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Synthetic Applications of 5-*Endo*-trigonal Cyclization, and Synthetic Studies Related to Puraquinonic Acid

by

Mousumi Sannigrahi 

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

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ABSTRACT

The first part of this thesis describes the application of a tandem radical cyclization to the formal synthesis of methyl *epi*-jasmonate. This sequence involves i) a 5-*exo*-digonal cyclization, ii) abstraction of a hydrogen, and iii) an unusual 5-*endo*-trigonal cyclization. The cyclization results in the formation of substituted cyclopentanes with good stereocontrol. Application of this sequence to material from the chiral pool was also studied, and the results of this work on the tandem radical process have been published (*J. Org. Chem.* **1999**, *64*, 2776).

The second part of this thesis describes synthetic studies on puraquinonic acid. Puraquinonic acid is a fungal metabolite which is known to induce cell differentiation in HL-60 cells. It contains an asymmetric center which is asymmetric due to substitution further away in molecule. This feature poses a significant synthetic problem. A model study was done to accommodate this feature. The route should make it possible to obtain the natural product in both racemic and optically pure forms. Also, a route towards the actual synthesis of puraquinonic acid was explored. A key intermediate was prepared, and it should lead to puraquinonic acid by the application of some straightforward chemical transformation.

ACKNOWLEDGMENTS

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

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5-*Endo*-Trigonal Radical Cyclization, Synthesis of Methyl *epi*-Jasmonate, and use of Material From the Chiral Pool

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LIST OF ABBREVIATIONS

AIBN.....2,2'-azobisisobutyronitrile

Bn.....benzyl

t-Bu.....*tert*-butyl

DBU.....1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ.....2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD.....diethyl azodicarboxylate

DIBAL.....diisobutylaluminum hydride

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

HMPA.....hexamethylphosphoric triamide

KHMDS.....potassium hexamethyldisilazane

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazane

MCPBA.....*m*-chloroperoxybenzoic acid

MOM.....methoxymethyl

MEM.....methoxyethoxymethyl

NMO.....4-methylmorpholine *N*-oxide

NMP.....1-methyl-2-pyrrolidinone

PCC.....pyridinium chlorochromate

PDC.....pyridinium dichromate

Ph.....phenyl

PMB.....*p*-methoxybenzyl

PPTS.....pyridinium *p*-toluenesulfonate

Pr.....propyl

Py.....pyridine

SEM.....2-(trimethylsilyl)ethoxymethyl

TBAF.....tetrabutylammonium fluoride

TBDPS.....*tert*-butyldiphenylsilyl

TBS.....*tert*-butyldimethylsilyl

TMS.....trimethylsilyl

Tf.....trifluoromethanesulfonyl

TFA.....trifluoroacetic acid

TFAA.....trifluoroacetic anhydride

THF.....tetrahydrofuran

TPAP.....tetra-*n*-propylammonium perruthenate

Ts.....*p*-toluenesulfonyl

PART I

5-*ENDO*-TRIGONAL RADICAL CYCLIZATION, SYNTHESIS OF METHYL *EPI*-JASMONATE, AND USE OF MATERIAL FROM THE CHIRAL POOL

5-*ENDO*-TRIGONAL RADICAL CYCLIZATION

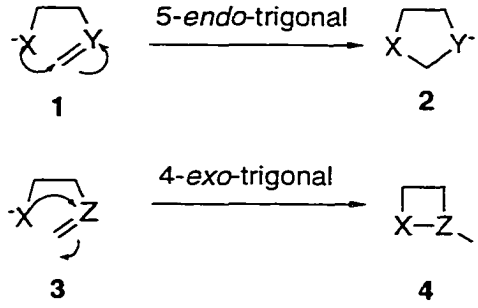
General

During the last 20 years radical reactions have become important for the generation of carbon-carbon bonds. Such reactions have characteristics that are different from polar processes. They occur under neutral conditions, and so acid- and base-labile groups are unaltered, and several common types of functional groups do not have to be protected during radical reactions. Another important feature is that steric congestion, which complicates and hinders ionic processes, does not play such a decisive role in radical chemistry.

A number of radical initiators are available which initiate reactions at low temperatures, and so radical reactions can be run under mild conditions.[1]

Most synthetic applications of radical chemistry in synthesis involve cyclizations, and in this regard the Baldwin rules[2,3] for ring closure and the Beckwith guidelines[4] are important in predicting the outcome of radical processes. In particular, 5-*endo* trigonal cyclizations are generally disfavored, but, as described below, an increasing number of such reactions are being discovered. Stereocontrolled tandem sequences of radical ring closures, giving rise to a variety of useful substrates, have been developed. Some of these sequences involve 5-*endo*-trigonal cyclization. The following literature review deals with the main transformations which have been accomplished using 5-*endo*-trigonal cyclization.

According to the Rules for Ring Closure, established by Baldwin[2,3] in 1976, a closure taking place through a 5-*endo*-trigonal pathway is a geometrically disfavored process when X is a first row element (Scheme 1). This rule is based on the

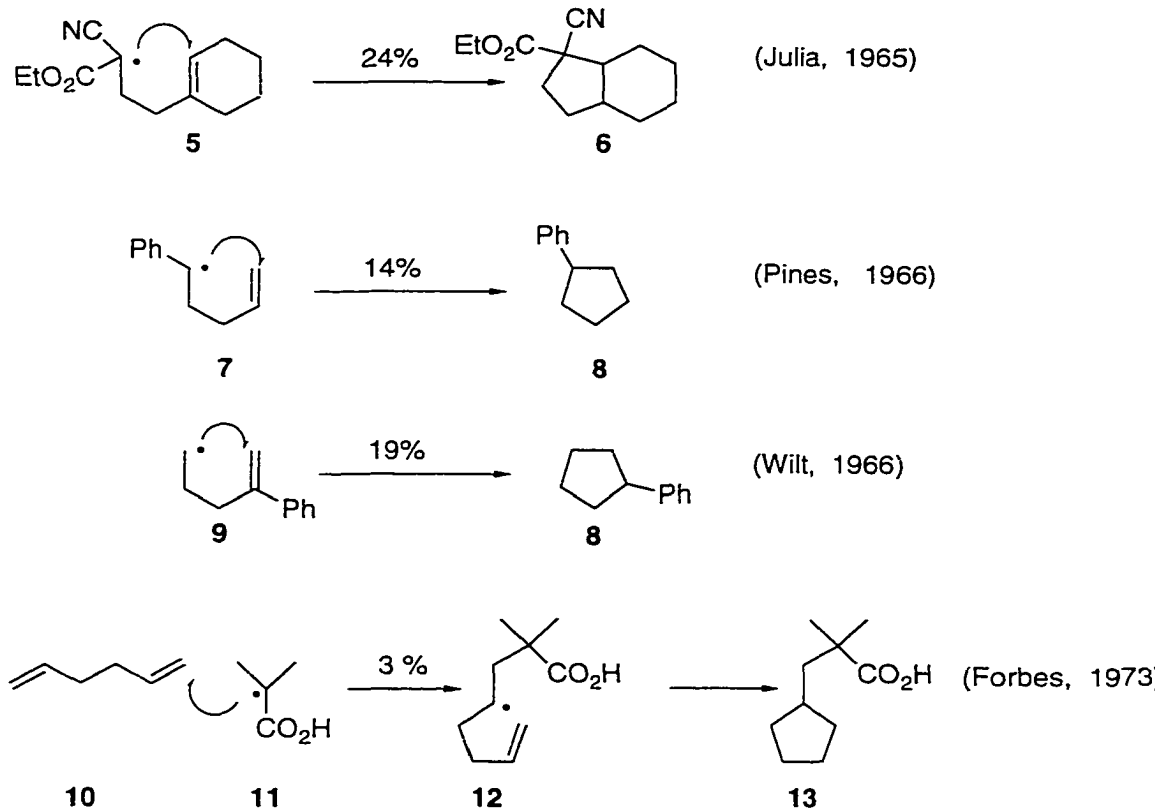


Scheme 1

premise that the transition state has to acquire a specific conformation for ring closure to occur. In analogy to the work done by Dunitz and Bürgi[5] on nucleophilic additions to carbonyls, Baldwin predicted the required angle of approach to be 109°. Thus, for 5-*endo*-trigonal cyclization a severe distortion of the bond angles and distances is required to achieve such a trajectory when the connecting chain involves first row elements. In such cases, the substrate may follow alternate reaction paths, such as 4-*exo*-trigonal cyclization (Scheme 1). The Beckwith Guidelines for radical reactions[4] support the general preference for 4-*exo* over 5-*endo* closures.

The reliability of this rule is demonstrated by the rare observation of 5-*endo*-trigonal cyclizations. The first examples of this process were found in the works of Julia,[6]

Pines,[7] Wilt[8] and Forbes[9] (Scheme 2). In each case low yields of the 5-*endo* closure product were obtained.



Scheme 2

However, in several cases, when X (Scheme 1) is a second row element, the above rule may be relaxed, and the 5-*endo* cyclization is efficient. The success in such cases is due to the larger atomic radii of second row elements and hence longer bond distances. The net result is that the required approach trajectory can be accommodated without undue strain. Studies involving closures in these circumstances have led to efficient routes to cyclopentanes and diquinanes, pyrrolizidinones, pyroglutamates, and spironucleosides,

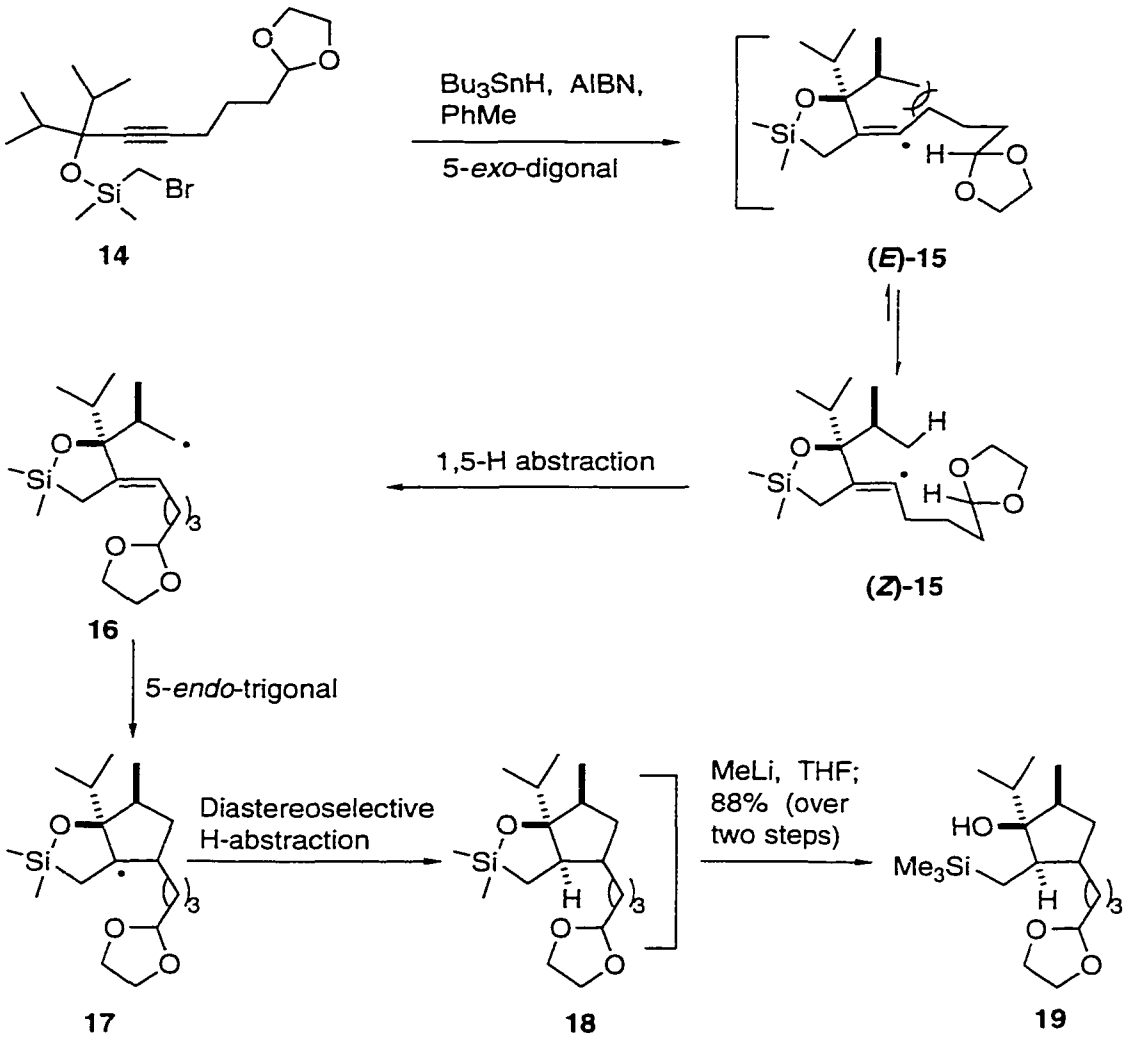
including several natural products.

5-*Endo*-Trigonal Cyclization by Carbon-Centered Radicals

(a) Use of an alkyl radical

Malacria and coworkers[10,11] have extensively developed a tandem radical cyclization sequence, which involves i) 5-*exo*-digonal cyclization, ii) diastereoselective 1,5-hydrogen transfer, and iii) a rarely-observed all-carbon 5-*endo*-trigonal cyclization (Scheme 3). This reaction sequence leads to products such as **19**, containing three new contiguous asymmetric centers.

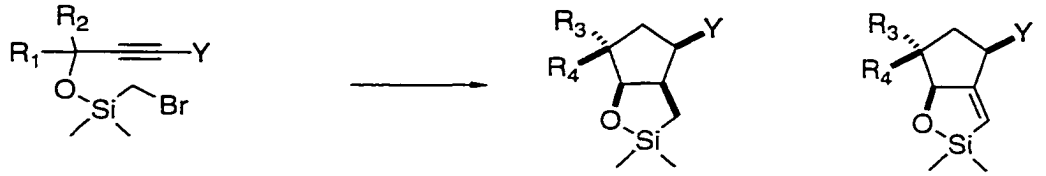
Upon treatment with Bu_3SnH, compound **14** underwent 5-*exo*-digonal cyclization to generate vinyl radical **15**, which exists in two forms, (*E*)-**15** and (*Z*)-**15**. Due to severe 1,3-allylic interactions in the *E*-vinylic intermediate **15**, the equilibrium shifts towards the more stable *Z* form. The highly reactive vinyl radical undergoes 1,5-hydrogen transfer by interaction with a non-activated C-H bond of **15**. The newly generated radical **16** then cyclizes by a 5-*endo*-trigonal pathway to give **17**. Diastereoselective quenching of the radical **17** produces the bicycle **18** which, on treatment with methyllithium, affords the cyclopentane **19**. The authors propose that the occurrence of the disfavored 5-*endo* process



Scheme 3

is due to a facilitating modification of the geometry brought about by steric repulsion between the isopropyl groups.

This hypothesis was later supported[11] by studying substrates which are sterically less demanding. For example, when the isopropyl groups were replaced by ethyl groups (Scheme 4, entry **20d**), the product of 5-*endo*-cyclization was isolated in lower yields.



20 **21** **22**

	R_1	R_2	R_3	R_4	Y	% **21**
20a	*i*-Pr	*i*-Pr	H	CH_3	*t*-Bu	88
20b	*i*-Pr	*i*-Pr	H	CH_3	Me_3Si	69
20c	*i*-Pr	*i*-Pr	H	CH_3	H	55
20d	Et	Et	H	H	*t*-Bu	21
20e	H	*t*-Bu	CH_3	CH_3	*t*-Bu	14
20f		$CH_2(CH_2)_2C(CH_3)_2$			CH_2OCPh_3	45

Scheme 4

The reaction was also found to be dependent on the bulk of the acetylenic substituent Y (Scheme 4). When compound **20a** (Y = *tert*-butyl) was subjected to similar experimental conditions, product **21b** was formed exclusively and in high yield, suggesting that no bimolecular reduction of the intermediate methylene radical had occurred. It was found that, when the bulky tris(trimethylsilyl)silane was employed instead of a stannane for the reaction **20a** → **21**, a complete reversal in the product ratio (**21**:**22**) was observed (10:90 *vs* 81:19). The observance of product **22** (arising from a β-elimination from an intermediate of type **17** (see Scheme 3) in the other cases (**20b-f**) was not mentioned in the paper.

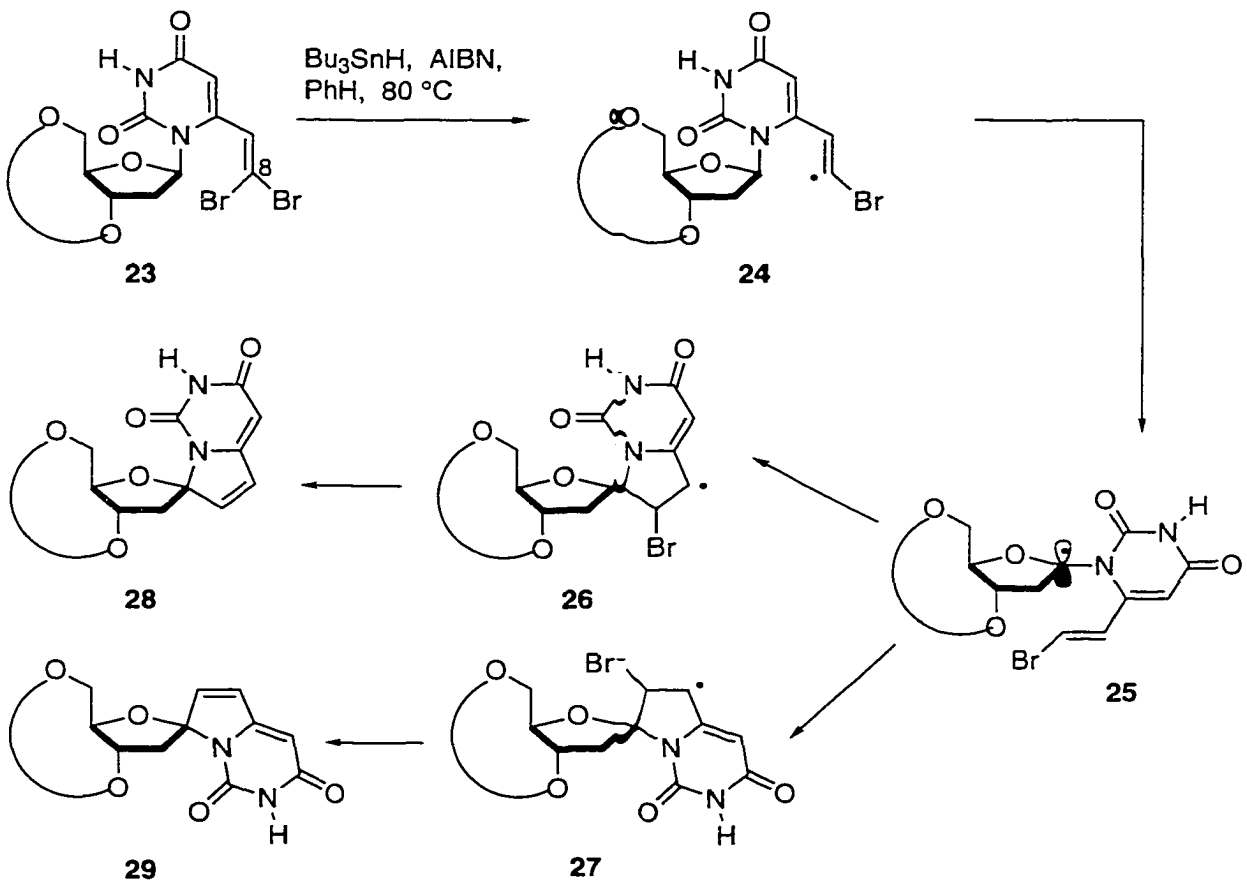
The sequence of Scheme 3 was also applied in the synthesis of polycyclic systems (see **20f**, Scheme 4).

(b) Use of a vinyl radical

5-*Endo*-trigonal ring closure has also been applied in

the synthesis of spironucleosides. The groups of Chatgilaloglu[12] and Tanaka[13] independently reported the first example of a nucleosidic anomeric radical (Scheme 5[12]).

The cascade summarized in Scheme 5 starts with bromine abstraction from C(8) by a stannyl or silyl radical to generate a highly reactive vinyl radical (**23** → **24**), followed by a 1,5 radical translocation to the anomeric position, a



Scheme 5

rare 5-*endo*-trigonal cyclization of the anomeric radical **25** onto the proximal double bond, and finally, product formation by bromine atom expulsion, giving **28** and **29** in a 2:1 ratio

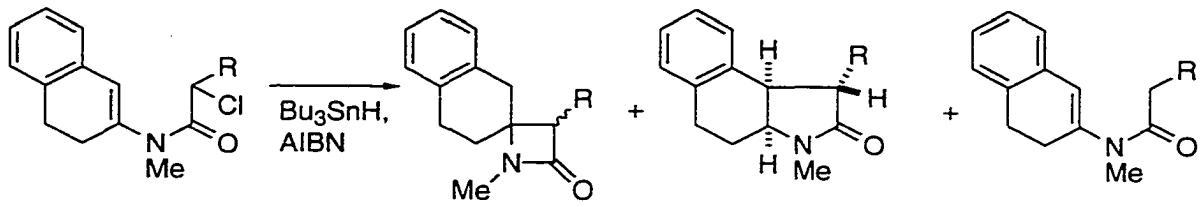
(25-44% yield). The stability of the anomeric radical **25** suggests that the 5-*endo*-trigonal cyclization is a relatively fast process, in this case. When the cascade was initiated using a 300-W visible light source, a better yield (78% combined) was obtained. The authors suggest that the stability of the intermediate radicals **26** and **27**, allows the cyclization to occur by the *endo* mode.

(c) Use of acyl radicals

Ikeda and coworkers have developed[14] an efficient route – based on 5-*endo*-trigonal closure – to various heterocycles containing a γ-lactam unit. Extensive studies on the factors that affect the cyclization process were also carried out.

Their methodology was first used to obtain a variety of γ-lactams (Scheme 6) by 5-*endo*-trigonal cyclization of *N*-vinylic α-chloroacetamides. When acetamides **30a-c**, were treated with Bu_3SnH and AIBN, a mixture of compounds **31a-c**, **32a-c** and **33a-c** was obtained. This study also found that the ratio of the product arising from 5-*endo*-trigonal cyclization and that from the competing 4-*exo*-trigonal closure is controlled by the electronic and steric effects imparted by the substituents on the radical center.

When R = H, intermediate **31a** predominates, as the benzylic radical, generated by 4-*exo* closure of **30a**, is more stable than the α-acylamino radical that results from the 5-*endo* mode of closure. However, if the substituent R in **30a-c** is a bulkier methyl or phenyl group, severe steric repulsion



30a R = H
30b R = Me
30c R = Ph

31a 50%
31b 42%
31c 0%

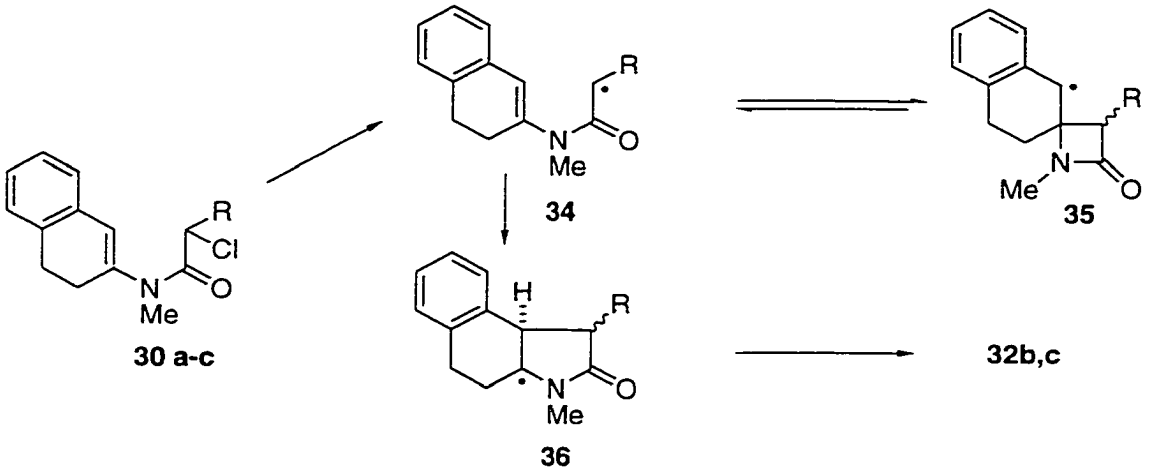
32a 0%
32b 35%
32c 76%

33a 32%
33b 19%
33c 0%

Scheme 6

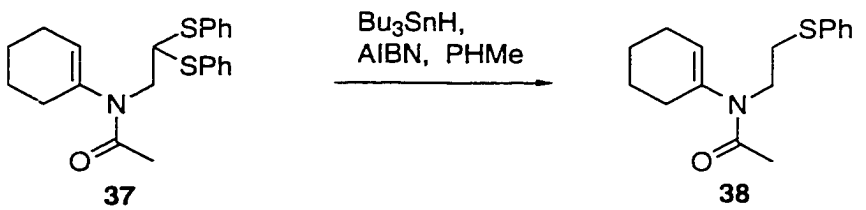
that develops between R and the neighboring gem-dialkyl group in the 4-*exo* pathway leads (Scheme 7) to increased amounts of **32b,c**.

Further work[15] showed that reversibility of the 4-*exo*-trigonal cyclization is a crucial factor in determining the product ratio. The 4-*exo*-trigonal cyclization is a kinetically favored process compared to the 5-*endo* closure in this case, but the benzylic radical **35** and the carbamoylmethyl radical **34** can equilibrate. In substrates where R = H, the reduction step is faster than equilibration, giving rise to β-lactams. However, in cases where R = Ph or Me, the presence of a radical stabilizing substituent (Ph or Me), slows reduction, and so ring opening of **35** to give **34** occurs, and the reduction step takes place only after the thermodynamically more stable **36** is formed by a 5-*endo*-trigonal cyclization. The above interpretation was supported by carrying out the reactions at different temperatures and studying the product ratio.[16] At a higher temperature, the rate of equilibration is increased, and the proportion of γ-lactam rises.



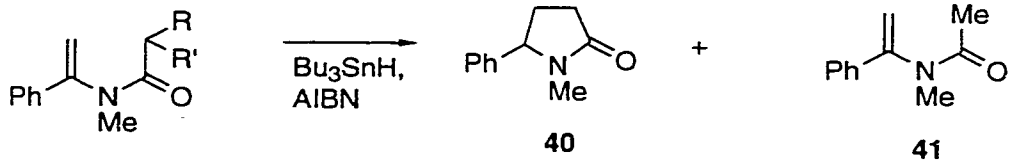
Scheme 7

The presence of the amide carbonyl group as part of the ring-closing chain was also found to be a necessary feature (Scheme 8) for effecting the cyclization.[14] When compound **37**, in which the amide carbonyl is not part of the potential ring-closing chain, was subjected to the standard conditions, only the reduced product **38** was obtained.



Scheme 8

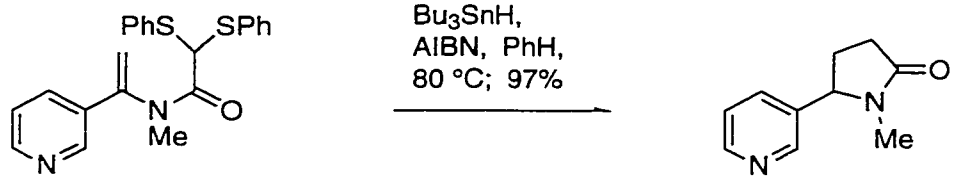
The above methodology was also extended to a study of the behavior of *N*-(1-arylethenyl)carbamoylmethyl radicals[17] (Scheme 9). The cyclization reaction was found to be highly dependent upon the nature of the radical precursor (see Scheme 9). The dithioacetal **39d** was found to be best suited



			40	41
39a	R = Cl	R = H	17%	18%
39b	R = Cl	R = Cl	0%	0%
39c	R = I	R = H	47%	12%
39d	R = SPh	R = SPh	75%	0%

Scheme 9

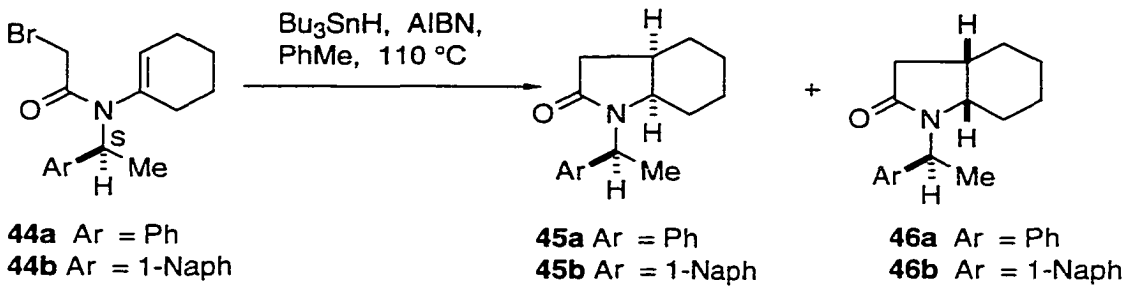
for this purpose, whereas the dichloro derivative **39b** failed to give any cyclization products, and much of the starting material was recovered. Racemic cotinine (**43**) was synthesized, using the above methodology (Scheme 10).



42 **43** (±)-cotinine

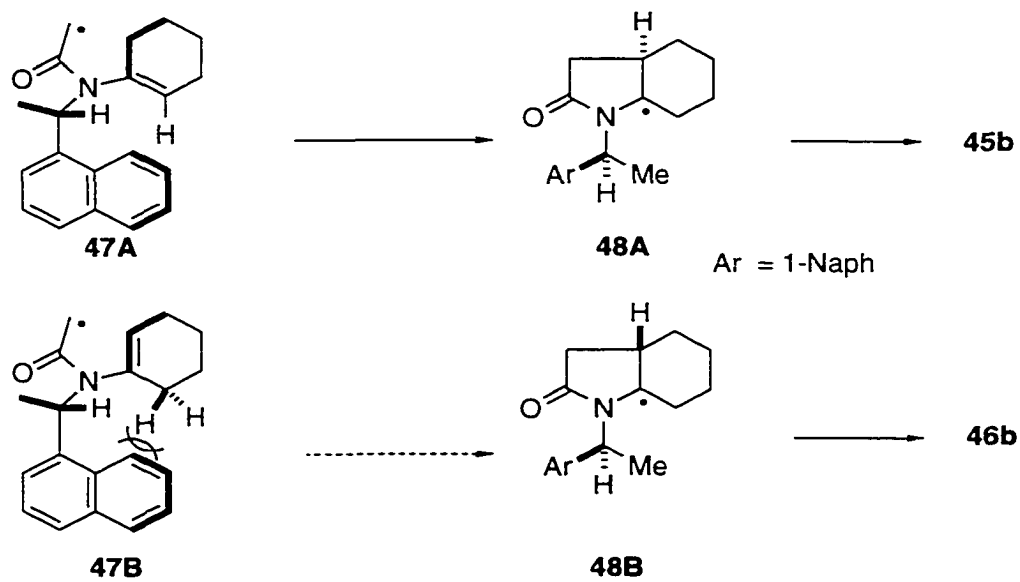
Scheme 10

In an effort to develop an asymmetric version of the above protocol, Ikeda's group[18] studied the cyclization of chiral *N*-(1-cycloalken-1-yl)-α-haloacetamides (Scheme 11), and the ring closure was designed so that the stereochemistry of the new asymmetric centers is controlled by 1,4 asymmetric induction by a chiral auxiliary on the nitrogen atom. When compound **44a** (Ar = Ph) was treated under the standard stannane reduction conditions, **45a** and **46a** were formed in



Scheme 11

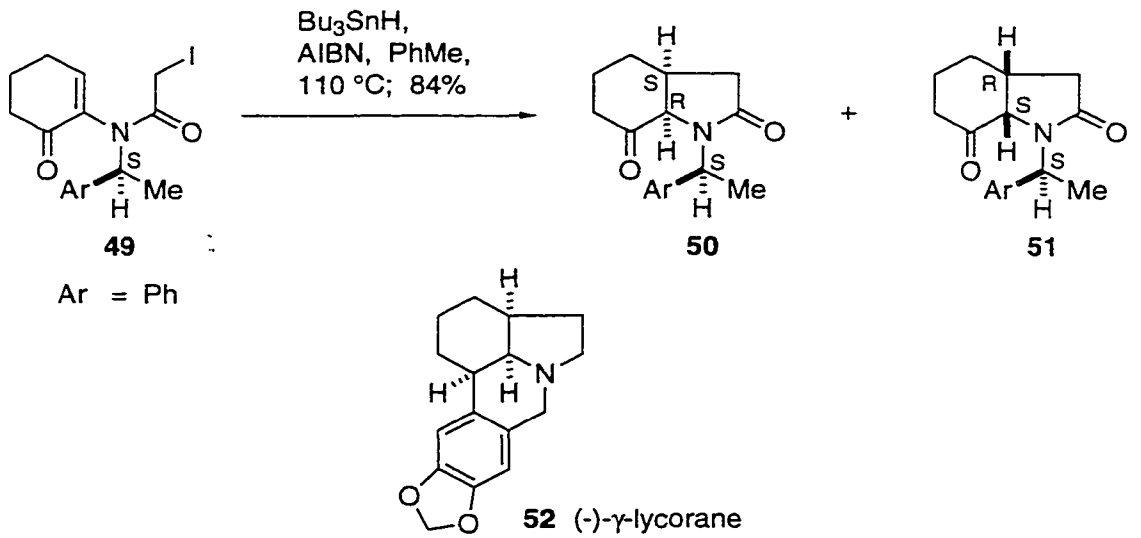
good yield, but the diastereoselectivity (3:2) was poor. When a sterically more demanding auxiliary, (*S*)-1-(1)-naphthylethyl was used, as in **44b**, the stereochemical outcome was improved (76:24), but the yield was poor (19%). Removal of the chiral auxiliary by hydrogenolysis of the mixture of **45b** and **46b** gave the corresponding amines, whose optical rotation indicated an ee of 77%. The observed diastereoselectivity was rationalized in the following way (Scheme 12).



Scheme 12

Compound **45b** is obtained by cyclization of the sterically favored conformer **47A**. Conformer **47A** produces intermediate **48A**, which subsequently abstracts hydrogen from the convex face to produce the *cis* ring fused product. In conformer **47B** steric repulsion between the C(8) hydrogen of the aromatic ring and one of the allylic hydrogens of the cyclohexene subunit makes this conformer less stable, and so the amount of **46b** is lowered (Scheme 12).

This result was applied in the total synthesis of the alkaloid (-)-γ-lycorane (**52**).[19] Enamine **49**, obtained from cyclohexane-1,2-dione, on exposure to Bu_3SnH, underwent radical cyclization by a 5-*endo*-trigonal route to give a 2:1 mixture



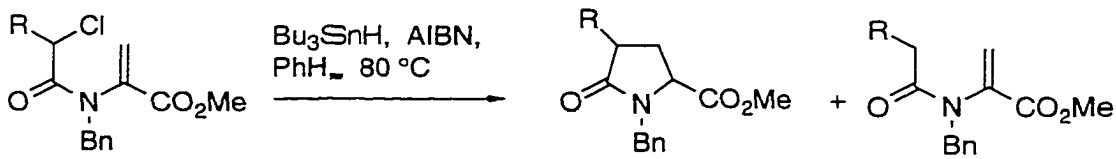
Scheme 13

of **50** and **51** (Scheme 13). The high combined yield (84%) of **50** and **51**, as compared to **45a** and **46b** (55%), may be explained in terms of the captodative[20] stabilizing effect of

the cyclized radical intermediate (-N-C·-C=O) in the case of **49**.

Goodall and Parsons, envisioned that substrates such as **53a-d**, when subjected to similar conditions as in the above cyclizations, should lead to the formation of pyroglutamates.[21] Pyroglutamates of type **54a-d**, with substituents R at C(4), are valuable intermediates in the synthesis of biologically important non-proteinogenic amino acids.

A series of α-chloroamides **53a-d**, prepared from DL-serine, on treatment with Bu_3SnH and AIBN, underwent 5-*endo*-trigonal cyclization to afford pyroglutamates **54a-d** in good yield (Scheme 14). The presence of the ester group served to increase the stability of the intermediate radicals by means of the captodative[20] effect.



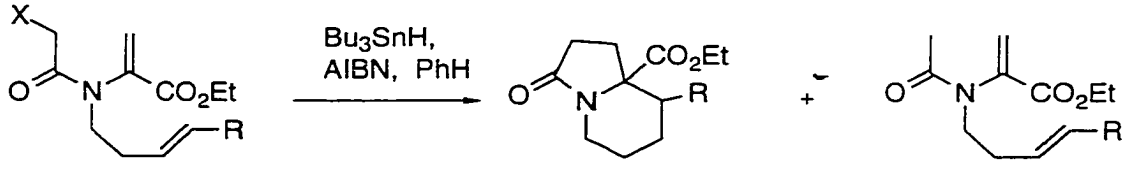
53a R = H	**54a** 52%	**55a** 13%
53b R = Me	**54b** 47%	**55b** -
53c R = Ph	**54c** 56%	**55c** -
53d R = Bn	**54d** 70%	**55d** -

Scheme 14

When R = H, CH, the simple reduction product was also observed. The authors make no comment as to why their reactions follow the 5-*endo* pathway. Presumably, the same

factors described above are involved. In addition, for the present case, a 4-*exo*-closure would be slowed because it would involve reaction at a fully substituted carbon.

In a related study, Baker *et al.*[22] also applied this unusual cyclization in an effort to synthesize indolizidinone and pyrrolizidinone alkaloids (Scheme 15). Some of these



56a R = H	X = Cl	**57a** 21%	**58a** 21%
56b R = Me	X = Cl	**57b** 27%	**58b** 27%
56C R = Me	X = I	**57c** 38%	**58c** 38%

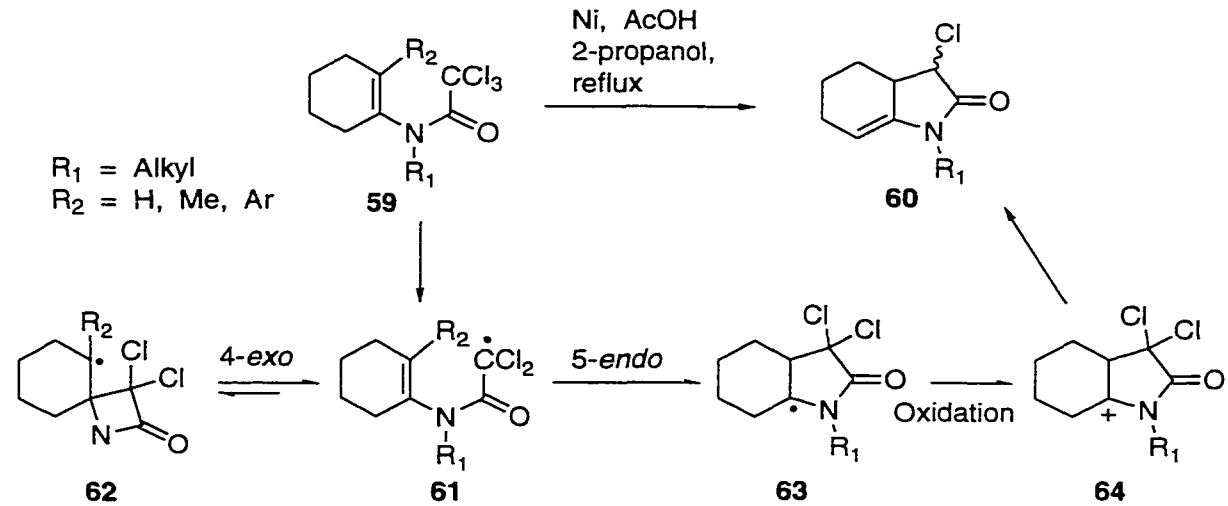
Scheme 15

alkaloids have important medicinal properties, and are common synthetic targets.

Various dehydroamino esters (Scheme 15) were treated with Bu_3SnH and catalytic amounts of AIBN. In each case a 5-*endo*-trigonal cyclization occurred, followed by a 5-*exo*- or 6-*endo* ring closure onto the pendant double bond (Scheme 15). The yields were better with iodides than with chlorides.

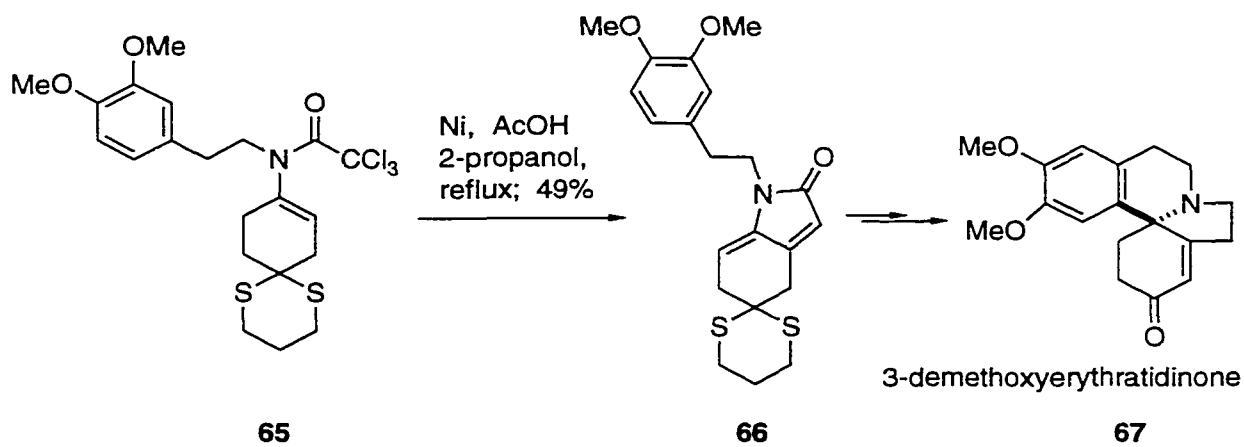
Zard *et al.*[23] used the normally disfavored 5-*endo*-trigonal cyclization to construct the crucial 5-membered ring (see Scheme 17) in a synthesis of the *erythrina* alkaloid 3-dimethoxyerythratidinone (**67**). The synthesis uses a novel method (Scheme 16) for generating radicals, previously developed by the Zard group. When trichloroacetamides (**59**)

were treated with nickel powder and acetic acid in refluxing 2-propanol, the compounds are first reduced to a radical intermediate (see **61**) which exclusively gives the *endo*-product, even when the 4-*exo* cyclization would lead to a resonance-stabilized, although more strained, radical (see **62**).



Scheme 16

For the synthesis of **67**, dithioketal **65** was subjected to...

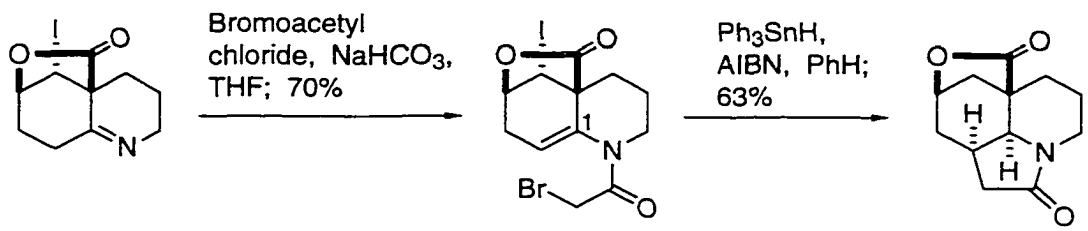


Scheme 17

the above radical cyclization conditions; it afforded the unsaturated lactam **66** in 49% yield, along with some (25%) of the simple reduction product ($CHCl_2$ instead of CCl_3).

Schultz and coworkers[24] have employed 5-*endo* trigonal cyclization of chiral enamide **69** to obtain lactams, which can potentially serve as models for kopsinine-type alkaloids (Scheme 18).

When compound **69**, itself prepared by *N*-acylation of **68**, was exposed to Bu_3SnH and AIBN, **70** was obtained in 63% yield



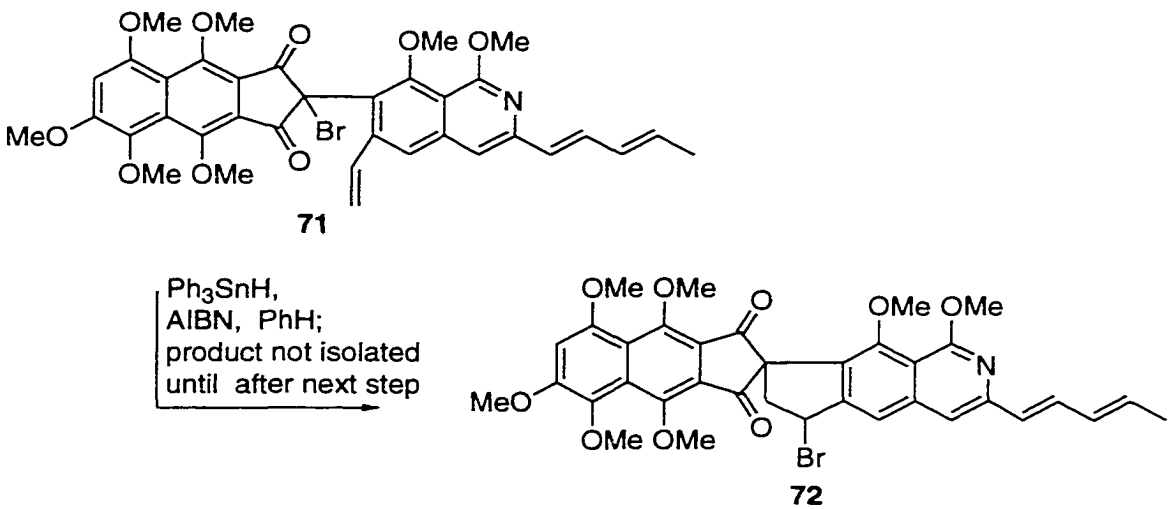
68 **69** **70**

Scheme 18

via a 5-*endo*-trigonal cyclization. It is interesting to note that the radical generated at C(1) in this process is reduced with complete β-facial selectivity. The selectivity is possibly the result of a transition state which ensures maximum overlap between the orbital carrying the radical and the enamide π bond. Such a transition state also requires the piperidine ring to be in the more favored chair conformation. Molecular modeling studies have also shown that the *cis* isomer **70** is 8.5 kcal/mol more stable than the corresponding *trans* isomer.

Rama Rao and coworkers have used 5-*endo*-trigonal closure

to generate the key spirocenter in their total synthesis of fredericamycin.[25] When a solution of Bu_3SnH and AIBN was added slowly to a refluxing solution of bromide **71**, spirocycle **72** was formed via a 5-*endo*-trigonal cyclization. No comment was made about the regiochemistry of this step (Scheme 19).



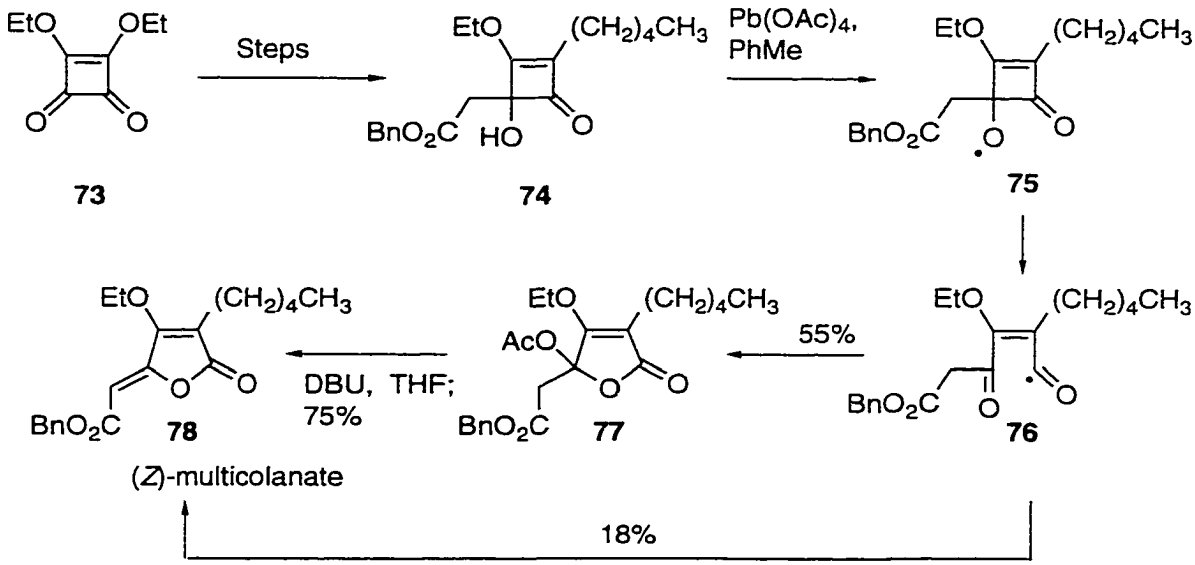
Scheme 19

(d) Use of a carbonyl radical

In another use of the 5-*endo* cyclization, Yamamoto *et al.*[26] developed a method to convert 4-hydroxy-2-cyclobutenones, which are readily available from diethyl squarate, into furanones (Scheme 20). Furanone-based natural products are known to possess various biological activities. The usefulness of this method was demonstrated by the synthesis of naturally-occurring (*Z*)-multicolanate (**78**).

Diethyl squarate was alkylated to obtain the hydroxy butenone **74**. Lead tetraacetate-induced oxidative

rearrangement (Scheme 20) gave **77** and **78** in a 3:1 ratio. The intermediate acetoxy tetronate **77** was converted efficiently into the natural product **78** by treatment with base.



Scheme 20

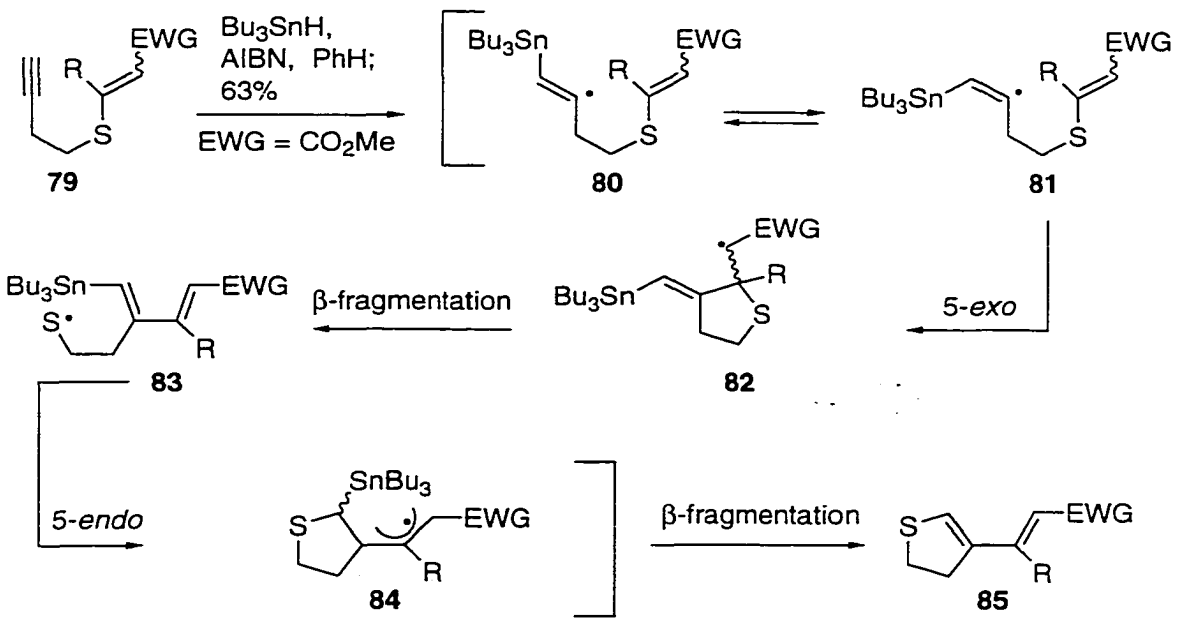
The oxidative rearrangement sequence is initiated by formation of the alkoxy radical **75** resulting from reaction of alcohol **74** with lead tetraacetate. This step is followed by a β-scission to produce the acyl intermediate **76**. 5-*Endo*-trigonal cyclization of the radical onto the carbonyl oxygen then produced the furanones **77** and **78**.

Other radical initiators such as ceric ammonium nitrate and manganese(III) acetate can also be used, but best results were obtained with lead tetraacetate.

(e) Use of a sulfur-centered radical

An example where a sulfur-centered radical undergoes 5-

endo-trigonal cyclization is found in Journet's synthesis of dihydrothiophene derivative **85**.[27] Compound **85** is obtained by a complex series of steps involving radical rearrangement and



Scheme 21

radical cyclization of sulfide **79** (Scheme 21). The process is initiated by addition of Bu_3SnH to the terminal triple bond. The newly-generated vinyl radical then equilibrates to the more stable *Z*-form, which undergoes 5-*exo*-trigonal cyclization and β-fragmentation to give **83**. The resulting sulfur radical then undergoes 5-*endo*-trigonal ring closure (**83** → **84**). The sequence is finally terminated by a β-fragmentation of the tin radical (**84** → **85**).

When the electron withdrawing group (ester) was replaced by a sulfone, no cyclization product was obtained because stannane addition to the double bond now occurs more rapidly

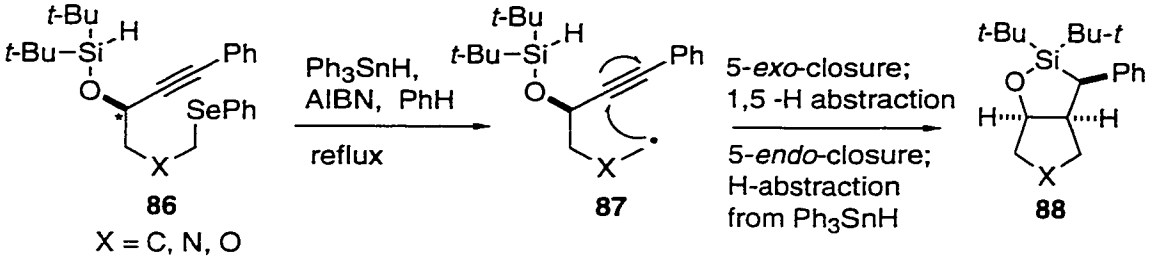
than to the triple bond.

(f) Use of silicon-centered radicals

Much of the chemistry involving silicon-centered radicals that undergo 5-*endo*-trigonal cyclization has been developed in this laboratory. The details of this work are discussed in the Results section of Part 1 (see later).

The methodology developed in this group (Scheme 22)[28-30] has been applied to a variety of substrates, leading to the efficient synthesis of substituted cyclopentanes, tetrahydrofurans, γ-lactones, pyrrolidines and chromanols, and natural products. One of the notable features of this series of transformations is the formation of three contiguous asymmetric centers in one step. Also, since the stereochemical outcome is controlled by the stereochemistry of the original hydroxyl group (see starred atom in **86**), this method can be been applied to the synthesis of optically pure compounds.[28,29]

The tandem radical process of Scheme 22 involves the following steps: i) 5-*exo*-digonal closure of radical **87** (produced from the selenide or bromide), giving rise to the vinyl radical; ii) a diastereoselective 1,5-hydrogen transfer and creation of a silicon centered radical and iii) an unusual 5-*endo*-trigonal cyclization, followed by hydrogen abstraction, to yield **88**, exclusively (Scheme 22).

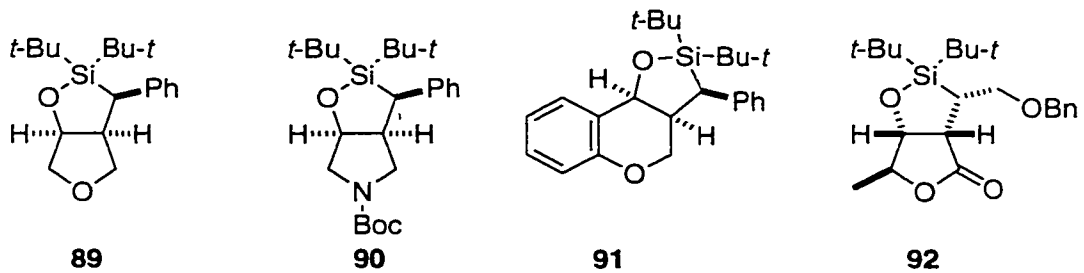


Scheme 22

The efficiency of the normally disfavored 5-*endo* process is due to the longer (compared with first row elements) O-Si bonds in the chain undergoing closure.

Initially, this methodology was developed to obtain substituted all-carbon 5-membered rings. These compounds could be obtained by cleaving the bicyclic products **88** (X = C) under a variety of conditions. The sequence of reactions shown in Scheme 22 was also successful when the *tert*-butyl groups on the cyclization precursor were replaced by phenyl or methyl groups.[30]

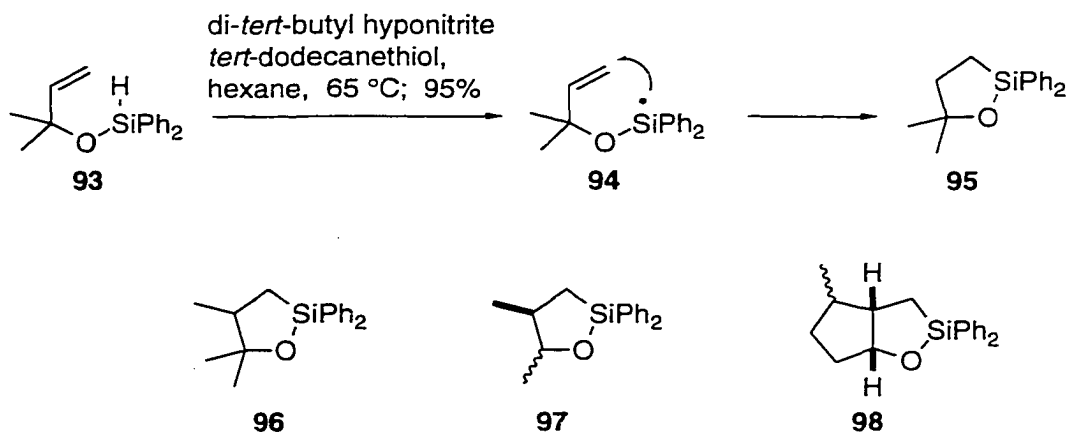
Further work (Scheme 23), using substrates were X is a heteroatom, was also carried out. Cyclization reactions occurred as before, and in good yields, giving rise to various five-membered heterocycles.



Scheme 23

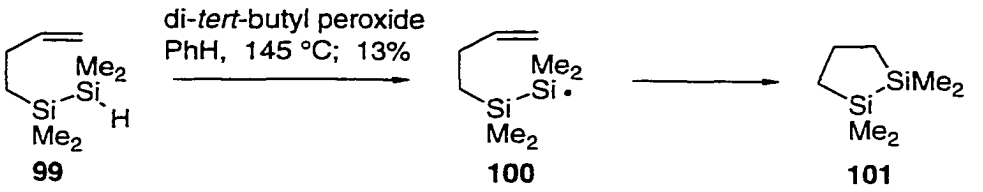
When an optically pure starting material was used, an optically pure lactone **92**, with three new contiguous asymmetric centers, was obtained (Scheme 23).

The preference of allyloxysilyl radicals to undergo 5-*endo*-trigonal cyclizations has also been observed in simple systems.[31,32] Thus, when hexane solutions of allyloxysilanes such as **93** were treated with catalytic amounts of *tert*-dodecanethiol and a radical initiator (di-*tert*-butyl hyponitrite), cyclic silane **95** could be obtained in 95% yield. This intermolecular thiol-catalyzed radical-chain hydrosilylation of alkenes represents a good route to cyclic organosilanes (Scheme 24).



Scheme 24

Barton and Revis[32] had also reported similar observations, but on disilanes such as **99** (see Scheme 25).



Scheme 25

Conclusion

As indicated in the above review, the normally disfavored 5-*endo*-trigonal mode of cyclization can be observed if certain special features are incorporated into the cyclization precursor. These features include the use of second-row elements, steric factors, or substitution that favors reversibility of an initial 4-*exo* closure.

SYNTHESIS OF METHYL *EPI*-JASMONATE

Methyl *epi*-jasmonate (**102**) is the main component responsible for the odor of jasmine oils. Originally, the epimer, methyl jasmonate, was erroneously thought to be responsible for the fragrance. Methyl jasmonate (**103**) was first isolated by Demole *et al.*[33] from the essential oil of *Jasmarinus grandiflorum* L. and characterized. Subsequently,[34] other members of the jasmonoid family (Figure 1), jasmonic acid (**104**) and methyl cucurbate (**105**) were isolated. The high price of jasmine absolute ($6000/kg) and high usage made it an important synthetic target.

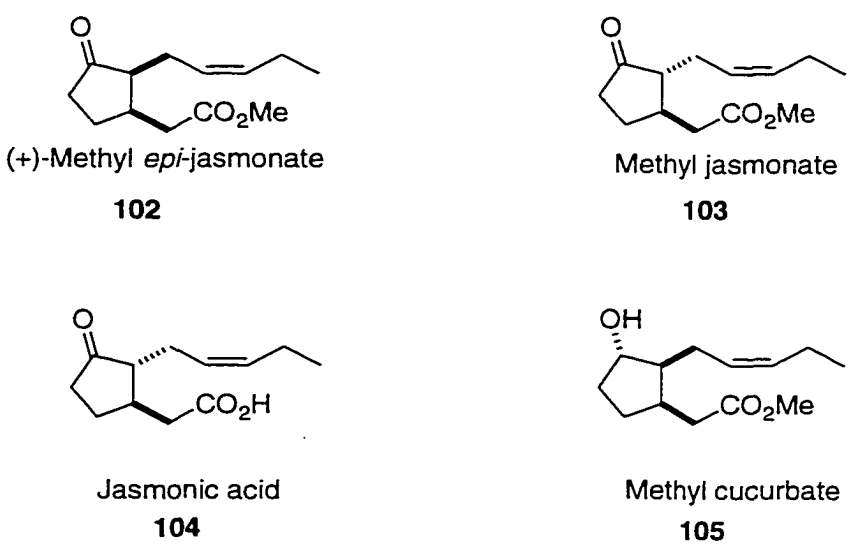


Figure 1 Jasmonoid family

The first isolation of methyl *epi*-jasmonate was reported by Baker *et al.*[35] from the hairpencils of the male oriental fruit moth, *Grapholitha molesta* B. The biosynthesis was reported[36] three years later.

It was not until 1984 that it was proven by Acree and Nishida[37] that (+)-**102** is the only stereoisomer of methyl jasmonate which is responsible for the characteristic odor, and that the other three stereoisomers are odorless.

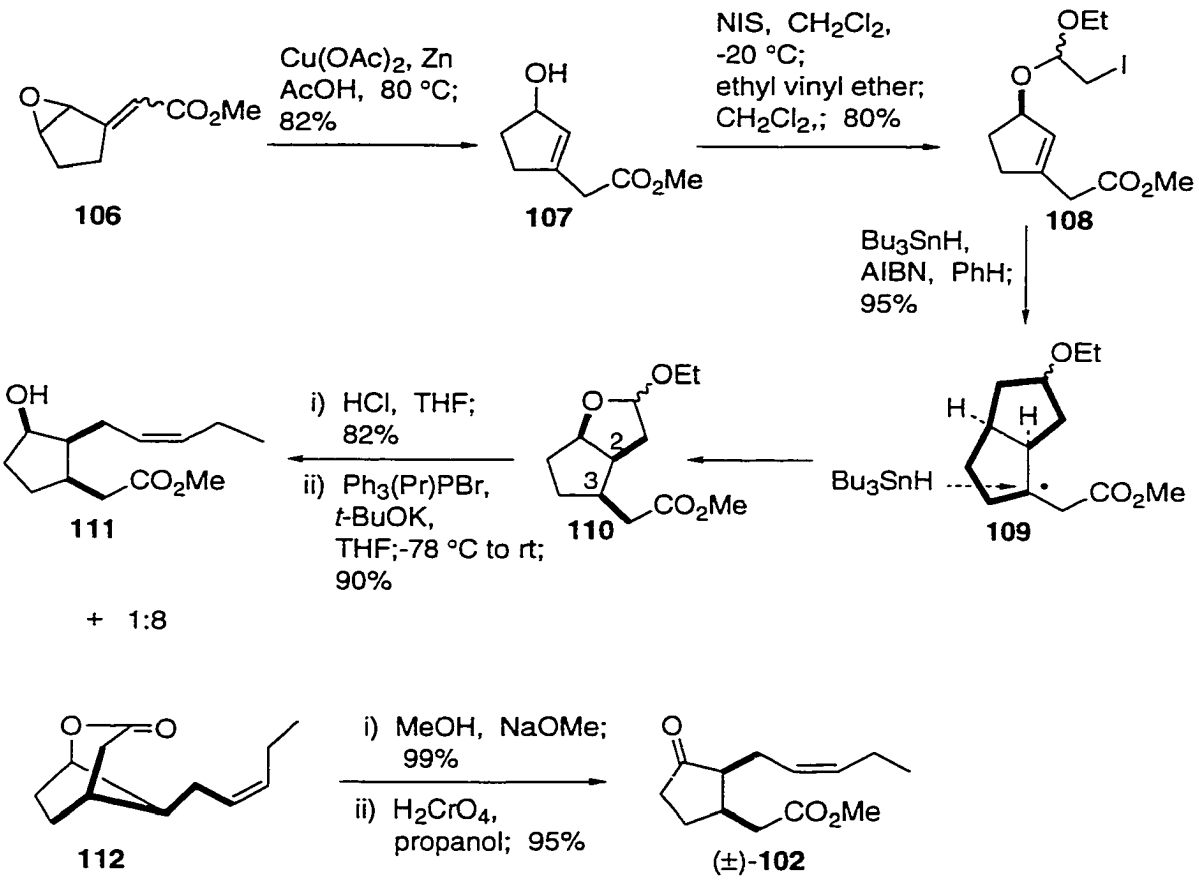
Methyl *epi*-jasmonate is also known to possess a range of plant regulatory and pheromonal properties.[35,38]

Several synthesis of methyl *epi*-jasmonate have been reported. The crucial step in each route is setting up the *cis* arrangement of the substituents at C(2) and C(3). Due to the presence of the carbonyl group in the 5-membered ring, the molecule has a tendency to equilibrate to the more stable *trans* stereochemistry.

The following section describes the various synthetic approaches reported in the literature, with special emphasis on the steps involved to acquire the desired *cis* configuration.

Stork and Ouerfelli[39] (Scheme 26) used a methodology developed in their group to set up the stereocenters in the appropriate fashion. Its application in the present case involved cyclization of haloacetals **108**, derived from the corresponding allylic alcohol.

Allylic alcohol **107**, prepared from epoxides **106**, was converted efficiently into iodoacetals **108**. Radical ring closure of **108** produced the bicyclic acetals **110** in high yield. The radical cyclization step controls the diastereoselectivity of the reaction. The radical generated from iodides **108**, on treatment with Bu_3SnH, undergoes 5-*exo*-

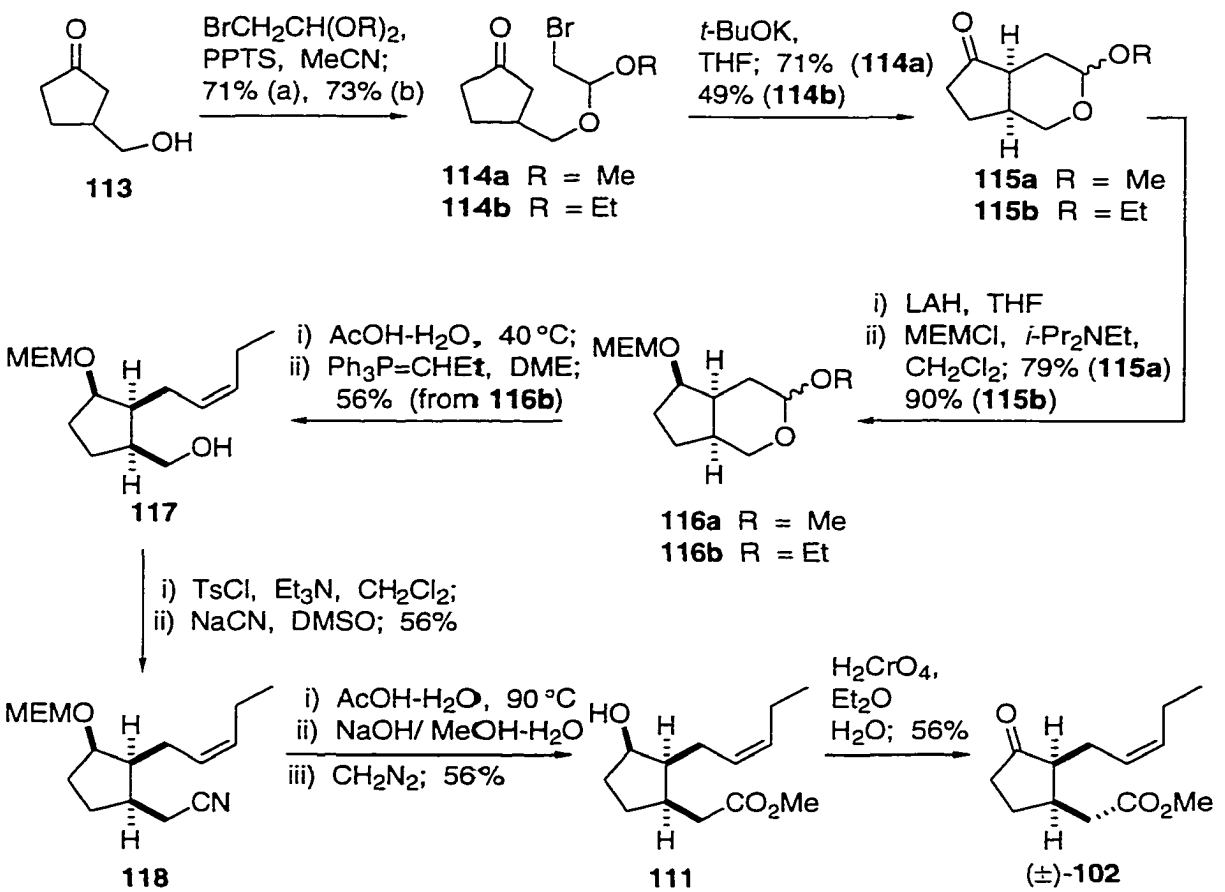


Scheme 26

trigonal ring closure, and the resulting radical **109** is trapped from the convex face, so as to give **110**. This possesses the desired *cis* arrangement of substituents at C(2) and C(3) (methyl *epi*-jasmonate numbering, Scheme 26).

Acid hydrolysis of acetals **110**, followed by a Wittig reaction, gave alcohol **111**, along with the related lactone **112**, the latter being the major product. The combined yield was 90%. Formation of lactone **112** proves the correctness of the stereochemical assignment to **110**. Methanolysis of **112** regenerates alcohol **111** which, on oxidation, gave (±)-methyl *epi*-jasmonate (**102**).

In a synthesis of (±)-methyl *epi*-jasmonate (**102**), Kitahara's group[40] (Scheme 27) made use of the inherent thermodynamic stability of the *cis*-fused acetals **115a,b** over the corresponding *trans* – a situation expected by analogy to the stability of the well-studied *cis*-1-hydrindanones. Keto



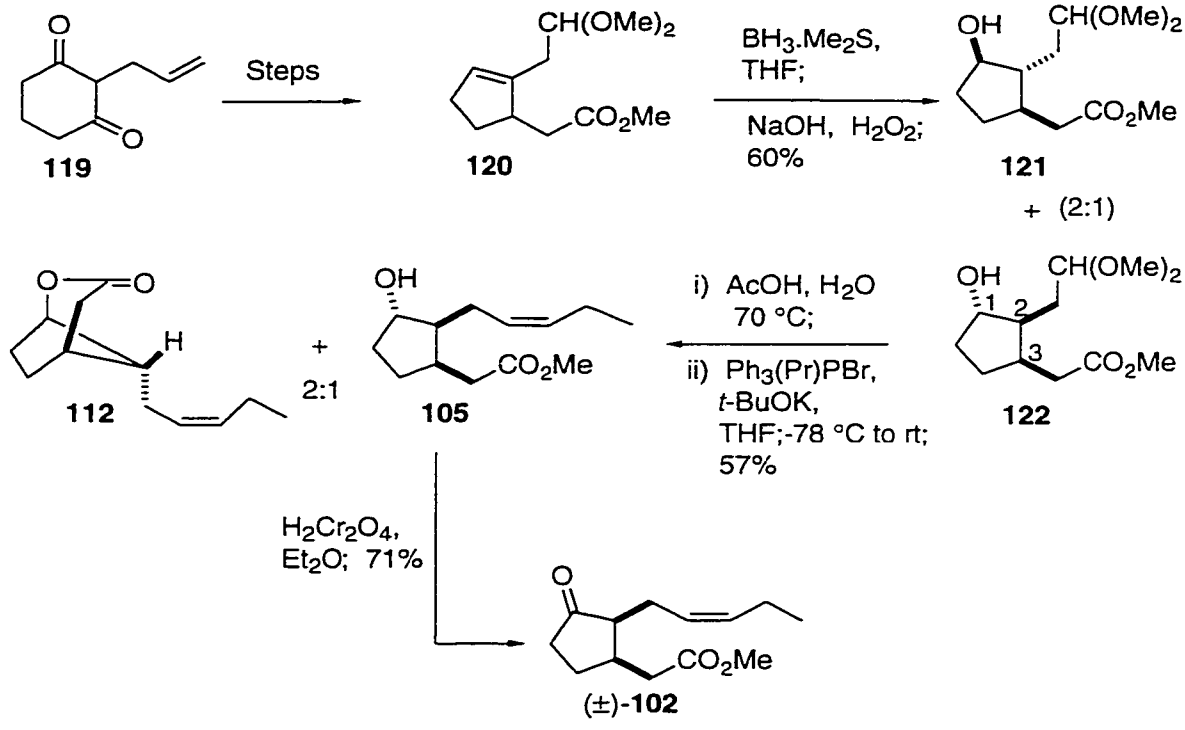
Scheme 27

alcohol **113** was easily converted into the bromoacetals **114a** or **114b**. Treatment of the bromoacetals with base gave a 2:1 mixture of the bicyclic compounds **115a** or **115b**. Epimerization after acetal ring cleavage was avoided by reducing the carbonyl and protecting the resulting alcohol

with a methoxyethoxymethyl (MEM) group (**115a,b** → **116a,b**, Scheme 27).

Acid hydrolysis of **116b** (experimental details for **116a** were not reported) produced the expected lactols which, when subjected to standard salt-free Wittig conditions (Scheme 27), gave the desired *Z* olefin **117**. The two-carbon arm incorporating the ester was obtained by a series of simple chemical transformations (**117** → **118** → **111**, Scheme 27). Finally, oxidation under mild conditions, using a two-phase system, gave (±)-**102** in an overall yield of 6%. The material was 97% pure, as judged by GC analysis.

In another synthesis (Scheme 28) of (±)-methyl *epi*-jasmonate by the same group,[41] the regio- and facial selectivity of a hydroboration-oxidation reaction served as a key element of the route. Olefin **120**, prepared in several steps from diketone **119**, when treated with a borane complex, followed by oxidative work up, gave a 1:2 mixture of the desired 2,3-*cis* alcohol **122** and its *cis* isomer **121**. Acid hydrolysis of the mixture gave the corresponding aldehydes which were then treated under salt-free Wittig conditions (Scheme 28). The resulting mixture was chromatographically separated, to obtain the desired product **105** in low yield (19%), along with the bridged lactone **112**. Alcohol **105**, was carefully oxidized to (±)-methyl *epi*-jasmonate (**102**). A

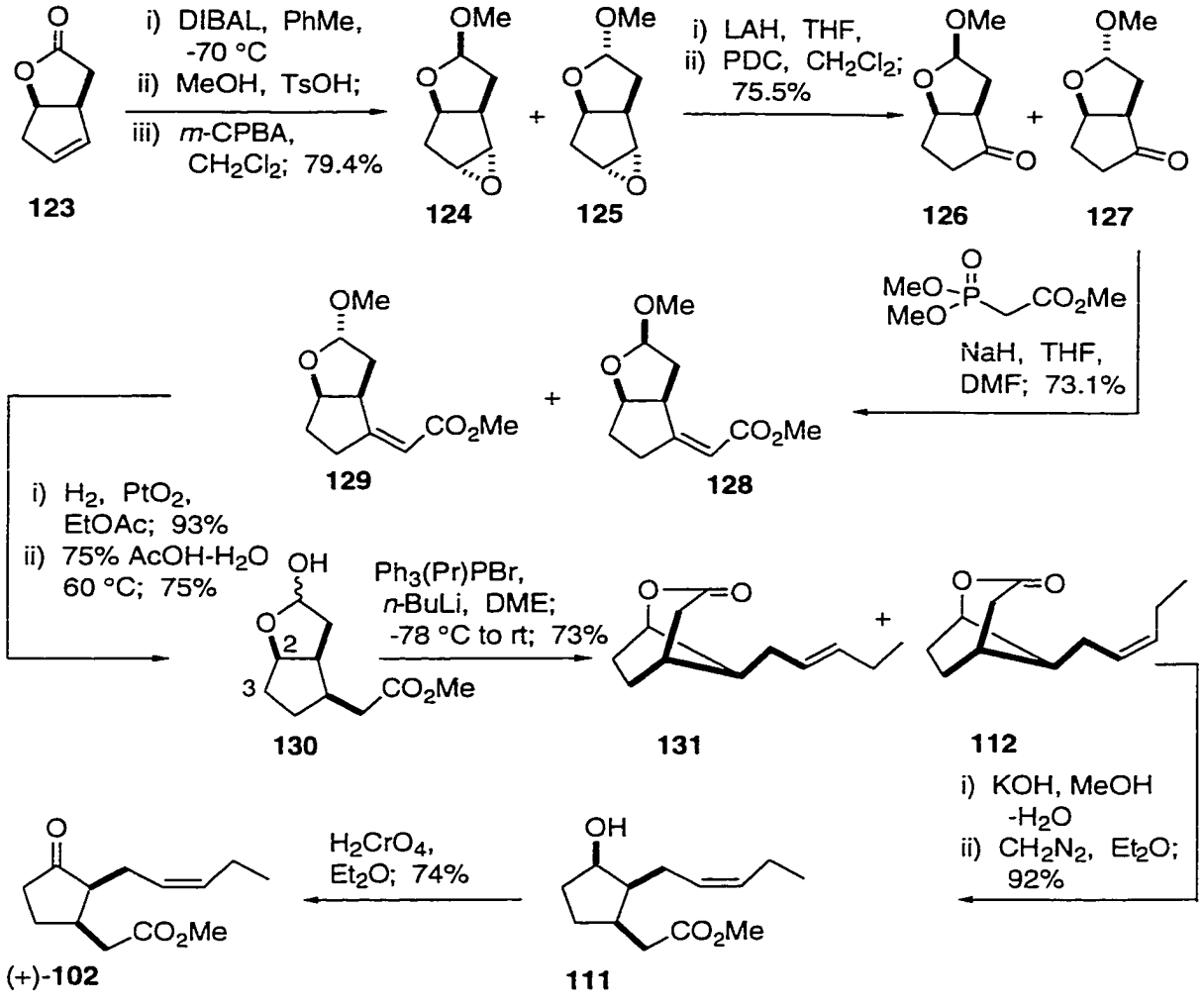


Scheme 28

small amount (12% of the total) of the *trans* isomer, methyl jasmonate, was also formed.

In a recent synthesis of (+)-methyl *epi*-jasmonate, an optically pure building block (**123**, Scheme 29) common in the synthesis of prostaglandins, was used by Kitahara's group.[42]

DIBAL reduction of (+)-**123**, followed by treatment with TsOH in methanol, gave the expected acetals, which where epoxidized, without separation, to produce **124** and **125**. Reduction of the epoxides gave an inseparable mixture of alcohols, which were oxidized to **126** and **127**. Attachment of the two-carbon unit was accomplished by a Horner-Emmons reaction with trimethyl phosphonoacetate. Facially selective



Scheme 29

hydrogenation proceeded smoothly and, as expected, from the convex face of the bicyclic system to give the *endo* products. These were hydrolyzed, giving lactols **130**. At this stage, with the required *cis* stereochemistry established, the remaining task of extending the C-2 chain was achieved by i) salt-free Wittig reaction of the lactols, giving an 89:11 *Z*:*E* mixture of chromatographically separable olefins, and ii) mild hydrolysis of the bridged lactone **112**, followed by esterification with diazomethane. As a result of these

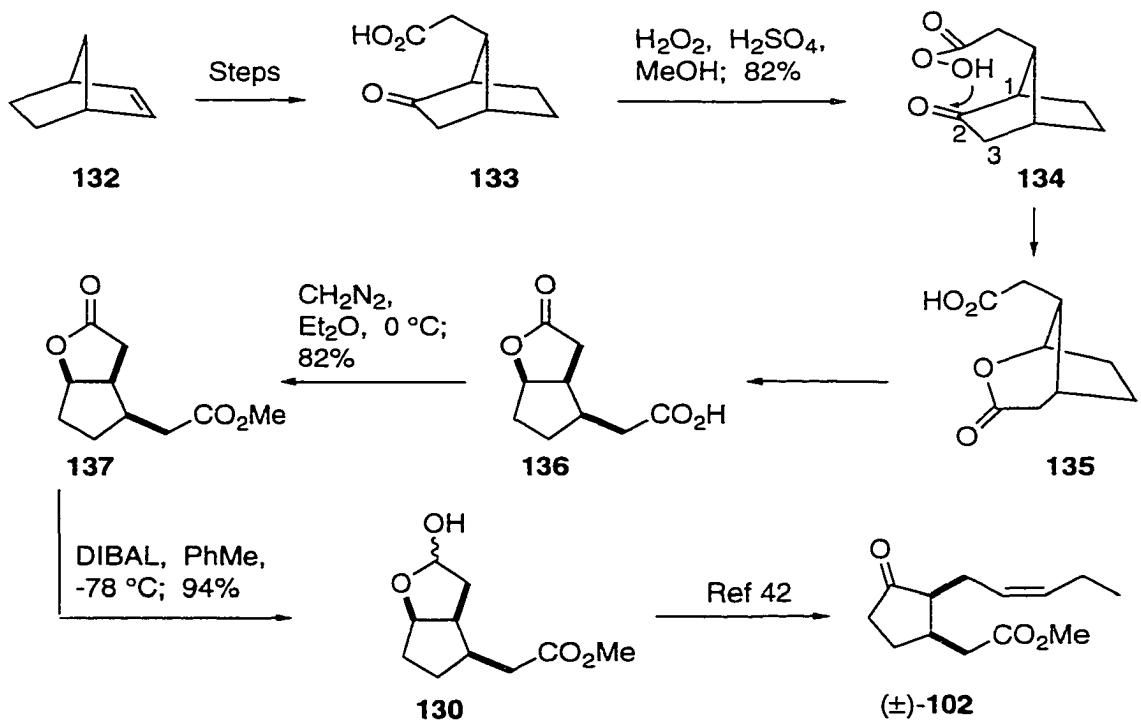
operations, ester **111** was formed with 100% ee. Two-phase oxidation under carefully controlled conditions gave (+)-**102**, which was 97% pure, as a small amount (3%) of the *trans* isomer was formed.

The unnatural isomer of methyl *epi*-jasmonate was synthesized similarly from (-)-**123**.

Lactone **136** has often seen service as an intermediate for the synthesis of methyl *epi*-jasmonate and other members of the jasmonoid family.

Seto and coworkers (Scheme 30) used **136** in their synthesis of racemic methyl *epi*-jasmonate.[43]

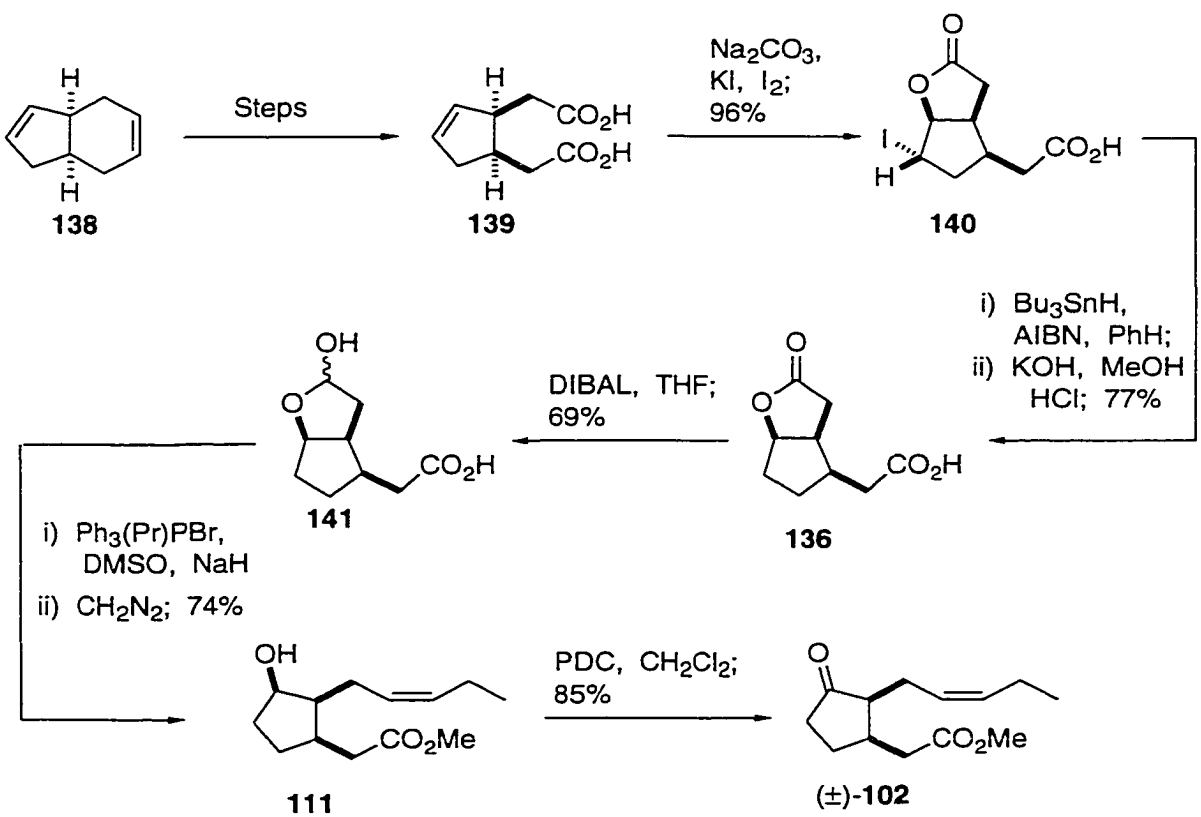
The route started with conversion of norbornene into acid **132**, using previously developed chemistry.[44] When



Scheme 30

compound **133** was treated with hydrogen peroxide in acidic methanol, contrary to previous reports, the C(1)-C(2) bond preferentially underwent rearrangement rather than the C(2)-C(3) bond, giving rise to **136**, via the peracid intermediate **135**. Esterification of **136** produced the γ-lactone **137**. Reduction of **137** gave lactols **130**, which were converted efficiently into methyl *epi*-jasmonate, using a set of chemical transformations also employed by Kitahara (*cf.* Scheme 29).[42]

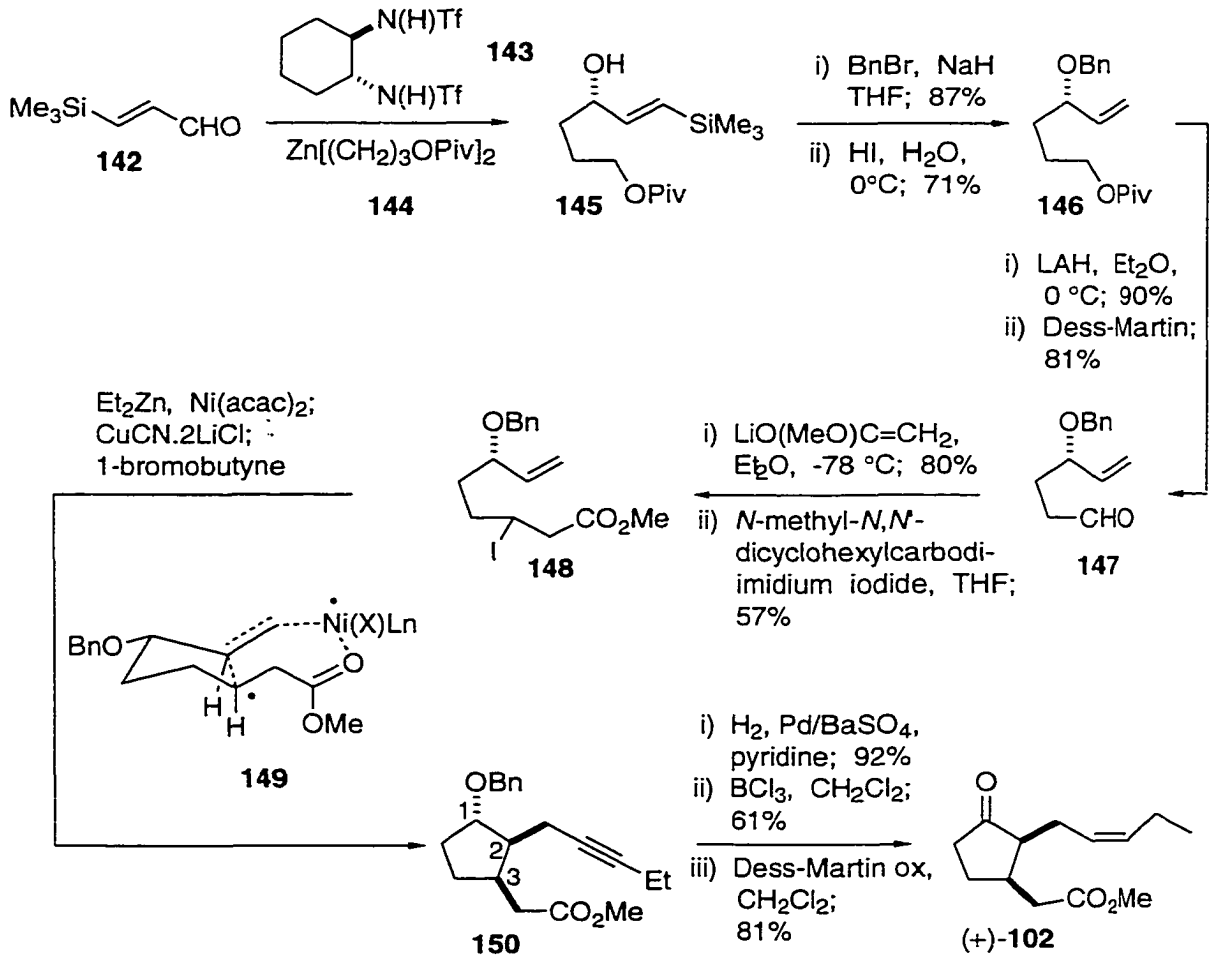
Crombie *et al.*[45] used the known diacid **139**,[46] itself made from hydrocarbon **138**, in their synthesis of racemic methyl *epi*-jasmonate (Scheme 31). Iodolactonization of **139**



Scheme 31

provided **140**, and stannane-mediated deiodination produced the bicyclic lactone **136**. DIBAL reduction then gave the lactols **141**, which were converted into methyl *epi*-jasmonate by a set of simple chemical transformations (**141** → **111** → **102**, Scheme 31). The Wittig reaction (**141** → **111**) did not proceed with complete stereoselectivity, and a chromatographically separable mixture of *Z* and *E* isomers of **111** was formed.

In Stadmüller and Knochel's synthesis of (+)-methyl *epi*-jasmonate,[47] three contiguous asymmetric centers are set up in a single step using a novel Ni-catalyzed cyclization (Scheme



Scheme 32

32).

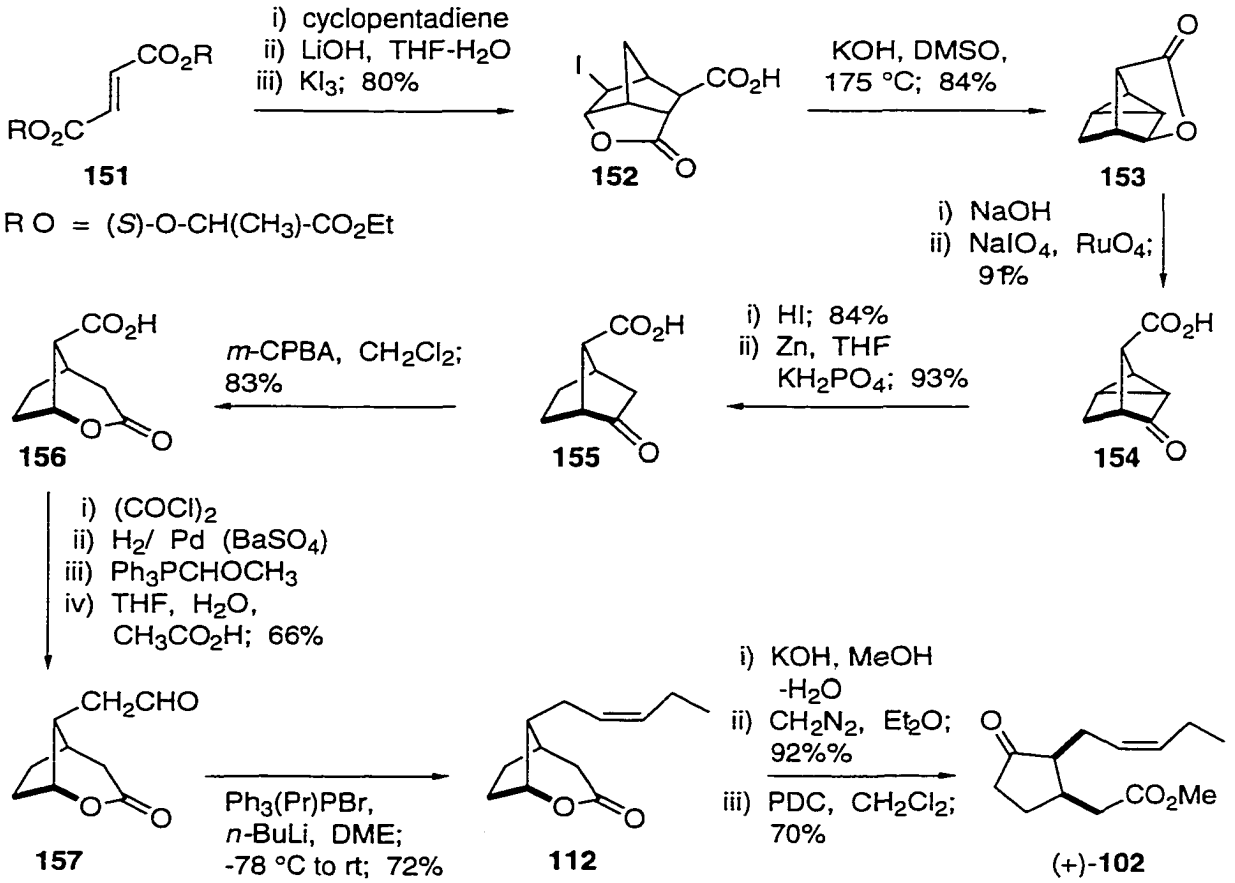
Alcohol **145** was obtained in good yield and reasonable enantiomeric purity (90% ee) by treatment of **142** with the dialkylzinc **144**, $Ti(i\text{-}PrO)_4$, and a catalytic amount of **143**. Benzylation of alcohol **145** and protodesilylation gave **146**, which was then converted into aldehyde **147**. At this point, condensation with the lithium enolate of methyl acetate, followed by replacement of the resulting hydroxyl by iodine, gave the cyclization precursor **148**, as a 1:1 mixture of diastereomers. In the cyclization step, iodides **148** undergo a stereoconvergent radical-mediated ring closure to give a cyclopentylmethylzinc derivative. This is transmetallated *in situ* using copper cyanide, and coupled with 1-bromobutyne. This set of reactions afforded **150** with 100% *trans* stereochemistry between C(1) and C(2) and 95:5 *cis*:*trans* selectivity between C(2) and C(3). The stereochemical outcome can be explained by assuming a chair-like transition state **149**, where all the substituents occupy a pseudoequatorial conformation. Coordination of Ni may serve to enhance the *cis* stereochemistry between C(2) and C(3).

Lindlar reduction of **150** then afforded an olefin (96% *Z*) which, on debenzylation and oxidation under *mild* conditions [to avoid epimerization at C(2)], gave the natural product (+)-**102**.

In one of the first asymmetric syntheses of methyl *epi*-jasmonate, Helmchen and coworkers,[48] used an intermediate (**154**), which could also serve as a building block leading to

other members of the jasmonoid family. This intermediate was readily available in multigram quantities by the route shown (Scheme 33).

Iodolactone **152** was obtained by enantioselective Diels-Alder



Scheme 33

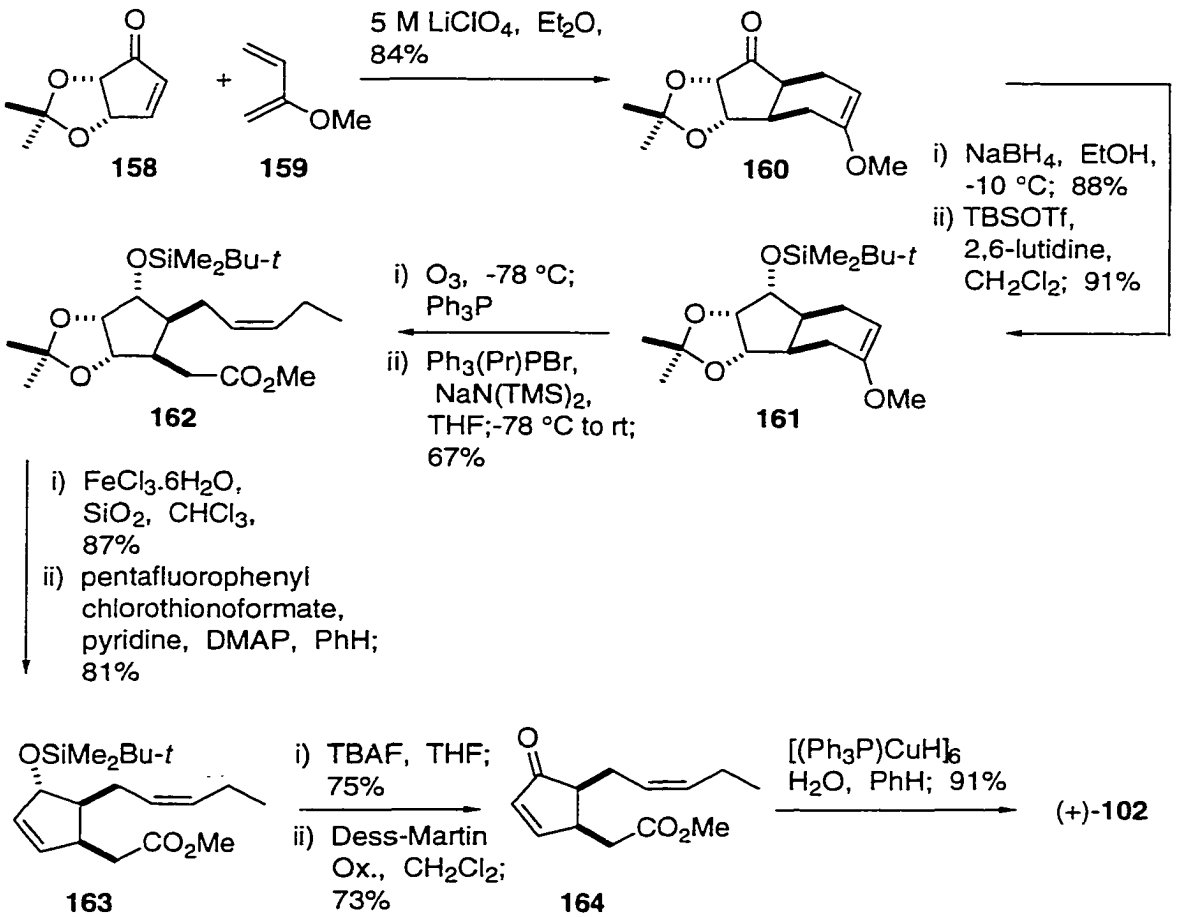
reaction of cyclopentadiene and ester **151**, followed by hydrolysis and iodolactonization. Thermally induced decarboxylation of the potassium salt of acid **152**, produced lactone **153**. Enantiopure **154** was then obtained by lactone opening and ruthenium tetroxide-catalyzed oxidation.

Treatment of **154** with concentrated hydriodic acid, followed by reduction of the resulting iodide with zinc, gave keto carboxylic acid **155**.

Baeyer Villiger oxidation of **155** served to introduce the oxygen at C(1) (**155** → **156**). Reduction of **156**, followed by Wittig reaction with (methoxymethylene)triphenylphosphorane, and subsequent hydrolysis of the resulting enol ethers, gave aldehyde **157**. The required *Z* olefin **112** was obtained by treating **157** with propylidenetriphenylphosphorane under salt-free Wittig conditions. Basic hydrolysis of the lactone then released the corresponding hydroxy acid which, on esterification, followed by oxidation under neutral conditions, gave (+)-methyl *epi*-jasmonate in good yield, along with trace amounts (96.4:0.6) of the *trans* isomer.

Another use of the enantioselective Diels-Alder reaction is seen in Bestmann's synthesis of (+)-methyl *epi*-jasmonate (Scheme 34).[49] The stereochemistry of the key step is controlled by the stereochemistry of the dienophile **158**, which is itself derived from D-tartaric acid. Lewis acid-catalyzed asymmetric Diels-Alder reaction of **158** with diene **159** gave adduct **160**, with the stereochemistry shown. In order to avoid epimerization α to the carbonyl, this group was first reduced diastereoselectively, and the resulting alcohol was protected as its silyl ether (**160** → **161**). Ozonolysis gave an aldehyde ester, which reacted under salt-free Wittig conditions to produce **162**. The Wittig reaction proceeded with complete *Z* stereoselectivity. Removal of the

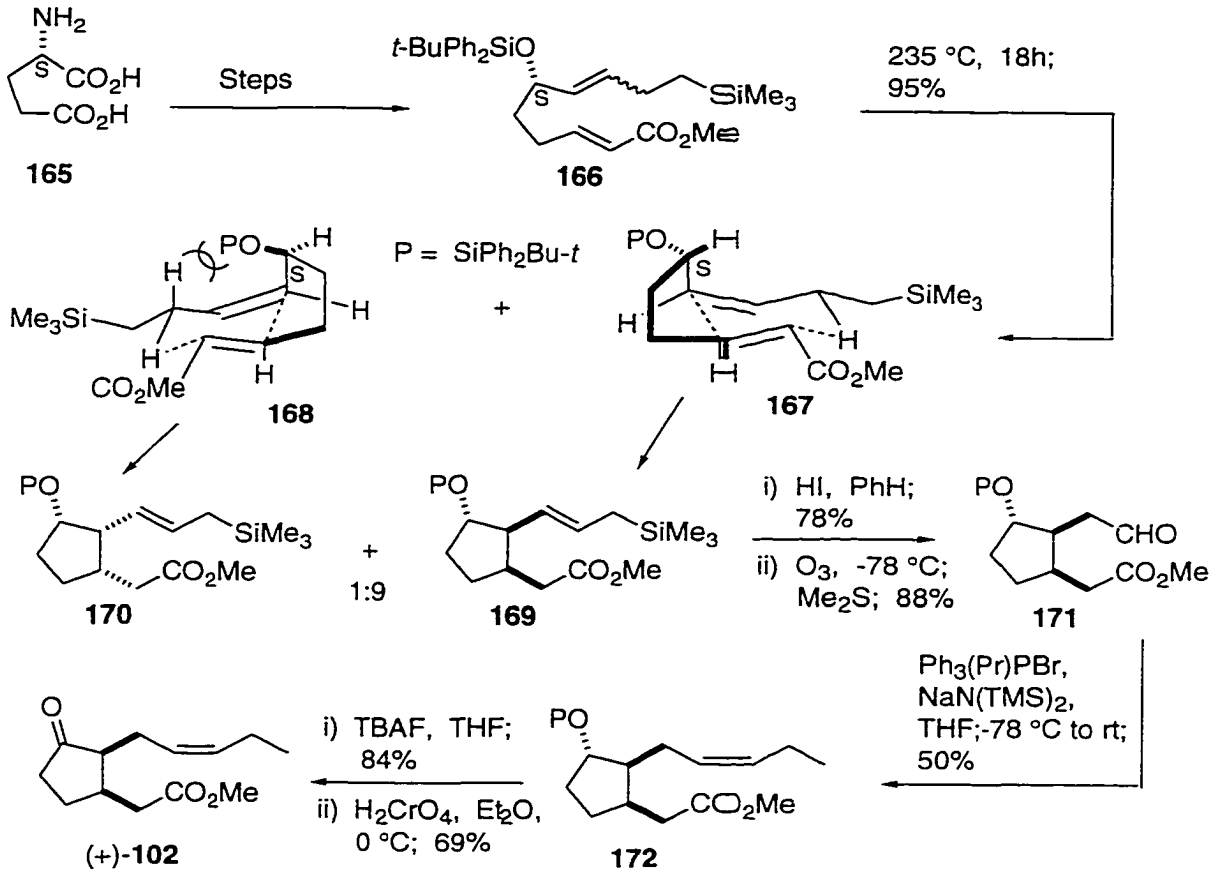
1,3-dioxolane group and Corey-Winter deoxygenation of the resulting vicinal diol gave olefin **163**. Finally, in order to be able to distinguish between the double bonds in a later step, the *t*-BuMe$_2$Si-protected alcohol was deprotected and oxidized to **164**. Selective reduction of the enone gave



Scheme 34

natural methyl *epi*-jasmonate (+)-**102**.

In an enantiospecific synthesis of (+)-methyl *epi*-jasmonate (Scheme 35), Sarkar and coworkers,[50] used an ene cyclization of the functionalized diene **166** to set up the essential asymmetric centers.



Scheme 35

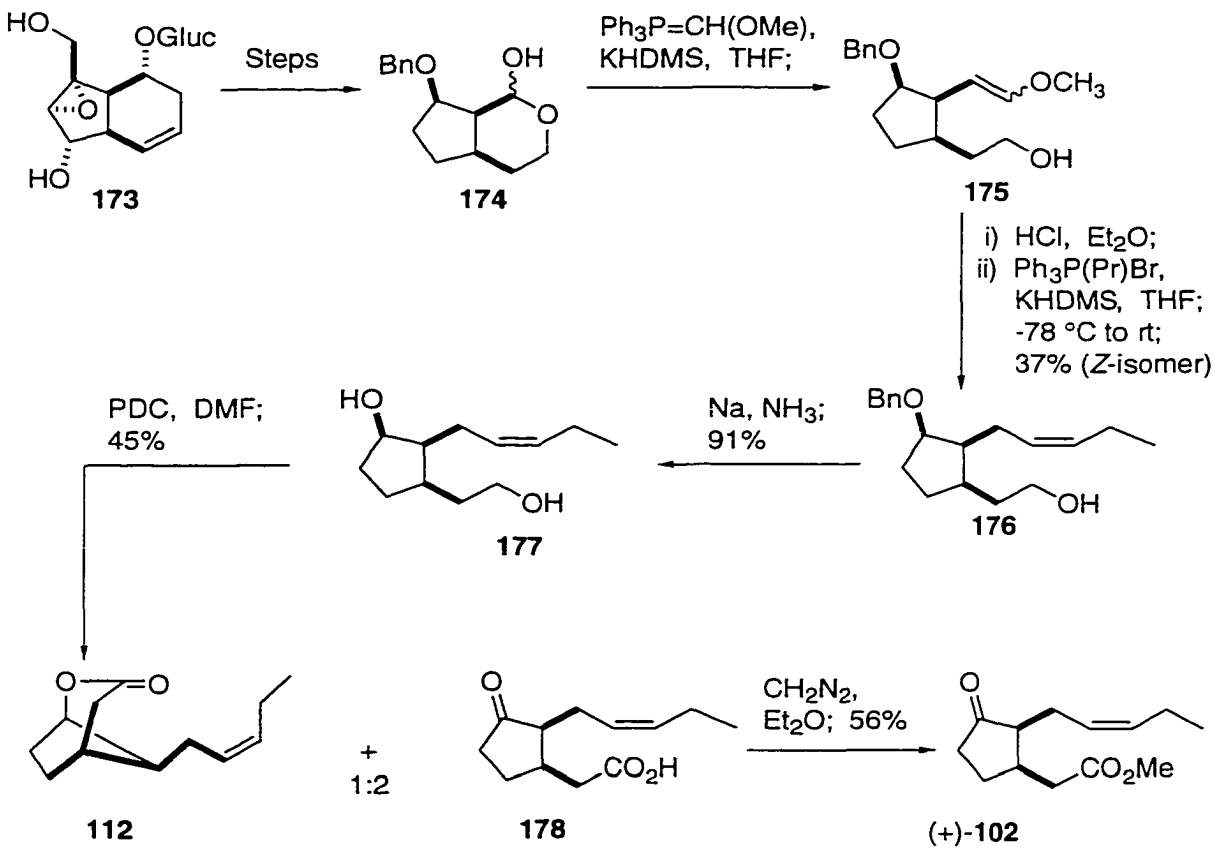
Diene **166** was synthesized from L-glutamic acid.[51] Ene reaction of **166** at 235 °C proceeded with high diastereoselectivity to give a 9:1 mixture of esters **169** and **170**. The stereoselectivity of the ene-reaction can be explained in terms of the possible transition states **167** and **168**. Transition state **167** gives rise to compound **169**, whereas the less stable **168**, where the alkoxy group is *endo*, gives **170**.

Double bond migration to the end of the upper pendant and ozonolysis, gave aldehyde. On Wittig olefination under salt-free conditions, **172** was formed, and desilylation,

followed by oxidation, gave (+)-**102** (87% ee).

A synthesis[52] of racemic material starting from racemic **166** had been achieved earlier, using the same route.

In Weinges and Lernhardt's[53] synthesis of (+)-methyl *epi*-jasmonate, catalpol **173**, a material from the chiral pool, was chosen as the starting point. Compound **173** was converted into lactols **174** by a literature procedure.[54] Wittig reaction with (methoxymethylene)triphenylphosphorane



Scheme 36

released the alcohol **175**. At this point, acid hydrolysis of the enol ethers, followed by treatment of the resulting aldehyde with propylidenetriphenylphosphorane under salt-free

conditions produced olefin **176** in good yield. Debenzylation (**176** → **177**), followed by oxidation, gave a 1:2 mixture of the bridged lactone **112** and the acid **178**. Esterification of **178** with diazomethane gave methyl *epi*-jasmonate (+)-**102**.

Conclusion

From the above review, it is clear that a number of approaches are available for preparing methyl *epi*-jasmonate, but all of them, inevitably, require the use of extremely mild conditions when the ketone carbonyl is released, in order to avoid epimerization, and it is probable that most synthetic material contains small amounts of the C(2) epimer.

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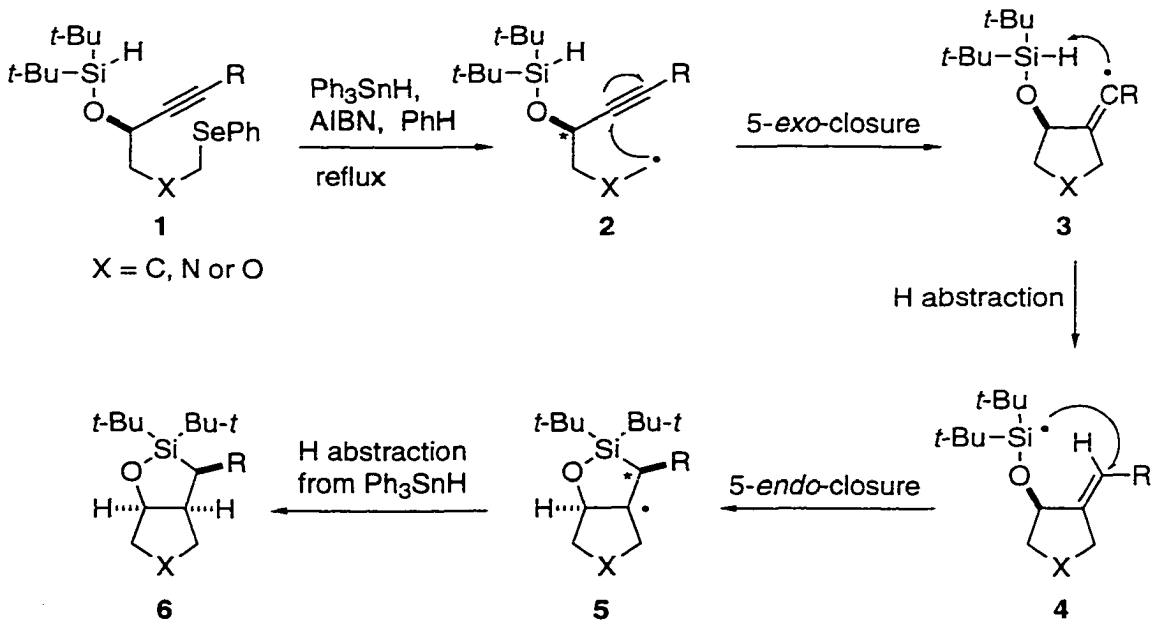
A FORMAL SYNTHESIS OF METHYL *EPI*-JASMONATE, AND USE OF MATERIAL FROM THE CHIRAL POOL

RESULTS AND DISCUSSION

Previous work in this laboratory resulted in the development of the radical cascade shown in Scheme 1. This cascade represents a method for making 5-membered rings in a stereocontrolled manner.[1] The essential steps require a starting material containing the following features: i) a radical precursor, ii) a radical acceptor (in this case a triple bond), and iii) a suitably placed silicon hydride, which will act as a hydrogen donor and generate a silicon-centered radical.



Scheme 1

The first step in the cascade involves generation of the alkyl radical **2**, by tin-mediated cleavage of the PhSe-C group. The radical undergoes 5-*exo*-digonal closure onto the triple bond, resulting in the creation of a 5-membered ring and a vinyl radical. This newly generated vinyl radical **3** then abstracts hydrogen from the silicon unit so as to create a silicon-centered radical. This, in turn, undergoes 5-*endo* cyclization onto the double bond to form a bicyclic system **5**, with a radical at the ring fusion position, as shown. Intermolecular hydrogen abstraction by this radical occurs exclusively from the less sterically hindered face, and generates the second stereocenter (**5** → **6**). Several key features of this cascade deserve comment. The first point is that the second cyclization occurs through a normally disfavored 5-*endo*-trigonal pathway. When a chain undergoing ring closure contains only first row elements, such processes are disfavored due to the severe distortion of the bond lengths and bond angles required for the preferred approach trajectory of the radical to the double bond.[2] However, in our case, the longer bond lengths associated with silicon make the preferred trajectory readily available. Cyclization reactions, like the one just described, involving silicon-centered radicals[3] are not common, but there is now a growing number of related examples actually involving carbon chains,[4] and these have been discussed in the review section of this thesis.

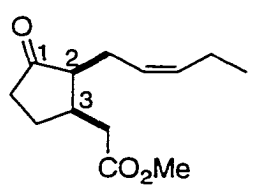
A second point about the cascade of Scheme 1 is that the

ring closure occurs stereoselectively, generating a second asymmetric center (see starred atom in **5**), although in our synthetic work described later, this center is destroyed during further elaboration. A third stereocenter is created when the reaction is quenched by hydrogen abstraction from the stannane. This process occurs exclusively from the convex face of the molecule.

Bicyclic compounds, such as **6**, where X is not a carbon but a heteroatom, have also been made by the same cascade process.[5]

Since the stereochemical consequences of the above reactions is controlled solely by the stereochemistry of the hydroxyl-bearing carbon, use of an optically pure alcohol should lead to the generation of enantiomerically pure compounds.

In the following discussion, I deal with the application of the method summarized in Scheme 1 to the synthesis of methyl *epi*-jasmonate (**7**), and I also illustrate the use of an optically pure starting material, obtained from the chiral pool.

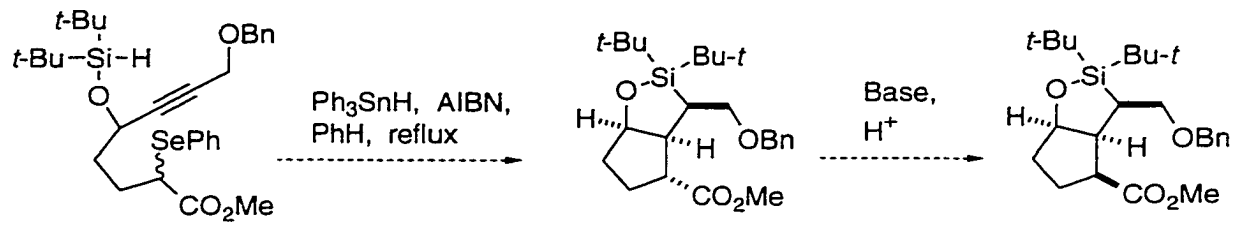


7

Figure 1 Methyl *epi*-jasmonate

Methyl *epi*-jasmonate

As mentioned earlier, the key structural feature of the natural product methyl *epi*-jasmonate (**7**) is a cyclopentane with the substituents at C(2) and C(3) in a *cis* relationship. We felt that this feature could be accommodated by the radical cascade of Scheme 1, by appropriate adjustment of the stereochemistry of the initial product. The radical cascade, when applied to a substrate **8** should give compound **9**. In principle, deprotonation of ester **9** by a suitable base, followed by kinetic reprotonation,



8 **9** **10**

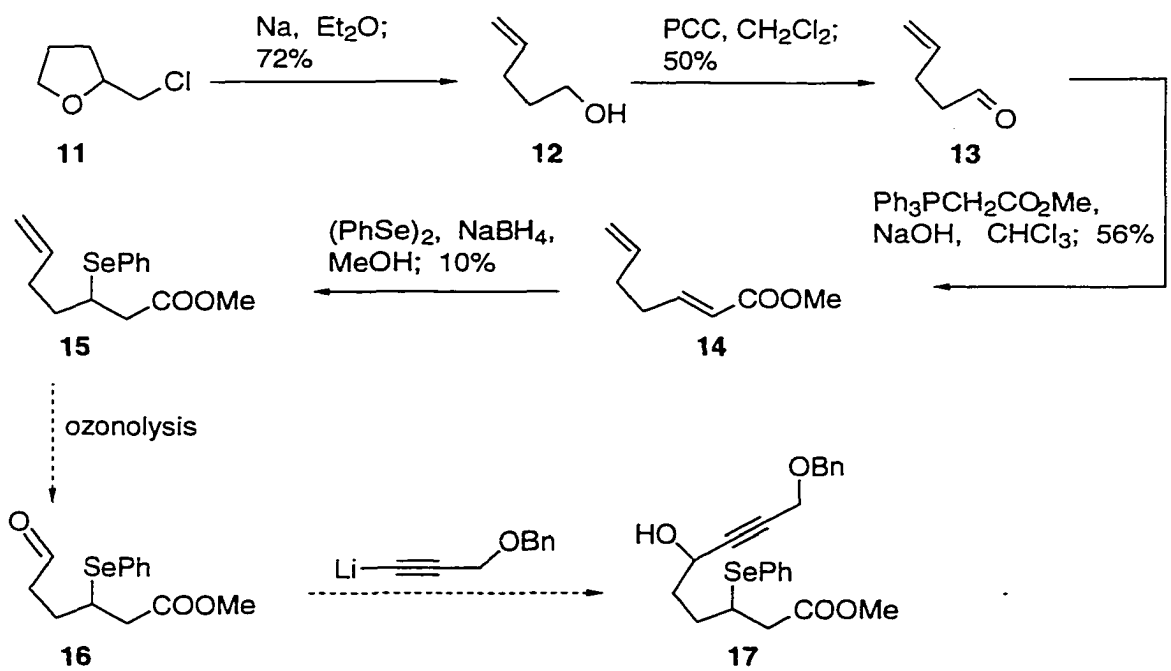
Scheme 2

should afford the all-*syn* trisubstituted cyclopentane system **10**. The deprotonation-reprotonation sequence would then extend the applicability of the radical cascade to the generation of *cis* substituted cylopentanes (Scheme 2).

An alternative way of achieving the same end would be to prepare a radical cyclization precursor such as **17** (Scheme 3), and then adjust the stereochemistry after cyclization by a dehydrogenation-hydrogenation sequence, as described later.

We examined the preparation of ester **17** first, and the compound was synthesized along the following lines.

The initial plan was to make selenide **16**, starting from furfuryl chloride. The latter was converted in good yield into the corresponding olefin (**11** → **12**) by dehydrohalogenation, using a literature procedure.[6] Oxidation of the alcohol led to the corresponding aldehyde **13**. The reaction appeared to be very clean, as judged by TLC examination, but isolation proved difficult due to the volatility of the aldehyde, and the isolated yield was low. Reaction of the aldehyde with the ylide derived from (carbomethoxymethyl)triphenylphosphonium bromide proceeded smoothly to give ester **14**, although in low yield (56%). Unfortunately, Michael addition of the anion $PhSe^-$ to the enone proceeded in unacceptable yield (10%), and so this route to selenide **15** was abandoned (Scheme 3). It had been

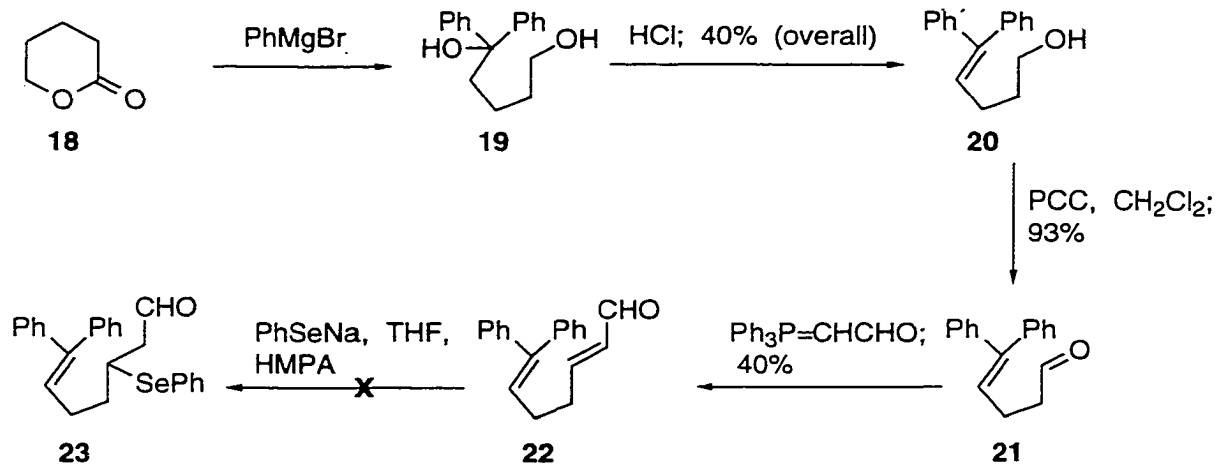


Scheme 3

our intention to ozonize **15** under conditions that would preserve the selenium unit,[7] and then elaborate aldehyde **16** into the key intermediate **17**.

To overcome the difficulty of isolating the volatile aldehyde **13**, and to make a more reactive Michael acceptor – by replacing the ester of **14** with an aldehyde group – we decided to modify the above route.

Starting from readily available δ-lactone **18**, the diol **19** was generated by Grignard reaction, and dehydrated

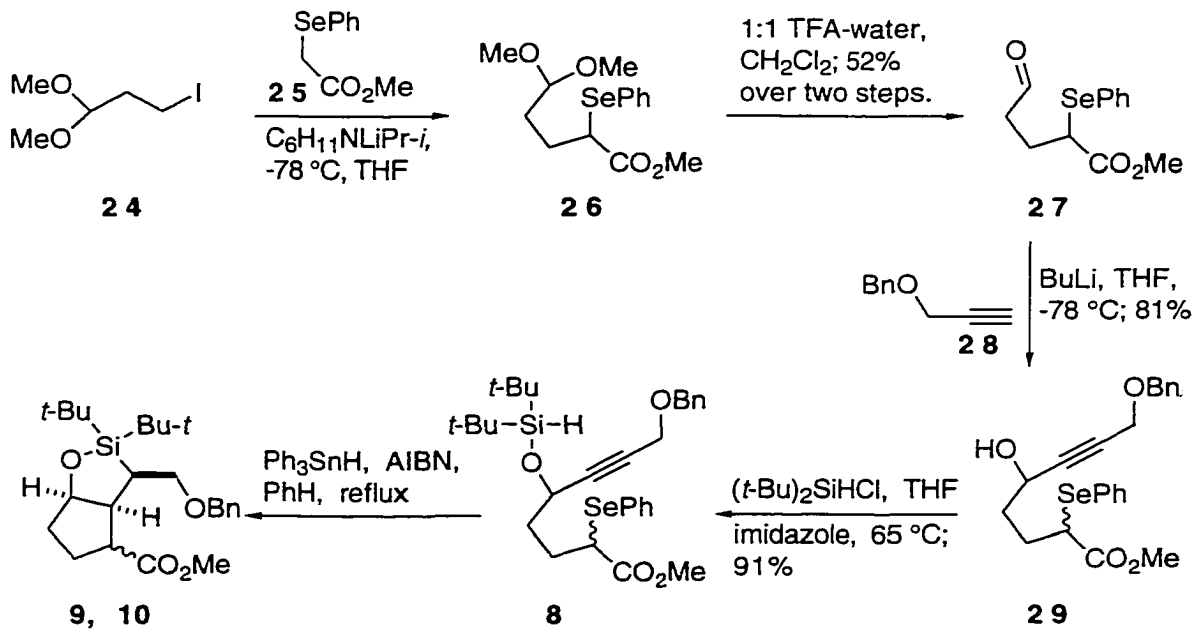


Scheme 4

selectively to obtain olefin **20** (Scheme 4).[8] Oxidation of the olefinic alcohol **20**, followed by Wittig homologation, gave the required aldehyde **22**. Next, we decided to install the radical precursor (PhSe) and cleave the remaining double bond. Unfortunately, our attempts to introduce the PhSe group by Michael addition were unsuccessful and so, at this point, we decided to base our approach to methyl *epi*-jasmonate on intermediate **8** (Scheme 2), this being a

substance that had already been prepared[9] in our laboratory. Of course, use of **8** would eventually entail the addition of an extra carbon.

The new reaction sequence started with alkylation of iodoacetal **24** with the anion derived from methyl(phenylseleno)acetate **25**, so as to give acetal **26**. This was best deprotected *in situ* using TFA, in order to liberate aldehyde **27**. Treatment of the aldehyde with the lithium anion of benzyl propargyl ether gave an inseparable mixture of alcohols **29**. Protection of the hydroxyl with di-*tert*-butylchlorosilane proceeded smoothly to yield the cyclization precursors **8**, and this material was then subjected to our standard conditions for radical cyclization. Slow addition of a benzene solution of Ph_3SnH and AIBN to a refluxing



Scheme 5

solution of **8** in the same solvent, proceeded smoothly, via sequential 5-*exo*-digonal cyclization, intramolecular hydrogen transfer, and 5-*endo* cyclization. The product of this sequence was a mixture of diastereomeric esters **9** and **10**. The stereochemistry of the products could not be established at this stage because the compounds were inseparable and the material contained tin residues. However, we expected that the 5-*exo*-digonal ring closure would take place preferentially via conformation **30**, in which the ester group is *trans* to the O-Si unit.

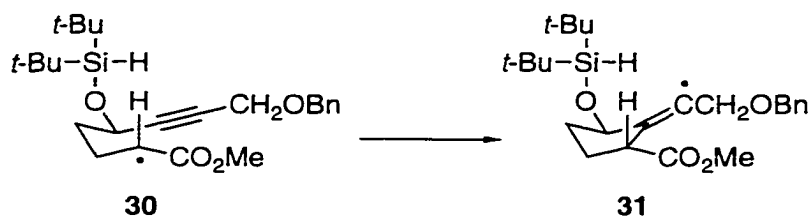
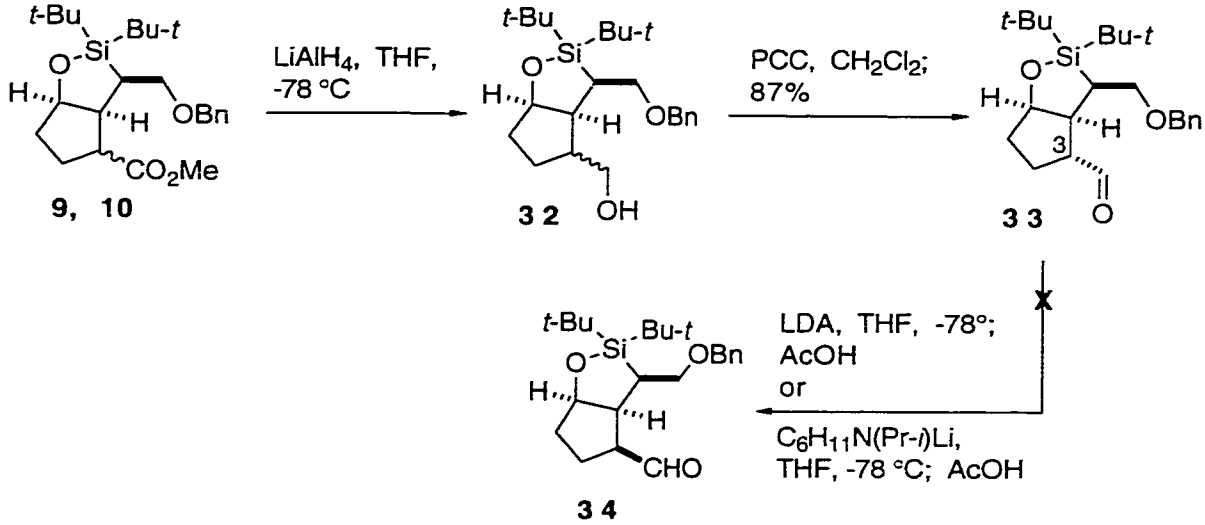


Figure 2 Favored Conformation

Previously, when the mixture of esters **9** and **10** had been treated with $BF_3.Et_2O$,[9a] attack on the silicon by fluoride ion led to expulsion of the OBn group, so that an olefin was formed.[9b] This olefin was isolated as a single isomer and the stereochemistry, which was assigned on the basis of ^1H NMR measurements,[9b] indicated that the major isomer of the **9,10** mixture would likewise have the ester group *trans* to the silicon unit.

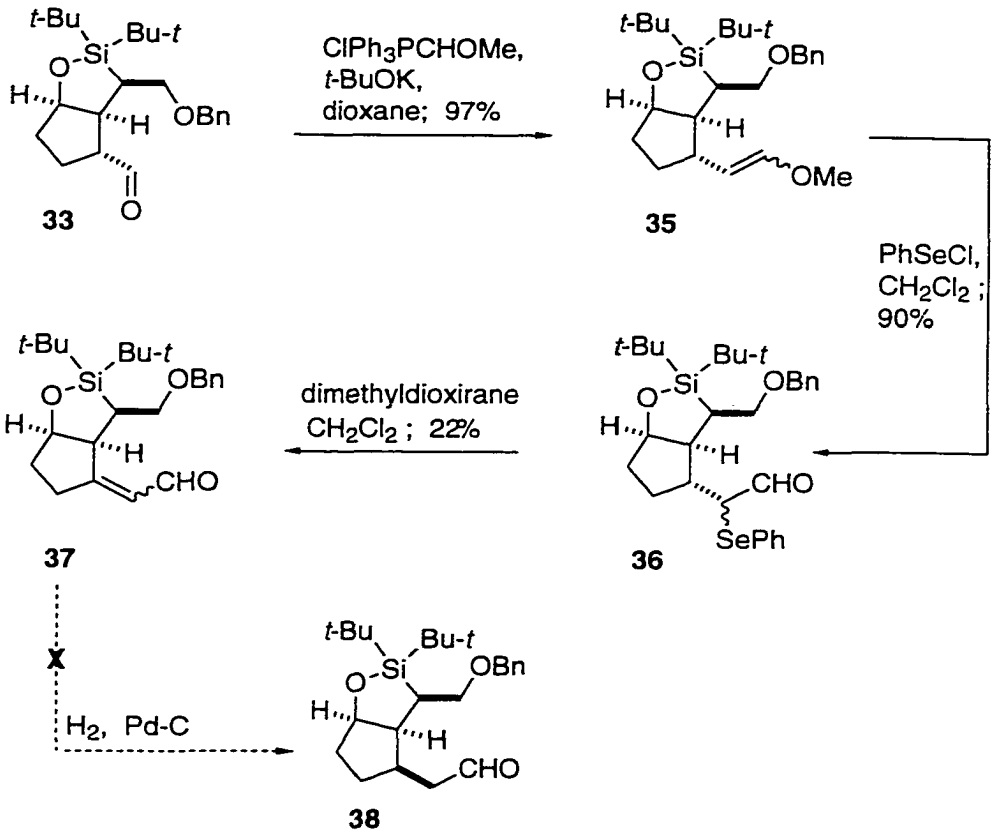
In order to obtain methyl *epi*-jasmonate all the substituents on the cyclopentane ring must be *cis*, and so stereochemical adjustment of the major radical cascade



Scheme 6

product was necessary. We anticipated that this could be done easily by oxidation of alcohols **32**, followed by base-induced epimerization at C(3). Surprisingly, when aldehyde **33** was treated with lithium isopropylcyclohexylamide in THF or with LDA, followed in each case by addition of acetic acid, not even trace amounts of the C(3) epimer could be detected, the starting material being recovered unchanged. Hence we decided to use an indirect approach, summarized in Scheme 7.

This new line of attack involved elongation of the chain at C(3) by one carbon (**33** → **35**), followed by introduction of selenium and selenoxide elimination (**35** → **36** → **37**) (Scheme 7). These steps would give a substituted exocyclic olefin (**37**), and hydrogenation of the double bond would be expected to proceed from the less hindered convex face of the bicycle,

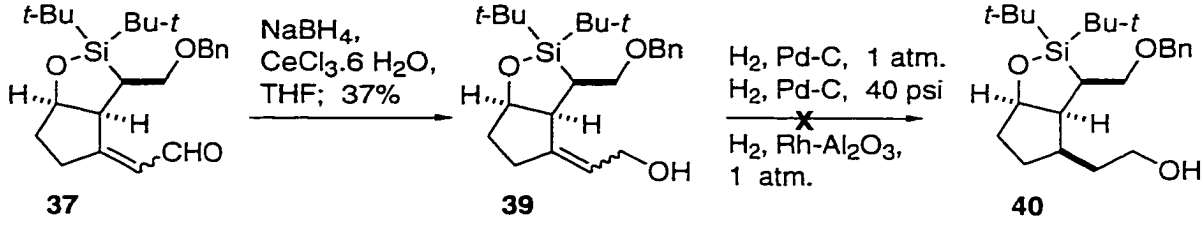


Scheme 7

thus generating the desired relative stereochemistry at the contiguous asymmetric centers of **38**.

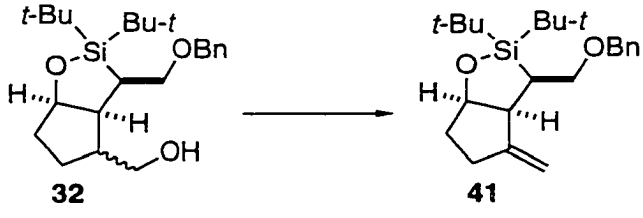
Conversion of aldehyde **33** into the enol ethers **35** proceeded without event and in high yield. Treatment of the ethers with PhSeCl gave selenides **36** but, to our surprise, the selenoxide elimination was inefficient and gave **37** in only 22% yield. Nevertheless, we proceeded with the hydrogenation step. However, we failed to saturate the double bond, and indeed, did not even observe debenzylation. At the time we did not establish if a catalyst poison was present, but instead, we decided to try the reduction on the

corresponding alcohols **39** (Scheme 8). In the event, attempts to reduce the double bond of the allylic alcohols under several different conditions (see Scheme 8) were unsuccessful.



Scheme 8

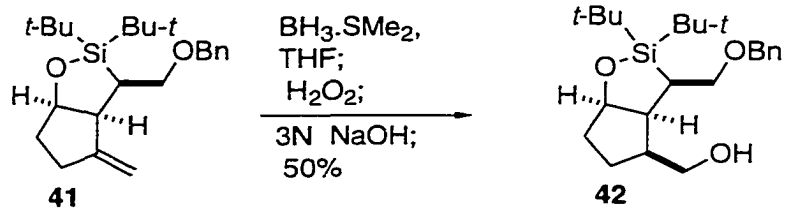
Finally we decided to convert alcohols **32** into olefin **41** (Scheme 9) and reinstall the hydroxyl group by hydroboration and oxidation. The hydroboration should be not only regio-selective, in accordance with Markovnikov's rule, but the reagent should also approach the olefin from the less hindered convex face; thereby the overall process would invert the stereochemistry at C(3) (see Scheme 10). Conversion of alcohols **32** into the corresponding *o*-nitro-



Conditions	Yield
i) a) MsCl, CH_2Cl_2; Et_3N; b) DBU, reflux	20%
ii) a) *o*-$O_2NC_6H_4SeCN$, Bu_3P, THF; 89%	10%
b) H_2O_2 or *m*-CPBA; i-Pr_2NH, CH_2Cl_2	or 7%
iii) a) Ph_2PCl, Imidazole I_2, CH_2Cl_2 ; 50%	0
b) DBU, reflux	
iv) a) Tf_2O, Pyridine, DMAP; 65%	SM
b) DBU, reflux	

Scheme 9

phenyl selenides proceeded in high yield, but elimination of the selenoxide was sluggish. To test our proposed route, we

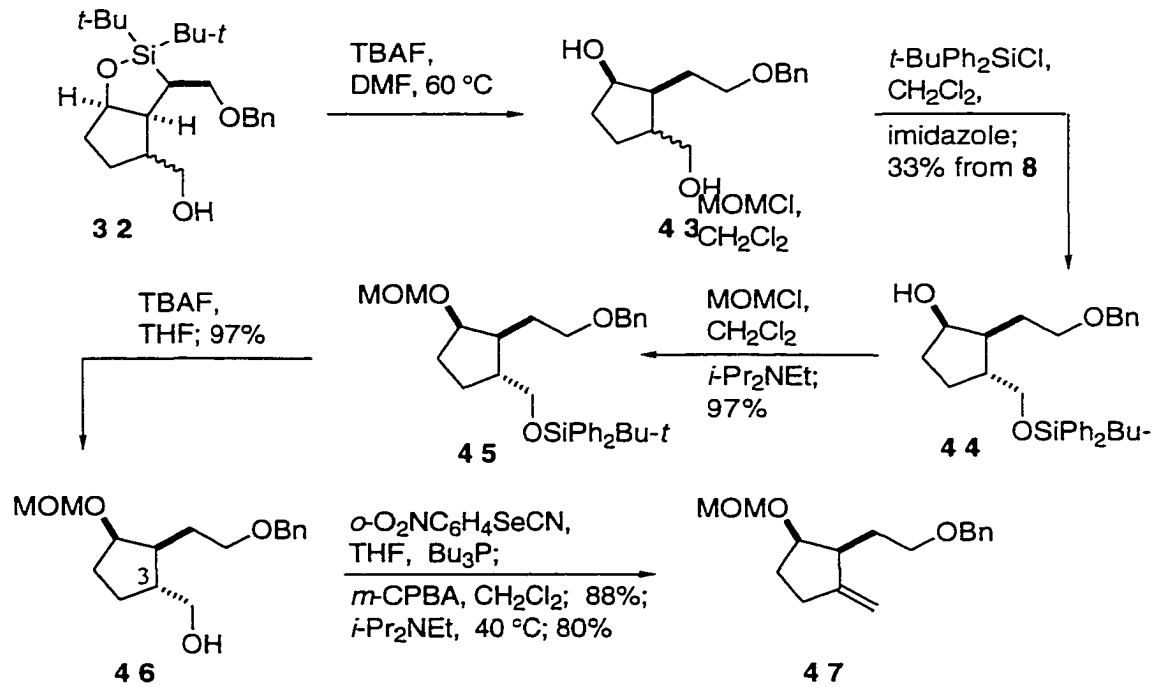


Scheme 10

decided to proceed with the hydroboration-oxidation sequence, despite the low yields in the previous step. Under standard conditions the olefin could be converted into the desired alcohol **42**, which was obtained as a single isomer in 50% yield (Scheme 10).

Our next task was to improve the yields of the olefin formation (**32** → **41**). We decided to convert the alcohol into various leaving groups and use a base to effect elimination. Several leaving groups were examined, and in each case (see Scheme 9) conversion of the hydroxyl into the leaving group was quite easy, but difficulties were again encountered in the elimination step. It occurred to us that the elimination process might be easier if the *tert*-butyl groups were removed and the rigid convex shape of the molecule were altered. To this end, a protodesilylation method developed by Stork,[10] was applied. This involves simultaneous cleavage of both the C-Si and O-Si bonds (Scheme 11). Treatment of bicyclic alcohols **32** with an excess of TBAF in warm (60 °C) DMF gave the trisubstituted cyclopentane **43**. Selective protection of

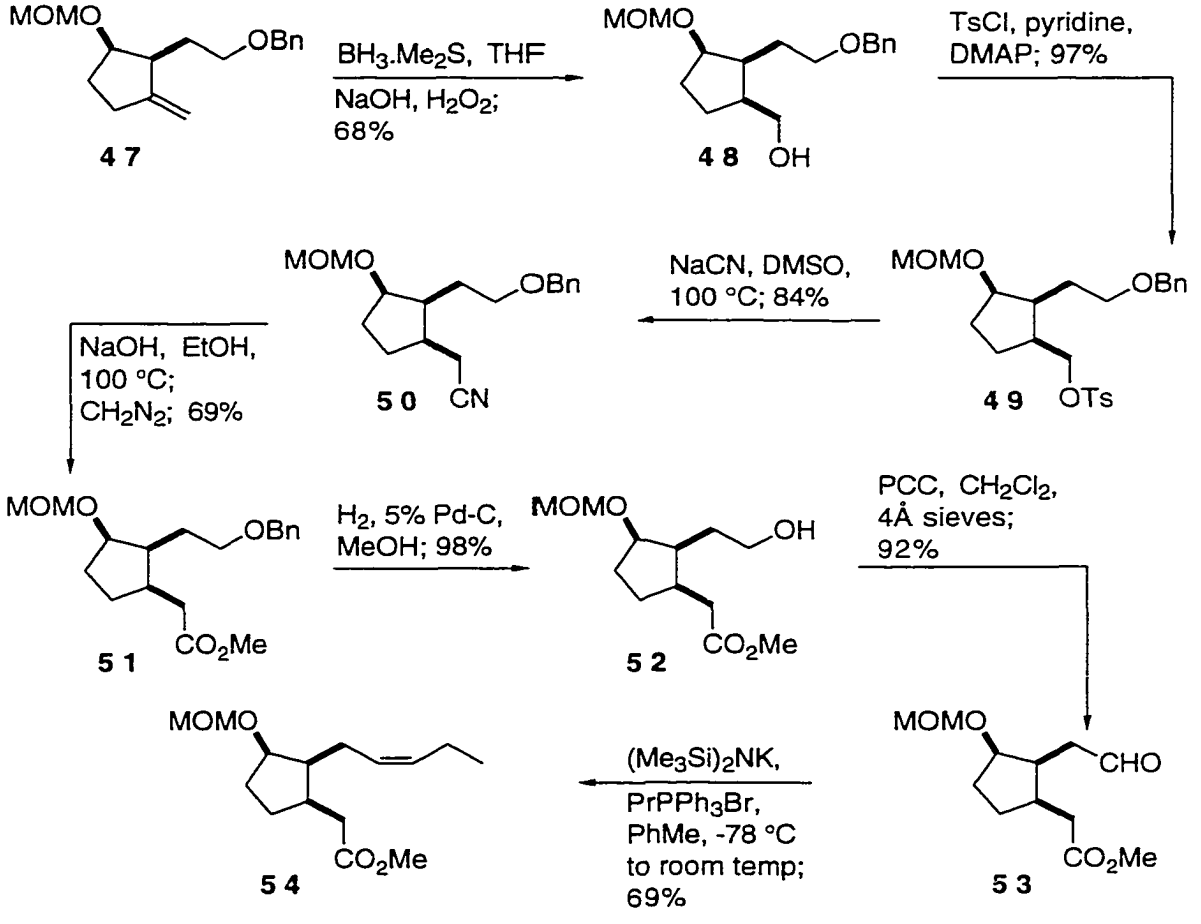
the primary hydroxyl, using *t*-$BuPh_2SiCl$, gave pure silyl ether **44**. It should be noted that this compound is the first pure substance obtained since the cyclization step, as unidentified tin species were present in the precursors (phenyl groups were evident in the ^1H NMR spectra). The yield of **44** was 33% over four steps. The hydroxyl of **44** was protected as its methoxymethyl (MOM) ether, and the resulting compound (**45**) was then desilylated under standard conditions to release alcohol **46**. Transformation of the alcohol into the selenide was done as before, and we were pleased to observe that when the selenide was oxidized with *m*-CPBA and treated with Hünig's base, olefin **47** could be obtained in very good yield (80%). Hydroboration of the olefin at -20 °C



Scheme 11

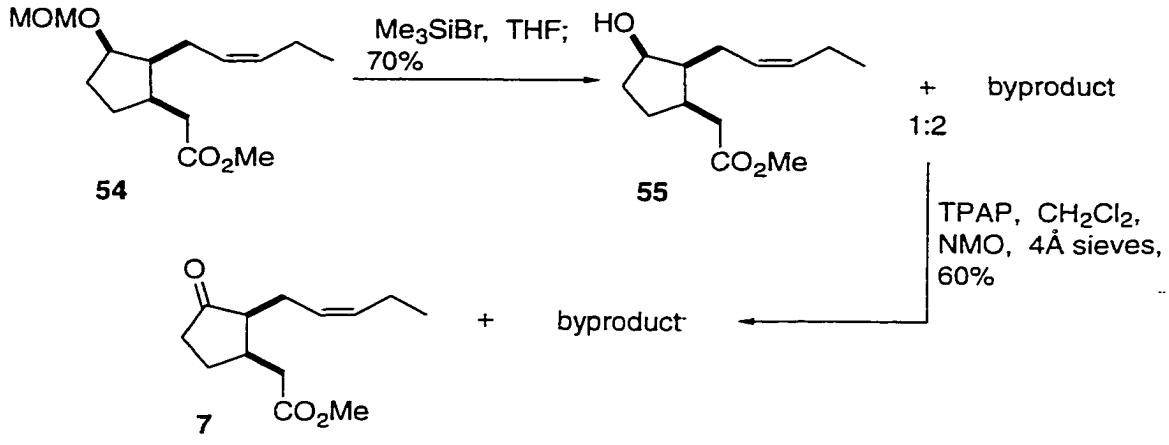
with borane-dimethyl sulfide complex, followed by oxidation with alkaline hydrogen peroxide, gave the desired alcohol **48** (Scheme 12). The reaction leading to alcohol **48** was completely selective both facially and regiochemically, so that the relative stereochemistry of the substituents was the same as in the target natural product.

A number of standard chemical transformations were then necessary to extend the hydroxyl-bearing arm to the desired length. The alcohol was converted into tosylate **49**, and the



Scheme 12

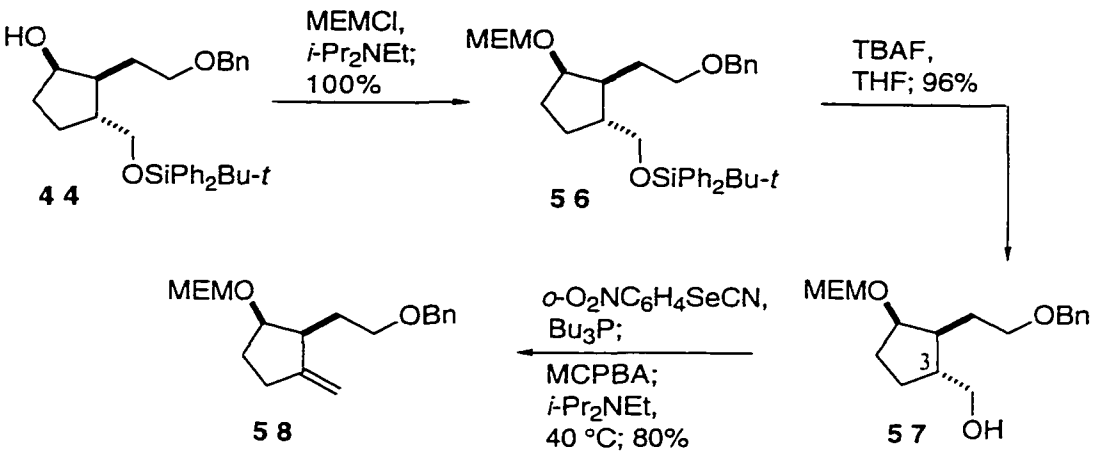
leaving group was then displaced by cyanide anion. Attempted hydrolysis of the resulting nitrile **50** under mild conditions (40 °C, aqueous base) failed to give any product, although at an elevated temperature (100 °C), using ethanolic base (3 N NaOH), the corresponding acid could be obtained in satisfactory yield. The crude acid was directly transformed into its methyl ester **51** by treatment with diazomethane. Hydrogenolysis of the benzyl group occurred at room temperature and at 1 atmosphere to give alcohol **52**. PCC oxidation then served to generate the corresponding aldehyde **53**, and this was treated with the salt-free Wittig reagent derived from triphenylpropylphosphonium bromide, using well established conditions.[11] The reaction gave *Z*-olefin **54** exclusively and in good yield (Scheme 12). The NMR spectra of **54** was totally free of signals expected for the *E* isomer.[12] The remaining tasks at this stage were to remove the MOM ether protecting group and to oxidize the resulting alcohol. Surprisingly, treatment of ether **54** with Me_3SiBr gave an inseparable mixture of the desired product along with a byproduct. Proton NMR analysis of the mixture showed the absence of the MOM group. In the hope of being able to remove the unwanted material at the next stage, the alcohol was oxidized with TPAP to give **7** and a byproduct. A single spot was observed by thin layer chromatography using various eluents, but the ^1H NMR spectrum showed the presence of the natural product along with an impurity derived from the last transformation in approximately a 1:2 ratio (Scheme 13).



Scheme 13

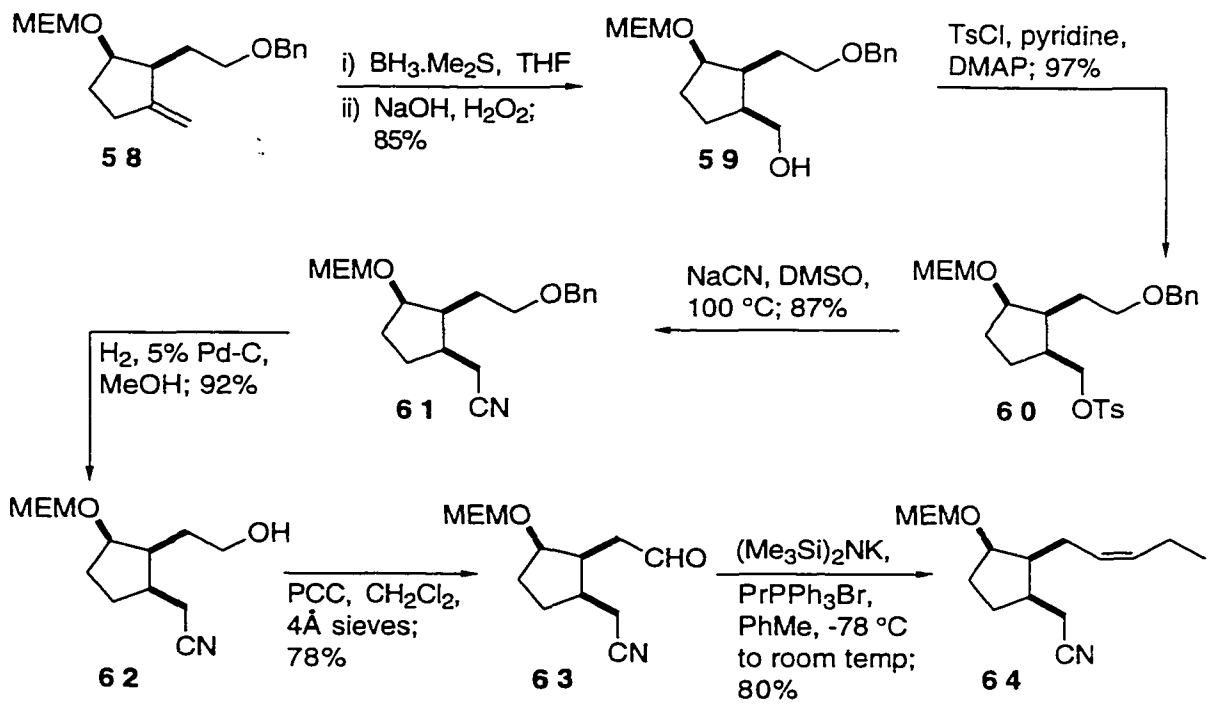
The byproduct, which could not be separated for characterization, might have been formed (during cleavage of the MOM group) by capture of the intermediate oxonium ion by the pendant olefin.

At this stage, it was clear that we needed to repeat the original sequence, with a protecting group that could be more easily removed (Scheme 14). We chose the 2-methoxyethoxy-methyl (MEM) as the unit to protect the secondary hydroxyl of compound **44** (**44** → **56**, Scheme 14). Desilylation of **56** with an excess of TBAF at room temperature gave alcohol **57**, which was readily converted into its *o*-nitrophenyl selenide. Peracid oxidation of the selenide gave the exocyclic olefin **58** in very good yield. Next, hydroboration-oxidation regenerated the hydroxymethyl group with the correct stereochemistry, as expected from our experiments in the MOM



Scheme 14

series. Tosylation of the resulting alcohol **59**, followed by displacement with cyanide, gave us the desired product **61** (Scheme 15). Removal of the benzyl group by hydrogenolysis released alcohol **62** which, on PCC oxidation, gave the corresponding aldehyde **63**. When the aldehyde was treated

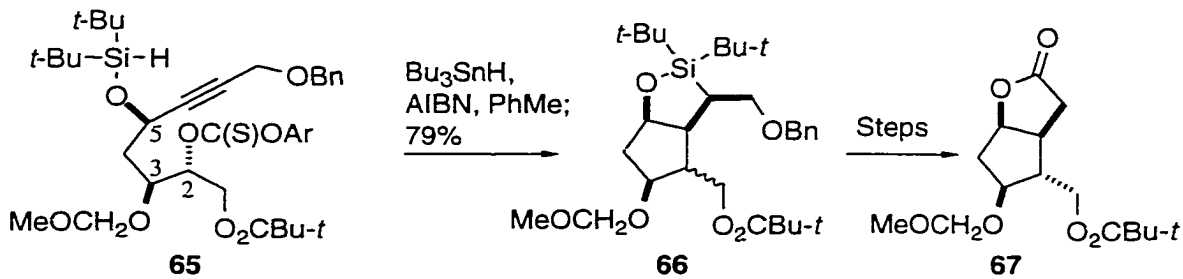


Scheme 15

with the salt free Wittig reagent generated from triphenylpropylphosphonium bromide, the *Z*-olefin **64** was obtained exclusively. Compound **64** (Scheme 15) is a substance that has been converted by others[13] into racemic methyl *epi*-jasmonate ester (see Scheme 27 in review section). Thus the synthesis of **64**, constitutes a formal synthesis of methyl *epi*-jasmonate.

APPLICATION OF THE RADICAL CASCADE TO MATERIAL FROM THE CHIRAL POOL

Other work in this laboratory resulted in the synthesis of **65**, which was transformed eventually into **67**.[9a] This compound is a derivative of the Corey lactone. The designa-



Scheme 16

tion "Corey lactone" has been used in recent literature to refer to a variety of hydroxyl-protected derivatives of general structure **68**. Such compounds serve as advanced intermediates commonly used in the synthesis of prostaglandins.[14] The prostaglandin family consists of a large

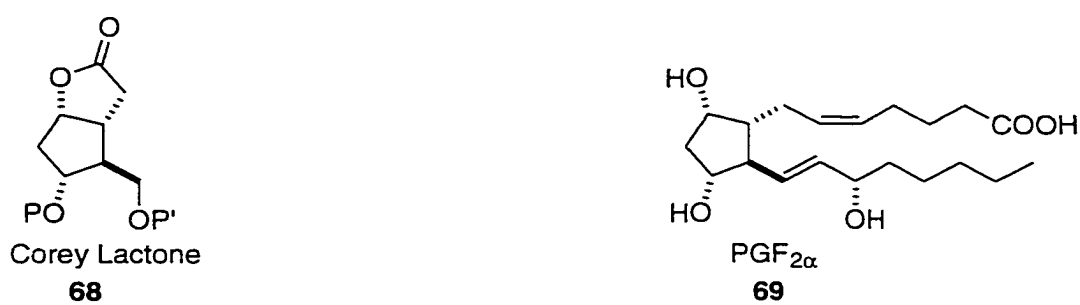


Figure 4 Corey Lactone and $PGF_{2\alpha}$

number of members but, common to all of them is a

cyclopentane ring with two side chains. The derivative **67** is related to the prostaglandin $PGF_{2\alpha}$ (**69**), as the relative stereochemistry about the cyclopentane subunit is the same in both compounds.

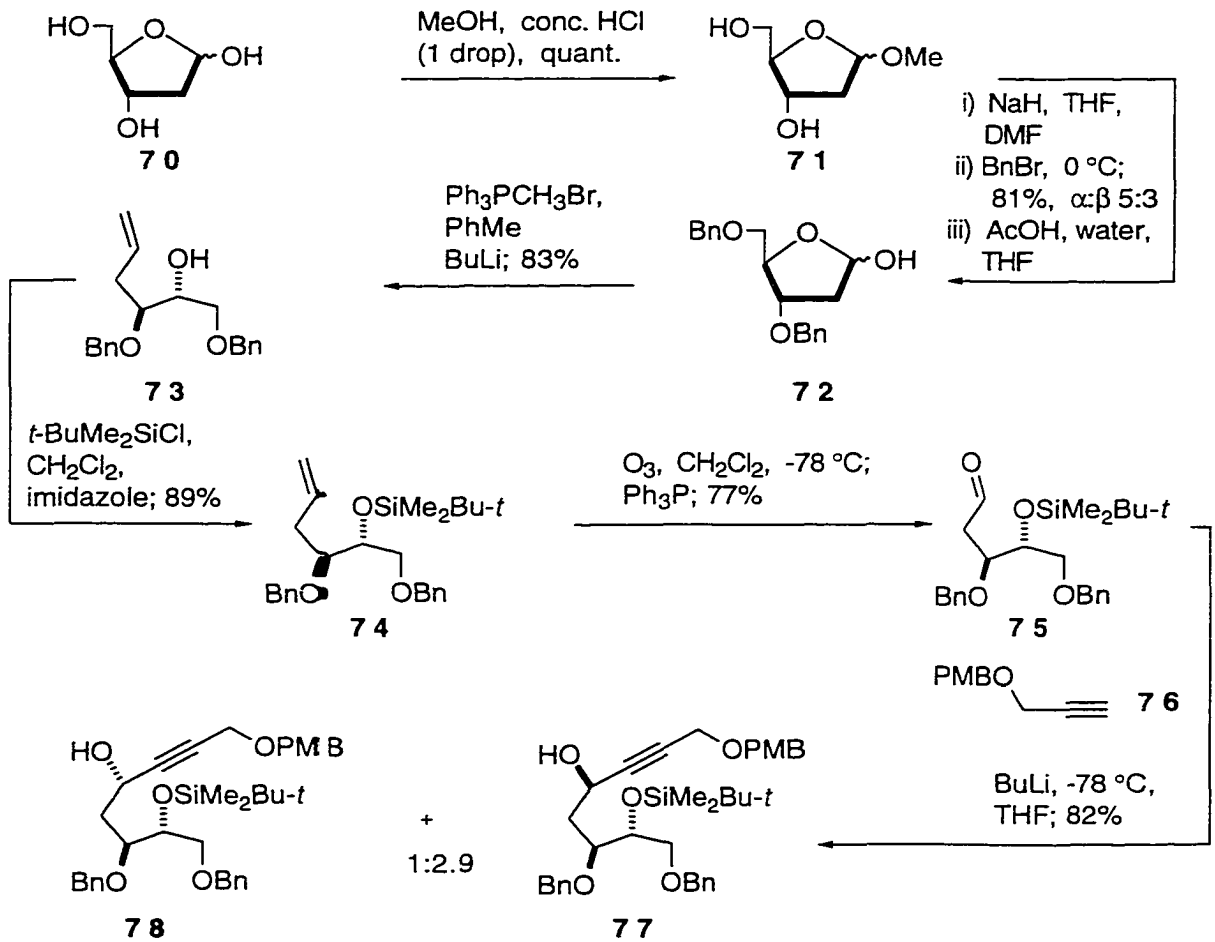
Previous work,[9] using the tandem radical process described in Scheme 1, but starting with **65**, gave the bicyclic product **66**, which was elaborated into the desired lactone **67**.

The stereochemistry of **65** at C(2) was assigned on the basis of my own experiments, described later, but my initial task was to apply the radical cyclization route (see Scheme 1) to the synthesis of optically pure **67**.

2-Deoxy-D-ribose, was chosen as the starting material because it contains the appropriate oxygen functionality for conversion into **67**. The material is also cheap and readily available, and it was chosen for this reason, even though the eventual lactone (**67**) would have the unnatural stereochemistry.

2-Deoxy-D-ribose (**70**) was first treated with methanol containing a catalytic amount of HCl, so as to trap the lactol unit as its methyl glycosides.[15] Protection of the remaining hydroxyls as benzyl ethers by a known procedure,[16] and acid hydrolysis of the resulting methyl glycosides, regenerated the lactol unit, to give **72**. Homologation of the lactol by Wittig reaction produced the hydroxy olefin **73** in very good yield (83%). Protection of the hydroxyl group with *t*-$BuMe_2SiCl$ (**73** → **74**), followed by ozonolysis in the

presence of an internal indicator (Sudan II red[17]) gave aldehyde **75**. Treatment of the aldehyde with the lithium anion derived from *p*-methoxybenzyl propargyl ether (**76**), proceeded diastereoselectively to a 1:2.9 mixture of alcohols **77** and **78**. These could be separated by careful (slow development) column chromatography. Both alcohols were

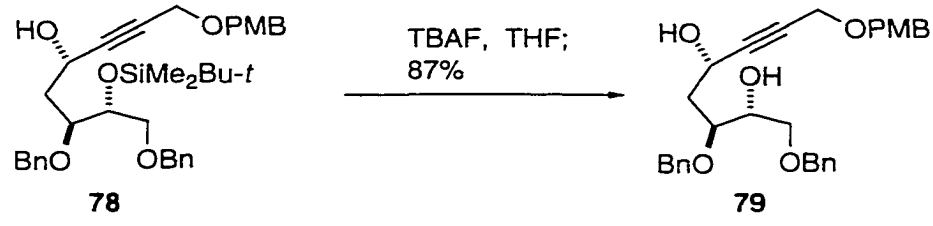


Scheme 17

desilylated easily, using TBAF to release the corresponding diols **79** and **80** (Scheme 18 and 19). We later found that conversion of alcohols **77** and **78** into the corresponding diols

made them more readily separable, and in subsequent runs, separation was delayed until that point.

The next task was to protect the propargylic hydroxyl selectively with the crucial *t*-Bu_2SiH unit. Fortunately, when **80** (the major diol) was treated with *t*-Bu_2SiHCl, the propargylic hydroxyl was protected at a much higher rate than



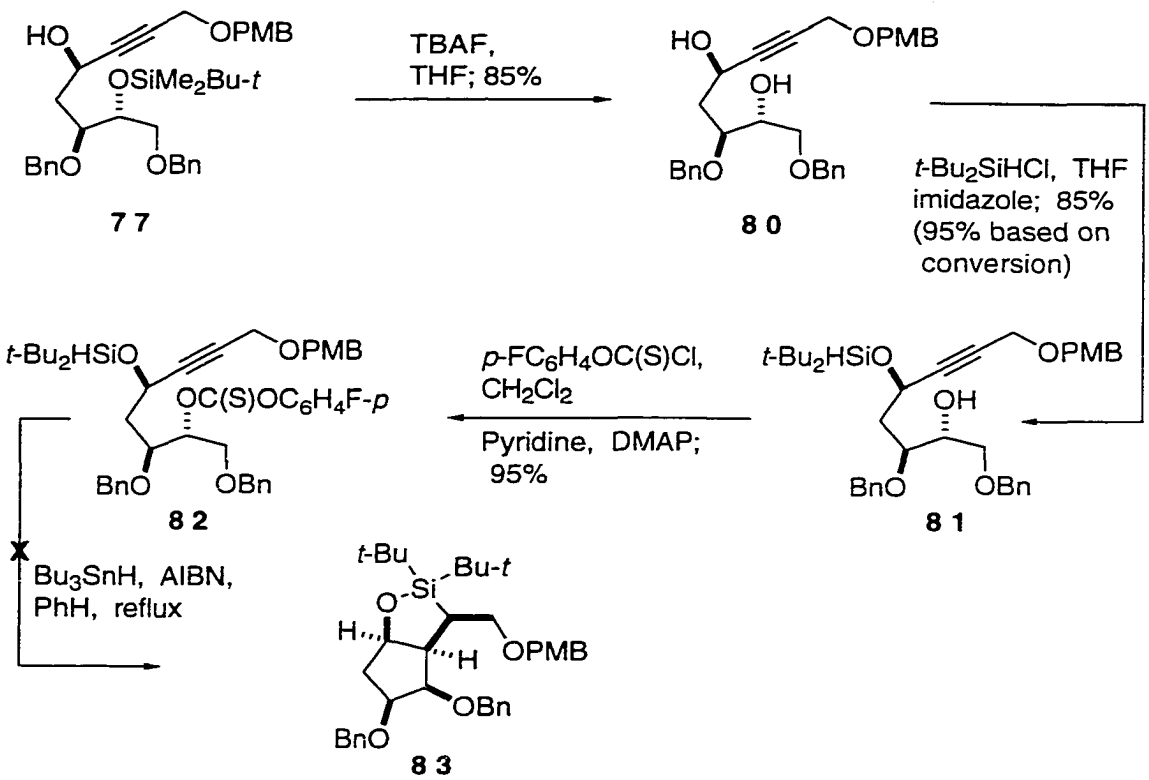
78 **79**

Scheme 18

the secondary hydroxyl (**80** → **81**). The reaction was monitored closely by TLC, and quenched at the first indication of the *bis*-silylated product. If necessary, the *bis*-silylated material could, in principle, be easily recycled, by treatment with TBAF. The regioselectivity observed in the monosilylation is probably due to the higher accessibility of the propargylic hydroxyl, due to the linear geometry of the adjacent alkyne.

The remaining task was to install the radical precursor, and to this end, the alcohol was esterified with *p*-$FC_6H_4OC(S)Cl$. Reaction proceeded smoothly to give **82** in excellent yield.

Unfortunately, when we tried our radical cyclization sequence, by slow addition of Bu_3SnH and AIBN to a refluxing



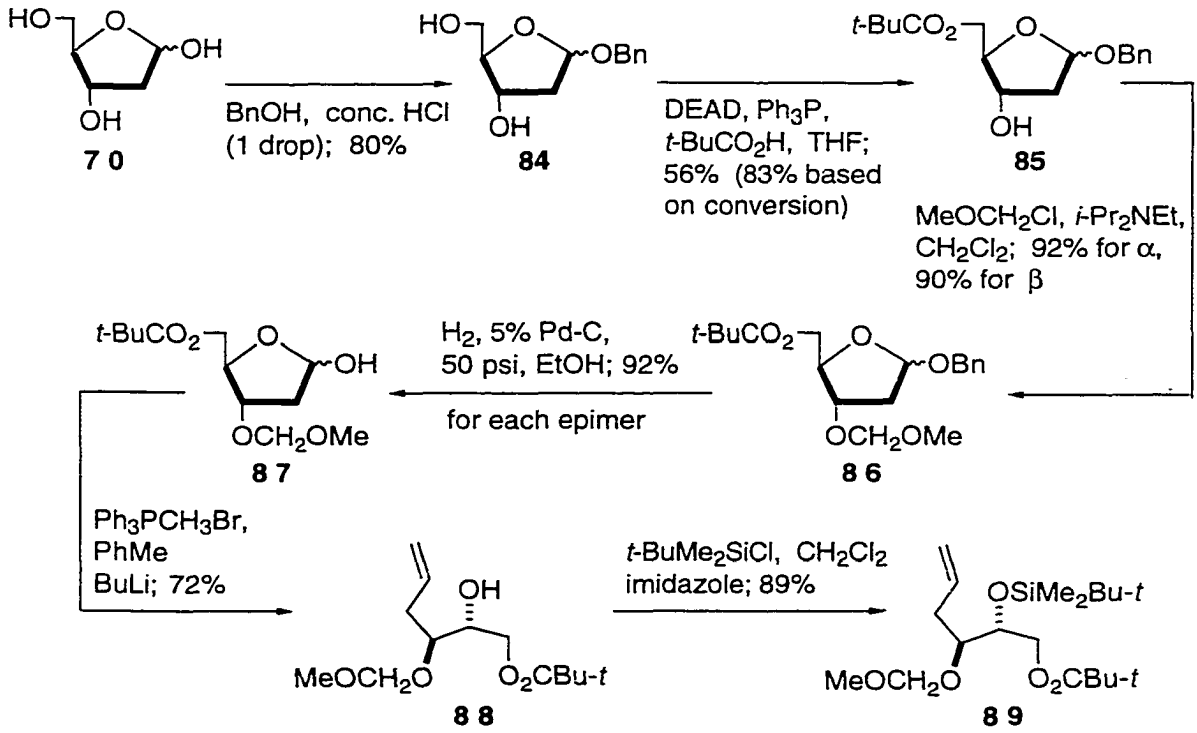
Scheme 19

solution of **82**, a complex mixture, which included some starting material, was obtained. Efforts to overcome this problem by varying the concentration and amount of stannane, were unsuccessful. We were unable to identify any of the reaction products and are unsure as to why this reaction failed. We assume that the presence of the benzyl group was responsible, but how it exerted an effect is unclear.

In prior work,[9] **65** had been found to undergo smooth cyclization. As **65** is similar to **82**, but with the hydroxyl groups protected differently, we decided to use the same protecting groups as in **65** for cyclization of material derived from 2-deoxy-D-ribose.

At this point we needed to solve another stereochemical

problem which remained unanswered during the synthesis of the racemic Corey lactone derivative **67**. The route used to make **65** ensured that the oxygen substituents at C(3) and C(5) are *syn*, but the relative stereochemistry with respect to the C(2) oxygen was unknown. To assign this stereochemistry, we decided to convert 2-deoxy-D-ribose into a compound with the same relative stereochemistry as implied by structure **65**. This choice of carbohydrate is appropriate as the C(2) stereochemistry in the final product is already set in the starting sugar. Spectroscopic comparison of the sugar-derived material with **65**, made by the prior route, would then allow us to make the stereochemical assignment at C(2) to the racemic compound. At the same time, formation of **65** (or a stereoisomer) would illustrate application of the radical



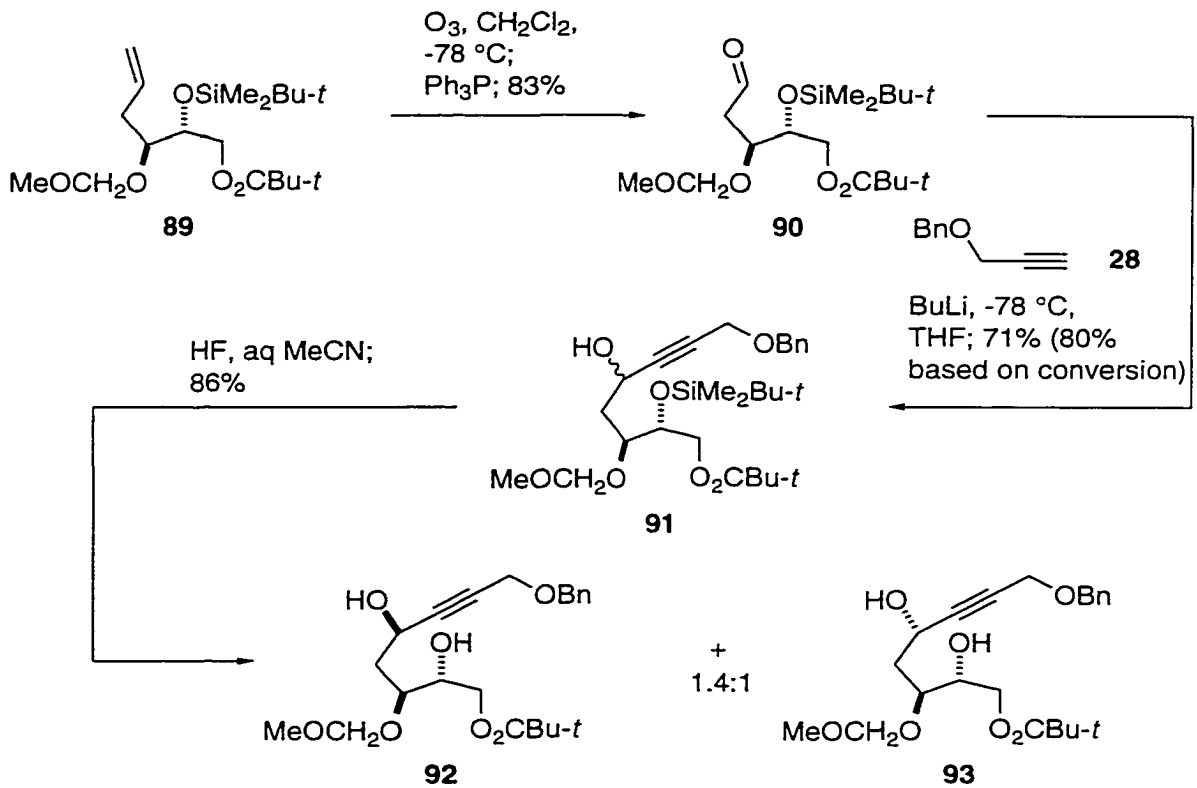
Scheme 20

cascade of Scheme 1 to material from the chiral pool.

Thus the failure of the radical cyclization with **82**, gave us the opportunity not only to use material from the chiral pool but also to settle at the same time the stereochemical assignment to **65**, made by the prior route.

When we attempted to convert 2-deoxy-D-ribose into the benzyl glycosides **84**, using a method very similar to the one used for methyl glycosides **71**, we were confronted with the problem of removing the excess of solvent (benzyl alcohol), but after several attempts, we managed to optimize the experimental conditions. Pivaloylation of the C(5) hydroxyl of the glycosides, using standard conditions (*t*-BuCOCl, pyridine) gave the mono-pivaloylated and bis-pivaloylated products in a 1:1 ratio. This outcome is presumably due to the absence of functionality at C(2), thereby making the hydroxyl at C(3) readily accessible. In substrates such as D-ribose the primary hydroxyl is routinely protected in the presence of the other secondary hydroxyls. Fortunately, when we tried a Mitsunobu reaction,[18] using *t*-$BuCO_2H$, much better selectivity was obtained, and the resulting α and the β epimers of the product **85** were fully separated at this point. The anomeric configuration was assigned by a TROESY NMR (600 MHz) experiment which established the stereochemistry of **85**-α. The C(3) hydroxyl of the separate monopivaloylated compounds **85**α and **85**β were protected as a MOM ether. Catalytic hydrogenolysis of the *O*-benzyl group failed to give any of the desired alcohol at 1 atmosphere. Increasing the

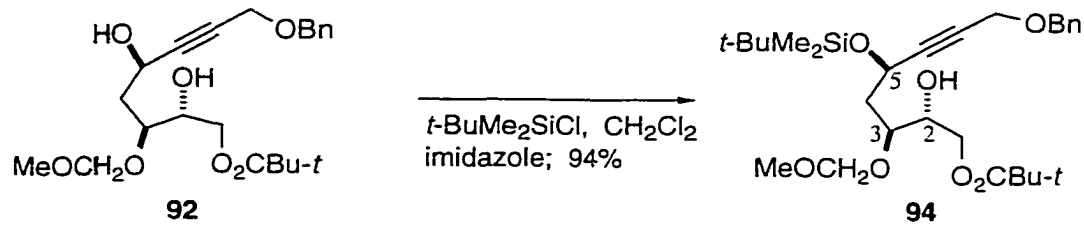
pressure (50 psi) and prolonging the reaction time gave a mixture of isomeric lactols **87**, in equilibrium with the open chain isomer. The stereochemistry at the anomeric center is, of course, destroyed in the next step. Homologation of **87** with the Wittig salt of methyltriphenylphosphonium bromide then produced olefin **88** in good yield. Silylation of the hydroxyl with *t*-BuMe$_2$SiCl (**88** → **89**), followed by ozonolytic cleavage (Scheme 21) of the double bond, gave us the intermediate **90**



Scheme 21

required for introduction of the acetylenic unit. Reaction of **90** with the anion derived from benzyl propargylic ether (**28**), afforded a 1:1.4 mixture of chromatographically

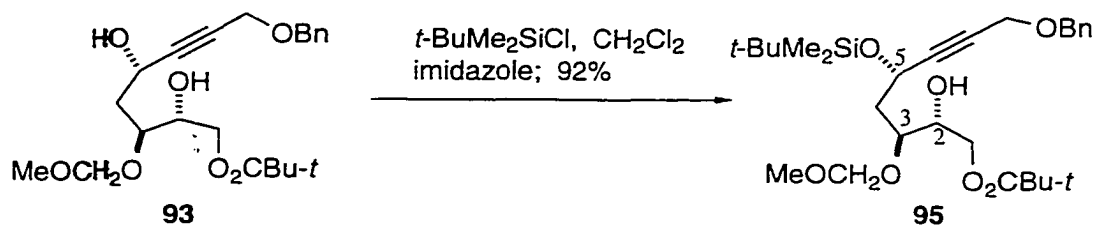
inseparable acetylenic alcohols **91**. The mixture was desilylated, using hydrofluoric acid, to give diols **92** and **93**, which were chromatographically separable. As before,



92 **94**

Scheme 22

silylation with *t*-$BuMe_2SiCl$ proceeded with very high regioselectivity, in favor of the propargylic hydroxyl. Both **94** and **95** were produced in over 90% yield (Schemes 22 and 23), although it is interesting to note that the reaction times for each isomer were quite different.



93 **95**

Scheme 23

The major product **94** was found to be spectroscopically (^1H and ^{13}C NMR) identical to the corresponding racemic compound, which was an intermediate in the synthesis of **65**.[9a] In the optically pure series, the material (**94**) obtained from 2-deoxy-D-ribose has the absolute stereochemistry at C(2) and C(3) preset, as shown. The relative stereochemistry at C(3) and C(5) in the racemic series, was set by the synthetic

route used. Thus, the relative stereochemistry at C(2), C(3) and C(5) in the racemic series is established.

As the major products of the two routes are structurally identical, the relative stereochemistry of racemic **65** and the relative stereochemistry of (+)-**94**, obtained from 2-deoxy-D-ribose, can be assigned as shown in Schemes 16 and 22, respectively. Since racemic **94** had been converted into the racemic Corey lactone derivative **67**,[9a] the route from the sugar constitutes a formal synthesis of optically pure **67**. As mentioned earlier the lactone route from the sugar would have the unnatural prostaglandin stereochemistry.

Experimental

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[19] 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 (120 °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. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was 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. Then air was sucked through for 1 min. 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), 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[20] or *p*-anisaldehyde,[21] 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 tetrahydrofuran (THF) and Et_2O were distilled from sodium and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, and pyridine were distilled from CaH_2.

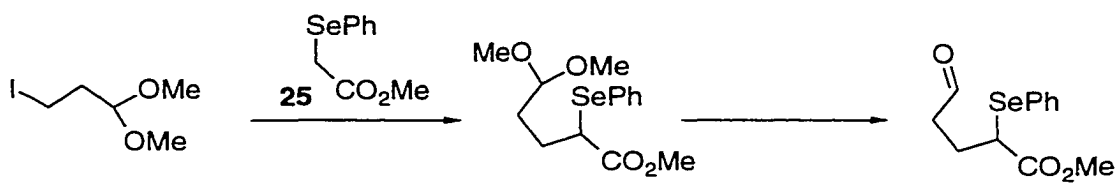
FT-IR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

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

Microanalyses were performed by the microanalytical laboratory of this Department.

Methyl 5-Oxo-2-(phenylseleno)pentanoate (27).



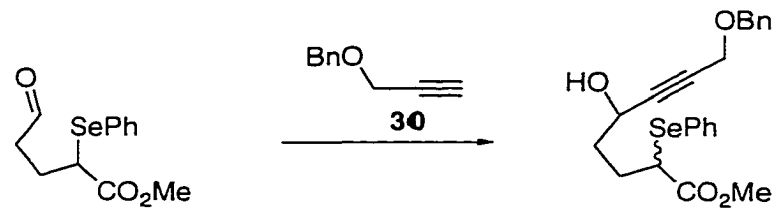
24 **26** **27**

BuLi (2.5 M in hexanes, 6.3 mL, 16 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of cyclohexylisopropylamine (2.59 mL, 15.7 mmol) in THF (7 mL).

After 15 min, ester **25** (3.27 g, 14.3 mL) in THF (5 mL) was added dropwise, and stirring was continued at -78 °C for 30 min. The resulting enolate solution was taken up into a syringe and added in a stream to a stirred solution of iodide **24** (3.27 g, 14.3 mmol) in dry DMSO (20 mL). The reaction mixture was stirred for 3 h, diluted with water (100 mL), and extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine, and dried (Na_2SO_4). Evaporation of the solvent gave a yellow residue which was dissolved in CH_2Cl_2 (40 mL). Aqueous TFA (50%, 30 mL) was added, and the heterogeneous mixture was stirred vigorously until the starting material had disappeared (TLC control, silica gel, 15:85 EtOAc-Hexane). The solution was cooled to 0 °C and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (4 x 100 mL, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 27 cm), using 15:85 EtOAc-hexane, gave **27** (2.11 g, 52%) as a pure (^1H NMR, 300 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 1727 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.0-2.15 (m, 2 H), 2.61 (td, J = 7.2, 1.08 Hz, 2 H), 3.65-3.71 (m, 4 H), 7.25-7.42 (m, 3 H), 7.55-7.65 (m, 2 H), 9.7 (t, J = 1.1 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 24.5 (t'), 42.3 (t'), 42.7 (d'), 52.4 (q'), 127.7 (s'), 129.1 (d'), 129.5 (d'), 136.2 (d'), 173.0 (s'), 201.0 (s'); exact mass *m/z* calcd for $C_{12}H_{14}O_3Se$ 286.01075, found 286.01080. Anal. Calcd for $C_{12}H_{14}O_3Se$: C 50.54, H 4.95.

Found: C 50.685, H 5.071.

Methyl (2*R,5*R**)- and (2*R**,5*S**)-(±)-5-Hydroxy-8-(phenylmethoxy)-2-(phenylseleno)-6-octynoate (29).**

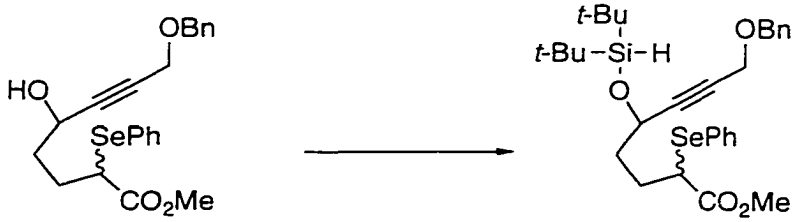


27 **29**

BuLi (1.6 M in hexanes, 21.0 mL, 34 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of benzyl propargyl ether[22] (4.92 g, 33.7 mmol) in dry THF (50 mL). After 15 min, aldehyde **27** (3.84 g, 13.5 mmol) in dry THF (20 mL plus 10 mL as a rinse) was added dropwise at -78 °C. After 2 h, the cold reaction mixture was poured into water (150 mL), and extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 x 22 cm), using 1:3 EtOAc-hexane, gave alcohol **29** (4.74 g, 81%) as a pure (^1H NMR, 200 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 1728, 3435 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.61-2.20 (m, 5 H), 3.55-3.75 (m, 4 H), 4.20 (s, 2 H), 4.32-4.50 (m, 1 H), 4.55 (s, 2 H), 7.21-7.45 (m, 8 H), 7.51-7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.4 (t'), 35.7 (t'), 42.9 (d'), 52.0 (q'), 57.3 (t'), 61.6 (d'), 71.6 (t'), 81.0 (s'), 87.0 (s'), 127.5 (s'), 127.8 (d'),

128.0 (d'), 128.4 (d'), 128.6 (d'), 129.0 (d'), 135.7 (d'), 137.2 (s'), 173.2 (s'). Anal. Calcd for $C_{22}H_{23}O_4Se$: C, 61.25; H, 5.61. Found: C, 61.42; H, 5.47.

Methyl (2*R,5*R**)- and (2*R**,5*S**)-(±)-5-[[Bis(1,1-dimethylethyl)silyl]oxy]-8-(phenylmethoxy)-2-(phenylseleno)-6-octynoate (8).**



29 **8**

t-Bu_2SiHCl (2.30 mL, 11.4 mmol) was added dropwise to a stirred solution of alcohol **29** (3.92 g, 9.09 mmol) and imidazole (1.24 g, 18.2 mmol) in dry THF (50 mL). The resulting white slurry was stirred and refluxed for 12 h, allowed to cool to room temperature, poured into water (100 mL), and extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 24 cm), using 5:95 EtOAc-hexane, gave an inseparable mixture (^{13}C NMR) of diastereomeric compound **8** (4.74 g, 91%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1732, 2093 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz), δ 0.85-1.10 (m, 18 H), 1.65-2.20 (m, 4 H), 3.60-3.75 (m, 4 H), 4.10 (s, 1 H), 4.15-4.25 (t, J = 1.4 Hz, 2 H), 4.50-4.65 (m, 3 H), 7.20-

7.42 (m, 8 H), 7.52-7.65 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 19.9 (s'), 20.3 (s'), 27.4 (q'), 27.7 (t'), 36.4 (t'), 36.5 (t'), 43.1 (d'), 43.2 (d'), 52.0 (q'), 57.3 (t'), 65.6 (d'), 71.3 (t'), 81.1 (s'), 81.2 (s'), 86.7 (s'), 127.6 (s'), 127.7 (s'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 128.5 (d'), 129.0 (d'), 135.7 (d'), 135.7 (d'), 137.5 (s'), 173.1 (s'); exact mass *m/z* calcd for $C_{30}H_{42}O_4SeSi$ 574.2018, found 574.2017. Anal. Calcd for $C_{30}H_{42}O_4SeSi$: C, 62.81; H, 7.38. Found: C, 62.80; H, 7.32.

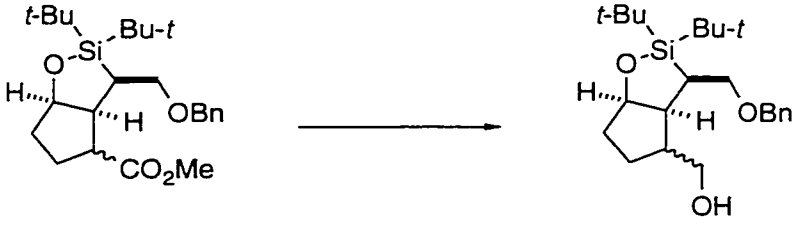
Methyl (3α,3aβ,4α,6aβ)- and (3α,3aβ,4β,6aβ)-(±)-2,2-Bis(1,1-dimethylethyl)hexahydro-3-[(phenylmethoxy)methyl]-2*H*-cyclopent[*d*]-[1,2]oxasilole-4-carboxylate (9, 10).

8 **9, 10**

A solution of Ph_3SnH (1.24 g, 3.50 mol) and AIBN (50.0 mg, 0.30 mmol) in dry PhH (20 mL) was added dropwise over 6 h (syringe pump) to a stirred and refluxing solution of **8** (1.69 g, 2.95 mmol) in dry PhH (150 mL). Refluxing was continued for an additional 1.5 h after the addition, and the mixture was then allowed to cool to room temperature. Evaporation of

the solvent, and flash chromatography of the residue over silica gel (4 x 20 cm), using 5:95 EtOAc-hexane, gave a crude mixture of **9** and **10**. The material was used directly in the next step, without full characterization, because it was found impossible to separate the desired compound from tin residues and from monocyclized (^{1}H NMR) product.

(3α,3aβ,4α,6aβ)- and (3α,3aβ,4β,6aβ)-(±)-2,2-Bis-(1,1-dimethylethyl)hexahydro-3-[(phenylmethoxy)-methyl]-2*H*-cyclopent[*d*]-[1,2]oxasilol-4-yl]methanol (32).

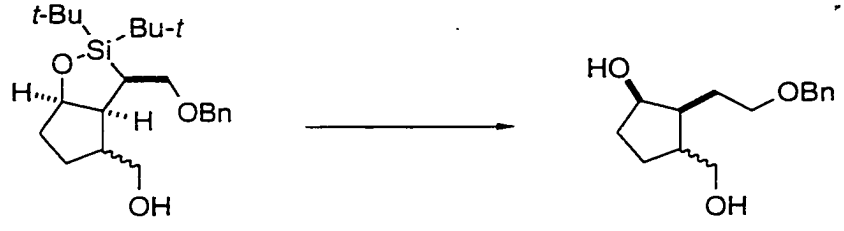


9, 10 **32**

A solution of crude **9**, **10** (3.24 g, 7.75 mmol) in dry THF (25 mL plus 5 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) slurry of $LiAlH_4$ (294.0 mg, 7.750 mmol) in dry THF (20 mL). Stirring was continued for 15 min, and MeOH (2 mL), $Na_2SO_4.10H_2O$ (2.0 g), Celite (5.0 g) and H_20 (2 mL) were then added, in that order, and the cold bath was removed. Stirring was continued for 30 min, and the resulting slurry was filtered through a pad of Celite, using EtOAc (TLC control, silica, 1:4 EtOAc-hexane). Evaporation of the filtrate and flash chromatography of the residue over

silica gel (4 x 22 cm), using 1:4 EtOAc-hexane, gave alcohols **32** (2.54 g, 84%), which were used directly for the next step without full characterization, because it was found impossible to separate the desired compound from tin residues and from monocyclized product at this stage. We depict **32** arbitrarily as a mixture of isomers, but we do not know for a fact whether one of the impurities is the isomer or a totally different compound.

(1α,2α,3β)- and (1α,2α,3α)-(±)-3-Hydroxymethyl-2-[2-(phenylmethoxy)ethyl]cyclopentanol (43).

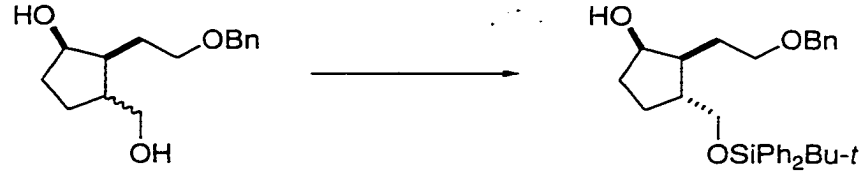


32 **43**

TBAF (1 M in THF, 30 mL, 30 mmol) was added dropwise to a stirred solution of impure alcohol **32** in DMF (30 mL). The mixture was heated at 60 °C for 3 h, allowed to cool to room temperature, poured into water (60 mL), and then extracted with EtOAc until extraction was complete (TLC control, silica, 3:1 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 24 cm), using 3:1 EtOAc-hexane, gave diols **43**, along with inseparable material derived from the monocyclized product. Diol **43** was

used directly for the next step without full characterization.

(1α,2α,3β)-(±)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-[2-(phenylmethoxy)ethyl]cyclopentanol (44).



43 **44**

Imidazole (362.3 mg, 5.321 mmol) and *t*-$BuPh_2SiCl$ (0.97 mL, 3.70 mmol) were added successively to a stirred solution of impure diols **43** in dry CH_2Cl_2 (15 mL), and stirring was continued for 1 h, by which time reaction was complete (TLC control, silica, 15:85 EtOAc-hexane). The mixture was poured into water (20 mL), and extracted with CH_2Cl_2 (4 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 (2.5 x 24 cm), using 15:85 EtOAc-hexane, gave alcohol **44** (400.0 mg, 33% over 4 steps) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3450 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.05 (s, 9 H), 1.40-2.08 (m, 8 H), 2.65 (m, 1 H), 3.4-3.7 (m, 4 H) 4.23 (m, 1 H), 4.5 (s, 2 H), 7.21-7.50 (m, 11 H), 7.58-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.5 (s'), 26.6 (t'), 27.0 (q'), 29.2 (t'), 33.4 (t'), 45.5

(d'), 47.7 (d'), 66.9 (t'), 70.8 (t'), 73.7 (t'), 74.8 (d'), 127.9 (d'), 128.0 (d'), 128.7 (d'), 129.9 (d'), 134.4 (s'), 135.9 (d'), 138.6 (s'). Anal. Calcd for $C_{31}H_{40}O_3Si$: C, 76.18; H, 8.25. Found: C, 75.40; H, 8.25.

(1α,2β,3β)-(±)-[(1,1-Dimethylethyl)diphenyl[[3-(methoxymethoxy)-2-[(2-phenylmethoxy)ethyl]cyclopentyl]methyl]oxy]silane (45).

44 **45**

i-Pr_2NEt (0.38 mL, 2.19 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **44** (714.6 mg, 1.460 mmol) in CH_2Cl_2 (25 mL). After 15 min, MOMCl (0.17 mL, 2.19 mmol) was added dropwise over 5 min, and stirring was continued for 1 h. The cold bath was removed, stirring was continued for 12 h, and the mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (4 x 50 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 EtOAc-hexane, gave the protected alcohol **45** (757.7 mg, 97%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3070, 1199 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.05 (s, 9 H), 1.51-2.08 (m, 8 H), 3.35 (s, 3 H), 3.42-3.70 (m, 4 H), 4.0-4.06 (m, 1 H), 4.42 (s, 2

H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, J = 6.7 Hz, 2 H), 7.20-7.45 (m, 10 H), 7.62-7.71 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 19.5 (t'), 26.1 (t'), 27.0 (q'), 28.7 (t'), 31.0 (t'), 43.4 (d'), 45.3 (d'), 55.6 (q'), 67.0 (t'), 69.8 (t'), 73.0 (t'), 80.5 (d'), 95.6 (t'), 127.7 (d'), 127.9 (d'), 128.0 (d'), 128.5 (d'), 129.9 (d'), 134.4 (s'), 136.0 (d'), 139.4 (s'); exact mass *m/z* calcd for $C_{33}H_{44}O_4Si$ 532.30086, found (M - *t*-Bu - OCH_2OCH_3) 414.20151. Anal. Calcd for $C_{33}H_{44}O_4Si$: C 74.39, H 8.32. Found: C 74.26, H 8.47.

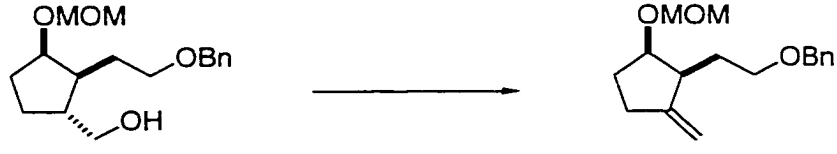
(1α,2β,3β)-(±)-3-(Methoxymethoxy)-2-[2-(phenylmethoxy)ethyl]cyclopentanemethanol (46).

45 **46**

TBAF (1.0 M in THF, 2.7 mL, 2.7 mmol) was added dropwise to a stirred solution of silylated alcohol **45** (707.4 mg, 1.320 mmol) in dry THF (15 mL). Stirring was continued for 20 h, by which time the reaction was complete (TLC control, silica, 3:4 EtOAc-hexane). The mixture was diluted with water (50 mL) and extracted with EtOAc (4 x 50 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 3:4 EtOAc-hexane, gave **46** (380.9 mg, 97%) as a pure (^1H NMR, 400 MHz), colorless oil:

FTIR (CH_2Cl_2 cast) 3431 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.35-2.01 (m, 9 H), 3.30 (s, 3 H), 3.42-3.60 (m, 4 H), 4.00-4.05 (m, 1 H), 4.49 (s, 2 H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, J = 6.7 Hz, 2 H), 7.21-7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.3 (t'), 28.8 (t'), 31.0 (t'), 43.8 (d'), 45.4 (d'), 55.6 (q'), 66.4 (t'), 69.8 (t'), 73.20 (t'), 80.6 (d'), 95.7 (t'), 127.9 (d'), 128.2 (d'), 128.7 (d'), 139.2 (s'); exact mass *m/z* calcd for $C_{17}H_{26}O_4$ 294.18309, found (M - OCH_3) 262.15689. Anal. Calcd for $C_{17}H_{26}O_4$: C 69.36, H 8.90. Found: C 68.89, H 8.79.

(2α,3α)-(±)-1-(Methoxymethoxy)-3-methylene-2-[2-(phenylmethoxy)ethyl]cyclopentane (47).



46 **47**

Bu_3P (0.32 mL, 1.31 mmol) was added dropwise over 5 min to a stirred solution of alcohol **46** (190.0 mg, 0.650 mmol) and 2-nitrophenyl selenocyanate (297.1 mg, 1.308 mmol) in dry THF (5 mL). The resulting red solution was stirred for 3 h, at which stage no starting material remained (TLC control, silica, 1:5 EtOAc-hexane). The solvent was evaporated and the crude product, which could not be easily purified, was used directly in the next step.

A stirred solution of the crude selenide in dry CH_2Cl_2

(5 mL) was cooled to -10 °C and *m*-CPBA (225.8 mg, 1.310 mmol) was added in one portion. Stirring was continued for 1 h, *i*-Pr_2NH (0.18 mL, 1.31 mmol) was added, and the mixture was refluxed for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm), using 1:5 EtOAc-hexane, gave **47** (158.0 mg, 88%) as a pure (^1H NMR, 300 MHz), yellow oil: FTIR (CH_2Cl_2 cast) 3070, 1653 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.57-1.92 (m, 4 H), 2.32-2.55 (m, 3 H), 3.3 (s, 3 H), 3.52-3.67 (m, 2 H), 4.02-4.12 (m, 1 H), 4.47 (s, 2 H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, *J* = 6.7 Hz, 2 H), 4.82-4.92 (d of multiplets, *J* = 24.0 Hz, 2 H), 7.20-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (t'), 29.5 (t'), 29.7 (t'), 46.0 (d'), 55.7 (q'), 69.2 (t'), 73.1 (t'), 79.3 (d'), 95.6 (t'), 105.2 (t'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 139.3 (s'), 154.1 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{24}NaO_3$ (M + Na) 299.16231, found 299.16231. Anal. Calcd for $C_{17}H_{24}O_3$: C 73.88, H 8.75. Found: C 73.72, H 9.07.

(1α,2α,3α)-(±)-3-(Methoxymethoxy)-2-[2-(phenylmethoxy)ethyl]cyclopentanemethanol (48).

47 **48**

$BH_3.SMe_2$ (10.0 M in THF, 0.10 mL, 0.98 mmol) was added

dropwise to a stirred and cooled (-20 °C) solution of olefin **47** (136.0 mg, 0.492 mmol) in dry THF (2.5 mL). After 30 min, the solution was warmed to 0 °C (by replacing the acetone-dry ice bath with an ice bath). Stirring was continued for 1 h, the ice bath was removed, and stirring was continued for 30 min. The mixture was cooled to 0 °C, and NaOH (3 N, 0.33 mL) was added dropwise, followed by 30% aqueous H_2O_2 (0.12 mL), and stirring was continued for 30 min. The mixture was diluted with Et_2O (5 mL), washed with water (2 x 5 mL) and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 15:85 EtOAc-hexane, gave **48** (98.1 mg, 68%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3444 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.51-1.98 (m, 6 H), 2.05-2.3 (m, 2 H), 2.91 (dd, J = 7.4, 3.2 Hz, 1 H), 3.3 (s, 3 H), 3.39-3.65 (m, 4 H), 4.0-4.08 (m, 1 H), 4.49 (s, 2 H), 4.62 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, J = 6.7 Hz, 2 H), 7.20-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 25.1 (t'), 25.6 (t'), 30.9 (t'), 42.0 (d'), 43.6 (d') 55.9 (q'), 62.7 (t'), 70.0 (t'), 73.3 (t'), 80.1 (d'), 95.4 (t'), 127.8 (d'), 128.0 (d'), 128.6 (d'), 139.2 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{26}NaO_4$ (M + Na) 317.17288, found 317.17255.

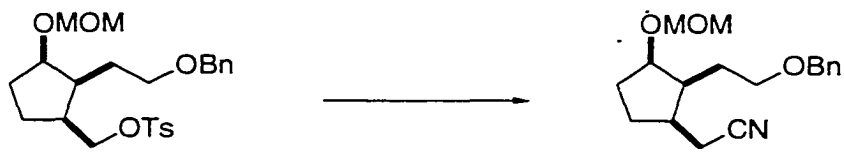
(1α,2α,3α)-(±)-[3-(Methoxymethoxy)-2-[2-(phenylmethoxy)ethyl]cyclopentyl]methyl 4-Methylphenylsulfonate (49).

48 **49**

p-TsCl (69.9 mg, 0.37 mmol) was added in one portion to a stirred solution of alcohol **48** (98.1 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) containing dry pyridine (0.5 mL). A catalytic amount of DMAP was tipped into the solution and the mixture was stirred overnight, by which time reaction was complete (TLC control, silica, 1:4 EtOAc-hexane). The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 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 18 cm), using 1:4 EtOAc-hexane, gave **49** (144 mg, 97%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1188 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.49-1.81 (m, 6 H), 1.92-2.08 (m, 1 H), 2.25-2.39 (m, 1 H), 2.45 (s, 3 H), 3.21 (s, 3 H), 3.4-3.6 (m, 2 H), 3.90-4.15 (m, 3 H), 4.39-4.51 (m, 4 H), 7.22-7.39 (m, 7 H), 7.71-7.80 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 21.7 (q'), 25.5 (t'), 26.9 (t'), 30.6 (t'), 39.7 (d'), 43.9 (d'), 55.6 (q'), 69.5 (t'), 73.2 (t'), 73.8 (t'), 79.8 (d'), 95.6 (t'), 127.8 (d'), 127.9 (d'), 128.2 (d'), 128.6 (d'), 130.1 (d'), 133.6 (s'), 139.2

(s'), 145.1 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{24}H_{32}NaO_6S$ (M + Na) 471.181731, found 471.181890. Anal. Calcd for $C_{24}H_{32}O_6S$: C 73.88, H 8.75. Found: C 73.72, H 9.07.

(1α,2α,3α)-(±)-3-(Methoxymethoxy)-2-[2-(phenylmethoxy)ethyl]cyclopentaneacetonitrile (50).



49 **50**

A solution of tosylate **49** (121.6 mg, 0.270 mmol) and NaCN (14.6 mg, 0.30 mmol) in dry DMSO (5 mL) was heated at 100 °C for 1 h, allowed to cool to room temperature, diluted with water (10 mL), and extracted with Et_2O (5 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 20 cm), using 1:3 EtOAc-hexane, gave **50** (69.4, 84%) as a pure (^1H NMR, 300 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 2244 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.6-2.1 (m, 7 H), 2.30-2.50 (m, 3 H), 3.29 (s, 3 H), 3.48-3.55 (m, 2 H), 3.98-4.05 (m, 1 H), 4.49 (s, 2 H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, *J* = 6.7 Hz, 2 H), 7.2-7.5 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 20.4 (t'), 25.7 (t'), 29.6 (t'), 30.8 (t'), 38.0 (d'), 44.8 (d'), 55.05 (q'), 69.6 (t'), 73.3 (t'), 73.6 (t'), 81.0 (d'), 95.8 (t'), 120.8 (s'), 127.9 (d'),

128.0 (d'), 128.7 (d'), 139.2 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{18}H_{25}NNaO_3$ (M + Na) 326.17321, found 326.17348.

Methyl (1α,2α,3α)-(±)-3-(Methoxymethoxy)-2-[2-(phenylmethoxy)ethyl]cyclopentaneacetate (51).

50 **51**

NaOH (137.6 mg, 3.440 mmol) in water (0.5 mL) was added to a solution of nitrile **50** (259.5 mg, 0.856 mmol) in EtOH (2 mL). The mixture was heated at 100 °C for 12 h, allowed to cool to room temperature, diluted with water (10 mL), acidified with 10% aqueous hydrochloric acid, and extracted with CH_2Cl_2 (5 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was redissolved in Et_2O (2 mL) and CH_2N_2 was added dropwise with stirring until a yellow color persisted. Evaporation of the solvent, and flash chromatography of the residue over silica gel (1 x 20 cm), using 1:4 EtOAc-hexane, gave ester **51** (210.0 mg, 69%) as a pure (^1H NMR, 300 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 1736 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.42-1.52 (m, 1 H), 1.60-1.91 (m, 5 H), 1.95-2.05 (m, 1 H), 2.25-2.50 (m, 3 H), 3.32 (s, 3 H), 3.45-3.55 (m, 2 H), 3.6 (s, 3 H), 3.95-4.05 (m, 1 H), 4.49 (s, 2

H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, J = 6.7 Hz, 2 H), 7.23-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 25.8 (t'), 29.7 (t'), 30.9 (t'), 36.8 (t'), 37.1 (d'), 44.1 (d'), 51.5 (q'), 55.6 (q'), 69.9 (t'), 73.2 (t'), 80.2 (d'), 95.8 (t'), 127.8 (d'), 128.0 (d'), 128.6 (d'), 139.4 (s'), 174.6 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{28}O_5Na$ (M + Na) 336.43200, found 336.19301.

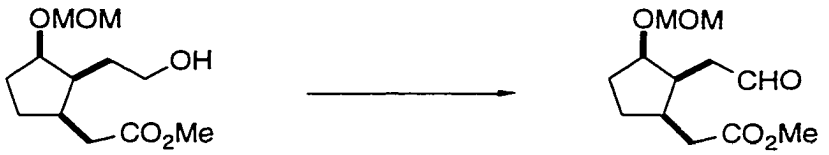
Methyl (1α,2α,3α)-(±)-2-(2-Hydroxyethyl)-3-(methoxymethoxy)cyclopentaneacetate (52).

51 **52**

5% Pd-C (3.0 mg) was added to a stirred solution of ester **51** (20.0 mg, 0.06 mmol) in MeOH (1 mL). The reaction flask was flushed with H_2 (3 x 1 min), and stirring was continued under hydrogen (balloon) until all the starting material was consumed (*ca* 30 min, TLC control, silica, 3:2 EtOAc-hexane). The mixture was filtered through a pad of silica gel (1 x 2 cm), using EtOAc (15 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 10 cm), using 3:2 EtOAc-hexane, gave **52** (14.3 mg, 98%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3444, 1736 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.49-1.61 (m, 2 H), 1.71-1.89 (m, 5 H), 1.95-2.05 (m, 1 H),

2.25-2.50 (m, 3 H), 3.32 (s, 3 H), 3.61-3.70 (m, 2 H), 3.62 (s, 3 H), 4.00-4.10 (m, 1 H), 4.58 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, J = 6.7 Hz, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 28.6 (t'), 29.3 (t'), 30.6 (t'), 36.8 (t'), 37.2 (d'), 44.1 (d'), 51.6 (q'), 55.7 (q'), 62.4 (t'), 80.4 (d'), 95.8 (t'), 174.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{22}O_5Na$ (M + Na) 269.13649, found 269.13639.

Methyl (1α,2α,3α)-(±)-3-(Methoxymethoxy)-2-(2-oxoethyl)cyclopentaneacetate (53).



52 **53**

A mixture of PCC (55.8 mg, 0.26 mmol) and powdered 4 Å molecular sieves (30 mg) was added to a stirred solution of alcohol **52** (49.2 mg, 0.20 mmol) in dry CH_2Cl_2 (4 mL). Stirring was continued for 4 h, by which time oxidation was complete (TLC control, silica, 2:3 EtOAc-hexane), and the mixture was applied directly to a column (1 x 15 cm) of silica gel. The column was developed, using 2:3 EtOAc-hexane, to give aldehyde **53** (45.0 mg, 92%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1736 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.41-1.50 (m, 1 H), 1.72-1.89 (m, 3 H), 2.25-2.70 (m, 6 H), 3.32 (s, 3 H), 3.62 (s, 3 H), 4.05-4.15 (m, 1 H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, J = 6.7 Hz, 2 H), 9.81

(t, J = 1.7 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 28.8 (t'), 30.2 (t'), 36.7 (t'), 36.7 (d'), 39.9 (t'), 40.9 (d'), 51.7 (q'), 55.7 (q'), 79.8 (d'), 96.0 (t'), 173.7 (s'), 202.2 (d'). All attempts to obtain a mass spectrum of the aldehyde, gave a spectrum of the corresponding acid: exact mass (HR electrospray) m/z calcd for $C_{12}H_{22}O_6Na$ (M + Na) 283.11576, found 283.11568.

Methyl [1α,2α,3α,(*Z*)]-(±)-3-(Methoxymethoxy)-2-(2-pentenyl)cyclopentaneacetate (54).

53 **54**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.9 mL, 0.45 mmol) was added to a stirred slurry of triphenylpropylphosphonium bromide (177.8 mg, 0.461 mmol) in dry PhMe (1 mL). The mixture was stirred for 1 h and the resultant bright red solution was then left undisturbed for 1 h. The supernatant liquid was drawn up into a syringe and an aliquot (*ca* 2.0 mL, 0.3 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of aldehyde **53** (26.0 mg, 0.11 mmol) in dry PhMe (1 mL). The temperature was maintained at -78 °C for 1 h and then the cold bath was removed. Stirring was continued overnight, leading to a colorless solution and the formation of Ph_3PO. The solvent was evaporated and the residue was

dissolved in CH_2Cl_2 (0.5 mL). The solution was applied directly to a flash chromatography column of silica gel (1 x 10 cm), and the column was developed using 1:4 EtOAc-hexane, to give olefin **54** (20.0 mg, 70%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2245 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J = 7.0 Hz, 3 H), 1.49-2.61 (m, 12 H), 3.33 (s, 3 H), 3.65 (s, 3 H), 4.00-4.08 (m, 1 H), 4.60 (AB q, $\Delta\nu_{AB}$ = 35.0 Hz, J = 7.2 Hz, 2 H), 5.25-5.5 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (q'), 20.8 (t'), 22.8 (t'), 29.2 (t'), 30.6 (t'), 36.5 (d'), 36.5 (t'), 47.5 (d'), 51.35 (q'), 55.4 (q'), 80.0 (d'), 95.6 (t'), 128.0 (d'), 132.2 (d'), 174.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{26}O_4Na$ (M + Na) 293.17288, found 293.17251.

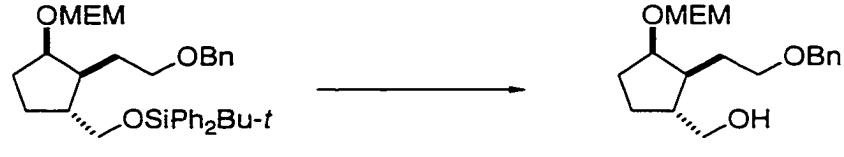
(1α,2β,3β)-(±)-[(1,1-Dimethylethyl)diphenyl[[2-[(2-phenylmethoxy)ethyl]-3-[(2-methoxyethoxy)methoxy]-cyclopentyl]methyl]oxy]silane (56).

44 **56**

i-Pr_2NEt (1.37 mL, 7.91 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **44** (1.28 g, 2.63 mmol) in CH_2Cl_2 (10 mL). After 15 min, MEMCl (0.90 mL, 7.91 mmol) was added dropwise over 5 min and stirring was continued for 1 h. The cold bath was removed, stirring was continued for

12 h, and the mixture was diluted with water (100 mL), and extracted with CH_2Cl_2. 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 EtOAc-hexane, gave **56** (1.51 g, 100%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1199, 3070 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.05 (s, 9 H), 1.50-2.10 (m, 8 H), 3.35 (s, 3 H), 3.40-3.70 (m, 8 H), 4.10-4.20 (m, 1 H), 4.47 (s, 2 H), 4.64 (AB q, $\Delta\nu_{AB}$ = 18.2 Hz, J = 6.8 Hz, 2 H), 7.20-7.45 (m, 10 H), 7.60-7.70 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 19.5 (t'), 26.1 (t'), 27.0 (q'), 28.7 (t'), 31.0 (t'), 43.4 (d'), 45.3 (d'), 59.0 (q'), 67.0 (t'), 67.4 (t'), 69.8 (t'), 72.2 (t'), 73.0 (t'), 80.5 (d'), 94.6 (t'), 127.7 (d'), 127.9 (d'), 128.0 (d'), 128.6 (d'), 129.9 (d'), 134.4 (s'), 136.0 (d'), 139.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{35}H_{48}NaO_5Si$ (M + Na) 599.3169, found 599.3171.

(1α,2β,3β)-(±)-3-[(2-Methoxyethoxy)methoxy]-2-[2-(phenylmethoxy)ethyl]cyclopentanemethanol (57).

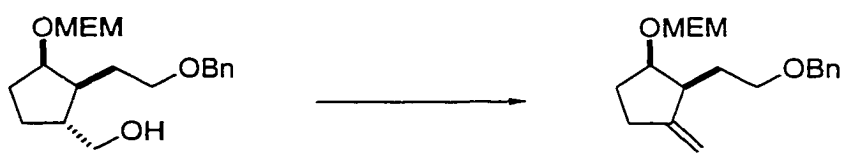


56 **57**

TBAF (1.0 M in THF, 4.6 mL, 4.6 mmol) was added dropwise to a stirred solution of **56** (1.33 g, 2.30 mmol) in dry THF (40 mL). Stirring was continued for 20 h, by which time

reaction was complete (TLC control, silica, 3:4 EtOAc-hexane). The mixture was diluted with water (100 mL) and extracted with EtOAc. 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 3:4 EtOAc-hexane, gave **57** (758 mg, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3445 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.20-2.10 (m, 9 H), 3.30 (s, 3 H), 3.40-3.70 (m, 8 H), 4.00-4.10 (m, 1 H), 4.50 (s, 2 H), 4.66 (AB q, $\Delta\nu_{AB}$ = 18.2 Hz, J = 6.8 Hz, 2 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 26.2 (t'), 28.8 (t'), 30.8 (t'), 43.7 (d'), 45.4 (d'), 59.0 (q'), 66.4 (t'), 67.4 (t'), 69.8 (t'), 72.2 (t'), 73.2 (t'), 80.6 (d'), 94.6 (t'), 127.9 (d'), 128.1 (d'), 128.7 (d'), 139.1 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{30}NaO_5$ (M + Na) 361.1991, found 361.1989.

(2α,3α)-(±)-1-[(2-Methoxyethoxy)methoxy]-3-methylene-2-[2-(phenylmethoxy)ethyl]cyclopentane (58).



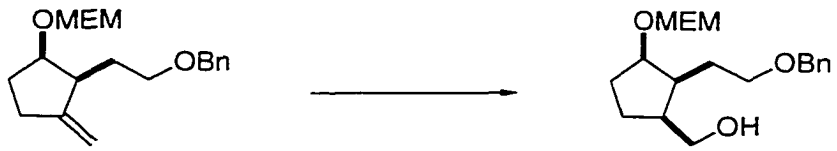
57 **58**

Bu_3P (0.11 mL, 0.45 mmol) was added dropwise over 5 min to a stirred solution of **57** (76.4 mg, 0.22 mmol) and 2-nitrophenyl selenocyanate (102.5 mg, 0.45 mmol) in dry THF (2 mL). The resulting red solution was stirred for 3 h, at

which stage no starting material remained (TLC control, silica, 1:5 EtOAc-hexane). The solvent was evaporated and the crude selenide was used directly in the next step.

A stirred solution of the crude selenide in dry CH_2Cl_2 (5 mL) was cooled to -10 °C and *m*-CPBA (78.0 mg, 0.45 mmol) was added in one portion. Stirring was continued for 1 h, *i*-Pr_2NH (0.06 mL, 0.45 mmol) was added, and the mixture was refluxed for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 18 cm), using 1:5 EtOAc-hexane, gave **58** (57.8 mg, 80%) as a yellow oil: FTIR (CH_2Cl_2 cast) 1652, 3070 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.60-2.00 (m, 4 H), 2.35-2.60 (m, 3 H), 3.30 (s, 3 H), 3.40-3.60 (m, 6 H), 4.07-4.09 (m, 1 H), 4.43 (AB q, $\Delta\nu_{AB}$ = 11.5 Hz, J = 11.9 Hz, 2 H), 4.64 (AB q, $\Delta\nu_{AB}$ = 38.3 Hz, J = 6.9 Hz, 2 H), 4.80 (d, J = 2.1 Hz, 1 H), 4.86 (d, J = 2.1 Hz, 1 H), 7.20-7.45 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 27.3 (t'), 29.5 (t'), 29.6 (t'), 46.0 (d'), 58.9 (q'), 67.5 (t'), 69.2 (t'), 72.1 (t'), 73.1 (t'), 79.3 (d'), 94.5 (t'), 105.2 (t'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 139.4 (s'), 154.1 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{28}NaO_4$ (M + Na) 343.1885, found 343.1889.

(1α,2α,3α)-(±)-3-[(2-Methoxyethoxy)methoxy]-2-[2-(phenylmethoxy)ethyl]cyclopentanemethanol (59).

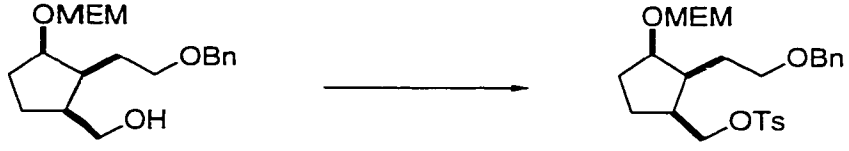


58 **59**

$BH_3.SMe_2$ (10.0 M in THF, 0.21 mL, 2.10 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of **58** (337.3 mg, 1.053 mmol) in dry THF (5 mL). After 30 min, the solution was warmed to 0 °C (by replacing the acetone-dry ice bath with an ice bath). Stirring was continued for 1.0 h, the ice bath was removed, and stirring was continued for 30 min. The mixture was cooled to 0 °C, and NaOH (3 N, 0.70 mL) was added dropwise, followed by 30% aqueous H_2O_2 (0.24 mL), and stirring was continued for 30 min. The mixture was diluted with Et_2O (10 mL), washed with water (2 x 10 mL) and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 15:85 EtOAc-hexane, gave **59** (303.0 mg, 85%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3453 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.60-1.90 (m, 6 H), 2.05-2.20 (m, 1 H), 2.20-2.30 (m, 1 H), 2.85 (dd, J = 7.8, 3.0 Hz, 1 H), 3.30 (s, 3 H), 3.40-3.70 (m, 8 H), 4.00-4.10 (m, 1 H), 4.41 (s, 2 H), 4.67 (AB q, $\Delta\nu_{AB}$ = 30.3 Hz, J = 6.9 Hz, 2 H), 7.20-7.45 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 25.2 (t'), 25.6 (t'), 30.9 (t'), 42.0 (d'), 43.6 (d') 59.0 (q'), 62.8 (t'), 67.7 (t'), 70.0 (t'), 72.1 (t'),

73.3 (t'), 80.1 (d'), 94.3 (t'), 127.8 (d'), 128.0 (d'), 128.7 (d'), 139.2 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{30}NaO_5$ (M + Na) 361.1991, found 361.1989.

(1α,2α,3α)-(±)-[3-[(2-Methoxyethoxy)methoxy]-2-[2-(phenylmethoxy)ethyl]cyclopentyl]methyl 4-Methylphenylsulfonate (60).

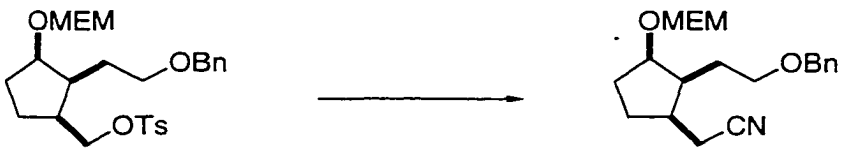


59 **60**

p-TsCl (304.4 mg, 1.596 mmol) was added in one portion to a stirred solution of **59** (180.0 mg, 0.532 mmol) in CH_2Cl_2 (5 mL) containing dry pyridine (0.5 mL). A catalytic amount of DMAP was tipped into the solution, and the mixture was stirred overnight, by which time reaction was complete (TLC control, silica, 1:4 EtOAc-hexane). The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. 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 18 cm), using 1:4 EtOAc-hexane, gave **60** (254 mg, 97%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1188 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.50-1.90 (m, 6 H), 1.95-2.10 (m, 1 H), 2.25-2.40 (m, 1 H), 2.45 (s, 3 H), 3.25 (s, 3 H), 3.40-3.60 (m, 6 H), 3.90-4.00 (m, 2 H), 4.10 (dd, J = 9.4, 5.5 Hz, 1 H), 4.42 (s, 2 H), 4.57 (AB q, $\Delta\nu_{AB}$ = 33.5 Hz, J = 6.9 Hz, 2

H), 7.20-7.40 (m, 7 H), 7.70-7.80 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 21.5 (q'), 25.3 (t'), 26.7 (t'), 30.3 (t'), 39.5 (d'), 43.7 (d') 58.8 (q'), 67.2 (t'), 69.4 (t'), 72.0 (t'), 73.0 (t'), 73.4 (t'), 79.6 (d'), 94.3 (t'), 127.6 (d'), 127.8 (d'), 128.0 (d'), 128.5 (d'), 123.0 (d'), 133.5 (s'), 139.0 (s'), 145.0 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{36}NaO_7S$ (M + Na) 515.2080, found 515.2083.

(1α,2α,3α)-(±)-3-[(2-Methoxyethoxy)methoxy]-2-[2-(phenylmethoxy)ethyl]cyclopentaneacetonitrile (61).



60 **61**

A solution of **60** (195.5 mg, 0.397 mmol) and NaCN (136.5 mg, 2.8 mmol) in dry DMSO (2.5 mL) was heated at 100 °C for 1 h, allowed to cool to room temperature, diluted with water (15 mL), 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 (1.5 x 20 cm), using 1:3 EtOAc-hexane, gave **61** (115.4 mg, 87%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 2244 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.60-2.10 (m, 7 H), 2.30-2.50 (m, 3 H), 3.35 (s, 3 H), 3.40-3.70 (m, 6 H), 4.00-4.10 (m, 1 H), 4.40 (s, 2 H), 4.62 (AB q, $\Delta\nu_{AB}$ = 25.7 Hz, J = 6.9 Hz, 2 H), 7.20-7.50 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.4 MHz) δ 20.4 (t'),

25.8 (t'), 29.6 (t'), 30.7 (t'), 38.0 (d'), 44.8 (d'), 59.1 (q'), 67.6 (t'), 69.6 (t'), 72.2 (t'), 73.4 (t'), 80.1 (d'), 94.7 (t'), 120.9 (s'), 127.99 (d'), 128.02 (d'), 128.7 (d'), 139.2 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{20}H_{29}NNaO_4$ (M + Na) 370.1994, found 370.2003.

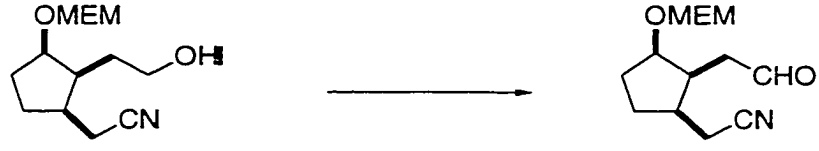
(1α,2α,3α)-(±)-2-(2-Hydroxyethyl)-3-[(2-methoxyethoxy)methoxy]cyclopentaneacetonitrile (62).

61 **62**

5% Pd-C (9 mg) was added to a stirred solution of **61** (55.0 mg, 0.16 mmol) in MeOH (2 mL). The reaction flask was flushed with H_2, and stirring was continued under hydrogen (balloon) until all the starting material was consumed (*ca* 30 min, TLC control, silica, 3:2 EtOAc-hexane). The mixture was filtered through a pad of silica gel (1 x 2 cm), using EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 10 cm), using 3:2 EtOAc-hexane, gave **62** (38.5 mg, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3442 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.50-2.15 (m, 8 H), 2.30-2.50 (m, 3 H), 3.35 (s, 3 H), 3.45-3.75 (m, 6 H), 4.05-4.15 (m, 1 H), 4.62 (AB q, $\Delta\nu_{AB}$ = 14.7 Hz, J = 6.7 Hz, 2 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 20.4 (t'), 28.5 (t'), 29.3 (t'), 30.8 (t'), 38.1 (d'), 44.6 (d'), 59.0 (q'),

62.0 (t'), 67.7 (t'), 72.2 (t'), 80.3 (d'), 94.8 (t'), 120.8 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{13}H_{23}O_4NNa$ (M + Na) 280.1525, found 280.1524.

(1α,2α,3α)-(±)-3-[(2-Methoxyethoxy)methoxy]-2-(2-oxoethyl)cyclopentaneacetonitrile (63).



62 **63**

A mixture of PCC (56.8 mg, 0.26 mmol) and powdered 4 Å molecular sieves (20 mg) was added to a stirred solution of **62** (52.2 mg, 0.20 mmol) in dry CH_2Cl_2 (2 mL). Stirring was continued for 1 h, by which time oxidation was complete (TLC control, silica, 2:3 EtOAc-hexane), and the mixture was applied directly to a column (1 x 15 cm) of flash chromatography silica gel. The column was developed using 2:3 EtOAc-hexane, to give **63** (41 mg, 78%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1722, 2245 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.60-1.75 (m, 1 H), 1.80-2.05 (m, 3 H), 2.30-2.60 (m, 5 H), 2.65-2.80 (m, 1 H), 3.35 (s, 3 H), 3.42-3.62 (m, 4 H), 4.10-4.20 (m, 1 H), 4.58 (AB q, $\Delta\nu_{AB}$ = 30.5 Hz, J = 6.8 Hz, 2 H), 9.80 (t, J = 1.1 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 20.3 (t'), 29.2 (t'), 30.3 (t'), 37.3 (d'), 39.9 (t'), 41.0 (d'), 59.0 (q'), 67.6 (t'), 72.1 (t'), 79.7 (d'), 94.7 (t'), 120.1 (s'), 201.4 (d'); exact mass (HR electrospray) *m/z* calcd for

$C_{13}H_{21}NNaO_4$ (M + Na) 278.1373, found 278.1368.

[1α,2α(*Z*),3α]-(±)-3-[(2-Methoxyethoxy)methoxy]-2-(2-pentenyl)cyclopentaneacetonitrile (64).

63 **64**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.5 mL, 0.25 mmol) was added to a slurry of triphenylpropylphosphonium bromide (100.2 mg, 0.260 mmol) in dry PhMe (1 mL). The mixture was stirred for 1 h and the resultant bright red solution was then left undisturbed for 1 h. The supernatant liquid was drawn up into a syringe and an aliquot (*ca* 1.0 mL, 0.2 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of **63** (15.8 mg, 0.06 mmol) in dry PhMe (1 mL). The temperature was maintained at -78 °C for 1 h and then the cold bath was removed. Stirring was continued overnight, leading to a colorless solution and the formation of Ph_3PO. The solvent was evaporated and the crude residue was dissolved in CH_2Cl_2 (0.5 mL). The solution was applied directly to a column of flash chromatography silica gel (1 x 10 cm), and the column was developed using 1:4 EtOAc-hexane, to give **64** (14.0 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2245 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.60-2.30 (m, 9 H), 2.30-2.50 (m, 3 H), 3.37 (s, 3

H), 3.50-3.70 (m, 4 H), 4.00-4.10 (m, 1 H), 4.64 (AB q, $\Delta\nu_{AB}$ = 35.0 Hz, J = 6.9 Hz, 2 H), 5.25-5.5 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.3 (q'), 20.2 (t'), 21.0 (t'), 23.1 (t'), 29.5 (t'), 30.8 (t'), 37.6 (d'), 48.1 (d'), 59.0 (q'), 67.4 (t'), 72.1 (t'), 80.2 (d'), 94.9 (t'), 120.8 (s'), 127.5 (d'), 133.0 (d'); exact mass (HR electrospray) *m/z* calcd for $C_{16}H_{27}NNaO_3$ (M + Na) 304.1889, found 304.1887.

(2*R*,3*S*)-1,3-Bis(phenylmethoxy)-5-hexen-2-ol (73).

72 **73**

BuLi (2.5 M in hexanes, 6.4 mL, 16 mmol) was added dropwise to a stirred suspension of Ph_3PCH_3Br (5.59 g, 15.9 mmol) in dry PhMe (60 mL), and the resulting yellow slurry was stirred at room temperature for 3 h. A solution of lactols **72**[16] (2.01 g, 6.37 mmol) in dry PhMe (20 mL) was added dropwise by syringe pump over *ca* 20 min, and the mixture was then heated at 50 °C for 10 h. The mixture turned brown and a white solid formed. The mixture was cooled to room temperature, diluted with water (30 mL), and extracted with EtOAc. The combined organic extracts were washed with water, saturated aqueous NH_4Cl (20 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 22

cm), using 1:4 EtOAc-hexane, gave **73** (1.649 g, 83%) as a pale yellow oil: $[\alpha]^{25}_D$ = 31.8° (*c* 1.6, CH_2Cl_2): FTIR (CH_2Cl_2 cast) 3425 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.38-2.48 (m, 3 H), 3.52-3.71 (m, 3 H), 3.81-3.85 (m, 1 H), 4.52 (s, 2 H), 4.58 (AB q, $\Delta\nu_{AB}$ = 38.5 Hz, J = 11.3 Hz, 2 H), 5.05-5.18 (m, 2 H), 5.86-5.98 (m, 1 H), 7.23-7.39 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 35.0 (t'), 71.6 (d'), 71.8 (t'), 72.4 (t'), 73.7 (t'), 79.6 (d'), 117.3 (t'), 127.9 (d'), 128.0 (d'), 128.2 (d'), 128.6 (d'), 128.7 (d'), 135.3 (d'), 138.7 (s'), 139.1 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{20}H_{24}NaO_3$ (M + Na) 312.17255, found 312.17202.

(2*R*,3*S*)-[(1,1-Dimethylethyl)dimethyl][[1,3-bis-(phenylmethoxy)-5-hexen-2-yl]oxy]silane (74).

73 **74**

Imidazole (654.6 mg, 9.615 mmol) and *t*-$BuMe_2SiCl$ (1.268 g, 8.413 mmol) were added consecutively to a stirred solution of **73** (1.500 g, 4.808 mmol) in dry CH_2Cl_2 (40 mL). Stirring was continued at room temperature for 10 h, at which point all the starting material had been consumed (TLC control, silica, 1:5 EtOAc-hexane). The mixture was diluted with water (50 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with water (10 mL) and

brine (20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 24 cm), using 1:9 EtOAc-hexane, gave **74** (1.84 g, 89%) as a colorless oil: $[\alpha]^{25}_D$ = -9.58° (*c* 1.2, CH_2Cl_2); FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 2.33-2.38 (m, 2 H), 3.51-3.60 (m, 3 H), 3.92-3.95 (m, 1 H), 4.42-4.52 (m, 2 H), 4.57 (AB q, $\Delta\nu_{AB}$ = 41.2 Hz, *J* = 7.5 Hz, 2 H), 5.05-5.12 (m, 2 H), 5.84-5.96 (m, 1 H), 7.23-7.39 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -4.7 (q'), -4.3 (q'), 18.4 (s'), 26.0 (q'), 35.5 (t'), 72.4 (t'), 72.7 (t'), 73.5 (t'), 73.7 (d'), 80.9 (d'), 116.7 (t'), 127.7 (d'), 127.8 (d'), 128.0 (d'), 128.1 (d'), 128.5 (d'), 128.6 (d'), 136.1 (d'), 139.0 (s'), 139.4 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{26}H_{38}NaO_3Si$ (M + Na) 449.24879, found 449.24820.

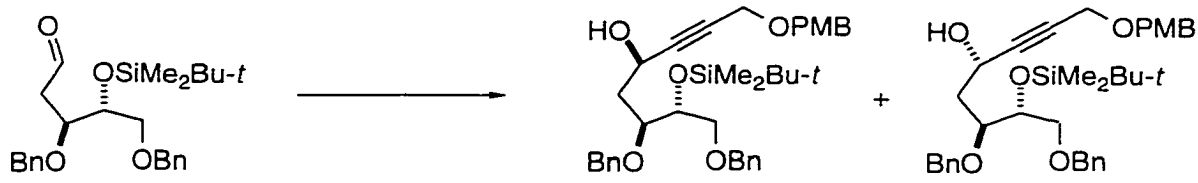
(3*S*,4*R*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3,5-bis(phenylmethoxy)pentanal (75).

74 **75**

Ozonized oxygen was bubbled through a stirred and cooled (-78 °C) solution of **74** (241.7 mg, 0.567 mmol) and Sudan III red (1 mg) in dry CH_2Cl_2 (10 mL) (protection from moisture by

Drierite tube). When all of the starting material was consumed (*ca* 10 min; discharge of the red color; TLC control, silica, 2:3 EtOAc-hexane), the solution was purged with oxygen for 10 min. Ph_3P (446.5 mg, 1.702 mmol) was added, the cooling bath was removed, and stirring was continued for 2 h, by which time the mixture had attained room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave **75** (186.9 mg, 77%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1723 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 2.55-2.70 (m, 2 H), 3.49-3.60 (m, 3 H), 4.01-4.15 (m, 1 H), 4.52 (s, 2 H), 4.57 (AB q, $\Delta\nu_{AB}$ = 41.2 Hz, J = 7.5 Hz, 2 H), 7.2-7.42 (m, 10 H), 9.78 (t, J = 6 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -4.6 (q'), -4.5 (q'), 18.4 (s'), 26.0 (q'), 44.8 (t'), 72.1 (t'), 72.5 (t'), 73.0 (d'), 73.7 (t'), 76.4 (d'), 128.0 (d'), 128.1 (d'), 128.2 (d'), 128.7 (d'), 138.7 (s'), 138.8 (s'), 201.8 (d'); exact mass (HR electrospray) *m/z* calcd for $C_{25}H_{36}NaO_4Si$ (M + Na) 451.22806, found 451.22765.

(4*R*,6*S*,7*R*)- and (4*S*,6*S*,7*R*)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-[(4-methoxyphenyl)methoxy]-6,8-bis(phenylmethoxy)-2-octyn-4-ol (77, 78).



75 **77** **78**

BuLi (2.5 M in hexanes, 3.1 mL, 7.7 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *p*-methoxybenzyl propargyl ether[23] (**76**) (1.347 g, 7.654 mmol) in THF (25 mL). Stirring at -78 °C was continued for 1 h, and then aldehyde **75** (1.310 g, 3.062 mmol) in THF (8 mL plus 2 mL as a rinse) was added dropwise. Stirring was continued for 2 h (TLC control, silica, 3:7 EtOAc-hexane), at which point no starting material remained. The cold bath was removed and, after 5 min, water (100 mL) was added. The mixture was extracted with EtOAc (4 x 100 mL), and the combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 28 cm), using 1:4 EtOAc-hexane, gave a separable mixture (2.9:1) of diastereomers **77** (1.11 g, 60%) and **78** (398.4 mg, 22%), each as a colorless oil.

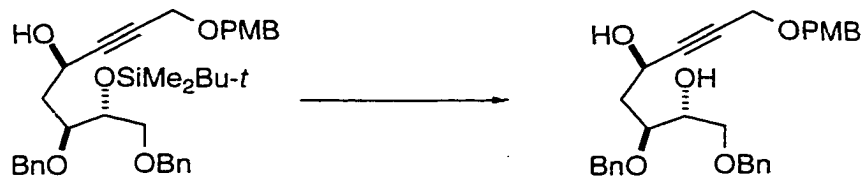
Compound **77** had: $[\alpha]^{25}_D$ = -16.0° (*c* 1.5, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3419 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.92 (s, 9 H), 1.82 (ddd, *J* = 14.7, 7.6,

2.9 Hz, 1 H), 2.10 (ddd, J = 24.6, 15.0, 2.4 Hz, 1 H), 2.99 (d, J = 7.3 Hz, 1 H), 3.51 (d, J = 5.6 Hz, 1 H), 3.78 (s, 3 H), 4.02-4.12 (m, 2 H), 4.18 (d, J = 1.7 Hz, 2 H), 4.48-4.52 (m, 6 H), 4.78 (d, J = 11.0 Hz, 1 H), 6.81-6.86 (m, 2 H), 7.21-7.38 (m, 12 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -4.7 (q'), -4.5 (q'), 18.4 (s'), 26.0 (q'), 37.3 (t'), 55.5 (q'), 57.4 (t'), 60.6 (d'), 71.5 (t'), 72.2 (t'), 72.9 (t'), 72.9 (d'), 73.6 (t'), 79.2 (d'), 80.9 (s'), 87.9 (s'), 114.0 (d'), 127.9 (d'), 128.0 (d'), 128.1 (d'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 129.9 (d'), 130.1 (s'), 138.6 (s'), 138.8 (s'), 159.7 (s'); exact mass (HR electrospray) m/z calcd for $C_{36}H_{48}NaO_6Si$ (M + Na) 627.31178, found 627.31107.

Compound **78** had: $[\alpha]^{25}_D$ = -33.8° (c 2.2, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3431 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 0.08 (s, 3 H), 0.13 (s, 3 H), 0.89 (s, 9 H), 1.91 (ddd, J = 14.4, 3.7, 1.7 Hz, 1 H), 2.04-2.14 (m, 1 H), 3.02 (d, J = 3.7 Hz, 1 H), 3.52 (d, J = 5.8 Hz, 2 H), 3.78 (s, 3 H), 4.02-4.06 (m, 1 H), 4.07-4.18 (m, 1 H), 4.15 (d, J = 1.7 Hz, 2 H), 4.44-4.58 (m, 5 H), 4.61-4.64 (m, 1 H), 4.72 (d, J = 3.9 Hz, 1 H), 6.81-6.86 (m, 2 H), 7.21-7.38 (m, 12 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -4.6 (q', two coincident peaks), 18.4 (s'), 25.9 (q'), 38.6 (t'), 55.5 (q'), 57.4 (t'), 61.0 (d'), 71.4 (t'), 72.1 (t'), 72.6 (t'), 73.0 (d'), 73.6 (t'), 79.6 (d'), 80.9 (s'), 87.6 (s'), 114.0 (d'), 127.9 (d'), 128.0 (d'), 128.3 (d'), 128.6 (d'), 129.9 (d'), 130.1 (s'), 138.7 (s', two coincident peaks), 159.7 (s'); exact mass (HR electrospray) m/z calcd for $C_{36}H_{48}NaO_6Si$ (M + Na) 627.31178, found 627.31165.

The relative stereochemistry of the two products was established by analogy with the arguments given in the Results and Discussion section for the corresponding MOM-protected compounds (**92** and **93**).

(2*R*,3*S*,5*R*)-8-[(4-methoxyphenyl)methoxy]-1,3-bis-(phenylmethoxy)-6-octyn-2,5-diol (80).

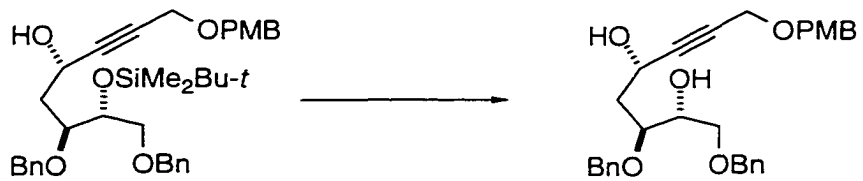


77 **80**

TBAF (1.0 M in THF, 3.6 mL, 3.6 mmol) was added dropwise to a stirred solution of silylated alcohol **77** (1.112 g, 1.823 mmol) in dry THF (25 mL). Stirring was continued for 20 h, by which time reaction was complete (TLC control, silica, 3:4 EtOAc-hexane). The mixture was diluted with water (40 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 3:4 EtOAc-hexane, gave diol **80** (1.542 mg, 85%) as a pure (^1H NMR, 400 MHz), colorless oil: $[\alpha]^{25}_D$ = -15.3° (*c* 1.5, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3433 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.01 (ddd, *J* = 14.5, 5.7, 4.7 Hz, 1 H), 2.12 (p, *J* = 7.3 Hz, 1 H), 2.88 (d, *J* = 4.0 Hz, 1 H), 3.23 (d, *J* = 5.0 Hz, 1 H), 3.58 (dd, *J* = 9.7, 6.5, Hz, 1 H), 3.62

(dd, J = 9.7, 4.0 Hz, 1 H), 3.76-3.79 (m, 1 H), 3.78 (s, 3 H), 3.95-4.00 (m, 1 H), 4.18 (s, 2 H), 4.48 (s, 3 H), 4.51 (s, 3 H), 4.62-4.65 (m, 1 H), 6.82-6.88 (m, 2 H), 7.21-7.38 (m, 12 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 38.9 (t'), 55.6 (q'), 57.5 (t'), 60.3 (d'), 71.4 (t'), 71.6 (t'), 72.1 (d'), 72.5 (t'), 73.7 (t'), 77.9 (d'), 81.2 (s'), 87.6 (s'), 114.0 (d'), 128.1 (d'), 128.2 (d'), 128.3 (d'), 128.7 (d'), 129.9 (d'), 130.0 (s'), 138.5 (s'), 138.55 (s'), 159.8 (s'); exact mass (HR electrospray) m/z calcd for $C_{30}H_{34}NaO_6Si$ (M + Na) 513.22531, found 513.22567.

(2*R*,3*S*,5*S*)-8-[(4-methoxyphenyl)methoxy]-1,3-bis-(phenylmethoxy)-6-octyn-2,5-diol (79).

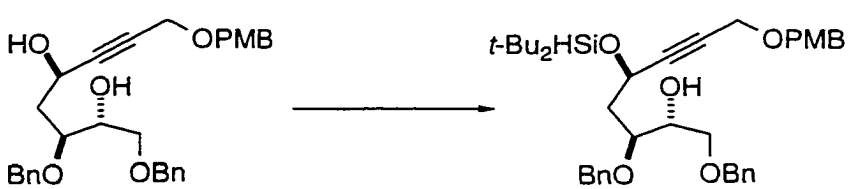


78 **79**

TBAF (1.0 M in THF, 1.3 mL, 1.3 mmol) was added dropwise to a stirred solution of silylated alcohol **78** (383.0 mg, 0.629 mmol) in dry THF (10 mL). Stirring was continued for 20 h, by which time reaction was complete (TLC control, silica, 3:4 EtOAc-hexane). The mixture was diluted with water (20 mL) and extracted with EtOAc (4 x 25 mL). The combined organic extract were washed with brine (20 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the

residue over silica gel (2 x 20 cm), using 3:4 EtOAc-hexane, gave diol **79** (266.0 mg, 87%) as a pure (^{1}H NMR, 400 MHz), colorless oil: $[\alpha]^{25}_D$ = -17.3° (*c* 3.1, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3423 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.85 (ddd, *J* = 14.7, 8.2, 3.5 Hz, 1 H), 2.05 (ddd, *J* = 14.7, 8.9, 3.3 Hz, 1 H), 2.48 (d, *J* = 3.8 Hz, 1 H), 2.82 (d, *J* = 6.7 Hz, 1 H), 3.52-3.61 (m, 2 H), 3.81 (s, 3 H), 3.91-4.01 (m, 2 H), 4.19 (s, 2 H), 4.51 (s, 3 H), 4.58 (s, 3 H), 4.60-4.68 (s, 3 H), 6.82-6.88 (m, 2 H), 7.21-7.38 (m, 12 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 38.1 (t'), 55.6 (q'), 57.4 (t'), 60.2 (d'), 71.2 (t'), 71.5 (t'), 71.8 (d'), 72.9 (t'), 73.7 (t'), 77.8 (d'), 81.1 (s'), 87.7 (s'), 114.0 (d'), 128.1 (d'), 128.2 (d'), 128.4 (d'), 128.7 (d'), 129.9 (d'), 130.1 (s'), 138.5 (s', two coincident peaks), 159.8 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{34}NaO_6Si$ (M + Na) 513.22531, found 513.22567.

(2*R*,3*S*,5*R*)-5-[[Bis(1,1-dimethylethyl)silyl]oxy]-8-[(4-methoxyphenyl)methoxy]-1,3-bis(phenyl-methoxy)-6-octyn-2-ol [(+)-81].

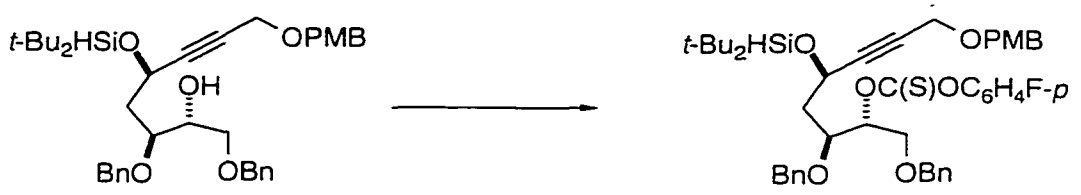


80 **81**

Imidazole (185.9 mg, 2.731 mmol) and *t*-Bu_2SiHCl (0.58

mL, 2.87 mmol) were added consecutively to a stirred solution of diol **80** (669.2 mg, 1.365 mmol) in dry THF (25 mL). Stirring was continued at room temperature for 3 h, at which point most (*ca* 90%) of the starting material had been consumed (TLC control, silica, 15:85 EtOAc-hexane). More imidazole (46.5 mg, 0.68 mmol) and *t*-Bu_2SiHCl (0.14 mL, 0.68 mmol) were added and stirring was continued. After 20 min, the bis-silylated product began to form. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (25 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 24 cm), using 15:85 EtOAc-hexane, gave (+)-**81** (730 mg, 85%, 95% based on conversion) as a colorless oil: $[\alpha]^{25}_D$ = -15.7° (*c* 2.9, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3442 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.98 (s, 9 H), 1.12 (s, 9 H), 1.91-1.98 (m, 1 H), 2.03-2.10 (m, 1 H), 2.52 (d, *J* = 4.0 Hz, 1 H), 3.58-3.61 (m, 2 H), 3.76-3.81 (m, 4 H), 3.96-4.00 (m, 1 H), 4.12-4.20 (m, 3 H), 4.51-4.62 (m, 6 H), 4.76-4.80 (m, 1 H), 6.81-6.86 (m, 2 H), 7.21-7.38 (m, 12 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 19.9 (s'), 20.2 (s'), 27.4 (q'), 40.0 (t'), 54.6 (q'), 57.4 (t'), 64.6 (d'), 71.4 (t'), 72.3 (d'), 72.9 (t'), 73.7 (t'), 77.6 (d'), 82.2 (s'), 87.1 (s'), 114.0 (d'), 128.1 (d'), 128.6 (d'), 128.7 (d'), 130.0 (d'), 130.2 (s'), 138.6 (s'), 139.0 (s'), 159.8 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{38}H_{52}NaO_6Si$ (M + Na) 655.34309, found 655.34327.

Thiocarbonic acid (2*R*,3*S*,5*R*)-*O*-5-[[Bis(1,1-dimethylethyl)silyl]oxy]-8-[(4-methoxyphenyl)methoxy]-1,3-bis(phenylmethoxy)-6-octyn-2-yl *O*-4-Fluorophenyl Ester (82).



81 **82**

p-$FC_6H_4OC(S)Cl$ (0.48 mL, 3.46 mmol) was added to a stirred solution of **81** (728.9 mg, 1.153 mmol) in dry CH_2Cl_2 (20 mL) containing pyridine (0.14 mL, 1.73 mmol) and DMAP (70.5 mg, 0.58 mmol). The resulting yellow solution was stirred for 18 h. At this point some starting material remained (TLC control, silica, 1:6 EtOAc-hexane). An additional portion of *p*-$FC_6H_4OC(S)Cl$ (0.08 mL, 0.58 mmol) was added and the mixture was stirred for 30 min, diluted with saturated aqueous NH_4Cl (25 mL), and extracted with CH_2Cl_2 (4 x 30 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (2 mL), and purified by flash chromatography over silica gel (3 x 40 cm), using 1:9 EtOAc-hexane, to give the thionoformate **82** (860 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ = -10.2° (*c* 2.8, CH_2Cl_2); FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.82 (s, 9 H), 1.10 (s, 9 H), 1.91-1.98 (m, 1 H), 2.04-2.16 (m, 1 H), 3.78-

3.85 (m, 5 H), 4.19-2.20 (m, 4 H), 4.43-4.45 (s, 2 H), 4.52-4.60 (m, 3 H), 4.68-4.80 (m, 2 H), 5.78-5.81 (m, 1 H), 6.82-6.88 (m, 2 H), 7.03-7.18 (m, 4 H), 7.21-7.38 (m, 12 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 19.9 (s'), 20.2 (s'), 27.4 (q'), 40.4 (t'), 54.6 (q'), 57.4 (t'), 64.5 (d'), 68.0 (t'), 71.4 (t'), 73.4 (t'), 73.7 (t'), 75.9 (d'), 82.5 (s'), 85.0 (d'), 86.7 (s'), 114.1 (d'), 116.8 (d') J_{C-C-F} = 23.5 Hz, 123.8 (d') $J_{C-C-C-F}$ = 8.3 Hz, 128.1 (d'), 128.4 (d'), 128.7 (d'), 128.8 (d'), 130.0 (d'), 130.2 (s'), 138.4 (s'), 138.6 (s'), 149.7 (s'), 159.8 (s'), 163.5 (s') J_{C-F} = 245.7 Hz, 195.2 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{45}H_{55}FNaO_7SSi$ (M + Na) 809.33195, found 809.33216.

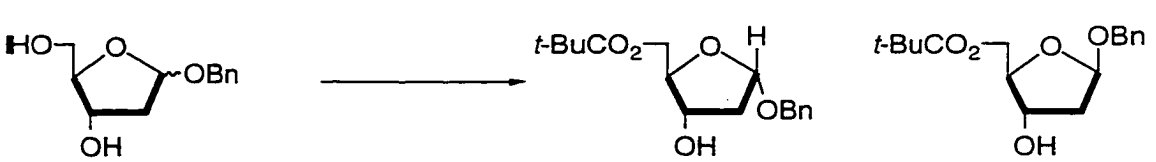
Phenylmethyl 2-Deoxy-α/β-D-*erythro*-pentofurano-side (84).

70 **84**

Concentrated hydrochloric acid (1 drop) was added to a stirred solution of 2-deoxy-D-ribose (415 mg, 3.09 mmol) in BnOH (7.5 mL). Stirring at room temperature was continued for 10 min (TLC control, silica, 1:9 MeOH-CH_2Cl_2), by which time reaction was over. Anhydrous $MgCO_3$ (415.0 mg) was added and the resultant slurry was stirred for 5 min, and then filtered through a sintered disc, the insoluble material

being washed with PhMe. The filtrate was evaporated at room temperature (water aspirator) and the remaining BnOH was removed at room temperature under diffusion pump vacuum (> 0.001 mm). The residue remaining after 24 h was dissolved in CH_2Cl_2 (1 mL), and purified by flash chromatography over silica gel (3 x 22 cm), using first 50:50 EtOAc-hexane (to remove remaining BnOH), followed by 1:9 MeOH-CH_2Cl_2, to give **84** (569.5 mg, 80%) as a colorless oil, which was a *ca* 5:3 (^{1}H NMR) inseparable mixture of anomers. A sample, highly enriched in one of the anomers, had: FTIR (CH_2Cl_2 cast) 3386 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05-2.20 (m, 1 H), 2.29-2.40 (m, 1 H), 2.61 (br s, 2 H), 3.60-3.78 (m, 2 H), 4.05-4.15 (m, 1 H), 4.50-4.60 (m, 2 H), 4.72-4.82 (m, 1 H), 5.34 (dd, *J* = 5.6, 2.1 Hz, 1 H), 7.28-7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 42.5 (t'), 63.6 (t'), 70.0 (t'), 72.2 (d'), 87.6 (d'), 103.7 (d'), 127.8 (d'), 128.0 (d'), 128.5 (d'), 137.2 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{16}NaO_4$ (M + Na) 247.0946, found 247.0947.

Phenylmethyl 2-Deoxy-5-*O*-(2,2-dimethylpropanoyl)-α-D-*erythro*-pentofuranoside (85α) and Phenylmethyl 2-Deoxy-5-*O*-(2,2-dimethylpropanoyl)-β-D-*erythro*-pentofuranoside (85β).



84 **85α** **85β**

A solution of diethyl azodicarboxylate (248.7 mg, 1.428 mmol) and *t*-$BuCO_2H$ (145.8 mg, 1.428 mmol) in dry THF (5 mL) was added to a stirred and warmed (60 °C) solution of alcohols **84** (320.1 mg, 1.428 mmol) and Ph_3P (374.5 mg, 1.428 mmol) in THF (2.5 mL), contained in a flask fitted with a condenser (Ar atmosphere). Stirring at 60 °C was continued for 3 h, the mixture was cooled to room temperature, and the solvent was evaporated. Flash chromatography of the residue [the material was taken up in CH_2Cl_2 (0.5 mL) and the solution was applied to the column] over silica gel (3 x 22 cm), using 1:4 EtOAc-hexane, gave **84** (86.4 mg, 27%), **85α** (94.1 mg, 22%) and **85β** (157.5 mg, 36%) (combined yield is 83%, based on conversion) as colorless oils. The stereochemical assignment was inferred from the assignment made to compound **85α** (see discussion).

Compound **85α** had: $[\alpha]^{25}_D$ = 104.5° (*c* 2.6, MeOH); FTIR (CH_2Cl_2 cast) 1731, 3508 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (s, 9 H), 2.02 (dd, *J* = 13.8, 0.6 Hz, 1 H), 2.20 (ddd, *J* = 13.8, 6.3, 4.8 Hz, 1 H), 2.74 (d, *J* = 10.6 Hz, 1 H), 4.00-4.18 (m, 3 H), 4.23 (dt, *J* = 2.0, 4.5 Hz, 1 H), 4.55 (d, *J* = 11.8 Hz, 1 H), 4.80 (d, *J* = 11.8 Hz, 1 H), 5.27 (dd, *J* = 5.5, 1.4 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 39.0 (s'), 41.5 (t'), 64.4 (t'), 69.5 (t'), 73.3 (d'), 85.5 (d'), 104.0 (d'), 128.0 (d'), 128.3 (d'), 128.8 (d'), 138.3 (s'), 178.4 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{24}NaO_5$ (M + Na) 331.1521, found 331.1528.

Compound **85β** had: $[\alpha]^{25}_D$ = -48.9° (*c* 1.7, MeOH); FTIR (CH_2Cl_2 cast) 1730, 3453 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (s, 9 H), 2.13 (dt, *J* = 13.5, 5.7 Hz, 1 H), 2.29 (ddd, *J* = 13.5, 6.8, 2.0 Hz, 1 H), 2.38 (br s, 1 H), 4.00-4.10 (m, 1 H), 4.17 (d, *J* = 5.8 Hz, 2 H), 4.40 (br s, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.74 (d, *J* = 5.4, 2.0 Hz, 1 H), 5.27 (dd, *J* = 5.4, 2.0 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 39.0 (s'), 42.0 (t'), 65.5 (t'), 69.7 (t'), 72.9 (d'), 84.3 (d'), 103.8 (d'), 127.9 (d'), 128.3 (d'), 128.7 (d'), 138.4 (s'), 178.7 .(s'); exact mass (HR electrospray) *m/z* calcd for $C_{17}H_{24}NaO_5$ (M + Na) 331.1521, found 331.1520.

Phenylmethyl 2-Deoxy-5-*O*-(2,2-dimethylpropanoyl)-3-*O*-(methoxymethyl)-α-D-*erythro*-pentofuranoside (86α).

85α **86α**

i-Pr_2NEt (0.18 mL, 134 mg, 1.04 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **85α** (106.5 mg, 0.346 mmol) in CH_2Cl_2 (6 mL). After 15 min, MOMCl (0.08 mL, 1.04 mmol) was added dropwise over 5 min, and stirring was continued for 1 h. The cold bath was removed, stirring was continued for 12 h, and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. 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 1:4 EtOAc-hexane, gave **86α** (112.2 mg, 92%) as a colorless oil: $[\alpha]^{25}_D$ = 106.6° (*c* 1.1, MeOH); FTIR (CH_2Cl_2 cast) 1728, 3435 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (s, 9 H), 2.05 (ddd, *J* = 14.1, 2.9, 1.4 Hz, 1 H), 2.27 (ddd, *J* = 14.1, 8.3, 5.5 Hz, 1 H), 3.30 (s, 3 H), 4.10-4.18 (m, 2 H), 4.20-4.30 (m, 2 H), 4.46 (d, *J* = 12 Hz, 1 H), 4.64 (AB q, $\Delta\nu_{AB}$ = 8.7 Hz, *J* = 6.9 Hz, 2 H), 4.77 (d, *J* = 12 Hz, 1 H), 5.27 (dd, *J* = 5.5, 1.4 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 39.0 (s'), 39.8 (t'), 55.7 (q'), 64.1 (t'), 69.5 (t'), 77.7 (d'), 81.6 (d'), 96.6 (t'), 103.6 (d'), 127.9 (d'), 128.2 (d'), 128.6 (d'), 138.8 (s'), 178.4 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{28}NaO_6$ (M + Na) 375.1784, found 375.1780. The anomeric configuration was assigned on the basis of a TROESY NMR (600 MHz) experiment.

Phenylmethyl 2-Deoxy-5-*O*-(2,2-dimethylpropanoyl)-3-*O*-(methoxymethyl)-β-D-*erythro*-pentofuranoside (86β).

85β **86β**

i-Pr_2NEt (0.12 mL, 0.71 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **85β** (72.8 mg,

2.63 mmol) in CH_2Cl_2 (5 mL). After 15 min, CH_3OCH_2Cl (0.90 mL, 57.1 mmol, 0.71 mmol) was added dropwise over 5 min, and stirring was continued for 1 h. The cold bath was removed, stirring was continued for 12 h, and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:4 EtOAc-hexane, gave **86β** (70.4 mg, 90%) as a colorless oil: $[\alpha]^{25}_D$ = -47.8° (*c* 0.9, MeOH); FTIR (CH_2Cl_2 cast) 1731 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (s, 9 H), 2.15 (dt, *J* = 13.5, 5.7 Hz, 1 H,), 2.35 (ddd, *J* = 13.5, 7.0, 1.9 Hz, 1 H), 3.30 (s, 3 H), 4.10-4.20 (m, 3 H), 4.20-4.25 (m, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.60 (s, 2 H), 4.74 (d, *J* = 11.7 Hz, 1 H), 5.27 (dd, *J* = 5.4, 1.9 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 39.0 (s'), 40.0 (t'), 55.6 (q'), 65.5 (t'), 69.6 (t'), 78.1 (d'), 82.4 (d'), 96.3 (t'), 104.0 (d'), 127.9 (d'), 128.3 (d'), 128.7 (d'), 138.4 (s'), 178.4 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{28}NaO_6$ (M + Na) 375.1784, found 375.1784.

2-Deoxy-5-*O*-(2,2-dimethylpropanoyl)-3-*O*-(methoxymethyl)-α/β-D-*erythro*-pentofuranose (87).

86α **87**

5% Pd-C (15.0 mg) was added to a solution of **86α** (472 mg, 1.34 mmol) in EtOH (95%, 15 mL), and the mixture was shaken in a Parr bottle under H_2 (50 psi) until all the starting material was consumed (*ca* 12 h, TLC control, silica, 2:3 EtOAc-hexane), the apparatus being opened periodically for examination by TLC. The mixture was filtered through a pad of silica gel (4 x 3 cm), using EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 15 cm), using 3:2 EtOAc-hexane, gave **87** (323.2 mg, 92%) as a colorless oil containing both anomers and small amounts of the open-chain isomer. These compounds were used directly in the next step.

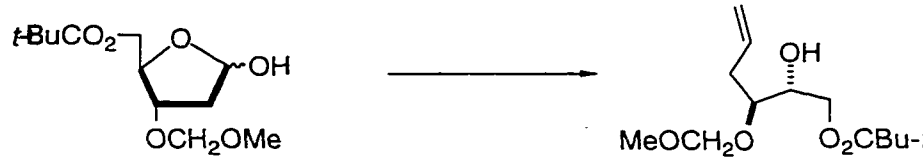
2-Deoxy-5-*O*-(1,1-dimethylpropanoyl)-3-*O*-(methoxymethyl)-α/β-D-*erythro*-pentofuranose (87).

86β **87**

5% Pd-C (10 mg) was added to a solution of **86β** (535.0 mg, 1.519 mmol) in EtOH (95%, 10 mL), and the mixture was shaken in a Parr bottle under H_2 (50 psi) until all the starting material was consumed (*ca* 12 h, TLC control, silica, 2:3 EtOAc-hexane), the apparatus being opened periodically for examination by TLC. The mixture was filtered through a

pad of silica gel (1 x 2 cm), using EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 10 cm), using 3:2 EtOAc-hexane, gave **87** (366.3 mg, 92%) as a colorless oil containing both anomers and small amounts of the open-chain isomer. These compounds were used directly in the next step.

(2*R*,3*S*)-2-Hydroxy-3-(methoxymethoxy)-5-hexenyl 2,2-Dimethylpropanoate (88).

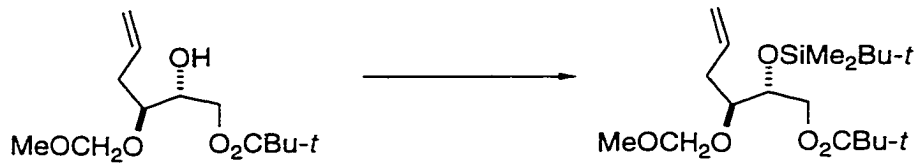


87 **88**

BuLi (2.5 M in hexanes, 2.5 mL, 6.3 mmol) was added dropwise to a stirred suspension of Ph_3PCH_3Br (2.223 g, 6.223 mmol) in dry PhMe (25 mL), and the resulting yellow slurry was stirred at room temperature for 3 h. A solution of lactols **87** (550.7 mg, 2.110 mmol) in dry PhMe (7.5 mL) was added dropwise by syringe pump, and the mixture was then heated at 50 °C for 10 h. The mixture turned brown and a white solid formed. The mixture was cooled to room temperature, diluted with water (30 mL), and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with water, saturated aqueous NH_4Cl (20 mL), and brine, and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 22 cm),

using 1:4 EtOAc-hexane, gave **88** (372.2 mg, 72%) as a pale yellow oil: $[\alpha]^{25}_D$ = 29.4° (*c* 1.2, MeOH); FTIR (CH_2Cl_2 cast) 1730, 3486 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.21 (s, 9 H), 2.40-2.50 (m, 2 H), 2.75 (d, *J* = 6.4 Hz, 1 H), 3.40 (s, 3 H), 3.60-3.70 (m, 1 H), 3.75-3.90 (m, 1 H), 4.10 (dd, *J* = 11.6, 6.8 Hz, 1 H), 4.20 (dd, *J* = 11.6, 3.6 Hz, 1 H), 4.64 (AB q, $\Delta\nu_{AB}$ = 8.2 Hz, *J* = 6.8 Hz, 2 H), 5.00-5.20 (m, 2 H), 5.75-6.00 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 27.4 (q'), 35.7 (t'), 39.1 (s'), 56.1 (q'), 65.7 (t'), 71.5 (d'), 80.1 (d'), 97.3 (t'), 117.6 (t'), 134.9 (d'), 179.0 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{13}H_{24}NaO_5$ (M + Na) 283.1521, found 283.1526.

(2*R*,3*S*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3-(methoxymethoxy)-5-hexenyl 2,2-Dimethylpropanoate (89).



88 **89**

Imidazole (197 mg, 2.89 mmol) and *t*-$BuMe_2SiCl$ (380 mg, 2.52 mmol) were added consecutively to a stirred solution of **88** (355.0 mg, 1.364 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued at room temperature for 10 h, at which point all the starting material had been consumed. The mixture was

diluted with water (10 mL) and extracted with EtOAc. The combined organic extracts were washed with water (10 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 22 cm), using 1:4 EtOAc-hexane, gave **89** (453.0 mg, 89%) as a colorless oil: $[\alpha]^{25}_D$ = -1.72° (*c* 0.9, MeOH); FTIR (CH_2Cl_2 cast) 1730 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.21 (s, 9 H), 2.30-2.40 (m, 2 H), 3.35 (s, 3 H), 3.65 (dt, *J* = 4.0, 6.0 Hz, 1 H), 3.82-3.85 (m, 1 H), 4.02 (dd, *J* = 11.4, 4.9 Hz, 1 H), 4.17 (dd, *J* = 11.4, 4.3 Hz, 1 H), 4.65 (AB q, $\Delta\nu_{AB}$ = 12.5 Hz, *J* = 6.7 Hz, 2 H), 5.00-5.20 (m, 2 H), 5.75-6.00 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -4.51 (q', two coincident peaks), 18.3 (s'), 26.0 (q'), 27.4 (q'), 35.5 (t'), 39.0 (s'), 56.0 (q'), 65.8 (t'), 72.6 (d'), 78.3 (d'), 96.5 (t'), 117.2 (t'), 135.6 (d'), 178.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{19}H_{38}NaO_5Si$ (M + Na) 397.2386, found 397.2396.

(2*R*,3*S*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3-(methoxymethoxy)-5-oxopentyl 2,2-Dimethylpropanoate (90).

89 **90**

Ozonized oxygen was bubbled through a stirred and cooled (-78 °C) solution of **89** (537.7 mg, 1.437 mmol) and Sudan III red (1 mg) in dry CH_2Cl_2 (10 mL) (protection from moisture by Drierite tube). When all of the starting material was consumed (*ca* 10 min; discharge of the red color; TLC control, silica, 2:3 EtOAc-hexane), the solution was purged with oxygen for 10 min. Ph_3P (753.7 mg, 2.873 mmol) was added, the cooling bath was removed, and stirring was continued for 2 h, by which time the mixture had attained room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm), using 1:4 EtOAc-hexane, gave **90** (420.9 mg, 83%) as a colorless oil: $[\alpha]^{25}_D$ = -16.9° (*c* 1.3, MeOH); FTIR (CH_2Cl_2 cast) 1732 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.21 (s, 9 H), 2.60-2.66 (m, 2 H), 3.35 (s, 3 H), 3.90-4.18 (m, 4 H), 4.65 (AB q, $\Delta\nu_{AB}$ = 23.0 Hz, *J* = 6.8 Hz, 2 H), 9.81 (t, *J* = 2.1 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -4.61 (q', two coincident peaks), 18.3 (s'), 25.9 (q'), 27.4 (q'), 39.0 (s'), 45.2 (t'), 56.0 (q'), 65.1 (t'), 72.6 (d'), 74.2 (d'), 96.7 (t'), 178.5 (s'), 201.2 (d'); a satisfactory mass spectrum could not be obtained.

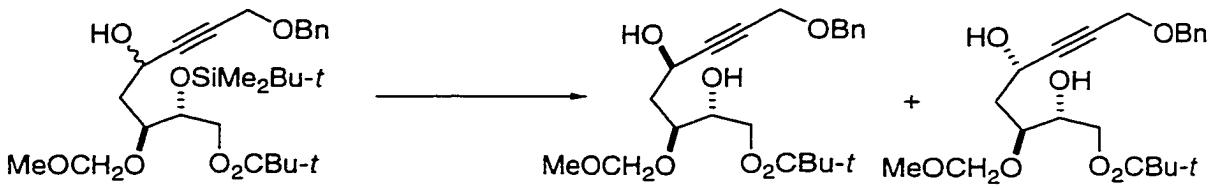
(2*R*,3*S*,5*R*)- and (2*R*,3*S*,5*S*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-3-(methoxymethoxy)-8-(phenylmethoxy)-6-octynyl 2,2-Dimethylpropanoate (91).

90 **91**

BuLi (2.5 M in hexanes, 1.1 mL, 2.8 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of benzyl propargyl ether (**28**[22]) (391.9 mg, 2.685 mmol) in THF (10 mL). Stirring at -78 °C was continued for 1 h, and then aldehyde **90** (378.0 mg, 1.073 mmol) in THF (3 plus 2 mL as a rinse) was added dropwise. Stirring was continued for 2 h (TLC control, silica, 2:3 EtOAc-hexane), at which point no starting material remained. The cold bath was removed and, after 5 min, water (10 mL) was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 22 cm), using 1:4 EtOAc-hexane, gave **90** (40 mg, 11%) and **91** (398.2 mg, 71%, or 80% based on conversion), each as a colorless oil. Compound **91** was isolated as a 1:1.4 mixture (^1H NMR, 400 MHz) of diastereoisomers: ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.10 and 0.11 (two s, 6 H in all), 0.90 (s, 9 H), 1.20

(s, 9 H), 1.80-2.20 (m, 2 H), 2.80 (d, J = 4.8 Hz) and 3.05 (d, J = 6.0 Hz) (the signals at 2.80 and 3.05 correspond to 1 H in all), 3.42 and 3.44 (two s, 3 H in all), 3.80-4.20 (m, 4 H), 4.25 and 4.26 (two s, 2 H in all), 4.52 (s, 2 H), 4.60-4.72 (m, 2 H), 4.72-4.80 (m, 1 H), 7.28-7.40 (m, 5 H).

(2*R*,3*S*,5*R*)- and (2*R*,3*S*,5*S*)-2,5-Dihydroxy-3-(methoxymethoxy)-8-(phenylmethoxy)-6-octynyl 2,2-Dimethylpropanoate (92, 93).



91 **92** **93**

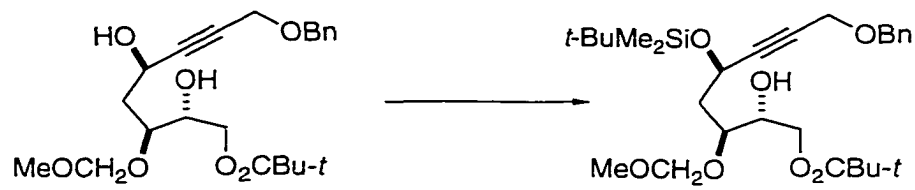
HF (48% in water, 0.4 mL, 11.2 mmol) was added to a stirred solution of **91** (251 mg, 0.48 mmol) in bench MeCN (5 mL). After 30 min, saturated aqueous $NaHCO_3$ (10 mL) was added dropwise, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 40 cm), using 1:4 EtOAc-hexane, gave **92** (98.1 mg, 50%), and **93** (69.8 mg, 35.5%) as a separable mixture (1.4:1.0) of diastereoisomers.

Compound **92** had: $[\alpha]^{25}_D$ = -15.36° (*c* 1.0, MeOH); FTIR (CH_2Cl_2 cast) 1728, 3436 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.21 (s, 9 H), 1.80-2.20 (m, 2 H), 2.60 (d, J = 5.0 Hz, 1 H), 3.10

(d, J = 5.0, 1 H), 3.35 (s, 3 H), 3.85-3.92 (m, 2 H), 4.00-4.25 (m, 4 H), 4.55 (s, 2 H), 4.60-4.68 (m, 3 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 39.0 (s'), 39.4 (t'), 56.3 (q'), 57.8 (t'), 60.2 (d'), 65.5 (t'), 71.8 (d'), 72.0 (t'), 78.4 (d'), 81.5 (s'), 87.3 (s'), 97.5 (t'), 128.1 (d'), 128.3 (d'), 128.7 (d'), 138.1 (s') 178.9 (s'); exact mass (HR electrospray) m/z calcd for $C_{22}H_{32}NaO_7$ (M + Na) 431.2046, found 431.2055.

Compound **93** had: $[\alpha]^{25}_D$ = -10.0° (c 1.4, MeOH); FTIR (CH_2Cl_2 cast) 1728, 3439 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (s, 9 H), 1.90 (ddd, J = 14.6, 9.0, 3.3 Hz, 1 H), 2.05 (ddd, J = 14.6, 9.0, 3.3 Hz, 1 H), 2.80 (d, J = 6.0 Hz, 1 H), 2.90 (d, J = 6.0 Hz, 1 H), 3.40 (s, 3 H), 3.80-3.84 (m, 1 H), 3.90-3.96 (m, 1 H), 4.16 (dd, J = 11.6, 6.7 Hz, 1 H), 4.18-4.21 (m, 3 H), 4.59 (s, 2 H), 4.60-4.68 (m, 1 H), 4.71 (AB q, $\Delta\nu_{AB}$ = 12.0 Hz, J = 6.7 Hz, 2 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 39.0 (s'), 39.1 (t'), 56.4 (q'), 57.8 (t'), 59.5 (d'), 65.4 (t'), 72.0 (d'), 72.0 (t'), 78.6 (d'), 81.0 (s'), 87.6 (s'), 98.1 (t'), 128.1 (d'), 128.3 (d'), 128.7 (d'), 138.1 (s') 178.9 (s'); exact mass (HR electrospray) m/z calcd for $C_{22}H_{32}NaO_7$ (M + Na) 431.2046, found 431.2057.

(2*R*,3*S*,5*R*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-2-hydroxy-3-(methoxymethoxy)-8-(phenylmethoxy)-6-octynyl 2,2-Dimethylpropanoate [(+)-94].

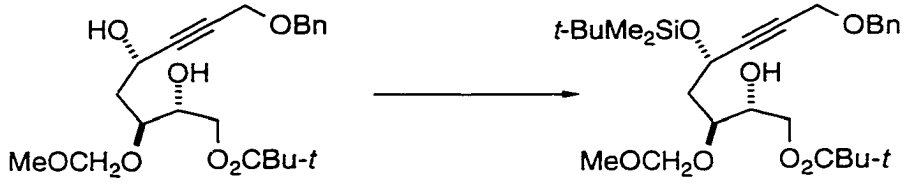


92 **94**

Imidazole (7.9 mg, 0.1 mmol) and *t*-$BuMe_2SiCl$ (34.8 mg, 0.23 mmol) were added consecutively to a stirred solution of diol **92** (23.5 mg, 0.06 mmol) in dry CH_2Cl_2 (3 mL). Stirring was continued at room temperature for 1 h, at which point all the starting material had been consumed and the bis-silylated product began to form. The mixture was diluted with water (2.5 mL) and extracted with EtOAc. The combined organic extracts were washed with water (2.5 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:4 EtOAc-hexane, gave (+)-**94** (28.3 mg, 94%) as a colorless oil: $[\alpha]^{25}_D$ = 7.81 (*c* 1.4, MeOH); FTIR (CH_2Cl_2 cast) 1730, 3442 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.14 (s, 3 H), 0.18 (s, 3 H), 0.90 (s, 9 H), 1.20 (s, 9 H), 1.91 (ddd, *J* = 14.1, 7.3, 4.2 Hz, 1 H), 2.09 (ddd, *J* = 14.0, 7.9, 5.9 Hz, 1 H), 3.15 (d, *J* = 6.4 Hz, 1 H), 3.39 (s, 3 H) 3.76-3.91 (m, 2 H), 4.09-4.23 (m, 4 H), 4.58 (s, 2 H), 4.60-4.72 (m, 3 H), 7.24-7.37 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -5.0. (q'), -4.4 (q'), 18.4 (s'), 25.9

(q'), 27.3 (q'), 39.0 (s'), 40.5 (t'), 56.2 (q'), 57.8 (t'), 60.9 (d'), 65.4 (t'), 71.8 (d'), 71.8 (t'), 78.9 (d'), 81.7 (s'), 87.5 (s'), 97.8 (t'), 128.1 (d'), 128.3 (d'), 128.7 (d'), 138.1 (s'), 178.7 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{28}H_{46}NaO_7Si$ (M + Na) 575.2911, found 575.2901.

(2*R*,3*S*,5*S*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-2-hydroxy-3-(methoxymethoxy)-8-(phenylmethoxy)-6-octynyl 2,2-Dimethylpropanoate [(-)-95].



93 **95**

Imidazole (14.3 mg, 0.21 mmol) and *t*-$BuMe_2SiCl$ (17.5 mg, 0.12 mmol) were added consecutively to a stirred solution of **93** (42.9 mg, 0.11 mmol) in dry CH_2Cl_2 (2.5 mL). Stirring was continued at room temperature for 10 h, at which point all the starting material had been consumed and the bis-silylated product began to form. The mixture was diluted with water (5 mL) and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:4 EtOAc-hexane, gave the C(5) epimer of (+)-**94**, i.e. (-)-**95** (50.4 mg, 92%) as a colorless oil: $[\alpha]^{25}_D$ = -17.6° (*c* 1.0, MeOH); FTIR (CH_2Cl_2 cast) 1730,

3438 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.14 (s, 3 H), 0.18 (s, 3 H), 0.90 (s, 9 H), 1.20 (s, 9 H), 1.88-1.95 (m, 2 H), 3.15 (d, J = 5.0 Hz, 1 H), 3.39 (s, 3 H), 3.80-3.86 (m, 2 H), 4.10-4.20 (m, 4 H), 4.59 (s, 2 H), 4.60-4.64 (m, 1 H), 4.71 (AB q, $\Delta\nu_{AB}$ = 12.0 Hz, J = 6.7 Hz, 2 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ -4.8 (q'), -4.7 (q'), 18.3 (s'), 25.9 (q'), 27.3 (q'), 39.0 (s'), 41.1 (t'), 56.2 (q'), 57.7 (t'), 59.8 (d'), 65.4 (t'), 71.8 (t'), 72.1 (d'), 79.3 (d'), 81.0 (s'), 88.2 (s'), 98.2 (t'), 128.0 (d'), 128.3 (d'), 128.7 (d'), 138.2 (s'), 178.7 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{28}H_{46}NaO_7Si$(M + Na) 545.2911, found 545.2910.

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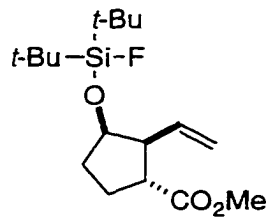

Figure 4 Olefinic Product

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(21) *p*-Anisaldehyde (15 drops) was added to concentrated H_2SO_4 (6 mL) and EtOH (94 mL).

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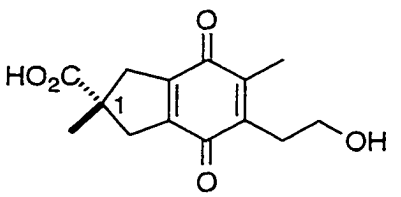
PART II

SYNTHETIC STUDIES RELATED TO PURAQUINONIC ACID

SYNTHETIC STUDIES RELATED TO PURAQUINONIC ACID

General Introduction

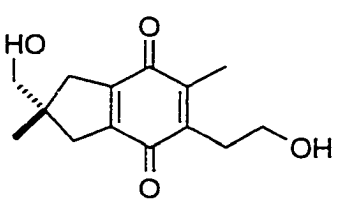
Puraquinonic acid (**1**), a norilludinane sesquiterpene, was isolated recently by Becker *et al.*[1] from the mycelial cultures of *Mycena pura*. It was found to induce cell differentiation in 30-40% of HL-60 cells at 380 μM concentration. This biological property makes it a potential candidate for the treatment of leukemias.[1]



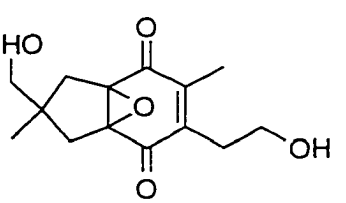
1

Figure 1 Puraquinonic acid

The structure was assigned on the basis of 2D NMR (HMBC and NOESY) spectroscopy,[1] but the stereochemistry at the asymmetric center has not yet been determined; the optical rotation has been reported, however. The value is +1 (*c* 1.0, $CHCl_3$).



Deliquinone **2**



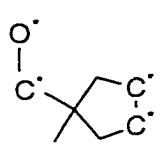
2,9-epoxydeliquinone **3**

Figure 2 Puraquinonic acid derivatives

Recently, several related natural products, such as deliquinone **2** – a C(1) reduced derivative of puraquinonic acid – and the corresponding epoxide, 2,9-epoxydeliquinone **3**, were isolated from *Russula delica*[2] and characterized. The biological properties of these substances have not yet been reported. Both are optically active. The optical rotation of **2** was reported to be -0.5 (*c* 0.6, MeOH) and that of **3** to be ± 1.0 (*c* 0.1, $CHCl_3$).

Puraquinonic acid and its derivatives possess a quaternary center which is asymmetric due to the substitution pattern further away in the molecule. This feature complicates the synthesis of such compounds.

A survey of the Beilstein database showed that a number of natural products possessing the structural unit **4** have been isolated, but few total syntheses have been reported. In Figure **3**, C* represents any substitution and the C*-O* and C*-C* bonds can be of any type. Likewise, a CASONLINE search [⇒ illud? and synth? and org/sc] for syntheses of members of the illudane class gave a similar result for compounds in which the quaternary center bears two different groups.

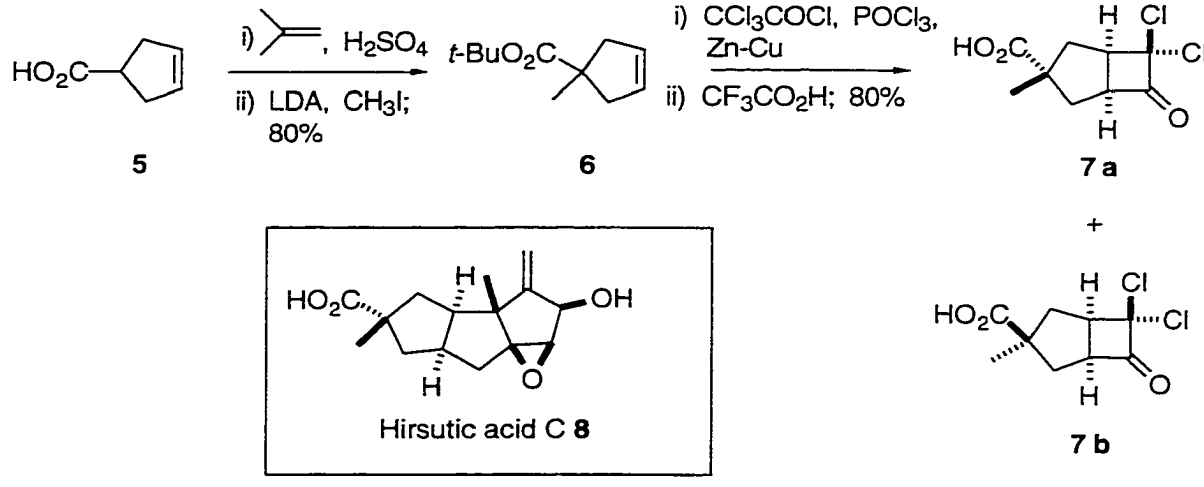


4

Figure 3 Model substructure **4**

The natural product hirsutic acid C (**8**) is an example

where the key feature of an asymmetric center, caused by the substitution further away, was found in the synthetic literature. Greene *et al.*[3,4] synthesized hirsutic acid C in both racemic and enantiomerically pure forms.

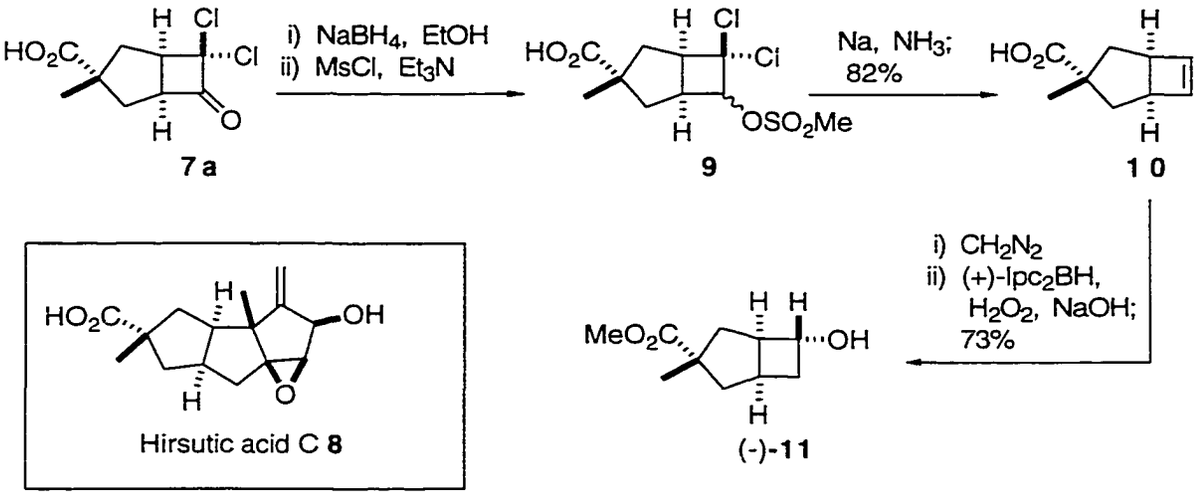


Scheme 1

In the synthesis[3] of racemic hirsutic acid C, the quaternary center was easily incorporated by alkylation of the starting acid **5**. Dichloroketene addition to the ester **6** proceeded diastereoselectively to produce a 3:1 mixture of **7a** and **7b**. The major isomer was subsequently converted into the desired natural product. Stereochemical assignments to **7a** and **7b** were based on further chemical derivatization of the minor isomer.

In the optically active series,[4] attempts to resolve racemic **7a** (Scheme 1), using the amine cinchonidine, gave very poor yields. In order to circumvent this problem, an alternative approach was used. Racemic keto acid **7a** was converted into the mesylates **9** (Scheme 2), and the crude

product was added to an excess of sodium in liquid ammonia.

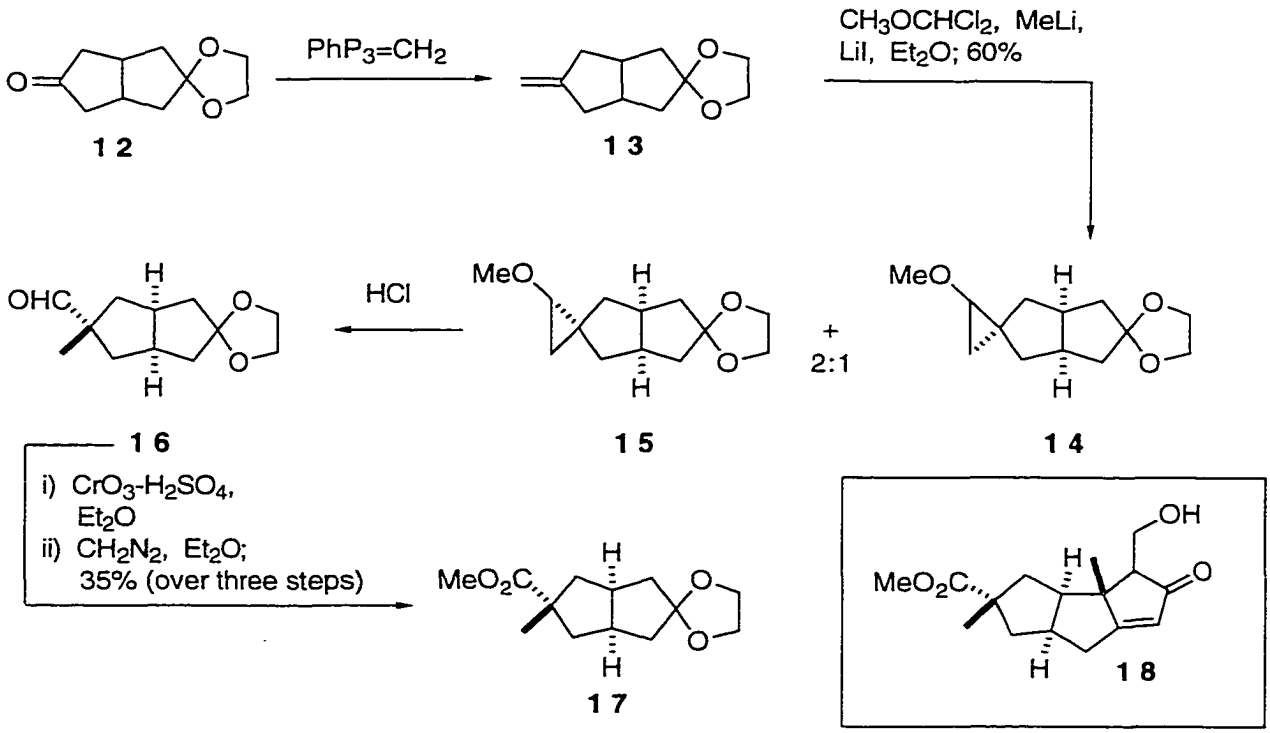


Scheme 2

Crystalline cyclobutene **10** was produced in high yield in this experiment. The *meso* olefin **10** was then desymmetrized using a procedure developed by Brown and coworkers.[5] This sequence involved asymmetric hydroboration with an excess of (+)-diisopinocampheylborane. The optical purity of the product **11** was found to be 92±5%. The stereochemical assignment was based on previous work on related compounds,[5] and the material was elaborated into the natural product hirsutic acid C.

In another study towards the synthesis of the hirsutane skeleton **18**, Sakan and coworkers[6] converted the monoketal **12** into the methylene derivative **13** (Scheme 3). Methoxycarbene addition to **13**, gave a 1:2 mixture of the *exo* and *endo* methoxycyclopropanes **14** and **15**. Chromatographic separation of the *exo* product, followed by acid cleavage of the cyclopropane ring, gave aldehyde **16** exclusively. This was

converted into the corresponding ester **17**, from which point the target **18** was easily reached.



Scheme 3

References and footnotes

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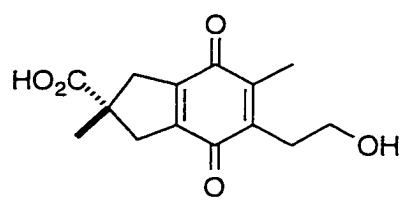
SYNTHETIC STUDIES RELATED TO PURAQUINONIC ACID

RESULTS AND DISCUSSION

The fungal metabolite puraquinonic acid (**1**) was isolated recently[1] and found to stimulate cell differentiation. This property suggests that it may serve as a lead compound for the design of anticancer drugs.[1]



1

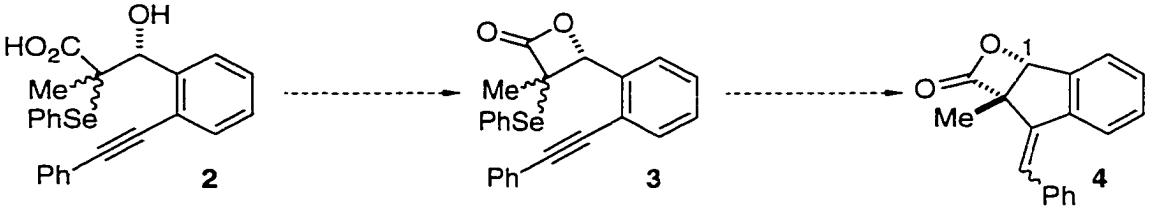
Figure 1 Puraquinonic acid

Puraquinonic acid contains a structural unit - the quaternary center - that presents a significant synthetic problem. The difficulty is due to the fact that the quaternary carbon is asymmetric, and the features of the molecule that are responsible for the asymmetry of this center are far removed from it. In principle, such an asymmetric center can be created if an adjacent, but temporary, asymmetric center is present during the appropriate steps of the work, and we decided to approach the synthesis based on this concept. Several exploratory studies were carried out, as described below, and these eventually

served to identify what we believe to be a very promising route that should afford optically active puraquinonic acid. At present the absolute stereochemistry of the natural product is not known, and our experimental work is designed to afford either enantiomer.

The β-lactone approach

Our first experiments were based on the ideas summarized in Scheme 1. If we could construct an optically pure lactone, such as **3**, starting from the corresponding hydroxy acid, then radical cyclization (**3** → **4**) would be expected to afford the tricyclic lactone shown in the Scheme. The lactone would, of necessity, have *cis* ring fusion, in accord



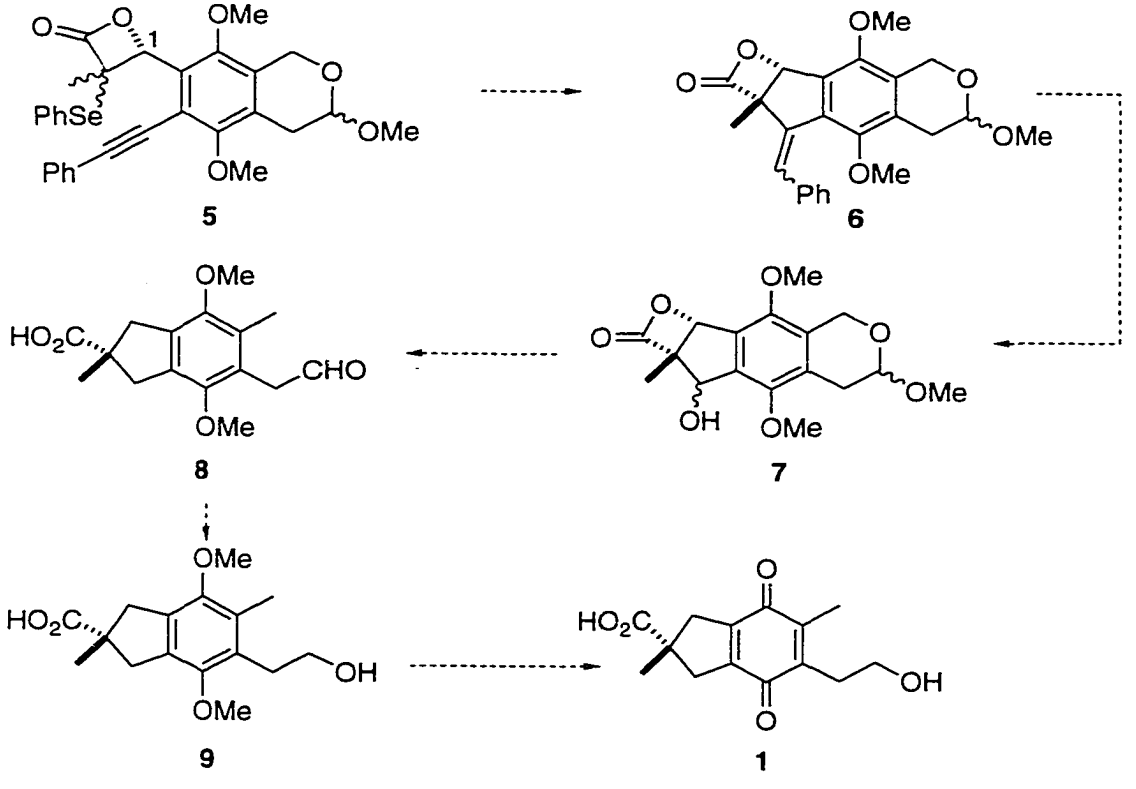
Scheme 1

with the general rules for ring fusion stereochemistry resulting from radical cyclization.[2] Consequently, the absolute stereochemistry at the hydroxyl-bearing carbon of **2** controls the stereochemical outcome of the whole process, and once the quaternary center has been set up, the C(1)-O bond in **4**, or a later intermediate, could be hydrogenolyzed.

We decided to test the plan on the simple system **2** itself. If we were successful in generating **4**, we would then

need to make some alterations to the model sequence, along the following lines.

In order to reach the natural product, we would begin with the synthesis of the protected lactol ethers **5**. Radical cyclization of **5** should produce **6**, with the appropriate stereochemistry at the quarternary center, determined in an absolute sense by the absolute stereochemistry at C(1) of **5**.



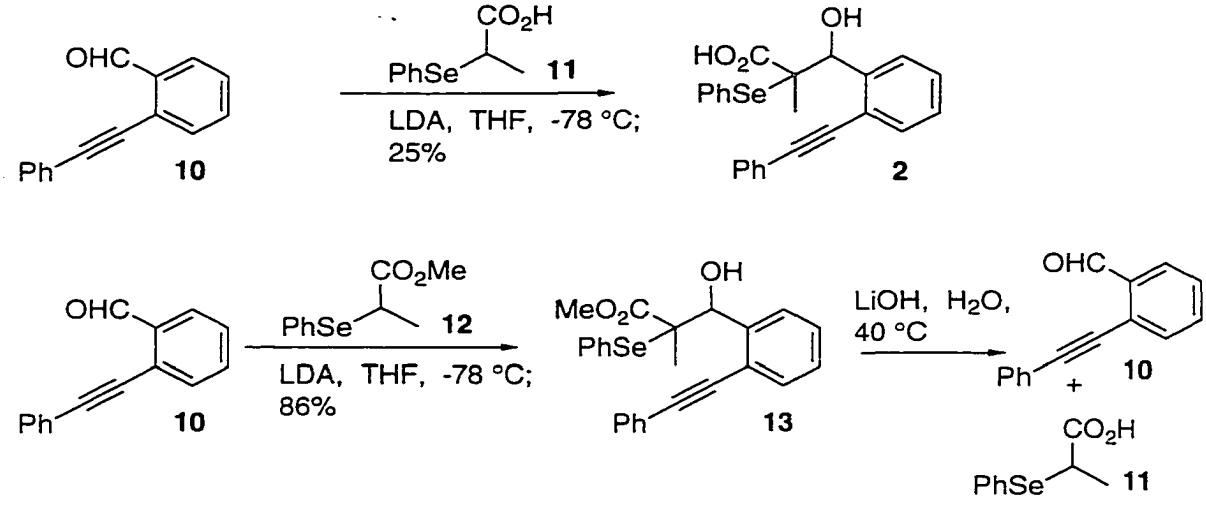
Scheme 2

Ozonolytic cleavage of the exocyclic double bond, followed by sodium borohydride reduction should give **7**, and at this point, catalytic hydrogenolysis of the benzylic oxygen functions should liberate aldehyde **8**. Reduction of the aldehyde, and DDQ (or CAN) oxidation of the dimethoxybenzene

unit (with or without temporary protection of the primary hydroxyl) would complete the synthesis (**9** → **1**).

Synthetic studies on the β-lactone route

As a model study, we prepared the hydroxy acids **13**, beginning with the condensation[3] of the known acid **11**[4] with aldehyde[5] **10**. The condensation (Scheme 3) gave very low yields (25%) and significant amounts of starting materials were recovered.

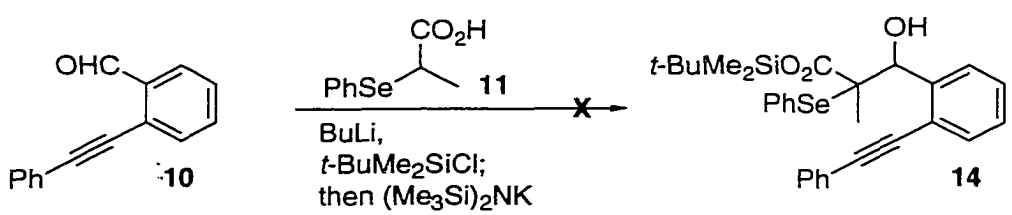


Scheme 3

From previous experiments on the synthesis of methyl *epi*-jasmonate, we knew that the use of methyl esters – as opposed to acids – led to much higher yields in similar condensations, and so we decided to work in the ester series (**10** → **13**); the carboxylic acid function required for β-lactone formation would then be obtained by hydrolysis. In the event, condensation of aldehyde **10** with the anion derived from phenylseleno ester **12**[6] gave the hydroxy esters **13** in

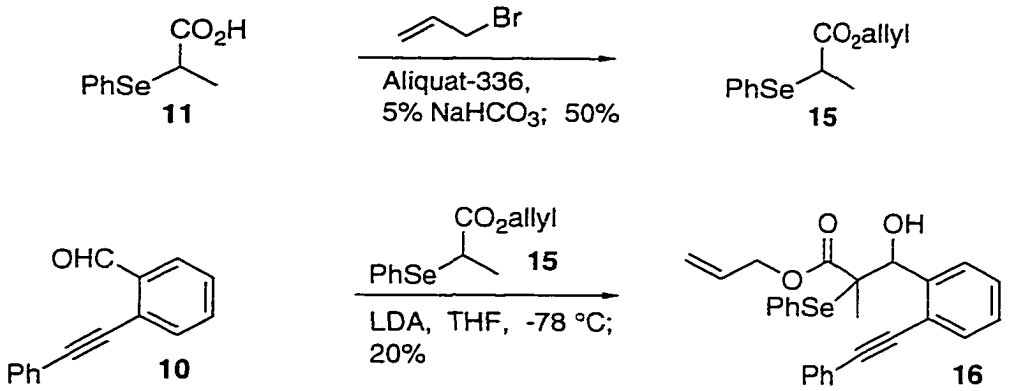
high yield (86%). Surprisingly, when we attempted to hydrolyze **13** with lithium hydroxide, the substrate underwent a retro-aldol reaction to give back aldehyde **10** and the product (**11**) of hydrolysis of the original seleno ester (Scheme 3).

In order to avoid the necessity for basic hydrolysis, we examined the use of a silyl ester, instead of a methyl ester. Protection of acid **11** with the *t*-$BuMe_2SiCl$ proceeded cleanly (as judged by TLC), but the product decomposed during the aqueous workup to give back the starting acid. *In situ*, protection of the acid, followed by attempted condensation with aldehyde **10**, also gave back extensive amounts of starting materials, and we failed to isolate the desired product **14** (Scheme 4).



Scheme 4

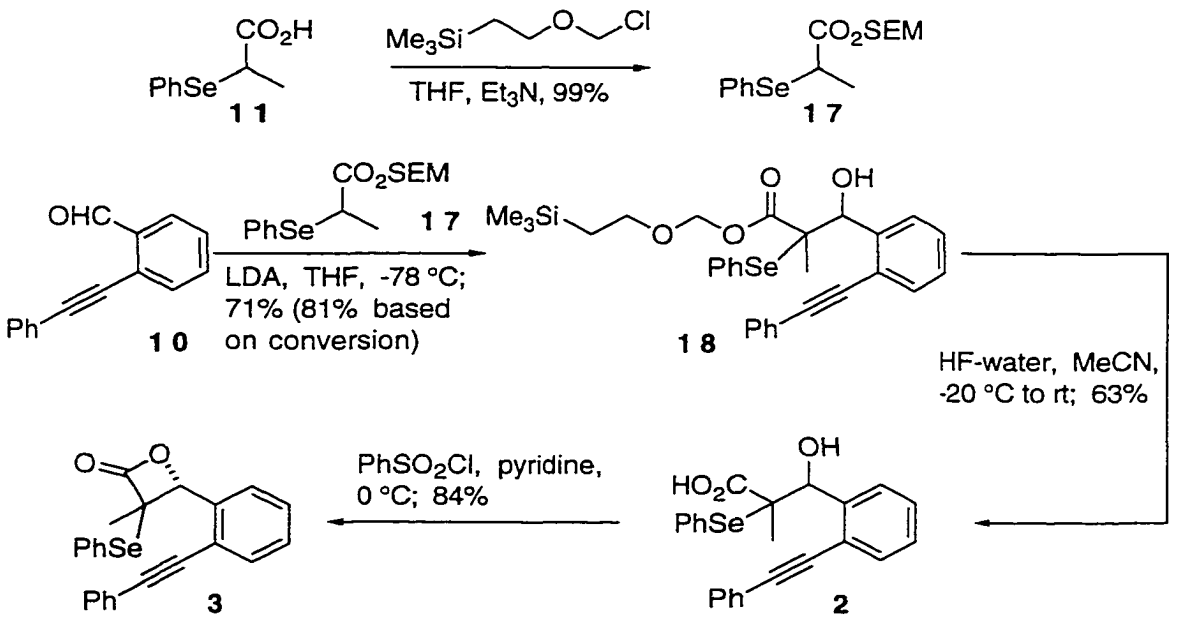
Next, we examined the use of an *O*-allyl ester, as the allyl group should be removable with a Pd reagent, without interfering with other functional groups present. Ester **15** could be obtained, although in low yield, by two-phase esterification of acid **11** with allyl bromide in the presence of sodium bicarbonate and Aliquat 336.[7] Unfortunately, condensation of allyl ester **15** with aldehyde **10** gave only a



Scheme 5

poor yield (20%) of the desired alcohols **16**.

Accordingly, we decided to try yet another protecting group. Esterification of acid **11** with $Me_3SiCH_2CH_2OCH_2Cl$ (SEMCl) produced ester **17**, quantitatively, and condensation with aldehyde **10** gave us the desired alcohols **18** in good yield (71%, or 81% corrected for recovered phenylseleno ester).

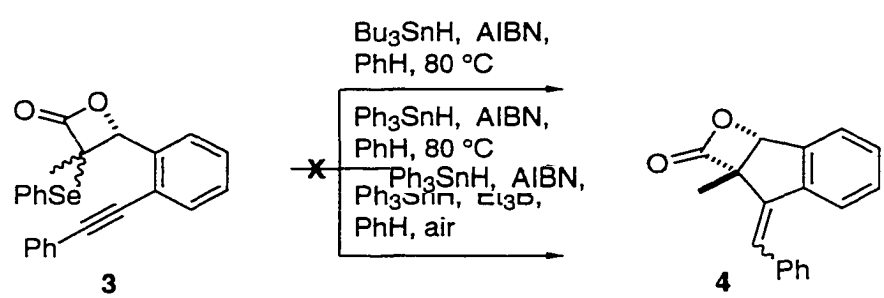


Scheme 6

Initial attempts at removing the silyl group,[8] using TBAF in DMPU were unsuccessful, but under harsher conditions (HF in MeCN),[9] the desired hydroxy acids **2** were obtained in 63% yield (Scheme 6).

With an acceptable route to the hydroxy acids in hand, our next task was to form the β-lactone. When hydroxy acids **2** were treated with phenylsulfonyl chloride in pyridine at 0 °C,[10] lactone **3** was produced in excellent yield (Scheme 6). We obtained a single lactone, even though the starting material was a mixture of stereoisomeric acids. At this point we were ready to try the key radical cyclization that would generate the quaternary center in a stereochemical sense that is controlled by the stereochemistry of the original alcohol **18**.

Slow addition of a solution of Bu_3SnH and AIBN to a refluxing solution of the potential cyclization precursor **3**, failed to give any one of the desired product. When Ph_3SnH was used, under similar conditions, decomposition of the starting material occurred. When the radical initiator was replaced by triethylborane, yet again, some starting material along with unidentified products were obtained. Attempts to



3 **4**

Scheme 7

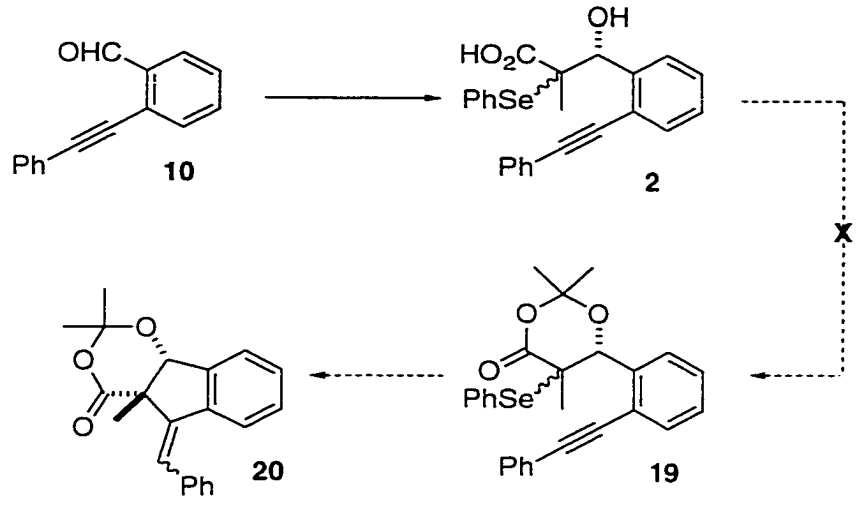
initiate the radical reaction with light (254 Å), also proved futile (Scheme 7).[11]

The outcome of these experiments was very disappointing, as an large number of radical cyclizations have been done in this laboratory, and we had no reason to expect that the present intended ring closures would present any difficulties.

At this point we felt, rightly or wrongly, that we had exhausted the possibilities using a β-lactone approach, as our substrate appeared to be unsuitable for the radical cyclization. Two features of the substrate might contribute to the failure of the radical steps. The highly strained β-lactone might decompose thermally or under the influence of a Lewis acid and, possibly, the rigidity of the system carrying the alkyne and β-lactone units might preclude adequately close approach of the carbons that must become linked.

One modification that we considered was to use a substrate such as **19**, where the four-membered lactone has been replaced by a more flexible six-membered unit (Scheme 8). The rules for ring fusion stereochemistry would still apply, so as to generate a quaternary center in the desired stereochemical sense.

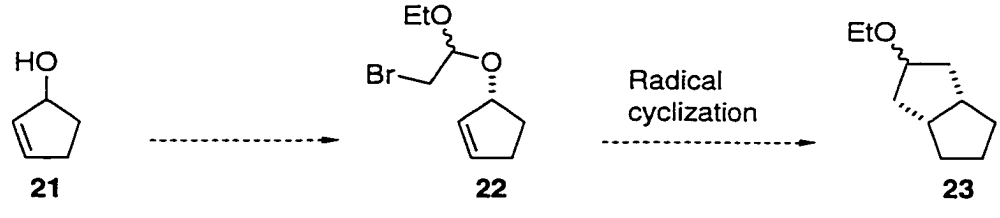
Attempts to link the carboxyl and hydroxyl of **2** failed (Scheme 8), and we subsequently found that similar difficulties had been observed by others on a related starting material.[12] In that case, however, use of bis(tri-



Scheme 8

methylsilyl)acetamide, instead of Me_3SiCl, afforded the desired cyclic material.

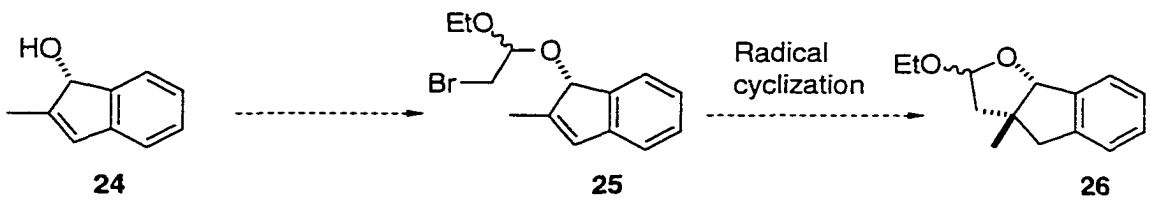
At this stage, we had recognized a different approach that looked sufficiently promising that we decided to stop our current work for the time being, in order to examine the new route, which was based on the Stork bromoacetal cyclization (Scheme 9).[13] Some years ago Stork *et al.*[13] had developed a method to synthesize compounds of type **23** by radical cyclization of bromoacetals **22**. On this basis, a



Scheme 9

substrate such as **25**, when subjected to the above methodology, should afford **26**. Again, the stereochemistry of

the newly-formed quarternary center would be controlled by the stereochemistry of the hydroxyl group in **24** (Scheme 10). The structure of **26** is such that it ought to be modifiable so as to generate the required carboxyl group.

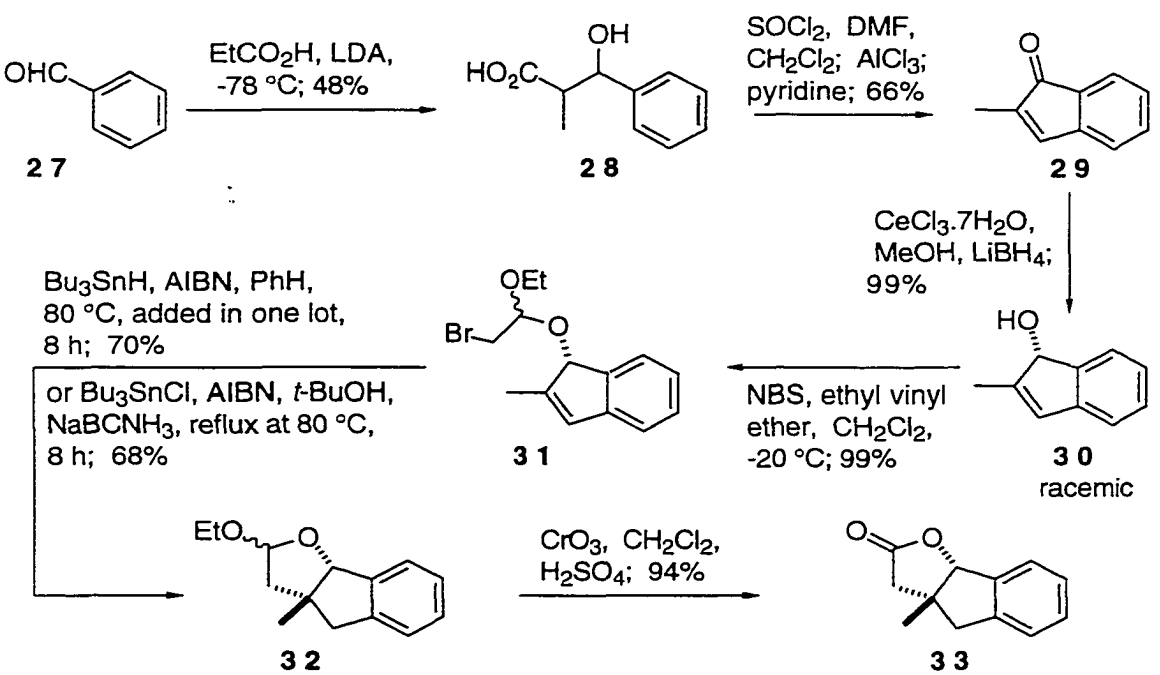


24 **25** **26**

Scheme 10

Model Studies on the Acetal Approach

2-Methylindenone (**29**) was made by a literature procedure,[14,15] starting from benzaldehyde (Scheme 11). Luche reduction of the carbonyl group gave the corresponding

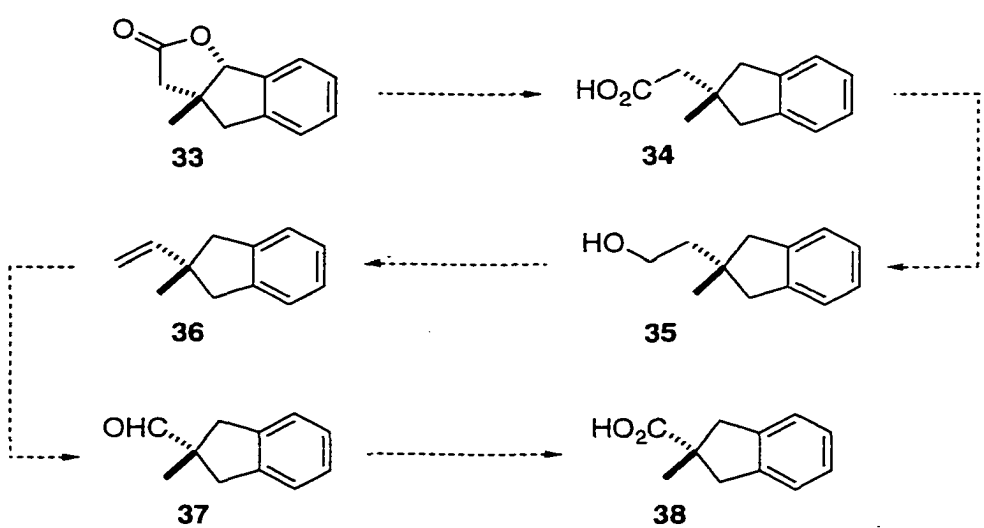


27 **28** **29** **30** racemic **31** **32** **33**

Scheme 11

indenol **30**, and this was smoothly converted into the required bromoacetals **31**.

Slow addition of a solution of Bu_3SnH and AIBN to a refluxing solution of **31** failed to give any of the desired cyclization product. Our next attempted cyclization involved the same reagents, but instead of slow addition, they were added in one lot. This modification led to the formation of a 1:4 diastereomeric mixture of the cyclic acetals **32** in 70% yield. In the hope of improving the yield, we tried the cyclization using catalytic amounts of Bu_3SnCl, AIBN and $NaBH_3CN$,[16] but the cyclized product was produced in a similar yield. As the two diastereomers of **32** were chromatographically inseparable and there was significant signal overlap in the ^1H NMR spectrum, we decided to convert the material into the corresponding lactone. Acid hydrolysis of acetals **32**, gave the corresponding lactols, and PCC oxidation



33 **34** **35** **36** **37** **38**

Scheme 12

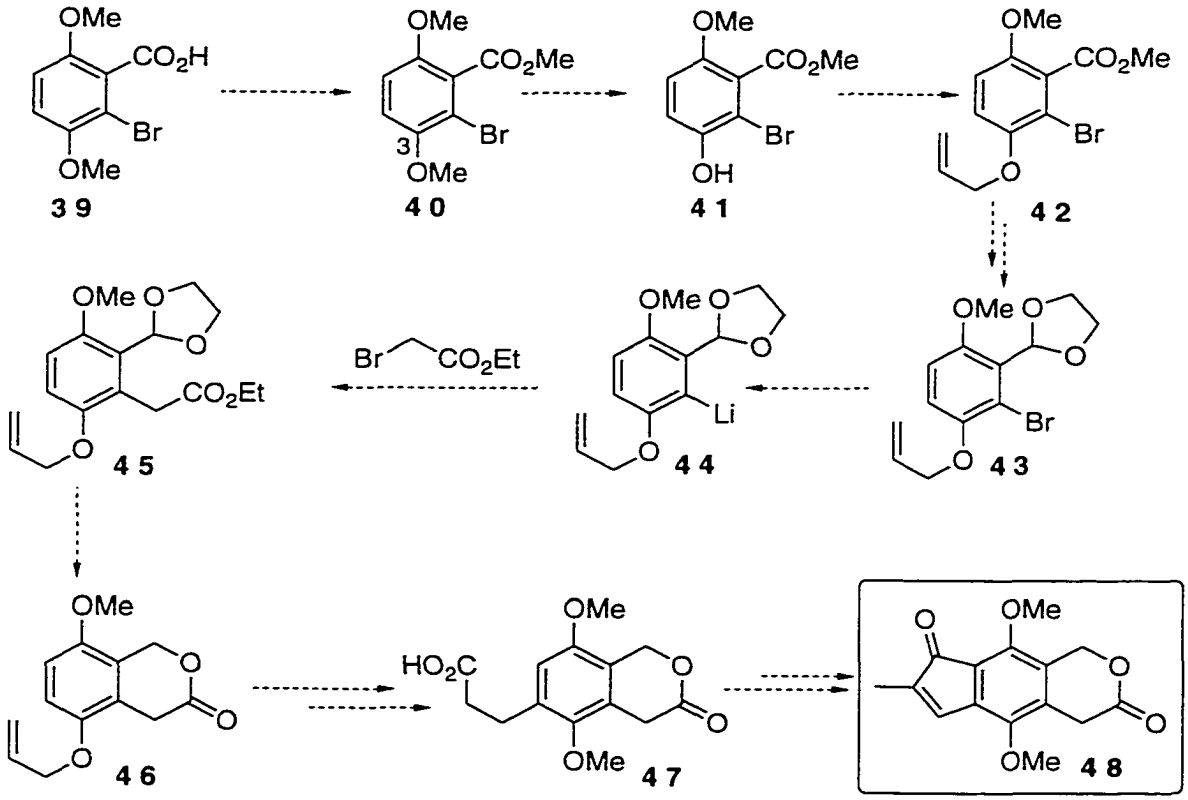
then gave the desired lactone **33**. The same transformation could also be achieved directly by treating **32** with freshly prepared Jones reagent.[16]

In principle, **33** could be degraded to a substance containing the required quarternary center by the sequence summarized in Scheme 12. We regarded the experiments of Scheme 11 as a reliable model on which to base the actual synthesis of the natural product, and we now proceeded to apply this approach to properly substituted substrates. To this end, we needed to prepare compound **38** (Scheme 13), or a synthetically equivalent material.

Synthesis of the substituted indenone system

Our initial plan (see Scheme 13) involved starting with the known bromide **39**,[17] which is available by a literature procedure from commercial 2,5-dimethoxybenzoic acid.

The bromo acid **39** was esterified (**39** → **40**). The next task was to selectively demethylate the C(3) ring oxygen so as to obtain phenol **41**. We had anticipated, of course, that this step might be difficult, as it was not clear what features of the molecule would control the selectivity of demethylation. The presence of the ester might be expected to favor removal of the C(6) *O*-methyl group, but we were not sure what role steric factors might play. We decided to try different boron-based reagents. If the demethylation was successful, the resulting phenol would then be protected as

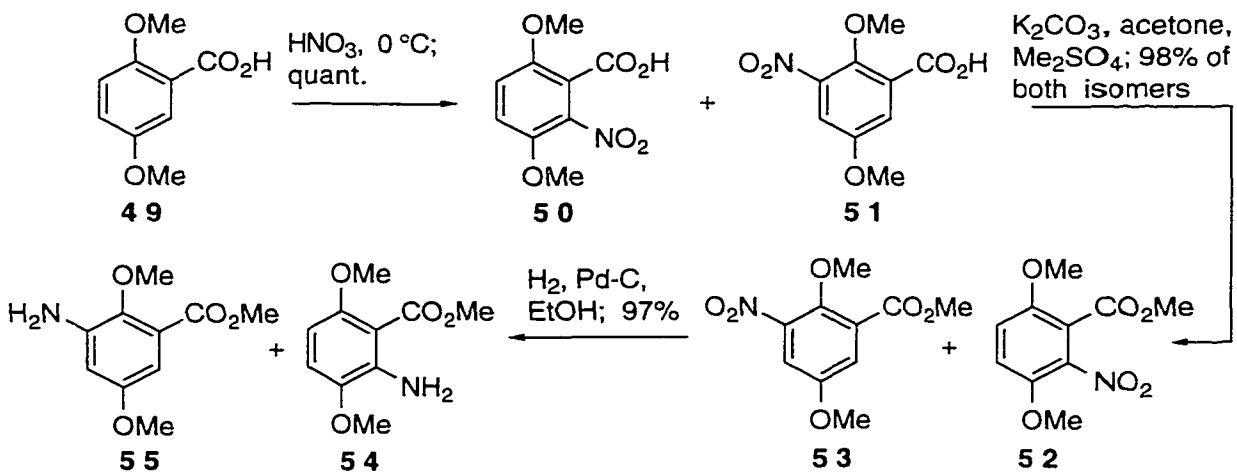


Scheme 13

an allyl ether (**41** → **42**), which would later serve the purpose of providing the extra substitution (by way of Claisen rearrangement) needed on the aromatic ring. The ester would next be reduced to the alcohol, reoxidized to the aldehyde, and protected as an acetal (**42** → **43**). Our plan then called for transmetallation of the bromide with BuLi, followed by treatment with ethyl bromoacetate, giving **45**. Deprotection of the aldehyde, followed by selective reduction, would then be expected to produce lactone **46**. We felt that Claisen rearrangement, followed by hydroboration-oxidation of the resulting olefin would give an alcohol, oxidizable to acid **47**. Finally, Friedel-Crafts acylation

should give the desired indenone **48**, which is suitably constituted for application of the radical closure sequence that we had already tested with a simple model (see Scheme 11). In connection with the proposed Friedel-Crafts reaction, we were aware that such processes can be done even on *O*-methyl ethers.[15]

The above plans were explored, as follows (Scheme 14). Nitration of 2,5-dimethoxybenzoic[18] acid gave a 5:1 mixture of **50** and **51**. Separation was not attempted at this stage, and the crude material was directly methylated to produce **52** and **53**. These esters could be completely separated, and the desired 2-nitro compound **52** was found to be the major product. Catalytic hydrogenation of **52** in ethanol gave amine **54**. When the above sequence (**49** → **54**) was carried out on a

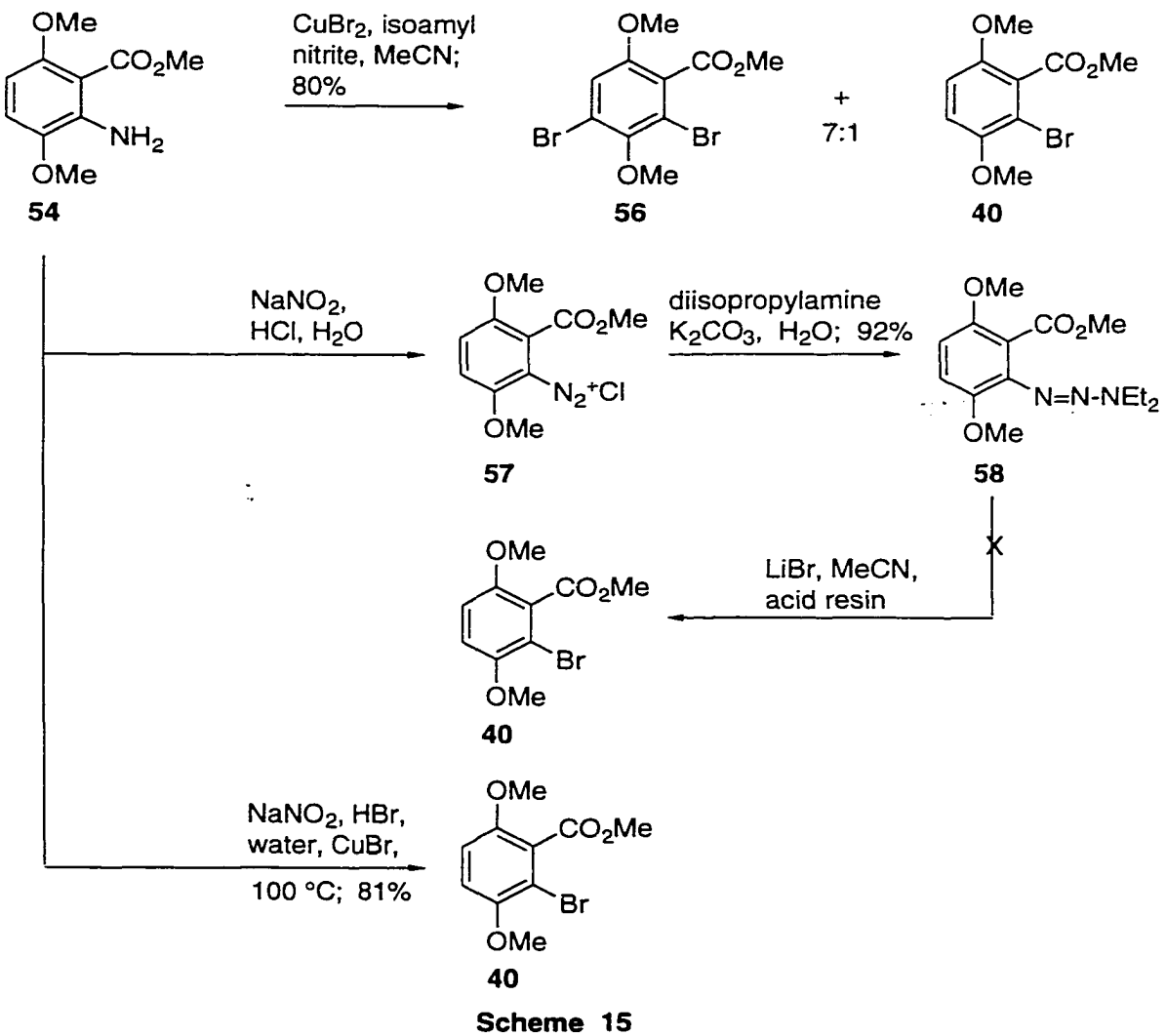


Scheme 14

large scale, the material was processed without isomer separation until the last step (formation of **54**), and at that point the required compound was isolated. This approach

allowed us to generate quite easily 5-7 g batches of the amine.

Our first attempt to diazotize the amine and convert it into bromide **40**, using $CuBr_2$ and isoamyl nitrite, gave us primarily the dibromide **56** (Scheme 15). We next tried a two-step literature[19] procedure that called for conversion of the amine into the triazo compound **58**. This intermediate was treated with LiBr in the presence of an acid resin, but none of the desired product was formed. Finally, we tried the

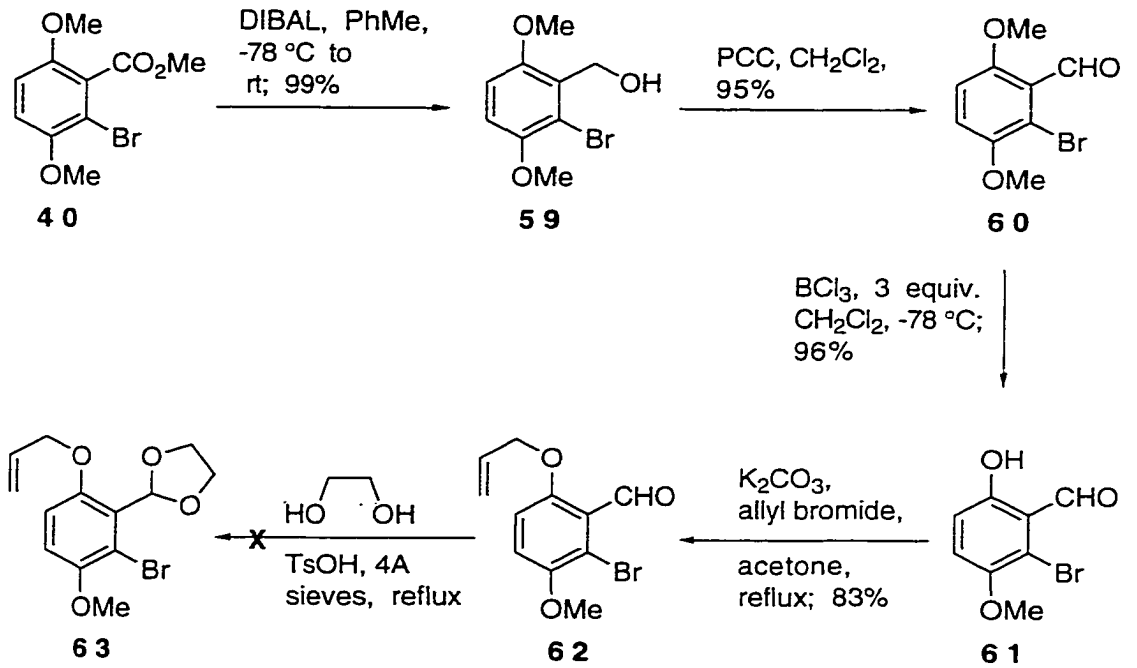


Scheme 15

classical Sandmeyer method, and were able to optimize the reaction conditions (Scheme 15). The amine was converted into the corresponding diazonium bromide, using an acidic $NaNO_2$ solution at 0 °C, and the bromide **40** was formed by heating with CuBr.

The next task was to demethylate compound **40** selectively at C(3), i.e. adjacent to the bromine. When **40** was exposed to BBr_3 (1.1 equivalent) for 5 min at -78°C none of the starting material was consumed. Increasing the temperature or the reaction time also did not lead to any reaction. When the temperature was raised to 40 °C, reaction occurred, but unfortunately, gave 42% of the doubly demethylated ester, along with some of the triply demethylated compound (2-bromo-3,6-dihydroxybenzoic acid).

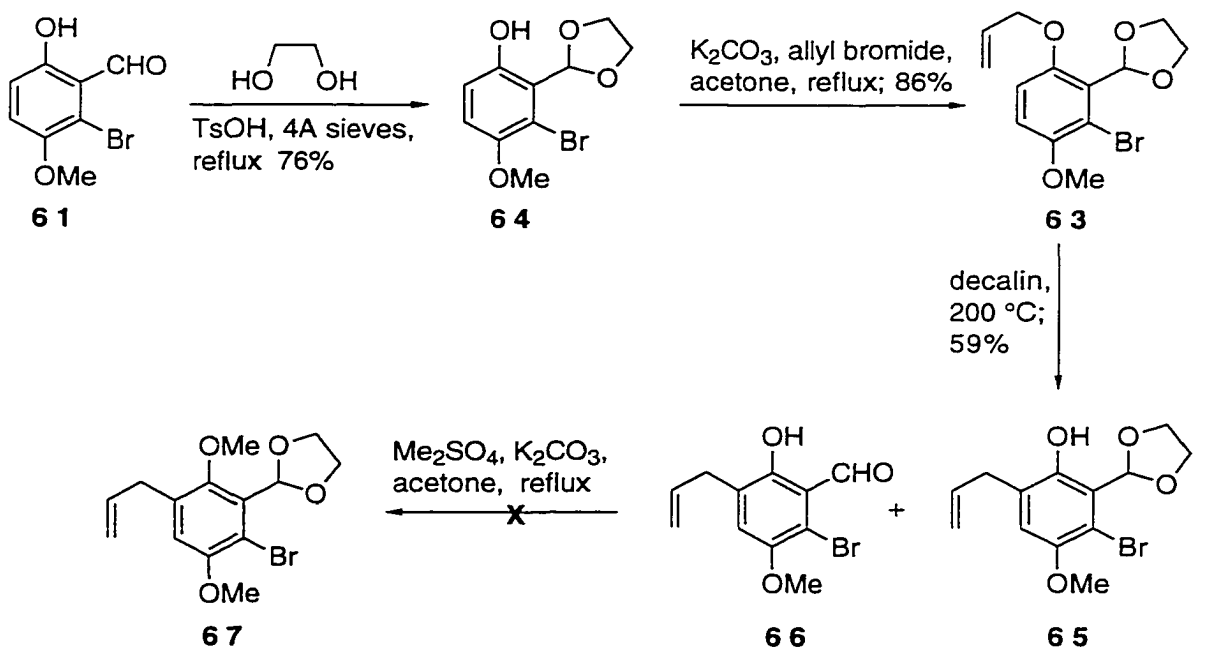
The above exploratory experiments indicated that the required selective demethylation would have to be controlled by the presence of some specific feature, and in this regard we noted that methoxy groups adjacent to an aldehyde or ketone can be removed selectively by BCl_3.[20] On the basis of this information, we converted ester **40** into the corresponding aldehyde **60**, by the standard sequence of DIBAL reduction and reoxidation (Scheme 16). Selective demethylation of the C(6) methoxy group (i.e., the one adjacent to the aldehyde) did indeed occur as anticipated, although the reaction required considerable optimization work (Scheme 16).



Scheme 16

Modified route

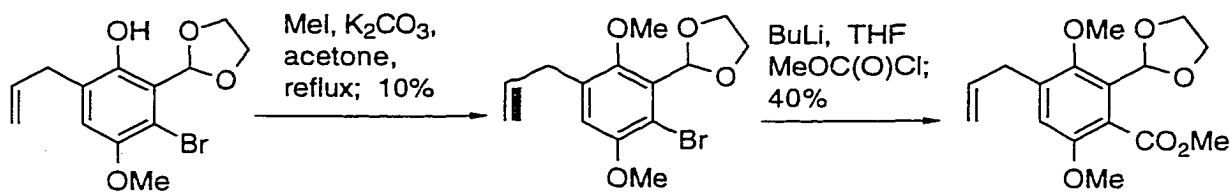
With phenol **61** in hand, we now proceeded to introduce an



Scheme 17

additional carbon substituent on the benzene ring, and for this purpose, the phenolic hydroxyl was allylated (**61** → **62**). Attempts to protect the aldehyde as its acetal **63** at this stage failed, and so we decided to carry out this transformation before the allylation.

Treatment of the hydroxy aldehyde **61** with ethylene glycol in the presence of a catalytic amount of TsOH (Scheme 17), gave acetal **64** in good yield. In exploratory experiments the derived allylated compound (**63**) was heated to a high temperature (200 °C); it underwent Claisen rearrangement to give the desired product **65**, together with some of the corresponding aldehyde **66** (Scheme 17) resulting from loss of the acetal group.

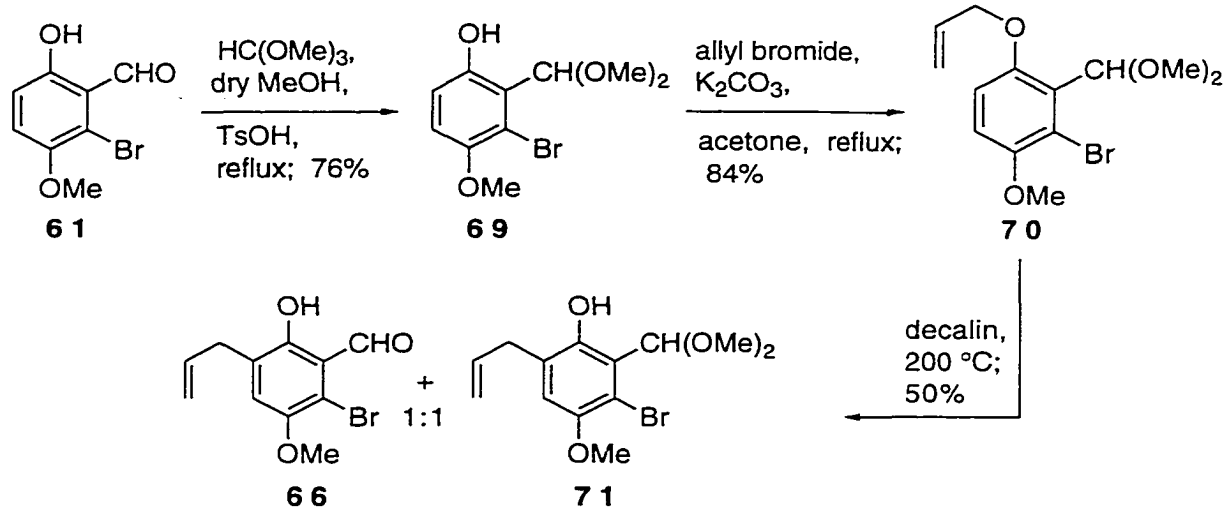


65 **67** **68**

Scheme 18

The next task was to protect the hydroxyl as a methoxy group but, unfortunately, in each attempt only a very small amount of the starting material was converted into the desired compound **67** (Scheme 18). Despite the low yield, we decided to try to replace the bromine by an ester group. Transmetallation of **67** with BuLi, followed by treatment with Mander's reagent, gave ester **68**, although in poor yield. Apart from the low yields in the methylation step, we also

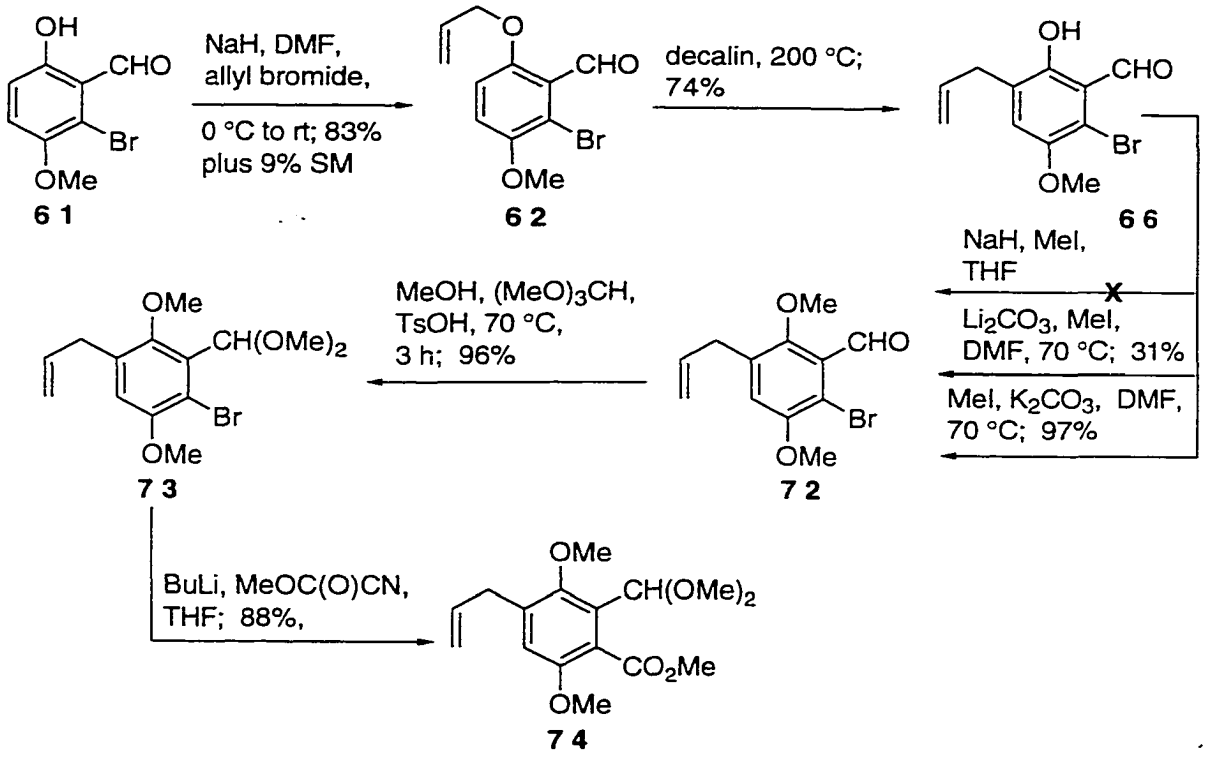
encountered solubility problems during purification of the compounds bearing the cyclic acetal unit. To circumvent these difficulties we decided to change the protecting group for the aldehyde to a dimethoxy acetal – chosen merely for convenience of preparation – and to try to find the best possible order of the three reactions involved: acetal protection, Claisen rearrangement, and methylation.



Scheme 19

Formation of the dimethyl acetal **69** (Scheme 19) was best effected by using trimethyl orthoformate in the presence of TsOH. The compound could be transformed smoothly into the allyl ether **70** in high yield, but Claisen rearrangement of **70** on a large scale produced an inseparable 1:1 mixture of the acetal **71** and aldehyde **66**. Obviously, we needed to try a different order of protection and Claisen rearrangement.

In our next attempt (Scheme 20), the hydroxy aldehyde **61**



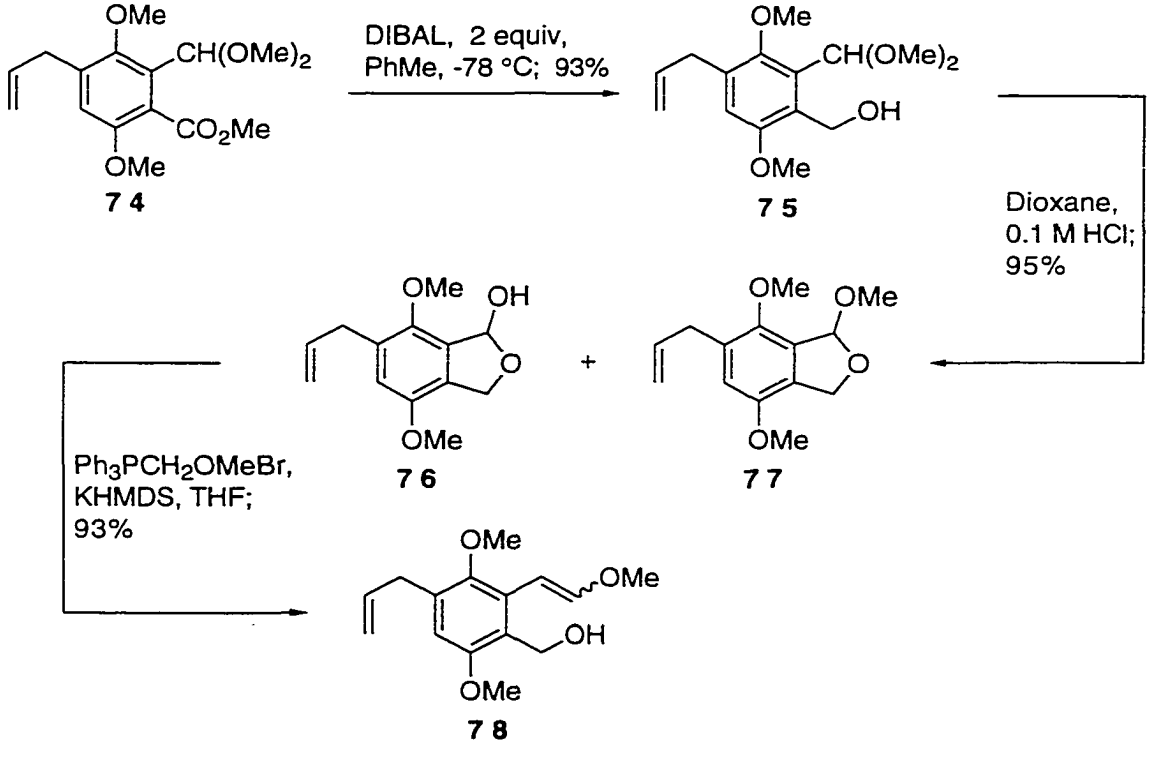
Scheme 20

was first converted into the allyl ether **62**.[21] Claisen rearrangement of this compound then gave the hydroxy aldehyde **66** in 74% yield.[22] All the Claisen rearrangements up to this point had been performed in decalin, and we now decided to try *N,N*-dimethylaniline, a commonly used solvent for Claisen rearrangements,[23] in the hope of increasing the yield. However, no significant improvement was observed; in fact the yield was actually about 10% lower in the amine solvent (Scheme 20).

Phenolic aldehyde **66** was best methylated (97%) by treatment with MeI and K_2CO_3 in DMF at 70 °C. The remaining step of protecting the aldehyde group as a dimethyl acetal (**72** → **73**) was accomplished as before, again in high yield

(96%). All our dimethoxy acetals were indeed much more soluble and easier to handle and purify than the corresponding cyclic acetals.

We could now direct our efforts to completion of the 6-membered ring characteristic of **48** (see earlier, Scheme 13), and the following simple transformations were carried out for this purpose: transmetallation of **73** with BuLi, followed by quenching of the lithiated product with MeOC(O)CN, gave ester **74** in 88% yield, and we were now ready to elaborate the side arms of puraquinonic acid.



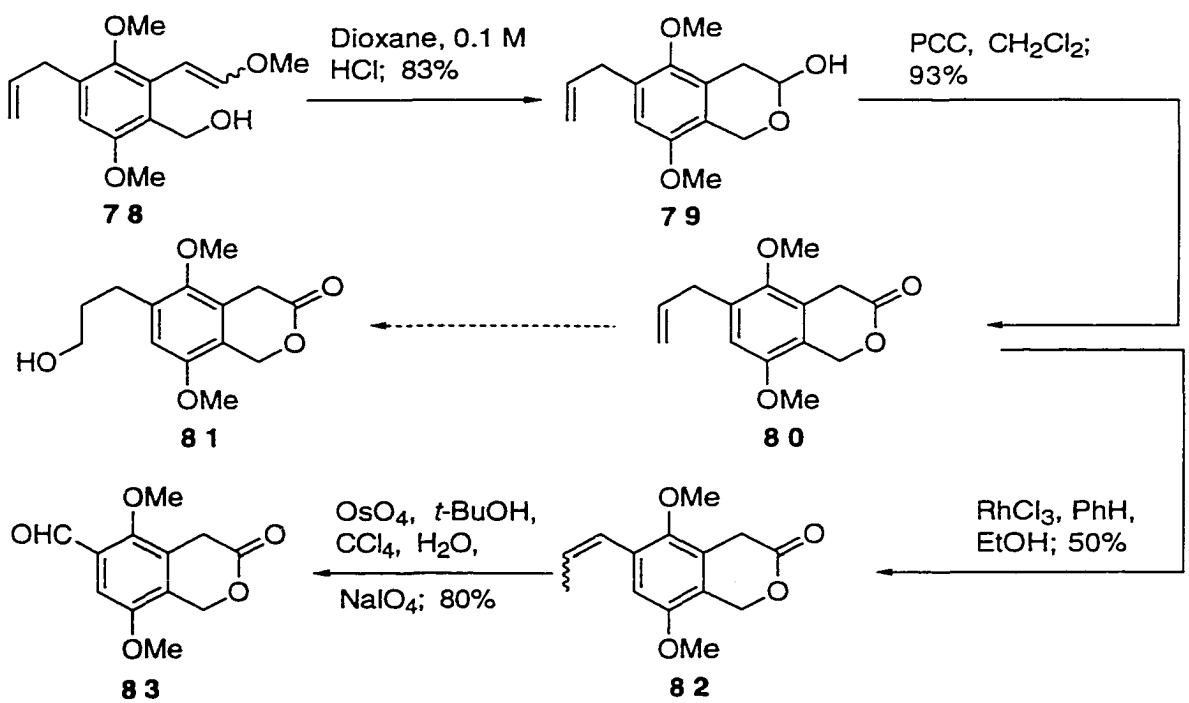
Scheme 21

Reduction of the ester with DIBAL gave alcohol **75** (Scheme 21). Attempts to remove the acetal using TFA in

aqueous chloroform resulted in isolation of acetal **77**. When **75** was stirred in acidic aqueous dioxane, the desired lactol **76** was obtained in 71% yield, together with a small amount (24%) of **77**. The latter could be recycled to obtain more of the desired lactol (Scheme 21).

Treatment of lactol **76** with the ylide generated by reaction of (methoxymethyl)triphenylphosphonium bromide and $(Me_3Si)_2NK$ gave a separable 2:1 mixture of the expected enol ethers **78**.[24] Each could be converted into the hemiacetal **79** efficiently by treatment with 0.1 N HCl in dioxane (Scheme 22). A small amount of the corresponding lactol methyl ether was also obtained.

At this stage we decided to proceed via the six-membered *lactone*, rather than the corresponding methyl *acetal*, since

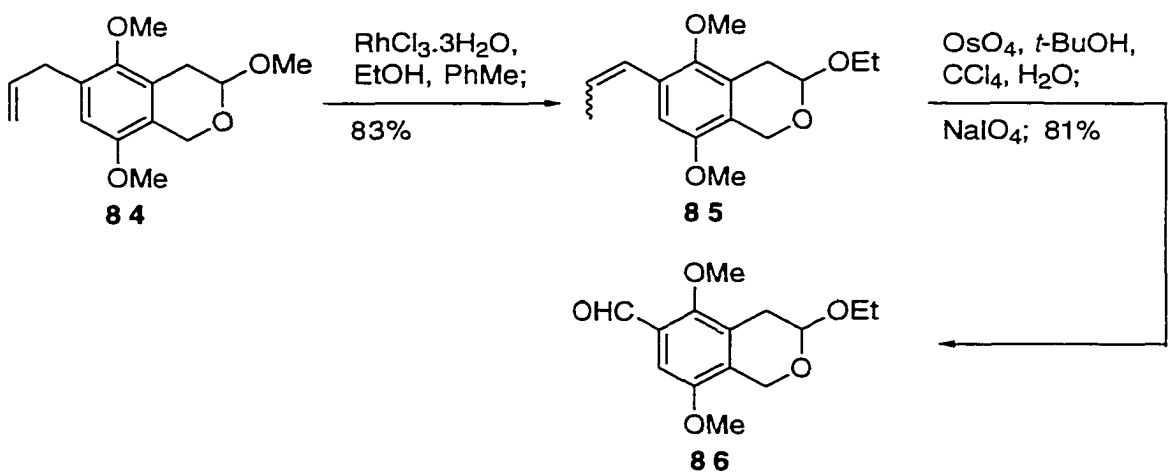


Scheme 22

the former was available to us more readily. In the event, this was an unwise decision, but it was possible to correct the error later. PCC oxidation of lactol **79** gave the lactone **80** in excellent yield. Initially, we decided that we would convert the allylic pendant of **80** into a hydroxypropyl group (see **81**) by hydroboration-oxidation, but examination of the literature revealed that the common regioselective borane reagents would also attack the lactone unit carbonyl.[25]

This difficulty could be avoided, in principle, by converting the allylic unit into an aldehyde which would then be condensed with the dilithium salt of propionic acid. To this end, the double bond in the side chain of **80** was moved into conjugation with the aromatic ring, by treatment with $RhCl_3.3H_2O$ in a PhMe-EtOH mixture (**80** → **82**) (Scheme 22). Dihydroxylation, followed by $NaIO_4$-mediated cleavage, gave aldehyde **83**.[26]

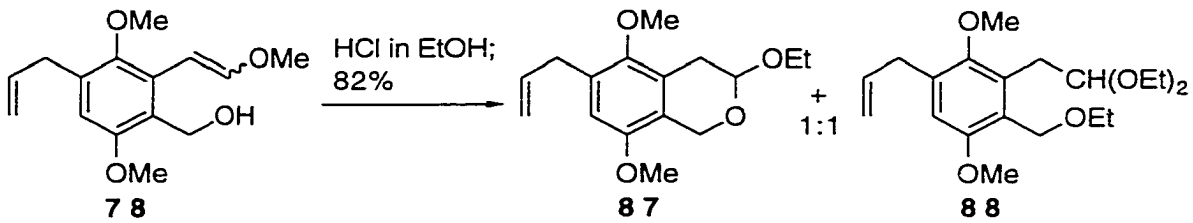
While these experiments were being carried out, we also pursued a modified route that avoided the possibility that



Scheme 23

the presence of the lactone carbonyl might make selective reaction at the aldehyde carbonyl difficult to achieve.

When **84**, obtained as a byproduct in the conversion of **78** into **79** (Scheme 22), was treated with $RhCl_3.3H_2O$ in a PhMe-EtOH mixture,[27] compounds **85** were obtained. Evidently, in addition to double bond isomerization, an alkoxy exchange with the solvent had taken place. Cleavage of the olefin with $OsO_4/NaIO_4$ gave the required aldehyde **86**.



78 **87** **88**

Scheme 24

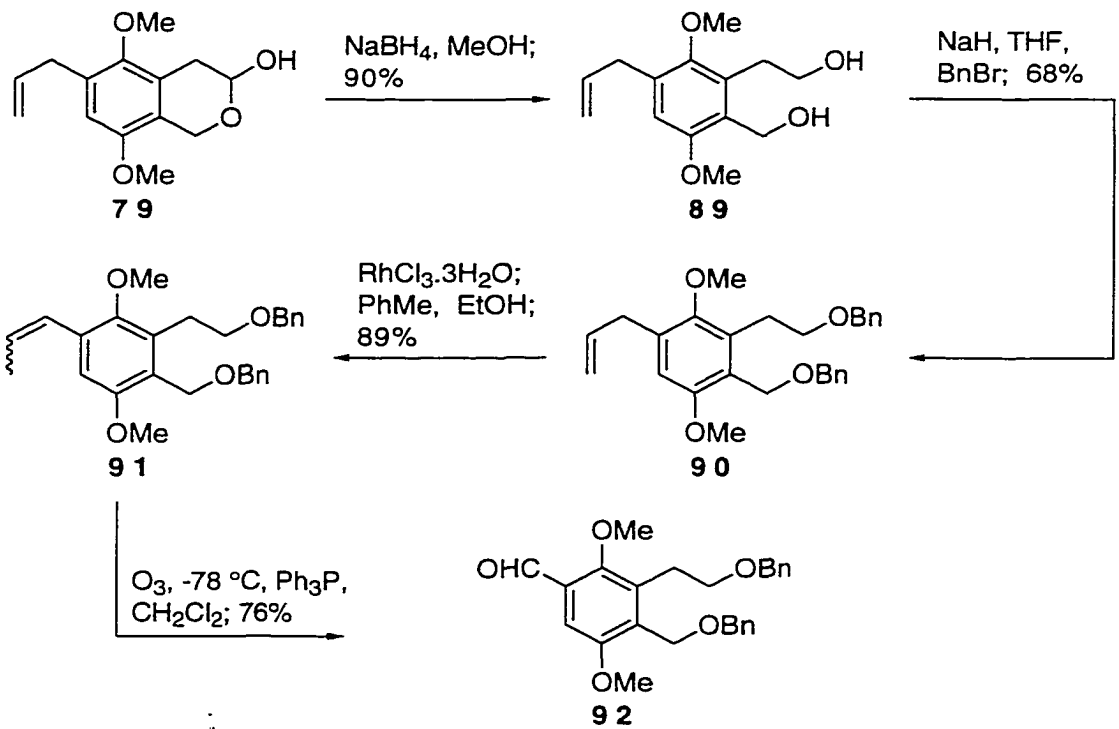
In order to obtain large amounts of **86**, or the corresponding methyl ether, we decided to treat the enol ether **78** with acid in ethanol. Unfortunately, this experiment gave a 1:1 mixture of **87** and **88** (Scheme 24), a transformation that is very easily understandable .

The bisbenzyl route

The foregoing experiments had given us extensive experience with the properties of the compound classes involved in our synthesis, and we were now in a position to modify the approach in a way which we expect will actually lead to the natural product.

Our modified route (Scheme 25) involves reduction of the

lactol (**79** → **89**) and protection of the resulting diol as a bisbenzyl ether (**89** → **90**). Conjugation of the olefin with the aromatic ring, followed by ozonolytic cleavage, would then give an aldehyde (**92**) suitable for elaboration into an indenone. These steps were easily accomplished.

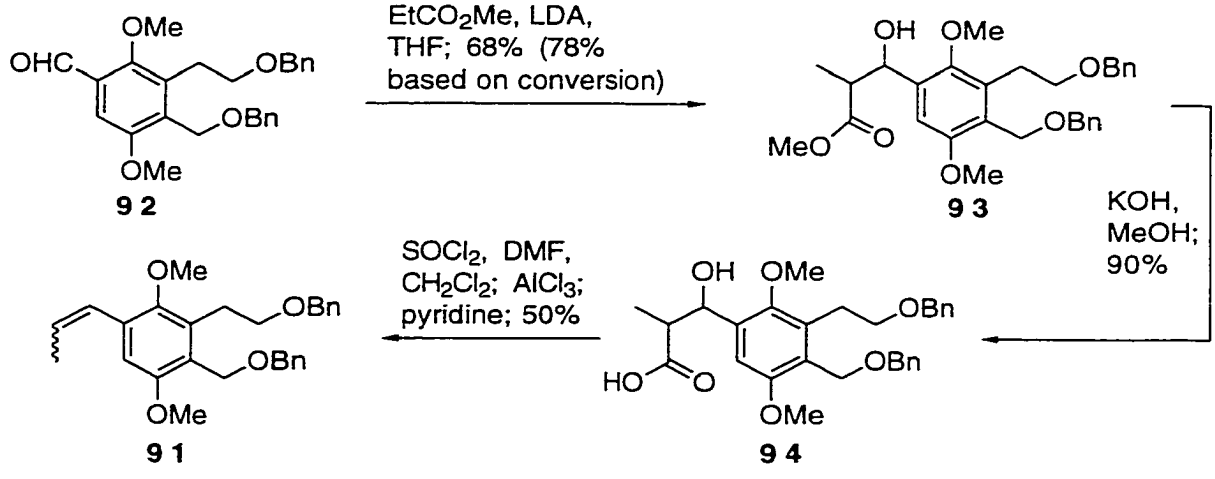


Scheme 25

Lactol **79** was readily reduced to the diol **89** in excellent yield. Protection of the diol with benzyl bromide gave the dibenzyl compound **90**, and the double bond in **90** was moved into conjugation, as before, in excellent yield. Ozonolysis then gave aldehyde **92**. Condensation of **92** with methyl propionate (Scheme 26) produced a diastereomeric mixture of alcohols **93**. Hydrolysis of the ester to the acid **94** proceeded without incident, and we were now ready to try

the crucial Friedel-Crafts acylation.

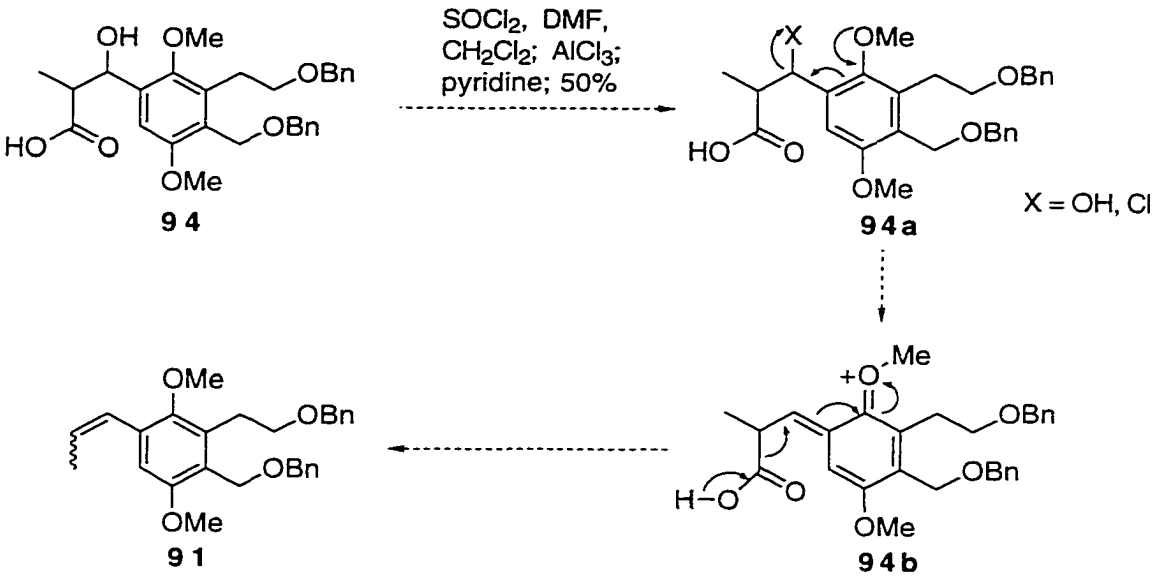
Compound **94** (which was used without full characterization) was treated under exactly the same conditions for Friedel Crafts acylation used in the model



Scheme 26

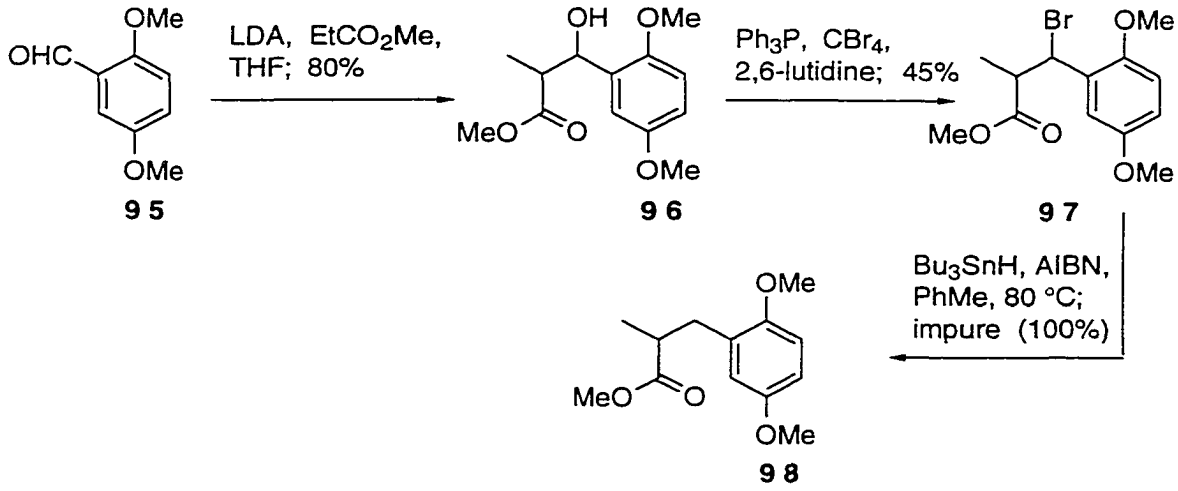
study with **28** (see Scheme 11). Unfortunately, none of the cyclized material was formed, but we isolated compound **91** (Scheme 26). Presumably, the methoxy group in **94** plays a role in this reaction. In the presence of the Lewis acid, the methoxy group β to the hydroxyl helps to expel the hydroxyl group or the corresponding chloride. This process is followed by decarboxylation and rearomatization (Scheme 27).

As we had reached an advanced stage in our synthesis, we decided to find a solution to the problem of constructing the 5-membered ring, using a model system, instead of valuable material from the main route.



Scheme 27

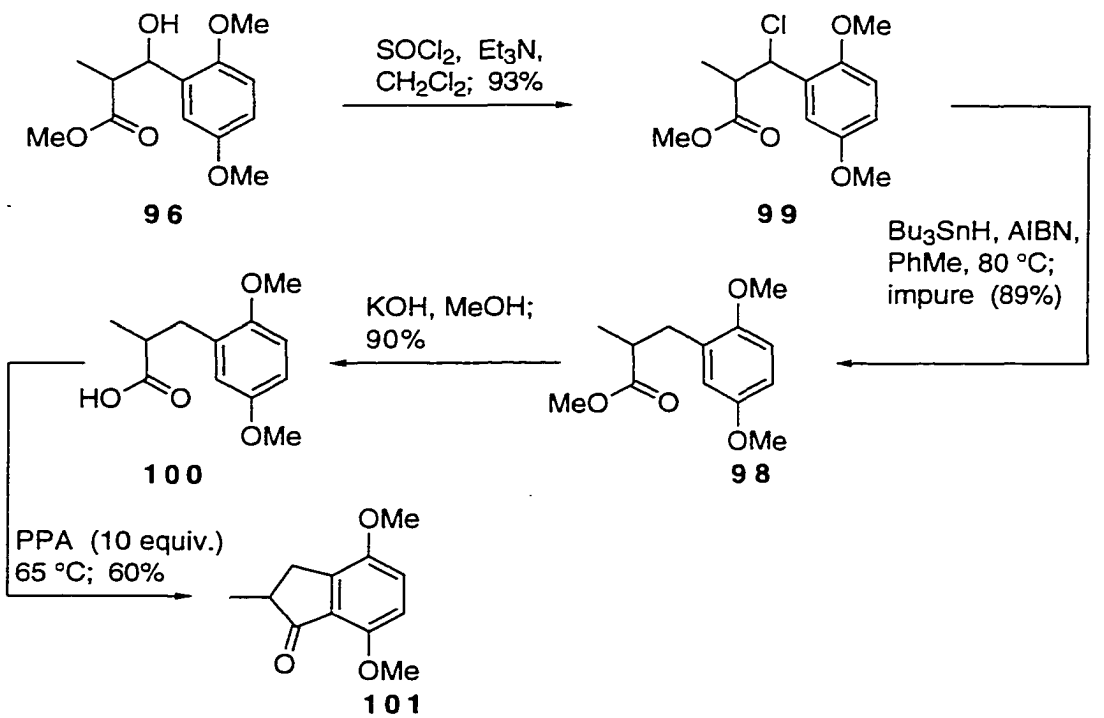
Our first approach in this effort (Scheme **28**) was to make **98**, a substrate which lacked the hydroxyl group of the main series (*cf.* **94**).



Scheme 28

Condensation of 2,5-dimethoxybenzaldehyde **95** with the lithium anion of ethyl propionate produced alcohols **96**. These could be converted easily into the bromides **97**[28] but

unfortunately, partial decomposition occurred during purification over silica gel. Stannane reduction of bromides **97** occurred readily to give the desired ester **98**. We had intended to convert **98** into the indanone **101**, but due to the instability of the bromide, we decided to make the chloro derivative instead.

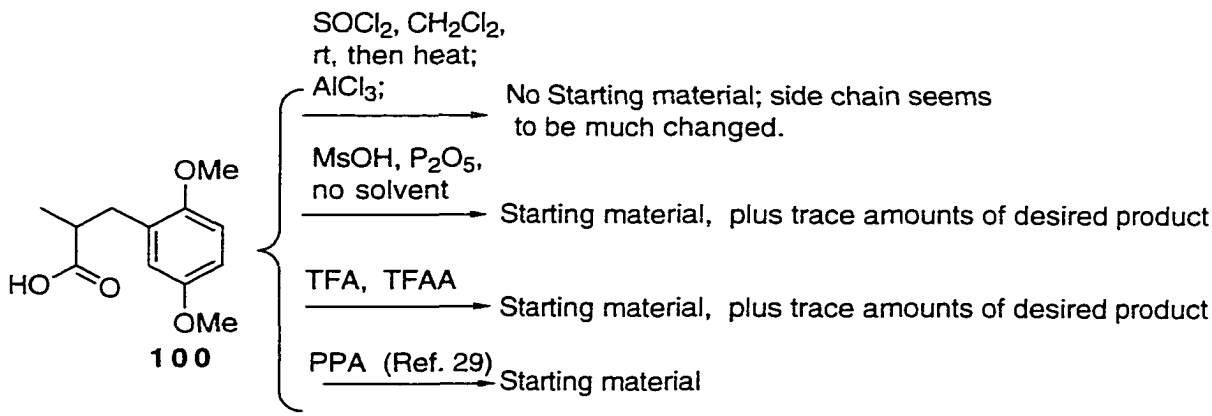


Scheme 29

Treatment of alcohol **96** with $SOCl_2$ in the presence of Et_3N gave chloride **99**, which could be isolated easily. Stannane reduction proceeded smoothly as before, to give ester **98**, and basic hydrolysis gave the acid **100**. Attempts to cyclize **100**, using polyphosphoric acid, prepared according to reference 29, failed, and we recovered only starting material. Other methods (TFA/TFAA, P_2O_5/methanesulfonic acid

or $SOCl_2/AlCl_3$) gave very small amounts of the desired product (Scheme 30).[14,15,30]

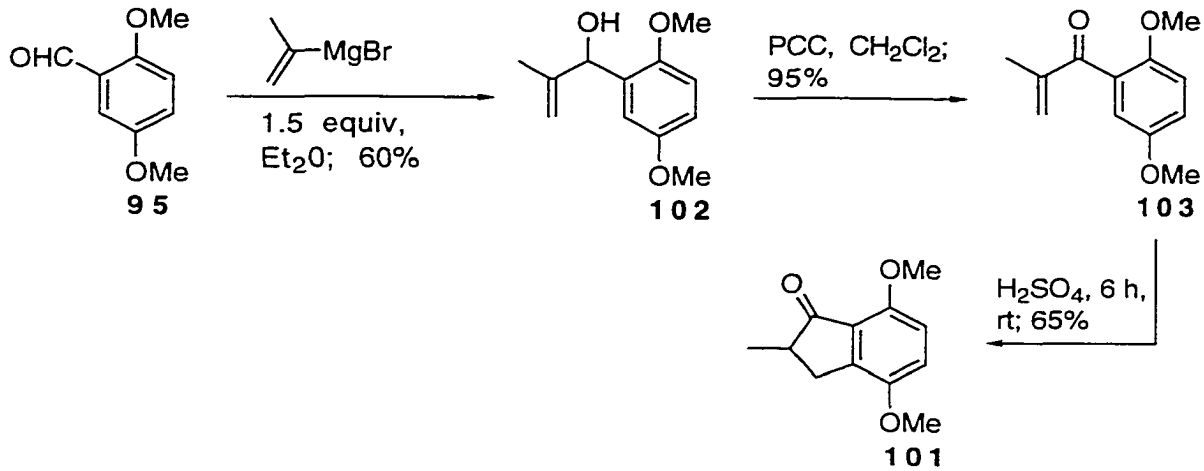
Finally, using freshly-prepared polyphosphoric acid, made according to a reference 28, and using it in large excess, gave the desired indanone **101** in 60% yield.



Scheme 30

During these latest model studies, we also considered using a Nazarov[31] reaction to construct the required 5-membered ring, and a simple model study (Scheme 31) quickly established that this was a very promising approach.

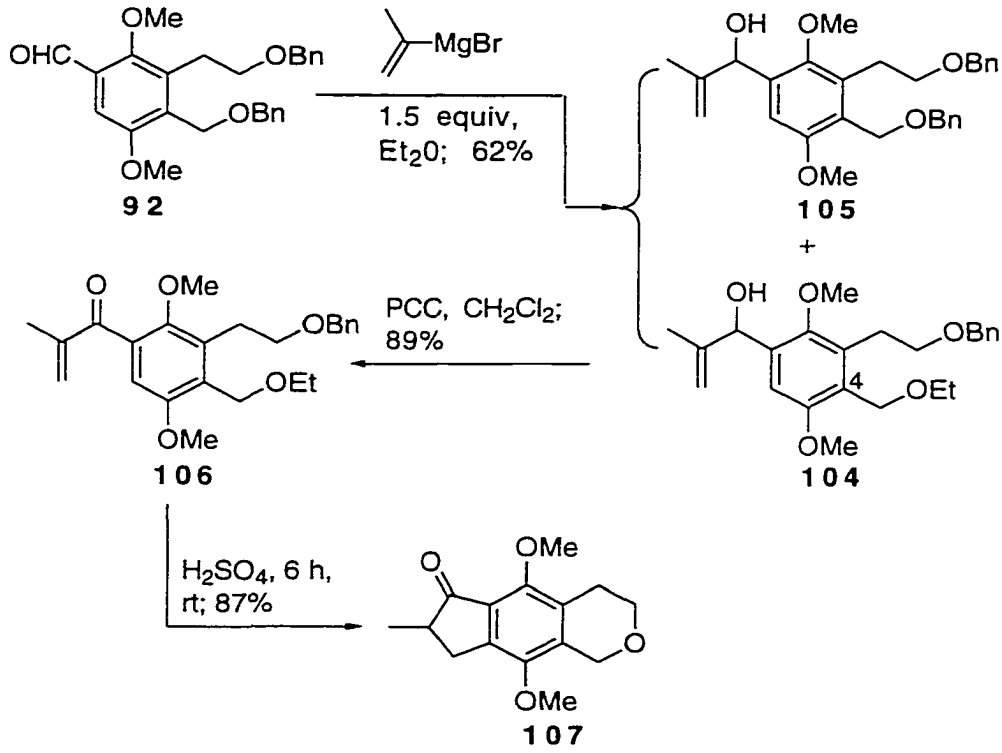
Aldehyde **95** was treated with isopropenylmagnesium bromide to obtain alcohol **102**, which was readily oxidized to ketone **103**. Treatment of the ketone with fuming $SnCl_4$ failed to produce any of the desired indanone **103**. However, when **103** was stirred with concentrated sulfuric acid for 1 day at room temperature, it underwent Nazarov cyclization to give **101** in 65% yield. It is known[31] that Nazarov cyclizations proceed more readily when the aromatic ring is highly substituted. Taking this factor into account leads us to



Scheme 31

believe that the most efficient route to our required indanone system will indeed be the use of an acid-mediated Nazarov cyclization.

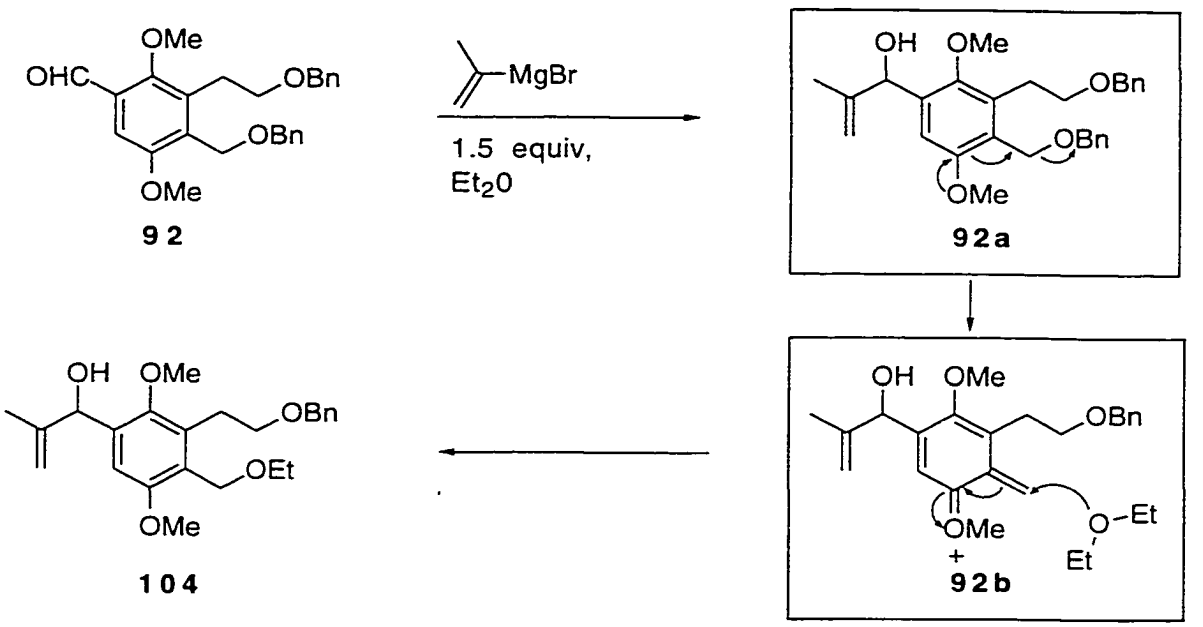
Grignard reaction of aldehyde **95** (Scheme 32) with isopropenylmagnesium bromide in ether gave a chromatographically separable mixture of two compounds. The major product (44%) was found to be **104**, where one of the benzyl groups had been replaced by an ethyl group. The minor product (18%) was the dibenzyl compound **105**. The major product (**104**) is presumably formed by expulsion of the OBn group from the carbon chain at C(4) by the oxygen lone pair on the adjacent methoxy group. The resulting species is then attacked by the solvent (Et_2O), followed by rearomatization (Scheme 33). It might be possible to vary the ratio of the products by adjusting the experimental conditions, but we have not tried this.



Scheme 32

Although in principle, either of the alcohols **104** or **105** could be processed further, we chose to continue our synthesis using the major product. PCC oxidation of **104** gave aldehyde **106**. When this aldehyde was stirred with concentrated sulfuric acid, not only did the Nazarov cyclization occur at a higher rate than in our model compound **103**, but a pyran ring was also generated. Formation of the pyran ring probably occurs via a process analogous to that outlined in Scheme 33 for an intermolecular reaction.

The unexpected formation of the pyran system does not alter the synthetic plan in any way, and further work in the group is aimed at converting **107** into puraquinonic acid along

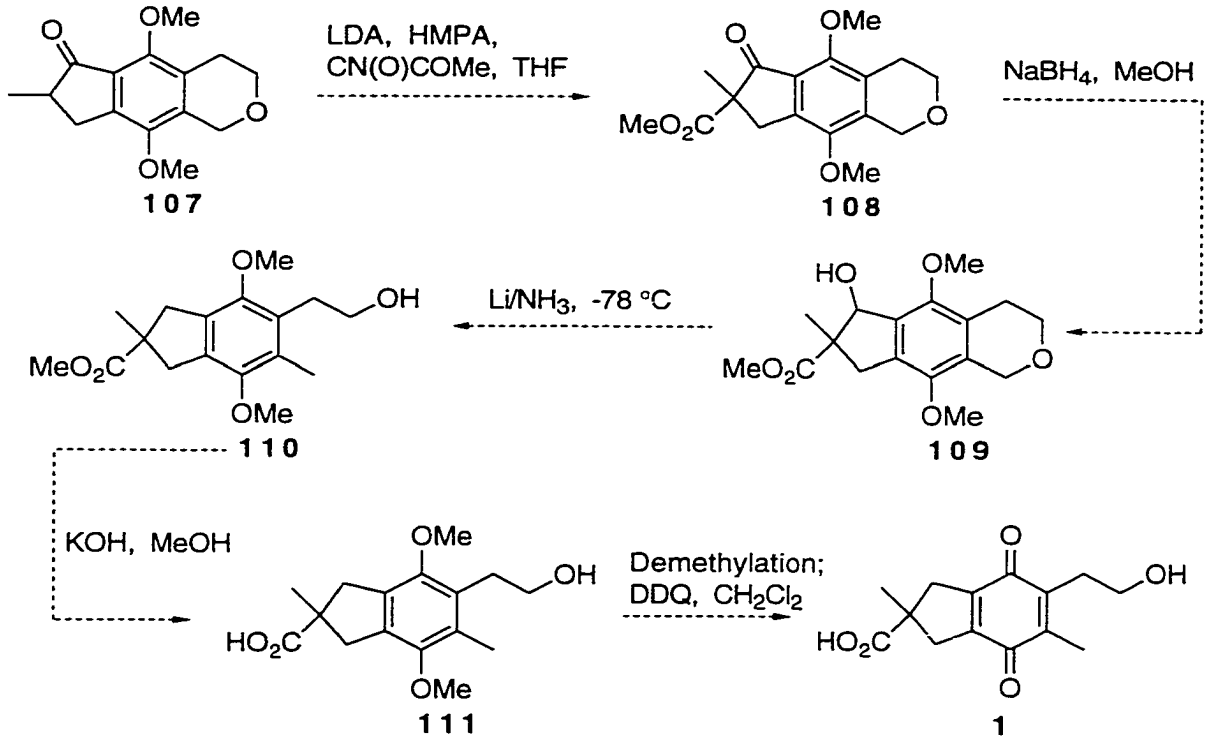


Scheme 33

the lines summarized in Scheme 34. This sequence will afford *racemic* puraquinonic acid, but we expect that intermediate **107** can be diverted to optically pure material by desaturation and asymmetric reduction of the ketone carbonyl. At that point, application of the procedure shown in Scheme 11 will generate the quaternary center, and the last steps of the synthesis will then require degradation of the lactol ether along the lines of Scheme 12.

Conclusion

As described above, we have developed methods, using model compounds related to puraquinonic acid, for constructing a quaternary carbon, and for making appropriate indanones. We expect that the methods are directly applicable to the main series leading to optically active



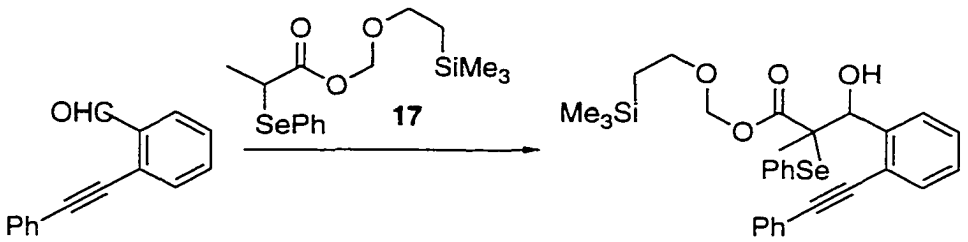
Scheme 34

puraquinonic acid, and work is currently under way in this laboratory to finish the synthesis in both the racemic and optically active series. For generation of optically pure material, a method will be needed for asymmetric reduction of ketone **107**, so that the approach of Scheme 11 can be applied. A number of reagents for asymmetric ketone reduction are available,[32] but other ways of constructing the derived optically pure alcohol are also being considered in the group.

Experimental

General Procedures. The same general procedures were used as described in part I of this thesis.

[2-(Trimethylsilyl)ethoxy]methyl 3-hydroxy-2-methyl-3-[2-(phenylethynyl)phenyl]-2-(phenylseleno)-propanoate (18).



10 **18**

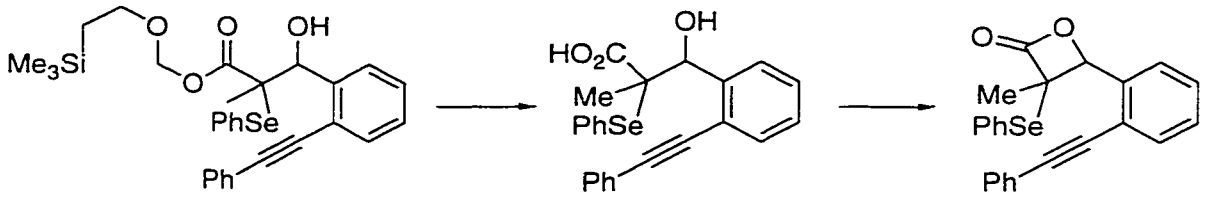
Ester **17** was generated in situ, as follows:

Acid **11** (400.0 mg, 1.721 mmol) was dissolved in dry THF (8 mL) and the mixture was stirred and cooled (0 °C). SEMCl (574 mg, 0.61 mL, 3.44 mmol) was added dropwise over 5 min, and the resulting white slurry was stirred for 3 h at 0 °C. The mixture was diluted with water (10 mL) and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 15:85 EtOAc-hexane, gave ester **17** (614.5 mg, 99%) as a pale yellow oil, which was used directly.

BuLi (2.5 M in hexanes, 0.8 mL, 1.9 mmol) was added

dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.26 mL, 1.87 mmol) in THF (5 mL). After 15 min, ester **17** (614.5 mg, 1.706) was added dropwise, and stirring was continued at -78 °C for 30 min. The resulting enolate solution was taken up into a syringe and added dropwise to a stirred room temperature solution of aldehyde **10** (386.6 mg, 1.877 mmol) in dry THF (1 mL). The mixture was stirred for 30 min, diluted with water (10 mL), and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 27 cm), using 1:4 EtOAc-hexane, gave a separable mixture (1:5) of alcohols **18** (689.5 mg, 71%, 81% corrected for recovered starting material) as a colorless oil. The major isomer had: FTIR (CH_2Cl_2 cast) 3475, 1727 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.02 (s, 9 H), 0.9-1.0 (m, 2 H), 1.4 (s, 3 H), 3.62-3.70 (m, 2 H), 4.18 (d, J = 6.7 Hz, 1 H), 5.32 (AB q, $\Delta\nu_{AB}$ = 41.5 Hz, J = 6.0 Hz, 2 H), 5.72 (d, J = 6.5 Hz, 1 H), 7.22-7.62 (m, 14 H); ^{13}C NMR (CD_2Cl_2, 75.3 MHz) δ -1.4 (q'), 18.3 (s'), 20.2 (q'), 56.9 (t'), 68.5 (t'), 75.7 (d'), 88.2 (s'), 90.4 (t'), 94.9 (s'), 123.3 (s'), 123.6 (s'), 126.7 (s'), 127.6 (d'), 128.3 (d'), 128.8 (d'), 128.9 (d'), 129.2 (d'), 129.9 (d'), 131.8 (d'), 132.4 (d'), 138.7 (d'), 141.7 (s'), 173.5 (s'); exact mass *m/z* calcd for $C_{30}H_{34}O_4Si^{80}Se$ 566.13916, found 566.13831.

3-Methyl-4-[2-(phenylethynyl)phenyl]-3-(phenylseleno)oxetan-2-one (3).



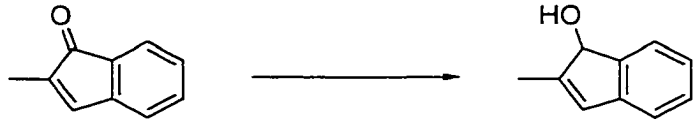
18 **2** **3**

HF (48% in H_2O, 0.5 mL) was diluted with MeCN (3 mL) and cooled (-20 °C). An aliquot (0.54 mL, 15% HF in MeCN-H_2O) of the solution was added dropwise to a stirred and cooled (-20 °C) solution of esters **18** (118.2 mg, 0.209 mmol) in MeCN (1 mL). The reaction was followed by TLC (silica, 1:1 EtOAc-hexane) and, after 2 h at -10 °C, since much of the starting material remained unreacted, an additional portion of HF (1 mL, 15% HF in MeCN-H_2O) was added, and the cooling bath was removed. Stirring was continued for an additional 1 h, by which time most of the starting material had been consumed. The mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), and the organic phase was washed with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to obtain acids **2** (57.4 mg, 63%) and recovered **18** (9.5 mg, 8%).

$PhSO_2Cl$ (0.07 mL, 0.58 mmol) was added dropwise to a stirred and cooled (-5 °C) solution of hydroxy acid **2** (83.3 mg, 0.19 mmol) in pyridine (2.5 mL). The brownish yellow

mixture was stirred at 0 °C for 18 h, diluted with water (5 mL), and extracted with Et_2O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:5 EtOAc-hexane, gave **3** (67.3 mg, 84%) as a yellow foam: FTIR (CH_2Cl_2 cast) 1829 cm^{-1}; 1H NMR (200 MHz) δ 1.31 (s, 3 H), 5.91 (s, 1 H), 7.25-7.51 (m, 9 H), 7.52-85 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 17.9 (q'), 59.8 (s'), 82.1 (d'), 88.3 (s'), 97.2 (s'), 122.8 (s'), 124.7 (s'), 127.0 (d'), 127.5 (s'), 130.5 (d'), 130.8 (d'), 131.3 (d'), 131.8 (d'), 133.8 (d'), 134.7 (d'), 138.7 (s'), 139.5 (d'), 173.3 (s'); exact mass *m/z* calcd for $C_{24}H_{18}O_2{}^{80}Se$ 418.04721, found 418.04776.

2-Methylinden-1-ol (30).



29 **30**

$CeCl_3.7H_2O$ (310.3 mg, 0.833 mmol) was added to a stirred and cooled (0 °C) solution of 2-methylindenone (100 mg, 0.69 mmol) in MeOH (8 mL). Stirring was continued for 15 min, and $LiBH_4$ (2 M in THF, 0.42 mL, 0.84 mmol) was added dropwise over 5 min. The cold bath was left in place, and stirring was continued for 1 h. Water (1 mL) was added and the

resultant slurry was filtered through a pad (1 x 2 cm) of Celite and washed with Et_2O (25 mL). The filtrate was concentrated (to *ca* 2 mL) and the resultant white suspension was extracted with Et_2O (5 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was redissolved in CH_2Cl_2 (2 mL) and purified by flash chromatography over silica gel (1 x 12 cm), using 1:9 EtOAc-hexane, to give **30** (102.9 mg, 99%) as a pure (^1H NMR, 300 MHz), white solid: mp 52.5 °C; FTIR (CH_2Cl_2 cast) 3031, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.83 (m, 1 H), 4.82 (d, J = 9.2 Hz, 3 H), 6.45 (s, 1 H), 7.11 (m, 2 H), 7.22 (m, 1 H), 7.41 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 75.3 MHz) δ 13.8 (q'), 79.2 (d'), 120.4 (d'), 123.5 (d'), 125.1 (d'), 127.0 (d'), 128.7 (d'), 143.5 (s'), 145.9 (s'), 149.1 (s'); exact mass *m/z* calcd for $C_{10}H_{10}O$ 146.07317, found 146.07309.

1-(2-Bromo-1-ethoxyethoxy)-2-methylindene (31).

30 **31**

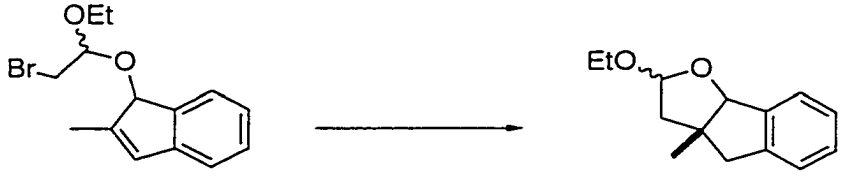
Alcohol **30** (100.0 mg, 0.681 mmol) was dissolved in CH_2Cl_2 (3.5 mL) and cooled (-20 °C) with stirring. In another flask a homogenous mixture of *N*-bromosuccinimide (187.9 mg, 1.055 mmol) and vinyl ethyl ether (88.4 mg, 0.12 mL, 1.23

mmol) in CH_2Cl_2 (8 mL) was prepared under Ar, taken up into a foil-wrapped syringe, and added dropwise over 8 min to the previous solution. All the flasks and syringes where protected from light in the last step. Stirring at -20 °C was continued for 3 h. At this point significant amounts (*ca* 30%) of the starting material remained. Another portion of *N*-bromosuccinimide (187.9 mg, 1.055 mmol) and ethyl vinyl ether (88.4 mg, 0.12 mL, 1.23 mmol) in CH_2Cl_2 (8 mL) was added, and stirring was continued for 30 min at -20 °C (TLC control, silica, 1:9 EtOAc-hexane).

The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with 10% aqueous $Na_2S_2O_3$ (10 mL) and water (10 mL), dried ($MgSO_4$), and evaporated. The residue was redissolved in CH_2Cl_2 (2 mL) and purified by flash chromatography over silica gel (2 x 22 cm), using 1:9 EtOAc-hexane, to give **31** (199.3 mg, 99%) as a colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05-1.21 (m, 3 H), 2.02-2.12 (m, 3 H), 3.26-3.41 (m, 2 H), 3.44-3.78 (m, 2 H), 4.70 (t, J = 5.2 Hz, 1 H), 4.82-5.0 (m, 1 H), 6.40 (d of broad m, J = 20 Hz, 1 H), 7.05-7.18 (m, 2 H), 7.21-7.28 (m, 1 H), 7.42-7.51 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.5 (q'), 14.6 (q'), 15.3 (q'), 15.4 (q'), 32.4 (t'), 33.0 (t'), 62.6 (t'), 63.4 (t'), 83.0 (d'), 84.0 (d'), 99.9 (d'), 101.1 (d'), 101.5 (d'), 120.4 (d'), 120.6 (d'), 124.3 (d'), 124.6 (d'), 125.0 (d'), 127.8 (d'), 128.8 (d'), 128.9 (d'), 142.7 (s'), 143.5 (s'), 143.8 (s'), 144.0 (s'), 146.1 (s'), 147.5 (s'); exact mass *m/z* calcd for $C_{14}H_{17}{}^{79}BrO_2$ 296.04120, found

296.04026.

***Cis*-2-Ethoxy-3,3a,4,8b-tetrahydro-2*H*-3a-methyl-indeno-[1,2-b]furan (32).**



31 **32**

Procedure A

Bromoacetal **31** (58.7 mg, 0.20 mmol), AIBN (3.3 mg) and Bu_3SnH (66.4 mg, 0.06 mL, 0.23 mmol) were dissolved in dry PhH (10 mL) and the reaction flask was lowered into a preheated oil bath (85 °C). Heating with stirring was continued until all the starting material was consumed (*ca* 8 h, TLC control, silica, 1:9 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 12 cm), using (1:9 EtOAc-hexane), gave **32** (30.7 mg, 70%) as a colorless oil. For characterization data, see following experiment.

Procedure B

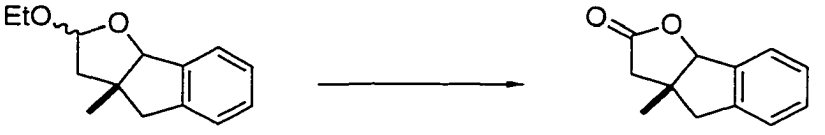
Bromoacetal **31** (293.4 mg, 1.000 mmol), AIBN (16.0 mg, 0.01 mmol), $NaBH_3CN$ (126.0 mg, 2.000 mmol) and Bu_3SnCl (0.03 mL, 0.10 mmol) were dissolved in *tert*-butyl alcohol (5.0 mL). The mixture was refluxed with stirring under nitrogen for 7

h. Then 3% aqueous NH_4OH was added and the solvent was evaporated. The residue was extracted with CH_2Cl_2 (3 x 3 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was redissolved in CH_2Cl_2 (0.5 mL) and purified by flash chromatography over silica gel (1 x 12 cm), using 1:9 EtOAc-hexane, to give **32** (148.4 mg, 68%) as a pure (^1H NMR, 360 MHz), colorless oil which was a 1:4 mixture of diastereomers. The minor diastereomer had: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.78 (t, J = 9.2 Hz, 3 H), 1.38 (s, 3 H), 2.01-2.15 (m, 2 H), 2.80 (d, J = 16.2 Hz, 1 H), 3.05 (d, J = 16.2 Hz, 1 H), 3.43-3.51 (m, 1 H), 3.80-3.89 (m, 1 H), 5.12 (s, 1 H), 5.18-5.20 (m, 1 H), 7.18-7.42 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 15.4 (q'), 26.0 (d'), 46.3 (t'), 48.0 (t'), 48.2 (s'), 48.8 (s'), 63.0 (t'), 93.0 (d'), 105.3 (d'), 125.2 (d'), 125.7 (d'), 127.0 (d'), 142.2 (s'), 142.5 (s'); exact mass (HR electrospray) m/z calcd for $C_{14}H_{18}NaO_2$ (M + Na) 241.12045, found 241.12014.

The major diastereomer had: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.21 (t, J = 9.2 Hz, 3 H), 1.41 (s, 3 H), 2.01-2.15 (m, 2 H), 2.81 (d, J = 21.6 Hz, 1 H), 3.39 (d, J = 21.6 Hz, 1 H), 3.16-3.20 (m, 1 H), 3.29-3.34 (m, 1 H), 5.08 (s, 1 H), 5.26 (m, 1 H), 7.18-7.42 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.6 (q'), 27.3 (d'), 46.5 (t'), 48.0 (t'), 48.2 (s'), 61.7 (s'), 93.0 (d'), 105.2 (d'), 124.8 (d'), 125.5 (d'), 126.5 (d'), 128.3 (d'), 128.7 (d'), 143.0 (s'), 143.1 (s'); exact mass (HR electrospray)

m/z calcd for $C_{14}H_{18}NaO_2$ (M + Na) 241.12045, found 241.12014.

***Cis*-3,3a,4,8b-Tetrahydro-2*H*-3a-methylindeno[1,2-b]furan-2-one (33).**



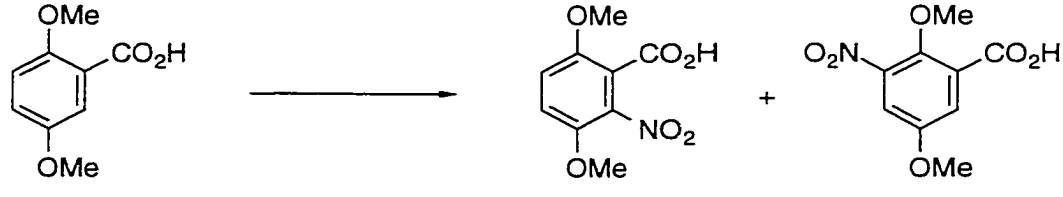
32 **33**

Ethers **32** (133.3 mg, 0.600 mmol) were dissolved in dry THF (2 mL), and AcOH-H_2O (10 mL, 2:8) was added dropwise to the mixture. Stirring was continued for 12 h, by which time a small amount of the starting material remained (TLC control, silica, 1:1 EtOAc-hexane). The mixture was warmed at 50 °C for 1 h, cooled to room temperature, and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 22 cm), using 15:85 EtOAc-hexane, gave the corresponding lactols (111.8 mg, 98%) as a white solid. The material was used directly in the next step.

A mixture of PCC (115.6 mg, 0.536 mmol) and powdered 4 Å molecular sieves (40.0 mg) was added to a stirred solution of lactol **32** (34.0 mg, 0.18 mmol) in dry CH_2Cl_2 (2.5 mL). Stirring was continued for 2 h, by which time oxidation was complete (TLC control, silica, 2:3 EtOAc-hexane). The mixture was applied directly to a column (1 x 15 cm) of

silica gel, and the column was developed using 1:9 to 2:3 EtOAc-hexane, to give lactone **33** (30.8 mg, 92%) as a pure (^{1}H NMR, 400 MHz), colorless oil which solidified on storage: mp 52 °C; FTIR (CH_2Cl_2 cast) 1776 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.38 (s, 3 H), 2.58 (m, 2 H), 3.1 (AB q, $\Delta\nu_{AB}$ = 57.3 Hz, J = 16.4 Hz, 2 H), 5.42 (s, 1 H), 7.25-7.50 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 26.3 (q'), 44.3 (t'), 46.4 (t'), 48.0 (s'), 94.7 (d'), 127.3 (d'), 128.2 (d'), 129.3 (d'), 131.7 (d'), 140.7 (s'), 144.7 (s'), 178.0 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{12}O_2$ 188.08372, found 188.08349.

3,6-Dimethoxy-2-nitrobenzoic acid (50) and 2,5-Dimethoxy-3-nitrobenzoic acid (51).



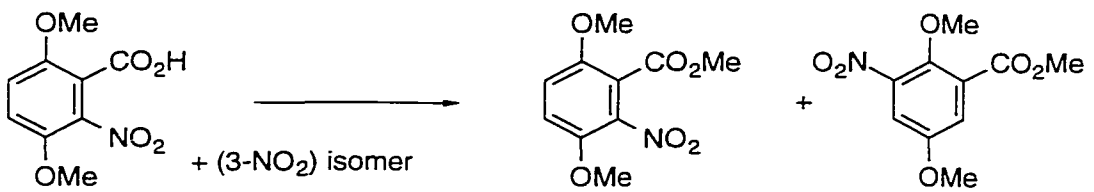
49 **50** **51**

The literature method[18] was modified.

HNO_3 (100 mL) was placed in a three-necked flask fitted with a low temperature thermometer and cooled to 0 °C. 2,5-Dimethoxybenzoic acid (10.0 g, 54.9 mmol) was added in small portions over 30 min with stirring (the temperature was not allowed to rise above 0 °C). The resulting yellow solution was stirred at 0 °C for another 3 h, and poured onto cracked

ice (300 mL). A yellow precipitate formed immediately. It was filtered off, air dried overnight, and dried further under oil-pump vacuum for 4 h to yield **50** and **51** (12.4 g, 100%) as a 5:1 mixture of isomers.

Methyl 3,6-Dimethoxy-2-nitrobenzoate (52) and Methyl 2,5-Dimethoxy-3-nitrobenzoate (53).



50 **52** **53**

K_2CO_3 (40.00 g, 290.0 mmol), dry acetone (250 mL), and Me_2SO_4 (18.4 g, 145 mmol, 13.3 mL) were added successively to the crude acid (26.40 g, 116.2 mmol) obtained from the previous step. The resulting orange colored solution was stirred for 12 h. The solvent was evaporated and the residue was kept under oil-pump vacuum for 12 h. The resulting yellow solid was redissolved in a small amount of EtOAc and purified by flash chromatography over silica gel (4 x 27 cm), using 15:85 EtOAc-hexane, to give esters **52** (23.0 g, 82%) and **53** (4.4 g, 16%). The major isomer **52** had: mp 118-119 °C; FTIR (CH_2Cl_2 cast) 1706, 1517, 1251 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.92 (s, 3 H), 3.96 (s, 3 H), 3.98 (s, 3 H), 7.45 (s, 1 H), 7.55 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 52.7 (q'), 56.9 (q'), 57.2 (q'), 109.5 (d'), 117.1 (d'), 125.1 (s'),

141.5 (s'), 146.2 (s'), 152.2 (s'), 165.1 (s'); exact mass *m/z* calcd for $C_{10}H_{11}O_6N$ 241.0586, found 241.05892.

The minor isomer **53** had: mp 102.5-103.5 °C; FTIR (CH_2Cl_2 cast) 1742, 1530, 1271 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.86 (s, 3 H), 3.88 (s, 3 H), 3.94 (s, 3 H), 7.08 (d, *J* = 9.4 Hz, 1 H), 7.11 (d, *J* = 9.4 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 53.1 (q'), 57.0 (q'), 57.2 (q'), 115.7 (d'), 116.1 (d'), 118.1 (s'), 145.3 (s'), 150.6 (s'), 163.4 (s'), 165.1 (s'); exact mass *m/z* calcd for $C_{10}H_{11}O_6N$ 241.05860, found 241.05902.

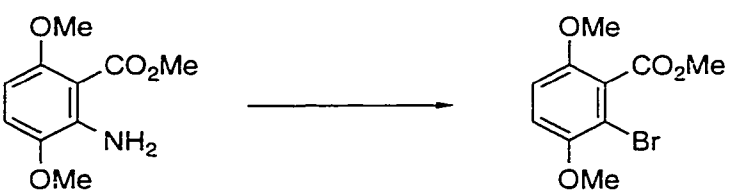
Methyl 2-Amino-3,6-dimethoxybenzoate (54).

52 **54**

10% Pd-C (25.0 mg) was added to a solution of ester **52** (1.50 g, 6.22 mmol) in EtOH (95%, 100 mL), and the mixture was shaken in a Parr bottle under H_2 (50 psi) until all the starting material was consumed (*ca* 12 h, TLC control, silica, 1:4 EtOAc-hexane). [The apparatus was opened periodically for examination by TLC]. The mixture was filtered through a pad (4 x 3 cm) of silica gel, using EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 15 cm), using 3:2 EtOAc-hexane,

gave amine **54** (1.266 g, 97%) as a pure (^{1}H NMR, 400 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 3489, 3379 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 3 H), 5.35 (broad s, 2 H), 6.15 (d, J = 8.8 Hz, 1 H), 6.75 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 51.9 (q'), 56.4 (q'), 56.5 (q'), 98.4 (d'), 105.0 (s'), 113.1 (d'), 140.7 (s'), 141.8 (s'), 154.1 (s'), 168.8 (s'); exact mass (HR electrospray) m/z calcd for $C_{10}H_{13}NNaO_4$ (M + Na) 234.07423, found 234.07467. Anal. Calcd for $C_{10}H_{13}N$: C 56.87, H 6.20, N 6.63. Found: C 56.71, H 6.31, N 6.61.

Methyl 2-Bromo-3,6-dimethoxybenzoate (40).



54 **40**

HBr (48% in water, 17.0 mL) was added to amine **54** (9.232 g, 43.75 mmol) and the mixture was stirred vigorously with a mechanical stirrer. The resulting white solid was broken up with a glass rod from time to time to allow reaction of the remaining amine. The slurry was further diluted with HBr (48% in water, 7.0 mL) and cooled (0 °C). A cooled (0 °C) solution of $NaNO_2$ (3.169 g, 45.94 mmol) in water (8.5 mL) was added dropwise by Pasteur pipette, maintaining a temperature below 5 °C. The resulting brownish-red solution was stored

in an ice-bath, and was added dropwise, using a Pasteur pipette, to a refluxing solution (100 °C) of $CuBr_2$ (4.14 g, 0.66 equiv) in HBr (48% in H_2O, 5.0 mL). The color of the reaction mixture changed from deep purple to black and later to brown. Upon completion of the addition, heating was continued for 10 min. The reaction mixture was cooled to room temperature and diluted with boiling Et_2O (10 mL). The aqueous layer was extracted with Et_2O (5 x 100 mL) until extraction was complete (TLC control, silica, 15:85 EtOAc-hexane). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The black crude material was redissolved in hot 4:1 EtOH-acetone, and applied directly to a column of flash chromatography silica gel (5 x 20 cm). The column was developed using 15:85 EtOAc-hexane, to give **40** (9.698 g, 81%) as a pure (^1H NMR, 400 MHz), white solid: mp 97 °C; FTIR (CH_2Cl_2 cast) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 3 H), 7.85 (AB q, $\Delta\nu_{AB}$ = 16.0 Hz, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.8 (q'), 56.6 (q'), 57.0 (q'), 109.9 (s'), 110.9 (d'), 113.1 (d'), 127.5 (s'), 150.3 (s'), 150.8 (s'), 166.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{10}H_{11}{}^{79}BrNaO_4$ (M + Na) 296.97384, found 296.97328. Anal. Calcd for $C_{10}H_{11}BrO_4$: C 43.66, H 4.03. Found: C 43.59, H 3.85.

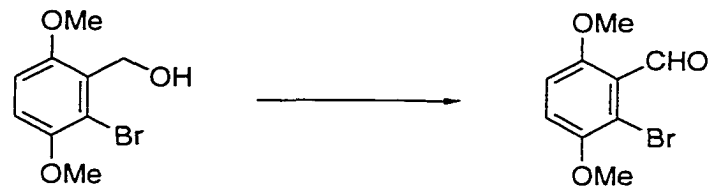
(2-Bromo-3,6-dimethoxyphenyl)methanol (59).

40 **59**

DIBAL (1.0 M in hexanes, 70.7 mL, 71 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ester **40** (9.692 g, 35.37 mmol) in dry PhMe (250 mL). The mixture was stirred at -78 °C for 2 h, warmed to 0 °C, and stirred for 1 h. Stirring was continued for another 6 h without recharging the ice bath. The solution was recooled (-78 °C), and MeOH (10 mL), $Na_2SO_4.10H_2O$ (4g), Celite (6.0 g) and water (2 mL) were added successively. The cold bath was removed and stirring was continued for 30 min. The slurry was filtered through a sintered disc funnel and washed with EtOAc (500 mL). The filtrate was concentrated and the residue was redissolved in a small amount of EtOAc and purified by flash chromatography over silica gel (5 x 20 cm), using 1:4 EtOAc-hexane, to give **59** (8.78 g, 99%) as a pure (^{1}H NMR, 400 MHz), white solid: mp 127-128 °C; FTIR (CH_2Cl_2 cast) 3489 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 2.44 (t, J = 7 Hz, 1 H), 3.82 (s, 6 H), 4.83 (d, J = 7 Hz, 2 H), 6.85 (s, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 56.6 (q'), 57.1 (q'), 60.6 (t'), 110.6 (d'), 112.0 (d'), 115.2 (s'), 130.5 (s'), 150.7 (s'), 153.0 (s'); exact mass (HR electrospray) m/z calcd for $C_9H_{11}{}^{79}BrNaO_3$ (M +

Na) 268.97892, found 268.97943. Anal. Calcd for $C_9H_{11}BrO_3$: C 43.75, H 4.49. Found: C 43.68, H 4.32.

2-Bromo-3,6-dimethoxybenzaldehyde (60).



59 **60**

A mixture of PCC (9.795 g, 45.52 mmol) and powdered 4 Å molecular sieves (3.0 g) was added to a stirred solution of alcohol **59** (8.012 g, 32.52 mmol) in dry CH_2Cl_2 (200 mL). Stirring was continued for 10 h, by which time oxidation was complete. The solvent was evaporated to approximately 50 mL and the slurry was filtered through a pad (5 x 3 cm) of silica gel which was washed with 1:1 EtOAc-hexane (400 mL, TLC control, silica, 1:1 EtOAc-hexane). The filtrate was evaporated and the residue was redissolved in CH_2Cl_2 (15 mL) and purified by flash chromatography over silica gel (5 x 15 cm), using 2:3 EtOAc-hexane, to give aldehyde **60** (7.530 g, 95%) as a pure (^{1}H NMR, 400 MHz), white solid: mp 99.5 °C; FTIR (CH_2Cl_2 cast) 1695 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 3.82 (s, 3 H), 3.84 (s, 3 H), 6.95 (d, J = 9.1 Hz, 1 H), 7.11 (d, J = 9.1 Hz, 1 H) 10.41 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 56.6 (q'), 57.2 (q'), 111.4 (d'), 114.8 (s'), 117.1 (d'), 124.8 (s'), 150.4 (s'), 155.4 (s'), 190.8 (d'); exact mass

(HR electrospray) *m/z* calcd for $C_9H_9{}^{79}BrNaO_3$ (M + Na) 266.96327, found 266.96351. Anal. Calcd for $C_9H_9BrO_3$: C 44.11, H 3.70. Found: C 43.94, H 3.26.

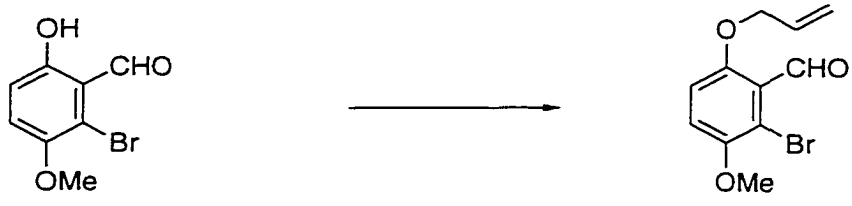
2-Bromo-6-hydroxy-3-methoxybenzaldehyde (61).

60 **61**

BCl_3 (1.0 M in hexanes, 59 mL, 59 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of aldehyde **60** (4.805 g, 19.69 mmol) in dry CH_2Cl_2 (200 mL). The resulting bright-red solution was stirred for 10 h without recharging the cold bath. The solution was recooled to 0 °C, and ice water (100 mL) was added slowly. The resulting deep yellow solution was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The yellow residue was redissolved in CH_2Cl_2 (5 mL) and purified by flash chromatography over silica gel (4 x 20 cm), using 15:85 EtOAc-hexane, to give **61** (4.317 g, 96%) as a pure (^1H NMR, 400 MHz), yellow solid: mp 89 °C; FTIR (CH_2Cl_2 cast) 1645 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.89 (s, 3 H), 6.95 (d, *J* = 9.1 Hz, 1 H), 7.21 (d, *J* = 9.1 Hz, 1 H) 10.41 (s, 1 H), 11.51 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 57.8 (q'), 116.4 (s'),

117.8 (d'), 118.3 (s'), 122.7 (d'), 149.7 (s'), 158.2 (s'), 198.6 (d'); exact mass *m/z* calcd for $C_8H_8{}^{79}BrO_3$ (M + H) 230.96568, found 230.96632. Anal. Calcd for $C_8H_7BrO_3$: C 41.59, H 3.05. Found: C 41.67, H 2.72.

2-Bromo-3-methoxy-6-(2-propenyloxy)benzaldehyde (62).

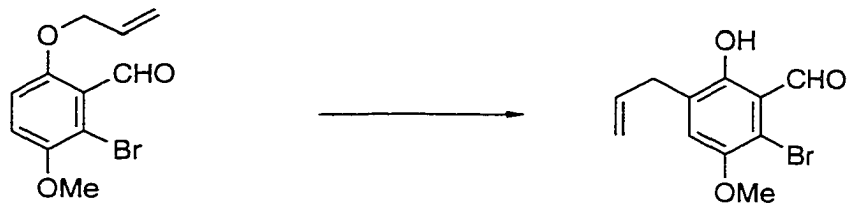


61 **62**

Aldehyde **61** (6.14 g, 26.59 mmol) in DMF (5 mL) was added dropwise to a stirred and cooled (0 °C) slurry of NaH (772.5 g, 30.58 mmol) in dry DMF (30 mL). The cold bath was removed and the resulting bright yellow slurry was stirred for 1 h. The solution was recooled to 0 °C and allyl bromide (4.60 mL, 53.2 mmol) was added dropwise. The cold bath was removed, and stirring was continued for 4 h. The reaction mixture was poured into brine (50 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with aqueous KOH (10%, 20 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. The pale yellow crude residue was redissolved in CH_2Cl_2 (5 mL) and purified by flash chromatography over silica gel (4 x 20 cm), using 1:4 EtOAc-hexane, to give **62** (6.01 g, 83%) as a pure (^1H NMR, 400 MHz), white, crystalline solid:

mp 77 °C; FTIR (CH_2Cl_2 cast), 1696 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.87 (s, 3 H), 4.57 (d, *J* = 6 Hz, 2 H), 5.29 (d, *J* = 12 Hz, 1 H), 5.43 (d, *J* = 18 Hz, 1 H), 6.00-6.09 (m, 1 H), 6.96 (d, *J* = 9 Hz, 1 H), 7.07 (d, *J* = 9 Hz, 1 H), 10.38 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 57.4 (q'), 70.8 (t'), 113.6 (d'), 113.7 (s'), 117.3 (d'), 118.0 (t'), 125.8 (s'), 133.0 (d'), 151.1 (s'), 154.8 (s'), 190.7 (d'); exact mass (HR electrospray) *m/z* calcd for $C_{11}H_{11}{}^{79}BrO_3Na$ (M + Na) 292.97892, found 292.97870.

2-Bromo-6-hydroxy-3-methoxy-5-(2-propenyl)benz-aldehyde (66).



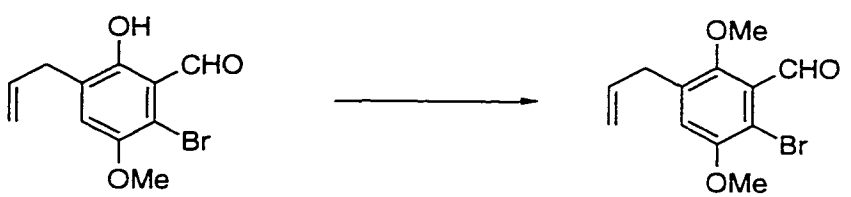
62 **66**

Trans decalin was degassed by several freeze-thaw cycles (liquid N_2/oil-pump vacuum).

A solution of aldehyde **62** (810.0 mg, 3.011 mmol) in degassed decalin (3 mL) was refluxed under Ar for 6.5 h and then cooled to room temperature. Flash chromatography of the mixture (without evaporation of the solvent) over silica gel (2 x 15 cm), using 1:12 EtOAc-hexane, gave phenol **66** (602.8 mg, 74%) as a pure, yellow oil: FTIR (CH_2Cl_2 cast) 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.40 (d, *J* = 6 Hz, 2 H), 3.87 (s, 3

H), 5.05-5.20 (m, 2 H), 5.85-6.07 (m, 1 H), 7.06 (s, 1 H), 10.40 (s, 1 H), 11.90 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 33.5 (t'), 57.9 (q'), 113.7 (s'), 116.8 (t'), 117.6 (s'), 123.2 (d'), 129.6 (s'), 135.6 (d'), 149.2 (s'), 156.3 (s'), 198.8 (d'); exact mass (HR electrospray) *m/z* calcd for $C_{11}H_{11}{}^{79}BrNaO_3$ (M + Na) 292.97892, found 292.97870.

2-Bromo-3,6-dimethoxy-5-(2-propenyl)benzaldehyde (72).

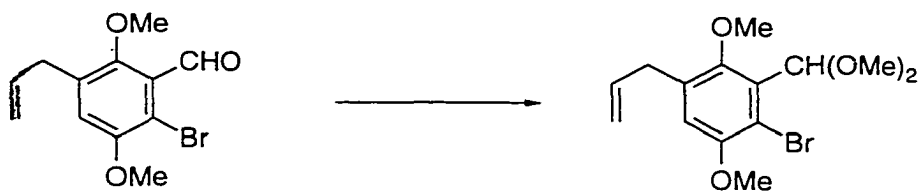


66 **72**

MeI (4.74 g, 2.08 mL, 33.4 mmol) was added dropwise to a stirred mixture of phenol **66** (1.808 g, 6.696 mmol) and K_2CO_3 (4.587 g, 33.37 mmol) in dry DMF (20 mL). The mixture was warmed to 70 °C and stirring was continued for 10 h at this temperature. The solids were filtered off and the filtrate was poured into brine (20 mL) and extracted with Et_2O (4 x 20 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1:4 EtOAc-hexane, gave aldehyde **72** (1.857 g, 97%) as a yellowish-white solid: mp 50 °C; FTIR (CH_2Cl_2 cast) 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.43 (dt, *J* = 6.5, 1.3 Hz, 2

H), 3.80 (s, 3 H), 3.90 (s, 3 H), 5.08-5.16 (m, 2 H), 5.90-6.00 (m, 1 H), 6.95 (s, 1 H), 10.38 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 33.7 (t'), 57.2 (q'), 63.9 (q'), 111.6 (s'), 116.9 (t'), 118.1 (d'), 129.7 (s'), 135.1 (s'), 136.4 (d'), 153.0 (s'), 153.6 (s'), 191.4 (d'); exact mass *m/z* calcd for $C_{12}H_{13}{}^{81}BrO_3$ 286.00275, found 286.00154.

1-Bromo-2-(dimethoxymethyl)-3,6-dimethoxy-4-(2-propenyl)benzene (73).

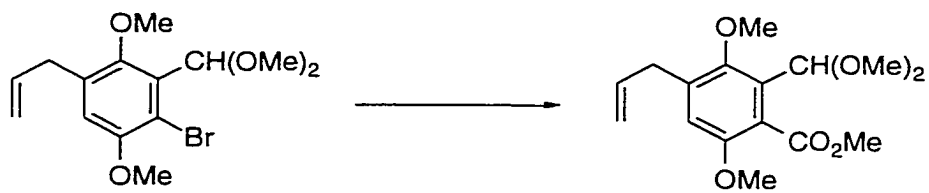


72 **73**

$CH(OMe)_3$ (3.00 mL, 27.4 mmol) was added dropwise to a stirred solution of aldehyde **72** (1.211 g, 4.248 mmol) in dry MeOH (3 mL) containing $TsOH.H_2O$ (5.0 mg). The mixture was warmed to 70 °C and stirring was continued for 3.5 h at this temperature. The mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 1:4 EtOAc-hexane, gave **73** (1.345 g, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.37 (d, *J* = 6.3 Hz, 2 H), 3.43 (s, 6 H), 3.71 (s, 3 H), 3.83 (s, 3 H), 5.07-5.16 (m, 2 H), 5.68 (s, 1 H), 5.90-6.04 (m, 1 H), 6.77 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.1 (t'), 56.0 (two overlapping q'), 57.0 (q'),

63.1 (q'), 105.4 (d'), 110.5 (s'), 114.0 (d'), 116.5 (t'), 132.1 (s'), 134.1 (s'), 137.0 (d'), 151.0 (s'), 152.9 (s'); exact mass *m/z* calcd for $C_{14}H_{19}{}^{79}BrO_4$ 330.0467138, found 284.00485 (M - C_2H_6O).

Methyl 3,6-Dimethoxy-2-(dimethoxymethyl)-4-(2-propenyl)benzoate (74).

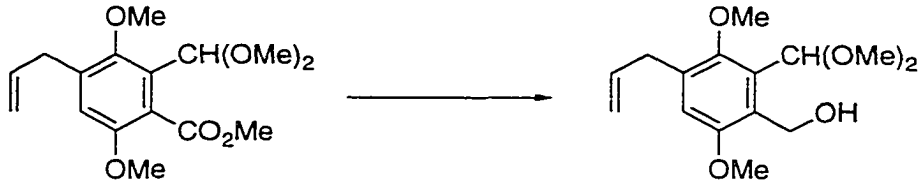


73 **74**

BuLi (1.6 M in hexanes, 3.7 mL, 9.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of bromide **73** (2.024 g, 6.116 mmol) in dry THF (50 mL), and the resultant pale brown solution was stirred at -78 °C for 25 min. MeOC(O)CN (0.85 mL, 10.7 mmol) in THF (0.85 mL) was then added dropwise over 5 min. Stirring was continued at -78 °C for 20 min, and the cold bath was removed. The mixture was allowed to warm to 0 °C, and was then diluted with water (20 mL), and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the pale yellow residue over silica gel (3 x 22 cm), using 1:3 EtOAc-hexane, gave ester **74** (1.673 g, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1737 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ

3.34 (s, 6 H), 3.44 (d, J = 6 Hz, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 5.09-5.15 (m, 2 H), 5.47 (s, 1 H), 5.91-6.02 (m, 1 H), 6.82 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.1 (t'), 52.1 (q'), 55.2 (q'), 56.7 (q'), 62.6 (q'), 101.6 (d'), 113.9 (d'), 116.6 (t'), 121.9 (s'), 130.4 (s'), 135.6 (s'), 136.9 (d'), 150.5 (s'), 152.7 (s'), 168.0 (s'); exact mass m/z calcd for $C_{16}H_{22}O_6$ 310.14163, found 310.14154.

[2-(Dimethoxymethyl)-3,6-dimethoxy-4-(2-propenyl)phenyl]methanol (75).

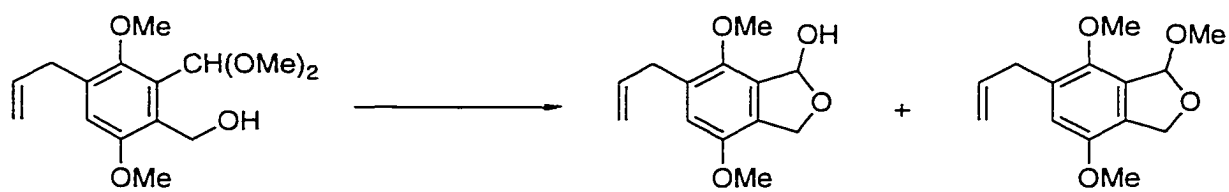


74 **75**

DIBAL (1.0 M in hexanes, 3.9 mL, 3.9 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ester **74** (596.8 mg, 1.925 mmol) in dry PhMe (20 mL). The mixture was stirred at -78 °C for 1 h and then DIBAL (1.0 M in hexanes, 1.9 mL, 1.9 mmol) was added, and stirring was continued for 1 h. The solution was recooled to -78 °C, and MeOH (3 mL), $Na_2SO_4.10H_2O$ (2.0 g), Celite (1.0 g) and water (1 mL) were added successively. The cold bath was removed and stirring was continued for 30 min. The slurry was filtered through a short pad of Celite on a sintered disc and the pad was washed with EtOAc (50 mL). The filtrate was evaporated

and the residue was dissolved in a small amount of EtOAc and purified by flash chromatography over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, to give **75** (504.9 mg, 93%) as a pure (^{1}H NMR, 400 MHz), white solid: FTIR (CH_2Cl_2 cast) 3430 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 2.97 (t, J = 6 Hz, 1 H), 3.44 (d, J = 6.5 Hz, 2 H), 3.48 (s, 6 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 4.81 (d, J = 6 Hz, 2 H), 5.08-5.10 (m, 1 H), 5.11-5.13 (m, 1 H), 5.61 (s, 1 H), 5.93-6.04 (m, 1 H), 6.76 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 34.3 (t'), 55.5 (t'), 56.4 (q'), 56.6 (q'), 62.9 (two q'), 103.9 (d'), 114.0 (d'), 116.2 (t'), 128.2 (s'), 131.7 (s'), 133.3 (s'), 137.3 (d'), 150.4 (s'), 155.0 (s'); exact mass m/z calcd for $C_{15}H_{22}O_5$, 282.14671, found 282.14673.

1,3-Dihydro-4,7-dimethoxy-6-(2-propenyl)isobenzofuran-1-ol (76) and 1,3-Dihydro-1,4,7-trimethoxy-6-(2-propenyl)isobenzofuran (77).



75 **76** **77**

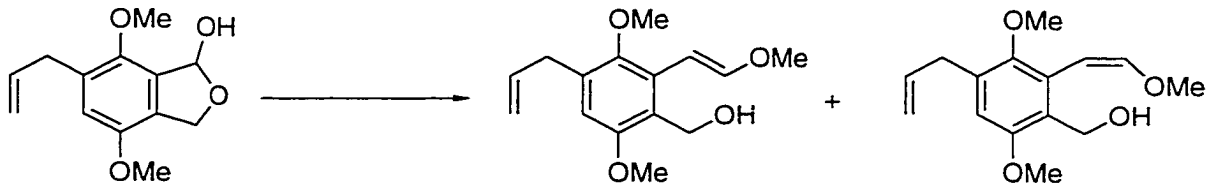
Dilute hydrochloric acid (0.1 M, 10 mL) was added dropwise to a stirred solution of acetal **75** (1.304 g, 4.624 mmol) in dioxane (10 mL). Stirring was continued for 12 h, by which time all the starting material had been consumed

(TLC control, silica, 2:3 EtOAc-hexane). The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 18 cm), using 1:4 EtOAc-hexane, gave lactol **76** (778.1 mg, 71%) as a white solid and acetal **77** (276.7 mg, 24%) as a colorless oil. Lactol **76** had: mp 157.5 °C; FTIR (CH_2Cl_2 cast) 3335 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.31-3.45 (m, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 4.88 (d, *J* = 12 Hz, 2 H), 5.01-5.18 (m, 2 H), 5.88-6.09 (m, 1 H), 6.59 (dd, *J* = 6, 1.8 Hz, 1 H), 6.7 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.4 (t'), 56.0 (q'), 61.4 (q'), 70.6 (t'), 101.0 (d'), 113.7 (d'), 115.7 (t'), 127.7 (s'), 132.3 (s'), 133.5 (s'), 137.6 (d'), 147.4 (s'), 149.7 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{13}H_{16}NaO_4$ (M + Na) 259.09463, found 259.09467.

Acetal **77** had: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.41 (s, 3 H), 3.42 (m, 2 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.82-5.15 (m, 4 H), 5.85-6.12 (m, 1 H), 6.25 (d, *J* = 3 Hz, 1 H), 6.68 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 35.9 (t'), 55.8 (q'), 57.5 (q'), 62.7 (q'), 72.3 (t'), 108.5 (d'), 115.2 (d'), 117.3 (t'), 129.8 (s'), 132.1 (s'), 134.7 (s'), 139.3 (d'), 149.0 (s'), 151.1 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{14}H_{18}NaO_4$ (M + Na) 273.11028, found 273.10998.

(*E*)-[3,6-dimethoxy-2-(2-methoxyethenyl)-4-(2-pro-

penyl)phenyl]methanol (*E*-78) and (*Z*)-[3,6-dimethoxy-2-(2-methoxyethenyl)-4-(2-propenyl)phenyl]methanol (*Z*-78).



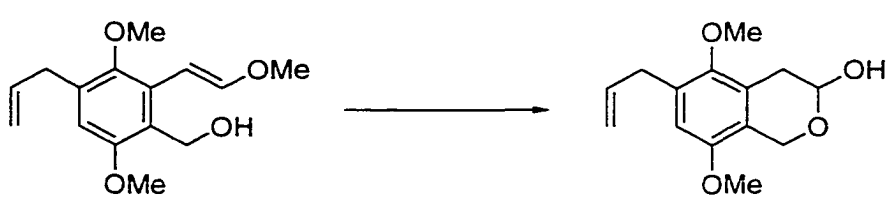
76 ***E*-78** ***Z*-78**

(Methoxymethyl)triphenylphosphonium bromide (511.3, 1.483 mmol) was placed in a long-necked flask and dry THF (2 mL) was added. The white slurry was stirred and cooled to -78 °C, and $(Me_3Si)_2NK$ (0.5 M solution in PhMe, 1.7 mL, 0.85 mmol) was added dropwise over 5 min. The resulting red slurry was stirred at -78 °C for 2 h, and a solution of lactol **76** (100.0 mg, 0.424 mmol) in dry THF (1 mL plus 1 mL as a rinse) was added dropwise. The resulting pale orange solution was stirred for 10 h without recharging the cold bath. The resulting white slurry was filtered off using a sintered disc, and washed with EtOAc (10 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:4 EtOAc-hexane, gave the isomeric enol ethers **(*E*)-78** (70.8 mg, 63%) and **(*Z*)-78** (33.5 mg, 30%) as colorless oils. Compound **(*E*)-78** had: FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.16 (t, *J* = 6.9 Hz, 1 H), 3.40 (dt, *J* = 1.4, 6.6 Hz, 2 H), 3.62 (s, 3 H), 3.71 (s, 3 H), 3.84 (s, 3 H), 4.65 (d, *J* = 6.9 Hz, 2 H),

5.05-5.14 (m, 2 H), 5.85 (d, J = 15 Hz, 1 H), 5.92-6.05 (m, 1 H), 6.61 (s, 1 H), 6.99 (d, J = 15 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 34.7 (t'), 56.1 (q'), 56.7 (q'), 58.0 (t'), 60.4 (q'), 98.0 (d'), 110.1 (d'), 115.9 (t'), 126.0 (s'), 130.8 (s'), 133.4 (s'), 137.7 (d'), 150.1 (s'), 153.1 (d'), 154.9 (s'); exact mass (HR electrospray) m/z calcd for $C_{15}H_{20}NaO_4$ (M + Na) 287.12593, found 287.12595.

Compound **(*Z*)-78** had: FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.78 (t, J = 6.9 Hz, 1 H), 3.40 (dt, J = 1.4, 6.6 Hz, 2 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.82 (s, 3 H), 4.54 (d, J = 6.9 Hz, 2 H), 5.05-5.14 (m, 2 H), 5.41 (d, J = 6.8 Hz, 1 H), 5.93-6.23 (m, 1 H), 6.25 (d, J = 6.8 Hz, 1 H), 6.67 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 34.5 (t'), 56.1 (q'), 59.2 (t'), 60.3 (q'), 61.0 (q'), 100.8 (d'), 111.3 (d'), 116.0 (t'), 127.7 (s'), 129.1 (s'), 133.0 (s'), 137.7 (d'), 148.4 (d'), 150.2 (s'), 154.8 (s'); exact mass (HR electrospray) m/z calcd for $C_{15}H_{20}NaO_4$ (M + Na) 287.12593, found 287.12572.

5,8-Dimethoxy-6-(2-propenyl)isochroman-3-ol (79).



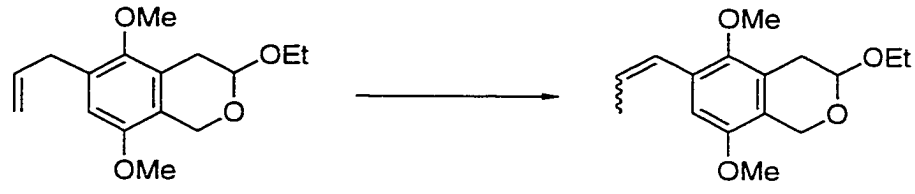
78 **79**

Dilute hydrochloric acid (0.1 M, 3 mL), was added

dropwise to a stirred solution of enol ethers **78** (250.0 mg, 0.946 mmol) in dioxane (10 mL). Stirring was continued for 12 h, by which time only one of the enol ethers (the *Z* isomer) had been converted into the corresponding lactol methyl ether while the other remain unchanged (TLC control, silica, 2:3 EtOAc-hexane). The reaction mixture was then heated at 60 °C for 3 h, by which point all the starting material had reacted (TLC control, silica, 2:3 EtOAc-hexane). the mixture was cooled to room temperature and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 1:2 EtOAc-hexane, gave **79** (196.4 mg, 83%) as a pure, colorless oil: FTIR (CH_2Cl_2 cast) 3404 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.71 (dd, J = 11.5, 5.2 Hz, 1 H), 3.00 (dd, J = 16.6, 3.6 Hz, 1 H), 3.08 (d, J = 4.5 Hz, 1 H), 3.39 (d, J = 6.6 Hz, 2 H), 3.65 (s, 3 H), 3.76 (s, 3 H), 4.66 (d, J = 16 Hz, 1 H), 4.85 (d, J = 16 Hz, 1 H), 5.05-5.14 (m, 2 H), 5.22-5.29 (m, 1 H), 5.93-6.03 (m, 1 H), 6.54 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 30.0 (t'), 34.4 (t'), 55.7 (q'), 60.7 (t'), 61.0 (q'), 92.4 (d'), 109.4 (d'), 115.8 (t'), 121.7 (s'), 126.2 (s'), 131.5 (s'), 137.8 (d'), 150.0 (s'), 151.6 (s'); exact mass *m/z* calcd for $C_{14}H_{18}O_4$ 250.12051, found 250.11985.

3-Ethoxy-5,8-dimethoxy-6-(1-propenyl)isochroman

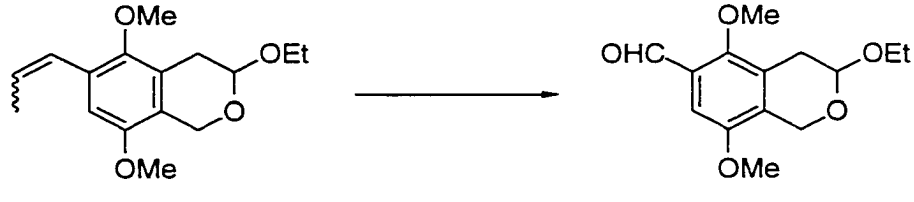
(85).



84 **85**

$RhCl_3.3H_2O$ (10.0 mg) was added to a stirred solution of olefin **84** (60.0 mg, 0.18 mmol) in dry 4:1 PhMe-EtOH (8 mL). The mixture was refluxed for 12 h, cooled, and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave an inseparable mixture of isomeric olefins **85** (43.5 mg, 69%) as a colorless oil: ^1H NMR (CD_2Cl_2, 200 MHz) δ (major isomer) 1.22 (t, J = 7 Hz, 3 H), 1.84 (dd, J = 7.0, 1.7 Hz, 3 H), 2.92-3.00 (m, 1 H), 3.50-3.62 (m, 1 H), 3.60 (s, 3 H), 3.78-3.91 (m, 1 H), 3.78 (s, 3 H), 4.62 (s, 2 H), 5.01 (t, J = 3 Hz, 1 H), 6.18-6.32 (m, 1 H), 6.58-6.69 (m, 1 H), 6.70 (s, 1 H).

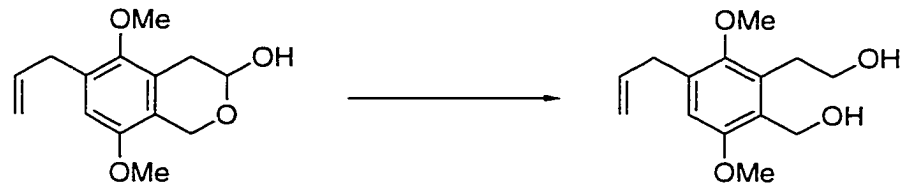
3-Ethoxy-5,8-dimethoxyisochroman-6-carbaldehyde (86).



85 **86**

OsO_4 (2.5% w/v in *t*-BuOH, 125.0 μL, 0.020 mmol) was added to a stirred mixture of **85** (43.5 mg, 0.17 mmol), *t*-BuOH (0.6 mL), CCl_4 (1.2 mL) and water (1.2 mL). After 15 min, $NaIO_4$ (90.0 mg, 0.42 mmol) was added in one portion, and stirring was continued for 2 h. Water (2 mL) was then added and the mixture was extracted with EtOAc (2 x 3 mL). The combined organic extracts were washed with water (2 mL), 10% $NaHSO_3$ (10 mL), and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 15:85 EtOAc-hexane, gave lactone **86** (36.63 mg, 81%) as a white solid: mp 105.5 °C; FTIR (CH_2Cl_2 cast) 1684 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.18 (t, *J* = 7.0 Hz, 3 H), 2.78-2.81 (m, 1 H), 2.92-3.00 (m, 1 H), 3.58-3.62 (m, 1 H), 3.82 (s, 3 H, 2 signals), 3.80-3.86 (m, 1 H), 4.71 (s, 2 H), 5.08 (t, *J* = 4 Hz, 1 H), 7.15 (s, 1 H), 10.38 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 15.3 (q'), 28.4 (t'), 54.3 (q'), 59.2 (t'), 63.8 (t'), 63.9 (q'), 96.3 (d'), 104.9 (d'), 127.68 (s'), 127.7 (s'), 132.3 (s'), 152.2 (s'), 156.4 (s'), 189.6 (d'); exact mass *m/z* calcd for $C_{14}H_{18}O_5$ 266.11542, found 266.11575.

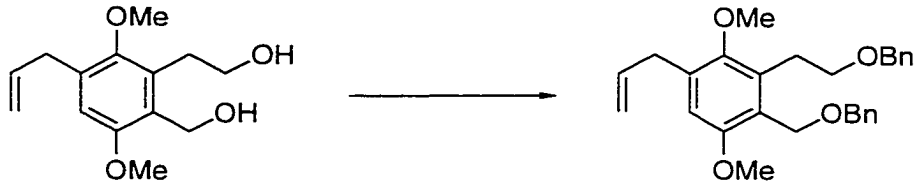
2-[(2-Hydroxymethyl)-3,6-dimethoxy-5-(2-propenyl)phenyl]ethanol (89).



79 **89**

$NaBH_4$ (35.6 mg, 0.94 mmol) was added in portions to a stirred and cooled (0 °C) solution of lactol **79** (156.0 mg, 0.624 mmol) in dry MeOH (8 mL). After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the MeOH was evaporated. The aqueous layer was extracted with Et_2O (3 x 8 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 1:1 EtOAc-hexane, gave **89** (141.0 mg, 90%) as a white solid: mp 73.5 °C; FTIR (CH_2Cl_2 cast) 3320 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.95 (t, *J* = 6.0 Hz, 2 H), 3.12 (broad s, 1 H), 3.41 (dt, *J* = 6.5, 1.3 Hz, 2 H), 3.51 (broad s, 1 H), 3.64 (s, 3 H), 3.76 (m, 2 H), 3.80 (s, 3 H), 4.61 (s, 2 H), 5.08-5.18 (m, 2 H), 5.85-6.05 (m, 1 H), 6.62 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 30.1 (t'), 34.5 (t'), 55.9 (q'), 56.1 (q'), 61.6 (q'), 62.8 (t'), 111.2 (d'), 116.2 (t'), 127.9 (s'), 133.2 (s'), 133.6 (s'), 137.4 (d'), 150.9 (s'), 154.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{14}H_{20}NaO_4$ (M + Na) 275.12593, found 275.12630.

1,4-Dimethoxy-3-[2-(phenylmethoxy)ethyl]-2-[(phenylmethoxy)methyl]-5-(2-propenyl)benzene (90).

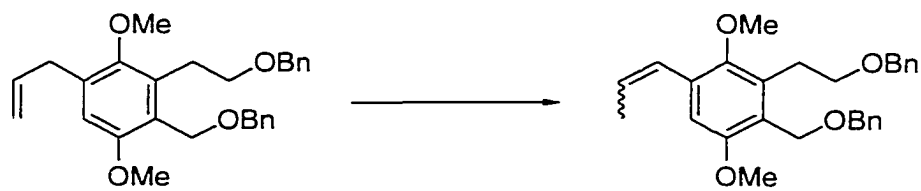


89 **90**

NaH (95% dispersion in mineral oil, 54.5 mg, 2.16 mmol) was added to a stirred and cooled (0 °C) solution of diol **89** (270.8 mg, 1.074 mmol) in dry THF (5 mL). BnBr (0.26 mL, 2.16 mmol) was added dropwise to the slurry and stirring was continued for 3 h without recharging the ice bath. The reaction was quenched with MeOH (0.5 mL), and then water (5 mL) was added. The aqueous layer was extracted with EtOAc (3 x 8 mL), and the combined extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 1:3 EtOAc-hexane, gave **90** (313.5 mg, 68%) as a colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.95-1.98 (m, 3 H), 3.02-3.09 (m, 2 H), 3.58-3.64 (m, 2 H), 3.68 (s, 3 H), 3.78 (m, 3 H), 4.40-4.61 (m, 6 H), 6.21-6.31 (m, 1 H), 6.60-6.68 (m, 1 H), 6.82-6.85 (m, 1 H), 7.22-7.39 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 20.0 (t'), 34.6 (t'), 56.3 (q'), 61.8 (q'), 63.6 (t'), 71.1 (t'), 72.7 (t'), 73.0 (t'), 111.4 (d'), 116.1 (t'), 124.9 (s'), 127.6 (d'), 127.7 (d'), 127.8 (d'), 128.1 (d'), 128.5 (d'), 128.55 (d'), 133.6 (s'), 134.0 (s'), 137.5 (d'), 139.4

(s'), 151.2 (s'), 155.0 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{28}H_{32}O_4$ 432.23007, found 432.23005.

(*Z*)- and (*E*)-1,4-Dimethoxy-3-[2-(phenylmethoxy)-ethyl]-2-[(phenylmethoxy)methyl]-5-(1-propenyl)benzene (91).

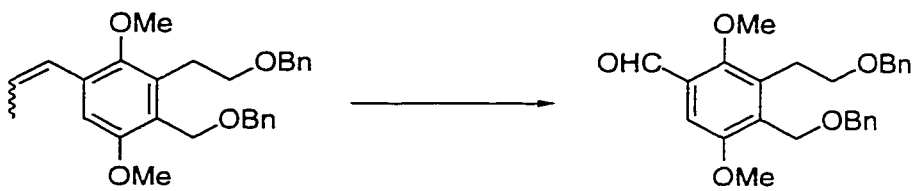


90 **91**

$RhCl_3.3H_2O$ (10.0 mg) was added to a stirred solution of olefin **90** (313.3 mg, 0.725 mmol) in dry 5:1 PhMe-MeOH (3 mL). The mixture was refluxed for 3 h, cooled and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave an inseparable mixture of isomeric olefins **91** (278.0 mg, 89%) as a colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.96-1.98 (m, 3 H), 3.00-3.12 (m, 2 H), 3.55-3.60 (m, 2 H), 3.64 (s, 3 H), 3.80 (s, 3 H), 4.40-4.62 (m, 6 H), 6.20-6.29 (m, 1 H), 6.61-6.70 (m, 1 H), 6.82-6.86 (m, 1 H), 7.23-7.39 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ (major isomer) 17.0 (q'), 29.4 (t'), 55.8 (q'), 63.5 (q'), 65.1 (t'), 67.5 (t'), 72.6 (t'), 74.5 (t'), 108.5 (d'), 125.5 (s'), 127.7 (d'), 128.9 (d'), 129.2 (d'), 129.4 (d'), 129.6 (d'), 133.2 (s'), 135.2 (s'), 140.9 (s'), 151.9 (s'), 156.6 (s'); exact mass *m/z* calcd for

$C_{28}H_{32}O_4$ 432.23007, found 432.23005.

2,5-Dimethoxy-3-[2-(phenylmethoxy)ethyl]-4-[(phenylmethoxy)methyl]benzaldehyde (92).

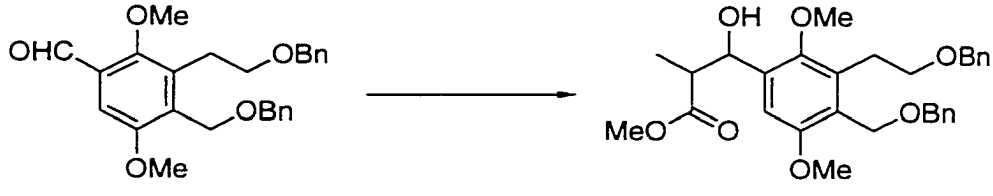


91 **92**

Ozonized oxygen was bubbled through a stirred and cooled (-78 °C) solution of olefin **91** (272.0 mg, 0.629 mmol) and Sudan II red (1 mg) in dry CH_2Cl_2 (4 mL) [protection from moisture (Drierite)]. When all of the starting material had been consumed (*ca* 10 min, discharge of the red color, and TLC control, silica, 2:3 EtOAc-hexane), the solution was purged with oxygen for 10 min. Ph_3P (330.0 mg, 1.258 mmol) was added, the cold bath was removed, and stirring was continued for 2 h, by which time the mixture had attained room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm), using 1:4 EtOAc-hexane, gave **92** (200 mg, 76%) as a pure oil; FTIR (CH_2Cl_2 cast) 1686 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.11 (t, J = 7.5 Hz, 2 H), 3.63 (t, J = 7.5 Hz, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.45 (s, 2 H), 4.55 (s, 2 H), 4.68 (s, 2 H), 7.18-7.48 (m, 11 H), 10.31 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 27.5 (t'), 56.4 (q'), 63.5 (t'), 65.4 (q'), 70.7

(t'), 73.1 (t'), 73.2 (t'), 107.4 (d'), 127.76 (d'), 127.84 (d'), 127.9 (d'), 128.2 (d'), 128.6 (d'), 129.5 (s'), 134.2 (s'), 135.6 (s'), 139.0 (s'), 139.1 (s'), 155.4 (s'), 157.1 (s'), 189.9 (d'); exact mass *m/z* calcd for $C_{26}H_{28}O_5$ 420.19366, found 420.19419.

Methyl 3-Hydroxy-3-[2,5-dimethoxy-3-[2-(phenylmethoxy)ethyl]-4-[(phenylmethoxy)methyl]phenyl]-2-methylpropanoate (93).

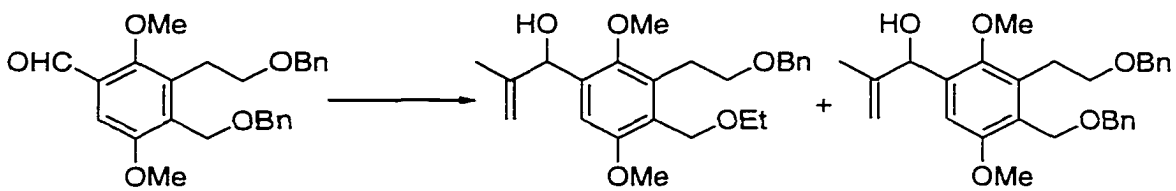


92 **93**

BuLi (2.5 M in hexanes, 0.17 mL, 0.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (60.6 μL, 0.43 mmol) in THF (0.4 mL). After 15 min, methyl propionate (35.0 mg, 38.2 μL, 0.40 mmol) was added dropwise, and stirring was continued at -78 °C for 30 min. The resulting enolate solution was taken up into a syringe and added dropwise to a stirred room temperature solution of aldehyde **92** (200.0 mg, 0.476 mmol) in dry THF (0.2 mL). The reaction mixture was stirred for 30 min, diluted with water (10 mL), and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica

gel (2 x 27 cm), using 15:85 EtOAc-hexane, gave an inseparable mixture of alcohols **93** (135.5 mg, 68%, 78% corrected for recovered starting material) as a colorless oil: FTIR (CH_2Cl_2 cast) 3453 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.0 (d, *J* = 7.2 Hz, 3 H), 2.80-3.15 (m, 3 H), 3.50-3.62 (m, 2 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.40-4.65 (m, 5 H), 5.15-5.18 (m, 1 H), 5.28 (s, 2 H), 6.8 (s, 1 H), 7.22-7.40 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.6 (q'), 15.5 (q'), 28.0 (t'), 47.1 (d'), 52.1 (d'), 56.3 (d'), 61.5 (d'), 62.6 (d'), 63.5 (t'), 66.1 (t'), 69.3 (d'), 71.0 (t'), 71.1 (d'), 72.9 (t'), 73.0 (t'), 108.0 (d'), 108.8 (d'), 126.7 (s'), 127.7 (d'), 127.8 (d'), 127.84 (d'), 128.2 (d'), 128.6 (d'), 134.0 (s'), 135.6 (s'), 139.3 (s'), 151.0 (s'), 155.5 (s'), 176.5 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{30}H_{36}NaO_7$ (M + Na) 531.23587, found 531.23548.

1-[4-Ethoxymethyl-2,5-dimethoxy-3-[2-(phenylmethoxy)ethyl]phenyl]-2-methyl-2-propen-1-ol (104) and 1-[2,5-Dimethoxy-3-[2-(phenylmethoxy)ethyl]-4-[(phenylmethoxy)methyl]phenyl]-2-methyl-2-propen-1-ol (105).



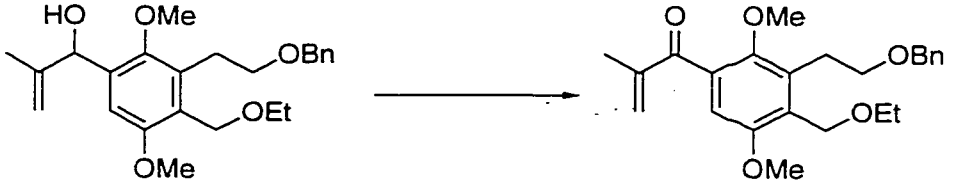
92 **104** **105**

Isopropenylmagnesium bromide (1.0 M in THF, 0.4 mL, 0.2 mmol) was added dropwise to a stirred and cooled (-10 °C) solution of aldehyde **92** (59.6 mg, 0.14 mmol) in Et_2O (2.5 mL). The mixture was stirred for 2 h, and then quenched with saturated aqueous NH_4Cl (2 mL). The organic extract was washed with water (5 mL), and the combined aqueous phases were extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 1:4 EtOAc-hexane, gave alcohols **104** (24.8 mg, 44%) and **105** (12.0 mg, 18%). Compound **104** had: FTIR (CH_2Cl_2 cast) 3425 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (t, J = 7 Hz, 3 H), 1.67 (s, 3 H), 2.28 (d, J = 4.5 Hz, 1 H), 3.05 (t, J = 9.0 Hz, 2 H), 3.55 (q, J = 7.0 Hz, 2 H), 3.62 (t, J = 9.0 Hz, 2 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 4.45 (m, 4 H), 5.00 (m, 1 H), 5.18 (m, 1 H), 5.41 (m, 1 H), 6.78 (s, 1 H), 7.21-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4 (q'), 19.5 (q'), 27.9 (t'), 56.3 (q'), 62.6 (q'), 63.5 (t'), 66.0 (t'), 71.0 (t'), 72.2 (d'), 72.8 (t'), 73.0 (t'), 108.6 (d'), 111.0 (s'), 126.6 (s'), 127.7 (d'), 127.8 (d'), 128.1 (d'), 128.5 (d'), 133.9 (s'), 136.0 (s'), 139.3 (s'), 147.2 (s'), 151.6 (s'), 155.3 (s'); exact mass m/z calcd for $C_{24}H_{32}O_5$ 400.22498, found 400.22517.

Compound **105** had: FTIR (CH_2Cl_2 cast) 3405 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (s, 3 H), 2.23 (d, J = 4.5 Hz, 1 H), 3.05 (t, J = 9.0 Hz, 2 H), 3.62 (t, J = 9.0 Hz, 2 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 4.45 (s, 2 H), 4.52 (s, 2 H), 4.61

(s, 2 H), 5.00 (m, 1 H), 5.18 (m, 1 H), 5.41 (d, J = 4.5 Hz, 1 H), 6.71 (s, 1 H), 7.21-7.38 (m, 10 H); exact mass (HR electrospray) m/z calcd for $C_{29}H_{34}NaO_5$ (M + Na) 485.23039, found 485.23056.

2-Methyl-1-[4-(ethoxymethyl)-2,5-dimethoxy-3-[2-(phenylmethoxy)ethyl]phenyl]propenone (106).

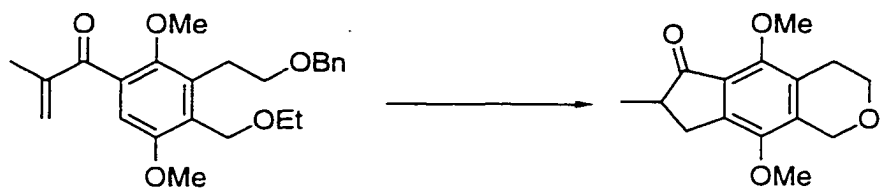


104 **106**

A mixture of PCC (18.7 mg, 0.09 mmol) and powdered 4 Å molecular sieves (9.0 mg) was added to a stirred solution of alcohol **105** (24.8 mg, 0.01 mmol) in dry CH_2Cl_2 (1.5 mL). Stirring was continued for 1 h, by which time oxidation was complete (TLC control, silica, 1:3 EtOAc-hexane). The mixture was applied directly to a column (1 x 15 cm) of silica gel, and the column was developed, using 1:4 EtOAc-hexane, to give ketone **106** (22.0 mg, 89%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2971 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, J = 7 Hz, 3 H), 2.02 (s, 3 H), 3.05 (t, J = 5.7 Hz, 2 H), 3.55 (q, J = 7.0 Hz, 2 H), 3.6 (s, 3 H), 3.62 (t, J = 7.9 Hz, 2 H), 3.78 (s, 3 H), 4.48-4.62 (m, 4 H), 5.62 (s, 1 H), 5.95 (s, 1 H), 6.62 (s, 1 H), 7.21-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4 (q'), 17.3 (q'),

27.8 (t'), 56.4 (q'), 62.9 (q'), 63.4 (t'), 66.2 (t'), 70.8 (t'), 73.0 (t'), 109.8 (d'), 127.7 (d'), 127.8 (d'), 128.6 (d'), 129.1 (s'), 130.0 (t'), 133.3 (s'), 134.3 (s'), 139.3 (s'), 144.9 (s'), 150.6 (s'), 154.1 (s'), 198.3 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{24}H_{30}NaO_5$ (M + Na) 421.19909, found 421.19876.

2,3,7,8-Tetrahydro-5*H*-4,9-dimethoxy-2-methyl-6-oxacyclopenta[b]naphthalen-1-one (107).



106 **107**

Ketone **106** (10.0 mg, 0.03 mmol) was dissolved in concentrated H_2SO_4 (0.1 mL) and the solution was stirred for 6 h. The resulting dark brown solution was diluted with water (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 8 cm), using 1:4 EtOAc-hexane, gave **107** (5.7 mg, 86%) as a pure (^1H NMR, 400 MHz), white solid: mp 123 °C; FTIR (CH_2Cl_2 cast) 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 7.2 Hz, 2 H), 2.60-2.71 (m, 2 H), 2.81 (t, J = 5.7 Hz, 2 H), 3.38 (q, J = 8.8 Hz, 1 H), 3.80 (s, 3 H), 3.86 (t, J = 5.8 Hz, 2 H), 3.87 (s, 3 H), 4.81

(s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.5 (q'), 22.9 (t'), 31.7 (t'), 42.4 (d'), 59.8 (q'), 61.4 (q'), 64.6 (d'), 64.7 (d'), 126.8 (s'), 127.4 (s'), 136.3 (s'), 142.2 (s'), 148.4 (s'), 152.0 (s'), 206.0 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{15}H_{18}NaO_4$ (M + Na) 285.11028, found 285.10978.

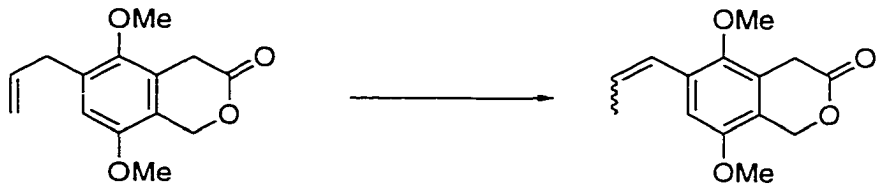
5,8-Dimethoxy-6-(2-propenyl)isochroman-3-one (80).

79 **80**

A mixture of PCC (54.5 mg, 0.25 mmol) and powdered 4 Å molecular sieves (40.0 mg) was added to a stirred solution of alcohol **79** (50.6 mg, 0.20 mmol) in dry CH_2Cl_2 (1.5 mL). Stirring was continued for 12 h, at which point some starting material still remained (TLC control, silica, 1:1 EtOAc-hexane). An additional portion of PCC (54.5 mg, 0.25 mmol) was added and stirring was continued for 1 h. The solvent was evaporated to approximately 0.5 mL and the resulting slurry was filtered through a pad (5 x 3 cm) of silica gel and washed with 1:1 EtOAc-hexane (5 mL), until all the product had been eluted (TLC control, silica, 1:1 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 2:3 EtOAc-

hexane, gave lactone **80** (46.8 mg, 93%) as a pure (^{1}H NMR, 400 MHz), white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.42 (d, *J* = 6 Hz, 2 H), 3.68 (s, br, 5 H), 3.81 (s, 3 H), 5.04-5.17 (m, 2 H), 5.36 (s, 2 H), 5.85-6.07 (m, 1 H), 6.63 (s, 1 H).

(*Z*)- and (*E*)-5,8-Dimethoxy-6-(1-propenyl)isochroman-3-one (82).

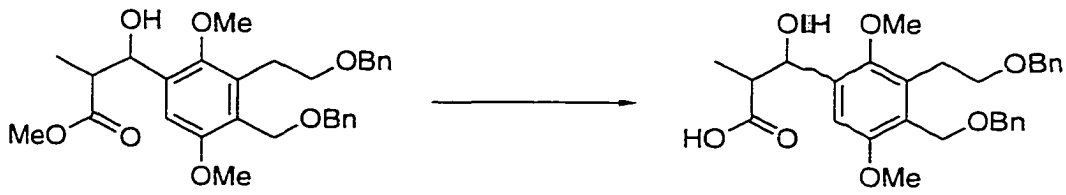


80 **82**

$RhCl_3.3H_2O$ (6.0 mg) was added to a stirred solution of olefin **80** (45.0 mg, 0.18 mmol) in dry 4:1 PhMe-EtOH (2 mL). The mixture was refluxed for 10 h, cooled and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave an inseparable mixture of isomeric olefins **82** (23.0 mg, 50%) as a white solid. The *trans* isomer had: ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.84 (dd, *J* = 7.0, 1.8 Hz, 3 H), 3.65 (s, 3 H), 3.67 (s, 2 H), 3.82 (s, 3 H), 5.37 (s, 2 H), 5.86-5.96 (m, 1 H), 6.49-6.58 (m, 1 H), 6.70 (s, 1 H).

The *cis* isomer had: ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.94 (dd, *J* = 6.6, 1.7 Hz, 3 H), 3.67 (s, 3 H), 3.70 (s, 2 H), 3.84 (s, 3 H), 5.35 (s, 2 H), 6.22-6.34 (m, 1 H), 6.58-6.67 (m, 1 H), 6.85 (s, 1 H).

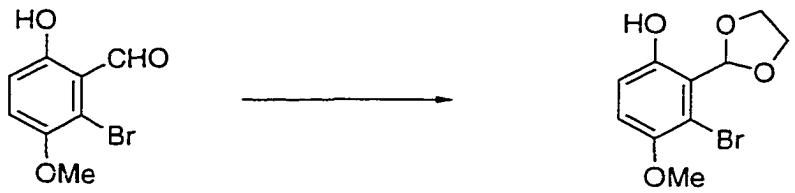
3-Hydroxy-3-[2,5-dimethoxy-3-[2-(phenylmethoxy)-ethyl]-4-[(phenylmethoxy)methyl]phenyl] -2-methylpropanoic acid (94).



93 **94**

Coarsely powdered KOH (15.0 mg, 0.27 mmol) was added to a swirled solution of ester **93** (45.0 mg, 0.09 mmol) in MeOH (0.25 mL) and water (0.1 mL). The reaction mixture was allowed to stand undisturbed for 12 h and then neutralized with 10% aqueous hydrochloric acid. The aqueous layer was extracted with CH_2Cl_2 (3 x 2.5 mL), and the combined organic extracts were washed with water (2.5 mL) and brine, and dried ($MgSO_4$). Evaporation of the solvent gave **94** (39.2 mg, 90%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (d, J = 6 Hz, 3 H), 2.91-3.15 (m, 2 H), 3.50-3.74 (m, 4 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 4.47-4.63 (m, 6 H), 5.42 (d, J = 2.7 Hz, 1 H), 6.98-7.02 (m, 1 H), 7.21-7.40 (m, 10 H).

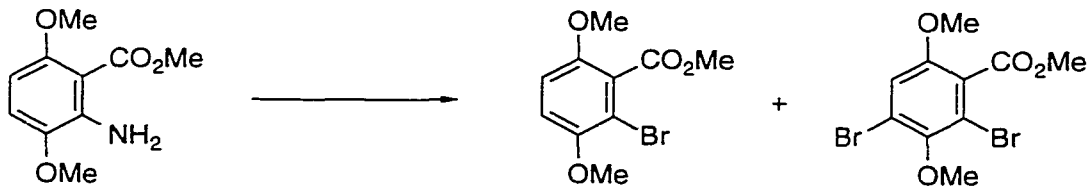
3-Bromo-2-(1,3-dioxolan-2-yl)-4-methoxy-1-benzenol (64).



61 **64**

Aldehyde **61** (509.0 mg, 2.200 mmol), ethylene glycol (273.1 mg, 4.4 mmol), and TsOH.$2H_2O$ (10.0 mg) were dissolved in dry PhH (15 mL). The reaction flask was attached to a Dean-Stark apparatus fitted with a condenser, and the reaction mixture was refluxed (oil bath at 125 °C) for 10 h, and cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm), using (1:3) EtOAc-hexane, gave **61** (40 mg, 8%) and **64** (462.2 mg, 76% or 84% based on conversion) as a pure (^{1}H NMR, 400 MHz), pale yellow solid: ^{1}H NMR (400 MHz) δ 3.8 (s, 3 H), 4.05-4.15 (m, 2 H), 4.20-4.25 (m, 2 H), 6.18 (s, 1 H), 6.80 (d, J = 8.5 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H), 8.42 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 57.4 (q'), 65.3 (t'), 105.8 (d'), 114.0 (s'), 115.1 (d'), 117.1 (d'), 119.3 (s'), 149.9 (s'), 151.9 (s'). Anal. Calcd for $C_{10}H_{11}BrO_4$: C 43.66, H 4.03. Found: C 43.5083, H 3.93.

Methyl 2-Bromo-3,6-dimethoxybenzoate (40) and Methyl 2,4-Dibromo-3,6-dimethoxybenzoate (56).

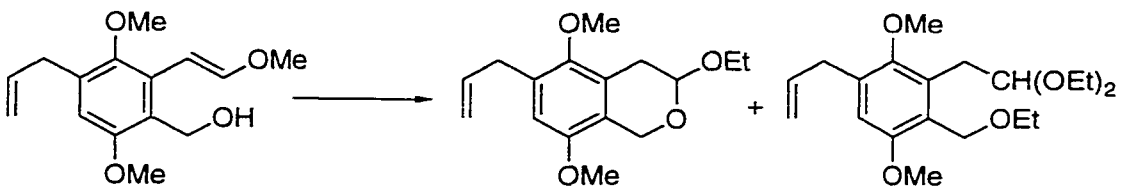


54 **40** **56**

Oven-dried (110 °C), anhydrous $CuBr_2$ (397.2 mg, 1.778 mmol), was placed in a flask fitted with a condenser. Freshly distilled MeCN (4.5 mL) was added with stirring, followed by isoamyl nitrite (0.30 mL, 2.22 mmol), and the resulting green solution was stirred and warmed at 65 °C. A solution of amine **54** (312.7 mg, 1.482 mmol) in MeCN (0.75 mL) was added dropwise, resulting in a brown solution and effervescence. After bubbling had subsided (*ca* 5 min), the mixture was allowed to cool to room temperature, and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with 20% aqueous hydrochloric acid (10 mL), water (10 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:1 EtOAc-hexane, gave dibromide **56** (368.2 mg, 70%) and the desired monobromide **40** (40.7 mg, 10%). The dibromide had: mp 56-57 °C; FTIR (CH_2Cl_2 cast) 1740 cm^{-1}; ^1H NMR (400 MHz) δ 3.81 (s, 3 H), 3.91 (m, 3 H), 4.00 (m, 3 H), 7.15 (s, 1 H); exact mass (HR electrospray) *m/z* calcd for $C_{10}H_{10}{}^{79}Br_2NaO_4$ (M + Na)

374.88435, found 374.8842. The monobromide data were the same as those reported before.

3-Ethoxy-5,8-dimethoxy-6-(2-propenyl)isochroman (87) and 3-[(2,2-Diethoxyethyl]-2-(ethoxymethyl)-1,4-dimethoxy-5-(2-propenyl)benzene (88).



78 **87** **88**

Ethanolic HCl (0.20 mL) was added to a stirred solution of enol ethers **78** (50.0 mg, 0.19 mmol). Stirring was continued for 12 h and the mixture was neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with water (10 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave acetal **87** (21.0 mg, 40%) and acetal **88** (27.0 mg, 42%). Compound **87** had: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (300 MHz) δ 1.21 (t, J = 6.8 Hz, 3 H), 2.70-2.98 (m, 2 H), 3.38 (d, J = 7.2 Hz, 2 H), 3.51-3.61 (m, 1 H), 3.62 (s, 3 H), 3.75 (s, 3 H), 3.78-3.90 (m, 1 H), 4.65 (s, 2 H), 4.98 (t, J = 4.0 Hz, 1 H), 5.05-5.12 (m, 2 H), 5.91-6.05 (m, 1 H), 6.51 (s, 1 H); exact mass (HR electrospray) m/z calcd for

$C_{16}H_{22}NaO_4$ (M + Na) 301.14158, found 301.14190.

Compound **88** had: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (300 MHz) δ 0.75 (t, *J* = 6 Hz, 3 H, 2 peaks), 1.18 (t, *J* = 6 Hz, 3 H), 3.05 (d, *J* = 6 Hz, 2 H), 3.31-3.65 (m, 8 H), 3.70 (s, 2 H), 3.75 (s, 2 H), 4.55 (s, 2 H), 4.71 (t, *J* = 3 Hz, 1 H), 5.05-5.18 (m, 2 H), 5.85-6.15 (m, 1 H), 6.6 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 15.5 (q'), 15.54 (q'), 32.65 (t'), 34.7 (t'), 56.4 (q'), 61.55 (q'), 63.7 (t'), 66.0 (t'), 104.4 (d'), 111.7 (d'), 116.0 (t'), 125.8 (s'), 132.6 (s'), 133.5 (s'), 137.65 (d'), 151.44 (s'), 154.9 (s'); exact mass *m/z* calcd for $C_{20}H_{32}O_5$ 352.22498, found 352.22476.

Methyl 3-Hydroxy-3-(2,5-dimethoxyphenyl)-2-methylpropanoate (96).

95 **96**

BuLi (2.5 M in hexanes, 3.9 mL, 9.8 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.15 mL, 1.45 g, 10.3 mmol) in THF (9.3 mL). After 15 min, freshly distilled methyl propionate (828 mg, 0.90 mL, 9.39 mmol) in THF (2.5 mL) was added dropwise, and stirring was continued at -78 °C for 40 min. The resulting enolate solution was taken up into a syringe and added at a fast

dropwise rate to a stirred solution of 2,5-dimethoxybenzaldehyde (1.871 g, 11.27 mmol) in dry THF (2.5 mL). Stirring was continued for 45 min, and the mixture was diluted with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 18 cm), using 1:4 EtOAc-hexane, gave a mixture of diastereomeric alcohols **96** (2.299 g, 80%) as a colorless oil. The material was used directly for the nest step, without characterization.

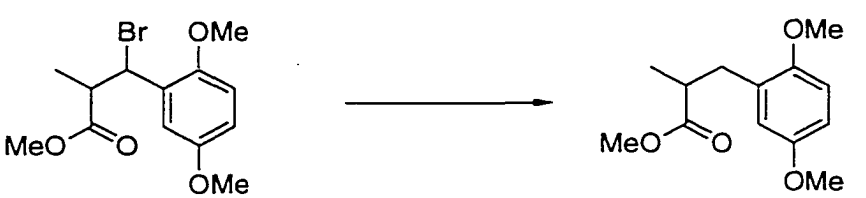
Methyl 3-Bromo-3-(2,5-dimethoxyphenyl)-2-methyl-propanoate (97).

96 **97**

Ph_3P (870.9 mg, 3.320 mmol) was added to a stirred solution of alcohols **96** (421.7 mg, 1.660 mmol) in MeCN (12 mL). After 5 min a homogenous mixture was obtained, and 2,6-lutidine (17.2 mg, 19.4 mL, 0.17 mmol) was added, followed by CBr_4 (1.101 g, 3.320 mmol). The resulting orange solution was stirred for 45 min, poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 20 mL). The combined

organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 12 cm), using (1:4 EtOAc-hexane), gave **97** (240.1 mg, 45%) as a pale brown oil that was a 3:2 mixture of diastereomers. ^1H NMR measurements and TLC examination showed that this product undergoes slight decomposition on contact with silica gel. The material, which was used directly for stannane reduction without full characterization, had: ^1H NMR (minor diastereomer) δ 1.01 (d, J = 6.0 Hz, 3 H), 3.41-3.50 (m, 1 H), 3.51 (s, 3 H), 3.78 (s, 3 H), 3.88 (s, 3 H), 5.55 (d, J = 12.0 Hz, 1 H), 6.91-7.15 (m, 3 H); ^1H NMR (major diastereomer) δ 1.41 (d, J = 6.0 Hz, 3 H), 3.21-3.39 (m, 1 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 3.88 (s, 3 H), 5.65 (d, J = 12.0 Hz, 1 H), 6.81-6.88 (m, 3 H).

Methyl 3-(2,5-Dimethoxyphenyl)-2-methylpropanoate (98).

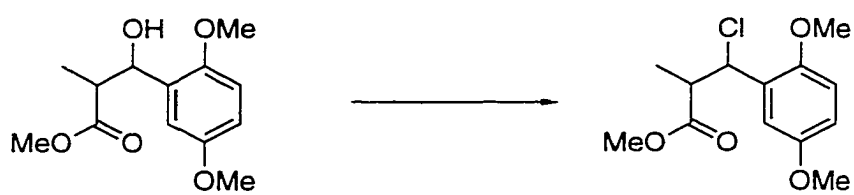


97 **98**

Bu_3SnH (0.24 mL, 0.91 mmol) and AIBN (10.0 mg) were added to a solution of bromide **97** (240.1 mg, 0.758 mmol) in PhH (10 mL), and the mixture was refluxed and stirred for 2 h. Evaporation of the solvent and flash chromatography of

the residue over silica gel (1.5 x 12 cm), using 1:9 EtOAc-hexane, gave **98** (216.1 mg, 100%) as a colorless oil containing inseparable tin residues: FTIR (CH_2Cl_2 cast) 1735 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (d, J = 7 Hz, 3 H), 2.75 (dd, J = 13.2, 7.6 Hz, 1 H), 2.86 (sextet, J = 7 Hz, 1 H), 3.01 (dd, J = 13.2, 6.7 Hz, 1 H), 3.61 (s, 3 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 6.66-6.70 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 17.1 (q'), 34.9 (t'), 39.9 (d'), 51.6 (q'), 55.9 (q'), 56.1 (q'), 111.5 (d'), 111.9 (d'), 117.4 (d'), 129.3 (s'), 152.3 (s'), 153.7 (s'), 176.9 (s'); exact mass *m/z* calcd for $C_{13}H_{18}O_4$ 238.12051, found 238.11999.

Methyl 3-Chloro-3-(2,5-dimethoxyphenyl)-2-methyl-propanoate (99).



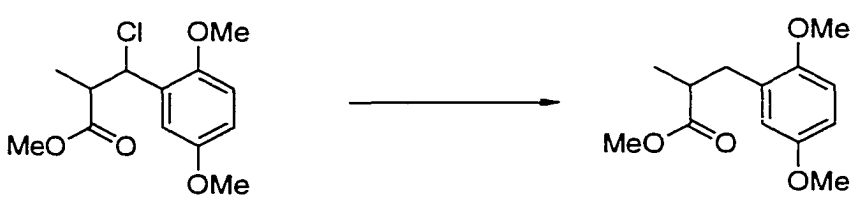
96 **99**

Et_3N (0.21 mL, 1.51 mmol) was added to a stirred solution of alcohol **96** (255.7 mg, 1.007 mmol) in CH_2Cl_2 (10 mL). $SOCl_2$ (180 mg, 0.11 mL, 0.17 mmol) was added dropwise and stirring was continued for 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue

over silica gel (2.5 x 12 cm), using (1:4 EtOAc-hexane), gave **99** (253.0 mg, 93%) as a colorless oil. The material was a 3:2 diastereomeric mixture. The minor diastereomer had: FTIR (CH_2Cl_2 cast) 1739 cm^{-1}; ^1H NMR (300 MHz) δ 0.98 (d, J = 7.0 Hz, 3 H), 3.12-3.25 (m, 1 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 5.12 (d, J = 10.7 Hz, 1 H), 6.91-7.15 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 15.8 (q'), 48.7 (d'), 52.2 (d'), 56.0 (q'), 56.55 (q'), 58.0 (q'), 112.7 (d'), 114.5 (d'), 115.0 (d'), 128.1 (s'), 151.4 (s'), 154.2 (s'), 174.7 (s'); exact mass m/z calcd for $C_{13}H_{17}{}^{35}ClO_4$ 272.08383, found 272.08096.

The major diastereomer had: FTIR (CH_2Cl_2 cast) 1739 cm^{-1}; ^1H NMR (300 MHz) δ 1.28 (d, J = 6.0 Hz, 3 H), 3.12-3.25 (m, 1 H), 3.61 (s, 3 H), 3.79 (s, 3 H), 3.87 (s, 3 H), 5.71 (d, J = 10.7 Hz, 1 H), 6.81-6.86 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 13.1 (q'), 46.0 (d'), 52.1 (d'), 56.0 (q'), 56.5 (q'), 59.5 (q'), 112.2 (d'), 114.2 (d'), 115.0 (d'), 129.1 (d'), 150.5 (s'), 153.9 (s'), 173.5 (s'); exact mass m/z calcd for $C_{13}H_{17}{}^{35}ClO_4$ 272.08383, found 272.08096.

Methyl 3-(2,5-dimethoxyphenyl)-2-methylpropanoate (98).



99 **98**

Bu_3SnH (0.30 mL, 1.12 mmol) and AIBN (12.0 mg) were added to a solution of chloride **96** (253.3 mg, 0.930 mmol) in dry PhH (20 mL), and the mixture was refluxed with stirring for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 12 cm), using 1:6 EtOAc-hexane, gave **98** (213.1 mg, 89%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1735 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (d, *J* = 7 Hz, 3 H), 2.75 (dd, *J* = 13.2, 7.6 Hz, 1 H), 2.86 (sextet, *J* = 7 Hz, 1 H), 3.01 (dd, *J* = 13.2, 6.7 Hz, 1 H), 3.61 (s, 3 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 6.66-6.70 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 17.1 (q'), 34.9 (t'), 39.9 (d'), 51.6 (q'), 55.9 (q'), 56.1 (q'), 111.5 (d'), 111.9 (d'), 117.4 (d'), 129.3 (s'), 152.3 (s'), 153.7 (s'), 176.9 (s'); exact mass *m/z* calcd for $C_{13}H_{18}O_4$ 238.12051, found 238.11999.

3-(2,5-Dimethoxyphenyl)-2-methylpropanoic acid (100).

98 **100**

Coarsely powdered KOH (58.2 mg, 1.00 mmol) was added to a swirled solution of ester **98** (82.2 mg, 0.35 mmol) in MeOH (1.0 mL) and water (0.2 mL). The mixture was allowed to

stand undisturbed for 12 h and then neutralized with 10% aqueous hydrochloric acid. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were washed with water (10 mL) and brine, and dried ($MgSO_4$). Evaporation of the solvent gave **100** (70.0 mg, 90%) as a white solid: mp 53 °C; FTIR (CH_2Cl_2 cast) 2938, 1704 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (d, *J* = 7.0 Hz, 3.0 H), 2.75 (dd, *J* = 13.2, 7.6 Hz, 1 H), 2.86 (sextet, *J* = 7.0 Hz, 1 H), 3.01 (dd, *J* = 13.2, 6.7 Hz, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 6.77-6.70 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 16.7 (q'), 34.3 (t'), 39.4 (d'), 55.6 (q'), 55.7 (q'), 111.1 (d'), 111.2 (d'), 117.2 (d'), 128.6 (s'), 151.7 (s'), 153.25 (s'), 182.8 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{12}H_{16}NaO_4$ (M + Na) 247.09463, found 247.09458.

4,7-Dimethoxy-2-methylindan-1-one (101).

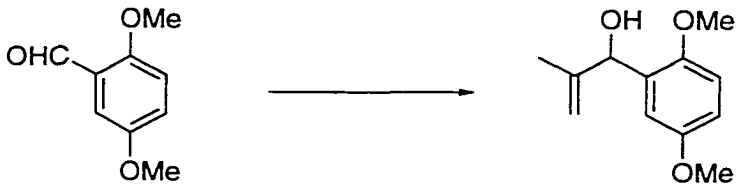
100 **101**

P_2O_5 (282.0 mg) was added to orthophosphoric acid (85%, d 1.7 g/mL, 0.13 mL, 218 mg), and the mixture was heated for 30 min (Ar atmosphere) at 200 °C (oil-bath) in a flask fitted with a reflux condenser and containing a magnetic stirring bar.[33] The mixture was then cooled to room temperature, and

used as follows.

Acid **100** (34.0 mg, 0.15 mmol) was added to freshly prepared polyphosphoric acid (500.0 mg). The greyish-white reaction mixture was heated to 65 °C with stirring, at which point it became a yellow solution. Heating was continued for 8 h and the reaction flask was removed from the oil bath and allowed to cool to room temperature. Water (2 mL) was added and the slurry was extracted with EtOAc (3 x 10 mL), and the combined extracts were washed with water (10 mL) and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a white solid. This was redissolved in CH_2Cl_2 (0.25 mL) and purified by flash chromatography over silica gel (1 x 8 cm), using 2:3 EtOAc-hexane, to give **101** (18.9 mg, 60%) as a pure, white solid: FTIR (CH_2Cl_2 cast) 1707 cm^{-1}; ^1H NMR (400 MHz) δ 1.24 (d, J = 7.4 Hz, 3 H), 2.55 (ddd, J = 17.1, 3.7, 0.5 Hz, 1 H), 2.60-2.71 (m, 1H), 3.23 (dd, J = 17.7, 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.86 (s, 2 H), 6.82 (AB q, $\Delta\nu_{AB}$ = 91.0 Hz, J = 8.7 Hz, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 16.9 (q'), 31.3 (t'), 42.1 (d'), 55.8 (q'), 56.0 (q'), 109.5 (d'), 116.6 (d'), 125.5 (s'), 144.2 (s'), 150.4 (s'), 151.9 (s'), 207.5 (s'); exact mass m/z calcd for $C_{12}H_{14}O_3$ 206.09430, found 206.09475.

1-(2,5-Dimethoxyphenyl)-2-methyl-2-propen-1-ol (102).



95 **102**

Isopropenylmagnesium bromide (1.0 M in THF, 3.3 mL, 3.3 mmol) was added dropwise to a stirred and cooled (0 °C) solution of aldehyde **95** (500.0 mg, 3.012 mmol) in Et_2O (20 mL). The reaction was followed by TLC (silica, 1:3 EtOAc-hexane) and, after 2 h, since much (*ca* 50%) of the starting material remained unreacted, an additional portion of isopropenylmagnesium bromide (1.5 mL, 1.5 mmol) was added. Stirring was continued for an additional 2 h, by which point more of the starting material had been consumed. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the organic phase was washed with water (5 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 1:4 EtOAc-hexane, gave alcohol **102** (375.8 mg, 60%), along with unreacted starting material (30%). Alcohol **102** had: ^1H NMR (400 MHz) δ 2.71 (s, 3 H), 2.63 (br s, 1 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.93 (s, 1 H), 5.21 (s, 1 H), 5.34 (s, 1 H), 6.79-6.89 (m, 3 H). ^{13}C NMR

(CD_2Cl_2, 75.5 MHz) δ 19.7 (q'), 55.9 (q'), 56.3 (q'), 73.0 (d'), 110.5 (t'), 112.3 (d'), 113.2 (d'), 114.0 (d'), 132.0 (s'), 146.9 (s'), 151.6 (s'), 154.2 (s'); exact mass *m/z* calcd for $C_{12}H_{16}O_3$ 208.10944, found 208.10938.

2-[2,5-Dimethoxyphenyl] 2-propenyl ketone (103).

102 **103**

A mixture of PCC (450.7 mg, 2.091 mmol) and powdered 4 Å molecular sieves (100.0 mg) was added to a stirred solution of alcohol **102** (334.6 mg, 1.743 mmol) in dry CH_2Cl_2 (4 mL). Stirring was continued for 1 h, by which time oxidation was complete (TLC control, silica, 1:3 EtOAc-hexane), and the mixture was applied directly to a column (1 x 15 cm) of silica gel. The column was developed using 1:4 EtOAc-hexane, to give ketone **103** (315.0 mg, 95%) as a pure (^1H NMR, 300 MHz), colorless oil which solidified on storage in a refrigerator: mp 31 °C; FTIR (CH_2Cl_2 cast) 1664 cm^{-1}; δ 2.04 (s, 3 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 5.65 (m, 1 H), 5.92 (m, 1 H), 6.77-6.91 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 17.12 (q'), 55.82 (q'), 56.47 (q'), 112.96 (d'), 114.10 (d'), 116.35 (d'), 128.93 (t'), 129.97 (s'), 145.00 (s'), 151.04 (s'), 153.24 (s'), 198.21 (s'); exact mass *m/z* calcd for

$C_{12}H_{14}O_3$ 206.09430, found 206.09449.

4,7-Dimethoxy-2-methylinden-1-one (101).

103 **101**

Ketone **103** (24.8 mg, 0.12 mmol) was dissolved in concentrated H_2SO_4 (0.2 mL) and the mixture was stirred for 24 h. The resulting dark brown solution was diluted with water (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic extracts were washed with water (2 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 8 cm), using 1:4 EtOAc-hexane, gave ketone **101** (16.1 mg, 65%) as a pure (^1H NMR, 360.1), white solid, spectroscopically identical with material obtained previously.

References and footnotes

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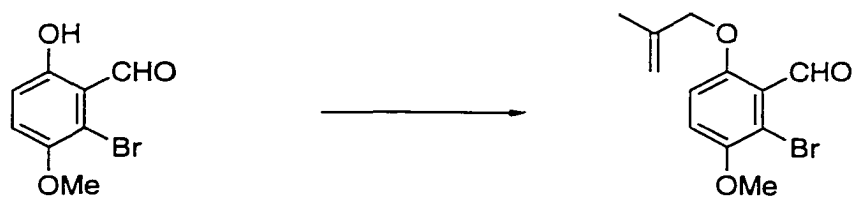
(22) A similar experiment was done with the 2-methyl-2-propenyl ether corresponding to **62**:

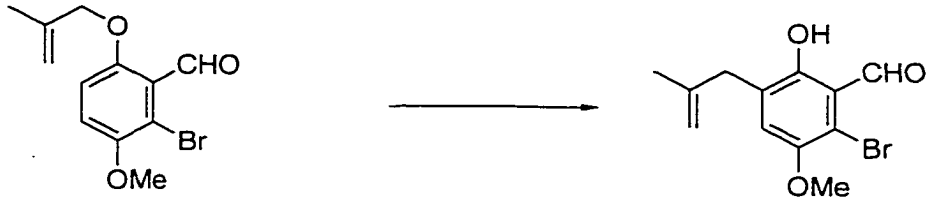
2-Bromo-3-methoxy-6-(2-methyl-2-propenyloxy)-benzaldehyde (A).



61 **A**

Aldehyde **61** (96.7 mg, 0.42 mmol) in DMF (0.25 mL) was added dropwise to a cooled (0 °C) slurry of NaH (11.6 mg, 0.48 mmol) in dry DMF (0.5 mL). The cold bath was removed, and the bright yellow slurry was stirred for 1 h, and then recooled to 0 °C. 3-Bromo-2-methylpropene (0.84 mL, 0.84 mmol) was added dropwise, the cold bath was removed, and stirring was continued for 4 h. The reaction mixture was poured into brine (5 mL) and extracted with Et_2O (4 x 5 mL). The combined organic extracts were washed with aqueous KOH (10%, 8 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The pale yellow crude residue was redissolved in CH_2Cl_2 (0.5 mL) and purified by flash chromatography over silica gel (1.5 x 20 cm), using 1:4 EtOAc-hexane, to give **A** (95.2 mg, 80%) as a pure (^1H NMR, 400 MHz), white, crystalline solid: FTIR (CH_2Cl_2 cast) 1696 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.82 (s, 3 H), 3.88 (s, 3 H), 4.51 (s, 2 H), 4.99-5.12 (m, 2 H), 7.01 (dd, J = 24.0, 6.6 Hz, 2 H), 10.41 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 19.4 (q'), 57.4 (q'), 73.5 (t'), 113.1 (t'), 113.4 (d'), 113.8 (s'), 117.4 (s'), 125.8 (s'), 151.1 (s'), 154.8 (s'), 190.7 (d'); exact mass (HR electrospray) m/z calcd for $C_{12}H_{13}{}^{79}BrNaO_3$ (M + Na) 306.99457, found 306.99436.

2-Bromo-6-hydroxy-3-methoxy-5-(2-methyl-2-propenyl)benzaldehyde (B).



A **B**

A solution of aldehyde **A** (51.0 mg, 0.18 mmol) in degassed decalin (0.75 mL) was refluxed under Ar for 6.5 h and then cooled to room temperature. Flash chromatography of the mixture (without evaporation of the solvent) over silica gel (1 x 15 cm), using 1:12 EtOAc-hexane, gave phenol **B** (31.2 mg, 61%) as a pure, yellow oil: FTIR (CH_2Cl_2 cast) 1696 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.72 (s, 3 H), 3.36 (s, 2 H), 3.85 (s, 3 H), 4.66-4.71 (m, 1 H), 4.83-4.86 (m, 1 H), 7.13 (s, 1 H), 10.41 (s, 1 H), 11.87 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 22.4 (s'), 37.1 (t'), 57.9 (q'), 112.4 (t'), 114.0 (s'), 117.7 (s'), 123.7 (d'), 129.2 (s'), 144.0 (s'), 149.2 (s'), 156.6 (s'), 198.8 (d'); exact mass *m/z* calcd for $C_{12}H_{13}{}^{79}BrO_3$ 284.00479, found 284.00463.

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