UNIVERSITY OF ALBERTA

Radical Cyclization Methodology and Total Synthesis of the Otteliones and Halichlorine

by

Dazhan Liu

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Department of Chemistry

Edmonton, Alberta

Fall 2008

Your file Votre référence
ISBN: 978-0-494-46363-5
Our file Notre référence
ISBN: 978-0-494-46363-5

To my family

ABSTRACT

The first chapter of this thesis describes the development of a general indirect method for effecting radical cyclization onto a benzene ring. This process achieves the oxidative radical cyclization by converting a phenol into a cross-conjugated ketone, and then performing the radical cyclization and rearomatization steps. This method forms five-, six-, and seven-membered heterocyclic rings fused to phenols. Modification allows both formation of non-phenolic products, and the introduction of alkyl or aryl substituents on the aromatic ring.

The second chapter describes the total synthesis of antitumor agents ottelione A & B. It was started with a model study, which gave the cores of both otteliones in 4 or 5 steps. With the success of the model study, a racemic synthesis was finished based on a selective ring close metathesis. To further improve the stereoselectivity in building the tetra-substituted five-membered ring, two different approaches were developed. By using either an asymmetric cyclopropanation of 2-cyclopentenone, or by elaboration of D-ribose, optically pure otteliones A and B were successfully prepared.

The last chapter of this thesis describes the total synthesis of marine natural product halichlorine, which was found to selectively inhibit the induction of VCAM-1. The azaspiro core of halichlorine was assembled by aldol condensation, radical cyclization and stereoselective cuprate addition. The quinolizidine ring system in halichlorine was concisely established by application of the Morita-Baylis-Hillam reaction, followed by a spontaneous cyclization. Finally the 15-membered lactone ring was formed using the Keck macrolactonization conditions.

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. D. L. J. Clive for his superb guidance and constant encouragement during the course of my Ph.D. program, and for his assistance during the preparation of this Thesis.

My thanks go to all group members, past and present, for their friendship and useful discussions and for creating an enjoyable and inspiring research environment.

My thanks are also extended to the support staff (IR, MS, NMR, elemental analysis labs, glass blowing, electronic, machine and chemical shops) for their valuable help and advice.

Finally, I would like to thank my family for their support, encouragement, patience and understanding.

TABLE OF CONTENTS

CHAPTER 1

FORMAL RADICAL CYCLIZATION ONTO BENZENE RINGS

CHAPTER 2

SYNTHESIS OF THE CORE STRUCTURES OF OTTELIONES A AND B, SYNTHESIS OF RACEMIC OTTELIONES A AND B AND SYNTHESIS OF OPTICALLY PURE OTTELIONES A AND B

CHAPTER 3

SYNTHESIS OF HALICHLORINE

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
DABCO	1,4-diazabicyclo[2,2,2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
Dess-Martin	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxo-3(H)-one
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	ethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	*N*-(3-dimethylamino)propyl-*N*-ethylcarbodiimde
Et	ethyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
Im	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride

LDA	lithium diisopropylamide
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Min	minute(s)
μM	micormolar
MOM	(methoxymethoxy)methyl
Mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
nM	nanomolar
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pM	picomolar
PPTS	pyridinium *p*-toluenesulfonic acid
RCM	ring closing metathesis
SM	starting material
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl

Tol	*p*-toluene-
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

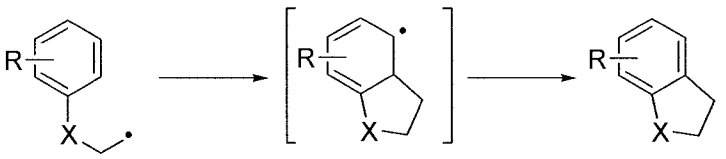
Chapter 1

Formal Radical Cyclization onto Benzene Rings

1 INTRODUCTION

1.1 General

While the cyclization of sp^3 and sp^2 carbon radicals onto double and triple bonds is an integral part of synthetic methodology, radical cyclization onto benzene rings along the lines summarized in Scheme 1 is a far less developed subject, notwithstanding the fact that it can be useful in preparing important benzo-fused compounds. Examples where the acceptor aromatic ring is a heterocycle are fairly well-known[1] and, for benzene rings, there is a growing number of reports[2,3] in which the attacking radical is sp^2 hybridized. However, there does not appear to be a general method to deal with direct closure of sp^3 hybridized carbon onto carbocyclic aromatic rings.

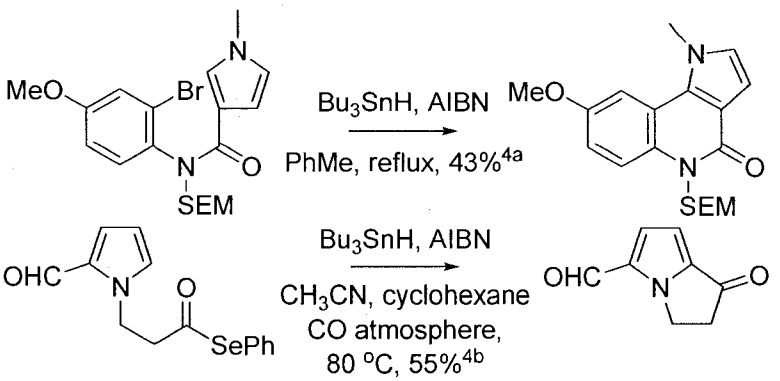


Scheme 1

1.2 Radical Cyclization onto Heteroaromatic Rings

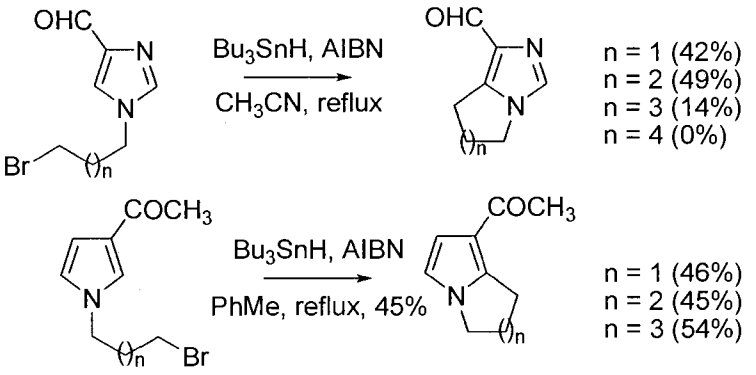
The addition of radicals onto heteroaromatic rings is well described in the literature, and several methods have been devised to affect such cyclizations, with Bu_3SnH-mediated reactions being the most explored.

Aryl and acyl radicals may be cyclized onto pyrroles containing electron withdrawing groups,[4] though the reaction of acyl radicals requires the use of an atmosphere of CO to prevent decarbonylation (Scheme 2).



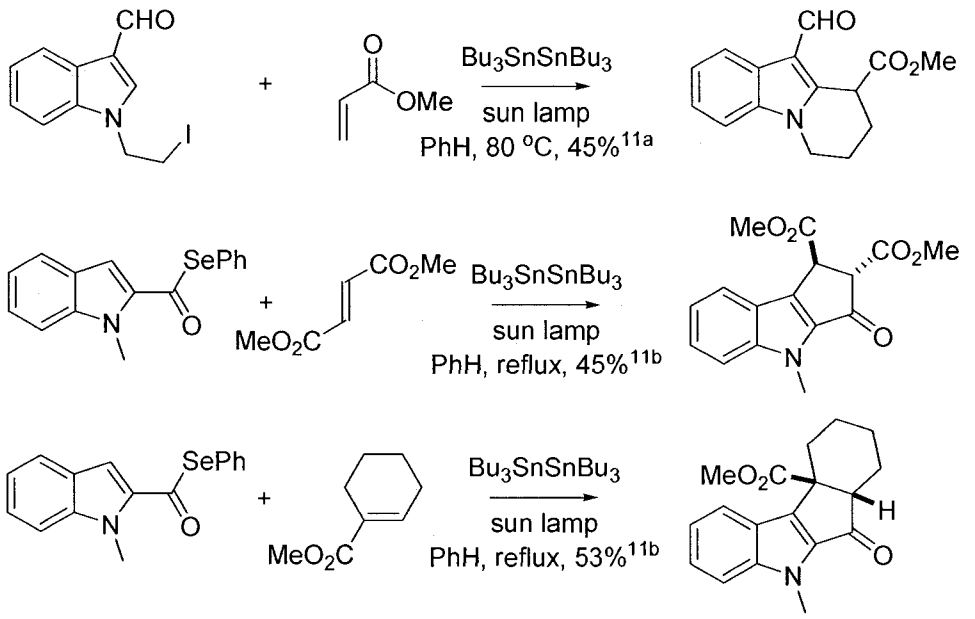
Scheme 2

Carbon radicals that are sp^3 hybridized have been reported to cyclize onto imidazoles and pyrroles having suitable electron withdrawing groups.[5] Under the standard conditions with Bu_3SnH, using syringe pump addition, 5- to 7-membered rings can be formed in modest yield (Scheme 3).



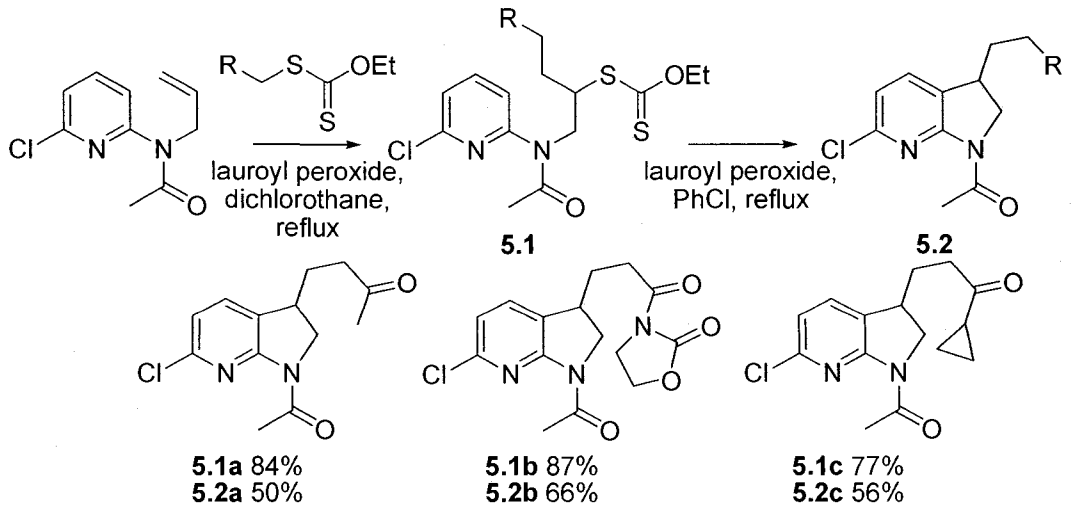
Scheme 3

In the presence of π-radical stabilizing groups, radical cyclization onto indoles,[6] pyridines,[7] pyridinium[8] salts, pyrazoles[5,9] and triazoles[10] can also be accomplished. By using non-reductive conditions (Bu_6Sn_2, *hv*), the ethylindole and the acylindole radicals undergo cascade addition-cyclization sequences with a series of electron-deficient alkenes (Scheme 4).[11] This annulation process provides straightforward access to cyclopenta[*b*]indoles in acceptable yield.[11b]



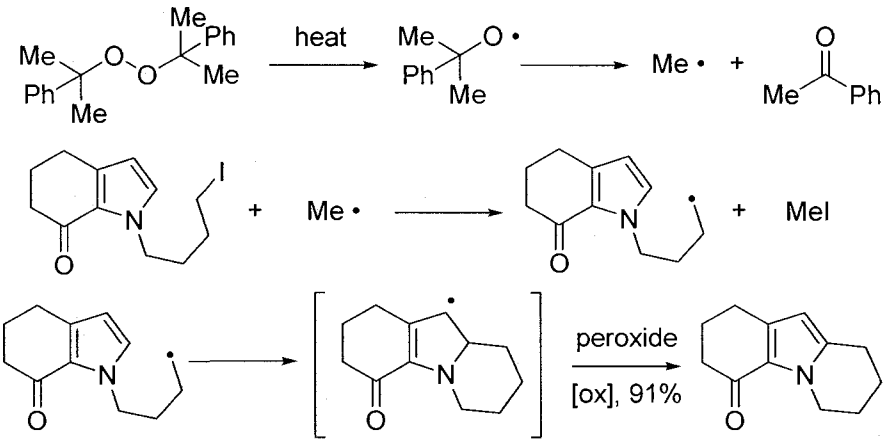
Scheme 4

While Bu_3SnH-mediated reactions are the most explored method for radical cyclization onto heterocycles, a few tin-free protocols have also been developed. Upon exposure to lauroyl peroxide in 1,2-dichloroethane or chlorobenzene, radicals generated from a xanthate group cyclize onto 2-chloro-6-aminopyridines (Scheme 5).[7b]



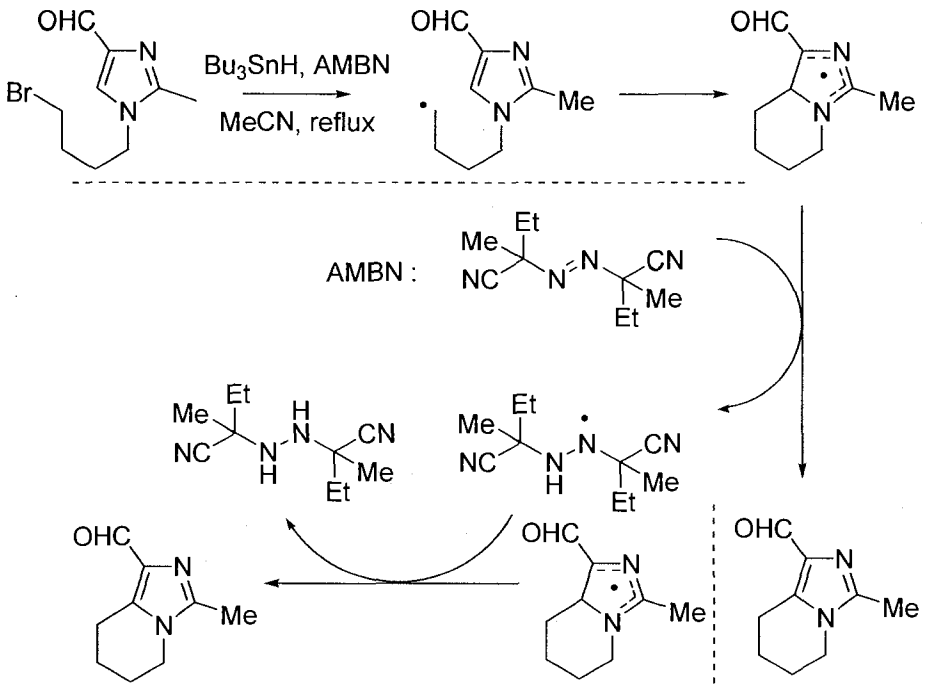
Scheme 5

Dicumyl peroxide was also found to be effective in various cyclization processes onto heterocycles.[6c] By using 1.5 equivalents of dicumyl peroxide, radicals generated from the alkyl iodide side chain cyclized onto various aromatic systems including pyrrole, indole, isoquinolone and pyridine.[6c] The proposed mechanism is shown in Scheme 6. In these radical cyclizations using stoichiometric amounts of peroxide, the peroxide is believed to be acting both as the initiator and the oxidant that regenerates the aromatic system.



Scheme 6

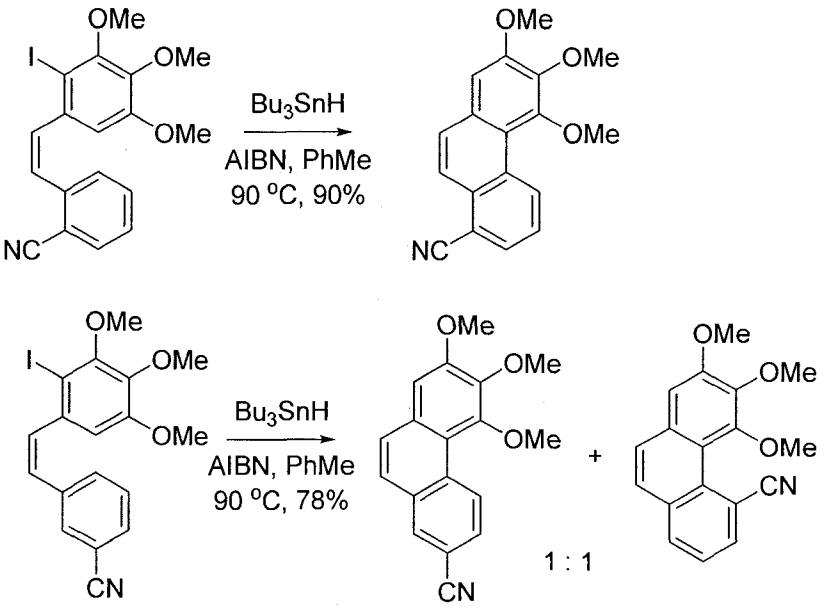
For those cyclizations onto aromatic rings using Bu_3SnH and AIBN, it is quite possible that the resulting relatively stable-radicals are also oxidized by loss of hydrogen (H) in a rearomatization process instead of being reduced by Bu_3SnH. The mechanism for the rearomatization has been the subject of considerable discussion.[12] Curran[13] has suggested that the need for an excess of initiator may be due to oxidation of the cyclohexadienyl radicals by the initiator, or by an initiator-derived radical. Recent detailed mechanistic studies from the Bowman laboratory[14] also pointed out that the predominant reaction sequence involves the initiator acting as an oxidizing agent in the sense shown in (Scheme 7), but the exact details remain unclear.



Scheme 7

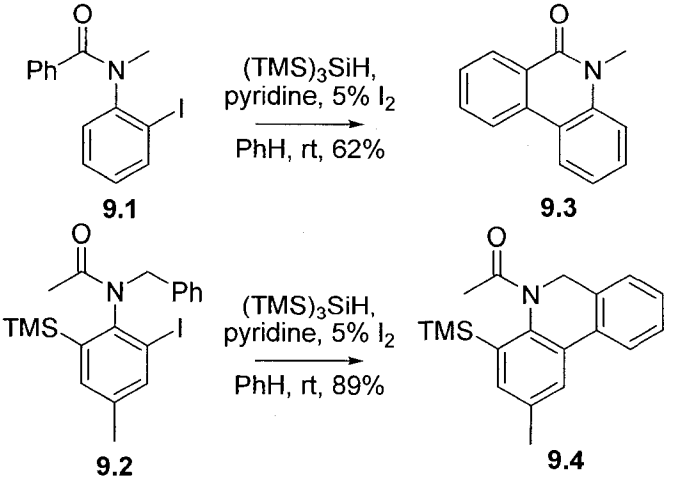
1.3 Cyclizations of vinyl or aryl radicals onto benzene rings

Many examples of radical cyclization of aryl radicals to form polyaromatic products have be examined.[2,15] Intramolecular additions of aryl radicals onto various arenes have been shown to proceed efficiently under standard radical cyclization conditions.[16] The radical acceptor may be electron-rich, unsubstituted or electron-deficient, and when this is substituted at C-2, cyclization occurs to C-6 exclusively (see Scheme 8).



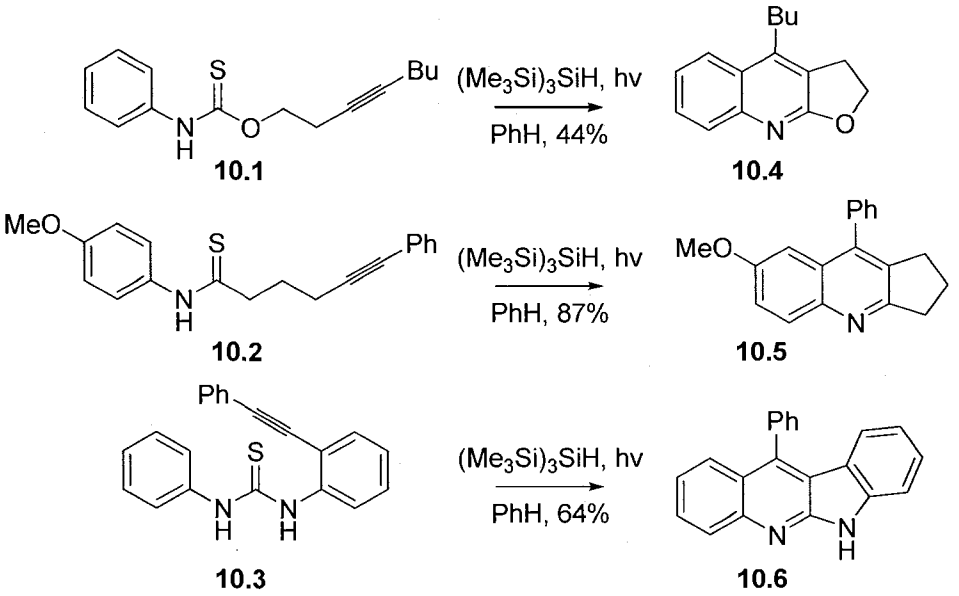
Scheme 8

Aryl iodides have been found to cyclize onto benzene rings under mild conditions.[17] With 5% I_2 as initiator and 1.2 equivalent of tris(trimethylsilyl)silane, compounds **9.1** and **9.2** provided exclusively the corresponding cyclized products **9.3** (62%) and **9.4** (89%) at room temperature in benzene (Scheme 9). The use of Bu_3SnH and AIBN gave lower yields in this type of reaction.



Scheme 9

Cascade radical annulations of thiocarbamates **10.1**, thioamides **10.2**, and thioureas **10.3** provide direct routes to carbocyclic and heterocyclic fused quinolines **10.4-10.6** (Scheme 10).[3a] These reactions provide access to products that are not readily made through imidoyl radical chemistry[18] when the needed imidoyl radical precursors are not available or not stable.

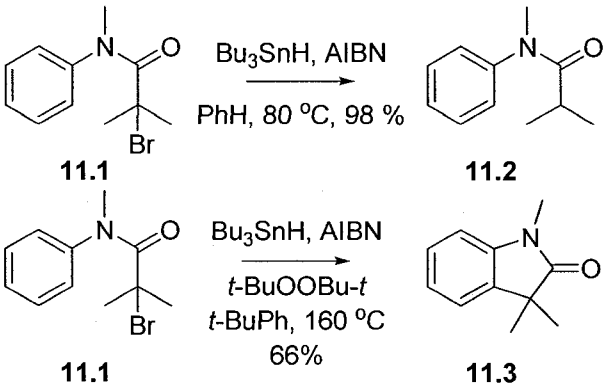


Scheme 10

1.4 Cyclization of sp^3 hybridized radicals onto benzene rings

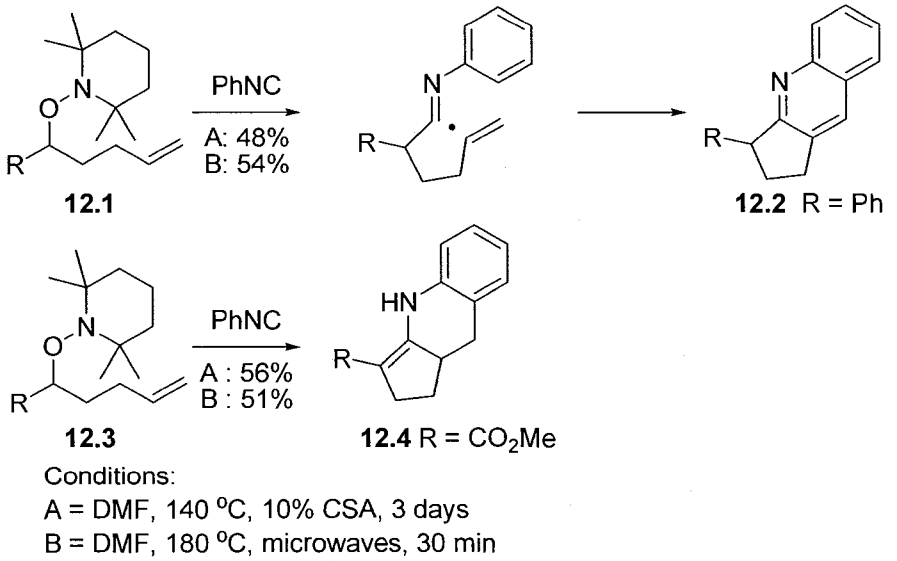
1.4.1 Attack on a Benzene Ring using Standard Radical Cyclization Conditions

When **11.1** was treated with Bu_3SnH and AIBN at 80 °C (Scheme 11), only reduced compound **11.2** was isolated (98% yield by GC analysis).[12a] By adding a catalytic amount of di-*tert*-butyl peroxide to **11.1** and 0.1 M Bu_3SnH in *tert*-butylbenzene at 160 °C, the cyclized product **11.3** was obtained in 66% yield.



Scheme 11

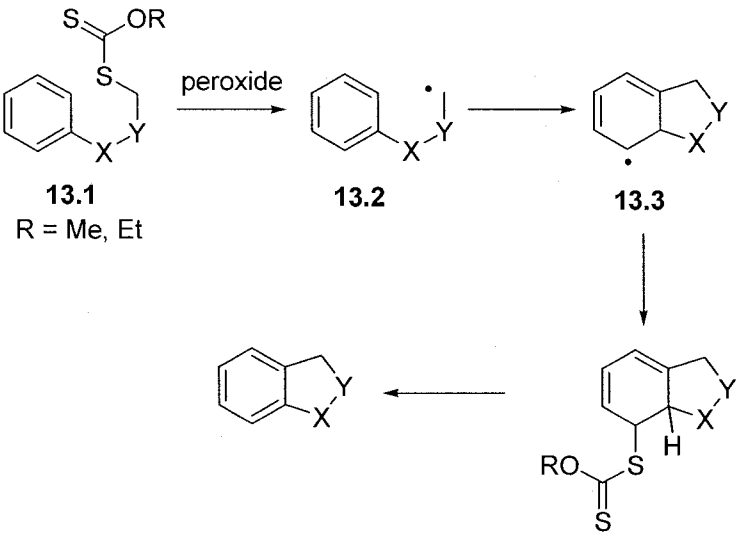
Alkoxyamines are reported as clean sources for the generation of *C*-centered radicals.[19] By thermolysis at 140 °C with 10% CSA for 3 days or using microwave-induced heating at 180 °C for 30 min, a series of quinolines was synthesized from alkoxyamines and various aryl isonitriles. Depending on the substituent R, oxidation to dihydro-1*H*-cyclopenta[*b*]quinolines (**12.1** → **12.2**) or tautomerization to tetrahydro-1*H*-cyclopenta[*b*]quinolines occurs (**12.3** → **12.4**).



Scheme 12

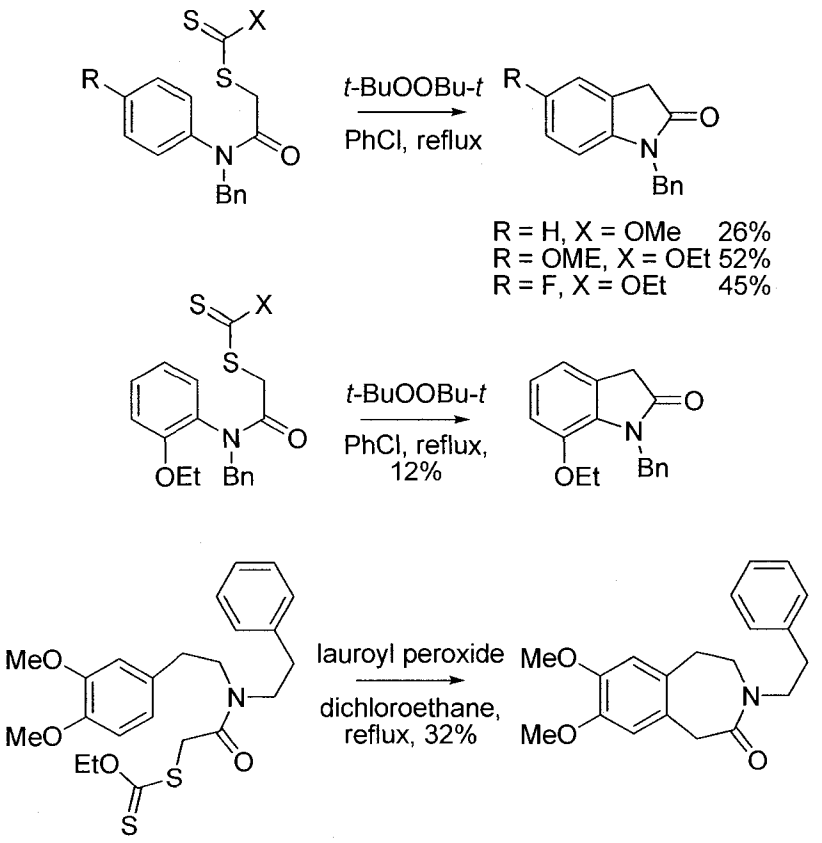
1.4.2 Application of the Xanthate Method

Zard *et al.* have published a series of papers reporting direct radical cyclization onto an aromatic ring.[20] This powerful method relies on the formation of a radical that is more stable than Me· (or Et·, if an ethyl xanthate is used) (Scheme 13).[20i] The conditions used strongly favor oxidative rearomatization over competing pathways. Another factor facilitating this process is that the xanthate (**13.1**) and the derived radical (**13.2**) exist in equilibrium; if they react with each other they produce **13.1** again.



Scheme 13

This process is proposed to generate the radical intermediate reversibly, a situation which allows the radical to be temporarily captured if it does not undergo the required cyclization onto an aromatic ring. Some typical examples including the preparation of a seven-membered ring[20f] are shown in Scheme 14.

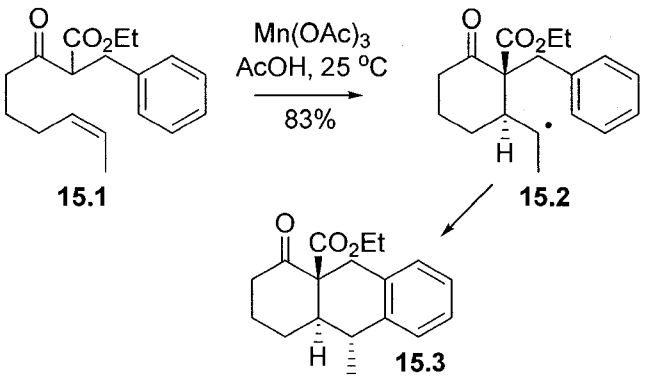


Scheme 14

Limits to this methodology include use of stoichiometric peroxide and high reaction temperatures. These factors are incompatible with sensitive functional groups.

1.4.3 Cyclization of Radicals from β-Dicarbonyl Compounds

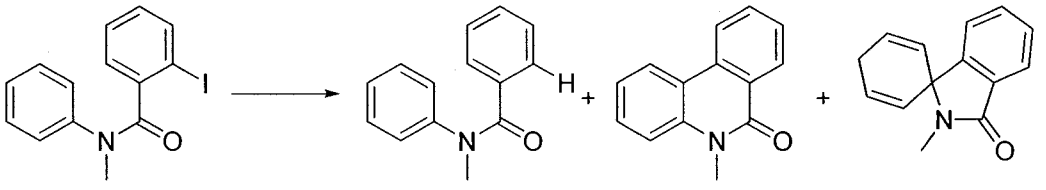
β-Keto esters and related dicarbonyl compounds are oxidized to radicals at 25-70 °C using $Mn(OAc)_3$ in acetic acid.[21] Polycyclization reactions may achieved by this method. Oxidative cyclization of **15.1** with $Mn(OAc)_3$ in acetic acid generates a cyclohexanemethyl radical **15.2**. This adds to the aromatic ring to provide **15.3** as a single stereoisomer in 83% yield (Scheme 15).[22]



Scheme 15

1.5 Radical Cyclization onto an Aromatic Ring without Rearomatization of the Ring

Crich *et al.* have developed conditions where the intermediate cyclohexadienyl radical is trapped without aromatization (Scheme 16).[12c] The method uses catalytic PhSeSePh which, in the presence of Bu_3SnH, generates benzeneselenol. The selenol facilitates hydrogen atom donation to the intermediate cyclohexadienyl radical and leads to cyclohexadienes. Without the presence of PhSeSePh less than 5% of cyclohexadiene product (**16.4**) is obtained together with 37% of starting material (**16.1**) and 23% of reduction product (**16.2**). There is a 1000-fold difference in rate constants for hydrogen atom abstraction from stannanes[23] and selenols[24] by alkyl radicals, with the abstraction from selenols being the faster process.



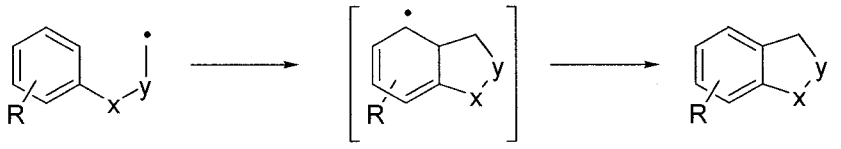
16.1	**16.2**	**16.3**	**16.4**
A : Bu_3SnH, AIBN, PhH, reflux recovered **16.1** 37%	23%	12%	<5%
B : Bu_3SnH, AIBN, 15% PhSeSePh, PhH, reflux, recovered **16.1** 0%	22%	22%	43%

Scheme 16

2 RESULTS AND DISCUSSION

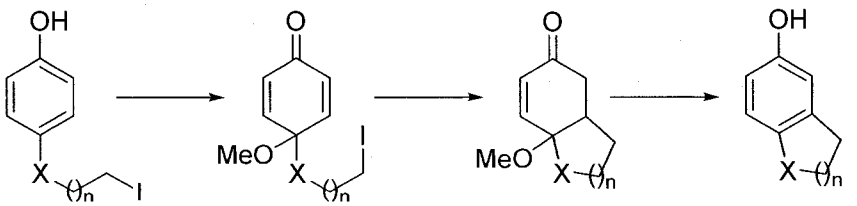
2.1 Research Objectives

The oxidative cyclization of an alkyl radical onto a benzene ring, as shown in Scheme 17 (X,Y = linking chain), would offer a useful route to benzo-fused compounds. As discussed in the introduction to this chapter, this is a known process; however, the only method that appears general is Zard's xanthate method, which sometimes needs quite harsh reaction conditions (refluxing in chlorobenzene) and the use of stoichiometric peroxide.



Scheme 17

Preliminary studies from this research group[25] established an indirect method for achieving the overall transformation shown in Scheme 17 along the lines summarized in Scheme 18. The essential steps involve conversion of a phenol into a cross-conjugated dienone (**18.1** → **18.2**), which readily undergoes classical radical closure. The product is then rearomatized by treatment with acid (**18.3** → **18.4**).

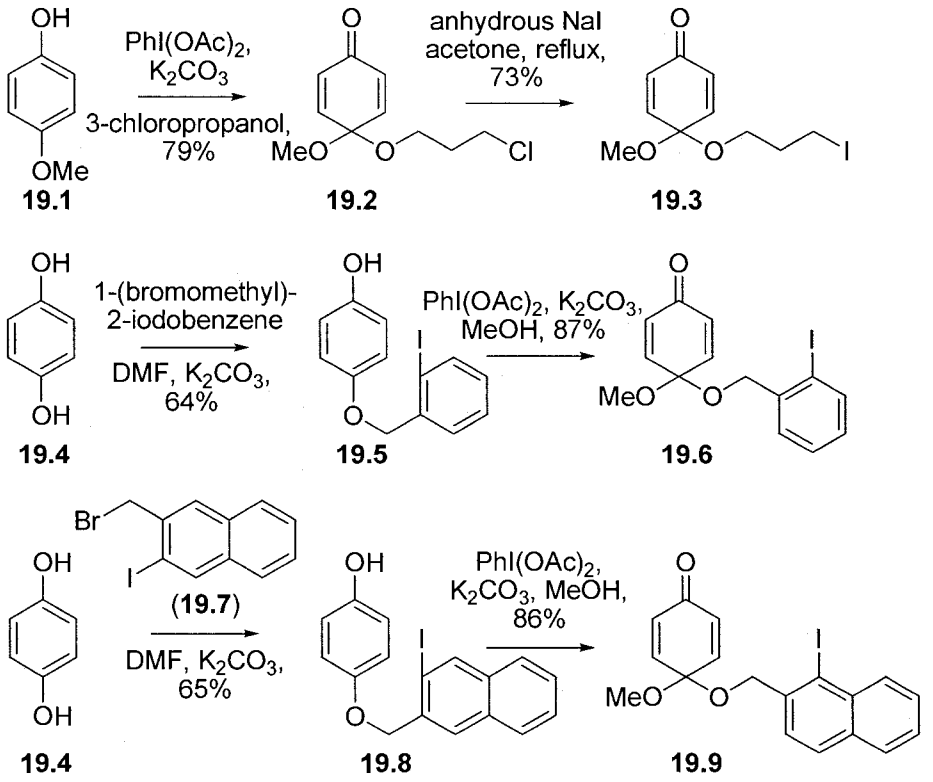


18.1 **18.2** **18.3** **18.4**

Scheme 18

2.2 Radical Cyclization of Cross-Conjugated Ketones and Rearomatization

The cross-conjugated ketones are available by oxidation of *p*-methoxyphenols in the presence of an excess of an α,ω-halo alcohol. In some of the cases yields were better when the alcohol was used as the solvent. Alternatively, the starting phenol can carry a *p*-alkoxy group already bearing a homolyzable substituent, and in that case the oxidation is done in MeOH. Typical examples of these approaches are shown in Scheme 19. $PhI(OAc)_2$ (*ca* 1.1 equiv) is used as the oxidizing agent.



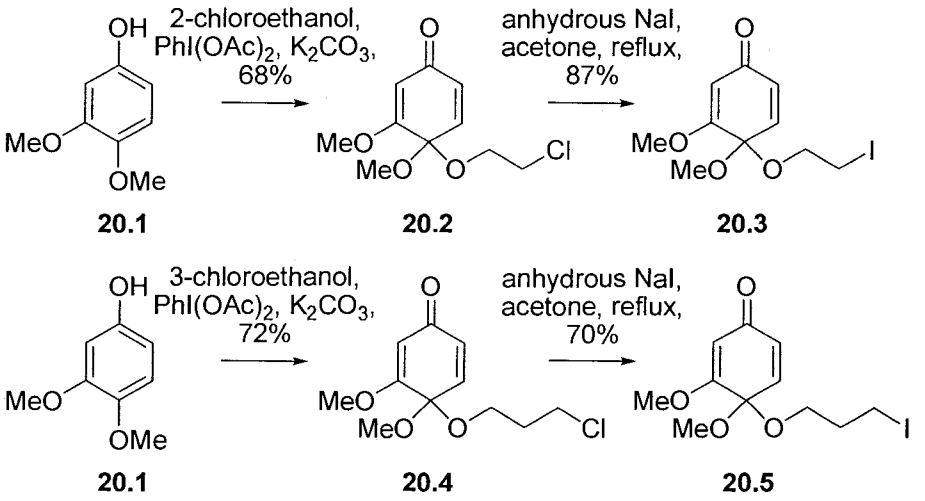
Scheme 19

The intermediate quinone ketals are sensitive to acid, and so the oxidation must be done in the presence of K_2CO_3 (*ca* 2.2 equiv),[26] and during chromatographic purification a small amount of Et_3N should be added to all solvents used. Generally, chloro alcohols

are satisfactory, and the resulting chlorides can be converted into the corresponding iodides by heating with anhydrous NaI.

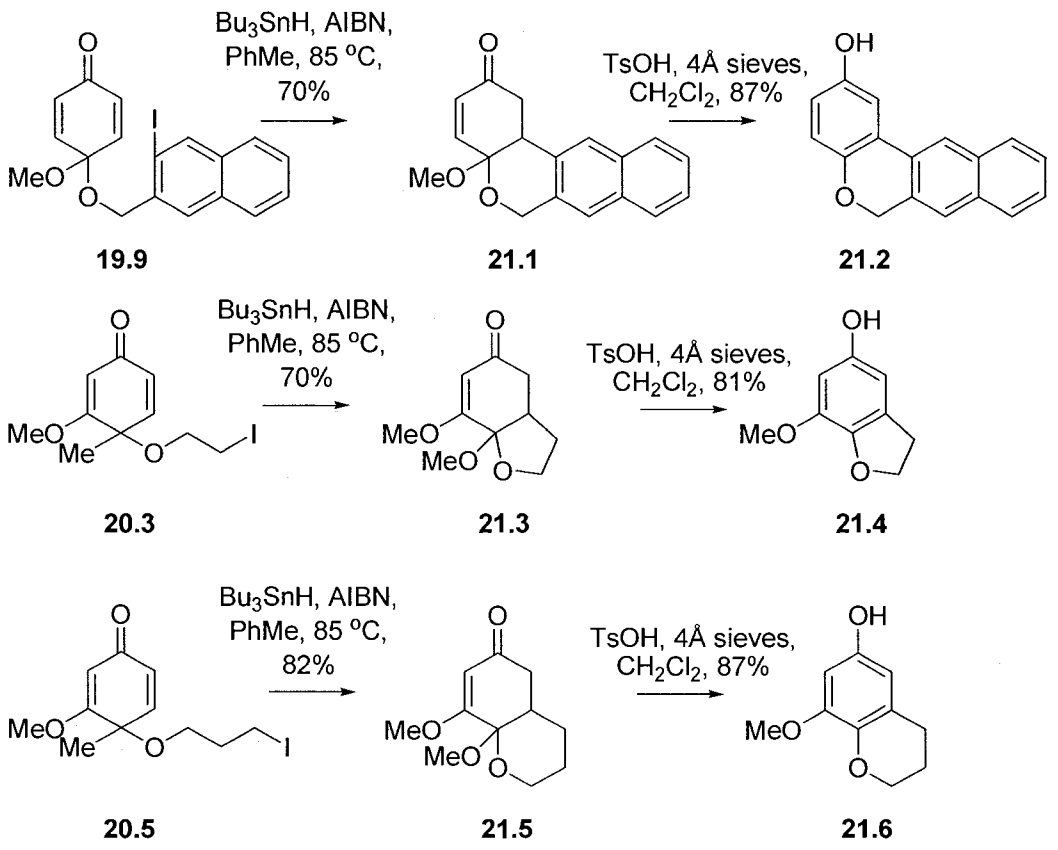
In those cases where a phenol, bearing a ω-haloalkoxy group in the *para* position, is readily available (**19.5**), then oxidation in MeOH is an alternative route. This is experimentally convenient because the excess of solvent is easily removed. Iodides **19.5** and **19.8** were made by alkylating hydroquinone with the appropriate benzylic bromide.

The examples in Scheme 20 establish that the general oxidation also works satisfactorily when an additional methoxy substituent is present.



Scheme 20

The radical cyclizations proceeded without incident (see Scheme 21) when dilute toluene solutions of stannane (0.07-0.12 M) and initiator (0.005-0.011 M) were added over 3-5 h to a hot (85 °C) solution (0.030-0.040 M) of the substrate in the same solvent. We arbitrarily avoided refluxing the solvent, and suspect, on the basis of a single experiment, that our milder conditions give a better result. Yields were generally above 75%. It appears necessary to use iodides in these reactions because the rate of homolysis of a C-Cl bond is too low and other reaction pathways intervene.



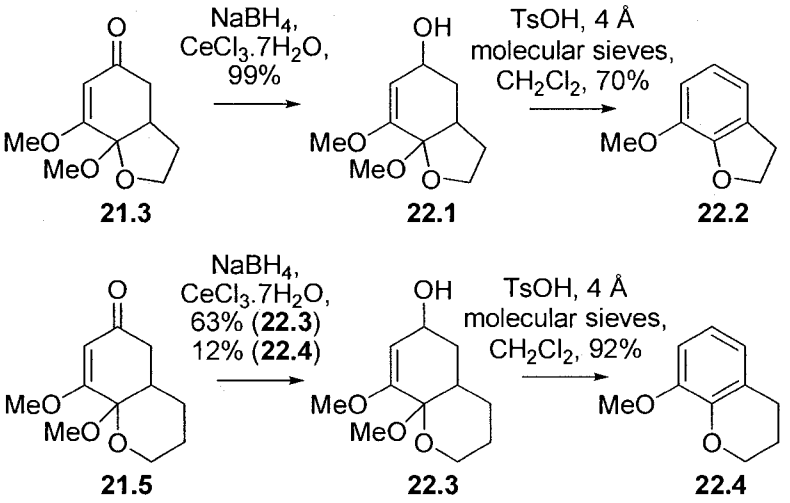
Scheme 21

The last step of the overall sequence is acid-catalyzed aromatization, and in all the examples we examined the methoxy group is expelled in preference to the heterocyclic oxygen. $TsOH{\cdot}H_2O$ is usually satisfactory, and yields for the aromatization are generally above 80%. The aromatization of **21.3** and **21.5** was arbitrarily done in the presence of 4Å molecular sieves.

2.3 Manipulation of the Radical Cyclization Products before Aromatization

As illustrated in Scheme 21, our general process affords phenols; it can, however, be modified easily so as to produce products with hydrogen, alkyl, or aryl groups in place of the normal phenolic hydroxyl.

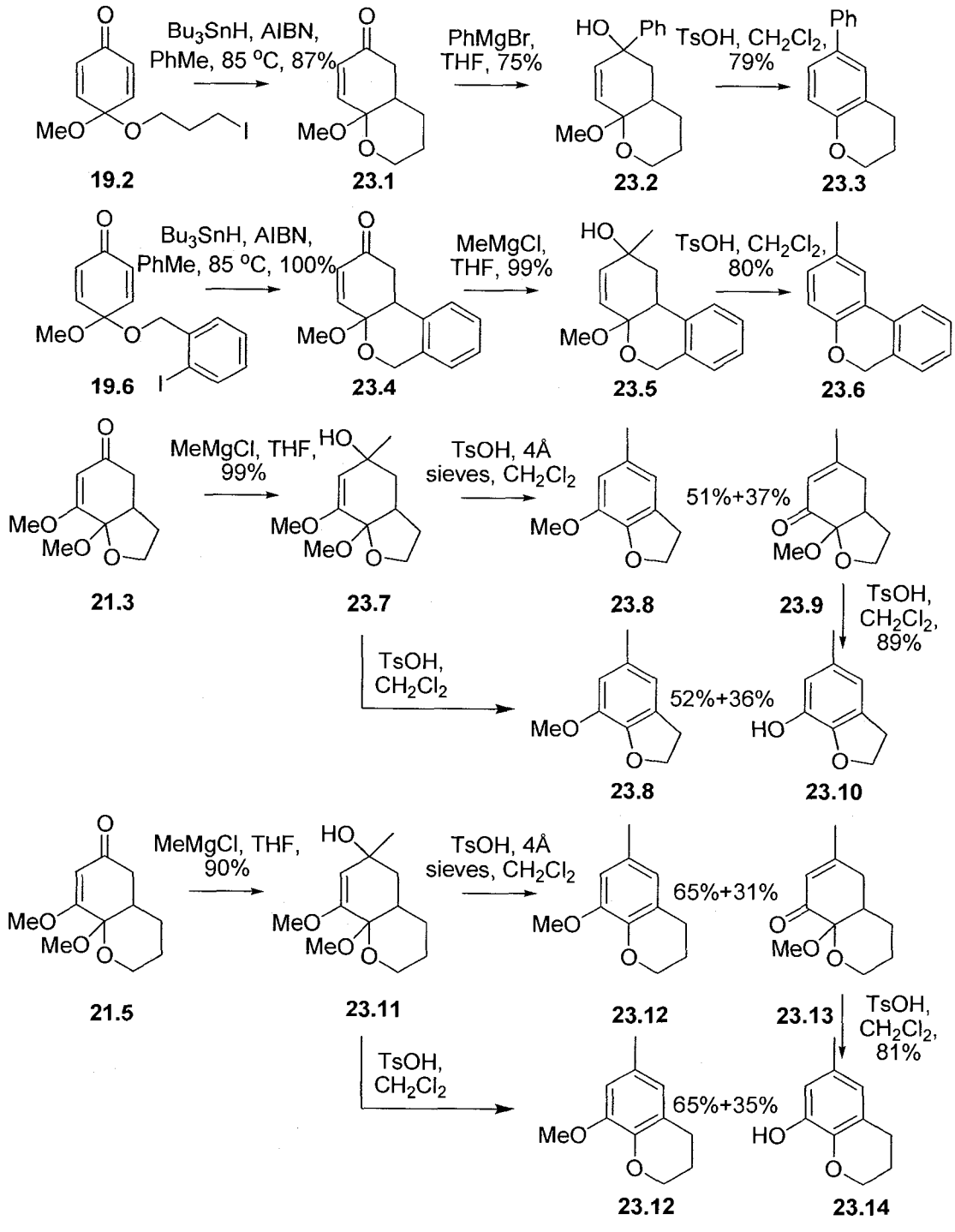
Reduction of the radical cyclization products with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ proceeds normally and aromatization of the resulting alcohols results in loss of the hydroxyl group (Scheme 22). In the case of **22.3**, aromatization occurs so easily that silica chromatography of the reduction product **22.3** gives some of the aromatized product **22.4**, while corresponding treatment of **22.1** is devoid of such complications.



Scheme 22

When the radical cyclization products are treated with a Grignard reagent, a tertiary alcohol is, of course, formed (see Scheme 23), and aromatization gives products carrying an alkyl or aryl group originating from the Grignard reagent.

Acid treatment of **23.7** and **23.11** gives results that depend on the precise conditions. In the presence of 4Å molecular sieves, aromatization and formation of an intermediate enone occurs (**23.7** → **23.8** + **23.9**; **23.11** → **23.12** + **23.13**) and both the aromatized methyl ethers (**23.8**, **23.12**) and the enones (**23.9**, **23.13**) can be isolated. In the absence of molecular sieves, the normal aromatization products (**23.8**, **23.12**) are formed along with the corresponding phenols (**23.10**, **23.14**) resulting from aromatization of the enone (**23.9**, **23.13**). The enones can themselves be aromatized (**23.9** → **23.10**, 89%; **23.13** → **23.14**, 81%).


Bu3SnH, AIBN,
PhMe, 85 °C, 87%
PhMgBr,
THF, 75%
TsOH, CH2Cl2,
79%
19.2
23.1
23.2
23.3
Bu3SnH, AIBN,
PhMe, 85 °C, 100%
MeMgCl,
THF, 99%
TsOH, CH2Cl2,
80%
19.6
23.4
23.5
23.6
MeMgCl, THF,
99%
TsOH, 4Å
sieves, CH2Cl2
51%+37%
21.3
23.7
23.8
23.9
TsOH,
CH2Cl2,
89%
TsOH,
CH2Cl2
52%+36%
23.8
23.10
MeMgCl, THF,
90%
TsOH, 4Å
sieves, CH2Cl2
65%+31%
21.5
23.11
23.12
23.13
TsOH,
CH2Cl2,
81%
TsOH,
CH2Cl2
65%+35%
23.12
23.14

Scheme 23

3 CONCLUSION

The radical methodology[27] described above represents a powerful method for making benzo-fused oxygen heterocycles.

The methodology allows the formation of five-, six- and seven-membered oxygen heterocyclic rings fused onto phenols. The approach is amenable to a number of modifications. We have developed modifications allowing construction of non-phenolic aromatic species and/or the introduction of alkyl or aryl substituents on the aromatic ring, giving access to substitution patterns not easily accessible by other methods.

4 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (140 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

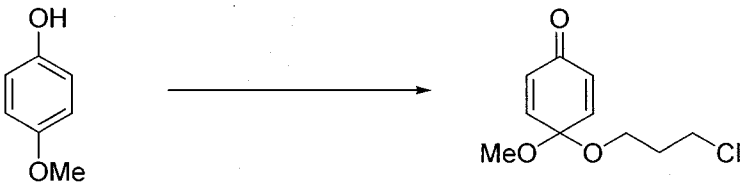
Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N, *i*-Pr_2NEt and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$. Acetone was distilled from K_2CO_3.

FT-IR measurements were made from the specified solvent using KBr plates.

The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, as based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

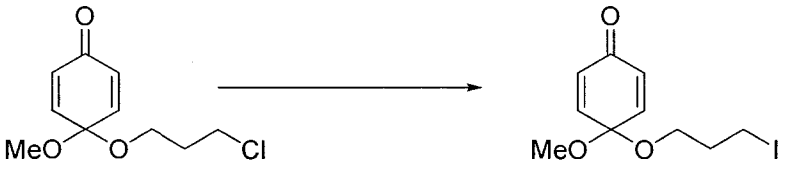
4-(3-Chloropropoxy)-4-methoxycyclohexa-2,5-dienone (19.2).



19.1 **19.2**

$PhI(OAc)_2$ (760 mg, 2.36 mmol) and K_2CO_3 (662 mg, 4.73 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, a solution of **19.1** (327 mg, 2.63 mmol) in 3-chloropropanol (2.5 mL) was injected dropwise over *ca* 1 min. Stirring was continued for 35 min and the mixture was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum for *ca* 12 h. Flash chromatography of the residue over silica gel, using 10% to 20% EtOAc-hexane mixtures, gave **19.2** (402 mg, 79%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2942, 2890, 1687, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03 (quintet, J = 6.1 Hz, 2 H), 3.36 (s, 3 H), 3.65 (t, J = 6.1 Hz, 2 H), 3.73 (t, J = 6.1 Hz, 2 H), 6.18-6.32 (m, 2 H), 6.73-6.84 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 32.7 (t), 41.4 (t), 50.6 (q), 59.2 (t), 92.5 (s), 130.0 (d), 143.5 (d), 185.0 (s); exact mass *m/z* calcd for $C_{10}H_{13}{}^{35}ClO_3$ 216.05533, found 216.05520.

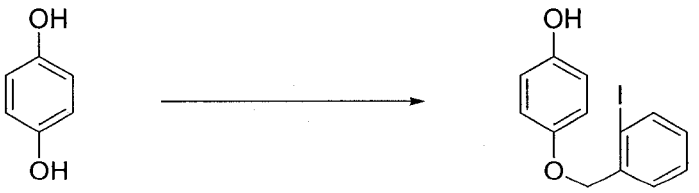
4-(3-Iodopropoxy)-4-methoxycyclohexa-2,5-dienone (19.3).



19.2 **19.3**

Acetone (2 mL, dried over K_2CO_3) was added to a mixture of **19.2** (0.10 g, 0.46 mmol) and anhydrous NaI (0.69 g, 4.6 mmol). The mixture was stirred and refluxed for 20 h, cooled and partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20:80 Et_3N-EtOAc-hexane, gave **19.3** (104 mg, 73%) as an oil: FTIR ($CHCl_3$, cast) 2939, 1689, 1675, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02-2.12 (m, 2 H), 3.28 (t, J = 6.1 Hz, 2 H), 3.63 (t, J = 6.1 Hz, 2 H), 6.23-6.31 (m, 2 H), 6.78-6.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 2.8 (t), 33.4 (t), 50.7 (q), 62.3 (t), 92.6 (s), 130.1 (d), 143.5 (d), 185.0 (s); exact mass m/z calcd for $C_{10}H_{13}IO_3$ 307.99094, found 307.99092.

4-(2-Iodobenzyloxy)phenol (19.5).

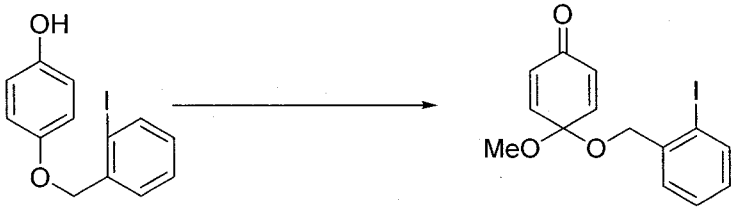


19.4 **19.5**

1-(Bromomethyl)-2-iodobenzene (1.07 g, 3.59 mmol) in dry DMF (9 mL plus 1 mL as a rinse) was added dropwise over 25 min to a stirred mixture of hydroquinone

(1.98 g, 18.0 mmol) and K_2CO_3 (1.24 g, 8.97 mmol) in DMF (40 mL), and stirring was continued at 60 °C for 12 h. The mixture was poured into water, neutralized with 10% aqueous hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum overnight. Flash chromatography of the residue over silica gel, using EtOAc-hexane mixtures from 5% EtOAc-hexane to 30% EtOAc-hexane, gave **19.5** (0.747 g, 64%) as a solid: mp 158-160 °C; FTIR (CH_2Cl_2, cast) 3364, 1565, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.52 (s, 1 H), 5.00 (s, 2 H), 6.72-6.80 (m, 2 H), 6.82-6.91 (m, 2 H), 7.03 (t, J = 8 Hz, 1 H), 7.37 (t, J = 8 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H), 7.86 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.7 (t), 97.2 (s), 116.0 (d), 116.1 (d), 128.3 (d), 128.6 (d), 129.4 (d), 139.2 (d), 139.3 (s), 149.8 (s), 152.6 (s); exact mass *m/z* calcd for $C_{13}H_{11}IO_2$ 325.98038, found 325.97992.

4-(2-Iodobenzyloxy)-4-methoxycyclohexa-2,5-dienone (19.6).



19.5 **19.6**

$PhI(OAc)_2$ (709 mg, 2.20 mmol) and K_2CO_3 (607 mg, 4.40 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. MeOH (10 mL) was added, and a solution of **19.5** (652 mg, 2.00 mmol) in MeOH (5 mL) was injected dropwise over *ca* 5 min. Further portions of MeOH (2 x 2 mL) were used as a rinse, which was added rapidly. Stirring was continued for 40 min and the black mixture was quenched by

addition of saturated aqueous $NaHCO_3$. The mixture was partitioned between water and Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 90:10:2 hexane-EtOAc-Et_3N, gave **19.6** (623 mg, 87%) as an oil: FTIR (neat) 3054, 2939, 1689, 1673, 1638, 1617 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.46 (s, 3 H), 4.65 (s, 2 H), 6.26-6.34 (m, 2 H), 6.87-6.94 (m, 2 H), 6.98 (td, J = 7.3, 2.0 Hz, 1 H), 7.33 (td, J = 7.5, 1.2 Hz, 1 H), 7.42 (br d, J = 7.5 Hz, 1 H), 7.80 (dd, J = 8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 50.8 (q), 68.9 (t), 92.8 (s), 97.4 (s), 128.4 (d), 128.7 (d), 129.4 (d), 127.0 (d), 139.1 (d), 139.7 (s), 143.2 (d), 185.0 (s); exact mass *m/z* calcd for $C_{14}H_{13}IO_3$ 355.99094, found 355.99133.

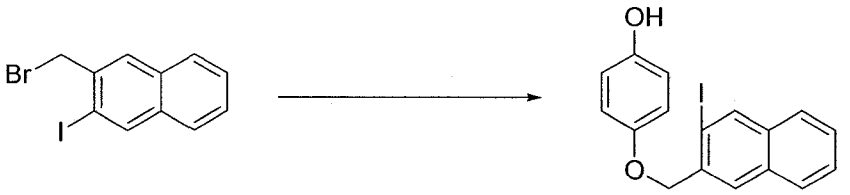
2-Bromoethyl-3-iodonaphthalene (19.7).

19.7

A solution of HBr in AcOH (40%, 25 mL) was added dropwise to a flask containing the 3-iodo-2-naphthalenemethanol (400 mg, 1.41 mmol) immersed in an ice bath. The ice bath was removed and stirring was continued at overnight. The mixture was evaporated under waterpump vacuum (*ca* 80 °C), and the residue was taken up in Et_2O. The solution was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using hexane, gave **19.7** (240 mg, 49%) as a solid: mp 95-97 °C; FTIR (CH_2Cl_2 cast) 3044, 1488, 1202, 974 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.74 (s, 2 H), 7.47-7.49 (m, 2 H), 7.66-7.68 (m, 1 H), 7.73-7.76 (m, 1 H), 7.91 (s, 1 H), 8.37 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (t), 96.3 (s), 126.5 (d), 127.0 (d), 127.4 (d), 127.9 (d), 129.4 (d), 132.8 (s), 134.5 (s), 136.3 (s), 139.6 (d);

exact mass *m/z* calcd for $C_{11}H_8I^{81}BrO$ 347.88336, found 347.88368.

4-[(3-Iodonaphthalen-2-yl)methoxy]phenol (19.8).



19.7 **19.8**

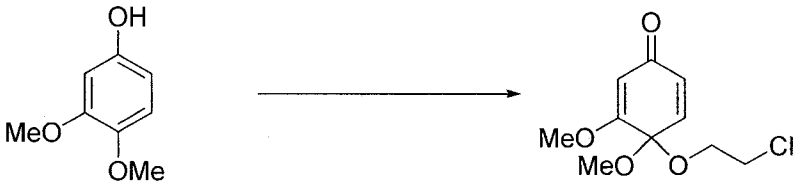
A solution of **19.7** (0.23 g, 0.66 mmol) in THF (3 mL) was added dropwise over 25 min to a stirred mixture of hydroquinone (364 mg, 3.30 mmol) and K_2CO_3 (229 mg, 1.66 mmol) in THF (10 mL), and a further portion of THF (1 mL) was used as a rinse, which was added quickly. The flask was transferred to an oil bath, and stirring was continued overnight at 60 °C. The mixture was cooled, poured into water, neutralized with 10% hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc-hexane, gave **19.8** (164 mg, 65%) as a solid: mp 124-126 °C; FTIR (CH_2Cl_2 cast) 3368, 3051, 1204, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.68 (s, 1 H), 5.09 (s, 2 H), 6.76-6.79 (m, 2 H), 6.89-93 (m, 2 H), 7.46-7.50 (m, 2 H), 7.69-7.72 (m, 1 H), 7.77-7.80 (m, 1 H), 7.93 (s, 1 H), 8.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.8 (t), 94.2 (s), 116.1 (d), 116.3 (d), 126.5 (d), 126.7 (d), 126.8 (d), 127.4 (d), 128.0 (d), 132.7 (s), 134.3 (s), 135.4 (s), 138.6 (d), 149.9 (s), 152.7 (s); exact mass *m/z* calcd for $C_{17}H_{13}IO_2$ 375.99603, found 375.99672.

4-[(3-Iodonaphthalen-2-yl)methoxy]-4-methoxycyclohexa-2,5-dienone (19.9).

19.8 **19.9**

$PhI(OAc)_2$ (164 mg, 0.510 mmol) and K_2CO_3 (140 mg, 1.02 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath, the contents were stirred, and MeOH (6 mL) was added. A solution of **19.8** (160 mg, 0.420 mmol) in MeOH (4 mL) was injected dropwise over *ca* 5 min, using MeOH (2 mL) as a rinse, which was added rapidly. Stirring was continued for 2 h and the mixture was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was partitioned between water and Et_2O. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 2:15:90 Et_3N-EtOAc-hexane, gave **19.9** (147 mg, 86%) as an oil: FTIR (CH_2Cl_2 cast) 3053, 1638, 1383, 1105, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.45 (s, 3 H), 4.74 (s, 2 H), 6.32 (dt, J = 10, 1.5 Hz, 2 H), 6.95 (dt, J = 10, 1.5 Hz, 2 H), 7.44-7.50 (m, 2 H), 7.66-7.69 (m, 1 H), 7.76-7.79 (m, 1 H), 7.84 (s, 1 H), 8.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 50.9 (q), 68.8 (t), 93.0 (s), 94.3 (s), 126.5 (d), 126.8 (d), 126.8 (d), 127.3 (d), 127.9 (d), 130.1 (d), 132.7 (s), 134.3 (s), 135.8 (s), 138.6 (d), 143.2 (d), 185.1 (s); exact mass *m/z* calcd for $C_{18}H_{15}O_3I$ 406.00659, found 406.00562.

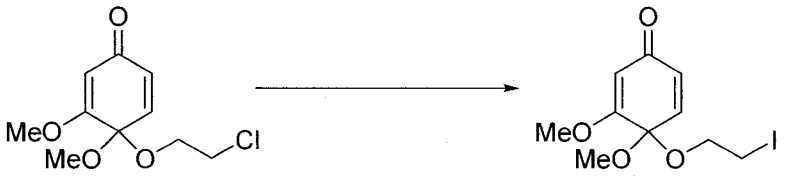
4-(2-Chloroethoxy)-3,4-dimethoxycyclohexa-2,5-dienone (20.2).



20.1 **20.2**

$PhI(OAc)_2$ (0.23 g, 0.71 mmol) and K_2CO_3 (197 mg, 1.43 mmol), were tipped into a flask which was then closed by a septum and flushed with N_2. After 5 min, 2-chloroethanol (1 mL) was injected and, after a further 10 min, a solution of **20.1** (100 mg, 0.650 mmol) in 2-chloroethanol (2.5 mL) was added dropwise over *ca* 6 min. A further portion of 2-chloroethanol (1 mL) was used as a rinse. Stirring was continued for 1 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was maintained under oil pump vacuum overnight in order to remove the excess of 2-chloroethanol. Flash chromatography of the residue over silica gel, using 1:40:60 Et_3N-EtOAc-hexane, gave **20.2** (151 mg, 68%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3076, 2942, 1308, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.27 (s, 3 H), 3.52-3.56 (m, 2 H), 3.67-3.72 (m, 5 H), 5.55 (d, J = 2 Hz, 1 H), 6.22 (dd, J = 10.4, 2 Hz, 1 H), 6.52 (d, J = 10.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.5 (t), 51.5 (q), 56.0 (q), 64.1 (t), 93.8 (s), 104.0 (d), 131.0 (d), 140.1 (d), 168.8 (s), 185.9 (s); exact mass *m/z* calcd for $C_{10}H_{13}{}^{35}ClO_4$ 232.05023, found 232.05016.

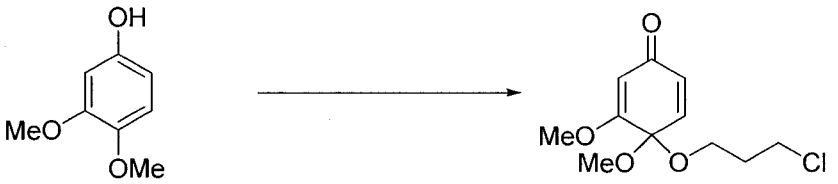
4-(2-Iodoethoxy)-3,4-dimethoxycyclohexa-2,5-dienone (20.3).



20.2 **20.3**

Dry acetone (10 mL) was added to a stirred mixture of **20.2** (420 mg, 1.81 mmol) and dry NaI (2.71 g, 18.1 mmol) and the mixture was refluxed for 48 h, cooled and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc-hexane, gave **20.3** (511 mg, 87%) as a yellow oil, which was used directly in the radical cyclization.

4-(3-Chloropropoxy)-3,4-dimethoxycyclohexa-2,5-dienone (20.4).

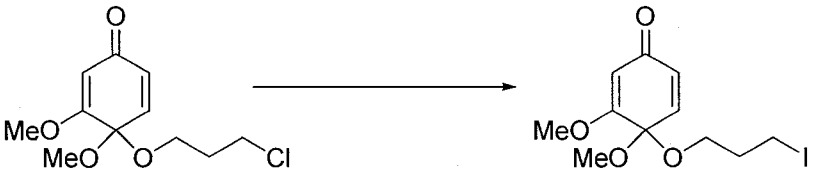


20.1 **20.4**

$PhI(OAc)_2$ (940 mg, 2.93 mmol) and K_2CO_3 (810 mg, 5.85 mmol) were placed in a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, 3-chloropropanol (1 mL) was injected and, after a further 10 min, a solution of **20.1** (410 mg, 2.66 mmol) in 3-chloropropanol (4 mL) was added dropwise over *ca* 15 min. A further portion of 3-

chloropropanol (1 mL) was used as a rinse. Stirring was continued for 3 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was maintained under oil pump vacuum overnight in order to remove the excess of 3-chloropropanol. Flash chromatography of the residue over silica gel, using 1:30:70 Et_3N-EtOAc-hexane, gave **20.4** (479 mg, 72%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2942, 1667, 1355, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95-1.99 (m 2 H), 3.27 (s, 3 H), 3.46-3.50 (m, 1 H), 3.56-3.62 (m, 3 H), 3.76 (s, 3 H), 5.60 (d, J = 1 Hz, 1 H), 6.26 (dd, J = 10.4, 0.8 Hz, 1 H), 6.51 (d, J = 10.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.5 (t), 41.4 (t), 51.5 (q), 56.0 (q), 60.1 (t), 94.1 (s), 104.4 (d), 131.4 (d), 140.7 (d), 169.0 (s), 186.0 (s); exact mass *m/z* calcd for $C_{11}H_{15}{}^{37}ClO_4$ 248.06294, found 248.06351.

4-(3-Iodopropoxy)-3,4-dimethoxycyclohexa-2,5-dienone (20.5).

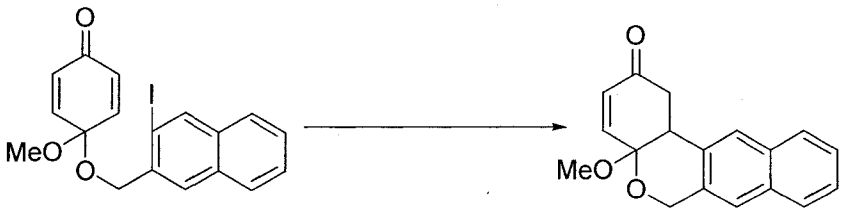


20.4 **20.5**

Dry acetone (15 mL) was added to a stirred mixture of **20.4** (990 mg, 4.01 mmol) and dry NaI (6.00 g, 40.1 mmol) and the mixture was refluxed for 24 h, cooled and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 2:50:50 Et_3N-EtOAc-hexane, gave **20.5** (948 mg, 70%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2939,

1668, 1227, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01 (quintet, J = 6.4 Hz, 2 H), 3.22-3.27 (m, 5 H), 3.42 (dt, J = 10, 5.6 Hz, 1 H), 3.52 (dt, J = 10, 5.6 Hz, 1 H), 3.78 (s, 3 H), 5.61 (d, J = 2 Hz, 1 H), 6.28 (dd, J = 10.4, 2 Hz, 1 H), 6.53 (d, J = 10.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.17 (t), 33.1 (t), 51.5 (q), 56.2 (q), 63.1 (t), 94.0 (s), 104.4 (d), 131.4 (d), 140.7 (d), 168.9 (s), 186.0 (s); exact mass *m/z* calcd for $C_{11}H_{15}IO_4$ 338.00153, found 338.00146.

4a-Methoxy-6,12b-dihydro-1*H*,4a*H*-naphtho[2,3-*c*]-chromen-2-one (21.1).

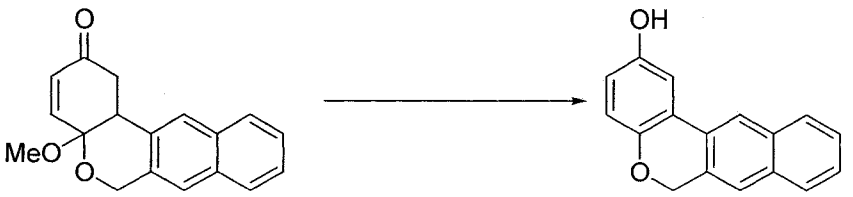


19.9 **21.1**

A solution of Bu_3SnH (0.12 mL, 0.42 mmol) and AIBN (7 mg, 0.04 mmol) in PhMe (10 mL) was added over 3 h (syringe pump) to a stirred and heated (80 °C) solution of **19.9** (143 mg, 0.350 mmol) in PhMe (50 mL). Heating at 80 °C was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2:20:80 Et_3N-EtOAc-hexane, gave **21.1** (70 mg, 70%) as an oil: FTIR (CH_2Cl_2 cast) 3053, 1631, 1270, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.81 (ddd, J = 16.5, 5, 0.5 Hz, 1 H), 2.90 (dd, J = 16.5, 10.5 Hz, 1 H), 3.49 (s, 3 H), 3.53 (dd, J = 10.5, 5 Hz, 1 H), 5.03 (AB q, $\Delta\nu_{AB}$ = 9.2 Hz, J = 14.9 Hz, 2 H), 6.10 (d, J = 10, 0.5 Hz, 1 H), 6.94 (d, J = 10.5 Hz, 1 H), 7.40-7.44 (m, 2 H), 7.54 (s, 1 H), 7.60 (s, 1 H), 7.73-7.78 (m, 2 H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.8 (q), 43.2 (t), 49.6 (d), 63.6 (t), 95.8 (s), 122.6 (d), 125.9 (d), 126.1 (d), 126.2 (d), 127.3 (d), 127.5 (d), 130.4 (d), 130.8 (s), 132.2 (s), 132.7 (s), 132.7 (s), 143.1 (d), 197.9 (s); exact mass *m/z* calcd for $C_{18}H_{16}O_3$

280.10995, found 280.10993.

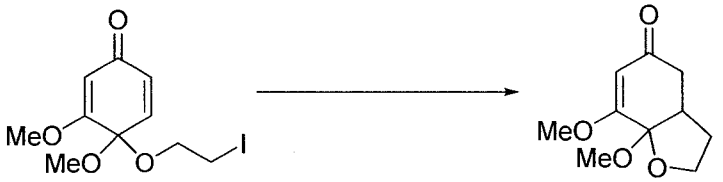
6*H*-Naphtho[2,3-*c*]chromen-2-ol (21.2).



21.1 **21.2**

TsOH·H_2O (5 mg) was added to a stirred mixture of **21.1** (68 mg, 0.24 mmol) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (7 mL) and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc-CH_2Cl_2, gave **21.2** (53 mg, 87%) as a colorless solid: mp 200-201 °C; FTIR (CH_2Cl_2 cast) 3452, 3048, 1489, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.55 (s, 1 H), 5.19 (s, 2 H), 6.74 (dd, J = 9, 3 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 3 Hz, 1 H), 7.42-7.48 (m, 2 H), 7.60 (s, 1 H), 7.76-7.80 (m, 1 H), 7.84-7.88 (m, 1 H), 8.05 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.0 (t), 109.9 (d), 116.6 (d), 118.5 (d), 120.9 (d), 123.2 (d), 123.8 (s), 126.2 (two coincident d), 127.5 (d), 128.0 (s), 128.1 (d), 130.6 (s), 132.9 (s), 133.5 (s), 149.4 (s), 150.6 (s); exact mass *m/z* calcd for $C_{17}H_{12}O_2$ 248.08372, found 248.08336.

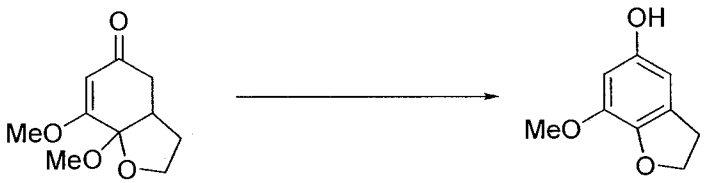
7,7a-Dimethoxy-2,3,3a,7a-tetrahydro-4*H*-benzofuran-5-one (21.3).



20.3 **21.3**

A solution of Bu_3SnH (0.96 mL, 3.6 mmol) and AIBN (58 mg, 0.36 mmol) in PhMe (15 mL) was added over 3 h (syringe pump) to a stirred and heated (85 °C) solution of **20.3** (960 mg, 2.96 mmol) in PhMe (40 mL). Heating at 85 °C was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2% Et_3N in EtOAc, gave **21.3** (417 mg, 70%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2944, 2834, 1664, 1612, 1317 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69-1.80 (m, 1 H), 2.20-2.28 (m, 1 H), 2.37 (dd, J = 16.4, 7.4 Hz, 1 H), 2.54 (dd, J = 16.4, 7.4 Hz, 1 H), 2.78 (quintet, J = 6.8 Hz, 1 H), 3.37 (s, 3 H), 3.71 (s, 3 H), 4.00-4.10 (m, 2 H), 5.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.3 (t), 38.8 (t), 40.9 (d), 51.3 (q), 56.1 (q), 68.1 (t), 102.9 (d), 103.7 (s), 171.3 (s), 196.6 (s); exact mass *m/z* calcd for $C_{10}H_{14}O_4$ 198.08920, found 198.08962.

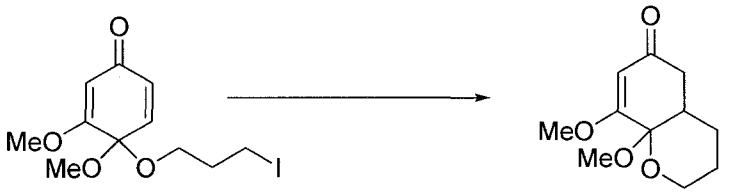
7-Methoxy-2,3-dihydrobenzofuran-5-ol (21.4).[28]



21.3 **21.4**

TsOH·H_2O (3 mg) was added to a stirred mixture of **21.3** (18 mg, 0.091 mmol) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc-CH_2Cl_2, gave **21.4**[28] (12 mg, 81%) as a solid: mp 110-111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.15 (t, J = 8.7 Hz, 2 H), 3.80 (s, 3 H), 4.57 (t, J = 8.7, 2 H), 5.09 (s, 1 H), 6.30-6.34 (m, 2 H).

8,8a-Dimethoxy-3,4,4a,8a-tetrahydro-2*H*,5*H*-chromen-6-one (21.5).



20.5 **21.5**

A solution of Bu_3SnH (0.90 mL, 3.3 mmol) and AIBN (55 mg, 0.28 mmol) in PhMe (15 mL) was added over 3 h (syringe pump) to a stirred and heated (85 °C) solution of **20.5** (940 mg, 2.78 mmol) in PhMe (60 mL). Heating at 85 °C was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2:50:50 Et_3N-EtOAc-hexane, gave **21.5** (486 mg, 82%) as a yellow solid: mp 62-64 °C; FTIR (CH_2Cl_2 cast) 2941, 1662, 1219, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42-1.48 (m, 1 H), 1.54-1.59 (m, 2 H), 1.81-1.86 (m, 1 H), 2.22 (dt, J = 14.4, 4.8 Hz, 1 H), 2.30 (dd, J = 16.8, 4.8 Hz, 1 H), 2.67 (dd, J = 16.8, 4.8 Hz, 1 H), 3.34-3.44 (m, 4 H), 3.72 (s, 3 H), 3.88-3.92 (m, 1 H), 5.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0 (t), 26.0 (t), 37.4 (d), 40.3 (t), 51.2 (q), 55.9 (q), 64.1 (t), 97.1 (s), 104.7 (d), 171.4 (s), 197.8 (s); exact mass *m/z* calcd for $C_{11}H_{16}O_4$ 212.10486, found 212.10487.

8-Methoxychroman-6-ol (21.6).

21.5 **21.6**

$TsOH{\cdot}H_2O$ (5 mg) was added to a stirred mixture of **21.5** (58 mg, 0.27 mmol) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc-CH_2Cl_2, gave **21.6** (43 mg, 87%) as a colorless solid: mp 74-76 °C; FTIR (CH_2Cl_2 cast) 3425, 2934, 1496, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93-1.96 (m, 2 H), 2.67 (t, J = 6.4 Hz, 2 H), 3.76 (s, 3 H), 4.17 (t, J = 5.2 Hz, 2 H), 5.08 (s, 1 H), 6.01 (s, 1 H), 6.26 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3 (t), 24.8 (t), 55.7 (q), 66.6 (t), 98.3 (d), 106.8 (d), 123.0 (s), 138.1 (s), 148.8 (s), 148.8 (s); exact mass *m/z* calcd for $C_{10}H_{12}O_3$ 180.07864, found 180.07888.

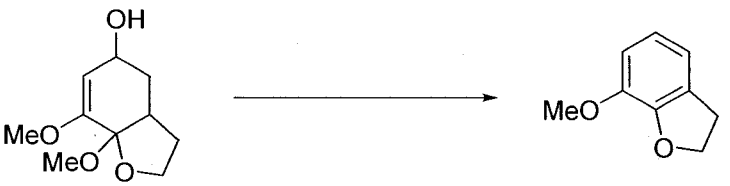
7,7a-Dimethoxy-2,3,3a,4,5,7a-hexahydrobenzofuran-5-ol (22.1).

21.3 **22.1**

$CeCl_3{\cdot}7H_2O$ (188 mg, 0.510 mmol) and $NaBH_4$ (57 mg, 1.5 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **21.3** (100 mg, 0.505 mmol) in dry

MeOH (20 mL). The cooling bath was removed and stirring was continued for 2 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using EtOAc, gave **22.1** (99 mg, 99%) as an oil, which was largely, if not exclusively, a single isomer: FTIR (CH_2Cl_2 cast) 3405, 2940, 1231, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31-1.40 (m, 1 H), 1.58-1.65 (m, 2 H), 1.93-2.00 (m, 1 H), 2.24-2.42 (m, 2 H), 3.26 (s, 3 H), 3.57 (s, 3 H), 3.99-4.11 (m, 2 H), 4.37 (br s, 1 H), 4.84 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.7 (t), 38.0 (t), 41.5 (d), 51.4 (q), 54.7 (q), 66.9 (d), 67.7 (t), 103.9 (d), 104.9 (s), 153.4 (s); exact mass *m/z* calcd for $C_{10}H_{16}O_4$ 200.10486, found 200.10533.

7-Methoxy-2,3-dihydrobenzofuran (22.2).[29]

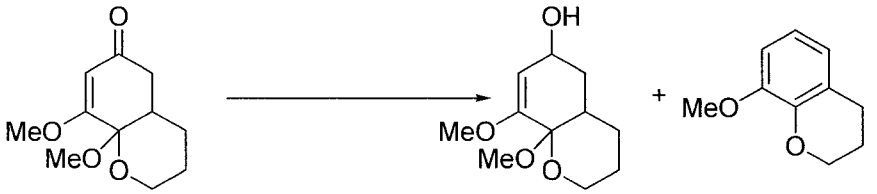


22.1 **22.2**

$TsOH{\cdot}H_2O$ (5 mg) was added to a stirred mixture of **22.1** (36 mg, 0.18 mmol) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 9:1 EtOAc-hexane, gave **22.2**[29] (19 mg, 70%) as a colorless solid: mp 46-48 °C; FTIR (CH_2Cl_2 cast) 2960, 1617, 1359, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.21 (t, J = 8.8 Hz, 2 H), 3.85 (s, 3 H), 4.60 (t, J = 8.8 Hz, 2 H), 6.71-6.81 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.3 (t), 55.9 (q), 71.6 (t), 111.1 (d), 117.1 (d), 120.9 (d), 128.0 (s), 144.6 (s), 148.3 (s); exact mass *m/z* calcd for $C_9H_{10}O_2$ 150.06808, found

150.06820.

8-Methoxy-3,4,4a,5,6,8a-2*H*-chromen-6-ol (22.3) and 8-Methoxychroman (22.4).[30]

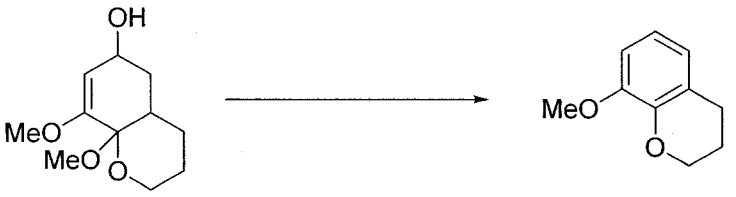


21.5 **22.3** **22.4**

$CeCl_3 \cdot 7H_2O$ (0.13 g, 0.35 mmol) and $NaBH_4$ (40 mg, 1.1 mmol) were added to a stirred and cooled (0 °C) solution of **21.5** (75 mg, 0.35 mmol) in dry MeOH (15 mL). The ice bath was removed and stirring was continued for 2 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 9:1 EtOAc-hexane, gave **22.3** (49 mg, 63%) and **22.4** (6.8 mg, 12%), both as oils. Alcohol **22.3** had: FTIR (CH_2Cl_2 cast) 3407, 2940, 1656, 1286 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.37 (m, 1 H), 1.46-1.52 (m, 1 H), 1.63-1.80 (m, 2 H),1.84-1.88 (m, including a doublet at δ 1.85, J = 5.2 Hz, 3 H in all), 1.96-2.03 (m, 1 H), 3.29 (s, 3 H), 3.55 (s, 3 H), 3.65-3.70 (m, 1 H), 3.84 (td, J = 11.6, 2.8 Hz, 1 H), 4.36 (br s, 1 H), 4.84 (d, J = 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (t), 24.6 (t), 32.9 (d), 35.6 (t), 51.3 (d), 54.7 (q), 62.6 (t), 67.0 (q), 97.1 (s), 103.8 (d), 155.3 (s); exact mass *m/z* calcd for $C_{11}H_{18}O_4$ 214.12051, found 214.12019.

Compound **22.4**[30] had: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.00-2.04 (m, 2 H), 2.80 (t, J = 8.8 Hz, 2 H), 3.87 (s, 3 H), 4.28 (t, J = 6.4 Hz, 2 H), 6.68-6.79 (m, 3 H).

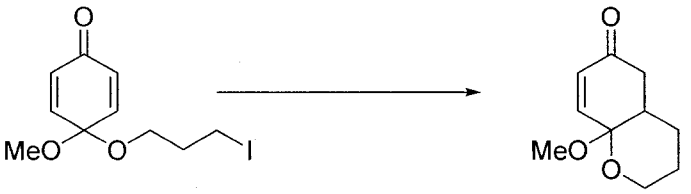
8-Methoxychroman (22.4).[30]



22.3 **22.4**

$TsOH{\cdot}H_2O$ (5 mg) was added to a stirred solution of **22.3** (45 mg, 0.21 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 3:1 EtOAc-hexane, gave **22.4** (32 mg, 92%) as an oil.

8a-Methoxy-3,4,4a,8a-tetrahydro-2*H*,5*H*-chromen-6-one (23.1).

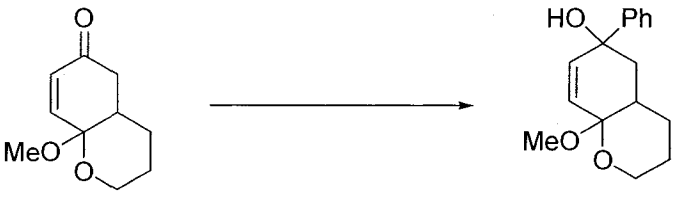


19.2 **23.1**

A solution of Bu_3SnH (88 μL, 0.33 mmol) and AIBN (5 mg, 0.03 mmol) in PhMe (5 mL) was added over 5 h (syringe pump) to a stirred and heated (85 °C) solution of **19.2** (78 mg, 0.25 mmol) in PhMe (20 mL). Heating was continued for 1 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2:15:85 Et_3N-EtOAc-hexane, gave **23.1** (40 mg, 87%) as an oil: FTIR (CH_2Cl_2, cast), 3044, 2946, 2877, 1686, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36-

1.49 (m, 2 H), 1.67-1.78 (m, 2 H), 2.04-2.11 (m, 1 H), 2.19-2.24 (m, 1 H), 2.36-2.41 (m, 1 H), 2.65-2.71 (m, 1 H), 3.37 (s, 3 H), 3.62-3.67 (m, 1 H), 3.72-3.78 (m, 1 H), 6.01 (dd, J = 10.3, 0.8 Hz, 1 H), 6.79 (d, J = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3 (t), 24.3 (t), 37.0 (d), 40.1 (t), 48.5 (q), 61.8 (t), 95.4 (s), 130.6 (d), 144.2 (d), 199.5 (s); exact mass *m/z* calcd for $C_{10}H_{14}O_3$ 182.09430, found 182.09428.

8a-Methoxy-6-phenyl-3,4,4a,5,6,8a-hexahydro-2*H*-chromen-6-ol (23.2).



23.1 **23.2**

PhMgBr (1 M in THF, 0.60 mL, 0.60 mmol) was added at a fast dropwise rate to a stirred solution of **23.1** (55 mg, 0.30 mmol) in THF (5 mL). Stirring was continued for 2 h and the mixture was cooled to 0 °C and quenched with water. The solvent was evaporated and the residue was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20:30 Et_3N-EtOAc-hexane, gave **23.2** (60 mg, 75%) as a colorless solid: mp 131-133 °C; FTIR (CH_2Cl_2 cast) 3406, 3033, 2862, 1490, 1274, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.32 (m, 2 H), 1.68-1.81 (m, 3 H), 1.96-2.06 (m, 1 H), 2.19 (s, 1 H), 2.44 (t, J = 13.2 Hz, 1 H), 3.36 (s, 3 H), 3.60-3.68 (m, 2 H), 5.85 (dd, J = 5.2, 2 Hz, 1 H), 6.07 (d, J = 5.2, 1 H), 7.23-7.27 (m, 3 H), 7.47 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2 (t), 24.4 (t), 33.5 (d), 42.5 (t), 48.0 (q), 61.5 (t), 74.8 (s), 96.0 (s), 126.0 (d), 126.8 (d), 127.4 (d), 128.2 (d), 135.6 (d), 144.6 (s); exact mass *m/z* calcd for $C_{16}H_{20}O_3$

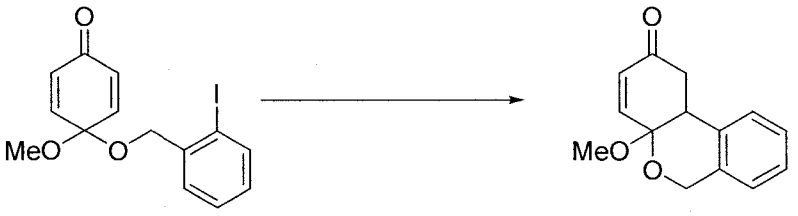
260.14124, found 260.14086.

6-Phenylchroman (23.3).[31]

23.2 **23.3**

TsOH·H_2O (10 mg) was added to a stirred solution of **23.2** (48 mg, 0.18 mmol) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was then partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:4 CH_2Cl_2-hexane, gave **23.3**[31] (31 mg, 79%) as a colorless solid: mp 43-44 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.01-2.06 (m, 2 H), 2.85 (t, J = 6.8 Hz, 2 H), 4.22 (t, J = 5.2 Hz, 2 H), 6.86 (d, J = 8.2 Hz, 1 H), 7.26-7.34 (m, 3 H), 7.38-7.42 (m, 2 H), 7.52-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (t), 25.0 (t), 66.6 (t), 117.0 (d), 122.4 (s), 126.0 (d), 126.5 (d), 126.7 (d), 128.4 (d), 128.6 (d), 133.3 (s), 141.0 (s), 154.6 (s); exact mass *m/z* calcd for $C_{15}H_{14}O$ 210.10446, found 210.10445.

4a-Methoxy-6,10b-dihydro-1*H*,4a*H*-benzo[*c*]chromen-2-one (23.4).



19.6 **23.4**

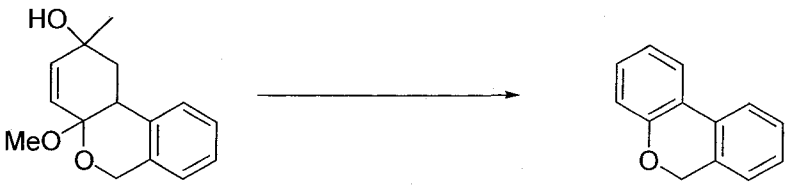
A solution of Bu_3SnH (187 mg, 0.640 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h (syringe pump) into a stirred and heated (95 °C) solution of **19.6** (191 mg, 0.540 mmol) in PhMe (15 mL). Heating was continued for 20 min after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:5:45 Et_3N-EtOAc-hexane, gave **23.4** (123 mg, 100%) as an oil, which was a single isomer (^{1}H NMR): FTIR ($CHCl_3$, cast) 2943, 2905, 2861, 1688, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64-2.75 (m, 2 H), 3.29 (dd, J = 10.8, 5.9 Hz, 1 H), 3.47 (s, 3 H), 4.88 (AB q, $\Delta\nu_{AB}$ = 19.6 Hz, J = 15.0 Hz, 2 H), 6.12 (dd, J = 10.4, 0.9 Hz, 1 H), 6.98 (d, J = 10.4 Hz, 1 H), 7.02-7.05 (m, 1 H), 7.09-7.12 (m, 1 H), 7.19-7.24 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.1 (d), 44.1 (t), 49.3 (q), 63.4 (t), 95.2 (s), 123.8 (d), 126.7 (d), 127.2 (d), 127.9 (d), 130.7 (d), 131.8 (s), 133.8 (s), 142.6 (d), 197.9 (s); exact mass *m/z* calcd for $C_{14}H_{14}O_3$ 230.09430, found 230.09417.

4a-Methoxy-2-methyl-1,2,6,10b-tetrahydro-4a*H*-benzo[*c*]chromen-2-ol (23.5).

23.4 **23.5**

MeMgCl (3 M in THF, 0.26 mL, 0.78 mmol) was added to a stirred solution of **23.4** (90 mg, 0.39 mmol) in THF (10 mL). Stirring was continued for 2 h. The mixture was cooled to 0 °C and quenched with water. The solvent was evaporated and the residue was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc-hexane, gave **23.5** (95 mg, 99%) as a colorless solid, which was a mixture of two isomers: mp 82-84 °C; FTIR (CH_2Cl_2 cast) 3411, 3064, 2940, 1285, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, signals for one isomer only) δ 1.30 (s, 0.5 H), 1.42 (s, 2.5 H), 1.93-1.98 (m, 2 H), 2.06 (s, 1 H), 2.87 (t, J = 8.4 Hz, 1 H), 3.37-3.39 (m, 3 H), 4.73-4.74 (m, 2 H), 5.89-5.92 (m, 2 H), 6.97 (d, J = 7.6 Hz, 1 H), 7.12-7.24 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, signals for one isomer only) δ 26.4 (q), 40.4 (d), 46.8 (t), 49.0 (q), 62.7 (t), 70.0 (s), 95.8 (s), 123.3 (d), 123.6 (d), 126.2 (d), 126.9 (d), 128.9 (d), 132.2 (s), 135.1 (s), 139.7 (d); exact mass *m/z* calcd for $C_{15}H_{18}O_3$ 246.12560, found 246.12590.

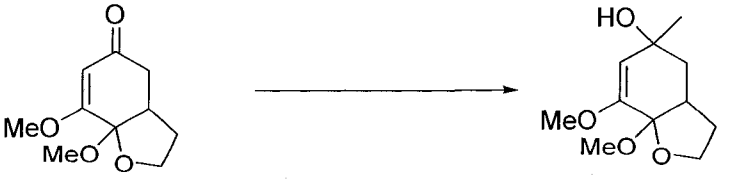
2-Methyl-6*H*-benzo[c]chromene (23.6).[32]



23.5 **23.6**

$TsOH{\cdot}H_2O$ (10 mg) was added to a stirred solution of **23.5** (92 mg, 0.37 mmol) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:9 EtOAc-hexane, gave **23.6**[32] (59 mg, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3 H), 5.09 (s, 2 H), 6.89 (d, J = 8 Hz, 1 H), 7.05 (dd, J = 8, 2 Hz, 1 H), 7.14 (d, J = 7.6 Hz, 1 H), 7.27 (td, J = 7.6, 1.2 Hz, 1 H), 7.36 (td, J = 7.6, 1.2 Hz, 1 H), 7.53 (d, J = 2H, 1 H), 7.70 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 68.5 (t), 117.1 (d), 121.9 (d), 122.6 (s), 123.6 (d), 124.6 (d), 127.5 (d), 128.3 (d), 130.1 (d), 130.3 (s), 131.3 (s), 131.6 (s), 152.6 (s).

7,7a-Dimethoxy-5-methyl-2,3,3a,4,5,7a-hexahydrobenzofuran-5-ol (23.7).

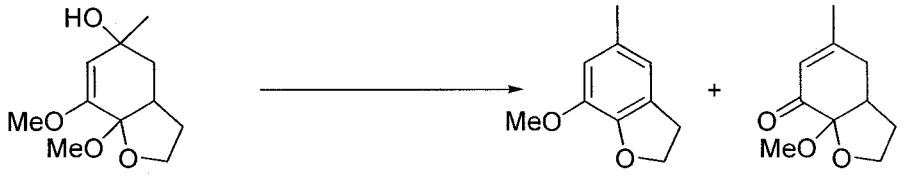


21.3 **23.7**

MeMgCl (3 M in THF, 0.15 mL, 0.45 mmol) was added to a stirred solution of **21.3** (30 mg, 0.15 mmol) in THF (5 mL), and stirring was continued for 2 h. The mixture

was cooled to 0 °C and quenched with water. The solvent was evaporated the residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 2:80:20 Et_3N-EtOAc-hexane, gave **23.7** (30 mg, 99%) as a colorless solid, which was a mixture of a major and a minor isomer: mp 74-75 °C; FTIR (CH_2Cl_2 cast) 3425, 2965, 1454, 1159, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3 H), 1.53-1.66 (m, 3 H), 1.81 (ddd, *J* = 12.8, 5.2, 1.2 Hz, 1 H), 2.28-2.36 (m, 1 H), 2.45-2.51 (m, 1 H), 3.28 (s, 3 H), 3.56 (s, 3 H), 4.02-4.09 (m, 1 H), 4.79 (d, *J* = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz, signals for major isomer only) δ 27.9 (d), 29.7 (t), 41.5 (q), 43.3 (t), 51.4 (q), 54.7 (q), 67.7 (t), 70.7 (s), 104.8 (s), 107.2 (d), 152.6 (s); exact mass *m/z* calcd for $C_{11}H_{18}O_4$ 241.12051, found 241.12060.

7-Methoxy-5-methyl-2,3-dihydrobenzofuran (23.8) and 5-Methyl-2,3,3a,7a-tetrahydro-4*H*-benzofuran-7-one (23.9).



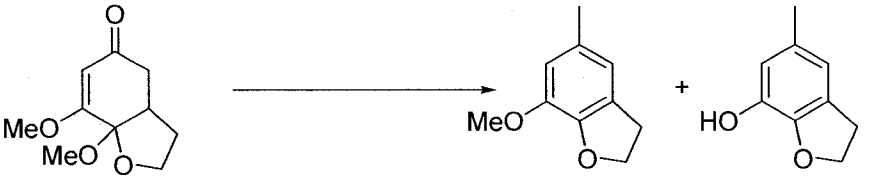
23.7 **23.8** **23.9**

TsOH·H_2O (5 mg) was added to a stirred solution of **23.7** (98 mg, 0.43 mmol) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (15 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with water. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 5:1 EtOAc-hexane, gave **23.8** (41 mg, 51%) as a colorless solid and **23.9** (33 mg, 37%) as an oil. **23.8** had: mp 46-48 °C; FTIR (CH_2Cl_2 cast) 2935, 1620, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3 H), 3.16 (t, *J* = 8.4 Hz, 2 H), 3.83 (s, 3 H), 4.57 (t, *J*

= 8.4 Hz, 2 H), 6.53 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q), 30.4 (t), 55.9 (q), 71.6 (t), 111.9 (d), 117.4 (d), 127.9 (s), 130.6 (s), 144.0 (s), 146.1 (s); exact mass *m/z* calcd for $C_{10}H_{12}O_2$ 164.08372, found 164.08344.

Enone **23.9** had: FTIR (CH_2Cl_2 cast) 2976, 1484, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70-1.74 (m, 1 H), 1.90 (s, 3 H), 2.19-2.26 (m, 2 H), 2.39-2.46 (m, 1 H), 2.64-2.66 (m, 1 H), 3.44 (s, 3 H), 3.94-4.05 (m, 2 H), 5.84 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3 (s), 30.4 (t), 33.6 (t), 43.5 (q), 51.9 (q), 67.3 (t), 101.4 (s), 125.3 (d), 160.0 (s), 192.4 (s); exact mass *m/z* calcd for $C_{10}H_{14}O_3$ 182.09430, found 182.09465.

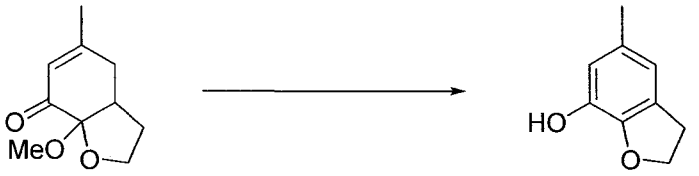
7-Methoxy-5-methyl-2,3-dihydrobenzofuran (23.8) and 5-Methyl-2,3-dihydrobenzofuran-7-ol (23.10).



23.7 **23.8** **23.10**

TsOH·H_2O (5 mg) was added to a stirred solution of **23.7** (28 mg, 0.14 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 3:1 EtOAc-hexane, gave **23.8** (12 mg, 52%) and **23.10** (6.8 mg, 36%) as colorless solids. Phenol **23.10** had: mp 95-97 °C; FTIR (CH_2Cl_2 cast) 3361, 3031, 1718, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (s, 3 H), 3.18 (t, *J* = 8.8 Hz, 2 H), 4.57 (t, *J* = 8.8 Hz, 2 H), 4.96 (s, 1 H), 6.40 (s, 1 H), 6.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 30.5 (d), 71.9 (d), 115.4 (d), 117.2 (d), 127.7 (s), 131.1 (s), 139.7 (s), 144.4 (s); exact mass *m/z* calcd for $C_9H_{10}O_2$ 150.06808, found 150.06840.

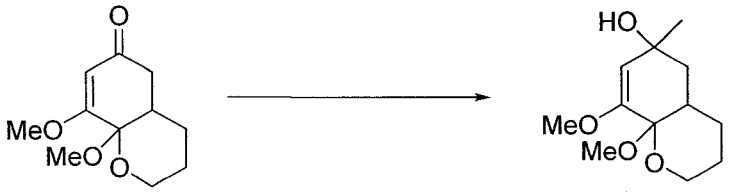
5-Methyl-2,3-dihydrobenzofuran-7-ol (23.10).



23.9 **23.10**

$TsOH{\cdot}H_2O$ (5 mg) was added to a stirred solution of **23.9** (30 mg, 0.16 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:3 EtOAc-hexane, gave **23.10** (22 mg, 89%) as a colorless solid.

8,8a-Dimethoxy-6-methyl-3,4,4a,5,6,8a-hexahydro-2*H*-chromen-6-ol (23.11).

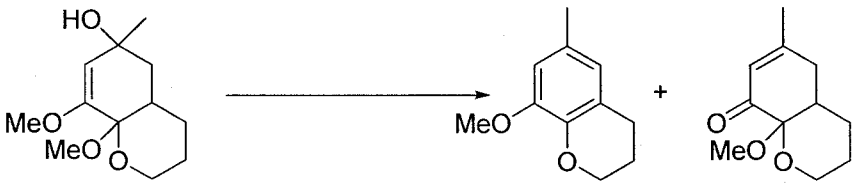


21.5 **23.11**

MeMgCl (3 M in THF, 0.47 mL, 1.4 mmol) was added to a stirred solution of **21.5** (0.10 g, 0.47 mmol) in THF (10 mL). Stirring was continued for 2 h. The mixture was cooled to 0 °C and quenched with water. The solvent was evaporated the residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 2:60:30 Et_3N-EtOAc-hexane, gave **23.11** (98 mg, 90%) as a yellow oil, which was a mixture of two

isomers: FTIR (CH_2Cl_2 cast) 3445, 1681, 1268, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.33 (m, 4 H), 1.42-1.47 (m, 1 H), 1.60-1.70 (m, 2 H), 1.84-2.07 (m, 4 H), 3.25 (s, 3 H), 3.49 (s, 3 H), 3.59-3.62 (m, 1 H), 3.80 (td, J = 11.2, 3.2 Hz, 1 H), 4.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz, signals for major isomer only) δ 20.6 (t), 24.5 (t), 28.8 (q), 33.2 (q), 41.0 (t), 51.3 (q), 54.6 (q), 62.6 (t), 70.1 (s), 97.1 (s), 107.6 (d), 153.6 (s); exact mass *m/z* calcd for $C_{12}H_{18}O_3$ (M - H_2O) 210.12560, found 210.12581.

8-Methoxy-6-methylchroman (23.12) and 8a-Methoxy-6-methyl-3,4,4a,8a-tetrahydro-2*H*,5*H*-chromen-8-one (23.13).



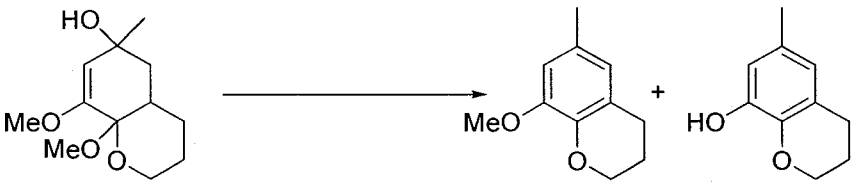
23.11 **23.12** **23.13**

TsOH·H_2O (5 mg) was added to a stirred mixture of **23.11** (95 mg, 0.42 mmol) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with water. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 2:30:70 Et_3N-EtOAc-hexane, gave **23.12** (49 mg, 65%) and **23.13** (26 mg, 31%) as oils. Chroman **23.12** had: FTIR (CH_2Cl_2 cast) 2932, 1495, 1221, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95-1.99 (m, 2 H), 2.24 (s, 3 H), 2.72 (t, J = 6.4 Hz, 2 H), 3.83 (s, 3 H), 4.22 (t, J = 5.2 Hz, 2 H), 6.45 (s, 1 H), 6.50 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0 (q), 22.2 (t), 24.7 (t), 55.7 (q), 66.7 (t), 110.0 (d), 121.7 (d), 122.4 (s), 128.9 (s), 141.9 (s), 148.0 (s); exact mass *m/z* calcd for $C_{11}H_{14}O_2$ 178.09938, found 178.09935.

Enone **23.13** had: FTIR (CH_2Cl_2 cast) 2938, 1681, 1152, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.62 (m, 4 H), 1.92 (s, 3 H), 2.03 (dd, J = 18.4, 2.4 Hz, 1 H),

2.16-2.19 (m, 1 H), 2.82 (dd, J = 11.2, 4.8 Hz, 1 H), 3.30 (s, 3 H), 3.51 (td, J = 11.2, 3.2 Hz, 1 H), 3.89-3.94 (m, 1 H), 5.83 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4 (q), 24.6 (t), 25.9 (t), 36.1 (t), 40.0 (d), 50.8 (q), 64.5 (t), 96.8 (s), 124.5 (d), 160.9 (s), 193.3 (s); exact mass *m/z* calcd for $C_{11}H_{16}O_3$ 196.10994, found 196.11006.

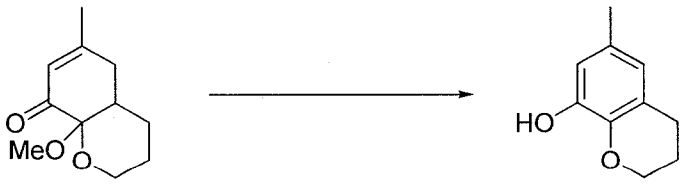
8-Methoxy-6-methylchroman (23.12) and 6-Methylchroman-8-ol (23.14).



23.11 **23.12** **23.14**

TsOH·H_2O (5 mg) was added to a stirred solution of **23.11** (84 mg, 0.37 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 3:1 EtOAc-hexane, gave **23.12** (43 mg, 65%) as an oil and **23.14** (21 mg, 35%) as a solid.

6-Methylchroman-8-ol (23.14).



23.13 **23.14**

TsOH·H_2O (5 mg) was added to a stirred solution of **23.13** (24 mg, 0.12 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2

and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 3:1 EtOAc-hexane, gave **23.14** (16 mg, 81%) as a colorless solid: mp 78-80 °C; FTIR (CH_2Cl_2 cast) 3450, 2955, 1501, 1214, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.97-1.99 (m, 2 H), 2.19 (s, 3 H), 2.71 (t, J = 6.4 Hz, 2 H), 4.18-4.21 (m, 2 H), 5.36 (s, 1 H), 6.38 (s, 1 H), 6.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (q), 22.6 (t), 24.2 (t), 66.8 (t), 112.9 (d), 120.8 (d), 122.0 (s), 129.6 (s), 139.6 (s), 144.5 (s); exact mass *m/z* calcd for $C_{10}H_{12}O_2$ 164.08372, found 164.08407.

5 REFERENCES AND FOOTNOTES

1 (a) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans 1* **2002**, 2747. (b) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron*, **2005**, *61*, 2689. (c) Majumdar, K. C.; Basut, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793.

2 Leading references to cyclization of aryl radicals onto aromatic rings: Clyne, M. A.; Aldabbagh, F. *Org. Biomol. Chem.* **2006**, *4*, 268.

3 Examples of cyclization of vinyl radicals onto aromatic rings: (a) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765. (b) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 3105. (c) Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.* **2005**, *70*, 10615.

4 (a) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951. (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*, **2001**, *42*, 7887.

5 (a) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937. (b) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111.

6 (a) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans 1* **1997**, 2639. (b) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795. (c) Menes-Arzate, M.; Martinez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001.

7 (a) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*, **2001**, *42*, 9061. (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. (c) Storey, J. M. D.; Ladwa, M. M. *Tetrahedron Lett.* **2006**, *47*, 381.

8 Murphy, J. A.; Sherborn, M. S. *Tetrahedron* **1991**, *47*, 4077.

9 Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *43*, 4191.

10 Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett.* **2000**, *41*, 381.

11 (a) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547.

12 (a) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119. (b) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977. (c) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765. (d) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991.

13 (a) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343. (b) Curran, D. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377.

14 Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Story, J. M. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 95.

15 (a) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1994**, *50*, 2107. (b) Ellis, M. J.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3180. (c) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S. *Tetrahedron* **1997**, *53*, 285. (d) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Pereira, A. M. D. L. *Tetrahedron* **1997**, *53*, 269. (e) Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209

16 (a) Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2002**, *43*, 3185. (b) Harrowven, D. C; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2002**, *43*, 3189.

17 Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706.

18 Fukuyama, T.; Chen, X. Q.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127.

19 Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875.

20 (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719. (b) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759. (c) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295. (d) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron*

Lett. **1999**, *40*, 2125. (e) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2000**, *39*, 731. (g) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 1692. (h) Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 2306. (i) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663.

21 Snider, B. B. *Chem. Rev.* **1996**, *96*, 339-363.

22 Mohan, R.; Kates, S. A.; Dombroski, M.; Snider, B. B. *Tetrahedron Lett.* **1987**, *28*, 845.

23 At 25 °C the rate constant for hydrogen abstraction from Bu_3SnH by a primary alkyl radical is 2.4 x 10^6 M^{-1} s^{-1}: Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

24 At 25 °C the rate constant for hydrogen abstraction from PhSeH by a primary alkyl radical is 2.1 x 10^9 M^{-1} s^{-1}: Newcomb, M.; Varick, T. R.; Ha, C.; Manek, M. B.; Yue, X. *J. Am. Chem. Soc.* **1992**, *114*, 8158.

25 Clive, D. L. J.; Fletcher, S. P.; Zhu, M. *J. Chem. Soc., Chem. Commun.* **2003**, 526.

26 Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.

27 Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282.

28 Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965.

29 Giraldi, P. N; Fojanesi, A.; Logemann, W.; Tosolini, G. P.; Dradi, E.; Bergamaschi, M. *Arzneim.-Forsch.* **1970**, *20*, 676.

30 Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Fujii, M.; Ishihama, H.; Uchida, Y. *Chem. Pharm. Bull.* **1987**, *35*, 632.

31 Deady, L. W.; Topson, R. D.; Vaughan, L. *J. Chem. Soc.* **1965**, 5718.

32 Cavill, G. W. K.; Dean, F. M.; Keenan, J. F. E.; McGookin, A.; Robertson, A.; Smith, G. B. *J. Chem. Soc.*, **1958**, 1544.

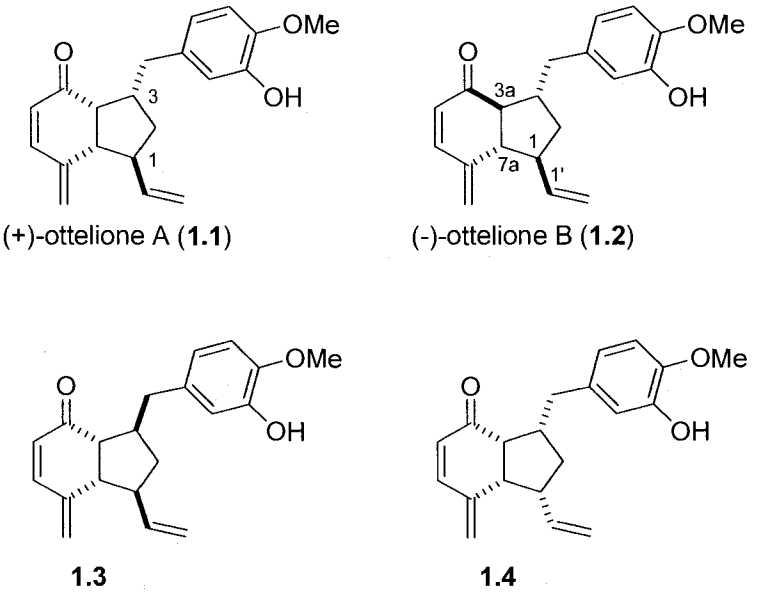
Chapter 2

Synthesis of the Core Structures of Otteliones A and B, Synthesis of Racemic Otteliones A and B and Synthesis of Optically Pure Otteliones A and B

1 INTRODUCTION

1.1 Isolation, Biological Activity and Structural Features of the Otteliones

The otteliones, designated as A (**1.1**)[1,2] and B (**1.2**)[1] are exceedingly powerful anticancer agents,[1] as judged by *in vitro* tests against a large panel of tumor cell lines. Both compounds were isolated from a freshwater plant, *ottelia alismoides*,[3] collected in Egypt,[1] but the amount of each obtained represented only 0.0009% of the dried weight of the sample. Structural studies were undertaken in America[1] and extensive NMR investigations served to identify the structure and relative stereochemistry of ottelione B, as shown in Scheme 1. In the case of ottelione A, however, these studies suggested the two possibilities **1.3** and **1.4**.



(+)-ottelione A (**1.1**) (-)-ottelione B (**1.2**)

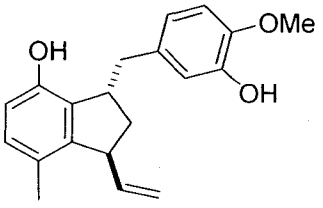
1.3 **1.4**

Scheme 1

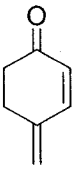
Ottelione A, was found to be identical to a compound, also isolated from *O. alismoides*, that had been described without any stereochemical assignment in a Rhone-Poulenc Rorer patent.[2] A later publication from the Rhone-Poulenc Rorer laboratories[4] assigned the relative stereochemistry shown in **1.1** to ottelione A, based on nOe

measurements, and this conclusion was subsequently confirmed by synthesis of the racemic compound.[5] Both the NMR structural work[1] and the investigations at Rhone-Poulenc Rorer,[2,4] were combined with biological evaluation which served to identify extremely strong anticancer activity. In the case of the evaluation[1] at the National Cancer Institute (USA) against a panel of *ca* 60 tumor cell lines, the impressive level of activity was quantified, and the compounds were found to have GI_{50} values in the sub-nanomolar to picomolar range. Ottelione B appears to be less potent than ottelione A. Ottelione A has been shown to inhibit tubulin polymerization and is able to disassemble preformed microtubules.[4] Some of the information available on the anticancer activity of the otteliones appears to have been reported only in a Ph.D. thesis[6] and in Abstracts of ACS National Meetings.[7] Ottelione B appears to be more selective towards some cancer cell lines than ottelione A.[6] Extracts of *O. alismoides* have also been reported to kill tubercular bacteria, and it was found in clinical trials that two cases of bilateral tuberculosis of the cervical lymph gland were cured in three months.[8]

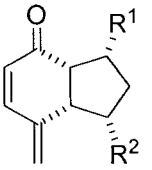
Examination of the structures of the otteliones raises the possibility that they might be prone to tautomerization to the aromatic compound **2.1** and, in fact, **2.1** was isolated along with **1.1**,[2] and is also cytotoxic; its tubulin activity, however, is only a fifth that of ottelione A.[4] A few extended dienone systems, such as **2.2**,[9,10] **2.3** and **2.4**[9c] have been known for many years; they were prepared under seemingly harsh conditions but do not readily aromatize.



2.1



2.2

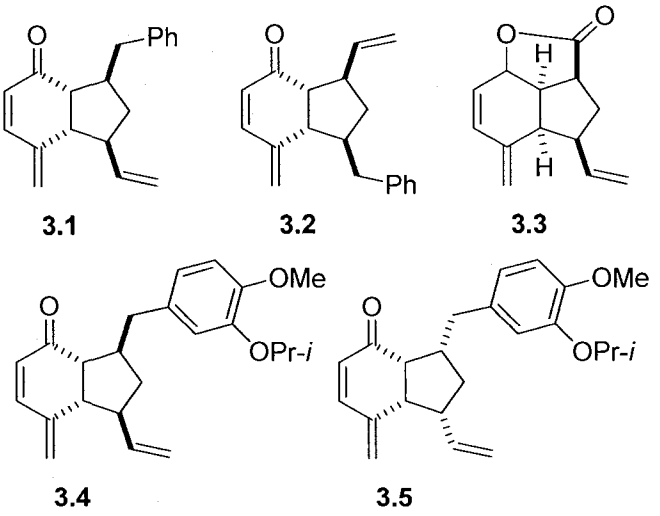


2.3 R^1 = vinyl, R^2 = H;
2.4 R^1 = H, R^2 = vinyl

Scheme 2

1.2 Other Synthetic Work on the Otteliones

The potent anticancer properties of the otteliones clearly make them important synthetic objectives. As mentioned above, synthetic studies played a role in establishing the structure of ottelione A. The majority[11] of the early synthetic work in this area was reported from Mehta's laboratory. Chemists in his group first prepared the model compounds (±)-**3.1**,[12] (±)-**3.2**,[12] and (-)-**3.3**.[13] With the experience thus gained, structure **1.1** was synthesized in racemic form and shown to correspond to ottelione A.[5] During the course of these studies the racemic *epi*-ottelione derivatives **3.4** and **3.5** were also prepared.[14] Finally, Mehta and Islam described the synthesis of both antipodes of otteliones A and B[15] and established that the natural compounds have the absolute configurations depicted by structures **1.1** and **1.2**.

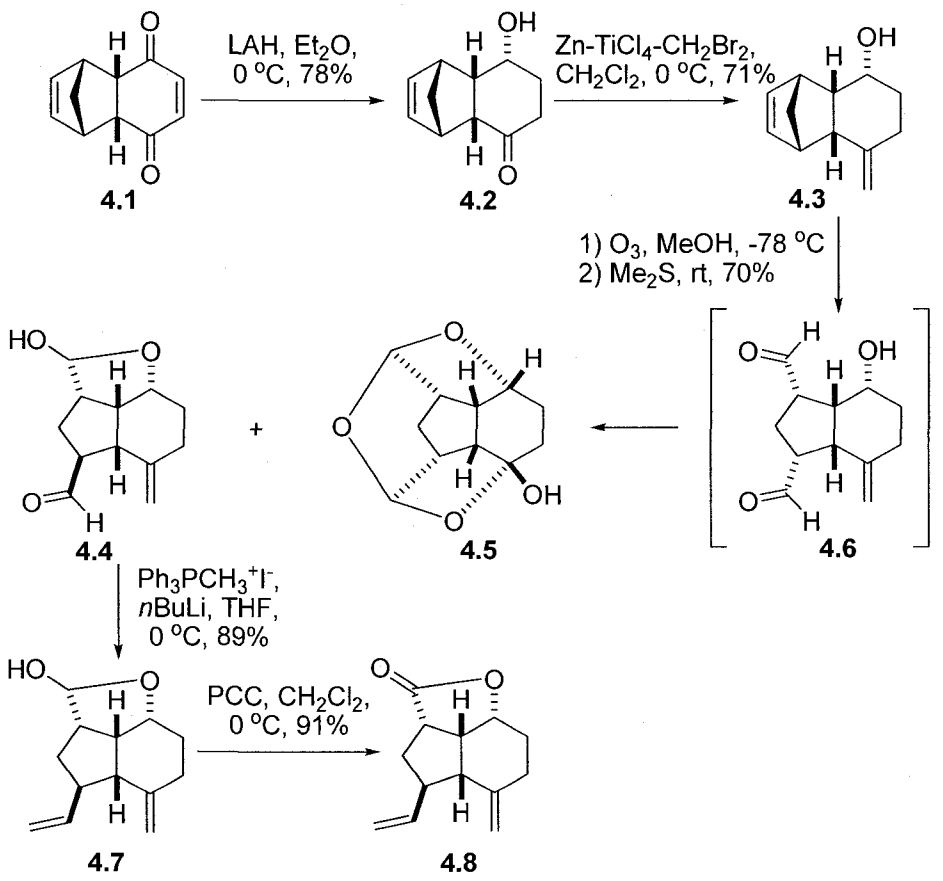


Scheme 3

At the same time, a Japanese group independently synthesized natural (+)-ottelione A and epimerized it to (-)-ottelione B.[16] The same group also prepared 3-*epi*-ottelione A in optically pure form.[17] A very recent paper[18] gives full details of the Japanese work including growth inhibition data and inhibitory activity against tubulin polymerization for (+)-ottelione A (**1.1**), (+)-3-*epi*-ottelione A and (+)-*O*-acetyl-3-*epi*-ottelione A; all are extremely potent in both respects, but may not act by the same mechanism.

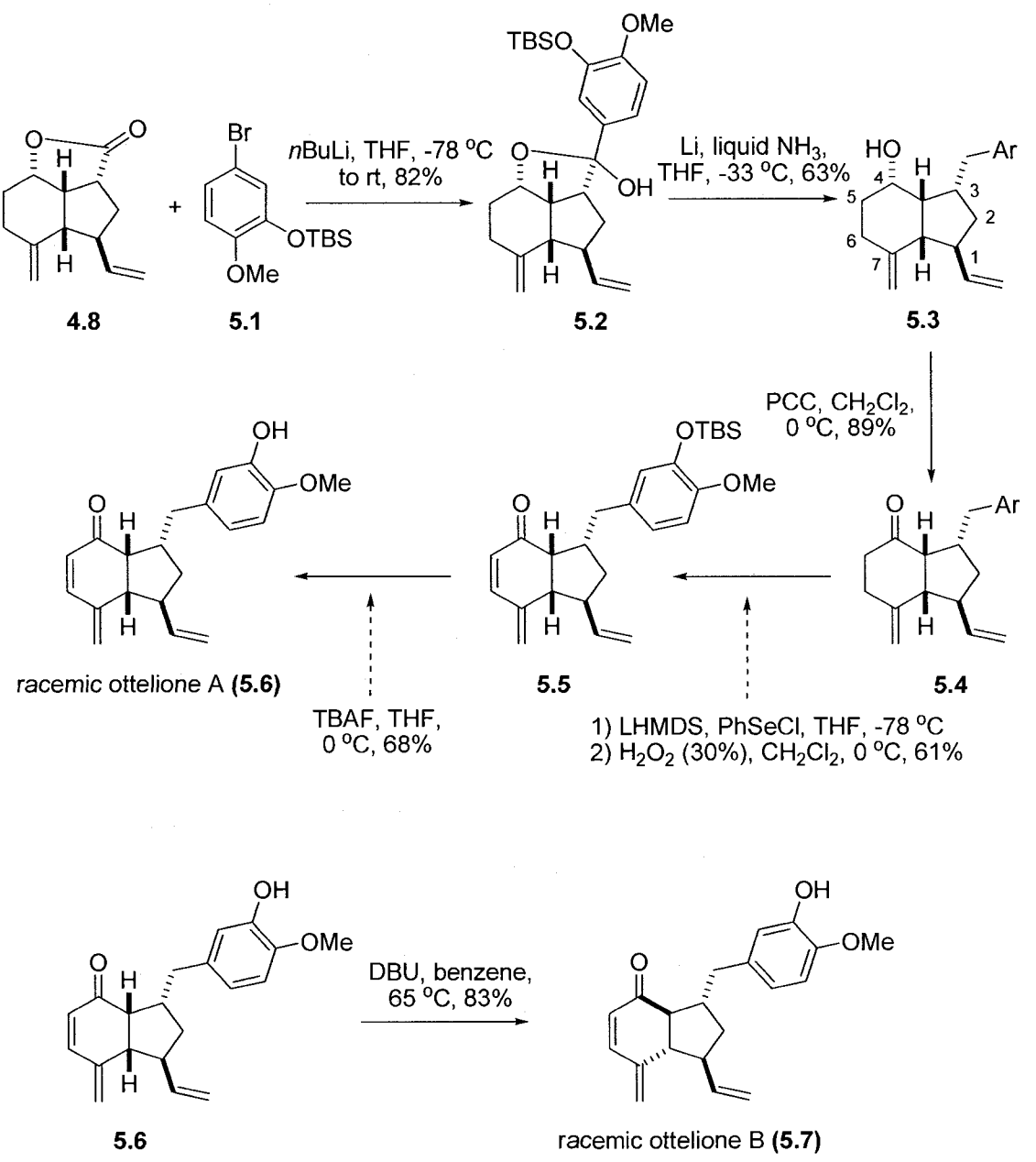
1.2.1 Total Synthesis of (±)-Otteliones A and B from Mehta's laboratory

Mehta and Islam's total synthesis of racemic ottelione A relied on a readily available Diels-Alder adduct (**4.1**) of cyclopentadiene and benzoquinone.[5] Partial reduction, followed by Lombardo methylenation gave **4.3**, which was subjected to controlled ozonolysis to deliver **4.4** and **4.5** in an 8:1 ratio. The lactol aldehyde **4.4** originated through the intramolecular capture of one of the aldehyde moieties of the intermediate dialdehyde **4.6**. Oxidative cleavage of both olefinic bonds of **4.3**, followed by a cascade intramolecular acetalization process, gave the minor product **4.5**. Wittig olefination of **4.4** installed the vinyl side chain of **4.7**. PCC oxidation of lactol **4.7** then gave lactone **4.8**, whose structure was confirmed by single-crystal X-ray analysis.



Scheme 4

With the four contiguous stereogenic centers all corresponding to the structure of ottelione A established, the synthesis continued with the addition of an organolithium reagent derived from **5.1**. The resulting adduct **5.2** was deoxygenated by lithium/ammonia reduction, which also released the C(4) hydroxyl group. PCC oxidation of **5.3** led to the cyclohexanone **5.4**, which was subjected to a phenylselenation-selenoxide elimination sequence to give the *cis*-fused dienone **5.5**. Fluoride-mediated deprotection of **5.5** provided racemic ottelione A (**5.6**), whose spectroscopic data matched those of the natural product. The authors also reported that synthetic ottelione A undergoes smooth epimerization to ottelione B (83%, **5.6**→**5.7**) on exposure to DBU. The NMR spectra of synthetic ottelione B were used to confirm the structure of the natural product.



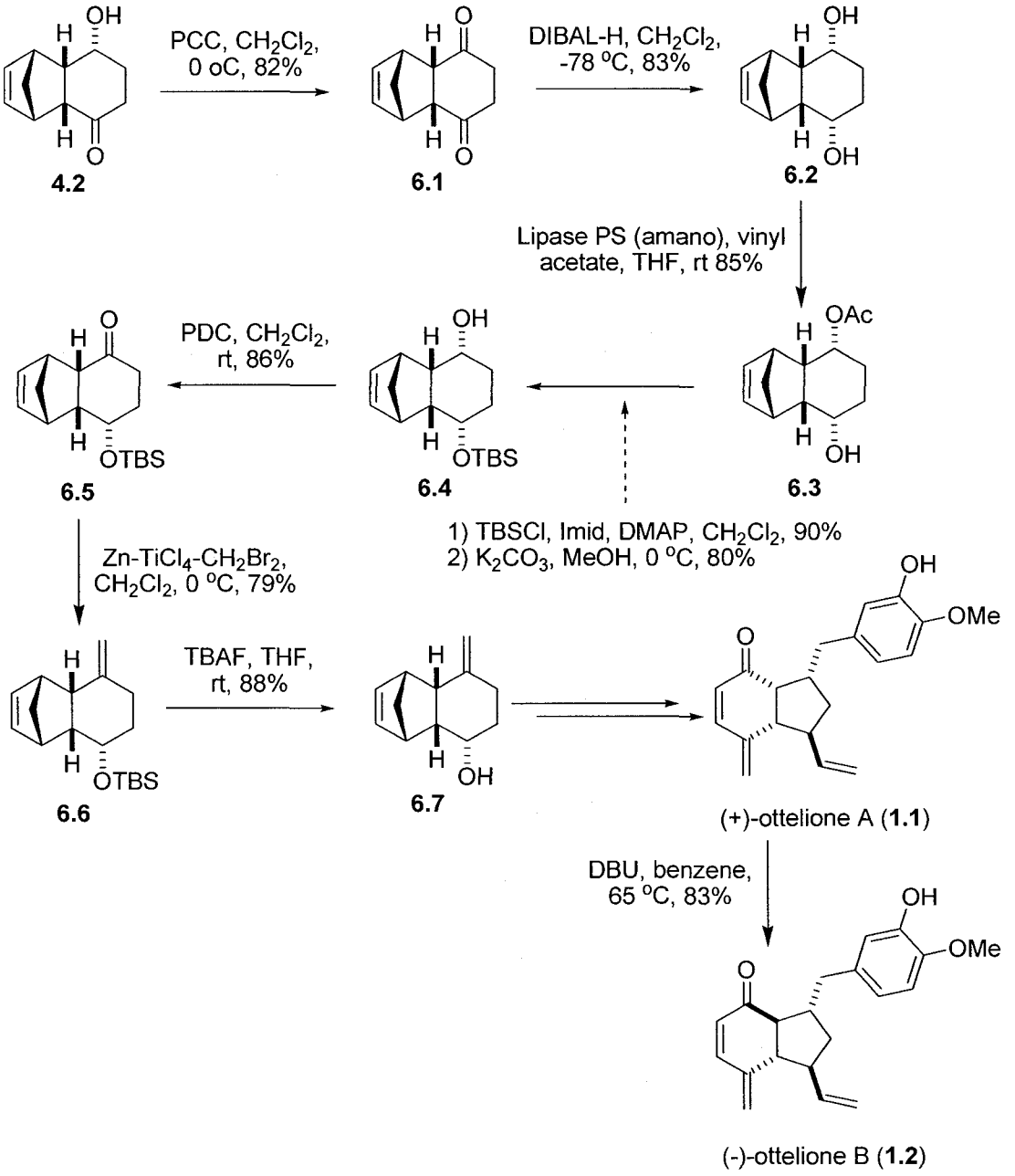
Scheme 5

1.2.2 Enantioselective Synthesis of (+)- and (-)- Ottelione A and (+)- and (-)- Ottelione B from Mehta's Laboratory

The enantioselective syntheses reported by Mehta and Islam were the first to establish the absolute configuration and to provide values for the specific rotations, which

were not mentioned in either of the isolation papers.[15] According to Mehta, Hoye et al. found ottelione A has a rotation of +14 (c 0.87, $CDCl_3$), and ottelione B a rotation of -276 (c 2.0, $CHCl_3$). The French group, in contrast, found that ottelione A has the opposite rotation, -20.8 (c 0.5, CH_2Cl_2). Mehta's work established the absolute configuration of ottelione A as **1.1** and ottelione B as **1.2**.[15]

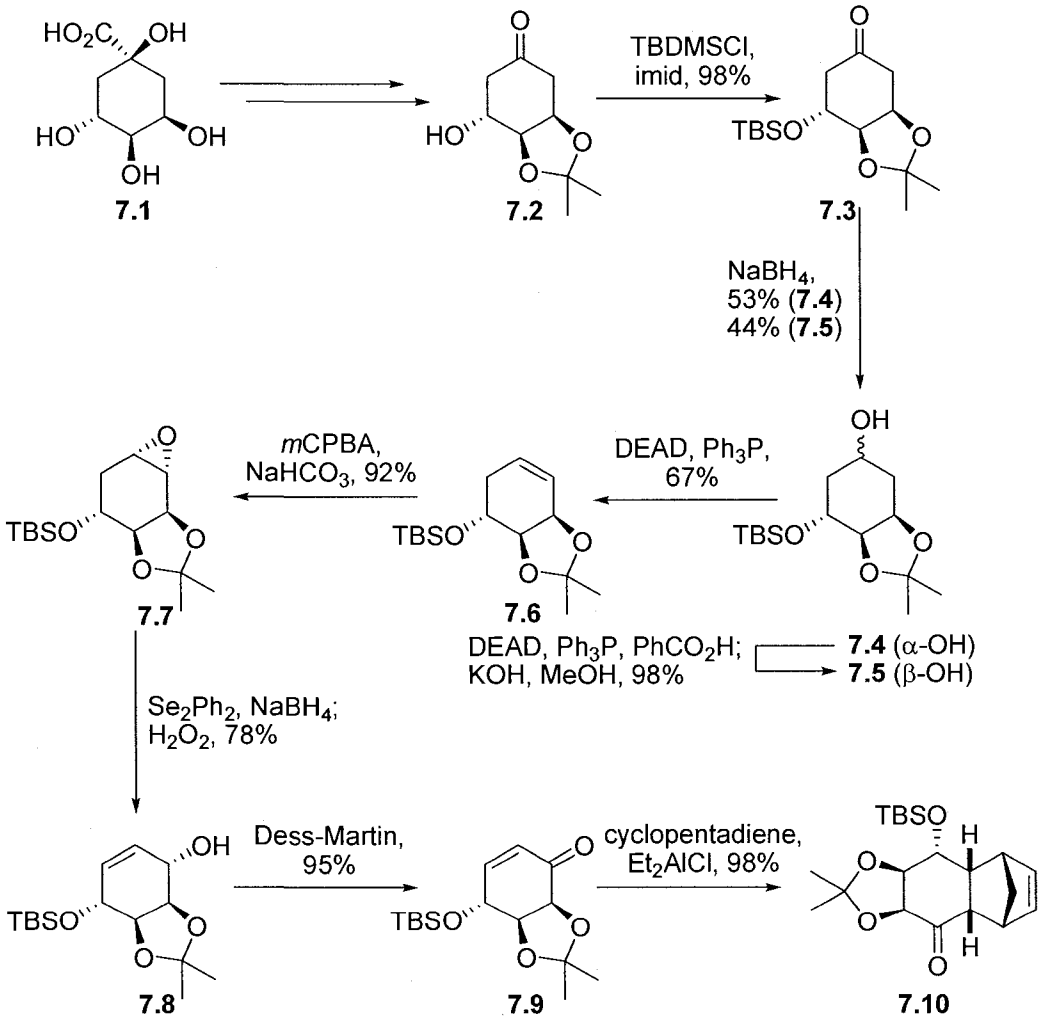
The key intermediate **6.2** was subjected to lipase-catalyzed transesterification to furnish enantiopure monoacetate **6.3** (Scheme 6). TBS protection of the hydroxyl group in **6.3**, followed by hydrolysis, gave **6.4**, which was further oxidized to the ketone **6.5**. Lombardo methylation and deprotection of the silyl group furnished **6.7**, from which point the route in Schemes 4 and 5 (from **4.3** to **5.6**) was followed to give synthetic (+)-ottelione A. This had a specific rotation of +19.2 (0.52, $CHCl_3$). The CD spectrum of synthetic ottelione A was also identical with that of the natural product. Treatment of synthetic (+)-ottelione A (**1.1**) with DBU furnished (-)-ottelione B with a specific rotation of -250 (c 0.24, $CHCl_3$). Ent-ottelione A had a specific rotation of -17 (c 0.4, $CHCl_3$) while ent-ottelione B had a specific rotation of +246 (c 0.4, $CHCl_3$).


PCC, CH2Cl2, 0 oC, 82%
DIBAL-H, CH2Cl2, -78 °C, 83%
Lipase PS (amano), vinyl acetate, THF, rt 85%
PDC, CH2Cl2, rt, 86%
1) TBSCl, Imid, DMAP, CH2Cl2, 90%
2) K2CO3, MeOH, 0 °C, 80%
Zn-TiCl4-CH2Br2, CH2Cl2, 0 °C, 79%
TBAF, THF, rt, 88%
DBU, benzene, 65 °C, 83%
4.2
6.1
6.2
6.3
6.4
6.5
6.6
6.7
(+)-ottelione A (1.1)
(-)-ottelione B (1.2)

Scheme 6

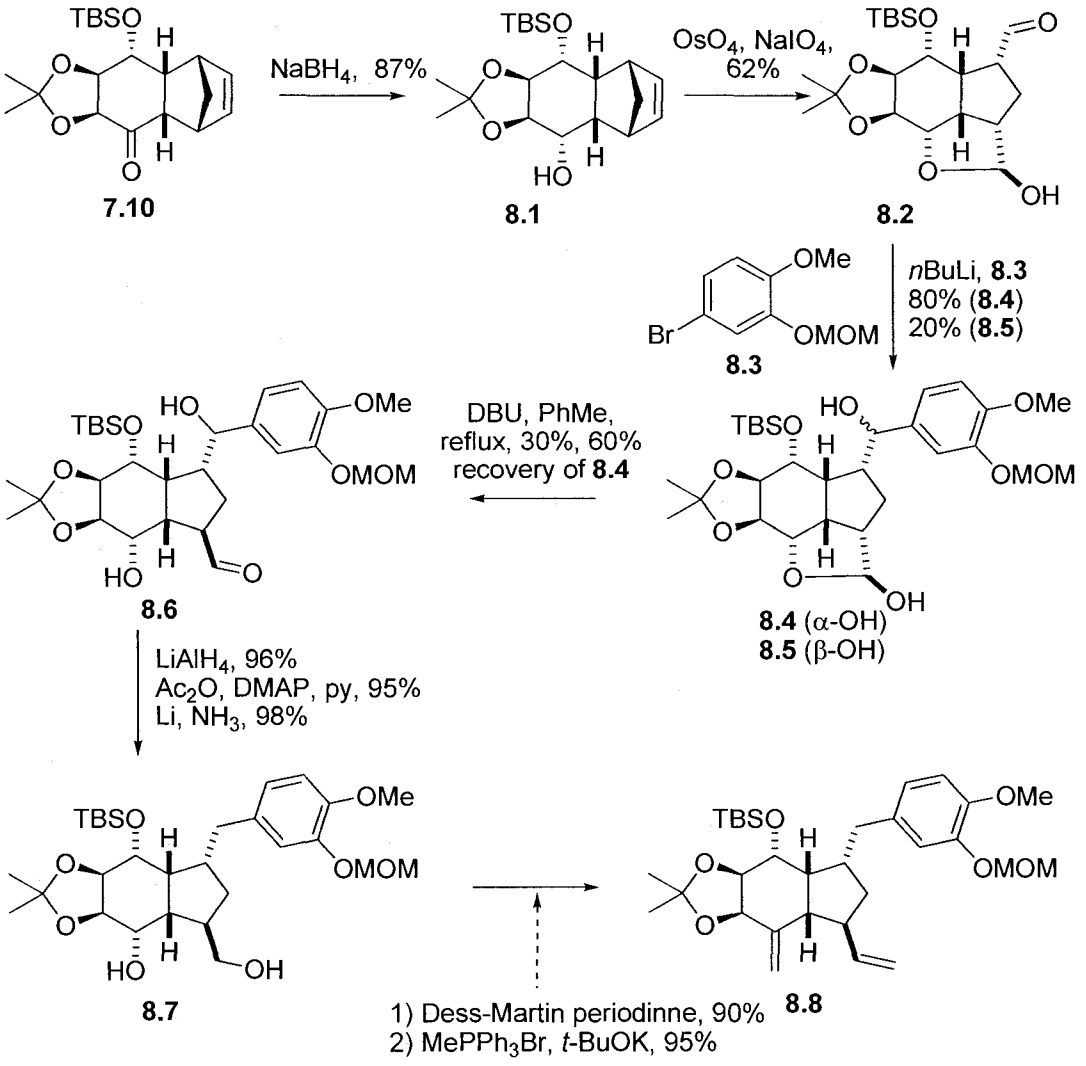
1.2.3 Synthetic Studies on Otteliones by Araki et al.

The synthesis starts with the known enantiomerically pure ketone **7.10** , which was prepared as shown in Scheme 7.[16] Commercially available (-)-quinic acid (**7.1**) was converted into **7.2**, according to literature procedures.[19] Standard transformations then provided **7.5**, which was dehydrated to olefin **7.6**. Epoxidation (**7.6**→**7.7**), followed by conversion to the allylic alcohol **7.8**, and oxidation gave **7.9**. The bridged system was then generated by Diels-Alder reaction with cyclopentadiene (**7.9**→**7.10**).



Scheme 7

Reduction of **7.10** (Scheme 8), followed by a Lemieux-Johnson oxidative cleavage (**8.1**→**8.2**), produced cyclic hemiacetal **8.2** by trapping of an intermediate dialdehyde. The remaining free aldehyde moiety reacted with the organolithium generated from **8.3**, to provide a separable mixture of alcohols **8.4** and **8.5**.



Scheme 8

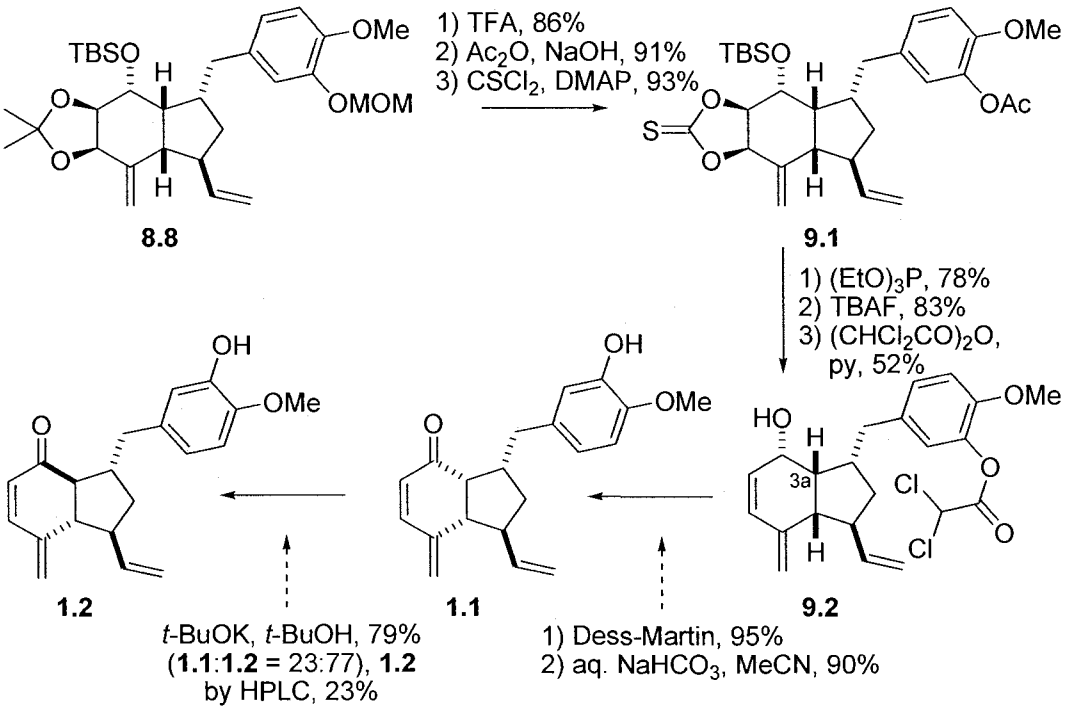
Next, the base-induced hemiacetal opening/epimerization of the formyl group of **8.4** to provide **8.6** was accomplished using DBU in refluxing toluene for 1.5 h. The yield was 30% under optimized conditions (extended reaction times caused decomposition),

and 60% unreacted **8.4** was recovered. This starting material **8.4** could be recycled four times to provide *ca* 65% yield of **8.6**. Treatment of the minor lactol **8.5** under identical conditions led to recovery of the starting material, and so the synthesis was carried on using only **8.4**.

Compound **8.6** was further converted to diol **8.7** in 89% overall yield by formyl group reduction, global acetylation, and reduction with a large excess (100 equiv.) of lithium in liquid ammonia at -78 °C. Double oxidation, followed by double Wittig methylenation then provided **8.8**.

The final stages that led to completion of the synthesis revolve around a multistep sequence to convert the three protected aliphatic hydroxyls in **8.8** into the highly sensitive 4-methylene-2-cyclohexeneone system. Acetonide deprotection was accompanied by removal of the MOM group on the phenolic hydroxyl under acidic conditions, and the latter was reprotected by chemoselective acetylation. Treatment of the resulting diol with thiophosgene gave cyclic thiocarbonate **9.1**. Reductive elimination of the thiocarbonate provided the diene system, and this step was followed by fluoride-mediated global deprotection, and reprotection of the phenolic hydroxyl as a dichloroacetate to give **9.2**. The choice of this protecting group was based on the fact that it could be cleanly removed later without epimerization at the C(3a) position. Alcohol **9.2** was converted into ottelione A by oxidation and careful deprotection. It was found that the specific rotation was +17.3 (*c* 0.55, $CHCl_3$), comparable to the value reported by Mehta and Islam.

Attempts to convert ottelione A (**1.1**) into ottelione B (**1.2**), using Mehta and Islam's conditions, gave an approximately equal mixture of **1.1** and **1.2**, rather than the claimed complete conversion. The Araki group found that epimerization was best accomplished by exposure to *t*-BuOK in *t*-BuOH at room temperature for 2 h; these conditions provided a 23:77 mixture of **1.1** and **1.2**. The isolation of **1.2** was accomplished by high performance liquid chromatography, with a chiral, nonracemic stationary phase.



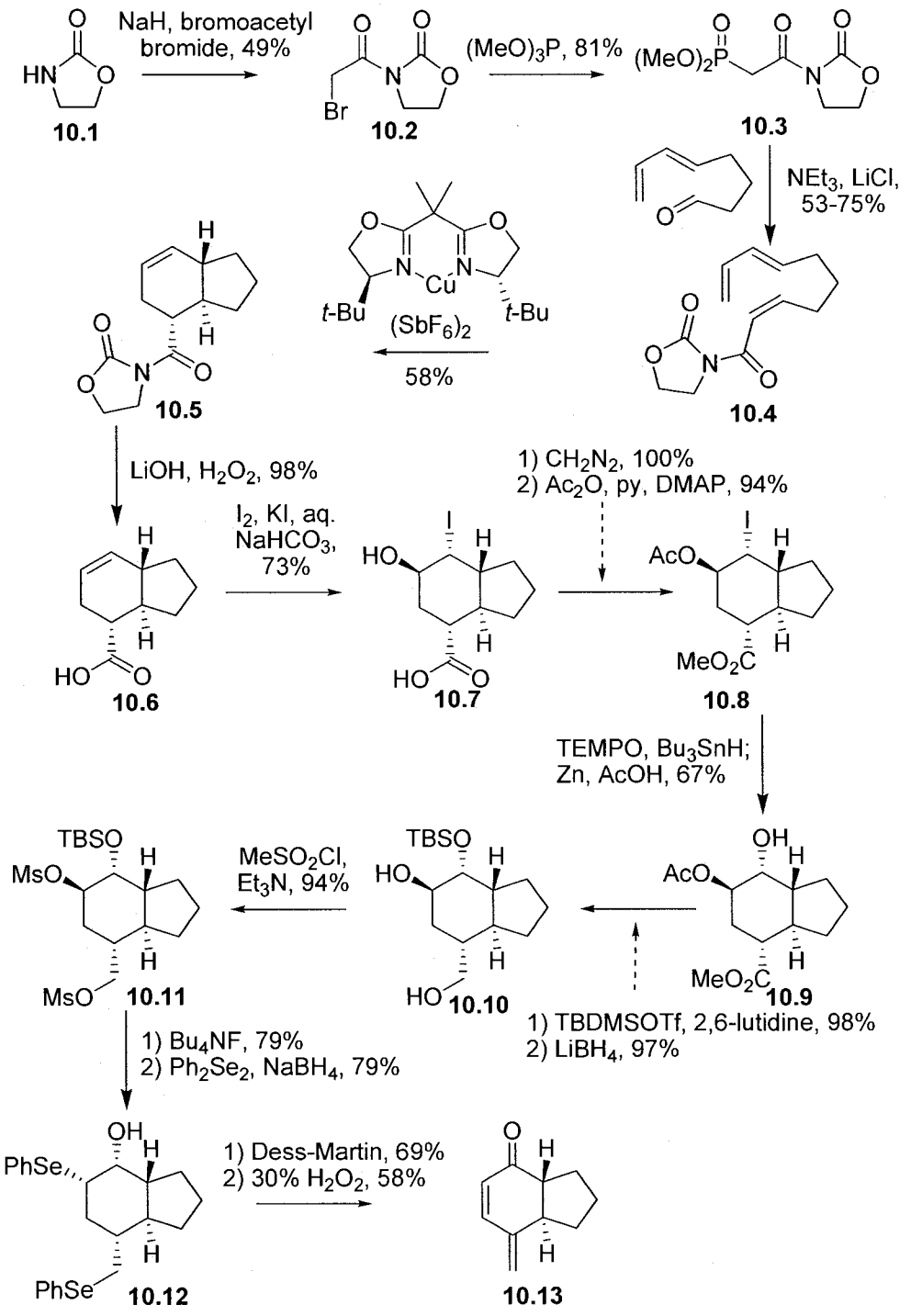
Scheme 9

Synthetic ottelione B was spectroscopically identical to the other reported data, but the optical rotation was -333.0 (*c* 0.18, $CHCl_3$), significantly higher than that reported by Hoye *et al.*[20] In Hoye's work, **1.2** was contaminated by **1.1** (**1.2**:**1.1** = 85:15) and the material had a specific rotation of -276 (*c* 2.0, $CHCl_3$). It is also clear that the synthetic ottelione B obtained by Mehta and Islam was contaminated by ottelione A; the Japanese chemists separated this impurity and our own efforts give the pure compound without the problems associated with contamination by ottelione A.

2 RESULTS AND DISCUSSION

2.1 Preliminary Synthetic Studies on the Core Structure of Ottelione B

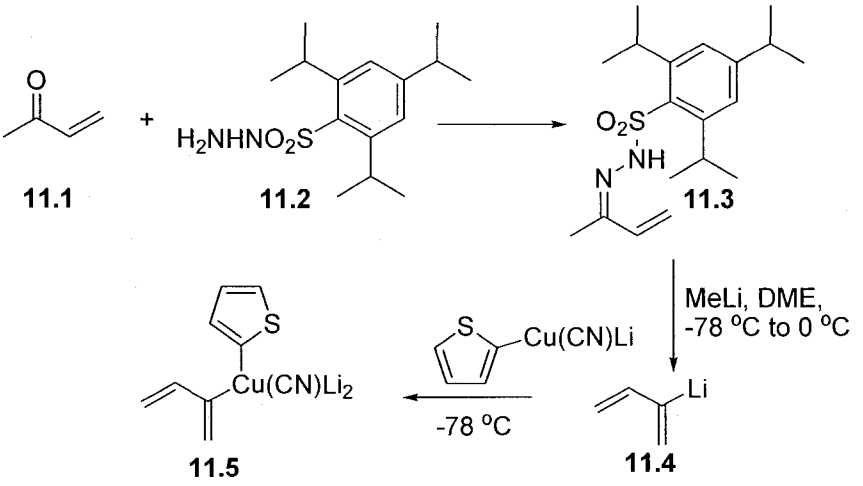
Synthetic studies on the otteliones were begun by a former group member before any total synthesis had been completed, and was initially aimed at **10.13**, the core structure of ottelione B. This model was eventually reached[21] by way of an intramolecular Diels-Alder reaction mediated by a chiral catalyst (Scheme 10). Just after that model study was completed, the short synthesis of both racemic otteliones was reported by Mehta and Islam,[5] and it did not seem appropriate to continue with the much longer route being pursued in this laboratory. However, about a year later when the syntheses of optically pure otteliones was published from two laboratories — both using the base-induced isomerization of ottelione A to ottelione B — it became clear that routes involving the A→B isomerization are not straightforward so that further synthetic work on the otteliones was clearly justified, especially in view of their exceptional anticancer potency. Therefore, we took up the project again but with a new plan and, as before, adopted the cautious approach of first making the core structures of both otteliones.[22]


NaH, bromoacetyl bromide, 49%
(MeO)3P, 81%
10.1
10.2
10.3
NEt3, LiCl, 53-75%
10.4
(SbF6)2
58%
t-Bu
t-Bu
Cu
10.5
LiOH, H2O2, 98%
I2, KI, aq. NaHCO3, 73%
1) CH2N2, 100%
2) Ac2O, py, DMAP, 94%
10.6
10.7
10.8
TEMPO, Bu3SnH; Zn, AcOH, 67%
MeSO2Cl, Et3N, 94%
10.9
10.10
10.11
1) TBDMSOTf, 2,6-lutidine, 98%
2) LiBH4, 97%
1) Bu4NF, 79%
2) Ph2Se2, NaBH4, 79%
1) Dess-Martin, 69%
2) 30% H2O2, 58%
10.12
10.13

Scheme 10

2.2 *Second Generation Route to the Core Structures*

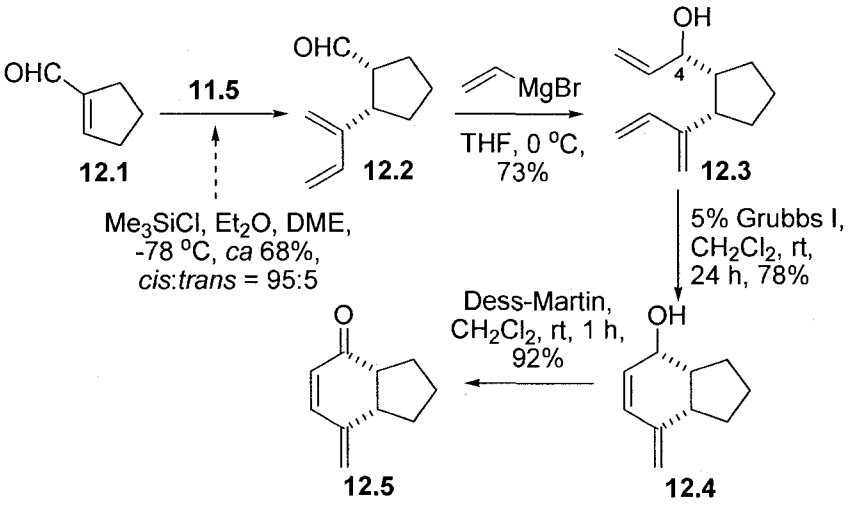
Methyl vinyl ketone **11.1** was converted into hydrazone **11.3**[23a] by reaction with (2,4,6-triisopropylbenzene)sulfonylhydrazine[24] and then, by reaction with MeLi, into 2-lithio-1,3-butadiene.[23] The resulting pink solution was added to a solution of lithium 2-thienylcyanocuprate[25] to form the mixed cuprate **11.5**.



Scheme 11

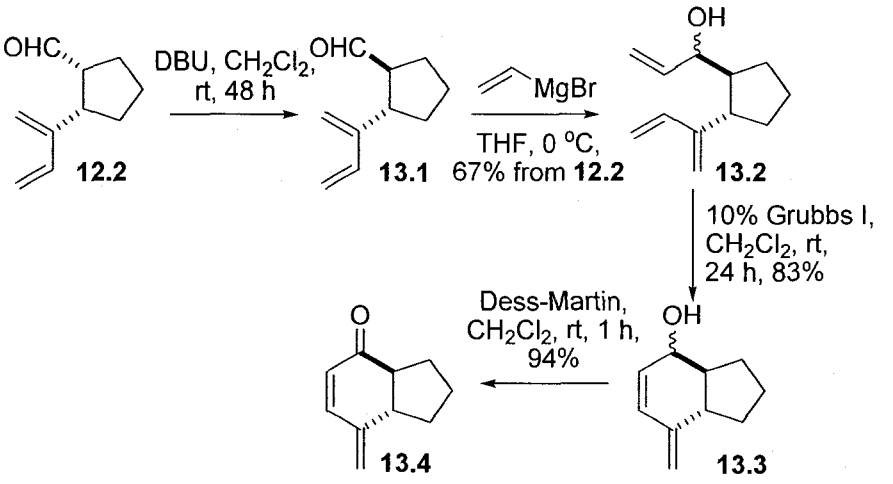
The readily available unsaturated aldehyde **12.1**[26] (Scheme 12) was subjected to conjugate addition, using the organocuprate **11.5** in the presence of Me_3SiCl.[27] After acidic workup the conjugate addition[28] gave a mixture of *cis* and *trans* isomers that was mainly (*ca* 95%) the desired *cis* compound **12.2**.

Reaction with vinylmagnesium bromide afforded alcohol **12.3** as a single isomer whose stereochemistry at C(4) (ottelione numbering) was not determined and is, in any case, inconsequential. In the presence of the Grubbs I catalyst (5 mol%) ring closing metathesis occurred to give **12.4** in 78% yield. This regiochemical outcome was expected, as preferential closure involving the less substituted double bond of a 1,3-diene unit has been observed previously.[29] Finally, Dess-Martin oxidation gave **12.5**, the core of ottelione A.



Scheme 12

The *trans* ring-fused core was then made from **12.2** (Scheme 13). To this end, the aldehyde was exposed to the action of DBU for 48 h at room temperature to produce material that was largely (*ca* 85% by ^{1}H NMR) the *trans* isomer **13.1**. Reaction with vinylmagnesium bromide proceeded without incident and it was possible to isolate **13.2** (67% yield) as a mixture of C(4) epimers in both of which the side arms on the five-membered ring were *trans*. Once again, ring closing metathesis with the Grubbs I catalyst was efficient (83%) and the resulting alcohols **13.3** were oxidized with the Dess-Martin reagent so as to produce **13.4**, the core of ottelione B. Even though **13.4** has a *trans* ring fusion the ring closing metathesis still involves preferential cyclization via the less substituted double bond of the 1,3-butadiene unit; this preference would appear to be general.

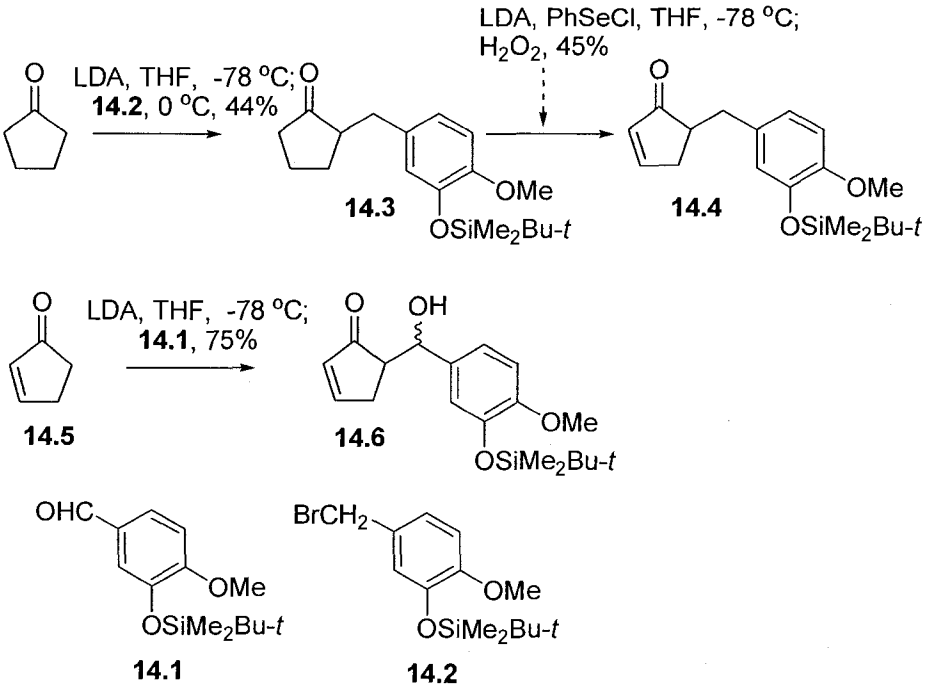


Scheme 13

With both the *cis* and *trans* ring fused models in hand we were able to examine briefly the possibility of epimerizing the *cis* into the *trans* isomer, but treatment with DBU in CH_2Cl_2, refluxing DME or refluxing PhMe did not effect epimerization to any significant extent.

2.3 Synthesis of Racemic Otteliones

At this stage of our studies the obvious next problem was to introduce substituents on the five-membered ring. Suitable precursors to the aromatic subunit appeared to be the readily available aldehyde **14.1**[30] and the derived bromide **14.2**.[31] Attempts to use the bromide for alkylation of 2-cyclopentenone or cyclopentanone were unpromising, but aldol condensation of 2-cyclopentenone[32] with aldehyde **14.1** worked well (**14.5**→**14.6**, 75%).



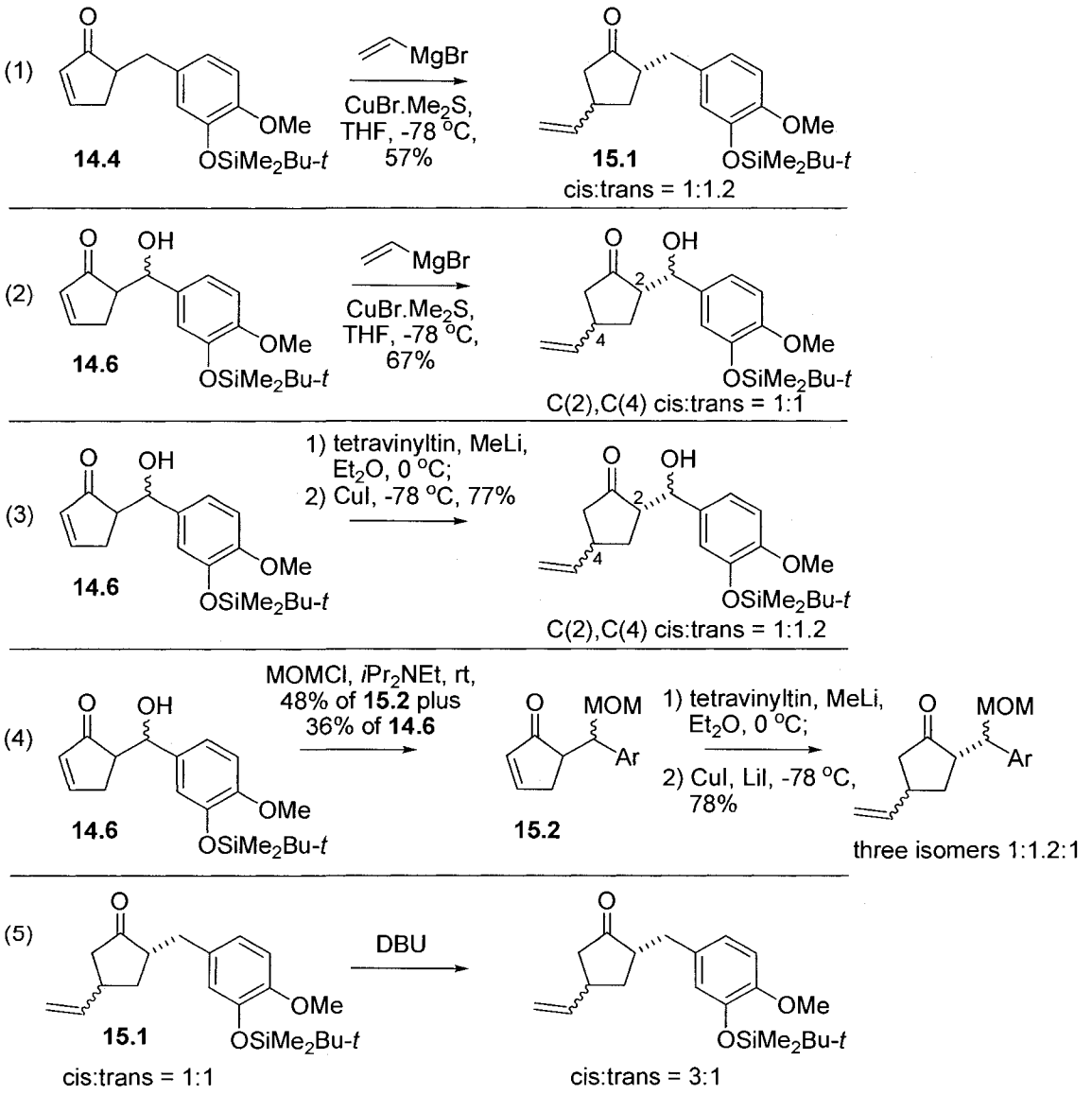
Scheme 14

Conjugate addition of the cuprate made from vinylmagnesium bromide and CuBr·SMe_2 complex to **14.4** gave a 1:1.2 mixture of *cis* and *trans* isomers, which were inseparable by chromatography (Scheme 15, entry 1). The same conditions were applied to the aldol condensation product **14.6**, which gave a similar result (67%, 1:1 mixture of *cis* and *trans* isomers, Scheme 15, entry 2). The use of vinyllithium and CuI with LiI did not improve the stereoselectivity (Scheme 15, entry 3). Protection of the benzylic hydroxyl group with MOMCl, followed by the treatment with vinyllithium and CuI, gave a mixture of three isomers in a 1:1.2:1 ratio, which also were not separable (Scheme 15, entry 4).

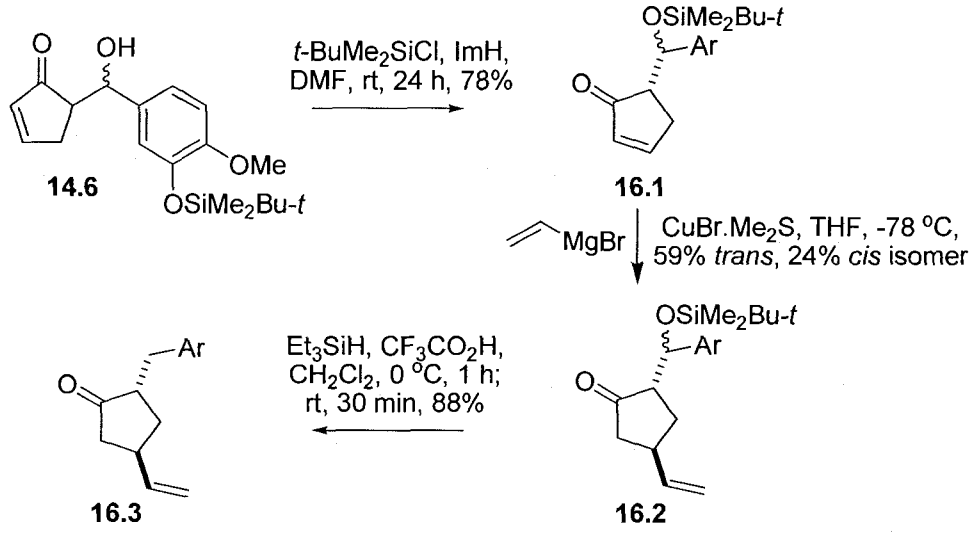
Attempted epimerization of **15.1** by DBU at various temperatures and in different solvents was found to favor the *cis* isomer, giving a 3:1 mixture of *cis* and *trans* isomers (Scheme 15, entry 5). The best conditions were found when *O*-silylated aldols **16.1** were treated with the cuprate made from vinylmagnesium bromide and CuBr·SMe_2 complex (Scheme 16). The conjugate addition in this case gave **16.2** in 59% yield, as well as the

corresponding material with *cis* substituents on the ring (24%). The *cis* isomers of **16.2** could be removed by chromatography. The desired product (**16.2**) was a 3:1 mixture epimeric at the siloxy-bearing carbon.

We note that little work has been done on the relative stability of *cis* and *trans* isomers of 2,4-disubstituted cyclopentanones, but the *cis* isomer appears to be more stable in those few cases examined.[33]

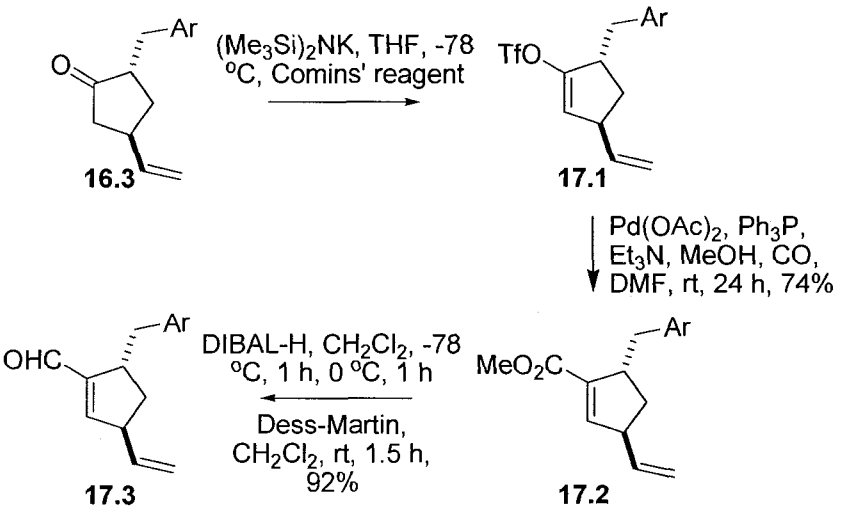


Scheme 15



Scheme 16

At this point the siloxy group was removed by the action of Et_3SiH[34] in the presence of CF_3CO_2H (**16.2→16.3**). Next, the ketone **16.3** was converted regioselectively into enol triflate[35] **17.1** (Scheme 17), and this was carbonylated[36] in the presence of MeOH so as to afford ester **17.2**. Over-reduction with DIBAL-H and Dess-Martin oxidation gave the key aldehyde **17.3**. This compound corresponds to aldehyde **12.1** used in our model studies on the core skeleton, but now carries the required peripheral substituents, and the stage was set for construction of the six-membered ring, which we hoped to accomplish by exactly the same procedure used for the models.

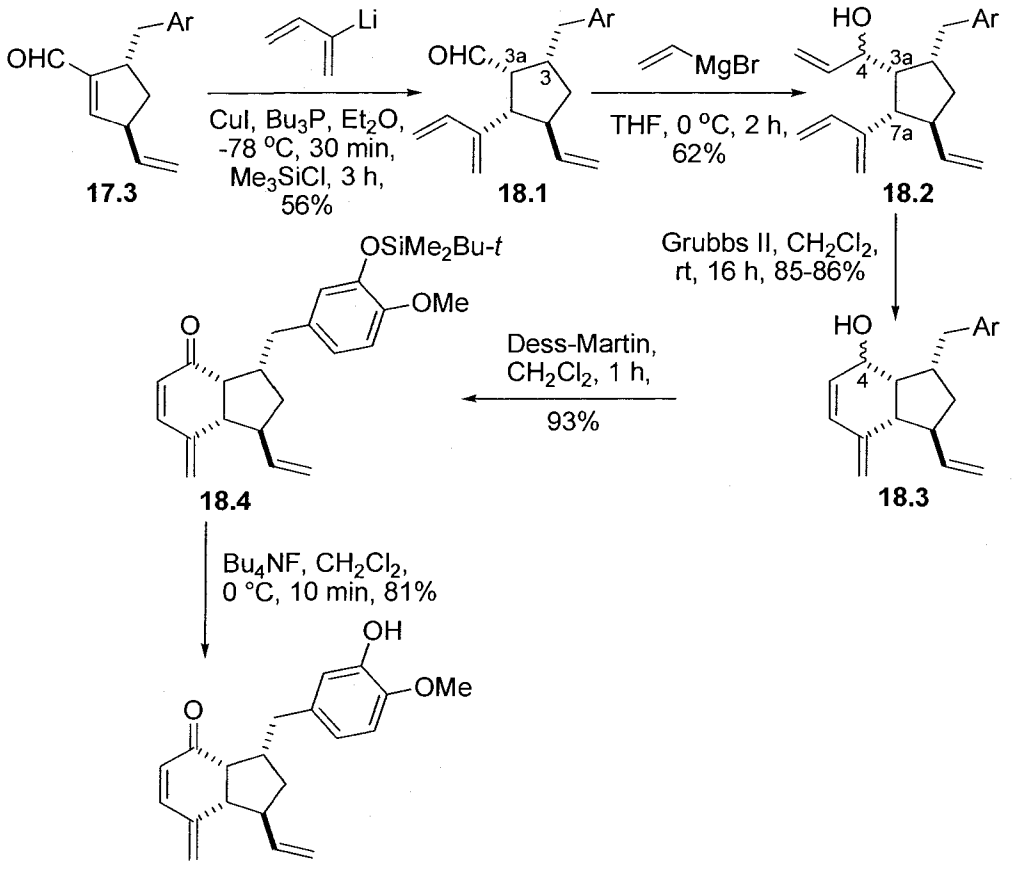


Scheme 17

The α,β-unsaturated aldehyde **17.3** was allowed to react with the mixed cuprate reagent **11.5** following the conditions developed during the model study. Unfortunately none of the desired product was isolated. After careful examination of the reaction conditions, the organocuprate derived from 2-lithio-1,3-butadiene[23] and $Bu_3P{\cdot}CuI$[37] was found to be effective for this transformation. This cuprate was allowed to react in the presence of Me_3SiCl[27] with enal **17.3** to give a crude product containing **18.1** and the corresponding C(3a) epimer, with **18.1** being the major product (7:1 to >10:1). Bu_3P was found to be crucial for this reaction; without Bu_3P no desired product was formed. However the excess of Bu_3P could not be easily removed, and a small amount of another unknown aldehyde (5-7% by ^1H NMR), possibly from the conjugate addition of the MeLi, was always found to be present in the crude product.

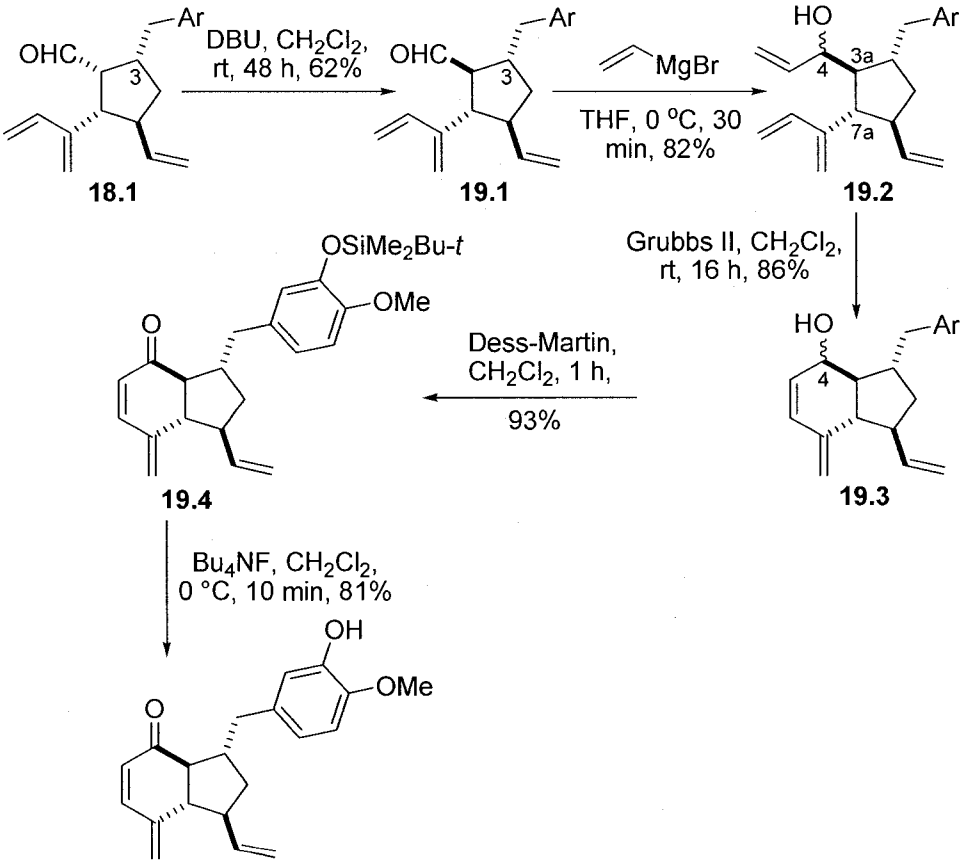
The crude material was treated with vinylmagnesium bromide and a mixture of the allylic alcohols **18.2** epimeric at C(4) was isolated. The minor isomer (14% yield) and the major isomer (48% yield) were individually subjected to the action of the Grubbs II[38] catalyst in CH_2Cl_2 at room temperature for 16 h. In both cases ring closing metathesis occurred in the desired fashion. The yield was high (85-86%) and the

presence of an additional double bond in the starting material as compared with our model system **12.3** did not introduce any complications. Based on the result of a single experiment with a mixture of the epimeric alcohols, the Grubbs I catalyst appears to work just as well. Dess-Martin oxidation of each alcohol to ketone **18.4** was likewise uneventful (90%), but the final deprotection of the resulting ketone **18.4** with Bu_4NF had to be monitored closely, as extended reaction time causes decomposition of the product. When performed in ice-cold CH_2Cl_2 for 10 min, the desilylation gives racemic ottelione A in 81% yield. Our first experiments were done in THF, but under these conditions, neither the starting material nor the desired product was obtained.



Scheme 18

Aldehyde **18.1** was then used to make ottelione B (Scheme 19). Epimerization at C(3a) was again achieved by the action of DBU, and aldehyde **19.1** could be isolated in 62% yield. Reaction with vinylmagnesium bromide gave **19.2** (83%) as an inseparable mixture of C(4) epimers. Once again, the ring closing metathesis worked well and without any sign of interference from the C(1) vinyl group. Dess-Martin oxidation of alcohols **19.3** [as a mixture of C(4) epimers] and controlled desilylation now presented no difficulties and we obtained pure racemic ottelione B. Its NMR spectra are clearly distinguishable from those of ottelione A.

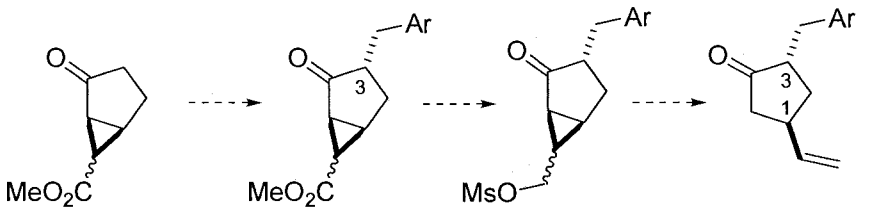


racemic ottelione B **(5.7)**

Scheme 19

2.4 Synthesis of Optically Pure Otteliones

The above synthesis of the racemic otteliones established that the ring closing metathesis procedure was a reliable method for the tetraenes we had used, but our experiments had also shown that setting up the *trans* stereochemistry of the C(1) and C(3) substituents by conjugate addition gives an unsatisfactory ratio of epimers. Our experiments also gave no guidance on how to make optically pure material. Careful consideration of these two problems — how to improve the *trans*/*cis* selectivity and how to obtain optically pure material suggested that starting materials of type **20.1** (or synthetically equivalent substances) might satisfy our requirements in all respects:[39] We anticipated that alkylation at C(3) would occur *anti* to the cyclopropyl group and, if the ester were converted into a leaving group (*cf* **20.2→20.3**), then reduction with SmI_2 might serve to open the cyclopropane and convert it into a vinyl group (*cf* **20.3→20.4**), the overall result being that the cyclopropane would initially serve as a steric shield and then as a vinyl precursor.

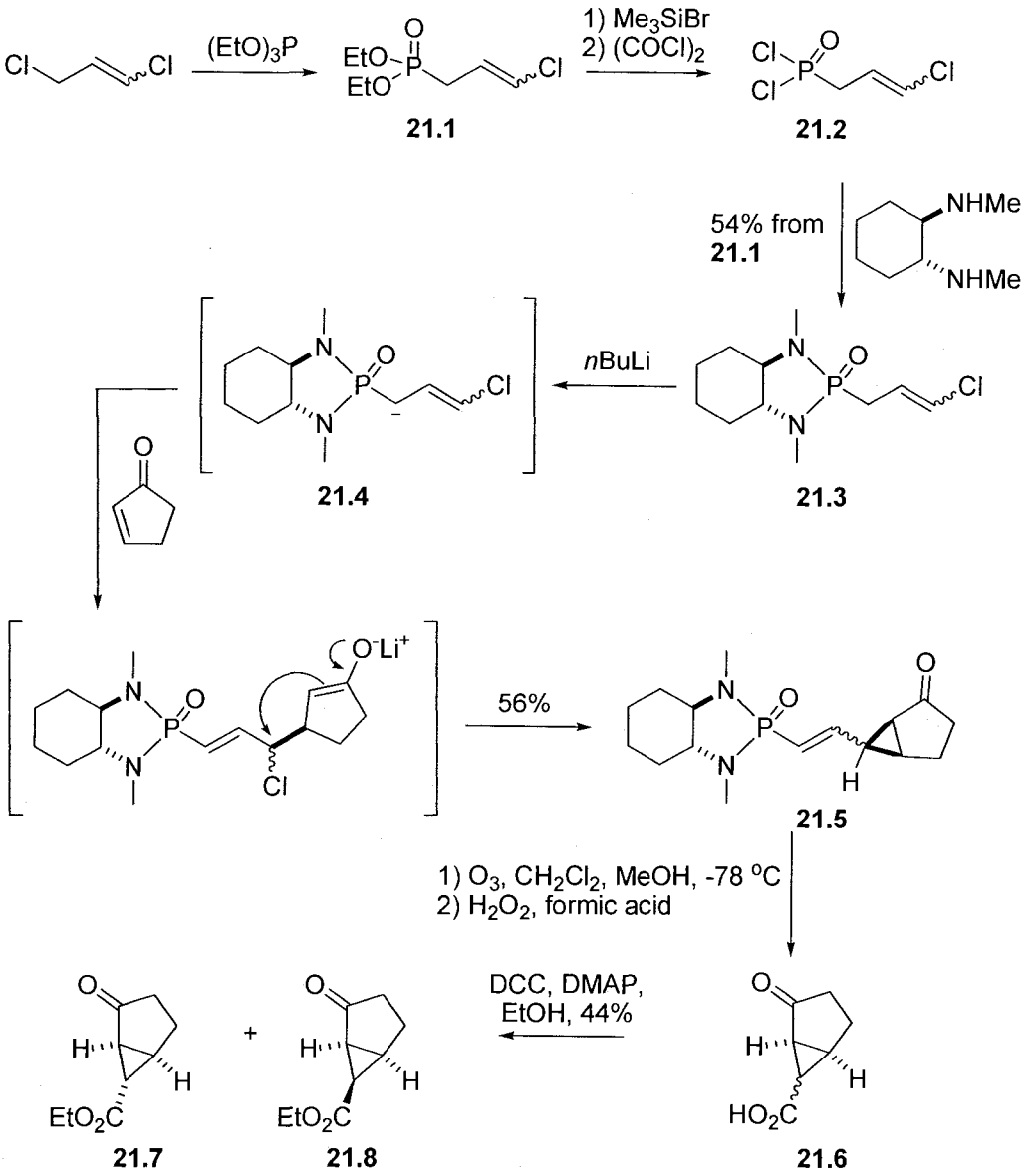


20.1 **20.2** **20.3** **20.4**

Scheme 20

A very convenient aspect of this plan was that optically pure compounds of type **20.1** and synthetically equivalent species were already available by literature methods. In particular, the asymmetric cyclopropanation method of Hanessian *et al.*[40] (Scheme 21) seemed well-suited to our needs. The allylphosphonate **21.1** was prepared from triethyl phosphite and 1,3-dichloropropene. After treatment with trimethylsilyl bromide and then

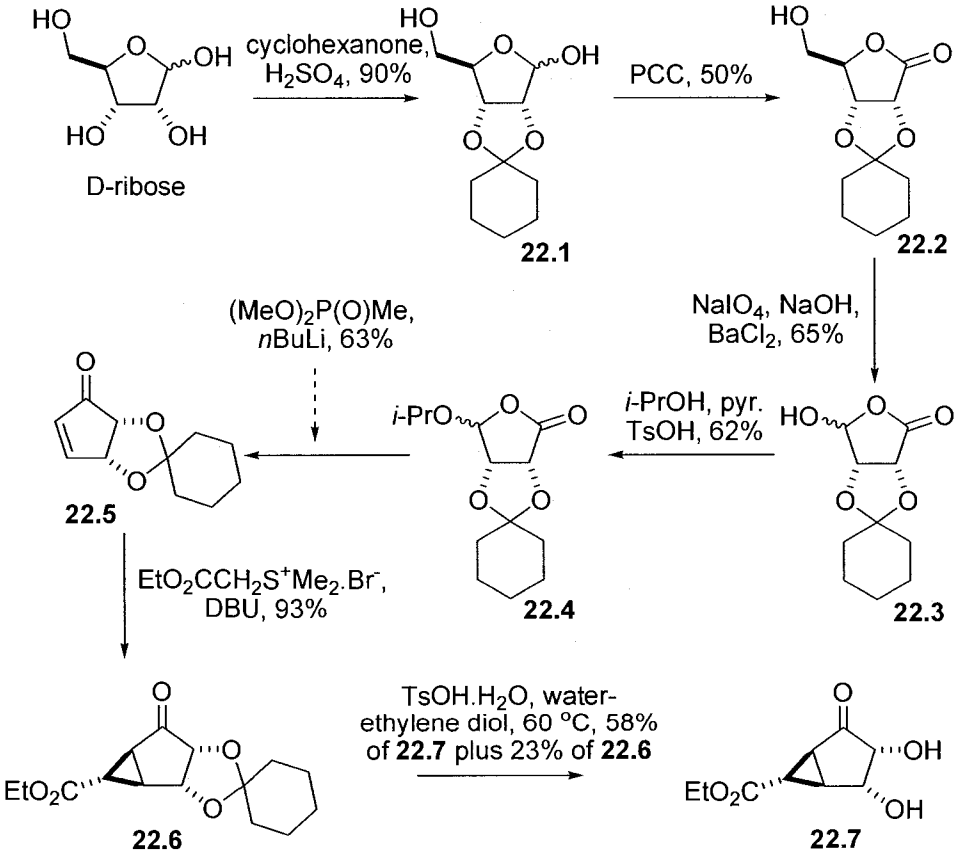
oxalyl chloride, the resulting crude chloroallylphosphonyl dichloride **21.2** was allowed to react with (1*R*,2*R*)-*N*,*N*'-dimethyl-1,2-cyclohexanediamine[41] to give chloroallylphosphonamide **21.3**. The highly stereocontrolled 1,4-addition of the derived anion **21.4** to cyclopentenone afforded cyclopropanated bicyclic product **21.5** in 56%. In addition to the two isomers shown by **21.5**, a small amount of another two isomers having the opposite stereochemistry at the cyclopentanone carbons was also produced, the ratio of **21.5** to this other pair being 10:1, as judged by ^{31}P-NMR. Ozonolysis, followed by oxidative workup, cleaved the phosphonamide part to give the corresponding acids **21.6** which, after esterification, gave the separable esters **21.7** and **21.8**.



Scheme 21

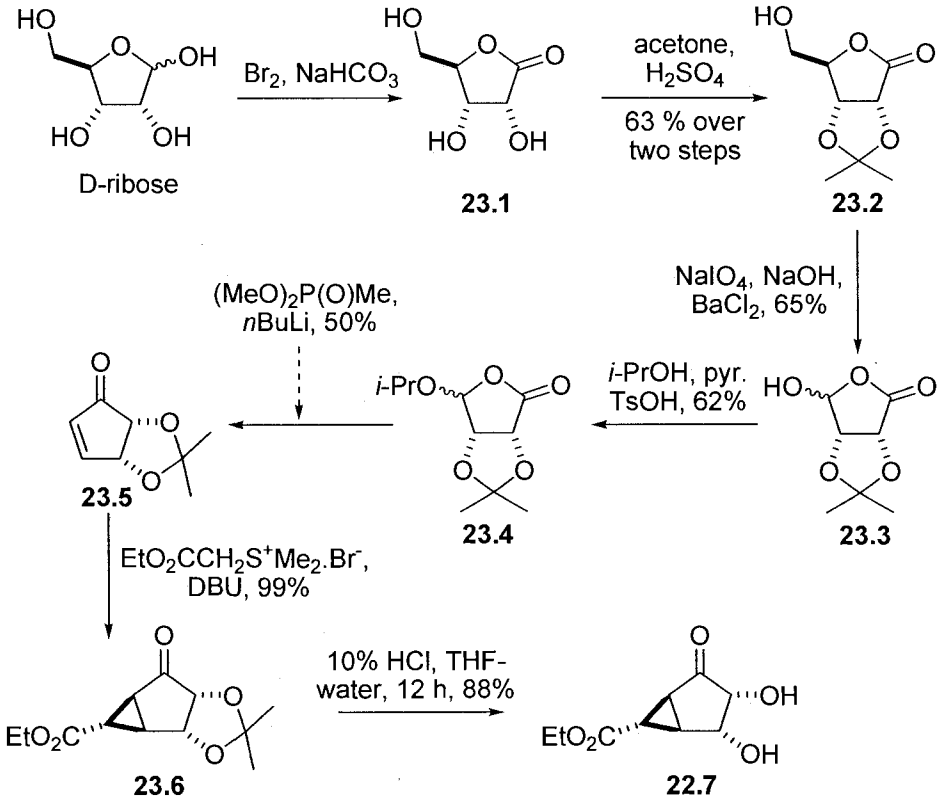
Several other routes toward **21.7** engaging D-ribose as starting material were also examined. The first route tested starts with protection of D-ribose with cyclohexanone under acidic conditions, followed by pyridinium chlorochromate oxidation to give D-ribonolactone **22.2**.[42] The free primary hydroxyl group in **22.1** was surprisingly preserved under the above oxidation conditions. Under basic conditions the lactone was opened and the resulting diol was oxidatively cleaved by sodium periodate to give

hydroxybutyrolactone **22.3**.[42] After treatment with isopropanol under acidic conditions, the resulting acetal **22.4** was subjected to an intramolecular Horner-Wadsworth-Emmons reaction to give the 2,3-dioxygenated cyclopentenone **22.5**.[43] With the cyclohexane ring blocking the bottom face of cyclopentenone **22.5**, the sulfonium ylide, generated *in situ* from (carboethoxymethyl)dimethylsulfonium bromide [$Me_2S^+CH_2CO_2EtBr^-$] in the presence of DBU, added stereospecifically to the top face of the cyclopentenone in excellent yield.[44] Various conditions were tested for deprotection of **22.6**; finally this was settled with the use of TsOH in the mixed solvents water-ethylene diol at 60 °C. Under these conditions the desired diol **22.7** was obtained in 58% yield and 23% of the starting ketal **22.6** was recovered.



Scheme 22

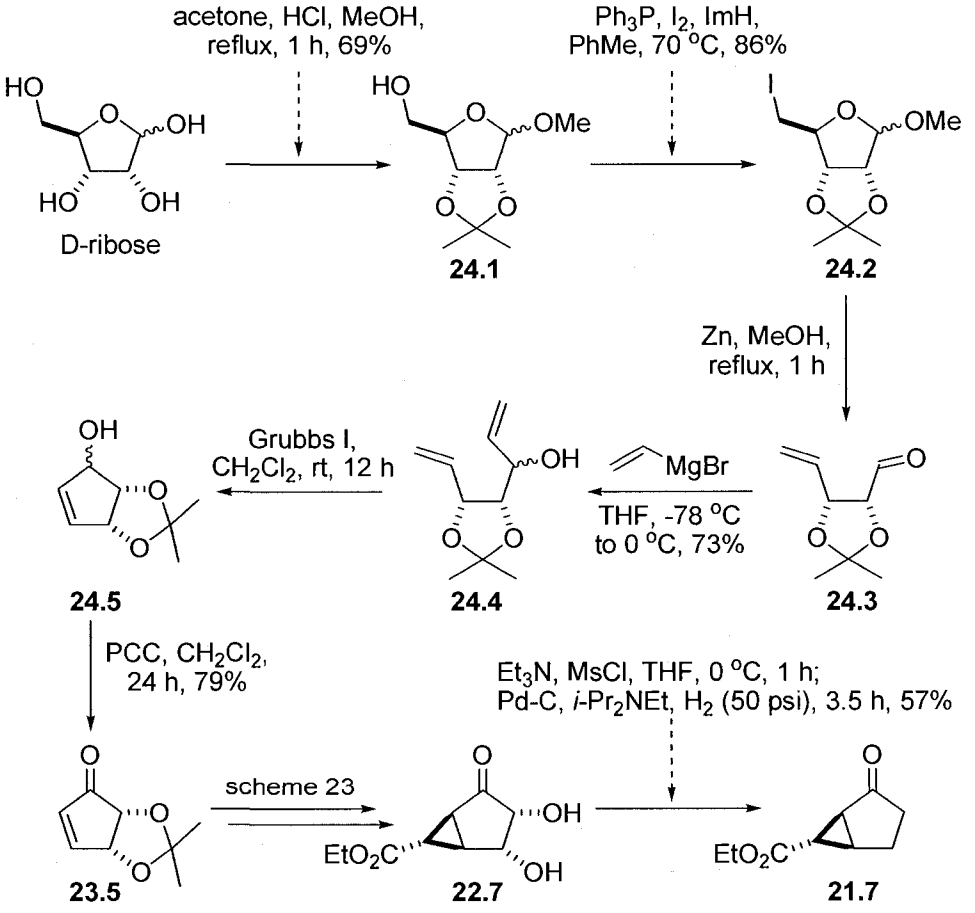
Due to the difficulty encountered with the last deprotection step, a second route (Scheme 23) was carried out by installing a 2,3-isopropylidene unit as protecting group. D-Ribose was first oxidized to D-ribonolactone, followed by protection with 2,2-dimethoxypropane in dry acetone under acidic conditions.[45] The resulting lactone **23.2** was subjected to similar transformations as those shown in Scheme 22 to give compound **23.6**.[46] Finally deprotection was performed with 10% HCl in THF-water to give the diol **22.7** in 88% yield.



Scheme 23

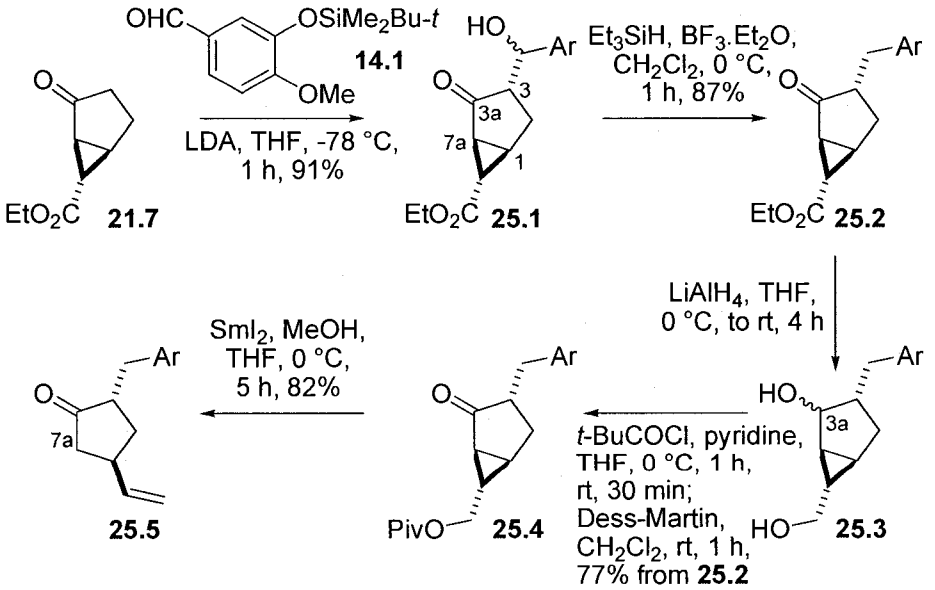
Further literature research suggested a third route towards intermediate **22.7**, also starting from D-ribose, which is summarized in Scheme 24.[47] Methyl 2,3-*O*-ispropylidene-D-ribofuranosides (**24.1**)[48] were converted into the corresponding iodides **24.2** using I_2/Ph_3P,[49] and treatment with Zn then generated aldehyde **24.3** which, without

purification, was treated with vinylmagnesium bromide. The resulting epimeric alcohols **24.4** underwent ring closing metathesis (**24.4→24.5**) in the presence of 1% Grubbs I catalyst. PCC oxidation took the route as far as enone **23.5**, and this was cyclopropanated in near quantitative yield by the sulfonium ylide method (see Scheme 23).[44] Acidic hydrolysis then liberated diol **22.7**, which was converted into the key compound **21.7** by dimesylation and reduction over Pd-C in the presence of Hünig's base. This last step may involve both hydrogenation and hydrogenolysis or merely two hydrogenation steps.[50] Most of our work was based on this last route from D-ribose because we then avoided the necessity of checking the optical purity of each batch.



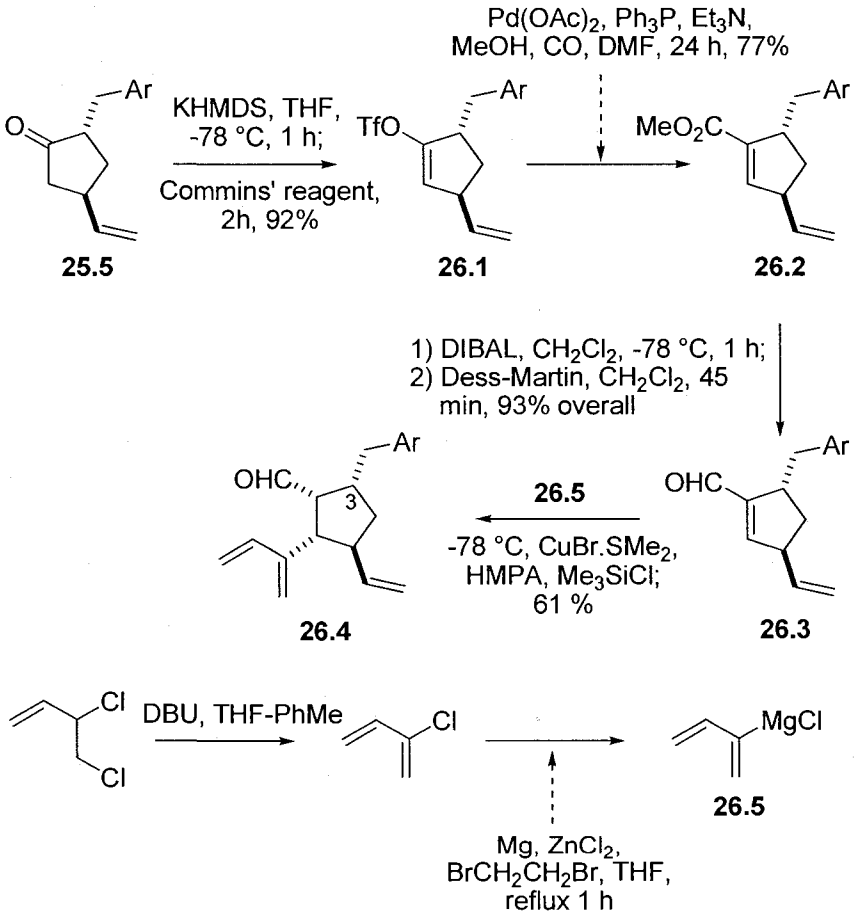
Scheme 24

With the cyclopropane in hand, the next task was to attach the aromatic subunit. Surprisingly, alkylation with bromide **14.2** gave a poor yield (42%), but aldol condensation with aldehyde **14.1**, followed by deoxygenation[51] (**21.7**→**25.1**→**25.2**) was satisfactory (79% overall). Reduction of both carbonyls (**25.2**→**25.3**), selective pivaloylation of the primary hydroxyl in **25.3**, and reoxidation of the remaining secondary hydroxyl, produced the cyclopropyl ketone **25.4** — the substrate for the crucial ring opening that would make the cyclopropyl unit discharge its last function by serving as a precursor to the C(1) vinyl group. On treatment below 0 °C with freshly-prepared SmI_2,[52] the desired change (**25.4**→**25.5**) occurred in good yield (82%)[53] and there remained only the conversion of ketone **25.5** into an aldehyde, before we would be at a point that overlaps structurally with our route to the racemic otteliones. The choice of a pivaloate for monoprotection of alcohols **25.3** was dictated by the greater selectivity in this protection as compared with the use of a benzoate, but the benzoate also underwent the samarium-induced reaction.



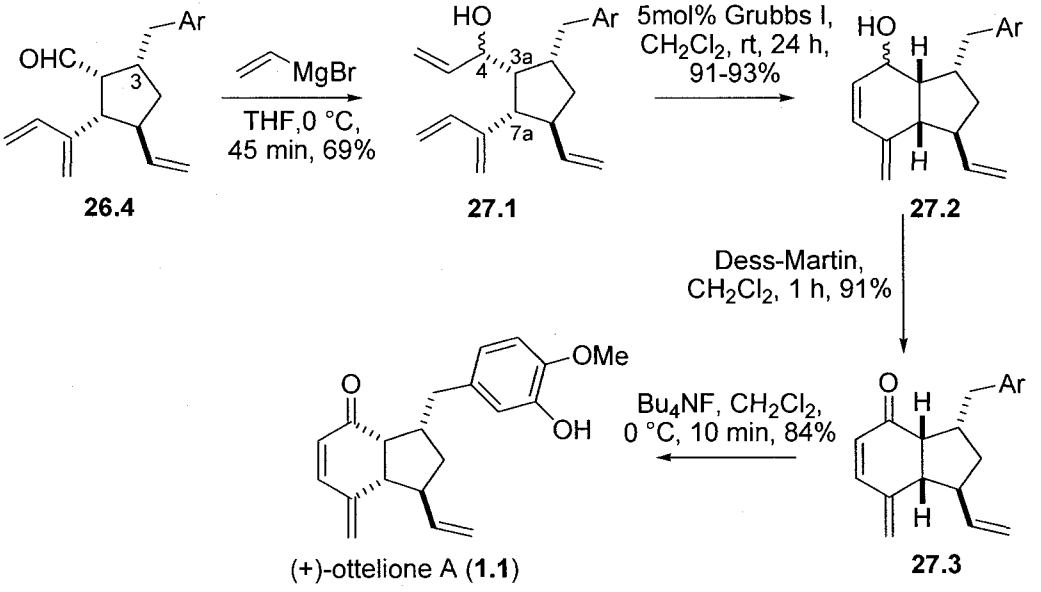
Scheme 25

Ketone **25.5** was deprotonated with $(Me_3Si)_2NK$ under kinetic conditions, and the enolate was quenched with Comins' reagent[35] to afford enol triflate **26.1**. This was carbonylated by a standard method[36] in the presence of MeOH so as to produce ester **26.2**. Reduction with DIBAL-H and reoxidation gave aldehyde **26.3**, from which point the procedure used to make racemic otteliones was followed, with minor variations (Schemes 26 and 27), except for the conjugate addition step (Scheme 26, **26.3**→**26.4**), which was done with the magnesium-derived cuprate **26.5**,[54] in the presence of both Me_3SiCl and HMPA.[55]



Scheme 26

Conjugate addition of cuprates to α,β-unsaturated aldehydes is not very common in the literature.[56] Compared with the conditions used in the model study and the synthesis of racemic otteliones, which were based on Shapiro reaction to generate the 2-lithio-1,3-butadiene,[23] our latest conditions gave the desired product without difficulties met in product purification. The conjugate addition occurred exclusively *trans* to the C(1) vinyl group and protonation gave mainly (7:1 to 10:1) the indicated stereochemistry (see **26.4**). The final product, (+)-ottelione A, had a specific rotation very close to the values reported by the Mehta[5] and Katoh[16,18] groups.



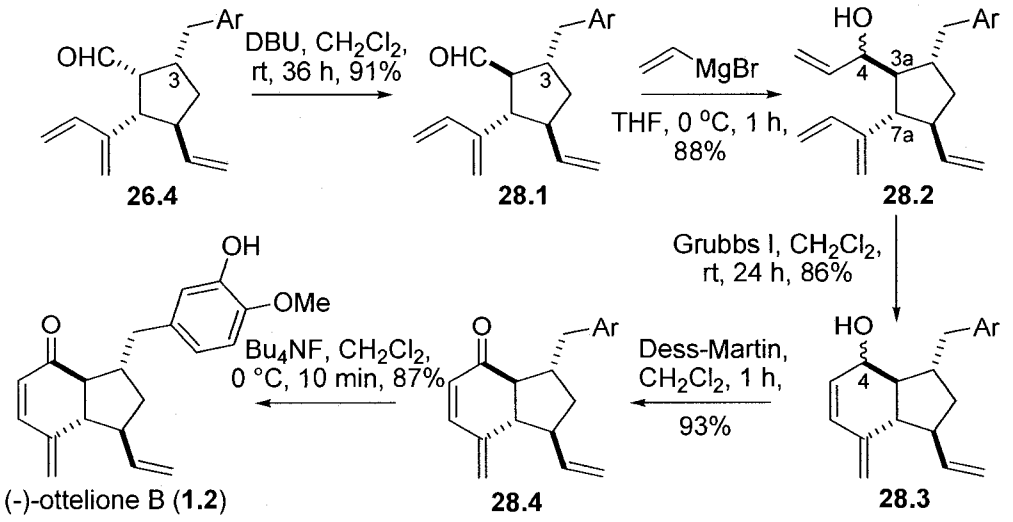
Scheme 27

As implied above, diversion of aldehyde **26.4** to (-)-ottelione B was done (Scheme 28) by the methods first used with racemic compounds.

Our sample of (-)-ottelione B formed crystals suitable for X-ray analysis, but the structure does not provide any obvious reason that would account for the absence of facile aromatization. The X-ray data (Figure 1) show that the six-membered ring is in a half chair conformation with the vinyl group oriented in such a way that the hydrogen atoms at

C(1') and C(7a) are *syn* and both of the C-H bonds at C(1') and C(7a) are parallel. The dihedral angle between the carbonyl group and the C(3a)-H bond is about 114°. We were unable to crystallize (+)-ottelione A.

The specific rotation of our material is close to that reported by Katoh and his colleagues[16,18] and the compound was easily shown by NMR measurements to be free of contamination by (+)-ottelione A.



Scheme 28

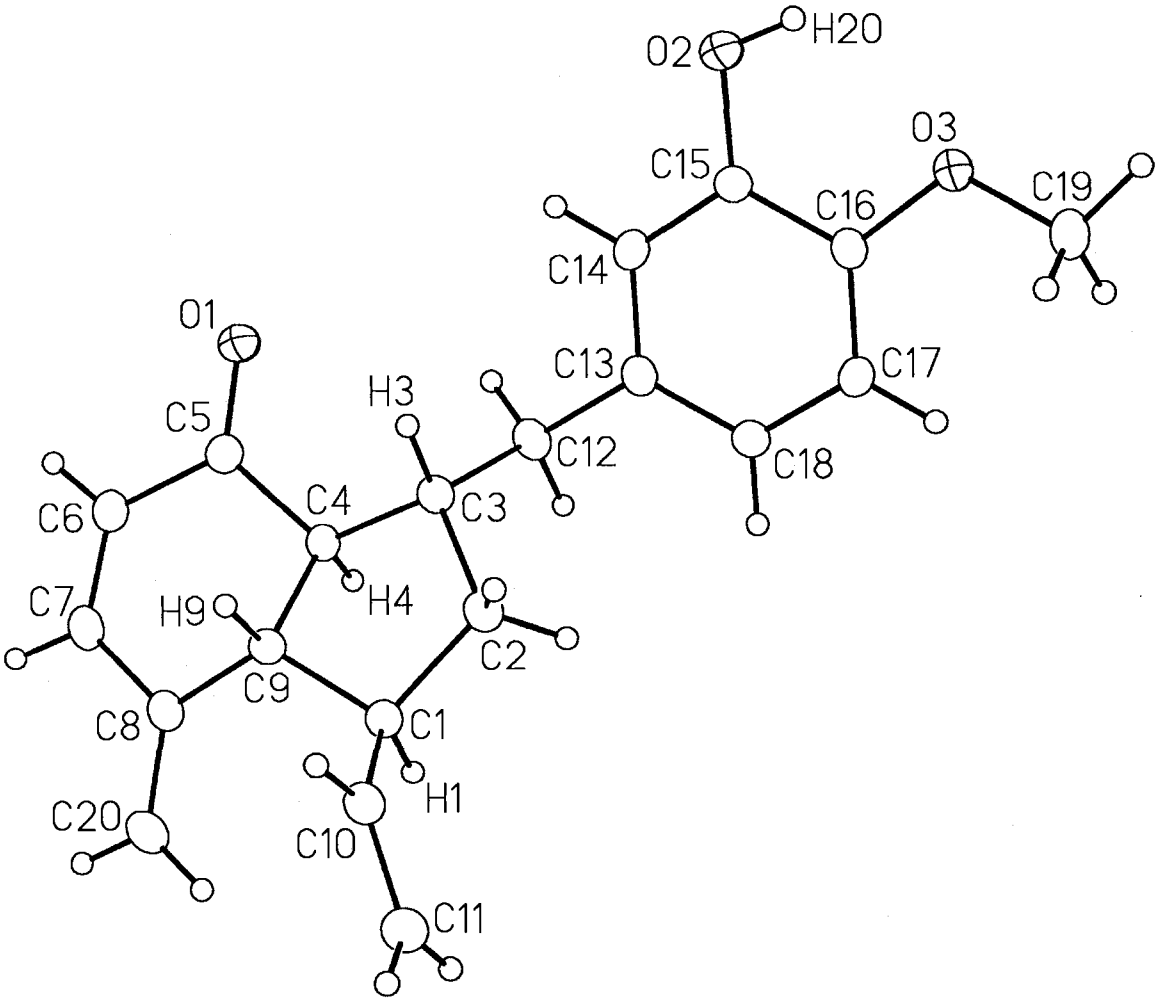


Figure 1 X-Ray structure of (-)-ottelione B (ORTEP diagram)

3 CONCLUSION

A short synthetic route toward the core structures of both otteliones A and B was developed. Compared with the earlier model study by a former researcher,[21] which gave the core of ottelione B in 16 steps and a total yield of 1.7%, the new route gave the core of ottelione A in 4 steps (36% overall) and the core of ottelione B in 5 steps (36% overall).

With the chemistry developed during the model study, the task of synthesis of racemic otteliones A and B was undertaken. Starting from commercially available cyclopentenone, racemic ottelione A was prepared in 13 steps (4.3% overall). The route towards racemic ottelione B, which shares a late-stage common intermedia with the synthesis of ottelione A, gave the desired product in 14 steps (3.5% overall).

In the synthesis of optical pure otteliones, a different strategy was applied to build the stereocenters on the cyclopentanone ring. Among the several routes examined, one route derived from D-ribose was favored due to its high efficiency. Optically pure ottelione A was prepared in 24 steps (1.7% overall) and optically pure ottelione B was prepared in 25 steps (1.9% overall). Professor Katoh's synthesis gave ottelione A in 30 steps (2.1% overall) and ottelione B in 31 steps (0.5% overall).

The synthetic method described here avoids difficulties encountered in epimerizing ottelione A to ottelione B, which was used in both Professor Mehta's and Professor Katoh's reports. Our X-ray structure of ottelione B appears to be the first such measurement for the otteliones, and the route illustrates a very convenient and apparently general level of discrimination between several double bonds in the ring closing metathesis step. A special feature of the synthesis is the use of a cyclopropane to shield one face of an attached ring and at a later stage to act as a precursor to a vinyl group. It is likely that our approach to the otteliones could also be used to prepare analogs of these very powerful anticancer agents.

4 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (140 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

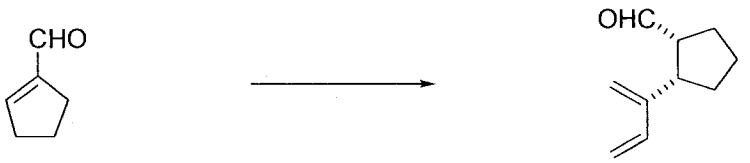
Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N, *i*-Pr_2NEt and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$. Acetone was distilled from K_2CO_3.

FT-IR measurements were made from the specified solvent using KBr plates.

The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, as based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

(1*R*,2*S*)-rel-2-(1-Methylene-2-propenyl)cyclopentanecarboxaldehyde (12.2).



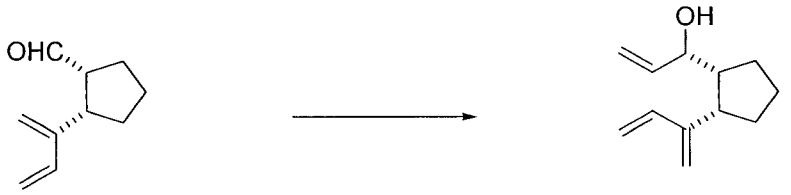
12.1 **12.2**

Methyl vinyl ketone was dried over anhydrous K_2CO_3 for 3 h, and then distilled at room temperature under reduced pressure (waterpump, 18 mmHg, protection from moisture) by using a receiver cooled in a dry ice-acetone bath (-78 °C). The freshly-distilled methyl vinyl ketone was dried over anhydrous Na_2SO_4 and used within a few h for conversion[23a] into a hydrazone with 2,4,6-tris(isopropyl)benzenesulfonylhydrazine.

MeLi (1.6 M solution in Et_2O, 0.87 mL, 1.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of the above hydrazone[23a] (0.23 g, 0.66 mmol) in dry DME (4 mL). The resulting yellow solution was stirred at -78 °C for 20 min, and then the dry ice-acetone bath was replaced by an ice bath. The mixture was stirred at 0 °C for 10 min, during which time the solution turned pink. The cooled pink solution (0 °C) was added dropwise via a short cannula (Ar pressure) to a stirred and cooled (-78 °C) solution of commercial lithium 2-thienylcyanocuprate (0.25 M solution in THF, 2.6 mL, 0.66 mmol), followed by dry Et_2O (5 mL). The mixture was stirred at -78 °C for 1 h and the resulting solution turned brown. Me_3SiCl (freshly distilled from CaH_2, 0.17 mL, 1.3

mmol) was added by syringe at a fast dropwise rate. The resulting solution turned yellow. A solution of 1-cyclopentenylcarboxaldehyde[26] (32 mg, 0.33 mmol) in Et_2O (1 mL plus 0.5 mL as a rinse) was added, and stirring was continued at -78 °C for 30 min. The dry ice-acetone bath was replaced by an ice bath and the mixture was stirred at 0 °C for 10 min. The flask was then transferred to a dry ice-acetone bath and AcOH (0.5 mL) was added. The dry ice-acetone bath was replaced by an ice bath and stirring was continued for 5 min. Water (5 mL) was added and the mixture was then filtered through a pad of Celite, using Et_2O (20 mL) was a rinse. The organic phase was washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) and filtered through a short column of silica gel, using 1:10 Et_2O-hexane. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 10 cm), using 1:10 Et_2O-hexane, gave **12.2** (34 mg, 68%) as a yellow liquid which contained two isomers (19:1) but was not absolutely pure and was not fully characterized: ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-1.90 (m, 5 H), 2.01-2.10 (m, 1 H), 3.01-3.20 (m, 2 H), 5.08 (s, 1 H), 5.16-5.19 (m, 2 H), 5.37 (d, J = 17.7 Hz, 1 H), 6.44 (dd, J = 11.0, 17.7 Hz, 1 H), 9.44 (d, J = 2.69 Hz, 1 H).

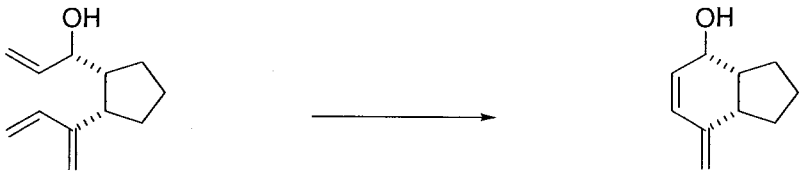
(1*R*,2*S*)-rel-α-Ethenyl-2-(1-methylene-2-propenyl)cyclopentanemethanol (12.3).



12.2 **12.3**

Vinylmagnesium bromide (1 M solution in THF, 0.27 mL, 0.27 mmol) was added to a stirred and cooled (0 °C) solution of aldehyde **12.2** (3:1 mixture of *cis* and *trans* isomers, 34 mg, 0.23 mmol) in THF (10 mL). The mixture was stirred at 0 °C for 1 h, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:10 Et_2O-hexane, gave **12.3** (22 mg, 73%) as a yellow liquid which was a single isomer: FTIR (CH_2Cl_2 cast) 3468, 3089, 2955, 898 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48-1.55 (m, 2 H), 1.69-1.87 (m, 5 H), 2.33 (ddt, J = 2.6, 6.5, 8.9 Hz, 1 H), 2.85-2.92 (m, 1 H), 4.21 (s, 1 H), 5.04 (td, J = 1.7, 10.6 Hz, 1 H), 5.12-5.23 (m, 4 H), 5.31-5.36 (d, J = 17.6 Hz, 1 H), 5.75 (ddd, J = 4.6, 10.6, 17.2 Hz, 1 H), 6.51 (dd, J = 10.9, 17.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.10 (s), 140.26 (d), 140.05 (d), 115.59 (t), 113.78 (t), 113.51 (t), 71.98 (d), 44.55 (d), 43.94 (d), 30.75 (t), 24.52 (t), 24.05 (t); exact mass *m/z* calcd for $C_{12}H_{18}O$ 178.13577, found 178.13549.

(3a*R*,7a*S*)-rel-2,3,3a,4,7,7a-Hexahydro-7-methylene-1*H*-inden-4-ol (12.4).

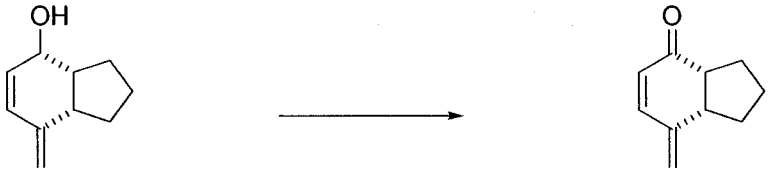


12.3 **12.4**

Ar was bubbled for *ca* 5 min through a stirred solution of alcohol **12.3** (44 mg, 0.25 mmol) in CH_2Cl_2 (30 mL) and Grubbs catalyst (first generation, 10 mg, 0.012 mmol) was added. The mixture was stirred at room temperature for 24 h and then evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:4 EtOAc-hexane, gave **12.4** (29 mg, 78%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3328, 2954, 2871, 1046

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43-1.51 (m, 2 H), 1.69-1.87 (m, 5 H), 1.92-1.97 (m 1 H), 2.72 (dd, *J* = 7.2, 17.5 Hz, 1 H), 3.96 (d, *J* = 6.8 Hz, 1 H), 4.94 (s, 1 H), 4.99 (s, 1 H), 5.76 (d, *J* = 9.9 Hz, 1 H), 6.13 (dd, *J* = 1.9, 9.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.83 (s), 131.13 (d), 129.48 (d), 113.73 (t), 68.13 (d), 46.83 (d), 43.11 (d), 31.96 (s), 28.49 (s), 21.83 (s); exact mass *m/z* calcd for $C_{10}H_{14}O$ 150.10446, found 150.10438.

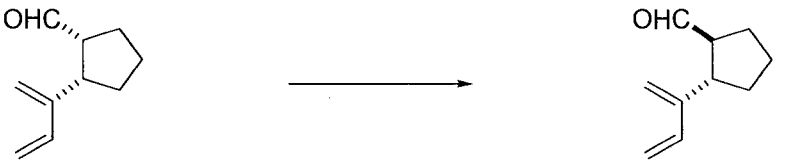
(3a*R*,7a*S*)-rel-1,2,3,3a,7,7a-Hexahydro-7-methylene-4*H*-inden-4-one (12.5).



12.4 **12.5**

Dess-Martin periodinane (0.13 g, 0.30 mmol) was added to a stirred solution of alcohol **12.4** (23 mg, 0.15 mmol) in CH_2Cl_2 (10 mL). Stirring at room temperature was continued for 1 h, and saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:10 Et_2O-hexane, gave **12.5** (21 mg, 92%) as an oil: FTIR (CH_2Cl_2 cast) 2953, 2871, 1664, 906 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53-1.66 (m, 3 H), 1.85-1.93 (m, 2 H), 2.20-2.25 (m, 1 H), 2.76 (dd, *J* = 7.8, 11.3 Hz, 1 H), 3.06 (dd, *J* = 7.8, 16.3 Hz, 1 H), 5.37 (d, *J* = 5.8 Hz, 2 H), 5.92 (d, *J* = 5.8 Hz, 1 H), 6.97 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8 (s), 145.5 (d), 143.4 (s), 126.6 (d), 120.4 (t), 49.2 (d), 44.4 (d), 33.6 (t), 27.7 (t), 23.0 (t); exact mass *m/z* calcd for $C_{10}H_{12}O$ 148.08882, found 148.08852.

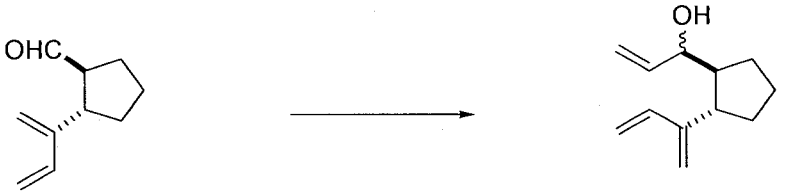
(1*R*,2*R*)-rel-2-(1-Methylene-2-propenyl)cyclopentanecarboxaldehyde (13.1).



12.2 **13.1**

DBU (48 mg, 0.32 mmol) was added to a stirred solution of aldehyde **12.2** (mainly *cis* isomer, 24 mg, 0.16 mmol) in CH_2Cl_2 (20 mL). Stirring at room temperature was continued until the trans/cis ratio was larger than 10:1 (usually 48 h, ^1H NMR control), and the solution was then washed with dilute hydrochloric acid (1 N, 8 mL), water (10 mL) and brine (10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a yellow oil, which was used directly in the next step.

(1*R*,2*R*)-rel-α-Ethenyl-2-(1-methylene-2-propenyl)cyclopentanemethanol (13.2).

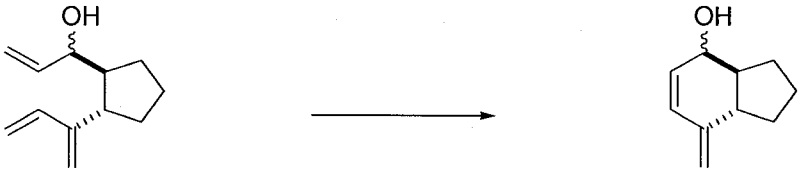


13.1 **13.2**

Vinylmagnesium bromide (1 M solution in THF, 0.19 mL, 0.19 mmol) was added dropwise to a stirred and cooled (0 °C) solution of crude aldehyde **13.1** in THF (10 mL). The mixture was stirred at 0 °C for 1 h, and then saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography

of the residue over silica gel (2 x 10 cm), using 1:10 Et_2O-hexane, gave **13.2** (19 mg, 67% over two steps) as a mixture of two isomers epimeric at the hydroxyl-bearing carbon: FTIR (CH_2Cl_2 cast) 3403, 2953, 2869, 990 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major isomer signals) δ 1.35-1.50 (m, 3 H), 1.59-1.69 (m, 2 H), 1.75-1.80 (m, 1 H), 1.97 (ddd, J = 4.4, 7.7, 13.0 Hz, 1 H), 2.10 (ddd, J = 4.4, 8.6, 16.3 Hz, 1 H), 2.72 (dd, J = 8.6, 17.2 Hz, 1 H), 4.08-4.10 (m, 1 H), 5.01-5.10 (m, 4 H), 5.22 (d, J = 17.0 Hz, 1 H), 5.37 (d, J = 17.5 Hz, 1 H), 5.88 (ddd, J = 5.9, 10.5, 17.0 Hz, 1 H), 6.37 (dd, J = 10.5, 17.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer signals) δ 149.9 (s), 140.5 (d), 138.9 (d), 114.4 (t), 113.5 (t), 113.4 (t), 74.2 (d), 49.3 (d), 43.2 (d), 34.0 (t), 26.2 (t), 24.4 (t); exact mass *m/z* calcd for $C_{12}H_{18}O$ 178.13577, found 178.13679.

(3a*R*,7a*R*)-rel-2,3,3a,4,7,7a-Hexahydro-7-methylene-1*H*-inden-4-ol (13.3).

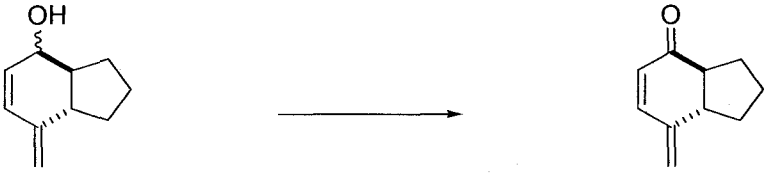


13.2 **13.3**

Ar was bubbled for *ca* 5 min through a stirred solution of alcohols **13.2** (19 mg, 0.11 mmol) in CH_2Cl_2 (20 mL) and Grubbs catalyst (first generation, 8.7 mg, 0.011 mmol) was added. The mixture was stirred at room temperature for 24 h and then evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:3 Et_2O-hexane, gave **13.3** (13 mg, 83 %) as a 3:1 mixture of two isomers. The major isomer was a colorless solid: mp 87-90 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34-1.43 (m, 1 H), 1.46-1.59 (m, 3 H), 1.71-1.83 (m, 2 H), 1.98-2.04 (m, 1 H), 2.09-2.14 (m, 2 H), 4.18 (s, 1 H), 4.08 (s, 1 H), 4.91 (s, 1 H), 5.73 (d, J = 9.8 Hz, 1H), 6.15 (dd, J = 2.0, 9.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (s), 133.9 (d), 131.1 (d), 109.9 (t), 74.6

(d), 51.7 (d), 45.5 (d), 29.0 (t), 27.3 (t), 22.1 (t). The minor isomer was not obtained pure, and the isomer mixture was carried forward.

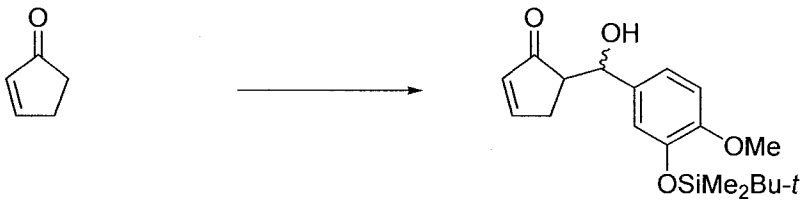
(3a*R*,7a*R*)-rel-1,2,3,3a,7,7a-Hexahydro-7-methylene-4*H*-inden-4-one (13.4).



13.3 **13.4**

Dess-Martin periodinane (75 mg, 0.18 mmol) was added to a stirred solution of alcohols **13.3** (13 mg, 0.088 mmol) in CH_2Cl_2 (10 mL). Stirring at room temperature was continued for 1 h, and saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:10 Et_2O-hexane, gave **13.4** (12 mg, 94%) as an oil: FTIR (CH_2Cl_2, cast) 2961, 2925, 2873, 2854, 1686, 1260, 1091, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.66-1.71 (m, 1 H), 1.75-1.82 (m, 3 H), 1.93-1.98 (m, 1 H), 2.03-2.07 (m, 1 H), 2.38-2.43 (m, 1 H), 2.53-2.58 (m, 1 H), 5.24 (s, 1 H), 5.33 (s, 1 H), 5.96 (d, J = 9.6 Hz, 1 H), 7.05 (d, J = 9.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (s), 147.1 (d), 145.5 (s), 128.8 (d), 116.4 (t), 54.1 (d), 47.6 (d), 27.6 (t), 23.3 (t), 21.6 (t).

(±)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]hydroxy-methyl]-2-cyclopentenone (14.6).

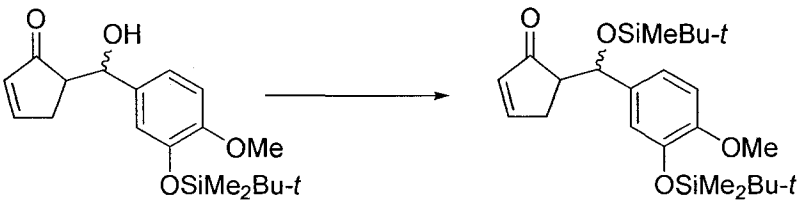


14.5 **14.6**

n-BuLi (2.5 M in hexane, 5.0 mL, 13 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.9 mL, 13 mmol) in THF (15 mL). Stirring was continued for 10 min, and the mixture was then cooled to -78 °C. 2-Cyclopenten-1-one (0.56 mL, 6.7 mmol) in THF (5 mL) was added dropwise, and stirring was continued for 15 min. 3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzaldehyde (**14.1**[30]) (2.23 g, 8.38 mmol) in THF (15 mL) was added dropwise and stirring was continued at -78 °C for 30 min. The mixture was then poured into an ice-cold mixture of Et_2O (30 mL) and saturated aqueous NH_4Cl (15 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:4 to 1:2 EtOAc-hexane, gave **14.6** (1.75 g, 75%) as a 5:3 mixture (^{1}H NMR) of two isomers: FTIR (CH_2Cl_2 cast) 3343, 2929, 2857, 1697, 1510, 1279, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer signals) δ 0.15 (s, 3 H), 0.16 (s, 3 H), 0.99 (s, 9 H), 2.43 (d, J = 4.8 Hz, 1 H), 2.49-2.64 (m, 1 H), 2.66-2.69 (m, 1 H), 2.74 (dd, J = 2.5, 5.0 Hz, 1 H), 3.80 (s, 3 H), 5.27-5.30 (m, 1 H), 6.20-6.23 (m, 1 H), 6.80-6.92 (m, 3 H), 7.73 (ddd, J = 2.6, 2.6, 5.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer signals) δ -4.64 (q), -4.60 (q), 18.4 (s), 25.7 (q), 29.9 (t), 52.0 (d), 55.5 (q), 71.5 (d), 111.9 (d), 118.7 (d), 119.6 (d),

134.2 (s), 135.0 (s), 144.9 (s), 150.3 (s), 165.6 (d), 210.9 (s); exact mass *m/z* calcd for $C_{19}H_{28}O_4Si$ 348.17569, found 348.17548.

(±)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy][3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-2-cyclopentenone (16.1).

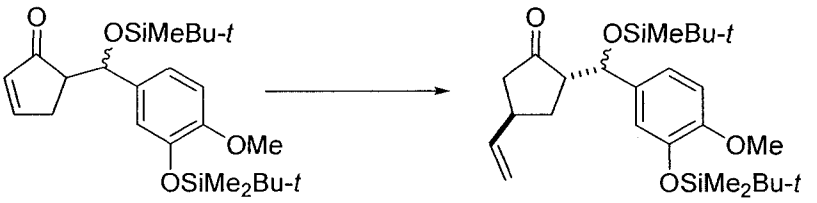


14.6 **16.1**

Imidazole (1.70 g, 25.0 mmol), followed by *t*-$BuMe_2SiCl$ (2.79 g, 18.5 mmol) were added to a stirred solution of **14.6** (4.30 g, 12.4 mmol) in DMF (16 mL), and stirring was continued for 24 h. Water (30 mL) and Et_2O (60 mL) were added and the mixture was extracted with Et_2O (4 x 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 25 cm), using 1:10 to 1:2 EtOAc-hexane, gave **16.1** [3.53 g, 78% corrected for recovered **14.6** (0.91 g)] as a mixture of two isomers (^{1}H NMR): FTIR (CH_2Cl_2 cast) 2955, 2928, 1710, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer signals) δ -0.04 (s, 3 H), 0.08 (s, 3 H), 0.10 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H), 0.98 (s, 9 H), 2.61 (ddd, *J* = 2.4, 2.4, 4.5 Hz, 2 H), 2.83 (dd, *J* = 4.5, 4.5 Hz, 1 H), 3.74 (s, 3 H), 5.23 (d, *J* = 4.6 Hz, 1 H), 5.92 (td, *J* = 2.1, 5.7 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 6.76 (dd, *J* = 2.1, 8.4 Hz, 1 H), 6.81 (d, *J* = 2.1 Hz, 1 H), 7.43 (td, *J* = 2.7, 5.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer signals) δ -5.13 (q), -4.83 (q), -4.75 (q), -4.67 (q), 18.2 (s), 18.4 (s), 25.7 (q), 25.8 (q), 30.4 (t), 53.4 (d), 55.3 (q), 73.1 (d), 111.2(d), 119.3 (d), 119.8 (d), 133.3 (s),

134.3 (d), 144.2 (s), 150.1 (s), 164.7 (d), 209.6 (s); exact mass *m/z* calcd for $C_{25}H_{42}O_4Si_2$ 462.26218, found 462.26183.

(2*R*,4*S*)-rel-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy][3-[[(1,1-dimethyl-ethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-4-ethenylcyclopentanone (16.2).

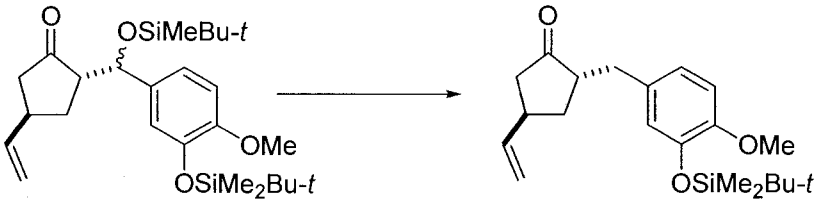


16.1 **16.2**

Vinylmagnesium bromide (1.0 M in THF, 15.8 mL, 15.8 mmol) was added to a stirred and cooled (-78 °C) suspension of CuBr·Me_2S (520 mg, 2.52 mmol) in THF (10 mL). The mixture was stirred for 20 min, and then **16.1** (2.91 g, 6.30 mmol) in THF (40 mL) was added over *ca* 2 h. Stirring was continued for 1 h, the dry ice-acetone bath was replaced by an ice bath and the mixture was stirred at 0 °C for 5 min. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:10 *t*-BuOMe-hexane, gave the C(2),C(4) *cis*-isomer (756 mg, 24%) and **16.2** (1.82 g, 59%) as a 3:1 mixture (^{1}H NMR) of two isomers epimeric at the siloxy-bearing carbon: FTIR (CH_2Cl_2 cast) 2955, 2930, 2858, 1714, 1511, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer signals) δ -0.11 (s, 3 H), 0.02 (s, 3 H), 0.11 (s, 3 H), 0.13 (s, 3 H), 0.87 (s, 9 H), 0.98 (s, 9 H), 1.78 (ddd, J = 7.2, 9.1, 13.4 Hz, 1 H), 2.00 (d, J = 7.7 Hz, 1 H), 2.04-2.11 (m, 1 H), 2.18-2.24 (m, 1 H), 2.89-2.33 (m, 1 H), 2.65-2.70 (m, 1 H), 3.76 (s, 3 H), 4.85-4.93 (m, 2 H), 5.05 (d, J = 4.7 Hz, 1 H), 5.70 (ddd, J = 6.3, 10.4, 16.9 Hz, 1 H), 6.72-6.83 (m, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$, major isomer signals) δ -4.95 (q), -4.86 (q), -4.77 (q), -4.74 (q), 18.0 (s), 18.0 (s), 25.6 (q), 25.7 (q), 29.9 (t), 37.1 (d), 44.7 (t), 55.3 (d), 55.7 (q), 72.9 (d), 111.3 (d), 113.6 (t), 119.2 (d), 119.5 (d), 134.4 (s), 140.8 (d), 144.5 (s), 150.1 (s), 217.9 (s); exact mass *m/z* calcd for $C_{27}H_{46}O_4Si_2$ 490.29346, found 490.29225.

(2*R*,4*S*)-rel-2-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-methyl]-4-ethenylcyclopentanone (16.3).

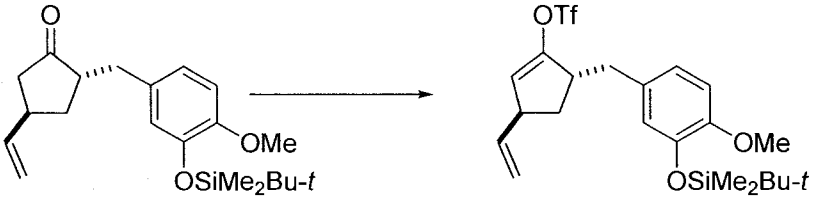


16.2 **16.3**

Et_3SiH (4.2 ml, 26 mmol), followed by CF_3CO_2H (0.98 mL, 13 mmol) in CH_2Cl_2 (5 mL) were added dropwise to a stirred and cooled (0 °C) solution of **16.2** (1.61 g, 3.29 mmol) in CH_2Cl_2 (40 mL). Stirring was continued for 1 h, the ice bath was removed, and stirring was continued for 30 min. The mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) with vigorous stirring, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:15 EtOAc-hexane, gave **16.3** (1.04 g, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2928, 1740, 1510, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 0.99 (s, 9 H), 1.88 (dd, *J* = 7.0, 7.0 Hz, 2 H), 2.21 (dd, *J* = 6.6, 18.2 Hz, 1 H), 2.34 (dd, *J* = 8.0, 18.4 Hz, 1 H), 2.46-2.53 (m, 2 H), 2.77-2.82 (m, 1 H), 2.93 (app q, *J* = 9.1 Hz, 1 H), 3.78 (s, 3 H), 4.99 (d, *J* = 1.4 Hz, 1 H), 5.02 (ddd, *J* = 1.4, 1.4, 6.0 Hz, 1 H), 5.83 (ddd, *J* = 6.4, 10.4, 17.2 Hz, 1 H), 6.65-6.70 (m, 2 H), 6.76 (d, *J* = 8.1 Hz, 1 H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ -4.65 (q), -4.63 (q), 18.4 (s), 25.7 (q), 33.9 (t), 35.2 (t), 36.8 (d), 43.9 (t), 48.6 (d), 55.5 (q), 112.1 (d), 114.0 (t), 121.7 (d), 122.1 (d), 132.0 (s), 140.7 (d), 144.9 (s), 149.5 (s), 219.6 (s); exact mass *m/z* calcd for $C_{21}H_{32}O_3Si$ 360.21207, found 360.21240.

1,1,1-Trifluoromethanesulfonic Acid (3*R*,5*R*)-rel-5-[[3-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-1-cyclopenten-1-yl Ester (17.1).

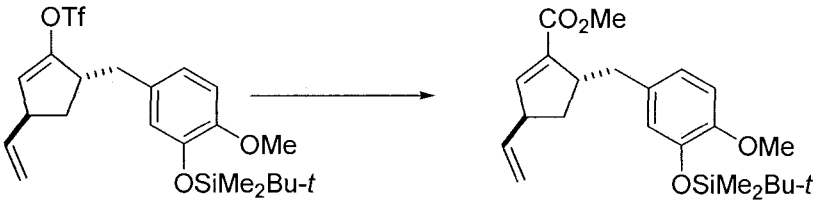


16.3 **17.1**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 8.0 mL, 4.0 mmol), followed by **16.3** (1.03 g, 2.86 mmol) in THF (6 mL plus 2 mL as a rinse) were added dropwise to THF (10 mL) at -78 °C. The mixture was stirred for 1 h. 2-[*N,N*-Bis(trifluoromethylsulfonyl)amino]-pyridine[35] (1.23 g, 3.43 mmol) in THF (4 mL) was added dropwise and stirring was continued for 1.5 h. The dry ice-acetone bath was then replaced by an ice bath and the mixture was stirred at 0 °C for 5 min. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:20 EtOAc-hexane, gave **17.1** (1.32 g, 93%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2954, 2930, 1212, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.16 (s, 3 H), 1.01 (s, 9 H), 1.76-1.83 (m, 1 H), 1.99 (ddd, J = 4.9, 8.5, 13.8 Hz, 1 H), 2.50 (dd, J = 8.5, 13.8 Hz, 1 H), 2.89 (dd, J = 4.1, 13.8 Hz, 1 H), 3.11-3.16

(m, 2 H), 3.79 (s, 3 H), 4.94-5.01 (m, 2 H), 5.58 (s, 1 H), 5.70 (ddd, J = 7.3, 10.1, 17.3 Hz, 1 H), 6.67 (d, J = 2.1 Hz, 1 H), 6.70 (d, J = 2.1, 8.2 Hz, 1 H), 6.78 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.69 (q), -4.67 (q), 18.4 (s), 25.7 (q), 33.9 (t), 37.0 (t), 43.0 (d), 44.3 (d), 55.5 (q), 112.0 (d), 114.4 (t), 118.6 (apparent q, J = 303.2 Hz), 119.9 (d), 121.8 (d), 122.2 (d), 130.9 (s), 140.0 (d), 144.9 (s), 149.6 (s), 151.8 (s); exact mass *m/z* calcd for $C_{22}H_{31}F_3O_5SSi$ 492.16135, found 492.16082.

(3*R*,5*R*)-rel-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-methyl]-3-ethenyl-1-cyclopentene-1-carboxylic Acid Methyl Ester (17.2).

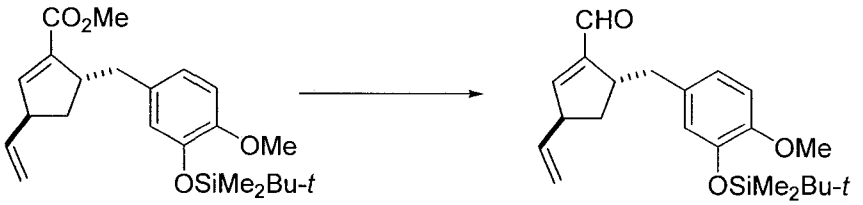


17.1 **17.2**

$Pd(OAc)_2$ (60 mg, 0.27 mmol), followed by Ph_3P (0.14 g, 0.53 mmol), Et_3N (0.74 ml, 5.3 mmol) and MeOH (4.3 ml, 0.11 mol) were added to a stirred solution of **17.1** (1.32 g, 2.67 mmol) in DMF (12 mL). The mixture was purged with CO for 10 min and stirred under CO (balloon filled with CO) at room temperature for 24 h. Et_2O (60 mL) was added, and the mixture was washed with water (2 x 25 mL). The aqueous phase was extracted with Et_2O (3 x 25 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:15 EtOAc-hexane, gave **17.2** (0.78 g, 73%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2952, 2929, 1718, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.73 (td, J = 8.4, 13.2 Hz, 1 H), 2.00 (ddd, J = 2.6, 7.8, 13.1 Hz, 1 H), 2.43 (dd, J = 8.8, 13.6 Hz, 1 H), 2.96 (dd, J = 3.9, 13.6 Hz, 1 H), 3.21-3.27

(m, 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.95 (d, J = 10.5, 1 H), 5.00 (d, J = 17.5 Hz, 1 H), 5.68 (ddd, J = 7.4, 10.2, 17.4 Hz, 1 H), 6.62 (s, 1 H), 6.67 (d, J = 2.0 Hz, 1 H), 6.70 (dd, J = 2.0, 8.2 Hz, 1 H), 6.76 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.65 (q), -4.62 (q), 18.5 (s), 25.8 (q), 35.9 (t), 38.4 (t), 45.5 (d), 48.0 (d), 51.4 (q), 55.6 (q), 111.9 (d), 114.4 (t), 122.1 (d), 122.3 (d), 132.9 (s), 139.4 (s), 139.8 (d), 144.6 (s), 146.4 (d), 149.3 (s), 165.5 (s); exact mass *m/z* calcd for $C_{23}H_{34}O_4Si$ 402.22263, found 402.22162.

(3*R*,5*R*)-rel-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-methyl]-3-ethenyl-1-cyclopentene-1-carboxaldehyde (17.3).



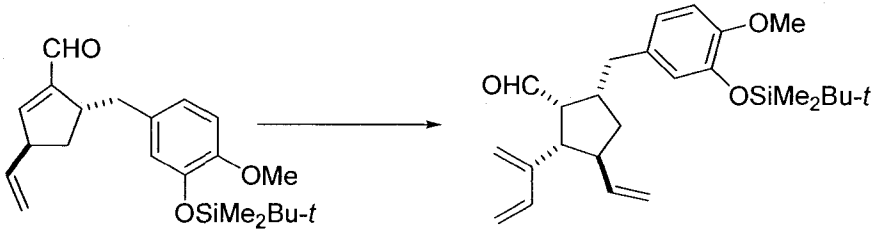
17.2 **17.3**

DIBAL-H (1.0 M in PhMe, 4.3 mL, 4.3 mmol) was added dropwise to a stirred and cooled (-78°C) solution of **17.2** (780 mg, 1.94 mmol) in CH_2Cl_2 (25 mL). Stirring was continued for 1.5 h, the dry ice-acetone bath was replaced by an ice bath and stirring was continued at 0 °C for 1 h. $Na_2SO_4 \cdot 10H_2O$ (2.0 g) was added, the cold bath was removed, and stirring was continued for 30 min. The mixture was then filtered through a pad of Celite (3 x 5), using CH_2Cl_2 (30 mL) as a rinse, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (25 mL).

Dess-Martin periodinane (986 mg, 2.32 mmol) was added to the CH_2Cl_2 solution, and the mixture was stirred for 1.5 h. Saturated aqueous $Na_2S_2O_3$ (8 mL) and saturated aqueous $NaHCO_3$ (4 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts

were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:15 EtOAc-hexane, gave **17.3** (665 mg, 92% from **17.2**) as a yellow oil: FTIR (CH_2Cl_2 cast) 2954, 2857, 1681, 1270 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.77 (td, J = 8.3, 13.3 Hz, 1 H), 2.04 (ddd, J = 3.0, 7.9, 13.3 Hz, 1 H), 2.40 (dd, J = 8.9, 13.6 Hz, 1 H), 2.99 (dd, J = 3.9, 13.6 Hz, 1 H), 3.26-3.33 (m, 2 H), 3.77 (s, 3 H), 4.99 (d, J = 10.5 Hz, 1 H), 5.04 (t, J = 1.3 Hz, 1 H), 5.70 (ddd, J = 7.4, 10.2, 17.4 Hz, 1 H), 6.64-6.66 (m, 2 H), 6.69 (dd, J = 2.1, 8.2 Hz, 1 H), 6.74 (d, J = 8.2 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.64 (q), 18.4 (s), 25.7 (q), 36.0 (t), 37.8 (t), 43.2 (d), 48.4 (d), 55.5 (q), 111.9 (d), 114.9 (t), 122.0 (d), 122.4 (d), 132.6 (s), 139.1 (d), 144.6 (s), 149.3 (s), 149.7 (s), 155.3 (d), 189.9 (s); exact mass *m/z* calcd for $C_{22}H_{32}O_3Si$ 372.21207, found 372.21164.

(1*R*,2*S*,3*S*,5*S*)-rel-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanecarboxaldehyde (18.1).



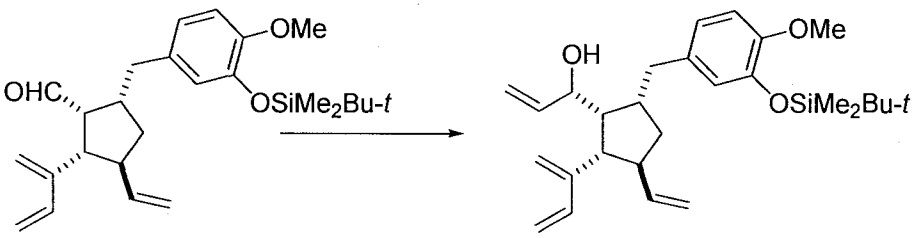
17.3 **18.1**

n-Bu_3P (0.40 mL, 1.59 mmol) was added to a stirred suspension of CuI (0.12 g, 0.65 mmol) in Et_2O (4 mL). The mixture was stirred for 10 min during which time a clear solution formed.[37]

MeLi (1.6 M in Et_2O, 0.86 mL, 1.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of methyl vinyl ketone *N*-(2,4,6-triisopropylbenzene)sulfonyl-

hydrazone[23a] (0.23 g, 0.65 mmol) in dry DME (2.5 mL). The resulting yellow solution was stirred for 30 min, and then the dry ice-acetone bath was replaced by an ice bath. The mixture was stirred at 0 °C for 15 min, and the resulting pink solution was recooled to -78°C. The above freshly prepared Bu_3P.CuI solution in Et_2O was added dropwise via a short cannula (argon pressure) to the above pink solution, and the mixture was stirred for 30 min at -78 °C. Me_3SiCl (0.12 mL, 0.96 mmol), followed by **17.3** (60 mg, 0.16 mmol) in Et_2O (3 mL) were added dropwise, and stirring at -78 °C was continued for 3 h. The solution was poured into an ice-cold mixture of Et_2O (15 mL) and saturated aqueous NH_4Cl (10 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were evaporated, and the residue was dissolved in CH_2Cl_2 (25 mL) and cooled in an ice bath. $TsOH{\cdot}H_2O$ (37 mg, 0.20 mmol) was added, and the mixture was stirred at 0 °C for 2 h. Another portion of $TsOH{\cdot}H_2O$ (19 mg, 0.10 mmol) was added, and stirring at 0 °C was continued for 30 min. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:20 EtOAc-hexane, gave crude **18.1** (42 mg, 56%) as a mixture of isomers [C(1),C(2) *cis*:*trans* > 10:1 (^{1}H NMR)] containing Bu_3P (0.2 equiv). Crude **18.1** was used directly in the next step.

(1*R*,2*S*,3*S*,5*S*)-rel-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-α,3-diethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanemethanol (18.2).



18.1 **18.2**

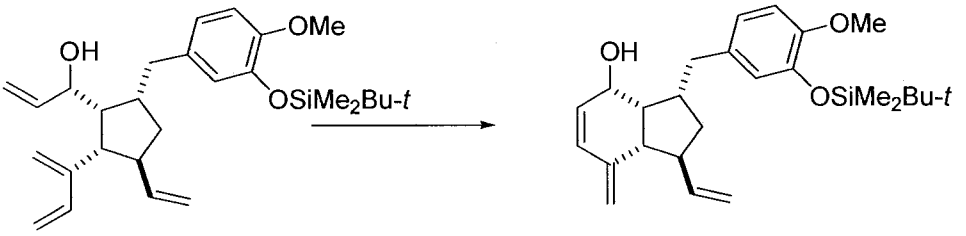
Vinylmagnesium bromide (1 M in THF, 0.50 mL, 0.50 mmol) was added to a stirred and cooled (0 °C) solution of crude **18.1** (42 mg, 0.090 mmol) in THF (2 mL). The mixture was stirred for 2 h, the cold bath was removed and stirring was continued for 0.5 h. Saturated aqueous NH_4Cl (4 mL), followed by water (1 mL) were added, and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 Et_2O-hexane, gave **18.2**-major isomer (20 mg, 48%) and **18.2**-minor isomer (5.6 mg, 14%).

Major isomer: FTIR (CH_2Cl_2 cast) 3559, 2953, 1511, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.16 (s, 3 H), 1.00 (s, 9 H), 1.44-1.52 (m, 2 H), 1.86-1.94 (m, 1 H), 2.47-2.61 (m, 3 H), 2.78-2.83 (m, 1 H), 2.96 (d, J = 9.9 Hz, 1 H), 3.09-3.15 (m, 1 H), 3.77 (s, 3 H), 4.30 (s, 1 H), 4.85 (d, J = 10.0 Hz, 1 H), 4.90 (d, J = 17.2 Hz, 1 H), 5.09 (t, J = 10.5 Hz, 2 H), 5.20 (d, J = 18.5 Hz, 2 H), 5.30 (d, J = 18.5 Hz, 2 H), 5.66 (ddd, J = 8.0, 9.6, 17.2 Hz, 1 H), 6.05 (ddd, J = 4.5, 10.4, 17.5 Hz, 1 H), 6.43 (dd, J = 10.9, 17.5 Hz, 1 H), 6.69-6.76 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.62 (q), -4.59 (q), 18.4 (s), 25.8 (q), 36.8 (t), 37.7 (t), 44.4 (d), 44.4 (d), 50.1 (d), 50.3 (d), 55.6 (q), 72.7 (d), 112.1 (t), 113.2 (t), 113.5 (t), 113.6 (t), 117.0 (t), 121.4 (d), 121.6 (d), 135.0 (s), 140.2

(d), 142.1 (d), 142.8 (d), 144.7 (s), 145.0 (s), 148.9 (s); exact mass *m/z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.29140.

Minor isomer: FTIR (CH_2Cl_2 cast) 3561, 2952, 1511, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.16 (s, 3 H), 1.00 (s, 9 H), 1.47-1.52 (m, 1 H), 1.67 (d, J = 4.5 Hz, 1 H), 1.86 (ddd, J = 6.8, 8.9, 13.1 Hz, 1 H), 2.35-2.40 (m, 1 H), 2.50 (ddd, J = 8.9, 10.9, 17.5 Hz, 2 H), 2.82-2.91 (m, 2 H), 3.01 (td, J = 8.5, 17.5 Hz, 1 H), 3.78 (s, 3 H), 4.27 (dd, J = 5.9, 10.9 Hz, 1 H), 4.86 (d, J = 10.0 Hz, 1 H), 4.92 (d, J = 17.5 Hz, 1 H), 5.13 (dd, J = 8.5, 10.3 Hz, 2 H), 5.24 (d, J = 16.7 Hz, 2 H), 5.32-5.40 (m, 2 H), 5.69 (ddd, J = 7.4, 10.2, 17.4 Hz, 1 H), 6.01 (ddd, J = 6.5, 10.9, 17.4 Hz, 1 H), 6.47 (dd, J = 10.9, 17.4 Hz, 1 H), 6.67-6.78 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.58 (q), 18.5 (s), 25.8 (q), 35.7 (t), 36.4 (t), 44.3 (d), 46.2 (d), 48.3 (d), 51.0 (d), 55.6 (q), 72.9 (d), 112.1 (d), 113.3 (t), 113.8 (t), 115.5 (t), 117.1 (t), 121.4 (d), 121.7 (d), 134.3 (s), 140.1 (d), 140.5 (d), 142.2 (d), 144.8 (s), 145.8 (s), 149.1 (s); exact mass *m/z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.28931.

(1*R*,3*R*,3a*S*,7a*R*)-rel-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-ol (18.3).



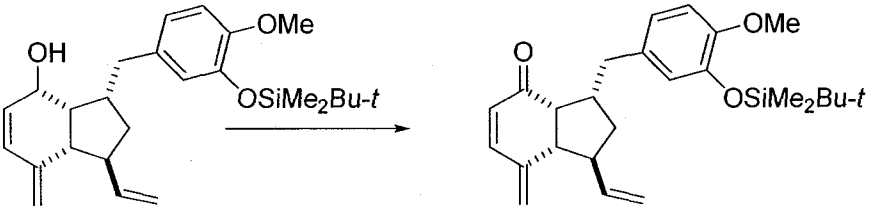
18.2 **18.3**

Ar was bubbled for *ca* 5 min through a stirred solution of alcohol **18.2** (major isomer, 9.8 mg, 0.022 mmol) in CH_2Cl_2 (3 mL), and Grubbs catalyst (second generation,[38] 0.9 mg, 0.001 mmol) was added. The mixture was stirred for 16 h and then

evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:6 EtOAc-hexane, gave **18.3** (7.8 mg, 85%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3367, 2930, 1512, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.00 (s, 9 H), 1.37 (d, J = 7.1 Hz, 1 H), 1.63-1.64 (m, 1 H), 1.77 (td, J = 10.6, 13.8 Hz, 1 H), 2.05 (td, J = 5.4, 8.4 Hz, 1 H), 2.24 (ddd, J = 6.1, 10.8, 19.2 Hz, 1 H), 2.39 (dd, J = 5.7, 10.8 Hz, 1 H), 2.46 (ddd, J = 5.5, 10.0, 19.0 Hz, 1 H), 2.61 (dd, J = 9.7, 13.8 Hz, 1 H), 3.03 (dd, J = 5.8, 13.8 Hz, 1 H), 3.78 (s, 3 H), 4.32 (t, J = 7.2 Hz, 1 H), 4.72 (s, 1 H), 4.79 (d, J = 17.1 Hz, 1 H), 4.89 (dd, J = 1.7, 10.1 Hz, 1 H), 4.90 (s, 1 H), 5.62 (ddd, J = 8.5, 9.9, 17.1 Hz, 1 H), 5.68 (d, J = 9.9 Hz, 1 H), 6.10 (dd, J = 1.7, 9.9 Hz, 1 H), 6.74-6.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.58 (q), 18.5 (s), 25.8 (q), 35.6 (t), 37.3 (t), 44.6 (d), 47.2 (d), 50.4 (d), 50.9 (d), 55.6 (q), 65.4 (d), 112.2 (d), 113.6 (t), 114.1 (t), 121.4 (d), 121.5 (d), 128.7 (d), 131.5 (d), 134.5 (s), 141.6 (s), 142.0 (d), 144.8 (s), 149.1 (s); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25867.

Ar was bubbled for *ca* 5 min through a stirred solution of alcohol **18.2** (minor isomer, 6.5 mg, 0.014 mmol) in CH_2Cl_2 (2.5 mL), and Grubbs catalyst (second generation,[38] 0.6 mg, 0.0007 mmol) was added. The mixture was stirred for 16 h and then evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **18.3** (5.3 mg, 86%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3485, 2953, 1510, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.03 (d, J = 6.4 Hz, 1 H), 1.65 (ddd, J = 6.0, 10.2, 13.1 Hz, 1 H), 1.98-2.08 (m, 2 H), 2.43-2.62 (m, 3 H), 2.85 (dd, J = 8.3, 13.7 Hz, 1 H), 2.95 (dd, J = 8.3, 13.7 Hz, 1 H), 3.78 (s, 3 H), 4.36 (dd, J = 5.5, 11.0 Hz, 1 H), 4.84-4.92 (m, 3 H), 5.01 (s, 1 H), 5.67-5.74 (m, 1 H), 5.93 (dd, J = 5.7, 9.7 Hz, 1 H), 6.19 (d, J = 9.7 Hz, 1 H), 6.74-6.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.59 (q), 18.5 (s), 25.8 (q), 36.2 (t), 37.9 (t), 44.6 (d), 44.9 (d), 48.6 (d), 49.9 (d), 55.6 (q), 64.4 (d), 112.1 (d), 113.8 (t), 115.8 (t), 121.4 (d), 121.5 (d), 128.2 (d), 131.5 (d), 135.1 (s), 142.1 (s), 143.7 (d), 144.8 (s), 148.9 (s); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25779.

(1*R*,3*R*,3a*S*,7a*R*)-rel-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-1,2,3,3a,7,7a-hexahydro-7-methylene-4*H*-inden-4-one (18.4).

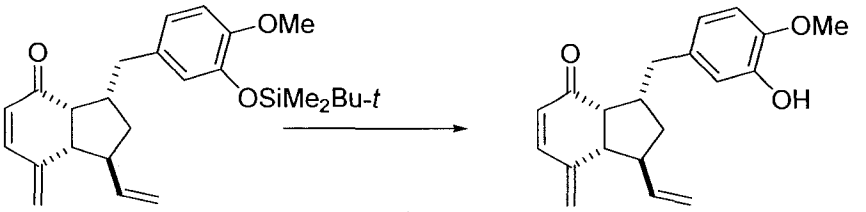


18.3 **18.4**

Dess-Martin periodinane (14 mg, 0.034 mmol) was added to a stirred solution of alcohol **18.3** [mixture of major isomer (7.8 mg) and minor isomer (4.2 mg), 0.028 mmol in all) in CH_2Cl_2 (5 mL). Stirring was continued for 1 h, and then saturated aqueous $Na_2S_2O_3$ (2 mL), followed by saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **18.4** (11 mg, 90%): FTIR (CH_2Cl_2 cast) 2953, 1665, 1510, 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 1.00 (s, 9 H), 1.53 (dd, J = 6.7, 13.5 Hz, 1 H), 1.71 (ddd, J = 7.2, 9.1, 13.1 Hz, 1 H), 2.43-2.52 (m, 2 H), 2.62 (td, J = 8.2, 16.4 Hz, 1 H), 2.79 (t, J = 8.2 Hz, 1 H), 2.86 (dd, J = 6.2, 8.2 Hz, 1 H), 3.02 (dd, J = 4.7, 12.3 Hz, 1 H), 3.76 (s, 3 H), 4.92-4.98 (m, 2 H), 5.32 (s, 2 H), 5.76 (ddd, J = 8.1, 10.1, 17.1 Hz, 1 H), 5.94 (d, J = 10.1 Hz, 1 H), 6.70-6.75 (m, 3 H), 6.98 (d, J = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.60 (q), 18.5 (s), 25.8 (q), 35.6 (t), 35.6 (t), 46.4 (d), 48.4 (d), 49.1 (d), 51.4 (d), 55.6 (q), 112.1 (d), 114.3 (t), 119.9 (t), 121.6 (d), 121.8 (d), 128.3 (d), 134.4 (s),

141.9 (d), 143.1 (s), 144.7 (s), 145.9 (d), 149.1 (s), 200.3 (s); exact mass *m/z* calcd for $C_{26}H_{36}O_3Si$ 424.24338, found 424.24330.

(1*R*,3*R*,3a*S*,7a*R*)-re1-Ethenyl-1,2,3,3a,7,7a-hexahydro-3-[(3-hydroxy-4-methoxyphenyl)methyl]-7-methylene-4*H*-inden-4-one (5.6).

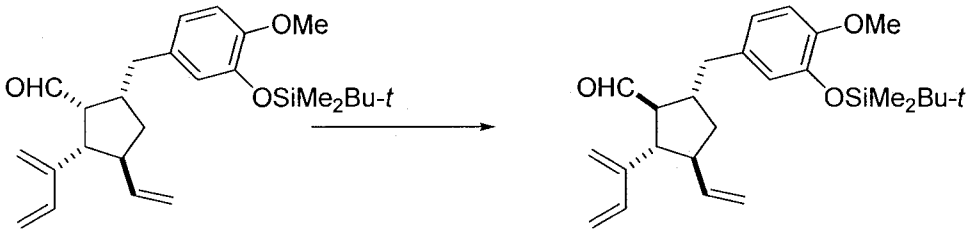


18.4 **5.6**

Bu_4NF (1.0 M in THF, 31 μL, 0.031 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **18.4** (11 mg, 0.026 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 15 min, water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 7 cm), using 1:4 EtOAc-hexane, gave **5.6** (6.4 mg, 81%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3418, 2932, 1659, 1510, 1273, 1130, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56-1.59 (m, 1 H), 1.73 (ddd, *J* = 7.1, 9.2, 13.5 Hz, 1 H), 2.48-2.54 (m, 2 H), 2.62 (td, *J* = 8.1, 16.4 Hz, 1 H), 2.79 (t, *J* = 8.2 Hz, 1 H), 2.86 (dd, *J* = 5.8, 8.1 Hz, 1 H), 3.03-3.09 (m, 1 H), 3.86 (s, 3 H), 4.92-4.98 (m, 2 H), 5.32 (d, *J* = 4.1 Hz, 2 H), 5.52 (s, 1 H), 5.76 (ddd, *J* = 8.2, 10.0, 16.8 Hz, 1 H), 5.93 (d, *J* = 9.9 Hz, 1 H), 6.68 (dd, *J* = 1.7, 8.2 Hz, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 6.78 (d, *J* = 1.7 Hz, 1 H), 6.98 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.7 (t), 35.8 (t), 46.3 (d), 48.6 (d), 49.0 (d), 51.4 (d), 55.9 (q), 110.5 (d), 114.4 (t), 114.9 (d), 119.9 (t), 120.2 (d), 128.3 (d), 135.1 (s), 141.8 (d), 142.9 (s), 144.7 (s), 145.3 (s), 145.9 (d), 200.3 (s); exact mass *m/z* calcd for $C_{20}H_{22}O_3$ 310.15689, found

310.15649. The compound is acid sensitive and so the solvent for NMR measurements was stored over anhydrous K_2CO_3.

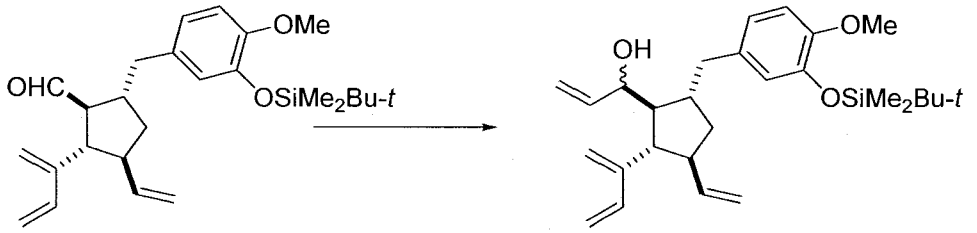
(1*R*,2*R*,3*R*,5*R*)-rel-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanecarboxaldehyde (19.1).



18.1 **19.1**

DBU (1.3 mg, 0.0087 mmol) was added to a stirred solution of crude **18.1** (54 mg, 0.087 mmol) in CH_2Cl_2 (8 mL). Stirring was continued for 24 h, and another portion of DBU (1.3 mg, 0.0087 mmol) was added. Stirring was continued until the trans/cis ratio was larger than 10:1 (usually 48 h, ^1H NMR control), and then the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:5 CH_2Cl_2-hexane, gave **19.1** as a yellow oil (23 mg, 62%, C(1),C(2) *trans*:*cis* > 10:1), which was used directly in the next step.

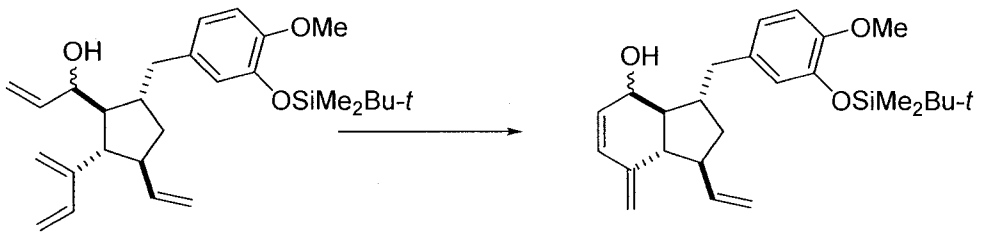
(1*R*,2*R*,3*R*,5*R*)-rel-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-α,3-diethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanemethanol (19.2).



19.1 **19.2**

Vinylmagnesium bromide (1 M in THF, 70 μL, 0.14 mmol) was added to a stirred and cooled (0 °C) solution of crude **19.1** (15 mg, 0.035 mmol) in Et_2O (3 mL). Stirring at 0 °C was continued for 30 min, and saturated aqueous NH_4Cl (4 mL), followed by water (1 mL) were added. The mixture was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:4 EtOAc-hexane, gave **19.2** (13 mg, 83%) as a 2:1 mixture (^{1}H NMR) of isomers epimeric at the hydroxyl-bearing carbon: FTIR (CH_2Cl_2 cast) 3467, 2929, 2857, 1510, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.41-1.45 (m, 1 H), 1.54-1.56 (m, 1 H), 1.66-1.67 (m, 1 H), 1.88-1.92 (m, 1 H), 2.16-2.26 (m, 1 H), 2.49-2.56 (m, 3 H), 2.68-2.72 (m, 1 H), 3.78 (s, 3 H), 4.03-4.10 (m, 1 H), 5.02-5.43 (m, 8 H), 5.61-5.68 (m, 1 H), 5.78-5.86 (m, 1 H), 6.33-6.40 (m, 1 H), 6.68-6.78 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer signals) δ -4.61 (q), 18.5 (s), 25.8 (q), 37.0 (t), 39.3 (d), 42.3 (t), 48.9 (d), 51.3 (d), 55.6 (q), 56.5 (d), 73.5 (d), 112.1 (d), 113.9 (t), 114.1 (t), 114.4 (t), 114.8 (t), 121.9 (d), 122.0 (d), 133.9 (s), 138.2 (d), 139.8 (d), 140.5 (d), 144.8 (s), 148.4 (s), 149.2 (s); exact mass *m/z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.29073.

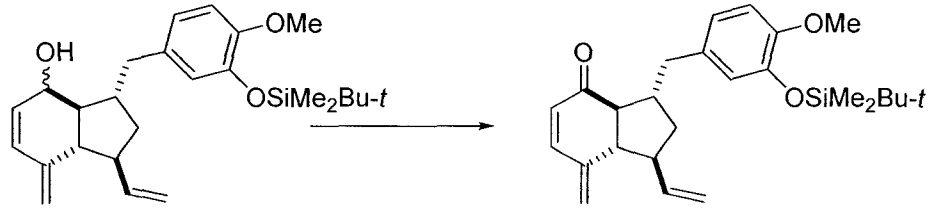
(1*R*,3*R*,3a*R*,7a*R*)-rel-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-ol (19.3).



19.2 **19.3**

Ar was bubbled for *ca* 10 min through a stirred solution of alcohol **19.2** (mixture of two isomers, 11 mg, 0.025 mmol) in CH_2Cl_2 (3 mL), and Grubbs catalyst (second generation,[38] 1 mg, 0.001 mmol) was added. The mixture was stirred for 12 h and then evaporated. Flash chromatography of the residue over silica gel (1 x 8 cm), using 1:10 EtOAc-hexane, gave **19.3** (9.0 mg, 86%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3379, 2929, 1511, 1270, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major isomer signals) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.28 (d, J = 6.4 Hz, 1 H), 1.42-1.51 (m, 1 H), 1.63-1.76 (m, 2 H), 2.09-2.21 (m, 2 H), 2.49 (dd, J = 8.8, 13.8 Hz, 1 H), 2.63-2.70 (m, 1 H), 3.01 (dd, J = 5.8, 13.8 Hz, 1 H), 3.78 (s, 3 H), 4.28 (s, 1 H), 4.87 (s, 1 H), 4.97 (d, J = 10.2 Hz, 1 H), 5.04-5.08 (m, 2 H), 5.64 (d, J = 9.7 Hz, 1 H), 5.74-5.83 (m, 1 H), 6.10 (dd, J = 1.5, 9.7 Hz, 1 H), 6.71-6.76 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer signals) δ -4.62 (q), -4.60 (q), 18.4 (s), 25.8 (q), 38.7 (t), 41.4 (t), 43.9 (d), 44.3 (d), 49.5 (d), 55.5 (q), 56.8 (d), 74.6 (d), 110.1 (t), 112.1 (d), 113.8 (t), 121.6 (d), 121.9 (d), 131.4 (d), 133.7 (d), 133.8 (s), 142.9 (d), 144.9 (s), 145.7 (s), 149.3 (s); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25955.

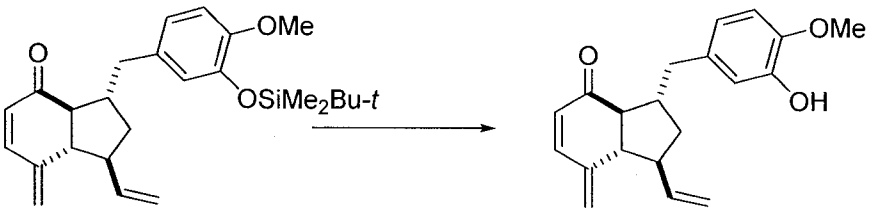
(1*R*,3*R*,3a*R*,7a*R*)-rel-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-1,2,3,3a,7,7a-hexahydro-7-methylene-4*H*-inden-4-one (19.4).



19.3 **19.4**

Dess-Martin periodinane (8.5 mg, 0.020 mmol) was added to a stirred solution of alcohols **19.3** (7.1 mg, 0.017 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 1 h, and then saturated aqueous $Na_2S_2O_3$ (2 mL), followed by saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 8 cm), using 1:10 EtOAc-hexane, gave **19.4** (6.6 mg, 93%) as an oil: FTIR (CH_2Cl_2 cast) 2953, 2930, 1681, 1512, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.99 (s, 9 H), 1.52-1.62 (m, 1 H), 1.78 (ddd, J = 6.8, 9.8, 13.9 Hz, 1 H), 2.27 (dd, J = 9.8, 13.9 Hz, 1 H), 2.36 (dd, J = 9.8, 13.4 Hz, 1 H), 2.45-2.56 (m, 2 H), 2.70 (td, J = 9.0, 18.8 Hz, 1 H), 3.11 (dd, J = 3.5, 13.4 Hz, 1 H), 3.78 (s, 3 H), 5.00 (d, J = 10.3 Hz, 1 H), 5.08 (d, J = 17.2 Hz, 1 H), 5.30 (s, 1 H), 5.44 (s, 1 H), 5.70-5.79 (m, 1 H), 5.94 (d, J = 9.7 Hz, 1 H), 6.71-6.75 (m, 3 H), 7.00 (d, J = 9.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.60 (q), -4.59 (q), 18.5 (s), 25.8 (q), 36.9 (t), 37.9 (d), 40.2 (t), 44.5 (d), 50.5 (d), 55.6 (q), 58.2 (d), 112.0 (d), 114.6 (t), 117.1 (t), 121.9 (d), 122.2 (d), 128.7 (d), 133.3 (s), 141.6 (d), 144.7 (s), 144.8 (s), 147.5 (d), 149.2 (s), 200.6 (s); exact mass *m/z* calcd for $C_{26}H_{36}O_3Si$ 424.24338, found 424.24399.

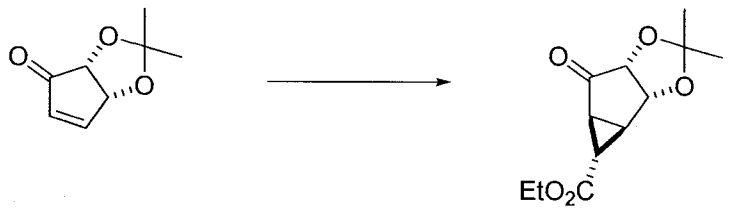
(1*R*,3*R*,3a*R*,7a*R*)-rel-1-Ethenyl-1,2,3,3a,7,7a-hexahydro-3-[(3-hydroxy-4-methoxyphenyl)methyl]-7-methylene-4*H*-inden-4-one (5.7).



19.4 **5.7**

Bu_4NF (1.0 M in THF, 20 μL, 0.020 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **19.4** (7.1 mg, 0.017 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 10 min, water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 7 cm), using 1:4 EtOAc-hexane, gave **5.7** (6.4 mg, 81%) as a colorless solid: mp: 139-141 °C; FTIR (CH_2Cl_2 cast) 3427, 2932, 1676, 1511, 1273, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (ddd, J = 8.1, 10.1, 13.5 Hz, 1 H), 1.79 (ddd, J = 6.8, 9.9, 13.9 Hz, 1 H), 2.27 (dd, J = 9.9, 13.9 Hz, 1 H), 2.35 (dd, J = 10.1, 13.5 Hz, 1 H), 2.48-2.55 (m, 2 H), 2.70-2.77 (m, 1 H), 3.15 (dd, J = 3.7, 13.5 Hz, 1 H), 3.86 (s, 3 H), 5.00 (dd, J = 1.2, 10.2 Hz, 1 H), 5.09 (d, J = 17.1 Hz, 1 H), 5.30 (s, 1 H), 5.45 (s, 1 H), 5.52 (s, 1 H), 5.74 (ddd, J = 8.1, 10.2, 17.1 Hz, 1 H), 5.95 (d, J = 9.7 Hz, 1 H), 6.69 (dd, J = 2.0, 8.2 Hz, 1 H), 6.76 (d, J = 8.2 Hz, 1 H), 6.81 (d, J = 2.0 Hz, 1 H), 7.00 (d, J = 9.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.0 (t), 38.0 (d), 40.7 (t), 44.6 (d), 50.6 (d), 56.0 (q), 58.4 (d), 110.6 (d), 114.7 (t), 115.4 (d), 117.1 (t), 120.5 (d), 128.8 (d), 134.2 (s), 141.6 (d), 144.8 (s), 144.9 (s), 145.3 (s), 147.6 (d), 200.6 (s); exact mass *m/z* calcd for $C_{20}H_{22}O_3$ 310.15689, found 310.15716.

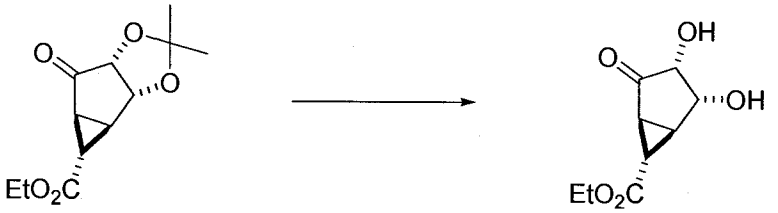
(3a*R*,3b*R*,4*S*,4a*S*,5a*R*)-Hexahydro-2,2-dimethyl-5-oxocyclopropa[3,4]cyclopenta[1,2-d]-1,3-dioxole-4-carboxylic Acid Ethyl Ester (23.6).



23.5 **23.6**

DBU (3.94 mL, 26.3 mmol) was added dropwise to a stirred solution of (carbethoxymethyl)dimethylsulfonium bromide (6.04 g, 26.1 mmol) in $CHCl_3$ (70 mL) at room temperature.[44] Stirring was continued for 30 min, and then the mixture was cooled in an ice bath. Enone **23.5**[47] (3.86 g, 25.1 mmol) in $CHCl_3$ (70 mL) was added dropwise, the cold bath was left in place but not recharged and stirring was continued for 24 h. CH_2Cl_2 (300 mL) was added, and the organic phase was washed by 5% HCl, water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:2 Et_2O-hexane, gave **23.6** (5.54 g, 92%) as a colorless oil: $[\alpha]_D$ = -354.9 (*c* 2.75, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2987, 2937, 1748, 1188 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3 H), 1.34 (s, 3 H), 1.42 (s, 3 H), 1.97 (dd, *J* = 3.2, 3.2 Hz, 1 H), 2.44 (dd, *J* = 2.8, 5.3 Hz, 1 H), 2.81 (dd, *J* = 3.8, 5.3 Hz, 1 H), 4.13-4.18 (m, 3 H), 4.79 (d, *J* = 4.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (q), 25.2 (q), 25.4 (q), 27.1 (d), 31.8 (d), 33.4 (d), 61.7 (t), 76.5 (d), 77.7 (d), 113.6 (s), 168.7 (s), 206.5 (s); exact mass *m/z* calcd for $C_{12}H_{16}O_5$ 240.09978, found 240.09969.

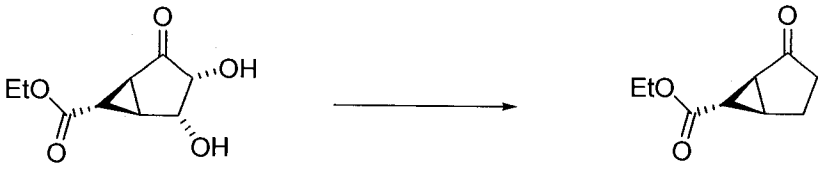
(1*R*,2*R*,3*R*,5*S*,6*S*)-2,3-Dihydroxy-4-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (22.7).[44]



23.6 **22.7**

Hydrochloric acid (10%, 10 mL) was added to a stirred solution of **23.6** (3.60 g, 15.0 mmol) in water (20 mL) and THF (20 mL). Stirring was continued for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:3 hexane-EtOAc, gave **22.7** (2.65 g, 88%) as a colorless solid: mp 73-75 °C; $[\alpha]_D$ = 77.1 (*c* 1.05, $CHCl_3$) [lit.[44] $[\alpha]_D$ = 74.0 (*c* 1.0, $CHCl_3$)]; FTIR (CH_2Cl_2 cast) 3315, 2980, 2894, 1717, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3 H), 2.32 (dd, *J* = 2.8, 3.7 Hz, 1 H), 2.37 (dd, *J* = 2.4, 6.0 Hz, 1 H), 2.75 (dd, *J* = 4.2, 6.0 Hz, 1 H), 3.49 (s, 1 H), 3.55 (s, 1 H), 3.96 (s, 1 H), 4.17 (q, *J* = 7.1, Hz, 2 H), 4.47 (d, *J* = 4.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 26.0 (d), 31.4 (d), 33.9 (d), 61.8 (t), 67.3 (d), 71.3 (d), 169.0 (s), 208.8 (s); exact mass *m/z* calcd for $C_9H_{12}O_5$ 200.06847, found 200.06803.

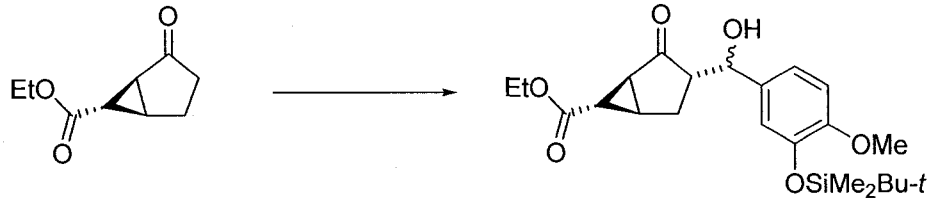
(1*S*,5*R*,6*S*)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (21.7).[44]



22.7 **21.7**

Et_3N (1.42 mL, 10.2 mmol), followed by $MeSO_2Cl$ (0.43 mL, 5.6 mmol) was added to a stirred and cooled (0 °C) solution of **21.7** (0.51 g, 2.6 mmol) in THF (15 mL). Stirring at 0 °C was continued for 1 h, and the resulting light yellow precipitate was filtered off. The solvents were evaporated and the residue was dissolved in EtOAc (25 mL). Pd/C (10%, 0.27 g), followed by *i*-Pr_2NEt (0.89 mL, 5.1 mmol) were added to the mixture, which was then shaken under H_2 (50 psi) in a Parr bottle for 2 h. Another portion of Pd/C (0.14 g) was added, and the reaction was continued at the same pressure for another 1.5 h. The mixture was filtered through a pad of Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **21.7** (0.24 g, 57%) as a colorless solid: mp 68-69 °C; $[\alpha]_D$ = 59.8 (*c* 1.32, MeOH) [lit. for enantiomer[57] $[\alpha]_D$ = -60 (*c* 1.34, MeOH)]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3 H), 1.97-2.10 (m, 4 H), 2.16-2.23 (m, 2 H), 2.46 (dd, *J* = 5.3, 8.8 Hz, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.4 (t), 26.5 (d), 29.2 (d), 31.9 (t), 35.8 (d), 61.2 (t), 170.4 (s), 211.7 (s).

(1*S*,3*S*,5*R*,6*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxy-phenyl]hydroxymethyl]-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (25.1).

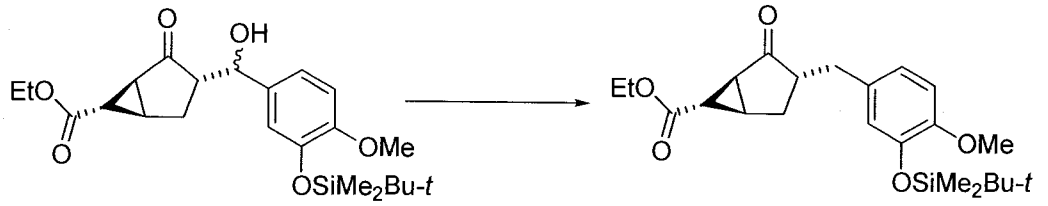


21.7 **25.1**

n-BuLi (1.6 M in hexane, 2.6 mL, 4.1 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.58 mL, 4.1 mmol) in THF (10 mL). Stirring was continued for 10 min, and the mixture was then cooled to -78 °C. Keto ester **21.7** (570 mg, 3.39 mmol) in THF (3 mL plus 0.5 mL as a rinse) was added dropwise, and stirring was continued for 30 min. 3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenz-aldehyde (**14.1**[30]) (1.09 g, 4.11 mmol) in THF (3 mL) was added dropwise and stirring was continued at -78 °C for 60 min. Saturated aqueous NH_4Cl (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave **25.1** (1.35 g, 91%) as a 1:1 mixture (^{1}H NMR) of two isomers: $[\alpha]_D$ = 13.4 (*c* 3.40, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3496, 2954, 2930, 1727, 1511, 1277, 849 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, signals for major isomer) δ 0.14-0.15 (m, 6 H), 1.00 (s, 9 H), 1.23-1.27 (m, 3 H), 1.76-1.86 (m, 1.5 H), 1.98 (t, *J* = 2.8 Hz, 0.5 H), 2.11 (t, *J* = 3.0 Hz, 0.5 H), 2.25 (d, *J* = 4.0 Hz, 0.5 H), 2.29-2.37 (m, 2 H), 2.42-2.50 (m, 1.5 H), 3.71 (s, 3 H), 4.11-4.17 (m, 2 H), 4.52 (s, 0.5 H), 4.55 (s, 0.5 H), 5.21 (s, 0.5 H), 6.78-6.84 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, signals for major isomer) δ -4.61 (q), -4.58 (q), 14.1 (q),

18.5 (s), 25.7 (q), 26.8 (q), 27.5 (d), 28.1 (d), 36.0 (d), 48.0 (d), 55.5 (q), 61.3 (t), 75.0 (d), 111.9 (d), 118.2 (d), 119.4 (d), 133.3 (s), 145.0 (s), 150.9 (s), 169.9 (s), 214.74 (s); exact mass *m/z* calcd for $C_{23}H_{34}O_6Si$ 434.21246, found 434.21153.

(1*S*,3*S*,5*R*,6*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-2-oxobicyclo[3.1.0]hexane-6-carboxylic Acid Ethyl Ester (25.2).

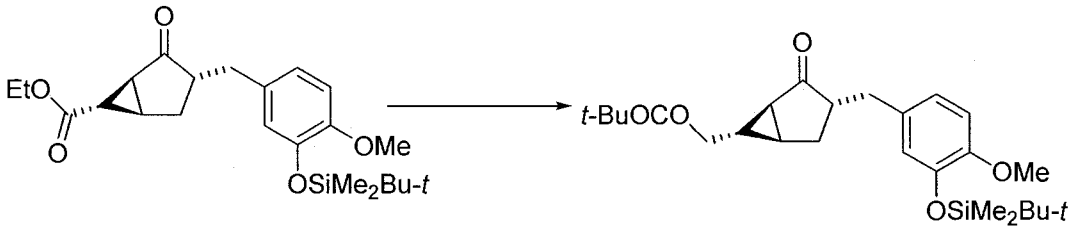


25.1 **25.2**

Et_3SiH (4.0 mL, 25 mmol), followed by $BF_3.Et_2O$ (0.79 mL, 6.2 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **25.1** (1.35 g, 3.11 mmol) in CH_2Cl_2 (25 mL). Stirring was continued for 1 h. Saturated aqueous $NaHCO_3$ (15 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 1:6 EtOAc-hexane, gave **25.2** (1.12 g, 87%) as a colorless oil: $[\alpha]_D$ = 8.65 (*c* 1.65, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2931, 2857, 1730, 1512, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 0.99 (s, 9 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.92 (ddd, *J* = 5.2, 8.8, 12.8 Hz, 1 H), 2.04 (t, *J* = 2.8 Hz, 1 H), 2.13-2.29 (m, 2 H), 2.32-2.34 (m, 2 H), 2.39-2.42 (m, 1 H), 3.04 (dd, *J* = 3.8, 13.6 Hz, 1 H), 3.77 (s, 3 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 6.61-6.66 (m, 2 H), 6.74 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.64 (q), -4.61 (q), 14.1 (q), 18.4 (s), 25.7 (q), 27.4 (d), 27.6 (d), 29.5 (t), 34.7 (t), 35.8 (d), 43.5 (d), 55.5 (q), 61.2 (t),

112.2 (d), 121.5 (d), 121.8 (d), 131.8 (s), 144.9 (s), 149.5 (s), 170.4 (s), 211.7 (s); exact mass *m/z* calcd for $C_{23}H_{34}O_5Si$ 418.21756, found 418.21677.

2,2-Dimethylpropanoic Acid [(1*S*,3*S*,5*S*,6*S*)-3-[[3-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-2-oxobicyclo[3.1.0]hex-6-yl]methyl Ester (25.4).

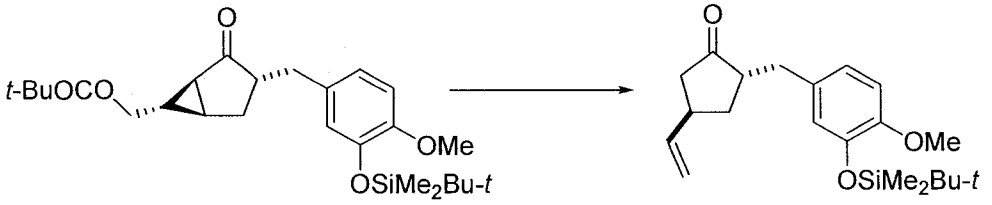


25.2 **25.4**

$LiAlH_4$ (0.87 g, 23 mmol) was added to a stirred and cooled (0 °C) solution of **25.2** (3.20 g, 7.66 mmol) in THF (140 mL). The ice bath was removed, and stirring was continued for 4 h. $Na_2SO_4 \cdot 10H_2O$ (24 g) was added, and the solution was diluted with CH_2Cl_2 (50 mL). Stirring was continued for 20 min, and then the mixture was filtered through a pad of Celite (5 x 6 cm), using CH_2Cl_2 (30 mL) as a rinse. The filtrate was dried (Na_2SO_4) and evaporated. The residue was dissolved in THF (100 mL) and the solution was cooled to 0 °C. Pyridine (3.7 mL, 46 mmol), followed by *t*-BuCOCl (1.9 mL, 15 mmol) were added dropwise with stirring. The ice bath was left in place, but not recharged, and stirring was continued for 1.5 h, the mixture having reached room temperature after 1 h. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:3 hexane-EtOAc, gave a colorless oil which was dissolved in CH_2Cl_2 (60 mL).

Dess-Martin periodinane (3.25 g, 7.66 mmol) was added to the above solution, and the mixture was stirred for 1 h. Saturated aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added. The mixture was stirred for 5 min, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:6 EtOAc-hexane, gave **25.4** (2.72 g, 77%) as a yellow oil: $[\alpha]_D$ = -27.7 (*c* 0.53, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2956, 2858, 1728, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.14 (s, 3 H), 1.00 (s, 9 H), 1.19 (s, 9 H), 1.67-1.72 (m, 1 H), 1.80-1.86 (m, 2 H), 1.95 (dd, *J* = 5.2, 9.2 Hz, 1 H), 2.09 (dd, *J* = 7.2, 13.2 Hz, 1 H), 2.23-2.30 (m, 2 H), 3.01-3.08 (m, 1 H), 3.76 (s, 3 H), 3.89 (dd, *J* = 6.4, 11.6 Hz, 1 H), 4.03 (dd, *J* = 6.4, 11.6 Hz, 1 H), 6.61-6.66 (m, 2 H), 6.73 (d, *J* = 8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.64 (q), -4.61 (q), 18.4 (s), 24.7 (d), 25.7 (q), 26.1 (d), 27.1 (q), 29.7 (t), 32.5 (d), 34.8 (t), 38.8 (s), 43.8 (d), 55.5 (q), 64.6 (t), 112.1 (d), 121.5 (d), 121.8 (d), 132.3 (s), 144.9 (s), 149.4 (s), 178.3 (s), 212.9 (s); exact mass *m/z* calcd for $C_{26}H_{40}O_5Si$ 460.26450, found 460.26488.

(2*S*,4*R*)-2-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-methyl]-4-ethenylcyclopentanone (25.5).

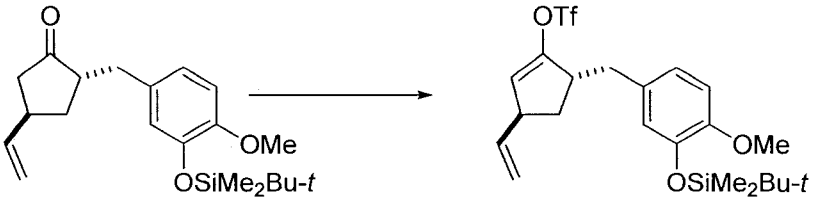


25.4 **25.5**

SmI_2 solution (80 mL, 0.2 M in THF, concentration calculated on the basis of the amount of 1,2-diiodoethane used, assuming 100% yield, 16 mmol) was added dropwise

to a stirred and cooled (0 °C) solution of **25.4** (1.94 g, 4.22 mmol) in 10:1 THF-MeOH (5.5 mL). Stirring at 0 °C was continued for 2 h, and another portion of SmI_2 solution (20 mL) was added. Stirring at 0 °C was continued for 3 h, and water (15 mL) was added. A few drops of 10% HCl were added to dissolve the white precipitate. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:10 EtOAc-hexane, gave **25.5** (1.25 g, 82%) as a colorless oil: $[\alpha]_D$ = -97.0 (*c* 1.15, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2954, 2930, 1740, 1511, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.88 (dd, *J* = 7.0, 7.0 Hz, 2 H), 2.21 (dd, *J* = 6.4, 18.4 Hz, 1 H), 2.34 (dd, *J* = 7.8, 18.4 Hz, 1 H), 2.46-2.53 (m, 2 H), 2.77-2.82 (m, 1 H), 2.93 (apparent q, *J* = 9.0 Hz, 1 H), 3.78 (s, 3 H), 4.99 (d, *J* = 1.5 Hz, 1 H), 5.02 (ddd, *J* = 1.4, 1.4, 6.0 Hz, 1 H), 5.83 (ddd, *J* = 6.3, 10.0, 17.5 Hz, 1 H), 6.65-6.70 (m, 2 H), 6.76 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.67 (q), -4.65 (q), 18.4 (s), 25.7 (q), 33.8 (t), 35.2 (t), 36.8 (d), 43.9 (t), 48.6 (d), 55.5 (q), 112.1 (d), 114.0 (t), 121.6 (d), 122.0 (d), 132.0 (s), 140.6 (d), 144.9 (s), 149.5 (s), 219.6 (s); exact mass *m/z* calcd for $C_{21}H_{32}O_3Si$ 360.21207, found 360.21273.

1,1,1-Trifluoromethanesulfonic Acid (3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-1-cyclopenten-1-yl Ester (26.1).

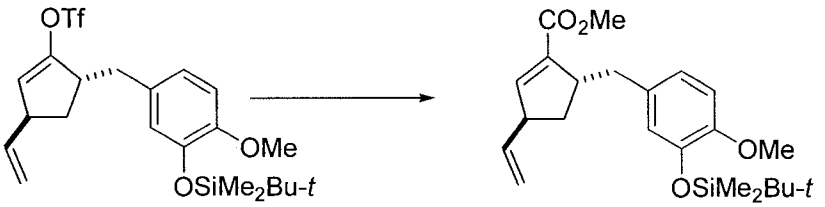


25.5 **26.1**

A solution of **25.5** (990 mg, 2.75 mmol) in THF (5 mL plus 1 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of $(Me_3Si)_2NK$ (0.5 M in PhMe, 7.1 mL, 3.6 mmol) in THF (10 mL). Stirring was continued for 1 h and 2-[*N,N*-bis(trifluoromethanesulfonyl)amino]pyridine[35] (1.28 g, 3.57 mmol) in THF (5 mL plus 1 mL as a rinse) was added dropwise. Stirring was continued for 2 h and the cold bath was then replaced by an ice bath. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:20 EtOAc-hexane, gave **26.1** (1.25 g, 92%) as a yellow oil: $[\alpha]_D$ = 59.9 (*c* 2.60, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2955, 2931, 1213, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.01 (s, 9 H), 1.76-1.83 (m, 1 H), 1.99 (ddd, *J* = 5.5, 7.5, 13.5 Hz, 1 H), 2.50 (dd, *J* = 9.0, 13.5 Hz, 1 H), 2.89 (dd, *J* = 4.1, 13.5 Hz, 1 H), 3.13 (d, *J* = 6.5 Hz, 2 H), 3.79 (s, 3 H), 4.94-5.01 (m, 2 H), 5.58 (s, 1 H), 5.70 (ddd, *J* = 8.0, 9.5, 17.0 Hz, 1 H), 6.67-6.72 (m, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.68 (q), -4.66 (q), 18.4 (s), 25.7 (q), 33.9 (t), 37.0 (t), 43.0 (d), 44.3 (d), 55.5 (q), 112.0 (d), 114.4 (t), 118.6 (apparent q, *J* = 320 Hz), 119.9 (d), 121.9 (d), 122.2

(d), 130.9 (s), 140.0 (d), 144.9 (s), 149.6 (s), 151.8 (s); exact mass *m/z* calcd for $C_{22}H_{31}F_3O_5SSi$ 492.16135, found 492.16030.

(3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-methyl]-3-ethenyl-1-cyclopentene-1-carboxylic Acid Methyl Ester (26.2).

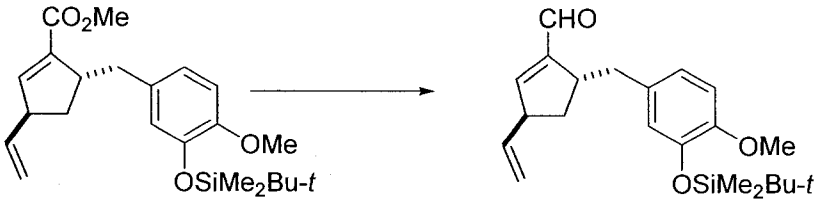


26.1 **26.2**

$Pd(OAc)_2$ (57 mg, 0.25 mmol), followed by Ph_3P (0.13 mg, 0.50 mmol), Et_3N (0.50 mL) and MeOH (3 mL) were added to a stirred solution of **26.1** (1.24 g, 2.52 mmol) in DMF (8 mL). The mixture was purged with CO for 10 min (via a needle below the solvent surface) and stirred under CO (balloon filled with CO) at room temperature for 24 h. Et_2O (40 mL) was added, and the mixture was washed with water (2 x 25 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:20 EtOAc-hexane, gave **26.2** (0.78 g, 77%) as a yellow oil: $[\alpha]_D$ = 52.2 (*c* 1.80, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2955, 2930, 1719, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.73 (td, *J* = 8.4, 13.2 Hz, 1 H), 2.00 (ddd, *J* = 2.4, 7.6, 13.2 Hz, 1 H), 2.43 (dd, *J* = 8.8, 13.6 Hz, 1 H), 2.96 (dd, *J* = 4.0, 13.6 Hz, 1 H), 3.21-3.27 (m, 2 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.97-5.01 (m, 2 H), 5.68 (ddd, *J* = 7.2, 10.0, 17.2 Hz, 1 H), 6.62 (s, 1 H), 6.67 (d, *J* = 2.0 Hz, 1 H), 6.70 (dd, *J* = 2.0, 8.4 Hz, 1 H), 6.76 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.66 (q), -4.63 (q), 18.4 (s), 25.7 (q), 35.9 (t), 38.4 (t), 45.5 (d), 48.1 (d), 51.4

(q), 55.5 (q), 111.9 (d), 114.4 (t), 122.1 (d), 122.3 (d), 132.9 (s), 139.4 (s), 139.8 (d), 144.6 (s), 146.4 (d), 149.3 (s), 165.5 (s); exact mass *m/z* calcd for $C_{23}H_{34}O_4Si$ 402.22263, found 402.22372.

(3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]-methyl]-3-ethenyl-1-cyclopentene-1-carboxaldehyde (26.3).

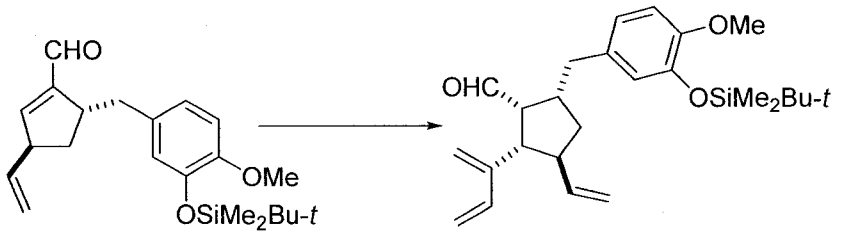


26.2 **26.3**

DIBAL-H (1.0 M in CH_2Cl_2, 1.2 mL, 1.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **26.2** (220 mg, 0.547 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h. $Na_2SO_4 \cdot 10H_2O$ (2.0 g) was added, the cold bath was removed, and stirring was continued for 30 min. The mixture was then filtered through a pad of Celite (3 x 5 cm), using CH_2Cl_2 (30 mL) as a rinse. The filtrate was evaporated and the residue was dissolved in CH_2Cl_2 (25 mL). Dess-Martin periodinane (0.28 g, 0.66 mmol) was added, and the mixture was stirred for 45 min. Saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (4 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:10 EtOAc-hexane, gave **26.3** (189 mg, 93%) as a colorless oil: $[\alpha]_D$ = 72.4 (*c* 1.25, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2954, 2857, 1682, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.15 (s, 3 H), 1.00 (s, 9 H), 1.77 (td, *J* = 8.4, 13.2 Hz, 1 H), 2.04 (ddd, *J* = 3.2, 8.0, 13.6 Hz, 1 H), 2.40 (dd, *J* = 9.2, 13.6 Hz, 1 H),

2.99 (dd, J = 4.0, 13.6 Hz, 1 H), 3.26-3.33 (m, 2 H), 3.77 (s, 3 H), 4.98-5.05 (m, 2 H), 5.70 (ddd, J = 7.2, 10.0, 17.2 Hz, 1 H), 6.64-6.70 (m, 3 H), 6.74 (d, J = 8.0 Hz, 1 H), 9.80 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.64 (q), -4.61 (q), 18.5 (s), 25.6 (q), 36.0 (t), 37.8 (t), 43.3 (d), 48.4 (d), 55.5 (q), 111.9 (d), 115.0 (t), 122.0 (d), 122.4 (d), 132.6 (s), 139.0 (d), 144.6 (s), 149.3 (s), 149.7 (s), 155.3 (d), 189.9 (s); exact mass *m/z* calcd for $C_{22}H_{32}O_3Si$ 372.21207, found 372.21199.

(1*R*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-3-ethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanecarboxaldehyde (26.4).



26.3 **26.4**

Chloroprene solution was prepared by slight modification of a literature procedure.[58]

DBU (7.2 mL, 48 mmol) was added to a stirred and cooled (0 °C) solution of 3,4-dichloro-1-butene (5.0 g, 40 mmol) in PhMe (15 mL). The ice bath was removed, and stirring was continued for 2 h. THF (2 mL) and water (1 mL) were added to dissolve the precipitate, and stirring was continued for 2 h. The organic phase was washed with water, 5% hydrochloric acid, saturated aqueous $NaHCO_3$ and brine, and then dried ($MgSO_4$). The drying agent was filtered off; using Et_2O as a rinse and a small amount of CaH_2 was added to the filtrate. The mixture was kept (no stirring) at room temperature

for 30 min, THF (20 mL) and 1,2-dibromoethane (0.50 mL) were added and most of the clear solution (*ca* 40 mL) was taken up into a syringe.

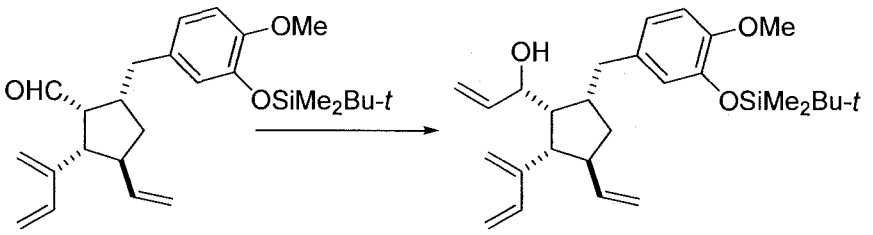
1,2-Dibromoethane (0.20 mL) was added to a stirred suspension of Mg (1.65 g) in THF (5 mL). The solution was refluxed for 10 min, cooled to room temperature and $ZnCl_2$ (1.20 mL, 1 M in THF), followed by the above chloroprene solution (5 mL) were added. The solution was stirred and heated until initiation occurred. The remaining chloroprene solution was added dropwise at a rate to maintain the reaction mixture at reflux, and refluxing was continued for 1 h after the addition was complete. The concentration of this Grignard solution was approximately 0.4 M as determined (^{1}H NMR) by reaction with an excess of PhCHO.

The above chloroprene Grignard solution (0.4 M in THF-PhMe, 1.2 mL, 0.49 mmol) was added to a stirred and cooled (-78 °C) suspension of CuBr·Me_2S (27 mg, 0.13 mmol) in THF (5 mL). The mixture was stirred for 20 min and HMPA (0.11 mL, 0.63 mmol) was then added.

Me_3SiCl (84 μL, 0.64 mmol) was added to **26.3** (0.12 g, 0.33 mmol) in THF (4 mL), and the resulting solution was added dropwise to the above organocopper solution over 10 min by syringe. Stirring at -78 °C was continued for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were stirred at 0 °C, and CF_3CO_2H (0.40 mL) was added. Stirring was continued for 1 h and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:10 Et_2O-hexane, gave **26.4** [87 mg, 61%, containing < 10% of the C(3a),C(7a) *trans* isomer (^{1}H NMR)] as a colorless oil: $[\alpha]_D$ = -47.4 (*c* 0.51, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2953, 2856, 1720, 1511, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, signals for C(3a),C(7a) *cis* isomer **26.4** only) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.81 (ddd, *J* = 6.5, 9.0, 13.5 Hz, 1 H), 2.04 (ddd, *J* = 9.5, 9.5, 13.5 Hz, 1 H), 2.50-2.59 (m, 2 H), 2.68

(dd, J = 6.0, 12.5 Hz, 1 H), 2.88 (dd, J = 6.5, 11.0 Hz, 1 H), 3.06 (dd, J = 6.0, 11.0 Hz, 1 H), 3.22 (ddd, J = 7.0, 10.5, 17.5 Hz, 1 H), 3.78 (s, 3 H), 4.95-5.01 (m, 2 H), 5.08-5.12 (m, 2 H), 5.23 (d, J = 18.0 Hz, 2 H), 5.71 (ddd, J = 7.4, 10.5, 16.6 Hz, 1 H), 6.35 (dd, J = 11.0, 17.5 Hz, 1 H), 6.65-6.76 (m, 3 H), 9.62 (d, J = 4.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, signals for C(3a),C(7a) *cis* isomer **26.4** only) δ -4.60 (q), 18.5 (s), 25.8 (q), 36.1 (t), 36.8 (t), 43.2 (d), 44.3 (d), 49.0 (d), 55.6 (q), 56.8 (d), 112.2 (d), 113.7 (t), 114.4 (t), 116.4 (t), 121.2 (d), 121.6 (d), 133.6 (s), 139.4 (d), 140.9 (d), 142.3 (s), 144.9 (s), 149.2 (s), 204.9 (d); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.29821.

(1*R*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-α,3-diethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanemethanol (27.1).



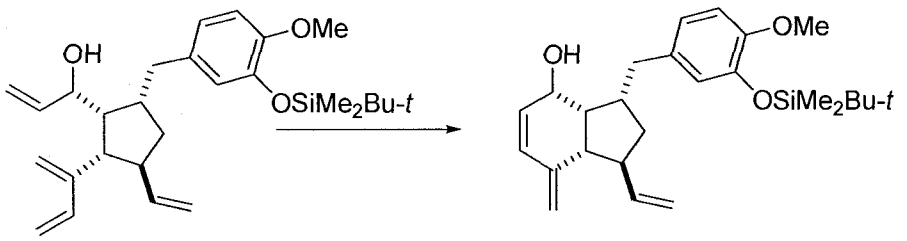
26.4 **27.1**

Vinylmagnesium bromide (1 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **26.4** (77 mg, 0.18 mmol, C(3a),C(7a) *cis*/*trans* = 7/1) in THF (5 mL) and the mixture was stirred for 45 min. Saturated aqueous NH_4Cl (4 mL) and water (3 mL) were added, and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:5 EtOAc-hexane, gave **27.1** as a mixture of two isomers epimeric at the hydroxyl-bearing carbon (major isomer, 41 mg, 50%, minor isomer, 15 mg, 19%). The major isomer had:

$[\alpha]_D$ = -70.8 (*c* 0.40, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3566, 2953, 1512, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3 H), 0.16 (s, 3 H), 1.00 (s, 9 H), 1.44-1.52 (m, 2 H), 1.90 (ddd, *J* = 8.5, 10.0, 13.0 Hz, 1 H), 2.46-2.60 (m, 3 H), 2.80 (dd, *J* = 7.0, 11.0 Hz, 1 H), 2.96 (dd, *J* = 2.8, 12.5 Hz, 1 H), 3.12 (ddd, *J* = 7.5, 10.5, 17.5 Hz, 1 H), 3.77 (s, 3 H), 4.30 (s, 1 H), 4.85 (d, *J* = 10.0 Hz, 1 H), 4.91 (d, *J* = 17.5 Hz, 1 H), 5.09 (t, *J* = 11.5 Hz, 2 H), 5.20 (d, *J* = 19.5 Hz, 2 H), 5.28-5.32 (m, 2 H), 5.66 (ddd, *J* = 7.5, 10.0, 17.5 Hz, 1 H), 6.04 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1 H), 6.43 (dd, *J* = 11.0, 17.5 Hz, 1 H), 6.69-6.76 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.61 (q), -4.58 (q), 18.5 (s), 25.8 (q), 36.8 (t), 37.7 (t), 44.4 (d), 44.4 (d), 50.1 (d), 50.3 (d), 55.6 (q), 72.8 (d), 112.1 (d), 113.2 (t), 113.5 (t), 113.6 (t), 117.0 (t), 121.4 (d), 121.6 (d), 135.0 (s), 140.2 (d), 142.1 (d), 142.8 (d), 144.7 (s), 145.1 (s), 148.9 (s); exact mass *m/z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.29092.

The minor isomer had: $[\alpha]_D$ = -59.5 (*c* 0.30, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3487, 2953, 1511, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.16 (s, 3 H), 1.00 (s, 9 H), 1.44-1.55 (m, 1 H), 1.67 (d, *J* = 4.0 Hz, 1 H), 1.86 (ddd, *J* = 7.0, 8.5, 13.0 Hz, 1 H), 2.35-2.40 (m, 1 H), 2.47-2.53 (m, 2 H), 2.83-2.89 (m, 2 H), 3.01 (td, *J* = 8.5, 18.0 Hz, 1 H), 3.78 (s, 3 H), 4.27 (dd, *J* = 5.5, 11.0 Hz, 1 H), 4.87 (d, *J* = 10.5, 1 H), 4.91 (d, *J* = 17.0 Hz, 1 H), 5.13 (dd, *J* = 9.5, 10.5 Hz, 2 H), 5.24 (d, *J* = 16.5 Hz, 2 H), 5.34-5.40 (m, 2 H), 5.69 (ddd, *J* = 7.5, 10.5, 17.5 Hz, 1 H), 6.01 (ddd, *J* = 6.5, 10.5, 17.5 Hz, 1 H), 6.47 (dd, *J* = 11.0, 17.5 Hz, 1 H), 6.68-6.77 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.61 (q), -4.58 (q), 18.5 (s), 25.8 (q), 35.7 (t), 36.4 (t), 44.3 (d), 46.3 (d), 48.3 (d), 51.0 (d), 55.6 (q), 72.9 (d), 112.1 (d), 113.3 (t), 113.8 (t), 115.5 (t), 117.1 (t), 121.4 (d), 121.7 (d), 134.3 (s), 140.1 (d), 140.5 (d), 142.2 (d), 144.8 (s), 145.8 (s), 149.1 (s); exact mass *m/z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.29129.

(1*S*,3*S*,3a*R*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-ol (27.2).



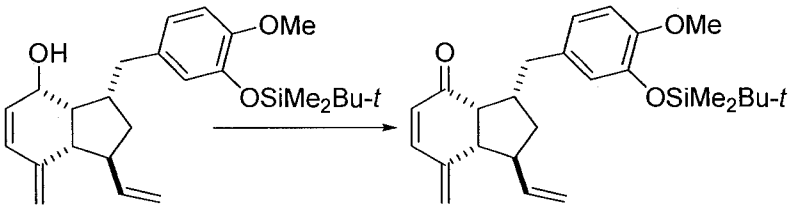
27.1 **27.2**

Ar was bubbled for *ca* 5 min through a stirred solution of **27.1** (major isomer, 30 mg, 0.067 mmol) in CH_2Cl_2 (4 mL), and Grubbs catalyst (first generation, 2.7 mg, 0.0033 mmol) was then added. The mixture was stirred for 24 h and then evaporated. Flash chromatography of the residue over silica gel (1.5 x 12 cm), using 1:5 EtOAc-hexane, gave **27.2** (26 mg, 93%) as a colorless oil: $[\alpha]_D$ = -32.7 (*c* 0.63, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3403, 2929, 1512, 881 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.00 (s, 9 H), 1.37 (d, *J* = 7.0 Hz, 1 H), 1.64 (ddd, *J* = 5.5, 9.0, 14.5 Hz, 1 H), 1.77 (td, *J* = 10.5, 14.0 Hz, 1 H), 2.05 (td, *J* = 5.5, 8.5 Hz, 1 H), 2.24 (ddd, *J* = 6.0, 10.5, 19.0 Hz, 1 H), 2.39 (dd, *J* = 5.5, 10.5 Hz, 1 H), 2.46 (ddd, *J* = 5.5, 10.0, 19.0 Hz, 1 H), 2.61 (dd, *J* = 9.5, 13.5 Hz, 1 H), 3.03 (dd, *J* = 6.0, 14.0 Hz, 1 H), 3.78 (s, 3 H), 4.32 (broad s, 1 H), 4.72 (s, 1 H), 4.79 (d, *J* = 17.0 Hz, 1 H), 4.89 (dd, *J* = 1.5, 10.0 Hz, 1 H), 4.92 (s, 1 H), 5.62 (ddd, *J* = 8.5, 10.5, 17.0 Hz, 1 H), 5.68 (d, *J* = 10.0 Hz, 1 H), 6.10 (dd, *J* = 2.0, 10.0 Hz, 1 H), 6.74-6.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.59 (q), 18.5 (s), 25.8 (q), 35.6 (t), 37.3 (t), 44.6 (d), 47.2 (d), 50.4 (d), 50.9 (d), 55.6 (q), 65.4 (d), 112.2 (d), 113.6 (t), 114.1 (t), 121.4 (d), 121.5 (d), 128.7 (d), 131.5 (d), 134.5 (s), 141.6 (s), 142.0 (d), 144.8 (s), 149.1 (s); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25793.

Ar was bubbled for *ca* 5 min through a stirred solution of alcohol **27.1** (minor isomer, 7.0 mg, 0.015 mmol) in CH_2Cl_2 (2 mL), and Grubbs catalyst (first generation, 0.6 mg, 0.00078 mmol) was then added. The mixture was stirred for 24 h and then evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:10

EtOAc-hexane, gave **27.2** (6.1 mg, 91%) as a colorless oil: $[\alpha]_D$ = 37.0 (*c* 0.20, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3490, 2954, 1511, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.99 (s, 9 H), 1.03 (d, *J* = 6.5 Hz, 1 H), 1.65 (ddd, *J* = 6.0, 10.0, 13.0 Hz, 1 H), 1.98-2.08 (m, 2 H), 2.42-2.51 (m, 2 H), 2.58 (ddd, *J* = 6.5, 10.5, 19.5 Hz, 1 H), 2.85 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.95 (dd, *J* = 8.5, 13.5 Hz, 1 H), 3.78 (s, 3 H), 4.36 (dd, *J* = 5.5, 11.0 Hz, 1 H), 4.84-4.91 (m, 3 H), 5.01 (s, 1 H), 5.70 (ddd, *J* = 9.5, 9.5, 17.0 Hz, 1 H), 5.93 (dd, *J* = 6.0, 9.5 Hz, 1 H), 6.19 (d, *J* = 9.5 Hz, 1 H), 6.74-6.79 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.60 (q), 18.5 (s), 25.8 (q), 36.2 (t), 37.9 (t), 44.6 (d), 45.0 (d), 48.6 (d), 49.9 (d), 55.6 (q), 64.4 (d), 112.1 (d), 113.8 (t), 115.8 (t), 121.4 (d), 121.5 (d), 128.2 (d), 131.5 (d), 135.2 (s), 142.2 (s), 143.7 (d), 144.8 (s), 148.9 (s); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25904.

(1*S*,3*S*,3a*R*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-1,2,3,3a,7,7a-hexahydro-7-methylene-4*H*-inden-4-one (27.3).

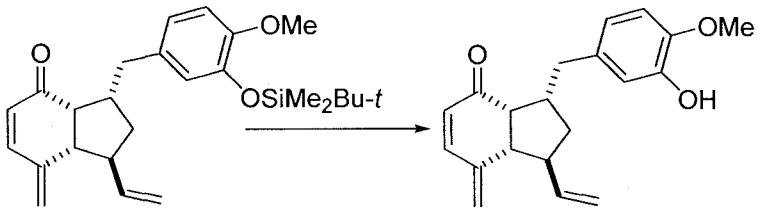


27.2 **27.3**

Dess-Martin periodinane (12 mg, 0.028 mmol) was added to a stirred solution of alcohols **27.2** (10 mg, 0.024 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 1 h, and then saturated aqueous $Na_2S_2O_3$ (1 mL), followed by saturated aqueous $NaHCO_3$ (1 mL) were added. The mixture was stirred for 5 min, diluted with water (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4)

and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:10 EtOAc-hexane, gave **27.3** (9.1 mg, 91%) as an oil: $[\alpha]_D$ = 14.6 (*c* 0.35, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2953, 1666, 1510, 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 0.99 (s, 9 H), 1.51-1.56 (m, 1 H), 1.71 (ddd, *J* = 7.1, 9.1, 13.1 Hz, 1 H), 2.43-2.52 (m, 2 H), 2.62 (td, *J* = 8.2, 16.4 Hz, 1 H), 2.79 (t, *J* = 8.2 Hz, 1 H), 2.86 (dd, *J* = 6.1, 8.2 Hz, 1 H), 3.02 (dd, *J* = 4.7, 12.3 Hz, 1 H), 3.77 (s, 3 H), 4.92-4.98 (m, 2 H), 5.33 (s, 2 H), 5.76 (ddd, *J* = 8.1, 10.1, 17.1 Hz, 1 H), 5.94 (d, *J* = 10.1 Hz, 1 H), 6.70-6.75 (m, 3 H), 6.98 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.61 (q), 18.5 (s), 25.8 (q), 35.6 (t), 35.6 (t), 46.4 (d), 48.4 (d), 49.1 (d), 51.4 (d), 55.6 (q), 112.1 (d), 114.4 (t), 119.9 (t), 121.6 (d), 121.8 (d), 128.3 (d), 134.4 (s), 141.9 (d), 143.1 (s), 144.7 (s), 146.0 (d), 149.1 (s), 200.3 (s); exact mass *m/z* calcd for $C_{26}H_{36}O_3Si$ 424.24338, found 424.24383.

(1*S*,3*S*,3a*R*,7a*S*)-1-Ethenyl-1,2,3,3a,7,7a-hexahydro-3-[(3-hydroxy-4-methoxyphenyl)methyl]-7-methylene-4*H*-inden-4-one (1.1).

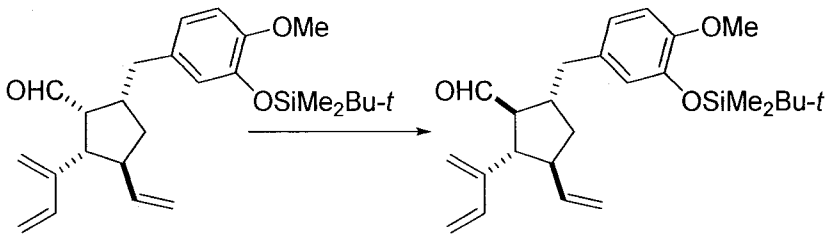


27.3 **1.1**

Bu_4NF (1.0 M in THF, 22 μL, 0.022 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **27.3** (9.1 mg, 0.022 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 5 min, and another portion of Bu_4NF (1.0 M in THF, 1.5 μL, 0.0015 mmol) was added. The mixture was stirred at 0 °C for a further 5 min. Water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over

silica gel (1.5 x 7 cm), using 1:20 EtOAc-CH_2Cl_2, gave **1.1** (5.6 mg, 84%) as a colorless oil: $[\alpha]_D$ = 19.7 (*c* 0.28, $CHCl_3$) [lit.[16,18] $[\alpha]_D$ = 17.3 (*c* 0.55, $CHCl_3$); lit.[15] $[\alpha]_D$ = 19.2 (*c* 0.52, $CHCl_3$)]; FTIR (CH_2Cl_2 cast) 3417, 2917, 1658, 1510, 1273, 1130, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54-1.59 (m, 1 H), 1.73 (ddd, *J* = 7.1, 9.2, 13.5 Hz, 1 H), 2.48-2.53 (m, 2 H), 2.62 (td, *J* = 8.1, 16.4 Hz, 1 H), 2.79 (t, *J* = 8.2 Hz, 1 H), 2.86 (dd, *J* = 5.8, 8.1 Hz, 1 H), 3.03-3.09 (m, 1 H), 3.86 (s, 3 H), 4.92-4.98 (m, 2 H), 5.32 (d, *J* = 4.1 Hz, 2 H), 5.52 (s, 1 H), 5.76 (ddd, *J* = 8.2, 10.0, 16.8 Hz, 1 H), 5.93 (d, *J* = 9.9 Hz, 1 H), 6.68 (dd, *J* = 1.7, 8.2 Hz, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 6.78 (d, *J* = 1.7 Hz, 1 H), 6.98 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.7 (t), 35.9 (t), 46.3 (d), 48.6 (d), 49.0 (d), 51.4 (d), 56.0 (q), 110.5 (d), 114.4 (t), 115.0 (d), 119.9 (t), 120.3 (d), 128.3 (d), 135.1 (s), 141.8 (d), 143.0 (s), 144.7 (s), 145.3 (s), 145.9 (d), 200.3 (s); exact mass *m/z* calcd for $C_{20}H_{22}O_3$ 310.15689, found 310.15721. The compound is acid sensitive and so the solvents for NMR and optical rotation measurements were stored over anhydrous K_2CO_3.

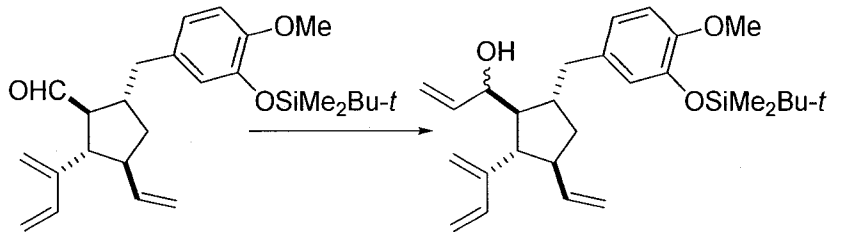
1*S*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxy-phenyl]methyl]-3-ethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanecarbox-aldehyde (28.1).



26.4 **28.1**

DBU (1 drop) was added to a stirred solution of **26.4** (42 mg, 0.099 mmol) in CH_2Cl_2 (7 mL). Stirring was continued until the trans/cis ratio was larger than 10:1 (usually 36 h, ^1H NMR control), and then the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:10 EtOAc-hexane, gave **28.1** (38 mg, 91%), as a yellow oil: $[\alpha]_D$ = -15.3 (*c* 0.30, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2930, 2857, 1722, 1511, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.69-1.82 (m, 2 H), 2.57-2.64 (m, 4 H), 2.69 (td, *J* = 8.5, 17.0 Hz, 1 H), 2.84 (t, *J* = 9.5 Hz, 1 H), 3.77 (s, 3 H), 4.93-4.98 (m, 2 H), 5.06 (d, *J* = 13.5 Hz, 2 H), 5.18 (s, 1 H), 5.30 (d, *J* = 17.5 Hz, 1 H), 5.68 (ddd, *J* = 7.5, 10.0, 17.0 Hz, 1 H), 6.31 (dd, *J* = 11.0, 18.0 Hz, 1 H), 6.67-6.77 (m, 3 H), 9.39 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.65 (q), 18.5 (s), 25.7 (q), 36.9 (t), 40.7 (t), 40.8 (d), 48.3 (d), 49.0 (d), 55.5 (q), 63.4 (d), 112.1 (d), 114.5 (t), 114.5 (t), 115.0 (t), 121.7 (d), 122.1 (d), 132.5 (s), 137.7 (d), 139.9 (d), 144.9 (s), 146.3 (s), 149.5 (s), 202.1 (d); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25882.

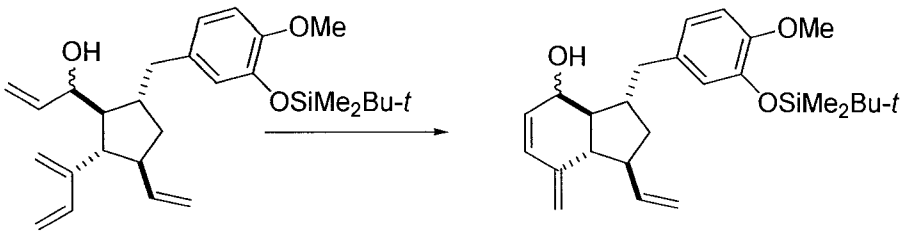
(1*S*,2*S*,3*S*,5*S*)-5-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxy-phenyl]methyl]-α,3-diethenyl-2-(1-methylene-2-propen-1-yl)cyclopentanemethanol (28.2).



28.1 **28.2**

Vinylmagnesium bromide (1 M in THF, 0.20 mL, 0.20 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **28.1** (36 mg, 0.085 mmol) in THF (4 mL). Stirring at 0 °C was continued for 1 h, and saturated aqueous NH_4Cl (4 mL), followed by water (1 mL) were added. The mixture was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:10 EtOAc-hexane, gave **28.2** (34 mg, 88%) as a 5:3 mixture (^{1}H NMR) of two isomers epimeric at the hydroxyl-bearing carbon: $[\alpha]_D$ = -116.3 (*c* 0.25, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3531, 2930, 2857, 1511, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6 H), 1.01 (s, 9 H), 1.46 (broad s, 1 H), 1.53-1.59 (m, 1 H), 1.66-1.67 (m, 1 H), 1.88-1.92 (m, 1 H), 2.16-2.26 (m, 1 H), 2.49-2.56 (m, 3 H), 2.68-2.75 (m, 1 H), 3.78 (s, 3 H), 4.02 (s, 0.5 H), 4.10 (s, 0.5 H), 5.02-5.43 (m, 8 H), 5.61-5.68 (m, 1 H), 5.78-5.86 (m, 1 H), 6.33-6.40 (m, 1 H), 6.68-6.78 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, signals for major isomer) δ -4.61 (q), 18.5 (s), 25.7 (q), 37.0 (t), 39.3 (d), 42.3 (t), 48.9 (d), 51.3 (d), 55.6 (q), 56.5 (d), 73.5 (d), 112.1 (d), 113.9 (t), 114.1 (t), 114.4 (t), 114.8 (t), 121.9 (d), 122.0 (d), 133.9 (s), 138.2 (d), 139.8 (d), 140.5 (d), 144.8 (s), 148.4 (s), 149.2 (s); exact mass *m/z* calcd for $C_{28}H_{42}O_3Si$ 454.29031, found 454.28975.

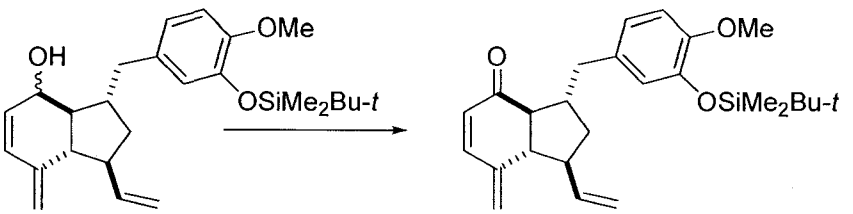
(1*S*,3*S*,3a*S*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-ol (28.3).



28.2 **28.3**

Ar was bubbled for *ca* 10 min through a stirred solution of alcohols **28.2** (25 mg, 0.055 mmol) in CH_2Cl_2 (5 mL), and Grubbs catalyst (first generation, 4.5 mg, 0.0055 mmol) was added. The mixture was stirred for 20 h and then evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 1:6 EtOAc-hexane, gave **28.3** (20 mg, 86%) as a mixture of two isomers epimeric at the hydroxyl-bearing carbon: $[\alpha]_D$ = -132.3 (*c* 0.16, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3397, 2929, 1511, 1270, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major isomer signals) δ 0.15 (s, 6 H), 1.00 (s, 9 H), 1.31 (broad s, 1 H), 1.42-1.51 (m, 1 H), 1.63-1.76 (m, 2 H), 2.09-2.21 (m, 2 H), 2.49 (dd, *J* = 8.8, 13.8 Hz, 1 H), 2.63-2.70 (m, 1 H), 3.01 (dd, *J* = 5.8, 13.8 Hz, 1 H), 3.78 (s, 3 H), 4.28 (s, 1 H), 4.87 (s, 1 H), 4.97 (d, *J* = 10.2 Hz, 1 H), 5.04-5.08 (m, 2 H), 5.64 (d, *J* = 9.7 Hz, 1 H), 5.74-5.83 (m, 1 H), 6.10 (dd, *J* = 1.5, 9.7 Hz, 1 H), 6.71-6.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer signals) δ -4.64 (q), -4.61 (q), 18.5 (s), 25.8 (q), 38.7 (t), 41.4 (t), 43.9 (d), 44.3 (d), 49.5 (d), 55.5 (q), 56.7 (d), 74.6 (d), 110.1 (t), 112.1 (d), 113.8 (t), 121.6 (d), 121.9 (d), 131.4 (d), 133.8 (d), 133.9 (s), 142.9 (d), 144.9 (s), 145.7 (s), 149.3 (s); exact mass *m/z* calcd for $C_{26}H_{38}O_3Si$ 426.25903, found 426.25945.

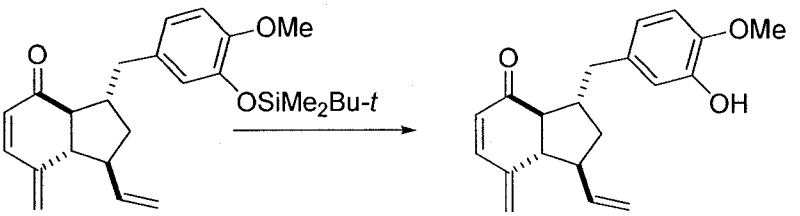
(1*S*,3*S*,3a*S*,7a*S*)-3-[[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methoxyphenyl]methyl]-1-ethenyl-1,2,3,3a,7,7a-hexahydro-7-methylene-4*H*-inden-4-one (28.4).



28.3 **28.4**

Dess-Martin periodinane (29 mg, 0.068 mmol) was added to a stirred solution of **28.3** (mixture of two isomers, 24 mg, 0.056 mmol) in CH_2Cl_2 (4 mL). Stirring was continued for 1 h, and then saturated aqueous $Na_2S_2O_3$ (3 mL), followed by saturated aqueous $NaHCO_3$ (2 mL) were added. The mixture was stirred for 5 min, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 7 cm), using 1:10 EtOAc-hexane, gave **28.4** (22 mg, 93%) as an oil: $[\alpha]_D$ = -248.8 (*c* 0.27, $CHCl_3$); FTIR (CH_2Cl_2 cast) 2952, 2929, 1682, 1511, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.99 (s, 9 H), 1.52-1.62 (m, 1 H), 1.78 (ddd, *J* = 6.8, 9.8, 13.9 Hz, 1 H), 2.27 (dd, *J* = 9.8, 13.9 Hz, 1 H), 2.36 (dd, *J* = 9.8, 13.4 Hz, 1 H), 2.45-2.56 (m, 2 H), 2.70 (td, *J* = 9.0, 18.8 Hz, 1 H), 3.11 (dd, *J* = 3.6, 13.4 Hz, 1 H), 3.78 (s, 3 H), 5.00 (d, *J* = 10.3 Hz, 1 H), 5.08 (d, *J* = 17.5 Hz, 1 H), 5.30 (s, 1 H), 5.44 (s, 1 H), 5.74 (ddd, *J* = 8.1, 10.2, 17.3 Hz, 1 H), 5.94 (d, *J* = 9.7 Hz, 1 H), 6.71-6.75 (m, 3 H), 7.00 (d, *J* = 9.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.61 (q), -4.59 (q), 18.5 (s), 25.8 (q), 36.9 (t), 37.9 (d), 40.3 (t), 44.5 (d), 50.5 (d), 55.6 (q), 58.2 (d), 112.0 (d), 114.6 (t), 117.1 (t), 122.0 (d), 122.2 (d), 128.7 (d), 133.3 (s), 141.6 (d), 144.7 (s), 144.8 (s), 147.5 (d), 149.2 (s), 200.6 (s); exact mass *m/z* calcd for $C_{26}H_{36}O_3Si$ 424.24338, found 424.24366.

(1*S*,3*S*,3a*S*,7a*S*)-1-Ethenyl-1,2,3,3a,7,7a-hexahydro-3-[(3-hydroxy-4-methoxyphenyl)methyl]-7-methylene-4*H*-inden-4-one (1.2).



28.4 **1.2**

Bu_4NF (1.0 M in THF, 34 μL, 0.034 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **28.4** (12 mg, 0.028 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 10 min, water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 7 cm), using 1:4 EtOAc-hexane, gave **1.2** (7.6 mg, 87%) as a colorless solid: mp 141-142 °C [lit.[16,18] 142.2-143.0 °C]; $[\alpha]_D$ = -331.4 (*c* 0.18, $CHCl_3$) [lit.[16,18] -333.0 (*c* 0.18, $CHCl_3$)]; FTIR (CH_2Cl_2 cast) 3431, 2927, 1676, 1511, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (ddd, *J* = 8.1, 10.1, 13.5 Hz, 1 H), 1.79 (ddd, *J* = 6.8, 9.9 , 13.8 Hz, 1 H), 2.27 (dd, *J* = 9.9, 13.9 Hz, 1 H), 2.35 (dd, *J* = 10.1, 13.5 Hz, 1 H), 2.48-2.55 (m, 2 H), 2.70-2.77 (m, 1 H), 3.15 (dd, *J* = 3.7, 13.5 Hz, 1 H), 3.86 (s, 3 H), 5.00 (dd, *J* = 1.2, 10.2 Hz, 1 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 5.30 (s, 1 H), 5.45 (s, 1 H), 5.53 (s, 1 H), 5.74 (ddd, *J* = 8.1, 10.2, 17.1 Hz, 1 H), 5.95 (d, *J* = 9.7 Hz, 1 H), 6.69 (dd, *J* = 2.0, 8.2 Hz, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.81 (d, *J* = 2.0 Hz, 1 H), 7.00 (d, *J* = 9.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.0 (t), 37.9 (d), 40.6 (t), 44.5 (d), 50.5 (d), 56.0 (q), 58.3 (d), 110.5 (d), 114.6 (t), 115.4 (d), 117.1 (t), 120.5 (d), 128.7 (d), 134.2 (s), 141.6 (d), 144.8 (s), 144.8 (s), 145.3 (s), 147.6 (d), 200.6 (s); exact mass *m/z* calcd for $C_{20}H_{22}O_3$ 310.15689, found 310.15659.

5 REFERENCES AND FOOTNOTES

1 Ayyad, S.-E. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. *J. Org. Chem.* **1998**, *63*, 8102.

2 Leboul, J.; Provost, J. WO 96/00205.

3 Cook, C. D. K.; Symoens, J.-J.; Urmi-König, K. *Aquatic Botany* **1984**, *18*, 263.

4 Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Mol. Pharmacol.* **2000**, *57*, 553. This publication identifies what is here called ottelione A as substance PRP112378.

5 Mehta, G.; Islam, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2396.

6 Lewis, H. J. Ph.D. Dissertation, University of Minnesota, Minnesota, 2005 (*Diss. Abstr. Int. B* **2005**, *66*, 2073).

7 (a) Scully, S. L.; Ghose, S.; Marine, S.; Islam, K.; Hoye, T. R.; Mehta, G.; Sreerama, L. "Abstracts of Papers", 233rd ACS National Meeting, Chicago, IL, March 25-29, 2007, CHED-1052. (b) Dechaine, J. L.; Lewis, H. J.; Ayyad, S.-E. N.; Hoye, T. R.; Sreerama, L. "Abstracts of Papers", 225th ACS National Meeting, New Orleans, LA, March 23-27, 2003, CHED-959.

8 Li, H.; Li, H.; Qu, X.; Zhao, D.; Shi, Y.; Guo, L.; Yuan, Z. *Zhongguo Zhongyao Zazhi* (*Chin. J. Chin. Mat. Med.* **1995**, *20*(2), 115-6, 128. (*Chem. Abstr.* 95298204).

9 The dienone system of the otteliones is very rare: for examples, see: (a) Birch, A. J. *Proc. R. Soc. N. S. W.* **1949**, *83*, 245. (b) Jung, M. E.; Rayle, H. L. *Synth. Commun.* **1994**, *24*, 197. (c) Murray, D. F.; Baum, M. W.; Jones, M., Jr. *J. Org. Chem.* **1986**, *51*, 1.

10 Dienone **2.2** undergoes both 1,4- and 1,6-addition with cuprates: Wild, H. *J. Org. Chem.* **1994**, *59*, 2748.

11 For other synthetic work, see: (a) Hanson, G. H.; Hoye, T. R.; Burke, S. D. "Abstracts of Papers", 234th ACS National Meeting, Boston, MA, August 19-23,

2007, AEI-092. (b) Kabrhel, J. E. Ph.D. Dissertation, University of Minnesota, Minnesota, 2006 (*Diss. Abstr. Int. B* 2007, *67*, 4425); (c) reference 7b. (d) Judd, A. S. Ph.D. Dissertation, University of Minnesota, Minnesota, 1999 (*Diss. Abstr. Int. B* **2000**, *60*, 5522). (e) reference 6. (f) Trembleau, L.; Patiny, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 6377. (g) Hoye, T. R.; Lewis, H. J.; Ayyad, S.-E. N.; Hans, J. J. "Abstracts of Papers", 224th National Meeting of the American Chemical Society, Boston, MA, Aug 18-22, 2002, ORGN-854.

12 Mehta, G.; Srinivasa Reddy, D. *Chem. Commun.* **1999**, 2193.

13 Mehta, G,; Islam, K. *Synlett* **2000**, 1473.

14 Mehta, G.; Islam. K. *Org. Lett.* **2002**, *4*, 2881.

15 Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 6733.

16 Araki, H.; Inoue, M.; Katoh, T. *Org. Lett.* **2003**, *5*, 3903.

17 Araki, H.; Inoue, M; Katoh, T. *Synlett* **2003**, 2401.

18 Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. *Chem. Eur. J.* **2007**, *13*, 9866.

19 Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.

20 See footnote 18 in reference 16.

21 Clive, D. L. J.; Fletcher, S. P. J. Chem. Soc., *Chem. Commun.* **2002**, 1940.

22 Clive, D. L. J.; Liu, D. *Tetrahedron Lett.* **2005**, 46, 5305

23 (a) Brown, P. A.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans 1* **1986**, 1129. (b) Brown, P. A.; Jenkins, P. R. *Tetrahedron Lett.* **1982**, *23*, 3733. (c) *cf.* Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

24 Cusak, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157.

25 Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

26 Kozikowski, A. P.; Tückmantel, W. *J. Org. Chem.* **1991**, *56*, 2826.

27 (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett. 1985*, **26**, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

28 Kende, A. S.; Jungheim, L. N. *Tetrahedron Lett. 1980*, **21**, 3849.

29 Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

30 Pettit, G. R.; Singh, S. B.; Cragg, G. M. *J. Org. Chem.* **1985**, *50*, 3404.

31 Sing, S. B.; Pettit, G. R. *J. Org. Chem.* **1989**, *54*, 4105.

32 *Cf.* Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110.

33 (a) Harispe, M.; Méa, D.; Horeau, A.; Jacques, *J. Bull. Soc. Chim. Fr.* **1963**, 472. (b) Varech, D.; Jacques, *J. Bull. Soc. Chim. Fr.* **1969**, 3505. (c) Sprung, I.; Anhalt, K.; Wahren, U.; Schulze, K. *Monatsh. Chem.* **1999**, *130*, 341.

34 *Cf.* Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *47*, 10807.

35 Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

36 (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109. (b) *cf* Cacchi, S.; Ciatinni, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931.

37 Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1247.

38 Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV)-dichloride.

39 Clive, D. L. J.; Liu, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 3738.

40 Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393.

41 Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754.

42 Liu, D.; Caperelli, C. A. *Synthesis* **1991**, 933.

43 Mariën, C. L.; Esmans, E. L.; Lemière, F.; Dommisse, R. A. *Synth. Commun.* **1997**, *27*, 205.

44 (a) Domínguez, C.; Ezquerra, J.; Prieto, L.; Espada, M.; Pedregal, C. *Tetrahedron Asymmetry* **1997**, *8*, 511. (b) Collado, I.; Domínguez, C.; Ezquerra, J.; Pedregal, C.; Monn, J. A. *Tetrahedron Lett.* **1997**, *38*, 2133.

45 Williams, J. D.; Kamath, V. P.; Morris, P. E. *Org. Synth.* **2005**, *82*, 75.

46 Sano, H.; Sugai, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1143.

47 (a) Smith, A. B.; Han, Q.; Breslin, P. A. S.; Beuchamp, G. K. *Org. Lett.* **2005**, *7*, 5075. (b) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993.

48 Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853.

49 (a) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849. (b) Palmer, A. M.; Jäger, V. Eur. *J. Org. Chem.* **2001**, *66*, 1293.

50 Kalwinch, I.; Metten, K.-H.; Brückner, R. *Heterocycles* **1995**, *40*, 939.

51 Orfanopoulos, M.; Smonou, I. *Synth. Commun.* **1988**, *18*, 833.

52 (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

53 For related opening of cyclopropyl ketones, see: (a) Beerli, R.; Brunner, E. J.; Borschberg, H.-J. *Tetrahedron Lett.* **1992**, *33*, 6449. (b) Nivlet, A.; Le Guen, V.; Dechoux, L.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 2115.

54 (a) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044. (b) Shea, K. J.; Pham, P. Q. *Tetrahedron Lett.* **1983**, *24*, 1003.

55 Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.

56 Clive, D. L. J.; Farina, V.; Beaulieu, P. L. *J. Chem. Soc., Chem. Commun.* **1981**, 643.

57 Moher, E. D. *Tetrahedron Lett.* **1996**, *37*, 8637.

58 Cottrell, L.; Golding, B. T.; Munter, T.; Watson, W. P. *Chem. Res. Toxicol.* **2001**, *14*, 1552.

Chapter 3

Synthesis of Halichlorine

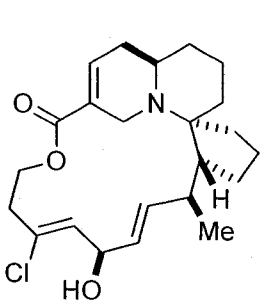
1 INTRODUCTION

1.1 General

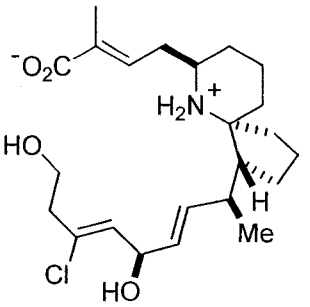
In 1996 Uemura and co-workers reported the isolation and structural characterization of two novel alkaloids.[1,2] Halichlorine (**1.1**),[1] which was isolated from the black marine sponge *Halichondria okadai* Kadota collected in Japanese waters, was found to inhibit the expression of VCAM-1 (vascular cell adhesion molecule-1) with an IC_{50} of 7 μg/mL. VCAM-1 is a member of the immunoglobulin superfamily[3] expressed on the surface of endothelium cells. It is induced by various inflammatory stimuli, and mediates leukocyte-endothelial cell adhesion and signal transduction. However, when the stimulus cannot be properly eliminated, this beneficial response can lead to a chronic and detrimental inflammatory process.[4] Therefore the regulation of leukocyte infiltration by inhibition of VCAM-1 is expected to have therapeutic potential in treating various inflammatory disorders and autoimmune diseases.[5] It has also been found that the adhesive function of VCAM-1 is used by cancer cells in the metastatic process.[6]

Halichlorine is crystalline and was isolated in 3.5×10^{-7} % yield, corresponding to 70.8 mg from 200 kg of wet sponge. The structure[1] was assigned on the basis of extensive spectroscopic measurements, but the absolute configuration was established by the results of a partial degradation,[7] and subsequently confirmed by the Danishefsky[8] synthesis.

Pinnaic acid (**1.2**)[2], whose structure clearly resembles that of halichlorine, was isolated from an Okinawan bivalve *Pinna muricata* in very small amount (1 mg from 10 kg of the bivalves). Pinnaic acid was found to inhibit a cytosolic phospholipase $cPLA_2$ with an IC_{50} of 0.2 μM.



1.1



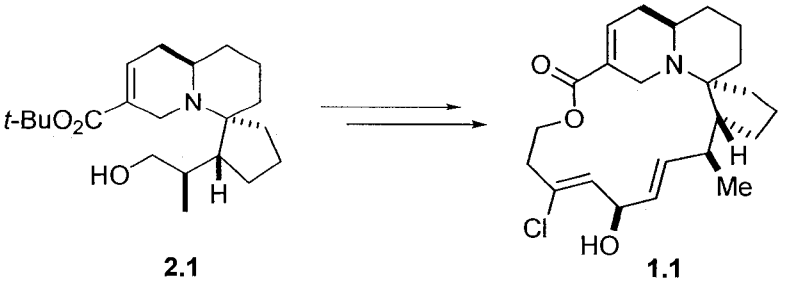
1.2

Scheme 1

Halichlorine has attracted considerable attention in the synthetic community due to its intriguing structure and biological activities. A large number of groups have published their respective approaches, including two total syntheses. Most of those synthetic efforts have been extensively covered in a specific review.[9] and only the two total syntheses and the most recent synthetic effects will be discussed in the following sections.

1.2 Reported Total Syntheses of Halichlorine

The first total synthesis of (+)-halichlorine was reported from Danishefsky's laboratory[8] in 1999. Following that report work on formal total synthesis aimed at the key intermediate **2.1** used in Danishefsky synthesis has been described. In 2004 a total synthesis of (±)-halichlorine was reported by Christie and Heathcock.[10]



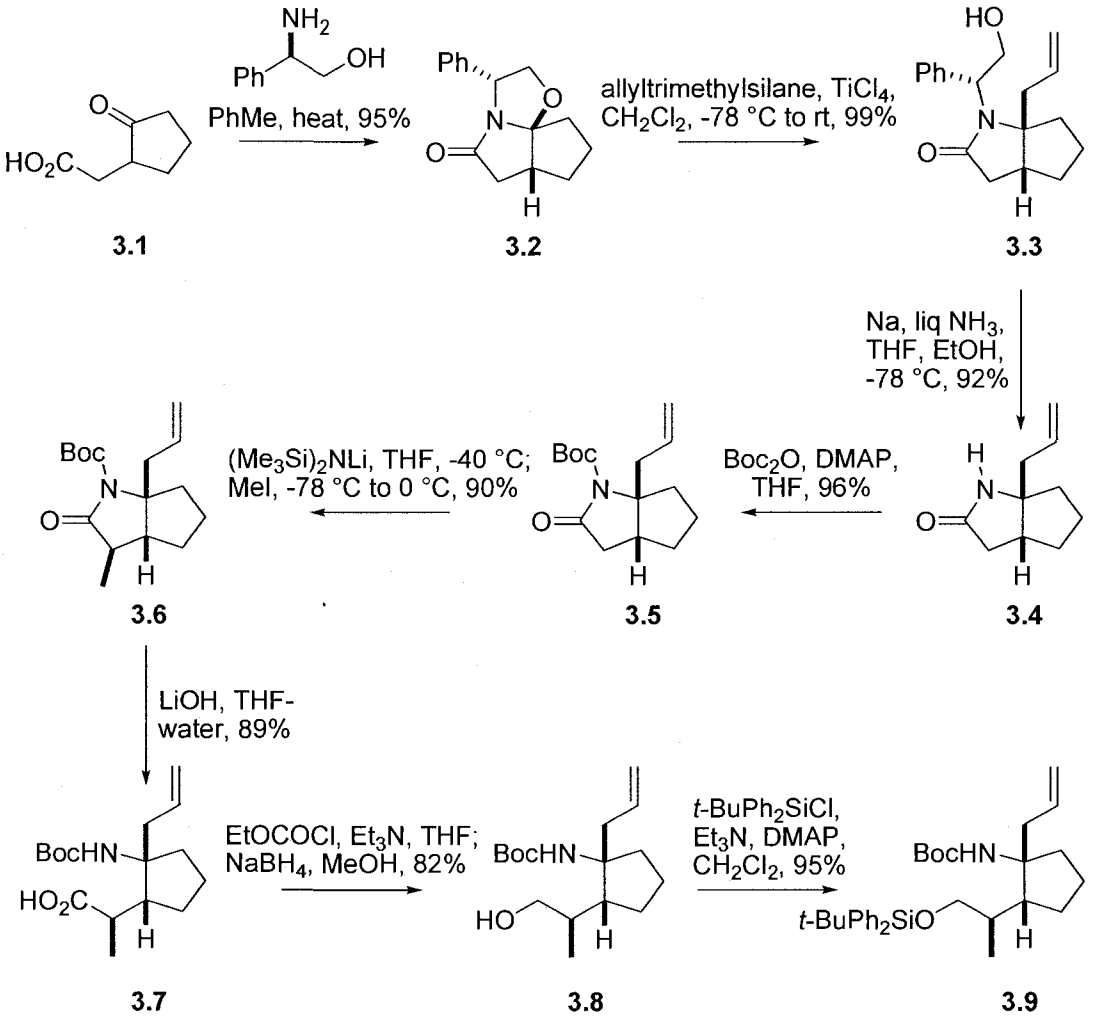
2.1 **1.1**

Scheme 2

1.2.1 Studies in Danishefsky's Laboratory[8, 11]

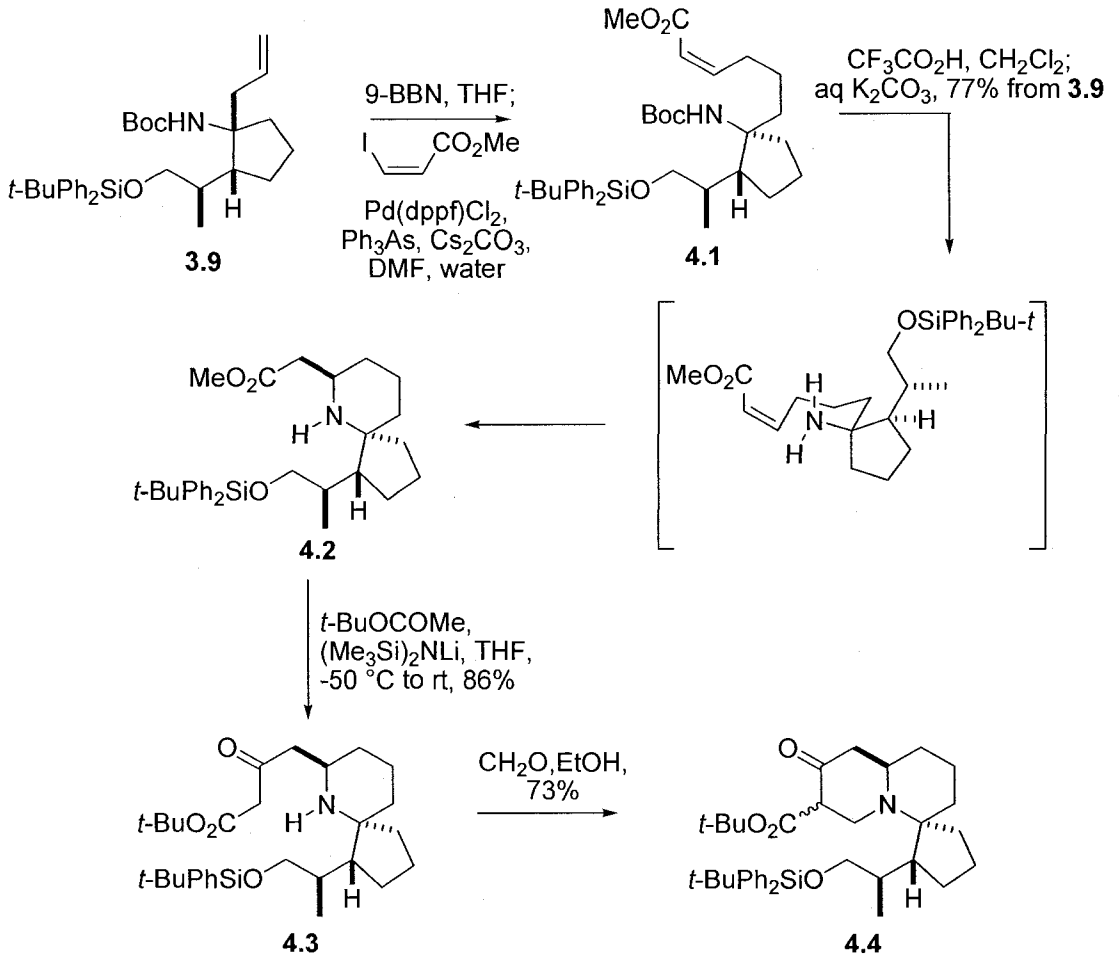
The first report in the halichlorine field from the Danishefsky laboratory[11] described an asymmetric synthesis of the spiroquinazoline core (Scheme 3). Their synthesis started with the known "Meyers-lactam"[12] **3.2**, which was prepared from racemic carboxylic acid **3.1** and D-(-)-phenylglycinol. Treatment of **3.2** with excess allyltrimethylsilane in the presence of titanium tetrachloride furnished lactam **3.3** in virtually quantitative yield. Following reductive debenzylation and protection of the nitrogen atom (**3.3** → **3.5**), the resulting bicyclic lactam **3.5** was methylated stereoselectively from the convex face (**3.5** → **3.6**). Reduction of **3.6** to the desired primary alcohol **3.8** could not be done directly, but was accomplished by hydrolysis to an acid which was then activated as the mixed anhydride and reduced with sodium borohydride. At this point the resulting primary hydroxyl was protected by silylation (**3.8** → **3.9**).

The allylic side chain was now elongated (**3.9** → **4.2**) by hydroboration and Suzuki coupling of the resulting borane with methyl *Z*-3-iodoacrylate. When the nitrogen was deprotected by the action of CF_3CO_2H, followed by neutralization with K_2CO_3, spontaneous intramolecular Michael addition occurred, to afford the spirotricycle **4.2** in good overall yield (77% from **3.9**). A two-carbon chain extension of **4.2** through a crossed Claisen condensation, followed by a Mannich closure with formaldehyde, gave **4.4** as a mixture of diastereoisomers.



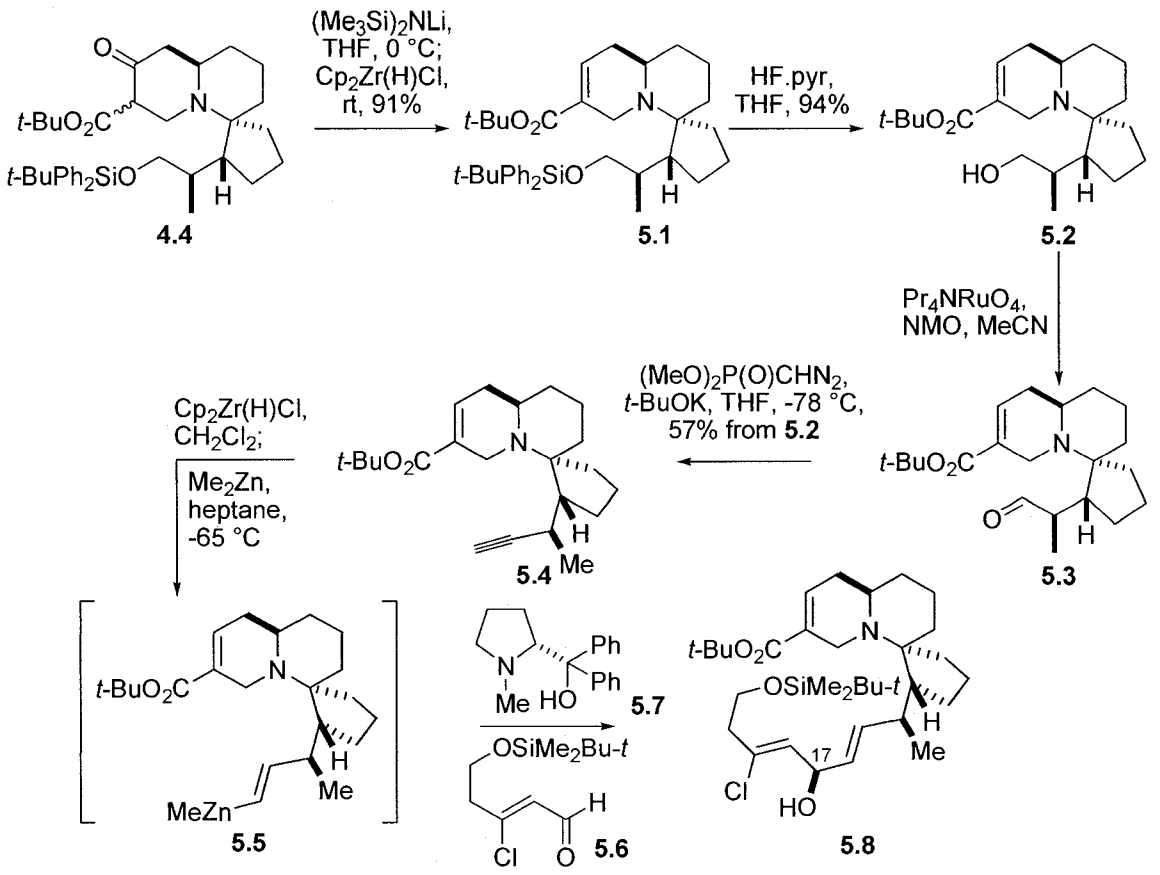
Scheme 3

Desaturation of **4.4** was achieved by formation of an enolate and reaction with $Cp_2Zr(H)Cl$[13] to give **5.1**. Desilylation gave alcohol **5.2**, which was then oxidized to the corresponding aldehyde **5.3**. This seemingly simple oxidation step required extensive effort, and was eventually achieved by use of Pr_4NRuO_4 in the presence of an excess of NMO.



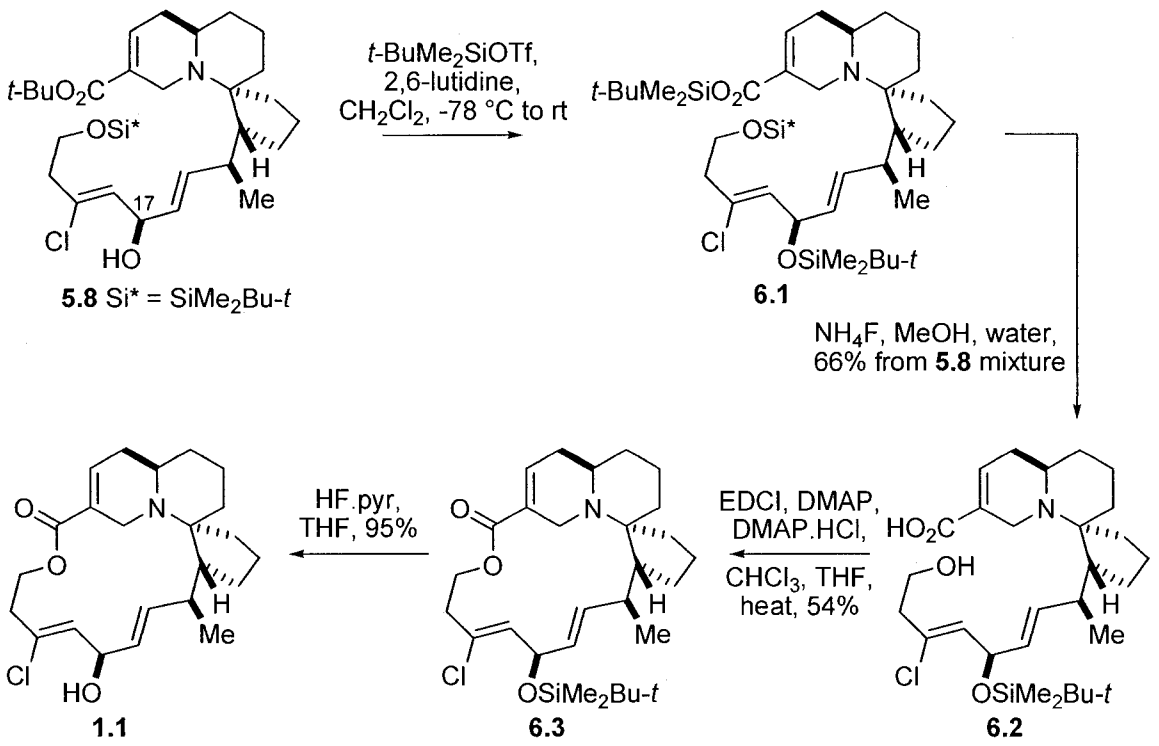
Scheme 4

Homologation of the aldehyde moiety of **5.4** could be done by using the Gilbert reagent (**5.3** → **5.4**), though all attempts to conduct variations of the Horner-Wadsworth-Emmons methodology with **5.3** were unsuccessful. The terminal alkyne was subjected to hydrozirconation and metal exchange with Me_2Zn (**5.4** → **5.5**). The resulting zinc species coupled smoothly with aldehyde **5.6**[14] in the presence of the optically pure amino alcohol **5.7**,[15] to afford a 4:1 mixture of the desired 17*R* epimer **5.8** and the corresponding 17*S* epimer, which is not shown. In the absence of a chiral additive, a 1:1 ratio of the 17*R* and 17*S* isomers was obtained.



Scheme 5

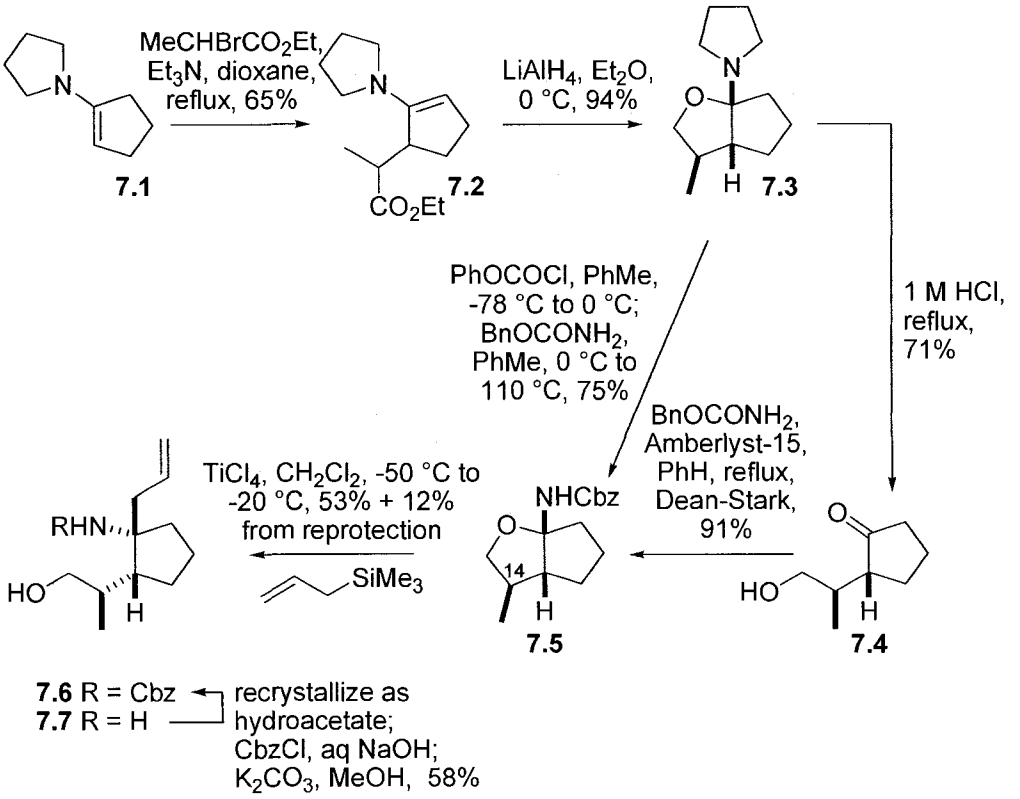
Treatment of **5.8** with *t*-BuMe$_2$SiOSO$_2$CF$_3$ generated the corresponding silyl ester of the carboxylic acid, while the secondary hydroxyl at C(17) was also protected as a silyl ether. Exposure of **6.1** to ammonium fluoride in aqueous methanol cleaved the silyl groups from the carboxyl and primary alcohol, but left the secondary silyl ether intact (**6.1** → **6.2**). At this point, macrolactonization under Keck conditions[16] and separation of the C(17) epimers gave **6.3**. The total synthesis was completed by deprotection with HF/pyridine to afford synthetic (+)-halichlorine **1.1**.



Scheme 6

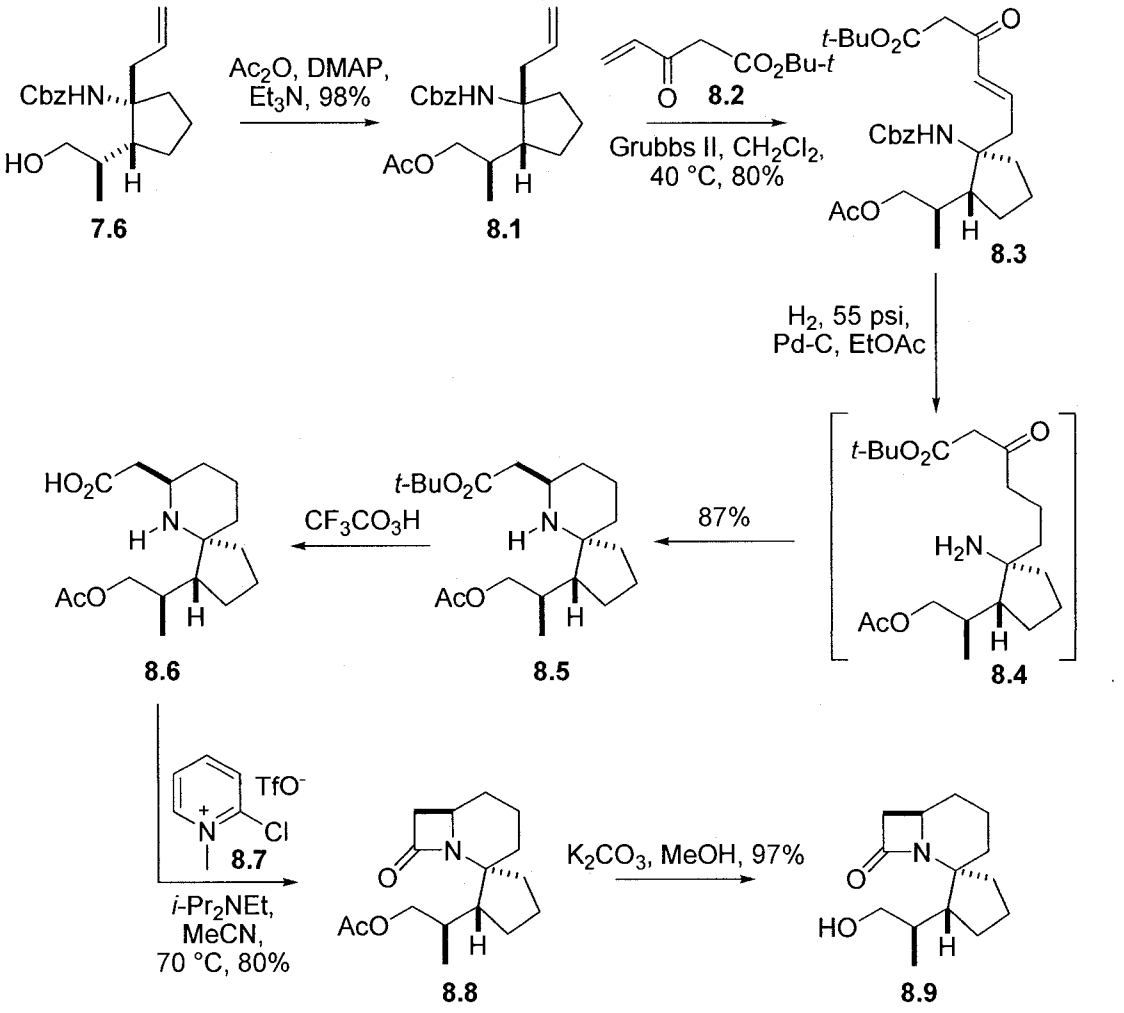
1.2.2 Studies in Heathcock's Laboratory[10]

The synthetic route reported by Christie and Heathcock began (Scheme 7) with the preparation of the keto alcohol **7.4** as a 2:1 mixture of diastereoisomers, according to a published procedure[17] (**7.1** → **7.4**). Condensation of this mixture of diastereomeric keto-alcohols with benzyl carbamate provided the *cis*-fused bicyclic carbamates **7.5**, epimeric at C(14), in a 6:1 ratio. The major epimer has the methyl substituent *exo* at C(14), as shown. The intermediate **7.3** can be converted directly into **7.5** by successive reaction with PhOCOCl and $BnOCONH_2$. Addition of a solution of carbamate **7.5** to a mixture of allyltrimethylsilane and $TiCl_4$ provided alcohol **7.6** as the major product. The by-product amino alcohol **7.7** was converted into alcohol **7.6** by acylation with excess benzyl chloroformate followed by hydrolysis of the carbonate group that was formed.



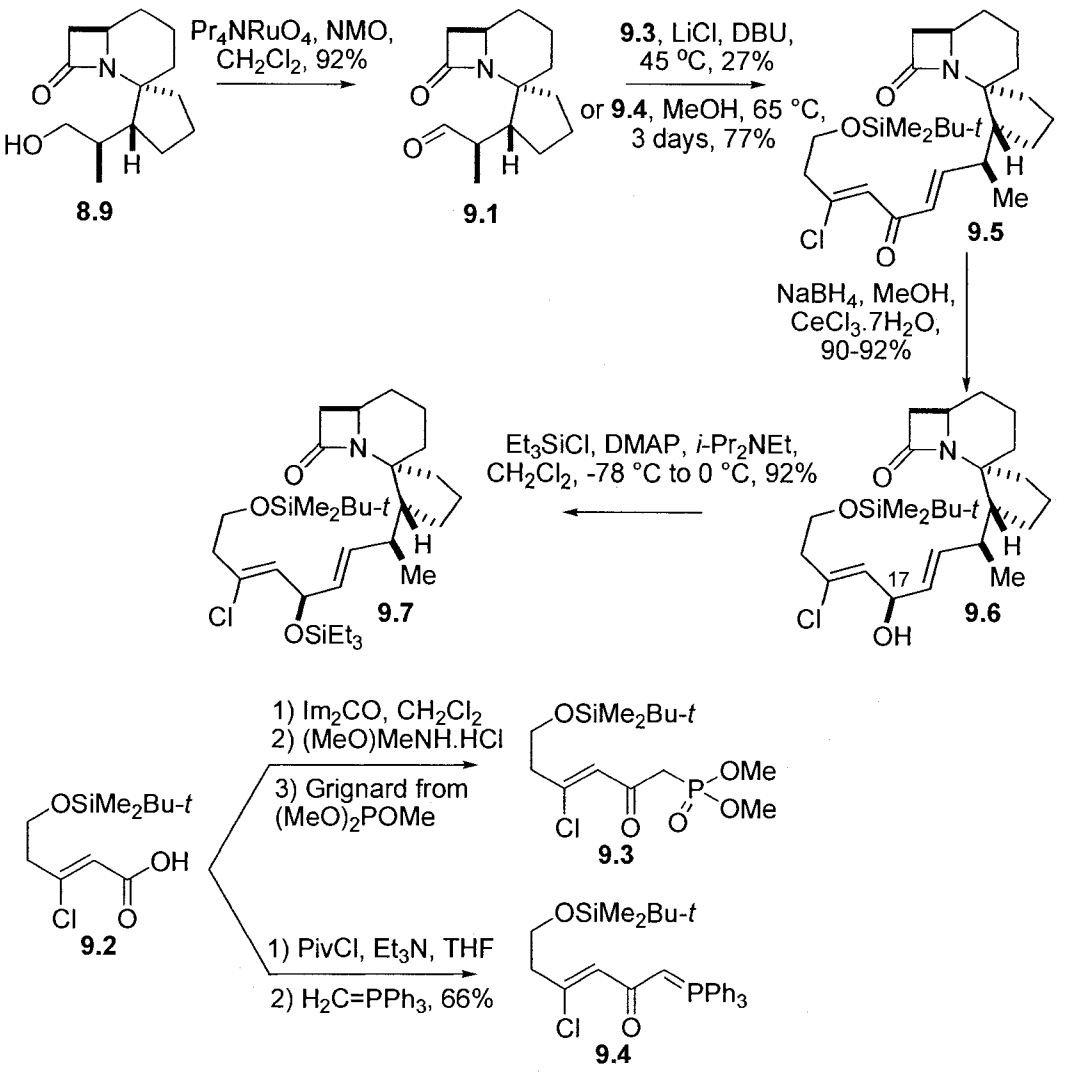
Scheme 7

After acetylation of the primary hydroxyl group in **7.6**, allyl derivative **8.1** was subjected to olefin cross metathesis with Nazarov ester **8.2** and Grubbs' second-generation metathesis catalyst to efficiently produce the *E*-olefin **8.3**. Hydrogenation of the double bond and removal of the nitrogen protecting group using a palladium catalyst produced the amino ketone **8.4**, and this underwent spontaneous cyclization to **8.5**, which was obtained as a single isomer. Due to the predictable difficulty in protection of the hindered proximal nitrogen in **8.5**, it was decided to use a β-lactam group for simultaneous protection of the nitrogen atom and the C(5) side chain. To this end, amino ester **8.5** was converted to the corresponding amino acid with trifluoroacetic acid, and then treatment with the modified Mukaiyama reagent **8.7**[18] gave the β-lactam **8.8** in good yield. Acetate cleavage produced alcohol **8.9**, whose structure was confirmed by single-crystal X-ray analysis.



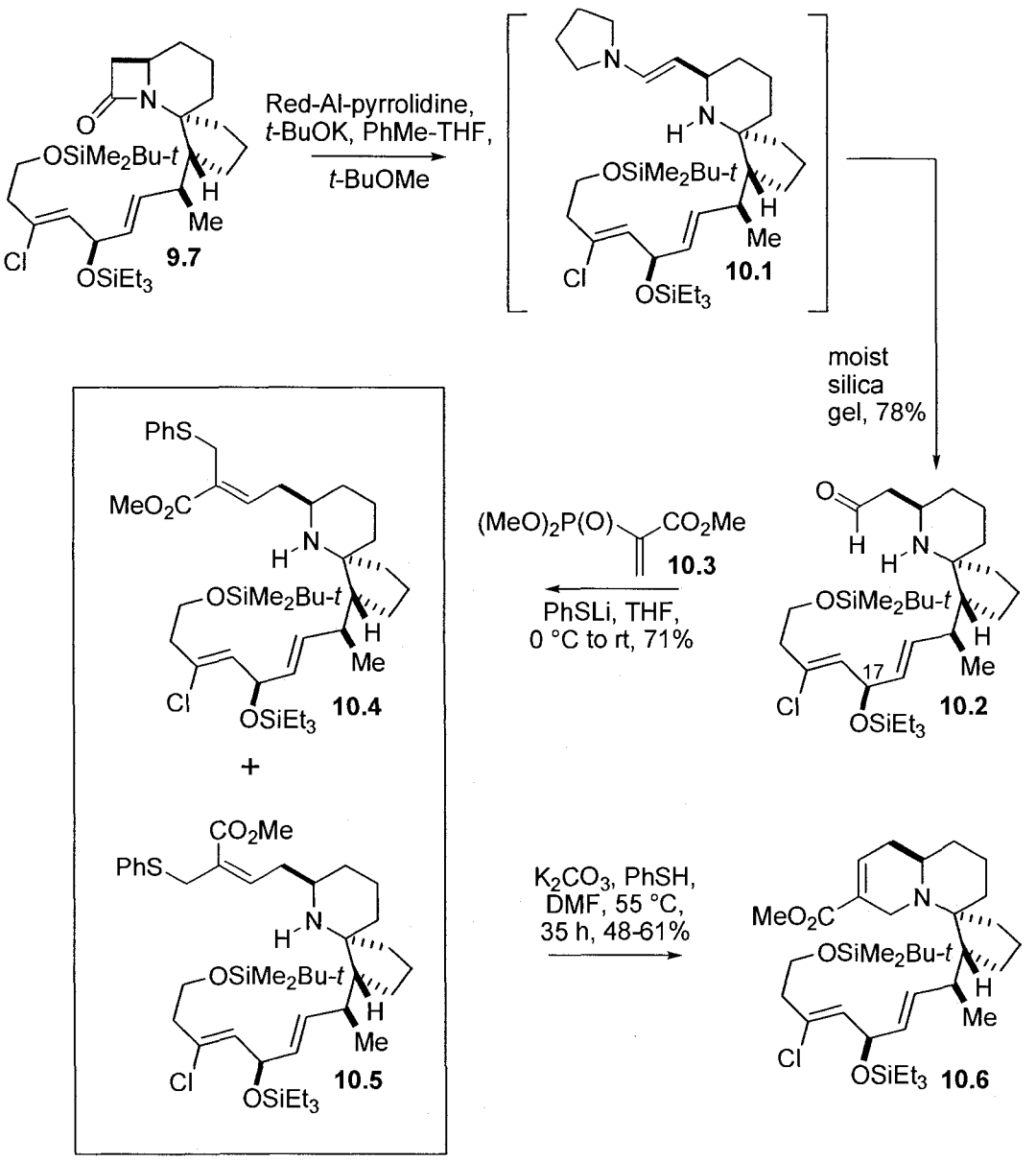
Scheme 8

Oxidation of alcohol **8.9** with Pr_4NRuO_4 and NMO gave the corresponding aldehyde **9.1**. Attempted Horner-Wadsworth-Emmons reaction of aldehyde **9.1** with known phosphonate[14] **9.3** produced the desired dienone **9.5** in ~25% yield. By switching to phosphorane **9.4** which, like phosphonate **9.3**, was prepared from **9.2**, the yield of dienone **9.5** was improved to 77%. Reduction of the ketone group in **9.5** could be achieved under Luche's conditions to give a 5:2 mixture favoring the desired diastereomer **9.6**. (*S*)-Alpine-Hydride was found to favor the undesired isomer in a ratio of ca 2:1. Silylation using Et_3SiCl with Hünig's base gave compound **9.7**.



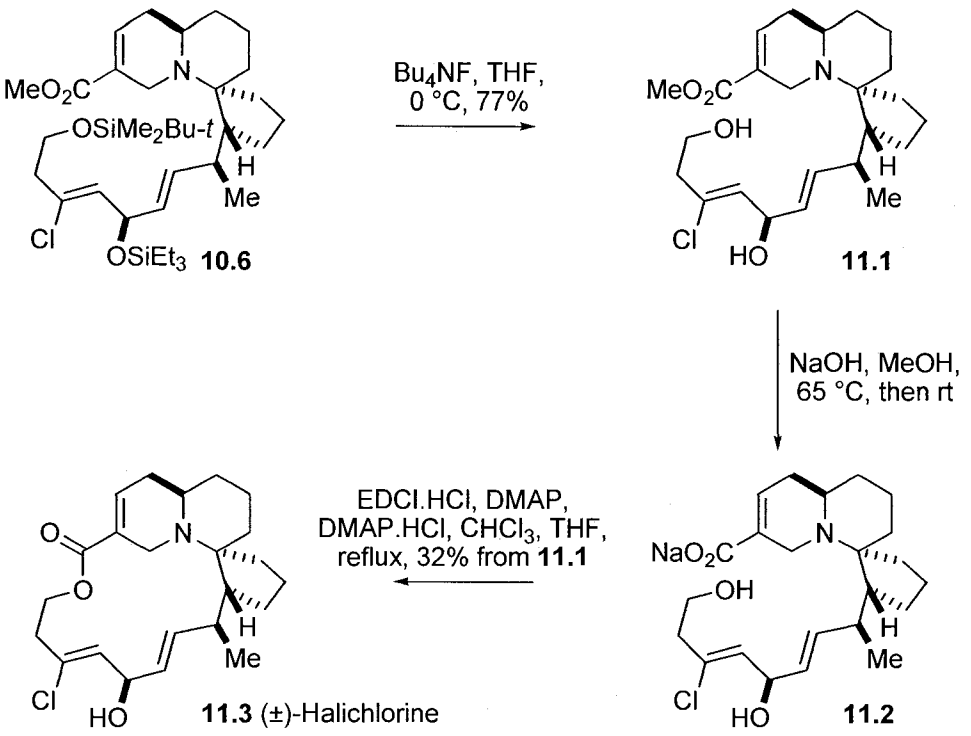
Scheme 9

The next task was to convert the β-lactam into amino aldehyde **10.2**, and the most effective reagent for this transformation was found to be Red-Al modified by treatment with pyrrolidine and *t*-BuOK.[18] Enamine **10.1** was believed to be the intermediate, which readily decomposed to **10.2** on contact with silica gel. The aldehyde **10.2** was then converted to a mixture of the two thioethers **10.4** and **10.5** by reaction with trimethyl phosphonoacrylate **10.3** and PhSLi. Upon heating with PhSH and K_2CO_3, the mixture of **10.4** and **10.5** gave directly the hexahydroquinolizine **10.6**.



Scheme 10

The silicon protecting groups in **10.6** were then cleaved with Bu_4NF, and saponification of the ester **11.1** gave the sodium salt **11.2**. The final step — the formation of the macrolactone — was achieved in 32% yield by use of the EDCI·HCl, DMAP-DMAP·HCl combination[16]. The racemic halichlorine **11.3** was crystalline, and the first X-ray crystal structure of the alkaloid was obtained.

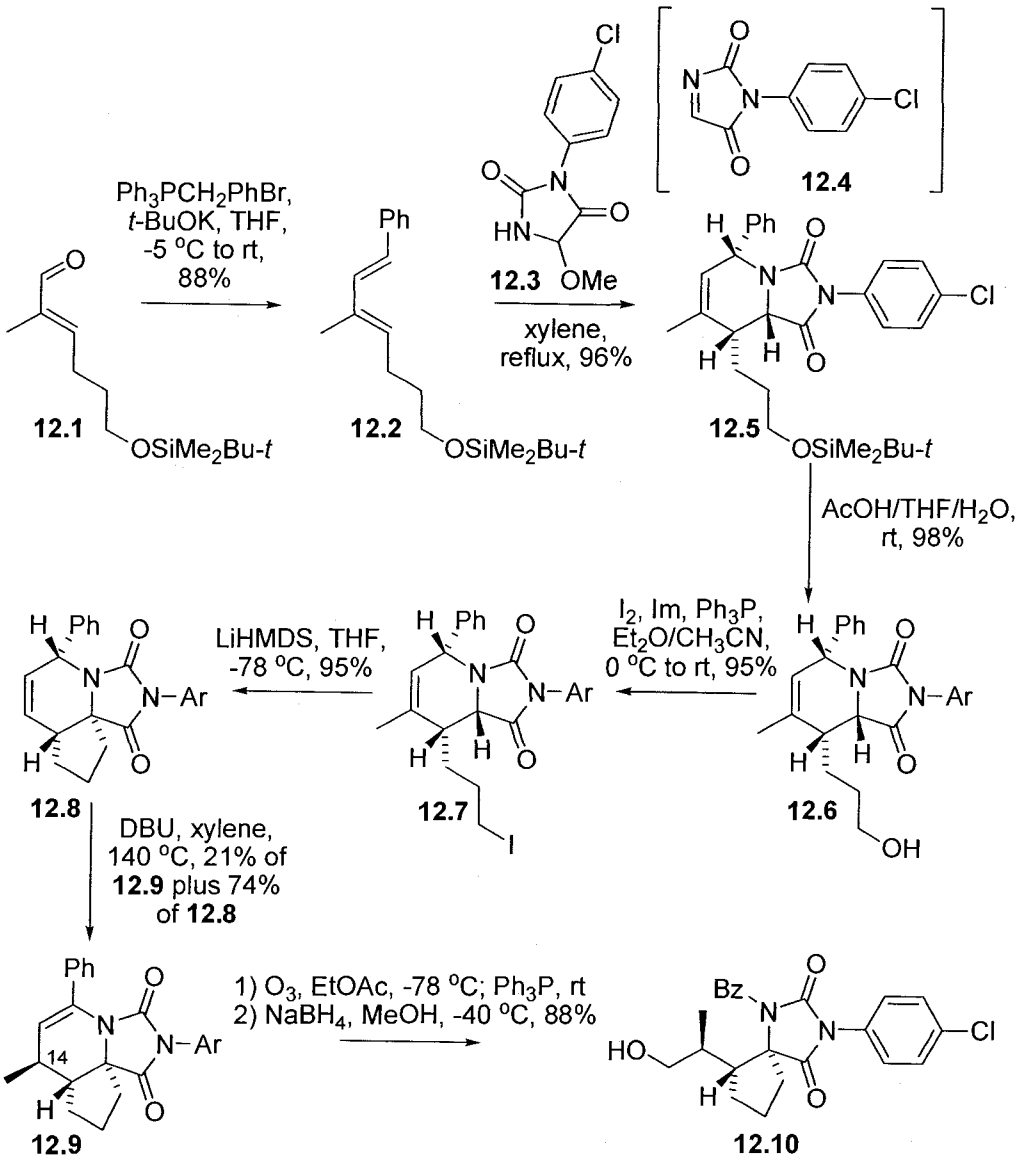


Scheme 11

1.3 Recent Synthetic Studies on Halichlorine

1.3.1 Studies in Kim's Laboratory

Kim and coworkers reported a new approach to cyclic α,α-disubstituted α-amino acid derivatives based on a hetero Dies-Alder reaction.[19] The known heterodienophile **12.4**, which was generated *in situ* from 3-(4-chlorophenyl)-5-methoxyhydantoin (**12.3**), reacted with diene **12.2** to give the desired Dies-Alder adduct **12.5** in excellent yield (96%). After desilylation and iodination under standard conditions, iodide **12.7** was treated with LiHMDS at -78 °C to afford the *cis*-fused tricyclic hydantoin **12.8**. Isomerization of the double bond in **12.8** was performed using DBU in xylene at 140 °C to give 21% of **12.9** plus 74% of starting material **12.8**. Unfortunately the configuration at C(14) in **12.9** was opposite to that of halichlorine. Finally olefin **12.9** was converted to spirobicycle **12.10** by ozonolysis and reduction.

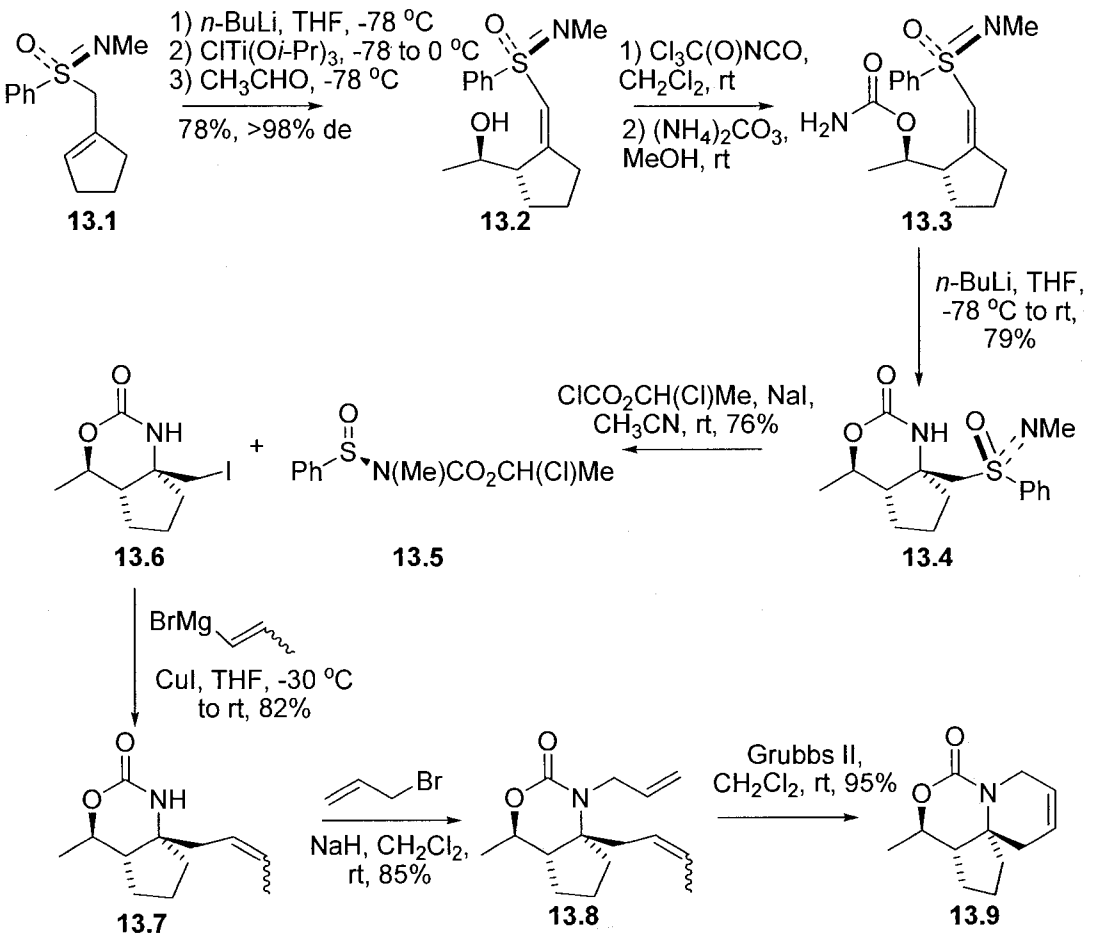


Scheme 12

Although the above method represents an approach to spirocycles considerable development would be needed for application to halichlorine.

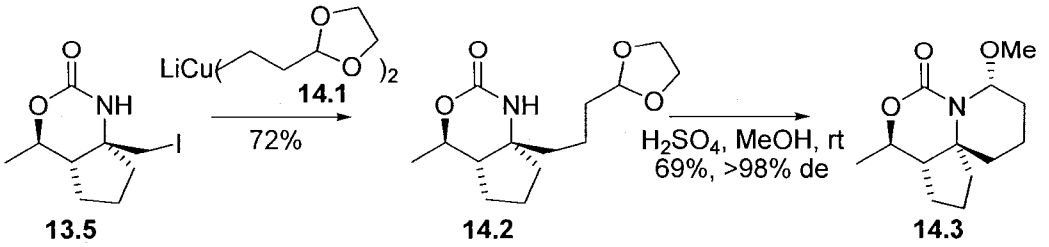
1.3.2 Studies in Gais's Laboratory

Gais and coworkers reported a modular asymmetric synthesis of several azaspirocycles based on the sulfoximine auxiliary.[20] In principle, this approach could be applied to the synthesis of natural products like halichlorine. Lithiation of the *R*-configured cyclic allylic sulfoximine **13.1**, followed by the treatment with $ClTi(OPr\text{-}i)_3$, furnished the corresponding titanium complex, which reacted with acetaldehyde to give homoallylic alcohol **13.2** with high regioselectivity (>98%). Treatment of alcohol **13.2** with trichloroacetyl isocyanate and subsequent hydrolysis of the corresponding *N*-trichloroacetyl carbamate furnished carbamate **13.3**. The crude carbamate was treated with *n*-BuLi to give oxazinone **13.4**. The next task was to remove the chiral sulfoximine, which was accomplished by treatment with $ClCO_2CH(Cl)Me$ in the presence of NaI to give sulfinamide **13.5** and iodide **13.6**. The reaction of iodide **13.6** with 1-propenylmagnesium bromide in the presence of CuI furnished alkene **13.7**. Attachment of an unsaturated substituent at the N atom was accomplished upon treatment of carbamate **13.7** with allyl bromide to give diene **13.8**. Finally ring closing metathesis furnished the azaspirocycle **13.9** in high yield (95%).



Scheme 13

It is also possible to access azaspirocycles with a functional group at the α-position by modifying the above approach. To this end, iodide **13.5** was treated with functionalized cuprate **14.1** to give acetal **14.2**. This was treated with H_2SO_4 in methanol to furnish the tricyclic acetal **14.3** with a 6-azaspiro[4,5]decane skeleton.



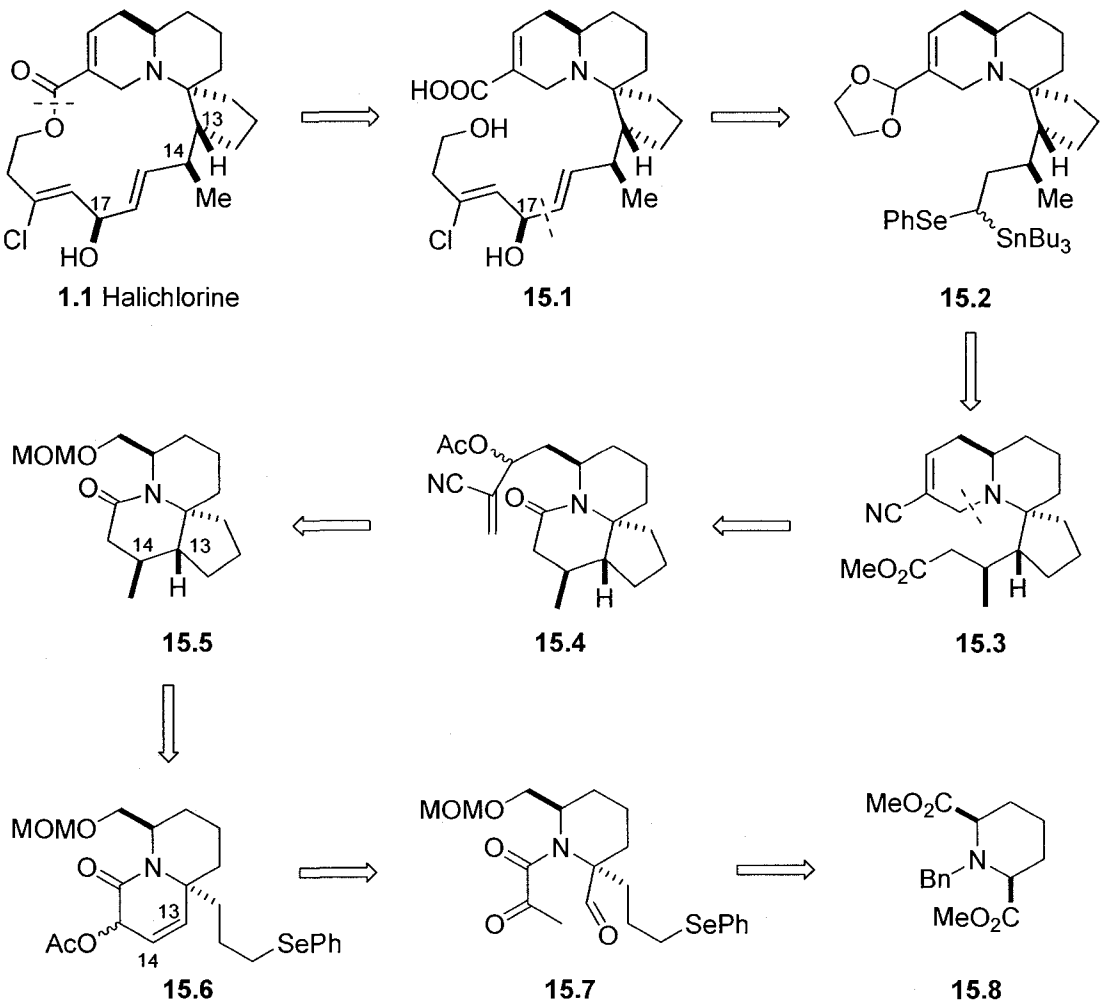
Scheme 14

2 RESULTS AND DISCUSSION

2.1 Synthesis of azaspirobicyclic core of halichlorine

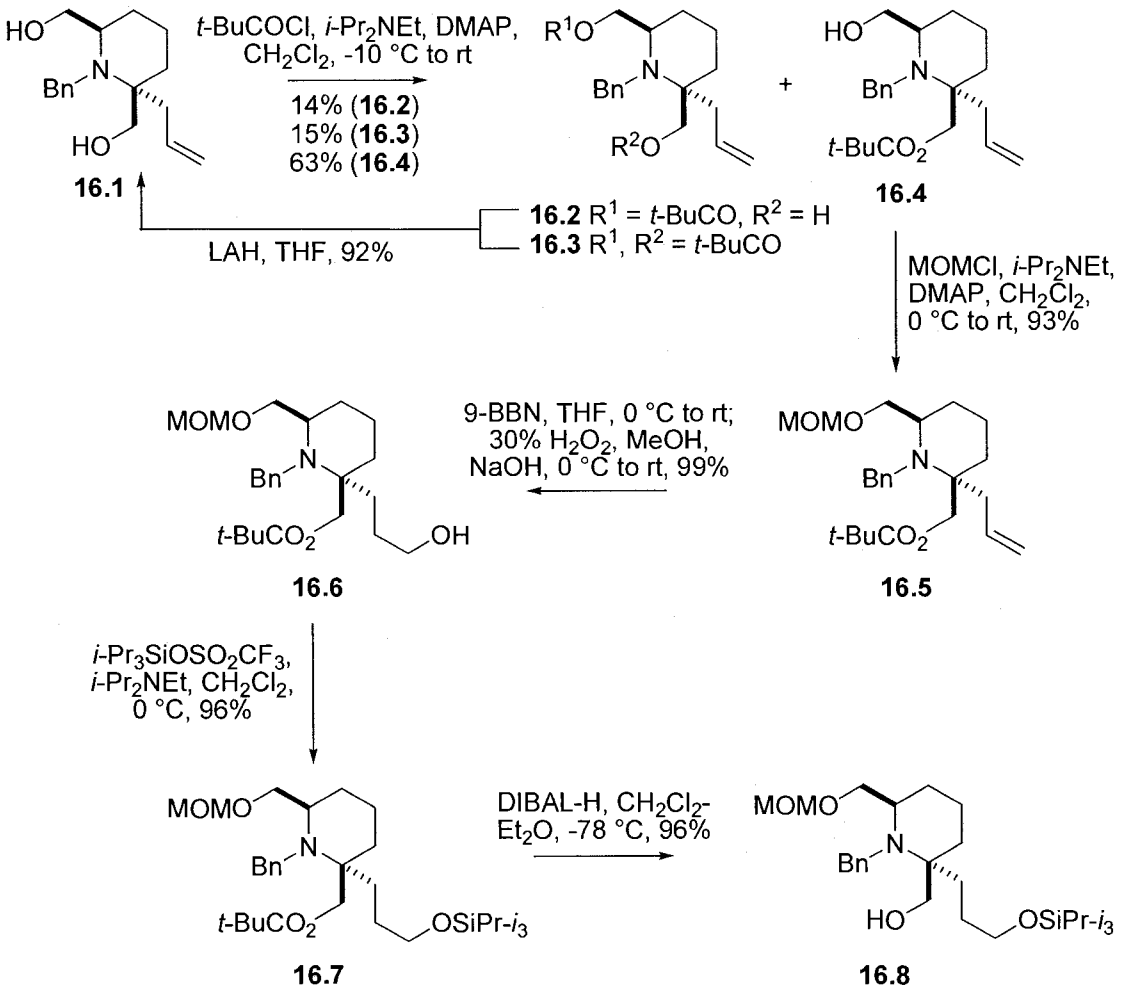
A number of exploratory studies that lead to spiro compounds resembling the core structure of halichlorine have been reported from the Clive group.[21] A former researcher[21c] has developed a route to the known carboxylic acid **15.1**,[8] which is two steps away from the final product. Since I joined this project, I repeated most of the steps to improve the efficiency of the synthesis, and I successfully prepared the final product halichlorine. A brief outline of the total synthesis is shown in Scheme 15, and then the route is discussed in more detail.

Carboxylic acid **15.1** could be accessed from the organolithium compound prepared from stannane selenide **15.2**. Compound **15.2** was made from the α,β-unsaturated nitrile **15.3**, which was itself derived from amide **15.4** by an intramolecular addition-elimination process. Amide **15.4** was prepared from the MOM ether **15.5**. The C(14) methyl group of this compound had been introduced by conjugated addition, and the spiro ring containing C(13) had been installed by radical cyclization. Compound **15.6** was then prepared from **15.7**, which was eventually made from readily the available[22] piperidine bis-ester **15.8**.



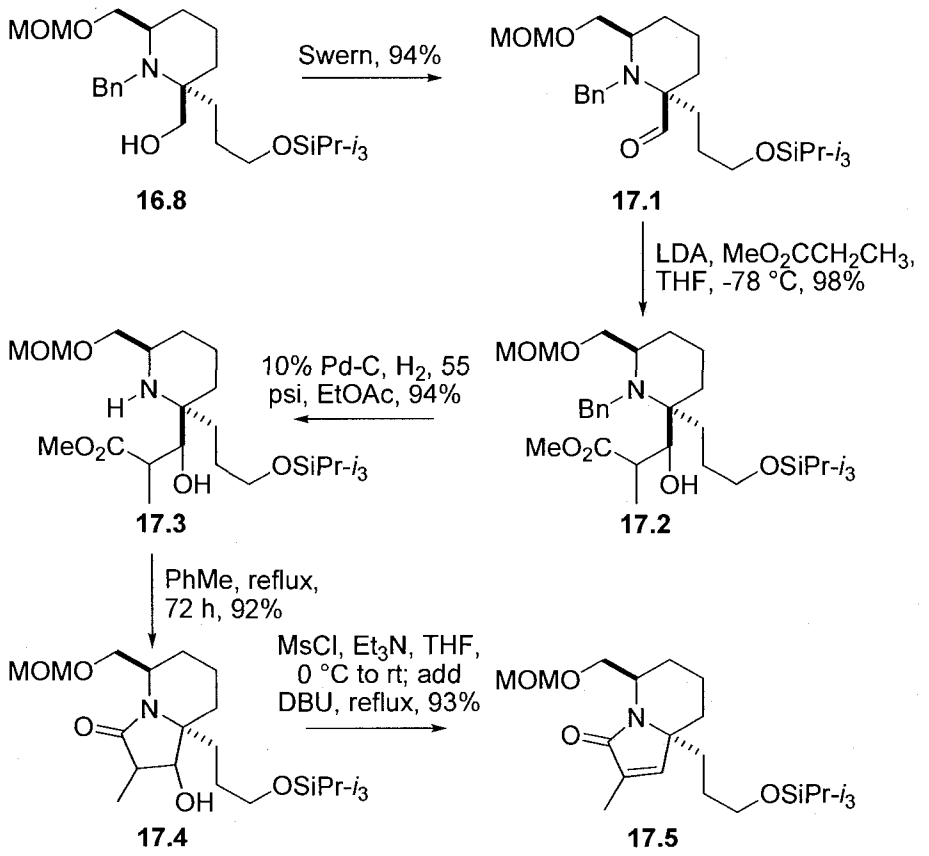
Scheme 15

Our synthesis started with diol **16.1**, which can be prepared from the known bis-ester **15.8** in two steps.[21b] Acylation with *t*-BuCOCl in the presence of Hünig's base and DMAP gave the mono-pivaloylation product **16.4** as the major product (63%). It is worth noting that the more hindered hydroxyl was acylated selectively. The regioisomer **16.2** (14%) and the bis-acylated compound **16.3** (15%) could be recycled back to diol **16.1** in 92% yield upon treatment with LAH. Protection of the remaining hydroxyl as a MOM ether, and hydroboration generated alcohol **16.6** in excellent yield (99%). The primary hydroxyl was then protected by silylation (**16.6** → **16.7**), followed by DIBAL reduction to give alcohol **16.8**.



Scheme 16

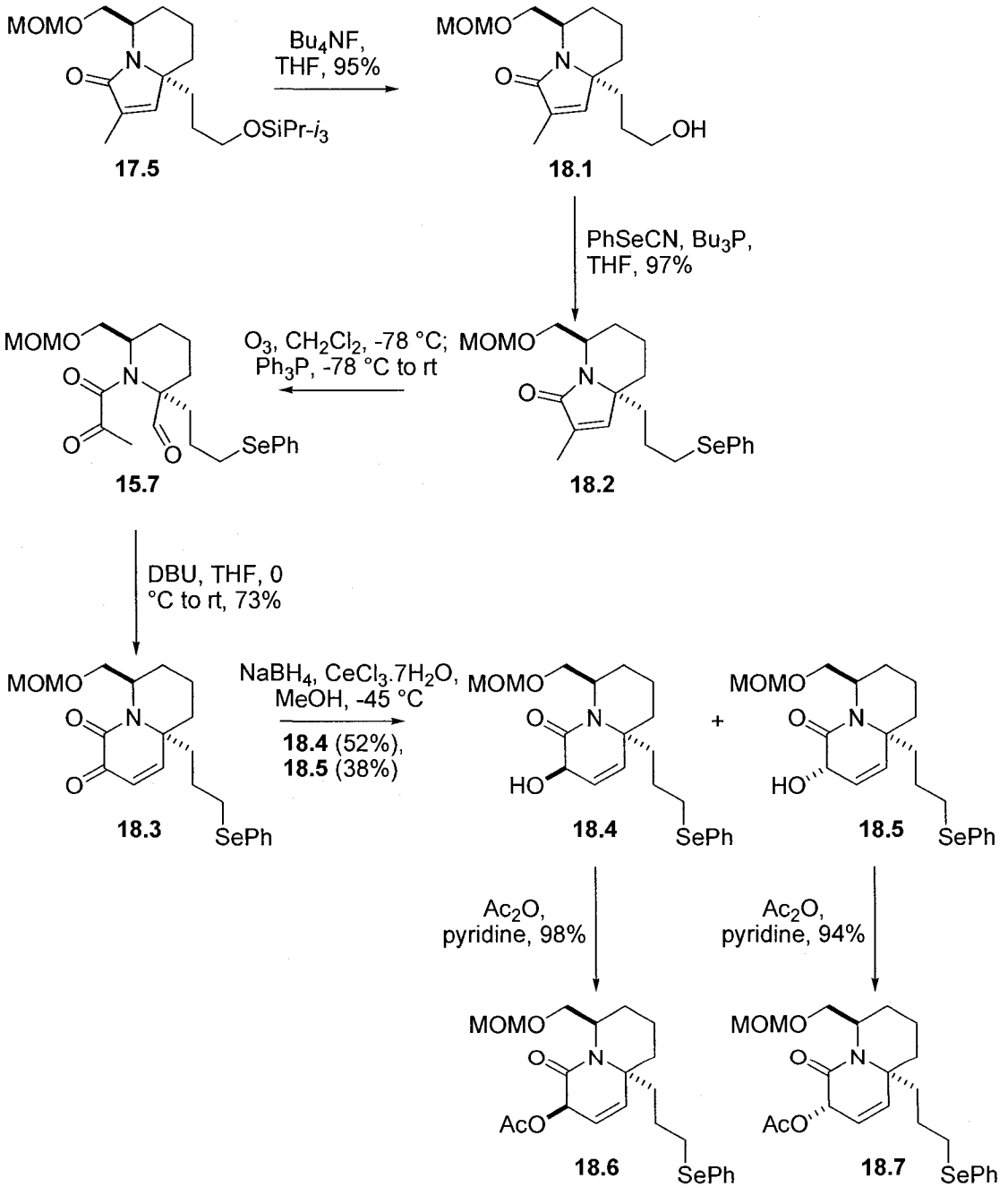
Alcohol **16.8** was oxidized to aldehyde **17.1**, which was then condensed with the anion made from methyl propionate. This experiment gave a separable mixture of two isomers (**17.2**). Without separation, the mixture was treated directly under standard hydrogenation conditions (Pd/C, H_2, 55 psi) to give amines **17.3**. Prolonged heating of a solution of **17.3** in PhMe resulted in smooth cyclization to afford a mixture of two lactams **17.4**. Again without separation, the isomeric mixture was subjected to mesylation, followed by elimination using DBU in refluxing THF, so as to give **17.5** as a single isomer in excellent yield (93%).



Scheme 17

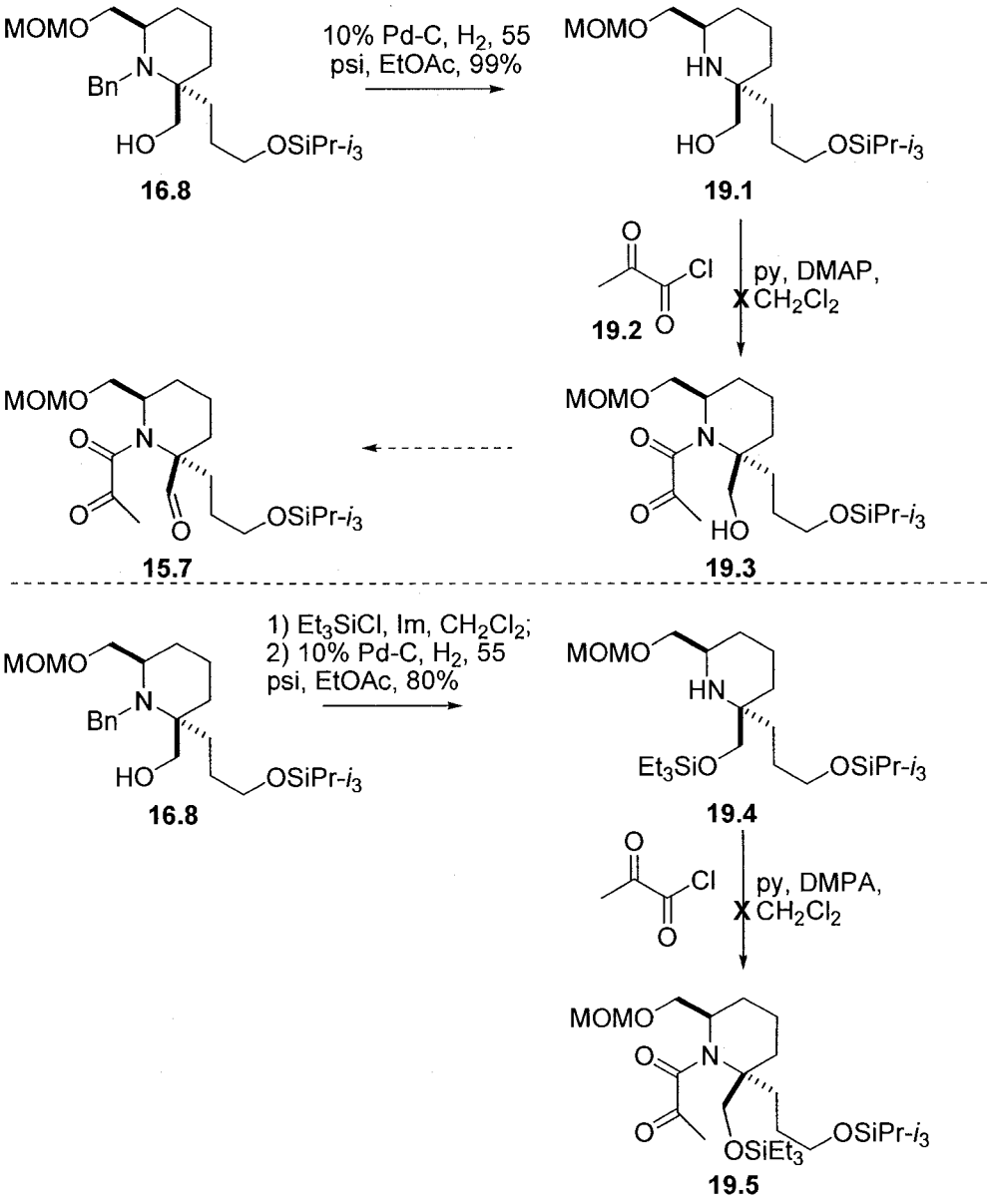
Desilylation of **17.5** released the primary alcohol, which was easily converted in the standard way to the corresponding phenyl selenide (**18.2**). The selenide **18.2** was then ozonized at a low temperature (-78 °C) and the cold ozonolysis mixture was treated with Ph_3P. When the solution was allowed to warm to room temperature both the ozonide and the intermediate selenoxides were reduced so that it was possible to isolate the tricarbonyl compound **15.7**. This procedure is based on the fact that selenoxides do not normally fragment rapidly at a low temperature but are reduced rapidly by phosphines, the net result being that a PhSe group can survive ozonolysis conditions even though the selenide is temporarily oxidized. DBU-mediated intramolecular aldol condensation of **15.7** provided enone **18.3**. Early studies by former researchers in this group indicated that the

radical cyclization of selenide **18.3** does not work unless the conjugated ketone is first reduced. This reduction gives two separable alcohols **18.4** and **18.5**, which are then protected as acetates (**18.6** and **18.7**).



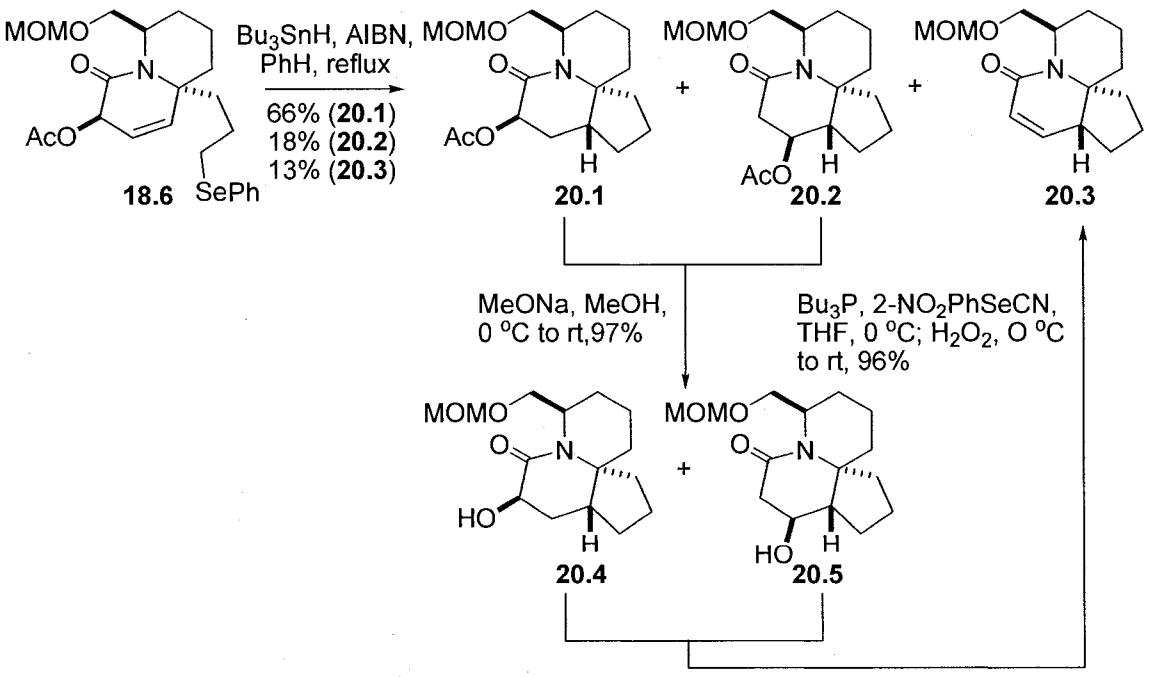
Scheme 18

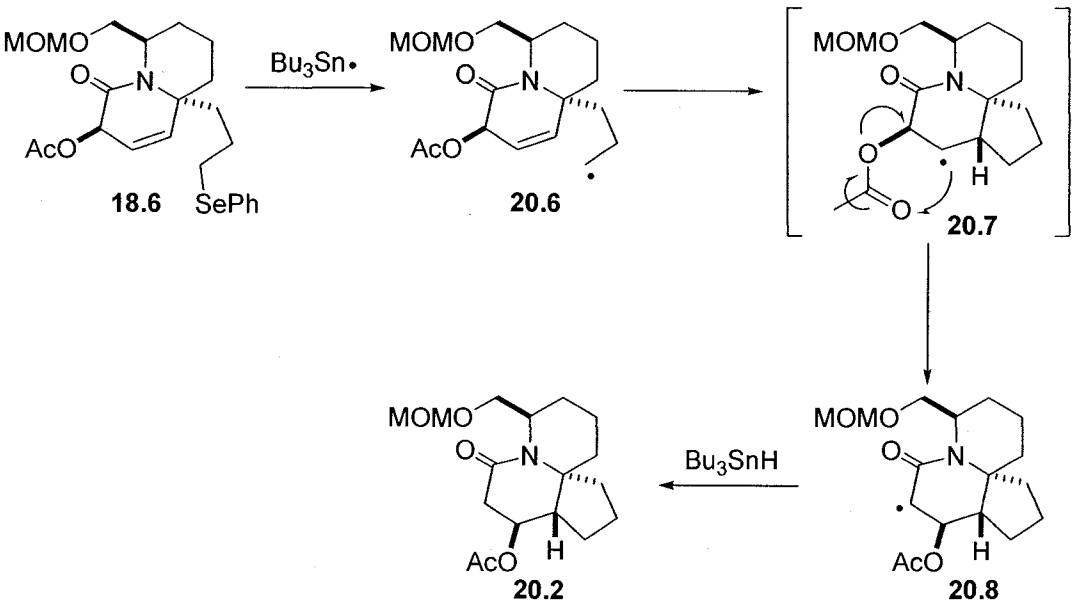
In my own work a different route to the tricarbonyl compound **15.7** was briefly explored (Scheme 19). Debenzylation of **16.8** by hydrogenation provided amino alcohol **19.1**. Several attempts to couple **19.1** with pyruvic acid chloride **19.2** gave back the starting material **19.1**. Protection of the free hydroxyl in **19.1** did not change the outcome (**19.4** → **19.5**). One possible reason for the difficulty in the coupling is the steric congestion around the nitrogen atom.



Scheme 19

Standard radical cyclization conditions were applied to acetate **18.6** (which I prepared by the prior route developed in this group) to give three products (Scheme 20). The major one is the expected acetate **20.1**, isolated in 66% yield. The second acetate (**20.2**), which was isolated in 18% yield, probably arose from the rearrangement of the intermediate **20.7** after the cyclization (**20.6** → **20.8**).[23] Unsaturated lactam **20.3** was also isolated in 13% yield. The cyclization is very sensitive to the reaction conditions. By switching benzene with toluene and keeping the reaction temperature at 80 °C, no desired product was obtained. Using THF as solvent at refluxing temperature gave the desired acetate **20.1** in 66% yield, but no rearranged acetate **20.2** or unsaturated lactam **20.3** could be found. Hydrolysis of a mixture of the two acetates (**20.1** and **20.2**), using MeONa in MeOH, gave the corresponding alcohols **20.4** and **20.5**. Introduction of a double bond by sequential phenylselenation and oxidative elimination then led to the unsaturated lactam **20.3** in excellent yield (96%).





Scheme 20

The other acetate **18.7** was also subjected to the above reaction sequence to afford the same lactam **20.3** (Scheme 21). The yield of each transformation is very close to the corresponding yield in the acetate **18.6** series. Although the rearranged acetate **21.2** was not characterized as it was always obtained together with some lactam **20.3**, acetate **20.2** and the corresponding alcohol **20.5** were fully characterized and the X-ray structure of **20.5** was obtained (Figure 1).

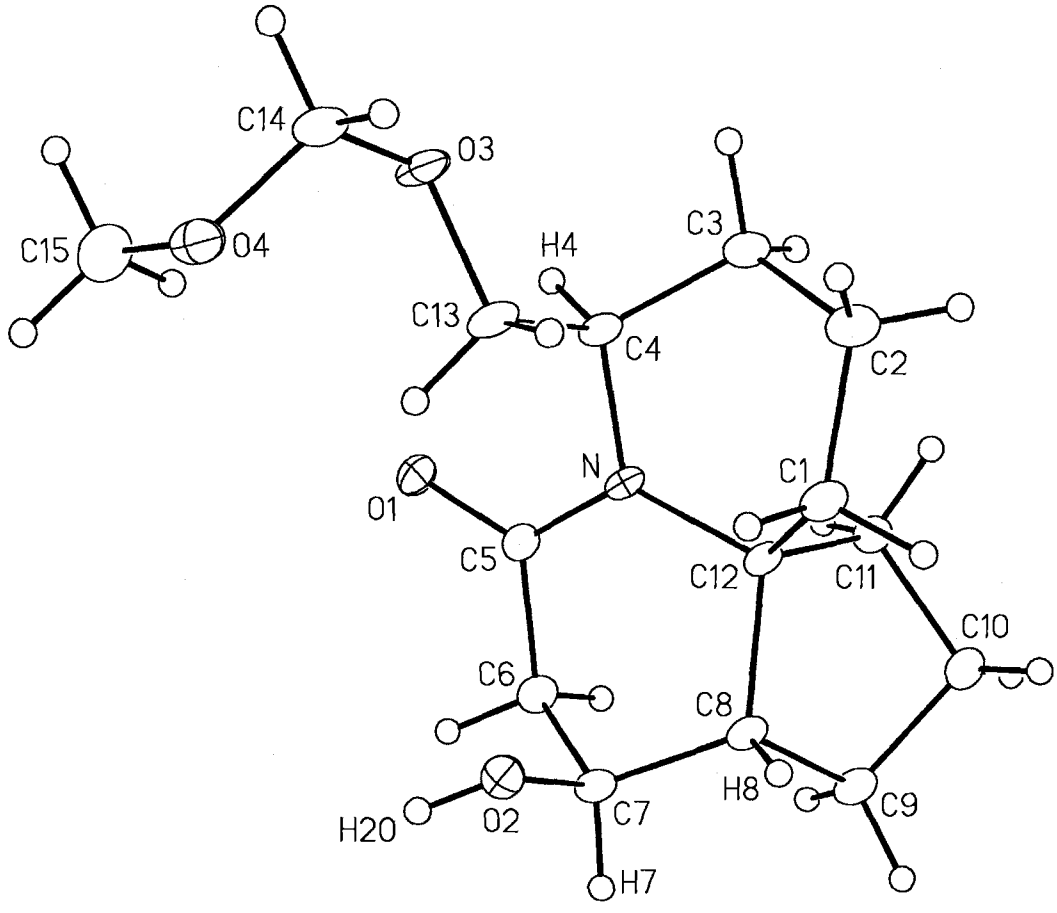
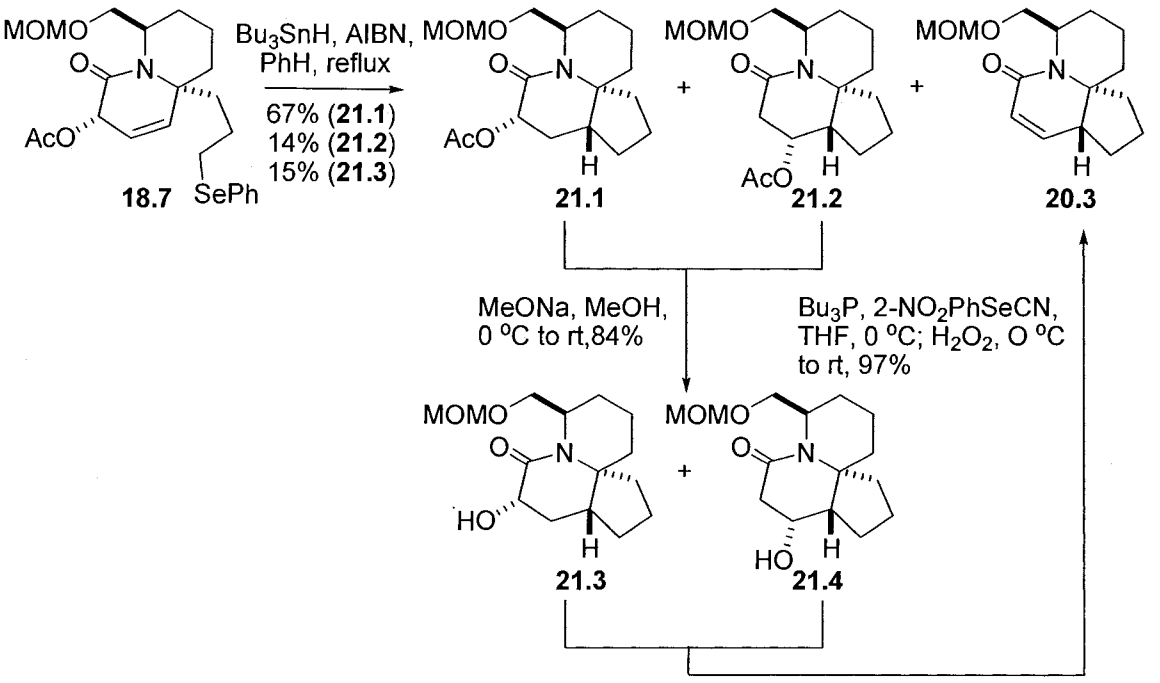


Figure 1 X-ray structure of **20.5** (ORTEP diagram)

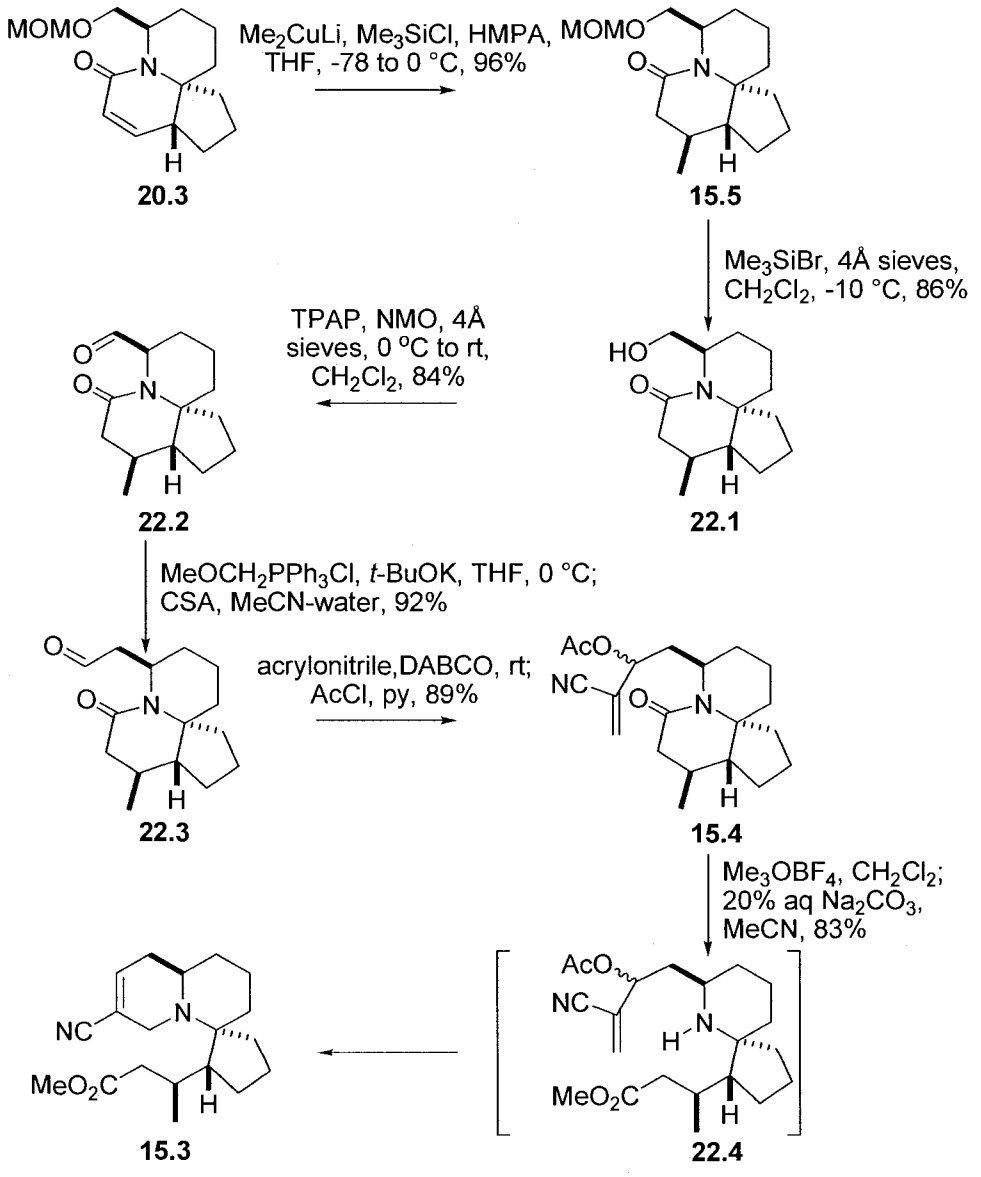


Scheme 21

With the unsaturated lactam **20.3** in hand, the next task was to install the methyl group at the β position. This was achieved by using lithium dimethylcuprate in the presence of Me_3SiCl and HMPA. The MOM protection group in **15.5** was then cleaved using Me_3SiBr at a low temperature (-10 °C) to give the primary alcohol **22.1**. Oxidation of alcohol **22.1** was problematic, but could be accomplished using TPAP and NMO in the presence of 4Å molecular sieves. Conditions such as the Swern oxidation or the Dess-Martin oxidation did not provide any of the desired product. The next task was to extend the aldehyde side chain **22.2** by one more carbon. Compound **22.2** was subjected to the standard Wittig homologation conditions by treating it with Ph_3CH_2OMeCl and *t*-BuOK. After hydrolysis, using camphorsulfonic acid in MeCN-water, aldehyde **22.3** was obtained in 92% yield over two steps.

Several approaches towards the tricyclic hexahydroquinolizine **15.3** had been tried by former researchers in the Clive group, and the best result[24] was obtained by first subjecting aldehyde **22.3** to a Baylis-Hillman-Morita reaction with acrylonitrile, followed

by acetylation to give allylic acetates **15.4**. Then *O*-methylation with Me_3OBF_4, followed by basic hydrolysis, furnished exclusively a single compound which was identified as the desired target hexahydroquinolizine **15.3**, indicating that the intramolecular Michael addition and elimination occurred spontaneously upon *in situ* formation of intermediate **22.4**.

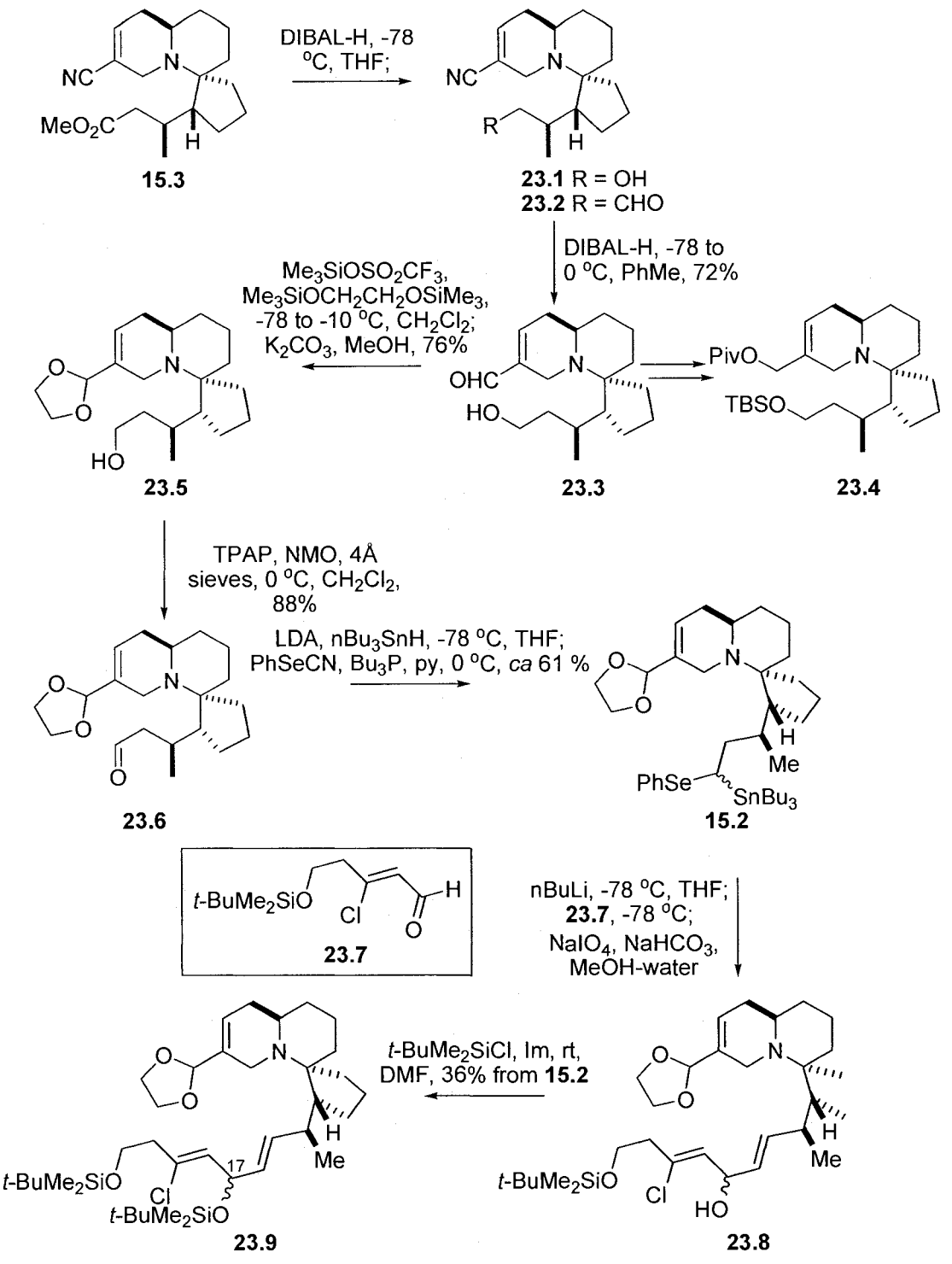


Scheme 22

2.2 Total synthesis of halichlorine

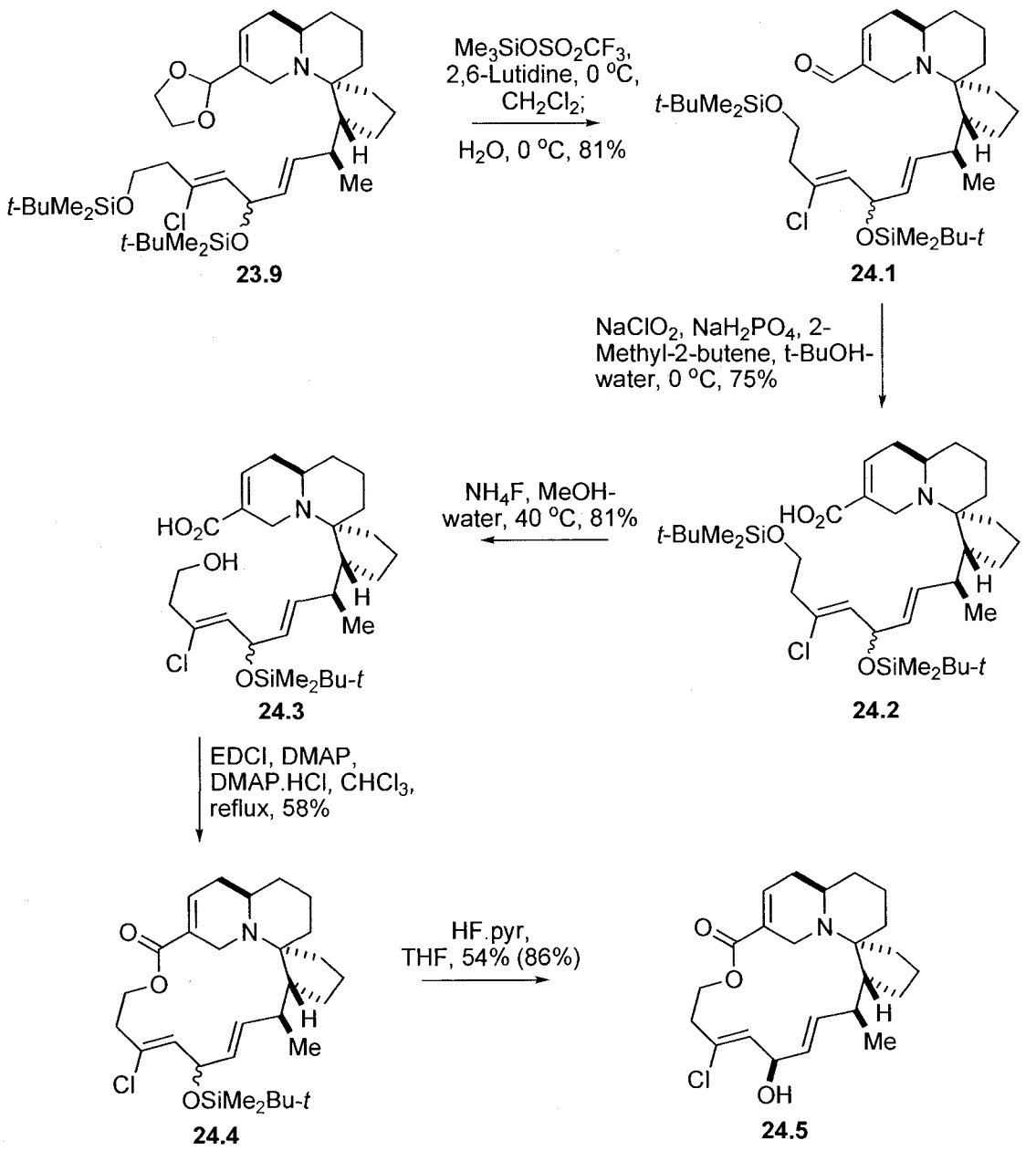
With key intermediate **15.3** in hand, the next task was to reduce both nitrile and ester groups. When a solution of nitrile ester **15.3** in THF was treated with DIBAL-H at -78 °C, the ester group could be reduced selectively to give a mixture of the corresponding nitrile alcohol and nitrile aldehyde (**23.1** and **23.2**). After workup, a solution of **23.1** and **23.2** in PhMe was treated with DIBAL-H to afford the desired aldehyde alcohol **23.3** in 72% yield over two steps. Treatment of a solution of nitrile ester **15.3** in CH_2Cl_2 or PhMe with excess DIBAL-H gave the desired aldehyde alcohol **23.3** in slightly lower yield (62%). The original plan was to protect the newly formed alcohol in **23.3** at this stage, and then reduce the aldehyde and then protect the resulting alcohol to give **23.4**. However, in order to shorten the route, it was decided to protect the aldehyde in **23.3** first, and then manipulate the lower side arm (Scheme 23).

To this end, aldehyde alcohol **23.3** was treated with 1.1 equiv of $Me_3SiOSO_2CF_3$ and an excess of 1,2-bis(trimethylsiloxy)ethane at a low temperature (-78 to -10 °C), and then subjected to hydrolysis, using K_2CO_3 in MeOH-water, to afford the desired acetal **23.5**. Oxidation with TPAP and NMO gave aldehyde **23.6**, which was treated with Bu_3SnLi[25] to form the expected α-hydroxystannanes. This material was used without purification, and was treated with PhSeCN and Bu_3P in the presence of pyridine (**23.6** → **15.2**). The resulting stannane selenides **15.2** were subjected to transmetallation with *n*-BuLi in THF to generate the corresponding organolithium, which reacted with known aldehyde **23.7**[14] to afford a mixture containing several isomers. Without separation, this mixture was treated with $NaIO_4$, which oxidatively eliminated the selenide, to form the allylic alcohols **23.8**. The secondary hydroxyl in **23.8** was protected as its silyl ether (**23.9**). Based on the ^1H NMR spectrum, **23.9** is a mixture (ca 4:1) of two isomers, presumably epimeric at C(17).


DIBAL-H, -78 °C, THF;
15.3
23.1 R = OH
23.2 R = CHO
DIBAL-H, -78 to 0 °C, PhMe, 72%
Me3SiOSO2CF3, Me3SiOCH2CH2OSiMe3, -78 to -10 °C, CH2Cl2; K2CO3, MeOH, 76%
23.5
23.3
23.4
TPAP, NMO, 4Å sieves, 0 °C, CH2Cl2, 88%
LDA, nBu3SnH, -78 °C, THF; PhSeCN, Bu3P, py, 0 °C, ca 61 %
23.6
15.2
23.7
nBuLi, -78 °C, THF; 23.7, -78 °C; NaIO4, NaHCO3, MeOH-water
t-BuMe2SiCl, Im, rt, DMF, 36% from 15.2
23.9
23.8

Scheme 23

Removing the acetal protection group without affecting the silyl ether could be achieved by using the $Me_3SiOSO_2CF_3$ and 2,6-lutidine combination.[26] Under acidic conditions (AcOH/THF/water or PPTS in acetone) the primary silyl ether was cleaved first. A former researcher in this group[21d] had established that aldehyde **24.1,** which was a mixture of two isomers [*ca* 1.7:1 (^{1}H NMR)] prepared by a different route, could be oxidized to acid **24.2**[8] with $NaClO_2$. Selective cleavage of the primary silyl ether using ammonium fluoride in aqueous methanol gave **24.3**, which underwent macrolactonization under Keck conditions[16] to afford macrolactone **24.4**. Chromatographic separation of the C(17) isomers could be achieved at this stage, but it was decided to carry both isomers to the next desilylation step (**24.4** $\rightarrow$ **24.5**). After removing the last protection group, using HF buffered with pyridine, the major isomer **24.5** was found to be identical to the natural product halichlorine (^{1}H/^{13}C NMR, IR, MS).[27] The minor isomer was not collected due to its extremely small quantity. The isolated yield of **24.5** from the mixture **24.4** is 54%, which is 86% based on the proportion of the major isomer in **24.4**.


Me3SiOSO2CF3,
2,6-Lutidine, 0 °C,
CH2Cl2;
H2O, 0 °C, 81%
23.9
24.1
NaClO2, NaH2PO4, 2-
Methyl-2-butene, t-BuOH-
water, 0 °C, 75%
NH4F, MeOH-
water, 40 °C, 81%
24.3
24.2
EDCI, DMAP,
DMAP.HCl, CHCl3,
reflux, 58%
HF.pyr,
THF, 54% (86%)
24.4
24.5

Scheme 24

3 CONCLUSION

The synthetic route described above starts with readily available diol **16.1** and constitutes a new route to the marine natural product halichlorine, which is 40 steps long. Key manipulations are: (1) the radical cyclization to make the spiro system, (2) stereospecific cuprate addition to introduce the methyl group at C(14), (3) the intramolecular conjugate displacement to generate the second six-membered ring, and (4) Keck macrolactonization to form the 15-membered lactone ring.

Currently a new approach toward optical pure halichlorine has been started, and this is based on a chiral amino acid as starting material.

4 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven (140 °C) for at least 3 h before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N, *i*-Pr_2NEt and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$. Acetone was distilled from anhydrous K_2CO_3.

FT-IR measurements were made from the specified solvent using KBr plates.

The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

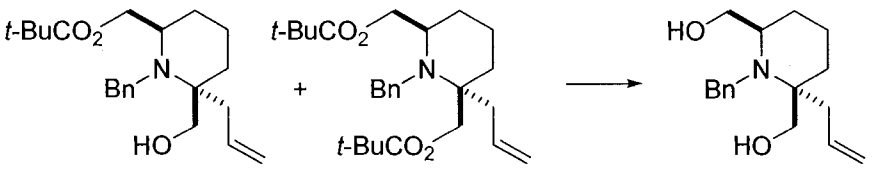
2,2-Dimethylpropanoic Acid (2*R*,6*R*)-6-(Hydroxymethyl)-1-(phenylmethyl)-2-(2-propenyl)-2-piperidinylmethyl Ester (16.4).

16.1 **16.4**

t-BuCOCl (3.7 mL, 30 mmol) was added dropwise over *ca* 2 h to a stirred and cooled (-30 to -25 °C) solution of diol **16.1** (7.83 g, 28.5 mmol), *i*-Pr_2NEt (9.93 mL, 57.0 mmol) and DMAP (70 mg, 0.57 mmol) in CH_2Cl_2 (205 mL). After the addition the cold bath was removed and stirring was continued for 2 h. Saturated aqueous NH_4Cl (80 mL) and Et_2O (250 mL) were then added. The organic phase was washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 10% to 15% EtOAc-hexane, gave alcohol **16.4** (6.42 g, 63%) as a solid:[21e] mp 77-78 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9 H), 1.17 (s, 1 H), 1.43-1.69 (m, 6 H), 2.45 (ddd, *J* = 14.0, 7.2, 0.8 Hz, 1 H), 2.56 (dd, *J* = 14.0, 7.2 Hz, 1 H), 2.72-2.76 (m, 1 H), 3.25 (ddd, *J* = 12.0, 9.3, 2.8 Hz, 1 H), 3.45-3.53 (m, 2 H), 4.02 (d, *J* = 11.9 Hz, 1 H), 4.10 (d, *J* = 11.9 Hz, 1 H), 4.31 (d, *J* = 16.7 Hz, 1 H), 5.10-5.16 (m, 2 H), 5.75 (dddd, *J* = 16.5, 10.5, 10.5, 0.5 Hz, 1 H), 7.14-7.20 (m, 1 H), 7.25-7.30 (m, 2 H), 7.39 (d, *J* = 7.3 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5 (t), 27.2 (q), 28.3 (t), 30.8 (t), 32.7 (t), 38.9 (s), 52.8 (t), 59.7 (s), 60.4 (d), 64.1 (t), 70.4 (t), 118.1 (t), 126.4 (d),

126.8 (d), 128.8 (d), 134.1 (d), 142.8 (s), 178.2 (s); exact mass *m/z* calcd for $C_{22}H_{34}NO_3$ 360.2533; found 360.2530.

(2*R*,6*R*)-1-(Phenylmethyl)-2-(2-propenyl)-2,6-piperidinedimethanol (16.1).



16.2 **16.3** **16.1**

$LiAlH_4$ (0.40 g, 10.5 mmol) was added to a stirred and cooled (0 °C) solution of **16.2** (0.90 g, 2.5 mmol) and **16.3** (0.57 g, 1.3 mmol) in THF (30 mL). Stirring was continued for 6 h with the cooling bath being left in place but not recharged. The mixture was diluted with CH_2Cl_2 (30 mL), cooled to 0 °C, and then $Na_2SO_4 \cdot 10H_2O$ (5 g) was added. The ice bath was removed and stirring was continued for 2 h. The mixture was filtered through a pad of Celite (2 x 4 cm), using CH_2Cl_2 (3 x 10 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 12 cm), using 1:1 EtOAc-hexane, gave **16.1** (0.96 g, 92%) as a colorless oil:[21e] FTIR (CH_2Cl_2 cast) 3380, 3024, 2937, 1636, 1602, 1451, 1051 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.40-1.80 (m, 6 H), 2.28 (dd, *J* = 14.0, 7.0 Hz, 1 H), 2.61 (dd, *J* = 14.0, 7.0 Hz, 1 H), 2.70-2.83 (m, 1 H), 3.32 (dd, *J* = 12.0, 3.5 Hz, 1 H), 3.41 (d, *J* = 11.0 Hz, 1 H), 3.44 (d, *J* = 16.5 Hz, 1 H), 3.53 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.64 (d, *J* = 11.0 Hz, 1 H), 4.28 (d, *J* = 16.5 Hz, 1 H), 5.09 (dd, *J* = 9.0, 0.5 Hz, 1 H), 5.13 (dd, *J* = 16.0, 2.0 Hz, 1 H), 5.78 (dddd, *J* = 16.5, 9.5, 9.5, 7.0 Hz, 1 H), 7.22 (dd, *J* = 9.0, 8.0 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8 (t), 29.0 (t), 30.0 (t), 32.7 (t), 52.4 (t), 60.8 (d), 61.5 (s), 65.3 (t), 67.5 (t), 117.9 (t), 126.8 (d), 127.1 (d), 129.1 (d), 134.3 (d), 142.5 (s); exact mass *m/z* calcd for $C_{17}H_{26}NO_2$ 276.1958; found 276.1959.

(2*R*,6*R*)-rel-[2-Allyl-1-benzyl-6-[(methoxymethoxy)methyl)piperidin-2-yl]]-methyl Pivaloate (16.5).

16.4 **16.5**

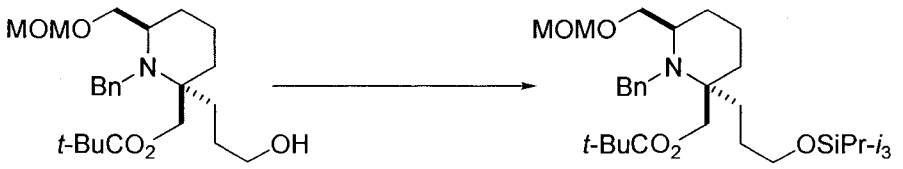
$MeOCH_2Cl$ (1.78 mL, 23.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16.4** (4.43 mg, 12.4 mmol), *i*-Pr_2NEt (8.61 mL, 49.4 mmol) and DMAP (60 mg, 0.49 mmol) in CH_2Cl_2 (120 mL). After the addition, the ice bath was removed and stirring was continued overnight. Water (35 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:10 EtOAc-hexane, gave **16.5** (4.64 g, 93%) as a colorless liquid:[21d] FTIR (CH_2Cl_2 cast) 1729, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 9 H), 1.47-1.65 (m, 5 H), 1.69-1.73 (m, 1 H), 2.40 (dd, *J* = 14.5, 7.5 Hz, 1 H), 2.52 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.91-2.94 (m, 1 H), 3.19 (s, 3 H), 3.25 (dd, *J* = 9.5, 7.5 Hz, 1 H), 3.50 (dd, *J* = 10.0, 3.5 Hz, 1 H), 3.89 (d, *J* = 16.5 Hz, 1 H), 3.97 (d, *J* = 5.0 Hz, 2 H), 4.10 (d, *J* = 16.5 Hz, 1 H), 4.28-4.32 (m, 2 H), 5.02-5.06 (m, 2 H), 5.77-5.85 (m, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.22-7.25 (m, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9 (t), 27.2 (q), 28.9 (t), 31.2 (t), 35.8 (t), 38.8 (s), 51.4 (t), 55.1 (d), 56.4 (q), 58.7 (s), 69.0 (t), 69.7 (t), 96.4 (t), 117.6 (t), 126.1 (d), 126.8 (d), 128.0 (d), 134.2 (d), 142.1 (s), 178.0 (s); exact mass *m/z* calcd for $C_{24}H_{38}NO_4$ (M + H) 404.280084 , found 404.280484.

(2*R*,6*R*)-rel-[1-Benzyl-2-(3-hydroxypropyl)-6-[(methoxymethoxy)methyl]-piperidin-2-yl]methyl Pivaloate (16.6).

16.5 **16.6**

9-BBN (0.5 M in THF, 41.6 mL, 20.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16.5** (4.19 g, 10.4 mmol) in THF (80 mL). The ice bath was removed after 15 min and stirring was continued overnight. The solution was recooled to 0 °C and MeOH (24.4 mL), NaOH (2 N, 70 mL) and H_2O_2 (30%, 12.2 mL) were added successively. After 15 min, the ice bath was removed and stirring was continued for 2.5 h. Brine (25 mL) and EtOAc (50 mL) were added, and the aqueous phase was extracted with EtOAc (3 x 40 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:3 EtOAc-hexane, gave **16.6** (4.33 g, 99%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 3436, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 9 H), 1.49-1.81 (m, 11 H), 2.97-3.01 (m, 1 H), 3.19 (s, 3 H), 3.29 (dd, J = 9.6, 7.2 Hz, 1 H), 3.52 (dd, J = 9.6, 3.6 Hz, 1 H), 3.57-3.61 (m, 2 H), 3.88 (d, J = 16.4 Hz, 1 H), 3.91 (d, J = 11.2 Hz, 1 H), 4.02 (d, J = 11.6 Hz, 1 H), 4.04 (d, J = 16.8 Hz, 1 H), 4.33 (d, J = 0.8 Hz, 2 H), 7.12-7.16 (m, 1 H), 7.22-7.26 (m, 2 H), 7.34-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9 (t), 26.9 (t), 27.1 (q), 27.5 (t), 28.0 (t), 30.3 (t), 38.8 (s), 50.6 (t), 55.1 (q), 55.7 (d), 58.5 (s), 63.4 (t), 68.7 (t), 69.6 (t), 96.3 (t), 126.2 (d), 126.9 (d) 128.1 (d), 142.1 (s), 178.2 (s); exact mass *m/z* calcd for $C_{24}H_{40}NO_5$ (M + H) 422.290649, found 422.290301.

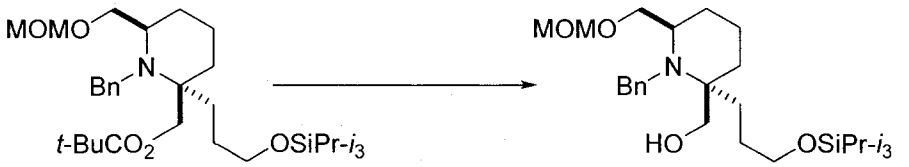
(2*R*,6*R*)-rel-[1-Benzyl-6-[(methoxymethoxy)methyl)]-2-[3-[(triisopropyl-silyl)oxy]propyl]piperidin-2-yl]methyl Pivaloate (16.7).



16.6 **16.7**

i-$Pr_3SiOSO_2CF_3$ (5.58 mL, 20.7 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16.6** (6.98 g, 16.5 mmol) and *i*-Pr_2NEt (7.20 mL, 41.3 mmol) in CH_2Cl_2 (140 mL). The mixture was stirred at 0 °C for 1 h, and then saturated aqueous NH_4Cl (80 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 1:10 EtOAc-hexane, gave **16.7** (9.19 g, 96%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93-1.08 (m, 21 H), 1.15 (s, 9 H), 1.48-1.72 (m, 9 H), 1.77-1.86 (m, 1 H), 2.92-2.97 (m, 1 H), 3.19 (s, 3 H), 3.28 (dd, *J* = 9.6, 7.6 Hz, 1 H), 3.53 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.60-3.67 (m, 2 H), 3.88-4.06 (m, 4 H), 4.32 (d, *J* = 2 Hz, 2 H), 7.13 (t, *J* = 7.2 Hz, 1 H), 7.22-7.25 (m, 2 H), 7.34 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9 (d), 17.6 (t), 17.7 (q), 27.1 (q), 27.9 (t), 28.3 (t), 30.6 (t), 38.7 (s), 50.8 (t), 55.0 (q), 55.6 (d), 58.2 (s), 63.8 (t), 68.5 (t), 69.8 (t), 96.3 (t), 126.1 (d), 126.9 (d) 128.0 (d), 142.1 (s), 178.2 (s); exact mass *m/z* calcd for $C_{33}H_{60}NO_5Si$ (M + H) 578.424078, found 578.423848.

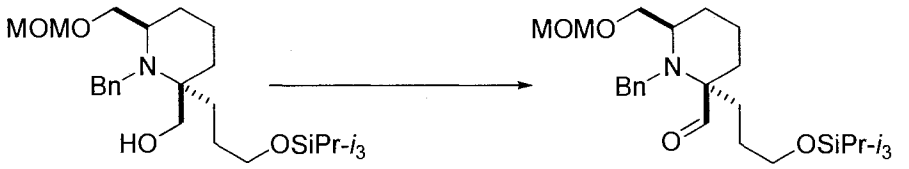
(2*R*,6*R*)-rel-[1-Benzyl-6-[(methoxymethoxy)methyl]-2-[3-[(triisopropyl-silyl)oxy]propyl]piperidin-2-yl]methanol (16.8).



16.7 **16.8**

DIBAL-H (1.0 M in hexane, 60.3 mL, 60.3 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **16.7** (11.6 g, 20.1 mmol) in Et_2O (250 mL). After the addition, stirring was continued for 30 min and then $Na_2SO_4 \cdot 10H_2O$ (60 g) was added. The cold bath was removed and stirring was continued overnight. The resulting thick white mixture was filtered through a pad of Celite (7 x 6 cm), using Et_2O (3 x 30 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 19 cm), using 1:4 EtOAc-hexane, gave **16.8** (8.88 g, 90%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93-1.12 (m, 21 H), 1.35-1.64 (m, 7 H), 1.73-1.92 (m, 3 H), 2.42-2.45 (m, 1 H), 2.90-2.95 (m, 1 H), 3.17 (s, 3 H), 3.21-3.29 (m, 2 H), 3.42 (dd, J = 10.0, 4.0 Hz, 1 H), 3.46 (d, J = 11.7 Hz, 1 H), 3.59 (d, J = 17.0 Hz, 1 H), 3.63-3.70 (m, 2 H), 4.12 (d, J = 17.0 Hz, 1 H), 4.22 (d, J = 6.5 Hz, 1 H), 4.28 (d, J = 6.5 Hz, 1 H), 7.16 (t, J = 7.0 Hz, 1 H), 7.26 (t, J = 7.5 Hz, 2 H), 7.34 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0 (d), 18.0 (q), 18.6 (t), 24.2 (t), 27.6 (t), 29.3 (t), 29.5 (t), 51.2 (t), 55.1 (q), 57.7 (d), 60.9 (s), 63.8 (t), 67.0 (t), 71.6 (t), 96.4 (t), 126.4 (d), 126.7 (d) 128.4 (d), 142.5 (s); exact mass *m/z* calcd for $C_{28}H_{52}NOSi$ (M + H) 494.366563, found 494.366820.

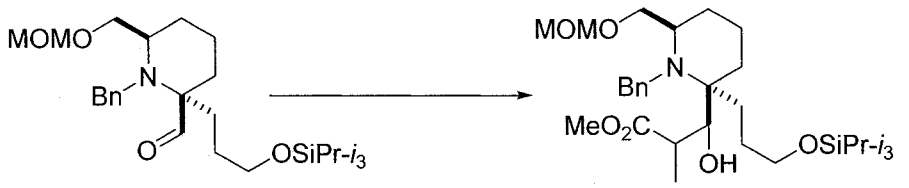
(2*R*,6*R*)-rel-[1-Benzyl-6-[(methoxymethoxy)methyl]-2-[3-[(triisopropyl-silyl)oxy]propyl]piperidine-2-carboxaldehyde (16.8).



16.8 **17.1**

Dry DMSO (4.22 mL, 59.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (2.36 mL, 27.1 mmol) in CH_2Cl_2 (150 mL). Stirring was continued for 10 min and then **16.8** (8.88 g, 18.0 mmol) in CH_2Cl_2 (110 mL) was added dropwise. Stirring was continued for 45 min, Et_3N (10.0 mL, 71.7 mmol) was added dropwise and stirring was continued for 30 min. The dry ice bath was removed and replaced with an ice bath, and stirring was continued for 30 min. Water (70 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:20 EtOAc-hexane, gave **17.1** (8.32 g, 94%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88-1.15 (m, 21 H), 1.48-1.85 (m, 10 H), 2.97-3.04 (m, 1 H), 3.18-3.22 (m, 4 H), 3.46 (dd, J = 9.5, 4.0 Hz, 1 H), 3.61-3.72 (m, 2 H), 3.89 (AB q, $\Delta\nu_{AB}$ = 10.0 Hz, J = 16.5 Hz, 2 H) 4.26 (AB q, $\Delta\nu_{AB}$ = 13.5 Hz, J = 6.5 Hz, 2 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 2 H), 7.36 (d, J = 7.5 Hz, 2 H), 9.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (d), 17.8 (t), 18.0 (q), 26.2 (t), 27.0 (t), 27.3 (t), 28.0 (t), 52.4 (t), 55.1 (q), 55.3 (d), 63.5 (s), 67.9 (t), 68.7 (t), 96.4 (t), 126.5 (d), 127.1 (d) 128.1 (d), 141.5 (s), 205.0 (d); exact mass *m/z* calcd for $C_{28}H_{49}NNaO_4Si$ (M + Na) 514.332858, found 514.332671.

Methyl (2*R*,3*R*)-rel-1-Benzyl-β-Hydroxy-6-[(methoxymethoxy)methyl]-α-methyl-2-[3-[(triisopropylsilyl)oxy]propyl]-2-piperidinepropanoate (17.2).



17.1 **17.2**

n-BuLi (1.6 M in hexane, 26.0 mL, 41.6 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (6.10 mL, 43.5 mmol) in THF (130 mL). Stirring was continued at -78 °C for 20 min and a solution of $C_2H_5CO_2Me$ (3.49 mL, 36.2 mmol) in THF (50 mL) was added dropwise. Stirring was continued for 1 h at -78 °C, and a solution of **17.1** (8.90 g, 18.1 mmol) in THF (45 mL) was then added dropwise. Stirring was continued for 30 min, saturated aqueous NH_4Cl (80 mL) was then added, and the mixture was extracted with Et_2O (3 x 80 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 15:100 EtOAc-hexane, gave a mixture of the two isomers of **17.2** (10.3 g, 98%). The less polar isomer had:[21d] FTIR (CH_2Cl_2 cast) 3479, 1736, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92-1.09 (m, 23 H), 1.18-1.66 (m, 7 H), 1.71-1.91 (m, 4 H), 2.82-2.89 (m, 1 H), 2.91-2.94 (m, 1 H), 3.21 (s, 3 H), 3.40 (dd, J = 9.6, 7.6 Hz, 1 H), 3.58-3.69 (m including singlet at δ 3.66, 7 H in all), 3.83 (d, J = 17.2 Hz, 1 H), 4.13 (d, J = 17.2 Hz, 1 H), 4.21 (d, J = 8.0 Hz, 1 H), 4.41 (AB q, $\Delta\nu_{AB}$ = 9.6 Hz, J = 6.4 Hz, 2 H), 7.11-7.15 (m, 1 H), 7.22-7.29 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (d), 17.91 (q), 17.93 (t), 18.1 (q), 27.6 (t), 28.2 (t), 28.9 (t), 29.7 (t), 38.3 (d), 51.8 (q), 52.1 (t), 55.2 (d), 56.4 (d), 62.5 (t), 64.2 (s), 69.8 (t), 81.1 (q), 96.4 (t), 126.0 (d), 127.0 (d), 128.0 (d), 141.0 (s), 178.4 (s); exact mass *m/z* calcd for $C_{32}H_{57}NNaO_6Si$ (M + Na) 602.385287, found 602.385996.

The more polar isomer had: FTIR (CH_2Cl_2 cast) 3495, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91-1.08 (m, 21 H), 1.24 (d, J = 7.2 Hz, 3 H), 1.33-1.89 (m, 10 H), 2.71-2.77 (m, 1 H), 3.04-3.09 (m, 2 H), 3.22 (s, 3 H), 3.45 (dd, J = 9.6, 7.2 Hz, 1 H), 3.58-3.64 (m including singlet at δ 3.61, 5 H in all), 3.70 (dd, J = 9.6, 5.6 Hz, 1 H), 3.95 (d, J = 16.4 Hz, 1 H), 4.11 (d, J = 6.0 Hz, 1 H), 4.16 (d, J = 16.4 Hz, 1 H), 4.42 (s, 2 H), 7.15 (t, J = 7.2 Hz, 1 H), 7.23-7.27 (m, 2 H), 7.32 (d, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9 (d), 14.7 (q), 17.6 (t), 18.0 (q), 24.9 (t), 27.1 (t), 28.8 (t), 29.6 (t), 41.6 (d), 51.5 (t), 51.6 (q), 54.4 (d), 55.2 (d), 62.4 (t), 63.8 (s), 70.0 (t), 76.1 (q), 96.3 (t), 126.3 (d), 127.1 (d), 128.2 (d), 141.8 (s), 177.0 (s); exact mass *m/z* calcd for $C_{32}H_{58}NO_6Si$ (M + H) 580.40279, found 580.40247.

Methyl (2*R*,3*R*)-rel-β-Hydroxy-6-[(methoxymethoxy)methyl]-β-methyl-2-[3-[(triisopropylsilyl)oxy]propyl]-2-piperidinepropanoate (17.3).

17.2 **17.3**

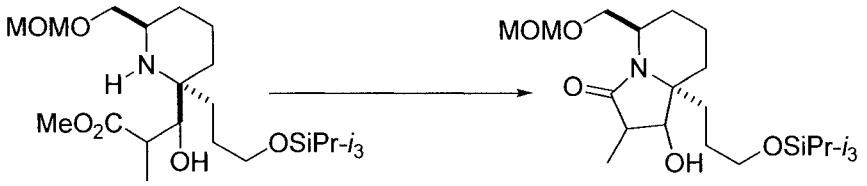
In this experiment the starting material was a mixture of isomers but previous work in this laboratory had used the individual components of **17.2**; hence, using **17.2** as an isomer mixture still allowed identification of each product as originating with the more polar or less polar component of **17.2**.

Pd/C (10 %, 2 g) was added to a solution of **17.2** (mixture of isomers) (9.53 g, 16.5 mmol) in EtOAc (40 mL) and the mixture was shaken in a Parr bottle under H_2 (55 psi) for 24 h. The mixture was filtered through a pad of Celite (5 x 4 cm) and the pad was washed with EtOAc (30 mL). Evaporation of the solvent and flash chromatography of

the residue over silica gel (5 x 30 cm), using 1:100 Et_3N-EtOAc, gave **17.3** as an oil which was a mixture of isomers (7.58 g, 94%). The secondary amine from the less polar isomer of **17.2** had:[21d] FTIR (CH_2Cl_2 cast) 3395, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85-1.12 (m, 21 H), 1.29 (d, J = 7.2 Hz, 3 H), 1.31-1.70 (m, 8 H), 1.88-2.02 (m, 2 H), 2.83-2.90 (m, 1 H), 2.95-3.02 (m, 1 H), 3.19-3.25 (m, 2 H), 3.34 (s, 3 H), 3.42 (dd, J = 9.2, 3.6 Hz, 1 H), 3.58-3.74 (m including singlet at δ 3.64, 5 H in all), 4.15 (br, s, 1 H), 4.58 (AB q, $\Delta\nu_{AB}$ = 5.1 Hz, J = 6.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9 (q), 17.3 (d), 18.0 (q), 19.7 (t), 27.0 (t), 27.3 (t), 28.1 (t), 29.7 (t), 39.2 (d), 49.4 (q), 51.5 (d), 55.1 (d), 57.5 (t), 63.5 (s), 73.2 (t), 78.8 (q), 96.5 (t), 176.2 (s); exact mass *m/z* calcd for $C_{25}H_{52}NO_6Si$ (M + H) 490.356392, found 490.356122.

The secondary amine from the more polar isomer of **17.2** had:[21d] FTIR (CH_2Cl_2 cast) 3400, 1741, 1690, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-1.09 (m, 21 H), 1.16 (d, J = 6.9 Hz, 3 H), 1.34-1.66 (m, 9 H), 1.84-1.95 (m, 1 H), 2.70-2.79 (m, 1 H), 2.92-3.00 (m, 1 H), 3.19 (t, J = 9.0 Hz, 1 H), 3.31 (s, 3 H), 3.39-3.49 (m, 2 H), 3.61-3.70 (m including singlet at δ 3.63, 5 H in all), 3.71-3.77 (m, 1 H), 4.56 (AB q, $\Delta\nu_{AB}$ = 6.2 Hz, J = 6.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.87 (q), 12.59 (d), 17.89 (q), 19.60 (t), 26.47 (t), 27.19 (t), 27.78 (t), 29.35 (t), 40.65 (d), 49.50 (d), 51.47 (q), 55.10 (d), 57.72 (s), 63.38 (t), 72.92 (t), 74.93 (q), 96.46 (t), 175.99 (s); exact mass *m/z* calcd for $C_{25}H_{52}NO_6Si$ (M + H) 490.35584, found 490.35595.

(5*R*,8a*R*)-rel-Hexahydro-1-hydroxy-5-[(methoxymethoxy)methyl-2-methyl]-8a-[3-[(triisopropylsilyl)oxy]propyl]indolizin-3(2*H*)-one (17.4).

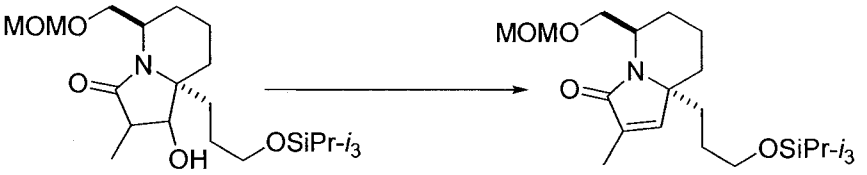


17.3 **17.4**

A solution of amine ester **17.3** (mixture of two isomers, 9.08 g, 8.48 mmol) in PhMe (450 mL) was refluxed for 72 h and the solution was then cooled and evaporated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 1:1 to 2:1 EtOAc-hexane, gave lactam **17.4** (7.83 g, 92%) as a colorless oil which was a mixture of two isomers. These could be identified from prior experiments starting with a single isomer of **17.3**. The lactam from the less polar series had:[21d] FTIR (CH_2Cl_2 cast) 3400, 1668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90-1.10 (m, 21 H), 1.15 (d, J = 7.5 Hz, 3 H), 1.35-1.89 (m, 11 H), 2.61-2.67 (m, 1 H), 3.33 (s, 3 H), 3.39-3.44 (m, 1 H), 3.61-3.67 (m, 2 H), 4.03-4.07 (m, 2 H), 4.24 (dd, J = 9.9, 4.3 Hz, 1 H), 4.62 (s, 2 H)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.7 (d), 12.0 (q), 18.1 (q), 18.7 (t), 26.9 (t), 27.7 (t), 27.8 (t), 28.9 (t), 40.5 (d), 52.8 (d), 55.3 (q), 63.0 (s), 65.7 (t), 68.7 (t), 72.0 (d), 96.8 (t), 174.7 (s); exact mass *m/z* calcd for $C_{24}H_{47}NNaO_5Si$ (M + Na) 480.312122, found 480.312161.

The lactam from the more polar series had: FTIR (CH_2Cl_2 cast) 3398, 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95-1.16 (m, 21 H), 1.21 (d, J = 7.0 Hz, 3 H), 1.30-1.88 (m, 11 H), 2.27-2.34 (m, 1 H), 3.11-3.17 (m, 1 H), 3.32 (s, 3 H), 3.65-3.73 (m, 2 H), 3.76 (d, J = 9.0 Hz, 1 H), 4.05-4.09 (m, 1 H), 4.22-4.25 (m, 1 H), 4.59-4.64 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.1 (q), 13.8 (d), 18.1 (q), 20.3 (t), 26.2 (t), 27.4 (t), 28.2 (t), 28.8 (t), 43.2 (d), 54.4 (q), 55.2 (d), 63.2 (s), 64.1 (t), 69.4 (t), 77.5 (d), 96.6 (t), 174.5 (s); exact mass *m/z* calcd for $C_{24}H_{48}NO_5Si$ (M + H) 458.32963, found 458.32964.

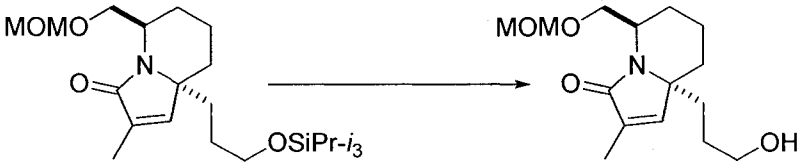
(5*R*,8a*R*)-rel-6,7,8,8a-Tetrahydro-5-[(methoxymethoxy)methyl]-2-methyl-8a-[3-[(triisopropylsilyl)oxy]propyl]indolizin-3(5*H*)-one (17.5).



17.4 **17.5**

Et_3N (23.9 mL, 0.171 mol) and MsCl (7.95 mL, 0.103 mol) were added successively to a stirred and cooled (0 °C) solution of the mixture of isomeric alcohols **17.4** (7.82 g, 16.3 mmol) and DMAP (35 mg, 0.29 mmol) in THF (370 mL). The solution was stirred at 0 °C for 30 min, and then the ice bath was removed, and DBU (25.6 mL, 0.171 mol) was added dropwise. Stirring was continued for 30 min and the mixture was then refluxed for 12 h. The solution was cooled to room temperature and brine (100 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 30 cm), using 1:3 EtOAc-hexane, gave **17.5** (7.00 g, 93%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1687, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93-1.28 (m, 25 H), 1.54-1.75 (m, 3 H), 1.81 (s, 3 H), 1.82-1.95 (m, 3 H), 3.25-3.32 (m, 1 H), 3.35 (s, 3 H), 3.56-3.64 (m, 2 H), 4.11 (dd, J = 10.4, 8.0 Hz, 1 H), 4.56 (dd, J = 10.0, 5.2 Hz, 1 H), 4.69 (AB q, $\Delta\nu_{AB}$ = 21.2 Hz, J = 6.4 Hz, 2 H), 6.55-6.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.9 (q), 11.9 (q), 18.0 (q), 20.3 (d), 26.4 (d), 27.6 (d), 29.8 (d), 34.9 (d), 53.9 (q), 55.2 (d), 63.0 (s), 64.5 (t), 68.4 (t), 96.8 (t), 134.2 (s), 145.6 (d), 170.0 (s); exact mass *m/z* calcd for $C_{24}H_{45}NNaO_4Si$ (M + Na) 462.301557, found 462.301493.

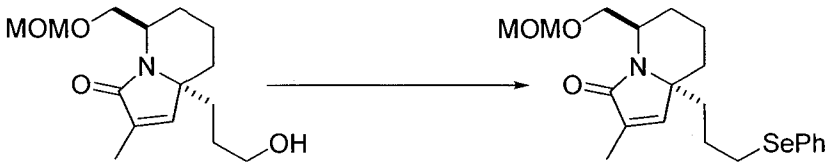
(5*R*,8a*R*)-rel-8a-(3-Hydroxypropyl)-5-[(methoxymethoxy)methyl]-2-methyl-6,7,8,8a-tetrahydroindolizin-3(5*H*)-one (18.1).



17.5 **18.1**

Bu_4NF (1.0 M in THF, 23.0 mL, 23.0 mmol) was added to a stirred solution of **17.5** (7.00 g, 15.4 mmol) in THF (150 mL). Stirring was continued for 1 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 100% EtOAc, gave alcohol **18.1** (4.29 g, 95%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 3418, 1671, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09-1.30 (m, 4 H), 1.49-1.73 (m, 4 H), 1.79-2.00 (m including singlet at δ 1.80, 6 H in all), 3.26-3.34 (m, 1 H), 3.35 (s, 3 H), 3.56 (t, J = 6.3 Hz, 2 H), 4.06 (dd, J = 10.2, 7.8 Hz, 1 H), 4.59 (dd, J = 10.2, 5.7 Hz, 1 H), 4.72 (AB q, $\Delta\nu_{AB}$ = 21.3 Hz, J = 6.3 Hz, 2 H), 6.54-6.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.9 (q), 20.3 (t), 26.2 (t), 27.4 (t), 29.6 (t), 35.1 (t), 54.0 (q), 55.3 (d), 62.4 (t), 64.5 (s), 68.5 (t), 96.9 (t), 134.4 (s), 145.5 (d), 170.1 (s); exact mass *m/z* calcd for $C_{15}H_{25}NNaO_4$ (M + Na) 306.168128, found 306.168099.

(5*R*,8a*R*)-rel-6,7,8,8a-Tetrahydro-5-[(methoxymethoxy)methyl]-2-methyl-8a-[3-(phenylseleno)propyl]-3(5*H*)-indolizinone (18.2).



18.1 **18.2**

PhSeCN (2.92 mL, 23.6 mmol) and Bu_3P (5.89 mL, 23.6 mmol) were added successively to a stirred and cooled (0 °C) solution of **18.1** (4.45 g, 15.7 mmol) in THF (150 mL). Stirring at 0 °C was continued for 2.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:3 to 1:1 EtOAc-hexane, gave **18.2** (6.47 g, 97%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1681, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08-1.23 (m, 2 H), 1.32-1.43 (m, 2 H), 1.52-2.00 (m, 9 H), 2.78-2.93 (m, 2 H), 3.13-3.32 (m, 1 H), 3.36 (s, 3 H), 4.10 (dd, J = 10.1, 8.0 Hz, 1 H), 4.53 (dd, J = 10.0, 5.4 Hz, 1 H), 4.69 (AB q, $\Delta\nu_{AB}$ = 15.8 Hz, J = 6.4 Hz, 2 H), 6.50-6.51 (m, 1 H), 7.22-7.27 (m, 3 H), 7.44-7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.9 (q), 20.3 (t), 23.3 (t), 28.1 (t), 29.7 (t), 31.1 (t), 35.0 (t), 54.0 (q), 55.3 (d), 64.4 (s), 68.4 (t), 96.8 (t), 126.9 (d), 129.0 (d), 130.0 (s), 132.7 (d), 134.4 (s), 145.3 (d), 169.9 (s); exact mass *m/z* calcd for $C_{21}H_{29}NNaO_3{}^{80}Se$ (M + Na) 446.12049, found 446.12095.

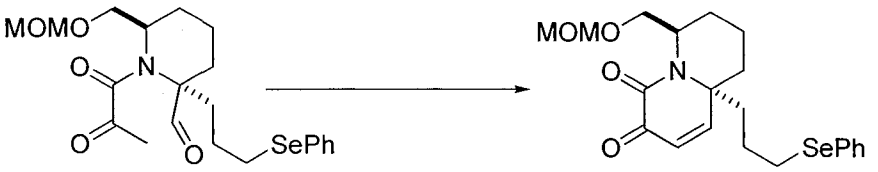
(2*R*,6*R*)-rel-1-(1,2-Dioxopropyl)-6-[(methoxymethoxy)methyl]-2-[3-(phenylseleno)propyl]-2-piperidinecarboxaldehyde (15.7).

18.2 **15.7**

A solution of **18.2** (0.539 g, 1.27 mmol) in CH_2Cl_2 (40 mL) was cooled to -78 °C and a steady stream of O_3 in O_2 (dried by passing through trap at -78 °C) was bubbled through the solution for 30 min. Then the mixture was flushed with O_2 for 20 min to remove the excess of O_3, and Ph_3P (1.20 g, 4.72 mmol) was tipped in. The mixture was stirred for 1 min, and was then poured into a cooled (-78 °C) round bottom storage flask (500 mL with magnetic stir bar in it) using CH_2Cl_2 (*ca* 3 mL) as a rinse. The mixture was stirred at -78 °C while a further 6 batches were processed.

Another solution of **18.2** (0.539 g, 1.27 mmol) in CH_2Cl_2 (40 mL) was subjected to ozonolysis following the above conditions. After the addition of Ph_3P (1.20 g, 4.72 mmol), the mixture was transferred to the same 500 mL round bottom flask using CH_2Cl_2 (*ca* 3 mL) as a rinse. After 5 more experiments carried out using the same amounts of starting material and reagents, the storage flask contained all the reaction solutions. The cooling bath was left in place but not recharged and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:3 to 1:1 EtOAc-hexane, gave ketoaldehyde **15.7** as a colorless oil which was used directly in the next step.

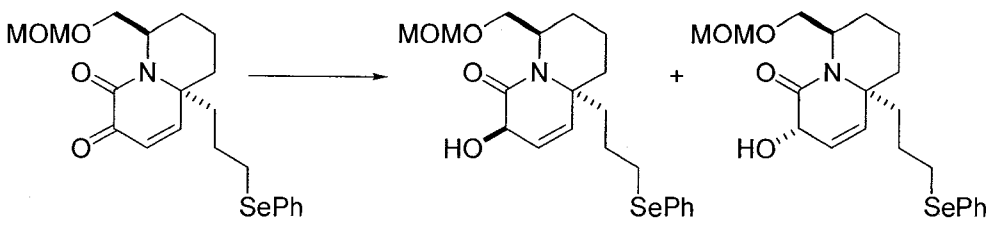
(6*R*,9a*R*)-rel-1,3,4,9a-Tetrahydro-4-[(methoxymethoxy)methyl]-9a-[3-(phenylseleno)propyl]-2*H*-quinolizine-6,7-dione (18.3).



15.7 **18.3**

DBU (7.4 mL, 50 mmol) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of the above ketoaldehyde **15.7** in THF (170 mL). The ice bath was left in place but not recharged and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 3:1 EtOAc-hexane, gave α,β-unsaturated ketoamide **18.3** (4.89 g from 12 combined batches, total 6.47 g of **18.2**, 73% over two steps) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1747, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42-1.73 (m, 5 H), 1.83-2.07 (m, 4 H), 2.44-2.59 (m, 1 H), 2.80-3.00 (m, 2 H), 3.34 (s, 3 H), 3.44-3.58 (m, 1 H), 4.06-4.20 (m, 2 H), 4,62 (AB q, $\Delta\nu_{AB}$ = 11.4 Hz, J = 6.4 Hz, 2 H), 6.36 (d, J = 10.2 Hz, 1 H), 6.83 (d, J = 10.2 Hz, 1 H), 7.23-7.28 (m, 3 H), 7.43-7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7 (t), 23.5 (t), 26.7 (t), 27.4 (t), 34.1 (t), 37.3 (t), 55.4 (q), 56.3 (d), 64.4 (s), 69.4 (t), 96.8 (t), 126.4 (d), 127.2 (d), 129.2 (d), 129.5 (s), 132.8 (d), 156.1 (d), 158.5 (s), 179.1 (s); exact mass *m/z* calcd for $C_{21}H_{27}NNaO_4{}^{80}Se$ (M + Na) 460.09975, found 460.09940.

(3*R*,6*R*,9a*R*)-rel-3,6,7,8,9,9a-Hexahydro-3-hydroxy-6-[(methoxymethoxy)-methyl]-9a-[3-(phenylseleno)propyl]-4*H*-quinolizin-4-one (18.4) and (3*R*,6*S*,9a*S*)-rel-3,6,7,8,9,9a-Hexahydro-3-hydroxy-6-[(methoxymethoxy)methyl]-9a-[3-(phenyl-seleno)propyl]-4*H*-quinolizin-4-one (18.5).



18.3 **18.4** **18.5**

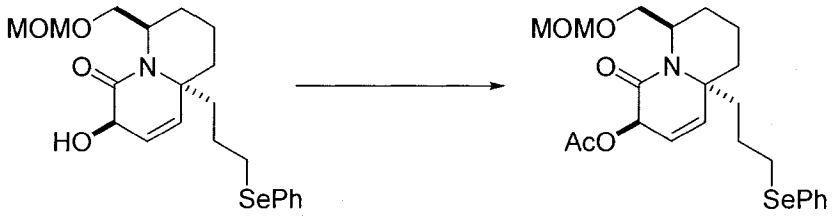
$CeCl_3.7H_2O$ (3.25 g, 8.72 mmol) was tipped into a stirred and cooled (-45 °C) solution of **18.3** (3.46 g, 7.92 mmol) in MeOH (100 mL). Stirring was continued for 20 min and then $NaBH_4$ (0.45 g, 12 mmol) was added in one portion. Stirring was continued at -45 °C for 30 min. Acetone (10 mL) was added and the mixture was allowed to warm to room temperature over 2 h, the cold bath being left in place, but not recharged. Saturated aqueous NH_4Cl (15 mL) and EtOAc (20 mL) were added, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:1 to 2:1 EtOAc-hexane, gave the less polar isomer **18.4** (1.81 g, 52%) and the more polar isomer **18.5** (1.32 g, 38%) as colorless oils.

The less polar isomer **18.4** had:[21d] FTIR (CH_2Cl_2 cast) 3369, 1632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.49-1.92 (m, 9 H), 2.03-2.11 (m, 1 H), 2.82-2.92 (m, 2 H), 3.33 (s, 3 H), 3.59 (br, s, 1 H), 3.75-3.86 (m, 3 H), 4.41 (t, J = 2.1 Hz, 1 H), 4.60 (AB q, $\Delta\nu_{AB}$ = 13.7 Hz, J = 6.4 Hz, 2 H), 5.49 (dd, J = 9.9, 2.8 Hz, 1 H), 5.84 (dd, J = 2.0, 10.0 Hz, 1 H), 7.22-7.25 (m, 3 H), 7.44-7.46 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.3 (t), 23.8 (t), 24.8 (t), 27.8 (t), 34.5 (t), 36.6 (t), 53.6 (q), 55.3 (d), 62.9 (s), 65.0 (d), 68.8 (t), 96.6 (t), 125.3 (d), 127.1 (d), 129.1 (d), 129.8 (s), 132.7 (d), 132.8 (d), 170.8 (s); exact mass *m/z* calcd for $C_{21}H_{29}NNaO_4{}^{80}Se$ (M + Na) 462.11540, found 462.11530.

The more polar isomer **18.5** had:[21d] FTIR (CH_2Cl_2 cast) 3372, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38-1.88 (m, 8 H), 1.95-2.01 (m, 1 H), 2.35-2.42 (m, 1 H), 2.87-2.98 (m, 2 H), 3.34 (s, 3 H), 3.41-3.47 (m, 1 H), 3.62 (s, br, 1 H), 4.07 (dd, J = 10.0,

3.5 Hz, 1 H), 4.14 (dd, J = 10.0, 8.5 Hz, 1 H), 4.39 (dd, J = 3.1, 1.9 Hz, 1 H), 4.62 (AB q, $\Delta\nu_{AB}$ = 7.5 Hz, J = 6.4 Hz, 2 H), 5.57 (dd, J = 10.2, 2.0 Hz, 1 h), 5.88 (dd, J = 10.2, 3.2 Hz, 1 H), 7.22-7.27 (m, 3 H), 7.46-7.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8 (t), 23.7 (t), 27.7 (t), 28.0 (t), 35.0 (t), 36.8 (t), 55.28 (q), 55.31 (d), 63.3 (s), 65.2 (d), 70.1 (t), 96.6 (t), 123.9 (d), 126.9 (d), 129.0 (d), 130.2 (s), 132.7 (d), 134.4 (d), 171.5 (s); exact mass m/z calcd for $C_{21}H_{30}NO_4{}^{80}Se$ (M + H) 440.13346, found 440.13358.

(3*R*,6*R*,9a*R*)-rel-3-(Acetyloxy)-3,6,7,8,9,9a-hexahydro-6-[(methoxymethoxy)-methyl]-9a-[3-(phenylseleno)propyl]-4*H*-quinolizin-4-one (18.6).

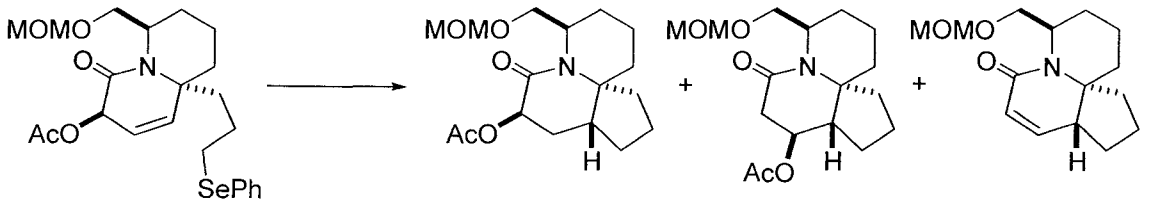


18.4 **18.6**

Ac_2O (1.6 mL, 17 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the less polar alcohol **18.4** (1.81 g, 4.12 mmol) in pyridine (16 mL). The ice bath was removed and the solution was stirred overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 16 cm), using 1:2 EtOAc-hexane, gave acetate **18.6** (1.94 g, 98%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1747, 1667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48-1.78 (m, 8 H), 1.85-1.90 (m, 1 H), 2.14 (s, 3 H), 2.19-2.25 (m, 1 H), 2.82-2.94 (m, 2 H), 3.31 (s, 3 H), 3.56-3.59 (m, 1 H), 3.84 (dd, J = 9.8, 3.7 Hz, 1 H), 3.96 (dd, J = 9.8, 8.6 Hz, 1 H), 4.58 (AB q, $\Delta\nu_{AB}$ = 14.1 Hz, J = 6.3 Hz, 2 H), 5.58-5.65 (m, 3 H), 7.20-7.26 (m, 3 H), 7.45-7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.7 (t), 20.9 (q), 24.3 (t), 25.1 (t), 27.8 (t), 35.6 (t), 35.8 (t), 54.5 (q), 55.3 (s), 63.3 (d), 66.2 (d), 69.5 (t), 96.6 (t), 122.1 (d), 127.0 (t), 129.1 (t), 129.9 (s), 132.8 (d),

135.1 (d), 165.6 (s), 170.2 (s); exact mass *m/z* calcd for $C_{23}H_{31}NNaO_5{}^{80}Se$ (M + Na) 504.12597, found 504.12613.

(4*R*,7*R*,8a*R*,11a*S*)-rel-7-Acetyloxydecahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.1), (4*R*,8*S*,8a*S*,11a*S*)-rel-8-Acetyloxy-decahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.2) and (4*R*,8a*R*,11a*S*)-rel-1,2,3,4,8a,9,10,11-Octahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.3).



18.6 **20.1** **20.2** **20.3**

Bu_3SnH (0.53 mL, 2.0 mmol) and AIBN (65 mg, 0.40 mmol) in PhH (25 mL) were added over 10 h (syringe pump) to a refluxing solution of **18.6** (0.64 g, 1.3 mmol) in PhH (260 mL). After the addition, the solution was refluxed for 4 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexane, gave acetate **20.1** (566 mg, 66%, combined yield of two identical batches), **20.2** (151 mg, 18%, combined yield of two identical batches) and α,β-unsaturated lactam **20.3** (89 mg, 13%, combined yield of two identical batches) as colorless oils.

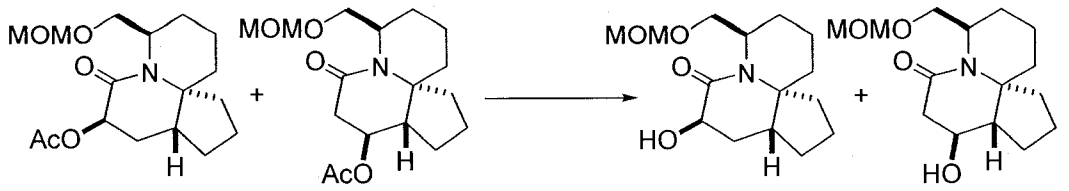
Acetate **20.1** had:[21d] FTIR (CH_2Cl_2 cast) 1694, 1667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47-2.05 (m, 15 H), 2.13 (s, 3 H), 3.33 (s, 3 H), 3.71 (dd, J = 9.6, 3.8 Hz, 1 H), 3.77 (t, J = 9.3 Hz, 1 H), 3.85-3.89 (m, 1 H), 4.60 (AB q, $\Delta\nu_{AB}$ = 19.25 Hz, J = 6.34 Hz, 2 H), 5.24 (dd, J = 10.9, 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.2 (t), 21.0 (q),

23.0 (t), 23.5 (t), 30.1 (t), 30.5 (t), 35.6 (t), 38.3 (t), 42.6 (d), 53.7 (q), 55.2 (d), 67.2 (s), 67.3 (d), 69.0 (t), 96.6 (t), 168.5 (s), 170.3 (s); exact mass *m/z* calcd for $C_{17}H_{27}NNaO_5$ (M + Na) 348.17814, found 348.17824.

Acetate **20.2** had: FTIR (CH_2Cl_2 cast) 2948, 2879, 1737, 1653, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46-2.02 (m, 17 H), 2.20 (ddd, J = 12.2, 5.7, 2.7 Hz, 1 H), 2.42 (dd, J = 16.7, 7.3 Hz, 1 H), 2.67 (dd, J = 16.7, 3.7 Hz, 1 H), 3.36 (s, 3 H), 3.77 (dd, J = 9.7, 4.1 Hz, 2 H), 3.81 (dd, J = 8.6, 8.6 Hz, 1 H), 3.91 (ddd, J = 10.6, 8.2, 4.1 Hz, 1 H), 4.63 (AB q, $\Delta\nu_{AB}$ = 17.0 Hz, J = 6.4 Hz, 2 H), 4.92 (ddd, J = 6.8, 6.4, 3.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.99 (t), 21.11 (q), 22.91 (t), 23.69 (t), 28.52 (t), 36.40 (t), 36.47 (t), 38.14 (t), 50.29 (d), 53.80 (d), 55.26 (q), 66.35 (s), 68.95 (t), 70.39 (d), 96.62 (t), 168.30 (s), 170.26 (s); exact mass *m/z* calcd for $C_{17}H_{27}O_5N$ 325.18893, found 325.18878.

The α,β-unsaturated lactam **20.3** had:[21d] FTIR (CH_2Cl_2 cast) 1664, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57-2.16 (m, 12 H), 2.38-2.42 (m, 1 H), 3.38 (s, 3 H), 3.68-3.71 (m, 2 H), 4.22-4.27 (m, 1 H), 4.66 (AB q, $\Delta\nu_{AB}$ = 16.0 Hz, J = 6.4 Hz, 2 H), 5.84 (dd, J = 9.8, 2.2 Hz, 1 H), 6.21 (dd, J = 9.8, 2.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (t), 22.1 (t), 22.6 (t), 30.9 (t), 33.1 (t), 36.6 (t), 46.7 (d), 50.7 (q), 55.2 (d), 65.2 (s), 68.8 (t), 96.6 (t), 124.0 (d), 142.4 (d), 163.4 (s); exact mass *m/z* calcd for $C_{15}H_{23}NNaO_3$ (M + Na) 288.15702, found 288.15708.

(4*R*,7*R*,8a*R*,11a*S*)-rel-Decahydro-7-hydroxy-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.4) and (4*R*,8*S*,8a*S*,11a*S*)-rel-Decahydro-8-hydroxy-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.5).



20.1 **20.2** **20.4** **20.5**

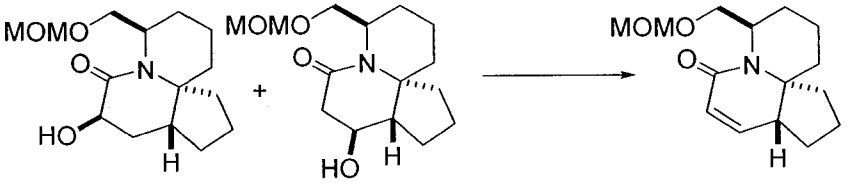
MeONa (1.23 g, 22.8 mmol) was added in one portion to a stirred and cooled (0 °C) solution of the less polar series acetate **20.1** plus the C(8) isomer **20.2** (0.930 g, 2.86 mmol) in MeOH (35 mL). Stirring at room temperature was continued overnight and then brine (30 mL) was added. The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:1 EtOAc-hexane, gave a mixture of alcohols **20.4** and **20.5** (0.79 g, 97%) as a colorless oil. A small sample of **20.4** was obtained by flash chromatography over silica gel using 1:1 EtOAc-hexane.

Alcohol **20.4** had:[21d] FTIR (CH_2Cl_2 cast) 3434, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26-2.09 (m, 16 H), 3.38 (s, 3 H), 3.71 (d, J = 6.9 Hz, 2 H), 4.02-4.13 (m, 2 H), 4.66 (AB q, $\Delta\nu_{AB}$ = 13.7 Hz, J = 6.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.9 (t), 22.4 (t), 23.2 (t), 30.9 (t), 32.6 (t), 34.8 (t), 39.3 (t), 42.9 (d), 52.7 (q), 55.3 (d), 64.6 (d), 66.5 (s), 68.4 (t), 96.6 (t), 173.6 (s); exact mass *m/z* calcd for $C_{15}H_{26}NO_4$ (M + H) 284.18563, found 284.18574.

MeONa (62 mg, 1.2 mmol) was added in one portion to a stirred and cooled (0 °C) solution of acetate **20.2** (37 mg, 0.12 mmol) in MeOH (3 mL). Stirring at room temperature was continued for 8 h and then brine (3 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 8 cm), using 10% MeOH in EtOAc, gave **20.5** (29 mg, 90%) as a colorless solid: mp 64-65 °C; FTIR (CH_2Cl_2 cast) 3386, 2948, 1627 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50-1.59 (m,

4 H), 1.73-1.84 (m, 7 H), 1.99-2.05 (m, 1 H), 2.20-2.23 (m, 1 H), 2.38 (dd, J = 16.5, 7.8 Hz, 1 H), 2.61-2.67 (m, 2 H), 3.35 (s, 3 H), 3.78 (dd, J = 14.0, 8.5 Hz, 2 H), 3.89 (dd, J = 13.2, 8.0 Hz, 2 H), 4.62 (AB q, $\Delta\nu_{AB}$ = 5.9 Hz, J = 6.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.3 (t), 23.0 (t), 24.3 (t), 28.7 (t), 36.5 (t), 37.9 (t), 40.1 (t), 53.2 (d), 53.7 (d), 55.3 (d), 66.7 (s), 68.3 (q), 69.4 (t), 96.5 (t), 169.8 (s); exact mass *m/z* calcd for $C_{15}H_{25}NO_4$ 283.17834, found 283.17821.

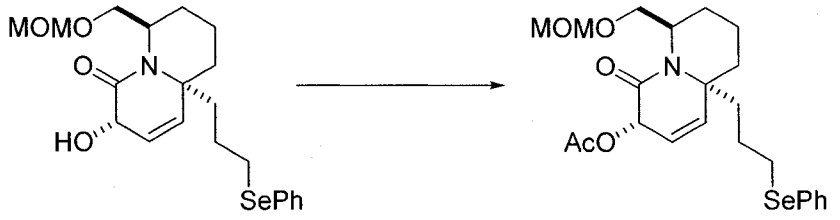
(4*R*,8a*R*,11a*S*)-rel-1,2,3,4,4a,9,10,11-Octahydro-4-[(methoxymethoxy)-methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.3).



20.4 **20.5** **20.3**

Bu_3P (0.90 mL, 3.6 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **20.4** and **20.5** (0.786 g, 2.78 mmol) and 2-nitrophenylselenocyanate (0.820 g, 3.61 mmol) in dry THF (100 mL). The mixture was stirred at 0 °C for 1 h, and then H_2O_2 (30%, 3 mL) was added dropwise at 0 °C. The cold bath was removed and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 1:1 to 2:1 EtOAc-hexane, gave **20.3** (0.706 g, 96%) as an oil.

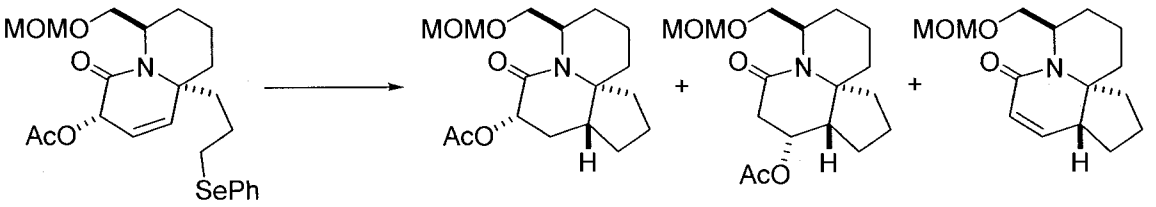
(3*R*,6*S*,9a*S*)-rel-3-Acetyloxy-3,6,7,9,9a-hexahydro-6-[(methoxymethoxy)-methyl]-9a-[3-(phenylseleno)propyl]-4*H*-quinolizin-4-one (18.7).



18.5 **18.7**

Ac_2O (1.2 mL, 13 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the more polar alcohol **18.5** (1.32 g, 3.01 mmol) in pyridine (10 mL). The ice bath was removed and the solution was stirred overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 16 cm), using 1:2 EtOAc-hexane, gave acetate **18.7** (1.36 g, 94%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1747, 1669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.46-1.54 (m, 2 H), 1.60-1.83 (m, 6 H), 1.92-1.99 (m, 1 H), 2.06 (s, 3 H), 2.30-2.37 (m, 1 H), 2.86-2.99 (m, 2 H), 3.33 (s, 3 H), 3.46-3.51 (m, 1 H), 3.97 (dd, J = 3.3, 10.0 Hz, 1 H), 4.10 (dd, J = 9.9, 8.8 Hz, 1 H), 4.61 (AB q, $\Delta\nu_{AB}$ = 11.6 Hz, J = 6.3 Hz, 2 H), 5.49 (dd, J = 3.9, 1.0 Hz, 1 H), 5.71 (dd, J = 10.2, 1.0 Hz, 1 H), 5.81 (dd, J = 10.1, 4.0 Hz, 1 H), 7.20-7.26 (m, 3 H), 7.45-7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (t), 20.9 (q), 24.0 (t), 26.5 (t), 27.9 (t), 35.2 (t), 36.9 (t), 55.0 (q), 55.3 (d), 63.2 (s), 66.5 (d), 70.0 (t), 96.7 (t), 121.0 (d), 126.9 (d), 129.0 (d), 130.0 (s), 132.7 (d), 137.7 (d), 166.0 (s), 170.1 (s); exact mass *m/z* calcd for $C_{23}H_{32}NO_5{}^{80}Se$ (M + H) 482.14402, found 482.14414.

(4*R*,7*S*,8a*R*,11a*S*)-rel-7-Acetyloxydecahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (21.1), (4*R*,8*R*,8a*S*,11a*S*)-rel-8-Acetyloxy-decahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (21.2) and (4*R*,8a*R*,11a*S*)-rel-1,2,3,4,8a,9,10,11-Octahydro-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.3).

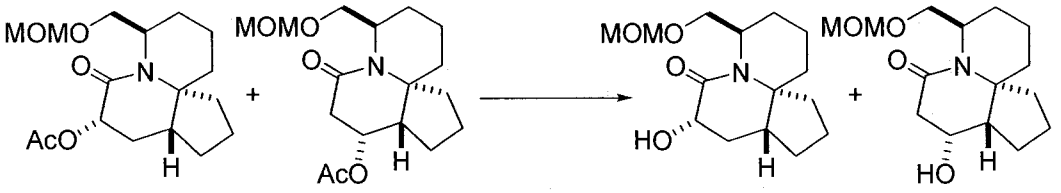


18.7 **21.1** **21.2** **20.3**

Bu_3SnH (0.57 mL, 2.1 mmol) and AIBN (69 mg, 0.42 mmol) in PhH (25 mL) were added over 12 h (syringe pump) to a refluxing solution of acetate **18.7** (0.678 g, 1.41 mmol) in PhH (280 mL). After the addition, the solution was refluxed for 3 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexane, gave acetate **21.1** (0.611 g, 67%, combined yield of two identical batches), **21.2** (0.114 g, 14%, combined yield of two identical batches) and α,β-unsaturated lactam **20.3** (0.126 g, 15%, combined yield of two identical batches) as colorless oils.

Acetate **21.1** had:[21d] FTIR (CH_2Cl_2 cast) 1738, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31-2.09 (m, 14 H), 2.11 (s, 3 H), 2.22-2.27 (m, 1 H), 3.32 (s, 3 H), 3.40-3.46 (m, 1 H), 3.93 (dd, J = 10.0, 3.0 Hz, 1 H), 4.06 (dd, J = 1.0, 8.8 Hz, 1 H), 4.60 (AB q, $\Delta\nu_{AB}$ = 12.2 Hz, J = 6.4 Hz, 2 H), 5.10 (dd, J = 12.2, 4.7 Hz, 1 H)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (t), 21.0 (q), 22.9 (t), 26.3 (t), 31.4 (t), 31.6 (t), 35.7 (t), 37.7 (t), 43.5 (d), 55.2 (q), 57.3 (d), 68.3 (s), 68.7 (d), 70.3 (t), 96.6 (t), 169.2 (s), 170.4 (s); exact mass *m/z* calcd for $C_{17}H_{28}NO_5$ (M + H) 326.19620, found 326.19637.

(4*R*,7*S*,8a*R*,11a*S*)-rel-Decahydro-7-hydroxy-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (21.3) and (4*R*,8*R*,8a*S*,11a*S*)-rel-Decahydro-7-hydroxy-4-[(methoxymethoxy)methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (21.4).

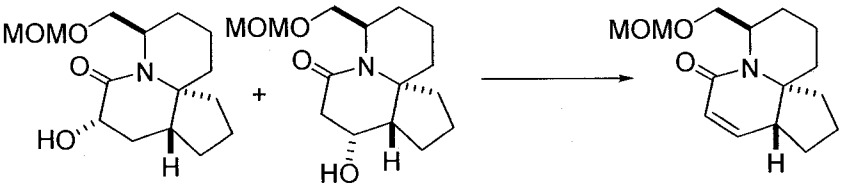


21.1 **21.2** **21.3** **21.4**

MeONa (0.97 g, 18 mmol) was added in one portion to a stirred and cooled (0 °C) solution of acetate **21.1** and the C(8) isomer **21.2** (0.736 g, 2.26 mmol) in MeOH (30 mL). Stirring at room temperature was continued overnight and then brine (30 mL) was added. The aqueous phase was extracted with EtOAc (3 x 25 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:1 EtOAc-hexane, gave a mixture of alcohols **21.3** and **21.4** (0.537 g, 84%) as a colorless oil. The individual alcohols had been isolated in prior experiments.[21d]

Alcohol **21.3** had:[21d] FTIR (CH_2Cl_2 cast) 3435, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30-1.37 (m, 1 H), 1.42-1.93 (m, 11 H), 2.00-2.06 (m, 1 H), 2.09-2.14 (m, 1 H), 2.23-2.27 (m, 1 H), 3.34 (s, 3 H), 3.47-3.53 (m, 1 H), 3.83 (dd, J = 12.3, 5.0 Hz, 1 H), 3.99-4.02 (m, 2 H), 4.62 (AB q, $\Delta\nu_{AB}$ = 14.1 Hz, J = 5.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.4 (t), 22.9 (t), 26.7 (t), 31.6 (t), 33.4 (t), 36.0 (t), 37.5 (t), 43.5 (d), 55.3 (d), 57.3 (q), 67.5 (d), 68.5 (s), 70.0 (t), 96.7 (t), 174.0 (s); exact mass *m/z* calcd for $C_{15}H_{25}NNaO_4$ (M + Na) 306.16758, found 306.16795.

(4*R*,8a*R*,11a*S*)-rel-1,2,3,4,8a,9,10,11-Octahydro-4-[(methoxymethoxy)-methyl]-6*H*-cyclopenta[*i*]quinolizin-6-one (20.3).



21.3 **21.4** **20.3**

Bu_3P (0.61 mL, 2.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohols **21.3** and **21.4** (0.530 g, 1.87 mmol) and 2-nitrophenylselenocyanate (0.550 g, 2.42 mmol) in dry THF (80 mL). The mixture was stirred at 0 °C for 1 h, and then H_2O_2 (30%, 3 mL) was added dropwise at 0 °C. The cold bath was removed and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 2:1 EtOAc-hexane, gave **20.3** (0.482 g, 97%) as a colorless oil.

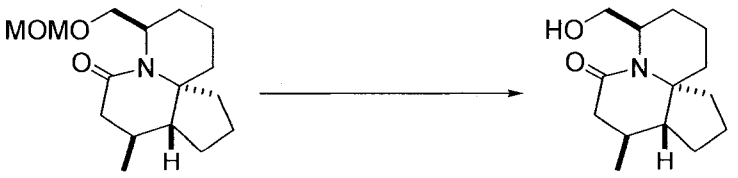
(4*R*,8*S*,8a*R*,11a*S*)-rel-Decahydro-4-[(methoxymethoxy)methyl]-8-methyl-6*H*-cyclopenta[*i*]quinolizin-6-one (15.5).

20.3 **15.5**

MeLi (1.6 M in Et_2O, 10.1 mL, 6.31 mmol) was added dropwise to a stirred and cooled (0 °C) suspension of CuI (purified by Soxhlet extraction overnight with dry THF, followed by drying under vacuum, all with protection from light) (1.54 g, 8.09 mmol) in

THF (25 mL). Stirring was continued at this temperature for 10 min, and then the mixture was cooled to -78 °C. A solution of Me_3SiCl (1.03 mL, 8.06 mmol), HMPA (1.41 mL, 8.10 mmol) and the α,β-unsaturated amide **20.3** (0.715 g, 2.70 mmol) in THF (5 mL plus 1 mL as a rinse) was added dropwise. Stirring at -78 °C was continued for 30 min, and then the mixture was warmed to 0 °C over 30 min by removing the solid carbon dioxide from the cold bath. Saturated aqueous NH_4Cl (20 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 2:1 EtOAc-hexane, gave **15.5** (0.724 g, 96%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3 H), 1.29-1.78 (m, 12 H), 1.88 (dd, J = 17.2, 11.5 Hz, 1 H), 1.97-2.00 (m, 1 H), 2.26-2.30 (m, 1 H), 2.34 (dd, J = 17.1, 3.8 Hz, 1 H), 3.34 (s, 3 H), 3.39-3.44 (m, 1 H), 3.89 (dd, J = 9.9, 3.1 Hz, 1 H), 4.06 (dd, J = 9.9, 8.5 Hz, 1 H), 4.61 (AB q, $\Delta\nu_{AB}$ = 13.1 Hz, J = 6.3 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (d), 20.7 (t), 23.3 (t), 26.0 (t), 30.5 (t), 31.6 (q), 36.3 (t), 38.4 (t), 40.9 (t), 53.4 (d), 55.2 (d), 56.7 (q), 68.5 (s), 70.8 (t), 96.6 (t), 173.2 (s); exact mass *m/z* calcd for $C_{16}H_{28}NO_3$ (M + H) 282.20637; found 282.20639.

(4*R*,8*S*,8a*R*,11a*S*)-rel-Decahydro-4-(hydroxymethyl)-8-methyl-6*H*-cyclopenta[*i*]quinolizin-6-one (22.1).

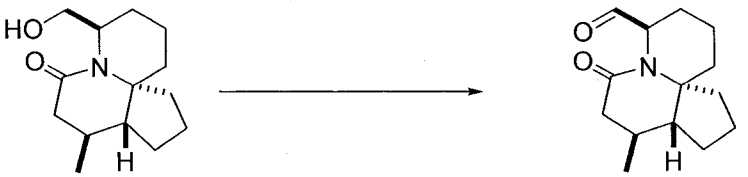


15.5 **22.1**

Me_3SiBr (0.45 mL, 3.5 mmol) was added dropwise to a stirred and cooled (-10 °C) mixture of ether **15.5** (97 mg, 0.35 mmol), 4Å molecular sieves (*ca* 50 mg) and

CH_2Cl_2 (2 mL). Stirring was continued for 1.5 h and then aqueous Na_2CO_3 (10% w/v, 0.5 mL) was added. The cold bath was removed and stirring was continued for 30 min and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using EtOAc, gave alcohol **22.1** (70 mg, 86%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 3363, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 3 H), 1.27-1.78 (m, 12 H), 1.89-1.99 (m, 2 H), 2.28-2.34 (m, 1 H), 2.43 (dd, J = 17.2, 3.6 Hz, 1 H), 3.28-3.33 (m, 1 H), 3.70 (dd, J = 12.6, 5.8 Hz, 1 H), 3.85 (dd, J = 12.6, 1.7 Hz, 1 H), 5.23 (dd, J = 10.4, 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0 (d), 21.4 (t), 22.6 (t), 26.6 (t), 29.3 (t), 30.7 (q), 34.9 (t), 38.8 (t), 41.6 (t), 53.5 (d), 60.2 (d), 63.9 (s), 69.9 (t), 172.6 (s); exact mass *m/z* calcd for $C_{14}H_{23}NNaO_2$ (M + Na) 260.162649, found 260.162559.

(4*R*,8*S*,8a*R*,11a*S*)-rel-Decahydro-8-methyl-6-oxo-6*H*-cyclopenta[*i*]quinolizine-4-carboxaldehyde (22.2).

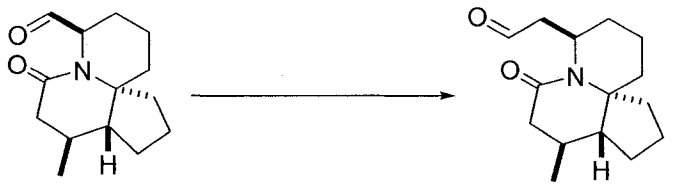


22.1 **22.2**

4Å Molecular sieves (*ca* 300 mg) and NMO (0.178 g, 1.52 mmol) were added successively to a stirred solution of alcohol **22.1** (0.120 g, 0.506 mmol) in CH_2Cl_2 (3.5 mL). Stirring was continued for 5 min, and the mixture was cooled to 0 °C. *n*-Pr_4NRuO_4 (36 mg, 0.10 mmol) was then added. Stirring was continued at 0 °C for 30 min, the ice bath was removed and stirring was continued for 2 h. The reaction mixture was directly loaded onto a column of flash chromatography silica gel (2 x 10 cm) made up with 2:1

EtOAc-hexane, and the column was developed using 2:1 EtOAc-hexane, to obtain aldehyde **22.2** (100 mg, 84%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 1722, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.5 Hz, 3 H), 1.22-1.33 (m, 1 H), 1.43-1.83 (m, 10 H), 1.91-2.07 (m, 3 H), 2.20-2.24 (m, 1 H), 2.42 (dd, J = 17.3, 3.5 Hz, 1 H), 3.34-3.37 (m, 1 H), 9.46 (s, br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4 (d), 20.4 (t), 23.1 (t), 23.7 (t), 30.3 (t), 31.3 (q), 35.3 (t), 38.5 (t), 39.0 (t), 52.8 (d), 62.5 (d), 67.7 (s), 172.7 (s), 201.7 (d); exact mass *m/z* calcd for $C_{14}H_{22}NO_2$ (M + H) 236.165054, found 236.165107.

(4*R*,8*S*,8a*R*,11a*S*)-rel-Decahydro-8-methyl-6-oxo-6*H*-cyclopenta[*i*]quinolizine-4-acetaldehyde (22.3).



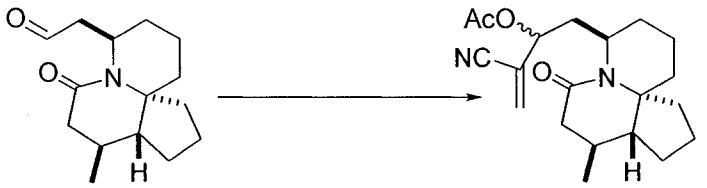
22.2 **22.3**

t-BuOK (0.550 g, 4.90 mmol) was added to a stirred and cooled (0 °C) suspension of $MeOCH_2PPh_3Cl$ (1.84 g, 5.37 mmol) in THF (12 mL). Stirring at 0 °C was continued for 30 min and then aldehyde **22.2** (0.210 g, 0.894 mmol) in THF (2 mL plus 0.5 mL as a rinse) was added dropwise over 1 min. The solution was stirred at 0 °C for 2 h, the ice bath was removed and stirring was continued overnight. Saturated aqueous NH_4Cl (5 mL) was added and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was partially purified by passing it through a silica gel column (2 x 10 cm), using 1.5:1 EtOAc-hexane, and the crude product was used directly in the next step.

CSA (50 mg) was added to a solution of the above crude product in MeCN (5 mL) containing water (2.5 mL). Stirring was continued overnight and saturated aqueous

Na_2CO_3 (5 mL) was then added. Stirring was continued for 30 min and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave aldehyde **22.3** (0.20 g, 92% over two steps) as a colorless solid:[21d] mp 69-70 °C; FTIR (CH_2Cl_2 cast) 1720, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 3 H), 1.26-2.01 (m, 14 H), 2.28-2.35 (m, 2 H), 2.81 (ddd, J = 17.3, 6.8, 1.3 Hz, 1 H), 3.42 (ddd, J = 17.3, 7.1, 1.2 Hz, 1 H), 3.80-3.88 (m, 1 H), 9.70 (s, 1 H); exact mass *m/z* calcd for $C_{14}H_{24}NO_2$ (M + H) 250.180704, found 250.180932.

(4*R*,8*S*,8a*R*,11a*S*)-rel-2-Cyano-1-[[decahydro-8-methyl-6-oxo-6*H*-cyclopenta-[*i*]quinolizin-4-yl]methyl]-2-propenyl Acetate (15.4).



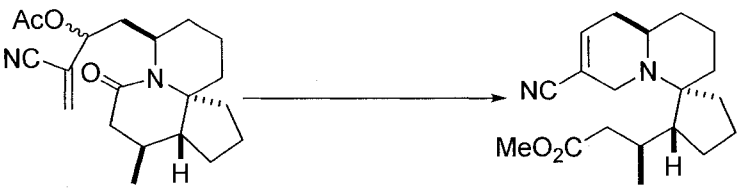
22.3 **15.4**

A mixture of aldehyde **22.3** (0.200 g, 0.803 mmol), DABCO (0.720 g, 6.42 mmol), and acrylonitrile (5 mL) was stirred at room temperature for 5 days. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 10 cm), using 1.5:1 EtOAc-hexane, gave a mixture of epimers which was used directly in the next step.

The above mixture was dissolved in CH_2Cl_2 (7 mL) and the solution was cooled to 0 °C. Pyridine (0.39 mL, 4.8 mmol) and AcCl (0.28 mL, 3.9 mmol) were added successively and the mixture was stirred at 0 °C for 30 min. The ice bath was removed and stirring was continued for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 1:1 EtOAc-hexane, gave acetates **15.4**

(0.255 g, 89% over two steps) as a colorless oil, which was an inseparable mixture of two isomers:[21d] FTIR (CH_2Cl_2 cast) 2223, 1746, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (mixture of two isomers) δ 0.88 (d, J = 6.2 Hz, 3 H), 0.90 (d, J = 6.2 Hz, 3 H), 1.24-2.03 (m, 29 H), 2.067 (s, 3 H), 2.071 (s, 3 H), 2.14-2.26 (m, 3 H), 2.33 (t, J = 4.5 Hz, 1 H), 2.39 (t, J = 4.2 Hz, 1 H), 2.74-2.84 (m, 1 H), 2.97-3.06 (m, 1 H), 3.19-3.37 (m, 2 H), 5.21-5.32 (m, 2 H), 5.97-6.05 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of two isomers) δ 19.1 (d), 19.2 (d), 20.9 (t), 21.0 (q), 21.1 (q), 21.7 (t), 23.5 (t), 27.4 (t), 28.4 (t), 30.6 (t), 30.9 (t), 31.6 (q), 31.9 (q), 35.8 (t), 36.0 (t), 37.1 (t), 37.4 (t), 38.4 (t), 39.0 (t), 41.3 (t), 41.8 (t), 52.8 (d), 53.51 (d), 53.52 (d), 53.8 (d), 68.9 (s), 69.3 (s), 71.4 (d), 71.8 (d), 116.25 (s), 116.28 (s), 122.90 (s), 123.0 (s), 133.0 (t), 133.4 (t), 169.78 (s), 169.85 (s), 174.8 (s), 175.2 (s); exact mass *m/z* calcd for $C_{20}H_{28}N_2NaO_3$ (M + Na) 367.19921, found 367.19917.

Methyl (β*R*,1*R*,2*S*,9'a*S*)-rel-7'-Cyano-1',2',3',6',9',9'a-hexahydro-β-methyl-spiro[cyclopentane-1,4'-[4*H*]quinolizine]-2-propanoate (15.3).

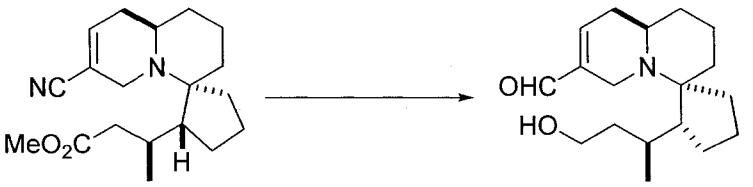


15.4 **15.3**

Commercial $Me_3O^+BF_4^-$ (0.52 g, 3.5 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 2,6-di-*tert*-butyl-4-methylpyridine (0.88 g, 4.3 mmol) and lactam **15.4** (mixture of two isomers, 0.245 g, 0.712 mmol) in CH_2Cl_2 (7 mL). The ice bath was removed and stirring was continued for 2 h. The solvent was then evaporated. The residue was taken up in MeCN (14 mL) and cooled to 0 °C, and aqueous Na_2CO_3 (20% w/v, 7 mL) was added. The ice bath was removed and the mixture was stirred

vigorously for 3 h. The aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:5 EtOAc-hexane, gave the tertiary amine **15.3** (0.176 g, 83%) as a colorless solid:[21d] mp 67-69 °C; FTIR (CH_2Cl_2 cast) 2217, 1735, 1654 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.70 (m, 1 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.96-1.26 (m, 8 H), 1.39-1.60 (m, 6 H), 1.81-1.84 (m, 1 H), 2.06-2.12 (m, 1 H), 2.16-2.21 (m, 1 H), 2.77 (d, J = 16.1 Hz, 1 H), 3.10 (d, J = 16.0 Hz, 1 H), 3.16 (d, J = 13.6 Hz, 1 H), 3.39 (s, 3 H), 5.87-5.89 (m, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 20.2 (d), 21.5 (t), 21.6 (t), 23.5 (t), 29.3 (t), 31.9 (q), 35.5 (t), 41.3 (t), 49.13 (t), 49.17 (t), 50.8 (d), 52.3 (d), 56.6 (q), 67.4 (s), 111.5 (s), 118.2 (s), 141.1 (d), 173.1 (s); exact mass *m/z* calcd for $C_{19}H_{29}N_2O_2$ (M + Na) 317.22235, found 317.22189.

(1*R*,2*S*,9'a*S*)-rel-1',2',3',6',9',9'a-Hexahydro-2-[(1*R*)-3-hydroxy-1-methylpropyl]spiro[cyclopentane-1,4'-[4*H*]quinolizine]-7'-carboxaldehyde (23.3).



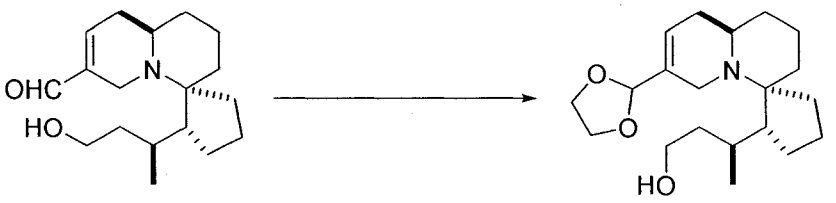
15.3 **23.3**

DIBAL-H (1.0 M in CH_2Cl_2, 0.23 mL, 0.23 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ester **15.3** (36.9 mg, 0.116 mmol) in THF (2 mL). Stirring at -78 °C was continued for 1 h, and then acetone (0.1 mL) and $Na_2SO_4 \cdot 10H_2O$ (250 mg) were added. Stirring was continued at room temperature for 2.5 h, and then the mixture was filtered through a pad of Celite (2 x 3 cm), using EtOAc (3 x 8 mL). The filtrate was evaporated to give a residue which was kept under oil pump vacuum for 1 h

and used directly in the next step without further purification. The material was a mixture of the expected cyano aldehyde **23.2** and the corresponding cyano alcohol **23.1** (TLC).

DIBAL-H (1.0 M in CH_2Cl_2, 0.46 mL, 0.46 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of above residue in PhMe (2 mL). The mixture was stirred at -78 °C for 30 min, and was then warmed to 0 °C over 45 min by slowly removing the lumps of dry ice from the cold bath. Stirring was continued at 0 °C for 15 min, and then acetone (0.1 mL) and $Na_2SO_4 \cdot 10H_2O$ (500 mg) was added. The cold bath was removed and stirring was continued for 2.5 h, and then the mixture was filtered through a pad of Celite (2 x 3 cm), using EtOAc (3 x 8 mL). The combined organic extracts were evaporated and flash chromatography of the residue over silica gel (2 x 10 cm), using EtOAc, gave alcohol **23.3** (25 mg, 72%) as a colorless oil:[21d] FTIR (CH_2Cl_2, cast) 3345, 1680 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.83 (d, J = 6.8 Hz, 3 H), 1.07-1.41 (m, 9 H), 1.43-1.76 (m, 3 H), 1.81-2.19 (m, 7 H), 2.81 (dd, J = 16.5, 2.6 Hz, 1 H), 3.46-3.69 (m, 3 H), 3.99 (s, 1 H), 6.00-6.03 (m, 1 H), 9.20 (s, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 21.0 (d), 22.0 (t), 23.6 (t), 29.4 (t), 30.9 (d), 32.7 (t), 35.9 (t), 40.5 (t), 45.1 (t), 53.7 (q), 57.8 (d), 61.7 (t), 67.9 (s), 139.9 (s), 146.3 (d), 191.2 (d); exact mass *m/z* calcd for $C_{18}H_{30}NO_2$ (M + H) 292.22711, found 292.22706.

(β*R*,1*R*,2*S*,9'a*S*)-rel-1',2',3',6',9',9'a-Hexahydro-7'-(1,3-dioxolan-2-y)-β-methylspiro[cyclopentane-1,4'-[4H]quinolizine]-2-propan-3-ol (23.5).



23.3 **23.5**

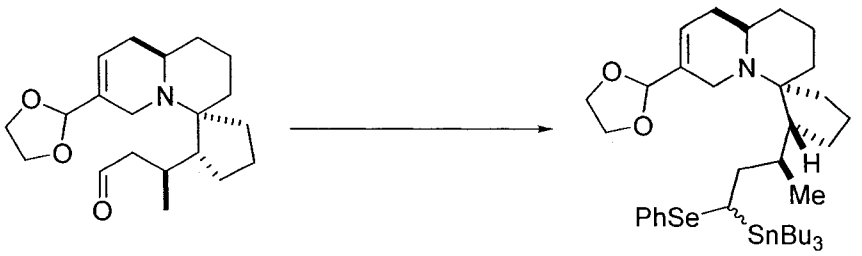
$Me_3SiOSO_2CF_3$ (24 μL, 0.13 mmol) and 1,2-bis(trimethylsiloxy)ethane (0.20 mL, 0.82 mmol) were added successively to a stirred and cooled (-78 °C) solution of aldehyde **23.3** (35 mg, 0.12 mmol) in CH_2Cl_2 (1 mL). The cooling bath was left in place but not recharged until the temperature reached -10 °C (about 1 h). Stirring at this temperature was continued for 3 h, and then saturated aqueous K_2CO_3 solution (0.2 mL) followed by MeOH (2 mL) were added. The mixture was stirred at room temperature overnight, diluted with brine (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using EtOAc, gave **23.5** (30 mg, 76%) as an oil: FTIR (CH_2Cl_2 cast) 3407, 2930, 2870, 1081 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 3 H), 1.24-1.76 (m, 12 H), 1.83-1.90 (m, 2 H), 1.99-2.19 (m, 4 H), 2.30-2.35 (m, 1 H), 2.42-2.45 (m, 1 H), 2.84 (dd, J = 15.5, 2.4 Hz, 1 H), 3.10 (d, J = 15.5 Hz, 1 H), 3.61 (ddd, J = 10.5, 10.5, 3.3 Hz, 1 H), 3.66-3.70 (m, 1 H), 3.86-4.02 (m, 4 H), 5.17 (s, 1 H), 5.84 (dd, J = 4.7, 4.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.41 (d), 21.88 (t), 23.54 (t), 28.81 (t), 30.82 (d), 33.10 (t), 33.62 (t), 33.63 (t), 34.74 (t), 39.99 (t), 45.79 (t), 54.08 (q), 58.08 (d), 61.92 (t), 65.21 (t), 65.27 (t), 67.49 (s), 104.95 (d), 125.43 (d), 133.23 (s); exact mass *m/z* calcd for $C_{20}H_{33}O_3N$ 335.24603, found 335.24620.

(β*R*,1*R*,2*S*,9'a*S*)-rel-1',2',3',6',9',9'a-Hexahydro-7'-(1,3-dioxolan-2-yl)-β-methylspiro[cyclopentane-1,4'-[4H]quinolizine]-2-propanal (23.6).

23.5 **23.6**

4Å Molecular sieves (*ca* 40 mg) and NMO (19 mg, 0.16 mmol) were added successively to a stirred solution of alcohol **23.5** (27 mg, 0.081 mmol) in CH_2Cl_2 (1.0 mL). Stirring was continued for 5 min, the mixture was then cooled to 0 °C and *n*-Pr_4NRuO_4 (5.6 mg, 0.016 mmol) was added. Stirring was continued at 0 °C for 30 min, and then the reaction mixture was directly loaded onto a column of flash chromatography silica gel (1 x 5 cm) made up with EtOAc. The column was developed using EtOAc to obtain **23.6** (24 mg, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2935, 2869, 1721, 1081 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, J = 6.7 Hz, 3 H), 1.53 (qd, J = 13.1, 3.6 Hz, 1 H), 1.35-1.44 (m, 6 H), 1.51-1.59 (m, 2 H), 1.70-1.77 (m, 2 H), 1.92-2.03 (m, 2 H), 2.07-2.13 (m, 3 H), 2.30-2.38 (m, 2 H), 2.85 (dd, J = 15.6, 2.5 Hz, 1 H), 3.07 (d, J = 15.6 Hz, 1 H), 3.15 (dd, J = 15.6, 2.5 Hz, 1 H), 3.86-4.00 (m, 4 H), 5.14 (s, 1 H), 5.82 (s, 1 H), 9.57 (t, J = 2.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.78 (t), 22.16 (d), 23.70 (t), 28.57 (t), 29.84 (d), 32.97 (t), 33.76 (t), 33.78 (t), 34.97 (t), 46.27 (t), 51.38 (t), 54.27 (q), 58.52 (d), 65.25 (t), 65.29 (t), 67.24 (s), 105.13 (d), 125.62 (d), 133.28 (s), 204.04 (d); exact mass *m/z* calcd for $C_{20}H_{31}O_3N$ 333.23041, found 333.23063.

(1*R*,2*S*,9'a*S*)-rel-7'-[1,3-Dioxolan-2-yl]-1',2',3',6',9',9'a-hexahydro-2-[(1*R*)-1-methyl-3-(phenylseleno)-3-(tributylstannyl)propyl]spiro[cyclopentane-1,4'-[4*H*]-quinolizine] (15.2).



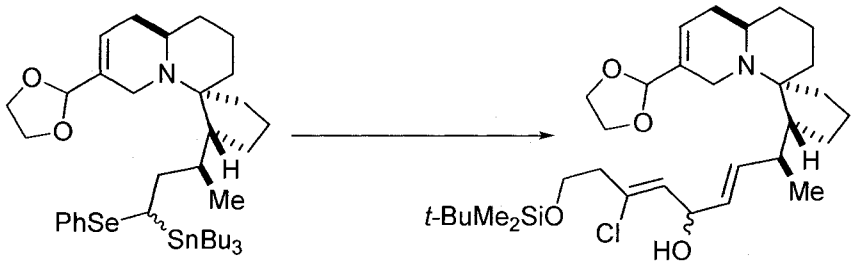
23.6 **15.2**

n-BuLi (2.5M in hexane, 0.14 mL, 0.35 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.055 mL, 0.39 mmol) in THF (0.5 mL). Stirring was continued at this temperature for 10 min, and then Bu_3SnH (0.11 mL, 0.39 mmol) was added. Stirring was continued at this temperature for 15 min, and then the ice bath was replaced by a dry ice-acetone bath. A solution of aldehyde **23.6** (24 mg, 0.071 mmol) in THF (0.5 mL plus 0.5 mL as a rinse) was added, and stirring was continued at -78 °C for 1 h. The mixture was quenched by addition of saturated aqueous NH_4Cl (2 mL), the cold bath was removed and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give an oily residue which was kept under oil pump vacuum for 1 h and used directly in the next step without further purification.

Pyridine (0.1 mL), PhSeCN (52 μL, 0.42 mmol) and Bu_3P (0.11 mL, 0.42 mmol) were added successively dropwise to a stirred and cooled (0 °C) solution of the above crude hydroxystannane in THF (1 mL). The ice bath was removed and the mixture was stirred for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 100% hexane to 10:1 hexane-EtOAc, gave selenides **15.2** contaminated by impurities (*ca* 33 mg, 61% over two steps) as a yellowish oil: FTIR (CH_2Cl_2 cast) 2954, 2927, 1463, 1079 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 12 H), 1.01 (dd, J = 15.9, 7.4 Hz, 6 H), 1.33 (dd, J = 14.8, 7.4 Hz, 9 H), 1.49-1.55 (m, 11 H), 1.60-1.70 (m, 3 H), 1.78-2.10 (m, 6 H), 2.35 (td, J = 12.4, 2.6 Hz, 2 H), 2.79 (dd, J = 15.6, 1.8 Hz, 1 H), 3.02 (d, J = 16.1 Hz, 1 H), 3.12 (dd, J = 12.2, 4.7 Hz, 1 H),

3.86-3.96 (m, 4 H), 5.13 (s, 1 H), 5.81 (s, 1 H), 7.18-7.25 (m, 3 H), 7.48 (d, J = 7.1 Hz, 2 H); exact mass *m/z* calcd for $C_{38}H_{62}NO_2{}^{80}Se^{120}Sn$ (M - H) 764.29623, found 764.29662.

(1*R*,2*S*,9'a*S*)-rel-2-[(1*R*,2*E*,5*Z*)-6-Chloro-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-1-methyl-2,5-octadienyl]-7'-[1,3-dioxolan-3-yl]-1',2',3',6',9',9'a-hexahydrospiro[cyclopentane-1,4'-[4*H*]quinolizine] (23.8).



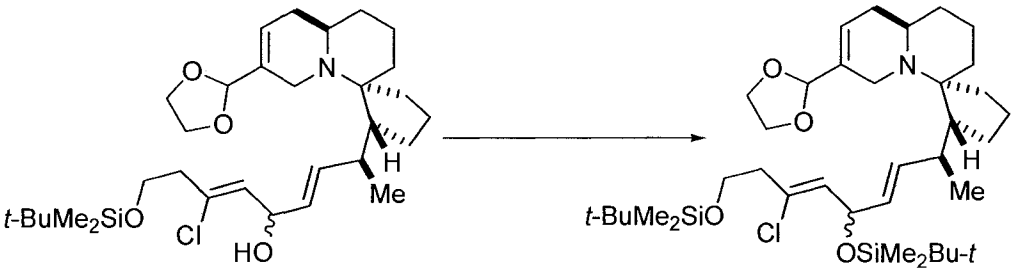
15.2 **23.8**

n-BuLi (2.5 M in hexane, 0.080 mL, 0.20 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of the selenide stannane mixture **15.2** (39 mg, 0.050 mmol) in THF (0.5 mL). Stirring at -78 °C was continued for 30 min and then aldehyde **23.7** (53 mg, 0.21 mmol) in THF (0.5 mL plus 0.5 mL as a rinse) was added dropwise. Stirring at -78 °C was continued for 30 min. Saturated aqueous NH_4Cl (2 mL) was then added and the mixture was extracted with EtOAc (3 x 7 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:4 to 1:1 EtOAc-hexane, gave the selenide which was dissolved in MeOH (2 mL).

Powdered $NaHCO_3$ (32 mg), $NaIO_4$ (32 mg, 0.15 mmol) and water (0.4 mL) were added successively to the above solution and stirring was continued for 24 h. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x

10 cm), using 1:4 to 1:1 EtOAc-hexane, gave alcohol **23.8** as a colorless oil, which was used directly in the next step: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer only) δ 0.059 (s, 6 H), 0.89 (s, 9 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.10-1.26 (m, 3 H), 1.33-1.52 (m, 7 H), 1.71-1.95 (m, 4 H), 2.05-2.14 (m, 2 H), 2.35-2.39 (m, 1 H), 2.46-2.60 (m, 3 H), 2.84 (dd, J = 15.6, 2.7 Hz, 1 H), 3.10 (d, J = 15.6 Hz, 1 H), 3.78-3.82 (m, 2 H), 3.88-4.00 (m, 4 H), 5.03 (t, J = 7.2 Hz, 1 H), 5.16 (s, 1 H), 5.43 (dd, J = 15.6, 6.6 Hz, 1 H) 5.63 (d, J = 7.8 Hz, 1 H), 5.79-5.85 (m, 1 H), 6.04 (dd, J = 15.6, 7.6 Hz, 1 H); exact mass *m/z* calcd for $C_{31}H_{53}{}^{35}ClNO_4Si$ (M + H) 566.34269, found 566.34258.

(1*R*,2*S*,9'a*S*)-rel-2-[(1*R*,2*E*,5*Z*)-6-Chloro-4,8-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-1-methyl-2,5-octadienyl]-7'-[1,3-dioxolan-3-yl]-1',2',3',6',9',9'a-hexahydrospiro[cyclopentane-1,4'-[4*H*]quinolizine] (23.9).

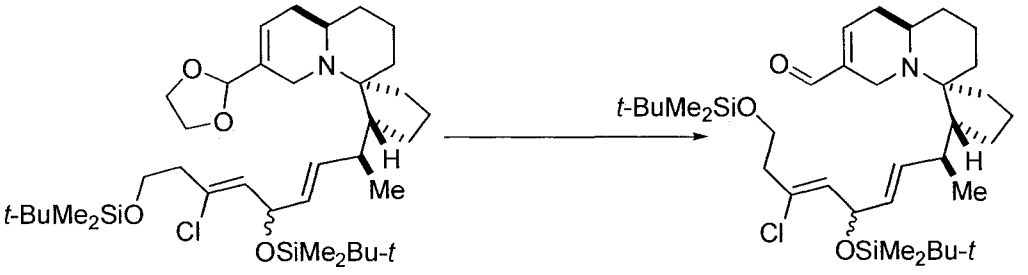


23.8 **23.9**

Imidazole (32 mg, 0.47 mmol) and *t*-$BuMe_2SiCl$ (38 mg, 0.25 mmol) were added successively to a stirred solution of the above alcohol **23.8** in DMF (*ca* 1 mL), and stirring was continued for 48 h. Water (5 mL) was added and the mixture was extracted with Et_2O (4 x 8 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 8 cm), using 1:10 to 1:4 EtOAc-hexane, gave **23.9** (12.4 mg, 36% over three steps) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2928, 2857, 1102, 836 cm^{-1}; ^{1}H NMR (500

MHz, $CDCl_3$, major isomer only) δ 0.059 (s, 12 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.15-1.16 (m, 2 H), 1.34-1.49 (m, 6 H), 1.56 (d, *J* = 12.7 Hz, 1 H), 1.72 (m, 1 H), 1.80 (m, 1 H), 1.88-1.96 (m, 2 H), 2.04-2.10 (m, 2 H), 2.34-2.38 (m, 1 H), 2.50 (t, *J* = 6.7 Hz, 3 H), 2.82 (dd, *J* = 15.7, 2.3 Hz, 1 H), 3.09 (d, *J* = 15.7 Hz, 1 H), 3.74-3.80 (m, 2 H), 3.88-3.99 (m, 4 H), 5.01 (t, *J* = 6.8 Hz, 1 H), 5.16 (s, 1 H), 5.37 (dd, *J* = 15.6, 5.8 Hz, 1 H), 5.54 (d, *J* = 7.9 Hz, 1 H), 5.82-5.87 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer only) δ -5.30 (q), -4.58 (q), -4.55 (q), -3.58 (q), 18.28 (s), 19.59 (s), 21.92 (t), 23.61 (t), 25.88 (q), 28.87 (t), 32.55 (t), 32.54 (t), 35.29 (t), 35.41 (d), 42.88 (t), 45.51 (t), 45.53 (t), 53.24 (q), 58.11 (d), 60.73 (t), 65.17 (t), 65.26 (t), 67.10 (s), 71.34 (d), 105.21 (d), 124.82 (d), 127.73 (d), 129.59 (s), 130.73 (d), 133.58 (s), 138.31 (d);exact mass *m/z* calcd for $C_{37}H_{67}{}^{35}ClNO_4Si_2$ (M + H) 680.42917, found 680.42966.

(1*R*,2*S*,9'a*S*)-rel-2-[(1*R*,2*E*,5*Z*)-6-Chloro-4,8-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-1-methyl-2,5-octadienyl]-1',2',3',6',9',9'a-hexahydrospiro[cyclo-pentane-1,4'-[4*H*]quinolizine]-7'-carboxaldehyde (24.1).

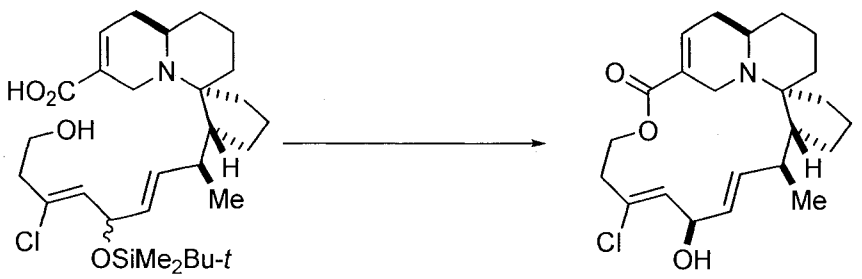


23.9 **24.1**

2,6-Lutidine (5 μL, 0.04 mmol) and $Me_3SiOSO_2CF_3$ (5 μL, 0.03 mmol) were added successively to a stirred and cooled (0 °C) solution of **23.9** (4.0 mg, 0.006 mmol) in CH_2Cl_2 (0.8 mL). Stirring was continued at this temperature for 1 h (TLC showed the disappearance of the starting material), and then water (*ca* 1.5 mL) was added. The

mixture was stirred at 0 °C for 15 min, and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 5 cm), using 1:10 EtOAc-hexane, gave **24.1** (3.0 mg, 81%) as a colorless oil:[21d] FTIR (CH_2Cl_2 cast) 2954, 2929, 1686, 1103, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (1.6:1 mixture of two isomers) δ 0.04 (s, 12 H), 0.88 (s, 18 H), 0.95-0.97 (two doublets at δ 0.96, 0.95, J = 6.5, 7.0 Hz, 3 H in all), 1.07-1.67 (m, 9 H), 1.75-1.97 (m, 3 H), 2.03-2.20 (m, 2 H), 2.27-2.40 (m, 3 H), 2.50 (t, J = 6.4 Hz, 2 H), 2.83-2.87 (m, 1 H), 3.45 (d, J = 15.2 Hz, 1 H), 3.75-3.79 (m, 2 H), 4.98-5.02 (m, 1 H), 5.23-5.32 (m, 1 H), 5.52-5.55 (m, 1 H), 5.69 (ddd, J = 15.83, 8.2, 1.0 Hz, 0.38 H), 5.81 (ddd, J = 15.5, 7.6, 1.1 Hz, 0.6 H), 6.70-6.73 (m, 1 H), 9.38 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (1.6:1 mixture of two isomers, major isomer peaks only) δ -5.3 (q), -4.6 (q), -4.5 (q), -4.4 (q), 18.3 (s), 19.9 (d), 21.7 (t), 23.6 (t), 25.9 (q), 29.0 (t), 32.7 (t), 33.4 (t), 36.1 (d), 36.8 (t), 41.1 (t), 42.8 (t), 45.1 (t), 53.3 (q), 58.2 (d), 60.6 (t), 67.2 (s), 71.4 (d), 127.9 (d), 129.7 (s), 130.7 (d), 138.0 (d), 140.5 (s), 147.7 (d), 192.3 (d); exact mass *m/z* calcd for $C_{35}H_{63}{}^{35}ClNO_3Si_2$ (M + H) 636.40296, found 636.40287.

(4*R*,12*Z*,14*R*,15*E*,17*S*,17a*R*,20a*S*)-rel-12-Chloro-1,2,3,4,10,11,14,17,17a,18,-19,20-dodecahydro-14-hydroxy-17-methyl-8*H*-4,7-ethanylylidene-6*H*-cyclopenta[f]-pyrido[1,2-e][1,5]oxaazacyclopentadecin-8-one [(±)-Halichlorine (24.5)].



24.3 **24.5**

N-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (68 mg, 0.35 mmol) was added to a stirred solution of DMAP (77 mg, 0.63 mmol) and DMAP·HCl (88 mg, 0.55 mmol) in $CHCl_3$ (10 mL), and the resulting solution was heated at reflux. A solution of acid **24.3** (3.4 mg, 6.3 μmol) in $CHCl_3$ (1 mL) was added to the above solution over 5 h (gas-tight syringe, syringe pump). After the addition two rinses of $CHCl_3$ (0.1 mL plus 0.1 mL) were added, and the solution was refluxed for a further 1 h. Heating was stopped and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 6 cm), using 1:3 EtOAc-hexane, gave **24.4** (1.9 mg, 58%) as a mixture of two isomers which was used directly in the next step.

HF·pyridine (*ca* 1.2 N, 0.2 mL) was added to a stirred solution of **24.4** (1.9 mg, 3.7 μmol) in THF (2.5 mL), and stirring was continued for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 6 cm), using 2:1 EtOAc-hexane, gave **24.5** (the more polar spot, 0.8 mg, 54%, 86% based on the amount of the correct isomer in the starting material) as a colorless oil: FTIR (CH_2Cl_2 cast) 3407, 2929, 2872, 1715, 1659, 1295 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.01 (d, J = 6.8 Hz, 3 H), 1.13 (d, J = 12.2 Hz, 1 H), 1.30 (m, 1 H), 1.43 (ddd, J = 12.0, 10.0, 3.0, 1 H), 1.50 (dddd, J = 13.0, 13.0, 13.0, 4.5 Hz, 1 H), 1.62-1.80 (m, 8 H), 1.95-2.03 (m, 1 H), 2.15-2.21 (m, 1 H),

2.55 (d, J = 14.5 Hz, 1 H), 2.63 (dd, J = 19.5, 2.0 Hz, 1 H), 2.73 (dq, J = 7.1, 6.8 Hz, 1 H), 2.86 (ddd, J = 14.5, 12.5, 4.5 Hz, 1 H), 3.10-3.14 (m, 1 H), 3.21 (d, J = 17.5 Hz, 1 H), 3.44 (d, J = 17.5 Hz, 1 H), 3.98 (ddd, J = 11.5, 4.5, 2.0 Hz, 1 H), 4.62 (ddd, J = 14.5, 11.5, 3.0 Hz, 1 H), 5.03 (dd, J = 6.5, 4.5 Hz, 1 H), 5.35 (dd, J = 15.5, 4.0 Hz, 1 H), 5.57 (d, J = 7.5 Hz, 1 H), 5.75 (dd, J = 15.0, 8.5 Hz, 1 H), 7.03 (br s, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 18.1, 22.1, 22.3, 24.6, 24.9, 27.1, 32.1, 33.5, 33.7, 38.7, 41.8, 51.8, 51.9, 62.3, 69.5, 70.9, 128.3, 128.8, 129.7, 133.1, 136.9, 139.2, 167.6; exact mass *m/z* calcd for $C_{23}H_{33}{}^{35}ClNO_3$ (M + H) 406.21435, found 406.21437. The spectra were identical to those published for halichlorine.[1,10,27]

The incorrect isomer of the starting material was separated, but no attempt was made to recycle it (by oxidation and reduction).

5 REFERENCES AND FOOTNOTES

1 Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.

2 Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.

3 (a) Springer, T. A. *Cell* **1994**, *76*, 301. (b) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068.

4 Foster, C. A. *J. Allergy Clin. Immunol.* **1996**, S270.

5 Boschelli, D. H.; Kramer, J. B.; Khatana, S. S.; Sorenson, R. J.; Connor, D. T.; Ferin, M. A.; Wright, C. D.; Lesch, M. E.; Imre, K.; Okonkwo, G. C.; Schrier, D. J.; Conory, M. C.; Ferguson, E. F.; Woelle, J.; Saxena, U. *J. Med. Chem.* **1995**, *38*, 4597.

6 (a) Vidal-Vanaclocha, F.; Fantuzzi, G.; Mendoza, L.; Fuentes, A. M.; Anasagasti, M. J.; Martin, J.; Carrascal, T.; Walsh, P.; Reznikov, L. L.; Kim, S.-H.; Novick, D.; Rubinstein, M.; Dinarello, C. A. *Proc. Nat. Acad. Sci. U.S.A.* **2000**, *97*, 734. (b) Wu, T-C. *Cancer Res.* **2007**, *67*, 6003.

7 Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861.

8 Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542.

9 Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483.

10 Christie, H. S.; Heathcock, C. H. *Proc. Nat. Acad. Sci.* **2004**, *101*, 12079.

11 Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513.

12 Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813.

13 Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1992**, *33*, 7461.

14 Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739.

15 (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257.

16 Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

17 Carlsson, S.; El-Barbary, A. A.; Lawesson, S.-O. *Bull. Chim. Belg.* **1980**, *89*, 643.

17 Flomer, J. J., Acero, C., Thai, D. L., Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170.

18 Abe, T.; Haga, T.; Negi, S.; Morita, Y.; Takayanagi, K.; Hamamura, K. *Tetrahedron* **2001**, *57*, 2701.

19 Kim, H.; Seo, J. H.; Shin, K. J.; Kim, D. J.; Kim, D. *Heterocycles* **2006**, *70*, 143.

20 Adrien, A.; Gais, H-J.; Kohler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 2155.

21 (a) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. (b) Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 2879. (c) Clive, D. L. J.; Wang, J.; Yu, M. *Tetrahedron Lett.* **2005**, *46*, 2853. (d) Yu, M. PhD Dissertation, University of Alberta, Edmonton, Alberta, 2006. (e) Yeh, V. S. C. PhD Dissertation, University of Alberta, Edmonton, Alberta, 2001.

22 Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332.

23 Crich, D.; Yao, Q. W.; Filzen, G. F. *J. Am. Chem. Soc.* **1995**, *117*, 11455.

24 Clive, D. L. J.; Yu, M.; Li, Z. *Chem. Commun.* **2005**, 906.

25 Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

26 Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930.

27 We thank Professor H. Arimoto (Tohoku University) for a copy of the ^{13}C NMR spectrum of natural halichlorine.