ELSEVIER

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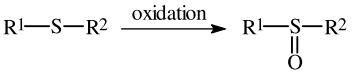
Contents

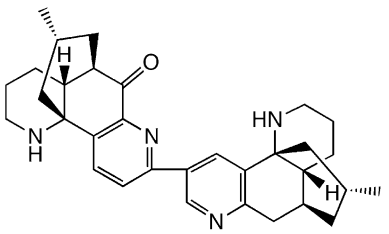
REPORT



The oxidation of sulfides to sulfoxides by halogen-mediated oxidation has been reviewed. The report contains 180 references, 28 tables and 34 schemes.

ARTICLES

A new dimer of $C_{16}N_2$ type alkaloid, complanadine B (**1**), and two new $C_{16}N$ type alkaloids, obscurumines A (**2**) and B (**3**), have been isolated from the club moss *Lycopodium complanatum* and *L. obscurum*, respectively. Complanadine A (**4**) isolated together with **1** induced secretion of neurotrophic factors from human astrocytoma cells.



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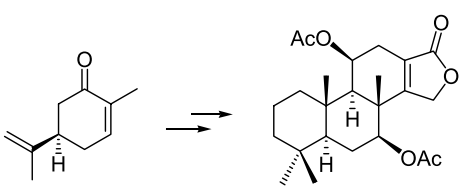
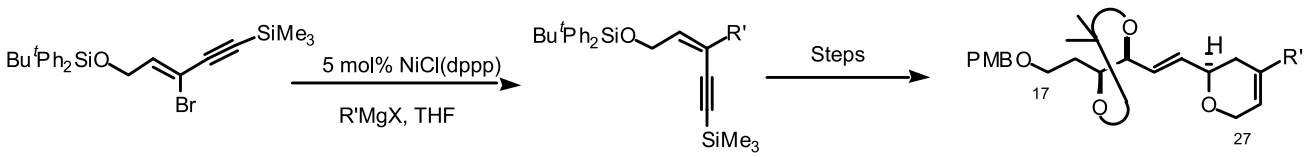
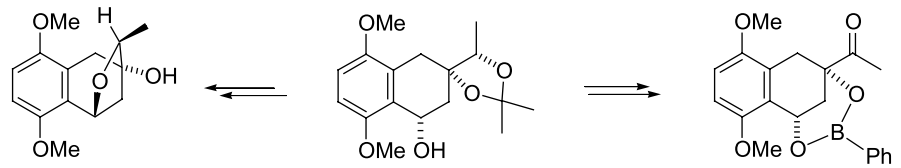
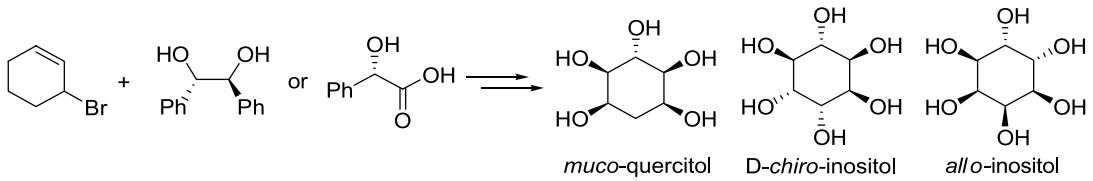


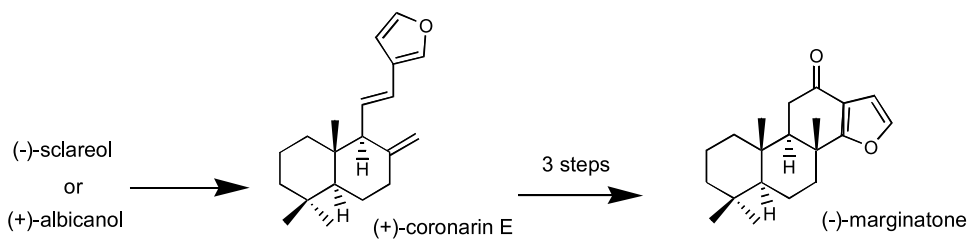
(*R*)-Carvone (+)-Dorisenone C

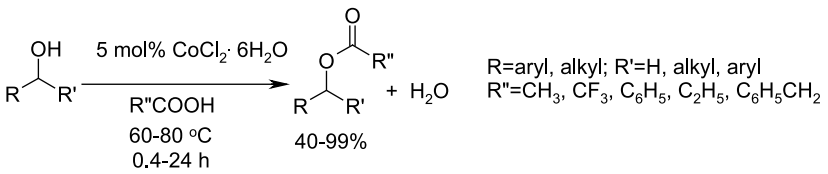
A diastereoselective synthesis of the oxygenated spongiane diterpene (+)-dorisenone C from carvone is described.

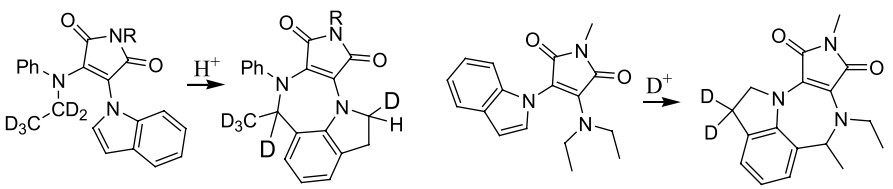


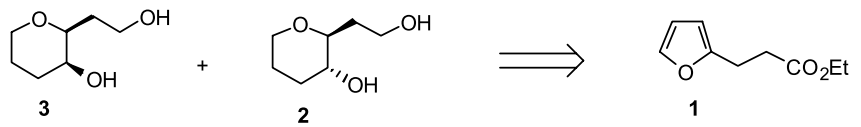


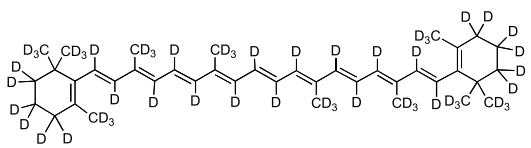


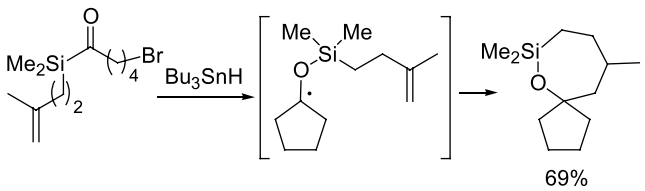


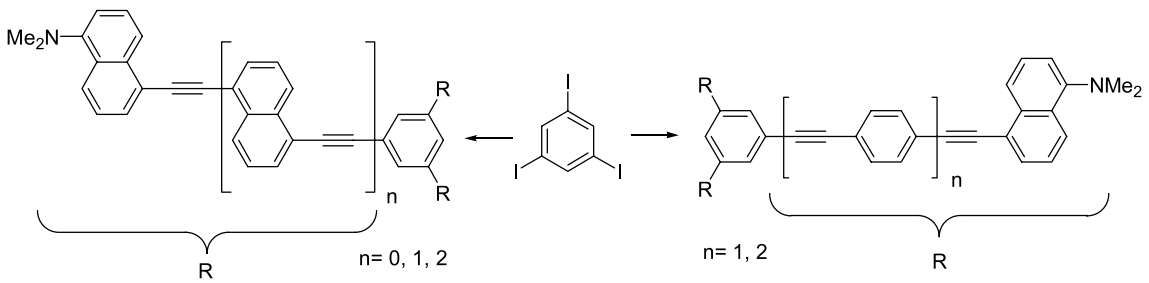


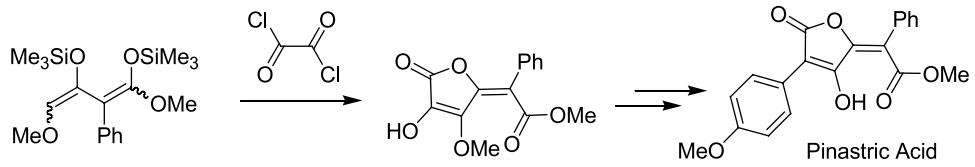


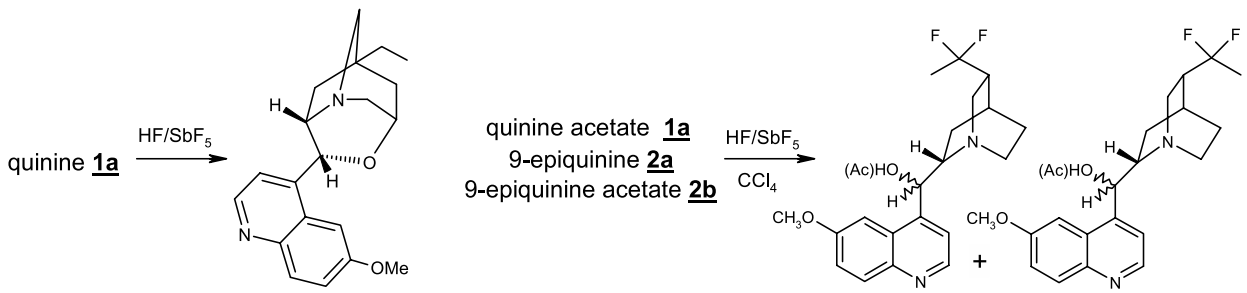


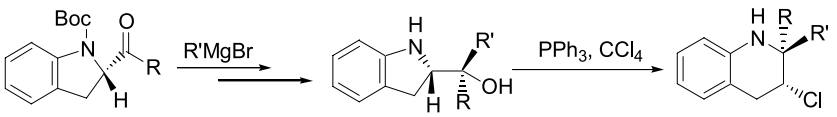


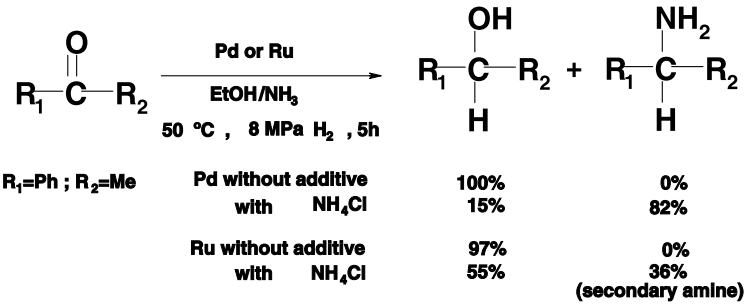


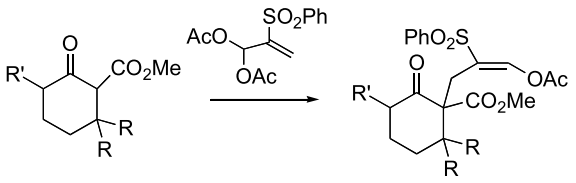


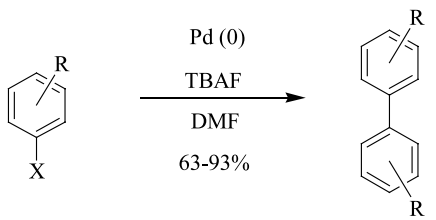


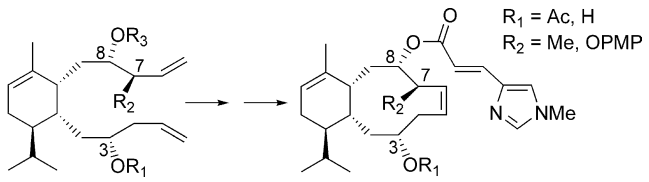


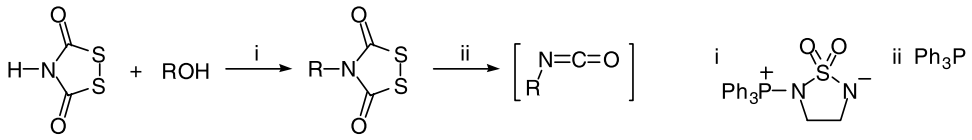




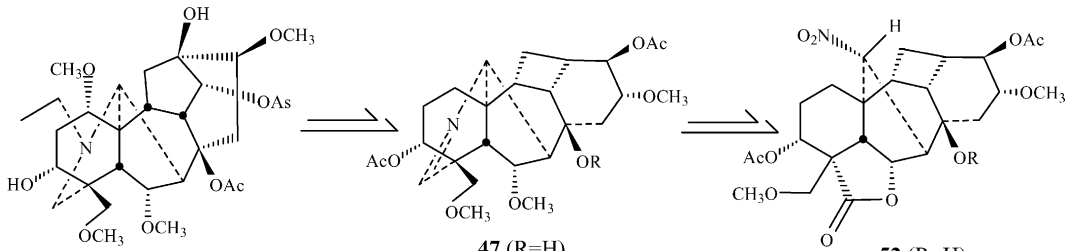








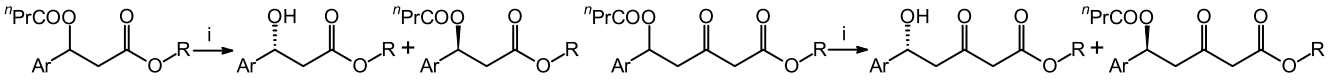
1,2,4-Dithiazolidine-3,5-dione can be used as a protected form of an isocyanate in modified Mitsunobu reactions of a wide range of alcohols.



3 yunaconitine

47 (R=H)
50 (R=Ac)

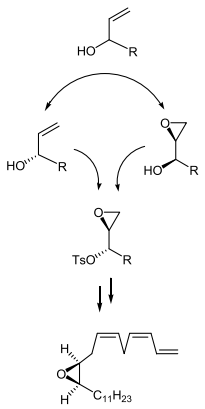
52 (R=H)
53 (R=Ac)

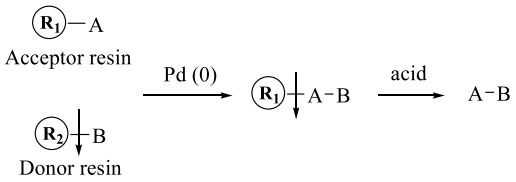


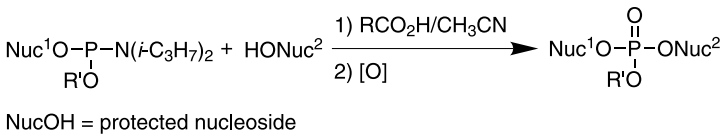
R=Me, Et, *i*-Pr, Bu; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..
(i) *CRL*/P_2O-H_2O; 30 °C; 24h

R=Me, Et; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..
(i) *CRL*/P_2O-H_2O; 30 °C; 24h

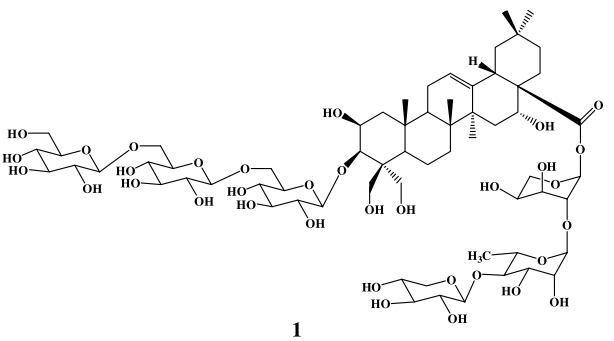
A simple and convenient method was reported for the preparation of optically active β-hydroxy-β-arylpropionates, δ-hydroxy-δ-aryl-β-oxo-pentanoates and their butyryl derivatives via CRL-catalyzed hydrolysis. The optically active products are potential precursors of some chiral pharmaceuticals and natural products.







Bioassay-directed fractionation of the antiviral active fraction of the roots of *Platycodon grandiflorum* leads to the isolation of three new triterpenoid saponins, platycosides G1–G3 (**1**–**3**), as well as two known saponins, platycodin D3 (**4**), and platycoside E (**5**). The structures of the new compounds were elucidated on the basis of their spectral data and chemical evidences. The isolated saponins were tested for their antiviral activities.



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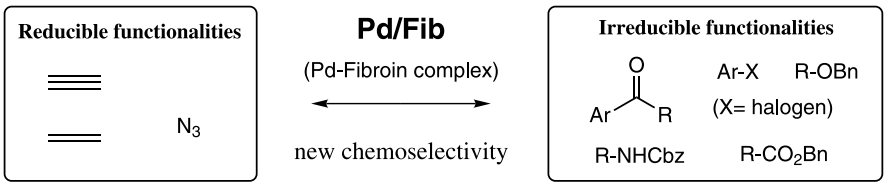

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Oxidation of sulfides to sulfoxides. Part 1: Oxidation using halogen derivatives

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Dedicated to Professor Józef Drabowicz

Contents

1. Introduction

The oxidation of sulfides to sulfoxides is of significant importance in organic chemistry, both for fundamental research and for a wide range of applications. The synthesis of sulfoxides was reported for the first time by Märcker in 1865 and, since then, a number of methods have been developed for the conversion of sulfides into sulfoxides. Although comprehensive reviews on the oxidation of sulfides to sulfoxides have been published in the past,[1–8]

Keywords: Oxidation; Sulfides; Sulfoxides.
Abbreviations: BIO, benziodazole oxide; bromamine-B, sodium salt of *N*-bromobenzenesulfonamide; BTMA–Br_3, benzyltrimethylammonium tribromide; (*tert*-butylperoxy)-iodane, 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one; $C_6H_5I(OTs)OH$, (*p*-toluenesulfonyloxy)hydroxyiodobenzene; CAN, ceric ammonium nitrate; chloramine-B, sodium salt of *N*-chlorobenzenesulfonamide; CTAB, cetyltrimethylammonium bromide; CTMATB, cetyltrimethylammonium tribromide; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBTA, (+)-dibenzoyl-D-tartaric acid; HBDS, hexabutyldistannoxane; HFIP, hexafluoro-2-propanol; HMTAB, hexamethylenetetramine–Br_2 complex; MCPBA, *m*-chloroperoxybenzoic acid; NBA, *N*-bromoacetamide; NBB, *N*-bromobenzamide; NBS, *N*-bromosuccinimide; NCA, *N*-chloroacetamide; NCS, *N*-chlorosuccinimide; PDAIS, poly(diacetoxyiodo)styrene; PIDA, phenyliodine(III) diacetate; PTAB, phenyltrimethylammonium tribromide; TBAPI, tetrabutylammonium periodate; TEAB, tetraethylammonium bromide; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl; TS, transition state; $VO(acac)_2$, vanadyl acetylacetonate.
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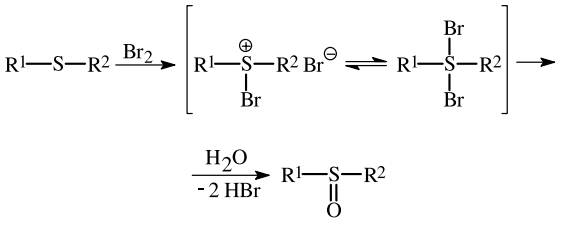
a vast number of procedures have been accumulated since that time, in particular during the last 20 years.[9–17]

There are several reagents available for this key transformation. Unfortunately, most of these reagents are not satisfactory. They are either harmful or expensive, and a simple procedure is not easily available, because of the over-oxidation of sulfoxides to sulfones. Despite the careful control of the reaction temperature, reaction time and the relative amounts of oxidants, it is difficult to avoid completely such over-oxidation.[18–20] As the sulfoxides are important for C–C bond formation and functional group transformations, the search for newer methods for the selective oxidation of sulfides to sulfoxides has continued.

In this review, we have considered the methods of halogen-mediated oxidation of sulfides to sulfoxides, but complementary data concerning other oxidizing agents have also been incorporated in a few cases, where they seemed useful. Despite this, the halogens and their derivatives have been considered as environmentally unfriendly, although their advantages are low price, easy handling, commercial availability, and relatively high stability. The mechanism of the halogen oxidation of sulfides to sulfoxides is still being developed, especially of those oxidants, which are impregnated on inorganic supports, which work efficiently under solvent-free conditions, and which are effective in asymmetric oxidations.

2. Oxidation of sulfides with molecular halogens

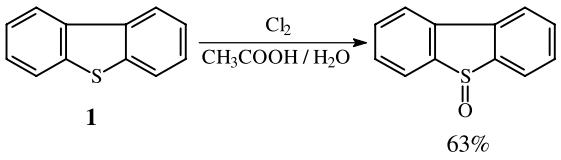
Molecular halogens form halosulfonium salts with organic sulfides that subsequently hydrolyze to sulfoxides, as shown in Scheme 1.[5,7,21–23]



Scheme 1.

Aqueous solutions of halogens have been used for the oxidation of sulfides since 1907.[24] This method has been widely explored and studied. It was recognized very early on that undesirable sidereactions very often predominate over the sulfoxide formation. In the case of oxidation of aryl sulfides with molecular chlorine, chlorination of the aromatic ring was also observed. Chlorine in an acetic acid–water mixture, however, oxidizes the sulfide **1** to the corresponding sulfoxide in acceptable yields (Scheme 2).[4]

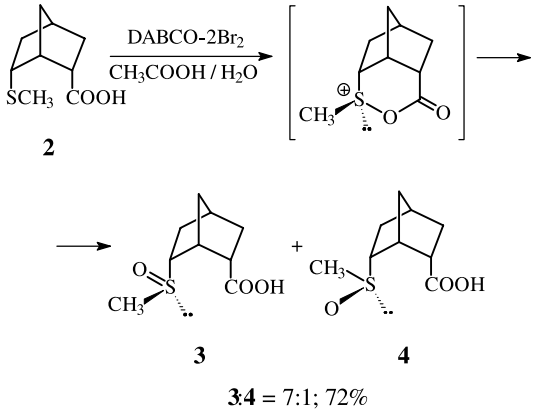
The biggest disadvantage of the utilization of molecular bromine in the oxidation of sulfides is the formation of byproducts such as sulfonic or sulfinic acids and bromo-substituted sulfides or sulfones. In this method, hydrogen bromide is considered to be responsible for the unwanted reactions. These may be easily prevented by carrying out the



Scheme 2.

oxidation under suitable conditions (Table 1). Shaabani[25] and Choudhary[26] used a hexamethylenetetramine–Br_2 complex (HMTAB), while Oae et al.[27] used complexes of bromine with tertiary amines (e.g. pyridine or 1,4-diazabicyclo[2.2.2]octane (DABCO)), acting as HBr acceptors.

Glass et al.[28–30] reported that the DABCO–$2Br_2$ complex diastereoselectively oxidized sulfides to sulfoxides in aqueous acetic acid. In this reaction, controlled by a neighboring hydroxyl or carboxyl group, the diastereomeric sulfoxides **3** were obtained from **2** in 72% yield (Scheme 3). For comparison, oxidation of the *endo* acid **2** with peracetic acid in ethyl acetate or with *m*-chloroperbenzoic acid in dichloromethane afforded a mixture of the diastereomeric sulfoxides **3** and **4** in a 5:1 ratio in 84% yield.[30]



Scheme 3.

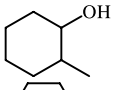
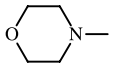
Drabowicz et al.[21] carried out the oxidation with bromine in a biphasic medium (CH_2Cl_2/H_2O), using potassium bicarbonate as the HBr acceptor (Table 1).

Ali et al.[31] demonstrated that bromine can also be utilized as an oxidant for the conversion of sulfides into sulfoxides on hydrated silica gel in dichloromethane (Table 1).

Ueno et al.[32] reported the oxidation of sulfides to sulfoxides with bromine under anhydrous conditions. They found that the addition of hexabutyldistannoxane (HBDS) to the reaction mixture afforded sulfoxides in high yields without sulfone contamination, even in the presence of an excess of the reagent (Scheme 4). This procedure is especially useful for sulfides having long, hydrophobic alkyl chains, for which solubility problems are often encountered in the oxidations in water or water/organic solutions.

Elnagar and Davis[33] employed aqueous bromine chloride

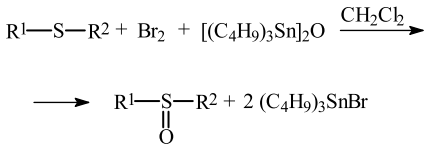
Table 1. Oxidation of sulfides R^1-S-R^2 to sulfoxides R^1-SO-R^2 with bromine under various reaction conditions

Reaction conditions	R^1	R^2	Yield [%]
HMTAB/$CHCl_3$/H_2O[a]	*n*-C_3H_7	*n*-C_3H_7	91
	C_6H_5	CH_3	93
	C_6H_5	C_6H_5	13
	$C_6H_5CH_2$	$C_6H_5CH_2$	95
Br_2/pyridine/H_2O/CH_3COOH[b]	C_6H_5	C_6H_5	95
	$C_6H_5CH_2$	C_6H_5	65
	p-$CH_3C_6H_4$	CH_3	85
PTAB/pyridine/H_2O[c]	*n*-C_3H_7	*n*-C_3H_7	84
	C_6H_5	CH_3	85
	C_6H_5	C_6H_5	89
	p-$(NO_2)C_6H_4$	CH_3	86
	p-$(COOH)C_6H_4$	C_6H_5	93
	$(CH_2)_4$		69
Br_2/H_2O/CH_2Cl_2/$KHCO_3$[d]	CH_3	*n*-C_3H_7	85
	CH_3	*n*-C_4H_9	90
	C_6H_5	CH_3	97
	C_6H_5	C_6H_5	95
	$C_6H_5CH_2$	$C_6H_5CH_2$	97
Br_2/H_2O/CH_2Cl_2/hydrated silica gel[e]	CH_3	CH_2=$CHCH_2$	87
	C_6H_5	CH_3	100
	C_6H_5	C_2H_5	98
	C_6H_5	C_6H_5	60
	p-$CH_3C_6H_4$	CH_3	95
Br_2/HBDS/CH_2Cl_2[f]	CH_3	CH_2Cl	78
	C_6H_5	CH_3	85
	C_6H_5	C_6H_{13}	85
	C_6H_5	C_6H_5	18
	C_6H_5	$C_6H_5CH_2$	82
	$C_6H_5CH_2$	$C_6H_5CH_2$	92
	C_6H_5		87
	C_6H_5		92
BTMA-Br_3/NaOH/H_2O/CH_2Cl_2[g]	*n*-C_3H_7	*n*-C_3H_7	89
	i-C_3H_7	*i*-C_3H_7	94
	n-C_4H_9	C_2H_5	98
	C_6H_5	C_6H_5	32 (73[h])
	C_6H_5	$C_6H_5CH_2$	53 (80[h])
	$C_6H_5CH_2$	CH_3	97
	$C_6H_5CH_2$	$C_6H_5CH_2$	84 (87[h])
	$(CH_2)_5$		66
CTMATB/CH_3CN/H_2O[i]	CH_3	CH_3	78
	$C_{16}H_{33}$	C_2H_5	95
	$(CH_3CO)OC_2H_4$	C_2H_5	89
	$(OH)C_2H_4$	C_5H_{11}	85
	C_6H_5	CH_3	93
	C_6H_5	*n*-C_5H_{11}	95
	C_6H_5	$C_6H_5CH_2$	94
	$C_6H_5CH_2$	$C_6H_5CH_2$	92

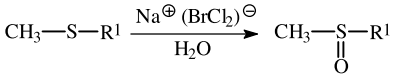
[a] Ref. 25.
[b] Ref. 27.
[c] Ref. 35.
[d] Ref. 21.
[e] Ref. 31.
[f] Ref. 32.
[g] Ref. 34.
[h] BTMA-Br_3/NaOH/H_2O/1,2-$C_2H_4Cl_2$, reflux.
[i] Ref. 37.

solutions stabilized with halide salts as the oxidizing agent for sulfides (Scheme 5). From among sodium, potassium, lithium, calcium and magnesium chlorides and bromides, sodium chloride is the most preferred salt for stabilization of the bromine chloride oxidant. An especially recommended reagent is an aqueous solution of $Na^+(BrCl_2)^-$, prepared by dissolving BrCl in an aqueous NaCl solution. Selective oxidation in this system is achieved by the use of protic solvents such as alcohols or aqueous alcohols. In anhydrous halogenated hydrocarbons, bromination of the aromatic ring of aryl sulfides takes place as a competitive reaction.

As a substitute for bromine in the bromine-mediated oxidation reactions of sulfides to sulfoxides, quaternary



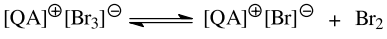
Scheme 4.



R^1	%
C_6H_5	87
p-$CH_3C_6H_4$	88

Scheme 5.

ammonium polybromides $[QA]^+[Br_3]^-$ have also been used (Scheme 6 and Table 1).[34–37]



Scheme 6.

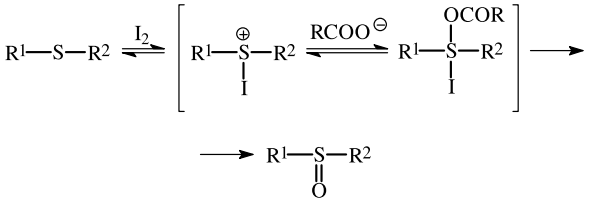
Cetyltrimethylammonium tribromide (CTMATB) provides a selective, mild and efficient oxidation of various sulfides to sulfoxides without affecting hydroxy or acetate groups.[37] The reaction is performed in a mixed acetonitrile–water solution with a 1:1.2 molar ratio of sulfide to CTMATB.

The oxidation with benzyltrimethylammonium tribromide (BTMA-Br_3) and aqueous sodium hydroxide is carried out in dichloromethane or 1,2-dichloroethane at room temperature or under reflux, respectively.[34] The advantage of this method is that the endpoint of the reaction can be recognized by a fading of the coloration on completion of the reaction. A limitation of this procedure is its failure in the preparation of unsaturated sulfoxides, since a double bond undergoes bromine addition under these reaction conditions.[34]

Typical reaction conditions for the oxidation with phenyltrimethylammonium tribromide (PTAB) involve the use of an aqueous pyridine solution at room or lower temperatures.[35]

Bravo et al.[38] have explored the use of bromine as a catalyst in the oxidation of sulfides to sulfoxides with H_2O_2 in CH_2Cl_2/H_2O and found that the oxidation in this system is strongly dependent on the structure of the sulfides. With H_2O_2 and catalytic amounts of Br_2 (10-fold less than H_2O_2), diaryl sulfides are not oxidized and only bromination of the aryl rings takes place. Dialkyl sulfides, however, give the corresponding sulfoxides with good yields and selectivity, while phenyl alkyl sulfides show both types of behavior, namely S-oxidation of the sulfide and C-bromination of the aryl ring. Under these reaction conditions, the bromination of the aromatic ring competes with the electrophilic attack of bromine on the sulfur atom in the sulfides to form a bromosulfonium cation. Hydrolysis of the bromosulfonium species provides the sulfoxides and HBr, and the latter acid is re-oxidized by H_2O_2 to Br_2, with regeneration of the catalyst.

In the chemical literature, there are relatively few examples of the use of molecular iodine for the oxidation of sulfides, because the reaction has been found to be relatively slow. Iodine oxidation of sulfides, however, is strongly catalyzed by certain nucleophiles.[39,40] Young et al. have reported the carboxylate-catalyzed oxidation of sulfides with iodine.[41,42] This reaction occurs through the formation of an intermediate sulfur–iodine complex, which subsequently undergoes hydrolysis to give the corresponding sulfoxide (Scheme 7).



Scheme 7.

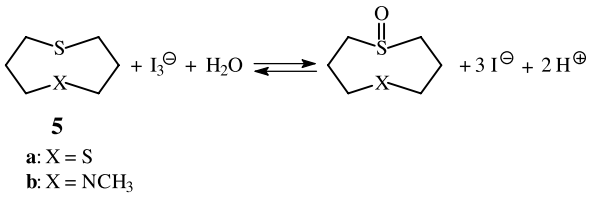
The application of a mercury(II) oxide–iodine reagent for the mild and selective oxidation of alkyl and cyclic sulfides to the corresponding sulfoxides was reported by Orito et al.[43] The reaction proceeds via the formation of the iodosulfonium cation, followed by replacement of the iodine atom with oxygen from the HgO. This oxidation is carried out in CH_2Cl_2 at room temperature and is usually complete within 30 min. Under these conditions, primary and secondary alkyl sulfides, including dibenzyl sulfide, are readily oxidized to the corresponding sulfoxides as the exclusive products. The six-membered cyclic sulfide, pentamethylene sulfide, was selectively oxidized to the sulfoxide in almost quantitative yield, whereas tetramethylene sulfide gave only a low yield of the corresponding sulfoxide (Table 2). Oxidation of di-*tert*-butyl sulfide, trimethylene sulfide, dithianes, and diphenyl sulfides failed to yield the sulfoxides. The oxidation rates of monophenyl sulfides were slower than those of dialkyl sulfides, and prolongation of the reaction time to a few hours was necessary.

Table 2. Formation of sulfoxides R^1-SO-R^2 using an HgO-I_2 reagent in CH_2Cl_2[43]

R^1	R^2	Yield [%]
n-C_3H_7	n-C_3H_7	95
n-C_4H_9	n-C_4H_9	94
i-C_3H_7	i-C_3H_7	92
s-C_4H_9	s-C_4H_9	92
$C_6H_5CH_2$	$C_6H_5CH_2$	94
C_6H_5	CH_3	85
C_6H_5	$C_6H_5CH_2$	92
p-ClC_6H_4	CH_3	92
$(CH_2)_5$		94
$(CH_2)_4$		38

Doi et al.[44] have reported the application of an aqueous I_2 solution to the oxidation of mesocyclic sulfides to the sulfoxides. At pH 3.5, the oxidation of 1,5-dithiacyclooctane (**5a**) to the monosulfoxide is 95% complete in 2 min,

whilst, when the pH is lowered to 1.5, the reaction can be completely reversed. The same reversible processes are also observed for 5-methyl-1-thia-5-azacyclooctane (**5b**) and its sulfoxide. It was proposed that these unique sulfide–sulfoxide interconversions were promoted by neighboring groups, the mesocyclic sulfides effectively catalyzing both the oxidation and the reduction reactions (Scheme 8).[44]



Scheme 8.

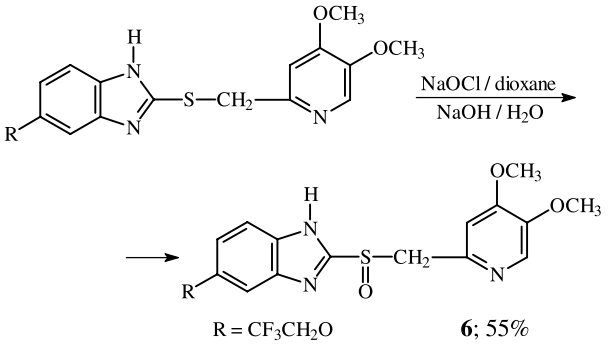
3. Oxidation of sulfides with hypochlorites

3.1. Sodium and calcium hypochlorites

Sodium hypochlorite in various solvents efficiently oxidizes cyclic, vinyl and aryl sulfides to the corresponding sulfoxides.[45] Oxidation of long-chain aliphatic sulfides with sodium hypochlorite, however, goes rather unselectively, a significant amount of the sulfone being obtained along with the required sulfoxide.

Sodium hypochlorite is stable only in dilute aqueous solutions. A critical consideration in the application of NaOCl as an oxidant is the pH of its solution. In strongly alkaline conditions (pH>12), OCl^- is the predominant form of positive chlorine and, because the hypochlorite ion is insoluble in organic solvents, phase-transfer catalysts are needed at this pH range to effect the oxidation reaction in biphasic media. Below pH 11, however, the equilibrium amount of HOCl becomes significant. Hypochlorous acid is soluble in polar organic solvents (e.g. CH_2Cl_2) and no phase-transfer catalyst is therefore necessary to effect the oxidation in the pH range 10–11. Below pH 10, molecular chlorine becomes a significant component, and the reactivity of the aqueous NaOCl solutions can be attributed to that of Cl_2.[6,46]

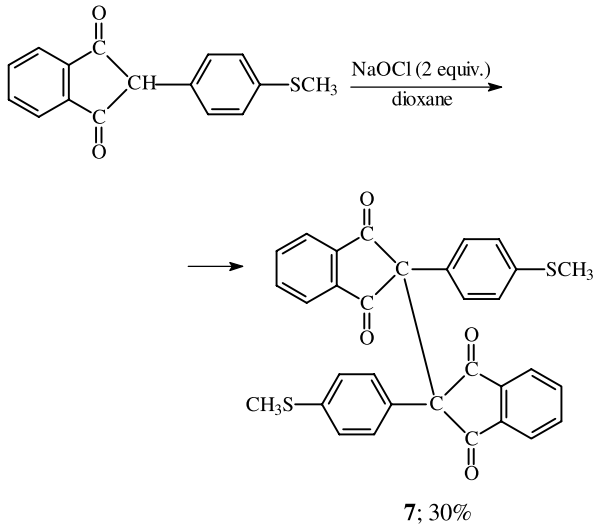
In alkaline media at pH>10, in methanol, ethanol, dioxane or DMSO as the solvent, sodium hypochlorite was used for the production of pharmacologically active compounds



Scheme 9.

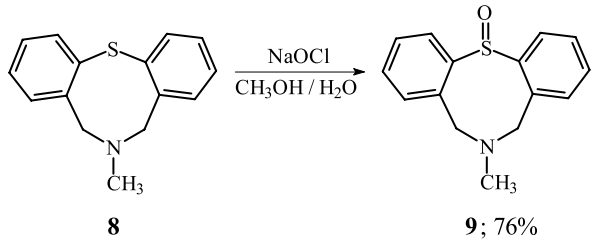
containing a sulfoxide group.[47,48] Under these reaction conditions, sulfinylfluoroalkoxy-substituted benzimidazoles such as **6**, useful as gastric acid secretion inhibitors, were synthesized (Scheme 9).[48]

Mitka et al.[49] have described the application of NaOCl in the oxidation of 2-(4-methylsulfanylphenyl)-indano-1,3-dione. Unexpectedly, no sulfide group oxidation was observed in this reaction. Instead, the dimer **7** was formed, with no apparent effect on the sulfide group (Scheme 10).



Scheme 10.

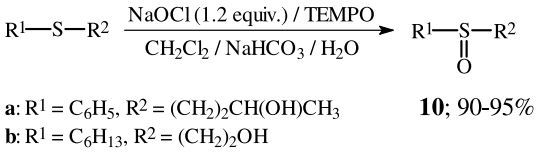
Selective oxidation of a dibenzo[*b*,*g*][1,5]thiazocine (**8**) was described by Ohkata et al.[50] The sulfoxide **9** is obtained by the oxidation of **8** in methanol with an aqueous sodium hypochlorite solution at −78 °C (Scheme 11). Oxidation of **8** with sodium periodate afforded a mixture of the sulfoxide **9** (12%) and the *N*-oxide of **8** (72%), whilst, in the oxidation with H_2O_2 in refluxing acetic acid, **9** was not obtained, but the sulfone was the major product.



Scheme 11.

trans-2-Benzylidene-2,3-dihydro-5-methylbenzo[*b*]thiophen-3-one, on reaction with sodium hypochlorite solution, the pH of which had been adjusted to 4–6, and *cis*-thiacyclooct-4-ene, on reaction with 1.3 equiv of NaOCl, gave the corresponding sulfoxides in over 80% yields without affecting the C=C bonds.[45,51] The actual oxidant in these examples was hypochlorous acid.

The application of NaOCl as a practical synthetic reagent

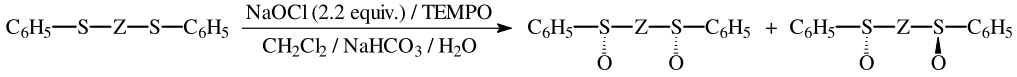


a: $R^1 = C_6H_5$, $R^2 = (CH_2)_2CH(OH)CH_3$
b: $R^1 = C_6H_{13}$, $R^2 = (CH_2)_2OH$

10; 90-95%

Scheme 12.

Sulfides can also be oxidized efficiently to the corresponding sulfoxides using calcium hypochlorite. The advantage of the calcium salt over sodium hypochlorite is its better stability at ambient temperature and its ease of handling as a solid.[59] A variety of alkyl and aryl alkyl sulfides can be selectively oxidized to the sulfoxides with calcium hypochlorite in yields exceeding 70%. Di-*n*-butyl sulfide gives



11a-f ***meso*-12a,b** ***rac*-12c-f**

a: $Z = (CH_2)_2$ **b**: $Z = (CH_2)_3$ **c**: $Z = (CH_2)_4$ **d**: $Z = (CH_2)_5$ **e**: $Z = (CH_2)_6$ **f**: $Z = (CH_2)_2CHCH_3$

Scheme 13.

for sulfide oxidation involves its use in a two-phase system with a phase-transfer catalyst.[52] Skarżewski and Siedlecka applied an oxoammonium salt, generated from 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), as the phase-transfer catalyst.[53–55] Despite the fact that this system is highly efficient and selective for the oxidation of primary alcohols, the authors have found that, under the conditions applied, the hydroxyl group in the aryl or alkylsulfinylalcohols **10a**,**b** remains unaffected (Scheme 12).

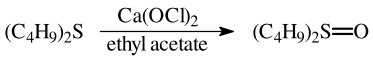
Oxidation of the disulfides **11a–f** with 1.2 equiv of NaOCl leads to the corresponding mono- or disulfoxides. When 2.2 equiv of the oxidizing agent are applied, 1,*x*-bis-(phenylthio)alkanes **11a–f** are converted into the corresponding disulfoxides **12a–f** in yields of 84–100%. In the case of **11a**,**b**, the disulfoxides **12a**,**b** are formed in 90–98% yields diastereoselectively (Scheme 13 and Table 3).[55]

Table 3. Oxidation of disulfides **11a–f** to sulfoxides **12a–f** with 2.2 equiv of sodium hypochlorite[55]

Product		Yield [%]	Ratio of diastereomers
12a	$(CH_2)_2$	~100	>49:1
12b	$(CH_2)_3$	80	9:1
12c	$(CH_2)_4$	98	1.2:1
12d	$(CH_2)_5$	93	1:1.1
12e	$(CH_2)_6$	96	1:1
12f	$(CH_2)_2CHCH_3$	84	3:2

Nevertheless, if **11a** was oxidized with 2.2 equiv of *m*-chloroperoxybenzoic acid (MCPBA)[56] or H_2O_2/H_2SO_4/*i*-PrOH,[57] no diastereoselectivity was observed.

Ramsden et al.[58] examined the usefulness of methyltri-*n*-octylammonium chloride as a phase-transfer catalyst for the hypochlorite oxidation of lipophilic sulfides. The sulfoxidation in the presence of the phase-transfer catalyst is nearly complete in 20 min with high selectivity, compared to 5 h in its absence.



13; 100%

Scheme 14.

the corresponding sulfoxide **13** in quantitative yield (Scheme 14), whereas, dibenzyl sulfide is inefficiently converted into dibenzyl sulfoxide (25% yield).[60]

Hirano et al.[61] reported that calcium hypochlorite and moist alumina in dichloromethane is a mild, inexpensive and convenient reagent for the conversion a broad range of sulfides into the sulfoxides. The $Ca(OCl)_2$-moist alumina system tolerates various functional groups, such as carbonyl groups in aldehydes and ketones, nitriles, halides, ethers, hydroxyls, olefinic and allylic double bonds, etc. In a view of its easy availability, mild reaction conditions, high chemoselectivity and high yield of sulfoxide products, this system may be treated as a very efficient oxidizing agent (Table 4). It should be noted, however, that, in the absence of alumina or in the presence of dry alumina, no reaction was observed in the tested oxidation of thioanisole.[61]

Table 4. Oxidation of sulfides (1 mmol) to sulfoxides R^1-SO-R^2 using $Ca(OCl)_2$-moist alumina (1 g) in CH_2Cl_2 (10 mL)[61]

R^1	R^2	Yield [%]
n-C_3H_7	*n*-C_3H_7	73
i-C_3H_7	*i*-C_3H_7	60
n-C_4H_9	*n*-C_4H_9	88
s-C_4H_9	*s*-C_4H_9	84
C_6H_{13}	C_6H_{13}	92
C_8H_{17}	CH_3	90
C_8H_{17}	C_8H_{17}	85
C_6H_5	CH_3	90
C_6H_5	C_2H_5	93
C_6H_5	C_6H_5	91
C_6H_5	$C_6H_5CH_2$	88
p-(CHO)C_6H_4	CH_3	94
p-(CH_2OH)C_6H_4	CH_3	81
C_6H_5	CH_2Cl	91
C_6H_5	$(CH_2)_2Cl$	94
C_6H_5	$(CH_2)_2OH$	85
C_6H_5	CH_2=CH	65
CH_2=$CHCH_2$	CH_2=$CHCH_2$	91
	$(CH_2)_5$	72
	$(CH_2)_2O(CH_2)_2$	85

3.2. *t*-Butyl hypochlorite

The oxidation of sulfides with *t*-butyl hypochlorite is very well established and can be used to prepare either the cyclic or acyclic sulfides.[62–65] The reaction of sulfides with *t*-butyl

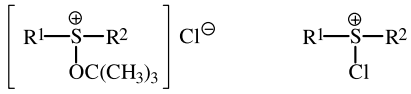
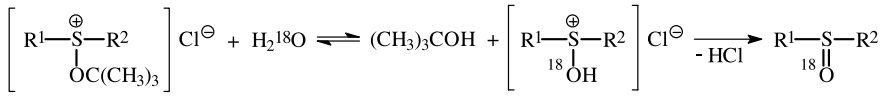


Figure 1.

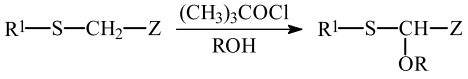


Scheme 15.

hypochlorite leads to the formation of an alkoxysulfonium intermediate, which then decomposes to the sulfoxides.[5,7,23] It was found that the oxidation of diphenyl sulfide with an equimolar quantity of *t*-butyl hypochlorite in dioxane, containing 2 equiv of $H_2^{18}O$, gave the sulfoxide in which 60% of the oxygen came from the labelled water.[23] The author concluded that, in the oxidation of sulfides with *t*-butyl hypochlorite, either the alkoxysulfonium or the chlorosulfonium species are the most likely intermediates (Fig. 1).

It is also possible, however, that the labelled sulfoxide is formed by solvation of the alkoxysulfonium intermediate, as shown in Scheme 15.

It should be noted that the reactions of propargyl or (methoxycarbonyl)methyl sulfides with *t*-butyl hypochlorite in an alcoholic solvent provide the corresponding α-alkoxy sulfides rather than the sulfoxides (Scheme 16).[5,7,23]



Z = C≡CH; $COOCH_3$

Scheme 16.

4. Oxidation of sulfides with chlorites and bromites

Although sodium chlorite ($NaClO_2$) alone is inefficient for sulfide oxidation in aprotic solvents, it has been disclosed that a (salen)manganese(III) complex[66] and manganese(III) acetylacetonate[14] are catalysts for the oxidation reaction in the presence of chromatographic and moist alumina, respectively. In the absence of the catalyst, no perceptible reaction takes place, and, in the absence of the alumina, the reaction is sluggish. The choice of the reaction medium is important. In the case of a (salen)manganese(III) catalyst, the reaction yield is influenced by the solvent in the following order: CH_2Cl_2 > acetone > CCl_4, $CHCl_3$, benzene > CH_3CN.

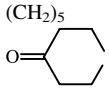
From among the solvents examined in the manganese(III) acetylacetonate-catalyzed oxidation, acetone is clearly the solvent of choice in terms of the ease of reaction, selectivity and yield of the sulfoxide. Under the conditions used, the chemical yields of sulfoxides are generally high and functional groups, such as hydroxyl, formyl, allyl, etc. remain unaffected (Table 5).

The oxidation of sulfides to sulfoxides with sodium bromite is often highly selective.[67] This procedure avoids the oxidation of other potentially reactive groups (Table 6). Another advantage of this method is that the reaction is easily monitored by the color change from an initial yellow to almost colorless.[68]

Iijima and Kyō[69] found that quinoxaline sulfides gave the corresponding sulfoxides **14** in 69–88% yields in the reaction with sodium bromite in acetic acid solution (Scheme 17).

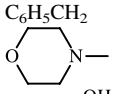
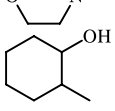
Sodium bromite acts as a selective and efficient oxidant in the presence of inorganic support materials, such as aluminas, zeolites, silica gel and clays.[70–72] Oxidation of dialkyl, alkyl aryl, diaryl and cyclic sulfides with sodium

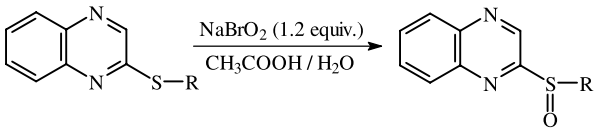
Table 5. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with $NaClO_2$[14,66]

R^1	R^2	Yield [%]	
		A	B
n-C_3H_7	n-C_3H_7	85	88
n-C_4H_9	n-C_4H_9	87	89
i-C_4H_9	i-C_4H_9	82	83
n-C_6H_{13}	n-C_6H_{13}	76	84
n-C_8H_{17}	CH_3	80	79
CH_2=$CHCH_2$	CH_2=$CHCH_2$	70	69
C_6H_5	CH_3	89	93
C_6H_5	C_6H_5	85	95
$C_6H_5CH_2$	$C_6H_5CH_2$	79	87
p-$(CH_2OH)C_6H_4$	CH_3	81	91
p-$(CHO)C_6H_4$	CH_3	91	91
p-$(CH_3O)C_6H_4$	CH_3	83	88
p-$(NO_2)C_6H_4$	CH_3	82	98
p-ClC_6H_4	CH_3	90	92
	$(CH_2)_4$	66	90
	$(CH_2)_5$	72	84
		66	94

(A) At 20 °C; 0.2 mmol of sulfide, 1 ml of CH_2Cl_2, 0.2 g of alumina, and 0.002 mmol of (salen)manganese(III) complex, Ref. 66; (B) at 20 °C; 0.2 mmol of sulfide, 1 ml of acetone, 0.2 g of moist alumina, and 0.002 mmol of manganese(III) acetylacetonate, Ref. 14.

Table 6. Formation of sulfoxides R^1-SO-R^2 in reactions of sulfides with $NaBrO_2$[68]

R^1	R^2	Yield [%]
n-C_4H_9	n-C_4H_9	89
C_6H_5	C_6H_5	78
C_6H_5	$C_6H_5CH_2$	97
C_6H_5	CH_2=$CHCH_2$	90
C_6H_5CH=CH	$C_6H_5CH_2$	97
C_6H_5		93
C_6H_5		80



14

R	%
CH_3	69
C_2H_5	88
$(CH_3)_2CH$	72
$C_6H_5CH_2$	69
C_6H_5	70

Scheme 17.

bromite in the presence of wet montmorillonite, kaolin[73] and zeolite[72] in dichloromethane affords the sulfoxides in comparable and satisfactory yields (Table 7).

Besides sodium, calcium and potassium bromites, bromous acid was also successfully applied for the preparation of sulfoxides in high yield and selectivity, without the risk of oxidation of the non-target functional groups or over-oxidation to sulfones.[74]

5. Oxidation of sulfides with bromates

Both alkyl and aryl sulfides can be efficiently oxidized to the sulfoxides using sodium bromate in combination with NH_4Cl in aqueous acetonitrile.[75] In the presence of $Mg(HSO_4)_2$, however, sodium bromate oxidation occurs in dry acetonitrile.[76] Alkyl and aryl sulfides are also oxidized with $NaBrO_3$–$Mg(HSO_4)_2$ under solvent-free conditions, but, in *n*-hexane, only the alkyl sulfides undergo sulfoxidation (Table 8).

Moreover, it has been shown that sodium bromate in the presence of catalytic amounts of ceric ammonium nitrate (CAN) is able to oxidize dialkyl and diaryl sulfides to the corresponding sulfoxides without over-oxidation to the sulfones.[77]

6. Oxidation of sulfides with iodo-compounds

6.1. Hypervalent iodine(III) reagents

Hypervalent iodine(III) reagents have been extensively used in organic syntheses, due to their low toxicity and ease of handling.[6,78–81] In 1949, Ford–Moore first described the selective oxidation of sulfides with iodosobenzene ($C_6H_5I{=}O$).[82] Iodosobenzene alone, however, is not a reactive oxidant,[83] but its reactivity may be accelerated by Lewis acids [e.g. $BF_3{\cdot}(C_2H_5)_2O$], and in a limited number of solvents, such as dichloromethane and acetonitrile.[80,81]

Several reports have shown that hypervalent iodine(III) oxidation using $C_6H_5I{=}O$–$(RCO)_2O$,[40,84–86] $C_6H_5I{=}O$–C_6H_5SeOOH,[87] $C_6H_5I(OTs)OH$,[88] $C_6H_5I(OTs)OCH_3$,[89] $C_6H_5I{=}O$–metalloporphyrin,[90–92] $C_6H_5I{=}O$–metallosalen,[93–95] $C_6H_5I{=}O$–clays,[96] $C_6H_5I{=}O$–cationic

Table 7. Oxidation of sulfides (1 mmol) to sulfoxides R^1-SO-R^2 with $NaBrO_2$ in the presence of wet clay minerals (**1g**)[72,73]

R^1	R^2	Yield [%]		
		A	B	C
n-C_3H_7	*n*-C_3H_7	80	82	79
i-C_3H_7	*i*-C_3H_7	80	79	72
n-C_4H_9	*n*-C_4H_9	78	74	80
s-C_4H_9	*s*-C_4H_9	74	78	79
n-C_6H_{13}	*n*-C_6H_{13}	78	89	75
n-C_8H_{17}	CH_3	70	73	82
C_6H_5	CH_3	78	80	82
C_6H_5	C_6H_5	73	79	75
$C_6H_5CH_2$	$C_6H_5CH_2$	74	80	67
p-$(CH_3O)C_6H_4$	CH_3	70	82	75
p-$(NO_2)C_6H_4$	CH_3	71	72	80
$(CH_2)_4$		74	80	84

(A) Montmorillonite, Ref. 73; (B) kaolin, Ref. 73; (C) zeolite, Ref. 72.

Table 8. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with $NaBrO_3$–$Mg(HSO_4)_2$[76]

R^1	R^2	Yield [%]		
		A	B	C
CH_3	CH_3	85	90	87
C_2H_5	C_2H_5	85	85	84
n-C_4H_9	*n*-C_4H_9	90	90	80
n-C_8H_{17}	*n*-C_8H_{17}	90	90	85
$C_6H_5CH_2$	$C_6H_5CH_2$	85	75	70
C_6H_5	CH_3	90	—	80
C_6H_5	C_2H_5	85	—	88
C_6H_5	C_6H_5	45	—	45
$C_6H_5CH_2$	C_6H_5	75	—	55
p-BrC_6H_4	CH_3	88	—	90
p-$(NO_2)C_6H_4$	CH_3	85	—	85

(A) CH_3CN; (B) *n*-hexane; (C) solvent-free conditions.

surfactants,[97] and $C_6H_5I{=}O$–KBr[98] is effective for the selective oxidation of sulfides to sulfoxides in various solvents.

For asymmetric oxidation of aryl methyl sulfides to the corresponding sulfoxides, $C_6H_5I{=}O$ was employed as an oxidant in the presence of L-tartaric anhydrides. The reaction occurred in moderate optical yields (i.e. 30–53%),[40] comparable to those reported for iodine(III)-tartrate polymers.[86]

It is interesting to note that the oxidation of sulfides to sulfoxides with iodosobenzene is catalyzed by benzeneselenic acid, but not by other protic acids such as acetic or benzoic acid.[87]

(*p*-Toluenesulfonyloxy)hydroxyiodobenzene [C_6H_5-I(OTs)OH] was found to be the effective oxidant in the iodosobenzene oxidation of sulfides in the presence of catalytic amounts of *p*-toluenesulfonic acid (TsOH).[99] If this reaction is performed in acetonitrile at room temperature, iodosobenzene reacts first with TsOH to form C_6H_5-I(OTs)OH, and the C_6H_5I(OTs)OH subsequently oxidizes sulfides to yield the sulfoxides, iodobenzene and TsOH. The TsOH-catalyzed iodosobenzene oxidation of sulfides is noteworthy for its mild reaction conditions, high yields and lack of over-oxidation products (Table 9).

Table 9. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with $C_6H_5I{=}O$ catalyzed by TsOH[99]

R^1	R^2	Yield [%]
C_6H_5	CH_3	82
C_6H_5	C_2H_5	81
C_6H_5	C_6H_5	92
C_6H_5	$C_6H_5CH_2$	96
$C_6H_5CH_2$	$C_6H_5CH_2$	91
p-$CH_3C_6H_4$	CH_3	81
p-ClC_6H_4	CH_3	80
p-$(NO_2)C_6H_4$	CH_3	99

Oxidation of sulfides to sulfides with C_6H_5I(OTs)OH was reported by Xia and Chen.[88] This mild and non-toxic oxidant can be used for the highly selective oxidation of sulfides to sulfoxides with excellent yields, under very mild conditions and without a catalyst (Table 10).

Table 10. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with C_6H_5-I(OTs)OH in CH_2Cl_2 at room temperature[88]

R^1	R^2	Yield [%]
C_6H_5	C_2H_5	95
C_6H_5	*n*-C_4H_9	97
C_6H_5	$C_6H_5CH_2$	~100
p-ClC_6H_4	C_2H_5	84
p-ClC_6H_4	*n*-C_4H_9	88
p-ClC_6H_4	*o*-$CH_3C_6H_4$	92
$C_6H_5CH_2$	$C_6H_5CH_2$	~100
$C_6H_5CH_2$	*n*-C_4H_9	94
$C_6H_5CH_2$	*p*-$CH_3C_6H_4$	~100

Iodosobenzene in dichloromethane, in the presence of catalytic amounts of chlorotetraphenylporphyrinato-Fe(III) and –Mn(III) complexes, oxidizes effectively only dialkyl sulfides to sulfoxides in 89–94% yields.[90] Under the same reaction conditions, diaryl sulfides gave the sulfoxides in moderate yields (59–75%), and over-oxidation to the sulfones (7–14%) took place.[90,91] Chloroporphyrinato-Fe(III) complexes accelerate the oxidation of dibutyl, dibenzyl, and diphenyl sulfides more than the analogous Mn(III) complexes. The yield of the sulfoxide in the chloroporphyrinato-Fe(III)-catalyzed oxidation was, however, slightly lower than that in the chloroporphyrinato-Mn(III)-catalyzed oxidation. Moreover, the oxidation of cyanomethyl phenyl sulfide with differently substituted oxidant and porphyrinato-Fe(III) catalyst resulted in C–S bond cleavage, but S-oxidation (59–71%) always predominated over S-dealkylation (4–9%).[90,91] It was also found that $C_6H_5I{=}O$ and a chlorotetraphenylporphyrinato-Fe(III) complex supported on the surface of silica gel acts as a good oxidant of alkyl aryl sulfides. In this system, the over-oxidation of sulfoxides to sulfones is suppressed, because of the complete adsorption of the sulfoxides on the inert support.[92]

Salicylidene–ethylenediamines, commonly known as salens, form stable complexes with transition metals. These metal-Schiff base complexes in combination with iodosobenzene as the oxidant offer a viable access to sulfoxides and sulfones under fluorous biphasic conditions and related methodologies.[100–102]

Cavazzini et al.[95] tested (salen)manganese(III) complexes in the preliminary oxidations of alkyl aryl sulfides with $C_6H_5I{=}O$ under fluorous biphasic conditions. Achiral (salen)manganese(III) complexes, used at 0.01 equiv relative to sulfide/$C_6H_5I{=}O$, effectively catalyze the oxidation of phenyl, *p*-nitrophenyl, and *p*-bromophenyl methyl sulfides, with good sulfoxide selectivities ($\geq$90%). The catalytic activity and selectivity were unaffected after three consecutive cycles. The application of chiral (salen)manganese(III) complexes for the enantioselective catalytic oxidation of alkyl aryl sulfides is, however, rather limited, because in many examples the enantioselectivity was $<$5% ee.

The oxidation of various sulfides to sulfoxides with an iodosobenzene–(salen)chromium(III) complex was reported by Kim et al.[103] The complex, *N*,*N*-ethylenebis(3,5-di-*tert*-butylsalicylideneiminato)chromium(III) chloride–$C_6H_5I{=}O$, in CH_2Cl_2 was found to transform dialkyl, alkyl aryl and diaryl sulfides to the sulfoxides with $>$90% yield. Electron-withdrawing substituents on the phenyl ring of methyl phenyl sulfides slightly suppress the yield of sulfoxides, whilst chloro and methyl substituents do not affect the reaction yield (Table 11).

Table 11. Yields of sulfoxides R^1-SO-R^2 obtained using a $C_6H_5I{=}O$–(salen)Cr(III) complex in CH_2Cl_2[103]

R^1	R^2	Yield [%]
n-C_3H_7	*n*-C_3H_7	96
C_8H_{17}	C_8H_{17}	94
C_6H_5	CH_3	99
C_6H_5	C_6H_5	91
p-ClC_6H_4	CH_3	98
p-$(NO_2)C_6H_4$	CH_3	90
p-$(CN)C_6H_4$	CH_3	91

The oxidation of aryl methyl sulfides with oxo(salen)-iron(III) complexes in acetonitrile was reported by Sivasubramanian et al.[104] Kinetic studies of the iodosobenzene–(salen)iron(III) oxidation indicate an oxygen-transfer mechanism from the iodosobenzene to the complex in the rate-determining step. Recently, a systematic study of the kinetics and mechanism of the oxidation of organic sulfides to sulfoxides with oxo(salen)manganese(V),[105–107] oxo(salen)chromium(V)[108] and oxo(salen)ruthenium(V)[104] complexes has been reported.

Application of $C_6H_5I{=}O$ supported on dry clays as an efficient oxidant of alkyl aryl sulfides to the corresponding sulfoxides was described by Kannan et al.[96] This oxidation may be carried out in a suspension in acetonitrile or in the solid state. The yields of sulfoxides under the suspension conditions for a 1:1 ratio of clay to $C_6H_5I{=}O$ (by weight) were in the range from 51% for *n*-butyl phenyl sulfoxide to 100% for *i*-propyl phenyl and methyl anisyl sulfoxides. The results of the oxidation of sulfides with 1:1 and 1:2 ratios of clay to $C_6H_5I{=}O$ (by weight), under the solid-state reaction conditions, indicated that the yield of sulfoxides increases with an increase in the $C_6H_5I{=}O$/clay ratio (Table 12).

Table 12. Yields of sulfoxides R^1-SO-R^2 obtained using $C_6H_5I{=}O$ in the presence of K10-montmorillonite in the solid state[96]

R^1	R^2	Yield [%] in clay:$C_6H_5I{=}O$	
		1:1	1:2
C_6H_5	CH_3	45	100
C_6H_5	CH_2CH_3	56	100
C_6H_5	*i*-C_3H_7	87	100
p-$(CH_3O)C_6H_4$	CH_3	89	100
p-$(COOH)C_6H_4$	CH_3	43	90
p-ClC_6H_4	CH_3	50	98
C_6H_5	$CH_2C_6H_5$	76	100
p-ClC_6H_4	$CH_2C_6H_5$	65	93
C_6H_5	C_6H_5	37	80

Tohma at al.[97] reported a mild and efficient oxidation of sulfides using iodosobenzene activated with a catalytic amount of the cationic surfactant, cetyltrimethylammonium bromide (CTAB), in solvents ranging from water to wet hydrocarbons. The oxidation of methyl *p*-tolyl sulfide with $C_6H_5I{=}O$–CTAB in water affords the sulfoxide in quantitative yield at room temperature. The results of the oxidation of various sulfides to the corresponding sulfoxides in toluene–water (500:1) using $C_6H_5I{=}O$–CTAB are summarized in Table 13.

Table 13. Yields of sulfoxides R^1-SO-R^2 obtained using $C_6H_5I{=}O$–CTAB in toluene–water (500:1) mixture[97]

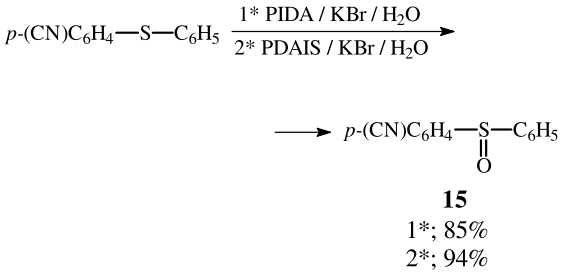
R^1	R^2	Yield [%]
o-$CH_3C_6H_4$	CH_3	89
o-$(CH_3O)C_6H_4$	CH_3	100
C_6H_5	C_2H_5	100
$C_6H_5CH_2$	CH_3	100
C_6H_5	$C_6H_5CH_2$	90
$C_6H_5CH_2$	$C_6H_5CH_2$	95
$(CH_2)_5$		78

The results obtained using the combined reagent $C_6H_5I{=}O$–KBr for the oxidation of various sulfides are summarized in Table 14.[98]

Table 14. Yields of sulfoxides R^1-SO-R^2 obtained using $C_6H_5I{=}O$ (1.5 equiv)–KBr (1.0 equiv) in water[98]

R^1	R^2	Yield [%]
p-$CH_3C_6H_4$	CH_3	100
$C_6H_5CH_2$	CH_3	95
C_6H_5	C_6H_5	100
p-$CH_3C_6H_4$	C_6H_5	94
p-$(CN)C_6H_4$	C_6H_5	25
p-$(NO_2)C_6H_4$	C_6H_5	Trace

These results indicate that this reaction is not applicable for the synthesis of diaryl sulfoxides having an electron-withdrawing group (e.g. CN or NO_2) on the aryl ring. Oxidation of the diaryl sulfide to the corresponding sulfoxide **15**, however, occurs in good yield using phenyliodine(III) diacetate (PIDA), or poly(diacetoxy-iodo)styrene (PDAIS) in the presence of KBr in water (Scheme 18).[98,109]



Scheme 18.

Phenyliodine(III) diacetate (PIDA) oxidation of aliphatic, aromatic and heterocyclic sulfides to sulfoxides involves the use of acetic acid as the solvent.[4,5,7] The reaction mechanism and kinetics have been studied by several researchers.[22,85] PIDA in wet $CHCl_3$ (99%) and poly-(diacetoxyiodo)styrene (PDAIS) oxidize di-*n*-butyl sulfide to the sulfoxide in 84% yield. In the oxidation of diaryl sulfides with PDAIS, however, the major product was the sulfone, whilst that in the case of PIDA was the sulfoxide.[109] Abe et al.,[110,111] Ley et al.[112,113] and Tohma et al.[114,115] have demonstrated that the polymer-supported hypervalent iodine(III) reagents are expected to be useful in the pharmaceutical and agrochemical industries, due to their versatility and low toxicity.

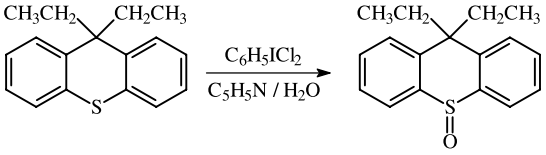
Varma et al. have developed alumina-supported PIDA for the oxidation of sulfides under solvent-free conditions upon

Table 15. Yields of sulfoxides R^1-SO-R^2 obtained using alumina-supported PIDA under microwave conditions[116]

R^1	R^2	Yield [%]
i-C_3H_7	*i*-C_3H_7	80
n-C_4H_9	*n*-C_4H_9	82
n-$C_{12}H_{25}$	CH_3	88
C_6H_5	CH_3	82
C_6H_5	C_6H_5	88
$C_6H_5CH_2$	C_6H_5	86
$C_6H_5CH_2$	$C_6H_5CH_2$	90
$(CH_2)_4$		82
O		85

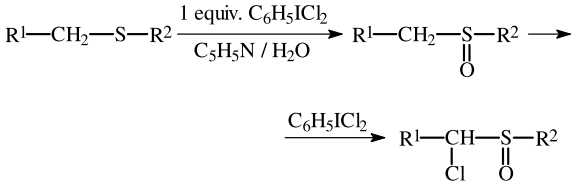
microwave irradiation.[116] From among the various solid supports ranging from acidic to basic surfaces, neutral alumina provided the best results in terms of the yields (80–90%) and the formation of fewer byproducts (Table 15).

Iodobenzene dichloride, which also belongs to the class of hypervalent iodine(III) reagents, was found to be useful for the conversion of aliphatic, aromatic or heterocyclic sulfides into the corresponding sulfoxides.[117] 9,9-Diethylthioxanthene was oxidized to the corresponding sulfoxide **16** with 88% yield (Scheme 19), whilst, for the synthesis of the 9,9-dibenzyl derivative, this method failed, probably because of the steric effects of the benzyl groups.



16; 88%

Scheme 19.



Scheme 20.

$C_6H_5ICl_2$ is not commercially available, due to its lack of stability, but it can be prepared easily from iodobenzene[118] or iodosobenzene.[119] Despite the fact that $C_6H_5ICl_2$ is a more powerful oxidant than metaperiodates, sulfones are not formed in the iodobenzene dichloride oxidation of sulfides. Prolonged exposure of sulfides having at least one hydrogen at the α-carbon atom to an excess of the oxidant, however, led to the α-chlorosulfoxides (Scheme 20).[120]

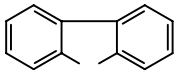
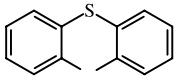
Müller and Godoy[121] reported the application of $RuCl_2(PPh_3)_3$ as a catalyst for the oxidation of sulfides with derivatives of iodosobenzene and iodoxybenzene. The derivatives studied contained electron-withdrawing substituents in the aromatic ring of C_6H_5IO and $C_6H_5IO_2$. With *p*-nitroiodosobenzene or *m*-iodosylbenzoic acid, dibenzyl sulfide is converted efficiently into the sulfoxide. The oxidation of dibenzyl sulfide proceeds sluggishly with $C_6H_5IO_2$, whilst with *o*-(COOH)C_6H_4I=O or *p*-(NO_2)-$C_6H_4IO_2$, no reaction takes place (Table 16). On the other hand, the oxidation of phenylethynyl methyl sulfide depends on the amount of oxidant. With a slight excess of C_6H_5I=O (1.3 equiv), a mixture of the sulfoxide (63%) and sulfone (14%) was obtained, with 2.5 equiv of the oxidant, the sulfone was formed quantitatively, whilst with 5 equiv, the phenylethynyl methyl sulfide was oxidized to benzoic acid.[79,121]

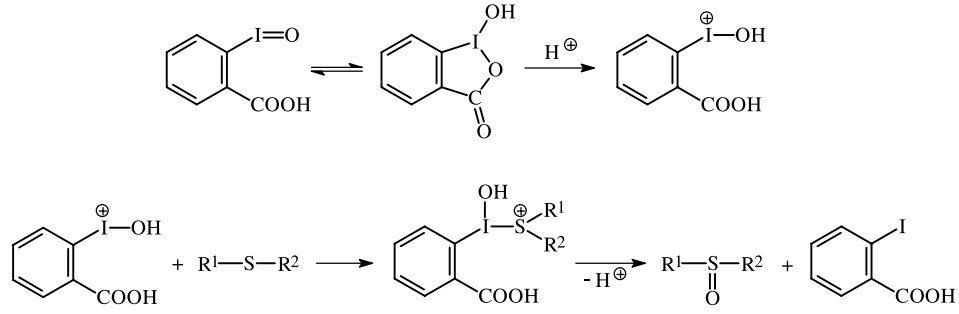
o-Iodosylbenzoic acid, which is inactive for the oxidation of dibenzyl sulfide in the C_6H_5I=O/Ru-system, appears to be an efficient oxidant of dibenzyl sulfide, as well as various other sulfides, in acidic conditions (Table 17).[122] In acetic acid, containing some sulfuric acid as a catalyst, *o*-iodosylbenzoic acid generates the reactive iodonium species responsible for the oxidation process (Scheme 21). Acidity also helps to prevent over-oxidation of the sulfoxide, since the protonated sulfoxide is more resistant to oxidation.

Table 16. Oxidation of dibenzyl sulfide with C_6H_5I=O and $C_6H_5IO_2$ derivatives catalyzed by $RuCl_2(PPh_3)_3$[121]

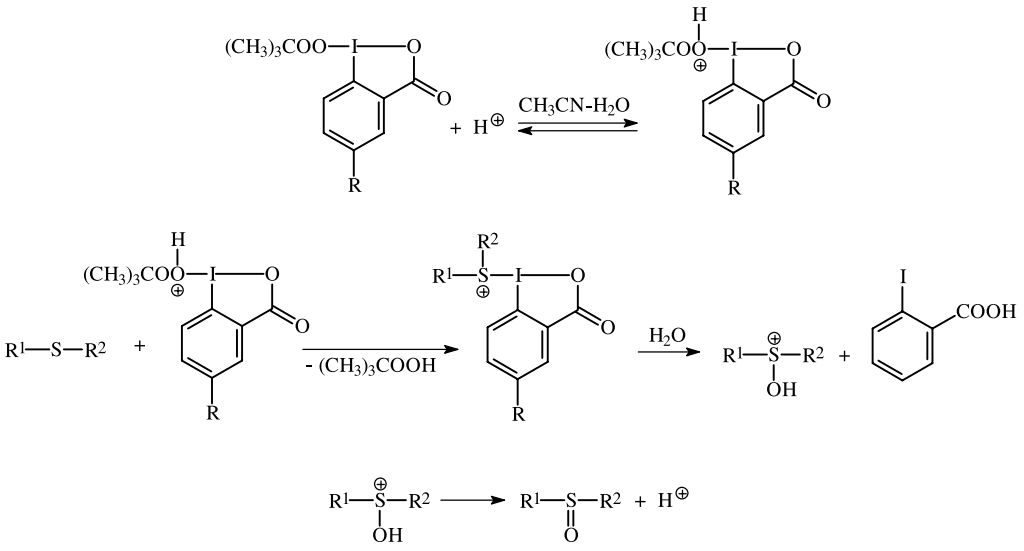
Oxidant	Sulfoxide [%]	Sulfone [%]
C_6H_5I=O	88	12
p-$(NO_2)C_6H_4I$=O	98	2
m-(COOH)C_6H_4I=O	90	—
$C_6H_5IO_2$	10	—
o-(COOH)C_6H_4I=O	—	—
p-$(NO_2)C_6H_4IO_2$	—	—

Table 17. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with *o*-iodosylbenzoic acid in acidic conditions[122]

R^1	R^2	Yield [%]
n-$C_{12}H_{25}$	*n*-$C_{12}H_{25}$	96
C_6H_5	C_6H_5	72
$C_6H_5CH_2$	C_6H_5	93
$C_6H_5CH_2$	$C_6H_5CH_2$	98
p-ClC_6H_4	*p*-ClC_6H_4	98
p-$(NO_2)C_6H_4$	C_6H_5	95
		98
		96



Scheme 21.



Scheme 22.

1-(*tert*-Butylperoxy)-1,2-benziodoxol-3(1*H*)-one [(*tert*-butylperoxy)-iodane],[123] prepared by the reaction of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one with *tert*-butyl hydroperoxide in the presence of $BF_3 \cdot (C_2H_5)_2O$ in chloroform,[124,125] was found to be another hypervalent iodine(III) oxidant of various types of sulfides to sulfoxides. In this reaction, the choice of solvent is important. The best results are achieved in acetonitrile–water (5:1) and dichloromethane. Moreover, the rate of oxidation in acetonitrile–water is much increased either by the addition of an acidic catalyst [e.g. $BF_3 \cdot (C_2H_5)_2O$] at room temperature (A), or by carrying out the reaction at 50 °C (B) (Table 18). For the oxidation of sulfides in acetonitrile–water, an ionic mechanism has been proposed (Scheme 22), while the oxidation in dichloromethane probably occurs by a free radical mechanism.[123]

Table 18. Yields of sulfoxides R^1-SO-R^2 obtained using (*tert*-butylperoxy)-iodane in CH_3CN–H_2O (5:1)[123]

R^1	R^2	Yield [%]	
		A	B
n-C_4H_9	$C_6H_5CH_2$	100	78
i-C_4H_9	$C_6H_5CH_2$	87	80
s-C_4H_9	$C_6H_5CH_2$	90	75
$C_6H_5CH_2$	$C_6H_5CH_2$	85	78
C_5H_{11}	C_6H_5	99	82
CH_2=$CHCH_2$	C_6H_5	82	77
p-$(CH_3O)C_6H_4$	CH_3	79	90

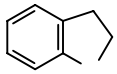
(A) Oxidant (1.1 equiv), $BF_3 \cdot Et_2O$ (0.3 equiv), 25 °C, N_2; (B) oxidant (1.2 equiv), 50 °C, air.

6.2. Hypervalent iodine(V) reagents

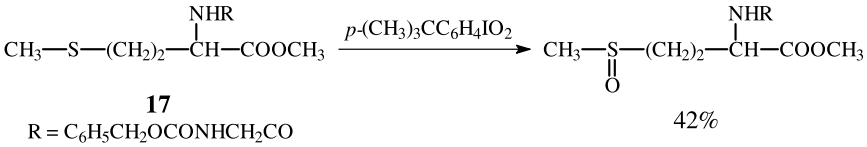
Iodoxybenzene ($C_6H_5IO_2$) and its derivatives are mild oxidants, but in the presence of a suitable catalyst their reactivity is increased.[79]

Oxidation of dialkyl, alkyl aryl and diaryl sulfides to sulfoxides with iodoxybenzene can be catalyzed by Brønsted and Lewis acids and by trichloroacetic anhydride.[126] Iodoxybenzene in the presence of catalytic amounts of vanadyl acetylacetonate [$VO(acac)_2$], oxidized some sulfides, but over-oxidation also occurred and several byproducts were formed.[127] In the presence of tartaric acid derivatives and a catalyst, however, iodoxybenzene affords chiral aryl alkyl sulfoxides quantitatively with moderate optical yields (Table 19).[128,129] The best chemical and optical yields are obtained in the presence of di-(2-methoxybenzoyl)-L-tartaric acid and cetyltrimethylammonium bromide (CTAB) in toluene–H_2O mixtures. The solubilization and activation of $C_6H_5IO_2$ by both CTAB and a chiral tartaric acid were found to be indispensable for the enhancement of the oxidation.[128] The oxidation of sulfides in water in the presence of (+)-dibenzoyl-D-tartaric acid (DBTA) requires the use of catalytic amounts of $MgBr_2$.[129] From among the bromides tested (i.e. LiBr, NaBr, $CaBr_2$, $BaBr_2$, $ZnBr_2$, and $MgBr_2$), $MgBr_2$ appears to be the most effective catalyst for the hypervalent iodine(V) sulfoxidation. The use of other tartaric acids or other chiral

Table 19. Catalytic oxidation of sulfides to sulfoxides R^1-SO-R^2 using $C_6H_5IO_2$[128,129]

R^1	R^2	Yield, % [ee, %]	
		A	B
m-$CH_3C_6H_4$	CH_3	—	100 [63]
p-$CH_3C_6H_4$	CH_3	100 [53]	100 [59]
p-BrC_6H_4	CH_3	100 [58]	—
m-$(NO_2)C_6H_4$	CH_3	94 [64]	100 [61]
p-$(NO_2)C_6H_4$	CH_3	91 [72]	100 [60]
p-$(CN)C_6H_4$	CH_3	100 [65]	97 [56]
p-$(CH_3O)C_6H_4$	CH_3	100 [46]	84 [63]
C_6H_5	CH_3	—	100 [60]
p-$(NO_2)C_6H_4$	C_2H_5	90 [57]	—
C_6H_5	$(CH_2)_2OH$	—	100 [43]
2-Naphthyl	CH_3	90 [51]	—
		88 [38]	100 [52]

(A) $C_6H_5IO_2$ (50 mol%) di-(2-methoxybenzoyl)-L-tartaric acid (10 mol%) in the presence of CTAB (20 mol%) in toluene-H_2O (60:1). Ref. 128; (B) $C_6H_5IO_2$ (55 mol%)-DBTA (10 mol%) in the presence of $MgBr_2$ (20 mol%) in water. Ref. 129.



Scheme 23.

components, such as chiral carboxylic, sulfonic, or phosphonic acids, did not improve the enantiomeric excess of chiral aryl methyl sulfoxides. By examination of the reaction using a variety of oxidants, it was established that the oxidation of *p*-tolyl methyl sulfide with common water-soluble oxidants, such as H_2O_2 or cumene hydroperoxide, was complete almost immediately, but without asymmetric induction.

4-*tert*-Butyl-iodoxybenzene was used as an efficient oxidant for the side-chain modification of methionine derivatives,[130] the methyl ester **17**, on treatment with 1.2 equiv of 4-*tert*-butyl-iodoxybenzene, giving the corresponding sulfoxide in 42% yield (Scheme 23). Conformational analysis of the methionine sulfoxide derivatives in solution was studied by Schenck et al.[131]

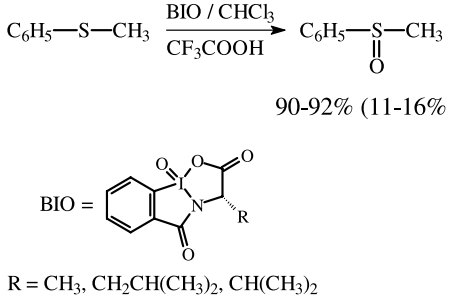
Shukla et al.[132] reported an efficient and rapid procedure for the sulfoxidation of sulfides substituted with different functional groups. In this procedure, *o*-iodoxybenzoic acid is used as an oxidant in the presence of tetraethylammonium bromide (TEAB) as a catalyst. An advantage of this method is the short reaction time (i.e. in several examples, the reaction was complete in 20 min to 2 h), mild reaction conditions and no over-oxidation to the sulfones (Table 20).

Table 20. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with *o*-iodoxybenzoic acid (1.1 equiv) in the presence of TEAB in $CHCl_3$–H_2O (100:1) at room temperature[132]

R^1	R^2	Yield [%]
C_2H_5	C_2H_5	98
n-C_4H_9	*n*-C_4H_9	98
C_6H_5	CH_3	97
C_6H_5	$(CH_2)_2CN$	98
C_6H_5	$CH(CH_3)(CH_2)_2OH$	97
C_6H_5	C_2H_5	97
C_6H_5	C_6H_5	98
$C_6H_5CH_2$	C_6H_5	96
p-$CH_3C_6H_4$	CH_3	95
p-ClC_6H_4	CH_3	93
p-$CH_3C_6H_4$	C_2H_5	97

Preliminary results on the application of benziodazole oxide (BIO) for the oxidation of sulfides indicate that BIO is a very convenient oxidizing reagent.[133] BIO and other cyclic derivatives of pentavalent iodine reagents may be prepared by the oxidation of 2-iodobenzamides with potassium bromate or OXONE®. The BIO and its derivatives are soluble in dichloromethane and other non-polar organic solvents. Non-symmetric sulfides are oxidized with BIO to chiral sulfoxides with moderate enantioselectivity (Scheme 24).

In recent years, moist HIO_3 has been employed for the oxidation of sulfides to sulfoxides. With this reagent, diphenyl, methyl phenyl and dibenzyl sulfides are oxidized to the corresponding sulfoxides in 92–95% yields, but the oxidation of sulfides with C=C bonds failed to yield the sulfoxides.[134]



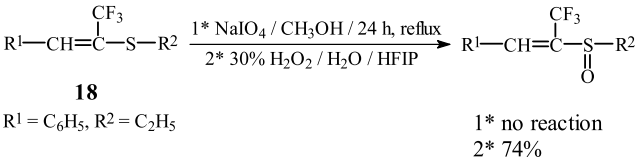
Scheme 24.

6.3. Periodates

From among the periodates, sodium periodate appears to be the most frequently used oxidant for the transformation of a variety of sulfides to the sulfoxides. Periodic acid HIO_4 and its dihydrate (paraperiodic acid), H_5IO_6, have also been applied.[6,135]

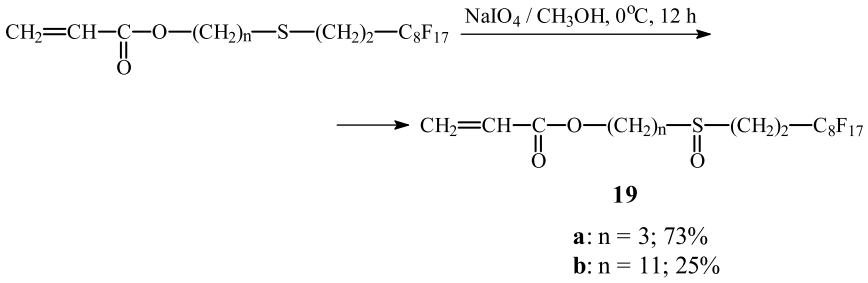
The oxidation of sulfides with sodium periodate is usually carried out using equimolar amounts of the oxidant in water at low temperatures. An excess of sodium periodate or higher temperatures results in over-oxidation to the sulfones. For organic substrates that are insoluble in water, an organic co-solvent (e.g. CH_3OH, C_2H_5OH, 1,4-dioxane, acetone, acetonitrile or THF) may be used.[136–139]

Problems appear in the oxidation of fluoroalkyl sulfides with sodium periodate. For the reaction of trifluoromethyl vinyl sulfides such as **18** with sodium periodate in methanol, no oxidation was observed, even after refluxing the solution for 24 h. Selective and efficient oxidation of **18** occurs at room temperature when aqueous H_2O_2 in hexafluoro-2-propanol (HFIP) is used (Scheme 25).[19]



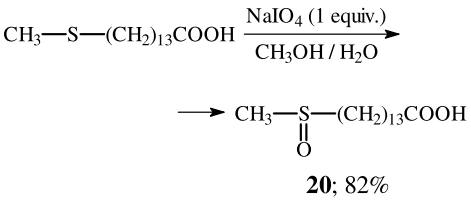
Scheme 25.

Pées et al.[140] reported the application of $NaIO_4$ for the oxidation of fluoroalkylsulfenyl acrylates. The reaction is instantaneous at 0 °C in methanol, giving the corresponding sulfoxides **19a**,**b**, which may be applied for synthesis of water- and oil-repellent polymers used in textile treatments (Scheme 26).



Scheme 26.

Oxidation of methylthioalkanoic acids, potentially active as cardiac inotropic and antifungal agents, with $NaIO_4$ (1 equiv) gives the corresponding methylsulfinylalkanoic acids in good yields.[141] The reaction of 14-methylthiotetradecanoic acid afforded the corresponding 14-methylsulfinyltetradecanoic acid (**20**), as illustrated in Scheme 27.



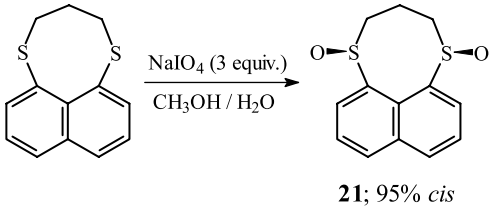
Scheme 27.

Spaltenstein et al.[142] oxidized sulfur-bridged peptides to the corresponding sulfoxides using sodium periodate in methanol–water mixtures. These sulfoxides were evaluated as potential HIV protease inhibitors and were found to be inactive within the limits of the assay.

Methylthiodeoxyuridine, which belongs to a group of compounds with antiviral properties, was oxidized with 1 equiv of $NaIO_4$ at 0 °C for 4 h to afford the sulfoxide in 66% yield. The product, however, appears to be inactive as an antiviral agent.[143]

Chadha et al.[144] investigated the application of alkyl and cyclic sulfoxides as inhibitors of alcohol dehydrogenase and ethanol metabolism in the liver. The target sulfoxides were obtained by oxidation with aqueous sodium periodate solution. Of the sulfoxides tested, the cyclic derivatives turned out to be better inhibitors than the non-cyclic compounds.

Acyclic dithioethers, such as 2,5-dithiahexane, 2,6-dithiaheptane, and 2,7-dithiaoctane, were oxidized with $NaIO_4$ in methanol–water mixtures at room temperature to give the corresponding mono-oxides in 42, 32, and 40% yields,



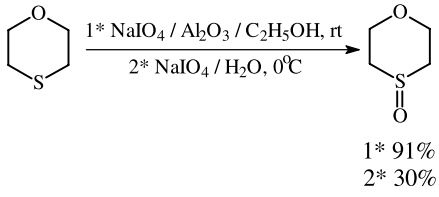
Scheme 28.

respectively.[145] Oxidation of 2-methyl-, 2-phenyl-, and 2-*tert*-butyl-1,3-dithianes with $NaIO_4$ at low temperature gave the *trans*-1-sulfoxides exclusively.[56,146] Oxidation of naphtho[1,8-*b*,*c*]-1,5-dithiocin, using an excess of $NaIO_4$ at room temperature, results in 95% yield of the *cis*-1,5-disulfoxide (**21**) (Scheme 28).[147,148]

Attempts to isomerize the *cis*-disulfoxide **21** to the *trans*-isomer were, however, unsuccessful. The disulfoxide **21** underwent no change in methanol saturated with HCl, whilst, with trimethyloxonium tetrafluoroborate, it produced a monosulfone, which, upon treatment with sodium periodate in aqueous methanol, afforded a sulfoxide–sulfone in quantitative yield.[23,149]

An alternative to the use of water, or water-alcoholic solutions of $NaIO_4$, is the use of $NaIO_4$ supported on inert inorganic materials. Solid oxidants based on silica gel, acidic alumina and other porous materials are an important class of supported reagents used for the selective oxidation of sulfides.[150]

Sodium periodate supported on acidic alumina was found to be a useful reagent for the oxidation of thiomorpholine to the sulfoxide in ethanol.[151,152] It should be noted, however, that the oxidation of thiomorpholine in water by $NaIO_4$ alone afforded the sulfoxide in only 30% yield (Scheme 29).[144]



Scheme 29.

Under microwave conditions, a variety of symmetrical and unsymmetrical sulfides have been oxidized selectively to the sulfoxides using sodium periodate supported on wet silica.[153,154] The optimal ratio of the sulfide to periodate for the complete conversion of sulfides into sulfoxides is 1:1.7 (Table 21), an excess of periodate affording the corresponding sulfones.

Blaskó et al.[155] investigated the effect of anionic micelles of sodium dodecyl sulfate on the periodate oxidation of dipropyl, dibutyl and methyl 4-methoxyphenyl sulfides.

Table 21. Yields of sulfoxides R^1-SO-R^2 obtained using an $NaIO_4$–wet silica system (1.7 equiv) under microwave conditions[153]

R^1	R^2	Yield [%]
n-C_4H_9	n-C_4H_9	76
$C_{12}H_{25}$	CH_3	80
C_6H_5	CH_3	80
C_6H_5	C_6H_5	85
$C_6H_5CH_2$	C_6H_5	83
$C_6H_5CH_2$	$C_6H_5CH_2$	80
$(CH_2)_4$		82

They found that this surfactant inhibits the oxidation reaction, because of the low solubility of the periodate ions in the micellar interior.

Hsieh-Wilson et al.[156] reported that the antibody 28B4 catalyzed the periodate-dependent oxidation of nitrobenzyl methyl sulfide to the corresponding sulfoxide. This reaction was initially examined to extend the antibody catalysis.[157,158] On the basis of kinetic studies, a mechanism for the oxidation was proposed. The transition state (TS) in the periodate-dependent oxygenation of sulfides can occur either via sulfur attack on the periodate oxygen (TS1), or by initial addition to the iodine center (TS2), followed by the oxygen transfer (Fig. 2).[159,160] The antibody active sites stabilized the developing charge on both the sulfur and the periodate ion in the transition state.

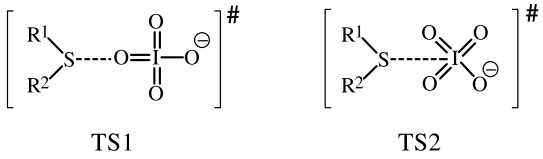


Figure 2.

From among the periodates, tetrabutylammonium periodate (TBAPI) was also found to be an efficient reagent for the selective oxidation of sulfides. The water-insoluble TBAPI is useful for homogeneous oxidations in non-aqueous solvents, due to its good solubility in common organic solvents and its insolubility in water.[5,7,161] Treatment of sulfides with TBAPI in refluxing chloroform provides the sulfoxides selectively and in good yields. An advantage of this method is that the sulfoxides are easily purified from the unreacted TBAPI by simple filtration through a column filled with silica gel. Using this reagent, the oxidation is complete in 2 h for tetrahydrothiophene and in 8 h for diphenyl sulfide (Table 22).[161]

Table 22. Oxidation of sulfides to sulfoxides R^1-SO-R^2 using 1 equiv of TBAPI in $CHCl_3$[161]

R^1	R^2	Yield [%]
p-$CH_3C_6H_4$	CH_3	86
p-$CH_3C_6H_4$	n-C_4H_9	85
p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	70
C_6H_5	C_6H_5	72
$(CH_2)_4$		90

Venkatachalapathy et al.[162] demonstrated the application of clays as supports for TBAPI in the periodate oxidation of sulfides to sulfoxides (Table 23). This reagent is much more efficient and faster when compared to the corresponding oxidation by the unsupported periodates[159] or a TBAPI/$AlCl_3$ mixture.[163]

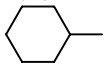
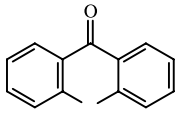
Table 23. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with clay-supported TBAPI[162]

R^1	R^2	Yield [%]
C_6H_5	CH_3	98
C_6H_5	C_2H_5	98
C_6H_5	n-C_3H_7	96
C_6H_5	i-C_3H_7	95
C_6H_5	n-C_4H_9	89
p-$CH_3C_6H_4$	CH_3	85 (52[a])
p-$(CH_3O)C_6H_4$	CH_3	94 (51[a])
p-$(COOH)C_6H_4$	CH_3	79

[a] Absence of clay.

Firouzabadi et al. investigated the oxidation of various sulfides with TBAPI in the presence of Lewis acids, such as $AlCl_3$, in refluxing acetonitrile and found that, under these conditions the sulfoxides were formed without over-oxidation (Table 24). It was also found that $BF_3\cdot(C_2H_5)_2O$ was ineffective.[163]

Table 24. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with TBAPI/$AlCl_3$ in refluxing acetonitrile[163]

R^1	R^2	Yield [%]
C_6H_5	CH_3	70
$C_6H_5CH_2$	n-C_4H_9	75
$C_6H_5CH_2$	$C_6H_5CH_2$	75
$C_6H_5CH_2$	C_6H_5	75
p-$(NO_2)C_6H_4$	C_6H_5	60
$C_6H_5CH_2$		73
		65

Kim et al.[164] applied periodic acid hydrate (H_5IO_6) in the presence of $FeCl_3$ as a mild and highly efficient oxidant system for the oxidation of sulfides to sulfoxides in CH_3CN. Under these conditions, the oxidation of p-bromothioanisole, for example, gives the corresponding sulfoxide in 99% yield within 1.5 min, while the oxidation without $FeCl_3$ takes 17 min to afford the same yield. $FeCl_3$ therefore catalyzes the oxidation with H_5IO_6 in a CH_3CN medium and

Table 25. Oxidation of sulfides to sulfoxides R^1-SO-R^2 using H_5IO_6 (1.1 mmol) in the presence of $FeCl_3$ (0.03 mmol) in CH_3CN[164]

R^1	R^2	Yield [%]
n-C_3H_7	n-C_3H_7	99
n-C_4H_9	n-C_4H_9	99
C_6H_5	CH_3	99
C_6H_5	C_2H_5	99
C_6H_5	C_6H_5	96
$C_6H_5CH_2$	CH_3	99
$C_6H_5CH_2$	C_6H_5	99
$C_6H_5CH_2$	$C_6H_5CH_2$	99
p-$CH_3C_6H_4$	CH_3	99
p-BrC_6H_4	CH_3	99
p-$(CN)C_6H_4$	CH_3	97
p-$(NO_2)C_6H_4$	CH_3	96
$(CH_2)_2O(CH_2)_2$		64

the optimum quantity of $FeCl_3$ was found to be about 3 mol% (Table 25).

7. Oxidation of sulfides with halogenated derivatives

7.1. *N*-Haloamides

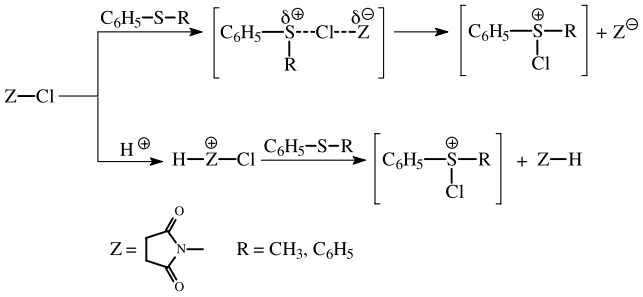
The scope and limitations of the use of *N*-halogenated amides for the oxidation of sulfides to sulfoxides, including *N*-bromocaprolactam, *N*-chloronylon-6,6, chloramines, bromamines, *N*-halosuccinimides, etc. have been reviewed earlier.[2,4,5,7]

The kinetics and mechanism of the oxidation of sulfides with *N*-bromoacetamide (NBA) in the presence of Hg(II) salts suggest that both NBA and the sulfide form complexes with Hg(II) ions and that these complexes participate in the rate-determining step, the formation of a halosulfonium cation, which hydrolyses to the sulfoxides.[165] The formation of a halosulfonium cation is also the rate-determining step in the oxidation of sulfides with *N*-chloroacetamide (NCA),[166] although in the oxidation with *N*-chloroamides the addition of Hg(II) is not necessary.[167]

Chowdhury et al.[168] studied the kinetics of the oxidation of sulfides with *N*-bromobenzamide (NBB) in acetic acid–water in the presence of perchloric acid and postulated that protonated NBB is the reactive species. The oxidation with NBB does not require the presence of Hg(II) as a bromine scavenger, in contrast to the NBA-mediated oxidation of sulfides.

Harville et al.[169] found that the treatment of aliphatic and aromatic sulfides with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) in a large volume of anhydrous methanol gave the corresponding sulfoxides in 62–93% yields. In all instances, an incremental addition of the *N*-halosuccinimides to the solution of the sulfide was preferred, in order to minimize the sulfone formation. Dialkyl and alkyl aryl sulfides oxidized with NBS in aqueous media undergo C–S bond cleavage, but aromatic sulfides are oxidized cleanly to the sulfoxides under the same reaction conditions. Oxidation of tetrahydrothiopyran-4-ones with NBS in a tetrahydrofuran–methanol–water solution affords the corresponding sulfoxides in 80–88% yields.[170]

A kinetic study of the oxidation of aryl methyl and diaryl sulfides with NCS in a mixed acetonitrile–water solvent containing 0.001 M perchloric acid has indicated that NCS and its protonated form are the oxidizing species (Scheme 30). Kinetic measurements of arylmercaptoacetic acids, however, show that, in this case, only NCS appears to be the active species.[171]

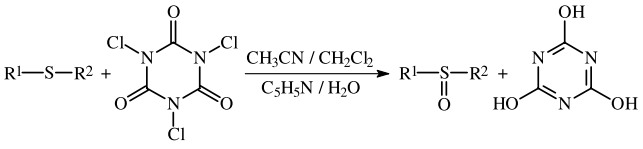


Scheme 30.

Trichloroisocyanuric acid was reported by Xiong et al. to be a selective and convenient oxidant of aryl methyl and diaryl sulfides to the sulfoxides (Scheme 31).[172] Table 26 shows the results of their oxidation of sulfides with trichloroisocyanuric acid in an acetonitrile–dichloromethane–pyridine mixture. Traces of water in the reaction mixture affected the rate of oxidation, excessive water reduced the rate, whilst anhydrous conditions made the reaction slow.

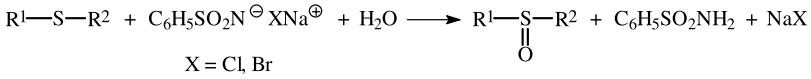
Table 26. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with trichloroisocyanuric acid[172]

R^1	R^2	Yield [%]
C_6H_5	CH_3	85
p-$CH_3C_6H_4$	CH_3	89
p-ClC_6H_4	CH_3	84
C_6H_5	C_6H_5	85
$C_6H_5CH_2$	$C_6H_5CH_2$	90
p-$(NO_2)C_6H_4$	C_6H_5	91



Scheme 31.

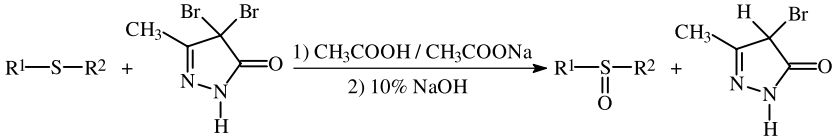
The Os(VIII)-catalyzed oxidation of sulfides in an alkaline medium with the sodium salt of *N*-chlorobenzenesulfonamide (chloramine-B)[173] and *N*-bromobenzenesulfonamide (bromamine-B)[174] was reported by Meenakshisundaram et al. (Scheme 32). It was found that the amount of sulfoxide formed in the oxidation with chloramine-B corresponds to the amount of chloramine-B consumed, which confirmed that the sulfides react with the oxidant in a 1:1 molar ratio. In this reaction, the reactivity of the dialkyl sulfides decreases in the order: $(C_2H_5)_2S > (CH_3)_2S > (i\text{-}C_3H_7)_2S > (n\text{-}C_4H_9)_2S > (t\text{-}C_4H_9)_2S$. Structure-reactivity relationships employing some *ortho*-, *meta*-, and *para*-substituted aryl methyl sulfides reveal that electron-releasing groups increase the sulfide reactivity, while electron-withdrawing substituents inhibit the oxidation rate.[173]



Scheme 32.

7.2. Other halo-derivatives

The application of *N*-chlorobenzotriazole and *N*-bromoamines to the sulfoxidation of sulfides has been reviewed previously.[2,4,5,7]



Scheme 33.

Table 27. Oxidation of sulfides to sulfoxides R^1-SO-R^2 with 4,4-dibromo-3-methylpyrazol-5-one[175]

R^1	R^2	Yield [%]
$C_6H_5CH_2$	CH_3	89
$C_6H_5CH_2$	C_6H_5	79
$C_6H_5CH_2$	$C_6H_5CH_2$	92
$C_6H_5CH_2$	$CH_2COOC_2H_5$	84

Recently, Mashraqui et al.[175] have reported that 4,4-dibromo-3-methylpyrazol-5-one in acetic acid is able to oxidize selectively sulfides to the sulfoxides in 79–92% yield (Scheme 33 and Table 27). 4,4-Dibromo-3-methylpyrazol-5-one, a stable crystalline solid, appears to be an electrophilic bromine carrier in acidic solutions, which reacts with sulfides to give the expected sulfoxides without contamination from the sulfones.

Russian researchers[176–179] have reported the oxidation of sulfides to the sulfoxides using chlorine dioxide. Kutchin et al.[179] found that gaseous ClO_2, as well as its aqueous solutions, can be used for the efficient oxidation of sulfides to the sulfoxides, with slight over-oxidation to the sulfones (2–3%) (Table 28). In their tested oxidation of dioctyl sulfide in an organic solvent with a 1:0.5 molar ratio of sulfide to ClO_2, the yields of sulfoxide were solvent dependent and varied in the range from 60% in acetone or diethyl ether to 80% in carbon tetrachloride and 90% in dichloromethane.[177] The oxidation of dimethyl, dipropyl and di-isobutyl sulfides in dichloromethane, carbon tetrachloride and ethyl acetate also gave satisfactory results in terms of the sulfoxide yields (90–95%) and purity.[178]

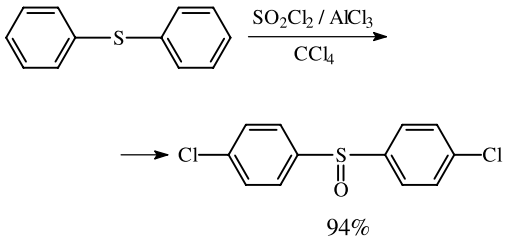
Table 28. Oxidation of sulfides to sulfoxides R^1-SO-R^2 using ClO_2 (0.5 equiv) at room temperature[179]

R^1	R^2	Yield [%]	
		A	B
n-C_3H_7	*n*-C_3H_7	93	95
i-C_4H_9	*i*-C_4H_9	88	95
n-C_8H_{17}	*n*-C_8H_{17}	89	92
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	—	94
p-BrC_6H_4	*p*-BrC_6H_4	97	98

(A) Gaseous ClO_2; (B) water solution of ClO_2.

Sulfuryl chloride oxidizes sulfides to the sulfoxides at low temperatures, but the oxidation takes place at ambient temperature in the presence of wet silica gel in dichloromethane.[4,5,7]

Savin et al.[180] reported a method for preparing 4,4-dichlorodiphenyl sulfoxide by the simultaneous chlorination and oxidation of diphenyl sulfide with sulfuryl chloride. This procedure involves the use of an SO_2Cl_2 solution in carbon tetrachloride in the presence of aluminium chloride at 0–5 °C (Scheme 34). The target 4,4-dichlorodiphenyl sulfoxide is used in the manufacture of sulfur-containing polymers.



Scheme 34.

8. Conclusions

This paper has reviewed the achievements in the halogen-mediated oxidation of sulfides to sulfoxides in the last 20 years. It is evident that tremendous progress has been made within this period of time. The environmental and economic significance of the oxidation of sulfides to the corresponding sulfoxides continues to inspire the research and development of novel, environmentally safe and efficient oxidation systems. Essentially, improvements have been made in the development of solvent-free and catalytic oxidation systems.

Sodium bromate combined with $Mg(HSO_4)_2$, iodosobenzene supported on dry clays, or alumina-supported phenyliodine(III) diacetate are especially recommended reagents for an efficient solvent-free oxidation of sulfides to sulfoxides. Periodic acid hydrate in the presence of $FeCl_3$ (which oxidizes dialkyl, alkyl aryl and diaryl sulfides to the sulfoxides almost quantitatively within 1.5 min), and calcium hypochlorite in the presence of moist alumina in dichloromethane (which tolerates various functional groups, such as carbonyl in aldehydes and ketones, nitriles, halides, ethers, hydroxyls, and olefinic and allylic double bonds, etc.), are the next recommended oxidizing agents.

Currently, in the catalytic sulfoxidation of sulfides, hypervalent iodine(III) and iodine(V) reagents activated with anhydrides and acids, metalloporphyrin and metallosalen complexes, cationic surfactants, and potassium bromide have been successfully used. These systems in the presence of chiral catalysts permitted an enantioselective oxidation of sulfides to the sulfoxides, but in

many cases with a mild enantioselectivity. The best chemical and optical yields are afforded by iodoxybenzene in the presence of di-(2-methoxybenzoyl)-L-tartaric acid and cetyltrimethylammonium bromide (CTAB) in toluene–H_2O mixtures.

The biggest disadvantage of the utilization of halogen-mediated systems in the oxidation of sulfides is the formation of byproducts such as sulfonic or sulfinic acids, and halogen-substituted sulfides and sulfones. The low price, ease of handling, commercial availability, and the relatively high stability of these oxidants, as well as the simple oxidation reaction procedures, however, ensure that the halogen oxidations of sulfides to the sulfoxides are still widely applied on a laboratory and industrial scale.

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Biographical sketch

Piotr Kowalski is a Professor at the Department of Chemistry of Cracow University of Technology in Kraków (Poland). He also works as a research consultant in synthesis and analysis of drugs at PLIVA *Kraków* Pharmaceutical Company. He received his Ph.D. in organic chemistry from Cracow University of Technology in 1977. His doctoral thesis was completed under the supervision of Professor W. Czuba. He received a habilitation degree for studies of electrophilic substitution reactions of 2-aminopyridines from A. Mickiewicz University, Poznań (Poland) in 1995. His research interests concentrate on azaheterocyclic compounds chemistry and medicinal chemistry, but his recent projects of PLIVA provided the motivation to write this review.

Katarzyna Ossowska was born in 1978 in Cracow, Poland. She received her M.S. degree in organic chemistry from Cracow University of Technology in 2002. Thereafter she joined the Synthesis Laboratory at PLIVA *Kraków* Pharmaceutical Company. Her research interest is focused on synthesis of drugs.

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Complanadine B, obscurumines A and B, new alkaloids from two species of *Lycopodium*

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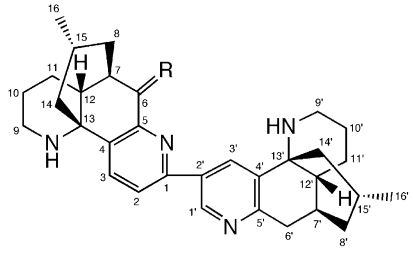
Abstract—A new dimer of $C_{16}N_2$ type alkaloid, complanadine B (**1**), and two new $C_{16}N$ type alkaloids, obscurumines A (**2**) and B (**3**), have been isolated from the club moss *Lycopodium complanatum* and *L. obscurum*, respectively. The structures and stereochemistry of **1**–**3** were elucidated by combination of 2D NMR spectra and chemical transformation. Complanadine A (**4**) isolated together with **1** induced secretion of neurotrophic factors from human astrocytoma cells.

1. Introduction

The *Lycopodium* alkaloids represent a large family of plant constituents obtained from the club moss belonging to Lycopodiaceae.[1] These structurally diverse alkaloids often possess unusual skeletons, and many of them continue to be of interest from biogenetic[2] and biological points of view[3] as well as providing challenging targets for total synthesis.[4] In recent ten years, much efforts have been devoted to preparation of structurally simplified analogues and derivatives with the tricyclic skeleton of huperzine A as a promising lead compound of acetylcholinesterase inhibitors.[5]

Recently, we have isolated some new types of alkaloids from extracts of the genus *Lycopodium* collected in Japan,[6–14] and biomimetic transformation through a modified Polonovski reaction has been examined.[15] With an aim to isolate structurally interesting alkaloids and key intermediates to clarify the biogenetic pathway, purification of extracts of *Lycopodium complanatum* and *L. obscurum* (Lycopodiaceae) led to isolate three new alkaloids, complanadine B (**1**) from *L. complanatum*, and obscurumines A (**2**) and B (**3**) from *L. obscurum*. This paper describes the isolation and structure elucidation of **1**–**3** and releasing activity of neurotrophic factors from human astrocytoma cells by complanadine A (**4**).



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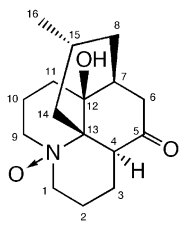
4: R=H_2



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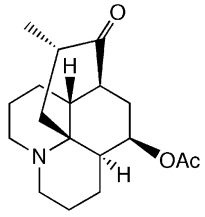

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The club moss of *L. complanatum* was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 10 with sat. Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an LH-20 column ($CHCl_3$/MeOH, 1:1) followed by an amino silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give complanadine B (**1**, 0.0002%) together with known alkaloids, complanadine A (**4**)[7] and lycopodine.[16]

Keywords: *Lycopodium*; Alkaloid; Dimer; Neurotrophic factors; Astrocytoma cells.
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The club moss of *L. obscurum* was extracted by the same procedure as described above, and $CHCl_3$ soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 1:0→0:1, and then $CHCl_3$/MeOH, 1:0→0:1). The fraction eluted with hexane/EtOAc (4:1) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give obscurumine B (**3**, 0.0006%) together with known alkaloids, lobscurinol,[16] des-*N*-methyl-β-obscurine,[16] and lycofawcine.[17] The fraction eluted with hexane/EtOAc (7:3) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) followed by C_{18} HPLC (20% CH_3CN/0.1% TFA) to give obscurumine A (**2**, 0.0001%).

Complanadine B {**1**, $[\alpha]_D^{23}$ −13° (*c* 0.5, MeOH)} showed the pseudomolecular ion peak at *m/z* 497 $(M+H)^+$ in the FABMS, and the molecular formula, $C_{32}H_{40}N_4O$, was established by HRFABMS (*m/z* 497.3259, $[M+H]^+$, Δ −2.1 mmu). IR absorptions implied the presence of amine and conjugated ketone (3322 and 1697 cm^{-1}, respectively) functionalities. ^{13}C NMR data (Table 1) revealed 32 carbon signals due to one carbonyl carbon, six sp^2 quaternary carbon, four sp^2 methines, two sp^3 quaternary carbons, six sp^3 methines, eleven sp^3 methylenes, and two methyl groups. Among them, four olefinic carbons [δ_c 146.02 (d), 150.51 (s), 155.00 (s), and 160.94 (s)] assignable to nitrogen-bearing carbons were elucidated to form two trisubstituted pyridine rings together with the remaining six olefinic carbons [δ_c 126.59 (d), 133.76 (s), 133.84 (d), 138.00 (s), 138.33 (d), and 143.63 (s)], while two quaternary carbons (δ_c 58.02 and 58.22) and two methylenes (δ_c 42.00; δ_H 2.48 and 2.82, and δ_c 42.13; δ_H 2.50 and 2.79) were ascribed to those attached to a nitrogen (Table 1). Since seven out of fifteen unsaturations were accounted for, **1** was inferred to possess eight rings. The gross structure of **1** was elucidated by analyses of 2D NMR data including ^1H-^1H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Fig. 1). Each pair of these ^1H and ^{13}C NMR signals (Table 1) seemed to be due to each half moiety (parts A and B) of a dimeric compound. In part A, connectivities of C-2 to C-3, C-7–C-8, C-9–C-12, C-14–C-16, C-7 to C-12, and C-8 to C-15 were revealed by the ^1H-^1H COSY and HOHAHA spectra. The presence of a 2, 3, 6-trisubstituted pyridine ring was elucidated from HMBC correlations of H-3 (δ_H 8.26) to C-1 and C-5, and H-2 (δ_H 8.31) to C-4. HMBC correlations of H-8 and H-12 to C-6 (δ_C 202.49) suggested the presence of a ketone at C-6 connected to C-7. The presence of a piperidine ring (N-9 and C-9–C-13) was deduced from the HMBC correlation of H-9 to C-13 (δ_c 58.22) through a nitrogen atom. HMBC cross-peaks of H-12 to C-4, and H_2-14 to C-13 and C-4 revealed connectivities from C-12 to C-4 and from C-14 to C-4 through C-13, constructing a lycodine-type ring system (part A). On the other hand, the corresponding ^1H-^1H COSY, HOHAHA, and HMBC correlations were also observed for part B (Fig. 1). HMBC correlations of H-1′ to C-2′, C-3′, and C-5′, and H-3′ to C-1′ and C-5′ indicated the existence of a 2, 3, 5-trisubstituted pyridine ring, constructing another lycodine-type ring system (part B).

Table 1. ^1H (δ_H) and ^{13}C NMR Data (δ_C) of Complanadine B (**1**) in CD_3OD at 300 K

	δ_H [int. mult, *J* (Hz)]	δ_C	HMBC (^1H)
1		155.00	**3**, **3′**
2	8.31 (1H, d, 8.3)	126.59	
3	8.26 (1H, d, 8.3)	138.33	
4		143.63	**2**, **12**, **14a**
5		150.51	**3**
6		202.49	**8a**, **12**
7	2.82 (1H, m)	52.70	
8a	1.61 (1H, dt, 3.9, 13.0)	39.71	**16**
8b	1.93 (1H, brd, 13.4)		
9a	2.48 (1H, dt, 2.7, 12.5)	42.00	
9b	2.82 (1H, t, 14.3)		
10	1.68 (2H, m)	27.30	**9a**, **9b**
11a	1.22 (1H, m)	27.10	**9a**, **9b**
11b	1.60 (1H, m)		
12	2.04 (1H, brd, 12.3)	48.10	**8b**
13		58.22	**9b**, **14a**
14a	1.52 (1H, t, 12.3)	48.96	**16**
14b	1.70 (1H, 1H, m)		
15	1.31 (1H, m)	27.56	**14a**, **16**
16	0.87 (3H, d, 6.4)	22.12	
1′	9.07 (1H, d, 2.1)	146.02	**3′**
2′		133.76	**1′**
3′	8.81 (1H, d, 2.1)	133.84	**1′**
4′		138.00	**14′a**
5′		160.94	**1′**, **3′**, **6′a**, **6′b**
6′a	2.74 (1H, m)	35.75	**8′a**
6′b	3.22 (1H, dd, 6.9, 19.0)		
7′	2.18 (1H, m)	34.71	**12′**
8′a	1.43 (1H, dt, 3.9, 13.0)	44.73	**6′b**, **16′**
8′b	1.83 (1H, brd, 13.4)		
9′a	2.50 (1H, dt, 2.7, 12.5)	42.13	
9′b	2.79 (1H, t, 14.3)		
10′	1.68 (2H, m)	27.30	**9′a**, **9′b**
11′a	1.20 (1H, m)	27.30	**9′a**, **9′b**
11′b	1.60 (1H, m)		
12′	1.79 (1H, 12.6)	44.23	**6′b**, **8′b**
13′		58.02	**9′b**, **14′a**
14′a	1.39 (1H, t, 12.2)	51.61	**8′b**, **16′**
14′b	1.59 (1H, m)		
15′	1.20 (1H, m)	27.00	**14b′**, **16′**
16′	0.82 (3H, d, 6.4)	22.37	

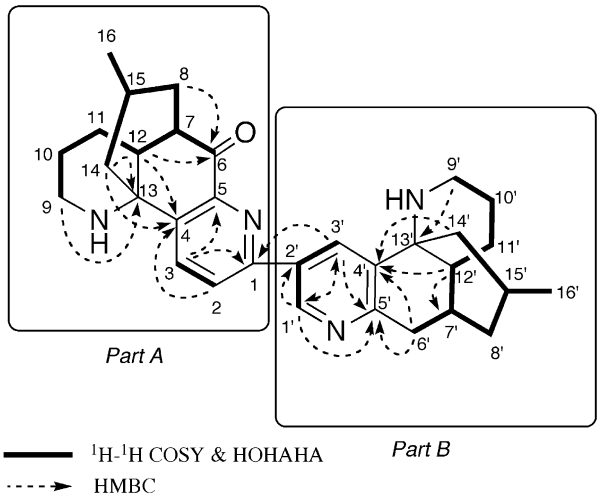

Figure 1. Selected 2D NMR correlations for complanadine B (**1**).

The connection between each pyridine ring in parts A and B was provided by the HMBC correlation of H-3′ (δ_H 8.81) to C-1 (δ_c 155.00), thus giving rise to the connectivity of C-1 to C-2′. NOESY correlations of H-2/H-3′ and H-2/H-1′ (Fig. 2) also supported the connectivity between parts A and B. Thus, the gross structure of complanadine B (**1**) was assigned as a new alkaloid consisting of lycodine and

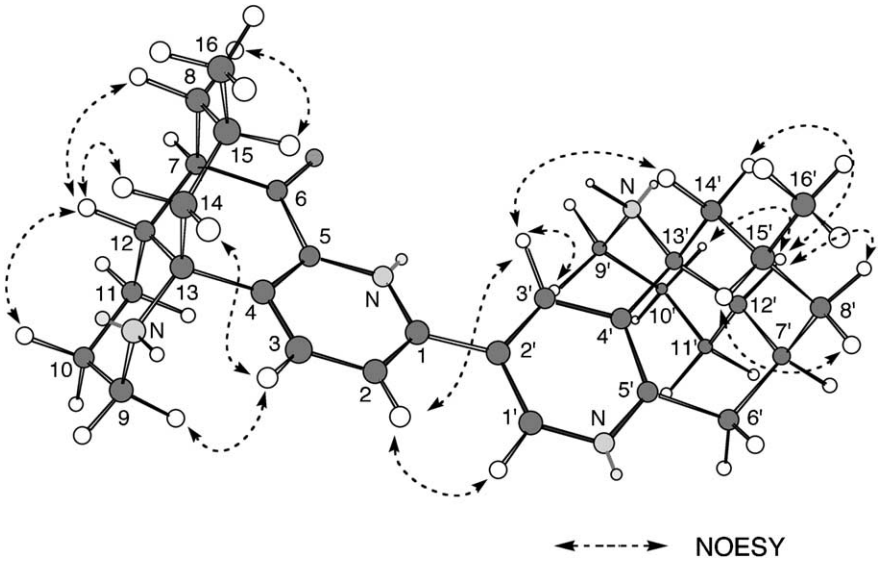

Figure 2. Selected NOESY correlations and relative stereochemistry for complanadine B (**1**).

6-oxolycodine units, in which C-1 in 6-oxolycodine was connected to C-2′ in lycodine.[18]

The phase sensitive NOESY spectrum of **1** showed cross-peaks as shown in computer-generated 3D drawing (Fig. 2). The relative configurations at C-7, C-12, C-13, and C-15 in part A were based on NOESY correlations of H-12/H_b-10, H-3/H_b-14, H_a-8/H-15, and H_b-8/H-12, while the piperidine and cyclohexane (C-7, C-8, and C-12–C-15) rings adopted both chair conformations. On the other hand, a NOESY correlation of H′-15/H'_a-8 was also observed in addition of the corresponding NOESY correlations for part B. Thus, the relative stereostructure of complanadine B (**1**) was assigned as shown in Figure 2. The CD spectrum [λ_{max} 230 (θ-9200), 260 (4000), 290 (3300), 315 (2300), and 350 (−2000) nm] of **1** in MeOH was similar to those [complanadine A (**4**): λ_{max} 260 (θ 4500), 285 (1500), 295 (2000), and 315 (3000) nm; lycodine: λ_{max} 250 (θ 5000), 280 (3000), and 325 (3000) nm] of complanadine A (**4**) and lycodine except for a negative CD curve at 350 nm.[7] According to the anti-octant sector rule[19] applied to aromatic conjugated ketones, absolute configurations of the 6-oxolycodine part were assigned as 7*R*, 12*R*, 13*R*, and 15*R*.

HRFABMS data (*m/z* 280.1918, $[M+H]^+$, Δ +0.6 mmu) of obscurumine A (**2**) indicated the molecular formula, $C_{16}H_{25}NO_3$. IR absorptions implied the presence of hydroxy (3330 cm^{-1}) and ketone (1670 cm^{-1}) functionalities. The ^{13}C NMR (Table 3) spectrum of **2** revealed signals due to three quaternary carbons ($sp^2\times1$ and $sp^3\times2$), three methines (sp^3), nine methylenes, and one methyl, implying that the structure of **2** was similar to that of lycodoline.[19] The molecular formula was larger than that of lycodoline by one oxygen unit. Detailed analyses of 2D NMR (^1H–^1H COSY, HOHAHA, HMQC, and HMBC) spectra of **2** and comparison of the ^{13}C chemical shifts of C-1, C-9, and C-13 (δ 64.3, 60.8, and 73.1, respectively) in **2** with those (δ 47.8, 47.9, and 67.8, respectively) of lycodoline indicated the presence of an N-oxide functionality for **2**. Oxidation of lycodoline with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the N-oxide derivative, whose spectral data and the $[\alpha]_D$ value were identical with those of natural obscurumine A (**2**). Thus, obscurumine A (**2**) was concluded to be the N-oxide of lycodoline.[20]

HRESIMS data [*m/z* 306.2073, $(M+H)^+$, Δ +0.4 mmu] of obscurumine B (**3**) revealed the molecular formula, $C_{18}H_{27}NO_3$. IR absorptions implied the presence of ketone (1705 and 1738 cm^{-1}) functionalities. The ^{13}C NMR (Table 3) spectra of **3** gave signals including three quaternary carbons ($sp^2\times2$ and $sp^3\times1$), five sp^3 methines, eight methylenes, and two methyls, suggesting that **3** had a similar backbone skeleton to that of fawcettiine.[21] In the ^{13}C NMR spectrum of **3** appeared signals due to the oxygen bearing carbon at δ_C 71.54 (d) and two ketone carbonyl carbons at δ_C 169.57 and 217.03. The gross structure of **3** was elucidated by 2D NMR (^1H-^1H COSY, HOHAHA, HMQC, and HMBC) data (Fig. 3). The ^1H-^1H COSY and HOHAHA spectra revealed connectivities of C-1 to C-7, C-9 to C-12, C-7 to C-12, and C-14 to C-16. These partial units were connected to each other through C-8 and C-13 on the basis of HMBC correlations of H-15 to C-7 and C-8, H-4 and H-14 to C-12, and H-4, H-9, and H-14 to C-13. The connection of C-1 to C-9 through a nitrogen was indicated by the HMBC correlation of H-1 to C-9. Thus, obscurumine B (**3**) was elucidated to be 8-dehydro form of fawcettiine.[21]

The relative stereochemistry of **3** was deduced from cross-peaks observed in the phase sensitive NOESY spectrum as shown in computer-generated 3D drawing (Fig. 3). Chair conformations of a cyclohexane ring (C-4–C-7 and C-12–C-13) and two piperidine rings (N-1, C-1–C-4, and C-13, and N-1, C-9–C-13) were suggested by NOESY correlations as shown in Figure 3. NOESY correlations of H_3-16 to H-12 indicated a boat conformation of cyclohexanone ring (C-7–C-8 and C-12–C-15). Thus, the relative stereo-structure of obscurumine B (**3**) was assigned as shown in Figure 3.

There are a few reports on natural products with two pyridine rings connected between α and β positions such as α, β-dipyridyl[22] and nicotelline,[23] which are minor alkaloids

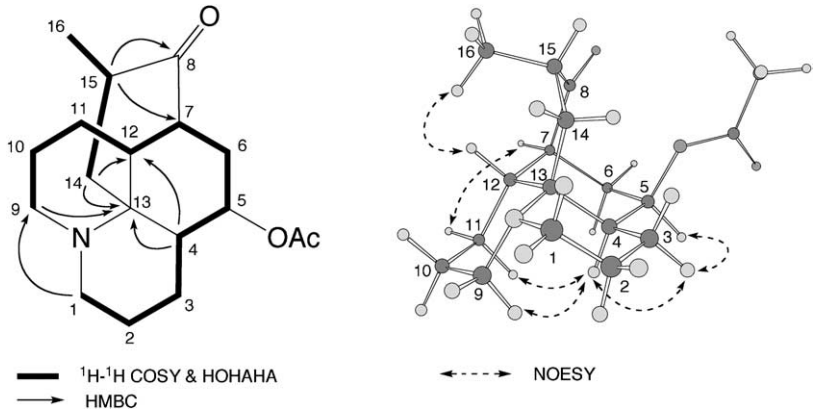

Figure 3. Selected 2D NMR correlations and relative stereochemistry for obscurumine B (**3**).

found in various *Nicotiana* species. Biogenetically, complanadines A (**4**) and B (**1**) may be produced through coupling of two 2,5-dihydropyridine rings like biosynthesis of α, β-dipyridyl.[24]

Human astrocytoma cells (glial cell line) were incubated for 2 days with complanadine A (**4**), and then rat pheochromocytoma (PC-12) cells were cultivated for 2 days in the conditioned 1321N1 culture medium. The culture medium has been shown to contain neurotrophic factors synthesized in 1321N1 cells, which promote the differentiation of PC-12 cells. The culture medium conditioned with 1–10 μM complanadine A (**4**) and 100 nM phorbol 12-myristate 13-acetate (PMA), which is an activator of neurotrophic factor biosynthesis, dose-dependently induced neurite extension in PC-12 cells (Fig. 4). These results indicate that complanadine A (**4**) induced secretion of neurotrophic factors from 1321N1 cells and the released neurotrophic factors promote neuronal differentiation of PC-12 cells.[25] Neurite outgrowth could not be evaluated for complanadine B (**1**) because of small amount of **1**. However, effect of **1** on neurotrophic factor biosynthesis in 1321N1 human astrocytoma cells was examined by a semiquantitative RT-PCR method,[25] in which enhancement of the mRNA expression for NGF was observed.

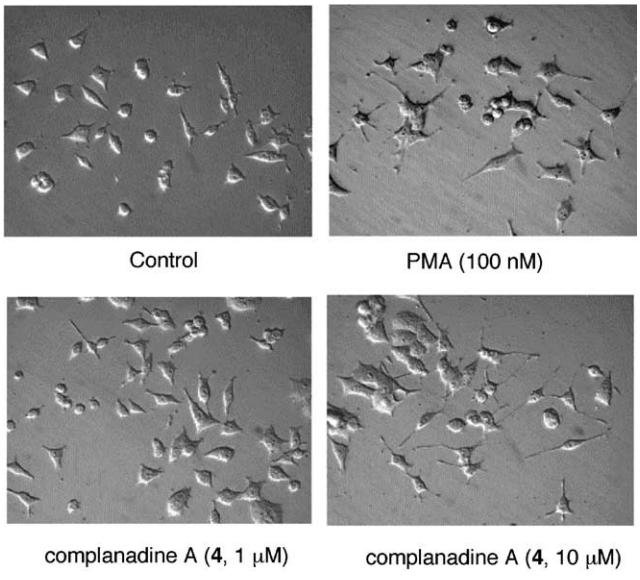

Figure 4. Glial cell-mediated morphological change of PC-12 cells by complanadine A (**4**).

2. Experimental

2.1. General experimental procedures

Optical rotations were measured on a JASCO P-1030 polarimeter. UV spectra were recorded on a Shimadzu UV1600PC spectrophotometer and IR spectra on a Jasco FTIR-230 spectrometer. ^{1}H and 2D NMR spectra were recorded on a 600 MHz spectrometer at 300 K, while ^{13}C NMR spectra were measured on a 150 MHz spectrometer. Each NMR sample of complanadine B (**1**) and obscurumine A (**2**) was prepared by dissolving 1.0 mg in 30 μL of CD_3OD and obscurumine B (**3**) dissolving 1.0 mg in 30 μL of $CDCl_3$ in 2.5 mm micro cells (Shigemi Co. Ltd, Tokyo, Japan). Chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) and $CDCl_3$ (δ_H 7.26 and δ_C 77.0) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. ^{1}H-^{1}H COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 t_1 increments. NOESY and HOHAHA spectra in the phase-sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. For HMQC spectra in the phase-sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with the *Z*-axis PFG, a 50 ms delay time was used for long-range C-H coupling. Zero-filling to 1 K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. FABMS were measured on a JEOL JMS-HX110 by using glycerol as the matrix.

2.1.1. Plant material. The club moss *Lycopodium complanatum* and *L. obscurum* were collected in Hokkaido in 2002. The botanical identification was made by Mr. N. Yoshida, Health Sciences University of Hokkaido. Each voucher specimen has been deposited in the herbarium of Hokkaido University.

2.1.2. Extraction and isolation. The club moss of

L. complanatum (1.4 kg) was extracted with MeOH, and the extract (76 g) was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 10 with sat. Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials (0.2 g) were subjected to an LH-20 column ($CHCl_3$/MeOH, 1:1) followed by an amino silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give complanadine B (**1**, 3.3 mg, 0.0002%), complanadine A[7] and lycopodine.[16]

The club moss (1.2 kg) of *L. obscurum* was extracted with MeOH (1 L×3). The MeOH extract (58 g) was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, after being adjusted at pH 10 with sat. Na_2CO_3, were partitioned with $CHCl_3$. $CHCl_3$ soluble materials (0.9 g) were subjected to an amino silica gel column (hexane/EtOAc, 1:0→0:1, and then $CHCl_3$/MeOH, 1:0→0:1). The fraction eluted with hexane/EtOAc (4:1) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give obscurumine B (**3**, 7.7 mg, 0.0006%), lobscurinol,[16] des-*N*-methyl-β-obscurine,[16] and lycofawcine.[17] The fraction eluted with hexane/EtOAc (7:3) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) followed by C_{18} HPLC (YMC Pack ODS-AM, 5 μm, YMC LTD., 10× 250 mm; eluent, 20% CH_3CN/0.1% TFA; flow rate, 2 mL/min; UV detection at 210 nm) to give obscurumine A (**2**, 1.4 mg, 0.0001%).

2.1.3. Complanadine B (1). Colorless solid; $[\alpha]_D^{24}$ −13° (*c* 0.5, MeOH); IR (neat) ν_{max} 3322, 2921, 1731, and 1697 cm^{-1}; UV (MeOH) λ_{max} 211 (ε 8000) and 268 nm (12000); ^1H and ^{13}C NMR data (Table 1); FABMS *m/z* 497 $[M+H]^+$; HRFABMS *m/z* 497.3259 [M+H; calcd for $C_{32}H_{41}N_4O$, 497.3280].

2.1.4. Obscurumine A (2). Colorless solid; $[\alpha]_D^{23}$ −44° (*c* 0.1, MeOH); IR (neat) ν_{max} 3330, 2960, and 1670 cm^{-1}; ^1H and ^{13}C NMR data (Tables 2 and 3); FABMS *m/z* 280 $[M+H]^+$; HRFABMS *m/z* 280.1918 [M+H; calcd for $C_{16}H_{26}NO_3$, 280.1912].

Table 2. ^1H NMR Data of obscurumines A (**2**) and B (**3**) at 300 K

	2[a]	**3**[b]
1a	2.92 (1H, dd, 4.8, 13.3)	2.64 (1H, m)
1b	3.62 (1H, dt, 5.0, 13.5)	3.29 (1H, dt, 3.3, 14.0)
2a	1.91 (1H, m)	1.41 (1H, m)
2b	1.98 (1H, m)	1.90 (1H, m)
3a	1.69 (1H, m)	1.44 (1H, m)
3b	2.12 (1H, brd, 14.3)	1.74 (1H, m)
4	3.30 (1H, m)	2.40 (1H, brd, 12.5)
5		4.91 (1H, brd, 1.9)
6a	2.36 (1H, dd, 1.7, 17.1)	1.93 (1H, m)
6b		1.96 (1H, m)
7	2.77 (1H, m)	2.29 (1H, brd, 2.2)
8	1.37 (1H, brd, 12.4)	
	2.01 (1H, m)	
9a	2.98 (1H, dd, 4.7, 12.8)	2.66 (1H, m)
9b	4.31 (1H, dt, 3.7, 13.0)	3.19 (1H, dt, 2.9, 12.4)
10a	1.81 (1H, brd, 6.7)	1.79 (1H, m)
10b	2.79 (1H, m)	1.87 (1H, m)
11a	1.53 (1H, brd, 13.5)	1.38 (1H, m)
11b	2.48 (1H, dt, 4.6, 13.7)	1.58 (1H, m)
12		2.19 (1H, brd, 11.4)
13		
14a	2.08 (1H, dd, 4.5, 13.4)	1.69 (1H, m)
14b	2.52 (1H, t, 12.2)	2.98 (1H, dd, 9.7, 14.0)
15	1.49 (1H, m)	2.77 (1H, m)
16	0.97 (3H, d, 6.2)	1.28 (3H, d, 7.7)
18		1.89 (3H, s)

[a] CD_3OD.
[b] $CDCl_3$.

Table 3. ^{13}C NMR Data of obscurumines A (**2**) and B (**3**) in $CDCl_3$ at 300 K

	2[a]	**3**[b]
1	64.29	47.57
2	22.0	18.89
3	18.69	22.76
4	49.00[c]	31.53
5	209.16	71.54
6	44.84	29.85
7	42.52	47.31
8	36.44	217.03
9	60.76	46.76
10	17.41	24.78
11	30.32	22.34
12	74.65	38.31
13	73.08	56.01
14	30.64	38.05
15	25.94	40.22
16	22.79	22.54
17		169.57
18		20.75

[a] CD_3OD.
[b] $CDCl_3$.
[c] Overlapped with solvent signals.

2.1.5. Obscurumine B (3). Colorless solid; $[\alpha]_D^{24}$ −63° (*c* 0.5, MeOH); IR (neat) ν_{max} 2930, 1738, and 1705 cm^{-1}; ^1H and ^{13}C NMR data (Tables 2 and 3); FABMS *m/z* 306 $[M+H]^+$; HRFABMS *m/z* 306.2073 [M+H; calcd for $C_{18}H_{28}NO_3$, 306.2069].

2.1.6. Chemical transformation of lycodoline to obscurumine A (2). To a solution of lycodoline (1.2 mg) in CH_2Cl_2 (200 μl) was added *m*-CPBA (1.5 mg). The mixture was allowed to stand for 150 min at 0 °C. After evaporation of solvent, the residue was applied to an amino silica gel column to give a compound (0.4 mg), whose spectral data and $[\alpha]_D$ value were identical with those of obscurumine A (**2**).

2.1.7. Evaluation of neurite outgrowth.[25] Human astrocytoma cells (glial cell line) were incubated for 2 days with 1–10 μM complanadine A (**4**) and 100 nM phorbol 12-myristate 13-acetate (PMA), and then rat pheochromocytoma (PC-12) cells were cultivated for 2 days in the conditioned 1321N1 culture medium. Cell morphology was assessed under a phase-contrast microscope. Neurite extension from PC-12 cells was regarded as an index of neuronal differentiation.

2.1.8. Semiquantitative RT-PCR.[25] Total RNA from 1321N1 cells was extracted by using a total RNA extraction kit, and semiquantitative RT-PCR was carried out by using a RT-PCR kit. NGF mRNA expression was examined as described previously.[25]

Acknowledgements

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Syntheses of oxygenated spongiane diterpenes from carvone. Synthesis of dorisenone C

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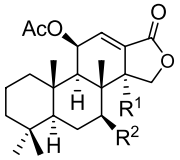
Abstract—The synthesis of dorisenone C, a representative member of the spongiane-type diterpene family, is described. The synthesis follows a B→AB→ABC→ABCD approach and is based on the initial preparation of the previously known hydroxy-aldehyde **14** (AB rings) from *R*-(−)-carvone, followed by an intramolecular Diels–Alder reaction between an oxygenated diene moiety and an acetylenic dienophile for the construction of the C ring (compound **22**), and adequate manipulation of the Diels–Alder adduct functionality for completion of the spongiane framework.

1. Introduction

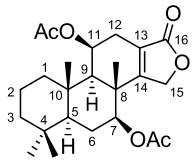
A large number of spongiane diterpenoids have been isolated from marine organisms such as sponges and nudibranchs,[1] which use them as defensive agents against predators. Most of these compounds show interesting biological properties, particularly cytotoxic activity.[2] Some of the spongianes with the highest levels of cytotoxic activity have been isolated from the Japanese marine mollusc *Chromodoris obsoleta* (Chromodorididae). This small group of spongianes, generically known as dorisenones, have a γ-butenolide moiety at the D-ring and additional polar groups, OH or AcO, at C-7, C-11 and/or C-14 positions of the spongiane framework, for example, dorisenones A (**1**), B (**2**), C (**3**) and D (**4**), and show strong cytotoxicity against several cell lines.[3]



1: R^1=OH, R^2=OAc

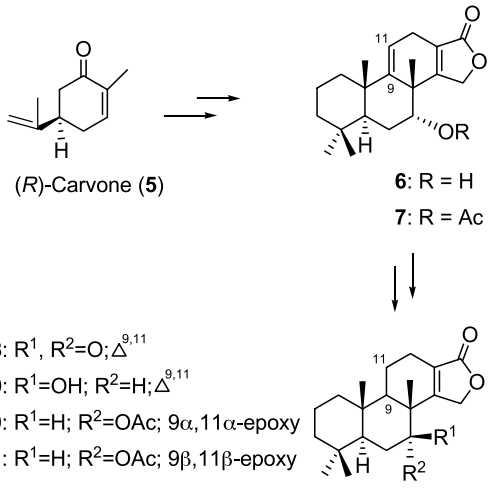
2: R^1=OH, R^2=H

4: R^1=H, R^2=OAc



3

Because of the interesting biological properties shown by most of the spongiane diterpenes, a relatively important amount of synthetic work has been done to prepare the spongiane framework in an efficient way and several natural spongianes have been successfully synthesized.[4] As a part of our research work related to the synthesis of biologically active terpene-type compounds starting from carvone (**5**), we recently described the synthesis of several oxygenated spongiane diterpenes functionally related to natural dorisenones, for example, compounds **6–11** (Scheme 1).[5] In spite of the close similarity between some of these compounds and the dorisenones, we were unable to transform them into any of these natural spongianes due



Scheme 1.

Keywords: Terpene; Spongiane; Synthesis; Carvone; Diels–Alder reaction; Retro-ene reaction; Propargylic ether.
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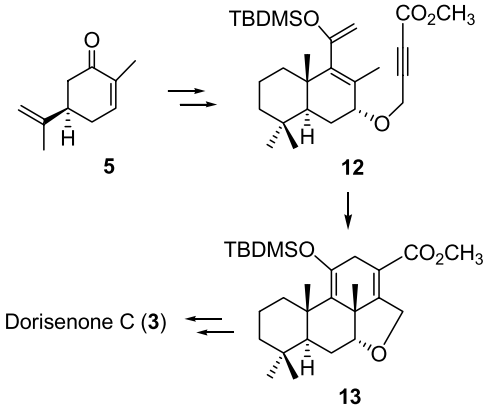
to the difficulties found in introducing the oxygenated functionalization at the C-11 position once the tetracyclic spongiane framework had been completed, for example, functionalization of the C9–C11 double bond of compounds such as **6** or **7**. In this short paper, we describe the adaptation of the approach previously used for the conversion of carvone (**5**) into spongiane-type compounds for the preparation of natural dorisenones, and in particular the synthesis of one representative member of this group of polyoxygenated spongiane diterpenes, dorisenone C (**3**).

2. Results and discussion

It was initially thought that the synthesis of dorisenone C (**3**) could be undertaken from a *trans*-decalin such as **12** (Scheme 2), which incorporates an oxygenated diene moiety



Scheme 2.

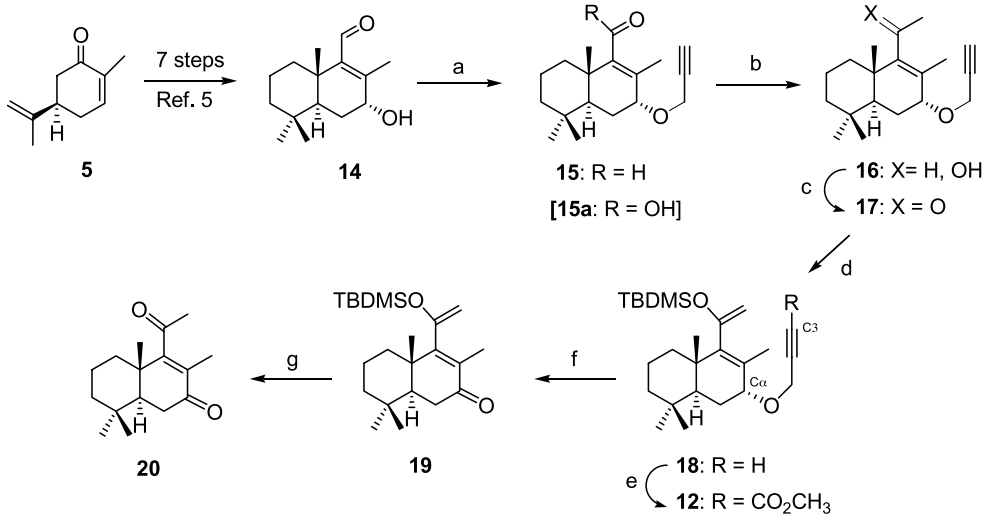
and a tethered acetylenic side chain that could afford the ABC ring system of the spongiane framework through an intramolecular Diels–Alder reaction. It was expected that the resulting adduct, for example, **13**, should have all the positions around the C-ring adequately functionalised for further elaboration of the γ-lactone D-ring and successful completion of the functionalization of target dorisenone C and related C-7 and C-11 oxygenated spongianes.[†]

2.1. Preparation of the ABC ring system

The synthesis of **13** begins with the preparation in seven steps, starting from (*R*)-(−)-carvone (**5**), of the γ-hydroxy-aldehyde **14**, following our established procedure (Scheme 3).[5] O-propargylation of the hydroxyl group of **14** with propargyl bromide under phase-transfer conditions proceeded straightforwardly to afford the propargyl ether **15** in 82% yield after silica gel chromatography. It should be mentioned that the aldehyde moiety of **15** was very easily oxidized to the corresponding carboxylic group during the work up procedure to give the acid **15a**; this air-oxidation was avoided by adding a small amount of a radical inhibitor to the reaction mixture, previously to the work up process (see Section 4).

A mixture of diastereomeric alcohols (**16**) was obtained when the propargyl ether **15** was treated with an excess of MeLi in THF. These, without necessity of separation, were directly oxidized to the corresponding methyl ketone **17** using Swern reaction conditions in 81% overall yield for the two steps. Conversion of **17** to the *tert*-butyldimethylsilyl enol ether **18** was accomplished in good yield by treatment with TBDMS triflate and triethylamine at low temperature. Finally, the synthesis of the required IMDA-adduct precursor **12** was completed in 90% yield by treating of **18** with lithium hexamethyldisilazane and trapping the resulting acetylide anion with methyl cyanoformate.

Heating a solution of **12** in toluene under the conditions previously used with the related system with a



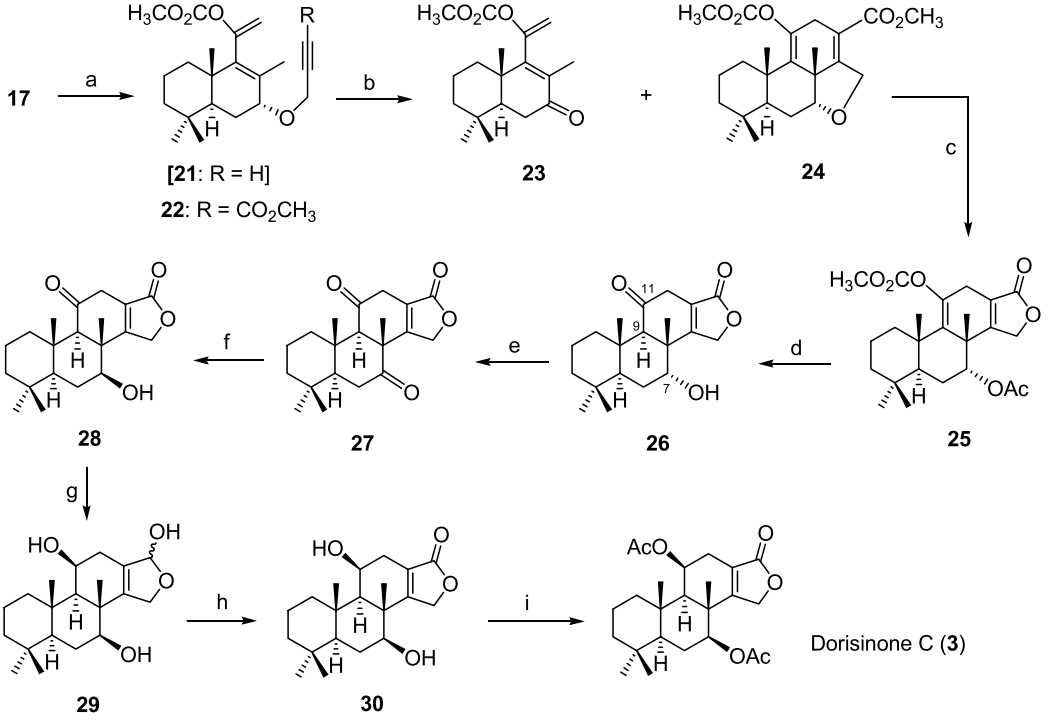
Scheme 3. Reagents and conditions: (a) $BrCH_2C{\equiv}CH$, 60% NaOH, Bu_4NI, rt, 3 h, 82%; (b) MeLi, THF, −78 °C, 30 min, 92%; (c) DMSO–$(COCl)_2$, CH_2Cl_2, −60 °C then Et_3N, 81%; (d) TBDSCl, Et_3N, C_6H_6, rt, 1.5 h, 86%; (e) LHMDS, THF, −40 °C, 20 min then CH_3OCOCN, 90%; (f) toluene, 180 °C, 72 h; (g) PTSA, acetone–H_2O, 56 °C, 2 h, 60% from **12**.

[†] Tetracyclic compounds have been named as spongiane derivatives, following the usual numbering used in the terpene field (see structure **3**). Systematic IUPAC nomenclature and numbering is used for all bicyclic compounds as given by the ChemDraw program (v 6.0.1) (CambridgeSoft Corp., Cambridge, MA).

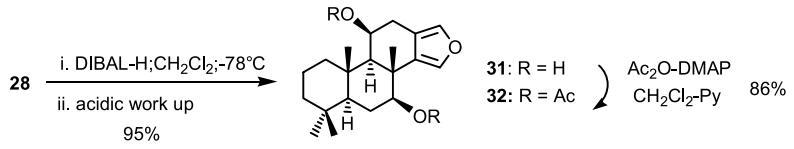
non-oxygenated diene moiety,[5] resulted in complete recovery of the starting material, no transformation or degradation of **12** was appreciated under these conditions. Transformation of **12** only took place at much high temperatures (e.g., 180–190 °C), almost 72 h being required for its complete consumption. However, the only compound formed under these conditions was not the desired Diels–Alder adduct, but rather the ketone **19**, which was unequivocally identified as such after hydrolysis of the acid-labile silyl enol ether moiety to the corresponding carbonyl group. The global yield for the two-step conversion of **12** into diketone **20** was about 60%.

The unexpected formation of compound **19** from **12** in the above reaction represents an example of the previously known retro-hetero-ene rearrangement of propargylic ethers,[6] a thermally induced reaction that proceeds through a concerted [1,5]-H shift pathway. The inertia of **12** to undergo the IMDA was somewhat unexpected but could be attributed to the strong non-bonding interaction that probably exists in the s-*cis* conformation of the diene moiety between the *tert*-butyldimethylsilyloxy group and the C-5 position of the decaline frame, which strongly destabilizes the intramolecular Diels–Alder reaction transition state. The relatively smooth conditions under which the formation of the ketone **19** took place contrast sharply with the high temperatures usually required for this kind of retro-ene rearrangement, which generally occurs under flash vacuum pyrolysis conditions (reaction temperatures range from 300 to 450 °C). Related propargylic esters have previously been heated at temperatures in the range of 200–300 °C without substantially experiencing a similar transformation.[7] A plausible explanation for the enhanced reactivity of the propargylic ether moiety of **12** may be found in the stabilization produced by the substituents at both extremes of the propargylic ether system in the transition state of the retro-ene reaction, in which the carbon atom donating the hydrogen (the allylic position, C_α) becomes more positive and the carbon accepting the migrating hydrogen (the carbon atom bonded to the electron-withdrawing methoxycarbonyl group, C_3) becomes more negative.[8]

In view of the unexpected behaviour of the oxygenated diene **12**, we decided to prepare an alternative IMDA-adduct precursor with a less sterically demanding group at the diene moiety, so the preparation of the dienol carbonate **22** was undertaken (Scheme 4).[9] The synthesis of **22** proved much more difficult than expected. Transformation of the methyl ketone group of **17** into the corresponding enol carbonate moiety, to give **21**, was readily effected by treatment of **17** with LDA in THF and dimethyl pyrocarbonate, but all attempts to perform the methoxycarbonylation of **21** to obtain the desired Diels–Alder adduct precursor **22** were unsuccessful. The initial efforts to obtain **22** in a single operation by sequential treatment of **17** with a large excess of LDA in THF and dimethyl pyrocarbonate also failed, and **21** was also the main product formed under these conditions. It was found after some experimentation, however, that this transformation could be achieved in a relatively efficient way by sequential treatment of **17** with three equivalents of a 1:1 mixture of LDA–BuLi in THF at −78 °C and an excess of methyl chloroformiate. By following this procedure, **22** was obtained in 67–70% yield after chromatographic purification. Heating this compound under similar conditions as described above for **12** gave a



Scheme 4. Reagents and conditions: (a) for **21**: LDA, THF, −78 °C then $(CH_3OCO)_2O$ and warm to rt, 2 h, 67%. For **22**: LDA–BuLi, THF, −78 to 0 °C, 2 h, then CH_3OCOCl, −78 to −10 °C, 1.5 h, 67%; (b) toluene, 195 °C, 96 h, 56% of **23** and 31% of **24**; (c) ZnI_2, Ac_2O, rt, 72 h, 82%; (d) $NaOCH_3$, CH_3OH, −20 °C, 5 days, 96%; (e) Jones reagent, acetone, 0 °C, 5 min., 92%; (f) BH_3–THF, THF, 0 °C, 2 h, 99%; (g) DIBAL-H, THF, −78 °C, 2 h; (h) MnO_2, CH_2Cl_2, overnight, 71% from **28**; (i) Ac_2O, DMAP, CH_2Cl_2–Py, rt, overnight, 80%.



Scheme 5.

roughly 2:1 mixture of the corresponding retro-ene rearrangement product and the required Diels–Alder adduct, **23** and **24**, respectively, in 87% combined yield. Both compounds were easily separated by column chromatography and the structure and stereochemistry of **24** unequivocally established by conventional NMR methods. It seems, based on the result obtained in the above reaction, that the steric size of the methyl carbonate group, although sensibly lower than the *tert*-butyldimethylsilyloxy group, was still determinant in destabilizing the transition state (TS) of the IMDA reaction, such that the competitive retro-ene reaction was still dominant. Unfortunately, several attempts to introduce an even less voluminous group at the diene moiety of the Diels–Alder adduct precursor, for example a methoxy group, were unsuccessful.

2.2. Construction of the D ring and further functionalization of the spongiane framework

In spite of the rather low yield of the adduct obtained in the above IMDA reaction, given the limitations imposed by the competitive retro-ene reaction, this result was considered a relative success considering the previous difficulties found for the introduction of the oxygen functionality at the C ring of the spongiane skeleton. The compound **24** seemed adequately functionalized to readily complete the preparation of target dorisenone C, so we turned our attention towards the elaboration of the γ-lactone D-ring, thus completing the spongiane framework, and the modification of the functionalization at the C-7 and C-11 positions (spongiane numbering). Paralleling our previous approach, the first task was readily accomplished in a single operation by treatment of the Diels–Alder adduct **24** with acetic anhydride and zinc iodide at room temperature.[10] Under these conditions, regioselective ring-opening of the dihydrofuran ring followed by in situ lactonization took place to give directly the spongiane-type compound **25** in 82% yield.

Hydrolysis of both the methyl carbonate and acetate groups was smoothly effected in very high yield by treatment of **25** with methanolic sodium methoxide at −20 °C for several days. The conditions of this reaction were somewhat critical to ensure a good yield of the hydroxy ketone **26**; under these conditions, not only hydrolysis of both ester groups took place, but also equilibration of the initially formed mixture of epimers at C-9 to the thermodinamically most stable 9α-isomer. The correct stereochemistry of **26** at the C-9 position was established unambiguously by NMR spectroscopy, the NOE enhancements observed between Me-8β (irradiated) and Me-10β being of special significance, as well as between H-9 (irradiated) and H-12α, H-1α and, particularly, H-5α.

Transformation of **26** into dorisenone C (**3**) required inversion of the axial hydroxyl group at C-7, stereoselective reduction of the C-11 carbonyl group to the axial alcohol and acetylation of the two hydroxyl groups. The first task was accomplished by oxidation of **26** with the Jones reagent in acetone followed by reduction of the resulting ketone **27** using the diborane–THF complex at 0 °C. The overall yield for this two-step process was 92%. As an alternative, the reduction of **27** to **28** was also effected using $NaBH_4$ in MeOH, although with a slightly lower yield. The β-orientation of the 7-OH group in **28** was also established from its spectroscopic data; for example, the ^{13}C NMR signal due to C-5 which is shifted substantially downfield with reference to the equivalent signal in the alcohol **26** (53.4 and 46.7 ppm, respectively) due to the absence of the γ-effect exerted by the axial oriented OH group in the latter. Also the coupling constant pattern observed for H-7 (dd, $J=$ 11.3, 4.0 Hz) is in agreement with an axial orientation for this hydrogen atom.

Reduction of the C-11 carbonyl group of **28** was somewhat more complicated. Treatment of ketone **28** with diborane, $NaBH_4$, $NaBH_4$–$CeCl_3$ or Bu_4NBH_4 under different reaction conditions always resulted in the recovering of unaltered starting material. On the other hand, the use of DIBAL-H in CH_2Cl_2 at low temperature led to a smooth reduction of both the C-11 ketonic and the C-15 lactonic carbonyl groups to furnish the dihydroxy lactol **29** in good yield. Given the high acid lability of the γ-lactol **29**, this was not purified but immediately oxidized to regenerate the γ-lactone moiety by treatment with MnO_2 in CH_2Cl_2 at room temperature.[11] The global yield for the conversion of **28** into the dihydroxy γ-lactone **30** was 71%.‡ The stereochemistry of the new stereogenic centre generated at C-11 was deduced from analysis of ^1H and ^{13}C NMR spectral data. For example, the H-11 proton appeared in the ^1H NMR spectrum of **30** as a broad triplet with an average width ($W_{1/2}=9$ Hz), which can only results from an equatorially oriented hydrogen, indicating the β (axial) orientation of the 11-hydroxyl group (Scheme 5).

Finally, the synthesis of dorisenone C (**3**) was completed by acetylation of both hydroxyl groups by treatment of the dihydroxy lactone **30** with an excess of acetic anhydride and 4-dimethylaminopyridine in a mixture of CH_2Cl_2-pyridine

‡ The dihydroxy furan **31** (see Scheme 5) was always isolated as a secondary product of this transformation, in variable amounts that depended on the work up procedure followed. This compound is originated by dehydration of the intermediate lactol **29**; in fact, it can be obtained in excellent yield directly from compound **28** by reduction with DIBAL-H at low temperature followed by acidic workup (see Section 4). This compound was readily acetylated by treatment with Ac_2O–DMAP in CH_2Cl_2–Py to give the diacetate **32**, the D-ring aromatic analogue of dorisenone C. The compounds **31** and **32** belong to the subgroup of spongianes with a D furan ring, for example, furanospongianes,[12] and are the first spongianes of this type that are functionalized at the C-7 and C-11 positions.

at room temperature. The data of the synthetic sample were in complete agreement with those reported earlier for the natural product. Since the optical rotation of **3** agreed well with that reported {$[\alpha]_D$ +30.1° (lit.[3] $[\alpha]_D$ +35.5°)}, the synthesis described here establishes the absolute configuration of natural dorisenone C as shown in formula **3** (5*S*,7*S*,8*R*,9*R*,10*S*,11*S*).

3. Conclusion

In conclusion, the diastereoselective synthesis of the spongiane diterpene dorisenone C (**3**) starting from (*R*)-(−)-carvone has been realized for the first time following a B→AB→ABC→ABCD approach. In spite of the relatively low yield obtained in the key step, due to an unexpected retro-hetero-ene rearrangement of a propargylic ether that competes with the desired IMDA reaction between a dienol carbonate moiety and an acetylenic dienophile, the route is short and relatively efficient and could be used, with minor modifications, for the preparation of other related members of this group of natural spongianes.

4. Experimental

4.1. General information

All melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured as KBr pellets or liquid films. Elemental analyses were performed by servicio de semimicroanalisis of S.C.S.I.E. (Valencia); final purification of all products for microanalysis was done by preparative HPLC on a μ-Porasil column. Mass spectra were obtained by electron impact (EI) at 70 eV. ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 300 or 400 MHz, and NMR ^{13}C spectra at 75 or 100 MHz. ^{1}H spectra were referenced to residual $CHCl_3$ (δ 7.26) and ^{13}C spectra to the central component of the $CDCl_3$ triplet at δ 77.0. Carbon substitution degrees were established by DEPT pulse sequences. A combination of COSY, HMQC, and NOE experiments was utilized when necessary for the assignment of ^{1}H and ^{13}C chemical shifts. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh. All operations involving air-sensitive reagents were performed under an inert atmosphere of dry argon using syringes, oven-dried glassware, and freshly distilled and dried solvents.

4.2. Synthesis of the ABC ring system from carvone

4.2.1. (3*R*,4a*S*,8a*S*)-3-Hydroxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde (14). Hydroxy-aldehyde **14** was prepared from (*R*)-(−)-carvone (**5**) in 7 steps and 40–45% overall yield as we described previously in Ref. 5.

4.2.2. (3*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-3-prop-2-ynyloxy-3,4,4a,5,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde (15). A heterogeneous mixture of alcohol-aldehyde **14** (93.3 mg, 0.396 mmol), TBAI (75 mg, 0.188 mmol), propargyl bromide (660 μL, 5.94 mmol) and aq 60% NaOH (432 μL) was vigorously stirred at room temperature for 3 h. The reaction mixture was poured into 2 M HCl cooled at 0 °C and extracted with hexane (containing a small amount of the radical inhibitor 2,6-di-*tert*-butil-4-methylphenol to avoid oxidation of the aldehyde group). The combined hexane extracts were washed with water and brine, dried with $MgSO_4$, and concentrated under vacuum. Column chromatography, using hexane–ethyl acetate (95:5) as eluent, afforded the propargyl ether **15** (88.8 mg, 82%) as a colourless oil. $[\alpha]_D^{26}$ +23.5° (0.9, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3303, 2923, 2866, 2118, 1720, 1675, 1057; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (1H, s, CHO), 4.31 (1H, dd, J=15.9, 2.3 Hz, OCH), 4.21 (1H, dd, J=15.9, 2.3 Hz, OCH′), 3.92 (1H, br d, J=3.9 Hz, H-3), 2.47 (1H, dd, J=2.3, 2.3 Hz, CC–H), 2.37 (1H, ddd, J=12.3, 4.5, 2.7 Hz, H-4α), 2.117 (3H, s, Me–C_2), 1.94 (1H, br d, J=14.0 Hz, H-8β), 1.34 (1H, ddd, J=14.7, 2.8, 2.8 Hz, H-4a), 1.154 (3H, s, Me–C_{8a}), 1.03 (1H, ddd, J=14.0, 13.2, 2.8 Hz, H-8α), 0.901 (3H, s, Meβ–C_5), 0.864 (3H, s, Meα–C_5); ^{13}C NMR (75 MHz) δ 194.1 (CHO), 147.5 (C_2), 145.9 (C_1), 79.8 (*C*CH), 76.5 (C_3), 74.8 (C*C*H), 56.7 (OCH_2), 45.8 (C_{4a}), 41.2 (C_6), 38.3 (C_{8a}), 35.6 (C_8), 33.0 (Meα–C_5), 32.9 (C_5), 22.5 (C_4), 21.6 (Meβ–C_5), 18.73 (C_7), 18.65 (Me–C_{8a}), 17.0 (Me–C_2); MS (EI) *m*/*z* 274 (M^+, 46), 245 (M^+-29, 100), 235 (40), 119 (58); HRMS *m*/*z* calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1941. Anal. Calcd for $C_{18}H_{26}O_2$: C 78.79, H 9.55; found: C 78.85, H 9.61.

Occasionally, when the radical inhibitor was not used during the workup procedure, the corresponding acid, **15a**, was isolated as the main product (up to 85% isolated yield).

Data for **15a** [(3*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3-prop-2-ynyloxy-3,4,4a,5,6,7,8,8a-octahydro-naphthalene-1-carboxylic acid]. $[\alpha]_D^{28}$ +44.6° (1.3, $CHCl_3$); IR $\nu_{máx}$/cm^{-1} (film) 3600–3100, 3306, 2930, 2868, 1720, 1056; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (1H, dd, J=16.0, 2.5 Hz, OCH), 4.17 (1H, dd, J=16.0, 2.5 Hz, OCH′), 3.91 (1H, br d, J=3.8 Hz, H-3), 2.43 (1H, dd, J=2.5, 2.5 Hz, CC–H), 1.94 (1H, br d, J=14.1 Hz, H-8β), 1.818 (3H, s, Me–C_2), 1.178 (3H, s, Me–C_{8a}), 0.908 (3H, s, Meβ–C_5), 0.870 (3H, s, Meα–C_5); ^{13}C NMR (75 MHz) δ 173.3 (COOH), 142.1 (C_2), 130.8 (C_1), 80.1 (*C*CH), 75.3 (C_3), 74.3 (C*C*H), 56.2 (OCH_2), 45.2 (C_{4a}), 41.3 (C_6), 37.5 (C_{8a}), 36.3 (C_8), 32.84 (Meα–C_5), 32.80 (C_5), 23.2 (C_4), 21.5 (Meβ–C_5), 18.7 (Me–C_{8a}), 18.6 (C_7), 18.5 (Me–C_2); MS (EI) *m*/*z* 290 (M^+, 20), 275 (M^+-15), 251 (49), 245 (M^+-CO_2H, 58), 189 (40), 119 (100); HRMS *m*/*z* calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1880.

4.2.3. 1-[(3*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-3-prop-2-ynyloxy-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl]-ethanone (17). A solution of aldehyde **15** (62.1 mg, 0.225 mmol) in THF (1.2 mL) was treated dropwise at −78 °C with an ethereal solution of MeLi (0.3 mL, 1.6 M, 0.48 mmol). After being stirred for 30 min at the same temperature, the mixture was quenched by the addition of saturated aq solution of NH_4Cl, diluted with water and extracted with ethyl ether. Work up and purification of the residue by flash column chromatography on silica gel with

hexane–ethyl acetate (8:2) as eluent afforded a 4:1 mixture of diastereomeric alcohols **16** (60.4 mg, 92%) as an oil. IR ν_{max}/cm^{-1} (film) 3500–3300, 3310, 2926, 2865, 1727, 1462, 1369, 1061; ^1H NMR (300 MHz) for the major diastereomer of **16** {1-[(3*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3-prop-2-ynyloxy-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl]-ethanol}, deduced from the ^1H NMR of the mixture, δ 4.63 (1H, q, $J=6.8$ Hz, *H*COH), 4.26 and 4.14 (2H, an AB system, two dd, $J=15.9$, 2.4 Hz, OCH_2), 3.75 (1H, br s, H-3), 2.41 (1H, dd, $J=2.4$, 2.4 Hz, CC–H), 1.959 (3H, s, Me–C_2), 1.411 (3H, d, $J=6.8$ Hz, *Me*–CHOH), 0.931 (3H, s, Me–C_{8a}), 0.897 (3H, s, Meβ–C_5), 0.853 (3H, s, Meα–C_5); ^{13}C NMR (75 MHz) δ 149.4 (C_1), 129.6 (C_2), 80.4 (*C*CH), 77.3 (C_3), 74.1 (C*C*H), 65.7 (CHOH), 56.0 (OCH_2), 46.1 (C_{4a}), 41.1 (C_6), 39.9 (C_{8a}), 36.2 (C_8), 33.1 (Meα–C_5), 33.0 (C_5), 23.0 (Me–CHOH), 22.7 (C_4), 21.8 (Meβ–C_5), 19.0 (C_7), 18.4 (Me–C_{8a}), 17.9 (Me–C_2); MS (EI) *m/z* 290 (M^+, 1), 275 (M^+-15, 13), 245 (100), 119 (57); HRMS *m/z* calcd for $C_{19}H_{30}O_2$ 290.2246, found 290.2234.

A solution of DMSO (58 μL, 0.76 mmol) in CH_2Cl_2 (130 μL) was added to a solution of oxalyl chloride (37.5 μL, 0.40 mmol) in CH_2Cl_2 (200 μL) at −78 °C, and the mixture was stirred for a few min. A solution of the above mixture of alcohols **16** (60.4 mg, 0.208 mmol) in CH_2Cl_2 (225 μL) was added, and the mixture was stirred at −60 °C for 30 min. Et_3N (277 μL, 1.96 mmol) was added to the solution, which was stirred at −60 °C for 15 min then warmed and maintained at 0 °C for 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic phases were successively washed with a 1 M solution of HCl, 5% aq $NaHCO_3$, water and brine and dried over anhydrous $MgSO_4$, filtered and the solvents evaporated under vacuum. Purification by column chromatography, using hexane–ethyl acetate (9:1) as eluent, afforded the methyl ketone **17** (48.6 mg, 81%) as an oil. $[\alpha]_D^{23}$ +40.0° (2.4, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2927, 2866, 1727, 1692, 1459, 1349, 1245, 1073, 1054; ^1H NMR (400 MHz) δ 4.27 (1H, dd, $J=16.0$, 2.5 Hz, OCH), 4.17 (1H, dd, $J=16.0$, 2.3 Hz, OCH′), 3.83 (1H, br d, $J=4.1$ Hz, H-3), 2.43 (1H, dd, $J=2.4$, 2.3 Hz, CC–H), 2.273 (3H, s, Me–CO), 1.674 (3H, s, Me–C_2), 1.123 (3H, s, Me–C_{8a}), 0.912 (3H, s, Meβ–C_5), 0.857 (3H, s, Meα–C_5); ^{13}C NMR (75 MHz) δ 209.3 (CO), 151.1 (C_2), 125.5 (C_1), 80.2 (*C*CH), 75.8 (C_3), 74.3 (C*C*H), 56.3 (OCH_2), 45.2 (C_{4a}), 41.4 (C_6), 38.3 (C_5+C_{8a}), 36.9 (C_8), 33.6 (Meα–C_5), 32.9 (*CH*$_3$CO), 23.2 (C_4), 21.5 (Meβ–C_5), 18.6 (C_7), 18.5 (Me–C_{8a}), 17.8 (Me–C_2); MS (EI) *m/z* 288 (M^+, 28), 273 (M^+-15, 6), 249 (57), 245 (M^+-CH_3CO, 47), 190 (31), 149 (100), 119 (83); HRMS *m/z* calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2099. Anal. Calcd for $C_{19}H_{28}O_2$: C 79.12; H 9.78; found: C 79.30, H 9.62.

4.2.4. *tert*-Butyl-dimethyl-{1-[(3*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3-prop-2-ynyloxy-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl]-vinyloxy}-silane (18).

Et_3N (28 μL, 0.20 mmol) and *tert*-butyldimethylsilyl triflate (28 μL, 0.122 mmol) were added to a solution of methyl ketone **17** (27.6 mg, 0.10 mmol) in benzene (0.6 mL) at 5 °C. After stirring at room temperature for 1.5 h, the mixture was poured into saturated aq $NaHCO_3$, extracted with hexane, and worked up as usual. Column chromatography on silica gel, previously deactivated by washing with 0.1% Et_3N in hexane and using the same mixture as eluent, gave the enol silyl ether **18** (33.1 mg, 86%) as an oil. ^1H NMR (300 MHz, C_6D_6) δ 4.36 (1H, br s, =CH), 4.02 (1H, br s, =CH′), 4.00 (1H, dd, $J=16.0$, 2.5 Hz, OCH), 3.88 (1H, dd, $J=16.0$, 2.3 Hz, OCH′), 3.76 (1H, br d, $J=4.1$ Hz, H-3), 2.037 (3H, s, Me–C_2), 1.99 (1H, dd, $J=2.3$, 2.5 Hz, CC–H), 0.946 (12H, s, *t*-*Bu*Si and Me–C_{8a}), 0.856 (3H, s, Me–C_5), 0.842 (3H, s, Me′–C_5), 0.181 and 0.177 (6H, two s, *Me*$_2$Si); ^{13}C NMR (100 MHz, C_6D_6) δ 155.8 (O*C*=CH_2), 146.7 (C_1), 128.2 (C_2), 127.9 (=CH_2), 81.1 (*C*CH), 76.2 (C_3), 74.0 (C*C*H), 55.9 (OCH_2), 45.9 (C_{4a}), 41.9 (C_6), 33.1 (Meα–C_5), 32.3 (C_5), 30.2 (C_8), 29.5 (C_{8a}), 25.8 (*Me*$_3$CSi), 23.7 (C_4), 21.9 (Meβ–C_5), 23.1 (Me–C_{8a}), 19.4 (C_7), 18.2 (Me$_3$*C*Si), 14.4 (Me–C_2), −4.4 and −4.5 (Me_2Si).

4.2.5. 4-{4-(2*R*,4a*S*,8a*S*)-[1-(*tert*-Butyl-dimethyl-silanyloxy)-vinyl]-3,4a,8,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-2-yloxy}-but-2-ynoic acid methyl ester (12).

A solution of compound **18** (25.6 mg, 0.063 mmol) in THF (0.6 mL) at −40 °C was treated dropwise with a solution 0.5 M of LiHMDS in THF (256 μL, 0.128 mmol). After 20 min, the reaction mixture was treated with methyl cyanoformate (11.2 mg, 12 μL, 0.131 mmol) and stirred at the same temperature for 1 h. Saturated aq $NaHCO_3$ was added, and the aq phase was extracted with hexane. Usual work up followed by purification by column chromatography, as described above for **18**, afforded the acetylenic ester **12** (26.4 mg, 90%) as a colourless oil. ^1H NMR (300 MHz, C_6D_6) δ 4.31 (1H, d, $J=1$ Hz, =CH), 3.97 (1H, d, $J=1$ Hz, =CH′), 3.83 and 3.73 (2H, two d, $J=17.1$ Hz, OCH_2), 3.61 (1H, br d, $J=3.7$ Hz, H-2), 3.19 (3H, s, CH_3O), 1.974 (3H, s, Me–C_3), 0.914 (12H, s, *t*BuSi and Me–C_{4a}), 0.832 (3H, s, Me–C_8), 0.814 (3H, s, Me′–C_8), 0.145 and 0.139 (6H, two s, *Me*$_2$Si); ^{13}C NMR (75 MHz, C_6D_6) δ 155.6 (O*C*=CH_2), 153.6 (CO_2), 147.0 (C_4), 130.7 (C_3), 129.0 (=CH_2), 85.0 (*C*CCO), 77.1 (C_2), 78.1 (C*C*CO), 55.6 (OCH_2), 52.0 (CH_3O), 45.9 (C_{8a}), 41.9 (C_7), 33.1 (Meα–C_8), 32.3 (C_8), 30.2 (C_5), 29.8 (C_{4a}), 25.8 (*Me*$_3$CSi), 23.7 (C_1), 23.0 (Me–C_{4a}), 21.9 (Meβ–C_8), 19.3 (C_6), 18.2 (Me$_3$*C*Si), 14.3 (Me–C_3), −4.46 and −4.55 (Me_2Si); HRMS *m/z* calcd for $C_{27}H_{44}O_4Si$ 460.3009, found 460.3011.

4.2.6. (4a*S*,8a*S*)-4-Acetyl-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-1*H*-naphthalen-2-one (20).

Formation of compound **18**. A solution of **12** (16.8 mg, 0.036 mmol) in degassed anhydrous toluene (2 mL) was heated in a vacuum sealed ampoule (previously silylated with 1,1,1,3,3,3-hexamenthyldisilazane in ether) at 180–190 °C for 72 h. Evaporation of the solvent under reduced pressure afforded a yellowish residue of crude ketone **19** (16.0 mg) that was used in the subsequent step without purification. ^1H NMR (300 MHz, C_6D_6) δ 4.28 (1H, br s, =CH), 3.89 (1H, br s, =CH′), 2.52 (^1H dd, $J=17.7$, 3.8 Hz, H-1α), 2.30 (1H, dd, $J=17.7$, 14.3 Hz, H-1β), 2.079 (3H, s, Me–C_3), 0.900 (12H, s, *t*BuSi and Me–C_{4a}), 0.681 (3H, s, Me–C_8), 0.622 (3H, s, Me′–C_8), 0.123 and 0.112 (6H, two s, *Me*$_2$Si).

Hydrolysis of compound **19**. A solution of the above obtained ketone **19** and a catalytic amount of PTSA in 1.5 mL of acetone (containing 3% of water) was stirred at 56 °C for 2 h. The solvent was evaporated under vacuum,

the oily residue was treated with saturated aq $NaHCO_3$, extracted with ether, and worked up as usual to give a solid residue that was purified by column chromatography, using hexane–ethyl acetate (9:1) as eluent, to afford the diketone **20** (6.8 mg, 60% from **12**) as a white solid. Mp 85–87 °C (from cold hexane); $[\alpha]_D^{28}$ +65.5° (1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2945, 2924, 2868, 2848, 1696, 1665, 1455, 1358, 1219, 1204; ^1H NMR (400 MHz, $CDCl_3$) δ 2.54 (1H, dd, J=17.9, 3.9 Hz, H-1α), 2.42 (1H, dd, J=17.9, 14.0 Hz, H-1β), 1.84 (1H, dd, J=14.0, 3.9 Hz, H-8a), 2.34 (3H, s, CH_3CO), 1.44 (1H, dd, J=11.8, 3.8 Hz, H-5), 1.660 (3H, s, Me–C_3), 1.328 (3H, s, Me–C_{4a}), 0.932 (3H, s, Meβ–C_8), 0.899 (3H, s, Meα–C_8); ^{13}C NMR (75 MHz) δ 205.8 (C_2), 200.3 (*C*OCH_3), 166.1 (C_4), 126.5 (C_3), 50.5 (C_{8a}), 40.8 (C_7), 39.0 (C_{4a}), 36.0* (C_5), 35.2* (C_1), 33.1 (C_8), 32.7 (*C*H_3CO), 32.4 (Meα–C_8), 21.1 (Meβ–C_8), 18.7 (C_6), 18.3 (Me–C_{4a}), 12.1 (Me–C_3); MS (EI) *m*/*z* 248 (M^+, 16), 206 (100), 135 (71); HRMS *m*/*z* calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1764. Anal. Calcd for $C_{16}H_{24}O_2$: C 77.38, H 9.74; found: C 77.95, H 9.75.

4.2.7. Carbonic acid methyl ester 1-[(3*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-3-prop-2-ynyloxy-3,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl]-vinyl ester (21). A solution of ketone **17** (15 mg, 0.051 mmol) in anhydrous THF (0.6 mL) was added dropwise into a 0.5 M solution of LDA in THF (0.3 mL, 0.15 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 10 min and then at 0 °C for a further 10 min. The mixture was cooled down to −78 °C, treated with freshly distilled dimethyl pyrocarbonate (21 μL, 0.19 mmol) and then allowed to warm to room temperature over 2 h while stirring. The mixture was diluted with hexane, washed with saturated aq NH_4Cl, water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the product purified by column chromatography, using hexane–ethyl acetate (9:1) as eluent, to afford enol carbonate **21** (12 mg, 67%) as a colourless oil. $[\alpha]_D^{22}$ −17.9° (1.8, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3293, 2951, 2922 2861, 1759, 1440, 1271, 1231, 1211, 1188, 1052; ^1H NMR (300 MHz, C_6D_6) δ 5.25 (1H, d, J=1.4 Hz, =CH), 4.55 (1H, d, J=1.4 Hz, =CH′), 3.98 (1H, dd, J=16.0, 2.5 Hz, OCH), 3.87 (1H, dd, J=16.0, 2.5 Hz, OCH′), 3.74 (1H, br d, J=4.0 Hz, H-3), 3.296 (3H, s, CH_3O), 2.00 (1H, t, J=2.5 Hz, CC–H), 2.166 (3H, s, Me–C_2), 1.124 (3H, s, Me–C_{8a}), 0.848 (3H, s, Me–C_5), 0.806 (3H, s, Me′–C_5); HRMS *m*/*z* calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2192.

4.2.8. 4-[(2*R*,4a*S*,8a*S*)-4-(1-Methoxycarbonyloxy-vinyl)-3,4a,8,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-2-yloxy]-but-2-ynoic acid methyl ester (22). A solution of methyl ketone **17** (44.7 mg, 0.154 mmol) in anhydrous THF (1.4 mL) was added dropwise to a solution of LDA and BuLi in THF [prepared from diisopropylamine (65 μL, 0.460 mmol), BuLi (575 μL of a 1.6 M solution in hexanes, 0.92 mmol) in 1.7 mL of THF] at −78 °C. The mixture was stirred at this temperature for 2 h and then allowed to slowly warm to 0 °C. It was cooled down again to −78 °C and treated with excess methyl chloroformiate (100 μL, 1.63 mmol). The reaction mixture was allowed to warm to −10 °C over 1.5 h, after which the reaction was quenched with saturated NH_4Cl solution. Extraction with diethyl ether was followed by washing of the organic layers with water and brine. The combined organic fractions were dried over Na_2SO_4 and the solvent reduced in vacuum. The crude oil was purified by column chromatography, using hexane–ethyl acetate (9:1) as eluent, to yield the product **22** (42 mg, 67%) as a colourless oil. $[\alpha]_D^{22}$ +20.3° (2.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2954, 2866, 2237, 1763, 1720, 1439, 1267, 1233, 1215, 1194, 1047; ^1H NMR (300 MHz, C_6D_6) δ 5.24 (1H, d, J=1.4 Hz, =CH), 4.54 (1H, d, J=1.4 Hz, =CH′), 3.84 and 3.75 (2H each, each d, J=17.1 Hz, OCH_2), 3.60 (1H, br d, J=3.8 Hz, H-2), 3.296 (3H, s, *C*H_3OCO_2), 3.240 (3H, s, *C*H_3OCO), 2.124 (3H, s, Me–C_3), 1.099 (3H, s, Me–C_{4a}), 0.850 (3H, s, Me–C_8), 0.800 (3H, s, Me′–C_8); ^{13}C NMR (75 MHz, C_6D_6) δ 153.6 (O*C*=CH_2), 152.2 (OCO_2), 142.7 (CO_2), 133.7 (C_3+C_4), 105.7 (=CH_2), 84.7 (*C*CCO), 78.3 (C*C*CO), 77.1 (C_2), 55.8 (OCH_2), 54.3 (*C*H_3OCO_2), 52.1 (*C*H_3OCO), 45.8 (C_{8a}), 41.6 (C_7), 38.1 (C_8), 37.5 (C_5), 33.1 (Meα–C_8), 33.0 (C_{4a}), 23.7 (C_1), 21.8 (Meβ–C_8+Me–C_3), 19.5 (Me–C_{4a}), 19.1 (C_6); MS (EI) *m*/*z* 404 (M^+, 1), 389 (3), 329 (33), 328 (100), 313 (9), 231 (12), 199 (3); HRMS *m*/*z* calcd for $C_{23}H_{32}O_6$ 404.2199, found 404.2256.

4.2.9. (5a*R*,8*S*,10a*S*)-1-Methoxycarbonyloxy-7,7,10a,10c-tetramethyl-2,5a,6,6a,7,8,9,10,10a,10c-decahydro-4*H*-5-oxa-acephenanthrylene-3-carboxylic acid methyl ester (24). A solution of dienol carbonate **22** (41.0 mg, 0.101 mmol) in degassed anhydrous toluene (3 mL) was heated in a vacuum sealed glass ampoule at 195 °C for 96 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel, using a 9:1 mixture of hexane–ethyl acetate as eluent, to afford in order of elution the ketone **23** (17.4 mg, 56%) as a colourless oil and the Diels–Alder adduct **24** (12.6 mg, 31%) as a yellowish oil.

Data for **23**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (1H, d, J=2.3 Hz), 4.76 (1H, d, J=2.3 Hz, H), 3.827 (3H, s), 2.55 (^1H dd, J=18.1, 4.5 Hz), 2.43 (1H, dd, J=18.1, 13.6 Hz), 1.897 (3H, s), 1.191 (3H, s), 0.933 (3H, s), 0.888 (3H, s); ^{13}C NMR (75 MHz) δ 200.9 (C_3), 158.6 (O*C*=CH_2), 152.9 (OCO_2), 150.1 (C_1), 133.9 (C_2), 106.1 (=CH_2), 55.2 (CH_3O), 50.3 (C_{4a}), 41.0 (C_6), 39.2 (C_{8a}), 36.2 and 35.5 (C_8 and C_4), 33.2 (C_5), 32.5 (Meα–C_5), 21.3 (Meβ–C_5), 18.7 (C_7), 18.5 (Me–C_{8a}), 13.7 (Me–C_2); MS (EI) *m*/*z* 306 (M^+, 0.2), 247 (0.5), 215 (2.5), 159 (8), 139 (77), 105 (55), 91 (100), 77 (91); HRMS *m*/*z* calcd for $C_{18}H_{26}O_4$ 306.1831, found 306.1846.

Data for **24**: $[\alpha]_D^{21}$ +7.2° (0.3, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2956, 2867, 1757, 1716, 1439, 1283, 1248, 1204, 1122, 1020, 757; ^1H NMR (300 MHz, C_6D_6) δ 5.15 (1H, dd, J=14.5, 2.5 Hz, H-4α), 4.31 (1H,dd, J=14.5, 3.6 Hz, H-4β), 3.58 (1H, dd, J=4.1, 1.9, H-5a), 3.58 (1H, d, J=20.5 Hz, H-2α), 3.301 (3H, s, *C*H_3OCO_2), 3.273 (3H, s, *C*H_3OCO), 3.23 (1H, ddd, J=20.5, 3.6, 2.5 Hz, H-2β), 2.51 (1H, ddd, J=13.3, 3.6, 2.5 Hz, H-10β), 2.02 (1H,br d, J=13.3 Hz, H-6α), 1.70 (^1H ddd, J=13.2, 13.0, 3.8 Hz, H-10α), 1.121 (3H, s, Me–C_{10a}), 1.048 (3H, s, Me–C_{10c}), 0.894 (3H, s, Meβ–C_7), 0.735 (3H, s, Meα–C_7); ^{13}C NMR (75 MHz, C_6D_6) δ 165.4 (CO_2), 164.4 (C_{3a}), 154.2 (OCO_2), 143.3 (C_1), 137.3 (C_{10b}), 120.0 (C_3), 82.3 (C_{5a}), 68.9 (C_4), 54.6 (*C*H_3OCO_2), 51.1 (*C*H_3OCO), 47.8 (C_{10c}), 43.4 (C_{6a}), 41.7 (C_8), 40.3 (C_{10a}), 38.8 (C_{10}), 33.6 (C_7), 33.3 (Meα–C_7), 31.8 (C_2), 25.3 (Me–C_{10c}), 24.2 (C_6), 22.0 (Meβ–C_7), 20.3 (Me–C_{10a}), 19.1 (C_9); MS (EI) *m*/*z* 404 (M^+, 8), 387 (18), 357

(41), 313 (17), 251 (100), 238 (55), 237 (55), 193 (32), 123 (33), 91 (27), 69 (34), 59 (48); HRMS *m/z* calcd for $C_{23}H_{32}O_6$ 404.2199, found 404.2128.

4.3. Construction of the D ring and further functionalization of the spongiane framework

4.3.1. 7α-Acetoxy-11-methoxycarbonyloxy-spongia-9(11),13-dien-16-one (25). A mixture of the adduct **24** (17.85 mg, 0.043 mmol) and ZnI_2 (18.8 mg, 0.058 mmol) in acetic anhydride (0.8 mL) was stirred at rt for 72 h. The reaction mixture was poured into water and extracted with ether. The organic extracts were washed with aq $NaHCO_3$, brine and dried. Chromatography of the residue obtained after evaporation of the solvent, using hexane–acetate (8:2) as eluent, afforded the lactone **25** (15.6 mg, 82%) as an oil. $[\alpha]_D^{24}$ +24.0° (0.3, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2954, 2926, 1760, 1735, 1271, 1234, 1019, 680; ^1H NMR (300 MHz, C_6D_6) δ 4.61 (1H, dd, *J*=3.8, 1.9 Hz, H-7), 4.29 (1H, ddd, *J*=16.6, 2.5, 2.5 Hz, H-15), 4.11 (1H, ddd, *J*=16.6, 3.4, 1.6 Hz, H′-15), 3.278 (3H, s, CH_3OCO_2), 3.13 (1H, ddd, *J*=21.5, 2.5, 1.6 Hz, H-12), 2.99 (1H, ddd, *J*=21.5, 3.4, 2.5 Hz, H′-12), 2.50 (1H, ddd, *J*=12.8, 3.2, 3.2 Hz, H-1β), 1.93 (1H, ddd, *J*=13.0, 3.2, 2.0 Hz, H-6α), 1.74 (1H, ddd, *J*=13.0, 12.8, 3.8 Hz, H-1α), 1.439 (3H, s, CH_3CO), 1.146 (3H, s, Me–C_{10}), 0.849 (3H, s, Me–C_8), 0.703 (3H, s, Meβ–C_4), 0.649 (3H, s, Meα–C_4); ^{13}C NMR (75 MHz, C_6D_6) δ 171.2 (C_{16}), 169.5 (CH_3CO), 163.2 (C_{14}), 153.5 (OCO_2), 141.6 (C_{11}), 134.3 (C_9), 122.4 (C_{13}), 74.3 (C_7), 67.9 (C_{15}), 54.7 (CH_3OCO_2), 45.1 (C_5), 44.2 (C_8), 42.3 (C_{10}), 41.2 (C_3), 39.2 (C_1), 33.6 (C_4), 33.4 (Meα–C_4), 28.4 (Me–C_8), 26.4 (C_{12}), 22.5 (Meβ–C_4), 22.3 (C_6), 21.5 (CH_3CO), 20.3 (Me–C_{10}), 19.4 (C_2); MS (EI) *m/z* 432 (M^+, 0.3), 390 (40), 372 (33), 357 (47), 314 (100), 289 (41), 275 (97), 261 (65), 250 (23), 223 (42); HRMS *m/z* calcd for $C_{24}H_{32}O_7$ 432.2148, found 432.2134.

4.3.2. 7α-Hydroxy-11-oxo-spongia-13-en-16-one (26). A solution of enol carbonate **25** (14.2 mg, 0.033 mmol) in anhydrous MeOH (0.44 mL) was treated with a 2% solution of sodium methoxide in MeOH (0.44 mL) at −40 °C. After being left at −20 °C in the fridge for 5 days, the mixture was poured into cold water, acidified by addition of 5% HCl, stirred for 5 min at rt and extracted with diethyl ether. The diethyl ether solution was washed with 10% aq solution of $NaHCO_3$ and water, dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed over silica gel using hexane–ethyl acetate (7:3) as eluent to give the hydroxy ketone **26** (10.5 mg, 96%) as a white solid. Mp 287–289 °C (with decomp; at 240–244 °C prism like crystals were transformed into needle like crystals) (from cold MeOH); $[\alpha]_D^{22}$ −131.1° (0.4, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3500–3350, 2924, 2868, 2850, 1760, 1700, 1390, 1223, 1068, 1017; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (1H, ddd, *J*=16.7, 3.2, 1.9 Hz, H-15α), 4.82 (1H, ddd, *J*=16.7, 3.0, 2.3 Hz, H-15β), 3.99 (1H, br d, *J*=1.9 Hz, H-7), 3.13 (1H, ddd, *J*=20.7, 2.5, 2.5 Hz, H-12α), 2.93 (1H, br d, *J*=20.7 Hz, H-12β), 2.81 (1H, s, H-9), 2.22 (1H, ddd, *J*=13.0, 4.5, 3.2 Hz, H-1β), 1.89 (1H, ddd, *J*=15.1, 13.4, 2.3 Hz, H-6β), 1.75–1.61 (2H, m, H-2 and H-6α), 1.49–1.36 (3H, m, H′-2, H-3 and H-5), 1.274 (3H, s, Me–C_{10}), 1.20 (1H, m overlapped with Me–C_8, H-3′), 1.181 (3H, s, Me–C_8), 0.858 (3H, s, Meβ–C_4), 0.852 (3H, s, Meα–C_4), 0.85 (1H, m overlapped with Me–C_4, H-1α); ^{13}C NMR (100 MHz) δ 206.4 (C_{11}), 172.6 (C_{16}), 168.4 (C_{14}), 122.4 (C_{13}), 71.4 (C_7), 69.0 (C_{15}), 60.7 (C_9), 46.7 (C_5), 45.8 (C_8), 41.9 (C_3), 38.6 (C_1), 38.1 (C_{12}), 37.2 (C_{10}), 33.2 (Meα–C_4), 32.7 (C_4), 26.4 (C_6), 23.0 (Me–C_8), 21.6 (Meβ–C_4), 18.0 (C_2), 16.1 (Me–C_{10}); MS (EI) *m/z* 332 (M^+, 17), 314 (52), 299 (37), 288 (32), 271 (23), 231 (15), 166 (100), 123 (34), 91 (13), 69 (24); HRMS *m/z* calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1998. Anal. Calcd for $C_{20}H_{28}O_4$: C 72.26, H 8.49; found: C 72.54, H 8.51.

4.3.3. 7,11-Dioxo-spongia-13-en-16-one (27). A solution of alcohol **26** (9.6 mg, 0.028 mmol) in acetone (1 mL) was treated at 0 °C with a few drops of the Jones reagent[13] (until persistence of the orange colour) and stirred for 5 min. The mixture was treated with a few drops of MeOH, poured into water and extracted with ethyl acetate. The organic phase was washed with diluted $NaHCO_3$ solution and brine. After drying and concentration, the residue was chromatographed, using hexane–ethyl acetate (7:3) as eluent, to give diketone **27** (8.8 mg, 92%) as a white solid. Mp 216–219 °C with decomp (the compound was crystallized by slow evaporation from CH_2Cl_2 solution); $[\alpha]_D^{22}$ −107.1° (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2919, 2850, 2850, 1761, 1748, 1709, 1670, 1389, 1341, 1187, 1095, 1070, 1016; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (1H, ddd, *J*=18.7, 3.2, 2.5 Hz, H-15), 5.12 (1H, ddd, *J*=18.7, 3.2, 2.3 Hz, H′-15), 3.16 (1H, ddd, *J*=21.5, 3.2, 2.3 Hz, H-12), 3.01 (1H, ddd, *J*=21.5, 3.2, 2.5 Hz, H′-12), 2.71 (1H, s, H-9), 2.63 (1H, dd, *J*=16.6, 15.6 Hz, H-6β), 2.49 (1H, dd, *J*=15.6, 2.8 Hz, H-6α), 2.35 (1H, ddd, *J*=13.3, 4.7, 3.0 Hz, H-1β), 1.454 (3H, s, Me–C_8), 1.364 (3H, s, Me–C_{10}), 1.30 (1H, br d, *J*=2.8, H-5), 0.891 (3H, s, Meα–C_4), 0.872 (3H, s, Meβ–C_4), 0.84 (1H, ddd, *J*=13.3, 13.3, 3.3 Hz, H-1α); ^{13}C NMR (75 MHz) δ 208.7 (C_{11}), 203.7 (C_7), 171.8 (C_{16}), 165.0 (C_{14}), 123.5 (C_{13}), 71.2 (C_{15}), 66.1 (C_9), 53.5 (C_5), 53.3 (C_8), 41.4 (C_3), 38.6 (C_1), 37.9 (C_{12}), 36.7 (C_{10}), 35.9 (C_6), 33.5 (C_4), 32.6 (Meα–C_4), 24.0 (Me–C_8), 20.9 (Meβ–C_4), 17.8 (C_2), 15.4 (Me–C_{10}); MS (EI *m/z* 330 (M^+, 76), 312 (32), 287 (52), 194 (44), 165 (34), 123 (91), 109 (100), 91 (43), 69 (70); HRMS *m/z* calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1832.

4.3.4. 7β-Hydroxy-11-oxo-spongia-13-en-16-one (28). A solution of BH_3–THF complex (1 M solution in THF, 108 μL, 0.108 mmol) was added at 0 °C to a solution of diketone **27** (9.0 mg, 0.027 mmol) in THF (0.8 mL) and the mixture was stirred at the same temperature for 2 h, after which H_2O (0.2 mL) was carefully added to the mixture at 0 °C. After the solution had been stirred at room temperature for 5 min, it was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was chromatographed on silica gel, using hexane–ethyl acetate (3:2) as eluent, to give hydroxyl-ketone **28** (9.0 g, 99%) as a solid. Mp 271 °C (at 230 °C the original crystals were transformed into needle like crystals which melt with decomposition at 271 °C) (from cold MeOH); $[\alpha]_D^{20}$ −67.9° (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3630–3500, 2922, 2868, 2850, 1760, 1740, 1715, 1462, 1071, 1051, 1009; ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (1H, ddd, *J*=18.2, 2.6, 2.6 Hz, H-15α), 4.94 (1H, ddd, *J*=18.2, 2.6, 2.6 Hz, H-15β), 3.81 (1H, dd, *J*=11.3, 4.0 Hz, H-7), 3.12 (1H, ddd, *J*=20.9, 2.6, 2.6 Hz, H-12α),

2.97 (1H, ddd, $J=20.9$, 2.6, 2.6 Hz, H-12β), 2.27 (1H, s, H-9), 2.22 (1H, ddd, $J=12.8$, 4.3, 3.0 Hz, H-1β), 1.85 (1H, ddd, $J=13.0$, 4.5, 2.1 Hz, H-6), 1.265 (3H, s, Me–C_{10}), 1.146 (3H, s, Me–C_8), 0.879 (3H, s, Meα–C_4), 0.860 (3H, s, Meβ–C_4), 0.72 (1H, ddd, $J=13.0$, 13.0, 3.6 Hz, H-1α); ^{13}C NMR (75 MHz) δ 205.2 (C_{11}), 172.4 (C_{16}), 168.4 (C_{14}), 122.2 (C_{13}), 75.4 (C_7), 70.6 (C_{15}), 65.4 (C_9), 53.4 (C_5), 45.7 (C_8), 41.6 (C_3), 38.6 (C_1), 38.0 (C_{12}), 36.7 (C_{10}), 33.3 (Meα–C_4), 32.1 (C_4), 28.3 (C_6), 21.6 (Meβ–C_4), 17.9 (C_2), 16.7 and 16.4 (Me–C_8 and Me–C_{10}); MS (EI) *m/z* 332 (M^+, 58), 317 (16), 288 (26), 271 (5), 166 (100), 123 (47), 91 (21), 69 (43); HRMS *m/z* calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1967.

4.3.5. 7β,11β-Dihydroxy-spongia-13-en-16-one (30). A solution of hydroxyl-ketone **28** (8.2 mg, 0.025 mmol) in anhydrous CH_2Cl_2 (0.7 mL) was treated with DIBAL-H (1.0 M solution in cyclohexane; 110 μL, 0.11 mmol) at −78 °C. The solution was stirred at the same temperature for 2 h, a few drops of MeOH were added and the reaction mixture was allowed to warm to 0 °C, after which it was treated with a solution of sodium tartrate (60 mg, 0.31 mmol) in H_2O (0.75 mL) and extracted with CH_2Cl_2. The organic phase was washed with diluted $NaHCO_3$ solution and water. After drying and concentration, the residue, containing the acid labile hemiacetal **29**, was used directly in the next step without purification.

A mixture of the residue obtained in above reaction (8.25 mg), MnO_2 (50 mg) and CH_2Cl_2 (0.6 mL) was stirred overnight at rt. The mixture was filtered through Celite and the solvent was removed under vacuum to give a residue that was purified by chromatography, using hexane–ethyl acetate (3:2) as eluent, to give the dihydroxy lactone **30** (5.6 mg, 71% for the two steps) as a white solid. Mp 275–277 °C (from cold MeOH); $[\alpha]_D^{24}$ −15.0° (0.15, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3500–3050, 2922, 2853, 1751, 1742, 1721, 1456, 1441, 1384, 1075, 1054, 989, 970, 882; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (1H, ddd, $J=18.3$, 3.4, 1.9 Hz, H-15), 4.91 (1H, ddd, $J=18.3$, 2.6, 2.6 Hz, H′-15), 4.77 (1H, dd, $J=3.8$, 3.8 Hz, H-11), 3.49 (1H, ddd, $J=11.3$, 6.7, 4.4 Hz, H-7), 2.45 (1H, dddd, $J=18.1$, 3.8, 3.4, 2.6 Hz, H-12), 2.36 (1H, br dd, $J=18.1$, 1.9 Hz, H′-12), 1.503 (3H, s, Me–C_8), 1.45 (1H, d, $J=6.7$ Hz, HO–C_7), 1.277 (3H, s, Me–C_{10}), 0.872 (3H, s, Meα–C_4), 0.867 (3H, s, Meβ–C_4); ^{13}C NMR (100 MHz) δ 174.6 (C_{16}), 168.2 (C_{14}), 120.8 (C_{13}), 76.5 (C_7), 71.3 (C_{15}), 64.4 (C_{11}), 56.5 (C_9), 54.6 (C_5), 42.7 (C_8), 41.6 (C_3), 39.8 (C_1), 37.7 (C_{10}), 33.3 (C_4), 33.3 (Meα–C_4), 29.7 (C_{12}), 28.9 (C_6), 21.2 (Meβ–C_4), 18.3 (C_2), 17.7 (Me–C_{10}), 15.7 (Me–C_8); MS (EI) *m/z* 334 (M^+, 4), 316 (47), 298 (26), 271 (27), 283 (13), 192 (33), 175 (100), 167 (62), 123 (61), 109 (46), 69 (61); HRMS *m/z* calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2130.

4.3.6. 7β,11β-Diacetoxy-spongia-13-en-16-one (dorisenone C, 3). DMAP (4.4 mg, 0.036 mmol) was added to a solution of the diol **30** (4.8 mg, 0.014 mmol), acetic anhydride (80 μL, 0.82 mmol), and pyridine (67 μL) in dry dichloromethane (0.4 mL) and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with ethyl acetate and then washed successively with 5% HCl, 5% $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated to afford a residue which was purified on silica gel, eluting with hexane–ethyl acetate (8:2) to give pure diacetate **3** (4.8 mg, 80%) as an amorphous solid that could not be induced to crystallize. $[\alpha]_D^{24}$ +30.1° (0.2, $CHCl_3$) (lit.[3] $[\alpha]_D^{27}$ +35.5°); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, br s, H-11), 4.85 (1H, ddd, $J=16.9$, 2.6, 2.6 Hz, H-15β), 4.68 (1H, dd, $J=11.0$, 4.2 Hz, H-7), 4.51 (1H, ddd, $J=16.9$, 2.4, 2.4 Hz, H-15α), 2.45 (2H, br s, H_2-12), 2.136 (3H, s, CH_3CO_2-C_{11}), 2.051 (3H, s, CH_3CO_2-C_7), 1.87 (1H, br d, $J=12.4$ Hz, H-1β), 1.87 (1H, m, H-6α),1.574 (3H, s, Me–C_8), 1.53 (1H, m, H-6β), 1.090 (3H, s, Me–C_{10}), 1.43 (1H, br d, $J=13.5$ Hz, H-3β), 1.15 (1H, ddd, $J=13.5$, 14.5, 3.6 Hz, H-3α), 0.96 (1H, br d, 12.7, H-5), 0.880 (3H, s, Meα–C_4), 0.835 (3H, s, Meβ–C_4); ^{13}C NMR (100 MHz) δ 173.4 (C_{16}), 170.0 ($CH_3CO_2C_{11}$), 169.9 ($CH_3CO_2C_7$), 165.5 (C_{14}), 121.9 (C_{13}), 78.4 (C_7), 69.6 (C_{15}), 65.6 (C_{11}), 55.6 (C_9), 54.3 (C_5), 41.5 (C_8), 41.4 (C_3), 39.5 (C_1), 37.7 (C_{10}), 33.3 (C_4), 33.1 (Meα–C_4), 29.2 (C_{12}), 24.5 (C_6), 21.6 ($CH_3CO_2C_{11}$), 21.5 ($CH_3CO_2C_7$), 21.2 (Meβ–C_4), 18.2 (C_2), 17.4 (Me–C_{10}), 17.3 (Me–C_8); MS (EI) *m/z* 419 ($M^+ + 1$, 1), 418 (M^+, 0.5), 358 (7), 343 (5), 298 (100), 283 (48), 188 (52), 175 (80), 149 (42), 123 (20); HRMS *m/z* calcd for $C_{24}H_{34}O_6$ (M^+) 418.2355, found 418.2350.

4.3.7. 7β,11β-Dihydroxy-spongia-13(16),14-diene (31). A solution of the hydroxyl-ketone **28** (6.6 mg, 0.021 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was treated with DIBAL-H (1.0 M solution in cyclohexane; 74 μL, 0.074 mmol) at −78 °C. The solution was stirred at the same temperature for 2 h and then quenched by the addition of aq saturated solution of NH_4Cl and extracted with ethyl acetate. The organic phase was washed with 5% HCl and water, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography, using hexane–ethyl acetate (8:2) as eluent, to afford the furan **31** (6.0 mg, 95%) as a solid. Mp 194–199 °C (crystals were obtained from a CH_2Cl_2 solution by slow evaporation); $[\alpha]_D^{24}$ −1.6° (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3600–3050, 2917, 2853, 1727, 1445, 1042, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, d, $J=1.7$ Hz, H-15), 7.15 (1H, dd, $J=2.6$, 1.5 Hz, H-16), 4.72 (1H, br s, H-11), 3.52 (1H, dd, $J=11.3$, 4.1 Hz, H-7), 2.78 (1H, ddd, $J=16.9$, 1.5, 0.9 Hz, H-12β), 2.69 (1H, dddd, $J=16.9$, 2.6, 1.7, 1.5 Hz, H-12α), 1.575 (3H, s, Me–C_8), 1.063 (3H, s, Me–C_{10}), 0.874 (3H, s, Meα–C_4), 0.855 (3H, s, Meβ–C_4); ^{13}C NMR (75 MHz) δ 138.6 (C_{16}), 137.6 (C_{15}), 131.5 (C_{14}), 116.7 (C_{13}), 79.7 (C_7), 65.7 (C_{11}), 57.1 (C_9), 54.9 (C_5), 41.7 (C_3), 40.2 (C_1), 40.1 (C_8), 37.8 (C_{10}), 33.3 (C_4), 33.3 (Meα–C_4), 32.6 (C_{12}), 29.1 (C_6), 21.5 (Me–C_{10}), 21.2 (Meβ–C_4), 18.5 (C_2), 17.7 (Me–C_8); MS (EI) *m/z* 318 (M^+, 100), 300 (4), 285 (25), 267 (10), 162 (15), 123 (23); HRMS *m/z* calcd for $C_{20}H_{30}O_3$ 318.2245, found 318.2265.

4.3.8. 7β,11β-Diacetoxy-spongia-13(16),14-diene (32). The diol **31** (5 mg) was acetylated as described above for **30**. Purification by chromatography, using hexane–ethyl acetate (8:2) as eluent, afforded the diacetate **32** (5.4 mg, 86%) as a colourless oil. $[\alpha]_D^{24}$ +28.9° (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2924, 2850, 1734, 1373, 1235, 1215, 1039; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (1H, d, $J=1.5$ Hz, H-15), 7.09 (1H, s, H-16), 5.77 (1H, br d, $J=4.0$ Hz, H-11), 4.69 (1H, dd, $J=11.1$, 4.0 Hz, H-7), 2.85 (1H, br d, $J=16.4$ Hz, H-12β), 2.65 (1H, ddd, $J=16.4$, 4.3, 1.6 Hz,

H-12α), 2.186 (3H, s, CH_3CO_2–C_{11}), 2.034 (3H, s, CH_3CO_2–C_7), 2.00 (1H, m, H-6β), 1.89 (1H, br d, J= 12.2 Hz, H-1β), 1.631 (3H, s, Me–C_8), 1.285 (1H, s, H-9), 1.063 (3H, s, Me–C_{10}), 1.00 (1H, dd, J=12.6, 2.5 Hz, H-5), 0.88 (1H, m overlapped with Meβ–C_4, H-1α), 0.878 (3H, s, Meα–C_4), 0.838 (3H, s, Meβ–C_4); ^{13}C NMR (100 MHz) δ 170.5 and 170.3 (2xCH_3CO_2), 137.5 (C_{16}), 137.1 (C_{15}), 131.7 (C_{14}), 116.5 (C_{13}), 81.9 (C_7), 67.2 (C_{11}), 56.2 (C_9), 54.6 (C_5), 41.6 (C_3), 40.0 (C_8), 39.0 (C_1), 37.8 (C_{10}), 33.4 (C_4), 33.2 (Meα–C_4), 28.4 (C_{12}), 24.8 (C_6), 21.7 and 21.6 (2×CH_3CO_2), 21.2 (Meβ–C_4), 18.4 (C_2), 22.7 (Me–C_{10}), 17.4 (Me–C_8); MS (EI) m/z 402 (M^+, <0.5), 342 (100), 282 (35), 267 (41), 207 (31), 145 (12); HRMS m/z calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2422.

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Stereoselective preparation of trisubstituted (*Z*)-alkenes; synthesis of the C17–C27 fragment of (−)-laulimalide

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Abstract—A Ni-catalyzed cross-coupling reaction of (*Z*)-5-(*tert*-butyldiphenylsilyl)oxy-3-bromo-1-trimethylsilyl-3-penten-1-yne (**1**) with alkyl Grignard reagent gives (*Z*)-3-alkyl-5-(*tert*-butyldiphenylsilyl)oxy-1-trimethylsilyl-3-penten-1-ynes (**2**) stereospecifically in good yields. The (*Z*)-enyne **2a** is transformed in four steps to (*Z*)-3-methyl-5-silyloxy-3-pentenal (**3**), which is coupled with ketophosphonate **4** to give enone **13**. The η-hydroxyallyl methanesulfonate derived from **13** is cyclized to 3,6-dihydro[2*H*]pyran by an intramolecular SN2′ reaction stereoselectively, furnishing a C17–C27 carbon unit of (−)-laulimalide.

1. Introduction

Stereocontrolled synthesis of tricarbon-substituted (*Z*)-alkenes is important for the synthesis of organic molecules. Since the configuration of the (*Z*)-structural unit in the molecule can fix the shape, two substituted carbon branches located in the *cis* relation of olefin play a specific role either in the constitution of the macro-lactone ring structure or to fix the conformation of acyclic structure, as shown in Figure 1. In fact, a methyl substituted (*Z*)-alkenyl unit can be observed in the structures of biologically important natural products, e.g. in macrolides, such as (−)-laulimalide, (−)-zampanolide, haterumalide NA, and (+)-lasonolide A[1] as well as in acyclic marine natural products, such as (−)-discodermolide, callystatin A and (−)-ratjadone.[2]

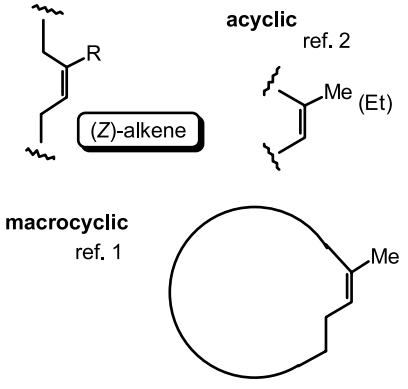
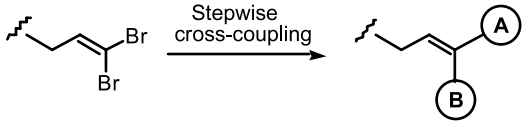


Figure 1.

Stepwise stereospecific cross-coupling of 1,1-dibromo-1-alkene, as shown in Scheme 1, is a potential method for the geometrically controlled synthesis of trisubstituted alkenes.[3] We reported carbon conjugated trisubstituted alkenes by this method.[4] More recently, we have reported that Pd-catalyzed cross-coupling reaction of 3-bromo-3-en-1-yne can afford both the (*E*)- or (*Z*)-trisubstituted alkenes stereoselectively.[5] In particular, isomerization of the (*Z*)-alkenyl–palladium complex to the (*E*)-alkenyl–palladium complex via cumulenyl–palladium complex intermediate in CH_2Cl_2 or DMF and subsequent cross-coupling in Sonogashira and Stille coupling is especially useful for the synthesis of the tricarbon-substituted conjugated (*Z*)-alkenyl unit, as shown in Scheme 2. After finding this unique isomerization, we have reinvestigated our results obtained previously by Ni-catalyzed Kumada–Tamao–Corriu coupling reaction of bromoenyne,[4a] and have found that the reaction proceeded completely with an inversion of the stereochemistry and have made a correction of the misassignment of the stereochemistry.[6] In this paper, we report the detail of this unique stereospecific synthesis of the (*Z*)-alkenyl unit by Kumada–Tamao–Corriu cross-coupling



Scheme 1.

Keywords: Bromoenyne; Trisubstituted (*Z*)-alkene; (−)-Laulimalide; SN2′ reaction; 3,6-Dihydro[2*H*]pyran.
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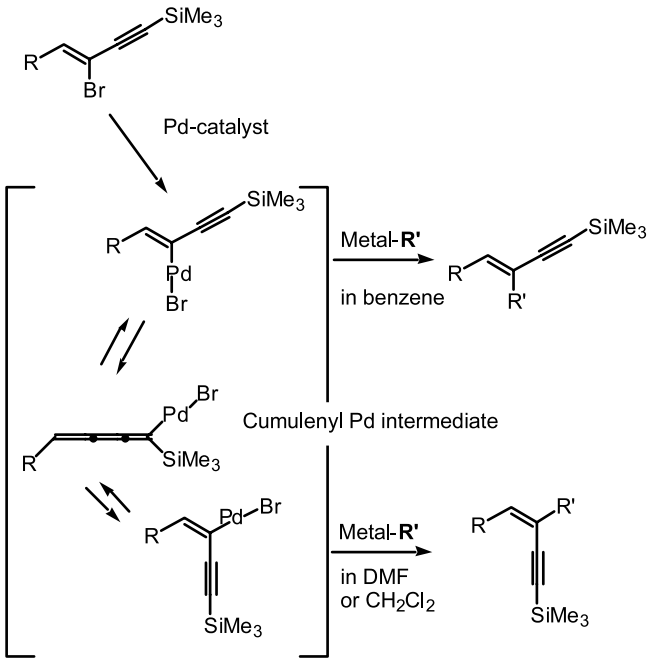


Scheme 2.

of 3-bromo-3-en-1-yne and efficient access to the C17–C27 fragment of (−)-laulimalide by means of the (*Z*)-alkenyl product.

2. Results and discussion

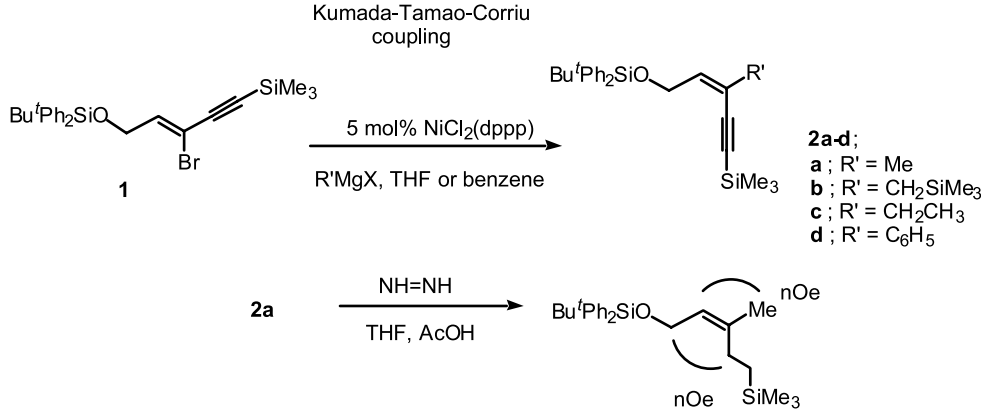
2.1. Kumada–Tamao–Corriu coupling of (*Z*)-3-bromo-1-trimethylsilyl-3-penten-1-yne

Although the Pd-catalyzed cross-coupling reactions of (*Z*)-5-(*tert*-butyldiphenylsilyl)oxy-3-bromo-1-trimethylsilyl-3-penten-1-yne (**1**) with terminal alkyne, vinylboronic acid or vinylstannane proceeded with retention of the configuration in benzene under Sonogashira, Suzuki and Stille conditions,[4,5] we have recently reported the Sonogashira and Stille reactions of **1** undergo with inversion of the configuration in CH_2Cl_2 or DMF. We have proposed this unusual isomerization mechanism by a 1,3-rearrangement of the σ-alkenyl–palladium complex through the cumulenyl–palladium intermediate shown in Scheme 2.[5] Upon careful reinvestigation of our previous results, this inversion was found to occur exclusively in the Ni-catalyzed Kumada–Tamao–Corriu coupling of **1** with ethylmagnesium bromide to give only (*Z*)-enyne. The coupling was carried out either in THF, ether or benzene with alkylmagnesium halide in the presence of 5–10 mol% of $NiCl_2$(dppp). The yields were quite good with methyl and trimethylsilylmethylmagnesium halide in 84 and 74% yields for **2a** and **2b**, respectively. With ethylmagnesium bromide, the yield of **2c** was 61% along with a small amount of enyne dimer and a reduced product by β-hydride elimination. The reaction with phenylmagnesium bromide gave **2d** poorly in less than 20% yield. The stereochemistry of **2** was confirmed by an NOE experiment after chemoselective reduction of trimethylsilylethyne to trimethylsilylethane with diimide,[7] as shown in Scheme 3, and also conversion to a dihydropyran ring in the later stage. It is interesting that the isomerization by the 1,3-rearrangement can take place depending on the solvent in the case of Pd catalyzed reactions, although the corresponding rearrangement takes place in most solvents in Ni-catalyzed cross-coupling reaction to give an isomerized alkene. Since a geometrically pure trisubstituted (*Z*)-alkene is an important functional group in organic synthesis, this method will be useful not only for the synthesis of the (*Z*)-enyne but also for that of a trisubstituted alkene. In fact, a functionalization of the trimethylsilylethynyl unit is possible such as to lead to other functional groups including ethenyl, hydroxyethyl, formylmethyl, and carboxymethyl, which can be used for the dihydropyran synthesis in Section 2.2.

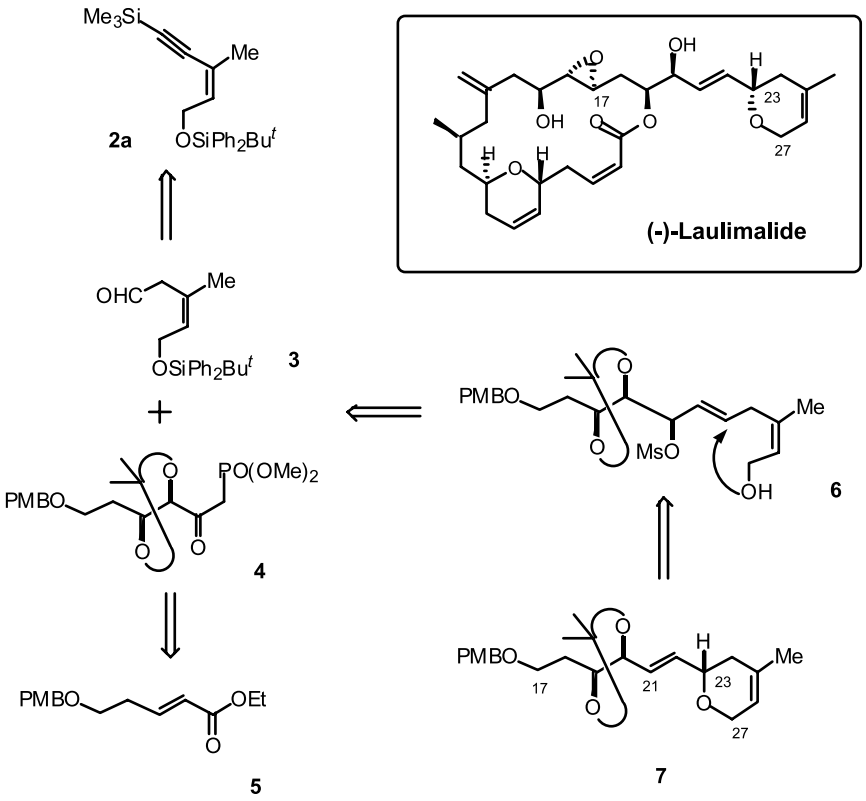
2.2. Synthetic plan for the C17–C27 fragment of (−)-laulimalide

(−)-Laulimalide is a marine natural product, possessing a high degree of cytotoxicity in a number of human cancer cell lines.[8] Although several elegant total syntheses have been achieved,[9] the 4-methyl-3,6-dihydro[2*H*]pyran ring located in the C23–C27 carbon chain, is prepared mostly by ring closing metathesis[9a,c,e–h] and/or by hetero Diels–Alder reaction.[9b,d]

We planned to use the above (*Z*)-enyne unit for the preparation of 4-methyl-3,6-dihydropyran. The structure of (−)-laulimalide and its synthetic plan for the C17–C27 carbon skeleton including the pyran ring are outlined in



Scheme 3.



Scheme 4.

Scheme 4. Reaction steps include a manipulation of aldehyde **3** from trimethylsilyethynyl alkene **2a** and the Horner–Wadsworth–Emmons reaction of ketophosphonate **4** being derived from **5** with aldehyde **3** giving the α,β-unsaturated ketone. The resultant enone will lead to dihydropyran **7** in three steps via cyclization of allyl methanesulfonate **6** by an intramolecular anti-S_N2' reaction.

2.3. Preparation of aldehyde 3

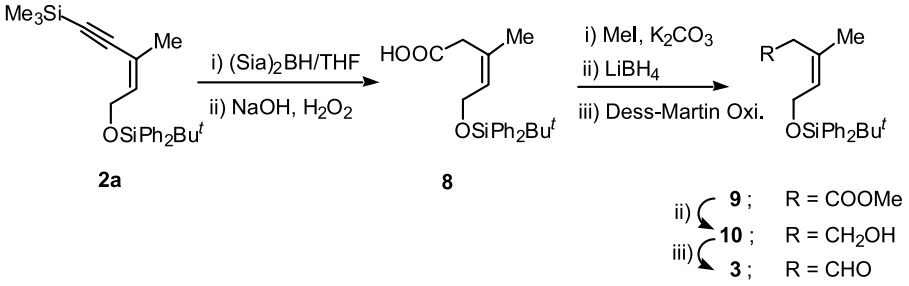
Conversion of **2a** to aldehyde **3** required four steps. First, hydroboration of the terminal alkyne and successive oxidation by Zweifel's method[10] gave carboxylic acid **8** in 72% yield. This acid was led to the methyl ester by treatment with iodomethane in the presence of K_2CO_3 to give **9** quantitatively. Reduction of the ester with $LiBH_4$ in THF afforded alcohol **10** in 79% yield. Oxidation of **10** with Dess-Martin periodinane gave aldehyde **3** quantitatively (Scheme 5).

2.4. Preparation of ketophosphonate 4 and Horner–Wadsworth–Emmons reaction

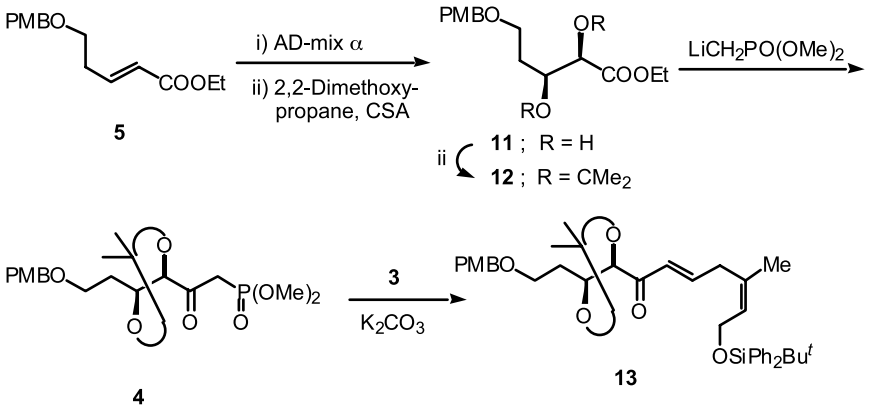
The synthesis of the C17–C20 carbon chain started from α,β-unsaturated ester **5**.[11] Sharpless asymmetric dihydroxylation of **5** using AD-mix-α gave diol **11** in 96% yield with 99% ee after recrystallization.[12] After a protection of the diol as an acetonide by 2,2-dimethoxypropane in the presence of CSA, the reaction of acetonide **12** with lithium salt of dimethyl methylphosphonate gave ketophosphonate **4** in 80% yield in two steps. Horner–Wadsworth–Emmons reaction of **4** with **3** in the presence of K_2CO_3 in THF and water[13] gave enone **13** in 70% yield (Scheme 6).

2.5. Ring formation of 3,6-dihydro[2*H*]pyran

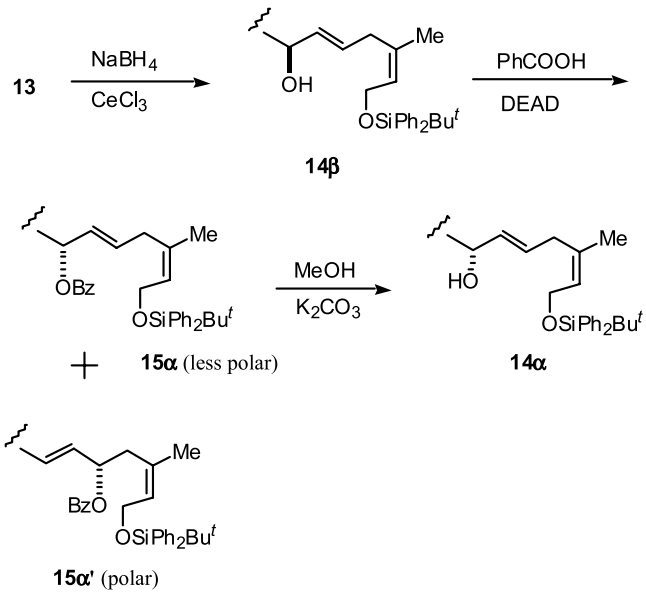
The precursors for the cyclization to 3,6-dihydro[2*H*]pyran were prepared from **13**. Although a reduction of ketone with certain hydride reagents such as $LiAl(O^tBu)_3H$ or DIBAL-H gave a lower selectivity along with the 1,4-reduction product, that with $NaBH_4$ in the presence of $CeCl_3$



Scheme 5.



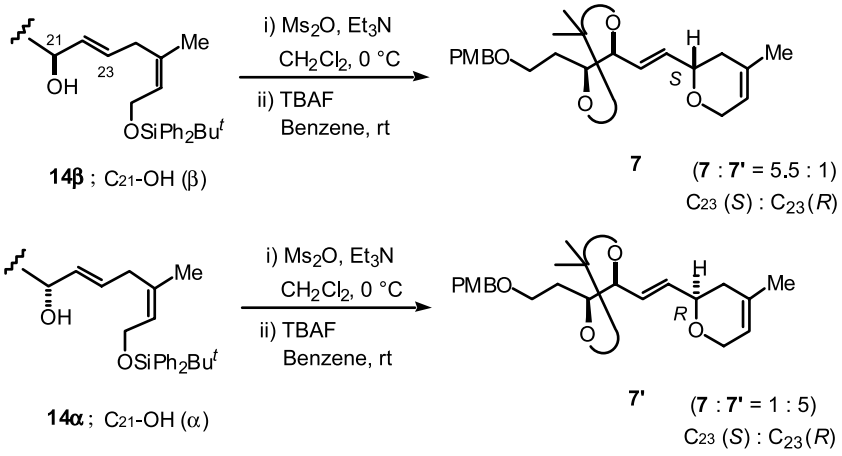
Scheme 6.



Scheme 7.

at −78 °C gave β-allylic alcohol **14**β in 80% yield selectively, with a >10:1 ratio. An β-alcohol was predominantly produced as was reported in the similar function system.[14] The other stereoisomer was prepared by an inversion of this chiral alcohol using Mitsunobu reaction. Mitsunobu reaction of **14**β with benzoic acid in the presence of diethyl diazodicarboxylate (DEAD) gave a 1:1 mixture of **15**α (C21 benzoate) and **15**α′ (C23 benzoate) in 81% yield, which were separated by HPLC. The less polar compound **15**α was obtained with a >10:1 diastereomeric ratio over the other diastereomer **15**β. Meanwhile, the regioisomer **15**α′ contained its diastereomer **15**β′ with a 20% diastereomeric ratio. Finally, methanolysis of **15**α gave **14**α in 97% yield (Scheme 7).

Treatment of **14**β with methanesulfonic anhydride in the presence of triethylamine in CH_2Cl_2 at 0 °C gave the corresponding methanesulfonate quantitatively. Without purification, it was subjected to an S_N2' reaction. When the methanesulfonate was treated with TBAF in benzene, (*S*)-dihydropyran **7** was obtained along with its diastereomer **7**′ in 60% yield with a 5.5:1 ratio. This reaction may be explained as follows. As soon as the deprotection of the silyl group with TBAF occurred, a generated oxygen nucleophile attacks the C23 carbon from *si*-face to form the pyran ring and simultaneous elimination of the methanesulfonate produces the (*E*)-alkenyl bond and (*S*)-chiral center in an anti-S_N2' fashion. The undesired (*R*)-isomer was produced via a S_N1' type reaction in a 15% diastereomeric ratio. On the other hand, the opposite stereochemistry took place in the same reaction of **14**α in which dihydropyran **7**′ was obtained for the most part along with **7** in 61% yield with a 5:1 ratio. Tosylate or nosylate of **14**α did not work well. In



Scheme 8.

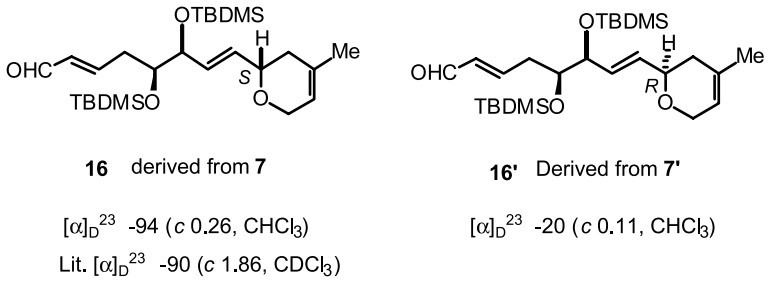


Figure 2.

both cases, substitutions proceeded well in benzene in about 5:1 ratio but gave a lower ratio in THF (Scheme 8).

The stereochemistry of 3,6-dihydro[2*H*]pyran was confirmed after a conversion to the fragment that Wender et al. used for their total synthesis of (−)-laulimalide.[9d] Functionalization and two-carbon extension by seven-step reactions from **7** reached α,β-unsaturated aldehyde **16**.[15] The proton NMR of the Wender's α,β-unsaturated aldehyde **16** was exactly matched with that of the major isomer being derived from **7**. Its specific degree −94 (*c* 0.26, $CHCl_3$) was quite close to that of the Wender's intermediate [−90 (*c* 1.86, $CDCl_3$)]. On the other hand, the specific degree of its diastereomer **16′** derived from **7′** was found to be −20 (*c* 0.11, $CHCl_3$) (Fig. 2).

3. Conclusion

A Ni-catalyzed cross-coupling reaction of **1** with alkyl Grignard reagent gave alkylated (*Z*)-enyne **2** with inversion of the initial configuration stereospecifically. A ring construction of 3,6-dihydro[2*H*]pyran was achieved by an intramolecular S_N2' reaction of η-hydroxyallyl methanesulfonate. The substitution reaction accompanied with chirality transfer effectively gave the C17–C27 carbon unit of (−)-laulimalide.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded at 300 or 400 MHz and at 75 or 100 MHz, respectively. Melting points were obtained on a melting point apparatus and were uncorrected. Mass spectra were recorded using electron impact (EI) ionization at 70 or 20 eV or chemical ionization (CI) with isobutene gas. Silica gel (70–230 mesh) was used for flash chromatography. Analytical thin-layer chromatography (TLC) was performed on glass pre-coated with silica gel (0.25 mm thickness). High performance liquid chromatography (HPLC) was carried out on a UV spectrophotomeric detector (254 nm) to which a 20×250 mm size column packed with silica gel was attached. All experiments were carried out under an argon atmosphere. THF and ether were dried over sodium/benzophenone ketyl, and CH_2Cl_2 was dried over P_2O_5, and they were distilled prior to use. The solvent extracts were dried over $MgSO_4$, and the solutions were evaporated under reduced pressure. AD-mix-α was purchased from Sigma-Aldrich chemical company.

4.2. Kumada–Tamao–Corriu coupling of bromoenyne with Grignard reagents

To a mixture of bromoenyne **1** (1.42 g, 3 mmol) and $NiCl_2$(dppp) (81 mg, 5 mol%) in THF (7.5 mL) was dropped a THF solution of MeMgBr (0.93 M, 9.6 mL) at 0 °C. Then the cooling bath was removed and the mixture was stirred at room temperature. After 1–4 h, the mixture was quenched with water and extracted with hexane (two times). The combined extracts were washed with satd NH_4Cl, water, and brine. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography to give **2** as an oil. Reaction time; 4 h for **2a**, 1 h for **2b**, 1.5 h for **2c** and 1.0 h for **2d**. Eluents for chromatography; 5% benzene in hexane for **2a**, 3% EtOAc in hexane for **2b**, 2% EtOAc in hexane for **2c** and 10% benzene in hexane for **2c**.

4.2.1. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-3-methyl-1-trimethylsilyl-3-penten-1-yne (2a). Oil, 84% yield. R_f=0.5 (20% benzene in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (9H, s), 1.06 (9H, s), 1.83 (3H, q, *J*=1.3 Hz), 4.42 (2H, dq, *J*=6.2, 1.3 Hz), 5.88 (1H, td, *J*=6.2, 1.3 Hz), 7.34–7.42 (6H, m), 7.67–7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.13, 19.2, 22.7, 26.9, 63.2, 103.4, 118.7, 127.6, 127.7, 129.5, 133.9, 135.5, 137.8. IR (film) cm^{-1}: 2137. MS (EI) *m/z*: 406 (M^+). HR-MS (EI) *m/z*: 406.2144 (calcd for $C_{25}H_{34}OSi_2$: 406.2148).

4.2.2. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-5-trimethylsilyl-1-(trimethylsilyl)methyl-3-penten-1-yne (2b). Oil, 74% yield. R_f=0.53 (3% ^{t}BuOMe in hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (9H, s), 0.05 (9H, s), 1.05 (9H, s), 1.60 (2H, s), 4.43 (2H, d, *J*=6.3 Hz), 5.70 (1H, t, *J*=6.3 Hz), 7.34–7.41 (6H, m), 7.67–7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5, −0.2, 19.3, 26.9, 27.3, 63.3, 104.2, 121.1, 127.6, 128.3, 129.5, 134.0, 134.8, 135.5. MS (EI) *m/z*: 478 (M^+). HR-MS (EI) *m/z*: 478.2539 (calcd for $C_{28}H_{42}OSi_3$: 478.2544).

4.2.3. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-3-ethyl-1-trimethylsilyl-3-penten-1-yne (2c). Oil, 61% yield. R_f=0.53 (20% benzene in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (9H, s), 1.06 (9H, s), 1.06 (3H, t, *J*=7.7 Hz), 2.11 (2H, q, *J*=7.3 Hz), 4.46 (2H, d, *J*=6.2 Hz), 5.88 (1H, t, *J*=6.2 Hz), 7.37–7.42 (6H, m), 7.67–7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0, 12.9, 19.3, 27.0, 29.8, 63.3, 99.8, 125.2, 128.0, 128.4, 129.6, 134.0, 135.7, 136.3. IR (film) cm^{-1}: 2141. MS (EI) *m/z*: 420 (M^+). HR-MS (EI) *m/z*: 420.2300 (calcd for $C_{26}H_{36}OSi_2$: 420.2305).

4.2.4. (*Z*)-5-(*tert*-Butyldiphenylsilyl)oxy-3-phenyl-1-trimethylsilyl-3-penten-1-yne (2d). Oil, 17% yield. R_f= 0.34 (2% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (9H, s), 1.09 (9H, s), 4.68 (2H, d, J=6.2 Hz), 6.58 (1H, t, J=6.2 Hz), 7.25–7.45 (9H, m), 7.53–7.59 (2H, m), 7.68–7.75 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.10, 19.3, 26.8, 63.9, 101.0, 123.0, 126.1, 127.7, 127.9, 128.3, 129.6, 133.7, 135.6, 137.0, 137.9. IR (film) cm^{-1}: 2141. MS (EI) *m*/*z*: 468 (M^+). HR-MS (EI) *m*/*z*: 468.2298 (calcd for $C_{30}H_{36}OSi_2$: 468.2305).

4.3. Preparation of the C23–C27 carbon chain

4.3.1. (*Z*)-5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-pentenoic acid (8). To a THF solution of borane (70 mmol) in THF (75 mL) was added 2-methyl-2-butene (14.8 mL, 140 mmol) dropwise at −15 °C and the mixture was stirred at 0 °C for 2 h. This mixture was recooled to −40 °C, and a THF (20 mL) solution of **2a** (9.43 g, 23.2 mmol) was dropped. The mixture was allowed to warm up to −3 °C gradually during 3 h, and then quenched with MeOH (30 mL) carefully at −10 °C. The whole mixture was further stirred for an additional 30 min at −10 °C. Aq sodium hydroxide (70 mL of 3 M solution) and hydrogen peroxide (24 mL of 30% solution) were added to the mixture at the same temperature. After stirring for 30 min, the mixture was acidified with aq HCl (1 M solution) at the same temperature and allowed to warm up to room temperature. The reaction mixture was extracted with EtOAc three times, and the extracts were washed with aq sodium thiosulfate, water, and brine successively. After drying over $MgSO_4$, the extract was condensed and the residual oil was purified by column chromatography on silica gel eluted with EtOAc to give carboxylic acid **8** (6.15 g) in 72% yield as a colorless oil. R_f=0.61 (40% EtOAc in hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.80 (3H, d, J= 1.3 Hz), 2.93 (2H, s), 4.19 (2H, dd, J=6.4, 1.1 Hz), 5.63 (1H, t, J=6.4 Hz), 7.36–7.44 (6H, m), 7.66–7.70 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.9, 26.8, 37.8, 60.7, 127.7, 128.4, 129.7, 130.6, 133.5, 135.6, 176.0. IR (neat) cm^{-1}: 3071, 3049, 2931, 2858, 1712, 1428, 1111, 1057. CI-MS (CI) *m*/*z*: 369 (M^++H), 367, 311, 233, 199, 189, 113. HR-MS (CI): *m*/*z* 369.1877 (calcd for $C_{22}H_{29}O_3Si$: 369.1886).

4.3.2. Methyl (*Z*)-5-(*tert*-butyldimethylsilyl)oxy-3-methyl-3-pentenoate (9). To a mixture of **8** (6.79 g, 18.4 mmol) and iodomethane (3.44 mL, 55.3 mmol) in anhydrous acetone (100 mL) was added anhydrous powdered potassium carbonate (12.7 g, 92 mmol), and the mixture was stirred for 5 h at room temperature. Then, it was quenched with satd NH_4Cl (10 mL) and the whole was condensed to a half volume under a reduced pressure. The mixture was extracted with ether and the extract was washed with brine, and dried over $MgSO_4$. Solvent was removed and the residual oil was chromatographed on silica gel eluted with 5% EtOAc in hexane to give **9** (7.0 g) as a colorless oil in quantitative yield. R_f=0.22 (5% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.77 (3H, d, J=1.3 Hz), 2.87 (2H, s), 3.59 (3H, s), 4.21 (2H, d, J=6.4 Hz), 5.58 (1H, td, J=6.4, 1.3 Hz), 7.35–7.44 (6H, m), 7.64–7.70 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.9, 26.8, 37.5, 51.8, 60.8, 127.6, 128.4, 129.6, 130.0, 133.8, 135.6, 171.5. IR (neat) cm^{-1}: 3071, 3049, 2932, 2857, 1741, 1429, 1110, 1057. MS (EI) *m*/*z*: 382 (M^+), 325, 213, 199, 105, 95. HR-MS (EI): *m*/*z* 382.1967 (calcd for $C_{23}H_{30}O_3Si$: 382.1964).

4.3.3. (*Z*)-5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-penten-1-ol (10). $LiBH_4$ (1.25 g, 57 mmol) was added to a solution of **9** (7.28 g, 19 mmol) in THF (100 mL) at 0 °C by several portions, and the reaction was continued for 15 h at room temperature. Then, water was added and the mixture was extracted with ether several times. The combined extracts were washed with water, brine and dried over $MgSO_4$, and concentrated. The residual oil was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give **10** (5.36 g) in 79% yield. Colorless oil, R_f=0.60 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.74–1.76 (3H, m), 2.24 (2H, t, J= 6.2 Hz), 3.61 (2H, t, J=6.2 Hz), 4.15 (2H, d, J=7.1 Hz), 5.58 (1H, t, J=7.1 Hz), 7.36–7.44 (6H, m), 7.68–7.72 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.5, 26.8, 35.2, 59.9, 60.1, 126.8, 127.7, 128.3, 129.7, 133.6, 135.6. IR (neat) cm^{-1}: 3392, 3071, 3048, 2931, 2857, 1472, 1428, 1112, 1062. MS (EI) *m*/*z*: 354 (M^+), 297, 267, 219, 199, 152, 78. HR-MS (EI): *m*/*z* 354.2020 (calcd for $C_{22}H_{30}O_2Si$: 354.2015).

4.3.4. (*Z*)-5-(*tert*-Butyldimethylsilyl)oxy-3-methyl-3-penten-1-al (3). To a solution of **10** (2.76 g, 7.75 mmol) in CH_2Cl_2 (75 mL) was added Dess-Martin periodinate (4.94 g, 11.65 mmol) in an ice bath. After the addition, the bath was removed and the mixture was stirred for 30 min at room temperature. Then the mixture was quenched with satd sodium thiosulfate and satd $NaHCO_3$, and the whole mixture was extracted with ether three times. The combined extracts were washed with water and brine and dried over $MgSO_4$. Solvent was removed under a reduced pressure to give a crude aldehyde **3** which was used for the next Hornor–Wadsworth–Emonns reaction without further purification. R_f=0.86 (20% EtOAc in hexane). ^{1}H NMR (300 MHz, C_6D_6) δ 1.26 (9H, s), 1.55 (3H, s), 2.54 (2H, d, J=2.0 Hz), 4.23 (2H, d, J=6.3 Hz), 5.73 (1H, t, J= 6.3 Hz), 7.30–7.40 (6H, m), 7.85–7.92 (4H, m), 9.10 (1H, t, J=2.0 Hz).

4.4. Preparation of the C17–C27 ketophosphonate

4.4.1. Ethyl (2*R*,3*S*)-2,3-dihydroxy-5-(4-methoxybenzyl) oxypentanoate (11). A suspension of AD-mix-α (25.1 g, 1.40 g/mol) in a 1:1 mixture of ^{t}BuOH and water (180 mL) was stirred for 15 min at room temperature, and then $MeSO_2NH_2$ (1.70 g, 17.9 mmol) and unsaturated ester **5** (4.73 g, 17.9 mmol) were added to the mixture at 0 °C. After being stirred for 1 day at the same temperature, the reaction mixture was quenched with satd sodium thiosulfate and extracted with EtOAc three times. The extracts were combined and washed with dil. HCl, water and brine. The organic extract was dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel eluted with 40% EtOAc in hexane to give **11** (5.14 g) in 96% yield which was recrystallized by isopropyl ether to give pure colorless crystals over 99% ee.

Mp 39–40 °C (from diisopropyl ether) lit. mp 40 °C.[12] R_f= 0.22 (50% EtOAc in hexane). $[\alpha]_D^{22}$ −2.0 (*c* 1.19, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, *J*=7.1 Hz), 1.79–1.87 (1H, m), 1.99–2.07 (1H, m), 2.90–3.02 (1H, br), 3.18–3.24 (1H, br), 3.62–3.74 (2H, m), 3.80 (3H, s), 4.06 (1H, brs), 4.14–4.19 (1H, m), 4.24–4.32 (2H, m), 4.46 (2H, s), 6.88 (2H, d, *J*=6.6 Hz), 7.25 (2H, d, *J*=6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 33.2, 55.3, 61.9, 67.8, 71.6, 73.0, 73.6, 113.8, 129.4, 129.9, 159.3, 173.2.

4.4.2. Ethyl (4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl) oxyethyl]-[1,3]dioxolan-4-carboxylate (12). A mixture of diol **11** (4.4 g, 14.7 mmol) and CSA (1.13 g, 4.42 mmol) was stirred in 2,2-dimethoxypropane at rt for 3 h. After an addition of aq $NaHCO_3$, the reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residual oil was chromatographed on silica gel eluted with 10% EtOAc in hexane to give acetonide **12** (4.03 g) in 80% yield. A colorless oil, R_f=0.48 (20% EtOAc in hexane). $[\alpha]_D^{25}$ −19.1 (*c* 1.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*=7.1 Hz), 1.44 (3H, s), 1.46 (3H, s), 1.96 (1H, dddd, *J*=14.1, 7.7, 5.9, 5.7 Hz), 2.10 (1H, dddd, *J*=14.1, 7.7, 6.6, 4.4 Hz), 3.54–3.66 (2H, m), 3.80 (3H, s), 4.13–4.32 (4H, m), 4.43 (2H, s), 6.87 (2H, d, *J*=8.8 Hz), 7.25 (2H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 25.7, 27.1, 33.6, 55.3, 61.3, 66.3, 72.6, 76.5, 79.1, 110.7, 113.7, 129.2, 130.4, 159.1, 170.7. IR (neat) cm^{-1}: 2988, 2936, 2866, 1757, 1736, 1613, 1586, 1513, 1372, 1249, 1099, 1036. MS (EI) *m/z*: 338 (M^+), 323, 280, 262, 233, 177, 189, 136. HR-MS (EI): *m/z* 338.1727 (calcd for $C_{18}H_{26}O_6$: 338.1729).

4.4.3. Dimethyl 2-{(4*R*,5*S*)-2,2-dimethyl-5-(4-methoxybenzyl)oxyethyl-[1,3]dioxolan-4-yl}-2-oxo-ethyl-1-phosphonate (4). To a solution of lithium salt of dimethyl methylphosphonate generated from dimethyl methylphosphonate (3.40 g, 27.4 mmol) with ^{n}BuLi (1.57 M in hexane solution, 15.1 mL) at −78 °C in anhydrous THF (100 mL), a THF (20 mL) solution of ester **12** (4.03 g, 11.9 mmol) was added dropwise at −78 °C and the mixture was stirred for 30 min at the same temperature. Satd NH_4Cl was added to the mixture and it was extracted with EtOAc. The organic extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by column chromatography on silica gel eluted with EtOAc to give **4** (4.96 g) with a quantitative yield. A colorless oil. R_f=0.65 (EtOAc). $[\alpha]_D^{25}$ +22.2 (*c* 1.54, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.44 (3H, s), 1.88–1.99 (1H, m), 2.02–2.11 (1H, m), 3.25 (1H, dd, *J*=21.8, 14.5 Hz), 3.44 (1H, dd, *J*=22.5, 14.5 Hz), 3.53–3.64 (2H, m), 3.77 (3H, d, *J*=6.0 Hz), 3.79 (3H, d, *J*=6.0 Hz), 3.80 (3H, s), 4.17 (1H, d, *J*=7.7 Hz), 4.22 (1H, ddd, *J*=11.7, 7.7, 7.5 Hz), 4.42 (2H, s), 6.86 (2H, d, *J*=8.8 Hz), 7.24 (2H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.1, 33.6, 35.8, 37.2, 52.9, 53.0 (d, *J*=6.5 Hz), 53.2 (*J*=6.1 Hz), 66.2, 72.6, 75.1, 84.8, 84.8, 110.5, 113.6, 113.7, 129.3, 130.4, 159.1, 201.6 (d, *J*=7.2 Hz). IR (neat) cm^{-1}: 3473, 2988, 2955, 2856, 1717, 1613, 1514, 1250, 1033. MS (EI) *m/z*: 416 (M^+), 350, 340, 272, 237, 222, 176. HR-MS (EI): *m/z* 416.1601 (calcd for $C_{19}H_{29}O_8P$: 416.1600).

4.5. Preparation of the C17–C27 carbon chain

4.5.1. (2*E*,5*Z*)-7-(*tert*-Butyldiphenylsilyl)oxy-1-{(4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl)oxyethyl]-[1,3]-dioxolan-4-yl}-5-methyl-hepta-2,5-dien-1-one (13). A mixture of ketophosphonate **4** (1.94 g, 4.66 mmol), crude aldehyde **3** (3.1 mmol), and anhydrous powdered K_2CO_3 (856 mg, 6.2 mmol) was stirred in a 1:1 mixture of THF–water (40 mL) at room temperature. After 3 h, the reaction was quenched with satd NH_4Cl, and extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give **13** (1.4 g) in 70% yield. A colorless oil. R_f=0.30 (15% EtOAc in hexane). $[\alpha]_D^{29}$ 2.6 (*c* 1.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.34 (3H, s), 1.43 (3H, s), 1.68 (3H, d, *J*=1.3 Hz), 1.87–1.96 (1H, m), 1.98–2.07 (1H, m), 2.74 (2H, d, *J*=6.8 Hz), 3.49–3.62 (2H, m), 3.78 (3H, s), 4.15–4.18 (4H, m), 4.39 (2H, s), 5.54 (1H, td, *J*=6.4, 1.3 Hz), 6.44 (1H, dt, *J*=15.8, 1.6 Hz), 6.83 (1H, dt, *J*=15.8, 6.8 Hz), 6.84 (2H, d, *J*=8.8 Hz), 7.21 (2H, d, *J*=8.8 Hz), 7.35–7.44 (6H, m), 7.65–7.69 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.5, 26.1, 26.8, 27.2, 33.6, 35.4, 55.3, 60.6, 66.3, 72.5, 75.7, 84.1, 110.2, 113.7, 125.7, 127.2, 127.7, 129.2, 129.6, 130.4, 133.0, 133.7, 135.6, 146.7, 159.1, 197.5. IR (neat) cm^{-1}: 3070, 2932, 2857, 1692, 1617, 1587, 1513, 1248, 1110. MS (EI) *m/z*: 642 (M^+), 585, 459, 433, 199, 143. HR-MS (EI): *m/z* 642.3380 (calcd for $C_{39}H_{50}O_6Si$: 642.3376).

4.5.2. (2*E*,5*Z*)-(1*R*)-7-(*tert*-Butyldiphenylsilyl)oxy-1-{(4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl)oxyethyl]-[1,3]dioxolan-4-yl}-5-methyl-hepta-2,5-dien-1-ol (14β). To a stirred mixture of **13** (1.75 g, 2.72 mmol) and $CeCl_3$ heptahydrate (1.52 g, 4.08 mmol) in methanol (28 mL), $NaBH_4$ (154 mg, 4.08 mmol) was added at −78 °C by several portions during 1 h. Then, the cooling bath was removed and the mixture was allowed to warm up to room temperature. Water was added and the mixture was extracted with EtOAc. The organic extract was washed with water and brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane. Alcohol **14**β (1.41 g) was obtained in 80% yield with a >10:1 diastereomeric ratio. A colorless oil, R_f=0.29 (20% EtOAc in hexane). $[\alpha]_D^{24}$ −9.4 (*c* 1.56, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.39 (6H, s), 1.67 (3H, d, *J*=1.1 Hz), 1.73–1.91 (2H, m), 2.59 (2H, t, *J*=6.5 Hz), 3.48–3.58 (2H, m), 3.63 (1H, dd, *J*=7.7, 4.8 Hz), 3.80 (3H, s), 3.97 (1H, dd, *J*=7.9, 4.0 Hz), 3.98 (1H, dd, *J*=7.9, 4.8 Hz), 4.20 (2H, d, *J*=6.4 Hz), 4.41 (2H, s), 5.37 (1H, dd, *J*=15.3, 6.8, 1.1 Hz), 5.46 (1H, t, *J*=6.4 Hz), 5.54 (1H, dtd, *J*=15.3, 6.5, 1.1 Hz), 6.87 (2H, d, *J*=8.8 Hz), 7.23 (2H, d, *J*=8.8 Hz), 7.36–7.42 (6H, m), 7.67–7.71 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.4, 26.8, 27.1, 27.4, 33.6, 35.1, 55.2, 60.6, 66.8, 72.3, 72.7, 75.0, 83.7, 108.9, 113.7, 125.7, 127.6, 129.2, 129.6, 129.7, 130.4, 131.1, 133.9, 135.1, 135.6, 159.1. IR (neat) cm^{-1}: 3466, 3070, 2932, 2857, 1613, 1514, 1248, 1109, 1039. MS (EI) *m/z*: 644 (M^+), 629, 587, 443, 388, 313, 295, 213, 199. HR-MS (EI): *m/z* 644.3541 (calcd for $C_{39}H_{52}O_6Si$: 644.3533).

4.6. Mitsunobu reaction of 14β with benzoic acid; preparation of 15α and 15α′

To a mixture of **14**β (926 mg, 1.44 mmol), benzoic acid (352 mg, 2.88 mmol), and triphenylphosphine (755 mg, 2.88 mmol) in benzene, diethyl diazodicarboxylate (1.25 mL, 40% in toluene solution) was dropped in an ice bath. After the mixture was stirred for 1 h at the same temperature, water was added and the mixture was extracted with ether. The ethereal extract was washed with water, and brine and dried over $MgSO_4$. After the solvent was removed, the crude product was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane. A 1:1 mixture of C21 and C23 benzoates, **15**α and **15**α′ (871 mg) were obtained in 81% yield. They were separated by HPLC with 15% EtOAc in hexane as an eluent (12 mL/min).

4.6.1. Compound 15α. Colorless oil (less polar isomer, retention time 11.9 min), R_f=0.57 (20% EtOAc in hexane) $[\alpha]_D^{25}$ −18.6 (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s), 1.30 (3H, s), 1.38 (3H, s), 1.63 (3H, d, *J*= 1.1 Hz), 1.90–2.00 (2H, m), 2.60 (2H, d, *J*=6.4 Hz), 3.50–3.62 (2H, m), 3.77 (3H, s), 3.93 (1H, dd, *J*=8.0, 3.5 Hz), 4.04 (1H, td, *J*=8.0, 3.7 Hz), 4.17 (2H, dd, *J*=6.4, 1.1 Hz), 4.39 (2H, s), 5.44 (1H, t, *J*=6.4 Hz), 5.52–5.67 (3H, m), 6.82 (2H, d, *J*=8.8 Hz), 7.19 (2H, d, *J*=8.8 Hz), 7.33–7.44 (8H, m), 7.53–7.59 (1H, m), 7.64–7.68 (4H, m), 8.02–8.05 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.3, 26.8, 26.9, 27.4, 34.0, 35.1, 55.2, 60.6, 66.6, 72.5, 74.4, 75.2, 82.0, 109.3, 113.7, 125.3, 125.9, 127.6, 128.4, 129.1, 129.5, 129.7, 130.2, 130.5, 133.0, 133.6, 133.9, 134.8, 135.6, 159.1, 165.4. IR (neat) cm^{-1}: 2932, 2857, 1722, 1613, 1514, 1249, 1110. MS (EI) *m/z*: 748 (M^+), 733, 691, 634, 615, 313, 295, 199. HR-MS (EI): *m/z* 748.3788 (calcd for $C_{46}H_{56}O_7Si$: 748.3795).

4.6.2. Compound 15α′. Colorless oil (polar isomer, retention time 13.5 min), R_f=0.57 (20% EtOAc in hexane). The diastereomeric ratio of (*S*)- and (*R*)-benzoates was 4:1. The spectral data are described for only the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.37 (3H, s), 1.38 (3H, s), 1.76 (3H, d, *J*=1.1 Hz), 1.75–1.85 (2H, m), 2.13 (1H, dd, *J*=13.9, 4.8 Hz), 2.45 (1H, dd, *J*=13.9, 9.0 Hz), 3.44–3.57 (2H, m), 3.70–3.78 (1H, m), 3.79 (3H, s), 4.01 (1H, dd, *J*=8.2, 6.4 Hz), 4.11 (1H, dd, *J*=12.8, 5.7 Hz), 4.28 (1H, dd, *J*=12.8, 7.3 Hz), 4.35 (2H, s), 5.47 (1H, dd, *J*=7.3, 5.7 Hz), 5.54–5.60 (1H, m), 5.70 (1H, dd, *J*=15.5, 6.4 Hz), 5.77 (1H, dd, *J*=15.5, 6.2 Hz), 6.84 (2H, d, *J*=8.8 Hz), 7.19 (2H, d, *J*=8.8 Hz), 7.31–7.44 (8H, m), 7.47–7.53 (1H, m), 7.64–7.69 (4H, m), 7.88–7.93 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 24.0, 26.8, 26.9, 27.2, 32.0, 37.2, 55.3, 60.8, 66.6, 72.2, 72.6, 77.9, 81.3, 108.7, 113.7, 127.6, 128.3, 128.3, 129.2, 129.5, 129.6, 129.6, 130.1, 130.4, 132.2, 132.3, 132.9, 133.9, 135.6, 159.1, 165.4. IR (neat) cm^{-1}: 3070, 2932, 2858, 1720, 1613, 1514, 1269, 1249, 1110. MS (EI) *m/z*: 748 (M^+), 733, 691, 633, 615, 313, 295, 213. HR-MS (EI): *m/z* 748.3790 (calcd for $C_{46}H_{56}O_7Si$: 748.3795).

4.6.3. (2*E*,5*Z*)-(1*S*)-7-(*tert*-Butyldiphenylsilyl)oxy-1-{(4*R*,5*S*)-2,2-dimethyl-5-[2-(4-methoxybenzyl)oxyethyl]-[1,3]dioxolan-4-yl}-5-methyl-hepta-2,5-dien-1-ol (14α). A mixture of benzoate **15**α (120 mg, 0.16 mmol) and powdered K_2CO_3 (111 mg, 0.8 mmol) in methanol (1.6 mL) was stirred for 2 h at room temperature. The mixture was poured into cold water and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. After solvent was removed, the residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane to give alcohol **14**α (100 mg) in 97% yield. Colorless oil, R_f=0.52 (30% EtOAc in hexane). $[\alpha]_D^{23}$ −8.3 (*c* 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.36 (3H, s), 1.37 (3H, s), 1.67 (3H, d, *J*=1.5 Hz), 1.75–1.84 (1H, m), 1.86–1.95 (1H, m), 2.59 (2H, d, *J*=6.4 Hz), 3.50–3.60 (2H, m), 3.68 (1H, dd, *J*=8.1, 4.6 Hz), 3.79 (3H, s), 4.00 (1H, td, *J*=8.1, 3.7 Hz), 4.15 (1H, td, *J*=6.1, 0.9 Hz), 4.20 (2H, dd, *J*=6.6, 1.2 Hz), 4.41 (2H, s), 5.39–5.48 (2H, m), 5.54 (1H, dtd, *J*=15.4, 6.6, 1.1 Hz), 6.86 (2H, d, *J*= 8.6 Hz), 7.23 (2H, d, *J*=8.6 Hz), 7.36–7.44 (6H, m), 7.66–7.70 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.4, 26.8, 27.0, 27.3, 34.2, 35.1, 55.3, 60.7, 66.9, 71.8, 72.7, 74.8, 83.2, 108.6, 113.8, 125.7, 127.6, 128.9, 129.3, 129.6, 130.4, 130.7, 133.9, 135.2, 135.6, 159.2. IR (neat) cm^{-1}: 3450, 3033, 2932, 2857, 1613, 1514, 1428, 1249, 1110, 1040. MS (EI) *m/z*: 644 (M^+), 629, 587, 388, 313, 295, 213, 199. HR-MS (EI): *m/z* 644.3528 (calcd for $C_{39}H_{52}O_6Si$: 644.3533).

4.6.4. Stereoselective dihydropyran ring formation by SN2′ reaction; preparation of 7 and 7′. A mixture of alcohol **14** (α or β, 0.2 mmol), triethylamine (1.4 mmol) and methanesulfonic anhydride (1 mmol) was stirred in CH_2Cl_2 (2 mL) at 0 °C for 1 h. A cold water was added to the mixture, and it was extracted with ether. The ethereal layer was quickly washed with aq $NaHCO_3$, water, and brine and dried over $MgSO_4$. Evaporation of solvent and residue was dissolved in benzene (1 mL). To this solution a THF solution of tetrabutylammonium fluoride (1 M, 1 mL) was added and the mixture was stirred for overnight at room temperature. Then, the mixture was quenched with water and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane to give a colorless oil. A 5.5:1 mixture of **7** and **7′** was obtained from **14**β in 60% yield, and a 1:5 mixture was obtained from **14**α in 61% yield. The mixture of **7** and **7′** were not separable by column chromatography, TLC, and HPLC. A mixture of **7** and **7′**. Colorless oil, R_f=0.36 (20% EtOAc in hexane). IR (neat) cm^{-1}: 2933, 2853, 1613, 1514, 1247, 1091, 1037. MS (EI) *m/z*: 388 (M^+), 370, 330, 312, 267, 209, 160, 136. HR-MS (EI): *m/z* $[M]^+$ 388.2251 (calcd for $C_{23}H_{32}O_5$: 388.2250). ^{1}H NMR and ^{13}C NMR are following; **7**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.40 (3H, s), 1.69 (3H, brs), 1.77–1.95 (3H, m), 1.99–2.08 (1H, m), 3.51–3.63 (2H, m), 3.80 (3H, s), 3.83 (1H, td, *J*=8.2, 4.0 Hz), 4.00–4.06 (1H, m), 4.06 (1H, dd, *J*=8.2, 7.5 Hz), 4.11–4.22 (2H, m), 4.43 (2H, s), 5.41 (1H, brs), 5.70 (1H, ddd, *J*=15.6, 7.5, 1.3 Hz), 5.87 (1H, ddd, *J*=15.6, 5.4, 0.5 Hz), 6.86 (2H, d, *J*=8.8 Hz), 7.25 (2H, d, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 26.9, 27.2, 32.0, 35.6, 55.2, 65.6, 66.7, 72.6, 73.1, 77.8, 81.9, 108.6, 113.7, 119.6, 127.4, 129.2, 130.5, 131.3, 135.4, 159.1. **7′**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 1.40 (3H, s), 1.69 (3H, brs), 1.78–1.94 (3H, m), 2.01–2.11 (1H, m), 3.51–3.64 (2H, m), 3.80 (3H, s), 3.79–

3.84 (1H, m), 3.98–4.03 (1H, m), 4.07 (1H, t, $J=7.7$ Hz), 4.12–4.23 (2H, m), 4.43 (2H, s), 5.41 (1H, brs), 5.69 (1H, ddd, $J=15.7$, 7.2, 1.5 Hz), 5.90 (1H, ddd, $J=15.7$, 5.1, 0.9 Hz), 6.87 (2H, d, $J=8.8$ Hz), 7.25 (2H, d, $J=8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 27.0, 27.3, 32.1, 35.6, 55.3, 65.7, 66.8, 72.7, 72.9, 78.0, 81.8, 108.6, 113.8, 119.7, 127.1, 129.3, 130.5, 131.4, 135.0, 159.1.

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A stereoselective synthesis of a chiral anthracyclinone AB-synthon from a carbohydrate precursor

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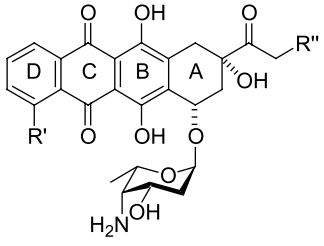
Abstract—Reaction of tetralinol **5** with phenylboronic acid removed the isopropylidene group with concomitant formation of phenylboronate **12**. Oxidation of the latter with PCC gave keto–ester **13**, a key intermediate in the synthesis of enantiopure anthracyclinones. Attempts at cleavage of the isopropylidene group in **5** by the usual procedures led first to substitution and epimerization at the benzylic position, then removal of the acetonide followed by formation of the cyclic ether **11a** as the final product.

1. Introduction

Anthracycline antibiotics, such as doxorubicine (**1**) and daunomycine (**2**), possess potent antitumor activity with proven clinical effectiveness against various types of human solid tumors and leukemias.[1] On the other hand they exhibit undesired side effects, notably dose-related cardiotoxicity, myelosuppression[2] and intrinsic as well as acquired resistance,[3] hampering their utility for cancer chemotherapy. The search for active compounds of the anthracycline type, with improved therapeutic properties, has resulted in a strong interest in the synthesis of analogues not available by biosynthetic methods, for example, idarubicine (**3**).[4]



1 R' = OMe, R'' = OH
2 R' = OMe, R'' = H
3 R' = R'' = H

Several strategies have been developed for the construction of the tetracyclic skeleton of the anthracyclinone, the aglycone of the antibiotic.[5] Amongst them, the approach originally reported by Wong et al.,[6] based on annelation of the CD-rings to the AB-synthon of the anthracyclinone is particularly efficacious. Consequently, it has been applied in numerous syntheses of anthracyclinones[7] and prompted[8] continuing interest in the development of various methodologies for preparation of AB-ring building blocks.

Recently, we have published a total synthesis of idarubicinone (**6**) using the AB + CD coupling methodology. A new chiral building block for rings A and B, tetralinol **5**, was obtained in 13 steps from L-rhamnose (**4**) (Scheme 1).[9]

In this paper, we describe the transformation of tetralinol **5** into the phenylboronic acid ester **13** (Scheme 4). It should be pointed out that ester **13** has been obtained before, albeit as a racemate,[10] and was used in the synthesis of racemic aglycons of modified anthracyclines.[11] Thus the present communication on the synthesis of ester **13** with (*S*) configuration at C-1 and C-3, which ultimately become C-7 and C-9, respectively, in the A-ring of the target molecule, opens a new route to chiral anthracyclinones with the natural (7*S*,9*S*) absolute configuration which is essential for their biological activity.[12]

2. Results and discussion

2.1. Nucleophilic substitution at C-1 in tetralinol 5

At first we attempted a transformation of tetralinol **5** to ketodiol **7** which appeared to be straightforward. Protection

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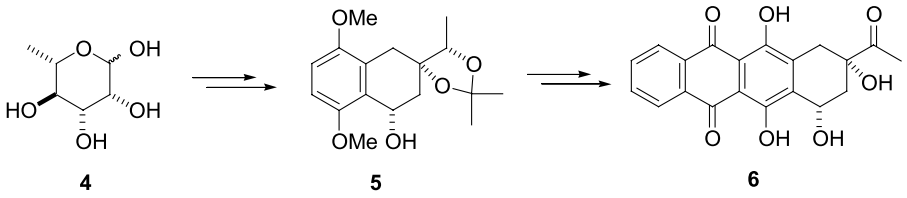
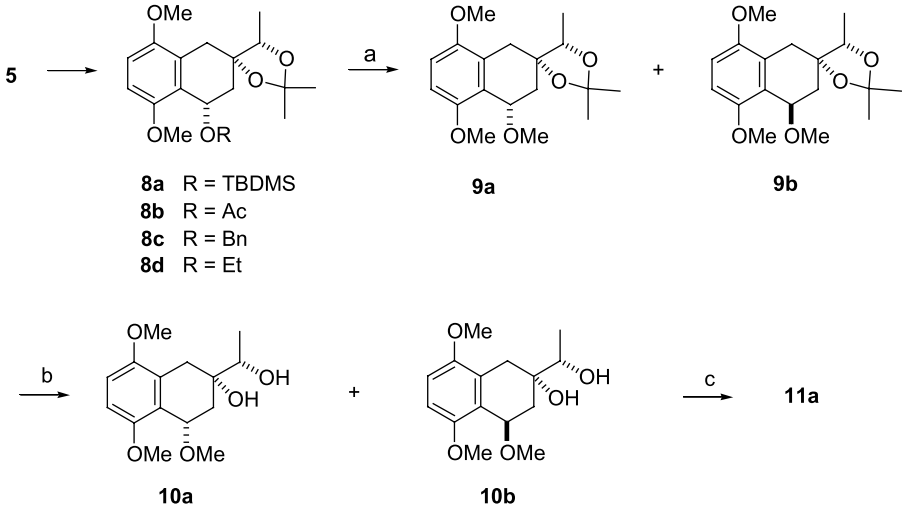
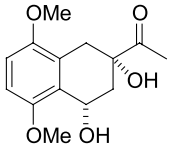


Scheme 1.

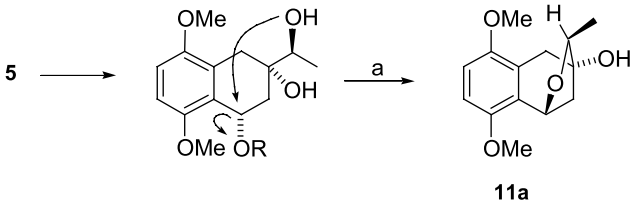


Scheme 2. (a) **8a**, PPTS, MeOH, ⇅, 2 h, chromatography: **9a**, 28%, **9b**, 42%; (b) PPTS, MeOH, ⇅, 24 h, chromatography: **10a**, 45%, **10b**, 36%; (c) PPTS, MeOH, ⇅, 48 h, 65%.

of the benzylic hydroxyl at C-1, cleavage of the isopropylidene group followed by oxidation of the secondary hydroxyl in the side chain should furnish the desired compound **7** (presumably with a protected C-1 hydroxyl). However, removal of the isopropylidene group without affecting the substituent at C-1 was unsuccessful. The benzylic substituent at C-1 proved to be susceptible to nucleophilic attack even under mild conditions. For example, the *tert*-butyldimethylsilyl derivative **8a**, on treatment with methanol in the presence of pyridinium *p*-toluenesulfonate (PPTS) at room temperature (24 h) or at reflux (2 h), gave a mixture of epimeric methyl ethers **9a** and **9b**, without cleavage of the isopropylidene group. The latter could be removed after prolonged reaction time yielding epimeric diols **10a** and **10b**. Other protecting groups of the C-1 hydroxyl, acetyl (**8b**), benzyl (**8c**) and ethyl (**8d**), did not change the course of the reaction. Other procedures recommended for the cleavage of acetonides[13] (80% AcOH/THF, 80% TFA/THF, I_2/methanol, *p*-toluenesufonic acid/methanol) did not yield the desired product. Reaction conditions in which the presence of a potentially nucleophilic solvent was avoided led to intramolecular substitution at C-1. Thus, treatment of silyl derivative **8a** with Fe–SiO_2 in chloroform[14] gave a tricyclic ether **11a** as the sole isolated product in 70% yield (Scheme 2). Apparently, the cleavage of the isopropylidene group was immediately followed by intramolecular nucleophilic attack of the secondary hydroxyl of the side chain at C-1 leading to the formation of ether **11a** (Scheme 3). It should be mentioned that ether **11a** was also the main final product of the attempted isopropylidene group cleavage of ketal **5** or its derivatives **8a–d** carried out in various (vide supra) reaction conditions.



The gross structure of the tricyclic ether **11a** was deduced from its analytical data (^{1}H NMR, MS, HRMS) and the ^{1}H NMR spectrum of its acetate **11b**. Single-crystal X-ray analysis of ether **11a** unequivocally confirmed the structure and established its stereochemistry as shown in Figure 1. In the crystal structure of **11a** there are characteristic O–H···O hydrogen bonds between the hydroxyl groups and the tetrahydrofuran ring oxygen atoms of the molecules related by translation along the *a*-axis. The O–H, H···O and O···O distances are: 0.82(6), 1.98(6) and 2.784(4) Å, respectively, while the hydrogen bond angle is of 166(6)°.[15]



Scheme 3. (a) $FeCl_3/SiO_2$, $CHCl_3$, RT, 5 h, 70%.

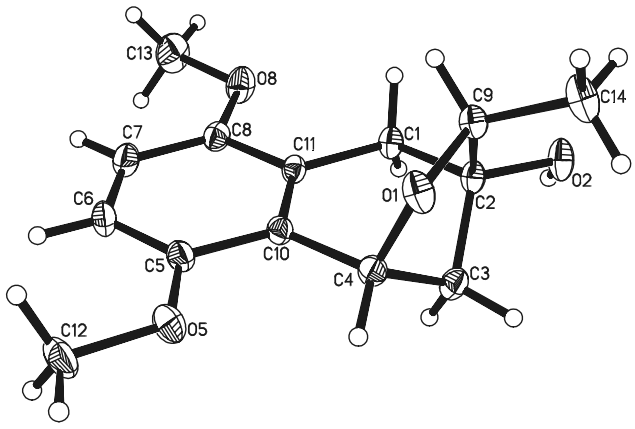
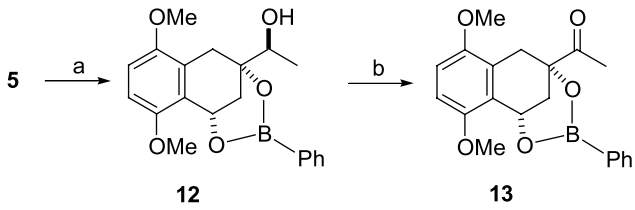


Figure 1. The ORTEP drawing of ether **11a** showing the numbering of the atoms. The non-hydrogen atoms are shown as 30% probability ellipsoids.

2.2. Phenylboronate 13

The foregoing results demonstrated that in the course of the cleavage of the isopropylidene group of ketal **5** (or its derivatives **8a**–**d**) it is difficult to avoid substitution at C-1. Elimination of an external nucleophile leaves room for the intramolecular reaction. It became apparent that the problem could be solved if removal of the isopropylidene group in ketal **5** occurred with concomitant protection of the hydroxyl at C-1. To this end we turned our attention to phenylboronic acid, which could serve as an acidic catalyst for cleavage of the ketal grouping and at the same time act as a protecting group for the two hydroxyls. For our purpose, a particularly important feature of phenylboronic acid as a protecting group was its tendency to form esters with 1,3-diols rather then 1,2-diols, as was demonstrated in case of the unprotected racemic triol **5**.[11] Therefore, esterification of the C-1 and C-3 hydroxyls should prevail over C-3 and C-1′, thus ensuring the protection of the C-1 position. Indeed, reaction of ketal **5** with phenylboronic acid in toluene gave phenylboronate **12**. The crude ester **12**, homogenous on TLC, was oxidized with pyridinium chlorochromate (PCC) affording ketoester **13** in good yield, after purification by flash chromatography. The structure of compound **13** was confirmed by its spectroscopic (^{1}H NMR, HRMS) data. Moreover the ^{1}H NMR and MS spectra of ketoester **13** were in agreement with the data reported for the racemate (Scheme 4).[11]



Scheme 4. (a) $PhB(OH)_2$, *p*-TsOH, toluene, 40–50 °C, 2 h; (b) PCC, CH_2Cl_2, 3 Å MS, RT, 1 h, 70%.

In summary, a method for the preparation of chiral AB-ring building block **13** has been developed. Since racemic compound **13** was used before as a key intermediate in the synthesis of anthracyclinones,[11] the present development accomplishes a formal synthesis of enantiopure idarubicinone and daunomycinone with natural absolute stereochemistry.

3. Experimental

3.1. General procedures

Melting points were determined in capillary tubes and are uncorrected ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 spectrometer at 200 MHz using TMS as an internal reference. IR spectra were recorded for $CHCl_3$ solutions on a Perkin–Elmer FTIR spectrometer. Mass spectra (MS and high resolution mass spectra (HRMS) were obtained using a Finnegan MAT 8200 instrument. Thin-layer chromatography was performed using precoated aluminum plates (Merck Kieselgel 60 F_{254}) and visualized with UV light or acidic molybdate(IV)-cerium sulfate reagent. Solvents and reagents were purified before use according to standard procedures.[16]

Compounds **8a**, **8b**, **8c** and **8d** were obtained from tetralinol **5** according to standard procedures and their structures were confirmed by spectroscopic data.

3.1.1. (4*S*,4′*S*,5*S*)-4′-*tert*-Butyldimethylsilyloxy-5′,8′-dimethoxy-2,2,5-trimethyl-3′,4′-dihydro-1′*H*-spiro-[dioxolane-4,2′-naphthalene) (8a). Colourless oil, $[\alpha]_D$ +17.5 (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 6.65 (AB, $\Delta\delta_{6',7'}$=14.0 Hz, $J_{6',7'}$=9.0 Hz, 2H, H-6′, H-7′); 5.25 (t,1H, H-4′); 3.83 (q, $J_{5,Me}$=7.0 Hz, 1H, H-5) 3.76 and 3.75 (2s, 23H, 2OCH_3); 3.10 (d, $J_{1'a,1'b}$=16.1 Hz, 1H, H-1′a); 2.75 (d, 1H, H-1′b); 2.19 (dd, $J_{3'a,3'b}$=14.3 Hz, $J_{3'a,4'}$=4.2 Hz, 1H, H-3′a); 1.80 (dd, $J_{3'b,4'}$=4.6 Hz,1H, H3′b); 1.48 and 1.37 (2s, 23H, >$C(CH_3)_2$); 0.96 (d, 3H, 5-CH_3); 0.87 (s, 9H, –$C(CH_3)_3$); 0.14 and −0.04 (2s, 23H, 2Si–CH_3). IR: ν_{max} 1602, 1488, 1464, 1101, 828 cm^{-1}. HRMS: calcd for $C_{23}H_{38}O_6Si$ (M^+): 422.248853; found: 422.248476.

3.1.2. (4*S*,4′*S*,5*S*)-4′-Acetoxy-5′,8′-dimethoxy-2,2,5-trimethyl-3′,4′-dihydro-1′*H*-spiro[1,3-dioxolane-4,2′-naphthalene] (8b). White solid, mp 126–127.5 °C, $[\alpha]_D$ −3.9 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 6.72 (AB, $\Delta\delta_{6',7'}$=21.5 Hz, $J_{6',7'}$=8.8 Hz, 2H, H-6′, H-7′), 6.24 (dd, $J_{3'a,4'}$=5.6 Hz, $J_{3'b,4'}$=3.2 Hz, 1H, H-4′), 4.01 (q, $J_{5,Me}$=6.6 Hz, 1H, H-5), 3.77 and 3.73 (2s, 23H, 2OCH_3), 2.98 (dd, $J_{1'a,1'b}$=17.4 Hz, $J_{1'a,3'b}$=1.7 Hz, 1H, H-1′a), 2.58 (d, 1H, H-1′b), 2.18 (ddd, $J_{3',3'b}$=14.7 Hz, $J_{3'b,4'}$=3.1 Hz, 1H, H-3′b), 2.05 (s, 3H, $COCH_3$), 1.97 (dd, 1H, H-3′a), 1.45 and 1.34 (2s, 23H, 2CH_3), 1.21 (d, 3H, 5-CH_3); IR: ν_{max} 1723, 1485, 1374, 1289, 1100 cm^{-1}. HRMS: calcd for $C_{19}H_{26}O_6$ (M^+): 350.172938; found: 350.172587.

3.1.3. (4*S*,4′*S*,5*S*)-4′-Benzyloxy-5′,8′-dimethoxy-2,2,5-trimethyl-3′,4′-dihydro-1*H*-spiro[1,3-dioxolane-4,2′-naphthalene] (8c). White solid, mp 82–83.5 °C, $[\alpha]_D$ −11.7 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.38–7.18 (m, 5H, –C_6H_5), 6.69 (AB, $\Delta\delta_{6',7'}$=15.1 Hz, $J_{6',7'}$=8.9 Hz, 2H, H-6′, H-7′), 5.04 (dd, $J_{3'a,4'}$=4.2 Hz, $J_{3'b,4'}$=3.1 Hz, 1H, H-4′), 4.52 (AB, $\Delta\delta_{a,b}$=11.2 Hz, $J_{a,b}$=12.2 Hz, 2H, –OCH_2–), 3.82 (q, $J_{5,Me}$=6.2 Hz, 1H, H-5), 3.77 and 3.74 (2s, 23H, 2OCH_3), 3.21 (d, $J_{1'a,1'b}$=15.7 Hz, 1H, H-1′a), 2.78 (d, 1H, H-1′b), 2.40 (dd, $J_{3'a,3'b}$=14.8 Hz, 1H, H-3′b), 1.72 (dd, 1H, H-3′a),

1.51 and 1.40 (2s, 23H, $2CH_3$), 0.98 (d, $J_{5,Me}=6.2$ Hz, 3H, 5-CH_3); IR: ν_{max} 2837, 1602, 1489, 1261, 1099 cm^{-1}; MS: *m/z* (%) 398 (83), 292 (82), 270 (75), 234 (92), 233 (35), 204 (34), 192 (68), 179 (100), 91 62); HRMS: calcd for $C_{24}H_{30}O_5$ (M^+): 398.20932; found: 398.20863.

3.1.4. (4*S*,4′*S*,5*S*)-4′-Ethoxy-5′,8′-dimethoxy-2,2,5-trimethyl-3′,4′-dihydro-1′*H*-spiro[1,3-dioxolane-4,2′-naphthalene] (8d). White solid, mp 69–71 °C, $[\alpha]_D+0.75$ (*c* 1, $CHCl_3$). ^1H NMR: δ 6.73 (AB, $\Delta\delta_{6',7'}=10.8$ Hz, $J_{6',7'}=8.7$ Hz, 2H, H-6′, H-7′); 4.95 (dd, $J_{3'a,4'}=4.22$, $J_{3'b,4'}=3.3$ Hz, 1H, H-4); 3.83 (q, $J_{5,Me}=6.4$ Hz, 1H, H-5); 3.78 and 3.77 (2s, 23H, $2OCH_3$); 3.62–3.38 (m, 2H, –OCH_2–); 3.16 (d, $J_{1'a,1'b}=15.6$ Hz, 1H, H-1′a); 2.72 (d, 1H, H-1′b); 2.35 (dd, $J_{3'a,3'b}=14.9$ Hz, 1H, H-3b); 1.7 (dd, 1H, H-3a); 1.44 and 1.39 (2s, 23H, $2CH_3$); 1.15 (t, $J=$ 7.1 Hz, 3H, –CH_3); 0.96 (d, 3H, 5′-Me); IR: ν_{max} 2837, 1601, 1489, 1261, 1100 cm^{-1}; MS: *m/z* (%) 336 (49), 246 (21), 232 (23), 215 (22), 208 (100), 179 (26), 86 (21); HRMS: calcd for $C_{19}H_{28}O_5$ (M^+): 336.19366; found: 336.19371.

3.1.5. (2*S*,4*R*,9*S*)-4,2-Epoxymethano-5,8-dimethoxy-9-methyl-1,2,3,4-tetrahydronapthalen-2-ol (11a). To a solution of silyl derivative **8a** (254 mg, 0.6 mmol) in chloroform (5 mL) $FeCl_3$–SiO_2 (11 mg) was added and resulting suspension was kept, with stirring, at room temperature for 5 h. Then reaction mixture was filtered, the solvent removed on a rotatory evaporator and the residue subjected to flash chromatography on a silica gel column in hexane–ethyl acetate (8:2) solution to afforded ether **11a** (111 mg, 74%) as a white solid, mp 211–213 °C, $[\alpha]_D$ −72.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 6.68 (s, 2H, H-6, H-7); 5.44 (d, $J_{3,4}=5.43$ Hz, 1H, H-4); 3.83 (q, $J_{9,CH3}=$ 6.42 Hz, 1H, H-9); 3.78 and 3.60 (2s, 23H, 2OMe); 3.05 (dd, $J_{1a,1b}=17.03$ Hz, $J_{1a,3a}=1.64$ Hz, 1H, H-1a); 2.94 (d, 1H, H-1b); 2.31(ddd, $J_{3a,3b}=10.44$, 1H, H-3a); 1.86 (d, 1H, H-3b); 1.18 (d, 3H, CH_3); IR: ν_{max} 3412, 1489, 1261, 1142, 1064 cm^{-1}; HRMS: calcd for $C_{14}H_{18}O_4$ (M^+): 250.12051; found: 250.12150.

3.1.6. (2*S*,4*R*,9*S*)-2-Acetoxy-4,2-epoxymethano–5,8-dimethoxy-9-methyl-1,2,3,4-tetrahydronaphthalene (11b). Reaction of hydroxy-ester **11a** with acetic anhydride–pyridine mixture (1: 1) and catalytic amount of 4-dimethylaminopyridine, after usual work-up, gave acetate **11b** as a white solid, $[\alpha]_D$ −55.5 (*c* 0.5, $CHCl_3$). ^1H NMR: δ 6.67 (s, 2H, H-6, H-7); 5.45 (d, $J_{3,4}=5.5$ Hz, 1H, H-4); 4.24 (q, $J_{9,CH3}=6.2$ Hz, 1H, H-9); 3.76 and 3.75 (2s, 23H, 2OMe); 3.56 (dd, $J_{1a,1b}=17.0$ Hz, $J_{1a,3a}=1.65$ Hz, 1H, H-1a); 3.18 (d, 1H, H-1b); 2.41 (ddd, $J_{3a,3b}=10.6$ Hz, 1H, H-3a); 2.25 (d, 1H, H-3b); 2.09 (s, 3H, $COCH_3$); 1.15 (d, 3H, –CH_3); IR: ν_{max} 1735, 1489, 1371, 1265, 1128 cm^{-1}; HRMS: calcd for $C_{19}H_{26}O_6$ (M^+) 350.172938; found: 350.193004.

3.1.7. (4*S*,4′*S*,5*S*)-(4*S*,4′*R*,5*S*)-Trimethoxy-2,2,5-trimethyl-3′,4′-dihydro-1*H*-spiro[1,3-dioxolane-4,2′-naphthalene] (9a and 9b). To a solution of silyl derivative **8a** (200 mg, 0.46 mmol) in methanol–water (19: 1) solution was added pyridinium *p*-toluenesulfonate (50 mg). After stirring for 2 h under reflux the mixture was washed with sodium hydrogen carbonate, brine, dried and the solvent evaporated. The residue, consisting mainly of two components (TLC), was subjected to flash chromatography on a silica gel column in hexane–ethyl acetate (8:2) solution to give as less polar component isomer **9b** (62 mg, 42%) as a white solid, mp 74–76 °C. ^1H NMR: δ; 6.70 (AB, $\Delta\delta_{6',7'}=$ 11.3 Hz, $J_{6',7'}=8.9$ Hz, 2H, H-6′, H-7′) 4.68 (dd, $J_{3'a,4'}=$ 5.0 Hz, $J_{3'b,4'}=2.4$ Hz, 1H, H-4′); 4.10 (q, $J_{5,Me}=6.2$ Hz, 1H, H-5); 3.80, 3.77 and 3.39 (3s, 3s, 3OMe); 3.12 (dd, $J_{3'a,3'b}=17.0$ Hz, $J_{1'a,3'b}=1.3$ Hz, 1H, H-1′a); 2.52 (d, 1H, H-1′b); 2.25 (dm, 1H, H-3′b); 2.08 (dd, 1H, H-3′a); 1.47 and 1.38 (2s, 23H, $>C(CH_3)_2$); 1.14 (d, 3H, 5-CH_3). IR: ν_{max} 2837, 1605, 1482, 1260, 1092 cm^{-1}; MS: *m/z* (%) 322 (57), 215 (22), 194 (100), 189 (20), 179 (28), 86 (24), 59 (30); HRMS: calcd for $C_{18}H_{26}O_5$ (M^+): 322.17801; found: 322.17957.

Further elution of the column with the same solvent afforded the more polar isomer **9a** (42 mg, 28%) as a white solid, mp 81–82 °C; ^1H NMR: δ 6.70 (AB, $\Delta\delta_{6',7'}=12.3$ Hz, $J_{6',7'}=$ 8.9 Hz, 2H, H-6′, H-7′), 4.90 (dd, $J_{3'a,4'}=3.9$ Hz, $J_{3'b,4v}=$ 3.2 Hz, 1H, H-4′); 3.79 (q, $J_{5,Me}=6.2$ Hz, 1H, H-5); 3.77 (s, 6H, 2OMe); 3.30 (d, $J_{1'a,1'b}=15.6$ Hz, 1H, H-1′a); 3.25 (s, 3H, OMe); 2.64 (d, 1H, H-1′b); 2.38 (dd, $J_{3'a,3'b}=15.1$ Hz, 1H, H-3′b); 1.66 (dd, 1H, H-3′a); 1.49 and 1.38 (2s, 23H, $2CH_3$); 0.94 (d, 3H, 5-Me); IR: ν_{max} 2836, 1601, 1489, 1465, 1371, 1102, 1102 cm^{-1}; MS: *m/z* (%) 322 (57), 215 (21), 194 (100), 179 (28), 86 (25); HRMS: calcd for $C_{18}H_{26}O_5$ (M^+): 322.17801; found: 322.17912.

3.1.8. (2*S*,4*S*)-(2*S*,4*R*)-2-[(1*S*)-1-Hydroxyethyl]-4,5,8-trimethoxy-1,2,3,4-tetrahydronaphthalen-2-ol (10a and 10b). A solution of silyl derivative **8a** (250 mg, 0.57 mmol) and pyridinium *p*-toluenesulfonate (70 mg) in methanol–water (19:1, 30 mL) was refluxed with stirring for 24 h. The reaction mixture was worked up as in previous experiment and the residue, containing mainly two components was subjected to flash chromatography on a silica gel column in hexane–ethyl acetate (1:1) solution to give the less polar diol **10a** (73 mg, 45%) as a white solid, mp 97–99 °C; ^1H NMR: δ 6.73 (AB, $\Delta\delta_{6,7}=7.8$ Hz, $J_{6,7}=$ 8.9 Hz, 2H, H-6, H-7); 4.97 (s, 1H, 2-OH); 4.78 (dd, $J_{3a,4}=$ 3.4 Hz, $J_{3b,4}=2.5$ Hz, 1H, H-4), 3.81, 3.75 and 3.49 (3s, 33H, 3OMe), 3.7 (q, $J_{1'Me}=6.4$ Hz, 1H, H-1′), 3.02 (dd, $J_{1a,1b}=18.0$ Hz, $J_{1a,3b}=2.0$ Hz, 1H, H-1a); 2.59 (dt, $J_{3a,3b}=14.6$ Hz, 1H, H-3b); 2.40 (d, 1H, H-1b), 1.49 (dd, 1H, H-3a), 1.26 (d, 3H, CH_3); IR: ν_{max} 3441, 1603, 1484, 1464, 1093 cm^{-1}; HRMS: calcd for $C_{15}H_{22}O_5$ (M^+): 282.14673; found: 282.14636.

Further elution of the column with the same solvent furnished the more polar diol **10b** (56 mg, 36%) as a white solid, mp 89–91 °C; ^1H NMR: δ 6.72 (AB, $\Delta\delta_{6,7}=$ 8.9 Hz, $J_{6,7}=9.0$ Hz, 2H, H-6, H-7), 4.66 (dd, $J_{1,2a}=$ 5.0 Hz, $J_{1,2b}=2.5$ Hz, 1H, H-1), 3.82, 3.76 and 3.49 (3s, 3H, 3OMe), 3.47 (q, $J_{1',2'}=6.6$ Hz, 1H, H-1′), 3.03 (dd, $J_{4a,4b}=$ 17.1 Hz, $J_{4a,2b}=1.7$ Hz, 1H, H-4a), 2.53 (d, 1H, H-4b); 2.43 (dt, $J_{2a,2b}=14.5$ Hz, 1H, H-2b), 1.82 (dd, 1H, H-2a), 1.22 (d, 3H, CH_3); IR: ν_{max} 3412, 1602, 1485, 1464, 1110 cm^{-1}; HRMS: calcd for $C_{15}H_{22}O_5$ (M^+): 282.14673; found: 282.14695.

3.1.9. (1*S*,3*S*)-3-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,3-diyl phenylboronate (13). To a

solution of tetralinol **5** (1.07 g, 3.47 mmol) in toluene (25 mL) were added phenylboronic acid (555 mg, 4.55 mmol) and *p*-toluenesulfonic acid (20 mg) and the mixture was stirred under an argon atmosphere at 40–50 °C for 2 h. The solution was diluted with ether (100 mL), washed with sodium hydrogen carbonate solution, brine, dried and solvent evaporated to give (1*S*,3*S*)-3-[(1*S*)-1-hydroxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,3-diyl phenylboronate (**12**) as thick oil, homogenous in TLC. ^{1}H NMR: δ 7.80–7.75 (m, 2H, aromatic), 7.45–7.25 (m, 3H, aromatic), 6.70 (s, 2H, H-6, H-7), 5.67 (dd, $J_{1,2a}$= 3.4 Hz, $J_{1,2b}$=2.3 Hz, 1H, H-1), 3.88 and 3.77 (2s, 23H, 2OCH$_3$), 3.87 (q, $J_{1',Me}$=6.4 Hz, 1H, H-1′), 3.11 (dd, $J_{4a,4b}$=18.5 Hz, $J_{2a,4a}$=1.9 Hz, 1H, H-4a), 2.73 (d, $J_{4a,4b}$= 18.5 Hz, 1H, H-4b), 2.38 (ddd, $J_{2a,2b}$=13.7 Hz, $J_{1,2a}$= 3.4 Hz, $J_{2a,4a}$=1.8 Hz, 1H, H-2a), 1.81 (dd, 1H, H-2b), 1.40 (d, 3H, –CH$_3$). Crude hydroxy-ester **12** was dissolved in freshly distilled dichloromethane (20 mL) and stirred at 40 °C under an argon atmosphere with pyridinium chlorochromate (3.0 g) and 3 Å molecular sieves (3.3 g) for 1 h. The reaction mixture was cooled, diluted with anhydrous ether (150 mL), filtered through a pad of Celite® and evaporated. Flash chromatography of the residue on silica gel column in ether solution yielded keto–ester **13** (859 mg, 70%). ^{1}H NMR: δ 7.79–7.85 (m, 2H, aromatic), 7.25–7.40 (m, 3H, aromatic), 6.75 (s, 2H, H-6, H-7), 5.68 (t, J= 2.8 Hz, 1H, H-1), 3.89 and 3.76 (2s, 23H, 2OCH$_3$), 3.08 (AB, $\Delta\delta_{4a,4b}$=23.8 Hz, $J_{4a,4b}$=18.2 Hz, 2H, H-4a, H-4b), 2.54 (s, 3H, COCH$_3$), 2.34 (d, J=2.9 Hz, 2H, H-2a, H-2b); MS: *m/z* (%) 352 (37), 231 (20), 230 (100), 215 (82), 205 (21), 177 (30); HRMS: calcd for $C_{20}H_{21}O_5B$ (M^+) 352.14819; found: 325.14564.

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Synthesis of enantiopure cyclitols from (±)-3-bromocyclohexene mediated by intramolecular oxyselenenylation employing (*S,S*)-hydrobenzoin and (*S*)-mandelic acid as chiral sources

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Abstract—Reaction of 3-bromocyclohexene with (*S,S*)-hydrobenzoin and (*S*)-mandelic acid and subsequent intramolecular oxyselenenylation of the resulting allylic ethers followed by oxidation–elimination afforded the valuable *cis*-fused bicyclic olefins, (1*S*,3*S*,4*S*,6*R*)-3,4-diphenylbicyclo[4,4,0]-2,5-dioxa-7-decene and (1*S*,3*S*,4*R*)-3-phenyl-4a,7,8,8a-tetrahydro-benzo[1,4]dioxan-2-one, respectively. Further stereoselective transformation of these *cis*-fused bicyclic olefins afforded the enantiopure cyclohexitols, *muco*-quercitol, D-*chiro*-inocitol and *allo*-inocitol.

1. Introduction

Cyclitols have recently attracted a great deal of attention due to their diverse biological activities and their versatilities as synthetic intermediates.[1] Polyhydroxy cyclohexanes, such as inositols and quercitols, and polyhydroxy cyclohexenes, such as conduritols, belong to a family of cyclitols (Fig. 1). These compounds can exist in a number of different stereoisomers; inositols, quercitols, and conduritols have 9, 16, and 6 possible stereoisomers, respectively. Among them, the inositols have been studied the most because of their important biological properties.[2] For example, D-*myo*-inositol 1,4,5-trisphosphate is a second messenger that controls many cellular processes by generating internal calcium signals.[3] Also, D-*chiro*-inositol is considered to be one of the significant constituents of putative insulin mediators.[4] Aminocyclohexitols and aminocyclopentitols, which are nitrogen analogs of cyclitols, have also been the focus of much attention in recent years mainly because of their glycosidase inhibitory activities.[5]

A great deal of effort has been devoted to the development of various methodologies for the synthesis of enantiopure cyclitols and their derivatives.[1a–d,6] Recently, the synthesis

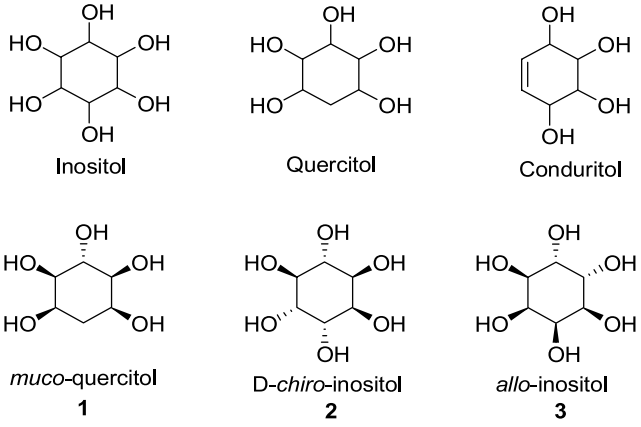

Figure 1.

of enantiopure cyclitols was achieved by transformation of other cyclitols by some groups.[7] The microbial oxidation of halobenzens was employed by Hudlicky et al. in the preparation of inositols.[8] The ring-closing metathesis (RCM) reaction has also been applied in the asymmetric synthesis of cyclitols using sugars,[9] tartrates,[10] and polyhydroxyl allylsilanes[11] as chiral building blocks. The Ferrier-II rearrangement[12] and the free radical cyclization[13] of sugar derivatives are other useful methods developed by Ikegami and Yadav et al., respectively. In addition, the reduction of arylsilanes in combination with the asymmetric dihydroxylation reported by Landais and co-workers

Keywords: 3-Bromocyclohexene; Intramolecular oxyselenenylation; Oxidation–elimination; Cyclohexitols.
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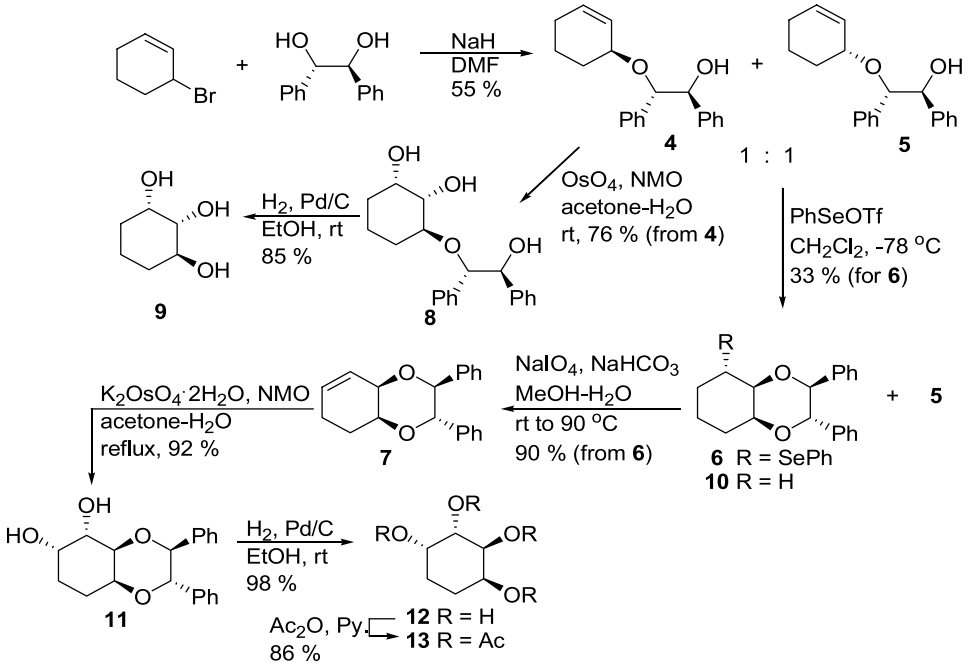
provides an easy access to cyclitols.[14] Even though there are a number of methods available for the asymmetric synthesis of cyclitols, they are generally target-specific and limited in applications. In this regard, there still remains a need for developing new methodologies that employ cheap and simple starting materials to accommodate structurally diverse cyclitol derivatives. Furthermore, it is highly desirable to develop a method that can also be applied to the synthesis of other functionalized cyclic compounds such as five-membered cyclopentitols and amino group-containing aminocyclitols. We have previously reported the preliminary work on the synthesis of enantiopure cyclitols from the cyclohexene mediated by sequential oxyselenenylation.[15] Herein we report the facile synthesis of biologically important cyclitols, *muco*-quercitol (**1**), D-*chiro*-inositol (**2**), and *allo*-inositol (**3**), from (±)-3-bromocyclohexene. The key reaction step features the application of (*S*,*S*)-hydrobenzoin and (*S*)-mandelic acid, as the source of oxygen atom and chirality in the stereoselective *cis*-diol formation of the cyclohexene ring system.

2. Results and discussion

Treating 3-bromocyclohexene with (*S*,*S*)-hydrobenzoin, which was pre-treated with sodium hydride, in DMF afforded an inseparable mixture of diastereomeric allylic ethers **4** and **5** in a ratio of 1 to 1 as shown in Scheme 1. Intramolecular oxyselenenylation of the mixture of **4** and **5** with PhSeOTf, which was generated in situ from PhSeBr and AgOTf in CH_2Cl_2, produced only a *cis*-fused bicyclic phenylselenenyl dioxane **6** in 33% yield, based on the mixture, along with the unreacted **5**. Both regiochemistry and stereochemistry were completely controlled in this intramolecular oxyselenenylation step. It is noteworthy to mention that the intermolecular oxyselenenylation of both cyclic[16] and acyclic[17] allylic alcohols usually provides 1,3-diol derivatives rather than 1,2-diol derivatives. Oxidation of selenide **6** with $NaIO_4$ in the presence of $NaHCO_3$, and subsequent *syn* elimination of the resulting selenoxide provided a valuable intermediate, bicyclic olefin **7**, in 90% yield. To better understand why the compound **5** is unreactive towards the cyclization under the oxyselenenylation condition, we have considered the transition state model for the intramolecular cyclization. The episelenonium ion, which would be the first intermediate that forms during the cyclization step, can possess either the conformation **5A** or **5B** (Fig. 2). The conformation **5B** is expected to be less favorable since there is a non-bonding interaction between one of the phenyl groups and the pseudoaxial hydrogen at the C-6 position. Thus, it is speculated that the conformation **5A** is the pre-dominant species under the given reaction conditions. In order for the conformation **5A** to achieve the *trans*-1,2-diaxial opening of the episelenonium ion, the hydroxyl group should attack the C-3 carbon leading to a seven-membered cyclic ring formation. Since it is unfavorable to form a seven-membered cyclic ring system, perhaps the cyclization of the allylic ester **5** does not occur under our intramolecular oxyselenation reaction conditions.

Absolute and relative stereochemistry at the newly generated stereocenters of the allylic ether **4** and the bicyclic olefin **7** was determined by their transformation to known compounds as shown in Scheme 1. Dihydroxylation of pure olefin **4** with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO),[18] and subsequent hydrogenolysis of the resulting diol **8** afforded the triol **9**. The absolute configuration of **9** was assigned on the basis of its ^1H NMR spectrum and by comparing its specific rotation with the reported value of an authentic material.[19] Therefore, the configuration of allylic carbon of the compound **4** was assigned as *S*. Reduction of the selenide **6** with Bu_3SnH gave compound **10**. Dihydroxylation of the olefin **7** with NMO in the presence of a catalytic



Scheme 1.

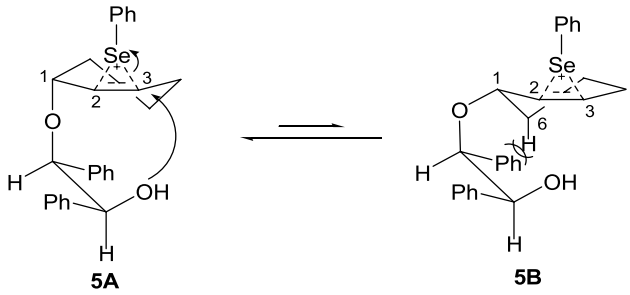


Figure 2.

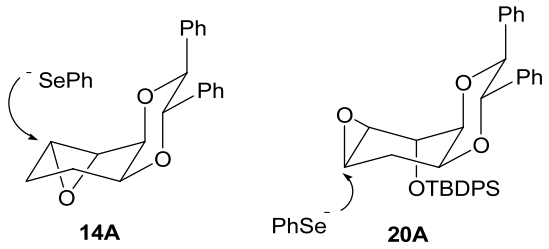
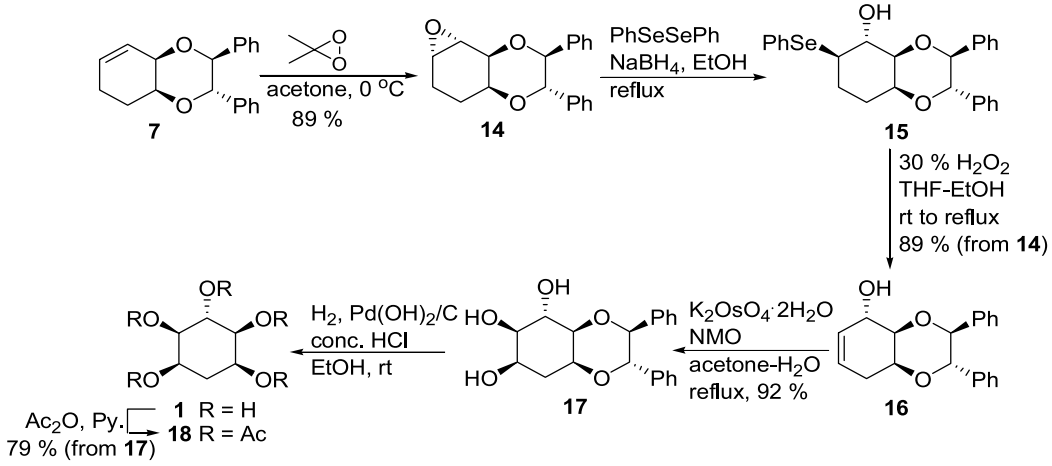


Figure 3.

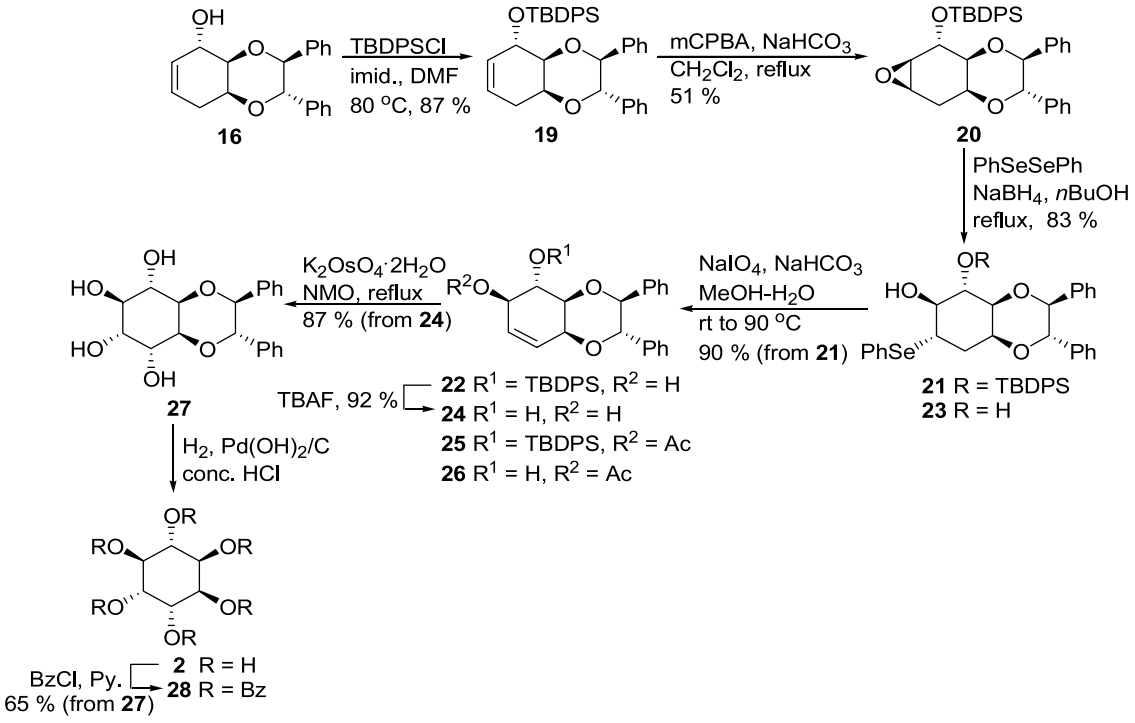
amount of $K_2OsO_4 \cdot 2H_2O$, and subsequent hydrogenolysis of the resulting diol **11** gave the tetrol **12**, which was converted to the tetraacetate **13** by acetylation. The relative stereochemistry of **7** was easily determined as *cis* by examining the ^{1}H NMR spectrum of **10** and by comparing the ^{1}H NMR of **13** with that of its known racemate.[20] Consequently, the configurations of the bicyclic olefin **7** at the C-1 and C-2 carbon centers were unambiguously determined to be *S* and *R*, respectively.

Epoxidation of **7** with dimethyldioxirane (DMDO) in acetone at 0 °C afforded the epoxide **14** in 89% yield, in which the major isomer has an epoxide ring *trans* to the dioxane ring, along with a small amount (ca. 5%) of the *cis* isomer (Scheme 2). On the other hand, treating **7** with MCPBA in methylene chloride gave the epoxide **14** with a lower stereoselectivity where a mixture of *trans* and *cis* isomers was obtained in a ratio of 7:3. Treating **14** with sodium benzeneselenoate, which was generated in situ from diphenyldiselenide (DPDS) and $NaBH_4$, gave the hydroxyselenide **15** in an excellent yield. Exclusive formation of **15** can be explained by the fact that the stable conformation of the bicyclic ring system **14** would be one (**14A**) with two bulky phenyl groups in the diequatorial position. The diaxial opening of the epoxide ring with PhSeNa should be regiospecific as shown in Figure 3. Oxidation of **15** with H_2O_2 followed by the elimination provided the allylic alcohol **16** in a high yield. Attempt to convert the epoxide **14** to the allylic alcohol **16** by employing the trialkysilyl triflate and the organic base[21] was not satisfactory. Dihydroxylation of **16** with NMO in the presence of a catalytic amount of $K_2OsO_4 \cdot 2H_2O$ occurred from the opposite face of the allylic hydroxyl group in **16** to afford exclusively the triol **17** in 92% yield. Hydrogenolysis of **17** with Pearlman's catalyst provided *muco*-quercitol (**1**), whose spectroscopic data and physical properties were identical with those of an authentic one. The structure of **1** was further confirmed by transforming it to the known pentaacetate **18**.[22]

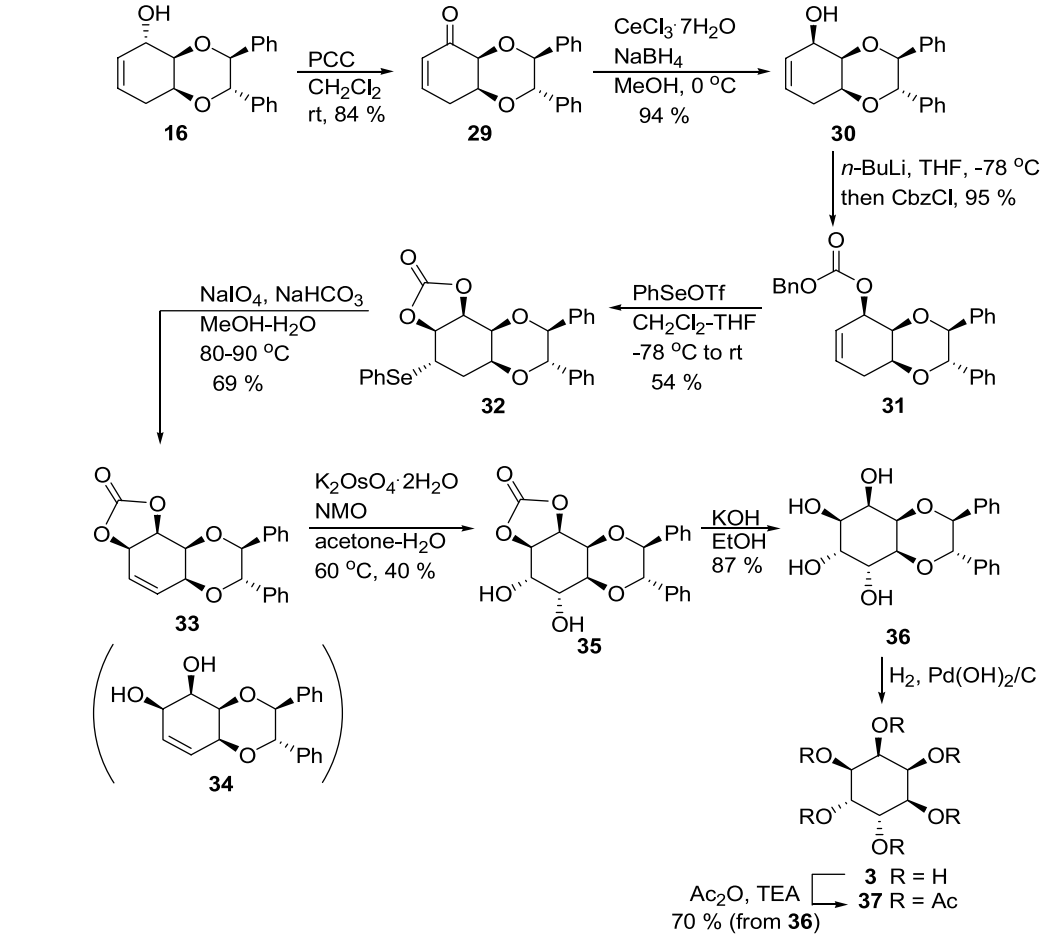
Protection of the hydroxyl group in **16** with sterically demanding *tert*-butyldiphenylsilyl (TBDPS) group and subsequent epoxidation of the resulting silyl ether **19** with MCPBA afforded the desired *trans*-epoxide **20** (*trans* to the OTBDPS group) along with *cis*-epoxide (*trans*/*cis*=3:2) in 85% yield (Scheme 3). However, epoxidation of **16**, its methyl ether, and benzyl ether with MCPBA gave the undesired *cis*-epoxide as the major product. Regiospecific diaxial opening of the epoxide ring **20**, of which stable conformation would be **20A** with two phenyl groups in the diequatorial position as shown in Figure 3, with sodium benzeneselenoate afforded the hydroxyselenide **21** in 83% yield as a mixture of two rotational isomers (3:2) about one of the single bonds in OTBDPS group. The mixture of two rotamers, **21a** and **21b**, was easily separated by flash column chromatography, and no isomerization was detected at room temperature. Oxidation of each rotamer of **21** with $NaIO_4$ followed by elimination of the resulting selenoxide also gave a stable and separable mixture of rotamers of the allylic alcohol **22** (**22a**/**22b**=3:2). One evidence for the rotational isomerism in compounds **21** and **22** can be acquired by removing the TBDPS group. Deprotection of each rotamer **21** (**21a** and **21b**) with tetrabutylammonium fluoride gave the identical diol **23** that did not show rotational isomerism. Similarly, the diol **24**, obtained from each rotamer of **22**, did not show rotational isomerism. It is,



Scheme 2.



Scheme 3.

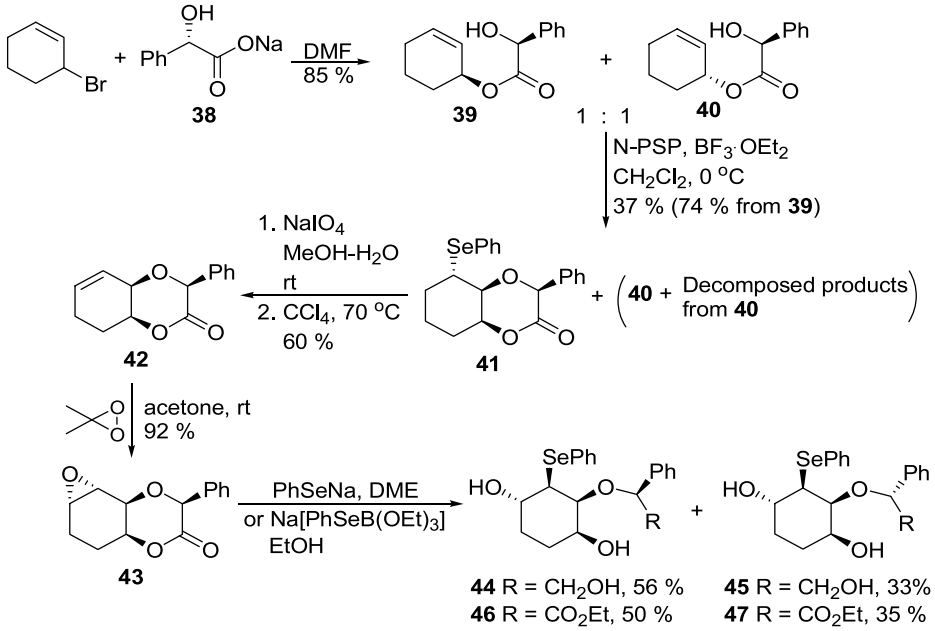


Scheme 4.

however, known that the TBDPS group can migrate among different hydroxyl groups resulting the formation of regioisomers.[23] In order to clarify whether that the isomers **22a** and **22b** are rotamers or regioisomers, the compound was acetylated to give **25** followed by desilyation. This reaction sequence provided **26** as a single compound indicating that the mixtures of compounds **21** and **22** were two rotational isomers. Dihydroxylation of **24** with $K_2OsO_4\cdot 2H_2O$ and NMO followed by hydrogenolysis of the resulting tetrol **27** with palladium hydroxide on carbon (Degussa type) in the presence of a trace amount of concentrated HCl gave D-*chiro*-inositol (**2**), of which physical properties are identical with those of authentic. Perbenzoate **28**[24] was prepared for further characterization of **2**.

Oxidation of the allylic alcohol **16** with pyridinium chlorochromate, and subsequent stereoselective reduction of the resulting ketone **29** with $NaBH_4$ in the presence of $CeCl_3$[25] provided the allylic alcohol **30** that has a hydroxyl group at the pseudoequatorial position (Scheme 4). The benzyl carbonate **31** was obtained in 95% yield by treating alkoxide of **30** with benzyl chloroformate. The Selenium (II) mediated cyclization of **31** was carried out with PhSeOTf in methylene chloride at −78 °C to afford the cyclic carbonate **32** in 54% yield. Upon oxidation with $NaIO_4$ in the presence of $NaHCO_3$ followed by elimination, the olefin **33** was obtained along with a small amount of the diol **34**, which was formed by hydrolysis of the cyclic carbonate group of **33**. Dihydroxylation of the olefin **33** with $K_2OsO_4\cdot 2H_2O$ and NMO followed by hydrolysis of the resulting dihydroxy carbonate **35** with KOH gave the tetrol **36**. Hydrogenolysis of **36** gave *allo*-inositol (**3**) which was converted to the known hexaacetate **37**.

The (*S*)-mandelic acid sodium salt was used to transform 3-bromocyclohexene in DMF to inseperable 1:1 mixture of diastereomeric allylic ethers **39** and **40** in 85% yield as shown in Scheme 5. Intramolecular oxyselenenylation of the mixture of **39** and **40** with *N*-(phenylseleno)phthalimide (*N*-PSP) in the presence of a catalytic amount of $BF_3\cdot OEt_2$ provided the bicyclic oxyselenide **41** (74% from **39**) and the unreacted **40** along with the decomposed by-products. A similar reasoning as that of **5** can be used to explain why the compound **40** is unreactive towards the oxyseleneylation condition (Fig. 2). Oxidation of the selenide **41** with $NaIO_4$ in methanol followed by elimination of the resulting selenoxide in carbon tetrachloride at 70 °C provided the olefin **42**. Epoxidation of the olefin **42** with dimethyldioxirane gave exclusively the epoxide **43**, in which the epoxide ring is *trans* to the dioxanone ring, in 92% yield. Ring opening of the epoxide **43** with PhSeNa afforded the hydroxyselenide **44** and its epimer **45**, both of which are undesired regioisomers. Attempts to synthesize desired hydroxyselenide by ring opening of the epoxide **43** using $Na[PhSeB(OEt)_3]$, PhSeSePh/Na, PhSeH/NaH, or PhSeH/$BF_3\cdot OEt_2$ were not successful. For example, reaction of **43** with $Na[PhSeB(OEt)_3]$ gave the undesired hydroxyselenide



Scheme 5.

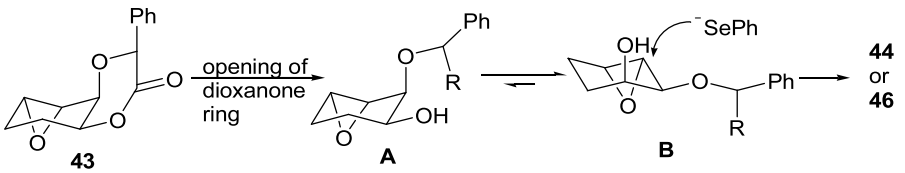
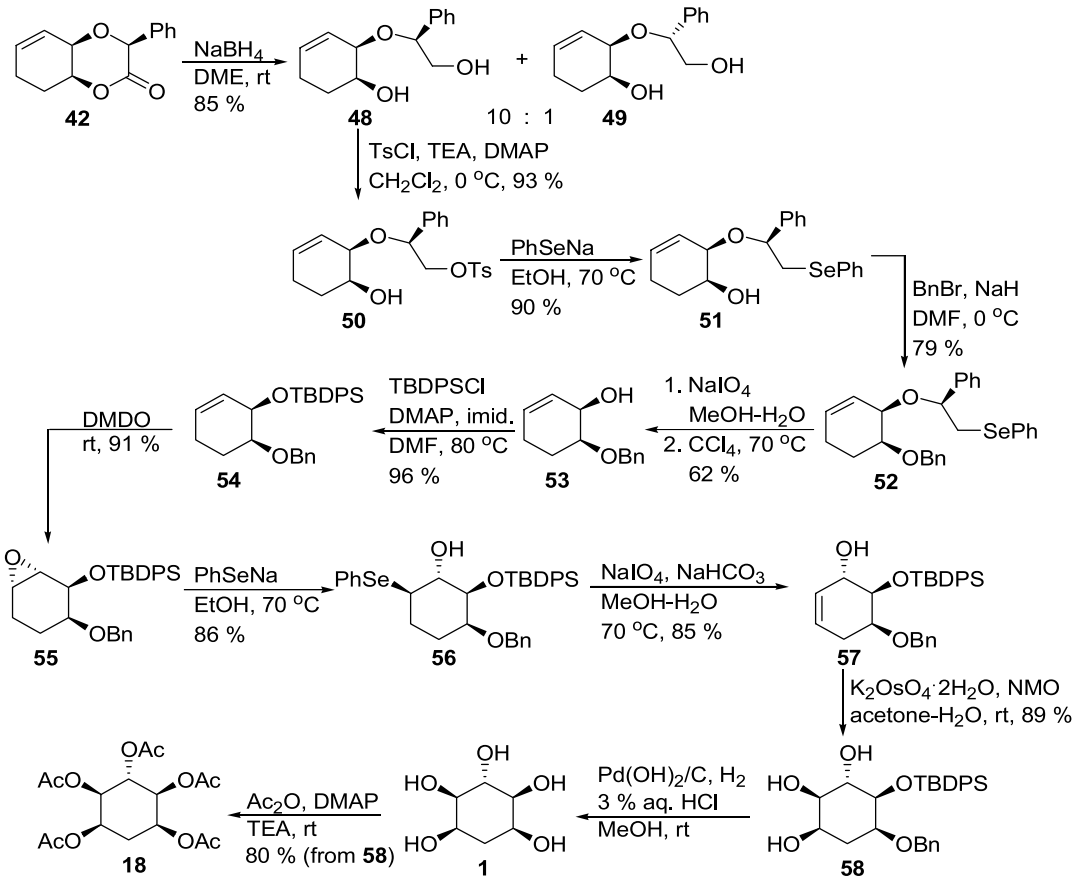


Figure 4.



Scheme 6.

46 and its epimer **47**. Formation of the undesired hydroxyselenides **44** and **46** can be explained by assuming that the dioxanone ring was opened prior to the diaxial opening of the epoxide by the $PhSe^-$ anion attack as shown in Figure 4. Once the lactone ring has been opened, the conformation **B** with the bulky benzylic ether group in the equatorial position is expected to be more stable than conformation **A** with that group in the axial position. Therefore, diaxial opening of the epoxide **B** with $PhSe^-$ would give the undesired hydroxyselenides **44** and **46**.

Before epoxidation of **42**, we decided to remove the dioxanone ring of **42**. It would be more desirable to produce a differentially protected cyclohexene diol than to make cyclohexene diol directly by nonselective cleavage of **42** by using Na/NH_3 or H_2-Pd/C. Treatment of **42** with $NaBH_4$ in DME provided diol **48** and a small amount of its epimer **49** (10:1) in 85% yield (Scheme 6). Tosylation of the primary hydroxyl group of **48** and subsequent displacement of the resulting tosylate **50** with PhSeNa provided the selenide **51** in high yield. Benzylation of the hydroxyl group of **51** and subsequent oxidation of the resulting benzyl-protected selenide **52** followed by elimination of the resulting selenoxide and a concomitant cleavage of enol ether afforded the allylic alcohol **53**. Protection of the hydroxyl group with bulky TBDPS group and subsequent epoxidation of the resulting allylic TBDPS ether **54** with dimethyldioxirane afforded exclusively the epoxide **55**, in which the epoxide ring is *trans* to the OTBDPS group. The ring opening reaction of the epoxide **55** with PhSeNa was completely regio- and stereoselective to provide exclusively the desired oxyselenide **56**. Regio- and stereoselectivity of this ring opening reaction of the epoxide **55** can be explained by assuming that the conformation **55A** with the OTBDPS group at the axial position is more favorable over the conformation **55B** with the OTBDPS group at the equatorial position (Fig. 5).[26] Oxidation of the selenide **56** with $NaIO_4$ in the presence of $NaHCO_3$ followed by elimination of the resulting selenoxide provided the allylic alcohol **57** in 85% yield. Dihydroxylation of the olefin **57** with $K_2OsO_4 \cdot 2H_2O$ and NMO occurred from the opposite face of the allylic hydroxyl group to afford exclusively the triol **58** in 89% yield. Hydrogenolysis of **58** with palladium hydroxide in the presence of aqueous 3% HCl directly gave *muco*-quercitol (**1**) in an excellent yield.[27] Further characterization of **1** was performed by its transformation to the known pentaacetate **18**.[22]

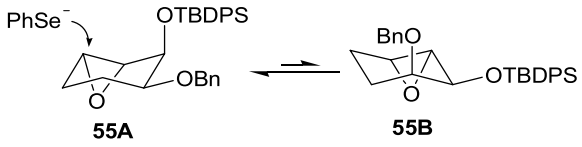


Figure 5.

3. Conclusion

We have synthesized *muco*-quercitol (**1**), D-*chiro*-inositol (**2**), and *allo*-inositol (**3**) from the (±)-3-bromocyclohexene

mediated by sequential oxyselenenylation. We also developed a novel method for the stereoselective construction of the *cis*-diol functionality into the cyclohexane ring from 3-bromocyclohexene, by employing (*S*,*S*)-hydrobenzoin and (*S*)-mandelic acid. Particularly, our methodology has shown that the use of 3-bromocyclohexene as the starting material is more convenient in the preparation of the versatile intermediate **6** than that of cyclohexene. In addition, we have found that the mixtures in **21** and **22** are rotational isomers resulting from introducing a bulky TBDPS group, not the regioisomers resulting from the migration of silyl group to the next hydroxyl group. On the synthetic route to *muco*-quercitol (**1**) from 3-bromohexene and (*S*)-mandelic acid, we have gained an easy access to the useful key intermediates such as differentially protected cyclohexene diol **53** and **57**, and demonstrated their versatility in the synthesis of enantiopure cyclohexitols. The usefulness of these compounds will be further demonstrated in the preparation of other important natural products.

4. Experimental

4.1. General

All reactions were conducted under a positive pressure of dry argon with dry, freshly distilled solvents unless otherwise noted. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Melting points are uncorrected. IR spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer. NMR spectra were recorded on a Bruker 250 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter.

4.1.1. (1*S*,2*S*,1′*S*)- and (1*S*,2*S*,1′*R*)-2-(Cyclohex-2′-enyloxy)-1,2-diphenylethanol (4 and 5). To a solution of (*S*,*S*)-hydrobenzoin (2.37 g, 0.01 mol) in DMF (60 mL) was added NaH (0.96 g, 0.2 mol). After stirring 5 min at rt, 3-bromocyclohexene (2.09 g, 0.02 mol) was added. The resulting solution was stirred further 1 h at rt, then quenched with H_2O and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give a mixture (1.63 g, 55%) of **4** and **5**: R_f=0.31 (hexane/EtOAc, 7:1).

4.1.2. (1*S*,2*S*,3*S*)-3[(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethoxy]-1,2-cyclohexanediol (8). To a solution of compound **4** (130 mg, 0.44 mmol) in acetone (8 mL) and H_2O (2 mL) were added NMO (63 mg, 0.54 mmol) and a catalytic amount of OsO_4 at rt. After stirring for 24 h at rt, the reaction mixture was quenched with $NaHSO_4$ (10 mg), and diluted with H_2O and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 3:2) to give the title compound **8** (109 mg, 76%) as a white solid. R_f=0.23 (hexane/EtOAc, 1:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13–1.26 (m, 1H), 1.31–1.53 (m, 3H), 1.71–1.77 (m, 1H), 1.95–1.99 (m, 1H), 2.67 (br s, 1H), 3.12 (br s, 1H), 3.45–3.52 (m, 2H), 3.72 (br s, 1H), 3.96–3.99 (m, 1H), 4.37 (d, J=7.8 Hz, 1H), 4.65 (d, J=7.8 Hz, 1H), 7.00–7.06 (m, 4H), 7.13–7.21 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.3, 27.9, 29.6, 69.2, 74.5, 76.1, 78.1, 83.9, 127.1, 127.7, 127.9, 128.2, 128.3, 138.1, 139.3. FAB HRMS calcd for $C_{20}H_{24}O_4Na$ $(M+Na)^+$: m/z 351.1572. Found: 351.1556.

4.1.3. [1*S*-(1α,2α,3β)]-Cyclohexanetriol (9). A solution of compound **8** (65 mg, 0.20 mmol) and Pd/C (78 mg, 5% Pd) in EtOH (3 mL) was vigorously stirred at 50–55 psi under H_2 gas. After stirring for 8 h at rt, the reaction mixture was passed through Celite pad and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 3:1) to give the title compound **9** (22 mg, 85%) as a white solid. R_f=0.15 (EtOAc only); mp 125–126 °C; $[\alpha]_D$=+70.2 (c 0.65, H_2O); ^{1}H NMR (250 MHz, D_2O) δ 1.22–1.37 (m, 1H), 1.43–1.66 (m, 3H), 1.71–1.79 (m, 1H), 1.82–1.89 (m, 1H), 3.38 (dd, J=3.0, 8.2 Hz, 1H), 3.70–3.79 (m, 1H), 3.97–4.02 (m, 1H); ^{13}C NMR (63 MHz, D_2O) δ 19.3, 31.1, 32.4, 71.0, 71.1, 76.9. Anal. calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.41; H, 9.21.

4.1.4. (1*S*,3*S*,4*S*,6*S*,7*R*)-3,4-Diphenyl-7-phenylselenobicyclo[4,4,0]-2,5-dioxadecane (6). To a solution of the mixture of compounds **4** and **5** (1.63 g, 5.5 mmol) and PhSeBr (1.61 g, 6.8 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added a THF (5 mL) solution of AgOTf (1.88 g, 7.3 mmol). After stirring for 30 min at −78 °C, the reaction mixture was warmed to rt, then diluted with CH_2Cl_2 and neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 14:1) to give the title compound **6** (0.81 g, 33%) as a white solid. R_f=0.45 (hexane/EtOAc, 7:1); mp 174–177 °C; $[\alpha]_D$=−34.45 (c 0.43, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.81–1.92 (m, 3H), 2.16–2.27 (m, 1H), 2.43–2.56 (m, 1H), 3.78 (s, 3H), 4.27 (s, 1H), 4.39 (d, J=9.3 Hz, 1H), 4.71 (d, J=9.3 Hz, 1H), 6.98–7.00 (m, 4H), 7.15–7.18 (m, 6H), 7.26–7.28 (m, 3H), 7.56–7.59 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.4, 24.6, 26.6, 45.6, 70.4, 76.5, 76.7, 85.2, 127.6, 127.7, 127.9, 128.05, 128.11, 128.2, 129.4, 133.8, 137.9, 138.0; IR ($CHCl_3$, film) 1216, 1097 cm^{-1}. HRMS calcd for $C_{26}H_{26}O_2Se$ $(M)^+$: m/z 450.1098. Found: 450.1099.

4.1.5. (1*S*,3*S*,4*S*,6*R*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxadecane (10). To a solution of compound **6** (90 mg, 0.20 mmol) in the presence of a catalytic amount of AIBN in benzene (3 mL) was slowly added (n-Bu)$_3$SnH (108 μL, 2 equiv). After the resulting solution was degassed by bubbling N_2 gas, it was heated to reflux for 3 h and was allowed to rt. The reaction mixture was concentrated to remove benzene. The residue was dissolved in 10% aqueous KF solution (5 mL) and ether (5 mL), then it was stirred for further 10 min at rt. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **10** (56 mg, 95%) as a white

solid. R_f=0.38 (hexane/EtOAc, 9:1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.18–2.07 (m, 7H), 2.48 (dq, J_d=12.7 Hz, J_q=3.7 Hz, 1H), 3.87 (m, 1H), 4.18 (d, J=2.0 Hz, 1H), 4.44 (d, J=9.3 Hz, 1H), 4.70 (d, J=9.3 Hz, 1H), 7.01–7.10 (m, 4H), 7.18–7.29 (m, 6H). HRMS calcd for $C_{20}H_{22}O_2$ $(M)^+$: m/z 294.1620. Found: 294.1691.

4.1.6. (1*S*,3*S*,4*S*,6*R*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-7-decene (7). A solution of compound **6** (0.17 g, 0.38 mmol) and $NaIO_4$ (0.21 g, 0.96 mmol) in methanol (20 mL) and H_2O (3 mL) in the presence of $NaHCO_3$ (40 mg, 0.48 mmol) was stirred for 10 min at rt and for 48 h at 90 °C. After removal of methanol by evaporation, the concentrated solution was diluted with H_2O and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **7** (98 mg, 90%) as a white solid. R_f=0.42 (hexane/EtOAc, 7:1); mp 149–152 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.78–1.82 (m, 1H), 2.10–2.29 (m, 1H), 2.34–2.38 (m, 1H), 2.61–2.68 (m, 1H), 4.05 (dt, J_d=13.0 Hz, J_t=3.5 Hz, 1H), 4.38 (t, J=4.4 Hz, 1H), 4.48 (d, J=9.1 Hz, 1H), 4.75 (d, J=9.1 Hz, 1H), 5.84 (m, 1H), 6.00 (m, 1H), 7.02–7.05 (m, 4H), 7.12–7.25 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.5, 26.2, 70.5, 72.6, 77.2, 84.9, 125.1, 127.8, 128.1, 133.4, 138.0, 138.2. HRMS calcd for $C_{20}H_{20}O_2$ $(M)^+$: m/z 292.1463. Found: 292.1466.

4.1.7. (1*S*,3*S*,4*S*,6*S*,7*S*,8*S*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-7,8-decanediol (11). To a solution of compound **7** (50 mg, 0.11 mmol) in acetone (4 mL) and H_2O (1 mL) were added NMO (32 mg, 0.27 mmol) and a catalytic amount of $K_2OsO_4\cdot 2H_2O$ at rt. After the resulting solution was heated to reflux for 20 h, it was allowed to rt and quenched with $NaHSO_4$ (10 mg). After stirring for further 10 min at rt, the reaction mixture was diluted with H_2O and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:2) to give the title compound **11** (54 mg, 92%) as a white solid. R_f=0.20 (hexane/EtOAc, 1:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.73–1.87 (m, 3H), 2.42–2.54 (m, 1H), 2.63 (br s, 1H), 3.03 (br s, 1H), 3.98–4.04 (m, 2H), 4.17–4.22 (m, 2H), 4.38 (d, J=9.3 Hz, 1H), 4.68 (d, J=9.3 Hz, 1H), 6.95–7.01 (m, 4H), 7.14–7.22 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.9, 26.2, 68.6, 69.7, 72.2, 76.8, 77.0, 85.2, 127.6, 127.9, 128.11, 128.13, 128.2, 128.3, 137.7. FAB HRMS calcd for $C_{20}H_{22}O_4Na$ $(M+Na)^+$: m/z 349.1416. Found: 349.1436.

4.1.8. [1*S*-(1α,2α,3β,4β)]-Cyclohexanetetrol (12). Compound **11** (47 mg, 0.14 mmol) was subjected to the same reaction conditions as that for the preparation of **9** from **8**. The reaction mixture was purified by flash column chromatography (CH_2Cl_2/MeOH, 2:1) to give the title compound **12** (20 mg, 98%) as a white solid. R_f=0.45 (CH_2Cl_2/MeOH, 2:1); ^{1}H NMR (250 MHz, D_2O) δ 1.54–1.65 (m, 4H), 3.63 (br s, 2H), 3.87 (br s, 2H); ^{13}C NMR (63 MHz, D_2O) δ 25.7, 70.0, 72.4. Anal. calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.44; H, 8.28.

4.1.9. (1*S*,3*S*,4*S*,6*R*,7*S*,8*S*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-7,8-epoxydecane (14). A solution of compound **7** (98 mg, 0.34 mmol) and dimethyldioxirane (2 equiv, ca. 0.05 M) in acetone (20 mL) was stirred for 3 h at 0 °C. The reaction mixture was concentrated by removing acetone. The residue was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **14** (94 mg, 89%) as a white solid. R_f=0.30 (hexane/EtOAc, 10:1); mp 153–155 °C; $[\alpha]_D$=−126.9 (c 0.11, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.56 (s, 1H), 2.04–2.25 (m, 1H), 2.50–2.52 (m, 1H), 2.54–2.57 (m, 1H), 3.28 (t, J=3.4 Hz, 1H), 3.35 (t, J=2.6 Hz, 1H), 4.00 (m, 1H), 4.46 (d, J=9.3 Hz, 1H), 4.58 (s, 1H), 4.69 (d, J=9.3 Hz, 1H), 7.00–7.06 (m, 4H), 7.16–7.22 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.8, 23.2, 52.4, 55.6, 69.7, 71.9, 76.8, 85.0, 127.7, 127.8, 128.2, 137.7, 137.8. Anal. calcd for $C_{20}H_{20}O_3$: C, 77.89; H, 6.53. Found: C, 77.78; H, 6.50.

4.1.10. (1*S*,3*S*,4*S*,6*R*,7*S*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-8-decen-7-ol (16). To a solution of compound **14** (109 mg, 0.35 mmol) in EtOH (15 mL) was slowly added a solution of DPDS (66 mg, 0.21 mmol) and $NaBH_4$ (16 mg, 0.42 mmol) in EtOH (5 mL). After the resulting solution was heated to reflux for 4 h, it was allowed to rt. To this solution were added THF (10 mL) and 30% H_2O_2 (1 mL). The resulting solution was stirred at rt until TLC analysis showed no intermediate **15**, at which point it was heated to reflux for 6 h, then it was allowed to rt. The reaction mixture was diluted with EtOAc and neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give the title compound **16** (97 mg, 89%) as a white solid. R_f=0.43 (hexane/EtOAc, 1:1); mp 154–156 °C; $[\alpha]_D$=+3.0 (c 0.20, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.31–2.41 (m, 1H), 3.04 (t, J=10.1 Hz, 1H), 4.22–4.33 (m, 3H), 4.48 (d, J=9.4 Hz, 1H), 5.83 (d, J=1.1 Hz, 1H), 5.97 (s, 1H), 6.95–6.99 (m, 2H), 7.02–7.06 (m, 2H), 7.14–7.21 (m, 6H). Anal. calcd for $C_{20}H_{20}O_3$: C, 77.89; H, 6.53. Found: C, 77.55; H, 6.68.

4.1.11. (1*S*,3*S*,4*S*,6*R*,7*S*,8*R*,9*R*)-3,4-Diphenylbicyclo-[4,4,0]-2,5-dioxa-7,8,9-decan-triol (17). Compound **16** (84 mg, 0.27 mmol) was subjected to the same reaction conditions as that for the preparation of **11** from **7**. The reaction mixture was purified by flash column chromatography (hexane/EtOAc, 1:7) to give the title compound **17** (86 mg, 92%) as a white solid. R_f=0.38 (hexane/EtOAc, 1:7); mp 220–222 °C; $[\alpha]_D$=−50.5 (c 0.11, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16–1.24 (m, 1H), 1.64–1.68 (m, 1H), 3.70 (s, 1H), 3.94–4.00 (m, 2H), 4.70 (d, J=9.4 Hz, 1H), 4.78 (d, J=9.3 Hz, 1H), 7.08–7.10 (m, 4H), 7.12–7.22 (m, 6H). Anal. calcd for $C_{20}H_{22}O_5$: C, 70.15; H, 6.47. Found: C, 70.18; H, 6.69.

4.1.12. *muco*-Quercitol pentaacetate (18) from 17. To a solution of compound **17** (12 mg, 0.035 mmol) in EtOH (3 mL) were added a catalytic amount of $Pd(OH)_2$/C and 2 drops of conc. HCl. After stirring for 2 h at rt under H_2 (1 atm), the reaction mixture was passed through Celite pad, which was washed with EtOH several times. The filtrate was concentrated thoroughly under vacuum to give *muco*-Quercitol (**1**) as a white solid. Without any further purification, **1** was dissolved in pyridine (2 mL). To this solution was added Ac_2O (0.5 mL). After stirring for 12 h at rt, the reaction mixture was diluted with EtOAc. The

organic layer was washed with aqueous 1 N HCl solution several times, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:3) to give the title compound **18** (11 mg, 79%) as a white solid. R_f=0.43 (hexane/EtOAc, 2:3); mp 162–164 °C; $[\alpha]_D$=0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.85–1.94 (dt, J_d=15.8 Hz, J_t=3.4 Hz, 1H), 2.03 (s, 6H), 2.05 (s, 3H), 2.10 (s, 1H), 2.29–2.38 (dt, J_d=15.8 Hz, J_t=4.2 Hz, 1H), 4.97–5.02 (dd, *J*=9.4, 3.5 Hz, 2H), 5.34–5.38 (dt, J_d=3.7 Hz, J_t=3.6 Hz, 2H), 5.62–5.70 (t, *J*=9.4 Hz, 1H); IR ($CHCl_3$, film) 1749, 1242 cm^{-1}. Anal. calcd for $C_{16}H_{22}O_{10}$: C, 51.33; H, 5.92. Found: C, 51.36; H, 5.98.

4.1.13. (1*S*,3*S*,4*S*,6*S*,7*S*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-7-*tert*-butyldiphenylsilyloxy-8-decene (19). A solution of compound **16** (66 mg, 0.21 mmol), TBDPSCl (115 mg, 0.42 mmol) and imidazole (29 mg, 0.42 mmol) in DMF (3 mL) was stirred for 14 h at 80 °C. The reaction mixture was allowed to rt, quenched with water and dilute with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 12:1) to give the title compound **19** (101 mg, 87%) as a white solid. R_f=0.68 (hexane/EtOAc, 4:1); $[\alpha]_D$=+1.78 (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10 (s, 9H), 2.31-2.41 (m, 1H), 3.04 (t, *J*=10.1 Hz, 1H), 4.13 (s, 1H), 4.26 (d, *J*=9.7 Hz, 2H), 4.43 (s, 1H), 4.66 (d, *J*=9.4 Hz, 1H), 5.52 (s, 1H), 5.83 (s, 1H), 6.90 (d, *J*=5.7 Hz, 2H), 7.02 (d, *J*=3.9 Hz, 2H), 7.13–7.20 (m, 6H), 7.35–7.43 (m, 5H), 7.67–7.72 (m, 5H). Anal. calcd for $C_{36}H_{38}O_3Si$: C, 79.08; H, 7.00. Found: C, 79.00; H, 7.01.

4.1.14. (1*S*,3*S*,4*S*,6*S*,7*S*,8*R*,9*R*)-3,4-Diphenylbicyclo-[4,4,0]-2,5-dioxa-7-*tert*-butyldiphenylsilyloxy-8,9-epoxy-decane (20). A solution of compound **19** (43 mg, 0.079 mmol), mCPBA (41 mg, 0.24 mmol) and $NaHCO_3$ (16 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) was heated to reflux for 20 h. The reaction mixture was allowed to rt, then diluted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/$CHCl_3$/EtOAc, 20:5:1) to give the title compound **20** (23 mg, 51%) and its diastereomer (14 mg, 32%) as a white solid, respectively. R_f=0.40 (hexane/$CHCl_3$/EtOAc, 20:5:1); $[\alpha]_D$=−22.3 (*c* 0.74, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 9H), 2.30 (m, 1H), 2.73 (t, *J*=12.9 Hz, 1H), 3.01 (t, *J*=1.7 Hz, 1H), 3.31 (t, *J*=4.4 Hz, 1H), 3.99 (s, 1H), 4.12 (d, *J*=9.3 Hz, 1H), 4.30–4.35 (m, 1H), 4.47 (s, 1H), 4.56 (d, *J*=9.3 Hz, 1H), 6.92–7.00 (m, 4H), 7.12–7.20 (m, 6H), 7.37–7.44 (m, 6H), 7.65–7.72 (m, 4H). FAB HRMS calcd for $C_{36}H_{38}O_4SiNa$ $(M+Na)^+$: *m*/*z* 585.2437. Found: 585.2442.

4.1.15. (1*S*,3*S*,4*S*,6*S*,7*S*,8*S*,9*S*)-3,4-Diphenylbicyclo-[4,4,0]-2,5-dioxa-7-*tert*-butyldiphenylsilyloxy-9-phenyl-selenodecan-8-ol (21). To a solution of compound **20** (25 mg, 0.044 mmol) in *n*-BuOH (3 mL) was slowly added a solution of DPDS (10 mg, 0.031 mmol) and $NaBH_4$ (2 mg, 0.062 mmol) in *n*-BuOH (3 mL). After the resulting solution was heated to reflux for 24 h, it was allowed to rt, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give the title compound **21a** (16 mg, 50%) and **21b** (10 mg, 33%) as a white solid, respectively. Compound **21a**: R_f=0.44 (hexane/EtOAc, 7:1); $[\alpha]_D$=−48.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.04 (s, 1H), 3.16 (td, J_t=9.4 Hz, J_d=3.7 Hz, 1H), 3.52 (d, *J*=9.5 Hz, 1H), 3.81 (d, *J*=3.0 Hz, 2H), 3.98 (d, *J*=9.5 Hz, 1H), 4.11 (d, *J*=2.1 Hz, 1H), 4.33 (d, *J*=9.5 Hz, 1H), 4.66 (d, *J*=9.5 Hz, 1H), 4.89 (dt, J_d=4.6 Hz, J_t=3.0 Hz, 1H), 6.81 (m, 2H), 6.92 (m, 2H), 7.12–7.18 (m, 6H), 7.25–7.29 (m, 4H), 7.40–7.48 (m, 6H), 7.65 (m, 2H), 7.72 (m, 2H), 7.81 (m, 1H). Anal. calcd for $C_{42}H_{44}O_4SiSe$: C, 70.07; H, 6.16. Found: C, 70.01; H, 6.52. Compound **21b**: R_f=0.28 (hexane/EtOAc, 7:1); $[\alpha]_D$=−21.3 (*c* 0.28, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.90 (d, *J*=12.8 Hz, 1H), 2.35 (d, *J*=6.0 Hz, 1H), 3.44 (td, J_t=8.7 Hz, J_d=3.9 Hz, 1H), 3.59 (s, 1H), 4.17 (d, *J*=1.7 Hz, 2H), 4.29 (s, 1H), 4.45 (d, *J*=9.2 Hz, 1H), 4.63–4.74 (m, 2H), 7.05–7.25 (m, 14H), 7.31–7.40 (m, 7H), 7.62–7.70 (m, 4H).

4.1.16. 23: Desilylation of silyl ether 21a and 21b. To a solution of compound **21a** (or **21b**) (20 mg, 0.028 mmol) in THF (3 mL) was added *n*-Bu_4NF (83 μL, 0.083 mmol, 1.0 M solution in THF). After stirring for 5 h at rt, the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the same compound **23** (12 mg, 90%) from **21a** and **21b** as a white solid. R_f=0.35 (hexane/EtOAc, 2:1); $[\alpha]_D$=+5.5 (*c* 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.95–1.99 (m, 1H), 2.86 (s, 1H), 3.38–3.42 (m, 2H), 3.66–3.71 (m, 1H), 3.83 (d, *J*=5.1 Hz, 1H), 4.19 (s, 2H), 4.65 (d, *J*=9.7 Hz, 1H), 4.71–4.75 (m, 1H), 4.86 (d, *J*=9.7 Hz, 1H), 6.96–6.99 (m, 4H), 7.17–7.22 (m, 6H), 7.30–7.33 (m, 3H), 7.58–7.62 (m, 2H). HRMS calcd for $C_{26}H_{26}O_4Se$ $(M)^+$: *m*/*z* 482.0996. Found: 482.0997.

4.1.17. (1*S*,3*S*,4*S*,6*S*,7*S*,8*R*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-7-*tert*-butyldiphenylsilyloxy-decen-8-ol (22). Compound **21** (32 mg, 0.04 mmol) was subjected to the same reaction conditions as that for the preparation of **7** from **6**. The reaction mixture was purified by flash column chromatography (hexane/EtOAc, 5:1) to give the title compound **22a** (13 mg, 54%) and **22b** (9 mg, 36%) as a white solid, respectively. Compound **22a**: R_f=0.50 (hexane/EtOAc, 5:1); $[\alpha]_D$=−5.0 (*c* 0.08, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.08 (d, *J*=5.4 Hz, 9H), 2.96 (d, *J*=10.1 Hz, 1H), 3.88 (s, 1H), 4.11–4.33 (m, 3H), 4.72 (d, *J*=9.1 Hz, 1H), 4.89 (s, 1H), 5.98 (d, *J*=10.5 Hz, 1H), 6.23 (d, *J*=8.1 Hz, 1H), 6.89 (d, *J*=5.7 Hz, 2H), 7.00 (d, *J*=4.1 Hz, 2H), 7.15–7.18 (m, 6H), 7.39–7.45 (m, 5H), 7.63–7.68 (m, 5H). HRMS calcd for $C_{36}H_{38}O_4Si$ $(M)^+$: *m*/*z* 562.2539. Found: 562.2542. Compound **22b**: R_f=0.23 (hexane/EtOAc, 5:1); $[\alpha]_D$=+31.3 (*c* 0.14, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 9H), 4.02 (d, *J*=18.0 Hz, 2H), 4.24 (s, 1H), 4.48 (d, *J*=9.0 Hz, 1H), 4.57 (s, 1H), 4.63 (d, *J*=9.0 Hz, 1H), 5.85 (d, *J*=9.6 Hz, 1H), 5.94 (d, *J*=9.5 Hz, 1H), 7.04–7.10 (m, 6H), 7.18–7.25 (m, 6H), 7.42–7.45 (m, 4H), 7.72–7.76 (m, 4H).

4.1.18. 25a: Acetylation of allylic alcohol 22a. To a solution of compound **22a** (10 mg) in pyridine (2 mL) was

added Ac_2O (0.5 mL). After stirring for 2 h, the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with aqueous 1 N HCl several times, dried over $MgSO_4$ and concentrated to give **25a** (11 mg). R_f=0.51 (hexane/EtOAc, 5:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10 s, 9H), 1.98 (s, 3H), 4.16–4.17 (m, 1H), 4.21–4.22 (m, 1H), 4.33 (d, J=8.9 Hz, 1H), 4.50 (d, J=8.9 Hz, 1H), 4.83 (d, J=3.4 Hz, 1H), 5.14 (s, 1H), 6.09 (s, 2H), 7.37–7.70 (m, 20H). FAB HRMS calcd for $C_{38}H_{40}O_5SiNa$ $(M+Na)^+$: m/z 627.2543. Found: 627.2522.

4.1.19. 25b: Acetylation of allylic alcohol 22b. R_f=0.41 (hexane/EtOAc, 5:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.91 (s, 3H), 4.01 (s, 1H), 4.29 (s, 1H), 4.48–4.50 (m, 2H), 4.62 (d, J=4.5 Hz, 1H), 5.23 (br s, 1H), 5.86 (d, J=5.3 Hz, 1H), 5.92 (d, J=5.3 Hz, 1H), 7.02–7.78 (m, 20H). FAB HRMS calcd for $C_{38}H_{40}O_5SiNa$ $(M+Na)^+$: m/z 627.2543. Found: 627.2525.

4.1.20. 26: Desilylation of silyl ether 25a and 25b. Compound **25a** (or **25b**) (4 mg) was subjected to the same reaction conditions as that for the preparation of **23** from **21a** and **21b** to give the same compound **26** (2 mg). R_f=0.1 (hexane/EtOAc, 5:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.13 (s, 3H), 3.34 (br s, 1H), 4.17–4.21 (m, 1H), 4.30–4.33 (m, 1H), 4.47 (d, J=8.9 Hz, 1H), 4.55 (d, J=8.9 Hz, 1H), 4.72 (d, J=3.4 Hz, 1H), 5.13 (br s, 1H), 6.06–6.10 (m, 2H), 6.99–7.22 (m, 10H). FAB HRMS calcd for $C_{22}H_{22}O_5Na$ $(M+Na)^+$: m/z 389.1365. Found: 389.1381.

4.1.21. (1*S*,3*S*,4*S*,6*R*,7*S*,8*R*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-9-decen-7,8-diol (24). To a solution of compound **22** (12 mg, 0.02 mmol) in THF (3 mL) was added *n*-Bu_4NF (64 μL, 0.064 mmol, 1.0 M solution in THF). After stirring for 5 h at rt, the reaction mixture was quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give the title compound **24** (6 mg, 92%) as a white solid. R_f=0.40 (hexane/EtOAc, 1:1); $[\alpha]_D$=+23.0 (c 0.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90 (s, 1H), 3.12 (d, J=11.6 Hz, 1H), 3.98 (d, J=10.0 Hz, 1H), 4.32 (s, 1H), 4.43 (d, J=9.1 Hz, 1H), 4.74 (d, J=9.2 Hz, 2H), 5.96 (d, J=10.4 Hz, 1H), 6.24–6.27 (m, 1H), 6.94–7.03 (m, 4H), 7.15–7.23 (m, 6H). HRMS calcd for $C_{20}H_{20}O_4$ $(M)^+$: m/z 324.1361. Found: 324.1359.

4.1.22. (1*S*,3*S*,4*S*,6*R*,7*S*,8*S*,9*R*,10*R*)-3,4-Diphenylbicyclo-[4,4,0]-2,5-dioxadecan-7,8,9,10-tetrol (27). Compound **24** (24 mg, 0.074 mmol) was subjected to the same reaction conditions as that for the preparation of **17** from **16**. The reaction mixture was purified by flash column chromatography (EtOAc only) to give the title compound **27** (22 mg, 87%) as a white solid. R_f=0.28 (EtOAc); $[\alpha]_D$=−68.1 (c 0.32, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.31 (s, 1H), 3.54 (s, 1H), 3.98 (d, J=13.9 Hz, 2H), 4.08–4.16 (m, 2H), 4.29–4.47 (m, 4H), 4.78 (d, J=9.4 Hz, 2H), 6.89 (d, J=6.1 Hz, 2H), 7.01 (d, J=6.4 Hz, 2H), 7.16–7.23 (m, 6H). Anal. calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.18. Found: C, 67.00; H, 6.27.

4.1.23. D-*chiro*-Inocitol hexabenzoate (28). To a solution of compound **27** (11 mg, 0.031 mmol) in EtOH (3 mL) were added a catalytic amount of $Pd(OH)_2$/C and 2 drops of conc. HCl. After stirring for 2 h at rt under H_2 (1 atm), the reaction mixture was passed through Celite pad, which was washed with EtOH several times. The filtrate was concentrated thoroughly under vacuum to give *chiro*-Inocitol (**2**) as a white solid. Without any further purification, **2** was dissolved in pyridine (2 mL). To this solution was added BzCl (0.5 mL). After stirring for 12 h at rt, the reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous 1 N HCl solution several times, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the title compound **28** (16 mg, 65%) as a white solid. R_f=0.30 (hexane/EtOAc, 2:1); $[\alpha]_D$=+69.9 (c 0.30, $ClCH_2$-CH_2Cl); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.03–6.08 (m, 2H), 6.09–6.14 (m, 2H), 6.29–6.34 (m, 2H), 7.27–7.34 (m, 8H), 7.42–7.49 (m, 4H), 7.56 (t, J=7.5 Hz, 4H), 7.67 (t, J=7.4 Hz, 2H), 7.83–7.92 (m, 8H), 8.16 (d, J=7.2 Hz, 4H). Anal. calcd for $C_{48}H_{36}O_{12}$: C, 71.63; H, 4.50. Found: C, 71.61; H, 4.56.

4.1.24. (1*S*,3*S*,4*S*,6*R*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-8-decen-7-one (29). To a solution of compound **16** (20 mg, 0.065 mmol) in CH_2Cl_2 (10 mL) was added PCC (43 mg, 0.20 mmol). After stirring for 3 h at rt, the reaction mixture was diluted with H_2O and CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give the title compound **29** (17 mg, 84%) as a white solid. R_f=0.3 (hexane/EtOAc, 3:1); mp 191–192 °C; $[\alpha]_D$=−134.7 (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.57–2.66 (m, 1H), 3.35–3.46 (m, 1H), 4.43–4.46 (m, 2H), 4.52 (d, J=9.3 Hz, 1H), 4.81 (d, J=9.3 Hz, 1H), 6.21 (d, J=9.9 Hz, 1H), 6.97–7.05 (m, 4H), 7.16–7.26 (m, 7H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.4, 71.0, 77.4, 78.0, 84.1, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 129.2, 137.0, 149.2, 194.0; IR ($CHCl_3$, film) 1679 cm^{-1}. Anal. calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.38; H, 5.85.

4.1.25. (1*S*,3*S*,4*S*,6*R*,7*R*)-3,4-Diphenylbicyclo[4,4,0]-2,5-dioxa-8-decen-7-ol (30). To a solution of compound **29** (16 mg, 0.053 mmol) and $CeCl_3 \cdot 7H_2O$ (24 mg, 0.064 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (3.0 mg, 0.074 mmol). After stirring for 10 min at 0 °C, the reaction mixture was diluted with H_2O and EtOAc. The organic layer was separated, passed through Celite pad, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 5:1) to give the title compound **30** (15 mg, 94%) as a white solid. R_f=0.27 (hexane/EtOAc, 3:1); mp 105–106 °C; $[\alpha]_D$=−85.5 (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.28–2.39 (m, 1H), 2.72 (s, 1H), 2.96–3.08 (m, 1H), 4.22–4.30 (m, 1H), 4.36 (d, J=4.5 Hz, 1H), 4.48 (s, 1H), 4.49 (d, J=9.4 Hz, 1H), 4.76 (d, J=9.4 Hz, 1H), 5.68 (d, J=10.3 Hz, 1H), 5.78–5.85 (m, 1H), 6.96–7.06 (m, 4H), 7.19–7.26 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.5, 67.5, 70.0, 74.9, 76.6, 85.4, 124.9, 127.7, 128.0, 128.1, 128.26, 128.31, 128.6, 137.4, 137.6; IR ($CHCl_3$, film) 3551, 3428, 3059, 2920, 2879 cm^{-1}. Anal. calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.87; H, 6.60.

4.1.26. Carbonic acid benzyl ester 2,3-diphenyl-2,3,4a,5,8,8a-hexahydro-benzo[1,4]dioxin-5-yl ester (31). To a solution of compound **30** (15 mg, 0.050 mmol) in THF (4 mL) at −78 °C was added *n*-BuLi (31 μL, 0.050 mmol, 1.6 M in hexanes). After stirring for 10 min at −78 °C, CbzCl (26 mg, 0.15 mmol) was added. The resulting solution was stirred for 10 min at −78 °C, then quenched with water and diluted with CH_2Cl_2. The organic layer was separated, passed through Celite pad, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **31** (21 mg, 95%). R_f=0.29 (hexane/EtOAc, 7:1); $[\alpha]_D$=−8.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.33–2.40 (m, 1H), 3.06–3.16 (m, 1H), 4.24–4.30 (m, 1H), 4.46 (d, *J*=9.4 Hz, 1H), 4.64 (s, 1H), 4.71 (d, *J*=9.4 Hz, 1H), 5.13 (s, 2H), 5.44 (s, 1H), 5.65 (d, *J*=10.2 Hz, 1H), 5.93–5.99 (m, 1H), 6.93–7.05 (m, 4H), 7.12–7.25 (m, 11H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.8, 69.4, 69.7, 72.8, 73.7, 76.8, 84.9, 123.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.6, 135.3, 137.5, 137.7, 154.8; IR ($CHCl_3$, film) 3029, 2921, 1735, 1252 cm^{-1}. Anal. calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.92; H, 5.98.

4.1.27. 7,8-Diphenyl-4-phenylselenyl-octahydro-1,3,6,9-tetraoxa-cyclopenta[a]naphthalene-2-one (32). To a solution of PhSeBr (24 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added a THF (1.5 mL) solution of AgOTf (31 mg, 0.12 mmol). To this solution was added the compound **31** (24 mg, 0.054 mmol). After stirring for 20 min at −78 °C, the reaction mixture was warmed to rt, diluted with CH_2Cl_2 and neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give the title compound **32** (15 mg, 54%). R_f=0.3 (hexane/EtOAc, 3:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.05–2.14 (m, 1H), 3.03–3.21 (m, 1H), 4.18–4.27 (m, 2H), 4.42–4.57 (m, 3H), 4.73–4.77 (m, 1H), 4.96–5.02 (m, 1H), 6.81–6.82 (m, 2H), 6.84–6.97 (m, 2H), 7.11–7.26 (m, 7H), 7.34–7.39 (m, 3H), 7.62–7.63 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 37.7, 68.0, 72.0, 74.0, 77.37, 77.44, 85.0, 126.9, 127.1, 127.9, 128.1, 128.3, 128.7, 129.2, 129.3, 129.9, 134.8, 135.4, 136.4, 136.9, 154.3; IR ($CHCl_3$, film) 1807, 1740, 1591 cm^{-1}.

4.1.28. 7,8-Diphenyl-3a,5a,7,8,9a,9b-hexahydro-1,3,6,9-tetraoxa-cyclopenta[a]naphthalene-2-one (33). Compound **32** (15 mg, 0.030 mmol) was subjected to the same reaction conditions as that for the preparation of **7** from **6**. The reaction mixture was purified by flash column chromatography (hexane/EtOAc, 3:1) to give the title compound **33** (7 mg, 69%) as a white solid. R_f=0.65 (hexane/EtOAc, 1:4); mp 237–238 °C; $[\alpha]_D$=89.9 (*c* 0.15, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.50 (d, *J*=2.1 Hz, 1H), 4.54–4.61 (m, 3H), 4.89 (dd, *J*=3.3, 3.2 Hz, 1H), 5.05–5.08 (m, 1H), 6.25 (d, *J*=10.4 Hz, 1H), 6.34–6.40 (m, 1H), 6.81–6.84 (m, 2H), 6.98–7.01 (m, 2H), 7.06–7.26 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 68.8, 69.4, 70.7, 73.5, 78.9, 83.8, 123.8, 127.3, 127.8, 127.9, 128.1, 128.2, 128.6, 134.9, 136.5, 136.9, 154.6; IR ($CHCl_3$, film) 1802, 1642, 1350, 1144, 1088, 1047 cm^{-1}. HRMS calcd for $C_{21}H_{18}O_5$ $(M)^+$: *m*/*z* 350.1154. Found: 350.1155.

4.1.29. 4,5-Dihydroxy-7,8-diphenyl-octahydro-1,3,6,9-tetraoxa-cyclopenta[a]naphthalene-2-one (35). To a solution of compound **33** (20 mg, 0.057 mmol) in acetone (4 mL) and H_2O (1 mL) were added NMO (66 mg, 0.57 mmol) and $K_2OsO_4\cdot 2H_2O$ (10 mg, 0.02 mmol) at rt. After the resulting solution was stirred for 48 h at 60 °C, it was allowed to rt and quenched with $NaHSO_4$ (10 mg). After stirring for further 10 min at rt, it was diluted with H_2O and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:4) to give the title compound **35** (9 mg, 40%) as a white solid. R_f=0.35 (hexane/EtOAc, 1:4); mp 83–90 °C (decom.); $[\alpha]_D$=−16.5 (*c* 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.78–2.94 (m, 2H), 4.13 (s, 1H), 4.50–4.62 (m, 4H), 4.85 (s, 2H), 4.99 (s, 1H), 6.78–6.82 (m, 2H), 7.01–7.02 (m, 2H), 7.17–7.26 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 68.2, 70.1, 71.9, 72.5, 73.9, 77.9, 78.9, 84.8, 127.1, 127.9, 128.2, 128.3, 128.9, 136.1, 136.5, 154.1; IR ($CHCl_3$, film) 3425, 2922, 2357, 1802 cm^{-1}.

4.1.30. 2,3-Diphenyl-octahydro-benzo[1,4]dioxine-5,6,7,8-tetrol (36). To a solution of compound **35** (9 mg, 0.023 mmol) in EtOH (2 mL) was added KOH (3 mg, 0.046 mmol) at rt, and the resulting solution was heated to 60 °C. After stirring 4 h at 60 °C, the reaction mixture was allowed to rt, neutralized with 3 drops of aqueous 1 N HCl solution and diluted with H_2O and EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:4) to give the title compound **36** (7 mg, 87%) as a white solid. R_f=0.65 (CHCl3/MeOH, 2:1); mp 80–85 °C (decom.); $[\alpha]_D$=−9.7 (*c* 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.48 (s, 2H), 2.77 (d, *J*=4.8 Hz, 1H), 2.94 (d, *J*=3.8 Hz, 1H), 4.10–4.12 (m, 1H), 4.17–4.18 (m, 2H), 4.41–4.43 (m, 2H), 4.50 (s, 1H), 4.82 (d, *J*=4.7 Hz, 1H), 4.90 (d, *J*=4.7 Hz, 1H), 6.92–6.94 (m, 2H), 7.03–7.04 (m, 2H), 7.21–7.26 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 63.4, 66.9, 72.2, 73.1, 73.4, 76.8, 77.9, 85.8, 127.6, 127.9, 128.3, 128.5, 128.7, 128.8, 136.65, 136.70; IR ($CHCl_3$, film) 3368 cm^{-1}. Anal. calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.92; H, 5.98.

4.1.31. *allo*-Inositol hexaacetate (37). To a solution of compound **36** (7 mg, 0.02 mmol) in EtOH (2 mL) were added a catalytic amount of $Pd(OH)_2$/C. After stirring for 1 h at rt under H_2 (1 atm), the reaction mixture was passed through Celite pad, which was washed with EtOH several times. The filtrate was concentrated thoroughly under vacuum to give *allo*-Inositol (**3**) as a white solid. Without any further purification, **3** was dissolved in TEA (1 mL). To this solution were added Ac_2O (0.5 mL) and a catalytic amount of DMAP. After stirring for 3 h at rt, the reaction mixture was diluted with EtOAc. The organic layer was washed with saturated NH_4Cl solution several times, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the title compound **37** (6 mg, 70%) as a white solid. R_f= 0.35 (hexane/EtOAc, 1:1); $[\alpha]_D$=0 (*c* 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.07 (br s, 18H), 5.33 (m, 2H), 5.46 (m, 4H). Anal. calcd for $C_{18}H_{24}O_{12}$: C, 50.00; H, 5.59. Found: C, 50.12; H, 5.51.

4.1.32. (1*S*,1′*S*)- and (1*S*,1′*R*)-Cyclohex-2′-enyl hydroxyphenylacetate (39 and 40). To a solution of (+)-mandelic acid (2.0 g, 13.1 mmol) in DMF (60 mL) was added NaH (60%, 0.58 g, 14.5 mmol). After stirring 1 h at rt, 3-bromocyclohexene (2.32 g, 14.4 mmol) was added. The resulting solution was stirred further 8 h at rt, and diluted with EtOAc. The organic layer was washed with saturated NH_4Cl solution, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give a mixture (2.59 g, 85%) of **39** and **40** as a yellow oil. R_f=0.25 (hexane/EtOAc, 7:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50–2.01 (m, 6H), 3.59–3.64 (t, J=6.3 Hz, 1H), 5.13–5.16 (d, J=6.1 Hz, 1H), 5.29–5.31 (m, 1H), 5.47–5.75 (m, 1H), 5.83–6.00 (m, 1H), 7.28–7.44 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.4, 18.8, 24.80, 24.83, 27.9, 28.2, 70.0, 70.5, 72.97, 73.00, 124.68, 124.71, 126.48, 126.51, 128.3, 128.5, 133.4, 133.8, 138.6, 138.7, 173.4, 173.5; IR ($CHCl_3$, film) 3460, 1730, 1453, 1183, 1098, 1065, 1006, 907, 736 cm^{-1}. Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.43; H, 6.84.

4.1.33. (1*S*,3*S*,4*S*,5*S*)-3-Phenyl-5-phenylselenyl-hexahydro-benzo[1,4]dioxin-2-one (41). To a solution of the mixture of **39** and **40** (0.53 g, 2.3 mmol) and NPSP (0.82 g, 2.7 mmol) in CH_2Cl_2 (20 mL) was slowly added $BF_3\cdot OEt_2$ (34 μL, 0.27 mmol) at 0 °C. The resulting solution was stirred for 20 min at 0 °C, diluted with CH_2Cl_2 and neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 7:1) to give the title compound **41** (0.33 g, 37%) as a yellow oil. R_f=0.25 (hexane/EtOAc, 7:1); $[\alpha]_D$=+3.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48–1.77 (m, 4H), 1.84–1.95 (m, 1H), 2.09–2.16 (m, 1H), 3.55–3.58 (m, 1H), 4.26–4.31 (m, 1H), 4.37–4.42 (dd, J=8.2, 2.7 Hz, 1H), 5.46 (s, 1H), 7.23–7.64 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.6, 27.9, 30.4, 43.3, 67.0, 75.3, 80.8, 127.0, 127.2, 128.4, 128.6, 128.8, 129.2, 135.8, 136.0, 167.0; IR ($CHCl_3$, film) 1743, 1223, 1065 cm^{-1}. Anal. calcd for $C_{20}H_{20}O_3Se$: C, 62.02; H, 5.20. Found: C, 62.04; H, 5.39.

4.1.34. (1*S*,3*S*,4*R*)-3-Phenyl-4a,7,8,8a-tetrahydro-benzo[1,4]dioxan-2-one (42). To a solution of compound **41** (1.40 g, 3.60 mmol) in MeOH (60 mL) and H_2O (10 mL) at rt was added $NaIO_4$ (1.86 g, 8.70 mmol). The resulting solution was stirred at rt until TLC analysis showed no starting material **41**, at which point it was concentrated thoroughly to remove the solvents (MeOH and H_2O). The residue was dissolved in CCl_4 (60 mL), and the solution was heated to 70 °C. After stirring 5 h at 70 °C, it was allowed to rt and diluted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to give the title compound **42** (0.50 g, 60%) as a yellow oil. R_f=0.45 (hexane/EtOAc, 3:1); $[\alpha]_D$=−53.3 (*c* 3.2, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.76–1.89 (m, 1H), 1.95–2.14 (m, 2H), 2.26–2.40 (m, 1H), 4.14–4.20 (m, 1H), 4.88 (m, 1H), 5.46 (s, 1H), 5.72–5.76 (m, 1H), 5.98–6.05 (m, 1H), 7.32–7.50 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.8, 24.6, 65.0, 74.4, 75.1, 123.1, 126.8, 128.7, 128.9, 132.6, 135.6, 167.8; IR ($CHCl_3$, film) 1730, 1387, 1229, 1104, 1045 cm^{-1}. Anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.05; H, 6.24.

4.1.35. (1*S*,4*S*,6*S*,7*S*,8*R*)-6-Phenyl-hexahydro-1,4,7-trioxa-cyclopropa-[a]naphthalene-5-one (43). A solution of compound **42** (25 mg, 0.1 mmol) and dimethyldioxirane (2 equiv, ca. 0.05 M) in acetone (10 mL) was stirred for 2 h at rt. The reaction mixture was concentrated by removing acetone. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to give the title compound **43** (23 mg, 92%) as a colorless oil. R_f=0.38 (hexane/EtOAc, 3:1); $[\alpha]_D$=−53.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44–1.59 (m, 1H), 1.64–1.75 (m, 1H), 1.95–2.04 (m, 1H), 2.10–2.24 (m, 1H), 3.32–3.34 (dd, J=3.5, 1.7 Hz, 1H), 3.40–3.41 (d, J=2.5 Hz, 1H), 3.91–3.95 (m, 1H), 4.58–4.60 (d, J=3.9 Hz, 1H), −5.53 (s, 1H), 7.36–7.47 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.4, 19.5, 52.4, 53.1, 60.9, 75.0, 75.6, 127.1, 128.9, 129.0, 134.7, 166.4; IR ($CHCl_3$, film) 1749, 1229, 1058 cm^{-1}. Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.28; H, 5.76.

4.1.36. (1*S*,2*S*,3*R*,4*S*,1′*S*)-2-(2-Hydroxy-1-phenyl-ethoxy)-3-phenylselanyl-cyclohexane-1,4-diol (44) and (1*S*,2*S*,3*R*,4*S*,1′*R*)-2-(2-hydroxy-1-phenyl-ethoxy)-3-phenylselanyl-cyclohexane-1,4-diol (45). To a solution of compound **43** (220 mg, 0.9 mmol) and DPDS (420 mg, 1.3 mmol) in DME (4 mL) was added $NaBH_4$ (120 mg, 3.1 mmol). After stirring for 3 h at rt, the reaction mixture was quenched with water, diluted with EtOAc. The organic layer was washed with saturated NH_4Cl solution several times, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:10) to give the title compound **44** (204 mg, 56%) and **45** (119 mg, 33%) as a colorless oil, respectively. Compound **44**: R_f=0.40 (hexane/EtOAc, 1:10); $[\alpha]_D$=+22.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13–1.28 (m, 1H), 1.76–2.03 (m, 3H), 2.50 (s, 1H), 2.91–3.02 (m, 1H), 3.37–3.83 (m, 7H), 4.43–4.47 (dd, J=7.4, 3.7 Hz, 1H), 7.26–7.66 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 26.9, 27.0, 47.6, 67.2, 73.1, 73.6, 76.0, 79.5, 126.1, 126.2, 127.3, 128.7, 128.9, 129.2, 137.0, 137.7; IR ($CHCl_3$, film) 3434, 1578, 1453, 1058 cm^{-1}. Anal. calcd for $C_{20}H_{24}O_4Se$: C, 58.97; H, 5.94. Found: C, 58.98; H, 5.98. Compound **45**: R_f=0.25 (hexane/EtOAc, 1:10); $[\alpha]_D$=−15.7 (*c* 3.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26–1.80 (m, 4H), 2.89–3.00 (m, 1H), 3.51–3.61 (m, 4H), 3.83–3.91 (t, J=9.8 Hz, 1H), 3.95 (m, 1H), 4.20 (br s, 2H), 4.47–4.52 (dd, J=7.7, 4.3 Hz, 1H), 7.12–7.65 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 27.4, 30.1, 48.3, 68.5, 73.5, 76.9, 79.7, 85.2, 126.2, 126.9, 127.8, 128.3, 128.4, 129.2, 136.4, 140.2; IR ($CHCl_3$, film) 3427, 1578, 1453, 1440, 1223, 1052 cm^{-1}. Anal. calcd for $C_{20}H_{24}O_4Se$: C, 58.97; H, 5.94. Found: C, 58.98; H, 5.98.

4.1.37. (1*S*,2*R*,1′*S*)-2-(2-Hydroxy-1-phenyl-ethoxy)-cyclohex-3-enol (48) and (1*S*,2*R*,1′*R*)-2-(2-hydroxy-1-phenyl-ethoxy)-cyclohex-3-enol (49). To a solution of compound **42** (0.31 g, 1.30 mmol) in DME (10 mL) was added $NaBH_4$ (0.10 g, 2.70 mmol). After stirring 1 h at rt, the reaction mixture was diluted with EtOAc and neutralized with saturated NH_4Cl solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography

(hexane/EtOAc, 1:3) to give the title compound **48** (0.24 g, 77%) and conpound **49** (24 mg, 8%) as a colorless oil, respectively. Compound **48**: R_f=0.28 (hexane/EtOAc, 1:3); $[\alpha]_D$=+37.5 (*c* 1.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.73–1.84 (m, 1H), 1.89–2.05 (m, 2H), 2.17–2.29 (m, 1H), 2.55 (m, 2H), 3.53–3.79 (m, 3H), 4.04 (s, 1H), 4.63–4.68 (dd, *J*=8.5, 3.8 Hz, 1H), 5.65–5.71 (m, 1H), 5.80–5.86 (m, 1H), 7.32–7.39 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.1, 23.8, 66.3, 67.4, 74.4, 80.5, 127.0, 127.4, 128.6, 128.9, 130.9, 138.8; IR ($CHCl_3$, film) 3421, 1453, 1229, 1111, 1051 cm^{-1}. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.75; H, 7.75. Compound **49**: R_f=0.35 (hexane/EtOAc, 1:3); $[\alpha]_D$=−164.9 (*c* 2.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.26–2.15 (m, 4H), 3.23 (br s, 2H), 3.54–3.63 (m, 1H), 3-65-3.76 (m, 2H), 4.36 (m, 1H), 4.67–4.72 (dd, *J*=8.3, 4.3 Hz, 1H), 5.75–5.88 (m, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.3, 24.4, 64.2, 67.8, 76.2, 81.3, 126.7, 126.9, 128.2, 128.6, 131.6, 139.4; IR ($CHCl_3$, film) 3375, 1453, 1433, 1104, 1058 cm^{-1}. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.73; H, 7.70.

4.1.38. (1*S*,2*R*,1′*S*)-Toluene-4-sulfonic acid 2-(6-hydroxy-cyclohex-2-enyloxy)-2-phenyl-ethyl ester (50). To a solution of compound **48** (118 mg, 0.50 mmol) and DMAP (19 mg, 0.16 mmol) in CH_2Cl_2 (20 mL) and TEA (10 mL) at 0 °C was added TsCl (96 mg, 0.50 mmol). After stirring 1 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated NH_4Cl solution several times, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the title compound **50** (183 mg, 93%) as a colorless oil. R_f=0.33 (hexane/EtOAc, 2:1); $[\alpha]_D$=+63.4 (*c* 2.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.63–1.76 (m, 1H), 1.85–2.00 (m, 2H), 2.17–2.26 (m, 1H), 2.28–2.31 (d, *J*=5.5 Hz, 1H), 2.44 (s, 2H), 3.48-3.55 (m, 1H), 3.99–4.00 (m, 1H), 4.04–4.16 (m, 2H), 4.74–4.79 (dd, *J*=7.4, 4.5 Hz, 1H), 5.61–5.67 (m, 1H), 5.78–5.83 (m, 1H), 7.26–7.39 (m, 7H), 7.72–7.75 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.8, 22.1, 23.5, 66.0, 72.9, 75.0, 77.2, 127.0, 128.0, 129.0, 129.1, 130.0, 131.0, 133.1, 137.2, 145.0; IR ($CHCl_3$, film) 3421, 1355, 1177, 1098 cm^{-1}. Anal. calcd for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23; S, 8.25. Found: C, 64.84; H, 6.24; S, 8.71.

4.1.39. (1*S*,2*R*,1′*S*)-2-(1-Phenyl-2-phenylselanyl-ethoxy)-cyclohex-3-enol (51). To a solution of compound **50** (184 mg, 0.5 mmol) in EtOH (10 mL) at rt was added $NaBH_4$ (54 mg, 1.4 mmol) and DPDS (222 mg, 0.7 mmol). After stirring for 3 h at 70 °C, the reaction mixture was quenched with water and concentrated to remove EtOH. The aqueous solution was neutralized with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to give the title compound **51** (160 mg, 90%) as a colorless oil. R_f=0.55 (hexane/EtOAc, 3:1); $[\alpha]_D$=+29.5 (*c* 3.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.64–1.75 (m, 1H), 1.83–1.98 (m, 2H), 2.23–2.35 (m, 1H), 2.38–2.39 (d, *J*=4.0 Hz, 1H), 3.09–3.15 (dd, *J*=12.5, 4.5 Hz, 1H), 3.32–3.41 (dd, *J*=12.5, 8.8 Hz, 1H), 3.43–3.50 (m, 1H), 3.96 (s, 1H), 4.68–4.73 (dd, *J*=8.8, 4.5 Hz, 1H), 5.61–5.67 (m, 1H), 5.77–5.82 (m, 1H), 7.23–7.51 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.0, 23.9, 35.8, 66.0, 74.6, 79.4, 126.7, 127.0, 127.2, 128.5, 128.9, 129.2, 130.9, 132.5, 141.5; IR ($CHCl_3$, film) 3421, 1098 cm^{-1}. Anal. calcd for $C_{20}H_{22}O_2Se$: C, 64.34; H, 5.94. Found: C, 64.34; H, 5.95.

4.1.40. (1*S*,2*R*,1′*S*)-Benzoic acid 2-(1-phenyl-2-phenylselanyl-ethoxy)-cyclohex-3-enyl-ester (52). To a solution of compound **51** (87 mg, 0.2 mmol) in DMF (5 mL) at 0 °C was added NaH (60%, 12 mg, 0.3 mmol). After stirring for 30 min at 0 °C, benzyl bromide (47 mg, 0.3 mmol) was added. The resulting solution was stirred for 12 h at 0 °C, diluted with EtOAc and washed with saturated NH_4Cl solution several times. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **52** (86 mg, 79%) as a yellow oil. R_f=0.38 (hexane/EtOAc, 10:1); $[\alpha]_D$=−26.8 (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.66–1.71 (m, 1H), 1.94–2.10 (m, 2H), 2.37–2.40 (m, 1H), 3.11–3.15 (dd, *J*=12.3, 4.8 Hz, 1H), 3.33-3.39 (dd, *J*=12.2, 8.4 Hz, 1H), 3.54–3.56 (m, 1H), 4.00 (m, 1H), 4.50–4.53 (d, *J*=6.1 Hz, 1H), 4.61–4.64 (d, *J*=6.1 Hz, 1H), 4.65–4.66 (m, 1H), 5.65–5.67 (m, 1H), 5.78–5.80 (m, 1H), 7.22–7.48 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.5, 24.2, 36.0, 71.7, 73.4, 74.2, 79.4, 126.0, 126.8, 127.1, 127.4, 127.8, 128.2, 128.3, 128.6, 129.1, 130.8, 131.3, 132.4, 139.4, 142.0; IR ($CHCl_3$, film) 1578, 1480, 1453, 1104 cm^{-1}. HRMS calcd for $C_{27}H_{28}O_2Se$ $(M)^+$: *m*/*z* 464.1255. Found: 464.1252.

4.1.41. (1*S*,6*S*)-6-Benzyloxy-cyclohex-2-enol (53). Compound **52** (110 mg, 0.2 mmol) was subjected to the same reaction conditions as that for the preparation of **42** from **41**. The reaction mixture was purified by flash column chromatography (hexane/EtOAc, 7:1) to give the title compound **53** (30 mg, 62%) as a yellow oil. R_f=0.35 (hexane/EtOAc, 3:1); $[\alpha]_D$=−120.7 (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.69–1.71 (m, 1H), 1.88–2.03 (m, 2H), 2.24–2.27 (m, 1H), 2.51–2.52 (d, *J*=5.1 Hz, 1H), 3.95 (m, 2H), 4.63–4.65 (d, *J*=11.7 Hz, 1H), 4.68–4.71 (d, *J*=11.7 Hz, 1H), 5.71–5.73 (m, 1H), 5.88–5.90 (m, 1H), 7.30–7.36 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.1, 26.6, 67.0, 71.1, 73.9, 124.8, 127.9, 128.6, 131.9, 138.5; IR ($CHCl_3$, film) 3430, 1216, 1074 cm^{-1}. HRMS calcd for $C_{13}H_{16}O_2$ $(M)^+$: *m*/*z* 204.1150. Found: 204.1168.

4.1.42. (1*R*,6*S*)-(6-Benzyloxy-cyclohex-2-enyloxy)-*tert*-butyl-diphenyl-silane (54). A solution of compound **53** (40 mg, 0.2 mmol) and TBDPSCl (82 mg, 0.3 mmol) in the presence of DMAP (7 mg, 0.06 mmol) and imidazole (40 mg, 0.6 mmol) in DMF (5 mL) was stirred for 12 h at 80 °C. The reaction mixture was allowed to rt, dilute with EtOAc and washed with saturated NH_4Cl solution several times. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 15:1) to give the title compound **54** (83 mg, 96%) as a colorless oil: R_f=0.50 (hexane/EtOAc, 15:1); $[\alpha]_D$=−55.2 (*c* 4.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.42–1.49 (m, 1H), 1.70–1.81 (m, 1H), 1.91–2.17 (m, 2H), 3.81 3.84 (t, *J*=3.5 Hz, 1H), 3.94–4.00 (dt, J_d=10.5 Hz, J_t=3.1 Hz, 1H), 4.62–4.67 (d, *J*=12.2 Hz, 1H), 4.77–4.82 (d, *J*=12.2 Hz, 1H), 5.53–5.75 (m, 2H), 7.20–7.43 (m, 11H), 7.70–7.74 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.4, 25.0, 26.3, 27.2,

72.3, 72.6, 74.2, 126.0, 127.3, 127.6, 127.7, 128.3, 129.66, 129.69, 130.7, 134.3, 134.7, 135.0, 136.0, 139.6; IR ($CHCl_3$, film) 1216, 1111 cm^{-1}. HRMS calcd for $C_{29}H_{34}O_2SiNa$ $(M+Na)^+$: *m/z* 465.2226. Found: 465.2253.

4.1.43. (1*R*,2*R*,3*S*,6*R*)-(3-Benzyloxy-7-oxa-bicyclo[4,1,0]-hept-2-yloxy)-*tert*-butyl-diphenyl-silane (55). Compound **54** (96 mg, 0.2 mmol) was subjected to the same reaction conditions as that for the preparation of **43** from **42**. The reaction mixture was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **55** (91 mg, 91%) as a colorless oil. R_f=0.50 (hexane/EtOAc, 10:1); $[\alpha]_D$=−5.3 (*c* 4.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.12–1.17 (m, 1H), 1.51–1.64 (m, 1H), 1.72–1.83 (m, 1H), 2.01–2.14 (m, 1H), 3.17–3.18 (d, *J*=3.8 Hz, 1H), 3.22–3.25 (t, *J*=3.3 Hz, 1H), 3.53–3.54 (d, *J*=2.8 Hz, 1H), 4.00–4.04 (m, 1H), 4.54–4.59 (d, *J*=12.0 Hz, 1H), 4.61–4.66 (d, *J*=12.0 Hz, 1H), 7.17–7.44 (m, 11H), 7.64–7.72 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.5, 20.5, 23.4, 27.2, 52.7, 54.5, 68.0, 72.3, 76.3, 127.5, 127.6, 127.7, 127.8, 128.4, 129.6, 129.7, 134.1, 134.5, 136.0, 136.2, 138.5; IR ($CHCl_3$, film) 1427, 1216, 1111 cm^{-1}. HRMS calcd for $C_{29}H_{35}O_3Si$ $(M+H)^+$: *m/z* 459.2355. Found: 459.2348.

4.1.44. (1*R*,2*R*,3*S*,6*R*)-3-Benzyloxy-2-(*tert*-butyl-diphenyl-silanyloxy)-6-phenylselanyl-cyclohexanol (56). Compound **55** (32 mg, 0.07 mmol) was subjected to the same reaction conditions as that for the preparation of **51** from **50**. The reaction mixture was purified by flash column chromatography (hexane/EtOAc, 10:1) to give the title compound **56** (37 mg, 86%) as a colorless oil. R_f=0.35 (hexane/EtOAc, 10:1); $[\alpha]_D$=−7.9 (*c* 3.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.25–1.36 (m, 1H), 1.56–1.66 (m, 1H), 1.83–1.90 (m, 1H), 2.00–2.18 (m, 1H), 2.90–3.01 (m, 2H), 3.07–3.12 (dd, *J*=9.2, 2.4 Hz, 1H), 4.04–4.12 (dd, *J*=10.3, 9.4 Hz, 1H), 4.16 (m, 1H), 4.22–4.26 (d, *J*=12.2 Hz, 1H), 4.37–4.42 (d, *J*=12.1 Hz, 1H), 7.13–7.78 (m, 20H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.4, 26.7, 27.1, 31.9, 47.7, 68.3, 71.4, 71.6, 84.2, 127.5, 127.6, 127.7, 127.9, 128.4, 129.1, 129.6, 129.8, 133.6, 134.4, 134.9, 136.1, 136.4, 136.9, 138.3; IR ($CHCl_3$, film) 3414, 1216, 1111 cm^{-1}. HRMS calcd for $C_{35}H_{40}O_3SeSi$ $(M)^+$: *m/z* 616.1912. Found: 616.1918.

4.1.45. (1*S*,5*S*,6*R*)-5-Benzyloxy-6-(*tert*-butyl-diphenyl-silanyloxy)-cyclohex-2-enol (57). A solution of compound **56** (30 mg, 0.05 mmol) and $NaIO_4$ (32 mg, 0.2 mmol) in methanol (6 mL) and H_2O (1 mL) in the presence of $NaHCO_3$ (8 mg, 0.1 mmol) was stirred for 10 min at rt, and then for 10 h at 70 °C. After removal of methanol by evaporation, the aqueous solution was diluted with H_2O and CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to give the title compound **57** (19 mg, 85%) as a colorless oil. R_f= 0.40 (hexane/EtOAc, 3:1); $[\alpha]_D$=+65.6 (*c* 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.94–1.95 (d, *J*= 3.1 Hz, 1H), 2.01–2.04 (m, 1H), 2.18–2.22 (m, 1H), 3.38–3.39 (d, *J*=6.6 Hz, 1H), 4.25 (s, 1H), 4.40–4.42 (d, *J*= 11.9 Hz, 1H), 4.60 (s, 1H), 4.63–4.65 (d, *J*=11.9 Hz, 1H), 5.57–5.59 (m, 1H), 5.70–5.72 (m, 1H), 7.25–7.74 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.5, 27.1, 33.4, 67.6, 69.3, 71.6, 83.1, 126.0, 127.7, 128.5, 129.8, 133.8, 134.7, 136.0, 136.2, 138.7; IR ($CHCl_3$, film) 3421, 1624, 1111 cm^{-1}. HRMS calcd for $C_{29}H_{34}O_3SiNa$ $(M+Na)^+$: *m/z* 481.2175. Found: 481.2163.

4.1.46. (1*R*,2*R*,3*S*,4*R*,5*S*)-5-Benzyloxy-4-(*tert*-butyl-diphenyl-silanyloxy)-cyclohex-1,2,3-triol (58). To a solution of compound **57** (23 mg, 0.05 mmol) in acetone (4 mL) and H_2O (1 mL) were added NMO (47 mg, 0.4 mmol) and $K_2OsO_4 \cdot 2H_2O$ (5 mg, 0.01 mmol) at rt. After stirring for 30 h at rt, $NaHSO_4$ (10 mg) was added. The reaction mixture was stirred for further 10 min at rt, then diluted with H_2O and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:3) to give the title compound **58** (22 mg, 89%) as a colorless oil. R_f=0.30 (hexane/EtOAc, 1:3); $[\alpha]_D$=+1.2 (*c* 0.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.44–1.50 (m, 1H), 2.25–2.32 (dt, J_d=11.0 Hz, J_t=4.0 Hz, 1H), 2.48 (m, 1H), 2.87 (m, 1H), 3.05–3.08 (d, *J*=8.5 Hz, 1H), 3.35–3.43 (m, 1H), 3.98–4.31 (m, 6H), 7.00–7.74 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.4, 27.2, 33.1, 70.7, 71.5, 72.1, 75.5, 77.4, 81.8, 127.5, 127.6, 127.7, 128.0, 128.4, 130.1, 130.2, 133.0, 136.3, 136.6, 138.0; IR ($CHCl_3$, film) 3441, 1631, 1117, 1071 cm^{-1}. HRMS calcd for $C_{29}H_{36}O_5Si$ $(M)^+$: *m/z* 492.2332. Found: 492.2318.

4.1.47. *muco*-Quercitol pentaacetate (18) from 58. To a solution of compound **58** (10 mg, 0.02 mmol) in EtOH (3 mL) were added a catalytic amount of $Pd(OH)_2/C$ and 3% aqueous HCl solution. After stirring for 24 h at rt under H_2 gas (1 atm), the reaction mixture was passed through Celite pad, which was washed with EtOH several times. The filtrate was concentrated thoroughly under vacuum to give *muco*-Quercitol (**1**) as a white solid. Without any further purification, **1** was dissolved in TEA (1 mL). To this solution were added Ac_2O (0.5 mL) and a catalytic amount of DMAP. After stirring for 3 h at rt, the reaction mixture was diluted with EtOAc. The organic layer was washed with saturated NH_4Cl solution several times, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to give the title compound **18** (6 mg, 80%) as a white solid. The spectroscopic data and physical properties of the pentaacetate **18** were completely identical with those of **18** obtained from **17**.

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18. Although compound **4** was obtained as an inseparable mixture with its diastereomer **5** in the present work, pure **4** could be obtained by the procedure of our previous work, see: Ref. 15.
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Synthesis of the marine furanoditerpene (−)-marginatone

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Abstract—A synthesis of the marine labdane furanoditerpene (−)-marginatone **1** has been accomplished by a short sequence of reactions starting from (+)-coronarin E **5**. The key step is the stereocontrolled-intramolecular electrophilic cyclisation of the (+)-dihydrocoronarin E **6**, to the tetracyclic marginatane skeleton **7**, which is subsequently functionalized by allylic oxidation to give **1**. As (+)-coronarin E **5** was previously synthesized from (−)-sclareol **10**, the herein reported preparation constitutes the first formal total synthesis of (−)-marginatone **1**, by which its absolute configuration has been confirmed.

1. Introduction

(−)-Marginatone **1** (Fig. 1) is a furanoditerpene, isolated from the marine sponge *Aplysilla glacialis*, collected from the west coast of Canada in 1991.[1] This spongian derivative contains the tetracyclic marginatane skeleton, which was first encountered in marginatafuran **2**, isolated from specimens of the northwestern Pacific common dorid nudibranch *Cadlina luteomarginata*[2] and also has been found later in a sponge, belonging to the genus *Aplysilla*.[3] From the skin extracts of the same dorid nudibranch, another marginatane metabolite the 20-acetoxy marginatone **3** was isolated.[3] *C. luteomarginata*, a rich source of terpenoid metabolites, is a delicate shell less mollusk, feeding mainly on a variety of marine sponges.[3–5] It sequesters selected metabolites from sponges in its diet and stores them in glands on its dorsum and in the skin, where they are used to thwart predators, since itself lacks any obvious protection. Thus, the metabolite content of *Cadlina luteomarginata* depends on its source and presents geographic variability relative to its dietary sources. The origin of furanoditerpenes found in this nudibranch is the dietary sponges of *Aplysilla sp*.

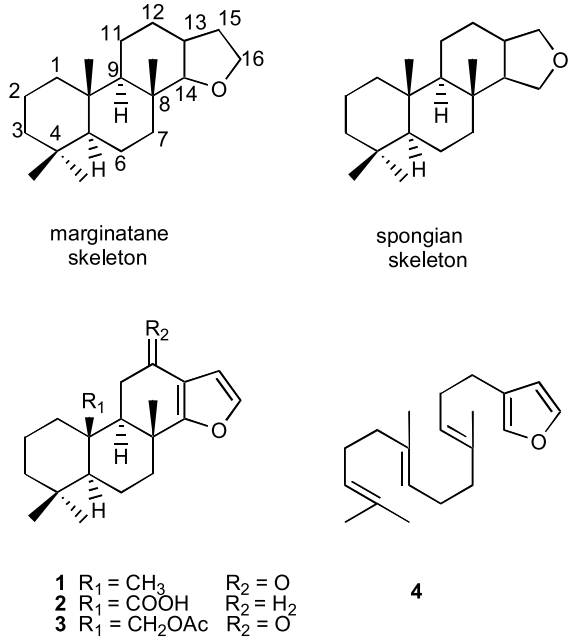

Figure 1.

The marginatane skeleton has been synthesized previously by Sharma[6] and Nishizawa,[7] during their studies on biomimetic cyclisations of ambliofuran **4**. Nevertheless, the characterisation of the new products and the associated spectroscopic data were insufficient. Quite recently, Zoretic obtained a functionalized tricarbocyclic synthon, using a radical-initiated cyclisation, on which subsequently created the furan-ring of the marginatane skeleton.[8] In the above syntheses, the marginatane derivatives were obtained in racemic form. There is no report on a total or formal total synthesis of an optically active marginatane derivative, which would provide the decisive confirmation of the absolute stereochemistry of this class of natural furanoditerpenes.

In this paper, we present the synthesis of enantiomerically pure (−)-marginatone **1**. The key intermediate of our

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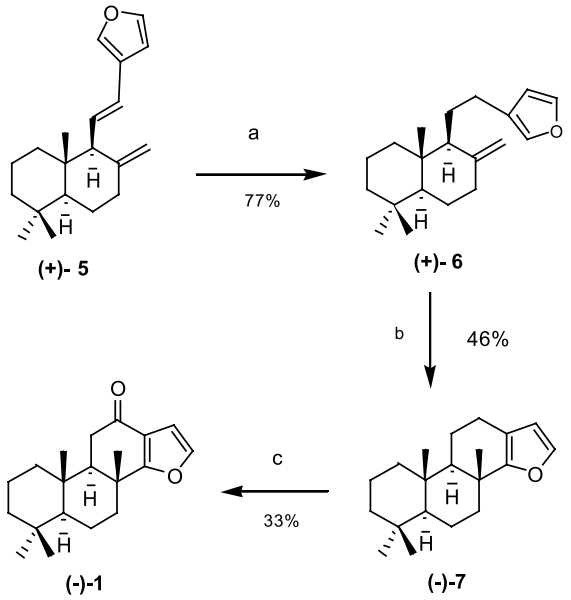
synthetic plan is the furanolabdane terpene, (+)-coronarin E **5**, a versatile precursor for the construction of the tetracyclic marginatane skeleton (outlined in Scheme 1).



Scheme 1. Synthesis of (−)-marginatone **1**. Reagents and conditions: (a) $HCOONH_4$, Pd/C 10%, MeOH reflux (77%); (b) $BF_3\cdot Et_2O$, CH_2Cl_2, room temperature (46%); (c) *t*-BuOOH 70%, aq NaOCl 5%, AcOEt, 0 °C, (33%).

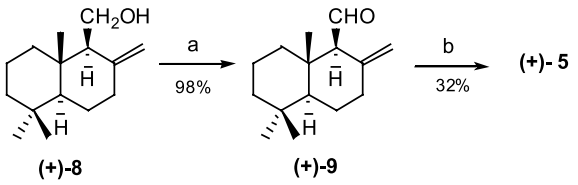
(+)-Coronarin E **5** has been isolated from various medicinal plants[9] and its absolute stereochemistry was elucidated by its synthesis from (−)-sclareol[10] and recently from (+)-manool,[11] confirming the normal labdane absolute stereochemistry 5*S*, 9*S* and 10*S*.

Partial reduction of the side chain double bond of (+)-coronarin E **5** to (+)-dihydrocoronarin E **6** and a subsequent intramolecular electrophilic cyclisation led to the desired tetracyclic derivative **7** with the marginatane skeleton, on which an allylic oxidation gave the target molecule (−)-marginatone **1**. By this route, the absolute stereochemistry of the natural (−)-marginatone was confirmed as to be the normal marginatane structure 5*S*,8*R*,9*S*,10*S*.

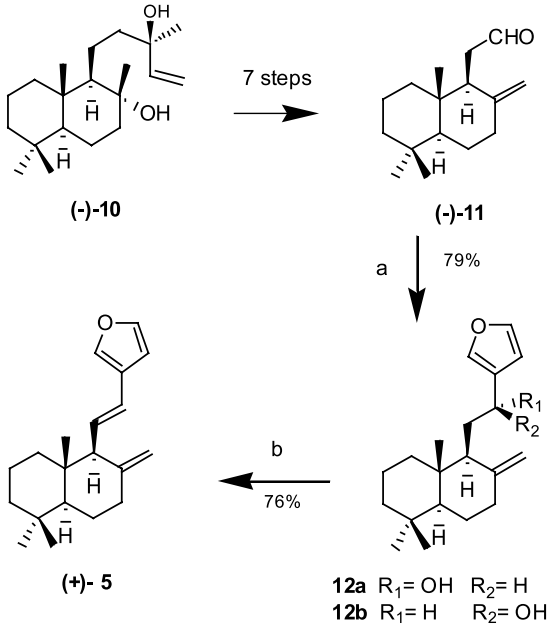
It must be noted that (−)-dihydrocoronarin E **6** is a marine natural product, isolated from the marine sponge of genus *Cacospongia*, collected from the Philipinnes,[12] whose absolute configuration was recently elucidated,[11] while our work was in progress.

The starting material for our synthesis, (+)-coronarin E **5**, was prepared from synthetic (+)-albicanol **8** by a procedure that could be applied as well to the synthesis of the opposite enantiomer, given that (−)-albicanol is available[13] (Scheme 2). Larger quantities of (+)-coronarin E **5** were also prepared from natural (−)-sclareol **10**, by minor modifications of the reported procedures[10] (Scheme 3).

In order to explore the best conditions for the cyclisation and especially the allylic to the furan oxidation, for which no reports have been found in the literature, the easily

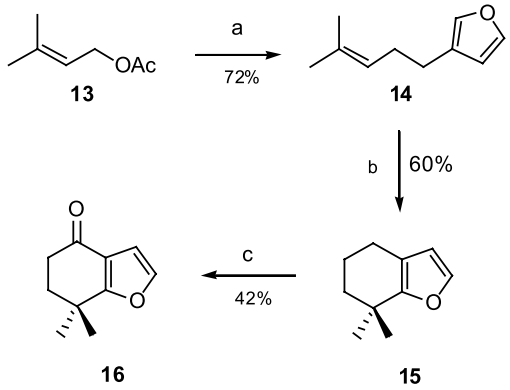


Scheme 2. Reagents and conditions: (a) $CrO_3\cdot Py$, CH_2Cl_2 (98%); (b) triphenylphosphonium-3-furylmethyl chloride, *n*-BuLi, THF, −78 °C (32%).



Scheme 3. Reagents and conditions: (a) 3-bromofuran, *n*-BuLi, Et_2O (79%, (**12a**+**12b**); (b) HMPA, reflux, (76%).

available[14] perillene **14**, possessing structural similarity with the upper part of the dihydrocoronarin E **6** (Scheme 4), was chosen as a model structure.



Scheme 4. Reagents and conditions: (a) 3-furylmethylmagnesium chloride, Li_2CuCl_4, THF, 0 °C (72%); (b) BF_3 Et_2O, CH_2Cl_2, room temperature (60%); (c) aq *tert*-butylhydroperoxide 70%, aq NaOCl 5%, 0 °C (42%).

The formal total synthesis of (−)-marginatone **1**, described herein constitutes the first synthesis of an optically active marginatane derivative, by which the absolute

stereochemistry of this class of natural marine products is confirmed.

2. Results and discussion

As point of departure for the synthesis of (−)-marginatone **1**, (+)-coronarin E **5** was used. We decided to undertake the synthesis of the starting material **5**, as depicted in Scheme 2, from the synthetic enantiomer (+)-albicanol **8**, bearing the (5*S*,9*S*,10*S*) stereochemistry. The total synthesis of both enantiomers of **8** has been reported by us.[13] Thus, oxidation of (+)-albicanol **8** was achieved with pyridinium chlorochromate (PCC) in methylene chloride at room temperature and gave almost quantitatively the unstable (−)-albicanal **9**,[15,16] which was used in the next step without purification. Wittig reaction of the aldehyde **9** with the triphenylphosphonium-3-furylmethylide gave (+)-coronarin E **5** as a gum, in 25% yield after purification by column chromatography. The spectral data[10a,11] and the optical rotation of the obtained product were in good agreement with those found in the literature. ($[\alpha]_D^{20}$ +24.2 (*c* 0.245, $CHCl_3$), lit.[9a] $[\alpha]_D$ +22.3 (*c* 0.44, $CHCl_3$)).

Taking into account the multi-step synthesis of (+)-albicanol **8** and the low yield of the above Wittig reaction, the synthesis of (+)-coronarin **5** from natural (−)-sclareol **10**, through (−)-γ-bicyclohomofarnesal **11**, was also undertaken (Scheme 3). Several syntheses of this versatile intermediate **11** have been reported.[17–19] Oxidative side chain degradation of (−)-sclareol **10**, by a slight modification of the procedure reported by Zahra[17] (7 steps, 52% from sclareol), which is the most suitable for large scale preparation, gave the ambergris odorant, (−)-γ-bicyclohomofarnesal **11**. The 8a-OH group of sclareol was protected as an acetate, which was easily removed under basic conditions. Optical rotation of compound **11** thus obtained $[\alpha]_D^{20} = -24.5$ (*c* 0.35, $CHCl_3$) was in accordance with the literature value (lit.[18] $[\alpha]_D^{21} = -25.5$ (*c* 1.07, $CHCl_3$)).

The coupling reaction of **11** with fleshy prepared 3-lithiofuran[20] led to a mixture of two diastereoisomeric alcohols **12a** and **12b**[10a,11] in a ratio of 1:2.5 (Scheme 3), in 78% overall yield. The above alcohols were readily separated by column chromatography over silica gel. Only **12a** could be obtained in crystalline form from hexane. Diastereoisomeric pure alcohols **12** or their mixture could be used indifferently to the next step, because dehydration removes the center of asymmetry.

It was reported that dehydration of **12a** and **12b** with 2,6-lutidine in the presence of a sulfonyl chloride gave (+)-coronarin E **5** in high yield (70%).[10a,11] In our hands, the above reported conditions gave (+)-coronarin E **5** in yields ≤20%. This dehydration proceeded much better by refluxing the alcohols **12** in HMPA.[21] Indeed, by this procedure one major product was obtained, which after purification by column chromatography on silica gel gave pure (+)-coronarin E **5** in 76% yield. The obtained **5** exhibited spectral properties and optical rotation similar to those reported for the product isolated from natural sources[9] ($[\alpha]_D^{20} = +25.3$ (*c* 0.45, $CHCl_3$) (lit.[9a] $[\alpha]_D = +22.3$ (*c* 0.44, $CHCl_3$)).

Sequentially to our synthetic plan, selective reduction of the conjugate to the furan ring double bond of (+)-coronarin E **5** was attempted (Scheme 1). Classical hydrogenation with H_2 and 10% Pd/C or 5% Pd/C as catalyst at room temperature, proved no regioselective, because all double bonds of the molecule, including furan ring, were reduced in few minutes. A recent reinvestigation on the use of ammonium formate as an active hydrogen donor for the selective reduction of the double bond of conjugated carbonyl compounds,[22] prompted us to use this procedure. Thus, ammonium formate in the presence of Pd/C (10%) as a catalyst, regioselectively reduced the conjugated double bond of (+)-coronarin E **5** to (+)-dihydrocoronarin E **6**, without affecting the exocyclic methylene and the vulnerable furan ring. The above reduction at room temperature requires large quantities of catalyst and long reaction times (2 days), and subsequently some full hydrogenation of **5** takes place. However, by refluxing a methanolic solution of **5** and the reduction reagents, with control of the progress of the reaction by TLC, the reaction was completed in a few hours, giving pure **6** in 77% yield. The spectral data of the product are identical to those quoted in the literature[12] for the natural product, but the optical rotation measured for **6**, $[\alpha]_D^{20} = +42.6$ (*c* 0.155, $CHCl_3$) was of opposite sign to that originally reported by Ireland[12] for the dihydrocoronarin isolated from a marine sponge, $[\alpha]_D^{20} = -22.0$ (*c* 0.14, $CHCl_3$). The present synthesis starting from (−)-sclareol **10**, via (−)-γ-bicyclohomofarnesal **11** and (+)-coronarin E **5**, confirms that our synthetic furanolabdane derivative (+)-dihydrocoronarin **6** has the normal labdane absolute stereochemistry (5*S*,9*S*,10*S*), and that the compound isolated by Ireland possesses the *ent*-**6** structure (5*R*,9*R*,10*R*). Antipodal stereochemistry has already been reported by Mungai for **6**, isolated from a terrestrial plant, but the absence of optical rotation value does not allow a firm conclusion for the absolute stereochemistry.[23] It must be noted that earlier studies on labdane diterpenes correlate positive optical rotation for normal labdane series and negative optical rotation for those with the *ent*-labdane structure.[24]

The first trial for the cyclisation of **6** mediated by $SnCl_4$ in benzene at room temperature or at reflux, as it is described for the cyclisation of ambliofuran,[7] failed to give distinct products. Since the above multi-stage synthesis afforded a very small quantity of **6**, we have chosen a structural model for the study of the cyclisation and the subsequent allylic oxidation step. The easily available synthetic perillene **14** (Scheme 4),[14] demonstrating a similar structure to the upper part of dihydrocoronarin E **6**, was the ideal choice. Perillene **14** was conveniently prepared by coupling the prenyl acetate **13** with the 3-furylmethyl magnesium chloride in the presence of Li_2CuCl_4 as the catalyst.[25] This reaction gave significant amounts of unreacted prenyl acetate, but no γ-substitution product was detected.

The cyclisation of perillene **14**, was studied by three reagents under various conditions. The results are summarized in Table 1. $SnCl_4$ in refluxing benzene or at room temperature gave a complex hydrocarbon mixture, from

Table 1. Model cyclisation of perillene **14**

Reagent	Ratio reagent/substrate	Solvent[a]	Temperature (°C)	Yield (%)
$SnCl_4$	2.0	C_6H_6	Reflux	—
$SnCl_4$	2.0	C_6H_6	−10 °C–room temperature	—
$SnCl_4$	0.15	CH_2Cl_2	−40 °C–room temperature	18
p-TsOH·H_2O	0.2	CH_2Cl_2	Reflux	48
$BF_3 \cdot Et_2O$	0.3	CH_2Cl_2	Room temperature	60

[a] Substrate concentration in all attempts was 0.04 M.

which no interesting compounds have been isolated. Only a small amount of the tetrahydrobenzofuran derivative **15** was obtained using $SnCl_4$ in anhydrous methylene chloride at low temperature. Use of *p*-TsOH·H_2O in refluxing methylene chloride gave similar results to those reported by Czeskis for the cyclisation of perillene.[26] The best results were obtained by the use of $BF_3 \cdot Et_2O$ as catalyst, in anhydrous methylene chloride at room temperature, affording the tetrahydrobenzofuran **15** in 60% yield.

The first approach for the oxidation of derivative **15**, was achieved using common reagents employed for allylic oxidation, bearing in mind that the furan ring could undergo oxidation as well. Attempts with chromium (VI) compounds, such as Na_2CrO_4[27a] in acetic acid or acetic anhydride, and CrO_3–pyridine complex[27b] completely destroyed the furan ring. Two milder oxidations with *m*-chloroperoxybenzoic acid and air,[28] and with $KMnO_4$ on a solid support of $CuSO_4 \cdot 5H_2O$[29] led also to products without the furan unit. Finally, the desired allylic oxidation was conveniently achieved, using aqueous tertbutylhydroperoxide and aqueous NaOCl at 0 °C.[30] Under these conditions the furan ring was not affected and the benzofuranone **16** was isolated in good yield (42%). No extensive study was made to improve the yield of the above oxidation. As far as we know, this is the first example of an oxidation at the α-alkyl position of a furan derivative.

Returning to our initial plan and using the protocol that gave the best results for the cyclisation of perillene, (+)-dihydrocoronarin E **6** was treated with $BF_3 \cdot Et_2O$ in anhydrous CH_2Cl_2 at room temperature to afford (−)-marginata-13,15-diene **7** in 46% yield. It should be noted that the cyclisation of dihydrocoronarin E **6** is regiocontrolled, giving the 2,3-substituted furan and no trace of 3,4-substituted furan derivatives, with the spongian skeleton (Fig. 1) have been detected. This fact is explained by the pronounced nucleophilicity of the C2-position in the furan ring.[31] Similar results have been obtained in the cyclisation of dendrolasin to give pallescensin A.[32]

The ^1H NMR spectrum of **7** is in complete agreement with a marginatane skeleton, having a 2,3-disubstituted furan ring and the *trans-anti-trans* structure.[1,2] The construction of the tetracyclic marginatane skeleton, with high stereoselectivity of the *trans-anti-trans* fused ABC ring system, can be explained by a synchronous intramolecular electrophilic cyclisation, during which the more favorable approach of the furan ring to the C8 carbon atom from the less hindered α-face of the molecule, creates the axial C8 methyl group with the β-configuration.

Finally, allylic oxidation of **7**, under the previously tested conditions on the model system, afforded (−)-marginatone **1** in 33% yield. The spectroscopic data of the synthetic product were identical to those reported for the natural product, isolated from the marine sponge *A. glacialis*.[1] Optical rotation of the synthetic compound was found to be $[\alpha]_D^{20} = -26.0$ (*c* 0.365, $CHCl_3$), which is in good accordance with the rotation of the natural (−)-marginatone (lit.[1] $[\alpha]_D^{20} = -16.0$ (*c* 0.4, $CHCl_3$)).

3. Conclusion

In conclusion, the first formal total synthesis of the natural (−)-marginatone **1**, from the naturally occurring (+)-coronarin E **5**, has been described. The essential electrophilic cyclisation of dihydrocoronarin **6** and the new oxidation of the methylene in the 3-position of the furan ring, were initially investigated in the model compound perillene **14** and in the corresponding tetrahydrobenzofuran derivative **15**, respectively. The reported synthesis of (−)-marginatone **1** establishes its absolute stereochemistry to be (5*S*,8*R*,9*S*,10*S*).

4. Experimental

4.1. General

All reagents are commercially available and used us supplied. Solvents for synthesis were distilled and dried before use. (+)-Albicanol **8** was prepared according to the literature.[13] (−)-Sclareol **10** was a gift from Vioryl S. A. Athens, Greece. Melting points were determined on a Büchi 510 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 343 digital polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were registered on a Perkin–Elmer 7200 spectrophotometer in 5% CCl_4 solutions. NMR spectra were recorded on a Varian Mercury spectrometer at 200 MHz for ^1H and at 80 MHz for ^{13}C, using $CDCl_3$ as solvent. Chemical shifts values are reported in ppm relative to residual chloroform, δ_H 7.27 and δ_C 77.0, respectively. Mass spectra were obtained on a Hewlett–Packard 5890–5970 GC–MS system. Column chromatography was carried out using Merck silica gel 60 (0.063–0.2 mm). Dry-column flash chromatography was carried out using Merck silica gel 60 (<0.063 mm). Thin layer chromatography (TLC) was performed on 0.25 mm Merck DC Alufolien Kieselgel 60 (F_{254}) and it was visualised by UV light or spraying with methanolic solution of H_2SO_4 (8%) or alkaline $KMnO_4$.

4.2. Synthesis of (+)-coronarin E from (+)-albicanol

4.2.1. (1*S*,4a*S*,8a*S*)-1-Naphthalenecarboxaldehyde,decahydro-5,5,8a-trimethyl-2-methylene [(−)-albicanal] (9). Pyridinium chlorochromate (0.645 g, 3 mmol) was stirred for 15 min in CH_2Cl_2 (15 mL). A solution of (+)-albicanol **8** (0.220 g, 1.0 mmol) in CH_2Cl_2 (5 mL) was slowly added at room temperature. Stirring was continued at room temperature until the starting material was disappeared on TLC. Diethyl ether (25 mL) was added and the reaction mixture was stirred at room temperature for 15 min. The supernatant solution was filtered through a short silica gel column and the solvent was evaporated under reduced pressure at room temperature, to give **9** (0.210 g, 95%) as a colorless oil, homogeneous in TLC; $[\alpha]_D^{20}=-64.5$ (*c* 1.12, $CHCl_3$); [lit.[16] $[\alpha]_D^{20}=-67.3$ (*c* 1.83, $CHCl_3$)]; IR ν_{max}/cm^{-1} 3080, 2950, 1720, 1640, 890; ^1H NMR δ 0.80 (3H, s), 0.83 (3H, s), 1.08 (3H, s), 1.15 (2H, m), 1.50 (1H, m), 1.62 (1H, m), 2.04 (1H, m), 2.38 (2H, m), 4.42 (1H, s), 4.84 (1H, s), 9.80 (1H, d, $J=4.0$ Hz).

4.2.2. [(5*S*,9*S*,10*S*)-11(*E*)]-15,16-Epoxy-8(17),11,13(16),14-labdatetraene [(+)-coronarin E] (5).

4.2.2.1. (a) 3-Furylmethyltriphenylphosphonium chloride. A solution of 3-furylmethyl chloride (2.40 g, 24 mmol), prepared from 3-furylmethanol,[33] and triphenylphosphine (6.30 g, 24 mmol) in benzene (30 mL) was refluxed for 48 h. Filtration of the white precipitate and washing by diethylether (2×50 mL) gave the 3-furylmethyltriphenylphosphonium chloride (3.90 g, 43%) as a white crystalline solid; mp 282–284 °C dec. [lit.[34] 283–287 °C dec.]. More of the salt can be obtained by adding into the filtrate additional triphenyl phosphine (3.15 g, 12 mmol) and refluxing for another 48 h.

4.2.2.2. (b) Wittig reaction. A solution of *n*-BuLi 1.6 M in hexane (0.7 mL, 1.1 mmol) was added dropwise into a stirred suspension of the above phosphonium salt (0.416 g, 1.1 mmol) in anhydrous THF (10 mL) at −78 °C, under nitrogen. The resulting brown-red mixture was stirred for 20 min at the same temperature and then a solution of **9** (0.210 g, 0.95 mmol) in anhydrous THF (5 mL) was added dropwise. The reaction mixture was stirred for an additional 1 h at −78 °C, brought to 0–4 °C and left overnight in the refrigerator. The total was poured into water (15 mL) and extracted with diethyl ether (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with petroleum ether 40–60 °C) and the major product (+)-coronarin E **5** was obtained as a gum homogeneous on TLC (86 mg, 32%); $[\alpha]_D^{20}=+24.2$ (*c* 0.245, $CHCl_3$) [lit.[9a] $[\alpha]_D=+22.3$ (*c* 0.44, $CHCl_3$); lit.[11] $[\alpha]_D^{24}=+25.0$ (*c* 1.7, $CHCl_3$)]; IR ν_{max}/cm^{-1} 3083, 2962, 2930, 1641, 969, 893, 872; ^1H NMR δ 0.86 (6H, s), 0.90 (3H, s), 2.12 (1H, td, $J=4.4$, 13.2 Hz), 2.40–2.48 (2H, m), 4.54 (1H, d, $J=1.8$ Hz), 4.77 (1H, d, $J=1.8$ Hz), 5.99 (1H, dd, $J=9.6$, 15.8 Hz), 6.21 (1H, d, $J=15.8$ Hz), 6.56 (1H, br s), 7.37 (2H, br s); ^{13}C NMR δ 15.0, 19.1, 22.0, 23.4, 33.6, 33.6, 36.8, 39.1, 40.8, 42.3, 54.8, 61.5, 107.6, 108.0, 121.7, 124.5, 128.3, 139.6, 143.3, 150.2; MS *m*/*z* 284 (M^+, 80%), 269 (6), 199 (4), 160 (17), 147 (100), 95 (27), 91 (32), 81 (64).

4.3. Synthesis of (+)-coronarin E from (−)-sclareol

4.3.1. (1*S*,4a*S*,8a*S*)-1-Naphthaleneacetaldehyde, decahydro-5,5,8a-trimethyl-2-methylene [(−)-γ-bicyclohomofarnesal] (11). Following the described procedure[17] (−)-sclareol **10** (15.4 g, 0.05 mol) was degraded to the title compound **11** (4.0 g, 32%) which was obtained as colorless oil: $[\alpha]_D^{20}=-24.5$ (*c* 0.350, $CHCl_3$) [lit.[18] $[\alpha]_D^{21}=-25.5$ (*c* 1.07, $CHCl_3$)]; IR ν_{max}/cm^{-1} 3086, 2935, 1727, 1643, 901, 887; ^1H NMR δ 0.72 (3H, s), 0.83 (3H, s), 0.91 (3H, s), 1.77 (1H, m), 2.10 (1H, td, $J=4.9$, 12.4 Hz), 2.32–2.51 (4H,m), 4.40 (1H, s), 4.83 (1H, s), 9.64 (1H, dd, $J=1.4$, 2.6 Hz); ^{13}C NMR δ 14.5, 19.2, 21.7, 23.8, 33.5, 37.4, 38.8, 39.3, 39.8, 41.9, 50.9, 55.2, 108.0, 148.5, 203.5.

4.3.2. (5*S*,9*S*,10*S*)-15,16-Epoxy-12-hydroxy-labda-8(17)-13(16),14-triene (12). A solution of *n*-BuLi 1.6 M in hexane (2.0 mL, 3.2 mmol) was added dropwise into a stirred solution of 3-bromofuran (0.380 g, 2.69 mmol) in anhydrous Et_2O (15 mL) at −78 °C under argon atmosphere. After 15 min, to the solution of 3-lithiofuran thus obtained, a solution of **11** (0.50 g, 2.13 mmol) in anhydrous Et_2O (15 mL) was added slowly. Stirring was continued for additional 2 h at -78 °C. Then, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the mixture was allowed to reach room temperature. The organic phase was separated and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to afford the two diastereoisomeric alcohols, **12a** (elution with petroleum ether–diethyl ether 6:1; 0.150 g, 23%) and **12b** (elution with petroleum ether–diethyl ether 4:1; 0.36 g, 56%). Alcohol **12a** was crystallized from n-hexane to give white needles: mp 70–71 °C; $[\alpha]_D^{20}=+45.9$ (*c* 0.49, $CHCl_3$) [lit[11] $[\alpha]_D^{20}=+19.0$ (*c* 1.0, $CHCl_3$)]; IR ν_{max}/cm^{-1} 3623, 3081, 2946, 1641, 891, 874; ^1H NMR δ 0.69 (3H, s), 0.82 (3H, s), 0.89 (3H, s), 2.06 (1H, td, $J=5.2$, 12.8 Hz), 2.43 (1H, ddd, $J=2.5$, 3.9, 12.7 Hz), 4.48 (1H, d, $J=1.6$ Hz), 4.69 (1H, m) 4.88 (1H, d, $J=1.4$ Hz), 6.42 (1H, dd, $J=1.2$, 2.6 Hz), 7.39 (2H, d, $J=1.8$ Hz); ^{13}C NMR δ, 14.6, 19.3, 21.6, 24.3, 32.6, 33.3, 33.5, 38.2, 39.0, 39.2, 42.0, 52.3, 55.3, 65.2, 106.4, 108.5, 130.2, 138.4, 143.2, 149.0.

The alcohol **12b** was obtained as a colorless oil: $[\alpha]_D^{20}=+8.5$ (*c* 0.495, $CHCl_3$) [lit[11] $[\alpha]_D^{20}=+13.0$ (*c* 1.2, $CHCl_3$)]; IR ν_{max}/cm^{-1} 3619, 3082, 2932, 2870, 1641, 894, 874; ^1H NMR δ 0.69 (3H, s), 0.78 (3H, s), 0.83 (3H, s), 2.37 (1H, ddd, $J=2.4$, 4.0, 12.6 Hz), 4.68 (1H, m), 4.71 (1H, d, $J=1.4$ Hz), 4.88 (1H, d, $J=1.4$ Hz), 6.41 (1H, dd, $J=0.8$, 1.8 Hz), 7.32 (1H, br s), 7.38 (1H, br s); ^{13}C NMR δ 14.5, 19.2, 21.6, 24.2, 31.8, 33.4, 33.4, 38.1, 38.7, 39.4, 41.9, 52.8, 55.2, 65.9, 106.6, 108.2, 128.7, 139.6, 143.3, 148.8.

4.3.3. [(5*S*,9*S*,10*S*)-11(*E*)]-15,16-Epoxy-8(17),11,13(16),14-labdatetraene [(+)-coronarin E] (5). A solution of a mixture of **12a** and **12b** (0.450 g, 1.49 mmol) in HMPA (27 mL) was refluxed for 5 h. Then, the reaction mixture was allowed to reach room temperature, poured into water and extracted with Et_2O (4×20 mL). The combined organic extracts were washed with brine, dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (elution with petroleum ether) to afford the (+)-coronarin E **5** (0.320 g, 76%) as a white gum: $[\alpha]_D^{20} = +25.5$ (*c* 0.45, $CHCl_3$). All spectroscopic data are identical to the previously obtained compound from (−)-albicanal **9**.

4.4. (5*S*,9*S*,10*S*)-15,16-epoxy-8(17),13(16),14-labdatriene [(+)-dihydrocoronarin E] (6)

To a stirred solution of (+)-coronarin E **5** (0.240 g, 0.84 mmol) in MeOH (17 mL), a small amount of catalyst 10% Pd/C (15 mg) was added, followed by ammonium formate (0.100 g, 1.59 mmol) and the reaction mixture was refluxed. Control of the progress of the reaction by TLC was performed every 30 min. After every control, the same quantity (0.100 g 1.59 mmol) of ammonium formate was added. The reaction was completed in 5 h, when 0.74 g ammonium formate (11.8 mmol) have been added in total. The mixture was allowed to reach room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was dissolved in Et_2O (25 mL). The ether solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (elution with petroleum ether) to afford (+)-dihydrocoronarin E **6** (0.184 g, 77%) as a colorless oil: $[\alpha]_D^{20} = +42.6$ (*c* 0.155, $CHCl_3$) [lit.[11] $[\alpha]_D^{24} = +23.0$ (*c* 2.00, $CHCl_3$)]; IR ν_{max}/cm^{-1} 3084, 2930, 1641, 891, 873; ^1H NMR δ 0.70 (3H, s), 0.82 (3H, s), 0.88 (3H, s), 2.00 (1H, td, J=5.1, 12.8 Hz), 2.25 (1H, m), 2.42–2.58 (2H, m), 4.58 (1H, s), 4.88 (1H, s), 6.28 (1H, s), 7.21 (1H, s), 7.36 (1H, t, J=1.7 Hz); ^{13}C NMR δ 14.5, 19.4, 21.7, 23.6, 24.1, 24.4, 33.6, 33.6, 38.3, 39.0, 39.6, 42.1, 55.4, 56.0, 106.2, 111.0, 125.4, 138.6, 142.6, 148.5.

4.5. Synthesis of the 7,7-dimethyl-6,7-dihydro-1-benzofuran-4(5*H*)-one (16)

4.5.1. 3-(4-Methyl-3-pentenyl)furan [perillene] (14). To a stirred suspension of magnesium (3.00 g, 123 mmol) and anhydrous THF (20 mL), a crystal of iodine and 2 drops of 1,2-dibromoethane were added under argon atmosphere, to initiate the reaction. Then, a solution of 3-chloromethylfuran[33] (2.91 g, 29 mmol) in anhydrous THF (30 mL) was added dropwise at a rate to keep the reaction mixture at 30–35 °C. After the addition, stirring was continued for 1.5 h at room temperature, and then left to decant for 30 min without stirring. The supernatant solution of 3-furylmethylmagnesium chloride thus obtained, was added in 2 min, via syringe, to a stirred solution of 3-methyl-2-butenyl acetate (1.98 g, 15.4 mmol) in anhydrous THF (15 mL) at 0 °C under argon atmosphere in the presence of Li_2CuCl_4[25] (17 mL 0.1 M in anhydrous THF, 1.7 mmol). The total was stirred at the same temperature for 1 h and left at room temperature overnight. Then, it was poured into saturated aqueous NH_4Cl (40 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (elution with petroleum ether) to afford unchanged 3-methyl-2-butenyl acetate (0.94 g, 7.3 mmol) and perillene **14** (0.88 g, 72% based on the consumed acetate) as a colorless oil; IR ν_{max}/cm^{-1} 2972, 2921, 2859, 1673, 1027, 873, 719; ^1H NMR δ 1.60 (3H, s), 1.70 (3H, s), 2.24 (2H, q, J=7.3 Hz), 2.46 (2H, t, J=7.5 Hz), 5.16 (1H, tq, J=1.5, 6.9 Hz), 6.29 (1H, s), 7.22 (1H, br s), 7.35 (1H, br s); ^{13}C NMR δ 25.0, 25.7, 28.5, 111.0, 123.8, 124.9, 132.1, 138.8, 142.5.

4.5.2. 7,7-Dimethyl-4,5,6,7-tetrahydro-1-benzofuran (15). To a stirred solution of **14** (0.60 g, 4.00 mmol) in anhydrous CH_2Cl_2 (100 mL), a solution of $BF_3 \cdot Et_2O$ (0.08 mL, 0.65 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise at room temperature under argon atmosphere. After 1 h, additional $BF_3 \cdot Et_2O$ (0.08 mL, 0.65 mmol) in anhydrous CH_2Cl_2 (3 mL) was added to the bright red reaction mixture which was stirred 2 h more at room temperature. The total was poured into cold H_2O (50 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ 5%, followed by brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by dry-column flash chromatography (elution with petroleum ether) to afford the tetrahydrobenzofuran **15** as a colorless oil (0.36 g, 60%);[26] IR ν_{max}/cm^{-1} 2967, 2934, 2853, 1503, 1457, 1160, 892, 697; ^1H NMR δ 1.25 (6H, s), 1.59–1.83 (4H, m), 2.41 (2H, t, J=6.1 Hz), 6.16 (1H, d, J=2.2 Hz), 7.24 (1H, d, J=2.0 Hz); ^{13}C NMR δ 20.5, 22.7, 27.7, 30.3, 39.4, 110.1, 115.0, 140.0, 157.4; MS *m*/*z* 150 (M^+, 21%), 135 (100), 117 (9), 107 (8), 91 (28), 79 (26), 77 (16), 55 (14).

4.5.3. 7,7-Dimethyl-6,7-dihydro-1-benzofuran-4(5*H*)-one (16). To a vigorously stirred solution of **15** (80 mg, 0.53 mmol) in ethyl acetate (2 mL) and aqueous *tert*-butyl hydroperoxide 70% (0.4 mL, 2.9 mmol), small drops of aqueous NaOCl 4–5% (commercial bleach, 2 mL) were added slowly, at 0 °C during 45 min. Then, aqueous $NaHSO_3$ 10% (5 mL) was added and the total was stirred at room temperature for 30 min. Then the organic phase was separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by dry-column flash chromatography (elution with petroleum ether–diethyl ether 1:1) to afford **16** (36 mg, 42%) as a colorless oil; IR ν_{max}/cm^{-1} 2973, 2933, 2862, 1683, 1160, 1126, 909, 697; ^1H NMR δ 1.38 (6H, s), 2.00 (2H, dd, J=5.9, 6.9 Hz), 2.58 (2H, dd, J=6.1, 7.1 Hz), 6.63 (1H, d, J=1.8 Hz), 7.32 (1H, d, J=1.8 Hz); ^{13}C NMR δ 25.9, 26.3, 35.4, 37.9, 106.3, 118.8, 142.5, 172.9, 194.6; MS *m*/*z* 164 (M^+, 46%), 149 (100), 136 (16), 121 (51), 108 (43), 93 (25), 91 (25), 77 (32). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.94; H, 7.23.

4.6. (5*S*,8*R*,9*S*,10*S*)-Marginata-13,15-diene (7)

To a stirred solution of (−)-dihydrocoronarin E **6** (0.150 g, 0.52 mmol) in anhydrous CH_2Cl_2 (20 mL) a solution of $BF_3 \cdot Et_2O$ (0.01 mL, 0.08 mmol) in anhydrous CH_2Cl_2 (1 mL) was added dropwise at room temperature under argon atmosphere. After 1 h, additional $BF_3 \cdot Et_2O$

(0.01 mL, 0.08 mmol) in anhydrous CH_2Cl_2 (1 mL) was added to the bright red reaction mixture and stirring was continued for 3 h. The reaction was monitored by the disappearance of the olefinic protons of **6** in the ^1H NMR spectrum. Then, the total was poured into cold H_2O (20 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ 5%, followed by brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by dry column flash chromatography (elution with petroleum ether) to afford (−)-marginata-13,15-diene **7** as a colorless oil (69 mg, 46%); $[\alpha]_D^{20}=-40.0$ (*c* 0.365, $CHCl_3$); IR ν_{max}/cm^{-1} 2935, 2870, 2852, 1264, 874; ^1H NMR δ 0.86 (3H, s), 0.88 (3H, s), 0.92 (3H, s), 1.21 (3H, s), 2.20–2.54 (6H, m), 6.11 (1H, d, $J=1.8$ Hz), 7.19 (1H, d, $J=1.8$ Hz); ^{13}C NMR δ 16.4, 18.3, 18.5, 19.1, 21.3, 22.5, 22.9, 33.3, 33.4, 37.1, 39.8, 42.2, 56.8, 56.9, 109.9, 113.5, 140.0, 159.9; MS *m/z* 286 (M^+, 24%), 271 (100), 201 (6), 147 (61), 137 (56), 105 (14), 95 (22), 81 (23). Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.55. Found: C, 83.69; H, 10.38.

4.7. (5*S*,8*R*,9*S*,10*S*)-Marginata-13,15-diene-12-one [(−)-marginatone] (1)

To a vigorously stirred solution of **7** (43 mg, 0.15 mmol) in ethyl acetate (1 mL) and aqueous tert-butyl hydroperoxide 70% (0.12 mL, 0.87 mmol), small drops of aqueous NaOCl 4–5% (commercial bleach, 0.8 mL) were added slowly at 0 °C during 15 min. Then, aqueous $NaHSO_3$ 10% (2 mL) was added to the reaction mixture and stirring was continued at room temperature for 30 min. Then, the organic phase was separated and the aqueous phase was extracted with Et_2O (3×2 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by dry column flash chromatography (elution with petroleum ether–diethyl ether 1:1) to afford **1** (15 mg, 33%) as a white solid which was recrystallized from *n*-hexane to give white shiny crystals. Mp 167–168 °C; $[\alpha]_D^{20}=-26.0$ (*c* 0.365, $CHCl_3$) [lit.[1] $[\alpha]_D^{20}=-16.0$ (*c* 0.4, $CHCl_3$)]; IR ν_{max}/cm^{-1} 2930, 2858, 1681, 1047, 717; ^1H NMR δ 0.86 (3H, s), 0.89 (3H, s), 0.99 (3H, s), 1.29 (3H, s), 1.90 (1H, dd, $J=4.9$, 11.5 Hz), 2.26–2.60 (3H, m), 6.60 (1H, d, $J=2.2$ Hz), 7.26 (1H, d, $J=2.0$ Hz); ^{13}C NMR δ 16.0, 17.9, 18.2, 20.5, 21.3 33.2, 35.3, 35.5, 37.4, 39.3, 41.8, 56.0, 56.5, 106.2, 118.2, 142.2, 176.0, 195.2; MS *m/z* 300 (M^+, 53%), 285 (27), 258 (26), 176 (32), 163 (90), 161 (87), 149 (77), 147 (100), 137 (62), 135 (53), 109 (56), 91 (76), 81 (54), 79 (49), 77 (56), 69 (70). Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.81; H, 9.55.

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Cobalt(II)-catalyzed direct acetylation of alcohols with acetic acid

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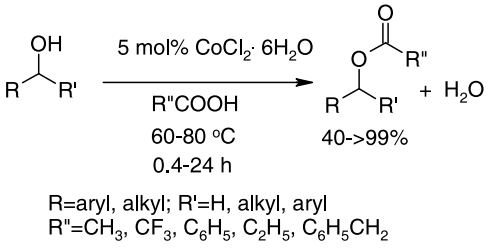
Abstract—Cobalt(II) chloride hexahydrate ($CoCl_2 \cdot 6H_2O$) efficiently catalyzes the acetylation of alcohols with AcOH in high yields. This protocol is also effective with other carboxylic acids, trifluoroacetic acid, propanoic acid, phenylacetic acid and benzoic acid, affording the corresponding acylated products in moderate to good yields. Removal of water is not necessary in these reactions. The catalyst can be filtered and recycled without loss of activity.

1. Introduction

Esterification of alcohols with carboxylic acids is among the fundamental and routinely used functional transformations in organic chemistry.[1] Traditionally, it is performed using mineral or sulfonic acids as catalysts in the presence of excess of either the alcohol or carboxylic acid to shift the equilibrium to the product side.[2] The use of strong mineral acids, however, leads to waste streams posing environmental problems for industrial processes. Alternatively, alcohols can be converted to the corresponding esters with carboxylic acids in the presence of a stoichiometric amount of DEAD[3] or DCC,[4] but these methods are uneconomical. Similarly, processes using anhydrides or acid chlorides are also significantly expensive routes compared to use of carboxylic acids.[5,6] Thus, from an industrial standpoint, there is a necessity to develop new methods for the esterification of alcohols with carboxylic acids. Graphite bisulfate has been used as a catalyst for the condensation of alcohols with carboxylic acids.[7] Later, microwave irradiation coupled with *p*-toluenesulfonic acid,[8] metal triflates,[9a–c] anhydrous $FeCl_3$,[9d] $HfCl_4 \cdot (THF)_2$[10a] and distannoxane[10b–c] have been studied for this purpose. Although most of these methods have been shown to be efficient, the catalysts involved are either expensive or water sensitive or both and are destroyed during the work-up procedure.[7–10]

Cobalt(II) chloride has recently been shown by Iqbal et al.[11] and ourselves[12] to catalyze condensation of β-ketoesters with aldehydes,[11a] cleavage of ethers,[11b] acylation of anisoles,[11c] conversion of allylic alcohols to amides,[11d] allylation of 1,3-dicarbonyl compounds,[11e] acylal synthesis,[11f] tosylation of alcohols[12a] and acetal synthesis.[12b] Since this catalyst is readily available, mild Lewis acid, inexpensive and less toxic, its further exploration to other functional group transformations will be quite useful. Herein we report the direct acetylation of alcohols with AcOH using cobalt(II) chloride hexahydrate ($CoCl_2 \cdot 6H_2O$) as a recyclable catalyst in high yields (Scheme 1). Other carboxylic acids, trifluoroacetic acid, phenylacetic acid, propanoic acid and benzoic acid, are also effective with this system affording the corresponding acylated products in moderate to good yields.



Scheme 1.

2. Results and discussion

Acetylation of benzyl alcohol **2a** was first studied with AcOH in acetonitrile. The reaction occurred to afford benzyl acetate **3a** in 45% yield when the reaction mixture was allowed to stir at 60 °C for 8 h over 5 mol% $CoCl_2 \cdot 6H_2O$ and 5 equiv of AcOH (Table 1, entry 1 and method A). Alternatively, the reaction could be driven to completion within 1 h in >99% yield of **3a** by performing the reaction in AcOH (method B). A control experiment of method A

Keywords: Acylation; Alcohol; Carboxylic acid; Cobalt(II) chloride; Catalyst.
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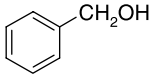
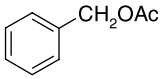
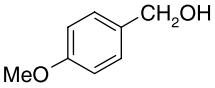
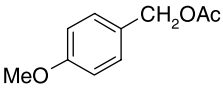
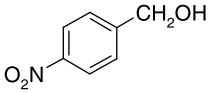
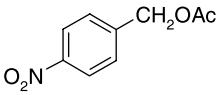
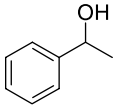
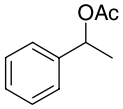
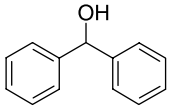
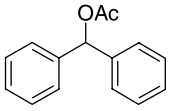
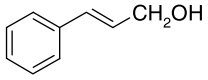
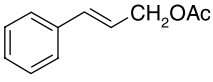
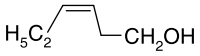
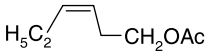
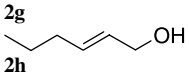
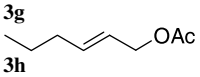
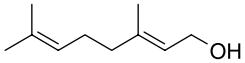
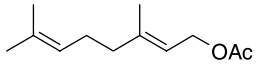
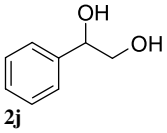
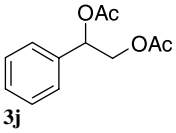
Table 1. Cobalt(II) catalyzed direct acetylation of benzylic and allylic alcohols with acetic acid

Entry	Substrate	Temp. (°C)	Time (h)	Product	Yield (%)[a,b]
1	 **2a**	60 60	8.0 1.0	 **3a**	45[c] 98
2	 **2b**	60	0.4	 **3b**	99
3	 **2c**	60	2.2	 **3c**	95
4	 **2d**	80	8.0	 **3d**	95
5	 **2e**	80	6.5	 **3e**	95
6	 **2f**	60	8.0	 **3f**	97
7	 **2g**	60	10.0	 **3g**	97
8	 **2h**	60	18.0	 **3h**	65
9	 **2i**	60	10.0	 **3i**	89
10	 **2j**	80	6.0	 **3j**	68

[a] Isolated yield.
[b] Substrate (3 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and AcOH (1.5–3.0 mL) were stirred for the appropriate time and temperature.
[c] Substrate (1 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and AcOH (5 mmol) were stirred in acetonitrile (1 mL) for the appropriate time and temperature.

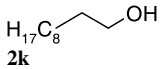
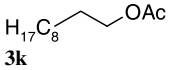
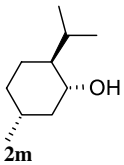
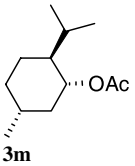
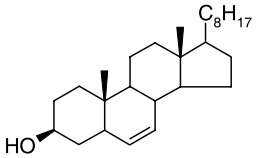
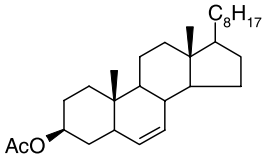
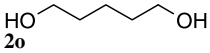
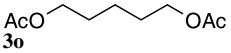
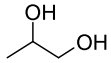
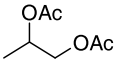
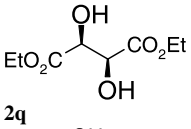
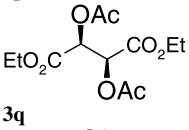
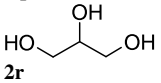
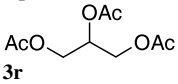
showed no reaction in the absence of cobalt salt, but, 12% of **3a** was obtained with method B.

To evaluate the scope of this reaction, acetylation of other alcohols was studied (Tables 1 and 2). Aromatic alcohols, 4-methoxy- and 4-nitrobenzyl alcohols, phenylethanol, diphenylmethanol and phenylglycol, were converted to the corresponding acetates in high yields (Table 1, entries 2–5 and 10). Allylic alcohols, cinnamyl alcohol, *cis*- and *trans*-hex-2-ene-1-ols and geraniol, were transformed to the respective acetates without affecting the carbon–carbon double bonds (Table 1, entries 6–9). Saturated alcohols, decanol, 2-butanol, (−)-menthol, cholesterol, pentane-1,5-diol, propane-1,2-diol, diethyl L-tartrate and 1,2,3-trihydroxypropane, took slightly longer reaction time compared to aromatic and allylic alcohols to afford the corresponding acetates (Table 2, entries 1–8). It is noteworthy that optically active alcohols did not undergo racemization. The reactivity of primary alcohols was greater compared to secondary alcohols. However, all hydroxy groups were acetylated in polyols. Acetylation of *tert*-alcohol, *tert*-butanol, and phenol was also studied but no reaction was observed (Table 2, entry 9).

Other carboxylic acids, trifluoroacetic acid, propanoic acid, benzoic acid and phenylacetic acid, were next studied for the acylation of benzyl and decyl alcohols (Table 3). Using method B, the reactions of trifluoroacetic acid and propanoic acid were studied to afford the corresponding acylated products **4a–b** and **4e–f** in high yields. In contrast, the reactions of benzoic acid and phenylacetic acid were investigated in acetonitrile to give the respective benzoates **4c–d** and **4g–h** in moderate yields (method A). These results suggest that this protocol can be applied for the acylation of alcohols with different carboxylic acids.

Regarding the mechanism, whether the reaction takes place

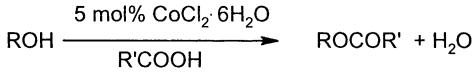
Table 2. Cobalt(II) catalyzed acetylation of saturated alcohols

Entry	Substrate	Temp. (°C)	Time (h)	Product	Yield (%)[a,b]
1	 **2k**	60	8	 **3k**	94
2	 **2l**	60	18	 **3l**	89
3	 **2m**	60	23	 **3m**	91
4	 **2n**	80	19	 **3n**	31[c]
5	 **2o**	60	14	 **3o**	95
6	 **2p**	80	15	 **3p**	92
7	 **2q**	80	24	 **3q**	56
8	 **2r**	80	23	 **3r**	68
9	 **2s**	80	20	No reaction	—

[a] Substrate (3 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and AcOH (1.5–3.0 mL) were stirred for the appropriate time and temperature.
[b] Isolated yield.
[c] Substrate (1 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and AcOH (5 mmol) were stirred in 1,2-dichloroethane (2 mL).

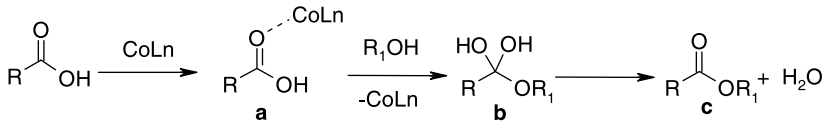
either by Lewis acid or Lewis acid assisted Brønsted acidity via intermediate **5**,[13] the acetylation of 4-methoxybenzyl alcohol was studied using a catalytic amount of HCl at 60 °C. The reaction took place efficiently affording a 2:1 mixture of 4-methoxybenzyl acetate and di(4-methoxybenzyl) ether in >99% yield at 0.3 h. In contrast, the corresponding $CoCl_2 \cdot 6H_2O$ catalyzed process afforded only 4-methoxybenzyl acetate with >99% selectivity. Furthermore, the FT-IR spectrum of the recovered cobalt salt was identical with that of $CoCl_2 \cdot 6H_2O$. Additionally, when the acetylation of 4-methoxybenzyl alcohol was studied with $Co(OAc)_2 \cdot 4H_2O$ as a catalyst, no significant effect was

Table 3. Cobalt(II) catalyzed acylation of alcohols with carboxylic acids



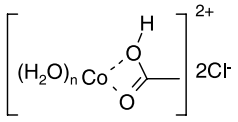
Entry	R	Temp. (°C)	Time (h)	R′	ROCOR′ (%)[a]
1	$C_6H_5CH_2$–**2a**	60	1.0	CF_3–(**4a**)	95[b]
2		60	1.2	C_2H_5–(**4b**)	93[b]
3		80	14.0	C_6H_5–(**4c**)	47[c]
4		80	15.0	$C_6H_5CH_2$– (**4d**)	44[c]
5	$H_{21}C_{10}$–**2k**	60	7.0	CF_3–(**4e**)	95[b]
6		60	8.5	C_2H_5–(**4f**)	93[b]
7		80	15.0	C_6H_5–(**4g**)	43[c]
8		80	18.0	$C_6H_5CH_2$–(**4h**)	40[c]

[a] Isolated yield.
[b] Substrate (1 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and carboxylic acid (1 mL) were stirred.
[c] Substrate (1 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and carboxylic acid (5 mmol) were stirred in acetonitrile (1 mL).



Scheme 2.

observed. These studies clearly suggest that the present methodology may take place by Lewis acid catalyzed process as shown in Scheme 2 and not by Lewis acid assisted Brønsted acidity.



5

To study the recyclability of the catalyst, the reaction mixture of benzyl alcohol **2a** and AcOH was treated with diethyl ether and water (Table 4). The organic layer was separated and successively washed with saturated $NaHCO_3$ solution, brine and water to provide benzyl acetate **3a** in >98% yield. The aqueous layer was concentrated under reduced pressure and the recovered cobalt(II) salt was further investigated for the acetylation of benzyl alcohol **2a** with AcOH under the same reaction conditions. As usual, the reaction occurred and the corresponding acetate **3a** was obtained in >97% yield. This process was repeated two times without loss of activity of the catalyst and the results are summarized in Table 4.

Table 4. Recycling of the catalyst

Run[a]	Benzylacetate [%]	Catalyst recovery [%]
1	>98	>99
2	>97	>98
3	>96	>97

[a] Benzyl alcohol (3 mmol), $CoCl_2 \cdot 6H_2O$ (5 mol%) and AcOH (1.5 mL) were stirred for 1 h at 60 °C.

3. Conclusions

The use of $CoCl_2 \cdot 6H_2O$ as a recyclable catalyst has been shown for the direct acetylation of alcohols using AcOH only as the acetyl source in high yields. These reaction conditions are also suitable for the esterification of alcohols with other carboxylic acids. Removal of water is not necessary in these reactions.

4. Experimental

4.1. General methods

$CoCl_2 \cdot 6H_2O$ was obtained from Loba India Ltd, Bombay. Alcohols and carboxylic acids were purchased either from Aldrich or Fluka and used without further purification. NMR spectra were recorded on DRX-300 (300 MHZ for ^1H and 75.5 MHZ for ^{13}C) spectrometer. Chemical shifts are given in δ units relative to the tetramethyl silane (TMS) signal as an internal reference. Coupling constants (J) are reported in hertz. IR spectra were recorded on Nicolet impact 410 spectrometer. Optical rotation was measured on Perkin Elmer Model 343 Polarimeter. Elemental analysis was conducted using Perkin Elmer 2400 series II CHNS analyzer. Column chromatography was preformed on silicagel (60–120 mesh) using ethyl acetate and hexane as eluent.

General procedure for the acylation of alcohols: method A. A solution of $CoCl_2 \cdot 6H_2O$ (5 mol%), alcohol (1 mmol) and carboxylic acid (5 mmol) in acetonitrile (1 mL) was stirred for the appropriate time and temperature (see Table 1 and 3). The reaction mixture was then cooled to room temperature and the aqueous acetonitrile was removed on a rotary evaporator under reduced pressure. The residue was treated with diethyl ether (10 mL) and water (1 mL). The organic layer was successively washed with saturated $NaHCO_3$ solution (3×5 mL), brine (2×5 mL) and water (2×5 mL). Drying (Na_2SO_4) and evaporation of the solvent under reduced pressure provided a residue which was passed through a short pad of silica gel (60–120 mesh) using ethyl acetate and hexane as eluent to provide the analytically pure acylated product. Concentration of the aqueous layer under reduced pressure provided the catalyst which can be recycled without loss of activity.

Method B. A solution of $CoCl_2 \cdot 6H_2O$ (5 mol%), alcohol (3 mmol) and AcOH (1.5–3.0 mL) was stirred for the appropriate time and temperature (see Table 1–4). The reaction mixture then treated with diethyl ether (25 mL) and water (2 mL). The organic layer was subjected to the work up and purification procedure as described in method A to provide the analytically pure acylated product. Concentration of the aqueous layer under reduced pressure afforded the catalyst (>99%) whose FT-IR spectrum was identical with that of $CoCl_2 \cdot 6H_2O$.

The following compounds are known and spectral data are consistent with those reported in the literature: benzyl acetate (**3a**),[19b] 4-methoxybenzyl acetate (**3b**),[6h] 4-nitrobenzyl acetate (**3c**),[6h] α-methylbenzyl acetate (**3d**),[6h] diphenylmethyl acetate (**3e**),[6h] cinnamyl acetate (**3f**),[19b] *trans*−2-hexenyl acetate (**3h**),[19a] geranyl acetate (**3i**),[19a] phenyl-1,2-ethyl diacetate (**3j**),[6j] decyl acetate (**3k**),[13] butyl-2-acetate (**3l**),[14] (−)-menthyl acetate (**3m**),[19a] cholesteryl acetate (**3n**),[19c] pentane-1,5-diacetate (**3o**),[6j] diethyl (L)-tartrate diacetate (**3q**),[15] 1,2,3-propyl triacetate (**3r**),[19a] benzyl trifluoroacetate (**4a**),[16] benzyl propanoate (**4b**),[17] benzyl benzoate (**4c**),[19b] decyl propanoate (**4f**),[18a] decyl benzoate (**4g**).[18b]

The following acetylated products are not reported in the literature.

4.1.1. *cis*-3-Hexenyl acetate (3g). Colorless liquid. Yield 97%. ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.5 Hz), 2.02 (s, 3H), 2.06–2.11 (m, 2H), 2.33–2.40 (m, 2H), 4.05 (t, 2H, J= 6.9 Hz), 5.27–5.35 (m, 1H), 5.46–5.54 (m, 1H); ^{13}C NMR

($CDCl_3$) δ 13.8, 20.2, 20.4, 26.4, 63.5, 123.4, 134.1, 170.5; IR (neat) 1741 cm^{-1}. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.58; H, 9.94.

4.1.2. Propane-1,2-diacetate (3p). Colorless liquid. Yield 92%. ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, $J=6.6$ Hz), 2.06 (s, 3H), 2.08 (s, 3H), 4.05 (dd, 1H, $J=6.6$, 11.7 Hz), 4.17 (dd, 1H, $J=3.6$, 12.0 Hz), 5.08–5.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.4, 20.7, 21.1, 66.0, 68.2, 170.4, 170.7; IR (neat) 1742 cm^{-1}. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.50; H, 7.53.

4.1.3. Benzyl phenylacetate (4d). Colorless liquid. Yield 44%. ^1H NMR ($CDCl_3$) δ 3.6 (s, 2H), 5.1 (s, 2H), 7.2–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 41.8, 67.0, 127.4, 128.5, 128.8, 129.6, 133.3, 134.2, 136.1, 171.5; IR (neat) 1750 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.64; H, 6.25.

4.1.4. Decyl trifluoroacetate (4e). Colorless liquid. Yield 95%. ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, $J=7.0$ Hz), 1.28–1.37 (m, 14H), 1.73–1.76 (m, 2H), 4.3–4.4 (t, 2H, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 23.0, 25.9, 28.4, 29.8, 29.9, 32.2, 68.5, 157.2, 157.7, 158.0, 158.2, 171.9; IR (neat) 1794 cm^{-1}. Anal. Calcd for $C_{12}H_{21}O_2F_3$: C, 56.68; H, 8.32. Found: C, 56.66; H, 8.33.

4.1.5. Decyl phenylacetate (4h). Colorless liquid. Yield 40%. ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, $J=6.8$ Hz), 1.3–1.5 (m, 14H), 1.5–1.7 (m, 2H), 3.6 (s, 2H), 3.9–4.2 (t, 2H, $J=6.8$ Hz), 7.1–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.6, 23.2, 29.3, 29.4, 29.7, 29.8, 30.0, 32.3, 65.3, 127.2, 128.7, 129.4, 134.4, 171.7; IR(neat) 1751 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.22; H, 10.18.

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Diazepines[1,4] annelated with indoline and maleimide from 3-(di)alkylamino-4-(indol-1-yl)maleimides: mechanism of rearrangement and cyclization

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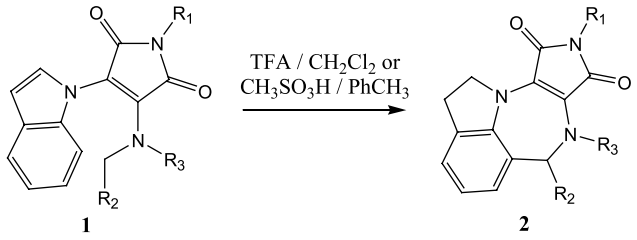
Abstract—The mechanism of cyclization of 3-(di)alkylamino-4-(indol-1-yl)maleimides to diazepine[1,4] derivatives was elucidated using deuterium labeled precursors.

1. Introduction

In our previous paper[1] we have described an unusual cyclization of 3-(di)alkylamino-4-(indol-1-yl)maleimides (**1**) by protic acids leading to the diazepines[1,4] with annelated indoline and maleimide nuclei (**2**) (Fig. 1).



1 **2**

Figure 1.

We assumed that the cyclization proceeds via three steps (Fig. 2): (1) protonation of the indole nucleus at position 3 (**4**); (2) hydride shift from the carbon atom adjacent to the nitrogen atom to position 2 of the protonated indole nucleus. This shift leads to the formation of indoline and iminium ion moieties (**5**); (3) electrophilic attack of the iminium ion at position 7 of the indoline nucleus resulting in protonated diazepine derivative **6**. Presented herein are the results of the experiments performed to test this hypothesis.

2. Results and discussion

Treatment of 3-diethylamino-4-(indol-1-yl)-1-methylmaleimide **8** with TFA in CH_2Cl_2 gave diazepine derivative **9**.[1] Similarly, the dideuterated product **10** was obtained in 80% yield when CF_3CO_2D was used (Fig. 3).

The ^1H and ^{13}C NMR spectra of compounds **9** and **10** were compared (Table 1).

The ^1H NMR spectrum of **10** was more straightforward than that obtained for **9**. Instead of a three hydrogen multiplet in the range δ 3.1–3.25 the single hydrogen multiplet at δ 3.17 was present. The latter was coupled with three hydrogen triplet at δ 1.08. This fact allows us to identify this signal as one of the hydrogens of the methylene group attached to N7. The signals corresponding to the hydrogens at C2 (position-3 of the indoline subfragment) were absent. The signal corresponding to the hydrogens at C1 (position-2 of indoline subfragment) at δ 4.44 was a broad singlet instead of complex multiplet at δ 4.43–4.49 in the spectrum of **9**. The other parameters of ^1H NMR spectra of **9** and **10** were similar. In the ^{13}C NMR spectrum of **9** the singlet signal of C2 atom at δ 28.2 was present; in contrast, in the ^{13}C NMR spectrum of **10** a multiplet (a doublet of triplets $J=30.5$, 19.8 Hz) at δ 27.4–28.1 was detectable. Thus, we conclude that the product of cyclization of indolylmaleimide **8** by CF_3CO_2D (compound **10**) has two deuterium atoms at position 2 (position 3 of indoline subfragment). This finding supports the hypothesis that the first step of cyclization is the protonation of the indole nucleus at position 3.

We next set out to find the source of hydrogen at C1 in the

Keywords: Cyclization; Hydride shift; Mechanism; Indole.
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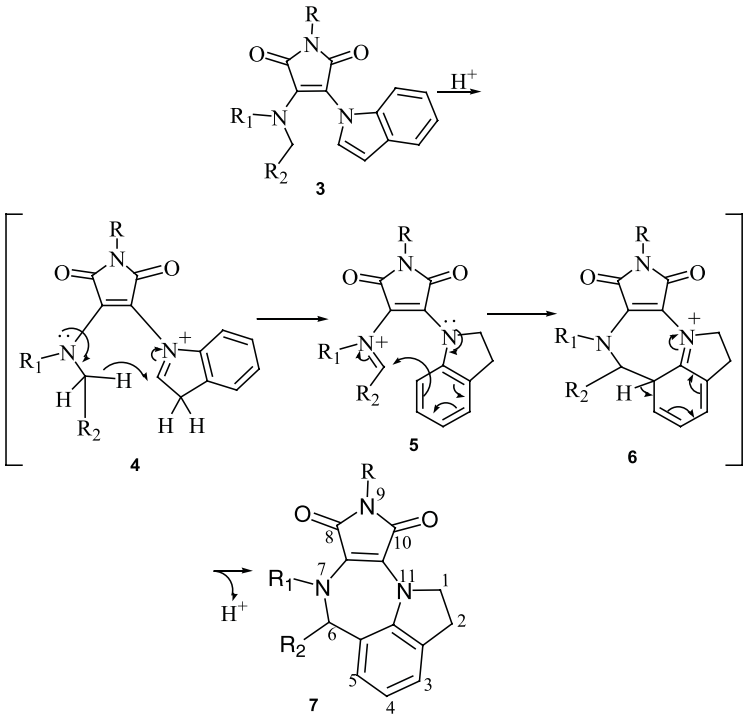

Figure 2.

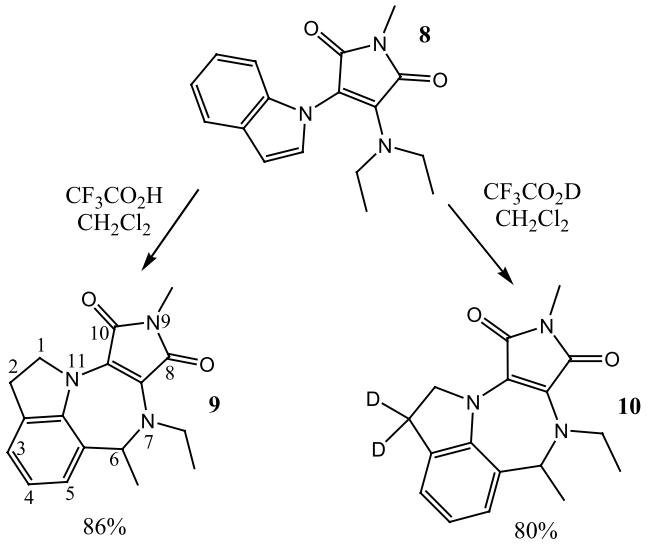

Figure 3.

cyclization products **2**. 1-Benzyl-3-[(d_5-ethyl)anilino]-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione **15** was used as a model compound in this experiment. Sodium d_5-ethylate prepared from d_6-ethanol **11** and NaH in THF was treated with TosCl to give d_5-ethyl tosylate **12**. *N*-(d_5-Ethyl)aniline **13** was obtained by the reaction of **12** with an excess of aniline. The reaction of **13** with 3-bromo-4-(indole-1-yl)maleimide **14** in DMF in the presence of Huenig base yielded **15**. According to the EI-MS spectrum and ^{1}H NMR data of **15** the percentage of deuterium incorporation was 97%. The signals corresponding to the carbon atoms of the ethyl group of non-deuterated **15** were observed in the ^{13}C NMR spectrum as low intensity singlets at δ 13.7 and 46.6. Thus the percentage of deuterium incorporation in **12**, **13**, and **14** can be evaluated as more than 97%.

The synthesis of indolinodiazepine derivative **17** from indolomaleimide **16** was described previously.[1] Indolomaleimide **15** was treated with TFA in CH_2Cl_2 and the cyclization product **18** was isolated as described for compound **17**.[1] The ^{1}H and ^{13}C NMR spectra of **18** were compared with the spectra of non-deuterated indolinodiazepine **17** (Table 2) and demonstrate that compound **18** contains as an admixture about 15% of non-deuterated compound **17**. ^{1}H NMR spectra of compounds **17** and **18** were very close. However, in ^{1}H NMR spectrum of **18** the signals of an admixture of **17** [hydrogen atom at C6 (one hydrogen quadruplet at δ 5.31), methyl group at C6 (three hydrogen doublet at δ 1.42) and one of the signals corresponding to hydrogens at C1 (doublet of triplets at δ 4.55)] were observed with the relative intensity of 15%; and the signal of another C1–H hydrogen at δ 4.35 was a triplet whereas in compound **17** it was a quadruplet. In the ^{13}C NMR spectrum of **18** C6–*C*H$_3$ methyl carbon signal, as well as the signals of C6 and C1, were observed as multiplets at δ 21.1, 50.2, and 56.7 instead of singlets at δ 20.3, 48.3 and 55.1, respectively. The signals of carbon atoms of non-deuterated product were also detectable as low intensity singlets at δ 22.3, 50.5 and 57.1. EI-MS data show that compound **18** contains the admixtures of the corresponding tetra-deutero derivative (~25%) and non-deutero compound **17** (~13%) (Fig. 4).

Altogether, our data demonstrate that, in the cyclization of compound **15**, the deuterium atom migrates from the position adjacent to nitrogen of *N*-(d_5-ethyl)aniline residue to position-2 of the indole nucleus. This model confirms the mechanism of the cyclization process suggested in our previous study.[1]

Table 1. The differences in NMR spectra of compounds **9** and **10**[a]

Compound **9**	Commentary	Compound **10**	Commentary
^{1}H NMR, δ, ppm			
3.1–3.25, 3H, m	C2–H_2 and one of the hydrogens of N7–CH_2 group	3.17, 1H, m	One of the hydrogens of N7–CH_2 group
4.43–4.49, 2H, m	C1–H_2	4.44, 2H, br s	C1–H_2
^{13}C NMR, δ, ppm			
28.2, s	*C*2	27.4–28.1, m	*C*2

[a] The spectra were registered in $CDCl_3$.

Table 2. Differences in NMR spectra of compounds **17** and **18**[a]

Compound **17**	Compound **18**	Commentary
^{1}H NMR		
1.42, 3H, d	Less intensive	C6–*C*H_3
4.45, 1H, q	4.34, 1H, t	C1–H_a
4.55, 1H, dt	Less intensive	C1–H_b
5.31, 1H, q	Less intensive	C6–*H*
^{13}C NMR		
20.3, s	21.1, m	C6–*C*H_3 (C6–*C*D_3)
48.3, s	50.2, m	*C*1
55.1, s	56.7, m	*C*6

[a] The spectra were registered in DMSO-d_6.

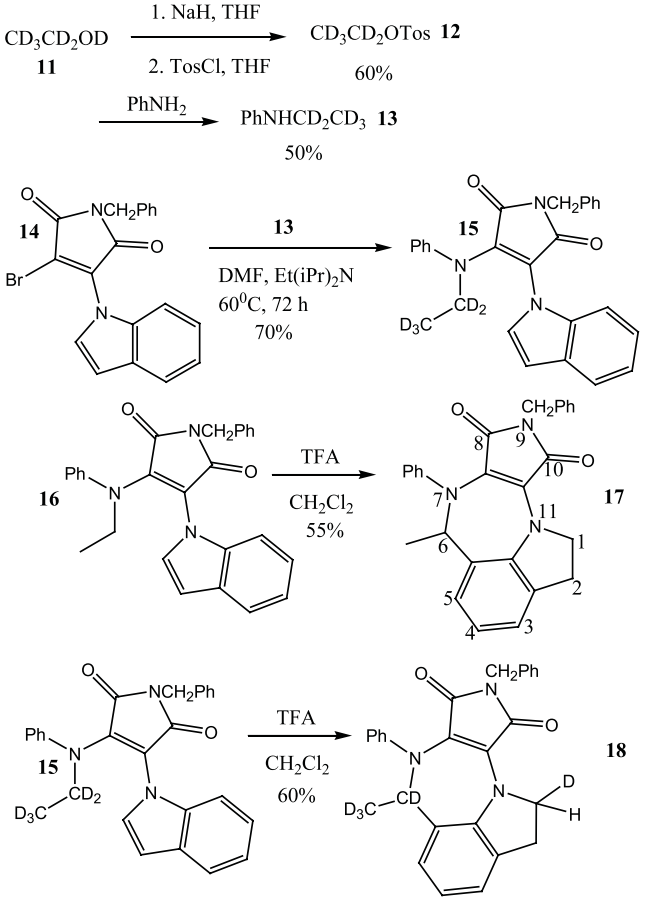

Figure 4.

3. Experimental

3.1. General

NMR spectra were recorded with Varian VXR-400 instrument at 400 MHz (^{1}H NMR) or at 75 MHz (^{13}C NMR) with internal references. Chemical shifts are given in ppm and coupling constants in Hz. Assignment of the signals was based on the decoupling experiments for ^{1}H NMR and APT-experiments for ^{13}C NMR spectra, the signals corresponding to the quaternary carbon atoms are marked (q). Electron impact mass-spectra (EI-MS) were obtained on an SAQ 710 Finnigan instrument at 70 eV (direct introduction, ion source temperature 150 °C). HRMS mass spectra were registered on a MAT 8430 Finnigan instrument with data operating system SS-300 (EI, 70 eV, direct introduction, ion source temperature 250 °C). Analytical TLC was performed on Kieselgel F254 plates (Merck) and column chromatography on Silica Gel Merck 60. Mps were determined on a Buchi SMP-20 apparatus and are uncorrected. Extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Solvents and reagents were obtained from commercial suppliers unless otherwise specified.

3.1.1. d_5-Ethyl tosylate (12). d_6-Ethanol (5.1 ml, 77.5 mmol) was added dropwise at 0 °C to the stirred suspension of NaH (2.4 g, 100 mmol) in THF (35 ml). The resulting suspension was stirred for 30 min at ambient temperature and treated with TosCl (19 g, 100 mmol) dissolved in THF (20 ml). The reaction mixture was stirred overnight, and the solvent was evaporated. The residue was dissolved in Et_2O–1 N HCl mixture (1:1, 100 ml). Organic phase was washed with $NaHCO_3$ solution (30 ml), water (30 ml), brine (30 ml) dried over Na_2SO_4 and evaporated. The residue was chromatographed (*n*-heptane–EtOAc, 20:1) to give **12** as an oil that crystallized upon standing at 0 °C for 7 days as colorless crystals (12.4 g, 61 mmol, 70%); mp 32–34 °C (*n*-heptane–EtOAc, 20:1); R_f 0.35 (*n*-heptane–EtOAc, 5:1); δ_H ($CDCl_3$) 2.4 (3H, s, PhCH_3), 7.3 (2H, d, Ph), 7.74 (2H, d, Ph); δ_C ($CDCl_3$) 13.2–13.9 (m, –CD_2*C*D_3), 21.4 (Ph*C*H_3) 65.7–66.1 (m, –CD_2CD_3), 127.6 (2C), 129.6 (2C), 133.0 (q), 144.5 (q) *m/z* (EI-MS) M^+ 205 (100), $M^+ - OCD_2CD_3$ 155 (85), 91 $M^+ - C_2D_5OSO_2$ (40%).

3.1.2. *N*-(d_5-Ethyl)aniline (13). The mixture of aniline (5 g, 54 mmol) and **12** (5.5 g, 27 mmol) was stirred at ambient temperature until no starting **12** could be detected by TLC. The reaction mixture was diluted with Et_2O (100 ml) and extracted with 2 N HCl (2×50 ml). The extracts were washed with $CHCl_3$ (50 ml), pH was adjusted to 12 with 2 N NaOH solution, and the amines were extracted with Et_2O

(2×75 ml). The extracts were dried over NaOH and evaporated. **13** was separated from the starting aniline by column chromatography (*n*-heptane→*n*-heptane–Et_3N, 20:1) to give **13** as a dark oil (2.3 g, 18.4 mmol, 50%); δ_H ($CDCl_3$) 3.5 (1H, br s, N*H*), 6.66 (3H, d, Ph), 6.76 (2H, t, Ph), 7.24 (3H,t, Ph); δ_C ($CDCl_3$) 13.6–14.1 (m, $-CD_2CD_3$), 37.1–37.5 (m, $-CD_2CD_3$), 112.5 (2C), 117.0, 129.0 (2C), 148.3 (q).

3.1.3. 2-Dideutero-1,2-dihydro-7-ethyl-6,9-dimethyl-6*H*-pyrrolo[3′,4′:2,3][1,4]diazepino[6,7,1-*hi*]indole-8,10-(7*H*,9*H*)-dione (10). A solution of 3-(diethylamino)-4-(1*H*-indol-1-yl)-1-methyl-1*H*-pyrrole-2,5-dione **8** (300 mg, 1 mmol) in CH_2Cl_2 (5 ml) was treated with CF_3CO_2D (1 ml). The reaction mixture was left to stir overnight and then poured into a mixture of EtOAc (50 ml) and aq $NaHCO_3$ (30 ml), the organic layer was separated, washed with aq $NaHCO_3$ (30 ml), water (30 ml), brine (30 ml) dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (*n*-heptane→*n*-heptane–acetone, 10:1) to give **10** as a dark violet solid (240 mg, 0.8 mmol, 80%); mp 80–82 °C (cyclohexane); R_f 0.41 (*n*-heptane–EtOAc, 3:1); *m*/*z* (EI HRMS) M^+ 299.1614 ($C_{17}H_{17}D_2N_3O_2$ requires 299.1601) (100), M^+-CH_3 284 (80), $M^+-NCH_2CH_3$ 256 (28), $M^+-C(O)NCH_3$ 241 (50%).

3.1.4. 1-Benzyl-3-[*N*-(d_5-ethyl)aniline]-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione (15). To the solution of 1-benzyl-3-bromo-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione **14** (1.1 g, 2.7 mmol) in DMF (10 ml) were added *N*-(d_5-ethyl)aniline (0.5 g, 3.9 mmol) and ethyldiisopropylamine (1 ml). The reaction mixture was stirred at 60 °C for 72 h and diluted with EtOAc (50 ml) and water (20 ml). The organic layer was separated and washed with 1 N HCl (2×10 ml), aq $NaHCO_3$ (10 ml), water (10 ml), brine (10 ml), dried and evaporated. The residue was purified by chromatography (*n*-heptane–EtOAc, 15:1) to give **15** as red crystals (0.8 g, 1.9 mmol, 70%); mp 112–114 °C (*n*-heptane–EtOAc); R_f 0.42 (*n*-heptane–EtOAc, 6:1); *m*/*z* (EI HRMS) M^+ 426.2087 ($C_{27}H_{18}D_5N_3O_2$ requires 426.2099) (100), M^+-CD_3 408 (11%).

3.1.5. 9-Benzyl-1,6-dideutero-2-hydro-6-(d_3-methyl)-7-phenyl-6*H*-pyrrolo[3′,4′:2,3][1,4]diazepino [6,7,1-*hi*]indole-8,10(7*H*,9*H*)-dione (18). To the stirred solution of **15** (200 mg, 0.48 mmol) in CH_2Cl_2 (20 ml) was added TFA (2 ml) and the mixture was left to stir for 8 h. The reaction mixture was diluted with EtOAc (60 ml) and washed with aq $NaHCO_3$ (3×20 ml), water (20 ml) and brine; dried and evaporated, the residue was chromatographed (*n*-heptane→*n*-heptane–acetone, 10:1) to give **18** as a dark violet solid (120 mg, 60%); mp 139–141 °C (cyclohexane), R_f 0.24 (*n*-heptane–EtOAc 6:1); *m*/*z* (EI HRMS) M^+ 426.2085 ($C_{27}H_{18}D_5N_3O_2$ requires 426.2099) (100%), *m*/*z* (EI-MS) M^+ 426 (100), M^+ (non-deuterated) 421 (15), M^+-CD_3 408 (30), M^+ (non-deuterated) $-CH_3$ 406 (9%).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.005

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The furan approach to oxacycles. Part 3: Stereoselective synthesis of 2,3-disubstituted tetrahydropyrans

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Abstract—Commercially available furan **1** was converted to 2,3-*trans* and 2,3-*cis*-disubstituted tetrahydropyrans **2** and **3** using a highly efficient route to oxacycles, based on the oxidation of the furan ring with singlet oxygen. Tetrahydropyrans **2** and **3** could be easily separated by column chromatography.

1. Introduction

The stereoselective preparation of 2,3-disubstituted tetrahydropyrans is an important synthetic goal since they are structural units that are present in a wide variety of bioactive natural products.[1] Due to their biological potency and structural complexity the fused cyclic polyether class of natural products such as brevetoxins A and B[2] or ciguatoxin[3] (Fig. 1) have received much attention. Their unusual molecular architecture, a series of fused cyclic ethers having regular *trans–syn–trans* stereochemistry, has stimulated numerous iterative routes[4] and represent indeed challenging synthetic targets for organic chemists.

2. Discussion

We recently described the synthesis of seven-membered oxacycles using either methoxyallene[5] or furan[6] as starting material. We now describe the stereoselective synthesis of 2,3-disubstituted tetrahydropyrans using the furan approach. Synthesis of **2** and **3** can be accomplished according to the reaction sequence shown in Scheme 1.

Commercially available furan **1** (Avocado Research Chemicals Ltd) reacted with LAH in ether to give alcohol **4** in 89% yield. Alcohol **4** was protected to afford silylether **5**. Oxidation of **5** with singlet oxygen followed by treatment with acetic anhydride in pyridine, afforded butenolide **6** in 89% yield (2 steps). Treatment of **6** with TBAF led to the bicyclic compound **7** through an intramolecular Michael addition (yield 81%). Finally after much experimentation (see Table 1), the best conditions for opening bicyclic lactone **7** were found: On reaction with LAH (10 equiv) in the presence of $BF_3 \cdot OEt_2$, **7** afforded a 89% yield of diols **2**[7,8] and **3**[7] which could be easily separated by column chromatography.

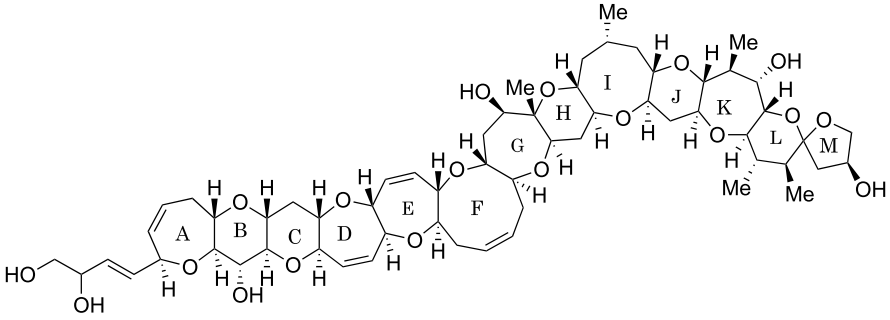

Figure 1. Ciguatoxin.

Keywords: Furan; Singlet oxygen; Tetrahydropyran; Oxacycles; Marin toxins.
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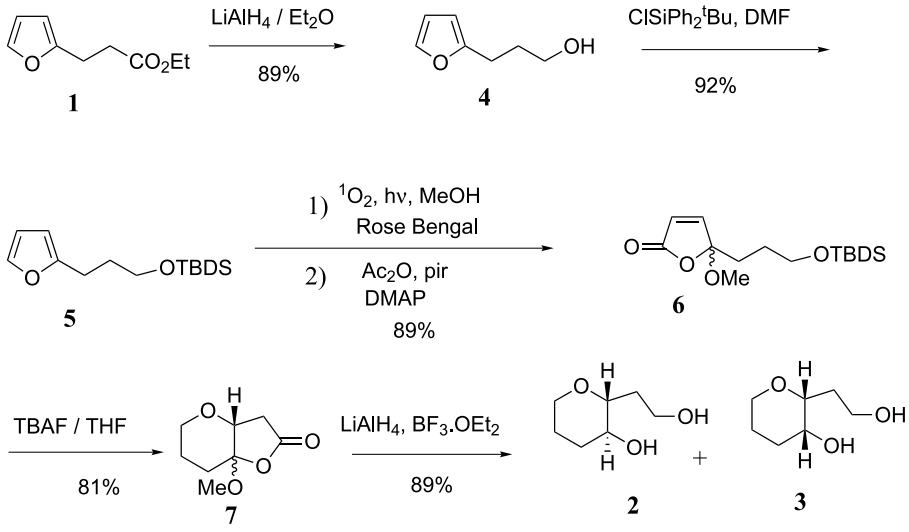


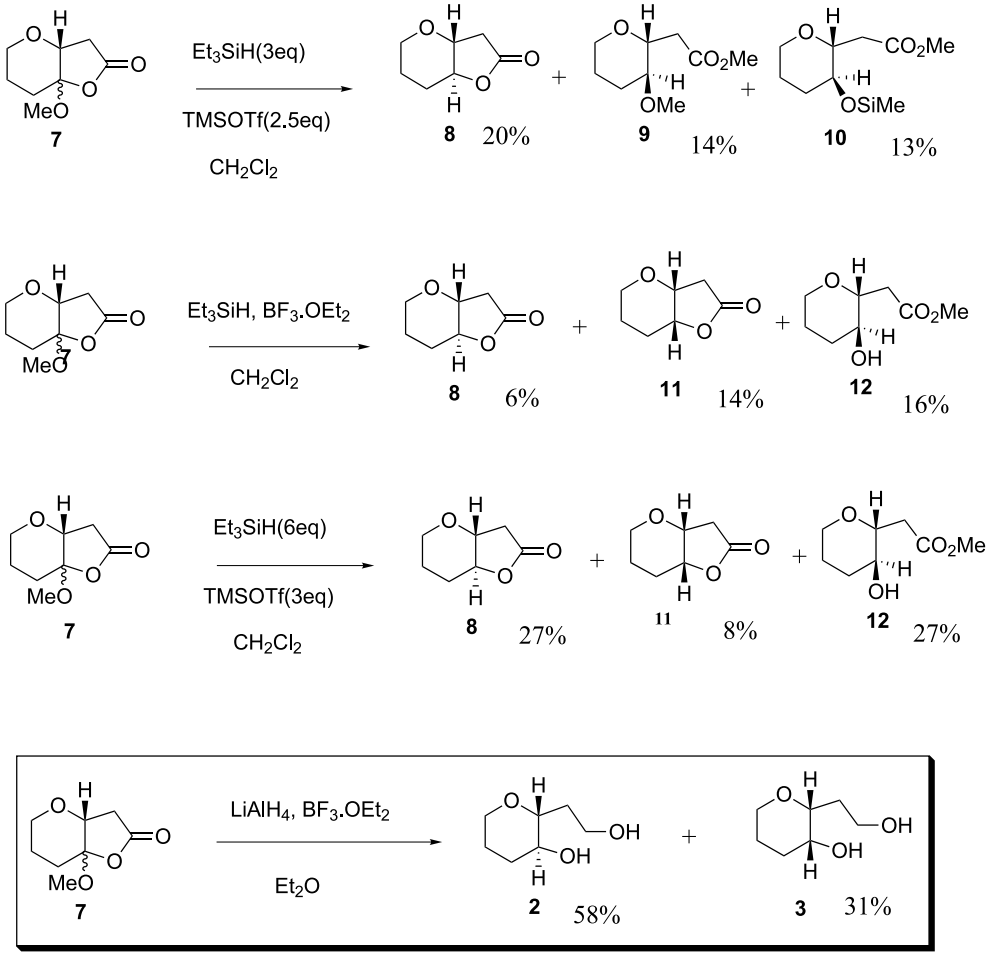
Scheme 1.

At this point, we were not able to distinguish between the two diols **2** and **3** so we decided to assign their stereochemistry using chemical correlation. The stereochemistry of *trans* and *cis* bicyclic lactones **8** and **11** (Table 1) was established using NOE experiments and 3D NMR techniques (Fig. 2).

Opening of these lactones with LAH led to diols whose spectroscopic data were identical to diols **2** and **3**, respectively (Scheme 2).

Recrystallization of diol **2** using a mixture of hexane and ethyl acetate afforded crystals which were subjected to

Table 1



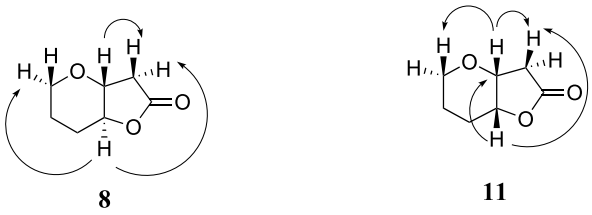
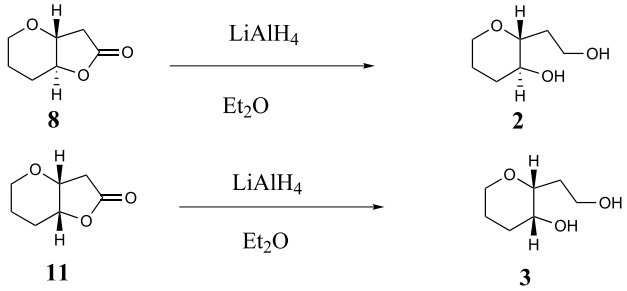


Figure 2. NOE correlations for **8** and **11**.



Scheme 2.

X-ray crystallographic analysis, thus establishing the structure to be that shown in Figure 3 and already determined by chemical correlation.

In conclusion, a new and efficient method for the stereoselective synthesis of *trans* and *cis* 2,3-disubstituted tetrahydropyrans from a commercially available furan derivative has been developed. The stereochemistry of diols **2** and **3** has been unambiguously assigned using chemical correlation and X-ray crystallographic analysis.[8] With a view towards an iterative approach to polycyclic ethers, diol **2** could be an excellent starting material. Both **2** and **3** are attractive synthons in diversity-oriented synthesis[9] or possible building blocks for new types of ionophores with C_2-symmetry.[10] Work is now in progress towards the enantioselective synthesis of highly substituted tetrahydropyrans starting from furans possessing a chiral side chain.

3. Experimental

3.1. General

Silica gel (230 mesh) was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75.47 MHz) were recorded in a Bruker AMX 300 spectrometer, using TMS as internal standard (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60 F254, 0.25 mm).

3.1.1. 3-(2-Furyl)propanol (4). To an ice cooled solution of furan **1** (7.3 g, 43.4 mmol) in dry ether (70 mL) was added LAH (3.3 g, 86.8 mmol) in small portions. At the end of the addition the mixture was stirred for 12 h at room temperature. Excess of hydride was destroyed by dropwise addition of water at 0 °C. The resulting white precipitate was filtered off and the organic phase was separated. The aqueous phase was extracted with ether (3×30 mL) and the combined organic phases were washed with brine (3×100 mL), dried (Na_2SO_4), filtered and concentrated affording 4.8 g of compound **4** [89%, yellowish oil, R_f: 0.50 (40% AcOEt/hexane)] which was used in the next reaction without further purification.; ^{1}H NMR ($CDCl_3$, δ): 7.28 (1H, dd, J=1.8, 0.7 Hz, CH), 6.26 (1H, dd, J=3.1, 1.8 Hz, CH), 5.99 (1H, dd, J=3.1, 0.8 Hz, CH), 3.64 (2H, t, J=6.4 Hz, CH_2), 2.71 (2H, t, J=7.5 Hz, CH_2), 1.88 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, δ): 155.49 (C), 140.78 (CH), 110.00 (CH), 104.86 (CH), 61.68 (CH_2), 30.80 (CH_2), 24.15 (CH_2); HRMS (EI) calcd for $C_7H_{10}O_2$ 126.0680, found 126.0677.

3.1.2. 2-(3-*tert*-Butyldipenylsilyloxypropyl)furan (5). To a solution of alcohol **4** (4.84 g, 38.4 mmol) in DMF (48 mL) was added imidazol (3.1 g, 46.1 mmol) and *tert*-butyl-diphenylsilylchloride (TBDS)(12.67 g, 46.1 mmol). The mixture was stirred at room temperature for 1 h, quenched

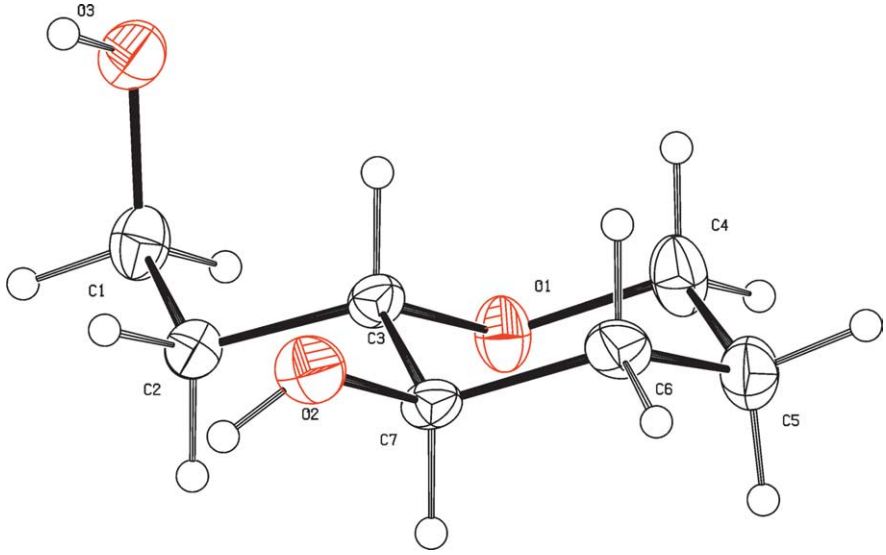


Figure 3. X-ray structure of **2**.

with aqueous NH_4Cl solution and extracted with diethyl ether (3×50 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated to afford a residue which was chromatographed on silica gel using 2% EtOAc/hexane as eluent giving 12.9 g of furan **9** [92%, yellow oil, R_f:0.82 (20% EtOAc/hexane)]. ^{1}H NMR ($CDCl_3$, δ): 7.69 (4H, dd, J=5.8, 1.6 Hz, CH_o–Ph), 7.42 (6H, m, $CH_{p,m}$–Ph), 7.30 (1H, m, CH), 6.28 (1H, dd, J=2.9, 1.7 Hz, CH), 5.97 (1H, dd, J=2.6, 2.00 Hz, CH), 3.72 (2H, m, CH_2), 2.78 (2H, t, J=7.7 Hz, CH_2-1), 1.91 (2H, m, CH_2), 1.08 (9H, s, CH_3–^{t}Bu); ^{13}C NMR ($CDCl_3$, δ): 155.91 (C), 140.72 (CH), 135.54 (CH_o–Ph), 133.84 (C–Ph), 129.55 (CH_p–Ph), 127.61 (CH_m–Ph), 110.43 (CH), 104.77 (CH), 62.89 (CH_2), 30.81 (CH_2), 26.82 (CH_3–^{t}Bu), 24.35 (CH_2), 19.22 (C–^{t}Bu); HRMS (EI) calcd for $C_{18}H_{19}O_2Si$ [M−3×CH_3] 308.1187, found 308.1190.

3.1.3. 5-[3-(*tert*-Butyldiphenylsilyloxi)propyl]-5-methoxy-5*H*-furan-2-one (6). To a solution of furan **5** (12.89 g, 35.38 mmol) in dry methanol (200 mL) was added Rose bengal (837 mg). The mixture was purged several times with O_2 (balloon), cooled to −78 °C and irradiated with a 200 W lamp for 7 h, stirring under oxygen atmosphere. The mixture was allowed to reach room temperature and the solvent was evaporated. The residue was rapidly passed through a column using 50% EtOAc/hexane in order to get rid of the catalyst. After solvent evaporation the residue was dissolved in pyridine (90 mL), acetic acid (23 mL) and DMAP (catalytic) were added and the mixture stirred at room temperature overnight. MeOH (100 mL) was added and stirring continued for 30 min. The methanol was rotatory evaporated and ether (200 mL) added. The pyridine was removed using a 10% aqueous solution of $CuSO_4$ (4×100 mL). The ethereal phase was dried over Na_2SO_4 and the solvent concentrated giving a residue which was chromatographed on silica gel using 15% EtOAc/hexane as eluent affording 12.6 g of butenolide **6** [89%, yellow oil, R_f: 0.33 (20% EtOAc/hexane)]. ^{1}H NMR ($CDCl_3$, δ): 7.81 (4H, m, H_o–Ph), 7.56 (6H, m, $H_{m,p}$–Ph),7.24 (1H, d, J=5.7 Hz, =CH), 6.36 (1H, d, J=5.7 Hz, =CH), 3.83 (2H, t, J=6.1 Hz, CH_2), 3.37 (3H, s, CH_3O), 2.18 (2H, m, CH_2), 1.80 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, δ): 170.32 (CO), 153.89 (CH), 135.94 (CH_o–Ph), 134.13 (C–Ph), 130.06 (CH_p–Ph), 128.08 (CH_m–Ph), 125.22 (CH), 111.58 (C), 63.64 (CH_2), 51.54 (CH_3O), 33.95 (CH_2), 27.27 (CH_3–^{t}Bu), 26.82 (CH_2), 19.61 (C–^{t}Bu); HRMS (EI) calcd for $C_{19}H_{21}O_4Si$ [M−3×CH_3] 354.1243, found 354.1219.

3.1.4. 6-Methoxy-2,7-dioxabicyclo[4.3.0]nonan-8-one (7). To a solution of butenolide **6** (5.62 g, 13.69 mmol) in dry THF (207 mL) was added dropwise tetrabutylammonium fluoride (13.69 mL of 1.0 M solution in THF, 13.69 mmol) and the mixture was stirred at room temperature for 5 h. Aqueous saturated solution of $NaHCO_3$ (220 mL) was added and the product extracted with ethyl acetate (3×130 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated giving a residue which was chromatographed on silica gel using 20% EtOAc/hexane as eluent, affording 1.9 g of bicyclic lactone **7** [81%, yellow oil, R_f: 0.45 (30% EtOAc/hexane)]. ^{1}H NMR ($CDCl_3$, δ): 3.88 (1H, d, J=4.4 Hz); 3.85 (1H, m), 3.37 (1H, dd, J=11.7, 1.7 Hz), 3.33 (3H, s, OCH_3), 2.88 (1H, dd, J=17.2, 4.4 Hz), 2.52 (1H, m), 2.33 (1H, d, J=17.2 Hz), 1.75 (1H, m), 1.66 (2H, m); ^{13}C NMR ($CDCl_3$, δ): 176.00 (CO), 104.61 (C), 76.48 (CH), 65.39 (CH_2), 49.35 (CH_3O), 37.02 (CH_2), 27.16 (CH_2), 21.52 (CH_2); HRMS (EI) calcd for $C_8H_{12}O_4$ 172.0736, found 172.0743.

3.2. Obtention of compounds 8–12 by reduction of bicyclic lactone 7 with Et_3SiH–TMSOTf[11a] and Et_3SiH–$BF_3\cdot Et_2O$[11b]

Reduction of **7** *with Et_3SiH–TMSOTf.* To a solution of **7** (175 mg, 1.02 mmol) in dry dichloromethane (26 mL) was added dropwise Et_3SiH (0.98 mL, 6.12 mmol) and TMSOTf (0.58 mL, 2.86 mmol) and the mixture stirred at room temperature for 4 days. A few drops of pyridine and water (25 mL) were added and the product extracted with ethyl acetate (3×30 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated giving a residue which was chromatographed on silica gel using 25% EtOAc/hexane as eluent, affording 39 mg of **8** [27%, colourless oil, R_f: 0.69 (70% EtOAc/hexane)], 11 mg of **11** [8%, colourless oil, R_f: 0.41 (70% EtOAc/hexane)] and 48 mg of **12** [27%, colourless oil, R_f: 0.18 (70% EtOAc/hexane)].

Reduction of **7** *with Et_3SiH–$BF_3\cdot Et_2O$.* To a solution **7** (167 mg, 0.97 mmol) in dry dichloromethane (25 mL) was added dropwise Et_3SiH (0.47 mL, 2.92 mmol) and $BF_3\cdot Et_2O$ (0.30 mL, 2.33 mmol) and the mixture stirred at room temperature for 48 h. A few drops of pyridine and water (25 mL) were added and the product extracted with dichloromethane (2×25 mL). The aqueous phase was saturated with NaCl and extracted with dichloromethane (2×25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated giving a residue which was chromatographed on silica gel using 35% EtOAc/hexane as eluent, affording 9 mg of **8** [6%, colourless oil, R_f: 0.69 (70% EtOAc/hexane)], 19 mg of **11** [14%, colourless oil, R_f: 0.41 (70% EtOAc/hexane)] and 26 mg of **12** [16%, colourless oil, R_f: 0.18 (70% EtOAc/hexane)].

3.2.1. *trans*-2,7-Dioxabicyclo[4.3.0]nonane-8-one (8). ^{1}H NMR ($CDCl_3$, δ): 4.02 (1H, dd, J=11.8, 3.25 Hz), 3.82 (1H, m,), 3.55 (2H, m), 2.72 (1H, dd, J=15.8, 6.9 Hz), 2.59 (1H, dd, J=15.8, 12.2 Hz), 2.31 (1H, m), 1.81 (2H, m), 1.7 (1H, m).^{13}C NMR ($CDCl_3$, δ): 172.55 (CO), 80.38 (CH), 79.07 (CH), 68.89 (CH_2), 35.66 (CH_2), 28.20 (CH_2), 24.71 (CH_2). HRMS (EI) calcd for $C_7H_{10}O_3$ 142.0630, found 142.0624.

3.2.2. *trans*-(6-Methoxy-2-oxacyclohexyl)methylacetate (9). ^{1}H NMR ($CDCl_3$, δ): 3.85 (1H, m), 3.66 (3H, s, CH_3OCO), 3.53 (1H, td, J=8.8, 3.7 Hz), 3.34 (1H, m), 3.31 (3H, s, CH_3O), 2.90 (1H, td, J=10, 4.3 Hz), 2.80 (aH, dd, J=15.1, 3.7 Hz), 2.40 (1H, dd, J=15.1, 8.5 Hz), 2.25 (1H, m), 1.66 (2H, m), 1.28 (1H, m).^{13}C NMR ($CDCl_3$, δ): 172.07 (CO), 78.59 (CHOMe), 77.69 (CH), 67.79 (CH_2), 56.16 (CH_3O), 51.58 (CH_3OCO), 37.99 (CH_2), 28.33 (CH_2), 25.09 (CH_2). HRMS (EI) calcd for $C_8H_{13}O_3$ [M−CH_3O] 157.0865.1243, found 157.0873.

3.2.3. *trans*-[6-(Trimethylsilyloxy)-2-oxacyclohexyl]-methylacetate (10). ^{1}H NMR ($CDCl_3$, δ): 3.84 (1H, m), 3.67 (3H, s, CH_3OCO), 3.50 (1H, td, J=8.9, 3.4 Hz), 3.34

(1H, m), 3.30 (1H, m), 2.76 (1H, dd, $J=15.1$, 3.42 Hz), 2.32 (1H, dd, $J=15.1$, 9.0 Hz), 1.97 (1H, d, $J=9.3$ Hz), 1.64 (2H, m), 1.45 (1H, m), 0.08 (9H, s, $(CH_3)_3Si$). ^{13}C NMR ($CDCl_3$, δ): 172.19 (CO), 79.42 (CH), 70.85 (CH), 67.84 (CH_2), 51.59 (CH_3O), 8.02 (CH_2), 33.30 (CH_2), 25.5 (CH_2), 0.3 $(CH_3)_3Si$); HRMS (EI) calcd for $C_{10}H_{19}O_4Si$ [M−CH_3] 231.1053, found 231.1059.

3.2.4. *cis*-2,7-Dioxabicyclo[4.3.0]nonane-8-one (11). ^1H NMR ($CDCl_3$, δ): 4.37 (1H, t, $J=2.6$ Hz), 4.20 (1H, dd, $J=4.2$, 2.4 Hz), 3.91 (1H, m), 3.42 (1H, m), 2.68 (1H, dd, $J=17.2$, 4.6 Hz), 2.53 (1H, d, $J=17.2$ Hz), 2.34 (1H, d, $J=13.6$ Hz), 1.85 (2H, m), 1.48 (1H, m); ^{13}C NMR ($CDCl_3$, δ): 176.2 (CO), 76.8 (CH), 72.8 (CH), 65.8 (CH_2), 39.0 (CH_2), 24.7 (CH_2), 19.2 (CH_2); HRMS (EI) calcd for $C_7H_{10}O_3$ 142.0630, found 142.0624.

3.2.5. *trans*-[6-Hydroxy-2-oxacyclohexyl]methylacetate (12). ^1H NMR ($CDCl_3$, δ): 3.90 (1H, m), 3.53 (1H, td, $J=8.8$, 3.7 Hz), 3.36 (1H, m), 3.34 (3H, s, CH_3O), 2.93 (1H, m), 2.87 (1H, dd, $J=15.4$, 3.7 Hz), 2.87 (1H, dd, $J=15.4$, 8.4 Hz), 2.28 (1H, m), 1.67 (2H, m), 1.29 (1H, m); ^{13}C NMR ($CDCl_3$, δ): 176.3 (CO), 78.5 (CHO), 77.3 (CH), 67.9 (CH_2), 56.3 (CH_3O), 37.9 (CH_2), 28.3 (CH_2), 25.0 (CH_2); HRMS (EI) calcd for $C_8H_{12}O_3$ [M−H_2O] 156.0786, found 156.0791.

3.3. Reduction of 7 using LAH, $BF_3\cdot OEt_2$: obtention of *trans*-2-(6-hydroxy-2-oxacyclohexyl)ethanol (2) and *cis*-2-(6-hydroxy-2-oxacyclohexyl)ethanol (3)

To a solution of **7** (179 mg, 1.04 mmol) in dry ether (15 mL) was added $BF_3\cdot OEt_2$ (0.32 mL, 2.5 mmol) and the mixture stirred for 40 min at room temperature. $LiAlH_4$ (396 mg, 10.44 mmol) was added in portions to the ice-cooled mixture which was stirred at room temperature for 19 h. The reaction was carefully quenched with cold water to destroy excess of hydride. After filtration and solvent evaporation the residue was chromatographed on silica gel using 20–80% EtOAc/hexane as eluent to afford 89 mg of **2** (58%) and 47 mg of **3** (31%).

3.3.1. Compound 2. ^1H NMR ($CDCl_3$, δ): 3.89 (1H, m), 3.80 (2H, m), 3.58 (2H, m), 3.19 (1H, m), 2.11 (1H, m), 2.03 (1H, m), 1.80 (1H, m), 1.69 (2H, m), 1.40 (1H, m); ^{13}C NMR ($CDCl_3$, δ): 82.4 (CH), 70.1 (CH), 67.7 (CH_2), 60.5 (CH_2), 35.3 (CH_2), 32.5 (CH_2), 25.5 (CH_2); HRMS (EI) calcd for $C_7H_{14}O_3$ 146.0943, found 146.0936.

3.3.2. Compound 3. ^1H NMR ($CDCl_3$, δ): 4.02 (1H, m), 3.81 (2H, m), 3.58 (2H, m), 3.52 (1H, m), 2.00 (2H, m), 1.71 (2H, m), 1.44 (2H, m); ^{13}C NMR ($CDCl_3$, δ): 79.6 (CH), 68.6 (CH_2), 67.1 (CH), 60.6 (CH_2), 34.3 (CH_2), 30.5 (CH_2), 20.1 (CH_2); HRMS (EI) calcd for $C_7H_{12}O_2$ [M−H_2O] 128.0837, found 128.0834.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.001

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8. X-ray crystal structure analysis of **2**: Bruker Smart CCD diffractometer, Mo K_α-radiation ($\lambda=0.71073$ Å), T 293(2) K. Crystal size: $0.36\times0.22\times0.20$ mm^3, colourless irregular prism, space group $C2/c$, monoclinic, $a=18.175(4)$ Å, $b=5.6732(13)$ Å, $c=15.521(4)$ Å, $\beta=102.577(4)°$, $V=1562.0(6)$ Å^3, $Z=8$, $\rho_{cal}=1.243$ g/cm^3, θ range = 2.30–28.01°, 4096 reflections collected, 1753 independent ($R_{int}=0.0544$), empirical absorption correction (SADABS [1], $T_{min}=0.530$, $T_{max}=1.000$) 93 parameters, final R indices [$I>2\sigma$], $R=0.0472$, $wR=0.0832$, GOF = 0.827. Structure solution: direct methods (SHELXS97 [2]), refinement on F2 (SHELXL97 [2]). H atoms were calculated. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Centre No. CCDC 238929.

Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; (fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk).

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Preparation of highly deuterated zeaxanthin, lycopene, and β-carotene from fully deuterated mevalonate using engineered *Escherichia coli*

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Abstract—Carotenoids are important natural pigments produced by various microorganisms and plants. Specific deuterium-labeling of these compounds is invaluable in biochemical and physiochemical research. In this paper, preparation of highly deuterated zeaxanthin, lycopene, and β-carotene using engineered *Escherichia coli* with fully deuterated mevalonate is described. Also described are physico-chemical properties of the obtained deuterated carotenoids.

1. Introduction

Carotenoids are the most common, naturally occurring terpenoid pigments, and are widely distributed in nature, where they fulfill essential biological functions. These pigments have many different biological functions, such as species-specific coloration, photo protection, and light harvest, and they serve as precursors for phytohormones. All carotenoids are biosynthesized according to the well-known isoprenoid pathway.[1] Two pathways, the mevalonate[2] and the 2-*C*-methyl-D-erythritol 4-phosphate (MEP)[3] pathways, lead to the formation of the first isoprene intermediate, isopentenyl diphosphate (IPP). In archaea, fungi, animals and plants except plastids, IPP is synthesized via mevalonate from acetyl-CoA as a starting precursor. In eubacteria and plant plastids, IPP biosynthesis proceeds via an initial condensation reaction between pyruvate and glyceraldehyde-3-phosphate followed by several additional reaction steps. The discovery of the eubacterial MEP pathway has provided the means for engineering the isoprenoid flux to improve carotenoid productivity.[4]

The MEP pathway is known to function for growth in *Escherichia coli*. Recently, several groups described the construction of doubly-engineered *E. coli* with the disruption of a gene of a certain enzyme involved in the MEP pathway and the introduction of the genes responsible for the key enzymes in the mevalonate pathway.[5] *E. coli* DK223/pTMV20 was constructed in this manner,[6] that is, the 1-deoxy-D-xylulose 5-phosphate reductoisomerase (*dxr*) gene was disrupted[7] and a plasmid pTMV20[5b] carrying the genes of three enzymes responsible for the formation of IPP was introduced. Moreover, the third genetic manipulation was envisioned by introducing another plasmid harboring, for example, a series of the genes involved in the carotenoid biosynthesis,[8] by which carotenoids were thus expected to be produced only from the supplemented mevalonate. When fully deuterated mevalonolactone-d_9 (MVL-d_9, 97% atom ^{2}H), the synthesis of which had been described previously,[9] is supplemented to the culture of such a triply engineered strain, the carotenoids to be produced should be highly deuterated.

In fact, we recently communicated the preparation of highly- and multiply-deuterated zeaxanthin by using such a triply-engineered *E. coli* and fully deuterated mevalonate.[6] In this paper, we describe an easily accessible way for preparation of highly deuterated carotenoids, zeaxanthin,

Keywords: Carotenoids; Biosynthesis; Isotope labeling; Engineered *Escherichia coli*.
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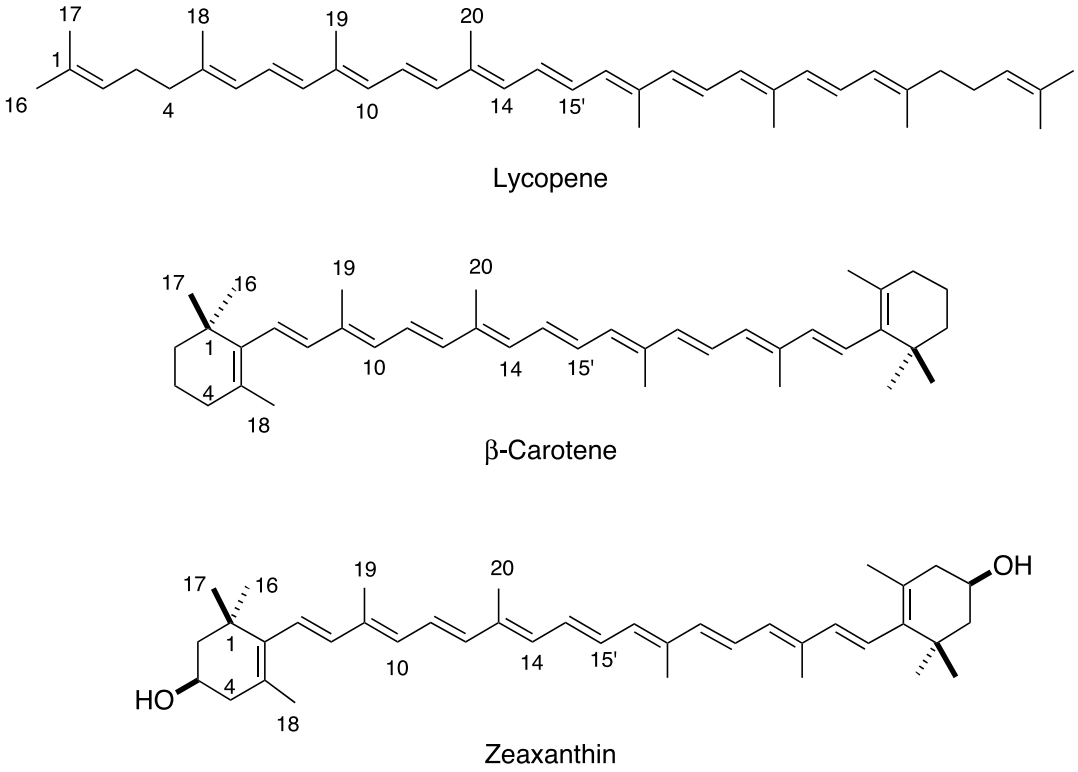

Figure 1. Structures of carotenoids.

lycopene, β-carotene (Fig. 1) by using engineered *E. coli* with fully deuterated mevalonate in full detail. Also described are physico-chemical properties of the obtained deuterated carotenoids.

2. Results and discussion

2.1. Preparation of multiply deuterated zeaxanthin

Firstly, *E. coli* DK223/pTMV20 was transformed with a plasmids, pACCAR25ΔcrtX[8a] for zeaxanthin production by standard electroporation. The transformant was cultured in the presence of MVL-d_9 and the biosynthesized zeaxanthin was extracted and purified by repeated chromatography as described in Section 4.

The EI-MS spectra of the obtained deuterated zeaxanthin and a non-labeled specimen are shown in Figure 2. While the molecular ion peak of non-labeled zeaxanthin was observed at *m/z* 568, signal clusters were observed for the deuterated zeaxanthin at much higher molecular ion regions than the corresponding non-labeled specimen, that is, the molecular ion peak was observed as a cluster of isotopomers between *m/z* 605–622. Thus, the deuterated zeaxanthin was proved to be biosynthesized only from the supplemented MVL-d_9. This fact appears to suggest that the whole mevalonate pathway including IPP isomerase was viable.[10] In addition, the clustered M^+ ion clearly implies variable deuterium content in each molecule. This appears to be due to the exchange of hydrogen at the methyl group of intermediary dimethylallyl diphosphate (DMAPP) during the IPP-DMAPP isomerase reaction and accordingly at the C-4 methylene group of IPP as well. Thus, once a proton is incorporated into the freely rotating C-4 methyl group of DMAPP, the reverse reaction from DMAPP to IPP should afford (*E*)- and (*Z*)-protonated IPP equally as shown in Figure 3.

Further, ^{1}H NMR spectra were then taken under the deuterium decoupled conditions to look at the carotenoid formation (Fig. 4). First, no proton incorporation was observed at H-10 and H-14 of zeaxanthin,[11] again confirming that no endogenous non-labeled IPP was formed. This implies that the stereochemistry of deprotonation–reprotonation at C-2 of IPP catalyzed by IPP isomerase, and that of deprotonation catalyzed by prenyl transferase affording geranylgeranyl diphosphate, must be the same. Removal of

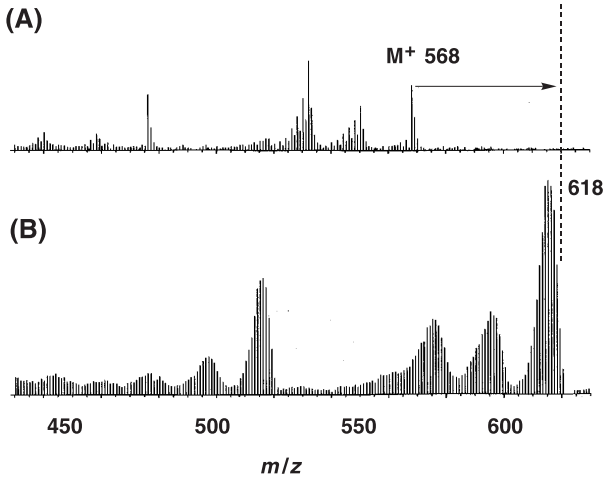

Figure 2. EI-MS spectra of (A) non-labeled zeaxanthin; (B) multiply deuterated zeaxanthin.

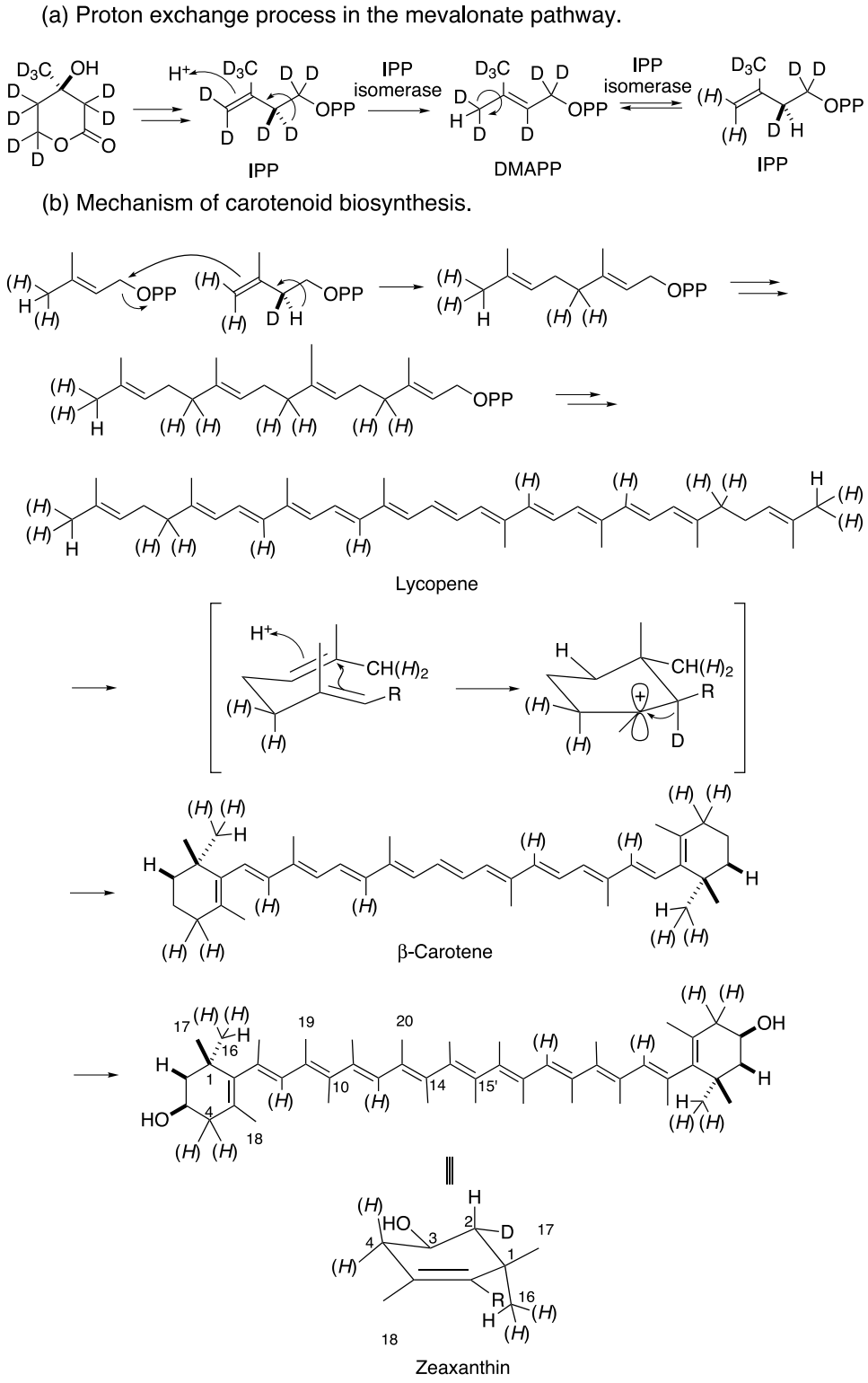

Figure 3. Biosynthetic pathway of carotenoids.

the *proR* proton on the corresponding C-2 methylene group of IPP has recently been demonstrated for the *E. coli* IPP isomerase and farnesyl diphosphate synthase by Poulter et al.[12]

Since the ring formation from lycopene is triggered by the electrophilic attack of a proton to the terminal double bond, one protium (originated from the medium) must reside at C-2 of the resulting zeaxanthin. Accordingly, the proton signal due to H-2 observed at δ 1.41, together with the hydroxy signal at δ 0.73 (D_2O exchangeable), are logical internal intensity references. The C-18, -19 and -20 methyl signals appeared as weak singlet of approximately 6% protium incorporation, which correspond well with the

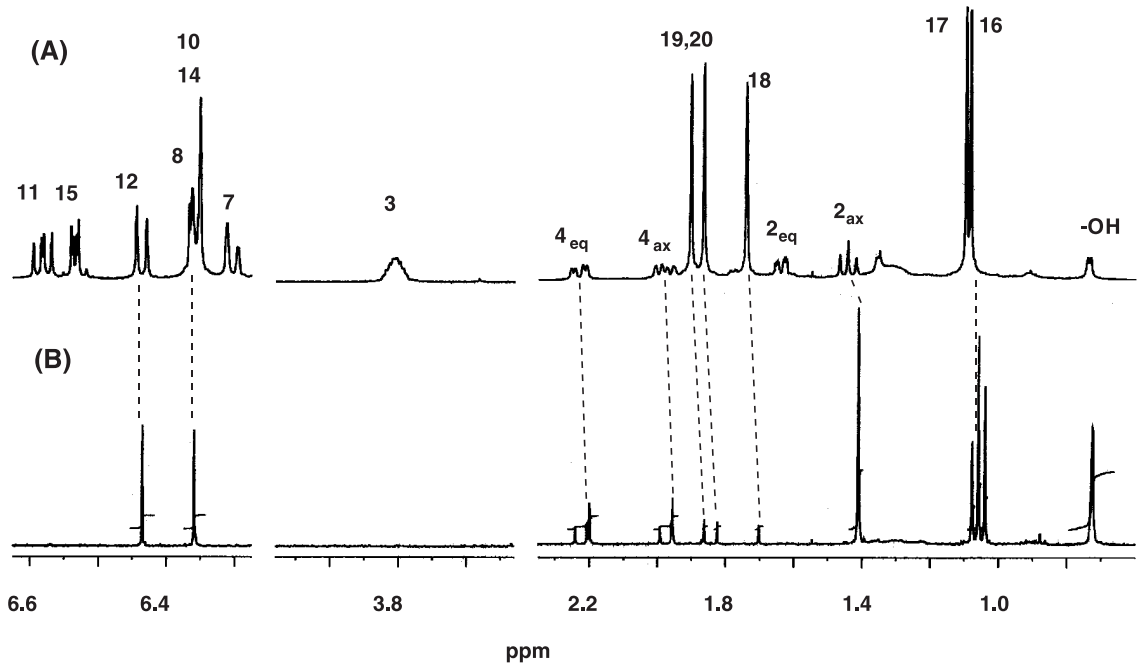

Figure 4. (A) ^{1}H NMR spectrum of non-labeled zeaxanthin; (B) deuterium decoupled ^{1}H NMR spectrum of multiply deuterated zeaxanthin.

original ^{2}H content of the supplemented MVL-d_9. Olefinic signals were observed only for H-8 at δ 6.32 and for H-12 at δ 6.47, both of which are singlets with 23% protium-incorporation. The C-4 protons were observed as two singlets of equal intensity at δ 1.96 and 2.20 and a pair of doublets at δ 1.98 and 2.22 ($J=17$ Hz). Total incorporation was 23%, in which half of the incorporated protium was ascribable to the singlets. These results suggest that the C-4 methylene group of IPP in the metabolic pool of this particular culture was 23% protium-labeled and that no stereochemical differentiation took place. Apparently, the significant equilibrium between IPP and DMAPP afforded a statistically averaged incorporation of protium into the methylene group. Further, despite the fact that the C-17 methyl signal was not identified due to signal overlapping, the C-16 methyl signal was observed as a cluster of three singlets at δ 1.04 (CHD_2, 56% protium-incorporated), 1.06 (CH_2D, 79%) and 1.08 (CH_3, 40%). High turnover between IPP and DMAPP was verified by the extensive incorporation of protium at the C-16 methyl group.

The cryptic stereochemistry of the cyclization of lycopene to β-carotene was elucidated without difficulty (Fig. 3). Essentially no protium was incorporated into the equatorial position at C-2, the signal of which should have appeared, if any, at around δ 1.6. Instead, as mentioned above, an intense singlet signal, which was ascribable to the axial proton, was observed at δ 1.41. Further, the protium-incorporated methyl group at C-1 was determined to be axially oriented after comparison with the non-labeled specimen. It appeared therefore that protonation to the *Si*-face of the C-1/C-2 double bond and the subsequent backside attack of the C-5/C-6 double bond, followed by deprotonation at C-6, gave the well-established β-carotene ring system. These results were completely consistent with that previously reported.[13]

2.2. Preparation of multiply deuterated lycopene, and β-carotene

As described above, we were successful to demonstrate the preparation of highly- and multiply-deuterated zeaxanthin by using the triply-engineered *E. coli* and MVL-d_9. A similar approach using *E. coli* lacking the cyclase and oxidase genes (*crtY* and *crtZ*) was estimated to conveniently provide highly deuterated lycopene and β-carotene, respectively. Thus, *E. coli* DK223 (pTMV20) was separately transformed with pACCRT-EIB[8c] and pACCAR16ΔcrtX[8b] for lycopene and β-carotene production, respectively. The transformants were cultured in the presence of MVL-d_9 and the biosynthesized lycopene and β-carotene were extracted and purified by repeated chromatography.

The mass spectra of the obtained deuterated lycopene and β-carotene were also shown in Figure 5. In both cases, the molecular ion peaks were observed as a cluster of isotopomers, as in the case of multiply deuterated zeaxanthin, between *m/z* 560–591 (non-labeled M^+ *m/z* 536) for deuterated lycopene and between *m/z* 560–589 (non-labeled M^+ *m/z* 536) for β-carotene.

The ^{2}H decoupled ^{1}H NMR spectra of the biosynthesized lycopene and β-carotene are shown in Figure 6. In the spectrum of the deuterated lycopene, the incorporation of protons from medium was clearly observed at C-4, -8, -12, and 16, which is obviously due to the interconversion between IPP and DMAPP as in the case of zeaxanthin. While in the case of β-carotene, in addition to the

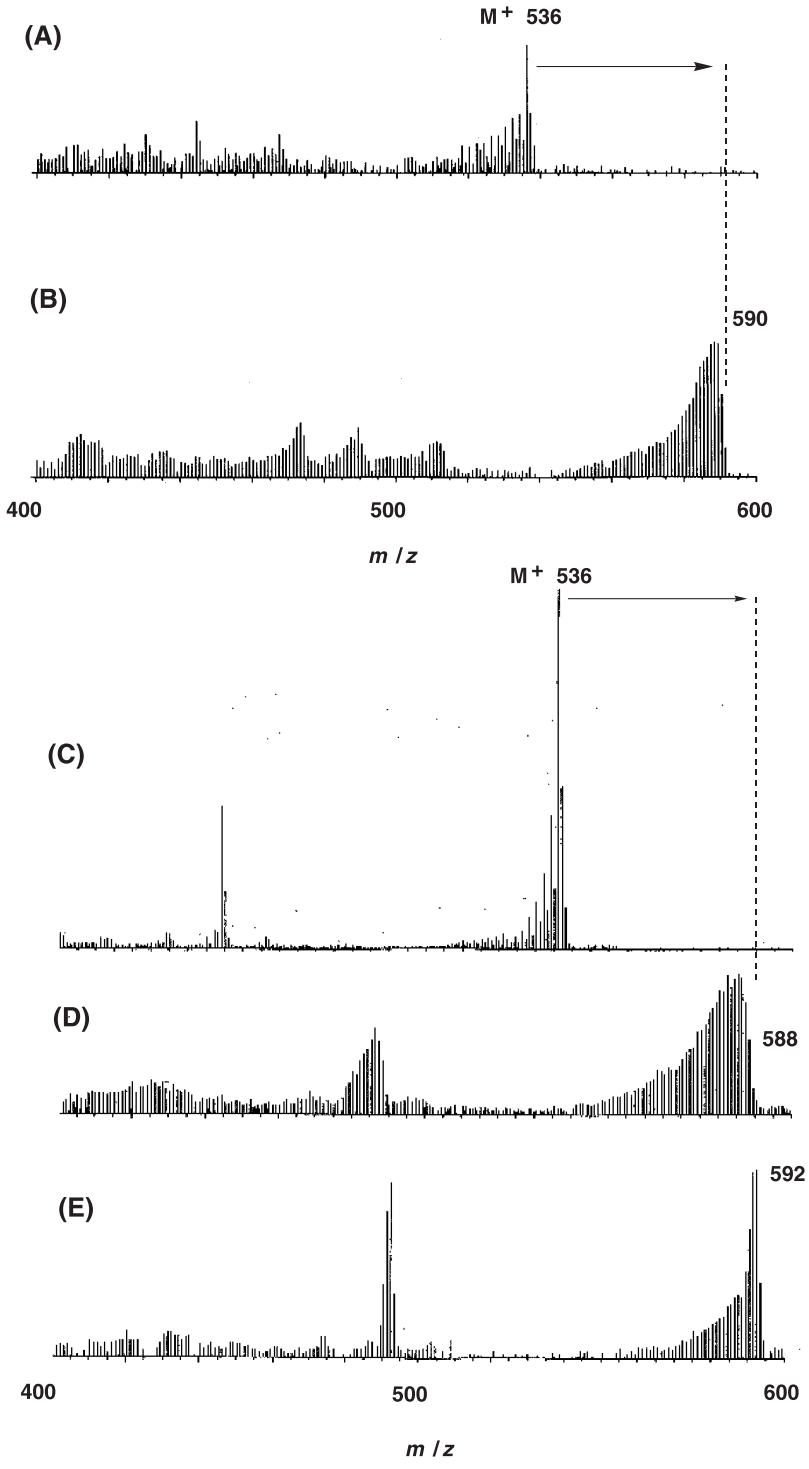

Figure 5. EI-MS spectra of (A) non-labeled lycopene; (B) multiply deuterated lycopene; (C) non-labeled β-carotene; (D) multiply deuterated lycopene; (E) uniformly deuterated β-carotene.

incorporated protons by IPP isomerase at C-4, -8, -12 and -16, the proton signal due to H-2 was observed at δ 1.45. As described in the biosynthesis of zeaxanthin, since the ring formation from lycopene is triggered by the electrophilic attack of a proton to the terminal double bond, one protium (originated from the medium) must reside at C-2. These results were completely consistent with the results of zeaxanthin as described above and the previously reported biosynthetic mechanism of carotenoids.[13]

2.3. Preparation of uniformly deuterated β-carotene

We were successfully developed a practical preparation method of highly deuterated carotenoids. This methodology can be meritorious for mechanistic enzymology, particularly, the key transformation involving proton attack and/or proton quench as observed in the present study as well as in terpene cyclase reactions,[14] by analyzing the protons to be incorporated from the culture medium. However, in turn,

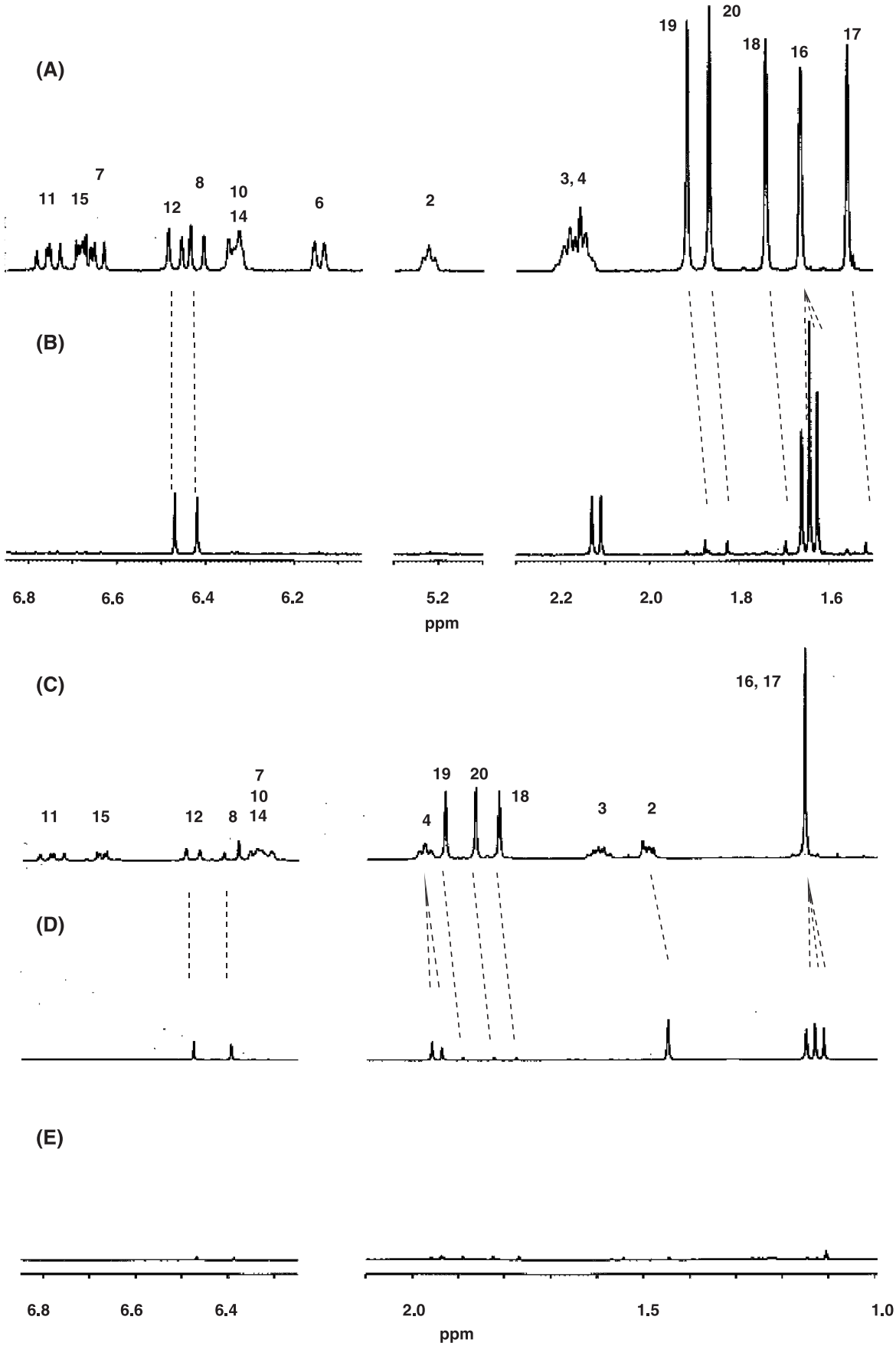

Figure 6. (A) ^{1}H NMR spectrum of non-labeled lycopene; (B) deuterium decoupled ^{1}H NMR spectrum of multiply deuterated lycopene; (C) ^{1}H NMR spectrum of non-labeled β-carotene; (D) deuterium decoupled ^{1}H NMR spectrum of multiply deuterated β-carotene; (E) deuterium decoupled ^{1}H NMR spectrum of uniformly deuterated β-carotene.

considering a view point for the preparation of uniformly deuterated carotenoids which are apparently useful in carotenoid chemistry, the incoming protium must be significantly reduced. We show here an example in which the incoming protium from the culture can be successfully reduced by the combination of the feeding of MVL-d_9 and the cultivation in deuterium oxide. The cultivation of *E. coli* DK223 (pTMV20, pACCAR16ΔcrtX) was carried out for 108 h at 30 °C in deuterium oxide (99 atom%) in the presence of MVL-d_9. Prolonged cultivation of *E. coli* was required under these conditions. The biosynthesized β-carotene were extracted and purified by repeated chromatography.

The mass spectra of the obtained β-carotene are also shown in Figure 5. As can be seen in Figure 5, the most abundant molecular ion peak appeared at *m/z* 592, which is 56 atom mass unit higher than the non-labeled β-carotene ($C_{40}H_{56}$). Thus, the most abundant isotopomer of the obtained β-carotene was found to be 100% deuterated. The ^2H decoupled ^1H NMR spectrum of the obtained β-carotene is also shown in Figure 6. The ^1H NMR signal intensities were significantly reduced, which further confirmed the extremely high deuterium incorporation. The averaged deuterium content of the obtained β-carotene was estimated to be at least 95% atom ^2H at each position from these spectra.

2.4. Chromatographic behavior

In general, replacement of C–H bond of hydrocarbons with C–^2H bond results in a less lipophilic molecule and this effect becomes more pronounced as the content of deuterium in the molecule increases, since the C–H bond has a higher oscillation frequency than the C–^2H bond. The higher oscillation frequency creates an increased electromagnetic field, which induces a field of opposite charge in surrounding molecules, thereby causing increased van der Waals forces.[15] Such a deuterium isotope effect is frequently observed when an isotopically labeled compound is subjected to a separation procedure, such as chromatography. It is sometimes possible to resolve molecules that contain the isotope label from those molecules which do not contain label. The lipophilicity or hydrophobicity of isotopomers can now easily be assessed by observing their chromatographic behaviors by using reverse phase liquid chromatography.[16] Thus, the obtained deuterated carotenoids were compared with the corresponding non-labeled counterparts. With reversed-phase C18 columns, it was possible to resolve deuterated carotenoids from the corresponding non-deuterated analogs. As shown in Figure 7, in all instances the deuterated compounds eluted ahead of its non-labeled analog indicating that van der Waals forces are operational during the separation process as in the cases of various hydrocarbons including some carotenes.[16,17] These results may provide the potential importance of deuterium isotope effects on noncovalent interactions between these deuterated catotenoids for application to biological systems.

2.5. Visible absorption spectra

During chromatographic analysis of the deuterated carotenoids, we noticed that the absorption spectra in the visible regions of the deuterated carotenoids are slightly different from those of the corresponding non-labeled specimen. Careful examination indicated that all of the obtained deuterated carotenoids showed a shift in maximum absorption to shorter wavelength, which are illustrated in Figure 8. The shifts in peak position are the order of 2–3 nm. Thus, the replacement of hydrogen by deuterium in these molecules results in distinct change in visible absorption spectra. A similar absorption maximum shift was already reported in several deuterated carotenoids.[18] Although the detailed mechanism is not clear at present, the differences in

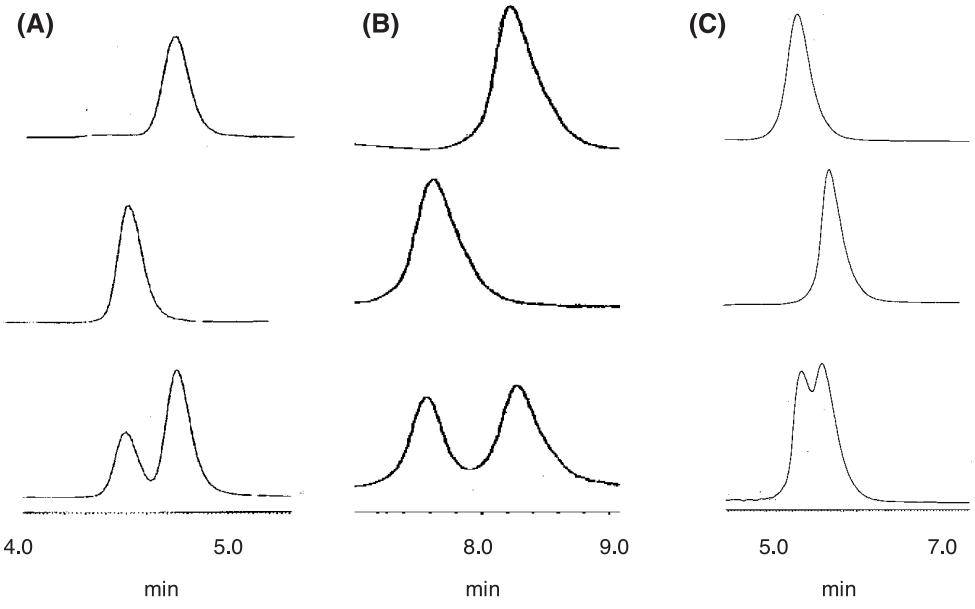

Figure 7. Reverse phase (C_{18}) HPLC separation of non-labeled and deuterated carotenoids. (A) zeaxanthin; (B) β-carotene; (C) lycopene; top, non-labeled; middle, multiply deuterated; bottom, co-injection. HPLC analysis was performed with a PEGASIL ODS column (Senshu, 4.6×250 mm) eluted with acetonitrile for zeaxanthin or acetonitrile–THF (10:1) for lycopene and β-carotene at a flow rate 1.2 ml/min at 45 °C.

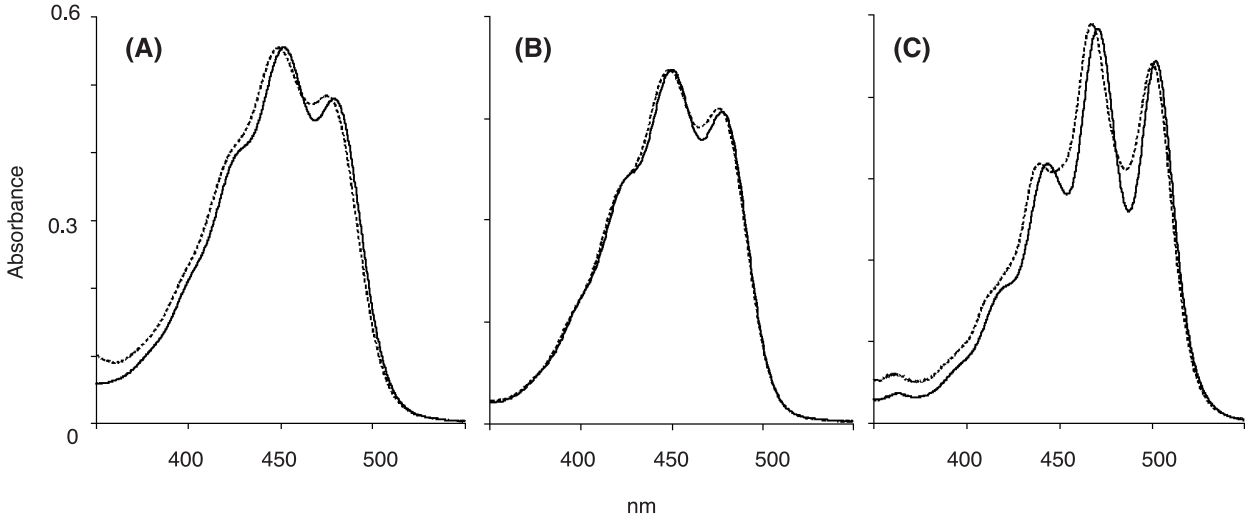

Figure 8. UV–visible spectra of non-labeled and deuterated carotenoids. (A) Zeaxanthin in ethanol; (B) β-carotene in hexane; (C) lycopene in hexane. Solid line, non-labeled; Dashed line, multiply deuterated.

visible absorption may due to the electric transitions coupled to the vibrational modes of the molecule.

3. Conclusion

We were successfully developed a practical preparation method of highly deuterated carotenoids by using engineered *E. coli* with fully deuterated mevalonate. The present study clearly demonstrate versatile potential of the present methodology for the mechanistic enzymology as well as preparation of uniformly and highly deuterated carotenoids. Preparation of fully deuterated carotenoids such as α- and β-carotene and lutein had been reported by cultivation of green algae in deuterated water, however, the algae had been cultured sometimes for a periods of more than a year, and the deuterated carotenoids were frequently obtained as a complex mixture.[19] The increased availability of highly deuterated carotenoids by the present methodology can stimulate diverse research including materials science, photochemistry, biochemistry of this class of isoprenoids as well as the application of isotope-dilution (tracer) methodology in such an important nutrient metabolism.[20]

4. Experimental

4.1. General

^{1}H NMR spectra were taken with a Bruker DRX-500 spectrometer. C_6D_6 was used as solvent and tetramethylsilane as internal standard. Signal assignment was made by comparison with literature data.[11] Mass spectra were obtained by using a JEOL AX-505H spectrometer. UV–Vis spectra were recorded on a Shimadzu UV-160A spectrophotometer. Racemic MVL-d_9 (97% atom D) was prepared by us and was used throughout in this study.[9a]

4.2. Construction of genetically-engineered *E. coli* for carotenoid biosynthesis

DNA manipulations were performed as described in the literature.[21] *E. coli* DK223/pTMV20[6,7] was transformed with pACCAR25ΔcrtX[8a] for zeaxanthin production, with pACCAR16ΔcrtX[8b] for β-carotene production or with pACCRT-EIB for lycopene production,[8c] respectively.

4.3. Bacterial culture, extraction and purification of pigments

4.3.1. Multiply deuterated zeaxanthine. *E. coli* DK223 (pTMV20, pACCAR25ΔcrtX) was cultured for 48 h at 30 °C in LB medium (Bacto Tryptone 10 g; yeast extract 5 g; NaCl 10 g; water 1 L) supplemented with MVL-d_9 (0.5 g/L), in the presence of kanamycin (10 mg/L), ampicillin (50 mg/L), chloramphenicol (30 mg/L), and isopropyl 1-thio-β-D-galactopyranoside (238 mg/L). The harvested cells (wet weight; 20 g) were extracted with cold acetone to give 248 mg of crude extract, which was then chromatographed over silica gel with $CHCl_3$-methanol (9:1) to afford 22 mg of zeaxanthin. Final purification was done by preparative HPLC (4.6×250 mm; Senshu PEGASIL ODS; CH_3CN) to give pure deuterated zeaxanthin (5.2 mg).

4.3.2. Multiply deuterated lycopene. *E. coli* DK223 (pTMV20, pACCART-EIB) was cultured for 25 h at 30 °C in LB medium supplemented with MVL-d_9 (0.5 g/L) in the presence of kanamycin (10 mg/L), ampicillin (50 mg/L), chloramphenicol (30 mg/L), and isopropyl 1-thio-β-D-galactopyranoside (238 mg/L). The harvested cells (wet weight; 17 g) were extracted with cold acetone to give 76 mg of crude extract, which was then chromatographed over silica gel with hexanes-$CHCl_3$ (1:1) to afford 2.5 mg of lycopene. Final purification was done by preparative HPLC (4.6×250 mm; Senshu PEGASIL ODS; CH_3CN–THF (10:1)) to give pure deuterated lycopene (1.5 mg).

4.3.3. Multiply deuterated β-carotene. *E. coli* DK223 (pTMV20, pACCAR16ΔcrtX) was cultured for 28 h at 30 °C in LB medium supplemented with MVL-d_9 (0.5 g/L) in the presence of kanamycin (10 mg/L), ampicillin (50 mg/L), chloramphenicol (30 mg/L), and isopropyl 1-thio-β-D-galactopyranoside (238 mg/L). The harvested cells (wet weight; 22 g) were extracted with cold acetone to give 160 mg of crude extract, which was then chromatographed over silica gel with hexanes–ethyl acetate (10:1) to afford 8.6 mg of β-carotene. Final purification was done by preparative HPLC (4.6×250 mm; Senshu PEGASIL ODS; CH_3CN–THF (10:1)) to give pure deuterated β-carotene (3.0 mg).

4.3.4. Uniformly deuterated β-carotene. *E. coli* DK223 (pTMV20, pACCAR16ΔcrtX) was cultured for 108 h at 30 °C in a medium containing Bacto Tryptone 10 g, yeast extract 5 g, NaCl 10 g in deuterium oxide 1 L (99 atom%) in the presence of MVL-d_9 (0.5 g/L), kanamycin (10 mg/L), ampicillin (50 mg/L), chloramphenicol (30 mg/L), and 1-thio-β-D-galactoside (238 mg/L). The harvested cells (wet weight; 2.5 g) were extracted with cold acetone to give crude extract, which was then chromatographed over silica gel with hexanes–ethyl acetate (10:1) to afford 2.0 mg of β-carotene. Final purification was done by preparative HPLC (4.6×250 mm; Senshu PEGASIL ODS; CH_3CN–THF (10:1)) to give pure uniformly deuterated β-carotene (1.0 mg).

Acknowledgements

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The study of intramolecular tandem radical cyclizations of acylsilanes with radicalphiles attached on silicon

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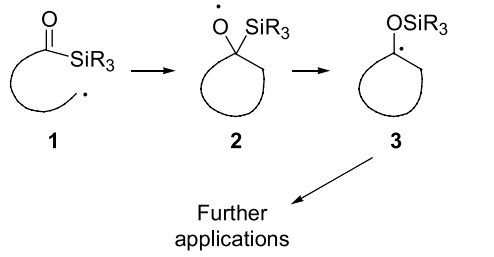
Abstract—Radical cyclizations of acylsilanes with radicalphilic pendant introduced on silicon proceeded in a tandem fashion to give spiro products containing a cyclic silyl ether skeleton. Because the alkoxysilyl group can be replaced with a hydroxy group through oxidation, the spiro silyl ethers can be converted into diols. In the case with a radical intermediate carrying 2-oxa-3-sila-6-heptenyl skeleton, products derived from 1,7-*endo* cyclization were obtained in good yields.

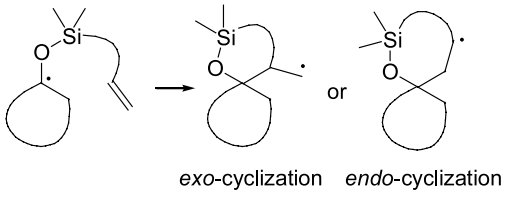
1. Introduction

Radical reactions are now widely used as important tools to construct carbon–carbon bonds.[1] Among various radical reactions, radical additions to carbonyl generate alkoxy radicals that are prone to undergo β-scission to regenerate the carbonyl functionality.[2] Yet this seemingly deleterious property can be manipulated to yield ring-expansion[3,4] and acylation[4–7] products. The cyclized alkoxy radicals can also be trapped intermolecularly or intramolecularly by hydrogen,[8] phosphorous,[9] boron[10] and tin.[11,12]

Several years ago, we initiated a study of intramolecular radical cyclizations of acylsilanes (Scheme 1).[13] In this type of cyclizations, radical **1** adds intramolecularly to the carbonyl of the acylsilane functionality[14] to give a β-silyl substituted alkoxy radical **2**. A facile radical-Brook rearrangement[15,16] occurs to afford an α-silyloxy radical **3**. In this fashion, the radical carbonyl cyclization reaction can also be driven irreversibly towards ring formation. Depending on the reaction conditions[13c] and structural features[13b,d,f,j] the intermediate α-silyloxy radical **3** can be converted to different products. One possibility (Scheme 2) involves the design of a radicalphile tethered to the silicon atom in such a way that the α-silyloxy radical can undergo further cyclization.[13f] The alkoxy silane moiety in the resulting silacycles can be considered as a hydroxy group equivalent.[17] Through oxidative hydrolysis, the silacycles can be opened to give diols. Now we wish to report the full investigation of this approach.



Scheme 1.



Scheme 2.

2. Results and discussion

As shown in Scheme 3, we choose to synthesize acylsilanes **8** and **9**. These acylsilanes contain allyl and homoallyl group attached on silicon. The strategy developed by Brook[18] and Corey[19] was used in the synthesis. We first prepared 2-silyl-1,3-dithianes **5a** (83%), **5b** (64%) and **5c** (68%) from the silylation of 1,3-dithiane (**4**) with the corresponding chlorosilanes. However when we used the same method for the preparation of dithiane **5d**, small amount of double

Keywords: Acylsilanes; Tandem radical cyclizations; Alkoxysilane; Brook rearrangement.
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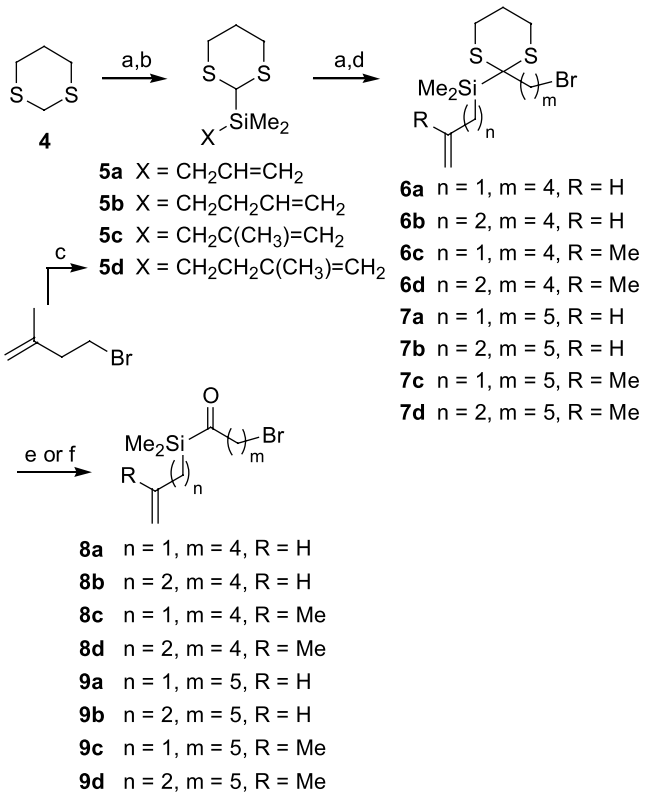
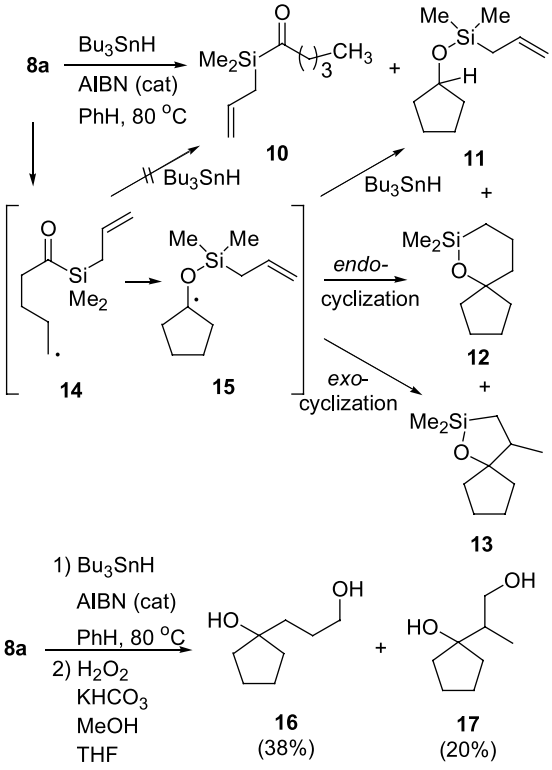
bond positional isomerization product was always present and difficult to remove. This was probably caused by the presence of small amount of hydrochloric acid in chlorodimethyl(3-methyl-3-butenyl)silane. We therefore switched to use an in situ generation method for the preparation of the chlorosilane under a slightly basic condition.[20] The Grignard reagent prepared from 4-bromo-2-methylbutene in THF was treated with chlorodimethyl(dimethylamino)-silane followed by the addition of acetyl chloride. To the chlorodimethyl(3-methyl-3-butenyl)silane solution thus prepared was added the anion generated from 1,3-dithiane to afford pure 2-silyldithiane **5d** in 38% without the formation of its double bond positional isomer.



Scheme 3. Reagents and conditions: (a) BuLi, THF, 0 °C; (b) (CH_2=$CHCH_2$)Me_2SiCl for **5a** (83%), (CH_2=$CHCH_2CH_2$)Me_2SiCl for **5b** (64%), and (CH_2=$CMeCH_2$)Me_2SiCl for **5c** (68%); (c) (i) Mg, THF, (ii) Me_2NSiMe_2Cl, (iii) AcCl, (iv) **4**, BuLi (**5d**, 39%); (d) $Br(CH_2)_mBr$, −20 °C, 1 h, for **6c** (52%), **6d** (51%), **7c** (66%), and **7d** (85%); (e) CAN (4 equiv), H_2O/MeOH/CH_2Cl_2, −20 °C, for **8a** (33% from **5a**); CAN (3 equiv), H_2O/CH_3CN, $NaHCO_3$, 0 °C, 10 min, for **8c** (37%), **8d** (80%), **9c** (38%), and **9d** (64%); (f) $(CF_3COO)_2IPh$ (1.7 equiv), $NaHCO_3$, CH_3CN/H_2O, −20 °C, for **8b** (36% from **5b**), **9a** (52% from **5a**), and **9b** (43% from **5b**).

The 2-silyl-1,3-dithianes were then alkylated with 1,4-dibromobutane or 1,5-dibromopentane to afford bromides **6** and **7**. Due to the presence of nucleophilic sulfur atoms in the molecule, the bromides are not stable. Although these bromides can be isolated and purified, it is best to hydrolyze the dithiane moiety once the crude bromides are obtained. In the case of the hydrolysis of **6a**, **6c**, **6d**, **7c**, and **7d**, ceric ammonium nitrate (CAN) in wet methanol or acetonitrile[21] was used as the reagent to give acylsilane **8a**, **8c**, **8d**, **9c**, and **9d**. Iodobenzene bistrifluoroacetate[22] was used in the hydrolysis of **6b**, **7a**, and **7b** to give **8b**, **9a**, and **9b**, respectively. The yields for the preparation of acylsilanes **8** are lower. This probably reflects the lower stability of the corresponding bromides **6** because in these compounds intramolecular attack of sulfur at the bromo-substituted carbon goes through a favored six-membered ring transition state. In contrast, the homologous bromides **7** contain one more methylene unit and the intramolecular nucleophilic attack by sulfur is more difficult.

The radical cyclization of acylsilane **8a** (Scheme 4) was performed by slow addition (1 h) of a benzene solution of tributyltin hydride (1.2 equiv) and AIBN (0.05 equiv) to a solution of **8a** in refluxing benzene. The concentration with respect to **8a** was 0.05 M. Although there may be four possible products **10**–**13**, acylsilane **10**, derived from hydrogen abstraction of the initial radical **14**, was not observed. This is expected, because radical 1,5-cyclizations of acylsilanes are very fast processes, and straight reduction products are generally not observed.[13h,i] Cyclopentyl ether **11** derived from hydrogen abstraction of α-silyloxy radical **15** was observed in 8% by GC analysis. For the purpose of GC comparison, an authentic sample of ether **11** was prepared from the silylation of cyclopentyl alcohol with allyldimethylsilyl chloride. Radical intermediate **15** can undergo *endo*- and *exo*-cyclization to give spiro silyl ethers **12** and **13**, respectively. However, due to the volatility of these silyl ethers, we were only able to isolate the major product **12** in 46% yield. We believe some portion of **12** was lost during concentration. As mentioned earlier, the C–Si bond of the alkoxysilyl group can be oxidatively cleaved to result in the replacement of the silyl group with a hydroxy group.[17] Therefore, we decided to treat the crude cyclization product mixture directly with hydrogen peroxide and potassium hydrogen carbonate in a mixture of methanol

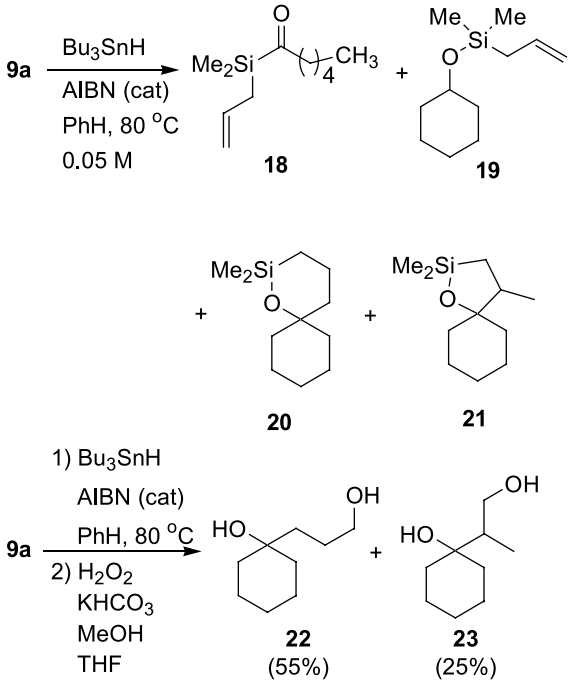


Scheme 4.

and THF.[23] In this way, we isolated 38% of diol **16** and 20% of diol **17**. Since diols **16** and **17** must be derived from silyl ethers **12** and **13**, respectively, this result showed that the *endo*-cyclization mode is the preferred process for the cyclization of α-silyloxy radical **15**. The ratio of the yields of the two diols, **16/17**=1.9/1, then reflects the *endo*/*exo* cyclization rate ratio of radical **15**.

In the cyclization of 5-hexenyl radical it is well-known that 5-*exo* cyclization is preferred over 6-*endo* cyclization.[1] In contrast, it was found that the replacement of C-3 of 5-hexenyl radical with a silicon atom directed the cyclization to 6-*endo* cyclization almost exclusively.[24] This preference is actually derived from the diminished 5-*endo* cyclization rate of the β-dimethylsilyl substituted radical.[24a] It was proposed by Wilt et al.[24a] that this phenomenon was due to the longer Si–C bond and the preferred ground state conformation making the radical more difficult to approach the internal carbon of the olefin. Our cyclization belongs to a 2-oxa-3-sila-5-hexenyl radical system that is rarely found in the literature. The cyclization results of acylsilane **8a** indicate that the presence of the silicon atom in this system also affects the mode of ring closure in favor of 6-*endo* cyclization albeit in a lower *endo*/*exo* ratio comparing with the 3-sila-5-hexenyl radical system. Although there is no adequate information in the literature to estimate the effect of the conformation of the silyloxy substituted radical, it can be speculated that the shorter C–O and Si–O bonds have important contribution influencing the *endo*/*exo* cyclization ratio of 2-oxa-3-sila-5-hexenyl radical.

Similarly, the reaction of acylsilane **9a** (Scheme 5) with tributyltin hydride at a concentration of 0.05 M gave a mixture of straight reduction product **18**, monocyclic product **19**, and two tandem cyclization products **20** and **21**. Direct treatment of the crude cyclization mixture under the oxidation conditions stated above afforded diols **22** and **23** in 55 and 25% yields, respectively. Gas chromatographic analysis of the crude cyclization mixture showed the straight reduction product **18** was present in about 7%, and the monocyclic product **19** was present in about 5%. For the purpose of comparison, authentic sample of **18** was isolated in 51% yield by performing the cyclization reaction at a more concentrated condition of 0.5 M. The silyl ether **19** was prepared from the reaction of cyclohexanol with allyldimethylsilyl chloride.



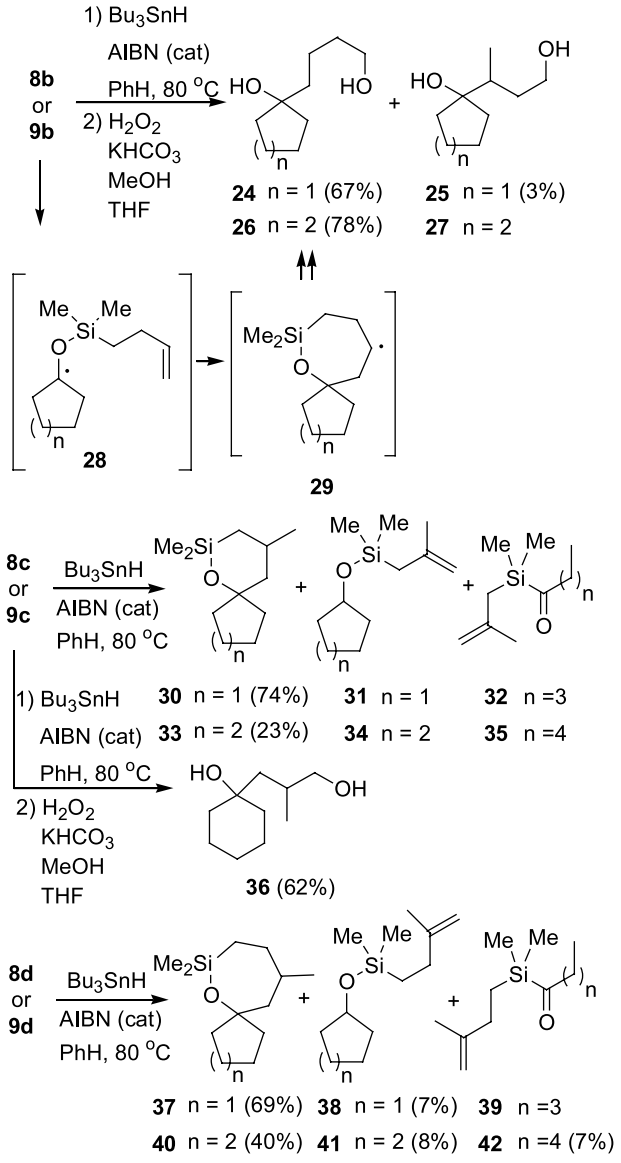
Scheme 5.

For the cyclization of acylsilane **9a**, the ratio of *endo*/*exo* cyclizations of the intermediate α-silyloxy substituted radical extrapolated from the ratio of diols **22/23** is 2.2/1. This *endo*/*exo* cyclization ratio is about the same as in the case of the cyclization of acylsilane **8a**. Therefore, the regioselectivity of the second ring formation is not strongly influenced by the pre-existing five- or six-membered ring. In the cyclization of **9a**, more straight reduction product was obtained. This reflects the slower 1,6-cyclization rate for acylsilanes as observed previously.[13i]

With a homoallyl group attached to the silicon atom, the two-step radical cyclization–oxidation sequences performed on acylsilanes **8b** and **9b** (Scheme 6) gave diols **24** (67%) and **26** (78%), respectively, as the major products. Small amount of diol **25** (3%) was isolated for the reaction of acylsilane **8b**. For the homologous acylsilane **9b**, diol **27** was not detected. These results indicate that the 2-oxa-3-sila-6-heptenyl radical intermediates **28** undergo 1,7-*endo* cyclization in preference. In the case of acylsilane **9b**, GC analysis of the crude radical cyclization product indicated the presence of 10% of straight reduction product and 12% of monocyclic silyl ether. Since the amount of monocyclic product is not much different from those obtained in the case of **8a** and **9a**, the 1,7-*endo* cyclization appears to be quite efficient. Previously, a similar 2,4-dioxa-3-sila-6-heptenyl radical system has also been reported by Myers, Gin and Rogers to give 1,7-*endo* cyclization predominantly.[25]

We also studied the cyclization of acylsilane **8c** (Scheme 6) having 2-methylallyl substituent on silicon. The methyl group attached on the internal carbon of the olefin directed the radical cyclization of **8c** to afford the spiro silyl ether **30** in 74% yield as the only product. We did not detect the presence of monocyclic ether **31** or acylsilane **32**. Apparently the methyl group on the allyl moiety retarded the attack of the radical appreciably such that the 5-*exo* cyclization mode was completely suppressed.[26] In addition, the 6-*endo* cyclization led to the formation of a more stabilized tertiary radical. This factor may contribute an acceleration effect that makes this tandem cyclization so efficient.

In comparison, the homologous acylsilane **9c** under our standard radical cyclization condition gave 23% of the tandem cyclization product **33**. Again, 6-*endo* cyclization of the second cyclization step was the predominate process. Analysis of the crude cyclization mixture via ^{1}H NMR revealed the presence of monocyclic product **34** and straight reduction product **35**. The ratio of **33/34/35** determined by NMR integration was 87/8/5. The low yield of the spiro product **33** was due to the volatility and the extensive chromatographic processes for its purification. When the



Scheme 6.

crude product of the cyclization of **9c** was directly oxidized under the Tamao oxidation condition,[23] we were able to obtain the diol **36** in 62% yield. The formation of small amount of monocyclic silyl ether **34** in this system seems to indicate that the cyclization rate of the intermediate cyclohexyl radical is slightly slower than the corresponding cyclopentyl radical as in the case of acylsilane **8c**. We suspect that the allylic methyl group may exhibit repulsive interaction with the C(3)-methylene unit of the cyclohexyl group in the transition state (Fig. 1) of the second cyclization and thus slows down the rate.

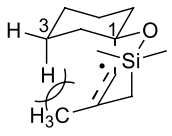


Figure 1. The proposed 1,6-*endo* cyclization transition state of the (2-methylallyl)silyloxy substituted cyclohexyl radical.

With a 3-methyl-3-butenyl group attached on silicon, the cyclizations of acylsilanes **8d** and **9d** gave exclusively 7-*endo* cyclization product for the second cyclization step. In the case of acylsilane **8d**, spiro silyl ether **37** was isolated in 69% yield in addition to 7% of monocyclic product **38**. Analysis of the crude product by ^{1}H NMR showed that straight reduction product **39** was not formed. The ratio of spiro silyl ether **37** and monocyclic silyl ether **38** in the crude product was 9/1 (**37**/**38**). The reaction of acylsilane **9d** with tributyltin hydride gave a 74/10/9 crude mixture of spiro silyl ether **40**, monocyclic silyl ether **41** and straight reduction product **42**, respectively. The spiro silyl ether **40** was isolated in 40% through silica gel column chromatography in addition to 6% of monocyclic product **41** and 7% of straight reduction product **42**. The presence of **42** reflected the slower rate of the initial 1,6-cyclization as described above. The lower ratio of spiro product **40** and monocyclic product **41** (74/10 by NMR) also showed that the pre-existing six-membered ring might influence the second 7-*endo* cyclization.

In summary, we have demonstrated that by introducing radicalphilic pendant on silicon, the radical cyclizations of acylsilanes can proceed in a tandem fashion. Because the alkoxysilyl group can be replaced with a hydroxy group through oxidation, the final cyclization products can be converted to give diols. In the case with a radical intermediate carrying 2-oxa-3-sila-6-heptenyl skeleton, products derived from 1,7-*endo* cyclization were obtained in good yields.

3. Experimental

3.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200, 300 or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75 or 100 MHz. Tetramethysilane ($\delta=0$ ppm) or $CHCl_3$ ($\delta=7.24$ ppm) were used as internal standards and $CDCl_3$ was used as the solvent. Benzene and THF were distilled from sodium benzophenone ketyl under N_2. Diisopropylamine and acetonitrile were dried with CaH_2 and distilled. The benzene used for cyclization reactions was deoxygenated by passing a gentle stream of argon through for 0.5 h before use. All reactions were performed under a blanket of N_2 or Ar. Lobar LiChroprep Si 60 (40–63 μm) pre-packed columns purchased from Merck were used for medium pressure liquid chromatography (MPLC). Gas chromatography was performed on a Shimadzu GC-8A apparatus with TCD using a 3.3 mm × 2 m column of 10% SE-30 on Chromosorb W (AW-DMCS), 80–100 mesh, and hydrogen as carrier gas.

3.1.1. 2-(Allyldimethylsilyl)-1,3-dithiane (5a). To a solution of 0.800 g (6.67 mmol) of 1,3-dithiane in 4.7 mL of dry THF cooled at 0 °C was added dropwise over 20 min a 1.64 N solution of butyllithium in hexane (5.29 mL, 8.67 mmol). The resulting solution was stirred at the same temperature for 40 min and then added over 30 min to a solution of 1.08 mL (7.38 mmol) of allylchlorodimethylsilane in 4.0 mL of dry THF cooled at 0 °C. The reaction mixture was stirred at the same temperature for 1 h and then

partitioned between 100 mL of ether and 50 mL of water. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed with MPLC using Lobar size B column (eluted with hexane/ethyl acetate, 99/1) to give 1.20 g (83%) of **5a** as a pale yellow liquid: IR (neat) 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 6H), 1.65 (d, J= 8 Hz, 2H), 1.88–2.15 (m, 2H), 2.68 (dt, J=14, 4 Hz, 2H), 2.84 (td, J=14, 4 Hz, 2H), 3.71 (s, 1H), 4.85 (br d, J= 10 Hz, 1H), 4.90 (br d, J=18 Hz, 1H), 5.76 (ddt, J=18, 10, 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4, 21.0, 26.1, 31.0, 33.0, 114.0, 133.7; HRMS calcd for $C_9H_{18}S_2Si$ m/z 218.0619, found 218.0621.

3.1.2. 2-((3-Buten-1-yl)dimethylsilyl)-1,3-dithiane (5b). According to the procedure for the preparation of **5a**, 1,3-dithiane (0.48 g, 4.0 mmol) reacted with 0.65 mL (4.0 mmol) of (3-buten-1-yl)chlorodimethylsilane[27] to afford 595 mg (64%) of **5b** as a pale yellow liquid: IR (neat) 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 6H), 0.70–0.82 (m, 2H), 1.88–2.15 (m, 4H), 2.68 (dt, J=14, 4 Hz, 2H), 2.85 (td, J=14, 4 Hz, 2H), 3.70 (s, 1H), 4.87 (br d, J=11 Hz, 1H), 4.98 (br d, J=17 Hz, 1H), 5.84 (ddt, J= 17, 11, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.8, 12.5, 26.2, 27.6, 31.1, 33.5, 113.0, 141.0; HRMS calcd for $C_{10}H_{20}S_2Si$ m/z 232.0775, found 232.0785.

3.1.3. 2-[Dimethyl(2-methyl-2-propenyl)silyl]-1,3-dithiane (5c). According to the procedure for the preparation of **5a**, 1,3-dithiane (0.217 g, 1.81 mmol) reacted with 0.35 mL (2.0 mmol) of chlorodimethyl(2-methyl-2-propen-1-yl)silane[28] to afford 275 mg (65%) of **5c** as a colorless liquid: IR (neat) 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 6H, $SiCH_3$), 1.70 (s, 2H, $SiCH_2$), 1.72 (s, 3H, $=CCH_3$), 1.93–2.16 (m, 2H, $SCH_2CH_2CH_2S$), 2.71 (dt, J= 14, 4 Hz, 2H, $SCH_{2(eq)}$), 2.87 (td, J=14, 2.4 Hz, 2H, $SCH_{2(ax)}$), 3.73 (s, 1H, SCHS), 4.55 (br s, 1H, $=CH_2$), 4.63 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.5 (CH_3), 24.8 (CH_2), 25.4 (CH_3), 26.3 (CH_2), 31.2 (CH_2), 33.6 (CH), 109.4 (CH_2), 142.3 (C); HRMS (FAB) calcd for $C_{10}H_{21}S_2Si$ $(M+H)^+$ m/z 233.0854, found 233.0836.

3.1.4. 2-[Dimethyl(3-methyl-3-butenyl)silyl]-1,3-dithiane (5d). A mixture of 0.358 g (14.9 mmol) of magnesium turnings and a few crystals of iodine in 1 mL of dry THF was stirred under argon until the iodine color disappeared. A solution of 1.38 mL (11.1 mmol) of 4-bromo-2-methyl-1-butene in 10 mL of dry THF was added to the mixture over a period of 25 min and stirred for another 15 min. The Grignard reagent prepared above was added dropwise over a period of 15 min to a cooled (0 °C) solution of 1.2 mL (6.93 mmol) of chlorodimethyl(dimethylamino)silane in 8 mL of dry THF. The reaction mixture was stirred for another 10 min at 0 °C followed by the addition of a solution of 0.50 mL (6.9 mmol) of acetyl chloride in 7 mL of dry THF over a period of 20 min at the same temperature. The resulting mixture was stirred for another 2.5 h at 0 °C to furnish a solution of dimethyl(3-methyl-3-buten-1-yl)silyl chloride. To another solution of 1.42 g (11.9 mmol) of 1,3-dithiane in 13 mL of dry THF cooled in an ice-water bath was added dropwise over 20 min a 1.5 N solution of butyllithium in hexane (9.40 mL, 14.1 mmol). This anion solution was then added to the silyl chloride solution prepared above at 0 °C over a period of 20 min, and the reaction mixture was stirred for 1.5 h at room temperature. The resulting mixture was poured into 20 mL of sat. ammonium chloride solution and extracted with 100 mL of ether. The organic layer was washed with water (100 mL× 2), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo to give 2.31 g of a yellow residue. The residue was chromatographed with MPLC using Lobar size B column (eluted with hexane/ethyl acetate, 98/2) to give 0.659 g (39%) of **5d** as a colorless liquid: IR (neat) 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 6H, $SiCH_3$), 0.80–0.85 (m, 2H, $SiCH_2$), 1.72 (s, 3H, $=CCH_3$), 1.95–2.14 (m, 4H, $SCH_2CH_2CH_2S$, and $=CCH_2$), 2.71 (dt, J=14, 4 Hz, 2H, $SCH_{2(eq)}$), 2.86 (td, J=14, 2.8 Hz, 2H, $SCH_{2(ax)}$), 3.73 (s, 1H, SCHS), 4.66 (br s, 1H, $=CH_2$), 4.70 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8 (CH_3), 11.6 (CH_2), 22.3 (CH_3), 26.3 (CH_2), 31.2 (CH_2), 31.5 (CH_2), 33.6 (CH), 108.6 (CH_2), 147.7 (C); HRMS (FAB) calcd for $C_{11}H_{22}S_2Si$ m/z 246.0932, found 246.0928.

3.1.5. 5-Bromo-1-(allyldimethylsilyl)-1-pentanone (8a). To a solution of 300 mg (1.38 mmol) of **5a** in 4.0 mL of dry THF cooled at 0 °C was added dropwise over 10 min a 1.46 N solution of butyllithium in hexane (1.23 mL, 1.79 mmol). The resulting solution was stirred at the same temperature for another 40 min and then added dropwise over 40 min to a solution of 0.33 mL (2.8 mmol) of 1,4-dibromobutane in 4.0 mL of dry THF cooled at −20 °C. The reaction mixture was stirred at −20 °C for 1 h and then partitioned between ether (60 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in a mixture of 2 mL of methanol and 2 mL of dichloromethane. To the resulting solution cooled at −20 °C was added over 7 min a solution of 3.10 g (5.66 mmol) of CAN in 6 mL of methanol and 0.31 mL of water. The resulting mixture was stirred at the same temperature for 5 min and then diluted with ether. The resulting mixture was filtered, and the filtrate was partitioned between 80 mL of ether and 35 mL of water. The organic phase was washed with brine (35 mL), dried ($MgSO_4$), and concentrated in vacuo to give 658 mg of a residual oil. The oil was chromatographed with MPLC over a Lobar size B column (eluted with hexane/ethyl acetate, 98/2) to give 120 mg (33%) of **8a** as a pale yellow liquid: IR (neat) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.19 (s, 6H), 1.53–1.72 (m, 4H), 1.72–1.87 (m, 2H), 2.60 (t, J=7 Hz, 2H), 3.36 (t, J=6.5 Hz, 2H), 4.81–4.93 (m, 2H), 5.72 (ddt, J=18, 10, 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.2, 20.5, 21.1, 32.2, 33.4, 48.0, 114.5, 133.0, 246.2; HRMS calcd for $C_{10}H_{19}{}^{81}BrOSi$ m/z 264.0368, found 264.0357.

3.2. General procedure for the preparation of acylsilanes 8b, 9a and 9b using iodobenzenebistrifluoroacetate for hydrolysis: 5-bromo-1-((3-buten-1-yl)dimethylsilyl)-1-pentanone (8b)

According to the procedure for the synthesis of **8a**, 0.70 g of **5b** (3.0 mmol) was alkylated with 0.72 mL (6.0 mmol) of 1,4-dibromobutane. The crude alkylation product was mixed with 1.76 g of sodium bicarbonate, 10 mL of acetonitrile, and 3 mL of water. To the resulting mixture

cooled at −20 °C was added slowly a solution of 2.2 g (5.1 mmol) of iodobenzenebistrifluoroacetate in 10 mL of acetonitrile. The reaction mixture was stirred at the same temperature for 5 min and then partitioned between 100 mL of ether and 50 mL of water. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give 1.7 g of a residual oil. The oil was chromatographed with MPLC over a Lobar size B column (eluted with hexane/ethyl acetate, 97/3) to give 298 mg (36%) of **8b** as a pale yellow oil: IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 6H), 0.70–0.85 (m, 2H), 1.51–1.87 (m, 4H), 1.93–2.13 (m, 2H), 2.59 (t, $J=7$ Hz, 2H), 3.34 (t, $J=7$ Hz, 2H), 4.70–5.03 (m, 2H), 5.79 (ddt, $J=17$, 11, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −4.8, 12.5, 20.6, 27.5, 32.2, 33.3, 47.6, 113.5, 140.4, 246.9; HRMS calcd for $C_{11}H_{21}{}^{81}BrOSi$ *m/z* 278.0524, found 278.0524.

3.2.1. 6-Bromo-1-(allyldimethylsilyl)-1-hexanone (9a). A pale yellow oil: IR (neat) 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.18 (s, 6H), 1.25–1.73 (m overlapped with d, $J=8$ Hz, 6H), 1.82 (quintet, $J=7$ Hz, 2H), 2.58 (t, $J=7$ Hz, 2H), 3.37 (t, $J=7$ Hz, 2H), 4.80–4.93 (m, 2H), 5.70 (ddt, $J=18$, 10, 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.2, 21.0, 21.2, 27.8, 32.6, 33.5, 48.8, 114.4, 133.1, 246.6; HRMS calcd for $C_{11}H_{21}{}^{81}BrOSi$ *m/z* 278.0525, found 278.0512.

3.2.2. 6-Bromo-1-((3-buten-1-yl)dimethylsilyl)-1-hexanone (9b). A pale yellow oil: IR (neat) 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 6H), 0.70–0.82 (m, 2H), 1.27–1.59 (m, 4H), 1.81 (quintet, $J=7$ Hz, 2H), 1.97–2.12 (m, 2H), 2.57 (t, $J=7$ Hz, 2H), 3.36 (t, $J=7$ Hz, 2H), 4.80–5.03 (m, 2H), 5.79 (ddt, $J=16$, 10, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −4.7, 12.6, 21.0, 27.5, 27.8, 32.6, 33.5, 48.5, 113.5, 140.5, 247.4; HRMS calcd for $C_{12}H_{23}{}^{81}BrOSi$ *m/z* 292.0681, found 292.0691.

3.2.3. 2-(4-Bromobutyl)-2-[dimethyl(2-methyl-2-propenyl)silyl]-1,3-dithiane (6c). According to the procedure for the synthesis of **8a**, 3.0 g (13 mmol) of **5c** was alkylated with 3.85 mL (32.3 mmol) of 1,4-dibromobutane to give 2.5 g (52%) of **6c** as a pale yellow liquid: IR (neat) 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.20 (s, 6H, $SiCH_3$), 1.60–1.69 (m, 2H), 1.71 (s, 3H, $=CCH_3$), 1.79 (s, 2H, $SiCH_2$), 1.81–1.94 (m, 3H), 1.99–2.08 (m, 1H), 2.16–2.25 (m, 2H), 2.44 (dt, $J=14$, 3.6 Hz, 2H, $SCH_{2(eq)}$), 3.00 (td, $J=14$, 2.8 Hz, 2H, $SCH_{2(ax)}$), 3.44 (t, $J=6.8$ Hz, 2H, CH_2Br), 4.53 (br s, 1H, $=CH_2$), 4.63 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.0 (CH_3), 23.6 (CH_2), 24.6 (CH_2), 25.1 (CH_2), 25.5 (CH_3), 26.4 (CH_2), 33.1 (CH_2), 33.6 (CH_2), 38.7 (C), 109.6 (CH_2), 142.6 (C); HRMS (FAB) calcd for $C_{14}H_{27}{}^{79}BrS_2Si$ *m/z* 366.0507, found 366.0500.

3.2.4. 5-Bromo-1-[dimethyl(2-methyl-2-propenyl)silyl]-pentan-1-one (8c). To a vigorously stirred cold (0 °C) mixture of 0.392 g (1.07 mmol) of **6c** and 0.553 g (6.59 mmol) of sodium bicarbonate in 10 mL of acetonitrile and 1 mL of water was added 1.47 g (2.69 mmol) of ceric ammonium nitrate in one portion. The resulting mixture was stirred for another 3 min at the same temperature and then quickly filtered over Celite. The filtrate was partitioned between 100 mL of ethyl acetate and 100 mL of water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.428 g of a residual oil. The oil was chromatographed with MPLC over a Lobar size B column (eluted with hexane/ethyl acetate, 98/2) to give 109 mg (37%) of **8c** as a pale yellow oil: IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 6H, $SiCH_3$), 1.60–1.72 (m overlapped with two s at 1.67 and 1.70, 7H, $=CCH_3$, $SiCH_2$ and others), 1.76–1.85 (m, 2H), 2.62 (t, $J=7$ Hz, 2H, $COCH_2$), 3.37 (t, $J=6.8$ Hz, 2H, CH_2Br), 4.50 (br s, 1H, $=CH_2$), 4.62 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −0.92 (CH_3), 20.8 (CH_2), 24.3 (CH_3), 32.3 (CH_2), 33.5 (CH_2), 46.7 (CH_2), 110.3 (CH_2), 142.2 (C), 244.5 (C); MS (rel intensity) *m/z* 277 (M^+, 2), 263 (6), 211 (11), 157 (24), 139 (38), 113 (90), 85 (40), 75 (100), 59 (92); HRMS calcd for $C_{11}H_{22}{}^{81}BrOSi$ $(M+H)^+$ *m/z* 279.0597, found 279.0602.

3.2.5. 2-(4-Bromobutyl)-2-[dimethyl(3-methyl-3-butenyl)-silyl]-1,3-dithiane (6d). According to the procedure for the synthesis of **8a**, 1.56 g (6.34 mmol) of **5d** was alkylated with 5.00 mL (37.3 mmol) of 1,4-dibromobutane to give 1.23 g (51%) of **6d** as a pale yellow liquid: IR (neat) 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 6H, $SiCH_3$), 0.84–0.92 (m, 2H, $SiCH_2$), 1.60–1.73 (m, 2H), 1.73 (s, 3H, $=CCH_3$), 1.85–1.96 (m, 3H), 2.02–2.08 (m, 3H), 2.17–2.24 (m, 2H, $=CCH_2$), 2.43 (dt, $J=14$, 3.6 Hz, 2H, $SCH_{2(eq)}$), 3.00 (td, $J=14$, 2.8 Hz, 2H, $SCH_{2(ax)}$), 3.44 (t, $J=6.4$ Hz, 2H, CH_2Br), 4.66 (br s, 1H, $=CH_2$), 4.70 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.2 (CH_3), 11.8 (CH_2), 22.4 (CH_3), 23.6 (CH_2), 25.2 (CH_2), 26.4 (CH_2), 32.1 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 36.6 (CH_2), 38.8 (C), 108.6 (CH_2), 148.0 (C); HRMS (FAB) calcd for $C_{15}H_{30}{}^{79}BrS_2Si$ $(M+H)^+$ *m/z* 381.0742, found 381.0741.

3.2.6. 5-Bromo-1-[dimethyl(3-methyl-3-butenyl)silyl]-pentan-1-one (8d). According to the procedure for the synthesis of **8c**, 0.12 g (0.31 mmol) of **6d** was hydrolyzed with 0.52 g (0.95 mmol) of ceric ammonium nitrate to give 72.3 mg (80%) of **8d** as a pale yellow liquid: IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 6H, $SiCH_3$), 0.81–0.87 (m, 2H, $SiCH_2$), 1.60–1.71 (m overlapped with a s at 1.70, 5H, CCH_3 and others), 1.76–1.84 (m, 2H), 1.95–2.01 (m, 2H, $=CCH_2$), 2.61 (t, $J=7$ Hz, 2H, $COCH_2$), 3.37 (t, $J=6.8$ Hz, 2H, CH_2Br), 4.67 (br s, 2H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6 (CH_3), 11.7 (CH_2), 20.8 (CH_2), 22.2 (CH_3), 31.5 (CH_2), 32.3 (CH_2), 33.5 (CH_2), 47.7 (CH_2), 109.0 (CH_2), 147.2 (C), 246.6 (C); HRMS (FAB) calcd for $C_{12}H_{24}{}^{79}BrOSi$ $(M+H)^+$ *m/z* 291.0780, found 291.0785.

3.2.7. 2-(5-Bromopentyl)-2-[dimethyl(2-methyl-2-propenyl)silyl]-1,3-dithiane (7c). According to the procedure for the synthesis of **8a**, 3.1 g (13.3 mmol) of **5c** was alkylated with 5.00 mL (37.3 mmol) of 1,5-dibromopentane to give 3.36 g (66%) of **7c** as a pale yellow liquid: IR (neat) 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 6H, $SiCH_3$), 1.42–1.55 (m, 4H), 1.70 (s, 3H, $=CCH_3$), 1.76 (s, 2H, $SiCH_2$), 1.86–1.95 (m, 3H), 1.98–2.06 (m, 1H), 2.15–2.21 (m, 2H), 2.43 (dt, $J=14$, 3.2 Hz, 2H, $SCH_{2(eq)}$), 2.99 (td, $J=14$, 2.8 Hz, 2H, $SCH_{2(ax)}$), 3.41 (t, $J=7.2$ Hz, 2H, CH_2Br), 4.51 (br s, 1H, $=CH_2$), 4.62 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.0 (CH_3), 23.6 (CH_2), 24.6 (CH_2), 25.1 (CH_2), 25.5 (CH_3), 27.1 (CH_2), 28.8 (CH_2), 32.7 (CH_2), 33.9 (CH_2), 37.5 (CH_2), 38.8 (C), 109.5 (CH_2), 142.6

(C); HRMS (FAB) calcd for $C_{15}H_{29}{}^{79}BrS_2Si$ *m/z* 380.0663, found 380.0663.

3.2.8. 6-Bromo-1-[dimethyl(2-methyl-2-propenyl)silyl]-hexan-1-one (9c). According to the procedure for the synthesis of **8c**, 3.31 g (8.68 mmol) of **7c** was hydrolyzed with 12.2 g (22.3 mmol) of ceric ammonium nitrate to give 0.97 g (38%) of **9c** as a pale yellow liquid: IR (neat) 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 6H, $SiCH_3$), 1.33–1.42 (m, 2H), 1.47–1.57 (m, 3H), 1.66 (s, 3H, $=CCH_3$), 1.69 (s, 2H, $SiCH_2$), 1.83 (quintet, $J=7.2$ Hz, 2H), 2.60 (t, $J=7$ Hz, 2H, $COCH_2$), 3.37 (t, $J=6.8$ Hz, 2H, CH_2Br), 4.48 (br s, 1H, $=CH_2$), 4.61 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.3 (CH_3), 21.2 (CH_2), 25.1 (CH_2), 25.2 (CH_3), 27.9 (CH_2), 32.7 (CH_2), 33.7 (CH_2), 48.8 (CH_2), 109.6 (CH_2), 141.7 (C), 246.4 (C); HRMS (FAB) calcd for $C_{12}H_{24}{}^{79}BrOSi$ $(M+H)^+$ *m/z* 291.0780, found 291.0774.

3.2.9. 2-(5-Bromopentyl)-2-[dimethyl(3-methyl-3-butenyl)-silyl]-1,3-dithiane (7d). According to the procedure for the synthesis of **8a**, 1.44 g (5.84 mmol) of **5c** was alkylated with 2.2 mL (16 mmol) of 1,5-dibromopentane to give 1.97 g (85%) of **7d** as a pale yellow liquid: IR (neat) 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.17 (s, 6H, $SiCH_3$), 0.85–0.91 (m, 2H, $SiCH_2$), 1.44–1.56 (m, 4H), 1.72 (s, 3H, $=CCH_3$), 1.85–1.94 (m, 3H), 1.95–2.07 (m, 3H), 2.16–2.22 (m, 2H, $=CCH_2$), 2.43 (dt, $J=13.5$, 4 Hz, 2H, $SCH_{2(eq)}$), 3.00 (td, $J=13.5$, 2.8 Hz, 2H, $SCH_{2(ax)}$), 3.41 (t, $J=6.8$ Hz, 2H, CH_2Br), 4.66 (br s, 1H, $=CH_2$), 4.70 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.1 (CH_3), 11.9 (2°), 22.3 (CH_3), 23.6 (CH_2), 25.2 (CH_2), 27.1 (CH_2), 28.8 (CH_2), 32.1 (CH_2), 32.7 (CH_2), 33.9 (CH_2), 37.5 (CH_2), 38.9 (C), 108.6 (CH_2), 148.0 (C); HRMS (FAB) calcd for $C_{16}H_{32}{}^{81}BrS_2Si$ $(M^+ + H)$ *m/z* 397.0878, found 397.0878.

3.2.10. 6-Bromo-1-[dimethyl(3-methyl-3-butenyl)silyl]-hexan-1-one (9d). According to the procedure for the synthesis of **8c**, 0.24 g (0.61 mmol) of **7d** was hydrolyzed with 0.99 g (1.8 mmol) of ceric ammonium nitrate to give 119 mg (64%) of **9d** as a pale yellow liquid: IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 6H, $SiCH_3$), 0.81–0.87 (m, 2H, $SiCH_2$), 1.38 (quintet, $J=7$ Hz, 2H), 1.53 (quintet, $J=7$ Hz, 2H), 1.70 (s, 3H, $=CCH_3$), 1.83 (quintet, $J=7$ Hz, 2H), 1.95–2.01 (m, 2H, $=CCH_2$), 2.60 (t, $J=7$ Hz, 2H, $COCH_2$), 3.38 (t, $J=7$ Hz, 2H, CH_2Br), 4.67 (br s, 2H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6 (CH_3), 11.7 (CH_2), 21.2 (CH_2), 22.2 (CH_3), 28.0 (CH_2), 31.6 (CH_2), 32.8 (CH_2), 33.7 (CH_2), 48.7 (CH_2), 108.9 (CH_2), 147.3 (C), 247.1 (C); HRMS (FAB) calcd for $C_{13}H_{26}{}^{79}BrOSi$ $(M+H)^+$ *m/z* 305.0936, found 305.0934.

3.3. General procedure for intramolecular radical cyclizations and oxidations: cyclization of 8a followed by oxidation. 1-(2-Hydroxy-1-methyl)ethylcyclopentanol (17)

To a refluxing solution of 150 mg (0.57 mmol) of **8a** in 2.5 mL of benzene was added via syringe pump over 2.5 h a solution of 0.18 mL (0.68 mmol) of tributyltin hydride and 5.0 mg (0.031 mmol) of AIBN in 6 mL of benzene. The resulting solution was heated for another 2 h and then cooled to room temperature. Gas chromatographic analysis (oven tempertature = 130 °C; flow rate = 28 mL/min) of the reaction mixture showed the presence of **11** ($t_R=6.4$ min), **13** ($t_R=7.3$ min), and **12** ($t_R=8.1$ min) in a ratio of 1:3:8.3, respectively. The reaction mixture was concentrated in vacuo. The residue was mixed with 626 mg (6.26 mmol) of potassium bicarbonate, 0.68 mL (23 mmol) of hydrogen peroxide, 8 mL of methanol, and 8 mL of THF. The resulting mixture was stirred at 66 °C for 19 h and then partitioned between 50 mL of dichloromethane and 30 mL of water. The aqueous phase was extracted with dichloromethane (50 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with hexane/ethyl acetate, 7/3, 6/4, 4/6 in sequence) to give 16 mg (20%) of the less polar **17** as a colorless oil: IR (neat) 3431 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (d, $J=7$ Hz, 3H), 1.38–1.95 (m, 9H), 3.00 (br s, 2H), 3.62 (dd, $J=10.5$, 5 Hz, 1H), 3.84 (dd, $J=10.5$, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8, 23.5, 23.8, 37.2, 39.2, 42.3, 66.9, 86.1; HRMS calcd for $C_8H_{16}O_2$ *m/z* 144.1150, found 144.1140. Continued elution gave 31 mg (38%) of the more polar **16**[12] as a pale yellow oil.

3.3.1. Cyclization of 9a followed by oxidation: 1-(3-hydroxypropyl)cyclohexanol (22) and 1-(2-hydroxy-1-methylethyl)cyclohexanol (23). According to the general procedure for cyclization and oxidation, the reaction of 100 mg (0.36 mmol) of **9a** afforded 14 mg (25%) of **23** as a colorless oil, and 31 mg (55%) of the more polar **22**.[29] **22**: ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.3, 25.8, 26.1, 37.5, 38.8, 63.3, 71.1. **23**: IR (neat) 3347 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (d, $J=7$ Hz, 3H), 1.02–1.75 (m, 11H), 2.56 (br s, 2H), 3.66 (dd, $J=11$, 6 Hz, 1H), 3.77 (dd, $J=11$, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.1, 21.6, 21.7, 25.7, 32.7, 36.5, 42.9, 65.4, 74.8; HRMS calcd for $C_9H_{18}O_2$ *m/z* 158.1307, found 158.1305.

3.3.2. Cyclization of 8b followed by oxidation: 1-(4-hydroxybutyl)cyclopentanol (24) and 1-(3-hydroxy-1-methylpropyl)cyclopentanol (25). According to the general procedure for cyclization and oxidation, the reaction of 250 mg (0.90 mmol) of **8b** afforded 4 mg (3%) of **25** as a colorless oil, and 96 mg (67%) of the more polar **24**.[12] **24**: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 23.8, 33.1, 39.7, 41.0, 62.7, 82.5. **25**: IR (neat) 3370 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (d, $J=7$ Hz, 3H), 1.20–1.95 (m, 13H), 3.55–3.70 (m, 1H), 3.73–3.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.7, 23.8, 23.9, 35.3, 38.3, 38.8, 39.7, 60.5, 85.2; HRMS calcd for $C_9H_{16}O$ $(M-H_2O)$ *m/z* 140.1201, found 140.1207.

3.3.3. Cyclization of 9b followed by oxidation: 1-(4-hydroxybutyl)cyclohexanol (26). According to the general procedure for cyclization and oxidation, the reaction of 70 mg (0.24 mmol) of **9b** afforded 31 mg (78%) of **26**[29]: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.2, 25.8, 29.7, 33.0, 37.4, 41.7, 62.7, 71.7.

3.3.4. Cyclization of 8c: 7,7,9-trimethyl-6-oxa-7-sila-spiro-[4.5]decane (30). According to the general procedure for cyclization, 181 mg (0.653 mmol) of **8c** reacted with 0.24 mL (0.85 mmol) of tributyltin hydride to give 95 mg

(74%) of **30** as a pale yellow liquid: IR (neat) 1456, 1252, 1029, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.23 (t, $J=14$ Hz, 1H, $SiCH_2$), 0.67 (br d, $J=14$ Hz, 1H, $SiCH_2$), 0.98 (d, $J=6.4$ Hz, 3H, $CHCH_3$), 1.29 (t, $J=13$ Hz, 1H, $CHCH_2$), 1.41–1.59 (m, 5H, $CHCH_2$ and others), 1.62–1.79 (m, 4H), 1.81–1.95 (m, 1H, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.20 (CH_3), 22.8 (CH_2), 23.2 (CH_2), 24.3 (CH_2), 26.4 (CH), 27.5 (CH_3), 38.5 (CH_2), 43.3 (CH_2), 47.8 (CH_2), 84.8 (C); MS (rel intensity) *m/z* 198 (M^+, 10), 183 (43), 169 (80), 156 (63), 141 (65), 127(81), 113 (14), 75 (100), 61 (23); HRMS calcd for $C_{11}H_{22}OSi$ 198.1434, found 198.1439.

3.3.5. Cyclization of 9c: 2,2,4-trimethyl-1-oxa-2-sila-spiro[5.5]undecane (33). According to the general procedure for cyclization, 353 mg (1.21 mmol) of **9c** reacted with 0.45 mL (1.7 mmol) of tributyltin hydride to give 58 mg (23%) of **33** as a pale yellow liquid: IR (neat) 1450, 1252, 1041, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 0.19 (t, $J=13$ Hz, 1H, SiCH), 0.66 (dq, $J=13$, 2 Hz, 1H, SiCH), 0.95 (d, $J=6.4$ Hz, 3H, $CHCH_3$), 1.00 (dd, $J=13$, 2 Hz, 1H, $CHCH_3$), 1.18–1.40 (m, 6H), 1.42–1.77 (m, 5H), 1.84–1.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.50 (CH_3), 1.55 (CH_3), 22.2 (CH_2), 22.4 (CH_2), 23.1 (CH_2), 24.1 (CH), 26.3 (CH_2), 27.6 (CH_3), 36.6 (CH_2), 42.1 (CH_2), 48.4 (CH_2), 74.1 (C); MS (rel intensity) *m/z* 212 (M^+, 40), 197 (27), 183 (37), 169 (100), 156 (81), 141 (45), 127 (89); 75 (66); HRMS calcd for $C_{12}H_{24}OSi$ 212.1591, found 212.1595.

3.3.6. Cyclization of 9c followed by oxidation: 1-(3-hydroxy-2-methylpropyl)cyclohexanol (36).[30] According to the general procedure for cyclization followed by direct oxidation, 308 mg (1.05 mmol) of **9c** reacted with 0.38 mL (1.4 mmol) of tributyltin hydride to give 112 mg (62%) of **36** as a pale yellow liquid: IR (neat) 3306 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76 (d, $J=6.8$ Hz, 3H, CH_3), 1.06–1.65 (m, 13H), 1.76–1.88 (m, 1H), 2.59 (br s, 1H, OH), 3.22 (dd, $J=10.4$, 9.2 Hz, 1H, OCH_2), 3.46 (dd, $J=10.4$, 3.6 Hz, 1H, OCH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8 (CH_3), 22.3 (CH_2), 22.6 (CH_2), 25.9 (CH_2), 30.9 (CH), 36.0 (CH_2), 40.1 (CH_2), 48.1 (CH_2), 69.2 (CH_2), 71.6 (C).

3.3.7. Cyclization of 8d: 7,7,10-trimethyl-6-oxa-7-sila-spiro[4.6]undecane (37) and (cyclopentyloxy)(dimethyl)(3-methyl-3-butenyl)silane (38). According to the general procedure for cyclization, 289 mg (0.99 mmol) of **8d** reacted with 0.35 mL (1.3 mmol) of tributyltin hydride to give 144 mg (69%) of **37** as a pale yellow liquid: IR (neat) 1457, 1251, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.62–0.67 (m, 2H, $SiCH_2$), 0.92 (d, $J=6$ Hz, 3H, $CHCH_3$), 1.22–1.33 (m, 1H, $CHCH_3$), 1.37–1.58 (m, 5H), 1.64–1.84 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.5 (CH_3), 1.1 (CH_3), 16.4 (CH_2), 23.5 (CH_2), 23.8 (CH_2), 25.3 (CH_3), 32.4 (CH_2), 33.1 (CH), 38.7 (CH_2), 43.6 (CH_2), 50.2 (CH_2), 84.8 (C); MS (rel intensity) *m/z* 212 (M^+, 26), 197 (23), 183 (100), 169 (61), 155 (41), 142 (44), 127 (64); 75 (57); HRMS calcd for $C_{12}H_{24}OSi$ 212.1591, found 212.1597. We also isolated 15 mg (7%) of **38** as a pale yellow liquid: IR (neat) 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 6H, $SiCH_3$), 0.68–0.75 (m, 2H, $SiCH_2$), 1.41–1.56 (m, 4H), 1.66–1.78 (m overlapped with a s at 1.71, 7H, CCH_3 and others), 1.96–2.03 (m, 2H, $CH_2C=$), 4.19 (quintet, $J=4.8$ Hz, 1H, OCH), 4.64 (br s, 1H, $=CH_2$), 4.68 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.4 (CH_3), 15.0 (CH_2), 22.3 (CH_3), 23.3 (CH_2), 31.3 (CH_2), 35.7 (CH_2), 74.3 (CH), 108.3 (CH_2), 148.3 (C); MS (rel intensity) *m/z* 212(M^+, 3), 197 (13), 143 (97), 111 (39), 101 (21), 85 (11), 75 (100), 67 (8), 59 (38); HRMS calcd for $C_{12}H_{24}OSi$ 212.1591, found 212.1595.

3.3.8. Cyclization of 9d: 8,8,11-trimethyl-7-oxa-8-sila-spiro[5.6]dodecane (40), (cyclohexyloxy)(dimethyl)(3-methyl-3-butenyl)silane (41) and 1-[dimethyl(3-methyl-3-butenyl)silyl]hexan-1-one (42). According to the general procedure for cyclization, 250 mg (0.82 mmol) of **9d** reacted with 0.29 mL (1.1 mmol) of tributyltin hydride to give 74 mg (40%) of **40** as a pale yellow liquid: IR (neat) 1449, 1252, 1053, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.57–0.63 (m, 2H, $SiCH_2$), 0.91 (d, $J=6.4$ Hz, 3H, $CHCH_3$), 1.16–1.50 (m, 10H), 1.54–1.68 (m, 3H), 1.71–1.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.07 (CH_3), 1.14 (CH_3), 16.0 (CH_2), 22.5 (CH_2), 22.8 (CH_2), 25.2 (CH_3), 26.3 (CH_2), 30.0 (CH), 32.4 (CH_2), 37.1 (CH_2), 41.7 (CH_2), 50.2 (CH_2), 74.1 (C); MS (rel intensity) *m/z* 226 (M^+, 56), 211 (14), 183 (100), 170 (33), 157 (72), 142 (28), 127 (37); 75 (81); HRMS calcd for $C_{13}H_{26}OSi$ 226.1747, found 226.1753. We also isolated 15 mg (8%) of **41** as a pale yellow liquid: IR (neat) 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 6H, $SiCH_3$), 0.68–0.75 (m, 2H, $SiCH_2$), 1.05–1.33 (m, 6H), 1.45–1.54 (m, 2H), 1.65–1.80 (m overlapped with a s at 1.71, 5H, $=CCH_3$ and others), 1.96–2.04 (m, 2H, $CH_2C=$), 3.49–3.57 (m, 1H, OCH), 4.64 (br s, 1H, $=CH_2$), 4.68 (br s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −1.3 (CH_3), 15.2 (CH_2), 22.3 (CH_3), 24.6 (CH_2), 25.7 (CH_2), 31.3 (CH_2), 36.2 (CH_2), 71.1 (CH), 108.3 (CH_2), 148.3 (C); MS (rel intensity) *m/z* 226 (M^+, 3), 211 (12), 157 (100), 143 (9), 127 (12), 111 (30), 99 (16), 75 (100), 59 (25); HRMS calcd for $C_{13}H_{26}OSi$ 226.1747, found 226.1754. In addition was isolated 13 mg (7%) of **42** as a pale yellow liquid: IR (neat) 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 6H, $SiCH_3$), 0.80–0.89 (m, 5H, $SiCH_2$ and others), 1.16–1.33 (m, 4H), 1.49 (quintet, $J=7.6$ Hz, 2H), 1.70 (s, 3H, $=CCH_3$), 1.94–2.02 (m, 2H, $=CCH_2$), 2.56 (t, $J=7.2$ Hz, 2H, $COCH_2$), 4.64–4.68 (two overlapped br s at 4.65 and 4.67, 2H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.5 (CH_3), 11.8 (CH_2), 14.1 (CH_3), 21.9 (CH_2), 22.2 (CH_3), 22.7 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 49.0 (CH_2), 108.9 (CH_2), 147.3 (C), 247.8 (C); HRMS (FAB) calcd for $C_{13}H_{27}OSi$ $(M+H)^+$ *m/z* 227.1831, found 227.1833.

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Carbon dendron nano-chains with π-extended conjugation based on end-capped *N*,*N*-dimethylamino in linear 1,4-phenylethynyl or in 1,5-naphthylethynyl subunits: fluorescence analysis

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Abstract—The synthesis of dendrons with the end-capped 5-(*N*,*N*-dimethylamino)naphthyl-1-ethynyl unit connected to conjugated naphthylethynyl or *p*-phenylethynyl chains, as the branches of the 1,3,5-substituted benzene core, have been undertaken by heterocoupling reaction between 1,3,5-triiodobenzene and the convenient end-capped 5-(*N*,*N*-dimethylamino)naphthylacetylene or 5-(*N*,*N*-dimethylamino)naphthylethynylphenylacetylene in the presence of the palladium–copper catalyst system, in excellent yields. The influence of the alternating naphthylethynyl–phenylethynyl chains on the fluorescence emission radiation, in the dendron structures, has been analyzed.

1. Introduction

Hyperbranched polymers and dendrimers are highly branched macromolecules that have received considerable attention.[1–5] Dendrimers are synthesized by multistep reactions requiring tedious purification, whereas hyperbranched polymers are prepared by one-step polymerization resulting in less regular structures. An undesirable feature of the one-step polymerization is the loss of control in molecular weight, accompanied by broad molecular weight distributions[6] and possible intramolecular cyclization.[7]

The convergent method for synthesizing dendrons and dendrimers had been reported by Hawker and Fréchet,[8] and this appeared to be the best method for making well-defined structures.

The area of highly conjugated, all-carbon and carbon-rich macromolecules continues to be of intense attention.[9] The synthesis and characterization of nanometer-sized conjugated molecules of precise length and constitution are of wide-spread interest, which is due to their inherent synthetic flexibility which permits the design of molecular architectures with important properties.[10,11] Molecules showing π-extended conjugation, in general, can present electroconductive, magnetic and optical properties.[12] A variety of potential applications such as artificial photosynthesis,[13] photocatalysis,[14] molecular photovoltaic cells,[15] molecular informatics,[16] and optoelectronic devices,[17,18] are beginning to emerge from this new field of research.

Conjugated systems integrated by 1,4-diethynyl or 1,3,5-triethynylphenyl units have been used in the preparation of aromatic oligomers bearing multiple ethynyl groups that exhibit electroluminescence properties,[19] poly(phenylvinylene) with fluorescence properties as well as dendrimers[20] with poly(yne) chain.[21] The triple bond play the role of a wire while the polyaromatic system behaves as an energy relay subunit.

We now report the controlled synthesis of a novel family of rigid conjugated dendron nanostructures with a controlled geometry and the fluorescence properties.

2. Results and discussion

The syntheses of the end-capped 5-(*N*,*N*-dimethylamino)-naphthylacetylenes (**1**, **2** and **3**) designed as the branches of the 1,3,5-benzene dendron structures were carried out by the heterocoupling between the terminal naphthylacetylene and 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol,[22] in presence of $PdCl_2(PPh_3)_2$ and Cu_2I_2 catalyst system, in NEt_3, Scheme 1.

Compound **1** was obtained by heterocoupling reaction between 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine and

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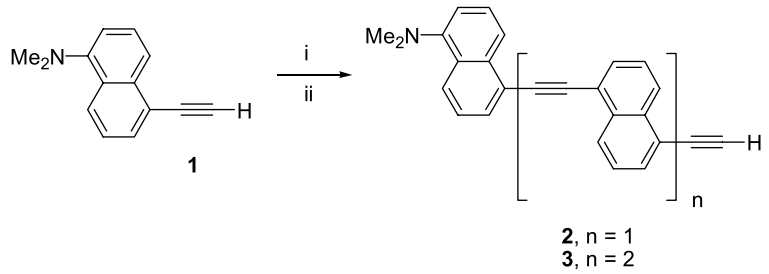


Scheme 1. (i) $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3, 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol. (ii) NaOH, toluene, at the reflux temperature.

2-methyl-3-butyn-2-ol in NEt_3, catalyzed by the palladium–copper system to give the propargyl intermediate, which by treatment with a catalytic amount of powdered NaOH in toluene, at the reflux temperature, gives **1** as a dark amber solid, in practically quantitative yield.

The naphthylacetylene homologue **2** was satisfactory obtained by the heterocoupling between the terminal acetylene **1** and 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol in NEt_3, catalyzed by the palladium–copper system, under a rigorous carbon dioxide atmosphere,[23] to give the propargyl intermediate, which by treatment with a catalytic amount of powdered NaOH in toluene at the reflux temperature gives **2**, as a yellow solid, in practically quantitative yield. Under the palladium catalytic conditions, compound **1** was really sensitive to the homocoupling reaction to give the 1,3-diyne derivative, which was avoided by use of a compatible carbon dioxide atmosphere.[23]

Compound **3** was obtained by the heterocoupling between the terminal acetylene **2** and 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol, in NEt_3 under argon atmosphere, catalyzed by the palladium–copper system, giving the propargyl intermediate, which by catalytic treatment with powdered NaOH, in toluene at the reflux temperature affords **3** in quantitative yield.

The end-capped 5-(*N*,*N*-dimethylamino)naphthylacetylenes (**1**–**3**) show fluorescence emission spectra with an important quantum yield in dichloromethane, Table 1.

The analysis of the fluorescence emission spectra allows to some remarkable facts: (i) compounds **1** and **2** show only a broad emission band while **3** shows two bands; (ii) the emission bands of the compound **2** and the first band of **3** show a normal Stokes shift for conjugated naphthalene rings, while **1** and the second band of **3** show a large anomalous Stokes shift; (iii) the fluorescence quantum yields are considerable though a significant slight decreasing for compound **2**. These dual fluorescence and fast intramolecular charge transfer (ICT) effect were observed in *N*,*N*-dialkylaminophenyl[24] or naphthyl[25] derivatives.

The end-capped 5-(*N*,*N*-dimethylamino)naphthalenes connecting with *p*-phenylethynyl chains as **5** and **7** were designed as the branches of the 1,3,5-benzene dendron structures. The synthesis was carried out by the heterocoupling between the appropriate terminal acetylene and 4-(*p*-iodophenyl)-2-methyl-3-butyn-2-ol,[26] Scheme 2.

Thus, 5-[(4-ethynyl-1-phenyl)ethynyl]-*N*,*N*-dimethylnaphthalen-1-amine (**5**) was obtained in excellent yield,[27] by the heterocoupling between the terminal acetylene **1** and 4-(*p*-iodophenyl)-2-methyl-3-butyn-2-ol in NEt_3, in the presence of the palladium–copper system, under a rigorous carbon dioxide atmosphere,[23] to give 4-(4-{[5-(*N*,*N*-dimethylamino)-1-naphthyl]ethynyl}-1-phenyl)-2-methyl-3-butyn-2-ol (**4**), which was treated with a catalytic amount of powdered NaOH in toluene, at the reflux temperature.

The naphthylacetylene **7** was satisfactory obtained by the heterocoupling between the terminal acetylene **5** and 4-(*p*-iodophenyl)-2-methyl-3-butyn-2-ol in NEt_3, under argon atmosphere, catalyzed by the palladium–copper system, yielding the propargyl intermediate **6**, followed the treatment with a catalytic amount of powdered NaOH in toluene, at the reflux temperature.

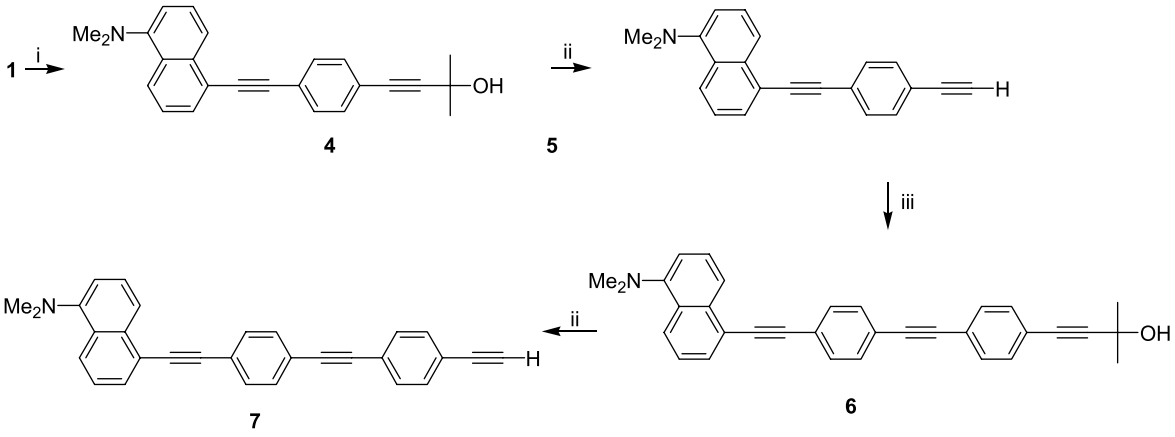
The ultraviolet–visible absorption and fluorescence emission spectra of the end-capped 5-(*N*,*N*-dimethylamino)-naphthalenes with *p*-phenylethynyl chains (**5** and **7**) are summarized in Table 2.

In contrast with the naphthylacetylenes **1**, **2** and **3** the conjugated naphthylethynylphenyl acetylenes **5** and **7** show fluorescence emission radiation with a large anomalous Stokes shift and the quantum yields strongly decreases.

Table 1. UV–vis and fluorescence spectra of compounds **1**, **2** and **3**

Compound	UV–vis[a] (CH_2Cl_2) λ_{max}, nm	ε (M^{-1} cm^{-1})	F[b] (CH_2Cl_2) λ_{max}, nm	Φ_f
1	336	2200	463	0.63[c]
2	343	23,100	397	0.55[d]
3	363	26,600	398 and 414	0.65[d]

[a] At room temperature.
[b] At room temperature and [c] $\cong 10^{-8}$ M.
[c] Fluorescence quantum yield in dichloromethane relative to quinine sulfate in 1 N H_2SO_4.
[d] Fluorescence quantum yield was in dichloromethane relative to 2-aminopyridine in 0.1 N H_2SO_4.



Scheme 2. (i) $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3, 4-(*p*-iodophenyl)-2-methyl-3-butyn-2-ol, CO_2 atmosphere. (ii) NaOH, toluene, at the reflux temperature. (iii) $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3, 4-(*p*-iodophenyl)-2-methyl-3-butyn-2-ol.

Table 2. UV–vis and fluorescence spectra of compound **5** and **7**

Compound	UV–vis[a] (CH_2Cl_2) λ_{max}, nm	ε (M^{-1} cm^{-1})	F[b] (CH_2Cl_2) λ_{max}, nm	Φ_f[c]
5	354	18,300	510	0.32
7	364	32,800	529	0.23

[a] At room temperature.
[b] At room temperature and [c] $\cong 10^{-8}$ M.
[c] Fluorescence quantum yield in dichloromethane relative to quinine sulfate in 1 N H_2SO_4.

Moreover, the quantum yield also decreases with the number of the ethynylphenyl units (**5** and **7**).

Now, the synthesis of the end-capped 5-(*N*,*N*-dimethylamino)naphthylethynyl dendrons with 1,3,5-trisubstituted benzene core and naphthylethynyl or *p*-phenylethynyl chains were satisfactory carried out by heterocoupling between the terminal naphthylacetylenes (**1**, **2** and **3**) or phenylacetylenes (**5** and **7**) and 1,3,5-triiodobenzene,[28] in NEt_3 under argon atmosphere, in the presence of the palladium–copper catalyst system.

Thus, the heterocoupling reaction between the terminal acetylenes (**1**–**3**) with 1,3,5-triiodobenzene affords 5-(*N*,*N*-dimethylamino)naphthylethynyl dendron nanostructures **8**–**10**, as orange solids: compound **8** ($n=0$) (85%) and compound **9** ($n=1$) (81%). Only for the heterocoupling between **1** and 1,3,5-triiodobenzene was necessary a rigorous carbon dioxide atmosphere, to avoid the homocoupled 1,3-butadiyne product,[23] while, the heterocoupling between the terminal acetylene **3** and 1,3,5-triiodobenzene was carried out under argon atmosphere, in pyridine at reflux temperature, giving **10** ($n=2$) in modest yield (30%), Scheme 3.

On the other hand, the synthesis of the end-capped 5-(*N*,*N*-dimethylamino)naphthylethynylphenylethynyl dendrons, with the more sterically alleviate *p*-phenylethynyl chains, was satisfactory carried out by heterocoupling between the terminal naphthylethynylphenylacetylenes (**5** and **7**) and 1,3,5-triiodobenzene, in NEt_3 under argon atmosphere, in the presence of the palladium–copper catalyst system. Compounds **11** ($n=1$, 79%) and **12** ($n=2$, 62%) were isolated as dark yellow solids, Scheme 4.

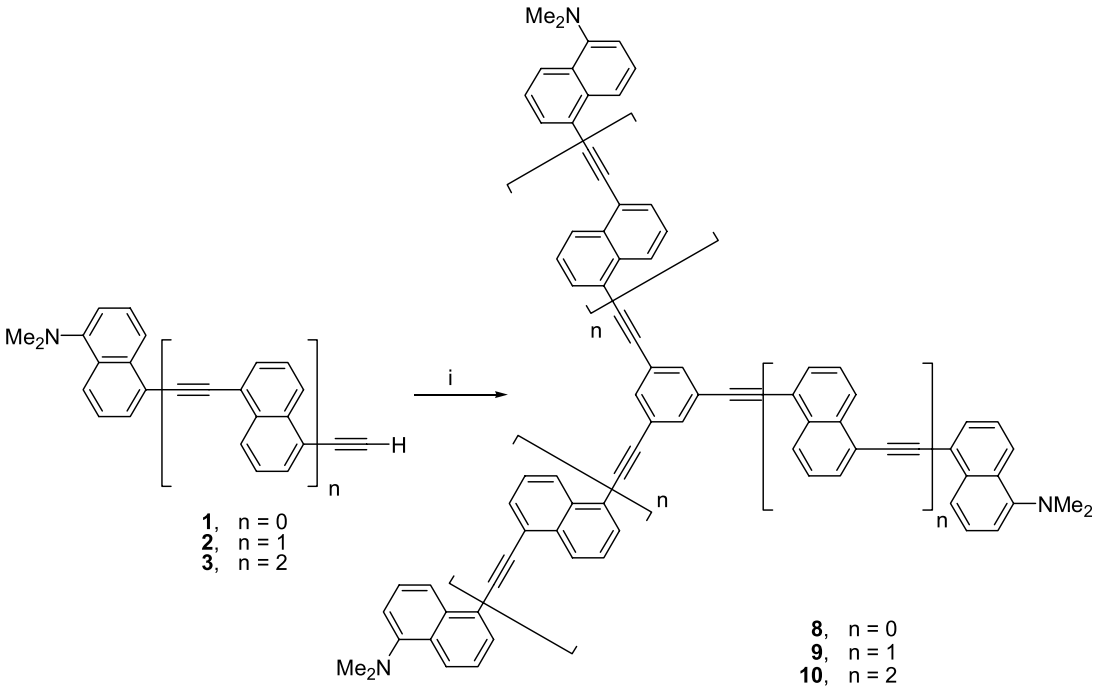
The ultraviolet–visible absorption and fluorescence emission spectra of the end-capped 5-(*N*,*N*-dimethylamino)-naphthylethynyl dendrons with 1,3,5-trisubstituted benzene core and naphthylethynyl or *p*-phenylethynyl chains are summarized in Table 3.

The conjugated compounds **8**–**12** show fluorescence emission radiation with a large anomalous Stokes shift as their terminal acetylene parents **1**, **2**, **3**, **5** and **7**. The quantum yields of the naphthylethynyl–naphthyl or naphthylethynyl–phenyl dendron families decrease with the conjugated size chain **8**–**10** and **11**–**12**. It has been postulated in *N*,*N*-dialkylaminophenyl or *N*,*N*-dialkylaminonaphthylderivatives, that the dimethylamino group undergoes an important twist relative to the conjugated system, giving large anomalous Stokes shift with quantum yield decreasing.[24,25] Hence the anomalous Stokes shift observed are due to an intramolecular charge transfer (ICT) or a twisted ICT (TICT) produced by the presence of the donor *N*,*N*-dimethylamino group.

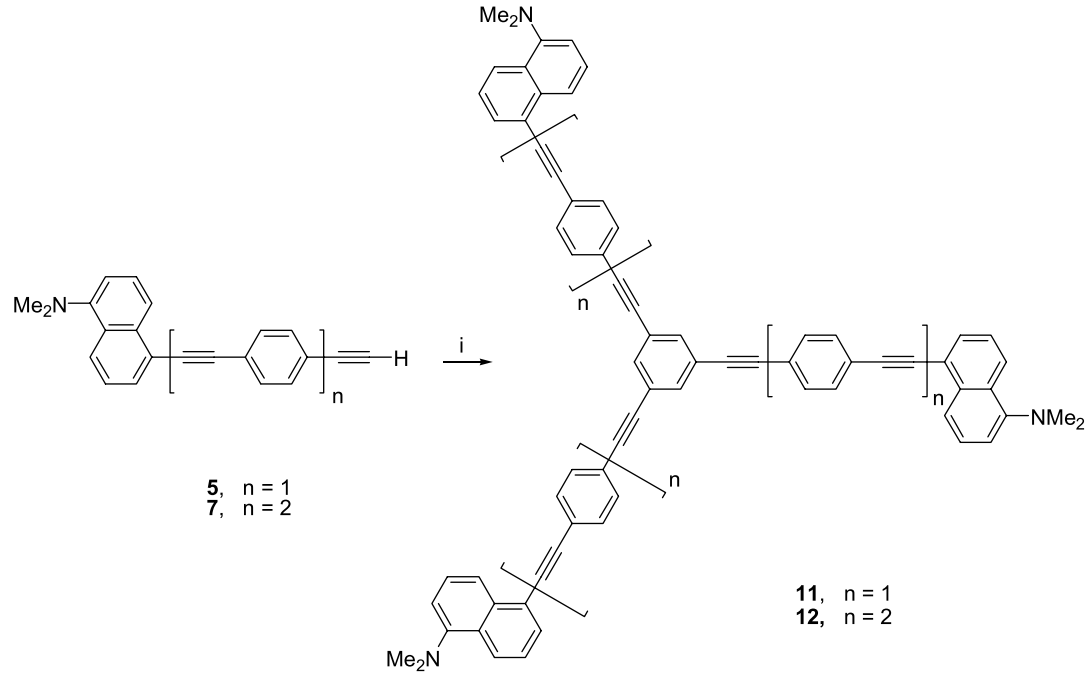
3. Conclusions

The synthesis of extended chain conjugated naphthylethynyl and phenylethynyl dendron structures have been designed to improve the fluorescent properties. The end-capped 5-(*N*,*N*-dimethylamino)naphthyl-1-ethynyl connected to conjugated phenylethynyl units show a constant quantum yield with the increasing of the number of phenylethynyl units.

An efficient divergent–convergent synthesis methodology for the preparation of dendrons with the end-capped 5-(*N*,*N*-dimethylamino)naphthyl-1-ethynyl moiety connected to



Scheme 3. (i) 1,3,5-Triiodobenzene, $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3.



Scheme 4. (i) 1,3,5-Triiodobenzene, $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3.

conjugated naphthylethynyl or *p*-phenylethynyl chains as the branches of the 1,3,5- substituted benzene core, have been carried out by the heterocoupling reaction between 1,3,5-triiodobenzene and the corresponding end-capped 5-(*N*,*N*-dimethylamino)naphthylacetylene or 5-(*N*,*N*-dimethylamino)naphthylethynylphenylacetylene in the presence of the palladium–copper catalyst system, in excellent yields. The naphthylethynyl–naphthyl and naphthylethynyl–phenyl conjugated families show fluorescence properties with a large anomalous Stoke shift due to a ICT or TICT effect due to the presence of the donor *N*,*N*-dimethylamino group. The quantum yields of the fluorescence emission radiation of the *N*,*N*-(dimethylamino)naphthylethynyl chains show an important decreasing with the conjugated size chain in the dendron structures.

Table 3. UV–vis and fluorescence spectra of the dendron structures **8**, **9**, **10**, **11** and **12**

Compound	UV–vis[a] (CH_2Cl_2) λ_{max}, nm	ε ($M^{-1}\,cm^{-1}$)	F[b] (CH_2Cl_2) λ_{max}, nm	Φ_f[c]
8	356	81,400	504	0.43
9	364	10,650	527	0.21
10	370	96,800	530	0.08
11	365	98,200	530	0.20
12	353	119,900	531	0.19

[a] At room temperature.
[b] At room temperature and [c] $\cong 10^{-8}$ M.
[c] Fluorescence quantum yield in dichloromethane relative to quinine sulfate in 1 N H_2SO_4.

4. Experimental

4.1. General

Melting points were determined in open capillaries using a Buchi or Reichert hot stage microscope and are uncorrected. IR spectra of solids were recorded as KBr pellets and IR spectra of oils were recorded as thin films on NaCl plates with a Bruker Vector 22 spectrophotometer, and the wave numbers are given in cm^{-1}. ^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker Aspect spectrometer. Chemical shifts are given in δ with TMS as an internal reference and constants coupling J are given in Hz, the solvent is $CDCl_3$. Mass spectra were recorded on a VG AutoSpec spectrometer at 70 eV and the MALDI-TOF spectra were recorded on a Bruker Reflex III spectrometer. The UV–vis spectra were recorded on a Hewlett–Packard 8453 spectrometer, frequencies are given in nm and ε in L mol^{-1} cm^{-1}. All fluorescence spectra were recorded at room temperature at 10^{-8} M on a SLM Aminco Bowman series 2, the fluorescence quantum yield was determined in dichloromethane on freshly prepared samples (air-equilibrated) with absorbances at the excitation wavelength (365 nm for the standard quinine sulfate). The samples quinine sulfate in 1 N H_2SO_4 and 2-aminopyridine in 0.1 N H_2SO_4 were employed as a standard ($\Phi_f=0.55$ and 0.66, respectively) to measure the fluorescence quantum yields, which were corrected taking into account the refractive indices of the solvents used. Yields are given after chromatography column separation on silica gel 60 (200–400 mesh) using the indicated solvents or solvent crystallization.

4.1.1. 5-Ethynyl-*N*,*N*-dimethylnaphthalen-1-amine (1).

4.1.1.1. (a) 4-[5-(*N*,*N*-Dimethylamino)-1-naphthyl]-2-methyl-3-butyn-2-ol (1a). General procedure for the cross-coupling reaction. To a solution of 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine (1 g, 3.4 mmol) and 2-methyl-3-butyn-2-ol (314 mg, 3.74 mmol) in freshly distilled $NHEt_2$ (or NEt_3) (40 mL), under argon atmosphere and at room temperature, was added $PdCl_2(PPh_3)_2$ (24 mg, 0.034 mmol) and Cu_2I_2 (0.5 mg, 0.003 mmol). The mixture was stirred for 15 h (monitored by TLC) and then, the amine was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution with a little amount of KCN, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration, the solvent was removed to give a brown solid, which was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (3:1). Compound **1a** was isolated as a dark amber oil, 840 mg (98%) yield. IR (film, cm^{-1}): 3398, 2220, 1409, 1165, 791. ^1H NMR ($CDCl_3$): δ 8.24 (d, 1H, $J=8.7$ Hz), 7.99 (d, 1H, $J=8.7$ Hz), 7.63 (d, 1H, $J=6.9$ Hz), 7.47 (t, 1H, $J=8.1$ Hz), 7.41 (dd, 1H, $J=6.9$, 8.7 Hz), 7.11 (d, 1H, $J=7.8$ Hz), 2.89 (s, 6H), 1.73 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.24, 134.64, 130.32, 128.58, 126.61, 125.01, 124.28, 120.75, 120.52, 114.49, 98.48, 80.69, 65.85, 45.29, 31.64. $C_{17}H_{19}NO$ (253.34). Anal. Calcd C 80.60, H 7.56, N 5.53. Found: C 80.74, H 7.44, N 5.68.

4.1.1.2. (b) 5-Ethynyl-*N*,*N*-dimethylnaphthalen-1-amine (1). General procedure for arylacetylenes. To a solution of **1a** (700 mg, 2.8 mmol) in anhydrous toluene (40 mL) was added finely powdered NaOH (12 mg, 0,28 mmol), under argon atmosphere, and the mixture was warmed at the reflux temperature for 10 h (monitored by TLC), and then filtered. The solvent was removed at reduced pressure and the solid residue was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:2) giving **1** as a dark amber solid, mp 50–51 °C, 545 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 229 (ε, 12,300), 254 (ε, 4800), 336 (ε, 2200). Fluorescence (CH_2Cl_2), λ_{max} (nm): 463 ($\phi=0.63$). IR (KBr, cm^{-1}): 3299, 2294, 1402, 791. ^1H NMR ($CDCl_3$): δ 8.46 (d, 1H, $J=$ 9.0 Hz), 8.31 (d, 1H, $J=8.4$ Hz), 7.93 (d, 1H, $J=7.2$ Hz), 7.64 (t, 1H, $J=7.8$ Hz), 7.56 (dd, 1H, $J=9.0$, 7.2 Hz), 7.21 (d, 1H, $J=7.5$ Hz), 3.65 (s, 1H), 2.89 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.15, 134.81, 131.05, 128.44, 126.77, 125.44, 124.10, 120.63, 119.92, 114.50, 82.21, 81.82, 45.06. COSY ($^1H/^1H$): 8.46/7.56/7.93/, 8.31/7.64/7.21. HETCORR ($^{13}C/^1H$): 131.05/7.93, 126.77/7.64, 125.44/8.46, 124.10/ 7.56, 120.63/8.31, 114.50/7.21. MS (70 eV): 195 (M^+, 100), 194 (43), 179 (7), 165 (3), 152 (31). $C_{14}H_{13}N$ (195.26). Anal. Calcd C 86.12, H 6.71, N 7.17. Found: C 85.92, H 6.86, N 7.02.

4.1.2. 5-[(5-Ethynyl-1-naphthyl)ethynyl]-*N*,*N*-dimethylnaphthalen-1-amine (2).

4.1.2.1. (a) 4-(5-{[5-(*N*,*N*-Dimethylamino)-1-naphthyl]ethynyl}-1-naphthyl)-2-methyl-3-butyn-2-ol (2a). General procedure for the cross-coupling reaction in CO_2 atmosphere. A dispersion of the components in dry triethylamine was placed in a Schlenk: compound **1** (100 mg, 0.51 mmol), 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol (171 mg, 0.51 mmol), NEt_3 (30 mL), $PdCl_2(PPh_3)_2$ (36 mg, 0.051 mmol) and Cu_2I_2 (1 mg, 0.0051 mmol). Then, carbonic dry-ice rods were added and maintained in slow sublimation until a white dense cloud was formed. The carbonic anhydride atmosphere was slowly displaced with an external stream of carbonic anhydride, bubbled through the dry triethylamine solution. The mixture was stirred at room temperature for 15 h (monitored by TLC) and then, the amine was removed under reduced pressure. The crude residue was washed with a

saturated aqueous ammonium chloride solution with a little amount of KCN, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration, the solvent was removed to give a brown solid, which was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (2:1). Compound **2a** was isolated as a pale yellow solid, mp 120–121 °C, 180 mg (87%) yield. IR (KBr, cm^{-1}): 3280, 2224, 1418, 1152, 782. ^1H NMR ($CDCl_3$): δ 8.57 (d, 1H, $J=8.4$ Hz), 8.34 (d, 1H, $J=7.5$ Hz), 8.32 (d, 1H, $J=7.8$ Hz), 8.26 (d, 1H, $J=8.7$ Hz), 7.92 (d, 1H, $J=6.9$ Hz), 7.88 (d, 1H, $J=7.5$ Hz), 7.72 (d, 1H, $J=7.2$ Hz), 7.62–7.49 (m, 4H), 7.16 (d, 1H, $J=7.5$ Hz), 2.93 (s, 6H), 1.76 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.41, 134.65, 133.18, 133.07, 130.99 (2C), 130.61, 128.75, 127.15, 126.87, 126.80, 126.19, 126.09, 125.30, 124.50, 121.67, 121.09, 120.99, 120.82, 114.65, 99.19, 93.37, 91.90, 80.10, 65.76, 45.34, 31.50. $C_{29}H_{25}NO$ (403.52). Anal. Calcd C 86.32, H 6.24, N 3.47. Found: C 86.49, H 6.34, N 3.56.

4.1.2.2. (b) 5-[(5-Ethynyl-1-naphthyl)ethynyl]-*N*,*N*-dimethylnaphthalen-1-amine (2). Following the general method used for the synthesis of **1**, a mixture of compound **2a** (100 mg, 0.25 mmol), anhydrous toluene (50 mL), and finely powdered NaOH (1 mg, 0.03 mmol) was stirred for 5 h and then filtered. The residual solid was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:1) giving **2** as a yellow solid, mp 145–147 °C, 86 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 235 (ε, 65,500), 343 (ε, 23,100). Fluorescence (CH_2Cl_2), λ_{max} (nm): 397 ($\phi=0.55$). IR (KBr, cm^{-1}): 3293, 2188, 2099, 1402, 787. ^1H NMR ($CDCl_3$): δ 8.61 (d, 1H, $J=8.4$ Hz), 8.42 (d, 1H, $J=8.4$ Hz), 8.32 (d, 1H, $J=8.7$ Hz), 8.26 (d, 1H, $J=8.1$ Hz), 7.93 (d, 1H, $J=6.9$ Hz), 7.88 (d, 1H, $J=7.5$ Hz), 7.82 (d, 1H, $J=7.5$ Hz), 7.64–7.49 (m, 4H), 7.17 (d, 1H, $J=7.8$ Hz), 3.52 (s, 1H), 2.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.40, 134.65, 133.43, 133.01, 131.80, 131.05, 130.61, 128.79, 127.68, 126.88, 126.82, 126.37, 126.03, 125.34, 124.49, 121.69, 121.07, 120.95, 120.26, 114.66, 93.43, 91.78, 82.39, 81.56, 45.36. HMQC ($^1H/^{13}C$): 8.61/127.68, 8.42/126.82, 8.32/125.34, 8.26/120.95, 7.93/131.05, 7.88/130.61, 7.82/131.80, 7.61/126.37, 7.58/126.03, 7.56/126.88, 7.52/124.49, 7.17/114.66. COSY ($^1H/^1H$): 8.61/7.58/7.82, 8.42/7.61/7.93, 8.32/7.52/7.88, 8.26/7.56/7.17. MS (70 eV): 345 (M^+, 100), 344 (19), 328 (10), 300 (21), 172 (12), 150 (18). $C_{26}H_{19}N$ (345.44). Anal. Calcd C 90.40, H 5.54, N 4.05. Found: C 90.48, H 5.28, N 4.89.

4.1.3. 5-({5-[(5-Ethynyl-1-naphthyl)ethynyl]-1-naphthyl}-ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (3).

4.1.3.1. (a) 4-{5-[(5-{[5-(*N*,*N*-Dimethylamino)-1-naphthyl]ethynyl}-1-naphthyl)ethynyl]-1-naphtyl}-2-methyl-3-butyn-2-ol (3a). Following the general method used for the synthesis of **1a**, a mixture of $PdCl_2(PPh_3)_2$ (173 mg, 0.25 mmol), Cu_2I_2 (5 mg, 0.025 mmol), compound **2** (850 mg, 2.46 mmol), 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol (826 mg, 2.46 mmol), and NEt_3 (200 mL) was stirred for 20 h. A flash chromatography on silica gel, eluting with hexane/ethyl acetate (2:1) giving **3a** as an orange solid, mp 238–240 °C, 1.2 g (88%) yield. IR (KBr, cm^{-1}): 3287, 2274, 2217, 1421, 1151, 780. ^1H NMR ($CDCl_3$): δ 8.65 (d, 1H, $J=8.1$ Hz), 8.61 (d, 1H, $J=7.8$ Hz), 8.58 (d, 1H, $J=8.4$ Hz), 8.38 (d, 1H, $J=8.4$ Hz), 8.34 (d, 1H, $J=8.4$ Hz), 8.29 (d, 1H, $J=7.8$ Hz), 7.97 (d, 2H, $J=6.3$ Hz), 7.96 (d, 1H, $J=6.6$ Hz), 7.91 (d, 1H, $J=7.2$ Hz), 7.76 (d, 1H, $J=7.5$ Hz), 7.70–7.51 (m, 6H), 7.19 (d, 1H, $J=6.9$ Hz), 2.96 (s, 6H), 1.77 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.49, 134.73, 133.24 (3C), 133.07, 131.23, 131.19, 131.12, 131.07, 130.66, 128.56, 127.45 (2C), 127.09 (2C), 126.92, 126.41, 126.31 (2C), 126.22, 125.39, 124.52, 121.86, 121.45 (2C), 121.15, 121.00, 120.95, 114.70, 99.28, 93.51, 92.67, 92.59, 91.90, 80.10, 65.94, 45.39, 31.68. $C_{41}H_{31}NO$ (553.70). Anal. Calcd C 88.94, H 5.64, N 2.53. Found: C 89.02, H 5.50, N 2.78.

4.1.3.2. (b) 5-({5-[(5-Ethynyl-1-naphthyl)ethynyl]-1-naphthyl}ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (3). Following the general method used for the synthesis of **1**, a mixture of compound **3a** (200 mg, 0.36 mmol), anhydrous toluene (40 mL), and finely powdered NaOH (1.4 mg, 0.036 mmol) was stirred for 10 h and then filtered. The residual solid was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:3) giving **3** as a pale orange solid, mp 210–211 °C, 177 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 235 (ε, 55,800), 363 (ε, 26,600). Fluorescence (CH_2Cl_2), λ_{max} (nm): 398, 414 ($\phi=0.65$). IR (KBr, cm^{-1}): 3293, 2219, 2083, 1420, 790. ^1H NMR ($CDCl_3$): δ 8.63 (d, 1H, $J=8.4$ Hz), 8.60 (d, 1H, $J=8.4$ Hz), 8.59 (d, 1H, $J=8.4$ Hz), 8.44 (d, 1H, $J=8.4$ Hz), 8.33 (d, 1H, $J=8.7$ Hz), 8.27 (d, 1H, $J=8.4$ Hz), 7.96 (d, 2H, $J=7.2$ Hz), 7.95 (d, 1H, $J=7.2$ Hz), 7.89 (d, 1H, $J=7.5$ Hz), 7.83 (d, 1H, $J=7.2$ Hz), 7.68–7.50 (m, 6H), 7.18 (d, 1H, $J=7.5$ Hz), 3.53 (s, 1H), 2.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.57, 134.74, 133.52, 133.22 (2C), 133.04, 131.90, 131.25 (2C), 131.17, 130.70, 128.82, 127.63, 127.49, 127.10, 127.05, 126.93, 126.44 (2C), 126.32, 126.18, 125.36, 124.56, 121.89, 121.50, 121.44, 121.16, 121.07, 120.42, 114.74, 93.53, 92.75, 92.53, 91.93, 82.47, 81.60, 45.42. MS (70 eV): 495 (M^+, 100), 494 (9), 441 (15), 316 (12), 277 (7), 247 (22). $C_{38}H_{25}N$ (495.62). Anal. Calcd C 92.09, H 5.08, N 2.83. Found: C 91.02, H 5.34, N 2.78.

4.1.4. 4-{4-[(4-{[5-(*N*,*N*-Dimethylamino)-1-naphthyl]-ethynyl}-1-phenyl)ethynyl]-1-phenyl}-2-methyl-3-butyn-2-ol (6). Following the general method used for the synthesis of **1a**, a mixture of $PdCl_2(PPh_3)_2$ (24 mg, 0.034 mmol), Cu_2I_2 (0.7 mg, 0.003 mmol), compound **5** (100 mg, 0.34 mmol), 4-(*p*-iodophenyl)-2-methyl-3-butyn-2-ol) (97 mg, 0.34 mmol), and NEt_3 (40 mL) was stirred for 12 h. A flash chromatography on silica gel, eluting with hexane/ethyl acetate (2:1) giving **6** as a yellow solid, mp 163–165 °C, 135 mg (88%) yield. IR (KBr, cm^{-1}): 3424, 2925, 2227, 1409, 1162, 838, 786. ^1H NMR ($CDCl_3$): δ 8.27 (d, 1H, $J=8.4$ Hz), 8.12 (d, 1H, $J=8.7$ Hz), 7.76 (d, 1H, $J=7.2$ Hz), 7.62 (d, 2H, $J=8.4$ Hz), 7.54 (d, 2H, $J=8.4$ Hz), 7.50 (dd, 1H, $J=8.7$ Hz, $J=7.5$ Hz), 7.49 (d, 2H, $J=8.4$ Hz), 7.48 (dd, 1H, $J=7.2$, 8.2 Hz), 7.41 (d, 2H, $J=8.4$ Hz), 7.14 (d, 1H, $J=7.5$ Hz), 2.90 (s, 6H), 1.63 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.32, 134.61, 131.55 (3C), 131.46, 130.49, 128.68, 126.76, 125.31, 124.41, 123.59, 122.89, 122.75 (2C), 120.86 (2C), 114.64, 95.67, 93.70, 90.91, 90.81, 90.15, 81.82, 65.54, 45.35, 31.28. $C_{33}H_{27}NO$ (453.58). Anal. Calcd C 87.38, H 6.00, N 3.09. Found: C 87.49, H 5.85, N 3.30.

4.1.5. 5-({4-[(4-Ethynyl-1-phenyl)ethynyl]-1-phenyl}-ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (7). Following the general method used for the synthesis of **1**, a mixture of compound **6** (100 mg, 0.22 mmol), anhydrous toluene (40 mL), and finely powdered NaOH (0.9 mg, 0.022 mmol) was stirred for 3 h and then filtered. The residual solid was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:2) giving **7** as a yellow-green solid, mp 151–152 °C, 86 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 232 (ε, 35,200), 264 (ε, 17,400), 337 (ε, 44,800), 364s (ε, 32,800). Fluorescence (CH_2Cl_2), λ_{max} (nm): 529 ($\phi=0.23$). IR (KBr, cm^{-1}): 3196, 2925, 2208, 2095, 1406, 839, 784. ^1H NMR ($CDCl_3$): δ 8.27 (d, 1H, $J=$ 8.4 Hz), 8.12 (d, 1H, $J=8.4$ Hz), 7.76 (d, 1H, $J=6.9$ Hz), 7.63 (d, 2H, $J=8.1$ Hz), 7.55 (d, 2H, $J=8.4$ Hz), 7.52 (dd, 1H, $J=8.4$, 7.2 Hz), 7.50 (s, 4H), 7.47 (dd, 1H, $J=6.9$, 8.4 Hz), 7.14 (d, 1H, $J=7.2$ Hz), 3.20 (s, 1H), 2.90 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.34, 134.60, 132.09, 131.60 (2C), 131.47, 130.51, 128.69, 126.79, 125.33, 124.54, 123.64, 123.51, 122.67, 122.05, 120.85 (2C), 114.64, 93.68, 91.12, 90.65, 90.13, 83.23, 79.03, 45.34. MS (70 eV): 395 (M^+, 100), 394 (9), 352 (8), 197 (18).$C_{30}H_{21}N$ (395.50). Anal. Calcd C 91.11, H 5.35, N 3.54. Found: C 91.28, H 5.54, N 3.38.

4.1.6. 1,3,5-Tri[(5-{*N*,*N*-dimethylamino}-1-naphthyl)-ethynyl]benzene (8). Following the general method used for the synthesis of **2a**, a mixture of $PdCl_2(PPh_3)_2$ (36 mg, 0.051 mmol), Cu_2I_2 (1 mg, 0.005 mmol), compound **1** (100 mg, 0.51 mmol), 1,3,5-triiodobenzene (77 mg, 0.17 mmol), and NEt_3 (30 mL) was stirred for 15 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:6) giving **8** as a dark orange solid, mp 193–195 °C, 95 mg (85%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 232 (ε, 180,940), 256s (ε, 111,500), 310 (ε, 85,500), 356 (ε, 81,400). Fluorescence (CH_2Cl_2), λ_{max} (nm): 504 ($\phi=0.43$). IR (KBr, cm^{-1}): 2208, 1400, 990, 789. ^1H NMR ($CDCl_3$): δ 8.33 (d, 3H, $J=8.7$ Hz), 8.22 (d, 3H, $J=7.8$ Hz), 7.93 (s, 3H), 7.83 (d, 3H, $J=6.9$ Hz), 7.58 (t, 3H, $J=$ 8.1 Hz), 7.51 (dd, 3H, $J=8.7$, 6.9 Hz), 7.17 (d, 3H, $J=$ 7.5 Hz), 2.93 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 151.35, 134.66, 134.02, 130.65, 128.69, 126.89, 125.46, 124.40, 120.89, 120.62 (2C), 114.67, 92.50, 89.34, 45.30. MS (70 eV): 657 (M^+, 100), 643 (3), 328 (13).$C_{48}H_{39}N_3$ (657.85). Anal. Calcd C 87.64, H 5.98, N 6.39. Found: C 87.50, H 6.11, N 6.51.

4.1.7. 1,3,5-Tri({5-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)-ethynyl]-1-naphthyl}ethynyl)benzene (9). Following the general method used for the synthesis of **1a**, a mixture of $PdCl_2(PPh_3)_2$ (93 mg, 0.13 mmol), Cu_2I_2 (3 mg, 0.013 mmol), compound **2** (250 mg, 0.73 mmol), 1,3,5-triiodobenzene (100 mg, 0.22 mmol), and NEt_3 (40 mL) was stirred for 20 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:4) giving **9** as an orange solid, mp 237–238 °C, 198 mg (81%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 239 (ε, 18,100), 364 (ε, 10,650). IR (KBr, cm^{-1}): 2206, 1435, 984, 783. Fluorescence (CH_2Cl_2), λ_{max} (nm): 527 ($\phi=0.21$). ^1H NMR ($CDCl_3$): δ 8.63 (d, 3H, $J=8.4$ Hz), 8.54 (d, 3H, $J=8.4$ Hz), 8.32 (d, 3H, $J=8.4$ Hz), 8.27 (d, 3H, $J=8.7$ Hz), 7.96 (d, 3H, $J=$ 5.7 Hz), 7.95 (s, 3H), 7.89 (d, 3H, $J=7.2$ Hz), 7.71–7.50 (m, 12H), 7.17 (d, 3H, $J=6.6$ Hz), 2.93 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 151.44, 134.67, 134.29, 133.19 (2C), 131.32, 131.90, 130.67, 128.82, 127.68, 126.94, 126.48, 126.26, 125.37, 124.54, 124.32, 121.86, 121.13, 121.01 (2C), 120.90, 114.68, 93.53, 93.03, 91.87, 88.88, 45.40. MS (FAB+): 1108 (M^+, 100). $C_{84}H_{57}N_3$ (1108.39). Anal. Calcd C 91.03, H 5.18, N 3.79. Found: C 90.92, H 5.31, N 3.62.

4.1.8. 1,3,5-Tri{[5-({5-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)ethynyl]-1-naphthyl}ethynyl)-1-naphthyl]-ethynyl}benzene (10). Following the general method used for the synthesis of **1a**, a mixture of $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), Cu_2I_2 (1.2 mg, 0.006 mmol), compound **3** (100 mg, 0.20 mmol), 1,3,5-triiodobenzene (30 mg, 0.07 mmol), and pyridine (40 mL) was stirred for 40 h at reflux. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:4) giving **6** as a pale orange solid, mp 212–214 °C, 93 mg (30%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 232 (ε, 193,400), 370 (ε, 96,800). Fluorescence (CH_2Cl_2), λ_{max} (nm): 530 ($\phi=0.08$). IR (KBr, cm^{-1}): 2223, 2200, 1420, 967, 780. ^1H NMR ($CDCl_3$): δ 8.82 (d, 3H, $J=8.4$ Hz), 8.65 (d, 3H, $J=8.7$ Hz), 8.54 (d, 3H, $J=8.4$ Hz), 8.32 (d, 3H, $J=8.1$ Hz), 8.30 (d, 3H, $J=$ 8.1 Hz), 8.26 (d, 3H, $J=8.1$ Hz), 8.02 (d, 3H, $J=7.2$ Hz), 8.01 (d, 3H, $J=7.2$ Hz), 7.96 (d, 6H, $J=6.6$ Hz), 7.89 (d, 3H, $J=7.2$ Hz), 7.75 (d, 3H, $J=7.2$ Hz), 7.72–7.50 (m, 18H), 7.17 (d, 3H, $J=7.8$ Hz), 2.93 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 151.52, 134.73, 133.26 (2C), 132.92 (2C), 132.46, 132.03, 131.71, 131.45, 131.19, 130.69, 128.88, 128.12, 127.84, 126.91, 126.78, 126.55, 126.29, 125.95 (2C), 125.90, 125.46, 124.52, 122.23, 122.04 (2C), 121.07 (2C), 120.97, 117.64, 114.73, 93.80, 93.68 (2C), 91.79 (2C), 91.46, 45.39. MS (FAB+): 1557 (M^+, 100). $C_{120}H_{75}N_3$ (1558.93). Anal. Calcd C 92.46, H 4.85, N 2.70. Found: C 92.39, H 4.97, N 2.53.

4.1.9. 1,3,5-Tri({4-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)-ethynyl]-1-phenyl}ethynyl)benzene (11). Following the general method used for the synthesis of **1a**, a mixture of $PdCl_2(PPh_3)_2$ (24 mg, 0.011 mmol), Cu_2I_2 (0.7 mg, 0.0013 mmol), compound **5** (100 mg, 0.34 mmol), 1,3,5-triiodobenzene (155 mg, 0.11 mmol), and NEt_3 (30 mL) was stirred for 72 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **11** as an dark yellow solid, mp 85–86 °C, 86 mg (79%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 230 (ε, 122,900), 262s (ε, 57,500), 337 (ε, 106,500), 365 (ε, 98,200). Fluorescence (CH_2Cl_2), λ_{max} (nm): 530 ($\phi=0.20$). IR (KBr, cm^{-1}): 2924, 2206, 1407, 961, 834, 786. ^1H NMR ($CDCl_3$): δ 8.29 (d, 3H, $J=$ 8.9 Hz), 8.14 (d, 3H, $J=8.1$ Hz), 7.77 (d, 3H, $J=6.9$ Hz), 7.70 (s, 3H), 7.64 (d, 6H, $J=8.5$ Hz), 7.57 (dd, 3H, $J=8.1$, 6.8 Hz), 7.55 (d, 6H, $J=8.5$ Hz), 7.49 (dd, 3H, $J=8.9$, 6.9 Hz), 7.15 (d, 3H, $J=6.8$ Hz), 2.91 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 151.33, 139.78, 134.56, 131.58 (2C), 130.52, 128.65, 126.78, 125.36, 124.41, 123.91, 122.21 (2C), 120.81, 120.73, 114.63, 93.59, 91.03, 90.30, 88.66, 45.32. MS (MALDI-TOF): 957.0. $C_{72}H_{51}N_3$ (958.21). Anal. Calcd C 90.25, H 5.36, N 4.39. Found: C 90.14, H 5.51, N 4.24.

4.1.10. 1,3,5-Tri{[4-({4-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)ethynyl]-1-phenyl}ethynyl)-1-phenyl]ethynyl}-benzene (12). Following the general method used for the synthesis of **1a**, a mixture of $PdCl_2(PPh_3)_2$ (6 mg,

0.008 mmol), Cu_2I_2 (0.2 mg, 0.0006 mmol), compound **7** (100 mg, 0.25 mmol), compound 1,3,5-triiodobenzene (37 mg, 0.08 mmol), and NEt_3 (40 mL) was stirred for 72 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **12** as an dark yellow solid, mp 209–210 °C, 65 mg (62%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 232 (ε, 94,500), 353 (ε, 119,900). Fluorescence (CH_2Cl_2), λ_{max} (nm): 531 ($\phi=0.19$). IR (KBr, cm^{-1}): 2924, 2207, 1407, 962, 835, 787. ^1H NMR ($CDCl_3$): δ 8.28 (d, 3H, $J=8.9$ Hz), 8.13 (d, 3H, $J=8.5$ Hz), 7.76 (d, 3H, $J=6.9$ Hz), 7.68 (s, 3H), 7.64 (d, 6H, $J=8.9$ Hz), 7.55–7.44 (m, 24H), 7.14 (d, 3H, $J=7.3$ Hz), 2.91 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 151.38, 139.28, 134.626, 131.64 (4C), 130.52, 128.76, 126.78, 125.39, 124.44, 123.94, 122.71 (4C), 120.90 (2C), 114.65, 93.71, 90.31, 90.86, 90.36, 90.19, 86.63, 45.35. MS (MALDI-TOF): 1258. $C_{96}H_{63}N_3$ (1258.57). Anal. Calcd C 91.62, H 5.05, N 3.34. Found: C 91.45, H 5.20, N 3.19.

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Synthesis of natural pulvinic acids based on a '[3+2] cyclization–Suzuki cross-coupling' strategy

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Abstract—A number of pulvinic acid natural products were prepared based on Suzuki cross coupling reactions of α-hydroxy-γ-alkylidenebutenolides which are readily available by cyclization of 1,3-bis-silyl enol ethers with oxalyl chloride. The formal total synthesis of pulvinic acid, atromentic acid, gomphidic acid and of 4-hydroxypulvinic acid, 4′-hydroxypulvinic acid and *iso*-gomphidic acid are reported. In addition, total syntheses of pinastric acid, xerocomic acid and variegatic acid were accomplished.

Pulvinic acids constitute a group of natural products containing a γ-alkylidenebutenolide ring system.[1] They have been isolated from several lichens and higher fungi and represent bright yellow and orange pigments. A number of regioselective and non-regioselective syntheses of unsymmetrical pulvinic acids have been reported.[2–4] For example, pulvinic acids are available by cleavage of one lactone moiety of pulvinic bis-lactones. The latter can be prepared, for example, by reaction of arylacetonitriles with diethyl oxalate[2a] or ethyl 2-chloro-2-oxoacetate[2b,c] or by biomimetic rearrangements of terphenylquinones.[2d] However, mixtures of regioisomeric products were obtained for reactions of unsymmetrical bis-lactones, due to the very similar chemical environment of the two lactone moieties. An alternative synthesis of permethylated pulvinic acids relies on Reformatsky-type reactions of maleic anhydrides.[3] Unfortunately, the yields are low and the procedure is relatively tedious, since the transformations have to be carried out over three steps ((a) Reformatsky condensation, (b) mesylation and (c) elimination). Pulvinic acids have been prepared also based on biomimetic transformations (Scheme 1).[4]

We and others have recently reported the functionalization of α-hydroxy-γ-alkylidenebutenolides, readily available by cyclization of 1,3-bis-silyl enol ethers[5,6] with oxalyl chloride,[7] by Stille and Suzuki cross coupling reactions.[8–11] The application of the Suzuki reaction allowed a convenient synthesis of the natural product vulpinic acid[2d,9] and of an analogue of the natural product norbadion A.[10] Herein, we wish to report the application of our methodology to the synthesis of the natural products pinastric acid,[2d,11] atromentic acid,[3,12] xerocomic acid,[4,13,14] variegatic acid[15,16b] and gomphidic acid[3,16] and of their analogues 4-hydroxypulvinic acid,[2d,3] 4′-hydroxypulvinic acid[2d,3] and *iso*-gomphidic acid.[3] The method reported herein allows a regioselective synthesis of pulvinic acids, since the aryl substituents are introduced independently from each other. In addition, the method is robust, the starting materials are readily available, the yields are good to very good and the number of steps is low.

1. Results and discussion

The reaction of methyl methoxyacetate (**1**) with the arylacetic esters **2a–d** afforded the β-ketoesters **3a–d** (Scheme 2, Table 1). The reaction of **3a–d** with NEt_3/Me_3SiCl gave the silyl enol ethers **4a–d**. The latter were transformed into the 1,3-bis-silyl enol ethers **5a–d**. The TMSOTf-catalyzed cyclization of **5a–d** with oxalyl chloride afforded the γ-alkylidenebutenolides **6a–d** with very good *E*-diastereoselectivity. The configuration of the exocyclic double bond was established based on NOESY measurements, on analogy to related findings[7–10] and on the transformation of **6** into natural products with known configuration (vide infra). The synthesis of **6a** and **6b** has been recently reported.[9,10] Butenolides **6a–d** were transformed into the corresponding triflates **7a–d**.

The Suzuki reaction of **7a** with (*p*-methoxyphenyl)boronic acid afforded *O*-methylpinastric acid (**10**) in 70% yield

Keywords: Butenolides; Cyclizations; Natural products; Pulvinic acids; Silyl enol ethers.
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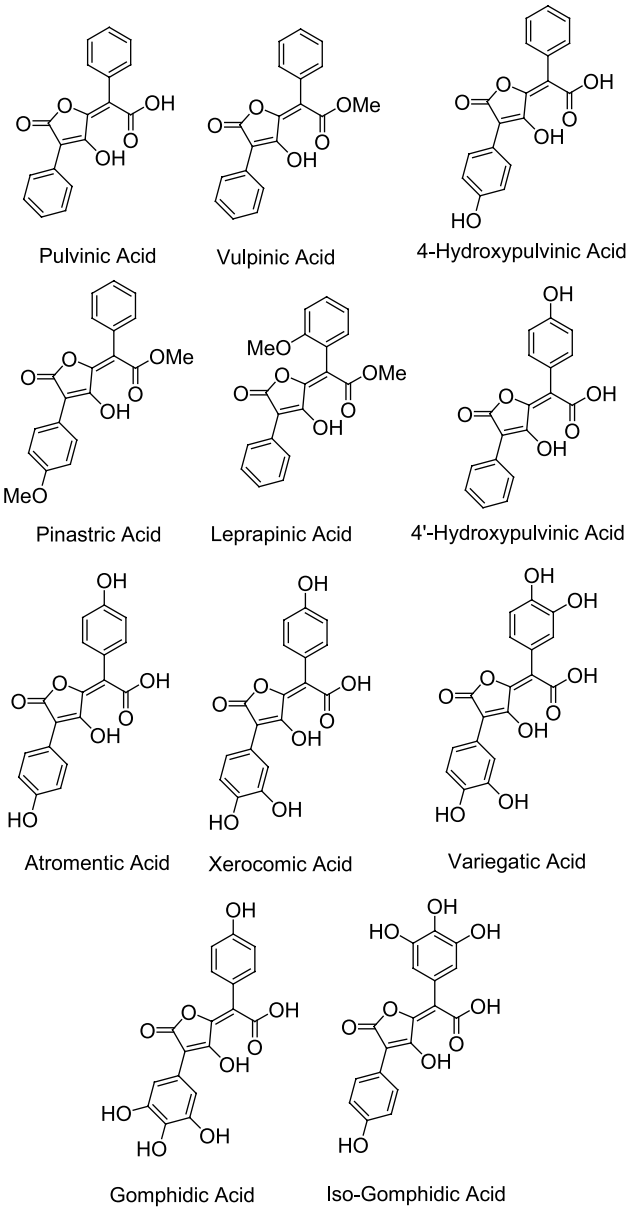
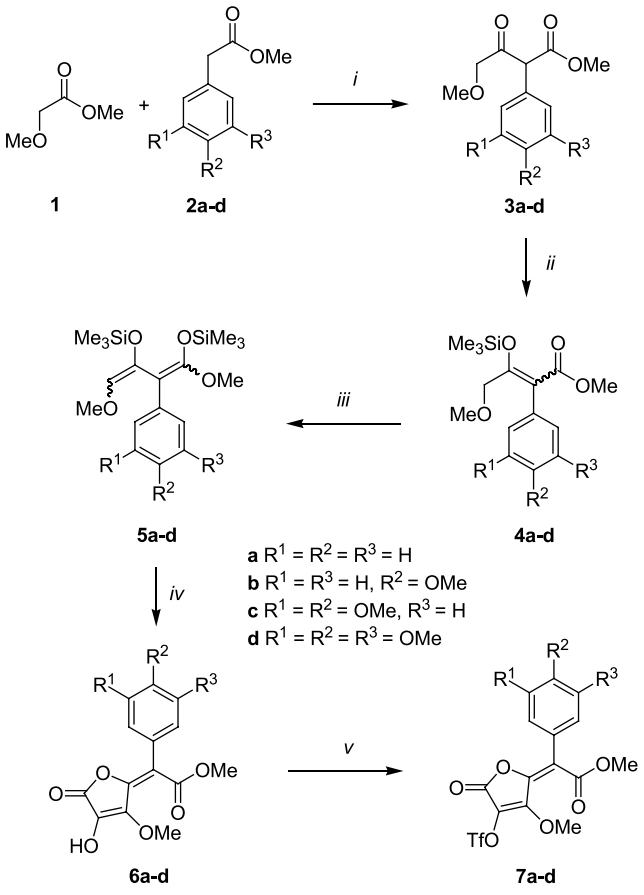


Scheme 1. Pulvinic acid natural products and analogues.



Scheme 2. Synthesis of butenolides **7a–d**: (i) (1) LDA, THF, (2) **2** (0.5 equiv), −78→20 °C; (ii) Me_3SiCl, NEt_3, toluene, 20 °C; (iii) (1) LDA, THF, −78 °C, (2) Me_3SiCl, −78→20 °C; (iv) oxalyl chloride, Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78→20 °C; (v) Tf_2O, pyridine, −78→−10 °C.

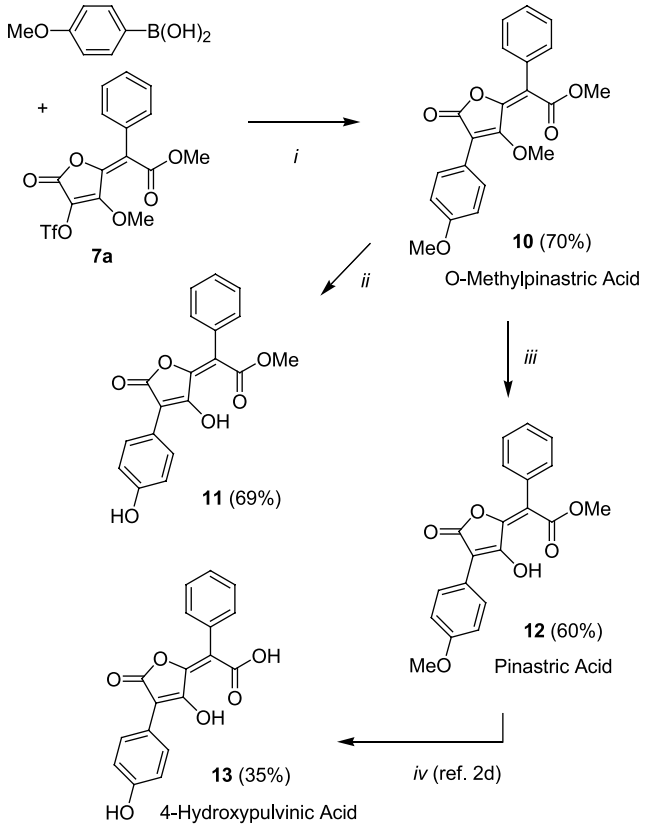
(Scheme 3). The configuration of the exocyclic double bond proved stable under the reaction conditions. Treatment of **10** with BBr_3 (4 equiv, 0 °C, 2 h) resulted in cleavage of both methyl ether groups to give **11** in 69% yield. However, the synthesis of pinastric acid required the regioselective cleavage of the butenolide methyl ether in the presence of the aryl methyl ether. Much to our satisfaction, treatment of **10** with only 1 equiv of BBr_3 (0 °C, 6 h) afforded pinastric acid (**12**) in 60% yield. The high regioselectivity of the reaction of **10** with BBr_3 can be explained (a) by chelation of BBr_3 to the ester carbonyl group (intermediate **A**, Scheme 4) and (b) by the better leaving group ability of the tetronate compared to the phenolate moiety. The chelation exerts a regiodirective bias and results in the activation and subsequent cleavage of the butenolide methyl ether (intermediate **B**). The spectroscopic data of pinastric acid **12** are identical with those reported in the literature.[2d] The transformation of **12** into 4-hydroxypulvinic acid (**13**) was accomplished earlier by Pattenden et al. by employment of Me_3SiI.[2d]

The Suzuki reaction of **7b** with phenylboronic acid gave butenolide **14a** in 85% yield (Scheme 5). The transformation of **14a** into 4′-hydroxypulvinic acid (**15a**) has been

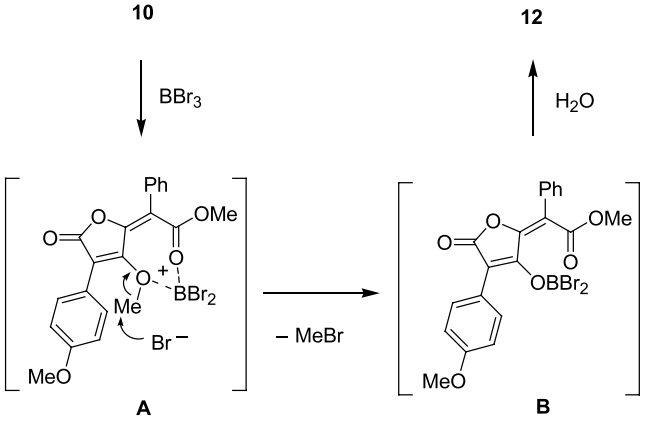
Table 1. Products and yields

3–7	R^1	R^2	R^3	% (**3**)[a]	% (**4**)[a]	% (**5**)[a]	% (**6**)[a]	% (**7**)[a]
a[b]	H	H	H	67	84	90	54	61
b[c]	H	OMe	H	58	90	95	57	77
c	OMe	OMe	H	62	83	89	61	66
d	OMe	OMe	OMe	62	72	96	61	74

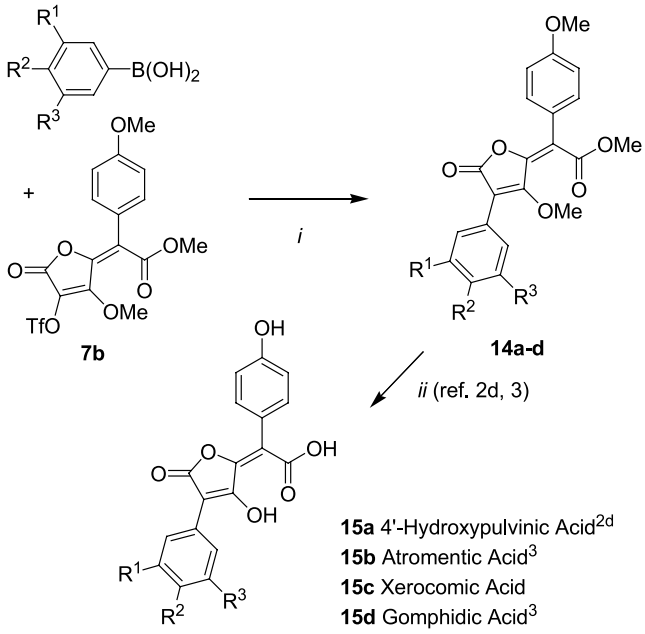
[a] Yields of isolated products, *E*/*Z*>98:2 for **6a–d** and **7a–d**.
[b] See Ref. 9.
[c] See Ref. 10.



Scheme 3. Synthesis of pinastric acid and 4-hydroxypulvinic acid: (i) $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux; (ii) BBr_3 (4 equiv), CH_2Cl_2, 0 °C; (iii) BBr_3 (1 equiv), CH_2Cl_2, 0 °C, 6 h; (iv) Me_3SiI, $CDCl_3$, 55 °C.



Scheme 4. Possible mechanism of the regioselective deprotection of **10**.



Scheme 5. Synthesis of pulvinic acids **15a–d**: (i) $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux; (ii) Me_3SiI, $CDCl_3$, 55 °C.

reported by Pattenden.[2d] Permethylatromentic acid (**14b**) was prepared in 62% yield by Suzuki reaction of **7b** with (4-methoxyphenyl)boronic acid. Treatment of **14b** with Me_3SiI has been reported to give atromentic acid (**15b**) in 70% yield.[3] The reaction of **7b** with (3,4-dimethoxyphenyl)boronic acid afforded permethylxerocomic acid (**14c**) in 81% yield. Treatment of **14c** with Me_3SiI afforded xerocomic acid (**15c**) in 72% yield. The Suzuki reaction of **7b** with (3,4,5-trimethoxyphenyl)boronic acid afforded permethylgomphidic acid (**14d**) in 88% yield. The Me_3SiI mediated transformation of **14d** into gomphidic acid (**15d**) has been reported to proceed in 65% yield.[3] All pulvinic acids were obtained as *E*-configured isomers. The spectroscopic data of all permethylated pulvinic acids were identical with those reported (Table 2).[2b,3]

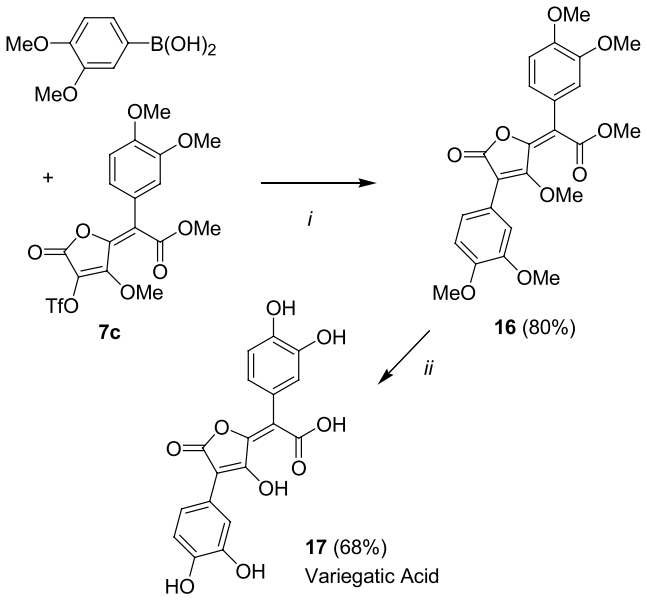
The synthesis of variegatic acid (**17**) was studied next (Scheme 6). The Suzuki reaction of **7c** with (3,4-dimethoxyphenyl)boronic acid gave permethylvariegatic acid (**16**) in 80% yield. Treatment of **16** with Me_3SiI afforded variegatic acid (**17**) in 68% yield. The spectroscopic data of the synthetic material were identical to those reported in the literature for the natural product.[14,16b]

The Suzuki reaction of **7d** with (4-methoxyphenyl)boronic

Table 2. Synthesis of pulvinic acids **15**

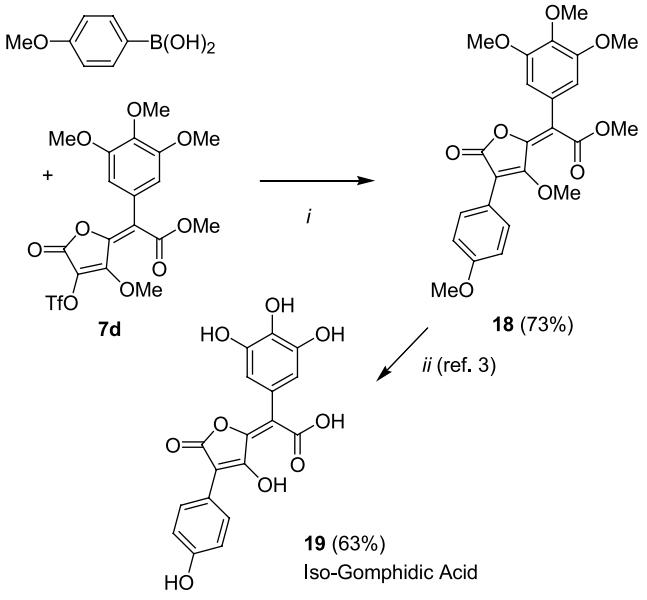
14, 15	R^1	R^2	R^3	%[a]
14a	H	H	H	85
14b	H	OMe	H	62
14c	OMe	OMe	H	81
14d	OMe	OMe	OMe	88
15a	H	H	H	34[2d]
15b	H	OH	H	70[3]
15c	OH	OH	H	72
15d	OH	OH	OH	65[3]

[a] Yields of isolated products, *E*/*Z* >98:2 for all products.



Scheme 6. Synthesis of variegatic acid: (i) $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux; (ii) Me_3SiI, $CDCl_3$, 55 °C.

acid afforded butenolide **18** in 73% yield (Scheme 7). The spectroscopic data of **18** are identical with those reported.[3] The transformation of **18** into *iso*-gomphidic acid (**19**) has been reported to proceed in 63% yield.[3]



Scheme 7. Synthesis of iso-gomphidic acid: (i) $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux; (ii) Me_3SiI, $CDCl_3$, 55 °C.

In summary, we have reported efficient formal syntheses of the natural products pulvinic acid, atromentic acid, and gomphidic acid and their analogues 4-hydroxypulvinic acid, 4′-hydroxypulvinic acid and iso-gomphidic acid. In addition, total syntheses of pinastric acid, xerocomic acid and variegatic acid were accomplished. The synthesis of pinastric acid relies on the regioselective deprotection of *O*-methylpinastric acid. The key steps of our synthetic strategy are firstly the synthesis of γ-alkylidenebutenolides by cyclization of 1,3-bis-silyl enol ethers with oxalyl chloride, a method previously developed by us, secondly the functionalization of the butenolides by Suzuki reactions and finally their transformation into natural products. All reactions are robust, easy to carry out and proceed in good yield and with excellent selectivity.

2. Experimental

2.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectral data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H_2O) or the electrospray ionization (ESI). For preparative scale chromatography silica gel (60–200 mesh) was used. Melting points are uncorrected.

2.2. Typical procedure for the synthesis of β-ketoesters (3a–d)

The reaction was carried out analogously to a known procedure.[10] The synthesis of **3a**,**b** has been reported earlier.[9,10] To a stirred solution of LDA (58.0 mmol) in THF (150 ml) was added methyl phenylacetate (8.10 ml, 57.6 mmol) at −78 °C. After stirring for 1 h methyl methoxyacetate (3.00 g, 28.8 mmol) was added. The temperature of the solution was allowed to rise to 20 °C during 12 h. A saturated aqueous solution of NH_4Cl was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3×150 ml). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **3a** as a colorless oil (4.58 g, 67%). The spectroscopic data are identical with those reported.[9]

2.2.1. Compound 3b. Starting with methyl methoxyacetate (9.00 g, 86.4 mmol), methyl (4-methoxyphenyl)acetate (27.90 ml, 172.9 mmol), LDA (172 mmol) and THF (432 ml), **3b** was isolated as a colourless solid (12.59 g, 58%), mp 55–56 °C. The spectroscopic data are identical with those reported.[10] ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.33$ (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.05 (d, 2H, $J=3.3$ Hz, CH_2), 4.89 (s, 1H, CH), 6.88 (dd, 2H, $J=2.1$, 1.5 Hz, ArH), 7.24 (dd, 2H, $J=2.1$, 1.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=52.32$, 54.98, 59.06 (CH_3), 59.60 (CH), 76.23 (CH_2), 114.04 (2C, CH), 123.59 (C), 130.42 (2C, CH), 159.36, 168.82, 201.80 (C); IR (KBr): $\tilde{\nu}=2953$ (s), 1748 (s), 1727 (s), 1610 (m), 1513 (s), 1441 (s), 1301 (m), 1251 (s), 1180 (m), 1161 (m), 832 (s) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 252.0 (M^+, 34), 219.9 (24), 179.0 (100), 147.4 (82), 77.4 (15), 45.1 (47); elemental analysis: calcd (%) for $C_{13}H_{16}O_5$ (252.26): C 61.89, H 6.39; found: C 61.55, H 6.00.

2.2.2. Compound 3c. Starting with methyl methoxyacetate (1.75 ml, 17.83 mmol), methyl (3,4-dimethoxyphenyl)-acetate (7.50 g, 35.67 mmol), LDA (35.66 mmol) and THF (90 ml), **3c** was isolated as a yellow oil (3.12 g, 62%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.36$ (s, 3H, OCH_3),

3.75 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.08 (d, 2H, $J=3.9$ Hz, CH_2), 4.88 (s, 1H, CH), 6.85 (s, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=51.77$, 55.07, 55.12. 58.47 (CH_3), 59.52 (CH), 75.69 (CH_2), 110.63, 111.88, 121.39 (CH), 123.61, 148.42 (2C), 168.26, 201.21 (C); IR (KBr): $\tilde{\nu}=3626$ (w), 3545 (w), 2949 (s), 2836 (m), 1749 (s), 1728 (s), 1595 (m), 1515 (s), 1460 (s), 1301 (m), 1262 (s), 1201 (s), 1146 (s), 1101 (m), 1026 (s) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 282.0 (M^+, 53), 209.0 (100), 181.1 (50), 150.0 (66), 45.1 (56); elemental analysis: calcd (%) for $C_{14}H_{18}O_6$ (282.29): C 59.56, H 6.42; found: C 59.20, H 6.48.

2.2.3. Compound 3d. Starting with methyl methoxyacetate (2.00 g, 19.2 mmol), methyl (3,4,5-trimethoxyphenyl)-acetate (9.24 g, 38.4 mmol), LDA (38.4 mmol) and THF (96 ml), **3d** was isolated as a colourless solid (3.70 g, 62%), mp 52 °C. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=3.36$ (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.82 (s, 9H, OCH_3), 4.11 (s, 2H, CH_2), 4.92 (s, 1H, CH), 6.58 (s, 2H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=52.12$, 55.68, 58.78 (2C), 60.04 (CH_3), 60.24 (CH), 76.05 (CH_2), 106.46 (2C, CH), 126.96, 137.72, 152.90 (2C), 168.34, 201.23 (C); IR (KBr): $\tilde{\nu}=3627$ (w), 3544 (w), 3452 (w), 2997 (s), 2942 (s), 2836 (s), 1752 (s), 1726 (s), 1591 (s), 1507 (s), 1462 (s), 1426 (s), 1318 (s), 1241 (s), 1199 (s), 1126 (s), 1104 (s), 730 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 312.1 (M^+, 68), 265.1 (9), 239.0 (100), 181.0 (32), 44.1 (37); elemental analysis: calcd (%) for $C_{15}H_{20}O_7$ (312.31): C 57.69, H 6.45; found: C 57.25, H 7.14.

2.3. Typical procedure for the synthesis of silyl enol ethers (4a–d)

The reaction was carried out analogously to a known procedure.[7b] The synthesis of **4a**,**b** has been reported earlier.[9,10] To a stirred benzene solution (10 ml) of **7** (4.50 g) was added triethylamine (4.50 ml, 32.4 mmol). After stirring for 2 h trimethylchlorosilane (4.60 ml, 36.4 mmol) was added. After stirring for 72 h, the solvent was removed in vacuo and to the residue was added Hexane (100 ml) to give a suspension. The latter was filtered under Argon atmosphere. The filtrate was distilled in vacuo to give **4a** as a colorless oil (5.00 g, 84%). The compound was used directly after its preparation. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.08$ (s, 9H, CH_3), 3.26 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2), 7.21–7.39 (m, 5H, ArH). The spectroscopic data are identical with those reported.[8]

2.3.1. Compound 4b. Starting with β-ketoester **3b** (6.0 g, 23.78 mmol), NEt_3 (5.28 ml, 38.05 mmol), TMSCl (5.38 ml, 42.80 mmol) and benzene (60 ml), **4b** was isolated as a yellow oil (7.00 g, 90%). The spectroscopic data are identical with those reported.[10] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.08$ (s, 9H, CH_3), 3.23 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.39 (s, 2H, CH_2), 6.78 (dd, 2H, $J=1.2$, 8.7 Hz, ArH), 7.07 (dd, 2H, $J=1.5$, 8.7 Hz, ArH).

2.3.2. Compound 4c. Starting with β-ketoester **3c** (3.0 g, 10.62 mmol), NEt_3 (2.36 ml, 17.00 mmol), TMSCl (2.41 ml, 19.11 mmol) and benzene (27 ml), **4c** was isolated as a yellow oil (3.15 g, 83%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.08$ (s, 9H, CH_3), 3.39 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.43 (s, 2H, CH_2), 6.79 (s, 3H, ArH).

2.3.3. Compound 4d. Starting with β-ketoester **3d** (3.26 g, 10.43 mmol), NEt_3 (2.40 ml, 16.70 mmol), TMSCl (2.38 ml, 18.79 mmol) and benzene (26 ml), **4d** was isolated as a yellow oil (2.73 g, 72%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (s, 9H, CH_3), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.81 (s,6H, OCH_3), 3.84 (s, 3H, OCH_3), 4.43 (s, 2H, CH_2), 6.45 (s, 2H, ArH).

2.4. Typical procedure for the synthesis of bis-silyl enol ethers (5a–d)

The reaction was carried out analogously to a known procedure.[7b] The synthesis of **5a**,**b** has been reported earlier.[9,10] To a stirred THF solution (100 ml) of LDA (20.4 mmol, 1.5 equiv) was added **4a** (4.00 g, 13.6 mmol) at −78 °C. After stirring for 1 h, trimethylchlorosilane (2.57 ml, 20.4 mmol) was added. The solution was allowed to warm to room temperature during 12 h with stirring. The solvent was removed in vacuo and to the residue was added Hexane (100 ml) to give a suspension. The latter was filtered under Argon atmosphere. The filtrate was distilled in vacuo to give **5a** as a colorless oil (4.50 g, 90%). The compound was used directly after its preparation. The spectroscopic data are identical with those reported.[9] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.04$ (s, 9H, CH_3), 0.31 (s, 9H, CH_3), 3.41 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 5.63 (s, 1H, =CH), 7.22–7.35 (m, 5H, ArH).

2.4.1. Compound 5b. Starting with **4b** (6.00 g, 18.5 mmol), LDA (27.7 mmol, 1.5 equiv), TMSCl (4.20 ml, 33.3 mmol) and THF (92 ml), **5b** was isolated as a yellow oil (7.00 g, 95%). The spectroscopic data are identical with those reported.[10] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.01$ (s, 9H, CH_3), 0.27 (s, 9H, CH_3), 3.45 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.77 (s,3H, OCH_3), 5.91 (s, 1H, =CH), 6.78 (d, 2H, $J=9.0$ Hz, ArH), 7.22 (d, 2H, $J=8.7$ Hz, ArH).

2.4.2. Compound 5c. Starting with **4c** (3.00 g, 8.46 mmol), LDA (13.54 mmol, 1.5 equiv), TMSCl (1.92 ml, 15.23 mmol) and THF (67 ml), **5c** was isolated as a yellow oil (3.25 g, 89%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.03$ (s, 9H, CH_3), 0.30 (s, 9H, CH_3), 3.46 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.85 (s,3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.62 (s, 1H, =CH), 6.79 (s, 3H, ArH).

2.4.3. Compound 5d. Starting with **4d** (2.70 g, 7.0 mmol), LDA (10.53 mmol, 1.5 equiv) and TMSCl (1.60 ml, 12.6 mmol) and THF (50 ml), **5d** was isolated as a yellow oil (3.0 g, 96%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.05$ (s, 9H, CH_3), 0.30 (s, 9H, CH_3), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 5.47 (s, 1H, CH), 6.61 (s, 2H, ArH).

2.5. Typical procedure for the synthesis of butenolides (6)

The reaction was carried out analogously to a known procedure.[7b] The synthesis of **6a**,**b** has been previously reported.[9,10] To a CH_2Cl_2 solution (60 ml) of oxalyl chloride (0.70 ml, 7.8 mmol) and of **5a** (2.20 g, 6.0 mmol)

was added a CH_2Cl_2 solution (5 ml) of Me_3SiOTf (0.6 ml, 3.6 mmol) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 12 h. After stirring for 2 h at 20 °C, a saturated aqueous solution of NaCl was added. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with an aqueous solution of HCl (10%), dried (Na_2SO_4) and filtered. The solvent of the filtrate was removed in vacuo and the residue was purified by column chromatography (silica gel, hexane/EtOAc) to give **6a** as a yellow solid (900 mg, 54%). The spectroscopic data were identical with those reported.[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.84 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 7.31–7.56 (m, 5H, ArH), 12.93 (s, 1H, OH); MS (EI, 70 eV): *m/z* (%)=276 (M^+, 100); elemental analysis: calcd for $C_{14}H_{12}O_6$ (276.25): C 60.87, H 4.38; found: C 60.62, H 4.52.

2.5.1. Compound 6b. Starting with **5b** (4.0 g, 10.08 mmol), oxalyl chloride (1.05 ml, 12.10 mmol), TMSOTf (0.55 ml, 3.02 mmol) and CH_2Cl_2 (100 ml), **6b** was isolated as a yellow solid (1.75 g, 57%), mp 163 °C. The spectroscopic data are identical with those reported.[10] ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ=3.83 (s, 6H, OCH_3), 4.16 (s, 3H, OCH_3), 6.98 (d, 2H, *J*=9.0 Hz, ArH), 7.49 (d, 2H, *J*=9.0 Hz, ArH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ=53.44, 56.34, 60.88 (CH_3), 115.62 (2C, CH), 125.65 (2C), 125.74 (C), 131.78 (2C, CH), 141.00, 144.43, 161.57, 165.59, 168.21 (C); IR (KBr): $\tilde{\nu}$=3309 (s), 2954 (w), 1736 (s), 1672 (s), 1634 (m), 1603 (m), 1514 (s), 1462 (m), 1377 (s), 1312 (m), 1258 (m), 1194 (s), 1142 (s), 1113 (s), 1057 (m), 831 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 305.9 (M^+, 100), 273.9 (54), 247.0 (84), 218.9 (25), 191.0 (28), 159.0 (32), 119.1 (15), 28.1 (68); elemental analysis: calcd (%) for $C_{15}H_{14}O_7$ (306.27): C 58.82, H 4.60; found: C 58.84, H 4.61.

2.5.2. Compound 6c. Starting with **5c** (3.25 g, 7.61 mmol), oxalyl chloride (0.80 ml, 9.14 mmol), TMSOTf (0.42 ml, 2.28 mmol) and CH_2Cl_2 (71 ml), **6c** was isolated as a yellow solid (1.55 g, 61%), mp 156–157 °C. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ=3.80 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 6.98 (d, 1H, *J*=8.5 Hz, ArH), 7.06 (dd, 1H, *J*=2.1, 8.5 Hz, ArH), 7.18 (d, 1H, *J*=2.1 Hz, ArH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ=53.46, 56.69, 56.80, 60.88 (CH_3), 113.08, 114.04 (CH), 114.94, 115.82 (C), 123.49 (CH), 125.75, 141.01, 144.37, 150.70, 151.64, 165.56, 168.16 (C); IR (KBr): ν=3327 (m), 2954 (w), 1743 (s), 1731 (s), 1671 (m), 1519 (m), 1374 (m), 1262 (m), 1132 (m), 1108 (m), 745 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 336.1 (M^+, 100), 277.1 (97), 249.1 (21), 150.1 (6); elemental analysis: calcd (%) for $C_{16}H_{16}O_8$ (336.29): C 57.14, H 4.79; found: C 56.76, H 5.13.

2.5.3. Compound 6d. Starting with **5d** (3.0 g, 6.56 mmol), oxalyl chloride (0.68 ml, 7.87 mmol), TMSOTf (0.35 ml, 1.96 mmol) and CH_2Cl_2 (61 ml), **6d** was isolated as a yellow solid (1.45 g, 61%), mp 129 °C; ^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ=3.79 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 4.17 (s, 3H, OCH_3), 6.82 (s, 2H, ArH); ^{13}C NMR (150 MHz, $(CD_3)_2CO$): δ=52.97, 56.69 (2C), 60.36, 60.75 (CH_3), 107.76 (2C, CH), 115.14, 125.57, 127.89, 140.19, 141.46, 143.60, 154.37, 154.43, 164.88, 167.41 (C); IR (KBr): $\tilde{\nu}$=3330 (s), 2953 (w), 1754 (s), 1727 (s), 1681 (s), 1655 (m), 1584 (m), 1508 (m), 1461 (m), 1422 (m), 1344 (m), 1312 (m), 1254 (m), 1138 (s), 1052 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 366.0 (M^+, 100), 312.0 (45), 279.0 (36), 239.0 (90), 181.1 (39), 45.0 (23); elemental analysis: calcd (%) for $C_{17}H_{18}O_9$ (366.30): C 55.74, H 4.95; found: C 55.92, H 5.27.

2.6. General procedure for the preparation of triflates (7)

The synthesis of **7a**,**b** has been reported.[9,10] To a dichloromethane solution (10 ml per 1 mmol of **6**) of butenolide **6** (1.0 equiv) and triflic anhydride (1.2 equiv) was added pyridine (2.0 equiv) at −78 °C. The solution was allowed to warm to −10 °C within 4 h. The product was isolated by rapid chromatography (silica gel, dichloromethane) of the reaction mixture.

2.6.1. Compound 7b. Starting with **6b** (980 mg, 3.19 mmol), triflic anhydride (0.65 ml, 3.82 mmol), pyridine (0.52 ml, 6.38 mmol) and CH_2Cl_2 (32 ml), **7b** was isolated as a yellow solid (1.06 g, 77%), mp 101–103 °C. The spectroscopic data are identical with those reported.[10] ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.28 (s, 3H, OCH_3), 6.93 (dd, 2H, *J*=2.1, 6.9 Hz, ArH), 7.58 (dd, 2H, *J*=2.1, 6.9 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=52.96, 55.41, 61.05 (CH_3), 113.97 (C), 114.50 (2C, CH), 118.40 (q, *J*=319.50 Hz, CF_3), 120.78, 122.50 (C), 131.27 (2C, CH), 135.60, 155.73, 160.18, 161.17, 165.97 (C); IR (KBr): $\tilde{\nu}$=2980 (w), 1787 (s), 1737 (s), 1663 (s), 1646 (m), 1602 (m), 1513 (m), 1428 (s), 1317 (m), 1290 (m), 1233 (s), 1213 (s), 1133 (m), 1087 (s), 1045 (s), 629 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 438.6 (M^+, 63), 304.9 (67), 249.0 (100), 220.9 (33), 205.9 (18), 135.0 (34), 28.0 (51); elemental analysis: calcd (%) for $C_{16}H_{13}O_9SF_3$ (437.74): C 43.90, H 2.99, S 7.32; found: C 43.86, H 3.17, S 7.41.

2.6.2. Compound 7c. Starting with butenolide **6c** (375 mg, 1.11 mmol), triflic anhydride (0.22 ml, 1.34 mmol), pyridine (0.19 ml, 2.24 mmol) and CH_2Cl_2 (11 ml), **7c** was isolated as a yellow solid (736 mg, 66%), mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.29 (s, 3H, OCH_3), 6.89 (d, 1H, *J*=8.5 Hz, ArH), 7.14 (dd, 1H, *J*=2.1, 8.5 Hz, ArH), 7.24 (d, 1H, *J*=2.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=53.04, 56.04 (2C), 61.11 (CH_3), 111.08, 112.25 (CH), 113.94 (C), 118.40 (q, *J*=319.5 Hz, CF_3), 120.83, 122.63 (C), 123.19 (CH), 135.69, 149.04, 150.99, 155.68, 160.13, 165.91 (C); IR (KBr): $\tilde{\nu}$=3600 (w), 1788 (s), 1734 (s), 1650 (s), 1521 (s), 1426 (s), 1295 (m), 1250 (s), 1137 (s), 1083 (s), 1056 (m), 615 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 467.8 (M^+, 40), 335.0 (18), 275.0 (100), 247.0 (25), 148.3 (20); elemental analysis: calcd (%) for $C_{17}H_{15}O_{10}SF_3$ (468.36): C 43.60, H 3.23; found: C 44.09, H 3.23.

2.6.3. Compound 7d. Starting with butenolide (655 mg, 1.79 mmol), triflic anhydride (0.37 ml, 2.14 mmol), pyridine (0.30 ml, 3.57 mmol) and CH_2Cl_2 (18 ml), **7d** was isolated as a yellow solid (659 mg, 74%), mp 143–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ=3.87 (s, 6H, OCH_3), 3.89 (s, 6H, OCH_3), 4.30 (s, 3H, OCH_3), 6.82 (s, 2H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ=53.25, 56.52 (2C), 61.13,

61.34 (CH_3), 107.15 (2C, CH), 114.37 (C), 118.40 (q, J= 319.50 Hz, CF_3), 120.88, 125.21, 136.90, 140.38, 153.51, 155.67, 160.15, 165.82 (C); IR (KBr): $\tilde{\nu}$=3580 (w), 2952 (w), 1791 (s), 1739 (s), 1654 (m), 1510 (m), 1425 (s), 1237 (m), 1220 (s), 1130 (s), 1086 (s), 1044 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 497.6 (M^+, 51), 364.9 (22), 304.9 (100), 250.9 (21), 69.9 (14), 28.0 (27).

2.7. General procedure for the synthesis of butenolides 10, 14a–d, 16 and 18 by Suzuki reactions

A dioxane solution (5 ml per 1 mmol of triflate) of triflate **3** (1.0 equiv), boronic acid (1.3 equiv), K_3PO_4 (1.5 equiv) and $Pd(PPh_3)_4$ (3 mol%) was refluxed for 4 h. A saturated aqueous solution of ammonium chloride was added. The organic and the aqueous layer were separated and the latter was extracted (3×) with ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc/hexane).

2.7.1. *O*-Methylpinastric acid (10). Starting with **7a** (125 mg, 0.30 mmol), (4-methoxyphenyl)boronic acid (60 mg, 0.39 mmol), potassium phosphate (102 mg, 0.48 mmol), tetrakis(triphenylphosphine) palladium (11 mg, 0.009 mmol) and dioxane (1.5 ml), **10** was isolated as a colourless solid (80 mg, 70%), mp 154 °C. The spectroscopic data are identical with those reported.[2d] ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.96 (dd, 2H, J=2.1, 6.9 Hz, ArH), 7.35–7.50 (m, 5H, ArH), 7.67 (dd, 2H, J= 1.8, 6.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.80, 55.35, 61.01 (CH_3), 108.63 (C), 114.05 (2C, CH), 115.95, 120.38 (2C, C), 128.76 (2C), 129.05, (2C),129.31, 131.10 (2C, CH), 141.62, 160.14, 161.90, 167.13, 167.97 (C); IR (KBr): $\tilde{\nu}$=2952 (w), 1774 (s), 1733 (s), 1628 (m), 1603 (s), 1513 (s), 1368 (m), 1300 (m), 1252 (s), 1164 (m), 1044 (m), 938 (m), 766 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 366.0 (M^+, 100), 334.9 (5), 306.9 (20), 279.0 (24), 251.0 (33), 146.5 (14), 119.0 (22); elemental analysis: calcd (%) for $C_{21}H_{18}O_6$ (366.369): C 68.84, H 4.83; found: C 68.64, H 4.83.

2.7.2. Permethyl-4′-hydroxypulvinic acid (14a). The reaction was carried out following the general procedure for Suzuki reactions. Starting with **7b** (150 mg, 0.34 mmol), phenylboronic acid (55 mg, 0.45 mmol), potassium phosphate (115 mg, 0.54 mmol), tetrakis(triphenylphosphine) palladium (12 mg, 0.01 mmol) and dioxane (1.7 ml), **14a** was isolated as a yellow solid (106 mg, 85%), mp 174 °C. The spectroscopic data are identical with those reported.[2d] ^{1}H NMR (600 MHz, $CDCl_3$): δ=3.76 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.93 (d, 2H, J=8.4 Hz, ArH), 7.39 (t, 3H, J=7.2 Hz, ArH), 7.43 (d, 2H, J=7.8 Hz, ArH), 7.51 (d, 2H, J=7.8 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ=52.93, 55.55, 61.43 (CH_3), 107.99 (C), 114.52 (2C, CH), 116.53, 123.69 (C), 128.63 (2C), 129.06, 130.08 (2C), 131.02 (2C, CH), 131.40, 140.21, 160.67, 163.02, 167.47, 168.05 (C); IR (KBr): $\tilde{\nu}$=3100 (w), 1768 (s), 1728 (s), 1624 (s), 1598 (s), 1511 (m), 1440 (w), 1367 (m), 1288 (s), 1257 (m), 1183 (m), 1159 (m), 1042 (m), 935 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 366.1 (M^+, 100), 307.0 (48), 251.1 (40), 165.0 (2), 89.0 (21); elemental analysis: calcd (%) for $C_{21}H_{18}O_6$ (366.36): C 68.84, H 4.83; found: C 68.51, H 5.12.

2.7.3. Permethylatromentic acid (14b). The reaction was carried out following the general procedure for Suzuki reactions. Starting with **7b** (200 mg, 0.45 mmol), (4-methoxyphenyl)boronic acid (90 mg, 0.59 mmol), potassium phosphate (155 mg, 0.72 mmol), tetrakis(triphenylphosphine) palladium (16 mg, 0.013 mmol) and dioxane (2.2 ml), **14b** was isolated as a yellow solid (110 mg, 62%), mp 168–169 °C. The spectroscopic data are identical with those reported.[3] ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.76 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 6.94 (t, 4H, J=8.9 Hz, ArH), 7.49 (d, 2H, J=8.7 Hz, ArH), 7.64 (d, 2H, J=9.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 52.68, 55.12, 55.28, 60.89 (CH_3), 108.03 (C), 113.93 (2C), 114.23 (2C, CH), 115.82, 120.51, 123.48 (C), 130.69 (2C), 130.95 (2C, CH), 140.15, 159.96, 160.32, 162.04, 167.31, 168.05 (C); IR (KBr): $\tilde{\nu}$=2957 (w), 1764 (s), 1732 (s), 1627 (m), 1599 (s), 1511 (s), 1459 (m), 1367 (m), 1288 (s), 1252 (s), 1160 (s), 1041 (m), 840 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 396.0 (M^+, 100), 337.0 (57), 281.0 (33), 223.0 (3), 119.1 (26), 28.1 (55); elemental analysis: calcd (%) for $C_{22}H_{20}O_7$ (396.40): C 66.66, H 5.08; found: C 67.31, H 5.45.

2.7.4. Permethylxerocomic acid (14c). The reaction was carried out following the general procedure for Suzuki reactions. Starting with **7b** (200 mg, 0.45 mmol), (4,5-dimethoxyphenyl)boronic acid (107 mg, 0.59 mmol), potassium phosphate (155 mg, 0.72 mmol), tetrakis(triphenylphosphine) palladium (16 mg, 0.013 mmol) and dioxane (2.2 ml), **14c** was isolated as a yellow solid (157 mg, 81%), mp 147–148 °C (lit.[13] mp 146–148 °C). The spectroscopic data are identical with those reported.[13] ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.91 (s, 9H, OCH_3), 6.94 (br, 3H, ArH), 7.10–7.40 (m, 2H, ArH), 7.65 (d, 2H, J=7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.73, 55.32, 55.88, 55.98, 60.91 (CH_3), 108.25 (C), 110.95, 112.46, 114.27 (2C, CH), 115.97, 120.76 (C), 122.76 (CH), 123.46 (C), 130.73 (2C, CH), 140.07, 148.76, 149.59, 160.37, 162.15, 167.31, 167.96 (C); IR (KBr): $\tilde{\nu}$=2952 (w), 1766 (s), 1728 (s), 1626 (m), 1601 (s), 1514 (s), 1462 (m), 1281 (s), 1257 (s), 1231 (s), 1185 (m), 1142 (s), 1047 (s), 1027 (m), 864 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 426.1 (M^+, 100), 367.1 (40), 311.0 (21), 148.2 (9), 69.8 (11); elemental analysis: calcd (%) for $C_{23}H_{22}O_8$ (426.40): C 64.78, H 5.20; found: C 64.32, H 5.63.

2.7.5. Permethylgomphidic acid (14d). The reaction was carried out following the general procedure for Suzuki reactions. Starting with **7b** (394 mg, 0.90 mmol), (3,4,5-trimethoxyphenyl)boronic acid (248 mg, 1.17 mmol), potassium phosphate (306 mg, 1.44 mmol), tetrakis (triphenylphosphine)palladium (32 mg, 0.027 mmol) and dioxane (4.5 ml), **14d** was isolated as a yellow solid (361 mg, 88%), mp 151–152 °C. The spectroscopic data are identical with those reported.[3] ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 6H, OCH_3), 3.91 (s, 3H, OCH_3), 6.77 (s, 2H, ArH), 6.94 (d, 2H, J=9.0 Hz, ArH), 7.65 (d, 2H, J=9.0 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): δ=52.94, 55.52, 56.43 (2C),

61.05, 61.25 (CH_3), 107.33 (2C, CH), 108.30 (C), 114.51 (2C, CH), 116.60, 123.60, 123.91 (C), 130.99 (2C, CH), 138.85, 140.07, 153.36 (2C), 160.68, 162.78, 167.42, 167.95 (C); IR (KBr): $\tilde{\nu}=3006$ (w), 2951 (w), 1768 (s), 1733 (s), 1623 (m), 1596 (s), 1508 (s), 1457 (m), 1372 (m), 1284 (s), 1262 (m), 1129 (s), 1043 (m), 842 (w) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 455.8 (M^+, 13), 396.6 (2), 287.9 (5), 183.8 (5), 152.4 (25), 69.9 (16), 28.0 (100); elemental analysis: calcd (%) for $C_{24}H_{24}O_9$ (456.40): C 63.16, H 5.30; found: C 63.44, H 5.81.

2.7.6. Permethylvariegatic acid (16). Starting with triflate **7c** (200 mg, 0.42 mmol) and 3,4-dimethoxyphenylboronic acid (101 mg, 0.55 mmol), potassium phosphate (145 mg, 0.68 mmol), tetrakis (triphenylphosphine)palladium (15 mg, 0.012 mmol) and dioxane (2.1 ml), **16** was isolated as a yellow solid (156 mg, 80%), mp 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.80$ (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 9H, OCH_3), 3.93 (s, 3H, OCH_3), 6.89 (d, 1H, $J=8.7$ Hz, ArH), 6.93 (d, 1H, $J=8.4$ Hz, ArH), 7.10 (d, 1H, $J=8.4$ Hz, ArH), 7.14 (dd, 1H, $J=2.1$, 8.4 Hz, ArH), 7.20 (dd, 1H, $J=2.1$, 8.7 Hz, ArH), 7.32 (d, 1H, $J=2.1$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=52.73$, 55.83 (2C), 55.91 (2C), 60.88 (CH_3), 108.28 (C), 110.86, 110.93, 111.92, 112.34 (CH), 115.96, 120.65 (C), 122.48, 122.71 (CH), 123.61, 140.20, 148.68, 148.83, 149.53, 150.08, 162.02, 167.21, 167.79 (C); IR (KBr): $\tilde{\nu}=2949$ (w), 2838 (w), 1771 (s), 1731 (s), 1600 (m), 1516 (s), 1462 (m), 1296 (m), 1261 (s), 1138 (s), 1024 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 455.9 (M^+, 100), 397.0 (36), 319.9 (57), 260.9 (42), 148.2 (14); elemental analysis: calcd (%) for $C_{24}H_{24}O_9$ (456.44): C 63.15, H 5.30; found: C 62.86, H 5.48.

2.7.7. Permethyl-*iso*-gomphidic acid (18). The reaction was carried out following the general procedure for Suzuki reactions. Starting with **7d** (300 mg, 0.60 mmol), (4-methoxyphenyl)boronic acid (120 mg, 0.78 mmol), potassium phosphate (206 mg, 0.96 mmol), tetrakis(triphenylphosphine) palladium (22 mg, 0.018 mmol) and dioxane (3.0 ml), **18** was isolated as a yellow solid (200 mg, 73%), mp 204–205 °C. The spectroscopic data are identical with those reported.[3] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.37$ (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.88 (s, 9H, OCH_3), 6.90 (s, 2H, ArH), 6.96 (d, 2H, $J=9.0$ Hz, ArH), 7.56 (d, 2H, $J=9.0$ Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=52.99$, 56.44 (3C), 61.09, 61.17 (CH3), 106.84 (2C, CH), 108.86, 114.05 (C), 114.22 (2C, CH), 115.94, 126.48, 128.22 (C), 131.25 (2C, CH), 139.56, 141.52, 144.51, 153.40, 162.09, 167.25, 167.91 (C); IR (KBr): $\tilde{\nu}=$ 2950 (w), 1773 (s), 1728 (s), 1632 (m), 1602 (m), 1578 (m), 1509 (s), 1455 (m), 1420 (m), 1342 (m), 1302 (m), 1256 (s), 1150 (m), 1127 (s), 953 (m), 644 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 456.1 (M^+, 100), 397.1 (34), 270.1 (99), 123.1 (61), 93.0 (51), 65.8 (15); elemental analysis: calcd (%) for $C_{24}H_{24}O_9$ (456.40): C 63.15, H 5.30; found: C 62.95, H 5.33.

2.7.8. Synthesis of butenolide (11). To a CH_2Cl_2 solution (3.0 ml) of **10** (55 mg, 0.15 mmol) was added BBr_3 (0.11 ml, 1.2 mmol) at 0 °C and the mixture was stirred for 2 h at 0 °C. An aqueous solution of HCl (5%) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc) to give **11** as a red solid (35 mg, 69%), mp 226–227 °C. ^{1}H NMR (300 MHz, acetone-d_6): $\delta=3.87$ (s, 3H, OCH_3), 6.89 (d, 2H, $J=9.0$ Hz, ArH), 7.24–7.41 (m, 5H, ArH), 8.07 (d, 2H, $J=9.0$ Hz, ArH); ^{13}C NMR (75 MHz, DMSO): $\delta=53.13$ (CH_3), 113.00 (C), 115.06 (2C, CH), 120.33 (C), 128.36 (3C), 128.56 (2C), 128.82 (2C, CH), 131.93, 147.08, 156.54 (2C), 167.67, 168.5 (2C, C); IR (KBr): $\tilde{\nu}=3375$ (s), 2925 (w), 2252 (w), 1746 (s), 1674 (m), 1599 (s), 1435 (m), 1301 (s), 1276 (s), 1179 (m), 1062 (s), 966 (m), 840 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 338.1 (M^+, 38), 306.1 (100), 250.1 (40), 194.0 (36), 144.8 (41), 89.0 (40); elemental analysis: calcd (%) for $C_{19}H_{14}O_6$ (338.31): C 67.45, H 4.17; found: C 67.36, H 4.88.

2.7.9. Synthesis of pinastric acid (12). To a CH_2Cl_2 (13 ml) solution of **10** (230 mg, 0.62 mmol) was added BBr_3 (0.06 ml, 0.62 mmol) at 0 °C, and the mixture was stirred for 6 h at 0 °C. An aqueous solution of HCl (5%) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel) to give pinastric acid (**12**) as an orange solid (130 mg, 60%), mp 203 °C. The spectroscopic data are identical with those reported.[2d] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.84$ (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.96 (d, 2H, $J=9.0$ Hz, ArH), 7.24–7.42 (m, 5H, ArH), 8.12 (d, 2H, $J=9.0$ Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=54.32$, 55.25 (CH_3), 105.25 (C), 113.90 (2C, CH), 115.17, 121.62 (C), 128.07 (2C), 128.47, 129.34 (2C), 129.93 (2C, CH), 132.06, 154.99, 158.56, 159.52, 166.08, 171.66 (C); IR (KBr): $\tilde{\nu}=$ 2960 (w), 2554 (w), 1771 (s), 1674 (s), 1601 (s), 1515 (s), 1457 (m), 1442 (m), 1308 (s), 1279 (s), 1255 (s), 1189 (m), 1064 (m), 960 (m), 843 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 352.0 (M^+, 37), 319.9 (100), 264.0 (41), 208.0 (54), 146.5 (8); elemental analysis: calcd (%) for $C_{20}H_{16}O_6$ (352.34): C 68.18, H 4.58; found: C 68.51, H 4.60.

2.7.10. Synthesis of xerocomic acid and variegatic acid. A solution of the corresponding permethylated pulvinic acid and trimethylsilyl iodide (10 equiv) in $CDCl_3$ (4 ml per 1 mmol of permethylated acid) sealed under argon in a NMR tube, was kept at 55 °C for ca. 72 h. The reaction was monitored by ^{1}H NMR. The solvent was removed in vacuo and the residue was dissolved in methanol. The solution was kept at 25 °C for 30 min and then the methanol was removed in vacuo. The residue was purified by chromatography (silica gel, benzene/ethyl acetate/formic acid=13:5:4).

2.7.11. Xerocomic acid (15c). Starting with permethylated xerocomic acid (100 mg, 0.23 mmol), trimethylsilyl iodide (0.33 ml, 2.34 mmol) and $CDCl_3$ (0.9 ml), **15c** was isolated as an orange solid (60 mg, 72%), mp 296 °C (lit.[4] 295–297 °C); ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta=6.89$ (d, 3H, $J=8.5$ Hz, ArH), 7.27 (d, 2H, $J=8.5$ Hz, ArH), 7.59 (dd, 1H, $J=2.1$, 8.5 Hz, ArH), 7.73 (d, 1H, $J=2.1$ Hz, ArH); ^{13}C NMR (150 MHz, $(CD_3)_2CO$): $\delta=104.50$ (C), 115.49 (2C), 116.10 (CH), 117.01 (C), 121.08 (CH), 122.64, 123.47 (C), 130.22, 132.63 (2C, CH), 145.64, 146.31, 155.30, 158.37, 160.44, 167.14, 174.28 (C); IR (KBr): $\tilde{\nu}=3263$ (s), 2956

(w), 2501 (w), 1739 (s), 1680 (m), 1600 (s), 1513 (m), 1370 (m), 1257 (s) cm^{-1}; IR (Nujol): 3174 (s), 2673 (w), 1736 (s), 1600 (s), 1460 (s), 1376 (s) cm^{-1}; UV–Vis (EtOH): λ_{max} (log ε)=258 (4.14), 405 (4.02); MS (EI, 70 eV): *m/z* (%): 356.0 (M^+, 2), 337.9 (6), 277.0 (3), 180.9 (4), 44.0 (90), 28.1 (100); elemental analysis: calcd (%) for $C_{18}H_{12}O_8$ (356.28): C 60.68, H 3.39; found: C 61.28, H 3.52.

2.7.12. Variegatic acid (17). Starting with permethylated variegatic acid (184 mg, 0.40 mmol), trimethylsilyl iodide (0.58 ml, 4.03 mmol) and $CDCl_3$ (1.6 ml), **17** was isolated as an orange yellow solid (102 mg, 68%), mp 235 °C; ^1H NMR (300 MHz, $(CD_3)_2CO$): δ=6.76 (dd, 1H, J=2.1, 8.1 Hz, ArH), 6.86 (d, 1H, J=8.1 Hz, ArH), 6.88 (d, 1H, J=8.5 Hz, ArH), 6.91 (d, 1H, J=2.1 Hz, ArH), 7.59 (dd, 1H, J=2.1, 8.5 Hz, ArH), 7.73 (d, 1H, J=2.1 Hz, ArH); ^{13}C NMR (150 MHz, $(CD_3)_2CO$): δ=104.20 (C), 115.49 (2C), 116.09 (CH), 117.30 (C), 118.56, 121.01 (CH), 122.78 (C), 123.26 (CH), 126.09, 145.20, 145.63, 146.23 (2C), 155.12, 160.82, 167.30, 174.25 (C); IR (KBr): $\tilde{\nu}$=3390 (s), 2968 (m), 1741 (s), 1606 (s), 1583 (m), 1520 (m), 1364 (m), 1275 (s), 1114 (w) cm^{-1}; UV–Vis (EtOH): λ_{max} (log ε)=275 (4.16), 408 (3.94); MS (EI, 70 eV): *m/z* (%): 372.1 (M^+, 3), 354.0 (94), 328.0 (56), 298.0 (46), 242.0 (41), 148.2 (100), 44.1 (97); elemental analysis: calcd (%) for $C_{18}H_{12}O_9$ (372.29): C 58.07, H 3.24; found: C 58.64, H 3.34.

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Rearrangement or *gem*-difluorination of quinine and 9-epiquinine and their acetates in superacid

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Abstract—In HF-SbF_5, quinine **1a** or its dihydrochloride rearranges into compound **3** (89%), the preferred conformation of the substrate favouring the observed cyclization. Under similar conditions epiquinine **2a** dihydrochloride yields in equal amounts two 10,10-difluoro derivatives, epimeric at C-3. In this case, the more stable conformation of the substrate in which the benzylic hydroxyl group is 'exo' to the quinuclidyl moiety, prevents the cyclisation. Similarly acetates **1b** and **2b** give the corresponding 10,10-difluoro derivatives epimeric at C-3. Formation of *gem*-difluoro compounds implies the formation of chloro intermediates at C-10 followed by an hydride abstraction, yielding an α-chloronium ion. This one is trapped by a fluoride ion and leads to the product by halogen exchange.

1. Introduction

Cinchona alkaloids quinine and quinidine have been used respectively as antimalaria and antiarrhythmic drugs.[1] More recently these compounds and derivatives have been reported as catalysts or (co)catalysts in a variety of enantioselective reactions.[2]

Quinine and quinidine are cleaved in acetic acid to yield quinicine.[1] In our research for new derivatives we were interested in an original approach using superacidic media. We have previously reported novel and selective reactions carried out in superacid HF-SbF_5 on various polyfunctional products.[3] Under these superacidic conditions, the reactivity of the substrates, being (poly)protonated, is dramatically modified compared to what is observed with conventional acids. In this paper we would like to report the reactivity of quinine **1a**, 9-epiquinine **2a**, and acetates **1b** and **2b** in superacid (Fig. 1).

2. Results and discussion

Table 1 shows that either quinine **1a** or its dihydrochloride in HF-SbF_5 at −30 °C yield almost quantitatively a sole rearranged product **3** (89%).[4] Under similar conditions, quinine acetate **1b**, 9-epiquinine **2a** and its corresponding acetate **2b** lead to a complex mixture, whereas in the presence of chloride ions in the media (CCl_4 or 2HCl), these compounds give *gem*-difluoro derivatives.

2.1. Reaction of quinine 1a (or its dihydrochloride 1a·2HCl)

2.1.1. Determination of structure. Mass spectrometry of compound **3** shows that the molecular weight (324) is identical to that of quinine **1a**. The determination of structure and conformation of compound **3** was made by extensive NMR analysis. ^1H and ^{13}C resonances were assigned by DEPT, COSY, NOESY, HMQC and HMBC data. The long range couplings and NOE interactions have been observed and are reported in Figure 2.

These data favour an anti conformation with the quinoline moiety in horizontal position due to the reduced rotation mobility about the C_4–C_4, bond as indicated. The structure of compound **3** has been confirmed by X-ray analysis (Fig. 2).

2.1.2. Formation of compound 3. In the reaction conditions, quinine **1a** is probably polyprotonated yielding ion **8** by N-protonation of the quinuclidine group and

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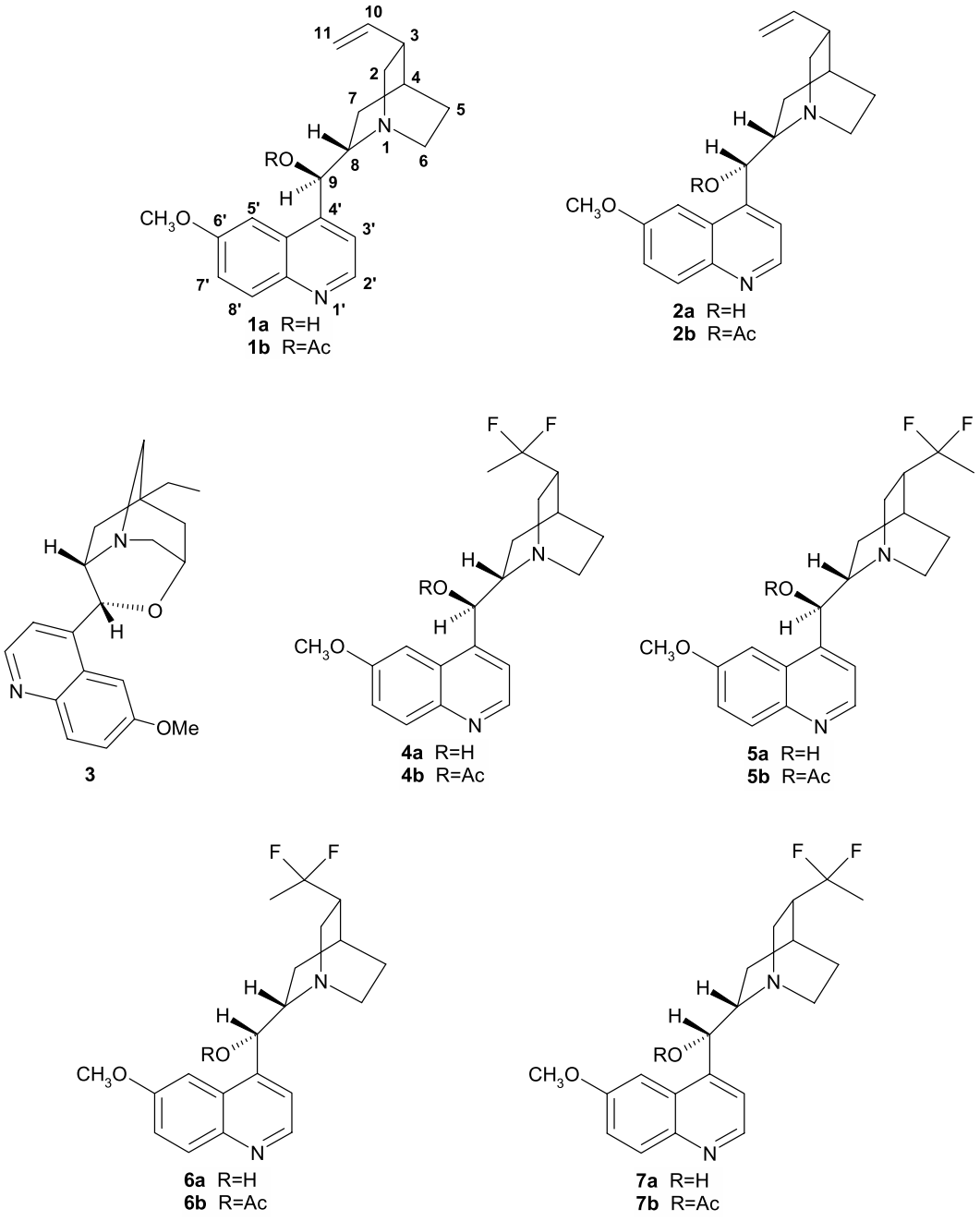


Figure 1.

diprotonation of the quinoline moiety at nitrogen and oxygen atoms, thus minimizing the interaction of the two positive charges (Scheme 1). Thus diprotonation disfavours the expected formation of benzylic ion by dehydratation of the protonated hydroxyl group (probably in equilibrium with the neutral form).

Table 1

Entry	Substrate	Product(s) (yield %)
1	**1a** or **1a**·2HCl (or CCl_4)	**3** (89)
2	**1b**	Complex mixture
3	**1b**·2HCl (or CCl_4)	**4b** (30)+**5b** (30)
4	**2a**	Complex mixture
5	**2a**·2HCl (or CCl_4)	**6a** (30)+**7a** (30)
6	**2b**	Complex mixture
7	**2b**·2HCl (or CCl_4)	**6b** (30)+**7b** (30)

Reaction conditions: HF/SbF_5, 10 min, −30 °C.

The following mechanism may be operative to account for the formation of compound **3**. Protonation of the C10–C11 double bond yields ion **9**. A rearrangement (**9**→**10**→**11**→**12**) implying a 1,2 hydride shift from C3 to C10, concerted with the migration of C4–C7 bond to C3, is followed by a 1,2 hydride shift to give ion **12**. The latter ion is trapped by the neutral hydroxyl group to give ether **3**, diprotonation of the quinoline moiety and N-protonation of the quinuclidyl group disfavouring the protonation of the hydroxyl group at C9. A non-concerted mechanism might lead either to ion **10** or to ion **13**, the latter leading to a product which has not been observed in the reaction.

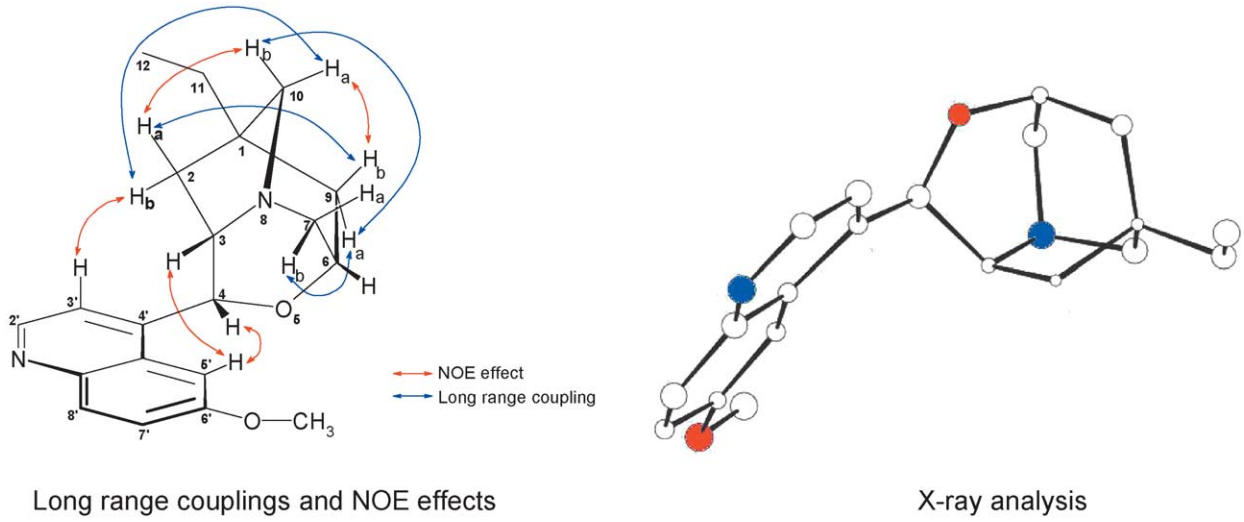
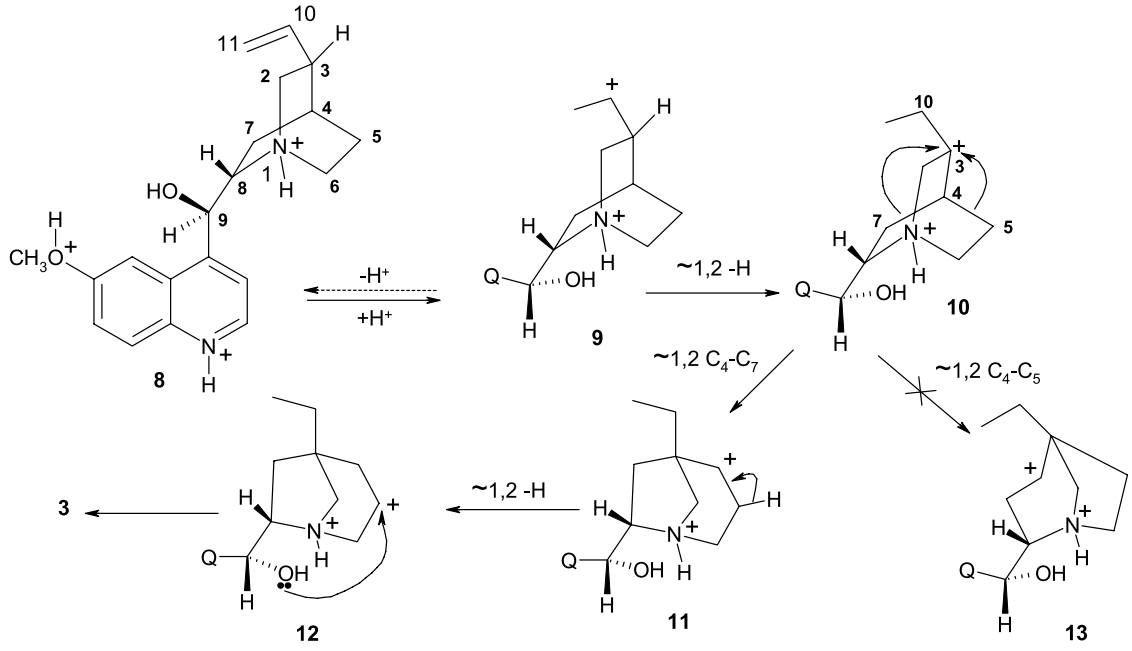


Figure 2.



Scheme 1.

2.2. Reaction of 9-epiquinine dihydrochloride 2a·2HCl

2.2.1. Determination of structure. 9-Epiquinine **2a** was prepared from quinine **1a** by the Mitsunobu reaction[5] and exhibits the expected NMR spectrometric data.[1c] Whereas 9-epiquinine **2a** gives a complex mixture in HF-SbF_5, the corresponding dihydrochloride **2a**·2HCl yields two new *gem*-difluoro derivatives **6a** (30%) and **7a** (30%).

Structures of **6a** and **7a** have been determined by NMR analysis and mass spectrometry. Whereas the quinoline moiety appears not to be modified when compared to compound **2a**, changes are observed in the upper part: disappearance of vinylic protons and presence of a difluorinated ethyl group characterized in ^{1}H NMR by a triplet at 1.51 ppm ($J=18.7$ Hz) for **6a** and at 1.54 ppm ($J=18.7$ Hz) for **7a**, and in ^{13}C NMR by a triplet at 125 ppm ($J=240$ Hz) for carbon 10 for both compounds. It should be noted that the ^{13}C NMR for compounds **6a** and **7a** are similar except for C5 and C7. For compound **6a**, C7 is more shifted than C5 as previously observed with quinine and its derivatives, whereas for compound **7a** C5 is more shifted than C7.[6] These data imply that compounds **6a** and **7a** are epimeric at C3. A Mitsunobu reaction, carried out with compounds **6a** and **7a**, gave **4a** and **5a**, respectively. The structure of compound **5a** has been determined by X-ray analysis confirming the proposed structure for compounds **4a**, **6a** and **7a** (Fig. 3).

2.2.2. Formation of compound 6a and 7a. Firstly, the importance of configuration at C9 on the reactivity of the substrates in superacid should be pointed out. Whereas quinine **1a** yields a single rearranged product **3**, 9-epiquinine **2a** gives, in the presence of chloride ions, two

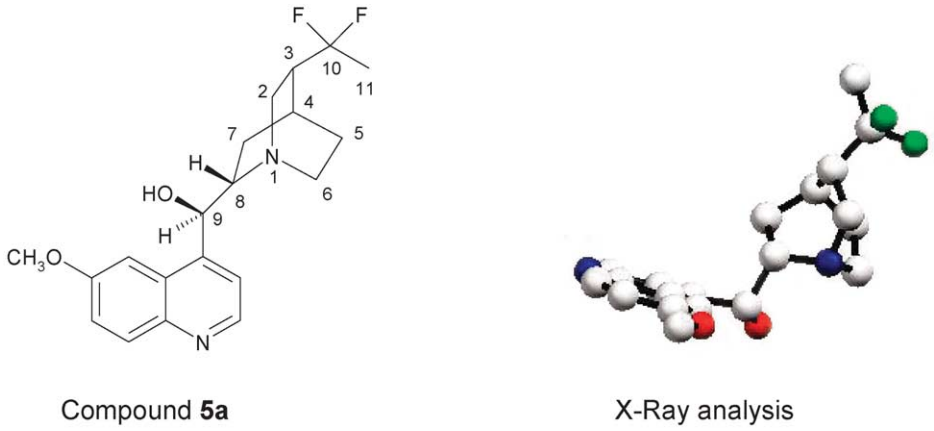
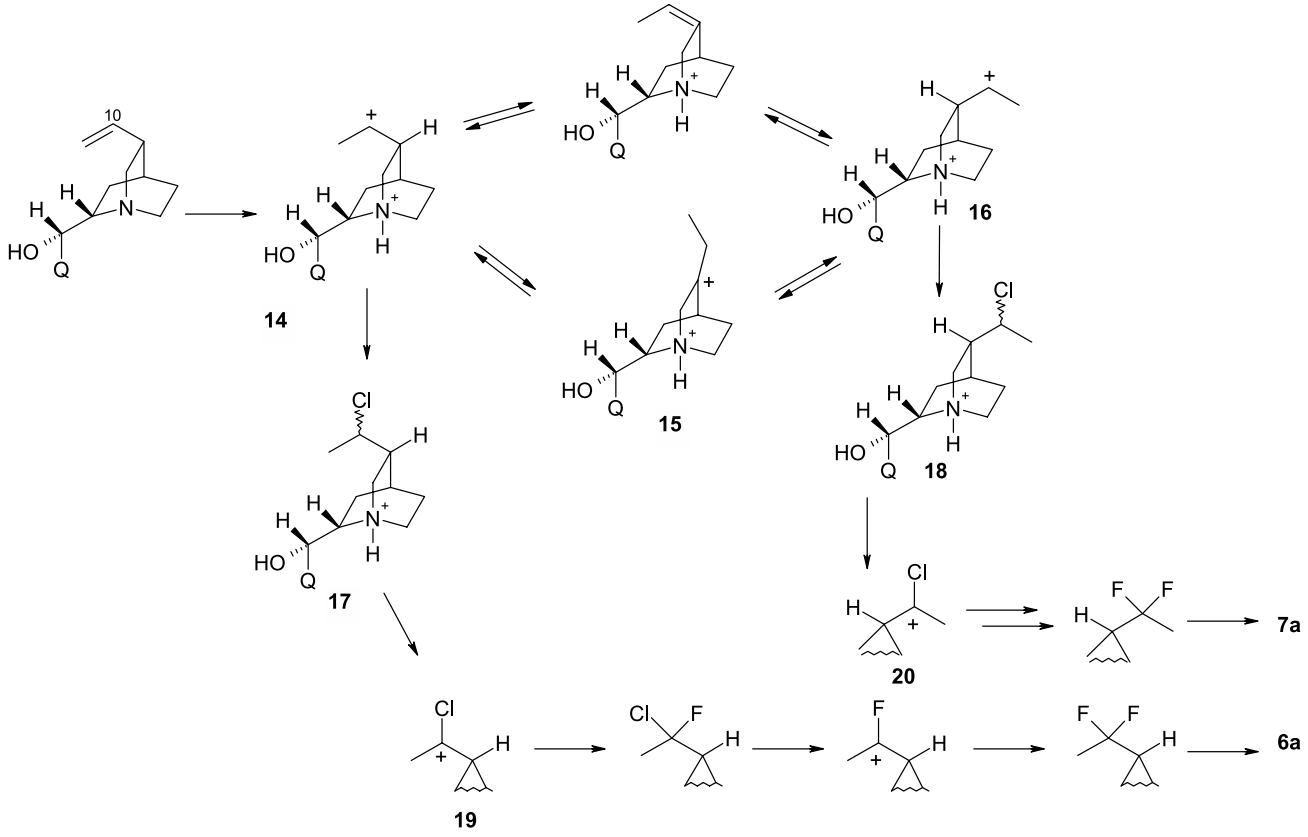


Figure 3.

gem-difluoro derivatives **6a** and **7a**. The postulated mechanism accounting for the formation of compounds **6a** and **7a** is similar to that postulated for the synthesis of *gem*-difluoroamines, from unsaturated amines such as anhydrovinblastine, precursor of Vinflunine (Javlor®), which is a novel anticancer agent.[7] This mechanism implies the formation of a carbenium ion **14** at C10 after protonation of the C10–C11 double bond (Scheme 2).

This ion can isomerize by a 1,2-hydride shift to tertiary ion **15** which is destabilized on account of the proximity of the protonated nitrogen atom. Ion **15**, after migration of hydrogen from C10 to C3 yields ion **14** and ion **16**, epimeric at C3. Another mechanism through a deprotonation–protonation process might also be operative for the formation of ions **14** and **16**. Trapping of these ions by the complex chloride SbF_5Cl^- involves the formation of intermediates **17** and **18**, chlorinated at C10. Hydride abstraction at C10 by the superacid HF-SbF_5 itself or by trichloromethyl ion CCl_3^+ in the presence of CCl_4,[7] gives mesomeric α-chlorocarbenium **19** and **20**, respectively which react with fluoride ions and lead by halogen exchange to the difluorinated products **6a** and **7a**. It has been shown that α-chloronium ions are stabilized by a chlorine atom



Scheme 2.

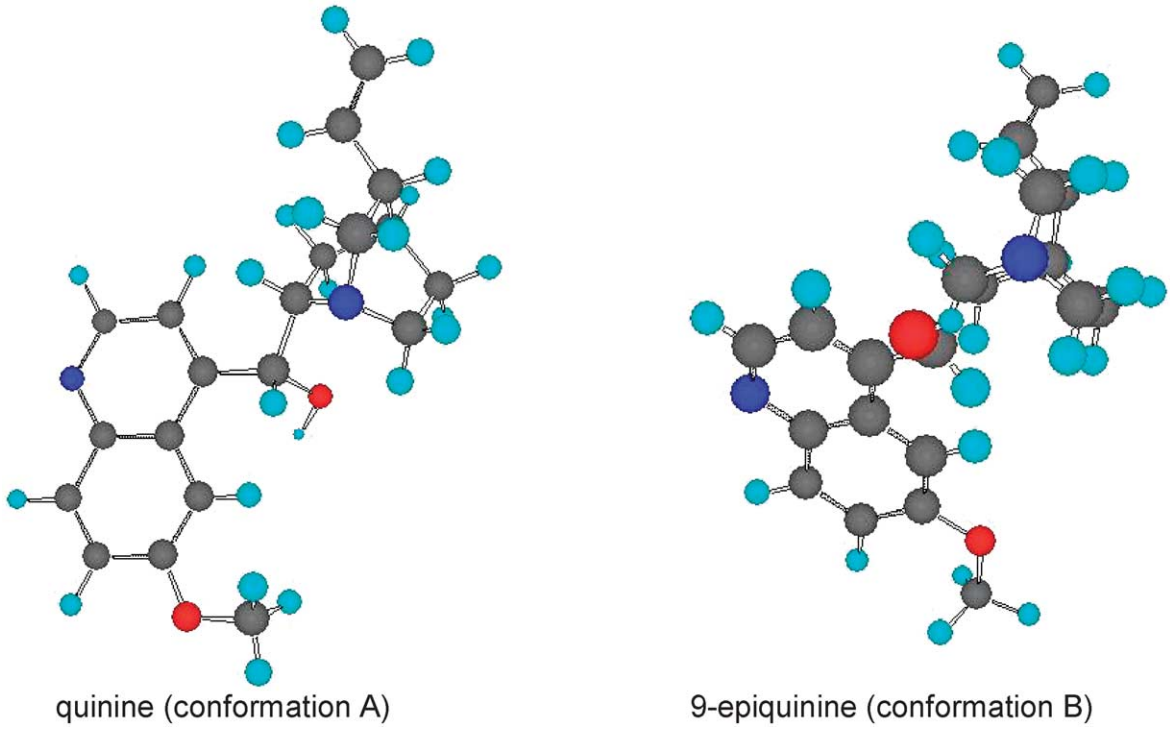


Figure 4.

which becomes π donor.[8] Unfortunately, it was not possible to isolate the assumed chloro intermediates **17** and **18**. In a similar reaction carried out with anhydrovinblastine, the corresponding chloroderivatives precursors of the *gem*-difluoro products, could be isolated and characterized.[7a]

2.2.3. Interpretation of the results. The different reactivity of quinine **1a** and 9-epiquinine **2a** in superacid can be explained by the two conformations of these substrates obtained by molecular modelisation, NMR and X-ray analysis.[9]

The more stable conformation of quinine **1a** and its hydrochloride is conformation A in which the hydroxyl group is under the quinuclidyl moiety, favouring the cyclisation following the rearrangement (Fig. 4). On the other hand, for 9-epiquinine **2a**, the preferred conformation is B, the hydroxyl group being 'exo' to the quinuclidyl group, thus preventing any cyclisation.

2.3. Reaction of quinine and 9-epiquinine acetates dihydrochloride 1b·2HCl or 2b·2HCl

Taking into account the cyclisation observed in the reaction of quinine dihydrochloride, we studied the reactivity of the corresponding acetate **1b** and its dihydrochloride in HF-SbF_5. Whereas acetate **1b** yields only a complex mixture, its dihydrochloride gives *gem*-difluoro derivatives **4b** (30%) and **5b** (30%), acylation of the hydroxyl preventing rearrangement and cyclisation. As expected, reaction of 9-epiquinine acetate dihydrochloride **2b**·2HCl yields the corresponding *gem*-difluoro compounds **6b** and **7b**. Reaction of acetates **6b** and **7b** with K_2CO_3 in methanol leads to the corresponding alcohols **6a** and **7a**, respectively. These compounds were also obtained by hydrolysis of acetates **4b** and **5b**, thus establishing the structures of **4b**, **5b**, **6b** and **7b**.

3. Biological activity

Gem-difluoro derivatives **6a** and **7a** have been tested in vitro on *Plasmodium falciparum* assay. The quinine-sensitive K1 or Thaï clones have been used to determine the influence of the two fluorine atoms at C10, and of the configuration at C3 on antimalaria activity. The IC_{50} values of quinine, chloroquine and *gem*-difluoro compounds **6a** and **7a** are reported in Table 2. The activity of the *gem*-difluoro derivatives appears to be comparable to that of quinine and chloroquinine.

Table 2

Substrate	IC_{50} (nM)	
	K1	Thaï
Quinine	50	22
Chloroquine	39.2	22.8
4a	100	24
5a	120	25

4. Conclusion

The study of the reactivity of cinchona alkaloids (quinine, 9-epiquinine) and their acetates in superacid media has showed the influence of the configuration of C-9.

With quinine **1a**, the more stable conformation, in which the benzylic hydroxyl group is under the quinuclidyl moiety, favours a new rearrangement not observed in usual acid conditions leading to an oxazapolycyclic compound.

In the case of 9-epiquinine, benzylic hydroxyl is 'exo' to the quinuclidyl moiety in the more stable conformation, preventing such a rearrangement. In the presence of chloride ions, two *gem*-difluoro derivatives, epimeric at C-3, are obtained.

By protection of the hydroxyl group of quinine by acetylation, no rearrangement is observed, but two *gem*-difluoro derivatives are obtained in the presence of chloride ions.

These results show the generality of this novel *gem*-difluorination, previously reported on amines and Vinca alkaloids.

5. Experimental

5.1. General methods

The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Reactions performed in superacid were carried out in a sealed Teflon® flask with a magnetic stirring. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out in anhydrous conditions leads as expected to the same results).

Yields refer to isolated pure products. ^{1}H and ^{13}C NMR were recorded on a 300 MHz Bruker spectrometer using $CDCl_3$ as solvent and TMS as internal standard.

Melting points were determined in a capillary tube and are uncorrected.

Mass spectra were measured in the electron impact mode (EI). High resolution mass spectra were performed on a Micromass ZABSpec TOF by the Centre Régional de Mesures Physiques de l'Ouest, Université Rennes.

All separations were done under flash-chromatography conditions on silica gel (15–40 μm).

Crystal data for **3** and **5a** were recorded at room temperature with a Nonius Kappa CDD diffractometer equipped with a graphite monochromator and an X-ray tube with a Mo anticathode (l=0.71069 Å). The structure was solved using direct methods[10] and refined using least square calculation.[11] The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 252807 for **3** and CCDC 252808 for **5a**.

Geometry optimizations were executed with Chem 3D by applying the AM1 and PM3 semi-empirical methods in MOPAC.

5.2. General procedure in superacidic media

To a mixture of SbF_5 (18 g, 0.082 mol) and HF (12 g, 0.6 mol) maintained at −30 °C in a Teflon® flask, was added quinine derivatives (3 mmol) with or without chloride source (2HCl, or CCl_4 (2 equiv)). The reaction mixture was magnetically stirred at the same temperature for 10 min. The reaction mixture was then neutralized with water/ice (300 mL) and sodium carbonate (100 g, 1 mol) and worked-up by usual manner. The products were isolated by column chromatography over SiO_2.

5.3. Reaction on quinine 1a

After reaction of quinine **1a** (972 mg, 3 mmol), following the general procedure, compound **3** (865 mg, 89%) was obtained as a white solid after flash chromatography eluted with the mixture CH_2Cl_2/MeOH/NH_3: 95/4.5/0.5 (v/v/v).

5.3.1. Compound 3. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (t, 3H, J=7.5 Hz, H-12), 1.21 (ddd, 1H, J=12.5, 9.8, 2.8 Hz, H-2a), 1.40 (m, 2H, H-11), 1.82 (m, 1H, H-9a), 1.84 (m, 1H, H-2b), 1.93 (dm, 1H, J=13.7 Hz, H-9b), 2.72 (broad s, 2H, H-10), 2.82 (dm, 1H, J=14 Hz, H-7a), 3.96 (s, 3H, O–CH_3), 3.99 (dm, 1H, J=14 Hz, H-7b), 4.10 (dm, 1H, J=9.8 Hz, H-3), 4.33 (broad s, 1H, H-6), 5.83 (broad s, 1H, H-4), 7.20 (d, 1H, J=2.0 Hz, H-5′), 7.36 (dd, 1H, J=7.7, 2.0 Hz, H-7′), 7.66 (d, 1H, J=4.4 Hz, H-3′), 8.03 (d, 1H, J=7.7 Hz, H-8′), 8.78 (d, 1H, J=4.4 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 9.8 (s, C-12), 29.6 (s, C-11), 38.4 (s, C-2), 42.2 (s, C-1), 42.3 (s, C-9), 54.4 (s, C-7), 56.1 (s, O–CH_3), 63.9 (s, C-3), 68.1 (s, C-10), 68.7 (s, C-4), 70.5 (s, C-6), 101.0 (s, C-5′), 119.5 (s, C-3′), 121.9 (s, C-7′), 126.5 (s, C-9′), 132.1 (s, C-8′), 144.2 (s, C-4′), 144.4 (s, C-10′), 148.1 (s, C-2′), 158.2 (s, C-6′). MS (70 eV), m/z (%): 324 (64), 309 (31), 295 (50), 282 (41), 252 (37), 83 (100). HRMS: $C_{20}H_{24}N_2O_2$ calculated: 324.1838, found: 324.1843. $[\alpha]_D$: −123.5° (c=0.2, $CHCl_3$, 20 °C). Mp: 83.6 °C.

Compound **3** was recrystallised in hexane/ether (80:20, v:v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{20}H_{24}N_2O_5$ molecular weight M=324.18, crystal system: orthorhombic, a=6.1430 (12) Å, b=17.355 (4) Å, c=18.305 (4) Å, volume of unit cell V=1951.5 (7) Å^3.

5.4. Reaction on 9-epiquinine 2a

After reaction of 9-epiquinine **2a** dihydrochloride (1.2 g, 3 mmol), following the general procedure, compounds **6a** (326 mg, 30%) and **7a** (326 mg, 30%) were isolated as oils after column chromatography eluted with the mixture AcOEt/petroleum ether/$HNEt_2$: 78/20/2 (v/v/v).

5.4.1. Compound 6a. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (m, 1H, H-7 endo), 1.51 (t, 3H, J=18.7 Hz, H-11), 1.56 (m, 1H, H-7 exo), 1.58 (m, 2H, H-5), 1.98 (m, 1H, H-3), 1.99 (m, 1H, H-4), 2.81 (m, 1H, H-6 exo), 3.14 (m, 2H, H-2), 3.17 (m, 1H, H-6 endo), 3.18 (m, 1H, H-8), 3.94 (s, 3H, –O–Me), 5.01 (d, 1H, J=10.0 Hz, H-9), 7.36 (dd, 1H, J=9.2, 2.7 Hz, H-7′), 7.38 (d, 1H, J=4.5 Hz, H-3′), 7.63 (d, 1H, J=2.7 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.73 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 22.5 (t, J=3 Hz, C-4), 23.0 (t, J=23 Hz, C-11), 25.9 (s, C-7), 28.8 (s, C-5), 40.7 (s, C-6), 42.3 (t, J=23 Hz, C-3), 50.5 (t, J=3 Hz, C-2), 55.5 (s, O–CH_3), 61.1 (s, C-8); 71.1 (s, C-9), 102.5 (s, C-5′), 120.1 (s, C-7′), 121.3 (s, C-3′), 124.8 (t, J=240 Hz, C-10), 128.1 (s, C-9′), 131.6 (s, C-8′), 144.1 (s, C-4′), 144.8 (s, C-10′), 147.6 (s, C-2′), 157.4 (s, C-6′). MS (70 eV), *m/z* (%): 362 (28), 189 (49), 174 (77), 146 (69), 82 (100). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. $[\alpha]_D$: 24.4° (c=1, MeOH, 20 °C).

5.4.2. Compound 7a. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (m, 1H, H-7), 1.25 (m, 1H, H-7), 1.26 (m, 1H, H-5), 1.54 (t, 3H, J=18.7 Hz, H-11), 2.00 (m, 1H, H-5), 1.98 (m, 1H, H-3), 1.99 (m, 1H, H-4), 2.86 (m, 1H, H-6 exo), 3.10 (m, 2H, H-2), 3.12 (m, 1H, H-8), 3.14 (m, 1H, H-6 endo), 3.92 (s, 3H, –O–Me), 5.04 (d, 1H, J=10.0 Hz, H-9), 7.36 (dd, 1H, J=9.2, 2.6 Hz, H-7′), 7.40 (d, 1H, J=4.5 Hz, H-3′), 7.67 (d, 1H, J=2.6 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.70 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 22.4 (s, C-5), 22.8 (t, J=4 Hz, C-4), 23.1 (t, J=23 Hz, C-11), 31.5 (s, C-7), 41.2 (s, C-6), 42.3 (t, J=23 Hz, C-3), 50.2 (t, J=4 Hz, C-2), 55.5 (s, –O–CH_3), 61.2 (s, C-8), 71.6 (s, C-9), 102.6 (s, C-5′), 120.2 (s, C-7′), 121.4 (s, C-3′), 125.2 (t, J=240 Hz, C-10), 128.0 (s, C-9′), 131.6 (s, C-8′), 144.2 (s, C-4′), 144.5 (s, C-10′), 147.5 (s, C-2′), 157.4 (s, C-6′). MS (70 eV), *m/z* (%): 362 (28), 189 (49), 174 (85), 146 (70), 82 (100). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. $[\alpha]_D$: −13.8° (c=1, MeOH, 20 °C).

5.5. Reaction on quinine acetate dihydrochloride 1b

After reaction of quinine acetate **1b** dihydrochloride (880 mg, 2 mmol), following the general procedure, compounds **4b** (240 mg, 30%) and **5b** (240 mg, 30%) were isolated as oils after column chromatography eluted with the mixture AcOEt/petroleum ether/$HNEt_2$: 28/70/2 (v/v/v).

5.5.1. Compound 4b. ^{1}H NMR (300 MHz, $CDCl_3$): 1.50 (m, 1H, H-7 endo), 1.52 (m, 1H, H-5), 1.56 (t, 3H, J=18.7 Hz, H-11), 1.74 (m, 1H, H-5), 1.99 (m, 1H, H-3), 2.03 (m, 1H, H-7 exo), 2.11 (s, 3H, H-13), 2.16 (m, 1H, H-4), 2.67 (m, 1H, H-6 exo), 2.93 (m, 2H, H-2), 3.16 (m, 1H, H-6 endo), 3.55 (m, 1H, H-8), 3.96 (s, 3H, –O–Me), 6.48 (d, 1H, J=7.5 Hz, H-9), 7.35 (dd, 1H, J=9.2, 2.5 Hz, H-7′), 7.38 (d, 1H, J=4.5 Hz, H-3′), 7.43 (d, 1H, J=2.5 Hz, H-5′), 8.01 (d, 1H, J=9.2 Hz, H-8′), 8.73 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.4 (s, 3H, C-13), 23.0 (t, J=3 Hz, C-4), 23.4 (t, J=22 Hz, C-11), 25.6 (s, C-7), 28.9 (s, C-5), 42.7 (s, C-6), 43.0 (t, J=22 Hz, C-3), 51.6 (t, J=3 Hz, C-2), 56.1 (s, –O–CH_3), 59.1 (s, C-8); 74.2 (s, C-9), 101.9 (s, C-5′), 119.6 (s, C-7′), 122.3 (s, C-3′), 125.2 (t, J=240 Hz, C-10), 127.4 (s, C-9′), 132.1 (s, C-8′), 145.2 (s, C-4′), 143.6 (s, C-10′), 147.7 (s, C-2′), 158.4 (s, C-6′), 170.4 (CO). HRMS: $C_{22}H_{26}N_2O_3F_2$ calculated: 404.1911, found: 404.1911. $[\alpha]_D$: −28.7° (c=0.9, MeOH, 20 °C).

5.5.2. Compound 5b. ^{1}H NMR (300 MHz, $CDCl_3$): 1.48 (m, 1H, H-5), 1.54 (t, 3H, J=18.7 Hz, H-11), 1.70 (m, 2H, H-7), 1.95 (m, 1H, H-4), 1.96 (m, 1H, H-3), 2.14 (s, 3H, H-13), 2.15 (m, 1H, H-5), 2.75 (m, 1H, H-6 exo), 2.89 (m, 2H, H-2), 3.11 (m, 1H, H-6 endo), 3.34 (m, 1H, H-8), 3.96 (s, 3H, –O–Me), 6.55 (d, 1H, J=6.7 Hz, H-9), 7.33 (d, 1H, J=4.5 Hz, H-3′), 7.39 (dd, 1H, J=9.1, 2.7 Hz, H-7′), 7.46 (d, 1H, J=2.7 Hz, H-5′), 8.02 (d, 1H, J=9.1 Hz, H-8′), 8.72 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.4 (s, C-13), 22.6 (s, C-5), 23.3 (t, J=4 Hz, C-4), 23.4 (t, J=23 Hz, C-11), 31.0 (s, C-7), 42.5 (t, J=23 Hz, C-3), 43.4 (s, C-6), 51.2 (t, J=4 Hz, C-2), 56.0 (s, O–CH_3), 59.2 (s, C-8), 74.0 (s, C-9), 101.9 (s, C-5′), 118.9 (s, C-3′), 122.2 (s, C-7′), 125.6 (t, J=240 Hz, C-10), 127.3 (s, C-9′), 132.2 (s, C-8′), 143.9 (s, C-10′), 145.1 (s, C-4′), 147.7 (s, C-2′), 158.4 (s, C-6′), 170.8 (CO). HRMS: $C_{22}H_{26}N_2O_3F_2$ calculated: 404.1911, found: 404.1911. $[\alpha]_D$: −74.9° (c=1, MeOH, 20 °C).

5.6. Reaction on epiquinine acetate dihydrochloride 2b

After reaction of epiquinine acetate **2b** dihydrochloride (350 mg, 0.8 mmol), following the general procedure, compounds **6b** (97 mg, 30%) and **7b** (97 mg, 30%) were isolated as oils after column chromatography eluted with the mixture AcOEt/petroleum ether/$HNEt_2$: 28/70/2 (v/v/v).

5.6.1. Compound 6b. ^{1}H NMR (300 MHz, $CDCl_3$): 0.75 (m, 1H, H-7), 1.52 (t, 3H, J=18.7 Hz, H-11), 1.53 (m, 3H, 2H-5, H-7), 1.93 (m, 2H, H-4, H-3), 2.08 (s, 3H, H-13), 2.77 (m, 1H, H-6), 3.13 (m, 2H, H-2), 3.33 (m, 1H, H-6), 3.61 (m, 1H, H-8), 3.97 (s, 3H, –O–Me), 6.41 (d, 1H, J=10 Hz, H-9), 7.40 (m, 2H, H-3′, H-7′), 7.58 (d, 1H, J=2.7 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.76 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.6 (s, C-13), 23.0 (s, C-4), 23.4 (t, J=28 Hz, C-11), 26.4 (s, C-7), 29.2 (s, C-5), 41.6 (s, C-6), 43.1 (t, J=23.4 Hz, C-3), 51.1 (s, C-2), 56.0 (s, –O–CH_3), 59.1 (s, C-8); 71.5 (s, C-9), 102.1 (s, C-5′), 121.0 (s, C-7′), 122.2 (s, C-3′), 128.1 (t, J=240 Hz, C-10), 128.2 (s, C-10′), 132.2 (s, C-8′), 141.3 (s, C-4′), 145.2 (s, C-9′), 147.9 (s, C-2′), 158.5 (s, C-6′), 170.8 (s, C═O).

5.6.2. Compound 7b. ^{1}H NMR (300 MHz, $CDCl_3$): 0.99 (m, 1H, H-7), 1.25 (m, 3H, H-7, 2H-5), 1.55 (t, 3H, J=18.7 Hz, H-11), 1.94 (m, 2H, H-3, H-4), 2.09 (s, 3H, H-13), 2.84 (m, 1H, H-6), 3.10 (m, 2H, H-2), 3.24 (m, 1H, H-6), 3.46 (m, 1H, H-8), 3.97 (s, 3H, –O–Me), 6.43 (d, 1H, J=10 Hz, H-9), 7.40 (m, 2H, H-3′, H-8′), 7.59 (d, 1H, 2.7 Hz, H-5′), 8.03 (d, 1H, J=9.2 Hz, H-8′), 8.75 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.6 (s, C-13), 22.7 (s, C-5), 23.1 (c, C-4) 23.2 (t, J=28 Hz, C-11), 32.1 (s, C-7), 41.7 (s, C-6), 42.5 (t, J=23 Hz, C-3), 50.8 (s, C-2), 56.0 (s, O–CH_3), 59.1 (s, C-8); 71.6 (s, C-9), 102.1 (s, C-5′), 120.9 (s, C-7′), 122.2 (s, C-3′), 125.6 (t, J=240 Hz, C-10), 128.1 (s, C-10′), 132.2 (s, C-8′), 142.1 (s, C-4′), 145.3 (s, C-9′), 147.8 (s, C-2′), 158.5 (s, C-6′), 170.7 (c, C═O).

5.7. Hydrolysis of compounds 4b and 5b

Compounds **4b** (or **5b**) was treated with K_2CO_3 (1.2 equiv) in a solution of MeOH/H_2O (7%). After being stirred for

2 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with AcOEt, washed, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give compounds **4a** as an oil (or **5a** as a yellow solid) (90%).

5.7.1. Compound 4a. ^{1}H NMR (300 MHz, $CDCl_3$): 1.44 (m, 1H, H-5), 1.49 (t, 3H, J=18.7 Hz, H-11), 1.54 (m, 1H, H-7 endo), 1.69 (m, 1H, H-7 exo), 1.74 (m, 1H, H-5), 1.89 (m, 1H, H-3), 2.05 (m, 1H, H-4), 2.57 (m, 1H, H-6 exo), 2.90 (m, 2H, H-2), 3.21 (m, 1H, H-8), 3.48 (m, 1H, H-6 endo), 3.87 (s, 3H, –O–Me), 5.44 (d, 1H, J=4.2 Hz, H-9), 7.24 (d, 1H, J=2.5 Hz, H-5′), 7.26 (dd, 1H, J=8.7, 2.6 Hz, H-7′), 7.38 (d, 1H, J=4.5 Hz, H-3′), 7.84 (d, 1H, J=8.7 Hz, H-8′), 8.36 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 23.0 (t, J=3 Hz, C-4), 23.1 (t, J=23 Hz, C-11), 22.6 (s, C-7), 28.5 (s, C-5), 42.7 (t, J=22 Hz, C-3), 43.1 (s, C-6), 51.4 (t, J=3 Hz, C-2), 55.6 (s, –O–CH_3), 59.6 (s, C-8); 71.9 (s, C-9), 101.6 (s, C-5′), 118.6 (s, C-3′), 121.4 (s, C-7′), 125.0 (t, J=240 Hz, C-10), 126.6 (s, C-9′), 131.0 (s, C-8′), 143.9 (s, C-10′), 148.3 (s, C-4′), 147.1 (s, C-2′), 157.6 (s, C-6′). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. $[\alpha]_D$: −102.8° (c=1.8, MeOH, 20 °C).

5.7.2. Compound 5a. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (m, 1H, H-7), 1.53 (t, 3H, J=18.7 Hz, H-11), 1.58 (m, 1H, H-5), 1.91 (m, 1H, H-3), 1.92 (m, 1H, H-5), 1.97 (m, 1H, H-7), 2.06 (m, 1H, H-4), 2.76 (m, 1H, H-6 exo), 2.95 (m, 1H, H-8), 3.71 (s, 3H, –O–Me), 2.96 (m, 2H, H-2), 3.67 (m, 1H, H-6 endo), 5.58 (d, 1H, J=4.2 Hz, H-9), 6.98 (d, 1H, J=2.7 Hz, H-5′), 7.20 (dd, 1H, J=9.2, 2.7 Hz, H-7′), 7.59 (d, 1H, J=4.5 Hz, H-3′), 7.84 (d, 1H, J=9.2 Hz, H-8′), 8.56 (d, 1H, J=4.5 Hz, H-2′).

^{13}C NMR (75 MHz, $CDCl_3$): 21.7 (s, C-5), 23.3 (t, J=23 Hz, C-11), 23.4 (t, J=4 Hz, C-4), 26.6 (s, C-7), 42.2 (t, J=23 Hz, C-3), 43.9 (s, C-6), 51.0 (t, J=4 Hz, C-2), 55.5 (s, –O–CH_3), 59.1 (s, C-8); 70.6 (s, C-9), 100.7 (s, C-5′), 118.2 (s, C-7′), 121.7 (s, C-3′), 125.3 (t, J=240 Hz, C-10), 126.1 (s, C-9′), 130.9 (s, C-8′), 143.5 (s, C-10′), 147.1 (s, C-2′), 148.3 (s, C-4′), 157.7 (s, C-6′). HRMS: $C_{20}H_{24}N_2O_2F_2$ calculated: 362.1806, found: 362.1789. Mp: 214 °C $[\alpha]_D$: −157.0° (c=1, MeOH, 20 °C).

Compound **5a** was recrystallized in CH_2Cl_2/hexane (20/80, v/v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{20}H_{24}N_2O_2F_2$, molecular weight M=362.42, crystal system: orthorhombic, a=7.14224 (3) Å, b=10.8005 (11) Å, c=23.583 (2) Å, volume of unit cell V=1819.2 (3) Å^3.

5.8. Synthesis of 9-epiquinine 2a by Mitsunobu reaction

A double-necked, round-bottomed flask was filled with quinine (4.05 g, 12.5 mmol) in anhydrous THF (70 mL) with 4-nitrobenzoic acid (4.18 g, 25 mmol) and PPh_3 (6.55 g, 25 mmol). The flask was cooled to 0 °C, and DEAD (3.93 mL, 25 mmol) was slowly added to maintain the temperature below 10 °C. Then the mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed in vacuo, and the residue was diluted with ether. The white precipitate was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$. The organic extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

The crude was treated with K_2CO_3 (1.2 equiv) in a solution of MeOH/H_2O (7%). Then the reaction mixture was stirred for 2 h and concentrated under reduced pressure. The residue was diluted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (AcOEt/$HNEt_2$: 98/2, v/v) gave 9-epiquinine **2a** (2.63 g, 65%) as an oil.

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Stereospecific synthesis of 2,2,3-trisubstituted tetrahydroquinolines: application to the total syntheses of benzastatin E and natural virantmycin

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Abstract—An efficient methodology for the synthesis of 2,2,3-trisubstituted tetrahydroquinolines has been developed, which involves the triphenylphosphine–CCl_4-mediated stereospecific rearrangement of α,α-disubstituted indoline-2-methanols **15** to 2,2,3-trisubstituted tetrahydroquinolines **26**. The rearrangement precursors **15** are readily prepared by the diastereoselective Grignard addition to 2-acylindolines **13**. The total syntheses of (+)-benzastatin E (**1**) and natural virantmycin (**2a**) were accomplished utilizing this methodology. This rearrangement reaction might afford some chemical precedent for the biogenetic pathway of the benzastatin family.

1. Introduction

The stereoselective construction of chiral quaternary carbon centers is one of the most difficult transformations in organic synthesis. The difficulty is magnified when quaternary stereogenic centers is involved.[1] Substituted tetrahydroquinolines and tetrahydroisoquinolines are compounds of great interest, because many biologically and pharmacologically active alkaloids bear this skeleton.[2] Chiral quaternary carbons are often essential for these compounds, and thus, the asymmetric synthesis of these ring systems has been the subject of intense research[3] though this still remains to be a challenging task. Few publications have described the enantioselective synthesis of isoquinoline derivatives containing C-1 quaternary stereocenter[4] or C-3 quaternary stereocenter.[5] Among them, Shibasaki et al. has recently reported an elaborate enantioselective synthesis of 1,1-disubstituted isoquinolines using a Reissert-type reaction.[4a] On the other hand, methods for asymmetric synthesis of quinoline derivatives with quaternary stereocenter has been relatively undeveloped. Recently, Mikami et al. has described an efficient enantioselective synthesis of quinolines bearing a C-3 quaternary stereocenter or a spiro ring, by the catalytic ene-type reaction of 1,7-enynes.[6] To the best of our knowledge, however, there has been no reports of a general, stereoselective synthesis of 2,2-disubstituted tetrahydroquinolines.

The benzastatin family and virantmycin are a novel class of indoline and tetrahydroquinoline alkaloids isolated from *Streptomyces nitrosporeous*.[7–10] Benzastatins show inhibitory activity against glutamate toxicity and lipid peroxidation in rat liver microsomes that can be used to prevent brain ischemia injury, and consists of indoline alkaloids such as benzastatin E, and tetrahydroquinoline alkaloids such as benzastatin C which are structurally related to virantmycin.[7,8] (−)-Virantmycin, a potent inhibitor towards RNA and DNA viruses, is a unique 2,2-disubstituted tetrahydroquinoline alkaloid with contiguous quaternary and tertiary stereocenters.[9,10] To date, several research groups have reported the total syntheses of (±)-virantmycin,[11,12] and the total synthesis of unnatural (+)-virantmycin was reported by Shirahama et al. in 1996.[13] The synthesis of natural occurring form of virantmycin, however, has not been accomplished.

Several biosynthetic pathways have been suggested for the benzastatin family based on the cooccurence of indolines and tetrahydroquinolines. Yoo et al. speculated that the simple benzastatin A is oxygenated at the double bond to form an intermediate epoxide, which can then undergo cyclization to form the indoline or the tetrahydroquinoline skeleton.[8] On the other hand, Yoo et al. proposed that the indoline and the tetrahydroquinoline skeletons can interconvert through an aziridine intermediate, demonstrated by the treatment of simple aziridine compound with anhydrous

Keywords: Diastereoselective Grignard addition; Benzastatin E; Rearrangement; Ring expansion reaction; Virantmycin.
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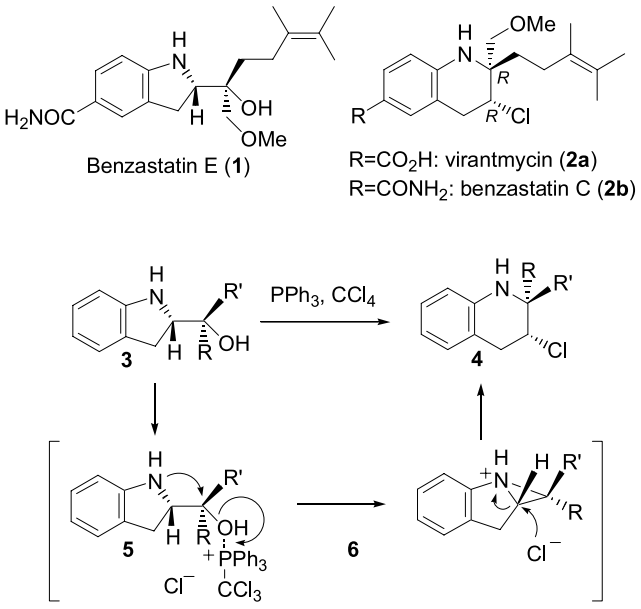
hydrogen chloride giving a mixture of indoline and tetrahydroquinoline.[14] This latter proposal indicates the biogenetic relationship between the indoline and the tetrahydroquinoline skeletons, and inspired us with the possibility of constructing the tetrahydroquinoline skeleton from indoline precursors via the intermediacy of aziridines, in a manner mimicking the biosynthetic process. Based on this proposed hypothesis, we designed the triphenylphosphine–CCl_4-mediated rearrangement from α,α-disubstituted indoline-2-methanol to 2,2,3-trisubstituted tetrahydroquinoline via the aziridine, followed by the ring opening attack of the chloride anion to the sterically less hindered carbon (Scheme 1). In this paper, we disclose the details of our development of stereoselective preparation of α,α-disubstituted indoline-2-methanols, and the stereospecific rearrangement of these precursors to furnish 2,2,3-trisubstituted tetrahydroquinolines, simultaneously constructing the contiguous quaternary and tertiary stereogenic centers. These methodologies were applied to efficient total syntheses of (+)-benzastatin E and natural virantmycin, which illustrates the utility of this methodology for the synthesis of various chiral indoline and tetrahydroquinoline alkaloids.[15,16]



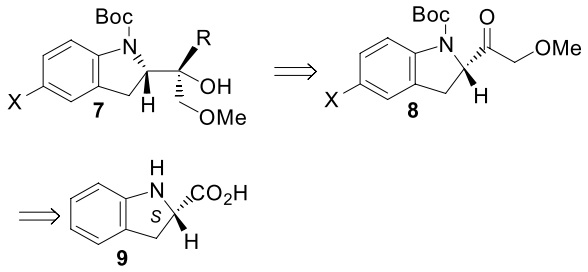
Scheme 1. Transformation of indolines to tetrahydroquinolines based on the proposed biosynthetic hypothesis.

2. Results and discussion

2.1. Diastereoselective synthesis of α,α-disubstituted indoline-2-methanols

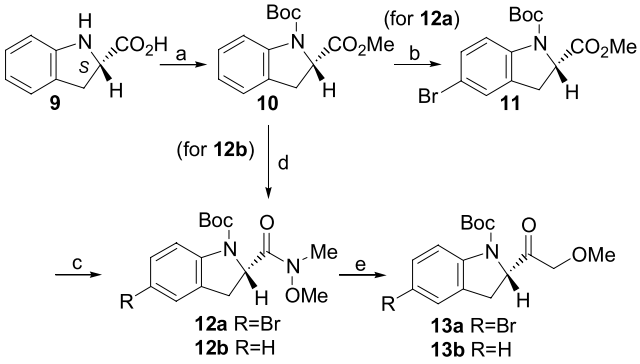
Our investigation of the stereospecific rearrangement of α,α-disubstituted indoline-2-methanols to 2,2,3-trisubstituted tetrahydroquinolines began with the development of a general route for the preparation of the rearrangement precursors. The synthetic scheme is outlined in Scheme 2. The key step, in terms of constructing the *tert*-alcohol moiety, is the diastereoselective Grignard addition to 2-acylindoline **8**.

The key intermediate 2-acylindoline **13** can be readily



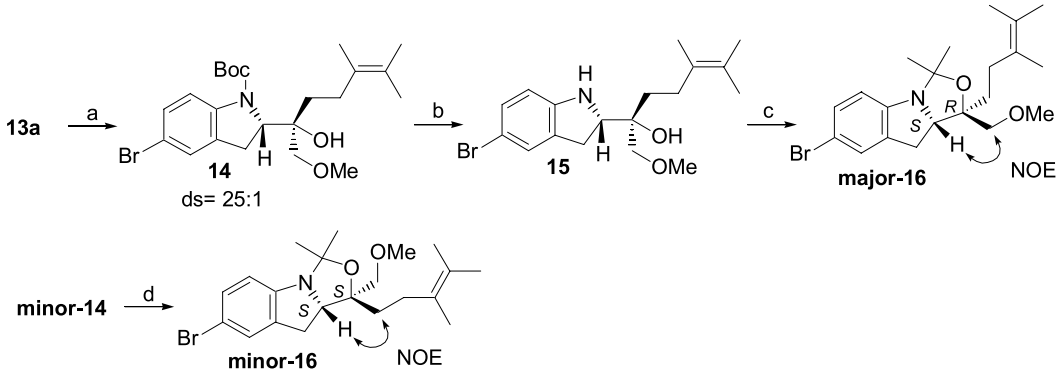
Scheme 2. Retrosynthetic analysis of α,α-disubstituted indoline-2-methanols **7**.

prepared from the commercially available (*S*)-(−)-indoline-2-carboxylic acid (**9**) as shown in Scheme 3. Carboxylic acid **9** was treated with sulfuric acid in methanol, followed by nitrogen protection with di-*tert*-butyl dicarbonate to provide methyl ester **10** in 92% yield. Bromination of **10** with NBS (1 equiv) in DMF afforded bromide **11** in 93% yield. The bromide was converted to Weinreb amide[17] **12a** by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and *i*-propylmagnesium chloride[18] in 83% yield. Coupling of methoxymethyl lithium,[19] derived from Sn–Li exchange of methyl tributylstannylmethyl ether, with **12a** afforded ketone **13a** in 61% yield. Simple 2-acylindoline **13b** with no substituent on the phenyl ring was obtained by directly converting **10** to Weinreb amide **12b** in 72% yield, followed by the coupling with methoxymethyl lithium to give **13b** in 56% yield.



Scheme 3. Reagents and conditions: (a) (i) MeOH, H_2SO_4, 80 °C; (ii) Boc_2O, CH_2Cl_2, rt, 92% (2 steps). (b) NBS, DMF, 0 °C, 93%. (c) *i*-PrMgCl, Me(MeONH)·HCl, THF, −20 to −10 °C, 83%. (d) *i*-PrMgCl, Me(MeONH)·HCl, THF, −20 to −10 °C, 72%. (e) $MeOCH_2Sn(n\text{-}Bu)_3$, *n*-BuLi, THF, −78 °C, 61% (**13a**), 56% (**13b**).

The Grignard addition to 2-acylindoline **13** proceeded with high diastereoselectivity and afforded the corresponding indoline-2-methanols in moderate to excellent yields.[20] In an initial experiment, reaction of 2-acylindoline **13a** with 3,4-dimethyl-3-pentenylmagnesium bromide[21] in THF at −78 °C furnished *tert*-alcohols in a 25:1 ratio of separable isomers (major-**14** and minor-**14**) (Scheme 4). The diastereoselectivity was determined by the HPLC analysis of the crude reaction mixture. The deprotection of the *N*-Boc group of major-**14** was achieved with HCO_2H/CH_2Cl_2 to give the rearrangement substrate, α,α-disubstituted indoline-2-methanol **15**. In order to determine the configuration of the newly created stereocenters, the *tert*-alcohols **14** were further converted to the corresponding



Scheme 4. Reagents and conditions: (a) 3,4-dimethyl-3-pentenylmagnesium bromide, THF, −78 °C, 91% (ds=25:1). (b) HCO_2H, CH_2Cl_2, 40 °C, 52%. (c) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 91%. (d) (i) HCO_2H, CH_2Cl_2, 40 °C, 76%; (ii) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 72%.

acetonides **16**. The absolute configuration of major-**14** was assigned as (9*S*,10*R*), and minor-**14** as (9*S*,10*S*), by the NOE experiment of the acetonides. The stereochemistry outcome of the diastereoselective Grignard addition can be rationalized by the Felkin–Anh model[22] depicted in Figure 1.

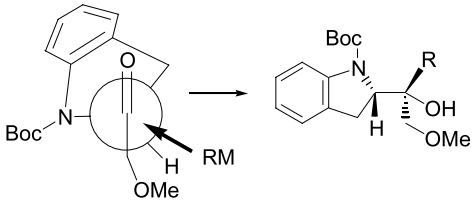


Figure 1. Diastereoselective Grignard addition.

To broaden the scope of this reaction, various 2-acylindolines were reacted with a series of Grignard reagents or alkyllithiums. The results are summarized in Table 1. In most cases, the reaction proceeded smoothly with high diastereoselectivities. It is noteworthy that either diastereomer can be easily obtained by exchanging the order of the metal reagent addition to Weinreb amide **12**, as shown in entries 1 and 2. The enantiomer of **14** can also be prepared by using (*R*)-(+)-indoline-2-carboxylic acid[23] as the starting material (entry 3). 2-Acylindolines with methoxymethyl group as the acyl group (**13a** and **13b**) reacted with variety of Grignard reagents and alkyllithiums, including vinyl Grignards (entries 8 and 9). However, the scope of the diastereoselective addition is somewhat limited when 2-acylindolines with alkyl groups (**13c**, **13e**–**h**) were applied as substrates. Alkyllithiums, such as methyllithium (entries 14 and 16), lithium phenylacetilide (entry 15) or phenyllithium (entry 17) reacts readily to furnish the corresponding *tert*-alcohols, whereas the Grignard reagents seemed to be less reactive. For example, **13h** does not react with methylmagnesium bromide under the standard conditions, resulting in the recovery of the starting material; the same applies to **13e** with 3-butenylmagnesium bromide, and **13f** with phenethylmagnesium chloride. All the obtained *tert*-alcohols **14** were converted to indoline-2-methanols **15** by the deprotection of the *N*-Boc group, thus efficiently providing the rearrangement precursors. The chiral HPLC analysis[24] of **15a** (the Boc-deprotected **14a**) shows that no racemization occurs during these manipulations (from **10** to **15**).

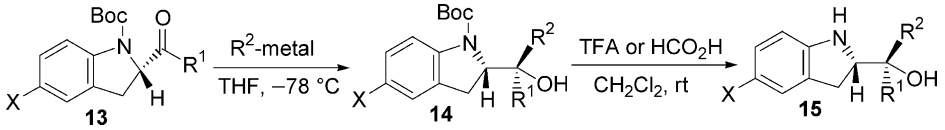
Furthermore, we satisfactorily accomplished the total synthesis of (+)-benzastatin E (**1**) in three steps from major-**16** as shown in Scheme 5. Benzastatin E (**1**) is the most potent inhibitor of glutamate toxicity using neuronal hybridoma N18-RE-105 among the benzastatin family.[8] The relative stereochemistry of **1** was elucidated by extensive NMR spectroscopic analysis, but the absolute stereochemistry was undetermined, leaving the question of which stereoisomer to aim at. Taking into account the proposed biosynthesis of benzastatins proceeding via the aziridine intermediate, the absolute configuration of indoline skeleton would be anticipated to reflect the configuration of tetrahydroquinolines such as (−)-virantmycin. Thus, one could speculate the absolute stereochemistry of benzastatin E to be 9*S*, and therefore the total synthesis of benzastatin E was carried out with major-**16**. Lithiation of major-**16** followed by the carboxylation with CO_2 provided **17**. Amidation of **17** with aqueous ammonia and 1,1′-carbonyldiimidazole (CDI) gave amide **18**. Removal of the acetonide protecting group from **18** with PPTS/MeOH furnished (+)-benzastatin E (**1**) $[\alpha]_D^{24}=+21.3$ (*c* 0.10, MeOH) (lit.[8] $[\alpha]_D^{18}=+17$ (*c* 0.1, MeOH))] in 64% yield. Spectral data (IR, ^{1}H NMR and ^{13}C NMR) for synthetic (+)-**1** are identical to that reported for the natural product. Therefore, the absolute stereochemistry of benzastatin E was confirmed as (9*S*,10*R*) as expected.

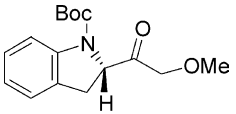
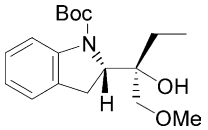
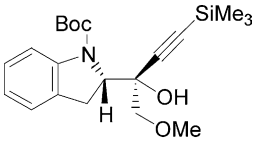
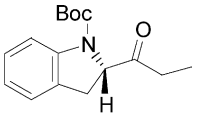
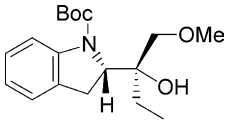
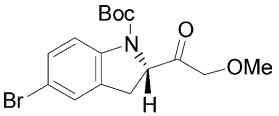
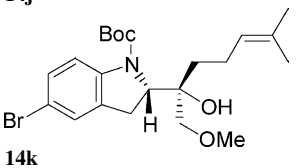
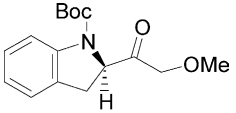
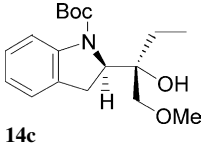
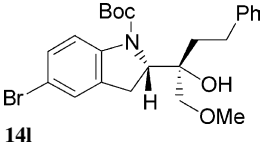
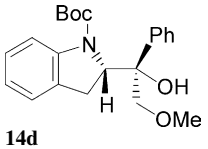
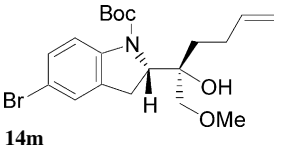
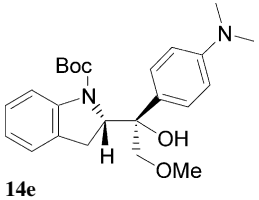
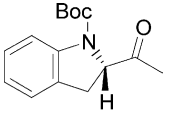
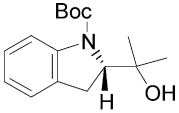
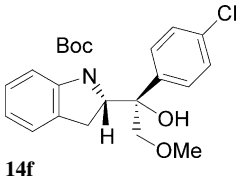
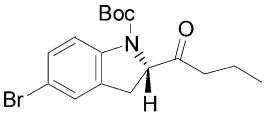
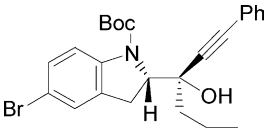
2.2. Stereospecific rearrangement from α,α-disubstituted indoline-2-ethanols to 2,2,3-trisubstituted tetrahydroquinolines

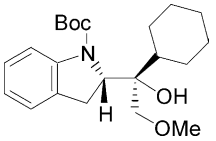
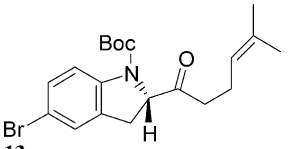
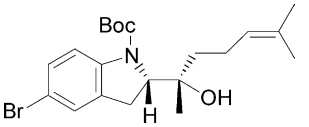
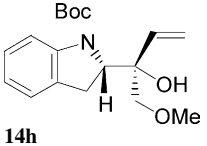
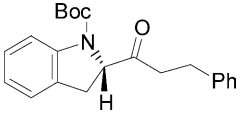
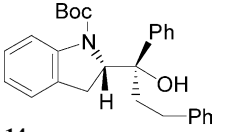
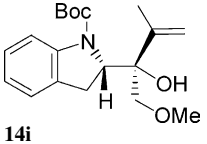
Having established the efficient method for the preparation of α,α-disubstituted indoline-2-methanols, the stereospecific rearrangement to 2,2,3-trisubstituted tetrahydroquinolines was investigated. Cossy et al. previously reported the ring-expansion reaction of *N*-benzylpyrrolidine-2-methanols to *N*-3-chloropiperidines using methanesulfonyl chloride, though they stated that no rearrangement occurs with α,α-disubstituted *N*-benzylpyrrolidine-2-methanols.[25] As speculated, this rearrangement did not proceed with our substrate **15a** resulting in crude mixture, probably due to the steric hindrance (Scheme 6).

Prior to the investigation of the rearrangement reaction of tertiary alcohols **15**, we decided to conduct a preliminary experiment with racemic α-monosubstituted

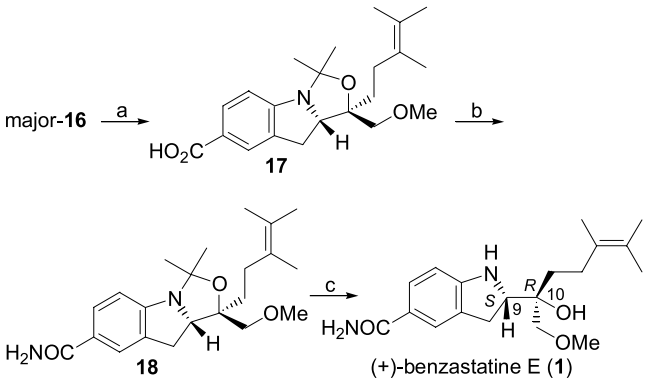
Table 1. Diastereoselective Grignard addition to 2-acylindolines **13**



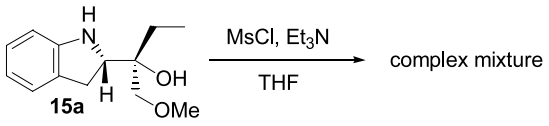
Entry	Substrate **13**[a]	Product **14**[b]	Yield[c]	Entry	Substrate **13**[a]	Product **14**[b]	Yield[c]
1	 **13b**	 **14a**	57% (16:1)[d]	10	**13b**	 **14j**	63 (38:1)
2[e]	 **13c**	 **14b**	86% (13:1)	11	 **13a**	 **14k**	67% (9:1)
3	 **13d**	 **14c**	62% (17:1)	12	**13b**	 **14l**	68% (8:1)
4	**13b**	 **14d**	94% (15:1)	13	**13b**	 **14m**	82% (11:1)
5	**13b**	 **14e**	84% (7:1)	14[e]	 **13e**	 **14n**	62%
6	**13b**	 **14f**	61% (9:1)	15[e]	 **13f**	 **14o**	85% (8:1)

7[f]	**13b**	 **14g**	85% (18:1)	16[e]	 **13g**	 **14p**	47% (10:1)
8	**13b**	 **14h**	97% (12:1)	17[e,g]	 **13h**	 **14q**	68% (38:1)
9	**13b**	 **14i**	100% (13:1)				

[a] Readily prepared from the corresponding Weinreb amide and either Grignard reagent or alkyllithium by the same method for preparation of **13** except for **13d**. Substrate **13d** was prepared from (*R*)-(+)-indoline-2-carboxylic acid.
[b] Absolute configuration of the major isomer was determined by NOE experiments of the corresponding acetonide derivative.
[c] Isolated yield of a mixture of diastereomers.
[d] Diastereomeric ratios determined by HPLC analysis of crude product mixtures.
[e] Alkyl lithium was used.
[f] 10 equiv of cyclohexylmagnesium bromide was used.
[g] 6 equiv of phenyllithium was used.

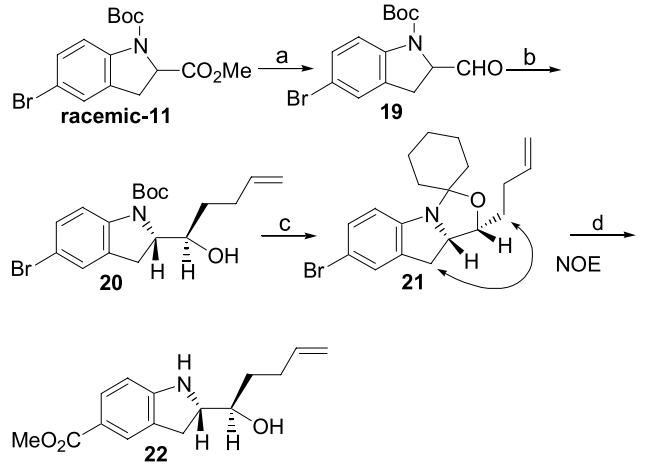


Scheme 5. Reagents and conditions: (a) *t*-BuLi, CO_2, Et_2O, −78 to 0 °C, 53%. (b) (i) CDI, 28%; (ii) aq NH_3, THF, rt, 74%; (c) PPTS, MeOH, rt, 64%.



Scheme 6. Attempt for the ring expansion using methanesulfonyl chloride.

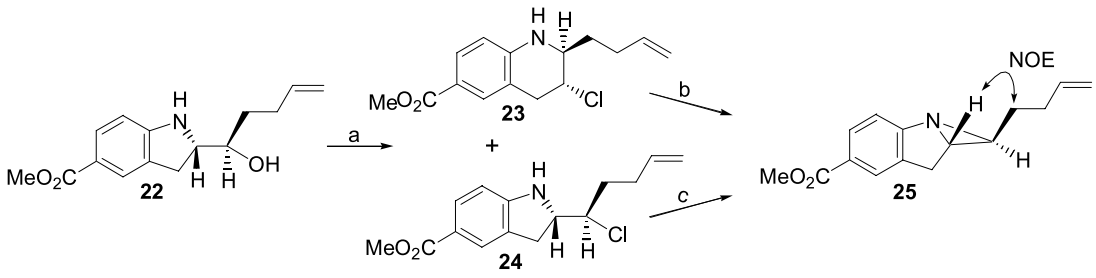
indoline-2-methanols. Synthesis of a representative substrate **22** is outlined in Scheme 7. Racemic ethyl ester **11** was converted to corresponding aldehyde **19** by reduction of **11** with LAH followed by Swern oxidization. In contrast to the Grignard reaction with 2-acylindolines **13** being highly diastereoselective, the Grignard reaction of the aldehyde **19** with 3-butenylmagnesium bromide proceeded in low diastereoselectivity. Lowering the reaction temperature to −87 °C was ineffective. The relative configuration of the Grignard adduct **20** was determined by the NOE experiment of the acetonide **21**, which was derived from **20** by deprotection of the *N*-Boc group, followed by the reaction with 1,1-dimethoxycyclohexane. The bromide on the phenyl ring of **21** was converted to a methyl ester group through a three step sequence, thus giving rise to the rearrangement precursor, α-monosubstituted indoline-2-methanol **22**.



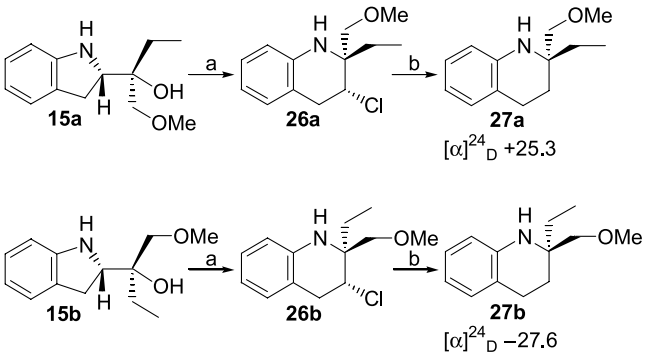
Scheme 7. Reagents and conditions: (a) (i) $LiAlH_4$, THF, −78 to 0 °C; (ii) SO_3·py, Et_3N, DMSO, CH_2Cl_2, 0 °C, 51% (2 steps). (b) 3-Butenylmagnesium bromide, THF, −78 °C, 75% (ds=3:1). (c) (i) TFA, CH_2Cl_2, 0 °C to rt, 59%; (ii) 1,1-dimethoxycyclohexane, *p*-TsOH, CH_2Cl_2, rt, 72%. (d) (i) *t*-BuLi, CO_2, Et_2O, −78 to 0 °C; (ii) $TMSCH_2N_2$, MeOH, 0 °C to rt; (iii) Amberlyst-15® ion exchange resin, MeOH, rt, 62% (3 steps).

Reaction of α-monosubstituted indoline-2-methanol **22** with PPh_3 (3 equiv) and CCl_4 (10 equiv) in CH_2Cl_2 at room temperature for 3 h delivered a 3:1 mixture of the desired rearrangement product **23** and Cl-substituted indoline **24** which was relatively unstable (the structure of **24** was characterized by ^1H NMR, ^{13}C NMR and EIMS) (Scheme 8).[26] The 5- and 6-membered ring of the products were confirmed by the HMBC experiments, and the relative stereochemistry was determined by the NOE experiment of the aziridine **25**, derived from **23** and **24** by: (1) formation of the aziridine ring by *t*-BuOK and (2) esterification of the resulting carboxylic acid. The indoline product **24** could be formed either by direct chlorination of the OH group of the substrate **22**, or via an aziridine intermediate as depicted in Scheme 1, in this case the chloride anion attacking the bridgehead carbon of the aziridine.

With the above result in mind, the triphenylphosphine–CCl_4-mediated rearrangement using α,α-disubstituted indoline-2-methanols **15a** and **15b** as substrates were initially examined. To our delight, treatment of **15a** with PPh_3 (3 equiv) and CCl_4 (10 equiv) in CH_2Cl_2 under reflux for 30 min afforded solely the desired rearrangement product tetrahydroquinoline **26a** as a single isomer in 63% yield (Scheme 9). Treatment of the diastereomer **15b** also gave **26b** as a sole isomer in 74% yield. Relative configurations of **26a** and **26b** were determined by comparison with the corresponding authentic racemic samples, reported by Shirahama et al.[12] Exposure of **26b** to $(n\text{-}Bu)_3SnH$ and azobisisobutyronitrile afforded the dechlorinated derivative **27b**, which was identical with the dechlorinated compound **27a** derived from **26a** except for the optical rotation. These results indicate that **26a** and **26b** have the opposite substituent orientation at C-2 position. The absolute configuration of **26a** was verified by the X-ray analysis as 2*R*,3*R* by the X-ray analysis of

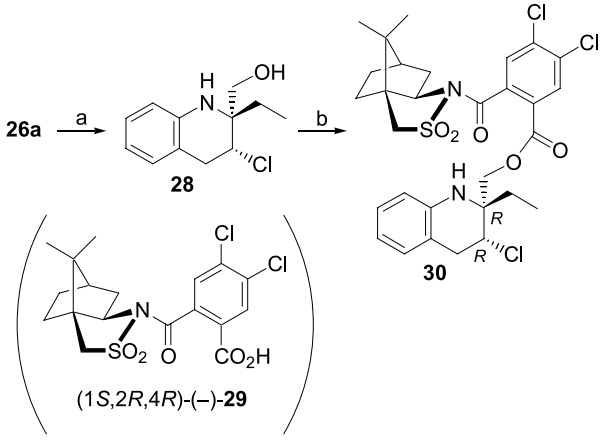


Scheme 8. Reagents and conditions: (a) PPh_3, CCl_4, CH_2Cl_2, rt, 91% (yield of a 3:1 mixture of **23** and **24**). (b) (i) *t*-BuOK, *t*-BuOH, 60 °C; (ii) $TMSCH_2N_2$, AcOH, MeOH, 0 °C to rt, 26% (2 steps). (c) (i) *t*-BuOK, *t*-BuOH, 60 °C; (ii) $TMSCH_2N_2$, AcOH, MeOH, 0 °C to rt, 47% (2 steps).



Scheme 9. Reagents and conditions: (a) PPh_3, CCl_4, CH_2Cl_2, 40 °C, 63%. (b) $(n\text{-}Bu)_3SnH$, AIBN, benzene, 80 °C, 95%. (c) PPh_3, CCl_4, CH_2Cl_2, 40 °C, 64%; (b) $(n\text{-}Bu)_3SnH$, AIBN, benzene, 80 °C, 75%.

(1*S*,2*R*,3*R*)-(−)-camphorsultam[27] derivative **30**, derived from **26a** in a two-step sequence (Scheme 10).[16] Moreover, no racemization occurred during the rearrangement, confirmed by the chiral HPLC analysis of **26a**.[28] In the light of these results, the rearrangement is considered to be stereospecific.[29]



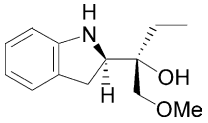
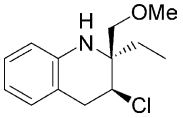
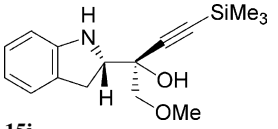
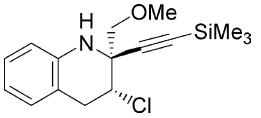
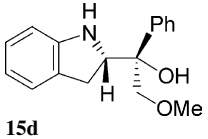
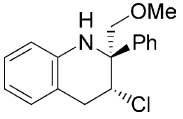
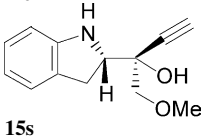
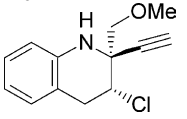
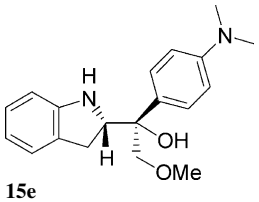
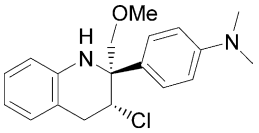
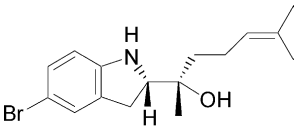
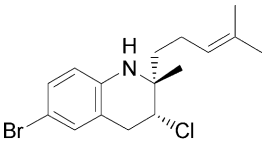
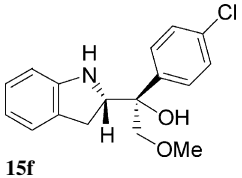
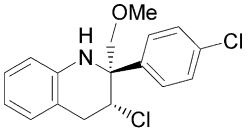
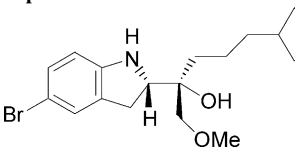
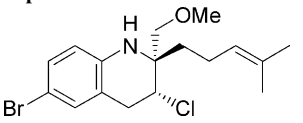
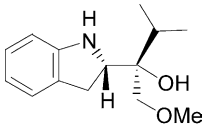
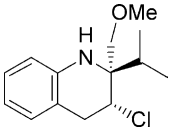
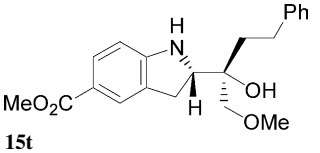
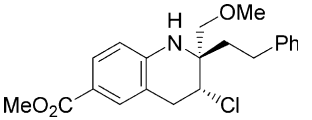
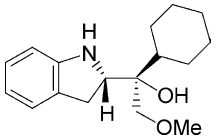
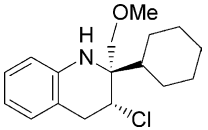
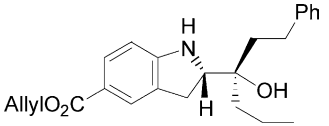
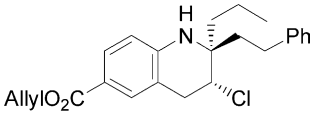
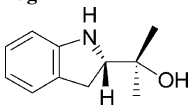
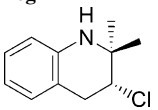
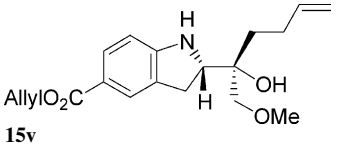
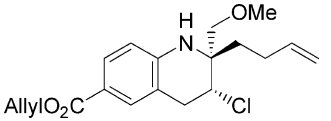
Scheme 10. Reagents and conditions: (a) $AlCl_3$, Me_2S, CH_2Cl_2, rt, 86%. (b) (1*S*,2*R*,4*R*)-(−)-**29**, DCC, DMAP, CH_2Cl_2, reflux, 64%.

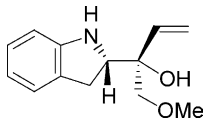
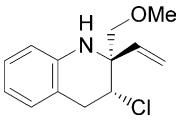
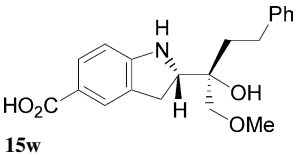
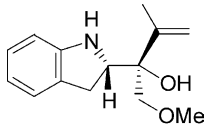
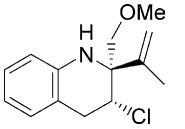
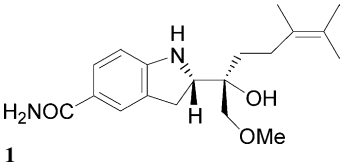
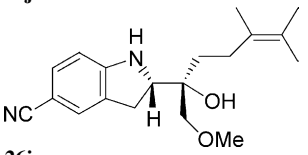
The utility of this rearrangement was investigated using various chiral indoline-2-methanol derivatives, as shown in Table 2. In most cases, the reactions provided single isomers in moderate to good yield.[30] The reaction of **15c** (enantiomer of **15a**) provided the antipode of **26a** (entry 1). Notably, the use of polymer-supported triphenylphosphine was also effective (entry 9). Unfortunately, the rearrangement was unsuccessful with some substrates. In the case of **15e**, a trace of rearrangement product **26e** was observed, but could not be isolated because of decomposition (entry 3). As shown in entries 17 and 18, the rearrangement proved to be quite sensitive to the substituent on the indoline aryl ring. Although the rearrangement proceeded smoothly with substrates with Br (entries 12 and 13) or ester groups (entries 14–16) substituted on the aryl ring, no reaction occurred with **15w** containing a carboxyl group (entry 17), and treatment of **1** resulted in the reduction of the amide group (entry 18).

Gratifyingly, the total synthesis of natural virantmycin was achieved utilizing our developed methodology for the construction of 2,2,3-trisubstituted tetrahydroquinolines (Scheme 11). Acylindoline **13b** was treated with iodine monochloride to afford **31** in 91% yield. Iodide **31** was subjected to diastereoselective Grignard addition with 2,3-dimethyl-3-pentenylmagnesium bromide[21] to give *tert*-alcohols **32** as a 19:1 mixture of separable isomers, as determined by HPLC analysis of the product mixture. The Boc protecting group of the major isomer was removed by treatment with HCO_2H to afford the rearrangement precursor **33**. The configurations of the newly created asymmetric centers in the Grignard adduct were determined by the NOE experiments of the acetonide derivative of **33**. Unfortunately, the rearrangement reaction was sluggish when **33** was subjected to the standard condition, giving a mixture of products including an undesired deiodinated product and an indole derivative (formed by dehydration followed by isomerization), along with the decomposition of the polysubstituted olefin (deduced from the disappearance of the olefinic carbon peak in the ^{13}C NMR spectrum). To overcome these problems we screened a number of aromatic and aliphatic phosphines, and found that the observed side reactions, such as reduction and isomerization to an indole, are suppressed to a certain extent with the usage of tri-*n*-butylphosphine as an alternative. As a result, tetrahydroquinoline **34** was provided as a single isomer in 45% yield by treating **33** with tri-*n*-butylphosphine and CCl_4. The tetrahydroquinoline **34** was carbonylated by reaction with 1 atm of CO in H_2O/DMF in the presence of catalytic $Pd(OAc)_2$ and K_2CO_3 to give (−)-virantmycin (**2a**) in 53% yield (80% based on recovered starting material). Synthetic **2a** was identical in all respects to natural virantmycin[10,13] [IR, ^1H NMR, ^{13}C NMR spectra, and $[\alpha]_D^{24} = -16.5$ (*c* 0.11, $CHCl_3$) (lit.[13] $[\alpha]_D^{18} = -11.1$ (*c* 0.175, $CHCl_3$))]. Our synthesis required only nine steps from the commercially available (*S*)-(−)-indoline-2-carboxylic acid (**9**).

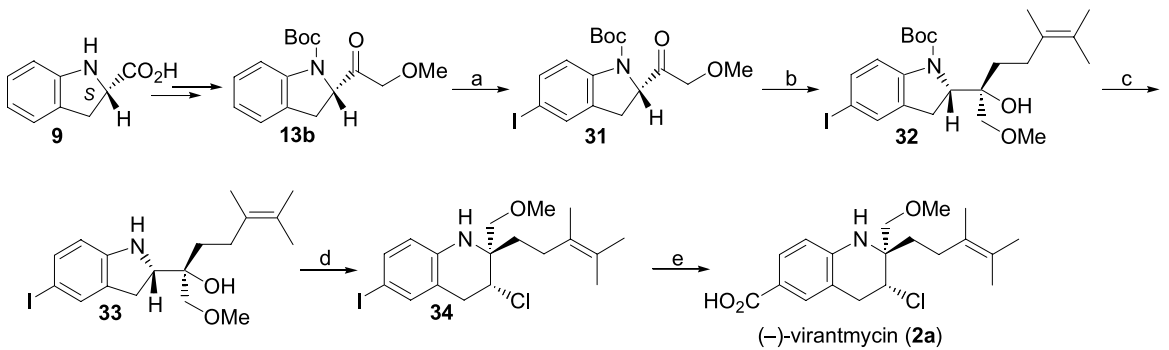
In summary, we have developed a new method for the synthesis of chiral 2,2,3-trisubstituted tetrahydroquinolines, involving the stereoselective preparation of α,α-disubstituted indoline-2-methanols, and its biomimetically inspired stereospecific rearrangement to tetrahydroquinolines in which contiguous quaternary and tertiary stereogenic centers are constructed in complete stereocontrol. The utility of this methodology for accessing various chiral indoline and tetrahydroquinoline alkaloids was clearly demonstrated by the total syntheses of benzastatin E and natural virantmycin.[31] The latter synthesis required only nine steps from the commercially available compound, which exhibits a sharp contrast to the previous syntheses of racemic and unnatural virantmycin. We believe that this stereospecific rearrangement reaction supports the biogenetic theory of benzastatin family involving the aziridine intermediate, though the alternative formation of these compounds via the epoxide intermediate cannot be ruled out without further biosynthetic experiments.

Table 2. Rearrangement from indolines **15** to tetrahydroquinolines **26**

Entry[a]	Substrate **15**	Product **26**[b]	Yield[c]	Entry[a]	Substrate **15**	Product **26**[b]	Yield[c]
1	 **15c**	 **26c**	63%	10	 **15j**	 **26j**	63%
2	 **15d**	 **26d**	63%	11	 **15s**	 **26s**	55%
3	 **15e**	 **26e**	Trace	12	 **15p**	 **26p**	62%
4	 **15f**	 **26f**	33%	13	 **15k**	 **26k**	41%
5	 **15r**	 **26r**	53%	14	 **15t**	 **26t**	50%
6	 **15g**	 **26g**	38%	15	 **15u**	 **26u**	52%
7	 **15n**	 **26n**	65%	16	 **15v**	 **26v**	46%

8	 **15h**	 **26h**	31%	17[d]	 **15w**	**26j**	No reaction
9	 **15i**	 **26i**	37% (44%)[e]	18	 **1**	 **26j**	61%

[a] All the reactions conducted were with Ph_3P (3 equiv) and CCl_4 (10 equiv), except for entry 9.
[b] The absolute stereochemistry was tentatively assigned by analogy with the reaction mechanism, except for **26c** (enantiomer of **26a**).
[c] Yield of isolated product after column chromatography.
[d] Racemic **15w** was used as a substrate.
[e] Polymer-supported triphenylphosphine was used.



Scheme 11. Reagents and conditions: (a) ICl, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C to rt, 91%. (b) 3,4-Dimethyl-3-pentenylmagnesium bromide, THF, −78 °C, 73% (ds=19:1). (c) HCO_2H, CH_2Cl_2, 50 °C, 59%. (d) (n-Bu)$_3$P, CCl_4, CH_2Cl_2, reflux, 45%. (e) CO 1 atm, K_2CO_3, $Pd(OAc)_2$, H_2O/DMF, rt, 53% (80% based on recovered starting material).

3. Experimental

3.1. General procedure

Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ containers. All other commercially obtained reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 or 500 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened. In the NMR spectral lists, chemical shifts which are assigned to the minor conformer are marked with an asterisk. Infrared spectra were recorded on a JASCO FT-IR-8900 spectrometer. Mass spectra were obtained on a JEOL HX-100, a SX-102A or a JMS-AX-505H mass spectrometer. Optical rotations were measured on a JASCO P-1030 polarimeter. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 F_{254} plates. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

3.2. Preparation of 2-acylindolines 13a, b

3.2.1. 1-*tert*-Butyl 2-methyl (2*S*)-indoline-1,2-dicarboxylate (10). To a solution of carboxylic acid **9** (20.0 g, 123 mmol) in MeOH (200 ml) was added sulfuric acid (15 ml) dropwise at room temperature. The mixture was stirred for 6 h at 80 °C. The solvent was removed in vacuo. The residue was neutralized with 15% NaOH aq, then extracted with AcOEt (100 ml×2). The combined organic extracts were washed with 1 N NaOH aq (50 ml×2), brine (50 ml), dried over Na_2SO_4, filtered and evaporated to give the corresponding methyl ester (20.3 g, 94%).

To a solution of methyl ester (20.3 g, 114 mmol) in CH_2Cl_2 (100 ml) was added Boc_2O (40.3 g, 185 mmol) in CH_2Cl_2 (100 ml) at room temperature. After stirring at room temperature overnight, the solvent was evaporated. Purification by silica gel column chromatography (hexane to hexane–AcOEt 1:1) gave **10** (31.4 g, 92% from **9**) as a colorless solid (mp 43–45 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) 1.50 (9H, br), 3.11 (1H, dd, J=4.0, 16.0 Hz), 3.50 (1H, dd, J=14.0, 16.0 Hz), 3.75 (3H, s), 4.87 (1H, br), 6.95 (1H, t, J=7.0 Hz), 7.11 (1H, d, J=7.0 Hz), 7.14–7.22 (1H, m), 7.49* (0.3H, br), 7.89 (0.7H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 31.9*, 32.7, 52.3, 60.4, 81.3, 82.3*, 114.6, 122.5, 124.3, 124.4, 127.9, 141.6*, 142.5, 151.6, 152.6*, 172.4; IR ($CHCl_3$) cm^{-1}: 2981, 1741, 1709, 1485, 1390, 1169; HRMS calcd for $C_{15}H_{19}NO_4$ $(M)^+$ 277.1314, found 277.1305. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.76; H, 6.70; N, 5.07; $[\alpha]_D^{24}=-70.6$ (c 0.84, $CHCl_3$).

3.2.2. 1-*tert*-Butyl 2-methyl (2*S*)-5-bromoindoline-1,2-dicarboxylate (11). NBS (8.79 g, 49.4 mmol) was added to a solution of **10** (13.7 g, 49.4 mmol) in DMF (50 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C. After addition of water (50 ml), the aqueous solution was extracted with AcOEt (50 ml×2). The combined organic extracts were washed with water (50 ml), brine (50 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) provided **11** (16.4 g, 93%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (9H, br), 3.09 (1H, d, J=16.5 Hz), 3.45–3.51 (1H, m), 3.75 (3H, s), 4.86 (1H, br), 7.22 (1H, s), 7.30 (1H, br d, J=7.0 Hz), 7.77 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1 (×3), 32.2, 52.3, 60.4, 81.6, 114.7, 115.9, 127.3, 130.1, 130.6, 141.7, 151.3, 171.9; IR ($CHCl_3$) cm^{-1}: 2981, 1745, 1709, 1477, 1377, 1312, 1257, 1159, 1025; HRMS calcd for $C_{15}H_{18}NO_4Br$ $(M)^+$ 355.0419, found 355.0418; $[\alpha]_D^{24}=-31.9$ (c 0.83, $CHCl_3$).

3.2.3. *tert*-Butyl (2*S*)-5-bromo-2-{[methoxy(methyl)-amino]carbonyl}indoline-1-carboxylate (12a). To a slurry of Me(MeO)NH·HCl (2.36 g, 24.3 mmol) and **11** (5.76 g, 16.2 mmol) in THF (20 ml) was added *i*-PrMgCl in THF (16.1 ml, 2.0 M) dropwise at −20 °C. The mixture was stirred for 20 min at −10 °C. To the reaction mixture were added Me(MeO)NH·HCl (2.36 g, 24.3 mmol) and *i*-PrMgCl in THF (16.1 ml, 2.0 M) at −20 °C. After stirring for 10 min at −10 °C, the reaction was quenched with satd NH_4Cl aq (80 ml) and extracted with AcOEt (70 ml×2). The combined organic solution was washed with brine (80 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 1:1) gave **12a** (5.2 g, 83%) as a colorless solid (mp 105–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers) δ 1.48 (6H, br s), 1.59 (3H, br s), 2.97 (1H, d, J=16.4 Hz), 3.22 (3H, s), 3.47 (1H, dd, J=11.6, 16.4 Hz), 3.75 (2H, br s), 3.81 (1H, br s), 5.20 (1H, br), 7.18 (1H, s), 7.28 (1H, br s), 7.35 (0.5H, br), 7.80 (0.5H, br d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 31.6*, 32.1, 32.6, 58.5*, 58.9, 61.3, 81.3, 82.3*, 114.5, 115.9, 127.2, 127.5, 130.5, 142.5, 151.5, 172.0; IR (KBr) cm^{-1}: 3000, 1702, 1679, 1478, 1378, 1320, 1256, 1161, 1029, 824; HRMS calcd for $C_{16}H_{21}N_2O_4BrNa$ $(M+Na)^+$ 407.0582, found 407.0583. Anal. Calcd for $C_{16}H_{21}N_2O_4Br$: C, 49.88; H, 5.49; N, 7.27; Br, 20.74. Found: C, 49.99; H, 5.50; N, 7.28; Br, 20.44; $[\alpha]_D^{24}=-89.4$ (c 0.90, $CHCl_3$).

3.2.4. *tert*-Butyl (2*S*)-2-{[methoxy(methyl)amino]carbonyl}indoline-1-carboxylate (12b). The procedure for the synthesis of **12a** was followed using **11** (7.03 g, 25.35 mmol), Me(MeO)NH·HCl (4.95 g, 50.7 mmol) and *i*-PrMgCl in THF (50.7 ml, 2.0 M) in THF (50 ml) to give **12b** (5.59 g, 72%) as a colorless solid (mp 109–111 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.49 (6H, br s), 1.60 (3H, br s), 2.99 (1H, br), 3.22 (3H, s), 3.49 (1H, dd, J=11.8, 15.8 Hz), 3.75 (2H, br s), 3.82 (1H, br s), 5 18 (1H, br), 6.91 (1H, t, J=7.6 Hz), 7.07 (1H, d, J=7.6 Hz), 7.17 (1H, br), 7.50* (0.4H, br), 7.92 (0.6H, br), ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers) δ 28.4 (×3), 32.0, 32.7, 58.3*, 58.8, 61.4, 80.9, 81.9*, 114.5, 122.1, 124.0, 124.5, 127.6, 128.0*, 129.0*, 142.1*, 143.0, 151.5, 152.5*, 171.6*, 172.3; IR (KBr) cm^{-1}: 2987, 1706, 1675, 1486, 1388, 1174, 757; HRMS calcd for $C_{16}H_{22}N_2O_4BrNa$ $(M+Na)^+$ 329.1477, found 329.1479. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.66; H, 7.28; N, 9.12; $[\alpha]_D^{24}=-117.0$ (c 0.46, $CHCl_3$).

3.2.5. *tert*-Butyl (2*S*)-5-bromo-2-(methoxyacetyl)indoline-1-carboxylate (13a). To a solution of $MeOCH_2Sn(n\text{-}Bu)_3$ (1.30 g, 3.90 mmol) in THF (10 ml) was added *n*-BuLi in hexane (3.90 ml, 1.6 M) dropwise at −78 °C. After stirring for 10 min at −78 °C, a solution of Weinreb amide **12a** (500 mg, 1.30 mmol) in THF (5 ml) was added to the reaction mixture at −78 °C. The mixture was stirred for 15 min at −78 °C and quenched with satd NH_4Cl aq (20 ml). The product was extracted with AcOEt (30 ml×2) and the organic solution was washed with brine (30 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 2:1) gave **13a** (295 mg, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (9H, br), 2.98 (1H, dd, J=4.4, 16.8 Hz), 3.44 (3H, s), 3.48 (1H, br), 4.16 (2H, br), 5.07 (1H, br), 7.21 (1H, s), 7.31 (1H, br), 7.79 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.9 (×3), 31.1*, 32.0, 60.3, 63.9*, 64.7, 75.8, 82.7, 115.7, 116.8, (×2), 128.2, 131.5, 142.7, 151.9, 205.0; IR ($CHCl_3$) cm^{-1}: 2981, 1707, 1478, 1372, 1256, 1153, 1106, 1023, 909; HRMS calcd for $C_{16}H_{20}NO_4Br$ $(M)^+$ 369.0576, found 369.0567; $[\alpha]_D^{24}=-53.9$ (*c* 1.07, $CHCl_3$).

3.2.6. *tert*-Butyl (2*S*)-2-(methoxyacetyl)indoline-1-carboxylate (13b). The procedure for the synthesis of **13a** was followed using **12b** (2.12 g, 6.92 mmol), $MeOCH_2Sn(n\text{-}Bu)_3$ (6.96 g, 20.76 mmol), *n*-BuLi in hexane (13.1 ml, 1.6 M) in THF (50 ml) to give **13b** (1.13 g, 56%) as a colorless solid (mp 58–60 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.50 (9H, br), 3.00 (1H, dd, J=4.5, 16.5 Hz), 3.43 (3H, s), 3.47 (1H, br), 4.18 (2H, br), 5.03 (1H, br), 6.94 (1H, t, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.19 (1H, br s), 7.48* (0.4H, br), 7.90 (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 30.9*, 31.7, 59.4, 63.3*, 64.0, 74.8, 75.4*, 81.6, 114.7 (×2), 122.6, 124.5, 127.9, 128.8*, 141.7*, 142.5, 151.4, 152.5*, 204.8; IR (KBr) cm^{-1}: 2976, 1732, 1704, 1488, 1395, 1154, 1111, 762; HRMS calcd for $C_{16}H_{21}NO_4Na$ $(M+Na)^+$ 314.1368, found 314.1373. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.91; H, 7.11; N, 4.84; $[\alpha]_D^{24}=-92.4$ (*c* 0.65, $CHCl_3$).

3.3. Investigation of the diastereoselective Grignard addition

3.3.1. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex-4-enyl]indoline-1-carboxylate (major-14). To a solution of ketone **13a** (282 mg, 0.761 mmol) in THF (10 ml) was added 3,4-dimethyl-3-pentenylmagnesium bromide in THF (freshly prepared from the corresponding bromide (714 mg, 0.457 mmol) and Mg (146 mg, 0.686 mmol)) dropwise at −78 °C. The mixture was stirred for 15 min at −78 °C. The reaction was quenched with satd NH_4Cl aq (20 ml) and extracted with AcOEt (20 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. The diastereoselectivity (25:1) was determined by HPLC analysis. Purification by silica gel column chromatography (hexane–AcOEt 5:1) gave major-**14** (323 mg, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (1H, dt, J=5.0, 13.0 Hz), 1.40 (1H, dt, J=5.0, 13.0 Hz), 1.47 (3H, s), 1.55 (3H, s), 1.56 (3H, s), 1.56 (9H, s), 1.95–2.06 (2H, m), 3.07 (1H, dd, J=2.0, 17.5 Hz), 3.27 (1H, dd, J=11.0, 17.5 Hz), 3.35 (3H, s), 3.40 (2H, s), 4.74 (1H, d, J=9.5 Hz), 7.25–7.33 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 19.7, 20.4, 27.9, 28.1 (×3), 29.7, 31.2, 59.2, 64.8, 76.2, 76.7, 82.2, 115.3, 117.6, 123.9, 127.0, 127.2, 129.6 (×2), 134.3, 142.0; IR ($CHCl_3$) cm^{-1}: 3554, 3373, 2983, 2927, 1672, 1477, 1371, 1255, 1164, 1016, 909; HRMS calcd for $C_{23}H_{34}NO_4BrNa$ $(M+Na)^+$ 490.1569, found 490.1571; $[\alpha]_D^{24}=-45.4$ (*c* 0.86, $CHCl_3$).

3.3.2. *tert*-Butyl (2*S*)-5-bromo-2-[(1*S*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex-4-enyl]indoline-1-carboxylate (minor-14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55–1.68 (2H, m), 1.58 (9H, s), 1.63 (6H, s), 1.65 (3H, s), 2.08–2.19 (2H, m), 2.98 (3H, s), 3.07 (1H, d, J=9.8 Hz), 3.15 (1H, d, J=9.8 Hz), 3.19–3.27 (2H, m), 4.65 (1H, dd, J=2.4, 10.2 Hz), 7.25 (2H, d, J=9.8 Hz), 7.31 (1H, br s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 18.3, 19.9, 20.5, 27.5, 28.3 (×3), 30.3, 33.2, 58.6, 66.0, 75.0, 76.2, 82.9, 115.6, 117.6, 124.0, 127.2, 127.6, 129.6, 135.0, 141.5, 155.2; IR (KBr) cm^{-1}: 3447, 2984, 2921, 2908, 2887, 2860, 1665, 1481, 1379, 1369; HRMS calcd for $C_{23}H_{34}NO_4BrNa$ $(M+Na)^+$ 490.1569, found 490.1567. Anal. Calcd for $C_{23}H_{34}BrNO_4$: C, 58.97; H, 7.32; N, 2.99; Br, 17.06. Found: C, 59.26; H, 7.20; N, 2.76; Br, 16.67; $[\alpha]_D^{24}=-77.5$ (*c* 0.98, $CHCl_3$); mp 103–106 °C.

3.3.3. (2*R*)-2-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-1-methoxy-5,6-dimethylhept-5-en-2-ol (15). To a solution of major-**14** (2.29 g, 4.89 mmol) in CH_2Cl_2 (10 ml) was added formic acid (20 ml) at room temperature. After stirring for 18 h at room temperature, the reaction mixture was neutralized with 15% NaOH aq and extracted with AcOEt (50 ml×2). The combined organic extracts were washed with brine (50 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1) yielded **15** (938 mg, 52%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.59 (2H, m), 1.64 (3H, s), 1.64 (3H, s), 1.66 (3H, s), 2.01 (1H, dt, J=5.5, 12.0 Hz), 2.15 (1H, dt, J=5.5, 12.0 Hz), 2.79 (1H, s), 2.90 (1H, dd, J=9.0, 15.5 Hz), 3.05 (1H, dd, J=10.5, 15.5 Hz), 3.39 (1H, d, J=9.5 Hz), 3.40 (3H, s), 3.49 (1H, d, J=9.5 Hz), 4.08 (1H, dd, J=9.0, 10.5 Hz), 4.26 (1H, br s), 6.49 (1H, d, J=8.5 Hz), 7.09 (1H, d, J=8.5 Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.9, 20.5, 28.1, 30.3, 32.8, 59.4, 65.9, 72.7, 78.1, 110.3, 110.5, 124.2, 127.1, 127.3, 129.7, 131.0, 149.7; IR ($CHCl_3$) cm^{-1}: 3405, 2924, 1604, 1481, 1247, 1166, 1111; HRMS calcd for $C_{18}H_{26}NO_2Br$ $(M)^+$ 367.1147, found 367.1150; $[\alpha]_D^{24}=-33.5$ (*c* 0.75, $CHCl_3$).

3.3.4. (1*R*,9a*S*)-7-Bromo-1-methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (major-16). To a solution of **15** (932 mg, 2.53 mmol) in CH_2Cl_2 (20 ml) was added 2,2-dimethoxypropane (3.11 ml, 25.3 mmol) and pyridinium *p*-toluenesulfonate (100 mg) at room temperature. The mixture was stirred for 4 h at room temperature. The solvent was concentrated in vacuo and satd $NaHCO_3$ aq (20 ml) was added to the residue. The product was extracted with AcOEt (20 ml×2) and the organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 5:1) gave major-**16**

(945 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (1H, dt, J=4.4, 13.2 Hz), 1.50 (3H, s), 1.51 (3H, s), 1.55 (3H, s), 1.57 (3H, s), 1.57–1.62 (1H, m), 1.65 (3H, s), 1.95 (1H, dt, J=4.4, 13.2 Hz), 2.05 (1H, dt, J=4.4, 13.2 Hz), 3.03 (1H, dd, J=9.8, 17.6 Hz), 3.09 (1H, dd, J=4.4, 17.6 Hz), 3.28 (1H, d, J=9.6 Hz), 3.38 (3H, s), 3.52 (1H, d, J=9.6 Hz), 4.34 (1H, dd, J=4.4, 9.8 Hz), 6.49 (1H, d, J=8.0 Hz), 7.09 (1H, dd, J=2.4, 8.0 Hz), 7.12 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.8, 20.5, 25.8, 28.1, 29.0, 29.2, 31.3, 59.5, 70.3, 76.3, 82.1, 94.8, 110.7, 113.0, 124.0, 127.3, 127.5, 129.4, 134.4, 147.8; IR ($CHCl_3$) cm^{-1}: 2928, 1596, 1474, 1371, 1259, 1118, 969, 862; HRMS calcd for $C_{21}H_{30}NO_2Br$ $(M)^+$ 407.1460, found 407.1470; $[\alpha]_D^{24}=+101.5$ (c 1.59, $CHCl_3$).

3.3.5. (1*S*,9a*S*)-7-Bromo-1-methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (minor-16). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (3H, s), 1.59–1.64 (1H, m), 1.63 (3H, s), 1.64 (3H, s), 1.66 (6H, s), 1.74–1.81 (1H, m), 2.04–2.17 (2H, m), 2.96 (1H, dd, J=10.3, 17.1 Hz), 3.08 (1H, d, J=9.8 Hz), 3.12 (1H, d, J=9.8 Hz), 3.19 (3H, s), 3.39 (1H, dd, J=2.9, 17.1 Hz), 4.17 (1H, dd, J=2.9, 10.3 Hz), 6.55 (1H, d, J=7.8 Hz), 7.12 (1H, d, J=7.8 Hz), 7.16 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 18.4, 19.9, 20.5, 25.8, 28.2, 28.6, 31.3, 34.9, 59.0, 70.1, 73.7, 82.4, 95.1, 111.1, 113.4, 124.1, 127.4, 127.5, 129.4, 134.4, 148.2; IR (KBr) cm^{-1}: 3429, 2983, 2928, 2913, 2896, 2863, 1596, 1472, 1337, 1250, 1105. Anal. Calcd for $C_{21}H_{30}BrNO_2\cdot 1/6H_2O$: C, 61.31; H, 7.43; N, 3.40; Br, 19.42. Found: C, 61.35; H, 7.29; N, 3.41; Br, 19.42; $[\alpha]_D^{24}=+98.9$ (c 0.66, $CHCl_3$); mp 68–70 °C.

3.4. Diastereoselective Grignard addition to 2-acylindolines 13

3.4.1. Preparation of 2-acylindolines 13c–h.

3.4.1.1. *tert*-Butyl (2*S*)-2-propionylindoline-1-carboxylate (13c). To a solution of **12b** (1.22 g, 3.98 mmol) in THF (5 ml) was added EtMgBr in Et_2O (4.0 ml, 3 M) dropwise at 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched with satd NH_4Cl aq (10 ml) and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 5:1) gave **13c** (611 mg, 56%) as a colorless solid (mp 74–76 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, t, J=6.5 Hz), 1.48 (9H, br), 2.53 (2H, br), 2.94 (1H, dd, J=5.0, 16.5 Hz), 3.48 (1H, br), 4.83 (1H, br), 6.95 (1H, t, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.20 (1H, br s), 7.91 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.35, 28.2 (×3), 30.5, 31.9, 66.3, 81.5, 114.7, 122.6, 124.4, 127.9, 142.6, 151.6, 160.9, 208.7; IR (KBr) cm^{-1}: 2978, 1720, 1700, 1485, 1397, 1322, 1151, 748; HRMS calcd for $C_{16}H_{21}NO_3$ $(M)^+$ 275.1521, found 275.1524. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.57; H, 7.61; N, 5.13; $[\alpha]_D^{24}=-80.2$ (c 0.32, $CHCl_3$).SO

3.4.1.2. *tert*-Butyl (2*R*)-2-(methoxyacetyl)indoline-1-carboxylate (13d). The procedure for the synthesis of **13a** was followed using enantiomer of **12b** (124 mg, 0.405 mmol), $MeOCH_2Sn(n\text{-}Bu)_3$ (407 mg, 1.215 mmol), n-BuLi in hexane (0.8 ml, 1.6 M) and THF (5 ml) to give **13d** (52 mg, 44%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.50 (9H, br), 3.00 (1H, dd, J=4.5, 16.5 Hz), 3.43 (3H, s), 3.47 (1H, br), 4.18 (2H, br), 5.03 (1H, br), 6.94 (1H, t, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 7.19 (1H, br s), 7.48* (0.4H, br), 7.90 (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 30.9*, 31.7, 59.4, 63.3*, 64.0, 74.8, 75.4*, 81.6, 114.7 (×2), 122.6, 124.5, 127.9, 128.8*, 141.7*, 142.5, 151.4, 152.5*, 204.8; IR (KBr) cm^{-1}: 2976, 1732, 1704, 1488, 1395, 1154, 1111, 762; HRMS calcd for $C_{16}H_{21}NO_4Na$ $(M+Na)^+$ 314.1368, found 314.1373; $[\alpha]_D^{24}=+69.3$ (c 0.32, $CHCl_3$).

3.4.1.3. *tert*-Butyl (2*S*)-2-acetylindoline-1-carboxylate (13e). The procedure for the synthesis of **13c** was followed using **12b** (1.3 g, 4.24 mmol), MeLi in diethyl ether (5.6 ml, 1.14 M) and THF (10 ml) to give **13e** (800 mg, 72%) as a colorless solid (mp 100–102 °C). ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.50 (9H, br), 2.15 (3H, br s), 2.97 (1H, dd, J=5.0, 16.5 Hz), 3.47 (1H, br), 4.78 (1H, br), 6.95 (1H, t, J=7.5 Hz), 7.12 (1H, d, J=7.5 Hz), 7.20 (1H, br s), 7.49* (0.4H, br), 7.90 (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 24.7, 25.6*, 28.2 (×3), 30.9*, 31.6, 66.8, 81.7, 114.8 (×2), 122.7, 124.5, 128.0, 142.5, 151.6, 206.2; IR (KBr) cm^{-1}: 2984, 1699, 1485, 1395, 1321, 1262, 1157, 752; HRMS calcd for $C_{15}H_{19}NO_3$ $(M)^+$ 261.1364, found 261.1360. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.90; H, 7.01; N, 5.40; $[\alpha]_D^{24}=-82.8$ (c 0.28, $CHCl_3$).

3.4.1.4. *tert*-Butyl (2*S*)-5-bromo-2-butyrylindoline-1-carboxylate (13f). The procedure for the synthesis of **13c** was followed using **12a** (1.0 g, 2.60 mmol), n-PrMgCl in diethyl ether (3.9 ml, 2.0 M) and THF (15 ml) to give **13f** (238 mg, 25%) as a colorless solid (mp 70–71 °C) along with the recovered **12a** (s27%). ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers) δ 0.92 (3H, t, J=7.4 Hz), 1.48 (6H, br s), 1.56–1.66 (5H, m), 2.38–2.46 (2H, br m), 2.92 (1H, dd, J=4.9, 17.1 Hz), 3.46 (1H, br), 4.85 (1H, br), 7.22 (1H, br s), 7.32 (1.4H, br), 7.79* (0.6H, br); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 14.0, 16.8, 28.4 (×3), 30.7*, 31.6, 39.7, 40.5*, 66.1*, 66.6, 82.1, 115.2, 116.4 (×2), 127.8, 130.4*, 131.1, 142.3, 152.0, 207.5; IR (KBr) cm^{-1}: 2976, 2962, 2934, 2874, 1712, 1701, 1480, 1374, 1155, 1143; HRMS calcd for $C_{17}H_{22}NO_3BrNa$ $(M+Na)^+$ 390.0681, found 390.0673. Anal. Calcd for $C_{17}H_{22}NO_3Br$: C, 55.44; H, 6.02; N, 3.80; Br, 21.70. Found: C, 55.63; H, 5.65; N, 3.75; Br, 21.67; $[\alpha]_D^{24}=-34.8$ (c 0.58, $CHCl_3$).

3.4.1.5. *tert*-Butyl (2*S*)-5-bromo-2-(5-methylhex-4-enoyl)indoline-1-carboxylate (13g). The procedure for the synthesis of **13c** was followed using **12a** (2.1 g, 5.45 mmol), 4-methyl-3-pentenylmagnesium bromide in THF (freshly prepared from the corresponding bromide (5.96 g, 36.6 mmol) and Mg (1.33 g, 54.8 mmol)) and THF (15 ml) to give **13g** (991 mg, 45%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, br), 1.65 (3H, s), 1.68 (3H, s), 2.26 (2H, q, J=7.2 Hz), 2.39–2.56 (2H, m), 2.91 (1H, dd, J=5.2, 16.8 Hz), 3.43 (1H, br t, J=14.0 Hz), 4.81 (1H, br), 5.11 (1H, dt, J=1.2, 7.6 Hz), 7.20 (1H, s), 7.30 (1H, d, J=7.2 Hz), 7.74 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.9, 25.7, 28.2 (×3), 31.3, 37.7, 66.4, 81.9, 114.9, 116.0, 122.3, 124.6, 127.3, 130.7, 132.9, 141.8, 151.3, 206.7; IR ($CHCl_3$) cm^{-1}: 2977, 2930, 1708, 1477,

1373, 1257, 1151; HRMS calcd for $C_{20}H_{26}NO_3BrNa$ $(M+Na)^+$ 430.0994, found 430.0969; $[\alpha]_D^{24}=-25.3$ (c 0.65, $CHCl_3$).

3.4.1.6. *tert*-Butyl (2*S*)-5-bromo-2-(3-phenylpropionyl)-indoline-1-carboxylate (13h). The procedure for the synthesis of **13c** was followed using **12a** (212 mg, 0.691 mmol), phenethylmagnesium chloride in THF (2.1 ml, 1.0 M) and THF (2 ml) to give **13h** (200 mg, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 1.52 (9H, br), 2.76 (1H, dd, $J=5.4$, 16.6 Hz), 2.80–2.93 (4H, m), 3.39 (1H, br), 4.85 (1H, br), 6.94 (1H, t, $J=7.3$ Hz), 7.06 (1H, d, $J=7.3$ Hz), 7.13–7.26 (6.5H, m), 7.89* (0.5H, br s); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 29.2, 31.5, 39.1, 39.9*, 66.5, 81.6, 114.8 (×2), 122.7, 124.5, 126.1, 128.0, 128.4 (×2), 128.5 (×2), 140.9, 142.5, 152.0, 207.0; IR ($CHCl_3$) cm^{-1}: 2980, 1725, 1700, 1487, 1394, 1158, 753; HRMS calcd for $C_{22}H_{25}NO_3$ $(M)^+$ 351.1835, found 351.1842; $[\alpha]_D^{24}=-68.5$ (c 1.05, $CHCl_3$).

3.4.2. Diastereoselective Grignard addition to 2-acylindolines 13.

3.4.2.1. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)propyl]indoline-1-carboxylate (14a). To a solution of **13b** (1.06 g, 3.64 mmol) in THF (10 ml) was added EtMgBr in THF (7.3 ml, 1.0 M) dropwise at −78 °C. The mixture was stirred for 15 min at −78 °C. The reaction was quenched with satd NH_4Cl aq (10 ml) and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. The diastereoselectivity (16:1) was determined by HPLC analysis. Purification by silica gel column chromatography (hexane–AcOEt 5:1) gave **14a** (2.1 mg, 57%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, $J=7.0$ Hz), 1.24–1.31 (1H, m), 1.35–1.38 (1H, m), 1.57 (9H, s), 3.03 (1H, dd, $J=2.0$, 16.5 Hz), 3.28 (1H, dd, $J=10.5$, 16.5 Hz), 3.64 (3H, s), 3.39 (1H, d, $J=10.0$ Hz), 3.41 (1H, d, $J=10.0$ Hz), 4.80 (1H, d, $J=9.5$ Hz), 6.95 (1H, t, $J=7.5$ Hz), 7.11–7.15 (2H, m), 7.45 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.26, 24.9, 28.3 (×3), 30.1, 59.3, 64.6, 76.0, 77.2, 82.1, 116.3 (×2), 122.8, 124.1, 126.9, 131.9, 142.8; IR ($CHCl_3$) cm^{-1}: 3373, 2981, 1667, 1484, 1382, 1331, 1287, 1165, 1115, 1015; HRMS calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$ 344.1838, found 344.1845; $[\alpha]_D^{24}=-62.1$ (c 0.80, $CHCl_3$).

Synthesis of compounds **14b–q** were carried out by the method similar to that used for **14a**.

3.4.2.2. *tert*-Butyl (2*S*)-2-[(1*S*)-1-hydroxy-1-(methoxymethyl)propyl]indoline-1-carboxylate (14b). The general procedure was followed using **13c** (584 mg, 2.12 mmol), $MeOCH_2Sn(n\text{-}Bu)_3$ (1.42 g, 4.24 mmol), n-BuLi in hexane (2.4 ml, 1.6 M) and THF (5 ml) to give **14b** (586 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, $J=7.8$ Hz), 1.58 (9H, s), 1.61–1.70 (2H, m), 2.83 (3H, s), 3.06 (1H, d, $J=9.0$ Hz), 3.13 (1H, dd, $J=2.0$, 16.0 Hz), 3.16 (1H, d, $J=9.0$ Hz), 3.25 (1H, dd, $J=10.4$, 16.0 Hz), 4.66 (1H, dd, $J=2.0$, 10.4 Hz), 6.96 (1H, t, $J=7.2$ Hz), 7.12–7.21 (2H, m), 7.45 (1H, br d, $J=6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.05, 27.2, 28.3 (×3), 30.4, 58.5, 65.3, 74.6, 76.2, 82.2, 114.5, 116.1, 122.8, 123.9, 126.4, 132.3, 142.0; IR ($CHCl_3$) cm^{-1}: 3385, 2981, 1659, 1484, 1387, 1165; HRMS calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$ 344.1837, found 344.1860; $[\alpha]_D^{24}=-78.5$ (c 0.43, $CHCl_3$).

3.4.2.3. *tert*-Butyl (2*R*)-2-[(1*S*)-1-hydroxy-1-(methoxymethyl)propyl]indoline-1-carboxylate (14c). The general procedure was followed using **13d** (51 mg, 0.175 mmol), EtMgBr in THF (0.35 ml, 1.0 M) and THF (1 ml) to give **14c** (35 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, $J=7.0$ Hz), 1.24–1.31 (1H, m), 1.35–1.38 (1H, m), 1.57 (9H, s), 3.03 (1H, dd, $J=2.0$, 16.5 Hz), 3.28 (1H, dd, $J=10.5$, 16.5 Hz), 3.64 (3H, s), 3.39 (1H, d, $J=10.0$ Hz), 3.41 (1H, d, $J=10.0$ Hz), 4.80 (1H, d, $J=9.5$ Hz), 6.95 (1H, t, $J=7.5$ Hz), 7.11–7.15 (2H, m), 7.45 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.26, 24.9, 28.3 (×3), 30.1, 59.3, 64.6, 76.0, 77.2, 82.1, 116.3 (×2), 122.8, 124.1, 126.9, 131.9, 142.8; IR ($CHCl_3$) cm^{-1}: 3373, 2981, 1667, 1484, 1382, 1331, 1287, 1165, 1115, 1015; HRMS calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$ 344.1838, found 344.1845; $[\alpha]_D^{24}=+52.7$ (c 0.32, $CHCl_3$).

3.4.2.4. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-2-methoxy-1-phenethyl]indoline-1-carboxylate (14d). The general procedure was followed using **13b** (353 mg, 1.21 mmol), PhMgBr in THF (2.4 ml, 1.0 M) and THF (3 ml) to give **14d** (418 mg, 94%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (9H, s), 2.85 (1H, d, $J=16.5$ Hz), 2.99 (1H, dd, $J=10.0$, 16.5 Hz), 3.28 (3H, s), 3.73 (1H, d, $J=10.0$ Hz), 3.87 (1H, d, $J=10.0$ Hz), 4.91 (1H, br), 6.90 (1H, t, $J=7.5$ Hz), 7.03 (1H, d, $J=7.5$ Hz), 7.11 (1H, t, $J=7.5$ Hz), 7.24 (1H, t, $J=7.5$ Hz), 7.33 (2H, t, $J=7.5$ Hz), 7.48 (3H, d, $J=7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (×3), 30.0, 59.4, 64.8, 77.9, 79.5, 81.4, 115.9 (×2), 122.7, 123.7, 125.6 (×2), 126.6, 127.1, 128.1, 128.2 (×2), 132.4, 142.3; IR ($CHCl_3$) cm^{-1}: 3549, 2981, 2932, 1685, 1602, 1484, 1381, 1282, 1258, 1166, 1135; HRMS calcd for $C_{22}H_{27}NO_4Na$ $(M+Na)^+$ 392.1838, found 392.1837; $[\alpha]_D^{24}=-41.7$ (c 0.53, $CHCl_3$).

3.4.2.5. *tert*-Butyl (2*S*)-2-[(1*R*)-1-(4-dimethylaminophenyl)-1-hydroxy-2-methoxyethyl]indoline-1-carboxylate (14e). The general procedure was followed using **13b** (253 mg, 0.87 mmol), 4-(*N*,*N*-dimethyl)aniline magnesium bromide in THF (3.5 ml, 0.5 M) and THF (2 ml) to give **14e** (300 mg, 84%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (9H, s), 2.89 (1H, d, $J=15.0$ Hz), 2.94 (6H, s), 2.98 (1H, dd, $J=10.0$, 15.0 Hz), 3.12 (1H, br s), 3.28 (3H, s), 3.71 (1H, d, $J=9.3$ Hz), 3.81 (1H, d, $J=9.3$ Hz), 4.85 (1H, br s), 6.72 (2H, d, $J=8.8$ Hz), 6.91 (1H, t, $J=7.3$ Hz), 7.05 (1H, d, $J=7.3$ Hz), 7.12 (1H, t, $J=7.3$ Hz), 7.34 (2H, d, $J=8.8$ Hz), 7.49 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7 (×3), 30.4, 40.8 (×2), 59.8, 65.2, 78.6, 79.5, 81.5, 112.6 (×2), 116.3 (×2), 123.0, 124.0, 126.6 (×2), 126.8, 130.2, 133.0, 143.5, 149.9; IR (thin film) cm^{-1}: 3554, 2977, 1695, 1615, 1522, 1484, 1382, 1369, 1167, 1135, 751; HRMS calcd for $C_{24}H_{33}N_2O_4$ $(M+H)^+$ 413.2440, found 413.2430; $[\alpha]_D^{24}=-52.9$ (c 0.29, $CHCl_3$).

3.4.2.6. *tert*-Butyl (2*S*)-2-[(1*R*)-1-(4-chlorophenyl)-1-hydroxy-2-methoxyethyl]indoline-1-carboxylate (14f). The general procedure was followed using **13b** (320 mg, 1.10 mmol), 4-chlorophenylmagnesium bromide in diethyl ether (2.2 ml, 1.0 M) and THF (3 ml) to give **14f** (265 mg,

61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (9H, s), 2.83 (1H, d, J=16.3 Hz), 3.02 (1H, dd, J=10.0, 16.3 Hz), 3.30 (3H, s), 3.44 (1H, br), 3.70 (1H, d, J=9.6 Hz), 3.82 (1H, d, J=9.6 Hz), 4.87 (1H, br), 6.92 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=7.3 Hz), 7.12 (1H, t, J=7.3 Hz), 7.29 (2H, d, J=8.6 Hz), 7.42 (2H, d, J=8.6 Hz), 7.45 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7 (×3), 30.4, 59.8, 65.0, 78.0, 79.6, 81.9, 116.3 (×2), 123.2, 124.1, 127.0, 127.5 (×2), 128.6 (×2), 132.4, 133.4, 141.1, 143.2; IR (KBr) cm^{-1}: 3457, 2978, 1689, 1485, 1381, 1369, 1168, 751; HRMS calcd for $C_{22}H_{27}ClNO_4$ $(M+H)^+$ 404.1629, found 404.1622; $[\alpha]_D^{24}=-62.8$ (c 0.44, $CHCl_3$).

3.4.2.7. *tert*-Butyl (2*S*)-2-[(1*R*)-1-cyclohexyl-1-hydroxy-2-methoxyethyl]indoline-1-carboxylate (14g). The general procedure was followed using **13b** (200 mg, 0.69 mmol), cyclohexylmagnesium bromide in THF (6.7 ml, 1.0 M) and THF (2 ml) to give **14g** (154 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.17 (4H, m), 1.52–1.57 (2H, m), 1.57 (9H, s), 1.65 (1H, br), 1.76 (3H, br), 1.88 (1H, br), 3.16–3.26 (2H, m), 3.30 (3H, s), 3.47 (1H, d, J=9.3 Hz), 3.53 (1H, d, J=9.3 Hz), 4.77 (1H, br), 6.94 (1H, t, J=8.0 Hz), 7.12 (2H, t, J=8.0 Hz), 7.47 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 27.2, 27.4, 27.4, 28.1 (×3), 28.7, 30.7, 44.2, 59.5, 64.0, 74.8, 78.1, 81.6, 116.5 (×2), 123.0, 124.1, 126.9, 133.2, 143.3; IR (thin film) cm^{-1}: 3551, 3393, 2977, 2928, 2854, 1697, 1485, 1387, 1169, 751; HRMS calcd for $C_{22}H_{34}NO_4$ $(M+H)^+$ 376.2488, found 376.2486; $[\alpha]_D^{24}=-47.9$ (c 0.71, $CHCl_3$).

3.4.2.8. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)prop-2-enyl]indoline-1-carboxylate (14h). The general procedure was followed using **13b** (200 mg, 0.69 mmol), vinylmagnesium bromide in THF (2.1 ml, 1.0 M) and THF (2 ml) to give **14h** (213 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (9H, s), 3.03 (1H, dd, J=2.0, 16.8 Hz), 3.27 (1H, dd, J=10.0, 16.8 Hz), 3.40 (3H, s), 3.43 (1H, d, J=9.6 Hz), 3.54 (1H, d, J=9.6 Hz), 4.74 (1H, d, J=10.0 Hz), 5.14 (1H, dd, J=1.2, 11.0 Hz), 5.42 (1H, dd, J=1.2, 17.2 Hz), 5.66 (1H, dd, J=11.0, 17.2 Hz), 6.94 (1H, t, J=7.2 Hz), 7.10–7.15 (2H, m), 7.44 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (×3), 29.8, 30.0, 59.5, 63.6, 78.7, 82.0, 116.1 (×2), 116.4, 122.8, 123.9, 126.9, 131.7, 136.8, 142.7; IR ($CHCl_3$) cm^{-1}: 3357, 2982, 2931, 1686, 1484, 1383, 1287, 1258, 1352, 1166, 1133, 1017, 936; HRMS calcd for $C_{18}H_{25}NO_4Na$ $(M+Na)^+$ 342.1681, found 342.1682; $[\alpha]_D^{24}=-56.6$ (c 0.69, $CHCl_3$).

3.4.2.9. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-2-methylallyl]indoline-1-carboxylate (14i). The general procedure was followed using **13b** (320 mg, 1.10 mmol), 2-methylallylmagnesium bromide in THF (6.6 ml, 0.5 M) and THF (5 ml) to give **14i** (380 mg, 100%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (9H, s), 1.84 (3H, s), 3.08–3.16 (2H, m), 3.37 (3H, s), 3.52 (1H, d, J=10.0 Hz), 3.75 (1H, d, J=10.0 Hz), 4.73 (1H, br), 5.09 (1H, s), 5.22 (1H, s), 6.96 (1H, t, J=7.5 Hz), 7.13–7.17 (2H, m), 7.52 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 28.2 (×3), 29.3, 59.3, 61.5, 75.7, 80.6, 81.2, 113.6, 116.0, 122.7, 123.6, 126.4, 132.6, 142.9, 145.2, 153.7; IR ($CHCl_3$) cm^{-1}: 3559, 2980, 2930, 1685, 1484, 1373, 1285, 1166, 1135, 1014, 911; HRMS calcd for $C_{19}H_{27}NO_4Na$ $(M+Na)^+$ 356.1838, found 356.1838; $[\alpha]_D^{24}=-53.1$ (c 0.23, $CHCl_3$).

3.4.2.10. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-3-trimethylsilanylprop-2-ynyl]indoline-1-carboxylate (14j). The general procedure was followed using **13a** (330 mg, 1.13 mmol), (trimethylsilylmethyl) magnesium bromide in THF (freshly prepared from trimethylsilylacetylene (0.96 ml, 6.79 mmol), MeMgBr in diethyl ether (1.13 ml, 3.40 mmol) and THF (1 ml)) and THF (5 ml) to give **14j** (280 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.13 (9H, s), 1.58 (9H, s), 3.05 (1H, d, J=16.5 Hz), 3.38 (1H, dd, J=10.5, 16.5 Hz), 3.47 (3H, s), 3.54 (1H, d, J=10.5 Hz), 3.66 (1H, d, J=10.5 Hz), 4.90 (1H, d, J=10.5 Hz), 6.95 (1H, t, J=7.5 Hz), 7.11 (1H, d, J=7.5 Hz), 7.13 (1H, t, J=7.5 Hz), 7.42 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.55 (×3), 28.2 (×3), 31.1, 59.8, 63.5, 75.0, 77.0, 82.5, 89.8, 102.7, 116.2 (×2), 122.8, 124.0, 126.7, 131.6, 142.5; IR ($CHCl_3$) cm^{-1}: 3317, 2981, 1664, 1484, 1383, 1251, 1165, 1135, 861, 845; HRMS calcd for $C_{21}H_{31}NO_4SiNa$ $(M+Na)^+$ 412.1920, found 412.1941; $[\alpha]_D^{24}=-68.8$ (c 0.35, $CHCl_3$).

3.4.2.11. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-5-methylhex-4-enyl]indoline-1-carboxylate (14k). The general procedure was followed using **13a** (1.20 g, 3.24 mmol), 4-methyl-3-pentenylmagnesium bromide in THF (freshly prepared from the corresponding bromide (2.5 g, 15.3 mmol) and Mg (550 mg, 23 mmol)) and THF (15 ml) to give **14k** (992 mg, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (1H, dt, J=5.0, 14.0 Hz), 1.34–1.40 (1H, m), 1.53 (3H, s), 1.56 (9H, s), 1.62 (3H, s), 1.91–1.97 (1H, m), 2.01–2.07 (1H, m), 3.04 (1H, d, J=16.5 Hz), 3.26 (1H, dd, J=10.5, 16.5 Hz), 3.33 (3H, s), 3.38 (2H, s), 4.76 (1H, d, J=10.5 Hz), 4.96 (1H, t, J=7.0 Hz), 7.21–7.24 (2H, m), 7.32 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 21.5, 25.5, 28.1 (×3), 29.7, 32.5, 59.2, 64.8, 76.8, 76.9, 82.3, 115.3, 117.5, 124.3, 127.0, 129.6, 131.3, 134.2, 142.0, 154.4; IR ($CHCl_3$) cm^{-1}: 3381, 2981, 2930, 1672, 1477, 1371, 1254, 1164; HRMS calcd for $C_{22}H_{32}NO_4BrNa$ $(M+Na)^+$ 476.1412, found 476.1412; $[\alpha]_D^{24}=-43.5$ (c 0.93, $CHCl_3$).

3.4.2.12. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-3-phenylpropyl]indoline-1-carboxylate (14l). The general procedure was followed using **13a** (1.0 g, 2.70 mmol), phenethylmagnesium chloride in THF (3.2 ml, 1.0 M) and THF (15 ml) to give **14l** (871 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (9H, s), 1.61–1.70 (2H, m), 2.54 (1H, dt, J=5.2, 11.8 Hz), 2.67 (1H, dt, J=5.2, 11.8 Hz), 3.04 (1H, d, J=16.9 Hz), 3.25 (1H, dd, J=10.3, 16.9 Hz), 3.32 (3H, s), 3.38 (2H, s), 4.77 (1H, d, J=10.3 Hz), 7.01 (2H, d, J=6.6 Hz), 7.07–7.27 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2 (×3), 29.3, 29.8, 34.6, 59.3, 65.0, 76.3, 76.7, 82.6, 115.5, 117.7, 125.6, 127.2, 128.2 (×2), 128.3 (×2), 129.8, 134.1, 141.9, 142.4, 154.6; IR (film) cm^{-1}: 3394, 2978, 2930, 1702, 1668, 1476, 1369, 1329, 1166, 1137, 757; HRMS calcd for $C_{24}H_{30}NO_4BrNa$ $(M+Na)^+$ 498.1256, found 498.1265; $[\alpha]_D^{24}=-37.8$ (c 1.03, $CHCl_3$).

3.4.2.13. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-(methoxymethyl)-pent-4-enyl]indoline-1-carboxylate

(14m). The general procedure was followed using **13a** (715 mg, 1.93 mmol), 3-butenylmagnesium chloride in THF (4.6 ml, 0.5 M) and THF (10 ml) to give **14m** (671 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28–1.36 (1H, m), 1.38–1.46 (1H, m), 1.57 (9H, s), 1.95–2.04 (1H, m), 2.13–2.24 (1H, m), 3.04 (1H, d, J=16.9 Hz), 3.26 (1H, dd, J=9.5, 16.9 Hz), 3.35 (3H, s), 3.38 (2H, s), 4.77 (1H, d, J=10.9 Hz), 4.87 (1H, d, J=10.9 Hz), 4.92 (1H, d, J=19.1 Hz), 5.66–5.76 (1H, m), 7.24–7.26 (2H, m), 7.32 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2, 28.2 (×3), 29.8, 31.6, 59.3, 64.9, 76.0, 76.7, 82.5, 114.2, 115.4, 117.6, 127.1, 129.8, 134.2, 138.8, 142.0, 154.2; IR (film) cm^{-1}: 3401, 2977, 2928, 1703, 1670, 1477, 1369, 1167, 1015, 815; HRMS calcd for $C_{20}H_{28}NO_4BrNa$ $(M+Na)^+$ 448.1100, found 448.1122; $[\alpha]_D^{24}=-50.8$ (c 1.06, $CHCl_3$).

3.4.2.14. *tert*-Butyl (2*S*)-2-(1-hydroxy-1-methylethyl)-indoline-1-carboxylate (14n). The general procedure was followed using **13e** (760 mg, 2.91 mmol), methyllithium in diethyl ether (7.7 ml, 1.1 M) and THF (10 ml) to give **14n** (500 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (3H, s), 1.22 (3H, s), 1.58 (9H, s), 2.84 (1H, d, J=16.5 Hz), 3.32 (1H, dd, J=10.5, 16.5 Hz), 4.51 (1H, d, J=10.5 Hz), 6.95 (1H, t, J=7.5 Hz), 7.12 (1H, d, J=7.5 Hz), 7.15 (1H, t, J=7.5 Hz), 7.47 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 26.8, 28.2 (×3), 30.9, 67.5, 74.3, 82.1, 116.2 (×2), 122.9, 124.1, 127.0, 131.4, 142.5; IR ($CHCl_3$) cm^{-1}: 3405, 2981, 1665, 1484, 1384, 1288, 1256, 1165, 1045, 1019; HRMS calcd for $C_{16}H_{23}NO_3Na$ $(M+Na)^+$ 300.1576, found 300.1568; $[\alpha]_D^{24}=-69.7$ (c 0.69, $CHCl_3$).

3.4.2.15. *tert*-Butyl (2*S*)-5-bromo-2-[(1*R*)-1-hydroxy-1-phenylethynylbutyl]indoline-1-carboxylate (14o). The general procedure was followed using **13f** (220 mg, 0.60 mmol), phenylacetyllithium in THF (1.8 ml, 1.0 M) and THF (5 ml) to give **14o** (240 mg, 85%) as a colorless solid (mp 122–124 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (3H, t, J=7.1 Hz), 1.58 (9H, s), 1.66–1.76 (3H, m), 1.80–1.86 (1H, m), 3.12 (1H, dd, J=1.7, 16.8 Hz), 3.42 (1H, dd, J=9.9, 16.8 Hz), 4.70 (1H, dd, J=1.7, 9.9 Hz), 6.88 (2H, d, J=7.3 Hz), 7.16–7.34 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 17.2, 28.5 (×3), 31.7, 42.2, 67.5, 75.7, 83.5, 84.7, 89.0, 115.9, 118.1, 122.6, 124.5, 127.4, 128.3 (×2), 128.4, 130.2, 131.8 (×2), 134.6, 142.2; IR (KBr) cm^{-1}: 3489, 2960, 2931, 2872, 1688, 1668, 1479, 1369, 1335, 1165, 757; HRMS calcd for $C_{25}H_{28}NO_3BrNa$ $(M+Na)^+$ 492.1150, found 492.1158. Anal. Calcd for $C_{25}H_{28}NO_3Br$: C, 63.83; H, 6.00; N, 2.98; Br, 16.99. Found: C, 63.98; H, 5.70; N, 2.99; Br, 16.90; $[\alpha]_D^{24}=-48.8$ (c 0.94, $CHCl_3$).

3.4.2.16. *tert*-Butyl (2*S*)-5-bromo-2-[(1*S*)-1-hydroxy-1,5-dimethylhex-4-enyl]indoline-1-carboxylate (14p). The general procedure was followed using **13g** (20 mg, 0.049 mmol), methyllithium in diethyl ether (0.13 ml, 1.1 M) and THF (2 ml) to give **14p** (10 mg, 47%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s), 1.47–1.54 (2H, m), 1.57 (9H, s), 1.63 (3H, s), 1.69 (3H, s), 2.12–2.21 (2H, m), 2.77 (1H, d, J=16.8 Hz), 3.30 (1H, dd, J=10.4, 16.8 Hz), 4.60 (1H, dd, J=2.4, 10.4 Hz), 5.12 (1H, t, J=6.4 Hz), 7.23–7.33 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 20.9, 21.5, 25.5, 28.1 (×3), 30.5, 39.2, 66.5, 75.9, 82.7, 115.4, 117.5, 124.2, 127.1, 129.9, 131.5, 133.6, 141.8, 155.0; IR ($CHCl_3$) cm^{-1}: 3437, 2979, 1668, 1477, 1372, 1163, 1015; HRMS calcd for $C_{21}H_{30}NO_3Br$ $(M)^+$ 423.1409, found 423.1400; $[\alpha]_D^{24}=-72.1$ (c 0.38, $CHCl_3$).

3.4.2.17. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1,3-diphenylpropyl]indoline-1-carboxylate (14q). The general procedure was followed using **13h** (17 mg, 0.048 mmol), phenyllithium in diethyl ether (0.3 ml, 0.94 M) and THF (1 ml) to give **14q** (14 mg, 68%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (9H, s), 2.19 (1H, dt, J=4.9, 12.7 Hz), 2.32 (1H, br), 2.45 (1H, dt, J=3.9, 12.7 Hz), 2.65 (1H, br), 2.87 (1H, d, J=16.1 Hz), 3.11 (1H, br), 4.90 (1H, d, J=9.3 Hz), 6.86 (1H, t, J=7.0 Hz), 6.97 (1H, d, J=7.0 Hz), 7.03 (1H, br), 7.11–7.26 (9H, m), 7.43 (2H, d, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5 (×3), 29.9, 30.9, 42.0, 67.9, 80.9, 82.3, 116.5 (×2), 123.3, 124.1, 125.9, 126.3, 127.0, 127.1, 127.6, 128.2, 128.3, 128.6 (×2), 128.6 (×2), 128.7, 132.2, 142.1, 142.9; IR (KBr) cm^{-1}: 2976, 2929, 1702, 1682, 1483, 1369, 1167, 751, 701; HRMS calcd for $C_{28}H_{32}NO_3$ $(M+H)^+$ 430.3282, found 430.2387; $[\alpha]_D^{24}=-59.6$ (c 1.40, $CHCl_3$).

3.5. Synthesis of (+)-benzastatin E (1)

3.5.1. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid (17). To a solution of major-**16** (919 mg, 2.25 mmol) in ether (15 ml) was added *t*-BuLi in pentane (6.0 ml, 1.5 M) dropwise at −78 °C. After stirring for 15 min at −78 °C, a portion of CO_2 (2.0 g) was added to the reaction mixture at −78 °C. After warming up to room temperature, the reaction was quenched with satd NH_4Cl aq (30 ml) and extracted with AcOEt (30 ml×2). The combined organic extracts were washed with brine (30 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 1:2) provided **17** (446 mg, 53%) as a colorless solid (mp 210–213 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (1H, dt, J=4.4, 13.2 Hz), 1.49 (3H, s), 1.54 (6H, s), 1.55 (3H, s), 1.56–1.65 (1H, m), 1.73 (3H, s), 1.95 (1H, dt, J=4.4, 13.2 Hz), 2.07 (1H, dt, J=4.4, 13.2 Hz), 3.06–3.10 (2H, m), 3.32 (1H, d, J=9.6 Hz), 3.40 (3H, s), 3.53 (1H, d, J=9.6 Hz), 4.45 (1H, dd, J=6.0, 9.6 Hz), 6.60 (1H, d, J=8.8 Hz), 7.74 (1H, s), 7.82 (1H, dd, J=1.6, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 20.6, 26.0, 28.0, 28.5, 28.9, 30.7, 59.6, 70.2, 75.9, 82.1, 93.9, 109.3, 118.7, 124.0, 126.5, 127.0, 130.8, 131.9, 132.5, 152.9, 171.8; IR (KBr) cm^{-1}: 2913, 1666, 1607, 1450, 1369, 1296, 1272, 1217, 1120, 827, 768; HRMS calcd for $C_{22}H_{31}NO_4$ $(M)^+$ 373.2253, found 373.2265; $[\alpha]_D^{24}=+223.5$ (c 0.42, $CHCl_3$).

3.5.2. (1*R*,9a*S*)-1-Methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxamide (18). To a solution of **17** (103 mg, 0.276 mmol) in THF (5 ml) was added 1,1′-carbonyldiimidazole (134 mg, 0.827 mmol) at room temperature. The mixture was stirred for 30 min at room temperature. 1,1′-Carbonyldiimidazole (134 mg, 0.827 mmol) was added and stirred for another 30 min at room temperature. 28% NH_3 aq (5.0 ml) was added to the reaction mixture at room

temperature and stirred for 12 h at this temperature. After addition of water (20 ml), the aqueous solution was extracted with AcOEt (20 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) gave **18** (76 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (1H, dt, J=5.5, 13.2 Hz), 1.48 (3H, s), 1.53 (6H, s), 1.55 (3H, s), 1.55–1.62 (1H, m), 1.71 (3H, s), 1.95 (1H, dt, J=5.5, 13.2 Hz), 2.06 (1H, dt, J=5.5, 13.2 Hz), 3.01–3.17 (2H, m), 3.31 (1H, d, J=9.6 Hz), 3.39 (3H, s), 3.53 (1H, d, J=9.6 Hz), 4.42 (1H, dd, J=5.2, 8.8 Hz), 5.90 (2H, br), 6.59 (1H, d, J=8.8 Hz), 7.49 (1H, dd, J=2.4, 8.8 Hz), 7.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 19.9 (×2), 20.6, 26.0, 28.0, 28.8, 28.9, 31.0, 59.6, 70.2, 76.0, 82.1, 94.2, 109.8, 123.0, 123.9, 124.1, 127.1, 132.1, 151.7, 169.4; IR ($CHCl_3$) cm^{-1}: 3534, 3417, 2928, 1663, 1609, 1492, 1444, 1370, 1272, 1118, 909; HRMS calcd for $C_{22}H_{32}N_2O_3Na$ $(M+Na)^+$ 395.2311, found 395.2313; $[\alpha]_D^{24}=+154.2$ (c 0.20, $CHCl_3$).

3.5.3. (+)-Benzastatin E (1). To a solution of **18** (70 mg, 0.188 mmol) in MeOH (5 ml) was added pyridinium *p*-toluenesulfonate (10 mg) at room temperature. The mixture was stirred for 3 h at room temperature. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt to AcOEt–MeOH 10:1) to give **1** (40 mg, 64%) as a colorless solid (mp 171–174 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (1H, dd, J=5.5, 14.0 Hz), 1.57 (1H, dd, J=4.5, 14.0 Hz), 1.64 (6H, s), 1.66 (3H, s), 2.01 (1H, dd, J=5.5, 13.0 Hz), 2.15 (1H, dd, J=4.5, 13.0 Hz), 2.70 (1H, br s), 2.97 (1H, dd, J=8.5, 16.0 Hz), 3.07 (1H, dd, J=11.0, 16.0 Hz), 3.42 (3H, s), 3.42 (1H, d, J=9.5 Hz), 3.52 (1H, d, J=9.5 Hz), 4.15 (1H, t, J=9.5 Hz), 4.65 (1H, br), 5.60 (2H, br), 6.58 (1H, d, J=7.5 Hz), 7.50 (1H, d, J=7.5 Hz), 7.55 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 20.0, 20.6, 28.2, 30.0, 32.7, 59.6, 66.2, 73.0, 78.4, 107.8, 123.1, 124.1, 124.5, 127.2, 128.0, 128.6, 154.5, 169.3; IR (KBr) cm^{-1}: 3416, 3312, 2918, 1645, 1606, 1441, 1380, 1262, 1112, 773; HRMS calcd for $C_{19}H_{29}N_2O_3$ $(M+H)^+$ 333.2178, found 333.2187. Anal. Calcd for $C_{19}H_{28}N_2O_3\cdot 0.3H_2O$: C, 67.55; H, 8.53; N, 8.29. Found: C, 67.48; H, 8.59; N, 8.24; $[\alpha]_D^{24}=+21.3$ (c 0.10, MeOH).

3.6. Stereoselective rearrangement from α,α-disubstituted indoline-2-methanols to 2,2,3-trisubstituted tetrahydroquinolines

3.6.1. Investigation of the rearrangement reaction with α-monosubstituted indoline-2-methanol 22.

3.6.1.1. *tert*-Butyl 5-bromo-2-formylindoline-1-carboxylate (19). To a solution of lithium aluminum hydride (1.67 g, 44.1 mmol) in THF (40 ml) was added racemic-**11** (7.85 g, 22.0 mmol) in THF (20 ml) dropwise at −78 °C. After stirring for 3 h at −40 °C, the reaction mixture was quenched with H_2O (1.7 ml), 5 N NaOH aq (1.7 ml), then H_2O (5.1 ml), and stirred at room temperature for 30 min. To the mixture was added magnesium sulfate (10 g) and AcOEt (30 ml), and the mixture was filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 6:1 to 1:1) gave the corresponding alcohol (6.00 g, 83%).

To a solution of alcohol (5.78 g, 15.5 mmol) in CH_2Cl_2 (150 ml) was added Et_3N (8.7 ml, 62.1 mmol), DMSO (7.3 ml, 102.5 mmol), and pyridine sulfur trioxide complex(7.41 g, 46.6 mmol) at 0 °C. After stirring at room temperature for 3 h, H_2O (150 ml) was added, and the product was extracted with CH_2Cl_2 (50 ml×3). The combined organic extracts were washed with brine (150 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 4:1 to 3:2) yielded aldehyde **19** (3.09 g, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (9H, br), 3.14 (1H, dd, J=4.9, 16.6 Hz), 3.38 (1H, br), 4.75 (1H, br), 7.26 (1H, s), 7.32 (1H, s), 7.78 (1H, br s), 9.63 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 28.2 (×3), 29.3, 60.0, 82.4, 115.2, 116.2 (×2), 127.6, 130.2*, 130.8, 141.6, 151.4, 198.3; IR (KBr) cm^{-1}: 3282, 3063, 2929, 1672, 1645, 1223, 751; HRMS calcd for $C_{14}H_{16}NO_3BrK$ $(M+K)^+$ 363.9951, found 363.9952.

3.6.1.2. *tert*-Butyl (2*S)-5-bromo-2-[(1*R**)-1-hydroxypent-4-enyl]indoline-1-carboxylate (20).** This diastereoselective Grignard addition was carried out by a method similar to that used for synthesis of **14a** with **19** (300 mg, 0.92 mmol), 3-butenylmagnesium bromide in THF (2.2 ml, 0.5 M) and THF (10 ml) to give **20** (264 mg, 75%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.44 (1H, m), 1.52–1.57 (1H, m), 1.57 (9H, s), 2.10–2.18 (1H, m), 2.27–2.31 (1H, m), 2.99 (1H, br), 3.20–3.25 (1H, m), 3.98 (1H, br), 4.49 (1H, br), 4.98 (1H, d, J=10.3 Hz), 5.05 (1H, dd, J=1.5, 15.6 Hz), 5.78–6.86 (1H, m), 7.24 (1H, s), 7.26 (1H, s), 7.47 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.6 (×4), 30.3, 31.6, 64.5, 73.3, 82.4, 115.4, 115.4, 116.8, 127.7, 130.3 (×2), 133.4, 138.4, 142.1; IR (liquid film) cm^{-1}: 3464, 2977, 2933, 1702, 1479, 1385, 1370, 1168, 1142; HRMS calcd for $C_{18}H_{24}NO_3BrNa$ $(M+Na)^+$ 404.08373, found 404.08407.

3.6.1.3. (1*R,9a*S**)-7-Bromo-1-but-3-enyl-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole-3-spiro-1′-cyclohexane (21).** To a solution of **20** (144 mg, 0.38 mmol) in CH_2Cl_2 was added TFA (1 ml) at 0 °C. After stirring at room temperature for 20 min, the reaction mixture was neutralized with satd $NaHCO_3$ aq and extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 9:1) gave the corresponding indoline-2-methanol (62 mg, 59%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.60 (2H, m), 2.08–2.18 (1H, m), 2.21 (1H, s), 2.24–2.31 (1H, m), 2.88 (1H, dd, J=9.5, 16.0 Hz), 3.00 (1H, dd, J=9.9, 16.0 Hz), 3.71–3.73 (1H, m), 3.82 (1H, br), 3.95 (1H, dt, J=3.7, 9.5 Hz), 4.96 (1H, d, J=9.6 Hz), 5.03 (1H, dd, J=1.8, 17.3 Hz), 5.76–5.86 (1H, m), 6.46 (1H, d, J=8.1 Hz), 7.06 (1H, br d, J=8.1 Hz), 7.13 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 30.2, 31.9, 64.5, 71.3, 110.7 (×2), 115.0, 127.5, 129.7, 131.3, 137.9, 149.4; IR (KBr) cm^{-1}: 3304, 3327, 2929, 2889, 1483, 1248, 920, 814; HRMS calcd for $C_{13}H_{16}NOBr$ $(M)^+$ 281.0415, found 281.0418.

To a solution of indoline-2-methanol (110 mg, 0.39 mmol) in CH_2Cl_2 was added 1,1-dimethoxycyclohexane (0.6 ml, 3.9 mmol) and *p*-TsOH (7 mg, 0.04 mmol) at room

temperature. The mixture was stirred at 30 min at room temperature. After concentration of the reaction mixture, purification by silica gel column chromatography (hexane–AcOEt 19:1 to 9:1) afforded **21** (102 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.21 (1H, m), 1.29–1.33 (1H, m), 1.42–1.63 (8H, m), 1.78 (1H, dt, J=4.2, 12.3 Hz), 2.00–2.03 (1H, m), 2.06–2.15 (1H, m), 2.19–2.26 (1H, m), 2.72 (1H, dd, J=9.5, 16.0 Hz), 3.07 (1H, dd, J=7.7, 16.0 Hz), 4.11 (1H, dd, J=5.9, 14.5 Hz), 4.32 (1H, dd, J=8.4, 14.5 Hz), 4.95 (1H, d, J=10.3 Hz), 5.01 (1H, dd, J=1.8, 17.3 Hz), 5.75–5.85 (1H, m), 6.64 (1H, d, J=8.5 Hz), 7.09 (1H, d, J=8.5 Hz), 7.14 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 23.9, 25.4, 30.2, 30.5, 30.8, 35.4, 37.2, 67.3, 74.4, 96.2, 113.6, 115.0, 117.9, 127.3, 129.3, 136.4, 138.0, 148.5; IR (liquid film) cm^{-1}: 2936, 2857, 1473; HRMS calcd for $C_{19}H_{24}NOBr$ (M)$^+$ 361.1041, found 361.1032.

3.6.1.4. Methyl (2*S)-2-[(1*R**)-1-hydroxypent-4-enyl]-indoline-5-carboxylate (22).** A method for the preparation of **17** was followed using **21** (115 mg, 0.32 mmol), *t*-BuLi in pentane (0.58 ml, 1.5 M) and THF (3 ml) to give the corresponding carboxylic acid (96 mg, crude yield 90%). The obtained carboxylic acid was used without further purification.

To a solution of crude carboxylic acid in MeOH (6 ml) was added $TMSCH_2N_2$ in hexane (2.5 ml, 2 M) at 0 °C. After stirring at room temperature overnight, the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 10:1) to give the corresponding methyl ester (92 mg, crude yield 92%). The obtained methyl ester was used without further purification.

To a solution of methyl ester in MeOH (1 ml) was added Amberlyst-15® ion exchange resin (10 mg) at room temperature. After stirring at room temperature for 4 h, the mixture was filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 7:3) gave **22** (51 mg, 62% from **21**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.66 (2H, m), 2.13 (1H, s), 2.15–2.23 (1H, m), 2.29–2.36 (1H, m), 3.01 (1H, dd, J=10.3, 16.1 Hz), 3.07 (1H, dd, J=9.8, 16.1 Hz), 3.78–3.80 (1H, m), 3.86 (3H, s), 4.07 (1H, dt, J=2.9, 9.3 Hz), 4.22 (1H, br s), 5.02 (1H, d, J=10.7 Hz), 5.09 (1H, d, J=16.6 Hz), 5.82–5.90 (1H, m), 6.59 (1H, d, J=8.8 Hz), 7.75 (1H, s), 7.78 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 30.1, 31.7, 51.6, 64.4, 71.8, 107.8, 115.2, 120.4, 126.7, 128.5, 130.6, 138.1, 155.0, 167.3; IR (KBr) cm^{-1}: 3404, 2932, 1676, 1616, 1307, 1276, 1121, 1090, 767; HRMS calcd for $C_{15}H_{19}NO_3$ (M)$^+$ 261.1365, found 261.1367.

3.6.1.5. Methyl (2*S,3*R**)-2-but-3-enyl-3-chloro-1,2,3,4-tetrahydroquinoline-6-carboxylate (23).** To a solution of **22** (10 mg, 0.038 mmol) in CH_2Cl_2 was added CCl_4 (0.04 ml, 0.42 mmol) and triphenylphosphine (30 mg, 0.11 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, and concentrated. The ratio of **23** and **24** (**23**:**24**=3:1) was determined by the ^{1}H NMR analysis of the crude residue. Purification by silica gel column chromatography (hexane–AcOEt 19:1 to 4:1) gave a mixture of **23** and **24** (**23**/**24**=3:1, total 9.7 mg, total yield 91%). Analytical sample was obtained by further purification by Lobar column chromatography (hexane–AcOEt 19:1). ^{1}H NMR (400 MHz, CD_3OD) δ 1.53–1.61 (1H, m), 1.63–1.72 (1H, m), 2.10–2.19 (1H, m), 2.21–2.28 (1H, m), 2.93 (1H, dd, J=5.9, 16.9 Hz), 3.22 (1H, dd, J=4.4, 16.9 Hz), 3.37–3.41 (1H, m), 3.76 (3H, s), 4.25 (1H, dd, J=5.5, 9.9 Hz), 4.95 (1H, d, J=10.3 Hz), 5.05 (1H, dd, J=1.5, 16.8 Hz), 5.76–5.86 (1H, m), 6.51 (1H, d, J=8.8 Hz), 7.54–7.58 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 30.3, 35.3, 35.3, 51.9, 56.5, 58.0, 113.6, 115.6, 116.9, 117.8, 130.6, 132.5, 139.1, 149.3, 169.3; IR (KBr) cm^{-1}: 3367, 1696, 1684, 1609, 1293, 1282, 1238. Anal. Calcd for $C_{15}H_{18}NO_2Cl$: C, 64.40; H, 6.49; N, 5.01; Cl, 12.67. Found: C, 64.10; H, 6.29; N, 4.97; Cl, 12.59.

3.6.1.6. Methyl (2*S)-2-[(1*R**)-1-chloropent-4-enyl]-indoline-5-carboxylate (24).** ^{1}H NMR (400 MHz, CD_3OD) δ 1.63–1.73 (1H, m), 1.90–1.98 (1H, m), 2.13–2.22 (1H, m), 2.29–2.38 (1H, m), 2.95 (1H, dd, J=7.3, 16.3 Hz), 3.19 (1H, dd, J=9.9, 16.3 Hz), 3.76 (3H, s), 3.87–3.91 (1H, m), 4.06–4.12 (1H, m), 4.96 (1H, d, J=10.2 Hz), 5.03 (1H, d, J=15.4 Hz), 5.74–5.84 (1H, m), 6.44 (1H, d, J=8.1 Hz), 7.59 (1H, d, J=1.5 Hz), 7.62 (1H, d, J=8.1 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 31.6, 33.9, 34.5, 52.0, 65.4, 67.4, 107.7, 116.0, 119.6, 126.8, 128.8, 132.0, 138.5, 157.4, 169.4; EI-MS *m*/*z* 279 (M)$^+$, 248, 224, 202, 188, 176, 144, 132, 117, 90, 77, 59, 41.

3.6.1.7. Methyl (1*S,7a*S**)-1-but-3-enyl-7,7a-dihydro-1*H*-azireno[1,2-*a*]indole-5-carboxylate (25).** To a solution of **23** (10 mg, 0.036 mmol) in *t*-BuOH (0.3 ml) was added *t*-BuOK in *t*-BuOH (0.05 ml, 1 M) at room temperature. After stirring at 60 °C for 3 h, the solvent was evaporated. To this residue was added MeOH (0.3 ml), followed by the addition of acetic acid in MeOH (0.36 ml, 0.1 N), then $TMSCH_2N_2$ in hexane (0.2 ml, 2 M) at 0 °C. The mixture was stirred at room temperature for 40 min. After addition of water (5 ml), the aqueous solution was extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 4:1) afforded **25** (1.6 mg, 26% from **23**) as a colorless oil.

Compound **25** was obtained from **24** (3.5 mg, 0.0125 mmol) by the similar procedure (1.4 mg, 47% from **24**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53–1.56 (1H, m), 1.66–1.71 (2H, m), 2.23–2.33 (2H, m), 2.89 (1H, td, J=3.2, 6.7 Hz), 3.29 (1H, dd, J=6.7, 16.9 Hz), 3.34 (1H, d, J=16.9 Hz), 3.89 (3H, s), 4.99 (1H, d, J=9.8 Hz), 5.06 (1H, d, J=18.6 Hz), 5.81–5.89 (1H, m), 7.28 (1H, s), 7.85–7.87 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 32.0, 32.8, 47.0, 52.2, 52.5, 115.5, 119.3, 126.8, 127.4, 129.8, 137.2, 137.9, 146.7, 162.6; IR (liquid film) cm^{-1}: 3386, 2922, 1718, 1611, 1438, 1275; HRMS calcd for $C_{15}H_{17}NO_2$ (M)$^+$ 243.1260, found 243.1267.

3.6.2. Investigation of the rearrangement reaction of indoline-2-methanols 15a, b to tetrahydroquinolines 26a, b.

3.6.2.1. (2*R*,3*R*)-3-Chloro-2-ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26a). Triphenylphosphine (135 mg, 0.420 mmol) was added to a solution of **15a** (31 mg, 0.14 mmol) and CCl_4 (135 µl, 1.40 mmol) in

CH_2Cl_2 (3 ml) at 40 °C. The mixture was stirred under reflux conditions for 30 min, and then concentrated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 2:1) gave tetrahydroquinoline **26a** (21 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz), 1.66 (1H, dq, J=7.3, 14.8 Hz), 1.76 (1H, dq, J=7.3, 14.8 Hz), 3.05 (1H, dd, J=6.6, 16.8 Hz), 3.30 (1H, dd, J=5.2, 16.8 Hz), 3.35 (3H, s), 3.48 (1H, d, J=9.2 Hz), 3.53 (1H, d, J=9.2 Hz), 3.99 (1H, br s), 4.33 (1H, dd, J=5.2, 6.6 Hz), 6.53 (1H, d, J=8.1 Hz), 6.63 (1H, t, J=8.1 Hz), 6.96 (1H, d, J=8.1 Hz), 7.01 (1H, t, J=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.1, 27.2, 33.9, 57.0, 57.6, 59.4, 73.5, 114.7, 117.2, 117.6, 127.4, 129.4, 142.3; IR ($CHCl_3$) cm^{-1}: 3422, 2972, 2935, 2896, 1607, 1588, 1482, 1312, 1260, 1112, 980, 960, 834; HRMS calcd for $C_{13}H_{18}NOCl$ $(M)^+$ 239.1077, found 239.1075; $[\alpha]_D^{24}=+7.2$ (c 0.45, $CHCl_3$).

3.6.2.2. (2*S*,3*R*)-3-Chloro-2-ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26b). The method for the synthesis of **26a** was followed with **15b** (100 mg, 0.45 mmol), PPh_3 (355 mg, 1.35 mmol) and CCl_4 (434 μl, 4.50 mmol) and CH_2Cl_2 (5 ml) to give **26b** (80 mg, 74%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.6 Hz), 1.72 (1H, dq, J=7.6, 14.5 Hz), 1.82 (1H, dq, J=7.6, 14.5 Hz), 3.09 (1H, dd, J=6.8, 16.5 Hz), 3.24 (1H, dd, J=4.8, 16.5 Hz), 3.35 (3H, s), 3.40 (1H, d, J=9.5 Hz), 3.42 (1H, d, J=9.5 Hz), 3.99 (1H, br s), 4.44 (1H, dd, J=4.8, 6.8 Hz), 6.57 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.97 (1H, d, J=8.0 Hz), 7.01 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.5, 25.4, 34.0, 57.5, 57.9, 59.3, 75.1, 115.0, 117.7, 117.8, 127.3, 129.3, 142.1; IR ($CHCl_3$) cm^{-1}: 3424, 2972, 2935, 2883, 1607, 1588, 1498. 1481, 1307, 1156, 1111, 962; HRMS calcd for $C_{13}H_{18}NOCl$ $(M)^+$ 239.1077, found 239.1081; $[\alpha]_D^{24}=-30.2$ (c 0.67, $CHCl_3$).

3.6.2.3. (2*S*)-2-Ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (27a). To a solution of **26a** (21 mg, 0.088 mmol) in benzene (5 ml) was added (n-Bu)$_3$SnH (0.047 ml, 0.175 mmol) and AIBN (catalytic) at room temperature. The mixture was stirred at 80 °C for 3 h. After concentration, satd KF aq was added, and the mixture was filtered. The product was extracted with AcOEt (5 ml×2), and the combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 5:1) afforded **27a** (17 mg, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J=9.0 Hz), 1.57–1.72 (4H, m), 2.70 (2H, t, J=8.0 Hz), 3.17 (1H, d, J=11.0 Hz), 3.35 (3H, s), 3.36 (1H, d, J=11.0 Hz), 3.99 (1H, br s), 6.49 (1H, dd, J=2.0, 9.0 Hz), 6.58 (1H, dt, J=2.0, 9.0 Hz), 6.95 (1H, d, J=9.0 Hz), 6.97 (1H, t, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.97. 23.4, 27.0, 29.1, 53.9, 59.3, 59.4, 114.2, 116.4, 120.3, 126.6, 128.9, 143.5; IR ($CHCl_3$) cm^{-1}: 3421, 2968, 2930, 1605, 1482, 1313, 1110; HRMS calcd for $C_{13}H_{19}NO$ $(M)^+$ 205.1467, found 205.1461; $[\alpha]_D^{24}=+25.3$ (c 0.31, $CHCl_3$).

3.6.2.4. (2*R*)-2-Ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (27b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J=9.0 Hz), 1.57–1.72 (4H, m), 2.70 (2H, t, J=8.0 Hz), 3.17 (1H, d, J=11.0 Hz), 3.35 (3H, s), 3.36 (1H, d, J=11.0 Hz), 3.99 (1H, br s), 6.49 (1H, dd, J=2.0, 9.0 Hz), 6.58 (1H, dt, J=2.0, 9.0 Hz), 6.95 (1H, d, J=9.0 Hz), 6.97 (1H, t, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.97. 23.4, 27.0, 29.1, 53.9, 59.3, 59.4, 114.2, 116.4, 120.3, 126.6, 128.9, 143.5; IR ($CHCl_3$) cm^{-1}: 3421, 2968, 2930, 1605, 1482, 1313, 1110; HRMS calcd for $C_{13}H_{19}NO$ $(M)^+$ 205.1467, found 205.1461; $[\alpha]_D^{24}=-27.6$ (c 0.31, $CHCl_3$).

3.6.2.5. (2*R*,3*R*)-3-Chloro-2-ethyl-2-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (28). To a solution of **26a** (131mg, 0.55 mmol) in CH_2Cl_2 (5 ml) was added $AlCl_3$ (364 mg, 2.73 mmol) and Me_2S (401 μl, 5.46 mmol) at room temperature. After stirring at room temperature for 31 h, satd $NaHCO_3$ aq (10 ml) was added and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 5:1 to 2:1) gave **28** (106 mg, 86%) as a colorless solid (mp 118–120 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.6 Hz), 1.72 (2H, q, J=7.6 Hz), 3.13 (1H, dd, J=8.0, 16.4 Hz), 3.28 (1H, dd, J=6.0, 16.4 Hz), 3.75 (2H, br d, J=3.6 Hz), 3.89 (1H, br s), 4.34 (1H, dd, J=6.0, 8.0 Hz), 6.57 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz), 7.03 (1H, t, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 27.5, 34.0, 57.5, 58.0, 64.0, 114.5, 118.0 (×2), 127.5, 129.2, 142.0; IR (KBr) cm^{-1}: 3393, 2267, 1493, 1315, 1046, 752; HRMS calcd for $C_{12}H_{16}NOCl$ $(M)^+$ 225.0920, found 225.0922. Anal. Calcd for $C_{12}H_{16}NOCl$: C, 63.85; H, 7.15; N, 6.21. Found: C, 63.82; H, 7.06; N, 6.24; $[\alpha]_D^{24}=+8.3$ (c 0.18, $CHCl_3$).

*(1S,2R,3R)-(−)-**30***. To a solution of **28** (5 mg, 0.0222 mmol) and **29** (14.4 mg, 0.0333 mmol) in CH_2Cl_2 (5 ml) was added DCC (6.9 mg, 0.0333 mmol) and DMAP (3 mg) at 50 °C. The mixture was stirred at 50 °C for 1 h, and then concentrated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) gave **30** as a colorless solid (9 mg, 64%). Recrystallization from ethanol gave an analytical sample (mp 212–215 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, s), 0.99 (3H, t, J=6.5 Hz), 1.20 (3H, s), 1.35–1.44 (2H, m), 1.55–1.69 (1H, m), 1.82–1.90 (1H, m), 1.92 (3H, br s), 2.12–2.20 (1H, m), 2.40–2.48 (1H, m), 3.17 (1H, dd, J=9.5, 17.0 Hz), 3.31 (1H, dd, J=5.5, 17.0 Hz), 3.39 (1H, d, J=14.0 Hz), 3.45 (1H, d, J=14.0 Hz), 4.04 (2H, br t, J=7.0 Hz), 4.36 (1H, dd, J=5.5, 9.5 Hz), 4.44 (1H, d, J=11.5 Hz), 4.51 (1H, d, J=11.5 Hz), 6.56 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.98 (1H, d, J=8.0 Hz), 6.99 (1H, t, J=8.0 Hz), 7.26 (1H, s), 7.50 (1H, s), 7.73 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.73, 19.9, 20.7, 26.4, 27.8, 33.1, 34.3, 37.7, 44.7, 47.7, 48.5, 53.1, 56.8, 57.3, 65.7, 67.1, 114.5, 117.5, 118.0, 127.6, 128.2, 129.0, 131.1, 131.5, 134.4, 135.0, 136.8, 142.4, 163.5, 165.2; IR (KBr) cm^{-1}: 3398, 2959, 1730, 1670, 1489, 1299, 1140, 1098, 750, 540; HRMS calcd for $C_{30}H_{33}N_2O_5Cl_3SNa$ $(M+Na)^+$ 661.1073, found 661.1071. Anal. Calcd for $C_{30}H_{33}N_2O_5Cl_3S\cdot 0.5H_2O$: C, 55.52; H, 5.28; N, 4.32. Found: C, 55.69; H, 5.02; N, 4.24; $[\alpha]_D^{24}=-40.9$ (c 0.29, $CHCl_3$).

3.6.3. Preparation of indoline-2-methanols 15 and the determination of the stereochemistry.

3.6.3.1. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybutan-2-ol (15a). To a solution of **14a** (650 mg,

2.02 mmol) in CH_2Cl_2 (3 ml) was added TFA (3 ml) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was neutralized with satd $NaHCO_3$ aq and extracted with AcOEt (10 ml×2). The combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 2:1) afforded **15a** (440 mg, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.7 Hz), 1.50–1.56 (1H, m), 1.62–1.69 (1H, m), 2.90 (1H, s), 2.92 (1H, dd, J=8.9, 17.5 Hz), 3.05 (1H, dd, J=10.9, 17.5 Hz), 3.38 (1H, d, J=9.8 Hz), 3.41 (3H, s), 3.49 (1H, d, J=9.8 Hz), 4.08 (1H, dd, J=8.9, 10.9 Hz), 4.24 (1H, br s), 6.65 (1H, d, J=7.5 Hz), 6.72 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.08 (1H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.94, 27.4, 30.5, 59.5, 65.6, 72.9, 78.1, 109.4, 118.8, 124.4, 127.1, 128.6, 150.5; IR ($CHCl_3$) cm^{-1}: 3485, 3405, 2975, 2932, 2893, 1609, 1486, 1467, 1247, 1110; HRMS calcd for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1490; $[\alpha]_D^{24}=-44.2$ (c 0.62, $CHCl_3$).

Compounds **15b–j**, **15n**, **15q** were prepared by the method similar to that used for the preparation of **15a**.

Compounds **15k** and **15p** were prepared by the method similar to that used for the preparation of **15**.

3.6.3.2. (2*S*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybutan-2-ol (15b). The general method was followed using **14b** (580 mg, 1.80 mmol) to give **15b** (350 mg, 88%) as a colorless solid (mp 49–51 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.8 Hz), 1.55–1.70 (2H, m), 2.37 (1H, s), 2.97 (1H, dd, J=10.1, 16.2 Hz), 3.02 (1H, dd, J=10.1, 16.2 Hz), 3.30 (1H, d, J=8.8 Hz), 3.36 (3H, s), 3.49 (1H, d, J=8.8 Hz), 3.95 (1H, br s), 4.05 (1H, t, J=10.1 Hz), 6.64 (1H, d, J=7.3 Hz), 6.71 (1H, t, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz), 7.08 (1H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.66, 28.6, 30.3, 59.4, 64.3, 74.0, 74.3, 109.6, 119.0, 124.6, 127.2, 129.0, 150.6; IR (KBr) cm^{-1}: 3468, 3320, 2919, 2883, 1489, 1463, 1111, 753; HRMS calcd for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1500. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.51; H, 8.40; N, 6.53; $[\alpha]_D^{24}=-21.7$ (c 0.43, $CHCl_3$).

3.6.3.3. (2*S*)-2-[(2*R*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybutan-2-ol (15c). The general method was followed using **14c** (210 mg, 0.65 mmol) to give **15c** (137 mg, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.7 Hz), 1.50–1.56 (1H, m), 1.62–1.69 (1H, m), 2.90 (1H, s), 2.92 (1H, dd, J=8.9, 17.5 Hz), 3.05 (1H, dd, J=10.9, 17.5 Hz), 3.38 (1H, d, J=9.8 Hz), 3.41 (3H, s), 3.49 (1H, d, J=9.8 Hz), 4.08 (1H, dd, J=8.9, 10.9 Hz), 4.24 (1H, br s), 6.65 (1H, d, J=7.5 Hz), 6.72 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.08 (1H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.94, 27.4, 30.5, 59.5, 65.6, 72.9, 78.1, 109.4, 118.8, 124.4, 127.1, 128.6, 150.5; IR ($CHCl_3$) cm^{-1}: 3485, 3405, 2975, 2932, 2893, 1609, 1486, 1467, 1247, 1110; HRMS calcd for $C_{13}H_{20}NO_2$ $(M+H)^+$ 222.1494, found 222.1490; $[\alpha]_D^{24}=+34.5$ (c 0.64, $CHCl_3$).

3.6.3.4. (1*R*)-1-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-2-methoxy-1-phenylethanol (15d). The general method was followed using **14d** (410 mg, 1.11 mmol) to give **15d** (264 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (1H, dd, J=8.8, 15.8 Hz), 2.68 (1H, dd, J=11.1, 15.8 Hz), 3.43 (3H, s), 3.49 (1H, d, J=9.9 Hz), 3.75 (1H, d, J=9.9 Hz), 3.77 (1H, s), 4.53 (1H, dd, J=8.8, 11.1 Hz), 4.51 (1H, br s), 6.66 (1H, d, J=7.3 Hz), 6.68 (1H, d, J=7.3 Hz), 6.92 (1H, d, J=7.3 Hz), 7.00 (1H, t, J=7.3 Hz), 7.29–7.31 (1H, m), 7.35–7.39 (2H, m), 7.50 (1H, s), 7.51–7.52 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 59.7, 67.0, 74.6, 82.2, 109.3, 119.0, 124.3, 125.1 (×2), 127.0, 127.0, 128.0 (×2), 128.2, 141.7, 150.4; IR ($CHCl_3$) cm^{-1}: 3405, 2930, 2894, 1732, 1610, 1486, 1089; HRMS calcd for $C_{17}H_{20}NO_2$ $(M+H)^+$ 270.1494, found 270.1491; $[\alpha]_D^{24}=-97.0$ (c 0.41, $CHCl_3$).

3.6.3.5. (1*R*)-1-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-[4-(dimethylamino)phenyl]-2-methoxy-ethanol (15e). The general method was followed using **14e** (126 mg, 0.31 mmol) to give **15e** (86 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (1H, dd, J=8.9, 16.1 Hz), 2.71 (1H, dd, J=13.9, 16.1 Hz), 2.96 (6H, s), 3.42 (3H, s), 3.47 (1H, d, J=9.8 Hz), 3.68 (1H, s), 3.72 (1H, d, J=9.8 Hz), 4.50 (1H, dd, J=8.9, 13.9 Hz), 4.52 (1H, br), 6.65 (2H, t, J=6.8 Hz), 6.73 (2H, d, J=8.8 Hz), 6.92 (1H, d, J=6.8 Hz), 6.99 (1H, t, J=6.8 Hz), 7.35 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.5, 40.8 (×2), 59.8, 67.6, 74.6, 82.8, 109.6, 112.4 (×2), 119.1, 124.6, 126.3 (×2), 127.4, 128.7, 129.9, 149.9, 151.0; IR (liquid film) cm^{-1}: 3403, 2888, 1614, 1523, 1486, 1083, 750; HRMS calcd for $C_{19}H_{25}N_2O_2$ $(M+H)^+$ 313.1916, found 313.1909; $[\alpha]_D^{24}=-97.4$ (c 0.45, $CHCl_3$).

3.6.3.6. (1*R*)-1-(4-Chlorophenyl)-1-[(2*S*)-2,3-dihydro-1*H*-indol-2-yl]-2-methoxyethanol (15f). The general method was followed using **14f** (150 mg, 0.37 mmol) to give **15f** (74 mg, 66%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (1H, dd, J=8.8, 15.9 Hz), 2.66 (1H, dd, J=10.7, 15.9 Hz), 3.42 (3H, s), 3.48 (1H, d, J=9.8 Hz), 3.68 (1H, d, J=9.8 Hz), 3.72 (1H, s), 4.45 (1H, br s), 4.50 (1H, t, J=9.8 Hz), 6.68 (2H, m), 6.94 (1H, d, J=7.6 Hz), 7.01 (1H, t, J=7.6 Hz), 7.34 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.2, 59.9, 66.7, 74.7, 81.9, 109.9, 119.6, 124.7, 127.1 (×2), 127.5, 128.5, 128.6 (×2), 133.3, 140.8, 150.7; IR (thin film) cm^{-1}: 3400, 2892, 1611, 1488, 1092, 753; HRMS calcd for $C_{17}H_{19}NO_2Cl$ $(M+H)^+$ 304.11043, found 304.11038; $[\alpha]_D^{24}=-92.6$ (c 0.25, $CHCl_3$).

3.6.3.7. (1*R*)-1-Cyclohexyl-1-[(2*S*)-2,3-dihydro-1*H*-indol-2-yl]-2-methoxyethanol (15g). The general method was followed using **14g** (150 mg, 0.40 mmol) to give **15g** (80 mg, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03–1.32 (5H, m), 1.56 (1H, tt, J=2.9, 12.2 Hz), 1.65 (1H, d, J=12.7 Hz), 1.71 (1H, d, J=12.2 Hz), 1.76–1.82 (2H, m), 2.07 (1H, d, J=12.7 Hz), 2.87 (1H, dd, J=8.4, 15.3 Hz), 3.05 (1H, dd, J=12.1, 15.3 Hz), 3.28 (1H, br s), 3.39 (3H, s), 3.45 (1H, d, J=9.3 Hz), 3.56 (1H, d, J=9.3 Hz), 4.18 (1H, dd, J=8.4, 12.1 Hz), 4.41 (1H, br s), 6.65 (1H, d, J=7.3 Hz), 6.7 (1H, t, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz), 7.08 (1H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 27.2, 27.3, 27.6, 28.2, 30.5, 45.1, 59.7, 66.4, 73.8, 78.2, 109.7, 119.1, 124.7, 127.4, 128.8, 150.9; IR (KBr) cm^{-1}: 3390, 2931, 2853, 1610, 1488, 1098, 760;

HRMS calcd for $C_{17}H_{25}NO_2$ $(M)^+$ 255.1885, found 275.1881; $[\alpha]_D^{24}=-36.6$ (*c* 0.58, $CHCl_3$).

3.6.3.8. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxybut-3-en-2-ol (15h). The general method was followed using **14h** (213 mg, 0.67 mmol) to give **15h** (107 mg, 73%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (1H, dd, $J=9.3$, 16.1 Hz), 2.97 (1H, dd, $J=10.3$, 16.1 Hz), 3.22 (1H, br s), 3.42 (1H, d, $J=9.3$ Hz), 3.43 (3H, s), 3.49 (1H, d, $J=9.3$ Hz), 4.15 (1H, t, $J=9.8$ Hz), 4.33 (1H, br s), 5.26 (1H, d, $J=10.2$ Hz), 5.52 (1H, d, $J=16.7$ Hz), 5.84 (1H, dd, $J=10.2$, 16.7 Hz), 6.65 (1H, d, $J=7.8$ Hz), 6.72 (1H, t, $J=7.8$ Hz), 7.03 (1H, t, $J=7.8$ Hz), 7.07 (1H, d, $J=7.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 59.5, 64.8, 74.4, 79.7, 109.4, 115.5, 118.9, 124.4, 127.1, 128.5, 137.1, 150.6; IR ($CHCl_3$) cm^{-1}: 3406, 2930, 2894, 1609, 1486, 1465, 1094; HRMS calcd for $C_{13}H_{18}NO_2$ $(M+H)^+$ 220.1338, found 220.1331; $[\alpha]_D^{24}=-34.6$ (*c* 0.28, $CHCl_3$).

3.6.3.9. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-3-methylbut-3-en-2-ol (15i). The general method was followed using **14i** (380 mg, 1.14 mmol) to give **15i** (232 mg, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (3H, s), 2.87 (1H, dd, $J=9.3$ Hz, 15.9), 2.97 (1H, dd, $J=10.7$, 15.9 Hz), 3.44 (1H, d, $J=9.2$ Hz), 3.44 (4H, s), 3.62 (1H, d, $J=9.2$ Hz), 4.27 (1H, t, $J=9.8$ Hz), 4.35 (1H, br s), 5.03 (1H, s), 5.25 (1H, s), 6.67 (1H, d, $J=7.0$ Hz), 6.73 (1H, t, $J=7.0$ Hz), 7.02–7.08 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 31.2, 59.5, 64.7, 75.7, 80.1, 109.3, 112.3, 118.9, 124.3, 127.0, 128.3, 144.3, 150.5; IR ($CHCl_3$) cm^{-1}: 3406, 2926, 2895, 1610, 1486, 1125, 1090; HRMS calcd for $C_{14}H_{20}NO_2$ $(M+H)^+$ 234.1494, found 234.1471; $[\alpha]_D^{24}=-46.5$ (*c* 0.22, $CHCl_3$).

3.6.3.10. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-4-trimethylsilanylbut-3-yn-2-ol (15j). The general method was followed using **14j** (280 mg, 0.72 mmol) to give **15j** (166 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (9H, s), 3.15 (1H, dd, $J=9.2$, 15.8 Hz), 3.21 (1H, dd, $J=8.4$, 15.8 Hz), 3.46 (4H, s), 3.58 (2H, s), 4.17 (1H, t, $J=9.2$ Hz), 4.34 (1H, br s), 6.63 (1H, d, $J=7.3$ Hz), 6.72 (1H, t, $J=7.3$ Hz), 7.01 (1H, t, $J=7.3$ Hz), 7.08 (1H, d, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.12 (×3), 32.5, 59.7, 64.6, 71.4, 78.6, 90.5, 103.7, 109.3, 118.9, 124.2, 127.0, 128.3, 150.3; IR ($CHCl_3$) cm^{-1}: 3403, 2962, 2933, 2899, 1609, 1486, 1252, 1123, 1083; HRMS calcd for $C_{16}H_{24}NO_2Si$ $(M+H)^+$ 290.1576, found 290.1585; $[\alpha]_D^{24}=-52.7$ (*c* 0.30, $CHCl_3$).

3.6.3.11. (2*R*)-2-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-1-methoxy-6-methylhept-5-en-2-ol (15k). The general method was followed using **14k** (990 mg, 2.18 mmol) to give **15k** (411 mg, 53%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.50 (1H, m), 1.54–1.60 (1H, m), 1.63 (3H, s), 1.70 (3H, s), 1.97–2.05 (1H, m), 2.10–2.18 (1H, m), 2.80 (1H, s), 2.90 (1H, dd, $J=8.8$, 15.9 Hz), 3.04 (1H, dd, $J=11.2$ Hz, 15.9), 3.37 (1H, d, $J=9.8$ Hz), 3.40 (3H, s), 3.48 (1H, d, $J=9.8$ Hz), 4.07 (1H, t, $J=9.8$ Hz), 4.26 (1H, br s), 5.11 (1H, br t, $J=7.3$ Hz), 6.49 (1H, d, $J=8.8$ Hz), 7.09 (1H, d, $J=8.8$ Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.9, 25.7, 30.4, 34.5, 59.4, 66.1, 72.8, 78.2, 110.3, 110.6, 124.1, 127.4, 129.8, 131.1, 131.9, 149.8; IR ($CHCl_3$) cm^{-1}: 3512, 3406, 2929, 1481, 1249, 1108; HRMS calcd for $C_{17}H_{24}NO_2BrNa$ $(M+Na)^+$ 376.0889, found 370.0890; $[\alpha]_D^{24}=-31.6$ (*c* 0.24, $CHCl_3$).

3.6.3.12. 2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]propan-2-ol (15n). The general method was followed using **14n** (500 mg, 1.80 mmol) to give **15n** (270 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.28 (3H, s), 3.01 (1H, dd, $J=9.8$, 15.7 Hz), 3.05 (1H, dd, $J=9.8$, 15.7 Hz), 3.85 (1H, t, $J=9.8$ Hz), 6.67 (1H, d, $J=7.2$ Hz), 6.74 (1H, t, $J=7.2$ Hz), 7.04 (1H, t, $J=7.2$ Hz), 7.10 (1H, d, $J=7.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 28.2, 30.9, 68.5, 70.7, 109.6, 119.2, 124.6, 127.2, 129.3, 150.7; IR ($CHCl_3$) cm^{-1}: 3393, 2978, 1608, 1487, 1467, 1247; HRMS calcd for $C_{11}H_{15}NO$ $(M)^+$ 177.1154, found 177.1157; $[\alpha]_D^{24}=-53.5$ (*c* 0.60, $CHCl_3$).

3.6.3.13. (2*S*)-2-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-6-methylhept-5-en-2-ol (15p). The general method was followed using **14p** (210 mg, 0.49 mmol) to give **15p** (98 mg, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.44–1.57 (2H, m), 1.64 (3H, s), 1.71 (3H, s), 2.03–2.10 (1H, m), 2.12–2.18 (1H, m), 2.95 (1H, dd, $J=9.2$ Hz, 16.0), 3.02 (1H, dd, $J=10.7$, 16.0 Hz), 3.88 (1H, t, $J=9.8$ Hz), 3.98 (1H, br), 5.14 (1H, br t, $J=6.8$ Hz), 6.48 (1H, d, $J=7.8$ Hz), 7.09 (1H, d, $J=7.8$ Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.1, 22.3, 25.6, 30.7, 40.6, 67.5, 72.7, 110.5, 110.7, 124.1, 127.5, 129.8, 131.5, 131.9, 149.8; IR ($CHCl_3$) cm^{-1}: 2978, 2918, 1481; HRMS calcd for $C_{16}H_{23}NOBr$ $(M+H)^+$ 324.0963, found 324.0956; $[\alpha]_D^{24}=-16.0$ (*c* 0.72, $CHCl_3$).

3.6.3.14. (1*R*)-1-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1,3-diphenylpropan-1-ol (15q). The general method was followed using **14q** (90 mg, 0.21 mmol) to give **15q** (69 mg, 100%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (1H, dt, $J=4.3$, 13.2 Hz), 2.15–2.22 (2H, m), 2.47 (1H, dd, $J=9.0$, 16.3 Hz), 2.76 (1H, dt, $J=4.3$, 12.7 Hz), 2.83 (1H, dd, $J=10.3$, 16.3 Hz), 2.96 (1H, s), 4.03 (1H, br s), 4.29 (1H, t, $J=10.0$ Hz), 6.67 (1H, d, $J=7.3$ Hz), 6.71 (1H, t, $J=7.3$ Hz), 6.93 (1H, d, $J=7.3$ Hz), 7.01 (1H, t, $J=7.6$ Hz), 7.10 (2H, d, $J=7.3$ Hz), 7.15 (1H, t, $J=6.8$ Hz), 7.24 (2H, t, $J=7.6$ Hz), 7.29 (1H, t, $J=6.8$ Hz), 7.4 (2H, t, $J=7.6$ Hz), 7.51 (2H, d, $J=6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.2, 31.7, 44.5, 69.1, 76.1, 110.4, 120.2, 124.9, 125.7 (×2), 125.9, 127.0, 127.4, 128.6 (×2), 128.6 (×2), 128.6 (×2), 129.6, 142.9, 143.0, 150.5; IR (KBr) cm^{-1}: 3466, 3362, 3027, 1486, 1245, 770, 700; HRMS calcd for $C_{23}H_{24}NO$ $(M+H)^+$ 330.18579, found 330.18813; $[\alpha]_D^{24}=-80.7$ (*c* 0.42, $CHCl_3$).

The configurations of the newly created asymmetric centers in **15** were determined by the NOE experiments of the corresponding acetonides. The acetonides **16a–b**, **16d–k**, **16p–q** were prepared by the method similar to that used for the preparation of major-**16**.

3.6.3.15. (1*R*,9a*S*)-1-Ethyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16a). The general method was followed using **15a** (30 mg, 0.14 mmol) to give **16a** (32 mg, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, t, $J=7.3$ Hz), 1.14–1.21 (1H, m), 1.49–1.62 (1H, m), 1.54 (3H, s), 1.67 (3H, s),

3.03 (1H, dd, J=9.7, 16.8 Hz), 3.09 (1H, dd, J=4.2, 16.8 Hz), 3.27 (1H, d, J=9.3 Hz), 3.39 (3H, s), 3.51 (1H, d, J=9.3 Hz), 4.34 (1H, dd, J=4.2, 9.7 Hz), 6.66 (1H, d, J=7.3 Hz), 6.72 (1H, t, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.10, 23.0, 25.5, 29.3, 31.3, 59.4, 69.6, 75.6, 82.0, 94.8, 111.9, 118.7, 124.2, 126.4, 131.8, 148.6; IR ($CHCl_3$) cm^{-1}: 2986, 2932, 2894, 1603, 1478, 1462, 1266, 1113; HRMS calcd for $C_{16}H_{23}NO_2$ $(M)^+$ 261.1729, found 261.1724; $[\alpha]_D^{24}=+135.6$ (c 0.78, $CHCl_3$).

3.6.3.16. (1*S*,9a*S*)-1-Ethyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16b). The general method was followed using **15b** (66 mg, 0.30 mmol) to give **16b** (56 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.3 Hz), 1.51 (3H, s), 1.66 (3H, s), 1.70–1.79 (2H, m), 2.97 (1H, dd, J=10.6, 16.8 Hz), 3.07 (1H, d, J=9.8 Hz), 3.17 (1H, d, J=9.8 Hz), 3.18 (3H, s), 3.34 (1H, dd, J=2.9, 16.8 Hz), 4.17 (1H, dd, J=2.9, 10.6 Hz), 6.69 (1H, d, J=7.5 Hz), 6.73 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.06 (1H, d, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.08, 26.0, 28.4, 28.7, 31.5, 59.0, 69.2, 73.5, 82.6, 95.1, 112.3, 119.1, 124.5, 126.7, 131.8, 148.9; IR ($CHCl_3$) cm^{-1}: 2987, 2931, 1603, 1478, 1461, 1264, 1106; HRMS calcd for $C_{16}H_{23}NO_2$ $(M)^+$ 261.1728, found 261.1725; $[\alpha]_D^{24}=+144.3$ (c 1.06, $CHCl_3$).

3.6.3.17. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-phenyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16d). The general method was followed using **15d** (33 mg, 0.12 mmol) to give **16d** (30 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (3H, s), 1.74 (3H, s), 2.67 (1H, dd, J=7.1, 16.1 Hz), 2.84 (1H, dd, J=9.3, 16.1 Hz), 3.43 (3H, s), 3.82 (2H, s), 4.61 (1H, dd, J=7.1, 9.3 Hz), 6.69 (1H, t, J=7.3 Hz), 6.73 (1H, d, J=7.3 Hz), 6.83 (1H, d, J=7.3 Hz), 7.00 (1H, t, J=7.3 Hz), 7.16–7.21 (3H, m), 7.31 (2H, d, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 31.7, 32.9, 59.7, 70.5, 79.7, 85.6, 97.5, 114.4, 121.1, 124.2, 126.4 (×2), 126.7, 126.8, 127.4 (×2), 132.6, 141.6, 148.9; IR ($CHCl_3$) cm^{-1}: 2930, 2894, 1477, 1258, 1102; HRMS calcd for $C_{20}H_{24}NO_2$ $(M+H)^+$ 310.1807, found 310.1812; $[\alpha]_D^{24}=-39.1$ (c 1.15, $CHCl_3$).

3.6.3.18. (1*R*,9a*S*)-1-(Methoxymethyl)-1-[4-(dimethylamino)phenyl]-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16e). The general method was followed using **15e** (50 mg, 0.16 mmol) to give **16e** (14 mg, 25%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.71 (3H, s), 2.70 (1H, dd, J=6.6, 16.1 Hz), 2.80 (1H, dd, J=9.1, 16.1 Hz), 2.89 (6H, s), 3.42 (3H, s), 3.74 (1H, d, J=9.8 Hz), 3.77 (1H, d, J=9.8 Hz), 4.59 (1H, dd, J=6.6, 9.1 Hz), 6.58 (2H, d, J=8.8 Hz), 6.69 (1H, t, J=7.8 Hz), 6.80 (2H, t, J=7.8 Hz), 6.99 (1H, t, J=7.8 Hz), 7.15 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 31.9, 33.6, 40.8 (×2), 59.9, 71.0, 80.2, 85.8, 97.4, 112.0 (×2), 114.8, 121.3, 124.6, 126.3, 126.8, 127.3 (×2), 133.5, 149.3, 149.6; IR (thin film) cm^{-1}: 2984, 2990, 1615, 1522, 1478; HRMS calcd for $C_{22}H_{29}N_2O_2$ $(M+H)^+$ 353.2229, found 353.2239; $[\alpha]_D^{24}=-58.2$ (c 0.47, $CHCl_3$).

3.6.3.19. (1*R*,9a*S*)-1-(4-Chlorophenyl)-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16f). The general method was followed using **15f** (43 mg, 0.14 mmol) to give **16f** (28 mg, 57%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (3H, s), 1,72 (3H, s), 2.63 (1H, dd, J=5.3, 16.2 Hz), 2.86 (1H, dd, J=9.0, 16.2 Hz), 3.41 (3H, s), 3.75 (1H, d, J=9.8 Hz), 3.79 (1H, d, J=9.8 Hz), 4.55 (1H, dd, J=5.3, 9.0 Hz), 6.67–6.73 (2H, m), 6.81 (1H, d, J=7.7 Hz), 6.69 (1H, t, J=7.7 Hz), 7.13 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 31.8, 32.8, 59.9, 70.6, 79.8, 85.3, 97.9, 114.5, 121.4, 124.6, 127.0, 127.8 (×2), 128.1 (×2), 132.3, 132.9, 140.5, 149.0; IR (thin film) cm^{-1}: 2987, 2929, 1478, 1092, 753; HRMS calcd for $C_{20}H_{23}NO_2Cl$ $(M+H)^+$ 344.14173, found 344.14187; $[\alpha]_D^{24}=-61.5$ (c 1.34, $CHCl_3$).

3.6.3.20. (1*R*,9a*S*)-1-Cyclohexyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16g). The general method was followed using **15g** (53 mg, 0.19 mmol) to give **16g** (45 mg, 74%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13–1.21 (5H, m), 1.40 (3H, s), 1.55 (3H, s), 1.59–1.73 (5H, m), 1.81 (1H, d, J=11.7 Hz), 2.95 (1H, dd, J=9.6, 16.2 Hz), 3.25 (1H, dd, J=8.1, 16.2 Hz), 3.38 (3H, s), 3.46 (1H, d, J=9.8 Hz), 3.53 (1H, d, J=9.8 Hz), 4.40 (1H, dd, J=8.1, 9.6 Hz), 6.70 (1H, d, J=7.6 Hz), 6.78 (1H, t, J=7.6 Hz), 7.04 (1H, t, J=7.6 Hz), 7.10 (1H, d, J=7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 26.9, 27.2, 27.2, 28.2, 29.6, 31.5, 31.6, 43.6, 59.6, 70.9, 77.0, 84.2, 95.4, 113.5, 120.4, 124.7, 127.2, 133.9, 148.5; IR (liquid film) cm^{-1}: 2924, 2853, 1481, 1104, 745; HRMS calcd for $C_{20}H_{29}NO_2$ $(M)^+$ 315.2198, found 312.2205; $[\alpha]_D^{24}=+73.6$ (c 0.62, $CHCl_3$).

3.6.3.21. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-vinyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16h). The general method was followed using **15h** (47 mg, 0.21 mmol) to give **16h** (56 mg, 100%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.79 (3H, s), 3.06–3.08 (2H, m), 3.43 (3H, s), 3.47 (1H, d, J=9.3 Hz), 3.51 (1H, d, J=9.3 Hz), 4.40 (1H, dd, J=4.9, 6.8 Hz), 4.98 (1H, d, J=18.5 Hz), 5.24 (1H, d, J=13.4 Hz), 5.75 (1H, dd, J=13.4, 18.5 Hz), 6.75 (2H, t, J=7.8 Hz), 7.01 (2H, t, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 30.2, 31.4, 59.7, 68.3, 77.6, 83.1, 96.5, 113.0, 115.7, 119.7, 124.5, 126.6, 131.2, 136.6, 148.5; IR ($CHCl_3$) cm^{-1}: 2931, 2894, 1712, 1604, 1478, 1461, 1105; HRMS calcd for $C_{16}H_{21}NO_2$ $(M)^+$ 259.1572, found 259.1575; $[\alpha]_D^{24}=+82.2$ (c 0.16, $CHCl_3$).

3.6.3.22. (1*R*,9a*S*)-1-Isopropenyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16i). The general method was followed using **15i** (36 mg, 0.15 mmol) to give **16i** (19 mg, 45%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.53 (3H, s), 1.54 (3H, s), 2.80 (1H, dd, J=9.5, 16.1 Hz), 3.04 (1H, dd, J=7.7, 16.1 Hz), 3.33 (3H, s), 3.52 (1H, d, J=9.9 Hz), 3.56 (1H, d, J=9.9 Hz), 4.21 (1H, dd, J=7.7, 9.5 Hz), 4.89 (1H, s), 5.01 (1H, s), 6.70 (1H, d, J=7.6 Hz), 6.73 (1H, t, J=7.6 Hz), 6.93–6.97 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 26.3, 32.0, 32.8, 59.6, 69.9, 78.3, 86.8, 97.4, 113.2, 115.1, 121.4, 124.5, 126.9, 133.7, 144.7, 148.8; IR ($CHCl_3$) cm^{-1}: 2928, 2895, 1477, 1560, 1095; HRMS calcd for $C_{17}H_{24}NO_2$ $(M+H)^+$ 274.1807, found 274.1811; $[\alpha]_D^{24}=+26.4$ (c 0.69, $CHCl_3$).

3.6.3.23. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-trimethylsilylethynyl-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole (16j). The general method was followed using **15j** (25 mg, 0.086 mmol) to give **16j** (22 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.15 (9H, s), 1.50 (3H, s), 1.73 (3H, s), 3.06 (1H, dd, J=9.9, 16.5 Hz), 3.26 (1H, dd, J=2.6, 16.5 Hz), 3.43 (3H, s), 3.51 (2H, s), 4.28 (1H, dd, J=2.6, 9.9 Hz), 6.62 (1H, d, J=7.7 Hz), 6.70 (1H, t, J=7.7 Hz), 6.94–7.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.39 (×3), 25.0, 30.8, 31.6, 60.2, 67.8, 75.4, 79.2, 91.3, 97.6, 103.8, 112.8, 119.4, 124.4, 126.3, 131.8, 148.4; IR ($CHCl_3$) cm^{-1}: 2961, 2931, 1479, 1461, 1266, 1251, 1106; HRMS calcd for $C_{19}H_{28}NO_2Si$ $(M+H)^+$ 330.1881, found 330.1887; $[\alpha]_D^{24}$ = +194.0 (c 0.44, $CHCl_3$).

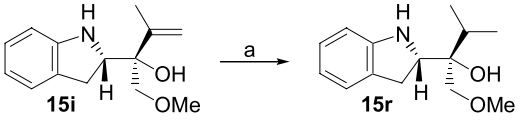
3.6.3.24. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-(4-methylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole (16k). The general method was followed using **15k** (436 mg, 1.23 mmol) to give **16k** (370 mg, 76%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (1H, dt, J=6.8, 12.7 Hz), 1.52 (3H, s), 1.54 (3H, s), 1.55–1.60 (1H, m), 1.63 (3H, s), 1.64 (3H, s), 1.91–1.97 (1H, m), 2.01–2.07 (1H, m), 3.02 (1H, dd, J=10.3, 17.3 Hz), 3.07 (1H, dd, J=4.7, 17.3 Hz), 3.29 (1H, d, J=8.8 Hz), 3.38 (3H, s), 3.53 (1H, d, J=8.8 Hz), 4.35 (1H, dd, J=4.7, 10.3 Hz), 4.99 (1H, br t, J=6.8 Hz), 6.50 (1H, d, J=7.8 Hz), 7.11 (1H, d, J=7.8 Hz), 7.13 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 21.8, 25.6, 25.7, 29.2, 30.8, 31.4, 59.6, 70.2, 76.2, 82.0, 94.9, 110.8, 113.0, 124.4, 127.5, 129.4, 131.4, 134.4, 147.9; IR ($CHCl_3$) cm^{-1}: 2629, 1474, 1259, 1112; HRMS calcd for $C_{20}H_{28}NO_2Br$ $(M)^+$ 393.1303, found 393.1303; $[\alpha]_D^{24}$ = +131.0 (c 0.36, $CHCl_3$).

3.6.3.25. (1*S*,9a*S*)-7-Bromo-1,3,3-trimethyl-1-(4-methylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16p). The general method was followed using **15p** (95 mg, 0.293 mmol) to give **16p** (86 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.49 (3H, s), 1.58–1.62 (2H, m), 1.64 (3H, s), 1.65 (3H, s), 1.70 (3H, s), 2.04–2.10 (2H, m), 2.93 (1H, dd, J=3.4, 17.1 Hz), 3.05 (1H, dd, J=10.3, 17.1 Hz), 4.15 (1H, dd, J=3.4, 10.3 Hz), 5.12 (1H, br t, J=6.8 Hz), 6.54 (1H, d, J=8.2 Hz), 7.12 (1H, d, J=8.2 Hz), 7.15 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 21.0, 22.8, 25.6, 25.8, 29.6, 31.6, 41.0, 70.0, 81.8, 94.3, 110.7, 113.1, 124.1, 127.5, 129.5, 131.8, 133.8, 148.2; IR ($CHCl_3$) cm^{-1}: 2985, 2931, 1474, 1381, 1370, 1256; HRMS calcd for $C_{19}H_{27}NOBr$ $(M+H)^+$ 364.1276, found 364.1259; $[\alpha]_D^{24}$ = +97.5 (c 0.47, $CHCl_3$).

3.6.3.26. (1*R*,9a*S*)-3,3-Dimethyl-1-phenethyl-1-phenyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (16q). The general method was followed using **15q** (23 mg, 0.070 mmol) to give **16q** (mg, 54%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, s), 1.76 (3H, s), 2.28–2.49 (3H, m), 2.61 (1H, dd, J=7.4, 16.1 Hz), 2.71 (1H, dd, J=8.6, 16.1 Hz), 2.79–2.86 (1H, m), 4.51 (1H, t, J=8.0 Hz), 6.73 (1H, t, J=7.4 Hz), 6.78 (1H, d, J=7.4 Hz), 6.84 (1H, d, J=7.4 Hz), 7.02 (1H, d, J=7.4 Hz), 7.13–7.34 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 30.5, 32.4, 34.0, 45.4, 75.9, 86.3, 97.6, 115.5, 121.9, 124.5, 125.9, 126.4 (×2), 126.8, 127.0, 128.0 (×2), 128.5 (×2), 128.6 (×2), 133.7, 142.9, 143.1, 149.5; IR (thin film) cm^{-1}: 3026, 2986, 2934, 1477, 1237, 1207, 747, 701; HRMS calcd for $C_{26}H_{28}NO$ $(M+H)^+$ 370.21709, found 370.21417; $[\alpha]_D^{24}$ = −32.0 (c 0.21, $CHCl_3$).

3.6.4. Preparation of 15r.

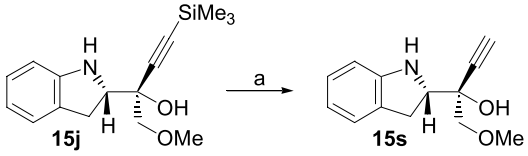
3.6.4.1. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-3-methylbutan-2-ol (15r). A solution of **15i** (50 mg, 0.214 mmol), 20 wt% $Pd(OH)_2$/C (50 mg) in methanol (5 ml) was stirred under H_2 atmosphere at room temperature for 2.5 h. $Pd(OH)_2$ was removed by filtration and the filtrate was evaporated. The resulting residue was purified by silica gel column chromatography (hexane–AcOEt 5:1) to give **15r** (32 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 1.90–1.96 (1H, m), 2.90 (1H, dd, J=8.0, 15.2 Hz), 3.03–3.09 (1H, m), 3.25 (1H, s), 3.41 (3H, s), 3.44 (1H, d, J=9.8 Hz), 3.58 (1H, d, J=9.8 Hz), 4.23 (1H, dd, J=8.0, 11.7 Hz), 4.42 (1H, s), 6.66 (1H, d, J=7.2 Hz), 6.72 (1H, t, J=7.2 Hz), 7.03 (1H, t, J=7.2 Hz), 7.10 (1H, d, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 17.3, 30.1, 33.7, 59.5, 66.0, 73.8, 77.2, 109.4, 118.9, 124.4, 127.1, 128.5, 150.7; IR (KBr) cm^{-1}: 3417, 3385, 2963, 2933, 1611, 1469, 1250, 1107; HRMS calcd for $C_{14}H_{22}NO_2$ $(M+H)^+$ 236.1651, found 236.1638; $[\alpha]_D^{24}$ = −51.2 (c 0.16, $CHCl_3$) (Scheme 12).



Scheme 12. Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, MeOH, rt, 63%.

3.6.5. Preparation of 15s.

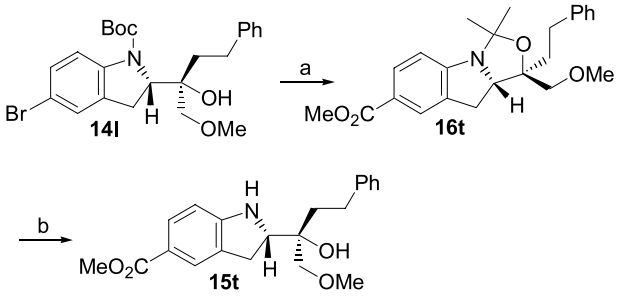
3.6.5.1. (2*R*)-2-[(2*S*)-2,3-Dihydro-1*H*-indol-2-yl]-1-methoxy-but-3-yn-2-ol (15s). To a solution of **15j** (91 mg, 0.314 mmol) in THF (1 ml) was added TBAF in THF (0.35 ml, 1 M) at room temperature. The mixture was stirred under the same temperature for 1 h. After addition of water, the aqueous solution was extracted with AcOEt. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. Purification by silica gel chromatography (hexane–AcOEt 5:1 to 2:1) gave **15s** (59 mg, 86%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (1H, s), 3.15 (1H, dd, J=10.0 Hz, 16.9), 3.21 (1H, dd, J=10.3, 16.9 Hz), 3.37 (1H, br s), 3.46 (3H, s), 3.55 (1H, d, J=9.8 Hz), 3.58 (1H, d, J=9.8 Hz), 4.19 (1H, t, J=9.5 Hz), 4.50 (1H, br), 6.65 (1H, d, J=7.5 Hz), 6.72 (1H, t, J=7.5 Hz), 7.01 (1H, t, J=7.5 Hz), 7.07 (1H, d, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.3, 59.7, 64.6, 71.4, 74.1, 78.4, 82.5, 109.6, 119.2, 124.4, 127.3, 128.3, 150.3; IR ($CHCl_3$) cm^{-1}: 3556, 3402, 3306, 2933, 2898, 1609, 1486, 1466, 1124, 1085; HRMS calcd for $C_{13}H_{15}NO_2Na$ $(M+Na)^+$ 240.1000, found 240.0986; $[\alpha]_D^{24}$ = −65.4 (c 0.15, $CHCl_3$) (Scheme 13).



Scheme 13. Reagents and conditions: (a) 1 M TBAF, THF, rt, 86%.

3.6.6. Preparation of 15t.

3.6.6.1. (1*R*,9a*S*)-1-(Methoxymethyl)-3,3-dimethyl-1-phenethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid methyl ester (16t). The procedure for the preparation of **15a** was followed using **14l** (868 mg, 1.82 mmol) to give the corresponding indoline-2-methanol (660 mg, 96%) (Scheme 14).



Scheme 14. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, rt, 96%; (ii) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, rt, 78%; (iii) *t*-BuLi, CO_2, Et_2O, −78 °C, 82%; (iv) $TMSCH_2N_2$, MeOH, ice bath, 95%. (b) PPTS, MeOH, rt, 95%.

The obtained indoline-2-methanol (64 mg, 1.70 mmol) was converted to the corresponding acetonide (554 mg, 78%) by the method similar to that used for the synthesis of major-**16**.

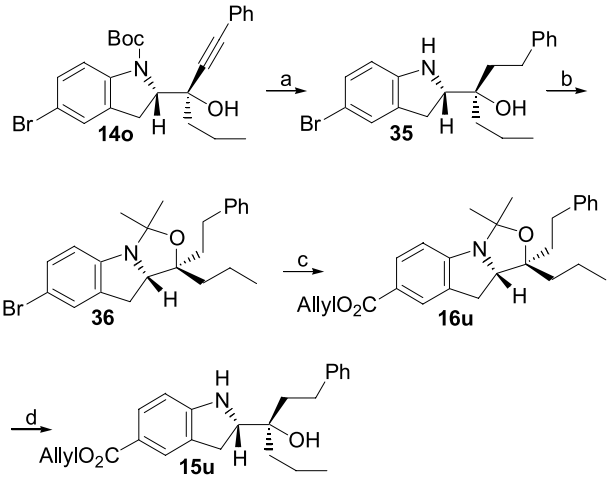
The conversion of the obtained acetonide (543 mg, 1.3 mmol) to the corresponding carboxylic acid (405 mg, 82%) was carried out by the method similar to that used for the synthesis of **17**.

The method for the synthesis of **22** was followed using the obtained carboxylic acid (300 mg, 0.79 mmol) to give **16t** (294 mg, 95%) as a colorless solid (mp 124–126 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (1H, dt, J=4.4, 13.0 Hz), 1.57 (3H, s), 1.75 (3H, s), 1.92 (1H, dt, J=5.4, 12.7 Hz), 2.59 (1H, dt, J=5.4, 13.0 Hz), 2.68 (1H, dt, J=4.4, 12.7 Hz), 3.07–3.08 (2H, m), 3.34 (1H, d, J=9.3 Hz), 3.39 (3H, s), 3.58 (1H, d, J=9.3 Hz), 3.83 (3H, s), 4.45 (1H, dd, J=6.3, 8.3 Hz), 6.58 (1H, d, J=8.3 Hz), 7.05 (2H, d, J=7.3 Hz), 7.12 (1H, t, J=7.3 Hz), 7.20 (2H, t, J=7.3 Hz), 7.65 (1H, s), 7.74 (1H, d, J=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 28.8, 29.7, 31.1, 32.7, 51.8, 59.9, 70.7, 76.4, 82.2, 94.7, 110.0, 120.4, 126.0, 126.4, 128.5 (×2), 128.6 (×2), 130.3, 132.1, 142.6, 152.7, 167.5; IR (KBr) cm^{-1}: 2938, 1699, 1607, 1273; HRMS calcd for $C_{24}H_{30}NO_4$ $(M+H)^+$ 396.21748, found 396.21800; $[\alpha]_D^{24}=+201.5$ (*c* 1.06, $CHCl_3$).

3.6.6.2. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(methoxymethyl)-3-phenylpropyl]-2,3-dihydro-1*H*-indole-5-carboxylic acid methyl ester (15t). The method for the synthesis of **1** was followed using **16t** (257 mg, 0.65 mmol) to give **15t** (220 mg, 95%) as a colorless solid (mp 129–130 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (1H, dt, J=5.1, 13.2 Hz), 1.83 (1H, dt, J=5.1, 13.2 Hz), 2.60 (1H, dt, J=5.1, 12.8 Hz), 2.69 (1H, s), 2.77 (1H, dt, J=5.1, 12.8 Hz), 2.91 (1H, dd, J=9.2, 15.8 Hz), 3.02 (1H, dd, J=10.6, 15.8 Hz), 3.39 (3H, s), 3.44 (1H, d, J=8.8 Hz), 3.51 (1H, d, J=8.8 Hz), 3.80 (3H, s), 4.14 (1H, t, J=9.5 Hz), 4.65 (1H, br s), 6.53 (1H, d, J=8.1 Hz), 7.17 (3H, m), 7.23–7.27 (2H, m), 7.67 (1H, s), 7.72 (1H, dd, J=1.5, 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.6, 29.9, 36.2, 51.5, 59.5, 66.1, 73.0, 78.0, 107.7, 120.0, 125.9, 126.0, 128.0, 128.2 (×2), 128.4 (×2), 130.6, 142.1, 155.1, 167.3; IR (KBr) cm^{-1}: 3431, 3370, 2949, 2905, 1699, 1611, 1437, 1285, 1269, 1092; HRMS calcd for $C_{21}H_{26}NO_4$ $(M+H)^+$ 356.1862, found 356.1846. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.71; H, 7.04; N, 3.89; $[\alpha]_D^{24}=-6.1$ (*c* 1.05, $CHCl_3$).

3.6.7. Preparation of 15u.

3.6.7.1. (3*R*)-3-[(2*S*)-5-Bromo-2,3-dihydro-1*H*-indol-2-yl]-1-phenylhexan-3-ol (35). A solution of **14o** (66 mg, 0.139 mmol), 10 wt% Pd/C (7 mg) in AcOEt (1 ml) was stirred under H_2 atmosphere at room temperature for 24 h. Pd/C was removed by filtration and the filtrate was evaporated. The resulting residue was purified by silica gel column chromatography (hexane–AcOEt 19:1) to give the crude reduced product (24 mg, crude yield 36%). The obtained product was used without further purification (Scheme 15).



Scheme 15. Reagents and conditions: (a) (i) H_2, Pd/C, AcOEt, rt; (ii) TFA, CH_2Cl_2, rt, 32% (2 steps). (b) 2,2-Dimethoxypropane, PPTS, CH_2Cl_2, 72%. (c) (i) *t*-BuLi, CO_2, Et_2O, −78 °C, 87%; (ii) allylbromide, K_2CO_3, DMF, rt, 89%. (d) PPTS, MeOH–CH_2Cl_2, rt, 92%.

Deprotection of the *N*-Boc group was carried out by the method similar to that used for the preparation of **15a** to give **35** (11 mg, 32% from **14o**) as a colorless solid (mp 128–129 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz), 1.27–1.50 (3H, m), 1.54–1.65 (2H, m), 1.78 (1H, dt, J=4.9, 12.9 Hz), 2.07 (1H, s), 2.51 (1H, dt, J=4.9, 12.9 Hz), 2.65 (1H, dt, J=4.9, 12.9 Hz), 2.82 (1H, dd, J=9.2, 16.0 Hz), 3.04 (1H, dd, J=10.2, 16.0 Hz), 3.17 (1H, br s), 3.94 (1H, t, J=9.9 Hz), 6.45 (1H, d, J=8.8 Hz), 7.03 (1H, d, J=8.8 Hz), 7.08–7.13 (4H, m), 7.18–7.23 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 17.1, 29.7, 30.0, 36.2, 39.9, 66.3, 73.7, 111.0, 111.1, 125.9, 127.6, 128.2 (×2), 128.4 (×2), 129.8, 131.7, 142.2, 149.5; IR (KBr) cm^{-1}: 3373, 3300, 2956, 2872, 1482, 1252; HRMS calcd for $C_{20}H_{25}NOBr$ $(M+H)^+$ 374.1119, found 374.1136. Anal. Calcd for $C_{20}H_{24}NOBr$: C, 64.17; H, 6.46; N, 3.74; Br,

21.35. Found: C, 64.26; H, 6.33; N, 3.72; Br, 21.29; $[\alpha]_D^{24} = -36.5$ (*c* 1.00, $CHCl_3$).

3.6.7.2. (1*R*,9a*R*)-7-Bromo-3,3-dimethyl-1-phenethyl-1-propyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (36). The method for the preparation of major-**16** was followed using **35** (4.8 mg, 0.013 mmol) to give **36** (3.8 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.3 Hz), 1.25–1.44 (4H, m), 1.49 (3H, s), 1.64 (3H, s), 1.68–1.72 (1H, m), 1.78–1.86 (1H, m), 2.53 (1H, dt, J=5.1, 12.9 Hz), 2.68 (1H, dt, J=4.4, 12.9 Hz), 2.95–2.97 (2H, m), 4.21 (1H, dd, J=5.9, 8.8 Hz), 6.41 (1H, d, J=8.8 Hz), 7.01–7.04 (4H, m), 7.08–7.12 (1H, m), 7.17–7.22 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 17.6, 25.7, 29.3, 29.5, 31.6, 34.0, 39.7, 70.9, 83.3, 94.1, 110.4, 112.4, 125.7, 127.6, 128.3 (×2), 128.4 (×2), 129.6, 133.9, 142.5, 147.7; IR (liquid film) cm^{-1}: 2958, 2933, 1476, 1367, 1262; HRMS calcd for $C_{23}H_{29}NOBr$ $(M+H)^+$ 414.1433, found 414.1454; $[\alpha]_D^{24} = +114.1$ (*c* 0.65, $CHCl_3$).

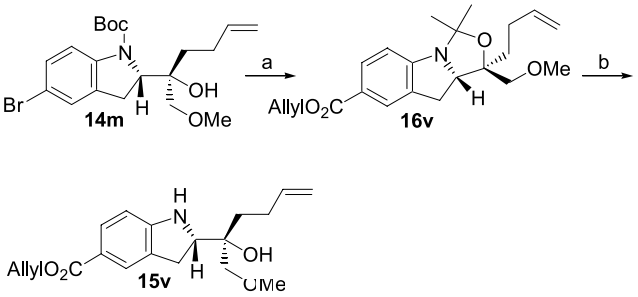
3.6.7.3. (1*R*,9a*R*)-3,3-Dimethyl-1-phenethyl-1-propyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid allyl ester (16u). Compound **36** (74 mg, 0.179 mmol) was converted to the corresponding carboxylic acid (59 mg, 87%) by the method similar to that used for the preparation of **17**.

To the solution of carboxylic acid (59 mg, 0.155 mmol) in DMF (1.2 ml) was added K_2CO_3 (32 mg, 0.23 mmol) and allyl bromide (0.02 ml, 0.236 mmol) at room temperature. After stirring at room temperature for 2 h, water (10 ml) was added. The product was extracted with diethyl ether (10 ml×2), and the combined organic extracts were washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 9:1) gave **16u** (58 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J=7.0 Hz), 1.27–1.49 (4H, m), 1.51 (3H, s), 1.65–1.73 (1H, m), 1.69 (3H, s), 1.79–1.87 (1H, m), 2.54 (1H, dt, J=4.7, 12.0 Hz), 2.69 (1H, dt, J=4.7, 13.2 Hz), 2.93–3.05 (2H, m), 4.29 (1H, dd, J=5.5, 9.9 Hz), 4.69–4.71 (2H, m), 5.20 (1H, d, J=9.5 Hz), 5.33 (1H, d, J=19.0 Hz), 5.92–6.01 (1H, m), 6.59 (1H, d, J=8.3 Hz), 7.00 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.3 Hz), 7.17 (2H, t, J=7.3 Hz), 7.61 (1H, d, J=1.7 Hz), 7.72 (1H, dd, J=1.7, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 17.6, 25.9, 28.6, 29.3, 30.9, 33.7, 39.3, 64.9, 70.9, 83.3, 93.3, 109.0, 117.6, 119.6, 125.7, 126.2, 128.2 (×2), 128.4 (×2), 130.4, 131.5, 132.7, 142.3, 152.3, 166.4; IR (liquid film) cm^{-1}: 2958, 2934, 2872, 1707, 1610, 1292, 1265, 1217, 1169; HRMS calcd for $C_{27}H_{34}NO_3$ $(M+H)^+$ 420.2539, found 420.2520; $[\alpha]_D^{24} = +209.8$ (*c* 0.57, $CHCl_3$).

3.6.7.4. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(2-phenylethyl)butyl]indoline-5-carboxylic acid allyl ester (15u). Method for the synthesis of **1** was followed using **16u** (56 mg, 0.133 mmol) to give **15u** (47 mg, 92%) as a colorless solid (mp 125–126 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (3H, t, J=7.3 Hz), 1.38–1.53 (2H, m), 1.55–1.61 (1H, m), 1.65–1.75 (2H, m), 1.90 (1H, dt, J=4.9, 13.2 Hz), 1.96 (1H, s), 2.62 (1H, dt, J=4.9, 13.2 Hz), 2.75 (1H, dt, J=4.9, 13.0 Hz), 2.98 (1H, dd, J=9.3, 15.9), 3.14 (1H, dd, J=10.7, 15.9 Hz), 4.10 (1H, t, J=9.8 Hz), 4.24 (1H, br s), 4.77–4.78 (2H, m), 5.26 (1H, d, J=11.7 Hz), 5.39 (1H, d, J=15.6 Hz), 5.99–6.07 (1H, m), 6.62 (1H, d, J=8.3 Hz), 7.19–7.22 (3H, m), 7.29–7.32 (2H, m), 7.77 (1H, s), 7.81 (1H, d, J=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 17.1, 29.6, 29.7, 36.3, 39.8, 65.0, 66.3, 74.1, 108.2, 117.6, 120.6, 125.9, 126.3, 128.2 (×2), 128.5 (×2), 128.8, 130.6, 132.7, 142.1, 155.0, 166.4; IR (KBr) cm^{-1}: 3452, 3309, 2950, 1682, 1614, 1269; HRMS calcd for $C_{24}H_{30}NO_3$ $(M+H)^+$ 380.2226, found 380.2246. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found: C, 75.83; H, 7.41; N, 3.70; $[\alpha]_D^{24} = -14.9$ (*c* 1.15, $CHCl_3$).

3.6.8. Preparation of 15v.

3.6.8.1. (1*R*,9a*S*)-1-But-3-enyl-1-(methoxymethyl)-3,3-dimethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]-indole-7-carboxylic acid allyl ester (16v). Compound **14m** (459 mg, 1.08 mmol) was converted to the corresponding indoline-2-methanol (290 mg, 83%) by the method similar to that used for the preparation of **15a** (Scheme 16).



Scheme 16. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, rt, 83%; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 72%; (iii) *t*-BuLi, CO_2, Et_2O, −78 °C, 83%; (iv) AllylBr, K_2CO_3, DMF, rt, 96%. (b) PPTS, MeOH, rt, 80%.

The obtained indoline-2-methanol (280 mg, 0.86 mmol) was converted to the corresponding acetonide (227 mg, 72%) by the method similar to that used for the synthesis of major-**16**.

Conversion of the obtained acetonide (206 mg, 0.56 mmol) to the corresponding carboxylic acid (154 mg, 83%) was carried out by the method similar to that used for the synthesis of **17**.

Method for the synthesis of **16u** was followed using the obtained carboxylic acid (128 mg, 0.39 mmol) to give **16v** (137 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.19 (1H, m), 1.53 (3H, s), 1.60–1.65 (1H, m), 1.68 (3H, s), 1.96–2.06 (1H, m), 2.08–2.17 (1H, m), 3.07–3.08 (2H, m), 3.29 (1H, d, J=8.8 Hz), 3.38 (3H, s), 3.51 (1H, d, J=8.8 Hz), 4.42 (1H, dd, J=6.2, 8.4 Hz), 4.77 (2H, dd, J=1.5, 5.9 Hz), 4.85 (1H, d, J=10.3 Hz), 4.91 (1H, dd, J=1.8, 19.0 Hz), 5.30 (1H, dd, J=1.5, 10.3 Hz), 5.39 (1H, dd, J=1.5, 19.0 Hz), 5.63–5.74 (1H, m), 5.98–6.08 (1H, m), 6.59 (1H, d, J=7.8 Hz), 7.2 (1H, d, J=1.5 Hz), 7.79 (1H, d, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 27.2, 28.5, 29.7, 30.7, 59.5, 64.9, 70.2, 75.9, 81.8, 94.2, 109.7, 114.2, 117.7, 120.0, 126.0, 130.1, 131.9, 132.7, 138.6, 152.6, 166.3; IR (liquid film) cm^{-1}: 2985, 2929, 1709, 1610, 1292, 1265, 1212, 1169, 1122; HRMS calcd for $C_{22}H_{29}NO_4Na$ $(M+Na)^+$ 394.1994, found 394.2021; $[\alpha]_D^{24} = +229.8$ (*c* 0.52, $CHCl_3$).

3.6.8.2. (2*S*)-2-[(1*R*)-1-Hydroxy-1-(methoxymethyl)-pent-4-enyl]indoline-5-carboxylic acid allyl ester (15v). Method for the synthesis of **1** was followed using **16v** (135 mg, 0.363 mmol) to give **15v** (96 mg, 80%) as a colorless solid (mp 132–134 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.65 (1H, m), 1.68 (1H, dt, J=5.5, 13.0 Hz), 2.06–2.13 (1H, m), 2.22–2.28 (1H, m), 2.70 (1H, s), 2.98 (1H, dd, J=8.8, 15.9 Hz), 3.07 (1H, dd, J=10.3, 15.9 Hz), 3.42 (1H, d, J=9.3 Hz), 3.43 (3H, s), 3.51 (1H, d, J=9.3 Hz), 4.17 (1H, t, J=9.8 Hz), 4.71 (1H, br s), 4.78 (2H, d, J=5.9 Hz), 4.99 (1H, d, J=8.8 Hz), 5.07 (1H, d, J=18.6 Hz), 5.27 (1H, d, J=11.7 Hz), 5.40 (1H, d, J=15.6 Hz), 5.80–5.88 (1H, m), 6.00–6.08 (1H, m), 6.58 (1H, d, J=8.8 Hz), 7.76 (1H, s), 7.81 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 29.8, 33.3, 59.4, 64.8, 66.0, 73.0, 78.0, 107.5, 114.6, 117.5, 119.8, 126.0, 128.0, 130.7, 132.7, 138.4, 155.2, 166.4; IR (KBr) cm^{-1}: 3434, 3284, 2907, 1681, 1613, 1271, 1234, 1117, HRMS calcd for $C_{19}H_{25}NO_4Na$ $(M+Na)^+$ 354.1691, found 354.1690. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.60; H, 7.58; N, 4.28; $[\alpha]_D^{24}=+4.6$ (c 0.27, $CHCl_3$).

3.6.9. Preparation of 15w.

3.6.9.1. (1*R,9a*S**)-7-Bromo-1-(methoxymethyl)-3,3-dimethyl-1-phenethyl-9,9a-dihydro-1*H*-[1,3]oxazolo-[3,4-*a*]indole (37).** Compound **14l** (868 mg, 1.82 mmol) was converted to the corresponding indoline-2-methanol (660 mg, 96%) by the method similar to that used for the preparation of **15a** (Scheme 17).

Method for the synthesis of major-**16** was followed using the obtained indoline-2-methanol (641 mg, 1.70 mmol) to give **37** (554 mg, 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, dt, J=4.6, 13.0 Hz), 1.55 (3H, s), 1.70 (3H, s), 1.92 (1H, dt, J=5.2, 13.0 Hz), 2.60 (1H, dt, J=5.2, 13.0 Hz), 2.69 (1H, dt, J=4.6, 13.0 Hz), 3.04 (1H, dd, J=9.3, 17.1 Hz), 3.09 (1H, dd, J=4.4, 17.1 Hz), 3.33 (1H, d, J=8.8 Hz), 3.39 (3H, s), 3.59 (1H, d, J=8.8 Hz), 4.39 (1H, dd, J=4.9, 7.8 Hz), 6.51 (1H, d, J=8.8 Hz), 7.07–7.11 (4H, m), 7.15 (1H, t, J=7.3 Hz), 7.22–7.27 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 29.3, 29.6, 31.4, 32.8, 59.6, 70.5, 76.4, 82.0, 95.2, 111.0, 113.1, 125.7, 127.6, 128.3 (×2), 128.3 (×2), 129.5, 134.3, 142.4, 147.8; IR ($CHCl_3$) cm^{-1}: 2931, 1475, 1259, 1109; HRMS calcd for $C_{22}H_{26}NO_4Br$ $(M)^+$ 415.1147, found 415.1128.

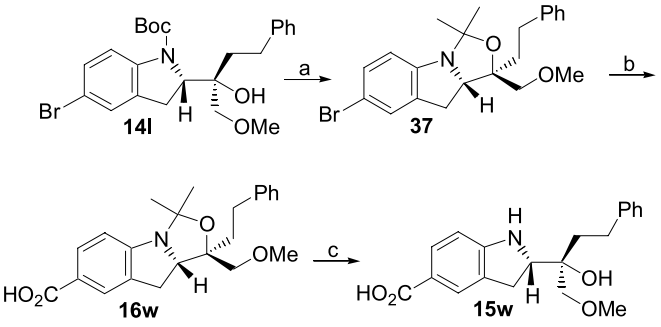
3.6.9.2. (1*R,9a*S**)-1-(Methoxymethyl)-3,3-dimethyl-1-phenethyl-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole-7-carboxylic acid (16w).** Method for the synthesis of **17** was followed using **37** (280 mg, 0.672 mmol) to give **16w** (159 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (1H, dt, J=3.9, 12.7 Hz), 1.59 (3H, s), 1.78 (3H, s), 1.96 (1H, dt, J=5.1, 12.7 Hz), 2.62 (1H, dt, J=5.1, 12.7 Hz), 2.69 (1H, dt, J=3.9, 12.7 Hz), 3.10–3.11 (2H, m), 3.37 (1H, d, J=9.3 Hz), 3.41 (3H, s), 3.61 (1H, d, J=9.3 Hz), 4.49 (1H, dd, J=6.2, 8.3 Hz), 6.61 (1H, d, J=8.8 Hz), 7.08 (2H, d, J=7.2 Hz), 7.14 (1H, t, J=7.2 Hz), 7.23 (2H, t, J=7.2 Hz), 7.72 (1H, s), 7.83 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 27.0, 28.5, 29.4, 30.7, 32.5, 59.7, 70.5, 76.0, 82.0, 94.3, 109.5, 119.0, 125.8, 126.8, 128.3 (×2), 128.4, 131.1, 132.0, 142.3, 153.0, 172.3; IR (KBr) cm^{-1}: 2984, 2929, 1672, 1607, 1270; HRMS calcd for $C_{23}H_{28}NO_4$ $(M+H)^+$ 382.2018, found 382.2009.

3.6.9.3. (2*S)-2-[(1*R**)-1-Hydroxy-1-(methoxymethyl)-3-phenylpropyl]-2,3-dihydro-1*H*-indole-5-carboxylic acid (15w).** Method for the synthesis of **22** was followed using **16w** (44 mg, 0.116 mmol) to give **15w** (20 mg, 51%) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ 1.80 (2H, t, J=8.8 Hz), 2.62–2.68 (1H, m), 2.73–2.79 (1H, m), 3.00 (1H, dd, J=9.8, 16.4 Hz), 3.11 (1H, dd, J=9.2, 16.4 Hz), 3.41 (3H, s), 3.47 (1H, d, J=9.3 Hz), 3.51 (1H, d, J=9.3 Hz), 4.16 (1H, t, J=9.8 Hz), 6.54 (1H, d, J=8.8 Hz), 7.14 (1H, t, J=7.2 Hz), 7.20 (2H, d, J=7.2 Hz), 7.25 (2H, t, J=7.2 Hz), 7.64 (1H, s), 7.68 (1H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 30.5, 30.6, 37.5, 59.6, 65.9, 75.3, 76.9, 108.0, 119.8, 126.7, 127.0, 129.3 (×2), 129.4 (×2), 129.6, 132.0, 144.1, 158.0, 170.9; IR (KBr) cm^{-1}: 3408, 2926, 1673, 1609, 1285, 1264; HRMS calcd for $C_{20}H_{24}NO_4$ $(M+H)^+$ 342.1705, found 342.1706.

3.6.10. Rearrangement from indoline-2-methanols 15 to tetrahydroquinolines 26.

Compounds **26c–d**, **26f–k**, **26n**, **26p**, **26r–v**, **15x** were obtained by the method similar to that used for the synthesis of **26a**.

3.6.10.1. (2*S*,3*S*)-3-Chloro-2-ethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26c). The general method was followed using **15c** (6.1 mg, 0.028 mmol) to give **26c** (5.4 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz), 1.66 (1H, dq, J=7.3, 14.8 Hz), 1.76 (1H, dq, J=7.3, 14.8 Hz), 3.05 (1H, dd, J=6.6, 16.8 Hz), 3.30 (1H, dd, J=5.2, 16.8 Hz), 3.35 (3H, s), 3.48 (1H, d, J=9.2 Hz), 3.53 (1H, d, J=



Scheme 17. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, rt, 96%; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 78%. (b) (i) t-BuLi, CO_2, Et_2O, −78 °C, 63%; (ii) Amberlyst-15® ion exchange resin, MeOH, rt, 51%.

9.2 Hz), 3.99 (1H, br s), 4.33 (1H, dd, J=5.2, 6.6 Hz), 6.53 (1H, d, J=8.1 Hz), 6.63 (1H, t, J=8.1 Hz), 6.96 (1H, d, J=8.1 Hz), 7.01 (1H, t, J=8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.1, 27.2, 33.9, 57.0, 57.6, 59.4, 73.5, 114.7, 117.2, 117.6, 127.4, 129.4, 142.3; IR ($CHCl_3$) cm^{-1}: 3422, 2972, 2935, 2896, 1607, 1588, 1482, 1312, 1260, 1112, 980, 960, 834; HRMS calcd for $C_{13}H_{18}NOCl$ $(M)^+$ 239.1077, found 239.1075; $[\alpha]_D^{24}=-6.9$ (c 0.32, $CHCl_3$).

3.6.10.2. (2*R*,3*R*)-3-Chloro-2-(methoxymethyl)-2-phenyl-1,2,3,4-tetrahydroquinoline (26d). The general method was followed using **15d** (14 mg, 0.052 mmol) to give **26d** (9.5 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (2H, m), 3.29 (3H, s), 3.93 (1H, d, J=8.8 Hz), 3.99 (1H, d, J=8.8 Hz), 4.57 (1H, t, J=3.5 Hz), 4.84 (1H, br s), 6.65 (1H, d, J=8.0 Hz), 6.72 (1H, t, J=8.0 Hz), 6.86 (1H, d, J=8.0 Hz), 7.10 (1H, t, J=8.0 Hz), 7.22–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 57.7, 59.6, 61.9, 78.7, 113.0, 116.2, 117.2, 125.8 (×2), 127.2, 127.5, 128.6 (×2), 129.6, 141.6, 142.9; IR ($CHCl_3$) cm^{-1}: 3437, 2926, 1606, 1484, 1316, 1271, 1109, 972; HRMS calcd for $C_{17}H_{18}NOCl$ $(M)^+$ 287.1073, found 287.1078; $[\alpha]_D^{24}=+142.0$ (c 0.20, $CHCl_3$).

3.6.10.3. (2*R*,3*R*)-3-Chloro-2-(4-chlorophenyl)-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26f). The general method was followed using **15f** (74 mg, 0.244 mmol) to give **26f** (26 mg, 33%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (1H, dd, J=3.7, 16.9 Hz), 2.82 (1H, dd, J=3.7, 16.9 Hz), 3.31 (3H, s), 3.89 (1H, d, J=8.8 Hz), 3.94 (1H, d, J=8.8 Hz), 4.53 (1H, t, J=3.7 Hz), 4.77 (1H, s), 6.67 (1H, t, J=7.6 Hz), 6.73 (1H, d, J=7.6 Hz), 6.88 (1H, d, J=7.6 Hz), 7.71 (1H, t, J=7.6 Hz), 7.28 (2H, d, J=8.8 Hz), 7.34 (2H, d, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.6, 57.7, 59.9, 62.0, 78.6, 113.7, 116.6, 118.0, 127.9 (×2), 128.1, 129.1 (×2), 130.1, 133.6, 141.7, 142.0; IR (thin film) cm^{-1}: 3428, 3380, 2924, 2896, 1488, 1110, 752; HRMS calcd for $C_{17}H_{17}NOCl_2$ $(M)^+$ 321.0687, found 321.0668; $[\alpha]_D^{24}=+109.2$ (c 0.35, $CHCl_3$).

3.6.10.4. (2*R*,3*R*)-3-Chloro-2-isopropyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26r). The general method was followed using **15r** (35 mg, 0.198 mmol) to give **26r** (25 mg, 65%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (6H, t, J=8.0 Hz), 2.00–2.07 (1H, m), 3.10 (1H, dd, J=7.0, 17.0 Hz), 3.26 (1H, dd, J=5.0, 17.0 Hz), 3.32 (3H, s), 3.53 (1H, d, J=9.0 Hz), 3.63 (1H, d, J=9.0 Hz), 4.03 (1H, br s), 4.48 (1H, dd, J=5.0, 7.0 Hz), 6.55 (1H, d, J=8.0 Hz), 6.65 (1H, t, J=8.0 Hz), 6.96 (1H, d, J=8.0 Hz), 7.01 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 17.7, 33.6, 34.4, 57.2, 58.8, 59.2, 73.3, 114.5, 117.3 (×2), 127.4, 129.1, 142.3; IR ($CHCl_3$) cm^{-1}: 3429, 2966, 2930, 1607, 1482, 1311, 1261, 1116, 980; HRMS calcd for $C_{14}H_{20}NOCl$ $(M)^+$ 253.1233, found 253.1232; $[\alpha]_D^{24}=+25.0$ (c 0.15, $CHCl_3$).

3.6.10.5. (2*R*,3*R*)-3-Chloro-2-cyclohexyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26g). The general method was followed using **15g** (80 mg, 0.290 mmol) to give **26g** (32 mg, 38%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16–1.40 (5H, m), 1.59–1.65 (2H, m), 1.77–1.83 (4H, m), 3.07 (1H, dd, J=6.4, 17.0 Hz), 3.28 (1H, dd, J=5.1, 17.0 Hz), 3.33 (3H, s), 3.51 (1H, d, J=9.3 Hz), 3.63 (1H, d, J=9.3 Hz), 4.06 (1H, br s), 4.50 (1H, t, J=5.1 Hz), 6.54 (1H, d, J=7.3 Hz), 6.65 (1H, dt, J=1.0, 7.3 Hz), 6.97 (1H, d, J=7.3 Hz), 7.01 (1H, t, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 27.3, 27.4, 27.5, 27.9, 34.6, 44.7, 57.3, 59.2, 59.5, 73.6, 114.7, 117.5, 117.5, 127.7, 129.5, 142.5; IR (KBr) cm^{-1}: 3402, 3365, 2926, 2852, 1487, 1099, 746; HRMS calcd for $C_{17}H_{24}NOCl$ $(M)^+$ 293.1546, found 293.1568; $[\alpha]_D^{24}=+11.6$ (c 0.46, $CHCl_3$).

3.6.10.6. (2*R*,3*R*)-3-Chloro-2-dimethyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26n). The general method was followed using **15n** (35 mg, 0.198 mmol) to give **26n** (25 mg, 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.32 (3H, s), 3.07 (1H, dd, J=9.0, 17.5 Hz), 3.23 (1H, dd, J=6.0, 17.5 Hz), 3.73 (1H, br s), 4.10 (1H, dd, J=6.0, 9.0 Hz), 6.51 (1H, d, J=8.0 Hz), 6.67 (1H, t, J=8.0 Hz), 6.98 (1H, d, J=8.0 Hz), 7.02 (1H, t, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 28.4, 34.8, 53.2, 62.6, 114.6, 117.7, 118.0, 127.5, 129.2, 142.4; IR ($CHCl_3$) cm^{-1}: 3473, 3415, 2972, 2936, 1608, 1588, 1497, 1485, 1462; HRMS calcd for $C_{11}H_{14}NCl$ $(M)^+$ 195.0815, found 195.0820; $[\alpha]_D^{24}=-28.9$ (c 0.34, $CHCl_3$).

3.6.10.7. (2*R*,3*R*)-3-Chloro-2-(methoxymethyl)-2-vinyl-1,2,3,4-tetrahydroquinoline (26h). The general method was followed using **15h** (32 mg, 0.146 mmol) to give **26h** (10.8 mg, 31%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (1H, dd, J=4.0 Hz, 17.5), 3.28 (1H, dd, J=4.0, 17.5 Hz), 3.41 (3H, s), 3.58 (1H, d, J=8.5 Hz), 3.63 (1H, d, J=8.5 Hz), 4.24 (1H, t, J=4.0 Hz), 4.32 (1H, br s), 5.26 (1H, d, J=9.5 Hz), 5.29 (1H, d, J=16.5 Hz), 5.89 (1H, dd, J=9.5, 16.5 Hz), 6.63 (1H, d, J=8.0 Hz), 6.66 (1H, t, J=8.0 Hz), 6.95 (1H, d, J=8.0 Hz), 7.05 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.0, 33.7, 56.3, 59.6, 60.4, 113.7, 116.6, 117.1, 117.6, 127.5, 129.6, 139.0, 141.6; IR ($CHCl_3$) cm^{-1}: 3433, 2927, 2897, 1608, 1590, 1482, 1313, 1271, 1115, 933; HRMS calcd for $C_{13}H_{16}NOCl$ $(M)^+$ 237.0920, found 237.0917; $[\alpha]_D^{24}=+72.4$ (c 0.22, $CHCl_3$).

3.6.10.8. (2*R*,3*R*)-3-Chloro-2-isopropenyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26i). The general method was followed using **15i** (48 mg, 0.206 mmol) to give **26i** (19 mg, 37%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, s), 2.86 (1H, dd, J=3.2, 16.8 Hz), 3.22 (1H, dd, J=3.6, 16.8 Hz), 3.41 (3H, s), 3.68 (1H, d, J=9.2 Hz), 3.76 (1H, d, J=9.2 Hz), 4.42 (1H, br t, J=2.8 Hz), 4.58 (1H, br s), 5.05 (1H, s), 5.07 (1H, s), 6.59 (1H, d, J=8.0 Hz), 6.63 (1H, t, J=8.0 Hz), 6.92 (1H, d, J=8.0 Hz), 7.04 (1H, t, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 33.6, 55.6, 59.5, 62.8, 76.6, 112.9, 115.8, 115.9, 117.1, 127.5, 129.6, 141.8, 144.9; IR ($CHCl_3$) cm^{-1}: 3456, 2926, 1609, 1502, 1483, 1315, 1275, 1112, 971, 914; HRMS calcd for $C_{14}H_{19}NOCl$ $(M+H)^+$ 252.1156, found 252.1160; $[\alpha]_D^{24}=+63.5$ (c 0.17, $CHCl_3$).

3.6.10.9. (2*R*,3*R*)-3-Chloro-2-(methoxymethyl)-2-trimethylsilanylethynyl-1,2,3,4-tetrahydroquinoline (26j). The general method was followed using **15j** (30 mg, 0.104 mmol) to give **26j** (20 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (9H, s), 3.24 (2H, d,

J=8.5 Hz), 3.41 (3H, s), 3.77 (2H, s), 4.35 (1H, br s), 4.36 (1H, t, J=8.5 Hz), 6.62 (1H, d, J=8.0 Hz), 6.68 (1H, t, J=8.0 Hz), 7.00 (1H, t, J=8.0 Hz), 7.05 (1H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.3 (×3), 33.0, 59.9, 64.8, 68.3, 77.9, 93.6, 108.8, 118.5, 124.1, 127.3, 127.8, 128.1, 150.3; IR ($CHCl_3$) cm^{-1}: 3410, 2962, 1610, 1485, 1468, 1403, 1251, 1096, 846; HRMS calcd for $C_{16}H_{22}$NOClSi $(M)^+$ 307.1159, found 307.1158; $[\alpha]_D^{24}$=+19.0 (c 0.14, $CHCl_3$).

3.6.10.10. (2*R*,3*R*)-3-Chloro-2-ethynyl-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline (26s). The general method was followed using **15s** (55 mg, 0.253 mmol) to give **26s** (33 mg, 55%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (1H, s), 3.24 (2H, d, J=9.0 Hz), 3.48 (3H, s), 3.76 (1H, d, J=10.5 Hz), 3.79 (1H, d, J=10.5 Hz), 4.30 (1H, br s), 4.40 (1H, t, J=9.0 Hz), 6.64 (1H, d, J=8.0 Hz), 6.70 (1H, t, J=8.0 Hz), 7.02 (1H, t, J=8.0 Hz), 7.06 (1H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.9, 59.8, 65.1, 67.3, 77.6, 109.1, 115.0, 118.9, 124.3, 127.4, 127.8, 129.6, 150.0; IR ($CHCl_3$) cm^{-1}: 3408, 3305, 2934, 1610, 1485, 1248, 1117, 1097, 968; HRMS calcd for $C_{13}H_{14}$NOCl $(M)^+$ 235.0764, found 235.0768; $[\alpha]_D^{24}$=−24.0 (c 0.30, $CHCl_3$).

3.6.10.11. (2*R*,3*R*)-6-Bromo-3-chloro-2-methyl-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydroquinoline (26p). The general method was followed using **15p** (45 mg, 0.139 mmol) to give **26p** (30 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.46–1.55 (1H, m), 1.57 (3H, s), 1.68 (3H, s), 1.72–1.80 (1H, m), 1.97–2.10 (2H, m), 3.05 (1H, dd, J=7.4, 16.8 Hz), 3.23 (1H, dd, J=5.6, 16.8 Hz), 3.83 (1H, br s), 4.11 (1H, dd, J=5.6, 7.4 Hz), 5.09 (1H, t, J=7.2 Hz), 6.38 (1H, d, J=9.6 Hz), 7.08 (1H, s), 7.09 (1H, d, J=9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 22.0, 24.8, 25.7, 34.0, 34.8, 55.2, 61.2, 109.0, 116.1, 119.8, 123.6, 130.0, 131.6, 132.0, 141.1; IR ($CHCl_3$) cm^{-1}: 3424, 2971, 2932, 1716, 1599, 1488, 1447, 1380, 1301, 1123; HRMS calcd for $C_{16}H_{21}$NClBr $(M)^+$ 341.0545, found 341.0544; $[\alpha]_D^{24}$=+37.4 (c 0.56, $CHCl_3$).

3.6.10.12. (2*R*,3*R*)-6-Bromo-3-chloro-2-(methoxymethyl)-2-(4-methylpent-3-enyl)-1,2,3,4-tetrahydroquinoline (26k). The general method was followed using **15k** (39 mg, 0.110 mmol) to give **26k** (17 mg, 41%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55–1.63 (1H, m), 1.59 (3H, s), 1.67 (3H, s), 1.69–1.75 (1H, m), 1.98–2.08 (2H, m), 3.02 (1H, dd, J=6.0, 17.5 Hz), 3.29 (1H, dd, J=4.5, 17.5 Hz), 3.36 (3H, s), 3.47 (1H, d, J=9.5 Hz), 3.52 (1H, d, J=9.5 Hz), 4.05 (1H, br s), 4.31 (1H, t, J=6.0 Hz), 5.07 (1H, br t, J=7.0 Hz), 6.42 (1H, d, J=9.0 Hz), 7.08 (1H, s), 7.09 (1H, d, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 21.6, 25.6, 33.6, 34.5, 56.6, 57.6, 59.3, 73.7, 109.0, 116.2, 119.2, 123.5, 130.2, 131.8, 132.1, 141.2; IR ($CHCl_3$) cm^{-1}: 3426, 2929, 1711, 1599, 1489, 1377, 1301, 1111, 977; HRMS calcd for $C_{17}H_{23}$NOClBr $(M)^+$ 371.0651, found 371.0655; $[\alpha]_D^{24}$=−11.6 (c 0.39, $CHCl_3$).

3.6.10.13. Methyl (2*R*,3*R*)-3-chloro-2-(methoxymethyl)-2-(2-phenylethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (26t). The general method was followed using **15t** (102 mg, 0.304 mmol) to give **26t** (45 mg, 50%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.87 (1H, m), 1.95–2.01 (1H, m), 2.58 (2H, t, J=8.4 Hz), 3.01 (1H, dd, J=6.6, 16.9 Hz), 3.23–3.28 (1H, m), 3.28 (3H, s), 3.46 (1H, d, J=9.2 Hz), 3.50 (1H, d, J=9.2 Hz), 3.74 (3H, s), 4.31 (1H, t, J=5.9 Hz), 4.39 (1H, s), 6.39 (1H, d, J=9.5 Hz), 7.05–7.10 (3H, m), 7.15–7.18 (2H, m), 7.60–7.62 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.3, 33.6, 37.0, 51.5, 56.3, 58.0, 59.4, 73.8, 113.7, 116.0, 118.8, 126.0, 128.2 (×2), 128.5 (×2), 129.6, 131.6, 141.4, 146.3, 167.1; IR (KBr) cm^{-1}: 3361, 2948, 1707, 1610, 1436, 1288, 1253, 1128, 1104; HRMS calcd for $C_{21}H_{24}NO_3ClK$ $(M+K)^+$ 412.1082, found 412.1074; $[\alpha]_D^{24}$=−29.4 (c 0.10, $CHCl_3$).

3.6.10.14. (2*S*,3*R*)-3-Chloro-2-phenethyl-2-propyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid allyl ester (26u). The general method was followed using **15u** (300 mg, 0.791 mmol) to give **26u** (164 mg, 52%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J=7.3 Hz), 1.25–1.32 (1H, m), 1.37–1.45 (1H, m), 1.55 (1H, dt, J=4.4, 12.8 Hz), 1.71 (1H, dt, J=4.4, 13.0 Hz), 1.78 (1H, dt, J=4.4, 13.0 Hz), 1.91 (1H, dt, J=5.9 Hz, 12.8), 2.60 (1H, dt, J=5.1, 12.6 Hz), 2.69 (1H, dt, J=5.1, 12.6 Hz), 3.10 (1H, dd, J=6.6, 17.3 Hz), 3.29 (1H, dd, J=5.1, 17.3 Hz), 4.05–4.10 (1H, m), 4.29 (1H, dd, J=5.1, 6.6 Hz), 4.72–4.73 (2H, m), 5.21 (1H, d, J=9.5 Hz), 5.34 (1H, d, J=19.1 Hz), 5.94–6.03 (1H, m), 6.42 (1H, d, J=8.1 Hz), 7.09–7.25 (5H, m), 7.69–7.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 16.0, 29.3, 33.5, 36.2, 37.9, 57.6, 58.3, 64.9, 113.5, 116.1, 117.6, 118.5, 126.0, 128.2, 128.5, 129.6 (×2), 131.7 (×2), 132.7, 141.5, 146.6, 166.3; IR (thin film) cm^{-1}: 3368, 2959, 2935, 2873, 1693, 1610, 1513, 1281, 1250, 1129; HRMS calcd for $C_{24}H_{29}NO_2Cl$ $(M+H)^+$ 398.1887, found 398.1914; $[\alpha]_D^{24}$=−2.2 (c 0.31, $CHCl_3$).

3.6.10.15. (2*R*,3*R*)-2-But-3-enyl-3-chloro-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid allyl ester (26v). The general method was followed using **15v** (83 mg, 0.250 mmol) to give **26v** (41 mg, 46%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70–1.76 (1H, m), 1.84–1.90 (1H, m), 2.16 (2H, q, J=7.8 Hz), 3.11 (1H, dd, J=6.3, 17.1 Hz), 3.36 (1H, dd, J=4.4, 17.1 Hz), 3.39 (3H, s), 3.54 (1H, d, J=9.3 Hz), 3.58 (1H, d, J=9.3 Hz), 4.35 (1H, t, J=5.4 Hz), 4.52 (1H, s), 4.78 (2H, d, J=5.8 Hz), 4.99 (1H, d, J=8.8 Hz), 5.06 (1H, d, J=14.7 Hz), 5.27 (1H, d, J=8.8 Hz), 5.39 (1H, d, J=18.6 Hz), 5.76–5.85 (1H, m), 6.00–6.08 (1H, m), 6.54 (1H, d, J=8.8 Hz), 7.74 (1H, s), 7.76 (1H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 33.8, 34.5, 56.4, 58.0, 59.6, 65.0, 73.9, 113.5, 115.0, 116.0, 117.7, 118.7, 129.7, 131.7, 132.7, 137.8, 146.2, 166.2; IR (liquid film) cm^{-1}: 3364, 2928, 1704, 1611, 1515, 1281, 1252, 1128, 1105; HRMS calcd for $C_{19}H_{25}NO_3Cl$ $(M+H)^+$ 350.1522, found 350.1526; $[\alpha]_D^{24}$=+17.1 (c 1.01, $CHCl_3$).

3.6.10.16. (2*S*)-2-[(1*S*)-1-Hydroxy-1-(methoxymethyl)-4,5-dimethylhex-4-enyl]indoline-5-carbonitrile (15x). The general method was followed using **1** (26 mg, 0.0782 mmol) to give **15**× (15 mg, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (1H, dt, J=5.0, 12.5 Hz), 1.55 (1H, dt, J=5.0, 12.5 Hz), 1.63 (6H, s), 1.65 (3H, s), 1.99 (1H, dt, J=5.0, 12.5 Hz), 2.15 (1H, dt, J=5.0, 12.5 Hz), 2.61 (1H, s), 2.96 (1H, dd, J=9.0, 16.5 Hz), 3.06 (1H, dd, J=11.0, 16.5 Hz), 3.42 (3H, s), 3.43 (1H, d,

J=9.0 Hz), 3.52 (1H, d, J=9.0 Hz), 4.15 (1H, t, J=9.5 Hz), 4.84 (1H, br s), 6.54 (1H, d, J=8.0 Hz), 7.25 (1H, s), 7.29 (1H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.9, 20.5, 28.0, 29.9, 32.6, 59.5, 66.0, 72.9, 78.4, 99.9, 108.0, 120.6, 124.6, 126.9, 127.8, 128.9, 133.0, 154.6; IR ($CHCl_3$) cm^{-1}: 3543, 3423, 2923, 2215, 1614, 1495, 1412, 1264, 1109, 972; HRMS calcd for $C_{19}H_{27}N_2O_2$ $(M+H)^+$ 315.2072, found 315.2065; $[\alpha]_D^{24}=+14.5$ (c 0.29, $CHCl_3$).

3.6.11. Synthesis of (−)-virantmycin.

3.6.11.1. *tert*-Butyl (2*S*)-5-iodo-2-(methoxyacetyl)-indoline-1-carboxylate (31). Iodine monochloride in CH_2Cl_2 (1.4 ml, 1.0 M) was added to a solution of **13b** (100 mg, 0.34 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (282 mg, 1.37 mmol) in CH_2Cl_2 (2 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt (10 ml), poured into $Na_2S_2O_3$ aq (10 ml) and the organic material was extracted with AcOEt(10 ml×2). The combined extracts were washed with 1 N HCl (20 ml), satd $NaHCO_3$ aq (20 ml) and brine (20 ml), dried over Na_2SO_4 and concentrated. Purification by silica gel flash chromatography (toluene–AcOEt 9:1) furnished **31** (130 mg, 91%) as a colorless solid (mp 72–74 °C). ^{1}H NMR (500 MHz, CD_3OD, two rotamers) δ 1.44–1.54 (9H, m), 2.96 (1H, br d, J=17.6 Hz), 3.41 (3H, s), 3.41–3.42 (1H, br m), 4.21 (2H, s), 5.09 (1H, dd, J=11.7, 4.9 Hz), 7.23* (0.3H, br s), 7.40 (1H, s), 7.44 (1H, d, J=8.8 Hz), 7.55 (0.7H, br s); ^{13}C NMR (125 MHz, CD_3OD) δ 28.5 (×3), 31.8, 59.8, 64.6, 76.1, 82.9, 117.3, 132.5, 134.7, 137.6 (×2), 144.2, 152.8, 206.2; IR ($CHCl_3$) cm^{-1}: 2981, 2935, 1708, 1693, 1476, 1371, 1152; HRMS calcd for $C_{16}H_{20}NO_4INa$ $(M+Na)^+$ 440.0335, found 440.0358; $[\alpha]_D^{24}=-46.0$ (c 0.82, $CHCl_3$).

3.6.11.2. *tert*-Butyl (2*S*)-2-[(1*R*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex-4-enyl]-5-iodoindoline-1-carboxylate (major-32). The prepared Grignard reagent (0.5 M THF solution, 7.8 ml) was added dropwise to a solution of **31** (813 mg, 1.95 mmol) in THF (3 ml) at −78 °C in N_2 atmosphere, and the reaction mixture was stirred at this temperature for 1 h. After the addition of satd NH_4Cl aq, the reaction mixture was allowed to warm to room temperature. The organic material was extracted with AcOEt (10 ml×2), and then the combined extracts were washed with brine (20 ml), dried over Na_2SO_4 and concentrated. Purification by silica gel flash chromatography (hexane–AcOEt 9:1) furnished the corresponding alcohol **32** (770 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (1H, dt, J=5.2, 12.7 Hz), 1.41 (1H, dt, J=5.2 Hz, 12.7), 1.52 (3H, s), 1.55 (3H, s), 1.57 (9H, s), 1.58 (3H, s), 1.99 (1H, dt, J=5.2, 12.7 Hz), 2.04 (1H, dt, J=5.2, 12.7 Hz), 3.08 (1H, dd, J=2.0, 16.9 Hz), 3.26 (1H, dd, J=10.3, 16.9 Hz), 3.35 (3H, s), 3.40 (2H, s), 4.73 (1H, br d, J=9.8 Hz), 7.24 (1H, br s), 7.43–7.44 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 19.8, 20.5, 28.1, 28.3 (×3), 29.6, 31.4, 59.3, 64.7, 76.3, 76.9, 82.4, 85.8, 118.3, 124.1, 127.4, 133.0, 134.8, 135.8 (×2), 142.8; IR ($CHCl_3$) cm^{-1}: 2983, 2928, 1687, 1672, 1475, 1370, 1164; HRMS calcd for $C_{23}H_{34}NO_4INa$ $(M+Na)^+$ 538.1431, found 538.1417; $[\alpha]_D^{24}=-36.3$ (c 0.46, $CHCl_3$).

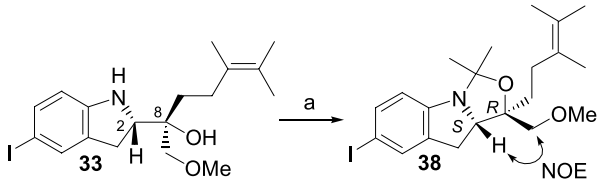
3.6.11.3. *tert*-Butyl (2*S*)-2-[(1*S*)-1-hydroxy-1-methoxymethyl-4,5-dimethylhex4-enyl]-5-iodoindoline-1-carboxylate (minor-32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (9H, s), 1.62 (6H, s), 1.65 (3H, s), 1.57–1.65 (2H, m), 2.11 (1H, dt, J=5.3, 12.5 Hz), 2.18 (1H, dt, J=5.3, 12.5 Hz), 2.88 (3H, s), 3.07 (1H, d, J=9.5 Hz), 3.15 (1H, d, J=9.5 Hz), 3.16–3.26 (2H, m), 4.64 (1H, dd, J=2.9, 10.2 Hz), 7.20–7.22 (1H, m), 7.43–7.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 19.9, 20.5, 27.6, 28.2, 28.3, 28.9, 30.2, 33.3, 58.7, 65.9, 75.0, 76.3, 77.4, 82.9, 85.9, 118.2, 124.1, 127.6, 133.1, 135.4, 135.6, 142.3; IR ($CHCl_3$) cm^{-1}: 2983, 2926, 1665, 1476, 1371, 1163; HRMS calcd for $C_{23}H_{34}NO_4INa$ $(M+Na)^+$ 538.1431, found 538.1437; $[\alpha]_D^{24}=-53.9$ (c 0.49, $CHCl_3$).

3.6.11.4. (2*R*)-2-[(2*S*)-2,3-Dihydro-5-iodo-1*H*-indol-2-yl]-1-methoxy-5,6-dimethylhept-5-en-2-ol (33). Formic acid (1 ml) was added to a solution of **32** (115 mg, 0.22 mmol) in CH_2Cl_2 (1 ml) at room temperature, and the mixture was stirred under reflux conditions for 2 h. The reaction mixture was poured into water, basified to pH 8 with $NaHCO_3$, and the organic material was extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography (hexane–AcOEt 3:2) to give **33** (55 mg, 59%) as a colorless solid (mp 104–106 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (1H, dt, J=5.1, 13.9 Hz), 1.55 (1H, dt, J=5.1, 13.9 Hz), 1.64 (3H, s), 1.66 (6H, s), 2.01 (1H, dt, J=5.1, 12.5 Hz), 2.15 (1H, dt, J=5.1, 12.5 Hz), 2.78 (1H, s), 2.89 (1H, dd, J=8.8, 16.1 Hz), 3.05 (1H, dd, J=11.0, 16.1 Hz), 3.39 (1H, d, J=9.5 Hz), 3.40 (3H, s), 3.49 (1H, d, J=9.5 Hz), 4.07 (1H, t, J=9.9 Hz), 4.28 (1H, br s), 6.41 (1H, d, J=8.1 Hz), 7.27 (1H, d, J=8.1 Hz), 7.33 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 20.1, 20.7, 28.3, 30.3, 33.0, 59.5, 66.0, 72.7, 78.3, 79.5, 111.2, 124.3, 127.1, 131.5, 133.0, 135.7, 150.3; IR ($CHCl_3$) cm^{-1}: 3513, 3407, 2925, 1602, 1479, 1417, 1248, 1112; HRMS calcd for $C_{18}H_{27}NO_2I$ $(M+H)^+$ 416.1087, found 416.1073. Anal. Calcd for $C_{18}H_{26}NO_2I$: C, 52.06; H, 6.31; N, 3.37; I, 30.56. Found: C, 52.08; H, 6.40; N, 3.55; I, 30.69; $[\alpha]_D^{24}=-25.9$ (c 0.19, $CHCl_3$).

3.6.11.5. (2*R*,3*R*)-3-Chloro-2-(3,4-dimethyl-pent-3-enyl)-6-iodo-2-methoxymethyl-1,2,3,4-tetrahydroquinoline (34). Tri-*n*-butylphosphine (140 μl, 0.54 mmol) was added dropwise to a solution of **33** (15 mg, 0.036 mmol) and carbon tetrachloride (110 μl, 1.08 mmol) in CH_2Cl_2 (2 ml) at reflux (bath temp. 55 °C) in N_2 atmosphere. The reaction mixture was stirred under reflux conditions for 1 h, and then concentrated. The resulting residue was purified by silica gel flash chromatography (hexane–AcOEt 19:1) to give **34** (7.1 mg, 45%) as a colorless solid (mp 98–100 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (3H, s), 1.57–1.62 (7H, m), 1.75 (1H, dt, J=5.2, 13.2 Hz), 2.00 (1H, dt, J=4.6, 12.2 Hz), 2.08 (1H, dt, J=4.6, 12.2 Hz), 3.02 (1H, dd, J=5.9, 17.1 Hz), 3.29 (1H, dd, J=5.9, 17.1 Hz), 3.36 (3H, s), 3.49 (1H, d, J=7.8 Hz), 3.53 (1H, d, J=7.8 Hz), 4.10 (1H, s), 4.31 (1H, t, J=5.9 Hz), 6.34 (1H, d, J=7.8 Hz), 7.26 (1H, s), 7.27 (1H, d, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.9, 20.6, 27.7, 33.0, 33.5, 56.4, 57.6, 59.4, 73.7, 78.1, 116.8, 119.8, 124.6, 126.7, 136.1, 137.7, 142.0; IR ($CHCl_3$) cm^{-1}: 2926, 1597, 1488, 1299, 1109; HRMS calcd for $C_{18}H_{25}NOClI$ $(M)^+$ 433.0670, found 433.0652; $[\alpha]_D^{24}=-10.3$ (c 0.64, $CHCl_3$).

3.6.11.6. (−)-Virantmycin (2a). A mixture of **34** (21 mg, 0.048 mmol), $Pd(OAc)_2$ (6.1 mg, 0.027 mmol) and K_2CO_3 (27 mg, 0.194 mmol) in 0.5 ml of H_2O and 0.5 ml of methanol was stirred vigorously at room temperature in 1 atm CO atmosphere for 18 h. After the addition of water, the organic material was extracted with AcOEt (5 ml×2). The combined organic extracts were washed with brine (10 ml), dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel flash chromatography (hexane–AcOEt 9:1 to 1:1) to give (−)-virantmycin (**2a**) as a yellow oil (9.0 mg, 53%) along with the recovered **34** (7.1 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (6H, s), 1.63 (3H, s), 1.61–1.67 (1H, m), 1.81 (1H, dt, J=4.9, 13.2 Hz), 2.01 (1H, dt, J=4.9, 12.2 Hz), 2.09 (1H, dt, J=4.9, 12.2 Hz), 3.12 (1H, dd, J=5.9, 17.6 Hz), 3.37 (1H, dd, J=4.9, 17.6 Hz), 3.39 (3H, s), 3.56 (1H, d, J=8.8 Hz), 3.58 (1H, d, J=8.8 Hz), 4.37 (1H, t, J=5.4 Hz), 4.65 (1H, br s), 6.54 (1H, d, J=7.8 Hz), 7.76–7.78 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 19.9, 20.6, 27.8, 33.5, 33.6, 56.2, 58.0, 59.4, 74.0, 113.5, 116.0, 117.6, 124.8, 126.5, 130.4, 132.4, 147.2, 171.6; IR ($CHCl_3$) cm^{-1}: 2926, 1710, 1675, 1609, 1290, 1132, 1111; HRMS calcd for $C_{19}H_{27}NO_3Cl$ $(M+H)^+$ 352.1679, found 352.1668; $[\alpha]_D^{24}=-16.5$ (c 0.11, $CHCl_3$).

3.6.11.7. Determination of the stereochemistry of major-32. The configurations of the newly created asymmetric centers in major-**32** was determined after NOE experiments of the acetonide **38**, which was derived from **33** by acetonization with 2,2-dimethoxypropane. As a result, major-**32** has (2*S*,8*R*) configuration (Scheme 18).



Scheme 18. Reagents and conditions: (a) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt, 64%.

3.6.11.8. (1*R*,9a*S*)-7-Iodo-1-methoxymethyl-3,3-dimethyl-1-(3,4-dimethylpent-3-enyl)-9,9a-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indole (38). Method for the synthesis of major-**16** was followed using **33** (17 mg, 0.041 mmol) to give **38** (12 mg, 64%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (1H, dt, J=4.2, 13.2 Hz), 1.50 (6H, s), 1.55–1.60 (7H, m), 1.65 (3H, s), 1.94 (1H, dt, J=4.9, 12.6 Hz), 2.05 (1H, dt, J=4.2, 12.6 Hz), 3.01 (1H, dd, J=10.3, 17.4 Hz), 3.07 (1H, dd, J=4.4, 17.4 Hz), 3.28 (1H, d, J=9.8 Hz), 3.38 (3H, s), 3.52 (1H, d, J=9.8 Hz), 4.33 (1H, dd, J=4.4, 10.3 Hz), 6.41 (1H, d, J=7.8 Hz), 7.27 (1H, d, J=7.8 Hz), 7.30 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 19.9, 20.5, 25.8, 28.1, 29.1, 29.1, 31.3, 59.6, 70.1, 76.3, 80.1, 82.2, 94.8, 113.7, 124.1, 127.4, 133.3, 135.0, 135.4, 148.5; IR ($CHCl_3$) cm^{-1}: 2928, 2862, 1474, 1258, 1117; HRMS calcd for $C_{21}H_{31}NO_2I$ $(M+H)^+$ 456.1399, found 456.1407; $[\alpha]_D^{24}=+68.4$ (c 1.20, $CHCl_3$).

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29. There is no direct evidence for the formation of aziridine intermediate **6**. A stepwise sequence may be possible (1. formation of tertiary chloride; 2. intramolecular cyclization to an aziridine; 3. ring opening by the attack of chloride anion). However, the tertiary chloride could not be obtained by treatment of **15a** with various chlorinating agents. Additionally, no aziridine compound was obtained by subjecting **15a** to Mitsunobu conditions. For the ring-opening reaction of an aziridine, such as **6**, with chloride anions to provide tetrahydroquinoline **4**, see Ref. 12.
30. All other products were highly polar materials which were not isolated.
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The effects of added ammonium chloride in the reductive amination of some carbonyl compounds over Ru and Pd catalysts

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Abstracts—The reductive amination of acetophenone, (+)-camphor, and 5α-cholestan-3-one over Ru and Pd metals as well as their carbon-supported catalysts gave corresponding amines together with alcohols as by-products. However, we found that the corresponding amines are selectively synthesized by the addition of ammonium chloride to the reaction system with depression of the formation of alcohol, as exemplified with acetophenone. Although alcohols are usually not formed over Pd with alicyclic ketones, the alcohols formation was effectively depressed over Ru in the presence of ammonium chloride. The effects of the additive on the stereoselectivity of the formation of amines are also discussed in the cases of (+)-camphor and 5α-cholestan-3-one.

1. Introduction

Reductive amination of carbonyl compounds with ammonia[1] is one of the most frequently used procedures in the preparation of amines. However, the reaction is complicated by the formation of primary, secondary or tertiary amines. Furthermore, the hydrogenation of carbonyl compounds to alcohols occurs as a significant side reaction. Therefore, the controlling of the reaction conditions is required for the selective synthesis of the desired amines. The product distribution may be influenced by the molar ratio of the carbonyl compound to ammonia, the molecular structure of the carbonyl compound, additives such as acids or bases, and the nature of catalysts.

In the preceding papers,[2–5] we reported that the reductive amination of carbonyl compounds over platinum metal catalysts exhibited different reactivity and selectivity according to the catalysts used and the compounds subjected to the reaction.

In the reductive amination, the carbonyl compound and ammonia first undergo an addition reaction to give a hemiaminal as an intermediate that may undergo hydrogenolysis directly to give a primary amine and/or be dehydrated to give an imine. The hydrogenation of the formed imine gives the primary amine (Scheme 1). In addition, the reaction between the primary amine formed and the imine or the carbonyl compounds may lead to formation of a secondary amine. Concurrently, simple hydrogenation of the carbonyl compound to give an alcohol may also occur.

In this paper the selective synthesis of the primary amine from the carbonyl compounds such as acetophenone (**I**), (+)-camphor (**II**) and 5α-cholestan-3-one (**III**) has been studied with unsupported and carbon-supported Ru and Pd as catalysts. The selective synthesis of the primary amine could be achieved with depression of the alcohol formation by the addition of ammonium chloride to the reaction system.

2. Results and discussion

The formation of primary amines in the reductive amination of carbonyl compounds proceeds via steps 1 and 2 or step 3 in Scheme 1. The reaction to give an imine (step 1) formation may be competitive with the formation of alcohols (step 7). Various additives have been used to promote the formation of the imine intermediate.[6] Previously, Alexander[7] reported the effect of additives in the reductive amination of acetophenone over an Adams Pt catalyst. The addition of ammonium chloride to the reaction system increased the yield of the primary amine with depression of formation of secondary amine. However, as reported previously, in the reductive amination of nonanal, the formation of secondary amine was not depressed and the yield of primary amine was not increased by addition of

Keywords: Reductive amination; Platinum metal catalysts; Acetophenone; (+)-Camphor; 5α-Cholestan-3-one.
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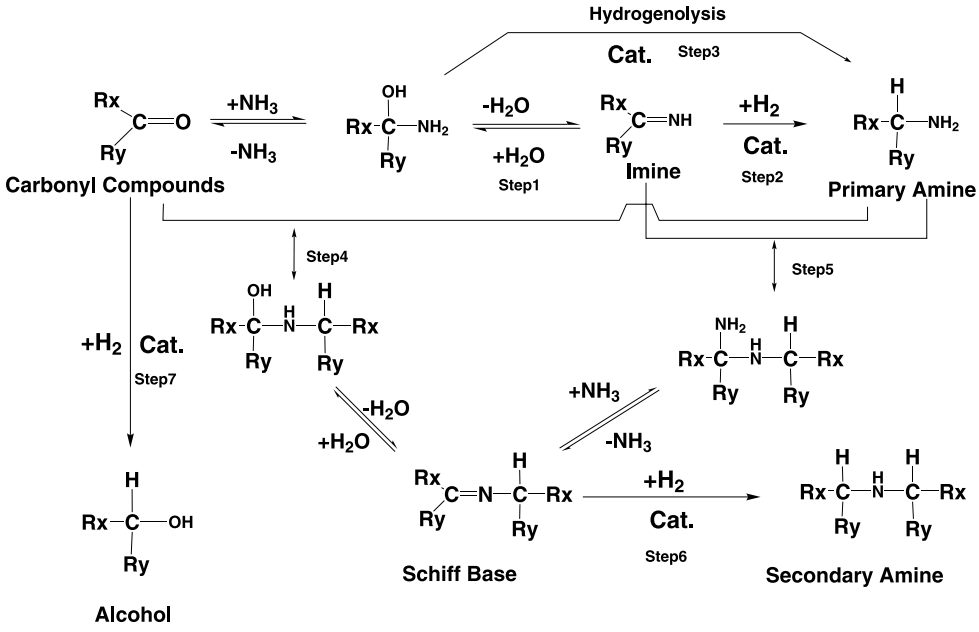


Scheme 1. Reductive amination of carbonyl compounds.

ammonium chloride over platinum metals including platinum as catalysts.[4]

In this study, we examined in detail the effects of the addition of ammonium chloride in the reductive amination of acetophenone (**I**), (+)-camphor (**II**), and 5α-cholestan-3-one (**III**) over Ru and Pd blacks as well as 5%Ru and 5%Pd on carbon as catalysts. The results are shown in Tables 1 and 2.

Although the formation of the secondary amine is usually very slight with alicyclic ketone in both the presence and absence of ammonium chloride, the secondary amine was obtained in 36 and 16% yields, respectively, with **I** over Ru black and with **II** over Pd black in the presence of ammonium chloride. This result is not consistent with those reported by Alexander with Adams Pt catalyst. Probably, it is due to the different properties of the catalysts used. The corresponding alcohols were also obtained by simple hydrogenation of the carbonyl compounds, in particular in the absence of ammonium chloride, as seen from the results in Tables 1 and 2. Thus, the formation of alcohols is markedly depressed by the addition of ammonium chloride.

It is well known that the dehydrative condensation reaction between a carbonyl compound and an amine or ammonia is promoted in acidic media. Therefore, it is suggested that the formation of the imine intermediate is promoted by the acidic function of ammonium chloride. Thus the amines are produced in preference to the corresponding alcohols.

2.1. The reductive amination of acetophenone (I)

Usually, over Pd black or 5% Pd–C catalysts the hydrogenation of **I** tends to give ethylbenzene by cleavage

Table 1. Reductive amination of carbonyl compounds over platinum metals

Substrate	Catalyst	Additive	Conversion (%)	Composition of reaction mixture/%							
				Primary amine		Alcohol		*N*-Alkylamine		Secondary amine	Schiff base
				A	B	A	B	A	B		
Acetophenone	Pd	None	100	0		100		0		0	0
		NH_4Cl	97	82		15		0		0	0
	Ru	None	97	0		97		0		0	0
		NH_4Cl	98[a]	0		55		0		36	0
(+)-Camphor	Pd	None	0	0	0	0	0	0	0	0	0
		NH_4Cl	86	55	10	1	0	3	0	16	1
	Ru	None	30	0	0	27	3	0	0	0	0
		NH_4Cl	79	23	34	4	1	3	1	7	4
5α-Cholestan-3-one	Pd	None	100	81	19	0	0	0	0	0	0
		NH_4Cl	100	79	21	0	0	0	0	0	0
	Ru	None	100	54	26	12	8	0	0	0	0
		NH_4Cl	100	82	16	1	1	0	0	0	0

Reaction conditions: acetophenone, 2.5×10^{-3} mol; H_2, 8 MPa; temp., 50 °C; time, 5 h. (+)-camphor, 5.0×10^{-3} mol; H_2, 8 MPa; temp., 200 °C; time, 5 h. 5α-cholestan-3-one, 2.0×10^{-4} mol; H_2, 6 MPa, temp., 50 °C, time, 4 h, additive. NH_4Cl, 0.2 g (3.73×10^{-3} mol) NH_3, 1.0 g (6.0×10^{-2} mol), catalyst, 1.0×10^{-2} g. A; *exo*- or β-position, B; *endo*- or α-position.

[a] Yield of α-methylcyclohexylalcohol as by-product was 7%.

Table 2. Reductive amination of carbonyl compounds over 5% carborn supported platinum metals

Substrate	Catalyst	Additive	Conversion (%)	Composition of reaction mixture/%							
				Primary amine		Alcohol		*N*-Alkylamine		Secondary amine	Schiff base
				A	B	A	B	A	B		
Acetophenone	Pd/C	None	100	0		100		0		0	0
		NH_4Cl	98	7		91		0		0	0
	Ru/C	None	96	5		91		0		0	0
		NH_4Cl	97	44		53		0		0	0
(+)-Camphor	Pd/C	None	88	67	0	0	0	11	0	4	5
		NH_4Cl	99	69	10	2	0	15	1	1	2
	Ru/C	None	94	1	6	37	18	9	22	0	0
		NH_4Cl	99	32	29	15	3	13	7	0	0
5α-Cholestan-3-one	Pd/C	None	100	78	22	0	0	0	0	0	0
		NH_4Cl	100	87	13	0	0	0	0	0	0
	Ru/C	None	100	73	18	4	5	0	0	0	0
		NH_4Cl	100	87	13	0	0	0	0	0	0

Reaction conditions: acetophenone, 2.5×10^{-3} mol; H_2, 8 MPa; temp., 50 °C; time, 5 h. (+)-Camphor, 5.0×10^{-3} mol; H_2, 8 MPa; temp., 200 °C; time, 5 h. 5α-Cholestan-3-one, 2.0×10^{-4} mol; H_2, 6 MPa, temp., 50 °C, time, 4 h. Additive; NH_4Cl. 0.2 g (3.73×10^{-3} mol). NH_3, 1.0 g (6.0×10^{-2} mol). Catalyst, 0.2 g. A; *exo*- or β-position, B; *endo*- or α-position.

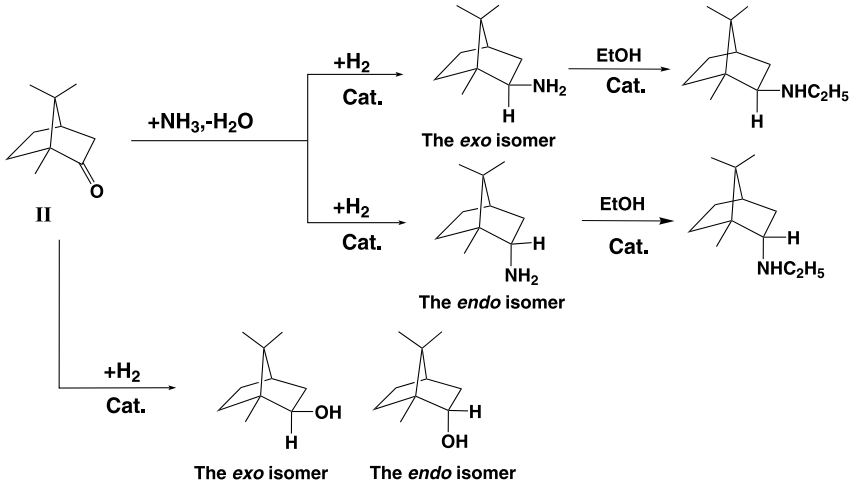
of the C–O bond together with 1-phenylethanol, but the addition of a small amount of organic bases such as morpholine or tetrahydroquinoline depresses the hydrogenolysis to give ethylbenzene.[8]

In the present reaction conditions of reductive amination, the hydrogenolysis did not occur and the yield of 1-phenylethanol was quantitative over both Pd black and 5% Pd–C. Over Pd black, however, the addition of ammonium chloride to the reaction system gave preferentially 1-phenyethylamine with depression of the formation of 1-phenylethanol, as can be seen in Table 1.

On the other hand, over 5% Pd–C the yield of 1-phenylethylamine was only 7.0% in the presence of ammonium chloride. Thus, a great difference was found between the results with Pd black and with 5% Pd–C. We suggest that the hydrogenation of the carbonyl compound may be much faster over highly dispersed palladium metal on carbon than over Pd black. Actually, the hydrogenation rate of **I** in the initial stage over 5% Pd–C was ten times as great as that with Pd black on the basis of unit weight of the metal. In contrast, the reaction of **I** with Pd black proceeded 7.5 times as rapidly in the presence of ammonium chloride as that without the additive. The reductive amination of **I** over Ru black or 5% Ru–C produced almost exclusively 1-phenylethanol. However, both the catalysts provided markedly different results in the formation of amines in the presence of ammonium chloride. On Ru black, bis(1-phenylethyl)-amine was obtained in a yield corresponding to a decrease in the yield of 1-phenylethanol, while on 5% Ru–C the yield of 1-phenylethylamine increased with the decrease in the yield of the benzyl alcohol. Thus, no primary amine was formed on Ru black and no secondary amine was produced on 5% Ru–C in the presence of ammonium chloride. In the reaction with Raney Ni, Robinson, Jr. and co-workers obtained 1-phenylethylamine in 44–52% yield,[9] whereas the yield of the amine was increased to 91% by the addition of small amounts of glacial acetic acid to the reaction mixture as described by another investigators.[10] On Pd black, the addition of ammonium acetate, instead of ammonium chloride, resulted in a decrease to 47% in the yield of 1-phenylethylamine.

2.2. The reductive amination of (+)-camphor (II)

In the reductive amination of **II** and cholestan-3-one(**III**) it is possible to observe not only the selectivity on the



Scheme 2.

formation of the amines and alcohols but also the stereoselectivity of the formation of stereoisomeric amines or alcohols. A higher reaction temperature of 200 °C was required to promote the reaction for the hindered ketone **II**.

The reaction with Pd black did not proceed at all in the absence of ammonium chloride while isobornylamine (the *exo* isomer) and bornyl amine (the *endo* isomer) (see Scheme 2) were obtained in 55% and 10% yields, respectively, in the presence of ammonium chloride (see Table 1). The yield of isobornyl alcohol was only 1%. Without ammonium chloride the appearance of Pd black has changed from a finely divided particle form (surface area: 33.4 m^2/g) before the reaction to a silvery white metallic form (surface area: 0.47 m^2/g) after the reaction. In the presence of ammonium chloride, the catalyst apparently did not change before and after the reaction, but the surface area of the Pd black was found to decrease to about 4–6 m^2/g. Evidently, the metallic Pd black suffered from an extreme sintering in the absence of the additive. It is of interest that the extreme sintering was prevented in the presence of ammonium chloride and the reductive amination of **II** proceeded smoothly. It is probable that the sintering was inhibited by a strong adsorption to the catalyst surface of the imine intermediate formed rapidly in the presence of ammonium chloride. It is known that the sintering of a platinum catalyst slowed down appreciably when the chloride ion content of the catalyst is maintained to about 1 wt%.[11] Therefore, it may be possible that the sintering of the Pd catalyst was also inhibited by the chloride ion from the ammonium chloride added.

On 5% Pd–C, the reductive amination proceeded readily both with or without ammonium chloride. However, the formation of the primary amine was further increased by the addition of ammonium chloride as can be seen from Table 2.

With respect to the stereoselectivity of the primary amine formed, isobornylamine (the *exo* isomer) was formed predominantly together with a small amount of bornylamine (the *endo* isomer) in the presence of ammonium chloride over both Pd black and 5% Pd–C. Unexpectedly, the *exo* isomer was exclusive over 5% Pd–C in the absence of ammonium chloride.

A high reaction temperature led to the formation of *N*-ethylbornylamines consisting of the *exo* and the *endo* isomers (see Scheme 2).

It is probable that the *N*-ethyl derivatives were formed by the reaction between the *exo* or the *endo* amine isomers and the acetaldehyde formed by the dehydrogenation of ethanol used as the solvent on the catalyst. It is noted that the stereoisomeric composition of the *N*-ethylamines is not much different from that of the amines.

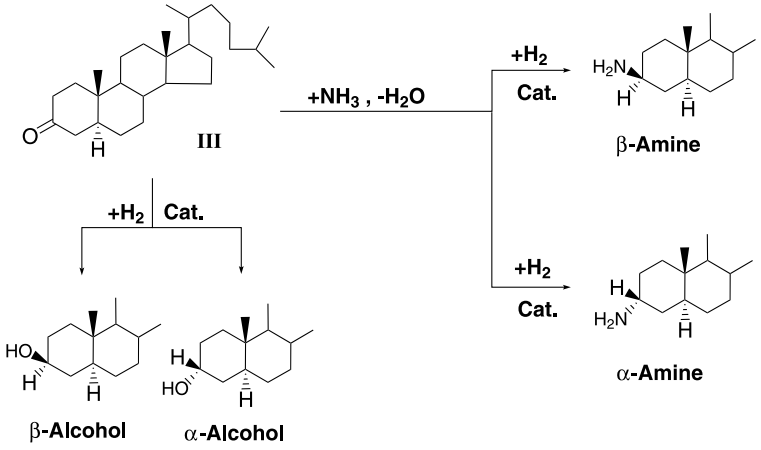
On Ru black and 5% Ru–C, the formation of the primary amine was also increased by the addition of ammonium chloride, while the alcohol was produced largely in the absence of ammonium chloride.

As described previously, the reductive amination of **II** with or without ammonium chloride over 5% Pd–C gave mainly the *exo* isomer. The thermodynamically more stable isomer of the primary amines is likely to be the *endo* isomer.[12] Thus over 5% Pd–C, the unstable *exo* isomer was formed predominantly with or without ammonium chloride. The formation of the *exo* isomer would probably result by the addition of hydrogen preferentially from a less hindered side (*endo* side) to the imine intermediate formed from **II**. On the other hand, the reductive amination of **II** in the presence of ammonium chloride over 5% Ru–C gave almost the same amounts of both the isomers. The formation of the *endo* isomer may be increased by increasing the addition of hydrogen to the more stable half-hydrogenated states of those formed from the imine intermediate.

2.3. The reductive amination of 5α-cholestan-3-one (III)

The reductive amination of **III** proceeded more smoothly under the addition of ammonium chloride than in the absence of the additive. Over Ru black and 5% Ru–C, the production of the alcohol was almost completely depressed by the addition of ammonium chloride.

With respect to the stereoselectivity of the steroid amine formed, the β-amino isomer (see Scheme 3) was obtained in larger amounts than the α-amino isomer (see Scheme 3) over both Pd black and 5% Pd–C.



Scheme 3. Reductive amination of 5α-cholestan-3-one.

Previously, Nishimura and co-workers reported[13] that the hydrogenation of **III** over Pd metal catalyst overwhelmingly gave the β-alcohol isomer. This result has been explained on the basis of an attractive interaction of the steroid α-face with the Pd catalyst. In the reductive amination, the structure of the steroid imine intermediate may be similar to that of **III**. Therefore it is presumed that the addition of hydrogen to the α-side of the steroid imine intermediate may occur predominantly, as in the hydrogenation of **III**.

The reductive amination of III over Ru and 5% Ru–C also gave the β-amino isomer in greater amounts than the α-amino isomer and the selectivity to the β-amino isomer further increased in the presence of ammonium chloride. It is probable that the stereochemistry is controlled more to give the β-amino isomer by the hydrogenation step of the steroid imine which would be produced more rapidly in the presence of ammonium chloride.

3. Experimental

Catalyst. The Pd or Ru metal catalysts were prepared by reducing the corresponding metal hydroxides (1.0 g) in distilled water (20 cm^3) for 30 min at room temperature and under 0.2–0.3 MPa of hydrogen pressure in a Parr hydrogenation apparatus. The metal black thus produced was washed with distilled water until the washing was neutral, and then dried in a desiccator under vacuum at room temperature.

Commercial 5% Pd or Ru on carbon catalysts were purchased from N.E.Chemcat Co., Ltd.

Material. Compound **I** (a purity of over 98%), compound **II** (a purity of over 98%) and compound **III** (a purity of over 97%) were purchased from Wako Pure Chemical Ind., Ltd, Tokyo, Tokyo Kasei Kogyo Co., Ltd Tokyo, and Aldrich Chemical Co., USA, respectively. These compounds in a purity of over 97–98% as judged by gas chromatography were used without further purification.

Reductive amination and analysis of reaction mixtures: A 30 cm^3 autoclave (for reaction of **I**) and a 100 cm^3 autoclave (for reaction of **II** and **III**) of an electromagnetically stirring type were charged with the catalyst (0.01 g of Pd or Ru metal, or 0.2 g of 5% Pd or Ru metal on carbon catalyst), the carbonyl compound [**I** (0.30 g, 2.5×10^{-3} mol), **II** (0.77 g, 5.0×10^{-3} mol), and **III** (0.077 g, 2.0×10^{-4} mol)], and 10–20 cm^3 of the solvent EtOH at an initial hydrogen pressure of 6-8 MPa. The temperature was maintained constant at 50 °C for **I**, at 200 °C for **II** and at 50 °C for **III**, during the reductive amination. Ammonia gas was led into chilled ethanol solvent (10–20 cm^3) through a soda-lime tube from the ammonia bomb and then the amount of ammonia dissolved [about 1.0 g (6.0×10^{-2} mol)] was determined by balance. Ammonium chloride [0.2 g (3.73×10^{-3} mol)] was added to the solvent. After the completion of the reaction, all products were analyzed by gas chromatography (SHIMADZU GC-14A) using a capillary column (25 m for reaction mixture of **I** and **II** and 50 m for reaction mixture of **III**) containing CBP1 and also identified by direct comparison with authentic samples. The temperature was raised to 260 °C at 5 °C/min after holding 60 °C for 20 min for the reaction mixture of **I**. For the reaction mixture of **II**, it was raised to 200 °C at 5 °C/min after holding at 70 °C for 10 minutes. The temperature was maintained constant at 280 °C for the reaction mixture of **III**. The structure of bornylamine (the *endo* isomer), isobornylamine (the *exo* isomer), and α- and β-5α-cholestan-3-amines produced from **II** and **III** were confirmed by GC-MS (JMS-Automass 150, JEOL Ltd, Tokyo) and ^{1}H NMR (Fourier Transform NMR Spectrometer Model R-90H, Hitachi, Ltd, Tokyo). The structure of *N*-ethylbornylamine and *N*-ethylisobornylamine were confirmed by measurements with GC-MS and ^{1}H NMR, and a related study[14] for their analysis. The surface area of Pd metal blacks was measured by SHIMADZU FLOW SORB II 2300, Shimadzu Co., Ltd Tokyo.

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Preparation of complex bridged bicyclic ring systems from 3,3-diacetoxy-2-phenylsulfonylpropene and β-keto esters

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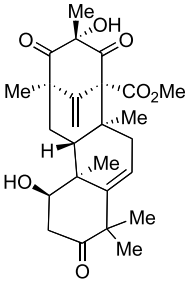
Abstract—The reaction of beta-keto esters with 3,3-diacetoxy-2-phenylsulfonylpropene affords bicyclic keto esters in good yields.

1. Introduction

The number of natural products bearing a phloroglucinol subunit has significantly increased in recent years.[1] Berkeleytrione (**1**) was isolated from *Penicillium* sp. found in the Berkeley Pit Lake in Butte, Montana and exhibits inhibitory activity against matrix metalloproteinase-3 and caspase-1.[2] Preaustinoid A (**2**) was isolated from *Melia azedarach* (Meliaceae) and exhibits broad bacteriostatic effects.[3] Nemorosone (**3**) was recently isolated and shows cytotoxic activity against epithelioid carcinoma (HeLa), epidermoid carcinoma (Hep-2), prostate cancer (PC-3) and central nervous system cancer (U251).[4] As part of a program to synthesize phloroglucinol-containing natural products,[5] we describe a useful synthesis of bridged bicyclic compounds.



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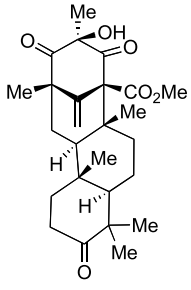

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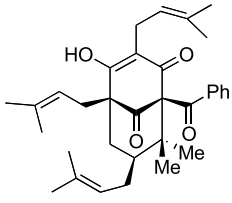

3

In a recent report[6] we described the preparation of bicyclic keto ester **5a** from **4a** by way of the versatile manganese mediated chemistry developed by Snider.[7] Bromination of **5a** with 3.5 equiv of NBS led to the isolation of bromo enone **6** in 55% yield. This reaction involves the intermediacy of a tribromide. Unfortunately, all attempts to produce **5b** from **4b** led only to undesired products (Scheme 1).

Michael addition of acrolein to **4c** led mainly to recovered **4c** plus polymeric products. The use of lower temperatures and radical inhibitors[8] failed to generate a bicyclic compound. This is in contrast to the successful Michael addition/intramolecular aldol reaction with acrolein and carbomethoxy cyclohexanone and is undoubtedly due to the steric hindrance of the geminal dimethyl group. Padwa has developed innovative methodology using sulfones as Michael acceptors.[9] We prepared annulation reagent **7** with the idea of performing two successive Michael additions to form a bridged bicyclic system followed by reductive elimination of the sulfone to generate a double bond. The three-step synthesis of **7** began with commercially available 3,3-diacetoxypropene. Addition of phenylsulfenyl chloride followed by oxidation of the sulfide with 2 equiv of MCPBA and elimination using diisopropylethylamine provided sulfone **7** in 80% overall yield on a 50 mmol scale (Scheme 2).

The Michael addition reaction of **7** was investigated with **4c**. Reaction of **4c** with 1 equiv of sodium hydride in THF at 25 °C followed by the addition of sulfone **7** furnished a 71% isolated yield of adduct **8** as one diastereomer by proton NMR. The stereochemistry of the methyl group relative to the quaternary center was not established since the next step would generate a bicyclic keto ester. Similarly, adducts **9–13** were generated. The *E*-stereochemistry of beta-acetoxy sulfone **8** was determined by a NOESY experiment (Scheme 3).

Cyclization of keto sulfone **8** using 1 equiv of potassium *tert*-butoxide at ambient temperature produced three

Keywords: β-Keto esters; *Penicillium*; Michael addition.
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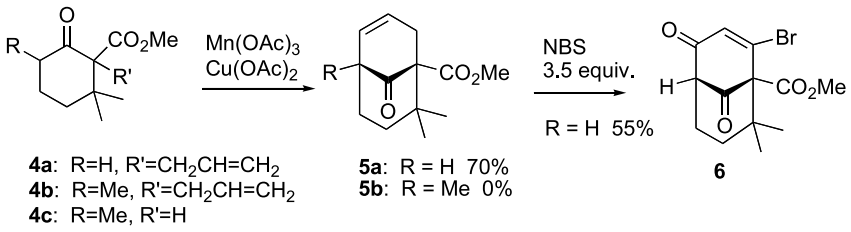
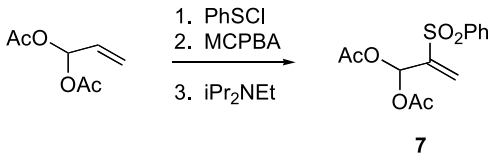


Scheme 1.

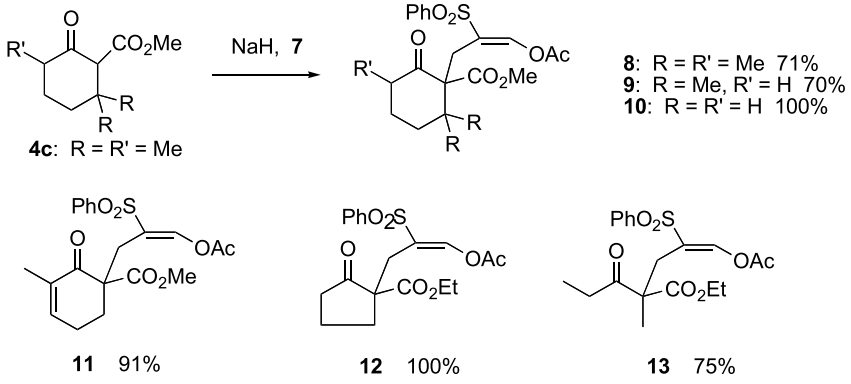


Scheme 2.

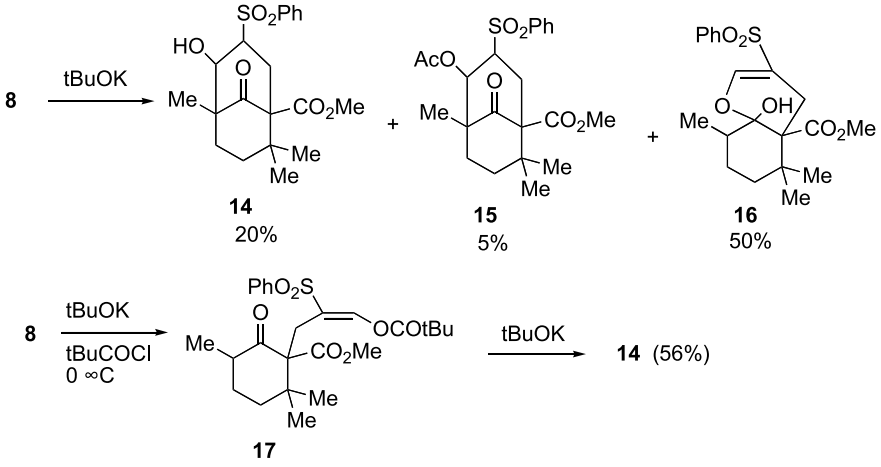
products, esters **14**, **15** and **16** in 20, 5 and 50% yields, respectively. The major product **16** was derived from the deacetylation of **8**. In order to enhance the yield of the cyclization products, acetate **8** was converted into pivalate **17** with potassium *tert*-butoxide followed by pivaloyl chloride at 0 °C in 80% yield. Reaction of **17** with potassium *tert*-butoxide in THF from 0 °C to room temperature afforded a 56% isolated yield of **14**, as a 1:0.8 mixture of hydroxy sulfone diastereomers (Scheme 4).

Cyclization of **9** also suffered from the labile acetoxy group. Initially, sulfone **9** was converted into tosylate **18** using potassium *tert*-butoxide and *para*-toluenesulfonyl chloride at 0 °C. Cyclization of **18** with potassium *tert*-butoxide afforded divinyl ether **20** in 90% yield. Sulfone **9** was then converted into pivalate ester **19** and cyclized to **21** (one diastereomer based on proton NMR) in 57% yield with KH in THF at 0 °C (Scheme 5).

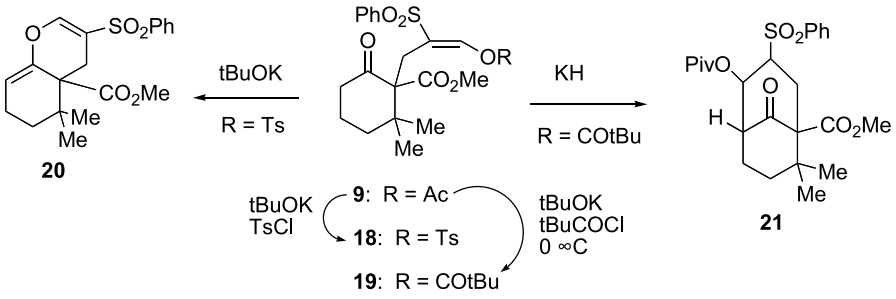
In view of the problems with acetate **9** and tosylate **18**, sulfones **10** and **11** were transformed directly into the pivalates and cyclized with potassium hydride in 40 and 83% yields, respectively. Interestingly, the reaction of the pivalate derived from **11** with potassium hydride gave a product derived from hydride addition to the enone system followed by cyclization to pivalate **23**, as one diastereomer based on proton NMR, in 83% yield (Scheme 6).



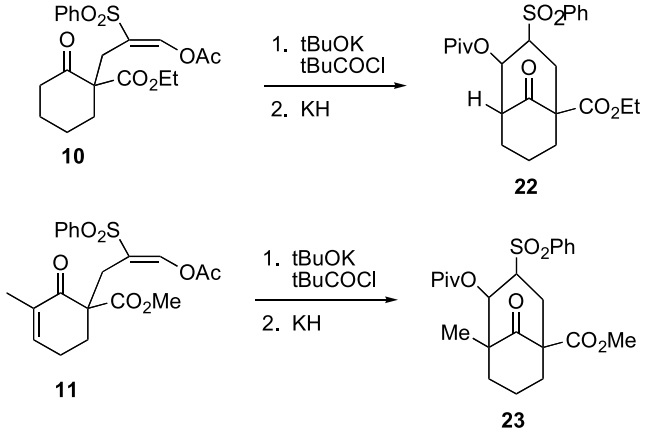
Scheme 3.



Scheme 4.

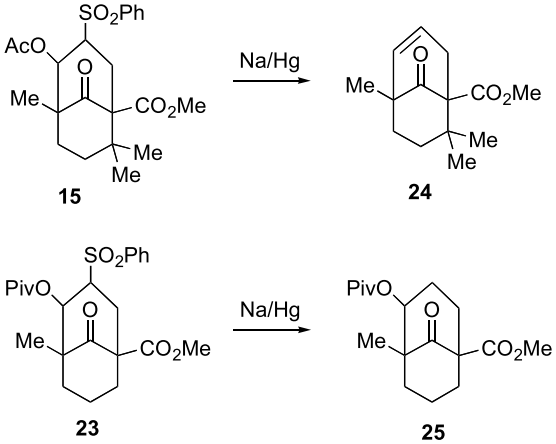


Scheme 5.



Scheme 6.

Acetoxy sulfone **15**, produced from alcohol **14** in 95% yield by acetylation with acetic anhydride and DMAP in methylene chloride at 25 °C, can be converted into the alkene **24** using sodium amalgam in MeOH in 57% yield.[10] Product **24** contains the bridgehead methyl group and bridgehead ester group present in **1** and **2**. Interestingly, pivalate **23** provided only desulfonated product **25** in 80% yield (Scheme 7).



Scheme 7.

In summary, the reaction of diacetoxy sulfone **7** with beta-keto esters provides a useful synthetic method for the preparation of complex bicyclic systems. The reactions are operationally convenient and amenable to scale up to produce gram quantities of bicyclic compounds.

2. Experimental

2.1. General

2.1.1. 3,3-Diacetoxy-2-phenylsulfonylpropene (7). To a mechanically stirred suspension of 6.8 g (0.05 mol) of *N*-chlorosuccinimide in 60 mL of dry methylene chloride at room temperature in a 250 mL flask equipped with a pressure-equalizing dropping funnel and an efficient condenser was added about 0.5 g of a total of 5.5 g (0.05 mol) of thiophenol. The mixture was then gently heated on a steam bath for 1–2 min until sulfenyl chloride formation commenced as evidenced by the intense orange coloration of the suspension. Once initiated, the remaining thiophenol was added dropwise at a rate sufficient to maintain the solvent at reflux. When the addition was complete (usually about 30 min were required), the homogeneous orange solution was stirred at room temperature for an additional 30 min. The suspension was then cooled to 0 °C and 8.7 g (0.055 mol) of 1,1-diacetoxy-2-propene was added in one portion. The mixture was then maintained at 0 °C until complete decoloration of the sulfenyl chloride suspension was observed (2 h). After warming to room temperature, the colorless suspension was filtered to remove the majority of the succinimide. Concentration of the combined filtrate and wash left a pale yellow oil which was diluted with 30 mL of hexane to precipitate the remainder of the succinimide. This suspension was let stand 1 h and then filtered, and the filtrate was evaporated to dryness which was pure enough to be used without further purification ^{1}H NMR (300 MHz, $CDCl_3$) 7.53–7.49 (m, 2H), 7.38–7.31 (m, 3H), 7.14 (d, $J=3.6$ Hz, 1H), 3.84–3.68 (m, 2H), 3.63–3.58 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H).

To a stirred solution of 4.4 g (0.02 mol) of chloro sulfide prepared above in 25 mL of dry methylene chloride, cooled to 0 °C under nitrogen, a solution of 2.2 equiv of *m*-chloroperbenzoic acid in 50 mL of methylene chloride was added dropwise. When the addition was complete, the mixture was stirred an additional 20 min and then filtered to remove the majority of the chlorobenzoic acid, which was washed with 30 mL of methylene chloride. The combined filtrate and wash was diluted with 50 mL of methylene chloride and then washed successively with 10% NaHCO3 (50 mL), 10% NaHSO3 (50 mL), 10% NaHCO3 again (50 mL), and saturated brine and finally dried (MgSO4), which was pure enough to be used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.94 (m, 2H),

7.76–7.60 (m, 3H), 7.23 (d, $J=3.0$ Hz, 1H), 4.17–3.94 (m, 2H), 3.88–3.83 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H).

A solution of 1.3 mL (7.5 mmol) of diisopropylethylamine in 50 mL of dry methylene chloride was added dropwise, under a nitrogen atmosphere, to a stirred solution of 2.3 g (6.9 mmol) of chlorosulfone at -10 °C. The reaction temperature was maintained at 0 °C for 2 h, then diluted with 40 mL of methylene chloride, washed with 25 mL each of chilled 1 N HCl, water, and brine, and finally dried over anhydrous magnesium sulfate. Crystallization with diethyl-ether/hexane gave compound **7** as a white solid, mp 72–73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92–7.89 (m, 2H), 7.69–7.54 (m, 3H), 7.39 (s, 1H), 6.75 (s, 1H), 6.36 (s, 1H), 1.96 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.95, 145.84, 139.68, 134.05, 129.53, 129.43, 128.55, 84.90, 20.61; HRMS (EI) *m/z* ($M-CH_3CO_2$) calcd for 239.03781, found 239.03830.

2.2. General procedure for Michael addition to 7

Keto ester (1 mmol) was added dropwise to the solution of sodium hydride (1 mmol) in THF (10 mL). After 20 min sulfone **7** (1 mmol) was added in one portion and stirred for another 1 h. The resulting mixture was neutralized with AcOH, which was dissolved in 20 mL of ether. The ether layer was washed with brine and dried over anhydrous $MgSO_4$. The crude material was purified by column chromatography.

2.2.1. Compound 8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, $J=3.3$ Hz, 1H), 7.88 (d, $J=7.8$ Hz, 2H), 7.67–7.52 (m, 3H), 3.67 (s, 3H), 3.31 (d, $J=16.8$ Hz, 1H), 2.90 (d, $J=16.8$ Hz, 1H), 2.23 (s, 3H), 1.87–1.34 (m, 4H), 0.92 (s, 6H), 0.74 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.44, 169.59, 166.20, 145.45, 139.58, 133.78, 129.58, 128.27, 123.20, 65.43, 51.43, 42.46, 40.53, 36.20, 30.56, 28.73, 26.28, 25.55, 20.75, 15.27; HRMS (EI) *m/z* calcd for 436.15558, found 436.15630.

2.2.2. Compound 9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.91 (d, $J=7.5$ Hz, 2H), 7.64–7.51 (m, 3H), 3.46 (s, 3H), 2.65–2.50 (m, 2H), 2.33–1.21 (m, 6H), 2.02 (s, 3H), 0.91 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.50, 170.76, 165.72, 142.24, 139.73, 133.47, 129.16, 128.04, 125.55, 66.73, 51.65, 44.17, 39.17, 36.25, 26.72, 26.62, 22.75, 22.53, 20.37; HRMS (EI) *m/z* calcd for 422.13993, found 422.14080.

2.2.3. Compound 10. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.87–7.83 (m, 2H), 7.63–7.50 (m, 3H), 4.26–4.17 (m, 2H), 2.90–2.76 (m, 2H), 2.52–1.56 (m, 8H), 2.20 (s, 3H), 1.32–1.24 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.27, 170.67, 165.89, 146.91, 139.82, 133.49, 129.30, 128.07, 124.08, 61.69, 59.98, 40.62, 35.11, 28.89, 27.07, 22.39, 20.59, 13.98; HRMS (EI) *m/z* calcd for 408.12428, found 408.12500.

2.2.4. Compound 11. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.81–7.76 (m, 2H), 7.58–7.43 (m, 3H), 6.57 (br s, 1H), 3.62 (s, 3H), 3.99 (d, $J=15.6$ Hz, 1H), 2.75 (d, $J=15.6$ Hz, 1H), 2.45–2.19 (m, 2H), 2.13 (s, 3H), 1.95–1.88 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.93, 171.22, 166.06, 146.92, 144.91, 139.65, 134.81, 133.71, 129.46, 128.30, 124.10, 56.08, 52.81, 30.20, 28.93, 23.67, 20.69, 16.84, 14.34.

2.2.5. Compound 12. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.87–7.83 (m, 2H), 7.64–7.51 (m, 3H), 4.19–4.08 (m, 2H), 3.09 (d, $J=15.6$ Hz, 1H), 2.63 (d, $J=15.6$ Hz, 1H), 2.39–2.30 (m, 2H), 2.22 (s, 3H), 2.03–1.91 (m, 2H), 1.21 (t, $J=6.9$ Hz 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.17, 171.14, 166.03, 146.31, 138.85, 133.79, 129.42, 128.49, 124.00, 62.00, 59.04, 37.53, 31.92, 27.70, 20.65, 19.86, 14.11.

2.2.6. Compound 13. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.84–7.81 (m, 2H), 7.63–7.49 (m, 3H), 4.28–4.09 (m, 2H), 3.05 (d, $J=15.6$ Hz, 1H), 2.84 (d, $J=15.6$ Hz, 1H), 2.61–2.2.45 (m, 2H), 2.20 (s, 3H), 1.33 (s, 3H), 1.27 (t, $J=7.2$ Hz, 3H), 1.06 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.45, 172.38, 166.02, 146.66, 139.27, 133.68, 129.38, 128.37, 124.22, 61.95, 58.62, 31.64, 28.75, 20.69, 18.64, 14.08, 8.365.

2.3. Procedure for cyclizations using *t*-BuOK

To a stirred solution of keto ester (1 mmol) in THF (10 mL) was added *t*-BuOK (1 mmol) in one portion at 0 °C. The mixture was stirred overnight at room temperature and dissolved in 20 mL of ether. The ether layer was washed with 10% aq. HCl, brine and dried over anhydrous $MgSO_4$. The crude material was purified by column choromatography.

2.3.1. Compound 14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.89 (m, 2H), 7.76–7.54 (m, 3H), 4.52 (d, $J=10.5$ Hz, 1H), 3.85 (s, 1H), 3.48 (s, 3H), 3.13–3.03 (m, 1H), 2.05–1.25 (m, 6H), 1.12 (s, 6H), 1.04 (s, 3H), 0.93(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.94, 170.13, 136.07, 134.92, 129.81, 129.35, 74.31, 66.17, 64.63, 52.29, 51.27, 42.93, 37.81, 29.30, 28.41, 26.48, 25.54, 20.90; HRMS (EI) *m/z* calcd for 394.14501, found 394.14570.

2.3.2. Compound 15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.83 (m, 2H), 7.71–7.56 (m, 3H), 5.62 (d, $J=11.4$ Hz, 1H), 3.68 (s, 3H), 3.45–3.33 (m, 1H),), 2.76 (dd, $J=14.7$, 4.8 Hz, 1H), 2.47 (d, $J=14.4$ Hz, 1H), 2.17–1.96 (m, 2H), 1.77–1.71 (m, 1H), 1.64 (s, 3H), 1.31–1.26 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.80, 170.86, 169.78, 139.47, 134.07, 129.50, 128.33, 74.83, 62.99, 61.07, 52.31, 49.84, 43.76, 38.08, 33.74, 26.59, 24.58, 22.87, 20.30, 17.63.

2.3.3. Compound 16. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.62–7.49 (m, 3H), 7.49 (d, $J=1.8$ Hz, 1H), 6.88 (d, $J=2.1$ Hz, 1H), 3.19 (s, 3H), 2.82–2.61 (m, 2H), 1.82–1.23 (m, 5H), 1.11–0.89 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.63, 152.20, 140.44, 132.87, 129.11, 127.55, 112.56, 105.36, 52.65, 52.22, 38.37, 36.04, 34.54, 27.70, 27.46, 25.60, 24.99, 13.39; HRMS (EI) *m/z* calcd for 394.14501, found 380.97603.

2.3.4. Compound 20. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2H), 7.65–7.52 (m, 3H), 7.46 (d, $J=2.4$ Hz, 1H), 5.59 (t, $J=4.2$ Hz, 1H), 3.28 (s, 3H), 2.82 (d, $J=15.6$ Hz,

1H), 2.33 (dd, $J=15.6$, 2.4 Hz, 1H), 2.17–2.09 (m, 2H), 1.63–1.55 (m, 1H), 1.33–1.28 (m, 1H), 0.98 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.44, 150.63, 147.13, 140.34, 133.15, 129.22, 127.92, 115.84, 109.73, 52.19, 51.04, 35.47, 33.90, 25.63, 24.23, 20.29; HRMS (EI) *m/z* calcd for 362.11880, found 362.11940.

2.4. Procedure for cyclizations using KH

To a stirred solution of potassium hydride (1 mmol) in THF (10 mL) was added diketone (1 mmol). The mixture was stirred overnight at room temperature and dissolved in 20 mL of ether. The ether layer was washed with 10% aq. HCl, brine and dried over anhydrous $MgSO_4$. The crude material was purified by column choromatography.

2.4.1. Compound 21. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2H), 7.72–7.56 (m, 3H), 5.40 (d, $J=10.8$ Hz, 1H), 4.12–4.00 (m, 2H), 3.49–3.39 (m, 1H),), 2.48–1.80 (m, 6H), 1.27–1.21 (m, 1H), 1.15–1.06 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.06, 177.39, 170.00, 138.41, 134.41, 129.68, 128.70, 73.82, 62.92, 61.18, 60.78, 54.22, 44.08, 38.71, 33.95, 28.62, 28.44, 27.00, 24.71, 22.73, 14.14; HRMS (EI) *m/z* calcd for 478.20253, found 478.20310.

2.4.2. Compound 22. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94–7.89 (m, 2H), 7.73–7.57 (m, 3H), 5.54 (dd, $J=10.5$ Hz, 0.9 Hz, 1H), 4.27–4.11 (m, 3H), 3.46–3.36 (m, 1H), 3.01–2.75 (m, 2H), 2.32 (br s, 1H), 2.28–1.51 (m, 6H), 1.18 (t, $J=10.2$ Hz 3H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.27, 177.41, 171.28, 138.23, 134.44, 129.69, 128.82, 73.26, 61.97, 60.19, 56.39, 55.01, 38.73, 38.06, 34.17, 29.03, 26.99, 17.70, 14.23; HRMS (EI) *m/z* calcd for 450.17123, found 450.17200.

2.4.3. Compound 23. Mp 168–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, $J=8.4$ Hz, 2H), 7.71–7.54 (m, 3H), 5.51 (d, $J=1.5$ Hz, 1H), 3.73 (s, 3H), 2.88 (br s, 1H), 2.67 (d, $J=$ 12.3 Hz, 1H), 2.49 (dd, $J=12.3$, 1.8 Hz, 1H), 2.31–1.81 (m, 6H), 1.27 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.59, 176.57, 170.40, 136.35, 134.57, 129.64, 129.48, 72.68, 65.73, 58.61, 55.46, 52.67, 39.45, 38.79, 31.21, 28.86, 26.81, 16.53, 15.14; HRMS (EI) *m/z* calcd for 450.17123, found 450.17190.

2.5. General procedure for pivaloyl group substitution

To a stirred solution of diketone (1 mmol) in THF (10 mL) was added *t*-BuOK (2 mmol) in one portion at 0 °C. The reaction temperature was maintained at 0 °C for 1 h, then trimethylacetyl chloride (2 mmol) was added. The resulting mixture was neutralized with AcOH, which was dissolved in 20 mL of ether. The ether layer was washed with brine and dried over anhydrous $MgSO_4$. The crude material was purified by column choromatography.

2.5.1. Compound 17. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, $J=0.9$ Hz, 1H), 7.84 (d, $J=8.7$ Hz, 2H), 7.62–7.49 (m, 3H), 3.65 (s, 3H), 3.21 (dd, $J=15.6$, 0.9 Hz, 1H), 2.99 (d, $J=15.6$ Hz, 1H), 2.04–1.38 (m, 4H), 1.25 (s, 9H), 1.00–0.95 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.02, 173.77, 170.68, 147.20, 140.17133.47, 129.30, 128.09, 124.61, 66.63, 51.52, 41.98, 41.23, 39.11, 36.17, 29.92, 27.53, 26.69, 26.26, 25.45, 15.41; HRMS (EI) *m/z* calcd for 478.20253, found 478.20320.

2.5.2. Compound 19. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.91 (d, $J=7.8$ Hz, 2H), 7.64–7.51 (m, 3H), 3.51 (s, 3H), 3.21–3.10 (m, 1H), 2.88 (dd, $J=15.9$, 1.2 Hz, 1H), 2.57 (d, $J=15.9$ Hz, 1H), 2.38–2.32 (m, 1H), 2.11–2.00 (m, 1H), 1.90–1.67 (m, 2H), 1.34–1.28 (m, 1H), 1.21 (s, 9H), 1.10 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.40, 174.50, 170.19, 145.62, 140.27, 133.29, 129.10, 128.18, 125.34, 67.25, 51.65, 43.79, 40.02, 39.13, 36.56, 26.74, 24.93, 22.86, 22.49; HRMS (EI) *m/z* calcd for 464.18688, found 464.18760.

2.6. Procedure for tosyl group substitution

To a stirred solution of diketone 9 (422 mg, 1 mmol) in THF (10 mL) was added *t*-BuOK (224 mg, 2 mmol) in one portion at 0 °C. The reaction temperature was maintained at 0 °C for 1 h, then *p*-toluenesulfonyl chloride (381 mg, 2 mmol) was added. The resulting mixture was neutralized with AcOH, which was dissolved in 20 mL of ether. The ether layer was washed with brine and dried over anhydrous $MgSO_4$. The crude material was purified by column choromatography.

2.6.1. Compound 18. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92–7.39 (m, 10H), 3.49 (s, 3H), 2.49 (s, 3H), 2.09–1.53 (m, 6H), 1.26–1.11 (m, 2H), 0.86 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.06, 169.82, 146.56, 143.13, 139.22, 133.60, 131.51, 130.15, 129.14, 128.51, 127.98, 126.70, 66.52, 51.78, 43.93, 38.85, 36.05, 26.50, 26.48, 22.49, 22.42, 21.90; HRMS (EI) *m/z* calcd for 534.13821, found 534.13900.

2.7. Procedure for aceoxysulfone elimination

The diketone 15 (43.6 mg, 0.1 mmol) in methanol (1 mL) and ethylacetate (0.5 mL) was stirred at 0 °C with 5% sodium amalgam. After 3 h, the mixture was poured into water (5 mL) and extracted with ether three times. The combined organic layer washed with brine and dried over anhydrous $MgSO_4$. The crude material was purified by column choromatography.

2.7.1. Compound 24. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dt, $J=9.3$, 3.6 Hz, 1H), 5.29 (d, $J=9.3$, 1H), 3.71 (s, 3H), 3.13–2.83 (m, 2H), 2.06–1.52 (m, 3H), 1.24–1.167 (m, 1H), 1.11 (s, 3H), 1.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.70, 171.64, 132.74, 127.86, 64.83, 51.86, 46.23, 42.73, 36.89, 36.20, 35.02, 25.46, 25.06, 21.85; HRMS (EI) *m/z* calcd for 236.14124, found 236.14170.

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Palladium-catalyzed homocoupling of aryl halides in the presence of fluoride

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Abstract—This report describes the fluoride-mediated homocoupling of aryl iodides and bromides catalyzed by palladium(0). This coupling protocol is tolerant of electron-donating and electron-withdrawing substitutents on the aryl halide, as well as *ortho* substitution. Optimum reaction conditions entail 10 mol% $Pd(dba)_2$, 3 equiv of tetrabutyl ammonium fluoride (TBAF) in DMF at 90 °C.

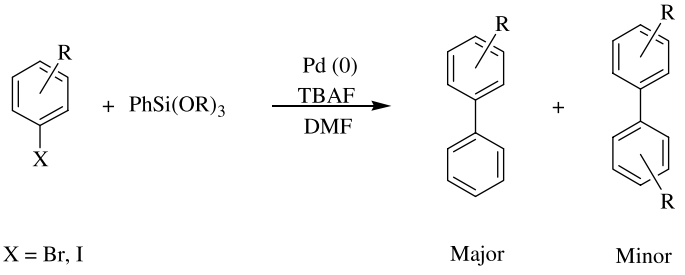
1. Introduction

Reductive dimerization of aryl halides is one of the venerable methods for the preparation of symmetrical biaryls. This reaction was first observed by Ullmann, over one hundred years ago.[1–3] The Ullmann reaction typically involves the homocoupling of an aryl halide mediated by a stoichiometric amount of copper at very high (>200 °C) temperatures. Improvements to this method have emerged in recent years which utilize other transition metals, including palladium and nickel, under milder conditions to affect the desired coupling reactions.[4–8] Other variants have utilized zinc as a reducing agent to regenerate a palladium(0) catalyst.[9–14] Under these conditions, homocoupling can be achieved at room temperature.

Our laboratory has focused on the palladium-catalyzed heterocoupling of aryl halides,[15–18] and triflates,[19,20] with aryl siloxanes (Hiyama coupling)[21] in the presence of tetrabutylammonium fluoride (TBAF) to form unsymmetrical biaryls (Scheme 1). During these studies, a minor biaryl by-product was observed arising from homocoupling of the aryl halide. This homocoupled by-product has been observed previously in other varients of the Hiyama coupling.[22,23] Optimization of the coupling reaction allowed for the exclusive formation of the desired heterocoupled product. However, we thought that it would also be possible to refine conditions that would facilitate the formation of the homocoupling product. This report details these studies and explores the scope and limitations of this homocoupling reaction.

2. Results and discussion

Fluoride-mediated homocoupling of aryl halide derivatives is not unprecedented.[4] In addition, Lemaire reported a tetrabutylammonium bromide promoted homocoupling



Scheme 1. Palladium-catalyzed cross-coupling of aryl siloxanes with aryl halides.

Keywords: Tetrabutylammonium fluoride; Aryl homocoupling; Ullmann coupling.
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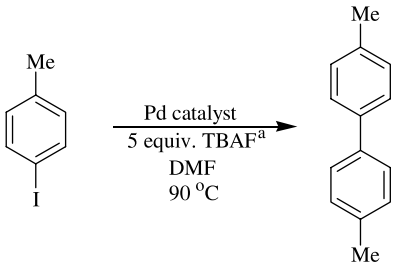
reaction catalyzed by palladium acetate.[24] Albanese has reported that electron deficient aryl iodides and bromides undergo homocoupling in the presence of TBAF and Pd catalysts.[4] However, in Albanese's study, the number of substrates studied was limited in number (seven examples), and was confined to electron-withdrawing substituents. In addition, *ortho*-substituted derivatives were reported to fail as coupling reagents. By comparison, in this study, we have investigated the scope and limitations of the coupling reaction and provide a protocol that will promote homocoupling of both electron-rich and electron-deficient arenes, including *ortho*-substituted derivatives.

Preliminary studies found that treatment of bromobenzene (or iodide) with 1.5 equiv of TBAF in the presence of 10 mol% $Pd(dba)_2$ gave biphenyl in modest yield. In addition, homocoupling only occurred when TBAF and Pd catalyst were present. For example, in the absence of fluoride, but in the presence of palladium, no homocoupled product was obtained. With these results in hand, experiments were conducted to optimize the reaction conditions for the homocoupling methodology and the results are summarized in Table 1.

Table 1. Optimization of the reaction conditions



Entry	Pd catalyst (mol%)	Phosphine (mol%)	Yield (%)[b]
1	$Pd(dba)_2$ (10)		92
2	$Pd(dba)_2$ (5)		27
3	$Pd(dba)_2$ (10)	PPh_3 (10)	43
4	$Pd(dba)_2$ (10)	PPh_3 (20)	54
5	$Pd(OAc)_2$ (10)		0[c]
6	$Pd(OAc)_2$ (10)	PPh_3 (10)	47
7	$Pd(OAc)_2$ (10)	PPh_3 (20)	58
8	$[Pd(allyl)Cl]_2$ (10)		0[d]
9	$[Pd(allyl)Cl]_2$ (10)	PPh_3 (10)	67
10	$[Pd(allyl)Cl]_2$ (10)	PPh_3 (20)	88

[a] 1.0 M TBAF in THF from Aldrich.
[b] Isolated yield.
[c] Starting material recovered unchanged.
[d] All starting material was reduced.

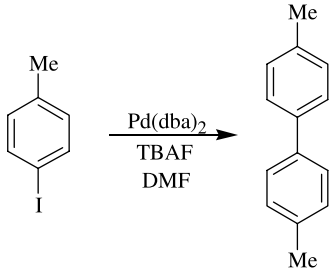
Under optimum conditions, *para*-iodotoluene underwent homocoupling in the presence of 5 equiv of fluoride in 92% isolated yield to generate the symmetrical biaryl (entry 1). Decreased yields of biaryl were obtained when the reaction was conducted in THF. The most obvious conclusions from the optimization studies were: (1) using $Pd(dba)_2$ as catalyst, that catalyst loading was critical to the yield of homocoupling (compare entries 1 and 2), and (2) that the presence of phosphine had a strongly deleterious effect on the reaction. What was unexpected from our studies was that allyl palladium chloride dimer was an inappropriate catatlyst with iodotoluene, giving no coupling product in the absence of phosphine. In the Albanese study,[4] allyl palladium chloride dimer (without phosphine!) was the catalyst of choice. Subsequent homocoupling experiments with $Pd(dba)_2$ indicated that this was the preferred catalyst in the homocoupling protocol. It was necessary to add a Pd(0) source to initiate the reaction, as no homocoupling was observed using Pd(II) (entry 5). However, palladium(0) could be generated in situ to effect moderate homocoupling (entries 6 and 7).[25,26]

As noted above, the addition of phosphine to $Pd(dba)_2$ significantly reduced the yield of homocoupled product (entries 3 and 4). The use of allyl palladium chloride dimer ($[Pd(\pi\text{-allyl})Cl]_2$) as catalyst gave anomolous results: in the absence of phosphine, all the aryl halide was reduced (entry 8). This is in contrast to the other Pd(II) catalyst (entry 5), which did not reduce the aryl halide. Increasing the mol% of phosphine led to an increase in the yield of homocoupled product (entries 8–10), presumably due to the reduction of Pd(II) to Pd(0) by the phosphine. The addition of phosphine moderates the activity of the catalyst, preventing the reduction pathway and favoring homocoupling. Despite similar yields of biaryl product for $Pd(dba)_2$ (entry 1) and $[Pd(\pi\text{-allyl})Cl]_2$: $2PPh_3$ (entry 10), the single component catalyst was used in the subsequent studies.

The homocoupling reaction of *p*-iodotoluene could be accomplished equally well using either a 1.0 M solution of TBAF in THF (Aldrich, ca. 5% H_2O) or crystalline $TBAF\cdot 3H_2O$ as the fluoride source. Apparently under these conditions, the small amount of water present in the fluoride reagent had no effect on the yield of the homocoupling reaction. This result is in stark contrast to the Albanese report which states that water must be rigorously excluded from the homocoupling if high yields of biaryl are to be obtained.

Having realized the optimum catalyst for the reaction, attention turned to evaluation of the optimum number of

Table 2. Yield of biaryl based on equivalents of TBAF in the homocoupling reaction[a]



Entry	Equivalents of TBAF	Yield (%)[b]
1	0	0
2	1	41
3	2	40
4	3	93
5	4	91
6	5	96
7	10	79

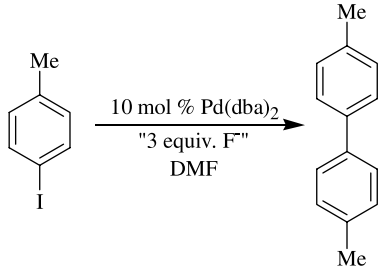
[a] Reactions were performed at 90 °C for 12 h. Mass balance is unreacted starting material.
[b] Isolated yield.

equivalents of TBAF to effect the homocoupling reaction. The results are presented in Table 2.

No homocoupling was observed in the absence of TBAF irrespective of the catalyst employed (entry 1). Increasing the equivalents of TBAF from one to three improved the yield of coupled product from 77 to 93%; however, there is no increase in the yield of biaryl until the addition of 10 equiv of TBAF, where the yield decreases. The TBAF used in these studies was added as a 1.0 M solution in THF. The decrease in yield at 10 equiv of TBAF is attributed to the large volume of THF that is also present, as earlier results had shown THF to be a poor solvent for the coupling reaction. Accordingly, if crystalline TBAF trihydrate is employed at 10 equiv, then no reduction in yield is observed (data not shown).

The next aspect of the reaction that was investigated was the source of the fluoride ion. It was thought that it might be possible to utilize an inexpensive alkali fluoride salt as an alternative to TBAF for the homocoupling reaction. As a result, a variety of fluoride salts were examined and the data is summarized in Table 3.

Table 3. Use of alkali fluoride salts in the palladium-catalyzed homocoupling reaction



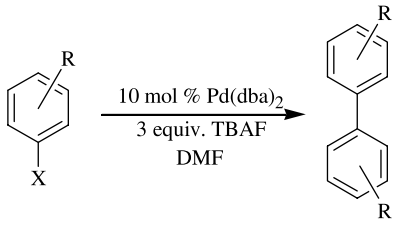
Entry	'F$^-$ source'	Yield (%)[a]
1	LiF	0[b]
2	NaF	0[b]
3	KF	0[b]
4	CsF	93[c] (37)[d]
5	TBAF·3H$_2$O	94
6	TMAF·4H$_2$O	92

[a] Isolated yield.
[b] Starting material was recovered unchanged.
[c] 10 equiv of CsF were added.
[d] 3.0 equiv of CsF were used. Remainder of starting material was recovered unchanged.

In most cases, the fluoride salts tested proved ineffective at promoting the homocoupling reaction (entries 1–3). In the case of CsF, however, moderate homocoupling was observed using three equivalents (entry 4). When the number of equivalents of CsF was increased to ten, homocoupling was observed to proceed in excellent yield. The successful homocoupling observed with CsF may be due to its higher solubility in DMF than the other alkali fluoride salts. Finally, crystalline TBAF trihydrate and tetramethylammonium fluoride (TMAF) affected the homocoupling reaction in a yield comparable to that of the 1.0 M TBAF solutions in THF (entries 5 and 6). Because of the large number of equivalents of CsF required to promote the homocoupling reaction, it was decided to use TBAF as the fluoride source in subsequent studies.

Finally, having determined the optimum conditions for the fluoride promoted homocoupling reaction, the scope and limitations of the homocoupling protocol was determined by employing a systematic investigation of the electronic and steric effects of substituents on the coupling reaction. The results of this study are presented in Table 4.

Table 4. Substituent effects in the homocoupling reaction[a]



Entry	X	R	Yield (%)[b]
1	I	H	86
2	I	4-Ac	78
3	I	4-OMe	93
4	I	2-OMe	89
5	I	2-NO$_2$	0[c]
6	I	4-Cl	68
7	Br	4-OMe	88
8	Br	2-OMe	72
9	Br	4-CN	0[c]
10	Br	4-CO$_2$Me	64[d]
11	Br	2-CO$_2$Me	0[c]
12	Br	4-Ac	88
13	Br	4-Me	82
14	Br	2,6-Dimethyl	0[e]
15	Br	2,6-Dimethoxy	0[e]
16	Br	2,3,4-Trimethoxy	63[d]
17	Br	I-Napthyl	84

[a] Reactions were performed at 90 °C for 12 h.
[b] Isolated yield.
[c] Starting material was reduced.
[d] Remainder of starting material was reduced.
[e] Starting material recovered.

In general, the reaction is tolerant of both electron-rich and electron-deficient aryl iodides and bromides. However, the presence of a nitro substituent resulted in the iodide being reduced (entry 5, compare with Albanese).[4] Acetyl (entries 2 and 12), chloro (entry 6) and carboxy methyl (entry 10) moieties coupled to provide symmetrical biaryls in modest to good yields. *Ortho*-substituted halides were found to couple efficiently (entries 4 and 8) including the electron-rich 2,3,4-trimethoxybromobenzene (entry 16). Di-*ortho* substitution was not tolerated (entries 14 and 15).

The results presented in Table 4 compare favorably to those obtained by Lemaire in his tetrabutylammonium bromide promoted, palladium-catalyzed homocoupling reaction of electron-donating and -deficient aryl iodides and bromides.[24] The contrast between our results and those previously reported by Albanese is likely due to the differences in catalyst and solvent employed as well as the source of TBAF. Our results clearly show that allyl palladium chloride dimer, the catalyst in Albanese's study, to be a poor catalyst for the generation of homocoupled

product. The Albanese study observed also a significant detrimental effect when hydrated TBAF was employed, as opposed to anhydrous TBAF. This may partially account for the poor activity of allyl palladium chloride (Table 1, entry 8) in our studies, as we made no attempt to dehydrate the TBAF. However, simply switching the catalyst to $Pd(dba)_2$ resulted in an excellent yield of homocoupled product, making the synthesis of anhydrous TBAF unnecessary.

In summary, a protocol for the homocoupling of aryl bromides and iodides has been developed that is based on palladium-catalyzed, fluoride-mediated reaction conditions. Unlike previous studies,[4] this protocol will function with both electron-rich and electron-deficient aryl substrates and gives good to excellent yields of biaryl product. Rigorous exclusion of water from the reaction was not necessary, and *ortho*-substitution was well tolerated. The application of this methodology to natural product total synthesis will be reported in due course.

3. Experimental

3.1. General experimental

Thin-layer chromatography (TLC) was performed on 0.25 mm Merck silica gel coated plates treated with a UV-active binder with compounds being identified by one or more of the following methods: UV (254 nm), vanillin/sulfuric acid charring. Flash chromatography was performed using thick walled columns and medium pressure silica gel (Whatman 200–425 mesh). Melting points were taken in Kimax soft glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406K) equipped with a calibrated thermometer. Melting points are corrected. Infrared spectra band positions are reported in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak). Nuclear magnetic resonance (400 MHz for ^1H, 100 MHz for ^{13}C) chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS). Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Dimethylformamide was distilled from calcium sulfate under reduced pressure and stored over molecular sieves. Bis(dibenzylideneacetone)palladium ($Pd(dba)_2$), and tetrabutyl ammonium fluoride (1 M solution in THF) were purchased from Aldrich and used as received. All glassware used in these reactions was either oven dried at 120 °C for 12 h or flame dried prior to use. All reactions were conducted under an atmosphere of argon. All compounds were determined to be >95% pure by ^1H NMR or GC analysis, unless otherwise noted. Previously reported compounds were characterized via ^1H and ^{13}C NMR and IR and compared to literature values.

3.2. Palladium-catalyzed homocoupling of aryl halides mediated by fluroide, representative procedure

Aryl halide (1.00 mmol) and $Pd(dba)_2$ (0.100 mmol) were combined in a round bottom flask and placed under argon. DMF (10 mL) was added, followed by TBAF (3.00 mL, 1.0 M in THF, 3.00 mmol). The reaction was then heated at 90 °C for 12 h. The light brown reaction mixture was poured into water (25 mL) and extracted three times with Et_2O (25 mL). The ethereal extracts were dried ($MgSO_4$) and the solvent evaporated. The crude product was then purified via column chromatography.

3.2.1. 4,4′-Dimethoxybiphenyl. Column chromatography (TLC R_f=0.31, 19:1 hexanes/EtOAc) yielded a white solid (93%) mp 177–178 °C (lit. 178–179 °C).[27] The ^1H and ^{13}C NMR and IR spectral data match those reported by Denmark.[27]

3.2.2. 2,2′-Dimethoxybiphenyl. Column chromatography (TLC R_f=0.21, 19:1 hexanes/EtOAc) yielded a white solid (89%) mp 153–154 °C (lit. 154–155 °C).[28] IR (CCl_4) 3070 (w), 3028 (w), 3002 (w), 2955 (m), 2933 (m), 2874 (w), 2856 (w), 2834 (w), 1505 (m), 1483 (m), 1261 (s), 1241 (s). The ^1H and ^{13}C NMR spectral data match those reported by Wan.[29]

3.2.3. 2,3,4,2′,3′,4′-Hexamethoxybiphenyl. Column chromatography (TLC R_f=0.23, 4:1 hexanes/EtOAc) yielded a white solid (63%) mp 125.5–126.8 °C (lit. 125–126 °C).[30] IR (CCl_4) 3002 (w), 2960 (m), 2940 (m), 2905 (m), 2833 (m), 1493 (s), 1462 (s), 1290 (s), 1228 (m), 1093 (s), 1007 (s). The ^1H and ^{13}C NMR spectral data match those reported by Banwell.[30]

3.2.4. 4,4′-Diacetylbiphenyl. Column chromatography (TLC R_f=0.33, 4:1 hexanes/EtOAc) yielded a white solid (88%) mp 188–189 °C (lit. 189–190 °C).[31] ^{13}C NMR ($CDCl_3$) δ 26.7, 127.4, 128.8, 136.6, 144.3, 197.6. The IR spectral data matches that reported by Stille.[31] The ^1H NMR spectral data matches that reported by Demark.[32]

3.2.5. 4,4′-Dicarbomethoxybiphenyl. Column chromatography (TLC R_f=0.23, 4:1 hexanes/EtOAc) yielded a white solid (64%) mp 215–216 °C (lit. 215–217 °C).[33] The ^1H NMR and IR spectral data match those reported by Tanaka.[7] The ^{13}C NMR spectral data matches that reported by Swadesh.[34]

3.2.6. 4,4′-Dimethylbiphenyl. Column chromatography (TLC R_f=0.44, pentane) yielded a white solid (92%) mp 119.5–120.6 °C (lit. 118–120 °C).[35] The ^1H and ^{13}C NMR spectral data match those reported by Kabalka.[35]

3.2.7. Biphenyl. Column chromatography (TLC R_f=0.54, pentane) yielded a white solid (86%) mp 69–71 °C (lit. 69–70 °C). The ^1H and ^{13}C NMR and IR spectral data match those reported by Koza.[36]

3.2.8. 4,4′-Dichlorobiphenyl. Column chromatography (TLC R_f=0.64, 19:1 hexanes/EtOAc) yielded a white solid (68%) mp 143.7–144.8 °C (lit. 142–144 °C).[36] The ^1H and ^{13}C NMR and IR spectral data match those reported by Koza.[36]

3.2.9. 1,1′-Binaphthyl. Column chromatography (TLC R_f=0.44, pentane) yielded a white solid (84%) mp 144.2–145.8 °C (lit. 144–145 °C).[9] IR (CCl_4) 3064 (w), 3043 (w), 3009 (w), 2960 (m), 2922 (m), 2853 (w), 1504 (w), 1383 (m). The ^1H and ^{13}C NMR spectral data match those reported by Jutand.[9]

3.2.10. 2,3,4-Trimethoxybromobenzene. Pyridinium hydrobromide perbromide (90%) (4.66 g, 13.1 mmol), was added in small portions over 30 min to a light red solution of 1,2,3-trimethoxybenzene (2.00 g, 11.9 mmol) and $FeCl_3 \cdot 6H_2O$ (50 mg 0.18 mmol) in Ac_2O (35 mL). The deep red solution was then heated at 55 °C for 5 min. The reaction was carefully poured into 100 mL of hot water. After cooling, the mixture was extracted with 50 mL of Et_2O ($\times 4$), dried ($MgSO_4$), and evaporated to yield a yellow oil. Column chromatography (TLC $R_f = 0.44$, 4:1 hexanes/EtOAc) produced a pale yellow oil (92%). IR (CCl_4) 3009 (m), 2960 (m), 2940 (s), 2898 (m), 2836 (m), 1580 (m), 1486 (s), 1462 (s), 1414 (s), 1293 (s), 1221 (s), 1096 (s), 1017 (s). ^{13}C NMR ($CDCl_3$) δ 56.2, 61.0, 61.1, 108.4, 108.6, 126.8, 151.0, 152.2, 153.3. The ^1H NMR spectral data matches that reported by Pettit.[37]

Acknowledgements

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Synthesis of novel, simplified, C-7 substituted eleutheside analogues with potent microtubule-stabilizing activity

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Abstract—The synthesis of a number of novel, simplified, C-7 substituted eleutheside analogues with potent tubulin-assembling and microtubule-stabilizing properties is described, using ring closing metathesis as the key-step for obtaining the 6–10 fused bicyclic ring system. The RCM precursors were synthesized starting from aldehyde **3** [prepared in six steps on a multigram scale from *R*-(−)-carvone in 30% overall yield] via multiple stereoselective Hafner–Duthaler allyltitanations and/or Brown allylborations. 'Second generation' RCM-catalyst **15** gave the desired ring closed ten-membered carbocycles as single *Z* stereoisomers in good yields. The RCM stereochemical course (100% *Z*) is likely to reflect thermodynamic control. Molecular mechanics and semi-empirical calculations also show that the *Z* stereoisomers of these ten-membered carbocycles are consistently more stable than the *E*. The crucial role of the homoallylic and allylic substituents and of their protecting groups for the efficiency of the RCM reactions is discussed. In particular, we have found that *p*-methoxyphenyl (PMP) protected allylic alcohols, the products of a stereoselective oxyallylation, are compatible with the RCM reaction and give better yields than the corresponding free allylic alcohols. One of the simplified analogues of the natural product (**44**, lacking inter alia the C-4/C-7 ether bridge) retains potent microtubule-stabilizing activity. However, the cytotoxicity tests did not parallel the potent tubulin-assembling and microtubule-stabilizing properties: limited cytotoxicity was observed against three common tumor cell lines (human ovarian carcinoma, human colon carcinoma and human leukemia cell lines, IC_{50} in the μM range), approximately two orders of magnitude less than paclitaxel (IC_{50} in the nM range). The mechanism of cell cycle arrest induced by compound **44** is similar to that obtained with paclitaxel.

1. Introduction

Sarcodictyins[1,2] A (**1a**) and B (**1b**) and eleutherobin[3,4] (**2**) (the 'eleutheside' family of microtubule-stabilizing drugs, Fig. 1) are active against paclitaxel resistant tumor cell lines and therefore hold potential as second generation microtubule-stabilizing anticancer agents.[4,5] The scarce availability of **1**–**2** from natural sources makes their total syntheses vital for further biological investigations.[5] To date, sarcodictyins A and B have been synthesized successfully by Nicolaou et al.[6] who have also exploited a similar route for accessing eleutherobin.[7] A subsequent report by Danishefsky and co-workers details an elegant alternative access to eleutherobin.[8] A number of partial syntheses and approaches have also been described.[9,10]

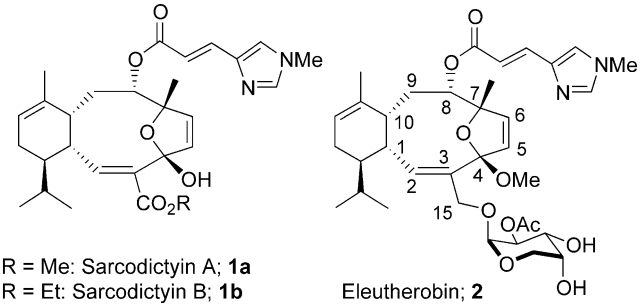

Figure 1. Marine diterpenoids sarcodictyin A (**1a**), B (**1b**) and eleutherobin (**2**).

The total syntheses of the eleutheside have generated very limited diversity in the diterpenoid core, with major variations reported only in the C-15 functionality and C-8

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side-chain.[5–8] We previously described the synthesis of a number of eleutheside analogues with potent tubulin-assembling and microtubule-stabilizing activity.[9h,m,n] However, the cytotoxicity assays did not parallel the potent tubulin-polymerizing properties: limited cytotoxicity was observed against three common tumor cell lines (human ovarian carcinoma and human colon carcinoma cell lines, IC_{50} in the μM range), two-to-three orders of magnitude less than paclitaxel (IC_{50} in the nM range).[9n] These results were attributed to an easy esterase-mediated hydrolytic cleavage of the *N*-methylurocanic ester side-chain in living cells (it is known that the natural eleuthesides are devoid of any cytotoxicity when the *N*-methylurocanic ester side-chain is lacking in position 8).[5] The simplified analogues, in fact, had an unsubstituted $–CH_2–$ in position 7, while natural eleutheSides have a fully substituted quaternary carbon, which is likely to hinder the hydrolysis of the adjacent ester at C-8.

In this paper, we describe the synthesis of a number of eleutheside analogues substituted at C-7, using ring closing metathesis (RCM) as the key-step for obtaining the 6–10 fused bicyclic ring. We also report the tubulin-polymerizing activities (ED_{50} and ED_{90} values) and the cytotoxicity tests (IC_{50} values) performed on these compounds using several different tumor cell lines.

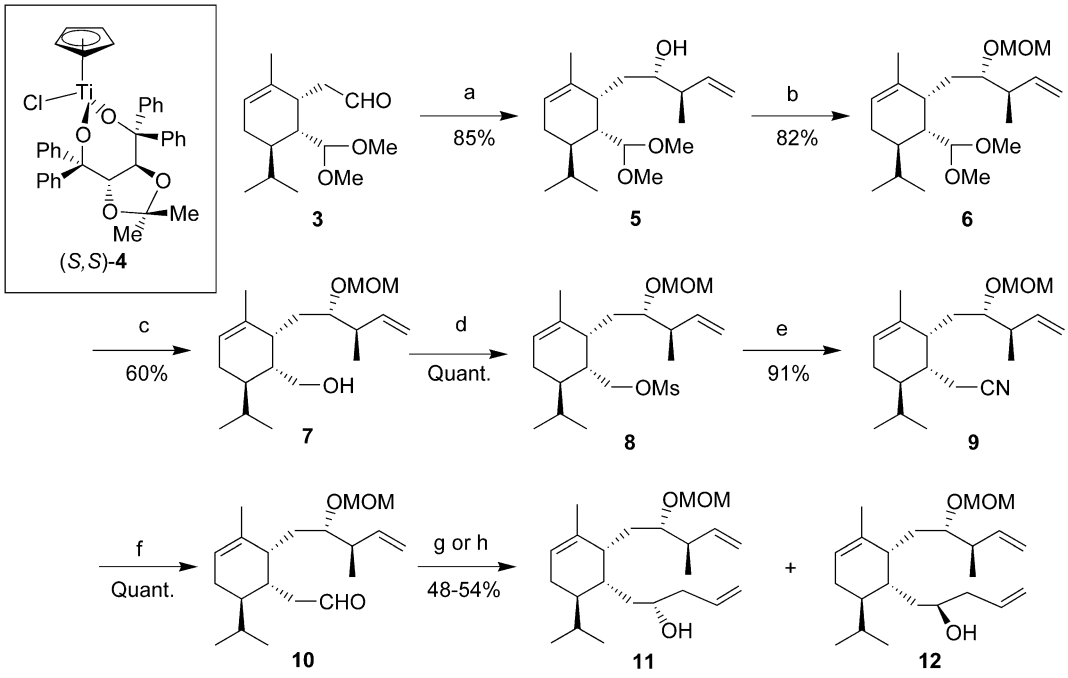
2. Results and discussion

2.1. Synthesis of the eleutheside analogues substituted at C-7

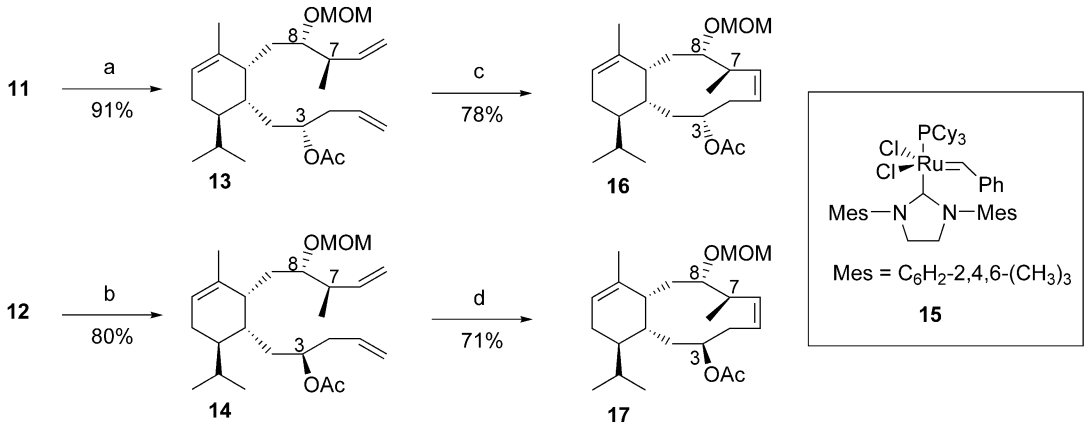
Aldehyde **3** (prepared in six steps on a multigram scale from *R*-(−)-carvone in 30% overall yield)[9a,g] was submitted to a stereoselective titanium-mediated Hafner–Duthaler crotylation,[11] generating alcohol **5** (Scheme 1).

The crotylation reaction proceeded in high yield (85%) and with complete stereocontrol in favor of the desired stereoisomer (diastereomeric purity >95% by ^1H and ^{13}C NMR).[12] After standard alcohol protection, an efficient and well established sequence of steps[8c] led to the homologated aldehyde **10**, on which a Brown allylation procedure was applied.[13] Addition of the allyl borane derived from (+)-α-pinene to aldehyde **10** gave a mixture of the two homoallylic alcohols (**11** and **12**) in a 3:1 ratio.[12] The use of the allyl borane derived from (−)-α-pinene gave the opposite stereochemical outcome (**11**/**12**=1:6).[12] Homoallylic alcohols **11** and **12** were acetylated and the resulting dienes (**13** and **14**) were subjected to ring closing metathesis[14] using the 'second generation' RCM-catalyst[15] **15** (CH_2Cl_2, reflux) to give the desired cyclized products **16** and **17** as single *Z* stereoisomers in 71–78% yields (Scheme 2). The stereochemistry at C-3 appears not to have a dramatic effect on the reaction, as similar yields were achieved. The *Z* stereochemistry of the double bond was unequivocally assigned by detection of the olefinic $^3J_{cis}$ coupling constant (10.8–10.9 Hz) in 400 MHz ^1H NMR experiments, and by detection of a NOE contact between these protons in 400 MHz NOESY experiments.

The reports that describe application of the RCM reaction to medium-sized—particularly ten-membered—rings, are still very rare, especially when dense functionality close to the reaction centre is involved.[16] The stereochemistry of the double bond created by our RCM reactions appears to be



Scheme 1. Reagents and conditions: (a) (i) 2-ButenylMgCl, (*S*,*S*)-TaddolCpTiCl [(*S*,*S*)-**4**], Et_2O, −78 to 0 °C; (ii) solution of **3** in Et_2O, −78 °C, 16 h; (iii) NH_4F (45% aqueous solution), rt, 4 h, 85% (>95% diastereomeric purity). (b) MOMCl, DIPEA, TBAI, CH_2Cl_2, rt, 16 h, 82%. (c) (i) $LiBF_4$, CH_3CN/H_2O (98/2), rt, 1 h; (ii) $NaBH_4$, EtOH, rt, 20 min, 60% over two steps. (d) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, quant. (e) KCN, 18-crown-6, MeCN, 80 °C, 5 h, 91%. (f) DIBAL-H, *n*-hexane/toluene (2/1), −78 °C, 40 min, quant. (g) (i) AllMgBr, ^{d}Ipc$_2$BOMe, Et_2O-THF, 0 °C to rt; (ii) solution of **10** in Et_2O, −78 °C 15 h, −78 to −20 °C 8 h; (iii) 6 N NaOH, H_2O_2, rt, 16 h, 48% (**11**/**12**=3:1). (h) (i) AllMgBr, ^{l}Ipc$_2$BOMe, Et_2O–THF, 0 °C to rt; (ii) solution of **10** in Et_2O, −78 °C 15 h, −78 to −20 °C 15 h; (iii) 6 N NaOH, H_2O_2, rt, 16 h, 54% (**11**/**12**=1:6).

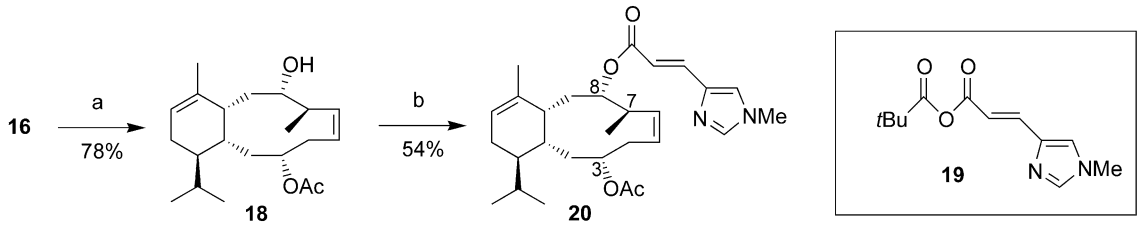


Scheme 2. Reagents and conditions: (a) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 91%. (b) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 80%. (c) **15** (6%), CH_2Cl_2, rt for 16 h, reflux for 7 h, 78% (100% *Z*). (d) **15** (6%), CH_2Cl_2, rt for 16 h, reflux for 7 h, 71% (100% *Z*).

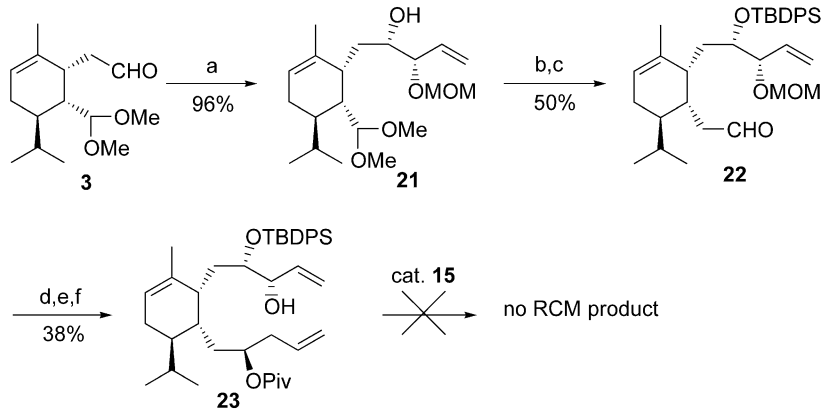
controlled in the desired sense (100% *Z*) by the structure of the new ten-membered carbocycles. This stereochemical course, which was found to be common to the cyclization of several related substrates (previously described)[9h,m,n,o] and of all the substrates reported in the present manuscript (vide infra), is likely to reflect thermodynamic control.[17] Molecular mechanics and semi-empirical calculations (see the relevant section below) also show that the *Z* stereoisomers of these ten-membered carbocycles are consistently more stable than the *E*.

A first simplified eleutheside analogue (**20**) was then synthesized from compound **16** using standard transformations (Scheme 3).

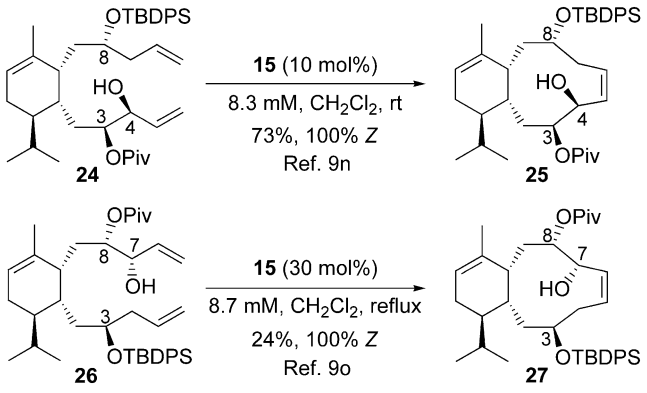
With the goal of synthesizing more C-7 functionalized eleutheside analogues, aldehyde **3** was oxyallylated using Brown's methodology [(*Z*)-γ-(methoxymethoxy)allyldiisopinocampheylborane from (−)-α-pinene][13d] in high yield (96%) and with excellent stereoselectivity (diastereomeric purity >95% by ^1H and ^{13}C NMR, Scheme 4).[12] Compound **21** was transformed into aldehyde **22** via a simple protection/deprotection/homologation sequence (analogous to the sequence described in Scheme 1). Aldehyde **22** was allylated using the allyl borane derived from (−)-α-pinene.[12,13] The protective groups were adjusted to give **23**, with a free allylic alcohol (a free alcohol in the allylic position is known to be important for promoting the cyclization).[9o,18,19] This time, 'second



Scheme 3. Reagents and conditions: (a) *p*-TSA, acetone, rt, 90 h, 78%. (b) **19** (Ref. 6b), $(CH_2Cl)_2$, Et_3N, DMAP, rt, 48 h, 54%.



Scheme 4. Reagents and conditions: (a) $^1Ipc_2BOMe$, AllOMOM, *sec*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C to rt, 16 h, 96% (>95% diastereomeric purity). (b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 16 h, 88%. (c) (i) AcOH/THF/H_2O (3/1/1), rt, 15 h, quant.; (ii) $NaBH_4$, EtOH, rt, 20 min, 71%; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 98%; (iv) KCN, 18-crown-6, CH_3CN, 80 °C, 6 h, 91%; (v) DIBAL-H, *n*-hexane/toluene (2/1), −78 °C, 45 min, 90%. (d) $^1Ipc_2BOMe$, AllMgBr, THF, −78 °C, 16 h, 52% (≥95% diastereomeric purity). (e) *t*-BuCOCl (PivCl), DMAP, CH_2Cl_2, 40 °C, 5 h, quant. (f) $BF_3{\cdot}Et_2O$, PhSH, CH_2Cl_2, −78 to −20 °C, 3 h, 73%.



Scheme 5.

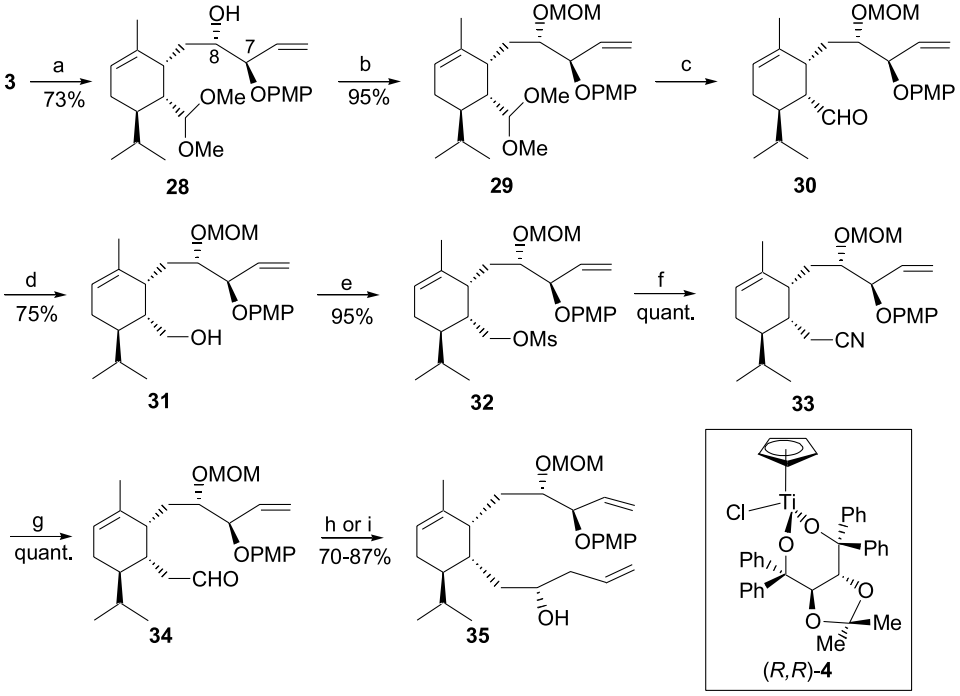
generation' RCM catalyst **15**[15] failed to provide the desired ring closed product, under a variety of experimental conditions.[9o]

This result is striking when compared to the analogous RCM reaction of diene **24** (Scheme 5), which proceeds smoothly to give the ring-closed product **25** in 73% isolated yield.[9n] Interconversion of the homoallylic O-protective groups of diene **23** gave the allylic alcohol **26** which did undergo cyclization to give **27**, albeit in a disappointing 24% yield.[9o]

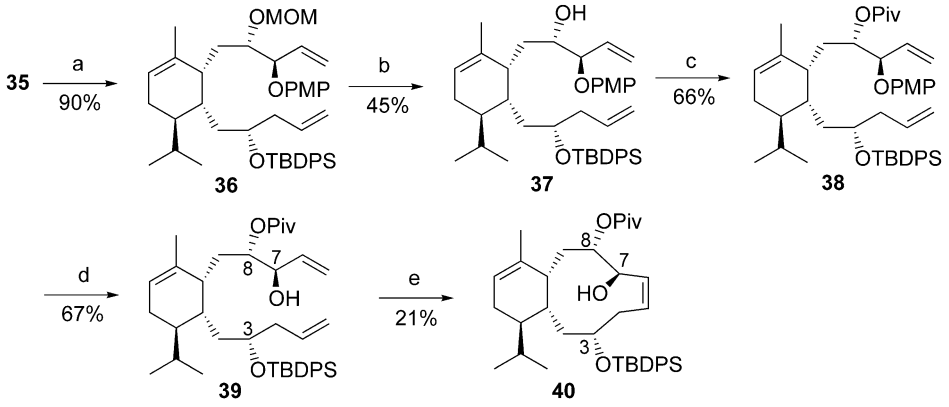
The rationale for this interconversion was that although the substitution pattern in compound **23** is the same as that shown by the successful cyclization precursor **24** (allylic alcohol, homoallylic OPiv and OTBDPS, Schemes 4 and 5), it is not the same with respect to the relationship between the groups [OH adjacent to OTBDPS (**23**) versus OH adjacent to OPiv (**24**)]. Again this observation demonstrates the importance of fine tuning the allylic and homoallylic alcohol protective groups for a successful RCM reaction.

At this point, we decided to change the stereochemistry at C-7, C-8 from *syn* to *anti*, hoping to influence the RCM performance[20] (Scheme 6). Aldehyde **3** was oxyallylated, using the (*S*,*S*)-TaddolCpTiCl complex (**4**),[11] to give the desired stereoisomer **28** in 73% isolated yield with complete stereocontrol (C-7, C-8 *anti* stereochemistry).[12] After standard alcohol protection as methoxymethyl ether (**29**, 95%), dimethylacetal deprotection ($LiBF_4$, CH_3CN/H_2O)[21] and $NaBH_4$ reduction (**31**, 75% over two steps), an efficient and well established sequence of steps[8c,9n] led to the homologated aldehyde **34** (95%). Using Brown allylboration (70%)[13] or better Hafner–Duthaler allyltitanation chemistry (87%),[11] the second olefin fragment was stereoselectively inserted in the south chain to give diene **35**.[12]

Protective group manipulations transformed diene **35** into the desired cyclization precursor **39** (C-7, C-8 *anti*) (Scheme 7) which had the same substitution and protection pattern as shown in compound **26** (C-7, C-8 *syn*). Reaction with the robust 'second generation' RCM-catalyst **15** gave a mixture of compounds, from which the cyclized product **40** could be isolated in a similarly poor yield (21%, Scheme 7). No significant difference was observed in the reactivity of the two diastereomers (**26** and **39**) in the RCM reaction.[20] It was noted, however, that if the RCM reaction was performed with the precursor PMP-protected allylic alcohol (**38**), higher yields could be obtained under similar reaction conditions (52%, 62% considering the recovered starting material, Scheme 8). This is, unexpectedly and unprecedentedly, a result in disagreement with the 'free allylic alcohol' effect,[9o,18,19] that is, allylic ethers are usually found



Scheme 6. Reagents and conditions: (a) *sec*-BuLi (1.3 M in cyclohexane), PMPOAllyl, (*S*,*S*)-TaddolCpTiCl [(*S*,*S*)-**4**], THF/Et_2O (57/43), −78 to 0 °C, 73%. (b) DIPEA, TBAI, MOMCl, CH_2Cl_2, 25 °C, 95%. (c) $LiBF_4$, CH_3CN/H_2O (98/2), 25 °C. (d) $NaBH_4$, EtOH, 25 °C, 75% over two steps. (e) MsCl, TEA, CH_2Cl_2, 0 to 25 °C, 95%. (f) KCN, 18-crown-6, CH_3CN, 80 °C, quant. (g) DIBAL-H, toluene/*n*-hexane (1/2), −78 °C, quant. (h) AllMgBr, $^dIpc_2BOMe$, Et_2O/THF (11/79), −78 °C, 70%. (i) AllMgBr, (*R*,*R*)-TaddolCpTiCl [(*R*,*R*)-**4**], Et_2O, −78 °C, 87%.



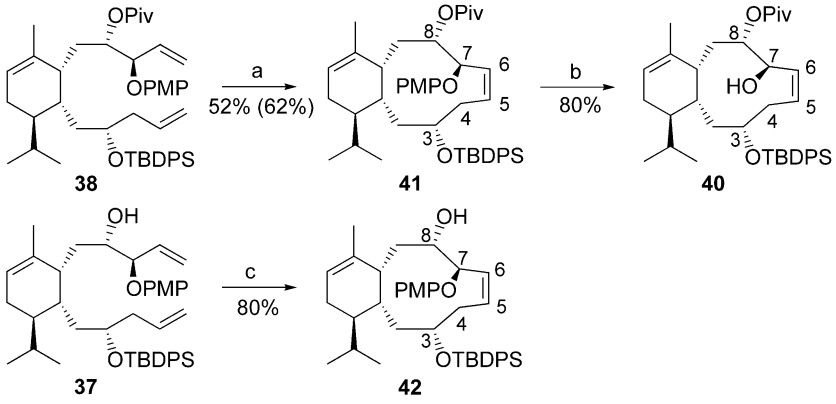
Scheme 7. Reagents and conditions: (a) imidazole, TBDPSCl, CH_2Cl_2, rt, 90%. (b) Me_2S, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C, 45%. (c) DMAP, PivCl, CH_2Cl_2, rt, 66%. (d) CAN, CH_3CN/H_2O (4/1), 0 °C, 67%. (e) **15** (10%), CH_2Cl_2, rt, 7.5 mM, 21% (100% *Z*).

to retard the RCM reaction while a rate acceleration is associated with allylic alcohols. Given the success of diene **38** in the RCM reaction, attempts were made to cyclize precursor **37**. Reaction of diene **37** with a free homoallylic alcohol and a PMP-protected allylic alcohol with the 'second generation' RCM-catalyst **15** gave the desired 6–10 fused bicycle **42** in 80% yield and 100% *Z*-selectivity (Scheme 8).

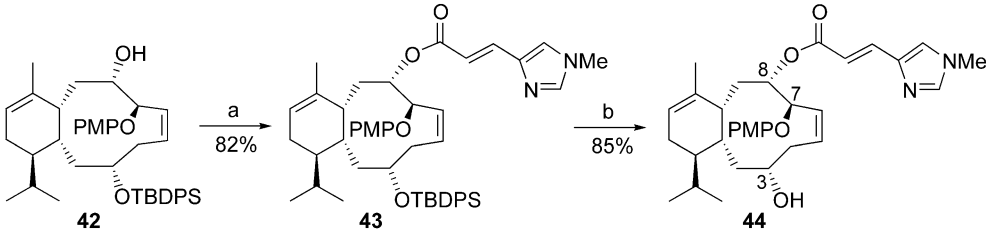
The improved results given by diene **37** compared to **38** may be due to the use of a higher boiling solvent.[22] An extensive analysis of compounds **41** and **42** was carried out using NMR spectroscopy. The olefinic $^3J_{cis}$ coupling constants suggested the *cis* configuration of the new double bonds ($^3J=11.4$ Hz for **41**, $^3J=11.4$ Hz for **42**). Furthermore, extensive NOESY experiments also suggested formation of the *Z*-olefin: a strong NOE was observed between C-7 methine and C-4 methylene protons and between H-5 and H-6.

At present, the reasons why the allylic OPMP group facilitates the RCM reaction are not completely understood. Sterically, the PMP can be considered relatively small, even smaller than a Me group (effective van der Waals radius of Ph = 1.62 Å compared to Me = 1.80 Å),[23] but definitely not smaller than a hydrogen. The true reason must be electronic, but difficult to rationalise.

A simplified eleutheside analogue (**44**) was then synthesized from compound **42** using standard transformations



Scheme 8. Reagents and conditions: (a) **15** (10%), CH_2Cl_2, reflux, 11 mM, 52% (62% considering the recovered starting material) (100% *Z*). (b) CAN, CH_3CN/H_2O (4/1), 0 °C, 80%. (c) **15** (10%), benzene, reflux, 10 mM, 80% (100% *Z*).



Scheme 9. Reagents and conditions: (a) **19** (Ref. 6b), $(CH_2Cl)_2$, Et_3N, DMAP, 80 °C, 82%. (b) TBAF, THF, rt, 85%.

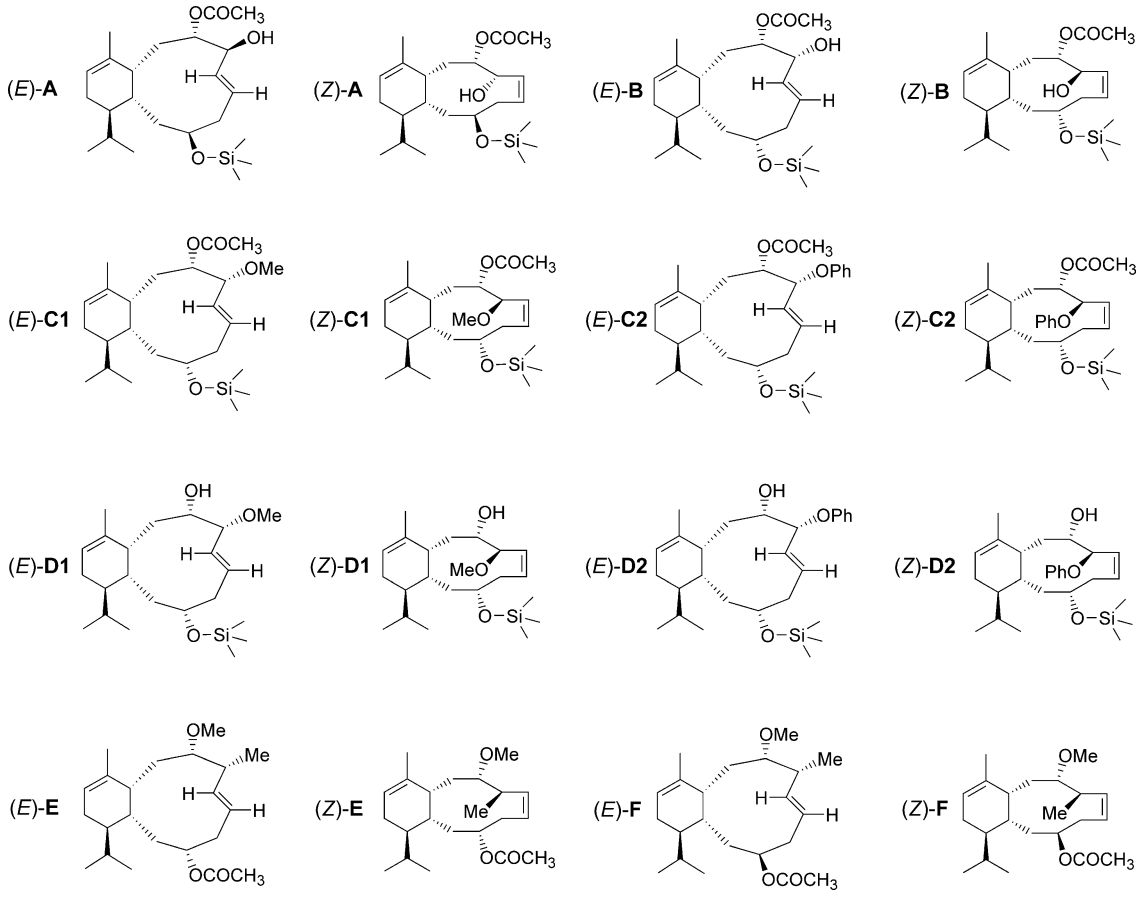


Figure 2. List of structures studied by molecular mechanics and semi-empirical PM3 calculations.

(Scheme 9). It is worth noting that the formation of the (*E*)-*N*-methylurocanic ester in refluxing 1,2-dichloroethane had a beneficial effect on the yield of **43** (82%).

2.2. Molecular mechanics and semi-empirical calculations

Molecular mechanics and semi-empirical PM3[24] calculations were undertaken in order to investigate if the stereochemical outcome of the various RCM reactions could possibly be due to thermodynamic control. Compounds **27**, **40**, **41**, **42**, **16** and **17** were simplified into structures **A**–**F** (*Z* and *E* stereoisomers, Fig. 2) in order to reduce the number of rotatable bonds and of low-quality torsional parameters,[25] by making the following changes in the protective groups: OPiv into OAc, OTBDPS into OTMS,[25] OPMP into either OMe (**C1** and **D1**) or OPh (**C2** and **D2**),[26] OMOM into OMe. Initially, conformational searches were carried out with MacroModel[27] (MM2*, $CHCl_3$ GB/SA) on each of the structures represented in Figure 2. In all cases, the *Z* stereoisomers of structures **A**–**F** were found to be consistently more stable than the corresponding *E* stereoisomers by ca. 1.8–12.7 kJ mol^{-1} (Table 1). The structures generated with MacroModel were then optimized at the PM3 level[24] with the Gaussian 03 package.[28] These calculations also show that the *Z* stereoisomers of structures **A**–**F** are more stable than the *E* stereoisomers, with energy differences ranging from 9.8 to 28.2 kJ mol^{-1} (Table 1). It is therefore highly likely that the selective formation of the *Z* ten-membered carbocycles in the RCM reactions is due to thermodynamic control.[17]

Table 1. Global minimum energy differences between the (*E*) and the (*Z*)-stereoisomers of structures **A**–**F**

Structure	E_E–E_Z (MM2*)[a]	E_E–E_Z (PM3)[a]
A	1.8	9.8
B	4.3	18.0
C1	6.6	17.4
C2	5.0	18.6
D1	7.4	12.3
D2	6.2	18.6
E	7.7	22.4
F	12.7	28.2

[a] Energy differences in kJ mol^{-1}.

Figure 3 shows the lowest energy conformers and relative energies of stereoisomer (*Z*)-**C1** (corresponding to **41**) and of stereoisomer (*E*)-**C1**, obtained at the PM3 level.

2.3. Biological assays

The effect of these new eleutheside analogues on the assembly of tubulin and on the stability of the formed microtubules was assessed at the University of Salford (UK), using the potent microtubule-stabilizing agent paclitaxel as a reference (Table 2).[2b,29] Eleutheside analogue **44** was shown to be at least as potent as paclitaxel. Microtubules were generated in the presence of $CaCl_2$ at 37 °C and were stable (i.e., did not depolymerize) at 10 °C. Although there is a general agreement that the

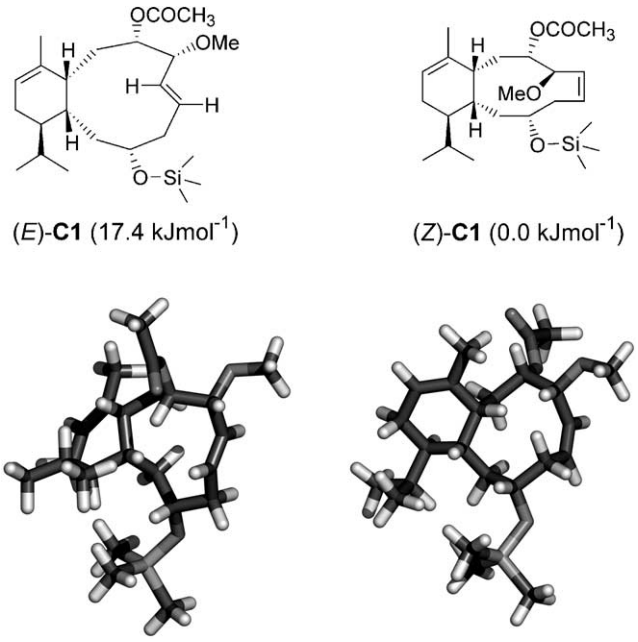


Figure 3. Lowest energy conformers and relative energies of stereoisomer (*Z*)-**C1** (corresponding to **41**) and of stereoisomer (*E*)-**C1**, obtained at the PM3 level.

Table 2. Tubulin polymerizing activities[a]

Compound	ED_{50} [μM]	ED_{90} [μM]
20	3.0	>20.0
44	0.1	0.5
Paclitaxel	1.0	2.5

[a] ED_{50}, effective dose that induces 50% tubulin polymerization; ED_{90}, effective dose that induces 90% tubulin polymerization (see Ref. 2b). ED values may vary depending on the tubulin batch (from pig brain): the same batch is used for the paclitaxel reference assay. For a more detailed experimental procedure, see Ref. 9n.

(*E*)-*N*-methylurocanic side-chain, the C-4/C-7 ether bridge, and the cyclohexene ring are important determinants of antimitotic activity,[5] it is interesting to note that this simplified analogue of the natural product (lacking inter alia the C-4/C-7 ether bridge) retains potent microtubule stabilizing activity. Given the dramatic impact that the furanose oxygen deletion is likely to have on the conformation of the ring system, the fact that some of these compounds retain activity comparable to paclitaxel in the tubulin polymerization assay is remarkable.[9n]

Table 3. Cytotoxicity assays: IC_{50} values on A2780, HCT116, K562 tumor cell lines[a]

Compound	IC_{50} [μM] (A2780)	IC_{50} [μM] (HCT116)	IC_{50} [μM] (K562)
20	10.9[b]	n.d.[c]	4.3[d]
44	1.9[b]	0.9[e]	2.3[d]

[a] IC_{50} values: concentration inhibiting cell growth by 50%. Cell proliferation was determined by the ATPlite assay (Perkin Elmer). A2780: human ovarian carcinoma cell line; HCT116: human colon carcinoma cell line; K562: human leukemia cell line.
[b] Paclitaxel IC_{50}=15 nM.
[c] Not determined.
[d] Paclitaxel IC_{50}=25 nM.
[e] Paclitaxel IC_{50}=7 nM.

However, the cytotoxicity assays did not parallel the potent tubulin-assembling and microtubule-stabilizing properties: limited cytotoxicity was observed for **44** (IC_{50} in the μM range) against three common tumor cell lines (human ovarian carcinoma, human colon carcinoma and human leukemia cell lines, Table 3),[30] approximately two orders of magnitude less than paclitaxel (IC_{50} in the nM range).

The mechanism of cell cycle arrest was studied in the case of compound **44**.[31] When tested on asynchronously proliferating HCT116 cells, compound **44** produced cell cycle perturbations similar to that obtained with paclitaxel: a 2.5-fold increase in the percentage of cells in G2/M phase (the mitotic phase) was observed with **44** at 4 μM and a 2-fold increase was obtained with paclitaxel at 50 nM.[31]

Despite their excellent microtubule-stabilizing activity, which is often superior to paclitaxel, and a mechanism of cell cycle arrest similar to that obtained with paclitaxel, high concentrations of our analogues (in the μM range) are needed to inhibit tumor cell growth.[9n] Thus, with this new class of eleutheside analogues, we succeeded, at least in part, in the separation of the tubulin mechanism from the cytostatic/cytotoxic action.[32] Although the application of these compounds as monotherapeutics in tumor indications will be limited, they might be of value as tools and wherever the stabilization of microtubules without other cell-toxic effects are advantageous. One of these potential applications might be the treatment of Alzheimer's disease.[33] It has been demonstrated very recently that paclitaxel protects very efficiently against β-amyloid toxicity in primary neurons.[34] This will open new therapeutic areas for compounds which are able to stabilize microtubules.

3. Experimental

3.1. General procedures

All reactions were carried out in flame-dried glassware under argon atmosphere. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_3CN (CaH_2), CH_2Cl_2 (CaH_2), $(CH_2Cl)_2$ (CaH_2), MeOH (CaH_2), Et_3N (CaH_2), *i*Pr_2EtN (CaH_2), $HN(TMS)_2$ (CaH_2), THF (Na), Et_2O (Na), benzene (Na), toluene (Na), *n*-hexane (Na). Organic extracts were dried over anhydrous Na_2SO_4. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness) or basic alumina supported on aluminium foils. TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm, following the procedure by Still and co-workers.[35] Proton NMR spectra were recorded on 400, 300, or 200 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ 7.26 ppm; d_6-DMSO, δ 2.50 ppm). The following abbreviations are used to describe spin multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br,

broad signal; dd, doublet of doublet; dt, doublet of triplet; ddd, doublet of doublet of doublet. Carbon NMR spectra were recorded on 400 (100 MHz), 300 (75 MHz) or 200 (50 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0). Infrared spectra were recorded on a standard Infrared Spectrophotometer; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter at the sodium D line. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. A Reserpine solution 100 pg/μL (about 100 count/s), 0.1% HCOOH/CH_3CN 1:1, was used as reference compound (Lock Mass).

3.1.1. (2*S*,3*R*)-1-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-3-methyl-pent-4-en-2-ol (5). To a cold (−78 °C), stirred suspension of (*S*,*S*)-**4**[11] (1.00 g, 1.63 mmol), in Et_2O (24.5 mL), was added 2-butenylmagnesium chloride (0.5 M in THF, 2.9 mL, 1.47 mmol). After stirring for 30 min, the resulting orange solution was warmed to 0 °C and stirred for 3 h, then recooled to −78 °C. A solution of aldehyde **3**[9a,g] (277 mg, 1.09 mmol) in Et_2O (6.0 mL) was added. After stirring for 15 h, the reaction mixture was treated with a NH_4F aqueous solution (45%, 10 mL) and stirred for further 4 h at room temperature. The organic phase was separated and the aqueous layer was extracted with iPr_2O (3×15 mL). The organic extracts were washed with brine. Purification of the crude by flash chromatography (*n*-hexane/EtOAc, 9/1) afforded compound **5** (285 mg, 85%) as a colourless oil. R_f=0.38 (*n*-hexane/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86–5.77 (m, 1H), 5.35 (br, 1H), 5.10–5.03 (m, 2H), 4.35 (d, 1H, J=5.5 Hz), 3.71–3.63 (m, 1H), 3.36 (s, 6H), 2.48 (br, 1H), 2.40 (br, 1H), 2.19–2.10 (m, 1H), 2.06–1.97 (m, 2H), 1.87–1.71 (m, 4H), 1.67 (s, 3H), 1.42 (ddd, 1H, J_1=14.6 Hz, J_2=10.1 Hz, J_3=3.3 Hz), 1.03 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.6 Hz), 0.83 (d, 3H, J=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.1, 136.6, 121.3, 115.2, 106.9, 71.8, 55.1, 54.4, 45.1, 39.8, 36.1, 34.5 (2C), 27.1, 24.5, 22.2, 21.0, 17.3, 16.0; FT-IR (CCl_4): ν 3632, 3583, 3487, 3077, 2961, 2832, 2675, 2290, 2002, 1847, 1638, 1558, 1463, 1386, 1259, 1216, 1159, 1111, 1073, 1007, 914; $[\alpha]_D^{20}$=+48.2 (c=1.03, EtOAc); HRMS (ESI): *m*/*z*: calculated for $C_{19}H_{34}NaO_3$: 333.2406 $[M+Na]^+$; found: 333.2410 (resolution 9000).

3.1.2. (4*R*,5*R*,6*R*)-5-Dimethoxymethyl-4-isopropyl-6-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-1-methyl-cyclohexene (6). To a stirred solution of compound **5** (993 mg, 3.20 mmol), in CH_2Cl_2 (8.1 mL) was added DIPEA (1.23 mL, 7.05 mmol) followed by TBAI (237 mg, 0.64 mmol) and chloromethyl methyl ether (487 μL, 6.41 mmol). After stirring for 15 h, the resulting brown solution was filtered through a plug of silica gel (eluting with CH_2Cl_2). Purification of the crude by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **6** (932 mg, 82%) as a colourless oil. R_f=0.6 (*n*-hexane/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddd, 1H, J_1=17.4 Hz, J_2=10.3 Hz, J_3=7.1 Hz), 5.28 (br, 1H), 5.08–4.97 (m, 2H), 4.78 (d, 1H, J=6.6 Hz), 4.70 (d, 1H, J=6.6 Hz), 4.29 (d, 1H, J=5.3 Hz), 3.80 (dt, 1H, J_1=9.7 Hz, J_2=3.2 Hz), 3.41 (s, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 2.50 (br, 1H), 2.34 (br, 1H), 2.11–1.60 (m, 9H), 1.36 (ddd, 1H, J_1=14.3 Hz, J_2=9.9 Hz, J_3=3.6 Hz), 1.04 (d, 3H, J=6.9 Hz), 0.91 (d, 3H, J=6.8 Hz), 0.82 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.2, 138.3, 120.2, 113.8, 107.0, 97.4, 81.4, 55.7, 55.1, 54.3, 42.0, 40.4, 36.3, 34.2, 32.1, 27.1, 24.4, 22.3, 21.3, 17.2, 14.4; FT-IR (CCl_4): ν 3075, 2959, 2931, 2842, 2830, 2674, 2291, 2009, 1831, 1736, 1639, 1558, 1464, 1442, 1376, 1369, 1259, 1214, 1152, 1103, 1078, 1049, 1013, 979, 914; $[\alpha]_D^{20}$=+74.0 (c=0.5, EtOAc); HRMS (ESI): *m*/*z*: calculated for $C_{21}H_{38}NaO_4$: 377.2668 $[M+Na]^+$; found: 377.2667 (resolution 10,000).

3.1.3. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-methanol (7). $LiBF_4$ (246 mg, 2.63 mmol) was dissolved in a mixture of CH_3CN/H_2O (5.2 mL, v/v: 98/2) and added to compound **6** (932 mg, 2.63 mmol). After stirring for 1 h, the reaction mixture was filtered through a plug of silica gel (eluting with CH_2Cl_2) and the filtrate concentrated in vacuo to give the crude aldehyde (768 mg), which was used without further purification. To a stirred solution of the crude aldehyde, in EtOH (28.0 mL), was added $NaBH_4$ (149 mg, 3.94 mmol). After stirring for 20 min, the reaction mixture was treated with NH_4Cl (1.41 g, 26.36 mmol) followed by Na_2SO_4 and iPr_2O, and stirred for further 20 min. The salts were removed by filtration and washed with iPr_2O. Purification by flash chromatography (*n*-hexane/EtOAc, 85/15) afforded alcohol **7** (505 mg, 60% over two steps) as a colourless oil. R_f=0.25 (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.93–5.72 (m, 1H), 5.34 (br, 1H), 5.16–5.01 (m, 2H), 4.75 (d, 1H, J=6.9 Hz), 4.69 (d, 1H, J=6.9 Hz), 3.75 (dd, 1H, J_1=11.2 Hz, J_2=5.1 Hz), 3.67–3.42 (m, 5H), 2.65–2.42 (m, 1H), 2.33 (br, 1H), 1.98–1.37 (m, 12H), 1.06 (d, 3H, J=6.9 Hz), 0.91 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.5, 137.4, 120.9, 115.1, 97.0, 81.3, 61.9, 55.9, 41.9, 41.6, 35.9, 34.2, 30.9, 24.2, 22.3, 21.1, 16.3, 14.1; FT-IR (CCl_4): ν 3633, 3513, 3080, 2961, 2931, 2824, 2290, 2004, 1846, 1736, 1638, 1543, 1463, 1417, 1386, 1369, 1259, 1216, 1150, 1101, 1040, 1008, 918; $[\alpha]_D^{20}$=+73.6 (c=0.7, EtOAc).

3.1.4. Methanesulfonic acid {(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-methyl ester (8). To a cold (0 °C), stirred solution of alcohol **7** (505 mg, 1.63 mmol), in CH_2Cl_2 (12.5 mL), was added Et_3N (680 μL, 4.88 mmol) followed by MsCl (189 μL, 2.44 mmol). After stirring at room temperature for 15 h, the solvent was evaporated under reduced pressure. Purification of the crude by filtration through a plug of silica gel (eluting with CH_2Cl_2) afforded mesylate **8** (634 mg, quant.) as a colourless oil. R_f=0.72 (CH_2Cl_2/EtOAc, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.94–5.74 (m, 1H), 5.33 (br, 1H), 5.18–5.03 (m, 2H), 4.75 (d, 1H, J=7.0 Hz), 4.70 (d, 1H, J=7.0 Hz), 4.30 (dd, 1H, J_1=9.9 Hz, J_2=7.2 Hz), 4.07 (dd, 1H, J_1=9.9 Hz, J_2=8.6 Hz), 3.70–3.58 (m, 1H), 3.43 (s, 3H), 3.03 (s, 3H), 2.63 (br, 1H), 2.39 (br, 1H), 2.26–2.07 (m, 1H), 1.96 (br, 2H), 1.75–1.20 (m, 7H), 1.05 (d, 3H, J=6.8 Hz), 0.92 (d, 3H, J=6.7 Hz), 0.87 (d, 3H, J=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3, 136.2, 120.8, 115.3, 96.7, 80.1, 69.2, 55.9, 41.0, 38.0, 37.3, 36.7, 33.9, 30.1,

27.2, 23.9, 22.1, 20.8, 17.8, 13.1; FT-IR (CCl_4): ν 2962, 2930, 2291, 2003, 1845, 1734, 1555, 1370, 1344, 1259, 1216, 1177, 1098, 1009; $[\alpha]_D^{20}=+21.0$ ($c=1.4$, EtOAc); HRMS (ESI): m/z: calculated for $C_{20}H_{37}NO_5S$: 406.2627 $[M+NH_4]^+$; found: 406.2622 (resolution 10,000).

3.1.5. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetonitrile (9). To a stirred solution of mesylate **8** (634 mg, 1.63 mmol), in CH_3CN (16.9 mL), was added 18-crown-6 (1.29 g, 4.89 mmol) followed by KCN (319 mg, 4.89 mmol). After stirring for 8 h at 80 °C, the solvent was evaporated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **9** (473 mg, 91%) as a colourless oil. $R_f=0.52$ (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85–5.76 (m, 1H), 5.35 (br, 1H), 5.21–5.05 (m, 2H), 4.73 (s, 2H), 3.58 (dt, 1H, $J_1=9.6$ Hz, $J_2=1.6$ Hz), 3.42 (s, 3H), 2.70 (br, 1H), 2.46–1.90 (m, 6H), 1.77–1.52 (m, 6H), 1.26 (ddd, 1H, $J_1=14.8$ Hz, $J_2=8.8$ Hz, $J_3=2.8$ Hz), 1.08 (d, 3H, $J=7.2$ Hz), 0.95 (d, 3H, $J=6.8$ Hz), 0.89 (d, 3H, $J=6.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.1, 135.1, 121.0, 119.8, 115.7, 96.9, 80.2, 55.9, 41.0, 39.5, 34.9, 34.7, 29.6, 27.3, 23.6, 22.1, 20.6, 18.9, 17.3, 13.2; FT-IR (CCl_4): ν 3081, 2963, 2892, 2847, 2823, 2290, 2247, 2004, 1847, 1638, 1558, 1463, 1426, 1388, 1372, 1257, 1217, 1151, 1101, 1041, 1006, 980, 920; $[\alpha]_D^{20}=+48.2$ ($c=1.33$, EtOAc); HRMS (ESI): m/z: calculated for $C_{20}H_{33}NaNO_2$: 342.2409 $[M+Na]^+$; found: 342.2419 (resolution 10,000).

3.1.6. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetaldehyde (10). To a cold (−78 °C), stirred solution of compound **9** (295 mg, 0.92 mmol), in toluene/*n*-hexane (15.0 mL, v/v: 1/2), was slowly added DIBAL-H (1.5 M in toluene, 6.1 mL, 9.20 mmol). After 45 min the reaction mixture was treated with EtOAc (7.5 mL) and an aqueous tartaric acid solution (1.0 M, 7.5 mL), and warmed to room temperature. After 1 h the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (5×10 mL). The organic extracts were washed with saturated $NaHCO_3$ aqueous solution (2×10 mL). The solvent was evaporated under reduced pressure to afford aldehyde **10** (296 mg, quant.) as a colourless oil, which was used without further purification. $R_f=0.2$ (CH_2Cl_2).

3.1.7. (*R*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (11) and (*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (12). To a cold (0 °C), stirred solution of ^{d}Ipc$_2$BOMe[13c] (1.0 M in THF, 2.4 mL, 2.42 mmol) was slowly added AllMgBr (1.0 M in Et_2O, 2.1 mL, 2.14 mmol). After stirring for 1 h at room temperature, the reaction mixture was cooled to −78 °C and aldehyde **10** (230 mg, 0.71 mmol) in Et_2O (2.8 mL) was added. After stirring for 15 h, the reaction mixture was warmed gradually to −20 °C during 8 h, and treated with an aqueous NaOH solution (6.0 M, 3.5 mL) and H_2O_2 (35%, 2.8 mL). After stirring for 16 h at room temperature, the organic phase was separated and the aqueous layer was extracted with iPr_2O (3×10 mL). A first flash chromatography (*n*-hexane/EtOAc, 9/1) afforded combined alcohols **11** and **12** as a mixture (48%). A second flash chromatography (CH_2Cl_2/iPr_2O, 95/5) afforded **11** (94 mg, 36%) and **12** (31 mg, 12%) as colourless oils (**11**/**12**=3:1).

Compound **11**. $R_f=0.32$ (CH_2Cl_2/iPr_2O, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.98–5.68 (m, 2H), 5.31 (br, 1H), 5.27–4.98 (m, 4H), 4.69 (s, 2H), 3.89–3.68 (m, 1H), 3.60–3.33 (m, 4H), 2.67 (br, 1H), 2.40–1.18 (m, 16H), 1.06 (d, 3H, $J=6.9$ Hz), 0.91 (d, 3H, $J=6.8$ Hz), 0.82 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.3, 137.0, 134.8, 121.0, 118.3, 115.2, 96.5, 80.7, 68.2, 55.8, 42.3, 41.1, 38.4, 35.1, 34.7, 34.5, 30.5, 27.0, 24.1, 22.7, 21.0, 17.4, 14.0; FT-IR (CCl_4): ν 3623, 3590, 3079, 2961, 2823, 2290, 1839, 1742, 1640, 1559, 1440, 1415, 1373, 1262, 1151, 1019, 918; $[\alpha]_D^{20}=+40.9$ ($c=0.98$, EtOAc); HRMS (ESI): m/z: calculated for $C_{23}H_{41}O_3$: 365.3056 $[M+H]^+$; found: 365.3065 (resolution 10,000).

Compound **12**. $R_f=0.44$ (CH_2Cl_2/iPr_2O, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.95–5.72 (m, 2H), 5.29 (br, 1H), 5.23–5.01 (m, 4H), 4.74 (s, 2H), 3.83–3.60 (m, 2H), 3.42 (s, 3H), 2.75–2.60 (m, 1H), 2.40–1.85 (m, 6H), 1.75–1.53 (m, 6H), 1.45–1.21 (m, 4H), 1.07 (d, 3H, $J=6.8$ Hz), 0.92 (d, 3H, $J=6.7$ Hz), 0.87 (d, 3H, $J=6.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.7, 136.3, 134.9, 120.8, 118.1, 115.0, 97.0, 80.2, 68.0, 55.9, 42.8, 41.2, 39.3, 34.2, 34.1, 32.5, 29.5, 27.4, 24.1, 22.3, 20.8, 19.9, 13.2; FT-IR (CCl_4): ν 3622, 3590, 3080, 2960, 2823, 2291, 2004, 1847, 1741, 1639, 1559, 1463, 1439, 1415, 1386, 1376, 1252, 1218, 1152, 1102, 1043, 1006, 980; $[\alpha]_D^{20}=+19.6$ ($c=0.87$, EtOAc); HRMS (ESI): m/z: calculated for $C_{23}H_{41}O_3$: 365.3056 $[M+H]^+$; found: 365.3061 (resolution 10,000).

Following the same procedure described above and using ^{l}Ipc$_2$BOMe[13c] as chiral auxiliary, the 2 epimeric alcohols were obtained in 54% yield and in a ratio **11**/**12**=1:6.

3.1.8. Acetic acid (*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl}-but-3-enyl ester (13). To a cold (0 °C), stirred solution of alcohol **11** (87 mg, 0.24 mmol), in CH_2Cl_2 (1.6 mL), was added Et_3N (66 μL, 0.48 mmol), followed by DMAP (2.9 mg, 0.024 mmol) and Ac_2O (34 μL, 0.36 mmol). After stirring for 30 min, the reaction mixture was warmed to room temperature and stirred for further 1 h. The reaction mixture was treated with a $NaHCO_3$ saturated aqueous solution (3 mL) and stirred for 15 min. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **13** (89 mg, 91%) as a colourless oil. $R_f=0.65$ (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.90–5.73 (m, 2H), 5.29 (br, 1H), 5.21–4.97 (m, 5H), 4.70 (s, 2H), 3.58–3.35 (m, 4H), 2.62 (br, 1H), 2.41–1.20 (m, 18H), 1.06 (d, 3H, $J=6.9$ Hz), 0.90 (d, 3H, $J=6.7$ Hz), 0.81 (d, 3H, $J=6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 140.3, 136.9, 133.8, 120.9, 117.7, 115.3, 96.5, 80.4, 71.4, 55.9, 41.1, 39.0, 38.4, 34.8, 34.4, 31.3, 30.4, 27.0, 24.0, 22.6, 21.2, 20.9, 17.6, 14.0; FT-IR (CCl_4): ν 3079, 2961, 2823, 2290, 2003, 1837, 1739, 1641, 1553, 1440, 1418, 1371, 1242, 1150, 1098, 1044, 918; $[\alpha]_D^{20}=+50.6$ ($c=1.03$, EtOAc); HRMS (ESI): m/z: calculated for

$C_{25}H_{46}NO_4$: 424.3421 $[M+NH_4]^+$; found: 424.3434 (resolution 10,000).

3.1.9. Acetic acid (*R*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-methyl-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl}-but-3-enyl ester (14). To a cold (0 °C), stirred solution of alcohol **12** (92 mg, 0.25 mmol), in CH_2Cl_2 (1.7 mL) was added Et_3N (70 μL, 0.50 mmol) followed by DMAP (3.1 mg, 0.025 mmol) and Ac_2O (36 μL, 0.38 mmol). After stirring for 30 min at 0 °C, the reaction was warmed to room temperature. After further 1 h, the reaction mixtures was filtered through a plug of silica gel (eluting with CH_2Cl_2). Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **14** (81 mg, 80%) as a colourless oil. R_f=0.50 (*n*-hexane/EtOAc, 9/1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.93–5.64 (m, 2H), 5.27 (br, 1H), 5.20–4.94 (m, 5H), 4.73 (s, 2H), 3.64 (dt, 2H, J_1=10.2 Hz, J_2=2.8 Hz), 3.41 (s, 3H), 2.75 (br, 1H), 2.42–2.20 (m, 3H), 2.06–1.20 (m, 15H), 1.09 (d, 3H, J=6.8 Hz), 0.87 (d, 3H, J=6.3 Hz), 0.84 (d, 3H, J=5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 140.6, 135.6, 133.6, 120.7, 117.7, 114.9, 97.3, 80.1, 71.0, 55.8, 41.3, 39.7, 39.5, 33.1, 31.3, 30.6, 29.1, 27.4, 23.9, 22.8, 22.1, 21.1, 20.6, 12.7; FT-IR (CCl_4): ν 3080, 2962, 2823, 2290, 2008, 1836, 1739, 1641, 1558, 1462, 1439, 1417, 1373, 1242, 1151, 1130, 1101, 1044, 940; $[\alpha]_D^{20}$=+9.6 (c=0.83, EtOAc); HRMS (ESI): *m/z*: calculated for $C_{25}H_{43}O_4$: 424.3421 $[M+H]^+$; found: 424.3439 (resolution 10,000).

3.1.10. Acetic acid (*Z*)-[(4*R*,4a*R*,6*S*,10*R*,11*S*,12a*R*)-4-isopropyl-11-methoxymethoxy-1,10-dimethyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (16). To a stirred solution of diene **13** (35 mg, 0.086 mmol), in degassed CH_2Cl_2 (8.0 mL), was added a solution of Grubbs catalyst **15** (4.4 mg, 5.2 μmol) in degassed CH_2Cl_2 (650 μL). After stirring for 15 h at room temperature, the reaction mixture was heated at 40 °C for 7 h. The reaction mixture was treated with DMSO (31 μL) and stirred for 15 h at room temperature under argon atmosphere. Purification by flash chromatography (*n*-hexane/EtOAc, 95/5) afforded compound **16** (25 mg, 78%) as a colourless oil. R_f=0.77 (*n*-hexane/EtOAc, 9/1, TLC runs twice); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (dt, 1H, J_1=10.8 Hz, J_2=5.0 Hz), 5.52 (dd, 1H, J_1=10.8 Hz, J_2=10.3 Hz), 5.30 (br, 1H), 5.13–5.05 (m, 1H), 4.73 (d, 1H, J=6.9 Hz), 4.61 (d, 1H, J=6.9 Hz), 3.79–3.72 (m, 1H), 3.42 (s, 3H), 2.94–2.84 (m, 1H), 2.70 (ddd, 1H, J_1=14.8 Hz, J_2=10.3 Hz, J_3=4.0 Hz), 2.24 (dt, 1H, J_1=14.8 Hz, J_2=4.3 Hz), 2.09–1.50 (m, 15H), 1.38 (br, 1H), 1.15 (d, 3H, J=6.6 Hz), 0.88 (d, 3H, J=6.8 Hz), 0.77 (d, 3H, J=6.7 Hz); ^{13}C NMR (50. MHz, $CDCl_3$): δ 170.4, 138.1, 134.1, 124.5, 120.8, 95.9, 81.6, 74.5, 55.8, 38.0, 37.4, 36.6, 34.3, 34.1, 32.1, 29.2, 27.1, 24.5, 24.0, 21.4, 21.0, 18.3, 15.5; FT-IR (CCl_4): ν 2961, 2931, 2290, 2004, 1847, 1735, 1558, 1464, 1370, 1245, 1218, 1150, 1099, 1042, 1008, 980; $[\alpha]_D^{20}$=+102.0 (c=0.83, EtOAc); HRMS (ESI): *m/z*: calculated for $C_{23}H_{38}NaO_4$: 401.2662 $[M+Na]^+$; found: 401.2659 (resolution 10,000).

3.1.11. Acetic acid (*Z*)-[(4*R*,4a*R*,6*R*,10*R*,11*S*,12a*R*)-4-isopropyl-11-methoxymethoxy-1,10-dimethyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (17). To a stirred solution of diene **14** (20 mg, 0.049 mmol), in degassed CH_2Cl_2 (4.6 mL), was slowly added a solution Grubbs catalyst **15** (2.5 mg, 3.0 μmol) in degassed CH_2Cl_2 (370 μL). The reaction mixture was stirred for 15 h at room temperature, then for 7 h at 40 °C and then for 15 h at room temperature. Further Grubbs catalyst **15** (1 mg) was added and then heated at 40 °C for 7 h. The reaction mixture was treated with DMSO (20 μL) and stirred for 15 h at room temperature under argon atmosphere. Purification by flash chromatography (*n*-hexane to *n*-hexane/EtOAc, 95/5) afforded compound **17** (13.1 mg, 71%) as a colourless oil. R_f=0.77 (*n*-hexane/EtOAc, 9/1, TLC runs twice); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46–5.40 (m, 2H), 5.33 (br, 1H), 5.24–5.15 (m, 1H), 4.72 (d, 1H, J=6.9 Hz), 4.60 (d, 1H J=6.9 Hz), 3.89–3.82 (m, 1H), 3.42 (s, 3H), 3.02–2.93 (m, 1H), 2.81–2.71 (m, 1H), 2.34–2.21 (m, 2H), 2.06 (s, 3H), 2.00–1.75 (m, 6H), 1.71–1.50 (m, 4H), 1.46–1.37 (m, 1H), 1.13 (d, 3H J=6.6 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.67 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 138.7, 133.6, 124.9, 120.9, 95.8, 81.4, 72.7, 55.8, 37.5, 37.0, 35.1, 34.5, 33.6, 32.4, 26.9, 26.4, 24.5, 24.4, 21.2, 21.0, 18.0, 14.7; FT-IR (CCl_4): ν 2961, 2930, 2290, 2003, 1847, 1740, 1558, 1458, 1369, 1246, 1149, 1098, 1042, 1008, 930; $[\alpha]_D^{20}$=+86.4 (c=0.56, EtOAc); HRMS (ESI): *m/z*: calculated for $C_{23}H_{38}NaO_4$: 401.2662 $[M+Na]^+$; found: 401.2657 (resolution 10,000).

3.1.12. Acetic acid (*Z*)-[(4*R*,4a*R*,6*S*,10*R*,11*S*,12a*R*)-11-hydroxy-4-isopropyl-1,10-dimethyl-3,4,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (18). To a stirred solution of compound **16** (6.4 mg, 0.017 mmol), in acetone (390 μL), was added *p*-TSA monohydrate (8.0 mg, 0.042 mmol). After stirring for 90 h at room temperature, the reaction mixture was filtered through a plug of silica gel (eluting with CH_2Cl_2). Purification by flash chromatography (*n*-hexane/EtOAc, 85/15) afforded alcohol **18** (4.4 mg, 78%) as an amorphous white solid. R_f=0.38 (*n*-hexane/EtOAc, 85/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (dt, 1H, J_1=11.0 Hz, J_2=4.8 Hz), 5.52 (dd, 1H, J_1=J_2=11.0 Hz), 5.31 (br, 1H), 5.11–5.04 (m, 1H), 3.92–3.84 (m, 1H), 2.84 (br, 1H), 2.76–2.67 (m, 1H), 2.29–2.22 (m, 1H), 2.07 (s, 3H), 2.03–1.93 (m, 1H), 1.88–1.48 (m, 11H), 1.39 (br, 1H), 1.17 (d, 3H, J=6.7 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 138.4, 133.3, 125.6, 121.3, 76.3, 75.0, 38.4, 38.0, 37.8, 37.0, 35.0, 32.6, 29.7, 27.6, 24.9, 24.4, 21.9, 21.4, 18.5, 15.9; FT-IR (CCl_4): ν 3631, 3455, 3015, 2961, 2931, 2847, 2290, 2003, 1847, 1734, 1558, 1452, 1370, 1245, 1218, 1102, 1010; $[\alpha]_D^{20}$=+88.4 (c=0.74, $CHCl_3$).

3.1.13. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid (*Z*)-[(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-acetoxy-1-isopropyl-4,7-dimethyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl] ester (20). To the mixed anhydride **19** (prepared according to Ref. 6b; 155 mg, 0.66 mmol) were added a solution of alcohol **18** (7.4 mg, 0.022 mmol) in $(CH_2Cl)_2$ (1.3 mL), followed by Et_3N (40 mg, 55 μL, 0.40 mmol) and DMAP (2.7 mg, 0.022 mmol). After stirring for 48 h at room temperature, the solvent was evaporated under reduced pressure. Purification by flash chromatography (*n*-hexane/EtOAc, 2/8) afforded compound **20** (5.6 mg, 54%) as a colourless oil. R_f=0.35 (*n*-hexane/

EtOAc, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, J=15.6 Hz), 7.47 (s, 1H), 7.09 (s, 1H), 6.58 (d, 1H, J=15.6 Hz), 5.67 (dt, 1H, J_1=10.8 Hz, J_2=5.0 Hz), 5.59 (dd, 1H, J_1=J_2=10.8 Hz), 5.31 (br, 1H), 5.21 (dt, 1H, J_1=11.5 Hz, J_2=3.0 Hz), 5.15–5.08 (m, 1H), 3.72 (s, 3H), 3.05–2.95 (m, 1H), 2.73 (ddd, 1H, J_1=14.6 Hz, J_2=10.8 Hz, J_3=4.0 Hz), 2.28 (dt, 1H, J_1=14.6 Hz, J_2=4.5 Hz), 2.14–1.25 (m, 16H) 1.06 (d, 3H, J=6.6 Hz), 0.87 (d, 3H, J=6.8 Hz), 0.78 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 167.2, 138.6, 137.6, 135.9, 133.6, 125.1, 122.4, 120.8, 116.3, 77.7, 74.3, 37.7, 37.5, 36.5, 33.7, 33.6, 32.0, 27.1, 24.5, 23.9, 22.7, 21.5, 21.0, 17.8, 14.1; FT-IR (CCl_4): ν 3016, 2961, 2929, 2873, 2856, 2291, 2003, 1847, 1734, 1708, 1645, 1548, 1458, 1387, 1370, 1297, 1245, 1218, 1162, 1103, 1008, 933; $[\alpha]_D^{20}$=+28.9 (c=0.56, EtOAc); HRMS (ESI): m/z: calculated for $C_{28}H_{41}N_2O_4$: 469.3061 $[M+H]^+$; found: 469.3070 (resolution 10,000).

3.1.14. (2*S*,3*R*)-1-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-3-(4-methoxy-phenoxy)-pent-4-en-2-ol (28). To a cold (−60 °C), stirred solution of 1-allyloxy-4-methoxy-benzene[36] (575.5 mg, 3.5 mmol) in THF (27.9 mL), was added *sec*-butyllithium (2.5 mL, 3.5 mmol, 1.3 M in cyclohexane). After stirring for 1.5 h, the resulting orange solution (colour is important) was transferred, via cannula, to a cold (−78 °C) suspension of (*S*,*S*)-**4**[11] (3.5 mmol, based on the amount of $CpTiCl_3$) in Et_2O (25.0 mL). The reaction mixture was stirred for 3 h (colour changed from yellow to orange and finally dark brown), and then was treated with a solution of aldehyde **3** (495 mg, 1.95 mmol) in THF (5.0 mL). After 16 h, the reaction mixture was warmed to 0 °C and then stirred for 8 h. The mixture was then treated with a NH_4F aqueous solution (45%, 100 mL) and stirred for further 16 h. After filtration through a pad of Celite® the organic phase was separated and the aqueous layer was extracted with iPr$_2$O (3×50 mL). Purification of the crude by flash chromatography on silica gel (petroleum ether/EtOAc, 9/1) gave a white foam (2.0 g) which was subjected to crystallization of Taddol from CCl_4. The solid was accurately washed and the mother liquors combined and concentrated, affording compound **28** (809 mg, impure of Taddol). A second purification by flash chromatography on basic alumina (toluene/CH_2Cl_2, 95/5) finally afforded pure **28** (598 mg, 73%) as colourless oil. R_f=0.40 (basic alumina plate, toluene/CH_2Cl_2, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.94–6.75 (m, 4H), 6.04–5.79 (m, 1H), 5.44–5.21 (m, 3H), 4.50–4.36 (m, 2H), 4.28–4.03 (m, 1H), 3.75 (s, 3H), 3.35 (s, 6H), 2.88 (d, 1H, J=4.5 Hz), 2.61–2.47 (m, 1H), 2.17–1.49 (m, 10H), 0.93 (d, 3H, J=6.3 Hz), 0.84 (d, 3H, J=6.3 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 153.9, 152.3, 136.4, 134.6, 121.4, 118.5, 117.4, 114.4, 106.9, 83.9, 70.5, 55.6, 55.3, 39.9, 36.0, 34.4, 32.4, 27.0, 24.4, 22.1, 21.0, 17.2; FT-IR (CCl_4): ν 3602, 3468, 2960, 2834, 2289, 1848, 1730, 1558, 1504, 1465, 1386, 1227, 1111, 929; $[\alpha]_D^{20}$=+51.8 (c=0.48, EtOAc); HRMS (ESI): calculated for $C_{25}H_{42}NO_5$: 436.3063 $[M+NH_4]^+$; found: 436.3066 (resolution 10,000).

3.1.15. 1-{(*R*)-1-[(*S*)-2-((1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl)-1-methoxy-methoxy-ethyl]-allyloxy}-4-methoxy-benzene (29). To a stirred solution of alcohol **28** (598 mg, 1.43 mmol) in CH_2Cl_2 (4.0 mL), was added DIPEA (1.5 mL, 8.58 mmol), TBAI (106 mg, 0.29 mmol) and MOMCl (543 μL, 7.15 mmol). After stirring for 7 h, the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (10 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **29** (628 mg, 95%) as a colourless oil. R_f=0.28 (basic alumina plate, iPr$_2$O/toluene, 5/95); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92–6.75 (m, 4H), 5.91 (ddd, 1H, J_1=17.1 Hz, J_2=10.7 Hz, J_3=6.3 Hz), 5.34–5.22 (m, 3H), 4.86 (s, 3H), 4.67 (br, 1H), 4.33 (d, 1H, J=5.3 Hz), 4.22–4.15 (m, 1H), 3.75 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 3.29 (s, 3H), 2.43 (br, 1H), 2.05–1.52 (m, 9H), 0.91 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 152.6, 137.9, 135.1, 120.3, 117.9, 117.3, 114.3, 107.0, 97.8, 83.3, 79.5, 55.6, 55.3, 54.3, 40.3, 36.3, 34.0, 31.8, 26.9, 24.4, 22.2, 21.2, 17.3; FT-IR (CCl_4): ν 2932, 2833, 2289, 2007, 1848, 1742, 1544, 1510, 1466, 1442, 1369, 1230, 1153, 1040, 926; $[\alpha]_D^{20}$=+59.7 (c=0.47, EtOAc); HRMS (ESI): calculated for $C_{27}H_{46}NO_6$: 480.3325 $[M+NH_4]^+$; found: 480.3318 (resolution 10,000).

3.1.16. (1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxy-methoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enecarbaldehyde (30). To a stirred solution of compound **29** (602 mg, 1.30 mmol) in CH_3CN/H_2O (7.6 mL, v/v: 98/2), was added $LiBF_4$ (122 mg, 1.30 mmol). After stirring for 6 h, the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (15 mL) and CH_2Cl_2 (10 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL) to give crude **30** (540 mg), which was used without further purification. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1), for analytical purposes, afforded pure **30** as a colourless oil. R_f=0.47 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.81 (d, 1H, J=3.9 Hz), 6.92–6.70 (m, 4H), 5.90–5.70 (m, 1H), 5.49–5.19 (m, 3H), 4.85–4.62 (m, 3H), 3.75 (s, 3H), 3.65 (dt, 1H, J_1=9.5 Hz, J_2=3.8 Hz), 3.31 (s, 3H), 2.72–2.45 (m, 2H) 2.15–1.65 (m, 9H), 0.94 (d, 3H, J=6.4 Hz), 0.84 (d, 3H, J=6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 206.9, 135.7, 134.4, 121.5, 118.8, 117.0, 114.4, 97.4, 81.9, 79.0, 55.6, 51.8, 37.5, 34.0, 30.1, 28.1, 24.2, 21.7, 20.7, 18.2; FT-IR (CCl_4): ν 2962, 2290, 1719, 1558, 1508, 1261, 1225, 1103, 1008, 980, 823; $[\alpha]_D^{20}$=+36.6 (c=0.13, EtOAc); HRMS (ESI): calculated for $C_{25}H_{40}NO_5$: 434.2906 $[M+NH_4]^+$; found: 434.2914 (resolution 10,000).

3.1.17. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxy-methoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-methanol (31). To a stirred solution of crude **30**, in EtOH (13.6 mL), was added $NaBH_4$ (74 mg, 1.95 mmol). After stirring for 20 min, the reaction mixture was treated with solid NH_4Cl (696 mg, 13.0 mmol), stirred for further 30 min, diluted with iPr$_2$O and dried over Na_2SO_4. Purification by flash chromatography (petroleum ether/EtOAc, 8/2) afforded compound **31** (408 mg, 75%, over two steps) as a colourless oil. R_f=0.15 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88–6.75 (m,

4H), 5.91 (ddd, 1H, $J_1=16.8$ Hz, $J_2=10.2$ Hz, $J_3=6.3$ Hz), 5.33–5.27 (m, 3H), 4.88 (d, 1H, $J=6.8$ Hz), 4.76 (d, 1H, $J=6.8$ Hz), 4.67–4.61 (m, 1H), 3.93 (dt, 1H, $J_1=9.6$ Hz, $J_2=3.3$ Hz), 3.82–3.71 (m, 4H), 3.63–3.54 (m, 1H), 3.39 (s, 3H), 2.43 (br, 1H), 2.07 (br, 1H), 2.00–1.47 (m, 10H), 0.91 (d, 3H, $J=6.8$ Hz), 0.84 (d, 3H, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 152.1, 137.1, 134.8, 121.0, 118.8, 117.2, 114.4, 97.6, 82.7, 79.8, 62.0, 56.0, 55.6, 41.3, 36.3, 34.2, 30.9, 27.0, 24.2, 22.2, 21.0, 16.6; FT-IR (CCl_4): ν 3514, 2961, 2933, 2896, 2290, 2003, 1857, 1544, 1507, 1259, 1228, 1105, 1041, 1008, 930; $[\alpha]_D^{20}=+61.2$ ($c=0.57$, EtOAc); HRMS (ESI): calculated for $C_{25}H_{42}NO_5$: 436.3063 $[M+NH_4]^+$; found: 436.3060 (resolution 10,000).

3.1.18. Methanesulfonic acid (1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl ester (32). To a cold (0 °C), stirred solution of alcohol **31** (367 mg, 0.88 mmol) in CH_2Cl_2 (7.0 mL), was added TEA (367 μL, 2.63 mmol) followed by MsCl (102 μL, 1.30 mmol). After 1 h, the reaction mixture was warmed to room temperature and stirred for 2 h. The solution was concentrated under reduced pressure and filtered through a plug of silica gel. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 8/2) afforded mesylate **32** (414 mg, 95%) as a colourless oil. $R_f=0.20$ (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89–6.76 (m, 4H), 5.87 (ddd, 1H, $J_1=16.2$ Hz, $J_2=10.4$ Hz, $J_3=5.8$ Hz), 5.37–5.29 (m, 3H), 4.85 (d, 1H, $J=6.9$ Hz), 4.78–4.70 (m, 2H), 4.34–4.13 (m, 2H), 3.85 (dt, $J_1=10.4$ Hz, $J_2=2.6$ Hz, 1H), 3.75 (s, 3H), 3.33 (s, 3H), 3.01 (s, 3H), 2.47 (br, 1H), 2.27–2.13 (m, 1H), 2.07–1.50 (m, 9H), 0.92 (d, 3H, $J=6.9$ Hz), 0.89 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 152.2, 135.8, 134.8, 120.9, 118.7, 117.1 (2C), 114.4 (2C), 97.5, 82.2, 79.1, 69.4, 55.8, 55.6, 37.7, 37.3, 37.1, 33.8, 30.0, 27.2, 23.9, 22.0, 20.7, 18.1; FT-IR (CCl_4): ν 2962, 2898, 2291, 2004, 1857, 1742, 1544, 1507, 1370, 1345, 1229, 1178, 1106, 1041, 1007, 979; $[\alpha]_D^{20}=+64.0$ ($c=0.48$, EtOAc); HRMS (ESI): calculated for $C_{26}H_{44}NO_7S$: 514.2839 $[M+NH_4]^+$; found: 514.2831 (resolution 10,000).

3.1.19. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetonitrile (33). To a stirred solution of mesylate **32** (410 mg, 0.83 mmol) in CH_3CN (8.0 mL), was added 18-crown-6 (1.09 g, 4.13 mmol) and KCN (269 mg, 4.13 mmol). After stirring for 2.5 h at 80 °C, the red solution was diluted with CH_2Cl_2 and filtered through a plug of silica gel. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **33** (353 mg, quant.) as a colourless oil. $R_f=0.31$ (petroleum ether/EtOAc, 8/2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.92–6.75 (m, 4H), 5.87 (ddd, 1H, $J_1=16.3$ Hz, $J_2=10.4$ Hz, $J_3=5.9$ Hz), 5.43–5.30 (m, 3H), 4.88–4.75 (m, 3H), 3.80–3.69 (m, 4H), 3.32 (s, 3H), 2.53 (br, 1H), 2.41–2.30 (m, 2H), 2.30–2.12 (m, 1H), 2.12–1.88 (m, 3H), 1.77–1.40 (m, 6H), 0.93 (d, 3H, $J=6.3$ Hz), 0.89 (d, 3H, $J=6.3$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.9, 152.0, 134.8, 134.7, 121.0, 119.8, 119.0, 117.0, 114.4, 97.7, 81.7, 79.2, 55.8, 55.6, 39.7, 34.4, 29.4, 27.3, 26.5, 23.6, 22.0, 20.5, 19.2, 17.3; FT-IR (CCl_4): ν 2961, 2934, 2896, 2847, 2834, 2290, 2003, 1857, 1558, 1507, 1465, 1441, 1427, 1388, 1370, 1250, 1228, 1182, 1152, 1106, 1066, 1041, 1006, 980; $[\alpha]_D^{20}=+23.9$ ($c=1.02$, EtOAc); HRMS (ESI): calculated for $C_{26}H_{38}NO_4$: 428.2801 $[M+H]^+$; found: 428.2811 (resolution 10,000).

3.1.20. {(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-acetaldehyde (34). To a cold (−78 °C), stirred solution of compound **33** (67 mg, 0.16 mmol) in toluene/*n*-hexane (2.55 mL, v/v: 1/2), was added DIBAL-H (1.5 M in toluene, 1.1 mL, 1.56 mmol). After stirring for 1 h, the reaction mixture was treated with EtOAc (1.3 mL) and an aqueous tartaric acid solution (1.0 M, 1.3 mL), then warmed to room temperature and stirred for further 1 h. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (5×5 mL). The organic extracts were washed with a saturated $NaHCO_3$ aqueous solution (2×5 mL) to give crude **34** (68 mg), which was used without further purification. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 14/1), for analytical purposes, afforded pure **34** (67 mg, quant.) as a colourless oil. $R_f=0.39$ (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, 1H, $J=2.2$ Hz), 6.89–6.74 (m, 4H), 5.87 (ddd, 1H, $J_1=17.1$ Hz, $J_2=10.7$ Hz, $J_3=6.0$ Hz), 5.38–5.24 (m, 3H), 4.86–4.70 (m, 3H), 3.80–3.67 (m, 4H), 3.31 (s, 3H), 2.53–2.29 (m, 4H), 2.07–1.85 (m, 3H), 1.73–1.60 (m, 4H), 1.60–1.46 (m, 1H), 1.35–1.23 (m, 1H), 0.95 (d, 3H, $J=6.7$ Hz), 0.84 (d, 3H, $J=6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 154.0, 152.2, 135.8, 134.9, 121.0, 118.7, 117.1, 114.4, 99.6, 82.1, 79.3, 55.8, 55.6, 43.3, 40.1, 34.7, 32.5, 29.8, 27.5, 23.9, 22.1, 20.8, 19.0; FT-IR (CCl_4): ν 2961, 2910, 2834, 2713, 2003, 1857, 1727, 1559, 1507, 1466, 1442, 1388, 1370, 1259, 1226, 1152, 1105, 1068, 1042, 1008, 980; $[\alpha]_D^{20}=+27.6$ ($c=0.46$, EtOAc); HRMS (ESI): calculated for $C_{26}H_{38}O_5$: 448.3063 $[M+NH_4]^+$; found: 448.3048 (resolution 10,000).

3.1.21. (*S*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (35). To a cold (0 °C), stirred solution of AllMgBr (1.0 M in Et_2O, 3.8 mL, 3.80 mmol) was added ^{d}Ipc$_2$BOMe[13c] (1.0 M in THF, 4.2 mL, 4.18 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h, cooled to −78 °C and treated with a solution of aldehyde **34** (545 mg, 1.27 mmol) in THF (10.0 mL). After stirring for 48 h, the reaction mixture was warmed to 0 °C and treated with a NaOH aqueous solution (6.0 M, 6.4 mL) and H_2O_2 (35%, 4.4 mL). After 3 h at room temperature, the mixture was heated to 50 °C and stirred for further 2 h. The organic phase was separated and the aqueous layer was extracted with EtOAc (3×10 mL). Purification of the crude by flash chromatography (petroleum ether/EtOAc, 85/15) afforded compound **35** (420 mg, 70%) as a colourless oil. For characterization and analytical data, see below.

3.1.22. (*S*)-1-{(1*R*,2*R*,6*R*)-6-Isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enyl}-pent-4-en-2-ol (35). To a cold (0 °C), stirred suspension of (*R*,*R*)-**4**[11] (0.53 mmol, based on the amount of $CpTiCl_3$) in Et_2O (6.0 mL), was added a solution of AllMgBr (1.0 M in Et_2O, 444 μL, 0.44 mmol). After stirring the brown-green solution for 1.5 h, the reaction mixture was cooled to −78 °C. To this solution

was added, via cannula, a solution of aldehyde **34** (96 mg, 0.22 mmol) in Et_2O (2.0 mL). The reaction mixture was stirred for 3 h, treated with a NH_4F aqueous solution (45%, 5 mL) and stirred for further 15 h at room temperature. The organic phase was separated and the aqueous layer was extracted with iPr_2O (3×10 mL). Purification of the crude by flash chromatography (petroleum ether/EtOAc, 85/15) afforded compound **35** (92 mg, 87%) as a colourless oil. R_f=0.38 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90–6.78 (m, 4H), 5.96–5.79 (m, 2H), 5.39–5.30 (m, 3H), 5.20–5.11 (m, 2H), 4.87 (d, 1H, J=6.8 Hz), 4.77 (d, 1H, J=6.8 Hz), 4.75–4.70 (m, 1H), 3.89–3.73 (m, 5H), 3.36 (s, 3H), 2.42–2.25 (m, 2H), 2.17–1.99 (m, 2H), 1.99–1.67 (m, 7H), 1.67–1.48 (m, 3H), 1.43–1.25 (m, 2H), 0.93 (d, 3H, J=6.7 Hz), 0.85 (d, 3H, J=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.9, 152.2, 136.5, 134.9, 134.7, 121.0, 118.7, 118.4, 117.2, 114.4, 97.4, 82.5, 79.4, 68.3, 55.8, 55.6, 42.2, 38.8, 34.7, 34.3, 34.1, 30.4, 27.2, 24.2, 22.5, 20.9, 18.0; FT-IR (CCl_4): ν 3585, 3403, 3028, 2961, 2290, 2004, 1855, 1548, 1506, 1465, 1441, 1386, 1368, 1260, 1227, 1150, 1103, 1010, 927; $[\alpha]_D^{20}$=+77.0 (c=1.04, EtOAc); HRMS (ESI): calculated for $C_{29}H_{44}NaO_5$: 495.30809 [M+Na]$^+$; found: 495.30596 (resolution 23,400).

3.1.23. *tert*-Butyl-((*S*)-1-{(1*R*,2*R*,6*R*)-6-isopropyl-2-[(2*S*,3*R*)-2-methoxymethoxy-3-(4-methoxy-phenoxy)-pent-4-enyl]-3-methyl-cyclohex-3-enylmethyl}-but-3-enyloxy)-diphenyl-silane (36). To a stirred solution of alcohol **35** (500 mg, 1.06 mmol) in CH_2Cl_2 (12.0 mL), was added imidazole (360 mg, 5.29 mmol) followed by TBDPSCl (581 mg, 2.11 mmol). After stirring for 16 h at room temperature, the solvent was removed under reduced pressure and the crude was purified by flash chromatography (petroleum ether/EtOAc, 25/1) to give compound **36** (677 mg, 90%) as a colourless oil. R_f=0.59 (petroleum ether/EtOAc, 8/2); HRMS (ESI): calculated for $C_{45}H_{66}NO_5Si$: 728.4710 [M+NH_4]$^+$; found: 728.4700 (resolution 10,000).

3.1.24. (2*S*,3*R*)-1-{(1*R*,5*R*,6*R*)-6-[(*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enyl]-5-isopropyl-2-methyl-cyclohex-2-enyl}-3-(4-methoxy-phenoxy)-pent-4-en-2-ol (37). To a cold (−20 °C), stirred solution of compound **36** (520 mg, 0.73 mmol) in CH_2Cl_2 (22.0 mL), was added Me_2S (209 mg, 3.36 mmol) and $BF_3\cdot OEt_2$ (550 mg, 3.88 mmol).[37] After 30 min (time control is essential), the reaction mixture was treated with a saturated $NaHCO_3$ aqueous solution (4.0 mL) and warmed to room temperature under vigorous stirring. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). Purification of the crude by flash chromatography (toluene/iPr_2O, 8/2) afforded compound **37** (219 mg, 45%) as a colourless oil. R_f=0.31 (toluene/iPr_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.69 (m, 4H), 7.47–7.35 (m, 6H), 6.91–6.81 (m, 4H), 5.94–5.81 (m, 2H), 5.39–5.29 (m, 2H), 5.17 (br, 1H), 5.01–4.94 (m, 2H), 4.38 (dd, 1H, J_1=6.7 Hz, J_2=4.1 Hz), 3.92–3.78 (m, 5H), 2.33–2.24 (m, 2H), 2.20–2.12 (m, 1H), 2.01–1.84 (m, 2H), 1.70–1.32 (m, 9H), 1.07 (s, 9H), 0.88 (d, 3H, J=6.7 Hz), 0.80 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 152.0, 136.0, 135.6, 135.3, 135.0, 134.6, 134.3, 129.5, 127.5, 121.1, 119.5, 117.4, 117.1, 114.5, 83.8, 70.9, 70.6, 55.7, 40.9, 38.8, 34.2, 33.4, 32.3, 31.2, 27.3, 27.0, 23.9, 22.3, 20.7, 19.4; FT-IR (CCl_4): ν 3400, 3072, 2963, 2905, 2290, 2001, 1854, 1558, 1442, 1413, 1296, 1219, 1018, 823; $[\alpha]_D^{20}$=+30.1 (c=0.77, EtOAc).

3.1.25. 2,2-Dimethyl-propionic acid (1*S*,2*R*)-1-{(1*R*,5*R*,6*R*)-6-[(*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-5-isopropyl-2-methyl-cyclohex-2-enylmethyl}-2-(4-methoxy-benzyl)-but-3-enyl ester (38). To a stirred solution of compound **37** (87 mg, 0.13 mmol), pyridine (1.0 mL) and DMAP (3.2 mg, 0.026 mmol) in CH_2Cl_2 (2.0 mL), was added PivCl (32 μL, 0.26 mmol). After stirring for 16 h at 40 °C, the reaction mixture was treated with a saturated NH_4Cl aqueous solution (5.0 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with water and brine. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **38** (65 mg, 66%) as a colourless oil. R_f=0.45 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.64 (m, 4H), 7.48–7.31 (m, 6H), 6.90–6.76 (m, 4H), 6.08–5.96 (m, 1H), 5.85 (ddd, 1H, J_1=17.1 Hz, J_2=10.6 Hz, J_3=6.4 Hz), 5.41–5.32 (m, 2H), 5.19–5.03 (m, 3H), 4.56 (dd, 1H, J_1=J_2=5.3 Hz), 3.94 (br, 1H), 3.77 (s, 3H), 2.37–2.27 (m, 1H), 2.21–2.11 (m, 1H), 2.06–1.97 (m, 1H), 1.96–1.84 (m, 1H), 1.75–1.41 (m, 6H), 1.41–1.26 (m, 3H), 1.13 (s, 9H), 1.07 (s, 9H), 0.79 (d, 3H, J=7.1 Hz), 0.77 (d, 3H, J=6.8 Hz); $[\alpha]_D^{20}$=+6.0 (c=0.95, EtOAc); HRMS (ESI): calculated for $C_{48}H_{67}O_5Si$: 751.4758 [M+H]$^+$; found: 751.4761 (resolution 12,000).

3.1.26. 2,2-Dimethyl-propionic acid (1*S*,2*R*)-1-((1*R*,5*R*,6*R*)-6-[(*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enyl]-5-isopropyl-2-methyl-cyclohex-2-enylmethyl)-2-hydroxy-but-3-enyl ester (39). To a cold (0 °C), stirred solution of compound **38** (20 mg, 0.03 mmol) in CH_3CN/H_2O (328 μL, v/v: 4/1), was added ceric ammonium nitrate (36 mg, 0.07 mmol).[38] After stirring for 1 h, the reaction mixture was filtered through a plug of silica (eluting with EtOAc). Purification of the crude by flash chromatography (toluene/iPr_2O, 95/5) afforded **39** (11 mg, 67%) as a colourless oil. R_f=0.31 (toluene/iPr_2O, 95/5); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74–7.65 (m, 4H), 7.47–7.32 (m, 6H), 6.07–5.72 (m, 2H), 5.38–4.84 (m, 6H), 4.14 (br, 1H), 3.88 (br, 1H), 2.40–1.80 (m, 4H), 1.73–1.05 (m, 29H), 0.78 (d, 3H, J=6.7 Hz), 0.76 (d, 3H, J=6.5 Hz).

3.1.27. 2,2-Dimethyl-propionic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenylsilanyloxy)-7-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (40). To a stirred solution of diene **39** (11 mg, 0.017 mmol) in degassed CH_2Cl_2 (2.1 mL), was slowly added a solution of Grubbs catalyst **15** (1.5 mg, 0.002 mmol) in CH_2Cl_2 (166 μL) and stirred for 24 h. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded **40** (2.2 mg, 21%) as a colourless oil. For characterization and analytical data, see below.

3.1.28. 2,2-Dimethyl-propionic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (41). To stirred a solution of diene **38** (50 mg, 0.066 mmol) in

CH_2Cl_2 (5.5 mL), was added, via syringe pump (during 45 min), a freshly prepared solution of Grubbs catalyst **15** (5.7 mg, 0.0066 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 15 h, the reaction mixture was heated to 40 °C for 24 h. Purification of the crude by flash chromatography (petroleum ether/CH_2Cl_2, 4/6) afforded the starting material **38** (7.7 mg) and the RCM product **41** (25 mg, 52%; 62% considering the recovered starting material) as a colourless oil. R_f=0.50 (petroleum ether/EtOAc, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.63 (m, 4H), 7.51–7.33 (m, 6H), 6.80–6.63 (m, 4H), 6.12 (dt, 1H, J_1=11.0 Hz, J_2=5.3 Hz), 5.71 (dd, 1H, J_1=11.0 Hz, J_2=9.6 Hz), 5.44 (dt, 1H, J_1=10.6 Hz, J_2=3.5 Hz), 5.23 (br, 1H), 4.97 (dd, 1H, J_1=9.6 Hz, J_2=2.7 Hz), 4.01 (br, 1H), 3.76 (s, 3H), 2.64–2.54 (m, 1H), 2.43–2.34 (m, 1H), 1.87–1.59 (m, 10H), 1.52–1.35 (m, 2H), 1.26 (s, 9H), 1.17–1.08 (m, 10H), 0.81 (d, 3H, J=6.8 Hz), 0.55 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 153.9, 151.6, 137.2, 135.9, 134.1, 133.9, 130.6, 129.7, 127.6, 121.0, 117.1, 114.4, 74.9, 74.1, 72.8, 55.6, 39.0, 37.6, 37.3, 36.2, 36.1, 33.2, 31.8, 27.2, 27.0, 26.9, 24.3, 23.8, 21.0, 19.2, 15.7; FT-IR (CCl_4): ν 3072, 2962, 2932, 2859, 2291, 2003, 1847, 1730, 1551, 1507, 1480, 1463, 1442, 1428, 1389, 1367, 1260, 1229, 1158, 1106, 1065, 1008, 980; $[\alpha]_D^{20}$=+137.7 (c=0.74, EtOAc); HRMS (ESI): calculated for $C_{39}H_{55}O_3Si$: 599.3921 [M-PMPOH+H]$^+$; found: 599.3918 (resolution 10,000).

3.1.29. 2,2-Dimethyl-propionic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenylsilanyloxy)-7-hydroxy-1-isopropyl-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (40). To a cold (0 °C), stirred solution of compound **41** (22 mg, 0.03 mmol) in CH_3CN/H_2O (1.0 mL, v/v: 4/1), was added ceric ammonium nitrate (35 mg, 0.064 mmol) in one portion.[38] After 15 min, the reaction mixture was diluted with CH_3CN and filtered through a plug of silica gel. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 8/2) afforded compound **40** (14.8 mg, 80%) as a colourless oil. R_f=0.45 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.61 (m, 4H), 7.49–7.35 (m, 6H), 6.01 (dt, 1H, J_1=11.1 Hz, J_2=5.2 Hz), 5.62 (dd, 1H, J_1=11.1 Hz, J_2=9.6 Hz), 5.27–5.17 (m, 2H), 4.60 (dd, 1H, J_1=9.6 Hz, J_2=2.9 Hz), 3.93 (br, 1H), 2.53–2.42 (m, 1H), 2.32–2.23 (m, 1H), 1.92–1.58 (m, 9H), 1.53–1.32 (m, 2H), 1.31–1.20 (m, 10H), 1.09 (s, 9H), 0.81 (d, 3H, J=6.8 Hz), 0.58 (d, 3H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 137.0, 135.9, 135.8, 134.3, 134.1, 129.6, 129.2, 129.1, 127.6, 127.5, 121.4, 76.6, 72.7, 68.5, 39.0, 37.9, 37.0, 35.9, 35.6, 32.9, 31.8, 27.2, 27.0, 24.3, 23.7, 21.0, 19.2, 16.2; FT-IR (CCl_4): ν 3448, 3072, 3051, 2962, 2931, 2859, 2291, 2003, 1847, 1731, 1558, 1480, 1462, 1428, 1389, 1368, 1262, 1218, 1156, 1104, 1009, 980; $[\alpha]_D^{20}$=+71.3 (c=0.94, EtOAc); HRMS (ESI): calculated for $C_{39}H_{56}NaO_4Si$: 639.38400 [M+Na]$^+$; found: 639.38421 (resolution 17,000).

3.1.30. (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-ol (42). To a stirred solution of compound **37** (12 mg, 0.018 mmol) in degassed benzene (1.66 mL), was added, via syringe pump (during 30 min), a freshly prepared solution of Grubbs catalyst **15** (1.5 mg, 0.0018 mmol) in benzene (0.14 mL). After 19 h at 80 °C, the reaction mixture was cooled at room temperature, treated with DMSO (5 μL) and stirred for 12 h. Purification of the crude by flash chromatography (petroleum ether/EtOAc, 9/1) afforded compound **42** (9.2 mg, 80%) as a colourless oil. R_f=0.78 (petroleum ether/EtOAc, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.66 (m, 4H), 7.48–7.33 (m, 6H), 6.79 (s, 4H), 6.11 (dt, 1H, J_1=11.4 Hz, J_2=5.1 Hz), 5.74 (dd, 1H, J_1=11.4 Hz, J_2=9.9 Hz), 5.23 (br, 1H), 4.90 (dd, 1H, J_1=9.9 Hz, J_2=2.6 Hz), 4.32–4.21 (m, 1H), 4.04–3.96 (m, 1H), 3.78 (s, 3H), 2.75 (s, 1H), 2.60–2.50 (m, 1H), 2.41–2.29 (m, 1H), 1.92–1.73 (m, 3H), 1.73–1.53 (m, 8H), 1.42–1.31 (m, 1H), 1.21–1.03 (m, 10H), 0.80 (d, 3H, J=6.8 Hz), 0.57 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 151.3, 137.2, 135.9, 134.2, 134.1, 130.8, 129.6, 127.6, 127.5, 127.0, 121.1, 117.3, 114.6, 77.6, 73.5, 72.6, 55.6, 38.0, 37.0, 35.9, 35.7, 33.3, 33.0, 27.2, 27.0, 24.3, 23.9, 19.2, 16.5, 14.0; FT-IR (CCl_4): ν 3400, 3072, 2962, 2859, 2290, 2003, 1852, 1742, 1558, 1428, 1389, 1258, 1219, 1105, 1066, 1007, 980; $[\alpha]_D^{20}$=+94.0 (c=0.92, EtOAc); HRMS (ESI): calculated for $C_{41}H_{54}NaO_4Si$: 661.36835 [M+Na]$^+$; found: 661.36917 (resolution 17,600).

3.1.31. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (43). To a stirred suspension of the mixed anhydride **19** (prepared according to Ref. 6b, 102 mg, 0.43 mmol) and of alcohol **42** (9.2 mg, 0.014 mmol) in $(CH_2Cl)_2$ (0.9 mL), was added DMAP (1.8 mg, 0.014 mmol) followed by TEA (40 μL, 0.29 mmol). After stirring for 1 h, the suspension (slightly more soluble) was heated to 80 °C for 2 h, cooled to room temperature overnight and heated to 80 °C for further 4 h. Purification by flash chromatography (petroleum ether/EtOAc, 1/9) afforded compound **43** (9.2 mg, 82%) as a clear yellowish oil. R_f=0.3 (petroleum ether/EtOAc, 2/8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.64 (m, 4H), 7.58 (d, 1H, J=15.7 Hz), 7.52 (s, 1H), 7.48–7.32 (m, 6H), 7.10 (s, 1H), 6.78–6.67 (m, 4H), 6.61 (d, 1H, J=15.7 Hz), 6.14 (dt, 1H, J_1=11.1 Hz, J_2=5.1 Hz), 5.81 (dd, 1H, J_1=11.1 Hz, J_2=10.5 Hz), 5.62–5.52 (m, 1H), 5.22 (br, 1H), 5.05–4.96 (m, 1H), 4.01 (br, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.66–2.54 (m, 1H), 2.44–2.33 (m, 1H), 1.91–1.02 (m, 22H), 0.78 (d, 3H, J=6.7 Hz), 0.54 (d, 3H, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.9, 154.1, 151.8, 138.6, 137.0, 136.0, 135.9, 134.2, 134.0, 130.4, 129.6, 127.7, 127.6, 127.5, 122.2, 121.0, 117.7, 116.5, 114.4, 75.4, 74.3, 72.7, 55.6, 37.9, 37.1, 36.1, 36.0, 33.6, 33.1, 32.0, 27.0, 26.5, 24.3, 23.7, 21.0, 19.3, 16.1; FT-IR (CCl_4): ν 2963, 2291, 2002, 1847, 1709, 1646, 1558, 1413, 1260, 1219, 1160, 1099, 1012; $[\alpha]_D^{20}$=+71.6 (c=0.92, EtOAc); HRMS (ESI): calculated for $C_{48}H_{61}N_2O_5Si$: 773.43443 [M+H]$^+$; found: 773.43474 (resolution 15,100); calculated for $C_{48}H_{60}N_2NaO_5Si$: 795.41637 [M+Na]$^+$; found: 795.41775 (resolution 15,100).

3.1.32. (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-acrylic acid (*Z*)-(1*R*,4a*R*,6*S*,7*R*,11*S*,12a*R*)-11-hydroxy-1-isopropyl-7-(4-methoxy-phenoxy)-4-methyl-1,2,4a,5,6,7,10,11,12,12a-decahydro-benzocyclodecen-6-yl ester (44). To a

stirred solution of compound **43** (10 mg, 0.013 mmol) in THF (0.5 mL), was added TBAF (1.0 M in THF, 52 μL, 0.057 mmol). After stirring for 19 h, the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (petroleum ether/EtOAc, 1/9) afforded compound **44** (5.9 mg, 85%) as a clear yellowish oil. R_f=0.15 (petroleum ether/EtOAc, 1/9); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 1H, J=15.7 Hz), 7.48 (s, 1H), 7.10 (s, 1H), 6.84–6.74 (m, 4H), 6.62 (d, 1H, J=15.7 Hz), 6.01 (dt, 1H, J_1=11.4 Hz, J_2=4.9 Hz), 5.86 (dd, 1H, J_1=11.4 Hz, J_2=9.5 Hz), 5.71–5.64 (m, 1H), 5.33 (br, 1H), 5.17 (dd, 1H, J_1=9.5 Hz, J_2=2.7 Hz), 4.05 (br, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.83–2.74 (m, 1H), 2.54–2.44 (m, 1H), 2.17–1.26 (m, 14H), 0.88 (d, 3H, J=6.8 Hz), 0.79 (d, 3H, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 154.3, 151.8, 138.9, 137.1, 136.1, 129.2, 128.4, 122.3, 121.1, 117.7, 116.4, 114.5, 75.4, 74.1, 71.7, 55.6, 37.9, 37.6, 36.2, 35.7, 33.6, 32.9, 32.3, 27.1, 24.5, 23.9, 21.0, 16.1; FT-IR (CCl_4): ν 3468, 2963, 2928, 2855, 2290, 2002, 1847, 1709, 1559, 1414, 1261, 1219, 1099, 1013; $[\alpha]_D^{20}$=+79.3 (c=0.30, EtOAc); HRMS (ESI): calculated for $C_{32}H_{43}N_2O_5$: 535.3166 $[M+H]^+$; found: 535.3165 (resolution 10,000).

3.1.33. Molecular mechanics and semi-empirical calculations. The potential energy surface of structures **A**–**F** (Z and E stereoisomers, Fig. 2) was searched using Monte Carlo[27b] conformational searches with MacroModel (v8.5)[27a] running on a 3.0 GHz Intel Pentium 4 with LINUX Red Hat 9 operating system. The calculations were performed with the MM2* force field using the GB/SA continuum solvent model for $CHCl_3$.[27c] Interconversion of ring structures was enabled using the ring-opening method of Still.[39] Ring closure bonds were defined for both the six and ten-membered rings present in structures **A**–**F**. Each search was run in blocks of 15,000 steps until convergence was reached, that is, no new structures were found and the global minimum energy remained constant throughout the search. Typically, 50,000–60,000 steps were enough to ensure convergence. Each new cycle used as input the results of the previous cycle and different ring-closure bond choices were used. During the search, structures with energy 20 kJ mol^{-1} higher than the current global minimum were discarded. Structures were fully minimized for up to 5000 steps until the gradient was less than 0.05 kJ Å mol^{-1} using the Polak Ribiere conjugate gradient method.[40] Redundant conformations were removed after heavy atom superimposition (RMSD cutoff=0.25 Å). The lowest energy conformers obtained with MacroModel for the Z and the corresponding E stereoisomers of structures **A**–**F** (using a 20.0 kJ mol^{-1} energy window from the global minima) were optimized at the PM3 level[24] using the Gaussian 03 package.[28]

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26. When an allylic aryl ether is present, there are low-quality parameters for the torsions: C(sp2)–C(sp3)–O(sp3)–C(sp2) [where a 00–C(sp3)–O(sp3)–00 is used] and Lp–O(sp3)–C(sp2)=C(sp2) [where a Lp–O(sp3)–C0*00 is used].
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Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, *Revision B.04* (Gaussian, Pittsburgh, PA, **2003**).

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A stereocontrolled route to protected isocyanates from alcohols

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Abstract—Full details are given for a modified Mitsunobu approach to the formation of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2** from a wide range of alcohols **10** with predominantly, inversion of configuration. The resulting products **2** can be regarded as protected isocyanates **6**.

1. Introduction

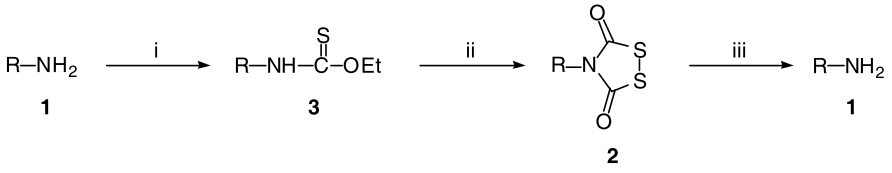
Amongst the plethora of protecting groups that have been developed for primary amines **1**,[1] the dithiasuccinoyl imide or 1,2,4-dithiazolidine-3,5-dione **2** (abbreviated to RNDts) stands out in that it can be cleaved under unusual conditions. For example, such imides **2** can be converted back into primary amines **1** using mild thiolysis, under basic conditions[2] or using phosphorus(III) reagents under partly aqueous conditions[3] (Scheme 1).

The 1,2,4-dithiazolidine-3,5-dione heterocycle is, however, stable under strongly acidic, mildly basic and photochemical cleavage conditions and hence, this group has been used in orthogonal protection strategies in peptide[4] and aminoglycoside[5] synthesis. *N*-Alkylated 1,2,4-dithiazolidine-3,5-diones **2** can be prepared from primary amines **1** via the treatment of their corresponding alkoxythiocarbamates **3** with chlorocarbonylsulfenyl chloride (Scheme 1).[6]

As an alternative, straightforward route to *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2**, we have recently shown that it is possible to use the parent heterocycle, 1,2,4-dithiazolidine-3,5-dione **4** and its corresponding potassium salt **5** as the nucleophile in substitution reactions with reactive alkyl halides. These studies have also highlighted the fact that such imides **2** can also be regarded as a masked form of an isocyanate **6**, which can be released on treatment with triphenylphosphine, under anhydrous conditions (Scheme 2).[7,8] In addition to representing a protected form of a primary amine therefore, alkylated 1,2,4-dithiazolidine-3,5-diones **2** are also versatile and potentially very useful, synthetic intermediates.

Our findings on the use of **4** in Mitsunobu-type alkylations of alcohols have also been reported (in preliminary form).[9] Herein, we give full experimental details and a discussion of the methods used in this synthetic procedure.

Imide derivatives and phthalimide in particular, have seen wide usage as nitrogen nucleophiles in Mitsunobu amination reactions.[10] In order to circumvent the problems that are sometimes encountered in the cleavage of *N*-alkylated phthalimides, a variety of other imide and related



Scheme 1. Reagents and conditions: (i) $EtOCS_2CH_2CO_2H$ or $EtOCS_2CSOEt$; (ii) ClCOSCl; (iii) $HOCH_2CH_2SH$, Et_3N or Ph_3P, H_2O.

Keywords: 1,2,4-Dithiazolidine-3,5-diones; Mitsunobu amination; Isocyanates; Urethanes; Amino acids.
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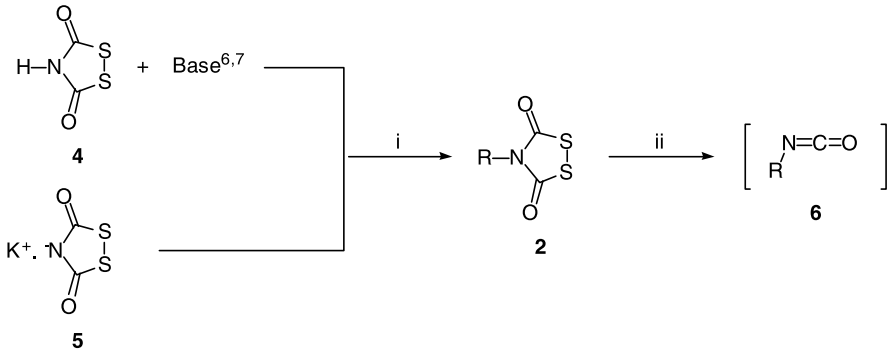
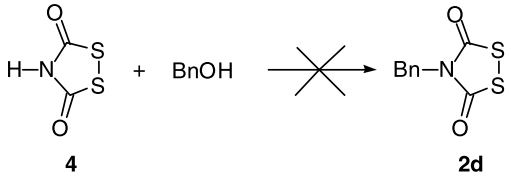


Scheme 2. Reagents and conditions: (i) R-Hal; (ii) Ph_3P, $PhCH_3$, $\triangle$.

derivatives have also been developed for use as protected amine nucleophiles.[11] The ability of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2** to act as protected amines or isocyanates, coupled with the remarkably high acidity of the parent heterocycle **4** ($pK_a = 2.85$),[7–9] suggested that conducting investigations into the behaviour of **4** under Mitsunobu amination conditions would be worthwhile.

2. Results and discussion

Initial experiments were carried out using benzyl alcohol, **4**, triphenylphosphine and diethyl azodicarboxylate (DEAD) (Scheme 3). As expected, these reaction conditions appeared only to result in degradation of **4**, presumably by reaction with triphenylphosphine and none of the desired product **2d** could be detected. An attempt to avoid this degradation by pre-mixing the triphenylphosphine and DEAD, followed by sequential addition of benzyl alcohol **10d** and **4**, also failed.



Scheme 3. Reagents and conditions: Ph_3P, $EtO_2C–N{=}N–CO_2Et$.

Castro et al. had reported the unexpected formation of betaine **7** in attempted Mitsunobu reactions with sulfamide **8** as the nucleophile (Fig. 1)[12] and showed that it could be used effectively to promote stereoselective Mitsunobu-type reactions between carboxylic and nitrogen acids and alcohols. Most importantly, Brummond and Lu showed that **7** could be used to mediate a Mitsunobu-type reaction with the phosphine-sensitive thiazolidinedione **9** (Fig. 1).[13]

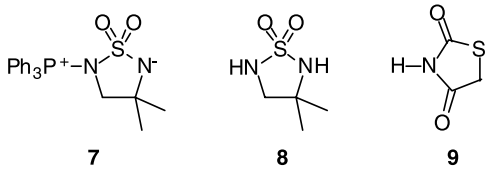
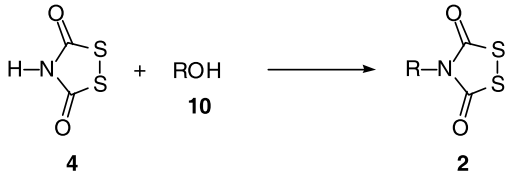


Figure 1.

We therefore carried out a systematic study of the use of **7** in reactions between **4** and a range of alcohols **10** (Scheme 4). These were chosen in order to compare results with those obtained in traditional and modified[14] Mitsunobu reactions with phthalimide.



Scheme 4. Reagents and conditions: **7**, CH_2Cl_2.

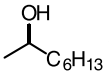
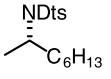
Initial experiments were carried out with three simple secondary alcohols. The results obtained are detailed in Table 1 with comparative yields and enantiomeric excesses, where available, being given for similar reactions of these alcohols with phthalimide under standard Mitsunobu conditions (Scheme 5) and using Barrett's imidate ester method (Scheme 6).

Isopropyl **10a** and *R*-*sec*-butyl **10b** alcohols gave an acceptable (51%) isolated yield of the corresponding *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2a** and **2b**, respectively. In the latter case, the ee of the product was found to be 71% and this is consistent with the observation that incomplete inversion is sometimes observed with betaine reagent **7**.[12] Whilst *R*-2-octanol **10c** gave a good yield of the desired product **2c**, we were unable to determine the enantiomeric excess by chiral HPLC, although further reactions of this product (see later) suggested that **2c** had an ee of 97%.

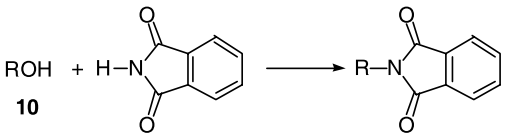
Analogous reactions of a number of allylic and benzylic alcohols were also investigated (Table 2).

Benzyl alcohol **10d** gave a very good (80%) yield of the desired *N*-alkylated 1,2,4-dithiazolidine-3,5-dione **2d**. A higher yield was expected from this reactive alcohol and indeed, this result is directly comparable with the 75% yield obtained in a standard Mitsunobu reaction between benzyl alcohol **10d** and phthalimide.[17] *R*-α-Methylbenzyl alcohol **10e** gave a lower yield (50%) of **2e** than that obtained for the corresponding phthalimide derivative (73%) produced using Barrett's imidate ester method.[14a] Interestingly however, both processes resulted in some racemisation, the products

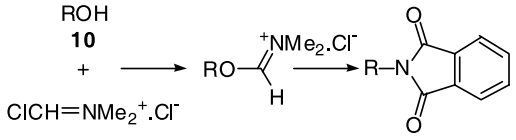
Table 1. Mitsunobu-type reactions with secondary alcohols

Alcohol **10** (equiv)[a]	Product **2**	Yield[b] (%)	ee (%)	Comparable reactions with phthalimide	
				Yield (%)	ee (%)
 **10a** (0.21)	 **2a**	51	—	[c]75[15] —[d]	— —
 **10b** (0.89)	 **2b**	51	71	[c]75 (±)[14] —[d]	— 92
 **10c** (0.93)	 **2c**	76	97[e]	[c]75[14] —[d]	>99 96

[a] Equivalent of **10** relative to **4**.
[b] Based on **10**.
[c] Using typical Mitsunobu conditions.
[d] Using Barrett's imidate ester method.
[e] Determined from urethane **11a** (see text).



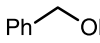
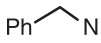
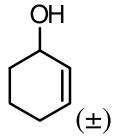
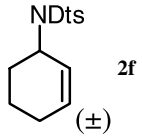
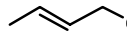
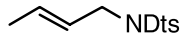
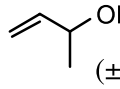
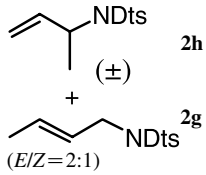
Scheme 5. Reagents and conditions: $R'O_2C–N{=}N–CO_2R'$, Ph_3P, solvent.



Scheme 6. Reagents and conditions: (i) CH_3CN, 0 °C; (ii) KPhth, 60–70 °C.

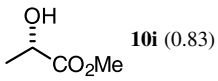
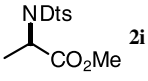
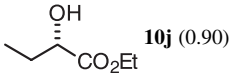
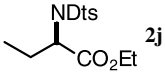
having similar ee's (70 and 72%, respectively), suggesting that Mitsunobu-type reactions of **10e** probably involve significant S_N1 character. Racemic 2-cyclohexen-1-ol **10f** gave a lower yield (38%) of the desired product **2f** although this is comparable with the imidate ester result obtained by Barrett et al. with potassium phthalimide (34%). In comparison, Sammes et al. have reported a 57% yield for the preparation of *N*-cyclohex-2-enyl phthalimide under standard Mitsunobu conditions.[18] Crotyl alcohol **10g** gave an acceptable yield of the desired product **2g** in an *E*/*Z* ratio which remained unchanged from the starting alcohol **10g**. For this alcohol, no products arising from allylic transposition could be detected. In contrast, racemic 3-buten-l **10h** gave a mixture of products in a relatively low (39%) yield. Here, the ratio of direct alcohol displacement/allylic transposition was found to be 2:1 with **2g** being obtained in

Table 2. Mitsunobu-type reactions with benzylic and allylic alcohols

Alcohol **10** (equiv)[a]	Product(s) **2**	Yield[b] (%)	ee (%)	Comparable reactions with phthalimide	
				Yield (%)	ee (%)
 **10d** (0.83)	 **2d**	80	—	[c]75[16] —[d]	— —
 **10e** (0.92)	 **2e**	50	71	—[c] [d]73[13a]	— 72
 **10f** (0.83)	 **2f**	38	—	[c]57 (±)[17] [d]34 (±)[13a]	— —
 **10g** (0.84)	 (*E*/*Z*=12:1) **2g**	57	—	—[c] —[d]	— —
 **10h** (1.00)	 (*E*/*Z*=2:1)	39 (overall)	—	—[c] [d]98 (±)[13a]	— —

[a] Equivalent of **10** relative to **4**.
[b] Based on **10**.
[c] Using typical Mitsunobu conditions.
[d] Using Barrett's imidate ester method.

Table 3. Mitsunobu-type reactions with hydroxyesters

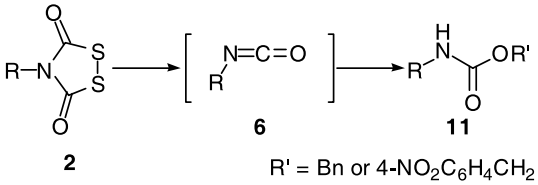
Alcohol 10 (equiv)[a]	Product 2	Yield[b] (%)	ee (%)	Comparable reactions with phthalimide	
				Yield %	ee %
 **10i** (0.83)	 **2i**	52	92	[c,d]45[18] [e]25[13b]	>99% —
 **10j** (0.90)	 **2j**	37	71	—[c] —[e]	— —

[a] Equiv. of **10** relative to **4**.
[b] Based on **10**.
[c] Using typical Mitsunobu conditions.
[d] Yield for reaction with *S*-ethyl lactate.
[e] Using Barrett's imidate ester method.

an *E*/*Z* ratio of 2:1. Interestingly, in comparison, Barrett et al. reported a very high (98%) yield in the imidate ester reaction of **10h** with potassium phthalimide, with no allylic transposition being observed.[14b]

In order to investigate our methodology in the context of the preparation of protected α- and β-amino acids, reactions between *S*-methyl lactate **10i** and *S*-ethyl 3-hydroxybutyrate **10j** and 1,2,4-dithiazolidine-3,5-dione **4** and betaine **7** were also carried out (Table 3).

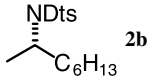
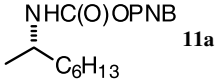
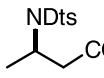
S-Methyl lactate **10i** gave a 52% yield of **2i**, with an enantiomeric excess of 92%. This result compares favourably with the analogous preparation of *S*-*N*-phthaloyl alanine ethyl ester under Mitsunobu conditions, using a solid-supported azodicarboxylate, where a 45% yield and > 99% ee have been reported for the reaction between *S*-ethyl lactate and phthalimide.[19] (Note: a 58% yield was originally reported for the standard Mitsunobu reaction between racemic ethyl lactate and phthalimide.[17]) In comparison, the reaction between *S*-methyl lactate **2i** and potassium phthalimide under imidate ester conditions, has been reported to give a low (25%) yield of *N*-phthaloyl alanine methyl ester with complete racemisation.[14b]



Scheme 7. Reagents and conditions: Ph_3P (1.00 equiv), R′OH (0.80–1.07 equiv), $PhCH_3$, reflux.

S-Ethyl 3-hydroxybutyrate **10j** gave a disappointing (37%) yield of the corresponding protected β-amino acid **2j** with some racemisation having occurred. The low yield, in this instance, is however, perhaps not surprising, given the propensity of such β-hydroxy esters to undergo elimination under Mitsunobu reaction conditions.[10a] Unfortunately, comparative literature data for reactions between phthalimide and 3-hydroxybutyrates are not available.

Table 4. Urethane preparation

Imide **2**	Alcohol (equiv)	Product **11**	Yield (%)	ee (%)	Imide **2** ee (%)
 **2b**	PNB–OH (0.80)	 **11a**	[a]92	97	[b]
 **2e**	Bn–OH (0.85)	 **11b**	[a]25	69	70
 **2e**	PNB–OH (0.85)	 **11c**	[a]79	69	70
 **2i**	Bn–OH (1.07)	 **11d**	[c]59	90	92
 **2j**	PNB–OH (1.05)	 **11e**	[c]89	71	71

[a] Based on benzylic alcohol.
[b] Could not be determined by chiral HPLC.
[c] Based on *N*-alkyl-1,2,4-dithiazolidine-3,5-dione **2**.

A number of the *N*-alkylated 1,2,4-dithiazolidine-3,5-dione products **2** were converted, through the intermediate (detectable but not isolated/characterised) isocyanates **6**, into urethane-protected amines **11** (Scheme 7).

Our previously reported procedure[8] was employed, in which a mixture of the *N*-alkylated 1,2,4-dithiazolidine-3,5-dione **2** was heated with an equimolar quantity of triphenylphosphine and a benzylic alcohol (0.80–1.07 equiv) in toluene, under reflux. Table 4 summarises the results of these studies, with yields being calculated, in all cases, from the minor component in the reaction.

As mentioned earlier, we had been unable to determine the enantiomeric excess in **2c**, which was derived from *R*-2-octanol but the enantiomers of the 4-nitrobenzyl urethane **11a** proved to be separable by chiral HPLC, indicating a 97% ee Importantly, for all of the urethanes **11** isolated, the enantiomeric excess was determined to be the same as the starting alcohol **10**, within experimental error, suggesting that the intermediate isocyanates **6** were configurationally stable under the reaction conditions employed.

The preparation of the urethane-protected alanine methyl ester derivative **11d** from the *S*-methyl lactate-derived 1,2,4-dithiazolidine-3,5-dione **2i** allowed us to confirm that inversion of configuration was the predominant pathway in the original Mitsunobu-type reaction. The formation of protected β-amino ester **11f** illustrates the potential use of the overall methodology in the synthesis of β-amino acids.

3. Conclusions

Overall, we have shown that the structurally simple heterocycle, 1,2,4-dithiazolidine-3,5-dione **4** provides an excellent isocyanate synthetic equivalent in Mitsunobu-type reactions using a wide variety of alcohols. The methodology developed has, therefore, significant potential to be of use in the synthesis of amines, ureas and also many nitrogen-containing heterocycles. The stability of this heterocyclic system to strongly acidic, mildly basic and photochemical conditions provides the possibility of carrying an isocyanate through a series of synthetic steps in a protected form, greatly expanding the number of possibilities for using this highly reactive functional group in synthesis.

4. Experimental

4.1. General

Enantiomeric excesses were determined by chiral HPLC, using a Chiralcel® OD™ column, eluting with 9:1 v/v hexane-propan-2-ol. Detection was carried out at a wavelength of 254 nm.

Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected.

Specific rotations were determined using an Optical Activity AA-1000 automatic polarimeter in a 1dm path length cell.

Infrared spectra were recorded using a Nicolet Magna 550 spectrometer with only major absorbances being quoted, using the abbreviations: w, weak; m, medium; s, strong and br, broad. Thin film samples were prepared by evaporation of a dilute chloroform sample of the compound on a sodium chloride plate.

^{1}H NMR spectra were obtained using Brücker AM300, ACF300 and Advance DRX400 spectrometers at operating frequencies of 300 and 400 MHz. Chemical shifts are quoted in ppm relative to tetramethylsilane with referencing to the residual protonated solvent peak. Coupling constants are given to the nearest 0.5 Hz. The abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad are used.

^{13}C NMR spectra were obtained using either a Brücker ACF300 or Brücker Advance DRX400 spectrometer at operating frequencies of 75 and 100 MHz, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane, with referencing to the solvent peak. Assignments are derived from DEPT editing.

Mass spectra were determined using Thermoquest Finnigan TRACE 2000 GC–MS and Micromass GCT instruments or by the EPSRC National Mass Spectrometry Service Centre, Swansea, UK in electron impact (EI), ammonia chemical ionisation (CI) and positive ion electrospray (ES^{+}) modes.

Analytical thin layer chromatography was carried out using glass or aluminium-backed plates coated with Merck Kieselgel 60 F_{254}, with plates being visualised by quenching of UV fluorescence or by staining with iodine or potassium permanganate as appropriate. Flash chromatography was carried out using BDH silica gel with particle size 40–63 μm.

Solvents and reagents were used as supplied commercially or purified using standard procedures as appropriate. Petroleum ether refers to the fraction of light petroleum ether boiling between 40 and 60 °C.

Solvents were removed under reduced pressure using a Büchi R110 Rotovapor, equipped with a water and/or dry ice condenser as appropriate.

4.2. Mitsunobu-type *N*-alkylation of 1,2,4-dithiazolidine-3,5-dione 4—general procedure

The alcohol **10** (typically *ca* 0.74 mmol) was added to a stirred solution of 1,2,4-dithiazolidine-3,5-dione **4** (typically 0.82 mmol) and betaine reagent **7**[12] in dichloromethane (2 cm^3) at room temperature. After stirring at this temperature for 18 h, the solvent was evaporated in vacuo and the resulting residue was purified by flash chromatography on silica gel (typically eluting with 90% petroleum ether–10% ethyl acetate) to give the *title compound* **2**.

4.2.1. 4-Isopropyl-1,2,4-dithiazolidine-3,5-dione 2a. Using

the general procedure above with isopropyl alcohol **10a** (300 μL, 3.93 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2a** (74 mg, 51%). as a colourless oil. Data as reported previously.[8]

4.2.2. *S*-4-*sec*-Butyl-1,2,4-dithiazolidine-3,5-dione 2b. Using the general procedure above with *R*-*sec*-butyl alcohol **10b** (67 μL, 0.73 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2b** (74 mg, 51%) as a colourless oil, 71% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +24 ($c=1$, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3044–2883 (w), 1736 (s), 1646 (s), 1454 (m), 1311 (w), 1223 (m), 1189 (w), 1034 (w), 949 (m) and 692 (s); δ_H (300 MHz; $CDCl_3$) 0.86 (3H, t, $J=8$ Hz, CH_3CH_2), 1.42 (3H, d, $J=8$ Hz, CH_3CH), 1.72–1.84 (1H, m, CH_AH_B), 1.94–2.06 (1H, m, CH_AH_B) and 4.39–4.49 (1H, m, C*H*); δ_C (100.6 MHz; $CDCl_3$) 14.2, 17.4 (*C*H_3), 32.3 (*C*H_2) and 56.6 (*C*H); *m*/*z* (EI) 191 (M^+, 12%), 135 (14), 99 (21), 73 (100) and 64 (33).

4.2.3. *S*-4-(1-Methylheptyl)-1,2,4-dithiazolidine-3,5-dione 2c. Using the general procedure above with *R*-2-octanol **10c** (120 μL, 0.76 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2c** (142 mg, 76%) as a brown oil, enantiomers inseparable by chiral HPLC; $[\alpha]_D^{21}$ +14 ($c=1$, $CHCl_3$); (Found M^+ (EI) 247.3810, $C_{10}H_{17}NO_2S_2$ requires 247.3795); ν_{max} (thin film)/cm^{-1} 3030–2834 (w), 1734 (s), 1685 (s), 1516 (w), 1375 (w), 1221 (m), 1136 (w) and 1059 (w); δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, $J=8$ Hz, CH_3CH_2), 1.11–1.36 (8H, complex, $(CH_2)_4$) 1.45 (3H, d, $J=8$ Hz, CH_3CH), 1.55–1.79 (1H, m, CH_AH_BCH), 1.94–2.12 (1H, m, CH_AH_BCH) and 4.42–4.58 (1H, m, C*H*); δ_C (75.1 MHz; $CDCl_3$) 14.0, 17.3 (*C*H_3), 22.5, 26.5, 28.8, 31.6, 32.2 ($(CH_2)_5$), 56.6 (*C*H) and 167.7 (*C*=O); *m*/*z* (EI) 247 (M^+, 7%), 155 (13), 135 (11), 129 (44) and 64 (100).

4.2.4. 4-Benzyl-1,2,4-dithiazolidine-3,5-dione 2d. Using the general procedure above with benzyl alcohol **10d** (70 μL, 0.68 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2d** (74 mg, 80%) as an off-white solid. Data as reported previously.[20]

4.2.5. *S*-4-(1-Phenylethyl)-1,2,4-dithiazolidine-3,5-dione 2e. Using the general procedure above with *R*-α-methylbenzyl alcohol **10e** (90 μL, 0.75 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2e** (90 mg, 50%), as a brown oil, 70% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −32 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 240.0168, $C_{10}H_{10}NO_2S_2$ requires 240.0153); ν_{max} (thin film)/cm^{-1} 3033–2844 (w), 1732 (s), 1630 (m), 1595 (m), 1554 (m), 1505 (w), 1426 (w), 1297 (m), 1190 (w), 1024 (w) and 723 (m); δ_H (400 MHz; $CDCl_3$) 1.78 (3H, d, $J=7$ Hz, CH_3), 5.73 (1H, q, $J=7$ Hz, C*H*) and 7.24–7.44 (5H, complex, phenyl-*H*); δ_C (100.6 MHz; $CDCl_3$) 16.0 (*C*H_3), 57.6 (*C*H), 128.3, 128.7, 128.9 (phenyl *C*H), 137.9 (phenyl *ipso*-*C*) and 167.8 (*C*=O); *m*/*z* (CI) 240 (MH^+, 9%), 192 (9), 164 (18), 151 (100) and 47 (87).

4.2.6. (±)-4-Cyclohex-2-enyl-1,2,4-dithiazolidine-3,5-dione 2f. Using the general procedure above with (±)-2-cyclohexen-1-ol **10f** (67 μL, 0.68 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2f** (56 mg, 38%), as a white solid; (Found MH^+ (CI) 216.0158, $C_8H_{10}NO_2S_2$ requires 216.0153); mp 89–91 °C; ν_{max} (thin film)/cm^{-1} 2980–2740 (w), 1646 (s), 1296 (m), 1167 (m) and 1134 (m); δ_H (400 MHz; $CDCl_3$) 1.62–2.25 (6H, complex, $(CH_2)_3$), 4.98–5.11 (1H, m, alkene C*H*), 5.46 (1H, dd, $J=2$, 12 Hz, NC*H*) and 5.89–6.01 (1H, m, alkene C*H*); δ_C (100.6 MHz; $CDCl_3$) 21.8, 24.0, 25.5 ($(CH_2)_3$), 56.3 (NCH), 124.4, 131.4 (alkene *C*H) and 167.3 (*C*=O); *m*/*z* (CI) 216 (MH^+, 16%), 164 (36), 136 (100) and 123 (24).

4.2.7. *E*-4-But-2-enyl-1,2,4-dithiazolidine-3,5-dione 2g. Using the general procedure above with crotyl alcohol **10g** (commercial *E*/*Z* mixture, 59 μL, 0.69 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2g** (74 mg, 57%), as a yellow oil; (Found MH^+ (CI) 189.9998, $C_6H_8NO_2S_2$ requires 189.9996); ν_{max} (thin film)/cm^{-1} 3060–2960 (m), 1718 (s), 1656 (m), 1420 (w), 1360 (w), 1340 (w), 1290 (m), 1140 (w), 1020 (w), and 980 (w); δ_H (400 MHz; $CDCl_3$) 1.70 (3H, dd, $J=1$, 6 Hz, CH_3), 4.28 (2H, dd, $J=1$, 7 Hz, CH_2), 5.38–5.55 (1H, m, alkene C*H*) and 5.76–5.89 (1H, m, alkene C*H*); δ_C (100.6 MHz; $CDCl_3$) 17.7 (*C*H_3), 47.7 (*C*H_2), 122.1, 132.9 (2×alkene *C*H) and 167.3 (*C*=O); *m*/*z* (CI) 190 (MH^+, 16%), 164 (18), 136 (100) and 98 (8). ^1H NMR indicated that the product contained a small quantity of *Z*-4-but-2-enyl-1,2,4-dithiazolidine-3,5-dione (*E*/*Z* ratio=12:1). The only ^1H NMR signals for this stereoisomer which could be positively identified were: δ_H (400 MHz; $CDCl_3$) 1.74 (3H, d, $J=$ 6 Hz, CH_3) and 4.40 (2H, d, $J=7$ Hz, CH_2).

4.2.8. (±)-4-(1-Methylallyl)-1,2,4-dithiazolidine-3,5-dione 2h and *E*/*Z*-4-but-2-enyl-1,2,4-dithiazolidine-3,5-dione 2g. Using the general procedure above with (±)-3-buten-2-ol **10h** (64 μL, 0.74 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.74 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave a 2:1 mixture of **2h** and **2g** (55 mg, 39%), as an oil; (Found MH^+ (CI) 189.9998, $C_6H_8NO_2S_2$ requires 189.9996); ν_{max} (thin film)/cm^{-1} 2926 (w), 1734 (m), 1686 (s), 1516 (w), 1311 (w), and 1059 (w); For **2h**: δ_H (400 MHz; $CDCl_3$) 1.56 (3H, d, $J=$ 6.8 Hz, CH_3), 5.00–5.08 (1H, m, NC*H*), 5.25–5.31 (2H, complex, CH=CH_2) and 6.07–6.18 (1H, m, C*H*=CH_2); δ_C (100.6 MHz; $CDCl_3$) 16.8 (*C*H_3), 57.4 (*C*H), 118.6 (CH=*C*H_2), 134.5 (*C*H=CH_2) and 167.2 (*C*=O); Data for **2g** as described above with the *E*/*Z* ratio being 1:2.

4.2.9. *R*-Methyl 2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl)propionate 2i. Using the general procedure above with *S*-methyl lactate **10i** (65 μL, 0.68 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2i** (78 mg, 52%), as an oil, 92% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +44 ($c=1$, $CHCl_3$). All other data as described previously for racemic **2i**.[8]

4.2.10. *R*-Ethyl 3-(3,5-dioxo-1,2,4-dithiazolidin-4-yl)-butyrate 2j. Using the general procedure above with

S-ethyl 3-hydroxybutyrate **10j** (98 μL, 0.74 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2j** (68 mg, 37%), as a yellow oil, 71% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −7 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 250.0210, $C_8H_{12}NO_4S_2$ requires 250.0208); ν_{max} (thin film)/cm^{-1} 1733 (m), 1635 (s), 1456 (w), 1375 (w), 1275 (m), 1173 (m), 1144 (m), 1068 (w), 804 (w) and 698 (m); δ_H (300 MHz; $CDCl_3$) 1.23 (3H, t, $J=7$ Hz, CH_3CH_2), 1.48 (3H, d, $J=7$ Hz, CH_3CH), 2.70 (1H, dd, $J=6$, 17 Hz, $CH_AH_BCO_2Et$), 3.18 (1H, dd, $J=9$, 17 Hz, $CH_AH_BCO_2Et$), 4.11 (2H, dq, $J=1$, 7 Hz, CH_2CH_3) and 4.88–4.96 (1H, m, CHN); δ_C (75.1 MHz; $CDCl_3$) 14.1, 17.4 (2×CH_3), 36.5 (CH_2CO_2Et), 51.7 (CHN), 61.0 (CH_2O) and 167.5, 170.2 (2×C=O); *m/z* (CI) 250 (MH^+, 7%), 206 (10), 204 (100), 156 (13), 116 (53) and 112 (27).

4.3. Urethane 11 formation from 4-alkylated 1,2,4-dithiazolidine-3,5-diones 2

A general procedure for urethane formation has been reported.[8]

4.3.1. *S*-(4-Nitrobenzyl)-1-methylheptyl carbamate 11a. Using the general procedure[8] with *S*-4-(1-methylheptyl)-1,2,4-dithiazolidine-3,5-dione **2b** (120 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and 4-nitrobenzyl alcohol (60 mg, 0.39 mmol) in toluene (2 cm^3) gave **11a** (111 mg, 92% based on 4-nitrobenzyl alcohol) as an oil, 97% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +23 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 309.1816, $C_{16}H_{25}N_2O_4$ requires 309.1814); ν_{max} (thin film)/cm^{-1} 3031–2856 (w), 1732 (s), 1611 (w), 1532 (s), 1452 (w), 1355 (s), 1243 (m), 1201 (m), 1111 (w), 1060 (w), 1024 (w), 740 (w) and 659 (s); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, d, $J=7$ Hz, CH_3CH), 1.14 (3H, d, $J=7$ Hz, CH_3CH), 1.18–1.49 (10H, complex, $(CH_2)_5$), 3.63–3.74 (1H, m, CHN), 4.66 (1H, br d, $J=8$ Hz, NH), 5.17 (2H, s, CH_2Ar) and 7.49, 8.20 (2×2H, AA′BB′, $J=9$ Hz, aryl-*H*); δ_C (100.6 MHz; $CDCl_3$) 14.1, 21.2 (2×CH_3), 22.6, 25.9, 29.1, 31.8, 37.1 ($(CH_2)_5$), 47.4 (CHN), 64.9 (CH_2Ar), 123.7, 128.0 (aryl *C*–H), 144.3, 147.5 (2×aryl *ipso C*) and 155.2 (C=O); *m/z* (CI) 309 (MH^+, 17%), 296 (19), 295 (100), 185 (8), 154 (60), 113 (13) and 106 (28).

4.3.2. *S*-Benzyl-1-phenylethylcarbamate 11b. Using the general procedure8 with *S*-4-(1-phenylethyl)-1,2,4-dithiazolidine-3,5-dione **2e** (140 mg, 0.59 mmol), triphenylphosphine (155 mg, 0.59 mmol) and benzyl alcohol (60 μL, 0.50 mmol) in toluene (2 cm^3) gave **11c** (32 mg, 25% based on benzyl alcohol) as an oily solid, 69% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −34 ($c=1$, $CHCl_3$) (literature $[\alpha]_D^{21}$ +44 ($c=0.59$, $CHCl_3$) for *R*-enantiomer[21]). All other data in agreement with literature values.[22]

4.3.3. *S*-(4-Nitrobenzyl)-1-phenylethyl carbamate 11c. Using the general procedure[8] with *S*-4-(1-phenylethyl)-1,2,4-dithiazolidine-3,5-dione **2e** (140 mg, 0.59 mmol), triphenylphosphine (155 mg, 0.59 mmol) and 4-nitrobenzyl alcohol (76 mg, 0.50 mmol) in toluene (2 cm^3) gave **11c** (118 mg, 79% based on 4-nitrobenzyl alcohol) as a brown oil, 69% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −41 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 301.1174, $C_{16}H_{17}N_2O_4$ requires 301.1188); ν_{max} (thin film)/cm^{-1} 3158–2839 (w), 1705 (s), 1606 (w), 1522 (s), 1450 (w), 1348 (s), 1240 (m), 1061 (m), 1014 (w), 852 (w), 739 (w) and 700 (m); δ_H (400 MHz; $CDCl_3$) 1.51 (3H, d, $J=7$ Hz, CH_3CH), 4.79–4.91 (1H, br m, CH), 5.08 (1H, br s, NH), 5.15, 5.17 (2×1H, AB, $J=14$ Hz, $ArCH_2$), 7.21–7.41 (5H, complex, phenyl-*H*) and 7.49, 8.20 (2×2H, AA′BB′, $J=8$ Hz, aryl-*H*); δ_C (100.6 MHz; $CDCl_3$) 22.4 (CH_3), 50.9 (CH), 65.2 (CH_2), 123.7, 125.9, 127.5, 128.2, 128.4 (aryl *C*–H), 143.1, 144.0 (2×aryl *ipso C*) and 155.0 (C=O); *m/z* (CI) 301 (MH^+, 5%), 295 (13), 280 (16), 279 (100), 201 (10) and 105 (37).

4.3.4. *R*-Benzyloxycarbonyl alanine methyl ester 11d. Using the general procedure[7] with *R*-methyl 2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) propionate **2i** (100 mg, 0.45 mmol), triphenylphosphine (120 mg, 0.46 mmol) and benzyl alcohol (50 μL, 0.48 mmol) in toluene (2 cm^3) gave **11d** (63 mg, 59% based on *R*-methyl 2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) propionate **2i**) as a white, powdery solid, 90% ee (determined by chiral HPLC); mp 45–46 °C (lit.[23] 47–48.5 °C); All other data in agreement with literature values.[23]

4.3.5. *R*-Ethyl 3-(4-nitrobenzyloxycarbonylamino) butyrate 11e. Using the general procedure[7] with *R*-ethyl 3-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) butyrate **2j** (150 mg, 0.60 mmol), triphenylphosphine (164 mg, 0.63 mmol) and 4-nitrobenzyl alcohol (96 mg, 0.63 mmol) in toluene (2 cm^3) gave **11e** (166 mg, 89% based on *R*-ethyl 3-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) butyrate **2j**) as a brown oil, 71% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +5 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 311.1235, $C_{14}H_{19}N_2O_6$ requires 311.1243); ν_{max} (thin film)/cm^{-1} 3050–2836 (w), 1734 (br s), 1608 (w), 1536 (s), 1456 (w), 1348 (s), 1247 (m), 1194 (w), 1109 (w), 1066 (m), 1028 (w), 852 (w) and 739 (w); δ_H (300 MHz; $CDCl_3$) 1.18 (3H, t, $J=7$ Hz, CH_3CH_2), 1.19 (3H, d, $J=7$ Hz, CH_3CH), 2.46 (2H, d, $J=6$ Hz, CH_2CH), 3.96–4.06 (1H, m, $CHCH_3$), 4.07 (2H, q, $J=7$ Hz, CH_2CH_3), 5.11 (2H, s, $ArCH_2$), 5.36 (1H, br d, $J=7$ Hz, NH) and 7.43, 8.14 (2×2H, AA′BB′, $J=9$ Hz, aryl-*H*); δ_C (75.1 MHz; $CDCl_3$) 14.6 (CH_3), 20.7 (CH_3), 40.7 ($CHCH_2$), 44.6 (NCH), 61.1 (CH_3CH_2), 64.3 $ArCH_2$), 124.1, 128.4 (aryl *C*–H), 144.5, 147.9 (2×aryl *ipso C*), 155.4 (urethane C=O) and 171.9 (ester C=O); *m/z* (CI) 311 (MH^+, 86%), 295 (23), 265 (100), 223 (12), 158 (24), 132 (18), 116 (77) and 112 (33).

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To seek an approach toward the chemical conversion of C_{19}-diterpenoid alkaloids to taxoids

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Abstract—This study, as a part of conversion of the C_{19}-diterpenoid alkaloids to the taxoids, described the search of a suitable route to the key intermediate B with four approaches (ABC, ACB, BCA, and CAB) designed and examined. In these cases, a new and efficient approach (CAB) toward the synthesis of the vital intermediates **51** or **52** has been developed. The key steps include the use of a semipinacol rearrangement treatment of **41** with NaOH/DMF under refluxing conditions for **30** min to afford **42**, and the rupture of the *N*-C-19 bond found in **45** or **48** to give **51** or **52**, respectively, through NBS imination followed by the creation of the oxaziridine **47** or the nitrone **50** and finally HIO_4 oxidation cleavages.

1. Introduction

Since Taxol® (paclitaxel, **1**)[1] and Taxotere® (docetaxel, **2**)[2] are currently two of the most exciting drugs in cancer chemotherapy,[3–4] efforts to synthesize taxol (**1**) have produced a wide variety of strategies for construction of the core structures[5] and to-date six total syntheses have been reported.[6–11] The diterpenoid alkaloids are a group of highly oxygenated complex natural products displaying a lot of interesting chemical reactions.[12] They were isolated mainly from both *Aconitum* and *Delphinium* plants (Ranunculaceae) as a rich source.[13] With careful skeletal analysis we have designed a strategy toward conversion of the C_{19}-diterpenoid alkaloids to the taxoids via a series of the degradational steps (Scheme 1). As showed in Scheme 1, the key steps for conversion from A (C_{19}-diterpenoid alkaloids) include mainly modifications of the A ring (de-amination, e.g. cleavage of the *N*-C-19 and *N*-C-17 bonds), the B ring (cleavage of the C-17–C-7 and C-10–C-11 bonds), and the C ring (C-10 or C-12 functionality and cleavage of the C-10–C-12 and C-12–C-13 bonds). After these cleavages to give the key intermediate D which was converted to the taxoids E via a cyclization by pinacol-like coupling developed by Swindell.[14]

On the basis of these considerations, our search for the starting materials has focused on the C_{19}-diterpenoid alkaloids from *Aconitum* species, which are widely distributed in southwest area of China.[15] Among the numerous naturally occurring this type alkaloids, only several compounds such as yunaconitine (**3**), indaconitine (**4**), and crassicauline A (**5**), etc. isolated from many plants are considered to be very useful.

In the course of studies on the chemistry of C_{19}-diterpenoid alkaloids,[16] we have broken through the key cleavages of rings A, B, and C in these alkaloids (Scheme 1, F). Although the results already have provided an important base for conversion into the taxoids, it takes still great effort to afford the vital intermediate **C** (Scheme 1). This is due to the most rigidly complex fused polycyclic system, chemical complexity derived from the *N*-atom, and strong dependence up on the substrates of the C_{19}-diterpenoid alkaloids. In an effort to seek an effective sequence allowed us to convert **A** obtained from the starting material yunaconitine (**3**) into the key intermediate C (Scheme 1) we describe in this paper a number of chemical transformation and other new findings for the purpose. To this end, four different lines of attack (approaches ABC, ACB, BCA, and CAB) designed according to modified sequence of the ring systems have been undertaken.

2. Results and discussion

2.1. Approach ABC

We reported that HIO_4 oxidation of the *N*,*O*-mixed acetal **6**

Keywords: C_{19}-diterpenoid alkaloid; Yunaconitine; N,19-*seco* C19-diterpenoid alkaloid; Semipinacol rearrangement; Imine; Oxaziridine; Nitrone; Taxoid.
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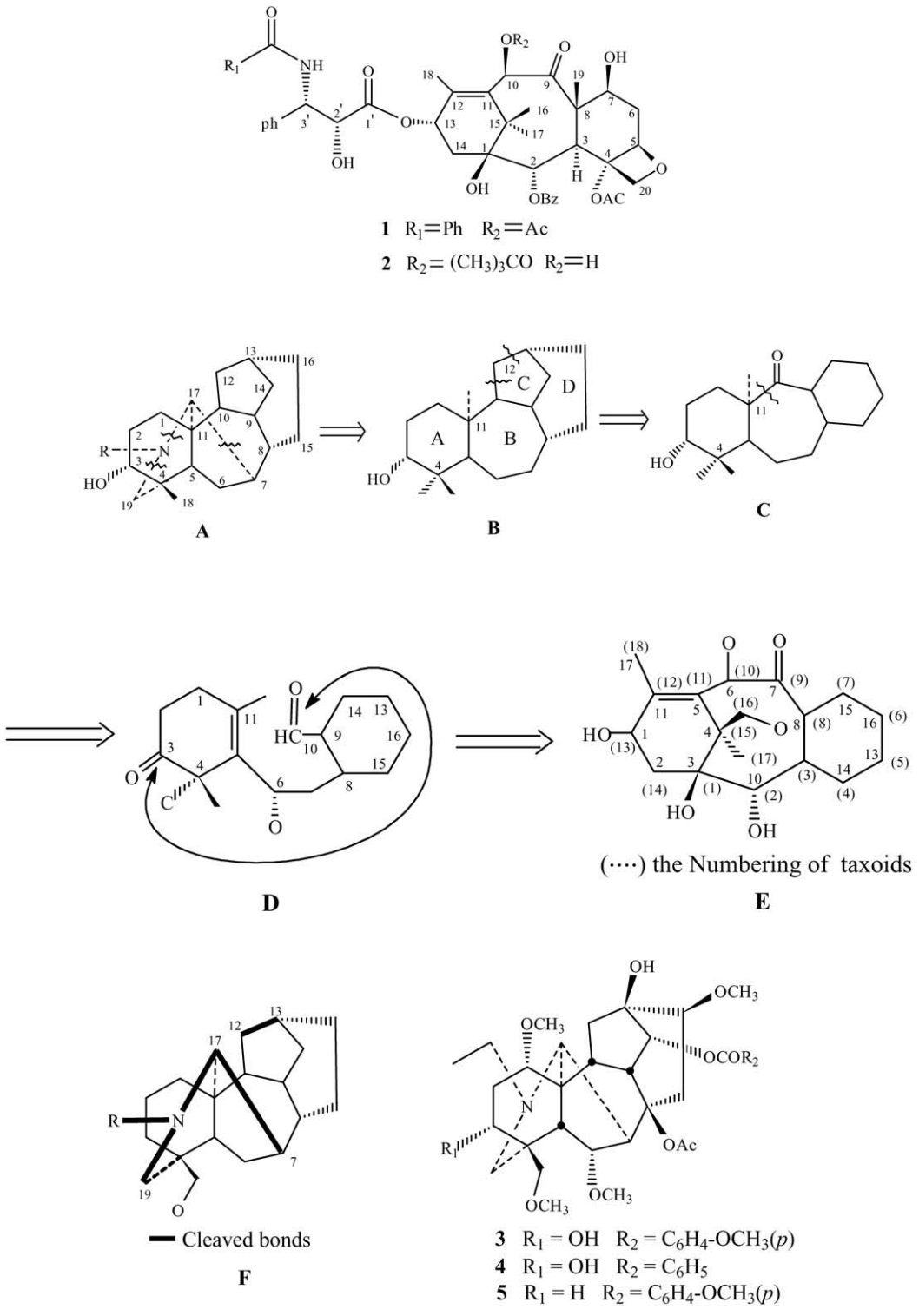
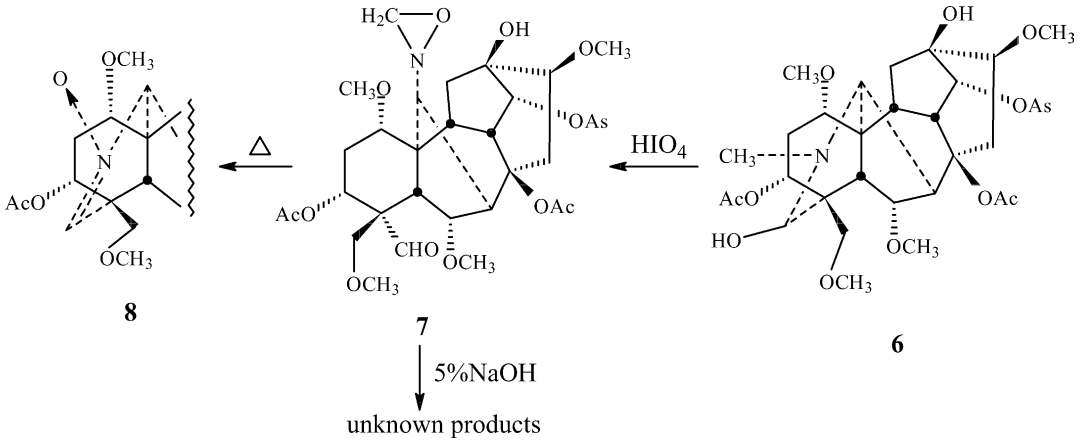


Scheme 1.

gave oxaziridine (**7**)[16t,17] which is unstable to acids, bases, and heating due to decomposition or formation of nitrone **8**[16t] probably because of participation of the hydroxyl at C-8 and the aldehyde group (Scheme 2). But an attempt to reduce the aldehyde group with $NaBH_4$–CH_3OH, or KBH_4–AcOH, which should permit avoiding reformation of the *N*-C-19 bond in **7** or **9**, gave only compounds **10** (49%) or **11** (73%), respectively. Treatment of **7** with K_2CO_3 in CH_3OH–H_2O afforded compounds **9** and **12** (ca.3:1) in 98% total yield (Scheme 3). The presence of *N*-CH_3 group in **10** and **11** was supported by the ^1H and ^{13}C NMR spectra (δ_H 2.60, s; δ_C 42.2, q for **10**; δ_H 2.64, s; δ_C 42.5, q for **11**). The ^{13}C NMR spectrum of **12** exhibited a distinctic lactam signal at δ_C 174.4 s. The afore-mentioned results might prove the aldehyde group in **7** to be recalcitrant mainly due to the bulkiness of hydroxyl or acetyl group at C-3 which was found in our subsequent research.[18]

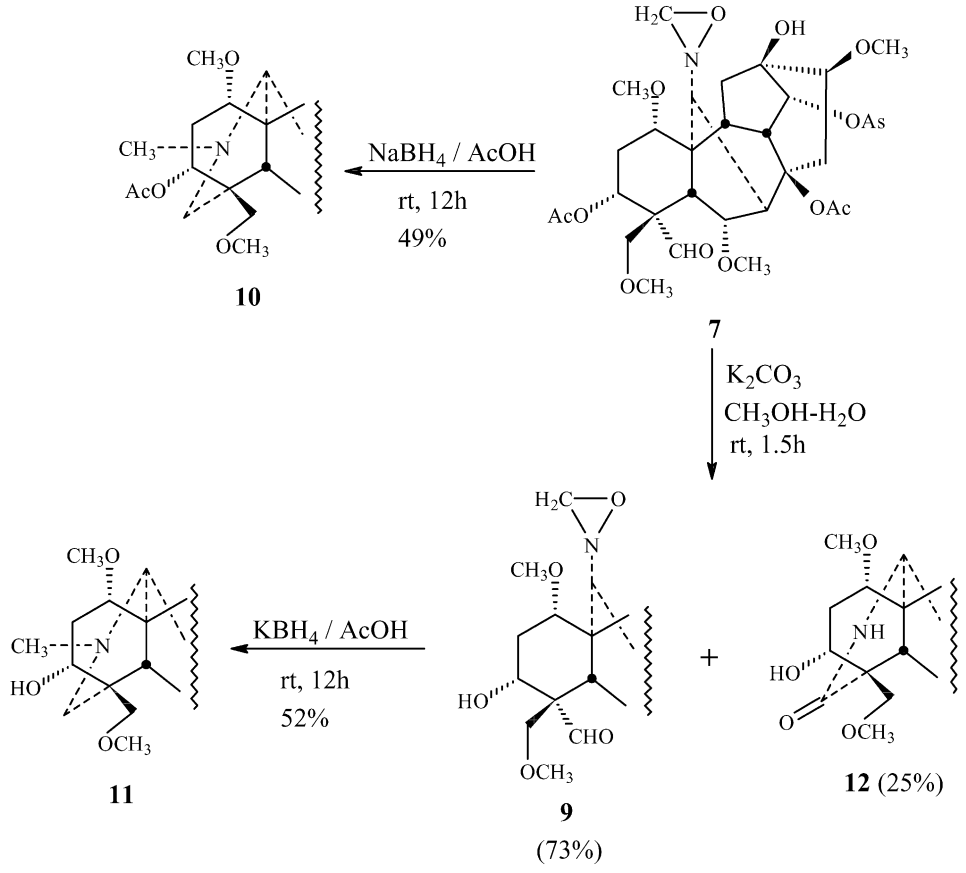


Scheme 2.

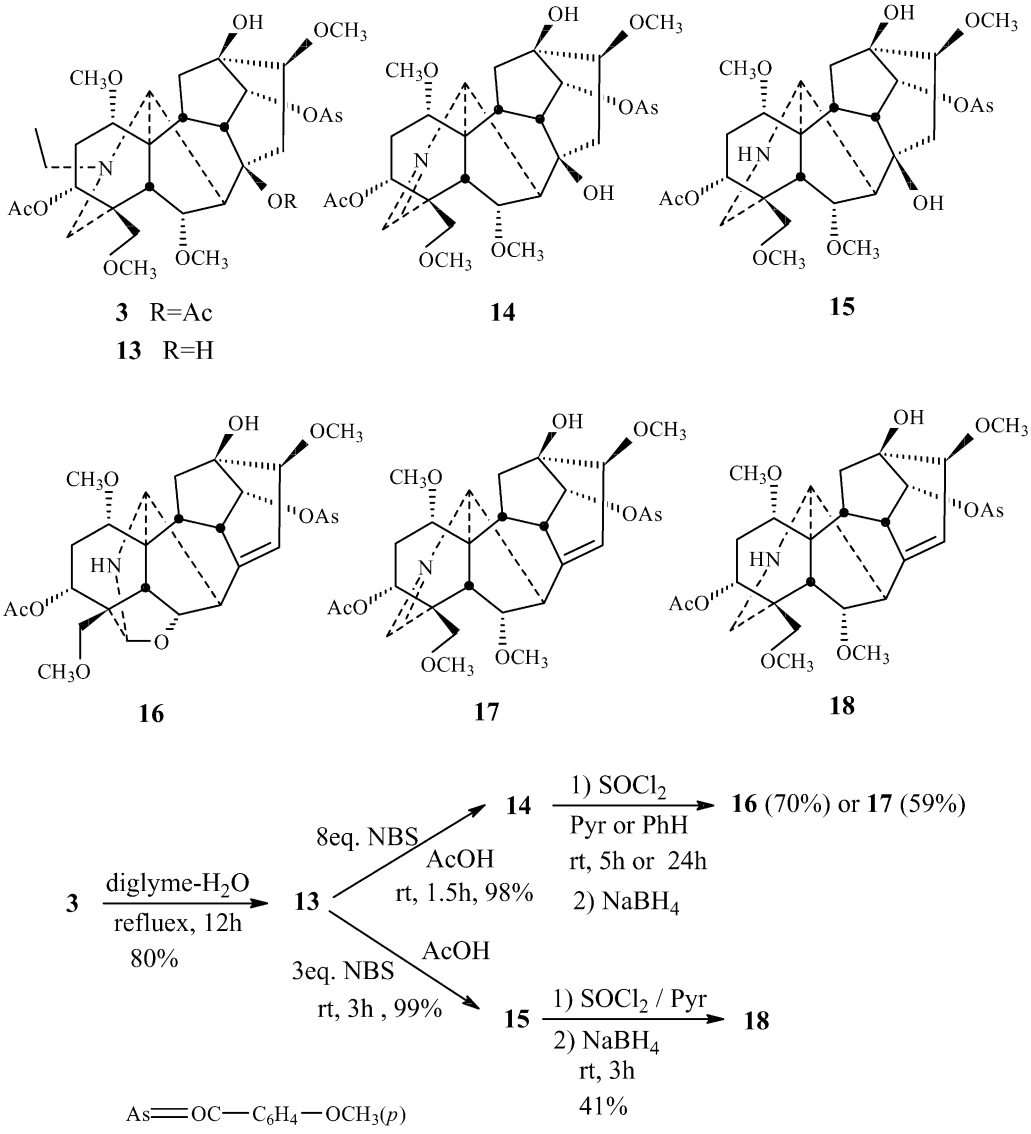
Our studies also showed that after the first fragmentation of C-7–C-17 bond in the molecule it is very difficult to prepare the *N*,19-*seco* compounds with the lower yield of the intermediate imines which are neccessary. Taking the findings into account, we decided prepare, at first, the imines such as **14** based on our developing protocol,[16i,t,v] followed by deamination and cleavaging the C-7–C-17 bond to give **B** (Scheme 1).

Selective hydrolysis of the starting material yunaconitine (**3**) in diglyme-H_2O (4:1) under refluxing conditions gave compound **13** which reacted with a mixture of glacial acetic acid and 8 equiv of NBS to give imine **14** in nearly quantitative yield, along with an important finds to be obviously enhancing the yield of imines using NBS/AcOH rather than NBS/*t*-BuOH previously reported by us,[16t] and the quantitative obtainment of *N*-deethyl product **15** with a three-fold amount of NBS (Scheme 4).

Attempted treatment of imine **14** with $SOCl_2$-pyridine or $SOCl_2$–C_6H_6 followed by $NaBH_4$ to fragment the C-7–C-17 bond via an intermediate 8-chlorro derivative, as previously reported by us,[16n,w] gave compounds **16** (70%) or **17** (59%) respectively. In the ^1H and ^{13}C NMR spectra of **16**, the signals at δ_H 5.66, d, $J=6.2$ Hz (H-15); δ_C 144.2 s (C-8), 116.7 d (C-15) for a trisubstituted double bond and at δ_H



Scheme 3.



Scheme 4.

4.83, dd, J=4.4, 2.0 Hz (H-6); δ_H 4.66, s (H-19); δ_C 87.6 d (C-19) for an *N*,*O*-mixed acetal moiety which also was supported by showing the correlation between H-6 and C-19 in the HMBC spectrum of **16**. The structure of **16** was established based on 2D NMR spectrum (Table 1). The ^{1}H NMR spectrum of **17** showed an imine signal at δ_H 7.47 (br s, H-19) and a trisubstituted double bond at δ_H 5.82 (d, J= 6.2 Hz, H-15). Interestingly, the *N*-deethyl compound **15** was exposed to $SOCl_2$ followed by $NaBH_4$ in similar procedure[16n,w] also produced the pyro product **18** (41%) instead of the desired 7,17-*seco* compound. This seems to show that the obtainment of 7,17-*seco* compounds, in our cases, required to meet simultaneously an anti-periplanar relationship between the lone pair of nitrogen atom and the C-8-Cl bond, and the tertiary amine patterns of the nitrogen atom.

2.2. Approach ACB

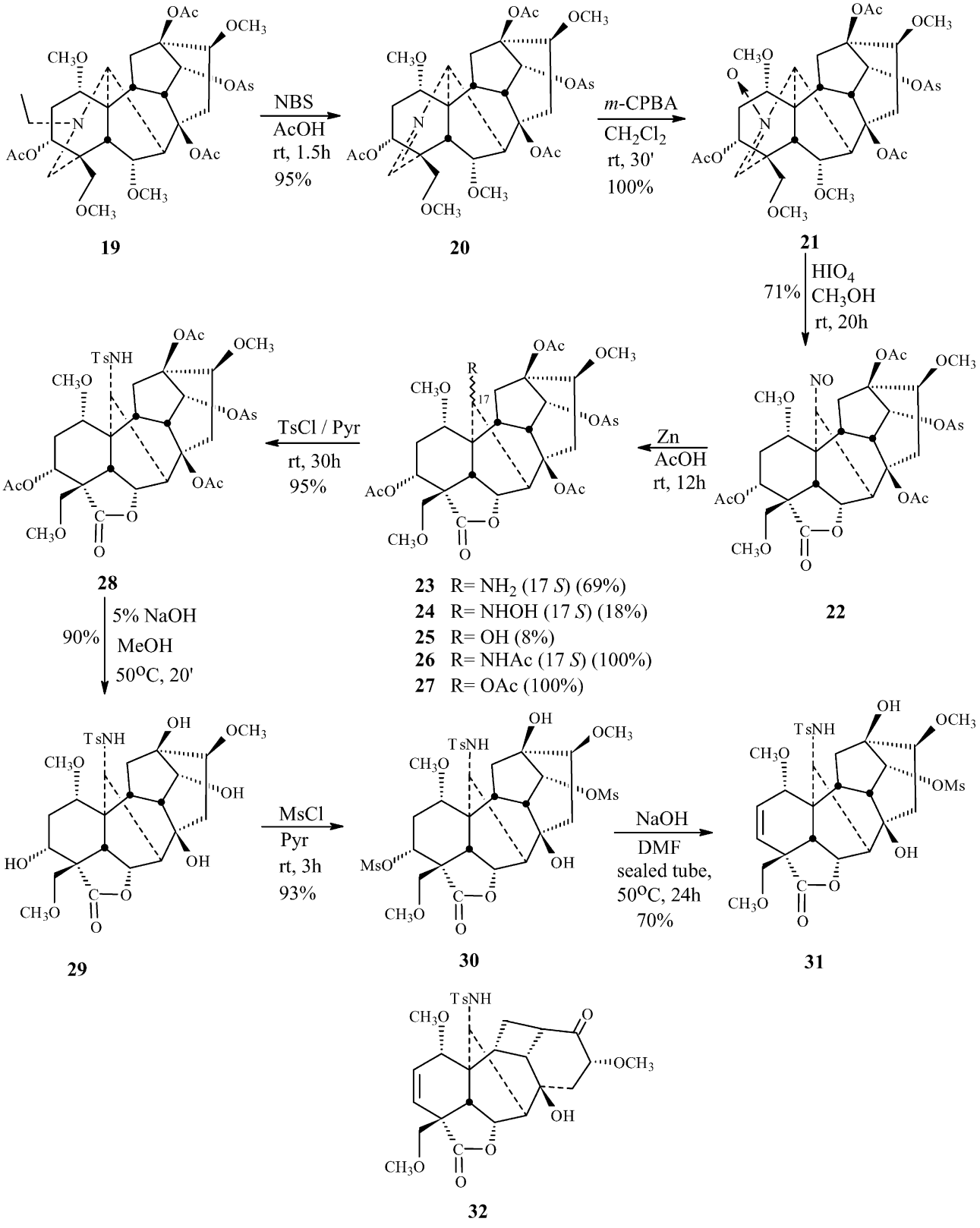
This approach was fashioned after the unsuccesseful ABC sequence. Attempt to strong alkaline rearrangement of the nitro compounds to the C-nor compounds by a reported method from this laboratory[16q,s] resulted in the complex products, which led us to try again reduction of the nitro group followed by protecting the amino group using TsCl. The 3,13-diacetylyunaconitine (**19**)[17] was exposed to NBS (8 equiv)-AcOH to give nearly quantitatively the imine **20** which was reacted with *m*-CPBA at room temperature to afford nitrone **21** (100%). An imine group (δ_H 6.72, d, J= 1.2 Hz, H-19; δ_C 135.4 d, C-19) was observed in the ^{1}H and ^{13}C NMR spectra of **21**. Treatment of **21** with molar excess of HIO_4 at room temperature gave the nitroso compound **22** as a blue amorphous powder. In the ^{1}H and ^{13}C NMR spectra of **22**, a γ-lactone moiety (δ_H 4.92, d, J=7.2 Hz (H-6β); δ_C 173.2 s (C-19)) was showed, and a methine carbon signal at δ_C 105.8 (d) can be assigned to C-17 bearing a nitroso group by comparison with those of the analogues.[16t] Reduction of **22** with Zn–conc. HCl gave the amine **23** (69%) together with the other two by-products **24** (18%) and **25** (8%) (Scheme 5). The carbon signals at δ_C 55.5 d (C-17) and 54.3 d (C-7) in **23** compared with those of **22** were obviously upfield-shifted (C-17: $\Delta\delta$-50.3; C-7: $\Delta\delta$-2.7). The MS spectrum of **24**, $C_{36}H_{45}O_{15}$ (HRMS), gave

Table 1. ^{1}H and ^{13}C NMR data for compound **16** (^{1}H: 400 MHz; ^{13}C: 100 MHz, $CDCl_3$)

No.	δ_C	δ_H Mult (J=Hz)	^{1}H–^{1}HCOSY	HMBC (H→C)
1	83.5 d	3.40 dd (6.0, 12.8)	H-2α, H-2β	C-17, C-1′, C-11, C-2, C-10
2	30.2 t	2.54 m (hidden)	H-2, H-1, H-3	C-1, C-3, C-4, C-11
		2.39 m	H-2, H-1, H-3	C-1, C-3, C-4, C-11
3	70.7 d	5.44 dd (6.8, 12.0)	H-2α, H-2β	C-19, C-18, C-4, C-5, C-2, 3-O*C*OCH$_3$
4	50.6 s	—	—	—
5	50.5 d	2.55 dd (hidden)	H-6, H-19 (w)	C-19, C-1, C-6, C-18, C-3, C-7, C-4, C-11, C-10
6	80.1 d	4.83 dd (2.0, 4.4)	H-5, H-17 (w)	C-19, C-17, C-4, C-5, C-11
7	56.4 d	3.10 br s	H-17	C-6, C-17, C-5, C-11, C-9
8	144.2 s	—	—	—
9	45.1 d	2.64 t (3.0)	H-10, H-14	C-8, C-15, C-13, C-14, C-11, C-12
10	48.2 d	2.23 m	H-12α, H-12β, H-9	C-8, C-1, C-17, C-11, C-9
11	49.0 s	—	—	—
12	37.9 t	1.99 dd (6.4, 14.8)	H-10, H-12	C-16, C-13, C-14, C-11, C-10
		1.92 dd (7.2, 14.8)	H-10, H-12	C-16, C-13, C-14, C-10, C-9
13	78.2 s	—	—	—
14	78.0 d	4.91 dd (0.8, 3.6)	H-9, H-16 (w)	C-16, C-13, C-9, C-1″, C-8
15	116.7 d	5.66 d (6.2)	H-16	C-16, C-14, C-7, C-9
16	83.4 d	3.40 (hidden)	H-15, H-14	C-8, C-15, C-13, C-14, -16′, C-12
17	68.3 d	3.27 br s (hidden)	H-7, H-6	C-19, C-1, C-6, C-5, C-11
18	74.5 t	3.23 ABq (9.2)	H-18 (δ 3.15)	C-19, C-3, C-18′, C-4, C-5
		3.15 ABq (9.2)	H-18 (δ 3.23)	C-19, C-3, C-18′, C-4, C-5
19	87.6 d	4.66 br s	—	C-6, C-18, C-17, C-4, C-5
1′	56.8 q	3.29 s	—	C-1′
16′	57.4 q	3.35 s	—	C-16′
18′	59.1 q	3.25 s	—	C-18′
O=C	170.3 s	2.05 s	—	-
CH$_3$	21.0 q	2.05 s	—	CO
O=C 1″	168.0 s	—	—	—
2″	122.5 s	—	—	—
7″ 3″	131.9 d	7.98 AA′BB′ (8.8)	H-4″	C-1″, C-5″, C-7″, C-2″, C-4″
6″ 4″	113.4 d	6.90 AA′BB′ (8.8)	H-3″	C-5″, C-6″, C-3″, C-2″
5″	163.3 s	—	—	—
OCH$_3$	55.3 q	3.85 s	—	C-5″

16

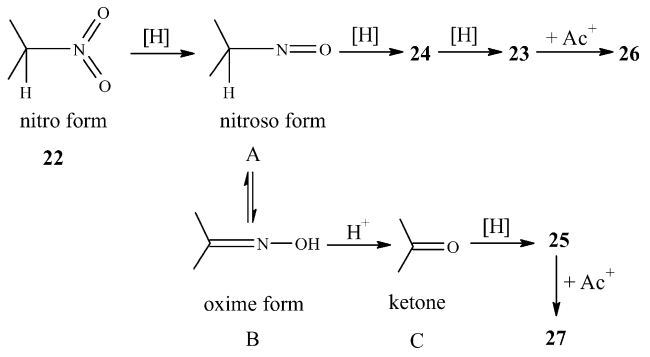
the molecular ion peak at m/z 731 which is 16 more unit than those of **23**. The ^{1}H and ^{13}C NMR spectra of **24** are very similar to those of **23**, except for C-17 (δ_C 64.5 d) being downfield-shifted by 9 ppm compared with those of **23**. From these facts mentioned above, the structure of **24** can be determined. The structure of **25** was established on the basis of the following key points: the odd molecular weight (m/z 716); a methine carbon signal at δ_C 74.7 (d) bearing to C-17; and a negative result to Dragendorff's reagent, which resulted from deamination. Acetylation of **23** and **25** with Ac_2O gave compounds **26** and **27**, respectively. In the ^{1}H NMR spectrum of **27**, an additional acetyl group was assigned at C-17 by the presence of the townfield signal at δ_H 5.03 (H-17) as compared with those of **25**. Apparently, configurations of C-17 in compounds **23**, **24**, and **26**, except for **25** and **27**, as the parent compound **22**, are deduced to be *S*. A plausible origin of these compounds **23**∼**27** can be rationalized mechanistically as shown in Scheme 6. Reduction of the nitro compound **22**, at first, gave the nitroso form A which was reduced again successively to give compounds **24** and **23**. In addition, there is an equilibration of the nitroso (A)-oxime (B) tautomerism.[19] Hydrolysis of B led to the ketone C, further reduction of C afforded **25**. Acetylation of **23** and **25** with AcOH resulted in obtainment of **26** and **27**, respectively. It is worth of note that the tautomerism between the nitroso and the oxime under alkaline condition was found by TLC detection (neutral silica gel GF_{254}: $CHCl_3$–MeOH=7:3, one spot; alkalized silica gel GF_{254}: $CHCl_3$–MeOH=95:5, two spots) and the NMR trial. When measuring the sample containing a few saturated Na_2CO_3 the ^{1}H and ^{13}C NMR spectra of **22** showed a distinctic signal at δ 155.7 (s) for the oxime group[16t], with ratio of about 3:1 based on the peak area of the H-14β signals at δ_H 4.99 for **22** and δ_H 4.84 for the oxime. Compound **23** was subjected to protection of the amino group, hydrolysis using 5% NaOH followed by sulfonation to give successively compounds **28** (95%), **29** (90%) and **30** (93%). The proton signal of H-17 (δ_H 5.66, d J=2.4 Hz) in the ^{1}H NMR spectrum of **28** compared with those of **23** was downfield-shifted due to the substitution of the OTs group. The ^{1}H and ^{13}C NMR spectra of **30** showed two OMs groups (δ_H 2.94, 2.97, each 3H, s; δ_C 38.1 q, 38.4 q), and the downfield-shift signals at δ_H 4.76 (1H, d, J=5.0 Hz, H-3β) and δ_H 4.43 (1H, d, J=4.2 Hz, H-14β) as compared with those of **29**. However, semipinacol rearrangement of **30** under various conditions (NaOH/DMF, reflux, 20 h[16q]; DBN/*o*-xylene, sealed tube, 180 °C, 12 h; NaOAc/HOAc, sealed tube, 150 °C, 24 h) resulted in formation of **31** (70%) rather than the desired product **32** (Scheme 5). This is incomprehensibly different from the results described in the literature.[16q]



Scheme 5.

2.3. Approach BCA

Owing to the unsuccesseve efforts described herein, we are forced to propose another approach BCA aiming at cleaving the C-7–C-17 bond using our developing protocol[16n,w] prior to modification of the ring C or A. According to the literature,[16w] the 7,17-*seco* compound **34** from **19** via **33** was prepared smoothly in 74% yield (Scheme 7). Its structure was established by spectral data and comparison with the authentic sample. Alkaline hydrolysis of **34**



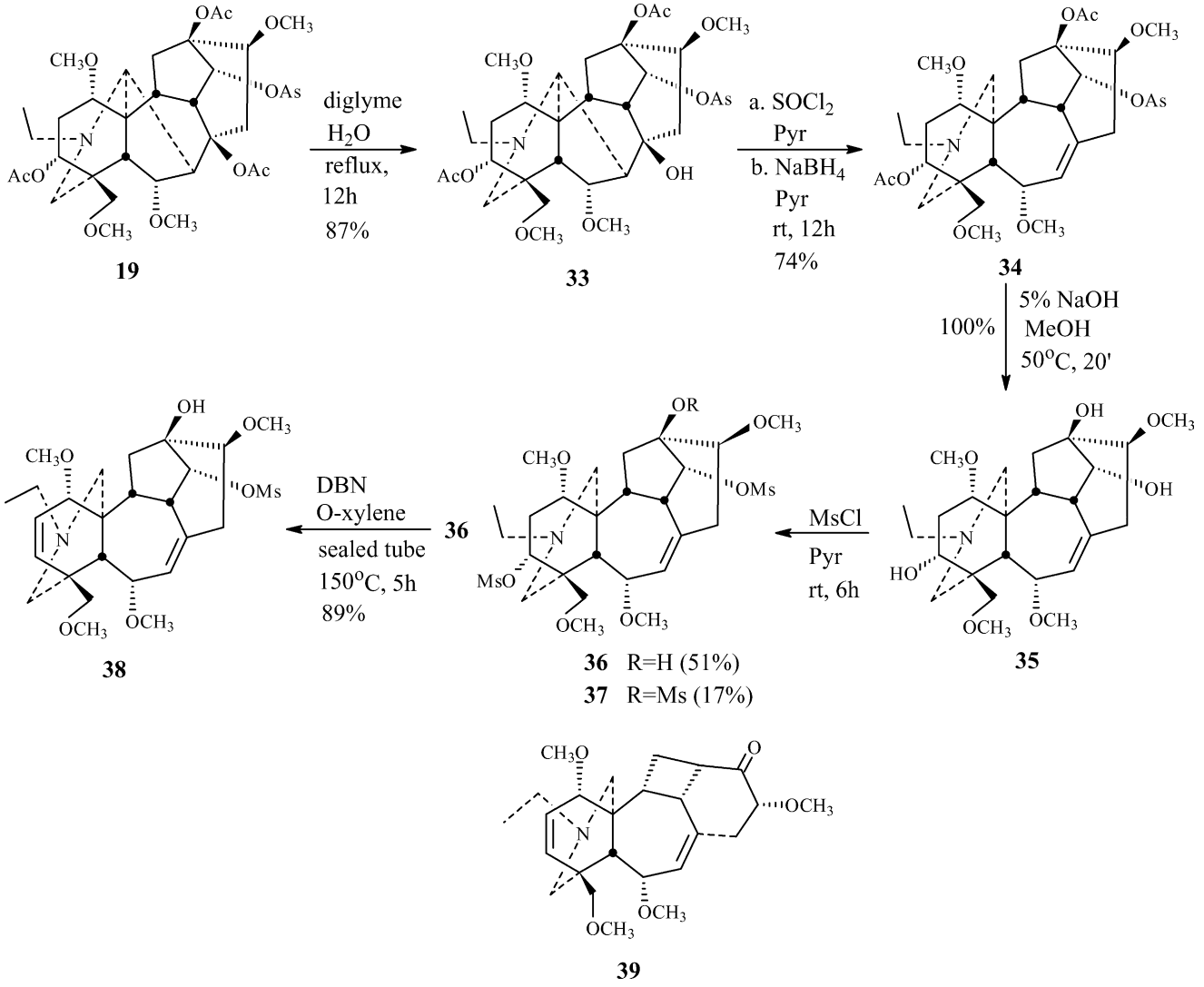
Scheme 6.

followed by sulfonation using MsCl/pyridine gave the desired product **36** (51%) along with the by-product **37** (17%) (Scheme 7). But, treatment of **36** under different conditions (DBN/ *o*-xylene, sealed tube, 180 °C; NaOH/ DMF, reflux, 12 h[16q]) gave compound **38** instead of the expected C-nor product **39** (Scheme 7). The ^{1}H and ^{13}C NMR spectra of **38** exhibited the presence of a disubstituted double bond (δ_H 5.92, dd, $J=9.8$, 2.0 Hz for H-3; 5.59, hidden for H-2; δ_C 136.8 d for C-2, 129.0 d for C-3), and a trisubstituted double bond (δ_H 5.61, hidden, H-7; δ_C 131.5 s, C-8; 125.7 d, C-7). Apparently the *N*,19-*seco* compound **30** in the approach ACB or the 7,17-*seco* compound **38** in the approach BCA approach was not an adequate form of semipinacol rearrangement probably due to harsh requirement on the substrates.

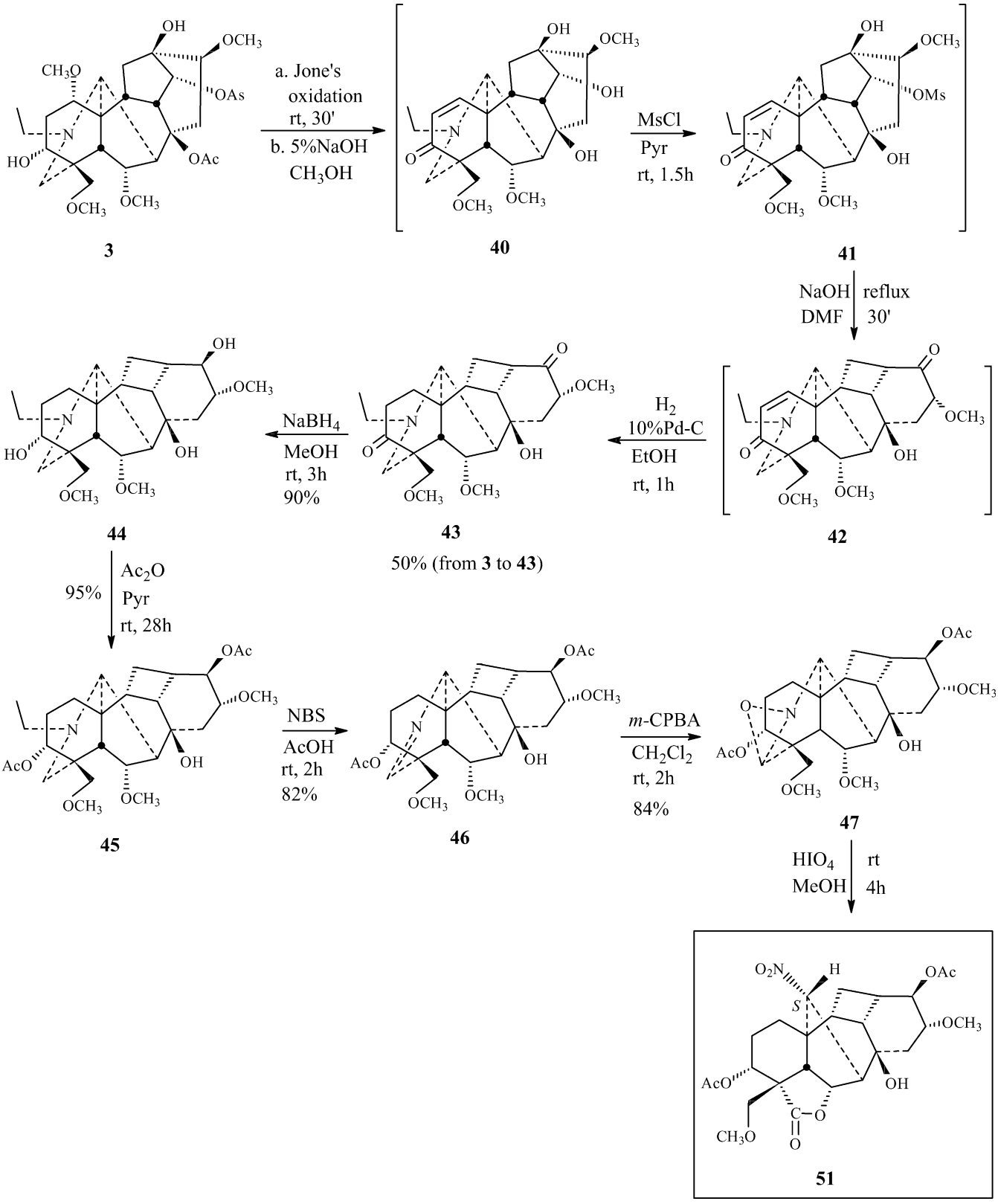
As mentioned above, all three approaches turned out to be ineffective and the last-mentioned method gave rise to the expected key intermediates **51** and **52**.

2.4. Approach CAB

The synthesis began with the starting material yunaconitine (**3**) afforded compound **43** in 50% overall yield through one-pot four step method[16s] including a key semipinacol rearrangement (Scheme 8). Its structure was determined by TLC comparison (silica gel GF_{254}, $CHCl_3$–MeOH=9:1) with the authentic sample. Reduction of **43** with $NaBH_4$ to avoid a negative participation of the keton group at C-3 followed by acetylation and subsequent formation of the imine afforded successively compounds **44**, **45**, and **46** in 70% overall yield in three steps from **43** to **46** (Scheme 8).



Scheme 7.



Scheme 8.

In the ^{1}H and ^{13}C NMR spectra of **46**, the signals at δ_H 7.39 (d, $J=1.2$ Hz, H-19) and δ_C 164.2 (d) (C-19) can be assigned to the imine group. The α-configuration of the hydroxyl group at C-3 in **44**, **45**, and **46** was supported from their larger $^{3}J_{2a,3a}$ coupling constant (9–13 Hz). In slight surprise, *m*-CPBA oxidation of **46** in an apotic media, e.g. CH_2Cl_2, resulted in formation of oxaziridine **47** in highly 84% yield where the addition to C=N is not favored presumably by participation of the more electron-donating hydroxyl group than the acetyl group as **49** at C-8.[20] The ^{1}H

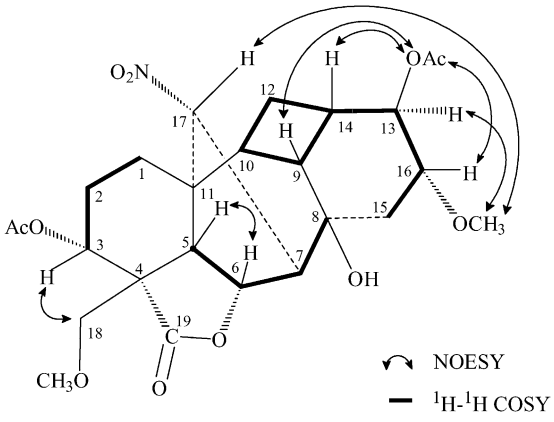


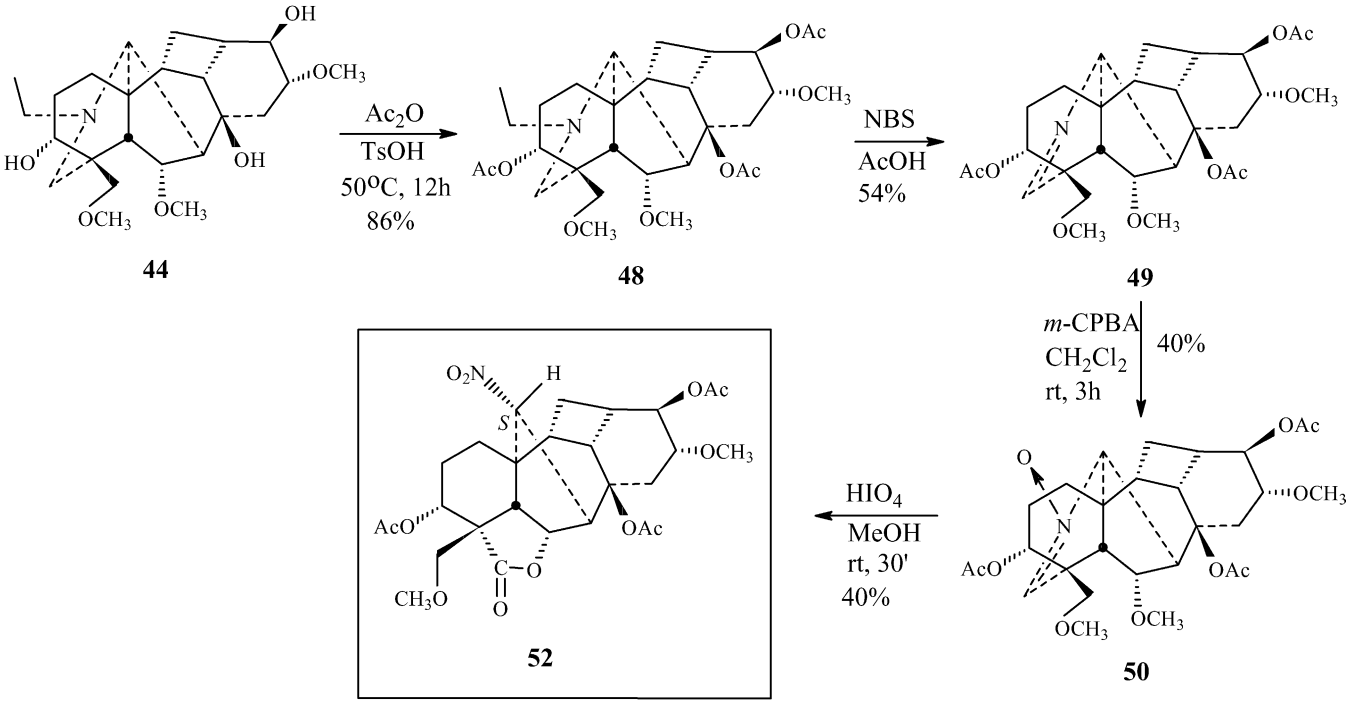
Figure 1. Key NOESY and ^{1}H–^{1}H COSY correlations of **51**.

and ^{13}C NMR spectra of **47** showed the absence of the imine or the nitrone group and the apparance of a methine carbon signal at δ_C 76.0 bearing an additional oxygen atom, together with consideration of the more 16 mass unit as compared with the molecular ion peak (*m*/*z* 491) of **46**, indicating that **47** had an oxaziridine moiety (δ_H 4.17, s, H-19; δ_C 76.0 d, C-19). In constract with **46**, treatment of triacetyl derivative **49** from **44** via **48** with *m*-CPBA under similar conditions afforded the desired nitrone **50** in modest yield of 40% which was oxidized using HIO_4 to the key intermediate **52** in only 40% yield. Wheres compound **47** was exposed to HIO_4 rather than bases or acids, where the decomposition was observed by bases, to give the analogue **51** in poor 26% yield differing from the report in the literature,[16t] indicating that obviously effect of the rearranged C-nor compounds such as **49** on formation of the nitrone. However, this is a new useful method for the ring opening of oxaziridines. In the ^{1}H and ^{13}C NMR spectra of **51** (Table 3) and **52** (see Section 4), the presence of γ-lactones [**51**: δ_H 5.63 (d, J=7.2 Hz, H-6β); δ_C 83.6 d (C-6), 177.7 s (C-19); **52**: δ_H 5.11 (d, J=7.2 Hz, H-6β); δ_C 81.9 d (C-6), 174.1 s (C-19)] was confirmed. Their IR spectra also showed absorption of the nitro groups (**51**: 1558–1378 cm^{-1}; **52**: 1550–1380 cm^{-1}). The α-orientation of H-13 in compounds **44**–**52** was deduced from the coupling constants ($J_{13,16}$=6.4–12 Hz) (see Section 4), especially including NOESY of **51** (Fig. 1), in which the correlations of OAc-13 (δ_H 2.18, 3H, s) with H-9β, H-14β, and H-16β as well as OCH_3-16α with H-13α and H-17 were observed. Similarly, α-configuration of the OAc group at C-3 in **51** also was confirmed due to the NOESY correlations between H-3β and H_2-18 (Fig. 1) as well as a larger $^3J_{2a,3a}$ coupling constant (9.2 Hz). The NOESY correlation of H-5β with H-6β in the NOESY spectrum of **51** suggested that the γ-lactone was located under the rings A and B, showing mechanically that the γ-lactone was formed prior to the *O*-demethylation of 6-OCH_3 group. The 2D NMR experiments (HMQC, ^{1}H–^{1}H COSY, HMBC, NOESY) of **51** further gave the assignments of all the ^{1}H and ^{13}C signals (Table 3). Comparison of the ^{13}C NMR spectra of **51** and **52** showed that there, as expected, are only minor differences mainly restricted to the vicinity of the C-8 function (Scheme 9).

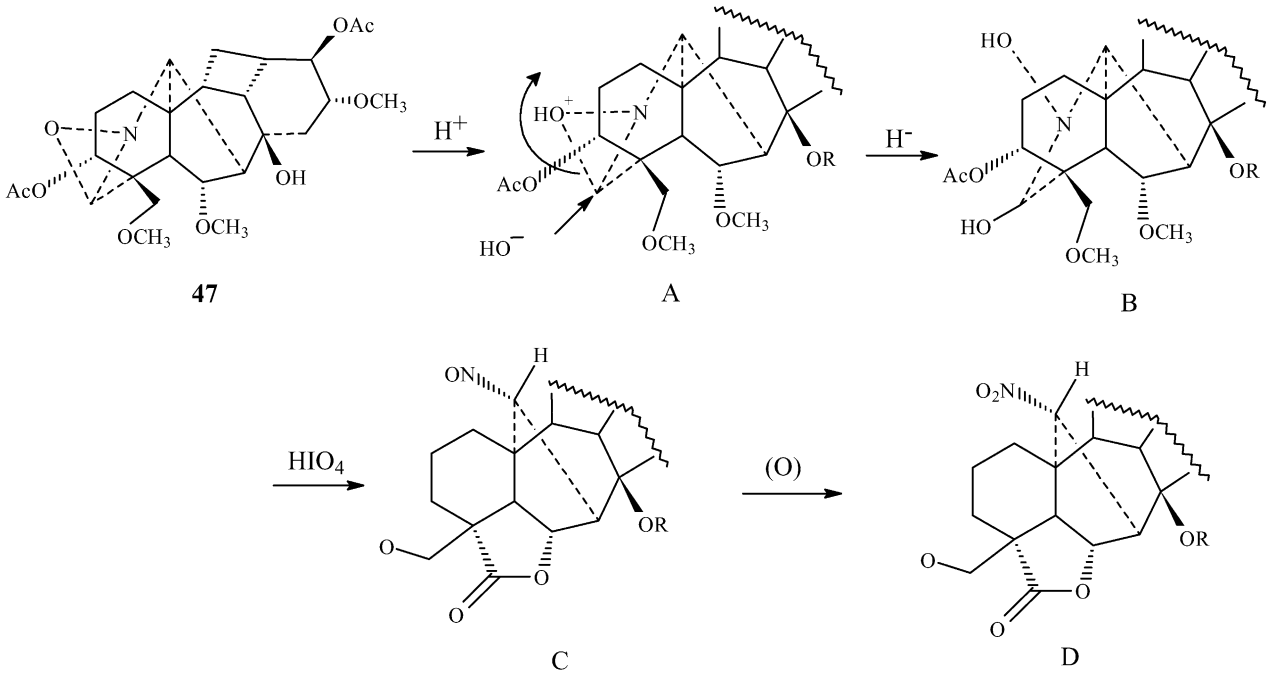
Compound **47** was converted into **51** presumably via a several step mechanism, the first step being protonation of H^+ to the oxygen atom (A), followed by an nucleophilic attack of OH^- to A and a subsequent glycol-like cleavage in company with formation of the γ-lacton moiety[16t] to afford C and its oxidized form D (Scheme 10).

3. Conclusion

This study, as a part of conversion of the C_{19}-diterpenoid



Scheme 9.



Scheme 10.

alkaloids to the taxoids, made us to drop the idea to seek a suitable route toward the key intermediate C (Scheme 1) with four approaches designed and examined based on our previous break-through results.

In the approach ABC (route 1), an attempt to reduce the aldehyde group in **7** using various regents failed mainly due to the bulkiness of hydroxyl or acetyl group at C-3. Formation of the key imines followed by cleaving the C-7–C-17 bond or preparation of the 7,17-*seco* compound using the secondary amine with respect of a protocol developed by this laboratory[16j,t,n,u,w] was then attempted.

Consequently, these were proved to be unsuccessful along with the obtainment of **16** having the new *N*,*O*-mixed acetal moiety. This seems to show that when preparing the 7,17-*seco* compounds it is necessary to meet both an anti-periplanar relationship between the lone pair of nitrogen atom and the C-8–Cl bond, as well as the tertiary pattern of the nitrogen atom in the substrates. In addition, an optimazed procedure was found to be very useful for imination or *N*-deethylation using 8 or 3 equiv of NBS, respectively with good application scope in the C_{19}-diterpenoid alkaloids.

The second approach (ACB) involves treatment of the nitroso **22** with Zn/AcOH–HCl to afford the desired compound **23** in high yield along with two interesting by-products **24** and **25**. After pretection of the amino group followed by hydrolysis and sulfonation the key compound **30** from **23** was obtained. However, to attempt conversion of **30** or **36** in the approach BCA (route 3) to the corresponding C-nor compoumd **32** or **39**, respectively, under various conditions via semipinacol rearrangement failed. This led to conclude that the *N*,19-*seco* compound **30** in the approach ACB or the 7,17-*seco* compound **36** in the approach BCA was not an adequate form of semipinacol rearrangement probably due to harsh requirement on the substrates.

Taking three unsuccessful approaches mentioned above into accunt, we offer the fourth approach CAB which at first involved in treatment of yunaconitine (**3**) using our method[16q] via semipinacol rearrangement to give the C-nor compound, and then, in cleaving the *N*-C-19 bond through three steps mainly including imination, formation of the oxaziridine or the nitrone, and HIO_4 oxidation fragmentation. Interestingly, an expected preparations of nitrone from **46** by *m*-CPBA oxidation resulted in the obtainment of oxaziridine **47** (84%) in constrast to those where *m*-CPBA oxidation of **49** led to produce nitrone **50** in moderate yield being much lower than those of *N*-oxidation of the imines from the substrates without the ring C rearrangment. Thus effect of the 8-OR (R=H, Ac) on formation of the nitrones or the oxaziridines was observed, which is worth to further research. Finally, we have found that treatment of oxaziridine **47** or nitrone **50** with HIO_4 afforded successively the key intermediate **51** or **52** in modest to moderate yield, which provided an important base for synthesis toward the vital intermediate C in Scheme 1. Further optimization of the reaction and application for synthesis of the key intermediates **51** and **52** are currently in progress.

In the course of our afore-mentioned studies, 43 C_{19}-diterpenoid alkaloids were obtained, of which 33 are structurely the new or novel compounds which were determined by spectral data (^1H and ^{13}C NMR, 2D NMR, HRMS).

4. Experimental

4.1. General

Melting points were determined on a Kofler block (uncorrected); optical rotations were measured in a 1.0 dm cell with a PE-314 polarimeter at 20±1 °C; IR spectra were

recorded on a Nicolet 200 SXV spectrometer; MS spectra were obtained with a Auto-Spec-3000 instrument; ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer, with TMS as internal standard; Silica gel GF_{254} and H (10–40 μm, Qingdao Sea Chemical Factory, China) were used for TLC and CC. Only key signals except for **16** and **51** in the ^{1}H NMR spectra are reported.

4.2. Approach ABC

4.2.1. Compounds 9 and 12. To a solution of compound **7** (100 mg, 0.14 mmol) in MeOH (5 mL), 10% K_2CO_3 (1 mL) was added the solution was stirred at room temperature for 1.5 h, then saturated NH_4Cl solution (80 mL) was added. Diluting (H_2O, 10 mL), extraction (CH_3Cl, 50 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98:2 to 95:5) afforded the pure products **9** (white amorphous powder, 69 mg, 73%) and **12** (white amorphous powder, 23 mg, 25%).

4.2.2. Compound 9. Mp 173–174 °C; R_f (95% $CHCl_3$–CH_3OH) 0.52; $[\alpha]_D^{20}=+28.5$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3469 (OH), 2939, 2828, 1718 (COO), 1649, 1608, 1514, 1460, 1260, 1102 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.36 (3H, s, 8-OAc), 3.00, 3.33, 3.42, 3.55, 3.87 (each 3H, s, OCH_3×5), 4.83 (1H, d, $J=4.4$ Hz, H-14β), 6.93, 8.00 (each 2H, AA′BB′, $J=8.4$ Hz, Ar-H), 10.3 (1H, s, H-19); δ_C (50 MHz, $CDCl_3$) 209.8 (C-19), 169.3 (*CO*CH_3), 165.3 (*CO*Ar), 163.5 (C-4″), 131.6 (C-2″, C-6″), 122.1 (C-1″), 113.7 (C-3″, C-5″), 83.3 (C-16), 83.1 (C-1), 82.7 (C-8), 81.8 (C-6), 78.0 (C-14), 76.2 (C-20), 75.7 (C-13), 74.1 (C-17), 71.5 (C-18), 67.9 (C-3), 59.3 (C-18′), 58.7 (C-16′), 57.1 (C-6′), 56.2 (C-1′), 55.3 (4′-OCH_3), 55.2 (C-4), 53.3 (C-7), 51.9 (C-11), 51.3 (C-5), 45.8 (C-10), 42.8 (C-9), 39.7 (C-15), 33.9 (C-2), 33.5 (C-12), 21.2 (CO*CH*$_3$); *m*/*z* (EI) 675 (3, M^+); HRMS (FAB): M^++H, found 676.2950, $C_{34}H_{46}NO_{13}$ requires 676.2969.

4.2.3. Compound 12. Mp 163–164 °C; R_f (95% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=+50.8$ (*c* 0.50, $CHCl_3$); ν_{max} (KBr) 3452 (OH), 2930, 1718 (COO), 1650, 1607, 1514, 1461, 1371, 1259, 1102 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.33 (3H, s, 8-OAc), 3.07, 3.29, 3.44, 3.50, 3.87 (each 3H, s, OCH_3×5), 4.00, 4.15 (each 1H, $J=9.2$ Hz, H_2-18), 4.84 (1H, d, $J=4.8$ Hz, H-4β), 6.93, 8.00 (each 2H, AA′BB′, $J=8.4$ Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 174.4 (C-19), 169.9 (*CO*CH_3), 166.0 (*CO*Ar), 163.5 (C-4″), 131.6 (C-2″, C-6″), 122.3 (C-1″), 113.6 (C-3″, C-5″), 82.8 (C-16), 82.7 (C-8), 82.6 (C-1), 80.5 (C-6), 78.9 (C-14), 76.3 (C-18), 75.0 (C-13), 68.5 (C-3), 58.9 (C-18′), 58.6 (C-16′), 57.9 (C-17), 57.1 (C-6′), 55.7 (C-1′), 55.3 (4″-OCH_3), 52.3 (C-11), 48.5 (C-4, C-7), 45.3 (C-9), 43.1 (C-5), 40.3 (C-10), 36.8 (C-15), 34.9 (C-12), 33.9 (C-2), 21.4 (CO*CH*$_3$); *m*/*z* (EI) 645 (4, M^+); HRMS (FAB): M^++H, found 646.2859, $C_{33}H_{44}NO_{12}$ requires 646.2864.

4.2.4. Compound 10. To a solution of compound **7** (200 mg, 0.28 mmol) in HOAc (12 mL), $NaBH_4$ (200 mg, 5.26 mmol) was added and the solution was stirred at room temperature for 12 h. After pouring into ice water (10 mL), the solution was basified with NH_4OH to pH 9. Extraction (CH_3Cl, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98.5:1.5) afforded the pure product (white amorphous powder, 94 mg, 49%). **10**: mp 135–136 °C; R_f (95% $CHCl_3$–CH_3OH) 0.54; $[\alpha]_D^{20}=+26.2$ (*c* 0.8, $CHCl_3$); ν_{max} (KBr) 3507 (OH), 2935, 1732 (COO), 1608, 1514, 1460, 1370, 1257, 1096 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.33 (3H, s, 8-OAc), 2.04 (3H, s, 3-OAc), 2.60 (3H, s, *N*-CH_3), 3.17, 3.18, 3.24, 3.50, 3.84 (each 3H, s, OCH_3×5), 4.06 (1H, d, $J=6.8$ Hz, H-6β), 4.85 (1H, d, $J=5.0$ Hz, H-14β), 4.90 (1H, t, $J=5.8$ Hz, H-3β), 6.90, 7.99 (each 2H, AA′BB′, $J=8.8$ Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 170.0 (*CO*CH_3), 169.7 (*CO*CH_3), 165.9 (*CO*Ar), 163.3 (C-4″), 131.6 (C-2″, C-6″), 122.5 (C-1″), 113.6 (C-3″, C-5″), 85.1 (C-8), 83.5 (C-16), 83.0 (C-1), 81.7 (C-6), 78.2 (C-14), 74.7 (C-13), 71.5 (C-18), 71.3 (C-3), 62.9 (C-17), 58.6 (C-16′, C-18′), 58.0 (C-6′), 56.4 (C-1′), 55.3 (4″-OCH_3), 49.9 (C-11, C-19), 48.2 (C-7), 45.5 (C-5), 45.0 (C-9), 42.4 (C-4), 42.2 (C-21), 40.4 (C-10), 39.1 (C-15), 35.3 (C-12), 31.8 (C-2), 21.5 (CO*CH*$_3$), 21.0 (CO*CH*$_3$); *m*/*z* (EI) 687 (10, M^+), 656 (65, M−OCH_3), 628 (55, M−OAc); HRMS (FAB): M^++H, found 688.3336, $C_{36}H_{50}NO_{12}$ requires 688.3333.

4.2.5. Compound 11. To a solution of compound **9** (100 mg, 0.15 mmol) in HOAc (8 mL), KBH_4 (100 mg, 1.85 mmol) was added and the solution was stirred at room temperature for 12 h. After pouring into ice water (10 mL), the solution was basified with conc. NH_4OH to pH 9. Extraction (CH_3Cl, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/95:5) afforded the pure product (white amorphous powder, 50 mg, 52%). **11**: mp 157–158 °C; R_f (90% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=+30.5$ (*c* 0.4, $CHCl_3$); ν_{max} (KBr) 3450 (OH), 2928, 1728 (COO), 1652, 1605, 1510, 1458, 1250, 1108 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.35 (3H, s, 8-OAc), 2.64 (3H, s, *N*-CH_3), 3.13, 3.29, 3.35, 3.56, 3.86 (each 3H, s, OCH_3×5), 4.87 (1H, d, $J=5.0$ Hz, H-14β), 6.93, 8.00 (each 2H, AA′BB′, $J=8.8$ Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 169.9 (*CO*CH_3), 166.1 (*CO*Ar), 163.5 (C-4″), 131.7 (C-2″, C-6″), 122.4 (C-1″), 113.8 (C-3″, C-5″), 84.8 (C-8), 83.2 (C-16), 82.7 (C-1), 81.4 (C-6), 78.2 (C-14), 74.6 (C-13), 71.0 (C-18), 70.7 (C-3), 64.4 (C-17), 59.0 (C-18′), 58.9 (C-16′), 57.9 (C-6′), 56.2 (C-1′), 55.3 (4″-OCH_3), 50.5 (C-11), 50.2 (C-19), 48.2 (C-7), 45.3 (C-9), 44.2 (C-5), 43.6 (C-4), 42.5 (C-21), 40.7 (C-10), 39.4 (C-15), 35.7 (C-12), 32.6 (C-2), 21.3 (CO*CH*$_3$); *m*/*z* (EI) 645 (6, M^+), 627 (11, M−H_2O), 614 (2, M−OMe); HRMS (FAB): M^++H, found 646.3232, $C_{34}H_{48}NO_{11}$ requires 646.3227.

4.2.6. Compound 13. To a solution of compound **3** (1.05 g, 1.50 mmol) in diglyme (80 mL), H_2O (20 mL) was added and the solution was heated at reflux for 13 h. Removal of solvent and column chromatography afforded the pure product (white amorphous powder, 785 mg, 80%), which was taken to next step directly.

4.2.7. Compound 14. To a solution of compound **13** (500 mg, 0.76 mmol) in HOAc (15 mL), NBS (1.08 g, 6.08 mmol) was added and the solution was stirred at room temperature for 1.5 h. After pouring into ice water (20 mL), the solution was basified with conc. NH_4OH to pH 10. Extraction ($CHCl_3$, 15 mL×3), drying (Na_2SO_4), and evaporation afforded the pure product (white amorphous

powder, 467 mg, 98%). **14**: mp 135–136 °C; R_f (90% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=+87.5$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3468 (OH), 2936, 1715 (COO), 1608, 1514, 1459, 1257, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.08 (3H, s, 3-OAc), 3.19, 3.24, 3.28, 3.40, 3.86 (each 3H, s, $OCH_3\times4$), 3.46, 4.16 (each 1H, ABq, $J=8.8$ Hz, H_2-18), 5.12 (1H, dd, $J=5.6$, 8.0 Hz, H-3β), 5.14 (1H, d, $J=4.8$ Hz, H-14β), 6.93, 8.00 (each 2H, AA′BB′, $J=8.4$ Hz, Ar-H), 7.45 (1H, d, $J=1.2$ Hz, 19-H); δ_C (100 MHz, $CDCl_3$) 170.2 (*CO*CH_3), 166.5 (*CO*Ar), 164.1 (C-19), 163.5 (C-4″), 131.7 (C-2″, C-6″), 122.1 (C-1″), 113.7 (C-3″, C-5″), 83.0 (C-16), 82.6 (C-6), 80.9 (C-1), 79.8 (C-14), 76.1 (C-13), 72.6 (C-3), 72.4 (C-18), 72.3 (C-8), 61.6 (C-17), 59.0 (C-7, C-18′), 58.3 (C-16′), 57.2 (C-6′), 55.9 (C-1′), 55.3 (4″-OCH_3), 50.4 (C-4), 49.9 (C-11), 46.4 (C-5), 44.7 (C-9), 41.9 (C-10), 40.8 (C-15), 35.7 (C-12), 30.4 (C-2), 21.9 (CO*CH*$_3$); *m/z* (EI) 629 (12, M^+), 570 (13, M−OAc); HRMS (FAB): M^++H, found 630.2911, $C_{33}H_{44}NO_{11}$ requires 630.2914.

4.2.8. Compound 15. To a solution of compound **13** (200 mg, 0.30 mmol) in HOAc (10 mL), NBS (162 mg, 0.91 mmol) was added and the solution was stirred at room temperature for 3 h. After pouring into ice water (20 mL), the solution was basified with conc. NH_4OH to pH 10. Extraction ($CHCl_3$, 15 mL×3), drying (Na_2SO_4), and evaporation afforded the pure product (white amorphous powder, 190 mg, 99%).

4.2.9. Compound 16. A solution of compound **14** (300 mg, 0.48 mmol) in pyridine (30 mL) was treated with $SOCl_2$ (2 mL) and stirred at room temperature for 5 h. Removal of solvent gave the residue, which was dissolved in MeOH (30 mL). To the solution $NaBH_4$ (300 mg) was added and this solution was stirred at room temperature for 3 h. Removal of solvent, basifying (NH_4OH, pH 9), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane–acetone/3:1) afforded the pure product (white amorphous powder, 200 mg, 70%). **16**: mp 132–133 °C; R_f (50% cyclohexane–acetone) 0.44; $[\alpha]_D^{20}=+17.6$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3465 (OH, NH), 2938, 2825, 1734 (COO), 1608, 1513, 1459, 1255, 1105 cm^{-1}; δ_H (400 MHz, $CDCl_3$) and δ_C (100 MHz, $CDCl_3$) see Table 1; *m/z* (ESI) 620 (100, M^+); HRMS (FAB): M^++H, found 598.2660, $C_{32}H_{40}NO_{10}$ requires 598.2652.

4.2.10. Compound 17. To a solution of compound **14** (35 mg, 0.056 mmol) in benzene (2 mL), $SOCl_2$ (0.3 mmol) was added and the solution was allowed to stand at room temperature for 24 h. After removal of solvent, the solution was neutralized with $NaHCO_3$ (5 mL). Extraction ($CHCl_3$, 3 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane–acetone/2:1) afforded the pure product (white amorphous powder, 20 mg, 59%). **17**: δ_H (200 MHz, $CDCl_3$) 2.06 (3H, s, 3-OAc), 3.21, 3.26, 3.29, 3.40, 3.85 (each 3H, s, $OCH_3\times5$), 4.94 (1H, d, $J=4.4$ Hz, H-14β), 5.00 (1H, dd, $J=4.6$, 8.8 Hz, H-3β), 5.82 (1H, d, $J=6.0$ Hz, 15-H), 6.90, 8.00 (each 2H, AA′BB′, $J=8.8$ Hz, Ar-H), 7.47 (1H, br s, H-19).

4.2.11. Compound 18. To a solution of compound **15** (50 mg, 0.08 mmol) in pyridine (3 mL), $SOCl_2$ (0.2 mL) was added and the solution was stirred at room temperature for 3 h. Evaporation in vacuum to dryness afforded a residue, which was dissolved in MeOH (10 mL). To the solution $NaBH_4$ (100 mg) was added and this solution was stirred at room temperature for 2 h. Removal of solvent gave the residue which was basified with 10% Na_2CO_3. Extraction ($CHCl_3$, 5 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98:2) afforded the pure product (white amorphous powder, 20 mg, 41%).**18**: mp 137–138 °C; R_f (95% $CHCl_3$–CH_3OH) 0.46; $[\alpha]_D^{20}=+122.5$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3466 (OH, NH), 2928, 1712 (COO), 1608, 1513, 1460, 1317, 1256, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.04 (3H, s, 3-OAc), 3.22, 3.25, 3.34, 3.38, 3.85 (each 3H, s, $OCH_3\times5$), 4.90 (1H, dd, $J=5.0$, 12.2 Hz, H-3β), 4.94 (1H, d, hidden, H-14β), 5.70 (1H, d, $J=6.2$ Hz, 15-H), 6.90, 8.00 (each 2H, AA′BB′, $J=8.8$ Hz, Ar-H); *m/z* (FAB) 614 (35, M^++H), 135 (100); HRMS (FAB): M^++H, found 614.2971, $C_{33}H_{44}NO_{10}$ requires 614.2965.

4.3. Approach ACB

4.3.1. Compound 20. To a solution of compound **19**[20] (2.20 g, 2.96 mmol) in HOAc (40 mL), NBS (4.22 g, 23.7 mmol) was added and the solution was allowed to stand at room temperature for 1.5 h. After pouring into ice water (50 mL), the solution was basified with conc. NH_4OH to pH 9. Extraction ($CHCl_3$, 20 mL×3), drying (Na_2SO_4), and evaporation afforded the pure product (white amorphous powder, 2.1 g, 95%). **20**: δ_H (200 MHz, $CDCl_3$) 1.29 (3H, s, 8-OAc), 2.05, 2.07 (each 3H, 3-OAc and 13-OAc), 3.09, 3.19, 3.24, 3.40, 3.86 (each 3H, s, $OCH_3\times5$), 5.12 (1H, d, $J=5.6$ Hz, 14β-H), 5.13 (1H, t, $J=7.0$ Hz, 3β-H), 6.90, 8.00 (each 2H, AA′BB′, $J=8.8$ Hz, Ar-H), 7.37 (1H, d, $J=1.0$ Hz, 19-H).The structure of **20** was identified by comparison of ^1H NMR and TLC (cyclohexane–acetone/1:1; $CHCl_3$–CH_3OH/9:1) with the authentic sample.

4.3.2. Compound 21. To a solution of compound **20** (2.00 g, 2.81 mmol) in CH_2Cl_2 (30 mL), *m*-CPBA (970 mg, 5.82 mmol) was added and the solution was stirred at room temperature for 30 min. To the reaction solution was added 10% Na_2CO_3 solution and the mixture was stirred vigorously. The organic layer was separated and the water layer was extracted with $CHCl_3$ (15 mL×2). Drying (Na_2SO_4), and evaporation afforded the pure product (white amorphous powder, 2.02 g, 100%). **21**: mp 175–176 °C; R_f (90% $CHCl_3$–CH_3OH) 0.42; $[\alpha]_D^{20}=+113.0$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 2937, 2828, 1736 (COO), 1608, 1514, 1461, 1257, 1104 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, 8-OAc), 2.06, 2.07 (each 3H, s, 3- and 13-OAc), 3.11, 3.22, 3.27, 3.42, 3.68 (each 3H, s, $OCH_3\times5$), 5.11 (1H, d, $J=5.2$ Hz, H-14β), 5.24 (1H, dd, $J=4.0$, 6.4 Hz, H-3β), 6.72 (1H, d, $J=1.2$ Hz, 19-H), 6.94, 8.03 (each 2H, AA′BB′, $J=8.8$ Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 170.4 (*CO*CH_3), 170.4 (*CO*CH_3), 169.1 (*CO*CH_3), 165.7 (*CO*Ar), 163.6 (C-4″), 135.4 (C-19), 131.8 (C-2″, C-6″), 122.0 (C-1″), 113.8 (C-3″, C-5″), 82.8 (C-8), 82.2 (C-16), 81.2 (C-1), 78.9 (C-6, C-14), 78.7 (C-13), 74.0 (C-3), 73.1 (C-17), 73.0 (C-18), 58.8 (C-18′), 58.3 (C-16′), 57.2 (C-6′), 56.1 (C-1′), 55.3 (4″-OCH_3), 54.2 (C-7), 51.5 (C-11), 45.3 (C-4), 43.3 (C-5), 41.2 (C-9), 39.3 (C-10), 38.4 (C-15), 35.3 (C-12), 28.4 (C-2), 21.2 (CO*CH*$_3$), 21.0 (CO*CH*$_3$), 20.9 (CO*CH*$_3$); *m/z* (EI) 729 (5, M^+), 697 (3), 654 (40); HRMS

(FAB): $M^+ + H$, found 730.3073, $C_{37}H_{48}NO_{14}$ requires 730.3075.

4.3.3. Compound 22. To a solution of compound **21** (550 mg, 1.33 mmol) in MeOH (25 mL), $HIO_4 \cdot 2H_2O$ (906 mg, 3.98 mmol) was added and the mixture was stirred at room temperature for 20 h. Removal of solvent, basifying (10% Na_2CO_3, 20 mL), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/70:1) afforded the pure product (blue crystal powder, 390 mg, 71%). **22**: mp 185–186 °C; R_f (97% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20} = +59.2$ (*c* 1.1, $CHCl_3$); ν_{max} (KBr) 2940, 2843, 1783 (γ-lactone), 1738 (COO), 1608, 1514, 1460, 1257, 1102 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.25 (3H, s, 8-OAc), 1.94, 2.07 (each 3H, s, 3 and 13-OAc), 3.07, 3.25, 3.33, 3.76 (each 3H, s, OCH_3×4), 4.92 (1H, d, J=7.2 Hz, H-6β), 4.99 (1H, d, J=4.6 Hz, H-14β), 5.21 (1H, dd, J=3.2, 12.8 Hz, H-3β), 6.84, 7.92 (each 2H, AA′BB′, J=8.4 Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 173.2 (C-19), 170.5 (*CO*CH_3), 170.1 (*CO*CH_3), 168.9 (*CO*CH_3), 165.8 (*CO*Ar), 163.6 (C-4″), 131.8 (C-2″, C-6″), 121.7 (C-1″), 113.7 (C-3″, C-5″), 105.8 (C-17), 82.1 (C-8, C-13), 81.6 (C-1, C-16), 79.3 (C-6), 78.2 (C-14), 75.1 (C-18), 68.3 (C-3), 59.5 (C-18′), 58.2 (C-16′), 57.2 (C-6′), 57.0 (C-7), 56.2 (C-1′), 55.4 (4″-OCH_3), 53.2 (C-5), 51.8 (C-11), 51.7 (C-4), 44.8 (C-9), 42.1 (C-10), 40.3 (C-15), 33.9 (C-12), 31.2 (C-2), 21.0 (CO*CH₃*), 21.0 (CO*CH₃*), 20.9 (CO*CH₃*); *m/z* (EI) 730 (25, $M^+ + H$), 699 (4, $M - OCH_3$), 670 (15); HRMS (FAB): $M^+ + H$, found 730.2714, $C_{36}H_{44}NO_{15}$ requires 730.2711.

4.3.4. Compounds 23, 24 and 25. To a solution of compound **22** (450 mg, 0.62 mmol) in HOAc (8 mL) and excess Zn dust (1.0 g), conc. HCl (1 mL) was added dropwise with stirring vigorously. The mixture was stirred at room temperature for 12 h. After filtration, the filtrate was poured into ice water (10 mL). Basifying (conc. NH_4OH, pH 9), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/200:1.5) afforded the pure product **23** (colorless crystal needle, 304 mg, 69%), **24** (white amorphous powder, 80 mg, 18%) and **25** (white amorphous powder, 35 mg, 8%).

4.3.5. Compound 23. Mp 244–245 °C; R_f (99% $CHCl_3$–CH_3OH) 0.58; $[\alpha]_D^{20} = +26.8$ (*c* 0.4, $CHCl_3$); ν_{max} (KBr) 3461 (OH), 2929, 2856, 1780 (γ-lactone), 1736 (COO), 1608, 1514, 1403, 1257, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (3H, s, 8-OAc), 2.03, 2.08 (each 3H, s, 3 and 13-OAc), 3.30, 3.32, 3.37, 3.84 (each 3H, s, OCH_3×4), 3.94 (1H, s, H-17), 4.77 (1H, d, J=6.2 Hz, H-6β), 5.02 (1H, d, J=5.0 Hz, H-14β), 5.04 (1H, dd, J=4.2, 9.6 Hz, H-3β), 6.90, 8.00 (each 2H, AA′BB′, J=8.8 Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 174.1 (C-19), 170.7 (*CO*CH_3), 170.4 (*CO*CH_3), 169.3 (*CO*CH_3), 165.9 (*CO*Ar), 163.6 (C-4″), 131.8 (C-2″, C-6″), 122.0 (C-1″), 113.8 (C-3″, C-5″), 82.6 (C-1, C-8, C-13), 81.1 (C-16), 79.7 (C-6), 76.6 (C-14), 74.6 (C-18), 67.9 (C-3), 59.4 (C-18′), 58.2 (C-16′), 56.5 (C-1′), 55.5 (C-17), 55.3 (4″-OCH_3), 54.3 (C-7), 51.8 (C-4), 51.3 (C-5), 50.6 (C-11), 44.5 (C-9), 41.8 (C-10), 40.9 (C-15), 34.2 (C-12), 30.2 (C-2), 21.2 (CO*CH₃*), 21.1 (CO*CH₃*), 21.0 (CO*CH₃*); *m/z* (FAB) 716 (100, $M^+ + H$), 656 (7, $M - OAc + H$); HRMS (FAB): $M^+ + H$, found 716.2918, $C_{36}H_{46}NO_{14}$ requires 716.2918.

4.3.6. Compound 24. Mp 191–192 °C; R_f (99% $CHCl_3$–CH_3OH) 0.52; $[\alpha]_D^{20} = +15.0$ (*c* 1.4, $CHCl_3$); ν_{max} (KBr) 3470 (OH), 2929, 2856, 1782 (γ-lactone), 1737 (COO), 1608, 1514, 1461, 1258, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (3H, s, 8-OAc), 2.03, 2.12 (each 3H, s, 3 and 13-OAc), 3.25, 3.29, 3.34, 3.84 (each 3H, s, OCH_3×4), 4.77 (1H, d, J=6.2 Hz, H-6β), 4.99 (1H, dd, J=3.8, 10.2 Hz, H-3β), 5.01 (1H, d, J=4.8 Hz, H-14β), 5.48 (1H, br s, NH-*OH*), 6.91, 8.00 (each 2H, AA′BB′, J=8.6 Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 174.1 (C-19), 170.6 (*CO*CH_3), 170.4 (*CO*CH_3), 169.2 (*CO*CH_3), 166.0 (*CO*Ar), 163.6 (C-4″), 131.8 (C-2″, C-6″), 122.0 (C-1″), 113.8 (C-3″, C-5″), 82.5 (C-8), 82.3 (C-13), 81.9 (C-1), 81.7 (C-16), 79.6 (C-6), 76.6 (C-14), 74.2 (C-18), 67.4 (C-3), 64.5 (C-17), 59.4 (C-18′), 58.3 (C-16′), 56.6 (C-1′), 55.4 (4″-OCH_3), 51.8 (C-4), 51.4 (C-7), 49.9 (C-11), 49.5 (C-5), 44.9 (C-9), 42.2 (C-10), 40.7 (C-15), 34.2 (C-12), 30.7 (C-2), 21.3 (CO*CH₃*), 21.1 (CO*CH₃*), 21.0 (CO*CH₃*); *m/z* (FAB) 732 (100, $M^+ + H$), 672 (15, $M - OAc + H$); HRMS (FAB): $M^+ + H$, found 732.2870, $C_{36}H_{46}NO_{15}$ requires 732.2867.

4.3.7. Compound 25. Mp 188–190 °C; R_f (99% $CHCl_3$–CH_3OH) 0.48; $[\alpha]_D^{20} = +45.8$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3461 (OH), 2928, 2856, 1778 (γ-lactone), 1733 (COO), 1608, 1514, 1461, 1259, 1099 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, s, 8-OAc), 2.02, 2.09 (each 3H, s, 3 and 13-OAc), 3.31×2, 3.35, 3.83 (each 3H, s, OCH_3×4), 4.06 (1H, s, H-17), 4.77 (1H, d, J=6.2 Hz, H-6β), 5.00 (1H, d, J=4.6 Hz, H-14β), 5.04 (1H, d, J=4.6, 12.0 Hz, H-3β), 6.90, 7.98 (each 2H, AA′BB′, J=8.6 Hz, Ar-H); δ_C (50 MHz, $CDCl_3$) 173.7 (C-19), 170.5 (*CO*CH_3), 170.3 (*CO*CH_3), 169.2 (*CO*CH_3), 165.9 (*CO*Ar), 163.6 (C-4″), 131.8 (C-2″, C-6″), 121.9 (C-1″), 113.8 (C-3″, C-5″), 82.3 (C-8), 82.2 (C-13), 81.8 (C-1), 81.6 (C-16), 79.6 (C-6), 76.5 (C-14), 75.4 (C-18), 74.7 (C-17), 67.3 (C-3), 59.4 (C-18′), 58.2 (C-16′), 56.6 (C-1′), 55.4 (4″-OCH_3), 54.9 (C-7), 51.8 (C-4), 51.1 (C-11), 50.6 (C-5), 43.6 (C-9), 41.4 (C-10), 40.6 (C-15), 34.1 (C-12), 31.8 (C-2), 21.2 (CO*CH₃*), 21.0 (CO*CH₃*), 21.0 (CO*CH₃*); *m/z* (FAB) 717 (20, $M^+ + H$), 657 (18, $M - OAc + H$); HRMS (FAB): $M^+ + H$, found 717.2753, $C_{36}H_{45}O_{15}$ requires 717.2758.

4.3.8. Compound 26. To a solution of compound **23** (30 mg, 0.04 mmol) in Ac_2O (2 mL), *p*-TsOH (20 mg) was added and the mixture was stirred at room temperature for 20 h. After pouring into ice water (5 mL), the solution was basified with conc. NH_4OH to pH 9. Extraction ($CHCl_3$, 5 mL×3), drying (Na_2SO_4) and evaporation afforded the pure product (white amorphous powder, 32 mg, 100%). **26**: mp 162–163 °C; R_f (75% cyclohexane–acetone) 0.55; $[\alpha]_D^{20} = +46.0$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3410 (*N*H), 2929, 1776 (γ-lactone), 1738 (COO), 1674 (CONH), 1608, 1514, 1461, 1259, 1099 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, 8-OAc), 2.01, 2.07, 2.16 (each 3H, s, OAc×3), 3.25, 3.37, 3.42, 3.86 (each 3H, s, OCH_3×4), 4.46 (1H, d, J=8.8 Hz, H-17), 4.84 (1H, d, J=6.4 Hz, H-6β), 5.02 (1H, dd, J=3.0, 8.0 Hz, H-3β), 5.06 (1H, d, J=5.2 Hz, H-14β), 5.72 (1H, brd, J=8.8 Hz, 17-*NH*Ac), 6.94, 8.03 (each 2H, AA′BB′, J=8.8 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 174.0 (C-19), 170.2 (*CO*CH_3), 170.0 (*CO*CH_3), 169.1 (*CO*CH_3),

169.0 (*CO*CH_3), 166.0 (*CO*Ar), 163.7 (C-4″), 131.9 (C-2″, C-6″), 122.0 (C-1″), 113.9 (C-3″, C-5″), 83.3 (C-1), 82.4 (C-8, C-13), 81.2 (C-16), 79.8 (C-6), 76.5 (C-14), 75.3 (C-18), 67.7 (C-3), 59.5 (C-18′), 58.5 (C-16′), 56.8 (C-1′), 55.4 (4″-OCH_3), 54.9 (C-17), 52.6 (C-7), 52.0 (C-4), 51.9 (C-5), 50.8 (C-11), 46.4 (C-9), 41.6 (C-10), 40.6 (C-15), 34.5 (C-12), 30.0 (C-2), 22.5 (CO*CH₃*), 21.2 (CO*CH₃*), 21.1 (CO*CH₃*), 21.0 (CO*CH₃*); *m/z* (EI) 758 (100, M^++H), 698 (33, M−OAc+H); HRMS (FAB): M^++H, found 758.3035, $C_{38}H_{48}NO_{15}$ requires 758.3024.

4.3.9. Compound 27. To a solution of compound **25** (20 mg, 0.03 mmol) in Ac_2O (2 mL), *p*-TsOH (10 mg) was added and the mixture was stirred at room temperature for 12 h. General work-up afforded the pure product (white amorphous powder, 21 mg, 100%). **27**: mp 157–158 °C; R_f (75% cyclohexane–acetone) 0.50; $[\alpha]_D^{20}=-82.0$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 2929, 1775 (γ-lactone), 1741 (COO), 1608, 1514, 1461, 1371, 1241, 1101 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, 8-OAc), 2.06, 2.07, 2.17 (each 3H, s, OAc×3), 3.28, 3.36, 3.42, 3.86 (each 3H, s, OCH_3×4), 4.79 (1H, d, *J*=6.4 Hz, H-6β), 5.03 (1H, hidden, H-17), 5.04 (1H, d, *J*=4.8 Hz, H-14β), 5.05 (1H, dd, *J*=4.0, 12.0 Hz, H-3β), 6.93, 8.03 (each 2H, AA′BB′, *J*=8.8 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 173.2 (C-19), 170.7 (*CO*CH_3), 170.2 (*CO*CH_3), 169.4 (*CO*CH_3), 168.8 (*CO*CH_3), 166.0 (*CO*Ar), 163.7 (C-4″), 131.9 (C-2″, C-6″), 122.0 (C-1″), 113.9 (C-3″, C-5″), 82.4 (C-8), 82.0 (C-13), 81.4 (C-1), 81.0 (C-16), 79.6 (C-6), 76.3 (C-14), 75.8 (C-17), 74.4 (C-18), 67.6 (C-3), 59.4 (C-18′), 58.4 (C-16′), 56.7 (C-1′), 55.4 (4″-OCH_3), 53.6 (C-7), 51.7 (C-5), 51.6 (C-4), 49.5 (C-11), 44.5 (C-9), 41.8 (C-10), 39.9 (C-15), 34.2 (C-12), 30.0 (C-2), 21.2 (CO*CH₃*), 21.2 (CO*CH₃*), 21.1 (CO*CH₃*), 21.0 (CO*CH₃*); *m/z* (ESI) 759 (40, M^++H); HRMS (FAB): M^++H, found 759.2870, $C_{38}H_{46}O_{16}$ requires 759.2864.

4.3.10. Compound 28. To a solution of compound **23** (300 mg, 0.42 mmol) in pyridine (15 mL), TsCl (240 mg, 1.26 mmol) was added and the solution was allowed to stand at room temperature for 30 h. Removal of solvent, basifying (10% Na_2CO_3, 20 mL), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/100:1) afforded the pure product as a white amorphous powder, 345 mg, (95%). **28**: mp 178–179 °C; R_f (98% $CHCl_3$–CH_3OH) 0.42; $[\alpha]_D^{20}=+5.5$ (*c* 1.7, $CHCl_3$); ν_{max} (KBr) 3466 (OH), 2939, 1778 (γ-lactone), 1740 (COO), 1607, 1514, 1460, 1371, 1258, 1101 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.27 (3H, s, 8-OAc), 1.96, 2.20 (each 3H, s, OAc×2), 2.41 (3H, s, Ar-CH_3), 3.17, 3.31, 3.45, 3.86 (each 3H, s, OCH_3×4), 4.84 (1H, d, *J*=6.4 Hz, H-6β), 5.00 (1H, d, *J*=5.0 Hz, H-14β), 5.09 (1H, dd, *J*=2.8, 7.8 Hz, H-3β), 5.66 (1H, d, *J*=2.4 Hz, H-17), 6.93, 8.00 (each 2H, AA′BB′, *J*=8.8 Hz, OAs), 7.32, 7.80 (each 2H, AA′BB′, *J*=8.4 Hz, Ts); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (FAB) 870 (20, M^++H), 810 (7, M−OAc+H); HRMS (FAB): M^++H, found 870.3013, $C_{43}H_{52}NO_{16}S$ requires 870.3007.

4.3.11. Compound 29. A solution of compound **28** (380 mg, 0.44 mmol) in 5% methanolic NaOH (15 mL) was heated at 50 °C for 20 min. Removal of solvent, diluting (H_2O, 30 mL), extraction (EtOAc, 20 mL×4), drying (Na_2SO_4) and evaporation afforded the pure product (colorless crystal needle, 240 mg, 90%). **29**: mp 234–235 °C; R_f (90% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=+56.4$ (*c* 0.5, CH_3OH); ν_{max} (KBr) 3427 (OH), 3108 (NH), 2928, 1768 (γ-lactone), 1601, 1460, 1377, 1330, 1096 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.40 (3H, s, Ar-CH_3), 2.97, 3.33, 3.43 (each 3H, s, OCH_3×3), 5.14 (1H, d, *J*=5.4 Hz, H-6β), 7.28, 7.73 (each 2H, AA′BB′, *J*=8.0 Hz, Ts); δ_C (50 MHz, CD_3COCD_3) see Table 2; *m/z* (FAB) 610 (100, M^++H); HRMS (FAB): M^++H, found 610.2327, $C_{29}H_{40}NO_{11}S$ requires 610.2322.

4.3.12. Compound 30. To a solution of compound **29** (300 mg, 0.49 mmol) in pyridine (10 mL), MsCl (0.20 mL, 2.57 mmol) was added and the solution was allowed to stand at room temperature for 3 h. Removal of solvent, diluting (H_2O), basifying (10% Na_2CO_3, pH 11), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4) and evaporation afforded the pure product as a white amorphous powder, 350 mg, (93%). **30**: mp 152–153 °C; R_f (95% $CHCl_3$–CH_3OH) 0.48; $[\alpha]_D^{20}=+19.4$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3507 (OH), 3320 (NH), 2935, 1771 (γ-lactone), 1639, 1460, 1350, 1176, 1094 cm^{-1}; δ_H (200 MHz, $CDCl_3$+CD_3OD) 2.28 (3H, s, Ar-CH_3), 2.94, 2.97 (each 3H, s, OMs×2), 3.05, 3.20, 3.26 (each 3H, s, OCH_3×3), 4.43 (1H, d, *J*=4.2 Hz, H-14β), 4.76 (1H, d, *J*=5.0 Hz, H-3β), 5.03 (1H, d, *J*=6.4 Hz, H-6β), 7.19, 7.58 (each 1H, AA′BB′, *J*=8.0 Hz, Ts); δ_C (50 MHz, $CDCl_3$+CD_3OD) see Table 2; *m/z* (FAB) 766 (100, M^++H); HRMS (FAB): M^++H, found 766.1869, $C_{31}H_{44}NO_{15}S_3$ requires 766.1873.

4.3.13. Compound 31. To a mixture of compound **30** (100 mg, 0.13 mmol) and anhydrous NaOAc (200 mg, 2.43 mmol) in sealed tube (20 mL), HOAc (3 mL) was added and the solution was stirred at 150 °C for 24 h. Diluting (ice water), basifying (NH_4OH, pH 10), extraction ($CHCl_3$, 5 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/25:1) afforded the pure product as a white amorphous powder, 80 mg, (70%). **31**: mp 232–233 °C; R_f (90% $CHCl_3$–CH_3OH) 0.51; $[\alpha]_D^{20}=-13.0$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3487 (OH), 3324 (NH), 2934, 1758 (γ-lactone), 1638, 1460, 1353, 1167, 1091 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.44 (3H, s, Ar-CH_3), 3.12, 3.25, 3.31, 3.41 (each 3H, s, OCH_3×3), 4.68 (1H, d, *J*=4.8 Hz, H-14β), 4.80 (1H, s, H-17), 5.12 (1H, d, *J*=7.2 Hz, H-6β), 5.92 (1H, dd, *J*=2.0, 10.4 Hz, H-2), 6.04 (1H, dd, *J*=1.6, 10.4 Hz, H-3), 7.31, 7.73 (each 1H, AA′BB′, *J*=8.8 Hz, Ts); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (FAB) 670 (85, M^++H); HRMS (FAB): M^++H, found 670.1988, $C_{30}H_{40}NO_{12}S_2$ requires 670.1992.

4.4. Approach BCA

4.4.1. Compound 33. To a solution of compound **19** (1.10 g, 1.48 mmol) in diglyme (40 mL), H_2O (10 mL) was added and the solution was heated at reflux for 12 h. Diluting (H_2O, 40 mL), basifying (NH_4OH, pH 10), extraction ($CHCl_3$, 20 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/50:1) afforded the pure product as a white amorphous powder, 900 mg, (87%), which was identified

Table 2. ^{13}C NMR data of compounds **28**, **29**, **30**, and **31**

Carbon	**28**	**29**	**30**	**31**
1	82.1 d	83.9 d	83.2 d	82.4 d
2	28.9 t	32.2 t	30.0 t	128.1 d
3	66.5 d	67.1 d	73.3 d	127.9 d
4	51.6 s	52.8 s	52.0 s	50.7 s
5	50.4 d	51.5 d	48.8 d	48.9 d
6	79.6 d	81.3 d	79.3 d	78.6 d
7	52.1 d	52.0 d	57.2 d	57.0 d
8	82.0 s	78.0 s	75.1 s	75.4 s
9	45.5 d	48.3 d	44.5 d	45.6 d
10	40.9 d	46.1 d	44.0 d	43.7 d
11	50.4 s	51.0 s	50.4 s	50.1 s
12	34.4 t	36.2 t	33.8 t	33.6 t
13	82.0 s	72.4 s	70.8 s	70.3 s
14	76.5 d	78.8 d	83.9 d	84.2 d
15	39.8 t	43.9 t	42.0 t	42.3 t
16	80.3 d	85.3 d	81.6 d	81.6 d
17	57.7 d	58.1 d	58.1 d	57.1 d
18	76.6 t	78.6 t	75.8 t	78.2 t
19	173.5 s	178.5 s	174.0 s	175.7 d
1′	56.6 q	56.3 q	56.1 q	56.6 q
16′	58.4 q	58.7 q	58.2 q	58.3 q
18′	59.4 q	59.4 q	59.0 q	59.4 q
O=C	170.2 s	—	—	—
|	170.2 s	—	—	—
CH_3	168.7 s	—	—	—
	21.1 q	—	—	—
	21.1 q	—	—	—
	21.0 q	—	—	—
SO_2	137.2 s	138.0 s	135.8 s	136.1 s
	129.3 d	130.3 d	129.4 d	129.5 d
	127.9 d	128.5 d	127.3 d	127.7 d
	143.4 s	144.0 s	143.7 s	143.6 s
CH_3	21.5 q	21.3 q	21.1 q	21.4 q
O=C	165.9 s	—	—	—
	121.8 s	—	—	—
	131.8 d	—	—	—
	113.8 d	—	—	—
	163.6 s	—	—	—
OCH_3	55.4 q	—	—	—
OMs	—	—	38.4 q	38.7 q
	—	—	38.1 q	—

by comparison with the authentic sample [TLC: cyclohexane–acetone/2:1; $CHCl_3$–CH_3OH/98:2].

4.4.2. Compound 34. To a solution of compound **33** (900 mg, 1.28 mmol) in pyridine (20 mL), $SOCl_2$ (1.0 mL) was added and the solution was stirred at room temperature for 12 h. To the reaction solution was added excess $NaBH_4$ and the reaction solution continued to stand at room temperature for 3 h. Removal of solvent, diluting (H_2O, 40 mL), basifying (conc. NH_4OH, pH 10), extraction ($CHCl_3$, 20 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane–acetone/4:1) afforded the pure product as a white amorphous powder, 650 mg, (74%), which was identified by comparison with the authentic sample [TLC: cyclohexane–acetone/2:1; $CHCl_3$–CH_3OH/96:4].

4.4.3. Compound 35. A solution of compound **34** (400 mg, 0.59 mmol) in 5% methanolic NaOH (15 mL) was heated at 50 °C for 20 min. Removal of solvent, diluting (H_2O, 50 mL), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4) and evaporation afforded the pure product (white amorphous powder, 274 mg, 100%). **35**: mp 92–93 °C; R_f (90% $CHCl_3$–CH_3OH) 0.42; $[\alpha]_D^{20} = +40.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3427 (OH), 2930, 1639, 1451, 1376, 1180, 1100 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, t, $J=7.2$ Hz, *N*-CH_2CH_3), 3.33, 3.33, 3.34, 3.45 (each 3H, s, OCH_3×4), 4.15 (1H, d, $J=2.8$ Hz, H-14β), 5.58 (1H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 133.5 (C-8), 126.8 (C-7), 85.4 (C-1, C-16), 82.6 (C-6), 79.8 (C-14), 77.8 (C-13), 74.3 (C-18), 70.5 (C-3), 59.1 (C-18′), 57.7 (C-16′), 57.6 (C-6′), 56.1 (C-1′), 52.1 (C-19), 51.6 (C-17), 49.5 (NCH_2CH_3), 43.9 (C-5), 43.7 (C-11), 42.2 (C-4), 41.6 (C-9), 40.9 (C-10), 38.9 (C-15), 38.5 (C-12), 35.3 (C-2), 12.0 (NCH_2CH_3); *m/z* (EI) 467 (15, M^+), 452 (100, $M-CH_3$), 436 (75, $M-OCH_3$), 378 (85); HRMS (FAB): $M^+ + H$, found 468.2959, $C_{25}H_{42}NO_7$ requires 468.2961.

4.4.4. Compounds 36 and 37. To a solution of compound

35 (220 mg, 0.47 mmol) in pyridine (15 mL), MsCl (0.14 mL, 1.80 mmol) was added and the solution was stirred at room temperature for 6 h. Removal of solvent, diluting (H_2O, 50 mL), basifying (10% Na_2CO_3, 20 mL), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/100:0.7) afforded the pure products as white amorphous powder (**36**: 150 mg, 51%; **37**: 55 mg, 17%).

4.4.5. Compound 36. Mp 113–114 °C; R_f (99% $CHCl_3$–CH_3OH) 0.56; $[\alpha]_D^{20}=+18.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3477 (OH), 2934, 1638, 1458, 1352, 1176, 1102 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, t, $J=7.2$ Hz, *N*-CH_2CH_3), 3.03, 3.07 (each 3H, s, OMs×2), 3.29, 3.37, 3.37, 3.34 (each 3H, s, OCH_3×4), 4.66 (1H, d, $J=2.0$ Hz, 14β-H), 4.83 (1H, dd, $J=6.4$, 11.6 Hz, H-3β), 5.56 (1H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 131.8 (C-8), 127.0 (C-7), 88.8 (C-14), 85.1 (C-16), 84.3 (C-1), 81.1 (C-6), 79.5 (C-3), 76.8 (C-13), 71.2 (C-18), 58.5 (C-18′), 57.8 (C-6′, C-16′), 56.1 (C-1′), 51.6 (C-19), 50.8 (C-17), 49.4 (NCH_2CH$_3$), 43.3 (C-11), 42.9 (C-5), 42.2 (C-4), 40.8 (C-9), 40.5 (C-10), 38.7 (C-15), 38.6 (C-12), 38.2 (OMs), 38.2 (OMs), 33.2 (C-2), 11.8 (NCH_2CH_3); *m*/*z* (EI) 623 (1, M^+), 608 (3, M−CH_3), 432 (100, M−OMs×2-H); HRMS (FAB): M^++H, found 624.2520, $C_{27}H_{46}NO_{11}S_2$ requires 624.2512.

4.4.6. Compound 37. Mp 110–111 °C; R_f (99% $CHCl_3$–CH_3OH) 0.5; $[\alpha]_D^{20}=+8.8$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 2938, 1639, 1459, 1355, 1170, 1105 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96 (1H, t, $J=7.2$ Hz, *N*-CH_2CH_3), 3.03, 3.10, 1.13 (each 3H, s, OMs×3), 3.29, 3.35, 3.37, 3.41 (each 3H, s, OCH_3×4), 4.83 (1H, dd, $J=5.2$, 11.6 Hz, H-3β), 4.90 (1H, br s, H-14β), 5.69 (1H, br s, H-7); δ_C (100 MHz, $CDCl_3$) 130.5 (C-8), 127.4 (C-7), 90.8 (C-13), 86.8 (C-14), 83.8 (C-1), 83.3 (C-16), 80.8 (C-6), 79.1 (C-3), 71.2 (C-18), 58.5 (C-18′), 57.7 (C-16′), 56.7 (C-6′), 56.0 (C-1′), 51.4 (C-19), 50.5 (C-17), 49.4 (NCH_2CH$_3$), 43.2 (C-11), 42.2 (C-4), 42.1 (C-5), 40.5 (C-9), 40.4 (C-10), 40.2 (OMs), 39.2 (C-15), 39.1 (C-12), 38.9 (OMs), 38.4 (OMs), 33.2 (C-2), 11.8 (NCH_2CH_3); *m*/*z* (EI) 701 (1, M^+), 605 (14, M−OMs-1), 510 (75, M−OMs×2-1), 414 (25, M−OMs×3-H-H); HRMS (FAB): M^++H, found 702.2287, $C_{28}H_{48}NO_{13}S_3$ requires 702.2288.

4.4.7. Compound 38. To a mixture of compound **36** (100 mg, 0.13 mmol) and *o*-xylene (2.5 mL) in sealed tube (20 mL), DBN (0.5 mL) was added and the solution was heated at 150 °C for 5 h. Removal of *o*-xylene and column chromatography (silica gel H, $CHCl_3$–CH_3OH/9:1) afforded the pure product (oil, 30 mg, 89%). **38**: mp 240–241 °C; R_f (80% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=-13.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3468 (OH), 3324, 2930, 1612, 1459, 1353, 1276, 1170, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, $J=$ 7.2 Hz, *N*-CH_2CH_3), 3.03 (3H, s, OMs), 3.30, 3.31, 3.36, 3.40 (each 3H, s, OCH_3×4), 4.65 (1H, d, $J=3.0$ Hz, H-14β), 5.59 (1H, dd, hidden, H-2), 5.61 (1H, br s, H-7), 5.92 (1H, dd, $J=2.0$, 9.8 Hz, H-3); δ_C (100 MHz, $CDCl_3$) 136.8 (C-2), 131.5 (C-8), 129.0 (C-3), 125.7 (C-7), 88.3 (C-14), 87.4 (C-1), 84.8 (C-16), 79.3 (C-6), 78.1 (C-18), 77.3 (C-12), 59.2 (C-18′), 58.1 (C-16′), 57.9 (C-6′), 56.4 (C-1′), 53.2 (C-19), 51.6 (C-17), 50.8 (NCH_2CH$_3$), 43.8 (C-5), 43.3 (C-4), 43.2 (C-11), 41.9 (C-9, C-10), 38.8 (C-12), 38.6 (C-15), 38.3 (OMs), 10.9 (NCH_2CH_3); *m*/*z* (EI) 527 (7, M^+), 521 (13, M−CH_3), 432 (100, M−OMs); HRMS (FAB): M^++H, found 528.2640, $C_{26}H_{42}NO_8S$ requires 528.2631.

4.5. Approach CAB

4.5.1. Compound 43. To a solution of yunaconitine (**3**) (1.55 g, 2.35 mmol) in acetone (10 mL), Jones reagent (3 mL, 8.22 mmol) was added dropwise under ice-water bath and the solution was stirred at room temperature for 30 min. Diluting (H_2O, 30 mL), basifying (conc. NH_4OH, pH 11), extraction ($CHCl_3$, 15 mL×4), drying (Na_2SO_4) and evaporation afforded the white amorphous powder, which was dissolved in 5% methanolic NaOH (15 mL) and heated at 50 °C for 30 min. Removal of solvent, diluting (H_2O, 30 mL), extraction ($CHCl_3$, 15 mL×3), drying (Na_2SO_4) and evaporation afforded the white amorphous powder (1.06 g, 100%). This residue (1.06 g, 2.35 mmol) was dissolved in pyridine (30 mL), MsCl (0.35 mL, 4.70 mmol) was added and the solution was stirred at room temperature for 1.5 h. Removal of solvent, diluting (H_2O, 30 mL), extraction ($CHCl_3$, 15 mL×3), drying (Na_2SO_4), and evaporation afforded the pure product (white amorphous powder, 1.17 g, 95%), which was dissolved in DMF (50 mL), NaOH (200 mg) was added and the solution was refluxed for 30 min. General work-up afforded the white amorphous powder (912 mg, 90%).

To a solution of the residue (912 mg, 2.12 mmol) in 95% EtOH (30 mL), 10% Pd–C (90 mg) was added and the solution was stirred under hydrogen steam at room temperature for 1 h. Filtration was evaporated under reduced pressure to give the pure product **43** (white amorphous powder, 915 mg, 100%), which was identified by comparison with the authentic sample [TLC: silica gel GF_{254}, cyclohexane–acetone/3:1; $CHCl_3$–CH_3OH/95:5].

4.5.2. Compound 44. To a solution of compound **43** (800 mg, 1.85 mmol) in MeOH (30 mL), $NaBH_4$ (500 mg, 13.15 mmol) was added and the solution was stirred at room temperature for 3 h. Removal of solvent, diluting (H_2O, 40 mL), extraction ($CHCl_3$, 15 mL×3), drying (Na_2SO_4), and evaporation afforded the pure product (white amorphous powder, 726 mg, 90%). **44**: mp 160–161 °C; R_f (90% $CHCl_3$–CH_3OH) 0.44; $[\alpha]_D^{20}=+12.5$ (*c* 0.2, $CHCl_3$); ν_{max} (KBr) 3426 (OH), 2930, 1649, 1459, 1379, 1203, 1175, 1101 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, t, $J=7.2$ Hz, *N*-CH_2CH_3), 3.32, 3.33, 3.39 (each 3H, s, OCH_3×3), 3.87 (1H, dd, $J=2.8$, 6.0 Hz, H-13), 4.08 (1H, dd, $J=2.4$, 9.6 Hz, H-3β); δ_C (100 MHz, $CDCl_3$) 84.3 (C-6), 77.7 (C-8), 77.0 (C-16), 76.7 (C-18), 74.4 (C-3), 64.6 (C-13), 62.8 (C-17), 59.0 (C-18′), 57.8 (C-16′), 56.0 (C-6′), 52.0 (C-7), 48.6 (NCH_2CH$_3$), 48.0 (C-5), 47.1 (C-19), 43.9 (C-11), 42.9 (C-9), 42.3 (C-4), 40.3 (C-10), 34.5 (C-15), 29.6 (C-14), 29.1 (C-12), 25.9 (C-2), 21.8 (C-1), 13.4 (NCH_2CH_3); *m*/*z* (EI) 437 (25, M^+), 422 (100, M−CH_3); HRMS (FAB): M^++H, found 438.2854, $C_{24}H_{40}NO_6$ requires 438.2856.

4.5.3. Compound 45. To a solution of compound **44** (700 mg, 1.60 mmol) in pyridine (30 mL), Ac_2O (3 mL) was added and the solution was heated at room temperature for 28 h. Removal of solvent, basifying (10% Na_2CO_3, 20 mL), extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), and evaporation afforded the pure product (white

amorphous powder, 791 mg, 95%). **45**: mp 72–73 °C; R_f (95% $CHCl_3$–CH_3OH) 0.46; $[\alpha]_D^{20}=+56.5$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3452 (OH), 2932, 1738 (COO), 1639, 1459, 1378, 1247, 1112, 1100 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, $J=6.8$ Hz, *N*-CH_2CH_3), 2.05, 2.13 (each 3H, s, OAc×2), 3.22, 3.34, 3.36 (each 3H, s, OCH_3×3), 4.97 (1H, dd, $J=5.2$, 12.4 Hz, H-3β), 5.22 (1H, dd, $J=6.4$, 7.2 Hz, H-13); δ_C (50 MHz, $CDCl_3$) 170.5 ($CO$$CH_3$), 170.2 ($CO$$CH_3$), 84.4 (C-6), 77.7 (C-8), 75.1 (C-3), 74.0 (C-16), 71.7 (C-18), 66.2 (C-13), 64.1 (C-17), 58.7 (C-18′), 57.9 (C-16′) 56.3 (C-6′), 51.8 (C-7), 48.4 (NCH_2CH_3), 48.0 (C-19), 46.2 (C-5), 43.7 (C-11), 42.3 (C-9), 41.4 (C-4), 40.0 (C-10), 36.5 (C-15), 29.6 (C-12), 29.4 (C-14), 25.9 (C-2), 22.8 (C-1), 21.1 ($CO$$CH_3$), 20.8 ($CO$$CH_3$), 13.3 ($NCH_2CH_3$); *m/z* (ESI) 522 (100, M^++H); HRMS (FAB): M^++H, found 522.3061, $C_{28}H_{44}NO_8$ requires 522.3067.

4.5.4. Compound 46. To a solution of compound **45** (760 mg, 1.45 mmol) in HOAc (40 mL), NBS (2.08 g, 11.77 mmol) was added and the solution was stirred at room temperature for 2 h. After pouring into ice water (50 mL), the solution was basified with conc. NH_4OH to pH 10. Extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/25:1) afforded the pure product (white amorphous powder, 585 mg, 82%). **46**: mp 110–111 °C; R_f (90% $CHCl_3$–CH_3OH) 0.41; $[\alpha]_D^{20}=+111.0$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3452 (OH), 2937, 1736 (COO), 1650 (C=N), 1461, 1378, 1246, 1210, 1108 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.06, 2.12 (each 2H, s, OAc×2), 3.28, 3.32, 3.34 (each 3H, s, OCH_3×3), 4.11 (each 1H, ABq, $J=8.8$ Hz, H_2-18), 4.04 (1H, dd, $J=1.2$, 6.8 Hz, H-6β), 3.59 (1H, s, H-17), 4.97 (1H, dd, $J=4.4$, 11.2 Hz, H-3β), 5.18 (1H, dd, $J=3.6$, 10.0 Hz, H-13), 7.39 (1H, d, $J=1.2$ Hz, H-19); δ_C (100 MHz, $CDCl_3$) 170.7 ($CO$$CH_3$), 169.8 ($CO$$CH_3$), 164.2 (C-19), 84.9 (C-6), 75.4 (C-8), 74.7 (C-16), 73.3 (C-3), 69.9 (C-18), 66.0 (C-13), 64.8 (C-17), 60.8 (C-7), 58.9 (C-18′), 57.9 (C-16′), 56.3 (C-6′), 49.8 (C-11), 45.2 (C-5), 43.5 (C-4), 42.9 (C-9), 39.2 (C-10), 36.0 (C-15), 29.3 (C-14), 26.4 (C-12), 26.3 (C-2), 23.5 (C-1), 20.9 ($CO$$CH_3$), 20.7 ($CO$$CH_3$); *m/z* (EI) 491 (15, M^+), 432 (100, M−OAc); HRMS (FAB): M^++H, found 492.2601, $C_{26}H_{38}NO_8$ requires 492.2597.

4.5.5. Compound 47. To a solution of compound **46** (520 mg, 1.06 mmol) in CH_2Cl_2 (35 mL), *m*-CPBA (367 mg, 2.12 mmol) was added and the solution was stirred at room temperature for 2 h. To the reaction mixture was added 10% Na_2CO_3 (20 mL) with stirring vigorously. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 mL×3). Drying (Na_2SO_4) and evaporation afforded the pure product (white amorphous powder, 450 mg, 84%). **47**: mp 117–118 °C; R_f (95% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=+52.8$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3452 (OH), 2931, 1739 (COO), 1460, 1378, 1245, 1210, 1108 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.10, 2.13 (each 3H, s, OAc×2), 3.28, 3.34, 3.38 (each 3H, s, OCH_3×3), 3.50, 4.18 (each 1H, ABq, $J=10.0$ Hz, H_2-18), 3.86 (1H, s, H-17), 3.88 (1H, dd, $J=2.4$, 8.8 Hz, H-6β), 4.17 (1H, s, H-19), 4.99 (1H, dd, $J=4.8$, 12.0 Hz, H-3β), 5.17 (1H, dd, $J=3.6$, 10.0 Hz, H-13); δ_C (100 MHz, $CDCl_3$) 170.6 ($CO$$CH_3$), 169.6 ($CO$$CH_3$), 83.7 (C-6), 77.0 (C-8), 76.0 (C-19), 74.8 (C-16), 73.1 (C-3), 68.7 (C-18), 66.1 (C-13), 65.0 (C-17), 58.8 (C-18′), 58.0 (C-7), 58.2 (C-16′), 56.3 (C-6′), 44.9 (C-11), 44.4 (C-4), 43.9 (C-5), 42.6 (C-9), 39.5 (C-10), 36.1 (C-15), 29.1 (C-14), 25.8 (C-12), 25.1 (C-2), 23.1 (C-1), 20.9 ($CO$$CH_3$), 20.8 ($CO$$CH_3$); *m/z* (EI) 507 (13, M^+), 492 (85, M−CH_3), 432 (100, M−CH_3–HOAc); HRMS (EI): M^+, found 507.2455, $C_{26}H_{37}NO_9$ requires 507.2468.

4.5.6. Compound 48. To a solution of compound **44** (45 mg, 0.10 mmol) in Ac_2O (2 mL), *p*-TsOH (50 mg) was added and the solution was heated at 50 °C for 12 h. Diluting (ice water), basifying (conc. NH_4OH, pH 10), extraction ($CHCl_3$, 5 mL×3), drying (Na_2SO_4) and evaporation afforded the pure product (white amorphous powder, 50 mg, 86%). **48**: mp 70–71 °C; R_f (95% $CHCl_3$–CH_3OH) 0.44; $[\alpha]_D^{20}=+48.1$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3451 (OH), 2934, 1738 (COO), 1459, 1375, 1244, 1112 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, t, $J=7.2$ Hz, *N*-CH_2CH_3), 2.02, 2.05, 2.14 (each 3H, s, OAc×3), 3.21, 3.32, 3.33 (each 3H, s, OCH_3×3), 4.97 (1H, dd, $J=6.4$, 11.6 Hz, H-3β), 5.26 (1H, dd, $J=3.2$, 8.8 Hz, H-13); δ_C (100 MHz, $CDCl_3$) 170.3 ($CO$$CH_3$), 170.2 ($CO$$CH_3$), 160.1 ($CO$$CH_3$), 89.4 (C-8), 85.0 (C-6), 75.3 (C-16), 73.9 (C-3), 71.6 (C-18), 66.9 (C-13), 63.0 (C-17), 58.6 (C-18′), 58.1 (C-16′), 56.7 (C-6′), 48.2 (C-7), 48.1 (NCH_2CH_3), 47.4 (C-19), 46.6 (C-5), 43.8 (C-11), 43.0 (C-9), 41.3 (C-4), 39.4 (C-10), 31.8 (C-15), 30.6 (C-14), 25.8 (C-2), 25.5 (C-12), 22.2 (C-1), 21.4 ($CO$$CH_3$), 21.1 ($CO$$CH_3$), 20.9 ($CO$$CH_3$), 13.2 ($NCH_2CH_3$); *m/z* (EI) 562 (10, M^+-H), 548 (10, M−CH_3), 503 (12, M−HOAc), 472 (40, M−OCH_3–HOAc), 444 (100, M−OAc×2-H); HRMS (EI): M^+, found 563.3081, $C_{30}H_{45}NO_9$ requires 563.3094.

4.5.7. Compound 49. To a solution of compound **48** (55 mg, 0.10 mmol) in HOAc (2 mL), NBS (139 mg, 0.78 mmol) was added and the solution was stirred at room temperature for 3 h. General work-up and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98:2) afforded the pure product as a white amorphous powder, 28 mg, (54%). **49**: mp 80–81 °C; R_f (95% $CHCl_3$–CH_3OH) 0.46; $[\alpha]_D^{20}=+98.0$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 2943, 1775 (COO), 1717 (COO), 1648 (C=N), 1432, 1375, 1241, 1108 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.00, 2.07, 2.13 (each 3H, s, OAc×3), 3.28, 3.31, 3.35 (each 3H, s, OCH_3×3), 4.97 (1H, dd, $J=4.8$, 12.0 Hz, H-3β), 5.22 (1H, dd, $J=4.0$, 8.0 Hz, H-13), 7.41 (1H, br s, H-19); δ_C (100 MHz, $CDCl_3$) 170.2 ($CO$$CH_3$), 169.8 ($CO$$CH_3$), 169.8 ($CO$$CH_3$), 164.0 (C-19), 86.5 (C-8), 85.5 (C-6), 75.3 (C-16), 73.1 (C-3), 69.6 (C-18), 67.4 (C-13), 63.1 (C-17), 58.8 (C-18′), 58.2 (C-16′), 57.8 (C-7), 57.0 (C-6′), 49.9 (C-11), 45.7 (C-5), 43.6 (C-4), 41.4 (C-9), 39.3 (C-10), 32.5 (C-15), 26.3 (C-2), 26.2 (C-12), 23.2 (C-1), 22.3 (C-14), 20.9 ($CO$$CH_3$), 20.9 ($CO$$CH_3$), 20.9 ($CO$$CH_3$); *m/z* (ESI) 533 (100, M^+); HRMS (FAB): M^++H, found 534.2707, $C_{28}H_{40}NO_9$ requires 534.2703.

4.5.8. Compound 50. To a solution of compound **49** (28 mg, 0.053 mmol) in CH_2Cl_2 (2 mL), *m*-CPBA (18 mg, 0.105 mmol) was added and the solution was stirred at room temperature for 30 min. General work-up and column chromatography (silica gel H, $CHCl_3$–CH_3OH/99:1) afforded the pure product as a white amorphous powder, 12 mg, (40%). **50**: mp 105–106 °C; R_f (96% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=+16.7$ (*c* 0.3, $CHCl_3$); ν_{max} (KBr)

Table 3. ^{1}H and ^{13}C NMR data of **51** (^{1}H: 400 MHz, ^{13}C: 100 MHz; $CDCl_3$)

No.	δ_H Mult (J=Hz)	δ_C	HMBC (H→C)
1	~1.80 m	22.6 t	C-2, C-10, C-11
2	1.50 m (α)	18.0 t	C-11
	1.80 m (β)		C-1, C-11
3	5.22 dd (9.2, 5.6)	66.4 d	C-1, C-2, C-4, C-5, C-18, C-19
4	—	52.2 s	—
5	2.54 m	48.0 d	C-7, C-17, C-18, C-19
6	5.63 d (7.2)	83.6 d	C-5, C-11, C-19
7	3.80 s	55.8 d	C-6, C-8, C-17
8	—	76.2 s	—
9	2.50 m	49.9 d	C-8
10	~2.30 m	37.4 d	C-5, C-8, C-9, C-14
11	—	49.7 s	—
12	1.40 m	24.9 t	C-9, C-11
13	5.05 dd (12.8, 3.2)	66.2 d	C-16, OO*C*CH$_3$ (δ_C 169.1)
14	3.02 m	29.1 d	C-8, C-10, C-12, C-16
15	~2.00 m	37.7 t	C-8, C-13, C-16
	~2.30 m		C-8, C-13, C-16
16	3.57 m	74.2 d	C-8
17	4.90 s	91.8 d	C-6, C-7, C-8
18	3.33 ABq (hidden)	77.1 t	C-19
	3.51 ABq (hidden)		C-19
19	—	177.7 s	—
16-OCH$_3$	3.33 s	56.4 q	C-16
18-OCH$_3$	3.33 s	59.4 q	C-18
3-OAc	2.02 s	170.2 s	OO*C*CH$_3$ (δ_C 170.2)
		20.9 q	
13-OAc	2.18 s	169.1 s	OO*C*CH$_3$ (δ_C 169.1)
		20.5 q	

2936, 1736 (COO), 1656, 1432, 1375, 1241, 1108 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.00, 2.08, 2.11 (each 3H, s, OAc×3), 3.28, 3.32, 3.39 (each 3H, s, OCH$_3$×3), 5.01 (1H, dd, J=6.4, 13.2 Hz, H-3β), 5.27 (1H, dd, J=3.6, 8.4 Hz, H-13), 6.17 (1H, br s, H-19); *m/z* (ESI) 572 (58, M$^+$+Na); HRMS (FAB): M$^+$+H, found 550.2656, $C_{28}H_{40}NO_{10}$ requires 550.2652.

4.5.9. Compound 51. To a solution of compound **47** (300 mg, 0.59 mmol) in MeOH (15 mL), excess $HIO_4 \cdot 2H_2O$ (800 mg, 3.76 mmol) was added and the mixture was stirred at room temperature for 4 h. Removal of solvent, basifying (10% Na_2CO_3, 30 mL), extraction ($CHCl_3$, 15 mL×4), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, petroleum ether–acetone/3:1) afforded the pure product **51** (white amorphous powder, 80 mg, 26%) and a by-product **47** (white amorphous powder, 120 mg, 40%). **51**: mp 114–115 °C; R_f (50% petroleum ether–acetone) 0.48; $[\alpha]_D^{20}=-1.70$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3450 (OH), 2941, 1780 (γ-lactone), 1740 (COO), 1558, 1461, 1378, 1243, 1107 cm^{-1}; δ_H (400 MHz, $CDCl_3$) and δ_C (100 MHz, $CDCl_3$) see Table 3; *m/z* (EI) 523 (4, M$^+$), 507 (3, M−CH$_3$), 463 (40, M−CH$_3$-*N*O$_2$), 419 (100); HRMS (EI): M$^+$, found 523.2057, $C_{25}H_{33}NO_{11}$ requires 523.2054.

4.5.10. Compound 52. To a solution of compound **50** (12 mg, 0.022 mmol) in MeOH (2 mL), excess $HIO_4 \cdot 2H_2O$ (50 mg, 0.23 mmol) was added and the mixture was stirred at room temperature for 12 h. A general work-up and column chromatography (silica gel H, $CHCl_3$–CH_3OH/100:1) afforded the pure product (white amorphous powder, 5 mg, 40%). **52**: mp 96–97 °C; R_f (98% $CHCl_3$–CH_3OH) 0.46; $[\alpha]_D^{20}=-28.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 2938, 1776 (γ-lactone), 1738 (COO), 1550, 1458, 1380, 1243, 1108 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.06, 2.07, 2.13 (each 3H, s, OAc×3), 3.33 (6H, s, OCH$_3$×2), 5.00 (1H, dd, J=4.0, 7.6 Hz, H-13), 5.24 (1H, dd, J=5.6, 9.2 Hz, H-3β), 5.11 (1H, d, J=7.2 Hz, H-6β), 5.49 (1H, s, H-17); δ_C (100 MHz, $CDCl_3$) 174.1 (C-19), 170.3 (*CO*CH$_3$), 170.1 (*CO*CH$_3$), 169.3 (*CO*CH$_3$), 89.0 (C-17), 84.1 (C-8), 81.9 (C-6), 76.7 (C-18), 75.1 (C-16), 67.1 (C-13), 66.7 (C-3), 59.3 (C-18′), 57.0 (C-16′), 56.1 (C-7), 51.5 (C-4), 51.1 (C-5), 49.5 (C-9), 49.4 (C-11), 37.0 (C-15), 36.9 (C-10), 29.2 (C-14), 24.7 (C-12), 21.9 (C-1, CO*CH$_3$*), 20.9 (CO*CH$_3$*), 20.5 (CO*CH$_3$*), 19.7 (C-2); *m/z* (ESI) 588 (58, M$^+$+Na); HRMS (EI): M$^+$, found 565.2160, $C_{27}H_{35}NO_{12}$ requires 565.2159.

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Candida Rugosa lipase-catalyzed kinetic resolution of β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates

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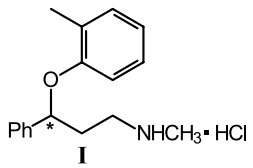
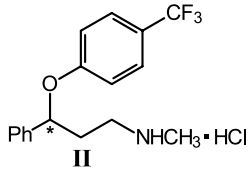
Abstract—A simple and convenient method was reported for the preparation of optically active β-hydroxy-β-arylpropionates, δ-hydroxy-δ-aryl-β-oxo-pentanoates and their butyryl derivatives via CRL-catalyzed hydrolysis. The optically active products are potential precursors of some chiral pharmaceuticals and natural products.

1. Introduction

Optically active β-hydroxy-β-arylpropionates and the derivatives thereafter are synthetically important and highly functionalized chiral synthons, of which the chiral β-hydroxy-β-arylpropionates are precursors of enantiopure pharmaceuticals including enantiomers of tomoxetine hydrochloride (**I**) and fluoxetine hydrochloride (**II**). The racemic **I** and **II** are pharmaceuticals for treatment of psychiatric disorders (depression, anxiety, alcoholism) and metabolic problems (obesity, bulimia).[1] Meanwhile, (*R*)-tomoxetine (**I**) is the first norepinephrine reuptake-inhibiting anti-depressant which does not possess strong affinity for either α- or β-adrenergic receptors.[1a,2]



I



II

On other hand, optically active δ-hydroxy-δ-aryl-β-oxo-pentanoates can be converted to 6-substituted-4-hydroxy lactones and also reacted with an equivalent of aldehydes via a tandem Knovenenagel reaction in the presence of $BF_3 \cdot Et_2O$ to give single diasetereomers of highly substituted tetrahydropyran-4-ones, which are key precursors of many natural products, such as compactin and mevinolin,[3] manoalide,[4] compaction and (+)-dihydrocompaction,[5] (−)-pestalotin,[6] bryostatin,[7] and so on.

Since optically active β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates have practical and potential uses in organic reactions and chiral pharmaceuticals, synthetic study of these molecules has therefore attracted considerable interest. The preparation of chiral β-hydroxy-β-arylpropionates was mainly focused on catalytic asymmetric[8] and biological reduction[9] of corresponding β-keto carboxylates. As examples for preparation of optically active δ-hydroxy-δ-aryl-β-oxo-pentanoates, 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene was reacted with chiral acetals through a distereselective addition[10] or with aldehydes via an asymmetric aldol condensation catalyzed by Ti(IV)/BINOL complex.[11] Another method used an enantioselective reaction of diketene with aldehydes through a chiral Schiff's base–titanium alkoxide complex.[12]

The drawbacks of above synthetic routes include harsh reaction conditions, expensive reagents, poor chemical yields and low optical purity.[8–12] An alternative way to synthesize these chiral molecules is based on biocatalytic kinetic resolution, which has attracted the interest of synthetic chemists because of the high-, regio- and stereoselectivity.[13] Our group has exploited baker's yeast-mediated enantioreduction for preparation of some optically active γ-hydroxy-β-ketophosphonates and δ-hydroxy-β-ketophosphonates.[14] In addition we also used *Candia Antartic* lipase B (CALB) and crude *Candia Rugosa* lipase

Keywords: β-Hydroxy-β-arylpropionates; δ-Hydroxy-δ-aryl-β-oxo-pentanoates; *Candia Rugosa* lipase (CRL); Enantioselectivity; Hydrolysis.
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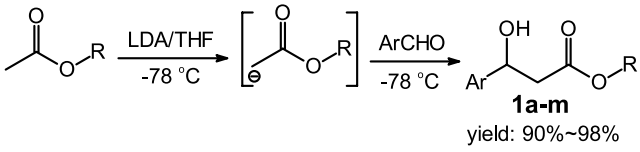
(CRL) to resolve hydroxyphophonates and aminophosphonates to obtain chiral compounds.[15]

In this paper, we wish to report our experimental results on CRL-catalyzed enantioselective hydrolysis and alcoholysis for the preparation of chiral hydroxycarboxylates bearing aryl groups.

2. Results and discussion

First, the racemic β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates were synthesized via a convenient and simple method with high yields (Schemes 1 and 2)

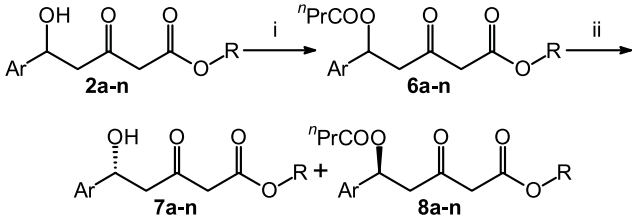


R=Me, Et, *i*-Pr, Bu; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

Scheme 1.

In our previous work,[15a,c,f] we successfully resolved β-hydroxy-β-arylethylphosphonates and δ-hydroxy-δ-aryl-β-oxo-butylphosphonates by crude CRL in diisopropyl ether. Because of the similarity of phosphonates and carboxylates, this strategy was successfully applied to resolve compounds **1a**–**m** and **2a**–**n**.

Direct butyrylation of **1a**–**m** and **2a**–**n** using DCC/butyric acid system afforded the butyryl derivatives in above 90% yields. The resulted products could be enantioselectively hydrolyzed to corresponding (*R*)-alcohols and (*S*)-esters by crude CRL in diisopropyl ether pre-equilibrated with 1.2 mol/L aqueous $MgCl_2$. (Schemes 3 and 4, Tables 1 and 2)



R=Me, Et; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

(i) $^{n}PrCO_2H$/DCC/DMAP(cat.)/CH_2Cl_2, rt, 1~2h;

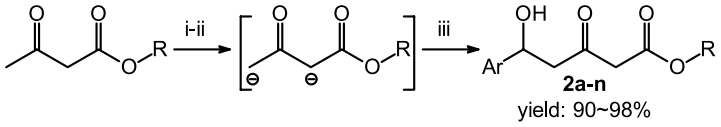
(ii) *CRL*/$^{i}Pr_2O$-H_2O, 30 °C, 24h.

Scheme 4.

Comparing the data in Table 1 with that of corresponding β-hydroxy-β-arylethylphosphonates,[15a,f] we found that the overall yields of CRL-catalyzed reaction were dramatically increased and reaction time was significantly shortened. However, the enantioselectivity of CRL decreased a little bit. Efforts to improve it by changing the bulky degree of the ester groups were unsuccessful.

Similar results were obtained and shown on Table 2. The enantioselectivity of CRL were very good in comparison to that for corresponding δ-hydroxy-δ-aryl-β-oxo-butylphosphonates.[15c]

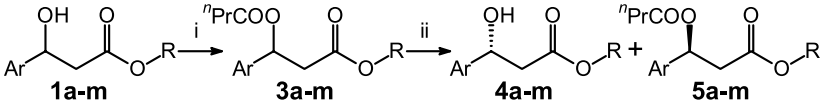
Due to the similarity of the substrates **3a**–**m** and **6a**–**n**, the enantioselectivity of the resolution reaction catalyzed by CRL are identical. Consequently, if the absolute configuration of one of the products **4a**–**m** and **5a**–**m** or **7a**–**n** and **8a**–**n** was determined, the stereochemistry of the other molecules could be deduced. Subsequently, the absolute configuration of hydrolyzed the ethyl β-hydroxy-β-phenyl-propionate (**4c**) and methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoate (**7a**) was determined by optical rotation. The optical rotation of **4c** is $[\alpha]_D^{20}=+48.7$ (*c* 1.4, $CHCl_3$) {literature[9a] (*S*)-**1c**: $[\alpha]_D^{20}=-50.8$ (*c* 1.0, $CHCl_3$) and literature[17] (*R*)-**1c**: $[\alpha]_D^{22}=+40.0$ (*c* 2.8, $CHCl_3$)} and **7a** is $[\alpha]_D^{20}=+58.1$ (*c*=1.0, $CHCl_3$) {literature[11a] (*R*)-**2a**:



R=Me, Et; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

(i) NaH/THF, 0 °C, 0.5h; (ii) BuLi/THF, ice-salt bath, 0.5h;
(iii) ArCHO/THF, ice-salt bath, 1.0~2.0h.

Scheme 2.



R=Me, Et, *i*-Pr, Bu; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

(i) $^{n}PrCO_2H$/DCC/DMAP(cat.)/CH_2Cl_2, rt, 1~2h; (ii) *CRL*/$^{i}Pr_2O$-H_2O, 30 °C, 24h.

Scheme 3.

Table 1. CRL catalyzed enantioselective hydrolysis of **3a–m**

Entry	R	Ar	Yield of **3** (%)	**4**		**5**		E^a
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
a	Me	C_6H_5	94	48	86.9	44	92.0	>68
b	Me	4-$MeOC_6H_4$	93	44	>99	47	92.0	>150
c	Et	C_6H_5	95	43	>99	48	91.9	>150
d	Et	4-MeC_6H_4	93	42	94.5	44	95.3	>100
e	Et	4-$MeOC_6H_4$	95	47	85.9	44	90.6	>60
f	Et	2-Furyl	91	51	75.1	40	90.2	>45
g	Et	2-ClC_6H_4	92	46	95.4	41	98.6	>150
h	Et	4-FC_6H_4	94	41	93.7	49	86.8	>100
i	Et	2,4-$Cl_2C_6H_3$	90	46	93.7	42	>99	>150
j	Et	4-$O_2NC_6H_4$	96	43	91.6	43	99.6	>150
k	*i*-Pr	C_6H_5	93	44	93.6	48	81.9	>50
l	*i*-Pr	4-$MeOC_6H_4$	92	45	75.7	46	76.7	>20
m	*n*-Bu	C_6H_5	95	42	93.0	47	86.8	>50

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[16]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS).

Table 2. CRL catalyzed enantioselective hydrolysis of **6a–n**

Entry	R	Ar	Yield of **6** (%)	**7**		**8**		E^a
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
a	Me	C_6H_5	92	46	97.0	47	99.9	>200
b	Me	4-MeC_6H_4	91	46	98.6	47	99.9	>200
c	Me	4-$MeOC_6H_4$	93	45	99.9	46	96.0	>200
d	Me	2-Furyl	94	54[c]	52.0	39[c]	98.1	>80
e	Me	2-BrC_6H_4	91	47	99.8	47	97.5	>200
f	Me	4-FC_6H_4	96	48	97.7	46	97.2	>200
g	Me	2,4-$Cl_2C_6H_3$	94	46	98.1	47	94.9	>200
h	Me	4-$O_2NC_6H_4$	93	46	99.9[d]	48	91.9	>200
i	Et	C_6H_5	94	47	99.7	47	99.7	>200
j	Et	4-MeC_6H_4	91	47	98.6	46	99.9	>200
k	Et	4-$MeOC_6H_4$	92	45	97.2	47	99.6	>200
l	Et	2-Furyl	94	46	89.6	48	84.9	>100
m	Et	2,4-$Cl_2C_6H_3$	93	45	99.1	49	99.9	>200
n	Et	4-$O_2NC_6H_4$	93	45	99.8	45	/[e]	/

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[16]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS).
[c] The reaction time was too long.
[d] The ee values of **7h** was determined by **8h**.
[e] **8n** can not be determined by chiral HPLC.

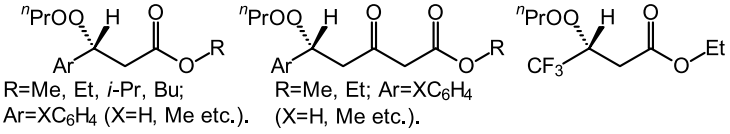
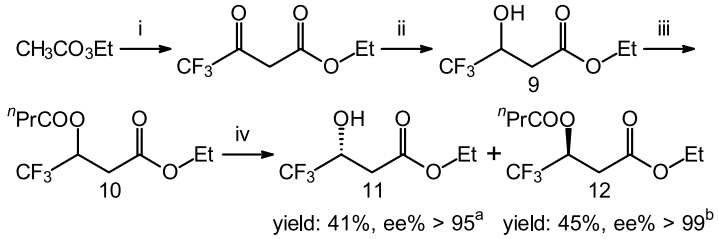


Figure 1. The preferential configuration of CRL-catalyzed hydrolysis.



a, the ee values of 11 was determined by ^{19}F NMR spectrum;
b, the ee values of 12 was determined by chiral HPLC.

(i) CF_3CO_2Et/EtONa/EtOH, reflux, 10h; (ii) $NaBH_4$, rt, 0.5h; (iii) $^nPrCO_2H$/DCC/DMAP(cat.)/CH_2Cl_2, rt, 1.5h; (iv) *CRL*/$^iPr_2O$-H_2O, 30 °C, 24h.

Scheme 5.

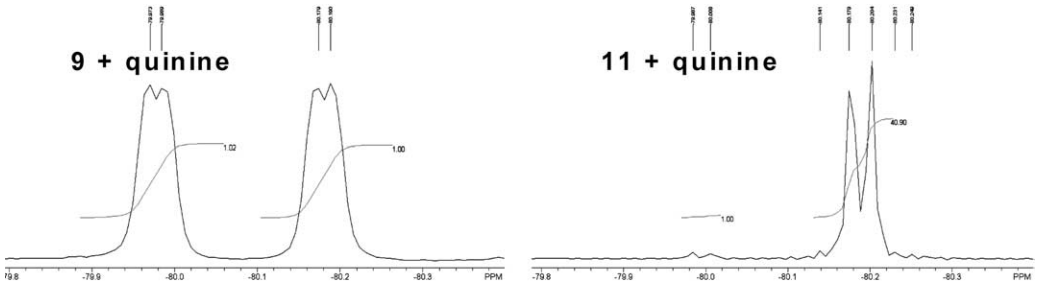


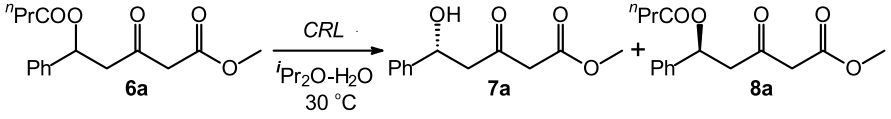
Figure 2. ^{19}F NMR spectrum of **9**+quinine and **11**+quinine.

$[\alpha]_D^{25}=+57.1$ ($c=1.0$, $CHCl_3$) and literature[11b] (*S*)-**2a** $[\alpha]_D^{25}=-46.0$ ($c=1.0$, $CHCl_3$)}.

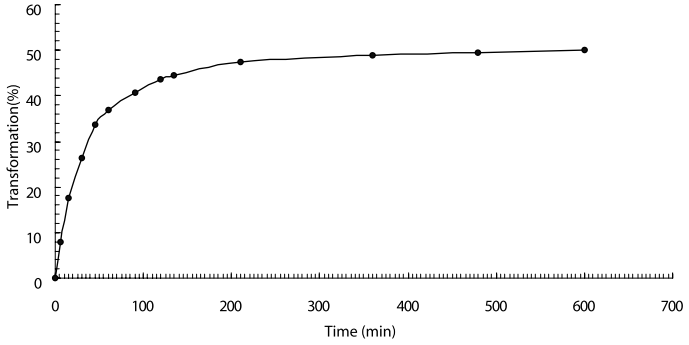
Based on the optical rotation data, the absolute configuration of products **4a**–**m** and **5a**–**m** or **7a**–**n** and **8a**–**n** was thus determined. So, the enantioselectivity of CRL-catalyzed hydrolysis of substrates **3a**–**m** and **6a**–**n** was consequently deduced (Fig. 1).

It was found that the enantioselectivity of CRL-catalyzed hydrolysis was kept almost identical. When the aryl group of β-hydroxy-β-arylethylphosphonates was replaced by a trifluoromethyl moiety,[15b] similar outcomes were observed. These trifluoromethyl analog are the precursors of novel fluorinated pharmaceuticals, such as the antidepressant beloxatone,[18] chiral ethyl 3-hydroxy-4,4,4-trifluorobutyrate was synthesized. (Scheme 5 and Fig. 2)

The absolute configuration of product **11** was also determined by optical rotation with an $[\alpha]_D^{20}=+20.8$ (c 0.7, $CHCl_3$) {literature[18c] (*S*)-**9**: $[\alpha]_D^{20}=-18.4$ (c 2.85, $CHCl_3$); literature[18b] (*R*)-**9**: $[\alpha]_D^{20}=+21.8$ (c 1.25, $CHCl_3$); literature[19] (*R*)-**9**: $[\alpha]_D^{25}=+20.1$ (c 1.2, $CHCl_3$)}. Based on the above data, the enantioselectivity of CRL-catalyzed hydrolysis was also deduced as shown in Figure 1.

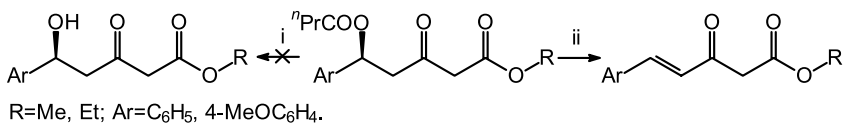


Scheme 6.



time (min)	transformation (%)	time (min)	transformation (%)	time (min)	transformation (%)	time (min)	transformation (%)
6	8.0	45	33.6	120	43.7	360	49.0
15	17.5	60	36.9	135	44.6	480	49.5
30	26.2	90	40.8	210	47.4	600	50.0

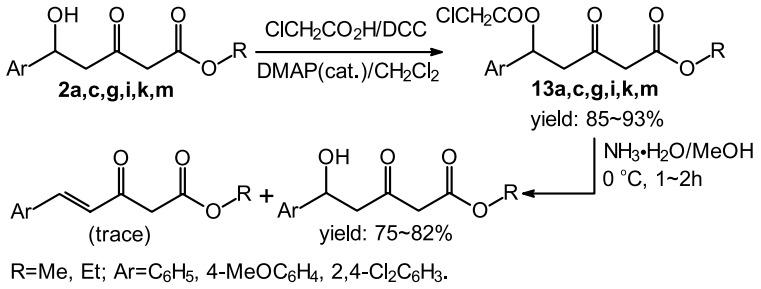
Figure 3. The curve between the transformation and reaction time of CRL-catalyzed hydrolysis of substrate **6a** (transformation was determined by ^{1}H NMR spectrum, because of big difference of chemical shift of δ-H between the product **7a** (δ_H: ~5.20 ppm) and **8a** (δ_H: ~6.20 ppm)).



R=Me, Et; Ar=C_6H_5, 4-$MeOC_6H_4$.

(i) lipase/H_2O; (ii) base/solvent.

Scheme 7.



Scheme 8.

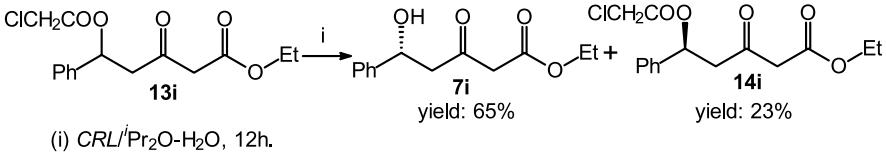
Due to the slow reaction rate of CRL-catalyzed hydrolysis of hydroxycarboxylates bearing aryl groups, we were able to investigate the kinetics of the transformation at 30 °C. (Scheme 6 and Fig. 3)

Although good results of CRL-catalyzed hydrolysis of δ-hydroxy-δ-aryl-β-oxo-pentanoates were achieved, we still met difficulty of transforming the chiral butyryl esters into corresponding optically active alcohols. Chemical hydrolysis only provided elimination products. It is necessary to point out that our trials to furnish this transformation by enzyme-catalyzed hydrolysis including CALB, IM, PS-30, PPL, GM as well as AY failed. (Scheme 7)

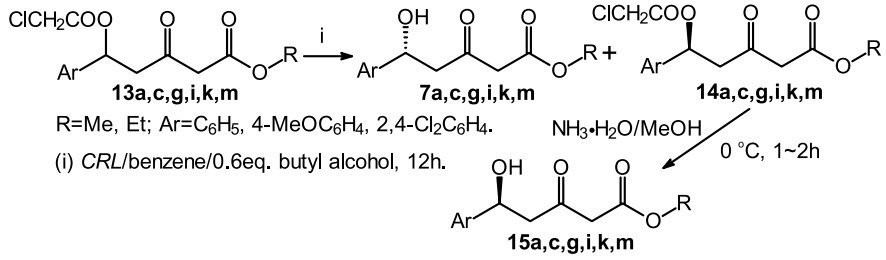
Some chloroacetyl esters were reported to transform into corresponding alcohols under weak basic conditions, such as Et_3N, $NH_3 \cdot H_2O$, K_2CO_3 etc.,[20] and such treatment also good for our substrates. The chloroacetyl esters formed by conventional method (DCC/chloroacetic acid) gave corresponding alcohols upon treatment with aqueous NH_3 in MeOH with excellent yield. (Scheme 8)

Since this method solved the problem of elimination of butyryl esters, and if the chloroacetyl esters could be resolved, the enantiomers of δ-hydroxy-δ-aryl-β-oxo-pentanoates were obtained.

Based on above idea, we first enantioselectively hydrolyzed the chloroacetyl esters catalyzed by crude CRL in diisopropyl ether preequilibrated with 1.2 M $MgCl_2$ solution. Although this enantioselective hydrolysis reaction successfully proceeded, the enantioselectivity was worse than their butyryl counterparts. (Scheme 9).



Scheme 9.

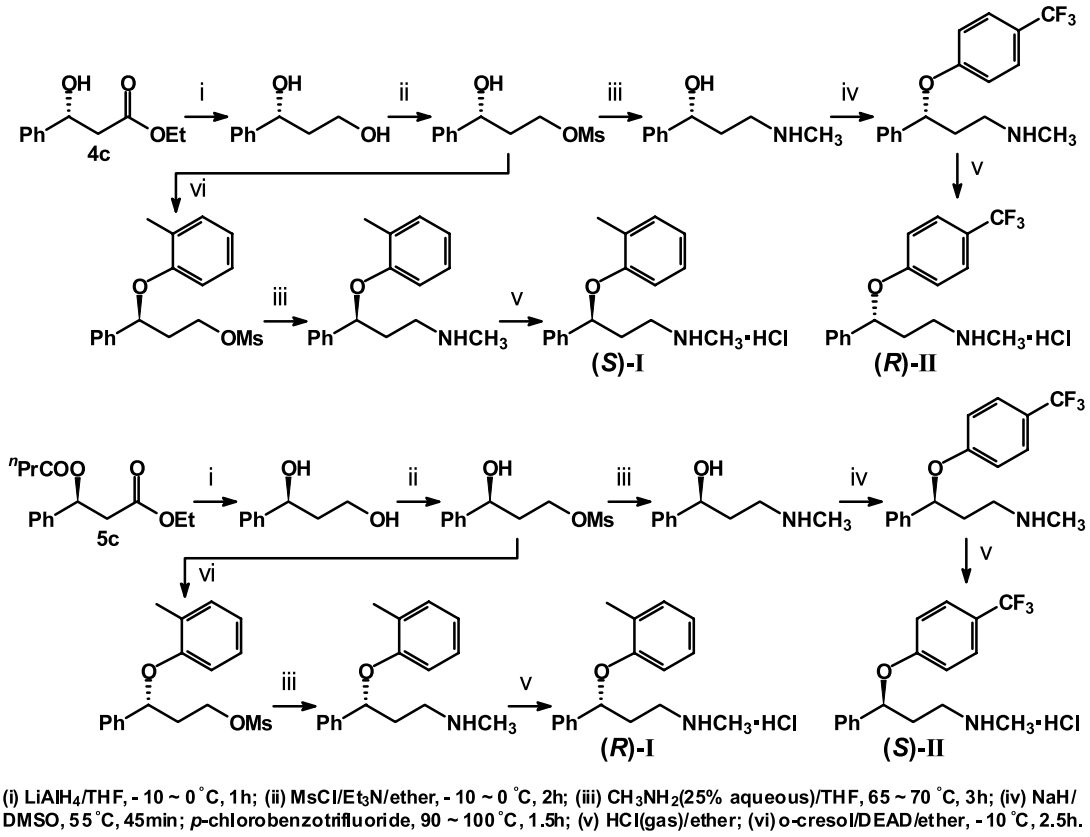


Scheme 10.

Table 3. CRL catalyzed enantioselective alcoholysis of **13a**,**c**,**g**,**i**,**k**,**m**

Entry	R	Ar	Yield of **14** (%)	**7**		**15**		E^a
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
a	Me	C_6H_5	48	45	78.6	76	88.7	>80
c	Me	4-$MeOC_6H_4$	49	46	86.5	78	94.9	>100
g	Me	2,4-$Cl_2C_6H_3$	46	43	92.0	70	90.6	>100
i	Et	C_6H_5	49	44	95.4	82	>99	>100
k	Et	4-$MeOC_6H_4$	49	45	96.7	79	>99	>100
m	Et	2,4-$Cl_2C_6H_3$	44	42	>99	71	97.3	>100

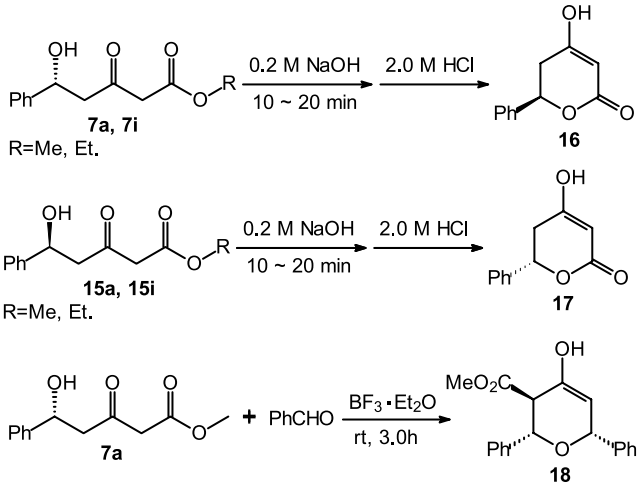
[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[16]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS).



Scheme 11.

Another alternative method to improve enantioselectivity was alcoholysis, and our group has prepared optically active 1- or 2-hydroxyalkanephosphonates through butyl alcoholysis reaction of corresponding chloroacetyl esters catalyzed by CALB and IM.[21] Fortunately, this method is successfully used in our substrates catalyzed by crude CRL. (Scheme 10 and Table 3).

After successful completion of the CRL-catalyzed hydrolysis/alcoholysis of substrates **3a**–**m**, **6a**–**n** and **13a**–**m**, we utilized the optically active products to synthesize some chiral pharmaceuticals and precursors of natural products. In the introduction, we stated the extremely useful chiral pharmaceuticals tomoxetine hydrochloride (**I**) and fluoxetine hydrochloride (**II**). We therefore selected one couple of the highest enantiomeric excess (**4c** and **5c**) to prepare them. We also transformed several chiral products (**7a**, **7i**, **15a** and **15i**) into optically active precursors of natural products, such as chiral 4-hydroxy-6-phenyll-5,6-dihydro-2-pyones (**16** and **17**) and methyl 4-oxo-2,6-diphenyl-tetrahydro-pyran-3-carboxylatete (**18**). (Schemes 11 and 12).



Scheme 12.

3. Conclusion

In summary, β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates were successfully resolved by CRL-catalyzed hydrolysis to furnish optically active β-hydroxy-β-arylpropionates, δ-hydroxy-δ-aryl-β-oxo-pentanoates and their butyryl derivatives, which are useful precursors of chiral pharmaceuticals, such as tomoxetine hydrochloride (**I**) and fluoxetine hydrochloride (**II**).

4. Experimental

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard); ^{19}F NMR spectra were taken on the same spectrometer using CF_3COOH as external standard.

CRL (901 units/mg) was purchased from Sigma Chemical Co.

The chiral liquid chromatography system: Waters 515 HPLC pump; UV Waters 2487 Dual λ Absorbance Detector, 254 nm; Penelson Network chromatography interface NCI 900, Turbohrom Navigator data station software; column dimensions: 0.46 cm×25 cm; the flow rate: 0.7 mL/min; eluent: hexane–isopropanol=9:1–8:2 (v/v).

4.1. General procedure for the preparation of β-hydroxy-β-arylpropionates 1a–m

To a solution of diisopropyl amine (1.82 g, 18 mmol) in dry THF (20 mL) was added butyllithium (in hexane 1.6 M, 11.3 mL, 18 mmol) at −78 °C under nitrogen. The mixture was kept at this temperature for 1 h, then a mixture of acetate (15 mmol) and dry THF (10 mL) was added at low temperature. After it stirred for 1 h at −78 °C, a mixture of aldehyde (18 mmol) and dry THF (10 mL) was added. After the mixture was stirred for another 1 h, saturated NH_4Cl solution was added and the aqueous layer was extracted with ethyl acetate (3×30 mL), the combined extracts were dried and evaporated in vacuum. The residue was subjected to flash chromatography to furnish the racemic β-hydroxy-β-arylpropionates **1a**–**m**.

4.2. General procedure for preparation of δ-hydroxy-δ-aryl-β-oxo-pentanoates (2a–n)

To a suspension of sodium hydride (80%, 0.54 g, 18 mmol) in dry THF (8 mL) was added acetoacetate (15 mmol) under nitrogen, after 30 min at rt, butyllithium (in hexane 1.6 M, 11.3 mL, 18 mmol) was added at −15–10 °C (ice-salt bath). The mixture was kept this temperature for 30 min, then aldehydes (18 mmol) was added at this temperature. After the mixture was stirred for 1–2 h at low temperature, saturated NH_4Cl (30 mL) was added and the aqueous was extracted with ethyl acetate (3×30 mL). The combined extracts was dried and evaporated in vacuum. The residues were subjected to flash chromatography to furnish the δ-hydroxy-δ-aryl-β-oxo-pentanoates (**2a**–**n**).

4.3. General procedure for the preparation of β-butyryloxy-β-arylpropionates (3a–m), δ-butyryloxy-δ-aryl-β-oxo-pentanoates (6a–n) and δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (15a,c,g,i,k,m)

In a 25 mL bottle were added substrates **1a**–**m** (or **2a**–**n**) (1 mmol), *n*-butyric acid (or chloroacetic acid) (1.2 mmol), DCC (248 mg, 1.2 mmol), DMAP (5 mg) and CH_2Cl_2 (10 mL). After the starting material was almost consumed at rt (about 1–2 h), diethyl ether (10 mL) was added and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the corresponding butyryl derivatives of which yields are listed in Tables 1 and 2.

4.4. General procedure of CRL-catalyzed enantioselective hydrolysis of β-butyryloxy-β-arylpropionates (3a–m)

Substrates **3a**–**m** (100 mg) and CRL (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 24 h at 30 °C, and filtered off the CRL that could be reuse and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **4a**–**m** and unreacted esters **5a**–**m**. The yields are listed in Table 1.

4.4.1. (3*R*) Methyl β-hydroxy-β-phenyl propionate (4a).[8i,22] Colorless oil; $[\alpha]_D^{20}=+46.9$ (*c* 1.2, $CHCl_3$). ν_{max}(liquid film) 3464, 3032, 2955, 1737, 1439, 1201, 1062, 1026, 763, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.27 (5H, m, C_6H_5), 5.14 (1H, dd, $J=7.5$, 8.7 Hz, PhC*H*CH_2), 3.73 (3H, s, OCH_3), 2.83–2.69 (2H, m, PhCHCH_2CO); *m*/*z* (EI) 180 (41, M^+), 120 (12), 107 (100), 105 (29), 79 (68), 77 (44), 51 (15), 43 (13%).

4.4.2. (3*S*) Methyl β-butyryloxy-β-phenyl propionate (5a). Colorless oil; $[\alpha]_D^{20}=-45.9$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3036, 2967, 2878, 1745, 1170, 1004, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.26 (5H, m, C_6H_5), 6.18 (1H, dd, $J=4.8$, 9.0 Hz, PhC*H*CH_2), 3.67 (3H, s, OCH_3), 2.97 (1H, dd, $J=9.0$, 15.6 Hz, PhCHCH_2CO), 2.76 (1H, dd, $J=5.4$, 15.6 Hz, PhCHCH_2CO), 2.29 (2H, t, $J=8.1$ Hz, $COCH_2CH_2CH_3$), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 0.91 (3H, t, $J=8.1$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 250 (1, M^+), 179 (100), 147 (20), 131 (14), 121 (37), 105 (62), 77 (16), 71 (47), 43 (33%). Found: C, 66.99; H, 7.31. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25.

4.4.3. (3*R*) Methyl β-hydroxy-β-(*p*-methoxyphenyl) propionate (4b).[23] Colorless oil; $[\alpha]_D^{20}=+36.4$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3482, 3003, 2955, 2839, 1738, 1614, 1515, 1249, 1033, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, $J=6.9$ Hz, C_6H_4), 6.82 (2H, d, $J=6.6$ Hz, C_6H_4), 5.02 (1H, dd, $J=4.5$, 9.3 Hz, ArC*H*CH_2), 3.74 (3H, s, CO_2CH_3), 3.65 (3H, s, OCH_3), 2.76–2.58 (2H, m, ArCHCH_2CO); δ_{13}C(75.5 MHz, $CDCl_3$) 173.07, 159.54, 135.31, 127.36, 114.28, 70.33, 55.64, 52.23, 43.70; *m*/*z* (EI) 210 (15, M^+), 179 (3), 137 (100), 135 (12), 109 (23), 94 (13), 77 (14), 65 (4%).

4.4.4. (3*S*) Methyl β-butyryloxy-β-(*p*-methoxyphenyl) propionate (5b). Colorless oil; $[\alpha]_D^{20}=-60.7$(*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2965, 2939, 2878, 1744, 1517, 1173, 832 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, $J=7.2$ Hz, C_6H_4), 6.87 (2H, d, $J=7.5$ Hz, C_6H_4), 6.13 (1H, dd, $J=5.4$, 9.3 Hz, ArC*H*CH_2), 3.80 (3H, s, CO_2CH_3), 3.66 (3H, s, OCH_3), 2.98 (1H, dd, $J=6.9$, 15.6 Hz, ArCHCH_2CO), 2.74 (1H, dd, $J=5.4$, 15.9 Hz, ArCHCH_2CO), 2.26 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.65–1.58 (2H, m, $COCH_2CH_2CH_3$), 0.90 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 280 (15, M^+), 209 (100), 193 (14), 151 (59), 137 (62), 135 (88), 119 (11), 77 (11), 71 (41%). Found: C, 64.15; H, 7.41. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19.

4.4.5. (3*R*) Ethyl β-hydroxy-β-phenyl propionate (4c).[8i,24] Colorless oil; $[\alpha]_D^{20}=+43.7$ (*c* 1.4, $CHCl_3$). ν_{max}(liquid film) 3461, 2984, 2938, 1734, 1197, 1162, 1028, 761, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 5.13 (1H, dd, $J=4.5$, 8.1 Hz, PhC*H*CH_2), 4.18 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.11 (1H, s, O*H*), 2.81–2.67 (2H, m, PhCHCH_2CO), 1.26 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m*/*z* (EI)

194 (100, M^+), 165 (6), 147 (13), 120 (19), 107 (97), 105 (65), 79 (49), 77 (38), 60 (11%).

4.4.6. (3*S*) Ethyl β-butyryloxy-β-phenyl propionate (5c). Colorless oil; $[\alpha]_D^{20}=-27.5$(*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3037, 2969, 2877, 1742, 1457, 1255, 1172, 1028, 763, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.26 (5H, m, C_6H_5), 6.18 (1H, dd, *J*=5.1, 9.0 Hz, PhC*H*CH_2), 4.10 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 2.95 (1H, dd, *J*=9.0, 15.3 Hz, PhCHCH_2CO), 2.74 (1H, dd, *J*=5.1, 15.9 Hz, PhCHCH_2CO), 2.30 (2H, t, *J*=7.8 Hz, CO$CH_2CH_2CH_3$), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 1.22 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 0.91 (3H, t, *J*=7.5 Hz, $COCH_2CH_2CH_3$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.7, 170.1, 139.9, 129.0, 128.7, 126.95, 72.3, 61.1, 42.0, 36.6, 18.8, 14.5, 14.0; *m/z* (EI) 264 (1, M^+), 193 (100), 147 (28), 131 (17), 121 (37), 105 (76), 77 (15), 71 (42), 43 (28%). Found: C, 68.18; H, 7.63. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63.

4.4.7. (3*R*) Ethyl β-hydroxy-β-(*p*-methylphenyl) propionate (4d).[8i,25] Colorless oil; $[\alpha]_D^{20}=+42.5$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3464, 2983, 2927, 1735, 1373, 1160, 1041, 819 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J*=8.4 Hz, C_6H_4), 7.16 (2H, d, *J*=7.8 Hz, C_6H_4), 5.09 (1H, dd, *J*=4.2, 9.0 Hz, ArC*H*CH_2), 4.17 (2H, q, *J*=7.5 Hz, OCH_2CH_3), 3.14 (1H, s, O*H*), 2.79–2.63 (2H, m, ArCHCH_2CO), 2.34 (3H, s, ArCH_3), 1.26 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 208 (31, M^+), 193 (14), 134 (7), 121 (100), 119 (42), 105 (9), 93 (38), 91 (34), 77 (17%).

4.4.8. (3*S*) Ethyl β-butyryloxy-β-(*p*-methylphenyl) propionate (5d). Colorless oil; $[\alpha]_D^{20}=-46.5$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2969, 2877, 1743, 1174, 1027, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J*=8.1 Hz, C_6H_4), 7.15 (2H, d, *J*=7.8 Hz, C_6H_4), 6.15 (1H, dd, *J*=5.7, 9.0 Hz, ArC*H*CH_2), 4.12 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 2.95 (1H, dd, *J*=7.2, 14.4 Hz, ArCHCH_2CO), 2.73 (1H, dd, *J*=5.1, 15.6 Hz, ArCHCH_2CO), 2.33 (3H, s, ArCH_3), 2.27 (2H, t, *J*=7.8 Hz, CO$CH_2CH_2CH_3$), 1.66–1.58 (2H, m, $COCH_2CH_2CH_3$), 1.22 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.90 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 278 (2, M^+), 207 (86), 191 (52), 149 (25), 145 (17), 119 (100), 177 (20), 91 (21), 71 (30), 43 (42%). Found: C, 69.07; H, 7.90. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97.

4.4.9. (3*R*) Ethyl β-hydroxy-β-(*p*-methoxylphenyl) propionate (4e).[8i,26] Colorless oil; $[\alpha]_D^{20}=+26.5$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 3461, 2981, 2908, 1732, 1613, 1515, 1249, 1176, 1035, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (2H, d, *J*=7.5 Hz, C_6H_4), 6.88 (2H, d, *J*=6.9 Hz, C_6H_4), 5.08 (1H, dd, *J*=4.2, 9.0 Hz, ArC*H*CH_2), 4.18 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 2.80–2.63 (2H, m, ArCHCH_2CO), 1.26 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 224 (12, M^+), 179 (4), 138 (9), 137 (100), 135 (18), 109 (18), 94 (8), 77 (10), 65 (3%).

4.4.10. (3*S*) Ethyl β-butyryloxy-β-(*p*-methoxylphenyl) propionate (5e). Colorless oil; $[\alpha]_D^{20}=-54.2$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2968, 2938, 2877, 1741, 1517, 1251, 1174, 1034, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, *J*=6.9 Hz, C_6H_4), 6.86 (2H, d, *J*=6.6 Hz, C_6H_4), 6.13 (1H, dd, *J*=5.7, 9.0 Hz, ArC*H*CH_2), 4.11 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 2.96 (1H, dd, *J*=9.3, 15.3 Hz, ArCHCH_2CO), 2.73 (1H, dd, *J*=4.8, 15.3 Hz, ArCHCH_2CO), 2.26 (2H, t, *J*=7.8 Hz, CO$CH_2CH_2CH_3$), 1.65–1.55 (2H, m, $COCH_2CH_2CH_3$), 1.21 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.88 (3H, t, *J*=7.5 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 294 (12, M^+), 223 (96), 207 (14), 177 (8), 161 (21), 150 (16), 137 (47), 135 (100), 119 (11), 71 (25%). Found: C, 65.26; H, 7.47. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53.

4.4.11. (3*R*) Ethyl β-hydroxy-β-furan-2-yl propionate (4f).[27] Colorless oil; $[\alpha]_D^{20}=+15.0$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3455, 2985, 2938, 1734, 1374, 1210, 1164, 1014, 742 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.36 (1H, m, C_4H_3O), 6.34–6.32 (1H, m, C_4H_3O), 6.28–6.26 (1H, m, C_4H_3O), 5.13 (1H, dd, *J*=4.8, 8.1 Hz, ArC*H*CH_2), 4.18 (2H, q, *J*=7.5 Hz, OCH_2CH_3), 3.43 (1H, s, O*H*), 2.94–2.78 (2H, m, ArCHCH_2CO), 1.27 (3H, t, *J*=7.2 Hz, OCH_2CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.13, 155.39, 142.47, 110.58, 106.55, 64.45, 61.24, 40.42, 14.44; *m/z* (EI) 184 (20, M^+), 155 (4), 137 (14), 110 (16), 97 (100), 95 (46), 88 (4), 69 (7), 60 (6%).

4.4.12. (3*S*) Ethyl β-butyryloxy-β-furan-2-yl propionate (5f). Colorless oil; $[\alpha]_D^{20}=-94.2$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2879, 1744, 1376, 1287, 1172, 1014, 746 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.37 (1H, m, C_4H_3O), 6.38–6.26 (3H, m, C_4H_3O, ArC*H*CH_2), 4.13 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 3.09 (1H, dd, *J*=8.4, 15.6 Hz, ArCHCH_2CO), 2.91 (1H, dd, *J*=5.7, 15.6 Hz, ArCHCH_2CO), 2.27 (2H, t, *J*=7.2 Hz, CO$CH_2CH_2CH_3$), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 1.23 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.91 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.71, 169.81, 151.76, 143.04, 110.72, 109.18, 65.01, 61.18, 38.13, 36.44, 18.72, 14.46, 13.84; *m/z* (EI) 254 (4, M^+), 183 (100), 167 (11), 137 (50), 121 (21), 115 (23), 110 (19), 95 (46), 71 (33), 43 (22%). Found: C, 61.43; H, 7.36. $C_{13}H_{18}O_5$ requires C, 61.41; H, 7.13.

4.4.13. (3*R*) Ethyl β-hydroxy-β-(*o*-chlorophenyl) propionate (4g).[28] Colorless oil; $[\alpha]_D^{20}=+80.3$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 3481, 2984, 2938, 1735, 1441, 1193, 1033, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.63 (1H, d, *J*=6.6 Hz, C_6H_4), 7.35–7.22 (3H, m, C_6H_4), 5.49 (1H, d, *J*=9.6 Hz, ArC*H*CH_2), 4.20 (2H, q, *J*=7.5 Hz, OCH_2CH_3), 3.63 (1H, s, O*H*), 2.86 (1H, dd, *J*=2.7, 16.8 Hz, ArCHCH_2CO), 2.58 (1H, dd, *J*=9.6, 16.5 Hz, ArCHCH_2CO), 1.28 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 228 (6, M^+), 193 (65), 147 (10), 143 (29), 141 (100), 139 (41), 113 (15), 105 (15), 88 (25), 77 (50), 60 (17%).

4.4.14. (3*S*) Ethyl β-butyryloxy-β-(*p*-methoxylphenyl) propionate (5g). Colorless oil; $[\alpha]_D^{20}=-5.6$ (*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 2970, 2938, 2878, 1751, 1375, 1172, 1019, 759 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.34 (2H, m, C_6H_4), 7.28–7.22 (2H, m, C_6H_4), 6.51 (1H, dd, *J*=5.1, 8.7 Hz, ArC*H*CH_2), 4.15 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 2.86–2.81 (2H, m, ArCHCH_2CO), 2.34 (2H, t, *J*=7.2 Hz, CO$CH_2CH_2CH_3$), 1.70–1.62 (2H, m, $COCH_2CH_2CH_3$), 1.24 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 0.93 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 299 (21, $M^+ + 1$), 263 (74), 227 (36), 211 (63), 193 (14), 175 (58), 169 (63), 165 (30), 139 (70), 71 (86), 43 (100%). Found: C, 60.21; H, 6.34. $C_{15}H_{19}O_4Cl$ requires C, 60.30; H, 6.41.

4.4.15. (3*R*) Ethyl β-hydroxy-β-(*p*-fluorophenyl) propionate (4h).[25] Colorless oil; $[\alpha]_D^{20}=+38.8$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3455, 2985, 2908, 1733, 1606, 1512, 1223, 1158, 838 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34 (2H, dd, *J*= 3.3, 9.0 Hz, C_6H_4), 7.03 (2H, t, *J*=6.6 Hz, C_6H_4), 5.10 (1H, dd, *J*=4.5, 8.1 Hz, ArC*H*CH_2), 4.18 (2H, q, *J*=7.5 Hz, O*C*H_2CH_3), 3.22 (1H, s, O*H*), 2.78–2.63 (2H, m, ArCHCH_2-CO), 1.26 (3H, t, *J*=7.2 Hz, OCH_2CH_3); *m/z* (EI) 212 (22, M^+), 195 (38), 165 (6), 153 (22), 138 (9), 125 (100), 123 (74), 97 (69), 88 (36), 77 (27), 60 (27%).

4.4.16. (3*S*) Ethyl β-butyryloxy-β-(*p*-fluorophenyl) propionate (5h). Colorless oil; $[\alpha]_D^{20}=-37.7$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2879, 1743, 1514, 1175, 1160, 838 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (2H, dd, *J*=5.4, 8.7 Hz, C_6H_4), 7.04 (2H, t, *J*=8.7 Hz, C_6H_4), 6.15 (1H, dd, *J*=5.4, 9.0 Hz, ArC*H*CH_2), 4.12 (2H, q, *J*=7.5 Hz, O*C*H_2CH_3), 2.96 (1H, dd, *J*=9.0, 15.9 Hz, ArCHCH_2CO), 2.73 (1H, dd, *J*=5.7, 15.9 Hz, ArCHCH_2CO), 2.28 (2H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$), 1.70–1.57 (2H, m, $COCH_2$-CH_2CH_3), 1.23 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.90 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 282 (10, M^+), 211 (96), 165 (31), 149 (20), 138 (7), 123 (100), 119 (8), 95 (10), 71 (77), 43 (87%). Found: C, 63.93; H, 6.96. $C_{15}H_{19}O_4F$ requires C, 63.82; H, 6.78.

4.4.17. (3*R*) Ethyl β-hydroxy-β-(*o*,*p*-dichlorophenyl) propionate (4i).[29] Colorless oil; $[\alpha]_D^{20}=+58.1$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3473, 2984, 2908, 1720, 1591, 1471, 1375, 1192, 868, 823 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (1H, d, *J*=8.7 Hz, C_6H_3), 7.35–7.26 (2H, m, C_6H_3), 5.42 (1H, dd, *J*=2.1, 9.6 Hz, ArC*H*CH_2), 4.17 (2H, q, *J*= 7.5 Hz, O*C*H_2CH_3), 2.82 (1H, dd, *J*=3.0, 16.5 Hz, ArCHCH_2CO), 2.53 (1H, dd, *J*=9.6, 16.5 Hz, ArCHCH_2-CO), 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.62, 139.13, 134.13, 132.29, 129.42, 128.54, 127.88, 67.01, 61.50, 60.85, 41.77, 14.51; *m/z* (EI) 263 (1, M^+), 227 (36), 177 (55), 175 (100), 173 (39), 139 (14), 111 (40), 88 (50), 75 (19), 43 (19%).

4.4.18. (3*S*) Ethyl β-butyryloxy-β-(*o*,*p*-dichlorophenyl) propionate (5i). Colorless oil; $[\alpha]_D^{20}=-12.3$ (*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 2970, 2938, 2878, 1708, 1475, 1376, 1168, 1022, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.23 (3H, m, C_6H_3), 6.44 (1H, dd, *J*=5.4, 8.1 Hz, ArC*H*CH_2), 4.15 (2H, q, *J*=6.9 Hz, O*C*H_2CH_3), 2.82–2.79 (2H, m, ArCHCH_2CO), 2.33 (2H, t, *J*=7.8 Hz, $COCH_2CH_2CH_3$), 1.70–1.61 (2H, m, $COCH_2CH_2CH_3$), 1.25 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.93 (3H, t, *J*= 6.9 Hz, $COCH_2CH_2CH_3$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.4, 169.7, 136.4, 134.8, 133.2, 130.0, 128.4, 127.9, 67.0, 61.3, 40.3, 36.4, 18.7, 14.5, 14.0; *m/z* (EI) 332 (1, M^+), 297 (7), 263 (26), 261 (39), 215 (10), 209 (9), 199 (10), 175 (32), 173 (43), 71 (100), 43 (60%). Found: C, 54.37; H, 5.65. $C_{15}H_{18}O_4Cl_2$ requires C, 54.07; H, 5.44.

4.4.19. (3*R*) Ethyl β-hydroxy-β-(*p*-nitrophenyl) propionate (4j).[30] Colorless oil; $[\alpha]_D^{20}=+23.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3480, 2985, 1732, 1522, 1349, 1195, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.22 (2H, d, *J*=6.9 Hz, C_6H_4), 7.57 (2H, d, *J*=9.0 Hz, C_6H_4), 5.24 (1H, dd, *J*=5.1, 7.5 Hz, ArC*H*CH_2), 4.20 (2H, q, *J*=6.9 Hz, O*C*H_2CH_3), 3.79 (1H, s, O*H*), 2.81–2.64 (2H, m, ArCHCH_2CO), 1.28 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 239 (30, M^+), 210 (17), 192 (34), 165 (29), 152 (75), 150 (100), 134 (10), 105 (21), 88 (46), 77 (34), 43 (22%).

4.4.20. (3*S*) Ethyl β-butyryloxy-β-(*p*-nitrophenyl) propionate (5j). Colorless oil; $[\alpha]_D^{20}=-36.6$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2878, 1743, 1608, 1526, 1349, 1169, 857 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.22 (2H, d, *J*= 6.9 Hz, C_6H_4), 7.55 (2H, d, *J*=7.5 Hz, C_6H_4), 6.22 (1H, dd, *J*=5.4, 8.1 Hz, ArC*H*CH_2), 4.14 (2H, q, *J*=6.9 Hz, O*C*H_2CH_3), 2.97 (1H, dd, *J*=8.7, 15.9 Hz, ArCHCH_2CO), 2.78 (1H, dd, *J*=5.7, 15.9 Hz, ArCHCH_2CO), 2.34 (2H, t, *J*=7.5 Hz, $COCH_2CH_2CH_3$), 1.71–1.58 (2H, m, $COCH_2$-CH_2CH_3), 1.24 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 0.92 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 309 (1, M^+), 264 (4), 238 (50), 222 (100), 192 (25), 176 (48), 150 (54), 134 (51), 103 (9), 71 (91), 43 (45%). Found: C, 58.42; H, 6.17; N, 4.74. $C_{15}H_{19}NO_6$ requires C, 58.25; H, 6.19; N, 4.53.

4.4.21. (3*R*) Isopropyl β-hydroxy-β-phenyl propionate (4k).[8i,31] Colorless oil; $[\alpha]_D^{20}=+39.4$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3462, 3033, 2983, 2937, 1731, 1455, 1375, 1198, 1109, 761, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.25 (5H, m, C_6H_5), 5.14–5.01 (2H, m, PhC*H*CH_2, O*C*$H(CH_3)_2$), 3.31 (1H, s, O*H*), 2.80–2.62 (2H, m, PhCHCH_2CO), 1.22 (6H, d, *J*=6.3 Hz, $OCH(CH_3)_2$); *m/z* (EI) 208 (15, M^+), 165 (41), 149 (11), 147 (19), 137 (7), 120 (7), 107 (100), 79 (50), 43 (23%).

4.4.22. (3*S*) Isopropyl β-butyryloxy-β-phenyl propionate (5k). Colorless oil; $[\alpha]_D^{20}=-41.8$(*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 3067, 2980, 2938, 1740, 1376, 1274, 1172, 1109, 1007, 763, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 6.18 (1H, dd, *J*=5.4, 9.0 Hz, PhC*H*CH_2), 5.04–4.95 (1H, m, O*C*$H(CH_3)_2$), 2.93 (1H, dd, *J*=9.0, 15.3 Hz, PhCHCH_2CO), 2.72 (1H, dd, *J*=5.1, 15.3 Hz, PhCHCH_2CO), 2.90 (2H, t, *J*=7.5 Hz, $COCH_2$-CH_2CH_3), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 1.20 (6H, t, *J*=7.5 Hz, $OCH(CH_3)_2$), 0.90 (3H, t, *J*=7.2 Hz, $COCH_2$-CH_2CH_3); *m/z* (EI) 278 (1, M^+), 207 (66), 165 (100), 147 (41), 131 (28), 120 (12), 105 (57), 71 (69), 43 (50%). Found: C, 69.06; H, 7.84. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97.

4.4.23. (3*R*) Isopropyl β-hydroxy-β-(*p*-methoxylphenyl) propionate (4l). Colorless oil; $[\alpha]_D^{20}=+32.1$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 3482, 2982, 2938, 2838, 1729, 1614, 1515, 1249, 1109, 1035, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, *J*=9.3 Hz, C_6H_4), 6.88 (2H, d, *J*= 9.3 Hz, C_6H_4), 5.15–5.01 (2H, m, ArC*H*CH_2, O*C*$H(CH_3)_2$), 3.80 (3H, s, O*C*H_3), 2.73 (1H, dd, *J*=8.7, 16.2 Hz, ArCHCH_2CO), 2.64 (1H, dd, *J*=3.9, 16.5 Hz, ArCHCH_2-CO), 1.23 (6H, d, *J*=6.0 Hz, $OCH(CH_3)_2$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.3, 159.5, 135.3, 127.4, 114.2, 70.4, 68.7, 55.6, 44.1, 22.1; *m/z* (EI) 238 (12, M^+), 195 (10), 179 (7), 137 (100), 135 (49), 109 (20), 94 (9), 77 (12), 43 (9%). Found: C, 65.31; H, 7.54. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61.

4.4.24. (3*S*) Isopropyl β-butyryloxy-β-(*p*-methoxylphenyl) propionate (5l). Colorless oil; $[\alpha]_D^{20}=-46.3$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 2979, 2938, 2878, 1740, 1614, 1517, 1376, 1303, 1174, 1110, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, *J*=6.6 Hz, C_6H_4), 6.86 (2H, d, *J*=6.6 Hz, C_6H_4), 6.13 (1H, dd, *J*=5.4, 9.3 Hz,

ArC*H*CH_2), 5.05–4.93 (1H, m, OC*H*$(CH_3)_2$), 3.79 (3H, s, OCH_3), 2.93 (1H, dd, J=9.0, 15.9 Hz, ArCHCH_2CO), 2.70 (1H, dd, J=5.7, 15.0 Hz, ArCHCH_2CO), 2.26 (2H, t, J=7.5 Hz, COC$H_2$$CH_2CH_3$), 1.65–1.58 (2H, m, $COCH_2$CH_2-CH_3), 1.19 (6H, t, J=6.6 Hz, OCH(CH_3)$_2$), 0.90 (3H, t, J=6.9 Hz, $COCH_2CH_2$CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.8, 169.7, 159.9, 131.9, 128.4, 114.3, 72.1, 68.5, 55.6, 42.1, 36.7, 22.1, 18.8, 14.0; *m*/*z* (EI) 308 (11, M^+), 237 (60), 195 (78), 177 (9), 161 (30), 150 (19), 137 (47), 135 (100), 119 (8), 71 (44), 43 (59%). Found: C, 66.21; H, 7.78. $C_{17}H_{24}O_5$ requires C, 66.21; H, 7.84.

4.4.25. (3*R*) *n*-Butyl β-hydroxy-β-phenyl propionate (4m).[8i,32] Colorless oil; $[\alpha]_D^{20}=+28.3$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 3464, 2962, 2935, 1733, 1271, 1195, 1165, 1061, 761, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 5.12 (1H, dd, J=4.5, 8.4 Hz, PhC*H*CH_2), 4.12 (2H, t, J=6.6 Hz, O$CH_2CH_2CH_2CH_3$), 3.22 (1H, s, O*H*), 2.77 (1H, dd, J=8.1, 15.9 Hz, PhCHCH_2CO), 2.69 (1H, dd, J=4.5, 16.5 Hz, PhCHCH_2CO), 1.63–1.56 (2H, m, OCH_2C$H_2CH_2CH_3$), 1.39–1.31 (2H, m, OCH_2CH_2CH_2-CH_3), 0.92 (3H, t, J=7.2 Hz, $OCH_2CH_2CH_2$CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.8, 143.1, 128.9, 128.1, 126.1, 70.7, 65.1, 43.8, 31.0, 19.5, 14.1; *m*/*z* (EI) 272 (48, M^+), 165 (14), 147 (27), 120 (18), 107 (100), 105 (85), 79 (50), 77 (34), 56 (19%).

4.4.26. (3*S*) *n*-Butyl β-butyryloxy-β-phenyl propionate (5m). Colorless oil; $[\alpha]_D^{20}=-32.9$(*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 2964, 2927, 2876, 1743, 1274, 1170, 1028, 763, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.27 (5H, m, C_6H_5), 6.17 (1H, dd, J=4.8, 9.3 Hz, PhC*H*CH_2), 4.08 (2H, t, J=6.3 Hz, O$CH_2CH_2CH_2CH_3$), 2.97 (1H, dd, J=9.0, 15.6 Hz, PhCHCH_2CO), 2.75 (1H, dd, J=5.1, 15.3 Hz, PhCHCH_2-CO), 2.29 (2H, t, J=7.5 Hz, COC$H_2CH_2CH_3$), 1.71–1.52 (4H, m, $COCH_2$CH_2CH_3, OCH_2C$H_2CH_2CH_3$), 1.40–1.28 (2H, m, OCH_2CH_2CH_2CH_3), 0.94–0.88 (6H, m, $COCH_2$-CH_2CH_3, $OCH_2CH_2CH_2$CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.7, 170.3, 139.9, 129.0, 128.7, 126.9, 72.4, 65.0, 42.0, 36.6, 31.0, 19.4, 18.89, 14.1, 14.0; *m*/*z* (EI) 293 (19, M^+), 221 (38), 205 (100), 163 (46), 147 (13), 105 (35), 77 (12), 71 (24), 57 (39%). Found: C, 69.67; H, 8.11. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27.

4.5. General procedure of CRL-catalyzed enantioselective hydrolysis of δ-butyryloxy-δ-aryl-β-oxo-pentanoates (6a–n)

Substrates **6a**–**n** (150 mg) and CRL (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 24 h at 30 °C, and filtered off the CRL that could be reuse and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **7a**–**n** and unreacted esters **8a**–**n**. The yields are listed in Table 2.

4.5.1. (5*R*) Methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7a).[33] Colorless oil; $[\alpha]_D^{20}=+58.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3497, 3064, 3033, 2956, 1745, 1714, 1439, 1327, 1156, 753, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 5.18 (1H, dd, J=5.7, 9.0 Hz, $COCH_2$-C*H*OH), 3.73 (3H, s, OCH_3), 3.51 (2H, s, COCH_2CO_2), 3.05–2.86 (3H, m, O*H*, COCH_2CHOH); *m*/*z* (EI) 222 (4, M^+), 204 (43), 149 (24), 144 (25), 131 (36), 116 (77), 107 (98), 105 (71), 79 (100), 77 (75), 43 (24%).

4.5.2. (5*S*) Methyl δ-butyryloxy-δ-phenyl-β-oxo-pentanoates (8a). Colorless oil; $[\alpha]_D^{20}=-36.5$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 3066, 2967, 2878, 1741, 1324, 1552, 1174, 753, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.26 (5H, m, C_6H_5), 6.20 (1H, dd, J=4.8, 8.7 Hz, $COCH_2$-C*H*OCO), 3.72 (3H, s, OCH_3), 3.46 (2H, s, COCH_2CO_2), 3.22 (1H, dd, J=8.7, 16.8 Hz, COCH_2CHOCO), 2.97 (1H, dd, J=4.8, 16.8 Hz, COCH_2CHOCO), 2.28 (2H, t, J=7.5 Hz, COC$H_2CH_2CH_3$), 1.68–1.58 (2H, m, $COCH_2$CH_2-CH_3), 0.90 (3H, t, J=7.5 Hz, $COCH_2CH_2$CH_3); *m*/*z* (EI) 274 (4, M^+-H_2O), 221 (39), 189 (52), 144 (15), 131 (27), 108 (88), 101 (27), 77 (22), 71 (100), 43 (81%). Found: C, 65.67; H, 7.02. $C_{16}H_{20}O_5$ requires C, 65.74; H, 6.90.

4.5.3. (5*R*) Methyl δ-hydroxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (7b). Colorless oil; $[\alpha]_D^{20}=+58.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3496, 3025, 2955, 1747, 1715, 1516, 1438, 1325, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, J=8.1 Hz, C_6H_4), 7.16 (2H, d, J=7.8 Hz, C_6H_4), 5.14 (1H, dd, J=3.3, 9.0 Hz, $COCH_2$C*H*OH), 3.73 (3H, s, OCH_3), 3.50 (2H, s, COCH_2CO_2), 2.99 (1H, dd, J=9.3, 17.1 Hz, COCH_2CHOH), 2.87 (1H, dd, J=3.6, 17.1 Hz, COCH_2CHOH), 2.34 (3H, s, ArCH_3); *m*/*z* (EI) 236 (4, M^+), 218 (33), 163 (16), 159 (10), 145 (23), 121 (100), 119 (40), 117 (14), 93 (52), 91 (47), 77 (25%). Found: C, 66.06; H, 7.03. $C_{13}H_{16}O_4$ requires C, 66.09, H, 6.83.

4.5.4. (5*S*) Methyl δ-butyryloxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (8b). Colorless oil; $[\alpha]_D^{20}=-46.4$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 2964, 2876, 1738, 1516, 1174, 1085, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, J=7.8 Hz, C_6H_4), 7.15 (2H, d, J=8.4 Hz, C_6H_4), 6.16 (1H, dd, J=5.1, 8.7 Hz, $COCH_2$C*H*OCO), 3.72 (3H, s, OCH_3), 3.45 (2H, s, COCH_2CO_2), 3.21 (1H, dd, J=8.7, 17.1 Hz, COCH_2CHOCO), 2.95 (1H, dd, J=4.8, 17.1 Hz, COCH_2-CHOCO), 2.33 (3H, s, ArCH_3), 2.28 (2H, t, J=7.2 Hz, COC$H_2CH_2CH_3$), 1.71–1.58 (2H, m, $COCH_2$CH_2CH_3), 0.89 (3H, t, J=7.2 Hz, $COCH_2CH_2$CH_3); *m*/*z* (EI) 288 (2, M^+-H_2O), 235 (35), 218 (9), 203 (43), 159 (7), 145 (27), 119 (100), 101 (17), 71 (60), 43 (37%). Found: C, 66.76; H, 7.20. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24.

4.5.5. (5*R*) Methyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7c).[11a] Colorless oil; $[\alpha]_D^{20}=+54.8$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 3496, 3003, 2957, 2840, 1746, 1715, 1615, 1515, 1250, 1033, 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27 (2H, d, J=9.0 Hz, C_6H_4), 6.87 (2H, d, J=8.4 Hz, C_6H_4), 5.12 (1H, dd, J=3.3, 9.3 Hz, $COCH_2$C*H*OH), 3.79 (3H, s, ArOCH_3), 3.73 (3H, s, CO_2CH_3), 3.50 (2H, s, COCH_2CO_2), 2.99 (1H, dd, J=9.0, 17.4 Hz, COCH_2CHOH), 2.85 (1H, dd, J=3.0, 17.4 Hz, COCH_2CHOH); *m*/*z* (EI) 252 (3, M^+), 234 (6), 179 (4), 161 (8), 137 (100), 135 (19), 109 (19), 94 (10), 77 (12), 65 (4%).

4.5.6. (5*S*) Methyl δ-butyryloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (8c). Colorless oil; $[\alpha]_D^{20}=-48.6$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2966, 2939, 2878, 1739, 1614, 1516, 1251, 1174, 1033, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, J=8.7 Hz, C_6H_4), 6.87 (2H, d, J=6.6 Hz,

C_6H_4), 6.15 (1H, dd, J=4.8, 9.0 Hz, $COCH_2CHOCO$), 3.79 (3H, s, $ArOCH_3$), 3.72 (3H, s, CO_2CH_3), 3.45 (2H, s, $COCH_2CO_2$), 3.22 (1H, dd, J=9.0, 17.1 Hz, $COCH_2$-CHOCO), 2.96 (1H, dd, J=5.1, 17.1 Hz, $COCH_2CHOCO$), 2.25 (2H, t, J=7.8 Hz, $COCH_2CH_2CH_3$), 1.63–1.56 (2H, m, $COCH_2CH_2CH_3$), 0.89 (3H, t, J=7.2 Hz, $COCH_2CH_2$-CH_3); *m/z* (EI) 322 (5, M^+), 251 (27), 234 (15), 219 (25), 207 (9), 161 (52), 137 (67), 135 (100), 101 (16), 71 (36%). Found: C, 63.11; H, 7.13. $C_{17}H_{22}O_6$ requires C, 63.34; H, 6.88.

4.5.7. (5*R*) Methyl δ-hydroxy-δ-furan-2-yl-β-oxo-pentanoates (7d).[34] Colorless oil; $[\alpha]_D^{20}=+23.2$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3482, 3124, 2957, 1745, 1716, 1439, 1327, 1151, 1012, 747 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.36 (1H, m, C_4H_3O), 6.34–6.32 (1H, m, C_4H_3O), 6.28 (1H, d, J=3.6 Hz, C_4H_3O), 5.20 (1H, dd, J=3.6, 8.7 Hz, $COCH_2CHOH$), 3.74 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2$-CO_2), 3.17 (1H, dd, J=9.0, 17.4 Hz, $COCH_2CHOH$), 3.03 (1H, dd, J=3.6, 17.4 Hz, $COCH_2CHOH$); *m/z* (EI) 212 (20, M^+), 180 (17), 152 (10), 139 (20), 121 (26), 116 (25), 110 (29), 97 (100), 95 (20), 69 (16%).

4.5.8. (5*S*) Methyl δ-butyryloxy-δ-furan-2-yl-β-oxo-pentanoates (8d). Colorless oil; $[\alpha]_D^{20}=-95.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2968, 2879, 1737, 1438, 1326, 1174, 1014, 749 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.36 (1H, m, C_4H_3O), 6.38–6.27 (3H, m, C_4H_3O, $COCH_2CHOCO$), 3.74 (3H, s, OCH_3), 3.49 (2H, s, $COCH_2CO_2$), 3.32 (1H, dd, J=8.4, 17.4 Hz, $COCH_2CHOCO$), 3.16 (1H, dd, J=5.4, 17.4 Hz, $COCH_2CHOCO$), 2.25 (2H, t, J=7.5 Hz, $COCH_2$-CH_2CH_3), 1.69–1.54 (2H, m, $COCH_2CH_2CH_3$), 0.89 (3H, t, J=7.5 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 282 (1, M^+), 211 (52), 179 (100), 162 (9), 137 (41), 121 (36), 101 (33), 94 (36), 71 (68), 43 (51%). Found: C, 59.59; H, 6.44. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43.

4.5.9. (5*R*) Methyl δ-hydroxy-δ-(*o*-bromophenyl)-β-oxo-pentanoates (7e). Colorless oil; $[\alpha]_D^{20}=+79.5$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3522, 2981, 2947, 2920, 1735, 1698, 1440, 1331, 1196, 1144, 1006, 749 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, d, J=6.6 Hz, C_6H_4), 7.51 (1H, d, J=7.8 Hz, C_6H_4), 7.35 (1H, t, J=7.5 Hz, C_6H_4), 7.13 (1H, t, J=7.2 Hz, C_6H_4), 5.49 (1H, dd, J=1.8, 9.6 Hz, $COCH_2CHOH$), 3.79 (3H, s, OCH_3), 3.54 (2H, s, $COCH_2$-CO_2), 3.09 (1H, dd, J=2.4, 17.7 Hz, $COCH_2CHOH$), 2.78 (1H, dd, J=9.6, 17.7 Hz, $COCH_2CHOH$); *m/z* (EI) 284 (14, M^+-H_2O), 282 (14, M^+-H_2O), 221 (11), 203 (54), 187 (48), 185 (69), 157 (20), 116 (100), 105 (20), 84 (26), 77 (78), 59 (19%). Found: C, 47.88; H, 4.56. $C_{12}H_{13}BrO_4$ requires C, 47.86; H, 4.35.

4.5.10. (5*S*) Methyl δ-butyryloxy-δ-(*o*-bromophenyl)-β-oxo-pentanoates (8e). Colorless oil; $[\alpha]_D^{20}=-0.92$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3066, 2967, 2937, 2877, 1743, 1438, 1250, 1174, 1086, 757 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54 (1H, d, J=8.1 Hz, C_6H_4), 7.37–7.28 (2H, m, C_6H_4), 7.15 (1H, dt, J=2.1, 8.1 Hz, C_6H_4), 6.47 (1H, t, J=6.3 Hz, $COCH_2CHOCO$), 3.73 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2CO_2$), 3.50 (2H, d, J=6.3 Hz, $COCH_2CHOCO$), 2.33 (2H, t, J=7.5 Hz, $COCH_2CH_2CH_3$), 1.71–1.59 (2H, m, $COCH_2CH_2CH_3$), 0.93 (3H, t, J=7.2 Hz, $COCH_2CH_2$-CH_3); *m/z* (EI) 301 (5, $M^+-{}^n$PrCO), 299 (5, $M^+-{}^n$PrCO), 291 (20), 269 (11), 209 (10), 203 (100), 183 (31), 101 (37), 71 (77), 59 (17), 43 (43%). Found: C, 51.98; H, 5.20. $C_{16}H_{19}BrO_5$ requires C, 51.77; H, 5.16.

4.5.11. (5*R*) Methyl δ-hydroxy-δ-(*p*-fluorophenyl)-β-oxo-pentanoates (7f). Colorless oil; $[\alpha]_D^{20}=+52.6$ (*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 3503, 2957, 1747, 1716, 1606, 1512, 1223, 840 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.28 (2H, m, C_6H_4), 7.03 (2H, t, J=6.9 Hz, C_6H_4), 5.15 (1H, dd, J=2.7, 9.0 Hz, $COCH_2CHOH$), 3.72 (3H, s, OCH_3), 3.50 (2H, s, $COCH_2CO_2$), 2.97 (1H, dd, J=9.0, 17.4 Hz, $COCH_2CHOH$), 2.87 (1H, dd, J=3.6, 17.4 Hz, $COCH_2$-$CHOH$); *m/z* (EI) 240 (2, M^+), 222 (27), 180 (9), 167 (21), 162 (15), 149 (32), 125 (100), 123 (65), 116 (64), 97 (77), 85 (25%). Found: C, 60.09; H, 5.63. $C_{12}H_{13}FO_4$ requires C, 60.00; H, 5.45.

4.5.12. (5*S*) Methyl δ-butyryloxy-δ-(*p*-fluorophenyl)-β-oxo-pentanoates (8f). Colorless oil; $[\alpha]_D^{20}=-31.7$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 2967, 2939, 2879, 1741, 1513, 1228, 1177, 1085, 839 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.31 (2H, m, C_6H_4), 7.03 (2H, t, J=6.9 Hz, C_6H_4), 6.17 (1H, dd, J=5.1, 8.7 Hz, $COCH_2CHOCO$), 3.72 (3H, s, OCH_3), 3.45 (2H, s, $COCH_2CO_2$), 3.22 (1H, dd, J=8.7, 16.8 Hz, $COCH_2CHOCO$), 2.97 (1H, dd, J=5.4, 17.1 Hz, $COCH_2CHOCO$), 2.27 (2H, t, J=7.2 Hz, $COCH_2CH_2CH_3$), 1.70–1.57 (2H, m, $COCH_2CH_2CH_3$), 0.90 (3H, t, J=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 292 (3, M^+-H_2O), 239 (69), 222 (16), 207 (100), 162 (14), 149 (36), 123 (90), 122 (38), 101 (41), 71 (83%). Found: C, 62.05; H, 6.30. $C_{16}H_{19}O_5F$ requires C, 61.93; H, 6.17.

4.5.13. (5*R*) Methyl δ-hydroxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7g). Colorless oil; $[\alpha]_D^{20}=+79.3$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3524, 2982, 2951, 1737, 1695, 1442, 1336, 1087, 1006, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (1H, d, J=8.1 Hz, C_6H_3), 7.36–7.27 (2H, m, C_6H_3), 5.49 (1H, dd, J=2.4, 9.6 Hz, $COCH_2CHOH$), 3.75 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2CO_2$), 3.06 (1H, dd, J=2.7, 17.7 Hz, $COCH_2CHOH$), 2.77 (1H, dd, J=9.9, 17.7 Hz, $COCH_2CHOH$); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 202.9, 167.7, 139.1, 134.1, 132.1, 129.4, 128.5, 128.0, 66.5, 52.9, 49.9, 49.8; *m/z* (EI) 274 (15, M^+-H_2O), 272 (23, M^+-H_2O), 237 (17), 177 (53), 175 (100), 173 (39), 147 (17), 116 (96), 111 (52), 84 (29), 74 (35%). Found: C, 49.60; H, 4.36. $C_{12}H_{12}Cl_2O_4$ requires C, 49.51; H, 4.15.

4.5.14. (5*S*) Methyl δ-butyryloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (8g). Colorless oil; $[\alpha]_D^{20}=-15.2$ (*c* 1.6, $CHCl_3$). ν_{max} (liquid film) 3095, 2967, 2878, 1745, 1592, 1774, 1247, 1172, 1103, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.24 (3H, m, C_6H_3), 6.45 (1H, dd, J=3.9, 8.4 Hz, $COCH_2CHOCO$), 3.74 (3H, s, OCH_3), 3.51 (2H, s, $COCH_2CO_2$), 3.18–3.03 (2H, m, $COCH_2CHOCO$), 2.32 (2H, t, J=7.5 Hz, $COCH_2CH_2CH_3$), 1.69–1.60 (2H, m, $COCH_2CH_2CH_3$), 0.92 (3H, t, J=7.2 Hz, $COCH_2CH_2$-CH_3); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 198.6, 173.4, 172.5, 136.4, 134.8, 132.9, 130.0, 128.3, 127.9, 68.1, 52.9, 51.7, 49.5, 47.7, 36.4, 18.7, 14.0; *m/z* (EI) 325 (3, M^+-Cl), 291 (15), 289 (23), 257 (32), 237 (29), 215 (9), 199 (12), 173 (46), 101 (39), 71 (100), 43 (55%). Found: C, 53.38; H, 5.07. $C_{16}H_{18}Cl_2O_5$ requires C, 53.20; H, 5.02.

4.5.15. (5*R*) Methyl δ-hydroxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (7h).[11] Colorless oil; $[\alpha]_D^{20}=+49.8$ (*c* 1.0, $CHCl_3$). ν_{max}(liquid film) 3535, 2959, 2893, 1735, 1707, 1514, 1347, 1190, 100, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, $J=9.0$ Hz, C_6H_4), 7.55 (2H, d, $J=8.7$ Hz, C_6H_4), 5.32 (1H, t, $J=6.0$ Hz, $COCH_2CHOH$), 3.75 (3H, s, OCH_3), 3.54 (2H, s, $COCH_2CO_2$), 2.99 (2H, d, $J=6.0$ Hz, $COCH_2CHOH$); *m/z* (EI) 250 (13, M^+-OH), 235 (44), 218 (21), 207 (14), 194 (14), 176 (27), 165 (20), 152 (75), 151 (90), 116 (100), 101 (32), 74 (64%).

4.5.16. (5*S*) Methyl δ-butyryloxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (8h). Colorless oil; $[\alpha]_D^{20}=-27.8$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2968, 2878, 1744, 1524, 1349, 1172, 1087, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.20 (2H, d, $J=6.9$ Hz, C_6H_4), 7.54 (2H, d, $J=6.6$ Hz, C_6H_4), 6.26 (1H, dd, $J=5.1$, 8.1 Hz, $COCH_2CHOCO$), 3.73 (3H, s, OCH_3), 3.48 (2H, s, $COCH_2CO_2$), 3.27 (1H, dd, $J=8.1$, 17.4 Hz, $COCH_2CHOCO$), 3.03 (1H, dd, $J=5.1$, 17.4 Hz, $COCH_2CHOCO$), 2.32 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.78–1.58 (2H, m, $COCH_2CH_2CH_3$), 0.91 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 319 (2, M^+-H_2O), 266 (29), 250 (29), 234 (53), 218 (63), 176 (55), 150 (43), 101 (40), 101 (16), 71 (100), 43 (56%). Found: C, 56.88; H, 5.84; N, 3.92. $C_{16}H_{19}NO_7$ requires C, 56.97; H, 5.68; N, 4.15.

4.5.17. (5*R*) Ethyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7i).[35] Colorless oil; $[\alpha]_D^{20}=+50.8$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3489, 3033, 2984, 2908, 1741, 1715, 1321, 1193, 1030, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 5.17 (1H, dd, $J=3.6$, 5.7 Hz, $COCH_2CHOH$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 2.99 (1H, dd, $J=9.0$, 17.1 Hz, $COCH_2CHOH$), 2.88 (1H, dd, $J=3.6$, 17.1 Hz, $COCH_2CHOH$), 1.26 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 236 (4, M^+), 218 (37), 189 (8), 162 (17), 144 (30), 131 (54), 130 (75), 107 (99), 105 (100), 84 (44), 79 (99), 77 (83%).

4.5.18. (5*S*) Ethyl δ-butyryloxy-δ-phenyl-β-oxo-pentanoates (8i). Colorless oil; $[\alpha]_D^{20}=-35.8$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3066, 2969, 2877, 1741, 1369, 1252, 1175, 1091, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.26 (5H, m, C_6H_5), 6.21 (1H, dd, $J=4.5$, 8.7 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.44 (2H, s, $COCH_2CO_2$), 3.23 (1H, dd, $J=9.0$, 17.1 Hz, $COCH_2CHOCO$), 2.98 (1H, dd, $J=4.5$, 17.1 Hz, $COCH_2CHOCO$), 2.28 (2H, t, $J=8.1$ Hz, $COCH_2CH_2CH_3$), 1.71–1.58 (2H, m, $COCH_2CH_2CH_3$), 1.27 (3H, t, $J=7.5$ Hz, OCH_2CH_3), 0.89 (3H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 306 (5, M^+), 251 (27), 234 (15), 219 (25), 207 (9), 161 (52), 137 (67), 135 (100), 101 (16), 71 (36%). Found: C, 66.34; H, 7.21. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24.

4.5.19. (5*R*) Ethyl δ-hydroxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (7j). Colorless oil; $[\alpha]_D^{20}=+47.9$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 3491, 2984, 1743, 1714, 1320, 1033, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, $J=8.1$ Hz, C_6H_4), 7.15 (2H, d, $J=8.4$ Hz, C_6H_4), 5.24 (1H, dd, $J=3.0$, 9.0 Hz, $COCH_2CHOH$), 4.18 (2H, q, $J=6.6$ Hz, OCH_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 2.99 (1H, dd, $J=9.0$, 17.1 Hz, $COCH_2CHOH$), 2.87 (1H, dd, $J=3.3$, 17.1 Hz, $COCH_2CHOH$), 2.33 (3H, s, $ArCH_3$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 250 (5, M^+), 232 (36), 163 (20), 145 (33), 130 (46), 121 (100), 119 (58), 93 (59), 91 (55), 77 (29%). Found: C, 67.04; H, 7.36. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25.

4.5.20. (5*S*) Ethyl δ-butyryloxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (8j). Colorless oil; $[\alpha]_D^{20}=-38.8$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2969, 2937, 2877, 1740, 1319, 1251, 1176, 1087, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, $J=8.1$ Hz, C_6H_4), 7.15 (2H, d, $J=7.8$ Hz, C_6H_4), 6.17 (1H, dd, $J=4.8$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.43 (2H, s, $COCH_2CO_2$), 3.22 (1H, dd, $J=8.4$, 16.8 Hz, $COCH_2CHOCO$), 2.96 (1H, dd, $J=4.8$, 16.8 Hz, $COCH_2CHOCO$), 2.33 (3H, s, $ArCH_3$), 2.27 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.70–1.56 (2H, m, $COCH_2CH_2CH_3$), 1.26 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.90 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 302 (4, M^+-H_2O), 249 (34), 232 (9), 203 (50), 159 (9), 145 (25), 119 (100), 91 (16), 71 (53), 43 (39%). Found: C, 67.30; H, 7.76. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55.

4.5.21. (5*R*) Ethyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7k).[36] Colorless oil; $[\alpha]_D^{20}=+42.9$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3502, 2983, 2839, 1741, 1515, 1249, 1033, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (2H, d, $J=6.9$ Hz, C_6H_4), 6.88 (2H, d, $J=6.6$ Hz, C_6H_4), 5.13 (1H, dd, $J=3.6$, 9.0 Hz, $COCH_2CHOH$), 4.19 (2H, q, $J=7.5$ Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 3.48 (2H, s, $COCH_2CO_2$), 3.00 (1H, dd, $J=9.0$, 17.4 Hz, $COCH_2CHOH$), 2.88 (1H, dd, $J=3.6$, 17.4 Hz, $COCH_2CHOH$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 266 (2, M^+), 248 (7), 179 (4), 161 (10), 137 (100), 135 (22), 109 (19), 94 (10), 77 (13%).

4.5.22. (5*S*) Ethyl δ-butyryloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (8k). Colorless oil; $[\alpha]_D^{20}=-47.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2968, 2938, 2877, 2840, 1739, 1614, 1516, 1251, 1175, 1034, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, $J=6.6$ Hz, C_6H_4), 6.86 (2H, d, $J=6.6$ Hz, C_6H_4), 6.16 (1H, dd, $J=5.1$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 3.43 (2H, s, $COCH_2CO_2$), 3.23 (1H, dd, $J=8.4$, 16.8 Hz, $COCH_2CHOCO$), 2.96 (1H, dd, $J=4.8$, 16.8 Hz, $COCH_2CHOCO$), 2.50 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.65–1.56 (2H, m, $COCH_2CH_2CH_3$), 1.28 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.89 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 336 (3, M^+), 265 (32), 248 (15), 219 (39), 207 (10), 161 (43), 137 (57), 135 (100), 71 (79), 43 (24%). Found: C, 64.18; H, 7.28. $C_{18}H_{24}O_6$ requires C, 64.27; H, 7.19.

4.5.23. (5*R*) Ethyl δ-hydroxy-δ-furan-2-yl-β-oxo-pentanoates (7l). Colorless oil; $[\alpha]_D^{20}=+32.2$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3484, 2985, 1741, 1716, 1370, 1321, 1151, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.36 (1H, m, C_4H_3O), 6.35–6.28 (2H, m, C_4H_3O), 5.21 (1H, dd, $J=3.6$, 8.4 Hz, $COCH_2CHOH$), 4.21 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.51 (2H, s, $COCH_2CO_2$), 3.18 (1H, dd, $J=8.7$, 17.7 Hz, $COCH_2CHOH$), 3.05 (1H, dd, $J=3.6$, 17.7 Hz, $COCH_2CHOH$), 1.29 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 226 (22, M^+), 180 (24), 152 (140), 139 (21), 130 (24), 121 (34), 110 (41), 97 (100), 95 (26), 84 (16%). Found: C, 58.20; H, 6.39. $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24.

4.5.24. (5*S*) Ethyl δ-butyryloxy-δ-furan-2-yl-β-oxo-pentanoates (8l). Colorless oil; $[\alpha]_D^{20}=-94.5$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2878, 1743, 1251, 1174, 1093, 1015, 748 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.28 (1H, m, C_4H_3O), 6.38–6.28 (3H, m, C_4H_3O, $COCH_2CHOCO$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 3.33 (1H, dd, $J=8.1$, 17.1 Hz, $COCH_2CHOCO$), 3.16 (1H, dd, $J=4.8$, 17.1 Hz, $COCH_2CHOCO$), 2.25 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.68–1.58 (2H, m, $COCH_2CH_2CH_3$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3), 0.90 (3H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 296 (1, M^+), 225 (48), 219 (7), 203 (50), 179 (100), 137 (40), 121 (24), 95 (19), 71 (34), 43 (30%). Found: C, 60.82; H, 6.95. $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.80.

4.5.25. (5*R*) Ethyl δ-butyryloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7m). Colorless oil; $[\alpha]_D^{20}=+75.3$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3320, 2979, 2938, 1747, 1712, 1473, 1407, 1135, 1030, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, d, $J=9.0$ Hz, C_6H_3), 7.57–7.28 (2H, m, C_6H_3), 5.50 (1H, dd, $J=2.1$, 9.3 Hz, $COCH_2CHOH$), 4.22 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.52 (2H, s, $COCH_2CO_2$), 3.42 (1H, d, $J=5.2$ Hz, $COCH_2CHOH$), 3.08 (1H, d, $J=16.2$ Hz, $COCH_2CHOH$), 1.30 (3H, t, $J=7.8$ Hz, OCH_2CH_3); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 203.0, 167.2, 139.1, 134.1, 132.1, 129.4, 128.6, 127.9, 66.5, 62.1, 50.1, 49.9, 14.5; *m*/*z* (EI) 288 (15, M^+-H_2O), 286 (22, M^+-H_2O), 251 (16), 212 (17), 199 (19), 175 (100), 147 (15), 130 (89), 111 (50), 88 (35), 75 (20%). Found: C, 51.26; H, 4.59; $C_{13}H_{14}Cl_2O_4$ requires C, 51.17; H, 4.62.

4.5.26. (5*S*) Ethyl δ-butyryloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (8m). Colorless oil; $[\alpha]_D^{20}=-16.8$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 2970, 2937, 2878, 1745, 1475, 1369, 1244, 1173, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.23 (3H, m, C_6H_3), 6.45 (1H, dd, $J=5.2$, 8.4 Hz, $COCH_2CHOCO$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.48 (2H, s, $COCH_2CO_2$), 3.09–2.98 (2H, m, $COCH_2CHOCO$), 2.32 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.69–1.60 (2H, m, $COCH_2CH_2CH_3$), 1.30 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.93 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 198.75, 172.45, 167.10, 136.45, 134.76, 132.93, 129.99, 128.31, 127.92, 68.12, 61.95, 49.78, 47.63, 36.46, 18.72, 14.54, 13.98; *m*/*z* (EI) 358 (1, M^+-H_2O), 356 (3, M^+-H_2O), 305 (19), 303 (29), 259 (34), 257 (51), 251 (37), 215 (16), 199 (17), 175 (36), 71 (100), 43 (56%). Found: C, 54.56; H, 5.39; $C_{17}H_{20}Cl_2O_5$ requires C, 54.41; H, 5.37.

4.5.27. (5*R*) Ethyl δ-hydroxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (7n). Colorless oil; $[\alpha]_D^{20}=+37.8$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3364, 3086, 2981, 1741, 1517, 1349, 1136, 1023, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, $J=8.7$ Hz, C_6H_4), 7.56 (2H, d, $J=8.7$ Hz, C_6H_4), 5.32 (1H, dd, $J=3.0$, 9.6 Hz, $COCH_2CHOH$), 4.22 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.52 (2H, s, $COCH_2CO_2$), 2.99 (2H, d, $J=6.3$ Hz, $COCH_2CHOH$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m*/*z* (EI) 263 (3, M^+-H_2O), 235 (66), 221 (33), 192 (13), 176 (32), 165 (24), 152 (78), 151 (93), 150 (100), 130 (91), 77 (42%). Found: C, 55.52; H, 5.39; N, 4.89. $C_{13}H_{15}NO_6$ requires C, 55.51; H, 5.38; N, 4. 98.

4.5.28. (5*S*) Ethyl δ-butyryloxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (8n). Colorless oil; $[\alpha]_D^{20}=-30.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2878, 1743, 1524, 1349, 1172, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, $J=8.1$ Hz, C_6H_4), 7.53 (2H, d, $J=8.7$ Hz, C_6H_4), 6.26 (1H, dd, $J=5.1$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.45 (2H, s, $COCH_2CO_2$), 3.26 (1H, dd, $J=8.4$, 17.7 Hz, $COCH_2CHOCO$), 3.00 (1H, dd, $J=5.4$, 17.7 Hz, $COCH_2CHOCO$), 2.31 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.69–1.59 (2H, m, $COCH_2CH_2CH_3$), 1.25 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.90 (3H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 333 (3, M^+-H_2O), 280 (26), 264 (25), 234 (56), 218 (64), 190 (23), 176 (59), 150 (40), 134 (25), 71 (100), 43 (75%). Found: C, 58.34; H, 5.82; N, 4.11. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.02; N, 3.99.

4.6. General procedure of CRL-catalyzed enantioselective alcoholysis of δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (13a,c,g,i,k,m) and chemical hydrolysis of chiral δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (14a,c,g,i,k,m)

Substrates **13a**,**c**,**g**,**i**,**k**,**m** (0.5 mmol), butyl alcohol (23 mg, 0.31 mmol) and CRL (30 mg) were added anhydrous benzene (3 mL). The mixture was stirred 12 h at 30 °C, and filtered off the CRL that could be reused and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **7a**–**m** and unreacted esters **14a**,**c**,**g**,**i**,**k**,**m**. The yields are listed in Table 3.

Chiral δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (**14a**,**c**,**g**,**i**,**k**,**m**) (0.1 mmol), methyl alcohol (3 mL) and ammonium hydroxide (5 drops) were stirred at 0 °C for 2 h, then ethyl acetate (5 mL) and brine (3 mL) were added, and water phase was washed with ethyl acetate (5 mL) again. The combined organic phase was dried and solvent was removed in vacuum, and the residue was subjected to flash chromatography to afford optical active **15a**,**c**,**g**,**i**,**k**,**m**. The yields are listed in Table 3.

4.6.1. (5*R*) Methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7a).[33] Colorless oil; $[\alpha]_D^{20}=+56.7$ (*c* 1.0, $CHCl_3$).

4.6.2. (5*S*) Methyl δ-chloroacetyloxy-δ-phenyl-β-oxo-pentanoates (14a). Colorless oil; $[\alpha]_D^{20}=-38.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3036, 2957, 1749, 1722, 1322, 1170, 993, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.26 (5H, m, C_6H_5), 6.27 (1H, dd, $J=4.5$, 8.4 Hz, $COCH_2CHOCO$), 4.06 (2H, s, $ClCH_2CO$), 3.72 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2CO_2$), 3.31 (1H, dd, $J=9.0$, 17.4 Hz, $COCH_2CHOCO$), 3.02 (1H, dd, $J=4.5$, 17.4 Hz, $COCH_2CHOCO$),; *m*/*z* (EI) 280 (13, M^+-H_2O), 221 (39), 204 (40), 189 (50), 144 (28), 131 (100), 105 (98), 101 (32), 77 (59), 59 (22%). Found: C, 56.55; H, 5.32. $C_{14}H_{15}ClO_5$ requires C, 56.29; H, 5.06.

4.6.3. (5*S*) Methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (15a).[33] Colorless oil; $[\alpha]_D^{20}=-54.3$ (*c* 1.2, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.4. (5*R*) Methyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7c).[11a] Colorless oil; $[\alpha]_D^{20}=+51.9$ (*c* 1.0, $CHCl_3$).

4.6.5. (5*S*) Methyl δ-chloroacetyloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (14c). Colorless oil; $[\alpha]_D^{20}=-49.7$ (*c* 2.0, $CHCl_3$). ν_{max} (liquid film) 3007, 2958, 2841, 1749, 1722, 1517, 1252, 1175, 1031, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32 (2H, d, $J=9.3$ Hz, C_6H_4), 6.88 (2H, d, $J=9.3$ Hz, C_6H_4), 6.23 (1H, dd, $J=4.8$, 8.7 Hz, $COCH_2CHOCO$), 4.03 (2H, s, $ClCH_2CO$), 3.80 (3H, s, $ArOCH_3$), 3.72 (3H, s, CO_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 3.31 (1H, dd, $J=8.7$, 17.4 Hz, $COCH_2CHOCO$), 3.01 (1H, dd, $J=4.5$, 17.4 Hz, $COCH_2CHOCO$); *m*/*z* (EI) 328 (3, M^+), 234 (22), 175 (18), 161 (100), 137 (61), 135 (46), 101 (15), 77 (20), 59 (12%). Found: C, 55.02; H, 5.51. $C_{15}H_{17}ClO_6$ requires C, 54.80; H, 5.21.

4.6.6. (5*S*) Methyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (15c).[11a] Colorless oil; $[\alpha]_D^{20}=-50.5$ (*c* 2.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.7. (5*R*) Methyl δ-hydroxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7g). Colorless oil; $[\alpha]_D^{20}=+73.3$ (*c* 2.4, $CHCl_3$).

4.6.8. (5*S*) Methyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (14g). Colorless oil; $[\alpha]_D^{20}=-13.7$ (*c* 1.9, $CHCl_3$). ν_{max} (liquid film) 3007, 2972, 2858, 1753, 1712, 1411, 1327, 1317, 1197, 1001, 865, 798 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.26 (3H, m, C_6H_3), 6.53 (1H, dd, $J=3.9$, 9.0 Hz, $COCH_2CHOCO$), 4.11 (2H, s, $ClCH_2CO$), 3.75 (3H, s, OCH_3), 3.51 (2H, s, $COCH_2CO_2$), 3.19 (1H, dd, $J=9.0$, 18.0 Hz, $COCH_2CHOCO$), 3.07 (1H, dd, $J=3.6$, 17.7 Hz, $COCH_2CHOCO$); $\delta_{13}C$ (75.5 MHz, $CDCl_3$) 198.4, 167.4, 166.2, 135.3, 135.3, 133.0, 130.1, 128.4, 128.1, 69.9, 52.9, 49.5, 47.3, 41.0; *m*/*z* (EI) 348 (9, M^+-H_2O), 257 (19), 237 (100), 199 (37), 175 (77), 137 (21), 101 (71), 77 (51), 59 (40%). Found: C, 46.02; H, 3.80. $C_{14}H_{13}Cl_3O_5$ requires C, 45.74; H, 3.56.

4.6.9. (5*S*) Methyl δ-hydroxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (15g). Colorless oil; $[\alpha]_D^{20}=-73.0$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.10. (5*R*) Ethyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7i).[35] Colorless oil; $[\alpha]_D^{20}=+47.6$ (*c* 1.3, $CHCl_3$).

4.6.11. (5*S*) Ethyl δ-chloroacetyloxy-δ-phenyl-β-oxo-pentanoates (14i). Colorless oil; $[\alpha]_D^{20}=-40.6$ (*c* 2.0, $CHCl_3$). ν_{max} (liquid film) 3067, 3036, 2985, 2910, 1745, 1721, 1411, 1370, 1171, 1030, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.27 (5H, m, C_6H_5), 6.28 (1H, dd, $J=4.5$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.06 (2H, s, $ClCH_2CO$), 3.43 (2H, s, $COCH_2CO_2$), 3.32 (1H, dd, $J=9.0$, 17.4 Hz, $COCH_2CHOCO$), 3.03 (1H, dd, $J=4.2$, 17.4 Hz, $COCH_2CHOCO$), 1.28 (3H, t, $J=7.2$ Hz, OCH_2CH_3); *m*/*z* (EI) 294 (9, M^+-H_2O), 259 (12), 218 (21), 189 (69), 145 (19), 131 (78), 107 (59), 105 (100), 77 (60), 51 (15%). Found: C, 57.50; H, 5.64. $C_{15}H_{17}ClO_5$ requires C, 57.61; H, 5.48.

4.6.12. (5*S*) Ethyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (15i).[35] Colorless oil; $[\alpha]_D^{20}=-46.6$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.13. (5*R*) Ethyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7k).[36] Colorless oil; $[\alpha]_D^{20}=+40.5$ (*c* 2.0, $CHCl_3$).

4.6.14. (5*S*) Ethyl δ-chloroacetyloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (14k). Colorless oil; $[\alpha]_D^{20}=-62.7$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2940, 2911, 2841, 1737, 1613, 1516, 1250, 1178, 1031, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, $J=6.9$ Hz, C_6H_4), 6.88 (2H, d, $J=7.2$ Hz, C_6H_4), 6.23 (1H, dd, $J=4.5$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.03 (2H, s, $ClCH_2CO$), 3.80 (3H, s, OCH_3), 3.47 (2H, s, $COCH_2CO_2$), 3.32 (1H, dd, $J=9.0$, 17.7 Hz, $COCH_2CHOCO$), 3.02 (1H, dd, $J=8.1$, 17.1 Hz, $COCH_2CHOCO$), 1.28 (3H, t, $J=7.5$ Hz, OCH_2CH_3); *m*/*z* (EI) 342 (2, M^+), 265 (4), 248 (14), 219 (20), 175 (16), 161 (100), 137 (96), 135 (92), 119 (12), 77 (29%). Found: C, 55.97; H, 5.60. $C_{16}H_{19}ClO_6$ requires C, 56.06; H, 5.59.

4.6.15. (5*S*) Ethyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (15k).[36] Colorless oil; $[\alpha]_D^{20}=-38.7$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.16. (5*R*) Ethyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7m). Colorless oil; $[\alpha]_D^{20}=+65.9$ (*c* 1.0, $CHCl_3$).

4.6.17. (5*S*) Ethyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (14m). Colorless oil; $[\alpha]_D^{20}=-6.8$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 31.05, 2980, 2939, 1763, 1741, 1710, 1413, 1314, 1186, 1089, 1029, 825 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.25 (3H, m, C_6H_3), 6.53 (1H, dd, $J=3.6$, 9.0 Hz, $COCH_2CHOCO$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.08 (2H, s, $ClCH_2CO$), 3.49 (2H, s, $COCH_2CO_2$), 3.19 (1H, dd, $J=9.0$, 17.7 Hz, $COCH_2CHOCO$), 3.02 (1H, dd, $J=3.9$, 17.7 Hz, $COCH_2CHOCO$), 1.30 (3H, t, $J=6.9$ Hz, $COCH_2CH_2CH_3$); $\delta_{13}C$ (75.5 MHz, $CDCl_3$) 198.4, 167.0, 166.2, 135.3, 135.3, 133.0, 130.2, 128.4, 128.1, 67.0, 62.1, 49.8, 47.3, 41.0, 14.5; *m*/*z* (EI) 362 (10, M^+-H_2O), 259 (19), 251 (100), 215 (13), 199 (40), 175 (72), 137 (19), 115 (30), 102 (15), 77 (55), 69 (18%). Found: C, 47.41; H, 4.19; $C_{15}H_{15}Cl_3O_5$ requires C, 47.21; H, 3.96.

4.6.18. (5*S*) Ethyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (15m). Colorless oil; $[\alpha]_D^{20}=-65.4$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.7. CRL-catalyzed enantioselective hydrolysis ethyl 3-butyryloxy-4,4,4-trifluorobutyrate (10)

4.7.1. Preparation of ethyl 3-hydroxy-4,4,4-trifluorobutyrate (9). Sodium (3.45 g, 0.15 mol) was dissolved in absolute ethanol (15 mL), and to this mixture was added CH_3CO_2Et (8.8 g, 0.10 mol) and CF_3CO_2Et (14.2 g, 0.10 mol). The mixture was heated under refluxed for 48 h, then cooled to rt and hydrolyzed with minimum of 10 N H_2SO_4, yielding a mixture of ester and its hydrate, bp 100–130 °C/760 mm Hg. Reduction of this mixture with $NaBH_4$ gave ethyl 3-hydroxy-4,4,4-trifluorobutyrate 15.4 g (83%).

4.7.2. Preparation of diethyl ethyl 3-butyryloxy-4,4,4-trifluorobutyrate (10). In a 25 mL bottle were added substrate **9** (0.186 g, 1 mmol), *n*-butyric acid (0.11 mL, 1.2 mmol), DCC (248 mg, 1.2 mmol), DMAP (5 mg) and CH_2Cl_2 (10 mL). After the starting material was almost consumed at rt (about 1–2 h), diethyl ether (10 mL) was added and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to give ethyl 3-butyryloxy-4,4,4-trifluorobutyrate 2.43 g (95%).

4.7.3. CRL-catalyzed enantioselective hydrolysis ethyl 3-butyryloxy-4,4,4-trifluorobutyrate (10). Substrate **10** (100 mg) and CRL (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 24 h at 30 °C, and filtered off the CRL that could be reused and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **11** (41%) and unreacted esters **12** (45%).

4.7.3.1. (3*R*) Ethyl 3-hydroxy-4,4,4-trifluorobutanozte (11).[19] Colorless oil; $[\alpha]_D^{20}=+20.8$ (*c* 0.7, $CHCl_3$). ν_{max} (liquid film) 3463, 2990, 2945, 1725, 1305, 1171, 1021, 880, 662 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.48–4.42 (1H, m, CF_3CHCH_2), 4.22 (2H,q, $J=7.5$ Hz, OCH_2CH_3), 3.60 (1H, s, O*H*), 2.78–2.63 (2H, m, CF_3CHCH_2), 1.30 (3H, t, $J=7.2$ Hz, OCH_2CH_3); $\delta_{19}F$ (120 MHz, $CDCl_3$) −80.21, −80.23; *m/z* (EI) 186 (2, M^+), 159 (24), 141 (100), 117 (27), 113 (16), 99 (10), 77 (8), 71 (28), 69 (14), 43 (51%).

4.7.3.2. (3*S*) Ethyl 3-butyryloxy-4,4,4-trifluorobutanozte (12). Colorless oil; $[\alpha]_D^{20}=+6.3$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 2976, 2943, 1882. 1768, 1747, 1183, 1139, 1049, 1027, 659 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.84–5.77 (1H, m, CF_3CHCH_2), 4.18 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 2.84–2.71 (2H, m, CF_3CHCH_2), 2.37 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.74–1.62 (2H, m, $COCH_2CH_2CH_3$), 1.26 (3H, t, $J=6.6$ Hz, OCH_2CH_3), 0.94 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); $\delta_{19}F$ (120 MHz, $CDCl_3$) −78.0, −78.0; *m/z* (EI) 256 (1, M^+), 228 (14), 211 (6), 187 (4), 141 (8), 123 (11), 71 (100), 70 (16), 43 (35%); HRMS (EI): M^+ found: 256.0918. $C_{10}H_{15}O_4F_3$ requires 256.0922.

4.8. Preparation of chiral tomoxetine hydrochloride (I) and fluoxetine hydrochloride (II)

4.8.1. Preparation of (1*R*) 1-phenylpropane-1,3-diol and (1*S*) 1-phenylpropane-1,3-diol. In a 50 mL flask were added (3*R*) ethyl β-hydroxy-β-phenyl propionate (**4c**) (0.39 g, 2 mmol) (or (3*S*) ethyl β-butyryloxy-β-phenyl propionate (**5c**) (0.53 g, 2 mmol)), THF (15 mL) and $LiAlH_4$ (0.11 g, 3 mmol) (or 0.18 g, 5 mmol). After the mixture was stirred at room temperature for 1 h, 5 mL aqueous HCl was added and THF was removed under reduced pressure. Then the solution was extracted with EtOAc (3×5 mL), the combine extracts were dried and evaporated in vacuum. The residue was subjected to flash chromatography to obtain (1*R*) 1-phenylpropane-1,3-diol 0.28 g, yield: 92%. (or (1*S*) 1-phenylpropane-1,3-diol 0.29 g, yield: 95%).

(1R) 1-Phenylpropane-1,3-diol.[9g,37] Colorless oil; $[\alpha]_D^{20}=+57.4$ (*c* 1.65, $CHCl_3$). ν_{max} (liquid film) 3349, 3032, 2974, 1494, 1454, 1050, 726, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.21 (5H, m, C_6H_5), 4.84 (1H, dd, $J=4.2$, 8.4 Hz, $PhCHCH_2$), 4.00 (1H, s, O*H*), 3.76–3.66 (2H, m, $CHCH_2CH_2OH$), 3.58 (1H, s, O*H*), 1.94–1.79 (2H, m, $PhCHCH_2CH_2$); *m/z* (EI) 152 (M^+, 19), 133 (11), 107 (100), 105 (32), 79 (72), 77 (49), 51 (13), 43 (7%).

(1S) 1-Phenylpropane-1,3-diol. Colorless oil; $[\alpha]_D^{20}=-57.4$ (*c* 1.20, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.2. Preparation of (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate and (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate. In a 25 mL flask were added (1*R*) 1-phenylpropane-1,3-diol (or (1*S*) 1-phenylpropane-1,3-diol) (0.30 g, 2 mmol), Et_3N (0.13 g, 3.6 mmol) and anhydrous Et_2O (10 mL), and at ice-salt bath the mixture of methanesulfonyl chloride (0.26 g, 2.3 mmol) and 5 mL Et_2O were added. After the mixture was stirred at this low temperature for 1 h, then at ice-water bath for another 2 h. The reaction was terminated through adding 10 mL saturated NH_4Cl. The water phase was extracted with EtOAc (3×5 mL), the combine extracts were dried and evaporated in vacuum. The residue was subjected to flash chromatography to obtain (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate (or (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate) 0.39 g, yield: 85%.

(3R) 3-Phenyl-3-hydroxypropyl methanesulfonate.[9g,37] Colorless oil; $[\alpha]_D^{20}=+21.5$ (*c* 2.00, $CHCl_3$). ν_{max} (liquid film) 3532, 3031, 2939, 1352, 1174, 975, 927, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 4.84 (1H, dt, $J=2.4$, 6.6 Hz, $PhCHCH_2$), 4.48–4.40 (1H, m, $CHCH_2CH_2O$), 4.28–4.21 (1H, m, $CHCH_2CH_2O$), 2.97 (3H, s, $CH_2OSO_2CH_3$), 2.62 (1H, s O*H*), 2.10 (2H, dd, $J=6.6$, 12.3 Hz, $PhCHCH_2CH_2$); *m/z* (EI) 230 (M^+, 2), 133 (47), 107 (100), 105 (66), 79 (71), 77 (43), 51 (9), 43 (3%).

(3S) 3-Phenyl-3-hydroxypropyl methanesulfonate. Colorless oil; $[\alpha]_D^{20}=-19.3$ (*c* 1.65, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.3. Preparation of (1*R*) 3-(methylamino)-1-phenyl-1-propanol and (1*S*) 3-(methylamino)-1-phenyl-1-propanol. A solution of (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate (or (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate) (0.23 g, 1 mmol) and methylamine (6 mL, 25% solution in water) in THF (6 mL) was heated at 60–65 °C in a pressure tube for 4 h. After cooling, the solvent was evaporated in vacuum. And the residue was dissolved in 8 mL aqueous HCl, then was extracted with EtOAc (1× 10 mL). The water phase was neutralized with Na_2CO_3 to alkaline (pH>10), and extracted with ether (3×10 mL). The combined extracts was dried and evaporated under reduced pressure to get (1*R*) 3-(methylamino)-1-phenyl-1-propanol (or (1*S*) 3-(methylamino)-1-phenyl-1-propanol) 0.133 g, yield: 80% (0.136 g, yield: 82%).

(1R) 3-(Methylamino)-1-phenyl-1-propanol.[9g,37] Colorless oil; $[\alpha]_D^{20}=+29.3$ (*c* 1.05, $CHCl_3$). ν_{max} (liquid film) 3402, 3032, 2825, 1469, 1194, 1045, 774, 704 cm^{-1}; δ_H

(300 MHz, $CDCl_3$) 7.41–7.21 (5H, m, C_6H_5), 4.93 (1H, dd, $J=3.0$, 9.0 Hz, PhC*H*CH_2), 2.92–2.81 (2H, m, $CHCH_2$-CH_2NH), 2.44 (3H, d, $J=4.2$ Hz, CH_2NHCH_3), 1.90–1.72 (2H, m, $PhCHCH_2CH_2$); *m/z* (EI) 165 (M^+, 9), 133 (7), 107 (3), 104 (12), 79 (9), 77 (17), 58 (11), 51 (7), 44 (100%).

(1S) 3-(Methylamino)-1-phenyl-1-propanol. Colorless oil; $[\alpha]_D^{20}=-23.0$ (*c* 1.55, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.4. Preparation of (*R*) fluoxetine and (*S*) fluoxetine. To a solution of (1*R*) 3-(methylamino)-1-phenyl-1-propanol (or (1*S*) 3-(methylamino)-1-phenyl-1-propanol) (83 mg, 0.5 mmol) in dry DMSO (3 mL) was added 80% NaH (30 mg, 1 mmol). The mixture was reacted at 55 °C for 30 min. Then trifluoromethyl-*p*-chlorobenzene (135 mg, 0.75 mmol) in 1 mL dry DMSO was added, the mixture was stirred at 90–100 °C for 1.5 h. After cooling dilution with ether, the mixture was washed with brine, dried and concentrated under vacuum. The residue was subjected to flash chromatography to obtain (*R*) fluoxetine (or (*S*) fluoxetine) 130 mg, yield: 84% (or 130 mg, yield: 84%).

(R) Fluoxetine.[9g,35] Colorless oil; $[\alpha]_D^{20}=+1.2$ (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3314, 3034, 2948, 2800, 1616, 1518, 1330, 1252, 1112, 1069 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42 (2H, d, $J=8.4$ Hz, C_6H_4), 7.34–7.25 (5H, m, C_6H_5), 6.90 (2H, d, $J=8.7$ Hz, C_6H_4), 5.31 (1H, dd, $J=4.8$, 8.4 Hz, PhC*H*CH_2), 2.75 (2H, t, $J=6.9$ Hz, $CHCH_2CH_2NH$), 2.44 (3H, s, CH_2NHCH_3), 2.25–2.17 (1H, m, $PhCHCH_2CH_2$), 2.08–1.99 (1H, m, $PhCHCH_2CH_2$), 1.86 (1H, s, N*H*); *m/z* (EI) 309 (M^+, 18), 251 (3), 183 (4), 104 (12), 164 (5), 148 (9), 104 (14), 91 (9), 77 (7), 44 (100%). Found: C, 66.29; H, 6.02; N, 4.77. $C_{17}H_{18}F_3NO$ requires C, 66.01; H, 5.87; N, 4.53.

(S) Fluoxetine. Colorless oil; $[\alpha]_D^{20}=-1.4$ (*c* 1.70, $CHCl_3$). Found: C, 66.07; H, 5.92; N, 4.80. $C_{17}H_{18}F_3NO$ requires C, 66.01; H, 5.87; N, 4.53. All of its other spectrums were identical with its enantiomer.

4.8.5. Preparation of (*R*) fluoxetine hydrochloride ((*R*)-II) and (*S*) fluoxetine hydrochloride ((*S*)-II). The oil (*R*) fluoxetine (or (*S*) fluoxetine) (42 mg, 0.14 mmol) was dissolved in ether and acidified with HCl (gas). The solution was concentrated to give a solid (*R*) fluoxetine hydrochloride ((*R*)-**II**) (or (*S*) fluoxetine hydrochloride ((*S*)-**II**)) 46 mg, yield: 98% (or 46 mg, yield: 98%).

(R) Fluoxetine hydrochloride ((*R*)-**II**).[9g,37] White solid; mp 140–141 °C; $[\alpha]_D^{20}=-10.1$ (*c* 1.00, $CHCl_3$); $[\alpha]_D^{20}=+12.0$ (*c* 1.00, H_2O). ν_{max} (liquid film) 3016, 2962, 2793, 2733, 2455, 1616, 1518, 1331, 1243, 1164, 1109, 1070, 843, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.64 (2H, s, N*H*,*H*Cl), 7.42 (2H, d, $J=8.4$ Hz, C_6H_4), 7.39–7.24 (5H, m, C_6H_5), 6.90 (2H, d, $J=8.7$ Hz, C_6H_4), 5.46 (1H, dd, $J=4.2$, 7.8 Hz, PhC*H*CH_2), 3.23–3.04 (2H, m, $CHCH_2CH_2NH$), 2.63 (3H, s, CH_2NHCH_3), 2.56–2.38 (2H, m, $PhCHCH_2CH_2$); *m/z* (EI) 309 (M^+-HCl, 6), 252 (1), 183 (2), 162 (2), 148 (4), 104 (8), 91 (5), 77 (4), 59 (4), 44 (100%). Found: C, 59.12; H, 5.50; N, 4.32. $C_{17}H_{19}ClF_3NO$ requires C, 59.05; H, 5.54; N, 4.05.

(S) Fluoxetine hydrochloride ((*S*)-**II**). White solid; mp 140–141 °C; $[\alpha]_D^{20}=+8.5$ (*c* 1.00, $CHCl_3$); $[\alpha]_D^{20}=+9.0$ (*c* 1.00, H_2O). Found: C, 59.09; H, 5.49; N, 4.73. $C_{17}H_{19}ClF_3NO$ requires C, 59.05; H, 5.54; N, 4.05. All of its other spectrums were identical with its enantiomer.

4.8.6. Preparation of (3*S*) 3-phenyl-3-(2-methylphenoxy)-propyl methanesulfonate and (3*R*) 3-phenyl-3-(2-methyl-phenoxy)propyl methanesulfonate. To a solution of PPh_3 (0.39 g, 1.5 mmol), *o*-cresol (0.22 g, 2 mmol) and anhydrous ether (8 mL) was added DEAD (40% solution in toluene, 0.66 g, 1.5 mmol) at ice-salt bath. After reacted at this temperature for 30 min, (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate (or (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate) (0.23 g, 1 mmol) was added to this reaction mixture. The mixture was kept this temperature for another 1 h, then at ice-water bath for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography to obtain (3*S*) 3-phenyl-3-(2-methylphenoxy)propyl methanesulfonate (or (3*R*) 3-phenyl-3-(2-methylphenoxy)propyl methanesulfonate) 0.26 g, yield: 80% (or 0.25 g, 78%).

(3S) 3-Phenyl-3-(2-methylphenoxy)propyl methanesulfonate.[37] Colorless oil; $[\alpha]_D^{20}=+7.8$ (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3065, 3030, 2938, 1493, 1357, 1239, 1176, 970, 753, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.25 (5H, m, C_6H_5), 7.20 (1H, d, $J=7.5$ Hz, C_6H_4), 6.96 (1H, t, $J=7.8$ Hz, C_6H_4), 6.81 (1H, t, $J=7.8$ Hz, C_6H_4), 6.60 (1H, d, $J=8.1$ Hz, C_6H_4), 5.33 (1H, dd, $J=4.5$, 8.4 Hz, PhC*H*CH_2), 4.51–4.35 (2H, m, $CHCH_2CH_2OSO_2$), 2.90 (3H, s, CH_2-OSO_2CH_3), 2.42–2.25 (2H, m, $PhCHCH_2CH_2$), 2.32 (3H, s, $ArCH_3$); *m/z* (EI) 320 (M^+, 3), 224 (4), 213 (2), 117 (100), 108 (7), 91 (7), 79 (6), 77 (6), 65 (2%).

(3R) 3-Phenyl-3-(2-methylphenoxy)propyl methanesulfonate. Colorless oil; $[\alpha]_D^{20}=-7.8$ (*c* 1.70, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.7. Preparation of (*S*) tomoxetine and (*R*) tomoxetine. The reaction process was identical with preparation of (1*R*) 3-(methylamino)-1-phenyl-1-propanol and (1*S*) 3-(methyl-amino)-1-phenyl-1-propanol. We obtained (*S*) tomoxetine 0.212 g, yield: 83% and (*R*) tomoxetine 0.209 g, yield: 82%.

(S) Tomoxetine.[35] Colorless oil; $[\alpha]_D^{20}=+36.8$ (*c* 0.50, $CHCl_3$). ν_{max} (liquid film) 3320, 3064, 2947, 2794, 1493, 1240, 1120, 750, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.22 (5H, m, C_6H_5), 7.12 (1H, d, $J=6.9$ Hz, C_6H_4), 6.96 (1H, t, $J=8.1$ Hz, C_6H_4), 6.77 (1H, t, $J=7.2$ Hz, C_6H_4), 6.60 (1H, d, $J=8.4$ Hz, C_6H_4), 5.59 (1H, dd, $J=4.2$, 8.1 Hz, PhC*H*CH_2), 2.80 (2H, t, $J=7.2$ Hz, $CHCH_2CH_2N$), 2.43 (3H, s, CH_2NHCH_3), 2.32 (3H, s, $ArCH_3$), 2.22–2.02 (3H, m, N*H*,$PhCHCH_2CH_2$); *m/z* (EI) 255 (M^+, 17), 151 (18), 148 (32), 108 (9), 104 (11), 91 (11), 77 (14), 44 (100%). Found: C, 80.21; H, 8.09; N, 5.52. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49.

(R) Tomoxetine. Colorless oil; $[\alpha]_D^{20}=-35.4$ (*c* 0.55, $CHCl_3$). Found: C, 80.00; H, 8.15; N, 5.62. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49. All of its other spectrums were identical with its enantiomer.

4.8.8. Preparation of (*S*) tomoxetine hydrochloride ((*S*)-I) and (*R*) tomoxetine hydrochloride ((*R*)-I). The reaction process was identical with preparation (*R*) fluoxetine hydrochloride ((*R*)-**II**) and (*S*) fluoxetine hydrochloride ((*S*)-**II**). And we obtained *S*) tomoxetine hydrochloride ((*S*)-**I**) 41 mg, yield: 99% and (*R*) tomoxetine hydrochloride ((*R*)-**I**) 41 mg, yield: 99%.

(S) Tomoxetine hydrochloride ((*S*)-**I**).[37] White solid; mp 162–163 °C; $[\alpha]_D^{20}=+40.9$ (*c* 1.18, $CHCl_3$); $[\alpha]_D^{20}=+43.1$ (*c* 1.00, MeOH); $[\alpha]_D^{20}=+42.6$ (*c* 1.18, EtOH). ν_{max} (liquid film) 3018, 2961, 2761, 2717, 1493, 1235, 1118, 1037, 767, 711 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.64 (2H, s, N*H*,*H*Cl), 7.34–7.21 (5H, m, C_6H_5), 7.10 (1H, d, $J=7.5$ Hz, C_6H_4), 6.94 (1H, t, $J=7.8$ Hz, C_6H_4), 6.77 (1H, t, $J=7.5$ Hz, C_6H_4), 6.59 (1H, d, $J=8.4$ Hz, C_6H_4), 5.37 (1H, t, $J=6.6$ Hz, PhC*H*CH_2), 3.15–3.11 (2H, t, $J=7.2$ Hz, $CHCH_2CH_2N$), 2.60 (3H, s, CH_2NHCH_3), 2.53–2.47 (2H, m, $PhCHCH_2CH_2$), 2.30 (3H, s, $ArCH_3$); *m/z* (EI) 255 (M^+-HCl, 5), 197 (1), 151 (9), 148 (16), 115 (3), 104 (7), 91 (7), 77 (8), 44 (100%). Found: C, 70.05; H, 7.85; N, 5.02. $C_{17}H_{22}ClNO$ requires C, 69.97; H, 7.60; N, 4.80.

(R) Tomoxetine hydrochloride ((*R*)-**I**). White solid; mp 161–162 °C; $[\alpha]_D^{20}=-34.9$ (*c* 1.18, $CHCl_3$); $[\alpha]_D^{20}=-39.0$ (*c* 1.00, MeOH); $[\alpha]_D^{20}=-38.4$ (*c* 1.18, EtOH). Found: C, 69.98; H, 7.75; N, 4.99. $C_{17}H_{22}ClNO$ requires C, 69.97; H, 7.60; N, 4.80. All of its other spectrums were identical with its enantiomer.

4.9. Prepraration of (*R*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (16) and (*S*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (17).[38]

In a 25 mL flask was added substrates **7a** or **7i** (**15a** or **15i**) (0.1 mmol) and 0.2 M solution of NaOH. After the mixture was stirred for 20 min, 2.0 M solution of HCl was added and the PH values <2. The solid was filtered and dried to get (*R*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (**16**) (or (*R*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (**17**)) 19 mg, yield: 98%.

(R) 4-Hydroxy-6-aryl-5,6-dihydro-2-pyones (**16**). White solid; mp 124–125 °C; $[\alpha]_D^{20}=+96.3$ (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3038, 2899, 1720, 1292, 1012, 756, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48–7.27 (5H, m, C_6H_6), 5.72 (1H, dd, $J=3.9$, 9.6 Hz, PhC*H*OCO), 3.69 (1H, d, $J=18.9$ Hz, COC*H*=COH), 3.49 (1H, d, $J=18.9$ Hz, COCH=CO*H*), 2.93 (2H, dq, $J=4.2$, 9.9, 18.3 Hz, PhC*H*CH_2C=); *m/z* (EI) 190 (64, M^+), 144 (2), 131 (4), 105 (72), 104 (100), 103 (28), 84 (58), 78 (28), 77 (32), 51 (9%). Found: C, 69.45; H, 5.50. $C_{11}H_{10}O_3$ requires C, 69.46; H 5.30.

(S) 4-Hydroxy-6-aryl-5,6-dihydro-2-pyones (**17**). White solid; mp 124–125 °C; $[\alpha]_D^{20}=-95.3$ (*c* 1.00, $CHCl_3$). Found: C, 69.29; H, 5.55. $C_{11}H_{10}O_3$ requires C, 69.46; H 5.30. All of its other spectrums were identical with its enantiomer.

4.10. Preparation of (*R*) methyl 4-oxo-2,6-diphenyl-tetrahydropyran-3-carboxylatete (18).[39]

In 25 mL flask was added substrate **7a** (111 mg, 0.5 mmol), benzaldehyde (66 mg, 0.63 mmol), $BF_3\cdot Et_2O$ (119 mg, 0.75 mmol) and CH_2Cl_2 (4 mL). After the mixture was reacted 3 h, ethyl acetate (35 mL) was added then washed with saturated $NaHSO_3$ solution (3×10 mL) and brine (2×10 mL). The organic phase dried and solvent was removed under reduced pressure, and the residues were purified by flash chromatography to give (*R*) methyl 4-oxo-2,6-diphenyl-tetrahydropyran-3-carboxylatete (**14**) 132 mg, yield: 85%.

Colorless oil; $[\alpha]_D^{20}=+23.7$ (*c* 1.30, $CHCl_3$). ν_{max} (liquid film) 3063, 3034, 2952, 1748, 1718, 1454, 1274, 1139, 1070, 761, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) .42–7.19 (10H, m, C_6H_5), 5.05 (1H, d, $J=10.8$ Hz, PhC*H*CHCO), 4.87 (1H, dd, $J=3.3$, 10.8 Hz, PhC*H*CH_2CO), 3.69 (1H, d, $J=10.8$ Hz, COC*H*CHPh), 3.57 (3H, s, OCH_3), 2.81–2.65 (2H, m, $PhCHCH_2CO$); *m/z* (EI) 310 (7, M^+), 278 (7), 233 (14), 204 (16), 201 (16), 172 (32), 145 (15), 131 (49), 104 (100), 77 (32%). Found: C, 73.52; H, 5.89. $C_{19}H_{18}O_4$ requires C, 73.53; H, 5.85.

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Concise total synthesis of (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-heneicosatriene, sex pheromone component of *Hyphantria Cunea*

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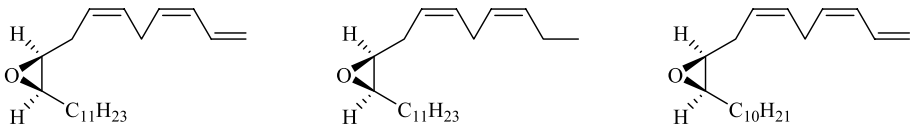
Abstract—The total synthesis of (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-heneicosatriene, sex pheromone component of *Hyphantria cunea*, using a convergent synthetic strategy, was achieved through the regioselective coupling of the two fragments, chiral epoxy tosylate and 1,4-diyne. The former fragment was synthesized in two efficient and convenient approaches starting from the same available material using Sharpless AE kinetic resolution as the key step.

1. Introduction

Optically active epoxides are an important class of natural products encountered as sex pheromones of Lepidopteran pests,[1] self-defensive substances against rice blast disease[2] and antifeedants.[3] The principal member of Lepidopteran epoxy pheromones, (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-henicosatriene **1**, featured a disubstituted chiral epoxide as the central structural element, was first assigned in 1989 in the sex pheromone gland of *Hyphantria cunea*[4] (Fig. 1). Subsequently, **1** was also found in the sex pheromone secretion of *Diacrisia oblique*.[5]

As compared with the synthesis of other members of chiral epoxide pheromones, the synthesis of **1** was more challenging due to the labile 1,3,6-triene subunit. To date, only two studies on the asymmetric synthesis of **1** have been published.[6] These methods suffered from some limitations, mostly importantly being long reaction sequences, very low total yield and/or uncontrolled semihydrogenation of conjugated terminal enyne. Our interest in the synthesis of **1** arises from several considerations. Firstly, due to the strong dependence of pheromone activity on the configuration, the stereoselective synthesis of **1** is of great interest and allows further exploration of the mechanism of pheromone–receptor interaction and the relationship between structure and biological activity. Furthermore, an efficient and concise procedure to **1** would make it possible to allow its use as a pest control agent in pheromone traps, which could lead to environmental-friendly pest management. Moreover, the novel structure itself poses intrinsic problems for a total synthesis. Herein, we describe a concise synthesis of **1**.



(9S, 10R)-**1** (9S, 10R)-**2** (9S, 10R)-**3**

Figure 1. Sex pheromone epoxy components of *Hyphantria cunea.*

Keywords: Sex pheromone; Hyphantria cunea; Total synthesis.
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2. Results and discussion

Our synthetic strategy was based on two main building blocks, that is, epoxy-tosylate (2*S*,3*S*)-**4** and 1,4-diyne **5** (Fig. 2). We envisaged that the former could be coupled with diynyl trifluoroborates which were readily generated in situ by the addition of $BF_3 \cdot Et_2O$ to diynyllithiums and mediated the regioselective ring cleavage of oxirane.[7] Our initial experiments involved the use of 1,4-heptdiyne **5a**. The coupling proceeded smoothly to afford the desired ring-opening product. In contrast, the coupling of (2*S*,3*S*)-**4** with **5b** under the similar condition had proven abortive. Repeated attempts by the modification of numerous experimental variations in base, reaction solvent and temperature, failed to furnish the product. Presumably, the introduction of electron-withdrawing vinyl led to the isomerization of molecules mainly due to deprotonation of a methylene between two triple bonds. To probe the effects of structural variations of 1,4-diyne on the course of coupling, additional two 1,4-diyne (**5c**, **5d**) were studied. Only **5d** underwent the coupling to deliver the desired product **6d**. In addition, 1,4-enyne **5e** was synthesized and employed in the coupling reaction. To our delight, we observed that (2*S*,3*S*)-**4** underwent, on treatment of **5e**, a smooth ring-opening to furnish **6e** (Fig. 3).

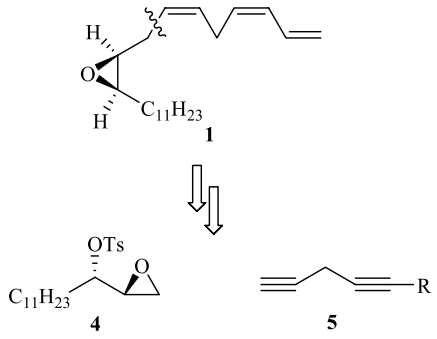
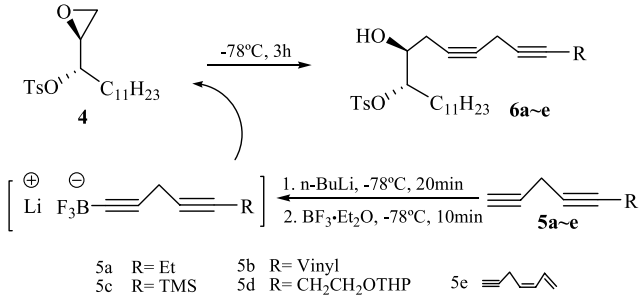


Figure 2. Retrosynthetic analysis of (9*S*,10*R*)-**1**.

As matters developed, it seemed that there were two possible routes to the target molecule, respectively derived from the intermediate **6e** and **6d** (Scheme 1). The former which might appear to be a more direct one, however, was not successful on the step of catalytic hydrogenation. We therefore adopt the route b employing **6d** as the intermediate. We found that the presence of THP protecting group in **6d** was unfavorable for the formation of oxirane. After removal of THP protecting group in **6d**, the resulting diol underwent cyclization in the presence of K_2CO_3 to afford **9** in good yield. The hydrogenation of **9** over Lindlar catalyst provided **10**, which was converted into the corresponding bromide **11**. The following elimination afforded the target molecule in good yield.

Expoxy tosylate (2*S*,3*S*)-**4** was a vital intermediate in the synthesis of epoxy pheromones and several approaches to it have been reported. However, the methods either employed expensive chiral catalyst system,[8] or were prohibitively lengthy and impractical for large scale preparation.[7b,9] Given those considerations, the present synthesis of (2*S*,3*S*)-**4** employed readily available material and utilized the Sharpless AE kinetic resolution as the key step (Scheme 2, (±)-**12**→(*S*)-**12**). In order to obtain (*S*)-**12** with high enantiomeric excess, the catalytic selectivities of various D-(−)-tartrate esters, diethyl (DET), diisopropyl (DIPT), dicyclohexyl (DCHT), dicyclododecyl tartrate (DCDT) were investigated, and the sterically demanding D-(−)-DCHT gave the best result.[10] Thus, the asymmetric epoxidation of alkenol (±)-**12** using D-(−)-DCHT as ligand gave (*S*)-**12** with excellent yield and enantioselectivity (98.2% ee) upon 50.8% completion of the reaction. Epoxidation on (*S*)-**12** with *m*-CPBA gave a 2:1 ratio of threo to erythro epoxy alcohols (3*S*)-**13**. The compound (3*S*)-**13** were converted into diastereomeric tosylates, which was flash chromatographed to afford (2*S*,3*S*)-**4**. To circumvent the drawbacks of kinetic resolution, on the other hand, we employed an inversion of the configuration[11] to convert (2*S*,3*R*)-**13**, the epoxy product of kinetic resolution, into (2*S*,3*S*)-**14** without the loss of material. Thus, the chemical yields were markedly beyond the 50% limitation set for kinetic resolution. The cleavage of the acetyl group in (2*S*,3*S*)-**14** provided the epoxy alcohols (2*S*,3*S*)-**13**, which were converted to (2*S*,3*S*)-**4** in good yield. The specific optical rotation of (2*S*,3*S*)-**4** was very close to that in the literature {$[\alpha]_D^{25} = +8.8$ ($c=1$, $CHCl_3$); lit.[8] $[\alpha]_D^{20} = +8.6$ ($c=1$, $CHCl_3$)}.

In conclusion, we have developed two efficient and convenient procedures for the synthesis of (2*S*,3*S*)-epoxy



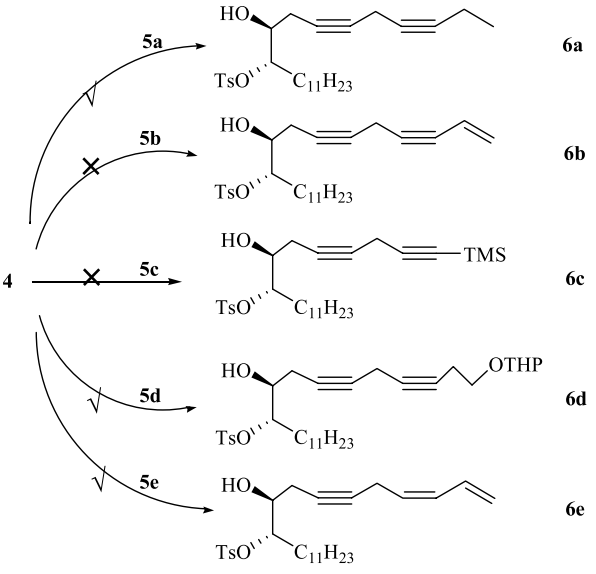
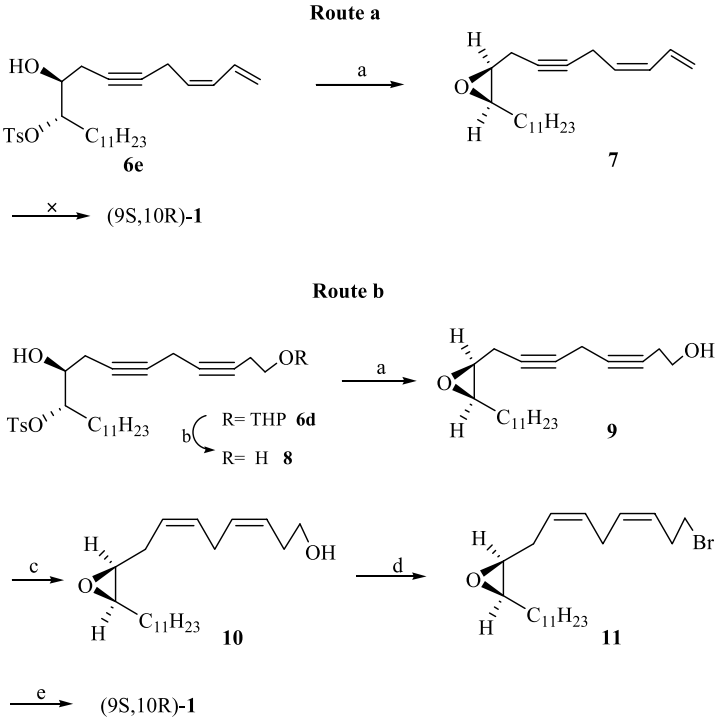
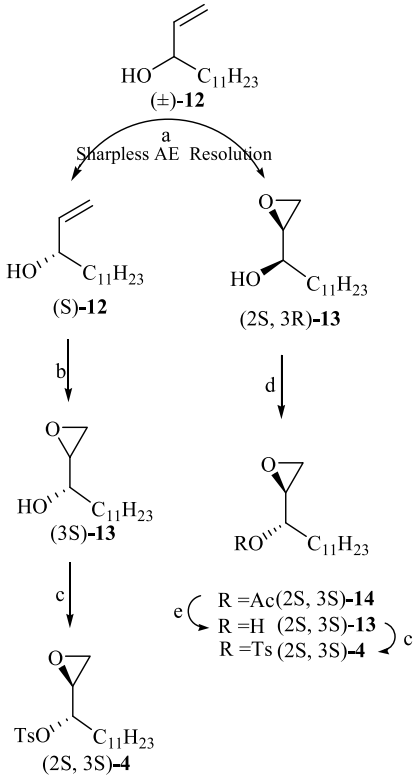


Figure 3. Coupling of various 1,4-diyne with (2*S*,3*S*)-**4**.



Scheme 1. Synthesis of (9*S*,10*R*)-**1**. Reagents and conditions: (a) K_2CO_3, CH_3OH, rt, 30 min; (b) PTSA, CH_3OH, rt, 5 h; (c) H_2, Pd-$CaCO_3$, quinoline, CH_3OH, rt; (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, 1 h; (ii) LiBr, $NaHCO_3$, THF, 8 h. (e) K_2CO_3, CH_3OH, rt, 48 h. PTSA, *p*-toluenesulfonic acid.



Scheme 2. Synthesis of (2*S*,3*S*)-**4**. Reagents and conditions: (a) 4 Å MS, D-(−)-DCHT, Ti(O-*i*-Pr)$_4$, TBHP, CH_2Cl_2, −20 °C (refrigerator); (b) *m*-CPBA, CH_2Cl_2, rt, 24 h; (c) (i) TsCl, powered KOH, Et_2O, −5 °C→0 °C, 3 h; (ii) flash chromatography employed to separate diastereoisomer; (d) AcOH, PPh_3, DIAD, THF, rt, 24 h; (e) K_2CO_3, CH_3OH, 0 °C, 1 h. D-(−)-DCHT, dicyclohexyl D-(−)-tartrate; TBHP, *tert*-butyl hydroperoxide; DIAD, diisopropyl azodicarboxylate.

tosylate starting from the same available material, and then explored the possibility of its coupling with 1,4-diyne or 1,4-enyne via alkylative epoxide rearrangement, through which (3*Z*,6*Z*,9*S*,10*R*)-9,10-epoxy-1,3,6-heneicosatriene **1**, the sex pheromone component of *Hyphantria cunea*, was successfully synthesized. The implementation of the new efficient approach to **1** would pave the way to the synthesis of other members of those highly stereoselective chemoreception insect pheromones or other structurally related polyacetylenic natural products.

3. Experimental

3.1. General methods

NMR spectra were recorded on a Bruker AMX-400 spectrometer using TMS as internal standard. All the coupling constants are reported in Hz. ^{13}C NMR spectra were recorded on the same instrument, and chemical shifts were measured relative to residual solvent resonances (δ ($CDCl_3$)=77.0). IR spectra were determined by Bruker Tensor 27 spectrometer. High-resolution mass spectra were obtained on a Micromass UK GCT-MS instrument with EI ionization methods. The optical rotations were determined for solution in $CDCl_3$ at 25 °C by using a Perkin–Elmer Model 241-Mc automatic polarimeter. Elemental microanalyses were performed by Italian Carloerba ST-2 analyzer. Melting points were determined on a Yanagimoto apparatus and were uncorrected. 1,4-Diyne and 1,4-enyne **5a**–**5e** were synthesized based on the general procedures described in the literature.[12] Anhydrous solvents were prepared as follows: THF and diethyl ether were freshly distilled under N_2 from Na/benzophenone. CH_2Cl_2 was

distilled under N_2 over CaH_2 and stored over 4 Å molecular sieves. Purification of products was performed by flash column chromatography on silica gel (200–300 mesh).

3.1.1. (*S*)-Tetradec-1-en-3-ol (*S*)-12 and (2*S*,3*R*)-1,2-epoxy-3-tetradecanol (2*S*,3*R*)-13. To a stirred and cooled (−20 °C) suspension of activated powered 4 Å molecular sieves (2.1 g) in 40 mL dry CH_2Cl_2 under nitrogen were added D-(−)-DCHT (0.44 g, 1.4 mmol) and Ti(O-*i*-Pr)$_4$ (0.284 g, 1 mmol) and stirred for 20 min. Then compound (±)-**12** (2.12 g, 10 mmol) and 0.4 mL *n*-dodecane (internal standard for GC monitoring of percent conversion) were added and stirred for further 30 min, during which a small aliquot (ca. 0.1 mL) was taken for a T_0GC sample. The reaction was then treated with a solution of TBHP in toluene (0.7 equiv, 3.3 M) added by gastight syringe. The reaction mixture was kept at −20 °C (refrigerator) and monitored by GC. When the conversion reached 50%, the reaction was quenched with an aqueous solution of $FeSO_4$ and citric acid and stirred for 30 min. The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed with saturated brine and dried over Na_2SO_4. The crude product was then purified by flash chromatography (petroleum ether/ether, 2/1) to give (*S*)-**12** (0.9 g, 87% based on 50.8% conversion) and (2*S*,3*R*)-**13** (1.06 g, 91% based on 50.8% conversion). (*S*)-**12**, a colorless oil, $[\alpha]_D^{25}=+5.5$ ($c=1$, $CHCl_3$), lit.[6b] $[\alpha]_D^{25}=+5.2$ ($c=1$, $CHCl_3$); IR (neat) ν 3390, 3020, 2930, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.86 (ddd, $^3J_{trans}=17.1$ Hz, $^3J_{cis}=10.4$ Hz, $^3J=6.3$ Hz, 1H, CH_2=C*H*), 5.18 (dt, $^3J_{trans}=17.1$ Hz, $^2J=^4J=1.4$ Hz, 1H, C*H*H=CH), 5.08 (dt, $^3J_{cis}=10.4$ Hz, $^2J=^4J=1.4$ Hz, 1H, CH*H*=CH), 4.05–4.12 (m, 1H, C*H*OH), 1.45–1.56 (m, 2H, CH_2CHOH), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.9$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 141.3, 114.3 (CH=CH_2), 73.2 (CHOH), 37.0, 31.9, 29.6, 29.5, 29.3, 25.3, 22.6, 14.0; Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.28; H, 13.12. (2*S*,3*R*)-**13**, white solid, mp 47–49 °C; $[\alpha]_D^{25}=-12.5$ ($c=1$, $CHCl_3$); IR (neat) ν 3310, 2910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81–3.83 (m, 1H, C*H*OH), 3.00–3.02 (m, 1H, oxirane CH), 2.81 (dd, $^2J=5.1$ Hz, $^3J=3.2$ Hz, 1H, oxirane CH_2), 2.72 (dd, $^2J=5.1$, $^3J=4.0$ Hz, 1H, oxirane, CH_2), 1.46–1.55 (m, 2H, CH_2CHOH), 1.26 (br, s,18H, $(CH_2)_9$), 0.88 (t, $J=6.7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 68.4 (CHOH), 54.6, 43.4 (CH(O)CH), 33.4, 31.9, 29.6, 29.5, 29.3, 25.2, 22.6, 14.0; Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.14.

3.1.2. (3*S*)-1,2-Epoxy-3-tetradecanol (3*S*)-13. A solution of (*S*)-**12** (2.12 g, 10 mmol) in 20 mL of anhydrous CH_2Cl_2 was cooled to 0 °C and stirred vigorously under nitrogen atmosphere. To this was added a solution of 75% *m*-CPBA (3.23 g, 14 mmol) in CH_2Cl_2. The resulting white mixture was warmed to room temperature and stirred for 24 h. The solution was filtered and washed with three 20 mL portions of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4. After the concentration and purification by flash chromatography (petroleum ether/ether, 2/1) epoxy alcohol (3*S*)-**13** (1.9 g, 84%) was obtained as a colorless oil which solidified upon standing at room temperature. The ratio of threo to erythro epoxy alcohols was determined to be ca. 2:1 by ^{1}H NMR integration of the carbinol methine proton resonances. IR (neat) ν 3310, 2910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 and 3.43 (2m, 1H, C*H*OH) (1:2), 2.96–3.04 (m, 1H, oxirane CH), 2.82 (dd, $^2J=4.9$ Hz, $^3J=4.1$ Hz, 1H, oxirane CH_2), 2.72 (dd, $^2J=4.9$ Hz, $^3J=2.7$ Hz, 1H, oxirane, CH_2), 1.55–1.60 (m, 2H, CH_2CHOH), 1.26 (br, s,18H, $(CH_2)_9$), 0.88 (t, $J=6.9$ Hz, 3H, CH_3); Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.14.

3.1.3. (2*S*,3*S*)-1,2-Epoxy-3-acetyloxytetradecane (2*S*,3*S*)-14. To a solution of the epoxy alcohol (2*S*,3*R*)-**13** (1.14 g, 5 mmol) in anhydrous THF (100 mL) was added AcOH (1.50 g, 25 mmol) and PPh_3 (5.24 g, 20 mmol), followed by the addition of diisopropylazodicarboxylate (3.03 g, 15 mmol) over a period of 5 min. The orange-red color of diisopropylazodicarboxylate faded immediately with slight liberation of heat. The solution was stirred at room temperature for 1 day. The mixture was diluted with ether (100 mL) then washed with H_2O and brine. The aqueous washings were extracted with ether (50 mL) and the extraction was washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed at reduced pressure. Flash chromatography (petroleum ether/ether, 5/1) of the residue afforded (2*S*,3*S*)-**14** (0.90 g, 67%) as a colorless oil. $[\alpha]_D^{25}=+2.7$ ($c=1$, $CHCl_3$); IR (neat) ν 2930, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.68–4.73 (m, 1H, C*H*OAc), 3.05–3.08 (m, 1H, oxirane CH), 2.82 (dd, $^2J=4.8$ Hz, $^3J=4.1$ Hz, 1H, oxirane CH_2), 2.63 (dd, $^2J=4.8$ Hz, $^3J=2.6$ Hz, 1H, oxirane CH_2), 2.08 (s, 3H, O=C*CH*$_3$), 1.63–1.66 (m, 2H, CH_2CHOAc), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.3 (O=C); 74.0 (CHOAc); 52.9, 44.8 (CH(O)CH); 31.8, 31.3, 29.5, 29.4, 29.3, 29.2, 25.1, 22.6, 20.9, 14.0; Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.92; H, 11.07.

3.1.4. (2*S*,3*S*)-1,2-Epoxy-3-tetradecanol (2*S*,3*S*)-13. To a solution of (2*S*,3*S*)-**14** (0.54 g, 2 mmol) in methanol (10 mL) was added anhydrous K_2CO_3 (0.5 g) at 0 °C while stirring. The mixture was stirred at 0 °C for 1 h, and then filtered. Concentration of the filtrate and purification by flash chromatography (petroleum ether/ether, 1/1) gave (2*S*,3*S*)-**13** (0.43 g, 94%) as a white solid, mp 40–42°C; $[\alpha]_D^{25}=+1.6$ ($c=1$, $CHCl_3$); IR (neat) ν 3310, 2910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.41–3.43 (m, 1H, C*H*OH), 2.97–2.99 (m, 1H, oxirane CH), 2.83 (dd, $^2J=4.8$ Hz, $^3J=4.2$ Hz, 1H, oxirane CH_2), 2.71 (dd, $^2J=4.8$ Hz, $^3J=2.7$ Hz, 1H, oxirane, CH_2), 1.57–1.61 (m, 2H, CH_2CHOH), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.8$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 71.7 (CHOH), 55.4, 45.1 (CH(O)CH), 34.3, 31.9, 29.6, 29.5, 29.4, 29.3, 25.3, 22.6, 14.0; Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.14.

3.1.5. (2*S*,3*S*)-1,2-Epoxy-3-tosyloxytetradecane (2*S*,3*S*)-4. To a solution of epoxy alcohols (3*S*)-**13** (2.28 g, 10 mmol) in 50 mL of anhydrous Et_2O was added tosylchloride (2.85 g, 15 mmol) and the mixture was cooled to −5 to −10 °C. Freshly and finely machine-powdered KOH (6 g) was added with efficient stirring over 15 min while maintaining the temperature between −5 and 0 °C. The mixture was stirred for additional 2 h at 0 °C and then poured into 50 mL of ice water. After vigorous shaking, the layers were separated. The organic layer and two ethereal

extracts were washed with brine and dried over anhydrous Na_2SO_4. Concentration and purification by flash chromatography (petroleum ether/ether, 2/1) yielded threo-epoxy tosylate (2*S*,3*S*)-**4** (1.72 g) as white solid and erythro-epoxy tosylate (0.94 g) as colorless oil. Threo-epoxy tosylate (2*S*,3*S*)-**4**, mp 66–68 °C; $[\alpha]_D^{25}=+8.8$ ($c=1$, $CHCl_3$), lit.[8] mp 71–72 °C, $[\alpha]_D^{20}=+8.6$ ($c=1$, $CHCl_3$); IR (KBr) ν 3050, 2925, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (d, $J=$ 8.3 Hz, 2H, 2,6-Ar), 7.32 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 4.34 (dt, $J=6.3$, 7.2 Hz, 1H, C*H*OTs), 3.03–3.06 (m, 1H, oxirane CH), 2.78 (t, $^2J=^3J=4.6$ Hz, 1H, oxirane CH_2), 2.63 (dd, $^2J=4.6$ Hz, $^3J=2.6$ Hz, 1H, oxirane CH_2), 2.44 (s, 3H, Ar–*CH_3*), 1.66–1.70 (m, 2H, C*H_2*CHOTs), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.5, 134.3, 129.6, 127.8 (Ar); 83.4 (CHOTs); 52.6, 44.8 (CH(O)CH); 31.9, 31.8, 29.5, 29.4, 29.2, 29.1, 24.8, 22.6, 21.6, 14.1; Anal. Calcd for $C_{21}H_{34}O_4S$: C, 65.93; H, 8.96. Found: C, 65.98; H, 8.93.

The same procedure as described above was applied for the conversion of (2*S*,3*S*)-**13** to (2*S*,3*S*)-**4**.

3.2. Typical procedure for the preparation of 6a, 6d and 6e

3.2.1. (*Z*,9*S*,10*S*)-9-Hydroxy-10-tosyloxyhenicosa-1,3-dien-6-yne 6e. A solution of **5e** (0.28 g, 3 mmol) in 15 mL of anhydrous THF was stirred at −78 °C as a solution of *n*-BuLi in hexanes (1 mL, 2.5 mmol) was added slowly by syringe. The resulting dark green solution was stirred for 15 min, and then $BF_3\cdot Et_2O$ (0.31 mL, 2.5 mmol) was added via syringe. After another 15 min, a solution of **4** (0.38 g, 1 mmol) in 4 mL of THF was added also by syringe, and the reaction mixture was stirred for further 3 h at −78 °C. The reaction mixture was then quenched with 10 mL saturated NH_4Cl. The aqueous layer was separated and extracted with ether (10 mL×2). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated to afford a brown residue which was purified through flash chromatography (petroleum ether/ether, 1/1) to give **6e** (0.37, 79%) as a colorless oil. $[\alpha]_D^{25}=-4.1$ ($c=1$, $CHCl_3$); IR (neat) ν 3524, 3080, 3030, 2925, 2285 (weak), 1645, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (d, $J=8.3$ Hz, 2H, 2,6-Ar), 7.33 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 6.63 (dddd, $^3J_{trans}=16.7$ Hz, $^3J_{cis}=10.2$ Hz, $^3J=10.7$ Hz, $^4J=1.0$ Hz, 1H, CH=CHC*H*=CH_2), 6.05 (t, $^3J=^3J_{cis}=10.7$ Hz, 1H, CH=C*H*CH=CH_2), 5.44 (dt, $^3J_{cis}=10.7$ Hz, $^3J=7.2$ Hz, 1H, C*H*=CHCH=CH_2), 5.25 (d, $^3J_{trans}=16.7$ Hz, 1H, CH=CHCH=C*H*H), 5.17 (d, $^3J_{cis}=10.2$ Hz, 1H, CH=CHCH=CH*H*), 4.62–4.67 (m, 1H, C*H*OTs), 3.76–3.80 (m, 1H, C*H*OH), 3.04 (dd, $^3J=7.2$ Hz, $^4J=1.8$ Hz, 2H, HC≡CC*H_2*C=CH), 2.44 (s, 3H, Ar–*CH_3*), 2.35–2.37 (m, 2H, C≡CC*H_2*CHOH), 1.50–1.70 (m, 2H, TsOCHC*H_2*), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.7, 134.1, 129.8, 127.9 (Ar); 131.3, 130.4, 126.3, 118.7 (2C=C); 84.7 (TsOCH); 81.0, 76.7 (C≡C); 70.4 (CHOH); 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 29.2, 24.9, 23.9, 22.7, 22.6, 21.7, 17.6, 14.1; HRMS (*m*/*z*) Calcd for $C_{28}H_{42}O_4S$ 474.2804, found 474.2801.

Compounds **6a** and **6d** were prepared in the same manner to that described above.

3.2.2. (9*S*,10*S*)-9-Hydroxy-10-tosyloxyhenicosa-3,6-diyne 6a. Colorless oil (0.40 g, 84%); $[\alpha]_D^{25}=-11.7$ ($c=$ 1, $CHCl_3$); IR (neat) ν 3410, 3065, 2925, 2210 (weak), 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (d, $J=8.3$ Hz, 2H, 2,6-Ar), 7.33 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 4.63–4.67 (m, 1H, C*H*OTs), 3.88 (dt, $J=3.9$, 6.9 Hz, 1H, C*H*OH), 3.11–3.13 (m, 2H, C≡CC*H_2*C≡C), 2.45 (s, 3H, Ar–C*H_3*), 2.34–2.37 (m, 2H, C≡CC*H_2*CHOH), 2.16–2.19 (m, 2H, C≡CC*H_2*-CH_3), 1.51–1.60 (m, 2H, TsOCHC*H_2*CH_2), 1.26 (br, s, 18H, $(CH_2)_9$), 1.12 (t, $J=7.5$ Hz, 3H, C≡CCH_2C*H_3*), 0.88 (t, $J=$ 6.8 Hz, 3H, CH_3); Anal. Calcd for $C_{28}H_{42}O_4S$: C, 70.85; H, 8.92. Found: C, 70.56; H, 8.68.

3.2.3. (9*S*,10*S*)-9-Hydroxy-10-tosyloxy-1-(tetrahydro-2*H*-pyran-2-yloxy)henicosa-3,6-diyne 6d. Colorless oil (0.42 g, 73%); $[\alpha]_D^{25}=-18.6$ ($c=1$, $CHCl_3$); IR (neat) ν 3430, 3065, 2925, 2216 (weak), 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (d, $J=8.2$ Hz, 2H, 2,6-Ar), 7.35 (d, $J=$ 8.2 Hz, 2H, 3,5-Ar), 4.63–4.66 (m, 2H, C*H*OTs, OC*H*O), 3.80–3.91 (m, 2H, C≡CCH_2C*H_2*OTHP), 3.69–3.73 (m, 1H, C*H*OH), 3.11–3.15 (m, 2H, C≡CC*H_2*C≡C), 2.49 (dt, $^3J=$ 7.1 Hz, $^5J=2.1$ Hz, 2H, HOCHC*H_2*C≡C), 2.45 (s, 3H, Ar–C*H_3*), 2.36 (t, $J=6.2$ Hz, 2H, C≡CC*H_2*CH_2OTHP), 1.50–1.80 (m, 8H, TsOCHC*H_2*, $(CH_2)_3$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.4$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.8, 134.1, 129.7, 127.9 (Ar); 98.7 (OCHO), 84.6 (TsOCH); 77.6, 75.7, 75.2, 68.5 (2C≡C); 70.3 (CHOH); 65.7, 62.2 ($2CH_2O$); 31.9, 30.6, 30.5, 29.6, 29.5, 29,3, 29.2, 25.4, 24.9, 23.8, 22.7, 21.6, 20.2, 19.4, 19.3, 14.1, 9.8, 9.6; Anal. Calcd for $C_{33}H_{50}O_6S$: C, 68.95; H, 8.77. Found: C, 68.77; H, 8.73.

3.2.4. (*Z*,9*S*,10*R*)-9,10-Epoxyhenicosa-1,3-dien-6-yne 7. To a solution of **6e** (0.47 g, 1 mmol) in 10 mL of anhydrous methanol was added anhydrous K_2CO_3 (0.4 g) with stirring at room temperature. After 30 min, the reaction mixture was filtered. Concentration of the filtrate and purification by flash chromatography (petroleum ether/diethyl ether, 10/1) afforded **7** (0.25 g, 82%) as a colorless oil which solidified upon standing at room temperature. $[\alpha]_D^{25}=+21.4$ ($c=1$, $CHCl_3$); IR (neat) ν 3030, 2925, 2285 (weak), 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63 (ddd, $^3J_{trans}=16.7$ Hz, $^3J_{cis}=$ 10.2 Hz, $^3J=10.7$ Hz, 1H, CH=CHC*H*=CH_2), 6.04 (t, $^3J=^3J_{cis}=10.7$ Hz, 1H, CH=C*H*CH=CH_2), 5.44 (dt, $^3J_{cis}=10.7$ Hz, $^3J=7.2$ Hz, 1H, C*H*=CHCH=CH_2), 5.24 (d, $^3J_{trans}=16.7$, 1H, CH=CHCH=C*H*H), 5.16 (d, $^3J_{cis}=10.2$ Hz, 1H, CH=CHCH=CH*H*), 3.06–3.12 (m, 3H, C≡CC*H_2*CH=CH, oxirane CH), 2.95 (dt, $J=4.2$, 5.5 Hz, 1H, oxirane CH), 2.52–2.58 (ddt, $^2J=17$ Hz, $^3J=$ 5.5 Hz, $^5J=2.7$ Hz, 1H, C≡CC*H*HCH(O)CH), 2.22–2.28 (ddt, $^2J=17$, $^3J=7.2$ Hz, $^5J=2.5$ Hz, 1H, C≡CCH*H*CH(O)CH), 1.50–1.56 (m, 2H, CH(O)CHC*H_2*), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 131.3, 130.3, 126.5, 118.5 (2CH=CH); 79.9, 75.4 (C≡C); 57.1, 55.3 (CH(O)CH); 31.9, 29.7, 29.6, 29.5, 29.3, 27.6, 26.5, 22.7, 18.8, 17.7, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{34}O$ 302.2610, found 302.2613.

3.2.5. (9*S*,10*S*)-1,9-Dihydroxy-10-tosyloxyhenicosa-3,6-diyne 8. PTSA (catalytic) was added to a solution of **6d** (1.15 g, 2 mmol) in 30 mL of methanol and stirred for 5 h at room temperature. Methanol was removed under reduced pressure and the residue was dissolved in ether. The ether

layer was washed with water, saturated aqueous $NaHCO_3$, brine respectively and dried over anhydrous Na_2SO_4. Concentration at reduced pressure and purification by flash chromatography (petroleum ether/ether, 1/4) afforded **8** (0.89 g, 91%) as a colorless oil. $[\alpha]_D^{25}=-8.6$ ($c=1$, $CHCl_3$); IR (neat) ν 3390, 3065, 2925, 2217 (weak), 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (d, $J=8.3$ Hz, 2H, 2,6-Ar), 7.35 (d, $J=8.3$ Hz, 2H, 3,5-Ar), 4.64–4.66 (m, 1H, C*H*OTs,), 3.79–3.82 (m, 1H, C*H*OH), 3.71 (t, $J=6.2$ Hz, 2H, C≡CCH$_2$C*H*$_2$OH), 3.13–3.15 (m, 2H, C≡CC*H*$_2$-C≡C), 2.42–2.47 (m, 5H, Ar–C*H*$_3$, HOCHC*H*$_2$C≡C), 2.36–2.38 (m, 2H, C≡CC*H*$_2$CH$_2$OH), 1.50–1.60 (m, 2H, TsOCHCH*H*$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.8, 134.1, 129.7, 127.8 (Ar); 84.6 (CHOTs); 77.3, 76.1, 75.8, 68.7 (2C≡C); 70.3 (CHOH); 61.0 (CH_2OH); 31.9, 30.5, 29.6, 29.5, 29.3, 29.2, 24.9, 23.7, 23.0, 22.9, 22.7, 21.6, 14.1, 9.8, 9.6; Anal. Calcd for $C_{28}H_{42}O_5S$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.74.

3.2.6. (9*S*,10*R*)-9,10-Epoxyhenicos-3,6-diyn-1-ol 9. The procedure described for the preparation of **7** was followed. White solid (0.26 g, 83%), mp 48–50 °C; $[\alpha]_D^{25}=+23.5$ ($c=1$, $CHCl_3$); IR (KBr) ν 3390, 2930, 2280 (weak) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (t, $J=6.2$ Hz, 2H, C*H*$_2$OH), 3.14–3.17 (m, 2H, C≡CC*H*$_2$C≡C), 3.11 (dt, $J=5.5$ Hz, 1.6, 1H, oxirane CH), 2.95 (dt, $J=4.5$, 5.5 Hz, 1H, oxirane CH), 2.29 and 2.52 (2m, 2H, C≡CC*H*$_2$CH(O)CH), 2.45 (tt, $^3J=6.2$ Hz, $^5J=2.3$ Hz, 2H, C≡CC*H*$_2$CH$_2$OH), 1.48–1.53 (m, 2H, CH(O)CHC*H*$_2$CH$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 77.1, 76.3, 76.2, 75.7 (2C≡C); 61.1 (CH_2OH); 57.1, 55.0 (CH(O)CH); 31.9, 29.6, 29.5, 29.4, 29.3, 27.5, 26.4, 23.1, 22.7, 18.7, 14.1, 9.8; HRMS (*m*/*z*) Calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2553.

3.2.7. (3*Z*,6*Z*,9*S*,10*R*)-9,10-Epoxyhenicos-3,6-dien-1-ol 10. Lindlar catalyst (5% palladium on $CaCO_3$, poisoned with lead, 15 mg) and 5 mg quinoline was placed in a 50 mL flask equipped with side arm and a rubber septum. The flask was alternately evacuated and filled with hydrogen several times. A solution of **9** (0.32 g, 1 mmol) in 20 mL of methanol was added via syringe and the suspension was stirred at room temperature until required amount of hydrogen gas (44.8 mL). The reaction mixture was filtered and concentrated under reduced pressure to afford **10** in almost quantitative yields. White solid, mp 39–42 °C; $[\alpha]_D^{25}=-2.5$ ($c=1$, $CHCl_3$); IR (neat) ν 3300, 3025, 2920, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.39–5.57 (m, 4H, C*H*=C*H*CH$_2$C*H*=C*H*) 3.66 (t, $J=6.3$ Hz, 2H, C*H*$_2$OH), 2.83–2.97 (m, 4H, C*H*(O)C*H*, CH=CHC*H*$_2$CH=CH), 2.25 and 2.39 (2m, 2H, CH=CHC*H*$_2$CH(O)CH), 2.35–2.41 (m, 2H, HC=CHC*H*$_2$CH$_2$OH), 1.46–1.55 (m, 2H, CH(O)CHC*H*$_2$CH$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.88 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 130.7, 130.3, 126.0, 124.6 (2C=C); 62.2 (CH_2OH); 57.2, 56.4 (CH(O)CH); 31.9, 30.9, 29.6, 29.5, 29.4, 27.8, 26.6, 26.3, 25.9, 22.7, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{38}O_2$ 322.2872, found 322.2874.

3.2.8. (3*Z*,6*Z*,9*S*,10*R*)-1-Bromo-9,10-epoxyhenicos-3,6-diene 11. To an ice-cooled solution of **10** (1.61 g, 5 mmol) in CH_2Cl_2 (30 mL) containing triethylamine (1.01 g, 10 mmol) was added methanesulfonyl chloride (0.74 g, 6.3 mmol) with stirring. The mixture was stirred for additional 1 h, and then washed with water. The methylene chloride solution was dried over anhydrous Na_2SO_4 and concentrated to give an oil residue. The residue was dissolved in dry THF (10 mL), and added anhydrous LiBr (1.72 g, 20 mmol) and $NaHCO_3$ (1.76 g, 15 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature and then filtered. Concentration of the filtrate and flash chromatography (petroleum ether/ether, 10/1) afforded **11** (1.57 g, 82%) as a colorless oil. $[\alpha]_D^{25}=+4.2$ ($c=1$, $CHCl_3$); IR (neat) ν 3030, 2925, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.41–5.54 (m, 4H, C*H*=C*H*CH$_2$C*H*=C*H*), 3.38 (t, $J=7.1$ Hz, 2H, C*H*$_2$Br), 2.79–2.96 (m, 4H, oxirane, CH=CHC*H*$_2$CH=CH), 2.63 (dt, $J=6.5$ Hz, 7.0, 2H, CH=CHC*H*$_2$CH$_2$Br), 2.29 and 2.37 (2m, 2H, CH(O)CHC*H*$_2$CH=CH), 1.50–1.55 (m, 2H, CH(O)-CHC*H*$_2$CH$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.89 (t, $J=6.6$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 130.5, 130.1, 126.5, 124.3 (2C=C); 57.3, 56.4 (CH(O)CH); 31.9, 30.8, 29.9, 29.6, 29.5, 29.4, 29.3, 26.0, 25.9, 22.6, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{37}OBr$ 384.2028, found 384.2031.

3.2.9. (3*Z*,6*Z*,9*S*,10*R*)-9,10-Epoxy-1,3,6-henicostriene 1. To a solution of **11** (0.38 g, 1 mmol) in 10 mL anhydrous methanol was added anhydrous K_2CO_3 (0.4 g) with stirring at room temperature. After 48 h, the reaction mixture was filtered. Concentration of the filtrate and purification by flash chromatography (petroleum ether/ether, 20/1) afforded **1** (0.26 g, 86%) as a colorless oil. $[\alpha]_D^{25}=-0.6$ ($c=3$, $CHCl_3$), lit.[6a] $[\alpha]_D^{16}=-0.41$ ($c=1.97$, $CHCl_3$); IR (neat) ν 3030, 2925, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.64 (dddd, $^3J_{trans}=16.8$ Hz, $^3J_{cis}=10.1$ Hz, $^3J=10.9$ Hz, $^4J=1.1$ Hz, 1H, CH=CHC*H*=CH$_2$), 6.01 (t, $J=10.9$ Hz, 1H, CH=C*H*CH=CH$_2$), 5.38–5.55 (m, 3H, C*H*=C*H*CH$_2$-C*H*=CH), 5.23 (dd, $^3J_{trans}=16.8$ Hz, $^2J=1.8$ Hz, 1H, CH=CHCH=C*H*H), 5.14 (d, $^3J_{cis}=10.1$ Hz, 1H, CH=CHCH=CH*H*), 2.80–2.96 (m, 4H, oxirane, CH=CHC*H*$_2$CH=CH), 2.29 and 2.39 (2m, 2H, CH(O)CHC*H*$_2$CH=CH), 1.55–1.60 (m, 2H, CH(O)-CHC*H*$_2$), 1.26 (br, s, 18H, $(CH_2)_9$), 0.89 (t, $J=6.7$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 131.8, 130.1, 129.9, 129.5, 124.4, 117.6 (3C=C); 57.2, 56.4 (CH(O)CH); 31.9, 29.9, 29.6, 29.5, 29.4, 29.3, 26.2, 26.0, 22.7, 14.1; HRMS (*m*/*z*) Calcd for $C_{21}H_{36}O$ 304.2766, found 304.2770.

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Development of resin-to-resin transfer reactions (RRTR) using Sonogashira chemistry☆

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Abstract—Sonogashira chemistry can be used according to the 'resin-to-resin transfer reaction' (RRTR) concept. Two fragments, one containing the halide moiety and the second one incorporating the alkyne functionality, are anchored on different solid supports using allyl and/or Wang-type linkages. Treatment with Pd(0) cleaves the allyl-linked fragment(s) which subsequently undergo Sonogashira coupling under the same conditions.

1. Introduction

Solid-phase synthesis, as pioneered by Merrifield, is the preferred route for synthesis of biologically important peptides.[1] This approach has been extended to other biopolymers, as well as to small organic molecules.[2] Over the past decade, solid-phase organic synthesis (SPOS) has attracted considerable attention because it offers several advantages with respect to classical solution-phase methods.[3] The solid-phase approach allows reactions to be driven to completion by using excess reagents which can be easily removed from desired intermediate products, bound to insoluble polymeric supports, by filtration and washing steps that occur without manipulative losses. Many organic reactions have been adapted to be effective with solid supports; these include peptide bond formation, Grignard reactions, Michael addition, multiple component condensation, diazotization, olefination, oxidation, reductive amination, cycloadditions, and metal-catalyzed cross-coupling.[4]

Combinatorial chemistry is an emerging field that allows for preparation of large libraries of chemical species using specified reaction sequences.[5] Synthesis is often followed up by high-throughput screening to identify those molecules that are biologically active. Combinatorial SPOS has proven to be a valuable tool in the drug discovery process due to easy work-up procedures and to the possibility of automation. Once a suitable scaffold can be created reproducibly, diversity may be introduced at every synthetic step, resulting in a large number of analogues.

Although several synthetic drugs possess structures with little resemblance to those of natural products, compounds originating from natural sources remain a major class of therapeutic agents. The design of libraries based on natural products as templates is an area of active interest.[6] However, to date only a small number of non-peptidic natural products have been accessed from simple precursors by SPOS.[7] To make libraries based on complex natural product templates, the use of semisynthetic approaches represents a good compromise between solution-phase and solid-phase strategies. An advanced intermediate is synthesized in solution, and is then attached to the support and used as a scaffold for combinatorial diversification at several positions.

An obviously advantageous option would be to develop a convergent approach for solid-phase synthesis of complex molecules, where two (or more) fragments of a molecule are synthesized separately on different supports, and then coupled via a 'resin-to-resin transfer reaction' (RRTR)[8] (Scheme 1).‡ Thus, each fragment can be diversified independently, increasing the overall number of possible analogues. This approach also circumvents problems that could be encountered with a linear SPOS strategy involving

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Keywords: Solid-phase organic synthesis; Resin-to-resin transfer reactions; Sonogashira coupling.
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‡ This article uses the 'RRTR' expression, coined by DeGrado and coworkers (Ref. 8b). As enunciated earlier by Patchornik (Ref. 8a), the overall concept is described by the moniker 'shadchan' chemistry.

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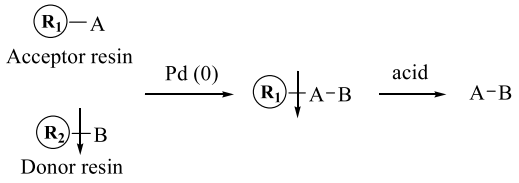


Scheme 1. Schematic representation of resin-to-resin transfer reactions.

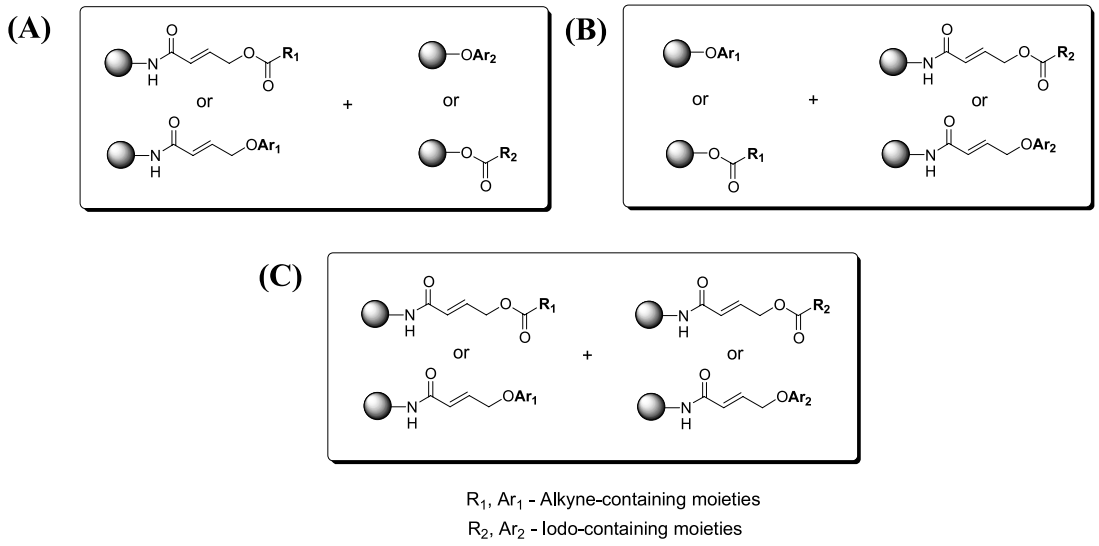
potentially incompatible reaction conditions. Although some triphasic reactions between two solid supports were explored in the 1970s as a way to probe mechanisms,[9] only a few examples have been reported that use RRTR for the construction of carbon–carbon bonds.[8]

The present work focuses on palladium-catalyzed cross-couplings as key reactions for condensation of two fragments. Such couplings have been applied successfully in the solid-phase mode, and are popular because of the generally mild conditions used that do not require strict exclusion of water or oxygen from solvent and atmosphere.[10] Specifically, Sonogashira coupling,[11] which involves coupling of aryl halides with alkynes, has been investigated. Solid-phase Sonogashira coupling was included as part of recently reported strategies to form furopyridines and furoquinolines.[12]

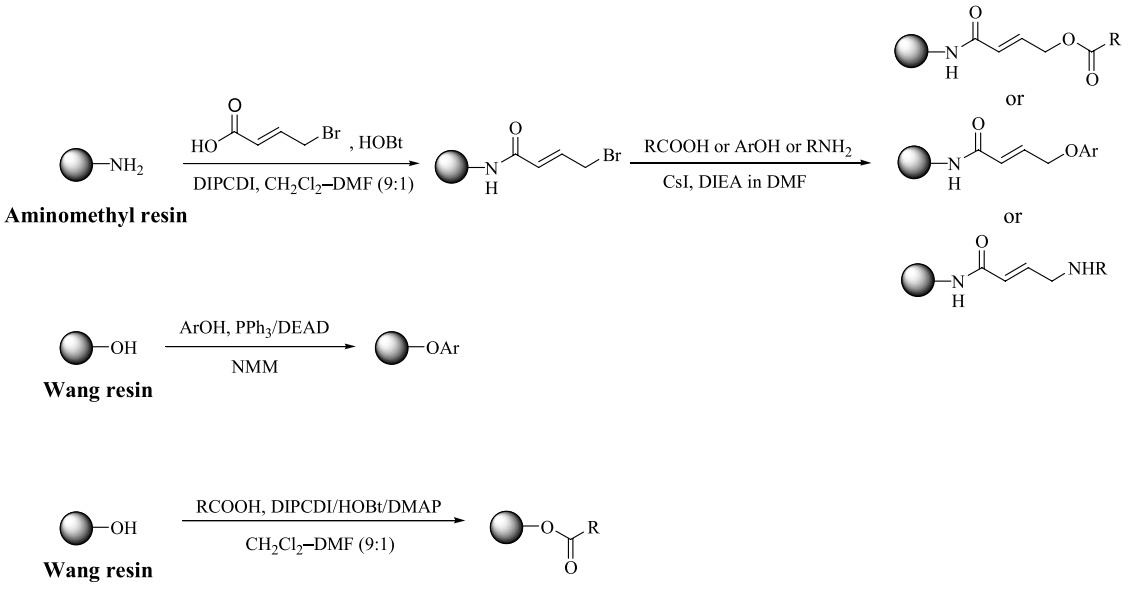
2. Results and discussion

2.1. Overall strategy

Three different strategies for resin-to-resin Sonogashira transfer can be envisaged (Scheme 2). These are: (A) attachment of an alkyne-substrate to an allyl resin, together with attachment of an iodo-containing molecule to a *p*-alkoxybenzyl ester (Wang) resin; (B) the opposite

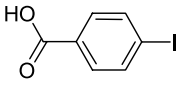
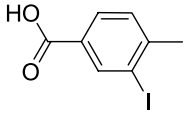
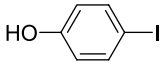
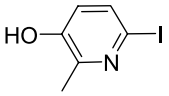
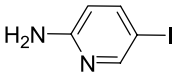
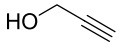


Scheme 2. Strategies for resin-to-resin Sonogashira transfer.



Scheme 3. Synthesis of starting resins.

Table 1. Efficiencies of loading various substrates onto solid supports[a]

Entry	Substrate	Yield (%)	
		Allyl resin[b]	Wang resin[c]
1		89	86
2		97	98
3		95[d]	70[d]
4		91	N.R.
5		92[d]	[e]
6		N.R.	96

[a] Anchoring chemistries are summarized in Scheme 3. Procedures are in Sections 4.1.3, 4.1.4, and 4.1.5. N.R. means no reaction.
[b] Yield determined by elemental analysis for residual Br, and compared to the theoretical loading.
[c] Yield determined by DMTCl test (Ref. 3) to measure the remaining free OH, which was compared to the theoretical loading.
[d] The reported yields involve two rounds of alkylation, following the procedure of Section 4.1.3.
[e] Not relevant because the substrate does not have a functional group that can react with Wang resin.

strategy, with the iodo-substrate anchored to an allyl resin and the alkyne moiety linked to Wang resin; and (C) attachment of both components to the solid support via an allyl linker. In the first two of these, Pd(0) treatment effects cleavage of a molecule from the allyl resin and also catalyzes the subsequent coupling to the second resin; later, TFA treatment releases the Sonogashira coupling product into solution. In the third strategy, both components are released upon exposure to Pd(0), and Sonogashira coupling occurs in solution.

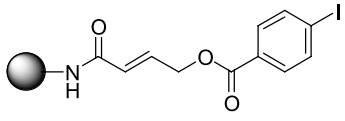
2.2. Synthesis of starting resins

RRTR strategies require appropriate 'donor' and 'acceptor' resins. For construction of the allyl resin, a 2-bromocrotonic acid linker[13] was added to an aminomethyl resin (1.6 mmol/g) by *N*,*N*′-diisopropylcarbodiimide (DIPCDI)-mediated coupling (Scheme 3). Carboxylic acids, phenols, and anilines were then loaded in the presence of CsI and *N*,*N*-diisopropylethylamine (DIEA) in *N*,*N*-dimethylformamide (DMF). For the 'acceptor' Wang-type resins (0.82–1.2 mmol/g), Mitsunobu coupling allowed for attachment of phenol and alcohol moieties, whereas carboxylic acids were loaded by treatment with DIPCDI, 1-hydroxybenzotriazole (HOBt), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP). In most cases, substrates were incorporated in moderate to excellent yields, after a single coupling or (occasionally) repeat coupling (Table 1). For allyl resins, yields ranged from 89 to 97%, whereas for Wang resin, yields were between 70 and 96%.

2.3. Cleavage efficiencies

Previous studies to optimize conditions for cleavage of amino acids and peptides from allyl resins have shown that nucleophiles such as morpholine and nBu$_3$SnH act as good allyl scavengers, and Pd(PPh$_3$)$_4$ is the catalyst that usually gives the best results.[14] Since a goal of this work was to effect concomitant cleavage/Sonogashira coupling, additional conditions reported for Sonogashira chemistry were explored.[11] These included the use of piperidine, DIEA, Et$_2$NH or Et$_3$N as bases, THF as solvent, and Pd(PPh$_3$)$_4$ or Pd(PPh$_3$)$_2$Cl$_2$ as catalysts. In the cases under consideration, cleavages from allyl resins were optimal, at

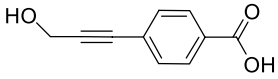
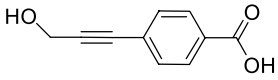
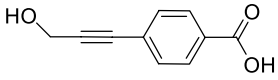
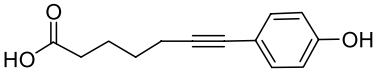
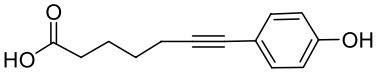
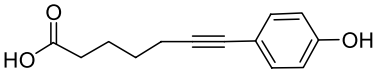
Table 2. Efficiencies of Pd(0)-mediated cleavages of resin-bound *p*-iodobenzoic acid[a]



Entry	Catalyst (equiv)	Base (mL)	Solvent (mL)	Time (h)	Temp (°C)	Purity (%)	Yield (%)
1	Pd(PPh$_3$)$_4$ (0.3)	Piperidine (1.0)	THF (1.0)	13	65	76	12
2	Pd(PPh$_3$)$_4$ (1.0)	Piperidine (1.0)	THF (1.0)	19	65	81	21
3	Pd(PPh$_3$)$_2$Cl$_2$ (2.0)	Piperidine (1.0)	THF (1.0)	18	50	75	15
4	Pd(PPh$_3$)$_4$ (1.0)	Morpholine (0.44)	CH$_2$Cl$_2$–H$_2$O (49:1) (5.0)	24	25	89	57
5	Pd(PPh$_3$)$_2$Cl$_2$ (2.0)	DIEA (0.6)	THF (6.0)	24	25	91	48
6	Pd(PPh$_3$)$_2$Cl$_2$ (2.0)	DIEA (2.8)	THF (6.0)	24	25	88	41
7	Pd(PPh$_3$)$_2$Cl$_2$ (2.0)	Et$_3$N (2.2)	THF (6.0)	24	25	—	0
8	Pd(PPh$_3$)$_2$Cl$_2$ (2.0)	Et$_2$NH (0.43)	THF (7.0)	24	25	75	14
9	Pd(PPh$_3$)$_2$Cl$_2$ (1.0)	Bu$_3$SnH (0.1)	CH$_2$Cl$_2$ (3.0)	24	25	82	8
10	Pd(PPh$_3$)$_4$ (0.15)	Morpholine (0.7)	THF–DMSO–0.5 N aqueous HCl (2:2:1) (1.25)	23	25	71	58
11	Pd(PPh$_3$)$_4$ (0.15)	Morpholine (2.7)	THF–0.5 N aqueous HCl) (1:1) (3.0)	19	25	67	43
12	Pd(PPh$_3$)$_2$Cl$_2$ (0.15)	Morpholine (2.7)	THF–DMSO–0.5 N aqueous HCl (2:2:1) (3.0)	24	25	76	14

[a] The substrate resin for cleavage (100 mg), prepared according to Section 4.1.2, was treated and analyzed further as described in Section 4.1.6. All equivalents are with respect to the theoretical maximum loading (1.6 mmol/g). Yield was calculated based on the weight of product obtained, normalized for the purity determined by analytical HPLC, and compared to the theoretical maximum based on the loading (1.6 mmol/g) of the starting resin.

Table 3. Sonogashira RRTR using Strategy A[a]

Entry	Product	Conditions	Purity (%)	Yield (%)
1		$Pd(PPh_3)_2Cl_2$ (2.0 equiv), CuI (0.1 equiv), DIEA (25 equiv), THF	81	34
2		$Pd(PPh_3)_4$ (1.0 equiv), CuI (0.1 equiv), morpholine (50 equiv), CH_2Cl_2–H_2O (49:1)	77	47
3		$Pd(PPh_3)_4$ (0.15 equiv), CuI (0.1 equiv), morpholine (50 equiv), THF–DMSO–0.5 N aqueous HCl (2:2:1)	86	7
4		$Pd(PPh_3)_2Cl_2$ (2.0 equiv), CuI (0.1 equiv), DIEA (25 equiv), THF	84	41
5		$Pd(PPh_3)_4$ (1.0 equiv), CuI (0.1 equiv), morpholine (50 equiv), CH_2Cl_2–H_2O (49:1)	71	26
6		$Pd(PPh_3)_4$ (0.15 equiv), CuI (0.1 equiv), morpholine (50 equiv), THF–DMSO–0.5 N aqueous HCl (2:2:1)	—	0

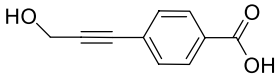
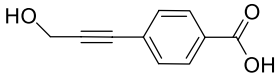
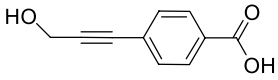
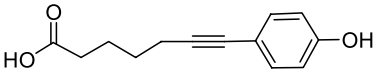
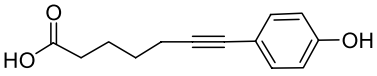
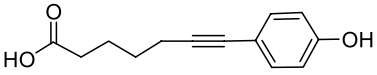
[a] The substrate resins (100 mg), prepared according to Sections 4.1.3 and 4.1.4, were treated and analyzed further as described in Section 4.1.7. All equivalents are with respect to the theoretical maximum loading (1.2 mmol/g). Cleavages were performed by treatment with TFA–CH_2Cl_2 (1:1) for 90 min. Purity refers to the relative area upon analytical HPLC of the main peak. Yield was calculated based on the weight of product obtained, normalized for the purity determined by analytical HPLC, and compared to the theoretical maximum based on the loading (1.2 mmol/g) of the starting resin.

25 °C with $Pd(PPh_3)_4$ and morpholine in CH_2Cl_2–H_2O (49:1) or THF–DMSO–0.5 N aqueous HCl (2:2:1) (Table 2, entries 4 and 10). The catalyst $Pd(PPh_3)_2Cl_2$, used in conjunction with DIEA in THF, also gave moderate yields (Table 2, entry 5). Elevated temperatures did not improve yields (Table 2, entries 1–3).

2.4. Resin-to-resin Sonogashira transfer reactions

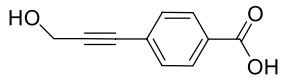
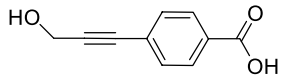
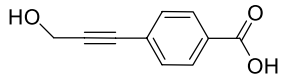
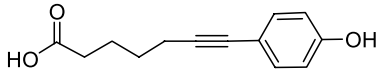
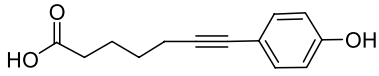
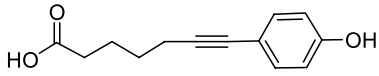
Conditions described in the previous section were studied for Sonogashira RRTR (Scheme 2; Tables 3–5). For strategy A (Table 3), where the alkyne moiety is linked to the allyl resin and the iodophenol moiety is anchored to Wang resin [eventually released, after RRTR, by treatment with TFA–CH_2Cl_2 (1:1)], the system $Pd(PPh_3)_4$/CuI/morpholine in THF–DMSO–0.5 N aqueous HCl (2:2:1), which was best for cleavage, gave very low yields for coupling (Table 3, entries 3 and 6). For two other systems tested, $Pd(PPh_3)_2Cl_2$/CuI/DIEA in THF and $Pd(PPh_3)_4$/CuI/morpholine in CH_2Cl_2–H_2O (49:1), overall yields ranged from 26 to 47% (Table 3, entries 1, 2, 4, and 5). For strategy B (Table 4), where the iodophenol is linked to the allyl resin,

Table 4. Sonogashira RRTR using strategy B[a]

Entry	Product	Conditions	Purity (%)	Yield (%)
1		$Pd(PPh_3)_2Cl_2$ (2.0 equiv), CuI (0.1 equiv), DIEA (25 equiv), THF	81	41
2		$Pd(PPh_3)_4$ (1.0 equiv), CuI (0.1 equiv), morpholine (50 equiv), CH_2Cl_2–H_2O (49:1)	74	44
3		$Pd(PPh_3)_4$ (0.15 equiv), CuI (0.1 equiv), morpholine (50 equiv), THF–DMSO–0.5 N aqueous HCl (2:2:1)	—	0
4		$Pd(PPh_3)_2Cl_2$ (2.0 equiv), CuI (0.1 equiv), DIEA (25 equiv), THF	83	28
5		$Pd(PPh_3)_4$ (1.0 equiv), CuI (0.1 equiv), morpholine (50 equiv), CH_2Cl_2–H_2O (49:1)	79	35
6		$Pd(PPh_3)_4$ (0.15 equiv), CuI (0.1 equiv), morpholine (50 equiv), THF–DMSO–0.5 N aqueous HCl (2:2:1)	—	0

[a] The substrate resins (100 mg), prepared according to Sections 4.1.3 and 4.1.4, were treated and analyzed further as described in Section 4.1.7. All equivalents are with respect to the theoretical maximum loading (1.2 mmol/g). Cleavages were performed by treatment with TFA–CH_2Cl_2 (1:1) for 90 min. Purity refers to the relative area upon analytical HPLC of the main peak. Yield was calculated based on the weight of product obtained, normalized for the purity determined by analytical HPLC, and compared to the theoretical maximum based on the loading (1.2 mmol/g) of the starting resin.

Table 5. Sonogashira RRTR using strategy C[a]

Entry	Product	Conditions	Purity (%)	Yield (%)
1		$Pd(PPh_3)_2Cl_2$ (2.0 equiv), CuI (0.1 equiv), DIEA (25 equiv), THF	78	47
2		$Pd(PPh_3)_4$ (1.0 equiv), CuI (0.1 equiv), morpholine (50 equiv), CH_2Cl_2–H_2O (49:1)	69	61
3		$Pd(PPh_3)_4$ (0.15 equiv), CuI (0.1 equiv), morpholine (50 equiv), THF–DMSO–0.5 N aqueous HCl (2:2:1)	82	21
4		$Pd(PPh_3)_2Cl_2$ (2.0 equiv), CuI (0.1 equiv), DIEA (25 equiv), THF	80	42
5		$Pd(PPh_3)_4$ (1.0 equiv), CuI (0.1 equiv), morpholine (50 equiv), CH_2Cl_2–H_2O (49:1)	79	55
6		$Pd(PPh_3)_4$ (0.15 equiv), CuI (0.1 equiv), morpholine (50 equiv), THF–DMSO–0.5 N aqueous HCl (2:2:1)	86	13

[a] The substrate resins (100 mg), prepared according to Section 4.1.3, were treated and analyzed further as described in Section 4.1.7. All equivalents are with respect to the theoretical maximum loading (1.6 mmol/g). Purity refers to the relative area upon analytical HPLC of the main peak. Yield was calculated based on the weight of product obtained, normalized for the purity determined by analytical HPLC, and compared to the theoretical maximum based on the loading (1.6 mmol/g) of the starting resin.

and the alkyne moiety is anchored to Wang resin, results were similar. Overall yields ranged between 28 and 44% in the two better systems, and were poor in the system optimized for cleavage.

Strategy C (Table 5) gave the overall best results. In this case, both substrates are anchored to allyl resins, and Pd(0) treatments effecting cleavage of the substrates and subsequent coupling in solution gave yields ranging from 42 to 61%. (Table 5, entries 1, 2, 4, and 5). Thus, Sonogashira coupling chemistry is more efficient when both components are free in solution.

Note that for the more successful RRTR sequences (Strategies A, B, C; Tables 3–5), palladium is required in levels equimolar or higher to the resin-bound substrate. Thus, it is difficult to establish whether or not the metal serves as a true catalyst. A mechanistic explanation for these empirical observations is not yet forthcoming.

3. Conclusions

The Sonogashira reaction has been evaluated as a transfer reaction between two resins for solid-phase synthesis. In transfer reactions, two converging fragments of a molecule are synthesized, each on a different support, and then coupled. The best results in the present studies were obtained when both substrates were anchored to allyl resins. Release of the two moieties by Pd(0), and subsequent coupling in solution gave up to 61% yield. This strategy, or variations thereof, should be applicable to SPOS of complex molecules, with the opportunity to avoid tedious purification of intermediates.

4. Experimental

4.1. General

Wang resin and aminomethyl resin, both based on 1% crosslinked polystyrene, were purchased from Novabiochem (Läufelfingen, Switzerland). CH_2Cl_2 was distilled from CaH_2, and tetrahydrofuran (THF) was distilled from sodium/benzophenone. Sonogashira couplings were carried out in capped vials under argon atmosphere. Analytical HPLC was performed on a Beckman instrument configured with two 112 pumps and a 165 wavelength variable detector, using a Vydac C18 analytical reversed-phase column (210TP54; 5 μm particle size; 300 Å; 0.46×25 cm) with UV detection at 220 and 280 nm. Linear gradients of 0.1% aqueous TFA–0.1% TFA in CH_3CN were run, at 1.2 mL/min flow rate, from 9:1 to 1:1 over 40 min. Preparative HPLC was carried out on a Waters instrument using a Vydac C18 semi-preparative reversed-phase column (218TP1010; 10 μm particle size; 300 Å; 1×25 cm) with UV detection at 220 and 280 nm, using H_2O and CH_3CN as eluents. Linear gradients of 0.1% aqueous TFA–0.1% TFA in CH_3CN were run, at 5.0 mL/min flow rate, from 9:1 to 1:1 over 60 min. ^1H NMR spectra were acquired on a Varian VI-500 spectrometer. Fast atom bombardment mass spectroscopy (FABMS) was performed on a VG7070E-HF mass spectrometer.

4.1.1. 2-Bromocrotonic acid. Following the literature,[13] crotonic acid (20 g, 0.23 mol) and *N*-bromosuccimide (NBS) (46 g, 0.25 mol) were dissolved in dry toluene (200 mL) and brought to reflux. 2,2′-Azobisisobutyronitrile (AIBN) (0.5 g, 3.7 mmol) was added, and reflux was continued for 2 h. Next, the reaction was cooled to 10 °C, filtered, and the filtrate was evaporated. Recrystallization

from cold CCl_4 gave the title product as a white crystalline solid (17.7 g, 47%). ^{1}H NMR ($CDCl_3$) δ 7.12 (dd, J=7.5, 1.5 Hz, 1H), 6.05 (dd, J=15.5, 1.5 Hz, 1H), 4.04 (dd, J=7.5, 1.5 Hz, 2H). FAB-MS *m/z* calcd 163.9, found 165.0 $[M+H]^+$.

4.1.2. Attachment of 2-bromocrotonic acid to aminomethyl resin. Title resin (1.0 g, 1.6 mmol/g) was washed with CH_2Cl_2 (3×2 min) and swollen in CH_2Cl_2–DMF (9:1) (6 mL). 2-Bromocrotonic acid (0.79 g, 4.8 mmol) and 1-hydroxybenzotriazole (HOBt) (0.74 g, 4.8 mmol) were dissolved in DMF (0.9 mL), and added to the resin. Next, reaction was initiated by addition of *N*,*N*′-diisopropylcarbodiimide (DIPCDI) (0.74 mL, 4.8 mmol), and the reaction proceeded for 24 h at 25 °C. The resin was washed with DMF (3×2 min) and CH_2Cl_2 (3×2 min) and the coupling was repeated once more. Yield: 98% (determined from DMTCl test[3]).

4.1.3. Representative procedure for loading of substrates onto 2-bromocrotonyl-resin.[15] The title resin (0.45 g, 1.6 mmol/g) was suspended in DMF (2 mL) and reacted with *p*-iodobenzoic acid (0.71 g, 2.88 mmol), cesium iodide (0.75 g, 2.88 mmol), and DIEA (0.50 mL, 2.88 mmol) at 40 °C overnight, in the presence of several (~10 spheres) 3 Å molecular sieves. Upon completion of the reaction, the sieves were separated manually with a tweezer, and the remaining brown resin was washed with DMF (3×1 min), MeOH (3×1 min), and CH_2Cl_2 (3×1 min), and dried in vacuo overnight. Yield: 89% (determined by elemental analysis on residual Br). The same overall procedure, applied to five other substrates, was carried out as summarized further in Table 1, with yields listed under the column 'Allyl resin'.

4.1.4. Representative procedure for loading of carboxylic acids onto Wang resin. Title resin (1.0 g, 1.0 mmol/g) was washed with CH_2Cl_2 (3×1 min) and DMF (3×1 min), and swollen in CH_2Cl_2–DMF (9:1). In a vial, *p*-iodobenzoic acid (0.99 g, 4.0 mmol) and HOBt (0.61 g, 4.0 mmol) were dissolved in DMF (2 mL), and added to the resin. Coupling was initiated by addition of DIPCDI (0.6 mL, 4.0 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) (12 mg, 0.1 mmol), and the reaction proceeded overnight at 25 °C. The resin was washed with DMF (3×2 min) and CH_2Cl_2 (3×2 min), and dried. Yield: 86% (determined from DMTCl test[3]). The same overall procedure, applied to 3-iodo-4-methylbenzoic acid, gave a 98% yield.

4.1.5. Representative procedure for loading of phenols onto Wang resin. Title resin (0.75 g, 0.82 mmol/g) was washed with CH_2Cl_2 (3×1 min) and DMF (3×1 min). In a round-bottom flask, *p*-iodophenol (2.75 g, 12.5 mmol) was dissolved in *N*-methylmorpholine (NMM) (50 mL), PPh_3 (3.28 g, 12.5 mmol) was added, and the suspension was stirred for 10 min until a clear solution was obtained. Next, diisopropylazadicarboxylate (DIAD) (1.80 mL, 11.3 mmol) was added dropwise, followed by addition of the Wang resin (0.75 g, 0.82 mmol/g). The reaction was mechanically stirred for 40 h at 25 °C, then washed with DMF (5×2 min) and CH_2Cl_2, (5×2 min), and finally dried. Yield: 70% (determined by DMTCl test[3]). The same overall procedure was unsuccessful for 6-iodo-2-picolin-5-ol, and gave a 96% yield for propargyl alcohol (Table 1).

4.1.6. Representative procedure for cleavage of *p*-iodobenzoic acid from allyl resin. Resin-bound iodobenzoic acid (100 mg), prepared according to Section 4.1.2, was combined with the reagents and solvents indicated in Table 2, as well as CuI (3 mg, 0.1 equiv). After reaction for the indicated time under ambient conditions or with heating, the resin was filtered. The filtrate was combined with H_2O (1 mL), and the organic phase was separated, washed with H_2O (3×1 mL) and brine (1×1 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH (1 mL) and injected in the HPLC. Purities reported on Table 2 refer to the relative area upon analytical HPLC of the main peak, which corresponded to an authentic standard of *p*-iodobenzoic acid.

4.1.7. General procedure for Sonogashira resin-to-resin transfer reactions. The procedures for the three strategies studied were essentially the same (see Tables 3–5). Resin-bound *p*-iodobenzoic acid (62.5 mg, 1.6 mmol/g) and resin-bound propargyl alcohol (100 mg, 1.2 mmol/g) were weighed in a vial, and the appropriate solvent (~5 mL) was added. After swelling the resins for 15 min, CuI (3 mg, 0.1 equiv) and the Pd catalyst (see Tables) were added, the vial was capped with a septum, and argon was flushed through for 15 min. The reaction mixture was agitated on a mechanical shaker for the appropriate time, and was then transferred to a polypropylene syringe. For strategies A and B, the reagents were drained and the resins were washed with THF (10×0.5 min), DMF (5×1 min), 0.02 M sodium diethyl dithiocarbamate in DMF (3×15 min), DMF (3×1 min) and CH_2Cl_2 (5×1 min). Cleavage was effected by treatment with TFA–CH_2Cl_2 (1:1) for 1 h. For strategy C, the reagents were drained and the resins washed with THF (10×0.5 min), DMF (5×1 min), and CH_2Cl_2 (5×1 min). The filtrate was evaporated, dissolved in EtOAc (2 mL) and washed with H_2O (3×2 mL), and brine (2×1 mL), dried ($MgSO_4$) and evaporated.

4.1.8. 4-(3-Hydroxy-1-propynyl)benzoic acid. After the experiment described in Table 5, entry 2, was carried out, the product mixture was concentrated and applied to preparative HPLC and eluted with H_2O–CH_3CN using experimental conditions described in Section 4.1, to provide the pure material which was characterized further: ^{1}H NMR (DMSO-d_6) δ 10.4 (broad s, 1H), 7.94 (d, J=8.4 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H), 4.24 (s, 2H). FAB-MS *m/z* calcd 176.0, found 176.9 $[M+H]^+$. This compound was obtained previously by Bumagin and co-workers[16] using an all-solution Sonogashira coupling.

4.1.9. 7-(4-Hydroxyphenyl)-6-heptynoic acid. After the experiment described in Table 5, entry 5 was carried out, a similar HPLC purification gave the characterizable material: ^{1}H NMR ($CDCl_3$) δ 6.83 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 2.34 (t, J=7.2 Hz, 2H), 1.98 (t, J=7.0 Hz, 2H), 1.52 (m, 4H). FAB-MS *m/z* calcd 218.1, found 219.3 $[M+H]^+$.

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Carboxylic acids as promoters for internucleotide-bond formation via condensation of a nucleoside phosphoramidite and a nucleoside: relationship between the acidity and the activity of the promoter

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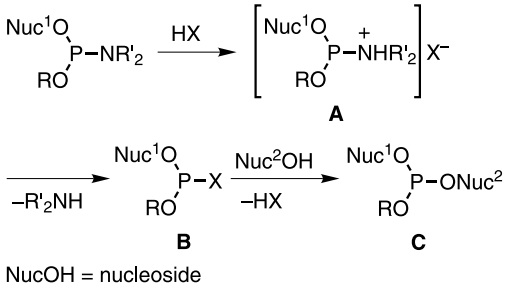
Abstract—The relationship between the activity and the acidity of a carboxylic acid as a promoter for condensation of a nucleoside phosphoramidite and a nucleoside was investigated. The investigation revealed that the acid, the p*K*a value of which in acetonitrile is less than 18, is capable of promoting the condensation reaction, and acid with a p*K*a value outside of this range does not serve as a promoter. In carboxylic acids serving as promoters, the ones with higher acidity generally show greater activity. In particular, acids with a p*K*a value less than ca. 16 (measured by a potentiometric method), such as trichloroacetic acid (p*K*a = 10.6), trifluoroacetic acid (p*K*a = 12.7), dichloroacetic acid (p*K*a = 13.2 or 15.8), and 2,4-dinitrobenzoic acid (p*K*a = 16.1), show high levels of activity higher than that of conventionally used 1*H*-tetrazole. These carboxylic acids generally serve as excellent promoters for both the liquid-phase and the solid-phase synthesis of oligonucleotides via phosphoramidite method.

1. Introduction

In nucleotide synthesis conducted via phosphoramidite method, one of the most important issues has been the invention of a useful promoter for the condensation of a nucleoside phosphoramidite and a nucleoside, forming an internucleotidic phosphityl linkage.[1] Previous investigations[2] have suggested that condensation using HX as a promoter can be achieved via mechanism shown in Scheme 1. Thus, the reaction is initiated by protonation of the phosphoramidite by HX. Then, the protonated phosphoramidite **A** undergoes the nucleophilic attack of X^-, which is generated in the first step, to produce an intermediate **B** with a P–X bond. Finally, this species reacts with a nucleoside to give a dinucleoside phosphite **C**. In this process, the rate-determining step is the condensation of the protonated phosphoramidite **A** and X^-. Accordingly, when HX is sufficiently acidic, thereby giving a high concentration of the protonated phosphoramidite, and X^- is sufficiently nucleophilic to react with the protonated phosphoramidite, HX becomes a promoter with high reactivity.[3]



Scheme 1. A suggested mechanism of condensation of a nucleoside phosphoramidite and a nucleoside using HX as a promoter.

Carboxylic acids may fulfil these requirements and accordingly are expected to serve as effective promoters for this reaction.[4] Currently, 1*H*-tetrazole and its derivatives are conventionally used as the promoters, kinds of which are limited. In contrast, there are many alternative carboxylic acids available. Therefore, in cases when carboxylic acids are useful, the choice of promoters is greatly increased.

Keywords: Nucleotides; Phosphoramidites; Carboxylic acids.
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Table 1. Activity of promoters[a]

Promoter	p*K*a value in CH_3CN[b]	Yield of **25** (%)	
		1 min	5 min
Trichloroacetic acid (**1**)	10.6	99	ND[c]
2,6-Dihydroxybenzoic acid (**2**)	12.6	ND	2
Trifluoroacetic acid (**3**)	12.7	82	99
Dichloroacetic acid (**4**)	13.2 or 15.8	90	99
2,4-Dinitrobenzoic acid (**5**)	16.1	81	99
Salicylic acid (**6**)	16.7	ND	0
3,5-Dinitrobenzoic acid (**7**)	17.0	55	76
2,6-Dichlorobenzoic acid (**8**)	17.6	46	74
2-Nitrobenzoic acid (**9**)	18.2	42	76
4-Nitrobenzoic acid (**10**)	18.7	ND	5
Benzoic acid (**11**)	20.7	ND	3
4-hydroxybenzoic acid (**12**)	20.8	ND	0
Acetic acid (**13**)	22.3	ND	0
1*H*-Tetrazole	14.5[d]	15	55
BIT	14.3[d]	97	ND

[a] Estimated by yield of the product **25** (^{31}P NMR measurement) obtained by 1- and/or 5-min reaction of **17** and **20**, followed by TBHP oxidation.
[b] Unless otherwise stated, the values were determined by the potentiometric method reported in Ref. 7.
[c] Not determined.
[d] Data determined by ^{13}C NMR analysis reported in Ref. 6.

Thus, it was considered of potential benefit to investigate the utility of carboxylic acids as promoters[5] of the condensation of a nucleoside phosphoramidite and a nucleoside. Furthermore, the present investigation is expected to provide potential solutions to the following important problem. As mentioned above, the promoter must be highly acidic. ?A3B2 tlsb=.01w?>However, it is difficult to anticipate how strong an acid must be in order to serve as an efficient promoter, because there are no systematic investigations of the relationship between the acidity and the activity of the promoter. The reason why there are no such investigations is that it is difficult to assess the acidity of the existing promoters such as the tetrazole derivatives[6] in acetonitrile, a solvent generally used for this type of reaction. In contrast, the p*K*a values of various carboxylic acids in acetonitrile have been reported in the literature.[7] Thus, an investigation of the activity of various kinds of carboxylic acids may provide us valuable information for solving the problem regarding how high acidity is required to an acid for serving as a good promoter. This paper describes the results of an investigation of these two subjects, that is, determining the utility of carboxylic acids as promoters for the formation of internucleotidic phosphite linkages using the phosphoramidite approach, and describing the relationship between the activity of the promoter and its acidity in acetonitrile.

2. Results and discussion

We selected carboxylic acids **1**–**13**, the acidities of which, when in acetnitrile, have been reported as shown in Table 1.[7] First, we screened these acids in terms of their ability to promote the condensation of the thymidine 3′-phosphoramidite **17** and the 5′-*O*-free thymidine **20**. Since the dinucleoside phosphite formed by this condensation reaction is too unstable to undergo various types of analysis, the activity of the promoter in this series of examinations was not determined at the stage of the formation of the phosphite. Consequently, we estimated the activity according to the yield of the dinucleoside phosphate **25**, which was quantitatively obtained by oxidizing the dinucleoside phosphite. The condensation reaction was carried out using **17** (48 μmol), **20** (40 μmol), and a promoter (48 μmol)[8] in the presence of powdery molecular sieves 3A[9] in acetonitrile (1 mL) (25 °C, 1–5 min), and the resulting phosphite product was converted to **25** by oxidation with a 1.0 M TBHP/toluene solution.[10] As a control experiment, the synthesis was also carried out in a similar manner using 1*H*-tetrazole or benzimidazolium triflate (BIT)[11] as a promoter for the first step. The yield of **25** was determined by ^{31}P NMR analysis. Table 1 lists the promoters examined, their p*K*a values in acetnitrile, and the respective yields of **25**.[12] The results indicated that the acidity of the promoter closely correlated with the activity of the promoter. Roughly, acids with p*K*a values in acetonitrile of less than 18.2 (measured by a potentiometric method) are capable of promoting such condensation, but acids bearing p*K*a values outside of this range do not serve as promoters. Among the acids capable of serving as promoters, those with smaller p*K*a values, that is, stronger acids, generally show higher reactivity, as shown in Figure 1. Acids with a p*K*a value lower than ca. 16 [e.g., trichloroacetic acid (p*K*a = 10.6), trifluoroacetic acid (p*K*a = 12.7), dichloroacetic acid (p*K*a = 13.2 or 15.8), and 2,4-dinitrobenzoic acid (p*K*a = 16.1)] show particularly favorable activity similar to that of BIT, and a higher level of activity than that achieved with 1*H*-tetrazole.[13] Surprisingly, no cleavage of the 5′-*O*-DMTr group was observed in the reactions, using trichloroacetic acid, trifluoroacetic acid, and dichloroacetic acid, which easily eliminate the DMTr protector in dichloromethane. Here, in order to avoid the detritylation, it is crucial to use the acid promoter in an equal molar amount or less than that of the phosphoramidite. When the acid promoter was used excessively, the detritylation took place to considerable extent. In spite of their low p*K*a values, 2-hydroxybenzoic acids, such as 2,6-dihydroxybenzoic acid (p*K*a = 12.6) and salicylic acid (p*K*a = 16.9), did not serve as good promoters.

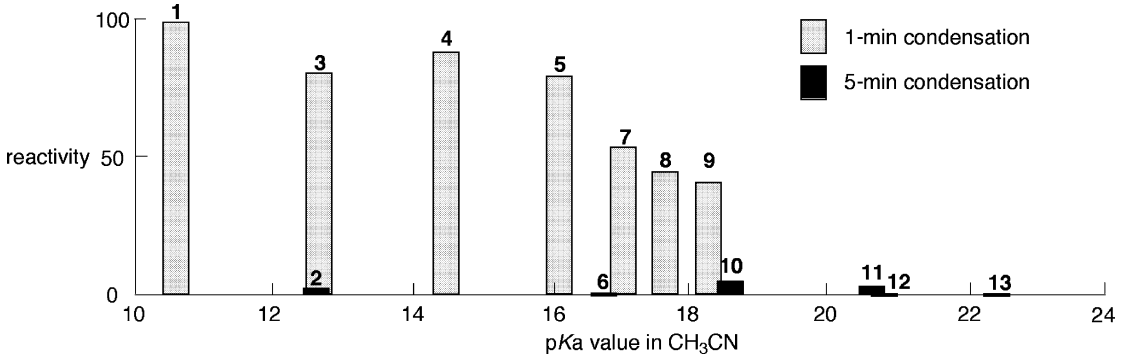
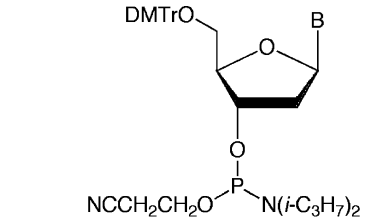
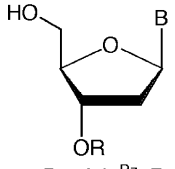


Figure 1. Relationship between p*K*a and reactivity of the promoter in CH_3CN estimated by yield of the product **25** (^{31}P NMR measurement) obtained by 1- or 5-min condensation of **17** and **20**, followed by TBHP oxidation. The p*K*a of **4** was plotted at the average value of the reported ones.

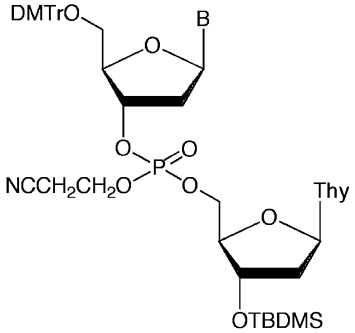
Using either of these acids as a promoter, the synthesis of **25** from **17** and **20** afforded the desired product in a lower than 10% yield, and gave many undesired products.



14, B = Ade^{Bz}
15, B = Cyt^{Bz}
16, B = Gua^{Ibu}
17, B = Thy

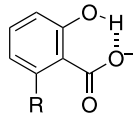


18, B = Ade^{Bz}; R = TBDMS
19, B = Gua^{Ibu}; R = TBDMS
20, B = Thy; R = TBDMS
21, B = Thy; R = CO(CH$_2$)$_2$CONH–CPG



22, B = Ade^{Bz}
23, B = Cyt^{Bz}
24, B = Gua^{Ibu}
25, B = Thy

It remains unclear why the reactions using a nonhydroxy-substituted benzoic acid or a 2-hydroxybenzoic acid as the promoter gave such different results from each, but the following explanation might account for the difference. By protonation, the nonhydroxy-substituted benzoic acid may produce a carboxylate with good nucleophilicity, and a reaction may take place with the activated phosphoramidite to form a sufficient amount of the phosphorous/carboxylic-mixed anhydride, which corresponds to the reactive species **B** shown in Scheme 1. In contrast, the 2-hydroxybenzoic acid may generate a carboxylate such as **26**, which lacks nucleophilicity, because the anionic carboxylic oxygen atom is masked by chelation with the hydrogen of the 2-hydroxy group. Therefore, the carboxylate function is not sufficiently capable of nucleophilically attacking the protonated phosphoramidite to form the reactive phosphorous/carboxylic-mixed anhydride.[14] Indeed, this interpretation of the results was supported by ^{31}P NMR studies of the reaction of **17** and 2,4-dinitrobenzoic acid or salicylic acid. Thus, the reaction of equimolar amounts of **17** (diastereomers; ^{31}P signals: δ 148.6 and 148.7 ppm) and 2,4-dinitrobenzoic acid in the absence of a nucleoside in CD_3CN formed the corresponding phosphorous/carboxylic mixed anhydride with a ^{31}P signal at δ 133.5 ppm [cf. $(n\text{-}C_4H_9O)_2POCOCH_3$: δ 132 ppm[4]]. This anhydride was then instantaneously consumed by the addition of **20** to quantitatively give the corresponding phosphite, producing a ^{31}P signal at δ 140 ppm. On the other hand, no formation of the phosphorous/carboxylic-mixed anhydride species was observed in the reaction using salicylic acid as the promoter. In this case, three ^{31}P signals appeared at δ 123.1, 123.3, and 123.7 ppm due to species other than the phosphorous/carboxylic-mixed anhydride.



26, R = H or OH

We next selected trichloroacetic acid and 2,4-dinitrobenzoic acid as the representative carboxylic acids, which showed high reactivity in the above-mentioned test, in order to investigate their general utility as promoters for internucleotide-linkage formation using nucleoside 3′-phosphoramidites other than **17**, such as **14**, **15**, and **16**. In this series of investigations, the reaction was carried out using 0.12 mmol of a nucleoside phosphoramidite, 0.10 mmol of a nucleoside, and 0.11 mmol of trichloroacetic acid or 0.12 mmol of 2,4-dinitrobenzoic acid in acetonitrile (1.0 mL) containing MS 3A, and thus the concentration of reactants (0.10–0.12 M) was higher than that (40–48 mM)

Table 2. Synthesis of dideoxyribonucleoside phosphates using **1** or **5** as a promoter

Amidite	Promoter	Product	Yield (%)[a]
14	**1**	**22**	99, 93[b]
14	**5**	**22**	99, 93[b]
15	**1**	**23**	98, 96[b]
15	**5**	**23**	99, 93[b]
16	**1**	**24**	98
16	**5**	**24**	99
17	**1**	**25**	99, 92[b]
17	**5**	**25**	99, 97[b]

[a] Estimated by ^{31}P NMR analysis.
[b] Isolated yield.

used in the above-mentioned test. The reaction using either acid as the promoter was completed in 5 min, and the subsequent oxidation with TBHP for 10 min gave dinucleoside phosphates **22**–**25** in excellent yields as shown in Table 2. In the preparation of these compounds, no side-reaction, not even depurination or detritylation, was detected.

The approach using trichloroacetic acid as the promoter could be applied to the solid-phase synthesis of oligonucleotides using the phosphormaidites **14**, **15**, **16**, and **17** as building blocks. For example, $^{5'}$GpApCpTpCpTpCpTpTpApGpCpTpApApT$^{3'}$ (**27**) was prepared starting from the nucleoside **21** attached to a controlled-pore glass (CPG) on an Applied Biosystems Model 392 DNA/RNA synthesizer, according to the procedure shown in Table 3. The synthesis was investigated, in which the coupling step was carried out by the following two methods: soon after mixing a 0.1 M solution of a phosphoramidite and a 0.08 M solution of trichloroacetic acid, the resulting mixture was delivered over 15 s (method A) or 30 s (method B) into the reaction column. As control experiments, we also carried out the synthesis where a 0.35 M (method C) or 0.08 M (method D) solution of 1*H*-tetrazole for the activation of the phosphoramidite was used in the coupling step and, after mixing this solution with a 0.1 M solution of a phosphoramidite, the resulting mixture was delivered over 30 s into the reaction column. Here, method C is a current standard method conventionally used, and was carried out for comparing efficiency of this method with that of the novel methods using trichloroacetic acid as the promoter. On the other hand, method D was carried out to investigate efficiency of 1*H*-tetrazole as the promoter in the synthesis using the low concentration (0.08 M) of solution, which is a suitable one for trichloroacetic acid. Method A and method B gave similar results and the target oligonucleotide **27** was produced in an 88% overall yield (a 99% average coupling yield) by both these two methods. As shown in Figure 2, HPLC analysis indicated that the purity of the product was satisfactorily high, even in the crude form. These results were similar to that obtained by method C and much better than that obtained by method D

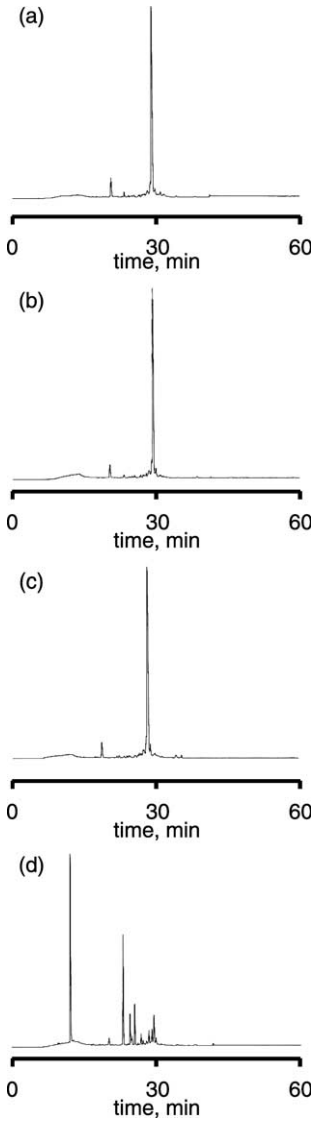


Figure 2. HPLC profile of the crude product of **27**. (a) Prepared by method A. (b) Prepared by method B. (c) Prepared by method C. (d) Prepared by method D. Conditions: column, COSMOSIL 5C_{18}-AR-II [4.6 (diameter) mm×25 (height) cm]; flow rate, 1.0 mL/min; detection, 254 nm; eluent and gradient, [A=a 100 mM triethylammonium acetate buffer solution in H_2O, B=a 20:80 mixture of H_2O and acetonitrile, 0–60 min with a linear gradient from A 100% to A 70%/B 30%]; temperature, 40 °C.

Table 3. Reaction sequence of the solid-phase synthesis

Step	Operation	Reagent(s)	Time (s)
1	Washing	CH_3CN	24
2	Detritylation	3% CCl_3COOH/CH_2Cl_2	77
3	Washing	CH_3CN	27
4	Coupling	0.1 M amidite/CH_3CN+0.08 M CCl_3COOH/CH_3CN	15–30
5	Washing	CH_3CN	14
6	Capping	Ac_2O/2,6-lutidine/THF (1:1:8)+*N*-methylimidazole/THF	15
7	Washing	CH_3CN	14
8	Oxidation	1.0 M *t*-C_4H_9OOH/toluene	30
9	Washing	CH_3CN	58

(see Fig. 2) to indicate that trichloroacetic acid has higher reactivity than that of 1*H*-tetrazole in the solid-phase synthesis.

3. Conclusion

In this study, we disclosed that various carboxylic acids serve as useful promoters for the formation of internucleotide linkage in acetonitrile via phosphoramidite approach. This investigation also revealed that the ability of a carboxylic acid (excluding a hydroxy-substituted carboxylic acid) to serve as a promoter depends on its p*K*a value in acetonitrile. Before the present study was conducted, it was assumed that strong acids such as trichloroacetic acid and trifluoroacetic acid could not be used as promoters, because the conjugate base, that is, the trichloroacetate or trifluoroacetate anion, would not exhibit sufficient nucleophilicity required for the promoter. However, this was fortunately not the case.[15] The present results indicated that, in considering the ability of carboxylic acids to serve as promoters, concern about the nucleophilicity of the corresponding carboxylate anions is unwarranted. In the case of carboxylic acids, acidity is the main factor controlling the promoter ability. In other words, it is possible to predict the ability of a carboxylic acid to serve as a promoter, provided its p*K*a value is known. In general, acids with low p*K*a value, that is, strong acids, have greater promoter activity, and acids with the p*K*a values lower than 16 (measured by a potentiometric method) exhibit the preferred reactivity. The result that trichloroacetic acid, with the p*K*a value of 10.6 in acetonitrile, served as an excellent promoter suggested that organosulfonic acids[16] or organophosphoric acids bearing similar acidity to that of trichloroacetic acid might also be used as promoters in the synthesis of nucleotides, according to a phosphoramidite strategy. Accordingly, investigation of the utility of organic acids other than carboxylic acids is ongoing in our laboratory. Results related to this topic will be reported in separate papers.

4. Experimental

4.1. General

Unless otherwise stated, the NMR spectra were obtained in $CDCl_3$ on a JEOL JNM-400 or ECA-500 instrument. The ^1H and ^{31}P NMR chemical shifts are described as values in ppm relative to $(CH_3)_4Si$ and 85% H_3PO_4, respectively. ESI-TOF HRMS spectra were measured using a Mariner spectrometer. HPLC analysis was carried out using a COSMOSIL 5C_{18}-AR-II column [Nacalai Tesque, 4.6 (diameter) mm×25 (height) cm] on a Waters 2695 Separations Module chromatograph with a Waters 2996 Photodiode Array Detector. Nacalai Tesque silica gel 60 (neutrality, 75 μm) was used for column chromatography. Unless otherwise stated, reactions were carried out at ambient temperature. Reactions requiring anhydrous conditions were carried out under an argon atmosphere in 10 or 20 mL Schlenk tubes dried by heating at 400 °C under reduced pressure (1–3 mm Hg). Trityl assay was carried out using a JASCO V-550 UV spectrometer. Solid-phase syntheses were conducted on an Applied Biosystems Model 392 DNA/RNA synthesizer using empty synthesis columns (TWIST from Glen Research).

4.2. Materials and solvents

Acetonitrile and CD_3CN were distilled from CaH_2. Powdery molecular sieves 3A (MS 3A) were used after drying the commercially supplied sieves (Nacalai Tesque) at 200 °C for 12 h. Other organic solvents were used after simple distillation of the commercially supplied solvents. Acetic acid purchased from Kishida was distilled from CrO_3 in the presence of acetic anhydride. Trichloroacetic acid supplied from Kishida was dried under reduced pressure (1–3 mm Hg) for >2 h before use. 2,6-Dihydroxybenzoic acid (Aldrich), trifluoroacetic acid (Kishida), dichloroacetic acid (Tokyo Kasei), 2,4-dinitrobenzoic acid (ACROS), salicylic acid (Kishida), 3,5-dinitrobenzoic acid (Tokyo Kasei), 2,6-dichlorobenzoic acid (Tokyo Kasei), 2-nitrobenzoic acid (Tokyo Kasei), 4-nitrobenzoic acid (Tokyo Kasei), 4-hydroxybenzoic acid (Kishida), benzoic acid (Nacalai Tesque), 1*H*-tetrazole (Wako), N^6-(benzoyl)-5′-*O*-(*p*,*p*′-dimethoxytrityl)-2′-deoxyadenosine 3′-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) (**14**) (Applied Biosystems Inc. or Glen Research), N^4-(benzoyl)-5′-*O*-(*p*,*p*′-dimethoxytrityl)-2′-deoxycytidine 3′-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) (**15**) (Applied Biosystems Inc. or Glen Research), N^2-(isobutyryl)-5′-*O*-(*p*,*p*′-dimethoxytrityl)-2′-deoxyguanosine 3′-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) (**16**) (Applied Biosystems Inc. or Glen Research), 5′-*O*-(*p*,*p*′-dimethoxytrityl)thymidine 3′-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) (**17**) (Applied Biosystems Inc. or Glen Research), and the thymidine derivative **21** attached to CPG (Applied Biosystems Inc.), were commercially supplied. The 3′-*O*-protected 2′-deoxyribonucleosides, **18**,[17] **19**,[17] and **20**,[18] a 1.0 M *tert*-butyl hydroperoxide/toluene solution,[19] and BIT[11b] were described in the literature or prepared by previously reported methods.

4.3. Screening of promoter reactivity

A mixture of the phosphoramidite **17** (35.8 mg, 48 μmol), the nucleoside **20** (14.2 mg, 40 μmol), and MS 3A (30 mg) in dry acetonitrile (0.8 mL) was stirred for 30 min. To this mixture was added an acetonitrile (0.2 mL) solution of a promoter (48 μmol). After 1 and/or 5 min, the reaction was quenched by the addition of diisopropylethylamine (16 μL, 96 μmol) and a 1.0 M toluene solution of TBHP (0.08 mL, 0.08 mmol); stirring was then continued for 10 min. The insoluble material was removed by filtration. The mixture was concentrated, and the resulting residue was dissolved in $CDCl_3$ (1 mL). An aliquot of the solution was subjected to ^{31}P NMR analysis to measure the product yield.

4.4. A typical procedure for the liquid-phase synthesis of dideoxyribonucleoside phosphates

A mixture of the phosphoramidite **17** (89.2 mg, 0.12 mmol), the nucleoside **20** (35.6 mg, 0.10 mmol), and MS 3A (60 mg) in dry acetonitrile (0.8 mL) was stirred for 30 min. An acetonitrile (0.2 mL) solution of trichloroacetic acid (18.0 mg, 0.11 mmol) or 2,4-dinitrobenzoic acid (25.6 mg, 0.12 mmol) was then added to the mixture,

which was stirred for an additional 5 min. To this mixture, a 1.0 M toluene solution of TBHP (0.24 mL, 0.24 mmol) was added, and stirring was continued for 10 min. The insoluble material was filtered off. Concentration of the filtrate afforded a crude product, which was purified by column chromatography (eluent, 20:1 CH_2Cl_2/CH_3OH) to afford **25** (986 mg, 97% yield): ^{31}P NMR (162 MHz) δ −3.33; HRMS (ESI^+) calcd for $C_{50}H_{62}N_5O_{14}PSiNa$ ($M+Na^+$) 1038.37, found 1038.37. The ^1H NMR spectrum (400 MHz) was identical to those of an authentic sample.[11b] Dideoxyribonucleoside phosphates **22**,[20] **23**,[20] and **24**[20] were prepared in a similar manner. ^1H NMR, ^{31}P NMR, and HRMS (ESI^+) spectral data of these compounds were as follows.

4.4.1. Compound 22. ^1H NMR (400 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.91 (s, 3H), 2.18–2.29 (m, 2H), 2.65–2.85 (m, 3H), 3.10–3.15 (m, 1H), 3.41–3.50 (m, 2H), 3.78, 3.79 (2 s, 6H), 4.01–4.46 (m, 7H), 5.30–5.34 (m, 1H), 6.14, 6.22 (2 t, 1H, J=6.8 Hz), 6.49–6.53 (m, 1H), 6.78–6.83 (m, 4H), 7.22–7.31 (m, 9H), 7.37–7.39 (m, 2H), 7.52–7.55 (m, 2H), 7.59–7.63 (m, 1H), 8.04, 8.06 (2 br, 2H), 8.14, 8.15 (2 s, 1H), 8.72, 8.75 (2 s, 1H), 9.16, 9.18 (2 s, 1H); ^{31}P NMR (162 MHz) δ −3.15, −3.22; HRMS (ESI^+) calcd for $C_{57}H_{66}N_8O_{13}PSi$ ($M+H^+$) 1129.43, found 1129.34.

4.4.2. Compound 23. ^1H NMR (400 MHz) δ 0.08, 0.09 (2 s, 6H), 0.89, 0.89 (2 s, 9H), 1.87, 1.90 (2 s, 3H), 2.14–2.41 (m, 3H), 2.67 (q, 1H, J=6 Hz), 2.76 (t, 1H, J=6 Hz), 2.94–2.99 (m, 1H), 3.43–3.53 (m, 2H), 3.79–3.80 (4 s, 6H), 3.98–4.03 (m, 1H), 4.11–4.31 (m, 4H), 4.37–4.42 (m, 2H), 5.13–5.18 (m, 1H), 6.19, 6.23 (2 t, 1H, J=6.4 Hz), 6.27–6.30 (m, 1H), 6.85–6.88 (m, 4H), 7.22–7.42 (m, 11H), 7.48–7.52 (m, 2H), 7.57–7.62 (m, 1H), 7.92–7.94 (m, 2H), 8.11–8.13(m, 1H), 9.23 (br, 1H), 9.25 (br, 1H); ^{31}P NMR (162 MHz) δ −3.11, −3.26; HRMS (ESI^+) calcd for $C_{56}H_{66}N_6O_{14}PSi$ ($M+H^+$) 1105.41, found 1105.44.

4.4.3. Compound 24. ^1H NMR (400 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.16–1.29 (m, 6H), 1.99, 2.05 (2 s, 3H), 2.27–2.42 (m, 2H), 2.64–2.82 (m, 5H), 3.30–3.42 (m, 2H), 3.73 (q, 1H, J=7.2 Hz), 3.79, 3.79 (2 s, 6H), 3.91–4.00 (m, 1H), 4.18–4.39 (m, 5H), 4.56–4.63 (m, 1H), 5.23–5.31 (m, 1H), 5.83–6.11 (m, 1H), 6.14–6.30 (m, 1H), 6.81–6.84 (m, 4H), 7.21–7.39 (m, 9H), 7.73, 7.73 (2 s, 1H), 9.02, 9.84 (2 s, 1H), 10.06, 10.54 (2 s, 1H), 12.21, 12.33 (2 s, 1H); ^{31}P NMR (162 MHz) −2.34, −3.04; HRMS (ESI^+) calcd for $C_{54}H_{68}N_8O_{14}PSi$ ($M + H^+$) 1111.44, found 1111.51.

4.5. Stability of purine nucleosides 18 and 19 to trichloroacetic acid in acetonitrile

A mixture of the nucleoside **18** (45.2 mg, 0.10 mmol) or **19** (46.9 mg, 0.10 mmol) and MS 3A (60 mg) in dry acetonitrile (0.8 mL) was stirred for 30 min. An acetonitrile (0.2 mL) solution of trichloroacetic acid (18 mg, 0.11 mmol) was then added to the mixture, which was stirred for an additional 30 min. To this mixture were added a $NaHCO_3$-saturated aqueous solution (ca. 2 mL) and dichloromethane (ca. 3 mL), and stirring was continued for 10 min. The lower organic layer was separated, dried over sodium sulfate, concentrated, and then subjected to HPLC analysis under the following conditions: column, COSMOSIL 5C_{18}-AR-II [4.6 (diameter) mm×25 (height) cm]; flow rate, 1.0 mL/min; detection, 254 nm; eluent and gradient, [A=a 1.0 mM ammonium acetate buffer solution in H_2O, B=a 0.2 mM ammonium acetate buffer solution in a 20:80 mixture of H_2O and acetonitrile, 0–90 min with a linear gradient from A 100% to A 70%/B 30%]; temperature, 40 °C. In both cases of **18** and **19**, only a peak due to the starting material was detected, indicating that **18** and **19** underwent no decomposition under the above reaction condition.

4.6. Solid-phase synthesis of $^{5'}$GpApCpTpCpTpCpTpTpApGpCpTpApApT$^{3'}$ (27)

Chain elongation of the oligodeoxyribonucleotide was carried out on a 0.2 μmol scale according to the reaction cycle shown in Table 3. The resulting fully protected oligonucleotide was exposed to concentrated ammonia at 25 °C for 2 h and then 55 °C for 12 h to afford the target compound: HRMS (ESI^-) of **27** calcd for $C_{156}H_{196}N_{54}O_{96}P_{15}$ ($M-3H^+$) 1608.96, found 1608.93.

4.7. NMR analysis of the reaction of 17 and 20 using 5 as a promoter

The phosphoramidite **17** (32.2 mg, 43 μmol) was weighed into a dry NMR tube equipped with a Young's tap and dissolved in CD_3CN (0.3 mL). To this sample, a solution of the carboxylic acid **5** (9.3 mg, 44 μmol) in CD_3CN (0.3 mL) was added with a syringe under an argon stream. The NMR tube was sealed by the Young's tap, and the ^1H and ^{31}P NMR spectra were recorded. After the measurements were carried out, a CD_3CN (0.3 mL) solution of the nucleoside **20** (13.0 mg, 37 μmol) was introduced into the tube in a similar manner for subsequent NMR analysis. The experiment was conducted in a similar manner with trichloroacetic acid or salicylic acid.

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8. In order to clearly observe a difference in the reactivity of the promoter, the reaction had to be carried out using a low (40–48 mM) concentration. At this concentration, the use of **17**, **20**, and a promoter at a molar ratio of 1.2:1.0:1.2 gave the highest product yield shown in Table 1. When the reaction was carried out using **17**, **20**, and a promoter in equimolar amounts, the product yield was slightly lower. For example, in the reaction using trichloroacetic acid as a promoter for 3 min, the yield of **25** was 84%.
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12. In the case using trichloroacetic acid as the promoter, reaction conditions including the amount of the promoter and concentration of the reactants affected the product yield. When the reaction was carried out using trichloroacetic acid in an equimolar amount to the phosphoramidite in a 40–48 mM solution, the 1-min reaction gave the highest product yield. The reaction for a longer period, for example, 5 min, led to some (ca. 5%) decomposition of the product to decrease the yield. In contrast, when the reaction was conducted using trichloroacetic acid in the amount less equivalent (ca. 0.9 equiv) to the phosphoramidite in a 0.10–0.12 M solution (see Table 2), no decomposition was observed after 5 min. The activity of the promoter decreased in solvents other than acetonitrile. For example, 2,4-dinitrobenzoic acid did not successfully carry out the condensation of **17** and **20** in 5 min in dichloromethane, toluene, THF, or DMF. In these cases, when the reaction was stopped at 5 min and then the resulting product was subjected to TBHP oxidation, **25** was obtained in only 81 (dichloromethane), 66 (toluene), 12 (THF), and 9% (DMF) yields, respectively.
13. The p*K*a values of 1*H*-tetrazole and BIT in acetonitrile are reported in Ref. 6 to be 14.5 and 14.3, respectively. Based on these p*K*a values, we can account for the reactivity of BIT observed in this study; however the reactivity of 1*H*-tetrazole appears to be too low, because 2,4-dinitrobenzoic acid, which has a higher p*K*a value, that is, lower acidity, showed much higher reactivity. This discrepant result might be explained as follows. The p*K*a values of the carboxylic acids and those of 1*H*-tetrazole and BIT were determined by fundamentally different methods, that is, a potentiometric method was used for the carboxylic acids, and a ^{13}C NMR method was employed for 1*H*-tetrazole and BIT; p*K*a values determined by such different methods might not be consistent. As a consequence, it might be irrelevant to discuss the relative reactivity of carboxylic acids and 1*H*-tetrazole on the basis of their p*K*a values reported to date.
14. The following explanation provides another conceivable reason. The carboxylate anion generated from 2-hydroxybenzoic acid has a hydroxy group that competes with the carboxylate anion in the reaction with the activated phosphoramidite. Accordingly, two types of reactive species, namely, a phosphorous/carboxylic-mixed anhydride and a phosphityl phenoxide, may be generated. Between these two species, the former may react with the 5′-*O*-free nucleoside to give the desired dinucleoside phosphite, but the latter may be inactive under these reaction conditions, that is, may remain stable without any changes. Accordingly, the subsequent oxidation would give a complex mixture of a variety of compounds. However, this possibility was excluded by the ^{31}P NMR analysis of the reaction of **17** and salicylic acid in the absence of the nucleoside **20**, which showed only scant formation of both the phosphorous/carboxylic-mixed anhydride and phosphityl phenoxide intermediates.
15. In order to determine whether the reaction of a phosphoramidite using trichloroacetic acid as an activator will form the corresponding phosphorous/carboxylic-mixed anhydride, we carried out ^{31}P NMR studies of the reaction of **17** and trichloroacetic acid; however, in this case, no evidence supporting the formation of the mixed acid anhydride was obtained. Therefore, in cases involving such a strong acid as a promoter, the condensation of a nucleoside 3′-phosphoramidite and a 5′-*O*-free nucleoside might not be achieved via phosphorous/carboxylic-mixed anhydride as the reactive intermediate, although the condensation might be achieved by direct attack of a nucleoside on the protonated phosphoramidite. The detailed mechanism of the condensation of a nucleoside phosphoramidite and a nucleoside using a strong carboxylic acid as a promoter is now under investigation.
16. For example, the p*K*a value of methanesulfonic acid in acetonitrile is ca. 10, which is similar to that of trichloroacetic acid (see, Ref. 7).
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New triterpenoid saponins from the roots of *Platycodon grandiflorum*

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Abstract—Bioassay-directed fractionation of the antiviral active fraction of the roots of *Platycodon grandiflorum* leads to the isolation of three new triterpenoid saponins, platycosides G1–G3 (**1**–**3**), as well as two known saponins, platycodin D3 (**4**), and platycoside E (**5**). The structures of the new compounds were elucidated on the basis of their spectral data and chemical evidences. The isolated saponins were tested for their antiviral activities against respiratory syncytial virus (RSV), herpes simplex type 1 virus (HSV-1) and influenza type A virus (Flu A). Compound **4** showed weak anti-RSV activity.

1. Introduction

The roots of *Platycodon grandiflorum* (Jacq.) A. DC. (Campanulaceae) have been used in antiphlogistic, antitussive and expectorant as a traditional Chinese medicine,[1] and it contains the abundance of saponins. Since Oshika first studied its saponin in 1918,[2] over 20 triterpenoid saponins have been reported.[3–10] Some of them showed anti-inflammatory, antitumor and immunomodulatory activities.[11–13] During our investigation of antiviral constituents from the traditional Chinese medicine,[14,15] the MeOH extract of the roots of *P. grandiflorum* exhibited the inhibitory effect against respiratory syncytial virus (RSV) (IC_{50} 44.1 μg/ml). The constituents of active MeOH extract were isolated by the bioassay-directed fractionation, and purified to yield three new trace triterpenoid saponins, platycosides G1–G3 (**1**–**3**), with two known platycodin D3 (**4**) and platycoside E (**5**) by preparative HPLC. In this paper, we report their structural determination and antiviral activities against HSV-1, RSV and Flu A.

2. Results and discussion

Platycoside G1 (**1**) was obtained as an amorphous powder, $[\alpha]_D^{20} = -11.2$ ($c = 0.32$, MeOH) The ^{13}C NMR spectrum of **1** showed signals corresponding to 64 carbons, which were sorted by DEPT experiments into six methyl, 15 methene, 35 methine, and eight quaternary carbons. Its molecular formula of $C_{64}H_{104}O_{34}$ was determined by HRFABMS. The spectral features and physicochemical properties revealed **1** to be a triterpenoid saponin. The IR spectrum exhibited absorptions at 3400 cm^{-1} (OH), 1742 cm^{-1} (ester carbonyl), and 1644 cm^{-1} (double bond). The five tertiary methyl groups (δ 1.01, 1.08, 1.12, 1.38, and 1.68) and one olefinic proton (δ 5.63, br s) were observed in the ^1H NMR spectrum. The ^{13}C NMR spectrum showed five sp^3 carbons at δ 17.4, 18.8, 24.4, 26.7, and 33.0, and two sp^2 olefinic carbons at δ 122.8 and 144.0, and five oxygenated methene and methine carbons at δ 68.6, 88.5, 73.7, 63.1 and 67.1 (see Table 2). The information of ^1H NMR spectrum coupled with ^{13}C NMR spectrum indicated that **1** possessed a 2β,3β,16α,23,24-pentahydroxyolean-12-ene-28-oic acidic aglycon.[9] The chemical shifts of C-3 (δ 88.5) and C-28 (δ 175.7) revealed that **1** was a bisdesmosidic glycoside. Thirty-four of 64 carbons were assigned to the oligosaccharide moieties. The ^1H and ^{13}C NMR spectra of **1** exhibited six sugar anomeric protons at δ 4.83 (d, J= 7.3 Hz), 4.74 (d, J=8.2 Hz), 5.03 (d, J=7.7 Hz), 6.43 (br s), 5.76 (br s), and 5.15 (δ, J=7.5 Hz) and carbons at δ 105.8, 104.7, 105.4, 93.3, 100.8, and 106.5 (see Tables 1 and 3). The monosaccharides were identified as arabinose, rhamnose, xylose, and glucose by TLC and a combination of DEPT, TOCSY, HMQC, and HMBC experiments, respectively. Comparing with NMR spectrum of platycoside E (**5**), the absence of apiose in **1** was also disclosed. Saponins **1** and **5** were further completely acid hydrolyzed in the parallel condition. The results exhibited that the

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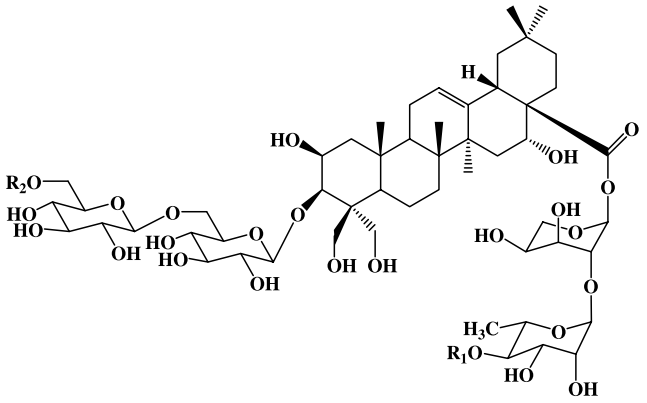
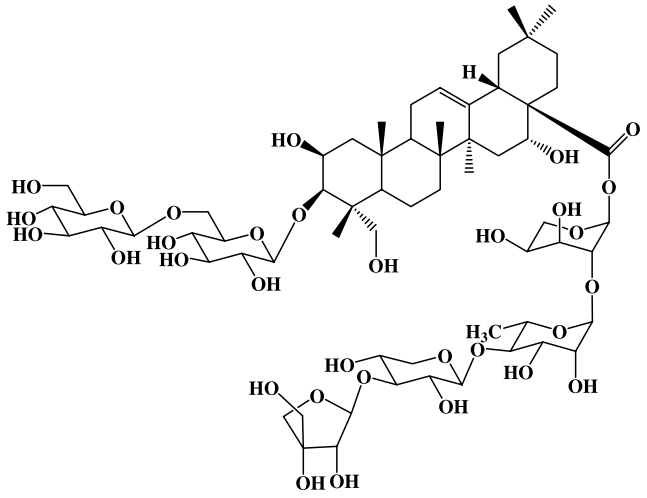


	R_1	R_2
1	− xyl	− glc
2	H	− glc
4	− xyl (3⟶1) api	H
5	− xyl (3⟶1) api	− glc



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sapogenin of **1** was identical with that of **5**, and the monosaccharides were confirmed. Their absolute configurations were determined to be L-rabinose, L-rhamnose, D-xylose, and D-glucose (ratio 1:1:1:3) by GLC analysis of the trimethylsilyl (TMSi) derivatives, respectively.[16] All the monosaccharides of **1** were in pyranose forms, as determined by their ^{1}H and ^{13}C NMR data and 2D NMR experiments. The β-anomeric configurations of the glucose and xylose units were determined by their $^3J_{H1,H2}$ coupling constants (7.3–8.2 Hz), and arabinose and rhamnose were determined as the α-configurations by the broad singlet of their anomeric protons. The sequence of the glycan part connected to C-3 of the aglycon was deduced from the following HMBC correlations: H-1‴ (δ 5.03) of terminal glucose with C-6″ (δ 70.1) of centre glucose, H-1″ (δ 4.74) of centre glucose with C-6′ (δ 70.6) of inner glucose, H-1′ (δ 4.83) of inner glucose with C-3 (δ 88.5) of aglycon (see Fig. 1). The second bisdesmosidic part at C-28 was established by the following HMBC information: the correlations between H-1 (δ 5.15) of xylose and C-4 (δ 83.3), H-1 (δ 5.76) of rhamnose and C-2 (δ 74.5) of arabinose, H-1 (δ 6.43) of arabinose and C-28 (δ 175.7) of the aglycon (see Fig. 1). On the basis of all the foregoing evidence, platycoside G1 (**1**) was elucidated as 3-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl-2β,3β,16α,23,24-pentahydroxyolean-12-ene-28-oic acid 28-*O*-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl (1→2)-α-L-arabinopyranoside.

Table 1. ^{1}H NMR spectroscopic data (δ) for the sugar moieties of **1–3** (400 MHz in pyridine-d_5)

H	**1**	**2**	**3**
Glucose (inner)			
1′	4.83 d (7.3)	4.80 d (7.6)	4.79 d (7.2)
2′	4.07 t (7.3)	4.00 t (7.6)	4.03–4.06 m
3′	4.02–4.04 m	3.95–3.96 m	
4′	3.82–3.90 m	3.87–3.87 m	3.88–3.96 m
5′	4.11 dd (3.8, 7.5)	4.10 dd (3.3, 7.4)	4.08–4.11 m
6′	5.01 br d (7.5)	4.80 br d (7.1)	5.01–5.15 m
	3.82–3.90 m	3.73–3.75 m	3.88–3.94 m
Glucose (centre)			
1″	4.74 d (8.2)	4.69 d (7.2)	
2″	4.02–4.04 m	3.95–3.96 m	
3″, 4″, 5″	4.18–4.21 m	4.08–4.16 m	
6″	4.74 br d (8.2)	4.71 br d (7.1)	
	3.82–3.90 m	3.73–3.75 m	
Glucose (terminal)			
1‴	5.03 d (7.7)	4.99 d (8.0)	4.92 d (7.6)
2‴	4.01 t (7.7)	3.95–3.96 m	3.88–3.94 m
3‴, 4‴	4.18–4.21 m	4.08–4.16 m	4.15–4.17 m
5‴	4.02–4.04 m	3.95–3.96 m	3.88–3.96 m
6‴	4.65 br d (8.0)	4.60 br d (6.8)	4.65 br d (7.7)
	3.82–3.90 m	3.73–3.75 m	3.88–3.94 m
Arabinose			
1	6.43 br s	6.45 br s	6.39 br s
2	4.48–4.51 m	4.38–4.45 m	4.65–4.70 m
3	4.82–3.90 m	3.87–3.87 m	3.88–3.94 m
4	4.36–4.38 m	4.38–4.45 m	4.23–4.28 m
5	4.46–4.48 m	4.51–4.55 m	4.40–4.45 m
	4.82–3.90 m	4.38–4.45 m	4.23–4.28 m
Rhamnose			
1	5.76 br s	5.73 br s	5.65 br s
2, 3	4.02–4.04 m	4.38–4.45 m	3.88–3.94 m
4, 5	4.36–4.38 m	4.22–4.28 m	4.23–4.28 m
6	1.71 d (5.2)	1.61 d (6.0)	1.63 (overlap)
Xylose			
1	5.15 d (7.5)		5.15 d (7.6)
2	4.02–4.04 m		4.03–4.06 m
3	4.82–3.90 m		3.88–3.94 m
4	4.18–4.21 m		4.15–4.17 m
5	3.48 t (10.1)		3.52 t (9.6)
Apiose			
1			6.26 br s
2			5.65 br s
3			—
4			4.15–4.17 m
			4.88 d (7.8)
5			4.23–4.28 m

The assignments are based upon DEPT, HMQC, and HMBC experiments. Overlapped signals are labeled with multiplicity (m). Coupling constants (*J* values in Hz) are shown in parentheses.

Platycoside G2 (**2**) was analysed to have the molecular formula of $C_{59}H_{96}O_{30}$ by its HRFAB mass spectrum and ^{13}C and DEPT NMR data. The ^{1}H and ^{13}C NMR signals of **2** were assigned by DEPT, TOCSY, HMQC, and HMBC

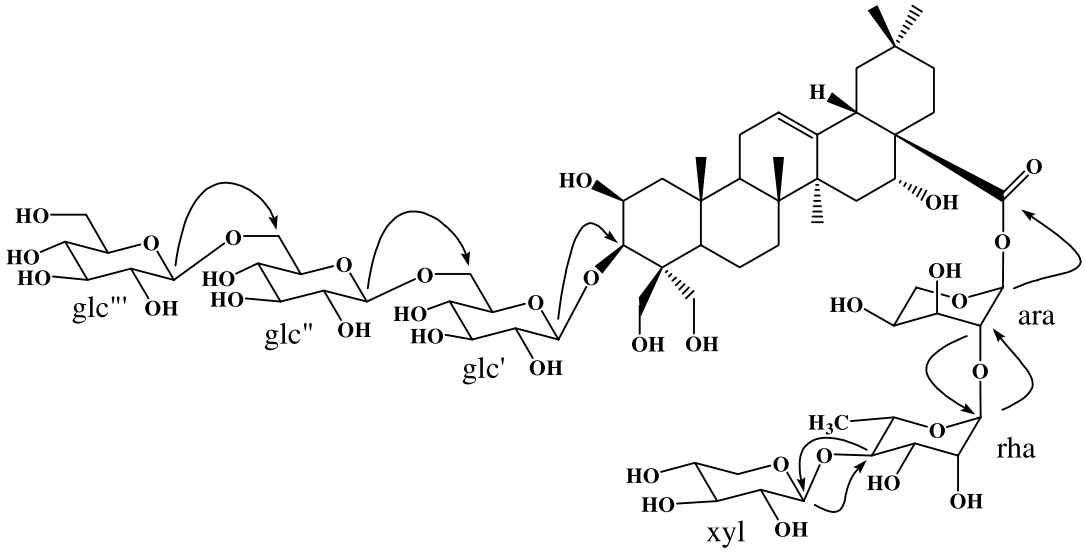

Figure 1. Key HMBC correlations for the sugar sequence of **1** (from H to C).

experiments. The comparison of the ^{1}H and ^{13}C NMR spectra of **2** with those of **1** clearly revealed that the sapogenin of **2** was in identical with that of **1**, and **2** were suggested to be a bisdesmosidic glycoside (see Tables 1–3). The anomeric proton and carbon signals of one xylosyl group in NMR spectra of **2** where disappeared, and the chemical shift of C-4 of rhamnose in **2** was shifted upfield from δ 83.3 to 74.0. By comparison with **1**, the configurations of the monosaccharides in **2** were assigned for β-glucose, α-arabiose, and α-rhamnose, respectively. The spectral data deduced that compound **2** was a dexylosyl platycoside G1. Comparing the spectral characteristic of **2** with **1**, the absolute configurations were supposed as L-rabinose, L-rhamnose, and D-glucose. On the basis of these results, platycoside G2 (**2**) was identified as 3-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl-2β,3β,16α,23,24-pentahydroxy-olean-12-ene-28-oic acid 28-α-L-rhamnopyranosyl-(1→2)-α-L-arabino-pyranoside.

Table 2. ^{13}C NMR spectroscopic data (δ) for the aglycon moieties of **1–3** (100 MHz in pyridine-d_5)[a]

C	1	2	3
1	45.0	45.2	44.4
2	68.6	70.0	69.7
3	88.5	88.8	84.5
4	47.8	47.5	43.1
5	47.3	47.0	47.9
6	19.1	19.2	18.7
7	33.2	33.7	33.6
8	40.2	40.5	40.5
9	44.7	48.1	48.0
10	37.7	37.9	37.4
11	23.7	24.0	24.4
12	122.8	122.6	123.2
13	144.0	144.1	144.4
14	42.1	42.4	42.6
15	35.8	36.0	36.5
16	73.7	73.8	74.3
17	49.4	49.7	49.9
18	41.3	41.5	41.6
19	47.8	47.4	47.4
20	30.6	30.9	31.3
21	35.8	36.0	36.3
22	32.4	32.0	32.6
23	63.1	63.2	66.3
24	67.1	66.0	15.6
25	18.8	19.1	18.0
26	17.4	17.6	17.9
27	26.7	27.0	27.6
28	175.7	175.6	176.1
29	33.0	33.3	33.6
30	24.4	24.8	25.2

[a] Assignments are based on HMQC, TOCSY and HMBC experiments.

Platycoside G3 (**3**) has a molecular formula of $C_{63}H_{102}O_{32}$ determined by HRFAB mass spectrum. The ^{1}H and ^{13}C NMR signals of **3** were assigned by DEPT, TOCSY, HMQC, and HMBC experiments. Comparing the ^{1}H and ^{13}C NMR signals of **3** with those of **4**, the chemical shift assignable to H-24 of **3** in the aglycon moiety was shifted upfield to δ 1.45, and the C-24 to δ 15.6. Other NMR signals of **3** were similar to those of **4** (see Tables 1–3). The ^{1}H and ^{13}C NMR spectra suggested that the aglycon of **3** was polygalacic acid.[9] The HMBC experiment of **3** indicated that the sugar sequence was also a bisdesmosidic glycoside, and comparison of the NMR spectrum of **3** with that of **4** showed that their glycans were the same. On the basis of the above results, **3** was concluded to be 3-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl-polygalacic acid 28-*O*-β-D-apiofuranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside.

All fractions and isolates, the MeOH extract of *P. grandiflorum* were tested for their antiviral activities against HSV-1, RSV and Flu A. All samples had no activity against HSV-1 and Flu A. The MeOH extract and fraction F02 showed moderate anti-RSV activity, and saponin **4** exhibited weak anti-RSV activity (see Table 4).

3. Experimental

3.1. General procedures

Optical rotations were measured with a JASCO DIP-370 digital polarimeter. IR absoption spectra were obtained with

Table 3. ^{13}C NMR Spectroscopic data (δ) for the sugar moieties of **1–3** (100 MHz in pyridine-d_5)[a]

C	1	2	3
Glucose (inner)			
1′	105.8	105.9	105.7
2′	74.8	74.7	75.5
3′	78.4	78.6	78.7
4′	72.0	72.5	72.2
5′	76.2	77.0	77.0
6′	70.6	70.1	70.8
Glucose (centre)			
1″	104.7	104.8	
2″	74.8	75.3	
3″	78.3	78.4	
4″	71.2	71.2	
5″	76.8	76.4	
6″	70.1	70.4	
Glucose (terminal)			
1‴	105.4	105.5	105.3
2‴	74.9	75.1	75.5
3‴	78.2	78.2	78.6
4‴	70.8	71.5	70.4
5‴	77.4	77.6	78.0
6‴	62.8	62.9	62.9
Arabinose			
1	93.3	93.4	93.7
2	74.5	75.1	75.5
3	71.7	70.7	71.8
4	66.0	65.5	66.3
5	62.8	62.6	63.2
Rhamnose			
1	100.8	101.4	101.4
2	70.9	72.2	72.3
3	72.4	72.3	73.0
4	83.3	74.0	83.9
5	68.3	70.1	68.9
6	18.1	18.6	18.7
Xylose			
1	106.5		106.8
2	75.7		75.6
3	78.0		85.0
4	69.8		70.1
5	67.1		67.2
Apiose			
1			111.4
2			78.3
3			80.7
4			75.5
5			65.6

[a] Assignments are based on HMQC, TOCSY and HMBC experiments.

Table 4. Anti-RSV activity of the triterpenoid saponins from *Platycodon grandiflorum*

Sample	RSV[a] IC_{50} (μg/mg)	CC_{50} (μg/mg)[b]	SI[c]
MeOH ext.	44.1	>200	4.5
Fraction F01	Inactive	>200	—
Fraction F02	25.0	>200	8.0
Fraction F03	Inactive	>200	—
1	Inactive	>200	—
2	Inactive	>200	—
3	Inactive	>200	—
4	200.0	>200	1.0
5	Inactive	>200	—
Ribavirin[d]	2.6	62.5	24.0

[a] IC_{50} is the concentration of the sample required to inhibit virus-induced CPE 50%.
[b] CC_{50} is the concentration of the 50% cytotoxic effect.
[c] SI is selectivity index = CC_{50}/IC_{50}.
[d] Ribavirin, an approved drug for the treatment of RSV infections in humans.

a Shimadzu IR-450 instrument as a film on KBr Disks. NMR spectra were obtained with a Bruker 400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C, respectively. Chemical shifts were reported in parts per million on the δ scale with TMS as the internal standard. FABMS were recorded on VG autospec 3000 system. Column chromatography was performed with silica gel (Qingdao Haiyang Chemical Group Co. Ltd, Qingdao, People's Republic of China), Diaion HP-20 (Mitsubishi Chemical, Japan), and ODS (100–200 mesh, Fuji Silysia Chemical Ltd, Japan). Reversed phase HPLC was carried out on a Agilent 1100 G1361A preparative pump, equipped with a Agilent 1100 G1315B Diode-array Detector, and Alltima C_{18} (250×22 mm, 10 μm), eluted with CH_3CN–H_2O (2:8) at a flow rate of 20 ml/min, with the UV detector set at 210 nm. GLC was carried out on a Shimadzu GC-7A, and column: Silicone OV-17 on Uniport HP 2%, 3 mm i.d.×2.1 m column; column temperature, initial temperature 140 °C for 16 min and rising 2 °C/min to final 170 °C; carrier gas, N_2, flow rate, 25 ml/min. TLC was performed on precoated Si gel 60 F_{254} plates (0.2 mm thick, Merck) with $CHCl_3$–MeOH–H_2O (7:3:1), $CHCl_3$–MeOH–H_2O–AcOH (7:3:1:1), $CHCl_3$–MeOH (9:1), and RP-18 F_{254} plates (0.2 mm thick, Merck) with MeOH–H_2O (6:4), and spots were detected by spraying with 10% ethanolic H_2SO_4 reagent.

3.2. Plant material

The roots of *Platycodon grandiflorum* (Jacq.) A. DC were collected in Hubei Province, PR China, in September 2003. The raw material was identified by Prof. Zhongzhen Zhao, Hong Kong Baptist University, Hong Kong, and a voucher specimen (CMED-0077-1) was deposited in the CMED-LAB of Hong Kong Jockey Club Institute of Chinese Medicine.

3.3. Extraction and isolation

The dried roots (933.8 g) were pulverized and extracted with MeOH for three times. The MeOH extract was concentrated in vacuum at 40 °C to give a residue (255.5 g), which was fractionated by CC on Diaion HP-20 eluting with H_2O 18 l, 50% MeOH 6 l, and MeOH 8 l, yield three fractions (F01-F03). Fraction F02 showed anti-RSV activity (see Table 4). This fraction was then subjected to silica gel, ODS CC, and purified by reversed phase HPLC to yield saponins **1** (123.5 mg, 0.013%), **2** (12.4 mg, 0.001%), **3** (18.0 mg, 0.002%), **4** (239.2 mg, 0.026%), and **5** (429.6 mg, 0.046%).

3.3.1. Platycoside G1 (1). White amorphous powder; $[\alpha]_D^{20} = -11.2$ ($c=0.3$, MeOH); IR (KBr) ν_{max}: 3400, 2920, 1742, 1644, 1040 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz): aglycon δ 1.01 (3H, s, H-29), 1.08 (3H, s, H-26), 1.12 (3H, s, H-30), 1.34 (1H, br d, $J=8.6$ Hz, H-15a), 1.38 (3H, s, H-25), 1.41–1.44 (4H, m, H-6, 7a, 19a), 1.55–1.58 (1H, m, H-7b), 1.68 (3H, s, H-27), 1.71–1.81 (2H, m, H-1a, 15b), 1.91–2.01 (5H, m, H-1b, 5, 11, 9), 2.15 (1H, br t, $J=9.6$ Hz, H-22a), 2.24 (1H, br d, $J=10.0$ Hz, H-21a), 2.35 (2H, t, $J=9.6$ Hz, H-21b, 22b), 2.77 (1H, t, $J=13.3$ Hz, H-19b), 3.53 (1H, t, $J=13.3$ Hz, H-18), 3.82–3.90 (m, H-23a), 4.01–4.04 (m, H-24), 4.46–4.55 (m, H-2, 3),

4.66 (1H, d, $J=8.0$ Hz, H-23b), 5.26 (1H, br s, H-16), 5.63 (1H, br s, H-12); Other ^{1}H and ^{13}C NMR data: see Tables 1–3; FAB-MS *m/z*: 1417 $[M+H]^+$; HRFABMS *m/z*: 1417.6490 $[M+H]^+$ (Calcd for $C_{64}H_{105}O_{34}$ 1417.6487).

3.3.2. Platycoside G2 (2). White amorphous powder; $[\alpha]_D^{20}=-50.6$ ($c=0.2$, MeOH); IR (KBr) ν_{max}: 3400, 2920, 1742, 1646, 1038 cm^{-1}; ^{1}H NMR (pyridine-d_5, 400 MHz): aglycon δ 0.94 (3H, s, H-29), 1.01 (3H, s, H-26), 1.06 (3H, s, H-30), 1.24 (1H, br d, $J=8.0$ Hz, H-15a), 1.34 (3H, s, H-25), 1.39–1.50 (4H, m, H-6, 7a, 19a), 1.63 (3H, s, H-27), 1.68–1.71 (1H, m, H-7b), 1.86–1.94 (7H, m, H-1, 5, 11, 9), 2.11–2.16 (1H, m H-22a), 2.19–2.33 (3H, m, H-21, 22b), 2.72 (1H, t, $J=13.3$ Hz, H-19b), 3.52 (1H, t, $J=13.3$ Hz, H-18), 3.85–3.87 (m, H- 23a), 3.95–3.96 (m, H-24), 4.51–4.44 (m, H-2, 3), 4.60 (1H, d, $J=8.0$ Hz, H-23b), 5.18 (1H, br s, H-16), 5.56 (1H, br s, H-12); Other ^{1}H- and ^{13}C NMR data: see Tables 1–3; FAB-MS *m/z*: 1285 $[M+H]^+$; HRFABMS *m/z*: 1285.6069 $[M+H]^+$ (Calcd for $C_{59}H_{97}O_{30}$ 1285.6065).

3.3.3. Platycoside G3 (3). White amorphous powder, $[\alpha]_D^{20}=-108$ ($c=0.3$, MeOH); IR (KBr) ν_{max}: 3400, 2920, 1742, 1646, 1038 cm^{-1}; ^{1}H NMR (pyridine-d_5, 400 MHz): aglycon δ 0.91 (3H, s, H-29), 1.05 (3H, s, H-26), 1.06 (3H, s, H-30), 1.25 (3H, s, H-25), 1.27(1H, br d, $J=8.0$ Hz, H-15a), 1.45 (3H, s, H-24), 1.47–1.50 (5H, m, H-6, 7a, 19a), 1.63 (3H, s, H-27), 1.68–1.76 (1H, m, H-7b), 1.86–2.11 (7H, m, H-1, 5, 9, 11, 15b), 2.20–2.29 (4H, m H-21, 22), 2.67 (1H, t, $J=13.2$ Hz, H-19b), 3.52 (1H, t, $J=13.3$ Hz, H-18), 3.88–3.94 (m, H-23a), 4.40–4.45 (m, H-2,3), 4.65–4.70 (m, H-23b), 5.15 (1H, br s, H-16), 5.46 (1H, br s, H-12); Other ^{1}H and ^{13}C NMR data: see Tables 1–3; FAB-MS *m/z*: 1371 $[M+H]^+$; HRFABMS *m/z*: 1371.6429 $[M+H]^+$ (calcd for $C_{63}H_{103}O_{32}$ 1371.6432).

3.4. Acid hydrolysis of platycosides G1 (1) and E (5)

Saponins **1** (25 mg) and **5** (30 mg) were heated in 1.5 ml of 1 M HCl (dioxane–H_2O, 1:1) at 96 °C for 3 h in a water bath, respectively, Dioxane was removed and the solution was extracted with EtOAc (2 ml×3), and removed EtOAc. The aglycons of **1** and **5** were consistent by comparing with TLC (silica gel plate, $CHCl_3$–MeOH–H_2O–AcOH 7:3:1:1, visualization by H_2SO_4 spray and then heated). The aqueous solution of acid hydrolysis of **1** was neutralized by passing through an Amberlite MB-3 resin column eluted with water, then concentrated and dried, and finally treated with 1-(trimethylsilyl)-imidozole at room temperature for 4 h. After the excess reagent was decomposed with H_2O, the reaction product was extracted with *n*-hexane (3 ml×2). The TMSi derivatives of the monosaccharides were identified as D-glucose, L-arabinose, L-rhamnose and D-xylose (3:1:1:1) by GLC analysis with authentic monosaccharides.

3.5. Viruses and cells

RSV strain Long, HSV-1 (15577) strain, and Madin Darby canine kidney (MDCK) cells were obtained from American Type Culture Collection. Flu A (H3N2) strain was obtained from Guangzhou, PR China; cytotoxicity assay and cytopathic effect reduction assay are corresponded with the reported methods.[15]

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Highly chemoselective hydrogenation method using novel finely dispersed palladium catalyst on silk-fibroin: its preparation and activity

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Abstract—A palladium–fibroin complex (Pd/Fib) was prepared by soaking silk-fibroin in MeOH solution of $Pd(OAc)_2$ for 2 days (under Ar atmosphere)—4 days (under air). $Pd(OAc)_2$ was gradually absorbed by fibroin and the rapid reduction of fibroin conjugated $Pd(OAc)_2$ proceeded with MeOH as a reductant at room temperature to be the Pd(0) complex. Pd/Fib catalyzed chemoselective hydrogenation of acetylenes, olefins and azides in the presence of aromatic ketones and aldehydes, halides, *N*-Cbz protective groups and benzyl esters which are readily hydrogenated using Pd/C or Pd/C(en) as a catalyst.

1. Introduction

Catalytic hydrogenation using a heterogeneous catalyst has been a powerful tool for functional group transformation in both the laboratory and industrial plant.[1] Pd/C, a heterogeneous catalyst, has many advantages over homogeneous catalysts, such as stability of the catalysts, ease of separation from the reaction mixture upon completion of the reaction, a good possibility of recyclability, cost reduction and high catalytic ability. However, the high catalytic activity of Pd/C makes it difficult to attain chemoselective reduction among some reducible functional groups. Recently, we reported several chemoselective hydrogenation methods using a Pd/C-ethylenediamine complex [Pd/C(en)].[2,3] Further development of novel catalysts for chemoselective hydrogenation methods will reinforce the versatility of synthetic processes.

On the other hand, the silk secreted from the silk gland of the silkworm *Bombyx mori* is composed of two principal components of proteins, fibroin and sericins, characterized by their solubility and stability in hot water, which enables the industrial degumming of the silk threads. Recently, fibroin and sericines have come to be considered a useful bio-material accounting for a wide variety of interesting properties such as in food, cosmetics, medical and biological materials, not to mention fibers.[4] In particular, fibroin is approximately 370 kDa molecular mass and consists of mainly glycine, alanine, serine and tyrosine, and very few residues of sulfur amino acids,[5] which can be a strong catalyst poison of metals.

The formation of fibroin heavy metal (Cu, Cr, Zn, Ni, Sn and so on) complexes has long been studied in connection with increasing the strength, weight and luster of heavy metal absorbed silk.[6] Many of the electron-rich functional groups in the protein easily bind with the metal surface, leading to the bioconjugate. During 1956–1962,[7] Akabori and co-workers reported silk protein-supported zero-valent metal catalyst for asymmetric hydrogenation. According to their reported procedure,[7b] silk fibroin was boiled for 8 min in 0.1 N AcOH containing $PdCl_2$ and the resulting chelate was reduced under hydrogen (80 kg/cm^2) in an autoclave. Based upon Akabori's preparation method,[7] fibroin of the silk fibroin-supported palladium catalyst was most likely denatured under the drastic reaction conditions for the reason that the fibroin was exposed to the strongly acidic conditions derived from liberating HCl from $PdCl_2$ in boiling 0.1 N AcOH. This could be due to the fact that the silk palladium-catalyzed asymmetric hydrogenations are inefficient inasmuch as the reproducibility of the method was invariably poor.[7] To our best knowledge, no applicable protein-supported metal catalyst has, as yet, been reported. Quite recently, Zhou et al. reported a core-shell nano-structured gold colloid-silk fibroin bioconjugate.[8] We report herein a preparation method of a novel Pd–fibroin (Pd/Fib)

Keywords: Silk-fibroin; Hydrogenation; Palladium catalyst; Chemoselective.
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catalyst under mild and nearly neutral reaction conditions and its application to highly chemoselective hydrogenation methods.[9]

2. Results and discussion

We chose $Pd(OAc)_2$ as a palladium source for the new Pd–fibroin catalyst (Pd/Fib) to avoid the strongly acidic conditions derived from released HCl from $PdCl_2$. The Pd absorption (1∼10 wt% of the silk fibroin) onto the silk fibroin was initiated by soaking silk fibroin [Fig. 1(a)] into a dark rust-colored MeOH solution of $Pd(OAc)_2$ [0.0235 mol/l, Fig. 1(b)] at room temperature in air. The colorless fibroin was time-dependently changed to black, which suggests the formation of zero-valent Pd. The liquid phase also changed gradually from rust to thoroughly colorless-clear [Fig. 1(c)–(e)] for 4 days, indicating the slow but complete adsorption of $Pd(OAc)_2$ on the silk fibroin and the rapid formation of the zero-valent Pd/Fib via oxidation of the silk fibroin or MeOH. Since no formation of black turbidity or silver mirror was observed during the deposition of Pd(0) onto the silk fibroin, it can be presumed that the formation of Pd(0) occurs only on the fibroin fiber. Although the preparation time of Pd/Fib could be reduced under Ar atmosphere, the preparation was carried out under atmospheric conditions from a practical standpoint. After simple filtration, the obtained Pd/Fib [Fig. 1(f)] was stable for more than three years at room temperature in air (in a capped vial) and is non-pyrophoric. The Pd/Fib can be used by cutting up the black yarn (Pd/Fib fiber) with scissors and is removed easily from the reaction mixture using a pair of tweezers or by simple filtration.

Figure 1. Preparation of Pd/Fib catalyst.

The quantitative analysis of the formation of acetic acid[10] and formaldehyde[11] was carried out to gain insight into the reduction of $Pd(OAc)_2$. For the reason that 90% of acetic acid and 70% of formaldehyde were determined from the filtered clear solution of Fig. 1(e), MeOH contributed to the reduction of $Pd(OAc)_2$ which was strongly adsorbed and coordinated by silk fibroin, while the Tyr and/or Ser residues of silk fibroin also display strong electron-donating

$$Pd(OAc)_2 \xrightarrow[MeOH,\ rt]{Fibroin} Pd(OAc)_2/Fib \xrightarrow[MeOH]{rt} Pd(0)/Fib + HCHO + 2AcOH$$

Scheme 1. Mechanism of Pd/Fib generation.

Figure 2. Silver mirror of palladium.

properties (Scheme 1). On the other hand, the formation of a silver mirror of palladium metal on the side face of the Erlenmeyer flask was observed when only the MeOH solution of $Pd(OAc)_2$ was allowed to stand in the absence of fibroin fiber at room temperature for 4 days (Fig. 2).

Scanning electron microscopy (SEM) images proved the high dispersion of amorphous palladium metal particles [Fig. 3(b)–(d)] on the smooth surface of the silk fibroin [Fig. 3(a)]. The variation of the Pd content only made a difference in the density of the Pd particles. This homogeneous dispersion was attributed to an interaction between the $Pd(OAc)_2$ and amino acids of the silk fibroin, increasing the resistance to the growth of the Pd cluster.[9]

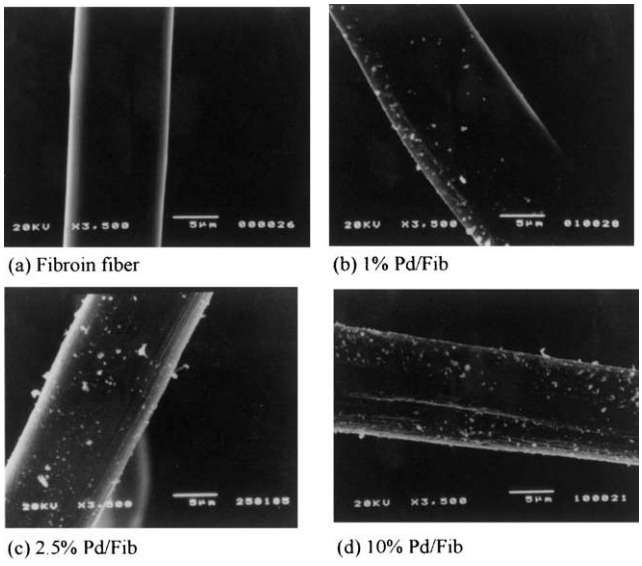
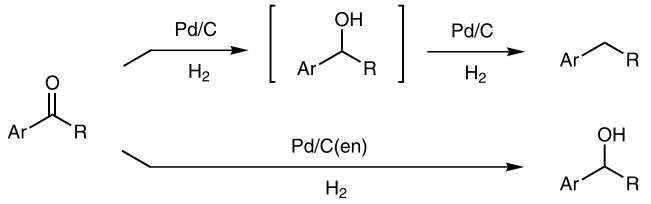


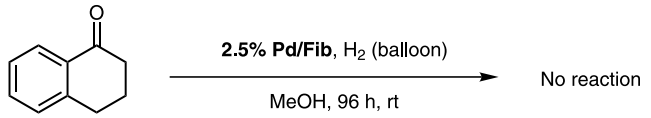
Figure 3. SEM image of original fibroin fiber (a), 1% (b), 2.5% (c) and 10% Pd/Fib (d).

It is well known that the Pd/C-catalyzed hydrogenation of aromatic carbonyls easily occurs to form methylene compounds via formation of the intermediary benzyl alcohol (Scheme 2).[1] Therefore, it is extremely difficult to achieve the chemoselective hydrogenation of olefin and acetylene functionalities leaving intact the aromatic ketone



Scheme 2. Reduction of aromatic carbonyl using Pd/C and Pd/C(en).

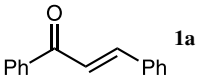
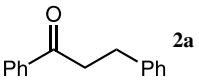
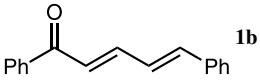
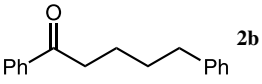
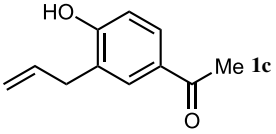
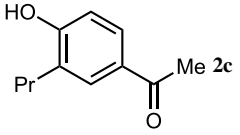
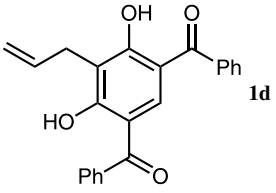
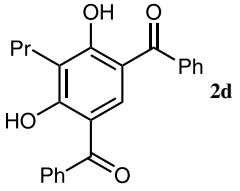
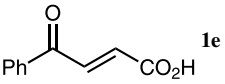
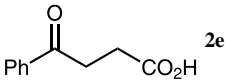
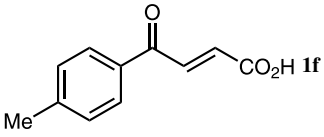
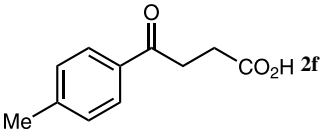
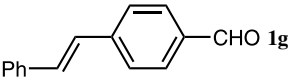
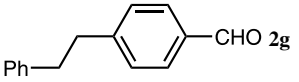
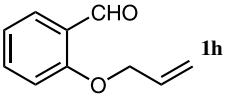
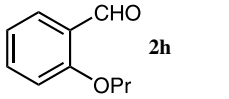
and aldehyde. Recently, we have reported a chemoselective hydrogenation method of aromatic carbonyls to form benzyl alcohols without hydrogenolysis of the intermediary benzyl alcohol using Pd/C(en) as a catalyst.[12] Following our interest in the use of Pd/Fib as a catalyst for the chemoselective hydrogenation, we found that 2.5% Pd/Fib surprisingly exhibited no catalyst activity toward the hydrogenation of aromatic carbonyl compounds (Scheme 3).



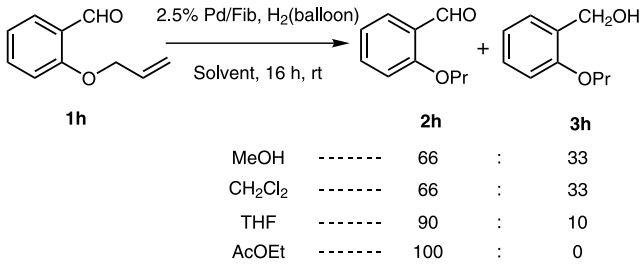
Scheme 3. Catalytic activity of 2.5% Pd/Fib toward the hydrogenation of aromatic ketone.

To explore the scope of the 2.5% Pd/Fib catalyst, the chemoselective hydrogenation of olefins in the presence of an aromatic carbonyl group within the molecule was carried out at room temperature (Table 1). Although aromatic ketones (**1a–1f**) were never reduced, hydrogenation activity of 2.5% Pd/Fib toward olefins is retained (entries 1–6). Moreover, the aromatic aldehyde (**1g**) was also stable under hydrogenation conditions using 2.5% Pd/Fib even under 5 atm pressure of hydrogen (entry 7). Although partial reduction of the aromatic aldehyde of *o*-allyloxybenzaldehyde (**1h**) was observed in MeOH, CH_2Cl_2 or THF as a solvent, the use of AcOEt as a solvent caused the perfect suppression of the reduction of the aromatic aldehyde group of **1h** (entry 8 and Scheme 4).

Table 1. Chemoselective hydrogenation of olefin in the presence of aromatic carbonyl using 2.5% Pd/Fib catalyst[a]

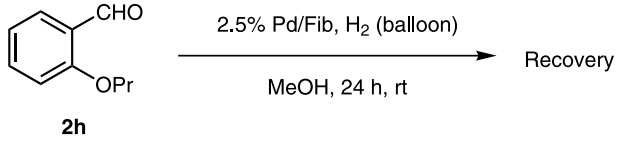
Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1a**	30	 **2a**	97 (99[c], 97[d])
2	 **1b**	3	 **2b**	100
3	 **1c**	37	 **2c**	99
4	 **1d**	46	 **2d**	74[e]
5	 **1e**	2	 **2e**	quant
6	 **1f**	10	 **2f**	99
7	 **1g**	24	 **2g**	100[c,e]
8	 **1h**	27	 **2h**	100[f]

[a] Unless otherwise specified, reactions were performed in 5 mL of MeOH under ambient hydrogen pressure at room temperature.
[b] Isolated yield.
[c] 5 atm pressure of hydrogen.
[d] The reaction was performed at 50 °C.
[e] 5 mL of CH_2Cl_2 was used as a solvent.
[f] 5 mL of AcOEt was used as a solvent.



Scheme 4. Solvent effect toward the hydrogenation of the aromatic aldehyde (**1h**).

While the aromatic aldehyde of **1g** was not reduced even under 5 atm pressure of hydrogen using 2.5% Pd/Fib catalyst in MeOH, the aldehyde of **1h** was partially reduced under ambient pressure of hydrogen in MeOH (entry 7 and Scheme 4). On the other hand, *o*-propyloxybenzaldehyde (**2h**) which possesses no olefin moiety was entirely recovered under the same hydrogenation conditions in MeOH (Scheme 5). According to these experimental results, the aldehyde of **1h** was partially reduced before the saturation of the olefin. Although the exact process of the partial reduction of **1h** is unclear, it has been proposed that



Scheme 5. Catalyst activity of 2.5% Pd/Fib toward the hydrogenation of aromatic aldehyde (**2h**) in MeOH.

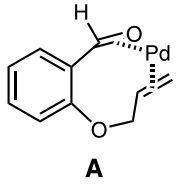


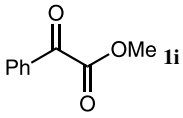
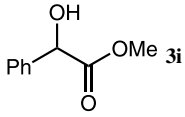
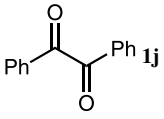
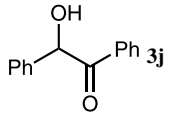
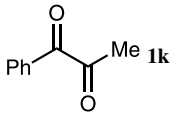
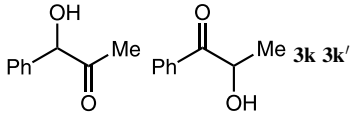
Figure 4. Cyclic coordination of **1h** with Pd (0).

the formation of a cyclic intermediate (**A**), which is obtained by the coordination of Pd metal with the olefin and aldehyde functionalities, is a key step of the competitive hydrogenation of the olefin and aldehyde of **2h** (Figure 4). Since the use of AcOEt as a solvent, which is a better ligand than the aromatic aldehyde of **2h**, should inhibit the formation of the cyclic intermediate (**A**), the selective hydrogenation was achieved in AcOEt.

While aromatic carbonyl groups were usually not reduced using 2.5% Pd/Fib (Table 1), aromatic ketones which possess ester or other ketone moieties at the α position were exceptionally reduced under the same conditions (Table 2). For example, methyl benzoylformate (**1i**), aromatic β-keto-ester, was reduced to the corresponding alcohol (**3i**). Regrettably, stereoselectivity of **3i** was extremely poor (only 4% ee). Benzil (**1j**) and 1-phenylpropane-1,3-dione (**1k**) which are aromatic 1,2-diketone were also reduced to the corresponding α-hydroxyketones. Again, we expected the formation of the neighboring-carbonyl group related cyclic palladium coordinated intermediate to be a key step of the exceptional reduction of the carbonyl group.

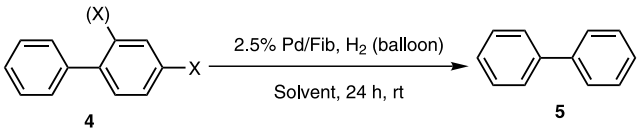
It is well known that aromatic chlorides are much less reactive than aromatic bromides and iodides toward the hydrogenation conditions and, hence, the dechlorination of aromatic chloride cannot readily be achieved and the hydrodechlorination reactions are very frequently incomplete but proceeded.[13] Needless to say, Pd/C(en)[2] or commercial Pd/C[1]-catalyzed chemoselective hydrogenation with retention of aromatic halides could not be accomplished,[13] whereas aromatic halides entirely tolerate the hydrogenation using 2.5% Pd/Fib (Table 3). Although partial hydrogenolysis of 4-chlorobiphenyl (**4b**) and 4-bromobiphenyl (**4c**) was observed in MeOH (entries 2 and 4), the use of THF as a solvent perfectly suppressed the partial hydrogenolysis (entries 3 and 5). 4-Fluorobiphenyl (**4a**) and 2-iodobiphenyl (**4d**) were stable under the hydrogenation conditions in MeOH.

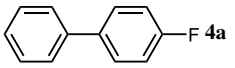
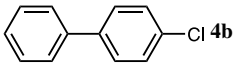
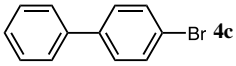
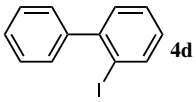
Table 2. Reducible aromatic carbonyls under the hydrogenation conditions using 2.5% Pd/Fib[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1i**	8	 **3i**	98
2	 **1j**	46	 **3j**	98[c]
3	 **1k**	43	 **3k** **3k′** (85 : 15)[e]	—[d]

[a] Unless otherwise specified, reactions were performed in 5 mL of MeOH under hydrogenation conditions at room temperature.
[b] Isolated yield.
[c] Under 5 atm pressure of hydrogen.
[d] Under 10 atm pressure of hydrogen.
[e] Determined by ^{1}H NMR (starting material was disappeared).

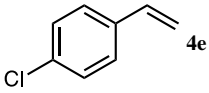
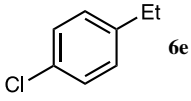
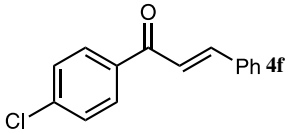
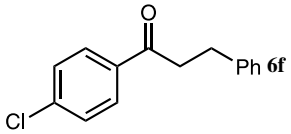
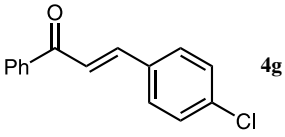
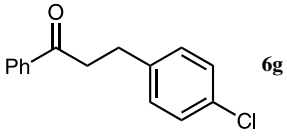
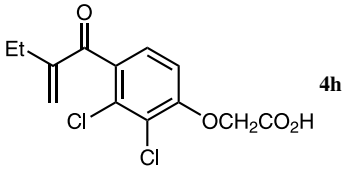
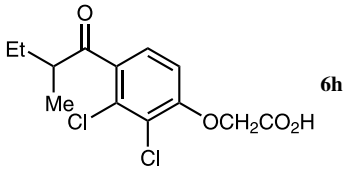
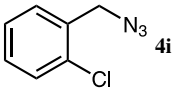
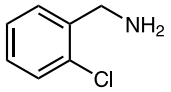
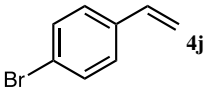
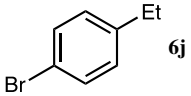
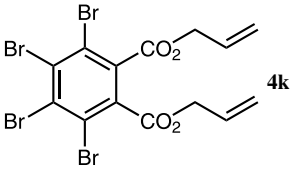
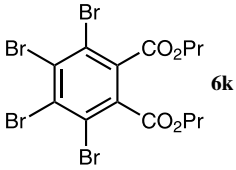
Table 3. Catalytic activity of 2.5% Pd/Fib toward the hydrogenolysis of aromatic halides



Entry	Substrate	Solvent	**4**:**5**[a]	Recovery (%)
1	 **4a**	MeOH	100:0	95
2	 **4b**	MeOH	95:5	—
3		THF	100:0	99
4	 **4c**	MeOH	84:16	—
5		THF	100:0	91
6	 **4d**	MeOH	100:0	98

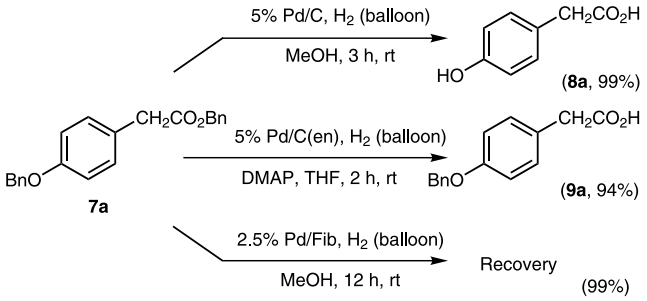
[a] Determined by ^{1}H NMR.

Table 4. Chemoselective hydrogenation of olefin and azide in the presence of aromatic halide using 2.5% Pd/Fib catalyst[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **4e**	24	 **6e**	100[c]
2	 **4f**	20	 **6f**	98
3	 **4g**	21	 **6g**	99[d]
4	 **4h**	12	 **6h**	100
5	 **4i**	24	 **6i**	91
6	 **4j**	24	 **6j**	100[c]
7	 **4k**	3	 **6k**	94

[a] Unless otherwise specified, reactions were performed in 5 mL of MeOH under ambient hydrogen atmosphere at room temperature.
[b] Isolated yield.
[c] Performed in CD_3OD as a solvent and determined by ^{1}H NMR.
[d] Performed in 15 mL of MeOH.

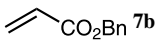
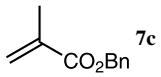
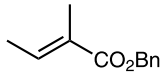
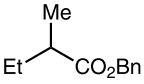
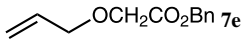
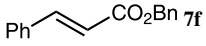
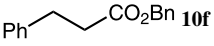
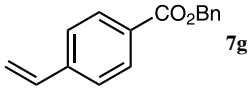
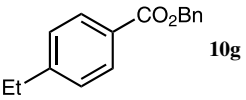
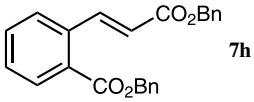
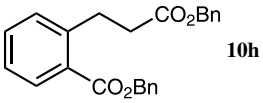
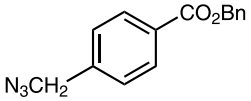
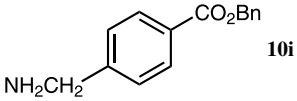
Consequently, the chemoselective hydrogenation of a variety of substrates containing aromatic halides and olefin or azide functions within a molecule was carried out at room temperature (Table 4). First, 4-chloro and 4-bromo styrenes (**4e** and **4j**) were hydrogenated using 2.5% Pd/Fib in CD_3OD because of the low boiling point of the products. Not only chloride but also bromide was never cleaved while the olefin was chemoselectively hydrogenated (entries 1 and 6). In addition, only the olefin moiety in compounds **4f–4h** containing aromatic chloride and ketone was selectively hydrogenated, to give the corresponding saturated compounds **6f–6h** (entries 2–4). The azide group of **4i** was also hydrogenated to the corresponding amine (**6i**) (entry 5). Furthermore, 2.5% Pd/Fib did not catalyze the hydrogenolysis of even multi-brominated aromatic bromide (**4k**) and the chemoselective hydrogenation of the olefins was achieved (entry 7). According to these results, 2.5% Pd/Fib catalyst is obviously applicable to the chemoselective hydrogenation of olefin and azide functions distinguishing the aromatic halides.



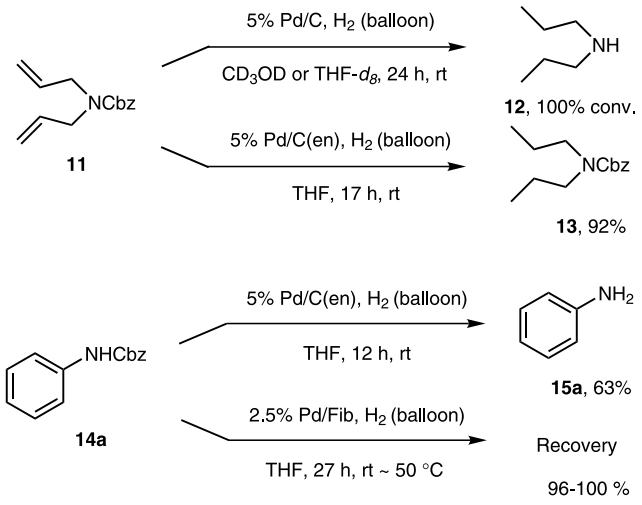
Scheme 6. Catalytic activity of Pd catalysts toward the hydrogenation of benzyl ether and ester.

Despite numerous literature precedents, chemoselective reduction of reducible functionalities such as alkynes, alkenes and azides remains a challenge in organic synthesis.[1] Especially, while benzyl ester or *N*-Cbz protective groups are widely used in organic synthesis, they are labile under hydrogenation conditions, and it is extremely difficult to keep such groups intact during a synthetic process involving hydrogenation steps.[14] In order to solve this problem, Misiti et al. have reported 3% Pd/C-catalyzed selective hydrogenation of a di-substituted olefin of γ-amino-α,β-unsaturated (conjugate) esters in the presence of a benzyl ester or *N*-Cbz protective group.[15] However, the method has limitation with regard to generality, and the stability of the benzyl esters and *N*-Cbz groups under the conditions was time-dependent.[15,16] During our efforts to extend the applicability of the Pd/Fib catalyst, we found that Pd/Fib indicates almost no catalytic activity towards the hydrogenolysis of benzyl ether and benzyl ester compared with Pd/C and Pd/C(en)[2a] (Scheme 6). The hydrogenolysis of 4-benzyloxyphenylacetic acid benzyl ester (**7a**) catalyzed by 2.5% Pd/Fib resulted in no reaction even after 12 h under ordinary hydrogen pressure (recovery of the starting material **7a** in 99%). On the other hand, the use of 5% Pd/C (Aldrich)[1] as a catalyst resulted in the hydrogenolysis of both the benzyl ether and the benzyl ester of **7a** to give the corresponding 4-hydroxyphenylacetic acid (**8a**) in 99% isolated yield. 5% Pd/C(en) catalyzed

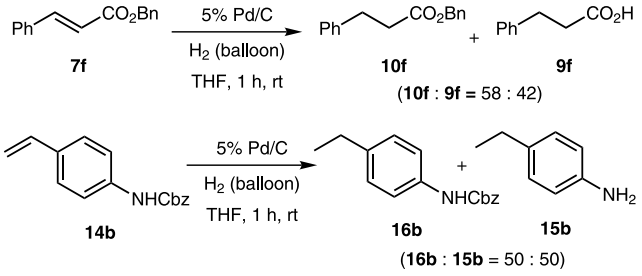
Table 5. Chemoselective hydrogenation of olefin and azide functionalities in the presence of a benzyl ester using 2.5% Pd/Fib catalyst[a]

1	Substrate	Solvent	Time (h)	Product	Yield (%)[b]
1	 **7b**	THF-d_8	7	$EtCO_2Bn$ **10b**	91[c]
2	 **7c**	THF-d_8	7	$iPrCO_2Bn$ **10c**	93[c]
3	 **7d**	MeOH	18	 **10d**	77[d]
4	 **7e**	MeOH	8	$PrOCH_2CO_2Bn$ **10e**	99
5	 **7f**	THF	24	 **10f**	98
6	 **7g**	MeOH	6	 **10g**	97
7	 **7h**	MeOH	12	 **10h**	100 (100)[e]
8	 **7i**	MeOH	17	 **10i**	100

[a] Unless otherwise specified, reactions were performed in 5 mL of the solvent under ambient hydrogen pressure at room temperature.
[b] Isolated yield.
[c] Performed in THF-d_8 (0.75 mL) and determined by ^1H NMR.
[d] Under 5 atm pressure of hydrogen.
[e] The reaction was performed at 50 °C.



Scheme 7. Catalytic activity of Pd catalysts toward the *N*-Cbz group of aliphatic and aromatic amines.



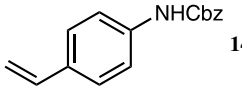
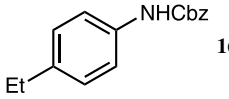
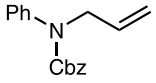
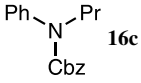
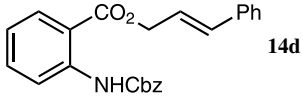
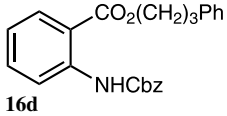
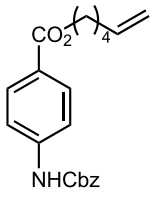
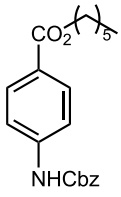
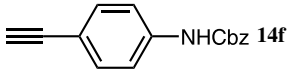
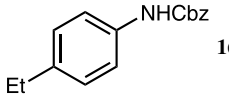
Scheme 8. Hydrogenation of **7f** and **14b** using commercial 5% Pd/C catalyst.

chemoselective hydrogenation of only the benzyl ester of **7a** with retention of the benzyl ether to give the corresponding 4-benzyloxyphenylacetic acid (**9a**) in 94% isolated yield.[2a] Judging from these results so far obtained, we are now in a position to disclose that the Pd/Fib catalyst is very efficient for chemoselective hydrogenation with retention of the benzyl ester within a molecule.

To explore the scope of the 2.5% Pd/Fib catalyst, the hydrogenation of a number of substrates containing a benzyl ester was investigated (Table 5). The terminal and internal olefin and azide functionalities were selectively reduced in the presence of α,β-unsaturated (conjugated) benzyl esters (**7b**–**7d**, **7f** and **7h**) (entries 1–3, 5 and 7), a non-conjugated benzyl ester (**7e**) (entry 4) and benzoic acid benzyl ester derivatives (**7g**, **7h** and **7i**) (entries 6, 7 and 8). A feature of the hydrogenation of benzyl ester derivatives is that the catalyst activity of Pd/Fib toward the benzyl esters is strongly influenced by the solvent. The benzyl esters of substrates **7b**, **7c** and **7f** were partially or completely hydrogenolized in MeOH as a solvent. However, no hydrogenolysis of the benzyl ester was observed in THF as a solvent as can be seen from entries 1, 2 and 5. On occasions when the partial hydrogenolysis of the benzyl ester of the substrate occurred in MeOH, the use of THF as a solvent gave satisfactory results (entries 1, 2 and 5).[2a,b,17,18]

N-Cbz (carbobenzoxy) protective groups are easily deprotected under hydrogenation conditions using Pd/C as a catalyst.[19] Recently, we reported the Pd/C(en) catalyzed-chemoselective hydrogenation with retention of the *N*-Cbz protective group of aliphatic amines although the chemoselective hydrogenation with retention of the aromatic

Table 6. Chemoselective hydrogenation of olefin and acetylene in the presence of aromatic *N*-Cbz group using 2.5% Pd/Fib catalyst[a]

Entry	Substrate	Solvent	Time (h)	Product	Yield (%)[b]
1	 **14b**	THF	5	 **16b**	92
2	 **14c**	MeOH	48	 **16c**	97
3	 **14d**	THF	34	 **16d**	99[c]
4	 **14e**	MeOH	22	 **16e**	100
5	 **14f**	MeOH	32	 **16f**	92[d]

[a] Unless otherwise specified, reactions were performed in 5 mL of the solvent under ambient hydrogen pressure at room temperature.
[b] Isolated yield.
[c] Under 10 atm pressure of hydrogen.
[d] Under 3 atm pressure of hydrogen.

N-Cbz groups or benzyl esters could not be accomplished.[2a,17,20] Although the hydrogenation of the substrate (**11**) containing an *N*-Cbz group of aliphatic amine and olefin functionalities within a molecule catalyzed by 5% Pd/C gave totally saturated and simultaneously deprotected product **12** as the sole product, the use of 5% Pd/C(en) catalyst in THF resulted in entirely chemoselective hydrogenation and the *N*-Cbz protective group was tolerated under the reaction conditions (Scheme 7). However, the *N*-Cbz protective group of an aromatic amine is easily deprotected under the same reaction conditions,[2a,17] for instance, the *N*-Cbz protective group of aniline (**14a**) was smoothly deprotected under the hydrogenation conditions using Pd/C(en) in THF.[2a,17] During our efforts to overcome this problem, we found that 2.5% Pd/Fib possesses no catalyst activity toward the hydrogenolysis of the aromatic *N*-Cbz group (**14a**) (Scheme 7).

The catalyst activity of 2.5% Pd/Fib toward reducible functionalities is much lower than the catalyst activity of Pd/C and Pd/C(en). The olefins of **7f** and **14b** were completely hydrogenated within an hour together with the partial hydrogenolysis of benzyl ester and *N*-Cbz, respectively (Scheme 8) with commercial 5% Pd/C as a catalyst, while the complete hydrogenation of the olefins required much longer time with Pd/Fib (24 and 5 h, respectively; Table 5, entry 5 and Table 6, entry 1). Therefore, some sterically hindered olefins such as **7d** (Table 5, entry 3), **14d** (Table 6, entry 3), *trans*-stilben (**17**) and some cinnamate type compounds (**18** and **19**) were irreducible under ambient pressure of hydrogen using the 2.5% Pd/Fib (Figure 5) with exceptional result (e.g. Table 5, entries 5 and 7). In addition, a competitive experiment using *cis*-Jasmone (**20**) which has a di-substituted *cis*-olefin and a tetra-substituted olefin as a substrate indicated that only the *cis*-olefin was chemoselectively reduced to the corresponding dihydrojasmone (**21**). Consequently, the hydrogenation using 2.5% Pd/Fib can distinguish between hindered and unhindered olefins and the chemoselective hydrogenation of unhindered olefin was efficiently achieved (Scheme 9).

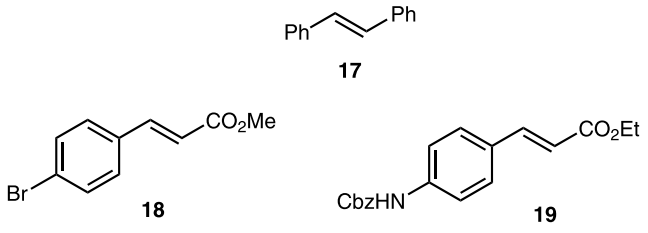
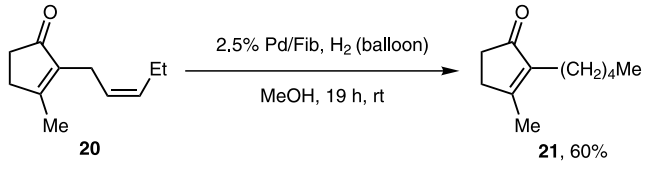


Figure 5. Irreducible olefins under ambient pressure of hydrogen using 2.5% Pd/Fib in MeOH.



Scheme 9. Chemoselective hydrogenation between two different olefins.

The chemoselectivity of the hydrogenation could be attributable to the catalyst poison effect of the coordinated silk fibroin support toward the zero valent palladium metal and the significant decrease in the active surface area of palladium metal by the formation of a minute cluster (Figure 3). In the Pd/Fib catalyst, the original affinity of palladium to aromatic carbonyls, halides, benzyl esters and *N*-Cbz protective groups was drastically and selectively reduced by fibroin.

3. Conclusion

Silk-fibroin supported palladium catalyst (Pd/Fib) was prepared by incipient wetness impregnation with a rust-colored MeOH solution of $Pd(OAc)_2$. After the palladium (II) was absorbed completely in the fibroin, the zero-valent Pd was formed on the fibroin fiber via oxidation by MeOH as a reductant. The Pd/Fib catalyst, black-colored yarn, shows chemoselectivity in hydrogenation of acetylene, olefin and azide functionalities in the presence of aromatic ketone, aldehyde and halide, benzyl ester and aromatic *N*-Cbz protective groups. These novel chemoselective hydrogenation methods using Pd/Fib should contribute to broad organic synthetic chemistry fields.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL AL 400 spectrometer, JEOL EX 400 spectrometer, or a JEOL GL 270 spectrometer with tetramethylsilane or residual protiated solvent used as a reference. Elemental analyses were performed by YANACO CHN CORDER MT-5 instrument. EI and FAB Mass spectra were taken on a JEOL JMS-SX102A instrument. SEM (Scanning Electron Microscopy) image were taken on a JEOL JSM-T330A. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM) according to the method of Still.[21] MeOH for HPLC and AcOEt dehydrated were purchased from Wako Pure Chemical Industries, Ltd. and used without purification. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. All other reagents were purchased from commercial sources and used without further purification.

4.1.1. Preparation of silk fibroin. Raw silk of *Bombyx mori* (10.0 g) wrapped in gauze was soaked in an aqueous solution (1.00 L) of Na_2CO_3 (500 mg, 6.02 mmol), $Na_2S_2O_4$ (100 mg, 0.57 mmol) and ethylenediaminetetraacetic acid dipotassium salt dihydrate (400 mg, 0.99 mmol) and boiled for an hour. The resulting silk was washed vigorously with water and dried in the shade to afford silk fibroin (7.83 g. Anal. Found: C, 47.57; H, 6.38; N, 18.37: sample 1.779 mg: ash 0.02 mg).

4.1.2. Preparation of 2.5% Pd/Fib. To a rust-colored solution of palladium acetate (1.06 g, 4.72 mmol) in MeOH (200 mL) at room temperature was soaked silk fibroin (20.0 g) for 4 days. The silk fiber changed gradually from white to black and the solution also changed gradually from rust to thoroughly colorless-clear. The resulting black fiber was filtered, washed vigorously with MeOH (500 mL), and

dried under reduced pressure to give the 2.5% Pd/Fib. [1] Anal. Found: C. 45.25; H, 5.99; N, 16.97: sample 1.92 mg: ash 0.01 mg. [2] Anal. Found: C. 46.56; H, 6.18; N, 17.95: sample 1.704 mg: ash 0.07 mg. [3] Anal. Found: C. 46.76; H, 6.25; N, 18.05: sample 1.766 mg: ash 0.04 mg.

4.1.3. Quantitative analysis of aldehyde.[10] To a solution of palladium acetate (52.7 mg, 0.23 mmol) in MeOH (10.0 mL) under Ar atmosphere at room temperature was soaked silk fibroin (1.00 g) for 4 days. The filtrate was diluted 200 times with distilled water. A mixture of the sample solution (5.00 mL) and acetylacetone solution (5.00 mL) which was prepared by distilled ammonium acetate (15.0 g), acetic acid (0.30 mL) and acetylacetone (0.20 mL) to the 100 mL with water was heated on a hot water bath for 10 min. The absorbance was determined by 254 nm. Calibration curve of formaldehyde was obtained by plotting peak size on the *y*-axis versus sample concentration on the *x*-axis for a series of samples with known concentrations using the data for the 1.25, 2.50 and 5.00 μg/mL standard solutions of formaldehyde.

4.1.4. Quantitative analysis of acetic acid.[11] To a solution of palladium acetate (52.7 mg, 0.23 mmol) in MeOH (10.0 mL) under Ar atmosphere at room temperature was soaked silk fibroin (1.00 g) for 4 days. The filtrate was diluted 10 times with distilled water. The solution was titrated with 0.01 N NaOH solution in the presence of phenolphthalein which was standardized by potassium hydrogen phthalate solution.

4.1.5. Formation of silver mirror of palladium. The MeOH (10.0 mL) solution of palladium acetate (52.7 mg, 0.23 mmol) was allowed to stand in the absence of fibroin fiber under Ar atmosphere at room temperature for 4 days. The formation of a silver mirror of palladium metal on the side face of the Erlenmeyer flask was observed.

4.1.6. Preparation of 1, 5 and 10% Pd/Fib. Silk fibroin (1.00 g) was soaked in a rust-colored solution of palladium acetate (1%: 21.2 mg, 5%: 106 mg, 10%: 211 mg) in MeOH (30.0 mL) at room temperature for 4 days. The resulting black fiber was filtered, washed vigorously with MeOH (100 mL), and dried under reduced pressure to give the 1% Pd/Fib. Anal. Found: C. 47.11; H, 6.18; N, 18.20: sample 2.309 mg: ash 0.08 mg. 5% Pd/Fib Anal. Found: C. 45.79; H, 6.02; N, 17.59: sample 1.934 mg: ash 0.09 mg. 10% Pd/Fib Anal. Found: C, 45.93; H, 6.04; N, 17.83: sample 1.797 mg: ash 0.13 mg.

4.1.7. Synthesis of substrate.

4.1.7.1. 2-Chlorobenzylazide (4i). To a solution of 2-chlorobenzylchloride (1.61 g, 10.0 mmol) in DMF (10.0 mL) at room temperature was added sodium azide (1.95 g, 30.0 mmol). The solution was stirred at room temperature for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 2-chlorobenzylazide (**4i**) as a colorless oil (1.03 g, 62%). ^{1}H NMR ($CDCl_3$): δ=7.29–7.43 (m, 4H), 4.26 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=133.8, 133.3, 130.0, 129.8, 129.6, 127.1, 52.3; MS (EI) *m*/*z* 167 (M^+, 38%), 140 (35%), 138 (99%), 127 (34%), 125 (100%), 111 (35%), 102 (36%), 89 (29%), 77 (56%), 75 (45%), 51 (37%), 50 (42%); HRMS (EI) Calcd for $C_{10}H_{12}O_2$ (M^+): 167.0250. Found: 167.0245.

4.1.7.2. Benzyl 4-benzyloxyphenylacetate (7a).[2a] To a solution of 4-benzyloxyphenylacetic acid (2.42 g, 10.0 mmol) and Et_3N (1.40 mL, 10.0 mmol) in THF (20.0 mL) at room temperature was added benzyl bromide (1.19 mL, 10.0 mmol). The solution was stirred at room temperature for 24 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ether (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography to afford benzyl 4-benzyloxyphenylacetate (**7a**) as a colorless solid (2.19 g, 88%). ^{1}H NMR ($CDCl_3$): δ=7.30–7.49 (m, 10H), 7.20 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 5.12 (s, 3H), 5.05 (s, 3H), 3.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=173.6, 159.8, 138.8, 138.8, 137.7, 132.3, 132.2, 130.4, 130.0, 130.0, 129.8, 129.3, 71.8, 68.4, 42.3; MS (EI) *m*/*z* 332 (M^+,), 242, 149, 91 (100%). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.49; H, 6.06. Found: C, 79.21; H, 6.10.

4.1.7.3. Benzyl allyloxyacetate (7e). To a solution of benzyl glycolate (0.83 g, 5.00 mmol) and NaH (240 mg, 6.00 mmol) in DMF (10.0 mL) was added allyl bromide (0.43 mL, 5.00 mmol). The solution was refluxed for 21 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford benzyl allyloxyacetate (**7e**) as a pale yellow oil (499 mg, 48%). ^{1}H NMR ($CDCl_3$): δ=7.37–7.33 (m, 5H), 5.96–5.86 (m, 1H), 5.29 and 5.23 (each d, *J*=171.1, 10.8 Hz, each 1H), 5.20 (s, 2H), 4.13 (s, 2H), 4.10 (d, *J*=5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=170.2, 135.4, 133.7, 128.6, 128.4, 127.6, 127.0, 118.2, 72.4, 67.1, 66.5; MS (FAB: Gly) *m*/*z* 207 (M^++H, 9%), 149 (7%), 131 (5%); HRMS (FAB: Gly) Calcd for $C_{11}H_{15}O_3$ (M^++H): 207.1021. Found: 207.1025.

4.1.7.4. Benzyl 4-vinylbenzoate (7g). To a solution of 4-vinylbenzoic acid (0.74 g, 5.00 mmol), EDC·HCl (1.15 g, 6.00 mmol) and DMAP (61.1 mg, 0.50 mmol) in CH_2Cl_2 (15.0 mL) was added benzyl alcohol (541 mg, 5.00 mmol). After the solution was refluxed for 1 h, the mixture was extracted with chloroform (50 mL×2) and water (50 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=100:1) to afford benzyl 4-vinylbenzoate (**7g**) as a pale yellow oil (0.93 g, 78%). ^{1}H NMR ($CDCl_3$): δ=8.03 (d, *J*=8.3 Hz, 2H), 7.47–7.34 (m, 7H), 6.75 (dd, *J*=10.7, 17.6 Hz, 1H), 5.86 and 5.38 (each d, *J*=17.6 Hz, each 1H), 5.36 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=116.2, 142.1, 136.1, 136.0, 130.0, 129.3, 128.6, 128.2, 128.2, 126.1, 116.5, 66.7; MS (EI) *m*/*z* 238 (M^+, 40%), 131

(100%), 91 (46%), 77 (15%); HRMS (EI) Calcd for $C_{16}H_{14}O_2$ (M^+): 238.0994. Found: 238.0985.

4.1.7.5. Benzyl 2-(benzyloxycarbonyl)cinnamate (7h). To a solution of 2-carboxycinnamic acid (0.96 g, 5.00 mmol), EDC·HCl (2.30 g, 12.0 mmol) and DMAP (112 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL) was added benzyl alcohol (1.08 g, 10.0 mmol). The solution was stirred at room temperature for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford benzyl 2-(benzyloxycarbonyl)cinnamate (**7h**) as a colorless oil (958 mg, 51%). ^{1}H NMR ($CDCl_3$): δ=8.52 (d, J=15.6 Hz, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.33–7.59 (m, 13H), 6.34 (d, J=15.6 Hz, 1H), 5.36 (s, 2H), 5.26 (s, 2H); ^{13}C NMR ($CDCL_3$): δ= 166.5, 166.2, 144.4, 136.5, 136.1, 135.6, 132.4, 130.9, 130.0, 129.4, 128.6, 128.4, 128.4, 128.2, 128.0, 120.8, 67.2, 66.3; MS (EI) *m/z* 372 (M^+, 5%), 28 (100%), 91 (100%), 105 (12%), 77 (10%), 44 (10%); HRMS (EI) Calcd for $C_{24}H_{20}O_4$ (M^+): 372.1364. Found: 372.13615.

4.1.7.6. Benzyl 4-azidomethylbenzoate (7i). To a solution of 4-hydroxymethylbenzoic acid (1.52 g, 10.0 mmol), Et_3N (1.70 mL, 12.0 mmol) in CH_2Cl_2 (10.0 mL) was added benzyl bromide (1.20 mL, 10.0 mmol). After the solution was stirred at room temperature for 23 h, the mixture was extracted with chloroform (100 mL) and water (100 mL). The organic layer was washed with sat. $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=2:1) to afford benzyl 4-hydroxymethylbenzoate[22] as a colorless solid (1.14 g, 47%). ^{1}H NMR ($CDCl_3$): δ=8.07 (d, J=8.3 Hz, 2H), 7.46–7.32 (m, 7H), 5.37 (s, 2H), 4.77 (d, J=5.9 Hz, 2H), 1.77 (t, J=5.9 Hz, OH). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.47; H, 5.92.

To a solution of benzyl 4-hydroxymethylbenzoate (0.30 g, 1.24 mmol) in CCl_4 (10.0 mL) was added Ph_3P (0.52 g, 2.00 mmol). The solution was refluxed for 18 h, after which time the solvent was removed under vacuum pressure. The residue was applied to a flash silica gel column chromatography (hexane/ether=50:1) to afford benzyl 4-chloromethylbenzoate[23] (0.26 g, 82%). ^{1}H NMR ($CDCl_3$): δ= 8.07 (d, J=8.3 Hz, 2H), 7.46–7.32 (m, 7H), 5.37 (s, 2H), 4.60 (s, 2H); MS (EI) *m/z* 262 (M^++2, 10%), 260 (M^+, 33%), 155 (32%), 153 (100%), 91 (64%).

To a solution of benzyl 4-chloromethylbenzoate (0.26 g, 0.96 mmol) in DMF (10.0 mL) was added NaN_3 (0.20 g, 3.00 mmol). The solution was stirred at room temperature for 12 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford benzyl 4-azidomethylbenzoate (**7i**) as a pale yellow oil (0.26 g, 98%). ^{1}H NMR ($CDCl_3$): δ=8.10 (d, J=7.8 Hz, 2H), 7.47–7.35 (m, 7H), 5.38 (s, 2H), 4.42 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=165.9, 140.5, 135.9, 130.2, 130.1, 128.6, 128.3, 128.2, 127.9, 66.8, 54.3; MS (EI) *m/z* 267 (M^+, 28%), 239 (50%), 160 (40%), 132 (96%), 91 (100%), 77 (35%); HRMS (EI) Calcd for $C_{15}H_{13}N_3O_2$ (M^+): 267.1008. Found: 267.1000.

4.1.7.7. *N*-(Benzyloxycarbonyl)diallylamine (11).[17] To a solution of diallylamine (1.94 g, 20.0 mmol) in CH_2Cl_2 (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (5.48 g, 22.0 mmol). The solution was stirred at room temperature for 7 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford *N*-(benzyloxycarbonyl)diallylamine (**11**) as a yellow oil (2.52 g, 55%). ^{1}H NMR ($CDCl_3$): δ=7.30–7.36 (m, 5H), 5.70–5.83 (m, 2H), 5.15 (s, 2H), 5.05–5.19 (m, 2H), 3.87–3.90 (m, 2H); HRMS (EI) Calcd for $C_{14}H_{18}NO_2$ (M^+): 232.1337. Found: 232.1346.

4.1.7.8. *N*-(Benzyloxycarbonyl)aniline (14a).[24] To a solution of aniline (0.46 g, 5.00 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.45 g, 6.00 mmol). After the solution was stirred at room temperature for 20 h, the mixture was extracted with ethyl acetate (150 mL) and water (100 mL×2). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford *N*-(benzyloxycarbonyl)aniline (**14a**) as a colorless solid (1.08 g, 95%). ^{1}H NMR ($CDCl_3$): δ= 7.65–7.25 (m, 1H), 7.06 (t, J=7.3 Hz, 1H), 6.72 (brs, NH), 5.20 (s, 2H). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.98; H, 5.61; N, 6.13.

4.1.7.9. *N*-Benzyloxycarbonyl-4-vinylaniline (14b).[17] To a solution of 4-vinylaniline (1.00 g, 8.39 mmol) in CH_2Cl_2 (10.0 mL) was added *N*-(benzyloxycarbonyloxy)-succinimide (2.45 g, 10.1 mmol). The solution was stirred at room temperature for 7 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford *N*-benzyloxycarbonyl-4-vinylaniline (**14b**) as a pale yellow solid (1.99 g, 92%). ^{1}H NMR ($CDCl_3$): δ=7.35–7.40 (m, 9H), 6.67 (dd, J=10.8, 17.6 Hz, 2H), 5.66 (d, J=17.6 Hz, 1H), 5.20 (s, 2H). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.79; H, 5.99; N, 5.54.

4.1.7.10. *N*-Allyl-*N*-(benzyloxycarbonyl)aniline (14c).[17] To a solution of *N*-allylaniline (1.33 g, 10.0 mmol) in CH_2Cl_2 (10.0 mL) was added *N*-(benzyloxycarbonyloxy)-succinimide (2.91 g, 12.0 mmol). The solution was stirred at room temperature for 7 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford

N-allyl-*N*-(benzyloxycarbonyl)aniline (**14c**) as a yellow oil (2.28 g, 85%). ^{1}H NMR ($CDCl_3$): δ=7.19–7.40 (m, 10H), 5.86–5.98 (m, 1H), 5.16 (s, 2H), 5.10–5.20 (m, 2H), 4.26–4.29 (m, 2H); HRMS (EI) Calcd for $C_{17}H_{17}NO_2$ (M^+): 267.1259. Found: 267.1250.

4.1.7.11. Cinnamyl *N*-(benzyloxycarbonyl)anthranilate (14d). To a solution of cinnamyl anthranilate (1.20 g, 5.00 mmol) and NaH (60% dispersion in mineral oil, 0.36 g, 9.00 mmol) in THF (20.0 mL) was added benzyl chloroformate (1.29 g, 9.00 mmol). After the solution was stirred at room temperature for 46 h, the mixture was extracted with ethyl acetate (100 mL) and phosphate buffer (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford cinnamyl *N*-(benzyloxycarbonyl)anthranilate (**14d**) as a colorless solid (1.15 g, 59%); mp 72–72.5 °C. ^{1}H NMR ($CDCl_3$): δ=10.59 (s, NH), 8.47 (d, J=7.8 Hz, 1H), 8.47 (d, J=7.8 Hz, 1H), 8.07 (d, J=7.8 Hz, 1H), 7.54 (t, J=7.8 Hz, 1H), 7.44–7.25 (m, 5H), 7.04 (t, J=7.8 Hz, 1H), 6.74 (d, J=15.9 Hz, 1H), 6.38 (dt, J=15.9, 6.3 Hz, 1H), 5.22 (s, 2H), 4.96 (d, J=6.3 Hz, 2H). Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.42; H, 5.52; N, 3.66.

4.1.7.12. 5′-Hexenyl 4-(benzyloxycarbonylamino)-benzoate (14e). To a solution of 4-aminobenzoic acid (1.37 g, 10.0 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (2.91 g, 12.0 mmol). The solution was stirred at room temperature for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL×2). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (chloroform/methanol=100:1) to afford 4-(benzyloxycarbonylamino)benzoic acid[25] as a fresh-colored solid (crude) (2.21 g, 81%). ^{1}H NMR (CD_3OD): δ=7.93 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.8 Hz, 2H), 7.42–7.30 (m, 5H), 5.19 (s, 2H); MS (EI) *m/z* 271 (M^+, 14%), 227 (11%), 91 (100%).

To a solution of 4-(benzyloxycarbonylamino)benzoic acid (1.63 g, 6.00 mmol), EDC·HCl (1.38 g, 7.20 mmol) and DMAP (0.60 g, 0.60 mmol) in CH_2Cl_2 (10.0 mL) was added 5-hexene-1-ol (601 mg, 6.00 mmol). After the solution was refluxed for 2 h, the mixture was extracted with CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (chloroform) to afford 5′-hexenyl 4-(benzyloxycarbonylamino)-benzoate (**14e**) as a colorless solid (1.27 g, 60%); mp 58–59 °C. ^{1}H NMR ($CDCl_3$): δ=7.99 (d, J=8.8 Hz, 2H), 7.47–7.35 (m, 7H), 6.93–6.87 (brs, NH), 5.87–5.77 (m, 1H), 5.22 (s, 2H), 5.03 and 4.98 (each d, J=17.1, 9.8 Hz, each 1H), 4.30 (t, J=7.1 Hz, 2H), 2.13 (q, J=7.1 Hz, 2H), 1.81–1.74 (m, 2H), 1.61–1.50 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=166.2, 152.8, 142.0, 138.4, 135.7, 130.9, 128.7, 128.5, 128.4, 125.3, 117.6, 114.8, 67.3, 64.8, 33.3, 28.2, 25.3; MS (EI) *m/z* 353 (M^+, 5%), 271 (7%), 227 (9%), 163 (34%), 146 (100%), 108 (24%), 91 (72%), 82 (42%), 44 (46%). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.31; H, 6.53; N, 3.91.

4.1.7.13. *N*-Benzyloxycarbonyl-4-ethynylaniline (14f).[26] To a solution of 4-ethynylaniline (0.58 g, 5.00 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (2.18 g, 9.00 mmol). The solution was stirred at room temperature for 36 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=10:1) to afford *N*-benzyloxycarbonyl-4-ethynylaniline (**14f**) as a flesh-colored solid (1.17 g, 93%); mp 98.5–99 °C. ^{1}H NMR ($CDCl_3$): δ=7.45–7.34 (m, 9H), 6.70 (brs, NH), 5.20 (s, 2H), 3.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ=152.9, 138.3, 135.8, 133.0, 128.7, 128.5, 128.4, 118.2, 116.9, 83.5, 76.5, 67.2; MS (EI) *m/z* 251 (M^+, 22%), 207 (12%), 91 (100%). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.63; H, 5.24; N, 5.49.

4.1.7.14. Methyl 4-bromocinnamate (18). To a solution of 4-bromocinnamic acid (2.27 g, 10.0 mmol) in DMF (5.00 mL) was added *N*,*N*-dimethylformamide dimethylacetal (13.3 ml, 100 mmol). The solution was stirred at room temperature for 24 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with sat. $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford methyl 4-bromocinnamate (**18**) as a colorless solid (1.53 mg, 64%); mp 88–93 °C. ^{1}H NMR ($CDCl_3$): δ=7.62 (d, J=15.9 Hz, 1H), 7.52 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.6 Hz, 2H), 6.43 (d, J=15.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=167.2, 143.5, 133.3, 132.1, 129.4, 124.5, 118.5, 51.8; MS (EI) *m/z* 242 (M^++H, 82%), 240 (M^+−H, 84%), 211 (97%), 209 (100%), 183 (24%), 181 (24%), 102 (86%). Anal. Calcd for $C_{10}H_9O_2Br$: C, 49.82; H, 3.76. Found: C, 49.83; H, 3.77.

4.1.7.15. Ethyl 4-(*N*-bezyloxyxcarbonylamino)cinnamate (19). To a solution of ethyl 4-aminocinnamate (761 mg, 4.00 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.16 g, 4.80 mmol). The solution was refluxed for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=10:1) to afford ethyl 4-(*N*-bezyloxyxcarbonylamino)cinnamate (**19**) as a colorless solid (405 mg, 31%); mp 119–121 °C. ^{1}H NMR ($CDCl_3$): δ=7.62 (d, J=15.9 Hz, 1H), 7.35–7.49 (m, 9H), 6.78 (s, 1H), 6.34 (d, J=15.9 Hz, 1H), 5.21 (s, 2H), 4.25 (q, J=7.2 Hz, 2H), 1.33 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=167.2, 153.0, 143.9, 139.6, 135.8, 129.7, 129.1, 128.7, 128.5, 128.4, 118.5, 116.9, 67.3, 60.4, 14.3; MS (EI) *m/z* 325 (M^+, 42%), 281 (20%), 91 (100%). Anal. Calcd for

$C_{19}H_{19}O_2NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.17; H, 5.94; N, 4.33.

4.1.8. General procedure of chemoselective hydrogenation using 2.5% Pd/Fib. After two vacuum/H_2 cycles to remove air from the round-bottom flask, a mixture of the substrate (1.00 mmol), 2.5% Pd/Fib (10 wt% of the substrate) in methanol (5.00 mL) was vigorously stirred at room temperature (ca. 20 °C) or at 50 °C under ambient pressure of hydrogen (balloon). The reaction mixture was filtered through a filter paper, and the filtrate was concentrated under reduced pressure to afford the product.

4.1.8.1. 3-Phenylpropiophenone (2a).[27] Yield 97% as a colorless solid; mp 74–75 °C. ^{1}H NMR ($CDCl_3$): δ=7.96 (d, J=7.3 Hz, 2H), 7.56 (t, J=7.3 Hz, 1H), 7.45 (t, J=7.3 Hz, 2H), 7.20–7.35 (m, 5H), 3.31 (t, J=7.6 Hz, 2H), 3.07 (t, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=199.2, 141.3, 136.9, 133.0, 128.6, 128.5, 128.4, 128.0, 126.1, 40.4, 30.1; MS (EI) m/z 210 (M^+, 65%), 105 (100%), 77 (40%). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.54; H, 6.68.

4.1.8.2. 1,5-Diphenylpentane-1-one (2b).[28] Yield 100% as a yellow oil. ^{1}H NMR ($CDCl_3$): δ=7.94 (d, J=7.3 Hz, 2H), 7.14–7.57 (m, 8H), 2.99 (t, J=7.3 Hz, 2H), 2.67 (t, J=7.6 Hz 2H), 1.68–1.84 (m, 4H); ^{13}C NMR ($CDCl_3$): δ=142.2, 137.0, 132.9, 128.5, 128.4, 128.3, 128.0, 125.8, 125.7, 38.4, 35.8, 31.1, 24.0; MS (EI) m/z 238 (M^+, 29%), 133 (34%), 120 (87%), 105 (100%), 91 (40%), 77 (60%); HRMS (EI) Calcd for $C_{17}H_{18}O$ (M^+): 238.1358. Found: 238.1365.

4.1.8.3. 4-Hydroxy-3-propylacetophenone (2c). Yield 99% as a green solid; mp 93–95 °C. ^{1}H NMR ($CDCl_3$): δ=7.79 (s, 1H), 6.91 and 7.73 (each d, J=8.3 Hz, each 1H), 2.64 (t, J=7.8 Hz, 2H), 2.58 (s, 3H), 1.64–1.69 (m, 2H), 0.97 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=198.7, 159.4, 131.2, 129.5, 129.1, 128.6, 115.1, 31.9, 26.2, 22.6, 13.9; MS (EI) m/z 178 (M^+, 30%), 163 (100%), 149 (23%). Anal. Calcd for $C_{11}H_{14}O_2 \cdot 1/10$: C, 73.39; H, 7.95. Found: C, 73.46; H, 7.95.

4.1.8.4. 2-Propyl-4,6-dibenzoylresorcinol (2d). Yield 74% as a light green solid; mp 167–169 °C. ^{1}H NMR ($CDCl_3$): δ=13.16 (s, 2H), 7.88 (s, 1H), 7.38–7.58 (m, 12H), 2.76 (t, J=7.6 Hz, 2H), 1.62–1.71 (m, 2H), 1.04 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=200.3, 167.4, 140.4, 137.5, 131.9, 128.8, 118.4, 112.0, 24.1, 21.6, 14.2; MS (EI) m/z 360 (M^+, 55%), 332 (24%), 331 (100%), 332 (24%), 253 (16%), 175 (33%), 105 (16%), 77 (16%). Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.44; H, 5.64.

4.1.8.5. 3-Benzoylpropionic acid (2e). Commercially available (Aldrich), 98% as a yellow solid; mp 117–119 °C. ^{1}H NMR ($CDCl_3$): δ=7.98 (d, J=7.4 Hz, 2H), 7.57 (t, J=7.4 Hz, 1H), 7.47 (t, J=7.4 Hz, 2H), 3.32 (t, J=6.6 Hz, 2H), 2.82 (t, J=6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=197.8, 178.5, 136.4, 133.3, 128.0, 33.1, 28.0; MS (EI) m/z 178 (M^+, 8%), 105 (100%), 77 (39%). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.55; H, 5.59.

4.1.8.6. 3-(4-Methylbenzoyl)propionic acid (2f). Commercially available (Aldrich), 99% as a light green solid; mp 129–131 °C. ^{1}H NMR ($CDCl_3$): δ=7.26 and 7.88 (each d, J=8.3 Hz, each 2H), 3.29 (t, J=6.6 Hz, 2H), 2.81 (t, J=6.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=197.5, 178.8, 144.1, 133.9, 129.3, 128.2, 33.0, 28.1, 21.6; MS (EI) m/z 192 (M^+, 10%), 119 (100%), 91 (32%), 65 (10%). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.72; H, 6.30. Found: C, 68.73; H, 6.27.

4.1.8.7. 4-(2-Phenylethyl)benzaldehyde (2g).[29] Yield 100% as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ=9.97 (s, 1H), 7.79 (d, J=8.3 Hz, 2H), 7.14–7.32 (m, 9H), 2.92–3.03 (m, 4H); ^{13}C NMR ($CDCl_3$): δ=192.0, 149.1, 140.9, 134.6, 129.9, 129.2, 128.4, 126.2, 38.0, 34.7; MS (EI) m/z 210 (M^+, 35%), 107 (28%), 91 (100%), 77 (25%). Anal. Calcd for $C_{15}H_{14}O \cdot 1/2H_2O$: C, 82.16; H, 6.89. Found: C, 82.51; H, 6.56.

4.1.8.8. 2-Propyloxybenzaldehyde (2h).[30] Yield 100% as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ=10.53 (s, 1H), 7.83 (dd, J=1.4, 7.9 Hz, 1H), 7.53 (dt, J=0.65, 7.9 Hz, 1H), 7.01 (t, J=7.9 Hz, 1H), 6.98 (d, J=7.9 Hz, 1H), 4.05 (t, J=6.8 Hz, 2H), 1.84–1.93 (m, 2H), 1.08 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=189.9, 189.8, 161.6, 135.9, 128.2, 120.5, 112.5, 70.0, 22.5, 10.5; MS (EI) 166 (M^++2, 25%), m/z 164 (M^+, 28%), 123 (65%), 121 (100%), 120 (35%), 57 (29%); HRMS (EI) Calcd for $C_{10}H_{12}O_2$ (M^+): 164.0837. Found: 164.0835.

4.1.8.9. Methylmanderate (2i). Commercially available (Aldrich), 98% as a colorless solid. ^{1}H NMR ($CDCl_3$): δ=7.30–7.43 (m, 5H), 5.18 (s, 1H), 3.76 (s, 3H).

4.1.8.10. Benzoin (2j). Commercially available (Aldrich), 98% as a colorless solid. ^{1}H NMR ($CDCl_3$): δ=7.92 (d, J=7.7 Hz, 2H), 7.53 (t, J=7.7 Hz, 1H), 7.40 (t, J=7.7 Hz, 2H), 7.34–7.27 (m, 5H), 5.96 (d, J=6.1 Hz, 1H), 4.55 (d, J=6.1 Hz, OH).

4.1.8.11. 4-Chloroethylbenzene (6e). Commercially available (TCI), 100%. ^{1}H NMR ($CDCl_3$): δ=7.14 and 7.22 (each d, J=8.3 Hz, each 2H), 2.59 (q, J=7.7 Hz, 2H), 1.86 (t, J=7.7 Hz, 3H); MS (EI) m/z 140 (M^+, 35%), 127 (31%), 125 (100%), 105 (40%).

4.1.8.12. 4′-Chloro-3-phenylpropiophenone (6f).[31] Yield 98% as a colorless solid; mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ=7.42, 7.89 (each d, J=8.3 Hz, each 2H), 7.19–7.32 (m, 5H), 2.37 (t, J=7.7 Hz, 2H), 3.06 (t, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=198.0, 141.0, 139.5, 135.2, 129.5, 128.9, 128.5, 128.4, 126.2, 40.4, 30.0; MS (EI) m/z 246 (M^+, 15%), 244 (55%), 141 (34%), 139 (100%), 111 (30%), 105 (15%), 91 (14%), 77 (13%); HRMS (EI) Calcd for $C_{15}H_{13}OCl$ (M^+): 244.0655. Found: 244.0661. Anal. Calcd for $C_{15}H_{13}OCl$: C, 73.62; H, 5.35. Found: C, 73.70; H, 5.21.

4.1.8.13. 3-(4-Chlorophenyl)propiophenone (6g).[32] Yield 99% as a light green solid; mp 53–55 °C. ^{1}H NMR ($CDCl_3$): δ=7.94 (d, J=6.8 Hz, 2H), 7.17–7.60 (m, 7H), 3.04 and 3.28 (each t, J=7.6 Hz, each 2H); ^{13}C NMR ($CDCl_3$): δ=198.8, 139.7, 133.1, 129.8, 129.5, 129.2, 128.5, 128.0, 122.5, 40.1, 29.3; MS (EI) m/z 244 (M^+,

48%), 105 (100%), 77 (42%). Anal. Calcd for $C_{15}H_{13}OCl$: C, 73.62; H, 5.35. Found: C, 73.66; H, 5.34.

4.1.8.14. 2,3-Dichloro-4-*sec*-pentanoylphenoxyacetic acid (6h).[33] Yield 100% as a colorless solid. ^{1}H NMR ($CDCl_3$): δ=6.80 and 7.27 (each d, J=8.6 Hz, each 2H), 4.81 (s, 2H), 3.17–3.82 (m, 1H), 1.75–7.82 (m, 1H), 1.41–1.47 (m, 1H), 1.17 (d, J=6.8 Hz, 3H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=206.6, 172.5, 155.5, 135.2, 131.4, 126.9, 110.8, 65.6, 46.8, 26.0, 15.6, 11.6; MS (FAB: Gly) m/z 307 (M^++2, 15%), 305 (M^+, 25%). Anal. Calcd for $C_{13}H_{14}O_4Cl\cdot 1/4H_2O$: C, 50.56; H, 4.74. Found: C, 50.64; H, 4.65.

4.1.8.15. 2-Chlorobenzylamine (6i). Commercially available (TCI), 91% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.18–7.39 (m, 4H), 3.94 (s, 2H), 2.57 (s, 1H); MS (EI) 265 (20%), 264 (18%), 230 (17%), 154 (19%) m/z 140 (M^+−1, 25%), 127 (29%), 125 (100%), 91 (25%), 89 (24%).

4.1.8.16. 4-Bromoethylbenzene (6j). Commercially available (TCI), 100%. ^{1}H NMR ($CDCl_3$): δ=7.17 and 7.44 (each d, J=8.3 Hz, each 2H), 2.66 (q, J=7.7 Hz, 2H), 1.26 (t, J=7.7 Hz, 3H).

4.1.8.17. Dipropyl 2,3,4,5-tetrabromophthalate (6k).[34] Yield 94% as a colorless solid; mp 61–62 °C. ^{1}H NMR ($CDCl_3$): δ=4.27 (t, J=6.6 Hz, 4H), 1.75 (m, 4H), 1.01 (t, J=7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ=164.8, 138.3, 135.4, 132.0, 122.7, 68.5, 21.7, 10.4; MS (EI) m/z 566 (M^+, 12%), 524 (9%), 483 (29%), 482 (40%), 481 (30%), 466 (60%), 465 (100%), 464 (65%), 420 (12%).

4.1.8.18. Benzyl propionate (10b). Commercially available (Aldrich), 91% determined by ^{1}H NMR. ^{1}H NMR (THF-d_8): δ=7.29–7.20 (m, 5H), 5.02 (m, 2H), 2.29–2.25 (m, 2H), 1.02 (t, J=7.8 Hz, 3H).

4.1.8.19. Benzyl isobutylate (10c). Commercially available (TCI), 93% determined by ^{1}H NMR. ^{1}H NMR (THF-d_8): δ=7.29–7.20 (m, 5H), 5.02 (s, 2H), 2.52–2.46 (m, 1H), 1.08 (d, J=7.0 Hz, 6H).

4.1.8.20. Benzyl 2-methylbutylate (10d).[35] 77% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.36–7.31 (m, 5H), 5.12 (s, 2H), 2.45–2.40 (m, 1H), 1.74–1.67 (m, 1H), 1.53–1.46 (m, 1H), 1.16 (d, J=7.2 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=176.6, 136.3, 128.5, 128.1, 128.0, 66.0, 41.1, 26.8, 16.6, 11.6; MS (EI) m/z 192 (M^+, 25%), 181 (67%), 180 (50%), 179 (40%), 165 (25%), 108, (20%), 91 (100%), 57 (43); HRMS (EI) Calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150. Found: 192.1156.

4.1.8.21. Benzyl propyloxyacetate (10e). Yield 99% as a light brown oil. ^{1}H NMR ($CDCl_3$): δ=7.37–7.33 (m, 5H), 5.20 (s, 2H), 4.12 (s, 2H), 3.49 (t, J=7.2 Hz, 2H), 1.69–1.60 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=170.5, 135.5, 128.5, 128.4, 73.5, 68.2, 66.4, 22.7, 10.4; MS (FAB, NBA) m/z 209 (M^++H, 20%); HRMS (FAB, NBA) Calcd for $C_{12}H_{17}O_3$ (M^++H): 209.1178. Found: 209.1172.

4.1.8.22. Benzyl 3-phenylpropionate (10f).[36] Yield 98% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.18–7.37 (m, 10H), 5.11 (s, 2H), 2.97 (t, J=7.8 Hz, 2H), 2.69 (t, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=173.0, 140.7, 136.2, 128.8, 128.6, 128.5, 126.6, 66.6, 36.1, 31.2; MS (EI) m/z 240 (M^+, 5%), 180 (60%), 149 (26%), 107 (78%), 91 (100%), 77 (15%); HRMS (EI) Calcd for $C_{16}H_{16}O_2$ (M^+): 240.1150. Found: 2240.1160.

4.1.8.23. Benzyl 4-ethylbenzoate (10g). Yield 97% as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ=8.00 (d, J=8.3 Hz, 2H), 7.46–7.25 (m, 7H), 5.36 (s, 2H), 2.70 (q, J=7.7 Hz, 2H), 1.25 (t, J=7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=166.5, 149.9, 136.2, 129.8, 128.5, 128.1, 127.9, 127.6, 126.1, 66.4, 28.9, 15.2; MS (EI) m/z 240 (M^+, 30%), 133 (100%), 91 (36%); HRMS (EI) Calcd for $C_{16}H_{16}O_2$ (M^+): 240.1150. Found: 224. 1139.

4.1.8.24. Benzyl-2-(benzyloxycarbonyl)propionate (10h). Yield 100% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.95 (d, J=7.2 Hz, 1H), 7.44–7.24 (m, 13H), 5.33 (s, 2H), 5.09 (s, 2H), 3.30 (t, J=7.7 Hz, 2H), 2.70 (t, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=172.8, 167.0, 142.5, 136.0, 135.9, 132.3, 131.2, 131.0, 129.3, 128.6, 128.5, 128.3, 128.3, 128.2, 128.2, 128.1, 126.5, 66.7, 66.2, 35.8, 29.9; MS (EI) m/z 374 (M^+, 3%), 265 (10%), 177 (53%), 149 (18%), 91 (100%); HRMS (EI) Calcd for $C_{24}H_{22}O_4$ (M^+): 374.1511. Found: 374.1518.

4.1.8.25. Benzyl 4-aminomethylbenzoate (10i).[37] Yield 100%. ^{1}H NMR ($CDCl_3$): δ=8.04 (d, J=8.3 Hz, 2H), 7.46–7.26 (m, 7H), 5.36 (s, 2H), 3.94 (s, 2H); MS (EI) m/z 241 (M^+, 20%), 240 (29%), 150 (40%), 134 (75%), 106 (100%), 91 (90%).

4.1.8.26. *N*-Benzyloxycarbonyl-4-ethylaniline (16b).[2a] Yield 97% as a pale yellow powder; mp 72–72.5 °C. ^{1}H NMR ($CDCl_3$): δ=7.41–7.26 (m, 7H), 7.13 (d, J=8.3 Hz, 2H), 6.60 (brs, NH), 5.19 (s, 2H), 2.60 (q, J=7.6 Hz, 2H), 1.21 (t, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=153.5, 139.6, 136.2, 135.4, 128.6, 128.3, 128.3, 119.0, 66.9, 28.2, 15.7.

4.1.8.27. *N*-Benzyloxycarbonyl-*N*-propylaniline (16c). Yield 97% as a light brown oil. ^{1}H NMR ($CDCl_3$): δ=7.37–7.19 (m, 10H), 5.14 (s, 2H), 3.64 (t, J=7.4 Hz, 2H), 1.59–1.43 (m, 2H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=155.5, 141.9, 136.8, 128.9, 128.3, 127.7, 127.5, 127.3, 126.6, 67.0, 52.1, 21.5, 11.1; MS (EI) m/z 269 (M^+, 30%), 196 (20%), 91 (100%); HRMS (EI) Calcd for $C_{17}H_{19}NO_2$ (M^+): 269.1420. Found: 269.1416.

4.1.8.28. 3-Phenylpropyl *N*-(benzyloxycarbonyl)-anthranilate (16d). Yield 99% as a pale yellow solid; mp 40–41 °C. ^{1}H NMR ($CDCl_3$): δ=10.59 (s, NH), 8.46 (d, J=7.8 Hz, 1H), 7.97 (d, J=7.8 Hz, 1H), 7.53 (t, J=7.8 Hz, 1H), 7.43–7.20 (m, 5H), 5.21 (s, 2H), 4.32 (t, J=7.0 Hz, 2H), 2.78 (t, J=7.0 Hz, 2H), 2.14–2.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=168.0, 153.4, 141.7, 140.9, 136.1, 134.5, 130.8, 128.5, 128.4, 128.2, 126.1, 118.8, 114.7, 66.8, 64.6, 32.3, 30.1; MS (EI) m/z 389 (M^+, 10%), 226 (9%), 208 (18%), 118 (40%), 117 (32%), 91 (100%); HRMS (EI) Calcd for $C_{24}H_{23}NO_4$ (M^+): 389.1633. Found: 389.1627.

4.1.8.29. Hexyl 4-(benzyloxycarbonylamino)benzoate (16e). Yield 100% as a colorless solid; mp 85–86 °C. ^{1}H NMR ($CDCl_3$): δ=7.99 (d, J=8.8 Hz, 2H), 7.47–7.34 (m, 7H), 6.86 (brs, NH), 5.22 (s, 2H), 4.29 (t, J=7.0 Hz, 2H), 1.78–1.71 (m, 2H), 1.43–1.32 (m, 6H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=166.2, 152.8, 141.9, 135.7, 130.9, 128.7, 128.5, 128.4, 125.4, 117.6, 67.4, 65.0, 31.5, 28.7, 25.7, 22.5, 14.0; MS (EI) *m/z* 355 (M^+, 18%), 311 (12%), 163 (44%), 146 (42%), 91 (100%); HRMS (EI) Calcd for $C_{21}H_{25}NO_4$ (M^+): 355.1784. Found: 355.1793.

4.1.8.30. Dihydrojasmone (21). Commercially available (TCI), 60% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=2.49–2.47 (m, 2H), 2.37–2.47 (m, 2H), 2.16 (t, J=7.3 Hz, 2H), 2.05 (s, 3H), 1.68–1.24 (m, 6H), 0.87 (t, J=7.3 Hz, 3H); MS (EI) *m/z* 166 (M^+, 15%), 151 (58%), 137 (30%), 123 (25%), 110 (100%), 105 (24%), 81 (24%), 67 (29%); HRMS (EI) Calcd for $C_{11}H_{18}O$ (M^+): 166.1358. Found: 166.1364.

4.1.9. General procedure of hydrogenation using 5% Pd/C or Pd/C(en) (Schemes 7 and 8). After two vacuum/H_2 cycles to remove air from the reaction tube, a mixture of the substrate (1.00 mmol), 5% Pd/C or Pd/C(en) (10 wt% of the substrate) in the solvent (1.00 mL) was vigorously stirred at room temperature (ca. 20 °C) or at 50 °C under ambient pressure of hydrogen (balloon). The reaction mixture was filtered using a membrane filter (Millipore Millex®-LG, 0.20 μm). The quantitative conversion of **11** and **14a**, and the product ratio of **7f** and **14b** were confirmed by ^{1}H NMR of the crude mixture.

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