=10.0, 8.5, 4.0 Hz, H4), 3.32–3.40 (m, 3H, H1, H5, H15), 3.89–3.92 (m, 1H, H1), 4.23–4.27 (m, 2H, H13), 4.37–4.40 (m, 1H, H11), 4.66–4.71 (m, 1H, H14), 5.11 (brd, 1H, J=10.5 Hz, H8), 5.15 (dt, 1H, J=17.0, 1.5 Hz, H8), 5.28 (dt, 1H, J=11.0, 1.5 Hz, H9), 5.30 (d, 1H, J=3.5 Hz, H12), 5.39 (dt, 1H, J=17.0, 1.5 Hz, H9), 5.88–5.94 (m, 1H, H7), 5.98 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H10), 7.24–7.38 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.46, 30.20, 36.81, 37.90, 55.71, 67.07, 67.65, 74.06, 79.06, 79.56, 79.88, 117.02, 117.49, 127.64, 129.16, 129.52, 135.05, 135.09, 136.49, 153.68, 171.21; FT-IR (film) ν 3480, 3074, 3029, 2933, 2855, 1770, 1713, 1642, 1604, 1496, 1481, 1454, 1392, 1350, 1211, 1097, 999, 920 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6$ 438.1893, found 438.1846; $[\alpha]_D^{22.6}$ +59.0° (c 1.85, $CHCl_3$).

4.4.8. 20,21-*syn*-15,21-*anti* Aldol product of 61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (brddd, 1H, J=23.5, 12.5, 4.5 Hz, H3), 1.56–1.72 (m, 2H, H2, H2), 2.24 (brdt, 1H, J=13.0, 3.5 Hz, H3), 2.30 (dt, 1H, J=15.0, 7.0 Hz, H6), 2.52 (d, 1H, J=8.0 Hz, OH), 2.81 (dd, 1H, J=13.5, 9.5 Hz, H13), 2.90–2.95 (m, 1H, H6), 3.12 (ddd, 1H, J=10.5, 8.5, 4.0 Hz, H4), 3.25–3.30 (m, 2H, H5, H13), 3.35 (td, 1H, J=12.0, 2.0 Hz, H1), 3.92 (brdd, 1H, J=11.0, 4.5 Hz, H1), 4.26 (dd, 1H, J=9.5, 3.5 Hz, H15), 4.32 (dd, 1H, J=9.0, 8.5 Hz, H15), 4.48–4.51 (m, 1H, H11), 4.78–4.83 (m, 1H, H14), 5.10 (brdd, 1H, J=10.0, 1.0 Hz, H8), 5.18 (brd, 1H, J=17.0, 1.5 Hz, H8), 5.28 (brd, 1H, J=11.5 Hz, H9), 5.35 (d, 1H, J=3.0 Hz, H12), 5.41 (brd, 1H, J=17.5 Hz, H9), 5.92–6.00 (m, 1H, H7), 5.99 (ddd, 1H, J=17.5, 11.0, 6.0 Hz, H10), 7.25–7.38 (m, 5H, Bn); FT-IR (film) ν 3525, 3073, 2938, 2855, 1775, 1715, 1640, 1497, 1454, 1393, 1352, 1275, 1215, 1099, 1052, 995 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.25, 28.97, 36.76, 37.79, 55.09,

66.99, 67.75, 73.68, 76.31, 76.46, 80.26, 116.58, 117.27, 127.61, 129.14, 129.64, 134.88, 135.83, 136.81, 153.76, 170.32; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6$ 438.1893, found 438.1879; $[\alpha]_D^{22.6}$ +115° (*c* 0.445, $CHCl_3$).

4.5. Stereocontrolled synthesis of the ABCDE ring moiety

4.5.1. Ester 65. To a solution of alcohol **40** (93.4 mg, 0.190 mmol) in THF (5 ml) and DMF (1.3 ml) was added NaH (60% dispersion in mineral oil, 15.2 mg, 0.381 mmol) at 0 °C. After stirring for 5 min, *t*-butyl bromoacetate (54.1 μl, 0.571 mmol) was added and the resulting mixture was stirred for 10 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10–5–1) to give ester **65** (106 mg, 0.175 mmol, 92%). **65**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H, *t*Bu), 1.49–1.60 (m, 1H, H10), 2.24 (dt, 1H, *J*=15.0, 8.0 Hz, H17), 2.32–2.37 (m, 2H, H4, H10), 2.61–2.67 (m, 2H, H4, H17), 3.09–3.16 (m, 2H, H8, H9), 3.26–3.32 (m, 2H, H5, H11), 3.37 (t, 1H, *J*=8.5 Hz, H6), 3.48 (td, 1H, *J*=9.5, 3.0 Hz, H16), 3.53 (t, 1H, *J*=8.5 Hz, H7), 3.87 (d, 2H, *J*=8.5 Hz, H12, H15), 4.00 (d, 1H, *J*=16.0 Hz, H21), 4.03 (brd, 1H, *J*=16.5 Hz, H1), 4.06 (d, 1H, *J*=16.5 Hz, H21), 4.31 (dd, 1H, *J*=15.5, 6.0 Hz, H1), 4.99 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 2H, *J*=11.5 Hz, CH_2=CH-, NAP), 5.09 (dd, 1H, *J*=17.5, 2.0 Hz, CH_2=CH–), 5.75–5.91 (m, 5H, H2, H3, H13, H14, H18), 7.43–7.48 (m, 2H, NAP), 7.55 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.26, 34.76, 36.73, 37.27, 67.95, 68.52, 73.34, 75.32, 78.59, 80.56, 81.11, 81.91, 81.97, 82.24, 83.60, 87.62, 116.96, 125.76, 126.01, 126.21, 126.42, 126.91, 127.80, 127.98, 128.02, 131.50, 131.71, 132.37, 133.11, 133.44, 135.23, 136.85, 169.21; FT-IR (film) ν 2977, 2876, 1750, 1452, 1368, 1301, 1228, 1131, 1098, 1008, 956, 915, 851, 817 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{36}H_{44}NaO_8$ 627.2934, found 627.2738; $[\alpha]_D^{24.5}$ +24.0° (*c* 0.460, $CHCl_3$).

4.5.2. Carboxylic acid 66. To a solution of ester **65** (66.1 mg, 0.109 mmol) in THF (3.3 ml) was added HCl (10 M, 1.64 ml, 16.4 mmol) at 0 °C. The mixture was warmed to 30 °C and stirred for 23 h. The reaction mixture was diluted with water and AcOEt. Aqueous phase was extracted with AcOEt and the combined organic phase was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=5–1) to give carboxylic acid **66** (48.4 mg, 88.2 μmol, 81%). **66**: colorless powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (q, 1H, *J*=11.5 Hz, H10), 2.26 (dt, 1H, *J*=15.0, 7.5 Hz, H17), 2.31–2.38 (m, 2H, H4, H10), 2.55–2.60 (m, 1H, H17), 2.63 (ddd, 1H, *J*=16.5, 7.5, 4.0 Hz, H4), 3.09–3.16 (m, 2H, H8, H9), 3.26–3.33 (m, 2H, H5, H11), 3.39 (t, 1H, *J*=9.0 Hz, H6), 3.52 (td, 1H, *J*=9.0, 3.5 Hz, H16), 3.54 (t, 1H, *J*=8.5 Hz, H7), 3.87 (brdd, 1H, *J*=8.5, 2.0 Hz, H12), 3.95 (brdd, 1H, J=8.5, 2.0 Hz, H15), 4.04 (brdd, 1H, *J*=15.5, 2.5 Hz, H1), 4.15 (d, 1H, *J*=16.5 Hz, H21), 4.24 (d, 1H, *J*=16.5 Hz, H21), 4.31 (dd, 1H, *J*=16.0, 6.0 Hz, H1), 4.99 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=12.0 Hz, NAP), 5.07 (brd, 1H, *J*=11.5 Hz, CH_2=CH–), 5.09 (brd, 1H, *J*=17.5 Hz, CH_2=CH–), 5.74–5.80 (m, 2H, H3, H13), 5.82–5.92 (m, 3H, H2, H14, H18), 7.44–7.47 (m, 2H, NAP), 7.54 (dd, 1H, *J*=9.0, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); FT-IR (KBr) ν 3026, 2961, 2885, 1742, 1602, 1436, 1355, 1261, 1094, 1024, 806 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{32}H_{36}NaO_8$ 571.2308, found 571.2390; $[\alpha]_D^{21.0}$ −1.1° (*c* 0.400, $CHCl_3$).

4.5.3. Amide 70. A solution of carboxylic acid **66** (48.4 mg, 88.2 μmol) and Et_3N (86.1 μl, 0.618 mmol) in CH_2Cl_2 (3 ml) was cooled to −78 °C. PivCl (109 μl, 0.882 mmol) was added and the mixture was stirred for 1 h at 0 °C to produce a mixed anhydride **67**. In another flask, to a solution of (*S*)-4-benzyl oxazolidinethione **68** (141 mg, 0.730 mmol) in THF (3 ml) was added *n*-BuLi (1.56 M solution in hexane, 340 μl, 0.529 mmol) at −78 °C. The solution was stirred for 15 min at −78 °C and transferred into the cooled solution of the mixed anhydride **67** *via* cannula at −78 °C. After stirring for 15 min at −78 °C, the mixture was warmed to 0 °C and the stirring was continued for an additional 1 h. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=5–4–3) and then HPLC to give amide **70** (32.4 mg, 44.8 μmol, 51%). **70**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.57 (m, 1H, H10), 2.27–2.36 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, *J*=16.5, 8.0, 4.0 Hz, H4), 2.65–2.71 (m, 1H, H17), 2.81 (dd, 1H, *J*=13.0, 9.5 Hz, auxiliary), 3.10–3.17 (m, 2H, H8, H9), 3.26–3.35 (m, 3H, H5, H11, auxiliary), 3.38 (t, 1H, *J*=8.0 Hz, H6), 3.54 (t, 1H, *J*=8.0 Hz, H7), 3.57 (td, 1H, *J*=8.0, 3.0 Hz, H16), 3.89 (brdd, 1H, *J*=9.0, 2.0 Hz, H12), 3.96 (brdd, 1H, *J*=9.0, 2.0 Hz, H15), 4.04 (brdd, 1H, *J*=16.0, 2.5 Hz, H1), 4.31 (dd, 1H, *J*=16.0, 6.0 Hz, H1), 4.37–4.42 (m, 2H, auxiliary), 4.95 (tt, 1H, *J*=10.0, 4.0 Hz, auxiliary), 4.99 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=17.5 Hz, H21), 5.05–5.08 (m, 1H, CH_2=CH–), 5.11 (brdd, 1H, *J*=17.5, 2.0 Hz, CH_2=CH–), 5.21 (d, 1H, *J*=18.0 Hz, H21), 5.75–5.80 (m, 1H, H3), 5.82 (dt, 1H, *J*=13.0, 2.0 Hz, H4), 5.85–5.89 (m, 1H, H2), 5.89 (dt, 1H, *J*=12.5, 2.5 Hz, H13), 5.89–5.95 (m, 1H, H18), 7.22–7.36 (m, 5H, auxiliary), 7.43–7.47 (m, 2H, NAP), 7.55 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.77, 36.76, 37.29, 37.68, 60.05, 68.53, 71.40, 71.60, 73.33, 75.34, 78.56, 80.57, 81.14, 81.88, 82.24, 83.50, 87.63, 117.12, 125.77, 126.02, 126.21, 126.42, 126.90, 127.70, 127.80, 128.00, 128.02, 129.25, 129.55, 131.49, 132.75, 133.12, 133.44, 135.08, 135.15, 136.84, 170.57, 184.84; FT-IR (film) ν 3027, 2878, 1714, 1367, 1330, 1207, 1167, 1096, 1011, 963, 911, 857, 818 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{42}H_{45}NNaO_8S$ 746.2764, found 746.2737; $[\alpha]_D^{22.0}$ +66.3° (*c* 0.530, $CHCl_3$).

4.5.4. Amide 71. A solution of carboxylic acid **66** (70.2 mg, 0.128 mmol) and Et_3N (154 μl, 1.11 mmol) in CH_2Cl_2 (5 ml) was cooled to −78 °C. PivCl (195 μl, 1.58 mmol)

was added and the mixture was stirred for 1 h at 0 °C to produce a mixed anhydride **66**. In another flask, to a solution (*S*)-4-benzyl oxazolidinone **69** (168 mg, 0.948 mmol) in THF (5 ml) was added *n*-BuLi (1.56 M solution in hexane, 506 μl, 0.79 mmol) at −78 °C. The solution was stirred for 15 min at −78 °C and transferred into the cooled solution of the mixed anhydride **67** *via* cannula at −78 °C. After stirring for 15 min at −78 °C, the mixture was warmed to 0 °C and the stirring was continued for an additional 30 min. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–5–1) to give amide **71** (87.4 mg, 0.123 μmol, 96%). **71**: colorless solid; mp 160 °C (hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (dd, 1H, J=11.5 Hz, H10), 2.26–2.37 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.66–2.67 (m, 1H, H17), 2.82 (dd, 1H, J=13.5, 10.0 Hz, auxiliary), 3.10–3.17 (m, 2H, H8, H9), 3.28 (td, 1H, J=9.0, 4.0 Hz, H5), 3.29–3.33 (m, 1H, H11), 3.35 (dd, 1H, J=13.0, 3.5 Hz, auxiliary), 3.38 (t, 1H, J=9.0 Hz, H6), 3.53 (t, 1H, J=8.5 Hz, H7), 3.56 (td, 1H, J=8.5, 2.5 Hz, H16), 3.89 (brdd, 1H, J=9.5, 2.0 Hz, H12), 3.96 (brdd, 1H, J=9.0, 2.0 Hz, H15), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.24 (dd, 1H, J=8.5, 3.0 Hz, auxiliary), 4.28–4.29 (m, 1H, auxiliary), 4.32 (dd, 1H, J=9.5, 6.0 Hz, H1), 4.67–4.72 (m, 1H, auxiliary), 4.71 (d, 1H, J=17.5 Hz, H21), 4.81 (d, 1H, J=18.0 Hz, H21), 4.99 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=11.5 Hz, NAP), 5.05–5.07 (m, 1H, CH_2=*CH*–), 5.11 (brdd, 1H, J=18.0, 2.0 Hz, CH_2=*CH*–), 5.75–5.95 (m, 5H, H2, H3, H13, H14, H18), 7.21–7.36 (m, 5H, auxiliary), 7.43–7.85 (m, 8H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.26, 22.79, 29.18, 30.07, 31.72, 34.77, 36.74, 37.28, 37.92, 45.03, 55.03, 62.22, 67.48, 68.52, 69.59, 73.34, 75.33, 76.94, 78.57, 80.56, 81.12, 81.96, 82.25, 83.49, 87.62, 117.06, 125.76, 126.01, 126.21, 126.43, 126.90, 127.65, 127.80, 127.99, 128.03, 129.19, 129.54, 131.47, 131.50, 132.67, 133.12, 133.44, 135.03, 135.17, 136.85, 153.54, 169.72; FT-IR (film) ν 3020, 2881, 1786, 1714, 1642, 1390, 1351, 1297, 1260, 1213, 1139, 1099, 1010, 976, 922, 858, 821, 755, 705 cm^{-1}; ESI-TOF MS $[M+NH_4]^+$ calcd for $C_{42}H_{49}N_2O_9$ 725.3438, found 725.3390; $[\alpha]^{22.0}_D$ +44.5° (*c* 1.03, $CHCl_3$).

4.5.5. Aldol reaction of 70. To a solution of Et_3N (102 μl, 0.732 mmol) in CH_2Cl_2 (2 ml) was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 366 μl, 0.366 mmol) at −78 °C. A solution of amide **70** (26.5 mg, 36.6 μmol) in CH_2Cl_2 (6 ml) was then added, and the resulting mixture was stirred for 30 min at −78 °C. To the resulting violet solution, freshly distilled acrolein (49.0 μl, 0.732 mmol) was added, and the stirring was continued for 20 min at −78 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1) to give a mixture of aldol products **72** and **73** (21.7 mg, 27.8 μmol, 76%) and recovery of **70** (4.0 mg, 5.5 μmol, 15%). The aldol products were further separated by HPLC to give 20,21-*syn*-15,21-*syn* isomer **73** (16.5 mg, 21.1 μmol, 58%) and 20,21-*anti*-15,21-*syn* isomer **72** (4.2 mg, 5.39 μmol, 15%). **72**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (dd, 1H, J=11.0 Hz, H10), 2.24–2.31 (m, 1H, H17), 2.31–2.36 (m, 2H, H4, H10), 2.43 (d, 1H, J=6.5 Hz, OH), 2.60–2.66 (m, 2H, H4, H17), 2.81 (dd, 1H, J=13.0, 10.0 Hz, auxiliary), 3.09–3.16 (m, 2H, H8, H9), 3.27 (td, 1H, J=10.0, 4.0 Hz, H5), 3.32–3.35 (m, 1H, H11), 3.36 (t, 1H, J=9.0 Hz, H6), 3.35–3.40 (m, 1H, auxiliary), 3.51 (t, 1H, J=8.5 Hz, H7), 3.56 (td, 1H, J=8.0, 3.0 Hz, H16), 3.88 (brdd, 1H, J=9.5, 2.5 Hz, H12), 4.02 (brdd, 1H, J=15.5, 2.5 Hz, H1), 4.11–4.14 (m, 1H, H15), 4.26 (brt, 1H, J=8.0 Hz, auxiliary), 4.30 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.36 (dd, 1H, J=9.5, 2.0 Hz, auxiliary), 4.50 (brdd, 1H, J=12.0, 6.0 Hz, H20), 4.85 (dddd, 1H, J=10.0, 7.0, 3.5, 2.0 Hz, auxiliary), 4.95 (d, 1H, J=12.5 Hz, NAP), 5.00 (d, 1H, J=12.0 Hz, NAP), 5.08 (dd, 1H, J=10.5, 2.0 Hz, CH_2=CH–), 5.12 (brdd, 1H, J=17.0, 2.0 Hz, CH_2=CH–), 5.27 (dt, 1H, J=11.0, 1.5 Hz, CH_2=CH–), 5.41 (dt, 1H, J=17.0, 1.5 Hz, CH_2=CH–), 5.76–5.79 (m, 2H, H3, H14), 5.84–5.93 (m, 3H, H2, H13, H18), 6.03 (ddd, 1H, J=17.0, 10.0, 5.0 Hz, H19), 6.70 (d, 1H, J=5.0 Hz, H21), 7.23–7.36 (m, 5H, auxiliary), 7.40–7.44 (m, 2H, NAP), 7.52 (dd, 1H, J=8.5, 2.0 Hz, NAP), 7.77–7.81 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.78, 36.72, 37.28, 37.85, 61.00, 68.54, 71.15, 73.32, 75.29, 78.47, 79.30, 80.52, 81.21, 82.20, 82.39, 83.57, 87.58, 117.25, 117.70, 125.74, 126.00, 126.19, 126.39, 126.88, 127.75, 127.79, 127.97, 128.02, 129.27, 129.60, 131.51, 131.83, 132.67, 133.10, 134.99, 135.07, 135.64, 136.85, 172.47; FT-IR (film) ν 3452, 2876, 1707, 1366, 1327, 1197, 1160, 1097, 962, 856, 818 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_9S$ 802.3026, found 802.3214. **73**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (dd, 1H, J=11.0 Hz, H10), 2.22 (brdt, 1H, J=15.0, 8.0 Hz, H17), 2.31–2.36 (m, 2H, H4, H10), 2.45 (d, 1H, J=8.5 Hz, OH), 2.58–2.64 (m, 1H, H17), 2.63 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.84 (dd, 1H, J=13.0, 10.0 Hz, auxiliary), 3.09–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, J=10.0, 4.0 Hz, H5), 3.33–3.40 (m, 3H, H6, H11, auxiliary), 3.52 (t, 1H, J=8.5 Hz, H7), 3.56 (td, 1H, J=9.0, 2.5 Hz, H16), 3.87 (ddt, 1H, J=9.0, 2.5, 2.0 Hz, H12), 4.01–4.05 (m, 2H, H1, H15), 4.30 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.31 (dd, 1H, J=9.5, 8.0 Hz, auxiliary), 4.37 (dd, 1H, J=9.0, 2.0 Hz, auxiliary), 4.54–4.58 (m, 1H, H20), 4.89 (dddd, 1H, J=9.5, 7.5, 3.5, 2.0 Hz, auxiliary), 4.95 (d, 1H, J=12.5 Hz, NAP), 5.00 (d, 1H, J=12.0 Hz, NAP), 5.08 (dd, 1H, J=10.5, 2.0 Hz, CH_2=CH–), 5.11 (brdd, 1H, J=17.5, 1.5 Hz, CH_2=CH–), 5.29 (dt, 1H, J=10.0, 1.5 Hz, CH_2=CH–), 5.41 (dt, 1H, J=17.5, 1.5 Hz, CH_2=CH–), 5.74–5.81 (m, 2H, H3, H14), 5.84–5.92 (m, 2H, H2, H18), 5.98–6.01 (m, 1H, H13), 6.02 (ddd, 1H, J=18.0, 11.0, 6.0 Hz, H19), 6.52 (d, 1H, J=3.0 Hz, H21), 7.23–7.36 (m, 5H, auxiliary), 7.40–7.45 (m, 2H, NAP), 7.52 (dd, 1H, J=9.0, 1.5 Hz, NAP), 7.80 (brt, 4H, J=8.5 Hz, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.78, 36.71, 37.25, 37.70, 61.06, 68.53, 71.14, 73.31, 75.28, 78.40, 80.27, 80.49, 81.23, 82.18, 82.68, 83.75, 87.57, 117.28, 117.59, 125.74, 126.00, 126.19, 126.38, 126.87, 127.75, 127.79, 127.97, 128.02, 129.26, 129.60, 131.51, 131.90, 132.46, 133.09, 133.42, 134.92, 135.07, 136.39, 136.84, 171.86; FT-IR (film) ν 3462, 3027, 2876, 1710, 1452, 1366, 1328, 1197, 1160, 1097, 1013, 961, 912, 857, 819 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_9S$ 802.3026, found 802.3301.

4.5.6. Synthesis of the ABCDE ring moiety (5) from 72. To a solution of amide **72** (4.2 mg, 5.4 μmol) in THF (1 ml) was added a solution of $NaBH_4$ (1.0 mg, 27 μmol) in water (0.25 ml). The mixture was stirred for 10 min at room temperature and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=2–1–0.5) to give a corresponding diol (2.7 mg, 4.6 μmol, 85%).

A solution of the diol (2.7 mg, 4.6 μmol) in CH_2Cl_2 (1 ml) was added the Grubbs catalyst **37** (0.4 mg, 0.457 μmol). The mixture was stirred for 30 min at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt=1–0.5–0.33) to give the ABCDE ring moiety **5** (2.1 mg, 3.7 μmol, 82%). **5**: colorless solid; mp 126–126.5 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (q, 1H, J=11.5 Hz, H10), 2.18–2.24 (brs, 2H, OH), 2.25–2.38 (m, 3H, H4, H10, H17), 2.63 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.67 (ddd, 1H, J=13.0, 9.5, 3.5 Hz, H17), 3.09–3.12 (m, 2H, H8, H9), 3.24 (ddd, 1H, J=12.0, 9.5, 4.5 Hz, H11), 3.28 (td, 1H, J=9.5, 4.0 Hz, H5), 3.37 (t, 1H, J=8.5 Hz, H6), 3.41 (m, 1H, H21), 3.52 (t, 1H, J=8.5 Hz, H7), 3.61 (td, 1H, J=9.0, 3.0 Hz, H16), 3.77–3.83 (m, 3H, H12, H22, H22), 4.04 (brdd, 1H, J=15.5, 2.5 Hz, H1), 4.14 (brdd, 1H, J=8.5, 2.5 Hz, H15), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.46 (brd, 1H, J=6.5 Hz, H20), 4.98 (d, 1H, J=12.5 Hz, NAP), 5.02 (d, 1H, J=12.5 Hz, NAP), 5.64 (dt, 1H, J=13.0, 2.5 Hz, H14), 5.71–5.81 (m, 4H, H2, H3, H13, H18), 5.86 (ddd, 1H, J=11.5, 6.0, 3.5 Hz, H19), 7.43–7.48 (m, 2H, NAP), 7.56 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.79–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.50, 34.59, 36.83, 64.48, 68.36, 70.20, 73.17, 75.15, 78.03, 80.47, 80.81, 81.09, 82.01, 84.70, 84.99, 87.46, 125.63, 125.87, 126.06, 126.30, 126.76, 126.84, 127.64, 127.84, 127.86, 130.89, 131.36, 132.96, 133.27, 134.89, 136.22, 136.62; FT-IR (film) ν 3399, 2875, 2360, 1367, 1260, 1093 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{33}H_{38}NaO_8$ 585.2465, found 585.2457; $[\alpha]_D^{21.0}$ −61.1° (c 0.82, $CHCl_3$).

4.5.7. Aldol reaction of 71. To a solution of Et_3N (50.4 μl, 0.362 mmol) in CH_2Cl_2 (2 ml) was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 181 μl, 0.181 mmol) at −78 °C. A solution of amide **71** (12.8 mg, 18.1 μmol) in CH_2Cl_2 (5 ml) was then added, and the resulting mixture was stirred for 30 min at −78 °C. To the resulting violet solution, freshly distilled acrolein (24.2 μl, 0.362 mmol) was added and the stirring was continued for 20 min at −78 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1) and then HPLC to give 20,21-*syn*-15,21-*syn* isomer **74** (9.9 mg, 13.0 μmol, 72%), a corresponding 20,21-*syn*-15,21-*anti* isomer (1.6 mg, 2.1 μmol, 12%), and recovery of **71** (1.3 mg, 1.9 μmol, 10%). **74**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (q, 1H, J=11.5 Hz, H10), 2.21 (brdt, 1H, J=15.5, 8.5 Hz, H17), 2.31–2.36 (m, 2H, H4, H10), 2.48 (d, 1H, J=7.5 Hz, OH), 2.59–2.63 (m, 1H, H17), 2.63 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.83 (dd, 1H, J=13.5, 9.5 Hz, auxiliary), 3.09–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, J=9.5, 4.0 Hz, H5), 3.32–3.39 (m, 3H, H6, H11, auxiliary), 3.51 (t, 1H, J=8.5 Hz, H7), 3.54–3.58 (m, 1H, H16), 3.87 (dq, 1H, J=8.5, 2.5 Hz, H12), 3.98 (dq, 1H, J=9.0, 2.5 Hz, H15), 4.02 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.23–4.25 (m, 2H, auxiliary), 4.30 (dd, 1H, J=15.0, 6.5 Hz, H1), 4.40–4.44 (m, 1H, H20), 4.68 (ddt, 1H, J=10.0, 7.0, 3.5 Hz, auxiliary), 4.95 (d, 1H, J=12.0 Hz, NAP), 5.00 (d, 1H, J=11.5 Hz, NAP), 5.07 (dd, 1H, J=10.5, 2.0 Hz, CH_2=CH–), 5.11 (dd, 1H, J=17.0, 2.0 Hz, CH_2=CH–), 5.28 (dt, 1H, J=11.0, 1.5 Hz, CH_2=CH–), 5.39 (dt, 1H, J=16.0, 1.5 Hz, CH_2=CH–), 5.41 (d, 1H, J=3.5 Hz, H21), 5.74–5.79 (m, 2H, H3, H14), 5.83–5.91 (m, 2H, H2. H18), 5.94–6.01 (m, 2H, H13, H19), 7.22–7.36 (m, 5H, auxiliary), 7.41–7.43 (m, 2H, NAP), 7.52 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.77–7.81 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.73, 36.68, 37.23, 37.88, 55.73, 67.10, 68.49, 73.26, 73.88, 75.24, 76.91, 78.33, 80.44, 80.85, 81.16, 82.15, 82.81, 83.60, 87.53, 117.26, 117.55, 125.71, 125.96, 126.16, 126.35, 126.83, 127.67, 127.75, 127.93, 127.98, 129.17, 129.55, 131.46, 131.89, 132.52, 133.06, 133.38, 134.86, 134.97, 136.44, 136.80, 153.60, 170.74; FT-IR (film) ν 3437, 3059, 3027, 2930, 2876, 1779, 1711, 1642, 1603, 1497, 1479, 1454, 1392, 1350, 1261, 1212, 1099, 1009 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_{10}$ 786.3254, found 786.3293; $[\alpha]_D^{20.5}$ +32.7° (c 0.800, $CHCl_3$). 20,21-*syn*-15,21-*anti* isomer: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (q, 1H, J=11.5 Hz, H10), 2.28 (brdt, 1H, J=15.0, 8.0 Hz, H17), 2.30–2.37 (m, 2H, H4, H10), 2.47 (d, 1H, J=8.5 Hz, OH), 2.63 (ddd, 1H, J=16.0, 7.5, 4.0 Hz, H4), 2.79 (dd, 1H, J=14.0, 9.0 Hz, auxiliary), 2.83–2.88 (m, 1H, H17), 3.08–3.14 (m, 2H, H8, H9), 3.25–3.34 (m, 3H, H5, H11, auxiliary), 3.37 (t, 1H, J=8.5 Hz, H6), 3.49–3.54 (m, 1H, H7, H16), 3.83–3.88 (m, 2H, H12, H15), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.24 (dd, 1H, J=8.5, 3.0 Hz, auxiliary), 4.30 (t, 1H, J=8.5 Hz, auxiliary), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.50–4.55 (m, 1H, H20), 4.74–4.79 (m, 1H, auxiliary), 4.98 (d, 1H, J=12.0 Hz, NAP), 5.02 (d, 1H, J=12.0 Hz, NAP), 5.06 (dd, 1H, J=10.5, 1.0 Hz, CH_2=CH–), 5.13 (dd, 1H, J=17.5, 2.0 Hz, CH_2=CH–), 5.30 (dt, 1H, J=10.5, 1.5 Hz, CH_2=CH–), 5.36 (d, 1H, J=3.5 Hz, H21), 5.42 (dt, 1H, J=17.5, 1.5 Hz, CH_2=CH–), 5.74 (dt, 1H, J=13.0, 2.5 Hz, H13), 5.75–5.80 (m, 1H, H3), 5.82 (dt, 1H, J=13.0, 2.5 Hz, H14), 5.85–5.94 (m, 2H, H2, H18), 6.01 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H19), 7.23–7.36 (m, 5H, auxiliary), 7.43–7.47 (m, 2H, NAP), 7.54 (d, 1H, J=8.0 Hz, NAP), 7.81–7.83 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.77, 36.72, 37.31, 37.78, 55.16, 67.02, 68.53, 73.30, 73.69, 75.36, 77.73, 78.26, 80.20, 80.44, 81.12, 82.17, 83.47, 87.63, 116.63, 117.66, 125.79, 126.04, 126.25, 126.48, 126.89, 127.64, 127.82, 128.04, 129.16, 129.65, 130.67, 131.52, 133.14, 133.47, 134.87, 135.73, 136.63, 136.78, 153.68, 169.81; FT-IR (film) ν 3503, 3027, 2927, 2874, 1778, 1714, 1639, 1603, 1454, 1392, 1351, 1216, 1099, 1006, 923, 856 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_{10}$ 786.3254, found 786.3272; $[\alpha]_D^{27.0}$ +62.6° (c 0.332, $CHCl_3$).

4.5.8. Diol 76. To a solution of amide **73** (18.0 mg, 23.1 μmol) in THF (2 ml) was added a solution of $NaBH_4$

(4.4 mg, 120 μmol) in water (0.5 ml). The mixture was stirred for 20 min at room temperature and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1–0.33) to give diol **75** (10.8 mg, 18.3 μmol, 79%).

A solution of the diol **75** (10.8 mg, 18.3 μmol) and Grubbs catalyst **37** (0.8 mg, 0.9 μmol) in CH_2Cl_2 (4 ml) was stirred for 1 h at room temperature. Et_3N was added and the mixture concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt=1–0.5–0.33) to give diol **76** (9.5 mg, 17 μmol, 92%). **76**: colorless solid; mp 175–177 °C (CH_2Cl_2–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (dd, 1H, J=11.5 Hz, H10), 2.13 (brs, 1H, 22-OH), 2.26 (brs, 1H, 20-OH), 2.27–2.37 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.09–3.18 (m, 3H, H8, H9, H17), 3.28 (td, 2H, J=10.0, 4.0 Hz, H5, H11), 3.37 (t, 1H, J=9.0 Hz, H6), 3.52 (brt, 1H, J=8.5 Hz, H7), 3.62–3.66 (m, 2H, H16, H21), 3.76–3.84 (m, 3H, H12, H22, H22), 4.03 (brdd, 1H, J=15.5, 2.5 Hz, H1), 4.11 (brdd, 1H, J=8.5, 2.5 Hz, H15), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.40 (brd, 1H, J=6.5 Hz, H20), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.03 (d, 1H, J=12.5 Hz, NAP), 5.67 (dt, 1H, J=13.0, 2.5 Hz, H14), 5.75–5.81 (m, 1H, H3), 5.80 (dt, 1H, J=12.5, 2.5 Hz, H13), 5.85–5.97 (m, 3H, H2, H18, H19), 7.43–7.48 (m, 2H, NAP), 7.54 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.80–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.47, 34.77, 37.05, 64.50, 68.52, 69.96, 73.35, 75.34, 78.39, 80.56, 81.03, 82.20, 82.71, 83.15, 84.92, 87.65, 125.79, 126.03, 126.22, 126.46, 126.92, 127.81, 128.00, 128.02, 128.05, 131.12, 131.52, 132.00, 132.03, 134.75, 134.76; FT-IR (film) ν 3415, 3025, 2879, 1450, 1366, 1264, 1092, 909, 857, 818, 733 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{33}H_{38}NaO_8$ 585.2464, found 585.2494; $[\alpha]_D^{24.1}$ −43.4° (*c* 1.14, $CHCl_3$).

4.5.9. TBS ether 77. To a solution of diol **76** (14.8 mg, 26.3 μmol) in CH_2Cl_2 (4 ml) were added imidazole (17.9 mg, 263 μmol) and TBSCl (19.8 mg, 132 μmol). The mixture was stirred for 30 min at room temperature and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–3–2) to give TBS ether **77** (14.8 mg, 21.9 μmol, 83%). **77**: colorless solid; mp 134–135 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 6H, TBS), 0.92 (s, 9H, TBS), 1.52 (dd, 1H, J=11.5 Hz, H10), 2.28–2.34 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.70 (d, 1H, J=4.5 Hz, 20-OH), 3.10–3.13 (m, 3H, H8, H9, H17), 3.24–3.30 (m, 2H, H5, H11), 3.37 (t, 1H, J=9.5 Hz, H6), 3.52 (brt, 1H, J=9.0 Hz, H7), 3.58–3.61 (m, 2H, H16, H21), 3.79 (d, 2H, J=5.5 Hz, H22, H22), 3.80–3.84 (m, 1H, H12), 4.03 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.08 (brdd, 1H, J=8.5, 2.0 Hz, H15), 4.30 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.40 (brd, 1H, J=4.5 Hz, H20), 4.98 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.64 (brd, 1H, J=12.5 Hz, H14), 5.75–5.84 (m, 2H, H3, H13), 5.84–5.91 (m, 3H, H2, H18, H19), 7.43–7.46 (m, 2H, NAP), 7.54 (brd, 1H, J=7.5 Hz, NAP), 7.80–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.36, −5.29, 18.37, 25.98, 33.38, 34.75, 37.03, 64.87, 68.48, 69.29, 73.35, 75.27, 76.90, 78.30, 80.62, 81.01, 82.22, 82.86, 85.08, 87.59, 125.72, 125.97, 126.19, 126.40, 126.88, 127.77, 127.94, 128.00, 130.66, 131.48, 132.43, 133.10, 133.43, 135.36, 136.86; FT-IR (film) ν 3467, 3020, 2952, 2929, 2882, 2858, 1602, 1509, 1470, 1462, 1363, 1300, 1257, 1216, 1091, 1008 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{39}H_{52}NaO_8Si$ 699.3329, found 699.3374; $[\alpha]_D^{24.5}$ −46.8° (*c* 1.02, $CHCl_3$).

4.5.10. Benzoate 78. To a solution of alcohol **77** (7.9 mg, 12 μmol) in toluene (2 ml) were added PPh_3 (15.3 mg, 58.4 μmol), BzOH (8.6 mg, 70 μmol) and DEAD (9.2 μl, 58 μmol). The mixture was stirred for 20 min at room temperature and quenched with water. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel=1 g, hexane–hexane/AcOEt=10–5) to give benzoate **78** (9.2 mg, 12 μmol, 100%). **78**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H, TBS), 0.04 (s, 3H, TBS), 0.88 (s, 9H, TBS), 1.53 (dd, 1H, J=11.0 Hz, H10), 2.28–2.37 (m, 3H, H4, H10, H17), 2.65 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.88 (ddd, 1H, J=13.5, 10.0, 3.5 Hz, H17), 3.09–3.15 (m, 2H, H8, H9), 3.27 (td, 1H, J=9.5, 5.0 Hz, H11), 3.29 (td, 1H, J=9.0, 4.5 Hz, H5), 3.38 (t, 1H, J=9.0 Hz, H6), 3.53 (t, 1H, J=8.5 Hz, H7), 3.68–3.73 (m, 3H, H16, H21, H22), 3.82–3.86 (m, 2H, H12, H22), 4.04 (brdd, 1H, J=15.0, 3.0 Hz, H1), 4.18 (brdd, 1H, J=9.0, 2.5 Hz, H15), 4.31 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.05 (d, 1H, J=11.5 Hz, NAP), 5.58 (ddd, 1H, J=8.5, 5.5, 1.5 Hz, H20), 5.64 (dt, 1H, J=12.5, 2.5 Hz, H14), 5.68 (dd, 1H, J=11.0, 5.5 Hz, H19), 5.78 (ddt, 1H, J=11.0, 8.0, 3.0 Hz, H3), 5.83–5.89 (m, 2H, H2, H18), 5.94 (dt, 1H, J=12.5, 3.0 Hz, H13), 7.43–7.64 (m, 4H, Bz, NAP), 7.81–7.86 (m, 4H, NAP), 8.02 (brd, 2H, J=7.5 Hz, Bz), 8.12 (dd, 2H, J=8.0, 1.0 Hz, Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.15, −5.10, 18.46, 26.06, 32.86, 34.78, 37.01, 64.34, 68.52, 71.76, 73.38, 75.31, 78.21, 80.80, 81.04, 81.69, 82.25, 84.73, 85.19, 87.62, 125.77, 126.01, 126.24, 126.46, 126.96, 127.81, 127.94, 127.98, 128.04, 128.59, 128.64, 129.76, 130.35, 130.61, 131.50, 132.85, 133.13, 133.30, 133.91, 135.21, 136.87, 165.38; FT-IR (film) ν 3030, 2931, 2883, 1724, 1693, 1603, 1453, 1415, 1319, 1268, 1091, 1023, 977, 908, 837, 775, 712 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{46}H_{56}NaO_9Si$ 803.3591, found 803.3536; $[\alpha]_D^{26.2}$ −35.4° (*c* 0.968, $CHCl_3$).

4.5.11. Synthesis of the ABCDE ring moiety 5 from 78. To a solution TBS ether **78** (16.9 mg, 21.6 μmol) in THF (2 ml) was added TBAF (1.0 M solution in THF, 65 μl, 65 μmol). After stirring for 1 h at room temperature, TBAF (65 μl, 65 μmol) was further added to the mixture and the stirring was continued for an additional 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=5–2) to give a corresponding alcohol (13.3 mg, 19.9 μmol, 92%). colorless solid; mp

143–144 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (q, 1H, J=11.5 Hz, H10), 2.25–2.37 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.70 (ddd, 1H, J=13.0, 9.5, 3.5 Hz, H17), 3.08–3.12 (m, 2H, H8, H9), 3.23 (ddd, 1H, J=12.0, 9.5, 4.5 Hz, H11), 3.27 (td, 1H, J=9.5, 4.0 Hz, H5), 3.37 (t, 1H, J=8.5 Hz, H6), 3.51 (brt, 1H, J=9.0 Hz, H7), 3.61–3.66 (m, 2H, H16, H21), 3.81 (ddd, 1H, J=9.0, 5.0, 2.5 Hz, H12), 4.03 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.15 (brdd, 1H, J=9.0, 2.5 Hz, H15), 4.30 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.39 (brdd, 1H, J=9.0, 4.5 Hz, H20), 4.59 (dd, 1H, J=11.5, 3.0 Hz, H22), 4.67 (dd, 1H, J=11.5, 6.0 Hz, H22), 4.97 (d, 1H, J=12.0 Hz, NAP), 5.03 (d, 1H, J=12.5 Hz, NAP), 5.59 (dt, 1H, J=12.5, 2.5 Hz, H14), 5.73–5.83 (m, 4H, H3, H13, H18, H19), 5.86 (ddt, 1H, J=12.0, 6.5, 3.0 Hz, H2), 7.43–7.49 (m, 4H, Bz, NAP), 7.54 (dd, 1H, J=8.0, 1.5 Hz, NAP), 7.58–7.61 (m, 1H, Bz), 7.80–7.84 (m, 4H, NAP), 8.09–8.11 (m, 2H, Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.67, 34.78, 36.99, 66.30, 68.52, 69.26, 73.32, 75.28, 78.10, 80.69, 81.01, 81.56, 82.18, 83.95, 84.70, 87.59, 125.77, 126.01, 126.22, 126.44, 126.92, 127.34, 127.80, 127.98, 128.02, 128.61, 129.94, 130.05, 130.30, 130.97, 131.51, 133.12, 133.38, 133.44, 135.17, 135.92, 136.83, 167.35; FT-IR (film) ν 3468, 3023, 2932, 2876, 1718, 1602, 1584, 1509, 1452, 1369, 1350, 1316, 1276, 1175, 1078, 1027 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{40}H_{42}NaO_9$ 689.2727, found 689.2797; $[\alpha]_D^{26.4}$ −90.6° (c 1.00, $CHCl_3$).

To a solution of the alcohol (9.0 mg, 14 μmol) in MeOH (2 ml) and THF (1 ml) was added K_2CO_3 (9.3 mg, 68 μmol). The mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=1–0.5–0.33) to give the ABCDE ring moiety **5** (7.0 mg, 12 μmol, 92%).

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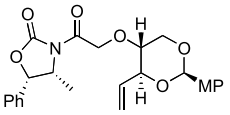
19. The numbering of carbon atoms in all compounds in this paper corresponds to that of CTX3C.
20. For instance, the corresponding oxazolidinone **A** did not give any coupling products, and instead decomposition of **A** occurred under various coupling conditions.



A

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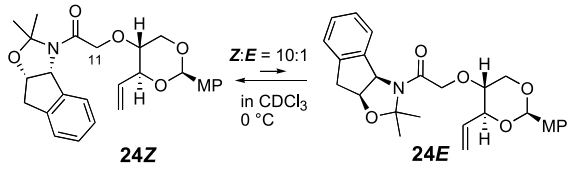
22. ^{1}H NMR of **24** suggested that **24** existed as a 10:1 equilibrium of amide rotamers (**24Z**:**24E**) in $CDCl_3$ at 0 °C because the major isomer showed NOE between the C11-methylene and indane aromatic proton. We assumed that this geometry was maintained in the enolate form.



24Z **24E**

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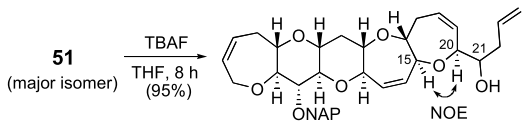
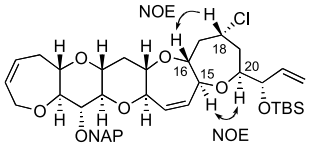
29. The C20-stereochemistry of the major isomer of **51** was identified by NOE experiments after removal of the TBS group.



30. The stereochemistry of the major isomer of **56** was assigned by NOE experiments.



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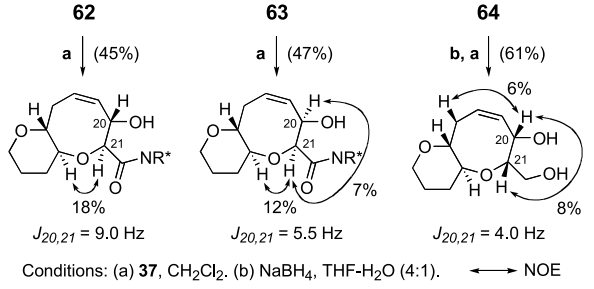

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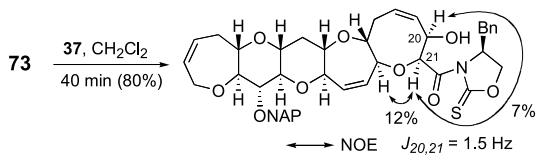
39. The C20- and C21-stereochemistries of **73** were confirmed by NMR after RCM.



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Synthesis of L-cyclopentenyl nucleosides using ring-closing metathesis and palladium-mediated allylic alkylation methodologies

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Abstract—The enantiomeric synthesis of L-cyclopentenyl nucleosides is described. The key intermediate (+)-cyclopentenyl alcohol (**8**) was prepared from methyl-α-D-galactopyranoside **1** using a ring closing metathesis reaction. Transformation of the allylic alcohol **8** into the allylic acetate (**9**) or carbonate (**10**), allows their coupling with purine and pyrimidine bases under Pd(0)-catalyzed Tsuji–Trost allylic alkylation's to yield **12a–c**. The Pd catalyzed reaction was found to require the use of $AlEt_3$.

1. Introduction

Carbocyclic nucleosides such as the naturally occurring aristeromycin[1] and neplanocin A,[2] lacking the labile glycosidic linkage between heterocycle and sugar, exhibit potent antitumor and antiviral activities. During the last decade, an enormous amount of work has focused on the search for novel natural and synthetic carbocyclic nucleosides possessing a satisfactory preclinical profile.[3] Among them, cyclobut A,[4] carbovir[5] and 6-cyclopropylaminopurine analogue[6] (1592, abacavir) are the most interesting compounds due to their effective anti-HIV activities. Abacavir has recently been approved by the FDA. The recent findings that a number of L-nucleosides, including (−)-(2′*R*,5′*S*)-1-(2-hydroxymethyloxathiolan-5-yl)cytosine (3TC),[7] β-L-thymidine[8] and β-L-2′-fluoro-5-methylarabinosyl uracil

(L-FMAU)[9] have shown promising antiviral activity, has triggered numerous developments in the modification of both the heterocyclic base and the sugar moiety of L-nucleosides.[10] For a number of years, we have been investigating the synthesis and antiviral studies of various D- and L-carbocyclic nucleosides, and we have recently reviewed the palladium-catalyzed routes to nucleosides.[11] A preliminary account of carba-L-furanose precursors has recently been reported by us.[12] We now report herein the combination of the metathesis and Pd(0) reactions to the synthesis of various purine and pyrimidine cyclopentenyl nucleosides, dealing with the synthetic details, NMR structural studies and confirmation of the formation of L-cyclopentenyl-carboxyclic ribonucleosides.

2. Results and discussion

The total synthesis of neplanocin and closely related derivatives has been fully described in the literature. Neplanocin A itself can be prepared from a bicyclic system,[13] or by an asymmetric Diels–Alder to yield a cyclopentadiene.[14] The most common synthesis of the compounds utilizes 2-cyclopenten-1-one, prepared either from (+)-γ-lactone-D-ribonic acid[15] or from the protected D-ribose via a ring-closing metathesis reaction.[16] Several optically active L- or D-carbocyclic nucleosides have also been prepared by the enzymatic resolution from racemic mixture.[17] No total enantioselective synthetic methods using a combination of Pd(0)-catalyzed reactions and metathesis had been reported to date. As both these methodologies have proven their effectiveness, it was of

Keywords: Metathesis; Palladium; Nucleosides; Allylic Alkylation.
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interest to employ a reaction sequence using both methods for the asymmetric synthesis of optically active L-cyclopentenyl nucleosides. A retrosynthetic analysis indicates that the L-cyclopentenyl nucleosides can be prepared by direct coupling of a nucleobase with the allylic alcohol moiety of the carbocycle using a palladium-catalyzed allylic alkylation (Tsuji–Trost reaction).[12,18]

2.1. Synthesis of the cyclopentenyl moiety

The cyclopentenyl precursor can be obtained from the known optically pure *tetra-O*-benzyl-D-galactopyranoside through a ring-closing metathesis step. This strategy holds the advantage of establishing three asymmetric centers onto the cyclopentenyl moiety (Scheme 1).

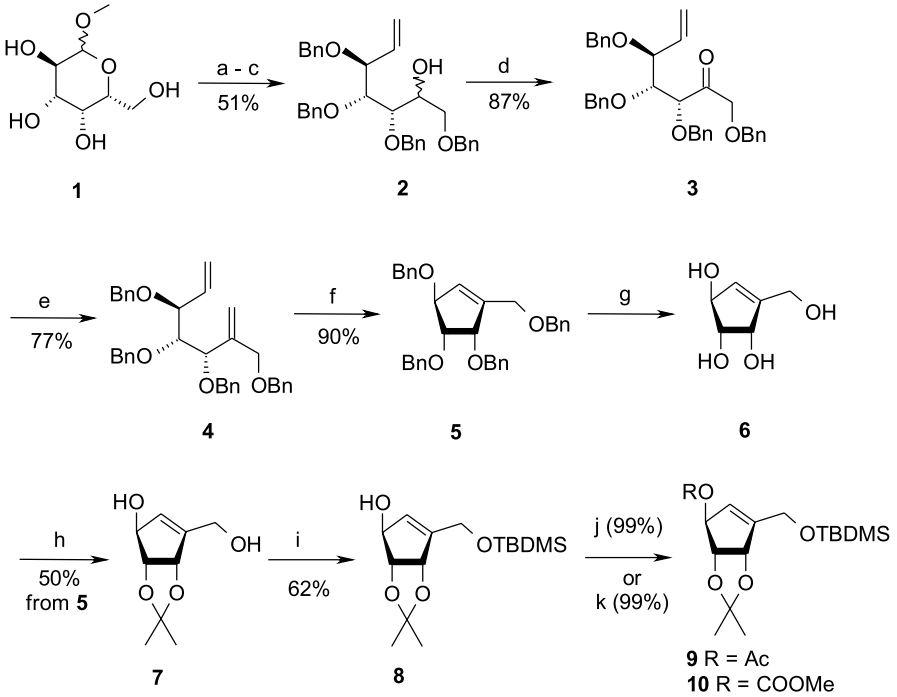
The appropriate functionalized precursor **9** was prepared on a preparative scale from the chiral methyl-α-D-galactopyranoside **1**, through the (+)-diene **4** as chiral key intermediate. After benzylation and demethylation on the anomeric position, treatment of **1** with methyltriphenyl phosphonium bromide, according to the procedure originally reported by Lancelin et al.[20] and subsequent oxidation gave optically pure L-tagatose (L-*lyxo*-hexulose) as a single isomer in 44% overall yield. A second Wittig reaction on **3** afforded the (+)-diene **4** in 77% yield. The ring-closing metathesis,[21] first key step of this reaction, was accomplished by exposure of diene **4** to 10 mol% of a second-generation ruthenium catalyst to yield the chiral cyclopentenyl analogue **5** in 90% yield.[11,22] Removal of the benzyl group using sodium metal in liquid ammonia and subsequent protection of the tetraol **6** gave the optically active allylic alcohol **8** (31% from 5). The allylic alcohol **8** which possess the same physico-chemical data than its (−)-counterpart [for (+)-**8**. $[\alpha]_D^{20} = +13.3$ (*c* 0.4, $CHCl_3$); for (−)-**8**. $[\alpha]_D^{20} = -12.8$ (*c* 1.84, $CHCl_3$)],[24] was converted either to the corresponding allylic acetate **9** or with methyl chloroformate in the presence of pyridine to the allylic carbonate **10**

2.2. Introduction of base via Tsuji–Trost reaction

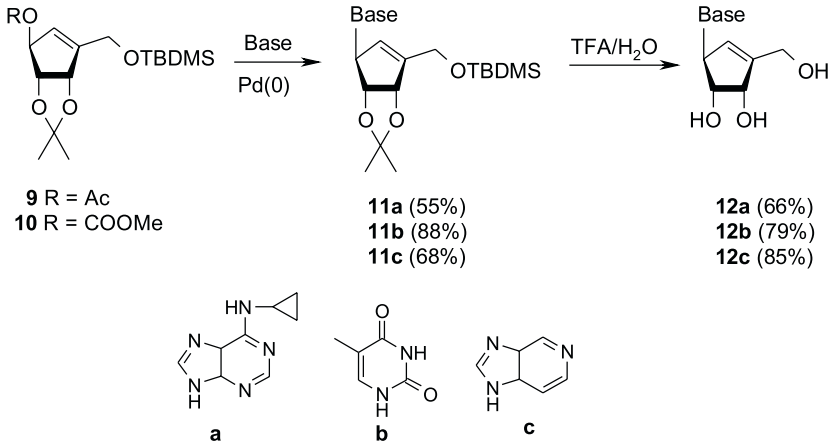
The coupling of the appropriate purine and pyrimidine bases (reaching L-nucleosides analogues **12a–c**) was carried out using the Pd(0)-catalyzed enantioselective Tsuji–Trost allylic amination and lead to the desired nucleosides (Scheme 2) with a global retention of configuration.[23] Unfortunately, in our hands, all attempts to introduce the heterocycle on **9** or on the more reactive allylic carbonate **10**, through an irreversible reaction, under various classical conditions [base (NaH, Et_3N), palladium catalyst/ligand ($Pd_2(dba)_3$, $Pd(PPh_3)_4$ in the presence of PPh_3 or dppf] led to the recovering of starting material.

The best compromise was obtained using triethylaluminium in combination with Pd(0) catalyst, for the preparation of L-cyclopentenyl nucleosides **11a–c** from the allylic carbonate **10**. Thus, reaction of **10** with appropriate purine and pyrimidine bases in the presence of Et_3Al and $Pd(PPh_3)_4$/dppf gave in moderate-to-good yields the enantiomeric L-nucleoside analogues **11a**, **11b** and **11c**, respectively (Table 1).

The purine analogues **11a** ((2-amino-6-cyclopropylamino)-purine) and **11c** (3-deazapurine) were obtained as unique *N*-9 isomer. The Pd-catalyzed coupling of an allylic acetate with a purine base can, in principle, lead to a mixture of *N-7* and *N-9* isomers. This problem, which is classic in



Scheme 1. Reagents and conditions: (a) NaH, BnBr, DMF; (b) AcOH, H_2SO_4 3 M; (c) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C to rt; (d) PCC, AcONa, MS 4 Å, CH_2Cl_2; (e) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C to rt; (f) Ruthenium catalyst of second generation[19] (10 mol%), benzene, 80 °C; (g) Na/NH_3 liq.; (h) dimethoxypropane, acetone, cat. *p*-TsOH, rt; (i) TBDMSCl, pyridine, 0 °C; (j) Ac_2O, pyridine; (k) MeOCOCl, DMAP, pyridine.



Scheme 2. Tsuji–Trost reaction and deprotection.

Vorbrüggen coupling of purines with sugars,[25] has been recognized only recently in Pd(0)-catalyzed couplings.[26] The best compromise, in agreement with Crimmins' work,[27] was obtained using a 6-aminocyclopropylpurine leading, in our hands, to the single *N-9* isomer.

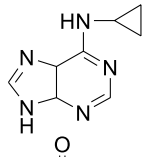
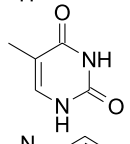
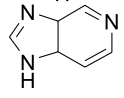
Finally those conditions applied to acetate derivative (**9**) afforded also expected compound in a same range of yield but after one night of reaction time instead of few hours for carbonate (**10**).

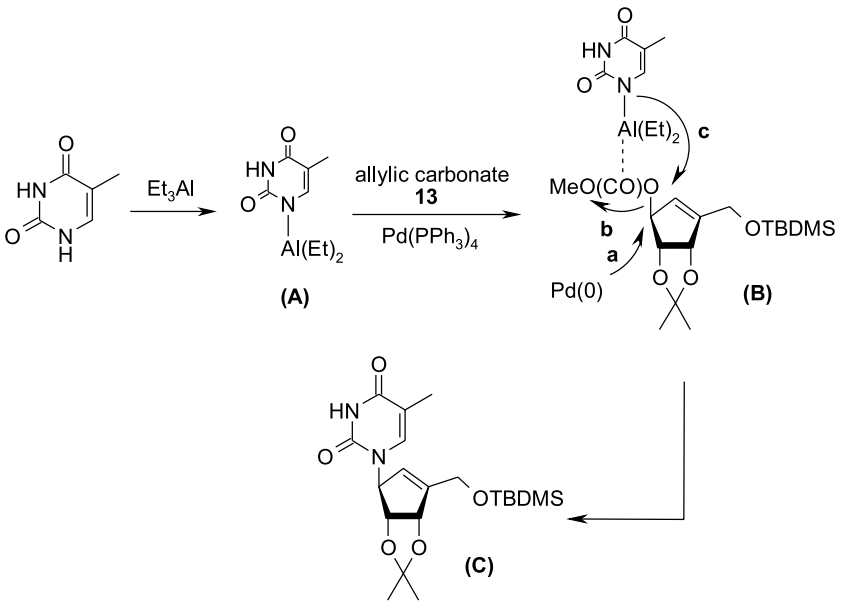
To assess the role of Et_3Al, we first confirmed that without the Pd catalyst or with another Lewis acid ($BF_3.Et_2O$, TMSOTf, $TiCl_4$), no reaction occurred. Thus, both the Pd(0) catalyst and triethylaluminium are necessary for the success of the heterocycle coupling. Et_3Al, like other organoaluminiums, can act as a Lewis acid to activate Lewis basic functionalities and also as a captor of electrophilic species by ethylation. Thus, we hypothesized that the in situ addition of Et_3Al on the nucleobase afforded a new aluminium amide species (**A**) which, acting as a Lewis acid, was able to activate the carbonate (or acetate) to form the transient π-allyl complex (step a) releasing the carbonate group (step b) and delivering in a regioselective manner the heterocycle (step c) through a concerted mechanism (Scheme 3). This hypothesis could be supported by the work from Yamamoto et al.[28] and Overman et al.[29] concerning the in situ formation of aluminium amide and from Shiohara et al.[30] describing a one-pot procedure for a pinacol-type 1,2-shift. By analogy, the transient unstable intermediate **B** can be postulated.

Compounds **11a–c** were deprotected with trifluoroacetic acid/H_2O to afford the corresponding nucleosides **12a–c**, in good yield. The nucleosides obtained were characterized by spectroscopic methods and these data compared to those obtained for the known D-isomers, L- or racemic forms. Furthermore, the configuration of compound **12b** at the C-1′ position, after the Tsuji–Trost heterocycle coupling has been unambiguously determined by NMR using 1D- and 2D-NOESY sequences (Fig. 1).

The 2D-NOESY spectra (relaxation delay 3 s, mixing time 0.8 s) showed correlation between the C_6-H proton (7.16) and the $C_{1'}$-H proton (5.33) owing to the free rotation around the C(1′)-N bond. Correlations were also seen between the C_6-H proton and the $C_{5'}$-H and $C_{2'}$-H proton, respectively, clearly indicating that the nucleobase was above the plane of the five-membered ring (e.g. β configuration). Assignment of ^1H and ^{13}C NMR signals were made on the basis of ^1H, ^{13}C, ^1H–^1H COSY, ^1H, ^{13}C COSY (gHMQC) and ^1H, ^{13}C-long range correlation spectra (gHMBC). The gHMBC spectrum optimized for a 5 Hz scalar coupling showed the expected cross-peaks between C_6-H proton and the carbon atoms within the nucleobase and also a cross-peak with carbon $C_{1'}$ indicating clearly the *N-1* regiochemisty of the nucleo-base allylic amination under Tsuji–Trost conditions. An interesting feature, the presence of a tautomeric form in the thymine

Table 1. Use of Et_3Al for Tsuji–Trost reaction

Entry	Nucleophile	R	Base	Catalyst/ligand	Product
1		COOMe	Et_3Al	$Pd(PPh_3)_4$/dppf	**11a** (55%)
2		COOMe	Et_3Al	$Pd(PPh_3)_4$/dppf	**11b** (88%)
3		COOMe	Et_3Al	$Pd(PPh_3)_4$/dppf	**11c** (68%)



Scheme 3. Proposed mechanism for Et_3Al action.

fragment of **12b** can be taken from the ^{13}C- and DEPT 135 spectra.

3. Conclusion

In summary, the enantioselective and total synthesis of L-cyclopentenyl nucleosides using ring-closing metathesis and palladium-mediated allylic alkylation methodologies has been realized and optimized. The synthesized compounds were evaluated in human PBM cells infected with HIV-1_{LAI},[32] against HBV in AD-38 cells. No significant activities were observed; the toxicities were also assessed, and these compounds did not exhibit any significant toxicity at concentration up to 100 μM in CEM, PBM, and Vero cells.[33]

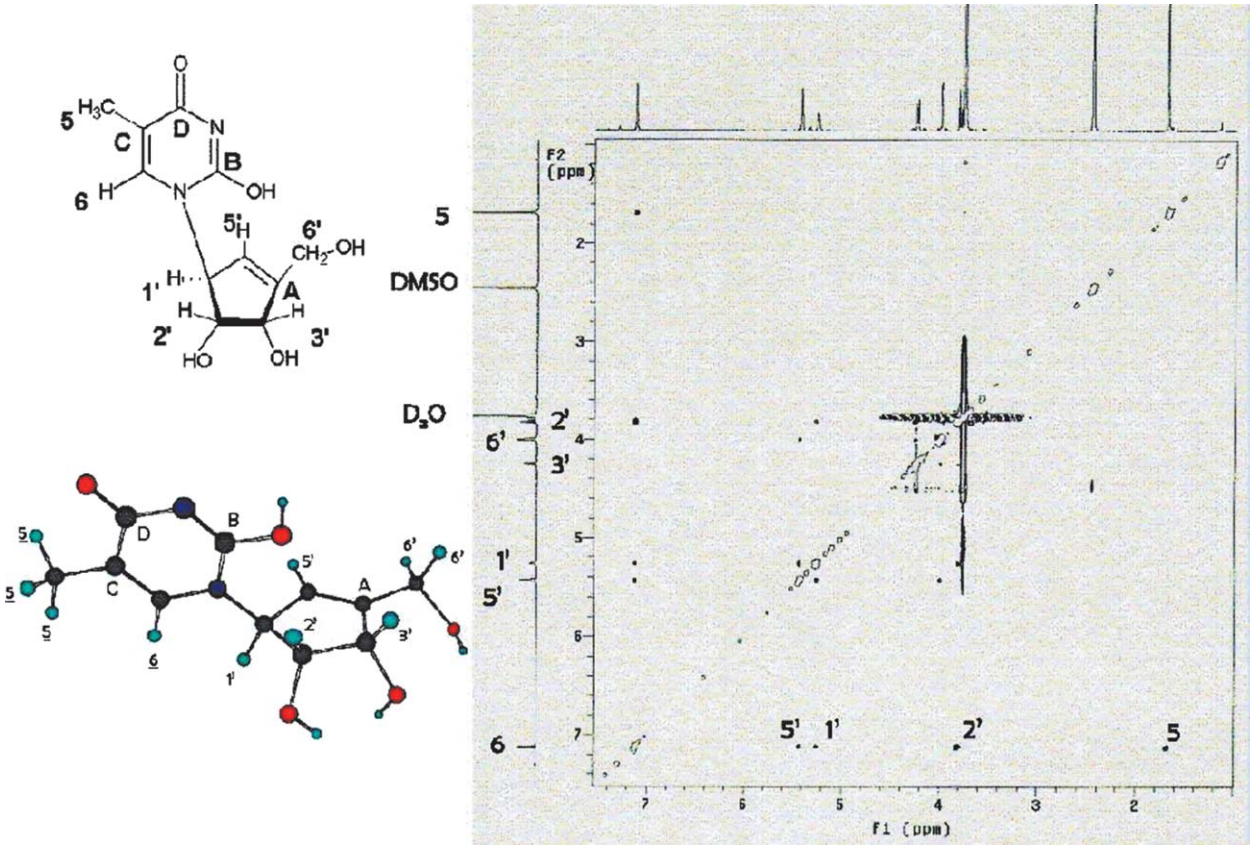


Figure 1. 2D-NOESY and an optimal configuration for **12b**.[31]

4. Experimental

4.1. General

Commercially available chemicals were reagent grade and used as received. THF was distilled from sodium/benzophenone ketyl; CH_2Cl_2 from CaH_2 immediately prior use and benzene over Na. The reactions were monitored by thin-layer chromatography (TLC), analysis using silica gel plates (Kieselgel 60 F_{254}, E. Merck). Compounds were visualized by UV irradiation and/or spraying with 20% H_2SO_4 in EtOH, followed by charring at 150 °C. Column chromatography was performed on Silica Gel 60 M (0.040–0.063 mm, E. Merck). The ^1H and ^{13}C NMR spectra were recorded on a a Bruker AVANCE DPX 250 and Varian $Inova_{Unity}$ 400 spectrometer (^1H 399.81 MHz, ^{13}C: 100.54 MHz) in (D_4) methanol and (D6)-DMSO, shift values in ppm relative to $SiMe_4$ as internal reference, unless otherwise stated; *J* in Hz. High Resolution Mass spectra were performed by the Centre Regional de Mesures Physiques de l'Ouest (University of Rennes, France).

4.2. Preparation of the cyclopentenyl moiety

4.2.1. 1,3,4,5-*tetra*-O-Benzyl-6,7-dideoxy-D-galacto-hept-6-en-2-ulose (3). A solution of the known alkene (**2**)[34] (0.31 g, 0.57 mmol) in CH_2Cl_2 (3 mL) was added to a suspension of NaOAc (0.28 g, 3.41 mmol), PCC (0.73 g, 3.41 mmol) and molecular sieve 4 Å (0.51 g).The reaction was stirred at room temperature for 2 h. After filtering off PCC salts and molecular sieve on a small chromatography column (CH_2Cl_2), the solvent was evaporated in vacuo and the residue was purified by flash chromatography (8/2 hexanes/EtOAc) to give **3** (0.26 g, 87%) as a colorless oil. $[\alpha]_D^{20} = +8.6$ (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40–7.10 (m, 20H), 5.85 (ddd, 1H, *J*=17.6, 10.3, 7.9 Hz), 5.36 (d, 1H, *J*=17.3 Hz), 5.29 (d, 1H, *J*=10.5 Hz), 4.72 (d, 1H, *J*=11.3 Hz), 4.58 (d, 1H, *J*=11.7 Hz), 4.57 (d, 1H, *J*=11.2 Hz), 4.49–4.27 (m, 7H), 4.21–4.16 (m, 1H), 4.14–4.07 (m, 1H), 3.94–3.89 (dd, 1H, *J*=4.7, 6.1 Hz); ^{13}C NMR (CDCl3) δ 207.8 (CO), 138.6, 138.4, 137.9, 137.6, 165.6 (CH), 128.9, 128.8, 128.7, 128.6, 128.43, 128.4, 128.3, 128.2, 128.1, 128.0, 120.1 (CH2), 83.2 (CH), 82.5 (CH), 81.2 (CH), 75.2 (CH2), 74.9 (CH2), 73.5 (CH2), 73.1 (CH2), 71.1 CH2); HRMS: C35H36O5Na, calcd *m/z* 559.6640, found, *m/z* 559.6646.

4.2.2. 3,4,5,7-*tetra*-O-Benzyl-1,2-didehydro-1,2,6-trideoxy-6-C-methylene-D-galacto-heptitol (4). To an ice-cold solution of methyltriphenylphosphonium bromide (1.78 g, 5.01 mmol) in THF (15 mL) was slowly added *n*-BuLi 1.6 M in hexane (2.91 mL, 4.67 mmol). The solution was stirred 30 min at 0 °C then 30 min at room temperature. After coming back at 0 °C, a solution of **3** (0.89 g, 1.66 mmol) in THF (10 mL) was added. The reaction was stirred at room temperature for 2 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 times) and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (9/1 hexanes/EtOAc) to give **4** (0.68 g, 77%) as a colorless oil. $[\alpha]_D^{20} = +32.4$ (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.30–6.90 (m, 20H), 5.80 (ddd, 1H, *J*=17.6, 10.3, 7.6 Hz), 5.43 (d, 1H, *J*=1.7 Hz), 5.29 (s, 1H), 5.20 (d, 1H, *J*=17.4 Hz), 5.13 (d, 1H, *J*=10.8 Hz), 4.55–4.33 (m, 6H), 4.21 (d, 1H, *J*=11.9 Hz), 4.10–3.98 (m, 5H), 3.49 (dd, 1H, *J*=7.8, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 144.5, 139.1, 139.0, 138.9, 138.8, 136.8 (CH), 129.4, 129.1, 128.8, 128.77, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 126.5, 126.3, 118.7 (CH_2), 116.0 (CH_2), 84.2 (CH), 80.7 (CH), 80.1 (CH), 75.4 (CH_2), 73.2 (CH_2), 71.1 (CH_2), 70.9 (CH_2), 70.8 (CH_2); HRMS: $C_{36}H_{38}O_4Na$, calcd *m/z* 557.2668, found, *m/z* 557.2666.

4.2.3. (1′*S*,2′*R*,3′*S*)-1,2,3-(Benzyloxy)-4-(benzyloxy methyl)-4-cyclopenten (5). A deoxygenated solution of **4** (3.6 g, 6.74 mmol) in freshly distilled benzene (100 mL) was refluxing during 4 h in presence of a ruthenium catalyst[11a] (10 mol%). After evaporation of the solvent, the residue was purified by flash chromatography (9/1 EP/EtOAc) to give **5** (3.07 g, 90%) as a colorless oil. $[\alpha]_D^{20} = +64.9$ (*c* 0.47, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35–7.15 (m, 20H), 5.99 (d, 1H, *J*=1.6 Hz), 4.86–4.84 (m, 1H), 4.65 (dd, 2H, *J*=1.6 Hz, 12.5 Hz), 4.55–4.54 (m, 5H), 4.34 (d, 1H, *J*=12.2 Hz), 4.31 (d, 1H, *J*=12.2 Hz), 4.02 (t, 1H, *J*=5.0 Hz), 3.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 142.3, 138.6, 138.4, 138.3, 138.1, 130.3 (CH), 128.44, 128.4, 128.3, 128.1, 128.0, 127.8, 127.75, 127.7, 127.6, 86.4 (CH), 84.4 (CH), 78.8 (CH), 72.7 (CH2), 72.3 (CH2), 71.9 (CH2), 71.5 (CH2), 67.2; HRMS: $C_{34}H_{34}O_4Na$, calcd *m/z* 529.2355, found, *m/z* 529.2359.

4.2.4. (1′*S*,2′*R*,3′*S*)-2,3-(Isopropylenedioxy)-4-(oxy methyl)-4-cyclopenten-1-ol (7). A solution of **5** (0.2 g, 0.38 mmol) in THF (2 mL) was added at −78 °C to a solution of liquid ammonia (20 mL) and sodium (0.1 g). The reaction was then refluxing during 2 h. After evaporation of ammonia and neutralization with solid NH_4Cl and MeOH, solvents were removed in vacuo. The residue was quickly purified by flash chromatography (7.5/2/0.5 EtOAc/MeOH/H_2O) to give **6**, and was directly used in the next step. A solution of compound **6**, 2,2-dimethoxypropane (0.24 mL) and *p*-TsOH (catalytic amount) in distilled acetone (4 mL) was stirred at room temperature overnight. After addition of solid Na_2CO_3, and evaporation of the volatiles, the residue was purified by flash chromatography (9/1 CH_2Cl_2/MeOH) to give **7** (35 mg, 50%) as a colorless oil. $[\alpha]_D^{20} = +15.8$ (*c* 0.7, $CHCl_3$), [lit. for D-isomer, $[\alpha]_D^{29} = -12.8°$ (*c* 1.8, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 5.73 (s, 1H), 5.19 (d, 1H, *J*=5.6 Hz), 4.69 (s, 1H), 4.51 (d, 1H, *J*=5.6 Hz), 4.31 (d, $1H_A$, J_{AB}=14.5 Hz), 4.24 (d, $1H_B$, J_{AB}=14.5 Hz), 3.16 (s, OH), 1.38 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.4, 127.7 (CH), 112.1, 86.4 (CH), 83.6 (CH), 79.8 (CH), 60.0 (CH_2), 27.3 (CH_3), 25.8 (CH_3); HRMS: $C_9H_{14}O_4Na$, calcd *m/z* 209.0790, found, *m/z* 209.0796.

4.2.5. (1′*S*,2′*R*,3′*S*)-2,3-(Isopropylenedioxy)-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclopenten-1-ol (8). A solution of **7** (0.04 g, 0.21 mmol) and TBDMSCl (36 mg, 0.26 mmol) in distilled pyridine (4 mL) was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by flash chromatography (9/1 hexanes/EtOAc) to give **8** (40 mg, 62%) as a colorless oil. $[\alpha]_D^{20} = +13.3$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.73 (s, 1H), 5.11 (d, 1H, *J*=5.5 Hz), 4.71 (s, 1H), 4.54 (d, 1H, *J*=5.5 Hz), 4.33 (d, $1H_A$, J_{AB}=15.8 Hz), 4.24 (d, $1H_B$, J_{AB}=

15.8 Hz), 2.01 (s, OH), 1.36 (s, 3H), 1.33 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 150.4, 127.4 (CH), 112.7, 87.6 (CH), 84.0 (CH), 80.7 (CH), 61.2 (CH_2), 28.2 (CH_3), 26.8 (CH_3), 26.7 ($CH_3\times3$), 19.2, −4.6 ($CH_3\times2$); HRMS: $C_{15}H_{28}O_4NaSi$, calcd *m/z* 323.1655, found, *m/z* 323.1650.

4.2.6. (1′*S*,2′*R*,3′*S*)-1-Acetoxy-2,3-(Isopropylenedioxy)-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclopentene (9). To a solution of **8** (0.037 g, 0.12 mmol) in pyridine (1 mL) were added Ac_2O (27 μL, 0.25 mmol) at 0 °C. The reaction was stirred at room temperature overnight. After evaporation of the volatiles, the residue was purified by flash chromatography (9/1 hexanes/EtOAc) to give **9** (42 mg, 99%) as a colorless oil. $[\alpha]_D^{20}=+51.3$ (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.71 (s, 1H), 5.53 (s, 1H), 5.08 (d, 1H, *J*= 5.5 Hz), 4.59 (d, 1H, *J*=5.5 Hz), 4.34 (d, $1H_A$, J_{AB}= 15.9 Hz), 4.25 (d, $1H_B$, J_{AB}=15.9 Hz), 2.04 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.1, 151.2, 125.5 (CH), 112.0, 83.7 (CH), 82.6 (CH), 81.8 (CH), 60.5 (CH_2), 27.0 (CH_3), 25.6 ($CH_3\times3$), 25.5 (CH_3), 20.6 (CH_3), 18.0, −5.1 ($CH_3\times2$); HRMS: $C_{17}H_{30}O_5NaSi$, calcd *m/z* 365.5015, found, *m/z* 365.5010.

4.2.7. (1′*S*,2′*R*,3′*S*)-1-(Methoxycarbonyloxy)-2,3-(isopropylenedioxy)-4-(*tert*-butyldimethylsilyloxy methyl)-4-cyclopentene (10). To a solution of **8** (0.05 g, 0.17 mmol) in CH_2Cl_2 (2 mL) were added distilled pyridine (18 μL), then methylchloroformate (80 μL) and DMAP (6.5 mg) at 0 °C. The reaction was stirred at room temperature for 4 h. After evaporation of the volatiles, the residue was purified by flash chromatography (9/1 hexanes/EtOAc) to give **10** (60 mg, 99%) as a colorless oil. $[\alpha]_D^{20}=+43.2$ (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.76 (s, 1H), 5.47 (s, 1H), 5.09 (d, 1H, *J*=5.6 Hz), 4.66 (d, 1H, *J*=5.6 Hz), 4.35 (d, $1H_A$, J_{AB}=16.0 Hz), 4.25 (d, $1H_B$, J_{AB}=16.0 Hz), 3.80 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.3, 152.7, 122.7 (CH), 112.7, 85.6 (CH), 84.0 (CH), 83.1 (CH), 60.5 (CH_2), 55.0 (CH_3), 27.5 (CH_3), 26.1 ($CH_3\times3$), 26.0 (CH_3), 18.5, −5.3 ($CH_3\times2$); HRMS: $C_{17}H_{30}O_6NaSi$, calcd, for *m/z* 381.1709, found, *m/z* 381.1715.

4.3. General procedure for the Pd(0)-catalyzed allylic alkylation of acetate (9) or carbonate (10)

To a solution of nucleobase (0.11 mmol) in DMF (2 mL) was added Et_3Al (111 μL, 1 N solution in hexane). After stirring at 60 °C for 45 min, a solution of (**9**) or (**10**) (0.05 mmol) in THF (2 mL), $Pd(PPh_3)_4$ (10 mol%) and dppf (5 mol%) were added and the reaction was stirred during 6 h at 60 °C. After evaporation of the volatiles, the residue was purified by flash chromatography on silica gel.

4.3.1. (1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclopenten-1-yl]-2*H*-6-(cyclopropylamino)-9*H*-purin-9-yl (11a). $[\alpha]_D^{20}=+47.3$ (*c* 0.6, MeOH); UV (MeOH) λ_{max} 268 nm; ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.12 (s, 1H), 5.94 (br s, NH), 5.77 (br s, 1H), 5.58 (br s, 1H), 5.28 (br s, 1H), 4.70 (d, 1H, *J*= 5.6 Hz), 4.35–4.51 (m, 2H), 2.99–3.11 (m, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.92 (br s, 9H), 0.59–0.71 (m, 4H), 0.10 (br s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.9, 153.7 (CH), 152.5, 138.0 (CH), 133.4, 131.8, 121.3 (CH), 112.8, 85.0 (CH), 83.7 (CH), 64.5 (CH), 60.5 (CH_2), 27.6 ($CH_3\times2$), 26.1 ($CH_3\times3$), 23.8 (CH), 18.5, 7.5 ($CH_2\times2$), −5.3 ($CH_3\times2$); HRMS: $C_{23}H_{35}N_5O_3NaSi$, calcd, for *m/z* 480.6429, found, *m/z* 480.6425.

4.3.2. (1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclopenten-1-yl]-thymine (11b). $[\alpha]_D^{20}=+105.2$ (*c* 0.9, MeOH); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1H), 6.80 (s, 1H), 5.56 (s, 1H), 5.41 (s, 1H), 5.16 (d, 1H, *J*=6 Hz), 4.57 (d, 1H, *J*=6 Hz), 4.38 (s, 2H), 1.89 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.9, 153.1, 150.8, 137.1 (CH), 121.5 (CH), 112.7, 110.9, 84.7 (CH), 83.4 (CH), 67.3 (CH), 60.5 (CH_2), 27.4 (CH_3), 26.0 ($CH_3\times3$), 25.9 (CH_3), 18.5, 12.6 (CH_3), −5.2 ($CH_3\times2$); HRMS: $C_{20}H_{32}N_2O_5NaSi$, calcd, for *m/z* 431.5642, found, *m/z* 431.5638.

4.3.3. (1′*S*,2′*R*,3′*S*)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclopenten-1-yl]-4*H*-imidazo[4,5-c]pyridine (11c). $[\alpha]_D^{20}=+51.2$ (*c* 0.7, MeOH); UV (MeOH) λ_{max} 255 nm; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.49 (s, 1H), 7.80 (d, 1H, *J*=6.6 Hz), 7.67 (d, 1H, *J*=6.6 Hz), 5.85 (s, 1H), 5.43 (s, 1H), 5.23 (d, 1H, *J*= 5.6 Hz), 4.59 (d, 1H, *J*=5.6 Hz), 4.44 (s, 2H), 1.47 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 156.0, 155.3, 144.8, 128.9 (CH), 128.0 (CH×2), 120.8 (CH), 114.1 (CH), 113.5, 86.1 (CH), 83.1 (CH), 78.9 (CH), 60.4 (CH_2), 27.3 (CH_3), 25.9 ($CH_3\times3$), 25.7 (CH_3), 18.5, −5.3 ($CH_3\times2$); HRMS: $C_{21}H_{31}N_3O_3Si$, calcd, for *m/z* 402.2213, found, *m/z* 402.2208.

4.4. General procedure for deprotection

A solution of protected compound in H_2O/TFA (1/2), was stirred at room temperature for 4 h. After evaporation of the volatiles, the residue was purified by flash chromatography (8/2 DCM/MeOH) to gave neplanocin analog.

4.4.1. (1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxy methyl-4-cyclopenten-1-yl]-2*H*-6-(cyclopropylamino)-9*H*-purin-9-yl (12a). $[\alpha]_D^{20}=+132.3$ (*c* 0.6, MeOH); UV (MeOH) λ_{max} 266 nm; ^{1}H NMR (DMSO-*d6*) δ 8.21 (s, 1H), 8.06 (s, 1H), 7.85 (m, NH), 5.67–5.70 (m, 1H), 5.31–5.39 (m, 1H), 5.17 (d, OH, *J*=6.7 Hz), 5.01 (d, OH, *J*= 5.8 Hz), 4.95 (t, OH, *J*=5.4 Hz), 4.41–4.43 (m, 1H), 4.26–4.33 (m, 1H), 4.10–4.17 (m, 2H), 3.05 (m, 1H), 0.64–0.73 (m, 2H), 0.56–0.61 (m, 2H); ^{13}C NMR (DMSO-*d6*) δ 157.7, 152.2, 150.1 (CH), 139.4 (CH), 138.4, 135.3, 124.4 (CH), 76.6 (CH), 72.2 (CH), 64.2 (CH), 58.6 (CH_2), 48.6 (CH), 6.5 (CH_2), 6.4 (CH_2); HRMS: $C_{14}H_{17}N_5O_3Na$, calcd, for *m/z* 326.3131, found, *m/z* 326.3127.

4.4.2. (1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxy methyl-4-cyclopenten-1-yl]-thymine (12b). A solution of **11b** (0.03 mmol) in H_2O/TFA (1 mL/2 mL), was stirred at room temperature for 4 h. After evaporation of the volatiles, the residue was purified by flash chromatography (8/2 CH_2Cl_2/MeOH). $[\alpha]_D^{20}=+90.3°$ (*c* 0.8, MeOH) [lit.[16] $[\alpha]_D^{27}=+94.5$ (*c* 0.7, MeOH)]; UV (MeOH) λ_{max} 272 nm; ^{1}H NMR (DMSO-*d6*+D_2O) δ 7.16 (s, 1H), 5.47–5.49 (m, 1H), 5.29–5.38 (m, 1H), 4.29 (d, 1H, *J*=5.4 Hz), 4.04–4.06 (m, 2H),

3.88 (t, 1H, $J=5.6$ Hz), 1.75 (s, 3H); ^{13}C NMR (DMSO-*d6*+D_2O) δ 164.8, 151.8, 138.3 (CH), 124.5 (CH), 110.03, 76.8 (CH), 72.5 (CH), 65.4 (CH), 59.1 (CH_2), 12.5 (CH_3); HRMS: $C_{11}H_{14}N_2O_5Na$, calcd, for *m/z* 278.2424, found, *m/z* 278.2429.

4.4.3. (1′*S*,2′*R*,3′*S*)-1-[2,3-Dihydroxy-4-hydroxy methyl-4-cyclopenten-1-yl]-4*H*-imidazo[4,5-c]pyridine (12c). $[\alpha]_D^{20}=+97.3°$ (*c* 0.7, MeOH); UV (MeOH) λ_{max} 266 nm; ^{1}H NMR (CD_3OD) δ 9.41 (s, 1H), 8.91 (s, 1H), 8.60 (d, 1H, $J=6.3$ Hz), 8.25 (d, 1H, $J=6.3$ Hz), 6.05–6.06 (m, 1H), 5.68–5.78 (m, 1H), 4.61 (d, 1H, $J=5.7$ Hz), 4.29–4.48 (m, 2H), 4.16 (t, 1H, $J=5.7$ Hz); ^{13}C NMR (CD_3OD) δ 157.2, 155.5, 144.3, 136.5 (CH), 136.1 (CH×2), 123.2 (CH), 113.3 (CH), 81.8 (CH), 81.6 (CH), 73.9 (CH), 60.3 (CH_2); HRMS: $C_{12}H_{13}N_3O_3Na$, calcd, for *m/z* 271.2535, found, *m/z* 271.2531.

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Asymmetric alkylation of glycine imine esters using solid supports preloaded with base

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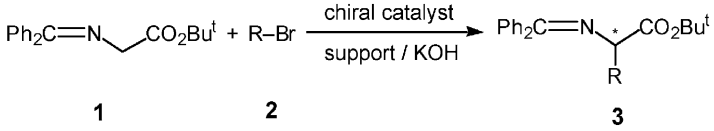
Abstract—Investigations into the use of solid supports preloaded with base for the asymmetric alkylation of a benzophenone-derived glycine-imine was described. Residual traces of water on the support dramatically accelerated the reactions to complete within a few minutes. The conditions employed in the present synthesis are mild, efficient and general.

1. Introduction

α-Amino acids are the important naturally occurring amino acids assembling into polypeptides with a wide range of vital biological functions, and hence the synthesis of optically active α-amino acids using a simple and easily scalable procedure remains an important synthetic challenge nowadays. The asymmetric alkylation of glycine imine esters for enantioselective synthesis of natural or unnatural amino acids using asymmetric phase transfer catalysis[1] has certainly gained solid success through recent extensive studies on the development of new catalysts[2] and modification of the reaction conditions.[3]

Generally, lower reaction temperatures provided higher enantioselectivity. Corey group had successfully used solid cesium hydroxide monohydrate as the basic phase in order to allow the use of lower temperatures (−60 to −80 °C) at which the aqueous phase of 50% aqueous KOH or NaOH can freeze and effectively stopping reaction.[2d] They achieved high asymmetric induction in the asymmetric phase-transfer alkylation of glycine imine esters. However, the vigorously stirring was essential to obtain rapid reaction, and the powdery cesium hydroxide monohydrate is a little expensive, while the inexpensive KOH or NaOH has very low surface area even in powder sate. In order to further improve the asymmetric alkylation using these bases, it is desirable to develop a new procedure that would have the possibility of acceleration of the reaction with high enantioselectivity and also allow an easy separation from the reaction mixture once the reaction has completed.

In our recent paper, we have developed a simple, efficient and practical method using commercially available solid supports preloaded with base to asymmetric alkylation of glycine imine ester (Scheme 1).[4] The alkylation product is readily obtained after simple extractive workup. Using the solid support with high sorptive surface area in this asymmetric reaction can avoid the problems associated with stirring of heterogeneous reaction mixture. The reaction on solid support proceeded rapidly with high yield and enantioselectivity, and moreover, it is possible for performing the asymmetric alkylation of glycine imine ester at lower temperatures using the inexpensive KOH. Heterogeneous organic reactions using inorganic solids as reaction media have been proven useful to chemists both in academia and in industry, because of their inexpensive nature and special catalytic attributes under heterogeneous reaction



Scheme 1.

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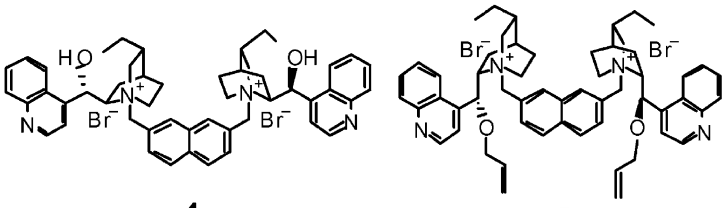

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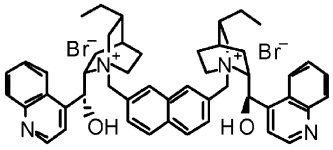

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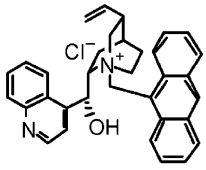

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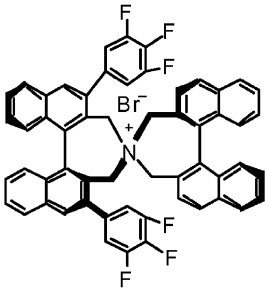

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conditions.[5] As part of our program to develop practical method that can be used in industrial processes, we further made more detailed studies on the method. In this work, by extending the above study, the factors of effect on the reaction enantioselectivity and reaction rate are explored.

2. Results and discussion

Preliminary experiments were carried out in order to determine the effects of different catalysts on the enantioselectivity and the reaction rate. The enantioselective efficiency of the catalysts was evaluated by the enantioselective alkylation of Schiff base **1**: the catalyst was mixed with **1** and benzyl bromide (**2a**) in dichloromethane. This particular assay reaction was chosen because it was known that the enantioselectivity of the imine **3** could be readily assessed by HPLC, and the absolute stereochemistry of this product was already known.[2d] The catalysts **4**, **5** and **6** were prepared according to the literature,[2h] the catalyst **7** is commercial available.[2c] The catalyst **4** is derived from cinchonine and the other three, **5**, **6** and **7** are derived from cinchonidine. The *N*-spiro type chiral C_2-symmetric quaternary ammonium bromide, catalyst **8** is commercially available.[2i] The reaction was monitored by TLC for disappearance of starting Schiff base **1**, a following simple workup that the solid support was washed with CH_2Cl_2 and the product was isolated directly by flash chromatography gave pure product. The enantiopurity was determined by HPLC analysis of the alkylated imine **3** by using a chiral column (Chiralcel OD) with hexane/2-propanol as solvent. The absolute configuration was assigned by the relative retention times of both enantiomers determined previously.[2]

As shown in Table 1, the catalysts **4**, **5**, **6** and **8** showed high enantioselectivity on solid support kaolin/KOH (81–84% ee, entries 1–3 and 5), whereas the rate of the reaction proved to be a little slow as estimated by TLC when catalyst **6** and **8** were used. However, when the reaction was carried out with the commercially available catalyst **7**, the product **3**

Table 1. Enantioselective alkylation of **1** with different catalysts and different solid supports [a]

Entry	Catalyst	Support	Time (h)	Yield (%)	Ee (%) (Config.)
1	**4**	Kaolin	1.0	97	81 (*R*)
2	**5**	Kaolin	0.5	97	82 (*S*)
3	**6**	Kaolin	6.5	86	84 (*S*)
4	**7**	Kaolin	0.5	91	72 (*S*)
5	**8**[b]	Kaolin	5.0	91	86 (*R*)
6	**5**	Aluminium oxide	3.5	90	84 (*S*)
7	**5**	Montmorillonite K10	24	90	86 (*S*)
8	**5**	Celite	140	50	62 (*S*)

[a] Unless otherwise specified, the reaction was carried out in air with **1** (0.05 mmol) and benzyl bromide (0.06 mmol) on the support/KOH (0.5 g, containing about 6 mmol of KOH per gram, no water) in the presence of the catalyst (0.005 mmol) at 20 °C. The starting materials and catalyst were dissolved in 0.1 ml of CH_2Cl_2.

[b] 0.001 mmol of catalyst **8** was used.

Table 2. Enantioselective alkylation of **1** with different base used to treat the kaolin supports[a]

Entry	Base (mmol/g)	Time (h)	Yield (%)	Ee (%)	Config.
1	KOH (2)	5.0	75	85	*S*
2	KOH (3)	0.75	88	88	*S*
3	KOH (5)	1.5	88	90	*S*
4	KOH (6)	2.0	89	91	*S*
5	KOH (7)	12	86	84	*S*
6	NaOH (6)	6.5	83	80	*S*
7	CsOH (6)	1.5	80	81	*S*

[a] The reaction was carried out in air with **1** (0.05 mmol) and benzyl bromide (0.06 mmol) on the kaolin/base (0.5 g, no water) in the presence of the catalyst **5** (0.005 mmol) at 20 °C. The starting materials and catalyst were dissolved in 0.1 ml of $PhCH_3/CHCl_3$ (5:5).

was obtained in a little low selectivity 72% ee (Table 1, entry 4). The preparation of (*R*)-**3** can use pseudo-enantiomertic catalysts **4** or **8**, while **5**, **6** and **7** can give corresponding (*S*)-enantiomer. The easily prepared catalyst **5** was chosen for the further investigation.

Further experiments involved using varying solid supports preloaded with KOH to probe the enantioselective alkylation of **1** in our assay reaction. It was found that the alkylation of imine **1** on solid supports preloaded with KOH, such as kaolin, aluminium oxide and montmorillonite K10 could be effected at 20 °C, giving similar enantioselection (82–86% ee, Table 1, entries 2, 6 and 7), while the reaction on montmorillonite K10 proved to be a little slow (24 h). These results showed that structural differences among the three solid supports maybe scarcely affected the enantioselectivity of the reaction. However, the reaction using solid support celite/KOH was far less effective resulting in low yield (50%) and low level of enantioselection (62% ee) after 140 h (Table 1, entry 8). The difference between celite/KOH and the other three solid supports maybe caused by the difference of the surface area in addition to the surface chemistry. The kaolin/KOH was chosen as solid support in the following studies. The support was recovered by washing with dichloromethane and drying to be recycled for use in subsequent reactions without decrease in activity over three cycles.

A study of the influence of base used to treat solid support kaolin on the enantioselective alkylation of **1** was performed using **5** as catalyst; the result being summarized in Table 2. The experiments involved using varying the amount of KOH on solid support and changing the inorganic base from KOH to NaOH or CsOH to measure the effect of these factors on the enantioselectivity with benzyl bromide (**2a**). The best enantioselection for the alkylated product was obtained when the amount of KOH on solid support kaolin was 6 mmol/g (Table 2, entry 4), while using NaOH or CsOH at the same condition led to a decrease on the enantioselection (Table 2, entries 6 and 7). Therefore, the solid support kaolin/KOH (containing about 6 mmol of KOH per gram) was used in the following reaction in this investigation.

In our previous paper, we have reported that the presence of CH_2Cl_2 in the reaction on the solid supports is crucial.[4] The amount of CH_2Cl_2 that can just dissolve the starting mixture and cannot make the support to form slurry was found to be best and yield the clean product. One of our initial aims of this work was to develop methodology that was as environmentally benign as possible, and so results of studies on effects of solvents which were used to dissolve the starting materials and catalyst on the enantioselective alkylation of **1** are presented in this paper.

Because the catalysts in this investigation easily dissolved in dichloromethane and chloroform, but did not dissolve very well in toluene, we chose to use somewhat more environmentally acceptable toluene mixed with other organic solvents to dissolve the starting materials and catalyst. It was found that the asymmetric alkylation could be carried out on the solid support kaolin/KOH in which the starting materials and catalyst dissolved in the mixture of toluene with dichloromethane or chloroform at different

Table 3. Effect of solvent on the enantioselective alkylation of **1**[a]

Entry	Solvent	Catalyst	Solvent (ml)	Time (h)	Yield (%)	Ee (%)	Config.
1	CH_2Cl_2	**5**	0.2	0.5	97	84	*S*
2	$PhCH_3/CH_2Cl_2$, 3:7	**5**	0.1	0.5	95	80	*S*
3	$PhCH_3/CH_2Cl_2$, 4:6	**5**	0.1	3.0	95	80	*S*
4	$PhCH_3/CH_2Cl_2$, 5:5	**5**	0.1	6.0	91	80	*S*
5	$PhCH_3/CHCl_3$, 5:5	**5**	0.1	2.0	89	91	*S*
6	$PhCH_3/CHCl_3$, 6:4	**5**	0.1	3.0	96	90	*S*
7	$PhCH_3/CHCl_3$, 6:4	**5**	0.15	4.0	99	92	*S*
8	$PhCH_3/CHCl_3$, 7:3	**5**	0.15	23	71	93	*S*
9	$PhCH_3/CH_3CN$, 7:3	**5**	0.1	0.67	96	72	*S*
10	$PhCH_3/CH_3CN$, 8:2	**5**	0.1	0.83	97	72	*S*
11	CH_2Cl_2	**7**	0.2	0.5	91	72	*S*
12	$PhCH_3/CHCl_3$, 5:5	**7**	0.1	1.5	91	89	*S*
13	CH_2Cl_2	**4**	0.2	2.0	97	81	*R*
14	$PhCH_3/CH_2Cl_2$, 3:7	**4**	0.1	0.75	92	79	*R*
15	$PhCH_3/CHCl_3$, 5:5	**4**	0.1	2.0	82	78	*R*
16	$PhCH_3/CH_3CN$, 8:2	**4**	0.1	0.33	91	57	*R*

[a] The reaction was carried out in air with **1** (0.05 mmol) and benzyl bromide (0.06 mmol) on the kaolin/KOH (0.5 g, containing about 6 mmol of KOH per gram, no water) in the presence of the catalyst (0.005 mmol) at 20 °C.

Table 4. Effects of temperature and residual water in the supports on the enantioselective alkylation of **1**[a]

Entry	Residual water (%)	Temp. (°C)	Solvent	Time (h)	Yield (%)	Ee (%)	Config.
1	25	20	$PhCH_3/CHCl_3$, 5:5	14	87	89	*S*
2	18	20	$PhCH_3/CHCl_3$, 5:5	4.0	85	88	*S*
3	16	20	$PhCH_3/CHCl_3$, 5:5	0.33	87	89	*S*
4	14	20	$PhCH_3/CHCl_3$, 5:5	0.03	89	87	*S*
5	12	20	$PhCH_3/CHCl_3$, 5:5	0.03	90	84	*S*
6	10	20	$PhCH_3/CHCl_3$, 5:5	0.03	91	80	*S*
7	7	20	$PhCH_3/CHCl_3$, 5:5	0.03	90	92	*S*
8[b]	7	20	$PhCH_3/CH_2Cl_2$, 7:3	0.16	90	94	*R*
9	2	20	$PhCH_3/CHCl_3$, 5:5	0.33	93	89	*S*
10[c]	2	20	$PhCH_3/CH_2Cl_2$, 5:5	0.5	91	86	*S*
11[c]	2	20	$PhCH_3/CHCl_3$, 5:5	0.5	90	90	*S*
12[b]	2	20	$PhCH_3/CH_2Cl_2$, 7:3	0.5	90	86	*R*
13[b]	2	20	$PhCH_3/CHCl_3$, 5:5	0.5	91	89	*R*
14	0	20	$PhCH_3/CHCl_3$, 5:5	2.0	89	91	*S*
15	0	0	$PhCH_3/CHCl_3$, 5:5	24	98	92	*S*
16	0	−30	$PhCH_3/CHCl_3$, 5:5	130	98	96	*S*
17	12	20	$PhCH_3/CHCl_3$, 5:5	0.5	89	90	*S*
18	12	−30	$PhCH_3/CHCl_3$, 5:5	1.5	92	92	*S*
19	12	20	$PhCH_3/CH_2Cl_2$, 3:7	0.08	89	83	*S*
20	12	20	$PhCH_3/CH_2Cl_2$, 3:7	1.0	94	88	*S*
21	12	−30	$PhCH_3/CH_2Cl_2$, 3:7	1.5	93	90	*S*
22	—[d]	20	$PhCH_3/CHCl_3$, 7:3	0.75	87	85	*S*
23	—[d]	0	$PhCH_3/CHCl_3$, 7:3	23	89	89	*S*

[a] Unless otherwise specified, the reaction was carried out in air with **1** (0.05 mmol) and benzyl bromide (0.1 mmol) on the kaolin/KOH (0.5 g, containing about 6 mmol of KOH per gram) in the presence of the catalyst **5** (0.005 mmol). The starting materials and catalyst were dissolved in 0.1 ml of $PhCH_3/CHCl_3$ (5:5).
[b] Catalyst **8** (0.001 mmol) was used instead of **5**.
[c] 0.001 mmol of catalyst **5** was used.
[d] The liquid–liquid reaction was carried out in air with glycine imine (**1**) (0.17 mmol) and benzyl bromide (0.85 mmol) in the presence of catalyst **5** (0.0017 mmol) in 50% aqueous KOH (0.25 ml)—$PhCH_3/CHCl_3$ (7:3, 0.75 ml) without support.

ratio. The level of enantioselectivity improved when the mixture of toluene and chloroform were used in comparison with those using only dichloromethane or the mixture of toluene and dichloromethane (Table 3, entries 1–8).

Successful reaction was also possible using the mixture of toluene and acetonitrile, the reaction proceeded rapidly with high conversion of starting material to product, however in these cases the obtained ee's were lower (Table 3, entries 9 and 10). The use of a slight excess amount (0.15 ml) of a mixture of toluene/chloroform (7/3, v/v) made the support slurry state, leading to the prolonged reaction time (23 h) for the alkylation of **1**, but the best enantioselection (93%) was achieved (Table 3, entry 8). Overall the variation of enantioselectivity with solvent type was obvious, and so it is likely that successfully making choice of suitable solvents could result in the improvement in enantioselectivity of the alkylation reaction.

If residual traces of water existed on the support, a dramatic acceleration effect on the rate of the reaction was observed (Table 4, entries 3–13). Particularly, the reaction was completed within 2 min at 20 °C on the kaolin/KOH support containing 7–14% (w/w) residual water (Table 4, entries 4–7). The similar enantioselections as the reaction on dry solid support kaolin/KOH were obtained with significant increase in the reaction rate (Table 4, entries 3–13 and 14). Lowering the concentration of catalyst **5** from 10 to 2 mol%, similar results were obtained without decrease on the enantioselection (Table 4, entries 9–11). The enantioselectivity achieved with 2 mol% of catalyst **8** being similar to that obtained with catalyst **5** (Table 4, compare entries 10, 11 with 12, 13). The enantioselectivity was further enhanced to 94% ee rapidly by performing the reaction using catalyst **8** on kaolin/KOH (Table 4, entry 8). It is showed that careful optimization of the reaction conditions could lead to significantly acceleration of the reaction with high enantioselectivities.

The residual water on solid support in excess of 18% (w/w) made the support slurry and deactivated, led to liquid–solid two phases in the reaction system instead of all the starting materials and catalyst absorbed on the solid support. In these cases, the yield and enantioselection decreased with prolonged reaction time (Table 4, entries 1 and 2).

The influence of the temperature on the enantioselectivity and rate of the alkylation reaction was probed. Alkylation of **1** with benzyl bromide was conducted at three different temperatures: 20, 0 and −30 °C. As expected, the best enantioselection for the alkylation product was obtained at the lower temperature (Table 4, entries 5 and 14–21).

For comparison purposes, the reaction was also carried out using aqueous 50% KOH in a mixture of toluene/chloroform without solid support under the similar conditions as for the solid support method. It was found that slight lower enantioselections were obtained under liquid–liquid phase transfer condition than the solid support method at 20 or 0 °C (Table 4, entries 14, 15, 22 and 23).

The effectiveness of the supports preloaded with base appears to be due to a combination of the factors: an increase in the effective surface area for reaction; the presence of pores which constrain both catalyst and reactant and thus act as microreactors. A small amount of solvent

Table 5. Enantioselective alkylation of **1** with different alkyl halides[a]

Entry	Alkyl halide	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)	Ee (%) (Config.)
1	**2a**: $PhCH_2Br$	**5** (10)	20	0.03	90	92 (*S*)
2		**5** (2)	20	0.03	89	92 (*S*)
3		**5** (2)	0	0.1	95	96 (*S*)
4[b]		**5** (1)	0	10	95	97 (*S*)
5		**7** (10)	0	0.16	90	92 (*S*)
6[c]		**7** (10)	rt	18	68	91 (*S*)
7		**8** (2)	0	0.18	89	96 (*R*)
8[d]		**8** (1)	0	2.0	79	99 (*R*)
9	**2b**: 4-Cl–$PhCH_2Br$	**5** (10)	20	0.05	90	90 (*S*)
10		**5** (2)	20	0.05	88	89 (*S*)
11	**2c**: (2-Naphthyl)CH_2Br	**5** (10)	20	0.03	83	92 (*S*)
12		**5** (2)	20	0.05	82	90 (*S*)
13	**2d**: $CH_2{=}CHCH_2Br$	**5** (10)	20	0.05	88	89 (*S*)
14		**5** (2)	20	0.05	85	87 (*S*)
15	**2e**: $CH_3(CH_2)_2CH_2I$	**5** (10)	20	0.15	80	90 (*S*)
16		**5** (2)	20	0.15	78	86 (*S*)
17	**2f**: $CH_3(CH_2)_4CH_2I$	**5** (10)	20	0.15	78	93 (*S*)
18		**5** (2)	20	0.15	76	93 (*S*)

[a] Unless otherwise specified, the reaction was carried out in air with **1** (0.05 mmol) and benzyl bromide (0.1 mmol) on the kaolin/KOH (0.5 g, containing about 6 mmol of KOH per gram, 7% water) in the presence of the catalyst (0.005 or 0.001 mmol). The starting materials and catalyst were dissolved in 0.1 ml of $PhCH_3/CHCl_3$ (5:5).

[b] The result of liquid–liquid reaction in Ref. 2h: the reaction was carried out in air with glycine imine (**1**) (0.17 mmol) and benzyl bromide (0.85 mmol) in the presence of catalyst **5** (0.0017 mmol) in 50% aqueous KOH (0.25 ml)—$PhCH_3/CHCl_3$ (7:3, 0.75 ml) without support.

[c] The result of liquid–liquid reaction in Ref. 2c: the reaction was carried out in air with glycine imine (**1**) (0.5 mmol) and benzyl bromide (0.6 mmol) in the presence of catalyst **7** (0.05 mmol) in 50% aqueous KOH (1 ml)—$PhCH_3$ (5 ml) without support.

[d] The result of liquid–liquid reaction in Ref. 2i: the reaction was carried out in air with glycine imine (**1**) (0.5 mmol) and benzyl bromide (0.6 mmol) in the presence of catalyst **8** (0.005 mmol) in 50% aqueous KOH (1 ml)—$PhCH_3$ (3 ml) without support.

contained in the solid support can provide a better internal diffusion of the reactants inside the pores. A synergistic interaction maybe exists between the components of solid support, leading to the formation of active sites, which control the reaction. In the case of commercial available solid supports without base treatment the active sites is absent. Further work is need, however, to elucidate the detailed mechanism.

With these preliminary studies completed, in order to demonstrate the utility of this method, attention was turned to conducting the enantioselective alkylation of **1** with other alkyl halides and the results summarized in Table 5 clearly demonstrate the general applicability of the present method. Rapid reaction rates were achieved with not only substituted benzyl bromide (**2b**) and 2-(bromomethyl)naphthalene (**2c**) but also allylic bromide (**2d**) and alkyl iodides (**2e**, **2f**). The catalyst was reduced to 2 mol%, showing no significant influence on the reaction rate and obtained ee's (entries 2, 10, 12, 14, 16 and 18). The reactions carried out with benzyl bromide (**2a**) using catalysts **5**, **7** and **8** at 0 °C were all much faster than the usual liquid–liquid reactions of the literatures[2c,h,i] with similar enantioselections, respectively (Table 5, entries 3–8).

3. Conclusion

We have developed a simple, convenient and practical method for the asymmetric alkylation of *N*-diphenylmethylene glycine *t*-butyl ester using solid support preloaded with base. The simple experimental and product isolation procedures combined with easy recovery and reuse of this support is expected to contribute to the development of clean and environmentally friendly strategy for the rapid preparation of optically active amino acids or related derivatives. Further studies on the optimization of the reaction conditions and the applications of this method to other asymmetric synthesis will be reported in due course.

4. Experimental

4.1. General

HPLC was carried out using a Waters 470 apparatus equipped with chiral columns. ^1H NMR spectra were measured on a JEOL JNM-GSX270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Mass spectra were carried out with a Perkin–Elmer ELAN 600. The solvents were of analytical grade. Catalysts **4**, **5** and **6** were prepared by a published procedure.[2h] The catalyst **7** (Aldrich), catalyst **8** (Aldrich) and all the supports: kaolin (Wako, cat. No. 117-00025), aluminium oxide (Merck, cat. No. 1011097, for chromatography, 90 standardized), montmorillonite K10 (Aldrich, cat. No. 28,1152-2, surface area 220–270 m^2/g, bulk density 300–370 g/l) and celite (Wako, cat. No. 537-02305, No. 545), were used as received.

4.2. General procedure for the preparation of solid support preloaded with base

Kaolin clay (3 g) was added to 4 ml of 25% KOH solution, and the mixture was sonicated for a period of 4 h then dried in a rotary evaporator for several hours (obtaining solid support with suitable residual water). Residual traces of water were removed from the support by irradiating with microwave for 15 min. The solid was ground to a powder.

The solid support thus prepared contains about 6 mmol of KOH per gram.

4.3. Typical procedure for alkylation of *N*-diphenylmethylene glycine *t*-butyl ester on solid support preloaded with base

A solution of *N*-diphenylmethylene glycine *t*-butyl ester (**1**) (0.05 mmol), benzyl bromide (**2a**) (0.06 mmol) and catalyst **5** (0.005 mmol) in CH_2Cl_2 (0.1 ml) was slowly added dropwise into kaolin/KOH (0.5 g, 51 equiv. KOH to **1**). The so-obtained solid was stilled at 20 °C. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with CH_2Cl_2 (2×5 ml) from the support. The extract was condensed with an evaporator and then the residue was purified by flash chromatography on silica gel (hexane/diethyl ether/triethylamine: 50/5/0.5) to afford the desired product (*S*)-α-benzyl *t*-butylglycinate benzophenone imine (**3a**) as a colorless oil. The entantiomeric excess was determined by HPLC (Chiralcel OD, hexane/2-propanol: 500:2.5, 1 ml/min, λ=254 nm, 23 °C). Spectral data are in agreement with literature values.[2d]

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Elimination reactions of glycosyl selenoxides

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Abstract—Glycosyl selenoxides, generated in situ from selenoglycosides by a Sharpless-type oxidation, undergo facile *syn* elimination leading to 2-hydroxy and 2-amino glycals in high yield.

1. Introduction

Glycosyl sulfoxides are extremely useful glycosyl donors, and have found wide application in oligosaccharide synthesis.[1] The thermal elimination of glycosyl sulfoxides has also recently been applied to the synthesis of 2-substituted glycals.[2] However, the chemistry of glycosyl selenoxides has not yet been the focus of extensive investigation.[3] As part of ongoing studies into expanding the synthetic utility of glycals[4–6] as starting materials for the synthesis of a variety of *C*-glycosides[7] we sought easy access to a wide range of 2-hydroxy and 2-amino substituted materials. Since existing synthetic routes to 2-hydroxy glycals are not particularly high yielding, attention turned to the possible use of the presumably facile elimination[8] of glycosyl selenoxides as a means of accessing these materials. Indeed the elimination of selenoxides had already been applied, both for the introduction of unsaturation into carbohydrates at positions other than at the anomeric centre,[9] and also for the synthesis of 2-deoxy furanoid materials.[10]

Glycosyl selenoxides should be available by oxidation of selenoglycosides, which have themselves found extensive use as glycosyl donors and are readily accessible in one-step from either the corresponding glycosyl acetates[11] or halides.[12] Thus it was envisaged that oxidation of a selenoglycoside would produce an anomeric selenoxide which could then undergo spontaneous in situ *syn* elimination to yield the corresponding 2-hydroxy glycal in a single step (Fig. 1). Since selenoxides undergo thermal elimination at considerably lower temperatures than sulfoxides[13] such a spontaneous elimination of a glycosyl selenoxide would advantageously obviate the need for isolation of any intermediates, and also eliminate the possibility of over-oxidation, which can be problematic in the case of glycosyl sulfoxides. Following a previous report on the use of glycosyl selenoxides as glycosyl donors[3] it was also decided to investigate the potential fate of glycosyl selenoxides if the 2-hydroxyl or 2-amino group was *cis* to the anomeric selenium, since in this case *syn* elimination would not be possible (Fig. 1). In this paper we provide full details[14] of the synthetic utility of 1,2-*trans* glycosyl selenoxides which smoothly eliminate in situ to allow the synthesis of 2-substituted glycals in very high yield, and we also outline some preliminary investigations into the fate of 1,2-*cis* glycosyl selenoxides.

2. Results and discussion

2.1. Synthesis of selenoglycosides

A variety of selenoglycoside substrates possessing various protecting group patterns were synthesized in order to test the general applicability of the proposed methodology. The known selenoglycosides **1a**,[11] **2a**,[11] **3a**,[15] **4a**,[15] **5a**,[11] **7a**,[11] **9a**,[11] and **11a**[11] were all accessed following previously published literature procedures. New selenoglycoside substrates were synthesized as follows (Scheme 1). Diacetonide **6a** was accessed directly from the known *manno* selenoglycoside tetraacetate **9**[16] by deacetylation with catalytic methoxide and immediate reprotection by treatment with dimethoxypropane and catalytic camphor sulphonic acid (74% yield). A variety of 2-amino selenoglycoside substrates were also synthesized. Thus, the phthalimido protected glucosamine selenoglycoside **8a** was synthesized from the known alcohol **14**[11] by treatment with acetic anhydride and pyridine (98% yield). In order to investigate

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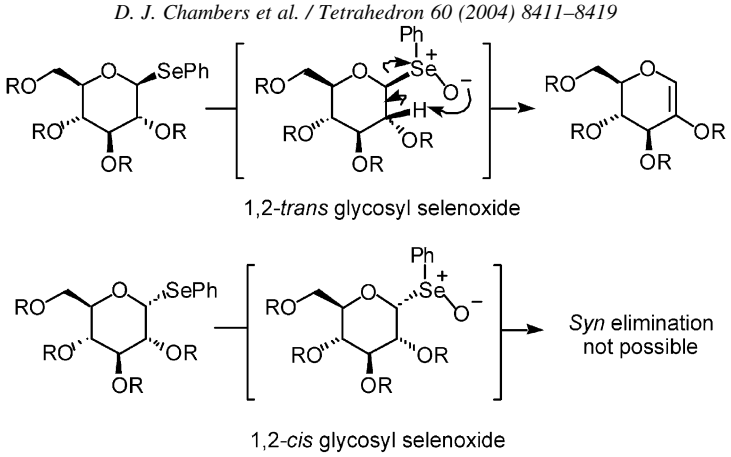
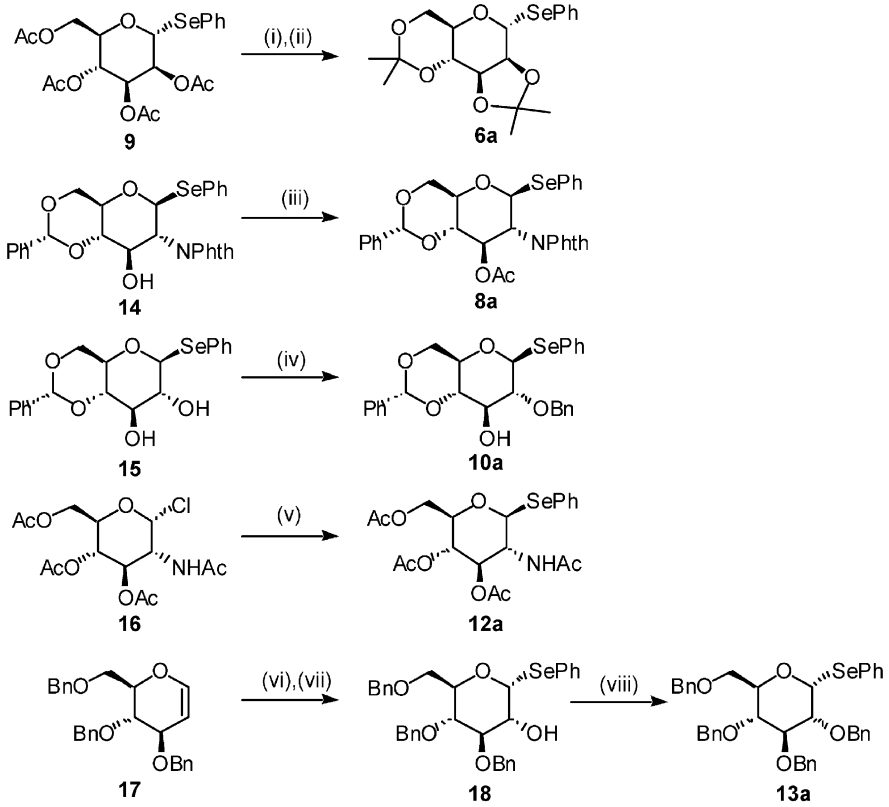


Figure 1.

whether free hydroxyl groups could be tolerated, the alcohol **10a**, possessing a free 3-hydroxyl, was accessed by selective benzylation of the known diol **15**[11] by treatment with benzyl bromide under phase transfer conditions (66% yield). To investigate the effect of variation of nitrogen protecting group the *N*-acetylglucosamine derivative **12a** was accessed from the chloride **16**[17] by treatment with diphenyl diselenide and sodium borohydride (62% yield). Finally, in order to investigate potential reactivity of a 1,2-*cis* selenoglycoside, the α-selenoglucoside **13a** was synthesized in two steps from tribenzyl glucal **17** as follows. Reaction with dimethyldioxirane in acetone yielded the α-epoxy glycal which was then reacted directly with selenophenol in THF to yield the α-gluco selenoglycoside **18**[18] (87% yield). Treatment of alcohol **18** with benzyl bromide and sodium hydride in DMF then produced the fully benzylated selenoglycoside **13a** (95% yield).

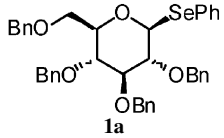
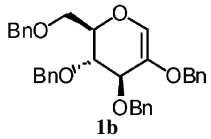
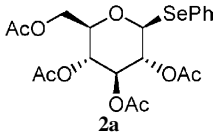
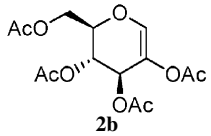
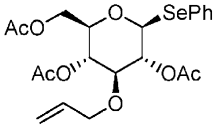
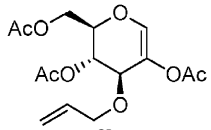
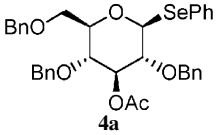
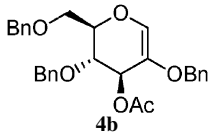
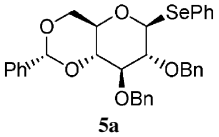
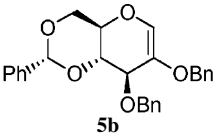
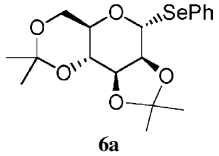
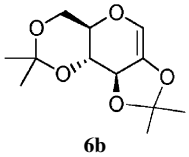
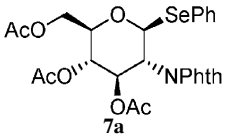
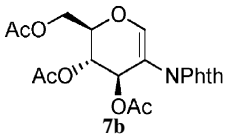
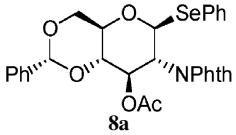
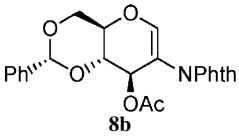
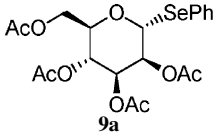
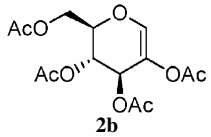
2.2. Oxidation and elimination reactions

Suitable reaction conditions were sought in order to achieve the desired oxidation and elimination reactions in a single step. Selenoglycoside **1a** was studied as a model compound and subjected to a variety of reaction conditions. Attempted oxidation of **1a** with either *meta*chloroperbenzoic acid (MCPBA) or periodate was not successful, and resulted either in decomposition of the substrate, or in the formation of multiple products. However, subjecting **1a** to Sharpless-



Scheme 1. (i) Na, MeOH; (ii) dimethoxypropane, camphor sulphonic acid, DMF, 60 °C, 240 mbar, 74% over two steps; (iii) Ac_2O, pyridine, 98%; (iv) BnBr, NaOH (aq), CH_2Cl_2, Bu_4NHSO_4, 66%; (v) PhSeSePh, $NaBH_4$, EtOH, 62%; (vi) dimethyldioxirane in acetone, CH_2Cl_2, 0 °C; (vii) PhSeH, THF, 87% over two steps; (viii) BnBr, NaH, DMF, 95%.

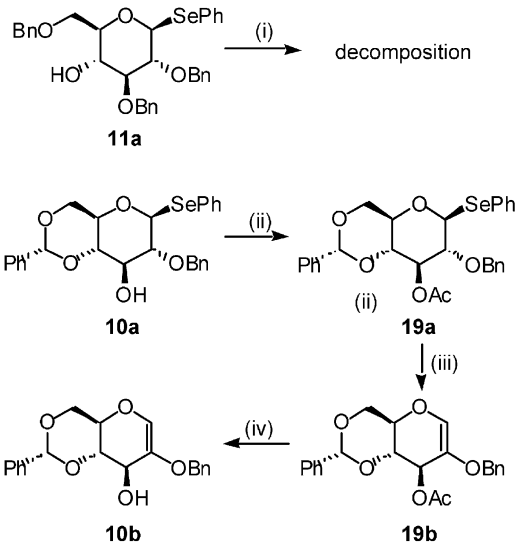
Table 1. Oxidation/elimination of 1,2-*trans* selenoglycosides

	Substrate	Glycal	Yield (%)
(a)	 **1a**	 **1b**	Quant.
(b)	 **2a**	 **2b**	99
(c)	 **3a**	 **3b**	90
(d)	 **4a**	 **4b**	95
(e)	 **5a**	 **5b**	91
(f)	 **6a**	 **6b**	86
(g)	 **7a**	 **7b**	Quant.
(h)	 **8a**	 **8b**	96
(i)	 **9a**	 **2b**	93

type oxidation conditions,[10,19] namely *tert*-butyl hydroperoxide and titanium tetra-isopropoxide, in the presence of di-*iso*propylethylamine as a base,[20] resulted in the formation of the desired 2-hydroxy glycal product **1b**[21] in quantitative yield. No intermediate selenoxide was observed either by NMR or thin layer chromatography (TLC), and the only isolated product was the desired glycal **1b** (Table 1).

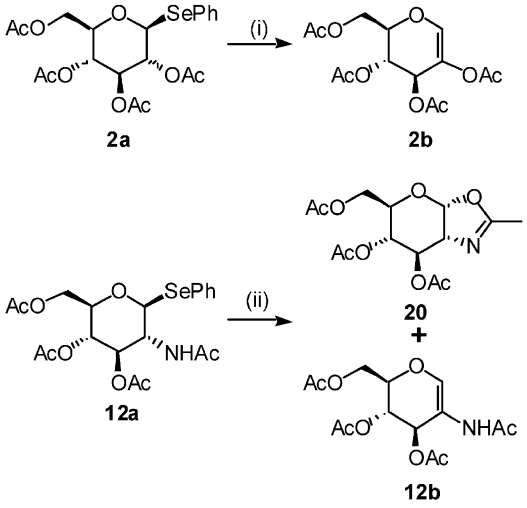
To test the generality of this process the fully protected selenoglycosides **2a**–**9a** were all subjected to these reaction conditions (Table 1). In all cases the desired glycal products **2b**–**8b** were produced in extremely high yield. The reaction worked equally well for the α-manno selenoglycosides **6a** and **9a**, and was compatible with fully protected substrates possessing acetate, benzyl, benzylidene, allyl and acetonide protection of hydroxyl groups. The reaction was also compatible with phthalimido protection of 2-amino selenoglycosides as demonstrated by the successful reaction of **7a** and **8a**.

Investigation then turned to the use of substrates that possessed free hydroxyl groups. Reaction of the alcohol **10a**, in which the 3-hydroxyl is free, under the optimized oxidation conditions outlined above, resulted in decomposition and the formation of multiple products by TLC. Since the desired glycal product of this reaction **10b** is an allylic alcohol, which itself may be oxidized under the reaction conditions, the oxidation of selenoglycoside **11a**, in which

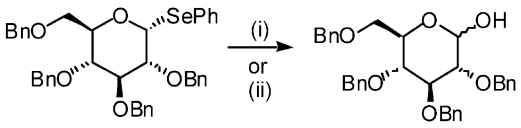


Scheme 2. (i) Ti(O*i*Pr)$_4$, Bu^{t}OOH, *i*Pr$_2$EtN, CH_2Cl_2, 0 °C; (ii) Ac_2O, pyridine, 96%; (iii) Ti(O*i*Pr)$_4$, Bu^{t}OOH, *i*Pr$_2$EtN, CH_2Cl_2, 0 °C, quantitative; (iv) NaOMe, MeOH, 99%.

the 4-hydroxyl was not protected, was also investigated. Unfortunately again this reaction resulted in decomposition and the formation of multiple products. To further investigate why decomposition was being observed, diacetone galactose was subjected to the oxidation conditions as a model alcohol. Unsurprisingly no reaction of the free hydroxyl was observed and the starting material recovered. In order to investigate if the reaction product was actually stable to the reaction conditions the glycal **10b** was synthesized in three steps from **10a** by acetylation to yield acetate **19a** (96% yield) which then smoothly underwent oxidation/elimination to yield glycal **19b** (quantitative) and then finally deacetylation to yield **10b** (99% yield, Scheme 2). Subjection of hydroxy glycal **10b** to the oxidation/elimination reaction conditions immediately resulted in decomposition. It can therefore be concluded that this selenoglycoside oxidation/elimination pathway can only be applied to fully protected substrates as the products



Scheme 3. (i) Ti(O*i*Pr)$_4$, Bu^{t}OOH, *i*Pr$_2$EtN, MeOH (10 equiv), CH_2Cl_2, 0 °C, quant.; (ii) Ti(O*i*Pr)$_4$, Bu^{t}OOH, *i*Pr$_2$EtN, CH_2Cl_2, 0 °C, 96%, ratio **12b**:**20**, 2.2:1.



Scheme 4. (i) Ti(O*i*Pr)$_4$, Bu^{t}OOH, *i*Pr$_2$EtN, CH_2Cl_2, 0 °C, 64%; (ii) Ti(O*i*Pr)$_4$, Bu^{t}OOH, *i*Pr$_2$EtN, MeOH (10 equiv), CH_2Cl_2, 0 °C, 35%.

of the elimination step decompose under the reaction conditions. The synthesis of **10b** outlined in Scheme 2 indicates that glycal products with free hydroxyl groups can be synthesized from selenoglycosides simply by the use of acetate protection/deprotection steps.

The only previous report in the literature on the chemistry of glycosyl selenoxides indicated that a glycosyl selenoxide had acted as an efficient glycosyl donor at low temperature.[3] In order to investigate the relative rates of the possible nucleophilic substitution versus elimination reactions the selenoglycoside **2a** was subjected to oxidation under the standard conditions at 0 °C in the presence of 10 equiv of methanol. Under these reaction conditions no methyl glycoside was obtained, the only product being the expected glycal **2b**, which was isolated in quantitative yield. (Scheme 3), indicating that at least at 0 °C elimination of a 1,2-*trans* glycosyl selenoxide competes effectively over any intermolecular nucleophilic substitution. However, the possibility of the anomeric selenoxide acting as a leaving group was confirmed by reaction of the *N*-acetyl protected selenoglycoside **12a**, which revealed competitive intramolecular substitution. In this case an inseparable mixture of the 2-amino glycal **12b** and the oxazoline **20** were isolated in 96% yield (ratio 2.2:1) (Scheme 3). This reaction also indicates that the efficient synthesis of 2-amino glycals by this route requires phthalimido or similar double protection of nitrogen.

Finally the potential fate of a 1,2-*cis* glycosyl selenoxide was investigated by oxidation of the α-selenoglucoside **13a**. Reaction under the standard conditions resulted in consumption of starting material and the formation of two more polar products as visualized by TLC.[22] However, attempted isolation of these products resulted in decomposition and the only material that could be isolated from the reaction mixture was the lactol **21** (Scheme 4). Moreover attempted in situ glycosylation by performing the reaction in the presence of 10 equiv of methanol also produced only lactol **21**, no methyl glycoside being observed. This result indicates that at least under these Sharpless-type oxidation conditions that glycosyl selenoxides have little potential to act as efficient and synthetically useful glycosyl donors.[23]

3. Summary and conclusion

Oxidation/elimination of 1,2-*trans* selenoglycosides using Sharpless type reaction conditions allows the high yielding synthesis of a wide variety of protected 2-hydroxy and 2-amino glycals. This methodology is advantageous to the alternative sulfoxide approach in that, neither isolation of intermediate oxidation products nor elevated temperatures are required, since formation of the desired glycal occurs

spontaneously subsequent to oxidation. However, this methodology is not applicable to selenoglycoside substrates possessing free hydroxyl groups. Moreover competitive intramolecular substitution of acetyl protected 2-amino glycosyl selenoxides results in substantial oxazoline formation, indicating double protection of 2-amino substituents is required for efficient reaction. However, intermolecular nucleophilic substitution under these conditions is not an efficient process, even for 1,2-*cis* selenoglycoside substrates, which cannot undergo 1,2-*syn* elimination. In this latter case only lactol products were observed.

4. Experimental

4.1. General methods

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Bruker AV 400 (400 MHz) spectrometer. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker AV 400 (100.6 MHz) spectrometer. Multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Infrared spectra were recorded on a Perkin–Elmer 150 Fourier Transform spectrophotometer. Low-resolution mass spectra were recorded on a Micromass Platform 1 using electrospray ionisation (ES), or on a Fisons AutoSpec-oaTof using chemical ionisation (CI). High-resolution mass spectra (electrospray) were performed on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer (ES), or (chemical ionisation) on a Fisons AutoSpec-oaTof (CI). Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical services of the Inorganic Chemistry Department, Oxford University. TLC was carried out on Merck Kieselgel 0.22–0.25 mm thickness glass-backed sheets, pre-coated with $60F_{254}$ silica. Plates were developed using 5% w/v ammonium molybdate in 2 M sulfuric acid. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Dichloromethane was distilled from calcium hydride. Petrol refers to the fraction of light petroleum ether boiling in the range 40–60 °C. All procedures were performed under an atmosphere of argon.

4.2. General experimental procedure for oxidation/elimination of selenoglycosides

The selenoglycoside (1 equiv) and *N*,*N*-diisopropylethylamine (1.7 equiv) were dissolved in anhydrous dichloromethane and the solution cooled to 0 °C. *tert*-Butyl hydroperoxide (5.5 M solution in decane, 2.3 equiv) was added drop-wise over a period of 5 min, and then titanium (IV) isopropoxide (1.0 equiv) was added. The reaction mixture was stirred under an atmosphere of argon for 2 h, after which time TLC indicated complete conversion of starting material to the product. The yellow solution was concentrated in vacuo, and purified by flash column chromatography.

4.3. 2,3,4,6-Tetra-*O*-benzyl-D-glucal 1b

Selenoglucoside **1a** (184.0 mg, 0.27 mmol, R_f 0.55 (petrol/ethyl acetate, 4:1)) was subjected to the general oxidation conditions to afford glucal **1b** (143.5 mg, quant., R_f 0.5) as a white crystalline solid, mp 65–66 °C (methanol) [lit. 68.5–69 °C];[21] $[\alpha]_D^{21}$ −7.5 (*c*, 1.0 in $CHCl_3$) [lit. $[\alpha]_D$ −6.2];[21] δ_H (400 MHz, $CDCl_3$) 3.71 (1H, dd, $J_{5,6}$=3.6 Hz, $J_{6,6'}$=10.8 Hz, H-6), 3.80 (1H, dd, $J_{5,6'}$=5.8 Hz, $J_{6,6'}$=10.8 Hz, H-6′), 3.92 (1H, dd, $J_{3,4}$=4.9 Hz, $J_{4,5}$=6.5 Hz, H-4), 4.09–4.13 (1H, m, H-5), 4.28 (1H, d, H-3), 4.50–4.78 (8H, m, 4×$PhCH_2$), 6.33 (1H, s, H-1), 7.25–7.39 (20H, m, 20×Ar-H).

4.4. 2,3,4,6-Tetra-*O*-acetyl-D-glucal 2b

Selenoglucoside **2a** (1.45 g, 2.98 mmol, R_f 0.3 (petrol/ethyl acetate, 2:1)) was subjected to the general oxidation conditions to afford glucal **2b** (0.966 g, 98%, R_f 0.25) as a white crystalline solid, mp 62–63 °C (ether/petrol) [lit. 61–62 °C (ether/petrol)];[24] $[\alpha]_D^{22}$ −25 (*c*, 1.2 in $CHCl_3$) [lit. $[\alpha]_D^{22}$ −33 (*c*, 1.24 in $CHCl_3$)];[24] δ_H (400 MHz, $CDCl_3$) 2.06, 2.10, 2.10 (12H, 3×s, 4×CH_3), 4.22 (1H, dd, $J_{5,6}$=3.2 Hz, $J_{6,6'}$=11.8 Hz, H-6), 4.35–4.45 (2H, m, H-5, H-6′), 5.23 (1H, dd, $J_{4,5}$=5.5 Hz, $J_{3,4}$=4.5 Hz, H-4), 5.56 (1H, d, $J_{3,4}$=4.5 Hz, H-3), 6.63 (1H, s, H-1).

Selenomannoside **9a** (200.7 mg, 0.41 mmol, R_f 0.35 (petrol/ethyl acetate, 2:1)) was subjected to the general oxidation conditions to afford glucal **2b** (126.2 mg, 93%, R_f 0.3) identical to the material described above.

4.5. 2,4,6-Tri-*O*-acetyl-3-*O*-allyl-D-glucal 3b

Selenoglucoside **3a** (132 mg, 0.27 mmol, R_f 0.25 (petrol/ethyl acetate, 2:1)) was subjected to the general oxidation conditions to afford glucal **3b** (80.1 mg, 90%, R_f 0.3) as a colourless oil; $[\alpha]_D^{23}$ −23 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1743 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.10, 2.12, 2.16 (9H, 3×s, 3×CH_3), 4.09–4.13 (3H, m, H-3, OCH_2-CH=CH_2), 4.22 (1H, dd, $J_{5,6}$=3.4 Hz, $J_{6,6'}$=12.0 Hz, H-6), 4.35–4.38 (1H, m, H-5), 4.45 (1H, dd, $J_{5,6'}$=7.8 Hz, $J_{6,6'}$=12.0 Hz, H-6′), 5.17–5.20 (2H, m, H-4, C=C$H_E$$H_Z$), 5.28 (1H, daq, ^3J=17.3 Hz, J=1.7 Hz, C=C$H_E$$H_Z$), 5.80–5.88 (1H, m, C$H$=$CH_2$), 6.60 (1H, s, H-1); δ_C (100.7 MHz, $CDCl_3$) 20.7, 20.8, 20.9 (3×q, 3×CH_3), 61.3 (t, C-6), 67.4 (d, C-4), 70.2 (t, OCH_2CH=CH_2), 70.6 (d, C-3), 74.0 (d, C-5), 117.6 (t, C=CH_2), 129.3 (s, C-2), 134.0 (d, C=CH_2), 137.4 (d, C-1), 169.6, 169.9, 170.6 (3×s, 3×C=O); *m*/*z* (ES^+) 351 ($M+Na^+$, 100), 346 ($M+NH_4^+$, 15%). (HRMS (ES^+) calcd for $C_{15}H_{20}O_8Na$ ($M+Na^+$) 351.1056. Found, 351.1055). (Found: C, 54.77; H, 6.30. $C_{15}H_{20}O_8$ requires C, 54.87; H, 6.14%.)

4.6. 3-*O*-Acetyl-2,4,6-tri-*O*-benzyl-D-glucal 4b

Selenoglucoside **4a** (9.69 g, 15.3 mmol, R_f 0.3 (petrol/ethyl acetate, 4:1)) was subjected to the general oxidation conditions to afford glucal **4b** (6.92 g, 95%, R_f 0.3) as a colourless oil; $[\alpha]_D^{24}$ +22 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film) 1741 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 3.69 (1H, dd, $J_{5,6}$=4.3 Hz, $J_{6,6'}$=10.6 Hz, H-6), 3.78 (1H, dd, $J_{5,6'}$=5.4 Hz, $J_{6,6'}$=10.6 Hz, H-6′), 3.97 (1H, dd, $J_{3,4}$=4.9 Hz, $J_{4,5}$=6.6 Hz, H-4), 4.11–4.16 (1H, m, H-5),

4.56, 4.59 (2H, ABq, J=11.8 Hz, $PhCH_2$), 4.65, 4.77 (2H, ABq, J=11.4 Hz, $PhCH_2$), 4.68, 4.72 (2H, 2×s, $PhCH_2$), 5.49 (1H, d, $J_{3,4}$=4.9 Hz, H-3), 6.37 (1H, s, H-1), 7.28–7.39 (15H, m, 15×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 21.1 (q, CH_3), 67.6 (t, C-6), 68.6 (d, C-3), 71.5, 72.7, 73.5 (3×t, 3×$PhCH_2$), 73.5 (d, C-4), 76.1 (d, C-5), 127.4, 127.7, 127.8, 127.9, 128.0, 128.4 (6×d, 15×Ar-C), 130.2 (d, C-1), 135.4, 136.9, 137.7, 137.8 (4×s, 3×Ar-C, C-2), 170.6 (s, C=O); m/z (ES^+) 497 ($M+Na^+$, 100), 492 ($M+NH_4^+$, 35%). (HRMS (ES^+) calcd for $C_{29}H_{30}O_6Na$ ($M+Na^+$) 497.1940. Found, 497.1931.)

4.7. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-glucal 5b

Selenoglucoside **5a** (106.8 mg, 0.18 mmol, R_f 0.4 (petrol/ethyl acetate, 4:1)) was subjected to the general oxidation conditions to afford glucal **5b** (71.2 mg, 91%, R_f 0.4) as a white crystalline solid, mp 121–123 °C (methanol); $[\alpha]_D^{21}$ −30 (c, 1.1 in $CHCl_3$) [lit. $[\alpha]_D$ +9.3 (c, 1.5 in $CHCl_3$)];[25] δ_H (400 MHz, $CDCl_3$) 3.79–3.85 (1H, m, H-5), 3.85–3.91 (1H, m, H-6), 4.15 (1H, dd, $J_{3,4}$=7.3 Hz, $J_{4,5}$=9.9 Hz, H-4), 4.42 (1H, dd, $J_{5,6'}$=4.4 Hz, $J_{6,6'}$=9.8 Hz, H-6′), 4.56 (1H, d, $J_{3,4}$=7.3 Hz, H-3), 4.77, 4.80 (2H, ABq, J=11.5 Hz, $PhCH_2$), 4.92, 4.96 (2H, ABq, J=12.0 Hz, $PhCH_2$), 5.65 (1H, s, $PhCHO_2$), 6.36 (1H, s, H-1), 7.31–7 58 (15H, m, 15×Ar-H).

4.8. Phenyl 2,3:4,6-*O*-di-*iso*-propylidene-1-seleno-α-D-mannopyranoside 6a

Tetraacetate **9**[16] (405.5 mg, 0.83 mmol) was dissolved in methanol (15 ml), and sodium methoxide (4.5 mg, 0.083 mmol) was added. The reaction mixture was stirred under an atmosphere of argon for 1 h, when TLC (ethyl acetate) indicated complete consumption of starting material (R_f 0.7) and formation of a single product (R_f 0.3). The mixture was concentrated in vacuo, and co-evaporated with toluene (2×30 ml). The residue was taken up in anhydrous DMF (10 ml). 2,2-Dimethoxypropane (0.41 ml, 3.33 mmol) and camphor sulphonic acid (39 mg, 0.17 mmol) were added, and the reaction mixture was stirred at 60 °C at reduced pressure (240 mbar) for 4 h. After this time, TLC (petrol/ethyl acetate, 2:1) indicated consumption of starting material (R_f 0) and formation of a major product (R_f 0.7). The mixture was concentrated in vacuo, and the residue taken up in ether (100 ml). The solution was washed with water (2×75 ml) and brine (2×75 ml of a saturated solution). The aqueous layers were extracted with ether (75 ml) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 6:1) to give diacetonide **6a** (246.0 mg, 74%) as a white crystalline solid, mp 109–110 °C (ether/petrol); $[\alpha]_D^{25}$ +188 (c, 1.0 in $CHCl_3$); ν_{max} (KBr disc) no significant peaks; δ_H (400 MHz, $CDCl_3$) 1.36, 1.46, 1.52, 1.56 (12H, 4×s, 4×CH_3), 3.73–3.79 (2H, m, H-6, H-6′), 3.86 (1H, dd, $J_{3,4}$=8.0 Hz, $J_{4,5}$=10.2 Hz, H-4), 3.92–3.98 (1H, m, H-5), 4.22 (1H, dd, $J_{2,3}$=5.4 Hz, $J_{3,4}$=8.0 Hz, H-3), 4.47 (1H, d, $J_{2,3}$=5.4 Hz, H-2), 6.07 (1H, s, H-1), 7.27–7.59 (5H, m, 5×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 18.8, 26.4, 28.3, 29.0 (4×q, 4×CH_3), 61.6 (t, C-6), 64.2 (d, C-5), 72.9 (d, C-4), 74.6 (d, C-3), 77.2 (d, C-2), 81.1 (d, C-1), 99.8, 109.8 (2×s, 2×O_2C), 128.1, 129.2, 134.5 (3×d, 5×Ar-C), 128.4 (s, Ar-C); m/z (CI^+) 401 (12%, $M+H^+$). (HRMS (CI^+) calcd for $C_{18}H_{25}O_5^{80}Se$ ($M+H^+$) 401.0867. Found, 401.0864). (Found: C, 54.16; H, 5.99. $C_{18}H_{24}O_5Se$ requires C, 54.14; H, 6.06%.)

4.9. 2,3:4,6-*O*-Di-*iso*-propylidene-D-glucal 6b

Selenomannoside **6a** (118.0 mg, 0.30 mmol, R_f 0.60 (petrol/ethyl acetate, 4:1)) was subjected to the general oxidation conditions to afford glucal **6b** (61.8 mg, 86%, R_f 0.65) as a pale yellow oil; $[\alpha]_D^{25}$ +44 (c, 1.1 in $CHCl_3$); ν_{max} (thin film) no significant peaks; δ_H (400 MHz, $CDCl_3$) 1.46, 1.47, 1.49, 1.56 (12H, 4×s, 4×CH_3), 3.60 (1H, dat, J=5.6, 10.4, 10.4 Hz, H-5), 3.83–3.93 (2H, m, H-4, H-6), 4.01 (1H, dd, $J_{5,6'}$=5.6 Hz, $J_{6,6'}$=11.1 Hz, H-6′), 4.60 (1H, dd, $J_{1,3}$=1.8 Hz, $J_{3,4}$=7.6 Hz, H-3), 6.22 (1H, d, $J_{1,3}$=1.8 Hz, H-1); δ_C (100.7 MHz, $CDCl_3$) 19.0, 25.3, 26.7, 28.9 (4×q, 4×CH_3), 62.0 (t, C-6), 67.3 (d, C-5), 71.1 (d, C-4), 73.6 (d, C-3), 99.6, 113.2, 134.1 (C-2, 2×$(CH_3)_2C$), 122.2 (d, C-1); m/z (CI^+) 243 ($M+H^+$, 100%). (HRMS (CI^+) calcd for $C_{12}H_{19}O_5$ ($M+H^+$) 243.1232. Found, 243.1235.)

4.10. 3,4,6-Tri-*O*-acetyl-2-phthalimido-D-glucal 7b

Selenoglucoside **7a** (150 mg, 0.26 mmol, R_f 0.2 (petrol/ethyl acetate, 1:1)) was subjected to the general oxidation conditions to afford glucal **7b** (120 mg, quant., R_f 0.15) as a colourless oil; $[\alpha]_D^{25}$ −26 (c, 1.1 in $CHCl_3$) [lit. $[\alpha]_D^{25}$ −15 (c, 0.2 in $CHCl_3$)];[26] δ_H (400 MHz, $CDCl_3$) 1.92, 2.11, 2.14 (9H, 3×s, 3×CH_3), 4.37 (1H, dd, $J_{5,6}$=3.5 Hz, $J_{6,6'}$=11.8 Hz, H-6), 4.50 (1H, dd, $J_{5,6'}$=6.7 Hz, $J_{6,6'}$=11.8 Hz, H-6′), 4.53–4.57 (1H, m, H-5), 5.31 (1H, at, J=4.4 Hz, H-4), 5.59 (1H, d, $J_{3,4}$=4.0 Hz, H-3), 6.76 (1H, s, H-1), 7.71–7.88 (4H, m, 4×Ar-H).

4.11. Phenyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-seleno-β-D-glucopyranoside 8a

Alcohol **14** (506 mg, 0.94 mmol) was dissolved in a mixture of acetic anhydride (4 ml) and pyridine (4 ml) and stirred under an atmosphere of argon. After 16 h, TLC (petrol/ethyl acetate, 2:1) indicated the consumption of starting material (R_f 0.3) and formation of a single product (R_f 0.4). The reaction mixture was poured into water, and extracted with DCM (6×25 ml). The combined organic layers were washed with hydrochloric acid (2×75 ml of a 1 M solution) and sodium bicarbonate (2×75 ml of a saturated solution), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 3:1) to give acetate **8a** (535 mg, 98%) as a white crystalline solid, mp 100–102 °C (ethyl acetate/petrol); $[\alpha]_D^{25}$ +1.9 (c, 1.1 in $CHCl_3$); ν_{max} (KBr disc) 1743, 1710 (s, 2×C=O); δ_H (400 MHz, $CDCl_3$) 1.87 (3H, s, CH_3), 3.72–3.85 (3H, m, H-4, H-5, H-6), 4.39–4.46 (2H, m, H-2, H-6′), 5.54 (1H, s, $PhCHO_2$), 5.89 (1H, at, J=9.4 Hz, H-3), 6.00 (1H, d, $J_{1,2}$=10.9 Hz, H-1), 7.21–7.86 (14H, m, 14×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 20.6 (q, CH_3), 55.4 (d, C-2), 68.6 (t, C-6), 70.5 (d, C-3), 71.6 (d, C-4), 79.0, 79.4 (2×d, C-1, C-5), 101.6 (d, $PhCHO_2$), 126.3, 128.3, 135.2, 136.8 (4×s, 4×Ar-C), 127.9, 128.2, 128.2, 128.5, 129.1, 129.2, 134.2, 135.2 (8×d, 14×Ar-C); m/z (ES^+) 602 (100, $M+Na^+$), 597 (85, $M+NH_4^+$), 580 (25%, $M+H^+$). (HRMS (ES^+) calcd for $C_{29}H_{29}O_7N_2^{80}Se$

($M+NH_4^+$) 597.1140. Found, 597.1136). (Found: C, 59.99; H, 4.56; N, 2.32. $C_{29}H_{25}O_7NSe$ requires C, 60.21; H, 4.36; N, 2.42%.)

4.12. 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-D-glucal 8b

Selenoglucoside **8a** (154 mg, 0.27 mmol, R_f 0.3 (petrol/ethyl acetate, 2:1)) was subjected to the general oxidation conditions to afford glucal **8b** (107.2 mg, 96%, R_f 0.2) as a white crystalline solid, mp 199–202 °C (ethyl acetate/petrol); $[\alpha]_D^{25}$ +8.6 (*c*, 1.1 in $CHCl_3$); ν_{max} (KBr disc) 1745, 1923 (s, C=O), 1664 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.88 (3H, s, CH_3), 3.94 (1H, at, J=10.1 Hz, H-6), 4.24–4.34 (2H, m, H-4, H-5), 4.49 (1H, dd, $J_{5,6'}$=4.8 Hz, $J_{6,6'}$=10.5 Hz, H-6′), 5.60 (1H, s, $PhCHO_2$), 5.97 (1H, d, $J_{3,4}$=6.6 Hz, H-3), 6.72 (1H, s, H-1), 7.27–7.50 (5H, m, 5×benzylidene Ar-H), 7.74–7.92 (4H, m, 4× phthalimide A-H); δ_C (100.7 MHz, $CDCl_3$) 20.6 (q, CH_3), 68.0 (t, C-6), 68.3 (d, C-3), 69.7, 77.4 (2×d, C-4, C-5), 101.7 (d, $PhCHO_2$), 107.2 (s, C-2), 123.7, 126.2, 128.3, 129.3, 134.4 (5×d, 9×Ar-C), 131.6, 136.6 (2×s, 3×Ar-C), 167.7, 170.5 (2×s, 2×C=O), 149.1 (d, C-1); *m/z* (ES^+) 444 ($M+Na^+$, 100), 439 ($M+NH_4^+$, 90%). (HRMS (ES^+) calcd for $C_{23}H_{23}N_2O_7$ ($M+NH_4^+$) 439.1505. Found, 439.1518). (Found: C, 65.50; H, 4.51; N, 3.31. $C_{23}H_{19}NO_7$ requires: C, 65.56; H, 4.54; N, 3.32%.)

4.13. Phenyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-seleno-β-D-glucopyranoside 10a

Diol **15** (8.66 g, 21.3 mmol) was dissolved in a mixture of DCM (150 ml) and sodium hydroxide (40 ml of a 5% aqueous solution). Benzyl bromide (2.5 ml, 21 mmol) and tetra-*N*-butylammonium hydrogen sulphate (1.44 g, 4.3 mmol) were added to the mixture, and the mixture stirred at 40 °C for 8 h. After this time, TLC (petrol/ethyl acetate, 4:1) indicated the consumption of starting material (R_f 0) and the formation of a major product (R_f 0.2) and a minor product (R_f 0.4). The reaction mixture was diluted with DCM (150 ml), and washed with water (2×250 ml). The organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 9:1→4:1) to afford the undesired dibenzylated compound (R_f 0.4, 1.24 g, 10%) as a white crystalline solid, and the desired alcohol **10a** (R_f 0.2), which was then further purified by recrystallisation (ethyl acetate/petrol) to yield a white crystalline solid (6.93 g, 66%), mp 120–122 °C; $[\alpha]_D^{21}$ −41 (*c*, 1.04 in $CHCl_3$); ν_{max} (KBr disc) 3467 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.57 (1H, br s, OH), 3.42–3.68 (3H, m, H-2, H-4, H-5), 3.77 (1H, at, J=10.3 Hz, H-6), 3.91 (1H, at, J=8.6 Hz, H-3), 4.38 (1H, dd, $J_{5,6'}$=4.9 Hz, $J_{6,6'}$=10.6 Hz, H-6′), 4.82, 4.95 (2H, ABq, J=10.3 Hz, CH_2Ph), 4.90 (1H, s, H-1), 5.53 (1H, s, $PhCHO_2$), 7.29–7.69 (15H, m, 15×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 68.6 (t, C-6), 71.1 (d, C-5), 75.3 (t, CH_2Ph), 75.6 (d, C-3), 80.3, 81.3 (2×d, C-2, C-4), 83.3 (d, C-1), 101.8 (d, $PhCHO_2$), 126.2, 128.0, 128.1, 128.2, 128.3, 128.3, 128.5, 129.1, 129.3, 134.6, 135.3, 136.9, 138.0 (10×d, 3×s, 18×Ar-C); *m/z* (CI^+) 499 (8%, $M+H^+$). (HRMS (CI^+) calcd for $C_{26}H_{27}O_5{}^{80}Se$ ($M+H^+$) 499.1024. Found, 499.1022.)

4.14. 2-*O*-Benzyl-4,6-*O*-benzylidene-D-glucal 10b

Acetate **19b** (1.12 g, 2.93 mmol) was dissolved in methanol (50 ml). Sodium methoxide (16 mg, 0.293 mmol) was added, and the mixture stirred under an atmosphere of argon for 1 h. After this time, TLC (petrol/ethyl acetate, 4:1) indicated formation of a single product (R_f 0.3) with no remaining starting material (R_f 0.4). The reaction mixture was concentrated in vacuo. The residue was taken up in DCM (100 ml) washed with water (2×75 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 4:1) to afford alcohol **10b** (986 mg, 99%) as a white crystalline solid, mp 133–134 °C (ethyl acetate/petrol); $[\alpha]_D^{22}$ +1.5 (*c*, 1.1 in $CHCl_3$); ν_{max} (KBr disc) 3498 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.77–3.86 (2H, m, H-5, H-6), 3.95 (1H, dd, $J_{3,4}$=7.4 Hz, $J_{4,5}$=9.9 Hz, H-4), 4.37–4.40 (1H, m, H-6′), 4.62 (1H, d, $J_{3,4}$=7.4 Hz, H-3), 4.69, 4.77 (2H, ABq, J=11.2 Hz, CH_2Ph), 5.60 (1H, s, $PhCHO_2$), 6.25 (1H, s, H-1), 7.35–7.54 (10H, m, 10×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 67.8, 68.3 (2×d, C-3, C-5), 68.3 (t, C-6), 71.3 (t, CH_2Ph), 80.0 (d, C-4), 101.5 (d, $PhCHO_2$), 126.3 (d, C-1), 127.7, 127.9, 128.3, 128.6, 129.2 (5×d, 10×Ar-C), 136.3, 126.9, 129.1 (3×s, 2×Ar-C, C-2); *m/z* (ES^+) 703 (2M+Na^+, 100), 358 ($M+NH_4^+$, 20%); (HRMS (ES^+) calcd for $C_{20}H_{24}O_5N$ ($M+NH_4^+$) 358.1654. Found, 358.1663). (Found: C, 70.60; H, 5.95. $C_{20}H_{20}O_5$ requires C, 70.58; H, 5.92%.)

4.15. Phenyl 3,4,6-tri-*O*-acetyl-2-*N*-acetylamino-2-deoxy-1-seleno-β-D-glucopyranose 12a

To a solution of diphenyldiselenide (2.35 g, 7.5 mmol) in ethanol (75 ml) was added sodium borohydride (780 mg, 21 mmol) under an atmosphere of argon. Chloride **16**[17] (5.00 g, 13.7 mmol) was dissolved in chloroform (25 ml), and the solution transferred to the reaction mixture via cannula. The mixture was stirred for 2 h, when TLC (ethyl acetate/petrol, 3:1) indicated complete consumption of starting material (R_f 0.5) and formation of a major product (R_f 0.3). The reaction mixture was diluted with DCM (300 ml), and washed with sodium hydroxide (300 ml of a 1 M solution) and brine (300 ml). The solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 1:2) to give acetate **12a** (4.11 g, 62%) as a white crystalline solid, mp 193–196 °C (ethyl acetate/petrol); $[\alpha]_D^{25}$ −29 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disc) 3298 (s, NH), 1758 (s, C=O), 1660 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.98, 2.02, 2.03, 2.08 (12H, 4×s, 4×CH_3), 3.65–3.69 (1H, m, H-5), 4.10–4.16 (1H, m, H-2), 4.15–4.23 (2H, m, H-6, H-6′), 5.00 (1H, d, $J_{1,2}$=10.5 Hz, H-1), 5.05–5.17 (2H, m, H-3, H-4), 5.56 (1H, d, $J_{NH,2}$=9.2 Hz, NH), 7.27–7.64 (5H, m, 5×Ar-H); δ_H (100.7 MHz, $CDCl_3$) 20.6, 20.6, 20.7 (3× q, 3×C(O)*C*H_3), 23.3 (q, $NHCH_3$), 54.0 (d, C-2), 62.4 (t, C-6), 68.3 (d, C-4), 73.6 (d, C-3), 76.9 (d, C-5), 82.7 (d, C-1), 128.3, 129.0 (2×d, 5×Ar-C), 127.9 (s, Ar-C), 169.3, 170.0, 170.6, 171.1 (4×s, 4×C=O); *m/z* (ES^+) 510 ($M+Na^+$, 100), 488 ($M+H^+$, 20%). (HRMS (ES^+) calcd for $C_{20}H_{25}NO_8Na^{80}Se$ ($M+Na^+$) 510.0643. Found, 510.0664).

4.16. 3,4,6-Tri-*O*-acetyl-2-*N*-acetylamino-2-deoxy-D-glucal 12b and methyl (3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-D]-Δ^2-oxazolidine 20

Selenoglucoside **12a** (161.6 mg, 0.33 mmol, R_f 0.4 (ethyl acetate)) was subjected to the general oxidation conditions to afford a 2.2:1 mixture (172.3 mg, 96%, R_f 0.3) of glucal **12b** and oxazolidine **20** as a pale yellow oil; ν_{max} (thin film) 1744, 1665 (2×s, amide I, amide II, N=C–O); δ_H (400 MHz, $CDCl_3$) data for **12b**: 2.03–2.14 (12H, m, 4×CH_3), 4.11–4.28 (1H, m, H-6), 4.35–4.43 (2H, m, H-5, H-6′), 5.22 (1H, at, J=4.7 Hz, H-4), 5.34 (1H, d, $J_{3,4}$=4.0 Hz, H-3), 6.94 (1H, s, NH), 7.41 (1H, s, H-1); data for **20**: 2.03–2.14 (12H, m, 4×CH_3), 3.60–3.65 (1H, m, H-3), 4.11–4.28 (2H, m, H-6, H-2), 4.35–4.43 (1H, m, H-6′), 4.93–4.97 (1H, m, H-4), 5.28 (1H, at, J=2.4 Hz, H-5), 5.99 (1H, d, $J_{1,2}$=7.5 Hz, H-1); δ_C (100.7 MHz, $CDCl_3$) data for **12b**: 21.1, 21.1, 21.3, 24.2 (4×q, 4×CH_3), 61.6 (t, C-6), 67.5, 67.8 (2×d, C-3, C-4), 73.6 (d, C-5), 111.6 (s, C-2), 140.8 (d, C-1), 169.2, 170.0, 170.9, 171.0 (4×s, 4×C=O); data for **20**: 14.3, 21.1, 21.3, 24.2 (4×q, 4×CH_3), 63.8 (t, C-6), 65.4 (d, C-2), 67.9 (d, C-3), 68.8 (d, C-4), 70.8 (d, C-5), 99.8 (d, C-1), 167.1, 169.6, 170.9, 172.1 (4×s, 3×C=O, C=N); *m/z* (ES^+) 352 ($M+Na^+$, 100%). (HRMS (ES^+) calcd for $C_{14}H_{19}NO_8Na$ ($M+Na^+$) 352.1008. Found, 352.1009.)

4.17. Phenyl 2,3,4,6-tetra-*O*-benzyl-1-seleno-α-D-glucopyranoside 13a

To a solution of selenoglucoside **18**[18] (1.01 g, 1.71 mmol) in anhydrous DMF (20 ml) was added benzyl bromide (0.30 ml, 2.56 mmol) and then sodium hydride (60% in mineral oil, 82 mg, 2.05 mmol). The reaction mixture was stirred under an atmosphere of nitrogen for 16 h, when TLC (petrol/ethyl acetate, 4:1) indicated consumption of starting material (R_f 0.2) and formation of a major product (R_f 0.4). The reaction mixture was quenched with methanol (6 ml), diluted with ether (100 ml) and washed with water (2×75 ml) and brine (2×75 ml of a saturated solution). The solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 6:1) to afford selenoglucoside **13a** (1.11 g, 95%) as a white crystalline solid, mp 71–72 °C (ether/petrol); $[\alpha]_D^{20}$ +162 (*c*, 0.9 in $CHCl_3$); ν_{max} (KBr disc) no significant peaks; δ_H (400 MHz, $CDCl_3$) 3.56 (1H, dd, $J_{5,6}$=1.8 Hz, $J_{6,6'}$=10.4 Hz, H-6), 3.71–3.80 (2H, m, H-4, H-6′), 3.84–3.88 (2H, m, H-2, H-3), 4.27 (1H, br dd, J=1.3, 10.1 Hz, H-5), 4.41, 4.59 (2H, ABq, J=12.1 Hz, $PhCH_2$), 4.52 (1H, d, J=10.9 Hz, PhCH), 4.67 (1H, d, J=11.7 Hz, PhCH), 4.79–4.88 (3H, m, 3×PhCH), 5.00 (1H, d, J=10.9 Hz, PhCH), 6.05 (1H, d, $J_{1,2}$=4.1 Hz, H-1), 7.17–7.61 (25H, m, 25×Ar-H); δ_C (100.6 MHz, $CDCl_3$) 68.3 (t, C-6), 72.7 (d, C-5), 72.4, 73.3, 75.1, 75.8 (4×t, 4×$PhCH_2$), 77.4 (d, C-4), 80.1, 83.2 (2×d, C-2, C-3), 85.8 (d, C-1), 127.4, 127.6, 127.6, 127.7, 127.9, 127.9, 127.9, 128.0, 128.2, 128.3, 128.4, 128.4, 128.9 (13×d, 25×Ar-C), 129.1, 137.6, 137.8, 138.2, 138.6 (5×s, 5×Ar-C); *m/z* (ES^+) 703 ($M+Na^+$, 100%). (HRMS (ES^+) calcd for $C_{40}H_{44}NO_5{}^{80}Se$ ($M+NH_4^+$) 698.2385. Found, 698.2380.)

4.18. Phenyl 3-*O*-acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-1-seleno-β-D-glucopyranoside 19a

Alcohol **10a** (1.84 g, 3.70 mmol) was dissolved in a mixture of acetic anhydride (20 ml) and pyridine (20 ml). The reaction mixture was stirred for 16 h under an atmosphere of argon. After this time, TLC (petrol/ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.3) and formation of a single product (R_f 0.4). The reaction mixture was poured into water, and extracted with DCM (4×50 ml). The organic layers were washed with hydrochloric acid (50 ml of a 1 M solution), sodium bicarbonate (50 ml of a saturated solution) and brine (50 ml of a saturated solution), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petrol/ethyl acetate, 6:1) to afford acetate **19a** (1.92 g, 96%) as a white crystalline solid, mp 148–149 °C (ethyl acetate/petrol); $[\alpha]_D^{21}$ −42 (*c*, 1.1 in $CHCl_3$); ν_{max} (KBr disc) 1730 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.97 (3H, s, CH_3), 3.51–3.62 (3H, m, H-2, H-4, H-5), 3.78 (1H, at, J=10.0 Hz, H-6), 4.39 (1H, dd, $J_{5,6}$=4.6 Hz, $J_{6,6'}$=10.5 Hz, H-6′), 4.61, 4.88 (2H, ABq, J=10.9 Hz, $PhCH_2$), 5.01 (1H, d, $J_{1,2}$=9.7 Hz, H-1), 5.38 (1H, at, J=9.1 Hz, H-3), 5.48 (1H, s, $PhCHO_2$), 7.28–7.68 (15H, m, 15×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 20.9 (q, CH_3), 68.6 (t, C-6), 71.4, 78.6, 79.8 (3×d, C-2, C-4, C-5), 74.4 (d, C-3), 75.0 (t, $PhCH_2$), 83.6 (d, C-1), 101.3 (d, $PhCHO_2$), 126.1, 128.0, 128.2, 128.2, 128.3, 128.5, 129.1, 129.2, 134.6 (9×d, 15×Ar-C), 136.9, 137.5 (2×s, 3×Ar-C), 169.7 (s, C=O); *m/z* (ES^+) 563 (100, $M+Na^+$), 558 (75%, $M+NH_4^+$). (HRMS (ES^+) calcd for $C_{28}H_{32}O_6N^{80}Se$ ($M+NH_4^+$) 558.1395. Found, 558.1378). (Found: C, 62.20; H, 5.23. $C_{28}H_{28}O_6Se$ requires C, 62.34; H, 5.23%.)

4.19. 3-*O*-Acetyl-2-*O*-benzyl-4,6-*O*-benzylidene-D-glucal 19b

Acetate **19a** (145 mg, 0.27 mmol, R_f 0.35 (petrol/ethyl acetate, 4:1)) was subjected to the general oxidation procedure to afford glucal **19b** (106.3 mg, quant., R_f 0.4) as a fluffy white crystalline solid, mp 125–127 °C (methanol); $[\alpha]_D^{22}$ −12 (*c*, 0.9 in $CHCl_3$); ν_{max} (KBr disc) 1745 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.14 (3H, s, CH_3), 3.82–3.92 (2H, m, H-5, H-6), 4.08 (1H, dd, $J_{3,4}$=7.9 Hz, $J_{4,5}$=9.8 Hz, H-4), 4.38–4.41 (1H, m, H-6′), 4.63, 4.82 (2H, ABq, J=11.6 Hz, $PhCH_2$), 5.57 (1H, s, $PhCHO_2$), 6.02 (1H, d, H-3), 6.34 (1H, s, H-1), 7.31–7.52 (10H, m, 10×Ar-H); δ_C (100.7 MHz, $CDCl_3$) 21.1 (q, CH_3), 68.0 (d, C-3), 68.3 (t, C-6), 69.0 (d, C-5), 71.8 (d, $PhCH_2$), 77.3 (d, C-4), 101.3 (d, $PhCHO_2$), 126.2, 127.3, 127.9, 128.3, 128.5, 129.2 (6×d, 10×Ar-C), 131.1 (d, C-1), 136.5, 136.7, 138.8 (3×s, 2×Ar-C, C-2), 170.7 (s, C=O); *m/z* (ES^+) 405 ($M+Na^+$, 60), 400 ($M+NH_4^+$, 95%); (HRMS (ES^+) calcd for $C_{22}H_{26}NO_6$ ($M+NH_4^+$) 400.1760. Found 400.1767). (Found: C, 69.09; H, 5.82. $C_{22}H_{22}O_6$ requires C, 69.10; H, 5.80%.)

4.20. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose 21

Selenoglucoside **13a** (113 mg, 0.17 mmol) and diisopropylethylamine (0.05 ml, 0.28 mmol) were dissolved in anhydrous DCM (6 ml) and the solution cooled to 0 °C. *tert*-Butylhydroperoxide (5.5 M in decane, 0.15 ml, 0.73 mmol)

was added drop-wise over 5 min, and then titanium(IV) isopropoxide (0.05 ml, 0.17 mmol) was added. The reaction mixture was stirred under an atmosphere of argon for 16 h, when TLC (petrol/ethyl acetate, 4:1) indicated consumption of starting material (R_f 0.5) and formation of two products (R_f 0.1, 0.05). The yellow solution was concentrated in vacuo, and purified by flash column chromatography (petrol/ethyl acetate, 6:1→2:1) to afford lactol **21** (R_f 0.4, 57.6 mg, 64%) as a white crystalline solid; δ_H (400 MHz, $CDCl_3$)[27] α anomer: 3.03 (1H, br s, OH), 3.52–3.73 (4H, m, H-2, H-4, H-6, H-6′), 3.98 (1H, at, $J=9.3$ Hz, H-3), 4.03–4.05 (1H, m, H-5), 4.13–4.98 (8H, m, 4×$PhCH_2$), 5.24 (1H, d, $J_{1,2}=3.5$ Hz, H-1), 7.12–7.53 (20H, m, 20×Ar-H); β anomer: 3.03 (1H, br s, OH), 3.41 (1H, dd, $J=7.7$, 8.9 Hz, H-2), 3.52–3.73 (4H, m, H-3, H-4, H-6, H-6′), 4.03–4.05 (1H, m, H-5), 4.13–4.98 (8H, m, 4×$PhCH_2$), 4.69–4.74 (1H, m, H-1), 7.12–7.53 (20H, m, 20×Ar-H).

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An investigation into the use of silica-supported bases within EOF-based flow reactors

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Abstract—Using a series of silica-supported bases, we demonstrate the synthesis of eight condensation products within an EOF-based flow reactor; in all cases, high yields (>99%) and product purity are obtained.

1. Introduction

Increased demand for the rapid preparation of small molecule libraries has led to renewed interest in the development of clean and efficient techniques for the synthesis of organic compounds. With this in mind, the miniaturisation of reaction technology is of particular interest to the pharmaceutical industry, where long term objectives include the desire to perform multiple functions such as synthesis, detection, screening and biological evaluation within a single integrated device, resulting in an overall reduction in the time taken to discover new lead compounds and put them into production.[1] To date, numerous compounds have been successfully synthesised within micro fabricated devices with many groups demonstrating advantages over traditional batch techniques such as greater reaction control, leading to increased conversions, selectivities and reduced reaction times.[2] Although many groups have begun the task of transferring synthetic methodology from batch to micro reactors, few have addressed the problems associated with product purification in continuous systems.[3] In order to tackle these problems, we were interested in the use of solid-supported reagents.[4]

1.1. Solid-supported reagents

Compared to solid-phase techniques,[5] where reaction intermediates are immobilised and cannot be fully characterised until cleaved from the support, the use of solid-supported reagents means that reaction products remain in solution, enabling reaction progress to be monitored. As the technique couples the advantages of both solid and solution-phase synthesis, the use of solid-supported reagents means that excess reagent can be employed in order to drive the reaction to completion, while the reagent can be easily removed from the reaction mixture. With the obvious similarities to solid-phase synthetic methodology, polymers have found widespread use in the preparation of solid-supported reagents;[6,7] other materials however include zeolites,[8] clays[9] and silicas.[10] Unlike certain polymers, silica exhibits no swelling in organic solvents and is thermally, chemically and mechanically stable; consequently, its use as a support is becoming more widespread. Due to the non-porous nature of the support, functionalisation is limited to the surface and as a result, reaction rate is not limited by reagent diffusion whilst enabling controlled, reproducible loading. In order to prevent any undesirable adsorption of materials onto the silica, any unfunctionalised silanol groups are end-capped. With this in mind, we were interested in investigating the incorporation of silica-supported reagents for continuous synthesis in a miniaturised flow reactor.

1.2. Knoevenagel condensation

The Knoevenagel reaction is defined as the condensation of an aldehyde or ketone with compounds that possesses an active methylene group. The reaction is brought about using organic bases such as primary or secondary amines.[11] The active methylene groups employed include nitro, cyano and acyl groups and in most cases, two groups are required in order to provide sufficient activation. As Scheme 1 illustrates, the primary product formed is the unsaturated product although, in some cases, further reaction may take place with a second molecule of the activated methylene compound resulting in a Michael addition to afford the bis product. With careful selection of the starting materials, enantioselective[12] and diastereoselective[13] condensation

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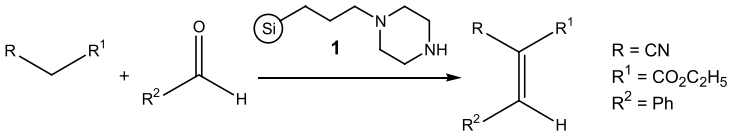

Scheme 1. General scheme illustrating the reaction of activated methylenes and aldehydes with a functionalised silica gel **1**.

products may be obtained. The main disadvantage associated with the Knoevenagel condensation is that the reactions do not proceed to completion and require purification to remove the organic base and its salt. Many alternatives exist, including acid catalysed condensations,[14] dry grind,[15] the use of microwave irradiation,[16] zeolites,[17] aluminium oxides[18] and the use of amino functionalised polymers[19] and silica gels.[20]

It was therefore proposed that by incorporation of a series of supported bases into a micro-fabricated device, that product purity could be increased while simultaneously maintaining the advantages associated with miniaturisation. Firstly, in order to compare the use of supported reagents within a flow reactor with traditional batch techniques, the reactions were initially performed in batch using both silica-supported and solution phase bases.

2. Results and discussion

As Scheme 1 illustrates, treatment of an activated methylene with a base **1** in the presence of an aldehyde, results in the preparation of an unsaturated product (Fig. 1).

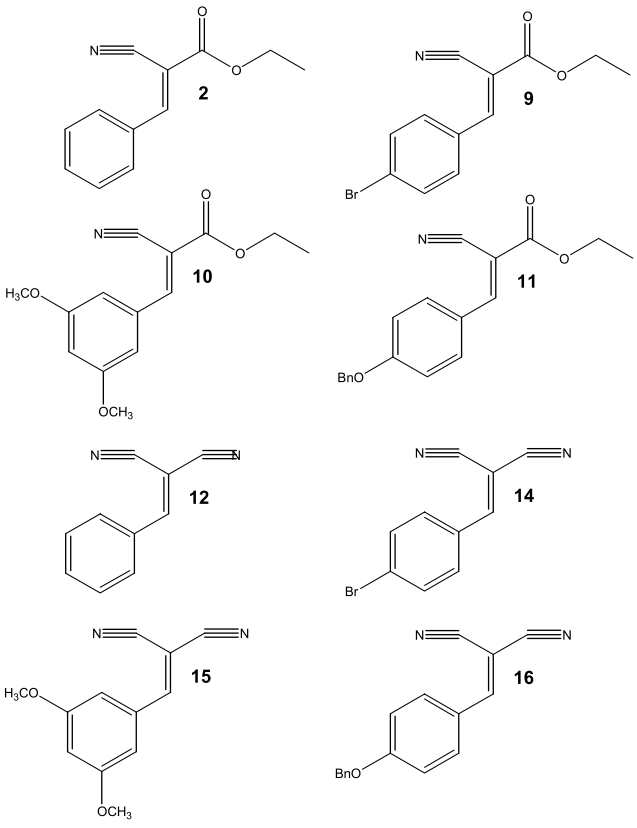

Figure 1. Synthetic targets for preparation in a miniaturised device.

Prior to investigating the incorporation of a silica-supported base within a flow reactor, using the preparation of 2-cyano-3-phenyl acrylic acid ethyl ester **2** as a model reaction, the rate of reaction was compared to a solution phase base at room temperature. As Figure 2 illustrates, compared to piperazine **3**, the rate of conversion is markedly reduced when 3-(1-piperazino)propyl-functionalised silica gel **1** is employed.

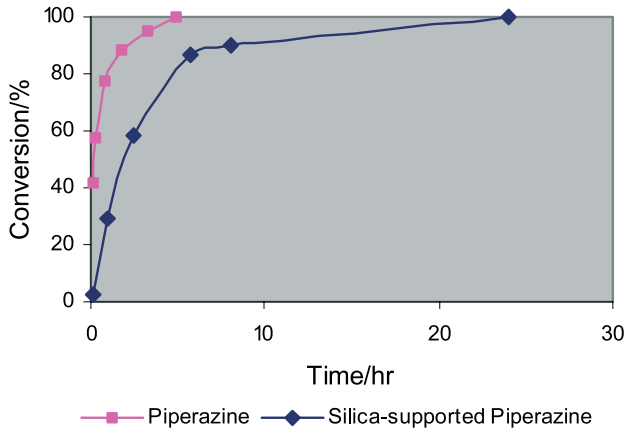

Figure 2. Graph illustrating the rate of conversion when employing solution-phase organic bases compared with solid-phase bases.

Having demonstrated the successful synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** using 3-(1-piperazino)propyl-functionalised silica gel **1**, the next step was to investigate reagent longevity. As Figure 3 illustrates, recycling the reagent results in a significant decrease in conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **2**. As the reaction is base catalysed and the reagent is end-capped to prevent fouling, the increase in reaction time was attributed to a loss of reagent as a result of recycling. In order to confirm this, the reaction was again investigated

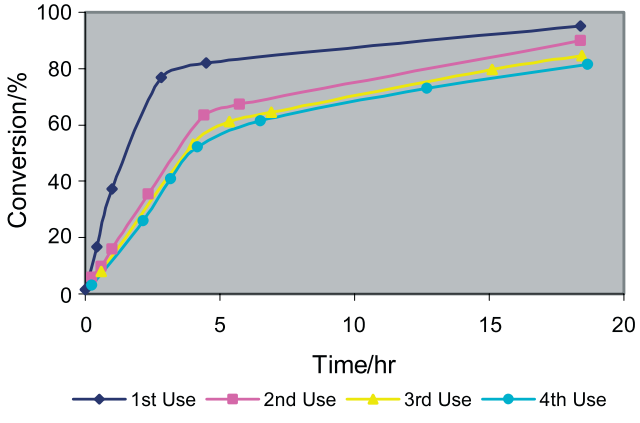

Figure 3. Graph illustrating the effect of recycling a solid supported reagent on the rate of conversion.

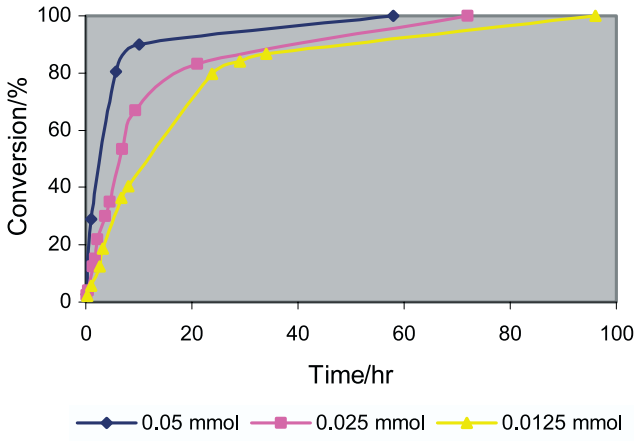

Figure 4. Graph illustrating the effect of base amount on the rate of conversion.

using varying amounts of 3-(1-piperazino)propyl-functionalised silica gel **1** (0.05–0.0125 mmol). As Figure 4 illustrates, as the quantity of base employed is decreased, the reaction time required increases, confirming the reduction in reaction rate is due to reagent loss. Having demonstrated the ability to recycle 3-(1-piperazino)propyl-functionalised silica gel **1**, the next step was to demonstrate its use in a micro fabricated device.

In order to evaluate the use of silica-supported reagents within an EOF-based system, a miniaturised flow reactor was investigated (Fig. 5). This approach not only enabled the reagents to be packed with ease but also provided a relatively inexpensive, versatile system. Although examples of pressure-driven systems have been reported within the literature, owing to its simplicity, the technique of electroosmotic flow (EOF) is demonstrated. The technique is advantageous as it is simple to use, requires no mechanical parts, enables reproducible pulse-free flow and most importantly, with respect to packed systems, generates minimal back-pressure.[21] As Figure 6 illustrates, when an ionisable surface such as glass, quartz or Teflon, comes in contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk liquid. A proportion of the counterions are adsorbed onto the surface, resulting in the formation of an immobile layer, and the remaining positive ions form a transient

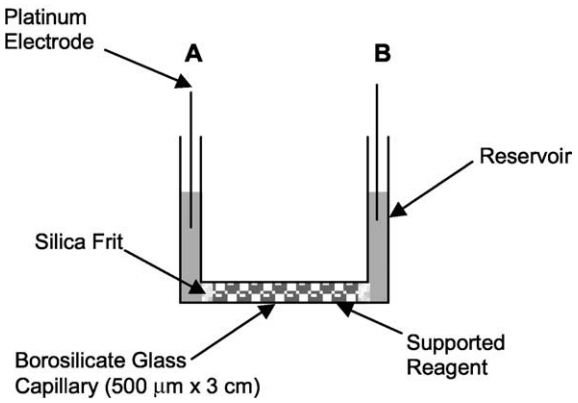

Figure 5. Schematic of the reaction set-up used for the evaluation of solid-supported reagents.

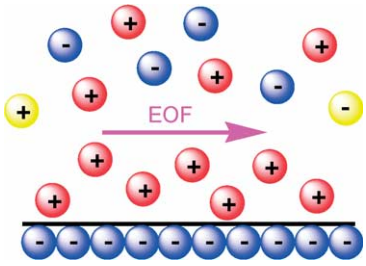

Figure 6. Schematic illustrating the principle of electroosmotic flow.

double layer. Application of an electric field causes the double layer to move towards the most negative electrode, inducing bulk flow within the microchannel.

To perform a reaction, the starting materials are passed over a silica-supported reagent using EOF, reacted for a specified time, collected in the product reservoir and analysed using a chromatographic technique. As Figure 5 illustrates, 5 mg of 3-(1-piperazino)propyl-functionalised silica gel **1** (4.75×10^{-3} mmol) was packed into a borosilicate glass capillary (500 μm×3 cm) and in order to prevent loss of the reagent, micro porous silica frits were placed at either end.[22] The capillary was then primed with MeCN to remove any air, ensuring the formation of a complete circuit, and the capillary attached to two glass reservoirs. The reagents were manipulated through the device via the application of a voltage to the platinum electrodes placed in the reagent reservoirs. As Figure 7 illustrates, a 1:1 mixture of benzaldehyde **4** and ethylcyanoacetate **5** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). Application of 333 and 0 V cm^{-1} resulted in the mobilisation of the reaction mixture through the packed bed at a flow rate of 0.5 μl min^{-1}.

After 20 min, the reaction products were collected in reservoir B, diluted with MeCN and analysed by GC-MS, whereby 98.3% conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **2** was obtained with respect to residual benzaldehyde **4** (Fig. 8). Consequently, in order to demonstrate the use of the aforementioned device for the continuous synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2**, the reactor was run continually over a period of 4.75 h (14 runs), whereby 0.025 g (0.124 mmol, 98.9%) of product **2** was prepared. As Table 1 illustrates, reproducible conversions of greater than 98% were obtained demonstrating device stability and reagent longevity. After analysis by GC-MS, the reaction products were collected and concentrated in vacuo, the crude product was then analysed by NMR. As Figure 9 illustrates, NMR confirms the successful

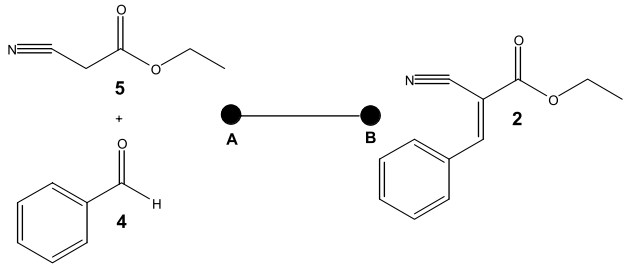

Figure 7. Schematic of the preparation of 2-cyano-3-phenyl acrylic acid ethyl ester **2** in an EOF-based miniaturised device.

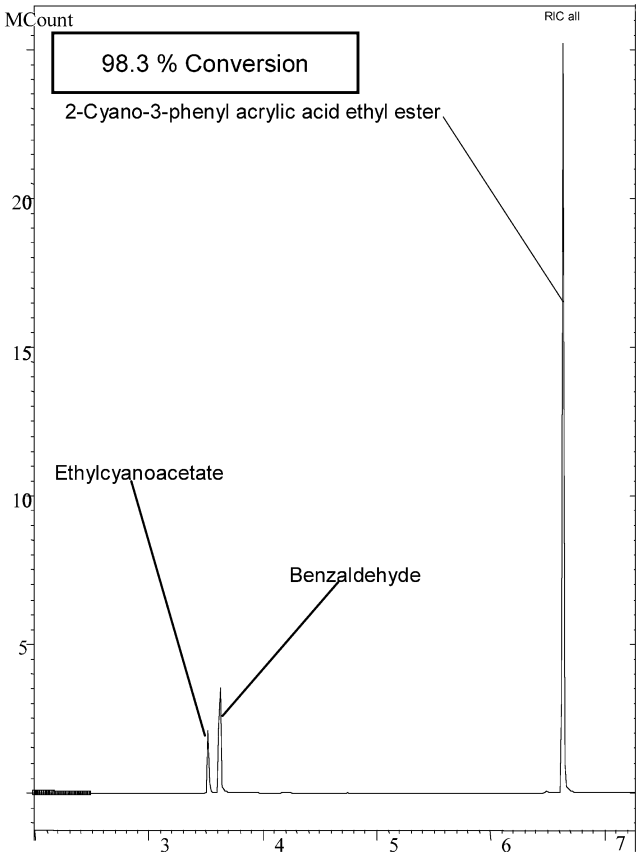

Figure 8. Chromatogram illustrating the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** within a micro reactor (98.3% conversion).

Table 1. Table illustrating device reproducibility over 4.7 h

Run No.	Conversion (%)
1	98.3
2	98.5
3	98.3
4	98.3
5	98.4
6	99.2
7	99.1
8	99.1
9	100.0
10	99.6
11	99.3
12	100.0
13	100.0
14	99.2
Mean=99.1%, % RSD=0.65	

synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** in high purity within a micro fabricated device without the need for further purification. Having demonstrated the ability to synthesise 2-cyano-3-phenyl acrylic acid ethyl ester **2**, the technique was repeated using 4-bromobenzaldehyde **6**, 3,5-dimethoxybenzaldehyde **7**, 4-benzyloxybenzaldehyde **8**, to afford the respective condensation products **9**, **10** and **11** in 99.5, 94.7 and 95.1% conversion respectively (Table 2).

Having successfully demonstrated the preparation of an array of condensation products, the technique was extended to the synthesis of 2-benzylidene malononitrile **12**. Using the aforementioned methodology, a 1:1 mixture of malononitrile **13** and benzaldehyde **4** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). As malononitrile **13** exhibits a greater electroosmotic mobility cf. ethylcyanoacetate **5**, the applied field was

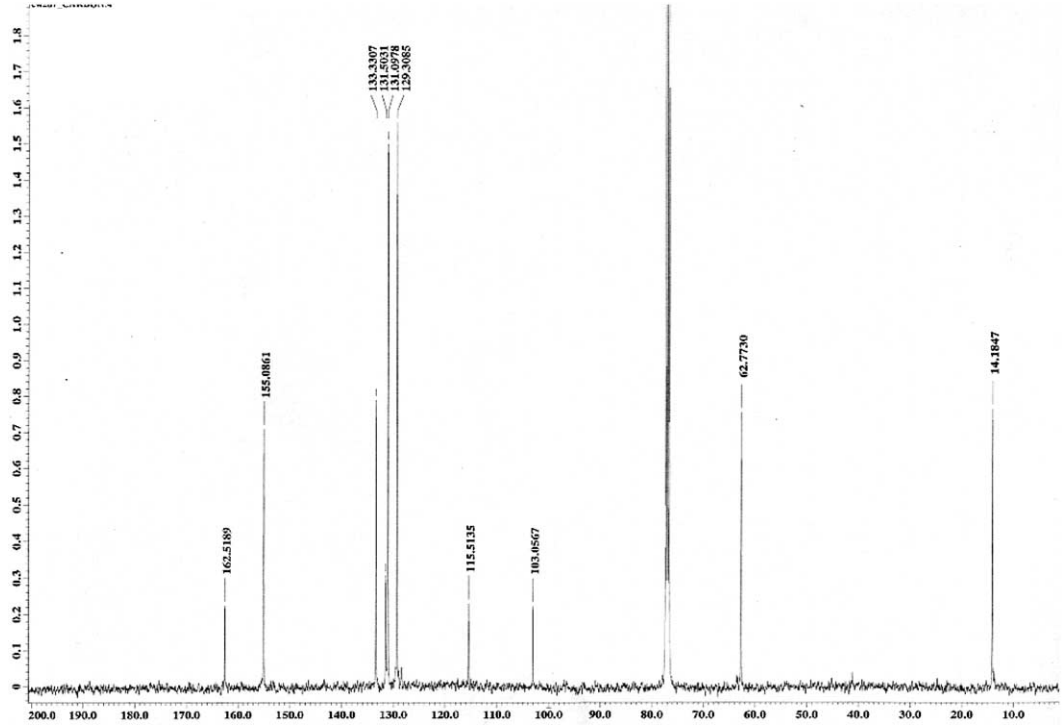

Figure 9. ^{13}C NMR of 2-cyano-3-phenyl acrylic acid ethyl ester **2** synthesised using a micro fabricated device.

Table 2. Summary of the conversions obtained in a micro fabricated device using 3-(1-piperazino)propyl-functionalised silica gel **1**

Product No.	Applied Field ($V\ cm^{-1}$)	Flow Rate ($\mu l\ min^{-1}$)	Conversion[a] (%)
2	333	0.5	99.1
9	333	0.3	99.5
10	333	0.3	94.7
11	333	0.5	95.1
12	167	1.0	96.9
14	167	0.5	96.3
15	167	0.7	97.8
16	167	1.0	99.7

[a] $\geq$10 replicates were performed for each compound.

reduced in order to obtain comparable flow rates. Application of 167 and 0 V cm^{-1} resulted in the mobilisation of the reaction mixture through the packed bed, at a flow rate of 1.0 µl min^{-1}, resulting in 96.9% conversion to 2-benzylidene malononitrile **12**. This was subsequently repeated using 4-bromobenzaldehyde **6**, 3,5-dimethoxybenzaldehyde **7**, 4-benzyloxybenzaldehyde **8**, to afford 2-(4-bromobenzylidene)-malononitrile **14** (96.9%), 2-(3,5-dimethoxybenzylidene)-malononitrile **15** (96.3%) and 2-(4-benzyloxybenzylidene)-malononitrile **16** (97.3%) respectively (Table 2). Again, ^{1}H and ^{13}C NMR spectra were obtained for all compounds synthesised within the device demonstrating excellent product purity. In all cases, no by-product formation was observed by GC-MS or NMR spectroscopy. The technique was subsequently repeated using the reagents; 3-(dimethylamino)propyl-functionalised silica gel **17** (1.50 mmol N g^{-1}), 3-aminopropyl-functionalised silica gel **18** (1.00 mmol N g^{-1}) and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidino)-propyl-functionalised silica gel **19** (2.4 mmol N g^{-1}) (Fig. 10) whereby 99.4, 100 and 99.3% conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **2** were obtained.

Previous work by Macquarrie et al.,[23] demonstrated the use of a 3-aminopropyl-functionalised silica surface in a heated, pressure-driven, aluminium micro reactor. Operating the device at 98 °C enabled 70% conversion of a 1:1 ethylcyanoacetate **5** and benzaldehyde **4** to 2-cyano-3-phenyl acrylic acid ethyl ester **2**. Compared to the work described herein, this approach is disadvantageous as solvent-free techniques are only suitable for the preparation of low viscosity compounds. Also, the elevated reaction temperatures employed, compromises device simplicity. This investigation therefore focussed on the preparation of an array of condensation products at room temperature, within an EOF-based micro fabricated device (Table 3).

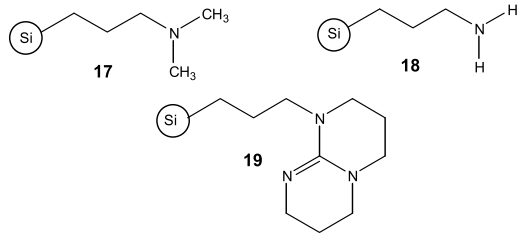

Figure 10. Schematic of 3-(dimethylamino)propyl-functionalised silica gel **17**, 3-aminopropyl-functionalised silica gel **18** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidino)propyl-functionalised silica gel **19**.

Table 3. Comparison of the conversions obtained for the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** using silica-supported bases **1**, **17**, **18** and **19**

Base	Applied field ($V\ cm^{-1}$)	Flow rate ($\mu l\ min^{-1}$)	Conversion[a] (%)
1	333	0.5	99.1
17	333	0.35	99.4
18	333	.35	100.0
19	333	0.80	99.3

[a] $\geq$10 replicates were performed for each compound.

Using four silica-supported bases, 3-(1-piperazino)propyl-functionalised silica gel **1**, 3-(dimethylamino)propyl-functionalised silica gel **17**, 3-aminopropyl-functionalised silica gel **18** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidino)propyl-functionalised silica gel **19**, enabled the synthesis of an array of condensation products in excellent conversions when the device was operated at flow rates of $<$1.0 µl min^{-1}. This technique is therefore suitable for the rapid synthesis of small quantities of compound for biological screening or the preparation of larger quantities by scaling-out.[24] The ability to prepare pure compounds in sufficient quantities to obtain structural information is also advantageous as it negates the need to prepare synthetic standards, whilst demonstrating the preparation of compounds of analytical purity. Compared to standard batch techniques employing solid supported reagents, the use of a continuous flow reactor is advantageous as reagents can be recycled without any loss upon filtration, resulting in more consistent conversions over extended periods of operation (Table 1 cf. Fig. 3). Localised concentration gradients enable reactions to be driven to completion without the need to employ large quantities of reagent, that is, 5 mg (4.75×10^{-4} mmol) in a micro reactor enables conversions in excess of 95% to be attained in minutes compared with $>$95 h in batch (Fig. 4, 0.0125 mmol).

3. Conclusions

In conclusion, we have demonstrated the successful incorporation of a series of silica-supported bases within an EOF-based micro-fabricated device, enabling the synthesis and characterisation of eight condensation products. Using the methodology described herein, further studies are currently underway within our laboratories to extend both the type of reagent and support employed, enabling more complex syntheses to be demonstrated.

4. Experimental

4.1. Materials and methods

All materials (analytical grade) were purchased from Aldrich and were used without purification. All NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Joel GX400 spectrometer and the chemical shifts are given in parts per million (ppm) with coupling constants given in Hertz (Hz). The following abbreviations are used to report NMR data; s=singlet, d=doublet, t=triplet, br s=broad singlet, m=

multiplet and C_0=quaternary carbon. Gas chromatography-mass spectrometry (GC-MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (2000) with a CP-Sil 8 (30 m) column (Phenomenex) and ultra high purity helium (99.999% Energas) carrier gas. Samples were analysed using one of the following methods; Method A: injector temperature 250 °C, helium flow rate 1.0 ml min^{-1}, oven temperature 60 °C for 1.0 min and then ramped to 270 °C at 35 °C min^{-1}, with a 3.0 min filament delay or; Method B: injector temperature 250 °C, helium flow rate 1.0 ml min^{-1}, oven temperature 60 °C for 1.0 min and then ramped to 270 °C at 20 °C min^{-1}, with a 3.0 min filament delay.

4.2. Batch reactions

4.2.1. General procedure for the solution-phase synthesis of Knoevenagel condensation products in batch. Piperazine **3** (0.09 g, 0.1 mmol) was added to a stirred solution of activated methylene (1.0 mmol) and aldehyde (1.0 mmol) in anhydrous MeCN (10 ml $mmol^{-1}$). After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of dilute HCl (50 ml, 0.1 M) and the reaction products extracted into DCM (3×50 ml). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, subsequent recrystallisation from DCM/hexane afforded the respective condensation product.

4.2.2. General procedure for the solid-phase synthesis of Knoevenagel condensation products in batch. 3-(1-Piperazino)propyl-functionalised silica gel **1** (1.9 mmol N g^{-1}, 200–400 mesh) (0.10 g, 0.1 mmol) was added to a stirred solution of activated methylene (1.0 mmol) and aldehyde (1.0 mmol) in anhydrous MeCN (10 ml $mmol^{-1}$). After stirring overnight, the reaction mixture was filtered and the filtrate concentrated in vacuo to afford the respective condensation product.

4.3. Micro-scale methodology

The reactions described herein were carried out using a single capillary device, as illustrated in Figure 5, with capillary dimensions of 500 μm i.d.×3.0 cm. To hold the supported reagent in place, micro porous silica frits were placed at either end of the capillary.[22] To mobilise reagents by EOF, platinum electrodes (0.5 mm o.d.×2.5 cm) were placed within the reagent reservoirs and voltages applied using a Paragon 3B high-voltage power supply (HVPS), capable of applying 0–1000 V to four pairs of outputs (Kingfield Electronics). Automation of the HVPS was achieved using an in-house LabVIEW™ program. To enable the results obtained to be attained using devices of different dimensions, voltages are reported as applied fields (V cm^{-1}), that is, voltage/capillary length. To monitor the progress of the reaction, experiments were conducted over a period of 20 min, after which, the product reservoir was analysed by GC-MS, whereby comparison of the amount of product with respect to residual aldehyde enabled the percentage conversion to be determined. In order to obtain NMR data on the compounds synthesised in the flow system, the reactors were operated continuously for 3–5 h, after which the reaction products were concentrated in vacuo and the crude compound analysed.

4.3.1. 2-Cyano-3-phenyl acrylic acid ester 2[25]. (0.0253 g, 98.9%) as a white solid; δ_H 1.41 (3H, t, J=7.0 Hz, CH_2CH_3), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 7.53 (3H, m, Ar), 7.99 (2H, m, Ar) and 8.26 (1H, s, CH); δ_C 14.2 (CH_3), 62.8 (CH_2), 103.1 (C_0CN), 115.5 (CN), 129.3 (2×CH), 131.0 (2×CH), 131.5 (C_0), 133.3 (CH), 155.1 (CH) and 162.5 (CO); *m/z* (EI) 202 (M^++1, 70%), 201 (100), 172 (80), 156 (90), 128 (75), 102 (55), 77 (50) and 51 (50); GC-MS retention time (Method A) R_T=6.63 min.

4.3.2. 3-(4-Bromophenyl)-2-cyano acrylic acid ethyl ester 9[26]. (0.0118 g, 99.5%) as a white solid; δ_H 1.40 (3H, t, J=7.3 Hz, CH_2CH_3), 4.39 (2H, q, J=7.3 Hz, CH_2CH_3), 7.65 (2H, d, J=8.7 Hz, Ar), 7.86 (2H, d, J=8.7 Hz, Ar) and 8.19 (1H, s, CH); δ_C 14.2 (CH_3), 62.9 (CH_2), 103.7 (C_0CN), 115.3 (CN), 128.3 (C_0Br), 130.3 (C_0), 132.3 (2×CH), 132.7 (2×CH), 153.6 (CH) and 162.3 (CO); 281 (M^++1, 90%), 280 (45), 279 (100), 251 (25), 200 (20), 154 (10), 127 (25), 100 (20) and 76 (20); GC-MS retention time (Method B) R_T=10.84 min.

4.3.3. 3-(3,5-Dimethoxyphenyl)-2-cyano acrylic acid ethyl ester 10[27]. (0.0109 g, 99.5%) as a white solid; δ_H 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 3.85 (6H, s, 2×OCH_3), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 6.65 (1H, m, Ar), 7.15 (2H, m, Ar) and 8.17 (1H, s, CH); δ_C 14.2 (CH_3), 55.7 (2×OCH_3), 62.8 (CH_2), 103.4 (C_0CN), 106.2 (CH), 108.6 (2×CH), 115.6 (CN), 133.1 (C_0), 155.2 (CH), 161.1 (2×C_0) and 162.5 (CO); 262 (M^++1, 20%), 261 (100), 189 (55), 161 (25) and 77 (10); GC-MS retention time (Method A) R_T=8.06 min.

4.3.4. 3-(4-Benzyloxyphenyl)-2-cyano acrylic acid ethyl ester 11. (0.0211 g, 99.1%) as a cream solid (Found C, 74.51; H, 5.77; N, 4.62. $C_{19}H_{17}O_3N$ requires C, 74.25; H, 5.58; N, 4.56%); δ_H 1.39 (3H, t, J=7.3 Hz, CH_2CH_3), 4.37 (2H, q, J=7.3 Hz, CH_2CH_3), 5.15, (2H, s, CH_2), 7.00 (2H, d, J=8.7 Hz, Ar), 7.40 (5H, m, Ar), 7.99 (2H, d, J=8.7 Hz, Ar) and 8.17 (1H, s, CH); δ_C 14.2 (CH_3), 62.5 (CH_2), 70.4 (C_0CH_2), 99.5 (C_0), 115.6 (2×CH), 124.6 (CN), 127.5 (2×CH), 128.4 (CH), 128.8 (2×CH), 133.7 (2×CH), 135.8 (C_0), 154.4, (CH), 162.9 (OC_0) and 163.1 (CO); 308 (M^++1, 5%), 307 (20), 91 (100) and 65 (20); GC-MS retention time (Method B) R_T=12.35 min.

4.3.5. 2-Benzylidene-malononitrile 12[25]. (0.0154 g, 100%) as a pale yellow solid; δ_H 7.55 (2H, m, Ar), 7.64 (1H, m, Ar), 7.79 (1H, s, CH) and 7.91 (2H, m, Ar); δ_C 83.0 (C_0), 112.6 (CN), 113.7 (CN), 129.7 (2×CH), 130.8 (2×CH), 131.0 (C_0), 134.7 (CH) and 159.9 (CH); 155 (M^++1, 20%), 154 (100), 127 (20) and 76 (10); GC-MS retention time (Method A) R_T=5.84 min.

4.3.6. 2-(4-Bromobenzylidene)-malononitrile 14[28]. (0.0349 g, 99.9%) as a pale yellow solid; δ_H 7.69 (2H, d, J=8.4 Hz, Ar), 7.72 (1H, s, CH) and 7.77 (2H, d, J=8.4 Hz, Ar); δ_C 83.6 (C_0), 112.3 (CN), 113.5 (CN), 129.7 (C_0Br), 130.0 (C_0), 131.8 (2×CH), 133.1 (2×CH) and 158.4 (CH); 235 (M^++1, 70%), 234 (100), 233 (95), 232 (90), 153 (25) and 77 (10); GC-MS retention time (Method B) R_T=9.65 min.

4.3.7. 2-(3,5-Dimethoxybenzylidene)-malononitrile 15[25].

(0.0240 g, 99.2%) as a yellow solid; δ_H 3.84 (6H, s, OCH_3), 6.70 (1H, m, Ar), 7.03 (2H, m, Ar) and 7.69 (1H, s, CH); δ_C 55.7 (2×OCH_3), 83.2 (C_0), 107.3 (CH), 108.3 (2×CH), 112.7 (CN), 113.7 (CN), 132.4 (C_0), 160.1 (CH) and 161.3 (2×C_0OCH_3); 215 ($M^+ + 1$, 25%), 214 (100), 186 (55), 171 (20), 155 (20), 142 (15), 114 (10) and 76 (10); GC-MS retention time (Method A) $R_T = 7.50$ min.

4.3.8. 2-(4-Benzyloxybenzylidene)-malononitrile 16[29]. (0.0235 g, 99.6%) as a pale yellow solid; δ_H 5.17 (2H, s, CH_2), 7.08 (2H, d, $J = 9.0$ Hz, Ar), 7.39 (5H, m, Ar), 7.64 (1H, s, CH) and 7.90 (2H, d, $J = 9.0$ Hz, CH); δ_C 70.6 (CH_2), 78.8 (C_0), 113.3 (CN), 114.4 (CN), 116.0 (2×CH), 124.2 (C_0), 127.5 (2×CH), 128.6 (CH), 128.9 (2×CH), 133.5 (2×CH), 135.5 (C_0), 158.8 (CH) and 163.9 (OC_0); 261 ($M^+ + 1$, 5%), 260 (5), 114 (10) and 91 (100); GC-MS retention time (Method B) $R_T = 11.97$ min.

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Efficient route to 20–32 membered macrocyclic crown diamides via ring closing metathesis

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Abstract—RCM of the appropriate bis-allyloxyacetanilides and bis-*o*-allyloxyphenoxyacetanilides led to an efficient synthetic approach to the corresponding macrocylic polyoxadiamides with 20- to 32-membered ring sizes in good to excellent yields using Grubbs' catalyst.

1. Introduction

There exists increasing interest in the synthesis of crown compounds and azacrown compounds due to their important diverse applications in supramolecular chemistry.[1,2] Of particular interest are crown compounds incorporating amide groups, since such groups modify the binding properties of the crown compounds with respect to alkali metal ions.[2,3] Recently, we reported efficient synthetic approaches towards polyaza-polyether-olefinic macrocyclic compounds of potential utility in supramolecular chemistry, using ring closing metathesis (RCM).[4] Moreover, some of our recently reported olefinic crown formazans prepared efficiently via RCM showed interesting applications in spectrophotometric determination of lithium ions.[5] Applications of RCM techniques has proved to be one of the most efficient synthetic approaches towards macrocyclic compounds.[6–16] However, application of such efficient macrocyclization technique for the synthesis of crown compounds are still limited.[4,10,17,18]

The present work describes the synthesis of macrocyclic polyethers containing amide groups inside the macrocyclic ring via RCM using Grubbs' catalyst **I** as the key macrocyclization step. The results obtained provide an efficient synthetic procedure towards macrocyclic crown diamides **1–5** with 20–26 membered rings and macrocylic polyoxadiamides **6–10** with 26–32 membered ring sizes (Fig. 1).

Keywords: Ring closing metathesis; 1,ω-Dienes; Bis-anilides; Diazapolyoxacycloalkenediones.
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2. Results and discussion

Scheme 1 illustrates our synthetic route to the precursor 1,ω-dienes **19–23** needed for the RCM synthesis of **1–5**. Thus, two routes were used to prepare compounds **19–23**. The first route involved acylation of *o*-aminophenol **11** with allyloxyacetyl chloride to afford the *o*-allyloxyacetamidophenol **12**. The latter was converted into its potassium salt **13** which was reacted with the appropriate dihalo or ditosylate derivatives **14–18** in DMF to give the corresponding 1,ω-dienes **19–23** in 40–50% yields. Alternatively, compounds **19–23** were obtained in 60–75% yields by reacting the appropriate bis-amines **24–28** with allyloxyacetyl chloride. RCM of the dienes **19–23** proceeded smoothly to give the corresponding macrocycles **1–5** in 62–93% yields with Grubbs' catalyst **I** (2–2.5 mol%) in refluxing CH_2Cl_2 for 3 h. The results are presented in Table 1.

On the other hand, the 1,ω-dienes **36–40** were readily obtained as outlined in Scheme 2. Thus, acylation of **24–28** with chloroacetyl chloride (**29**) afforded the corresponding bis-chloroacetamide derivatives **30–34**. Reacting the latter with the potassium salt of *o*-allyloxyphenol (**35**) afforded the desired 1,ω-dienes **36–40**. RCM of the dienes **36–40** proceeded smoothly to give the corresponding macrocycles **6–10** in 86–95% yields upon heating with Grubbs' catalyst **I** (1.5–2 mol%) in refluxing CH_2Cl_2 for 3 h. The results are presented in Table 2.

In all RCM reactions, the progress of the reaction was monitored by TLC and ^1H NMR spectroscopic analysis where no further increase in products was noticed after 3 h of reflux in CH_2Cl_2. The RCM products **1–10** were shown from their ^1H and ^{13}C NMR to consist of the *E* and *Z* isomers in different ratios as shown in Tables 1 and 2.

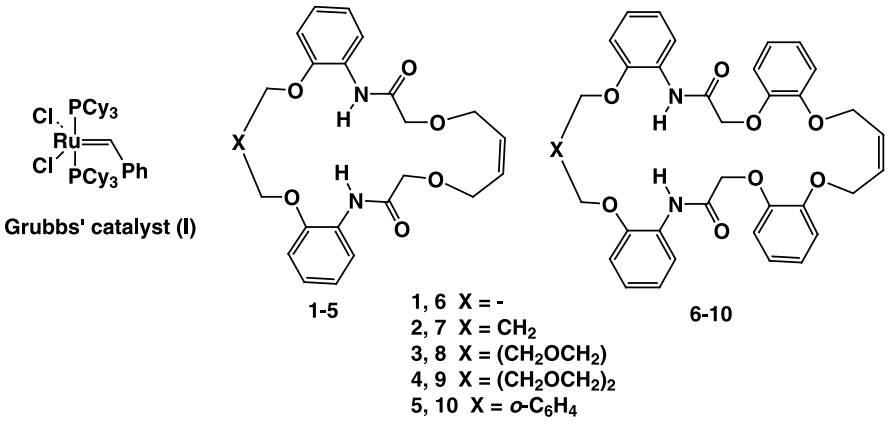
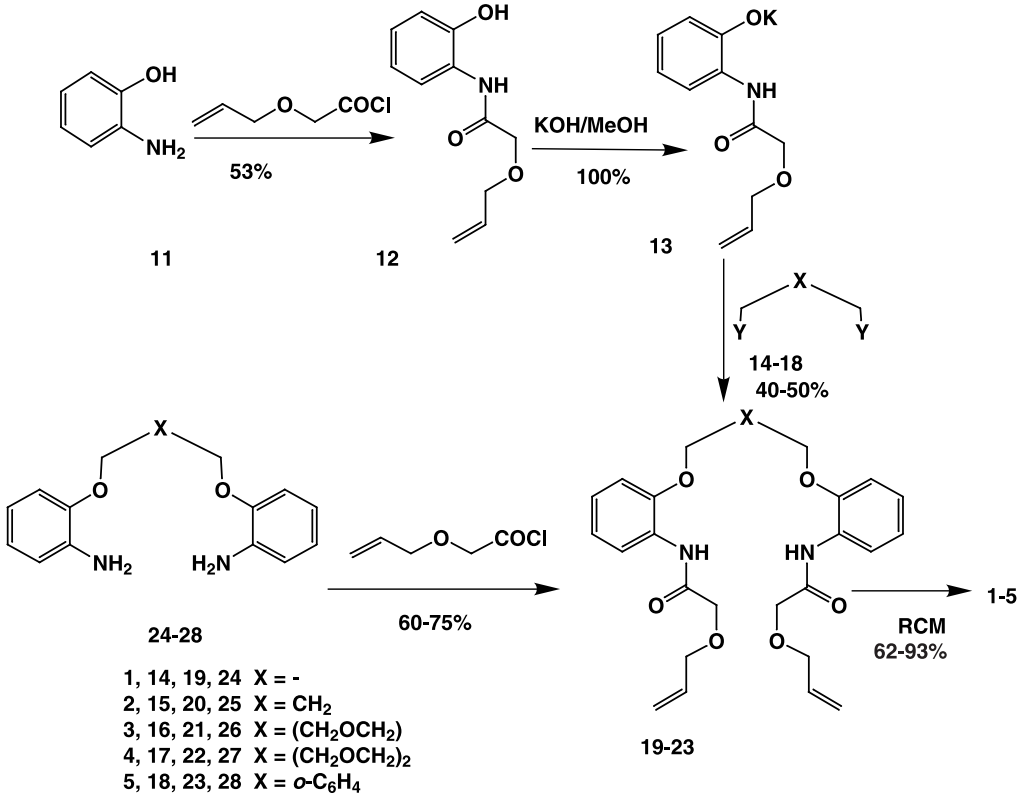


Figure 1.

The *E*:*Z* isomers of the olefinic crown diamides were readily assigned and their ratios were determined[4b] from the ^{1}H NMR and ^{13}C NMR spectra. The major products in most of the RCM reactions were shown to be the *E* isomers with the characteristic ^{13}C NMR signal of the OCH_2 (of the $OCH_2CH{=}CHCH_2O$), which appears more downfield than that for the corresponding *Z* isomer. On the contrary in the ^{1}H NMR spectra, the OCH_2 of *E* isomers appears as essentially a singlet and more upfield than that of the *Z* isomer which appears as a broad doublet ($J=3$–5 Hz). Also, in the ^{1}H NMR spectra, the CH═ of the *E* isomers appear as broad singlets and more downfield than those of the *Z* isomers which appear as triplets (Tables 1 and 2). An exception occurs in the ^{1}H NMR spectra of compound **7** where the CH═ of the *Z*-isomer appears more downfield than that of the *E*-isomer.

The present work describes an efficient synthetic access to macrocyclic crown-diamide derivatives, with potential diverse applications in supramolecular chemistry and as starting compounds for further synthetic transformations, utilizing the RCM techniques for the macrocyclization step. The examples of RCM presented here represent one of the most efficient macrocyclization reaction techniques for the synthesis of crown compounds. It also expands the utility of RCM methodology and its application to the synthesis of large-ring cyclic olefins with different functional groups.



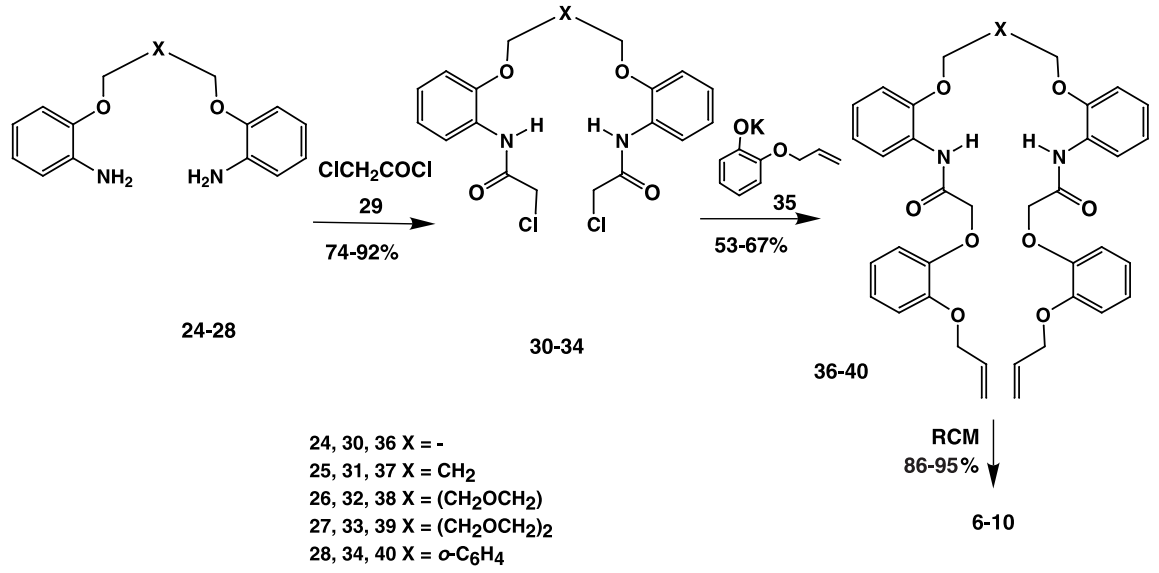
Scheme 1.

Table 1. Catalyst %, yields, *E*/*Z* ratios and characteristic ^{1}H NMR spectroscopy signals of macrocycles **1–5**

Entry	Substrate	Mol% catalyst/ substrate	Yield (%)	Product *E*:*Z* ratio	^{1}HNMR of *E*/*Z* products			*J* (Hz)
					NH	$OCH_2CH=$	$OCH_2CH=$	
1	**19**	2	62	**1**	9.11	4.18 (m)	6.04 (m)	
				1:1	9.03	4.29 (dd)	5.94 (tt)	1.1, 3.8
2	**20**	2.5	93	**2**	9.14	4.19 (m)	6.04 (m)	
				19:1	9.14	4.19 (d)	5.90 (t)	4.2
3	**21**	2	70	**3**	9.22	4.20 (s)	6.08 (s)	
				1:1	9.13	4.25 (d)	5.92 (t)	3.4
4	**22**	2	80	**4**	9.09	4.21 (s)	6.02 (s)	
				1:1	9.09	4.25 (d)	5.92 (t)	3.6
5	**23**	2.5	89	**5**	9.17	4.11 (s)	5.93 (br)	
				1.3:1	9.13	4.07 (d)	5.40 (t)	4

Table 2. Catalyst %, yields, *E*/*Z* ratios and characteristic ^{1}H NMR spectroscopy signals of macrocycles **6–10**

Entry	Substrate	Mol% catalyst/ substrate	Yield %	Product *E*:*Z* ratio	^{1}H NMR of *E*/*Z* products			*J* (Hz)
					NH	$OCH_2CH=$	$OCH_2CH=$	
1	**30**	1.5	91	**6**	9.53	4.39 (s)	6.06 (s)	
				4:1	9.23	4.70 (d)	5.87 (t)	3.5
2	**31**	2.0	92	**7**	9.63	3.85 (s)	5.64 (s)	
				3:1	9.24	4.75 (d)	5.90 (t)	3.2
3	**32**	1.5	86	**8**	9.24	4.47 (dd)	6.13 (m)	1.1, 2.0
				3:1	9.20	4.80 (d)	5.92 (t)	3.5
4	**33**	2.0	95	**9**	9.20	4.66 (s)	6.15 (s)	
				2:1	9.21	4.83 (d)	5.95 (t)	3.2
5	**34**	1.5	94	**10**	9.30	4.29 (d)	5.94 (t)	2.5
				2:1	9.27	4.55 (d)	5.69 (t)	3.2



Scheme 2

Scheme 2.

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded in KBr disks using Perkin Elmer System 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer. Mass spectra were measured on VG Auto-spec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on LECO CHNS-932 Elemental Analyzer. Allyloxyacetyl chloride[19] and the bis-diamines **24–28**[20] were prepared as reported in the literature.

3.1.1. *o*-Allyloxyacetamidophenol 12. To a cold (5 °C) solution of *o*-aminophenol (**11**) (1.3 g, 12 mmol) in sodium hydroxide solution (12 mmol in 4 mL water) was added allyloxyacetyl chloride[17] (1.35 g, 10 mmol) dropwise with stirring. The reaction mixture was kept stirring for 10 min and the resulting precipitate was filtered off. The filtrate was acidified with conc. HCl (1 mL) and the resulting colorless crystals were collected, washed several times with water and crystallized from EtOH/H_2O to give 1.1 g (53%) of **12**, colorless crystals, mp 121–123 °C. IR: 3371, 3304, 3089, 2961, 2917, 2870, 2741, 1663, 1615, 1593, 1549, 1457, 1377, 1283, 1249, 1204, 1148, 1107, 1097, 981, 917, 756. ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 2H, CH_2C═O), 4.19 (d, 2H, J=5.7 Hz, OCH_2CH═), 5.35 (d, 1H, J=10.4 Hz, CH_2=CH), 5.41 (d, 1H, J=17.8 Hz, CH_2=CH), 5.96 (m, 1H, =CH), 6.88 (dt, 1H, J=1.1, 7.5 Hz), 7.06 (m, 2H), 7.17 (t, 1H, J=7.5 Hz), 8.56, 8.99 (2s, 2H, NH, OH). LCMS; *m*/*z*: 208 (M+1). Anal. calcd for $C_{11}H_{13}NO_3$ (207.2): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.57; H, 6.43; N, 6.86.

3.2. Bis-*o*-allyloxyacetamidophenoxy derivatives 19–23. General procedures

A. Compound **12** (22 mmol) was added to a solution of KOH (0.13 g, 2.2 mmol) in methanol (10 mL). The mixture was then stirred at room temperature for 15 min and the solvent was then removed in vacuo. To the remaining potassium salt **13** was added DMF (5 mL) and the appropriate dihalo or ditosylate derivatives **14**–**18** (1 mmol). The reaction mixture was then heated under reflux for 5 min. The mixture was cooled, diluted with water (20 mL) and the precipitate was collected, washed with cold water and finally crystallized from petroleum ether (40–60).

B. To a solution of each of the appropriate bis-amine dihydrochlorides **24**–**28**[20] (1 mmol) in DCM (10 mL) at 0 °C was added dropwise TEA (3 mL) followed by a dropwise addition of a solution of allyloxyacetyl chloride[19] (0.28 g, 2.1 mmol) in DCM (10 mL) over a period of 30 min at 0 °C. The reaction mixture was then kept stirring at room temperature overnight. The mixture was then diluted with DCM (50 mL) and washed with hydrochloric acid (2 M, 100 mL), then twice with saturated sodium carbonate solution and finally with water. The organic layer was then dried over anhydrous sodium sulfate and evaporated to dryness. The remaining bis-anilides **19**–**23** were recrystallized from petroleum ether (40–60).

3.2.1. 1,2-Bis(*o*-allyloxyacetamidophenoxy)ethane 19. Yield 0.19 g (43%, A); 0.3 g (70%, B); colorless crystals, mp 89–90 °C. IR: 3384, 1690, 1649, 1534, 1452, 1249, 1206, 1116, 926, 748. ^{1}H NMR ($CDCl_3$): δ 3.87 (d, 4H, J=5.5 Hz, OCH_2CH═), 4.02 (s, 4H, OCH_2CH_2O), 4.45 (s, 4H, CH_2C═O), 4.95 (d, 2H J=10.4 Hz, CH_2═), 5.14 (dd, 2H, J=1.3, 17.2 Hz, CH_2═), 5.61 (m, 2H, CH═), 6.97 (d, 2H, J=7.6 Hz), 7.04 (t, 2H, J=7.6 Hz), 7.10 (dt, 2H, J=1.5, 7.6 Hz), 8.45 (dd, 2H, J=1.5, 7.6 Hz), 9.08 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 67.2, 69.7, 72.2, 111.1, 117.6, 120.0, 121.8, 124.0, 127.4, 132.5, 147.2, 167.6. LCMS; *m*/*z*: 441 (M+1). Anal. calcd for $C_{24}H_{28}N_2O_6$ (440.5): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.50; H, 6.32; N, 6.47.

3.2.2. 1,3-Bis(*o*-allyloxyacetamidophenoxy)propane 20. Yield 0.19 g (42%, A); colorless crystals, mp 93–95 °C. IR: 3385, 1690, 1601, 1534, 1454, 1250, 1207, 1114, 751. ^{1}H NMR ($CDCl_3$) δ 2.37 (quint, 2H, J=6.1 Hz, OCH_2CH_2), 4.09 (s, 4H, CH_2C═O), 4.09 (dd, 4H, J=1.4, 6.8 Hz, CH_2CH═), 4.27 (t, 4H, J=6.1 Hz, OCH_2CH$_2$), 5.23 (m, 2H, CH_2═), 5.35 (m, 2H, CH_2═), 5.89 (m, 2H, CH═), 6.92 (dd, 2H, J=1.3, 7.8 Hz), 7.01 (dt, 2H, J=1.3, 7.8 Hz), 7.07 (dt, 2H, J=1.7, 7.8 Hz), 8.43 (dd, 2H, J=1.7, 7.8 Hz), 9.04 (s, 2H, NH). LCMS; *m*/*z*: 455 (M+1). Anal. calcd for $C_{25}H_{30}N_2O_6$ (454.5): C, 66.06; H, 6.65; N, 6.16. Found: C, 66.21; H, 6.71; N, 6.22.

3.2.3. 1,5-Bis(*o*-allyloxyacetamidophenoxy)-3-oxapentane 21. Yield 0.23 g (47%, A), 0.3 g (61%, B); colorless crystals, mp 55–56 °C. IR: 3383, 3070, 2937, 1690, 1601, 1534, 1485, 1453, 1333, 1253, 1209, 1116, 1046, 927, 751. ^{1}H NMR ($CDCl_3$) δ 3.95 (t, 4H, J=4.7 Hz, $ArOCH_2CH_2O$), 4.24 (t, 4H, J=4.7 Hz, ArOCH_2CH_2O), 4.07 (s, 4H, CH_2C═O), 4.10 (dd, 4H, J=1.2, 5.0 Hz, CH_2CH═), 5.25, 5.36 (dd, 2H, J=1.0, 10.6 Hz, CH_2═), 5.36 (dd, 2H, J=1.6, 17.2 Hz, CH_2═), 5.94 (m, 2H, CH═), 6.92 (dd, 2H, J=1.5, 8.0 Hz), 7.04 (m, 4H), 8.42 (dd, 2H, J=1.5, 8.0 Hz), 9.04 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 68.3, 69.9, 72.4, 111.6, 117.9, 120.0, 121.6, 124.0, 127.3, 133.4, 147.3, 167.6. LCMS; *m*/*z*: 485 (M+1). Anal. calcd for $C_{26}H_{32}N_2O_7$ (484.6): C, 64.45; H, 6.66; N, 5.78. Found: C, 64.54; H, 6.65; N, 6.00.

3.2.4. 1,8-Bis(*o*-allyloxyacetamidophenoxy)-3,6-dioxaoctane 22. Yield, 0.23 g (43%, A), 0.4 g (75%, B), colorless crystals, mp 63–64 °C. IR: 3384, 3070, 2875, 1690, 1601, 1534, 1485, 1454, 1332, 1290, 1253, 1209, 1177, 1137, 1116, 1046, 928, 750. ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 4H, OCH_2CH_2O), 3.88 (t, 4H, J=4.8 Hz, $ArOCH_2CH_2O$), 4.08 (s, 4H, CH_2C═O), 4.12 (dd, 4H, J=1.3, 4.2 Hz, CH_2CH═), 4.19 (t, 4H, J=4.8 Hz, ArOCH_2CH_2O), 5.27 (dd, 2H, J=1.3, 10.4 Hz, CH_2═), 5.37 (m, 2H, CH_2═), 5.95 (m, 2H, CH═), 6.89 (dd, 2H, J=1.5, 8.0 Hz), 7.00 (m, 4H), 8.41 (dd, 2H, J=1.5, 8 Hz), 9.04 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 68.2, 69.7, 69.8, 71.0, 72.3, 111.4, 118.0, 119.9, 121.6, 123.7, 129.8, 133.4, 147.4, 167.6. Anal. calcd for $C_{28}H_{36}N_2O_8$ (528.6): C, 63.62; H, 6.86; N, 5.30. Found: C, 63.75; H, 6.77; N, 5.41.

3.2.5. 1,2-Bis(*o*-allyloxyacetamidophenoxymethyl)benzene 23. Yield, 0.25 g (48%, A), 0.35 g, (68%, B); colorless crystals, mp 72 °C. IR: 3387, 3069, 3028, 2935, 2892, 2852, 1689, 1600, 1534, 1484, 1454, 1331, 1290, 1250, 1205, 1114, 1046, 1006, 928, 750. ^{1}H NMR ($CDCl_3$) δ 3.97 (dd, 4H, J=0.8, 5.6 Hz, CH_2CH═), 4.01 (s, 4H, CH_2C═O), 5.06 (d, 2H, J=10.4 Hz, CH_2=CH), 5.16 (dd, 2H, J=1.1, 17.8 Hz, CH_2═CH), 5.23 (s, 4H, OC$H_2C_6H_4$), 5.68 (m, 2H, CH═), 6.9–7.06 (m, 6H), 7.43 (m, 2H), 7.57 (m, 2H), 8.44 (dd, 2H, J=1.0, 8.0 Hz), 9.03 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 68.2, 69.6, 72.2, 111.3, 117.9, 119.8, 121.7, 124.0, 127.1, 128.6, 128.8, 133.0, 134.4, 147.0, 167.4. LCMS; *m*/*z*: 517 (M+1). Anal. calcd for $C_{30}H_{32}N_2O_6$ (516.6): C, 69.75; H, 6.24; N, 5.42. Found: C, 69.62; H, 6.31; N, 5.55.

3.3. Bis-*o*-chloroacetamidophenoxy derivatives 30–34. General procedure

A mixture of the appropriate bis-amine dihydrochloride **24**–**28** (10 mmol) and sodium carbonate (3.7 g, 35 mmol) in

water (15 mL) was stirred for 10 min, then DCM (20 mL) was added and cooled to 5 °C. To this cold mixture was added dropwise with stirring a solution of chloroacetyl chloride (2.83 g, 25 mmol) in DCM (20 mL). The reaction mixture was stirred for 1 h and the organic layer was separated, evaporated in vacuo and the remaining precipitate was recrystallized from ethanol to give colorless crystals of compounds **30–34**.

3.3.1. 1,2-Bis(*o*-chloroacetamidophenoxy)ethane (30). Yield 2.94 g (74%); colorless crystals, mp 197–199 °C. IR: 3384, 3295, 3136, 3070, 2957, 1675, 1600, 1537, 1454, 1337, 1257, 1118, 1047, 751. ^{1}H NMR ($CDCl_3$) δ 4.13 (s, 4H, OCH_2CH_2O), 4.50 (s, 4H, $CH_2C{=}O$), 6.99 (dd, 2H, $J=1.2$, 8 Hz), 7.06 (dt, 2H, $J=1.5$, 8 Hz), 7.14 (dt, 2H, $J=1.5$, 8 Hz), 8.37 (dd, 2H, $J=1.5$, 8 Hz), 9.02 (s, 2H, NH). LCMS; *m/z*: 397 (M+1), 399 (M+3), 401 (M+5). Anal. calcd for $C_{18}H_{18}Cl_2N_2O_4$ (397.3): C, 54.42; H, 4.57; N, 7.05. Found: C, 54.44; H, 4.50; N, 7.17.

3.3.2. 1,2-Bis(*o*-chloroacetamidophenoxy)propane (31). Yield 3.36 g (82%); colorless crystals, mp 185–186 °C. IR: 3287, 3146, 3073, 3004, 2953, 2883, 1680, 1602, 1551, 1496, 1456, 1343, 1288, 1262, 1227, 1118, 998, 753, 680. ^{1}H NMR ($CDCl_3$) δ 2.43 (quint, 2H, $J=6$ Hz, $OCH_2CH_2CH_2O$), 4.21 (s, 4H, $CH_2C{=}O$), 4.34 (t, 4H, $J=6$ Hz, OCH_2CH_2), 6.96 (d, 2H, $J=7.8$ Hz), 7.02 (t, 2H, $J=7.8$ Hz), 7.12 (dt, 2H, $J=1$, 7.8 Hz), 8.35 (dd, 2H, $J=1$, 7.8 Hz), 9.04 (s, 2H, NH). LCMS; *m/z*: 411 (M+1), 413 (M+3), 415 (M+5). Anal. calcd for $C_{19}H_{20}Cl_2N_2O_4$ (411.3): C, 55.49; H, 4.90; N, 6.81. Found: C, 55.77; H, 5.07; N, 6.89.

3.3.3. 1,5-Bis(*o*-chloroacetamidophenoxy)-3-oxapentane (32). Yield 4.05 g (92%); colorless crystals, mp 115–117 °C. IR: 3375, 3062, 3003, 2928, 2876, 1677, 1604, 1536, 1488, 1459, 1408, 1338, 1256, 1117, 1051, 758. ^{1}H NMR ($CDCl_3$) δ 3.99 (t, 4H, $J=4.6$ Hz, $ArOCH_2CH_2O$), 4.26 (t, 4H, $J=4.6$ Hz, $ArOCH_2CH_2O$), 4.17 (s, 4H, $CH_2C{=}O$), 6.94 (d, 2H, $J=7.8$ Hz), 7.02 (t, 2H, $J=7.8$ Hz), 7.10 (dt, 2H, $J=1.2$, 7.8 Hz), 8.35 (dd, 2H, $J=1.2$, 7.8 Hz), 9.07 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ 44.0, 69.2, 69.8, 113.6, 121.5, 122.1, 125.8, 127.6, 149.4, 165.2. LCMS; *m/z*: 441 (M+1), 443 (M+3), 445 (M+5). Anal. calcd for $C_{20}H_{22}Cl_2N_2O_5$ (441.3): C, 54.43, H, 5.02, N, 6.35. Found: 54.37, H, 5.05, N, 6.37.

3.3.4. 1,8-Bis(*o*-chloroacetamidophenoxy)-3,6-dioxaoctane (33). Yield 4.0 g (83%); colorless crystals, mp 99–100 °C. IR: 3382, 3136, 3068, 3010, 2950, 2874, 1683, 1605, 1538, 1488, 1453, 1409, 1337, 1292, 1257, 1209, 1117, 1047, 929, 751. ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 4H, OCH_2CH_2O), 3.90 (t, 4H, $J=4.6$ Hz, $ArOCH_2CH_2O$), 4.19 (s, 4H, $CH_2C{=}O$), 4.22 (t, 4H, $J=4.6$ Hz, $ArOCH_2CH_2O$), 6.91 (d, 2H, $J=7.8$ Hz), 7.00 (t, 2H, $J=7.8$ Hz), 7.09 (dt, 2H, $J=1.1$, 7.8 Hz), 8.34 (dd, 2H, $J=1.1$, 7.8 Hz), 9.08 (s, 2H, NH). LCMS; *m/z*: 485 (M+1), 487 (M+3), 487 (M+5). Anal. calcd for $C_{22}H_{26}Cl_2N_2O_6$ (485.4): C, 54.44; H, 5.40; N, 5.77. Found: C, 54.45; H, 5.53; N, 5.98.

3.3.5. 1,2-Bis[*o*-(chloroacetamido)phenoxymethyl]benzene (34). Yield 3.65 g (77%); colorless crystals, mp 155–157 °C. IR: 3392, 3062, 3005, 2957, 2909, 2861, 1680, 1601, 1486, 1457, 1296, 1257, 1119, 1026, 749. ^{1}H NMR ($CDCl_3$) δ 4.12 (s, 4H, $CH_2C{=}O$), 5.28 (s, 4H, $CH_2C_6H_4$), 7.00 (d, 2H, $J=7.8$ Hz), 7.05 (t, 2H, $J=7.8$ Hz), 7.11 (dt, 2H, $J=1.3$, 7.8 Hz), 7.46 (m, 2H), 7.59 (m, 2H), 8.36 (dd, 2H, $J=1.3$, 8 Hz), 8.96 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ 43.9, 68.1, 113.4, 121.2, 123.1, 125.9, 127.2, 128.6, 128.7, 135.2, 149.5, 165.3. LCMS; *m/z*: 473 (M+1), 475 (M+3), 477 (M+5). Anal. calcd for $C_{24}H_{22}Cl_2N_2O_4$ (473.4): C, 60.90; H, 4.68; N, 5.92. Found: C, 61.11; H, 4.85; N, 5.88.

3.4. Compounds 36–40. General procedures

o-Allyloxyphenol (0.33 g, 2.2 mmol) was added to a solution of KOH (0.13 g, 2.2 mmol) in methanol (5 mL). The mixture was then stirred at room temperature for 15 min and the solvent was then removed in vacuo. To the remaining potassium salt **35** was added DMF (2 mL) and the appropriate dichloro derivatives **30–34** (1 mmol). The reaction mixture was then heated under reflux for 5 min. The mixture was cooled, diluted with water (20 mL) and the precipitate was collected, washed with cold water and finally crystallized from petroleum ether (40–60) to give colorless needles of compounds **36**, **37**. Compound **38–40** were purified by silica gel column chromatography [6:3:4 DCM/EtOAc/petroleum ether (40–60)].

3.4.1. 1,2-Bis[*o*-(*o*-allyloxyphenoxyacetamido)phenoxy] ethane (36). Yield 0.42 g (67%); colorless crystals, mp 126–127 °C. IR: 3387, 3069, 2927, 1690, 1600, 1536, 1501, 1454, 1254, 1205, 1120, 1051, 929, 747. ^{1}H NMR ($CDCl_3$) δ 4.31 (s, 4H, OCH_2CH_2O), 4.43 (d, 4H, $J=5.1$ Hz, $CH_2CH{=}$), 4.56 (s, 4H, $CH_2C{=}O$), 5.20 (d, 2H, $J=10.5$ Hz, $CH_2{=}$), 5.34 (d, 2H, $J=17.1$ Hz, $CH_2{=}$), 5.97 (m, 2H, =CH), 6.80 (m, 4H), 6.87 (m, 4H), 6.98 (m, 6H), 8.34 (m, 2H), 9.13 (s, 2H, NH). LCMS; *m/z*: 625 (M+1). Anal. calcd for $C_{36}H_{36}N_2O_8$ (624.7): C, 69.22; H, 5.81; N, 4.48. Found: C, 69.01; H, 5.90; N, 4.65.

3.4.2. 1,3-Bis[*o*-(*o*-allyloxyphenoxyacetamido)phenoxy]-propane (37). Yield 0.38 g (60%); colorless crystals, mp 120 °C. IR: 3391, 3069, 2933, 1690, 1599, 1535, 1499, 1453, 1253, 1204, 1118, 1052, 927, 747. ^{1}H NMR ($CDCl_3$) δ 2.16 (quint, 2H, $J=6.0$ Hz, OCH_2CH_2), 4.08 (t, 4H, $J=6$ Hz, OCH_2CH_2), 4.53 (d, 4H, $J=5.2$ Hz, $OCH_2CH{=}$), 4.64 (s, 4H, $CH_2C{=}O$), 5.22 (d, 2H, $J=10.6$ Hz, $CH_2{=}$), 5.36 (d, 2H, $J=17.2$ Hz, $CH_2{=}$), 5.99 (m, 2H, =CH), 6.73 (m, 2H), 6.96 (m, 12H), 8.36 (dd, 2H, $J=2.1$, 7.3 Hz), 9.13 (s, 2H, NH). LCMS; *m/z*: 639 (M+1). Anal. calcd for $C_{37}H_{38}N_2O_8$ (638.7): C, 69.58; H, 6.00; N, 4.39. Found: C, 69.48; H, 6.03; N, 4.28.

3.4.3. 1,5-Bis[*o*-(*o*-allyloxyphenoxyacetamido)phenoxy]-3-oxapentane (38). Yield 0.36 g (54%); pale yellow oil. IR: 3387, 3068, 2930, 2868, 1690, 1600, 1535, 1499, 1455, 1255, 1205, 1120, 1051, 928, 793, 749. ^{1}H NMR ($CDCl_3$) δ 3.76 (br, 4H, $ArOCH_2CH_2O$), 4.02 (br, 4H, $ArOCH_2CH_2O$), 4.56 (d, 4H, $J=4.8$ Hz, $OCH_2CH{=}$), 4.62 (s, 4H, $CH_2C{=}O$), 5.22 (d, 2H, $J=10.5$ Hz, $CH_2{=}$), 5.37 (d, 2H, $J=17.3$ Hz, $CH_2{=}$), 6.01 (m, 2H, =CH), 6.78 (d, 2H, $J=7.5$ Hz), 6.90 (m, 4H), 7.01 (m, 8H), 8.40 (d, 2H, $J=7.6$ Hz), 9.21 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 68.5, 69.7, 69.8, 70.5, 111.7, 114.2, 117.4, 117.9, 120.3, 121.4, 121.6, 123.7, 124.2, 127.2, 133.0, 147.4, 147.6, 149.3, 166.8. LC/MS; *m/z*: 669 (M+1). Anal. calcd for $C_{38}H_{40}N_2O_9$ (668.8):

C, 68.25; H, 6.03; N, 4.19. Found: C, 67.98; H, 5.97; N, 4.38.

3.4.4. 1,8-Bis[*o*-(*o*-allyloxyphenoxyacetamido)phenoxy]-3,6-dioxaoctane (39). Yield 0.38 g (53%); pale yellow oil, R_f=0.67. IR: 3387, 3069, 2925, 2876, 1688, 1600, 1534, 1501, 1455, 1256, 1209, 1120, 1050, 998, 929, 750. ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 4H, OCH_2CH_2O), 3.72 (t, 4H, J=4.8 Hz, $ArOCH_2CH_2O$), 4.13 (t, 4H, J=4.8 Hz, $ArOCH_2CH_2O$), 4.59 (d, 4H, J=5.2 Hz, OCH_2CH=), 4.65 (s, 4H, CH_2C=O), 5.24 (d, 2H, J=10.4 Hz, CH_2=), 5.39 (d, 2H, J=17.3 Hz, CH_2=), 6.04 (m, 2H, =CH), 6.91 (m, 6H), 6.99–7.09 (m, 8H), 8.41 (d, 2H, J=7.8 Hz), 9.23 (s, 2H, NH). LCMS; m/z: 713 (M+1). Anal. calcd for $C_{40}H_{44}N_2O_{10}$ (712.8): C, 67.40, H, 6.22, N, 3.93. Found: C, 67.40, H, 6.11, N, 4.05.

3.4.5. 1,2-Bis[*o*-(*o*-allyloxyphenoxyacetamido)phenoxymethyl]benzene (40). Yield 0.5 g (71%), colorless semi-solid. IR: 3391, 3068, 2922, 2856, 1690, 1600, 1535, 1501, 1455, 1255, 1206, 1119, 1049, 997, 928, 749. ^{1}H NMR ($CDCl_3$) δ 4.36 (d, 4H, J=5.3 Hz, OCH_2CH=), 4.59 (s, 4H, CH_2C=O), 5.10 (d, 2H, J=10.4 Hz, CH_2=), 5.18 (s, 4H, $OCH_2C_6H_4$), 5.25 (d, 2H, J=17.4 Hz, CH_2=), 5.87 (m, 2H, =CH), 6.84 (m, 6H), 6.89 (m, 2H), 6.99 (m, 6H), 7.16 (m, 2H), 7.43 (m, 2H), 8.42 (m, 2H), 9.23 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 68.4, 69.4, 70.2, 111.8, 113.8, 116.9, 117.7, 120.4, 121.2, 121.6, 123.5, 124.3, 127.2, 128.4, 128.6, 132.9, 134.3, 147.1, 147.3, 149.1, 166.8. LC/MS; m/z: 701 (M+1). Anal. calcd for $C_{42}H_{40}N_2O_8$ (700.8): C, 71.99, H, 5.75, N, 4.00. Found: C, 71.99, H, 5.69, N, 4.19.

3.5. Ring closing metathesis of 19–23, 36–40. General procedure

A solution of each of the substrates **19–23**, **36–40** (0.2 mmol) in DCM (25 mL) and Grubbs' catalyst (2.5–4 mg, ca. 1.5–2.5 mol% of the substrate) was heated under reflux for 3 h. The reaction mixture was then mixed with silica gel (100–200 mm, 0.5 g), stirred for 30 min, filtered and the silica was extracted twice with DCM (50 mL). After removing the solvent from the DCM extract, the remaining products were analyzed by ^{1}H NMR (Tables 1 and 2). Compounds **1**, **3**, **4**, **8** were purified by preparative thin layer chromatography [6:3:4 DCM/EtOAc/petroleum ether (40–60)]. All macrocycles **1–10** were characterized by their R_f values on TLC using the same solvent mixture where both *E* and *Z* isomers gave the same spot. The *E* and *Z* isomers of compound **10** were separated by fractional crystallization by leaving a CH_2Cl_2 solution of the mixture in a closed atmosphere containing petroleum ether (40–60). Other isomers were identified by their ^{1}H and ^{13}C NMR in their mixture.

3.5.1. Compound 1. (*E* and *Z*): Yield 51 mg (62%); colorless crystals, mp 169–171 °C, (R_f=0.32). IR: 3387, 3066, 2960–2904, 2852, 1691, 1601, 1536, 1483, 1456, 1332, 1256, 1201, 1120, 746. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 4.14 (s, 4H, OCH_2CH_2), 4.18 (m, 4H, CH_2CH=), 4.54 (s, 4H, CH_2C=O), 6.04 (m, 2H, =CH), 6.88 (dd, 2H, J=1.5, 7.8 Hz), 7.06 (m, 4H), 8.45 (dd, 2H, J=1.5, 7.8 Hz), 9.11 (s, 2H, NH). ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 4.12 (s, 4H, OCH_2CH_2), 4.29 (dd, 4H, J=1.1, 3.8 Hz, CH_2CH=), 4.50 (s, 4H, CH_2C=O), 5.94 (tt, 2H, J=1.1, 3.8 Hz, =CH), 6.86 (dd, 2H, J=1.5, 8 Hz), 7.06 (m, 4H), 8.42 (dd, 2H, J=1.5, 8 Hz), 9.03 (s, 2H, NH). LCMS: m/z=413 (M+1). Anal. calcd for $C_{22}H_{24}N_2O_6$ (412.5): C, 64.07; H, 5.87; N, 6.79. Found: C, 64.06; H, 5.92; N, 6.97.

3.5.2. Compound 2. (*E* and *Z*): 79 mg (93%); colorless crystals, mp 191–193 °C, (R_f=0.32). IR: 3374, 2963, 2889, 2870, 1681, 1603, 1542, 1490, 1456, 1408, 1336, 1291, 1252, 1212, 1115, 1040, 1016, 966, 817, 751. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 2.35 (quintet, 2H, J=7 Hz, OCH_2CH_2), 4.16 (s, 4H, CH_2C=O), 4.19 (m, 4H, CH_2CH=), 4.24 (t, 4H, J=7 Hz, OCH_2CH_2), 6.04 (m, 2H, =CH), 6.90 (d, 2H, J=7.8 Hz), 7.04 (m, 4H), 8.45 (d, 2H, J=7.8 Hz), 9.14 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 28.9, 65.1, 71.0, 71.6, 111.2, 119.7, 121.6, 124.0, 127.4, 127.9, 146.6, 167.15. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 2.35 (quintet, 2H, J=7 Hz, OCH_2CH_2), 4.16 (s, 4H, CH_2C=O), 4.19 (d, 4H, J=4.2 Hz, CH_2CH=), 4.24 (t, 4H, J=7 Hz, OCH_2CH_2), 5.90 (t, 2H, J=4.2 Hz, =CH), 6.90 (d, 2H, J=8 Hz), 7.04 (m, 4H), 8.39 (d, 2H, J=8 Hz), 9.14 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 29.6, 65.5, 67.1, 70.8, 111.5, 119.7, 121.6, 124.04, 127.3, 128.4, 147.2, 167.2. MS: m/z=426 (M^+, 70%). Anal. calcd for $C_{23}H_{26}N_2O_6$ (426.5): C, 64.78; H, 6.15; N, 6.57. Found: C, 64.50; H, 6.22; N, 6.61.

3.5.3. Compound 3. (*E* and *Z*): 64 mg (70%); colorless crystals, mp 141–142 °C, (R_f=0.35). IR: 3378, 3061, 2933, 2855, 1686, 1601, 1535, 1485, 1453, 1252, 1116, 752. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 3.94 (t, 4H, J=4.2 Hz, $ArOCH_2CH_2O$), 4.16, 4.20 (2s, 4H, 4H, CH_2C=O, CH_2CH=), 4.23 (t, 4H, J=4.2 Hz, $ArOCH_2CH_2O$), 6.08 (s, 2H, =CH), 6.91 (m, 2H), 7.04 (m, 4H), 8.43 (m, 2H), 9.22 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 68.9, 69.6, 70.8, 71.5, 112.1, 119.8, 121.8, 124.0, 128.1, 128.7, 147.2, 167.4. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 3.99 (t, 4H, J=4.8 Hz, $ArOCH_2CH_2O$), 4.07 (s, 4H, CH_2C=O), 4.23 (t, 4H, J=4.8 Hz, $ArOCH_2CH_2O$), 4.25 (d, 4H, J=3.4 Hz, CH_2CH=), 5.92 (t, 2H, J=3.4 Hz, =CH), 6.91 (m, 2H), 7.04 (m, 4H), 8.43 (m, 2H), 9.13 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 67.4, 68.6, 70.2, 70.8, 111.7, 119.8, 121.7, 124.0, 127.4, 127.8, 147.1, 167.1. LC/MS: m/z=457 (M+1). Anal. calcd for $C_{24}H_{28}N_2O_7$ (456.5): C, 63.15; H, 6.18; N, 6.14. Found: C 63.38, H 6.30, N 6.29.

3.5.4. Compound 4. (*E* and *Z*): 80 mg (80%); colorless crystals, mp 137–138 °C, (R_f=0.30). IR: 3379, 3023, 2929, 1690, 1600, 1535, 1454, 1252, 1116, 798. 752 cm^{-1}. ^{1}HNMR ($CDCl_3$) (*E* isomer): δ 3.79 (s, 4H, OCH_2CH_2O), 3.92 (t, 4H, J=4.1 Hz, $ArOCH_2CH_2O$), 4.14 (s, 4H, CH_2C=O), 4.20 (t, 4H, J=4.1 Hz, $ArOCH_2CH_2O$), 4.21 (s, 4H, CH_2CH=), 6.02 (s, 2H, =CH), 6.89 (m, 2H), 6.99 (m, 2H), 7.07 (m, 2H), 8.43 (m, 2H), 9.09 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 68.5, 69.7, 70.4, 70.9, 71.3, 111.3, 119.8, 121.5, 124.1, 128.4, 128.9, 147.3, 167.4. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 3.80 (s, 4H, OCH_2CH_2O), 3.91 (t, 4H, J=4.1 Hz, $ArOCH_2CH_2O$), 4.12 (s, 4H, (s, 4H, CH_2C=O), 4.21 (t, 4H, J=4.1 Hz, $ArOCH_2CH_2O$), 4.25 (d, 4H, J=3.6 Hz, CH_2CH=), 5.92 (t, 2H, J=3.6 Hz, =CH), 6.99 (m, 2H), 7.07 (m, 2H), 8.43 (m, 2H), 9.09 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 67.4, 68.6, 70.0, 70.5, 70.9, 110.9, 119.6, 121.4, 124.1, 128.1, 128.7, 147.3,

167.2. LCMS: $m/z=501$ (M+1). Anal. calcd for $C_{22}H_{32}N_2O_8$ (500.5): C, 62.39; H, 6.44; N, 5.60. Found: C, 62.56; H, 6.59; N, 5.78.

3.5.5. Compound 5. (*E* and *Z*): 87 mg (89%); colorless crystals, mp 202–204 °C, ($R_f=0.53$). IR: 3382, 3014, 2919, 2845, 1687, 1601, 1534, 1453, 1249, 1204, 1115, 1014, 752. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 4.11 (s, 8H, $CH_2C{=}O$, $CH_2CH{=}$), 5.36 (s, 4H, $OCH_2C_6H_4$), 5.93 (br, 2H, =CH), 6.80 (m, 2H), 7.03 (m, 4H), 7.39 (m, 2H), 7.47 (m, 2H), 8.40 (m, 2H), 9.17 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 68.5, 69.7, 70.6, 111.1, 119.9, 121.6, 124.0, 127.1, 128.0, 128.2, 128.6, 134.3, 146.7, 167.1. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 4.03 (s, 4H, $CH_2C{=}O$), 4.07 (d, 4H, $J=4$ Hz, $CH_2CH{=}$), 5.22 (s, 4H, $OCH_2C_6H_4$), 5.40 (t, 2H, $J=4$ Hz, =CH), 6.95 (m, 2H), 7.04 (m, 4H), 7.48 (m, 2H), 7.56 (m, 2H), 8.45 (m, 2H), 9.13 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 67.6, 68.1, 70.5, 111.4, 119.6, 121.8, 124.0, 127.3, 128.04, 128.7, 129.1, 134.1, 146.9, 167.3. LCMS: $m/z=488$ (M^+). Anal. calcd for $C_{28}H_{28}N_2O_6$ (488.6): C, 68.84; H, 5.78; N, 5.73. Found: C, 68.60; H, 5.81; N, 5.67.

3.5.6. Compound 6. (*E* and *Z*): 109 mg (91%); colorless crystals, mp 214 °C, ($R_f=0.38$). IR: 3380, 3070, 3005, 2926, 1691, 1599, 1537, 1500, 1452, 1254, 1206, 1120, 1043, 749. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 4.33 (s, 4H, OCH_2CH_2O), 4.39 (s, 4H, $OCH_2CH{=}$), 4.63 (s, 4H, $CH_2C{=}O$), 6.06 (s, 2H, =CH), 6.81–7.06 (m, 14H), 8.42 (dd, 2H, $J=1.0$ Hz, 7.7), 9.53 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer) δ 66.5, 68.6, 69.7, 112.0, 113.6, 115.9, 120.1, 121.3, 122.8, 123.2, 124.2, 127.9, 147.1, 147.2, 147.5, 149.1, 166.4. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 4.30 (s, 4H, OCH_2CH_2O), 4.57 (s, 4H, $CH_2C{=}O$), 4.70 (d, 4H, $J=$ 3.5 Hz, $OCH_2CH{=}$), 5.87 (t, 2H, $J=3.5$ Hz, =CH), 6.85–7.06 (m, 14H), 8.38 (dd, 2H, $J=2.2$ Hz, 7.5), 9.23 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 65.3, 66.5, 69.2, 113.6, 114.9, 115.6, 120.3, 121.4, 121.7, 122.7, 123.1, 124.1, 147.2, 147.3, 147.7, 148.5, 166.5. LCMS: $m/z=597$ (M+1, 100%). Anal. calcd for $C_{34}H_{32}N_2O_8$ (596.6): C, 68.45; H, 5.41; N, 4.70. Found: C, 68.71; H, 5.90; N, 4.90.

3.5.7. Compound 7. (*E* and *Z*): 112 mg (92%); colorless crystals, mp 220 °C, ($R_f=0.30$). IR: 3385, 3067, 2923, 1689, 1600, 1537, 1500, 1455, 1290, 1256, 1210, 1117, 1045, 1001, 911, 745. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 2.23 (quint, 2H, $J=5.4$ Hz, OCH_2CH_2), 3.85 (s, 4H, $OCH_2CH{=}$), 4.20 (t, 4H, $J=5.4$ Hz, OCH_2CH_2), 4.57 (s, 4H, $CH_2C{=}O$), 5.64 (s, 2H, =CH), 6.53 (d, 2H, $J=8$ Hz), 6.66 (d, 2H, $J=8$ Hz), 6.86–7.14 (m, 10H), 8.37 (d, 2H, $J=$ 7.8 Hz), 9.63 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer) δ 29.3, 63.3, 68.0, 73.1, 110.8, 113.5, 119.95, 120.2, 120.8, 121.3, 124.4, 124.6, 126.65, 128.0, 147.7, 148.4, 149.8, 167.0. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 2.27 (quint, 2H, $J=$ 6.5 Hz, OCH_2CH_2), 4.12 (t, 4H, $J=6.5$ Hz, OCH_2CH_2), 4.65 (s, 4H, $CH_2C{=}O$), 4.75 (d, 4H, $J=3.2$ Hz, $CH_2CH{=}$), 5.90 (t, 2H, $J=3.2$ Hz, =CH), 6.74 (m, 2H), 7.01 (m, 10H), 7.12 (m, 2H), 8.37 (m, 2H), 9.24 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer) δ 29.0, 65.5, 65.7, 69.0, 110.8, 114.1, 114.9, 120.0, 121.1, 121.8, 123.1, 124.3, 126.7, 128.2, 147.2, 147.4, 148.3, 166.3. LCMS; *m/z*: 611 (M+1). Anal. calcd for $C_{35}H_{34}N_2O_8$ (610.7): C, 68.84; H, 5.61; N, 4.59. Found: C, 68.98; H, 5.51; N, 4.70.

3.5.8. Compound 8. (*E* and *Z*): 110 mg (86%); colorless crystals, mp 138–140 °C ($R_f=0.36$). IR 3387, 3070, 2930, 2854, 1688, 1600, 1535, 1501, 1454, 1255, 1207, 1120, 1049, 748. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 3.90 (t, 4H, $J=$ 4.7 Hz, $ArOCH_2CH_2O$), 4.02 (t, 4H, $J=4.7$ Hz, $ArOCH_2CH_2O$), 4.47 (dd, 4H, $J=1.1$, 2.0 Hz, $OCH_2CH{=}$), 4.63 (s, 4H, $CH_2C{=}O$), 6.13 (m, 2H, =CH), 6.78 (m, 2H), 6.87 (m, 2H), 7.01 (m, 10H), 8.41 (m, 2H), 9.24 (s, 2H, NH). ^{13}C NMR (DEPT) ($CDCl_3$) (*E* isomer): δ 68.5 (CH_2), 68.8 (CH_2), 69.8 ($2CH_2$), 111.7 (CH), 113.9 (CH), 115.7 (CH), 120.5 (CH), 121.4 (CH), 121.5 (CH), 123.2 (CH), 124.3 (CH), 127.1 (C), 128.1 (CH), 147.4 (C), 147.6 (C), 148.7 (C), 166.4 (C). ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 3.80 (t, 4H, $J=4.7$ Hz, $ArOCH_2CH_2O$), 3.98 (t, 4H, $J=4.7$ Hz, $ArOCH_2CH_2O$), 4.65 (s, 4H, $CH_2C{=}O$), 4.80 (d, 4H, $J=$ 3.5 Hz, $OCH_2CH{=}$), 5.92 (t, 2H, $J=3.5$ Hz, =CH), 6.78 (m, 2H), 6.87 (m, 2H), 7.01 (m, 10H), 8.44 (m, 2H), 9.20 (s, 2H, NH). ^{13}C NMR (DEPT) ($CDCl_3$) (*Z* isomer): δ 65.2 (CH_2), 68.8 (CH_2), 69.8 (CH_2), 69.9 (CH_2), 111.6 (CH), 113.9 (CH), 115.7 (CH), 120.1 (CH), 121.4 (CH), 121.6 (CH), 123.27 (CH), 124.2 (CH), 127.1 (C), 128.2 (CH), 147.3 (C), 147.6 (C), 148.4 (C), 166.4 (C). LCMS: *m/z*: 641 (M+1). Anal. calcd for $C_{36}H_{36}N_2O_9$ (640.7): C, 67.49; H, 5.66; N, 4.73. Found: C, 67.59; H, 5.84; N, 4.75.

3.5.9. Compound 9. (*E* and *Z*): 130 mg (95%); colorless crystals, mp 202–204 °C, ($R_f=0.31$). IR: 3385, 3065, 2928, 2865, 1690, 1601, 1537, 1500, 1454, 1254, 1206, 1119, 1049, 747. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 3.57 (s, 4H, OCH_2CH_2O), 3.74 (t, 4H, $J=4.8$ Hz, $ArOCH_2CH_2O$), 4.14 (t, 4H, $J=4.8$ Hz, $ArOCH_2CH_2O$), 4.66 (s, 8H, $CH_2C{=}O$, $CH_2CH{=}$), 6.15 (s, 2H, =CH), 6.86–7.07 (m, 14H), 8.42 (d, 2H, $J=7.7$ Hz), 9.20 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 68.6, 68.7, 69.4, 69.8, 70.9, 112.0, 114.2, 115.7, 120.4, 121.5, 121.6, 123.2, 124.3, 127.3, 128.3, 147.5, 147.7, 148.7, 166.6. ^{1}H NMR ($CDCl_3$) (*Z* somer): δ 3.50 (s, 4H, OCH_2CH_2O), 3.73 (t, 4H, $J=4.8$ Hz, $ArOCH_2CH_2O$), 4.12 (t, 4H, $J=4.8$ Hz, $ArOCH_2CH_2O$), 4.64 (s, 4H, $CH_2C{=}O$), 4.83 (d, 4H, $J=3.2$ Hz, $CH_2CH{=}$), 5.95 (t, 2H, $J=3.2$ Hz, =CH), 6.86–7.07 (m, 14H), 8.42 (d, 2H, $J=7.7$ Hz), 9.21 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 65.2, 68.6, 69.5, 69.8, 70.9, 111.7, 114.0, 115.9, 120.4, 121.5, 121.6, 123.3, 124.3, 127.2, 128.5, 147.4, 147.6, 147.7, 166.6. LCMS: $m/z=685$ (M+1). Anal. calcd for $C_{38}H_{40}N_2O_{10}$ (684.8): C, 66.66; H, 5.89; N, 4.09. Found: C, 66.59; H, 5.73; N, 4.20.

3.5.10. Compound 10. (*E* and *Z*): 127 mg (94%); colorless crystals, mp 110 °C, ($R_f=0.38$). IR 3380, 3065, 2923, 2855, 1690, 1600, 1540, 1501, 1455, 1384, 1255, 1208, 1118, 1048, 921, 744. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 4.29 (d, 4H, $J=2.5$ Hz, $OCH_2CH{=}$), 4.58 (s, 4H, $CH_2C{=}O$), 5.25 (s, 4H, $OCH_2C_6H_4$), 5.94 (t, 2H, $J=2.5$ Hz, =CH), 6.81–7.09 (m, 16H), 7.37 (m, 2H), 8.41 (m, 2H), 9.30 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 68.2, 68.4, 70.0, 112.3, 113.2, 116.0, 120.3, 121.2, 121.6, 123.3, 124.3, 127.4, 128.3, 128.4, 129.2, 134.5, 147.1, 147.2, 148.7, 166.8. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 4.55 (d, 4H, $J=3.2$ Hz, $OCH_2CH{=}$), 4.62 (s, 4H, $CH_2C{=}O$), 5.26 (s, 4H, $OCH_2C_6H_4$), 5.69 (t, 2H, $J=3.2$ Hz, =CH), 6.85–6.95 (m, 10H), 7.3 (m, 4H), 7.11 (m, 2H), 7.43 (m, 2H), 8.45 (m, 2H), 9.27 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 65.0, 68.4, 69.2, 112.0, 113.2, 114.9, 120.3, 121.3, 121.8, 122.9, 124.3, 127.3,

127.8, 127.9, 128.2, 134.0, 146.9, 147.2, 148.2, 166.4. LCMS: $m/z=673$ (M+1). Anal. calcd for $C_{40}H_{36}N_2O_8$ (672.7): C, 71.42; H, 5.39; N, 4.16. Found: C, 71.30; H, 5.32; N, 3.92.

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Synthesis of mono *meso*-pyridyl 21,23-dithiaporphyrins and unsymmetrical non-covalent porphyrin dimers

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Abstract—A new method has been developed to synthesize 21,23-dithiaporphyrins having one pyridyl group at the *meso* position. The method required easily available unknown precursors and the condensation resulted in mono *meso*-pyridyl 21,23-dithiaporphyrins as single products in 8–11% yield. Two of the three mono *meso*-pyridyl N_2S_2 porphyrins were used to synthesize non-covalent unsymmetrical porphyrin dimers containing one N_2S_2 and one N_4 porphyrin cores.

1. Introduction

Porphyrins and metalloporphyrins provide an advantageous class of building blocks for the construction of large multi-component architectures because of their relatively facile synthesis, stability and diversity of properties. Several synthetic strategies are employed for the assembly of multiporphyrin systems. A wide variety of porphyrin arrays of ever-increasing size have been constructed by the traditional methodology of covalently linking porphyrins.[1] More recently, the incorporation of porphyrins into porphyrin assemblies via non-covalent interactions has proven to be an attractive method for array formation.[2] By controlling the choice of materials, the supramolecular structure of the array can be engineered. To a large extent, the majority of the self-assembling porphyrin arrays are based on metal–ligand interactions and *meso*-pyridyl porphyrins play a key role in this kind of array. There are several reports available on non-covalent porphyrin assemblies connected via pyridyl groups which are mostly concerned with normal porphyrin (N_4 core) systems.[3] The core-modified porphyrins with cores such as N_3S, N_3O, N_2S_2, N_2O_2, N_2SO exhibit unique chemistry and different properties from N_4 porphyrin systems.[4] Core-modified porphyrins with functional groups such as iodophenyl, ethynyl phenyl, pyridyl etc at *meso* positions are suitable building blocks to synthesize unsymmetrical porphyrin arrays.[5] We recently prepared heteroporphyrins building blocks having two iodophenyl and ethynyl phenyl groups at *meso* positions in a *cis* fashion and used them to construct covalently linked energy donor appended systems.[6] We also prepared *cis*-pyridyl porphyrin building blocks with N_3S and N_3O porphyrin cores and synthesized non-covalent unsymmetrical trimers containing one N_3S and two N_4 porphyrin cores.[7] The porphyrins with one functional group are more desirable and available synthetic reports in the literature are useful only to synthesize mono-functionalized N_3S and N_3O porphyrins.[8] To the best of our knowledge, there are no reports available on mono-functionalized 21,23-dithiaporphyrins (N_2S_2 core). In this paper, we report the synthesis of three N_2S_2 porphyrins with one pyridyl group at the *meso* position (Chart 1) and its use to further construct two novel unsymmetrical non-covalent dimers having two different porphyrin cores. These are the first examples of non-covalent porphyrin dimers with N_2S_2 and N_4 porphyrin cores.

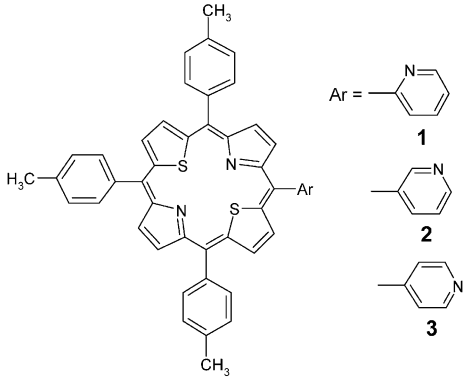

Chart 1. Mono *meso*-pyridyl 21,23-dithiaporphyrins.

Keywords: *meso*-Pyridyl porphyrins; Core-modified porphyrins; Non-covalent; Unsymmetrical array.
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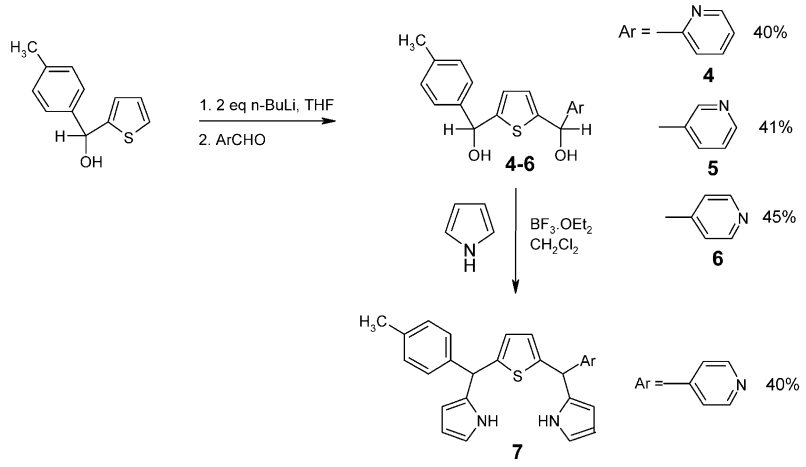


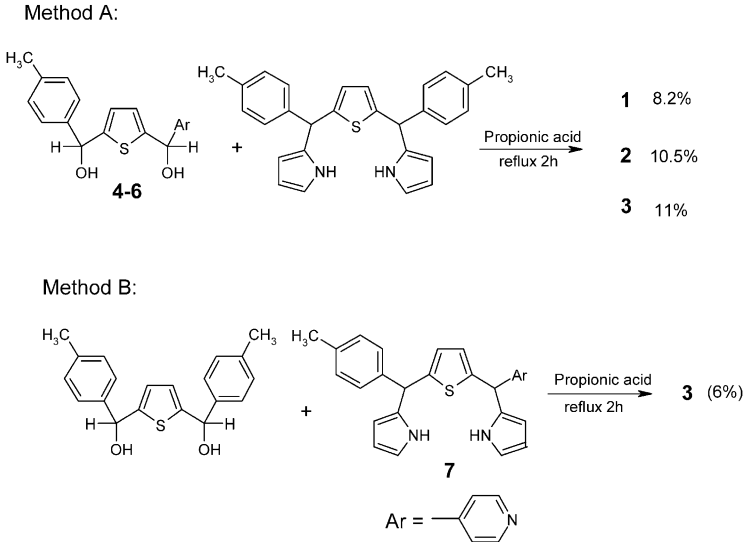
Scheme 1. General synthetic scheme of unsymmetrical diols **4–6** and unsymmetrical tripyrrin **7**.

2. Results and discussion

2.1. Unsymmetrical thiophene diols 4–6 and unsymmetrical tripyrrin 7

To synthesize mono *meso*-pyridyl 21,23-dithiaporphyrins, the unknown key precursors such as unsymmetrical thiophene diols and unsymmetrical 16-thiatripyrrins were required. The unsymmetrical thiophene diols **4–6** were synthesized in two steps starting with thiophene (Scheme 1). The desired thiophene mono-ol, 2-(*p*-tolylhydroxymethyl) thiophene[8b] was prepared by treating thiophene with 1 equiv. of *n*-BuLi followed by addition of 1.2 equiv. of *p*-tolualdehyde in THF at 0 °C. The TLC analysis of the crude mixture indicated the formation of desired mono-ol along with symmetrical diol and unreacted aldehyde. The mono-ol was separated from the mixture by column chromatography and afforded mono-ol in 65% yield. The thiophene mono-ol was then treated with 2 equiv. of *n*-BuLi followed by addition of pyridine 2- or 3- or 4-carboxaldehyde in THF at 0 °C. After work-up, the crude mixture containing the desired unsymmetrical diol along with some unreacted mono-ol and aldehyde was subjected to silica gel column chromatography. Since the unsymmetrical diols have two chiral centres, the TLC analysis showed the presence of an additional minor spot close to the major diol spot, which might be due to its diastereomer. However, we collected the major spot and used it for porphyrin reactions. Because the chirality is lost on porphyrin formation, no attempts were made to characterize the minor spot. The diols **4** and **5** were obtained in 40% yields and diol **6** was afforded as semi-solid in 45% yield. The unsymmetric nature of diols was clearly evident in their ^{1}H NMR spectra. The thiophene and CH protons which appear as singlets in the symmetrical diol[9] appeared as multiplets in diols **4–6** due to unsymmetrical substitution.

The unsymmetrical 16-thiatripyrrin **7** was prepared by treating 1 equiv. of unsymmetrical diol **6** with 40 equiv. of pyrrole in CH_2Cl_2 in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ (Scheme 1). The excess pyrrole was removed under vacuum and the TLC analysis showed only one major spot along with polymeric material at the bottom of the TLC plate. The crude compound was subjected to silica gel column chromatography and afforded **7** in 40% yield. The unsymmetric nature of **7** was clearly established by the



Scheme 2. Two general synthetic schemes for the preparation of mono *meso*-pyridyl 21,23-dithiaporphyrins **1–3**.

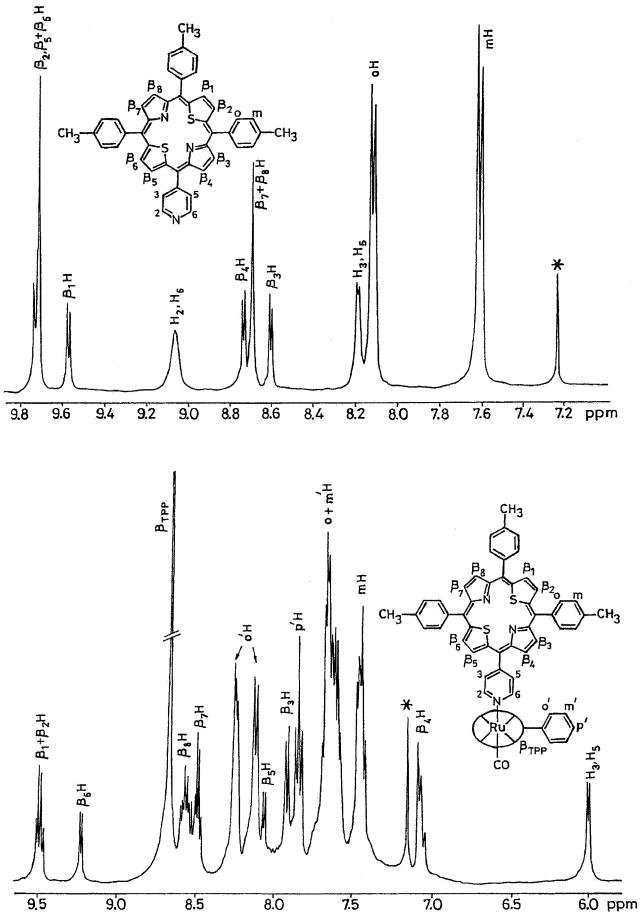


Figure 1. ^{1}H NMR spectra of **3** (top) and dimer **9** (bottom) recorded in $CDCl_3$.

splitting of thiophene and CH signals in the ^{1}H NMR spectra which appears as a singlet in symmetrical 16-thiatripyrrin.[10] The M^+ ion peak in the mass spectrum also confirmed the product.

2.2. Mono *meso*-pyridyl 21,23-dithiaporphyrins 1–3

To synthesize 21,23-dithiaporphyrins **1–3** with one 2- or 3- or 4-pyridyl functional group at the *meso* position (Chart 1), we followed any one of the two methods (Method A and B) shown in Scheme 2. Porphyrins **1–3** were synthesized by condensing 1 equiv. of unsymmetric thiophene diols **4–6**, respectively with 1 equiv. of the symmetrical 16-thiatripyrrin (5,10-ditolyl-16-thia-15,17-dihydrotripyrrin)[10] in propionic acid at refluxing temperature for 2 h (Method A). The propionic acid was removed under vacuum and washed thoroughly with slight warm water and dried in an oven at 100 °C. The crude black compounds of **1–3** were passed through silica gel column eluting with CH_2Cl_2/2%CH_3OH to remove the non-porphyrinic materials. The TLC analysis after the first column indicated the formation of the desired compound as the sole product. The crude compounds were subjected to second silica gel column chromatography using CH_2Cl_2 and the pure porphyrins were afforded as purple solids in 8–11% yields. Alternately porphyrin **3** was also prepared using unsymmetrical 16-thiatripyrrin **7**. One equivalent of unsymmetrical 16-thiatripyrrin **7** was condensed with 1 equiv. of symmetrical thiophene diol (2,5-(*p*-tolylhydroxymethyl) thiophene)[9] in propionic acid at refluxing temperature for 2 h (Method B). The crude compound obtained after usual work-up was purified by column chromatography and afforded **3** in 6% yield. Thus by following the method B, the porphyrin **3** was afforded in much lower yield than method A. Hence the synthesis of porphyrins **1** and **2** were not attempted using method B. However, both the methods are clean and the desired compounds were obtained as the single product. No scrambling was observed in these reactions.

The porphyrins **1–3** were characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, elemental analysis, infrared and absorption spectroscopies. The ^{1}H NMR spectrum of porphyrin **3** is presented in Figure 1(top) and the data of selected protons are presented in Table 1. In the ^{1}H NMR spectra, the thiophene and pyrrole protons of **1–3** appeared as two or three signals unlike S_2TPP[4] in which they appear as singlets. This is due to the unsymmetric substitution of porphyrins **1–3**. The presence of strong *m*/*z* peak at 692 confirmed the product. The absorption spectra of **1–3** showed four Q-bands (Fig. 2) and one Soret band and the extinction coefficients were almost comparable to that of S_2TPP (Table 2).

2.3. Non-covalent unsymmetrical dimers 8 and 9

Porphyrins with pyridyl groups at *meso* positions are ideal building blocks to synthesize non-covalent porphyrin arrays.[2,3] Since the heteroporphyrins with pyridyl groups at *meso*-positions are very few,[7,11] the chemistry remained unexplored. In general, *meso*-pyridyl N_4 porphyrins form non-covalent porphyrin arrays by co-ordinating with different metalloporphyrins (M=Zn, Mg, Ru, Rh etc.). However, our earlier study[7] with *cis*-pyridyl heteroporphyrins with N_3S cores showed that the N_3S porphyrins prefers to form non-covalent trimers with RuTPP(CO)(EtOH) but not with ZnTPP. Furthermore, *cis*-pyridyl N_3O porphyrins did not form non-covalent arrays with any metalloporphyrin. Thus, the chemistry of *meso*-pyridyl heteroporphyrins are core dependent and quite different from N_4 porphyrins.

The mono *meso*-pyridyl N_2S_2 porphyrins **1–3** were explored to construct non-covalent unsymmetrical dimers containing one N_2S_2 and one N_4 porphyrin cores. To synthesize unsymmetrical dimer **8**, we treated 1 equiv. of **2** with

Table 1. ^{1}H NMR Spectroscopy chemical shifts (δ in ppm) of selected protons in $CDCl_3$

Porphyrin	β-Pyrrole	β-Thiophene	2,6-Pyridyl	3,5/3,4-Pyridyl
2	8.61(d), 8.69(s), 8.75(d)	9.58(d), 9.71(s), 9.73(d)	9.06(bs), 9.50(bs)	7.80(m), 8.55(d)
8	6.84(d), 8.16(d), 8.64(d)	8.30(d), 9.38(d), 9.58(d), 9.62(d)	1.90(d), 2.22(s)	6.98(t), 7.38(d)
3	8.60(d), 8.69(s), 8.73(d)	9.57(d), 9.73(m)	9.07(bs)	8.19(m)
9	7.08(d), 7.92(d), 8.50(d), 8.58 (d)	8.06(d), 9.21(d), 9.47(d), 9.50(d)	1.92(d)	6.00(d)

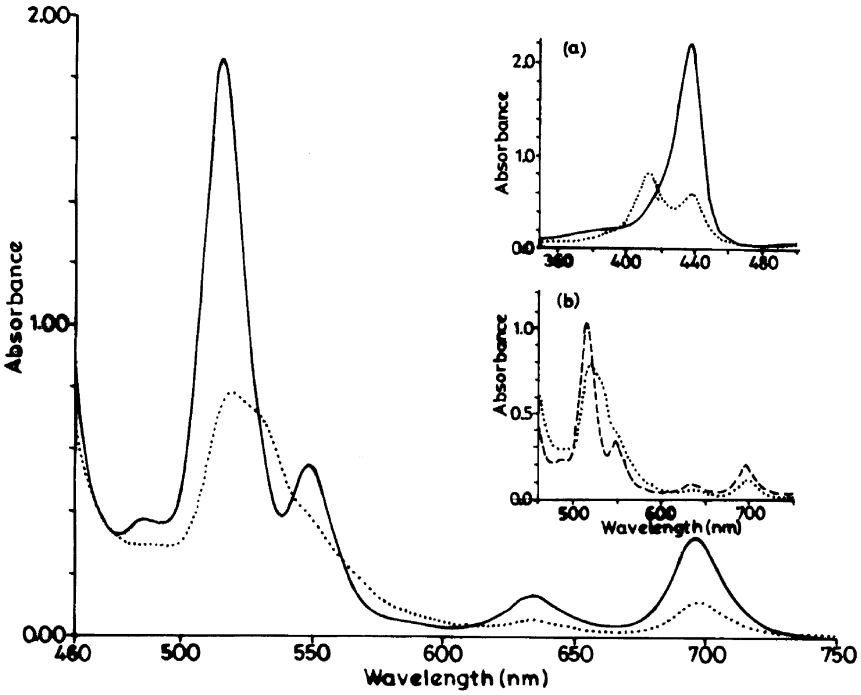
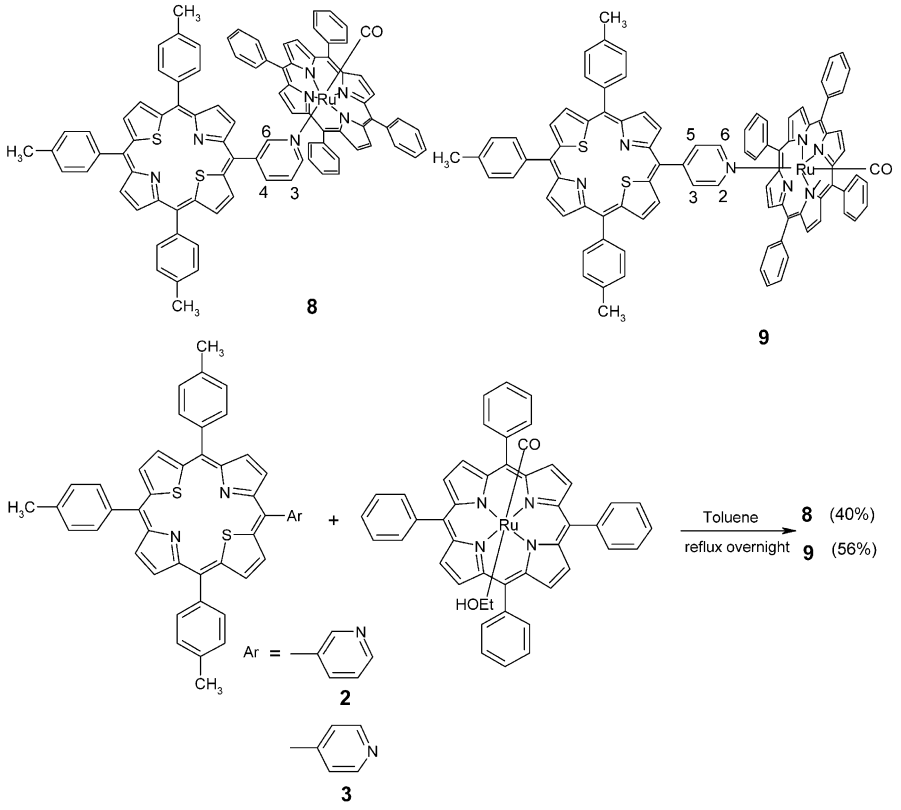


Figure 2. Q-bands and Soret band (inset a) absorption spectra of **3** (solid line) and **9** (dotted line). The inset b shows the absorption spectra of dimer **9** (dotted line) and 1:1 mixture of **3** and RuTPP(CO)(EtOH) (dashed line). All were recorded in toluene and the concentrations used were: Soret band, 5×10^{-6} M; and Q-bands, 5×10^{-5} M.

1 equiv. of RuTPP(CO)(EtOH) in toluene at refluxing temperature for 12 h (Scheme 3). As the reaction progressed, the colour of the reaction mixture changed from bright red to brownish red. The reaction progress was monitored with TLC and the reaction was stopped after complete disappearance of **2** as judged by TLC. The solvent was removed under vacuum and the crude compound was subjected to silica gel column chromatography using petroleum ether/dichloromethane (80:20). The fast moving unreacted RuTPP(CO)(EtOH) was removed and the desired dimer **8** was then collected with petroleum ether/dichloromethane (60:40) as a purple solid in 40% yield. Similarly, treating the porphyrin **3** with RuTPP(CO)(EtOH) under same conditions gave the dimer **9** in 56% yield (Scheme 3). Interestingly, porphyrin **1** did not form any dimer which may be due to steric hindrance. Furthermore, porphyrins **1**–**3** when treated with ZnTPP under different reaction conditions also did not form a dimer. The dimers **8** and **9** were highly soluble in most organic solvents and characterized by NMR spectroscopy, mass spectrometry, elemental analysis, infrared and Uv–visible spectroscopy. The ^{1}H NMR spectrum of dimer **9** comparing with monomer **3** shown in Figure 1 clearly demonstrated the formation of dimer. The signals of dimers **8** and **9** were composed of the parts of RuTPP and N_2S_2 porphyrin **2** and **3** respectively. The pyrrole and phenyl protons of the RuTPP part of dimers **8** or **9** appeared at almost the same chemical shifts of starting monomer RuTPP(CO)(EtOH). It is well-known that the porphyrin ring current changes the chemical shifts of the protons located near the porphyrin plane. The protons of mono pyridyl N_2S_2 porphyrin were shifted upfield from its parent porphyrin because of the RuTPP ring current. The pyrrole and thiophene protons of N_2S_2 porphyrin unit of dimers **8** and **9** were shifted upfield compared to their corresponding monomers **2** and **3**, respectively (Fig. 1 and Table 1). However, the maximum upfield shifts were observed for the 2,6- and 3,4-/3,5-pyridyl protons of the N_2S_2 porphyrin unit implying the coordination of pyridyl

Table 2. Absorption data of mono *meso*-pyridyl 21,123-dithiaporphyrins recorded in toluene

Porphyrin	Soret band λ (nm) ($\varepsilon\times10^{-4}$)	Absorption Q-bands λ (nm) ($\varepsilon\times10^{-3}$)			
		IV	III	II	I
1	437 (28.5)	515 (28.4)	549 (8.2)	634 (2.2)	697 (4.8)
2	437 (13.1)	515 (13.4)	549 (5.0)	634 (1.4)	697 (2.5)
3	437 (37.5)	515 (32.2)	549 (9.6)	634 (2.4)	697 (5.6)
8	438 (136.5)	520 (19.3)	552 (9.9)	635 (1.7)	698 (3.1)
	412 (204.3)	531 (sh)	567 (sh)		
1:1 Mixture of **2** and RuTPP(CO)(EtOH)	437 (128.6)	516 (15.5)	548 (7.7)	633 (2.4)	697 (3.3)
	413 (67.1)				
9	437 (204.2)	519 (28.1)	550 (sh)	634 (2.1)	697 (4.1)
	412 (292.9)	531 (sh)	567 (sh)		
1:1 Mixture of **3** and RuTPP(CO)(EtOH)	437 (217.1)	515 (26.8)	548 (8.8)	633 (2.5)	697 (5.1)
	411 (66.3)				



Scheme 3. Synthetic scheme for the preparation of non-covalent unsymmetrical dimer **8** and **9**.

group with central ruthenium ions. The large upfield shifts of 2,6-pyridyl protons compared with 3,4-/3,5-pyridyl protons indicate that these protons experienced large ring current effect of RuTPP because of their proximity to the RuTPP core. The elemental analysis and mass data were in agreement with dimer formation. IR measurements showed the $\nu_{(CO)}$ stretch at 1943 cm^{-1}. The absorption spectra of dimers **8** and **9** were compared with 1:1 mixture of RuTPP(CO)(EtOH) and **2** and **3**, respectively. The absorption spectra indicated that the dimers exhibited bands corresponding to both the units whereas, 1:1 mixture showed bands corresponds mainly to the mono-pyridyl N_2S_2 porphyrin unit. Furthermore, in the dimer **8** or **9**, the extinction coefficient of the Soret band of RuTPP unit was three times to that of the RuTPP unit of a 1:1 mixture, supporting the co-ordination of the pyridyl group of N_2S_2 porphyrin to the central ruthenium ion of the Ru(TPP)(CO) (Table 2).

3. Conclusions

In summary, we synthesized mono *meso*-pyridyl 21,23-dithiaporphyrins using readily available precursors. The porphyrins were obtained as single products in good yields by following any one of the two methods mentioned in this paper. The mono-*meso*-pyridyl porphyris were used to construct the non-covalent unsymmetrical porphyrin dimers containing N_4 and N_2S_2 porphyrin units. We are presently exploring the synthesis of other mono-functionalized 21,23-dithiaporphyrin building blocks for the synthesis of unsymmetrical covalent dimers using the methodology reported in this paper.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded using a Varian 400 MHz instrument using tetramethylsilane as an internal standard. Absorption and fluorescence spectra were obtained with Perkin–Elmer Lambda-35 and Lambda-55 instruments, respectively. The IR spectra were recorded with a Nicolet Impact-400 FT-IR spectrometer and the ES MS mass spectra were recorded with a Q-Tof micro (YA-105) mass spectrometer. Toluene, THF and diethylether were obtained from S.D. Fine chemicals, India, and were dried by standard procedures before use. All general chemicals were obtained from Qualigens, India. *p*-Tolualdehyde, thiophene, pyrrole, pyridine carboxaldehydes were obtained from Lancaster. Column chromatography was performed using 60–120 mesh silica obtained from Sisco Research Laboratories, India.

4.1.1. 2-(2-Pyridylhydroxymethyl)-5-(*p*-tolylhydroxymethyl) thiophene (4). A distilled diethylether (30 mL) was taken in a dry 250 mL three necked round-bottomed flask equipped with a rubber septum, gas inlet and gas outlet tube and a positive pressure of N_2 was maintained. A monool (2-(*p*-tolylyhydroxymethyl) thiophene) (1 g, 4.90 mmol) followed by *n*-BuLi (6.1 mL of ca. 15% solution in hexane) were added to it at 0 °C and stirring was continued for 1 h.

Then the ice-cold solution of 2-pyridine carboxaldehyde (0.93 mL, 9.79 mmol) in dry THF (20 mL) was added to the stirred solution. The reaction mixture was stirred at 0 °C for 15 min and then brought to room temperature. The reaction was quenched by adding an ice-cold NH_4Cl solution (50 mL, ca. 1 M). The organic layer was washed with water and brine solution and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator under reduced pressure to afford the crude compound. TLC analysis showed three major spots corresponding to the unreacted 2-pyridine carboxaldehyde, unreacted mono-ol and the desired diol **4**. In addition to the major spot of diol, we have also noted one minor spot just above the major diol spot, which was not characterized. The aldehyde, the mono-ol and the minor unidentified fractions were removed by silica gel column chromatography (1–3% CH_3OH/CH_2Cl_2) and the major diol fraction **4** was collected (609 mg, 40%) with 4% CH_3OH/CH_2Cl_2 as a white solid, mp 121–122 °C; [Found: C, 69.19; H, 5.20; N, 4.32; S, 10.11. $C_{18}H_{17}NO_2S$ requires C, 69.43; H, 5.50; N, 4.50; S, 10.30%]; R_f (4% CH_3OH/CH_2Cl_2) 0.51; ν_{max} (KBr) 3457, 3357, 3059, 2871, 1488, 1437, 1054, 806, 760, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.52–8.55 (1H, bs, pyridyl), 7.66 (1H, t, $J=7.5$ Hz, pyridyl), 7.28 (2H, d, $J=8.1$ Hz, *o*-tolyl), 7.20–7.22 (2H, m, pyridyl), 7.13 (2H, d, $J=8.1$ Hz, *m*-tolyl), 6.83 (1H, d, $J=4.4$ Hz, thiophene), 6.70 (1H, d, $J=4.4$ Hz, thiophene), 5.91 (2H, s, C*H*OH), 2.32 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 148.2, 147.6, 140.2, 137.8, 137.6, 129.3, 126.4, 126.3, 125.0, 124.5, 123.1, 121.6, 72.5, 70.9, 21.3; ES MS 312 (8 MH^+), 295 (12), 294 (100), 175 (10), 119 (18%).

4.1.2. 2-(3-Pyridylhydroxymethyl)-5-(*p*-tolylhydroxymethyl) thiophene (5). To a three-necked 250 mL round-bottomed flask containing mono-ol (1 g, 4.90 mmol) in ether (30 mL), was added *n*-BuLi (6.1 mL of a 15% solution in hexane) under the same experimental conditions as mentioned above. 3-Pyridine carboxaldehyde (0.93 mL, 9.67 mmol) in dry THF (20 mL) was added slowly to the reaction mixture followed by workup and chromatography to afford the desired diol **5** (624 mg, 41%) as a white solid, mp 120–122 °C; [Found: C, 69.12; H, 5.25; N, 4.37; S, 10.20. $C_{18}H_{17}NO_2S$ requires C, 69.43; H, 5.50; N, 4.50; S, 10.30%]; R_f (4% CH_3OH/CH_2Cl_2) 0.48; ν_{max} (KBr) 3440, 3352, 3050, 3020, 2868, 1600, 1481, 1432, 809, 761, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.23 (1H, bs, pyridyl), 8.16–8.18 (1H, m, pyridyl), 7.58–7.60 (1H, m, pyridyl), 7.21 (2H, d, $J=8.2$ Hz, *o*-tolyl), 7.04–7.06 (1H, m, pyridyl), 7.01 (2H, d, $J=8.2$ Hz, *m*-tolyl), 6.52 (1H, d, $J=4.4$ Hz, thiophene), 6.49 (1H, d, $J=4.4$ Hz, thiophene), 5.76 (2H, s, C*H*OH), 2.24 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 149.6, 147.9, 147.2, 144.7, 137.5, 134.9, 129.1, 128.3, 124.7, 124.3, 123.7, 123.5, 71.9, 69.7, 21.3; *m*/*z* (ES MS) 312 (8 MH^+), 294 (100), 219 (12), 174 (15), 119 (10), 102 (17%).

4.1.3. 2-(4-Pyridylhydroxymethyl)-5-(*p*-tolylhydroxymethyl) thiophene (6). The diol **6** was prepared following the same method given for diols **4** and **5** by adding *n*-BuLi (6.1 mL of a 15% solution in hexane) to mono-ol (1 g, 4.90 mmol) in diethylether (30 mL) followed by ice cold solution of 4-pyridine carboxaldehyde (0.93 mL, 9.79 mmol) in dry THF (20 mL). Purification of the crude product by silica gel column chromatography (4% CH_3OH/CH_2Cl_2) gave the desired diol **6** (685 mg, 45%) as an off-white semi-solid, mp 125–126 °C; [Found: C, 69.28; H, 5.41; N, 4.30; S, 10.18. $C_{18}H_{17}NO_2S$ requires C, 69.43; H, 5.50; N, 4.50; S, 10.30%]; R_f (4% CH_3OH/CH_2Cl_2) 0.47; ν_{max} (KBr) 3457, 3350, 3050, 3022, 2872, 1484, 1438, 1050, 806, 760, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.18 (2H, d, $J=8.8$ Hz, pyridyl), 7.21–7.25 (4H, m, tolyl), 7.06 (2H, d, $J=8.8$ Hz, pyridyl), 6.62 (1H, d, $J=5.2$ Hz, thiophene), 6.59 (1H, d, $J=5.2$ Hz, thiophene), 5.82 (2H, s, C*H*OH), 2.27 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 148.6, 146.4, 146.2, 140.7, 137.4, 129.4, 126.3, 124.7, 124.3, 123.1, 121.4, 71.9, 70.4, 21.1; *m*/*z* (ES MS) 312 (5 MH^+), 294 (100), 194 (32%).

4.1.4. 5-(4-Pyridyl)-10-(*p*-tolyl)15,17-dihydro-16-thiatripyrrin (7). A mixture of **6** (500 mg, 1.61 mmol) and pyrrole (4.5 mL, 64.3 mmol) were degassed by bubbling with N_2 for 10 min. $BF_3 \cdot OEt_2$ (202 μL, 1.61 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. The solution was diluted with CH_2Cl_2 (100 mL), then washed with 0.1 M NaOH, followed by water. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the unreacted pyrrole was removed by vacuum distillation at room temperature. TLC analysis of the crude mixture showed no other product formation except small amounts of polymeric material at the origin. The resulting dark yellow viscous liquid was purified by column chromatography (silica gel 60–120 mesh, ethyl acetate/petroleum ether (50:50) to afford tripyrrin **7** (263 mg, 40%) as an orange oily liquid; [Found: C, 76.44; H, 5.46; N, 10.10; S, 7.70. $C_{26}H_{23}N_3S$ requires C, 76.24; H, 5.66; N, 10.26; S, 7.83%]; R_f (50% ethyl acetate/petroleum ether) 0.49; ν_{max} (KBr) 3403, 3290, 3091, 2968, 2864, 1615, 1602, 1462, 1072, 861, 762, 741 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.40 (2H, d, $J=8.0$ Hz, pyridyl), 8.30 (2H, bs, N*H*), 7.60 (2H, d, $J=8.0$ Hz, pyridyl) 7.09–7.11 (4H, m, tolyl), 6.71–6.73 (4H, m, pyrrole), 6.54–6.56 (2H, m, pyrrole), 6.05 (1H, s, thiophene), 5.84 (1H, s, thiophene), 5.81 (1H, s, C*H*), 5.46 (1H, s, C*H*), 2.27 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 150.2, 147.7, 145.9, 137.3, 136.7, 133.3, 128.3, 128.2, 125.3, 122.9, 122.4, 121.3, 117.2, 108.2, 107.3, 45.7, 36.9, 21.1; *m*/*z* (ESMS) 409 (100 $M-H^+$), 394 (40), 252 (8), 237 (15), 239 (10), 169 (12%).

4.1.5. 5-(2-Pyridyl)-10,15,20-tris(*p*-tolyl)-21,23-dithiaporphyrin (1). A solution of **4** (367 mg, 1.18 mmol) and symmetrical 16-thiatripyrrin (5,10-ditolyl-16-thia-15,17-dihydrotripyrrin) (500 mg, 1.18 mmol) in 125 mL of propionic acid was refluxed for 3 h. The progress of the reaction was checked by absorption spectroscopy, which showed bands characteristic of the desired porphyrin. The excess propionic acid was removed under vacuum and the resultant black solid was washed several times with warm water and dried in an oven at 100 °C. The crude product was then purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (2:98) as eluent, to afford the desired porphyrin **1** (67 mg, 8.2%) as a purple solid, mp > 300 °C; [Found: C, 80.03; H, 4.95; N, 6.24; S, 9.44. $C_{46}H_{33}N_3S_2$ requires C, 79.82; H, 4.92; N, 6.07; S, 9.25%]; R_f (2% CH_3OH/CH_2Cl_2) 0.44; ν_{max} (KBr) 2929, 2864, 1456, 976, 794; δ_H (400 MHz, $CDCl_3$) 9.70–9.73 (4H, m, β-thiophene), 9.20–9.22 (1H, bs, pyridyl), 8.69–8.71 (4H, m, β-pyrrole), 8.27–8.29 (2H, m, pyridyl), 8.12–8.14 (6H, m, *o*-tolyl), 7.71–7.73 (1H, m, pyridyl), 7.60–7.62 (6H, m, *m*-tolyl),

2.70 (9H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 156.8, 149.5, 148.4, 147.9, 147.6, 138.4, 137.9, 136.2, 135.7, 135.0, 134.8, 134.5, 131.2, 130.3, 129.5, 128.3, 128.0, 122.6, 21.6; *m/z* (ES MS) 692 (100% M^+).

4.1.6. 5-(3-Pyridyl)-10,15,20-tris(*p*-tolyl)-21,23-dithiaporphyrin (2). Condensation of **5** (367 mg, 1.18 mmol) with symmetrical 16-thiatripyrrin (500 mg, 1.18 mmol) in propionic acid (125 mL) using similar reaction and purification methods as mentioned for **1**, gave the desired porphyrin **2** (86 mg, 10.5%) as a purple solid, mp > 300 °C; [Found: C, 79.64; H, 4.77; N, 6.20; S, 9.11. $C_{46}H_{33}N_3S_2$ requires C, 79.82; H, 4.92; N, 6.07; S, 9.25%]; R_f (2% CH_3OH/CH_2Cl_2) 0.46; ν_{max} (KBr) 2926, 2860, 1450, 982, 794; δ_H (400 MHz, $CDCl_3$) 9.73 (1H, d, $J=5.1$ Hz, β-thiophene), 9.71 (2H, s, β-thiophene), 9.58 (1H, d, $J=5.1$ Hz, β-thiophene), 9.50 (1H, bs, pyridyl), 9.06 (1H, bs, pyridyl), 8.74–8.76 (1H, d, $J=4.5$ Hz, β-pyrrole), 8.69 (2H, s, β-pyrrole), 8.61 (1H, d, $J=4.5$ Hz, β-pyrrole), 8.55 (1H, d, $J=7.5$ Hz, pyridyl), 8.13–8.15 (6H, m, *o*-tolyl), 7.79–7.81 (1H, m, pyridyl), 7.60–7.62 (6H, m, *m*-tolyl), 2.70 (9H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 156.7, 153.3, 149.1, 148.4, 148.1, 147.9, 147.7, 141.2, 140.1, 136.1, 135.9, 135.3, 134.8, 134.3, 133.7, 128.9, 128.3, 128.0, 122.8, 21.6; *m/z* (ES MS) 692 (100% M^+).

4.1.7. 5-(4-Pyridyl)-10,15,20-tris(*p*-tolyl)-21,23-dithiaporphyrin (3). Condensation of **6** (367 mg, 1.18 mmol) with symmetrical 16-thiatripyrrin (500 mg, 1.18 mmol) in propionic acid (125 mL) using similar reaction and purification methods as mentioned for **1**, gave the desired porphyrin **3** (90 mg, 11%) as a purple solid. The compound **3** was also prepared by following method B. Condensation of 2,5-bis (*p*-tolylhydroxymethyl) thiophene (200 mg, 0.617 mmol) with 5-(4-pyridyl)-10-(*p*-tolyl)-15,17-dihydro-16-thiatripyrrin **7** (253 mg, 0.617 mmol) in propionic acid followed by chromatography gave **3** (26 mg, 6.1%) as a purple solid, mp > 300 °C; [Found: C, 79.71; H, 4.77; N, 6.28; S, 9.10. $C_{46}H_{33}N_3S_2$ requires C, 79.82; H, 4.92; N, 6.07; S, 9.25%]; R_f (2% CH_3OH/CH_2Cl_2) 0.50; ν_{max} (KBr) 2930, 2860, 1455, 982, 798; δ_H (400 MHz, $CDCl_3$) 9.72–9.74 (3H, m, β-thiophene), 9.57 (1H, d, $J=5.2$ Hz, β-thiophene), 9.07 (2H, bs, pyridyl), 8.73 (1H, d, $J=4.8$ Hz, β-pyrrole), 8.69 (2H, s, β-pyrrole), 8.60 (1H, d, $J=4.8$ Hz, β-pyrrole), 8.18–8.19 (2H, m, pyridyl), 8.12–8.14 (6H, m, *o*-tolyl), 7.61–7.63 (6H, m, *m*-tolyl), 2.69 (9H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 157.0, 156.6, 155.1, 150.9, 149.8, 148.7, 148.5, 147.6, 146.9, 138.0, 136.1, 135.7, 135.1, 134.9, 134.7, 133.6, 129.5, 128.3, 21.6; *m/z* (ES MS) 692 (100% M^+).

4.1.8. Unsymmetrical non-covalent dimer (8). The dithiaporphyrin building block, **2** (20 mg, 0.0289 mmol) was dissolved in 30 mL of toluene in a two necked 100 mL round-bottomed flask and was purged with N_2 for 10 min. RuTPP(CO)(EtOH) (23 mg, 0.0289 mmol) was then added and the solution was refluxed with stirring overnight. The reaction was monitored with TLC and absorption spectroscopy. The TLC analysis after 12 h showed complete consumption of **2**, and absorption spectroscopy showed characteristic splittings and shifts in soret and in Q-bands. The heating was stopped and the solvent was removed under reduced pressure. The crude compound was purified by silica gel column chromatography using petroleum ether/dichloromethane (60:40) as solvent and afforded dimer **8** (17 mg, 40%) as a purple solid, mp > 300 °C; [Found: C, 76.30; H, 4.50; N, 6.70; S, 4.50. $C_{46}H_{33}N_3S_2$ requires C, 76.36; H, 4.29; N, 6.84; S, 4.47%]; R_f (60% pet ether/dichloromethane) 0.48; ν_{max} (KBr) 2930, 2858, 1943, 1443, 1358, 1267, 1177, 1021, 800, 755; δ_H (400 MHz, $CDCl_3$) 9.62 (1H, d, $J=4.8$ Hz, β-thiophene), 9.58 (1H, d, $J=4.8$ Hz, β-thiophene), 9.38 (1H, d, $J=4.8$ Hz, β-thiophene), 8.77 (8H, s, β-pyrrole of TPP), 8.64 (1H, d, $J=5.0$ Hz, β-pyrrole of **2**), 8.54 (4H, d, $J=8$ Hz, o'-Ph of TPP), 8.50 (4H, d, $J=8$ Hz, o'-Ph of TPP), 8.30 (1H, d, $J=4.8$ Hz, β-thiophene), 8.14 (2H, d, $J=5.2$ Hz, β-pyrrole of **2**), 7.58–7.64 (14H, m, *o*-tolyl of **2** + *m*-Ph of TPP), 7.42–7.50 (10H, m, *m*-tolyl of **2** + p'-Ph of TPP), 7.38 (1H, d, $J=4.4$ Hz, 4-pyridyl), 6.98 (1H, t, $J=2.0$, 4.4 Hz, 3-pyridyl), 6.84 (1H, d, $J=5.0$ Hz, β-pyrrole of **2**), 2.65 (9H, s, *Me*), 2.22 (1H, s, 6-pyridyl), 1.90 (1H, d, $J=2.0$ Hz, 2-pyridyl); δ_C (400 MHz, $CDCl_3$) 157.2, 156.0, 153.4, 152.0, 150.9, 148.5, 147.9, 147.6, 146.3, 146.1, 145.8, 144.5, 143.9, 142.7, 141.5, 139.2, 138.0, 136.7, 135.7, 134.6, 134.1, 132.5, 131.6, 128.9, 128.4, 125.3, 123.6, 120.3, 22.8, 21.6; *m/z* (ES MS) 1435 (15 M^+), 741 (40), 713 (10), 692 (100%).

4.1.9. Unsymmetrical non-covalent dimer (9). Compound **3** (20 mg, 0.0289 mmol) was treated with RuTPP(CO)(EtOH) (23 mg, 0.0289 mmol) in toluene under the same reaction condition as for **8** to yield the dimer **9** (23 mg, 56%) as a purple solid, mp > 300 °C; ν_{max} (KBr) 1943 (CO); δ_H (400 MHz, $CDCl_3$) 9.50 (1H, d, $J=4.8$ Hz, β-thiophene), 9.47 (1H, d, $J=4.8$ Hz, β-thiophene), 9.21 (1H, d, $J=4.8$ Hz, β-thiophene), 8.66 (8H, s, β-pyrrole of TPP), 8.58 (1H, d, $J=5.2$ Hz, β-pyrrole of **3**), 8.50 (1H, d, $J=5.2$ Hz, β-pyrrole of **3**), 8.20–8.30 (4H, m, o'-ph of TPP), 8.10–8.18 (4H, m, o'-phl of TPP), 8.06 (1H, d, $J=4.8$ Hz, β-thiophene), 7.92 (1H, d, $J=5.2$ Hz, β-pyrrole of **3**), 7.84 (4H, t, $J=7.6$ Hz, *p*-ph of TPP), 7.58–7.70 (m, m'-ph of TPP + *o*-tolyl of **3**), 7.43–7.47 (6H, m, *m*-tolyl of **3**), 7.08 (1H, d, $J=5.2$ Hz, β-pyrrole of **3**), 6.00 (2H, d, $J=2.4$ Hz, 3,5-pyridyl), 2.61 (6H, s, *Me*), 2.26 (3H, s, *Me*), 1.92 (2H, d, $J=2.4$ Hz, 2,6-pyridyl); δ_C (400 MHz, $CDCl_3$) 157.0, 156.6, 153.4, 152.2, 150.9, 149.8, 148.5, 147.6, 156.9, 146.3, 145.8, 143.9, 142.7, 141.5, 139.7, 139.2, 138.0, 136.1, 135.8, 134.1, 132.6, 132.1, 131.1, 129.0, 128.4, 126.3, 123.0, 119.3, 22.8, 21.6; *m/z* (ES MS) 1435 (17 M^+), 713 (10), 692 (100%).

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Phototransformations of some 3-alkoxy-2-styrylchromones: type II cyclisations of 1,4- and 1,6-biradicals

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Abstract—3-Alkoxy-2-styrylchromones on photo-irradiation with UV-light transform into oxetanopyrananones, pyranopyrones, pyranopyrananones and pyranoalcohols. The products formed have been found to depend upon the structure of alkoxy group (methyl, benzyl and allyls). Alkoxychromones containing a heterocyclic ring (thiophene, furan) in place of phenyl in the styryl group produced only pyranoalcohols as the photoproducts. The photo-conversions have been rationalized through an initial H-abstraction by the C=O group producing a 1,4-biradical. In allyloxy derivatives, cyclisations involve both 1,4- and 1,6-biradicals.

1. Introduction

3-Alkoxy-2-aryl(furan, thiophene or phenyl)chromones[1] and 2-alkoxy/alkyl-3-aryl-2-cyclohexenones[2] on photo-irradiation undergo cyclisations to angular cyclic products, with the involvement of the alkoxy chain and the aryl group. α-Alkoxy acyclic enones[3] with aryl substituents at the β-position have been found to photo-convert into cyclobutyl products without the involvement of the aryl group. The reason for this diversity between cyclic and acyclic compounds has been attributed to steric and conformational effects.[3] In a related study on 2-methyl-3-methoxychromones,[4,5] photo-irradiations have led to the formation of dimeric-oxetanols. Evidently, although the basic premise of the substrates is the same, the products formed are quite different and have been found to depend upon the substituents at the β-position of the enone moiety **1**.[1] In all these transformations, the primary reaction is the excitation of the C=O group that subsequently abstracts hydrogen from the α-substituents with the formation of 1,4-biradical[1,2] **2** (Scheme 1).

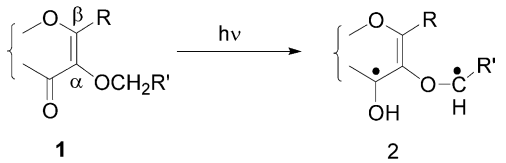
Earlier in a preliminary study, we reported the synthesis of some linear tricyclic pyranopyrones from the photolysis of 3-benzyloxy-2-styrylchromones.[6] With a view to better understanding how the interposing of a double bond between the aryl group at C-2 and the chromone moiety affect the reaction pathway, we present herein the results of detailed investigations on the various 3-alkoxy derivatives of 2-styrylchromones. The possibilities are:

(a) H-abstraction by C=O from O–C**H**$_2$ leading to products as reported earlier.[6]
(b) Styryl bond undergoes *cis–trans* isomerisation.
(c) The ethers, that can be considered as triene systems (styryl group coupled to the 2,3-double bond of chromone), undergo conrotatory photocyclisations to phenanthrenes.[7]

The substrates in the present study may undergo all these competing reactions or some may take preference over the others.

2. Results

The 3-alkoxy-2-styrylchromones were synthesised as follows. 5-Chloro-2-hydroxyacetophenone on condensation with cinnamaldehyde in the presence of NaOH/EtOH gave **3**



1 **2**

Scheme 1.

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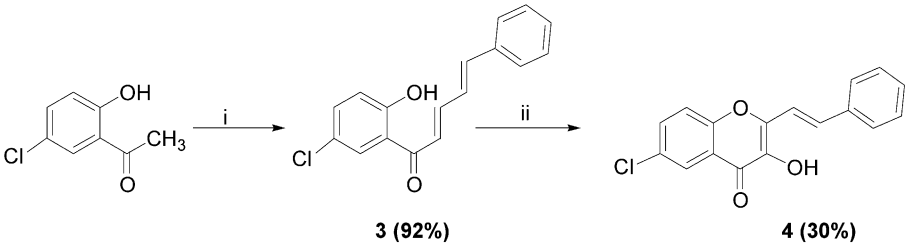
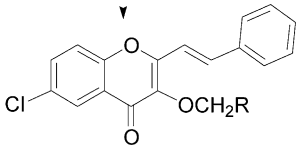


i ; C_6H_5-CH=CH-CHO/C_2H_5OH/NaOH, 0 °C

ii; KOH/H_2O_2 (30%)

iii; $K_2CO_3/CH_3COCH_3/Bu_4N^+I^-$/RX

iii



CH_3I	**5**, R = H	78%
$C_6H_5CH_2Cl$	**6**, R = C_6H_5	80%
CH_2=CH-CH_2Br	**7**, R = CH=CH_2	80%
CH_2=C(CH_3)-CH_2Cl	**8**, R = C(CH_3)=CH_2	75%
C(CH_3)$_2$=CH-CH_2Cl	**9**, R = CH=C(CH_3)$_2$	78%

Scheme 2.

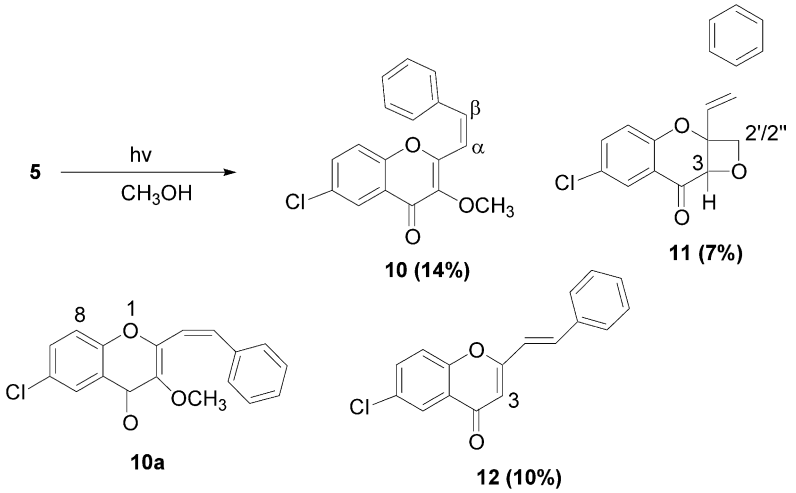
which under Algar-Flynn-Oyamada ($H_2O_2/^-OH$) conditions[8] was converted into 3-hydroxy-2-styrylchromone **4** that subsequently was alkylated to obtain ethers **5–9** (Scheme 2).

The 6-chloro-3-methoxy-2-styrylchromone **5** on photoirradiation with pyrex filtered UV light furnished three products **10**, **11** and **12** (Scheme 3).

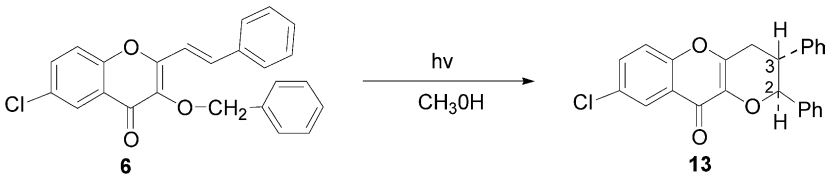
That the photoproduct **10** is a *cis* isomer of **5** became evident from $J_{\alpha,\beta}=12.0$ Hz (cf. **5**, $J_{\alpha,\beta}=16.0$ Hz). The chromone **10** could have two conformations **10** and **10a** (Scheme 3). Our preference for expression **10** over **10a** stems from the observation that H-8 in **10** appeared at δ 6.75 as compared to H-8 in **5** that was located at δ 7.40; such upfield shifting could be the result of shielding of H-8 by the phenyl of styryl group. An energy calculation[9] by MM2 also showed that **10** is 2 Kcal more stable than **10a**.

The oxetane **11** (C=O, 1693 cm^{-1}) exhibited H-3 at δ 5.05(s) and H-2′/H-2″ at δ 4.82 and 5.05 ($J=7.0$ Hz). The loss of 30 mass units (CH_2O) from the molecular ion *m/z* 312, further confirmed the presence of an oxetane ring in compound **11**. The demethoxylated product **12** showed in its ^{1}H NMR spectrum a signal at δ 6.30, characteristic[5] of the C-3 proton in chromones. The identity of the photoproduct **12** was further confirmed by synthesising an authentic sample of the compound through cyclisation of **3**.

The photoirradiation of 3-benzyloxy-2-styrylchromone **6** produced a linear tricyclic pyranopyrone **13** in 10% yield (Scheme 4) and no other compound could be isolated although TLC analysis of the photolysate showed some polymeric products. The reaction, here followed the same



Scheme 3.



Scheme 4.

route as reported by us previously on a chromone similar to **6**.[6] The *trans* disposition of two benzylic protons in **13** was confirmed by the observation of $J_{2,3}=7.0$ Hz.

Next in the study were included the allyloxy derivatives **7**, **8** and **9**. The photoirradiation of a methanolic solution of **7** with UV light (pyrex) furnished three tricyclic products, two linear **14**, **16** and one angular **15** (Scheme 5).

The structure of the linear tricyclic pyranopyrone **14** was confirmed as it is similar to the photoproduct **13** obtained from **6**; H-2 and H-3 are *trans* to each other, $J_{2,3}=6.8$ Hz. The angular tricyclic alcohol **15** did not exhibit any C=O absorption in its ir spectrum. The *trans* configuration of H_α and H_β was confirmed from $J_{\alpha,\beta}=16.0$ Hz; a D_2O shake confirmed the presence of the OH (^{1}H NMR spectra). The salient spectral features of linear pyranopyrananone (C=O, 1700 cm^{-1}) **16** are that H_α and H_β possess a *cis* configuration with $J_{\alpha,\beta}=12.0$ Hz (cf. **7** and **15** $J_{\alpha,\beta}=16.0$ Hz) and out of the three protons belonging to benzenoid ring A, H-9 appears at δ 5.95 (cf. **7**, H-8 δ 7.40). This latter observation could be due to a *cis* disposition of H_α and H_β so that the styryl group is disposed to shield H-9 (Fig. 1), a situation similar to that observed in **10**.

The other styryl chromones **8** and **9** behaved in a similar manner and furnished the products **17**–**18** (yield 10–12%),

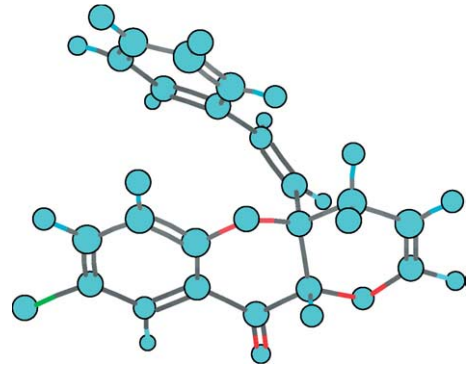
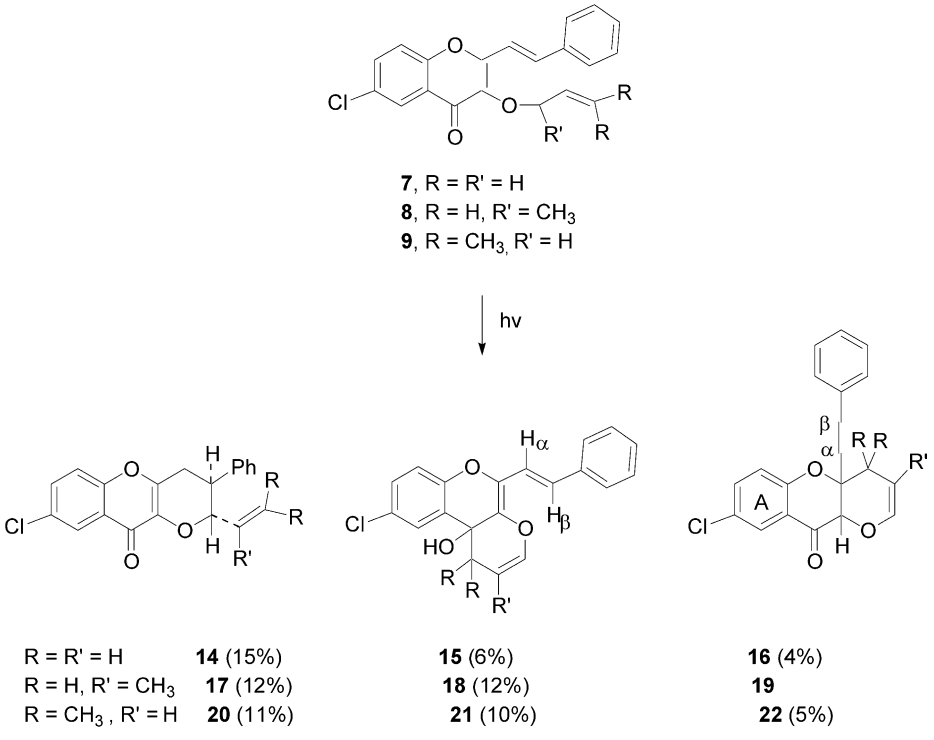


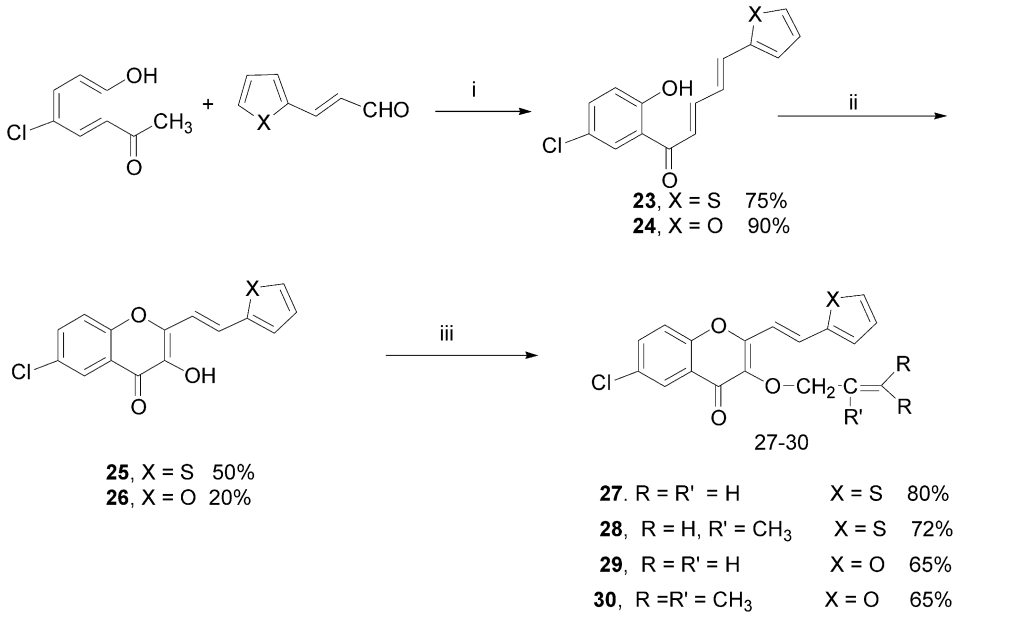
Figure 1. Energy minimized structure of **16**.

19 (trace amount) and **20**, **21** (yield 10–11%), **22** (yield 5%), respectively. It is rather intriguing to mention here that H-9 in **22** appeared at δ 7.07 and the styryl protons exhibited $J_{\alpha,\beta}=16.0$ Hz (cf. **16**, $J=12.0$ Hz H-9). For this diverse behaviour of pyranopyranones **19** and **22**, we are unable to offer any explanation. From the photolysate of **8**, the photoproduct **19** could not be isolated due to its extremely low yield although its formation could be seen from the ^{1}H NMR and ir spectra of the reaction mixture.

To seek further information on the photo-transformations occurring in allyloxystyrylchromones, the investigations



Scheme 5.



Scheme 6.

were extended to include the substrates **27**–**30** that were synthesised by following the sequence of reactions shown in Scheme 6. The purpose here was to investigate how the replacement of the phenyl ring by electron rich heterocyclic five-membered rings, furan and thiophene, affect the course of the reaction.

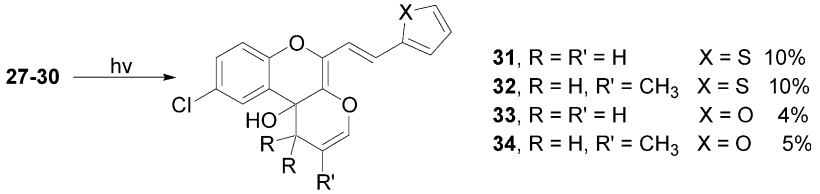
From the photolysate of the chromones **27**–**30**, the only compounds that could be isolated were angular tricyclic alcohols **31**, **32** (yield 10%), **30**, **34** (yield ~5%); in spite of our best efforts, no other products could be isolated (Scheme 7).

3. Discussion

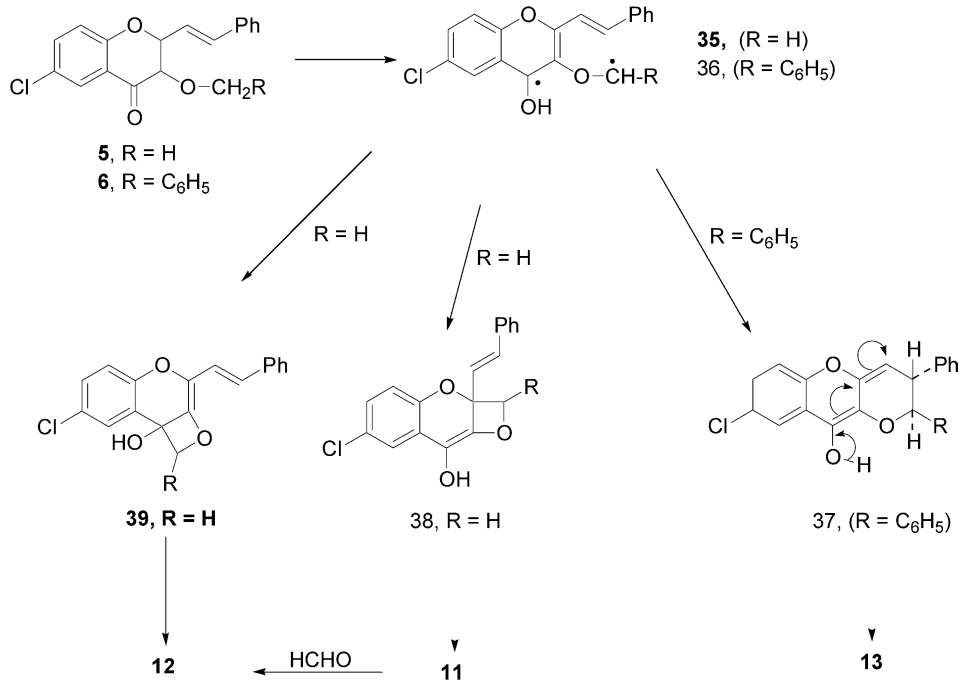
The photo conversions described above may be explained through an initial H-abstraction from the 3-alkoxy group by the photo excited C=O of the pyrone moiety that then results in the formation of a 1,4-biradical (Scheme 8).[1,2] In the photolysis of **5** and **6**, the diversity in the product formation may be rationalised on the basis of radical stability. The photolysis of **6** (R=C_6H_5) produces the benzyloxy radical **36** (R=C_6H_5) that consequently cyclises to produce **37** (R=C_6H_5), which by 1,5-hydrogen shift finally culminates in the formation of linear product **13**. Such a situation may not occur in the photolysis of **5** (R=H) where the alkoxy radical **35** (R=H) lacks the inherent stability of the benzyloxy radical **36** (R=C_6H_5). The 1,4-biradical **35** resulting from the photolysis of **5** may cyclise to give oxetanol **39** (R=H) that subsequently may cleave to furnish demethoxylated product **12**. Alternatively, the chromone **12** may be obtained through the extrusion of HCHO from oxetane[5,10] **11** that is formed from ketonisation of **38** (R=H).

Our preference for the formation of **12** from **11** rests on the following: (a) the oxetane **11** has been isolated and its photolysis led to its conversion into **12**, (b) envisaged instability of **39** where oxetanol is part of the fused system carrying an sp^2-hybridized carbon; **38** is only an enolic form of **11**. The formation of oxetane **11** finds corroboration from an earlier report where such intermediates have been isolated in the photolytic demethoxylation of 3-methoxy-2-cholesten-4-one.[11] In a previous report on the photolysis of 3-methoxy-2-methylchromones,[5] such demethoxylation has been rationalised through photoaddition of CH_3OH to the 2,3-double bond of pyrone, but no addition products whatsoever were isolated. In all probability the photoreaction there also might have occurred through the formation of oxetane followed by cleavage. It may be added here that the probability of the formation of products similar to **13** from **5**, and **12** from **6** can not altogether be excluded; perhaps these were formed in such small quantities that we were unable to isolate them.

The photo conversions of allyloxychromones **7**, **8** and **9**



Scheme 7.



Scheme 8.

offer an interesting proposition where the reaction followed a different course; here the photolysis produced two linear tricyclic pyranes and one angular tricyclic alcohol (Scheme 9). The reaction once again is envisaged to initiate through the formation of 1,4-biradical **40** which could undergo cyclisation to produce linear tricyclic pyranopyrone products: **7**→**14** (R=R′=H), **8**→**17** (R=H, R′=CH_3) and **9**→**20** (R=R′=CH_3); these are similar to **13** as obtained from the photolysis of **6**. Such similarity could very well be rationalised on the basis of almost equal stability[12] of allyl and benzyl radicals. Regarding the realisation of tricyclic alcohols (**15**, **18** and **21**) and pyranopyranones (**16**, **19** and **22**) it is understandable that these are formed (Scheme 9) by delocalisation in allyloxy radical **40** (1,4-biradical)↔**40a** (1,6-biradical)↔**40b** (1,6-biradical). Such behaviour of allyloxy radicals has not been observed in the past in our laboratory during the photolytic experiments on 3-allyloxy-2-arylchromones where instead of styryl group an aryl (phenyl, furyl, thiophene) moiety is present.[13] Although in 2-arylchromones where the allyloxy chain carries an electron-captive group (R=$COOCH_3$)[14] at the distal end, products are known to arise through delocalisation of initially formed allyloxy radicals. But, in these compounds no cyclisation similar to the one experienced by allyloxychromones **7**–**9** was observed. In a related study on 3-allyloxy-1,2-naphthaquinones,[15] the formation of a 1,6-biradical from the initially produced 1,4-biradical has been reported but no products similar to alcohol (**15**, **18** and **21**) as obtained in the present case were reported. In some other studies pertaining to photocyclisations involving 1,*n*-biradicals where the substrates did possess allylic moieties, no products involving isomerisations have been reported.[16]

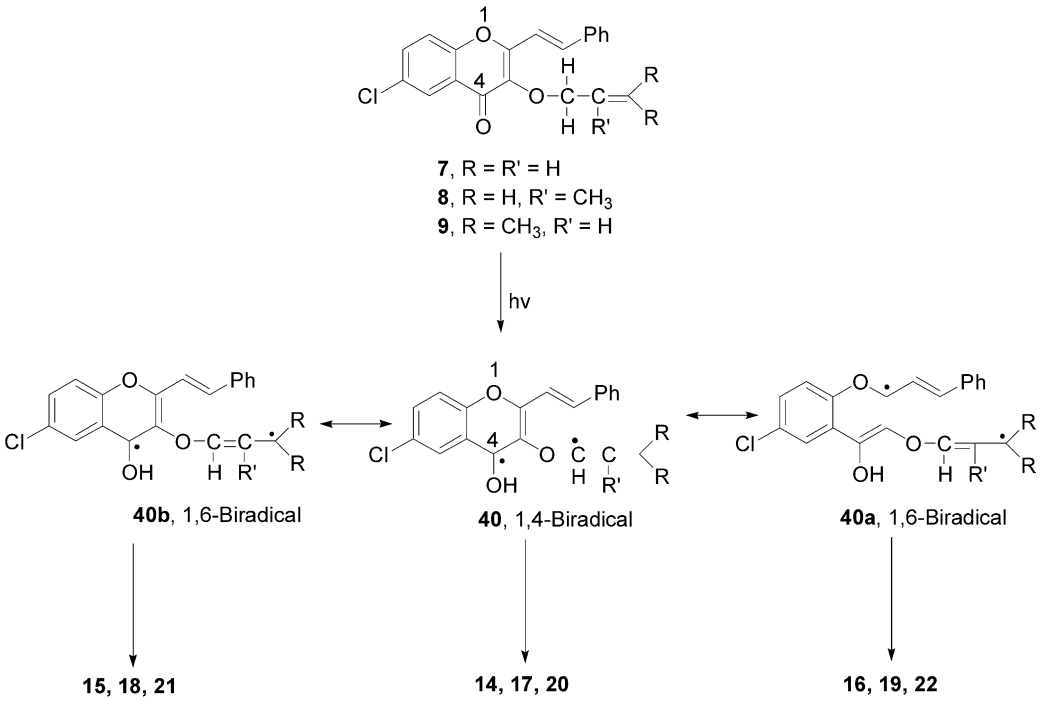
In the photocyclisation of chromones **27**–**30** carrying 5-membered heterocyclic rings (furan and thiophene), only angular tricyclic alcohols **31**–**34** could be isolated and no product similar to **14** and **16** were available. It is possible that some electronic factors may be operating that do not allow the formation of such products; or it may be the steric bulk of furan or thiophene rings as compared to phenyl ring that pushes the allyloxy group towards the C=O for instantaneous cyclisation leading to photoproducts **31**–**34**.

The energy minimised structures[9] of chromones **7** and **27** (Fig. 2) show that the distance between one of the hydrogens belonging to –O–CH_2– and **O** of C=O group in **27** is 2.887 Å and in **7** is 2.987 Å. This observation supports the notion that the allyloxy group in **27** is being pushed closer to the C=O facilitating the formation of angular products.

It is evident from the photo-products reported here that the alkoxychromones **5**–**9** and **27**–**30** did not undergo any conrotatory cyclisations; may be conrotatory ring closure of the type dominant in the triene systems,[7] here, is suppressed due to the blockade of the point of cyclisation in preference to more facile H-abstractions. Although a literature survey reveals that photocyclisations do take place even in those triene systems where the point of cyclisation carries a substituent[17] that is extruded during the reaction; 2-styrylchromones[18] have also been reported to undergo photocyclisations to angular tetracyclics.

4. Conclusions

From the above study it may be concluded that 3-alkoxy-2-styrylchromones undergo reactions through H-abstractions and no conrotatory ring closures were observed. The initially generated allyloxy radicals in the photolysis of 3-allyloxchromones produce mesomeric biradicals en route to products.



Scheme 9.

5. Experimental

Melting points reported are uncorrected. IR spectra were recorded on a Buck Scientific IR spectrophotometer using KBr pellets and UV spectra were recorded on U-2000 spectrophotometer. ^{1}H NMR spectra were recorded on a 300 or 90 MHz spectrometer using Me_4Si as internal standard. Mass spectra were recorded at 70 eV. TLC plates were coated with silica gel G suspended in MeOH–$CHCl_3$ silica gel (60–120 mesh) was used for column chromatography.

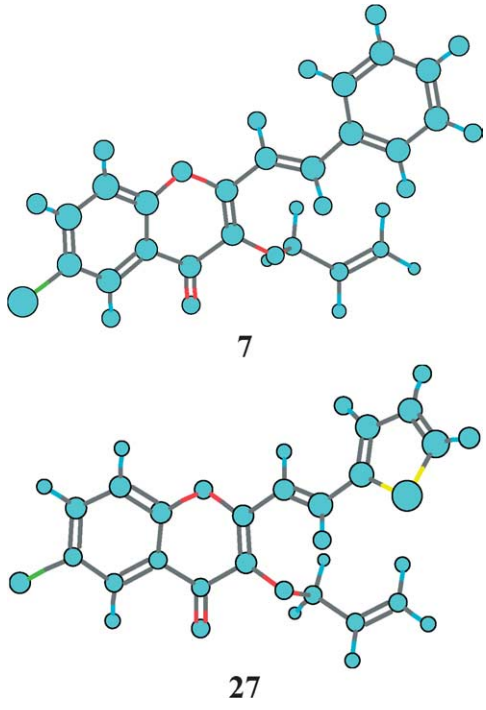


Figure 2. Energy minimized structures of **7** and **27**.

The percent yields reported in the photochemical reactions are calculated by excluding the recovered starting substrates.

5.1. Synthesis of chromones 5–9 and 27–30

5.1.1. 1-(5-Chloro-2-hydroxy-phenyl)-5-phenyl-penta-2,4-dien-1-one, 3. A solution of 5-chloro-2-hydroxyacetophenone (10.0 g, 59 mmol) and cinnamaldehyde (7.8 g, 58 mmol) in EtOH was mixed with powdered NaOH (3.0 g, 75 mmol) at 0 °C and the resulting dark red mixture was stirred for 12 h and thereafter was poured on ice-HCl to obtain **3** (15.35 g, 92%) as yellow solid, crystallised from EtOH, mp 151–152 °C; [Found: C, 71.48; H, 4.79. $C_{17}H_{13}ClO_2$ requires C, 71.71; H, 4.60]; ν_{max} (cm^{-1}) 3400 (–OH), 1640 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.68 (s, 1H), 7.76 (d, J=2.0 Hz, 1H), 7.60–6.80 (m, 11H).

5.1.2. 1-(5-Chloro-2-hydroxy-phenyl)-5-thiophen-2-yl-penta-2,4-dien-1-one, 23. Prepared using a procedure similar to above by taking 5-chloro-2-hydroxyacetophenone (5.0 g, 29.5 mmol).

Yellow solid (6.40 g, 75%), mp 125–127 °C; [Found: C, 61.69; H, 3.68. $C_{15}H_{11}ClO_2S$ requires C, 61.96; H, 3.81]; ν_{max} (cm^{-1}) 3254 (OH), 1639 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.80 (s, 1H), 7.79 (d, J=2.4 Hz, 1H), 7.70 (d, J=14.6 Hz, 1H), 7.66 (d, J=14.6 Hz, 1H), 7.41 (dd, J=2.4, 8.9 Hz, 1H), 7.36 (d, J=5.1 Hz, 1H), 7.20 (d, J=3.4 Hz, 1H), 7.06 (dd, J=3.7, 5.1 Hz, 1H), 6.97 (d, J=8.9 Hz, 1H), 6.88 (d, J=15.2 Hz, 1H), 6.83 (d, J=15.2 Hz, 1H).

5.1.3. 1-(5-Chloro-2-hydroxy-phenyl)-5-furan-2-yl-penta-2,4-dien-1-one, 24. Prepared using a procedure similar to above by taking 5-chloro-2-hydroxyacetophenone (5.0 g, 29.5 mmol).

Yellow solid (7.25 g, 90%), mp 150–152 °C; [Found: C, 65.35; H, 4.29. $C_{15}H_{11}ClO_3$ requires C, 65.58; H, 4.04]; ν_{max} (cm^{-1}) 3400 (OH), 1640 (C=O). ^1H NMR ($CDCl_3$): δ 12.16 (s, 1H), 7.78 (d, J=2.4 Hz, 1H), 7.70 (d, J=11.0 Hz, 1H), 7.65 (d, J=11.0 Hz, 1H), 7.50 (d, J=1.8 Hz, 1H), 7.42 (dd, J=2.4, 8.7 Hz, 1H), 7.11 (d, J=14.6 Hz, 1H), 6.96 (d, J=8.7 Hz, 1H), 6.84 (d, J=14.6 Hz, 1H), 6.57 (d, J=3.6 Hz, 1H), 6.49 (dd, J=3.6, 1.8 Hz, 1H).

5.1.4. 6-Chloro-3-hydroxy-2-styryl-chromen-4-one, 4. To a solution of **3** (2.0 g, 1 mmol) in MeOH (30 mL) mixed with powdered KOH (1.0 g, 25 mmol) 0 °C, was added H_2O_2 (30%, 5 mL) dropwise. The solution after stirring for 5 h was poured on ice-HCl to give light yellow precipitates, crystallised ($CHCl_3$–EtOH) to yellow needles (6.30 g, 30%), mp 225–227 °C; [Found: C, 68.59; H, 3.54. $C_{17}H_{11}ClO_3$ requires C, 68.35; H, 3.71]; ν_{max} (cm^{-1}) 3400 (OH), 1638 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 12.25 (s, 1H, –OH), 8.10 (d, J=2.0 Hz, 1H), 7.60–7.50 (dd, J=9.0, 2.0 Hz, 1H), 7.46–7.20 (m, 7H), 6.80 (d, J=17.0 Hz, 1H).

5.1.5. 6-Chloro-3-hydroxy-2-(2-thiophen-2-yl-vinyl)-chromen-4-one, 25. Prepared using a procedure similar to above.

Yellow needles (1.05 g, 50%), mp 238–240 °C; [Found: C, 59.38; H, 3.22. $C_{15}H_9ClO_3S$ requires C, 59.12; H, 2.98]; ν_{max} (cm^{-1}) 3271 (OH), 1632 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 12.10 (s, 1H), 8.18 (d, J=2.5 Hz, 1H), 7.58 (dd, J=8.9, 2.5 Hz, 1H), 7.60 (d, J=15.9 Hz, 1H), 7.50 (d, J=8.9 Hz, 1H), 7.37 (d, J=5.1 Hz, 1H), 7.28 (d, J=3.6 Hz, 1H), 7.11 (d, J=15.9 Hz, 1H), 7.07 (dd, J=3.6, 5.1 Hz, 1H).

5.1.6. 6-Chloro-3-hydroxy-2-(2-furan-2-yl-vinyl)-chromen-4-one, 26. Prepared using a procedure similar to above.

Yellow needles (0.42 g, 20%), mp 225–228 °C; [Found: C, 62.19; H, 2.92. $C_{15}H_9ClO_4$ requires C, 62.41; H, 3.14]; ν_{max} (cm^{-1}) 3400 (OH), 1641 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 11.99 (s, 1H), 8.14 (d, J=2.7 Hz, 1H), 7.58 (dd, J=8.7, 2.7 Hz, 1H), 7.52 (d, J=1.5 Hz, 1H), 7.44 (d, J=8.7 Hz, 1H), 7.35 (d, J=16.0 Hz, 1H), 7.28 (d, J=16.0 Hz, 1H), 6.64 (d, J=3.4 Hz, 1H), 6.50 (dd, J=1.5, 3.4 Hz, 1H).

5.1.7. 6-Chloro-3-methoxy-2-styryl-chromen-4-one, 5. A suspension of **4** (3.0 g, 10 mmol), CH_3I (2.1 g, 15 mmol), $Bu_4N^+I^-$ (2.0 g), freshly fused K_2CO_3 (2.0 g in dry acetone (25 mL) was refluxed for 1 h with continuous stirring. The colour of the solution changed from dark red to yellow. The reaction mixture was poured in HCl–H_2O. Subsequent filtration and evaporation of the solvent provided ether **5** (2.45 g, 78%) as pale yellow solid that was purified by percolating through a column of silica gel with pet. ether as eluent, mp 168 °C; [Found: C, 69.15; H, 4.29. $C_{18}H_{13}ClO_3$ requires C, 69.13; H, 4.19]; λ_{max} MeOH 351, 262 nm; ν_{max} (cm^{-1}) 1640 (C=O), 1615 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J=2.0 Hz, 1H), 7.55 (dd, J=9.0, 2.0 Hz, 1H), 7.50–7.20 (m, 8H), 4.00 (s, 3H); m/z 312 (M^+, 100%).

The chromones **6–9**, **27–30** were synthesised using benzyl chloride, allyl chloride, methyl allyl chloride and dimethyl allyl chloride by the procedure as used for compound **5**.

5.1.8. 3-Benzyloxy-6-chloro-2-styryl-chromen-4-one, 6. Pale yellow solid (3.12 g, 80%), mp 144–146 °C; [Found: C, 74.33; H, 4.71. $C_{24}H_{17}ClO_3$ requires C, 74.13; H, 4.41]; λ_{max} MeOH 351, 261 nm; ν_{max} (cm^{-1}) 1640 (C=O), 1615 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J=2.0 Hz, 1H), 7.70–7.50 (m, 13H), 7.35 (d, J=9.0 Hz, 1H), 5.26 (s, 2H); m/z 388 (M^+, 100%).

5.1.9. 3-Allyloxy-6-chloro-2-styryl-chromen-4-one, 7. Pale yellow solid (2.72 g, 80%), mp 134 °C; [Found: C, 70.69; H, 4.76. $C_{20}H_{15}ClO_3$ requires C, 70.90; H, 4.46]; λ_{max} MeOH 352, 264 nm; ν_{max} (cm^{-1}) 1640 (C=O), 1615 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J=2.0 Hz, 1H), 7.60–7.20 (m, 9H), 6.20–5.80 (m, 1H), 5.40–5.10 (m, 2H), 4.70 (d, J=6.0 Hz, 2H); m/z 338 (M^+, 100%).

5.1.10. 3-(2-Methyl)-allyloxy-6-chloro-2-styryl-chromen-4-one, 8. Pale yellow solid (2.66 g, 75%), mp 110 °C; [Found: C, 71.89; H, 4.46. $C_{21}H_{17}ClO_3$ requires C, 71.49; H, 4.86]; λ_{max} MeOH 351, 264 nm; ν_{max} (cm^{-1}) 1640 (C=O), 1615 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J=2.0 Hz, 1H), 7.70–7.30 (m, 9H), 5.10–4.95 (m, 2H), 4.65 (s, 2H),1.90 (s, 3H); m/z 352 (M^+, 100%).

5.1.11. 3-(3-Methyl)-allyloxy-6-chloro-2-styryl-chromen-4-one, 9. Pale yellow solid (2.87 g, 78%), mp 116–117 °C; [Found: C, 72.25; H, 5.54. $C_{22}H_{19}ClO_3$ requires C, 72.03; H, 5.22]; λ_{max} MeOH 351, 264 nm; ν_{max} (cm^{-1}) 1640 (C=O), 1615 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J=2.0 Hz, 1H), 7.65 (dd, J_0=9.0 Hz, 1H), 7.60–7.40 (m, 8H), 5.50 (m, 1H), 4.70 (d, J=7.0 Hz, 2H), 1.80 (s, 6H); m/z 366 (M^+, 100%).

5.1.12. 3-Allyloxy-6-chloro-2-(2-thiophen-2-yl-vinyl)-chromen-4-one, 27. Pale yellow solid (2.71 g, 80%), mp 123–125 °C; [Found: C, 62.97; H, 3.58. $C_{18}H_{13}ClO_3S$ requires C, 62.70; H, 3.80]; λ_{max} THF 390, 374, 271 nm; ν_{max} (cm^{-1}) 1640 (C=O), 1615 (C=C). ^1H NMR (300 MHz, $CDCl_3$): 8.18 (d, J=2.7 Hz, 1H), 7.65 (d, J=15.8 Hz, 1H), 7.60 (dd, J=2.7, 8.9 Hz, 1H), 7.46 (d, J=8.9 Hz, 1H), 7.38 (d, J=5.1 Hz, 1H), 7.29 (d, J=3.6 Hz, 1H), 7.15 (d, J=15.9 Hz, 1H), 7.09 (dd, J=3.6, 5.1 Hz, 1H), 6.08 (t{dd} J=6.0, 10.2, 16.5 Hz, 1H), 5.38 (t{dd} J=1.4, 2.7, 16.5 Hz, 1H), 5.28 (dd J=1.0, 10.2 Hz, 1H), 4.75 (dd, J=1.2, 6.0 Hz, 2H).

5.1.13. 3-(2-Methyl)-allyloxy-6-chloro-2-(2-thiophen-2-yl-vinyl)-chromen-4-one, 28. Pale yellow solid (2.54 g, 72%), mp 121–123 °C; [Found: C, 63.79; H, 3.91. $C_{19}H_{15}ClO_3S$ requires C, 63.59; H, 4.21]; λ_{max}THF 393, 376, 269 nm; ν_{max}(cm^{-1}) 1643 (C=O), 1620 (C=C). ^1H NMR (300 MHz, $CDCl_3$): 8.18 (d, J=2.4 Hz, 1H), 7.66 (d, J=16.0 Hz, 1H), 7.60 (dd, J=2.4, 9.0 Hz, 1H), 7.47 (d, J=9.0 Hz, 1H), 7.38 (d, J=5.0 Hz, 1H), 7.29 (d, J=3.6 Hz, 1H), 7.19 (d, J=16.0 Hz, 1H), 7.09 (dd, J=3.6, 5.0 Hz, 1H), 5.11 (s, 1H), 5.02 (d, J=1.1 Hz, 1H), 4.66 (s, 2H), 1.94 (s, 3H).

5.1.14. 3-Allyloxy-6-chloro-2-(2-furan-2-yl-vinyl)-chromen-4-one, 29. Pale yellow solid (2.22 g, 65%), mp 125–127 °C; [Found: C, 65.36; H, 3.49. $C_{18}H_{13}ClO_4$ requires C, 65.76; H,

3.99]; λ_{max} MeOH 343, 275 nm; ν_{max} (cm^{-1}) 1641 (C═O), 1624 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, J= 2.4 Hz 1H), 7.58 (dd, J=9.0, 2.4 Hz, 1H), 7.52 (d, J= 1.2 Hz, 1H), 7.3 (d, J=9.0 Hz, 1H), 7.30 (d, J=15.9 Hz 1H), 7.23 (d, J=15.9 Hz, 1H), 6.63 (d, J=3.3 Hz, 1H), 6.50 (dd, J=1.8, 3.3 Hz, 1H), 6.11 (m, 1H), 5.38 (br d, J= 18.0 Hz, 1H), 5.26 (br d, J=10.2 Hz, 1H), 4.76 (br d, J= 6.3 Hz, 2H).

5.1.15. 3-(2-Methyl)-allyloxy-6-chloro-2-(2-furan-2-yl-vinyl)-chromen-4-one, 30. Pale yellow solid (2.31 g, 65%), mp 125–126 °C; [Found: C, 66.29; H, 4.17. $C_{19}H_{15}ClO_4$ requires C, 66.58; H, 4.41]; λ_{max} MeOH 342, 258 nm; ν_{max} (cm^{-1}) 1642 (C═O), 1626 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J=2.4 Hz, 1H), 7.56 (dd, J= 8.8, 2.4 Hz, 1H), 7.48 (d, J=1.6 Hz, 1H), 7.41 (d, J= 8.8 Hz 1H), 7.26 (d, J=15.6 Hz, 1H), 7.17 (d, J=15.6 Hz, 1H), 6.63 (d, J=3.6 Hz, 1H), 6.51 (dd, J=1.6, 3.6 Hz, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 4.63 (s, 2H), 1.90 (s, 3H).

5.2. Photoirradiation of chromones 5–9 and 27–30

5.2.1. Photoirradiation of 6-chloro-3-methoxy-2-styryl-chromen-4-one, 5. A deoxygenated solution of **5** (600 mg) in dry MeOH (75 mL) was irradiated in a pyrex reactor under N_2 atmosphere for 90 min. The removal of solvent under reduced pressure yielded a red gummy viscous mass that was chromatographed over silica gel. The column was eluted with increasing proportion of benzene in pet. ether–benzene mixture yielding **10**, **11** and **12**.

Compound **10**. Pale yellow solid (63 mg, 14%), mp 152 °C. [Found: C, 68.83; H, 4.48. $C_{18}H_{13}ClO_3$ requires C, 69.13; H, 4.19]; ν_{max} (cm^{-1}) 1640 (C═O), 1620 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J=2.7 Hz, 1H), 7.43 (dd, J= 2.7, 9.0 Hz, 1H), 7.35 (m, 5H), 6.73 (d, J=9.0 Hz, 1H), 6.76 (d, J=12.0 Hz, 1H), 7.04 (d, J=12.0 Hz, 1H), 3.98 (s, 3H); *m/z* 312 (M^+, 100%).

Compound **11**. Creamy solid (32 mg, 7%), mp 112–114 °C; [Found: C, 69.43; H, 4.48. $C_{18}H_{13}ClO_3$ requires C, 69.13; H, 4.19]; λ_{max} MeOH 338, 253 nm; ν_{max} (cm^{-1}) 1693 (C═O), 1618 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J= 2.0 Hz, 1H), 7.65–7.20 (m, 8H), 6.87 (d, J=16.0 Hz, 1H), 5.05 (s, 1H), 5.02 (d, J=7.0 Hz, 1H), 4.82 (d, J=7.0 Hz, 1H); *m/z* 312 (M^+, 23%).

Compound **12**. Pale yellow solid (41 mg, 10%), mp 145–146 °C; [Found: C, 72.62; H, 3.48. $C_{17}H_{11}ClO_2$ requires C, 72.22; H, 3.92]; λ_{max} MeOH 334 nm; ν_{max} (cm^{-1}) 1640 (C═O), 1615 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 815 (d, J=2.0 Hz, 1H), 7.74 (d, J=15.0 Hz, 1H), 7.65 (m, 8H), 6.30 (s, 1H).

5.2.2. Photoirradiation of 3-benzyloxy-6-chloro-2-styryl-chromen-4-one, 6. A benzene solution of **6** (600 mg, 22 mmol) on photolysis for 3 h furnished **13**.

Compound **13**. White solid (45 mg, 10%), mp 210–211 °C; [Found: C, 74.43; H, 4.68. $C_{24}H_{17}ClO_3$ requires C, 74.13; H, 4.41]; λ_{max} MeOH 333, 287, 237 nm; ν_{max} (cm^{-1}) 1640 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J=2.0 Hz, 1H), 7.65 (dd, J=8.0, 2.0 Hz, 1H), 7.20 (m, 11H), 5.05 (d, J=7.0 Hz, 1H), 3.35 (m, 1H), 3.15 (d, J=8.0 Hz, 2H); *m/z* 388 (M^+ 18%).

5.2.3. Photoirradiation of 3-allyloxy-6-chloro-2-styryl-chromen-4-one, 7. A methanolic solution of **7** (1.0 g) on photolysis for 1 h furnished **14**, **15** and **16**.

Compound **14**. White solid (105 mg, 15%), mp 118–120 °C; [Found: C, 70.48; H, 4.18. $C_{20}H_{15}ClO_3$ requires C, 70.90; H, 4.46]; ν_{max} (cm^{-1}) 1642 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, J=2.6 Hz, 1H), 7.49 (dd, J=2.6, 9.0 Hz, 1H), 7.33–7.17 (m, 6H), 5.76–5.57 (m, 1H), 5.24 (d, J= 17.2 Hz, 1H), 5.08 (d, J=10.6 Hz, 1H), 4.53 (t, J=6.8, 7.2 Hz, 1H), 3.26–3.11 (m, 1H), 3.09–2.99 (m, 2H); *m/z* 338 (M^+, 100%).

Compound **15**. Pale yellow solid (42 mg, 6%), mp 98–100 °C; [Found: C, 70.57; H, 4.72. $C_{20}H_{15}ClO_3$ requires C, 70.90; H, 4.46]; λ_{max} MeOH 367, 294 nm; ν_{max} (cm^{-1}) 1610 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J= 2.0 Hz, 1H), 7.44 (dd, J=2.0, 9.0 Hz, 1H), 7.20–7.10 (m, 6H), 6.95 (d, J=9.0 Hz, 1H), 6.50 (d, J=16.0 Hz, 1H), 6.45 (d{t}, J=6.0{1.5}Hz, 1H), 5.10 (m, 1H), 3.90 (s, 1H), 3.10 (br d, J=1.5 Hz, 2H); *m/z*338 (M^+, 100%).

Compound **16**. White solid (28 mg, 4%), mp 118–120 °C; [Found: C, 70.62; H, 4.18. $C_{20}H_{15}ClO_3$ requires C, 70.90; H, 4.46]; λ_{max} MeOH 339 nm; ν_{max} (cm^{-1}) 1700 (C═O), 1615 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J=2.0 Hz, 1H), 7.30 (s, 5H), 7.05 (dd, J=2.0, 9.0 Hz, 1H), 6.50 (d, J= 12.0 Hz, 1H), 6.45 (d{t}, J=6.0, 1.5 Hz, 1H), 5.95 (d, J= 9.0 Hz, 1H), 5.70 (d, J=12.0 Hz, 1H), 4.85 (m, 1H), 4.70 (s, 1H), 2.90 (m, 2H).

5.2.4. Photoirradiation of 3-(2-methyl)-allyloxy-6-chloro-2-styryl-chromen-4-one, 8. A methanolic solution of **8** (1.0 g) on photolysis for 1 h furnished **17** and **18**.

Compound **17**. White solid (71 mg, 12%), mp 190–192 °C; [Found: C, 71.01; H, 4.48. $C_{21}H_{17}ClO_3$ requires C, 71.49; H, 4.86]; ν_{max} (cm^{-1}) 1642 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, J=2.6 Hz, 1H), 7.48 (dd, J=2.6, 9.0 Hz, 1H), 7.31–7.13 (m, 6H), 4.79 (d, J=4.0 Hz, 2H), 4.47 (d, J=9.2 Hz, 1H), 3.33–3.12 (m, 1H), 3.01 (dd, J=2.8, 8.2 Hz, 2H), 1.64 (s, 3H); *m/z* 352 (M^+, 100%).

Compound **18**. Pale yellow solid (73 mg, 12%), mp 88–90 °C; [Found: C, 71.19; H, 5.24. $C_{21}H_{17}ClO_3$ requires C, 71.49; H, 4.86]; λ_{max} MeOH 297, 265 nm; ν_{max} (cm^{-1}) 1615 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J= 2.0 Hz, 1H), 7.44 (dd, J=2.0, 9.0 Hz, 1H), 7.20–7.10 (m, 6H), 6.95 (d, J=9.0 Hz, 1H), 6.50 (d, J=16.0 Hz, 1H), 6.35 (m, 1H), 3.90 (s, 1H), 3.10 (s, 2H), 1.72 (s, 3H); *m/z* 352 (M^+, 100%).

5.2.5. Photoirradiation of 3-(3-methyl)-allyloxy-6-chloro-2-styryl-chromen-4-one, 9. A methanolic solution of **9** (1.0 g) on photolysis for 1 h furnished **20**, **21**and **22**.

Compound **20**. White solid (66 mg, 11%), mp 187–189 °C; [Found: C, 71.73; H, 5.63. $C_{22}H_{19}ClO_3$ requires C, 72.03; H, 5.22]; ν_{max} (cm^{-1}) 1640 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, J=2.0 Hz, 1H), 7.64 (dd, J=2.0, 9.0 Hz,

1H), 7.50–7.30 (m, 6H), 5.25 (d, 1H), 4.85–4.83 (m, 1H), 3.10–3.00 (m, 3H), 1.55 (s, 3H), 1.45 (s, 3H); *m/z* 366 (M^+, 100%).

Compound **21**. Pale yellow solid (60 mg, 10%), mp 80–82 °C; [Found: C, 71.92; H, 5.03. $C_{22}H_{19}ClO_3$ requires C, 72.03; H, 5.22]; λ_{max} MeOH 295, 268 nm; ν_{max} (cm^{-1}) 1612 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J= 2.0 Hz, 1H), 7.29 (dd, J=2.0, 9.0 Hz, 1H), 7.16 (m, 6H), 6.80 (d, J=9.0 Hz, 1H), 6.50 (d, J=16.0 Hz, 1H), 6.35 (d, J=6.0 Hz, 1H), 4.73 (d, J=6.0 Hz, 1H), 3.85 (s, 1H), 1.45 (s, 3H), 1.32 (s, 3H); *m/z* 366 (M^+, 100%).

Compound **22**. White solid (31 mg, 5%), mp 115–117 °C; [Found: C, 71.73; H, 5.56. $C_{22}H_{19}ClO_3$ requires C, 72.03; H, 5.22]; ν_{max} (cm^{-1}) 1698 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J=2.0 Hz, 1H), 7.46 (dd, J=2.0, 9.0 Hz, 1H), 7.24–7.20 (m, 5H), 7.07 (d, J=8.7 1H), 6.48 (d, J=16.2 Hz, 1H), 6.12 (d, J=16.2 Hz, 1H), 6.42 (d, J=6.0 Hz, 1H), 5.07 (s, 1H), 4.73 (d, J=6.0 Hz, 1H), 1.42 (s, 3H), 1.27 (s, 3H).

5.2.6. Photoirradiation of 3-allyloxy-6-chloro-2-(2-thiophen-2-yl-vinyl)-chromen-4-one, 27. A benzene solution of **27** (1.0 g) on photolysis for 1 h furnished **31**

Compound **31**. Pale yellow solid (61 mg, 10%), mp 128–30 °C; [Found: C, 62.27; H, 3.38. $C_{18}H_{13}ClO_3S$ requires C, 62.70; H, 3.80]; λ_{max} THF (ε) 407 nm (11700), 379 nm (14300), 315 nm (21400), 229 nm (25500); ν_{max} (cm^{-1}) 3630 (OH), 1633 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 11.68 (s, 1H), 7.70 (d, J=2.4 Hz, 1H), 7.43 (dd, J=2.4, 8.9 Hz, 1H), 7.17 (d, J=4.8, 1.0 Hz, 1H), 7.01 (d, J=1.0, 3.4 Hz, 1H), 6.98 (d, J=8.9 Hz, 1H), 6.95 (dd, J=4.8, 3.4 Hz, 1H), 6.93 (d, J=15.8 Hz, 1H), 6.65 (d, J=15.8 Hz, 1H), 6.51 (t{d}, J=1.2, 5.4 Hz, 1H), 5.12 (t{d}, J=3.0, 5.4 Hz, 1H), 3.11 (dd, J=1.2, 3.0 Hz, 2H); *m/z* 344 (M^+, 100%).

5.2.7. Photoirradiation of 3-(2-methyl)-allyloxy-6-chloro-2-(2-thiophen-2-yl-vinyl)-chromen-4-one, 28. A benzene solution of **28** (1.0 g) on photolysis for 1 h furnished **32**.

Compound **32**. Pale yellow solid (55 mg, 10%), mp 118–20 °C; [Found: C, 63.27; H, 4.47. $C_{19}H_{15}ClO_3S$ requires C, 63.59; H, 4.21]; λ_{max} THF (ε) 410 nm (11900), 380 nm (11400), 318 nm (28000), 228 nm (26900). ν_{max} (cm^{-1}) 3610 (OH), 1630 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 11.71 (s, 1H), 7.68 (d, J=2.6 Hz, 1H), 7.43 (dd, J=2.6, 8.9 Hz, 1H), 7.17 (d, J=4.9 Hz, 1H), 7.01 (d, J=3.3 Hz, 1H), 6.99 (d, J=15.9 Hz, 1H), 6.97 (d, J=8.9 Hz, 1H), 6.95 (dd, J=4.9, 3.3 Hz, 1H), 6.70 (d, J=15.9 Hz, 1H), 6.39 (d, J=1.4 Hz, 1H), 2.99 (br s, 2H), 1.73 (s, 3H); *m/z* 358 (M^+, 100%).

5.2.8. Photoirradiation of 3-allyloxy-6-chloro-2-(2-furan-2-yl-vinyl)-chromen-4-one, 29. A benzene solution of **29** (1.0 g) on photolysis for 1 h furnished **33**.

Compound **33**. Pale yellow solid (24 mg, 4%), mp 130 °C; [Found: C, 65.38; H, 3.59. $C_{18}H_{13}ClO_4$ requires C, 65.76; H, 3.99]; λ_{max} MeOH 310 nm; ν_{max} (cm^{-1}) 3434 (OH), 1628 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J=2.7 Hz, 1H), 7.43 (dd, J=2.7, 9.0 Hz, 1H), 7.43 (d, J=1.2 Hz, 1H), 7.01 (d, J=15.9 Hz, 1H), 6.98 (d, J=9.0 Hz, 1H), 6.50 (d{t}, J=6.0{1.5} Hz, 1H), 6.36 (dd, J=1.8, 3.6 Hz, 1H), 6.32 (d, J=15.9 Hz, 1H), 6.30 (d, J=3.3 Hz, 1H), 5.14–5.12 (m, 1H), 3.90 (br s, 1H), 3.07 (br s, 2H); *m/z* 328 (M^+, 100%).

5.2.9. Photoirradiation of 3-(2-methyl)-allyloxy-6-chloro-2-(2-furan-2-yl-vinyl)-chromen-4-one, 30. A benzene solution of **30** (1.0 g) on photolysis for 1 h furnished **34**.

Compound **34**. Pale yellow solid (30 mg, 5%), mp 118–120 °C; [Found: C, 66.29; H, 4.19. $C_{19}H_{15}ClO_4$ requires C, 66.58; H, 4.41]; λ_{max} MeOH 307 nm; ν_{max} (cm^{-1}) 3428 (OH), 1629(C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J=2.7 Hz, 1H), 7.44 (dd, J=2.7, 9.0 Hz, 1H), 7.35 (d, J= 0.9 Hz, 1H), 7.05 (d, J=15.9 Hz, 1H), 6.97 (d, J=9.0 Hz, 1H), 6.38–6.37 (m, 2H), 6.37 (d, J=15.9 Hz, 1H), 6.31 (d, J=3.0 Hz, 1H), 3.90 (s, 1H), 2.96 (br s, 2H), 1.72 (s, 3H); *m/z* 342 (M^+, 100%).

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An efficient approach to isoindolo[2,1-*b*][2]benzazepines via intramolecular [4+2] cycloaddition of maleic anhydride to 4-α-furyl-4-*N*-benzylaminobut-1-enes

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Abstract—Acylation of 4-α-furyl-4-*N*-benzylaminobut-1-enes with maleic anhydride gave 4-oxo-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid via amide formation followed by intramolecular Diels–Alder reaction of furan (IMDAF). The cycloaddition proceeded under mild reaction conditions (25 °C) and provided only the *exo*-adduct in quantitative yield. Treatment of this compound with PPA gave isoindolo[2,1-*b*][2]benzazepine derivatives via ring opening, aromatization and intramolecular electrophilic alkylation. In order to extend the scope of the reaction sequence, 7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acids were further transformed into useful synthetic intermediates.

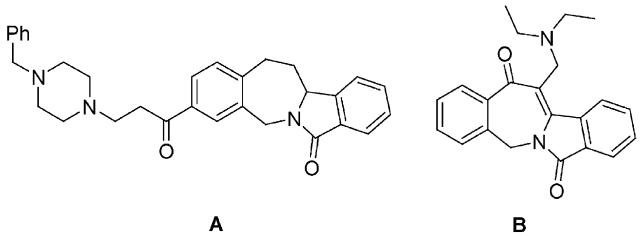
1. Introduction

Compounds with the isoindolo[2,1-*b*][2]benzazepine core are known to have important biological activities.[1,2] For example, 5,11b,12,13-tetrahydro-3-[1-oxo-3[1-(phenylmethyl)-4-piperidinyl]propyl]-7*H*-isoindolo[2,1-*b*][2]benzazepine-7-one (**A**) and 12-diethylaminomethyl-5*H*-isoindolo[2,1-*b*][2]benzazepine-7,13-dione (**B**) are known to have AChE-inhibiting activity[1a] and a protective effect against nitrogen-induced hypoxia[2] respectively (Scheme 1).

Although compounds with the isoindolo[2,1-*b*][2]benzazepine moiety show interesting biological properties, to the best of our knowledge, only two synthetic routes to isoindolo[2,1-*b*][2]benzazepines have been reported in the literature. The first route is based on the intramolecular Friedel–Crafts acylation of 2,3-dihydro-3-oxo-2-(phenylmethyl)-1*H*-isoindol-1-acetic acids[2] whereas the second one utilized the π-cyclization of *N*-acyliminium ions generated from *N*-alkenyl-3-hydroxyisoindolin-1-ones.[3] Both approaches involve many steps and yielded the desired products in moderate yields. Recently,[4] we reported a synthetic approach to substituted oxoisoindolo[2,1-*a*]quinolines from 4-α-furyl-4-*N*-arylaminobut-1-ens (homoallylamines) using an intramolecular Diels–Alder reaction of furan as the key transformation. As part of our continuing effort to investigate the reactivity of homoallylfuryl amines,[5] we extended this approach to prepare various polycyclic nitrogen heterocycles. In this paper we describe a three-step protocol for the synthesis of 7-oxotetrahydroisoindolo[2,1-*b*][2]benzazepine-8-carboxylic acids **5a-e** from readily available 4-α-furyl-4-*N*-benzylaminobut-1-enes **3a-e** (Scheme 2).

2. Results and discussion

The starting 4-*N*-benzylaminobut-1-enes **3a-e** were readily obtained by a two-step one-pot procedure.[5c] Condensation of benzylamines **1** with furaldehydes **2** gave the intermediate imines, which were immediately treated with



Scheme 1.

Keywords: Homoallylamines; Isoindolobenz-2-azepines; Intramolecular Diels–Alder reaction; IMDAF; Intramolecular electrophilic alkylation.
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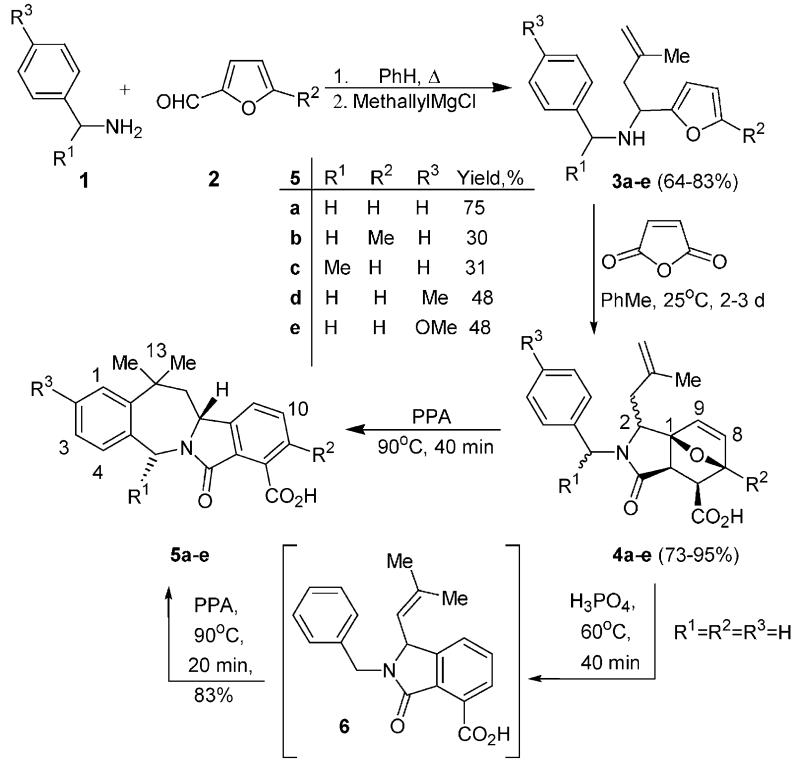


5	R^1	R^2	R^3	Yield,%
a	H	H	H	75
b	H	Me	H	30
c	Me	H	H	31
d	H	H	Me	48
e	H	H	OMe	48

Scheme 2.

methallylmagnesium chloride to provide the desired amines **3a**-**e** in good overall yields (Scheme 2). It is noteworthy that the α-methylbenzylamine derivative **3c** was isolated as a 1:1.1 mixture of diastereoisomers with (R^*,R^*)- and (R^*,S^*)-oriented methallyl and CH_3 (R^1) groups.

The reaction of homoallylamines **3a**-**e** with maleic anhydride[6] proceeded smoothly (toluene, rt, 2–3 days) to give the corresponding 3-benzyl-2-methallyl-3-aza-10-oxatricyclo [5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acids **4a**-**e** as a ~1:1 mixture of isomers at C-2. The products are formed via an initial *N*-acylation followed by the IMDA cycloaddition reaction sequence. The IMDA cycloaddition reaction was highly stereoselective and furnished only the *exo*-cycloadducts **4a**-**e**. Under the acylation reaction conditions, amine **3c** with two stereogenic centers gave a 1:5:10 mixture of *exo*-isomers, determined from the ^{1}H NMR spectrum of the crude product. No additional experiment was carried out to establish the relative stereochemistry of compound **4c**. The *exo*-configuration of Diels–Alder adducts **4a**,**c**-**e** (R^2=H) was confirmed by comparing the $^3J_{6\text{-H},7\text{-H}}$ value of compounds **4a**,**c**-**e** with the analogous bridged systems reported in the literature.[7] The reported $^3J_{6\text{-H},7\text{-H}}$ value for 6-H in molecules with an *endo*-orientation is <1 Hz whereas, the $^3J_{6\text{-H},7\text{-H}}$ value for 6-H in molecules with an *exo*-orientation is around 3 Hz. So the observed coupling constants for compounds **4a**,**c**-**e** ($^3J_{6\text{-H},7\text{-H}}$=0–0.8 Hz) unambiguously proves the *endo*-orientation of 6-H (and 5-H correspondingly). The stereochemistry of adducts **4b** (R^2=Me) can be surmised by analogy with compounds **4a**,**c**-**e**. We were unable to separate the isomer mixtures due to the insoluble nature of compound **4** in commonly used solvents.

Having successfully isolated compounds **4a**-**e** in high yields, we then proceeded to study the acid promoted ring opening/ ring forming sequence. Treatment of epoxyisoindolines **4a**-**e** with excess polyphosphoric acid (PPA) at 90 °C for 40 min smoothly promoted a 1,7-oxygen bridge opening/ aromatization/ intramolecular electrophilic cyclization sequence to give the isoindolobenzazepine carboxylic acids **5a**-**e** in 30–75% yields (Scheme 2). Treatment of compound **4a** with H_3PO_4 at 60 °C gave a mixture of the cyclized compound **5a** and the uncyclized double bond migration product **6** (~1:2). Isolation of intermediate **6** shows that the reaction sequence involves an initial cleavage of the 1,7-oxygen bridge followed by aromatization to give **6**. Electrophilic cyclization of pure isoindolone **6** under the action of PPA at 90 °C proceeds via formation of the thermodynamically stable tertiary carbocation and yields isoindolobenzazepine **5a** in 83% yield.

Compounds **5a**,**b**,**d**,**e** exist in the form of one conformer with the pseudo-axial orientation of 11b-H, as evidenced by ^{1}H NMR spectroscopic data. In particular, the vicinal coupling constant values $J_{11b,12A(ax)}$=12.0–14.0 Hz and $J_{11b,12B(eq)}$=2.5–2.9 Hz unambiguously prove the pseudo-axial orientation of 11b-H. Although heating isomeric mixtures of compound **4c** (R^1=Me) with PPA could lead to a mixture of two stereoisomers of compound **5c** (*cis*- and *trans*-configurations of the methyl group at C-5 and the proton at C-11b), to our surprise, acid **5c** was isolated as a single *cis*-isomer with the pseudo-equatorial orientation of the 5-CH_3 group and the pseudo-axial of the 11b proton.

The *cis*-structure of compound **5c** was confirmed by NOE. The NOE values (η) indicated an increase of H_i signal

intensity when H_j signal was saturated ($\eta_{Hi}\{H_j\}$, %). The values of $\eta_{11b\text{-}H}\{5\text{-}H\}=9.5\%$, on one hand, and $\eta_{5\text{-}H}\{11b\text{-}H\}=5\%$, on the other hand, proved that 11b-H and 5-H were situated on the one side of the benz-2-azepine ring plane.

The carboxylic acids **5a**-**e** are crystalline with high melting points and insoluble in most of the commonly used organic solvents. The low (~30%) yield of cyclization products **5b** and **5c** is explained by considerable resinification of reaction mixtures and losses during recrystallization from the *i*-PrOH–DMF mixture. Probably, the second (minor) *trans*-isomer of **5c** could be lost at the purification stage of the reaction mixture.

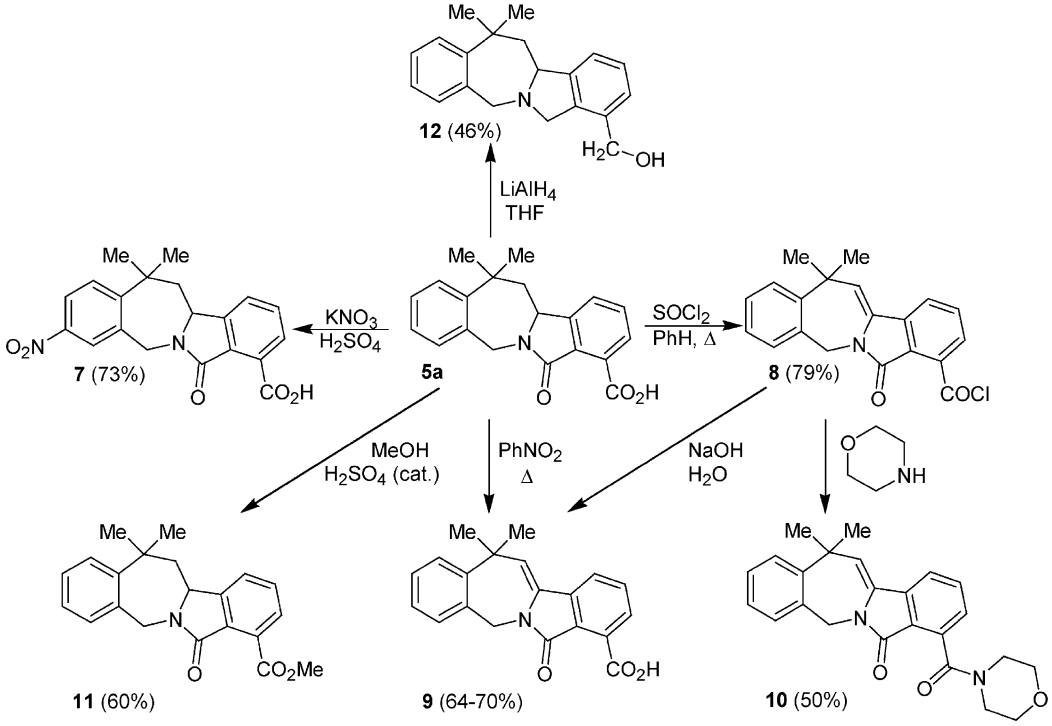
Having developed an efficient simple synthetic route for the isoindolo[2,1-*b*][2]benzazepine system, we turned our attention to further functionalize the system to make the reaction sequence synthetically useful. Accordingly, compound **5a** was chosen as the test substrate and subjected to various reaction conditions and the results are shown in Scheme 3.

As far as we know there is only one example of the aromatic electrophilic substitution of 7-oxoisoindolo[2,1-*b*][2]benzazepines.[8] The authors regioselectively acylated isoindolobenzazepines at the C-3 position with AcCl/$AlCl_3$ in boiling dichloroethane. Unfortunately, our attempts to acylate the isoindolobenzazepine carboxylic acid **5a** with excess Ac_2O/$AlCl_3$ in dichloromethane (or AcCl/$AlCl_3$ in dichloroethane or nitrobenzene) using the published procedure[8] met with failure.

Treatment of **5a** with potassium nitrate and concentrated sulfuric acid afforded the 3-nitro substituted azepine **7** as a single compound in 73% yield. The structure of compound **7** was confirmed by ^{1}H NMR spectroscopy, based on the multiplicities of proton signals of the nitro substituted benzene ring, and NOE values for the same protons. High NOE values were measured for the doublet signal δ 7.69 ($J_{ortho}=8.9$ Hz, NOE=13%) with 13-CH_3 saturation (δ 1.50), and for the doublet signal δ 8.30 ($J_{meta}=2.7$ Hz, NOE=18%) with 5-H_A saturation (δ 5.37) thus proving 1 and 4 position of the above mentioned aromatic protons, and 3 nitro substituent position.[9]

Heating acid **5a** in $PhNO_2$ smoothly oxidized the ring to give compound **9**. Heating compound **5a** with thionyl chloride in benzene gave the unexpected ring oxidized acid chloride **8**. We suppose, that the dehydrogenation occurs due to an oxidative action of $SOCl_2$ itself or products of its decomposition (SO_2, Cl_2). Several examples of similar dehydrogenation exist in the literature,[10] but in all cases the oxidation was carried out under basic conditions (pyridine, picoline). The structure of the acid chloride **8** was confirmed by ^{1}H and ^{13}C NMR spectra and by conversion into compound **9** by hydrolysis of acid chloride **8** with NaOH. The amide **10** and ester **11** were prepared from the acid chloride **8** and acid **5a**, respectively, in moderate yields. The reduction of **5a** with 8 mol equiv. lithium aluminum hydride in boiling THF gave alcohol **12** (Scheme 3).

In conclusion, this paper describes a simple and efficient synthetic approach to isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acids. The synthetic route involves intramolecular Diels–Alder cycloaddition of 4-α-furyl-4-*N*-benzylaminobut-1-enes with maleic anhydride followed by PPA acid-promoted intramolecular seven-membered ring formation sequence. This two-step synthetic sequence is very efficient and yielded the tetracyclic compounds in high



Scheme 3.

yields. Further functionalization of the acid was also examined. Considering the mild reaction conditions, and stereochemical control associated with the IMDA cycloaddition/ acid promoted cyclization reaction sequence, we believe that this methodology could be of use in organic synthesis for the preparation of polycyclic drug- and natural product-like molecules.

3. Experimental

All reagents were purchased from Acros Chemical Co. All solvents were used without further purification. Melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a UR-20 spectrometer in KBr pellets for solid or in thin film for oils. ^{1}H NMR spectra were recorded on a Bruker WP-200 or WH-400 spectrometers for solutions (2%) in deuteriochloroform or DMSO-D_6 at 30 °C and using TMS as internal standard. Chemical shifts are reported in ppm units, and coupling constants (J) are quoted in Hz. Abbreviations of coupling patterns: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), ddd (doublet doublet of doublets), ddt (doublet doublet of triplets), m (multiplet). Mass spectra were obtained by electron impact at 70 eV on a Varian MAT-112 spectrometer or Finnegan MAT95XL chromatomass spectrometer. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC silufol UV_{254} plates.

3.1. 4-(2-Furyl)-4-*N*-benzylaminobut-1-enes 3. Typical procedure

The freshly obtained[5c,9] aldimine (0.30 mol) was added slowly drop-wise at reflux to a stirred solution of methallylmagnesium chloride, prepared from methallyl chloride (41 mL, 0.45 mol) and magnesium turnings (22.0 g, 0.90 mol) in mixture THF–ether (1:1, 300 mL). After the addition of the Schiff base the reaction mixture was stirred for one hour at room temperature. The cooled reaction mixture was taken up in saturated aqueous NH_4Cl solution (300 mL) under ice cooling and extracted with ether (3×100 mL). The organic layer was dried $MgSO_4$ and concentrated. The residue was distilled in vacuo to give the products **3** as colourless oils.

3.1.1. 2-Methyl-4-(2-furyl)-4-*N*-benzylaminobut-1-ene (3a). Yield 83%; bp 158–160 °C/7 mm Hg; n_D^{20} 1.5350; IR 3320 (NH), and 1640 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 241 (1), 186 (50), 91 (100), 77 (32), 55 (9), 51 (16), 39 (22); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H, Me-2), 1.72 (brs, 1H, NH), 2.35–2.60 (m, 2H, H-3), 3.56 (d, 1H, NCH_AH$_B$, J=13.4 Hz), 3.77 (d, 1H, NCH$_A$$H_B$, J=13.4 Hz), 3.85 (dd, 1H, H-4, J=8.2, 6.4 Hz), 4.73 (brs, 1H, H-1), 4.79 (brs, 1H, H-1), 6.18 (dd, 1H, H-3′, J=3.1, 0.9 Hz), 6.31 (dd, 1H, H-4′, J=3.1, 1.8), 7.15–7.35 (m, 5H, Ph-H), 7.36 (dd, 1H, H-5′, J=1.8, 0.9). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.4 (C-2′), 142.2 (C$_{qu.}$-Ph), 141.4 (C-5′), 140.2 (C-2), 128.23 (2C, *orto*-Ph), 128.10 (2C, *meta*-Ph), 126.8 (*para*-Ph), 113.29 (C-1), 109.8 (C-3′), 106.4 (C-4′), 53.0 (C-4), 51.1 (CH_2N), 43.5 (C-3), 21.8 (Me-2). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.69; H, 7.86; N, 5.81.

3.1.2. 2-Methyl-4-(2-(5-methylfuryl))-4-*N*-benzylaminobut-1-ene (3b). Yield 34%; bp 158–159 °C/3 mm Hg; IR 3310 (NH), and 1640 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): [M−55 (–CH$_2$C(Me)=CH$_2$)]$^+$ 200 (57), 91 (100), 77 (8), 65 (15), 51 (10), 39 (20); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 3H, Me-2), 1.73 (brs, 1H, NH), 2.29 (brs, 3H, Me-5′), 2.41 (dd, 1H, H-3B, J=5.5, 13.8 Hz), 2.51 (dd, 1H, H-3A, J=8.9, 13.8 Hz), 3.57 (d, 1H, NCH_AH$_B$, J=13.4 Hz), 3.77 (dd, 1H, H-4, J=8.9, 5.5 Hz), 3.80 (d, 1H, NCH$_A$$H_B$, J=13.4 Hz), 4.76 (brs, 1H, H-1), 4.80 (brs, 1H, H-1), 5.89 (dq, 1H, H-4′, J=3.0, 1.0 Hz), 6.06 (d, 1H, H-3′, J=3.0 Hz), 7.17–7.37 (m, 5H, Ph–H). Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.00; H, 8.22; N, 5.47.

3.1.3. 2-Methyl-4-*N*-(α-methylbenzyl)-4-(2-furyl)aminobut-1-ene (3c). Mixture of two diastereoisomers in the ratio ~1:1.1, yield 79%; bp 150–155 °C/7 mm Hg; n_D^{20} 1.5274; IR 3305 (NH), and 1645 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): [M−55 (–CH$_2$C(Me)=CH$_2$)]$^+$ 200 (51), 105 (100), 96 (90), 79 (28), 77 (33), 55 (15), 41 (14), 39 (21); ^{1}H NMR ($CDCl_3$, 200 MHz) maj isomer δ 1.33 (d, 3H, *Me*CHN, J=6.5 Hz), 1.62 (s, 3H, Me-2), 1.68 (brs, 1H, NH), 2.43 (dd, 1H, H-3B, J=13.7, 7.1 Hz), 2.52 (dd, 1H, H-3A, J=13.7, 7.1 Hz), 3.74 (q, 1H, MeC*H*N, J=6.5 Hz), 3.90 (t, 1H, H-4, J=7.1 Hz), 4.68 (m, 1H, H-1), 4.75 (m, 1H, H-1), 6.06 (brd, 1H, H-3′, J=3.0, 0.8 Hz), 6.22 (dd, 1H, H-4′, J=3.0, 1.8 Hz), 7.29 (dd, 1H, H-5′, J=1.8, 0.8 Hz), 7.16–7.31 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.61 (C-2′), 145.74 (C$_{qu.}$-Ph), 142.2 (C-5′), 140.9 (C-2), 126.40 (2C, *ortho*-Ph), 128.10 (2C, *meta*-Ph), 126.58 (*para*-Ph), 113.0 (C-1), 109.7 (C-3′), 105.9 (C-4′), 55.1 (*C*HMe), 52.2 (C-4), 43.0 (C-3), 22.8 (CH*Me*), 22.1 (Me-2); min isomer δ 1.29 (d, 3H, *Me*CHNH, J=6.7 Hz), 1.45 (s, 3H, Me-2), 1.68 (brs, 1H, NH), 2.31 (dd, 1H, H-3B, J=13.5, 5.4 Hz), 2.45 (dd, 1H, H-3A, J=13.5, 9.1 Hz), 3.52 (dd, 1H, H-4, J=9.1, 5.4 Hz), 3.59 (q, 1H, MeC*H*N, J=6.7 Hz), 4.72 (m, 1H, H-1), 4.78 (m, 1H, H-1), 6.06 (brd, 1H, H-3′, J=3.0, 0.7 Hz), 6.29 (dd, 1H, H-4′, J=3.0, 1.7 Hz), 7.36 (dd, 1H, H-5′, J=1.7, 0.7 Hz), 7.16–7.31 (m, 5H, Ph-H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.56 (C-2′), 145.23 (C$_{qu.}$-Ph), 142.1 (C-5′), 141.2 (C-2), 126.48 (2C, *ortho*-Ph), 128.18 (2C, *meta*-Ph), 126.7 (*para*-Ph), 113.2 (C-1), 109.6 (C-3′), 106.2 (C-4′), 55.0 (*C*HMe), 51.0 (C-4), 43.9 (C-3), 24.5 (CH*Me*), 21.6 (Me-2); Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.02; H, 8.25; N, 5.50.

3.1.4. 2-Methyl-4-*N*-(4-methylbenzyl)-4-(2-furyl)aminobut-1-ene (3d). Yield 75%; bp 147–148 °C/2 mm Hg; n_D^{22} 1.5315; IR 3320 (NH), and 1645 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): [M−55 (–CH$_2$C(Me)=CH$_2$)]$^+$ 200 (31), 105 (100), 95 (18), 94 (13), 91 (22), 79 (21), 77 (26), 65 (11), 39 (35); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 3H, Me-2), 1.78 (brs, 1H, NH), 2.34 (s, 3H, *Me*-Ar), 2.43 (dd, 1H, H-3B, J=13.7, 5.7 Hz), 2.53 (ddd, 1H, H-3A, J=13.7, 8.7, 0.7 Hz), 3.52 (d, 1H, NCH_AH$_B$, J=13.0 Hz), 3.76 (d, 1H, NCH$_A$$H_B$, J=13.0 Hz), 3.85 (dd, 1H, H-4, J=8.7, 5.7 Hz), 4.75 (d, 1H, H-1, J=0.7 Hz), 4.80 (brs, 1H, H-1), 6.20 (brd, 1H, H-3′, J=3.0 Hz), 6.34 (dd, 1H, H-4′, J=3.0, 1.7 Hz), 7.13 (BB′, 2H, H-Ar), 7.16 (AA′, 2H, H-Ar), 7.39 (dd, 1H, H-5′, J=1.7, 0.7 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.3 (C-2′), 142.0 (C$_{qu.}$–C_6H_4Me), 141.2 (C-5′), 137.0 (C$_{qu.}$–C_6H_4Me), 136.1 (C-2), 128.8 (2C,

ortho-C_6H_4Me), 127.9 (2C, *meta*-C_6H_4Me), 113.1 (C-1), 109.7 (C-3′), 102.2 (C-4′), 50.7 (CH_2N), 52.8 (C-4), 43.3 (C-3), 20.9 ($C_6H_4\mathit{Me}$), 22.7 (Me-2); Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.00; H, 8.28; N, 5.52.

3.1.5. 2-Methyl-4-*N*-(4-methoxybenzyl)-4-(2-furyl)aminobut-1-ene (3e). Yield 71%; bp 162 °C/2 mm Hg; n_D^{22} 1.5381; IR 3310 (NH), and 1645 (C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): $[M-55\ (-CH_2C(Me)=CH_2)]^+$ 216 (28), 121 (100), 91 (11), 77 (18), 65 (8), 55 (7), 39 (12); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (brs, 3H, Me-2), 1.81 (brs, 1H, NH), 2.43 (brdd, 1H, H-3B, $J=13.7$, 5.9 Hz), 2.52 (dd, 1H, H-3A, $J=13.7$, 8.7 Hz), 3.50 (d, 1H, NCH_AH_B, $J=13.1$ Hz), 3.73 (d, 1H, NCH_AH_B, $J=13.1$ Hz), 3.79 (s, 3H, OMe), 3.84 (dd, 1H, H-4, $J=8.7$, 5.9 Hz), 4.74 (m, 1H, H-1), 4.80 (m, 1H, H-1), 6.20 (dd, 1H, H-3′, $J=3.2$, 0.8 Hz), 6.33 (dd, 1H, H-4′, $J=3.2$, 1.8 Hz), 6.85 (BB′, 2H, H-Ar), 7.18 (AA′, 2H, H-Ar), 7.39 (dd, 1H, H-5′, $J=1.8$, 0.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 158.5 ($C_{qu.}$–C_6H_4OMe), 156.4 (C-2′), 142.1 ($C_{qu.}$–C_6H_4OMe), 141.3 (C-5′), 132.2 (C-2), 129.2 (2C, *ortho*-C_6H_4OMe), 113.6 (2C, *meta*-C_6H_4OMe), 113.2 (C-1), 109.7 (C-3′), 106.3 (C-4′), 55.0 (MeO), 50.5 (CH_2N), 52.8 (C-4), 43.4 (C-3), 21.8 (Me-2); Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.49. Found: C, 75.29; H, 7.72; N, 5.19.

3.2. 4-Oxo-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acids (4). Typical procedure

Corresponding amine **3** (0.1 mol) was dissolved in 150 mL of toluene and an equimolar amount of maleic anhydride (0.1 mol, 9.8 g) was added in one portion. Reaction mixture was stirred for 30–60 h at room temperature and then crystalline product was filtered off, washed with toluene (2×100 mL), ether (2×80 mL) and dried at 100 °C to give desired products **4** as white solids.

3.2.1. 3-Benzyl-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4a). Ratio of isomers **A/B** ~1:1.6; yield 95%; mp 169–170 °C; IR 1710 (COOH), and 1640 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 339 (2), 284 (10), 204 (8), 194 (7), 120 (6), 99 (12), 91 (100), 78 (16), 65 (16), 51 (8), 39 (10); ^1H NMR ($CDCl_3$, 200 MHz) isomer **A** δ 1.71 (s, 3H, Me-2′), 2.40–2.55 (m, 2H, H-3′), 2.83 (d, 1H, H-6, $J=9.2$ Hz), 3.04 (d, 1H, H-5, $J=9.2$ Hz), 3.95 (dd, 1H, H-2, $J=8.2$, 5.5 Hz), 4.08 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 4.82 (brs, 1H, H-1′), 4.92 (brs, 1H, H-1′), 5.09 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 5.25 (d, 1H, H-7, $J=1.5$ Hz), 6.35 (dd, 1H, H-8, $J=5.8$, 1.5 Hz), 6.48 (d, 1H, H-9, $J=5.8$ Hz), 7.15–7.45 (m, 5H, H-Ph), 11.03 (brs, 1H, COOH); isomer **B** δ 1.71 (s, 3H, Me-2′), 2.40–2.55 (m, 2H, H-3′), 2.83 (d, 1H, H-6, $J=9.2$ Hz), 2.89 (d, 1H, H-7, $J=9.2$ Hz), 4.10 (dd, 1H, H-3, $J=8.1$, 6.6 Hz), 4.19 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 4.71 (brs, 1H, H-1′), 4.82 (brs, 1H, H-1′), 4.95 (d, 1H, CH_AH_BN, $J=15.0$ Hz), 5.29 (s, 1H, H-7), 6.28 (s, 2H, H-8 and H-9), 7.15–7.45 (m, 5?, H-Ph), and 11.03 (brs, 1H, COOH). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 74.80; H, 6.20; N, 4.13. Found: C, 74.80; H, 6.21; N, 4.10.

3.2.2. 3-Benzyl-7-methyl-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4b). Ratio of isomers **A/B** ~1:2; yield 89%; mp 174.5–175 °C; IR 1730 (COOH), and 1650 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 353 (10), 309 (3), 298 (53), 262 (23), 254 (6), 208 (10), 149 (15), 131 (5), 106 (10), 99 (20), 91 (100), 65 (18), 55 (13); ^1H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.69 (s, 6H, Me-2′ and Me-7), 2.31 (dd, 1H, H-3′A, $J=15.3$, 8.7 Hz), 2.50 (dd, 1H, H-3′B, $J=15.3$, 5.2 Hz), 2.83 (d, 1H, H-6, $J=8.7$ Hz), 3.09 (d, 1H, H-5, $J=8.7$ Hz), 3.96 (dd, 1H, H-2, $J=8.7$, 5.2 Hz), 4.11 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 4.82 (brs, 1H, H-1′), 4.91 (brs, 1H, H-1′), 5.10 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 6.12 (d, 1H, H-8, $J=5.7$ Hz), 6.54 (d, 1H, H-9, $J=5.7$ Hz), 7.20–7.35 (m, 5H, H-Ph), 9.38 (brs, 1H, COOH); isomer **B** δ 1.69 (s, 6H, Me-2′ and Me-7), 2.50 (m, 2H, H-3′), 2.82 (d, 1H, H-6, $J=8.6$), 2.93 (d, 1H, H-5, $J=8.6$ Hz), 3.98 (m, 1H, H-3), 4.15 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 4.71 (brs, 1H, H-1′), 4.80 (brs, 1H, H-1′), 5.01 (d, 1H, CH_AH_BN, $J=15.6$ Hz), 6.06 (d, 1H, H-8, $J=5.6$ Hz), 6.33 (d, 1H, H-9, $J=5.6$ Hz), 7.20–7.35 (m, 5H, H-Ph), 9.38 (brs, 1H, COOH). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.50; N, 3.97. Found: C, 71.39; H, 6.51; N, 3.98.

3.2.3. 2-Methallyl-4-oxo-3-(α-phenylethyl)-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4c). Ratio of isomers **A/B/C** ~10:5:1; yield 73%; mp 212–215 °C; IR 1730 (COOH), and 1660 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 353 (2), 298 (6), 186 (10), 120 (14), 105 (100), 96 (28), 91 (36), 77 (18), 65 (12), 51 (6), 39 (10); ^1H NMR ($CDCl_3$, 200 MHz) isomer **A** (maj) δ 1.58 (brs, 3H, Me-2′), 1.63 (d, 3H, MeCH, $J=7.3$ Hz), 1.90–2.15 (m, 2H, H-3′), 2.83 (d, 1H, H-6, $J=9.2$ Hz), 2.99 (d, 1H, H-5, $J=9.2$ Hz), 4.19 (dd, 1H, H-2, $J=10.1$, 4.0 Hz), 4.70 (brs, 1H, H-1′), 4.84 (brs, 1H, H-1′), 5.28 (d, 1H, H-7, $J=1.5$ Hz), 5.35 (q, 1H, C*H*Me, $J=7.3$ Hz), 6.37 (dd, 1H, H-8, $J=5.8$, 1.5 Hz), 6.46 (d, 1H, H-9, $J=5.8$v), 7.15–7.50 (m, 5H, H-Ph). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.50; N, 3.97. Found: C, 71.41; H, 6.48; N, 3.97.

3.2.4. 3-(4-Methylbenzyl)-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4d). Ratio of isomers **A/B** ~ 1:1.2; yield 92%; mp 109.5–111 °C; IR 1720 (COOH), and 1665 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 353 (9), 218 (36), 194 (17), 120 (33), 105 (100), 99 (15), 91 (10), 77 (16), 65 (7), 55 (9), 39 (9); ^1H NMR (DMSO-D_6, 400 MHz) isomer **A** δ 1.56 (s, 3H, Me-2′), 2.26 (s, 3H, Me-Ar), 2.36–2.52 (m, 2H, H-3′), 2.49 (d, 1H, H-6, $J=9.1$ Hz), 2.99 (d, 1H, H-5, $J=9.1$ Hz), 4.16 (dd, 1H, H-2, $J=10.1$, 4.5 Hz), 4.59 (d, 1H, CH_AH_BN, $J=15.3$ Hz), 4.63 (m, 1H, H-1′), 4.71 (m, 1H, H-1′), 4.80 (d, 1H, CH_AH_BN, $J=15.3$ Hz), 5.01 (d, 1H, H-7, $J=1.7$ Hz), 6.29 (dd, 1H, H-8, $J=5.8$, 1.7 Hz), 6.43 (d, 1H, H-9, $J=5.8$ Hz), 7.07–7.15 (m, 4H, H-Ar); isomer **B** δ 1.67 (s, 3H, Me-2′), 2.14 (dd, 1H, H-3′A, $J=13.9$, 9.0 Hz), 2.25 (s, 3H, Me-Ar), 2.40 (m, 1H, H-3′B), 2.49 (d, 1H, H-6, $J=9.1$ Hz), 2.82 (d, 1H, H-5, $J=9.1$ Hz), 3.68 (dd, 1H, H-2, $J=9.0$, 5.5 Hz), 3.99 (d, 1H, CH_AH_BN, $J=15.4$ Hz), 4.19 (d, 1H, CH_AH_BN, $J=15.4$ Hz), 4.77 (m, 1H, H-1′), 4.85 (m, 1H, H-1′), 4.97 (d, 1H, H-7, $J=1.7$ Hz), 6.39 (dd, 1H, H-8, $J=5.8$, 1.7 Hz), 6.54 (d, 1H, H-9, $J=5.8$ Hz), 7.07–7.15 (m, 4H, H-Ar). ^{13}C NMR (DMSO-D_6, 65 °C, 100.6 MHz) isomer **A** δ 173.5, 172.5, 140.5, 135.6, 132.2, 127.0, 56.1, 44.3, 38.1, 22.5, 158.9, 133.7, 128.8, 92.1, 90.6, 81.5, 81.4, 55.1, 50.7, 49.3, 45.9. Isomer **B** δ 173.6, 173.1, 139.8, 136.4,

127.8, 114.4, 56.3, 43.7, 34.5, 22.8, 158.9, 133.7, 128.8, 92.1, 90.6, 81.5, 81.4, 55.1, 50.7, 49.3, 45.9. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.50; N, 3.97. Found: C, 71.41; H, 6.49; N, 3.95.

3.2.5. 3-(4-Methoxybenzyl)-2-methallyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (4e). Ratio of isomers **A/B** ~1:3.1; yield 74%; mp 136.5–139 °C; IR 1715 (COOH), and 1695 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 369 (4), 314 (3), 248 (11), 234 (38), 216 (20), 175 (10), 150 (8), 136 (29), 121 (100), 91 (4), 77 (4); ^{1}H NMR (DMSO-D_6, 400 MHz) isomer **A** δ 1.57 (s, 3H, Me-2′), 2.15 (dd, 1H, H-3′A, J=13.1, 10.5 Hz), 2.39–2.56 (m, 1H, H-3′B), 2.47 (d, 1H, H-6, J=9.3 Hz), 2.81 (d, 1H, H-5, J=9.3 Hz), 3.72 (s, 3H, OMe), 4.15 (dd, 1H, H-2, J=10.5, 4.1 Hz), 4.16 (d, 1H, CH_AH$_B$N, J=15.5 Hz), 4.58 (d, 1H, CH$_A$$H_B$N, J=15.5 Hz), 4.64 (brs, 1H, H-1′), 4.72 (brs, 1H, H-1′), 5.01 (d, 1H, H-7, J=1.6 Hz), 6.29 (dd, 1H, H-8, J=5.8, 1.6 Hz), 6.43 (d, 1H, H-9, J=5.8 Hz), 6.86 (AB, 2H, H-Ar), 7.17 (AB, 2H, H-Ar); isomer **B** δ 1.67 (s, 3H, Me-2′), 2.39–2.56 (m, 2H, H-3′), 2.47 (d, 1H, H-6, J=9.3 Hz), 2.99 (d, 1H, H-5, J=9.3 Hz), 3.68 (dd, 1H, H-2, J=8.5, 5.5 Hz), 3.71 (s, 3H, OMe), 3.98 (d, 1H, CH_AH$_B$N, J=15.5 Hz), 4.79 (d, 1H, CH$_A$$H_B$N, J=15.5 Hz), 4.78 (brs, 1H, H-1′), 4.97 (d, 1H, H-7, J=1.5 Hz), 6.86 (brs, 1H, H-1′), 6.39 (dd, 1H, H-8, J=5.8, 1.5 Hz), 6.54 (d, 1H, H-9, J=5.8 Hz), 6.83 (AB, 2H, H-Ar), 7.17 (AB, 2H, H-Ar). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.31; H, 6.24; N, 3.82.

3.3. 13,13-Dimethyl-7-oxoisoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5). Typical procedure

A mixture of fine powdered adduct **4** (0.01 mol) and 40 mL of PPA (prepared from 30 g of P_2O_5 and 30 mL of 85% H_3PO_4) was stirred at 90 °C for 40 min (TLC control). Then the reaction mixture was cooled and poured into 100 mL of water. The obtained precipitate was filtered off washed with cold water (5×80 mL), isopropanol (2×30 mL) and dried in air. Then the crude product was purified by recrystallization (*i*-PrOH–DMF) in case of **5a**,**c**-**e** or on Al_2O_3 (1.5×3 cm, chloroform) in case of **5b** to give desired isoindolobenzazepines **5** as colorless crystals.

3.3.1. 13,13-Dimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5a). Yield 75%; mp 255–257 °C; IR 1700 (COOH), and 1680 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 321 (27), 306 (2), 278 (13), 277 (52), 276 (20), 275 (100), 131 (14), 115 (8), 103 (3), 91 (14), 77 (3); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.42 (dd, 1H, H-12A(ax), J=11.9, 14.0 Hz), 1.47 (s, 3H, Me-13), 1.57 (s, 3H, Me-13), 2.55 (dd, 1H, H-12B(eq), J=3.4, 14.0 Hz), 4.97 (d, 1H, H-5A, J=15.5 Hz), 5.13 (d, 1H, H-5B, J=15.5 Hz), 5.30 (dd, 1H, H-11b, J=3.4, 11.9 Hz), 7.21 (dd, 1H, H-1, J=1.6, 7.5 Hz), 7.37 (dt, 1H, H-2, J=1.1, 7.5 Hz), 7.37 (dt, 1H, H-3, J=1.6, 7.5 Hz), 7.41 (dd, 1H, H-4, J=1.1, 7.5 Hz), 7.82 (t, 1H, H-10, J=7.7), 7.99 (brd, 1H, H-11, J=7.7 Hz), 8.12 (dd, 1H, H-9, J=7.7, 0.7 Hz), 9.03 (brs, 1H, COOH). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 167.1 and 169.1 (s, C=O), 147.8, 147.2, 134.9, 128.1, 128.6 (s, C-Ar), 132.6, 131.9, 130.9, 128.3, 127.0, 126.62, 126.56 (d, C-Ar), 60.6 (d, C-11b), 46.8 (t, C-5), 45.6 (t, C-12), 37.5 (s, C-13), 32.3, 25.5 (q, Me-13). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.78; H, 5.90; N, 4.37.

3.3.2. 9,13,13-Trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5b). Yield 30%; mp 133.5–135 °C; IR 1710 (COOH), and 1660 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 335 (1), 291 (100), 276 (25), 262 (5), 248 (25), 235 (5), 172 (113), 160 (13), 146 (34), 131 (30), 115 (40), 91 (63), 77 (16), 65 (13), 39 (13); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 3H, Me-13), 1.60 (dd, 1H, H-12A(ax), J=14.0, 12.2 Hz), 1.61 (s, 3H, Me-13), 2.25 (dd, 1H, H-12B(eq), J=14.0, 3.0 Hz), 2.42 (s, 3H, Me-9), 4.69 (d, 1H, H-5A, J=15.6 Hz), 4.86 (dd, 1H, H-11b(ax), J=3.0, 12.2 Hz), 5.31 (d, 1H, H-5B, J=15.6 Hz), 7.16–7.42 (m, 6H, H-Ar), 7.63 (brs, 1H, COOH). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 166.0 (2C, COOH and C-7), 147.8, 144.1, 138.0, 137.2, 132.8, 132.0, 131.0, 128.2, 126.9, 126.7, 123.4, 122.6 (C-Ar), 59.2 (d, C-11b), 47.2 (t, C-5), 46.5 (t, C-12), 38.1 (s, C-13), 32.9 (q, C-9), 21.3, 26.1 (q, Me-13). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.14; H, 6.25; N, 4.17.

3.3.3. 5,13,13-Trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5c). Yield 31%; mp 209.5–211.5 °C; IR 1710 (COOH), and 1680 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 335 (8), 320 (100), 289 (17), 276 (23), 138 (6), 129 (10), 115 (7), 103 (4), 91 (7), 81 (4), 44 (36), 28 (22); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (brs, 3H, Me-13), 1.55 (s, 3H, Me-13), 1.81 (d, 3H, Me-5, J=7.4 Hz), 2.17 (dd, 1H, H-12A, J=14.7, 6.0 Hz), 2.70 (dd, 1H, H-12B, J=14.7, 6.0 Hz), 5.16 (t, 1H, H-11b, J=6.0 Hz), 5.94 (q, 1H, H-5, J=7.4 Hz), 7.21–7.45 (m, 4H, H-Ar), 7.73–7.79 (m, 2H, H-Ar), 8.43 (dd, 1H, H-9, J=7.4, 1.7 Hz), 15.80 (brs, 1H, COOH). ^{13}C NMR (DMSO-D_6, 50.3 MHz) δ 168.2 and 165.3 (C=O), 147.4, 145.6, 138.8, 129.5, 129.0 (s, C-Ar), 133.4, 132.4, 130.5, 128.3, 127.5, 127.0, 126.0 (d, C-Ar), 57.2 (d, C-11b), 53.3 (d, C-5), 44.5 (s, C-13), 39.2 (t, C-12), 32.8, 31.9, 23.5 (q, Me-13 and Me-5). Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.11; H, 6.28; N, 4.20.

3.3.4. 2,13,13-Trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5d). Yield 48%; mp 219–221 °C; IR 1705 (COOH), and 1695 (N-C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M$^+$ 335 (23), 291 (22), 289 (100), 207 (1), 159 (3), 144 (5), 129 (7), 115 (5), 91 (3), 77 (2); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.37 (dd, 1H, H-12A(ax), J=13.5, 11.7 Hz), 1.46 (s, 3H, Me-13), 1.55 (s, 3H, Me-13), 2.26 (s, 3H, Me-2), 2.53 (dd, 1H, H-12B(eq), J=2.6, 13.5 Hz), 4.91 (d, 1H, H-5A, J=15.4 Hz), 5.08 (d, 1H, H-5B, J=15.4 Hz), 5.28 (dd, 1H, H-11b(ax), J=2.6, 11.7 Hz), 7.00 (brd, 1H, H-3, J=7.4 Hz), 7.19 (brs, 1H, H-1), 7.24 (d, 1H, H-4, J=7.4 Hz), 7.81 (t, 1H, H-10, J=7.6 Hz), 7.99 (d, 1?, H-11, J=7.6 Hz), 8.12 (d, 1?, H-9, J=7.6 Hz). ^{13}C NMR (DMSO-D_6, 50.3 MHz) δ 167.6 and 165.5 (C=O), 148.4, 147.6, 137.9, 133.9, 132.9, 132.5, 132.1, 129.1, 128.7, 128.4, 127.2, 126.6, 60.3, 48.6, 47.3, 38.0, 32.8, 26.0, 21.7. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.12; H, 6.29; N, 4.18.

3.3.5. 2-Methoxy-13,13-trimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (5e). Yield 48%; mp 197–198?; IR 1705 (COOH), and 1695 (N-C=O) cm^{-1}; EI-MS (70 eV) m/z (rel. intensity): M^+ 351 (15), 334 (4), 305 (100), 290 (2), 175 (4), 160 (5), 145 (4), 131 (3), 115 (3), 91 (4), 44 (7), 28 (5); 1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (dd, ^{1}H, H-12A(*ax*), J=14.3, 12.2), 1.55 (s, 3H, Me-13), 1.64 (s, 3H, Me-13), 2.32 (dd, 1H, H-12B(*eq*), J=14.3, 3.3), 3.79 (s, 3H, OMe), 4.78 (d, 1H, H-5A, J=15.4), 5.06 (dd, 1H, H-11b(*ax*), J=12.2, 3.3), 5.24 (d, 1H, H-5B, J=15.4), 6.72 (dd, 1H, H-3, J=8.3, 2.6), 6.79 (d, 1H, H-1, J=2.6), 7.31 (d, 1H, H-4, J=8.3), 7.65 (dd, 1H, H-11, J=7.6, 1.1), 7.70 (t, 1?, H-10, J=7.6), 8.35 (dd, 1H, H-9, J=7.6, 1.1). ^{13}C NMR (DMSO-D6−CDCl3, 75.4 MHz) δ 172.4 and 170.1 (s, C=O), 164.3 (C-2), 153.8 (s), 152.8 (s), 137.7 (d), 137.6 (d), 137.3 (d), 133.9 (s), 133.6 (s), 132.20 (d), 132.16 (s), 119.2 (d), 115.1 (d), 65.9 (OMe), 60.2 (d, C-11b), 51.5 (t), 51.1 (t), 44.9 (s), 37.5 (q), 30.5 (q). Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.79; H, 5.98; N, 3.99. Found: C, 71.81; H, 5.99; N, 4.01.

3.3.6. 1-Oxo-2-benzyl-3-(2′-methylpropenyl)-1,2-dihydro-3*H*-isoindole-7-carboxylic acid (6). A mixture of fine powdered adduct **4a** (1.69 g, 5.0 mmol) and 25 mL of H_3PO_4 (85%) was stirred at 60 °C for 40–60 min (TLC control—before a disappearance of the initial compound spot). Then the reaction mixture was cooled and poured into 100 mL of water. The obtained precipitate was filtered off washed with cold water (5×80 mL) and dried. Then the crude product was washed with isopropanol (6×30 mL) and the solid fraction was discarded. The isopropanol solution was concentrated in vacuo and the formed precipitate was filtered off. The double recrystallization (heptane–ethyl acetate) gave desired isoquinoline **6** as colorless crystals, yield 13%; mp 149.5–150 °C; IR 1705 (COOH), and 1695 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 321 (43), 277 (100), 260 (4), 234 (4), 212 (6), 199 (14), 183 (4), 170 (9), 157 (4), 128 (8), 106 (7), 91 (49), 65 (5), 28 (8); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (d, 3H, Me-1′, J=1.3 Hz), 1.86 (d, 3H, Me-2′, J=1.3 Hz), 4.18 (d, 1H, CH_AH_BN, J=14.7 Hz), 4.80 (dt, 1H, H-3′, J=10.0, 1.3 Hz), 5.18 (d, 1H, H-3, J=10.0 Hz), 5.29 (d, 1H, CH_AH_BN, J=14.7 Hz), 7.25–7.35 (m, 5H, H-Ph), 7.46 (dd, 1H, H-4, J=7.7, 0.8 Hz), 7.67 (t, 1H, H-5, J=7.7 Hz), 8.36 (dd, 1H, H-6, J=7.7, 0.8 Hz). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.80; H, 5.94; N, 4.35.

3.3.7. 3-Nitro-13,13-dimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (7). Potassium nitrate (0.66 g, 6.5 mmol) was added in portion to a stirred solution of **5a** (2.00 g, 6.23 mmol) in 15 mL of sulfuric acid. Then the reaction mixture was stirred at 40 °C for 30 min and poured into 50 mL of water. The obtained precipitate was filtered off, washed with water to pH ~7 and dried in air. Then the crude product was purified by recrystallization (*i*-PrOH–DMF) to give the desired nitroderivative **7** as white crystals. Yield 73%; mp 240–242 °C; IR 1720 (COOH), 1690 (N–C=O), 1560 (NO_2 s), and 1380 (NO_2 as) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 366 (3), 322 (100), 204 (20), 190 (5), 176 (5), 144 (8), 129 (28), 115 (33), 109 (68), 103 (15), 91 (18), 77 (18), 73 (41), 63 (10), 51 (9), 44 (83), 33 (18); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.51 (s, 3H, Me-13), 1.52 (dd, 1H, H-12A(ax), J=14.3, 11.0 Hz), 1.62 (s, 3H, Me-13), 2.62 (dd, 1H, H-12B(eq), J=14.3, 3.5 Hz), 5.05 (d, 1H, H-5A, J=15.9 Hz), 5.34 (dd, 1H, H-11b(ax), J=11.0, 3.5 Hz), 5.37 (d, 1H, H-5B, J=15.9 Hz), 7.69 (d, 1H, H-1, J=8.9 Hz), 7.83 (t, 1H, H-10, J=7.6 Hz), 8.00 (d, 1H, H-11, J=7.6), 8.12 (d, 1H, H-9, J=7.6 Hz), 8.13 (dd, 1H, H-2, J=2.7, 8.9 Hz), 8.30 (d, 1H, H-4, J=2.7 Hz). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 25.1, 32.3 (q, Me-13), 38.5 (s, C-13), 46.1 (t, C-5), 44.8 (t, C-12), 60.4 (d, C-11b), 123.0 (d, C-2), 125.1 (d, C-4), 127.0 (d, C-11), 128.7 (d, C-1), 131.9 (d, C-9), 132.8 (d, C-10), 128.0, 128.8, 137.0, 145.6, 147.7, 155.3 (all s, 6C-Aryl), 165.0 (COOH), 167.4 (C-7). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.92; N, 7.65. Found: C, 65.59; H, 4.92; N, 7.67.

3.3.8. Chloroanhydride of 5,13-dihydro-13,13-dimethyl-7-oxo-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (8). Four molar equivalents of thionylchloride (1.79 mL, 25 mmol) were added to a suspension of acid **5a** (2.0 g, 6.23 mmol) in 50 mL of benzene. Then the reaction mixture was refluxed for 6 h. The precipitate formed on cooling of the reaction mixture was filtered off. The mother liquor was concentrated in vacuo and the formed precipitate was filtered off. The crystalline fractions were combined, washed with ether and recrystallized from chloroform–DMF to give the desired product **8** as yellow crystals. Yield 79%; mp 203–204 °C; IR 1700 (COCl), and 1668 (N–C=O and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 339 (6), 337 (18), 322 (100), 294 (25), 286 (8), 259 (23), 230 (15), 192 (13), 164 (6), 151 (6), 143 (35), 129 (20), 115 (46), 101 (15), 83 (5), 78 (25), 63 (10), 51 (13), 36 (30); ^{1}H NMR (DMSO-D_6, 200 MHz) δ 1.73 (s, 6H, Me-13), 5.26 (s, 2H, H-5), 6.43 (s, 1H, H-12), 7.20–7.50 (m, 4H, H-1,2,3,4), 7.80 (t, 1H, H-10, J=7.4 Hz), 8.01 (dd, 1H, H-11, J=7.4, 0.8 Hz), 8.20 (dd, 1H, H-9, J=7.4, 0.8 Hz). Anal. Calcd for $C_{20}H_{16}NO_2Cl$: C, 71.11; H, 4.75; N, 4.15. Found: C, 71.15; H, 4.74; N, 4.14.

3.3.9. 5,13-Dihydro-13,13-dimethyl-7-oxo-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (9). *Procedure A*. A mixture of chloroanhydride **8** (2.0 g, 5.93 mmol) and 10% solution of NaOH (30 mL) was stirred at 80 °C for 30 min. Then the reaction mixture was poured into 30 mL of water and acidified with 16% HCl to pH ~7. The obtained precipitate was filtered off, washed with water (3×100 mL) and dried in air. Recrystallization from *i*-PrOH–DMF gave the desired acid **9** as white crystals. Yield 70%.

Procedure B. A mixture of **5a** (2.0 g, 6.23 mmol) and nitrobenzene (20 mL) was refluxed for 4 h. After that the reaction mixture was concentrated in vacuo to half of its volume and the formed crystals were filtered off, washed with ether and dried in air. Then the crude product was purified by recrystallization (*i*-PrOH–DMF) to give desired dehydroderivative **9** as white crystals. Yield 64%; mp 285.5–287 °C; IR 1720 (COOH), and 1645 (N–C=O and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 319 (18), 304 (100), 276 (30), 260 (5), 245 (5), 230 (8), 217 (10), 204 (8), 189 (5), 174 (8), 143 (5), 130 (20), 115 (50), 109 (20), 102 (50), 91 (13), 77 (13), 63 (15), 51 (9), 39 (15); ^{1}H NMR (DMSO-D_6, 400 MHz) δ 1.69 (s, 6H, Me-13), 5.21 (s,

2H, H-5), 6.39 (s, 1H, H-12), 7.27 (dt, 1H, H-2, J=1.2, 7.4 Hz), 7.35 (dt, 1H, H-3, J=1.2, 7.4 Hz), 7.44 (dd, 1H, H-1, J=1.2, 7.4 Hz), 7.46 (dd, 1H, H-4, J=1.2, 7.4 Hz), 7.78 (t, 1H, H-10, J=7.7 Hz), 7.98 (dd, 1H, H-11, J=0.8, 7.7 Hz), 8.20 (dd, 1H, H-9, J=0.8, 7.7 Hz). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.24; H, 5.33; N, 4.39. Found: C, 75.24; H, 5.36; N, 4.41.

3.3.10. Morpholine amide of 5,13-dihydro-13,13-dimethyl-7-oxo-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (10). A mixture of chloroanhydride **8** (0.75 g, 2.23 mmol) and 10 mL of morpholine was refluxed for 4 h. Then the reaction mixture was cooling, poured into 30 mL of water and acidified with 15% hydrochloric acid. The formed precipitate was filtered off, washed with water (5×20 mL) and dried in air. The crude product was recrystallized (*i*-PrOH–DMF) to give the desired amide **10** as slightly-yellow crystals. Yield 50%; mp 223–224 °C; IR 1700 and 1638 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 388 (55), 373 (100), 345 (30), 302 (15), 288 (20), 275 (28), 259 (48), 245 (15), 230 (20), 216 (20), 202 (15), 189 (9), 172 (11), 158 (13), 143 (45), 136 (8), 130 (29), 115 (35), 102 (15), 91 (15), 86 (35), 73 (21), 56 (19), 44 (28); ^{1}H NMR (DMSO-D_6, 200 MHz) δ 1.74 (s, 3H, Me-13), 1.76 (s, 3H, Me-13), 3.05–4.05 (m, 8H, H-morpholine), 5.16 (d, 1H, H-5A, J=15.3 Hz), 5.26 (d, 1H, H-5B, J=15.3 Hz), 5.86 (s, 1H, H-12), 7.15–7.70 (m, 7H, H-Ar). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 166.7 and 164.4 (s, C=O), 147.5, 137.3, 134.3, 134.0, 133.3 (all s, C-Ar), 132.9, 131.6, 129.2, 127.7, 127.3, 126.1 (all d, C-Ar), 123.7 (s, C-11b), 120.7 (d), 118.0 (d, C-12), 66.4 (t, 2C), 47.4, 45.4, 42.3, 38.8 (s, C-13), 32.6 (q, 2C, Me-13). Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.23; H, 6.19; N, 7.22. Found: C, 74.24; H, 6.20; N, 7.25.

3.3.11. Methyl ether of 13,13-dimethyl-7-oxo-5,11b,12,13-tetrahydro-7*H*-isoindolo[2,1-*b*][2]benzazepine-8-carboxylic acid (11). A mixture of acid **5a** (2.00 g, 6.23 mmol), 30 mL of dry methanol and 0.05 mL of 96% sulfuric acid was refluxed for 6 h. After the reaction mixture was cooled, poured into water (80 mL) and extracted with ethyl acetate (3×30 mL). The organic phase was dried with $MgSO_4$ and concentrated. The crude product was recrystallized (hexane–ethyl acetate) to give the desired ester **11** as white crystals. Yield 60%; mp 167–169 °C; IR 1720 (O–C=O), and 1690 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 335 (35), 304 (6), 292 (5), 275 (100), 158 (11), 145 (6), 129 (15), 115 (18), 91 (28), 77 (8), 51 (2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 3H, Me-13), 1.60 (s, 3H, Me-13), 1.60 (dd, 1H, H-12A(ax), J=14.1, 12.0 Hz), 2.25 (dd, 1H, H-12B(eq), J=3.0, 14.1 Hz), 3.98 (s, 3H, COOMe), 4.68 (d, 1H, H-5A, J=15.5 Hz), 4.90 (dd, 1H, H-11b(ax), J=3.0, 12.0 Hz), 5.28 (d, 1H, H-5B, J=15.5 Hz), 7.14–7.55 (m, 7H). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 169.1 and 165.1 (s, C=O), 148.1 (2C, s), 136.9, 130.6, 128.6 (s, C-Ar), 132.8, 131.6, 129.1, 127.8, 127.49, 127.55, 125.7 (d, C-Ar), 60.1 (d, C-11b), 53.6 (q, OMe), 47.3 (t, C-5), 46.9 (s, C-13), 38.5 (t, C-12), 33.2, 26.3 (q, Me-13). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.11; H, 6.27; N, 4.18. Found: C, 75.11; H, 6.28; N, 4.20.

3.3.12. 5,11b,12,13-Tetrahydro-13,13-dimethyl-8-hydroxymethyl-7*H*-isoindolo[2,1-*b*][2] benzazepine (12). Eight molar equivalents of lithium aluminum hydride (0.90 g, 24.9 mmol) were added to a suspension of the acid **5a** (1.0 g, 3.10 mmol) in 40 mL of THF. The resulting reaction mixture was refluxed for 2 h. Then the excess $LiAlH_4$ was decomposed with water (50 mL). The obtained product was extracted with chloroform (4×50 mL). The organic extract was dried with $MgSO_4$ and concentrated. The crude product was recrystallized from hexane–ethyl acetate mixture to give the desired benzylic alcohol **12** as colorless crystals. Yield 46%; mp 146.5–148.5 °C; IR 3150 (OH) cm^{-1}; EI-MS (70 eV) *m/z* (rel. intensity): M^+ 293 (100), 278 (20), 250 (33), 237 (12), 218 (9), 202 (4), 174 (6), 161 (12), 146 (18), 131 (72), 91 (84), 77 (13), 55 (11), 39 (12); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 3H, Me-13A), 1.50 (s, 3H, Me-13B), 1.96–2.06 (m, CH_2−12), 3.72 (brd, 1H, H-5B, J=12.9 Hz), 3.92 (brd, 1H, H-5A, J=12.9 Hz), 3.96 (d, 1H, H-7B, J=14.0 Hz), 4.26 (m, CH_2OH), 4.26 (d, 1H, H-7A, J=14.0 Hz), 4.26 (m, 1H, H-11b), 7.05 (brd, 1H, J=7.2 Hz), 7.16–7.28 (m, 5H-Ar), 7.44 (brd, 1H, J=7.7 Hz). ^{13}C NMR (DMSO-D_6, 100.6 MHz) δ 147.7, 145.1, 138.6, 137.4, 136.3 (s, C-Ar), 131.0, 127.3, 126.74, 126.68, 126.0, 125.1, 119.7 (d, C-Ar), 65.8 (d, C-11b), 61.3 (t), 58.4 (t), 57.0 (t), 44.9 (q, C-13), 38.5 (C-12), 33.0, 28.2 (q, Me-13). Calcd for $C_{20}H_{23}NO$: C, 81.91; H, 7.85; N, 4.78. Found: C, 81.93; H, 7.86; N, 4.80.

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Syntheses of new polyamine dendrimer units via a tandem hydroformylation/reductive amination sequences

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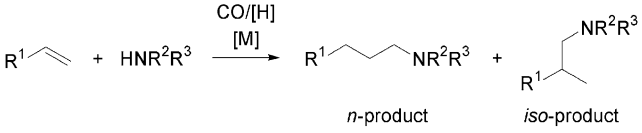
Abstract—Rh-catalyzed tandem hydroformylation/reductive amination sequences (hydroaminomethylation) starting from olefins are applied to the synthesis of new polyamine dendrimer units using both convergent and divergent strategies in solution as well as on solid support.

1. Introduction

Putrescine, spermidine and spermine and many other biogenic polyamines from plants and animals[1,2] as polycations at physiological pH play an important role in various biological processes such as cell regulation,[3,4] or DNA transfection.[5] They interact with nucleic acids, proteins and phospholipids and therefore affect DNA conformation and aggregation as well as membrane[5] or enzyme activitities.[6] The concentration of these polyamines is strictly regulated. Consequently selective analogues of naturally occurring polyamines offer a wide range of therapeutic potential, e.g. in treatment of cancer,[7] AIDS[8] or neurological diseases.[9]

Various methods for the synthesis and modification of linear polyamines are available,[10,11] among these alkylations including standard procedures as well as the Mitsunobu method, reduction of amides, nitriles, nitro compounds, azides and Schiff bases, and amine syntheses via conjugate addition. Polyamine modifications usually involve the number and type of nitrogen atoms, the chain length between these and changes in conformational rigidity by introducing cyclic units. Instead of linear polyamine chains, branched systems or highly branched systems like those in dendrimers can be envisaged. Thus dendrimer-like polyamines are of high interest due to their structural similarities with the natural products. A general strategy to synthesize dendrimer like polyamines was developed by Vögtle.[12] The sequence starts with an amine which is reacted with acrylonitrile in a Michael-type addition to form a saturated nitrile, which is reduced with $CoCl_2$ and $NaBH_4$ to give the primary amine.[12] As an example using this method Ganesh and co workers[13] synthesized pyrrolidyl polyamines with dendrimer like structures to stabilize DNA duplexes and triplexes. Other polyamine dendrimers were constructed using similar methodologies.[14] Alternatively Tomalia et al.[15] started from mesylated or tosylated aziridines to obtain protected polyethylenimines, which can be deprotected by acidic hydrolysis to yield the primary amine. Repetition of this sequence leads to polyethyleneamine dendrimers. Using these methods, polyamine dendrimers are also obtained by functionalization of the outer spheres as well as the core of preformed dendritic structures. The functionalization of the outer spheres is well examined and numerous examples are reported using various methods of amine synthesis.[16] Only rare examples, however, are known for a core functionalization of dendrimers starting from amphiphilic[17] and dendrimer-like[13] polyamines.

Recently hydroaminomethylation (Scheme 1), a rhodium-catalyzed reaction sequence combining hydroformylation of olefins and reductive amination of the resulting aldehydes under the same conditions, has been used in the synthesis of linear and cyclic polyfunctionalized amines including polyamines and azamacroheterocycles.[18] This method should also be applicable to dendrimer synthesis offering access to new structural features.



Scheme 1.

Keywords: Dendrimer units; Polyamines; Hydroformylation; Hydroaminomethylation; Reductive amination; Rh-Catalysis; Solid support.
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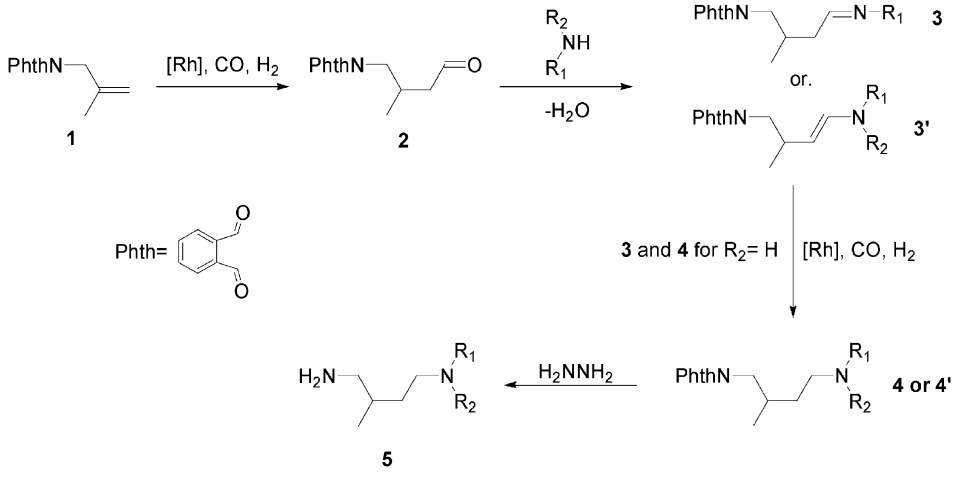
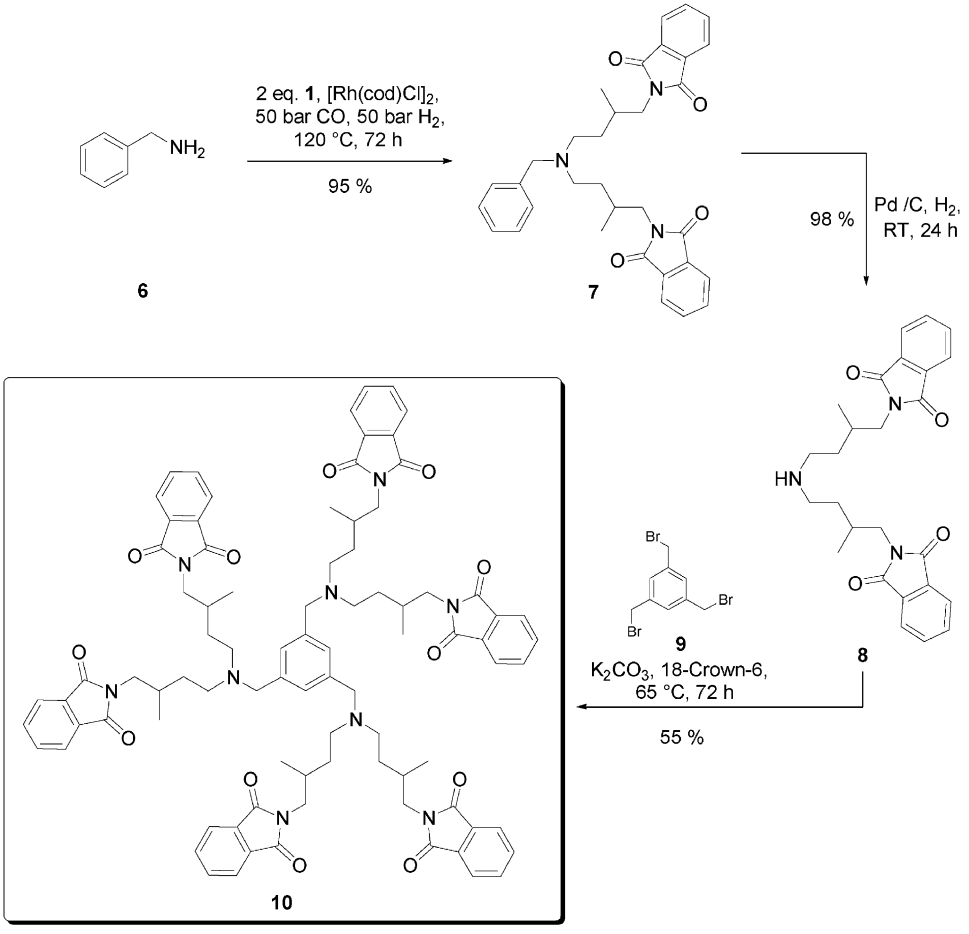
2. Results and discussion

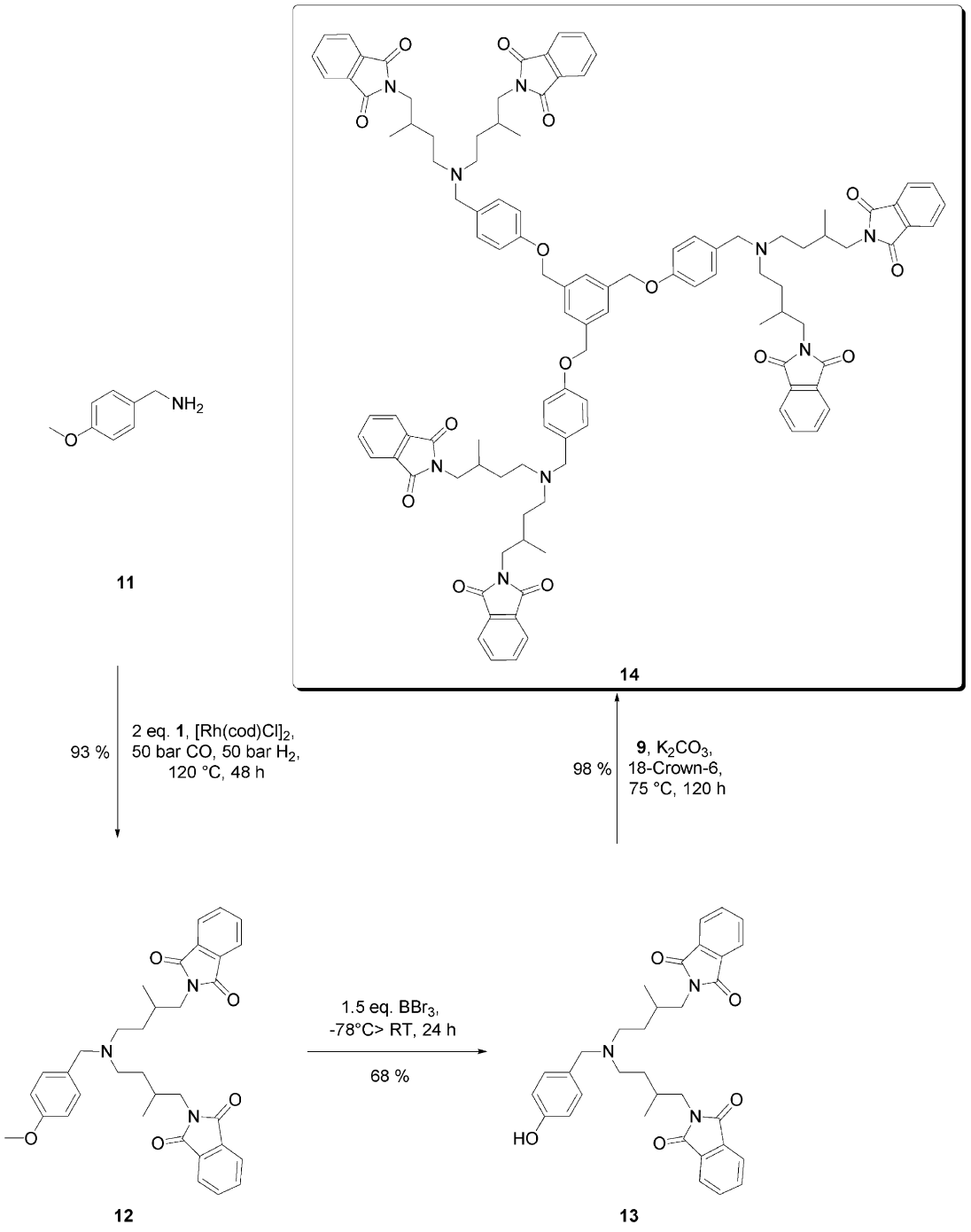
We here wish to report first applications of hydroaminomethylation in the synthesis of dendrimer-type polyamines both using convergent and divergent strategies. As building block the easily obtainable methallylphthalimide (**1**)[19] was used as the olefinic reaction partner bearing a protceted primary amino group which after deprotection provides the branching point for the next dendrimer generation. In principle numerous other linear, branched or cyclic unsaturated amines can be used. In our model studies the methallyl system was chosen, since there are no *n*/*iso*-selectivity problems to complicate the initial hydroformylation step (Scheme 2). This step is followed by a condensation of the aldehyde with a primary or secondary amine already present in the reaction mixture to give imine **3** or enamine **3′**. Finally reduction of the intermediate imine **3** or enamine **3′** under hydroformylation conditions forms



Scheme 2.



Scheme 3.



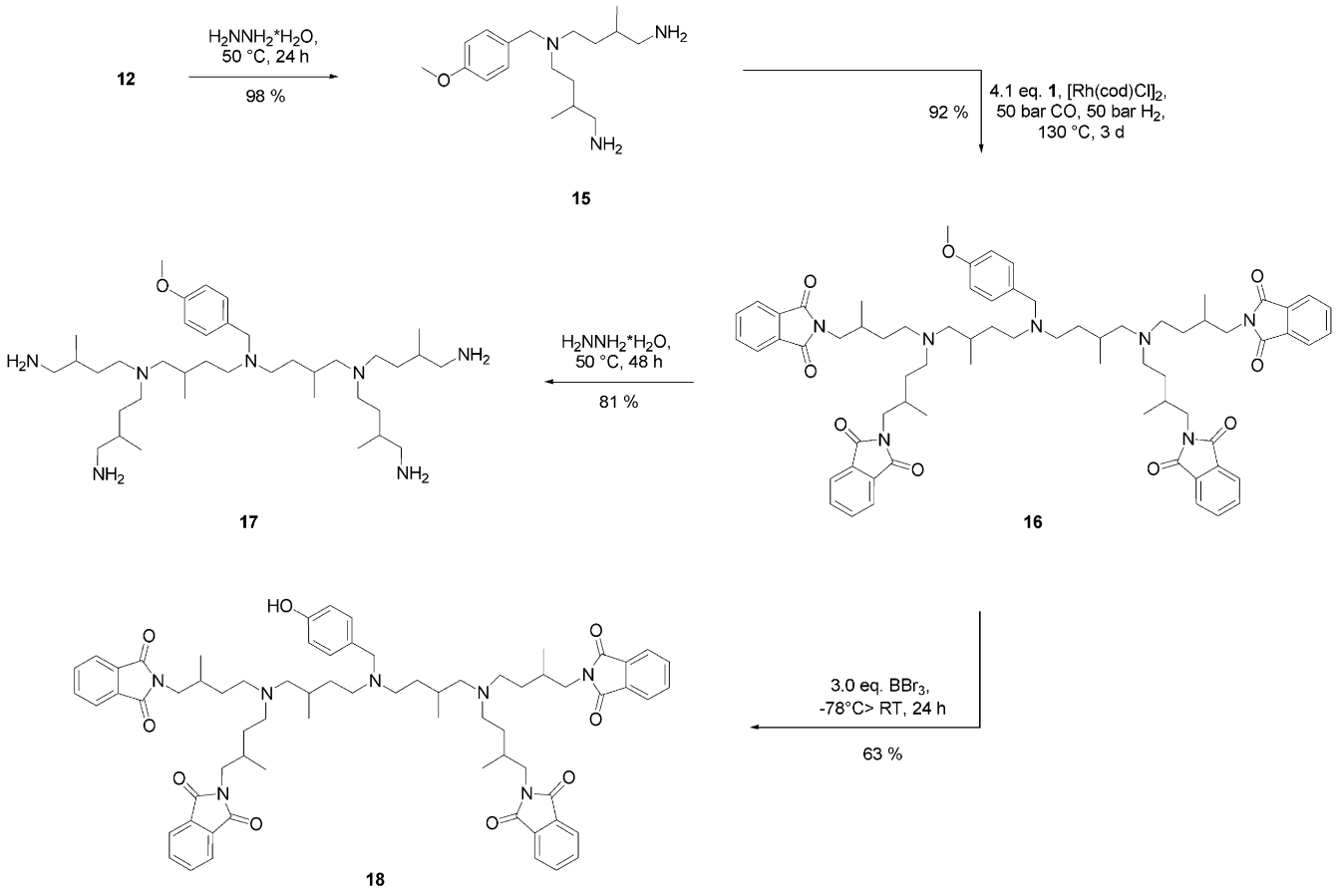
Scheme 4.

the saturated secondary or tertiary amine **4** resp. **4′**. Now the phthalimides **4** resp. **4′** can be deprotected by hydrazinolysis to give a primary amine **5** which establishes the branching point for the next generation via hydroaminomethylation and hydrazinolysis forming the growing dendrimer.

Using this method dendrimer units can be prepared by divergent and convergent strategies. Following a convergent strategy benzylamine (**6**) is converted under hydroaminomethylation conditions with 2.0 equiv of methallylphthalimide (**1**) to afford the orthogonally protected triamine **7** in very good yields. This step is performed in an autoclave under rhodium catalysis at 120 °C, 100 bar (CO/H_2; 1/1) in 72 h.

The phthalimide and benzyl protected compound **7** is debenzylated under reductive conditions with Pd/C under H_2 atmosphere to give **8** in nearly quantitative yield. The secondary amino group can then be attached to trihalide cores using general substitution conditions.[20] Thus alkylation with 1,3,5-tris(bromomethyl)benzene (**9**)[21] results in the polyamine dendrimer unit **10** in good yields (Scheme 3).

As an alternative, if using the *p*-methoxybenzyl protecting group, the phenolic function can be deprotected and used for



Scheme 5.

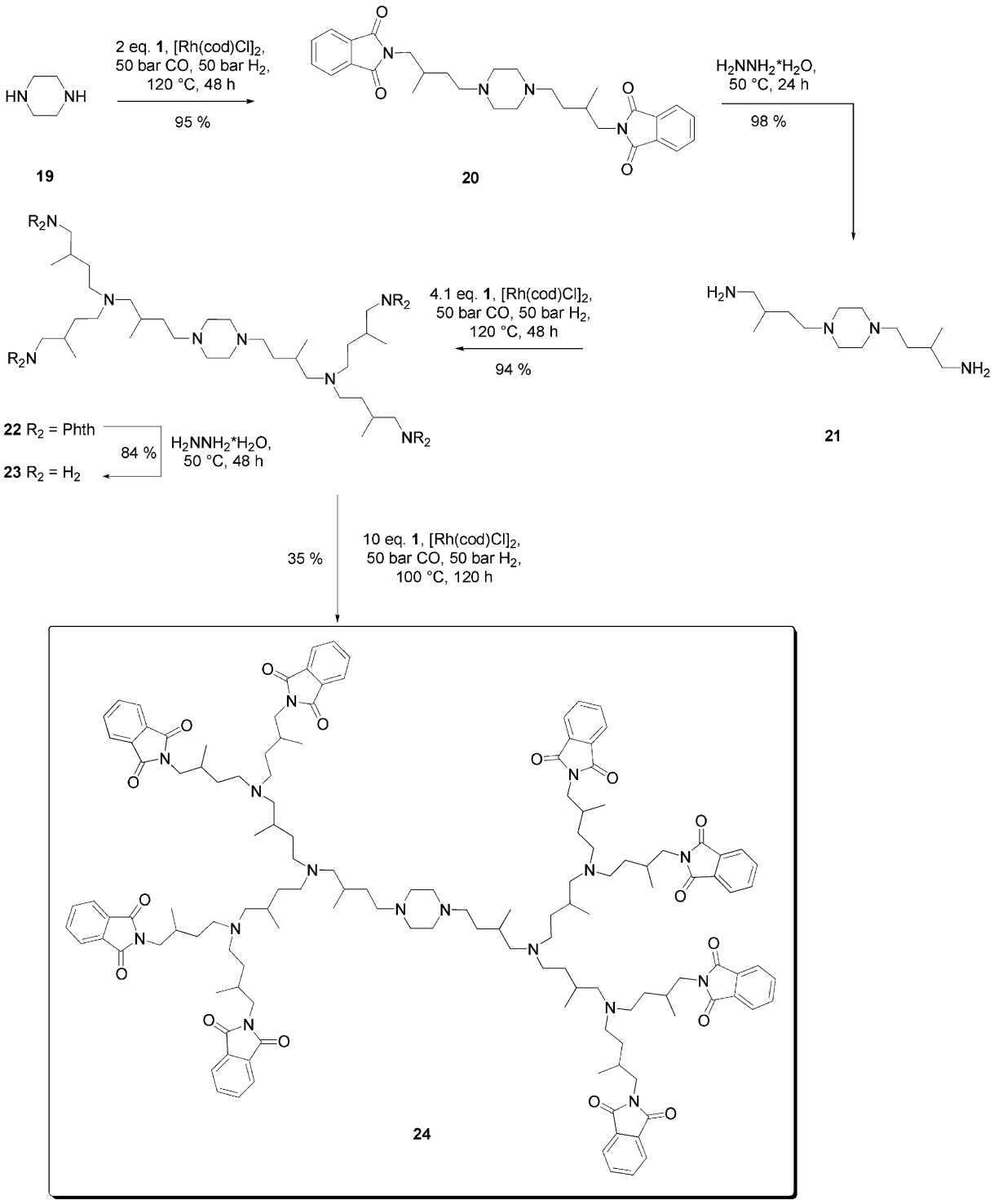
alkylation with a trihalide core **9**. For this the PMB protected triamine **12** is obtained via hydroaminomethylation of methallylphthalimide (**1**) in the presence of *p*-methoxybenzylamine (**11**). For demethylation, compound **12** is treated with 1.5 equiv BBr_3 at −78 °C.[22]

Using a standard procedure in polyether dendrimer synthesis[20] the activated polyamine dendron **13** react with the core 1,3,5-tris-(bromomethyl)benzene (**9**) in a nearly quantitative yield to give the dendrimer unit **14** with a polyamine scaffold around a polyether core (Scheme 4).

Following this strategy benzylamine (**6**) or *p*-methoxybenzylamine (**11**) can also be used as starting amine for larger dendron units such as **17**, obtained in an overall yield of 68% from *p*-methoxybenzylamine (**11**). Deprotection of **12** with hydrazine nearly quantitatively gives polyamine **15**. The second hydroaminomethylation to form **16** requires longer reaction times to give yields higher than 90%. The hydrazinolysis of **16** gives the second generation polyamine **17** in 81% yield. Whereas for demethylation of **12** 1.5 equiv BBr_3 were sufficient, the deprotection of **16** to give **18** needs 3 equiv BBr_3 for reasonable yields (Scheme 5).

Hydroaminomethylation procedures can also be used to construct larger polyamine dendrimer units such as **24**, synthesized in five steps following a divergent strategy starting from piperazine (**19**) as an diamine core. In the first step piperazine (**19**) is converted in an autoclave under rhodium catalysis at 120 °C, 100 bar (CO/H_2; 1/1) in 48 h with 2.0 equiv methallylphthalimide (**1**) to the solid diimide derivative **20** in 95% yield. Free tetraamine **21** is obtained after treatment of **20** with hydrazine at 50 °C. Interestingly, piperazine compounds of type **21** are used as heterocyclic analogues of spermine with pharmaceutical activities as anticancer agents or *N*-methyl-*D*-aspartate (NMDA) receptor modulators.[23]

The hydroaminomethylation protocol used for compound **21** with 4.1 equiv of methallylphthalimide (**1**) results in the tetraphthalimide **22** in 94% yield. Deprotection of **22** gives the symmetric polyamine **23** in 84% yield. Whereas up to this point the hydroaminomethylation steps proceeded with excellent yields, the outcome of further conversions of polyamine **23** with methallylphthalimide (**1**) under the usual conditions of hydroaminomethylation is strongly dependent on the amounts of catalyst used. With 0.3 mol% product **24** is obtained only in traces. The major product here is the alcohol formed via reduction of the hydroformylation product of methallylphthalimide (**1**). If lowering the catalyst amount to 0.05 mol% the aldehyde reduction can be suppressed and after 120 h reaction time the third generation polyamine product **24** is obtained in 35% yield. Thus reductive amination of the newly formed aldehyde with the amine groups here appears to be slower than the aldehyde reduction. Slowing down the hydroformylation by lowering the catalyst concentration reverses the relative rates of

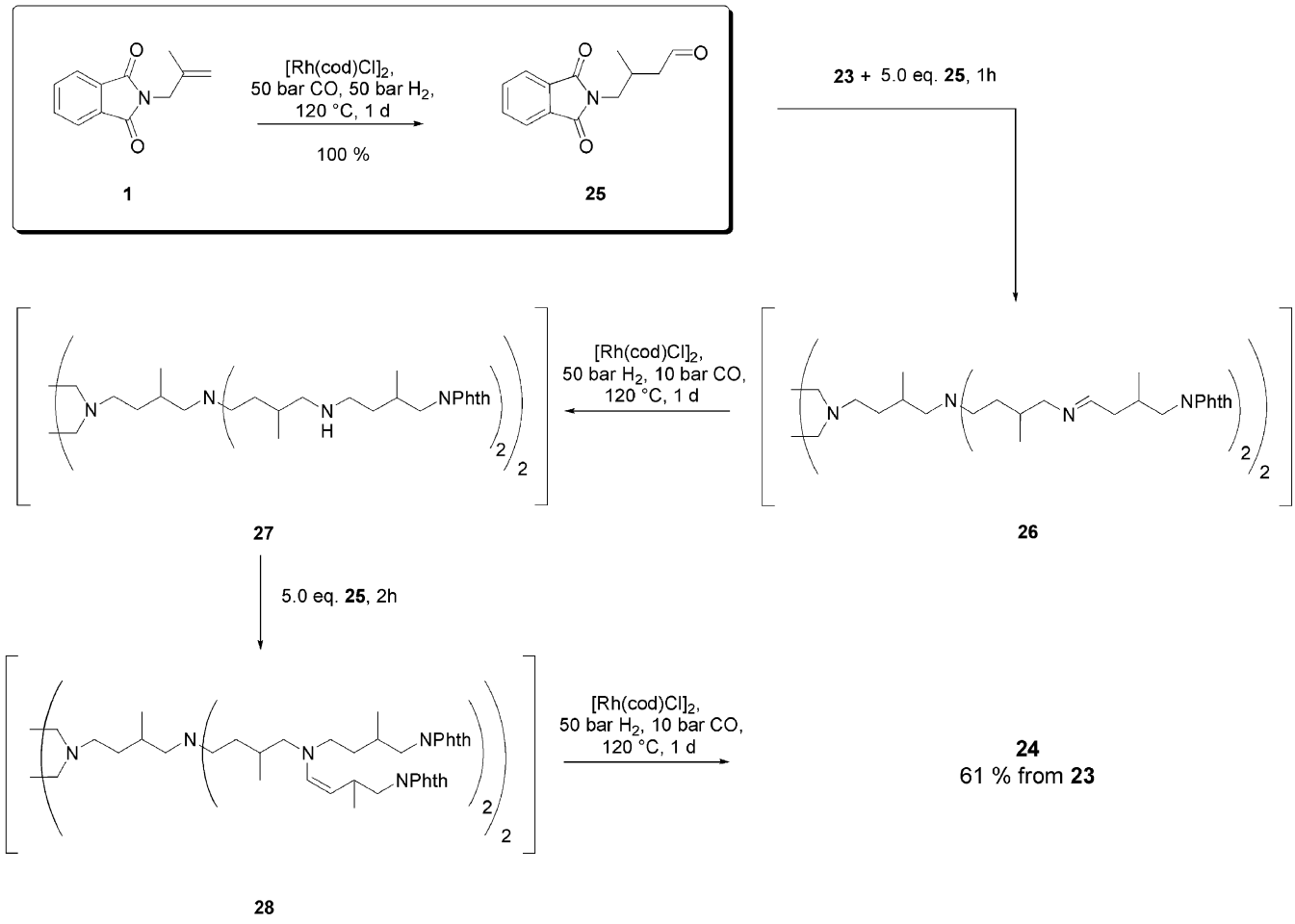


Scheme 6.

aldehyde reduction and reductive amination to give the desired product **24** (Scheme 6).

As an alternative route to achieve better yields of **24** the stepwise version of hydroaminomethylation can be used. For this first the aldehyde **25** is prepared in quantitative yields (Scheme 7). Subsequently this aldehyde **25** is added portion wise to the polyamine **23** and converted under reductive amination conditions stepwise to the product **24**. With this modification the yield of **24** can be optimized up to 61% (based on **23**).

Although in amine and polyamine syntheses on solid support reductive amination is a widely used method only few applications of hydroaminomethylation on solid support are reported.[24] For polyamines attached to solid supports either a preformed polyamine dendron can be linked to a polymer[25] or the dendritic structures are formed



Scheme 7.

directly on the polymer. Here we wish to present a first example of the latter method using the hydroaminomethylation/deprotection protocol. For this commercially available Wang-resin was functionalized with Fmoc-L-proline using the carbodiimide method and cleavage of the Fmoc group with piperidine in DMF to give the NH-functionalized resin **29**.

The secondary amine function of resin **29** was alkylated using 5 equiv methallylphthalimide (**1**) under hydroaminomethylation conditions. Mechanical destruction of the polymer beads was minimized by slow stirring and use of a glass insert in the autoclave. After workup the result of hydroaminomethylation to give resin **30** in nearly quantitative yield was confirmed by hydrolysis of the linker function of a sample probe [with TFA/DCM/H_2O (49/49/2)] and ^{1}H NMR and MS analysis of the cleavage product. The NMR investigation revealed no detectable diastereoselectivity during hydroformylation and formation of the new stereogenic centers. Resin **30** is deprotected by hydrazinolysis at room temperature. Treatment with 3 equiv $H_2NNH_2 \cdot H_2O$ in dry ethanol results in resin **31** bearing a primary amine function in 95% yield. This step again was monitored by hydrolytic cleavage of a sample probe and NMR and MS investigation. Similarly a second hydroaminomethylation sequence was found to proceed in very good yields to give the first branching point for a growing dendron unit on solid support (Scheme 8).

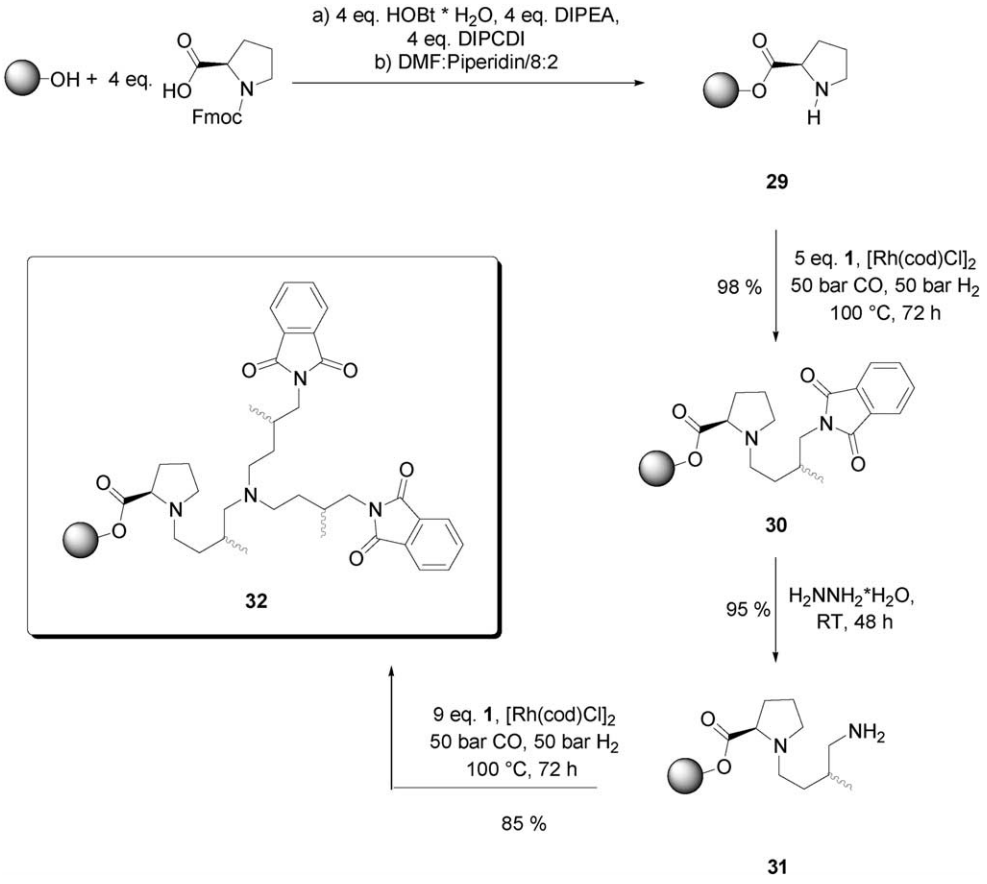
3. Conclusion

The results presented here show that hydroaminomethylation sequences can be used in solution or on solid support following divergent or convergent strategies to give polyamines in very good yields. This is demonstrated by using phthalimide protected methallylamine building blocks. According to earlier results, in principle, a variety of nonbranched, branched or cyclic unsaturated amine units can be used with high diversity. Similarly in the convergent strategies various core units can be used. Thus hydroaminomethylation allowing higher diversities than other established procedures is well suited as a new method for the generation of tertiary amines as branching points in dendrimer and solid phase synthesis.

4. Experimental section

4.1. General remarks

All general chemicals were purchased from commercial sources. The catalyst precursor $[Rh(cod)Cl]_2$ was prepared as previously described.[26] ^{1}H and ^{13}C NMR spectra were



Scheme 8.

recorded at room temperature with Bruker DRX 400 and DRX 500 spectrometers using $CDCl_3$ as solvent and TMS as an internal standard. The signals were assigned using APT, HH- and CH-correlation techniques. Infrared spectra were recorded with a Nicolet Impact 400 D spectrometer using neat compounds as films between NaCl or KBr plates or as disks with KBr. FAB-MS were recorded with a JEOL JMS-SX 102A spectrometer. MALDI-TOF-MS was carried out with a Voyager-DE Pro BioSpectrometerTM from PerSeptive Biosystems using a α-Cyano-4-hydroxycinnamic acid matrix. ESI-MS were recorded with a Finnigan (LC-Q). Elemental analyses were performed with a Leco CHNS-932 analyzer. Pressure reactions were carried out in autoclaves (type A, 250 ml, PTFE insert) from Berghof, Eningen and in a Parr stainless steel autoclave (250 ml). After charging the autoclave with the starting material, the catalyst precursor, the solvent, the reactor was flushed with argon, subjected to hydrogen and carbon monoxide, and heated to the required reaction temperature. Following the reaction, the solvent was removed by rotary evaporation and the catalyst was filtered off by passage through a small pad of neutral alumina (activity III). The products were purified by column chromatography on neutral alumina (activity III) gel from Merck (Darmstadt) or on silica gel 60 (70–230 mesh ASTM) from Macherey-Nagel GmbH & Co. KG.

4.2. Convergent route

4.2.1. Preparation of *N*-methallylphthalimide (1).[19] Freshly distilled methallylchloride (29.90 g, 330.00 mmol) was added dropwise to a well-stirred suspension of phthalimide (44.12 g, 300.00 mmol), anhydrous potassium carbonate (84.00 g, 608.00 mmol) and methyltrioctylammoniumchloride (5 ml) in dimethylformamide (160 ml), while maintaining the temperature at 20 °C in a water bath. After 20 h stirring, the slurry was poured into water (500 ml), the resulting precipitate was filtered, dried and crystallized from ethanol to give pure **1** (59.88 g, 297.58 mmol, 99%), mp 88 °C (lit. 87–88.[27]) ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=1.77 (s, 3H), 4.22 (s, 2H), 4.81 (s, 1H), 4.89 (s, 1H), 7.65–7.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=20.4, 43.2, 111.9, 123.3, 132.0, 134.0, 139.3, 168.1. IR (KBr), $\tilde{\nu}$ [cm^{-1}]=1124, 1188, 1327, 1383, 1393, 1428, 1443, 1467, 1610, 1713, 1769, 2920, 2973, 3095.

4.2.2. Preparation of benzyl-bis[4-(*N*-phthalimidyl)-3-methylbutyl]amine (7). Methallylphthalimide (**1**) (3.75 g, 18.64 mmol), Benzylamine (**6**) (1.00 g, 9.33 mmol) and $[Rh(cod)Cl]_2$ (15 mg, 0.33 mol%) were dissolved in 20 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated to 120 °C for 3 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate/hexane 1:5) to give 4.75 g (8.84 mmol, 95%) **7** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.80 (d, J=6.5 Hz, 6H), 1.21–1.32 (m, 2H), 1.50–1.61 (m, 2H), 1.96–2.05 (m, 2H), 2.35–2.55 (m, 4H), 3.35–3.60 (m, 6H), 7.11–7.30 (m, 5H), 7.65–7.90 (m, 8H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ [ppm]=17.4, 17.5, 30.8, 31.5, 44.1, 44.1, 51.2, 51.3, 58.6, 123.1, 126.7, 128.1, 128.8, 132.0, 133.8, 139.7, 168.6. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1157, 1171, 1188, 1264, 1318, 1335, 1366, 1380, 1397, 1434, 1453, 1467, 1641, 1705, 1715, 1773, 2856, 2873, 2930, 2960, 3028, 3060. HR-MS (FAB): for $C_{33}H_{35}N_3O_4$ calcd: 538.2706 $[M^+ + H]^+$, found: 538.2680 $[M^+ + H]^+$.

4.2.3. Preparation of bis[4-(*N*-phthalimidyl)-3-methylbutyl]amine (8). A mixture of **7** (240 mg, 0.45 mmol) and 10% palladium on carbon (100 mg with 50 w.-% water) in ethanol (120 mL) was stirred at room temperature under a hydrogen atmosphere for 24 h at atmospheric pressure. The catalyst was then filtered off and the organic phase was evaporated to give 195 mg (0.44 mmol, 98%) **8**. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.89 (d, J=6.7 Hz, 6H), 1.27–1.37 (m, 2H), 1.45–1.57 (m, 2H), 1.91–2.28 (m, 3H), 2.50–2.75 (m, 4H), 3.40–3.57 (m, 4H), 7.52–7.81 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.5, 30.8, 34.3, 43.9, 47.4, 123.1, 131.9, 133.8, 168.5. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=912, 1054, 1088, 1336, 1362, 1381, 1399, 1435, 1456, 1468, 1684, 1714, 1772, 2253, 2809, 2874, 2932, 3155, 3400, 3466. HR-MS (FAB): for $C_{26}H_{29}N_3O_4$ calcd: 448.2236 $[M^+ + H]^+$, found: 448.2235 $[M^+ + H]^+$.

4.2.4. Preparation of [3,5-bis({bis-[4-(*N*-phthalimidyl)-3-methyl-butyl]amino}methyl)benzyl]-bis[4-(*N*-phthalimidyl)-3-methyl-butyl]amine (10). A mixture of the 1,3,5-tris(bromomethyl)benzene (**9**) (150 mg, 0.42 mmol), **8** (941 mg, 2.10 mmol), potassium carbonate (1.16 g, 8.41 mmol), and 18-Crown-6 (222 mg, 0.84 mmol) in dry acetonitrile (100 ml) was refluxed under nitrogen for 3 days with vigorous stirring. The mixture was then cooled and evaporated to dryness under reduced pressure. Water (100 mL) was added to dissolve inorganic salts. After extraction with ethyl acetate and drying over sodium sulfate solvents were removed. The crude mixture was purified by column chromatography (silica gel, ethyl acetate) to give 333 mg (0.23 mmol, 55%) **10**. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm]=0.92 (d, J=6.7 Hz, 18H), 1.37–1.50 (m, 12H), 1.57–1.68 (m, 6H), 2.07–2.17 (m, 6H), 3.49–3.79 (m, 24H), 7.37–7.56 (m, 3H), 7.66–7.82 (m, 24H). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm]=17.6, 29.8, 36.9, 43.9, 53.0, 60.5, 123.1, 123.1, 123.2, 129.4, 132.0, 12.4, 133.9, 168.5, 168.7. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1056, 1361, 1382, 1399, 1436, 1468, 1712, 1772, 2933, 2964. MALDI-TOF-MS: for $C_{87}H_{93}N_9O_{12}$ calcd: 1456.70 $[M^+ + H]^+$, found: 1456.29 $[M^+ + H]^+$.

4.2.5. Preparation of *p*-Methoxybenzyl-bis[4-(*N*-phthalimidyl)-3-methylbutyl]amine (12). Methallylphthalimide (**1**) (7.25 g, 36.00 mmol), *p*-methoxybenzylamine (**11**) (2.47 g, 18.00 mmol) and $[Rh(cod)Cl]_2$ (20 mg, 0.45 mol%) were dissolved in 80 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 120 °C for 2 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate/hexane 1:5) to give 9.45 g (16.70 mmol, 93%) **12** as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.77 (d, J=6.5 Hz, 6H), 1.18–1.32 (m, 2H), 1.41–1.65 (m, 2H), 1.83–2.06 (m, 2H), 2.27–2.52 (m, 4H), 3.34–3.52 (m, 6H), 3.74 (s, 3H), 6.68–6.77 (m, 2H), 7.08–7.17 (m, 2H), 7.61–7.82 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.3, 17.4, 30.6, 30.6, 31.3, 31.4, 43.9, 44.0, 50.8, 50.9, 55.0, 57.6, 113.2, 113.5, 122.9, 129.8, 131.4 131.8, 133.6, 133.7, 158.4, 168.6. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1055, 1171, 1251, 1359, 1456, 1513, 1584, 1612, 1712, 1775, 2833, 2967, 3029, 3060, 3467, 3543. HR-MS (FAB): for $C_{34}H_{37}N_3O_5$ calcd: 568.2811 $[M^+ + H]^+$, found: 568.2788 $[M^+ + H]^+$.

4.2.6. Preparation of *p*-hydroxybenzyl-bis[4-(*N*-phthalimidyl)-3-methylbutyl]amine (13).[21] A solution of **12** (2.0 g, 3.52 mmol) in 50 mL of dry dichloromethane was cooled to −78 °C, and BBr_3 (1.32 g, 5.28 mmol in 10 ml dichloromethane) was added. After the mixture was stirred for 2 h at this temperature, the mixture was stirred for 18 h at room temperature. The BBr_3 was decomposed by addition of 10 mL of MeOH. The solvents were removed in vacuo, and the residue was suspended in water. The suspension was extracted with ethyl acetate. The crude mixture were purified by column chromatography (neutral alumina activity III, ethyl acetate) to give 1.33 g (2.40 mmol, 68%) **13** as a viscous brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.75–0.95 (m, 6H), 1.25–1.39 (m, 2H), 1.45–1.65 (m, 2H), 1.90–2.05 (m, 2H), 2.35–2.55 (m, 4H), 3.35–3.65 (m, 6H), 6.65–6.75 (m, 2H), 7.05–7.15 (m, 2H), 7.65–7.90 (m, 8H), (phenolic H is not visible). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.4, 17.5, 30.9, 31.2, 43.9, 44.0, 50.8, 57.8, 115.0, 123.2, 130.2, 131.9, 133.8, 154.9, 168.6. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1054, 1362, 1381, 1399, 1711, 1772, 2964, 3463. HR-MS (FAB): for $C_{33}H_{35}N_3O_5$ calcd: 554.2655 $[M^+ + H]^+$, found: 554.2628 $[M^+ + H]^+$.

4.2.7. Preparation of (4-{3,5-bis[4-({bis-[4-(*N*-phthalimidyl)-3-methyl-butyl]amino}methyl)-phenoxymethyl]benzyloxy}benzyl)-bis[4-(*N*-phthalimidyl)-3-methyl-butyl]amine (14). A mixture of the 1,3,5-tris(bromomethyl)benzene (**9**) (100 mg, 0.28 mmol), **13** (466 mg, 0.84 mmol), potassium carbonate (125 mg, 0.90 mmol), and 18-crown-6 (23 mg, 0.09 mmol) in dry acetonitrile (20 ml) was refluxed under nitrogen for 5 days with vigorous stirring. The mixture was then cooled and evaporated to dryness under reduced pressure. Water (20 mL) was added to dissolve inorganic salts. After extraction with ethyl acetate and drying over sodium sulfate solvents were removed. The crude mixture was purified by column chromatography (silica gel, ethyl acetate) to give 489 mg (0.28 mmol, 98%) **14**. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.76–0.83 (m, 18H), 1.24–1.32 (m, 6H), 1.47–1.58 (m, 6H), 1.74–1.88 (m, 6H), 1.96–2.02 (m, 6H), 2.40–2.46 (m, 6H), 3.41–3.54 (m, 18H), 4.92–5.09 (m, 6H), 6.79–6.96 (m, 6H), 7.06–7.24 (m, 6H), 7.29–7.40 (m, 3H), 7.66–7.83 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.4, 17.5, 30.9, 31.4, 44.0, 44.1, 51.0, 57.7, 69.7, 70.4, 113.4, 114.4, 114.8, 123.1, 129.2, 130.0, 132.0, 133.8, 137.9, 151.3, 168.6. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1053, 1239, 1359, 1381, 1398, 1434, 1467, 1510, 1611, 1712, 1771, 2930, 2959. ESI-MS: for $C_{108}H_{111}N_9O_{15}$ calcd: 1774.828 $[M^+ + H]^+$, found: 1774.823 $[M^+ + H]^+$.

4.2.8. Preparation of N^I-(4-Amino-3-methyl-butyl)-N^I-*p*-methoxybenzyl-3-methyl-butan-1,4-diamine (15). 12 (5.00 g, 8.80 mmol) and hydrazine hydrate (2.05 g, 40.95 mmol) in 50 ml dry ethanol were heated at 50 °C

for 24 h. The suspension was cooled and filtered. The filtrate was concentrated with a rotary evaporator. The residue was dissolved in 50 ml 2 N NaOH and extracted 3 times with 100 ml ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give **15** (2.66 g, 8.65 mmol, 98%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm]=0.85 (d, J=6.7 Hz, 6H), 1.12–1.30 (m, 6H), 1.31–1.60 (m, 4H), 2.28–2.71 (m, 8H), 3.34–3.59 (m, 2H), 3.75 (s, 3H), 6.75–6.96 (m, 2H), 7.15–7.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm]=17.4, 17.5, 31.3, 34.5, 48.3, 48.4, 51.3, 55.0, 57.7, 113.3, 129.8, 131.7, 158.3. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1038, 1170, 1247, 1300, 1376, 1463, 1511, 1611, 1662, 2853, 2923. HR-MS (FAB): for $C_{18}H_{33}N_3O$ calcd: 308.2707 $[M^+ + H]^+$, found: 308.2717 $[M^+ + H]^+$.

4.2.9. Preparation of {[*p*-methoxybenzyl-({bis-[4-(*N*-phthalimidyl)-3-methyl-butyl]amino}methyl-butyl) amino]methyl-butyl}-bis[(*N*-phthalimidyl)methyl-butyl]amine (16). Methallylphthalimide (**1**) (2.72 g, 13.50 mmol), **15** (1.00 g, 3.25 mmol) and $[Rh(cod)Cl]_2$ (10 mg, 0.30 mol%) were dissolved in 30 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 130 °C for 3 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate/hexane 1:1) to give 3.50 g (3.00 mmol, 92%) **16** as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.68–0.85 (m, 18H), 1.05–1.26 (m, 6H), 1.35–1.60 (m, 8H), 1.85–2.10 (m, 8H), 2.15–2.45 (m, 12H), 3.30–3.55 (m, 10H), 3.71 (s, 3H), 6.67–6.78 (m, 2H), 7.07–7.16 (m, 2H), 7.56–7.80 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.4, 17.4, 17.5, 17.6, 18.4, 18.4, 29.6, 29.7, 30.8, 30.9, 31.6, 31.7, 32.0, 43.9, 44.0, 44.1, 44.1, 51.3, 51.3, 51.7, 51.8, 51.9, 55.0, 57.2, 60.3, 61.8, 113.2, 123.0, 129.8, 131.7, 131.9, 133.7, 158.1, 168.4. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1053, 1087, 1171, 1188, 1246, 1356, 1380, 1398, 1435, 1467, 1510, 1622, 1712, 1773, 2803, 2932. HR-MS (FAB): for $C_{70}H_{85}N_7O_9$ calcd: 1168.6487 $[M^+ + H]^+$, found: 1168.6488 $[M^+ + H]^+$.

4.2.10. Preparation of N^I-(4-Amino-3-methyl-butyl)-N^I-{4-[{4-[bis(4-amino-3-methyl-butyl)amino]-3-methyl-butyl}-(4-methoxy-benzyl)amino]-2-methyl-butyl}-3-methyl-butane-1,4-diamine (17). 16 (560 mg, 0.48 mmol) and hydrazine hydrate (240 mg, 4.80 mmol) in 50 ml dry ethanol and 5 ml dry dichloromethane were heated at 50 °C for 48 h. The suspension was cooled and filtered. The filtrate was concentrated with a rotary evaporator. The residue was dissolved in 50 ml 8 N NaOH and extracted 10 times with 250 ml ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give **17** (250 mg, 0.39 mmol, 81%) as a yellow-orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.50–0.98 (m, 18H), 0.99–1.27 (m, 6H), 1.28–1.80 (m, 12H), 1.85–3.00 (m, 31H), 3.29–3.64 (m, 3H), 3.72 (s, 3H), 6.68–6.90 (m, 2H), 7.06–7.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.4, 17.5, 17.5, 17.6, 18.4, 18.5, 29.7, 29.7, 31.2, 31.3, 31.9, 32.0, 34.4, 47.9, 48.2, 48.3, 48.4, 51.1, 51.3, 52.2, 55.0, 60.3, 61.7, 113.2, 129.8, 129.8, 131.6, 158.2. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1007, 1029, 1079, 1158, 1272, 1374, 1462, 1668, 2806, 2924, 3296. HR-MS (FAB): for $C_{38}H_{77}N_7O$ calcd: 648.6268 $[M^+ + H]^+$, found: 648.6243 $[M^+ + H]^+$.

4.2.11. Preparation of {[*p*-hydroxybenzyl-({bis[4-(*N*-phthalimidyl)-3-methyl-butyl]amino}methyl-butyl) amino]methyl-butyl}-bis[(*N*-phthalimidyl)methyl-butyl] amine (18).[21] A solution of **16** (2.0 g, 1.71 mmol) in 50 mL of dry dichloromethane was cooled to −78 °C, and BBr_3 (1.29 g, 5.15 mmol in 10 ml dichloromethane) was added. After the mixture was stirred for 2 h at this temperature, the mixture was stirred for 18 h at room temperature. The BBr_3 was decomposed by addition of 10 mL of MeOH. The solvents were removed in vacuo, and the residue was suspended in water. The suspension was extracted with ethyl acetate. The crude mixture were purified by column chromatography (neutral alumina activity III, first ethyl acetate then methanol) to give 1.25 g (1.08 mmol, 63%) **18** as a viscous brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm]=0.68–0.89 (m, 18H), 1.00–1.26 (m, 6H), 1.35–1.60 (m, 8H), 1.80–2.15 (m, 9H), 2.20–2.60 (m, 11H), 3.30–3.55 (m, 10H), 6.67–6.85 (m, 2H), 7.05–7.20 (m, 2H), 7.55–7.85 (m, 16H), (phenolic H is not visible). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm]=17.4, 17.4, 17.5, 17.5, 18.3, 29.8, 30.8, 30.9, 31.4, 31.4, 31.5, 44.0, 44.1, 51.7, 51.8, 56.9, 60.6, 61.6, 115.7, 122.8, 123.1, 131.3, 131.8, 133.8, 148.2, 168.5. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1053, 1087, 1189, 1359, 1380, 1398, 1434, 1467, 1514, 1614, 1716, 1772, 2804, 2872, 2930, 2958, 3440. HR-MS (FAB): for $C_{69}H_{83}N_7O_9$ calcd: 1154.6331 $[M^+ + H]^+$, found: 1154.6372 $[M^+ + H]^+$.

4.3. Divergent route

4.3.1. Preparation of 4-bis(4-*N*-phthalimido-3-methyl-butyl)piperazine (20). Methallylphthalimide (**1**) (4.03 g, 20.00 mmol), piperazine (**19**) (862 mg, 10.00 mmol) and $[Rh(cod)Cl]_2$ (15 mg, 0.61 mol%) were dissolved in 50 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 120 °C for 2 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (silica gel, ethyl acetate/hexane 1:5) to give 4.91 g (9.51 mmol, 95%) **20** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.91 (d, J=6.7 Hz, 6H), 1.25–1.40 (m, 2H), 1.49–1.61 (m, 2H), 1.90–2.05 (m, 2H), 2.15–2.75 (m, 12H), 3.45–3.65 (m, 4H), 7.65–7.86 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.6, 31.4, 31.4, 44.1, 53.2, 56.3, 123.2, 132.0, 133.9, 168.6. IR (Film, NaCl), $\tilde{\nu}$ [cm^{-1}]=1053, 1161, 1354, 1379, 1399, 1433, 1466, 1610, 1725, 1771, 2688, 2814, 2879, 2937, 3463. EA: for $C_{30}H_{36}N_4O_4$ calcd: C=69.7%, H=7.0%, N=10.8%, found: C=69.7%, H=7.0%, N=10.5%. HR-MS (FAB): for $C_{30}H_{36}N_4O_4$ calcd: 517.2815 $[M^+ + H]^+$, found: 517.2782 $[M^+ + H]^+$.

4.3.2. Preparation of 4-[4-(4-amino-3-methyl-butyl) piperazin-1-yl]-2-methyl-butylamine (21). 4-Bis(4-N-phthalimido-3-methyl-butyl)piperazine (**20**) (4.30 g, 8.32 mmol) and hydrazine hydrate (1.25 g, 24.46 mmol) in 100 ml dry ethanol were heated at 50 °C for 24 h. The suspension was cooled and filtered. The filtrate was concentrated with a rotary evaporator. The residue was dissolved in 50 ml 8 N NaOH and extracted 3 times with 100 ml ethyl acetate. The combined organic layers were dried over

$MgSO_4$, filtered and concentrated to give 4-[4-(4-amino-3-methyl-butyl)-piperazin-1-yl]-2-methyl-butylamine (**21**) (2.09 g, 8.15 mmol, 98%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm]=0.75–0.85 (m, 6H), 1.09–1.29 (m, 6H), 1.33–1.42 (m, 2H), 1.43–1.54 (m, 2H), 2.01–2.58 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm]=17.4, 31.2, 34.9, 48.9, 53.1, 56.4. IR (film, KBr), $\tilde{\nu}$ [cm^{-1}]=1123, 1160, 1273, 1310, 1336, 1373, 1463, 1558, 1568, 1601, 1667, 2809, 2870, 2949, 3291, 3363. HR-MS (FAB): for $C_{14}H_{32}N_4$ calcd: 257.2705 $[M^+ + H]^+$, found: 257.2698 $[M^+ + H]^+$.

4.3.3. Preparation of {4-[4-(4-{bis[4-(*N*-phthalimidyl)-3-methyl-butyl]amino}-3-methyl-butyl)piperazin-1-yl]-2-methyl-butyl}-bis[4-(*N*-phthalimidyl)-3-methyl-butyl] amine (22). Methallylphthalimide (**1**) (1.75 g, 8.70 mmol), **21** (550 mg, 2.14 mmol) and $[Rh(cod)Cl]_2$ (10 mg, 0.47 mol%) were dissolved in 30 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 120 °C for 2 days. After cooling the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate/hexane 1:1) to give 2.25 g (2.01 mmol, 94%) **22** as a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm]=0.69–0.96 (m, 18H), 0.99–1.31 (m, 6H), 1.35–1.67 (m, 8H), 1.84–2.15 (m, 9H), 2.16–2.65 (m, 19H), 3.38–3.62 (m, 8H), 7.59–7.84 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm]=17.4, 17.5, 17.5, 17.6, 18.5, 29.8, 30.2, 30.8, 30.9, 31.6, 31.7, 32.1, 32.2, 44.0, 44.1, 44.1, 44.1, 51.9, 52.0, 52.0, 53.2, 56.7, 60.4, 123.1, 123.1, 131.9, 133.7, 133.8, 168.5. IR (Film, KBr), $\tilde{\nu}$ [cm^{-1}]=1269, 1356, 1379, 1398, 1414, 1467, 1614, 1716, 1772, 2808, 2873, 2930, 3058, 3467. HR-MS (FAB): for $C_{66}H_{84}N_8O_8$ calcd: 1117.6490 $[M^+ + H]^+$, found: 1117.6489 $[M^+ + H]^+$.

4.3.4. Preparation of N^1-(4-amino-3-methyl-butyl)-N^1-[4-(4-{4-[bis(4-amino-3-methyl-butyl)amino]-3-methyl-butyl}piperazin-1-yl)-2-methyl-butyl]-3-methyl-butane-1,4-diamine (23). 22 (500 mg, 0.45 mmol) and hydrazine hydrate (450 mg, 9.00 mmol) in 70 ml dry ethanol were heated at 50 °C for 48 h. The suspension was cooled and filtered. The filtrate was concentrated with a rotary evaporator. The residue was dissolved in 50 ml 8 N NaOH and extracted 10 times with 250 ml ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give **23** (224 mg, 0.38 mmol, 84%) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.68–0.93 (m, 18H), 0.99–1.20 (m, 7H), 1.26–1.80 (m, 23H), 1.91–2.10 (m, 4H), 2.13–2.44 (m, 19H), 2.44–2.67 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.4, 18.4, 18.9, 30.0, 31.2, 32.0, 34.4, 48.2, 48.3, 48.3, 48.4, 52.1, 53.1, 56.6, 60.2, 61.6. IR (Film, KBr), $\tilde{\nu}$ [cm^{-1}]=1007, 1029, 1079, 1158, 1272, 1374, 1462, 1668, 2806, 2923, 3290. HR-MS (FAB): for $C_{34}H_{76}N_8$ calcd: 597.6271 $[M^+ + H]^+$, found: 597.6287 $[M^+ + H]^+$.

4.3.5. Preparation of compound 24.

4.3.5.1. Method A. Methallylphthalimide (**1**) (0.30 g, 1.49 mmol), **23** (88 mg, 0.15 mmol) and $[Rh(cod)Cl]_2$ (0.2 mg, 0.05 mol%) were dissolved in 10 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 100 °C for 5 days. After cooling, the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate/hexane 10:1) to give 119 mg (51.60 μmol, 35%) compound **24** as a yellow wax. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.68–1.04 (m, 36H), 1.05–1.29 (m, 7H), 1.29–1.48 (m, 10H), 1.49–1.68 (m, 10H), 1.72–2.01 (m, 8H), 2.01–2.19 (m, 8H), 2.21–2.99 (m, 25H), 3.03–4.15 (m, 44H), 7.62–7.77 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.5, 17.9, 27.7, 29.8, 36.8, 36.9, 43.1, 43.8, 48.3, 60.3, 123.1, 131.8, 133.8, 168.6. IR (Film, KBr), $\tilde{\nu}$ [cm^{-1}]=1054, 1088, 1171, 1188, 1263, 1334, 1358, 1383, 1398, 1437, 1458, 1468, 1616, 1712, 1772, 2933, 2964, 3467. ESI-MS: for $C_{138}H_{180}N_{16}O_{16}$ calcd: 2320.01 $[M^+ + H]^+$, found: 2319.40 $[M^+ + H]^+$.

4.3.5.2. Method B. *Preparation of phthalimidyl-3-methyl-butyraldehyde* (**25**). Methallylphthalimide (**1**) (5.00 g, 24.85 mmol) and $[Rh(cod)Cl]_2$ (15 mg, 0.24 mol%) were dissolved in 50 ml of dry toluene and placed in the autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 120 °C for 1 day. After cooling, the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate) to give 5.73 g (24.80 mmol, 100%) **25** as a colorless wax. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm]=1.01 (d, J=6.8 Hz, 3H), 2.21–2.66 (m, 3H), 3.58–3.65 (m, 2H), 7.68–7.88 (m, 4H), 9.72 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm]=17.8, 30.0, 43.3, 48.5, 123.3, 131.9, 134.0, 168.6, 201.2.

Preparation of compound **24**.180 mg (0.74 mmol) **25**, 88 mg (0.15 mmol) **23** and $[Rh(cod)Cl]_2$ (5.0 mg, 1.35 mol%) were dissolved in 10 ml of dry toluene placed in the autoclave and stirred for 1 h at RT under Argon. The autoclave is then pressurized with 50 bar H_2 and 10 bar CO and heated at 120 °C for 1 day. After cooling and expanding the gases 180 mg (0.74 mmol) **25** is added and the mixture is stirred again for 2 h at RT under Argon. At last step the autoclave is pressurized again with 50 bar H_2 and 10 bar CO and heated at 120 °C for one more day. After cooling, the solvent was removed in a rotary evaporator and the crude mixture was purified by column chromatography (neutral alumina activity III, ethyl acetate/hexane 10:1) to give 208 mg (0.09 mmol, 61%) compound **24** as a yellow wax. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.68–1.04 (m, 36H), 1.05–1.29 (m, 7H), 1.29–1.48 (m, 10H), 1.49–1.68 (m, 10H), 1.72–2.01 (m, 8H), 2.01–2.19 (m, 8H), 2.21–2.99 (m, 25H), 3.03–4.15 (m, 44H), 7.62–7.77 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=17.5, 17.9, 27.7, 29.8, 36.8, 36.9, 43.1, 43.8, 48.3, 60.3, 123.1, 131.8, 133.8, 168.6. IR (Film, KBr), $\tilde{\nu}$ [cm^{-1}]=1054, 1088, 1171, 1188, 1263, 1334, 1358, 1383, 1398, 1437, 1458, 1468, 1616, 1712, 1772, 2933, 2964, 3467.ESI-MS: for $C_{138}H_{180}N_{16}O_{16}$ calcd: 2320.01 $[M^+ + H]^+$, found: 2319.40 $[M^+ + H]^+$.

4.4. Solid supported reactions

4.4.1. Preparation of L-proline-*Wang-yl*-ester (29).

4.4.1.1. Preparation of Fmoc-L-proline-*Wang-yl*-ester. A solution of Fmoc-L-proline (556 mg, 1.65 mmol),

diisopropylethylamine (DIPEA) (213 mg, 1.65 mmol), 1-hydroxybenzotriazolehydrate ($HOBt \cdot H_2O$) (253 mg, 1.65 mmol), diisopropylcarbodiimide (DIPCDI) (208 mg, 1.65 mmol) in 5 ml dry DMF was added to Wang resin (500 mg 0.82 mmol/g). The mixture was shaken at room temperature for 24 h. The resin was filtered, washed with DMF (5 times) and CH_2Cl_2 (5 times) and dried to constant weight in vacuo.

4.4.1.2. Deprotection of Fmoc-L-proline-*Wang-yl*-ester on solid support to form 29. A suspension of the obtained Fmoc-L-proline-*Wang-yl*-ester (550.0 mg) in DMF/piperidine (4:1, 6 ml) was shaken at room temperature for 30 min and filtered, washed with DMF (5 times) and CH_2Cl_2 (5 times) and dried to constant weight in vacuo.

4.4.2. Preparation of 1-[4-(*N*-phthalimidyl)-3-methyl-butyl]proline-*Wang-yl*-ester (30). Methallylphthalimide (**1**) (433 mg, 2.15 mmol), **29** (510 mg, 387.06 μmol) and $[Rh(cod)Cl]_2$ (2 mg, 0.38 mol%) were dissolved in 80 ml of dry toluene and placed with the glass inlet in the Parr autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 100 °C for 3 days. After cooling the resin was filtered, washed with DMF (5 times), CH_2Cl_2 (5 times), DMF (5 times), CH_2Cl_2 (5 times) and dried to constant weight in vacuo.

4.4.3. Confirmation of the structure of 1-[4-(*N*-phthalimidyl)-3-methyl-butyl]proline-*Wang-yl*-ester (30). A suspension of **30** (90 mg, 58.73 μmol) in $TFA/CH_2Cl_2/H_2O$ (49:49:2.5 ml) was shaken at room temperature for 60 min. The resin was filtered and the filtrate was evaporated in vacuo to give a diastereomeric mixture (1:1) of 1-[4-(*N*-phthalimidyl)-3-methyl-butyl]proline (19 mg, 57.51 μmol, 98%). ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.87–1.02 (m, 3H), 1.52–1.89 (m, 2H), 1.95–2.21 (m, 3H), 2.25–2.58 (m, 2H), 3.05–3.24 (m, 1H), 3.27–3.63 (m, 4H), 3.92–4.27 (m, 2H), 7.62–7.89 (m, 4H), 9.15 (bs, 1H). HR-MS (FAB): for $C_{18}H_{22}N_2O_4$ calcd: 331.1658 $[M^+ + H]^+$, found: 331.1673 $[M^+ + H]^+$.

4.4.4. Preparation of 1-(4-amino-3-methyl-butyl)proline-*Wang-yl*-ester (31). A suspension of **30** (500 mg, 326.18 μmol), hydrazine hydrate (76 mg, 1.50 mmol) in 3 ml dry ethanol was shaken at room temperature for 48 h. The resin was filtered and washed with DMF (5 times), CH_2Cl_2 (5 times), DMF (5 times), CH_2Cl_2 (5 times), diethylether (5 times), methanol (5 times), diethylether (5 times) and dried to constant weight in vacuo.

4.4.5. Confirmation of the structure of 1-(4-amino-3-methyl-butyl)proline-*Wang-yl*-ester (31). A suspension of **31** (94 mg, 67.03 μmol) in $TFA/CH_2Cl_2/H_2O$ (49:49:2.5 ml) was shaken at room temperature for 60 min. The resin was filtered and the filtrate was evaporated in vacuo to give a diastereomeric mixture (1:1) of 1-(4-amino-3-methyl-butyl)proline (13 mg, 64.91 μmol, 97%). ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.80–1.10 (m, 3H), 1.37–1.63 (m, 2H), 1.63–1.96 (m, 4H), 2.30–2.45 (m, 2H), 2.56–2.92 (m, 2H), 2.94–3.21 (m, 2H), 3.21–3.41 (m, 1H), 3.44–3.69 (m, 1H), 4.21–4.40 (m, 1H), (hydrogen of carboxyl group is not visible). HR-MS (FAB): for $C_{10}H_{20}N_2O_2$ calcd: 201.1603 $[M^+ + H]^+$, found: 201.1596 $[M^+ + H]^+$.

4.4.6. Preparation of 1-(4-{bis[4-(*N*-phthalimidyl)-3-methyl-butyl]amino}-3-methyl-butyl)proline-*Wang-yl*-ester (32). Methallylphthalimide (**1**) (131 mg, 0.65 mmol), **31** (100 mg, 71.29 μmol) and $[Rh(cod)Cl]_2$ (1 mg, 0.62 mol%) were dissolved in 80 ml of dry toluene and placed with the glass inlet in the Parr autoclave. The autoclave was pressurized with 100 bar CO/H_2 (1:1) and heated at 100 °C for 3 days. After cooling the resin was filtered, washed with DMF (5 times), CH_2Cl_2 (5 times), DMF (5 times), CH_2Cl_2 (5 times) and dried to constant weight in vacuo.

4.4.7. Confirmation of the structure of 1-(4-{bis[4-(*N*-phthalimid-yl)-3-methyl-butyl]amino}-3-methyl-butyl)-proline (32). A suspension of **32** (103 mg, 56.20 μmol) in $TFA/CH_2Cl_2/H_2O$ (49:49:2.5 ml) was shaken at room temperature for 60 min. The resin was filtered and the filtrate was evaporated in vacuo to give 1-(4-{bis-[4-(*N*-phthalimid-yl)-3-methyl-butyl]amino}-3-methyl-butyl)-proline (30 mg, 47.56 μmol, 85%) as a diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.76–1.01 (m, 9H), 1.12–1.30 (m, 2H), 1.41–1.59 (m, 3H), 1.63–1.81 (m, 3H), 1.84–2.10 (m, 6H), 2.65–2.77 (m, 2H), 2.81–2.92 (m, 2H), 2.97–3.14 (m, 4H), 3.19–3.35 (m, 1H), 3.39–3.52 (m, 3H), 3.57–3.65 (m, 1H), 4.20–4.38 (m, 1H), 7.77–8.00 (m, 8H), (hydrogen of carboxyl group is not visible). HR-MS (FAB): for $C_{36}H_{46}N_4O_6$ calcd: 630.3463 $[M^+ + H]^+$, found: 630.3417 $[M^+ + H]^+$.

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Synthesis of melampolides and *cis*,*cis*-germacranolides as natural herbicide models☆

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Abstract—The comparative study between the theoretical molecular properties of the starting materials and the yields in the transformation of melampolides to *cis*,*cis*-germacranolides using SeO_2/*t*-BuOOH (TBHP) as oxidant allows to establish a feasible relationship with their values of dipolar moment. Conditions for this transformation are optimized and some mechanistic considerations are made based in this finding. Cluster analysis of the phytotoxic activity of the melampolides and *cis*,*cis*-germacranolides obtained shows that the activity is greatly influenced by the spatial shape of the backbone, prevailing upon other factors such as the presence of reactive functional groups.

1. Introduction

Selenium dioxide is a soft and widely used reagent useful to get access to allylic alcohols and unsatured carbonyl systems from alkenes, among others. The mechanism is thought to proceed through a first 'ene' reaction rate-determining step, followed by a [2,3] sigmatropic rearrangement, and breakdown of the resultant selenium ester.[1] This subject has been recently revisited, so as kinetic isotope effects and theoretical calculations strongly supports the idea of an ene concerted reaction with SeO_2 itself as active oxidant rather than an ene-concerted process with a selenous ester, or even an electrophilic attack by $HSeO_2^+$. However, the isolation of some minor products suggests the presence of a minor pathway involving a stepwise ene reaction through reversible formation of a zwitterion followed by rate-limiting proton transfer.[2] In spite of its usefulness, some environmental and safety concerns have arisen because wastes contain high amounts of the metal. Thus, metal-catalyzed oxidation methods with alkyl-hydroperoxides as stoichiometric oxidant have been developed and are commonly used. Among them, the system SeO_2/*tert*-butyl-hydroperoxide (TBHP) has found extensive application in natural products synthesis as a soft and stereoselective reactive.[3,4]

Currently, we are interested in developing new models of agrochemicals based on phytotoxic allelochemicals.[5] The increasing incidence of resistant weeds to important herbicides classes such as *s*-triazines[6] and dinitroanilines[7] in addition to environmental concerns are pulling-on research on this field. As an alternative, Allelopathy is able to offer new lead compounds to be used as herbicides and several classes of compounds such as phenolics, alkaloids, and terpenes have been reported as phytotoxic.[8] Among them, germacranolides (Fig. 1) constitute a very interesting group because of the high number of compounds reported and their wide spectrum of biological activities that includes pharmacological,[9] cytotoxic,[10] fungicidal,[11] antibacterial,[12] and allelopathic activities.[13] Consequently, an important effort to synthesize the germacranolide skeleton has been made.[14] These efforts have been centred, mainly, in *trans*,*trans*-germacranolides, but little has been done about the chemistry and biological activity in the other subgroups.

Going on with our previous work in sesquiterpene lactones (SL) as potential lead herbicides[4,5,15] here in we report the

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Keywords: Allylic oxidation mechanism; Synthesis of sesquiterpenes; Melampolides; *cis*,*cis*-Germacranolides; Structure–activity relationship study (SAR).

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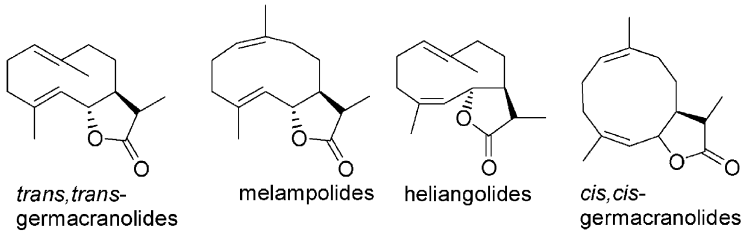


Figure 1. Main germacranolides backbones.

diasterospecific synthesis of several SL with melampolide and *cis*,*cis*-germacranolide skeletons using modified reaction conditions in the SeO_2–TBHP system[17] suitable for use in a Structure–Activity Relationship (SAR) study of their phytotoxicity.

2. Results and discussion

Metal-catalyzed oxidations with alkyl hydroperoxides can be divided into two categories depending on if the intermediate involved in the oxygen-transfer step is a peroxometal or an oxometal. In other words, the initial oxidizing agent could be the selenium dioxide itself, or the selenium-TBHP adduct. It is generally believed that this reaction proceeds through an initial ene reaction of SeO_2 with the olefin, followed by a [2,3] sigmatropic rearrangement, the resulting Se(II) being reoxidized by TBHP, and additional data supporting this vision has been published (Fig. 2).[16] In this case, only a catalytic amount of the metal is needed (typically, 2 mol%).[17]

When this reaction is carried out using the natural germacranolide costunolide (**1**) as substrate the amount of SeO_2 needed increases and the stereochemistry of the double bond changes in the final product from *E* to *Z* (compound **2**). In this case, a different mechanism with a bulky peroxometal intermediate *t*-BuOO–SeO_3H has been proposed (Fig. 3).[17]

This mechanism should certainly explain why the methyl group at C-10 reacts before the methylene position at C-9 in the germacranolide skeleton, instead of the accepted order $CH_2 > CH_3 > CH$.[16] The change in the stereochemistry of the double bond takes place through a rotation before the sigmatropic rearrangement occurs.

The reaction also yields as side-products the corresponding 14-oxoderivatives due to oxidation of the resulting hydroxyl group. This reaction has demonstrated to be useful in getting access to the melampolide and *cis*,*cis*-germacranolide skeletons, even though the yields obtained for *cis*,*cis*-germacranolides were low (around 10%).[5a]

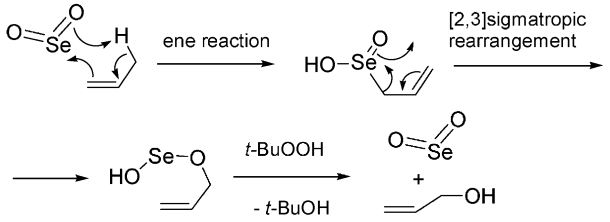


Figure 2. General mechanism of the SeO_2 allylic oxidation.

2.1. Synthesis and molecular modeling

In order to overcome these low yields and aiming also to perform a SAR study melampolides **2–8** were used as starting materials to obtain the corresponding *cis*,*cis*-germacranolides (Table 1) with different yields. Conditions for optimal yields were set to as SeO_2/TBHP (0.5:2 molar ratio) in a reflux of DCM using compound **4**. These conditions allow to minimize the amount of the 14-oxo-derivative. Best results were obtained with the 14-acetoxy- and 14-chloro-derivatives **4** and **5** respectively, followed by the oxo-melampolide **3** and the hydroxy-melampolide **2**. The 14-TBDMS derivative **6** gave the 14-oxoderivative **3** (53% yield) due to deprotection of the silyl group caused by the acid medium generated by the selenium salts and subsequent oxidation of the free hydroxyl. No change in the stereochemistry of the Δ(4–5) double bond was observed. Finally, lower or no yields were obtained with the epoxy-derivatives **7** and **8** (Table 1).

Theoretical ΔH_r° values as obtained using PM3 calculations (Table 2)[18] were in all cases about −42 Kcal/mol. This result supports the idea that the different reactivity observed for each substrate should not be related with the difference of energy between starting and final products. Consequently, factors affecting the transition states should arise as determining to explain the experimental data.

According to the mechanism proposed by Haruna and Ito[17] three transition states will consecutively take place during the reaction (Fig. 4): (a) a cyclic intermediate corresponding to the ene reaction step $E_1^\#$; (b) the eclipsed conformation of the selenium substituent and the double bond during the rotation step $E_2^\#$; and (c) that corresponding to the sigmatropic rearrangement $E_3^\#$. The conformational flexibility of the backbone in the different substrates and end products are mostly the same and are not influenced by substituents at the C-14 position. Otherwise, the reacting part of the melampolide (e.g. the double bond at C-4, C-5 and the C-15 methyl group) is the same for all starting compounds (**2–8**). Consequently, the activation energies corresponding to the rotation and rearrangement steps have to be similar in all cases and will not determine the different yields observed. Thus, we propose as a feasible working hypothesis that those factors affecting the energy of the first transition state ($E_1^\#$, ene reaction) would be crucial to explain the different results obtained and will also be in good agreement with the literature.[16]

A correlation between theoretical dipolar moments obtained

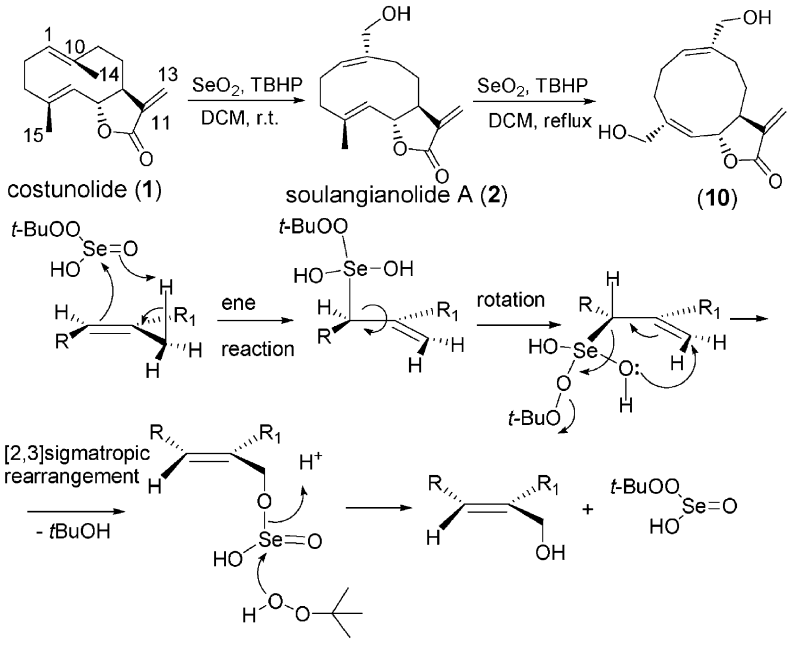
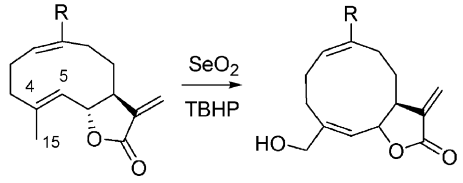


Figure 3. Mechanism proposed for the SeO_2-TBHP allylic oxidation.[17]

from PM3 calculations and the experimental yields can be observed (Table 1, Fig. 5): the lower the dipolar moment is, the higher the resulting yield. This correlation would be in good agreement with the hypothesis presented: the ene reaction is a concerted process where no new charges are generated; lower dipolar moments of starting material lead to lower dipolar moments in the transition state, and thus, transition states with lower polarities will be better dissolved in low polar solvents such as those used for these oxidations (DCM: $\mu = 1.60$ D; THF: $\mu = 1.63$ D). Accordingly, the solvation enthalpy contribution will be diminished and, consequently, the activation energy will also be lowered, thus favoring the reaction pathway. Compounds **4** and **5** present the lower dipolar moments and the higher yields while the free alcohol **2** and the 14-oxoderivative **3** render lower amounts of the *cis*,*cis*-germacranolide. Finally, the epoxiderivative **8**, with the highest value of dipolar moment, does not react at all (Table 1).



Compound **7** constitutes an exception to this correlation (Fig. 5), as the theoretical value of the dipolar moment does not match with the reactivity. However, experimental R_f values obtained by TLC show that real polarity of this compound should correspond to a value similar to those of compounds **2** and **8**, thus matching the correlation proposed.

The starting melampolide **2** was obtained from costunolide (**1**) using SeO_2/TBHP, along with the aldehyde **3** as side product.[5a,17] The acetylated derivative **4** was used as starting material for *cis*,*cis*-germacranolide large scale synthesis since it provided the best yields. Selective epoxidation using MCPBA at the C1–C10 (**18** and **19**) or the C4–C5 (**15**) double bonds in the *cis*,*cis*-germacranolide backbone was achieved through the introduction of a bulky steric demanding *tert*-butyl-dimethyl-silyl (TBDMS) group at C15 (**16**). However, steric hindrance induced by the C14-acetoxyl group in **16** did not allow direct epoxidation at C1–C10. So, selective deprotection of the acetoxy derivative at C14 was carried out using magnesium methoxide,[19] yielding the corresponding de-acetylated derivative (**17**) and traces of the enantiomerically pure Michael adduct at the unsatured lactone ring (**17b**). The stereochemistry of compound **17b** was unequivocally assigned as 11*S* through NOESY experiments. Epoxidation of the resulting free-hydroxyl compound **17** yielded both alpha (**18**) and beta

Table 1. Melampolide to *cis*,*cis*-germacranolides conversion using SeO_2/TBHP as oxidant system[a]

R	Starting material	Final product	Yield (%)	Dipolar moment (μ, D)
CH_2OH	**2**	**10**	10	4.34
CHO	**3**	**11**	24	4.45
CH_2OAc	**4**	**12**	57	3.78
CH_2Cl	**5**	**13**	43	4.04
$CH_2OTBDMS$[b]	**6**	**3**	53	4.70
1β,10β-Epoxy-derivatives				
CH_2OH	**7**	**14**	3	3.87
CH_2OAc	**8**	—	—	4.49

[a] SeO_2:TBHP molar relation (0.5:2), DCM, reflux.
[b] The reaction product was the carbaldehyde melampolide, with no change in the stereochemistry.

Table 2. Theoretical ΔH_f° and ΔH_r° (Kcal/mol) for some germacranolides as obtained from PM3 calculations[18]

Starting material	ΔH_f° (Kcal/mol)	End product	ΔH_f° (Kcal/mol)	ΔH_r° (Kcal/mol)
2	−94.8	**10**	−137.1	−42.3
3	−82.3	**11**	−124.4	−42.1
4	−136.6	**12**	−177.1	−40.5
5	−61.2	**13**	−101.2	−40.0
7	−106.8	**14**	−153.4	−46.6

(**19**) epoxide isomers. Finally, epoxidation of the double bond at C4–C5 only afforded one isomer (**15**) due to hindrance of the alpha face of the molecule by the lactone ring (Fig. 6). Epoxidation in the same position of the melampolide framework is not possible due to steric restrictions caused by the spatial disposition of the molecule.

2.2. Bioassays and SAR studies

The bioactive properties of sesquiterpene lactones have been attributed for a long time to the electrophilic properties of the α-methylene-γ-lactone moiety because it easily reacts with nucleophilic groups contained in important biomolecules.[20] A long discussion whether nucleophilic additions at the double bond of the lactone ring is the main factor causing bioactivity on sesquiterpene lactones is still on the literature. However, this feature might not be the only responsible of their bioactivity and we have recently reported positive bioactive sesquiterpene lactones without this functional group.[4,15a] The changes introduced in the basic melampolide and *cis*,*cis*-germacranolide frameworks attend to analyze the influence in the activity that the following criteria might have: (i) influence of reactive groups other than the α-methylene-γ-lactone group; (ii) influence of the spatial arrangement of the basic carbon framework; and (iii) importance of halogen-containing compounds, very common in pesticide and insecticide synthetic designs.[21] Consequently, compounds depicted in Figure 6 were synthesized according to the methodology described above and tested. Compounds **1** and **22–26** were previously tested[4] and have been introduced here by means of comparison and cluster analysis.

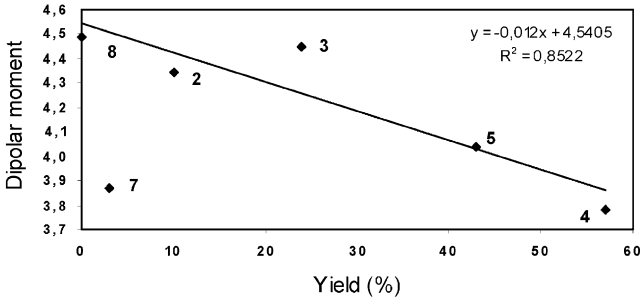


Figure 5. Correlation between dipolar moments of starting materials and the yields in the SeO_2/TBHP allylic oxidation.

Bioassays were carried out using the monocots *Triticum aestivum* L. and *Allium cepa* L., and the dicots *Lactuca sativa* L. and *Lepidium sativum* L. as target species, according to the methodology reported by our group[22] and

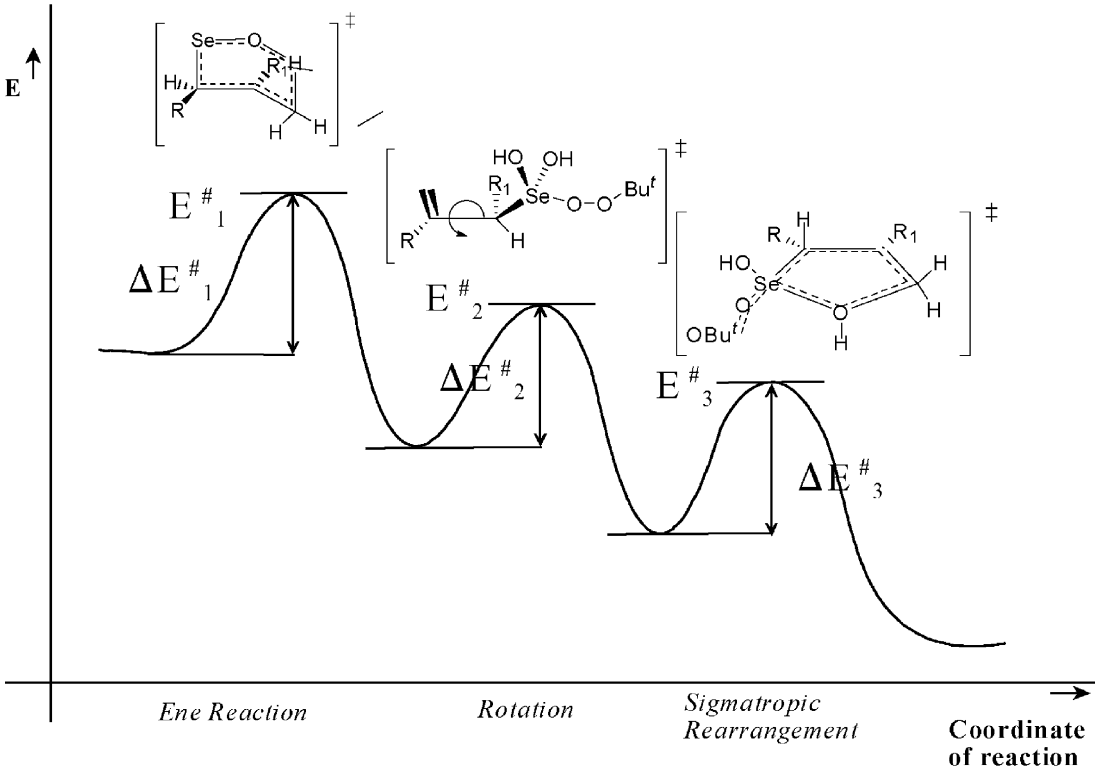


Figure 4. Activated states according to the proposed reaction mechanism.

Table 3. ^{1}H NMR data for listed compounds (400 MHz in $CDCl_3$, signal of the residual $CHCl_3$ centered at δ 7.25 ppm)[a]

H	3	4	5	6	8	9	10	11	12	12b
1	6.48 dd	5.48	5.59	5.42	2.90	4.48 m	5.49 dd	6.56	5.54	5.45
2α	2.40[b] m	2.12[b]	2.15[b]	2.11[b]	2.32 dddd	2.02[b] m	2.20[b]	2.76[b]	2.27[b]	2.40 dddd
2β	2.26[b] m	1.95[b]	1.99[b]	1.94[b]	1.19	1.56[b]	2.52[b]	2.54[b]	2.55[b]	2.60
3α	2.04 ddd	1.87 m	1.85 ddd	1.84 m	2.24 ddd	2.32[c] m	2.24[c] ddd	2.46 m	2.24[c]	2.51 ddd
3β	2.28 m	2.16	1.58	2.15	2.16	2.18[c] ddd	2.66[c] m	2.62 m	2.67[c]	2.83 ddd
5	4.97 brd	5.00	5.00	5.04	5.24 d	5.38 brd	5.48	5.50 d	5.49	6.32 brd
6	4.52 dd	4.54	4.58	4.58	4.59	4.62	5.19	5.07	5.18	5.35
7	2.26 ddddd	2.57	2.43	2.59	2.81	2.73	2.71 m	2.44	2.72	2.87
8α	2.86 dddd	2.26	2.36 m	2.33 dddd	2.16 m	2.28	2.08 dddd	2.42	2.07	2.07 m
8β	1.44 dddd	1.54	1.57	1.50	1.62	1.67	1.72	1.67	1.73	1.82
9α	2.38[c] m	2.17[c]	2.03[c]	2.18[c]	2.06	1.92[d]	2.60[d]	2.80	2.61	2.24 ddd
9β	1.95[c] m	2.07[c]	1.97[c]	2.01[c]	1.37 ddd	1.33[d]	2.30[d]	2.49 m	2.22	2.64
13a	5.41 d	5.39	5.46	5.40	5.41	5.42	5.58	5.58	5.39	5.69
13b	6.08 d	6.11	6.18	6.16	6.18	6.17	6.27	6.25	6.11	6.37
14	9.39 d	4.38	4.13	4.14	4.43	9.83 s	4.10 d	9.42	4.38	4.58
14′		4.55 d	3.99	4.00	3.91		4.05		4.55	4.43
15	1.83 d	1.83	1.84	1.84	1.85 s	1.91	3.99	4.04	3.98	9.38

H	13	14	15	16	17	17 b	18	19	20
1	5.61 dd	3.10 m	5.73 dd	5.54	5.48	5.48	3.17	3.09	6.47 ddd
2α	2.21[b] m	2.03[b]	2.19	2.17	2.17[b]	2.12 [b]	1.17	2.14	2.43 dddd
2β	2.54[b] m	1.76[b]	2.42	2.52	2.50[b]	2.46 [b]	2.43	2.61	2.26 dddd
3α	2.26 m	2.03[c]	2.28[b] ddd	2.20[b] m	2.18[c]	2.17 [b]	2.15	2.03	2.06 dd
3β	2.67 m	1.76[c]	1.88[b]	2.61[b]	2.54[c]	2.56 [b]	2.20	2.03	
5	5.49 d	5.52 dd	3.01 d	5.45 dd	5.44 brd	5.51 d	5.42	5.49	4.93
6	5.16 dd	5.20	4.28	5.17	5.18	5.07	5.04	5.19	4.58
7	2.66 m	2.83	2.86	2.70	2.68	2.20	2.76	2.82	1.67
8α	2.10 dddd	2.03 m	2.00 dddd	2.05 m	2.07 dddd	2.09	1.97	2.03	1.99 ddd
8β	1.74 dddd	1.76 m	1.80 dddd	1.72	1.71 dddd	1.63	1.76	1.74	1.42
9α	2.63 ddd	2.65 m	2.47 ddd	2.58 m	2.58 ddd	2.25	1.44	2.14	2.86 dddd
9β	2.44 m	2.21 ddd	2.24	2.25 m	2.31	2.52	2.38	2.61	2.33
13a	5.60 d	5.59	5.68	5.58	5.56	3.63	5.64	5.58	2.71 dd
13b	6.39 d	6.28	6.35	6.27	6.26	3.57	6.31	6.27	2.81 dd
14	4.09 d	3.80	4.62	4.59	4.10	4.05	3.90	3.81	9.43
14′	4.02 d	3.59	4.44	4.43	4.04	4.00	3.70	3.55	
15	3.99 s	4.03	3.78 d	3.96 s	3.96	3.98	4.07	4.00	1.86

4: CH_3–CO, δ 2.03, 3H, s; **6**: (CH_3)C–, δ 0.89, 9H, s; CH_3–, δ 0.05, 3H, s; CH_3–, δ 0.04, 3H, s; **8**: CH_3–CO, δ 2.09, 3H, s; **12**, **12b**: CH_3–CO, δ 2.03, 3H, s; **15**: 15′, δ 3.55, d, 1H; CH_3–CO, δ 2.03, 3H, s; **16–19**: (CH_3)C–, δ 0.90, 9H, s; CH_3–, δ 0.06, 3H, s; CH_3–, δ 0.05, 3H, s; **16**: CH_3–CO, δ 2.07, 3H, s; **17b**: OCH_3–, δ 3–34, 3H; (CH_3)C–, δ 0.89, 9H, s; CH_3–, δ 0.06, 3H, s; CH_3–, δ 0.05, 3H, s; **20**: *C*H_2–CH$_2$–N, δ 1.74, 4H, brs; H-11, δ 2.31, 1H, m; CH$_2$–*C*H_2–N, δ 2.61, 4H, brs.

[a] Multiplicities are not repeated if identical with the preceding column.
[b] Signals might be interchanged within the same column.
[c] Signals might be interchanged within the same column.
[d] Signals might be interchanged within the same column.

parameters analyzed were germination and root and shoot elongation.

Melampolides show, in general, low levels of phytotoxicity: only the root length of the dicots lettuce and cress was inhibited (Table 5). However, all values are below 20% inhibition. On the other hand, the aldehydes **3** and **9**, and the chlorinated compound **5** show good levels of stimulation of wheat germination. No significant activities where detected in onion.

Regarding *cis*,*cis*-germacranolides (Table 5), only the isomeric epoxides **18** and **19** present significant phytotoxic activity on lettuce germination. Other groups or substituents do not seem to increase these effects. The aldehyde **11** and the chlorinated derivative **13** present good levels of stimulation of wheat germination. Finally, the epoxide **18** and the acetoxy derivative **12** are the only *cis*,*cis*-germacranolides showing a weak inhibition on root lettuce, similar to those of melampolides.

According to these results and those previously published for similar sesquiterpene lactones with *trans*,*trans*-germacranolide structure,[15a] some conclusions can be established:

2.2.1. Influence of the conformation. Cluster analysis (or complete linkage analysis) is a powerful statistic tool used to compare and group data in categories attending to their similar bioactivity.[23] As a result, a hierarchy tree is obtained with those elements with lower differences of bioactivity among them falling closer or into the same subgroup. In our particular case, we combined data obtained for germination and growth of all three skeletal types (e.g. *trans*,*trans*-germacranolides, melampolides, and *cis*,*cis*-germacranolides) assayed with the four target species (lettuce, cress, onion, and wheat). The resulting grouping tree (Fig. 7) clearly separates previously tested *trans*,*trans*-germacranolides[15a] (compounds **1**, **22–24**, **26**, Fig. 7, group F_1) from melampolides and *cis*,*cis*-germacranolides (group F_2). The profiles of activity of the elements included in F_1 category are similar among them, and quite different from F_2. a general decreasing order of activity for germacranolides can be set to as *trans*,*trans*-germacranolides > melampolide > *cis*,*cis*-germacranolides.[24]

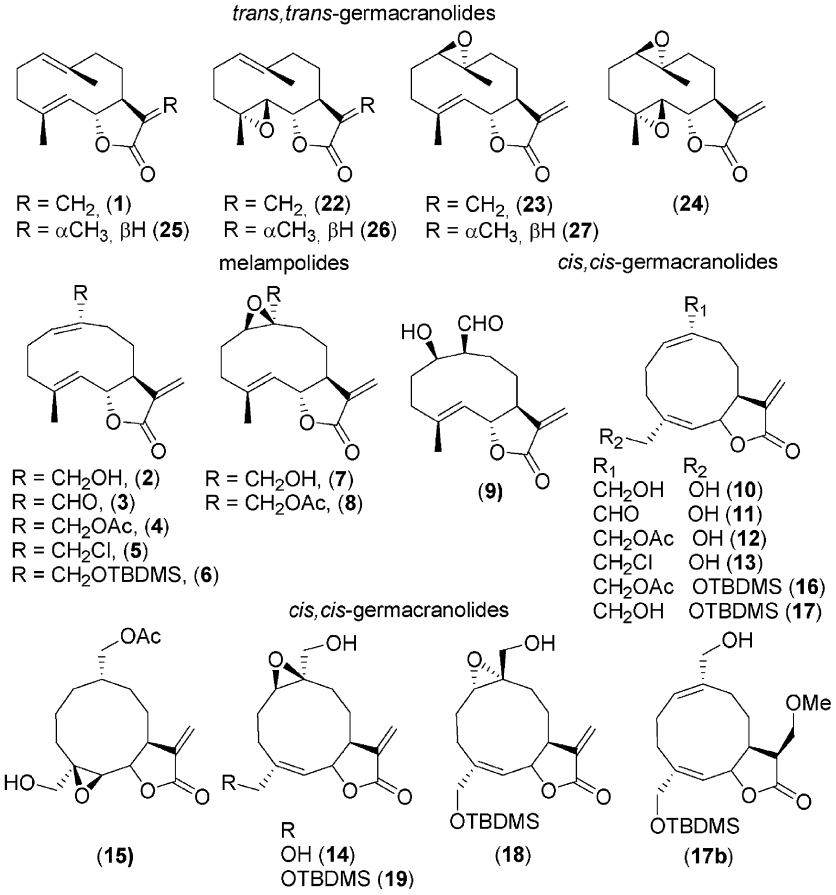


Figure 6. Germacranolides tested in the bioassays.

There is a clear correlation between the lost of activity and the change in the spatial disposition of the carbon framework—caused by the different stereochemistry in the two double bonds of the macrocycle. While *trans*,*trans*-germacranolides present a 'double-crown' like conformation (typical theoretical molecular volume $V=313$ Å^3), melampolides adopt a 'twisted' disposition (V(**2**)$=318$ Å^3), and *cis*,*cis*-germacranolides has a 'boat-like' conformation (V(**10**)$=335$ Å^3) (Fig. 8). Since all compounds present similar volumes, total steric demands are mostly the same for all of them. Thus, if the

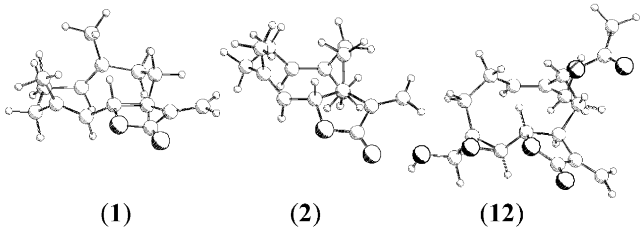


Figure 8. Minimum energy conformers as obtained by PM3 calculations.[21]

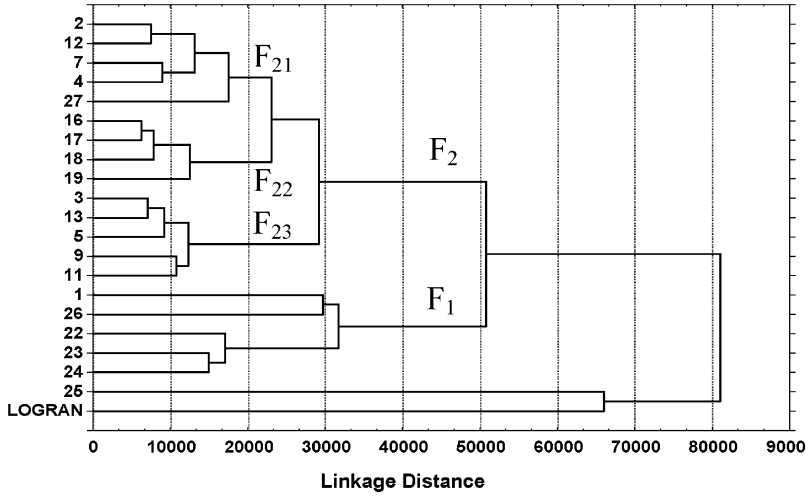


Figure 7. Complete linkage analysis (cluster) of the germacranolides tested.

Table 4. ^{13}C NMR data for listed compounds (100 MHz in $CDCl_3$, signal of the residual $CHCl_3$ centered at δ 77.0 ppm)[a]

C	3	4	5	6	8	9	10	11	12	12b
1	153.4 d	129.9	130.4	125.1[b]	62.6	71.4	125.5[b]	152.9	129.2	129.5
2	24.2[b] t	24.9	24.4	24.7	27.3	29.7[b]	24.3[c]	25.8[b]	24.6[b]	23.8[b]
3	37.1 t	38.1	38.1	38.5	34.3	35.5	26.5	25.6[b]	26.3	24.6
4	137.4 s	138.2	139.6 [b]	140.4	142.4	141.3	140.1[d]	138.4	140.1	141.0
5	126.1 d	125.3	125.3	125.0[b]	124.3	126.1	125.4[b]	126.3	126.5	150.0
6	80.7 d	80.6	80.3	80.8	79.3	79.6	78.1	77.9	77.9	77.3
7	45.5 d	45.3	45.4	45.5	46.0	44.1	43.8	43.6	43.8	42.9
8	26.1[b] t	25.1	25.1	25.2	24.1[b]	25.1	31.8	31.6	31.7	32.0
9	22.0 t	24.0	22.8	23.8	24.5[b]	17.4[b]	24.2[c]	22.1	24.4[b]	22.8[b]
10	144.7 s	135.8	137.6[b]	138.4	60.6	52.2 d	139.4[d] s	143.6	134.6	134.3
11	139.2 s	139.8	138.2	140.2	139.6	139.2	139.4[d]	139.4	139.5	138.1
12	170.2 s	170.7[b]	170.2	170.5	169.8[c]	171.1	170.1	170.1	170.1[c]	170.4[c]
13	119.3 t	118.8	119.2	118.6	119.2	119.3	122.6	123.3	122.7	123.9
14	195.6 d	67.5 t	48.9	66.7	67.1	203.8	66.2	195.3 d	67.3 t	67.2
15	16.9 q	17.1	17.2	17.2	17.4	16.9	66.2 t	66.3	66.3	194.1 d

C	13	14	15	16	17	17b	18	19	20
1	130.1 d	60.7	128.2	129.6	125.8	125.2	62.0	60.9	152.5
2	24.6[b] t	28.7	21.6	24.6	24.2[b]	24.4	22.4	30.3	25.4
3	26.2 t	23.6[b]	27.1	26.1	26.3	26.0	26.9[b]	23.5[b]	37.3
4	142.1 s			139.8	140.1	140.0	144.5	125.5	136.1
5	125.4 d	125.0	61.5	124.4	124.4	125.1	123.1	124.3	126.7
6	77.9 d	77.2	80.6	78.1	78.3	79.7	79.2	78.2	80.6
7	43.7 d	44.1	39.1	43.9	44.1	42.7	29.9	44.0	46.0
8	31.2 t	28.7	32.3	31.7	31.8	31.2	28.9	29.7	26.1
9	23.9[b] t	24.6[b]	25.1	24.6	24.4[b]	23.9	26.8[b]	24.7[b]	22.5
10	136.2 s	63.2	135.5	134.5	139.2[c]	139.6	63.9	63.2	145.4
11	139.5 s	139.2	138.3	139.6	139.8[c]	48.9 d	139.2 s	139.4	46.5 d
12	170.3 s	169.7	170.6[b]	170.8[b]	170.3	177.0	169.7	169.7	171.1
13	122.8 t	122.6	123.8	122.5	122.4	71.3	122.3	122.3	53.2
14	48.8 t	67.2	66.8	67.6	66.3	66.5	66.2	67.2	195.3 d
15	66.2 t	64.3	63.0	66.3	66.3	66.0	64.3	64.2	17.0 q

4: δ 20.9 q (CH_3–CO–); δ 170.3[a] s (CH_3–*C*O–); **6**: δ −5.2 q (CH_3–Si); δ −5.3 q (CH_3–Si); δ 25.9 q [$(CH_3)_3$C–Si)]; **8**: δ 20.7 q (CH_3–CO–); δ 170.5[b] s (CH_3–*C*O–); **12**: δ 20.9 q (CH_3–CO–); δ 171.1[b] s (CH_3–*C*O–); **12b**: δ 20.9 q (CH_3–CO–); δ 169.5[b] s (CH_3–*C*O–); **15**: δ 20.9 q (CH_3–CO–); δ 169.4[a] s (CH_3–*C*O–); **16**, **17**, **17b**, **18**, **19**: δ −5.3 q (CH_3–Si); δ −5.3 q (CH_3–Si); δ 18.4 s [$(CH_3)_3C$–Si)]; δ 25.9 q [$(CH_3)_3$C–Si)]; **16**: δ 20.9 q (CH_3–CO–); δ 170.0[a] s (CH_3–*C*O–); **17b**: δ 59.2 q (CH_3O–); **20**: δ 23.8 t [CH_2–CH_2–N]; δ 54.7 t [CH_2–CH_2–N].

[a] Multiplicities are not repeated if identical with the preceding column.
[b] Signals might be interchanged within the same column.
[c] Signals might be interchanged within the same column.
[d] Signals might be interchanged within the same column.

change in the shape of the backbone leads also to a change in the orientation of the reactive exocyclic double bond in the lactone ring (Fig. 8), this might be correlated with the decrease observed in the phytotoxicity.

2.2.2. Functional group influence. A second α,β-unsaturated carbonyl system at C-14 (compounds **3** and **11**) represents another possible reacting center for Michael nucleophilic additions. However, comparison of data from alcohols **2** and **10** and their corresponding aldehydes **3** and **11** show no increment in the phytotoxic activity. This is indicative that steric hindrance or stereoelectronic effects

Table 5. Bioactivity shown by melampolides and *cis*,*cis*-germacranolides in the Petri dish bioassay

	Lettuce			Cress			Wheat			Onion		
	G	R	S	G	R	S	G	R	S	G	R	S
Melampolides												
2		(−)	(−)	(−)	(−)	(+)	(−)	(+)	(+)		(−)(+)	(−)
3			(−)				+		(−)	(+)	(+)	
4		(−)	(+)	(−)	(−)	(+)					(−)(+)	
5							+		(−)	(+)	(+)	
7		(−)	(+)		(−)	+	(−)	+	(+)		(−)	
9			(−)				+			(+)	(+)	(+)
cis,*cis*-Germacranolides												
12		(−)	(+)	(−)	(−)	(+)		(+)	(+)			(+)
13		(−)	(+)				+		(−)	(+)		
15		(+)			+		(+)	−(+)	—	(+)		
16		(−)	(+)	(−)	(−)				(−)		(−)	
17			(+)	(−)	(−)	(−)	(−)		(−)	(−)	(−)	
18	—	—	(+)	(−)		(−)	(−)	(+)	—	(−)	(−)(+)	
19	—	(−)(+)	(+)	(−)		(−)		(+)	—		(+)	

G: Germination; R: Root Length; S: Shoot Length; blank: No active; (+), (−): stimulatory or inhibitory values below 20% at the maximum concentration tested (100 μM); +, −: stimulatory or inhibitory values between 20–40%.

dos not allow such a reaction. This hypothesis has been further tested trying to use pyrrolidine as molecular probe resembling amino groups of biomolecules. Reaction of pyrrolidine with compounds **3** and **11** led to the expected Michael adducts at the lactone ring (compounds **20** and **21**, respectively). However, no reaction products could be obtained in the unsaturated aldehyde system, thus supporting this idea. Note also that the non-conjugated aldehyde **9** remains inactive.

Halogen atoms are commonly present in pesticide formulation, where they have been usually introduced to increase the activity.[25] Otherwise, brominated and chlorinated derivatives are also frequently found in marine natural products showing high levels of biological activity.[26] However, the introduction of halogen atoms or even an epoxide ring do not add any increase of the phytotoxicity (compounds **5**, **7**, **8**, **14**, **15**, **18**, **19**), except for the isomeric epoxides *cis*,*cis*-germacranolide **18** and **19** which show an important increment of the phytotoxic activity, specially on lettuce germination. The different activity shown among epoxides at the C1–C10 in melampolides (**7**) and *cis*,*cis*-germacranolides (**18** and **19**) could relay on the different spatial disposition of the backbones, allowing an easier access in the last ones to the oxirane ring.

A deep look into the second group F_2, allows to differentiate three new subgroups: F_{22} includes only *cis*,*cis*-germacranolides with a TBDMS substituent at C-15, F_{23} groups both *cis*,*cis*-germacranolides and melampolides possessing a chlorine or carbaldehyde groups, and hydroxyl or acetoxyl containing compounds fall into the F_{21} category. Thus, the F_{22} subgroup resembles the sterically demanding TBDMS *cis*,*cis*-germacranolide derivatives.

3. Conclusions

We report an optimal relation SeO_2/TBHP to obtain *cis*,*cis*-germacranolides from melampolides as 1:4. Such a ratio is in good accordance with the proposed catalytic nature of SeO_2 in this reaction. Otherwise, to explain the change in the stereochemistry of the double bonds it is necessary to adopt a peroxometal intermediate reactive species in contrast to recently reported hypothesis,[2] at least for this system.

Also, a feasible relationship between the theoretical dipolar moment and the yield is observed, which mirrors the influence of the solvation energy in the first rate-determining ene reaction step. Compounds having low dipolar moments are better solvated in low polar solvents such as DCM or THF, thus favoring better yields.

Regarding the SAR study, it can be concluded as a general trend the decreasing order of activity *trans*,*trans*-germacranolides > melampolides > *cis*,*cis*-germacranolides. Such an order has been found to positively correlate with the progressive change in the carbon framework of the decalyne system and it is in good agreement with previous results.[15a] Cluster analysis has demonstrated to be a powerful tool to analyze profiles of activity and to group those compounds with similar bioactivity.

New nucleophilic reactive centers do not necessarily add additional biological inhibitory effects, unless they are quite accessible. In this sense, easily accessible oxirane rings seem to induce higher inhibiting activities (*cis*,*cis*-germacranolides **18** and **19**).

4. Experimental

4.1. General

All reagents and solvents were used as obtained from commercial suppliers, excepting compound **1**. Costunolide (**1**) was isolated by column chromatography from Costus Resin Oil (Pierre Chauvet, S. A.) and purified by recristallization from hexane/ethyl acetate mixtures. Solvents were distilled from glass prior to use. Column chromatography was performed on silica gel (35–75 mesh) and TLC analysis was carried out using aluminum-packed precoated silica gel plates. For HPLC, LiChrosorb silica 60 was used in the normal-phase mode with a differential refractometer (RI) in a Hitachi L-6020 HPLC instrument. ^1H and ^{13}C NMR spectra were recorded using a Varian UNITY-400 spectrometer at 400 MHz and 100 MHz, respectively, and using $CDCl_3$ as solvent. The resonance of residual chloroform at δ_H 7.25 ppm in the ^1H and δ_C 77.00 ppm for $CDCl_3$ in the ^{13}C spectra were used as internal references. Mass spectra were obtained by using a VG 1250 or a VG AUTOSPEC instruments at 70 eV. IR spectra were recorded on a Mattson 5020.

Soulangianolide A (**2**). 100 mg of costunolide (**1**) were dissolved in DCM (10 mL) and strongly stirred at room temperature with selenium dioxide (SeO_2, 24 mg, 0.5 equiv.). Then, *t*-butyl hydroperoxide (TBHP, 0.1 mL, 2 equiv.) was drop wise. After 1 h, filtering the reaction mixture through silica gel and the solvent evaporated under vacuum stopped the reaction. The crude of reaction was purified by CC using hexane/ethyl acetate mixtures as eluant, yielding **2** (62%) as a colorless oil and trace amounts of the 14-oxo-melampolide **3**. All spectral and physical data of 2 were in full agreement with those reported in the literature for 14-hydroxymelampolide.[5a]

4.1.1. 14-Oxomelampolide (3). ν_{max} (KBr) 1763 (carbonyl group), 1679 (aldehyde group), 1625 (double bond) cm^{-1}; HRMS: found $[M]^+$ 246.12549, $C_{15}H_{18}O_3$ requires 246.12560; FAB 246.137 $[M]^+$; EIMS, *m/z* (rel. int.): 231 $[M-CH_3]^+$ (1.1); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=8.4; 3α,3β=13.1; 3α,2β=11.7; 5,6=10.3; 6,7=9.6; 8α,8β=14.1; 8α,9β=12.8; 8α,9α=6.7; 8α,7=3.5; 8β,7=11.5; 8β,9β=5.9; 8β,9α=1.9; 13a,7=3.1; 13b,7=3.5; 14,9=1.7; 15,5=1.4; ^{13}C NMR data, see Table 4.

4.2. Acetylation

All acetylations were carried out by dissolving the compound in dry pyridine and adding an excess of acetic anhydride. After 24 h stirring, the reaction mixture was washed with a saturated aqueous solution of $CuSO_4$ to remove the excess of pyridine, yielding the corresponding acetyl derivatives quantitatively.

4.2.1. 14-Acetoxymelampolide (4). ν_{max} (KBr) 1768 (carbonyl group), 1730 (acetoxy carbonyl group), 1667 (double bond) cm^{-1}; HRMS: found $[M+1]^+$ 291.15991, $C_{17}H_{22}O_4$ requires 291.15963; EIMS, *m/z* (rel. int.): 291 $[M+1]^+$ (2.9), 231 $[M-AcOH]^+$ (100); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.6; 5,6=10.2; 6,7=9.4; 8α,8β=14.3; 8α,9β=13.1; 8α,9α=6.1; 8α,7=3.8; 8β,7=12.0; 8β,9β=4.5; 8β,9α=3.0; 13a,7=3.4; 13b,7=3.2; 14,14′=12.4; 15,5=1.3; ^{13}C NMR data, see Table 4.

4.2.2. (1*R*,10*S*)-14-Acetoxy-1,10-epoxymelampolide (8). ν_{max} (KBr) 1765 (carbonyl group), 1744 (acetoxy carbonyl group), 1678 (double bond) cm^{-1}; HRMS: found $[M]^+$ 306.14681, $C_{17}H_{22}O_5$ requires 306.14673; FAB 307.147 $[M+1]^+$; EIMS, *m/z* (rel. int.): 247 $[M-OAc]^+$ (36.0); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=4.3; 1,2β=10.1; 2α,2β=14.5; 2α,3α=1.6; 2α,3β=6.1; 3α,3β=12.7; 3α,2β=12.7; 5,6=10.5; 6,7=9.8; 8α,8β=17; 8β,7=12.4; 8β,9β=4.7; 8β,9α=3.1; 9α,9β=15.1; 9β,8α=13.8; 9β,8β=4.7; 13a,7=3.1; 13b,7=3.5; 14,14′=12.3; ^{13}C NMR data, see Table 4.

4.3. Chlorination of 14-hydroxymelampolide (2)

440 mg of compound **2** were dissolved in 4 ml of dried pyridine, followed by addition of tosyl chloride (TsCl, 414 mg, 1.2 equiv.) with stirring. After 22 h, the pyridine was removed under vacuum, and the crude was purified by CC, yielding 14-chloromelampolide **5** (80%).

4.3.1. 14-Chloromelampolide (5). ν_{max} (KBr) 1763 (carbonyl group), 1669 (double bond), 666 (C–Cl) cm^{-1}; HRMS: found $[M]^+$ 266.10748:266.10453, $C_{15}H_{19}ClO_2$ requires 266.10736:268.10441; FAB 266.097:268.564 $[M]^+$; EIMS, *m/z* (rel. int.): 251 $[M-CH_3]^+$ (3.0), 231 $[M-Cl]^+$ (4); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=9.3; 3α,3β=3α,2β=13.0; 3α,2α=1.9; 5,6=10.6; 6,7=9.4; 8α,8β=14.0; 8α,9β=13.8; 8α,9α=5.8; 8α,7=3.8; 8β,7=11.9; 8β,9β=4.7; 8β,9α=2.6; 13a,7=3.1; 13b,7=3.5; 14,14′=12.3; 15,5=1.0; ^{13}C NMR data, see Table 4.

4.4. Silylation of 14-hydroxymelampolide (2)

200 mg of **2** were dissolved in *N*,*N*-dimethylformamide (*N*,*N*-DMF, 4 mL), followed by addition of *t*-butyldimethylsilyl chloride (TBDMSCl, 273 mg, 2 equiv) and dry collidine (0.24 mL, 2 equiv.). After 24 h, the reaction was stopped by addition of water (4 mL) and the reaction mixture extracted with AcOEt (3×). The combined organic phases were dried with anhydrous sodium sulfate yielding 14-*t*-butyldimethylsilyloxy-melampolide **6** (99%).

4.4.1. 14-[*tert*-Butyl-dimethylsilyloxy]melampolide (6). ν_{max}/cm^{-1}: 1744 (carbonyl group), 1670 (double bond); HRMS: found $[M]^+$ 362.22759, $C_{21}H_{34}O_3Si$ requires 362.22772; FAB 361.232 $[M-1]^+$; EIMS, *m/z* (rel. int.): 305 $[M-C(CH_3)_3]^+$ (28.1), 277 $[M-C(CH_3)_3Si]^+$ (4.9); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=9.3; 5,6=10.6; 6,7=9.4; 8α,8β=14.0; 8α,9β=13.8; 8α,9α=5.8; 8α,7=3.8; 8β,7=11.9; 8β,9β=4.7; 8β,9α=2.6; 13a,7=3.1; 13b,7=3.5; 14,14′=12.3; 15,5=1.0; ^{13}C NMR data, see Table 4.

4.5. Epoxidations

All epoxidations were carried out as follows: to a solution of the starting compound (0.262 mmol) in sodium acetate buffered dried THF (8 mL) another solution of *m*-CPBA (0.290 mmol) in dried THF (4 ml) was drop wise while stirring. Reaction was monitored by TLC until no starting materials could be observed. Then, the reaction was stopped and the work-up was as follows: the reaction mixture was extracted with NaOH (aq) 5% (2×) and the organic phase washed with distilled water (2×). All the aqueous phases were re-extracted with ethyl acetate, and the combined organic phases were dried on anhydrous sodium sulfate. After separation by CC, (1*R*,10*R*)-1β,10β-epoxy-14-hydroxy-melampolide **7** was obtained from **2** in a crystalline form (62%). Spectral and physical data were in full agreement with those reported in the literature.[15a] Compound **15** was obtained from **12** with a 47% yield, and compounds **18** (42%) and **19** (56%) were obtained from **17**.

4.5.1. (4*R*,5*S*)-14-Acetoxy-4,5-epoxy-15-hydroxy-*cis*,*cis*-germacranolide (15). ν_{max} (KBr) 3483 (OH), 1762 (carbonyl group), 1738 (acetoxy carbonyl group), 1685 (double bond) cm^{-1}; HRMS: found $[M+1]^+$ 323.15048, $C_{17}H_{20}O_6$ requires 323.14946; EIMS, *m/z* (rel. int.): 323 $[M+1]^+$ (3.8), 263 $[M-AcO]^+$ (46.7), 245 $[M-AcO-H2O]^+$ (68.3); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=8.1; 3α,3β=14.1; 3α,2β=11.3; 3α,2α=7.4; 5,6=9.5; 6,7=3.5; 8α,8β=14.6; 8α,9β=12.9; 8α,7=5.0; 8α,9α=3.8; 8β,7=12.9; 8β,9β=4.9; 8β,9α=3.5; 9α,9β=14.8; 9β,8α=12.8; 13a,7=2.3; 13b,7=2.7; 14,14′=12.7; 15,15′=12.7; ^{13}C NMR data, see Table 4.

4.5.2. (1*S*,10*S*)-15-*t*-Butyldimethylsilyloxy-1,10-epoxy-14-hydroxy-*cis*,*cis*-germacranolide (18). ν_{max} (KBr) 3455 (OH), 1763 (carbonyl group), 1658 (double bond) cm^{-1}; HRMS: found $[M+1]^+$ 395.22762, $C_{21}H_{34}O_5Si$ requires 395.22538; EIMS *m/z* (rel. int.): 395 $[M+1]^+$ (8.8), 337 $[M-HC(CH_3)_3]^+$ (3.6); ^1H NMR data, see Table 3, *J* (Hz): 1,2α=11.0; 1,2β=3.2; 2α,2β=14.9; 2α,3α=2α,3β=4.3; 5,6=10.1; 6,7=3.6; 8α,8β=15.4; 8α,9β=9.6; 8α,7=3.7; 8α,9α=2.1; 9α,9β=15.1; 9α,8β=9.2; 13a,7=2.3; 13b,7=2.6; 14,14′=12.4; 14,8=5.1; 15,5=1.6; 15',5=1.9; ^{13}C NMR data, see Table 4.

4.5.3. (1*R*,10*R*)-15-*t*-Butyldimethylsilyloxy-1,10-epoxy-14-hydroxy-15-*cis*,*cis*-germacranolide (19). ν_{max} (KBr) 3477 (OH), 1764 (carbonyl group), 1660 (double bound) cm^{-1}; HRMS: found $[M+1]^+$ 395.22516, $C_{21}H_{34}O_5Si$ requires 395.22538; EIMS *m/z* (rel. int.): 395 $[M+1]^+$ (8.8), 337 $[M-HC(CH_3)_3]^+$ (3.6); ^1H NMR data, see Table 3, *J* (Hz): 2α,3α=2α,3β=4.4; 2α,2β=15.9; 5,6=11.3; 6,7=4.3; 13a,7=2.3; 13b,7=2.5; 14,14′=12.4; ^{13}C NMR data, see Table 4.

4.5.4. (1*R*,10*R*)-1,10-Epoxy-14-hydroxymelampolide (7) ring opening. 184 mg of compound **7** were dissolved in 10 ml of THF, followed by addition of boron trifluoride dihydrate ($BF_3 \cdot 2H_2O$, 0.15 mL, 2 equiv.). After 4 h, the reaction was stopped by adding water, the reaction mixture extracted with ethyl acetate (3×), and the combined organic phases were dried on anhydrous sodium sulfate. The crude

of reaction was purified by CC to afford (1*R*,10*S*)-1-hydroxy-14-oxomelampolide **9** (53%). The configuration at carbons C1 and C10 was assigned based on positive correlations found in the bidimensional NOESY experiment (H-5, H-7, H-10, H-1) that were in full agreement with the minimum energy conformer obtained by PM3 calculations.

4.5.5. (1*R*,10*S*)-1-Hydroxy-14-oxomelampolide (9). ν_{max} (KBr) 3463 (OH), 1759 (carbonyl group), 1722 (aldehyde group), 1665 (double bond) cm^{-1}; HRMS: found $[M+1]^+$ 265.14103, $C_{15}H_{20}O_4$ requires 265.14398; EIMS *m/z* (rel. int.): 265 $[M+1]^+$ (15.0), 247 $[M-H_2O]^+$ (46.9), 229 $[M-H_2O-CO]^+$ (89.8); ^{1}H NMR data, see Table 3, *J* (Hz): 1,10=11.8; 3α,3β=3β,2α=12.7; 5,6=6,7=10.1; 9α,9β=13.6; 9β,8α=13.6; 9β,8β=4.9; 13a,7=3.2; 13b,7=3.4; ^{13}C NMR data, see Table 4.

4.6. Oxidation of melampolides to *cis*,*cis*-germacranolides

Selenium dioxide (SeO_2, 0.5 equiv.) and TBHP (2 equiv.) were added to a DCM solution (7 mL) of compounds **2**–**8** (80 mg each). The reaction mixture was heated until reflux and strongly stirred over 8 h. Then, the reaction was stopped as it was for compound **2**, yielding **10** (10%), **11** (24%), **12** (57%), **13** (43%), and **14** (3%), respectively. Compound **8** did not react and compound **6** run deprotection of the silyl ether group and subsequent oxidation of the free hydroxyl group to yield **3** (53%). It was also possible to detect trace amounts of the 15-oxo-derivative **12b** using **4** as starting material. The low yields obtained for the rest of starting materials might be the cause for not detecting analogue compounds in the other systems assayed.

4.6.1. 14,15-Dihydroxy-*cis*,*cis*-germacranolide (10). ν_{max} (KBr) 3406 (OH), 1755 (carbonyl group), 1658 (double bond) cm^{-1}; HRMS: found $[M-H_2O]^+$ 246.12497, $C_{15}H_{18}O_3^+$ requires 246.12504; FAB 264.352 $[M]^+$; EIMS, *m/z* (rel. int.): 246 $[M-H_2O]^+$ (5.0), 228 $[M-2H_2O]^+$ (6.0); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.1; 5,6=9.5; 6,7=3.7; 8α,8β=14.3; 8α,9β=12.4; 8α,7=8α,9α=4.4; 8β,7=12.5; 8β,9β=4.7; 8β,9α=3.6; 9α,9β=14.4; 13a,7=2.4; 13b,7=2.7; 14,14′=12.6; ^{13}C NMR data, see Table 4.

4.6.2. 15-Hydroxy-14-oxo-*cis*,*cis*-germacranolide (11). ν_{max} (KBr) 3444 (OH), 1757 (carbonyl group), 1749 (aldehyde group), 1681 (double bond) cm^{-1}; HRMS: found $[M+1]^+$ 263.13237, $C_{15}H_{18}O_4$ requires 263.12833; EIMS, *m/z* (rel. int.): 263 $[M+1]^+$ (18.8), 245 $[M-H_2O]^+$ (100); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.1; 5,6=9.5; 6,7=3.8; 8α,8β=14.9; 8β,9β=4.8; 8β,9α=2.5; 13a,7=2.4; 13b,7=2.7; 14,1=1.3; ^{13}C NMR data, see Table 4.

4.6.3. 14-Acetoxy-15-hydroxy-*cis*,*cis*-germacranolide (12). ν_{max} (KBr) 3426 (OH), 1747 (carbonyl group), 1739 (acetoxy carbonyl group), 1636 (double bond) cm^{-1}; HRMS: found $[M]^+$ 306.14678, $C_{17}H_{22}O_5$ requires 306.14673; FAB 307.153 $[M+1]^+$; EIMS, *m/z* (rel. int.): 275 $[M-CH_2OH]^+$ (1.0), 246 $[M-CH_2OH-AcOH]^+$ (27.0); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.5; 5,6=9.6; 6,7=3.8; 8α,8β=14.5; 8α,9β=12.5; 8α,9α=8α,7=4.9; 8β,7=12.9; 8β,9β=4.9; 8β,9α=3.7; 13a,7=2.3; 13b,7=2.7; 14,14′=12.5; ^{13}C NMR data, see Table 4.

4.6.4. 14-Acetoxy-15-oxo-*cis*,*cis*-germacranolide (12b). ν_{max} (KBr) 1768 (aldehyde group), 1747 (carbonyl group), 1731 (acetoxy carbonyl group), 1689 (double bond) cm^{-1}; HRMS: found $[M]^+$ 304.13065, $C_{15}H_{20}O_5$ requires 304.13107; EIMS, *m/z* (rel. int.): 304 $[M]^+$ (1.4), 261 $[M-AcO]^+$ (1.7); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.8; 2α,2β=2α,3β=14.7; 5,6=9.2; 6,7=3.7; 8α,8β=14.5; 8α,9β=12.2; 8α,9α=5.5; 8β,7=12.6; 8β,9β=4.9; 8β,9α=5.4; 9α,9β=14.9; 13a,7=3.1; 13b,7=3.4; 14,14′=12.9; 15,5=1.3; ^{13}C NMR data, see Table 4.

4.6.5. 14-Chloro-15-hydroxy-*cis*,*cis*-germacranolide (13). ν_{max} (KBr) 3461 (OH), 1761 (carbonyl group), 1687 (double bond) cm^{-1}; HRMS: found $[M-Cl]^+$ 247.13336, $C_{15}H_{19}O_3Cl$ requires 247.13342; EIMS, *m/z* (rel. int.): 282 $[M]^+$ (1.0), 247 $[M-Cl]^+$ (46.7), 251 $[M-CH_2OH]^+$ (34.2); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=9.7; 5,6=9.6; 6,7=3.9; 8α,8β=14.5; 8α,9β=12.4; 8α,7=4.9; 8α,9α=4.9; 8β,7=12.7; 8β,9β=4.8; 8β,9α=3.7; 9α,9β=14.7; 13a,7=2.5; 13b,7=2.7; 14,14′=11.4; ^{13}C NMR data, see Table 4.

4.6.6. 14,15-Dihydroxy-1β,10β-epoxide-*cis*,*cis*-germacranolide (14). ν_{max} (KBr) 3504 (OH), 1763 (carbonyl group), 1660 (double bond) cm^{-1}; HRMS: found $[M]^+$ 280.13112, $C_{15}H_{20}O_5$ requires 280.13108; FAB 280.659 $[M]^+$; EIMS, *m/z* (rel. int.): 252 $[M-H_2O]^+$ (4.0), 244 $[M-2H_2O]^+$ (6.0); ^{1}H NMR data, see Table 3, *J* (Hz): 5,6=9.3; 6,7=4.4; 9α,9β=14.5; 9α,8β=9α,8α=9β,8β=4.3; 13a,7=2.3; 13b,7=2.6; 14,14′=12.4; ^{13}C NMR data, see Table 4.

4.7. Silylation of 12

30 mg of **12** were dissolved in N,N-dimethylformamide (3 mL), followed by addition while stirring of TBDMSCl (2 equiv., 25 mg) and collidine (2 equiv., 0.04 mL). After 24 h, the reaction was stopped as for compound **2** to afford the corresponding 14-acetoxy-15-*t*-butyldimethylsilyloxy-*cis*,*cis*-germacranolide **16** (99%).

4.7.1. 14-Acetoxy-15-*t*-butyldimethylsilyloxy-*cis*,*cis*-germacranolide (16). ν_{max} (KBr) 1767 (carbonyl group), 1730 (acetoxy carbonyl group), 1682 (double bond) cm^{-1}; HRMS: found $[M+1]^+$ 420.23107, $C_{21}H_{30}O_5Si$ requires 420.23320; EIMS, *m/z* (rel. int.): 420 $[M]^+$ (3.8), 361 $[M-AcO]^+$ (27.9), 303 $[M-AcO-HC(CH_3)_3]^+$ (12.6); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.8; 5,6=9.5; 6,7=3.7; 8α,8β=14.2; 8β,7=12.6; 8β,9β=4.7; 8β,9α=4.0; 13a,7=2.3; 13b,7=2.7; 14,14′=12.4; ^{13}C NMR data, see Table 4.

4.8. Deacetylation of 16

30 mg of **16** were dissolved in dried methanol (1 mL) under nitrogen atmosphere. Afterwards, magnesium methoxide (0.08 mL, dilution 7.4% wt. in MeOH) was added. After 24 h, the reaction was stopped by adding water, the reaction

mixture extracted with AcOEt (4×), and the combined organic phases washed with brine (4×) and dried with anhydrous sodium sulphate. The solvent was removed in vacuum. 15-*t*-Butyldimethylsilyloxy-14-hydroxy-*cis*,*cis*-germacranolide **17** was obtained with a 74% yield, along with traces of the corresponding Michael adduct **17b**.

4.8.1. 15-*t*-Butyldimethylsilyloxy-14-hydroxy-*cis*,*cis*-germacranolide (17). ν_{max} (KBr) 3442 (OH), 1755 (carbonyl group) cm^{-1}; HRMS: found $[M]^+$ 378.22259, $C_{21}H_{34}O_4Si$ requires 378.22264; FAB 379.124 $[M+1]^+$; EIMS, *m/z* (rel. int.): 361 $[M-H_2O]^+$ (3.8), 323 $[M-HC(CH_3)_3]^+$ (5.1); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=7.2; 5,6=9.6; 6,7=3.7; 8α,8β=14.3; 8β,7=12.7; 8β,9α=4.2; 13a,7=2.4; 13b,7=2.7; 14,14′=12.6; ^{13}C NMR data, see Table 4.

4.8.2. (11*S*)-15-*t*-Butyldimethylsilyloxy-11,13-dihydro-14-hydroxy-13-methoxy-*cis*,*cis*-germacranolide (17b). ν_{max} (KBr) 3446 (OH), 1768 (carbonyl group), 1658 (double bond) cm^{-1}; FAB 409.226 $[M-1]^+$; EIMS, *m/z* (rel. int.): 393 $[M-OH]^+$ (4.7), 353 $[M-C(CH_3)_3]^+$ (3.0); ^{1}H NMR data, see Table 3, *J* (Hz): 1,2α=1,2β=6.6; 5,6=9.2; 6,7=5.2; 8α,8β=14.1; 8β,7=12.9; 8β,9α=4.0; 8β,9β=4.6; 9α,9β=14.9; 9β,8α=4.0; 13,13′=9.3; 13,11=5.5; 13′,11=3–7; ^{13}C NMR data, see Table 4. The stereochemistry at C-11 was assigned based on positive nOe correlations found in the bidimensional NOESY experiment between H-6 and H-13.

4.9. Michael additions of pyrrolidine to compounds 3 and 11

0.15 mmol each of compounds **3** and **11** were dissolved in dry THF (0.5 mL) and the solution cooled in the freezer for 15 min. Pyrrolidine solution (21 mg, 0.3 mmol) in dry THF (0.5 mL) was added to the cooled solution and the mixture kept at room temperature during 20 h. The solvent was evaporated in vacuum and the crude of reaction purified on a Al_2O_3 column chromatography using DCM/MeOH (97:3) as eluant, to yield 75% of **20** and **21** in each case.[27] The stereochemistry of the adduct at C-11 was established as *R* for compound **20** since a positive nOe effect was observed for H-11 when the signal corresponding to H-6 was irradiated (% nOe: 2.8% for H-11, 2.8% for H-9, 1.2% for H-15, and 3.1 for H-8β). No positive nOe effects could be observed on the side chain signals when H-5 was irradiated (% nOe: 1.2% for H-1, 6.3% for H-2β, and 8.4% for H-7).

4.9.1. (11*R*)-14-Oxomelampolide pyrrolidine mono adduct (20). ν_{max} (KBr) 1768 (carbonyl group), 1658 (double bond) cm^{-1}; HRMS: found $[M]^+$ 317.196936, $C_{19}H_{26}NO_3$ requires 317.199094; EIMS, *m/z* (rel. int.): 317 $[M]^+$ (100.0), 288 $[M-CHO]^+$ (9.1), 246 $[M-C_4H_8N]^+$ (4.6); data, see Table 3, *J* (Hz): 1,2α=9.1; 1,2β=7.1; 2α,2β=12.4; 2α,3β=6.0; 2α,3α=3.1; 2β,3α=7.0; 2β,3β=2.1; 5,6=6,7=10.1; 8α,8β=14.2; 8α,9β=12.5; 8β,9β=1.9; 9α,9β=13.9; 13,13′=13.2; 13,11=4.0; 13′,11=5.2; ^{13}C NMR data, see Table 4.

4.9.2. 14-Oxo-15-hydroxy-*cis*,*cis*-germacranolide pyrrolidine mono adduct (21). ν_{max} (KBr) 3446 (OH), 1768 (carbonyl group), 1658 (double bond) cm^{-1}; HRMS: found $[M]^+$ 333.194748, $C_{19}H_{26}NO_4$ requires 333.194009; EIMS, *m/z* (rel. int.): 333 $[M]^+$ (5.0), 317 $[M-O]^+$ (100.0), 288 $[M-O-CHO]^+$ (10.7), 261 $[M-C_4H_9N]^+$ (6.9); ^{1}H NMR δ_H (400 MHz, CDCl3) 9.40 (d, 1H, *J*=1.4 Hz, H-14), 5.18 (brd, 1H, *J*=9.8 Hz, H-6), 5.65 (d, 1H, *J*=10.1 Hz, H-5), 6.54 (dd, 1H, *J*=8.3 Hz, H-1).

4.10. Germination and seedling growth bioassays[22]

Seeds of *Lactuca sativa* L. cv. Roman (lettuce), *Lepidium sativum* L. cv. Común (cress), *Allium cepa* L. cv. Valenciana (onion), and *Triticum aestivum* L. cv. Cortex (wheat) were obtained from FITÓ, S.L. (Barcelona, Spain). All undersized or damaged seeds were discarded and the assay seeds were selected for uniformity. Bioasays were carried out in 9 cm Ø plastic Petri dishes, using Whatman #1 filter paper as support. The general procedure for seedling bioassay was as follows: 25 seeds of each species were placed per dish, excepting *Triticum aestivum* (10 seeds per dish), with 5 mL of test soln, and incubated in the dark at 25 °C. Four replicates for each concentration were set up. Germination and growth time varied for each plant species: *L. sativum*, 3 days; *L. sativa* and *T. aestivum*, 5 days; and *Allium cepa*, 7 days. Test mother solutions (10^{-2} M) were prepared using dimethyl sulfoxide (DMSO) and then diluted to 10^{-4} M using 10 mM MES (2-[*N*-morpholino]ethanesulphonic acid). Following solutions were obtained by dilution maintaining the 0.5% DMSO percentage. Parallel controls were performed. All pH values were adjusted to 6.0 before bioassay. All products were purified prior to the bioassay using HPLC equipped with a refractive index detector. Minimum degree of purity was of 99% as extracted from the chromatograms.

4.11. Statistical treatment

Germination and root and shoot length were tested by Welch's test,[28] the differences between test solutions and controls being significant with $P<0.01$. Cluster analysis was performed using the Statistica package.[29] The analyses were recorded to all compounds tested using as variables germination index, and root and shoot growth.

4.12. Molecular modeling

Minimum energy conformations and molecular properties were obtained using MMX and PM3 calculations (PCMODEL ver 6.0, Serena Software, Bloomington, IN; MOPAC, ver. 6.00), respectively. Conformers were obtained using the randomize command in PCMODEL and the local minimum energy structures obtained were used for further semiempiric minimization with MOPAC using PM3 method. For semiempiric calculations the parameters PRECISE, GEOOK, and *T*=86400 were used. Theoretical ΔH_f° values produced by MOPAC allowed to discriminate among conformers and to obtain the minimum energy conformer in each case.

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Synthesis and reactivity of a 1,4-dihydropyrazine derivative

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Abstract—*N*,*N*-Bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine can be obtained in high yield by treatment of the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine with dimethylaminopyridine and potassium carbonate. This compound was used as substrate in Michael addition reactions with several types of nucleophiles. The electrochemical behaviour of this pyrazine derivative was also studied by cyclic voltammetry and by controlled potential electrolysis.

1. Introduction

Diazines constitute an important class of heterocyclic compounds present in several natural occurring compounds. Pyrazines are found in the luminescent chromophores of certain marine organisms,[1] in cephalostatins isolated from *Cephalodiscus Gilchrist* which are powerful anticancer agents,[2] in the fungal metabolite aspergillic acid[3] and in foods as potent flavour components.[4] 1,4-Dihydropyrazine is an important structural unit of certain redox-active biological molecules such as flavin coenzymes and several marine luciferines.[5] 1,4-Dihydropyrazine derivatives also constitute interesting electron donors in conducting charge transfer complexes and magnetic materials. The properties of 1,4-dihydropyrazines depend on the nature of the substituents and on the planarity of the ring. When planar, these ring systems can be considered 'anti-aromatic' due to cyclic 8π-electron conjugation.[5]

Recently, we have demonstrated the versatility of the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine [Tos-ΔAla(*N*-Boc)-OMe][6] as a substrate in Michael addition reactions. This compound is easily prepared in high yield from Tos-Ser-OMe by a di-*tert*-butylpyrocarbonate/dimethylaminopyridine [$(Boc)_2O$/DMAP] mediated dehydration.[6] Depending on the structure of the nucleophile, several types of compounds can be synthesized from Tos-ΔAla(*N*-Boc)-OMe, namely β-substituted alanine and dehydroalanine derivatives,[7] furanic amino acids, which by treatment with TFA yield dehydroproline derivatives[8] and α,-substituted β-sufinylamino acids.[8] It was also found that Tos-ΔAla(*N*-Boc)-OMe in the presence of DMAP undergoes a rearrangement to give the *E* isomer of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(4-toluenesulfonyl)-α,β-didehydroserine.[7] Here in, we describe the synthesis and discuss the reactivity of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine obtained from Tos-ΔAla(*N*-Boc)-OMe.

2. Results and discussion

When Tos-ΔAla(*N*-Boc)-OMe (compound **1**) was reacted with DMAP in acetonitrile in the presence of an excess of potassium carbonate the product obtained was *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine in 89% yield (compound **2**, Scheme 1). By sampling the reaction mixture and carrying out ^{1}H NMR analysis, it was found that the reaction proceeds via the formation of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-(4-toluenesulfinyl)-α,β-didehydroserine. Alternatively, compound **2** can be prepared in a one pot procedure from Tos-Ser-OMe by reacting with $(Boc)_2O$ and DMAP (0.1 equiv) in dry acetonitrile for 30 min and then adding K_2CO_3 (6 equiv) and more DMAP (1 equiv) (78% yield).

The presence of electron withdrawing substituents on 1,4-dihydropyrazine systems has a stabilizing effect thus allowing the preparation and isolation of such compounds.[5b] In the case of compound **2** the stabilizing effect of the ester groups is reinforced by the presence of the Boc groups on the nitrogen atoms. These groups are essential for stabilization of this 1,4-dihydropyrazine system since treatment of compound **2** with TFA gave 2,5-bis-methoxycarbonylpyrazine in 71% yield (compound **3**, Scheme 2). The methoxycarbonyl substituents in compound **3** cause the

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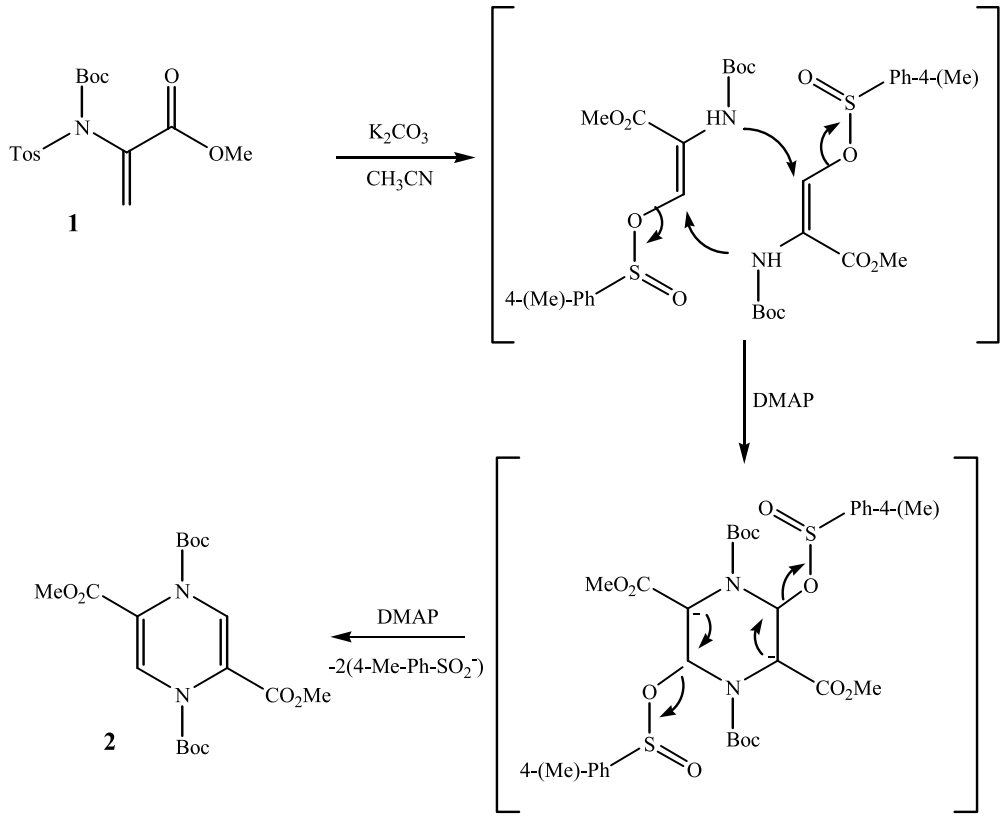
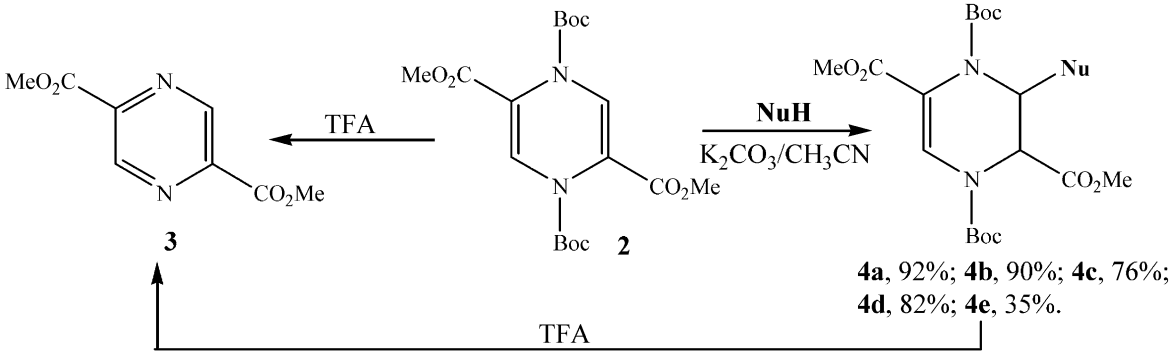


Scheme 1.



NuH: 1,2,4-triazole, **a**; 3-formylindole, **b**; 4-bromothiophenol, **c**; benzylamine, **d**; sodium methoxide, **e**.

Scheme 2.

aromatic protons to show a downfield shift in the ^{1}HNMR spectrum (9.42 ppm in $CDCl_3$) when compared with those of unsubstituted pyrazine (8.60 ppm in $CDCl_3$).[9]

The four electron-withdrawing groups of compound **2** made it possible to use this compound as an electrophile in Michael addition reactions. Thus, compound **2** was treated with several types of nucleophiles namely: 1,2,4-triazole, 3-formylindole, benzylamine, 4-bromothiophenol and sodium methoxide to give one of the diasteriomers of the corresponding 3-substituted-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine derivatives in good to high yields (compounds **4a**-**e**, Scheme 2). ^{1}H NMR spectra of these addition products at 25 °C in $CDCl_3$ showed **4a**-**e** to be rotameric mixtures with no coupling between the 2-H and 3-H protons which indicate that the diastereomer obtained corresponds to the *trans* isomer. ^{1}H NMR analysis of the Michael adducts show that the remaining vinylic proton suffers from a downfield shift (from 7.09 ppm to values ranging from 7.24 to 7.78 ppm). This has been found in other cases in which cyclic 8π-electron conjugated systems are reduced to non-aromatic compounds.[5b,10] Treatment of compounds **4c** and **4d** with TFA resulted in cleavage of the Boc groups and elimination of the nucleophile giving the pyrazine derivative **3** (76 and 74%, respectively). This indicates that the presence of electron withdrawing

substituents on the nitrogen atoms is also essential for stabilization of these non-aromatic tetrahydropyrazine systems.

The UV spectrum of compound **2** shows two absorption bands at 225 and 276 nm (extinction coefficients of 43,265 and 31,720 $M^{-1}\,cm^{-1}$) and is similar to the UV spectrum of compound **3** which shows absorption bands at the same wavelengths (extinction coefficients of 34,615 and 23,330 $M^{-1}\,cm^{-1}$) (Fig. 1).

Cyclic voltammetry of compound **2** between −1.0 and

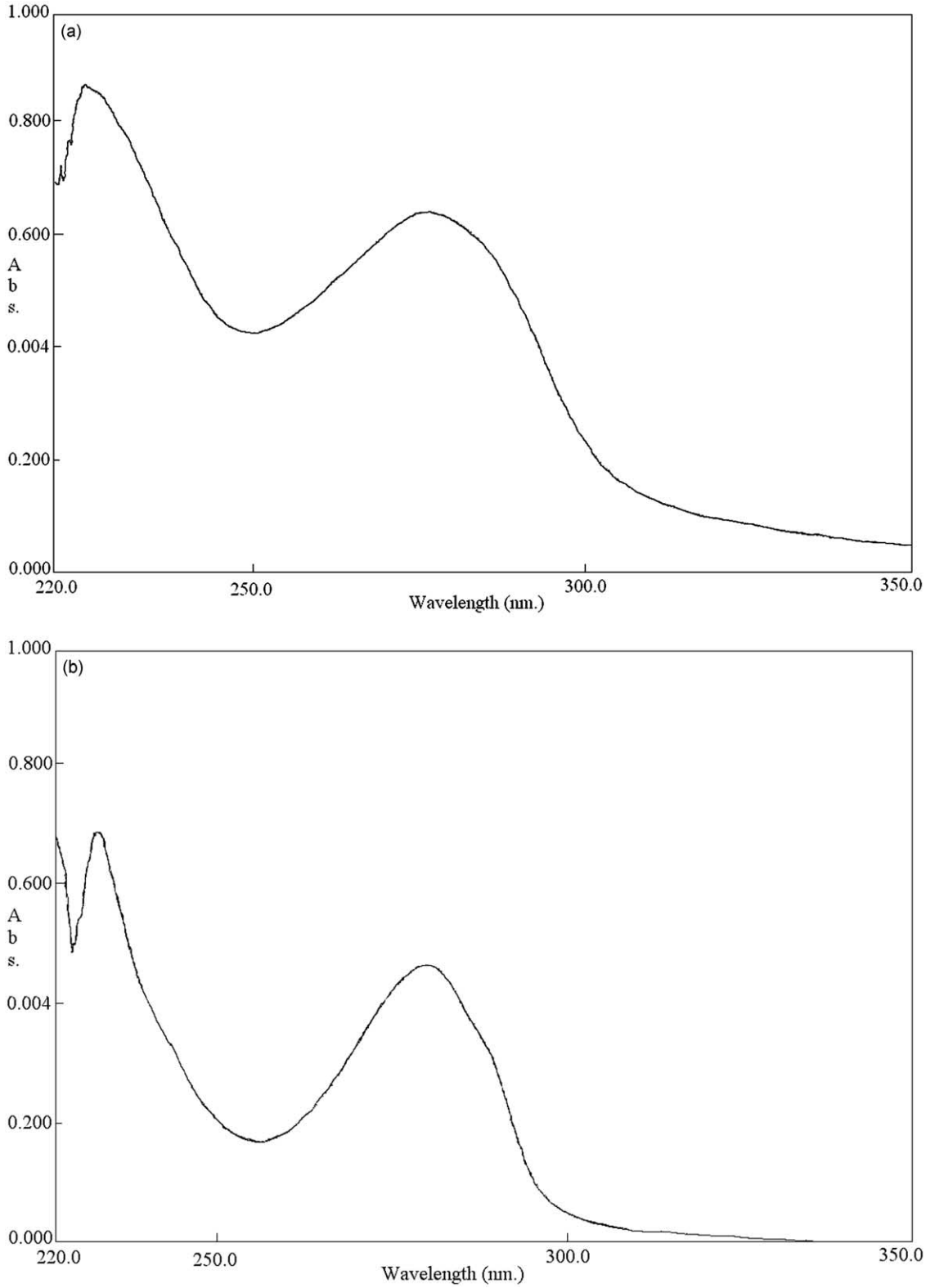


Figure 1. UV spectra of compounds **2** and **3** in dichloromethane.

1.8 V showed a single oxidation peak at 1.20 V versus SCE (Fig. 2). The oxidation potential described for *N*-ethyl-1,4-dihydropyrazine is −0.67 V versus SCE.[11] Thus, the high potentials for oxidation of compound **2** can be assigned to the electron-withdrawing effect of the substituents which makes the loss of electrons more difficult. A potential sweep from 0 to −2.8 V showed a reduction peak at −2.14 V versus SCE (Fig. 2).

The pyrazine derivative (compound **3**) shows no oxidation peak in the range between −1.0 and 1.8 V. A potential sweep from 0 to −2.8 V showed two reduction peaks at

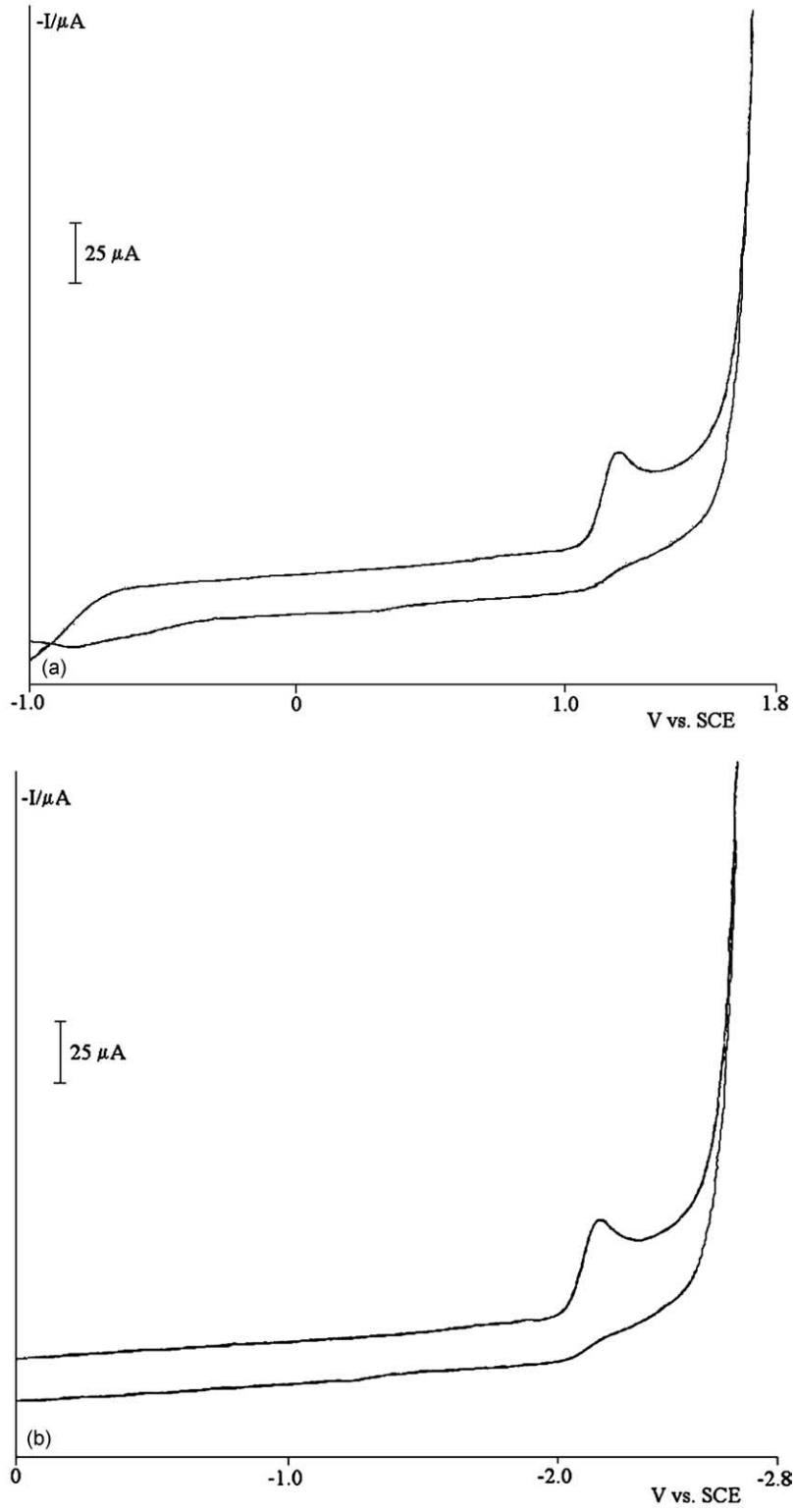


Figure 2. Cyclic voltammograms at a vitreous carbon electrode of a 0.005 mol dm^{-3} solution of compound **2** in DMF with 0.1 mol dm^{-3} Bu_4NBF_4 as supporting electrolyte at a sweep rate of 100 mV s^{-1} (SCE=standard calomel electrode).

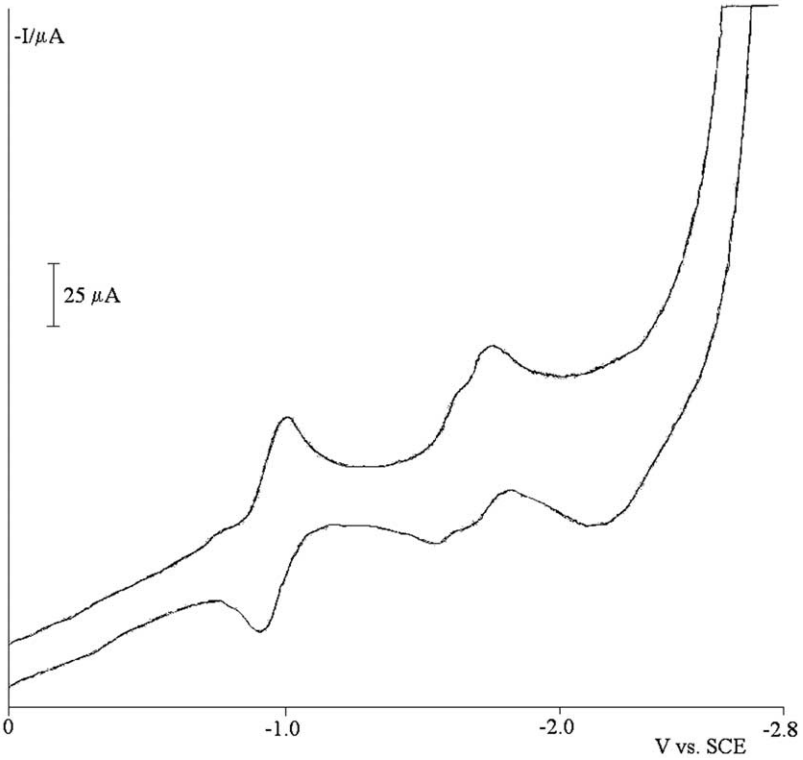


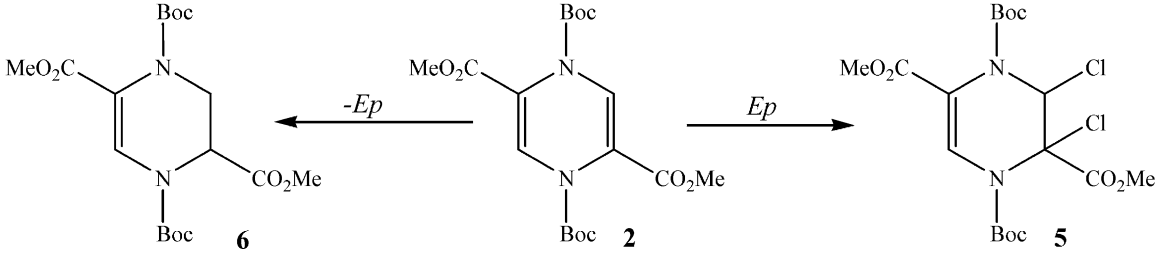
Figure 3. Cyclic voltammogram at a vitreous carbon electrode of a 0.005 mol dm^{-3} solution of compound **3** in DMF with 0.1 mol dm^{-3} Bu_4NBF_4 as supporting electrolyte at a sweep rate of 100 mV^{-1} (SCE=standard calomel electrode).

−1.00 and −1.82 V versus SCE (Fig. 3). Considering the electron-withdrawing effect of the substituents, the first reduction potential for 2,5-bis-methoxycarbonylpyrazine is in agreement with that found for: unsubstituted pyrazine (−2.16 versus SCE);[12] 2-carboxamide pyrazine (−1.75 V versus SCE);[13] and with the first reduction peak of chloropyrazine (−1.78 V versus SCE).[12]

In view of the cyclic voltammetry data obtained, controlled potential electrolysis of compound **2** at the oxidation and reduction peak potentials were carried out. In these reactions tetraethylammonium chloride was used as supporting electrolyte and triethylammonium chloride as electron donor. Oxidation of compound **2** gave one of the diastereomers of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,3-dichloro-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (compound **5**) in 91% yield (Scheme 3). The formation of this compound can be due to oxidation to give a radical cation which reacts with the chloride ions present in solution. Reduction of compound **2** gave as expected *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (compound **6**) in 55% yield (Scheme 3).

3. Conclusion

The common method for the synthesis of pyrazines involves the cyclocondensation of nitrogen nucleophiles onto α-dicarbonyl systems. We developed a new high yielding method for the synthesis of a 1,4-dihydropyrazine derivative from the methyl ester of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butoxycarbonyl)-α,β-didehydroalanine by treatment with DMAP and K_2CO_3. This compound was easily converted into 2,5-bis-carboxymethylpyrazine by treatment with TFA. The 1,4-dihydropyrazine derivative is also a good substrate for the diastereoselective synthesis of several tetrahydropyrazines, in good to high yields, either by Michael addition reactions or by controlled potential electrolysis. Several of these diazine derivatives can have biological activity since pyrazinamide is one of the front line agents against *M. Tuberculosis*,[14] some dihydropyrazines such as



Scheme 3.

2,3-dihydro-5,6-dimethylpyrazine showed DNA strand-breaking activity in plasmid[15] and tetrahydropyrazines have been used in the synthesis of a HIV protease inhibitor.[16]

4. Experimental

4.1. Materials and methods

Melting points were determined in a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus at 300 and 75.4 MHz, respectively. ^{1}H–^{1}H spin–spin decoupling and DEPT θ 45° were used. Chemical shifts are given in ppm and coupling constants in Hz. MS and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was performed on a LECO CHNS 932 elemental analyser.

The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey–Nagel silica gel 230–400 mesh. Petroleum ether refers to the boiling range 40–60 °C.

4.1.1. Synthesis of Tos-ΔAla(*N*-Boc)-OMe. The synthesis of these compounds was described in Ref. 6.

4.1.2. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine (2) from Tos-ΔAla(*N*-Boc)-OMe. To a solution of Tos-ΔAla(*N*-Boc)-OMe in acetonitrile (0.1 mol dm^{-3}), K_2CO_3 (6 equiv) was added, followed by 1 equiv of DMAP, with fast stirring at room temperature. The reaction was monitored by TLC, (diethyl ether/*n*-hexane, 1:1) and when no starting material nor Boc-ΔSer(*O*-toluenesulfinyl)-OMe was detected ($\approx$72 h), the solution was filtered and evaporated at reduced pressure (the same procedure but heating the reaction mixture under reflux allowed the reaction to be complete in 12 h). The residue obtained was partitioned between 200 cm^3 of diethyl ether and 100 cm^3 of $KHSO_4$ (1 mol dm^{-3}). The organic phase was thoroughly washed with $KHSO_4$ (1 mol dm^{-3}), $NaHCO_3$ (1 mol dm^{-3}) and brine (3$\times$50 cm^3 each), and dried over $MgSO_4$. Removal of the solvent afforded pure compound **2** (89%), mp 155.0–156.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.50 (18H, s, CH_3 2Boc), 3.80 (6H, s, 2CH_3 OMe), 7.09 (2H, s, 3-H+6-H); ^{13}C NMR ($CDCl_3$): 27.88, 52.27, 83.65, 119.82, 127.68, 148.82, 162.58; MS: *m*/*z* (%)=399 (14) [M$^+$+1], 398 (20) [M$^+$], 343 (36) [M$^+$−CO_2Me], 298 (6) [M$^+$−Boc], 198 (100) [M$^+$−2Boc]. Anal. Calcd for $C_{18}H_{26}N_2O_8$ (398.41): C 54.27; H 6.58; N 7.03; found C 54.42; H 6.72; N 6.94.

4.1.3. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,4-dihydropyrazine (2) from Tos-Ser-OMe. To a solution of Tos-Ser-OMe in dry acetonitrile (0.1 mol dm^{-3}), 0.1 equiv of DMAP were added, followed by Boc_2O (2.2 equiv) with fast stirring at room temperature. After reacting for 30 min more DMAP (1 equiv) was added and also K_2CO_3 (6 equiv). After reacting for approximately 3 days the same work-up as described above was carried out to give compound **2** (78% yield).

4.1.4. Synthesis of 2,5-bis-methoxycarbonylpyrazine (3). To a solution of compound **2** in dichloromethane (0.02 mol dm^{-3}), 10% trifluoroacetic acid was added with fast stirring at room temperature. The reaction was monitored by TLC, (diethyl ether/*n*-hexane, 1:1) and when no starting material was detected removal of the solvent afforded pure compound **3** (71%), mp 145.5–147.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 4.10 (6H, s, 2CH_3 OMe), 9.42 (2H, s, 3-H+6-H); ^{13}C NMR ($CDCl_3$): 53.55, 145.18, 145.52, 163.52. Anal. Calcd for $C_8H_8N_2O_4$ (196.16): C 48.98; H 4.11; N 14.28; found C 49.06; H 4.10; N 14.00.

4.1.5. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(triazol-1-yl)-1,2,3,4-tetrahydropyrazine (4a). To a solution of compound **2** in acetonitrile (0.1 mol dm^{-3}), K_2CO_3 (6 equiv) was added, followed by 1 equiv of 1,2,4-triazole, with fast stirring at room temperature. The reaction was monitored by TLC, (diethyl ether/*n*-hexane, 1:1) and when no starting material was detected ($\approx$16 h), the solution was filtered and evaporated under reduced pressure. The residue obtained was partitioned between 100 cm^3 of diethyl ether and 30 cm^3 of $NaHCO_3$ (1 mol dm^{-3}). The organic phase was washed with $NaHCO_3$ (1 mol dm^{-3}) and brine (2$\times$30 cm^3 each), and dried over $MgSO_4$. Removal of the solvent afforded compound **4a** as an enantiomeric mixture of the *trans* diastereomer (92%); oil; ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.48, 1.50 (36H, 2s, CH_3 Boc), 3.79, 3.81 (12H, 2s, CH_3 OMe), 5.93, 6.03, 6.93, 6.99 (4H, 4s, 2-H+3-H pyr.), 7.36, 7.57 (2H, 2s, 6-H pyr.), 7.92 (2H, s, 3-*H* or 5-*H* triaz.), 8.32 (2H, s, 3-*H* or 5-*H* triaz.); ^{13}C NMR ($CDCl_3$): 27.69, 27.83, 52.15, 53.12, 56.26, 57.40, 63.20, 83.79, 84.37, 122.46, 127.64, 148.50, 150.04, 152.26, 166.72; MS: *m*/*z* (%)=467 (7) [M$^+$], 367 (3) [M$^+$−Boc], 267 (24) [M$^+$−2Boc], 198 (100) [M$^+$−2Boc-triaz.]; HRMS found 467.2016, Calcd for $C_{20}H_{29}N_5O_8$ 467.2016.

4.1.6. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(3-formylindol-1-yl)-1,2,3,4-tetrahydropyrazine (4b). The same procedure described for the synthesis of compound **4a** was applied substituting 3-formylindole for 1,2,4-triazole. Removal of the solvent afforded compound **4b** as an enantiomeric mixture of the *trans* diastereomer (90%), mp 156.0–157.0 °C (from ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.48, 1.54 (36H, 2s, CH_3 Boc), 3.75, 3.84 (12H, 2s, CH_3 OMe), 5.40, 5.56 (2H, 2s, 2-H or 3-H pyr.), 7.23–7.58 (10H, m, 2-H or 3-H+6-H pyr.+2-H+5-H+6-H ind.), 7.73 (2H, d, *J*=7.5 Hz, 7-H ind.), 8.31 (2H, d, *J*=7.8 Hz, 4-H ind.), 9.95 (2H, s, C*H*O); ^{13}C NMR ($CDCl_3$): 27.73, 27.92, 52.12, 53.39, 57.01, 59.95, 83.76, 85.32, 110.33, 110.65, 119.27, 121.69, 122.13, 123.67, 124.84, 125.13, 134.17, 136.60, 150.41, 151.83, 163.91, 166.70, 184.94. Anal. Calcd for $C_{27}H_{33}N_3O_9$ (543.57): C 59.66; H 6.12; N 7.73; found C 59.87; H 6.18; N 7.78.

4.1.7. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(4-bromophenylsulfanyl)-1,2,3,4-tetrahydropyrazine (4c). The same procedure described for the synthesis of compound **4a** was applied substituting 4-bromothiophenol for 1,2,4-triazole. Removal of the solvent afforded compound **4c** as an enantiomeric mixture

of the *trans* diastereomer (76%), mp 137.0–138.5 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.34, 1.49, 1.57 (36H, 3s, C*H*$_3$ Boc), 3.69, 3.78 (12H, 2s, C*H*$_3$ OMe), 4.89, 5.08 (2H, 2s, 2-H or 3-H), 6.15, 6.21 (2H, 2s, 2-H or 3-H), 7.48 (8H, broad s, ArH), 7.56, 7.78 (2H, 2s, 6-H); ^{13}C NMR ($CDCl_3$): 27.66, 28.00, 51.83, 52.87, 57.30, 57.60, 58.23, 59.77, 82.41, 84.29, 108,52, 122.44, 130.50, 132.04, 135.32, 150.67, 151.22, 164.26, 167.27. Anal. Calcd for $C_{24}H_{31}N_2O_8SBr$ (587.48): C 49.07; H 5.32; N 4.77; S 5.46; found C 49.40; H 5.52; N 4.81; S 5.40.

4.1.8. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-(benzylamino)-1,2,3,4-tetrahydropyrazine (4d). The same procedure described for the synthesis of compound **4a** was applied substituting benzylamine for 1,2,4-triazole. Removal of the solvent afforded compound **4d** as an enantiomeric mixture of the *trans* diastereomer (82%), mp 106.5–107.5 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.42, 1.45, 1.52 (36H, 3s, C*H*$_3$ Boc), 3.70 (6H, s, C*H*$_3$ OMe), 3.80–3.92 (10H, m, C*H*$_3$ OMe + C*H*$_2$ Bn), 4.82, 4.97 (2H, 2s, 2-H or 3-H), 5.60, 5.65 (2H, 2s, 2-H or 3-H), 7.28–7.36 (10H, m, ArH), 7.50, 7.71 (2H, 2s, 6-H); ^{13}C NMR ($CDCl_3$): 27.87, 27.97, 49.47, 51.77, 52.57, 59.27, 60.55, 62.41, 81.58, 84.02, 121.51, 127.25, 128.43, 128.56, 139.17, 150.69, 152.75, 164.99, 167.85, 168.07. Anal. Calcd for $C_{25}H_{35}N_3O_8$ (505.56): C 59.39; H 6.98; N 8.31; found C 59.43; H 7.21; N 8.05.

4.1.9. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-3-methoxy-1,2,3,4-tetrahydropyrazine (4e). The same procedure described for the synthesis of compound **4a** was applied substituting sodium methoxide for 1,2,4-triazole. Removal of the solvent afforded compound **4e** as an enantiomeric mixture of the *trans* diastereomer (35%); oil; ^{1}H NMR ($CDCl_3$) (2 rotamers): 1.43, 1.47, 1.53 (36H, 3s, C*H*$_3$ Boc), 3.40 (6H, s, C*H*$_3$ COMe), 3.70, 3.79 (12H, 2s, C*H*$_3$ COOMe), 4.89, 5.05 (2H, 2s, 2-H or 3-H), 5.79, 5.84 (2H, 2s, 2-H or 3-H), 7.51, 7.72 (2H, 2s, 6-H), ^{13}C NMR ($CDCl_3$): 27.85, 28.01, 51.77, 52.70, 55.26, 58.78, 60.18, 77.96, 82.02, 83.56, 83.91, 107.85, 122.47, 150.81, 167.37; MS: *m*/*z* (%)=430 (8) [M^+], 230 (100) [M^+-2Boc], 199 (21) [M^+-2Boc-OMe]; HRMS found 430.1947, Calcd for $C_{19}H_{30}N_2O_9$ 430.1951.

4.1.10. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,3-dichloro-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (5). A solution of Et_4NCl (0.1 mol dm^{-3}; supporting electrolyte) and Et_3NHCl (0.04 mol dm^{-3}; proton donor) in MeCN was added to a two compartment, three-electrode cell. Compound **2** (99.5 mg, 0.25 mmol) was added to the anodic compartment and a cyclic voltammogram recorded. The potential was adjusted to a value 50 mV more positive than that corresponding to the CV peak and the electrolysis started, the reaction being monitored by HPLC. When all starting material had disappeared, the content of the anodic compartment was concentrated under reduced pressure and the residue partitioned between 100 cm^3 of ethyl acetate and 50 cm^3 of water. The organic phase was then washed with water and brine (3×30 cm^3 each) and dried over $MgSO_4$. The solution was filtered and the solvent removed to give a residue which was submitted to column chromatography using diethyl ether/*n*-hexane (1:2) as eluent to give compound **5** (106.8 mg, 91%), mp 119.5–121.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): 1.49, 1.53 (18H, 2s, C*H*$_3$ Boc), 3.82, 3.88 (6H, 2s, C*H*$_3$ OMe), 6.61 (1H, s, 3-H), 7.56 (1H, s, 6-H); ^{13}C NMR ($CDCl_3$): 27.70, 27.76, 52.24, 54.24, 68,71, 83.93, 85.91, 109.74, 122.00, 126.15, 148.79, 149.05, 163.20, 163.68; MS: *m*/*z* (%)=470 (1) [M^++2], 468 (1.3) [M^+], 368 (2) [M^+-Boc], 268 (57) [M^+-2Boc], 233 (63) [M^+-2Boc-Cl], 197 (100) [M^+-2Boc-2Cl]. HRMS found 468.1082, Calcd for $C_{18}H_{26}N_2O_8Cl_2$ 468.1066.

4.1.11. Synthesis of *N*,*N*-bis-(*tert*-butoxycarbonyl)-2,5-bis-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (6). The same procedure as described above was followed but adding compound **2** (99.5 mg, 0.25 mmol) to the cathodic compartment to give compound **6** (55.2 mg, 55.2%). ^{1}H NMR ($CDCl_3$): 1.41, 1.52 (18H, 2s, C*H*$_3$ Boc), 2.96–3.08 (1H, m, 3-H), 3.71, 3.78 (6H, s, 2C*H*$_3$ OMe), 4.68–4.90 (2H, m, 2-H + 3-H), 7.53 (1H, s, 6-H); ^{13}C NMR ($CDCl_3$): 27.82, 27.88, 42.27, 51.75, 52.62, 54.70, 55.98, 81.69, 83.58, 83.90, 109.60, 123.01, 150.52, 150.64, 169.00, 169.35; MS: *m*/*z* (%)=400 (4) [M^+], 200 (100) [M^+-2Boc], 167 (11) [M^+-2Boc-OMe], 141 (13) [M^+-2Boc-CO_2Me]; HRMS found 400.1857, Calcd for $C_{18}H_{28}N_2O_8$ 400.1846.

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Tripodal Ru(II) complexes with conjugated and non-conjugated rigid-rod bridges for semiconductor nanoparticles sensitization

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Abstract—Three tripodal Ru(II)-polypyridyl complexes have been synthesized as models to study long-range electron transfer in TiO_2 semiconductor nanoparticles thin films, in particular to study the effect of the conjugation of the bridge containing the Ru complex and for distance dependence studies. The tripodal sensitizers, which are 1,3,5,7-tetraphenyladamantane derivatives having three COOMe anchoring groups and one rigid-rod bridge substituted with a Ru(II) complex, are the longest prepared to date (Ru-to-footprint distance ~24 Å). Two have a rigid-rod bridge made of two *p*-ethynylphenylene units $(Ph\text{-}E)_2$ capped with a 4-2,2′-bipyridyl (bpy) ligand or a 5-1,10-phenanthrolinyl (phen) ligand for the Ru complex. The third tripod, which contains a bpy ligand for the Ru complex, has one bicyclo[2.2.2]octylene (Bco) unit in place of a *p*-phenylene (Ph) unit and is the first example of a tripodal sensitizer with a non-conjugated bridge.

1. Introduction

The photoexcitation of dyes covalently bound to TiO_2 nanoparticles thin films is an important step in dye-sensitized (Grätzel) solar cells and other optoelectronic systems based on wide band gap semiconductors.[1] Polypyridine complexes of Ru(II), the classical photosensitizing dyes for solar cells, are generally bound to the TiO_2 nanoparticles through anchoring groups directly attached on one or more ligands. Carboxylate (COOR) or phosphonate ($PO(OR)_2$) groups are frequently used for this purpose because they form strong bonds with TiO_2 surfaces.[1a] To bind the sensitizers, we[2] and others[3,4] have developed rigid linkers that have the shape of tripods and rigid-rods.[5] The design of linkers of varying complexity for the functionalization of semiconductor nanoparticle is a recent and promising development in this field.[6]

For clarity, in this paper we call bridge (b) the moiety that is placed between the anchoring groups (A) and the chromophore or sensitizer (S), and tripodal linker the molecule that contains both the bridge and the anchoring groups, as shown in Figure 1. Tripodal sensitizer, or tripod, is the tripodal linker capped with the Ru complex. We reported the study of tripodal sensitizers based on tetraphenylmethane and 1,3,5,7-tetraphenyladamantane, and having one *p*-ethynylphenylene (Ph-E) unit as the bridge carrying Ru-polypyridyl complexes.[2b–d] These molecules are rigid and stand perpendicularly to the surface when all three COOR anchoring groups are bound. Because of this binding geometry, the distance of the Ru complex from the semiconductor is fixed, and tripodal sensitizers are useful models to study interfacial electron transfer processes.

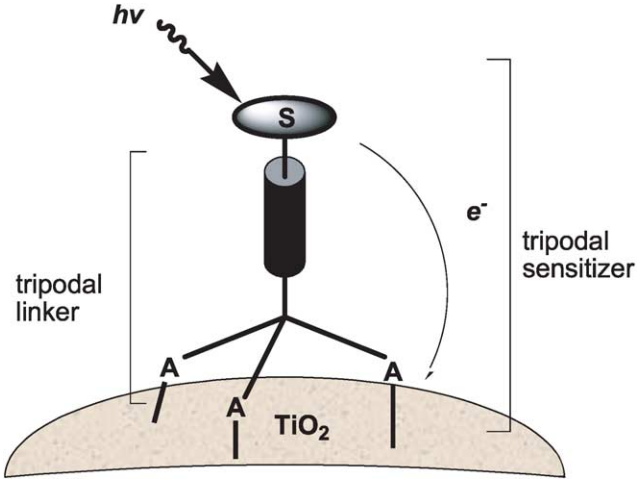

Figure 1. Schematic representation of the components of a tripodal sensitizer bound to a TiO_2 nanoparticle. These are: the sensitizing chromophore (S) and the tripodal linker, containing a rigid-rod bridge (b) and three anchoring groups (A).

Keywords: Titanium dioxide; Sensitization; ruthenium complexes; Tripods.
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The Ru-to-footprint distance (d) in our previous series of tripods was 15–18 Å.[2] In this paper we report the synthesis and characterization of the longest (d = 24 Å) tripods prepared to date and the first example of a tripodal sensitizer with a non-conjugated bridge (**1**, **2** and **3** in Figure 2). Both **1** and **2** contain a bridge made of two *p*-ethynylphenylene units, $(Ph\text{-}E)_2$, but differ in the ligands for the Ru complex (a phen ligand in **1** and a bpy ligand in **2**). Tripod **3** is analogous to the bpy-based **2**, but contains a bicyclo[2.2.2]-octylene unit (Bco) in the bridge in place of a *p*-phenylene (Ph) unit.[7]

The study of tripodal Ru-polypyridyl sensitizers bound to TiO_2 thin films has shown that the metal-to-ligand charge transfer (MLCT) excited state is localized on the bpy ligand attached to the bridge and that the bridge conjugation can influence the electron injection process.[2] This is not surprising, as the influence of $(Ph\text{-}E)_n$[8a–c] groups and other conjugated substituents[8d,9e] on the photophysical properties of Ru-polypyridyl complexes has been demonstrated. We observed this effect in the interfacial charge injection in **1** and **2** bound to TiO_2 thin films (**1**/TiO_2 and **2**/TiO_2).[2a] The electron injection in Ru complexes that are directly bound to the surface, for instance $Ru(dcb)(bpy)_2^{2+}$,[7] occurs in $\tau <$ 80 fs.[1a,9] As expected, slower rates were observed in **1**/TiO_2 and **2**/TiO_2.[2a] The kinetics were fit using bi-exponential decays,[1,9,10] with **1** injecting faster than **2**. In both cases, there was a slow ($\tau \sim 3$ ps) component ascribed to the long-range injection, together with a sub-picosecond component ($\tau \sim 240$ fs for **1**/TiO_2 and ~ 450 fs for **2**/TiO_2).[2a] The ultrafast component was rationalized considering the extensive π-conjugation of the bridge. The faster injection exhibited by the phen-based **1**/TiO_2 with respect to the bpy-based **2**/TiO_2 was attributed to the stronger electronic coupling between the phen ligand and the bridge.[2a,11] In summary, the study of **1** and **2** reinforced the concept that the conjugated bridge plays an important role in the interfacial electron injection. To probe this effect, we have now prepared **3**, which contains a non-conjugated bridge.

Hydrocarbon cage compounds that have been used to prepare non-conjugated bridges connecting an electron donor–acceptor[12] pair include cubane,[13] stellane,[14] adamantane,[15] [*n*]staffanes[16] and bicyclo[2.2.2]octane.[17,18] The use of rigid-rod molecules for this purpose has been reviewed.[19] We selected to incorporate one bicyclo[2.2.2]-octylene unit in the bridge because it is an excellent insulator of electronic effects,[17c] as shown by a comparison of the LUMO delocalization in the bridges of **2** and **3** (Figure 3).

At the same time, the replacement of a Ph with a Bco does not significantly change the length of the molecule (Figure 2, inset). These properties make **3** an ideal model to study the bridge conjugation effect on the rate of electron injection. Also, models **1**–**3** will be useful, together with other tripods, in distance dependence studies to investigate the mechanism(s) for the electron injection. In this paper we report the syntheses of **1** and **2** (for which we had reported preliminary data but not the synthesis) and the new model **3** through two different routes.

2. Synthesis

Scheme 1 shows the two synthetic routes employed. The key step in both routes, step 1, involves the monosubstitution of a tetrahedral precursor (**I**) to prepare a derivative having one group different from the other three. Since this is a statistical step, it requires a separation. The alkyne of the tripodal linker (**II**) is capped with the chromophore in the last step, so that a variety of tripodal sensitizers (**III**) can be prepared from this intermediate.

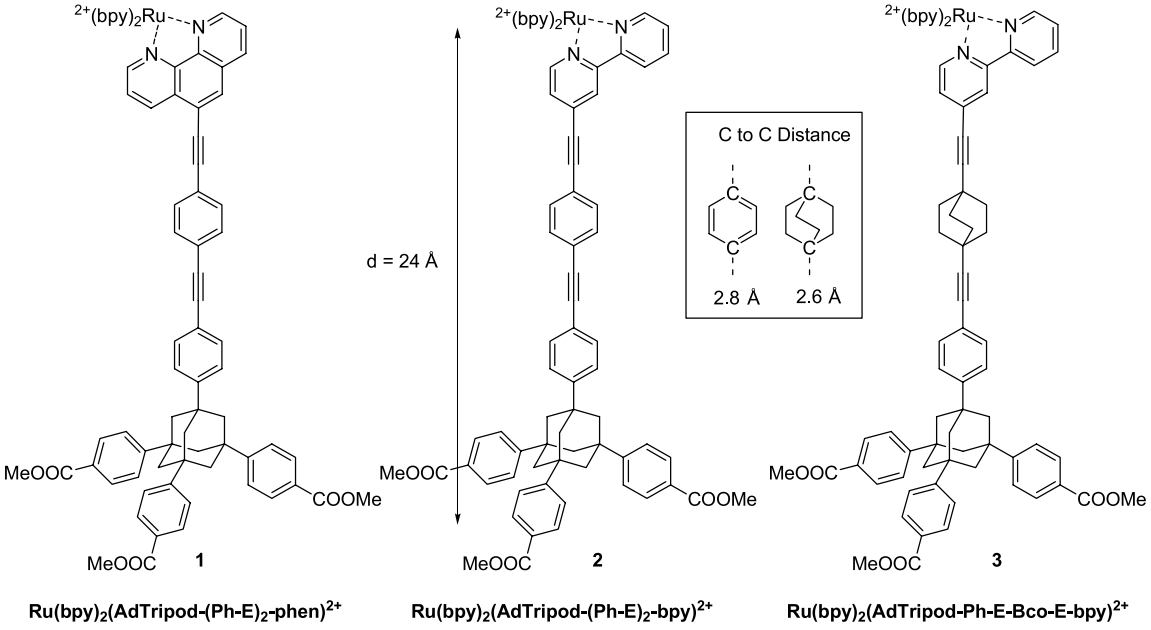


Figure 2. Tripodal sensitizers **1**, **2** and **3**. The counterion is PF_2^- in all cases. Note the phen ligand in **1** and bpy ligand in **2**. Tripod **3** contains a Bco unit that retains the axial symmetry and has the same length as a Ph unit (inset). The distance (d) of the Ru center to the footprint (the plane defined by the three surface-bound oxygen atoms) in **1**–**3** is 24 Å.[7]

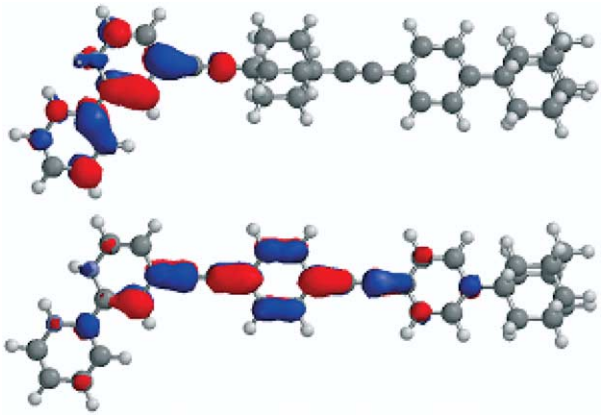


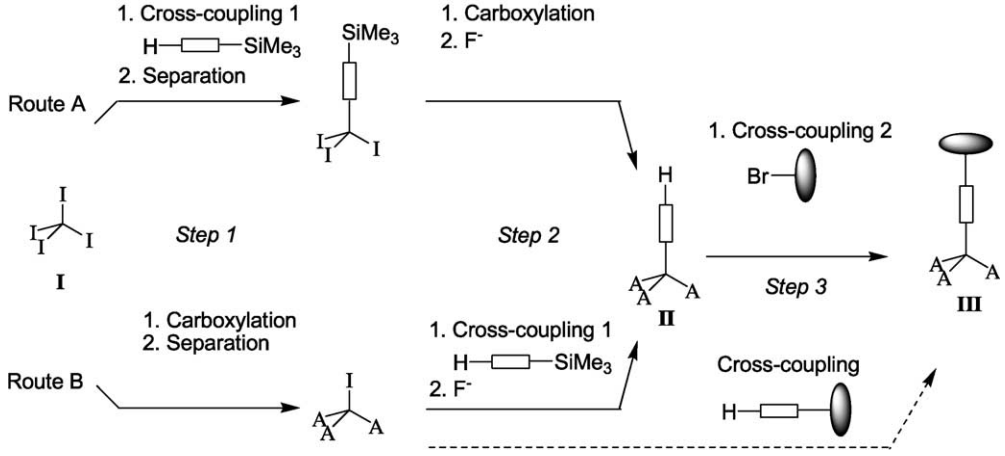
Figure 3. LUMO of a bpy-E-Bco-E-Ph bridge (top) and of a bpy-E-Ph-E-Ph bridge (bottom) connected to the adamantane core of the tripod (Spartan '02, Wavefunction, Inc.).

In Route A the rigid-rod bridge is introduced via cross-coupling in step 1 and the three remaining iodine groups are converted into anchoring groups via metal–halogen exchange and carboxylation in step 2. This order is reversed in route B. A potentially useful aspect of this reversal is that steps 2 and 3 can be combined by performing the cross-coupling with an ethynyl bridge carrying the chromophore (Scheme 1, dashed arrow).[20] Also, since the tricarboxylation is performed first, the bridge (with or without the chromophore) can be attached in a non-statistical cross-coupling to form **II**, thereby minimizing the loss of the valuable rigid-rod bridge. Results obtained with the two approaches are discussed below.

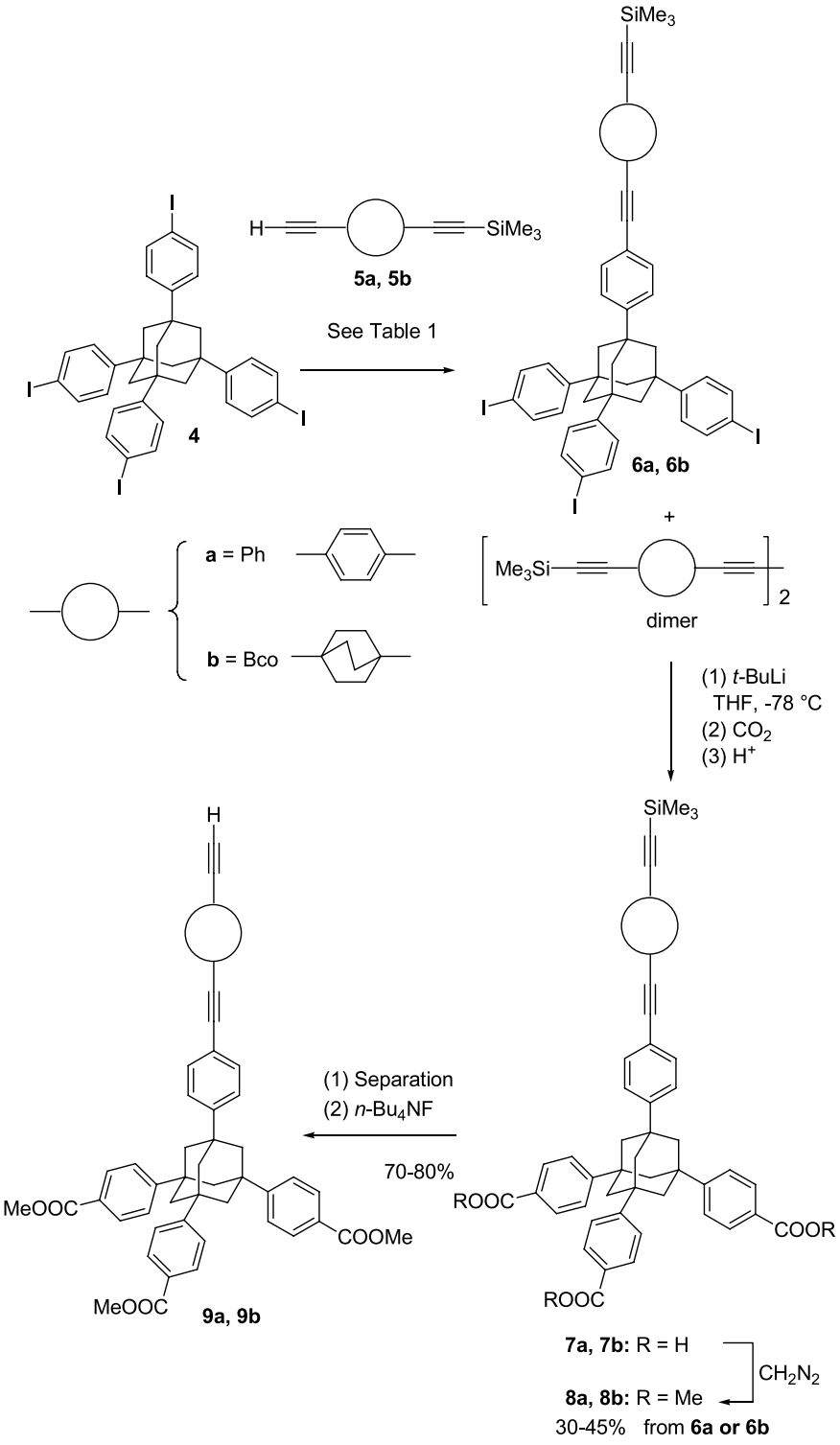
Route A (Schemes 2 and 3) follows the same sequence reported to prepare shorter tripods,[2c] but the use of longer bridges required different conditions in the first and last steps of the synthesis. In general, we observed that cross-coupling reactions proceeded in lower yields or were more sluggish as the size of the tripodal linker or of the bridge increased.

In the first step, 1,3,5,7-tetrakis(4-iodophenyl)-adamantane[21] (**4**) was reacted with 1-ethynyl-4-trimethylsilyl-ethynyl-benzene (**5a**)[5b] or 1-ethynyl-4-trimethyl-silylethynyl-bicyclo[2.2.2]octane (**5b**),[22] to afford monosubstituted **6a** or **6b**, respectively, in a Sonogashira cross-coupling reaction (Scheme 2).[23,24] Both mono-deprotected alkynes **5a** and **5b** were prepared from the corresponding 1,4-bis(trimethylsilyl)ethynes, using 1 equiv. of MeLi·LiBr complex as the nucleophile.[5b,25] The reaction was performed at −78 °C for **5a** and at rt for **5b**. In both cases the crude material was a 1:1 mixture (GC/MS) of the monodeprotected compound and the starting material, with only traces of dialkyne. After this mixture was employed in the cross-coupling step, the unreacted 1,4-bis(trimethyl-silyl)ethyne was easily isolated in pure form and used again. The Sonogashira conditions that we had used previously[2d] ($Pd(PPh_3)_2Cl_2$/CuI/*i*-Pr_2NH) resulted in almost complete dimerization of **5a** or **5b**. Dimerization of the alkyne, a common side reaction in Sonogashira reactions, is not a problem when the alkyne is added in large excess. In this case, **5a** and **5b** are added in equimolar amount to **4**, and **5b** is not expendable because it is prepared via a multistep synthesis.[20,21] Our experience with the synthesis of rigid-rod sensitizers prepared from **5a** and methyl 5-bromo-1,3-benzenedicarboxylate[5b] indicated that the use of $Pd(dba)_2$/CuI/PPh_3 under argon minimizes the dimerization of **5a**. By employing these conditions we were able to prepare **6a** and **6b** in 28–36% yields and to inhibit the dimerization (Table 1, entries 2 and 5).

For the synthesis of **6b**, we also used the cross-coupling procedure reported by Albinsson and coworkers (Table 1, entry 4),[18] but in our case the purification of the product was not practical. Although **4** and alkyne **5a** or **5b** were reacted in equimolar ratio, the step is statistical and di- and tri-substituted products and unreacted **4** were recovered together with monosubstituted **6a** or **6b**. The mono-substituted products **6a** and **6b** were both isolated in this step for characterization purposes. For preparative purposes, however, it is easier to remove unreacted **4** from the crude material and use this purified mixture in the following step. The di- and tri- substituted products are useful inter-mediates, and we are pursuing their conversion into di- and tri-chromophoric antennas. Metal–halogen exchange with *t*-BuLi followed by quenching with CO_2 and acidification afforded the acids **7a** (or **7b**), which are insoluble materials. Treatment with diazomethane and purification of the more soluble esters by column chromatography (or separation if the carboxylation is performed on the statistical mixture



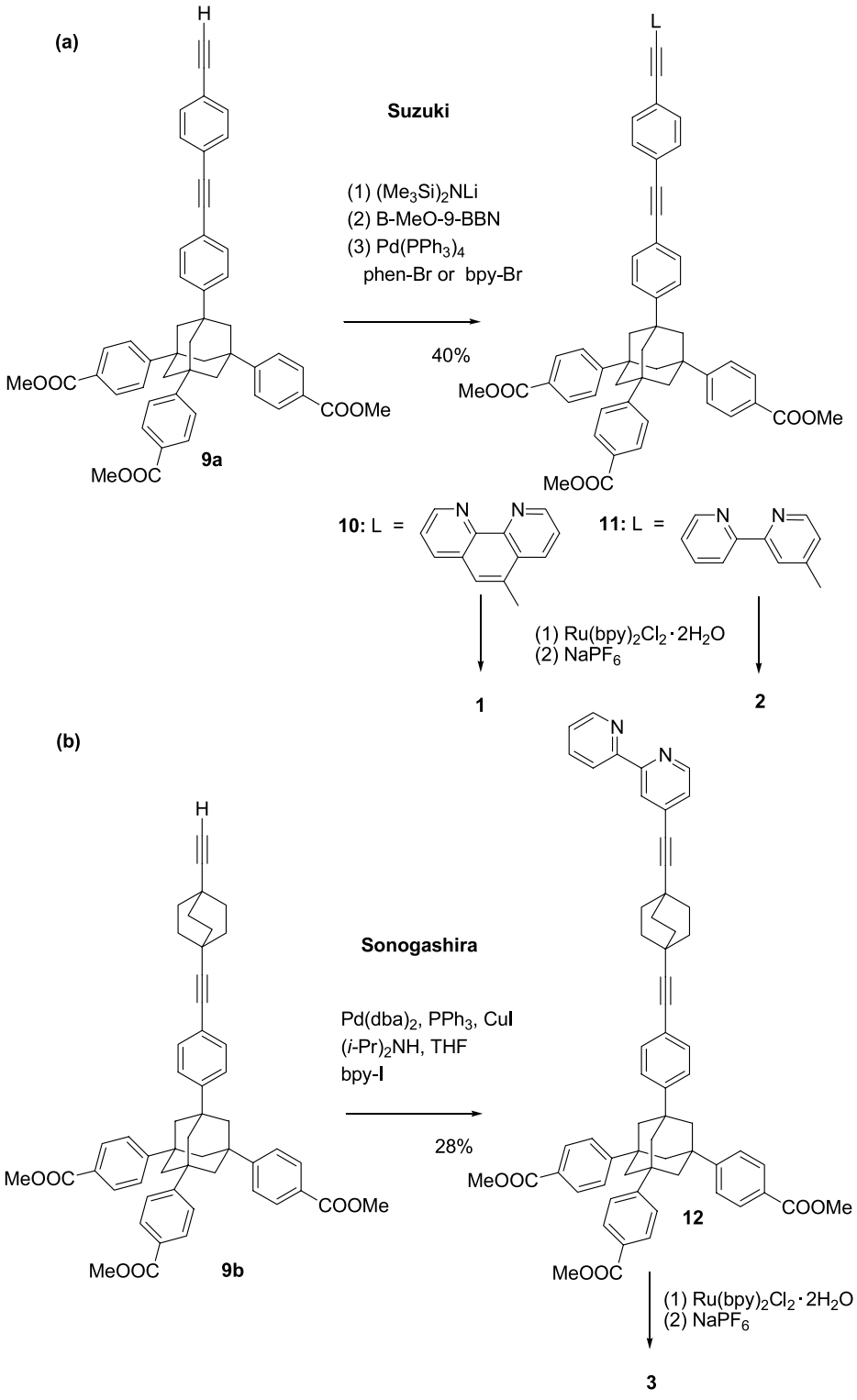
Scheme 1.



Scheme 2.

from the first step) afforded tricarboxylic esters **8a** or **8b**. The TMS-alkyne was deprotected using *n*-Bu_4NF to form alkyne **9a** or **9b**. The yield from **6a** or **6b** is 30–45%. ^1H NMR spectra showed a significant upfield shift of the alkyne proton in **9b** (δ_H (C≡C*H*)=2.10 ppm) compared to **9a** (δ_H (C≡C*H*)=3.17 ppm) suggesting that the terminal alkyne on the Bco unit is less acidic. This observation may account for the significantly lower reactivity of **9b**, and the need for two different cross-coupling procedures in the last step (Scheme 3a).

A Suzuki-type reaction[26] was employed to react **9a** with 4-bromo-2,2′-bipyridine[27] or 5-bromo-1,10-phenanthroline[28] to afford **11** and **10**, respectively. This procedure involves deprotonation of the alkyne, treatment with B-methoxy-9-BBN and then cross-coupling of the resulting



Scheme 3.

ethynylboronate with the aryl halide in the presence of Pd(0) catalyst. The Sonogashira reaction was avoided, because the presence of Cu(I) leads to the dimerization of **9a**. The non-conjugated ethyne **9b**, however, did not react in Suzuki conditions. The cross-coupling of **9b** required Sonogashira conditions and the more reactive 4-iodo-2,2′-bipyridine[29] (Scheme 3b). Tripodal linker **12** could be obtained only in this way, albeit only in 28% yields and with substantial dimerization of **9b**. Finally, the tripodal Ru(II) complexes **1**, **2** and **3** were prepared from the phen- or bpy-substituted tripodal linkers **10**, **11** and **12**, respectively.

Given our interest in tripodal sensitizers, we tested a potentially shorter route in which the anchoring groups are introduced first (Scheme 1, Route B). Carboxylation of **4** afforded a mixture of mono-, di- and tri-substituted esters.

Table 1. Reaction conditions for the cross-coupling reaction of **4** with alkyne **5a** or **5b**[a]

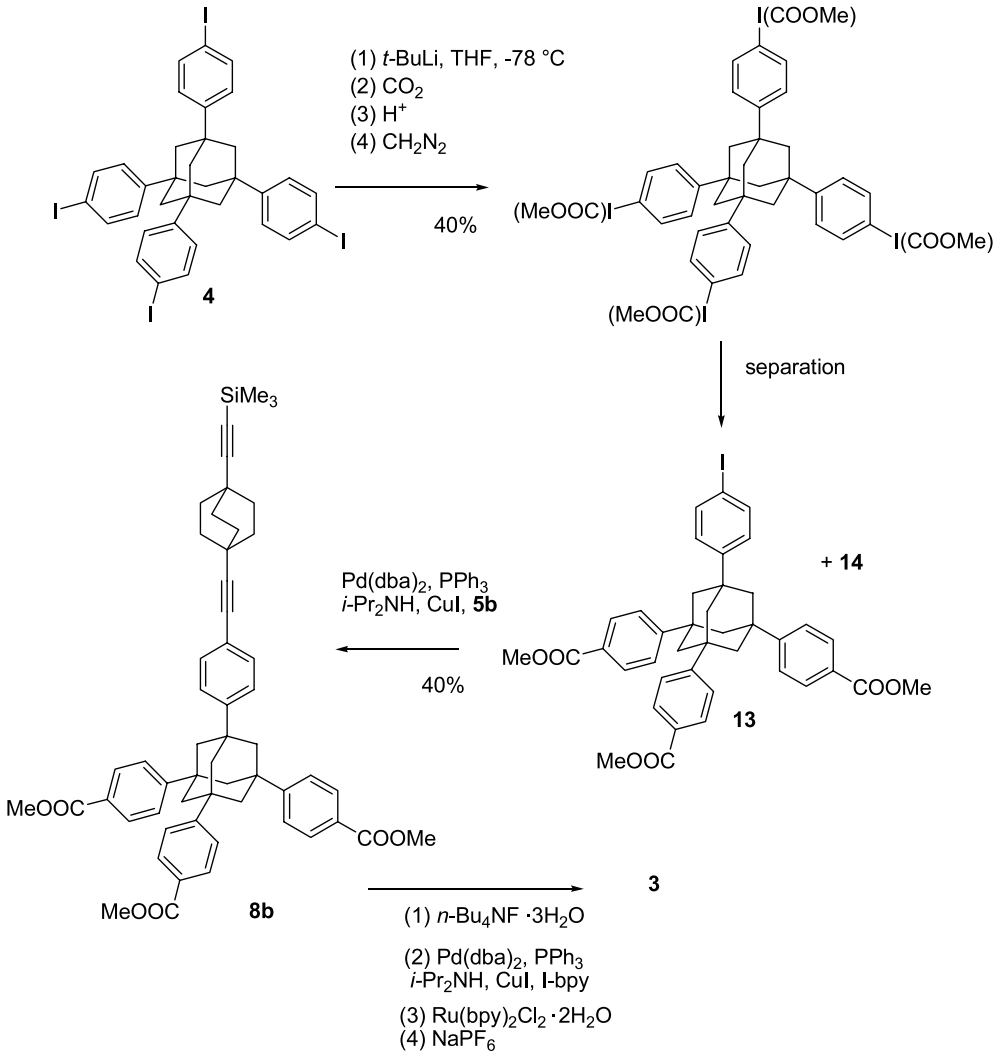
Entry	Alkyne[b]	Amine	Catalysts	Solvent	Product yield (%)	Dimer of **5a** or **5b** yield (%)
1	**5a**	Et_3N[c]	$Pd(dba)_2$, PPh_3, CuI	Benzene/THF	**6a** 30	15
2	**5a**	*i*-Pr_2NH[c]	$Pd(dba)_2$, PPh_3, CuI	Benzene/THF	**6a** 36	10
3	**5a**	*i*-Pr_2NEt[c]	$Pd(dba)_2$, PPh_3, CuI	Benzene/THF	**6a** Traces	34
4	**5b**	Piperidine[d]	$Pd(PPh_3)_4$	Piperidine[d]	**6b** 23[e]	25
5	**5b**	*i*-Pr_2NH[c]	$Pd(dba)_2$, PPh_3, CuI	THF	**6b** 28	20

[a] All reactions were performed at room temperature.
[b] The alkyne was added in 1–1.2 equiv. Any increase leads to more dimer.
[c] The amine was added in 20% excess with respect to **4**.
[d] The amine was used as the solvent.
[e] Piperidine was distilled in vacuo from the crude material.

Separation of this statistical mixture afforded **13**, which has one iodine available for the cross-coupling and three COOMe anchoring groups, in 15–20% yield from **4** (Scheme 4).

Although we could not separate compound **13** from an impurity, **14**, (See Supplementary data),[30] this crude material was used in the cross-coupling step with **5b** and unreacted **14** was separated from the product afterwards. Monosubstituted **9b** was thus obtained in ~40% yield from **13**. The tripodal sensitizer **3** was prepared from **9b** using the same procedures shown in Scheme 2.

In conclusion, Route B yielded **3** in the same overall yield as Route A (~6% for route A and ~6–8% for route B). The main advantage is that the cross-coupling step proceeds in higher yields (40%) and without wasting the precious bridge in a statistical reaction. We are currently improving this route and the use of a chromophore-substituted alkyne, as suggested in Scheme 1 (dashed line), is being explored.



Scheme 4.

Table 2. Absorption and fluorescence data for CH_3CN solutions of **1–3** and reference complexes

Entry	Sensitizer	λ_{abs} (nm) (ε, $M^{-1}\,cm^{-1}$)	[a]λ_F (nm)	τ (μs)	$\phi_F \times 10^{-2}$
1	**1**	449 (2.3×10^4)	606	1.4	10
2	**2**	463 (2.8×10^4)	638	2.2	12
3	**3**	456 (1.6×10^4)	624	1.6	14
4	[b]$Ru(bpy)_2(phen)^{2+}$	450	620		
5	[b]$Ru(bpy)_3^{2+}$	452	626	0.8[b]	

[a] The solutions were de-oxygenated by freeze-pump-thaw. $\lambda_{ex}=450$ nm.
[b] From Ref. 2b, in acetonitrile.

3. Solution photophysical properties of 1–3

The solution absorption and fluorescence data of tripodal sensitizers **1–3** are reported in Table 2, together with two reference complexes. A comparison of the absorption spectra between the bpy-based tripodal complexes **2** and **3**, shown in Figure 4, clearly shows an effect due to differences in the bridge structure.

The visible absorption spectra of **2** and **3** both displayed the broad band typical of the MLCT excited state at ~450 nm, while the $\pi \rightarrow \pi^*$ ligand-centered band at ~350 nm is present only in the spectrum of the bpy-tripod with the conjugated bridge (**2**) (Figure 4). The MLCT band for **2** was centered at 463 nm and red-shifted with respect to the same band in the spectrum of the bpy-tripod with the non-conjugated bridge (**3**) and of the reference $Ru(bpy)_3$. This shift was observed in the rt fluorescence spectra (Table 2). Specifically, the fluorescence spectrum of the bpy-based tripod with the conjugated bridge **2** was about 14 nm red-shifted with respect to the spectrum of the corresponding tripod with the Bco unit in the bridge, **3**, and of the reference $Ru(bpy)_3^{2+}$ (Table 2, entries 2, 3 and 5).

4. Summary

We have described the synthesis of three long (d=24 Å) tripodal Ru-polypyridyl sensitizers (**1–3**) via two synthetic routes. Although the overall yields from both routes are low, the compounds are of interest to study the effect of the bridging unit in electron transfer studies at nanoparticle interfaces, and the 'reversal' route B tested here may prove more useful that the method reported before. The bridge carrying the chromophore is conjugated in phen-based **1** and bpy-based **2**, and carries a bicyclo[2.2.2]octylene unit in bpy-based **3**. The photophysical study of **1**/TiO_2[2a] and **2**/TiO_2[2a], and the shorter tripods[2b–d] had suggested that the conjugated bridges influence the interfacial kinetic processes, and the models described here will allow to fully test this hypothesis.

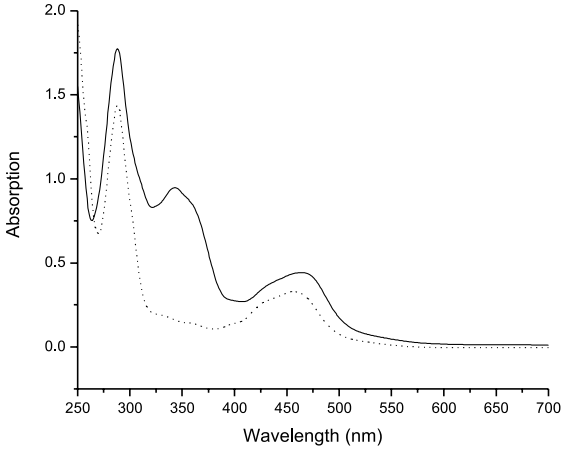


Figure 4. Absorption spectra of acetonitrile solutions of $Ru(bpy)_2(AdTripod\text{-}(Ph\text{-}E)_2\text{-}bpy)^{2+}$ **2** (—) and $Ru(bpy)_2(AdTripod\text{-}Ph\text{-}E\text{-}Bco\text{-}E\text{-}bpy)^{2+}$ **3** (- - -).

5. Experimental

5.1. General experimental methods

Instrumentation. ^1H (499.90 MHz) and ^{13}C (124.98 MHz) NMR spectra were obtained on a Varian INOVA 500 spectrometer and recorded in $CDCl_3$ unless otherwise noted. The ^1H spectra were referenced to Me_4Si, or to residual $CHCl_3$ (7.27 ppm) for the compounds containing the TMS group. The ^{13}C spectra were referenced to the central line of the solvent. Chemical shifts (δ) are given in parts per million (ppm) and reported to a precision of ± 0.01 ppm. Proton coupling constants (J) are given in Hz and reported to a precision of ± 0.1 Hz. High-resolution mass spectra (FAB-MS) and elemental analyses were obtained from commercial facilities. UV–vis absorbance data were collected on a VARIAN Cary-500 spectrophotometer, and photoluminescence (PL) measurements were performed on a VARIAN Cary-Eclipse Fluorescence Spectrophotometer. Measurements were run in CH_3CN in 1 cm quartz cuvettes. The solvent for the fluorescence spectra was de-oxygenated by three cycles of freeze-pump-thaw or by bubbling solvent-saturated nitrogen. The solutions were 0.005 mM (**2**) and 0.015 mM (**3**) in acetonitrile for the fluorescence spectra and 0.02 mM (**2** and **3**) for the absorption spectra. IR spectra were performed on a Mattson Research Series 1 FT-IR (KBr).

Materials and general procedures. All reactions were performed under nitrogen or argon atmosphere with glassware oven-dried and then flamed in vacuo unless otherwise specified. Column chromatography was performed using silica gel (40 μm average particle size). Thin layer chromatography (TLC) was performed using silica gel plates with fluorescent indicator and UV light as detection method. Phosphomolybdic 10% ethanolic solution and heat or iodine vapors were used as developing agents for compounds that do not absorb in the UV–vis (for instance **5b**). 'Standard workup' in the synthetic procedures refers to the following sequence: (a) the aqueous layer is extracted with the indicated solvent three times; (b) the organic layers are collected and dried over Na_2SO_4 anhyd; (c) the solvent is evaporated in vacuo on a rotary evaporator. Monoglyme

(1,2-dimethoxyethane) was distilled over sodium/benzophenone ketyl. THF (purchased anhydrous grade) was distilled over sodium/benzophenone ketyl. Benzene was distilled over sodium/benzophenone ketyl, CH_2Cl_2 was distilled over CaH_2, CBr_4 was recrystallized from ethanol and PPh_3 from hexane. We observed improved yields when we used CO_2(g) from a lecture bottle rather than generated from dry ice. Pd(0) catalysts were stored and handled in a glove box. The following solution reagents were purchased from Acros or Aldrich and were not titrated prior to use: *t*-BuLi (1.5 M solution in pentane), MeLi·LiBr complex (2.2 M solution in diethyl ether), Lithium bis(trimethylsilyl)amide (1.0 M solution in hexane), 9-methoxy-9-borobicyclo[3.3.3]nonane (B-methoxy-9-BBN, 1.0 M solution in hexane), *n*-BuLi (1.6 M solution in hexane). 4-Bromo-2,2′-bipyridine,[27] 5-bromo-1,10-phenanthroline,[28] 4-iodo-2,2′-bipyridine,[29] 1,3,5,7-tetrakis(4-iodophenyl)adamantane **4**,[21] **5a**[5b] and **5b**[22] were synthesized following literature procedures. *CAUTION*. To avoid explosion, diazomethane was prepared using exclusively glassware with smooth joints (Aldrich) from Diazald (Aldrich), MeOH, and KOH aq. following described procedures.[31]

5.2. Synthesis of tripodal sensitizers 1–3

5.2.1. 1,3,5-(4-Iodophenyl)-7-[4-(1-trimethylsilylethynyl-4-ethynyl-phenyl)phenyl]-adamantane (6a). A 1:1 mixture (GC/MS) of **5a**[5b] and 1,4-bis(trimethylsilylethynyl)-benzene (300 mg of mixture, 0.64 mmol of **5a**) was added to a solution of **4**[21] (515 mg, 0.54 mmol) in *i*-Pr_2NH (0.12 mL), benzene (25 mL) and THF (25 mL) at rt, followed by $Pd(dba)_2$ (18 mg, 0.027 mmol), PPh_3 (28 mg, 0.108 mmol), and CuI (10 mg, 0.054 mmol). The mixture was stirred at rt under nitrogen for 24 h and filtered. TLC ($CHCl_3$/hexane, 10/90) showed 5 spots corresponding to: 1,4-bis(trimethylsilylethynyl)-benzene (R_f=0.95), the dimer from **5a** (R_f=0.6), **4** (R_f=0.4), **6a** (R_f=0.26), di-substituted product (R_f=0.17). The mixture was separated by column chromatography ($CHCl_3$/hexane, 1/9) to afford **6a** (207 mg, 36%). Mp 194–196 °C. ^{1}H NMR δ_H: 7.68 (d, 6H, *J*=9.0 Hz, PhI), 7.51 (d, 2H, *J*=8.5 Hz), 7.44 (two s, 4H), 7.43 (d, 2H, *J*=8.5 Hz), 7.21 (d, 6H, *J*=9.0 Hz, PhI), 2.09 and 2.07 (two s, 12H, C*H*$_2$(Ad)), 0.25 (s, 9H, $SiMe_3$). ^{13}C NMR δ_C: 149.1, 148.4, 137.5, 131.9, 131.7, 131.3, 127.1, 125.0, 123.3, 122.8, 121.0, 104.6 (C≡C), 96.3 (C≡C), 91.7 (I-*C*), 91.1 (–C≡C–), 89.0 (–C≡C–), 46.7 (*C*H_2(Ad)), 39.2 and 39.0 (*C*(Ad)), −0.1 ($SiMe_3$). Anal. calcd for $C_{47}H_{41}I_3Si$: C, 55.64; H, 4.07. Found: C, 55.33; H, 4.29.

5.2.2. 1,3,5-(4-Iodophenyl)-7-[4-(1-trimethylsilylethynyl-4-ethynyl-[2.2.2]bicyclooctyl)phenyl]-adamantane (6b). A 1:1 mixture (GC/MS) of 1,4-bis(trimethylsilylethynyl)-bicyclo[2.2.2]octane and 1-ethynyl-4-trimethylsilylethynyl-bicyclo[2.2.2]octane (**5b**) (342 mg, ~0.58 mmol of **5b**) was added to a solution of **4** (535 mg, 0.57 mmol) in *i*-Pr_2NH (0.12 mL) and THF (80 mL) at rt, followed by $Pd(dba)_2$ (18 mg, 0.028 mmol), PPh_3 (28 mg, 0.108 mmol), CuI (10 mg, 0.054 mmol). The mixture was stirred at rt for 24 h and filtered. GC/MS shows the formation of dimer from **5b**. TLC ($CHCl_3$/hexane, 1/9) showed three spots: two were assigned to **4** (R_f=0.35) and **6b** (R_f=0.18). The mixture was separated by column chromatography ($CHCl_3$/hexane, 1/9) to afford **6b** (170 mg, 28%). ^{1}H NMR δ_H: 7.68 (d, 6H, *J*=8.5 Hz, PhI), 7.33 (s, 4H), 7.2 (d, 6H, *J*=8.5 Hz, PhI), 2.06 (s, 12H, C*H*$_2$ (Ad)), 1.83 (d, 12H, *J*=7.5 Hz, C*H*$_2$ (Bco)), 0.13 (s, 9H, $SiMe_3$). ^{13}C NMR δ_C: 148.7, 148.2, 137.7, 131.8, 127.4, 124.9, 122.1, 114.1 (C≡C), 96.7 (C≡C), 91.9 (I-*C*), 83.9 (C≡C), 80.5 (C≡C), 46.9 (*C*H_2(Ad)), 39.3 (*C*(Ad)), 32.0 (*C*H_2(Bco)), 27.1 and 26.9 (*C*(Bco)), 0.5 ($SiMe_3$). IR (cm^{-1}): 3032 (*ν*C–H(Ar)), 2942 and 2863 (*ν*C–H(aliph.)), 2155 (*ν*C≡C), 1509, 1485, 1454, 1393, 1356, 1247, 1002, 790.

5.2.3. 1,3,5-(4-Carboxyphenyl)-7-[4-(1-trimethylsilylethynyl-4-ethynyl-phenyl)phenyl]-adamantane (7a). To a solution of **6a** (580 mg, 0.57 mmol) in THF (20 mL) cooled to −78 °C was added dropwise over 20 min *t*-BuLi (5.5 mmol, 4.5 mL of a 1.5 M pentane solution). The mixture was stirred for an additional 15 min and CO_2 was bubbled into the reaction mixture. An abundant yellow precipitate formed. The cooling bath was removed, the mixture was allowed to warm to rt, and water (50 mL) and hexane (50 mL) were added. The clear aqueous layer was separated, cooled with a water/ice bath and acidified with ~10% HCl aq. A pale yellow precipitate formed. Standard workup with $CHCl_3$ afforded 0.42 g of a pale yellow powder. The crude material was used in the next step.

5.2.4. 1,3,5-(4-Carboxyphenyl)-7-[4-(1-trimethylsilylethynyl-4-ethynyl-[2.2.2]bicyclooctyl)phenyl]-adamantane (7b). This was prepared using the same procedure using **6b** (416 mg, 0.4 mmol) in THF (20 mL), *t*-BuLi (3.8 mmol, 2.5 mL of a 1.5 M pentane solution). The pale yellow precipitate was collected by filtration to afford 260 mg of crude material that was used in the next step.

5.2.5. 1,3,5-(4-Carbomethoxyphenyl)-7-[4-(1-trimethylsilylethynyl-4-ethynyl-phenyl)phenyl]-adamantane (8a). A solution of the mixture of acids (200 mg) in ethyl ether (10 mL) was treated with CH_2N_2 (see General). The solvent was removed in vacuo and the crude material was purified by column chromatography (AcOEt/hexane, 1/4) to afford 110 mg of **8a** (R_f=0.4) (yield from **6a** ~45%). Mp 196–198 °C. ^{1}H NMR δ_H: 8.04 (d, 6H, *J*=8.5 Hz, *Ph*COOMe), 7.56 (d, 6H, *J*=8.5 Hz, *Ph*COOMe), 7.53 (d, 2H, *J*=8.5 Hz), 7.47 (d, 2H, *J*=8.5 Hz), 7.45 and 7.44 (two s, 4H), 3.91 (s, 9H, COO*Me*), 2.20 (s, 12H, C*H*$_2$), 0.25 (s, 9H, $SiMe_3$). ^{13}C NMR δ_C: 166.9 (*C*OOMe), 153.8, 149.0, 131.9, 131.8, 131.4, 129.8, 128.3, 125.1 (two carbons), 123.3, 122.8, 121.1, 104.6 (C≡C), 96.3 (C≡C), 91.1 (C≡C), 89.0 (C≡C), 52.1 (COO*Me*), 46.6 (*C*H_2(Ad)), 39.6 and 39.3 (*C*(Ad)), −0.1 ($SiMe_3$). IR (cm^{-1}): 3037 (*ν*C–H(Ar)), 2951 and 2898 (*ν*C–H(aliph.)), 2156 (*ν*C≡C), 1931.5, 1724.3 (*ν*C=O), 1608 (*ν*C– C(Ar)), 1512, 1436, 1406, 1358, 1281 (*ν*C–O), 1192, 1110 (*ν*C–O), 1018, 866, 844 (*δ*Ar), 762. Anal. calcd for $C_{53}H_{50}O_6Si$: C, 78.49; H, 6.21. Found: C, 78.32, H, 6.11.

5.2.6. 1,3,5-(4-Carbomethoxyphenyl)-7-[4-(1-trimethylsilylethynyl-4-ethynyl-[2.2.2]bicyclooctyl)phenyl]-adamantane (8b). A solution of the mixture of acids (0.26 g) in ethyl ether (10 mL) was treated with CH_2N_2 (see General). TLC (AcOEt/hexane, 20/80) showed three spots, with **8b**

R_f=0.31. The mixture was purified by silica gel column chromatography (AcOEt/hexane, 1/4) to afford **8b** as a white powder (100 mg, yield from **6b** ~30%). ^{1}H NMR δ_H: 8.05 (d, 6H, J=8.5 Hz, *Ph*COOMe), 7.56 (d, 6H, J=8.5 Hz, *Ph*COOMe), 7.37 (s, 4H), 3.92 (s, 9H, COO*Me*), 2.19 (two s, 12H, CH_2(Ad)), 1.84 (two s, 12H, CH_2(Bco)), 0.14 (s, 9H, $SiMe_3$). ^{13}C NMR δ_C: 167.0 (*C*OOMe), 154.1, 148.1, 131.8, 130.0, 128.4, 125.3, 124.9, 122.2, 114.0 (C≡C), 96.6 (C≡C), 83.9 (C≡C), 80.4 (C≡C), 52.3 (COO*Me*), 46.9 and 46.8 (*C*H_2(Ad)), 39.8 and 39.3 (*C*(Ad)), 31.9 (*C*H_2(Bco)), 27.0 and 26.9 (*C*(Bco)), 0.5 ($SiMe_3$). IR (cm^{-1}): 2945 and 2864 (νC–H(aliph.)), 2162 (νC≡C), 1724 (ν C=O), 1932, 1611 (νC–C(Ar)), 1572, 1509, 1436, 1408, 1357, 1282 (νC–O), 1192, 1110 (νC–O), 1017, 961, 847 (δAr). HMRS (FAB) for $C_{55}H_{59}O_6Si$, MH^+= 843.4076.

5.2.7. 1,3,5-(4-Carbomethoxyphenyl)-7-[4-(1,4-bis-(ethynyl)phenyl)phenyl]-adamantane (9a). nBu$_4$NF·3H$_2$O (540 mg, 1.72 mmol) was added to a solution of **8a** (700 mg, 0.86 mmol) in CH_3CN (20 mL) and benzene (20 mL) at rt with stirring. After 1.5 h, water (20 mL) was added. Standard workup with CH_2Cl_2 and purification by column chromatography (AcOEt/hexane, 1/4) afforded **9a** as a white powder (R_f=0.3) (450 mg, Avg. yield for this step ~75%). Mp 214–216 °C. ^{1}H NMR δ_H: 8.04 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.56 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.54 (2H, d, J=8.5 Hz), 7.47 (m, 6H), 3.92 (s, 9H, COO*Me*), 3.17 (s, 1H, C≡C*H*), 2.21 and 2.20 (two s, 12H, CH_2(Ad)). ^{13}C NMR δ_C: 166.9 (*C*OOMe), 153.8, 149.1, 132.1, 131.8, 131.4, 129.8, 128.3, 125.1 (two carbons), 123.7, 121.8, 121.0, 91.2 (C≡C), 88.8 (C≡C), 83.3 (C≡C), 78.9 (C≡C), 52.1 (COO*Me*), 46.6 (*C*H_2(Ad)), 39.6 and 39.3 (*C*(Ad)). IR (cm^{-1}): 3302 (ν ≡C–H), 3037 (νC–H(Ar)), 2950 and 2919 (νC–H(aliph.)), 2849, 2565 (νC≡C), 2216.4 (νC≡C), 1931, 1724 (νC=O), 1611 (νC–C(Ar)), 1514, 1435, 1405, 1282 (νC–O), 1191, 1111 (νC–O), 1018, 837 (δAr), 765.0. Anal. calcd for $C_{50}H_{42}O_6$: C, 81.28; H, 5.73. Found: C, 80.99, H, 5.57.

5.2.8. 1,3,5-(4-Carbomethoxyphenyl)-7-[4-(1,4-bis-(ethynyl)[2.2.2]bicyclooctyl)phenyl]-adamantane (9b). This was prepared following the same procedure using **8b** (81 mg, 0.09 mmol) in CH_3CN (10 mL) and nBu$_4$NF·3H$_2$O (45 mg, 0.3 mmol). Column chromatography (AcOEt/hexane, 1/4) afforded **9b** as a white powder (R_f= 0.25) (53 mg, Avg. yield for this step ~75%). ^{1}H NMR δ_H: 8.04 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.56 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.37 (d, 4H, J=2.5 Hz), 3.92 (s, 9H, COO*Me*), 2.19 (two s, 12H, CH_2(Ad)), 2.10 (s, 1H, C≡C*H*), 1.85 (two s, 12H, CH_2(Bco)). ^{13}C NMR δ_C: 167.2 (*C*OOMe), 154.1, 148.2, 131.9, 130.0, 128.5, 125.3, 125.0, 122.2, 96.5 (C≡C), 91.4 (C≡C), 80.6 (C≡C), 68.3 (C≡C), 52.3 (COO*Me*), 46.9 and 46.8 (*C*H_2(Ad)), 39.8 and 39.3 (*C*(Ad)), 31.9 (*C*H_2(Bco)), 26.9 and 26.3 (*C*(Bco)). IR (cm^{-1}): 3302 (ν≡C–H), 3056 (νC–H(Ar)), 2943 and 2865 (νC–H(aliph.)), 2224 (νC≡C), 2107 (νC≡C), 1932, 1724 (νC=O), 1610 (νC–C(Ar)), 1571, 1508, 1438, 1406, 1356, 1282 (νC–O), 1193, 1110 (νC–O), 1018, 967, 898, 853 (δAr), 834 (δAr). HMRS (FAB) for $C_{52}H_{51}O_6$, MH^+=771.3690.

5.2.9. Ad-Tripod-(Ph-E)2-Phen (10). To a solution of **9a** (235 mg, 0.32 mmol) in THF (8 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (0.48 mmol, 0.48 mL of a 1 M hexane solution). After 30 min, B-methoxy-9-BBN (0.48 mmol, 0.48 mL of 1 M hexane) was added. After stirring 2 h at −78 °C, the solution was transferred via cannula to a second flask containing $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) and 5-bromo-1,10-phenanthroline[28] (90 mg, 0.35 mmol) in THF (5 mL). The reaction mixture was refluxed for 24 h, cooled to rt, and standard workup with CH_2Cl_2 afforded a crude material that was purified by column chromatography with the following sequence of eluents: (AcOEt/hexane, 1/4), CH_2Cl_2, (CH_2Cl_2/MeOH, 95/5) to afford **10** as a white powder (140 mg, 47%). Mp 187–189 °C. ^{1}H NMR δ_H: 9.28 (dd, 1H, J=3.0, 1.5 Hz, phen), 9.23 (dd, 1H, J=3.0, 1.5 Hz, phen), 8.86 (dd, 1H, J=8.5, 1.5 Hz, phen), 8.28 (dd, 1H, J=7.5, 1.5 Hz, phen), 8.13 (s, 1H, phen), 8.05 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.78 (q, 1H, J=4.5 Hz, phen), 7.68 (q, 1H, J=4.5 Hz, phen), 7.66 (d, 2H, J=8.5 Hz), 7.56 (m, 10H), 7.50 (d, 2H, J=8.5 Hz), 3.92 (s, 9H, COO*Me*), 2.21 (s, 12H, CH_2(Ad)). ^{13}C NMR δ_C: 166.88 (*C*OOMe), 153.8, 150.9, 150.6, 149.2, 145.7, 145.5, 136.1, 134.9, 131.8, 131.7 (two carbons), 130.8, 129.8, 128.3 (two carbons), 128.1, 125.1 (two carbons), 123.9, 123.6, 123.5, 122.2, 121.0, 119.8, 95.2 (C≡C), 91.6 (C≡C), 88.9 (C≡C), 87.5 (C≡C), 52.1 (COO*Me*), 46.7 (*C*H_2(Ad)), 39.6 and 39.3 (*C*(Ad)). IR (cm^{-1}): 3035 (νC–H(Ar)), 2946 and 2899 (νC–H(aliph.)), 2842, 2208 (νC≡C), 1930, 1721 (νC=O), 1611 (νC–C(Ar)), 1566, 1511, 1436, 1407, 1282 (νC–O), 1191, 1108 (νC–O), 1019, 835 (δAr), 766. Anal. calcd for $C_{62}H_{48}N_2O_6$: C, 81.20; H, 5.28; N, 3.05. Found: C, 80.62, H, 5.14, N, 2.71.

5.2.10. Ad-Tripod-(Ph-E)$_2$-Bpy (11). Tripodal ligand **11** was prepared using the same procedure using **9a** (150 mg, 0.20 mmol) in THF (5 mL), lithium bis(trimethylsilyl)-amide (0.23 mmol, 0.23 mL of a 1 M hexane solution), B-methoxy-9-BBN (0.23 mmol, 0.23 mL of a 1 M hexane solution), $Pd(PPh_3)_4$ (20 mg, 0.02 mmol), 4-bromo-2,2-bipyridine[27] (89 mg, 0.38 mmol) in THF (5 mL). The crude material was purified by silica gel column chromatography with the following sequence of eluents: (AcOEt/hexane, 1/4), CH_2Cl_2, (CH_2Cl_2/MeOH 95/5) to afford **11** as a white powder (108 mg, 60%). Mp 175–177 °C. ^{1}H NMR δ_H: 8.72 (d, 1H, J=4.5 Hz, bpy), 8.68 (d, 1H, J=5.5 Hz, bpy), 8.55 (s, 1H, bpy), 8.43 (d, 1H, J=8.0 Hz, bpy), 8.05 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.84 (td, 1H, J=8.0, 2.0 Hz, bpy), 7.57 (m, 12H), 7.49 (d, 2H, J=8.5 Hz), 7.41 (d, 1H, J=5.0 Hz, bpy), 7.35 (t, 1H, J=5.5 Hz, bpy), 3.92 (9H, s, COO*Me*), 2.21 (s, 12H, CH_2(Ad)). ^{13}C NMR δ_C: 166.9 (*C*OOMe), 156.1, 155.4, 153.8, 149.2, 149.2, 149.1, 137.1, 132.3, 131.9, 131.6, 129.8, 128.3, 125.2, 125.1, 125.0, 124.2, 124.1, 123.2, 121.9, 121.2, 121.0, 93.6 (C≡C), 91.6 (C≡C), 88.9 (C≡C), 88.8 (C≡C), 52.1 (COO*Me*), 46.7 (*C*H_2(Ad)), 39.6 and 39.3 (*C*(Ad)). IR (cm^{-1}): 3058 (νC–H(Ar)), 2948, 2897 and 2843 (νC–H(aliph.)), 2207 (νC≡C), 1926, 1722 (νC=O), 1610.0 (νC–C(Ar)), 1582, 1536, 1514, 1459, 1436, 1407, 1282 (νC–O), 1190, 1110 (νC–O), 1018, 836 (δAr), 761.6. Anal. calcd for $C_{60}H_{48}N_2O_6$: C, 80.70; H, 5.42; N, 3.14. Found: C, 79.98, H, 5.43, N, 2.4.

5.2.11. Ad-Tripod-Ph-E-Bco-E-Bpy (12). Terminal alkyne **9b** (260 mg, 0.34 mmol) was added to a solution of 4-iodo-2,2′-bipyridine[29] (115 mg, 0.4 mmol) in i-Pr$_2$NH (0.15 mL)

and THF (40 mL) at rt, followed by $Pd(dba)_2$ (15 mg, 0.02 mmol), PPh_3 (21 mg, 0.08 mmol), CuI (9.5 mg, 0.04 mmol). The mixture was refluxed for 2 days, then cooled to rt and filtered. TLC ($CHCl_3$/MeOH, 98/2) showed three spots: **9b** (R_f=0.45), 4-iodo-2,2′-bipyridine (R_f=0.25) and **12** (R_f=0.15). The crude material was separated by column chromatography with the following sequence of eluents: (AcOEt/hexane, 1/4), $CHCl_3$, ($CHCl_3$/MeOH 98/2) to afford **12** (170 mg, 28%). ^{1}H NMR δ_H: 8.69 (d, 1H, J=4.5 Hz, bpy), 8.58 (d, 1H, J=5.0 Hz, bpy), 8.39 and 8.37 (s, 2H, bpy), 8.04 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.82 (td, 1H, J=8.0, 2.0 Hz, bpy), 7.56 (d, 6H, J=8.5 Hz, *Ph*COOMe), 7.38 (s, 4H), 7.32 (t, 1H, J=5.5 Hz, bpy), 7.25 (dd, 1H, J=5.0, 1.5 Hz, bpy), 3.92 (s, 9H, COO*Me*), 2.19 (two s, 12H, C*H*$_2$(Ad)), 1.91 (s, 12H, CH_2). ^{13}C NMR δ_C: 167.1 (*C*OOMe), 156.2, 155.9, 154.1, 149.4, 149.2, 148.2, 137.2, 133.3, 131.9, 130.0, 128.5, 125.7, 125.3, 125.0, 124.1, 123.6, 122.2, 121.3, 101.8 (C≡C), 96.4 (C≡C), 80.6 (C≡C), 79.1 (C≡C), 52.3 (COO*Me*), 46.9 and 46.8 (*C*H$_2$(Ad)), 39.8 and 39.3 (*C*(Ad)), 31.9 and 31.8 (*C*H$_2$(Bco)), 27.2 and 27.0 (*C* (Bco)). IR (cm^{-1}): 3060 (νC–H(Ar)), 2946 and 2866 (νC–H(aliph.)), 2226 (νC≡C), 1931, 1724 (νC=O), 1611 (νC–C(Ar)), 1586, 1534, 1509, 1458, 1435, 1409, 1280 (νC–O), 1191, 1112 (νC–O), 1015, 841 (δAr).

5.2.12. Ru(bpy)$_2$(Ad-Tripod-(Ph-E)$_2$-Phen)$^{2+}$ 2PF$_6^-$ (1). A solution of **10** (97 mg, 0.105 mmol) in THF (2 mL) was added to a 1:1 mixture of ethanol/water (10 mL). To the solution, de-oxygenated by bubbling N_2 for ~30 min, was added $Ru(bpy)_2Cl_2\cdot 2H_2O$ (54 mg, 0.105 mmol). The mixture was refluxed for 6 h under nitrogen, cooled to rt and filtered. Addition of $NaPF_6$ to the filtrate formed a red precipitate, which was collected and washed with water several times to afford **1** (130 mg, 80%). ^{1}H NMR δ_H: (CD_3COCD_3): 9.19 (d, 1H, J=8.5 Hz, phen), 8.88 (d, 2H, J=5.0 Hz), 8.84 (t, 3H, J=6.0 Hz), 8.70 (s, 1H, phen), 8.53 (d, 1H, J=4.5 Hz), 8.49 (d, 1H, J=4.5 Hz), 8.27 (m, 2H), 8.18 (m, 4H), 8.03 (d, 6H, J=8.5 Hz, *Ph*COOMe), 7.96 (m, 4H), 7.80 (m, 8H), 7.76 (d, 2H, J=8.5 Hz), 7.66 (m, 4H), 7.61 (d, 2H, J=8.5 Hz), 7.40 (m, 2H), 3.88 (9H, s, COO*Me*), 2.33 and 2.32 (12H, two s, C*H*$_2$(Ad)). ^{13}C NMR δ_C: (CD_3COCD_3): 167.2 (*C*OOMe), 158.4, 158.2, 155.8, 154.2, 153.1, 151.6, 148.8, 148.5, 139.1, 139.0, 137.8, 136.4, 133.1, 132.7, 132.6, 131.6, 130.3, 129.0, 128.8, 128.7, 127.9, 127.8, 126.7, 126.6 (two carbons), 125.4, 125.3, 122.5, 121.3, 98.00 (C≡C), 93.0 (C≡C), 89.2 (C≡C), 86.8 (C≡C), 52.3 (COO*Me*), 47.0 (*C*H$_2$(Ad)), 40.7 and 40.4 (*C*(Ad)). IR (cm^{-1}): 3083 (νC–H(Ar)), 2951 and 2918 (νC–H(aliph.)), 2208 (νC≡C), 1930, 1719 (νC=O), 1609 (νC–C(Ar)), 1515, 1466, 1446, 1434, 1282 (νC–O), 1195, 1111 (νC–O), 1018, 842 (δ(Ar)), 765. Anal. calcd for $C_{82}H_{64}F_{12}N_6O_6P_2Ru$: C, 60.78; H, 3.98; N, 5.19. Found: C, 60.50, H, 3.97, N, 5.03. HRMS (FAB) calcd for $C_{82}H_{64}N_6O_6Ru$ 1330.3931, found 1330.3940.

5.2.13. Ru(bpy)$_2$(Ad-Tripod-(Ph-E)$_2$-Bpy)$^{2+}$ 2PF$_6^-$ (2). Complex **2** was prepared using the same procedure from **11** (70 mg, 0.075 mmol) in THF (2 mL), ethanol/water (10 mL), $Ru(bpy)_2Cl_2\cdot 2H_2O$ (40 mg, 0.075 mmol), $NaPF_6$ to afford 67 mg of **2** (56% yield). ^{1}H NMR δ_H: (CD_3COCD_3): 8.95 (d, 2H, J=9.0 Hz, bpy), 8.84 (d, 4H, J=8.0 Hz, bpy), 8.25–8.18 (m, 6H), 8.12–8.06 (m, 5H), 8.02 (6H, d, J=8.5 Hz, *Ph*COOMe), 7.81 (6H, d, J=8.5 Hz, *Ph*COOMe), 7.74 (2H, d, J=8.5 Hz), 7.65–7.58 (12H, m), 3.87 (9H, s, COO*Me*), 2.31 and 2.30 (two s, 12H, C*H*$_2$(Ad)). ^{13}C NMR δ_C: (CD_3COCD_3): 167.2 (*C*OOMe), 158.6, 158.1, 158.0, 157.9, 157.7, 155.6, 152.9, 152.8, 152.7, 152.6, 151.6, 139.2, 139.1, 139.0, 133.1, 133.0, 132.7, 132.5, 130.3, 129.7, 129.5, 129.4, 129.1, 129.0, 128.8, 126.9, 126.6, 126.5, 125.9, 125.7, 125.4, 121.8, 121.2, 97.9 (C≡C), 93.2 (C≡C), 89.1 (C≡C), 88.2 (C≡C), 52.2 (COO*Me*), 47.0 and 46.9 (*C*H$_2$(Ad)) 40.6 and 40.4 (*C*(Ad)). IR (cm^{-1}): 3081 (νC–H(Ar)), 2920 and 2849 (νC–H(aliph.)), 2208 (νC≡C), 1718 (νC=O), 1610 (νC–C(Ar)), 1570, 1513, 1469, 1439, 1282 (νC–O), 1192, 1113 (νC–O), 841 (δAr), 763. Calcd for $C_{80}H_{64}F_{12}N_6O_6P_2Ru$: C, 60.19; H, 4.04; N, 5.26. Found: C, 60.13, H, 3.97, N, 5.04. HRMS (FAB) calcd for $C_{80}H_{64}N_6O_6Ru$ 1306.3931, found 1306.3910.

5.2.14. Ru(bpy)$_2$(Ad-Tripod-Ph-E-Bco-E-Bpy)$^{2+}$ 2PF$_6^-$ (3). Complex **3** was prepared using the same procedure, but under argon, from **12** (44 mg, 0.047 mmol) in THF (~1 mL), ethanol/water (10 mL), $Ru(bpy)_2Cl_2\cdot 2H_2O$ (25 mg, 0.048 mmol) and $NaPF_6$ to afford 53 mg of **3** (70% yield). The precipitate was very fine and tended to form a suspension. ^{1}H NMR δ_H: (CD_3COCD_3): 8.90 (d, 1H, J=8.5 Hz, bpy), 8.83 (m, 4H, bpy), 8.74 (d, 1H, J=1.0 Hz, bpy), 8.24 (m, 5H, bpy), 8.17 (d, 1H, J=5.5 Hz, bpy), 8.07 (m, 10H), 7.79 (d, 6H, J=8.5 Hz, *Ph*COOMe), 7.61 (m, 7H), 7.44 (dd, 1H, J=6.0, 1.5 Hz, bpy), 7.36 (d, 2H, J=8.5 Hz), 3.87 (s, 9H, COO*Me*), 2.30 (two s, 12H, C*H*$_2$(Ad)), 1.93 (s, 12H, C*H*$_2$(Bco)). ^{13}C NMR (CD_3COCD_3) δ_C: 184.3, 167.2 (*C*OOMe), 158.4, 158.2, 158.1, 158.0, 157.8, 155.8, 152.9, 153.0, 152.8, 152.7, 139.1, 139.0, 134.2, 132.3, 130.4, 130.1, 129.1, 129.0, 128.8, 127.1, 126.5, 126.3, 125.7, 125.4, 122.5, 107.1 (C≡C), 96.4 (C≡C), 81.6 (C≡C), 78.7 (C≡C), 52.3 (COO*Me*), 47.2 and 47.0 (*C*H$_2$(Ad)), 40.7 and 40.3 (*C*(Ad)), 32.3 and 32.1 (*C*H$_2$(Bco)), 28.2 and 27.6 (*C*(Bco)). IR (cm^{-1}): 3083 (νC–H(Ar)), 2926, 2852 (νC–H(aliph.)), 2225 (νC≡C), 1924, 1718 (νC=O), 1610 (νC–C(Ar)), 1568, 1508, 1464, 1442, 1410, 1362, 1281 (νC–O), 1194, 1112 (νC–O), 1017, 842 (δAr). HRMS (FAB) calcd for $C_{82}H_{72}O_6N_6F_6PRu$ 1483.4199, found 1483.4216.

5.2.15. Synthesis of 8b via Route B (Scheme 4). To a solution of **4**[21] (470 mg, 0.5 mmol) in THF (20 mL) cooled to −78 °C, *n*-BuLi (2 mmol, 1.3 mL of a 1.5 M pentane solution) was added dropwise over 20 min with stirring. The mixture was stirred for additional 20 min and CO_2 was bubbled into the reaction mixture from a flask containing solid CO_2. An abundant yellow precipitate formed. The cooling bath was removed, the mixture was allowed to warm to rt, and water (50 mL) and hexane (50 mL) were added. The aqueous layer was separated, cooled with water/ice bath and acidified by addition of diluted HCl. A pale yellow precipitate formed. This was collected by filtration to afford 360 mg of crude material. This was dissolved in ethyl ether (10 mL), treated with CH_2N_2 (see General) and stirred for 2 h. TLC (AcOEt/hexane, 1/4) showed four spots: R_f=0.77, 0.63, 0.47 and 0.32 corresponding to mono-, di-, tri- and tetra-ester, respectively. The mixture of methyl esters was purified by column chromatography (AcOEt/hexane, 1/4) to afford 70 mg of **13** and **14** in ratio 1.5:1 (^{1}H NMR)

(yield of **13** ~15–20%). The mixture could not be separated by column chromatography or other methods, because both compounds had an identical R_f factor in a variety of eluents, and have identical solubility properties in a variety of solvents. ^{1}H NMR of **13** and **14** δ_H: ($CDCl_3$): 8.04 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.70 (d, J=9.0 Hz, PhI), 7.57 (s), 7.56 (d, 6H, J=9.0 Hz, *Ph*COOMe), 7.51 (d, J=7.0 Hz), 7.41 (t, J=7.5 Hz), 7.25 (d, J=8.0 Hz, PhI), 3.92 (s, 9H, COO*Me*), 2.19 (two s, 12H, CH_2(Ad)). ^{13}C NMR δ_C: ($CDCl_3$): 167.1 (*C*OOMe), 154.2, 153.9, 148.8, 148.5, 137.8, 130.0, 128.8, 128.5, 128.4, 127.4, 125.3, 125.1, 92.0, 52.3 (COO*Me*), 47.0; 46.9; 46.8 and 46.7 (CH_2(Ad)), 39.8; 39.7 and 39.3 (*C*(Ad)).

A 1:1 mixture (GC/MS) of **5b** (295 mg, ~0.56 mmol of **5b**) was added to a solution of mixture **13** and **14** (410 mg, ~0.56 mmol of **13**) in *i*-Pr_2NH (0.15 mL) and THF (30 mL) at rt, followed by $Pd(dba)_2$ (18.5 mg, 0.028 mmol), PPh_3 (29 mg, 0.11 mmol), and CuI (10 mg, 0.054 mmol). The mixture was stirred at rt for 24 h and filtered. GC/MS of the filtrate shows the formation of dimer from **5b**. TLC ($CHCl_3$/hexane, 1/9) showed two spots: **8b**, R_f=0.48 and **14**, R_f=0.45. The mixture was separated by column chromatography ($CHCl_3$/hexane, 1/9) to afford **8b** (110 mg, 40%). The spectral data were identical to those obtained for **8b** prepared though route A.

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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.2004.06.124

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Aurilide, a cytotoxic depsipeptide from the sea hare *Dolabella auricularia*: isolation, structure determination, synthesis, and biological activity

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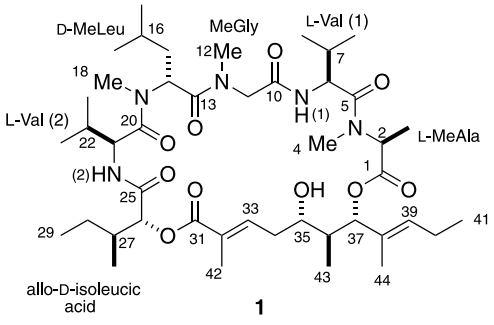
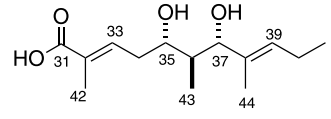
Abstract—The bioassay-guided fractionation of the cytotoxic constituents of the Japanese sea hare *Dollabella auricularia* led to the isolation of aurilide (**1**), a 26-membered cyclodepsipeptide. The gross structure of **1** was established by spectroscopic analysis including 2D NMR techniques. The absolute stereostructure was determined by chiral HPLC analysis of acid hydrolysates of **1** and by the enantioselective synthesis of a degradation product arising from a dihydroxylated fatty acid portion. The enantioselective synthesis of **1** was achieved in 12% overall yield (16 steps) and confirmed the absolute stereostructure of **1**. The cytotoxicity of **1** was evaluated using a synthetic sample, which was found to exhibit potent cytotoxicity against HeLa S_3 cells with an IC_{50} of 0.011 μg/mL. Further biological and pharmacological studies of **1** have been carried out by using synthetic **1**.

1. Introduction

In the 1960s, Pettit and co-workers began intensively investigating the cytostatic and antineoplastic constituents of the Indian Ocean sea hare *Dolabella auricularia*, resulting in the isolation of a number of novel peptide- and depsipeptide-type bioactive compounds termed dolastatins.[1] We have carried out the cytotoxicity-directed examination of the constituents of Japanese specimens of *D. auricularia* and isolated a variety of cytotoxic compounds.[2,3] As part of our study in search for cytotoxic compounds from this animal, the isolation, the structure, and the synthesis of aurilide (**1**), a cytotoxic depsipeptide, have been described in preliminary communications.[4,5] In this article, we report the isolation, the structure determination, and much improved synthesis of aurilide (**1**) together with a discussion of its biological activities, which were evaluated by using synthetic **1**.



1



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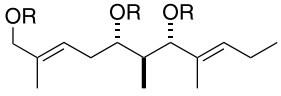

3 R = *p*-BrC_6H_4CO

Keywords: Aurilide; *Dolabella auricularia*; Depsipeptide; Cytotoxicity; Structure determination; Synthesis.
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2. Results and discussions

2.1. Isolation

The internal organs of the sea hare *D. auricularia*, collected from one site located on the coast of Azuri, Shima peninsula in Mie Prefecture, were extracted with MeOH, and the extracts were partitioned between H_2O and EtOAc. The EtOAc-soluble material was further partitioned between 9:1 MeOH/H_2O and hexane. The material obtained from the aqueous MeOH portion was subjected to cytotoxicity-guided fractionation by repetitive normal- and reversed-phase chromatography and by reversed-phase HPLC to afford aurilide (**1**) as a colorless powder in 1.9×10^{-7}% yield based on wet weight.

2.2. Gross structure

The NMR data (Table 1) coupled with a $[M+Na]^+$ peak at *m/z* 856.5432 ($\Delta+2.0$ mmu) in the HRFABMS of aurilide (**1**) suggested a molecular formula of $C_{44}H_{75}N_5O_{10}$. In the IR spectrum, there were observed bands at 3430, 1735, 1685, 1645, and 1245 cm^{-1} that were assigned to hydroxy, ester, and amide groups. The ^1H NMR data showed the presence of two amide NH groups (δ 7.77 and 6.55) and three *N*-methylamide groups (δ 3.25, 2.91, and 2.57), suggesting the peptidic nature of **1**. Resonances in the ^1H NMR spectrum were assigned by DQF-COSY, HSQC, and HMBC analyses, as shown in Table 1. Although the ^{13}C NMR spectrum could not be obtained due to the scarcity of the sample, carbon chemical shifts were mostly determined by HSQC and HMBC ($J_{CH}=6$ Hz) experiments. These spectroscopic data suggested the presence of five amino acid residues (two valines, *N*-methylglycine, *N*-methylalanine, and *N*-methylleucine), an isoleucic acid residue, and a dihydroxy acid portion (C31–C44). The low-field chemical shift of H-37 (δ 5.18) suggested that the acyloxy group is attached to C37. The stereochemistry of the two trisubstituted olefins of **1** was determined to be *E* on the basis of the ^{13}C chemical shifts of the respective vinyl methyls with *cis* steric interaction (δ_{C42} 12.4 and δ_{C44} 11.1).[6] The degree of unsaturation in **1** suggests the cyclic nature of this molecule. The HMBC correlations shown in Table 1 disclosed two sequences, Val(2)-MeLeu-MeGly and Val(1)-MeAla-**2**. The NOESY correlation of NH(2)/H-26 established the connectivity between isoleucic acid and Val(2). Further evidence for the connectivities of the partial structures could not be obtained from either HMBC experiments or the NOESY data. However, considering the peptidic nature of **1**, the carboxyl carbon (C31) of **2** must be bonded to the hydroxy oxygen atom of isoleucic acid and the carboxyl carbon (C10) of the MeGly should be connected to the amino nitrogen of Val(1). Thus, the gross structure of aurilide is unequivocally shown as **1**.

2.3. Stereochemistry

The absolute stereostructure of **1** was elucidated as follows. Acidic hydrolysis of **1** (9 M HCl, 110 °C, 72 h) followed by reversed-phase HPLC separation afforded four components, MeAla, Val, MeLeu, and isoleucic acid. The absolute configurations of the three components, Val, MeLeu, and isoleucic acid, were determined to be L, D, and allo-D, respectively, by the chiral HPLC analysis. The absolute configuration of MeAla was established to be L by HPLC analysis of the Marfey's derivative.[7] The absolute stereochemistry of three contiguous asymmetric carbons (C35, C36, and C37) in **1** was determined by the enantioselective

Table 1. NMR data for aurilide (**1**) in C_6D_6

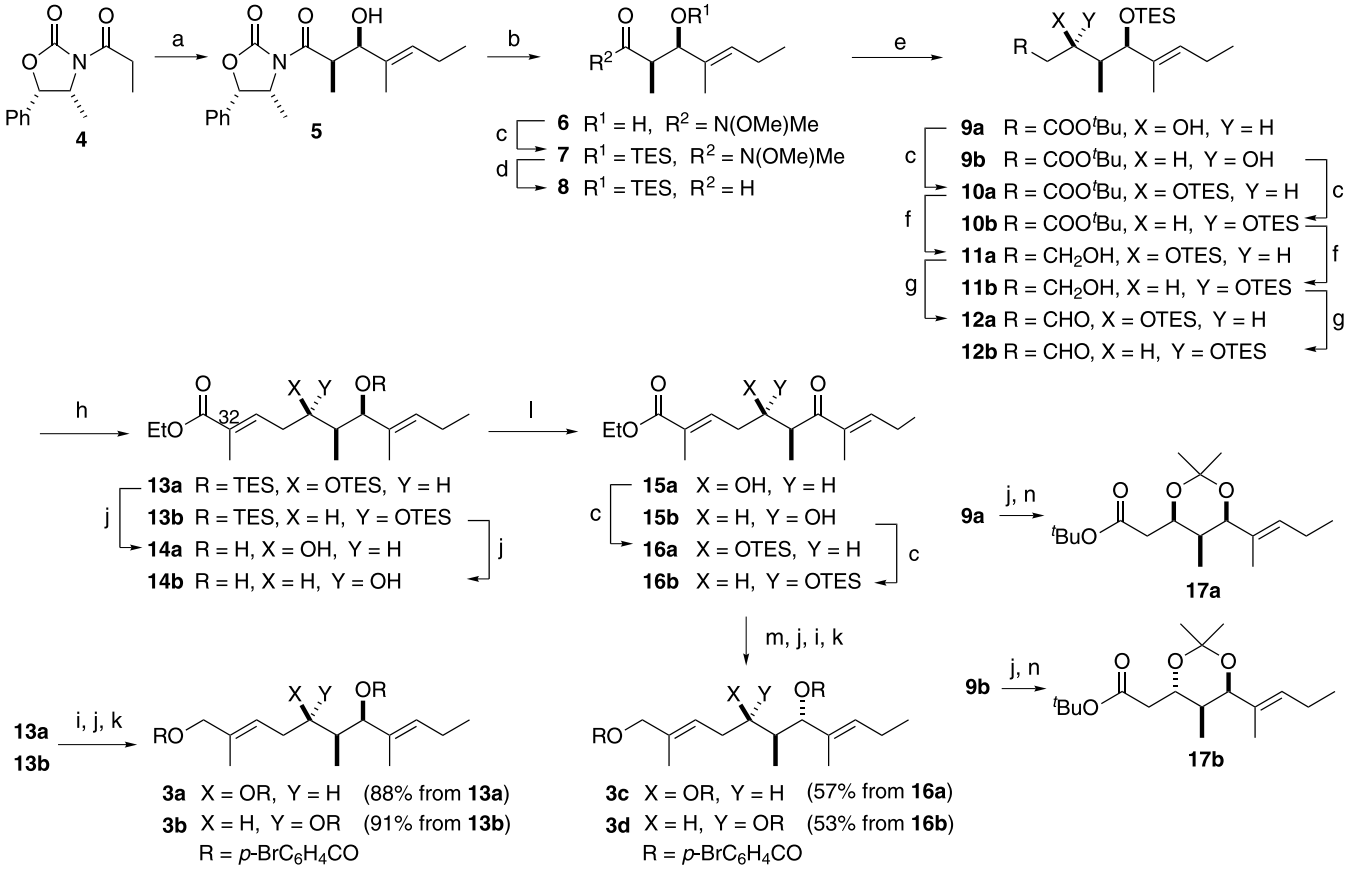
Position	^1H[a]	^{13}C[b]	HMBC[c]	Position	^1H[a]	^{13}C[b]	HMBC[c]
1		169.7	H-2, 3, 37	24	0.85 d (6.6)	18.5	H-23
2	3.10 q (7.0)	59.1	H-3, 4	25		170.0	H-26
3	1.24 d (7.0)	13.6	H-2	26	4.72 d (7.2)	78.5	H-30
4	2.57 s	36.5		27	2.08 m	36.9	H-26, 29, 30
5		172.0	H-2, 4, 6	28a	1.52 m	25.7	H-29, 30
6	5.17 dd (7.0, 7.0)	54.1	H-8, 9	28b	1.14 m		
7	2.08 m	32.7	H-6, 8, 9	29	0.83 t (7.7)	11.5	
8	1.16 d (7.0)	19.9	H-9	30	1.04 d (7.0)	14.8	H-26
9	1.33 d (7.0)	17.8	H-6, 8	31		169.52	H-42
10		169.47	H-11a, 11b	32		128[d]	H-42
11a	4.44 d (17.9)	51.4	H-12	33	7.77 m	145.4	H-34, 42
11b	3.84 d (17.9)			34	2.12 m	30.4	
12	3.25 s	36.4	H-11a, 11b	35	4.00 m	70.9	H-43
13		170.1	H-11b, 12, 14, 15b	36	2.00 m	40.7	H-37, 43
14	5.64 dd (7.0, 7.0)	52.4	H-15a, 15b, 19	37	5.18 d (11.4)	82.2	H-39, 43, 44
15a	2.23 ddd (14.6, 7.0, 7.0)	39.0	H-14, 17, 18	38		131.2	H-37, 40, 44
15b	1.52 ddd (14.6, 7.0, 7.0)			39	5.63 t (7.6)	134.0	H-37. 40, 41, 44
16	1.85 m	25.2	H-17, 18	40	1.95 dt (7.6, 7.6)	21.2	H-41
17	1.07 d (7.0)	23.3	H-15a, 15b, 18	41	0.89 t (7.6)	13.9	H-40
18	1.07 d (7.0)	22.9	H-15a, 15b, 17	42	1.90 s	12.4	
19	2.91 s	30.6	H-14	43	0.62 d (7.0)	9.7	
20		172.1	H-19, 21	44	1.55 s	11.1	H-37, 39
21	4.61 dd (8.8, 8.8)	54.6	H-23, 24	NH (1)	7.77 br d (7.0)		
22	1.98 m	31.1	H-21, 23, 24	NH (2)	6.55 br d (8.8)		
23	0.83 d (6.6)	19.3	H-24				

[a] Recorded at 600 MHz. Coupling constants (Hz) are in parentheses. The signal of one proton (OH) was not observed.
[b] Recorded at 150 MHz by using synthetic **1**.
[c] Recorded at 600 MHz. Parameters were optimized for $J_{CH}=6$ Hz.
[d] Overlapped with the solvent signal.

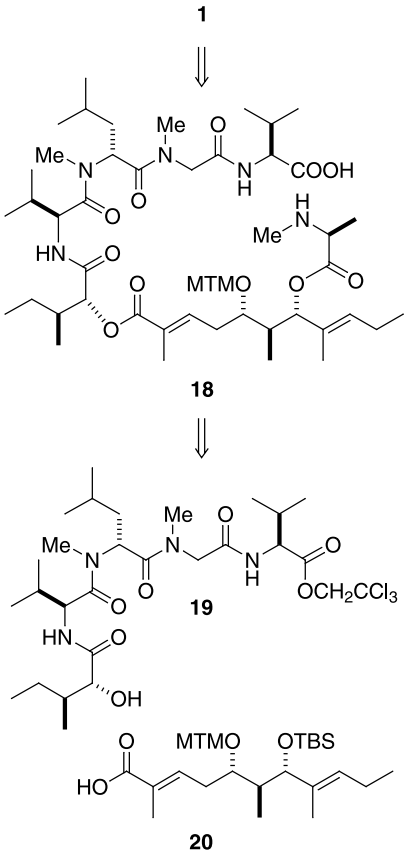
synthesis of tris(*p*-bromobenzoate) **3** that was obtained by the reduction of **1** ($LiAlH_4$, ether) followed by acylation (*p*-BrC_6H_4COCl, pyridine). Thus, the four possible diastereomeric tris(*p*-bromobenzoates) **3a**, **3b**, **3c**, and **3d** were synthesized as follows (Scheme 1). The Evans aldol reaction between imide **4**[8] and *trans*-2-methyl-2-pentenal afforded hydroxy imide **5** in 80% yield as a single diastereomer. Transamidation[9] of **5** (100%) followed by protection of the hydroxy group in **6** provided silyl ether **7** (100%). The amide group in **7** was reduced with DIBAL to give aldehyde **8** (91%). Treatment of **8** with $LiCH_2COO^tBu$ gave a mixture of diastereomeric alcohols **9a** (58%) and **9b** (40%), which could be separated by silica gel column chromatography. The stereochemistry of the hydroxy group in **9a** and **9b** was determined by ^1H and ^{13}C NMR analysis of the derived acetonides **17a** and **17b**, respectively.[10] The hydroxy group in **9a** was silylated to give silyl ether **10a** (99%), which was reduced to alcohol **11a** (94%). Swern oxidation[11] of alcohol **11a** afforded aldehyde **12a** (75%), the Horner–Emmons reaction of which with $(EtO)_2P(O)CH(Me)COOEt$ gave conjugated ester **13a** (88%) along with the 32*Z*-isomer (7%). Reduction of the ester moiety of **13a** followed by desilylation and acylation (*p*-BrC_6H_4COCl, pyridine) yielded tris(*p*-bromobenzoate) **3a** (88% in 3 steps). Tris(*p*-bromobenzoate) **3b** was synthesized from **9b** by the same sequence of reactions as described above. Two other diastereomers, **3c** and **3d**, were also prepared from **13a** and **13b**, respectively. Thus, deprotection of the TES group in **13a** and **13b** gave diols **14a** and **14b**, which were oxidized with MnO_2 to enones **15a** and **15b**, respectively. The hydroxy group of **15a** and **15b** was silylated to give silyl ethers **16a** and **16b**, which were transformed into **3c** and **3d** by the following sequence of reactions: (i) 1,2-reduction of the keto group, (ii) desilylation, (iii) DIBAL reduction, and (iv) *p*-bromobenzoylation. Among the four synthetic diastereomers, **3a**, **3b**, **3c**, and **3d**, the ^1H NMR and the CD spectra of **3d** were identical to those for natural **3**, establishing the absolute stereochemistry of **3**. On the basis of these findings, the complete stereostructure of aurilide was determined as shown in formula **1**.

2.4. Synthesis

Although aurilide (**1**) was isolated from a strongly cytotoxic fraction of the sea hare, the scarcity of the natural supply has prevented the evaluation of its cytotoxicity. To confirm the stereostructure of **1** and to obtain **1** in adequate quantities for biological and pharmacological studies, the enantioselective synthesis of aurilide (**1**) was carried out. A retrosynthetic analysis of aurilide (**1**) is shown in Scheme 2. A key step in the synthesis of aurilide (**1**) is the 26-membered ring



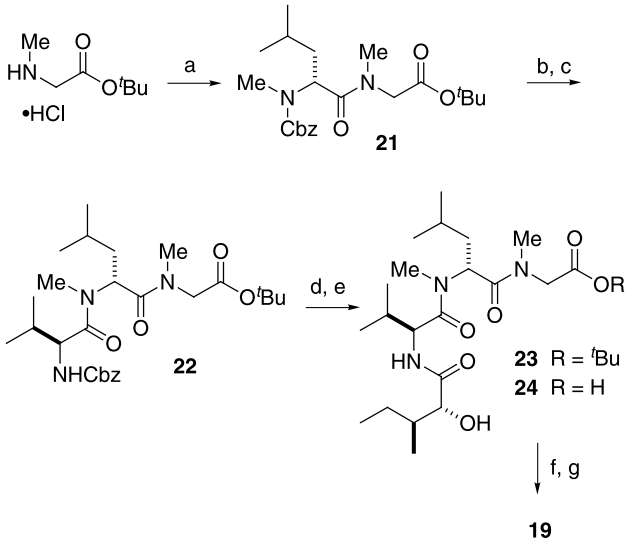
Scheme 1. *Reagents and conditions*: (a) Bu_2BOTf, Et_3N, *trans*-2-methyl-2-pentenal, CH_2Cl_2, −78 °C, 80%; (b) $Me_2AlN(Me)OMe$, THF, toluene, 0 °C, 100%; (c) TESCl, imidazole, DMF, rt, (**7**) 100%, (**10a**) 99%, (**10b**) 95%, (**16a**) 85%, (**16b**) 89%; (d) DIBAL, THF, hexane, −78 °C, 91%; (e) $LiCH_2COO^tBu$, THF, −78 °C, (**9a**) 58%, (**9b**) 40%; (f) DIBAL, CH_2Cl_2, hexane, −23 °C, (**11a**) 94%, (**11b**) 93%; (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, (**12a**) 75%, (**12b**) 84%; (h) $(EtO)_2P(O)CH(Me)COOEt$, NaH, DME, −23 °C, (**13a**) 88%, (**13b**) 86%; (i) DIBAL, CH_2Cl_2, hexane, −23 °C; (j) HF·pyridine, pyridine, THF, rt, (**14a**) 98%, (**14b**) 98%; (k) *p*-BrC_6H_4COCl, pyridine, rt; (l) MnO_2, CH_2Cl_2, rt, (**15a**) 69%, (**15b**) 60%; (m) $NaBH_4$, $CeCl_3\cdot H_2O$, EtOH, −23 °C; (n) $Me_2C(OMe)_2$, PPTS, acetone, rt.



Scheme 2. Retrosynthetic analysis of aurilide (**1**).

closure. We planned to construct the cyclic structure of **1** by the macrolactamization of amino acid **18**, which was synthesized from pentapeptide **19** and the protected dihydroxy acid **20**.

Pentapeptide **19** was prepared as follows (Scheme 3).

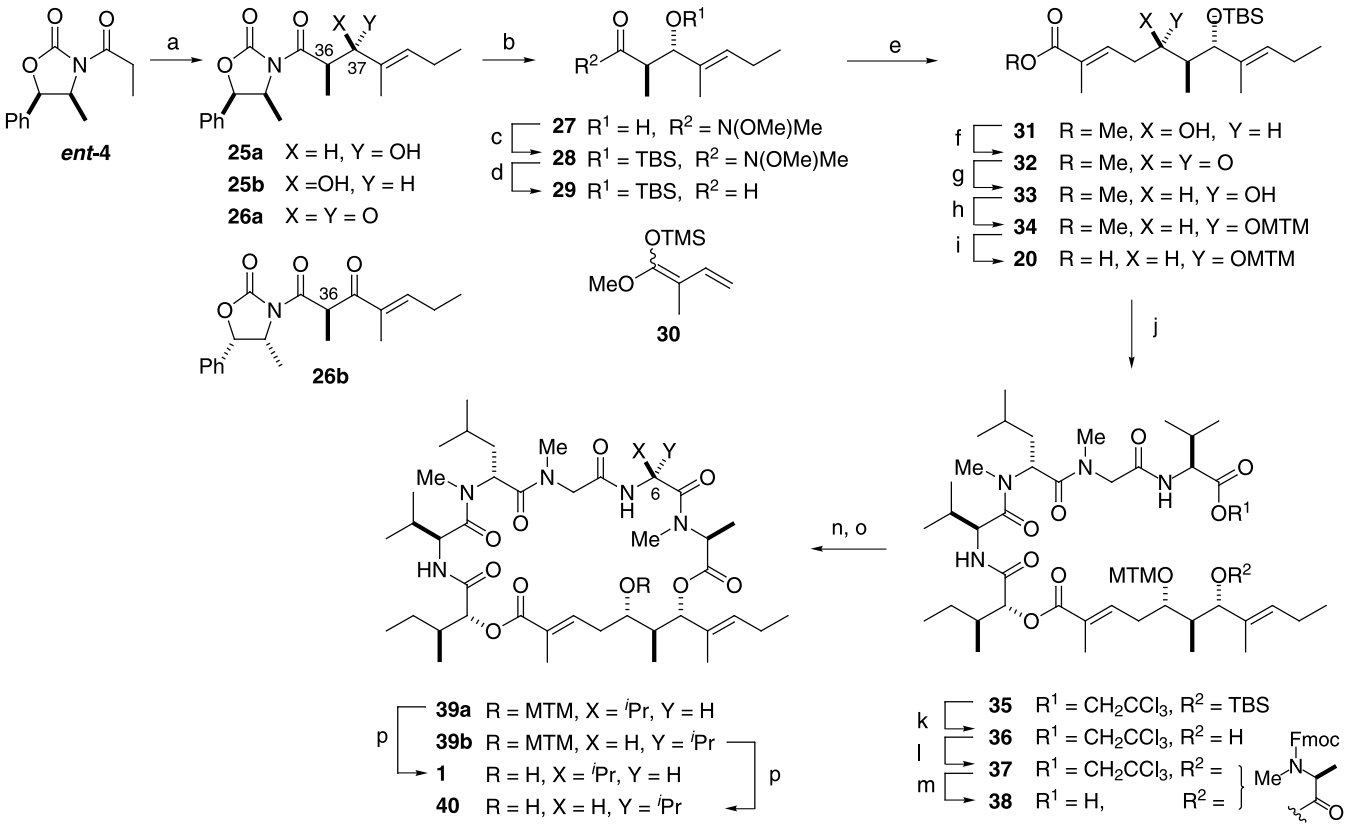


Scheme 3. *Reagents and conditions*: (a) Cbz-D-MeLeu, DEPC, Et_3N, DMF, 0 °C, 98%; (b) H_2, 10% Pd–C, EtOH, rt; (c) Cbz-L-Val, PyBOP, *i*-Pr_2EtN, CH_2Cl_2, rt, 92% (2 steps); (d) H_2, 10% Pd-C, EtOH, CH_2Cl_2, rt; (e) sodium salt of allo-D-isoleucic acid, EDCI·HCl, HOBt, DMF, rt, 95% (2 steps); (f) TMSOTf, 2,6-lutidine, 0 °C, 100%, (g) L-Val-OCH_2CCl_3, EDCI·HCl, HOBt, DMF, CH_2Cl_2, rt, 98%.

Condensation of *N*-methylglycine *tert*-butyl ester hydrochloride and *N*-Cbz-*N*-methyl-D-leucine using DEPC[12] gave dipeptide **21**. Deprotection of the Cbz group of **21** followed by coupling with *N*-Cbz-L-valine using (benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP)[13] afforded tripeptide **22**, which was converted into tetrapeptide **23** by condensation with sodium salt of allo-D-isoleucic acid[14] using EDCI·HCl[15] and 1-hydroxybenztriazole (HOBt).[16] Deprotection of the *tert*-butyl group (TMSOTf, 2,6-lutidine)[17] gave carboxylic acid **24**, which was condensed with L-valine 2,2,2-trichloroethyl ester to provide pentapeptide **19**.

Synthesis of the protected dihydroxy acid **20** began with an anti-selective aldol reaction (Scheme 4).[18] The aldol reaction between imide *ent*-**4** and *trans*-2-methyl-2-pentenal under Heathcock conditions afforded hydroxy imide **25a** (67%) along with the *syn*-isomer **25b** (14%). The stereochemistry of **25a** was determined as follows. Transamidation of **25a** and its *syn*-diastereomer **5** (Scheme 1), which was prepared by Evans aldol reaction, gave diastereomeric amides **27** (84%) and **6**, respectively, indicating that the relative stereochemistry between C36 and C37 in **25a** was *anti*. On the other hand, the oxidation of **25a** and **5** afforded diastereomeric ketones **26a** and **26b**, respectively, establishing that the absolute configuration of C36 in **25a** was *R*. From these results, the stereochemistry of **25a** was determined to be 36*R* and 37*S* (*anti*), as expected from the results of Heathcook and co-workers.[18] The hydroxy group in **27** was silylated to give silyl ether **28** (100%), the amide group of which was reduced with DIBAL to provide aldehyde **29** (93%). The vinylogous Mukaiyama aldol reaction[19] between **29** and silyl ketene acetal **30**[20] afforded methyl ester **31** in 87% yield as a single diastereomer.[21,22] This stereoselectivity can be explained by a transition state model proposed by Evans and co-workers.[23] Configuration inversion of the C35 hydroxy group in **31** was effected as follows: Dess–Martin oxidation[24] of **31** afforded ketone **32** (94%), and reduction of the resulting keto group in **32** stereoselectively ($\alpha/\beta=20/1$) proceeded to give alcohol **33** (82%), which had the desired stereochemistry at C35.[21] Protection of the hydroxy group in **33** was effected by treatment with DMSO, Ac_2O, and AcOH[25] to give (methylthio)methyl (MTM) ether **34** (74%) along with ketone **32** (10%). The ester group of **34** was hydrolyzed with LiOH in aqueous MeOH to afford the protected dihydroxy acid **20** in 89% yield.

The coupling reaction between pentapeptide **19** and the protected dihydroxy acid **20** was effected with EDCI·HCl and DMAP to provide ester **35** (91%), which was converted into alcohol **36** (100%). Esterification of **36** with *N*-Fmoc-*N*-methyl-L-alanine gave the *N*-methylalanine ester **37**[26] (94%), the 2,2,2-trichloroethyl group of which was removed to afford carboxylic acid **38** (97%). Deprotection of the Fmoc group in **38** followed by macrolactamization with EDCI·HCl and 1-hydroxy-7-azabenzotriazole (HOAt)[27] in CH_2Cl_2–DMF (10:1) provided lactam **39a** (66%) along with lactam **39b** (24%), which resulted from epimerization at C6. Macrolactamization with other reagents such as Bop-Cl,[28] PyBOP,[13] DPPA,[29] and EDCI·HCl and HOBt gave lactam **39a** in low yield. Finally, the MTM group in **39a** was removed with $AgNO_3$[30] to give aurilide (**1**) (93%), while



Scheme 4. *Reagents and conditions*: (a) Bu_2BOTf (2 equiv), *i*-Pr_2EtN, *trans*-2-methyl-2-pentenal, Et_2O, −100 °C→−78 °C, 67%; (b) $Me_2AlN(Me)OMe$, THF, toluene, 50 °C, 84%; (c) TBSCl, imidazole, DMF, rt, 100%; (d) DIBAL, THF, hexane, −78 °C, 93%; (e) **30**, $BF_3{\cdot}Et_2O$, CH_2Cl_2–Et_2O (10:1), −78 °C, 87%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 94%; (g) $NaBH_4$, MeOH, −23 °C, 82%; (h) DMSO, Ac_2O, AcOH, 40 °C, 74%; (i) LiOH, H_2O, MeOH, 30 °C, 89%; (j) **19**, EDCI·HCl, DMAP, CH_2Cl_2, rt, 91%; (k) HF·pyridine, pyridine, THF, 40 °C, 100%; (l) Fmoc-L-MeAla, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C, 94%; (m) Zn, NH_4OAc, THF, H_2O, rt, 97% (n) Et_2NH, MeCN, rt, (o) EDCI·HCl, HOAt, CH_2Cl_2–DMF (10:1), rt, (**39a**) 66%, (**39b**) 24% (2 steps); (p) $AgNO_3$, 2,6-lutidine, THF, H_2O, (**1**) 93%, (**40**) 97%.

6-*epi*-aurilide (**40**) was obtained (97%) from **39b** under identical conditions. Synthetic aurilide (**1**) was found to be identical to natural **1** in all respects, including the spectroscopic (UV, IR, ^1H NMR, MS, and $[\alpha]_D$) and chromatographic properties. Thus, the stereostructure of aurilide was unambiguously confirmed to be that shown in **1**. In comparison with the previous synthesis of **1** reported as a communication[5] in 1997 (overall yield 3.9%), the synthetic procedures have been much improved as regards the present synthesis of **1**, especially in terms of the vinylogous Mukaiyama aldol reaction and macrolactamization (overall yield 12%), resulting in a supply of **1** on a gram scale. The availability of an ample amount of **1** by synthesis enabled us to perform various biological and pharmacological studies of aurilide (**1**). Recently, Takahashi, Doi, and co-workers achieved a solid-phase library synthesis of aurilide (**1**) and related analogs.[31]

2.5. Biological activity

Aurilide (**1**) exhibited strong cytotoxicity against HeLa S_3 tumor cells with an IC_{50} value of 0.011 μg/mL, while the cytotoxicity of 6-*epi*-aurilide (**40**) ($IC_{50}>4$ μg/mL) was much weaker than that of **1**. These results indicated that the cytotoxicity of **1** depends markedly on the stereochemistry at C6 of **1**. Aurilide (**1**) was evaluated in vitro in the NCI 60 cell lines: **1** was found to exhibit a high level of cytotoxicity (the mean panel GI_{50} concentration was 0.12 μg/mL) against the tested cell lines and to be particularly active against ovarian, renal, and prostate cancer cell lines. Interestingly, **1** was not cytocidal but cyctostatic against leukemia cell lines. Aurilide (**1**) showed unusually high in vivo antitumor activity in the NCI's hollow fiber assays,[32] but did not have significant antitumor activity owing to toxicity in the in vivo human tumor xenograft tests. Aurilide (**1**) showed strong microtubule stabilization properties, but the mechanism was different from that of taxol, as determined by immunofluorescence analysis: aurilide (**1**) does not seem to interact directly with tubulin.

3. Conclusion

A novel cytotoxic 26-membered depsipeptide, aurilide (**1**), was isolated from the Japanese sea hare *Dolabella auricularia*. Its structure was established by a combination of spectroscopic analysis, chiral HPLC analysis, and organic synthetic methods. The enantioselective total synthesis of **1** was achieved in 12% overall yield (16 steps). Whereas the natural sample of **1** was obtained from the sea hare *D. auricularia* in sub-milligram quantities, the synthetic sample was available on a gram scale. Aurilide (**1**) was found to reveal a high level of cytotoxicity in vitro against the NCI 60 cell lines and show unusually high in vivo

antitumor activity in the NCI's hollow fiber assays, while **1** did not have significant antitumor activity in the in vivo human tumor xenograft tests. Recently, a structurally related cytotoxin, kulokekahalide-2, has been isolated from the cephalaspidean mollusk *Philinopsis speciosa*.[33]

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were measured at 270, 400 or 600 MHz for ^{1}H and 100 or 150 MHz for ^{13}C. *J* values are given in Hz. Both TLC analysis and preparative TLC were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820 MH and FL-60D, and E. Merck aluminum oxide 90 (activity II–III) were used for column chromatography unless otherwise noted. Organic solvents for anhydrous reactions were distilled from the following drying agents: THF and ether (Na-benzophenone ketyl), benzene (Na), triethylamine (calcium hydride), DMSO (calcium hydride under reduced pressure), CH_2Cl_2 (P_2O_5), acetone (anhydrous K_2CO_3), and MeOH (Mg). All moisture-sensitive reactions were performed under an atmosphere of nitrogen.

4.1.1. Extraction and isolation. Specimens of *D. auricularia* (31 kg wet wt) were collected by hand at a depth of 0–1 m on the coast of the Shima Peninsula, Mie Prefecture, Japan, in May 1993 and stored at −20 °C for several months until extraction. The specimens were separated into the internal organs and the thick outer skin, and the former (15.7 kg) was extracted with MeOH (32 L) at room temperature for 5 days. The methanolic extract was concentrated to ca. 2 L in vacuo and extracted with EtOAc (3×2 L). The EtOAc portion (77 g) was dissolved in 9:1 MeOH/H_2O (770 mL), and the solution was washed with hexane (2×770 mL). The aqueous MeOH portion (22.8 g) was chromatographed on silica gel (450 g), using 1:1 toluene/EtOAc (1.8 L) followed by EtOAc (1.8 L) as eluent. The fraction (1.35 g) eluted with EtOAc was then chromatographed on silica gel (70 g, 2:1 hexane/acetone) to give active fraction (447 mg, IC_{50} against HeLa S_3 cells = 3.26 μg/mL). Using the same procedure as described above, the sea hare (76 kg wet wt) collected in 1993 and 1994 were extracted and separated to yield an additional active fraction (2.51 g). They were combined and subjected to RP-MPLC (Develosil ODS 30/60, 70%→100% MeOH). The fraction (1.3 g) eluted with 83–93% MeOH was further separated by RP-MPLC (Develosil ODS 30/60, 80%→100% MeOH). The fraction (139 mg, IC_{50} = 0.45 μg/mL) eluted with 80–87% MeOH was chromatographed on silica gel (8 g, 15:1, 10:1, 5:1 $CHCl_3$–acetone, and acetone, successively). The fraction (48 mg, IC_{50} = 0.28 μg/mL) eluted with 5:1 $CHCl_3$–acetone was further separated by RP-HPLC [Develosil ODS-HG-5 (ϕ10×250 mm), MeCN–MeOH–H_2O 75:5:40→75:5:0, flow rate 2 mL/min]. The fraction (13.5 mg, IC_{50} = 0.091 μg/mL) eluted with 75:5:27–75:5:21 MeCN–MeOH–H_2O was separated by RP-HPLC [Develosil ODS-HG-5 (ϕ10×250 mm), 80% MeOH, flow rate 2 mL/min] to afford an active fraction (2.2 mg, IC_{50} = 0.047 μg/mL t_R = 33–40 min). Using the same procedure as described above, the sea hare (156 kg wet wt) collected in 1991–1995 were extracted and separated to yield an additional active fraction (6.6 mg). They were combined and further separated by RP-HPLC [Develosil ODS-HG-5 (ϕ20×250 mm), 70% MeCN, flow rate 5 mL/min]. The active fraction (1.7 mg, IC_{50} = 0.017 μg/mL, t_R = 47–55 min) was further purified by preparative TLC (silica gel 200×200×0.25 mm, benzene–acetone 3:1) followed by RP-HPLC [Develosil ODS-HG-5 (ϕ20×250 mm), 80% MeOH, flow rate 5 mL/min] to give aurilide (**1**) (0.5 mg, 1.9×10^{-7}%, t_R = 39 min) as a colorless powder. $[\alpha]_D^{25}$ = −17 (*c* 0.058, MeOH); UV (MeOH) λ_{max} 220 nm (sh) (ε 17000); IR ($CHCl_3$) 3430 (br), 1735, 1685, 1645, 1245 cm^{-1}; ^{1}H NMR data, see Table 1; HRMS (FAB) calcd for $C_{44}H_{75}N_5NaO_{10}$ $[(M+Na)^+]$ 856.5412, found 856.5432.

4.1.2. Absolute stereochemistry of the peptide moiety. Aurilide (**1**) (0.26 mg) was treated with 9 M HCl (0.1 mL) at 110 °C for 72 h. The product mixture was diluted with H_2O (1 mL), concentrated, and separated by RP-HPLC [Develosil ODS-HG-5 (ϕ4.6×250 mm), MeCN/H_2O/CF_3COOH 1:99:0.05 (20 min), 1:99:0.05 to 10:90:0.05 (20 min, linear gradient), and then 10:90:0.05 (20 min); flow rate, 1.0 mL/min; detection at 205 nm] to give *N*-methyl-alanine (t_R = 3 min), valine (t_R = 5 min), *N*-methyl leucine (t_R = 21 min), and isoluecic acid (t_R = 55 min). The absolute configurations of three components, MeAla, Val, and isoleucic acid were determined by chiral HPLC analysis: column, CHIRALPAK MA(+) (4.6×50 mm); solvent, 2 mM $CuSO_4$ for Val and MeLeu and 2 mM $CuSO_4$/MeCN 9:1 for isoleucic acid; flow rate, 1.0 mL/min; detection at 254 nm. The retention times (min) of the authentic samples: L-Val (8.0), D-Val (4.0), L-MeLeu (9.0), D-MeLeu (6.7), L-isoleucic acid (64), D-isoleucic acid (39), allo-L-isoleucic acid (52), and allo-D-isoleucic acid (32). A solution of *N*-methyl alanine derived from **1** in H_2O (50 μL) was treated with 1% solution of Marfey's reagent in acetone (20 μL) and 1 M $NaHCO_3$ (5 μL) at 40 °C for 1 h followed by addition of 2 M HCl (2.5 μL). The mixture was analyzed by RP-HPLC [Develosil ODS-HG-5 (4.6×250 mm); solvent, MeOH/0.02 M NaOAc (pH 4.0) 1:1; flow rate 1.0 mL/min; detection at 340 nm]. The retention times (min) of the authentic Marfey derivatives of MeAla: L-MeAla (5.3) and D-MeAla (6.3).

4.1.3. Degradation of aurilide. To a stirred solution of aurilide (**1**) (0.3 mg) in ether (0.2 mL) cooled at 0 °C was added 1 M solution of lithium aluminum hydride in ether (0.01 mL, 0.01 mmol), and the mixture was stirred at room temperature for 1.3 h. The reaction was quenched by addition of ice (1 g) and 1 M HCl, and the mixture was extracted with EtOAc (3×4 mL). The combined extracts were washed with 0.2 M HCl (1 mL), saturated aqueous $NaHCO_3$ (1 mL), and brine (2 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was dissolved in pyridine (0.2 mL) and reacted with *p*-bromobenzoyl chloride (50 mg, 0.23 mmol) at room temperature for 17 h. The mixture was diluted with 5% aqueous $NaHCO_3$ (2 mL), stirred at room temperature for 1 h, and extracted with ether (3×4 mL). The combined extracts were washed with 5% aqueous $NaHCO_3$ (2×3 mL), H_2O (3 mL), and brine (3 mL), successively, dried (Na_2SO_4), and concentrated.

The residual oil was purified by preparative TLC (silica gel 200×100×0.25 mm, hexane–acetone 3:1) followed by HPLC [Develosil 60-5 (ϕ10×250 mm), hexane–EtOAc–MeOH 20:1:0.1, flow rate 2 mL/min, detection UV_{254}] to give tris(*p*-bromobenzoate) **3** (0.05 mg) as a colorless powder: CD (MeOH) λ_{ext} 253 nm ($\Delta\varepsilon$ −56), 238 nm ($\Delta\varepsilon$ +94); ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (t, J=7.3 Hz, 3H), 0.86 (d, J=7.3 Hz, 3H), 1.50 (s, 3H), 1.54 (s, 3H), 1.80–1.89 (m, 2H), 2.44–2.40 (m, 2H), 2.58 (ddq, J=9.9, 4.4, 7.3 Hz, 1H), 4.42 (d, J=12.5 Hz, 1H), 4.48 (d, J=12.5 Hz, 1H), 5.49 (br t, J=7.3 Hz, 1H), 5.57 (d, J=9.9 Hz, 1H), 5.63–5.58 (m, 2H), 7.61 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H), 7.90 (d, J=8.4 Hz, 2H). The signals due to six protons in **3** were not observed due to the overlap with the solvent signals.

4.1.4. Hydroxy imide 5. To a stirred solution of imide **4** (1.36 g, 5.84 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C were added 1 M solution of dibutylboron triflate in CH_2Cl_2 (6.4 mL, 6.4 mmol) and triethylamine (1.19 mL, 8.56 mmol), successively. The reaction mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of *trans*-2-methyl-2-pentenal (0.45 mL, 3.9 mmol) in CH_2Cl_2 (2.0 mL, 1.5 mL rinse) was added, and the reaction mixture was stirred at −78 °C for 1.5 h and at 0 °C for 0.5 h. After the reaction was quenched by addition of 0.5 M phosphate buffer (pH 7, 10 mL) and MeOH (20 mL), 30% aqueous hydrogen peroxide (10 mL) in MeOH (20 mL) was added slowly, and the resulting solution was stirred at 0 °C for 1 h. The organic solvents were evaporated, and the mixture was cooled to 0 °C. Saturated aqueous $Na_2S_2O_3$ (15 mL) was added slowly, and the mixture was extracted with ether (2×50 mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–EtOAc 7:1→5:1→4:1) to give **5** (1.03 g, 80% from *trans*-2-methyl-2-pentenal) as colorless crystals along with recovered **4** (459 mg). **5**. mp 96–97 °C (pentane–ether). $[\alpha]_D^{31}$ = +30.6 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3600, 3530 (br), 1780, 1695, 1455, 1345, 1190, 955 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (d, J=6.6 Hz, 3H), 0.99 (t, J=7.6 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.63 (d, J=0.7 Hz, 3H), 2.08 (dq, J=7.6, 7.6 Hz, 2H), 2.75 (d, J=3.3 Hz, 1H), 3.99 (dq, J=4.0, 6.9 Hz, 1H), 4.36 (m, 1H), 4.77 (dq, J=7.3, 6.6 Hz, 1H), 5.55 (m, 1H), 5.67 (d, J=7.3 Hz, 1H), 7.27–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (q), 13.2 (q), 14.1 (q), 14.3 (q), 20.6 (t), 40.6 (d), 54.9 (d), 75.4 (d), 78.9 (d), 125.6 (d, 2C), 128.1 (d), 128.7 (d, 2C), 128.8 (d), 132.8 (s), 133.1 (s), 152.6 (s), 176.9 (s); MS (FAB) *m/z*, 354 $(M+Na)^+$; HRMS (FAB) calcd for $C_{19}H_{25}NNaO_4$ $[(M+Na)^+]$ 354.1681, found 354.1669. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.90; H, 7.60; N, 4.23. Found C, 68.84; H, 7.69; N, 4.19.

4.1.5. Amide 6. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (306 mg, 3.14 mmol) in THF (2 mL) cooled at −10 °C was added a 2.0 M solution of trimethylaluminum in toluene (1.5 mL, 3.0 mmol) dropwise. The resulting solution was stirred at 0 °C for 5 min and at room temperature for 15 min. The solution was recooled to 0 °C, and a solution of hydroxy imide **5** (516 mg, 1.56 mmol) in THF (3 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, and transferred into a vigrously stirred mixture of CH_2Cl_2 (7.5 mL) and 0.5 M HCl (7.5 mL) at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 50 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The organic layer and extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (20 g, hexane–EtOAc 3: 1→2:1→EtOAc) to give **6** (339 mg, 100%) as a colorless oil and 4-(*R*)-methyl-5-(*S*)-phenyl-2-oxazolidinone (272 mg) as colorless crystals. **6**. $[\alpha]_D^{27}$ = −8.0 (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3430 (br), 1630, 1460, 1420, 1390, 995 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (t, J=7.6 Hz, 3H), 1.10 (d, J=6.9 Hz, 3H), 1.59 (d, J=0.7 Hz, 3H), 2.06 (dq, J=7.6, 7.6 Hz, 2H), 3.07 (m, 1H), 3.20 (s, 3H), 3.72 (s, 3H), 3.80 (br d, J=1.0 Hz, 1H), 4.26 (m, 1H), 5.58 (tq, J=7.6, 0.7 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.3 (q), 13.4 (q), 14.1 (q), 20.8 (t), 32.0 (q), 33.3 (d), 61.5 (q), 75.3 (d), 128.0 (d), 132.1 (s). A signal due to carbonyl carbon was not observed; MS (FAB) *m/z* 238 $(M+Na)^+$; HRMS (FAB) calcd for $C_{11}H_{21}NNaO_3$ $[(M+Na)^+]$ 238.1420, found 238.1419.

4.1.6. Silyl ether 7. To a stirred solution of amide **6** (320 mg, 1.49 mmol) in DMF (2 mL) were added imidazole (295 mg, 4.33 mmol) and triethylsilyl chloride (0.3 mL, 1.8 mmol). The mixture was stirred at room temperature for 45 min and diluted with H_2O (6 mL), and the resulting mixture was extracted with hexane (4×8 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, hexane–EtOAc 8:1→5:1) to give **7** (489 mg, 100%) as a colorless oil. $[\alpha]_D^{26}$ = +0.9 (*c* 1.58, $CHCl_3$); IR ($CHCl_3$) 1650, 1460, 1420, 1385, 1065, 995, 865 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.57 (q, J=7.9 Hz, 6H), 0.88 (t, J=7.6 Hz, 3H), 0.92 (t, J=7.9 Hz, 9H), 1.18 (d, J=6.9 Hz, 3H), 1.59 (br s, 3H), 1.94 (dq, J=7.3, 7.6 Hz, 2H), 3.08 (s, 3H), 3.13 (m, 1H), 3.61 (s, 3H), 4.10 (d, J=9.2 Hz, 1H), 5.30 (br t, J=7.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 4.79 (t, 3C), 6.8 (q, 3C), 11.0 (q), 13.7 (q), 14.8 (q), 20.7 (t), 32.0 (q), 40.4 (d), 61.4 (q), 80.2 (d), 129.2 (d), 135.0 (s), 176.0 (s); MS (FAB) *m/z* 352 $(M+Na)^+$; HRMS (FAB) calcd for $C_{17}H_{35}NNaO_3Si$ $[(M+Na)^+]$ 352.2284, found 352.2293.

4.1.7. Aldehyde 8. To a stirred solution of silyl ether **7** (470 mg, 1.43 mmol) in THF (5 mL) cooled at −78 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (2.2 mL, 2.2 mmol) dropwise. The solution was stirred at −78 °C for 2 h, and the reaction was quenched by addition of acetone (0.2 mL). The solution was stirred at −78 °C for 5 min and then transferred into a vigorously stirred mixture of CH_2Cl_2 (20 mL) and 0.5 M tartaric acid (20 mL) at room temperature. The resulting two-phase mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (2×20 mL). The organic layer and the extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, hexane–EtOAc 50:1→30:1) to give **8** (350 mg, 91%) as a colorless oil. $[\alpha]_D^{26}$ = −2.3 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 2730, 1720, 1455, 1215, 1070, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (q,

J=7.8 Hz, 6H), 0.93 (t, J=7.8 Hz, 9H), 0.95 (t, J=7.8 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.57 (br s, 3H), 1.94–2.10 (m, 2H), 2.51 (ddq, J=2.0, 6.8, 6.8 Hz, 1H), 4.25 (d, J=6.8 Hz, 1H), 5.40 (br t, J=6.8 Hz, 1H), 9.66 (d, J=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8 (t, 3C), 6.8 (q, 3C), 9.2 (q), 12.0 (q), 13.8 (q), 20.7 (t), 51.0 (d), 77.9 (d), 129.4 (d), 134.2 (s), 204.7 (d); MS (FAB) m/z 293 $[(M+Na)]^+$; HRFABMS calcd for $C_{15}H_{30}NaO_2Si$ $[(M+Na)]^+$ 293.1913, found 293.1910.

4.1.8. Aldols 9a and 9b. To a 0.5 M solution of lithium diisopropylamide prepared from diisopropylamine (0.36 mL, 2.6 mmol), a 1.58 M solution of BuLi in hexane (1.6 mL, 2.5 mmol), and THF (3.0 mL) at −78 °C was added *tert*-butyl acetate (0.38 mL, 2.82 mmol), and the mixture was stirred at −78 °C for 25 min. A solution of aldehyde **8** (344 mg, 1.27 mmol) in THF (3 mL) was added, and the resulting mixture was stirred at −78 °C for 45 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (8 mL), and the mixture was extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 30 g, benzene→benzene–EtOAc 50:1) to give **9a** (286 mg, 58%) and **9b** (196 mg, 40%) as a colorless oil, respectively.

Compound **9a**. $[\alpha]_D^{26}$=+9.1 (c 1.36, $CHCl_3$); IR ($CHCl_3$) 3520 (br), 1715, 1455, 1370, 1240, 1155, 1010, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (q, J=7.8 Hz, 6H), 0.93 (d, J=6.8 Hz, 3H), 0.94 (t, J=7.8 Hz, 9H), 0.97 (t, J=7.8 Hz, 3H), 1.45 (s, 9H), 1.54 (br s, 3H), 1.98–2.11 (m, 3H), 2.26 (dd, J=3.9, 16.1 Hz, 1H), 2.49 (dd, J=9.3, 16.1 Hz, 1H), 2.71 (d, J=3.4 Hz, 1H), 4.00 (m, 1H), 4.01 (d, J=7.3 Hz, 1H), 5.40 (br t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 6.9 (q, 3C), 8.1 (q), 11.7 (q), 13.8 (q), 20.8 (t), 28.1 (q, 3C), 41.0 (t), 41.1 (d), 68.9 (d), 80.8 (s), 81.0 (d), 129.1 (d), 135.0 (s), 172.1 (s); MS (FAB) m/z 409 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{42}NaO_4Si$ $[(M+Na)^+]$ 409.2750, found 409.2729.

Compound **9b**. $[\alpha]_D^{26}$=−5.5 (c 1.36, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1715, 1460, 1370, 1240, 1155, 1010, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, J=7.8 Hz, 6H), 0.79 (d, J=6.8 Hz, 3H), 0.94 (t, J=7.8 Hz, 9H), 0.96 (t, J=7.8 Hz, 3H), 1.46 (s, 9H), 1.57 (br s, 3H), 1.73 (m, 1H), 2.03 (dq, J=7.3, 7.3 Hz, 2H), 2.39 (dd, J=9.3, 16.1 Hz, 1H), 2.45 (dd, J=2.9, 16.1 Hz, 1H), 3.48 (d, J=3.9 Hz, 1H), 3.86 (m, 1H), 4.13 (d, J=4.4 Hz, 1H), 5.36 (br t, J=7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8 (t, 3C), 6.9 (q, 3C), 10.2 (q), 12.8 (q), 13.4 (q), 20.8 (t), 28.1 (q, 3C), 39.7 (t), 41.9 (d), 69.6 (d), 78.2 (d), 81.0 (s), 128.2 (d), 134.9 (s), 172.7 (s); MS (FAB) m/z 409 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{42}NaO_4Si$ $[(M+Na)^+]$ 409.2750, found 409.2774.

4.1.9. Silyl ethers 10a and 10b. To a stirred solution of aldol **9a** (84.3 mg, 0.218 mmol) in DMF (0.2 mL) were added imidazole (68.0 mg, 1.00 mmol) and triethylsilyl chloride (0.07 mL, 0.42 mmol). The mixture was stirred at room temperature for 1.5 h and diluted with H_2O (2 mL), and the resulting mixture was extracted with hexane (3× 5 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–benzene 3:1→2:1) to give **10a** (105 mg, 99%) as a colorless oil. Using the same procedure as described above, **10b** (70.1 mg, 95%) was obtained from **9b** (40.0 mg, 0.15 mmol) as a colorless oil.

Compound **10a**. $[\alpha]_D^{27}$=+2.0 (c 1.20, $CHCl_3$); IR ($CHCl_3$) 1715, 1455, 1370, 1240, 1155, 1035, 1010, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52–0.62 (m, 12H), 0.92 (t, J=8.3 Hz, 9H), 0.93 (d, J=6.8 Hz, 3H), 0.95 (t, J=7.8 Hz, 9H), 0.98 (t, J=7.3 Hz, 3H), 1.45 (s, 9H), 1.53 (br s, 3H), 1.62 (m, 1H), 2.00 (ddq, J=7.3, 14.6, 7.3 Hz, 1H), 2.08 (ddq, J=7.3, 14.6, 7.3 Hz, 1H), 2.38 (dd, J=5.9, 14.6 Hz, 1H), 2.44 (dd, J=7.8, 14.6 Hz, 1H), 3.91 (d, J=8.8 Hz, 1H), 4.00 (ddd, J=2.0, 5.9, 7.8 Hz, 1H), 5.32 (br dd, J=7.3, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (t, 3C), 5.4 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 8.9 (q), 10.9 (q), 13.8 (q), 20.8 (t), 28.1 (q, 3C), 41.3 (d), 42.4 (t), 69.2 (d), 80.21 (s), 80.24 (d), 129.8 (d), 135.9 (s), 170.7 (s); MS (FAB) m/z 523 $(M+Na)^+$.

Compound **10b**. $[\alpha]_D^{26}$=−24.8 (c 0.81, $CHCl_3$); IR ($CHCl_3$) 1725, 1460, 1370, 1240, 1160, 1050, 1010 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.49–0.62 (m, 12H), 0.91 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.9 Hz, 9H), 0.93 (t, J=7.9 Hz, 9H), 0.96 (d, J=6.8 Hz, 3H), 1.43 (s, 9H), 1.60 (br s, 3H), 1.81 (m, 1H), 2.02 (dq, J=7.3, 7.3 Hz, 2H), 2.15–2.29 (m, 2H), 3.58 (d, J=8.9 Hz, 1H), 4.03 (ddd, J=3.6, 3.6, 7.6 Hz, 1H), 5.23 (br t, J=6.8 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.1 (t, 3C), 6.90 (q, 3C), 6.93 (q, 3C), 10.1 (q), 11.2 (q), 13.7 (q), 20.8 (t), 28.1 (q, 3C), 38.5 (t), 43.4 (d), 69.6 (d), 79.8 (s), 81.2 (d), 129.5 (d), 135.2 (s), 171.3 (s); MS (FAB) m/z 523 $(M+Na)^+$.

4.1.10. Alcohols 11a and 11b. To a stirred solution of silyl ether **10a** (70.7 mg, 0.141 mmol) in CH_2Cl_2 (1 mL) cooled at −23 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (0.72 mL, 0.71 mmol), and the mixture was stirred at −23 °C for 2 h. The reaction was quenched by addition of acetone (0.1 mL) and saturated aqueous Na/K tartrate (5 mL), and the mixture was stirred at room temperature for 45 min and extracted with hexane (3×8 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ether 9:1→5:1) to give **11a** (57.3 mg, 94%) as a colorless oil. Using the same procedure as described above, **11b** (51.8 mg, 93%) was obtained from **10b** (65.1 mg, 0.130 mmol) as a colorless oil.

Compound **11a**. $[\alpha]_D^{27}$=−0.4 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3630, 3480 (br), 1460, 1415, 1380, 1235, 1035, 1005, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, J=7.8 Hz, 6H), 0.59 (q, J=7.8 Hz, 6H), 0.91 (d, J=6.8 Hz, 3H), 0.92 (t, J=7.8 Hz, 9H), 0.95 (t, J=7.8 Hz, 9H), 0.97 (t, J=7.3 Hz, 3H), 1.51 (br s, 3H), 1.65 (ddq, J=3.4, 7.3, 6.8 Hz, 1H), 1.72–1.85 (m, 2H), 1.90 (br s, 1H), 1.93–2.12 (m, 2H), 3.61 (ddd, J=6.3, 6.3, 10.7 Hz, 1H), 3.71 (ddd, J=6.3, 6.3, 10.7 Hz, 1H), 3.77 (ddd, J=3.4, 5.9, 5.9 Hz, 1H), 3.93 (d, J=7.3 Hz, 1H), 5.34 (br t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (t, 3C), 5.4 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 9.5 (q), 11.6 (q),13.9 (q), 20.8 (t), 37.4 (t),

40.8 (d), 60.2 (t), 71.0 (d), 79.5 (d), 129.3 (d), 135.6 (s); MS (FAB) *m/z* 453 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{50}NaO_3Si_2$ $[(M+Na)^+]$ 453.3196, found 453.3196.

Compound **11b**. $[\alpha]_D^{30}=-31.4$ (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3510 (br), 1455, 1415, 1240, 1045, 1005, 870, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.60 (q, $J=7.8$ Hz, 6H), 0.92 (t, $J=7.8$ Hz, 9H), 0.94 (t, $J=7.3$ Hz, 3H), 0.95 (t, $J=7.8$ Hz, 9H), 0.97 (d, $J=6.8$ Hz, 3H), 1.48 (m, 1H), 1.60 (br s, 3H), 1.65 (m, 1H), 1.82 (ddq, $J=3.4$, 9.8, 6.8 Hz, 1H), 2.01 (dq, $J=7.3$, 7.3 Hz, 2H), 2.19 (br s, 1H), 3.59 (d, $J=9.8$ Hz, 1H), 3.60–3.74 (m, 3H), 5.22 (br t, $J=7.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.1 (t, 3C), 6.8 (q, 3C), 6.9 (q, 3C), 10.0 (q), 10.9 (q), 13.7 (q), 20.7 (t), 32.7 (t), 43.4 (d), 61.8 (t), 72.4 (d), 81.3 (d), 129.5 (d), 135.4 (s); MS (FAB) *m/z* 453 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{50}NaO_3Si_2$ $[(M+Na)^+]$ 453.3196, found 453.3180.

4.1.11. Aldehydes 12a and 12b. To a stirred solution of oxalyl chloride (0.020 mL, 0.23 mmol) in CH_2Cl_2 (1.0 mL) cooled at −78 °C was added a 1.4 M solution of DMSO in CH_2Cl_2 (0.50 mL, 0.71 mmol) dropwise. The resulting solution was stirred at −78 °C for 5 min, and a solution of alcohol **11a** (63.0 mg, 0.147 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min, and triethylamine (0.20 mL, 1.43 mmol) was added. The resulting mixture was stirred at −78 °C for 40 min, warmed to 0 °C, and stirred for 40 min. The mixture was diluted with H_2O (3 mL) and extracted with hexane (3× 6 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–CH_2Cl_2 2:1) to give **12a** (47.5 mg, 75%) as a colorless oil. Using the same procedure as described above, **12b** (42.5 mg, 84%) was obtained from **11b** (50.8 mg, 0.118 mmol) as a colorless oil.

Compound **12a**. $[\alpha]_D^{27}=+4.2$ (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 2730, 1720, 1460, 1415, 1240, 1035, 1005, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.57 (q, $J=7.8$ Hz, 6H), 0.92 (d, $J=6.8$ Hz, 3H), 0.92 (t, $J=7.8$ Hz, 9H), 0.94 (t, $J=7.8$ Hz, 9H), 0.98 (t, $J=7.3$ Hz, 3H), 1.53 (br s, 3H), 1.62 (ddq, $J=3.4$, 7.3, 6.8 Hz, 1H), 1.95–2.13 (m, 2H), 2.59 (ddd, $J=2.4$, 6.4, 16.1 Hz, 1H), 2.64 (ddd, $J=2.4$, 6.4, 16.1 Hz, 1H), 3.97 (d, $J=7.3$ Hz, 1H), 4.13 (ddd, $J=3.4$, 6.4, 6.4 Hz, 1H), 5.35 (br t, $J=6.8$ Hz, 1H), 9.75 (t, $J=2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (t, 3C), 5.3 (t, 3C), 6.89 (q, 3C), 6.92 (q, 3C), 9.4 (q), 11.6 (q), 13.8 (q), 20.2 (t), 42.3 (d), 49.8 (t), 68.2 (d), 79.0 (d), 129.6 (d), 135.6 (s), 201.7 (d); MS (FAB) *m/z* 451 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{48}NaO_3Si_2$ $[(M+Na)^+]$ 451.3040, found 451.3020.

Compound **12b**. $[\alpha]_D^{30}=-31.2$ (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 2730, 1725, 1460, 1415, 1240, 1055, 1005, 870, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.56 (q, $J=7.8$ Hz, 6H), 0.92 (t, $J=7.8$ Hz, 9H), 0.94 (t, $J=7.3$ Hz, 3H), 0.94 (t, $J=7.8$ Hz, 9H), 0.96 (d, $J=6.8$ Hz, 3H), 1.61 (br s, 3H), 1.88 (ddq, $J=3.4$, 9.3, 6.8 Hz, 1H), 2.02 (dq, $J=7.3$, 7.3 Hz, 2H), 2.24 (ddd, $J=2.0$, 2.4, 15.6 Hz, 1H), 2.46 (ddd, $J=3.4$, 9.3, 15.6 Hz, 1H), 3.55 (d, $J=9.3$ Hz, 1H), 4.09 (ddd, $J=2.4$, 3.4, 9.3 Hz, 1H), 5.23 (br t, $J=7.3$ Hz, 1H), 9.72 (dd, $J=2.0$, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.0 (t, 3C), 6.8 (q, 3C), 6.9 (q, 3C), 10.0 (q), 11.0 (q), 13.7 (q), 20.7 (t), 43.4 (d), 45.6 (t), 68.2 (d), 81.2 (d), 129.8 (d), 135.2 (s), 202.6 (d); MS (FAB) *m/z* 451 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{48}NaO_3Si_2$ $[(M+Na)^+]$ 451.3040, found 451.3044.

4.1.12. Conjugated esters 13a and 13b. To a stirred solution of triethyl 2-phosphonopropionate (110 mg, 0.462 mmol) in DME (1.8 mL) cooled at 0 °C was added NaH (10.9 mg of 60% dispersion in mineral oil, 0.273 mmol). The resulting solution was stirred at 0 °C for 5 min and at room temperature for 20 min and re-cooled to −20 °C. A solution of aldehyde **12a** (47.0 mg, 0.110 mmol) in DME (1 mL) was added dropwise, and the mixture was stirred at −10 °C for 1 h. Saturated aqueous NH_4Cl (4 mL) was added, and the mixture was extracted with hexane (3× 6 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 10 g, hexane–ether 100:1) to give **13a** (49.7 mg, 88%) as a colorless oil along with 32*Z* isomer of **13a** (4.1 mg, 7%). Using the same procedure as described above, **13b** (42.5 mg, 86%) was obtained from **12b** (41.5 mg, 0.097 mmol) as a colorless oil along with with 32*Z* isomer of **13b** (6.2 mg, 12%).

Compound **13a**. $[\alpha]_D^{26}=+18.8$ (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1460, 1370, 1280, 1220, 1095, 1005, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, $J=7.8$ Hz, 6H), 0.57 (q, $J=7.8$ Hz, 6H), 0.92 (d, $J=6.4$ Hz, 3H), 0.92 (t, $J=7.8$ Hz, 9H), 0.95 (t, $J=7.8$ Hz, 9H), 0.98 (t, $J=7.8$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.47 (br s, 3H), 1.56 (m, 1H), 1.83 (br s, 3H), 1.99 (ddq, $J=7.8$, 7.8, 14.6 Hz, 1H), 2.07 (ddq, $J=7.8$, 7.8, 14.6 Hz, 1H), 2.31 (ddd, $J=5.9$, 6.8, 14.6 Hz, 1H), 2.39 (ddd, $J=8.3$, 8.3, 14.6 Hz, 1H), 3.69 (ddd, $J=2.4$, 5.9, 8.3 Hz, 1H), 3.88 (d, $J=8.8$ Hz, 1H), 4.11–4.23 (m, 2H), 5.33 (br t, $J=6.8$ Hz, 1H), 6.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.5 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 9.0 (q), 10.9 (q), 12.6 (q), 13.8 (q), 14.2 (q), 20.8 (t), 35.2 (t), 40.9 (d), 60.4 (t), 71.4 (d), 80.4 (d), 129.0 (s), 130.0 (d), 135.7 (s), 138.8 (d), 167.9 (s); MS (FAB) *m/z* 535 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{56}NaO_4Si_2$ $[(M+Na)^+]$ 535.3615, found 535.3607.

32Z Isomer of **13a**. $[\alpha]_D^{30}=+1.4$ (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 1705, 1645, 1455, 1380, 1235, 1005, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52–0.61 (m, 12H), 0.90 (d, $J=6.8$ Hz, 3H), 0.92 (t, $J=7.8$ Hz, 9H), 0.95 (t, $J=7.8$ Hz, 9H), 0.97 (t, $J=7.3$ Hz, 3H), 1.30 (t, $J=7.3$ Hz, 3H), 1.48 (br s, 3H), 1.56 (m, 1H), 1.88 (d, $J=1.5$ Hz, 3H), 1.99 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 2.06 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 2.6 1–2.77 (m, 2H), 3.65 (ddd, $J=2.4$, 5.4, 8.3 Hz, 1H), 3.88 (d, $J=8.8$ Hz, 1H), 4.19 (q, $J=7.3$ Hz, 2H), 5.33 (br t, $J=7.3$ Hz, 1H), 5.82 (tq, $J=6.4$, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.5 (t, 3C), 6.9 (q, 3C), 7.0 (q, 3C), 8.9 (q), 11.1 (q), 13.9 (q), 14.2 (q), 20.8 (t), 20.9 (q), 35.6 (t), 40.7 (d), 60.1 (t), 72.0 (d), 80.2 (d), 128.5 (s), 129.7 (d), 135.6 (s), 138.3 (d), 167.9 (s); MS (FAB) *m/z* 535 $(M+Na)^+$.

Compound **13b**. $[\alpha]_D^{27}=-38.2$ (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1460, 1370, 1285, 1240, 1050, 1010 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 0.54 (q, J=7.8 Hz, 6H), 0.56 (q, J=7.8 Hz, 6H), 0.92 (t, J=7.8 Hz, 9H), 0.93 (t, J=7.8 Hz, 9H), 0.95 (t, J=7.3 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 1.27 (t, J=7.3 Hz, 3H), 1.59 (br s, 3H), 1.81 (d, J=1.0 Hz, 3H), 1.85 (ddq, J=3.4, 9.3, 6.8 Hz, 1H), 2.01 (dq, J=7.3, 7.3 Hz, 2H), 2.11 (ddd, J=2.9, 7.3, 15.1 Hz, 1H), 2.21 (ddd, J=7.3, 9.3, 15.1 Hz, 1H), 3.57 (ddd, J=2.9, 3.4, 9.3 Hz, 1H), 3.65 (d, J=9.3 Hz, 1H), 4.17 (q, J=7.3 Hz, 2H), 5.25 (br t, J=7.3 Hz, 1H), 6.78 (ddq, J=7.3, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.0 (t, 3C), 6.8 (q, 3C), 6.9 (q, 3C), 10.1 (q), 10.9 (q), 12.6 (q), 13.7 (q), 14.2 (q), 20.8 (t), 30.8 (t), 43.9 (d), 60.3 (t), 71.8 (d), 81.3 (d), 128.2 (s), 129.6 (d), 135.7 (s), 140.6 (d), 168.1 (s); MS (FAB) m/z 535 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{56}NaO_4Si_2$ $[(M+Na)^+]$ 535.3615, found 535.3605.

32Z isomer of **13b**. $[\alpha]_D^{27}=-46.9$ (c 0.58, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1455, 1415, 1375, 1050, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, J=7.8 Hz, 12H), 0.91 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.8 Hz, 9H), 0.93 (t, J=7.8 Hz, 9H), 0.95 (d, J=7.3 Hz, 3H), 1.31 (t, J=7.3 Hz, 3H), 1.56 (br s, 3H), 1.81 (m, 1H), 1.88 (d, J=1.0 Hz, 3H), 1.99 (dq, J=7.3, 7.3 Hz, 2H), 2.48–2.61 (m, 2H), 3.52 (ddd, J=3.9, 3.9, 7.8 Hz, 1H), 3.67 (d, J=9.3 Hz, 1H), 4.19 (q, J=7.3 Hz, 2H), 5.24 (br t, J=7.3 Hz, 1H), 5.97 (tq, J=6.8, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 5.1 (t, 3C), 6.87 (q, 3C), 6.89 (q, 3C), 10.1 (q), 10.9 (q), 13.7 (q), 14.3 (q), 20.8 (t), 20.9 (q), 31.6 (t), 43.8 (d), 60.0 (t), 72.3 (d), 81.0 (d), 127.3 (s), 129.3 (d), 135.5 (s), 141.5 (d), 168.0 (s); MS (FAB) m/z 535 $(M+Na)^+$.

4.1.13. Tris(*p*-bromobenzoates) 3a and 3b. To a stirred solution of conjugated ester **13a** (15.2 mg, 0.030 mmol) in CH_2Cl_2 (0.5 mL) cooled at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (0.12 mL, 0.12 mmol), and the mixture was stirred at −78 °C for 1.5 h. The reaction was quenched by addition of methanol (0.05 mL) and saturated aqueous Na/K tartrate (5 mL), and the mixture was stirred at room temperature for 1 h and extracted with EtOAc (3×6 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated to give a crude alcohol (14.1 mg) as a colorless oil, which was employed in the next experiment without purification. A solution of the crude alcohol (14.1 mg) in a 1:3:5 mixture of HF·pyridine, pyridine, and THF (0.5 mL) was stirred at room temperature for 45 min. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated to give a crude triol (8.9 mg) as a colorless oil, which was employed in the next experiment without purification. To a stirred solution of the crude triol (8.9 mg) in pyridine (0.2 mL) was added *p*-bromobenzoyl chloride (80.0 mg, 0.37 mmol). The mixture was stirred at room temperature for 13 h, diluted with hexane (1 mL), and filtered through a cotton plug, and the residue was washed with hexane (5 mL) The filtrate and the washings were combined and treated with 5% aqueous $NaHCO_3$ (3 mL) at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with hexane (2× 6 mL). The organic layer and the extracts were combined, washed with 5% aqueous $NaHCO_3$ (2×1 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–CH_2Cl_2 3:1→2:1→1:1) to give **3a** (20.7 mg, 88% from **13a**) as colorless crystals. Using the same procedure as described above, **3b** (13.5 mg, 90%) was obtained from **13b** (7.0 mg, 0.014 mmol) as a colorless oil.

Compound **3a**. mp 106.0–107.5 °C (hexane–CH_2Cl_2). $[\alpha]_D^{29}=+2.8$ (c 0.28, $CHCl_3$); CD (MeOH); λ_{ext} 253 ($\Delta\varepsilon$ +45.0), 236 nm ($\Delta\varepsilon$ −52.1); UV (MeOH) λ_{max} 244 nm (ε 54500); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1115, 1105, 1010, 940 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.81 (t, J=7.3 Hz, 3H), 1.17 (d, J=7.0 Hz, 3H), 1.56 (br s, 3H), 1.58 (br s, 3H), 1.82 (ddq, J=7.3, 15.0, 7.3 Hz, 1H), 1.91 (ddq, J=7.3, 15.0, 7.3 Hz, 1H), 2.21–2.28 (m, 2H), 2.61 (ddd, J=7.3, 7.3, 14.3 Hz, 1H), 4.54 (s, 2H), 5.28 (ddd, J=2.9, 6.6, 7.3 Hz, 1H), 5.43 (br ddq, J=7.3, 7.3, 1.1 Hz, 1H), 5.52 (br dd, J=7.3 Hz, 1H), 5.71 (d, J=8.1 Hz, 1H), 7.11–7.18 (m, 6H), 7.70–7.78 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9 (q), 12.0 (q), 13.6 (q), 14.3 (q), 20.8 (t), 30.1 (t), 37.1 (d), 70.2 (t), 74.4 (d), 81.6 (d), 123.4 (d), 128.0 (s), 128.11 (s), 128.12 (s), 129.0 (s), 129.1 (s), 129.3 (s), 129.8 (s), 130.9 (d, 2C), 131.02 (d, 2C), 131.04 (d, 2C), 131.70 (d, 2C), 131.72 (d, 2C), 131.8 (d, 2C), 132.6 (d), 133.6 (s), 164.8 (s), 164.9 (s), 165.5 (s); MS (FAB) m/z 810 $(M+Na)^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ $[(M+Na)^+]$ 810.9881, found 810.9853. Anal. calcd for $C_{35}H_{35}Br_3O_6$: C, 53.10; H, 4.46. Found C, 53.12; H, 4.42.

Compound **3b**. $[\alpha]_D^{29}=-0.4$ (c 1.04, $CHCl_3$); CD (MeOH) λ_{ext} 253 ($\Delta\varepsilon$ +191), 237 nm ($\Delta\varepsilon$ −88.8); UV (MeOH) λ_{max} 244 nm (ε 59400); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1105, 1100, 850 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (t, J=7.3 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.52 (s, 3H), 1.70 (s, 3H), 1.88 (dq, J=7.3, 7.3 Hz, 2H), 2.29 (ddd, J=3.7, 7.0, 15.2 Hz, 1H), 2.32–2.44 (m, 2H), 4.47 (d, J=12.5 Hz, 1H), 4.52 (d, J=12.5 Hz, 1H), 5.28 (ddd, J=3.7, 5.5, 9.2 Hz, 1H), 5.47 (br dd, J=7.0, 7.0 Hz, 1H), 5.58 (br t, J=7.3 Hz, 1H), 5.69 (d, J=6.6 Hz, 1H), 7.08 (d, J=8.4 Hz, 2H), 7.14–7.17 (m, 4H), 7.65 (d, J=8.4 Hz, 2H), 7.70 (d, J=8.4 Hz, 2H), 7.78 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6 (q), 12.5 (q), 13.8 (q), 14.3 (q), 20.9 (t), 28.6 (t), 37.9 (d), 70.1 (t), 74.9 (d), 79.4 (d), 124.1 (d), 128.02 (s), 128.04 (s), 129.01 (s), 129.04 (s), 129.3 (s), 130.6 (s), 130.92 (d, 2C), 130.97 (d, 2C), 131.02 (s), 131.05 (d, 2C), 131.64 (d, 2C), 131.65 (d, 2C), 131.7 (d, 2C), 132.9 (d), 133.6 (s), 164.7 (s), 165.1 (s), 165.4 (s); MS (FAB) m/z 810 $(M+Na)^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ $[(M+Na)^+]$ 810.9881, found 810.9885.

4.1.14. Diols 14a and 14b. A solution of conjugated ester **13a** (29.3 mg, 0.057 mmol) in a 1:3:5 mixture of HF·pyr-pyridine, pyridine, and THF (0.5 mL) was stirred at room temperature for 40 min. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (3×4 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane–ether 3:1→2:1) to give **14a** (15.9 mg, 98%) as a colorless oil. Using the same procedure as described above, **14b** (22.5 mg, 98%)

was obtained from **13b** (41.8 mg, 0.081 mmol) as a colorless oil.

Compound **14a**. $[\alpha]_D^{27}=+3.3$ (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3600, 3490 (br), 1700, 1650, 1460, 1280, 1250, 1105, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, $J=$ 6.8 Hz, 3H), 0.98 (t, $J=7.3$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.54 (br s, 3H), 1.68 (m, 1H), 1.86 (d, $J=1.0$ Hz, 3H), 2.06 (dq, $J=7.3$, 7.3 Hz, 2H), 2.27 (br s, 1H), 2.31 (ddd, $J=$ 7.3, 7.3, 15.1 Hz, 1H), 2.46 (m, 1H), 3.01 (br s, 1H), 3.98 (m, 1H), 4.17 (m, 1H), 4.18 (q, $J=7.3$ Hz, 2H), 5.45 (m, 1H), 6.81 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (q), 12.6 (q), 13.4 (q), 14.1 (q), 14.2 (q), 20.7 (t), 34.6 (t), 38.8 (d), 60.5 (t), 74.8 (d), 80.4 (d), 126.8 (d), 129.7 (s), 134.7 (s), 138.1 (d), 168.0 (s); MS (FAB) *m/z* 307 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{28}NaO_4$ $[(M+Na)^+]$ 307.1885, found 307.1902.

Compound **14b**. $[\alpha]_D^{27}=-0.3$ (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3600, 3480 (br), 1700, 1650, 1370, 1280, 1085, 1035, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J=$ 7.3 Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.54 (br s, 3H), 1.73 (m, 1H), 1.86 (br s, 3H), 2.06 (dq, $J=7.3$, 7.3 Hz, 2H), 2.40 (br s, 1H), 2.43 (m, 1H), 2.49 (ddd, $J=7.3$, 7.3, 15.1 Hz, 1H), 2.97 (br d, $J=2.0$ Hz, 1H), 3.79 (m, 1H), 4.18 (q, $J=7.3$ Hz, 2H), 4.34 (br s, 1H), 5.43 (br t, $J=7.3$ Hz, 1H), 6.84 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (q), 12.7 (q), 13.6 (q), 14.1 (q), 14.2 (q), 20.8 (t), 34.6 (t), 39.4 (d), 60.5 (t), 74.4 (d), 75.5 (d), 126.7 (d), 129.7 (s), 134.6 (s), 138.3 (d), 168.0 (s); MS (FAB) *m/z* 307 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{28}NaO_4$ $[(M+Na)^+]$ 307.1885, found 307.1870.

4.1.15. Enones 15a and 15b. To a stirred solution of diol **14a** (15.9 mg, 0.056 mmol) in CH_2Cl_2 (0.4 mL) was added MnO_2 (23.4 mg, 0.27 mmol), and the mixture was stirred at room temperature for 4 h. Manganese dioxide (107 mg, 1.24 mmol) was added, and the mixture was stirred at room temperature for 4 h. Further, MnO_2 (110 mg, 1.28 mmol) was added, and the mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (2 mL) and filtered through a pad of Celite, and the residue was washed with EtOAc (30 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, benzene–EtOAc 10:1→8:1) to give **15a** (10.9 mg, 69%) as a colorless oil. Using the same procedure as described above, **15b** (7.2 mg, 60%) was obtained from **15b** (12.0 mg, 0.042 mmol) as a colorless oil.

Compound **15a**. $[\alpha]_D^{27}=-11.4$ (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1700, 1650, 1640 (sh), 1460, 1370, 1280, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, $J=$ 7.3 Hz, 3H), 1.17 (d, $J=7.3$ Hz, 3H), 1.29 (t, $J=7.3$ Hz, 3H), 1.77 (br s, 3H), 1.86 (d, $J=1.0$ Hz, 3H), 2.28 (dq, $J=$ 7.3, 7.3 Hz, 2H), 2.31 (m, 1H), 2.43 (ddd, $J=7.3$, 7.3, 15.1 Hz, 1H), 3.23 (dq, $J=3.4$, 7.3 Hz, 1H), 3.33 (d, $J=$ 2.0 Hz, 1H), 4.02 (m, 1H), 4.19 (q, $J=7.3$ Hz, 2H), 6.62 (br t, $J=7.3$ Hz, 1H), 6.80 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2 (q), 11.8 (q), 12.7 (q), 13.0 (q), 14.3 (q), 22.6 (t), 33.6 (t), 42.2 (d), 60.5 (t), 70.9 (d), 129.9 (s), 135.6 (s), 137.6 (d), 145.8 (d), 167.9 (s), 207.2 (s); MS (FAB) *m/z* 305 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{26}NaO_4$ $[(M+Na)^+]$ 305.1729, found 305.1700.

Compound **15b**. $[\alpha]_D^{27}=-10.9$ (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 3600, 3480 (br), 1700, 1650, 1640, 1455, 1370, 1275, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, $J=$ 7.3 Hz, 3H), 1.20 (d, $J=6.8$ Hz, 3H), 1.29 (t, $J=7.3$ Hz, 3H), 1.77 (d, $J=1.0$ Hz, 3H), 1.79 (d, $J=1.0$ Hz, 3H), 2.28 (dq, $J=7.3$, 7.3 Hz, 2H), 2.35 (ddd, $J=7.3$, 7.8, 15.3 Hz, 1H), 2.41 (ddd, $J=7.3$, 7.8, 15.3 Hz, 1H), 3.33 (dq, $J=5.4$, 6.8 Hz, 1H), 3.38 (br s, 1H), 3.87 (m, 1H), 4.19 (q, $J=$ 7.3 Hz, 2H), 6.63 (br t, $J=7.3$ Hz, 1H), 6.82 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (q), 12.6 (q), 12.9 (q), 14.3 (q), 16.4 (q), 22.6 (t), 34.8 (t), 42.9 (d), 60.5 (t), 73.7 (d), 129.7 (s), 136.4 (s), 137.8 (d), 146.0 (d), 167.9 (s), 207.3 (s); MS (FAB) *m/z* 305 $(M+Na)^+$; HRMS (FAB) calcd for $C_{16}H_{26}NaO_4$ $[(M+Na)^+]$ 305.1729, found 305.1700.

4.1.16. Silyl ethers 16a and 16b. To a stirred solution of enone **15a** (10.4 mg, 0.037 mmol) in DMF (0.2 mL) were added imidazole (20.8 mg, 0.306 mmol) and triethylsilyl chloride (0.015 mL, 0.089 mmol). The mixture was stirred at room temperature for 2 h and diluted with H_2O (3 mL), and the resulting mixture was extracted with hexane (3×2 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (1 g, hexane–ether 8:1) to give **16a** (12.4 mg, 85%) as a colorless oil. Using the same procedure as described above, **16b** (8.7 mg, 89%) was obtained from **15b** (7.0 mg, 0.025 mmol) as a colorless oil.

Compound **16a**. $[\alpha]_D^{28}=-14.9$ (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1640 (sh), 1480, 1370, 1250, 1095, 1010, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (q, $J=$ 7.8 Hz, 6H), 0.96 (t, $J=7.8$ Hz, 9H), 1.04 (t, $J=7.3$ Hz, 3H), 1.11 (d, $J=6.8$ Hz, 3H), 1.28 (t, $J=7.3$ Hz, 3H), 1.71 (d, $J=1.5$ Hz, 3H), 1.73 (d, $J=1.0$ Hz, 3H), 2.23 (dq, $J=$ 7.3, 7.3 Hz, 2H), 2.25–2.31 (m, 2H), 3.30 (dq, $J=7.3$, 6.8, 1H), 4.08 (dt, $J=7.3$, 4.9 Hz, 1H), 4.12–4.23 (m, 2H), 6.55 (tq, $J=7.3$, 1.0 Hz, 1H), 6.84 (ddq, $J=7.3$, 7.3, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1 (t, 3C), 6.9 (q, 3C), 11.2 (q), 12.6 (q), 13.0 (q), 14.3 (q), 15.5 (q), 22.5 (t), 35.3 (t), 44.9 (d), 60.4 (t), 73.6 (d), 129.4 (s), 136.3 (s), 138.0 (d), 144.5 (d), 167.8 (s), 204.8 (s); MS (FAB) *m/z* 419 $(M+Na)^+$; HRMS (FAB) calcd for $C_{22}H_{40}NNaO_4Si$ $[(M+Na)^+]$ 419.2594, found 419.2574.

Compound **16b**. $[\alpha]_D^{27}=+51.6$ (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 1700, 1655, 1640 (sh), 1460, 1370, 1250, 1080, 1005, 945 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (q, $J=$ 7.8 Hz, 6H), 0.89 (t, $J=7.8$ Hz, 9H), 0.96 (d, $J=6.8$ Hz, 3H), 1.09 (t, $J=7.3$ Hz, 3H), 1.29 (t, $J=7.3$ Hz, 3H), 1.76 (d, $J=1.0$ Hz, 3H), 1.83 (br s, 3H), 2.26 (dq, $J=7.3$, 7.3 Hz, 2H), 2.30–2.43 (m, 2H), 3.41 (dq, $J=7.3$, 6.8 Hz, 1H), 4.12 (ddd, $J=3.9$, 5.9, 7.3 Hz, 1H), 4.20 (q, $J=7.3$ Hz, 2H), 6.63 (br t, $J=7.3$ Hz, 1H), 6.92 (ddq, $J=7.3$, 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9 (t, 3C), 6.8 (q, 3C), 11.5 (q), 12.7 (q), 13.1 (q), 13.6 (q), 14.3 (q), 22.5 (t), 33.4 (t), 45.1 (d), 60.4 (t), 73.3 (d), 129.2 (s), 136.8 (s), 138.4 (d), 144.5 (d), 168.0 (s), 204.5 (s); MS (FAB) *m/z* 419 (M+

Na)$^+$; HRMS (FAB) calcd for $C_{22}H_{40}NNaO_4Si$ [(M+Na)$^+$] 419.2594, found 419.2585.

4.1.17. Tris(*p*-bromobenzoates) 3c and 3d. To a stirred solution of silyl ether **16a** (5.1 mg, 0.013 mmol) in ethanol (0.2 mL) cooled at −78 °C were added $CeCl_3\cdot 7H_2O$ (26.6 mg, 0.071 mmol) and $NaBH_4$ (2.1 mg, 0.056 mmol), and the mixture was stirred at −78 °C for 1 h and −23 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL), and the resulting mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–ether 15:1→10:1) to give a diastereomeric mixture of alcohols (4.9 mg, α:β=6:1) as a colorless oil, which was employed in the next experiment without separation of the diastereomers. A solution of the diastereomeric mixture of alcohols (4.9 mg, α:β=6:1) in a 1:3:5 mixture of HF·pyr-pyridine, pyridine, and THF (0.5 mL) was stirred at room temperature for 30 min. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (3×5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated to give a crude diol (4.3 mg) as a colorless oil, which was employed in the next experiment without purification. To a stirred solution of crude diol (4.3 mg) in CH_2Cl_2 (0.3 mL) cooled at −78 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (0.08 mL, 0.078 mmol), and the mixture was stirred at −23 °C for 1.5 h. The reaction was quenched by addition of MeOH (0.05 mL) and saturated aqueous Na/K tartrate (4 mL), and the mixture was stirred at room temperature for 1 h and extracted with EtOAc (3 × 8 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ether 9:1→5:1) to give a crude triol (4.0 mg) as a colorless oil, which was employed in the next experiment without purification. To a stirred solution of the crude triol (4.0 mg) in pyridine (0.2 mL) was added *p*-bromobenzoyl chloride (80.0 mg, 0.37 mmol). The mixture was stirred at room temperature for 12 h, diluted with hexane (2 mL), and filtered through a cotton plug, and the residue was washed with hexane (5 mL) The filtrate and the washings were combined and diluted with 5% aqueous $NaHCO_3$ (3 mL), and the mixture was stirred at room temperature for 1 h. The layers were separated, and the aqueous layer was extracted with hexane (3×4 mL). The organic layer and the extracts were combined, washed with 5% aqueous $NaHCO_3$ (2×1 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–CH_2Cl_2 2:1→1:1→1:2) to give **3c** (5.5 mg, 57% from **16a**) as colorless crystals along with **3a** (1.0 mg, 10% from **16a**). Using the same procedure as described above, **3d** (6.6 mg, 53% from **16b**) was obtained from **16b** (6.3 mg, 0.016 mmol) as a colorless oil along with **3b** (1.2 mg, 9% from **16b**).

Compound **3c**. $[\alpha]_D^{29}=-10.6$ (*c* 0.36, $CHCl_3$); CD (MeOH); λ_{ext} 252 (Δε −172), 236 nm (Δε +126); UV (MeOH) λ_{max} 244 nm (ε 52100); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1115, 1100, 1010 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.82 (t, *J*=7.3 Hz, 3H), 0.98 (d, *J*=6.9 Hz, 3H), 1.55 (s, 6H), 1.86 (dq, *J*=7.3, 7.3 Hz, 2H), 2.17 (ddd, *J*=6.6, 7.3, 14.3 Hz, 1H), 2.28 (ddq, *J*=2.2, 9.9, 6.9 Hz, 1H), 2.60 (ddd, *J*=7.3, 7.7, 14.3 Hz, 1H), 4.49 (d, *J*=12.5 Hz, 1H), 4.53 (d, *J*=12.5 Hz, 1H), 5.46 (m, 1H), 5.54 (d, *J*=9.9 Hz, 1H), 5.63 (ddd, *J*=2.2, 6.6, 7.7 Hz, 1H), 5.63 (m, 1H), 7.07–7.12 (m, 4H), 7.14–7.18 (m, 2H), 7.66–7.77 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7 (q), 11.3 (q), 13.7 (q), 14.3 (q), 20.9 (t), 30.4 (t), 37.2 (d), 70.2 (t), 72.7 (d), 81.0 (d), 124.0 (d), 127.8 (s), 127.9 (s), 128.1 (s), 129.0 (s), 129.2 (s), 129.5 (s), 130.2 (s), 130.97 (d, 2C), 130.99 (d, 2C), 131.0 (d, 2C), 131.5 (d, 2C), 131.6 (d, 2C), 131.7 (d, 2C), 133.2 (d), 133.6 (s), 164.7 (s), 165.0 (s), 165.5 (s); MS (FAB) *m/z* 810 (M+Na)$^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ [(M+Na)$^+$] 810.9881, found 810.9884.

Compound **3d**. $[\alpha]_D^{30}=-5.4$ (*c* 0.37, $CHCl_3$); CD (MeOH); λ_{ext} 254 (Δε −57.0), 236 nm (Δε +91.1); UV (MeOH) λ_{max} 244 nm (ε 61400); IR ($CHCl_3$) 1715, 1590, 1485, 1395, 1270, 1115, 1105, 1010, 850 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 0.83 (t, *J*=7.3 Hz, 3H), 0.86 (d, *J*=7.3 Hz, 3H), 1.50 (s, 3H), 1.54 (s, 3H), 1.80–1.89 (m, 2H), 2.44–2.40 (m, 2H), 2.58 (ddq, *J*=4.4, 9.9, 7.3 Hz, 1H), 4.42 (d, *J*=12.5 Hz, 1H), 4.48 (d, *J*=12.5 Hz, 1H), 5.49 (br t, *J*=7.3 Hz, 1H), 5.57 (d, *J*=9.9 Hz, 1H), 5.58–5.63 (m, 2H), 7.11–7.17 (m, 6H), 7.61 (d, *J*=8.4 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 2H), 7.90 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (q), 11.6 (q), 13.7 (q), 14.2 (q), 20.9 (t), 28.0 (t), 37.8 (d), 70.1 (t), 74.8 (d), 81.7 (d), 124.4 (d), 128.0 (s), 128.1 (s), 128.2 (s), 129.0 (s), 129.1 (s), 129.2 (s), 130.2 (s), 130.9 (d, 2C), 131.0 (d, 2C), 131.1 (d, 2C), 131.6 (d, 2C), 131.7 (d, 2C), 131.8 (d, 2C), 132.8 (s), 133.4 (d), 164.9 (s), 165.1 (s), 165.4 (s); MS (FAB) *m/z* 810 (M+Na)$^+$; HRMS (FAB) calcd for $C_{35}H_{35}^{79}Br_3NaO_6$ [(M+Na)$^+$] 810.9881, found 810.9894.

4.1.18. Dipeptide 21. To a stirred solution of *N*-methylglycine *tert*-butyl ester hydrochloride (1.09 g, 5.08 mmol) and *N*-benzyloxycarbonyl-*N*-methyl-D-leucine (1.56 g, 5.60 mmol) in DMF (5 mL) cooled at 0 °C were added triethylamine (2.3 mL, 17 mmol) and diethylphosphoryl cyanide (0.84 mL, 2.20 mmol), successively. The reaction mixture was stirred at 0 °C for 3.5 h, diluted with EtOAc–benzene (1:2, 15 mL), washed with 5% aqueous citric acid (5 mL), saturated aqueous $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (62 g, hexane–EtOAc 6:1→3:1) to give **21** (2.03 g, 98%) as a colorless oil. $[\alpha]_D^{33}=+68.8$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1735, 1680, 1655, 1435, 1310, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78–0.98 (m, 6H), 1.42–1.76 (m, 12H), 2.78 (s, 0.3H), 2.84 (s, 0.7H), 2.89 (s, 1.9H), 2.91 (s, 0.5H), 2.94 (s, 1.0H), 3.08 (s, 1.6H), 3.87–4.03 (m, 2H), 4.74–5.23 (m, 3H), 7.28–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (q), 23.0 (q), 24.5 (d), 28.0 (q, 3C), 29.2 (q), 36.1 (q), 37.7 (t), 50.6 (t), 52.7 (d), 67.3 (t), 81.7 (s), 127.6 (d, 2C), 127.9 (d), 128.4 (d, 2C), 136.6 (s), 156.4 (s), 168.0 (s), 171.3 (s); MS (FAB) *m/z* 429 (M+Na)$^+$, 407 (M+H)$^+$; HRMS (FAB) calcd for $C_{22}H_{35}N_2O_5$ [(M+H)$^+$] 407.2546, found 407.2553.

4.1.19. Tripeptide 22. A mixture of dipeptide **21** (1.22 g,

3.00 mmol) and 10% Pd on carbon (244 mg) in EtOH (3 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the residue was washed with chloroform. The filtrate and the washings were combined and concentrated to give crude amine (782 mg) as a colorless oil. To a stirred solution of the crude amine (782 mg) and *N*-benzyloxycarbonyl-L-valine (1.41 g, 5.60 mmol) in CH_2Cl_2 (3.0 mL) cooled at 0 °C were added PyBOP (3.21 g, 6.17 mmol) and diisopropylethylamine (2.4 mL, 14 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with EtOAc (40 mL), washed with 10% aqueous citric acid (2×10 mL), H_2O (5 mL), saturated aqueous $NaHCO_3$ (2× 8 mL), H_2O (5 mL), and brine (8 mL) successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography (i. silica gel 150 g, hexane–EtOAc 4:1→3:1; ii. alumina 20 g, benzene–EtOAc 3:1) to give tripeptide **22** (1.31 g, 92% from **21**) as a colorless oil. $[\alpha]_D^{29}=+82.6$ (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3430, 1735, 1720, 1635, 1505, 1410, 1230, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, $J=6.8$ Hz, 1.05H), 0.82 (d, $J=6.3$ Hz, 1.05H), 0.86 (d, $J=6$,8 Hz, 1.95H), 0.85–0.98 (m, 7.95H), 1.40 (s, 9H), 1.30–1.73 (m, 3H), 1.94 (m, 1H), 2.84 (s, 1.05H), 2.91 (s, 1.95H), 3.00 (s, 3H), 3.70 (d, $J=$ 17.1 Hz, 0.35H), 3.84 (d, $J=16.6$ Hz, 0.65H), 3.95 (d, $J=$ 16.6 Hz, 0.65H), 4.57–4.98 (m, 1.35H), 5.02 (d, $J=12.7$ Hz, 0.35H), 5.04 (s, 1.3H), 5.06 (d, $J=12.7$ Hz, 0.35H), 5.31 (dd, $J=5.9$, 8.8 Hz, 0.35H), 5.49 (dd, $J=6.3$, 8.8 Hz, 0.65H), 5.61 (d, $J=8.8$ Hz, 1H), 7.22–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 [16.4] (q), 19.5 [19.6] (q), 22.0 [21.8] (q), 22.9 [23.0] (q), 24.5 [24.3] (d), 27.9 [27.8] (q, 3C), 30.4 [30.2] (q), 30.9 [31.0] (d), 36.0 [34.9] (q), 37.7 [37.9] (t), 50.6 [51.9] (t), 50.8 [49.8] (d), 55.78 [55.81] (d), 66.57 [66.60] (t), 81.5 [82.0] (s), 127.78 [127.82] (d, 2C), 127.85 [127.88] (d), 128.28 [128.30] (d, 2C), 136.34 [136.29] (s), 156.2 [156.1] (s), 167.7 [168.2] (s), 170.6 [170.7] (s), 171.7 [171.8] (s). The minor counterparts of doubled signals in the ratio of 1.9:1 are in brackets; MS (FAB) *m*/*z* 528 $(M+Na)^+$; HRMS (FAB) calcd for $C_{27}H_{43}N_3NaO_6$ $[(M+Na)^+]$ 528.3050, found 528.3049.

4.1.20. Tetrapeptide 23. A mixture of tripeptide **23** (3.56 g, 7.05 mmol) and 10% Pd on carbon (437 mg) in EtOH (20 mL) was stirred under a hydrogen atmosphere at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOH. The filtrate and the washings were combined and concentrated to give a crude amine (2.67 g) as a colorless oil. To a stirred solution of the crude amine (2.67 g), *allo*-D-isoleucic acid sodium salt (1.19 g, 7.78 mmol), and 1-hydroxybenzotriazole (1.88 g, 13.9 mmol) in DMF (14 mL) cooled at 0 °C was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (2.55 g, 11.7 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with EtOAc (150 mL), washed with 5% aqueous $NaHCO_3$ (20 mL), 10% aqueous citric acid (20 mL), H_2O (15 mL), and brine (20 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, benzene–acetone 6:1→3:1) to give **23** (3.25 g, 95% from **22**) as colorless crystals. mp 100.5–101.0 °C (hexane–EtOAc). $[\alpha]_D^{28}=+$ 58.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 3410, 1735, 1635, 1505, 1465, 1235, 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.79 (d, $J=6.9$ Hz, 1.95H), 0.82 (d, $J=6.8$ Hz, 1.05H), 0.86–1.04 (m, 15H), 1.18–1.90 (m, 6H), 1.45 (s, 3.15H), 1.47 (s, 5.85H), 2.05 (m, 1H), 2.77 (d, $J=5.6$ Hz, 0.65H), 2.79 (d, $J=5.6$ Hz, 0.35H), 2.90 (s, 1.05H), 3.00 (s, 1.95H), 3.06 (s, 3H), 3.72 (d, $J=18.2$ Hz, 0.35H), 3.92 (d, $J=16.8$ Hz, 0.65H), 4.00 (d, $J=16.8$ Hz, 0.65H), 4.05 (dd, $J=2.6$, 5.6 Hz, 1H), 4.54 (d, $J=18.2$ Hz, 0.35H), 4.84 (dd, $J=5.3$, 8.9 Hz, 0.35H), 4.90 (dd, $J=5.3$, 8.9 Hz, 0.65H), 5.37 (dd, $J=5.9$, 8.9 Hz, 0.35H), 5.55 (dd, $J=6.3$, 8.9 Hz, 0.65H), 6.81 (d, $J=8.9$ Hz, 0.35H), 6.88 (d, $J=8.9$ Hz, 0.65H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 [11.9] (q), 12.7 [12.6] (q), 17.25 [17.21] (q), 19.7 (q), 22.2 [22.0] (q), 22.9 [23.0] (q), 24.6 [24.5] (d), 26.2 [26.3] (t), 28.0 [27.9] (q, 3C), 30.7 [30.4] (q), 31.2 [31.0] (d), 36.0 [35.0] (q), 37.8 [37.9] (t), 38.6 [38.8] (d), 50.7 [52.0] (t), 51.1 [50.0] (d), 53.5 [53.8] (d), 73.9 (d), 81.8 [82.3] (s), 167.8 [168.4] (s), 170.5 [170.7] (s), 171.8 [172.0] (s), 173.5 [173.7] (s). The minor counterparts of doubled signals in the ratio of 1.9:1 are in brackets; MS (FAB) *m*/*z* 508 $(M+Na)^+$; HRMS (FAB) calcd for $C_{25}H_{47}N_3NaO_6$ $[(M+Na)^+]$ 508.3362, found 508.3386. Anal. calcd for $C_{25}H_{47}N_3O_6$: C, 61.80; H, 9.75; N, 8.65. Found C, 61.81; H, 10.0; N, 8.56.

4.1.21. Carboxylic acid 24. To a stirred solution of tetrapeptide **23** (181 mg, 0.373 mmol) in THF (4.0 mL) cooled at 0 °C were added 2,6-lutidine (0.26 mL, 2.23 mmol) and trimethylsilyl triflate (0.29 mL, 1.50 mmol), successively. The reaction mixture was stirred at 0 °C for 3 h, diluted with 1 M HCl (5 mL), and extracted with CH_2Cl_2 (5×8 mL). The extracts were combined, washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, $CHCl_3$–MeOH 100:1→60:1→40:1→20:1) to give carboxylic acid **24** (160 mg, 100%) as a colorless powder. $[\alpha]_D^{28}=+116$ (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3400, 3300 (br), 1730, 1640, 1520, 1465, 1410, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, $J=6.8$ Hz, 1.95H), 0.83 (d, $J=6.8$ Hz, 1.05H), 0.88–0.98 (m, 15H), 1.84–1.20 (m, 6H), 2.02 (m, 0.35H), 2.13 (m, 0.65H), 2.92 (s, 1.05H), 2.93 (s, 1.95H), 2.98 (s, 1.05H), 3.08 (s, 1.95H), 3.73 (d, $J=17.6$ Hz, 0.65H), 3.95 (d, $J=18.1$ Hz, 0.35H), 4.06 (d, $J=3.9$ Hz, 0.35H), 4.10 (d, $J=2.4$ Hz, 0.65H), 4.27 (d, $J=$ 18.1 Hz, 0.35H), 4.41 (d, $J=17.6$ Hz, 0.65H), 4.74 (dd, $J=8.3$, 8.8 Hz, 0.65H), 4.79 (dd, $J=6.8$, 9.3 Hz, 0.35H), 5.42 (dd, $J=7.3$, 7.3 Hz, 0.35H), 5.50 (dd, $J=7.3$, 7.3 Hz, 0.65H), 7.41 (d, $J=9.3$ Hz, 0.35H), 7.80 (d, $J=8.8$ Hz, 0.65H). Signals due to two protons (COOH, OH) were not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 [11.6] (q), 12.5 [13.1] (q), 18.0 [17.4] (q), 19.4 [19.5] (q), 22.4 [22.2] (q), 22.8 [23.0] (q), 24.6 [24.4] (d), 26.2 [26.0] (t), 30.6 [30.8] (d), 30.9 [30.5] (q), 36.1 [35.3] (q), 37.9 [38.1] (t), 38.4 [38.2] (d), 49.9 [50.7] (t), 51.7 [51.0] (d), 54.1 [54.0] (d), 74.0 [74.8] (d), 170.5 [169.9] (s), 171.0 [170.6] (s), 172.4 [171.9] (s), 174.8 [174.1] (s). The minor counterparts of doubled signals in the ratio of 1.9:1 are in brackets; MS (FAB) *m*/*z* 452 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{39}N_3NaO_6$ $[(M+Na)^+]$ 452.2737, found 452.2730. Anal. calcd for $C_{21}H_{39}N_3O_6$: C, 58.66; H, 9.32; N, 9.62. Found C, 58.70; H, 9.15; N, 9.78.

4.1.22. Pentapeptide 19. To a stirred solution of carboxylic acid **24** (154 mg, 0.359 mmol) and L-valine 2,2,2-trichloroethyl ester hydrochloride (125 mg, 0.442 mmol) in DMF

(0.5 mL) and CH_2Cl_2 (0.1 mL) cooled at 0 °C were added triethylamine (0.065 mL, 0.47 mmol), 1-hydroxybenzotriazole (73.0 mg, 0.541 mmol), and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (89.0 mg, 0.464 mmol), successively. The reaction mixture was stirred at room temperature for 2 h, diluted with EtOAc (20 mL), washed with 10% citric acid (2×4 mL), H_2O (4 mL) saturated aqueous $NaHCO_3$ (2×2 mL), brine (2 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane–acetone 3:1→2.5: 1) to give **19** (232 mg, 98%) as a colorless powder. $[\alpha]_D^{27}=+46.3$ (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 3420, 3360 (br), 1755, 1675, 1630, 1515, 1465, 1390, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, $J=6.8$ Hz, 2.55H), 0.81 (d, $J=6.8$ Hz, 0.45H), 0.85–1.07 (m, 21H), 1.23–1.90 (m, 6H), 2.05 (m, 1H), 2.32 (m, 1H), 2.89 (d, $J=4.9$ Hz, 0.15H), 2.93 (d, $J=4.9$ Hz, 0.85H), 2.96 (s, 0.45H), 3.10 (s, 3H), 3.12 (s, 2.55H), 3.93 (d, $J=17.1$ Hz, 0.15H), 3.99 (d, $J=15.6$ Hz, 0.85H), 4.06 (d, $J=15.6$ Hz, 0.85H), 4.13 (dd, $J=2.0$, 4.9 Hz, 1H), 4.27 (d, $J=17.1$ Hz, 0.15H), 4.62 (d, $J=11.7$ Hz, 1H), 4.64 (dd, $J=4.9$, 8.8 Hz, 0.85H), 4.69 (dd, $J=4.9$, 8.3 Hz, 0.15H), 4.82 (m, 0.15H), 4.85 (dd, $J=6.8$, 8.8 Hz, 0.85H), 4.90 (d, $J=11.7$ Hz, 0.85H), 4.92 (d, $J=11.7$ Hz, 0.15H), 5.29 (dd, $J=5.4$, 9.3 Hz, 0.15H), 5.47 (dd, $J=6.3$, 8.3 Hz, 0.85H), 6.74 (d, $J=8.8$ Hz, 0.85H), 6.82–6.89 (m, 0.3H), 6.93 (d, $J=8.8$ Hz, 0.85H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (q), 12.6 (q), 17.39 [17.25] (q), 17.41 [17.7] (q), 19.0 (q), 19.5 (q), 22.0 [21.8] (q), 22.9 [23.1] (q), 24.7 [24.6] (d), 26.2 (t), 30.59 [30.65] (d), 30.74 (q), 31.1 [30.9] (d), 36.5 (q), 37.7 [37.8] (t), 38.6 (d), 51.2 [50.7] (d), 52.6 [52.4] (t), 53.7 [54.0] (d), 57.0 [57.3] (d), 73.95 [74.00] (d), 74.35 [74.40] (t), 94.4 [94.3] (s), 168.6 [168.3] (s), 170.2 [170.7] (s), 171.8 [171.6] (s), 172.3 [172.4] (s), 173.6 [173.7] (s). The minor counterparts of doubled signals in the ratio of 5.7:1 are in brackets; MS (FAB) *m/z* 681 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{49}^{35}Cl_3N_4NaO_7$ [$(M+Na)^+$] 681.2564, found 681.2579. Anal. calcd for $C_{28}H_{49}Cl_3N_4O_7$: C, 50.90; H, 7.48; N, 8.49. Found C, 50.99; H, 7.52; N, 8.43.

4.1.23. Hydroxy imide 25a. To a stirred solution of imide *ent*-**4** (2.28 g, 9.48 mmol) in ether (28 mL) cooled at 0 °C were added dibutylboron triflate (4.75 mL, 19.0 mmol) and diisoprpylethylamine (1.90 mL, 10.9 mmol), successively. The reaction mixture was stirred at 0 °C for 30 min and cooled to −100 °C. A solution of *trans*-2-methyl-2-pentenal (1.35 mL, 11.8 mmol) in ether (8.0 mL, 2.0 mL rinse) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched by addition of trietylamine (2.0 mL, 14 mmol) and 0.5 M phosphate buffer (pH 7, 40 mL). The reaction mixture was stirred at room temperature for 20 min and extracted with ether (2× 50 mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, benzene–ether 80:1→40:1→20:1→10:1) to give **25a** (2.09 g, 67%) and *syn*-hydroxy imide **25b** (453 mg, 14%) as crystals, respectively.

Compound **25a**. Mp 89–90 °C (hexane–ether). $[\alpha]_D^{31}=-30.6$ (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3600, 3520 (br), 1780, 1695, 1455, 1370, 1345, 1190, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, $J=6.8$ Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H), 1.08 (d, $J=6.4$ Hz, 3H), 1.68 (br s, 3H), 2.05 (dq, $J=7.3$, 7.3 Hz, 2H), 2.63 (d, $J=6.4$ Hz, 1H), 4.10 (dd, $J=6.4$, 8.8 Hz, 1H), 4.15 (dq, $J=8.8$, 6.4 Hz, 1H), 4.79 (dq, $J=6.8$, 6.8 Hz, 1H), 5.44 (br t, $J=7.3$ Hz, 1H), 5.67 (d, $J=6.8$ Hz, 1H), 7.28–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7 (q), 13.9 (q), 14.3 (q), 14.8 (q), 20.8 (t), 40.6 (d), 55.2 (d), 78.9 (d), 81.2 (d), 125.6 (d, 2C), 128.3 (d), 128.7 (d, 2C), 131.3 (d), 133.2 (s), 133.7 (s), 153.4 (s), 176.5 (s); MS (FAB) *m/z* 332 $(M+H)^+$, 354 $(M+Na)^+$. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.90; H, 7.60; N, 4.23. Found C, 68.91; H, 7.78; N, 4.22.

Compound **25b**. mp 148–149 °C (hexane–ether). $[\alpha]_D^{31}=-17.8$ (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3600, 3530 (br), 1780, 1695, 1455, 1370, 1345, 1190, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 1.17 (d, $J=6.8$ Hz, 3H), 1.65 (br s, 3H), 1.97–2.13 (m, 2H), 2.56 (br s, 1H), 4.09 (dq, $J=3.4$, 6.8 Hz, 1H), 4.38 (d, $J=3.4$ Hz, 1H), 4.80 (dq, $J=6.8$, 6.8 Hz, 1H), 5.52 (m, 1H), 5.68 (d, $J=6.8$ Hz, 1H), 7.27–7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (q), 13.1 (q), 14.0 (q), 14.6 (q), 20.8 (t), 40.6 (d), 54.8 (d), 75.7 (d), 78.8 (d), 125.6 (d, 2C), 128.4 (d), 128.7 (d, 2C), 128.8 (d), 133.0 (s), 133.2 (s), 152.7 (s), 176.6 (s); MS (FAB) *m/z* 332 $(M+H)^+$, 354 $(M+Na)^+$. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.90; H, 7.60; N, 4.23. Found C, 68.84; H, 7.71; N, 4.25.

4.1.24. Amide 27. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.90 g, 19.5 mmol) in THF (3 mL) cooled at −15 °C was added a 2.0 M solution of trimethylaluminum in toluene (8.9 mL, 17.8 mmol) dropwise. The resulting solution was stirred at 0 °C for 5 min and at room temperature for 20 min. The solution was recooled to 0 °C, and a solution of hydroxy imide **25a** (1.55 g, 4.68 mmol) in THF (12 mL) was added. The reaction mixture was warmed to 50 °C, stirred for 1.5 h, and transferred into a vigorously stirred mixture of CH_2Cl_2 (20 mL) and 0.5 M HCl (20 mL) at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 50 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layer and extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (100 g, hexane–^{i}PrOH 40: 1→35:1→30:1→EtOAc) and FL-60D silica gel (100 g, hexane–ether 3:2→1: 1) to give **27** (846 mg, 84%) as a colorless oil and 4-(*S*)-methyl-5-(*R*)-phenyl-2-oxazolidinone (450 mg) as colorless crystals. **27**. $[\alpha]_D^{30}=-43.8$ (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3600, 3440 (br), 1640, 1460, 1390, 1220, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, $J=7.3$ Hz, 3H), 1.04 (d, $J=6.8$ Hz, 3H), 1.63 (br s, 3H), 2.05 (dq, $J=7.3$, 7.3 Hz, 2H), 2.95 (br s, 1H), 3.13 (m, 1H), 3.21 (s, 3H), 3.73 (s, 3H), 4.12 (d, $J=7.8$ Hz, 1H), 5.45 (br t, $J=7.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (q), 13.9 (q), 14.8 (q), 20.7 (t), 31.9 (q), 38.1 (d), 61.4 (q), 79.8 (d), 130.4 (d), 133.9 (s), 176.9 (s); MS (FAB) *m/z* 238 $(M+Na)^+$, 216 $(M+H)^+$; HRMS (FAB) calcd for $C_{11}H_{21}NNaO_3$ [$(M+Na)^+$] 238.1420, found 238.1422.

4.1.25. Silyl ether 28. To a stirred solution of amide **27** (1.34 g, 6.23 mmol) in DMF (6 mL) were added imidazole

(1.65 g, 24.2 mmol) and *tert*-butyldimethylsilyl chloride (1.62 g, 10.4 mmol). The mixture was stirred at room temperature for 3 h, diluted with H_2O (30 mL), and extracted with ether (4×40 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–EtOAc 10:1) to give **28** (2.22 g, 100%) as a colorless oil. $[\alpha]_D^{30}=-21.2$ (*c* 1.60, $CHCl_3$); IR ($CHCl_3$) 1650, 1460, 1390, 1250, 1060, 990, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.03 (s, 3H), 0.79 (s, 9H), 0.83 (d, $J=7.3$ Hz, 3H), 0.94 (t, $J=7.3$ Hz, 3H), 1.55 (br s, 3H), 1.98 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 2.04 (ddq, $J=7.3$, 14.6, 7.3 Hz, 1H), 3.14 (m, 1H), 3.16 (s, 3H), 3.72 (s, 3H), 4.13 (d, $J=9.8$ Hz, 1H), 5.35 (br dd, $J=7.3$, 7.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3 (q), −4.9 (q), 10.1 (q), 13.8 (q), 14.2 (q), 18.0 (s), 20.8 (t), 25.6 (q, 3C), 31.8 (q), 38.7 (d), 61.3 (q), 81.7 (d), 131.1 (d), 134.0 (s), 176.4 (s); MS (FAB) *m/z* 330 $(M+H)^+$; HRMS (FAB) calcd for $C_{17}H_{36}NO_3Si$ $[(M+H)^+]$ 330.2465, found 330.2463.

4.1.26. Aldehyde 29. To a stirred solution of silyl ether **28** (633 mg, 1.92 mmol) in THF (6.5 mL) cooled at −78 °C was added a 0.98 M solution of diisobutylaluminum hydride in hexane (3.9 mL, 3.8 mmol) dropwise. The solution was stirred at −78 °C for 1.5 h, and the reaction was quenched by addition of acetone (0.4 mL). The solution was stirred at −78 °C for 10 min and then transferred into a vigorously stirred mixture of CH_2Cl_2 (30 mL) and 0.5 M tartaric acid (30 mL) at room temperature. The resulting two-phase mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer and the extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–CH_2Cl_2 20:1→10:1) to give **29** (480 mg, 93%) as a colorless oil. $[\alpha]_D^{32}=-26.2$ (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 2720, 1720, 1470, 1460, 1255, 1060, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3H), 0.02 (s, 3H), 0.84 (s, 9H), 0.85 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 1.56 (br s, 3H), 1.95–2.12 (m, 2H), 2.55 (ddq, $J=2.9$, 8.8, 6.8 Hz, 1H), 4.05 (d, $J=8.8$ Hz, 1H), 5.36 (br dd, $J=7.3$, 7.3 Hz, 1H), 9.74 (d, $J=2.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (q), −4.5 (q), 10.6 (q), 11.0 (q), 13.7 (q), 18.1 (s), 20.8 (t), 25.7 (q, 3C), 50.1 (d), 80.6 (d), 130.8 (d), 133.8 (s), 205.4 (d); MS (EI) *m/z* 213 $[(M-C_4H_9)^+$, 100), 155 (20), 115 (30); HRMS (EI) calcd for $C_{11}H_{21}O_2Si$ $[(M-C_4H_9)^+]$ 213.1345, found 213.1311.

4.1.27. Methyl ester 31. To a stirred solution of aldehyde **29** (83.9 mg, 0.31 mmol) in CH_2Cl_2 (2.4 mL) and ether (0.24 mL) cooled at −78 °C were added 2-methyl-1-trimethylsiloxy-1-methoxy-1,3-butadiene (**30**) (0.2 mL, 1.01 mmol) and boron trifluoride diethyl etherate (0.06 mL, 0.49 mmol), successively. The reaction mixture was stirred at −78 °C for 2 h and diluted with THF–H_2O–0.3 M HCl (5:1:0.4, 4 mL). The mixture was stirred at room temperature for 15 min and then transferred into saturated aqueous $NaHCO_3$ (5 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with hexane (3×7 mL). The organic layer and the extracts were combined, washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on FL-60D silica gel (5 g, hexane–ether 10:1) to give **31** (104 mg, 87%) and as a colorless oil. $[\alpha]_D^{30}=+9.0$ (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1705, 1650, 1460, 1440, 1285, 1255, 1090, 1020, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.91 (d, $J=6.8$ Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H), 1.52 (br s, 3H), 1.68 (m, 1H), 1.84 (d, $J=1.0$ Hz, 3H), 2.05 (dq, $J=7.3$, 7.3 Hz, 2H), 2.21 (ddd, $J=6.3$, 6.3, 15.1 Hz, 1H), 2.39 (m, 1H), 3.30 (d, $J=2.9$ Hz, 1H), 3.72 (s, 3H), 4.00 (d, $J=4.9$ Hz, 1H), 4.02 (m, 1H), 5.46 (br dd, $J=7.3$, 7.3 Hz, 1H), 6.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (q), −4.5 (q), 11.5 (q), 12.6 (q), 12.7 (q), 13.9 (q), 18.0 (s), 20.8 (t), 25.9 (q, 3C), 33.7 (t), 39.1 (d), 51.7 (q), 70.6 (d), 82.3 (d), 128.86 (s), 128.90 (d), 133.9 (s), 139.3 (d), 168.5 (s); MS (FAB) *m/z* 407 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{40}NaO_4Si$ $[(M+Na)^+]$ 407.2594, found 407.2622.

4.1.28. Ketone 32. To a stirred solution of methyl ester **31** (1.32 g, 3.44 mmol) in CH_2Cl_2 (25 mL) was added Dess–Martin periodinane (2.29 g, 5.41 mmol). The mixture was stirred at room temperature for 1 h and diluted with ether (30 mL), saturated aqueous $Na_2S_2O_3$ (40 mL), and 0.5 M phosphate buffer (pH 7, 40 mL). The resulting mixture was stirred at room temperature for 30 min and extracted with ether (3×50 mL). The combined extracts were washed with H_2O (2×50 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (35 g, hexane–ether 15:1→8:1) to give **32** (1.23 g, 94%) as a colorless oil. $[\alpha]_D^{30}=-44.5$ (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 1710, 1650, 1460, 1435, 1255, 1090, 1050, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.05 (s, 3H), 0.80 (s, 9H), 0.81 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 1.55 (br s, 3H), 1.85 (d, $J=1.0$ Hz, 3H), 1.99–2.11 (m, 2H), 2.82 (dq, $J=9.8$, 6.8 Hz, 1H), 3.41 (d, $J=7.3$ Hz, 2H), 3.74 (s, 3H), 4.06 (d, $J=9.8$ Hz, 1H), 5.35 (br dd, $J=7.3$, 7.3 Hz, 1H), 7.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (q), −4.7 (q), 10.1 (q), 12.9 (q), 13.7 (q), 13.8 (q), 18.0 (s), 20.8 (t), 25.7 (q, 3C), 44.4 (t), 49.5 (d), 51.8 (q), 82.4 (d), 130.1 (s), 131.4 (d), 133.3 (d), 133.7 (s), 168.0 (s), 210.3 (s); MS (FAB) *m/z* 405 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{38}NaO_4Si$ $[(M+Na)^+]$ 405.2437, found 405.2447.

4.1.29. Alcohol 33. To a stirred solution of ketone **32** (234 mg, 0.613 mmol) in methanol (6 mL) cooled at −23 °C was added sodium borohydride (119 mg, 3.15 mmol). The mixture was stirred at −23 °C for 50 min, diluted with saturated aqueous NH_4Cl (20 mL), and extracted with hexane (4×20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 32 g, hexane-1,2-dichloroethane 3:1→2:1→1:1) to give **33** (193 mg, 82%) along with **31** (9.3 mg, 4%) as a colorless oil, respectively. **33**. $[\alpha]_D^{29}=-28.1$ (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 1705, 1650, 1460, 1435, 1255, 1095, 1040, 1020, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.09 (s, 3H), 0.65 (d, $J=6.9$ Hz, 3H), 0.89 (s, 9H), 0.96 (t, $J=7.6$ Hz, 3H), 1.56 (br s, 3H), 1.77 (m, 1H), 1.85 (d, $J=1.0$ Hz, 3H), 2.02 (dq, $J=7.6$, 7.6 Hz, 2H), 2.32 (ddd, $J=6.9$, 7.6, 15.8 Hz, 1H), 2.44 (m, 1H), 3.73 (s, 3H), 3.81 (m, 1H), 3.84 (d, $J=8.9$ Hz,

1H), 4.18 (br s, 1H), 5.30 (br t, J=7.6 Hz, 1H), 6.97 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.2 (q), −4.2 (q), 10.8 (q), 12.7 (q), 13.1 (q), 13.6 (q), 18.1 (s), 20.8 (t), 25.8 (q, 3C), 33.6 (t), 41.0 (d), 51.6 (q), 74.1 (d), 86.3 (d), 128.7 (s), 131.0 (d), 134.8 (s), 139.3 (d), 168.5 (s); MS (FAB) *m/z* 407 $(M+Na)^+$; HRMS (FAB) calcd for $C_{21}H_{40}NaO_4Si$ $[(M+Na)^+]$ 407.2594, found 407.2601.

4.1.30. (Methylthio)methyl ether 34. To a stirred solution of alcohol **33** (1.47 g, 3.83 mmol) in DMSO (28 mL) was added a 1:5.6 mixture of acetic acid and acetic anhydride (23 mL) at room temperature. The mixture was stirred at 40 °C for 3 h and diluted with hexane (54 mL) and 0.5 M phosphate buffer (pH 7, 90 mL). The layers were separated, and the aqueous layer was extracted with hexane (3× 30 mL). The organic layer and the extracts were combined, washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 130 g, hexane–ether 50:1→10:1) to give **34** (1.29 g, 74%) and **32** (174 mg, 10%) as a colorless oil, respectively. **34**. $[\alpha]_D^{28}$= −85.8 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 1710, 1650, 1460, 1435, 1280, 1250, 1055, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.01 (s, 3H), 0.71 (d, J=6.9 Hz, 3H), 0.88 (s, 9H), 0.96 (t, J=7.3 Hz, 3H), 1.54 (br s, 3H), 1.85 (d, J=1.3 Hz, 3H), 1.95–2.10 (m, 3H), 2.14 (s, 3H), 2.22–2.32 (m, 2H), 3.66 (d, J=9.2 Hz, 1H), 3.73 (s, 3H), 4.13 (ddd, J=3.0, 5.3, 7.9 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.63 (d, J=11.5 Hz, 1H), 5.29 (br dd, J=6.9, 6.9 Hz, 1H), 6.91 (ddq, J=6.9, 6.9, 1.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3 (q), −4.4 (q), 10.4 (q), 10.7 (q), 12.7 (q), 13.8 (q), 14.0 (q), 18.1 (s), 20.7 (t), 25.8 (q, 3C), 28.6 (t), 38.3 (d), 51.6 (q), 73.1 (t), 75.7 (d), 80.9 (d), 128.3 (s), 130.0 (d), 134.9 (s), 140.6 (d), 168.5 (s); MS (FAB) *m/z* 467 $(M+Na)^+$; HRMS (FAB) calcd for $C_{23}H_{44}NaO_4SSi$ $[(M+Na)^+]$ 467.2628, found 467.2623.

4.1.31. Carboxylic acid 20. To a stirred solution of (methylthio)methyl ether **34** (806 mg, 1.82 mmol) in MeOH (20 mL) was added 5 M LiOH (5 mL) at room temperature. The mixture was stirred at 30 °C for 11.5 h, acidified with 10% aqueous citric acid (60 mL), and extracted with ether (3×50 mL). The combined extracts were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 70 g, hexane–ether 8:1→2:1) to give **20** (691 mg, 89%) as a colorless oil. $[\alpha]_D^{28}$= −90.3 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3100 (br), 1685, 1645, 1460, 1290, 1250, 1105, 1055, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.02 (s, 3H), 0.72 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.96 (t, J=7.3 Hz, 3H), 1.54 (br s, 3H), 1.86 (br s, 3H), 1.95–2.11 (m, 3H), 2.15 (s, 3H), 2.23–2.38 (m, 2H), 3.67 (d, J= 9.3 Hz, 1H), 4.16 (ddd, J=3.4, 3.4, 8.8 Hz, 1H), 4.53 (d, J=11.7 Hz, 1H), 4.63 (d, J=11.7 Hz, 1H), 5.30 (br dd, J= 6.8, 6.8 Hz, 1H), 7.06 (m, 1H). A signal due to one proton (COOH) was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (q), −4.4 (q), 10.4 (q), 10.7 (q), 12.3 (q), 13.8 (q), 14.0 (q), 18.1 (s), 20.8 (t), 25.8 (q, 3C), 28.8 (t), 38.2 (d), 73.1 (t), 75.5 (d), 80.9 (d), 127.8 (s), 130.0 (d), 134.9 (s), 143.3 (d), 173.1 (s); MS (FAB) *m/z* 453 $(M+Na)^+$; HRMS (FAB) calcd for $C_{22}H_{42}NaO_4SSi$ $[(M+Na)^+]$ 453.2471, found 453.2495.

4.1.32. Ester 35. To a stirred solution of carboxylic acid **20** (1.02 g, 2.37 mmol) and pentapeptide **19** (3.57 g, 5.41 mmol) in CH_2Cl_2 (6.4 mL) were added 4-(dimethylamino)pyridine (179 mg, 1.46 mmol) and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (518 mg, 2.70 mmol), and the mixture was stirred at room temperature for 13 h. The mixture was diluted with EtOAc (120 mL), washed with 10% aqueous citric acid (40 mL), H_2O (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 200 g, benzene–acetone 15:1→9:1→3:1) to give **35** (2.31 g, 91%) as a colorless oil. $[\alpha]_D^{28}$= +14.7 (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 3420, 1755, 1710, 1680, 1640, 1510, 1460, 1250, 1140, 1055, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.01 (s, 0.45H), 0.02 (s, 2.55H), 0.71 (d, J=7.3 Hz, 3H), 0.79 (d, J=6.8 Hz, 2.55H), 0.83–1.01 (m, 33H), 1.05 (d, J=6.8 Hz, 0.45H), 1.54 (s, 3H), 1.18–1.75 (m, 5H), 1.90 (s, 3H), 1.92–2.12 (m, 5H), 2.08 (s, 0.45H), 2.10 (s, 2.55H), 2.20–2.40 (m, 3H), 2.95 (s, 0.45H), 3.01 (s, 0.45H), 3.03 (s, 2.55H), 3.07 (s, 2.55H), 3.57 (d, J=17.1 Hz, 0.15H), 3.66 (d, J=8.8 Hz, 1H), 3.80 (d, J=15.1 Hz, 0.85H), 4.13 (ddd, J=2.9, 2.9, 9.8 Hz, 1H), 4.21 (d, J=15.1 Hz, 0.85H), 4.35 (d, J= 17.1 Hz, 0.15H), 4.51 (d, J=11.7 Hz, 0.15H), 4.53 (d, J= 11.7 Hz, 0.85H), 4.57–4.64 (m, 2.85H), 4.69 (dd, J=5.4, 8.8 Hz, 0.15H), 4.73 (dd, J=6.8, 8.3 Hz, 0.15H), 4.81 (dd, J=4.9, 8.8 Hz, 0.85H), 4.89 (d, J=11.7 Hz, 0.85H), 4.91 (d, J=11.7 Hz, 0.15H), 5.00 (d, J=3.4 Hz, 0.15H), 5.20 (d, J=2.9 Hz, 0.85H), 5.25 (dd, J=6.8, 8.8 Hz, 0.15H), 5.30 (br t, J=6.8 Hz, 1H), 5.55 (dd, J=6.4, 8.8 Hz, 0.85H), 6.34 (d, J=8.8 Hz, 0.15H), 6.55 (d, J=8.8 Hz, 0.85H), 6.71 (d, J=8.8 Hz, 0.85H), 6.91 (d, J=8.3 Hz, 0.15H), 7.02 (br t, J=7.3 Hz, 0.85H), 7.04 (m, 0.15H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ −5.3 (q), −4.3 (q), 10.3 (q), 10.7 (q), 11.7 (q), 12.8 (q), 13.8 (q), 13.9 (q), 14.2 (q), 16.7 (q), 17.4 (q), 18.1 (s), 19.1 (q), 19.7 (q), 20.7 (t), 22.2 (q), 23.0 (q), 24.7 (d), 25.8 (q, 3C), 26.2 (t), 28.9 (t), 30.5 (d), 30.6 (q), 31.0 (d), 36.5 (q), 37.3 (d), 37.9 (t), 38.4 (d), 50.8 (d), 53.1 (t), 53.1 (d), 56.8 (d), 73.3 (t), 74.4 (t), 75.9 (d), 76.3 (d), 80.9 (d), 94.4 (s), 127.9 (s), 130.0 (d), 134.8 (s), 142.2 (d), 166.7 (s), 168.7 (s), 170.0 (s), 170.1 (s), 171.4 (s), 171.7 (s); MS (FAB) *m/z* 1093 $(M+Na)^+$; HRMS (FAB) calcd for $C_{50}H_{89}^{35}Cl_3N_4NaO_{10}SSi$ $[(M+Na)^+]$ 1093.5032, found 1093.5020.

4.1.33. Alcohol 36. Ester **35** (83.6 mg, 0.078 mmol) was dissolved in a 5:3:12 mixture of HF·pyridine, pyridine, and THF (2 mL). The solution was stirred at 40 °C for 12 h, diluted with EtOAc (4 mL), and poured into saturated aqueous $NaHCO_3$ (12 mL) cooled at 0 °C. The mixture was extracted with EtOAc (3×8 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, benzene–acetone 8:1→ 5:1) to give **36** (74.5 mg, 100%) as a colorless oil. $[\alpha]_D^{24}$= +38.3 (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3420, 3400 (br), 1755, 1710, 1680, 1630, 1510, 1460, 1410, 1240, 1140, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, J=6.8 Hz, 3H), 0.78 (d, J=6.8 Hz, 2.55H), 0.84 (d, J=7.3 Hz, 0.45H), 0.85–0.96 (m, 20.55H), 0.98 (d, J=6.8 Hz, 3H), 1.04 (d, J= 6.8 Hz, 0.45H), 1.16–1.48 (m, 3H), 1.53–1.75 (m, 2H), 1.58 (s, 3H), 1.91 (s, 3H), 1.90–2.10 (m, 5H), 2.15 (s, 0.45H),

2.16 (s, 2.55H), 2.28 (m, 1H), 2.40 (m, 1H), 2.53 (m, 1H), 2.87 (br s, 0.15H), 2.92 (br s, 0.85H), 2.94 (s, 0.45H), 3.03 (s, 3H), 3.06 (s, 2.55H), 3.58 (d, J=17.6 Hz, 0.15H), 3.71 (d, J=9.8 Hz, 0.85H), 3.74 (d, J=9.8 Hz, 0.15H), 3.79 (d, J=15.1 Hz, 0.85H), 4.16 (ddd, J=4.9, 5.4, 6.3 Hz, 1H), 4.21 (d, J=15.1 Hz, 0.85H), 4.47 (d, J=17.6 Hz, 0.15H), 4.61 (d, J=11.7 Hz, 1H), 4.59–4.73 (m, 3H), 4.75 (dd, J=7.8, 8.3 Hz, 0.15H), 4.82 (dd, J=8.9, 8.8 Hz, 0.85H), 4.89 (d, J=11.7 Hz, 0.85H), 4.92 (d, J=11.7 Hz, 0.15H), 5.11 (d, J=3.4 Hz, 0.15H), 5.24 (m, 0.15H), 5.27 (d, J=2.8 Hz, 0.85H), 5.30 (br t, J=6.8 Hz, 1H), 5.52 (dd, J=6.4, 8.8 Hz, 0.85H), 6.46 (d, J=8.8 Hz, 0.15H), 6.62 (d, J=9.3 Hz, 0.85H), 6.71 (d, J=8.3 Hz, 0.85H), 6.97 (d, J=8.3 Hz, 0.15H), 7.08 (br t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 10.3 (q), 11.4 (q), 11.7 (q), 12.7 (q), 13.9 (q), 14.0 (q), 14.3 (q), 16.9 (q), 17.4 (q), 19.1 (q), 19.6 (q), 20.7 (t), 22.2 (q), 23.0 (q), 24.7 (d), 26.1 (t), 30.0 (t), 30.60 (d), 30.63 (q), 31.2 (d), 36.5 (q), 37.2 (d), 37.8 (t), 38.3 (d), 51,1 (d), 52.8 (t), 53.3 (d), 57.0 (d), 73.4 (t), 74.4 (t), 76.1 (d), 77.6 (d), 80.9 (d), 94.4 (s), 127.7 (s), 130.6 (d), 135.0 (s), 141.4 (d), 166.5 (s), 168.7 (s), 169.9 (s), 170.1 (s), 171.6 (s, 2C); MS (FAB) m/z 979 $(M+Na)^+$; HRMS (FAB) calcd for $C_{44}H_{75}^{35}Cl_3N_4NaO_{10}S$ $[(M+Na)^+]$ 979.4166, found 979.4139.

4.1.34. *N*-Methylalanine ester 37. To a stirred solution of alcohol **36** (1.14 g, 1.19 mmol) in CH_2Cl_2 (4 mL) cooled at 0 °C were added *N*-Fmoc-*N*-methyl-L-alanine (578 mg, 1.78 mmol), 4-(dimethylamino) pyridine (78.7 mg, 0.644 mmol), and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (440 mg, 2.30 mmol), and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with EtOAc (120 mL), washed with 10% aqueous citric acid (40 mL), H_2O (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on alumina (20 g, benzene–EtOAc 1:1) and subsequently on silica gel (50 g, benzene–acetone 10:1→5:1) to give **37** (1.41 g, 94%) as a colorless powder. $[\alpha]_D^{31}=+11.7$ (c 1.07, $CHCl_3$); IR ($CHCl_3$) 3430, 3360 (br), 1750, 1690, 1640, 1510, 1450, 1400, 1310, 1235, 1150, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–1.02 (m, 30H), 1.15–1.75 (m, 5H), 1.42 (d, J=7.3 Hz, 3H), 1.54 (s, 0.6H), 1.56 (s, 2.4H), 1.90–2.13 (m, 4H), 1.90 (s, 3H), 2.07 (s, 0.6H), 2.10 (s, 2.4H), 2.23–2.41 (m, 4H), 2.92 (s, 3H), 2.95 (s, 0.6H), 3.02 (s, 0.6H), 3.03 (s, 2.4H), 3.06 (s, 2.4H), 3.58 (d, J=17.6 Hz, 0.2H), 3.80 (d, J=15.1 Hz, 0.8H), 3.85 (m, 1H), 4.21 (d, J=15.1 Hz, 0.8H), 4.22–4.94 (m, 7.4H), 4.62 (d, J=11.7 Hz, 1H), 4.80 (dd, J=5.4, 8.8 Hz, 0.8H), 4.89 (d, J=11.7 Hz, 1H), 5.02 (d, J=9.3 Hz, 1H), 5.20 (br d, J=2.4 Hz, 1H), 5.25 (br t, J=7.3 Hz, 0.2H), 5.45–5.50 (m, 1H), 5.55 (dd, J=6.8, 8.9 Hz, 0.8H), 6.45 (d, J=8.3 Hz, 0.2H), 6.59 (d, J=8.8 Hz, 0.8H), 6.61 (d, J=8.3 Hz, 0.2H), 6.71 (d, J=8.8 Hz, 0.8H), 6.88–7.02 (m, 1H), 7.26–7.78 (m, 8H); MS (FAB) m/z 1286 $(M+Na)^+$; HRMS (FAB) calcd for $C_{63}H_{92}^{35}Cl_3N_5NaO_{13}S$ $[(M+Na)^+]$ 1286.5376, found 1286.5390.

4.1.35. Carboxylic acid 38. To a stirred solution of *N*-methylalanine ester **37** (2.39 g, 1.89 mmol) in THF (75 mL) and 1 M NH_4OAc (15 mL) was added activated Zn powder (8.6 g, 132 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined, washed with 10% aqueous citric acid (2×30 mL), H_2O (30 mL), and brine (30 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, $CHCl_3$–MeOH 20:1) to give **38** (2.07 g, 97%) as a colorless powder. $[\alpha]_D^{30}=-11.2$ (c 1.12, MeOH); IR (KBr) 3400 (br), 1740 (sh), 1710, 1690, 1530, 1640, 1450, 1400, 1210, 1100, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 0.69–0.91 (m, 30H), 1.09–1.75 (m, 5H), 1.33 (d, J=7.3 Hz, 3H), 1.57 (br s, 3H), 1.81 (br s, 3H), 1.81–2.01 (m, 4H), 2.01 (br s, 3H), 2.04–2.30 (m, 4H), 2.82 (s, 3H), 2.94 (s, 3H), 2.97 (s, 3H), 3.83 (d, J=15.3 Hz, 1H), 4.01 (d, J=15.3 Hz, 1H), 4.20–4.80 (m, 9H), 4.91 (br s, 1H), 5.05 (br s, 1H), 5.37 (br t, J=6.8 Hz, 1H), 5.43 (dd, J=5.9, 9.8 Hz, 1H), 6.78–6.93 (m, 3H), 7.18–7.33 (m, 4H), 7.40–7.53 (m, 2H), 7.63–7.69 (m, 2H). A signal due to one proton (COOH) was not observed; MS (FAB) m/z 1156 $(M+Na)^+$; HRMS (FAB) calcd for $C_{61}H_{91}N_5NaO_{13}S$ $[(M+Na)^+]$ 1156.6232, found 1156.6240.

4.1.36. Lactam 39a. To a stirred solution of carboxylic acid **38** (427 mg, 0.377 mmol) in MeCN (20 mL) was added diethylamine (2 mL), and the mixture was stirred at room temperature for 2.5 h and concentrated. The residual oil was purified by column chromatography on silica gel (12 g, $CHCl_3$–MeOH 30:1→5:1) to give crude amino acid **18** (344 mg) as a colorless powder. To a stirred solution of crude amino acid **18** (344 mg) in CH_2Cl_2 (350 mL) and DMF (35 mL) cooled at 0 °C were added 1-hydroxy-7-azabenzotriazole (546 mg, 3.93 mmol) and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (734 mg, 3.84 mmol), and the mixture was stirred at room temperature for 40.5 h. The mixture was diluted with EtOAc (200 mL), washed with 10% aqueous citric acid (2×30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 40 g, benzene–acetone 10:1→5:1) to give **39a** (222 mg, 66%) and **39b** (80.8 mg, 24%) as a colorless powder, respectively.

Compound **39a**. $[\alpha]_D^{28}=+14.7$ (c 0.48, $CHCl_3$); IR ($CHCl_3$) 3420, 3360, 1735, 1700 (sh), 1685, 1645, 1510, 1460, 1410, 1280, 1250, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (major rotamer) δ 0.80 (d, J=6.8 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), 0.88 (d, J=6.8 Hz, 3H), 0.88–0.97 (m, 15H), 0.99 (d, J=6.8 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.24–1.74 (m, 5H), 1.41 (d, J=7.8 Hz, 3H), 1.59 (br s, 3H), 1.88–2.23 (m, 6H), 1.98 (br s, 3H), 2.09 (s, 3H), 2.32–2.45 (m, 2H), 2.96 (s, 3H), 2.98 (s, 3H), 3.09 (s, 3H), 3.47 (d, J=16.6 Hz, 1H), 4.08 (m, 1H), 4.11 (d, J=16.6 Hz, 1H), 4.54 (d, J=11.2 Hz, 1H), 4.58 (d, J=11.2 Hz, 1H), 4.65 (q, J=7.8 Hz, 1H), 4.84 (dd, J=8.9, 8.8 Hz, 1H), 4.93 (d, J=11.2 Hz, 1H), 4.94 (dd, J=3.7, 9.3 Hz, 1H), 4.99 (d, J=3.4 Hz, 1H), 5.27 (t, J=7.3 Hz, 1H), 5.51 (br t, J=6.8 Hz, 1H), 6.63 (d, J=8.8 Hz, 1H), 7.21 (dd, J=5.4, 8.8 Hz, 1H), 7.32 (d, J=9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 9.9 (q), 10.8 (q), 11.8 (q), 12.6 (q), 13.7 (q), 14.12 (q), 14.16 (q), 14.21 (q), 16.3 (q), 17.3 (q), 19.6 (q), 20.0 (q), 20.9 (t), 22.4 (q), 23.2 (q), 24.6 (d), 26.2 (t), 28.6 (t), 30.4 (q), 30.5 (d), 31.2 (d), 31.7 (q), 35.7 (q), 36.6 (d), 37.7 (d),

37.8 (t), 51.6 (t), 52.0 (d), 53.3 (d), 53.8 (d), 54.2 (d), 74.3 (t), 76.6 (d), 76.7 (d), 82.0 (d), 128.2 (s), 130.3 (s), 133.8 (d), 143.1 (d), 167.8 (s), 168.4 (s), 169.7 (s), 170.0 (s), 171.6 (s), 171.8 (s), 172.1 (s); MS (FAB) *m/z* 916 $(M+Na)^+$; HRMS (FAB) calcd for $C_{46}H_{79}N_5NaO_{10}S$ $[(M+Na)^+]$ 916.5445, found 916.5430.

Compound **39b**. $[\alpha]_D^{27}=-1.8$ (*c* 0.63, $CHCl_3$); IR ($CHCl_3$) 3410, 1740, 1710, 1695, 1635, 1510, 1465, 1410, 1240, 1095, 1090, 1050 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (major rotamer) δ 0.75 (d, $J=6.6$ Hz, 3H), 0.81 (d, $J=7.6$ Hz, 6H), 0.90 (d, $J=6.6$ Hz, 3H), 0.91–1.00 (m, 18H), 1.30 (m, 1H), 1.36–1.45 (m, 2H), 1.41 (d, $J=7.3$ Hz, 3H), 1.53 (m, 1H), 1.59 (br s, 3H), 1.74 (ddd, $J=7.3$, 7.3, 13.9 Hz, 1H), 1.87 (br s, 3H), 1.88–2.08 (m, 4H), 2.08 (s, 3H), 2.14 (m, 1H), 2.27 (m, 1H), 2.30–2.43 (m, 2H), 2.88 (s, 3H), 2.94 (s, 3H), 3.08 (s, 3H), 3.28 (d, $J=16.8$ Hz, 1H), 3.91 (m, 1H), 4.54 (d, $J=11.7$ Hz, 1H), 4.57 (d, $J=16.8$ Hz, 1H), 4.59 (d, $J=11.7$ Hz, 1H), 4.88 (dd, $J=4.8$, 8.9 Hz, 1H), 4.89 (dd, $J=5.1$, 8.9 Hz, 1H), 5.01 (d, $J=11.0$ Hz, 1H), 5.19 (q, $J=7.3$ Hz, 1H), 5.37 (d, $J=1.8$ Hz, 1H), 5.40 (dd, $J=7.3$, 7.3 Hz, 1H), 5.52 (br t, $J=7.3$ Hz, 1H), 6.67 (d, $J=8.9$ Hz, 1H), 6.97 (d, $J=8.9$ Hz, 1H), 7.01 (br dd, $J=7.3$, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 9.9 (q), 10.8 (q), 11.8 (q), 12.7 (q), 13.7 (q), 14.1 (q), 14.2 (q), 15.3 (q), 16.4 (q), 17.0 (q), 19.8 (q), 19.9 (q), 20.9 (t), 22.6 (q), 23.0 (q), 24.6 (d), 26.2 (t), 28.4 (t), 30.1 (q), 31.4 (d), 31.6 (q), 32.2 (d), 34.5 (q), 36.2 (d), 37.4 (d), 37.9 (t), 50.9 (d), 51.8 (d), 52.1 (t), 53.0 (d), 53.9 (d), 73.7 (t), 75.7 (d), 76.1 (d), 82.2 (d), 128.7 (s), 130.2 (s), 134.2 (d), 144.8 (d), 166.6 (s), 167.1 (s), 170.1 (s), 170.3 (s), 170.6 (s), 171.2 (s), 171.4 (s); MS (FAB) *m/z* 916 $(M+Na)^+$; HRMS (FAB) calcd for $C_{46}H_{79}N_5NaO_{10}S$ $[(M+Na)^+]$ 916.5445, found 916.5434.

4.1.37. Aurilide (1). To a stirred solution of lactam **39a** (654 mg, 0.732 mmol) in THF (16 mL) and H_2O (4 mL) were added 2,6-lutidine (1.7 mL, 14.6 mmol) and $AgNO_3$ (5.37 g, 31.6 mmol), and the mixture was stirred at 65 °C for 1 h. The mixture was diluted with EtOAc (30 mL) and filtered through a pad of Celite, and the residue was washed with EtOAc (50mL). The filtrate and the washings were combined, washed with 1 M HCl (30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, benzene–acetone 8:1→5:1→3:1) to give 1 (566 mg, 93%) as a colorless powder. Using the same procedure as described above, 40 (3.1 mg, 97%) was obtained from 39b (3.4 mg, 0.15 mmol) as a colorless powder. Synthetic 1. $[\alpha]_D^{27}=-20$ (*c* 0.057, MeOH); UV (MeOH) λ_{max} 220 nm (sh) (ε 21000); IR, ^1H NMR, and FABMS spectra were identical to those of natural 1; ^{13}C NMR, see Table 1; HRMS (FAB) calcd for $C_{44}H_{75}N_5NaO_{10}$ $[(M+Na)^+]$ 856.5411, found 856.5395.

Compound **40**. $[\alpha]_D^{29}=+11$ (*c* 0.062, MeOH); IR ($CHCl_3$) 3500 (br), 3410, 1735 (sh), 1710, 1695 (sh), 1635, 1510, 1460, 1410, 1240, 1195, 1090 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 0.72 (d, $J=7.0$ Hz, 1.65H), 0.73 (d, $J=6.6$ Hz, 1.35H), 0.76 (d, $J=6.3$ Hz, 1.35H), 0.77 (d, $J=6.3$ Hz, 1.65H), 0.79 (d, $J=7.0$ Hz, 1.35H), 0.83 (d, $J=7.3$ Hz, 1.65H), 0.83–1.00 (m, 18H), 1.03 (d, $J=7.0$ Hz, 1.65H), 1.06 (d, $J=7.3$ Hz, 1.35H), 1.12 (d, $J=7.0$ Hz, 1.35H), 1.19 (d, $J=7.0$ Hz, 1.65H), 1.20–1.33 (m, 2H), 1.42–1.62 (m, 3H), 1.52 (br s, 1.65H), 1.55 (br s, 1.35H), 1.76–1.95 (m, 4H), 1.98–2.48 (m, 4H), 2.02 (br s, 1.35H), 2.11 (s, 1.65H), 2.50 (s, 1.65H), 2.53 (d, $J=5.5$ Hz, 0.55H), 2.67 (s, 1.65H), 2.80 (s, 1.35H), 2.89 (s, 1.35H), 2.96 (s, 1.35H), 2.98 (s, 1.65H), 3.36 (d, $J=16.5$ Hz, 0.45H), 3.37 (d, $J=17.2$ Hz, 0.55H), 3.40 (d, $J=5.0$ Hz, 0.45H), 3.79 (m, 0.55H), 3.88 (m, 0.45H), 4.52 (d, $J=17.2$ Hz, 0.55H), 4.53 (q, $J=7.3$ Hz, 0.55H), 4.77 (q, $J=7.3$ Hz, 0.45H), 4.85 (d, $J=16.5$ Hz, 0.45H), 4.96 (dd, $J=5.1$, 8.4 Hz, 0.45H), 4.98 (t, $J=9.2$ Hz, 0.55H), 5.05 (dd, $J=4.8$, 9.2 Hz, 0.55H), 5.10 (dd, $J=4.8$, 8.1 Hz, 0.45H), 5.29 (d, $J=10.3$ Hz, 0.45H), 5.38 (dd, $J=3.7$, 7.4 Hz, 0.45H), 5.39 (d, $J=10.6$ Hz, 0.55H), 5.48 (br t, $J=7.3$ Hz, 0.55H), 5.51 (t, $J=7.3$ Hz, 0.55H), 5.57 (br t, $J=7.3$ Hz, 0.45H), 5.69 (d, $J=3.7$ Hz, 0.45H), 5.90 (d, $J=2.9$ Hz, 0.55H), 6.76–6.81 (m, 1H), 7.35–7.41 (m, 1H), 7.56 (br t, $J=7.3$ Hz, 0.55H), 7.70 (br t, $J=7.3$ Hz, 0.45H); ^{13}C NMR (150 MHz, C_6D_6) δ 11.2 (q), 11.7 (q), 11.9 (q), 12.9 [13.0] (q), 13.9 [13.8] (q), 14.1 [14.3] (q), 14.5 [14.7] (q), 16.5 [16.6] (q), 17.5 [18.4] (q), 19.6 [20.1] (q), 19.8 [20.2] (q), 21.07 [21.11] (t), 22.6 [20.9] (q), 23.1 [23.3] (q), 24.9 [25.3] (d), 26.6 [26.4] (t), 31.2 [29.9] (q), 31.4 [31.0] (d), 32.2 (d), 32.9 [31.4] (t), 35.3 (q), 36.0 [35.8] (q), 37.6 [37.0] (d), 38.6 [37.7] (t), 40.8 [40.5] (d), 51.4 [52.0] (d), 52.1 [52.2] (t), 53.7 (d), 54.1 [54.2] (d), 54.8 (d), 71.7 (d), 76.4 [76.8] (d), 82.5 [82.4] (d), 129.4 [129.3] (s), 131.5 [131.7] (s), 133.1 [133.2] (d), 141.7 [141.8] (d). The minor counterparts of doubled signals in the ratio of 1.2:1 are in brackets. Signals due to carbonyls which could not be assigned major or minor rotamer: δ 166.9, 167.1, 167.8, 168.2, 170.0, 170.3, 171.3, 172.2, 172.4, 173.6; MS (FAB) *m/z* 856 $(M+Na)^+$; HRMS (FAB) calcd for $C_{44}H_{75}N_5NaO_{10}$ $[(M+Na)^+]$ 856.5411, found 856.5393.

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New brassinosteroid analogs having nitrogenated functionalities at C_3 to provide more information about the brassinosteroid–receptor interaction

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Abstract—An efficient synthesis of different brassinosteroid derivatives with an azide or an amine function at C3 without any function at C2 and their biological activity evaluation in the rice lamina inclination test is described. The key step in the synthetic strategy involves a nucleophilic substitution by azide of an activated 3β-OH followed by reduction to amine. The activity elicited by **7** and **9** having an azide group, in contrast with the residual ones elicited by their corresponding amines, suggests that the 3α-OH group of an active brassinosteroid could act as acceptor in the putative hydrogen bonding interaction with the receptor/s.

1. Introduction

Brassinosteroids are potent plant growth regulators, which have an exciting potential use in agriculture for improving crops yield and quality, by helping the plant to overcome environmental stress and herbicidal injury.[1–3]

For a better understanding of the mode of action of such interesting compounds we have developed a methodology based on molecular modeling techniques. The results obtained until now are consistent with the fact that hydrogen bonding interaction can take place in the brassinosteroid-receptor complex to elicit activity.[4] Considering this, another point to be determined is whether each OH group present in an active brassinosteroid acts as an acceptor or as a donor in such hydrogen bonding interaction. Nevertheless, it is worthwhile mentioning that Bach et al.[5] suggest that there is substantial retention of activity when the OH group is modified because the new group is able to block the glucosydation, which seems to represent a metabolic deactivation pathway.[3]

Focusing on the C_3 position, different compounds having ketone,[6] fluorine[7] or methoxy[5] instead of 3α-OH have been reported. Further studies for more information about the type of receptor interaction in that position should be given.

In this communication, we present the synthetic strategy and bioactivity evaluation in the rice lamina inclination test (RLIT) towards different stigmastane brassinosteroid derivatives with an amine or an azide function at C3 in the A ring, without any function at C2. Moreover, the effect of these structural changes on bioactivity are discussed.

2. Results and discussion

2.1. Synthesis

The synthetic strategy developed to obtain the target compounds, having azide or amine at C3 (Scheme 1), has essentially consisted on introducing the nitrogenated functionality at C3, with the desired α-configuration, through a nucleophylic attack with sodium azide over an activated 3β-OH group, followed by reduction of the azide to amine. Thus, starting from stigmasterol (**1**), one of the best ways for introducing the 3β-OH consists on following the well-known procedure described by Takatsuto et al.,[8] in which the hydroxyketone **3** is obtained from stigmasterol (**1**) in five steps.

A crude of **3** was obtained in a yield of 61% starting from stigmasterol (**1**) with only a chromatographic purification of the cyclopropyl ketone intermediate **2**. Both diasteroisomers

Keywords: Brassinosteroids; Azide-amine derivatives; Plant growth regulators; Rice lamina inclination test.
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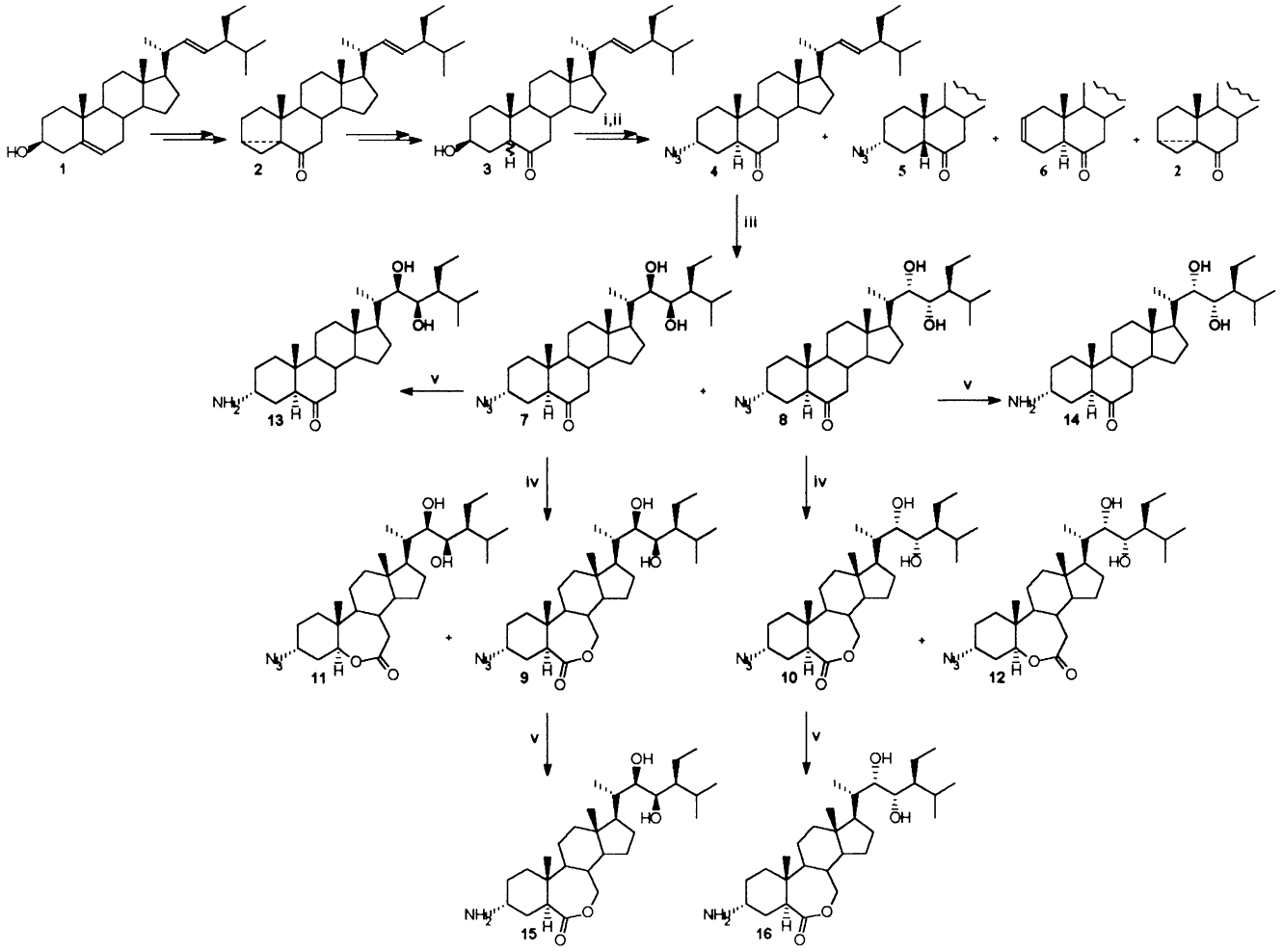

Scheme 1. Reagents and conditions: (i) MsCl, toluene/TEA, 5 h, 0 °C. (ii) NaN_3, DMF, 12 h, 90 °C. (iii) OsO_4/NMO/DHQD PHN/$Et_4N^+AcO^-$.$4H_2O$, THF/^{t}ButOH/H_2O, 264 h, 0 °C. (iv) CF_3COOOH, $CHCl_3$, 5 h, 0 °C. (v) PPh_3/H_2O, THF, 48–144 h, rt.

3a (A/B *trans* junction) and **3b** (A/B *cis* junction) were isolated after chromatographic purification of part of the crude, in a ratio of 16:1 (**3a/3b**), due to the higher thermodynamic stability of the A/B *trans* junction for such compounds.[9]

The next synthetic steps were performed without any purification of the crude, thus with the mixture of **3a** and **3b**.

The azide derivative **4** was synthesized by mesylation of **3**, treating the reaction crude (**3a**+**3b**) with MsCl/TEA at 0 °C during 5 h, followed by heating at 90 °C for 12 h with NaN_3/DMF. After chromatographic purification, the desired product **4** (74%) was obtained as well as its isomer **5** (7%) and the elimination products **2**+**6** (6%). The 3α configuration of the azide group of compound **4** was determined on the basis of the signal displayed at $\delta=3.99$ ppm (3β-H, $W_{1/2}=8.0$ Hz) in its ^{1}H NMR spectra.

Osmium-catalysed asymmetric dihydroxylation of the double bond of **4**, using methylmorpholine-4-oxide (NMO) as a cooxidant and dihydroquinidine 9-*O*-(9′-phenantryl)ether (DHQD PHN) as a chiral ligand[10] yield a mixture of **7** and **8**, which were isolated, after chromatographic purification, with an overall yield of 82% and a ratio of 1.12:1 (**7**:**8**). The dihydroxylation was carried out working with 0.33 equiv of chiral ligand, six times less than it was reported before.[11] This reduction involved a decrease of the ratio between the two feasible isomers (1.12:1 in front of 2.1:1).

Baeyer–Villiger oxidation[12] of compounds **7** and **8**, both of them treated separately with freshly prepared CF_3COOOH in $CHCl_3$, at 0 °C for 5 h gave, after chromatographic purification, **9** and **10**, respectively, with a yield of 30% for each one. Moreover, it was possible to identify their corresponding isomeric 6-oxo-7-oxa lactones (**11** and **12**), through spectral data analysis. The ratio obtained for both isomers was 1:1 in both cases (**9**:**11** and **10**:**12**) according to the expected.[13]

Finally, the reduction of the azides **7**, **8**, **9** and **10** to the amines **13**, **14**, **15** and **16** were carried out through the Staudinger reaction,[14] using PPh_3 to obtain the corresponding iminophosphoranes, which were hydrolyzed to amines because of the presence of water in the media. The amine derivatives **13**–**16** were obtained with an extremely high degree of conversion but with serious problems in their purification. The main drawback was the separation of the triphenylphosphine and its related by-products from the

Table 1. Activity data

Compound	1 μg/plant	0.5 μg/plant	0.1 μg/plant	0.05 μg/plant	0.02 μg/plant	0.01 μg/plant	Activity $-\log[\text{dose}]_{45°}$
7	75°±20°	64°±9°	30°±13°	24°±17°	—	17°±9°	0.65
8	1°±1°	—	—	—	—	—	Residual[a]
9	106°±10°	94°±5°	86°±5°	74°±10°	44°±18°	37°±16°	1.76
10	48°±30°	17°±10°	—	—	—	—	Residual[a]
13	23°±15°	—	—	—	—	—	Residual[a]
14	3°±2°	—	—	—	—	—	Residual[a]
15	55°±15°	31°±23°	16°±8°	—	—	—	Residual[a]
16	5°±2°	—	—	—	—	—	Residual[a]
17	85°±3°	76°±4°	59°±7°	65°±3°	—	46°±12°	1.91

[a] Residual: below to the limit of detection.

desired compounds. After a tedious purification process, **13–16** were achieved in 31–65% yield, depending on the compound.

2.2. Activity evaluation

A highly sensitive modified rice lamina inclination test (RLIT), using Bahia as a cultivar, based on the procedure developed by Takeno and Pharis[15] has been used to evaluate the activity data of the new synthesized compounds (Table 1).[4]

Figure 1 shows the dose-dependent activity curves of this bioassay obtained for **7** and **9** as well as (22*R*,23*R*)3α-22,23-trihydroxy-5α-stigmastan-6-one (**17**) (Fig. 2), which has already been synthesized and bioactivity evaluated in a different RLIT,[6,16] in order to compare its activity values.

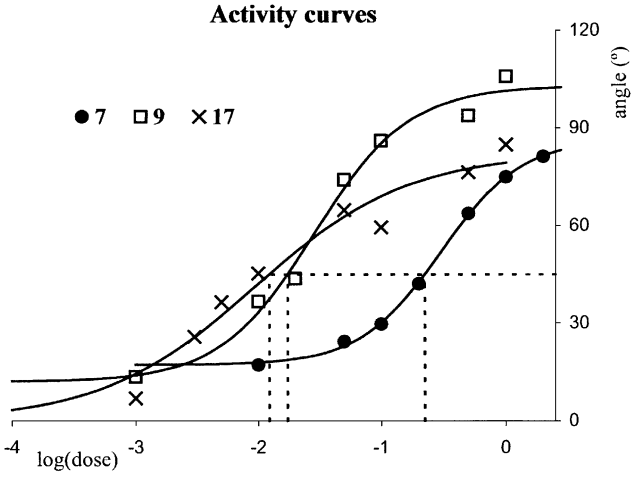

Figure 1. Dose-dependent activity curves for **7**, **9** and **17** and their activity data obtained interpolating at 45°.

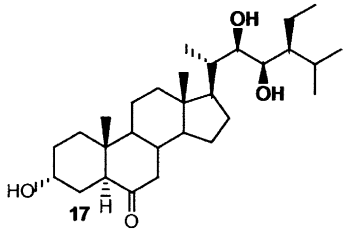

Figure 2.

3. Conclusions

From all the new analogs synthesized having a 3α-N_3 group, that act only as an acceptor in binding, only compounds **7** and **9** have elicited activity. Both contain a 22*R*,23*R* diol at the side chain and either a ketone (**7**) or a lactone (**9**) functionality in the B ring. The lack of activity for compounds **8** and **10** can be explained by the brassinosteroids having a 22*S*,23*S* diol at the side chain, which shows lower activity than their corresponding 22*R*,23*R*.

Moreover, all new analogs having a 3α-NH_2 group, which can act as a hydrogen bonding donor, have elicited residual activity with both the configuration of diol at the side chain and functionality in the B ring.

Considering the above results and the elicited activity by the 3α-N_3 derivatives **7** and **9**, in contrast with those elicited by their corresponding 3α-NH_2 analogs **13** and **15** compared with **17** suggests that the 3α-OH group present in the most active brassinosteroids could act as acceptor in the putative hydrogen bonding interaction of the brassinosteroid-receptor complex. This hypothesis is supported by the fact that compounds having ketone,[16] fluorine,[7] or methoxy[5] at C_3 have also elicited activity.

Although having another functionality different from free hydroxy groups to block the glucosydation pathway should also be taken into account,[5] it can also be noticed the importance of the different affinities of each compound with the receptor. In this sense, having an acceptor or a donor in the putative hydrogen bonding deserves to be considered. However, this question remains to be solved and further brassinosteroid analogs should be synthesized and bioactivity evaluated.

4. Experimental

4.1. Rice lamina inclination test (RLIT)

Seeds of Bahia rice cultivar were soaked in water and incubated in a growth chamber under a 16 h light/8 h darkness photoperiod at 30 °C for 2 days. The germinated seeds were planted on the surface of 0.5% aqueous agar medium and incubated under the above conditions for 4 days. Selected seedlings were treated with the brassinosteroid test solutions (95% ethanol) by applying them with a microsyringe (0.5 μL) onto the second lamina joint of the

plant sheath (10–12 plants). Treated and untreated (control) seedlings were returned to the growth chamber at 30 °C in the dark for 2 days. The interior angle between the leaf lamina of the second leaf and its leaf sheath was then measured. This procedure was repeated for 3 or 4 times for each dose tested and statistical parameters were calculated.

4.2. Synthesis

Melting points were determined using a Büchi 530 instrument and are uncorrected. IR spectra were obtained on a Nicolet Magna 560 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Gemini-300 (300 MHz) spectrometer using TMS as internal standard. The multiplicity of the signals in the ^{13}C NMR was determined using the Distorsionless enhancement polarization transfer (DEPT) sequence. Mass spectra of positive ions were obtained by chemical ionization (MS (CI), *m/z*), were run on a Helwett–Packard 5988-A instrument using methane as the carrier gas. High resolution mass spectra (HRMS (CI)) were measured on a Fisions VG-Altospec spectrometer. The progress of all reactions and column chromatography was monitored by TLC on silica gel $60F_{254}$ microplates (Macherey-Nagel (MN), Art 804023) and spots were detected by spraying with 50% sulfuric acid, followed by heating. Flash column chromatography was performed on 230–400 mesh MN silica gel. Medium-pressure chromatography was run on a Lichoprep Si 60 column (Merck) (silica gel 230–400 mesh). Dry solvents were distilled immediately before use. Petroleum ether refers to the fraction boiling at 40–65 °C.

4.2.1. (22*E*) 3α-Azido-5α-stigmast-22-en-6-one (4). A solution of **3** (0.99 g, 2.32 mmol) in anhydrous toluene (10 mL) and anhydrous TEA (2.7 mL) was treated with methanesulfonyl chloride (0.7 mL, 9.05 mmol). The mixture was stirred at 0 °C for 5 h and extracted with AcOEt. Then, the organic layer was washed with HCl (1 N), a saturated solution of $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. Removal of the solvent yielded the crude product (22*E*) 3β-mesyloxy-5ξ-stigmast-22-en-6-one (1.124 g). The crude solution (0.97 g) in dry DMF (8.2 mL) was treated with sodium azide (0.39 g, 6.0 mmol) under argon and heated to 90 °C for 12 h. The solvent was then evaporated to dryness and the mixture dissolved in AcOEt. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The mixture was purified by flash and medium-pressure chromatography (Cy/$CHCl_3$ (3:1)) to give **6** (11 mg, 1% from **3**), **2** (34 mg, 4% from **3**), **4** (676 mg, 74% from **3**) and **5** (45 mg, 5% from **3**).

4.2.1.1. (22*E*) 3α-Azido-5α-stigmast-22-en-6-one (4). Mp (petroleum ether): 118–119 °C; IR ν^{CHCl_3} cm^{-1}: 2956, 2870, 1708, 1368, 1173, 945; ^{1}H NMR ($CDCl_3$): 0.68 (18-H_3, 3H, s), 0.74 (19-H_3, 3H, s), 0.79 (27-H_3, 3H, d, J=6.6 Hz), 0.80 (29-H_3, 3H, t, J=7.5 Hz), 0.84 (26-H_3, 3H, d, J=6.6 Hz), 1.02 (21-H_3, 3H, d, J=6.6 Hz), 3.99 (3β-H, 1H, m), 5.02 (23-H, 1H, dd, J=15.0, 8.4 Hz), 5.15 (22-H, 1H, dd, J=15.0, 8.4 Hz); ^{13}C NMR ($CDCl_3$): 12.2 (C18 and C29), 12.6 (C19), 19.0 (C27), 21.0 (C11), 21.1 (C21 and C26), 24.0 (C15), 24.8 and 24.9 (C2 and C4), 25.4 (C28), 28.7 (C16), 31.9 (C25), 32.3 (C1), 37.9 (C8), 39.3 (C12), 40.4 (C20), 41.3 (C10), 42.8 (C13), 46.7 (C7), 51.2 (C24), 52.4 (C5), 53.7 (C9), 55.9 (C17), 56.9 (C14), 57.2 (C3), 129.6 (C23), 138.0 (C22), 211.7 (C6); MS (CI), *m/z* (%): 454 ([M+1]$^+$, 89), 453 ([M]$^+$, 64), 439 ([M+1-15]$^+$, 3), 427 (35), 426 (100), 411 (37), 410 (40), 382 (43), 341 (57), 340 (37), 314 (42), 313 (45), 312 (61), 386 (37), 273 (32). HRMS (CI): 454.3797 [M+1]$^+$, (Calcd 454.3797).

4.2.1.2. (22*E*) 3α-Azido-5β-stigmast-22-en-6-one (5). Mp (petroleum ether):131–132 °C; IR ν^{CHCl_3} cm^{-1}: 2955, 2934, 2869, 2092, 1700; ^{1}H NMR ($CDCl_3$): 0.67 (18-H_3, 3H, s), 0.79 (27-H_3, 3H, d, J=6.6 Hz), 0.80 (29-H_3, 3H, t, J=7.5 Hz), 0.84 (26-H_3, 3H, d, J=6.6 Hz), 0.86 (19-H_3, 3H, s), 1.02 (21-H_3, 3H, d, J=6.6 Hz), 3.32 (3β-H, 1H, m), 5.02 (23-H, 1H, dd, J=15.0, 8.4 Hz), 5.15 (22-H, 1H, dd, J=15.0, 8.4 Hz); ^{13}C NMR ($CDCl_3$): 12.2 (C18 and C29), 19.0 (C27), 20.8 (C11), 21.1 and 21.2 (C21 and C26), 23.3 (C19), 24.0 (C15), 25.4 (C28), 28.8 (C16), 31.9 (C25), 26.3, 34.1 and 34.5 (C1, C2 and C4), 37.1 (C8), 37.9 (C10), 39.5 (C12), 40.0 (C9), 40.4 (C20), 42.9 (C7 and C13), 51.2 (C24), 55.9 (C17), 56.9 (C14), 59.5 and 59.7 (C3 and C5), 129.7 (C23), 137.9 (C22), 212.6 (C6).

4.2.2. (22*R*,23*R*) 3α-Azido-22,23-dihydroxy-5α-stigmastan-6-one (7) and (22*S*,23*S*) 3α-azido-22,23-dihydroxy-5α-stigmastan-6-one (8). A solution of **4** (4.96 g, 10.94 mmol), OsO_4 (0.09 g, 0.37 mmol), dihydroquinidine 9-*O*-(9′-phenantryl) ether (1.83 g, 3.65 mmol), *N*-methylmorpholine-*N*-oxide (14.4 g, 108.0 mmol) and $Et_4N^+AcO^-\cdot nH_2O$ (2.05 g, 7.85 mmol) in THF (54 mL), *t*-ButOH (41 mL) and H_2O (9 mL) was stirred under argon atmosphere at 0 °C in the dark for 11 days. The mixture reaction was treated with a saturated solution of $Na_2S_2O_5$ (100 mL) and stirred at room temperature for 1 h. The reaction crude was then extracted with AcOEt, the organic phase was washed with water and brine, and dried over anhydrous $MgSO_4$. Removal the solvent yielded the crude product (11.88 g), which was purified by flash chromatography ($CHCl_3$/AcOEt 15:1) to give **7** (2.28 g, 43%) and **8** (2.06 g, 39%).

4.2.2.1. (22*R*,23*R*) 3α-Azido-22,23-dihydroxy-5α-stigmastan-6-one (7). Mp (petroleum ether): 143–144 °C; IR ν^{CHCl_3} cm^{-1}: 3496, 2940, 2869, 2109, 1703, 983; ^{1}H NMR ($CDCl_3$): 0.68 (18-H_3, 3H, s), 0.74 (19-H_3, 3H, s), 0.91 (21-H_3, 3H, d, J=6.3 Hz), 0.95 (29-H_3, 3H, t, J=7.5 Hz), 0.96 (27-H_3, 3H, d, J=6.9 Hz), 0.97 (26-H_3, 3H, d, J=6.9 Hz), 3.60 (22-H, 1H, m), 3.72 (23-H, 1H, m), 3.99 (3β-H, 1H, m); ^{13}C NMR ($CDCl_3$): 11.8 (C18), 11.9 (C21), 12.6 (C19), 13.4 (C29), 18.8 (C28), 19.4 (C27), 21.1 (C11), 21.2 (C26), 23.8 (C15), 24.7 and 24.9 (C2 and C4), 27.6 (C16), 28.8 (C25), 32.2 (C1), 36.9 (C20), 38.0 (C8), 39.4 (C12), 41.3 (C10), 42.8 (C13), 46.3 (C24), 46.6 (C7), 52.3 (C5), 52.5 (C17), 53.6 (C9), 56.6 (C14), 57.1 (C3), 72.7 (C23), 74.5 (C22), 211.7 (C6); MS (CI), *m/z* (%): 488 ([M+1]$^+$, 6), 470 ([M+1-18]$^+$, 3), 373 (100), 372 (52). HRMS (CI): 488.3838 [M+1]$^+$, (Calcd 488.3825).

4.2.2.2. (22*S*,23*S*) 3α-Azido-22,23-dihydroxy-5α-stigmastan-6-one (8). Mp (petroleum ether): 210–211 °C; IR ν^{CHCl_3} cm^{-1}: 3545, 3381, 2960, 2872, 2108, 2086, 1701; ^{1}H NMR ($CDCl_3$): 0.70 (18-H_3, 3H, s), 0.74 (19-H_3, 3H, s), 0.89 (27-H_3, 3H, d, J=6.9 Hz), 0.95 (26-H_3, 3H,

d, $J=6.9$ Hz), 0.97 (29-H_3, 3H, t, $J=7.5$ Hz), 1.04 (21-H_3, 3H, d, $J=6.9$ Hz), 3.60–3.62 (22-H and 23-H, 2H, m), 3.99 (3β-H, 1H, m); ^{13}C NMR ($CDCl_3$): 11.9 (C18), 12.6 (C19), 14.1 (C21), 14.5 (C29), 17.7 (C27), 18.5 (C28), 21.0 (C11), 21.7 (C26), 24.1 (C15), 24.7 and 24.9 (C2 and C4), 26.9 (C25), 27.8 (C16), 32.2 (C1), 37.8 (C8), 39.3 (C12), 41.2 (C10), 42.3 (C20), 43.4 (C13), 46.6 (C7), 49.6 (C24), 52.4 (C5), 52.6 (C17), 53.6 (C9), 56.3 (C14), 57.1 (C3), 70.6 (C23), 72.1 (C22), 211.6 (C6); MS (CI), *m/z* (%): 488 ([M+1]$^+$, 8), 470 ([M+1-18]$^+$, 4), 374 (37), 373 (100), 372 (48). HRMS (CI): 488.3833 [M+1]$^+$, (Calcd 488.3825).

4.2.3. (22*R*,23*R*) 3α-Azido-22,23-dihydroxy-6,7-*seco*-5α-stigmasta-6,7-lactone (9). A solution of **7** (650 mg, 1.38 mmol) in $CHCl_3$ (98 mL) at 0 °C was treated with a freshly prepared CF_3COOOH (12.7 mL) at 0 °C under argon atmosphere in the dark for 5 h. Then, a saturated solution of $Na_2S_2O_5$ (120 mL) was added and stirred for 1 h. Then, the mixture was treated with $NaHCO_3$ (s) and the organic layer was washed with brine, dried over $MgSO_4$ anhydrous and evaporated to dryness. The crude mixture was purified by medium-pressure chromatography (Cy/$CHCl_3$/AcOEt 3:2:1) to give **9** (207 mg, 30%) and another more polar fraction rich in **11**.

4.2.3.1. (22*R*,23*R*) 3α-Azido-22,23-dihydroxy-6,7-*seco*-5α-stigmasta-6,7-lactone (9). Mp (petroleum ether): 193–194 °C; IR ν^{CHCl_3} cm^{-1}: 3447, 2960, 2094, 1726, 1466, 1183, 757; ^{1}H NMR ($CDCl_3$): 0.71 (18-H_3, 3H, s), 0.90 (19-H_3, 3H, s), 0.90 (21-H_3, 3H, d, $J=6.3$ Hz), 0.96 (29-H_3, 3H, t, $J=7.5$ Hz), 0.96 (27-H_3, 3H, d, $J=6.9$ Hz), 0.97 (26-H_3, 3H, d, $J=6.9$ Hz), 3.02 (5α-H, 1H, dd, $J=12.3$, 4.2 Hz), 3.58 (22-H, 1H, m), 3.72 (23-H, 1H, m), 3.99 (3β-H, 1H, m), 4.03–4.14 (7-H_2, 2H, m). ^{13}C NMR ($CDCl_3$): 11.0 (C18), 12.0 (C21), 13.6 (C29), 14.9 (C19), 18.9 (C28), 19.5 (C27), 21.3 (C26), 22.2 (C11), 24.8 (C15), 25.3 (C2), 27.6 (C16), 28.9 (C25), 29.7 (C4), 33.8 (C1), 36.3 (C10), 37.0 (C20), 39.6 (C8), 39.7 (C12), 42.5 (C5), 42.5 (C13), 46.4 (C24), 51.3 and 58.3 (C9 and C14), 52.5 (C17), 56.7 (C3), 70.5 (C7), 72.8 (C23), 74.4 (C22), 175.9 (C6). MS (CI), *m/z* (%): 504 ([M+1]$^+$, 11), 486 ([M+1-18]$^+$, 9), 390 (68), 389 (100), 388 (83), 361 (43), 360 (72), 359 (82), 145 (31). HRMS (CI): 504.3815 [M+1]$^+$, (Calcd 504.3814).

4.2.3.2. (22*R*,23*R*) 3α-Azido-22,23-dihydroxy-5,6-*seco*-5α-stigmasta-6,5-lactone (11). Although it was not possible to isolate this compound in a high purity, the spectral data is consistent with its structure: ^{1}H NMR ($CDCl_3$): 0.71 (18-H_3, 3H, s), 0.90 (19-H_3, 3H, s), 0.90 (21-H_3, 3H, d, $J=6.3$ Hz), 0.96 (29-H_3, 3H, t, $J=7.5$ Hz), 0.96 (27-H_3, 3H, d, $J=6.9$ Hz), 0.97 (26-H_3, 3H, d, $J=6.9$ Hz), 2.44 (7-H, 2H, m), 3.58 (22-H, 1H, m), 3.71 (23-H, 1H, m), 4.03 (3β-H, 1H, m), 4.45 (5α-H, 1H, dd, $J=11.4$, 5.4 Hz).

4.2.4. (22*S*,23*S*) 3α-Azido-22,23-dihydroxy-6,7-*seco*-5α-stigmasta-6,7-lactone (10). Compound **8** (320 mg, 0.68 mmol) was treated in a similar way as described for compound **7**. The crude was purified by medium-pressure chromatography (Cy/$CHCl_3$/AcOEt 4:2:1) to give compound **10** (97 mg, 30%) and another more polar fraction rich in **12**.

4.2.4.1. (22*S*,23*S*) 3α-Azido-22,23-dihydroxy-6,7-*seco*-5α-stigmasta-6,7-lactone (10). Mp (petroleum ether): 87–89 °C; IR ν^{CHCl_3} cm^{-1}: 3446, 2955, 2094, 1726, 1184, 756; ^{1}H NMR ($CDCl_3$): 0.74 (18-H_3, 3H, s), 0.88 (27-H_3, 3H, d, $J=6.9$ Hz), 0.90 (19-H_3, 3H, s), 0.95 (26-H_3, 3H, d, $J=6.9$ Hz), 0.96 (29-H_3, 3H, t, $J=7.5$ Hz), 1.03 (21-H_3, 3H, d, $J=6.9$ Hz), 3.01 (5α-H, 1H, dd, $J=12.3$, 4.2 Hz), 3.59–3.61 (22-H and 23-H, 2H, m), 3.99 (3β-H, 1H, m), 4.14–4.04 (7-H_2, 2H, m); ^{13}C NMR ($CDCl_3$): 11.8 (C18), 14.2 (C21), 14.5 (C29),14.8 (C19), 17.8 (C27), 18.6 (C28), 21.8 (C26), 22.2 (C11), 25.2 and 25.3 (C2 and C15), 27.0 (C25), 27.9 (C16), 29.8 (C4), 33.8 (C1), 36.3 (C10), 39.5 (C8), 39.6 (C12), 42.3 (C20), 42.5 (C5), 43.2 (C13), 49.6 (C24), 52.6 (C17), 51.1 and 58.4 (C9 and C14), 56.3 (C3), 70.5 (C7), 70.6 (C23), 72.2 (C22), 175.8 (C6). MS (CI), *m/z* (%): 504 ([M+1]$^+$, 14), 486 ([M+1–18]$^+$, 11), 390 (67), 389 (100), 388 (88), 370 (21), 361 (46), 360 (68), 359 (100), 330 (31), 328 (32), 145 (51), 127 (31). HRMS (CI): 504.3820 [M+1]$^+$, (Calcd 504.3815).

4.2.4.2. (22*S*,23*S*) 3α-Azido-22,23-dihydroxy-5,6-*seco*-5α-stigmasta-6,5-lactone (12). Although it was not possible to isolate this compound in a high purity, the spectral data is consistent with its structure: IR ν^{CHCl_3} cm^{-1}: 3444, 2955, 2104, 1725, 1276, 756; ^{1}H RMN ($CDCl_3$): 0.73 (18-H_3, 3H, s), 0.88 (27-H_3, 3H, d, $J=6.9$ Hz), 0.90 (19-H_3, 3H, s), 0.95 (26-H_3, 3H, d, $J=6.9$ Hz), 0.96 (29-H_3, 3H, t, $J=7.5$ Hz), 1.03 (21-H_3, 3H, d, $J=6.9$ Hz), 2.49 (7-H, 2H, m), 3.59–3.61 (22-H and 23-H, 2H, m), 4.03 (3β-H, 1H, m), 4.44 (5α-H, 1H, dd, $J=11.4$, 5.4 Hz); ^{13}C NMR ($CDCl_3$): 11.7 (C18), 11.8 (C19), 14.1 (C21), 14.5 (C29), 17.8 (C27), 18.6 (C28), 21.8 (C26), 22.2 (C11), 24.8 and 25.6 (C2 and C15), 26.9 (C25), 27.4 (C16), 32.0 and 32.7 (C1 and C4), 34.8 (C8), 38.1 (C7), 39.6 (C12), 39.8 (C10), 42.3 (C20), 43.2 (C13), 49.6 (C24), 52.8 (C17), 55.1, 57.6 and 57.9 (C3, C9 and C14), 70.6 (C23), 72.0 (C22), 79.3 (C5), 174.6 (C6).

4.2.5. General procedure for the reduction of azides to amines

A solution of azide **7**-**10**, PPh_3 (1–1.5 equiv) and water (5–15 equiv) in THF was stirred at room temperature for 2–6 days. The solvent was evaporated to dryness. The crude mixture was purified by flash cromatography (AcOEt, AcOEt/MeOH 9:1, AcOEt/MeOH/NH_3 9:1:0.3) and the residue afforded was dissolved in $CHCl_3$ and the organic phase was treated with NaOH (1 M) and evaporated to dryness. Finally, solid was treated with a mixture of EtOH/H_2O at room temperature to give the amine **13**–**16**.

4.2.5.1. (22*R*,23*R*) 3α-Amino-22,23-dihydroxy-5α-stigmastan-6-one (13). Yield 65%. Mp (EtOH/H_2O): 190 °C (decomp.); IR ν^{CHCl_3} cm^{-1}: 3451, 3362, 3304, 2942, 2869, 1707, 1382, 756; ^{1}H NMR ($CDCl_3$): 0.68 (18-H_3, 3H, s), 0.73 (19-H_3, 3H, s), 0.91 (21-H_3, 3H, d, $J=6.3$ Hz), 0.95 (29-H_3, 3H, t, $J=7.5$ Hz), 0.96 (27-H_3, 3H, d, $J=6.9$ Hz), 0.97 (26-H_3, 3H, d, $J=6.9$ Hz), 3.38 (3β-H, 1H, m), 3.59 (22-H, 1H, m), 3.72 (23-H, 1H, m); ^{13}C NMR ($CDCl_3$): 12.0 (C18), 12.0 (C21), 12.6 (C19), 13.6 (C29), 18.9 (C28), 19.5 (C27), 21.2 (C11), 21.3 (C26), 23.9 (C15), 27.7, 27.7 and 28.0 (C2, C4 and C16), 28.9 (C25), 31.6 (C1), 37.0 (C20), 38.1 (C8), 39.6 (C12), 41.8 (C10), 42.8 (C13), 44.5 (C3), 46.3 (C24), 46.7 (C7), 51.5 (C5), 52.5 (C17), 53.6 (C9), 56.7 (C14), 72.7 (C23), 74.5 (C22), 212.8 (C6); MS (CI), *m/z*

(%): 462 ([M+1]$^+$, 88), 461 ([M]$^+$, 92), 447 ([M+1–15]$^+$, 3), 446 ([M−15]$^+$, 9), 444 ([M+1–18]$^+$, 19), 443 ([M−18]$^+$, 6), 347 (100), 346 (74), 345 (34). HRMS (CI): 461.3854 [M+1]$^+$, (Calcd 461.3842).

4.2.5.2. (22*S*,23*S*) 3α-Amino-22,23-dihydroxy-5α-stigmastan-6-one (14). Yield 63%. Mp (EtOH/H_2O): 146–147 °C; IR ν^{CHCl_3} cm^{-1}: 3437, 2948, 1707, 1382, 756; ^{1}H NMR ($CDCl_3$): 0.70 (18-H_3, 3H, s), 0.73 (19-H_3, 3H, s), 0.89 (27-H_3, 3H, d, J=6.9 Hz), 0.95 (26-H_3, 3H, d, J=6.9 Hz), 0.96 (29-H_3, 3H, t, J=7.5 Hz), 1.03 (21-H_3, 3H, d, J=6.9 Hz), 3.38 (3β-H, 1H, m), 3.60–3.61 (22-H and 23-H, 2H, m); ^{13}C NMR ($CDCl_3$): 12.0 (C18), 12.9 (C19), 14.2 (C21), 14.6 (C29), 17.8 (C27), 18.7 (C28), 21.1 (C11), 21.8 (C26), 24.3 (C15), 27.0 (C25), 27.7 and 27.9 (C2 and C4), 28.0 (C16), 31.6 (C1), 38.0 (C8), 39.6 (C12), 41.8 (C10), 42.3 (C20), 43.5 (C13), 44.5 (C3), 46.9 (C7), 49.6 (C24), 51.6 (C5), 52.6 (C17), 53.8 (C9), 56.5 (C14), 70.6 (C23), 72.1 (C22), 212.7 (C6); MS (CI), *m/z* (%): 462 ([M+1]$^+$, 86), 461 ([M]$^+$, 81), 447 ([M+1-15]$^+$, 5), 446 ([M−15]$^+$, 10), 444 ([M+1–18]$^+$, 22), 443 ([M−18]$^+$, 7), 347 (100), 346 (64), 345 (32), 317 (32), 281 (32), 131 (46). HRMS (CI): 462.3930 [M+1]$^+$, (Calcd 462.3920).

4.2.5.3. (22*R*,23*R*) 3α-Amino-22,23-dihydroxy-6,7-*seco*-5α-stigmasta-6,7-lactone (15). Yield 31%. Mp (EtOH/H_2O): 220–221 °C; IR ν^{CHCl_3} cm^{-1}: 3446, 2958, 1719, 1184, 755; ^{1}H NMR ($CDCl_3$): 0.71 (18-H_3, 3H, s), 0.89 (19-H_3, 3H, s), 0.90 (21-H_3, 3H, d, J=6.3 Hz), 0.95 (29-H_3, 3H, t, J=7.5 Hz), 0.96 (27-H_3, 3H, d, J=6.9 Hz), 0.97 (26-H_3, 3H, d, J=6.9 Hz), 3.15 (5α-H, 1H, dd, J=12.9, 3.9 Hz), 3.38 (3β-H, 1H, m), 3.58 (22-H, 1H, m), 3.75 (23-H, 1H, m), 4.08–4.10 (7-H_2, 2H, m); ^{13}C NMR ($CDCl_3$): 11.8 (C18), 12.0 (C21), 13.6 (C29), 14.9 (C19), 19.0 (C28), 19.6 (C27), 21.4 (C26), 22.3 (C11), 24.8 (C15), 27.7 and 28.2 (C2 and C16), 28.9 (C25), 32.7 and 32.8 (C1 and C4), 36.6 (C10), 37.0 (C20), 39.6 (C8), 39.8 (C12), 41.5 (C5), 42.6 (C13), 44.2 (C3), 46.4 (C24), 51.4 and 58.3 (C9 and C14), 52.5 (C17), 70.4 (C7), 72.8 (C23), 74.4 (C22), 176.7 (C6); MS (CI), *m/z* (%): 478 ([M+1]$^+$, 96), 477 ([M]$^+$, 20), 463 ([M+1–15]$^+$, 3), 462 ([M−15]$^+$, 9), 460 ([M+1–18]$^+$, 20), 363 (100), 362 (100), 346 (30), 333 (38). HRMS (CI): 478.3885 [M+1]$^+$, (Calcd 478.3896).

4.2.5.4. (22*S*,23*S*) 3α-Amino-22,23-dihydroxy-6,7-*seco*-5α-stigmasta-6,7-lactone (16). Yield 40%. Mp (EtOH/H_2O): 110.5–111.5 °C; IR ν^{CHCl_3} cm^{-1}: 3414, 2955, 2871, 1718, 755; ^{1}H NMR ($CDCl_3$): 0.73 (18-H_3, 3H, s), 0.88 (27-H_3, 3H, d, J=6.9 Hz), 0.91 (19-H_3, 3H, s), 0.95 (26-H_3, 3H, d, J=6.9 Hz), 0.96 (29-H_3, 3H, t, J=7.5 Hz), 1.03 (21-H_3, 3H, d, J=6.9 Hz), 3.18 (5α-H, 1H, dd, J=12.3, 4.3 Hz), 3.38 (3β-H, 1H, m), 3.59–3.61 (22-H and 23-H, 2H, m), 4.08–4.10 (7-H_2, 2H, m); ^{13}C NMR ($CDCl_3$): 11.8 (C18), 14.2 (C21), 14.6 (C29),14.9 (C19), 17.8 (C27), 18.7 (C28), 21.8 (C26), 22.2 (C11), 25.2 (C15), 27.0 (C25), 27.8 and 27.9 (C2 and C16), 32.2 and 32.7 (C1 and C4), 36.6 (C10), 39.5 (C8), 39.7 (C12), 41.4 (C5), 42.3 (C20), 43.2 (C13), 44.4 (C3), 49.5 (C24), 51.2 and 58.1 (C9 and C14), 52.6 (C17), 70.4 (C7), 70.8 (C23), 72.2 (C22), 176.6 (C6); MS (CI), *m/z* (%): 478 ([M+1]$^+$, 100), 477 ([M]$^+$, 18), 463 ([M+1–15]$^+$, 3), 462 ([M−15]$^+$, 5), 460 ([M+1–18]$^+$, 20), 363 (78), 362 (73). HRMS (CI): 478.3896 [M+1]$^+$, (Calcd 478.3896).

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9. Although the synthesis and spectral data of compound **3a** has already been published,[17] it has also been possible to isolate (22*E*) 3β-hydroxy-5β-stigmast-22-en-6-one (**3b**): IR ν^{CHCl_3} cm^{-1}: 3503, 3348, 2955, 2868, 1703; ^{1}H NMR ($CDCl_3$): 0.68 (18-H_3, 3H, s), 0.80 (29-H_3, 3H, t, J=7.2 Hz), 0.79 (27-H_3, 3H, d, J=6.6 Hz), 0.84 (26-H_3, 3H, d, J=6.6 Hz), 0.88 (19-H_3, 3H, s), 1.02 (21-H_3, 3H, d, J=6.6 Hz), 4.13 (3β-H, 1H, m), 5.02 (23-H, 1H, dd, J=15.0, 8.4 Hz), 5.14 (22-H, 1H, dd, J=15.0, 8.4 Hz); ^{13}C NMR ($CDCl_3$): 12.1 (C18), 12.2 (C29), 18.9 (C27), 21.0 (C26), 21.1 (C11), 21.2 (C21), 23.8 (C19), 24.0 (C15), 25.4 (C28), 28.8 (C16), 31.8 (C25), 27.2, 28.6 and 33.0 (C1, C2 and C4), 36.8 (C8), 38.1 (C10), 39.5 (C9), 39.6 (C12), 40.4 (C20), 42.9 (C13), 43.0 (C7), 51.2 (C24), 54.4 (C5), 55.9 (C17), 57.0 (C14), 64.7 (C3), 129.6 (C23), 137.9 (C22), 215.4 (C6)
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Synthesis and biological activities of 5′-ethylenic and acetylenic modified L-nucleosides and isonucleosides

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Abstract—Two series of 6′-halovinyl-adenosine stereoisomers including 5′-ethylenic and acetylenic substituted L-adenosine, 5′-ethylenic and acetylenic substituted isonucleosides were synthesized. In the L-nucleoside series, compounds **6b**, **8b**, **10b** and **13b** showed modest inhibition of SAH hydrolase (21, 44, 50 and 26% respectively) at 100 μM. The L-isomers of 5′-ethylenic and acetylenic modified isonucleoside **23**, **24** exhibited no activity for the inhibition of SAH hydrolase, however, the D-isomers **30** and **31** showed some activities in the same test (35 and 21%). It indicated clearly the strict stereochemical requirement for the substrate of SAH hydrolase. Compounds **6b**, **8b**, **8c**, **11b** exhibited modest to good inhibition effects on the growth of HeLa cells or Bel-7420 cells at 1 μM (64, 44, 53 and 82% respectively).

1. Introduction

Methylated 5′-cap structure plays an essential role for the stability of mRNA against phosphatases and ribonucleases, for proper binding to ribosomes, and for the promotion of splicing. Hence, an uncapped mRNA is much less likely to be translated into its respective protein. Since many types of viruses also require methylated 5′-capped mRNA for proper translation into proteins, interference with the formation of these 5′-caps could lead to the inhibition of replication.[1,2] The various methyltransferases which catalyze these reactions have been targeted for drug design. The normal cellular role of SAH hydrolase is regulating *S*-adenosyl-L-methionine dependent biological methylation reactions. *S*-Adenosyl-L-methionine is involved in the methylation of many biomolecules and SAH is a potent feedback inhibitor of crucial transmethylation enzymes.[3–5] De Clercq and Cools found that some adenosine analogues showed the inhibition of vaccinia virus replication and a good correlation between the antiviral effectiveness and their ability to inhibit SAH hydrolase.[6] According to the mechanism of the hydrolysis of SAH by SAH hydrolase, many adenosine analogues, including some acyclic sugar mimics, have been designed and displayed interesting broad-spectrum antiviral properties. These first-generation inhibitors act as substrates for the first step in the hydrolysis reaction, where, the enzyme oxidizes the 3′-hydroxyl group of SAH to ketone and converts the NAD^+ to NADH in the process.[7,8] However, some dihalohomovinyl adenosine analogues were reported as the inhibitors for the 'type II' inactivation of SAH hydrolase involving its '5′/6′-hydrolytic activity'. The type II inhibitors contain an electrophilic entity at 5′-position of adenosine which could bind covalently to the enzyme without prior oxidation at 3′-position.[9] This discovery may open a way to the rational design of antiviral and antitumour drugs. Many 5′-halovinyl adenosine analogues or its conjugated diene analogues and acetylenic analogues were reported.[10–15] It was suggested that enzyme-mediated addition of water across the 5′,6′-double bond could generate electrophilic acyl halids or α-halo ketone species that could undergo nucleophilic attack by proximal groups on the enzyme and addition of water across the 5′,6′-triple bond followed by tautomerization of the hydroxyvinyl intermediates could also generate similar electrophiles at the enzyme active site. L-Nucleosides are the enantiomers of the natural nucleosides. Among these

Keywords: Stereoisomers; Biological activity; L-Nucleoside series.

Abbreviations: Ado, adenosine; AIBN, 2,2′-azobisisobutyronitrile; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; ACN, acetonitrile; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DCM, dichloromethane; DEAD, diethyl azodicarboxylate; DIBAL-H, diisobutylaluminum hydride; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; Hcy, homocysteine; HBV, heptitis B virus; HIV, human immunodeficiency virus; HPLC, high-performance liquid chromatography; HRMS (TOF), high resolution mass spectrometry; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide; NAD^+, the oxidized form of NAD; NADH, the reduced form of NAD; NAD, nicotinamide–adenine dinucleotide; NMR, nuclear magnetic resonance; PBE, 20 mM phosphate buffer and 5 mM EDTA; Py, pyridine; RP-HPLC, reverse phase high-performance liquid chromatography; SAH, *S*-adenosyl-L-homocysteine; 3TC, (−)-β-L-1,3-oxathiolanyl-cytosine; TFA, trifluoroacetic acid; TMSOTf, trimethylsilyl trifluromethanesulfonate; Ts, toluenesulfonyl; TSA, *p*-toluenesulfonic acid; THF, tetrahydrofuran.

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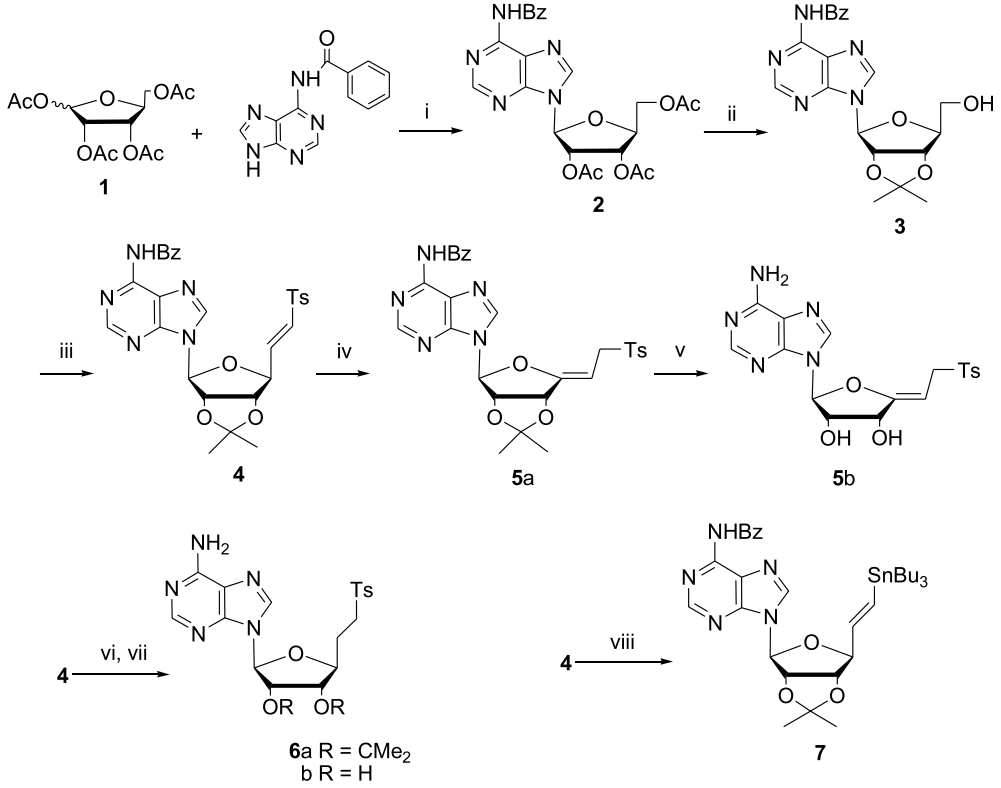
compounds, the separated enantiomer of L-2′-deoxy-3′-thiacytidine (3TC) demonstrated more potent activities against both HIV and HBV than their corresponding D-configuration counterparts with much less host toxicity.[16] Since then, a number of L-nucleoside analogues have been synthesized and biologically evaluated.[17–21] Isonucleosides represent a novel class of carbohydrate modified nucleosides in which the nucleobase is linked to various positions of ribose other than C-1′. We have reported a series of syntheses of isonucleosides.[22–25] The conformations of such L-nucleosides and isonucleosides exhibit profound changes compared to natural nucleosides. These alternations in conformation might be interesting to understand the recognition of L-nucleosides and isonucleosides as substrates by SAH hydrolase and explain the specific substrates requirement of SAH hydrolase. Herein, we report the synthesis of such L-nucleoside and isonucleoside analogues and their inactivation of SAH hydrolase.

2. Chemistry

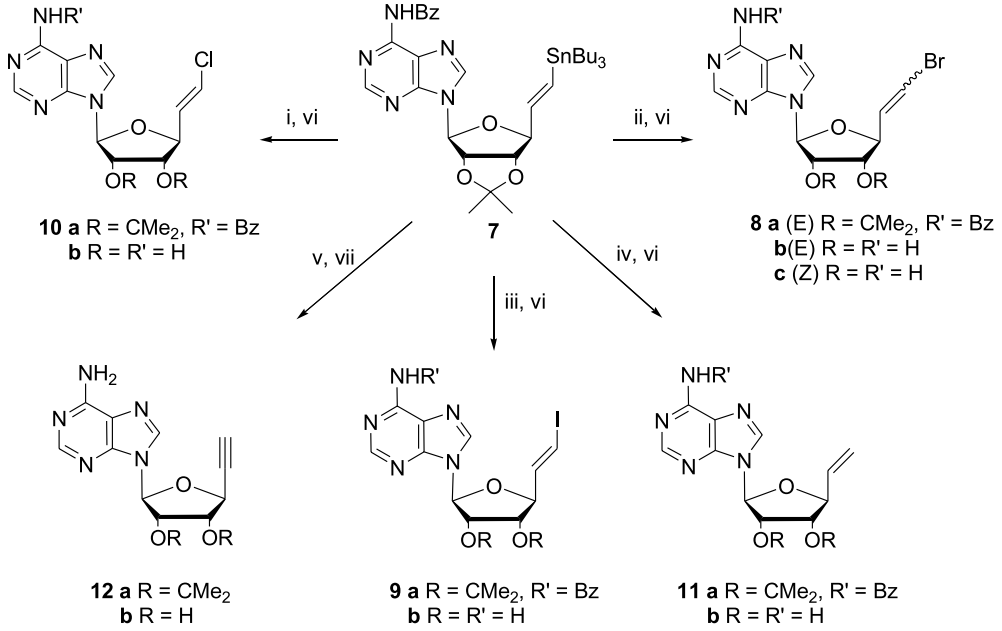
2.1. Synthesis of 5′-ethylenic and acetylenic substituted L-adenosine analogues

According to a known procedure, condensation of 1,2,3,5-tetra-*O*-acetyl-L-ribose **1** with benzoyl adenine provided the fully protected nucleoside **2** in 86% yield.[26] After removal of the acetyl groups, the 2′,3′-hydroxy groups of compound **2** were protected in the presence of $HC(OEt)_3$ and a catalytic amount of TSA at room temperature to give 6-*N*-benzoyl-2′,3′-*O*-isopropylidene-L-adenosine **3** in 81% yield. In order to synthesize the 5′-ethylenic adenosine, we tried first to isolate 5′-aldehyde adenosine after Moffatt oxidation of compound **3**. But many efforts failed due to the instability of 5′-aldehyde intermediate. However, the 5′-aldehyde intermediate in solution (without separation) could react with a stable Wittig reagent [(*p*-tolylsulfonyl)methylene]triphenyl phosphorane[27,28] to give compound **4** in 97% yield (Scheme 1). ^{1}H NMR data showed that compound **4** had *E*-form double bond signals at 5′ and 6′ position (δ=6.30, $H_{6'}$; δ=6.99, $H_{5'}$; $J_{5',6'}$=15.0 Hz). Isomerization of compound **4** was observed in basic condition. When compound **4** was treated with 1 M NaOH, a pure 6′-tosylallylic adenosine **5a** was obtained in 70% yield. **5a** was deprotected to give **5b** which can be confirmed by ^{13}C NMR, the double bond shifted to 4′,5′ position (δ=161.0, $C_{4'}$; δ=86.4, $C_{5'}$). According to the computer simulation, the *Z*-configuration of the double bond in compound **5b** is thermodynamicly more stable than the *E*-configuration. Treatment of **4** with sodium borohydride in aqueous methanol resulted in reduction of the tosylvinyl to give **6**a in 93% yield. Deprotection of **6a** gave **6b** in 54% yield.

Stannyldesulfonylation (Bu_3SnH/AIBN/toluene)[29] of **4** provided the 6-*N*-benzoyl-9-[6′-(*E*)-(tributylstannyl)-5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenine **7**. Compound **7** was reacted with *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS) and chlorine respectively to provide the 6-*N*-benzoyl-9-[6′-halo-5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenine **8a**, **9a**, **10a** (89, 98 and 77% respectively) and only *E*-form isomers were formed (Scheme 2).

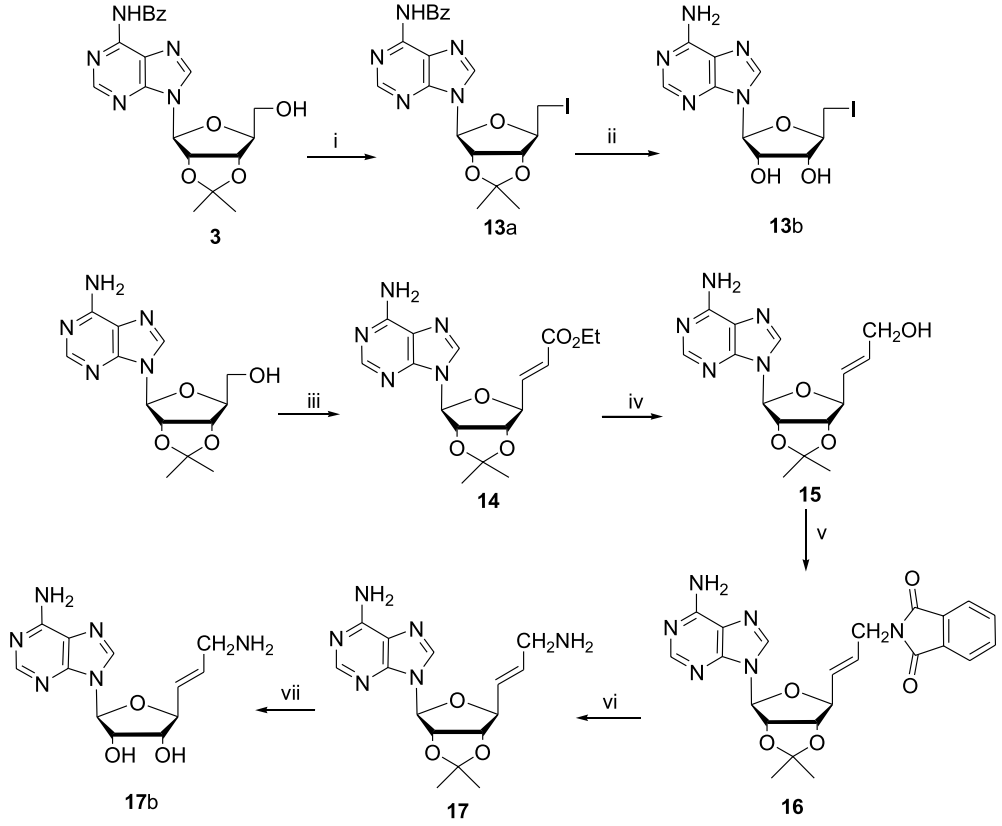


Scheme 1. Reagents and conditions: (i) BSA, 80 °C, DCE; TMSOTf, 80 °C, toluene. (ii) K_2CO_3/MeOH, rt; TSA, $HC(OEt)_3$, rt. (iii) DCC, $Cl_2CHCOOH$, DMSO; $TsCH{=}PPh_3$, rt. (iv) 1 N NaOH/H_2O, ACN, rt. (v) NH_3/MeOH, rt; CF_3COOH/H_2O, 0 °C. (vi) $NaBH_4$, MeOH/H_2O, rt. (vii) CF_3COOH/H_2O, 0 °C. (viii) Bu_3SnH, AIBN, toluene, reflux.



Scheme 2. Reagents and conditions: (i) Cl_2, DCM/CCl_4, −50 °C. (ii) NBS, DCM/CCl_4, −30 °C. (iii) NIS, DCM/CCl_4, −20 °C. (iv) NH_4F, EtOH, reflux. (v) $Pb(AcO)_4$, MeCN, rt. (vi) CF_3COOH/H_2O, 0 °C; NH_3/MeOH. (vii) NH_3/MeOH.

After deprotection, **8b**, **9b**, **10b** were obtained and in the case of compound **8a**, the deprotected product was a mixture of *E*- and *Z*-form isomers, *Z*-form isomer **8c** was separated in 16% yield. Destannnylation of **7** with ammonium fluoride in ethanol at reflux gave compound **11a** and treatment of **7** with lead tetraacetate in acetonitrile resulted in oxidative destannylation to give the 6-*N*-benzoyl-9-(5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′-ynofuranosyl) adenine **12a**. Deprotection of **11a** and **12a** provided **11b** and **12b** respectively (Scheme 2). To extend the structure types of 5′-modified L-nucleosides, 5′-iodo-L-adenosine **13b** was synthesized from compound **3** by the substitution of iodine



Scheme 3. Reagents and conditions: (i) Ph_3P, I_2, 1,4-dioxane, py, rt. (ii) NH_3/MeOH, rt; CF_3COOH/H_2O, 0 °C. (iii) DCC, DMSO, $Cl_2CHCOOH$, $EtO_2CCH{=}PPh_3$. (iv) DIBAL-H, DCM, −78 °C. (v) Phthalimide, Ph_3P, DEAD, THF, rt. (vi) CH_3NH_2/EtOH, rt. (vii) CF_3COOH/H_2O, rt.

Table 1. [1]HNMR Spectral data[a,b] of 5′-modified L-nucleosides

Compound	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[d] ($J_{3'-4'}$)	H4′[d] ($J_{4'-5'}$)	H5′[d] ($J_{5'-6'}$)	H6′[c] ($J_{6'-4'}$)	H2[e]	H8[e]	NH_2[f]	Others[e]
3[g]	5.94 (4.8)	5.23[h] (5.7)	5.13 (2.1)	5.78[d] (1.8)	3.81[i], 4.03[j]		8.07	8.79	9.04[k]	1.28, 1.66 (CH_3), 7.54–7.63[i] (Bz)
4[g]	6.17 (1.5)	5.50 (6.0)	5.22 (3.6)	4.86[i] (4.2)	6.99 (15.0)	6.30 (1.8)	8.08	8.60	9.23[k]	1.38, 1.60, 2.39[l] (CH_3), 7.21–7.64[i] (Bz)
5a[g]	6.24[e]	5.61[c] (6.0)	5.24[c]		4.85[h] (8.1)	3.84[d]	8.02	8.75	8.91[k]	1.52, 1.61, 2.39[l] (CH_3), 7.18–8.00[i] (Bz)
5b	6.00 (4.0)	4.56 (7.5)	4.52[c]		4.85[h] (5.5)	3.90[i]	8.07	8.14	7.35	2.31[l] (CH_3), 5.62 (OH3′) 5.71 (OH2′), 7.21–7.64[i] (Bz)
6a[g]	5.95 (2.4)	5.43 (6.3)	4.90 (3.9)	4.21[i] (7.2)	2.16[i] (8.4)	3.12[i]	7.87	8.19	7.27	1.35, 1.57, 2.44[l] (CH_3) 7.27–7.68[i] (Bz)
6b	5.79 (4.5)	4.63 (5.0)	4.10 (5.5)	3.90[i] (6.0)	1.95[i] (8.0)	3.34[i]	8.02	8.27	7.30	2.38[l] (CH_3), 5.23 (OH3′), 5.45 (OH2′), 7.44–7.75[i] (Bz)
7[g]	6.19 (1.8)	5.57 (6.3)	5.04 (3.0)	4.72 (6.0)	6.03 (18.9)	6.27[d] (1.2)	8.10	8.35	8.96[k]	1.37, 1.63 (CH_3), 0.79–1.52[i] (Bu_3Sn), 7.57–8.05[i] (Bz)
8a[g]	6.15 (1.5)	5.57 (6.3)	5.12 (3.3)	4.69 (6.0)	6.34–6.36[i]		8.10	8.83	9.03[k]	1.41, 1.63 (CH_3), 7.58–8.03[i] (Bz)
8b	5.90 (5.0)	4.70 (10.0)	4.19 (5.0)	4.36 (8.0)	6.56 (13.5)	6.71[c]	8.15	8.37	7.31	
8c	5.91 (6.0)	4.85 (5.0)	4.14 (3.5)	4.73 (8.0)	6.72[h] (7.0)	6.75[c]	8.15	8.37	7.31	
9a[g]	6.15 (1.5)	5.59 (6.3)	5.13 (3.0)	4.69 (6.9)	6.66 (14.7)	6.38[d]	8.08	8.84	8.97[k]	1.43, 1.63 (CH_3), 7.58–8.03[i] (Bz)
9b	5.89 (5.1)	4.70 (5.4)	4.18 (4.5)	4.32 (7.5)	6.85 (14.4)	6.67[d]	8.15	8.35	7.31	
10a[g]	6.14 (2.1)	5.56 (6.3)	5.10 (3.3)	4.71 (7.8)	6.08 (13.2)	6.23[d]	8.24	8.81	9.14[k]	1.40, 1.64 (CH_3), 7.54–8.03[i] (Bz)
10b	5.89 (4.5)	4.38 (8.3)	3.36–3.41		6.31 (13.0)	6.60[d]	8.15	8.36	7.31	
11a[g]	6.19 (1.5)	5.59 (6.3)	5.05 (3.6)	4.72 (6.9)	5.89[m] (17.1, 10.8)	5.16, 5.27	8.11	8.84	8.92[k]	1.42, 1.63 (CH_3), 7.57–8.03[i] (Bz)
11b	6.25 (5.0)	4.68[h] (5.0)	4.12[h] (4.5)	4.32[h] (6.5)	6.08[m] (17.0, 10.5)	5.19, 5.30	8.16	8.31	7.29	
12a[g]	6.28[e]	5.75[c] (5.7)	5.13 (1.2)	5.07[c]		2.44	8.30	8.82	9.07[k]	1.41, 1.58 (CH_3), 7.47–8.00[i] (Bz)
12b	5.94 (5.0)	4.78[h] (5.0)	4.35[h] (4.0)	4.55		3.75[c] (2.0)	8.21	8.32	7.59	
13a[g]	6.21 (2.4)	5.52 (5.7)	5.11 (3.3)	4.45[j] (10.2)	3.29, 3.46		8.19	8.83	9.08[k]	1.42, 1.64 (CH_3), 7.58–8.03[i] (Bz)
13b	5.90 (6.0)	4.80 (6.0)	4.16 (5.0)	3.98[j] (10.5)	3.45, 3.60		8.14	8.36	7.30	5.50 (OH3′), 5.79 (OH2′)
14[g]	6.13 (1.8)	5.56 (6.3)	5.14 (3.6)	4.81[i]	6.96 (15.6)	5.81[d] (1.5)	7.86	8.33	5.59	1.40, 1.63 (CH_3), 1.22[h] (H9′), 4.11[n] (H8′)
15[g]	6.10 (2.1)	5.85–5.86		4.72[i]	5.02 (6.3)	5.54[d] (2.1[o])	7.87	8.36	5.60	1.40, 1.63 (CH_3), 3.97[c,p] (H7′,2.4)
16[g]	6.07 (2.0)	5.49 (6.0)	4.98 (3.5)	4.68 (7.0)	5.84 (15.5)	5.73[j] (5.5)	7.85	8.25	5.47	1.37, 1.60 (CH_3), 7.72–7.85[i] (Bz)
17a	6.09 (1.5)	5.52 (5.7)	5.00 (3.3)	4.70 (6.3)	5.76–5.86[j]		7.89	8.35	5.80	1.39, 1.62 (CH_3), 3.28[e] (H7′), 1.99[f] (CH_2NH_2)
17b	5.94 (5.1)	4.66[h] (5.1)	4.14[h] (4.5)	4.37[h] (5.7)	6.07 (15.3)	5.77[j,p] (6.9)	8.19	8.35	5.80	3.46[c] (H7′)

[a]Chemical shifts(δ) in DMSO-d_6 at 300 MHz (unless otherwise noted). [b]'Apparent' first-order coupling constants (Hz, in parentheses). [c]Doublet (unless otherwise noted). [d]Doublet of doublets (unless otherwise noted). [e]Singlet (unless otherwise noted). [f]Broad singlet. [g]In $CDCl_3$. [h]Triplet (unless otherwise noted). [i]Multiplet. [j]Doublet of triplets. [k]NH. [l]$PhCH_3$. [m]Doublet of doublets of doublets. [n]Quartet. [o]$^3J_{H6'-H7'}$.

(Scheme 3). For the synthesis of compound **17b**, the 2′,3′-*O*-isopropylidene-L-adenosine was oxidized by Moffat reaction and followed by the treatment of Wittig reagent to give the α,β-unsaturated ester **14** in 50% yield. Reduction of compound **14** with DIBAL-H gave the allylic alcohol **15**, which was converted into phthalimide **16** by a Mitsunobu reaction in 81% yield. After the cleavage with methylamine, and deprotection with TFA, compound **17b** was obtained in 81% yield (Scheme 3). The ^1H and ^{13}C NMR data of L-adenosine derivatives were listed in Tables 1 and 2.

2.2. Synthesis of 5′-ethylenic and acetylenic substituted isonucleosides

The [5-(*R*)-dimethoxy-4-(*R*)-hydroxy-3(*S*)-adenin-9-yl]tetrahydrofuran **18** was synthesized starting from D-xylose[22]

Table 2. ^{13}C NMR Spectral data[a,b] of 5′-modified L-nucleosides

Compound	C2	C4	C5	C6	C8	C1′	C2′[c]	C3′[c]	C4′	C5′	C6′
5b[d]	152.8	149.1	119.1	156.1	139.3	88.2	71.9	69.4	161.0	86.4	52.6
6b[e]	152.5	149.1	119.3	156.1	144.4	88.0	72.7	72.6	81.6	21.1	51.6
7[f,g]	152.8	149.6	123.4	152.8	142.3	90.8	84.6	84.2	90.5	143.8	133.6
8b	152.6	149.3	119.2	156.1	140.0	87.6	73.4	72.6	83.6	136.0	109.9
8c	152.6	149.4	119.4	156.1	140.3	87.7	74.2	72.7	82.2	133.6	111.1
9b	152.6	149.3	119.2	156.1	143.7	87.6	73.2	72.6	85.7	140.0	82.1
10b	152.7	149.3	119.2	156.1	140.0	87.6	73.7	72.7	82.3	132.2	121.5
11b	152.8	149.5	119.0	156.1	139.9	87.6	73.9	72.8	84.8	136.7	117.1
12b	152.0	149.5	119.0	155.4	139.6	87.4	73.5	73.1	81.1	78.7	75.2
13b	152.7	149.5	119.1	156.1	139.9	87.4	73.2	72.7	83.9	7.8	
14[g,h]	153.2	152.6	122.6	155.4	140.0	90.6	84.3	83.9	86.3	143.4	131.9
15[g,i]	153.2	151.3	122.4	155.4	140.0	90.6	84.6	84.2	87.5	133.7	127.4
16[g,j]	153.1	149.4	123.4	155.6	139.9	90.5	84.5	84.1	87.2	132.0	120.2
17a[k]	153.2	149.5	120.2	155.5	139.9	90.4	84.6	84.2	87.7	136.0	126.4
17b[l]	152.8	149.5	119.2	156.1	139.8	87.5	73.9	72.8	83.5	133.6	124.7

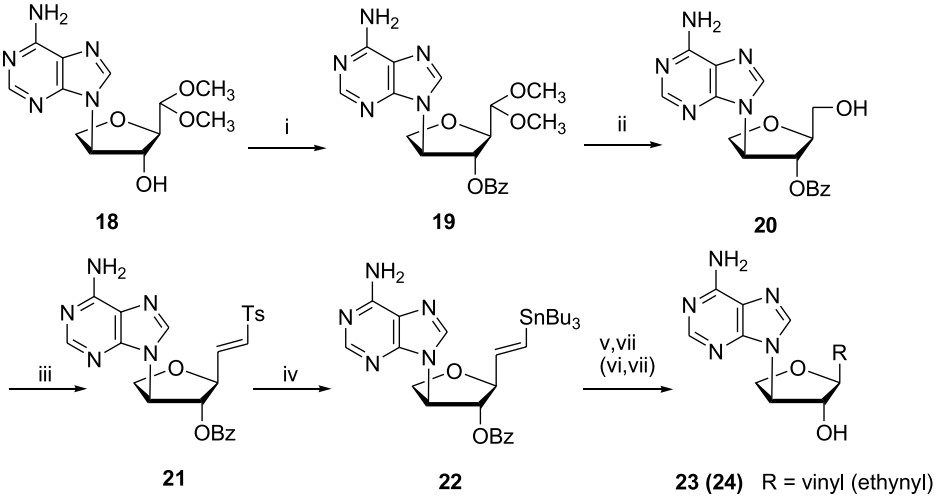
[a] Chemical shifts (δ) in DMSO-d_6 at 75 MHz.
[b] Proton-decoupled singlets.
[c] Assignment might be reversed.
[d] Peaks also at δ 21.5, 127.86, 129.3, 135.9, 144.0 ($PhCH_3$).
[e] Peaks also at δ 26.3, 127.7, 129.9, 135.9, 144.4 ($PhCH_3$).
[f] Peaks also at δ 9.4, 13.6, 27.2, 28.9 (Bu_3Sn); 25.4, 27.1, 114.5 (CMe_2); 127.8, 128.9, 132.8, 133.8, 164.3 (PhCO).
[g] In $CDCl_3$.
[h] Peaks also at δ 14.1, 60.6, 165.6 ($CO_2CH_2CH_3$); 25.3, 27.1, 114.7 (CMe_2).
[i] Peaks also at δ 25.4, 27.1, 114.5 (CMe_2); 62.4 (CH_2OH).
[j] Peaks also at δ 25.3, 27.0, 114.4 (CMe_2); 38.6 (CH_2NR); 123.4, 127.4, 130.4, 134.0 (Ph); 155.9, 167.0 (CO).
[k] Peaks also at δ 25.4, 27.1, 114.5 (CMe_2); 43.2 (CH_2NR).
[l] Peaks also at δ 63.1 (CH_2NR).

with a published procedure in our laboratory. Protection of **18** with benzoyl chloride gave compound **19**. One-pot reaction of **19** by treatment with 1% HCl/THF at 70–90 °C and followed by reduction with $NaBH_4$ provided the isonucleoside **20** in 52% yield. As the procedure described above, Moffatt oxidation was applied to **20** and followed by treatment with wittig reagent [(*p*-tolylsulfonyl)methylene]triphenylphosphorane to give the 6′-(*E*)-tosylvinyl derivative **21** in 85% yield. Stannyldesulfonylation (Bu_3SnH/AIBN/toluene) of **21** provided compound **22**. Compound **22** was treated in the presence of lead tetraacetate at ambient temperature to provide the 5′-vinyl isonucleoside **23**. Treatment of **22** with ammonium fluoride in ethanol at reflux gave the 5′-ethynyl isonucleoside **24** (Scheme 4). The compound **25**, enantiomer of isonucleoside **18**, were synthesized using our published procedure.[25]

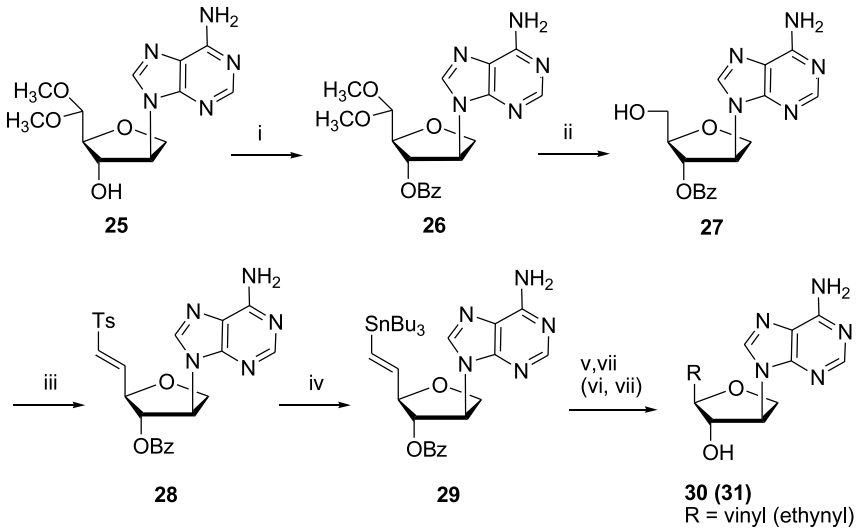
Using the similar procedure as described above, the syntheses of **30** and **31** were shown in Scheme 5. The ^1H and ^{13}C NMR data of iso-adenosine derivatives were listed in Tables 3 and 4.

2.3. Biological results and discussion

Compounds **5b**, **6b**, **8b**, **8c**, **9b**, **10b**, **11b**, **12b**, **13b**, **17b** and **23**, **24**, **30**, **31** were evaluated for the inactivation of SAH hydrolase and known active compound, 6′(*E*)-bromovinyl D-adenosine (**D–B**),[36] was used as control (Table 5). In the L-nucleoside series, compounds **6b**, **8b**, **10b** and **13b** showed modest inhibition of SAH hydrolase (21, 44, 50 and 26% respectively) at 100 μM. Compound **8c**, the *Z*-form isomer of **8b**, and compound **9b** exhibited no inhibition in this assay. Wnuk et al. reported the synthesis of 6′-(*E*) and



Scheme 4. Reagents and conditions: (i) BzCl, Py, 0–40 °C. (ii) 1% HCl, THF, 70–90 °C. (iii) DCC, DMSO, $Cl_2CHCOOH$; $TsCH{=}PPh_3$. (iv) Bu_3SnH, AIBN, toluene, reflux. (v) NH_4F, EtOH, reflux. (vi) $Pb(OAc)_4$, ACN, rt. (vii) $NaOCH_3$/MeOH, rt.



Scheme 5. Reagents and conditions: (i) BzCl, Py, 0–40 °C. (ii) 1% HCl, THF, 70–90 °C. (iii) DCC, DMSO, $Cl_2CHCOOH$; TsCH=PPh_3. (iv) Bu_3SnH, AIBN, toluene, reflux. (v) NH_4F, EtOH, reflux. (vi) $Pb(OAc)_4$, ACN, rt. (vii) $NaOCH_3$/MeOH, rt.

(*Z*)-halohomovinyl derivatives of adenosine and indicated that the order of inhibitory potency of these derivatives for the inactivation of *S*-adenosyl-L-homocysteine hydrolase was I > Br > Cl > F and *E* form > *Z* form.[14] However, in our L-nucleoside series, the inhibitory potency of SAH hydrolase was weaker than that of their D-isomers and the order of inhibitory potency seemed confusion. The activities of chloro-substituted derivative **10b** and the bromo partner **8b** were almost the same but iodo-substituted compound **9b** showed no activity. According to the mechanism studies on the inhibition of SAH hydrolase,[33] the acetylenic derivative of adenosine showed marked inhibition at 100 μM[14] but the L-isomer of 9-(5′,6′-dideoxy-β-D-ribo-hex-5′-ynofuranosyl)adenine **12b** was inactive at the same condition. The 5′-ethylenic and acetylenic modified isonucleoside analogues **23**, **24**, **30**, **31** were also evaluated in this assay. The L-isomers of 5′-ethylenic and acetylenic modified isonucleoside **23**, **24** exhibited no activity for the inhibition of SAH hydrolase, however, the D-isomers **30** and **31** showed some activities in the same test (35 and 21%). Computer modeling study showed that each pair of D- and L-enantiomer of 6′-halohomovinyl derivative of adenosine was fitted together by pairing base moiety and 5′-moiety (Fig. 1), but sugar ring was out from the model. L-5′-Ethylenic and acetylenic isonucleoside analogues could not fit to the 5′-acetylenic modified adenosine derivative but the D-isomer was more similar to the D-nucleoside partner (Fig. 2). In the cases of L-2′-deoxy-3′-thiacytidine (3TC) and other L-nucleoside antiviral drugs, the monophosphorylation of a nucleoside analogues was the crucial step for the biological activity and the certain kinase could recognize both of the D- and L-isomers without limitation of configuration,[30] however, this study indicated clearly the strict stereochemical requirement for the substrate of SAH hydrolase.[31]

Wnuk et al. reported the observation of a direct correlation of cytostatic activity with inhibition of SAH hydrolase and found that the most potent inhibitors of

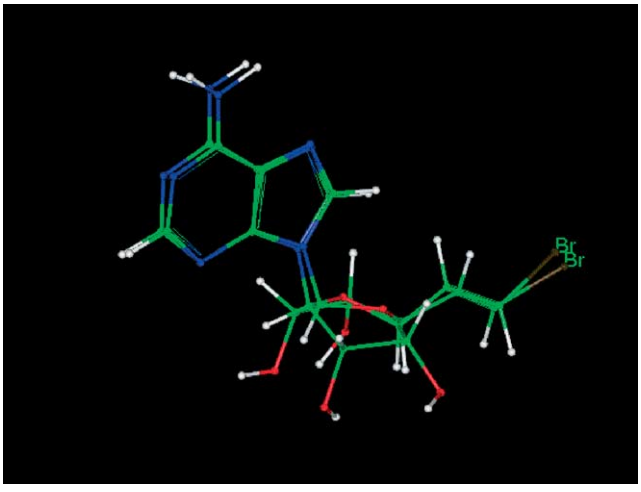


Figure 1. Overlap of structure of D- and L-6′(*E*)-bromovinyl adenosine. The modeling was performed based on the energy optimized structure. Enatiomers were fit together by pairing N3, N6, N7, N9, C5′ and C6′ (the modeling was performed on SGI Indy workstation and MSI Insight II was used).

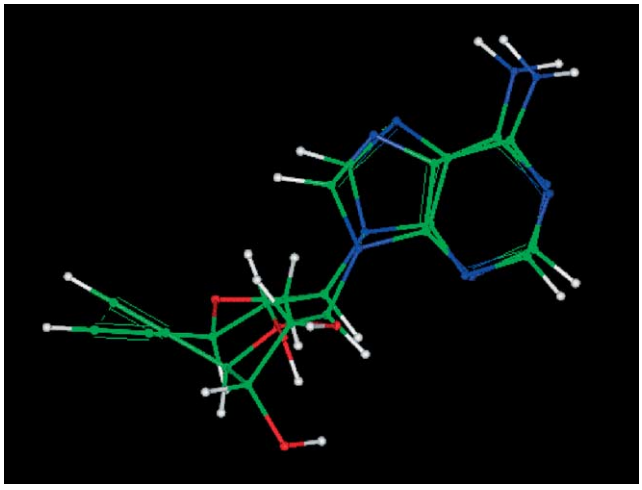


Figure 2. Overlap of structure of 6′-ethynyl D-adenosine. The modeling was performed based on the energy optimized structure. Enantiomers were fit together by pairing N3, N6, N7, N9, C5′ and C6′ (the modeling was performed on SGI Indy workstation and MSI Insight II was used).

Table 3. [1]HNMR Spectral data[a,b] of 5′-modified isonucleosides

Compound	H2′a[c,d] ($J_{2'-3'}$)	H2′b[e] ($J_{2'-3'}$)	H3′[e] ($J_{3'-4'}$)	H4′[e] ($J_{4'-5'}$)	H5′[e] ($J_{5'-6'}$)	H6′[e]	H2	H8	NH_2[f]	H7′	Others[g]
19	4.39 (6.0, 10.5)	4.29 (3.0)	5.72 (2.4)	5.32 (5.4)	4.28 (3.6)	4.77[c]	8.32	8.33	6.35[h]		3.51, 3.55[g] (OCH_3), 7.47–8.03[i] (Bz)
20	4.14 (5.7, 10.5)	4.04 (3.3)	5.75 (4.2)	5.34 (6.0)	4.08 (4.2)	4.36[c]	8.25	8.32	6.59[h]		7.42–8.01[i] (Bz)
21	4.44–4.46 (5.1, 10.5)		5.36 (7.5)	4.77[j] (4.5)	5.56 (3.0)	7.28[k] (15.0)	7.84	8.29	5.83[h]	6.80[d]	2.63[g] ($PhCH_3$), 7.27–8.03[i] (Bz)
22	4.44 (5.7, 10.5)	4.33 (2.7)	5.34[i] (7.8)	4.60[i] (4.5)	5.49 (4.5)	6.25[k]	8.01	8.39	5.69[h]	6.53[d]	0.94–1.48[i] (Bu_3Sn), 7.55–8.06[i] (Bz)
23[l]	4.19–4.20 (6.0, 10.5)		4.88 (6.0)	4.36 (6.5)	4.11[j] (6.5)	5.92[i,k] (17.5, 10.5)	8.13	8.14	7.24[h]	5.17	
24[l]	4.30 (5.7, 10.5)	4.20 (3.3)	4.59 (4.2)	4.85 (6.0)	4.40 (4.2)		8.14	8.15	7.25[h]	2.49[g]	6.20[g] (OH4′)
26	4.38 (6.0, 10.5)	4.29 (3.0)	5.73 (2.4)	5.33 (5.4)	4.28[c] (3.6)	4.79[c]	8.32	8.33	6.35[h]		7.47–8.03[i] (Bz)
28	4.44–4.46[c] (5.1, 10.5)		5.36 (7.8)	4.76 (4.5)	5.56 (3.0)	7.30[k] (15.0)	7.84	8.29	5.88[h]	6.83[e]	2.44[g] ($PhCH_3$), 7.27–8.03[i] (Bz)
29	4.44 (5.7, 10.5)	4.32 (2.7)	5.34 (7.8)	4.60[i] (4.5)	5.48 (4.8)	6.25[k] (19.2)	8.01	8.36	5.57[h]	6.53[e]	0.85–1.46[i] (Bu_3Sn), 7.27–8.05[i] (Bz)
30[l]	4.19[e] (6.0, 10.5)		4.88 (6.0)	4.36 (6.5)	4.11[j] (6.5)	5.92[i,k] (17.5, 10.5)	8.14	8.15	7.24[h]	5.17[e]	6.21[g] (OH4′)
31[l]	4.30 (5.0, 10.5)	4.20 (2.0)	4.59 (5.0)	4.85 (5.0)	4.40		8.14	8.15	7.25[h]	2.49[g]	

[a]Chemical shifts (δ) in $CDCl_3$ at 300 MHz (unless otherwise noted). [b]'Apparent' first-order coupling constants (Hz, in parentheses). [c]Doublet (unless otherwise noted). [d]$^2J_{H2'-H2'}$. [e]Doublet of doublets (unless otherwise noted). [f]Broad singlet. [g]Singlet (unless otherwise noted). [h]NH_2. [i]Multiplet. [j]Triplet (unless otherwise noted). [k]$^3J_{H6'-H7'}$. [l]In Me_2SO-d_6. [m]Doublet of triplets. [n]$^2J_{H6'-H6'}$. [o]$^2J_{H7'-H7'}$.

Table 4. [13]CNMR Spectral data[a,b] of 5′-modified isonucleosides

Compound	C2	C4	C5	C6	C8	CH_3	C2′	C3′	C4′	C5′	C6′	C7′
20[c,d]	152.5	149.3	118.6	156.0	139.3		70.4	60.5	79.1	84.4	59.9	
21[c,e]	153.3	149.8	119.6	155.5	140.2		70.9	59.9	81.6[f]	82.6[f]	128.3	144.7
22[c,g]	153.1	149.3	118.9	155.5	140.3		71.4	60.3	82.5	86.3	142.2	133.9
23	152.4	149.5	119.0	156.0	139.4		68.7	61.7	78.6	84.7	136.5	116.9
24	152.4	149.5	119.3	156.0	139.2		69.0	61.2	79.9	81.4	77.9	73.7
28[c,h]	153.3	149.8	119.6	155.6	140.2		70.9	59.9	81.5	82.6	128.3	144.7
29[c,i]	153.1	148.9	118.9	155.6	141.9		71.3	60.8	82.6	86.1	142.3	134.0
30	152.4	149.5	119.0	156.0	139.4		68.7	61.7	78.6	84.6	136.5	116.8
31	152.4	149.4	119.3	156.0	139.2		69.0	61.2	79.9	81.4	77.9	73.7

[a]Chemical shifts (δ) in DMSO-d_6 at 75 MHz. [b]Proton-decoupled singlets. [c]Peaks also at δ 128.5, 129.7, 133.8, 135.4, 166.1 (PhCO). [d]Peaks also at δ 128.8, 128.9, 129.5, 133.8, 165.2 (PhCO). [e]Peaks also at δ 12.6, 127.9, 128.6, 129.9, 130.0, 132.4, 134.0, 136.8, 138.3, 165.6 (PhCO). [f]Assignment might be reversed. [g]Peaks also at δ 9.5, 13.6, 17.5, 19.1, 26.8, 27.2 27.7, 27.8, 29.0, 29.7, (Bu_3Sn), 128.6, 129.9, 130.9, 133.8, 165.6 (PhCO). [h]Peaks also at δ 127.8, 128.6, 129.9, 130.0, 132.4, 134.0, 136.8, 138.3, 165.6 (PhCO). [i]Peaks also at δ 9.5, 13.6, 17.5, 19.2, 26.8, 27.2, 27.7, 29.0, 29.7 (Bu_3Sn), 128.8, 129.9, 130.9, 134.0, 165.6 (PhCO).

Table 5. Inhibition of *S*-adenosyl-L-homocysteine hydrolase by synthetic adenosine analogues[a]

Conc.\compound	D–B	6b	8b	10b	11b
100 μM	94%	21%	44%	50%	30%
10 μM	92%	—	10%	16%	—
1 μM	68%	—	—	—[b]	—
Conc\compound	**13b**	**23**	**24**	**30**	**31**
100 μM	26%	12%	20%	35%	21%
10 μM	24%	—	11%	16%	12%
1 μM	—	—	—	—	—

[a] The data shown are the average results of three experiments.
[b] Dash means no activity in this condition.

SAH hydrolase also showed the most potent cytostatic activities.[14] In our case, compounds **6b**, **8b**, **8c**, **9b**, **10b**, **11b**, **12b**, **13b**, **17b** and **23**, **24**, **30**, **31** were screened by culture of tumor cells (Table 6), only HeLa cells and Bel-7420 cells were sensitive to these compounds. Compounds **6b**, **8b**, **8c**, **11b** exhibited modest to good inhibition effects on the growth of HeLa cells or Bel-7420 cells at 1 μM (64, 44, 53 and 82% respectively), compounds **9b**, **12b** and **13b** were active at 10 μM (55, 64 and 73%). Therefore, the cytostatic activites of L-nucleoside and isonucleoside derivatives reported may correlate with inhibition of SAH hydrolase and other mechanisms.

3. Conclusions

The synthesis of stereoisomers of 6′-halovinyl modified adenosine analogues could explain the specific substrates requirement of SAH hydrolase. We designed and synthesized two series of 6′-halovinyl D-adenosine stereoisomers including 5′-ethylenic and acetylenic substituted L-adenosine and 5′-ethylenic substituted isonucleosides. In the L-nucleoside series, compounds **6b**, **8b**, **10b** and **13b** showed modest inhibition of SAH hydrolase (21, 44, 50 and 26% respectively) at 100 μM. The isonucleoside analogues **31**, **32** showed some weaker activities in the same test (35 and 21%). It indicated clearly the strict stereochemical requirement for the substrate of SAH hydrolase. Compounds **6b**, **8b**, **8c**, **11b** exhibited modest to good inhibition effects on the growth of HeLa cells or Bel-7420 cells at 1 μM (64, 44, 53 and 82% respectively), compounds **9b**, **12b** and **13b** were active at 10 μM (55, 64 and 73%). Therefore, the cytostatic activites of L-nucleoside and isonucleoside derivatives reported may correlate with inhibition of SAH hydrolase and other mechanisms.

Table 6. The inhibitory effect of 5′-modified L-nucleosides on Hela cells and Bel-7420 cells in vitro[a]

Compound	Tumor cell line	Conc. (μM)	Inhibition rate (%)
6b	Bel-7420	1.0	64
		10.0	81
8b	Hela	1.0	44
		10.0	67
8c	Hela	0.1	23
		1.0	53
		10.0	67
9b	Hela	1.0	22
		10.0	55
13b	Hela	1.0	10
		10.0	64
11b	Bel-7420	0.1	27
		1.0	82
12b	Bel-7420	1.0	35
		10.0	73

[a] The data shown are the average results of three experiments.

4. Experimental

4.1. General

Uncorrected melting points were determined on a XT-4A melting point apparatus. NMR spectra were recorded on a Varian 300 MHz spectrometer. Mass spectra were obtained on PE SCLEX QSTAR mass spectrometer. Elemental analyses were performed on Varian ELIII analyzer. Solvents were dried by reflux over CaH_2 and distilled before use, chromatographic purifications were carried out using silica gel (200–300 mesh, Qingdao chemicals). Preparative RP-HPLC was performed with spectra physics SP 8800 ternary pump system and Pynamax C_{18} columns.

4.1.1. 6-*N*-Benzoyl-2′,3′-*O*-isopropylidene-L-adenosine (3). Compound **2** (240 mg, 0.48 mmol) was dissolved in K_2CO_3/CH_3OH (20 mL), the resulting solution was stirred at ambient temperature for 1.2 h. The solution was neutralized to pH=7 with HCl/H_2O and then was evaporated, the residue was dissolved into acetone (20 mL) and TSA (400 mg, 2.1 mmol), triethyl orthoformate (0.5 mL, 2.9 mmol) were added. The mixture was stirred at ambient temperature overnight. The solution was neutralized with $NaHCO_3/H_2O$ and evaporated. The residue was partitioned ($CHCl_3/H_2O$), dried ($MgSO_4$) and evaporated. Purified on column chromatograph (EtOAc/acetone=4/1), **3** (161 mg, 81%) was obtained as a white foam. TOF-MS ($M^+ + H$): 412.

4.1.2. 6-*N*-Benzoyl-9-[5′,6′-dideoxy-2′,3′-*O*-isopropylidene-6′-(*p*-toluenesulfonyl)-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (4). A solution of **3** (375 mg, 0.91 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 564 mg, 2.7 mmol) in dried DMSO (2 mL) was cooled (0 °C) under argon, $Cl_2CHCOOH$ (38 μL, 0.47 mmol) was added, and stirred for 2 h at ambient temperature, then [(*p*-tolylsulfonyl)methylene]triphenyl phosphorane was added to the solution and stirred overnight. Oxalic acid dihydrate (453 mg, 3.6 mmol) in MeOH (4 mL) was added. After 30 min the dicyclohexylurea was filtered and washed with cold MeOH, and the combined filtrates were evaporated (in vacuo). The residue was partitioned ($EtOAc/H_2O$), the organic layer was washed with H_2O (3×10 mL), $NaHCO_3/H_2O$, and $NaCl/H_2O$, dried ($MgSO_4$) and evaporated. Purified on column chromatography, **4** (500 mg, 97%) was obtained as a white

solid. Mp 108–109 °C. HRMS (TOF) calcd for $C_{28}H_{28}N_5O_6S$ ($M^+ + H$): 562.1760; found: 562.1770.

4.1.3. 6-*N*-Benzoyl-9-[5′,6′-dideoxy-6′-(*p*-toluenesulfonyl)-β-L-ribo-hex-5′(*Z*)-enofuranosyl] adenosine (5a). To a stirred solution of **4** (181 mg, 0.32 mmol) in CH_3CN/H_2O (4:1, 10 mL) was added 1 M NaOH/H_2O(1 mL) and stirring was continued at ambient temperature for 4 h, the solution was concentrated to half volume and EtOAc (10 mL) and 0.05 M HCl/H_2O (2 mL) were added. The organic layer was washed with saturated $NaHCO_3$/H_2O, brine, dried (Na_2SO_4) and purified on column chromatograph to give **5a** (127 mg, 70%) as a white foam. Mp 103–104 °C. TOF-MS ($M^+ + H$): 562.

4.1.4. 9-[4′,5′-Dideoxy-6′-(*p*-toluenesulfonyl)-β-L-ribo-hex-5′(*Z*)-enofuranosyl] adenosine (5b). Compound **5a** (25 mg, 0.044 mmol) was dissolved in 15 mL saturated NH_3/CH_3OH solution, the resulting solution was stirred overnight at ambient temperature and evaporated, CF_3COOH/H_2O (9:1, 3 mL) was added to the residue and stirring was continued for 1 h at 0 °C (ice bath). After co-evaporation with EtOH (2×3 mL), the residue was separated with a short silica gel column (EtOAc→EtOAc/*i*-PrOH/H_2O, 20:1:2, upper layer), compound **5b** (12 mg, 64%) was collected as a white solid. Mp 115–117 °C. HRMS (TOF) calcd for $C_{18}H_{20}N_5O_5S$ ($M^+ + H$): 418.1185; found: 418.1152

4.1.5. 9-[2′,3′-*O*-Isopropylidene-6′-(*p*-toluenesulfonyl)-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (6a). To a stirred solution of **4** (12 mg, 0.021 mmol) in MeOH/H_2O (1:1, 3 mL) was added sodium borohydride (3 mg, 0.08 mmol). After 18 h at ambient temperature, the solution was concentrated to half volume and the residue was partitioned ($CHCl_3$/H_2O). The organic layer was washed with brine, H_2O, dried ($MgSO_4$), and evaporated. Purified on column chromatography (EtOAc/petroleum ether, 2:1), compond **6a** (9 mg, 93%) was obtained as a white foam. TOF-MS ($M^+ + H$): 460.

4.1.6. 9-[6′-(*p*-Toluenesulfonyl)-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (6b). The deprotection of **6a** was performed (as described for 5b) gave a white solid **6b** (11 mg, 55%). Mp 124–126 °C. HRMS (TOF) calcd for $C_{18}H_{22}N_5O_5S$ ($M^+ + H$): 420.1342; found: 420.1329.

4.1.7. 6-*N*-Benzoyl-9-[6′-(*E*)-(tributylstannyl)-5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (7). The oxygen in the solution of **4** (93 mg, 0.165 mmol) in toluene (10 mL) was removed by argon for 30 min, and Bu_3SnH (0.2 mL, 0.66 mmol) was added. Argon was passed through the solution continually for 15 min, and AIBN (70 mg, 0.33 mmol) was added. The solution was refluxed for 5 h and evaporated, and the residue was purified on column chromatography (EtOAc/petroleum ether, 1:3). Compound **7** (70 mg, 61%) was obtained as a colorless oil. Analysis calcd for $C_{33}H_{47}N_5O_4Sn$: C, 56.91; H, 6.80; N, 10.06; found: C, 57.07; H, 7.01; N, 9.66.

4.1.8. 6-*N*-Benzoyl-9-[6′-bromo-5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (8a). A solution of NBS (59 mg, 0.329 mmol) in CH_2Cl_2/CCl_4 (1:1, 10 mL) was added dropwise to a stirred solution of **7** (169 mg, 0.243 mmol) in CH_2Cl_2/CCl_4 (1:1, 6 mL) at −30 °C. After 30 min, the mixture was poured into saturated $NaHCO_3$/H_2O and extracted by $CHCl_3$. The combined organic phase was washed (brine), dried ($MgSO_4$), and evaporated, and the residue was purified on column chromotography (EtOAc/petroleum ether, 1:1) to provide **8a** (106 mg, 89%). TOF-MS ($M^+ + H$): 486.

4.1.9. 9-[6′-Bromo-5′,6′-dideoxy-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (8b). 9-[6′-Bromo-5′,6′-dideoxy-β-L-ribo-hex-5′(*Z*)-enofuranosyl] adenosine (8c). Deprotection of **8a** (35 mg, 0.072 mmol) (as described for **5b**) gave a residue that was purified by RP-HPLC (preparative column; program: 17% CH_3CN/H_2O for 1 h at 3 mL/min) to give **8b** (*E*) (15 mg, 61%, t_R=47 min. Mp 141–142 °C) and **8c** (*Z*) (4 mg, 16%, t_R=31 min. Mp 135–136 °C). **8b**. HRMS (TOF) calcd for $C_{11}H_{13}BrN_5O_3$ ($M^+ + H$): 342.0202; found: 342.0218; **8c**. TOF-MS ($M^+ + H$): 342.

4.1.10. 6-*N*-Benzoyl-9-[6′-iodo-5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (9a). A solution of NIS (70 mg, 0.312 mmol) in CH_2Cl_2/CCl_4 (1:1, 10 mL) was added dropwise to a stirred solution of **7** (150 mg, 0.216 mmol) in CH_2Cl_2/CCl_4 (1:1, 10 mL) at ∼−20 °C. After 1.5 h the slightly pink mixture was poured into saturated $NaHCO_3$/H_2O and extracted by $CHCl_3$, the combined organic phase was washed with 2% $NaHSO_3$/H_2O and brine, dried ($MgSO_4$), and evaporated. Purified on column chromatography (EtOAc/petroleum ether, 1:1) gave **9a** (113 mg, 98%). TOF-MS ($M^+ + H$): 534.

4.1.11. 9-[6′-Iodo-5′,6′-dideoxy-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (9b). Deprotection of **9a** (20 mg, 0.0375 mmol) (as described for **5b**) gave a residue, which was purified by RP-HPLC (preparative column; program: 17% CH_3CN/H_2O for 100 min at 3 mL/min) to give a white solid **9b** (8 mg, 54%, t_R=93 min. Mp 113–114 °C). HRMS (TOF) calcd for $C_{11}H_{13}N_5O_3I$ ($M^+ + H$): 390.0063; found: 390.0076.

4.1.12. 6-*N*-Benzoyl-9-[6′-chloro-5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (10a). Cl_2 was gently bubbled through a solution of **7** (35 mg, 0.05 mmol) in CH_2Cl_2/CCl_4 (1:1, 2 mL) at ∼−50 °C, and stirring was continued for 5 min. The solution was carefully washed ($NaHCO_3$/H_2O, 2% $NaHSO_3$/H_2O, and brine), dried ($MgSO_4$), and evaporated. Purified on column chromatography [EtOAc/petroleum ether, 1:1] gave **10a** (17 mg, 77%) as a white foam. Mp 80–83 °C. TOF-MS ($M^+ + H$): 512.

4.1.13. 9-[6′-Chloro-5′,6′-dideoxy-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (10b). Deprotection of **10a** (17 mg, 0.0385 mmol) (as described for **5b**) gave a residue which was purified by RP-HPLC (preparative column; program: 17% CH_3CN/H_2O for 60 min at 3 mL/min) to give a white solid **10b** (5 mg, 43%, t_R=54 min. Mp 140–141 °C). HRMS (TOF) calcd for $C_{11}H_{13}N_5O_3Cl$ ($M^+ + H$): 298.0707; found: 298.0690

4.1.14. 6-*N*-Benzoyl-9-[5′,6′-dideoxy-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′-enofuranosyl] adenosine (11a). A solution of **7** (200 mg, 0.287 mmol) and NH_4F (190 mg,

5.75 mmol) in anhydrous EtOH (15 mL) was refluxed for 19 h and evaporated. The residue was partitioned ($NaHCO_3$/H_2O/$CHCl_3$), and the organic layer was washed (brine), dried ($MgSO_4$), and concentrated. Purified on column chromatography (EtOAc/petroleum ether, 1:1) gave **11a** (116 mg, 99%) as a foam. TOF-MS ($M^+ + H$): 408.

4.1.15. 9-[5′,6′-Dideoxy-β-L-ribo-hex-5′-enofuranosyl] adenosine (11b). Deprotection of **11a** (20 mg, 0.049 mmol) (as described for 5b) gave a residue which purified by a short silica gel column (EtOAc→EtOAc/*i*-PrOH/H_2O, 20:1:2) to give **11b** (7 mg, 54%) as a white solid. Mp 160–161 °C. HRMS (TOF) calcd for $C_{11}H_{14}N_5O_3$ ($M^+ + H$): 264.1097; found: 264.1111

4.1.16. 9-[2′,3′-*O*-Isopropylidene-5′,6′-dideoxy-β-L-ribo-hex-5′-ynofuranosyl] adenosine (12a). A deoxygenated solution of **7** (341 mg, 0.49 mmol) in anhydrous CH_3CN (25 mL) under argon was treated with $Pb(OAc)_4$ (272 mg, 0.61 mmol), and stirred at ~0 °C (ice bath) for 5 h and then for 2 h at ambient temperature, the mixture was evaporated, the residue was partitioned ($NaHCO_3$/H_2O/$CHCl_3$) and the organic phase was washed ($NaHCO_3$/H_2O and brine), dried ($MgSO_4$), and evaporated. Purified on column chromatography (EtOAc/petroleum ether, 2:1) gave **12a** (105 mg, 71%) as a foam. TOF-MS ($M^+ + H$): 406.

4.1.17. 9-[5′,6′-Dideoxy-β-L-ribo-hex-5′-ynofuranosyl] adenosine (12b). Compound **12a** (20 mg, 0.066 mmol) was added to a solution of CF_3COOH/H_2O (9:1, 3 mL), the mixture was stirred for 1 h at ~0 °C and evaporated, co-evaporated with EtOH (2×3 mL), the residue was separated with a short silica gel column (EtOAc→EtOAc/*i*-PrOH/H_2O, 20:1:2). **12b** (8 mg, 46%) was collected as a solid. Mp 114–116 °C. HRMS (TOF) calcd for $C_{11}H_{12}N_5O_3$ ($M^+ + H$): 262.0940; found: 262.0922

4.1.18. 6-*N*-Benzoyl-9-[5′-deoxy-5′-iodo-2′,3′-*O*-isopropylidene-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (13a). To a stirred solution of **3** (233 mg, 0.56 mmol) in anhydrous dioxane (15 mL) containing anhydrous pyridine (0.1 mL, 1.12 mmol), triphenylphosphine (222 mg, 0.84 mmol), I_2 (220 mg, 0.84 mmol) were added and stirring was continued for 20 h at ambient temperature, methanol (1.0 mL) was added, and then the solvents were removed by evaporation. The residue was partitioned (EtOAc/H_2O), and the organic phase was washed (10% $Na_2S_2O_3$ and brine), dried (Na_2SO_4), and evaporated. Purified on column chromatography (EtOAc/petroleum ether, 1:1) gave **13a** (263 mg, 89%) as a foam. TOF-MS ($M^+ + H$): 522.

4.1.19. 9-[5′-Deoxy-5′-iodo-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (13b). Deprotection of **13a** (25 mg, 0.046 mmol) (as described for **5b**) gave a residue that purified by RP-HPLC (preparative column; program: 0–10% CH_3CN/H_2O for 3 min followed by a gradient of 10–40% for 50 min) to give **13b** as a white foam (8 mg, 45%, t_R= 34 min). HRMS (TOF) calcd for $C_{10}H_{13}N_5O_3I$ ($M^+ + H$): 378.0063; found: 378.0071.

4.1.20. 9-[5′,6′-Dideoxy-2′,3′-*O*-isopropylidene-6′-ethoxycarbonyl-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (14). 2′,3′-*O*-Isopropylidene-L-adenosine (500 mg, 1.63 mmol), DCC (1 g, 4.89 mmol) were added to a stirred solution of DMSO (4.5 mL) under argon, $Cl_2CHCOOH$ (78 μl, 0.96 mmol) was added at ~0 °C, and stirring was continued for 2 h at ambient temperature. $Ph_3P{=}CHCO_2Et$ (680 mg, 1.95 mmol) was added and the resulting mixture was stirred overnight. Oxalic acid dihydrate (1.1 g, 8.7 mmol) in MeOH (10 mL) was added, after 30 min the dicyclohexylurea was filtered and the filtrate was evaporated (in vacuo). The residue was partitioned (EtOAc/H_2O), the organic layer was washed with H_2O (3×40 mL), $NaHCO_3$/H_2O, and brine, dried (Na_2SO_4) and the solution was evaporated. Purified on column chromatography (EtOAc/petroleum ether, 2:1) gave **14** (306 mg, 50%) as a white solid. Mp 105–107 °C. HRMS (TOF) calcd for $C_{17}H_{22}N_5O_5$ ($M^+ + H$): 376.1621; found: 376.1608.

4.1.21. 9-[5′,6′-Dideoxy-2′,3′-*O*-isopropylidene-6′-hydroxymethyl-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (15). To **14** (306 mg, 0.816 mmol) in CH_2Cl_2 (10 mL), a 20% solution of DIBAL-H in toluene (5.25 mL, 8.16 mmol) was added drop wise. The mixture was stirred at −78 °C for 2 h, and then quashed with MeOH (10 mL). A saturated aqueous solution of potassium sodium tartrate monohydrate (80 mL) was added, and the resulting suspension was stirred vigorously for 16 h at ambient temperature, then extracted with EtOAc (3×100 mL). The combined organic phase were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 25:1) to give **15** (180 mg, 66%) as a white foam. HRMS (TOF) calcd for $C_{15}H_{20}N_5O_4$ ($M^+ + H$): 334.1515; found: 334.1538.

4.1.22. 9-[5′,6′-Dideoxy-2′,3′-*O*-isopropylidene-6′-phthalimido-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (16). DEAD (40% wt in toluene, 0.23 mL, 0.51 mmol) was added dropwise to a stirred suspension of **15** (170 mg, 0.51 mmol), phthalimide (75 mg, 0.51 mmol) and Ph_3P (133 mg, 0.51 mmol) in THF (3 mL). After stirring for 3 h at ambient temperature, the solvents were evaporated. Purified on column chromatography gave **16** (160 mg, 67%) as a white solid. Mp 198–200 °C. HRMS (TOF) calcd for $C_{23}H_{23}N_6O_5$ ($M^+ + H$): 463.1730; found: 463.1714.

4.1.23. 9-[5′,6′-Dideoxy-2′,3′-*O*-isopropylidene-6′-aminomethyl-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (17a). To phthalimide **16** (150 mg, 0.32 mmol), a solution of 30% $MeNH_2$ in EtOH (20 mL) was added and the mixture was stirred at 20 °C for 24 h. After evaporation in vacuo, the residue was separated with a silica gel column (CH_2Cl_2/MeOH, 35:1), compound **17** (101 mg, 93%) was collected as a colorless oil. HRMS (TOF) calcd for $C_{15}H_{21}N_6O_3$ ($M^+ + H$): 333.1675; found: 333.1693.

4.1.24. 9-[5′,6′-Dideoxy-6′-aminomethyl-β-L-ribo-hex-5′(*E*)-enofuranosyl] adenosine (17b). A solution of **17a** (28 mg, 0.084 mmol) in TFA-H_2O (5:2, 1.5 mL), was stirred at 20 °C for 2 h and then evaporated to dryness. The residue was dissolved with H_2O and purified by RP-HPLC (preparative column; program: a gradient of 0–10% CH_3CN/H_2O for 30 min at 3 mL/min) to give **17b** (20 mg, 81%, t_R=22 min) as a colorless foam. HRMS (TOF) calcd for $C_{12}H_{17}N_6O_3$ ($M^+ + H$): 293.1362; found: 293.1381.

4.1.25. [5-(*R*)-Dimethoxymethyl-4-(*R*)-benzoyloxy-3(*S*)-(adenine-9′-yl)]-tetrahydrofuran (19). A stirred solution of compound **18** (2.3 g, 8.0 mmol) in anhydrous pyridine (50 mL), benzoyl chloride (1.0 mL, 8.8 mmol) was added dropwise at 0 °C and stirring was continued for 3 h at 0 °C. The solvents were evaporated and the residue was partitioned (saturated $NaHCO_3/H_2O$/EtOAc), the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. Purified on column chromatography (EtOAc/petroleum ether, 2:1) gave **19** (2.1 g, 66%) as a colorless foam, and recovered **18** (0.56 g, 23%). HRMS (TOF) calcd for $C_{19}H_{22}N_5O_5$ ($M^+ + H$): 400.1621; found: 400.1618.

4.1.26. [5-(*S*)-Hydroxymethyl-4-(*R*)-benzoyloxy-3(*S*)-(adenine-9′-yl)]-tetrahydrofuran (20). Compound **19** (1.2 g, 3.0 mmol) was added to a mixed solution of THF (12 mL) and 1% HCl (12 mL). The resulting solution was stirred for 8 h at 90 °C, 2 N $NaOH/H_2O$ was used to neutralize the solution to pH = 7, $NaBH_4$ (370 mg, 9.2 mmol) was added and stirred at ambient temperature for 1 h. After neutralization with 1 N HCl/H_2O, the solution was evaporated to dryness and the residue was purified on silica gel column to give compound **20** (851 mg, 80%) as a colorless foam. HRMS (TOF) calcd for $C_{17}H_{18}N_5O_4$ ($M^+ + H$): 356.1359; found: 356.1349.

4.1.27. {5-(*S*)-[2(*E*)-*p*-Toluenesulfonylethylene]-4-(*R*)-benzoyloxy-3(*S*)-(adenine-9′-yl)}-tetrahydrofuran (21). A stirred solution of compound **20** (476 mg, 1.3 mmol), DCC (1.08 g, 5.9 mmol) in DMSO (3.5 mL), $Cl_2CHCOOH$ (66 μl, 0.7 mmol) was added dropwise at 0 °C (ice bath), stirring was continued for 2 h at ambient temperature, [(*p*-tolylsulfonyl)methylene]triphenyl phosphorane (900 mg, 7.2 mmol) was added and stirred overnight. MeOH (8 mL) was added and stirred for 30 min at room temperature, the resulted dicyclohexylurea was filtered and washed with cold MeOH, and the combined filtrates were evaporated (in vacuo). The residue was partitioned (EtOAc/H_2O), the organic layer was washed with H_2O (3×30 mL), $NaHCO_3$/H_2O, and brine, dried ($MgSO_4$) and evaporated. Purified on column chromatography gave **21** (350 mg, 51%) as a white solid. Mp 136–138 °C. HRMS (TOF) calcd for $C_{25}H_{24}N_5O_5S$ ($M^+ + H$): 506.1498; found: 506.1484.

4.1.28. {5-(*S*)-[2(*E*)-Tributylstannylvinyl]-4-(*R*)-benzoyloxy-3(*S*)-(adenine-9′-yl)}-tetrahydrofuran (22). A solution of **21** (320 mg, 0.6 mmol) in toluene (50 mL) was deoxygenated (argon, 30 min), and Bu_3SnH (0.67 mL, 2.2 mmol) was added. Deoxygenation was continued for 15 min, and AIBN (40 mg, 0.2 mmol) was added. The solution was refluxed for 6 h and evaporated, and the residue was purified by column chromatograph (EtOAc/petroleum ether, 2:1). The elution gave **22** (219 mg, 54%) as a colorless oil, and recovered **21** (85 mg, 26%). HRMS (TOF) calcd for $C_{30}H_{44}N_5O_3Sn$ ($M^+ + H$): 642.2466; found: 642.2449.

4.1.29. [5-(*S*)-(2-Vinyl)-4-(*R*)-hydroxy-3(*S*)-(adenine-9′-yl)]-tetrahydrofuran (23). A solution of compound **22** (76 mg, 0.12 mmol) in dried EtOH (10 mL), NH_4F (200 mg, 6.0 mmol), was added, the resulting solution was refluxed for 3 days, and then evaporated. The residue was purified by silica gel column (EtOAc/petroleum ether, 3:1) to give protected **23**. The product was dissolved in CH_2Cl_2 (10 mL) and catalytic amount of 30% NaOMe/MeOH was added under stirring. After stirred at room temperature for 1 h, the mixture was evaporated and purified by a silica gel column, to give **23** (9 mg, 68%) as a white solid. Mp 179–181 °C. HRMS (TOF) calcd for $C_{11}H_{14}N_5O_2$ ($M^+ + H$): 248.1147; found: 248.1152.

4.1.30. [5-(*S*)-(2-Ethynyl)-4-(*R*)-hydroxy-3(*S*)-(adenine-9′-yl)]-tetrahydrofuran (24). The procedure of reaction is the same as the synthesis for **12a**, but $Pb(OAc)_4$ (4 equiv to compound **22**) was added and stirring was continued for 3 days at ambient temperature. The procedure gave the residue no further purification for the removal of the benzoyl group. The procedure of deprotection was described as compound **23** that gave **24** (18 mg, 67%) as a colorless foam. HRMS (TOF) calcd for $C_{11}H_{12}N_5O_2$ ($M^+ + H$): 246.0991; found: 246.1005.

4.1.31. [5-(*S*)-Dimethoxymethyl-4-(*S*)-benzoyloxy-3(*R*)-(adenine-9′-yl)]-tetrahydrofuran (26). Similar to the synthesis of **19**, compound **26** was obtained in a yield of 85% as a white solid. Mp 183–185 °C.

4.1.32. [5-(*R*)-Hydroxymethyl-4-(*S*)-benzoyloxy-3(*R*)-(adenine-9′-yl)]-tetrahydrofuran (27). Similar to the synthesis of **20**, compound **27** was obtained in a yield of 70% as a colorless oil.

4.1.33. {5-(*R*)-[2(*E*)-*p*-Toluenesulfonylethylene]-4-(*S*)-benzoyloxy-3(*R*)-(adenine-9′-yl)}-tetrahydrofuran (28). Similar to the synthesis of **21**, compound **28** was obtained in a yield of 54% as a white solid. Mp 141–143 °C. HRMS (TOF) calcd for $C_{25}H_{24}N_5O_5S$ ($M^+ + H$): 506.1498; found: 506.1485.

4.1.34. {5-(*R*)-[2(*E*)-tributylstannylvinyl]-4-(*S*)-benzoyloxy-3(*R*)-(adenine-9′-yl)}-tetrahydrofuran (29). Similar to the synthesis of **22**, compound **29** was obtained in a yield of 63% as a white foam, with recovered **28** (29%). HRMS (TOF) calcd for $C_{30}H_{44}N_5O_3Sn$ ($M^+ + H$): 642.2466; found: 642.2427.

4.1.35. [5-(*R*)-(2-Vinyl)-4-(*S*)-hydroxy-3(*R*)-(adenine-9′-yl)]-tetrahydrofuran (30). Similar to the synthesis of **23**, compound **30** was obtained in a yield of 41% as a white solid. Mp 172–174 °C. HRMS (TOF) calcd for $C_{11}H_{14}N_5O_2$ ($M^+ + H$): 248.1147; found: 248.1143.

4.1.36. [5-(*R*)-(2-Ethynyl)-4-(*S*)-hydroxy-3(*R*)-(adenine-9′-yl)]-tetrahydrofuran (31). Similar to the synthesis of **24**, compound **31** was obtained in a yield of 64% as a white foam. HRMS (TOF) calcd for $C_{11}H_{12}N_5O_2$ ($M^+ + H$): 246.0991; found: 246.1002.

4.2. Purification of AdoHcy hydrolase and evaluation of the effectiveness of synthetic compounds

Recombination human placental AdoHcy hydrolase was purified from cell free extracts of *Escherichia coli* transformed with plasmid pPROK-19.[32] To evaluate the inhibitory potential of the compounds, different concentrations (0.01–100 μM) were preincubated with 10 μL (10 μg)

enzyme at 37 °C for 10 min at pH 7.4 in 240 μL PBE buffer. The mixture was then incubated with 50 μL Ado (10 mM) and 200 μL Hcy (10 mM) at 37 °C for 10 min. This reaction was terminated by addition of 20 μL sulfuric acid, and the mixture was cooled with ice bath. After centrifugalization (10,000 rpm for 5 min), the AdoHcy formed was analyzed by HPLC on a C-18 reversed-phase column (Diamonsil™; 250×4.6 mm). Elution was performed with a gradient: (94%A: 6% B, 1 mL/min) over 10 min. (mobile phase A was 0.1% CF_3COOH and mobile phase B was acetonitrile). Quantitative analysis of AdoHcy was monitored (UV) at 258 nm.

4.3. Assays for the inhibition on the growth of various tumor cells

Growth inhibition of the synthetic compounds to various tumor cells were determined by MTT and SRB assays.[34,35] Briefly, tumor cells ($1–2.5\times10^4$ cells mL^{-1}) were inoculated in 96-well culture plates (180 μL/well). After 24 h culture, 20 μL of culture medium containing synthetic compound of various concentrations were added to the wells, and RPMI-1640 medium in control cells, then the cells were incubated for 48 h. The growth inhibition of HL-60 cells were determined by MTT method, and the other cell lines were assayed by SRB method. The absorbance of each well was measured using a microculture plate reader at 570 nm (MTT) and 540 nm (SRB).

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The absolute configuration of peroxisomicines A1 and A2

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Abstract—Peroxisomicine A1 is a potentially antineoplastic compound isolated from the seeds of *Karwinskia parvifolia*. It is considered as a useful chemotype for the preparation of topoisomerase II targeted anticancer cells. Stereochemically, it is characterized by the presence of two stereocenters and a rotationally hindered and thus likewise stereogenic biaryl axis. In this contribution, the absolute configuration of peroxisomicine A1 and its epimer, peroxisomicine A2, was established by means of a five-step degradative procedure giving the respective *R*- and *S*-configured methyl 2-(2′-methyl-5′-oxotetrahydrofuryl)acetates. The configuration of the degradation product was obtained by means of optical rotation, ^{1}H NMR analysis using a chiral displacement reagent, and by experimental and quantum chemical circular dichroism (CD) investigations. Based on the results obtained here and considering our previous work on the relative configuration at centers versus axis of these compounds, peroxisomicine A1 resulted to be the *P*,3*S*,3′*S*-isomer and peroxisomicine A2 the *P*,3*R*,3′*S*-isomer.

1. Introduction

Peroxisomicine A1 (**1a**, PA1) is a biologically active hydroxyanthracenone isolated from the seeds of plants belonging to genus *Karwinskia* (Rhamnaceae).[1] On account of its high and selective toxicity towards different cell lines, peroxisomicine A1 (**1a**) has been tested as an antitumor drug;[2] it exhibited no mutagenic activity in peripheral blood lymphocytes.[3] Recently, it has been suggested that PA1 (**1a**) induces apoptosis[4] and **1a** was found to inhibit topoisomerase II but not topoisomerase I.[5] From the air-dried, ground fruits of *Karwinskia parvifolia*, several isomers of peroxisomicine A1 (**1a**) were isolated and purified.[6,7] However, the most abundant isomer, peroxisomicine A2 (**1b**, PA2), did not show the selective toxicity towards tumor cell lines that PA1 (**1a**) displayed.[1]

By means of X-ray crystallography, NMR data, and CD spectra[7,8] we have demonstrated that PA1 (**1a**) and PA2 (**1b**) are epimers at C-3. In this contribution we describe the determination of the full absolute stereostructures of these two unsymmetrically coupled dimeric[9] hydroxyanthracenones.

2. Results and discussion

The biologically active dimeric hydroxyanthracenones obtained from plants of the genus *Karwinskia* have so far presented stereochemical problems on account of the chiral centers within the dihydroxyanthracene subunits and the stereogenic axis between these two molecular moieties. Although several approaches have been used in similar compounds, none of them proved to be effective in the present case. On account of this, we report here the results obtained by applying a degradative procedure described earlier by Gill and coworkers.[10,11] In contrast to chiroptical methods, which are limited to monomeric hydroxyanthracenones, the chemical degradation and further identification of the butanolide obtained, offers a solution for the central chirality determination in coupled dihydroxyantracenones, as already pointed out by Gill et al.

By applying the degradative procedure to our peroxisomicines (Scheme 1), however, complex mixtures resulted and

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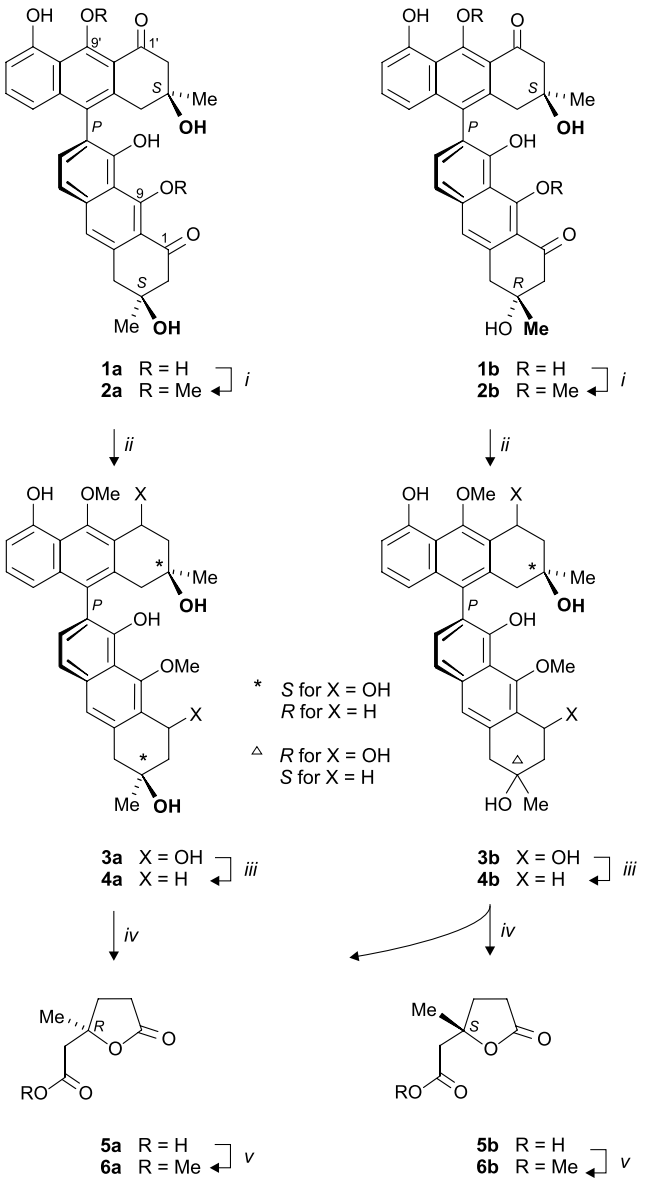


Scheme 1. Comparative stereoanalysis of PA1 (**1a**) and PA2 (**1b**), by *O*-protection, deoxygenation, and oxidative degradation. (i) CH_2N_2; (ii) $LiBH_4$; (iii) H_2, Pd/C; (iv) $RuCl_3$, $NaIO_4$; (v) CH_2N_2.

the yields were very poor. For this reason, the intermediates were not completely purified as suggested by Gill,[10] but only analyzed in a crude form, just to be sure of the nature of the compounds obtained in each step. The degradative procedure was carried out in parallel, on PA1 (**1a**) and its epimer PA2 (**1b**).

The first step in the degradation process was the blocking of 9-OH and 9′-OH to allow further reduction of the carbonyl function (C-1 and C-1′). It had previously been reported that all the procedures used to reduce the carbonyl in these molecules were unsuccessful.[12] It was therefore, anticipated that methylation of these OH groups should impart stability to the molecule and allow the reduction to proceed smoothly, by enhancement of the carbonyl reactivity.[12] The reaction conditions used were similar to those previously reported[12] to increase the proportion of the 9,9′-*O*-dimethylated PA1 obtained as the major component. This product, **2a**, was isolated and identified by means of ^{1}H NMR by comparison with the data published earlier.[12] The respective product originating from PA2 (**1b**) had not previously been reported. In the ^{1}H NMR spectrum of **2b**, the signals at 16.06 and 16.41, corresponding to the deshielded 9- and 9′-enolic protons of peroxisomicine A2 (**1b**) were absent and two new 3H singlets appeared at 4.06 and 4.13 ppm, instead. Isolation of these compounds was accomplished in order to make sure that the 9- and 9′-positions were fully *O*-methylated.

Reduction of the *O*-dimethylated compounds, **2a** and **2b**, posed no problem, in contrast to the reaction with the parent compounds, PA1 (**1a**) and PA2 (**1b**), themselves. The reduction was monitored by the disappearance of the carbonyl band at 1675 cm^{-1} in the IR spectra and appearance of a signal at 5.5 ppm in the ^{1}H NMR spectra corresponding to the benzylic protons H-1 and H-1′. In this reduction reaction, a mixture of the diastereoisomeric alcohols was obtained. Hydrogenolysis of the diastereomeric mixtures **3a** thus obtained from PA1 (**1a**) and **3b** originating from PA2 (**1b**), in a Parr apparatus gave the tetrahydroanthracenes **4a** and **4b**, respectively. While the methylenic signals were not clearly seen in the ^{1}H NMR spectrum of the reaction mixture, the disappearance of the signals at 5.5 ppm revealed the transformation of the secondary alcohols.

Oxidation of these compounds with sodium metaperiodate in the presence of ruthenium chloride gave, after the extractive procedure, the carboxylic acids **5a** and **5b**, which were immediately *O*-methylated. The resulting esters **6a** and **6b** were purified by low-pressure chromatography. However, the products still exhibited aromatic signals showing that the oxidation had been incomplete. This could originate from a too low catalytic activity of ruthenium, which forms a low-valence complex with the product of the reaction.[13] Acetonitrile is a good ligand for ruthenium, thus destroying the complex and returning the ruthenium to the cycle. According to this, complete oxidation was achieved when an excess of acetonitrile was added. Therefore, the butanolides obtained by applying the degradative procedure to PA1 (**1a**) and PA2 (**1b**) gave, after extractive purification, the carboxylic acids **5a** and **5b**, which were *O*-methylated and purified, resulting in the esters **6a** and **6b**, respectively.

For their stereoanalysis, ^{1}H NMR spectra were recorded with and without adding the Eu displacement reagent. The Me and OMe resonances of the butanolide obtained from PA1 (**1a**) appeared at δ 1.52 and 3.70 ppm, respectively. After addition of a chiral Eu(III) shift reagent, they resonated at lower fields (2.20 and 4.51 ppm, respectively), but, as expected, no signal splitting was observed, confirming our previous finding that the absolute configuration at C-3 and C-3′ is the same in this compound. By contrast, when the butanolide obtained from PA2 (**1b**) was analyzed after addition of the same displacement reagent, both signals, which were again shifted to lower field, were now resolved into two signals each (2.17 and 2.20 ppm for the methyl and 4.48 and 4.51 ppm for the methoxy signals) as expected from our previous finding that the configurations at C-3 and C-3′ in PA2 (**1b**) are opposite to each other.[8] The

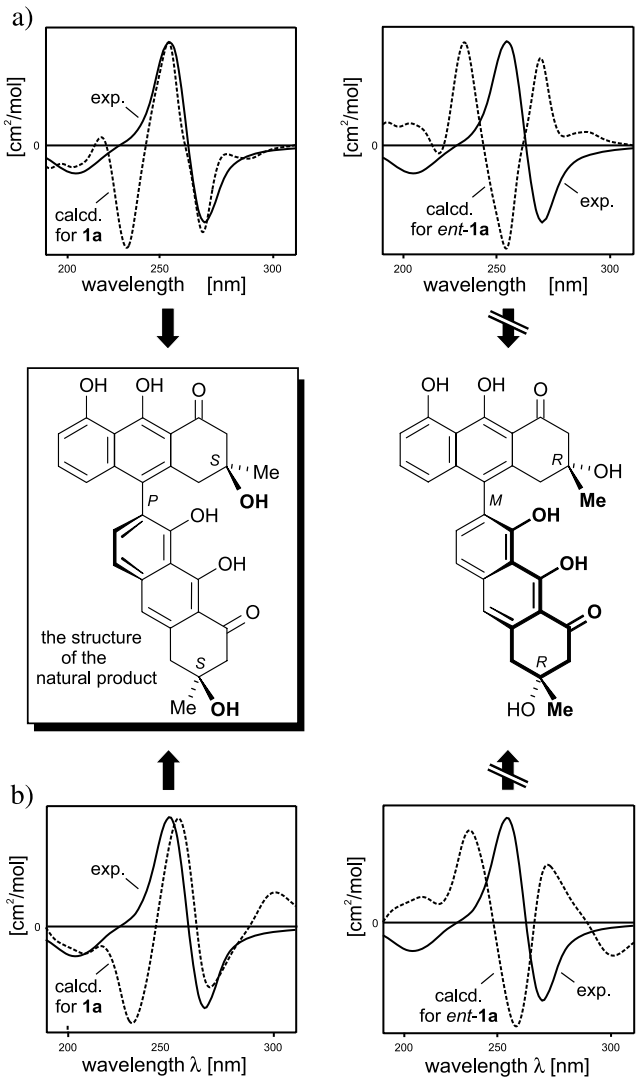
butanolide obtained from the degradation of PA1 (**1a**) showed a smaller displacement upon addition of the chiral Eu reagent, which, according to the literature,[10] hinted at the presence of the *R*-isomer. When a solution of the butanolide obtained from PA2 (**1b**) was added to the mixture of the butanolide obtained from PA1 (**1a**) and the displacement reagent, additional discrete resonances appeared at higher fields (2.17 and 4.48 ppm for the methyl and methoxy signals, respectively). It had previously been reported that the higher-field component of both signals corresponds to the (*S*)-butanolide,[10] showing unequivocally that this isomer arises from the degradation product obtained from PA2 (**1b**). With these results it was possible to demonstrate that the butanolide **6a**, originating from the degradation of PA1 (**1a**), is *R*-configured. Optical rotation unequivocally confirmed its absolute configuration.

Thus, the chirality of peroxisomicine A1 (**1a**) has been established here for the first time in complete stereochemical detail as being 3*S*,3′*S* and that of peroxisomicine A2 (**1b**) as 3*R*,3′*S*. Given the known configuration at the stereogenic centers relative to the axis, as deduced from X-ray diffraction and from NMR investigations,[7,8] the absolute axial configuration can thus be assigned to be *P*.[14]

To further confirm these results, quantum chemical circular dichroism (CD) calculations were performed. Arbitrarily starting with the (*P*)-atropo-diastereomer of **1a**, this molecule was submitted to a conformational analysis by means of the semiempirical AM1[15] method, resulting in 120 conformers within the relevant energetical range of 3 kcal/mol above the global minimum. For each optimized geometry a CD spectrum was calculated using the CNDO/S-CI[16] approach. The single CD curves thus obtained were added up and weighted in accordance to their respective heat of formation, that is, following the Boltzmann statistics, to give the overall theoretical spectrum, which was subsequently UV-corrected.[17] Its comparison with the experimental one of **1a** revealed a good agreement (Scheme 2a, left), whereas the likewise simulated CD curve for (*M*,3*R*,3′*R*)-**1a** showed a virtually opposite behavior (Scheme 2a, right), thus assigning **1a** to possess a *P*-configured chiral axis.

To further validate this structural elucidation, (*P*,3*S*,3′*S*)-**1a** was additionally submitted to a molecular dynamics (MD) simulation[18] using the MM3[19] force field at a virtual temperature of 600 K. For the geometries extracted from the trajectory of motion single CD spectra were computed using again the CNDO/S-CI[16] method. Subsequent summing up of these spectra and UV correction[17] delivered the overall simulated CD curve, which again corresponded with the measured CD spectrum of **1a** (Scheme 2b, left), while the likewise predicted curve for (*M*,3*R*,3′*R*)-**1a** was once again found to be virtually opposite (Scheme 2b, right). In consequence, both theoretical approaches led unambiguously to PA1 (**1a**) having a *P*-configured axis.

The similarity of the CD spectrum of peroxisomicine A2 (**1b**) with that of **1a** finally clearly established this epimeric molecule to be *P*-configured, too, again in agreement with the spectroscopic results described above.



Scheme 2. Attribution of the absolute configuration of PA1 (**1a**) by comparison of the experimental CD spectrum (in MeOH) with the spectra calculated for (*P*,3*S*,3′*S*)-**1a** and (*M*,3*R*,3′*R*)-**1a**; (a) according to the AM1-Boltzmann approach; (b) following the MM3-MD method.

3. Conclusion

The work described in this paper presents the combined approach to establish the stereochemical details of the epimeric biaryl natural products, peroxisomicines A1 and A2, by spectroscopic, chemical (here degradative), and computational methods (quantum chemical CD calculations). Accordingly, **1a** and **1b** have an identical configuration at C-3′ (both *S*) and at the rotationally hindered biaryl axis (both *P*), but differ at C-3, which is *S* for **1a** and *R* for **1b**. The results demonstrate the value of combining experimental and computational methods in attaining stereochemical information otherwise difficult to achieve.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on a Bruker

DPX-400 machine at 400.13 and 100.62 MHz, respectively, using $CDCl_3$ as the solvent. The IR spectra were recorded using a FT-IR Bruker Vector 22. Precoated silica gel 60 F254 and RP18 F254 (Merck, 0.2 mm thick) were used for TLC, spots being detected in the visible and UV, or by spraying with 5% KOH in ethanol. Low-pressure chromatography was accomplished on Lobar Lichroprep RP-18 material (40–63 μm) from Merck. Analytical HPLC was carried out on an HP 1090 DAD detector with a C-18 column 100×2.1 mm, 5 μm. Elution was accomplished with a mixture of acetonitrile, methanol, water, and acetic acid according to a methodology previously described.[20] Optical rotations were measured on a Perkin–Elmer 341 polarimeter at 22 °C. All reactions were performed using purified and dried solvents under an atmosphere of either N_2 or Ar. Reagents were from Aldrich and Sigma Chemical Co.

4.2. Isolation of peroxisomicines A1 (1a) and A2 (1b)

PA1 (**1a**) and PA2 (**1b**) were obtained from the fruits of *K. parvifolia* as previously described;[7] purity and identity were assessed by physico-chemical, chromatographic, and spectroscopic methods.

4.3. *O*-Methylation of PA1 (1a)

PA1 (**1a**) (100 mg) in ethanol (5 mL) was exposed to diazomethane (generated in situ by means of the diazald reagent using the Diazald® Kit from Aldrich) in an acetone dry ice bath for 45 min. The reaction mixture was extracted with ethyl acetate and the product precipitated with *n*-hexane. The resulting pale yellow residue (75 mg) was purified by means of CC (silica gel 60, ethyl acetate) to give ten fractions, which were combined according to TLC monitoring (the developing system was also ethyl acetate) to give three fractions. Only the fractions with an R_f value similar to that of the peroxisomicine-9,9′-di-*O*-methyl ether (**2a**) were purified and identified as previously described.[12]

4.4. Reduction of 9,9′-di-*O*-methylperoxomicine A1 (2a)

A mixture of the 9,9′-di-*O*-methyl ether **2a** of peroxisomicine A1 (**1a**) (70 mg) and lithium borohydride (60 mg dissolved in THF) was stirred at room temperature until the initial product had disappeared as shown by TLC and IR spectra. When the conversion was complete, methanol was added to the reaction vessel. The solvent was evaporated and the residue was redissolved with ethyl acetate, and then washed several times with water. The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent evaporated by distillation, reconstituted with ethyl acetate and the product precipitated with *n*-hexane. The pale yellowish residue **3a** (61 mg) was used in the following reaction without further purification.

4.5. Hydrogenolysis of the alcohol mixture 3a

The mixture of diastereomeric alcohols **3a** (40 mg) in methanol (10 mL) containing Pd/C (10%, 10 mg) was shaken under an atmospheric pressure of hydrogen (50 psi) in a Parr apparatus for 15 h at room temperature. The catalyst was filtered off and washed with methanol and the solvent was removed under reduced pressure. The residue was recovered with chloroform and precipitated with petroleum ether to obtain the crude tetrahydroanthracene **4a**.

4.6. Oxidation of the tetrahydroanthracene 4a

The crude tetrahydoanthracene **4a** (26 mg) was stirred with sodium metaperiodate (0.595 g) and a trace of ruthenium(III) chloride (3.7 mg) in a heterogeneous mixture of tetrachloromethane (3 mL), acetonitrile (3 mL), and water (4 mL) for 24 h. After this time, isopropanol (3.5 mL) was added to destroy the oxidizing agent followed by an excess of barium chloride. After 30 min of vigorous stirring, the mixture was filtered and the residue was washed with dichloromethane. The filtrate was extracted with dichloromethane, and then, with continuous stirring, with ether at room temperature during 24 h. Finally the dichloromethane and the ethereal extracts were combined, dried, and evaporated to yield an oil consisting of crude **5a**.

4.7. *O*-Methylation of 5a

The oily residue obtained after oxidation of **4a** was immediately exposed to an excess of ethereal diazomethane as described in the first reaction. After 1 h the excess of diazomethane was destroyed by dropwise addition of acetic acid and the solution was evaporated to dryness. The product was purified by means of low-pressure chromatography (Lobar, silica gel) under isocratic condition using ethyl acetate/*n*-hexane (3:2) as the eluent, with a flow rate of 3 mL/min. The fractions containing the methylated butanolide according to TLC (silica gel, ethyl acetate/*n*-hexane 3:2) were evaporated and recuperated with chloroform. The product **6a** was analyzed by means of ^{1}H NMR, showing data similar to those reported in the literature.[21]

4.7.1. Spectral data of the degradation product 6a. $\alpha_D^{25} = +9.3$ ($CHCl_3$).[21] ^{1}H NMR (400.13 MHz): $\delta = 1.52$ (s, 3H, CH_3-2), 2.13 (ddd, 1H, H-3), 2.42 (ddd, 1H, $J=$ 16.7 Hz, H-3′), 2.63 (ddd, 1H, H-4), 2.68 (ddd, 1H, H-4′), 2.74 (d, 2H, CH_2), 3.70 (s, 3H, CH_3O) ppm.

4.8. Analysis of 6a by means of ^{1}H NMR using a chiral shift reagent

To the butanolide **6a** placed in an NMR tube and dissolved in $CDCl_3$ (0.5 mL), 35, 70, and 105 μL of a 100 mg/mL solution of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]europium(III) were successively added. ^{1}H NMR spectra were recorded after each addition.

4.9. *O*-Methylation of PA2 (1b)

PA2 (**1b**, 80 mg) was *O*-methylated by a similar procedure as described above for PA1 (**1a**). The product was purified by means of gravitational column chromatography (silica gel, ethyl acetate). Fractions containing the 9,9′-di-*O*-methyl ether **2b** of peroxisomicine A2 (**1b**) were gathered, the solvent evaporated, the residue redissolved in ethyl acetate, and precipitated by addition of *n*-hexane.

4.9.1. Spectral data of the 9,9′-di-*O*-methyl ether 2b. MS-EI (70 eV): *m/z* (%)=542 (48) (M^+), 524 (100), 506 (10), 491 (20). ^{1}H NMR (400.13 MHz): δ=1.33 (s, 3H, CH_3-3′), 1.51 (s, 3H, CH_3-3), 2.86 (d, 1H, J=16.7 Hz, H-4′$_{ax}$), 2.87 (m, 2H, H-2′), 3.28 (m, 2H, H-2), 3.00 (d, 1H, J=16.72 Hz, H-4′$_{eq}$), 3.26 (d, 1H, J=16.1 Hz, H-4$_{eq}$), 3.29 (d, 1H, J=16.1 Hz, H-4$_{ax}$), 4.06 (s, 3H, OCH_3-9), 4.13 (s, 3H, OCH_3-9′), 6.81 (d, 1H, J=8.39 Hz, H-5′), 6.89 (d, 1H, J=7.67 Hz, H-7′), 7.31 (d, 1H, J=8.1 Hz, H-6), 7.33 (t, 1H, H-6′), 7.39 (d, 1H, J=8.5 Hz, H-5), 7.56 (s, 1H, H-10), 10.16 (s, 1H, OH-8′), 10.25 (s, 1H, OH-8) ppm.

4.10. Reduction of the 9,9′-di-*O*-methyl ether 2b

60 mg of **2b** were reduced by the same procedure as described for PA1 (**1a**), monitored by means of IR, leading to a mixture of the alcohols **3b**.

4.11. Hydrogenolysis of the alcohol mixture 3b

The hydrogenolytic deoxygenation was performed as explained for PA1 (**1a**) with 43 mg of the mixture **3b** to obtain 35 mg of the crude product **4b**.

4.12. Oxidation of the tetrahydroanthracene 4b

29 mg of the tetrahydroanthracene **4b** obtained from the previous reaction were oxidized as depicted above for **4a** as derived from PA1 (**1a**); the resulting carboxylic acid was immediately *O*-methylated to give the crude ester, which was purified by means of low-pressure chromatography (Lobar, C-18, isocratic). The product (1 mg, **6a/6b**) was analyzed by means of ^{1}H NMR (data identical to those of compound **6a**).

4.13. ^{1}H NMR analysis of the mixture 6a/6b obtained from PA1 (1b) by means of a chiral shift reagent

To the above butanolide, dissolved in $CDCl_3$ (0.5 mL), and placed in an NMR tube, 105 μL of a 100 mg/mL solution of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]europium(III) were added and the ^{1}H NMR spectrum was recorded.

4.14. ^{1}H NMR analysis of a mixture of the butanolide obtained from PA1 (1a) and the mixture of butanolides derived from PA2 (1b), by using a chiral shift reagent

To the butanolide **6a** in $CDCl_3$ (0.5 mL), 105 μL of a solution of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]europium(III) were added. After measurement of the ^{1}H NMR spectrum, 10 μL of the mixture of butanolides obtained from PA2 (**1b**) were added immediately and the ^{1}H NMR spectrum was registered again.

4.15. Computational

The conformational analysis was carried out on Silicon Graphics OCTANE R10000 workstations by means of the semiempirical AM1[15] method as implemented in the program package VAMP 6.5,[22] starting from preoptimized geometries generated by the TRIPOS[23] force field. The molecular dynamics simulation was performed at a virtual temperature of 600 K using the MM3[19] force field, as implemented in the molecular modeling package SYBYL.[23] The overall simulation time was 500 ps. The single geometries were extracted every 0.5 ps. The wave functions required for the calculation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/S-CI[16] calculations. These computations were carried out with Linux Pentium III workstations by the use of the BDZDO/MCDSPD[24] program package. In the case of the MD approach, the single CD spectra were added up arithmetically, whilst in the case of the conformational analysis, they were weighted following the Boltzmann statistics, according to the respective heat of formation. For a better visualization, the rotational strengths were transformed into $\Delta\varepsilon$ values and superimposed with a Gaussian band shape function.

Acknowledgements

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An imidazolium ionic liquid having covalently attached an oxime carbapalladacycle complex as ionophilic heterogeneous catalysts for the Heck and Suzuki–Miyaura cross-coupling

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Abstract—An oxime carbapalladacycle, analogous to that used as catalyst in homogeneous phase, has been derivatized to increase its ionophilicity by introducing an imidazolium group covalently attached through a chain at the complex. The resulting complex is soluble in 1-butyl-3-methylimidazolium ionic liquid (bmimPF_6) and not extractable by ether. The catalytic activity of this palladium complex in bmimPF_6 is, however, unsatisfactory and only increases marginally in bmimPF_6/supercritical CO_2. This limitation has been overcome by supporting this imidazolium palladium complex on high surface area Al/MCM-41 aluminosilicate, whereby a solid active catalyst for the Suzuki cross-coupling has been obtained. Reusability and stability over reuse for this Al/MCM-41-supported catalyst have been studied.

1. Introduction

A general tendency in catalysis is to transform a successful homogeneous catalytic reaction into a heterogeneous process in which the catalyst can be easily separated from the reaction mixture, allowing its reuse and the design of continuous flow operation.[1–3] Among the different approaches for this homogenous-to-heterogeneous transformation, one established strategy is to take advantage of the property of fluorous solvents to be immiscible with typical organic solvents at room temperature, but to become totally soluble at higher temperatures. In addition, fluorous liquids are normally poor solvents at room temperature, but the room-temperature solubility in them increases considerably by appending to the molecules a perfluorinated chain that accounts for above 20% of the molecular weight. The thermotropic property of fluorous solvents has been applied in heterogeneous catalysis by modifying conventional catalysts introducing fluorous pony tails, whose exclusive role is to increase the solubility in the fluorous phase while decreasing simultaneously the solubility in conventional organic solvents.

The use of ionic liquids is another topic of much interest in heterogenous catalysis.[4,5] Ionic liquids can dissolve many organic compounds but they are in turn immiscible in some apolar organic solvents such as alkanes or ethers. In those cases in which the catalyst is soluble in ionic liquids, but insoluble in alkanes or ethers, it would be also possible to develop a heterogeneous system in which the reaction is carried out in the ionic liquid, and the reaction products recovered by simple liquid–liquid extraction using alkanes or ethers.

Following a parallel strategy to that used in fluorous-phase catalysis,[6–13] our work here describes the modification of a carbapalladacycle catalyst aimed at increasing the 'ionophilicity' of the complex.[14–16] This has been achieved by introducing an imidazolium pony tail. The effect caused by the introduction of an imidazolium moiety in the catalyst can be termed as 'ionophilicity' (in analogy with the term 'fluoricity'[17]) and is used to describe the alteration of molecular properties of the catalysts, particularly their solubility, by increasing its affinity to ionic liquids and its ionic liquid behaviour. There are precedents in which molecules have been modified to enhance their ionophilicity.[18,19] This imidazolium-substituted carbapalladacycle has also been supported on a large-surface area support. Related precedents are those reporting the use of chloroaluminates of *N*,*N*′-dialkylimidazolium supported on MCM-41 silicate as solid Lewis acid catalysts.[20] In our case the counter-anion does not play the role of Lewis acid and the major point of our work being to devise a synthetic route to link covalently the imidazolium moiety and the palladium complex. We will show the results achieved with this cationic complex as heterogeneous catalysts under various conditions, addressing its reusability and stability.

Keywords: Palladium catalyst; Heterogeneous catalysis; Ionic liquids.
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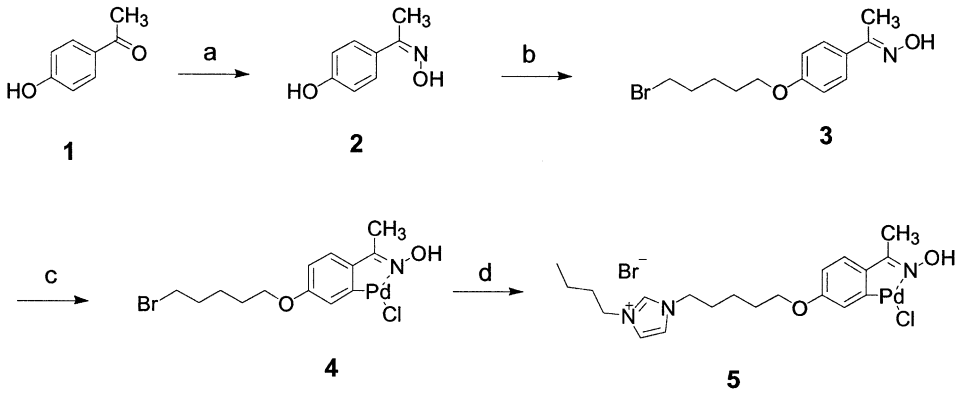


Scheme 1. Synthetic route followed for the preparation of oxime carbapalladacycle **5**. (a) NH_2OH, NaOAc, H_2O, reflux, 1 h; (b) 1,5-dibromopentane, K_2CO_3, acetone, reflux, 48 h; (c) Li_2PdCl_4, NaOAc, methanol, rt, 72 h; (d) 1-methylimidazole, THF, 50 °C, 72 h.

2. Results and discussion

Oxime carbapalladacycle with structure Pd-**2** has been reported by Nájera and co-workers as one of the most active palladium catalysts for the Suzuki–Miyaura cross-coupling of aryl halides and arylboronic acids.[21–24] The synthetic route followed to prepare its derivative palladium complex **5** is indicated in Scheme 1. Starting from 4-hydroxyacetophenone, the corresponding oxime was obtained and then reacted with 1,5-dibromopentane to obtain compound **3**. Of the various possibilities tested, the introduction of Pd^{2+} after formation of compound **3** was found as the most convenient. Palladium metal ion and its complexes are prone to undergo reduction with formation of black palladium metal under very mild conditions.[25] Therefore, the step in which the palladium complex is formed in the synthetic route has to be carefully selected to avoid palladium reduction. In our case, other alternatives and, particularly introduction of palladium in the last step after formation of the imidazolium moiety were found less desirable due to the formation of black palladium metal.

All the intermediates in the synthesis of complex **5** were characterized analytically and spectroscopically. As the most salient feature, we have seen that formation of the palladium–carbon bonds in the carbapalladacycle complex **4** produces a change in the number and pattern of the aromatic protons from A_2B_2 to ABM. Figure 1 shows the IR spectra of carbapalladacycles **4** and **5** compared to those of the parent complex Pd-**2** reported by Nájera and the starting oxime **2**. The most salient common feature is the absence of the C=N stretching vibration of the palladium complexes as compared to 1670 cm^{-1} recorded for the oxime precursors.

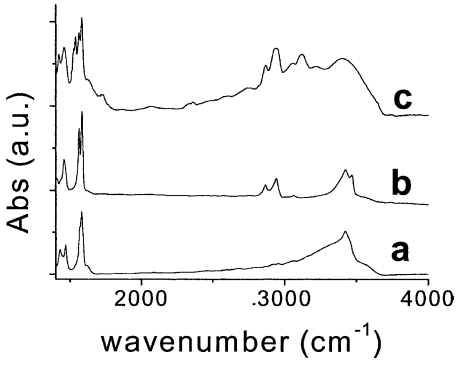


Figure 1. IR spectra of oxime carbapalladacycles recorded at room temperature in KBr (a) or dissolved in dichloromethane (b, c); (a) oxime carbapalladacycle Pd-**2**, (b) compound **4**, (c) compound **5**.

Besides ligand centred absorption bands, most transition metal complexes have in the visible region of the UV–Vis spectrum charge transfer transition bands that are specific of the metal-ligand orbital overlapping. As expected in view of the reports on the optical spectrum of the parent oxime carbapalladacycle, Figure 2 presents the UV–Vis spectra of complexes **4** and **5** showing two broad absorption bands at λ_{max} 300 and 350 nm that are absent in the ligand **3**. This is indicative that the co-ordinative ligand–metal bound has survived the nucleophilic substitution using N-methylimidazole.

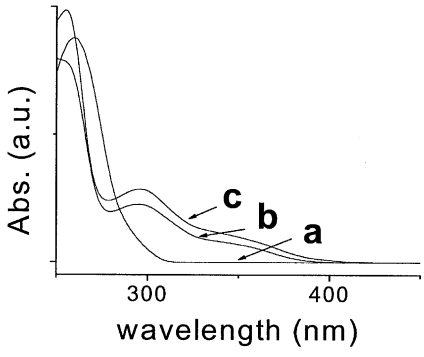


Figure 2. Transmission UV–Vis spectra in dichloromethane of **3** (a), **4** (c) and **5** (b).

When submitted to FAB-MS analysis, complexes **4** and **5** appear as monomeric species and the most characteristic feature corresponds to the molecular ion cluster arising from the natural isotopic distribution of Pd or Pd and Br. Based on FAB-MS, it has been reported that the simplest carbapalladacycles are dimeric species, in agreement with the

tendency of palladium to form tetra co-ordinated complexes. In our case, it may very well occur that the monomeric nature of complexes **4** and **5** arises from the co-ordination of palladium with terminal groups (Br in complex **4** and imidazolium in complex **5**), thus satisfying all the co-ordination positions around palladium. As expected, complex **5** is soluble in 1-butyl-3-methylimadozolium hexafluorophosphate ($bmim^+$ PF_6^-) as well as in halogenated organic solvents.

Complex **5** was also supported on Al/MCM-41 (Si/Al 13). The presence of AlO_4^{5-} tetrahedra replacing isomorphically SiO_4^{4-} in the framework of a silicate produces and excess of negative charge that requires the presence of charge balancing cations to maintain the electroneutrality of the solid.[3,26] Aluminosilicates are particularly suited as solid supports to adsorb and incorporate positively-charged organic cations such as complex **5**. It is expected that after adsorption, Coulombic interactions between complex **5** and the aluminosilicate will occur. The strength of this electrostatic interaction between complex **5** and Al/MCM-41 was determined by following the intensity of the IR bands corresponding to complex **5** after thermal treatment of **5**@Al/MCM-41 in a sealed cell under reduced pressure. It was observed that **5** remains adsorbed after thermal treatment at 300 °C under 10^{-2} Pa for prolonged periods. The diffuse reflectance UV–Vis spectrum shows the two characteristic charge transfer transition bands of the palladium complex (Fig. 3). Table 1 provides a comparison of the chemical analysis (Pd, C and N) and porosity of Al/MCM-41 before and after adsorption of complex **5**. In agreement with the assumption that **5** becomes adsorbed into the mesoporous channels of Al/MCM-41, the micropore volume and BET surface area becomes somewhat reduced with respect to the initial values measured for pristine Al/MCM-41, although the resulting **5**@Al/MCM-41 catalyst still exhibits the large surface area and porosity characteristic of the original support.

As indicated above, carbapalladacycle complex **5** was soluble in $bmimPF_6$ and it could not be extracted from this solution upon extensive liquid–liquid extraction with diethyl ether. A control using unmodified Najera's complex Pd-**2** showed that this procedure extracts a significant fraction of the parent complex from $bmim^+PF_6^-$ as evidenced visually by the observation of a yellow extract, thus, demonstrating that the ionophilicity principle based on the introduction of an imidazolium tag attached to the palladium complex serves to increase its affinity for imidazolium ionic liquids.

The activity of complex **5** as reusable catalyst for the Heck reaction (Eq. (1)) between styrene and halobenzenes was initially tested in $bmim^+PF_6^-$ and NaAcO as a base. A summary of the results are shown in Table 2. As it can be seen there, the results were in general disappointing in terms of conversion. The use of iodobenzene or deactivated bromobenzenes as reagents, an excess of NaAcO or a stronger base does not lead to satisfactory improvements in conversion. The best results were obtained using supercritical CO_2 as co-solvent in $bmimPF_6$ to decrease the viscosity of the medium and to promote diffusion. Unfortunately, even under these conditions the conversion was still far from optimum. Besides the Heck reaction, Suzuki coupling (Eq. (2)) of iodobenzene was also inefficiently catalyzed by complex **5** in ionic liquid (conversions below 10%, see Table 2 entry 8) and no further tests were carried out, particularly considering that iodobenzene is the most reactive reagent.

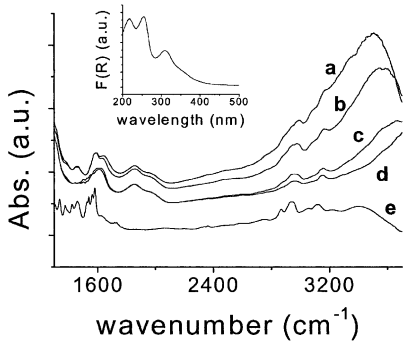


Figure 3. IR spectra of the **5**@Al/MCM-41 recorded at room temperature after outgassing for 1 h at: room temperature (a), 100 °C (b), 200 °C (c) and 300 °C (d) at 10^{-2} Pa. For the sake of comparison the IR spectrum of **5** recorded at room temperature is included (e). The inset shows the diffuse reflectance UV–Vis spectra (plotted as the Kubelka-Munk function of the reflectance, R) of **5**@Al/MCM-41.

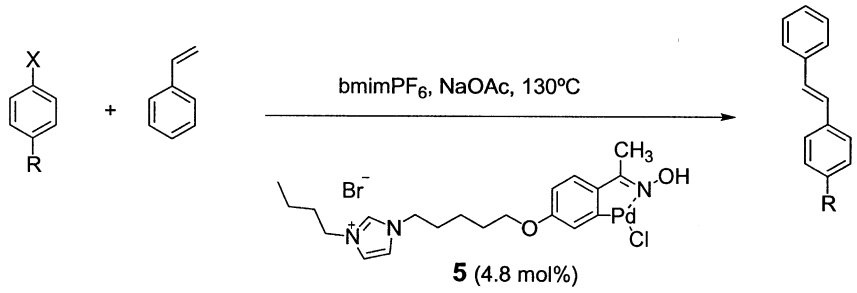
Table 1. Relevant analytical and physicochemical parameters of the Al/MCM-41 and **5**@Al/MCM-41

	Solid	
	Al/MCM-41	**5**@Al/MCM-41
Si/Al atomic ratio	13	13
BET surface area ($m^2 \times g^{-1}$)	781	692
Micropore volume ($cm^3 \times g^{-1}$)	0.419	0.358
Average pore diameter (Å)	38.3	33.9
Micropore area ($m^2 \times g^{-1}$)	518	439
Elemental analysis ($mmol \times g^{-1}$)	–	Pd: 0.042; C: 2.56; N: 0.42

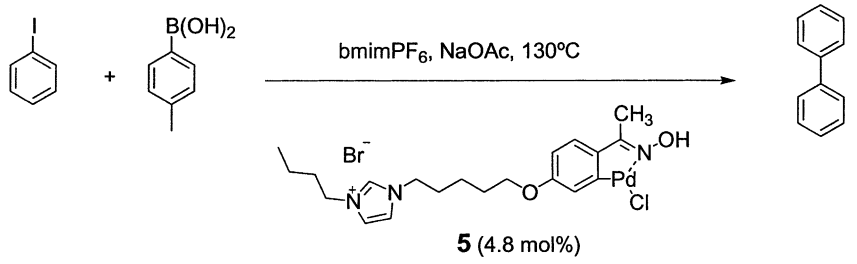
Table 2. Results for the Heck or Suzuki reaction of halobenzenes (1 mmol), styrene (Heck, 156 mg, 1.5 mmol) or tolylboronic acid (Suzuki, 102 mg, 1 mmol) and NaOAc (164 mg, 2 mmol) in a 5 wt% solution of **5** in $(bmim)PF_6$ (25 mg in 500 mg)) at 130 °C

Entry	Halobenzene	Time (h)	Yield (%)
1	Bromobenzene	24	3.4
2	Bromoacetophenone	72	25.7
3	Iodobenzene	5	17.3
4	Iodobenzene	5	1.6[a]
5	Iodobenzene	5	7.8[b]
6	Iodobenzene	5	8.1[c]
7	Iodobenzene	20	26.3[d]
8	Iodobenzene	5	8.4[e]

[a] $BmimCl^{-1}$ as solvent.
[b] K_2CO_3 as base.
[c] Six equivalents of NaOAc.
[d] Supercriticcl CO_2.
[e] Suzuki coupling.

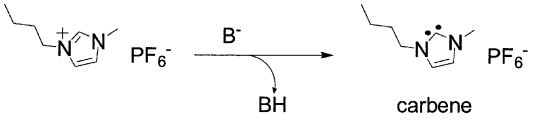


(1)



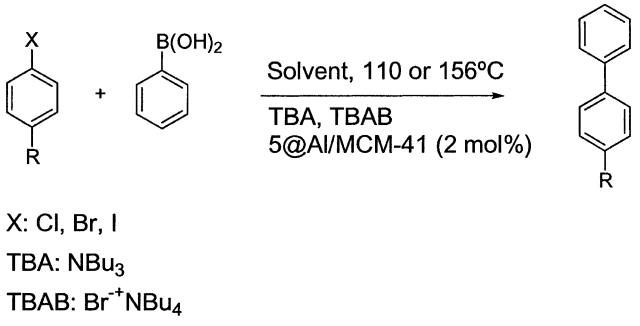
(2)

One possible explanation for the low activity of complex **5** in ionic liquids is based on the poor stability of imidazolium ionic liquids to bases. We and others have previously shown that ionic liquids have a limitation for NaOH catalyzed reactions due to the formation of a carbene arising from deprotonation of $bmim^+$ at the 2 position (Eq. (3)).[27,28] This carbene would co-ordinate with complex **5** and eventually would lead to its decomposition and formation of black palladium. Whatever the reasons, we tried to circumvent this problem by supporting complex **5** in Al/MCM-41. The resulting **5**@Al/MCM-41 powder can be used as solid catalyst in conventional organic solvents.



(3)

The activity of **5**@Al/MCM-41 was tested in toluene and dimethylformamide (DMF). These solvents were selected to determine the influence of polarity on the catalytic activity of **5**@Al/MCM-41. Table 3 lists conversion and selectivity data measured using this solid catalyst and tributylamine (TBA) as base for the Suzuki–Miyaura cross coupling between halobenzenes and phenylboronic acid (Eq. (4)). Noteworthy is the positive influence of the presence of tetrabutylammonium bromide (TBAB) on the activity and stability of the solid catalyst. Figures 4 and 5 compare the time conversion plot for the Suzuki coupling of p-haloacetophenone and phenylboronic acid either in toluene or DMF in the presence and absence of TBAB. The use of TBA^+ as additive was already reported by Nájera[23,29] and a likely rationalization of its influence compatible with our observations will be provided below.



(4)

As expected in view of the precedents, the activity of **5**@Al/MCM-41 was higher in a polar solvent like DMF than in toluene (see Table 3). Using DMF as solvent, bromo and even chlorobenzenes undergo Suzuki coupling promoted by **5**@Al/MCM-41. As expected, we notice however that the catalytic activity of **5**@Al/MCM-41 for chlorocompounds is lower than for bromoderivatives (see footnote a in Table 3). Moreover,

Table 3. Results for the Suzuki reaction of halobenzene (0.2 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), tributylamine (95 μL, 0.4 mmol), TBAB (32.2 mg, 0.1 mmol) in toluene at 110 °C or DMF at 156 °C (5 mL) for 72 h in the presence of **5**@Al/MCM-41 (85.1 mg)

Run	X	R	Solvent	Conversion (%)	Suzuki:homocoupling products
1	I	$COCH_3$	Toluene	>99	32:68
2	I	H	Toluene	51	51 (the same)
3	I	Br	Toluene	75	13:62
4	Br	$COCH_3$	DMF	>99	>99:0
5	Br	H	DMF	57	57:0
6[a]	Cl	$COCH_3$	DMF	87	87:0

[a] Double amount of catalyst.

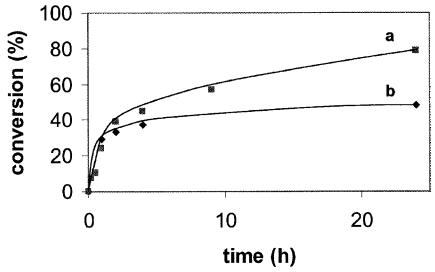


Figure 4. Time conversion plot for the Suzuki reaction of 4-haloacetophenone (49.2 mg, 0.2 mmol), phenylboronic acid (36.6 mg, 0.3 mmol) and tributylamine (95 μL, 0.4 mmol) in toluene (5 mL) at 110 °C in the presence (a, 32.2 mg, 0.1 mmol) or absence (b) of TBAB, using **5**@Al/MCM-41 (85.1 mg) as catalyst.

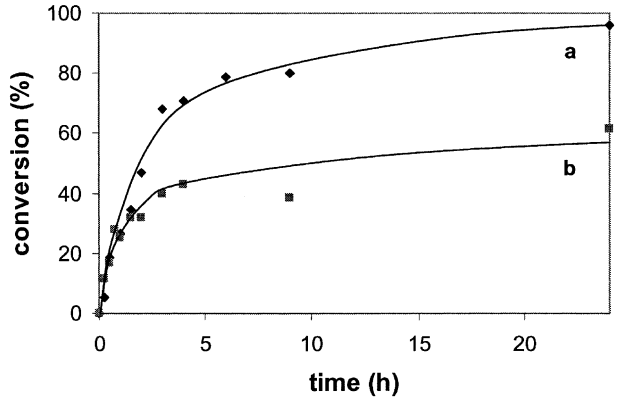


Figure 5. Time conversion plot for the Suzuki reaction of 4-haloacetophenone (39.8 mg, 0.2 mmol), phenylboronic acid (36.6 mg, 0.3 mmol) and tributylamine (95 μL, 0.4 mmol) in DMF (5 mL) at reflux temperature in the presence (a, 32.2 mg, 0.1 mmol) or absence (b) of TBAB, using **5**@Al/MCM-41 (85.1 mg) as catalyst.

the activity of **5**@Al/MCM-41 in DMF was very similar to that observed for the parent complex Pd-**2** in homogeneous phase in the same solvent and significantly higher under these conditions than an analogous catalyst previously prepared by us in which an oxime carbapalladacycle oxime was covalently bonded to MCM-41 through a chain[30] (Fig. 6). The latter catalyst can be used, however, for reactions in aqueous media, while the presently reported **5**@Al/MCM-41 is obviously inappropriate for reactions in water due to the ionic nature of the bonding between **5** and the Al/MCM-41 support.

The catalyst can be recovered from the reaction mixture by simple filtration and after washing with fresh solvent can be reused. Similar activity and selectivity were measured for **5**@Al/MCM-41 either in toluene or DMF after four consecutive reuses. Palladium analyses of the liquid phase and activity data upon reuse are given in Table 4.

When dealing with heterogeneous catalysts an important issue is to confirm that the activity is really due to the solid catalyst and not to a minor fraction of the active sites that under the reaction conditions migrates from the solid to the solution. To address the possibility of leaching, a reaction was initiated in the presence of **5**@Al/MCM-41, then the suspension filtered while still hot at 50% conversion and the clear solution after removal of the solid allowed to react further. If the activity is completely due to the solid catalyst, the reaction should stop in the absence of the solid. Figure 7 shows the results of the leaching study for **5**@Al/MCM-41 in where it can be considered that a percentage of 30% of the total conversion is due to the palladium dissolved from the solid into the solution. This leaching is confirmed by a gradual loss of palladium from the catalyst after being subject to several recycles (see Table 4).

The diffuse reflectance UV–Vis spectra of reused **5**@Al/MCM-41 shows a considerable decrease and eventually disappearance of the 350 nm band characteristic of the initial complex **5** in the first uses. This fact indicates that the complex is not completely stable under the reaction conditions and undergoes a progressive decomposition upon use probably by reduction and formation of palladium metal. Importantly, a reused **5**@Al/MCM-41 sample in which most of the complex has disappeared, as evidenced by the disappearance of the 350 nm band in the diffuse reflectance UV–Vis spectra, still contains over 70% of the initial palladium and showed high activity towards the Suzuki coupling (see Table 4, run 3). These data agree with the transformation during the reaction of most the palladium complex into highly-dispersed palladium metal particles on

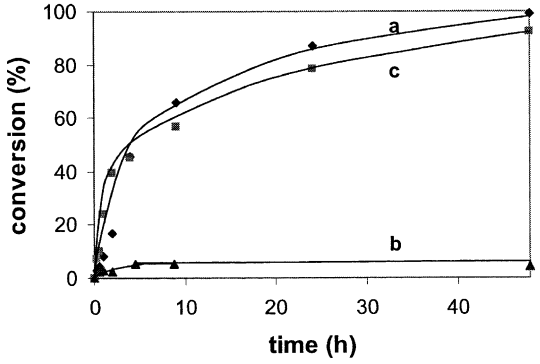


Figure 6. Time conversion plot for the Suzuki reaction of 4-haloacetophenone (49.2 mg, 0.2 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), tributylamine (95 μL, 0.4 mmol), TBAB (32.2 mg, 0.1 mmol) in toluene (5 mL) at 110 °C in the presence of **5**@Al/MCM-41 (a, 85.1 mg), **5** anchored covalently to MCM-41 (b, 121.2 mg) and the acetophenone carbapalladacycle oxime Pd-**2** (c, 1.16 mg) as catalysts.

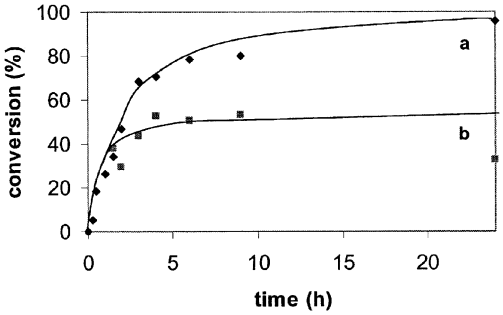


Figure 7. Time conversion plot for the Suzuki reaction of 4-haloacetophenone (39.8 mg, 0.2 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), tributylamine (95 μL, 0.4 mmol), TBAB (32.2 mg, 0.1 mmol) in DMF (5 mL) at reflux temperature in the presence of **5**@Al/MCM-41 as catalyst (a, 85.1 mg) and a twin run in which the solid was filtered in hot at 90 min (ca. conversion 40%) and allowing the clear solution to continue the reaction (b).

Table 4. Activity upon reuse of **5**@Al/MCM-41 for the Suzuki coupling of 4-iodoacetophenone (0.2 mmol) and phenylboronic acid (3.6 mg, 03 mmol) adding tributylamine (95 mL, 0.4 mmol) and TBAB (32.2 mg, 0.1 mmol) as co-catalysts in toluene at 110 °C

Run	Reuse	Conversion (%)	Suzuki:homocoupling products	Pd (mmol×g^{-1})	Loss of Pd[a] (% vs original)
1	0	88	17:71	0.043	<1
2	1	86	24:62	0.044	<1
3	2	90	20:70	0.033	21
4	3	86	18:70	0.028	33

[a] Fresh solid catalyst: 0.042 mmol×g^{-1}.

the high surface area Al/MCM-41 support. This hypothesis is also in agreement with the positive influence of TBAB on the catalytic activity. Recent reports[25,31–33] have shown that quaternary ammonium surfactants can be used to stabilize colloidal Pd nanoparticles that can be active for C–C coupling reactions provided that palladium agglomeration and the corresponding particle size growth is prevented. Large palladium metal particles, as those obtained when this noble metal is supported on activated carbon, are inert or considerably less active as Suzuki catalyst.

In summary, while the ionophilicity of an oxime carbapalladacycle can be significantly increased by introducing in the noble metal complex an imidazolium tag, the use of this catalyst in ionic liquid for the Heck and Suzuki reactions is limited by the requirement of basic conditions. Supporting this imidazolium modified carbapalladacycle catalyst on Al/MCM-41 is a viable methodology to increase the activity and reusability of the palladium catalyst in organic solvents. However, the oxime carbapalladacycle complex is not totally stable under the reaction conditions and as a result some palladium leaching from the solid to the solution occurs. These factors play a negative role on the long-term reusability of the system.

3. Experimental

The reagents and solvents were obtained from commercial sources and were used without further purification. GC was carried out on an HP 5890 instrument equipped with a 25 m capillary column of 5% phenylmethylsilicone. GC-MS was performed on an Agilent 5973N instrument equipped with the same column and conditions as GC. ^{1}H and ^{13}C NMR were recorded in a 300 MHz Bruker Avance instrument using $CDCl_3$ or d^6-DMSO as solvents and TMS as internal standard. Diffuse reflectance UV–Vis spectra were recorded on a Cary 5G adapted with a praying mantis accessory using $BaSO_4$ as reference. IR spectra were recorded on a Jasko 460plus spectrophotometer using sealed greaseless quartz cells with CaF_2 windows. Self-supported wafers (10 mg) were obtained by pressing the solid at 1 Ton×cm^{-1} for 5 min. Thermal treatments were carried out in sealed IR cells and the spectra recorded in a Nicolet 710 instrument at room temperature after outgassing at the corresponding temperature under 10^{-2} Pa. BET surface area and micropore volume were measured by isothermal nitrogen adsorption using a Micromeritics ASAP2000. The C and N content of the solids was determined by combustion chemical analysis using a Fisons CHNSO analyzer. The Pd content in Al/MCM-41 catalysts was determined by dissolving the aluminosilicate in a mixture of HF/HCl/HNO_3 conc. (30 mg in ca. 1:1:1 mL), diluting the solution in water (30 mL) and measuring by quantitative atomic absorption spectroscopy (Varian SpectrAA 10 plus). The Pd content in organic molecules was determined in the same way but dissolving the compound in a mixture of HCl/HNO_3 conc. (3 mg in ca. 1:1 mL) and diluting the solution in water/acetonitrile (95:5 v/v, 30 mL).

3.1. Preparation procedure of Al/MCM-41

To a solution of cetyl trimethylammonium bromide (3.68 g), tetramethylammonium hydroxide (8.49 g) in water (32.6 g) aluminium hydroxide (0.48 g) was added and the mixture was stirred (200 rpm) for 1 h. Silica (5 g, Aerosil, Degussa) was added and the mixture was stirred for 1 h more until homogeneous gelation was observed. A pH of 13.6 was measured and the gel was submitted to hydrothermal crystallization at 150 °C for 24 h. After this time the final pH was measured (11.6) and the solid was washed with distilled water (0.5 L per g). The solid was dried at 60 °C for 24 h and calcined (from room temperature up to 540 °C at a rate of 5 °C×min^{-1}, then the temperature maintained 10 h of which the first 4 h were purged under nitrogen flow and the rest under air flow) before use. The loss of weight in the calcination was ca. 40% and the final Si/Al molar ratio was ca. 15. The Si/Al atomic ratio was determined by chemical analysis.

3.1.1. Synthesis of 2. 4-Hydroxyacetophenone (3 g, 0.022 mol) was added to a solution of hydroxylamine hydrochloride (5.13 g, 0.074 mol) and sodium acetate (10.26 g, 0.125 mol) in water (26 mL). The solution was stirred at reflux temperature for 1 h. After this time, the aqueous solution was extracted exhaustively with diethyl ether. The organic phase was dried and the solvent evaporated under vacuum. To the resulting crude, hexane was added and 1-(4-hydroxyphenyl)ethanone oxime (**2**) starts to precipitate as a white solid (3.25 g, 0.0215 mol, 98%). IR (KBr, cm^{-1}): 3324, 1642, 1603, 1514, 1444, 1316, 1240, 1176, 940, 825, 589. ^{1}H NMR δ_H (ppm, 300 MHz, CD_3OD): 7.49 (2H, d, J=5 Hz), 6.77 (2H, d, J=5 Hz), 2.18 (3H, s). ^{13}C NMR δ_C (ppm, 300 MHz, CD_3OD): 159.9, 156.7, 130.2, 128.9, 116.5, 12.55. MS: m/z 151. Anal. calcd for $C_8H_9NO_2$ (151.15): C 63.5; H 5.95; N 9.26. Found: C 63.19; H 6.22; N 9.35.

3.1.2. Synthesis of 3. A solution of 4-hydroxyacetophenone oxime (1.51 g, 10 mmol) in acetone (100 mL) was added dropwise (2 mL/min) to a dispersion of 1,5-dibromopentane (10 mL, 73 mmol) and K_2CO_3 (4.14 g, 30 mmol) in acetone (20 mL) at reflux temperature. After complete addition, the mixture was heated 48 h. At this time the mixture was filtered, the solvent evaporated under vacuum and the crude

was submitted to partition in CH_2Cl_2/water. The organic phase was collected and CH_2Cl_2 evaporated under vacuum. The residue was treated with hexane (200 mL) and the product obtained by filtration under vacuum as a white solid (yield: 42%, purity by GC >99%). IR (KBr, cm^{-1}): 2939, 2866, 1674, 1599, 1575, 1560, 1510, 1311, 1255, 1170, 833, 588. ^1H NMR δ_H (ppm, 300 MHz, $CDCl_3$): 8.8 (1H, s), 7.6 (2H, d, $J=9$ Hz), 6.8 (2H, d, $J=9$ Hz), 4.0 (2H, t), 3.3 (2H, t), 2.3 (3H, s), 1.9 (2H, s), 1.8 (2H, s), 1.6 (2H, s). ^{13}C NMR δ_C (ppm, 300 MHz, $CDCl_3$): 159.9, 155.6, 129.0, 127.4, 114.4, 67.7, 33.5, 32.5, 29.0, 24.8, 12.1. MS (FAB): *m/z* 301–299 (peaks at 151, 134, 120, 94, 77, 69). Anal. calcd for $C_{13}H_{18}NO_2Br$ (300.22): C 52.0; H 6.0; N 4.7. Found: C 51.6; H 5.7; N 2.8.

3.1.3. Synthesis of 4. To a methanolic solution (5 mL) of Li_2PdCl_4 (786 mg, 3 mmol) and sodium acetate (246 mg, 3 mmol), a solution of **3** (602 mg, 2 mmol) in methanol (15 mL) was added. The mixture was stirred at room temperature for 72 h. Then, water was added (20 mL) and, after cooling, the cyclopalladate complex started to precipitate as a green solid (yield: 95%, purity by NMR 75%). IR (KBr, cm^{-1}): 3350, 2937, 2862, 1574, 1531, 1454, 1429, 1373, 1342, 1275, 1223, 1215, 1101, 1018, 966, 872, 804, 638, 555. ^1H NMR δ_H (ppm, 300 MHz, DMSO-d^6): 10.4 (1H, s), 9.8 (1H, s), 7.4 (1H, s), 7.2 (1H, d, $J=$ 15 Hz), 6.7 (1H, d, $J=15$ Hz), 4.0 (2H, s), 3.6 (2H, t), 2.2 (3H, s), 1.9 (2H, m), 1.7 (2H, m), 1.5 (2H, m). ^{13}C NMR δ_C (ppm, 300 MHz, DMSO-d^6): 167.5, 157.3, 154.7, 133.1, 128.3, 122.1, 111.8, 67.6, 35.5, 32.3, 29.1, 28.1, 24.6, 11.7. MS (FAB): isotopic distribution for M-Cl compatible with 1 Pd and 1 Br (%): *m/z* 402 (11), 403 (22), 404 (38), 405 (22), 406 (53), 407 (0), 408 (38), 409 (0), 410 (12); found: 19, 29, 43, 28, 53, 14, 37, 16, 13. Anal. calcd for $C_{13}H_{17}NO_2ClPd$ (441.08): C 35.0; H 3.8; N 3.2; Pd 24.0. Found: C 35.4; H 4.1; N 3.2; Pd 22.3.

3.1.4. Synthesis of 5. To a dark green solution of complex **4** (441 mg, 1 mmol) in THF (50 mL), 1-methylimidazole (239.1 μL, 246.3 mg, 3 mmol) was added. The solution turned bright green and was magnetically stirred in a pre-heated bath oil at 50 °C for three days. After this time the solvent was evaporated under vacuum. Then, diethyl ether was added (15 mL), the mixture was filtered. The crude of **5** obtained was dissolved in dichloromethane and filtered in order to remove any generated Pd black. The organic solvent was evaporated under vacuum and, after washing with diethyl ether (3×20 mL), a viscous green oil was obtained. The product was stored in dry atmosphere (480 mg, yield: 92%). IR (KBr, cm^{-1}): 3400, 3120, 2941, 2868, 1580, 1596, 1539, 1525, 1458, 1421, 1375, 1336, 1308, 1287, 1277, 1229, 1209, 1167, 1107, 1043, 1028, 962, 818, 741, 699, 660, 640, 621. ^1H NMR δ_H (ppm, 300 MHz, DMSO-d^6): 8.9 (1H, s), 8.2 (1H, s), 7.5 (1H, t, $J=1.5$ Hz), 7.4 (1H, s), 7.2 (1H, t, $J=9$ Hz), 6.9 (1H, d, $J=9$ Hz), 6.7 (1H, dd, $J=3$, 1.5 Hz), 3.9 (2H, t, $J=7$ Hz), 3.8 (2H, s), 3.7 (3H, d, $J=1.5$ Hz), 2.2 (3H, s), 1.7 (2H, m), 1.6 (2H, m), 1.4 (2H, m). ^{13}C NMR δ_C (ppm, 300 MHz, DMSO-d^6): 159.5, 154.7, 151.8, 140.5, 138.4, 136.9, 135.6, 122.6, 121.1, 109.4, 65.3, 55.3, 49.0, 45.6, 34.5, 32.1, 22.4. Anal. calcd for $C_{17}H_{23}N_3O_2BrClPd$ (523.20): C 39.0; H 4.4; N 8.0; Pd 20.3. Found: C 40.8; H 5.3; N 10.9; Pd 14.3.

3.2. Adsorption of 5 on Al/MCM-41

Palladium complex **5** (200 mg) was dissolved in ethanol/dichloromethane (2:1 v/v, 24 mL) and the solution was magnetically stirred (500 rpm) in a pre-heated bath oil at 40 °C in the presence of 2 g of previously dehydrated Al/MCM-41. After 24 h the mixture was filtered under vacuum and the solid was exhaustively Soxhlet-extracted with dichloromethane. The palid yellow solid was kept into a desicator for 24 h.

3.3. Typical procedure for reactions in ionic liquid

A 5 wt% mixture of complex **5** (25 mg) in $bmimPF_6$ (500 mg) was dissolved in dichloromethane (1 mL). The solvent was evaporated under reduced pressure and bromobenzene (105 μL, 157 mg, 1 mmol), styrene (172 μL, 156 mg, 1.5 mmol) and sodium acetate (164 mg, 2 mmol) were added. The mixture was magnetically stirred (200 rpm) in a pre-heated oil bath at 130 °C for 24 h. Then, the solution was cooled, extracted with diethyl ether ($5\times$ 5 mL) and the ethereal phase was concentrated and analysed by CG using nitrobenzene as external standard.

3.4. Typical procedure for reactions using 5@Al/MCM-41

4-Haloacetophenone (0.1 mmol), phenylboronic acid (18.3 mg, 0.15 mmol) and tetrabutylammoniun bromide (TBAB, 16.1 mg, 0.05 mmol) were placed into a double-necked round-bottom vessel. Toluene (2.5 mL) and tributylamine (47.5 μL, 37.1 mg, 0.2 mmol) were added and the solution was magnetically stirred in a pre-heated oil bath at 110 °C in the presence of **5**@AlMCM-41 (42.6 mg, 2 mol% of Pd). The course of the reaction was followed periodically by stopping the stirring for half a minute and taken aliquots (0.1 mL) that were analysed by GC. All the products were confirmed by CG-MS.

3.5. Leaching tests

Leaching of catalytically active species from the solid to the solution (which would act as homogeneous catalysts) was studied filtering the reaction at the time in which 25–50% of the expected yield was achieved. Filtration was carried out in a glass syringe coupled with a swinney 13 mm filter (Millipore) while the reaction was still hot in order to avoid palladium precipitation upon cooling. Then, the clear solution was allowed to react for additional 48 h. The course of the reaction was followed by analysing periodically the reaction mixture by GC. The results were compared with those obtained in the same conditions without removing the solid catalyst from the reaction mixture.

3.6. Recovery and reuse of the catalyst

After a typical reaction run (four times the amounts of reagents and catalyst than in a typical reaction procedure), the solid was separated by vacuum filtration in hot. Then, the solid was washed with dichloromethane (300 mL per 100 mg of solid) and was dried 30 min under reduced pressure. The dry solid was weighed and reused in a next run

adding the proportional amounts of reactants to keep the substrate-to-catalyst and the solvent-to-catalyst ratios constant throughout the series of reuses.

Acknowledgements

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Solid phase synthesis of 6-acylamino-1-alkyl/aryl-4-oxo-1, 4-dihydrocinnoline-3-carboxamides

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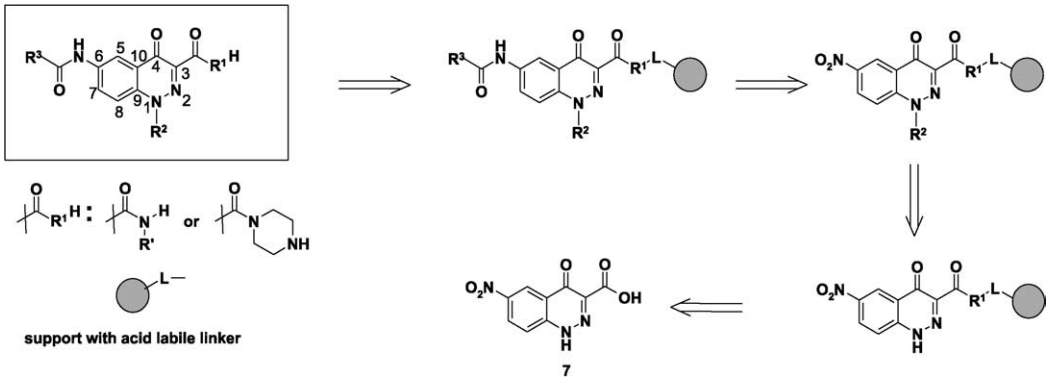
Abstract—6-Acylmino-1-alkyl/aryl-4-oxo-1,4-dihydrocinnoline-3-carboxamides were synthesized in parallel from 6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxylic acid. The latter formed amides with amines bound to polystyrene-based resins via acid-labile linkers. N1 and N2-alkylation, followed by alkyl migration yielded only N1-alkylated products. Reduction of the 6-nitro group and acylation concluded the synthesis.

Cinnolines and some of their heterocyclic analogs exhibit biological activity in various areas. After trypanocidal activity was discovered long ago,[1] antihypertensive, antithrombotic, antitumor, antisecretory,[2] as well as bactericidal, antihistaminic and insecticidal activities[3] have been demonstrated. Cinnolines have also been described as anxiolytic agents and benzodiazepine receptor antagonists.[4]

Our aim was to develop a robust synthesis of 1,3,6-trisubstituted cinnolines on solid phase, minimizing the steps on the solid phase not involved in the diversification of the scaffold. The first cinnolines were synthesized by von Richter[5] and a method based on that initial synthesis was shown to provide cinnolines with various substitution patterns on the allocycle, that is, C5-8, as well as on C3 and C4.[6] Unfortunately, N1-substituted cinnolines are not accessible by this route unless at least one derivatization step would be performed in solution phase. We also attempted to avoid Pd-mediated couplings,[6] that are often oxygen sensitive and may lead to Pd-contaminations in the final products. The principle of our solid-phase approach, allowing to exploit three diversity points on a cinnoline-scaffold is presented below (Scheme 1).

We intended to start from a readily available cinnoline precursor, commercially available resins and standard



Scheme 1. Retrosynthetic analysis of 1,3,6-trisubstituted cinnolines; R^1-H: primary amines or piperazine, R^2, R^3, R': alkyl or aryl groups.

Keywords: Cinnolines; Solid support; Alkylation; Arylation; Rearrangement; Reduction; Acylation; Reaction monitoring.
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[†] Work performed as partial requirement the degree: Master of Pharmaceutical Chemistry at the University of Genova, Italy.

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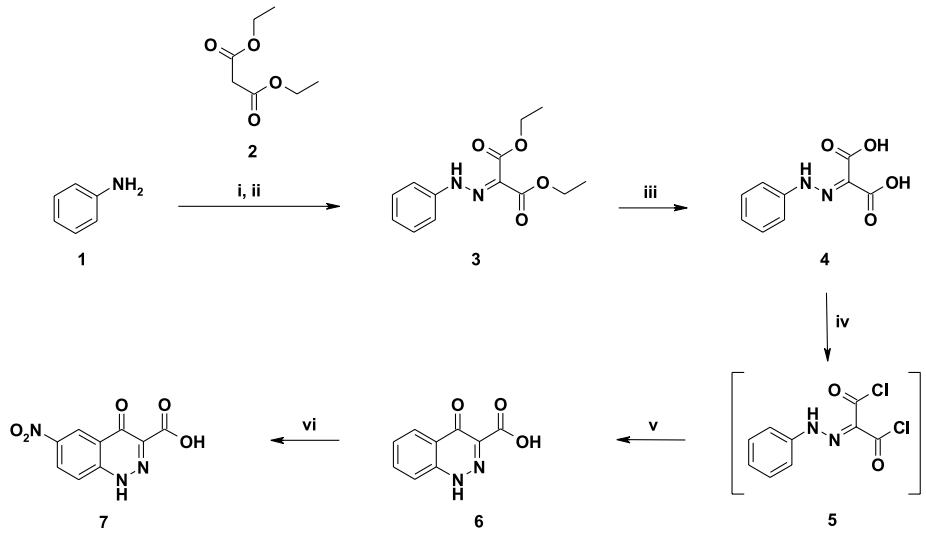
doi:10.1016/j.tet.2004.06.103



Scheme 2. (i): aq. HCl, rt quant.; (ii): (a) $NaNO_2$, HOAc, H_2O, EtOH, 0 °C; (b) **2**, 0° rt 12 h; (iii): (a) aq. NaOH; (b) aq. HCl; (iv): $SOCl_2$, 1,2-dichlorobenzene, reflux, 5 h, evaporation of excess $SOCl_2$; v: (a) $TiCl_4$, 90 °C, 12 h, evaporation; (b) aq. NaOH, filtration; (c) HCl, 66% from **1**; vi: HNO_3, H_2SO_4, reflux, 2 h.

reagents allowing the introduction of broad structural diversity.

We would initiate the synthesis by acylating resins bearing a wide variety of amines with **7** or an analog thereof. To introduce R^2, we intended to alkylate the cinnoline selectively on N1. Reduction of the nitro group at C6, followed by acylation of the resulting amino function would give the target compounds.

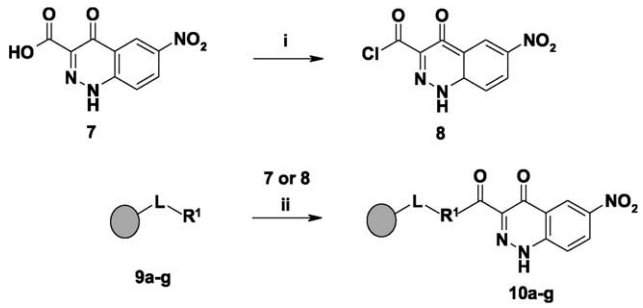
One potential problem of this synthetic path lies in the regioselectivity of the alkylation. We also needed to clarify, whether the alkylation should be performed prior to or after the acylation on C6–NH_2.

Initially, we needed to obtain sufficient quantities of the central building blocks **7** or **8** (Scheme 3), which could to be then bound to the solid phase. Among the main synthesis methods described in the literature for cinnolines,[7] we chose the large scale procedure of Barber et al.[8] Within this approach, the steps concerning the conversion of **4** to **6** (Scheme 2) had to be revisited, since neither 1,2-dichloroethane, nor chloroform were acceptable solvents for multigram scale preparations in our laboratories. Thus in a one-pot-procedure the diacid **4** was converted quantitatively into **5** using thionyl chloride in 1,2-dichlorobenzene. After evaporation of excess $SOCl_2$ under ambient pressure and without isolation of **5**, $TiCl_4$ was added to the crude reaction mixture to conclude the cyclization. Removal of all volatiles (including $TiCl_4$) in vacuo prior to the aqueous basic workup gave pure 4-oxo-1,4-dihydrocinnoline-3-carboxylic acid **6** in high yield as a yellow solid. The efficiency of the cyclization was found to be extremely important, since the subsequent nitration-conditions led to conversion of mesoxallic acid penylhydrazone to picric acid.[9,10] The latter provides a risk of explosion on shock, if dried.

Compound **6** was then nitrated to afford 6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxylic acid **7** in a mixture of fuming nitric acid and sulfuric acid, which compound **6** is soluble in. The yields of the nitration are determined, not by the conversion, but by the recovery of compound **7**, which possesses some aqueous solubility. Compound **7** was then converted to **8** (Scheme 3) and both were tested for their ability to couple to primary amines bound onto the polystyrene supports via appropriate acid labile linkers.

We used commercial Tr-supports bearing amines,[11] 2-methoxy-benzaldehyde (AMEBA),[12] and indole-3-carbaldehyde resins.[13] In the case of 2-methoxy-benzaldehyde and indole-3-carbaldehyde resins a set of amines was immobilized onto the polymers using reductive aminations. For the of 2-methoxy-benzaldehyde and indole-3-carbaldehyde resins, the linker was attached to the polystyrene matrix via a flexible spacer moiety, which allowed the use of NMR-spectroscopy to analyze the polymer-bound species.[14] On commercial Tr-supports the NMR-analysis of the polymer-bound species was not possible, due to strong vibrational and rotational constraints leading to long relaxation times. Thus, on-bead NMR revealed that conditions involving $NaBH_3CN$[13] or $NaBH(OAc)_3$ in presence of acetic acid,[15] or $NaBH_3CN$ with $Ti(OiPr)_4$[16] as dehydrating agent were equivalent for most amines.[17] To avoid problems caused by possible insoluble precipitates we chose the conditions described by Gordon et al.[15] to immobilize the amines.

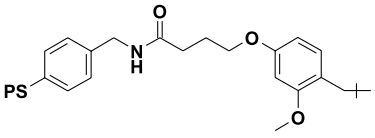
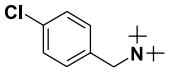
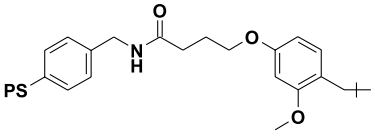
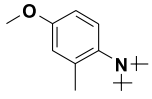
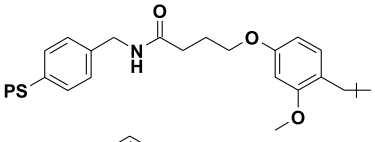
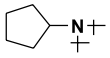
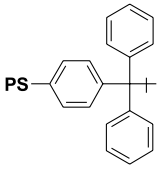
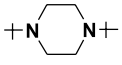
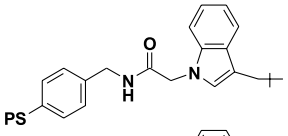
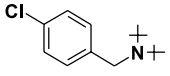
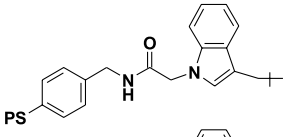
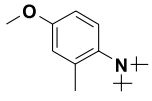
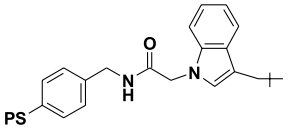
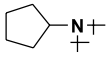
The acylation of polymer bound amines was then undertaken with **7** or **8**. All resins bearing the yellow 6-nitro-4-oxo-1,4-dihydrocinnolines are dark brown. After acidolytic cleavage of the cinnolies, followed by a quench of the polymer-bound linker cation with MeOH pale yellow resins were re-obtained. The reaction yields were obtained by on-bead NMR and after analysis of cleavage products. Variations in yields resulting from the method of determination become apparent (Table 1). The most efficient acylation could be accomplished with **7** in mixtures of dichloromethane and DMF after preactivation with carbonyl diimidazole (CDI) or preformation of the pentafluorophenyl ester. In turn, acylation with 6-nitro-4-oxo-1,4-dihydrocinnoline-3-carbonyl chloride **8** led to lower acylation efficiencies (Scheme 3, Table 1).



Scheme 3.

We found that macroscopic swelling may not be a clear indicator of functional group mobility on the polymer. Thus, DMF was often found to be favorable to obtain well resolved NMR-spectra over DCM, especially in case of polymer-bound cinnolines, despite of the greater macroscopic swelling observed in the latter solvent. Confocal microscopy revealed that beads of resins with high loading appear like dark circles with illuminated edges.[18] Even in cases, when on-bead NMR of a swollen resin indicated exhaustive modification of the resin bound functionalities (for instance acylation of AMEBA-resins), the apparent lack of fluorescence in the center of the beads must have been caused by fluorescence quenching of proximal chromophores, despite of them being fixed on the polymer. (Fig. 1) A quantification of the loading by confocal microscopy can therefore be ruled out. As expected, we found a dramatic difference in the fluorescence of the polymer bound substrates. This enables qualitative assessment, whether a polymer bound substrate was modified or not, the absorption or emission spectra are altered during the transformation.

Table 1. Acylation of support-bound amines with cinnoline-based acylating agents

	L–	R^1	Product	Method A	Method B	Method C
9a			**10a**	19[a]	45–50,[b] 55[a]	>95,[b] 62[a]
9b			**10b**	15–20[b]	74[a]	
9c			**10c**			96[a]
9d			**10d**		79[c]	95[a,d]
9e			**10e**			>80,[b] 93[a]
9f			**10f**			>80,[b] 97[c]
9g			**10g**			>80,[b] 95,[a] 81[e]

L, linker; PS, polystyrene, crosslinked with 1–2% divinylbenzene. (i) $POCl_3/PCl_5$, 95 °C, 2 h, 96%; (ii) Method A: **8**, DMF/DCM, sym. collidine, rt 16 h, (determined by on-bead NMR); Method B: **9a**, **7**, CDI, DMF sym. collidine, rt 16 h, loading: 45–50% of **10a** (determined by on-bead NMR with an error of 5% caused by the integation of overlapping signals); Method C: **9a–g**, **7**, DIC, pentafluorophenol, *N*-methylimidazole, DMF sym. collidine, rt 16 h, loading: **10a–g** (determined by weight of the cleavage products).

[a] Isolated yield after cleavage from resin; purity > 95% by HPLC-MS at 220 nm.

[b] Determined by on-bead NMR.

[c] Purity of isolated product after cleavage determined by HPLC-MS at 220 nm.

[d] Isolated as TFA salt.

[e] Purity determined by NMR of crude product after cleavage, side product is cyclopentyl ammonium trifluoroacetate.

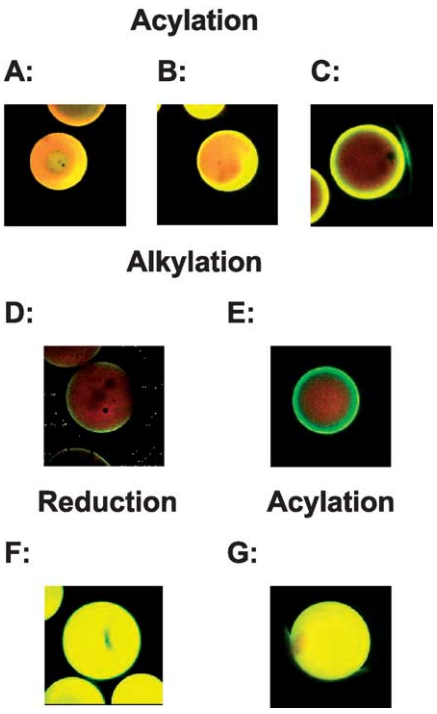


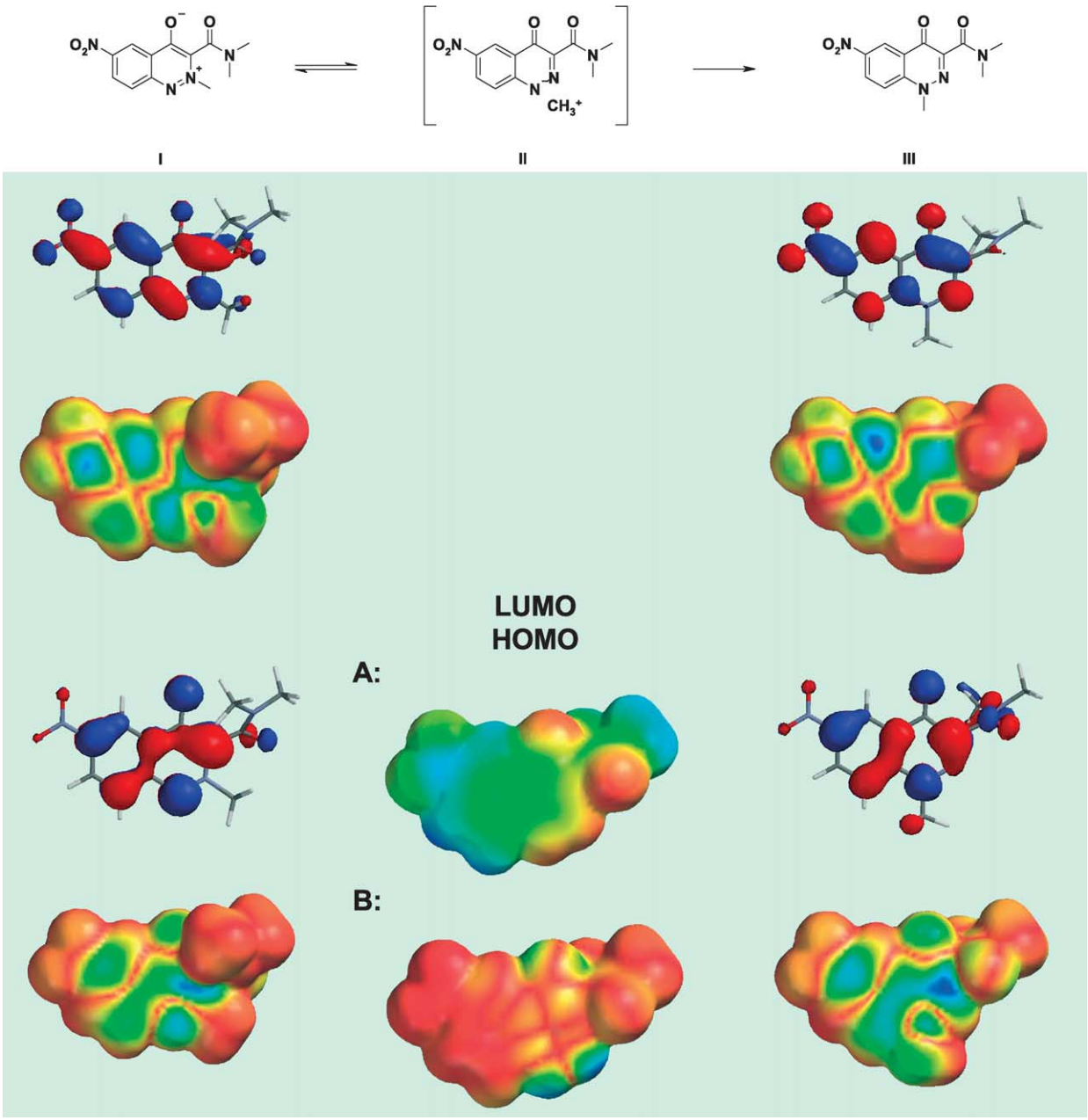
Figure 1. Example of confocal microscopy of some resins swollen in *N*-methyl imidazole (NMI). NMI was found to be favorable, since it is non-volatile and allows most polystyrene based resins to swell almost as much as in DCM. (A): **9a**; (B): **10a** with a loading of 15–20%; (C): **10a** with loading 45–50%; (D): **12b**, **13b** (alkylation products of **10a** with BnBr **11b**); (E): **12d**, **13d** (alkylation product of **10a** with MeI **11e**); (F): **14e** (product of reduction of **12d**, **13d** with Bu_4SH); (G): **17b** acylation product of **14b** with cyclopropanoyl chloride.

During all acyclations, the O4-function of the cinnolines did not require protection. Hartree-Fock calculations (Scheme 4) suggested[19] a low HOMO-value and therefore a low nucleophilicity at O4. As a consequence, various attempts to increase the solubility of **7** by O-silylation failed.[20] The same calculations suggested a large HOMO value at C3, which may facilitate ketene formation.[21] As a result, acylation of AMEBA and other amine resins under moderately basic conditions and nucleophilic catalysts, such as imidazole or pentafluorophenol reduce the amount of high molecular weight side products, which may be the result of ketene formation. In the case of acid chloride, but also of the DCI coupling, on-resin magic angle spinning NMR revealed considerable amounts of non-covalently bound cinnoline in presence of free, unacylated AMEBA resin. It appears that cinnoline residues on resin or in solution may aggregate or bind tightly to polystyrene. The resulting aggregates may be considered as 'non-covalent' cross links, which obscure the accessibility of resin functionalities.[22] The vicinity of cinnoline chromophores is supported by fluorescence quenching in the inner part of beads observed by confocal microscopy. The efficiency of active ester coupling procedures lies in the greater hydrophobicity of the active ester and its lower reactivity towards nucleophiles relative to acid chloride **8**. These features allow the active ester to diffuse deeply into the resin without being hydrolyzed to the very insoluble acid **7**, which is likely to form aggregates on its own or with other cinnoline residues already bound to the solid phase. Magic angle spinning on-bead NMR of 'acid chloride couplings' often revealed substantial quantities of **7**, which could neither react with proximal polymer-bound amino functions nor washed out with polar solvents such as NMP. To disrupt these aggregates, the washing procedure of resins **10a–d** is crucial. DMF or NMP washes have not been effective, however, special 'washing cocktails' such as DMSO/DCM 1/1 (v/v), DMF/2,4,6-collidine/H_2O 8/1/1 (v/v/v) or DMF/aqueous ammonia 4/1 (v/v) were necessary to elute all the non-covalently bound cinnoline.

The subsequent alkylation, prior to reduction of the 6-nitro-group, gave cleaner products than on N^6-acylated derivatives (Table 2). The reaction of **10a–g** with alkyl-halides in presence of K_2CO_3, Rb_2CO_3 and Cs_2CO_3 in DMF, silver salts, and also with alcohols under Mitsunobu conditions[23] gave for some alkyl halides initially a mixture of N1 and N2 alkylated products **12** and **13**, as indicated by ROESY-NMR spectra[24] on bead and analysis of cleavage products. Among the alkylations with alkaline carbonates, Rb_2CO_3 in DMF gave the most consistent yields and pure compounds. However, the use dry solvent and finely powdered, anhydrous carbonate-base was essential for a complete alkylation. Alkylations at ambient temperature with Huenig's base (DIPEA) in THF or DCM, as well as with Cs_2CO_3 in toluene at 45 °C were very sluggish.

Arylations of cinnoline could be performed on electron deficient heterocycles, such as 4-nitrofluorobenzene via nucleophilic aromatic substitution with the N1 of cinnoline acting as nucleophile. Some alkyl halides, such as 4-nitrobenzylbromide or phenacylbromide appear to give only the 1-alkyl or aryl isomer even before heating. In case of the alkylation with phenacylbromide (**11g**), the regioselectivity could not be altererd using AgOTf instead of Rb_2CO_3 as promotor. However, employing silver salts inhibits the oligomerization of phenacylbromide. O4-alkylation was not observed in any case. During heat treatment in polar solvents, used during the subsequent reductions, the N2-alkyl-cinnolines were found to convert into N1-alkyl-cinnolines **12** (Table 2).[25]

This rearrangement was assumed to progress intramolecularly or via a tight transition state, since it was found to be unaffected by even large excesses of nucleophiles, such as pyridine or HS^-, which could likely trap alkyl-cations or alkyl radicals.[26] In order to explain this rearrangement we performed, Hartree-Fock calculations on N1 and N2 methylated cinnoline-3-carboxamides: *N*,*N*,1-trimethyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (**III**) and 3-[(dimethylamino)carbonyl]-2-methyl-6-nitrocinnolin-2-ium-4-olate (**I**). The calculations indicated, that the absolute value of the LUMO of **III** was more or less uniformly localized across the bicyclic aromatic system, except for 1-Me-group, having a low LUMO-value and C5 having a high value. The value of HOMO of **III** displayed an equal distribution throughout the bicyclic molecule including the methyl group, which participates in the cinnoline π-system by hyperconjugation. Interestingly, C3 has a high HOMO-value. In turn, the LUMO of **I** displayed a large value on the methyl group. The HOMO of **I** has a low value on the methyl group, however and a large value on N1. The high value of the LUMO of the methyl-group of **I** indicates electron deficiency, which may facilitate heterolytic



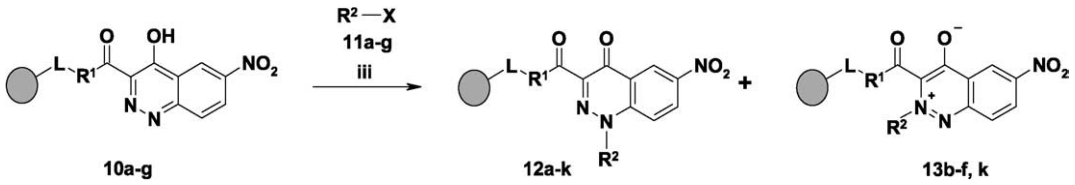
Scheme 4. The values of the HOMO and the LUMO of model molecules **I** and **III** as well as anion **II** (B) mapped onto the electron density of the molecule. The color ranges from red = value absolute value of orbital near 0 to blue = absolute value of orbital near 1. (A): For the anion **II** the localization of the negative charge is mapped onto the electron density. Also here color ranges from red = no density to blue = maximum density.

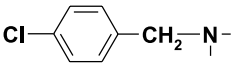
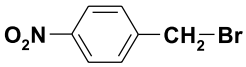
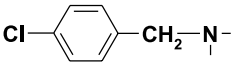
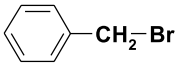
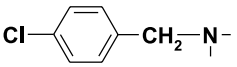
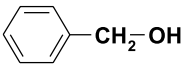
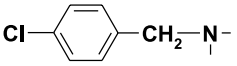
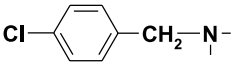
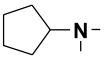
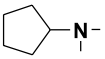
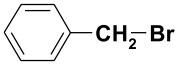
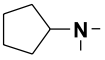
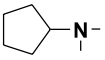
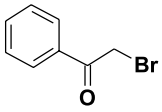
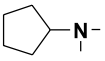
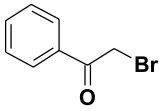
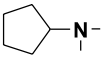
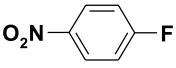
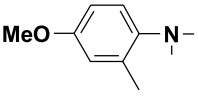
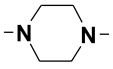
dissociation to a methyl cation and a cinnoline anion (**II**). In the latter, the largest negative charge on a 'non-oxygen'-atom is localized on N1, while the HOMO is mostly localized on N1 and N2. Therefore, it is likely that a charged electrophile, capable of forming a covalent bond, may attack N1 (Scheme 4).

Indeed, in reactions involving harder electrophiles such as phenacyl bromide (**11g**), 4-nitrobenzyl bromide (**11a**) and 4-nitrofluorobenzene (**11h**)[26,27] only the N1-alkylated or arylated compounds, respectively, **12h**, **12i** and **12a**, could be observed and isolated. A rearrangement involving homolytic dissociation of N3-phenacylated cinnoline may, however, not be ruled out. The free electron of the cinnolyl radical intermediate is mainly localized on C3, but also on O4 and N1. A recombination on N1 would be favored and would preserve aromaticity. During the course of our study, a selection of N-alkylated cinnolines were cleaved from the resin and analyzed, while others could be characterized on-bead by magic angle spinning NMR spectroscopy[15] (Table 2).

The reduction of the 6-nitro-group with $SnCl_2$[28] gave complex mixtures. In turn, the 6-nitro group of the cinnoline but also the nitro group of a nitrobenzylmoiety were cleanly reduced by Bu_4NSH[29] in pyridine/H_2O 9/1 (v/v) to give a 6-aminocinnoline. The reduction compounds **12** and **13** were performed in a polar solvent. Under the conditions of the reduction (pyridine/H_2O 9/1 (v/v), 80 °C, 48 h) the migration of N2-alkyl groups to N1 was also completed. The resulting amino group could be acylated with various

Table 2. Alkylation of support-bound cinnolines

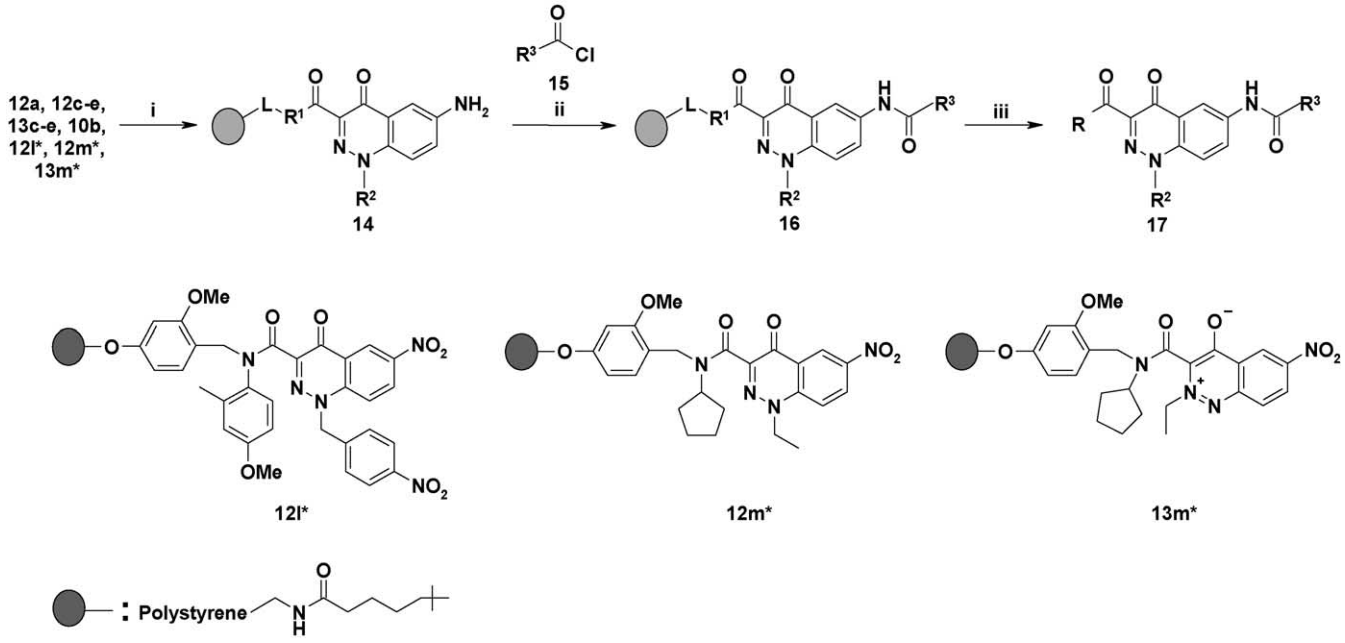


Entry	No	R^1	No		Product[a]	Conversion[b]	Purity[c]
1[d]	**10a**		**11a**		**12a**	71	71[e]
2[b]	**10a**		**11b**		**12b/13b**	>95	>95
3[f]	**10a**		**11c**		**12b/13b**	>95	>95
4[d]	**10e**		**11d**	Et–I	**12c/13c**	>95	84
5[d]	**10a**		**11e**	Me–I	**12d/13d**	>95	93
7[d]	**10c**		**11e**	Me–I	**12e/13e**	>95	>95
8[g]	**10g**		**11b**		**12f/13f**	92	92
9[d]	**10g**		**11f**	$H_2C{=}CH{-}CH_2{-}Br$	**12g**	90	90[i]
10[d,h]	**10g**		**11g**		**12h**	90	23
11[g]	**10g**		**11g**		**12h**	95	82
12[i]	**10g**		**11h**		**12i**	80	80[i]
13[d]	**10b**		**11e**	Me–I	**12j**	>95	72
14[d]	**10d**		**11e**	Me–I	**12k/13k**	70	70[i]

[a] In some reactions **12** and **13** are formed together.
[b] Based on LC-MS trace at 220 nm.
[c] Determined by LC-MS at 220 nm.
[d] Rb_2CO_3, DMF, 24 h, rt.
[e] rest is starting material.
[f] PPh_3, diisopropyl azadicarboxylate (DIPAC), THF.
[g] Collidine, AgOTf, DCM.
[h] Although there was high conversion of the cinnoline to 12 h, the product was impured by high molecular weight hydrophobic material being the result of base promoted polycondensation of **11g**.
[i] Rb_2CO_3, DMF/DMSO 1/1 (v/v), 4 days, 60 °C.

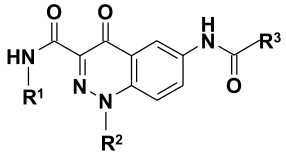
acid chlorides to afford the polymer-bound desired product. A random selection of the products were cleaved from the resin using TFA in DCM (Scheme 5).

Due to a side reaction caused by incomplete acylation of AMEBA-resins, during the alkylation or during the reduction, the desired cinnolines are sometimes contaminated by the products resulting from the reaction of polymer bound amines with acid chlorides **15**. Table 3 shows a random selection of some of the target compounds obtained

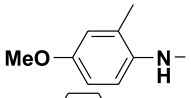
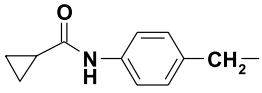
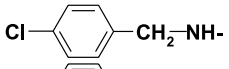
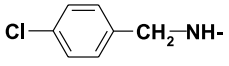
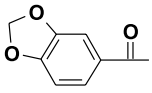
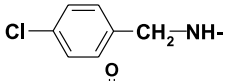
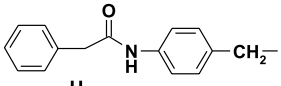
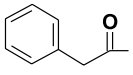
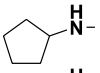
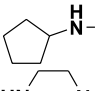
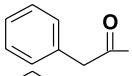
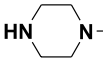
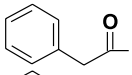
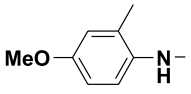
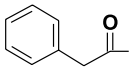


Scheme 5. (i): 1 M Bu_4NSH, pyridine/H_2O, 9:1 (v/v), 80 °C, 48 h; (ii): R_2COCl, DMF, NEt_3, rt; (a) TFA/DCM/Et_3SiH, 20:78:2 (v/v/v), 5×5 min; (b) add toluene to product solution prior to evaporation; compounds **12l***, **12m*** and **13m*** were not isolated. The synthesis was performed from the AMEBA resins without isolation of the intermediates.

Table 3. Tri-substituted cinnolines synthesized according to Scheme 5



17a-h

Entry	No	R^1–NH–	R^2	R^3	Yield[a]
1[b]	**17a**				60
2	**17b**		**Et–**		64
3	**17c**		**Me–**		45
4[c]	**17d**				
				40	
5	**17e**		**Me–**		88
7	**17f**		**Et–**		42
8	**17g**		**Me–**		65
9	**17h**		**H**		Nd.

[a] Isolated yield based on the initial amine loading.
[b] Product obtained from the 4-nitrobenzyl precursor **12l*** after reduction and exhaustive acylation.
[c] Product obtained from the 4-nitrobenzyl precursor **12a** after reduction and exhaustive acylation.

after cleavage from the resin. We performed preparative HPLC-purification, with all the compounds in Table 3, which is a general routine prior to submission to our biological assays.

1. Conclusion

We have shown a feasible route to derivatize cinnolines on solid phase. The current approach makes use of a readily accessible starting material. The key step of the solid phase derivatization is the equilibration of the alkyl N1 and the N2 alkylated cinnolines, which lies on the side of the N1-alkylated species. This approach, complements the method described by Braese et al.,[6] as it allows for the introduction of diversity elements in different positions of the cinnoline ring system. It can be used to provide a large number of diverse cinnoline derivatives, which are attractive for their activity in many medicinal indication areas.

2. Experimental

2.1. General

All solvents and reagents were purchased from Sigma-Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233, USA and Dr. Theodor Schuchardt & Company, Edward-Buchner Strasse 14-20, D-85662 Hohenbrunn, Germany.

Some reaction on solid supports were performed in a glass 'frit reactor' closed by a rubber septum, connected to an Ar-balloon. The bottom contains a P3-glass frit, leading to a narrow outlet, which can either be sealed by a small septum or rubber stopper, or fastened tightly onto a PTFE valve to perform.

Parallel synthesis including washings and cleavage were performed using a Mettler Bhodan Miniblock: Mettler-Toledo Bohdan Inc., 562 Bunker Court, Vernon Hills, IL 60610 USA.

For the reactions performed on beads, quantitative loading of the resin bound starting material was assumed. Large excesses of reagents were generally applied to assure pseudo first order kinetics.

2.2. MO-calculations

MO-calculations were performed using the 'Titan' molecular modeling program by Wavefunctions, Inc. 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA and Schroedinger, Inc. 1500 SW First Avenue, Suite 1180, Portland, OR 97201, USA.

The Hartree-Fock[19] calculations were performed on semi-empirical AM1 equilibrium geometry using 3-21G split valence basis set.[30]

2.2.1. 3-[(Dimethylamino)carbonyl]-2-methyl-6-nitrocinnolin-2-ium-4-olate (I).

Multiplicity: Singulet
Charge: Neutral
Energy (HOMO): −8.554 eV
Energy (LUMO): 0.098 eV
Dipole: 7.445 debye

2.2.2. II.

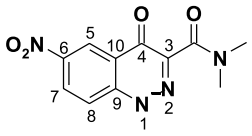
Multiplicity: Singulet
Charge: Anion
Energy (HOMO): −4.288 eV
Energy (LUMO): 4.230 eV
Dipole: 5.088 debye

Natural atomic populations and charges (Table 4).

2.2.3. *N*,*N*,1-Trimethyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (III).

Multiplicity: Singulet
Charge: Neutral
Energy (HOMO): −9.369 eV
Energy (LUMO): 0.792 eV
Dipole: 7.379 debye

Table 4. Natural atomic population and charges of intermediate II



Atom	Occupancy	Charge
C3	6.144071	−0.144071
C4	5.481241	0.518759
C10	6.235211	−0.235211
C9	5.772752	0.227248
C5	6.109730	−0.109730
H8	0.744287	0.255713
C6	6.004672	−0.004672
H5	0.707848	0.292152
C7	6.214790	−0.214790
H7	0.732420	0.267580
C8	6.269757	−0.269757
C11	5.193528	0.806472
O4(amide)	8.663858	−0.663858
N4(amide)	7.608281	−0.608281
C12(amide)	6.432754	−0.432754
H10(Me)	0.802522	0.197478
H11(Me)	0.768920	0.231080
H12(Me)	0.763315	0.236685
C13(amide)	6.424863	−0.424863
H3(Me)	0.801902	0.198098
H9(Me)	0.744813	0.255187
H15(Me)	0.802233	0.197767
N3(Nitro)	6.457914	0.542086
O2(Nitro)	8.445937	−0.445937
O3(Nitro)	8.432248	−0.432248
O1	8.710572	−0.710572
N2	**7.136560**	**−0.136560**
N1	**7.393001**	**−0.393001**
Total charge = −1		

2.3. Confocal microscopy

For the confocal laser scanning microscopy a Radiance 2000 Biorad mounted on a Zeiss optic was used. For the excitation a Krypton Ex 488-568 laser was used while for the emission the following set of filters were used.

D488/10, HQ 500LP-HQ 515/30, E 580LP HQ600/40, E600LP, 660LP.

About 5 mg of resin were suspended in NMI (*N*-methylimidazole) and allowed to stand for 2 h. In that time the resins were swollen. $CHCl_3$, which is a solvent allowing swelling of many polystyrene based resins were found to be too volatile to be useful. The resulting suspension was transferred on a microscopy plate and viewed. The filters were adjusted to afford a good contrast and accommodate the different intensity and wavelength of fluorescence of the support substrate.

2.4. Cleavages of compounds from resin

The cleavages were performed on 5–50 mg of resin. The resins, often prewashed as described in the corresponding reactions, were then washed with DCM (3×2 mL). The cleavage was performed with TFA/triethyl silane/DCM 20/2/78 (v/v/v), 5× (1 mL, 5 min). The product solutions are combined and toluene (2 mL) was added prior to the evaporation in a vacuum centrifuge. The dried down samples are resuspended in toluene (5 mL) and redried to remove residual triethyl silane. The crude products may be dissolved in DMSO or MeCN/H_2O 4/1 (v/v) and subjected to HPLC.

2.5. HPLC

HPLC/MS was performed on a Waters XTerra RP18 (4.6× 50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid/acetonitrile 95:5), and mobile phase B was H_2O/acetonitrile (5:95). Gradient from 10 to 90% B in 8 min, hold 90% B 2 min. UV detection at 220 and 254 nm. Flow rate 1 mL/min. Injection volume 10 μL. Full scan, mass range from 100 to 800 amu. Capillary voltage was 2.5 KV; Source temperature was 120 °C; Cone was 10 V. Retention Times are given in minutes at 220 or 254 nm. All final products **17a–h** have been purified by preparative HPLC on a Waters Xterra RP18 (19×100 mm, 5 μm) column using a Waters preparative HPLC 2525 equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, electrospray ionization, positive mode. Mobile phase A was water 0.1% formic acid, and Mobile phase B was acetonitrile. Gradient from 10 to 90% B in 8 min, hold 90% B 2 min. Flow rate 20 mL/min.

2.5.1. Mesoxaloyl dichloride phenylhydrazone[8b] (5). To mesoxalic acid phenylhydrazone (**3**) (3.53 g, 17.1 mmol) suspended in dry chloroform (21 mL) was added a solution of thionyl chloride (4 mL) in chloroform. The reaction mixture was heated to reflux for 5 h to a afford a red solution. The solution was evaporated to dryness under reduced pressure to yielded a brown brittle solid. An aliquot of this solid (2 mg) was dissolved in dry $CDCl_3$ to obtain NMR-spectra.

δ_H (300 MHz, $CDCl_3$) 7.33–7.39 (1H, m, Ph), 7.47–7.58 (4H, m, Ph), δ_C (75.5 MHz, $CDCl_3$) 118.9, 121.6, 124.4, 125.2, 140.2, 161.5, 161.8.

An aliquot of the reaction mixture was treated with methanol to afford dimethyl (phenylhydrazono)malonate (**18**) and was then subjected to LC/MS. The derivative **18** of the desired product was 97% of the products detectable by HPLC-MS: C-18-column 10–90% MeCN in 1% aq. TFA, 4.97 min; ESI-MS: (MH^+) 237, ($M-H^-$) 235.

2.5.2. 4(1*H*)-Oxocinnoline 3-carboxylic acid (6) by a one-pot-procedure. The reaction was performed in a five-nacked, flask with an overhead stirrer and, optionally, a reflux condenser or distillation bridge. To 2-(phenylhydrazono)malonate (**4**) (20 g, 96 mmol) suspended in 1,2 dichlorobenzene (100 mL) was added a solution of $SOCl_2$ (20 mL, 0.24 7 mol) in 1,2 dichlorobenzene (60 mL) within 15 min. The reaction mixture (dark red solution, with little precipitate) was heated to 70 °C for 5 h. The excess $SOCl_2$ was distilled off under ambient pressure. 50 mL of the 1,2 dichlorobenzene was removed under reduced pressure. (bp: 50 °C). To the stirred, concentrated solution was added a solution of $TiCl_4$ (20 mL) in 1,2-dichlorobenzene (40 mL) within 1 h. The reaction suspension was stirred at 90 °C for 14 h. Subsequently, the $TiCl_4$ and then the 1,2 dichlorobenzene were evaporated in vacuo.

The resulting brown solid was extracted several times with small portions of hot aq. NaOH (4 M, 90 °C, total volume: 200 mL). The resulting suspension was passed through 'Dicalite' or 'Hyflow' The product precipitated into conc. HCl (37%, 1.5 L) while being agitated. 4-Hydroxycinnoline-3-carboxylic acid[8a,b] was filtered off and dried in vacuo over P_4O_{10}/KOH. Yield: 11.7 g (66%). **6**: δ_H (300 MHz DMSO-D_6) 7.68, (1H, m), 7.86 (1H, d, $J=8.6$ Hz, C8*H* cinnoline), 7.99 (1H, m), 8.23 (1H, dd, $J=8.1$, 1.4 Hz, C7*H* cinnoline); δ_C (75.5 MHz, DMSO-D_6) 118.84, 124.67, 124.83, 128.71, 135.95, 141.80, 163.94, 171.83; ESI-MS: (MH^+) 191, ($M-H^-$) 189.

2.6. Caution!

If the isolated product contains more than approximately 30% of 2-(phenylhydrazono)malonate it is not suitable for the nitration. The hydrazone forms picric acid under the nitration conditions. Minor impurities of picric acid do not co-precipitate within the work-up of the nitration product in the next step. In most cases, however, the precipitated

product from the previous stage has a purity of about 95% (HPLC at 220 nm).

2.6.1. 6-Nitro-4(1*H*)-oxocinnoline 3-carboxylic acid (7). The nitration of the cinnoline was performed according to Barber et al.[8b] 4(1*H*)-oxy-cinnoline-3-yl-carboxylic acid (**6**) 10 g, 52.59 mmol) was added in portions at 0 °C to H_2SO_4 (96%, 40 mL). Then HNO_3 (90%, 20 mL) was added. The reaction mixture was refluxed (85 °C) for 50 min. The reaction mixture may foam during the first 15 min. Then evolution of NO_2 is observed. The progress of the reaction was monitored by HPLC/MS. When the starting material was converted completely, the reaction mixture (orange) was cooled down to 22 °C and poured on crashed ice (500 mL). The product precipitates as a yellow solid. After it has been verified that the precipitate does not contain picric acid, the product was dried in vacuo over P_4O_{10}. The yield of 4-hydroxy-6-nitrocinnoline-3-carboxylic acid: (8.31 g, 67.2%).

Compound **7**: δ_H (300 MHz DMSO-D_6) 7.89 (1H, d, J= 9.2 Hz, C8*H* cinnoline), 8.58 (1H, dd, J=9.2, 2.4 Hz, C7*H* cinnoline), 8.81 (1H, d, J=2.4 Hz, C5*H* cinnoline); δ_C (75.5 MHz, DMSO-D_6) 120.32, 121.20, 123.85, 129.11, 140.78, 144.19, 144.06, 163.91, 168.88; ESI-MS: (MH^+) 236, ($M-H^-$) 234.

2.6.2. 6-Nitro-4(1*H*)-oxy-cinnoline-3-yl-methanoyl chloride (8). To compound **7** (2.07 g, 8.8 mmol) was added $POCl_3$ (4.09 mL, 43.8 mmol), then PCl_5 (3.67 g, 17.6 mmol). The reaction mixture was stirred at 95 °C for 2 h. The insoluble product was removed by filtration and washed with dry diethyl ether. Yield: 2.14 g (96%).

It could be analyzed after formation of a piperidide derivative: to **8** (20 mg) dissolved in DCM (2 mL) was added piperidine (100 μL) the reaction solution was extracted 10% aq. formic acid. The aq. layer was neutralized with 2 N NaOH and extracted again with 5 mL DCM. The combined DCM-phases were dried over Na_2SO_4 and the evaporated to dryness in vacuo.

δ_H (300 MHz $CDCl_3$) 1.71–1.93 (m), 3.40–3.64 (m), 8.15 (1H, d, J=9 Hz, C8*H* cinnoline), 8.40 (1H, dd, J=9, 3 Hz, C7*H* cinnoline), 9.19 (1H, d, J=3 Hz, C5*H* cinnoline); δ_C (75.5 MHz, $CDCl_3$) δ 23.97, 26.10, 31.22, 52.96, 121.63, 125.10, 129.46, 138.28, 145.08, 152.65, 167.30, 168.40; ESI-MS: (MH^+) 303.

2.7. Attachment of cinnoline to the polymeric support

We determined the loading of the resins by on-bead HMS-NMR and by NMR and after cleavage of an aliquot of product.

2.8. Loading of resin determined by cleavage

To 20 mg of resin were put into a 5 mL polypropylene tube, equipped with a PTFE-frit and placed onto a Visiprep Vacuum Manifold™ (Supelco, Supelco Park, Bellafonte, PA 16823-0048, USA). A solution of TFA/DCM 1/4 (v/v) (1 mL) was added and allowed to stand for 1 h at rt. The resin was filtered and washed three times with the TFA-solution. All filtrates were combined and evaporated to dryness. The resulting residues were weighed and analyzed. The yields in Table 1 were based on the theoretical loading indicated by the manufacturer of the starting resin.

The theoretical loadings of the used resins. Piperazine-Tr-resin (Novabiochem): 1 mmol/g. 4(4-Formyl)-2-methoxy-phenoxy)butyryl-resin (Novabiochem): 0.86 mmol/g. Indole-resin: 1.13 mmol/g.

2.9. For example: synthesis of 10a by the 'acid chloride method'

6-Nitro-4-oxo-1,4-dihydrocinnoline-3-carbonyl chloride **8** (593 mg, 2.52 mmol), dissolved in 2 mL dry DMF was added to a AMEBA-resin bearing 4-chlorobenzylamine **9a** (500 mg, 0.42 mmol) in DCM (8 mL). Subsequently dry collidine (2 mL) was added and the suspension shaken for 16 h. The resin was washed with eight alternating washes of DMSO/DCM 1/1 (v/v); DMF/2,4,6-collidine/H_2O 8/1/1 (v/v/v) or DMF/aq. ammonia 4/1 (v/v) (3 mL each) then with three alternating washes of MeOH and DCM (3 mL each).

On-bead IR: 1611 cm^{-1} (C=O), 1340 cm^{-1} (N=O).

On-bead NMR reveals a coupling yield of 15–20%, TFA-cleavage: 20–30% of **10a**. ESI-MS: (MH^+) 359, ($M-H^-$) 357.

Magic angle spinning 500 MHz on-bead NMR of partially acylated AMEBA-resin bearing a mixture of **9b** and **10b** (Fig. 2).

2.10. Example for the synthesis of 10a by CDI-activation of 7

To 6-nitro-4(1*H*)-oxy-cinnoline-3-yl-carboxylic acid **7** (593 mg, 2.52 mmol) dissolved in 2 mL dry DMF was added sym. collidine (1.5 mL) and CDI (409 mg, 252 mmol). This solution was added to a suspension of AMEBA-resin bearing 4-chlorobenzylamine **9a** (100 mg, 0.084 mmol) preswollen for 30 min in dry DMF (4 mL). The suspension was shaken for 24 h at 25 °C. The resin was washed with The resin was washed with eight alternating washes of DMSO/DCM 1/1 (v/v); DMF/2,4,6-collidine/H_2O 8/1/1 (v/v/v) or DMF/aq. ammonia 4/1 (v/v) (3 mL each) then with three alternating washes of MeOH and DCM (3 mL each).

On-bead IR: 1600 cm^{-1} (C=O), 1335 cm^{-1} (N=O).

On-bead NMR revealed a coupling yield of 45–50%,

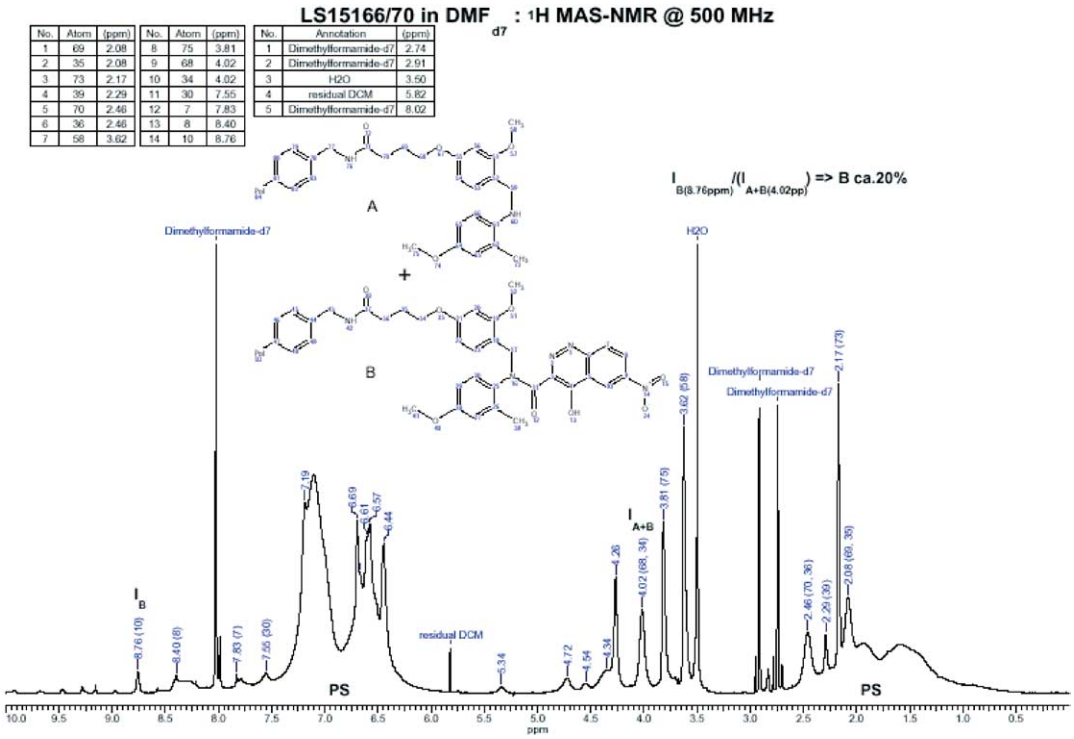


Figure 2. On-bead NMR of crude **9b** and **10b** synthesized by the acid-chloride method.

TFA-cleavage: 50–60% of **10a**. The product was poorly soluble in MeOH, DMF, DMSO, H_2O, MeCN and DCM, thus on-bead NMR provides a good method to obtain an NMR-spectrum (Fig. 3).

On-bead magic angle spinning NMR: δ_H (500 MHz, $CDCl_3$) 2.08 (2H, CH_2 spacer), 2.47 (2H, CH_2 spacer), 3.95–4.1 (2H, CH_2OAr, spacer); 4.4–4.75 (CH_2 linker and 4-chlorobenzyl), 7.93 (1H, C8*H* cinnoline), 8.26 (1H), H1 (cinnoline), 8.53 (1H, C7*H* cinnoline), 8.90 (1, H, C5*H* cinnoline). The loading can be estimated by comparing the integration of the signals of the spacer at 2.47 and 3.95–41 ppm with the integration of the cinnoline peaks. The product is identical to the one obtained after cleavage of **10e**.

2.11. Acylation of the polymer-bound amine using the pentafluorophenol ester of 7

To 6-nitro-4(1*H*)-oxy-cinnoline-3-yl-carboxylic acid **7** (235 mg, 1 mmol) pentafluorophenol (430 mg, 2.33 mmol), DMAP (2 mg, 0.016 mmol) and 6 mL of DCM was added 1,3-diisopropylcarbodiimide (DIC) (0.5 mL, 403 mg, 3.19 mmol). After 30 min all of the

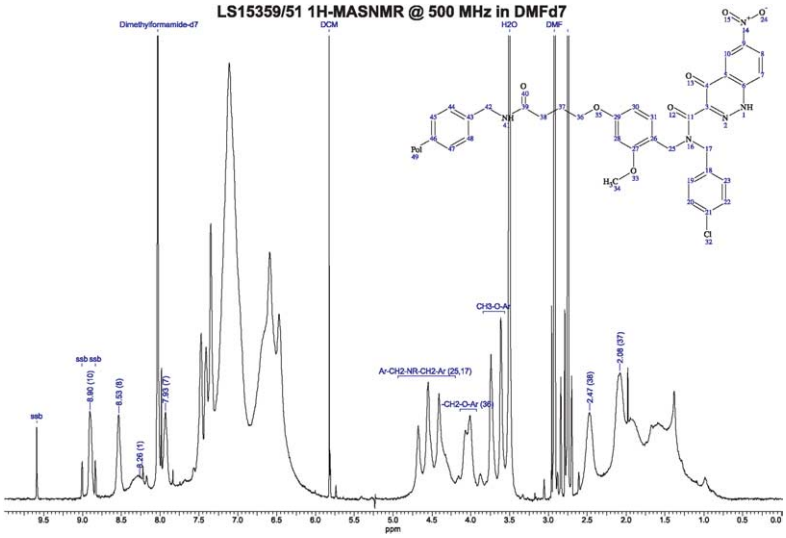


Figure 3. On-bead NMR of crude **10a** synthesized by CDI-activation of **7**.

cinnoline was converted in the pentafluorophenyl ester yielding a clear, brown solution. To this solution was added 1 mL of symmetrical collidine. The solution was then brought to 10 mL with DCM. 2.5 mL of this solution was then added to 50 mg of polystyrene resin bearing amines with a loading of 0.8–1.1 mmol/g. The reaction time and the workup of the resin was performed as described under the CDI coupling procedure. On bead NMR reveales acylation of the resin as indicated in Table 1.

2.11.1. *N*-(4-Methoxy-2-methylphenyl)-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (from 10b, 10f). δ_H (300 MHz, DMSO-D_6) 2.34 (3H, s, C2*Me* 4-methoxy 2-methylanilide), 3.73 (3H, s, O*Me* 4-methoxy 2-methylanilide), 6.78 (1H, dd, $J=9$, 3 Hz, C5*H* 4-methoxy 2-methylanilide), 6.86 (1H, d, $J=3$ Hz, C3*H* 4-methoxy 2-methylanilide); 7.93–7.98 (2H, m, C8*H* cinnoline, C6*H* 4-methoxy 2-methylanilide), 8.60 (1H, dd, $J=10$, 1 Hz, C7*H* cinnoline), 8.9 (1H, d, $J=1$ Hz, 1H, C5*H* cinnoline), 11.25 (1H, s, N*H* amide); ESI-MS: (MH^+) 355, ($M-H^-$) 353.

2.11.2. 4-Oxo-3-(piperazin-1-ylcarbonyl)-1,4-dihydrocinnolin. TFA (from 10d). δ_H (300 MHz, DMSO-D_6) 3.07 (2H, m, *piperazine*), 3.20 (2H, m, *piperazine*), 3.56 (2H, m, *piperazine*), 3.84 (2H, m, *piperazine*), 7.75 (1H, d, $J=9$ Hz, C8*H* cinnoline), 8.57 (1H, dd, $J=9$, 3 Hz, C7*H* cinnoline), 8.77 (1H, d, $J=3$ Hz, C5*H* cinnoline), 9.02 (2H, broad s, N*H*); ESI-MS: (MH^+) 304, ($M-H^-$) 302.

2.11.3. *N*-(4-Chlorobenzyl)-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (from 10e). This spectrum was recorded in a supersaturated solution in DMSO. The following amide is poorly soluble in all common solvents and gives tailing peaks in RP-HPLC.

δ_H (300 MHz, DMSO-D_6) 4.54 (2H, d, $J=6$ Hz, *p*-C_6H_4Cl–CH_2), 7.40 (4H, m, *p*-Cl–C_6H_4–CH_2), 7.78 (2H, d, $J=9$ Hz, C8*H* cinnoline), 8.58 (1H, dd, $J=9$, 2 Hz, C7*H* cinnoline), 8.85 (1H, d, $J=2$ Hz, C5*H* cinnoline), 9.62 (1H, t, $J=6$ Hz, *p*-Cl–C_6H_4–CH_2–N*H*CO); ESI-MS (MH^+) 359, ($M-H^-$) 357.

2.11.4. *N*-Cyclopentyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (from 10g). δ_H (300 MHz, DMSO-D_6) 1.38–1.75 (6H, m, *cis*C2*H*, *cis*C5*H*, C3H_2, C4H_2, cyclopentyl), 1.79–2.07 (2H, m, *trans*C2*H*, *trans*C5*H*, cyclopentyl), 4.05–4.41 (1H, m, C1*H*, cyclopentyl), 7.89 (1H, d, $J=9$ Hz, C8*H* cinnoline), 8.40–8.67 (1H, dd, C7*H* cinnoline, $J=9$, 2 Hz), 8.84 (1H, d, $J=2$ Hz, C5*H* cinnoline), 9.20 (1H, d, $J=9$ Hz, N*H*); ESI-MS: (MH^+) 302, ($M-H^-$) 301.

2.12. General procedure for alkylation of polymer-bound cinnolines using Rb_2CO_3

Rb_2CO_3 (82 mg, 355 μmol) was dissolved in anhydrous DMF (3 mL), and the resulting solution was added to resin **10a–10d** (71 μmol). After 15 min of swelling the alkyl halide (for example benzyl bromide 41 μL, 355 μmol) was added and the resin suspension was shaken for 24 h. The resin was washed with five alternating washes of water and DMF (3 mL each) then with five alternating washes of MeOH and DCM (3 mL each).

2.12.1. *N*-(4-Chlorobenzyl)-6-nitro-1-(4-nitrobenzyl)-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12a). The spectrum was recorded 24 h after onset of the reaction: δ_H (300 MHz, $CDCl_3$) 4.65 (2H, d, *p*-Cl–$C_6H_4CH_2$), 5.88 (2H, s, *p*-NO_2–$C_6H_4CH_2$); 7.28 (4H, m, *p*-Cl–C_6H_4), 7.40 (2H, d, $J=8$ Hz, C2*H*, C6*H* 4-nitrobenzyl), 7.49 (1H, d, $J=9$ Hz, C8*H* cinnoline), 8.22 (2H, d, $J=8$ Hz, C3*H*, C5*H* 4-nitrobenzyl), 8.45 (1H, dd, $J=2$, 9 Hz, C7H cinnoline), 9.19 (1H, d, $J=2$ Hz, C5*H* cinnoline); 9.98 (1H, t, CON*H*CH_2) HPLC/MS: C-18-column 10–90% MeCN in 1% aq. TFA, 6.63 min; ESI-MS: (MH^+) 494.

2.12.2. Mixture of *N*-(4-chlorobenzyl)-1-ethyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12c) and 3-{[(4-chlorobenzyl)amino]carbonyl}-2-ethyl-6-nitrocinnolin-2-ium-4-olate (13c). The spectrum was recorded 20 h after onset of the reaction: Two isomers were found, the major amounting to 73% and the minor to 27% of the mixture. δ_H (300 MHz, $CDCl_3$) 1.62 (3H, t, $J=7$ Hz, CH_3CH_2-N major isomer), 1.72 (3H, t, $J=7$ Hz, CH_3CH_2-N minor isomer), 4.64–4.77 (2H, m, *p*-Cl–$C_6H_4CH_2$ both isomers), 4.72 (2H, q, $J=7$ Hz, CH_3CH_2-N major isomer), 5.31 (2H, q, $J=7$ Hz, CH_3CH_2-N minor isomer), 7.3–7.36 (4H, m, *p*-Cl–$C_6H_4CH_2$ both isomers) 7.77 (1H, d, $J=10$ Hz, C8*H* cinnoline, major isomer) 8.04 (1H, d, $J=9$ Hz, C8*H* cinnoline, minor isomer), 8.52 (1H, dd, $J=2$, 9 Hz, C7*H* cinnoline, minor isomer), 8.62 (1H, dd, $J=3$, 10 Hz, C7*H* cinnoline major isomer), 9.20 (1H, d, $J=2$ Hz, C5*H* cinnoline, minor isomer), 9.27 (1H, d, $J=3$ Hz, C5*H* cinnoline, major isomer) HPLC-MS: C-18-column 10–90% MeCN in 1% aq. TFA, 8 min; 5. 87 min major isomer (70%) ESI-MS: (MH^+) 387.20; 6.02 min minor isomer (30%) ESI-MS: (MH^+) 387. The composition of the mixture does not change upon standing at rt in $CDCl_3$ for three days.

2.12.3. Mixture of *N*-(4-chlorobenzyl)-1-methyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12d) and 3-{[(4-chlorobenzyl)amino]carbonyl}-2-methyl-6-nitrocinnolin-2-ium-4-olate (13d). The spectrum was recorded 53 h after onset of the reaction: two isomers were found the major amounting to 68% and the minor to 32% of the mixture. δ_H (300 MHz, $CDCl_3$) 4.31 (3H, s, *Me*, both isomers), 4.62 (2H, d, $J=5.7$ Hz, *p*-Cl–$C_6H_4CH_2$, minor isomer) 4.63 (2H, d, $J=5.7$ Hz, *p*-Cl–$C_6H_4CH_2$, major isomer), 7.26–7.29 (4H, m, *p*-Cl–$C_6H_4CH_2$, both isomers), 7.68 (1H, d, $J=9.3$ Hz, C8*H* cinnoline), 8.56 (1H, dd, $J=2.6$, 9.2 Hz, C7*H* cinnoline, both isomers), 9.15 (1H, d, $J=2.6$ Hz, C5*H* cinnoline, minor isomer), 9.20 (1H, d, $J=2.6$ Hz, C5*H* cinnoline, major isomer), 9.74 (1H, t, CON*H*, minor isomer), 9.94 (1H, t, CON*H*, major isomer), HPLC: C-18-column 10–90% MeCN in 1% aq. TFA, 5.33 min major isomer (68%); ESI-MS: (MH^+) 373; 5.6 min minor isomer (32%); ESI-MS: (MH^+) 373.

2.12.4. Mixture of *N*-cyclopentyl-1-methyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12e) and 3-[(cyclopentylamino)carbonyl]-2-methyl-6-nitrocinnolin-2-ium-4-olate (13e). The spectrum was recorded 24 h after

onset of the reaction: two isomers were found the major amounting to 68% and the minor to 32% of the mixture. δ_H (300 MHz, $CDCl_3$) 1.59–1.78 (4H, m, C3H_2, C4H_2 cyclopentyl, both isomers), 1.79–1.86 (2H, m, *cis*C2*H*, *cis*C5*H* cyclopentyl, both isomers), 2.01–2.15 (2H, m, *trans*C2*H*, *trans*C5*H* cyclopentyl, both isomers), 4.32 (3H, s, *Me*, major isomer), 4.40 (1H, m, C1*H* cyclopentyl, minor isomer), 4.49 (1H, m, C1*H*, cyclopentyl, major isomer), 4.87 (3H, s, *Me*, minor isomer), 7.76 (1H, d, $J=9.2$ Hz, C8*H* cinnoline, major isomer), 8.02 (1H, d, $J=9.2$ Hz, C8*H* cinnoline, minor isomer), 8.51 (1H, dd, $J=2.6$, 9.2 Hz, C7*H* cinnoline, minor isomers), 8.65 (1H, dd, $J=2.6$, 9.2 Hz, C7*H* cinnoline, major isomers), 9.21 (1H, d, $J=2.6$ Hz, C5*H* cinnoline, minor isomer), 9.27 (1H, d, $J=2.6$ Hz, C5*H* cinnoline, major isomer), 10.00 (1H, d, CON*H* minor isomer), 10.15 (1H, d, CON*H* minor isomer). HPLC: C-18-column 10–90% MeCN in 1% aq. TFA, 8 min; 4.17 min minor isomer; ESI-MS: (MH^+) 317, ($M-H^-$) 315; 4.45 min major isomer; ESI-MS: (MH^+) 317.

2.12.5. 1-Allyl-*N*-(cyclopentyl)-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12g). The spectrum was recorded 48 h after the onset of the reaction: δ_H (300 MHz, $CDCl_3$) 1.61–1.72 (4H, m, C3H_2, C4H_2 cyclopentyl), 1.75–1.82 (2H, m, *cis*C2*H*, *cis*C5*H* cyclopentyl), 2–2.13 (2H, m, *trans*C2*H*, *trans*C5*H* cyclopentyl), 4.5 (1H, m, C1*H* cyclopentyl), 5.27, 5.32 (3H, m, $H_2C{=}CHCH_2$, (*E*)*H*HC=CHCH$_2$), 5.42 (1H, d, $J=$ 10.6 Hz, (*Z*)*H*HC=CHCH$_2$), 6.0–6.11 (1H, m, $J=5.3$, 10.6, 17.2 Hz, $H_2C{=}CHCH_2$), 7.74 (1H, d, $J=9.6$ Hz, C8 *H* cinnnoline, major isomer), 8.59 (1H, dd, $J=2.7$, 9.6 Hz, C7*H* cinnoline), 9.27 (1H, d, $J=2.6$ Hz, C5*H* cinnoline), 9.92 (1H, d, N*H* minor isomer) HPLC/MS: C-18-column 10–90% MeCN in 1% aq. TFA: 5.23 min; ESI-MS: (MH^+) 343.

2.12.6. *N*-Cyclopentyl-6-nitro-4-oxo-1-(2-oxo-2-phenylethyl)-1,4-dihydrocinnoline-3-carboxamide (12h). The spectrum was recorded 48 h after theonset of the reaction: δ_H (300 MHz, $CDCl_3$) 1.63–1.84 (6H, m, C3H_2, C4H_2, *cis*C2*H*, *cis*C5*H* cyclopentyl), 2.05–2.15 (2H, m, *trans*C2*H*, *trans*C5*H* cyclopentyl), 4.44 (1H, m, C1*H* cyclopentyl), 6.13 (2H, s, CH_2COPh), 7.39 (1H, d, $J=9.3$ Hz, C8*H* cinnnoline), 7.58 (2H, t, $J=7.9$ Hz, C3*H*, C5*H* phenyl), 7.73 (1H, t, $J=7.9$ Hz, C4*H*, phenyl), 8.02 (2H, d, $J=7.9$ Hz, C2*H*, C6*H* phenyl), 8.52 (1H, dd, $J=2.7$, 9.3 Hz, C7*H* cinnoline), 9. 29 (1H, d, $J=2.6$ Hz, C5*H*, cinnoline); HPLC/MS: C-18-column 10–90% MeCN in 1% aq. TFA, 6.03 min; ESI-MS: (MH^+) 421.

2.12.7. *N*-Cyclopentyl-6-nitro-1-(4-nitrophenyl)-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12i). Rb_2CO_3 (82 mg, 355 μmol) was suspended in anhydrous DMF/DMSO 1/1 (v/v) (3 mL), and the resulting solution was added to resin **10c** (71 μmol). After 15 min of swelling 4-nitro-fluorobenzene (77 mg, 3.55 μmol) was added and the resin suspension was shaken for 60 h at 60 °C. The resin was washed with five alternating washes of water and DMF (3 mL each) then with five alternating washes of MeOH and DCM (3 mL each).

δ_H (300 MHz, DMSO-D_6) 1.4–1.75 (6H, m, C3H_2, C4H_2, *cis*C2*H*, *cis*C5*H* cyclopentyl), 1.9–2 (2H, m, *trans*C2*H*, *trans*C5*H* cyclopentyl), 4.24 (1H, m, C1*H* cyclopentyl), 7.54 (1H, d, $J=9.6$ Hz, C8*H* cinnnoline), 8.0 (2H, d, $J=$ 9.2 Hz, C2*H*, C6*H* 4-nitrophenyl), 8.47 (1H, dd, $J=2.7$, 9.6 Hz, C7*H*, cinnoline), 8.57 (2H, d, $J=9.2$ Hz, C3*H*, C5*H*, 4-nitrophenyl), 8.91 (1H, d, $J=2.6$ Hz, C5*H* cinnoline), 9.05 (1H, d, N*H*); HPLC/MS: C-18-column 10–90% MeCN in 1% aq. TFA 10 min, 5.97 min; ESI-MS: (MH^+) 424.

2.12.8. *N*-(4-Methoxy-2-methylphenyl)-1-methyl-4-oxo-6-nitro-1,4-dihydrocinnoline-3-carboxamide (12j). δ_H (300 MHz, DMSO-D_6) 2.34 (3H, s, C2*Me* 4-methoxy 2-methylanilide), 3.73 (3H, s, *Me*O 4-methoxy 2-methylanilide), 6.78 (1H, dd, $J=9$, 3 Hz, C5*H* 4-methoxy 2-methylanilide), 6.86 (1H, d, $J=3$ Hz, C3*H* 4-methoxy 2-methylanilide), 7.93–7.98 (2H, m, C8*H* cinnoline, C6*H* 4-methoxy 2-methylanilide), 8.60 (1H, dd, $J=10$, 1 Hz C7*H* cinnoline), 8.9 (1H, d, $J=1$ Hz, C5*H* cinnoline), 11.25 (1H, s, CON*H*); ESI-MS: (MH^+) 355, ($M-H^-$) 353.

2.12.9. 1-Methyl-6-nitro-3-(piperazin-1-ylcarbonyl)cinnolin-4(1*H*)-one (12k) and 2-methyl-6-nitro-3-(piperazin-1-ylcarbonyl)cinnolin-2-ium-4-olate (13k). δ_H (300 MHz, DMSO-D_6) 3.20 (2H, m, *piperazine*, both isomers), 3.23 (2H, m, *piperazine*, both isomers), 3.56–3.60 (2H, m, *piperazine*, both isomers), 3.83–3.86 (2H, m, *piperazine*, both isomers), 4.16 (3H, s, *Me* major isomer); 4.33 (3H, s, *Me*, minor isomer), 8.06 (1H, d, $J=9.6$ Hz, C5H, cinnoline, major isomer), 8.07 (1H, d, $J=9.7$ Hz, C5*H* cinnoline, minor isomer), 8.48 (1H, dd, $J=2.7$, 9.7 Hz, C7*H*, cinnoline, minor isomer), 8.61 (dd, $J=2.6$, 9.7 Hz, C7*H*, cinnoline, major isomer), 8.8 (1H, 2d, $J=2.6$ Hz, C8H cinnoline, both isomers); 9.14 (s, N*H*) HPLC-MS: C-18-column 0–60% MeCN in 1% aq. TFA, min; 2.5 min both isomers; ESI-MS: ($M-H^-$) 316.

2.13. Example for alkylation of polymer-bound cinnolines using Mitsunobu conditions

Triphenyl phosphine (119 mg, 454 μmol) was dissolved in

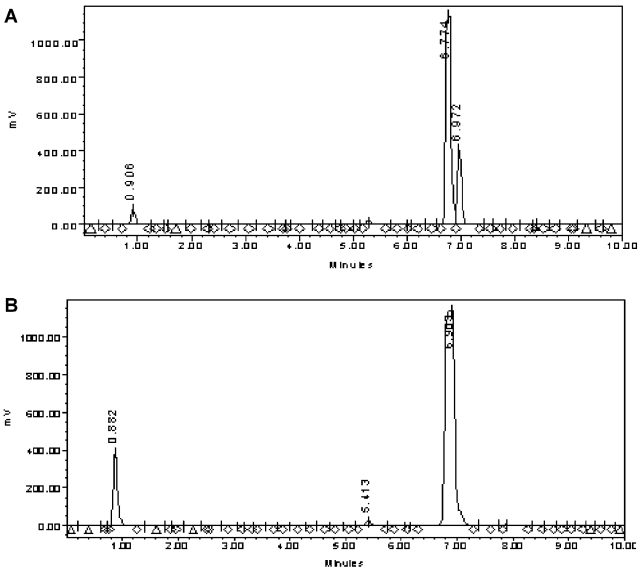


Figure 4. (A) Rearrangement of the resin bearing **12b** and **13b** after 16 h; (B) after 27 h at rt (almost all **13b** is consumed, Figure 5)

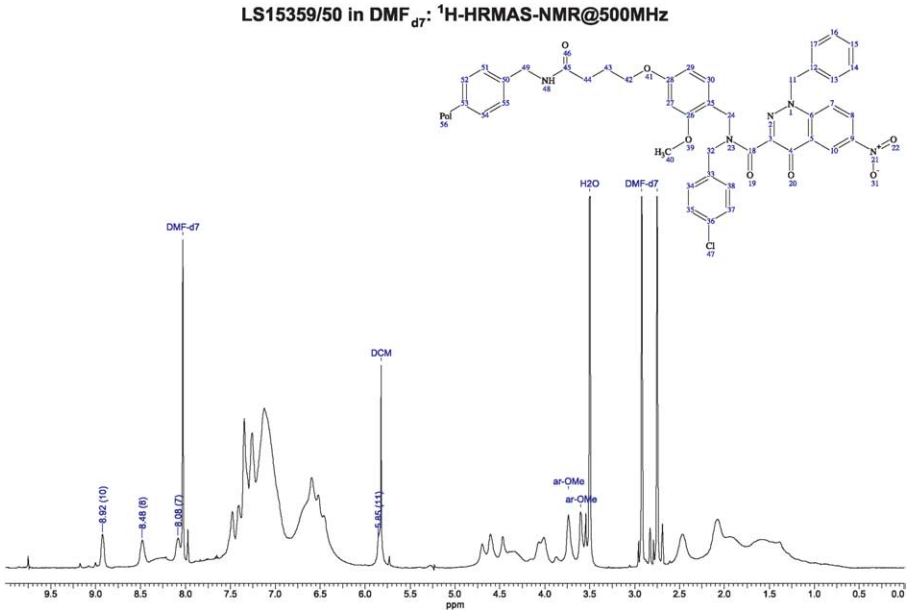


Figure 5. On-bead NMR of crude 1-benzyl-*N*-(4-chloro-benzyl)-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxomide (**12b**).

dry THF (1 mL). At 0 °C diisopropylazo dicarboxylate (DIPADC) and (92 mg, 454 μmol) and benzylic alcohol (74 μL, 454 μmoL) was added and the resulting solution added to resin **10a** (80 mg, 56 μmol) preswollen in 0.5 mL of THF. The resin suspension was shaken for 24 h. The resin was washed with five alternating washes of water and DMF (3 mL each) then with five alternating washes of MeOH and DCM (3 mL each). The product mixture was found to be and behave like the mixture of the alkylations with alkyl halides (Figs. 4 and 5).

2.13.1. 1-Benzyl-*N*-(4-chlorobenzyl)-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12b). On-bead magic angle spinning NMR: δ_H (500 MHz DMF-D_7) 5.85 (2H, PhCH_2), 8.08 (1H, C8*H* cinnoline), 8.48 (1H, C7*H* cinnoline), 8.92 (1H, C5*H* cinnoline). On-bead magic angle spinning ROESY NMR indicated the position of the benyzl group is bound to N1 of the cinnoline.

NMR-spectrum after TFA-cleavage: δ_H (300 MHz, DMSO-D_6) 4.58 (2H, d, J=6.2 Hz, *p*-Cl$C_6H_4CH_2$), 5.85 (2H, s, CH_2Ph), 7.24–7.38 (9H, m, *p*-Cl$C_6H_4CH_2$, CH_2Ph), 7.69 (1H, d, J=9.6 Hz, C8*H* cinnoline), 8.48 (1H, dd, J=2.6, 9.2 Hz, C7*H* cinnoline), 9.23 (1H, d, J=2.6 Hz, C5*H*, cinnoline), 9.94 (NH). HPLC-MS analysis of an aliquot cleaved from the resin revealed two peaks. ESI-MS: (MH^+) 449, ($M-H^-$) 447.09. After 27 h in H_2O/MeCN 1/4 (v/v) only one peak was detectable by HPLC-MS. The compounds were identical to the ones obtained using the Rb_2CO_3 and the AgOTf-procedure.

2.13.2. Mixture of 1-benzyl-*N*-cyclopentyl-6-nitro-4-oxo-1,4-dihydrocinnoline-3-carboxamide (12f) and 2-benzyl-3-[(cyclopentylamino)carbonyl]-6-nitrocinnolin-2-ium-4-olate (13f) using AgOTf. AgOTf (103 mg, 0.4 mol) was dissolved in anhydrous DCM/2,4,6-collidine 1/1 (v/v) (3 mL), and the resulting solution was added to resin **10c** (71 μmol). After 15 min of swelling benzyl bromide 41 μL, 355 μmol) was added and the resin suspension was shaken for 24 h in the dark. A precipitation of AgBr began 15 min after the addition of benzyl bromide. After 24 h the reaction mixture was consumed by gel-like AgBr precipitation. The resin was washed pyridine (5×3 mL each) to dissolve the AgBr. The resin was washed with five alternating washes of water and DMF (3 mL each) then with five alternating washes of MeOH and DCM (3 mL each).

The spectrum was recorded 24 h after onset of the reaction: Two isomers were found the major amounting to 68% and the minor to 32% of the mixture. δ_H (300 MHz $CDCl_3$) 1.5–1.7 (6H, m, *cis*C2*H*, *cis*C5*H*, C3H_2, C4H_2, cyclopentyl, both isomers), 1.8–2.0 (2H, m, *trans*C2*H*, *trans*C5*H* (cyclopentyl, both isomers), 4.32 (1H, m, C1*H* cyclopentyl, minor isomer), 4.45 (1H, m, C1*H* cyclopentyl, major isomer), 5.36 (2H, s, PhCH_2, major isomer), 6.50 (2H, s, PhCH_2, minor isomer), 7.18–7.29 (4H, m, C2*H*, C3*H*, C5*H*, C6*H* Ph, both isomers), 7.37 (1H, m, C4*H* Ph, both isomers), 7.63 (1H, d, J=9.2 Hz, C8*H* cinnnoline, major isomer), 8.01 (1H, d, J=9.2 Hz, C8*H*, cinnoline, minor isomer), 8.41 (1H, dd, J=2.6, 9.2 Hz, C7*H* cinnoline, major isomers), 8.44 (1H, dd, J=2.6, 9.2 Hz, C7*H* cinnoline, minor isomer), 9.12 (1H, d, J=2.6 Hz, C5*H* cinnoline, minor isomer), 9.18 (1H, d, J=2.6 Hz, C5*H* cinnoline, major isomer), 9.9 (1H, d, N*H* minor isomer), 9.93 (1H, d, N*H* (minor isomer). HPLC-MS: C-18-column 10–90% MeCN in 1% aq. TFA, 6.05 major isomer; ESI-MS: (MH^+) 393; minor 6.37 min minor isomer; ESI-MS: (MH^+) 393.

The composition of the mixture changed slowly towards the major isomer upon standing in DMSO at rt.

2.14. Reduction of nitrated cinnolines

To resin bearing alkylated or non-alkylated nitrocinnoline

(400 mg), suspended in pyridine/water 9/1 (v/v) (8 mL), was added Bu_4NHS (1.11 g, 4.02 mmol) the reaction mixture was shaken for 16 h at 80 °C. The resin was washed with five alternating washes of water and DMF (3 mL each) then with five alternating washes of MeOH and DCM (3 mL each). An aliquot of the resin was subjected to cleavage with TFA.

2.14.1. 6-Amino-3-{[(4-chlorobenzyl)amino]carbonyl}-4-hydroxy-1-methylcinnolin-1-ium trifluoroacetate (14a). δ_H (600 MHz DMSO-D_6) 4.20 (3H, s, N1*Me* cinnoline), 4.55–4.54 (2H, d, $J=3$ Hz, *p*-$ClC_6H_4CH_2$), 6.12 (2H, broad s, NH_2), 7.23 (2H, m, C5*H*, C7*H* cinnoline), 7.36 (2H, m, C2*H*, C6*H* 4-chlorobenzyl), 7.38–7.40 (2H, m, C3*H*, C5*H* 4-chlorobenzyl), 7.76–7.75 (1H, d, C8*H* cinnoline), 10.43 (1H, t, $J=3$ Hz, CON*H*), On-bead IR: 1335 cm^{-1} (N═O), 1350 cm^{-1} (N═O); ESI-MS: (MH^+) 357.

2.15. Acylation of the aniline bound to the polymeric support

To resin bearing aminocinnolin (120 mg) suspended in DCM (2 mL) was added DIPEA (71 μL, 330 μmol), DMAP (2 mg) and cyclopropylcarbonylchloride (30 μL, 330 μmol) the reaction mixture was shaken for 16 h.

The resin was washed with five alternating washes of water and DMF (3 mL each) then with five alternating washes of MeOH and DCM (3 mL each).

2.15.1. 6-[(Cyclopropylcarbonyl)amino]-1-({4-[(cyclopropylcarbonyl)amino]cyclohexa-2,4-dien-1-yl}methyl)-*N*-(4-methoxy-2-methylphenyl)-4-oxo-1,4-dihydrocinnoline-3-carboxamide (17a). δ_H (500 MHz DMSO-D_6) 0.75 (4H, m, CH_2 cyclopropyl), 0.81 (4H, d, $J=6.1$ Hz, CH_2 cyclopropyl), 1.73, 1.8 (2H, 2m, C1*H*, cyclopropyl), 2.38 (3H, s, C2*Me* 4-methoxy 2-methylanilide), 3.74 (3H, s, O*Me* 4-methoxy 2-methylanilide), 4.85 (2H, s, ArCH_2N1 cinnoline), 6.81 (1H, dd, $J=8.8$, 2.9 Hz, C5*H* 4-methoxy 2-methylanilide), 6.88 (1H, d, $J=2.9$ Hz, C3*H* 4-methoxy 2-methylanilide), 7.26 (1H, d, $J=8.5$ Hz, C3*H*, C5*H* (4-cyclopropanecarboxamido*phenyl*methyl), 7.54 (2H, d, $J=8.5$ Hz, C2*H*, C6*H* (4-cyclopropanecarboxamido*phenyl*-methyl), 7.96 (1H, dd, C7*H* cinnoline), 7.99 (1H, d, C8*H* cinnoline), 8.12 (1H, d, $J=8.8$ Hz, C6*H* 4-methoxy 2-methylanilide), 8.72 (1H, d, $J=2$ Hz, C5*H* cinnoline), 10.21, 10.72, 11.89 (3H, 3 broad s, CON*H*). HRMS (FABS): MH^+ 566.2379, $C_{32}H_{31}N_5O_5$ requires 566.2398.

2.15.2. *N*-(4-Chlorobenzyl)-6-[(cyclopropylcarbonyl)amino]-1-ethyl-4-oxo-1,4-dihydrocinnoline-3-carboxamide (17b). δ_H (600 MHz DMSO-D_6) 0.84 (4H, dd, $J=7.6$, 3.4 Hz, CH_2 cyclopropyl); 1.43 (3H, t, $J=7.2$ Hz, CH_2Me), 1.81 (1H, m, C*H*CO cyclopropylcarbonyl), 4.55 (2H, d, $J=6.1$ Hz, *p*-$ClC_6H_4CH_2$), 4.63 (2H, q, $J=7.2$ Hz, CH_2Me), 7.39 (4H, m, *p*-$ClC_6H_4CH_2$), 8.05 (1H, d, $J=9.3$ Hz, C8*H* cinnoline); 8.11 (1H, dd, $J=9.3$, 2.4 Hz, C7*H* cinnoline), 8.55 (1H, d, $J=2.4$ Hz, C5*H* cinnoline), 10.1 (1H, t, $J=6.0$ Hz, *p*-$ClC_6H_4CH_2NHCO$), 10.72 (1H, broad s, CON*H* cyclopapanecarboxamide); HRMS (FABS): MH^+, found 425.1387 $C_{22}H_{21}ClN_4O_3$ requires 425.1375.

2.15.3. 6-[(1,3-Benzodioxol-5-ylcarbonyl)amino]-*N*-(4-chlorobenzyl)-1-methyl-4-oxo-1,4-dihydrocinnoline-3-carboxamide (17c). δ_H (600 MHz DMSO-D_6) 4.26 (3H, s, *Me*), 4.56 (2H, d, *p*-$ClC_6H_4CH_2$) 5.86 (2H, d, OCH_2O), 7.08 (1H, d, $J=8.3$ Hz, C7*H*, 1,3-benzodioxol-5-yl), 7.39 (4H, m, *p*-$ClC_6H_4CH_2$), 7.56 (1H, d, $J=1.5$ Hz, C4*H* 1,3-benzodioxol-5-yl), 7.63 (1H, dd, $J=8.3$, 1.5 Hz, C6*H* 1,3-benzodioxol-5-yl), 8.01 (1H, d, $J=9.3$ Hz, C8*H* cinnoline), 8.33 (1H, dd, $J=9.4$, 2.3 Hz, C7*H* cinnoline), 8.75 (d, $J=2.4$ Hz, C5*H* cinnoline), 10.12 (1H, t, $J=6.0$ Hz, *p*-$ClC_6H_4CH_2NHCO$), 10.54 (1H, broad s, CON*H* 6-[(1,3-benzodioxol-5-ylcarbonyl)amino]); HRMS (FABS): MH^+, found 491.1102. $C_{25}H_{19}ClN_4O_5$ requires 491.1117.

2.15.4. *N*-(4-Chlorobenzyl)-4-oxo-6-[(phenylacetyl)amino]-1-{4-[(phenylacetyl)amino]benzyl}-1,4-dihydrocinnoline-3-carboxamide (17d). δ_H (600 MHz DMSO-D_6) 3.59–3.68 (4H, m, PhCH_2CO), 4.56 (2H, d, *p*-$ClC_6H_4CH_2$), 5.78 (2H, m, ArCH_2N1 cinnoline), 7.23 (2H, d, $J=8.5$ Hz, C2*H*, C6*H* 4-[(phenylacetyl)amino]*phenyl*methyl), 7.27–7.34 (12H, m, *Ph*CH_2CO), 7.54 (2H, d, $J=8.5$ Hz, C3*H*, C5*H* 4-[(phenylacetyl)amino]*phenyl*methyl); 7.9 (1H, d, $J=9.5$ Hz, C8*H* cinnoline), 7.98 (1H, dd, $J=9.5$, 2.4 Hz, C7*H* cinnoline), 8.57 (1H, d, $J=2.4$ Hz, C5*H* cinnoline), 10.03 (1H, t, $J=6.0$ Hz, *p*-$ClC_6H_4CH_2NHCO$), 10.19 (1H, broad s, CON*H* 4-[(phenylacetyl) *amino*]phenylmethyl), 10.67 (1H, CON*H*C6 cinnoline); HRMS (FABS): MH^+ found 670.2208. $C_{39}H_{32}ClN_5O_4$ requires 670.2216.

2.15.5. *N*-Cyclopentyl-6-[(cyclopropylcarbonyl)amino]-1-methyl-4-oxo-1,4-dihydrocinnoline-3-carboxamide (17e). δ_H (600 MHz DMSO-D_6) 0.78–4.23 (17H, m, H*C*, CH_2 cyclopropyl, cyclopentyl, N1*Me* cinnoline), 7.95 (1H, d, $J=9.3$ Hz, C8*H* cinnoline), 8.09 (1H, dd, $J=9.3$, 2.4 Hz, C7*H* cinnoline), 8.55 (1H, d, $J=2.4$ Hz, C5*H* cinnoline), 9.76 (1H, d, $J=7.1$ Hz, CON*H*C_5H_9), 10.7 CON*H*C_3H_5); HRMS (FABS): MH^+, found 355.1773. $C_{19}H_{22}N_4O_3$ requires 355.1765.

2.15.6. *N*-Cyclopentyl-1-ethyl-4-oxo-6-[(phenylacetyl)amino]-1,4-dihydrocinnoline-3-carboxamide (17f). δ_H (600 MHz DMSO-D_6) 1.42 (3H, t, $J=7.2$ Hz, *Me*CH_2), 1.44–1.98 (8H, m, CH_2 cyclopentyl), 3.71 (2H, m, PhCOCH_2), 4.23 (1H, m, C1*H* cyclopentyl), 4.62 (2H, q, $J=7.2$ Hz, MeCH_2), 7.22–738 (5H, m, *Ph*), 8.04 (1H, dd, $J=9.3$ Hz, C8*H* cinnoline), 8.08 (dd, $J=9.3$, 2.2 Hz, C7*H* cinnoline), 8.58 (1H, d, $J=2.4$ Hz, C5*H* cinnoline), 9.75 (1H, d, $J=7.1$ Hz, CO*H*NC_5H_9); 10.69 (1H, s, CON*H*); HRMS (FABS): MH^+, found 419.2082. $C_{24}H_{26}N_4O_3$ requires 419.2078.

2.15.7. *N*-[1-Methyl-4-oxo-3-(piperazin-1-ylcarbonyl)-1,4-dihydrocinnolin-6-yl]-2-phenylacetamide (17g). δ_H (500 MHz DMSO-D_6) 2.6, 2.72 (4H, 2m, C3H_2, C5H_2 piperazine), 3.15, 3.52 (4H, 2m, C2H_2, C6H_2 piperazine), 3.69 (2H, m, PhCOCH_2), 4.08 (3H, s, N1*Me* cinnoline), 7.22–7.27 (1H, m, C4*H* Ph), 7.30–7.37 (4H, m, C2*H*, C3*H*, C5*H*, C6*H* Ph); 7.82 (2H, d, $J=9.3$ Hz, C8*H* cinnoline), 8.06 (1H, dd, $J=9.3$, 2.5 Hz, C7*H* cinnoline), 8.45 (d, $J=2.4$ Hz, C5*H* cinnoline), 10.68 (1H, s, CON*H* phenylacetamide); HRMS (FABS): MH^+, found 406.1885. $C_{22}H_{23}N_5O_3$ requires 406.1874.

2.15.8. *N*-(4-Methoxy-2-methylphenyl)-4-oxo-6-[(phenylacetyl)amino]-1,4-dihydrocinnoline-3-carboxamide (17h). δ_H (500 MHz DMSO-D_6) 2.53 (3H, s, C2*Me* 4-methoxy 2-methylanilide), 3.69 (2H, s PhCOCH_2), 3.73 (3H, s, *Me*O 4-methoxy 2-methylanilide), 6.76 (1H, dd, J= 8.9, 2.7 Hz, C5*H* 4-methoxy 2-methylanilide), 6.82 (1H, d, J=2.7 Hz, C3*H* (4-methoxy 2-methylanilide), 7.25 (1H, t, J=7.1 Hz, C4*H* Ph); 7.35 (4H, m, C2*H*, C3*H*, C5*H*, C6*H* Ph), 7.87 (2H, m, C8*H* cinnoline, C6*H* 4-methoxy 2-methylanilide), 8.24 (1H, s, CON*H* 4-methoxy 2-methylanilide), 8.25 (1H, d, 9.73 Hz, C7*H* cinnoline), 8.56 (1H, s, C5*H* cinnoline), 10.44 (1H, s, CON*H* phenacetylamide), 12.93 (1H, s, N*H* cinnoline); HRMS (FABS): MH^+, found 443.1723. $C_{25}H_{22}N_4O_4$ requires 443.1714.

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