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TITANIUM-INDUCED DICARBONYL COUPLING AND THE CHEMICAL DEGRADATION OF MEVINOLIN AND COMPACTIN

by

CHENGZHI ZHANG

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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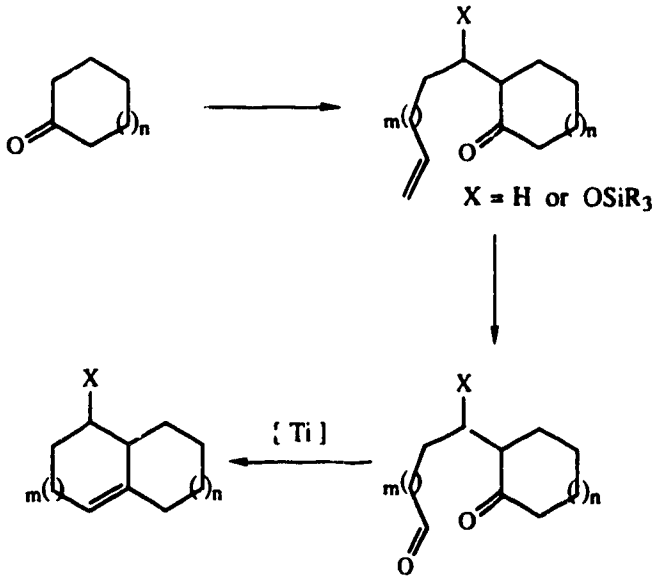
To my wife and my parents

ABSTRACT

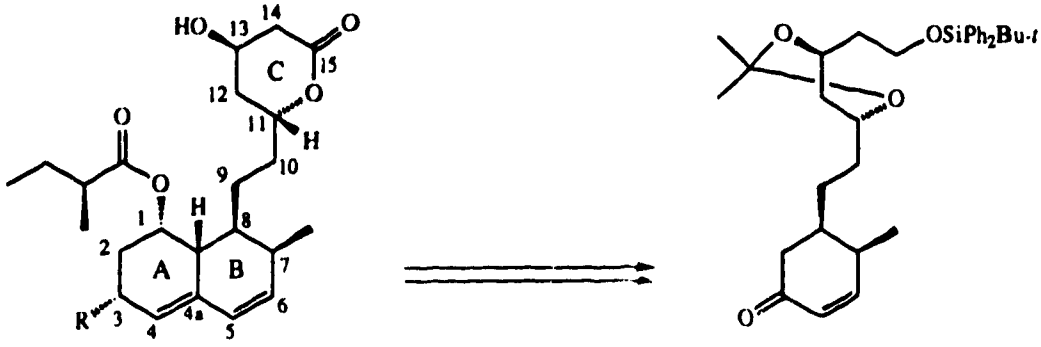
The first part of this Thesis describes the development of a new low-valent titanium reagent and its use in a general method of annulation (Scheme A). The reagent is *formally* a Ti(I) species and, unlike other low-valent titanium species, it can be used with highly oxygenated substrates.



Scheme A

The second part of the thesis describes the degradation of both mevinolin (**1a**) and compactin (**1b**) into the enone **2**. This enone had previously been made by total synthesis and it can be converted into a range of analogues of **1a** in which ring A is modified. The degradation reported here therefore

makes available a number of semisynthetic analogues.



1a R = H
1b R = Me

2

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I would like to express my gratitude to Professor D. L. J. Clive for his advice and encouragement during the course of my research, and for his assistance in the preparation of this thesis.

I thank Dr. K. S. Keshava Murthy and Douglas W. Hayward for several results mentioned in the first section of the thesis. (Experimental details for that work are not included here, as this thesis describes only the author's research.)

The help of the Technical Staff of the Chemistry Department is greatly appreciated; in particular the NMR and Mass Spectral Technical Staffs provided considerable assistance with high-field NMR and mass spectral measurements, respectively.

I would like to thank my friends and co-workers for frequent helpful discussions and advice. I am specially grateful to Michel Cantin, Sylvain Daigneault, Nola Etkin, Hartford Manning, Martin Postema, Dr. Yong Tao, and Dr Peter Vernon.

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Most importantly, I want to thank my wife, Xiuying Sun and my son, Tenghao Zhang, for their constant support.

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LIST OF ABBREVIATIONS

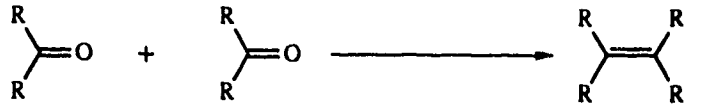
CIMS	chemical ionization mass spectrum
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
DMF	*N*,*N*-dimethylformamide
FABMS	fast atom bombardment mass spectrum
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidide
MCPBA	*m*-chloroperoxybenzoic acid
NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butylhydroperoxide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOTMS	trimethylsilyl triflate
TMS	trimethylsilyl

Chapter I

Low-Valent Titanium Reagents for Dicarbonyl Coupling

Introduction

During an experimental survey[1,2,3] of reductions with T(III), McMurry sought to examine the effect of $TiCl_3$ on the behavior of $LiAlH_4$, it being known that the presence of metal salts altered the behavior of the hydride. On adding benzophenone to a slurry formed by reaction of $LiAlH_4$ with $TiCl_3$ in THF, he found that tetraphenylethylene was formed in high yield. This type of reaction, in which carbonyl compounds — usually ketones or aldehydes — are coupled by use of low-valent titanium to produce olefins (Scheme 1), has



R = aliphatic or aromatic

Scheme 1

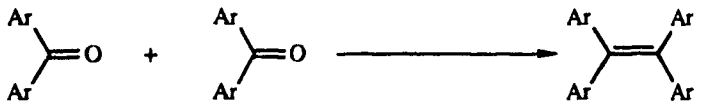
served for many years as an extremely useful procedure and is usually known as the McMurry reaction.[4] The active reagent is referred to[5,6,7,8] as a Ti(0) species, and the scope of the method has been examined in detail. A number of reviews [1,2,4] are available and the essential characteristics of the process are as follows:

Types of Carbonyl Compounds Coupled

(a) Intermolecular Reactions[9,10,11]

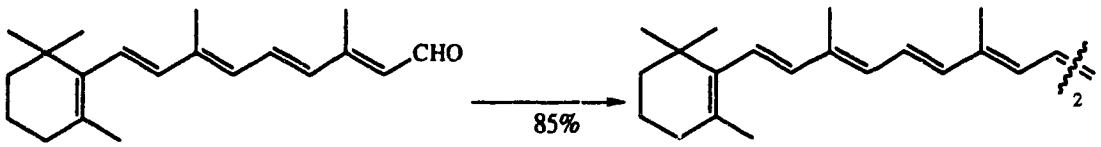
In the original report[3] aryl (Ar_2CO), aralkyl [Ar(R)CO],

and alkyl [R(R')CO] ketones were shown to give the corresponding olefins (Scheme 2),[3] as did aryl aldehydes.[3]



Scheme 2

Unsaturated ketones[2] and aldehydes also undergo the reaction. For example, retinal gives β-carotene in 85% yield (Scheme 3).[3] In the case of aldehydes and aralkyl ketones the



Retinal β-Carotene

Scheme 3

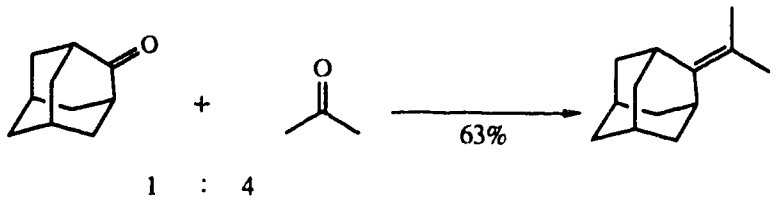
products are sometimes formed with exclusive *E*-geometry,[3] and sometimes[2,12] isomer mixtures are obtained.

At the same time that McMurry was studying the dicarbonyl coupling two related reports appeared describing the use of systems based on $TiCl_4/Zn$[13] and $TiCl_4/Mg$.[14]

(b) Cross Coupling Reactions[9,15,16,17]

McMurry examined the possibility of making unsymmetrical olefins by coupling two different carbonyl compounds.[9,16] A mixture of symmetrical and unsymmetrical olefins was obtained

but, if one component is used in excess, the reaction affords unsymmetrical olefins in good yield. For example, use of a 1:4 mixture of adamantanone and acetone gave the cross coupling product in 63% yield (Scheme 4) with little (12%)

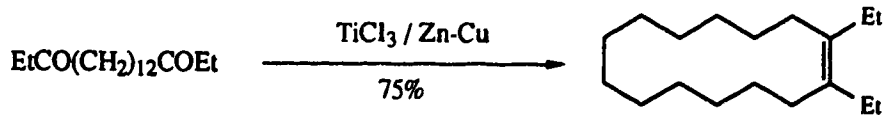


Scheme 4

bisadamantylidene. Unsymmetrical products are formed efficiently when one of the starting ketones is a diaryl ketone. Unsymmetrical olefins are also available from diaryl ketones and aralkyl ketones ($TiCl_3$/Li/DME).[18]

(c) Intramolecular Reactions[9]

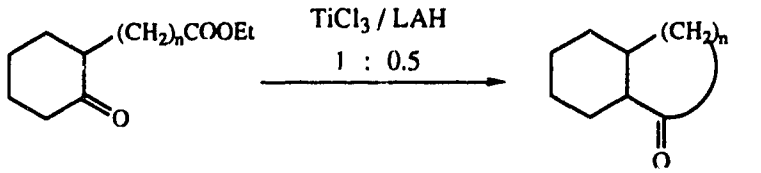
The coupling reaction works in an intramolecular sense and, when an α,ω-dicarbonyl compound — a dialdehyde, diketone, or keto aldehyde — is added slowly (e.g., over 24 hours) to a slurry of the titanium reagent (prepared from $TiCl_3$ and Zn(Cu) couple), then a cyclic olefin is formed in high yield (Scheme 5). Ring sizes 3 to 16 and 22 have been



Scheme 5

prepared and the ketone terminus can be aliphatic or aromatic.[9,19,20] Even strained olefins are accessible.[21,22,23]

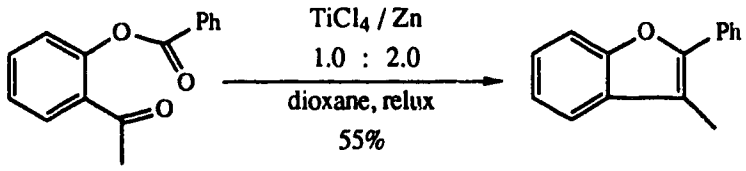
The cyclization of α,ω-keto *esters* (Scheme 6)[24,25] can be



n = 2, 3, 5, 6, 11 50-80%

Scheme 6

accomplished by using a reagent prepared from $LiAlH_4$, $TiCl_3$ and triethylamine, and ring sizes from 4 to 14 have been generated. Reagent made from $TiCl_3$ and Zn(Cu) couple does work, but the yields are lower. The $TiCl_4$/Zn (1:2) system has been used to prepare furans (Scheme 7).[26] Other examples



Scheme 7

of the use of base have been reported.[27]

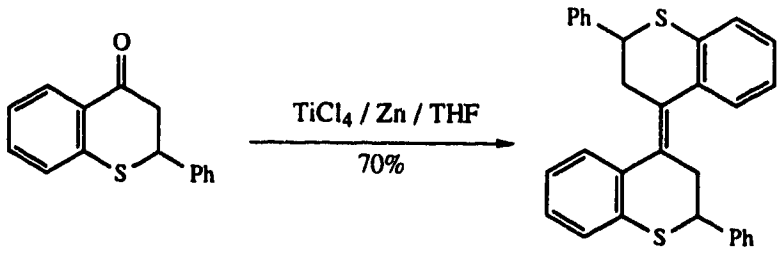
Types of Reagent

Representative examples of the types of reducing agents

that have been used are listed in Table 1, which also gives the ratios of the components in the reaction, as well as the solvents and products.

The K(3.2 mole):$TiCl_3$(1 mole) system is better than the reagent made from $LiAlH_4$ for coupling of aliphatic ketones, the $LiAlH_4$ reagent being erratic for this purpose.[46]

Reagent made form Zn(Cu) couple and $TiCl_3$ removes ethylene ketal groups,[9] but is compatible with the presence of phosphorus (as phosphine).[47] Reagent prepared from $TiCl_4$ and Zn is compatible with the presence of sulfur[48,49] and selenium (Scheme 8). The $TiCl_3$/K system can be used to deoxygenate phenols derivatized as their diethyl phosphate esters.[35]



Scheme 8

Table 1

Coupling Reagents and Proportions

Coupling Reagents	Compound Used	Moles $TiCl_n$ per mole Carbonyl	Reaction Conditions	Product	Yield (%)	Ref
$TiCl_4$/Zn 1:2.0	PhCHO	1.5	THF, 0°C	Pinacol	98	13
$TiCl_4$/Zn 1:2.0	PhCHO	1.5	Dioxane, reflux	Alkene	98	13
$TiCl_4$/Zn 1:2.0	**1**	1.5	THF, reflux	Alkene	71	28
$TiCl_4$/Zn 1:2.0	**2**	2.8	THF, reflux	Alkene	56-91	28
$TiCl_4$/Zn pyridine 1:2.0	**3**	1.07	THF, reflux	Alkene	25	29
$TiCl_4$/Zn/ pyridine --:--	**4**	---	THF, 0°C	Pinacol	71	30
$TiCl_4$/Zn 1:2.0	$PhCH_2CH_2CHO$	1.5	THF, reflux	Pinacol	86	13
$TiCl_4$/Mg(Hg) 1:2.0	cyclohexanone	1.5	THF, 0°C	Pinacol	93	31
$TiCl_4$/Mg(Hg) 1:2.70	**5**	1.5	THF, 0°C	Pinacol	90	31

Table 1 Continued

Coupling Reagents	Compound Used	Moles $TiCl_n$ per mole Carbonyl	Reaction Conditions	Product	Yield (%)	Ref
$TiCl_4$/Mg/ t-BuOH 1:1.0:2.0	(-)-carvone	2.0	THF, 5°C	Pinacol	70	32
$TiCl_4/C_8K$ 1:4.0	**6**	1.0		Alkene	84	33
$TiCl_4/C_8K$/ pyridine 1:4:1	cyclohexanone	2.0		Alkene	75	33
$TiCl_4$/LAH/Et_3N 1:0.4:0.15	**7**	6.8	---	**8**	100	34
$TiCl_3$/K 1:3.5	Adamantane	4.0	THF, reflux	Alkene	91	9
$TiCl_3$/K 1:3.0	$ArOP(O)(OEt)_2$	0.67	THF, reflux	Ar-H		35
$TiCl_3$/K 1:3.2	$Ph_2C=O$	1.0-5.0	THF, r.t.	Alkene	92-97	5
$TiCl_3$/K 1:3.2	cyclohexanone	1.0-5.0	THF, reflux	Alkene	86-90	5
$TiCl_3$/Li 1:3.5	cyclohexanone & benzophenone	4	DME reflux	Cyclohex-ylidenedi-phenyl-methane	78	16

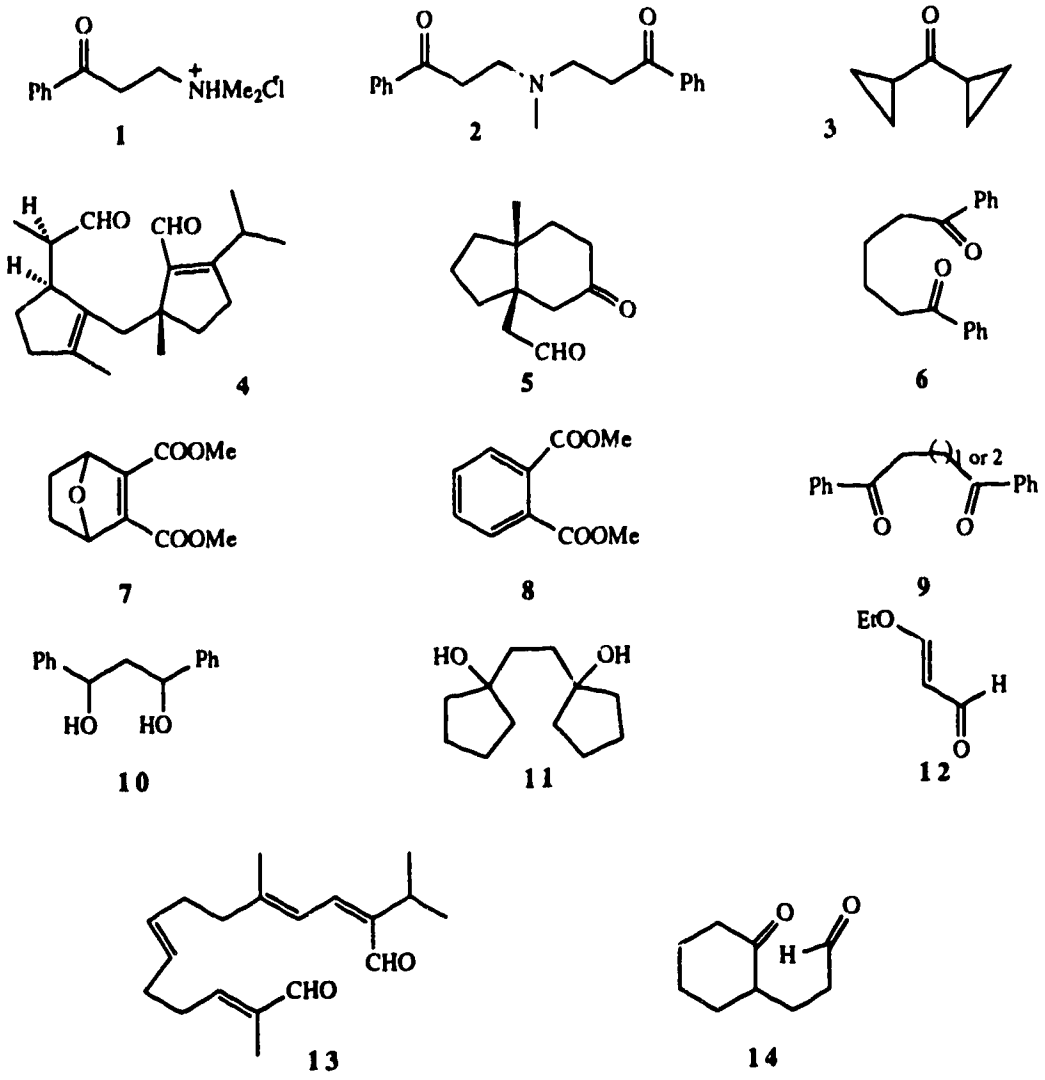
Table 1 Continued

Coupling Reagents	Compound Used	Moles $TiCl_n$ per mole Carbonyl	Reaction Conditions	Product	Yield (%)	Ref
$TiCl_3$/Mg 1:1.7	$Ph_2C=O$	1.0-5.0	THF, r.t	Alkene	94-99	5
$TiCl_3$/Mg 1:1.7	cyclohexanone	1.0-5.0	THF, reflux	Alkene	88-90	5
$TiCl_3/LiAlH_4$ 1:0.5	$Ph_2C=O$	1.0-5.0	THF, r.t.	Alkene	91-99	5
$TiCl_3/LiAlH_4$ 1:0.5	cyclohexanone	1.0-5.0	THF, reflux	Alkene	66-72	5
$TiCl_3/LiAlH_4$ 1:0.43	**9**	2.3	THF, reflux	Alkene	40-61	36
$TiCl_3/LiAlH_4$ 1:0.28	**10**	6.63 (Ti/OH)	THF, reflux or DME, reflux	1,2-Diphenyl-cyclo-propane	40	37
$TiCl_3/LiAlH_4$ 1:0.5	**11**	2.0 (Ti per OH)	THF, 0°C	Diene	90	38
$TiCl_3/LiAlH_4$ 1:0.5	**12**	1	THF	Pinacol		39
$TiCl_3(DME)_2$/ Zn-Cu 1:3.85	cyclohexanone	4.0	DME, reflux	Alkene	97	40

Table 1 Continued

Coupling Reagents	Compound Used	Moles $TiCl_n$ per mole Carbonyl	Reaction Conditions	Product	Yield (%)	Ref
$TiCl_3(DME)_2$/ Zn-Cu 1:3.85	cyclohexanone	2.0	DME, reflux	Alkene	75	40
$TiCl_3(DME)_2$/ Zn-Cu 1:3.85	tetradecanedial	4.0	DME, reflux	Alkene	80	40
$TiCl_3(DME)_2$/ Zn-Cu 1:3.0	Tetradecanedial	7.5	DME, 25°C	Pinacol	89	41
$TiCl_3/C_8K$ 1:3.0	cyclohexanone	4.0	THF, reflux	Alkene	79	42
$TiCl_3/C_8K$ 1:2.0	cyclohexanone	--	--	Pinacol	64	43
$TiCl_3(DME)_2$/ Zn-Cu --:--	**13**		DME, -40°C	Pinacol	46	44
Cp_2TiCl_2 1:0.75	**14**	3.0	THF 50°C	pinacol	49	31
$(n\text{-}C_6H_6)_2Ti$	$R_2C{=}O$ R = Me or Ph	2.0	THF reflux	Alkene	100	45
$(n\text{-}C_6H_6)_2Ti$	Benzil	2.0	THF reflux	Diphenyl-acetylene	96	45

The Strutures for Some Compounds in Table 1



Scheme 9

Mechanism

An early suggestion[3] was that a ketyl radical anion is formed from the carbonyl substrate and a Ti(II) species, and the ketyl then dimerizes (Scheme 10). The resulting pinacol

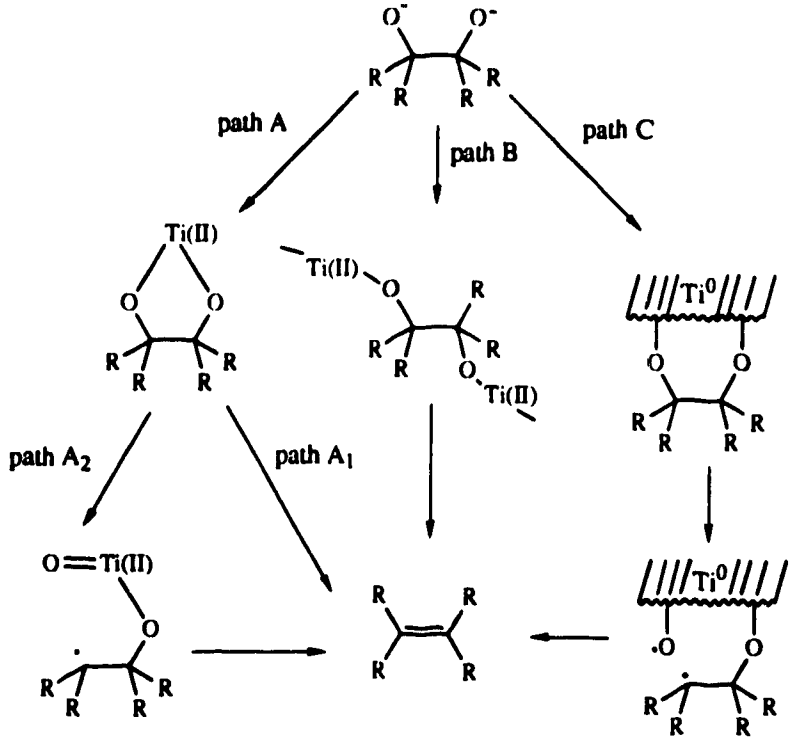
Scheme 10

alkoxide reacts with the titanium reagent to form the olefin and TiO_2. Evidence to support this suggestion is the isolation of pinacols when the reaction is not allowed to proceed to completion. In fact, the reaction can be run under conditions in which pinacols are formed in good yield.[30,50,41] When the presumed intermediate pinacols were subjected to the standard reaction conditions, the expected olefins were formed.[50] Collapse of the pinacols was taken to be the rate-determining step in the carbonyl coupling process, simply on the basis that the pinacols could be isolated.

Shortly afterwards the mechanistic proposal was changed, to invoke Ti(0),[9] but the idea of having pinacols as intermediates was retained, as the experimental results in that regard (i.e., the isolation of pinacols) were still valid.

It was found that *Z/E* double bond isomers are produced when starting from stereochemically pure 1,2-diols and, on this basis, the proposal was made that the deoxygenation is not concerted. Double bonds are not isomerized by the titanium reagent, unless the bonds are very strained.[2,25] The mechanism by which the intermediate 1,2-dioxygenated species is converted into olefins attracted McMurry's interest.[2] He

considered three possibilities (Scheme 11):

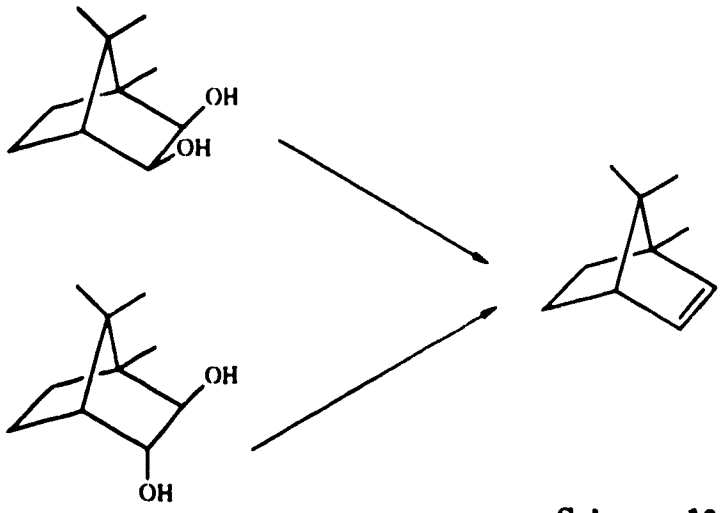


Scheme 11

In path A the deoxygenation occurs through a five-membered transition state, while in path B, the intermediate is one in which each of the two oxygens is attached to a different titanium atom. McMurry's path C was very vaguely defined and, presumably differs from path B mainly in the valence state of the attached titanium atoms. In suggesting this mechanistic scheme the valency of the active titanium species is not specifically dealt with.

The involvement of a five-membered intermediate was eliminated by showing that two stereochemically fixed diols

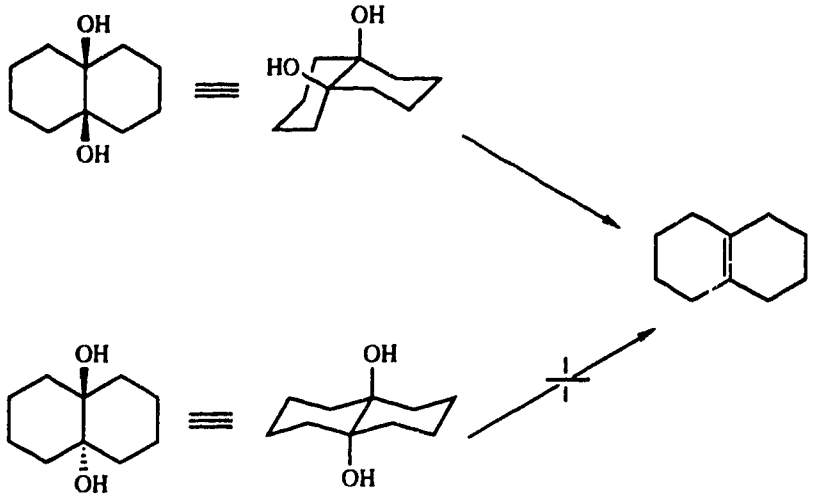
(*cis*- and *trans*-camphane diols, Scheme 12) both react with



Scheme 12

the $TiCl_3/LiAlH_4$ reagent at a similar rate, whereas, with lead tetraacetate, the rate difference is about 10^6, the *cis* isomer reacting faster.

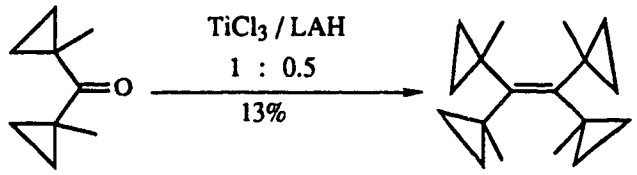
Path B could also be eliminated by experiments which revealed a great difference in behavior between *cis*- and *trans*-9,10-decalindiols. The cis isomer gave the expected olefin but the *trans* isomer was inert (Scheme 13). These observations were taken to mean that both oxygens must be



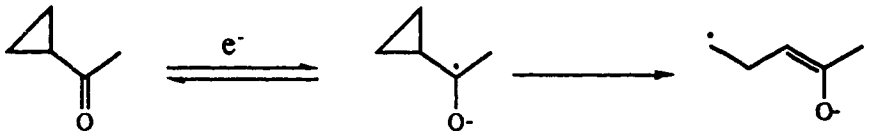
Scheme 13

able to bind to a common titanium surface. Thus, path C is left and represents the working hypothesis.

One observation against an intermediate ketyl radical anion is the fact that cyclopropyl ketones can be converted into olefins[51] (Scheme 14) even though it is known that ketyl radical anions formed from cyclopropyl ketones isomerize rapidly as shown in Scheme 15.[52]



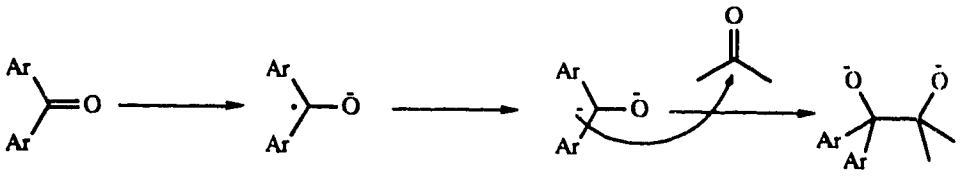
Scheme 14



Scheme 15

The difference between the reduction potential values

for diaryl ketones and aliphatic ketones has led to the suggestion of an ionic mechanism (Scheme 16).[16]



Scheme 16

Nature of the Reagent

The coupling reaction with low-valent titanium reagents is a heterogeneous process and so a mechanistic study is a difficult undertaking, but a detailed investigation was reported by a Belgian group,[5,6,7] and some progress has been made at least in defining satisfactory conditions for carrying out the reaction. A central question is the valence state of the titanium, but this can not yet be answered clearly.

Benzophenone and cyclohexanone were used[5] as models for the coupling of aromatic and aliphatic ketones, respectively. The work was a pioneering effort in the field but, in searching for the best conditions, the Belgian group did not carry out a full optimization study. Consequently, their experiments did not reveal conditions for the global maximum yield (see discussion section on our own optimization work). The use of Li, K, and $LiAlH_4$ for reduction of $TiCl_3$ was examined, best results being obtained with the proportions listed in Table 2.

Table 2

The Optimized Ratios

Reducing agent	$TiCl_3$:reducing agent	$TiCl_3$:ketone
Li	1:3.2	1:1
K	1:3.2	1:1
Mg	1:1.7	1:1
$LiAlH_4$	1:0.5	1:1

It was stressed that it is important to ensure that the reduction of the $TiCl_3$ is carried out to completion.[53] This may not always be easy; as it is reasonable to suspect that the reducing agent (Li, K, $LiAlH_4$) becomes coated with insoluble titanium particles. All the systems in Table 2 performed very well, suggesting that "rather similar" species are formed in each case. In retrospect, we believe, on the basis of our own investigations, that this is not necessarily a valid conclusion, since the behavior of benzophenone (and probably also cyclohexanone) is not very sensitive to the nature of the titanium reagent.

In each experiment the black color of titanium persists at the end of the coupling process and so titanium dioxide was not regarded as an end product. However, we think that the white color of the dioxide could easily be obscured by a

slight excess of the black reagent, although we never saw in our own experiments any evidence that the mixtures became paler in color.

A number of solvents were tested, the range of possibilities being limited to hydrocarbons and ethers by the reactive nature of the titani agent and the reducing agents used in its preparation. Benzene, cyclopentadiene, hexane, furan, thiophene, pyridine, anisole, THF, glyme, diglyme, and diethyl ether were tried. Generation of the low-valent titanium could be done with Na and Mg in THF only, but with Li, K, and $LiAlH_4$ the whole reaction (including the dicarbonyl coupling) could also be accomplished in glyme, diglyme, and diethyl ether. In pyridine the reagent seemed to form in all the solvents tried, but no dicarbonyl coupling took place. When diethyl ether was the solvent, a metallic mirror formed on the walls of the flask but olefins were still formed in reasonable yield.

THF performed best in all cases studied and the initial concentration of $TiCl_3$ (from 0.04 M to 0.67 M) had little effect (at least on the yield of tetraphenylethylene).

No systematic study of the influence of the ratio of reducing agent to $TiCl_3$ had previously been undertaken, and best results were now found for the ratios specified in Table 2. With the benefit of hindsight, it is important to stress that the tabulated results refer to a 1:1 ratio of $TiCl_3$ to ketone and, as we discuss later, this is not the most suitable ratio (at least with our reagents).

The first three entries in Table 2 are formally consistent with the formation of Ti(0), the requirement for a slight excess of the metal over the theoretical amount being attributed to the presence of impurities such as $TiCl_4$ and titanium oxychlorides.

The situation for the $TiCl_3/LiAlH_4$/THF combination is less clear cut. It is known that titanium *tetra*chloride reacts with $LiAlH_4$ according to the stoichiometry of Scheme 17.[54] but it is not clear what titanium species is formed with a $TiCl_3$:$LiAlH_4$ ratio of 1:0.5, for which maximum yields were found (Table 3). On the basis of circumstantial evidence, the Belgian chemists suggest that the *formal* oxidation state is Ti(I) in this case.

$$5TiCl_3 + 3LiAlH_4 \longrightarrow 5Ti(0) + 3Al(0) + 12HCl + 3LiCl$$

Scheme 17

Using the $TiCl_3$/reducing agent ratios found to be the best when the $TiCl_3$/ketone ratio is 1:1 (see Table 2), the ratio of $TiCl_3$ to ketone was optimized in three cases, and the results are shown in Table 3.

Table 3

The Optimized Ratios for $TiCl_3$/Carbonyls[54]

Reagent	$TiCl_3$:ketone
$TiCl_3$/Li (1:3.2)	Not specified
$TiCl_3$/K (1:3.2)	Not specified
$TiCl_3$/Mg (1:1.7)	1:1
$TiCl_3/LiAlH_4$ (1:0.5)	1:1 (for benzophenone)
$TiCl_3/LiAlH_4$ (1:0.5)	4:1 (for cyclohexanone)

It is speculated that a titanium surface containing the metal in a variety of valence states becomes bonded to the ketone. A radical anion forms on the surface and dimerizes. Then, by an unspecified pathway, the resulting pinacolate is converted into an olefin.

The Belgian study served to define certain facts: The type of solvent, the ratio of reducing agent to titanium halide, and the ratio of titanium halide to ketone are all important factors. A full optimization study was not undertaken, and the precise nature of the low-valent titanium has eluded definition. As a working hypothesis, the reaction is regarded as proceeding through a ketyl radical anion. If this is postulated to be formed on the surface of the reagent then the objection to such an intermediate (formation of

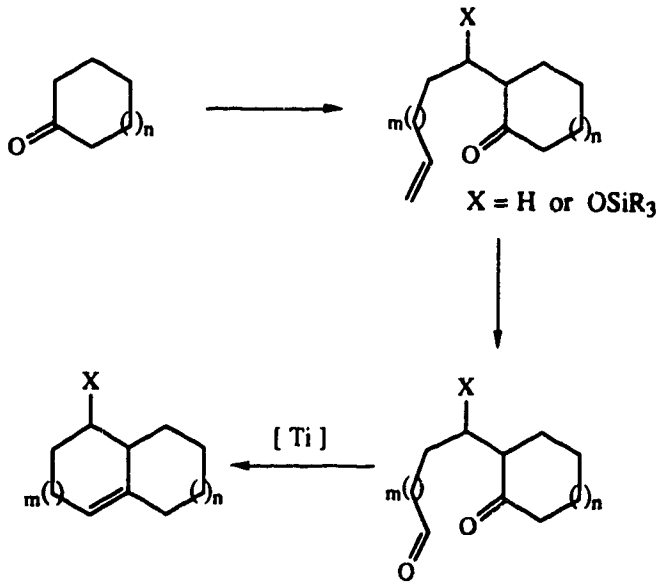
olefins from cyclopropyl ketones, as described above) becomes less of an objection, as the behavior of such species on a surface is not known. Pinacolates must be intermediates because pinacols can be isolated when the reaction is run under very mild conditions.[41]

Applications in Organic Synthesis

A large number of applications of the titanium-induced dicarbonyl coupling have been reported in organic synthesis,[4a] but, until the work from this laboratory was published[55] there were only a few isolated reports in which the substrate was even moderately oxygenated.[56] A probable reason for this can be found in the experiments done in this laboratory (see later).

Discussion

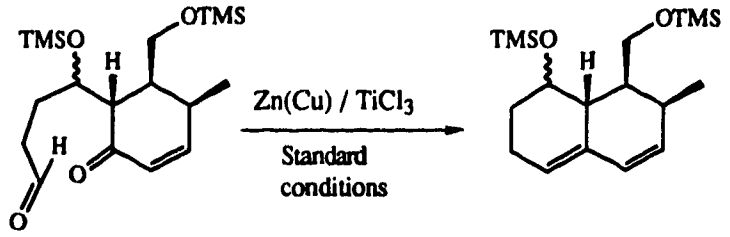
This section of the thesis deals with the development and application of some new low-valent titanium reagents in which the metal has a formal valency of one. These reagents can be used in a general method of annulation, as summarized in Scheme 18,[57] and, unlike those conventional low-valent titanium species which we have tested, our reagents also work when the substrates are highly oxygenated.



Scheme 18

The starting point for our research is based on a model study[58] for the synthesis[55] of compactin and mevinolin that was carried out in this laboratory several years ago.

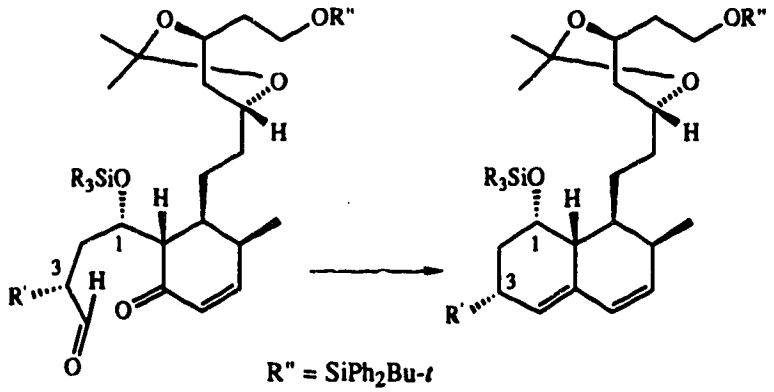
Compounds **15** were treated under standard conditions[9] with the titanium reagent prepared from $TiCl_3$ and Zn(Cu) couple (Scheme 19). The desired products (**16**) were formed in about 72% yield and, on the basis of this promising result, the



15 **16**

Scheme 19

synthetic work was continued to the stage of the complex keto aldehydes **17a** and **17b** (Scheme 20). However, when the same conditions for titanium-induced coupling that had been



R" = $SiPh_2Bu$-*t*

17a R = Me; R' = H; both epimers at C-1

17b R = Et; R' = H; both epimers at C-1

17c R = Et; R' = Me; 1-*S* only

17d R = Et; R' = Et; 1-*S* only

18a-d (R, R' have values corresponding to those in **17a-d**

Scheme 20

successful with the models **15**, were applied to **17a**, none of the desired products **18a** were obtained. At a much later stage in the present investigation (see below[59]) some **18a** was isolated, but, when initially tried, the reaction was unsuccessful. A spectroscopic check was, of course, made for the presence of compounds in which one or more of the protecting groups had been lost, but which, nevertheless, had the hexahydronaphthalene substructure of **18a**. The reagent made in the reported manner[3,46] from $TiCl_3$ and $LiAlH_4$ was also examined, but again, as far as could be judged, the hexahydronaphthalenes **18a** were not formed.

At this point in the program to synthesize mevinolin, a full examination was made of the literature on the McMurry reaction and it became clear that, among the many applications, very few involved highly oxygenated substrates.[56] Indeed, the process had been reported not to work if the starting material contained an ethylene ketal group.[9,60]

Professor McMurry, who was consulted about the difficulties with the conversion of **17a** into **18a**, pointed out that his reagent, as usually prepared [i.e. from $TiCl_3$ and Zn(Cu) couple] contains Lewis acids, and he had suspected, from his own work, that these acids are responsible for degrading acetals. He had reported[24] (although not for a highly oxygenated substrate) the use of reagent supplemented with triethylamine. When the

$LiAlH_4/TiCl_3$ procedure was repeated (using **17b**), but in the presence of an excess of triethylamine[24] (to quench Lewis acid sites), compounds **18b** could be obtained — but only in yields of 30-35%. The experiments were repeated several times with different proportions of amine in the hope of increasing the yield because the reaction was a crucial one in the approach to mevinolin and compactin. None of these efforts was successful and it was decided to accept the poor yield. Consequently, a large supply of **17a** was built up so that enough material would be available to take the product of the titanium coupling all the way to compactin.

In the meantime other modifications of the titanium reagent were examined, and it was decided to use potassium graphite (C_8K)[42] as the intermediate reducing agent, because this substance would not introduce additional Lewis acid species — as do Zn(Cu) couple and $LiAlH_4$. Moreover, C_8K would probably react more completely[5,6,7,33] than lumps of metallic potassium since the metal is uniformly distributed within a large number of graphite particles. The first experiment (carried out by Dr K.S. Keshava Murthy), in which **17b** was treated with an excess of reagent prepared by the action of C_8K (3 moles) on $TiCl_3$ (1 mole), afforded the desired products **18b** in 71% yield, but the next few attempts to reproduce this result gave yields of 0 to 35%. All the weighings for these experiments had been done in a glove bag and it was suspected that unintentional exposure of the very air-sensitive C_8K or $TiCl_3$ to atmospheric oxygen or to

moisture had altered the stoichiometry from the intended level. Therefore, the effect of changing the proportions of all the ingredients in the conversion of **17b** into **18b** was investigated, and it was quickly established by Dr. Keshava Murthy that good yields are obtained by using C_8K (2 moles) and $TiCl_3$ (1 mole) per 0.058 — 0.062 mole of dicarbonyl substrate. The results of these early experiments in the mevinolin/compactin series are shown in Table 4.

TABLE 4[a]

Coupling Results for Mevinolin/Compactin Series

Entry	Substrate	$TiCl_3:C_8K$	Substrate:$TiCl_3$	Yield
a	**17b**	1.00:4.07	1.00:10.00	0%
b	**17b**	1.00:3.00	1.00:10.00	30%
c	**17b**	1.00:2.09	1.00:17.14	85%
d	**17c**	1.00:2.53	1.00: 9.89	22%
e	**17c**	1.00:2.14	1.00: 9.97	42%
f	**17c**	1.00:2.11	1.00:16.40	86%
g	**17d**	1.00:1.97	1.00:17.20	89%

Footnote to Table 4

[a]**All reactions were run in 1,2-dimethoxyethane (DME).**

In each case the low-valent titanium reagent was generated by heating C_8K and $TiCl_3$ in refluxing DME for an arbitrary period of 2 hours, followed by slow addition (over

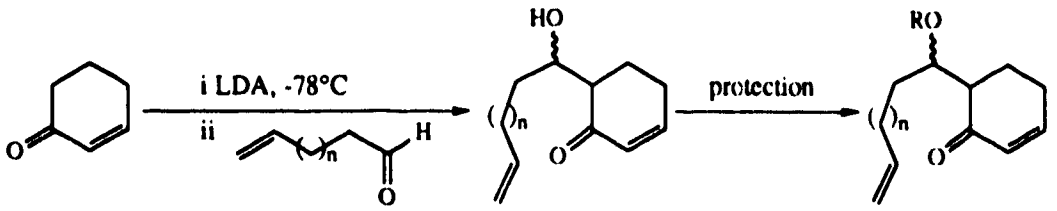
ca. 9 hours) of the dicarbonyl compound at room temperature, and then a further period (*ca.* 5 hours) at reflux. When the reaction was monitored by thin layer chromatography it was discovered that an intermediate is formed during the addition, but most of the final product is generated in the reflux period. These conditions were routinely used in the compactin,[55] mevinolin,[55] and 3-ethylcompactin[61] series, i.e., with **17b-d** [see Tables 4 and 8 (the latter is on pages 34 — 36)]. No epimerization takes place α to the aldehyde group in **17c**[55] or **17d**.[61]

The above experiments represent a general method for annulation and this is summarized in Scheme 18 (see above). The method involves attaching a chain, carrying a potential, or actual, carbonyl group α to the carbonyl of a cyclic ketone. Then, after unmasking the pendant carbonyl (if necessary), the two carbonyls are coupled to generate a bicyclic olefin. The titanium reagent has been tested in the demanding case represented by the natural products chemistry (**17→18**) discussed above, and it was clearly worthwhile to extend the method and to demonstrate its generality.

We have studied a number of examples (see later, Table 8, page 34) in whicn we used several different methods for attaching the carbonyl side chain. The early experiments were done with the $C_8K/TiCl_3$ reagent, but later we employed other reducing agent/titanium halide combinations that are easier to handle.

Preparation of the Substrates for Titanium Coupling

In some of our examples we used an aldol condensation to attach the pendant chain α to the ketone carbonyl. Scheme 21

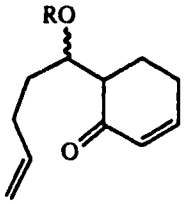
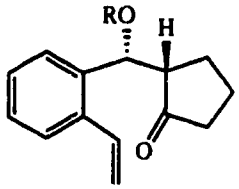
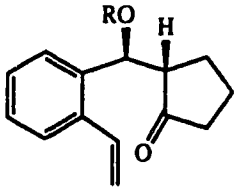
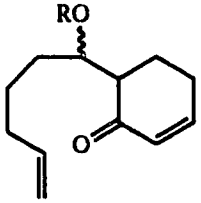


Scheme 21

illustrates the general approach and the compounds made are listed in Table 5. It should be noted that the hydroxyl must be protected, and for this purpose silylation or acetylation are suitable.

Table 5

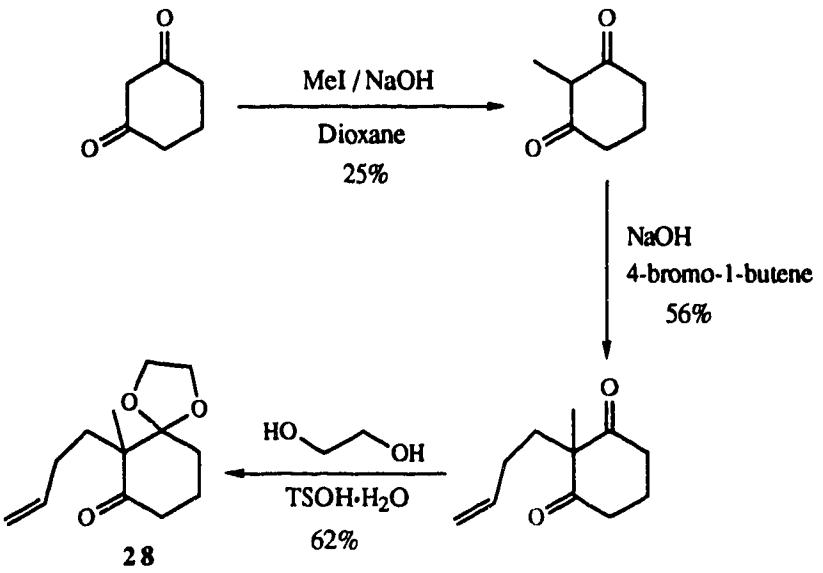
Products from Aldol Condensation

Structure	Yield from Condensation	Yield from Protection
	19 R = H, 82%	20 R = Et_3Si, 88%
	21 R = H, —	22 R = Et_3Si, 46%[a]
	23 R = H, —	24 R = Et_3Si, 30%[a]
	25 R = H, 75%	26 R = Et_3Si, 81% 27 R = Ac, 88%

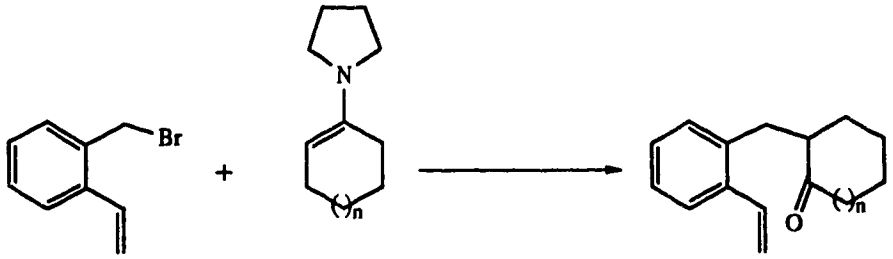
Footnote toTable 5

[a]The yield is over the two steps. The two compounds were separated and obtaind in the indicated yields.

A second method for making substrates for the titanium coupling is by direct enolate alkylation. The protected diketone **28** was assembled in this way (Scheme 22), and, in a related process, enamine alkylation was used (Scheme 23).



Scheme 22

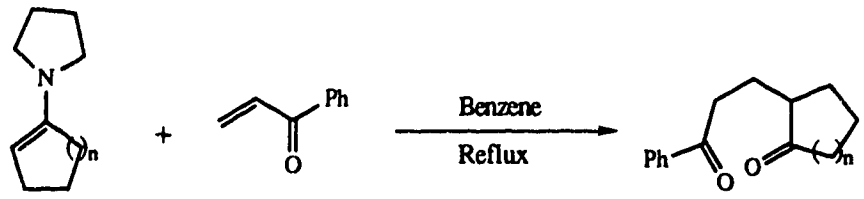


29, n = 1, 34%

30, n = 2, 95%

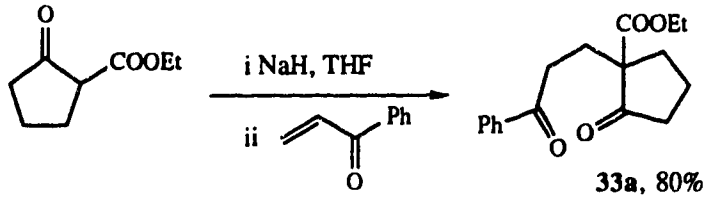
Scheme 23

We have also applied Michael addition, as shown in Schemes 24, 25, and 26, the last procedure (Scheme 26) being a little more involved than the others.



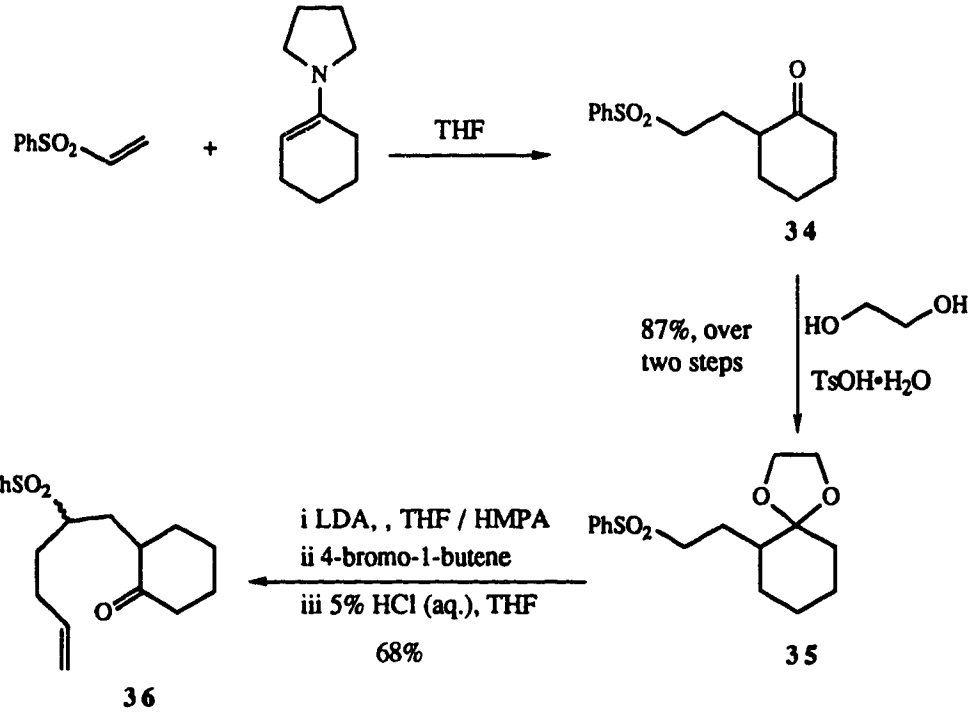
31a, n = 1, 79%
32a, n = 2, 86%

Scheme 24



33a, 80%

Scheme 25



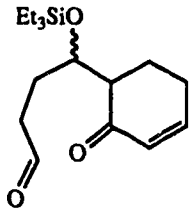
Scheme 26

Apart from those cases where the second carbonyl was not already present in the newly introduced side chain (Schemes

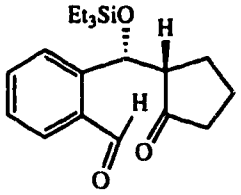
21, 22, 23, and 26), an extra step was needed to generate that carbonyl. This was done in two ways: Ozonolysis was used for aldehydes **17a-d**, **20a**, **37a**, **38a**, **22a**, **24a**, **29a**, and **30a**, as shown in Table 6.

Table 6

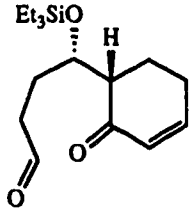
Dicarbonyls from Ozonolysis



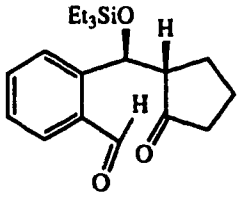
20a, 79%



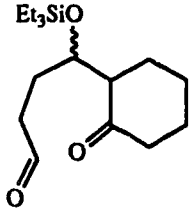
22a, 91%



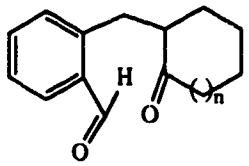
37a, 60%[a]



24a, 98%



38a, 83%



29a, n = 1, 84%

30a, n = 2, 95%

Footnote to Table 6.

[a]The starting material was a single isomer.

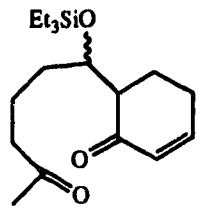
Isomer **37a** was obtained simply by chromatographic separation of the ozonolysis products (**20a**) of compounds **20**.

Compounds **38a** (see Table 6) were prepared by hydrogenation of compounds **20a**.

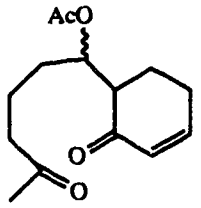
The other method for generating the second carbonyl group is by Wacker oxidation[62] (see Table 7). The best experimental procedure[62] for this involves treatment of the olefin with oxygen in DMF-H_2O in the presence of a catalytic amount of $PdCl_2$ and a stoichiometric quantity of CuCl.

Table 7

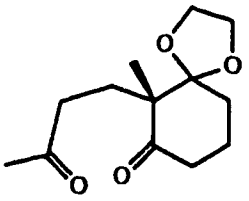
Products from Wacker Oxidation



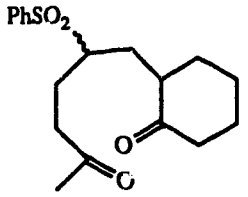
26a, 75%



27a, 87%



28a, 70%



36a, 85%

The Titanium Coupling

Our results for the titanium coupling are collected in Table 8.

Table 8

Titanium Induced Annulation Results [a]

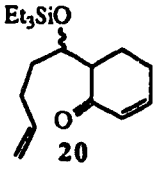
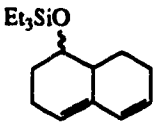
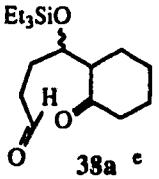
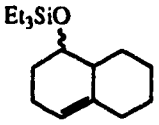
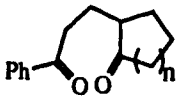
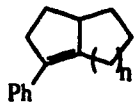
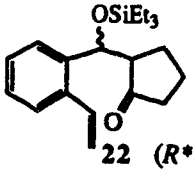
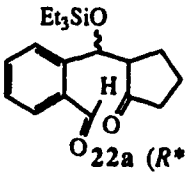
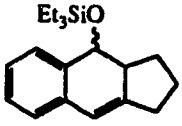
Carbonyl Substrate	Method [b]	Product	Yield
17b	A; rt [c]	**18b**	85%
17a	B; rt	**18a**	71%
17c	A; rt [c]	**18c**	86%
17d	A; rt [d]	**18d**	89%
 **20**	 **20a** [e]	A	 **20b** [e]	82%
	37a (*R**, *R**) [f]	C	**37b** (*R**, *S**)	71-86%
	37a (*R**, *R**) [f]	D	**37b** (*R**, *S**)	65%
	 **38a** [e]	A	 **38b** [e]	64%
	 **31a** n = 1	A	 **31b** n = 1	86%
	32a n = 2	A	**32b** n = 2	87%
 **22** (*R**,*S**)	 **22a** (*R**, *S**)	A	 **22b** (*R**, *R**)	50%
24 (*R**,*S**)	**22a** (*R**, *S**)	A [g]	**22b** (*R**, *R**)	64% [g]
	24a (*R**, *R**)	A	**24b** (*R**, *S**)	51%
	24a (*R**, *R**)	A [g]	**24b** (*R**, *S**)	67% [g]

Table 8 (continued)

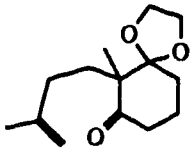
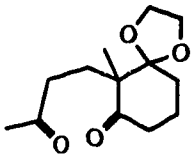
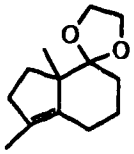
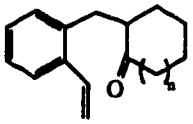
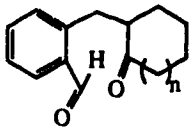
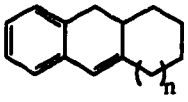
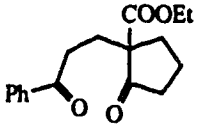
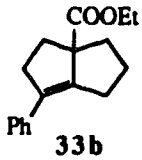
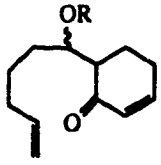
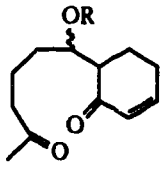
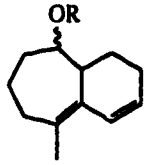
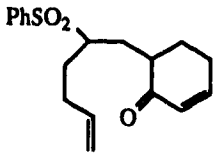
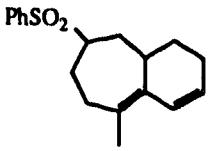
Starting Materials	Carbonyl Substrate	Method [b]	Product	Yield
				
28	**28a**	A [h]	**28b**	75% [h]
	28a	B [h]	**28b**	69% [h]
				
29a n = 1	**29a** n = 1	A	**29b** n = 1	81%
30a n = 2	**30a** n = 2	A	**30b** n = 2	86%
				
	33a	A	**33b**	61%
	33a	B	**33b**	69%
	33a	C	**33b**	66-73%
				
26 R = $SiEt_3$	**26a** R = $SiEt_3$	A	**26b** R = $SiEt_3$	74% [i]
27 R = Ac	**27a** R = Ac	B	**27b** R = Ac	58% [j]

Table 8 (continued)

Carbonyl Substrate	Method	Product	Yield
			
36	**36a**	B	**36b** [j]	39%
Benzophenone **37a**	C	Tetraphenylethylene **37b**	84% [k]
Cyclohexanone **38a**	C	Cyclohexylidene-cyclohexane **38b**	56%
38a	A	**38b**	58%
Cyclododecanone **39a**	A	Cyclododecylidene-cyclododecane **39b**	85%

Footnotes to Table 8.

(a) Yields refer to isolated compounds.
(b) A = $C_8K/TiCl_3$/DME; B = $Na/C_{10}H_8/TiCl_4$/THF; C = Na(Hg)/$TiCl_4$/DME; D = Na-K/$TiCl_4$/THF.
(c) See reference 55.
(d) See reference 61.
(e) Mixture of both isomers.
(f) The relative configuration at the two stereogenic centers is specified. Note that (*R*,R**)-(±)-**37a** gives the (*R*,S**)-(±)-product (without any epimerization). There is a corresponding change in notation when **22a** and **24a** are converted into their respective products. The stereochemical assignments to **37b**, **22b**, and **24b** (and hence to their precursors) follow from a consideration of the coupling constants for the CHOSi signals.
(g) Dioxane was used as the solvent and the dicarbonyl compound was added at reflux.
(h) See also Table 9.
(i) Combined yield of the separated [(*R*,R**)-(±)- and (*R*,S**)-(±)-] isomers.
(j) A single isomer of undetermined stereochemistry.
(k) See also Tables 10 and 11.

In our initial experiments the $C_8K/TiCl_3$ system was used for the dicarbonyl coupling. The dicarbonyl compound had

been added at room temperature with **17a-d**, but we generally added the material at reflux. We have not made a systematic study of the effect of the temperature during the addition period, but we have examined modifications of the reagent that avoid, as far as possible, the need to weigh compounds as highly air-sensitive as C_8K and $TiCl_3$. (Such materials are best handled in a dry box.) For this reason we evaluated sodium-naphthalene ($Na/C_{10}H_8$) as the reducing agent because stock solutions are easily dispensed by syringe techniques, and $TiCl_4$ as the titanium halide because this compound is a distillable liquid. We also examined 40% w/w sodium amalgam (Na/Hg)[63] and 17% w/w sodium-potassium alloy (Na-K).[64] Both of these reducing agents are liquids and they were both used with $TiCl_4$. As in the case of the original formulation (see Table 4), a particular ratio of reducing agent and $TiCl_4$ was required for optimum results, except with Na(Hg). Our results on the influence of the proportions of the ingredients are shown in Table 9, and the ratio

TABLE 9[a]

Intramolecular Coupling of 28a to 28b

	System	$TiCl_n$:Reductant	Substrate:$TiCl_n$	Yield
a	Na/N*/$TiCl_4$/THF/**28a**	1.00:4.20	1.00:17.00	21%
b	Na/N*/$TiCl_4$/THF/**28a**	1.00:3.50	1.00:17.00	41%
c	Na/N*/$TiCl_4$/THF/**28a**	1.00:2.98	1.00:17.40	61%
d	Na/N*/$TiCl_4$/THF/**28a**	1.00:2.78	1.00:15.90	67%
e	Na/N*/$TiCl_4$/THF/**28a**	1.00:2.66	1.00:17.40	70%
f	Na/N*/$TiCl_4$/THF/**28a**	1.00:2.00	1.00:17.00	23%
g	C_8K/$TiCl_3$/DME/**28a**	1.00:2.07	1.00:16.85	75%
h	C_8K/$TiCl_3$/DME/**28a**	1.00:3.50	1.00:10.05	28%
i	Zu(Cu)/$TiCl_3(DME)_2$/DME/**28a**	1.00:2.00	1.00:17.06	62%

TABLE 9 (continued)

Intramolecular Coupling of 28a to 28b

	System	$TiCl_n$:Reductant	Substrate:$TiCl_n$	Yield
j	Zu(Cu)/$TiCl_3(DME)_2$/DME/**28a**	1.00:1.02	1.00:17.00	69%
k	Zu(Cu)/$TiCl_3$/DME/**28a**	1.00:2.30	1.00:22.25	67%
l	Zu(Cu)/$TiCl_3$/DME/**28a**	i.00:1.00	1.00:16.85	72%
m	Zu(Cu)/$TiCl_3(DME)_2$/DME/**28a**	1.00:2.28	1.00:22.45	70%
n	Zu(Cu)/$TiCl_3(DME)_2$/DME/**28a**	1.00:3.14	1.00: 7.80	70%
o	Na(Hg)/$TiCl_4$/DME/**28a**	1.00:2.00	1.00:17.00	67%
p	Na(Hg)/$TiCl_4$/DME/**28a**	1.00:2.70	1.00:17.00	69%
q	Na(Hg)/$TiCl_4$/DME/**28a**	1.00:3.00	1.00:17.00	63%
r	Na(Hg)/$TiCl_4$/DME/**28a**	1.00:3.50	1.00:17.00	56%
s	Na(Hg)/$TiCl_4$/DME/**28a**	1.00:4.20	1.00:17.00	63%

Footnote to Table 9. N* = naphthalene.

corresponds closely to the formal production of titanium(I). In each case the reagent had to be used in substantial excess, just as had been found with the $C_8K/TiCl_3$ system.

With Na(Hg) the choice of solvent is important (as judged by experiments with **28a**); the reactions were cleaner when run in DME than in THF.

We also examined a few intermolecular cases (see Table 8, **37a** — **39a**), but, although we did not carry out an extensive study, the ratios with both $Na/C_{10}H_8/TiCl_4$ and $C_8K/TiCl_3$ (see later) seem to be important. At a later date we examined the subject in detail with benzophenone (see below, and Tables 11).

In reactions involving aldehydes, we have gained the impression (not specifically proven by deliberate experiments) that the compounds should be free of the corresponding acids, and so the aldehydes were always protected from air.

In some cases (see Table 8) prolonged reaction times (e.g., for **38b, 22b, 24b, 28b**) or use of a higher boiling solvent (dioxane instead of DME) are advantageous (**22b, 24b**).

When the $Na/C_{10}H_8/TiCl_4$/THF system is used, relatively large amounts of naphthalene must be separated from the desired product, and this can be difficult in some cases, unless the product has a very high boiling point. In that case the naphthalene can be removed by sublimation. Of course, if the product is quite polar, chromatographic

separation is straightforward. However, in the hope of simplifying product isolation, we tried 1-(dimethylamino)-naphthalene,[65] which, of course, is extractable into acid. Unfortunately, significant cleavage of the sp^2-carbon nitrogen bond occurs under the reaction conditions so that the product mixtures still contain substantial amounts of naphthalene. Ideally, the amine could be used in catalytic quantities, but when this was tried we found that reduction of $TiCl_4$ was incomplete in THF at room temperature, even after sonication[66] for 24 hours.[67]

An attempt at sonochemical dispersion[66] of potassium metal in DME, with the intention of then adding $TiCl_4$, was unsuccessful, lumps of potassium[68] still being visible after several hours. In retrospect, we should have used toluene, in which such dispersion has been reported,[69] but this solvent was not examined.[53] However, Na(Hg) was tried successfully (see Tables 8 and 9), and here the problem of separating naphthalene does not arise.

As shown in Table 8, the reaction generally worked well with simple examples and so we sought a very sensitive substrate that could be used as a test case. Compounds **17a-d** were too valuable for this purpose, and we already knew that our $C_8K/TiCl_3$ reagent was superior to the classical species, at least with **17b** as the substrate. Compound **28a** was chosen as a more accessible example than **17a-d**. It was reported[60] that **28a** does not undergo intramolecular coupling with the standard Zn(Cu) couple/$TiCl_3$ reagent.

Our $C_8K/TiCl_3$ reagent worked well with **28a** (75%, Table 9) and so did reagent generated from Na/naphthalene and $TiCl_4$ (70%) (see Table 9 above). In both cases [$C_8K/TiCl_3$ and Na/naphthalene/$TiCl_4$] the yield was sensitive to the ratio of the components in the reaction mixture but, surprisingly, when we used Na(Hg) as the intermediate reducing agent, there was little dependence (within the range we studied) on the ratio of amalgam to $TiCl_4$ (at a constant $TiCl_4$/substrate ratio of 17:1).

At this point in our investigation it was reported[40] that use of a $TiCl_3$-DME complex[70] (instead of $TiCl_3$, with Zn(Cu) couple yielded an improved formulation of the classical reagent, and it was important to compare our low-valent titanium species with the new one. In the event, our experiments (see Table 9) showed that **28a** is not a very demanding material in the present context, because the intramolecular coupling works well with all the reagents we tried, *including* the standard Zn(Cu) couple/$TiCl_3$. We could detect (see Table 9) no significant advantage with the DME complex, although it appears to be less air-sensitive than $TiCl_3$ itself, but we did find that with $C_8K/TiCl_3$ and $Na/C_{10}H_8/TiCl_4$, and only with these, the outcome of the intramolecular coupling is very sensitive to the ratio of the components. The product **28b** is inert to C_8K or to Zn(Cu) couple in refluxing DME, but an excess of C_8K, over and above the optimum amount, must be avoided during *formation* of the reagent.

We also carried out a short study of the coupling of benzophenone with the $C_8K/TiCl_3$ system and found, with the $C_8K/TiCl_3$ ratio fixed at 2.1:1, that a large excess of reagent is definitely required (see Table 10).

Table 10
Coupling of benzophenone with $C_8K/TiCl_3$/DME[a]

Entry	C_8K:$TiCl_3$	$TiCl_3$:Ph_2C=O	Yield of Ph_2C=CPh_2	Recovery of Ph_2C=O
a	2.23:1.00	1.94:1.00	33%	58%
b	2.04:1.00	4.11:1.00	79%	13%
c	2.10:1.00	8.00:1.00	91%	0%
d	2.99:1.00	8.21:1.00	89%	0%
e	4.46:1.00	6.00:1.00	<10%	--[b]

Footnotes to Table 10
[a]In a typical experiment, benzophenone (54.7 mg, 0.30 mmol) in DME (6 mL) was added in one portion to a refluxing mixture of the titanium reagent [from $TiCl_3$ (370.0 mg, 2.40 mmol) and C_8K (681.7 mg, 5.04 mmol)] in DME (10 mL). Refluxing was continued for 12 h.
Yields refer to isolated compounds.
[b]Not measured.

All the experiments hitherto had relied on a small number of tests in which the ratio of the components in the coupling reaction had been changed, and we felt it would be desirable to carry out a comprehensive optimization study in which the titanium/reducing agent and the titanium/substrate ratios are systematically varied over a wide range. This survey would have been prohibitively labor-intensive for an intramolecular coupling as some 80 experiments were contemplated, and each would involve addition of the

dicarbonyl compound over about 10 hours. We chose, therefore, to examine an intermolecular example (in which case the substrate is added in one portion), and we used benzophenone, since its reaction could be monitored easily by gas chromatography. We arbitrarily prepared the reagent by heating the components for 2 hours in refluxing THF. Our results are shown in Table 11. We appreciate that benzophenone is not particularly sensitive to the ratios but, nevertheless, the Table shows clearly that, for highest yields, the ratios that had been found largely by chance with **17b** are close to those that give a global maximum for benzophenone. Significant amounts of 1,2-diphenylethane are produced if the $Na/C_{10}H_8/TiCl_4$ ratio is greater than 3.2:1.[71]

A comparison of the results in Tables 10 and 11 suggests that the active species (and/or its amount) in the $C_8K/TiCl_3$ and $Na/C_{10}H_8$ systems are different, because the sensitivity of yield to ratios is not the same with both reagents.

Table 11[a]

Conditions for Benzophenone Coupling

$TiCl_4$/ Ph_2CO	Na-naphthalene/$TiCl_4$												
	2.00	2.20	2.40	2.60	2.70	2.80	3.00	3.10	3.20	3.40	3.60	3.80	4.00
2.00	33.3	45.6	38.2	38.7	46.8	53.3	56.9	71.9	65.4	48.9	52.0	53.9	42.5
4.00	54.7	57.4	80.6	70.4	83.3	69.4	81.9	83.1	71.9	79.5	55.1	47.6	40.8
6.00	82.1	80.3	82.9	85.1	86.1	100	100	98.8	69.2[b]	65.1	53.7	43.7	38.9
8.0	84.9	87.3	91.8	94.0	100[c]	100	100[d]	100	59.3	66.8	52.2	52.5	45.8[e]
9.0	82.2	90.0	92.4	95.4	100	100	100	94.2	58.6	70.6	55.9	50.5	46.5
10.0	76.6	94.3	96.7	98.4	100	100	100	91.0	62.4	69.4	58.2	48.5	47.5

[a]Yields determined by gc.

[b]In a preparative experiment with Na-naph/$TiCl_4$::3.19:1; $TiCl_4$:Ph_2C=O::5.0:1; yield = 72%.

[c]In a preparative experiment with Na-naph/$TiCl_4$::2.66:1; $TiCl_4$:Ph_2C=O::8.1:1; yield = 87%.

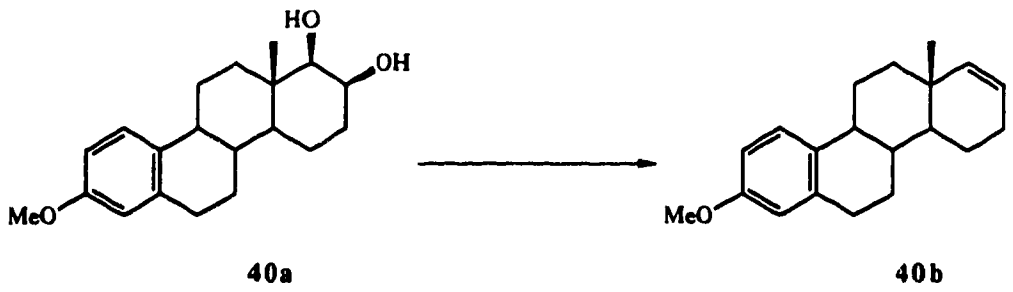
[d]In a preparative experiment with Na-naph/$TiCl_4$::3.00:1; $TiCl_4$:Ph_2C=O::8.1:1; yield = 82%.

[e]In a preparative experiment with Na-naph/$TiCl_4$::4.13:1; $TiCl_4$:Ph_2C=O::8.1:1; yield < 60%.

Conclusion

In view of the successful coupling of **28a** with the classical Zn(Cu) couple/$TiCl_3$ reagent (see Table 9), our remaining supply of **17b** from the compactin series was subjected (by Dr K. S. Keshava Murthy) to the classical Zn(Cu) couple/$TiCl_3$ method. This experiment had been tried earlier, of course, but this time, with the benefit of considerable experience in handling low-valent titanium reagents, the desired product was indeed isolated, although in less than 40% yield. We conclude, therefore, that our reagents do have advantages over the conventional [so-called titanium(0) species], and are appropriate to try with highly oxygenated substrates.[56d] Our reagents, with the possible exception of that made from Na(Hg), are clearly different in behavior from other titanium species we have examined, and they [Zn/$TiCl_3$ and $Na/C_{10}H_8/TiCl_4$] are mild enough for application to compounds of type **3**. The Na(Hg)/$TiCl_4$ reagent has not been tested with **3** but its performance is adequate with **28a**.

Finally, we were curious to establish whether vicinal diols can be converted into olefins with the present reagents,[72] but this point was examined only in a cursory manner. Vicinal diols can be isolated with typical McMurry reagents if the reaction is done under mild conditions.[44,30,41,50] In our case (experiment done by Sylvain Daigneault), the *cis* 1,2-diol **40a** gave the corresponding



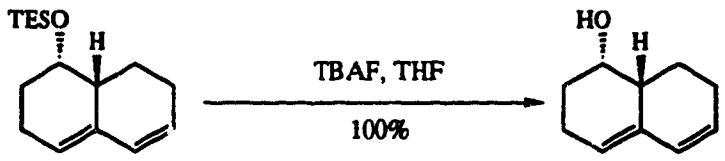
40a **40b**

Scheme 27

olefin when treated with the $C_8K/TiCl_3$ reagent. The yield was 92%, but the reaction was slow in boiling THF (67°C), and was best done in diglyme at 85°C.

We have also generated Ti(II) [from $TiCl_4$ (1 mole) and Na/naphthalene (2 mole)] and used the reagent to make 1,2-diphenyl-1,2-ethanediol.

Our last experiment related to the titanium work was the preparation of alcohol **41**. As described in the next chapter of the thesis, we needed a large amount of this alcohol (referred to as compound **25** in the next chapter) for model studies on the degradation of mevinolin and compactin. The compound was prepared by desilylation of **37b**, under standard conditions.



37b **41**

Scheme 28

Experimental Section

The same general procedures were followed as described previously,[73] all reactions involving titanium being done under argon.[74] Petroleum ether refers to material with bp 35 - 60°C. All aldehydes were checked for the absence of carboxylic acids and were carefully protected from air during use.

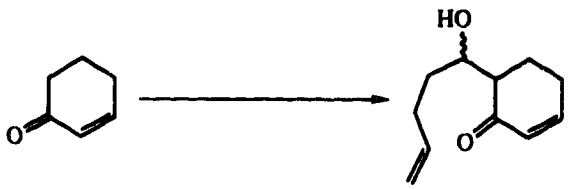
4-Pentenal.

4-Pentenol (17.23, 0.20 mol) in CH_2Cl_2 (30 mL) was added to a stirred suspension of PCC (64.67 g, 0.30 mol) in anhydrous CH_2Cl_2 (300 mL) under argon at room temperature over *ca* 10 min. After a further 10 min, the reaction flask was cooled by a cold-water bath , and the bath was removed 10 min later. Stirring was continued for 2 h (V.P.C. control, 10% OV-1, 90°C) and the mixture was then diluted with ether (300 mL) and filtered through a pad of Florisil. The insoluble residue was washed with ether (3 x 50 mL), the washings were filtered through the Florisil pad, and the solvent was removed by distillation through a 30-cm Vigreaux column. Spinning band distillation [bp 97°C (lit. [75] bp 102--104°C)] of the residue gave 4-pentenal (5.38 g, 32%) of greater than 98% purity (V.P.C.; 10% OV-1, 90°C): IR ($CHCl_3$ cast) 1713, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHZ) δ 2.30--2.70 (m, 4 H), 4.95--5.15 (m, 2 H), 5.75--5.95 (m, 1H), 9.80 (t, J = 1.50 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHZ) δ 26.02, 42.64, 115.57,

123.71, 201.77; exact mass, *m/z* 84.0572 (calcd for C_5H_8O, *m/z* 84.0572).

6-[1-(Triethylsilyl)oxy]-4-pentenyl-2-cyclohexen-1-one (20).

(a) 6-(1-Hydroxy-4-pentenyl)-2-cyclohexen-1-one.

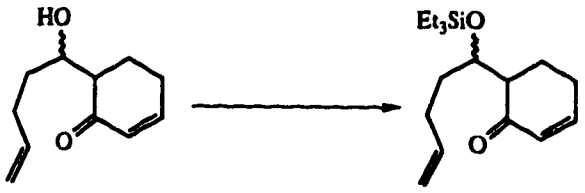


19

n-BuLi (1.6 M in hexanes, 34.4 mL, 55 mmol) was added dropwise to a stirred and cooled (0°C) solution of *i*-Pr_2NH (8.5 mL, 60.6 mmol) in dry ether (100 mL). Stirring at 0°C was continued for 10 min and the mixture was then cooled to -78°C. 2-Cyclohexen-1-one (4.82 mL, 49.8 mmol) was added over *ca.* 20 min. The resulting yellow solution was stirred at -78°C for 60 min, and 4-pentenal[76] (5.90 mL, 59.7 mmol) was then added in one portion, followed, after 10 min, by glacial acetic acid (8.6 mL, 150.2 mmol). The mixture was left to warm to room temp and was then diluted with water (100 mL). The layers were separated, and the aqueous phase was extracted with ether (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 3:7 EtOAc--hexane gave the desired aldols **19** (7.3749 g, 82%) as an apparently homogeneous (TLC, silica, 3:7 EtOAc--

hexane) oil: IR ($CHCl_3$ cast) 3450, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two diastereoisomers in a ratio of *ca.* 1:4) δ 1.35--1.85 (m, 3 H), 1.85--2.60 (m, 6 H), 2.68 (d, J = 6.0 Hz, 0.2 H; exchanges with D_2O), 3.85--3.96 (m, 0.80 H), 4.09 (dd, J = 3.0, 1.0, 0.8 H; exchanges with D_2O), 4.14--4.24 (m, 0.2 H), 4.90--5.10 (m, 2 H), 5.75--5.95 (m, 1 H), 5.95--6.10 (m, 1 H), 6.95--7.10 (m,1 H). [In the presence of D_2O the signal at 3.85--3.96 simplified to a doublet of triplets (J = 8.5, 3.0 Hz), and the signal at 4.14--4.24 also simplified to a doublet of triplets (J = 9.5, 4.5 Hz).] ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 24.98, 25.76, 29.21, 32.87, 51.57, 71.09, 114.63, 129.78, 138.49, 150.91, 203.43; (minor isomer) δ 17.99, 22.47, 30.40, 32.20, 55.20, 69.21, 114.79, 130.08, 138.26, 150.68, 201.76; exact mass, *m/z* calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1148. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.36; H, 9.10.

(b) 6-[[1-(Triethylsilyl)oxy]-4-pentenyl]-2-cyclohexen-1-one (20).



19 **20**

A general procedure[77] for triethylsilylation was used: Et_3SiCl (1.43 mL, 8.48 mmol) was added to a solution of the above aldols (764.3 mg, 4.24 mmol) in dry pyridine (10.0 mL).

The solution was heated at 60°C for 4 h, cooled to room temp, diluted with ether (60 mL) and extracted with 10% w/v $CuSO_4.5H_2O$ (4 x 20 mL). The combined aqueous extracts were back-extracted with ether (30 mL) and the combined ether extracts were washed with water (2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 EtOAc--hexane gave **20** (1.1078 g, 88.7%) as an apparently homogeneous (TLC, silica, 1:9 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 2959, 2876, 1677, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two isomers in a ratio of 1:4) δ 0.50--0.70 (m, 6 H), 0.85--1.05 (m, 9 H), 1.45--2.55 (m, 9 H), 4.38--4.48 (dt, *J* = 8.0, 4.0 Hz, 0.8 H), 4.48--4.54 (dt, *J* = 6.8, 2.5 Hz, 0.2 H), 4.90--5.10 (m, 2 H), 5.75--6.05 (m, 2 H), 6.90--7.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 4.89, 6.69, 21.85, 25.86, 30.53, 32.09, 53.38, 70.14, 114.09, 130.10, 138.42, 149.62, 199.21; (minor isomer) δ 20.95, 25.19, 29.92, 34.58, 50.61, 69.12, 114.39, 130.25, 137.99, 199.30; exact mass, *m/z* calcd for $C_{17}H_{30}O_2Si$ 294.2015, found 294.2011. Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.37; H, 10.33.

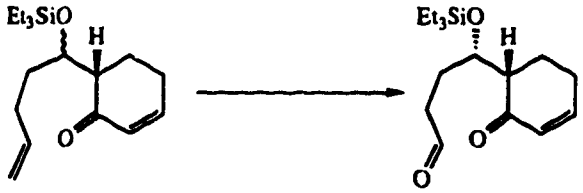
2-Oxo-γ-[(triethylsilyl)oxy]-3-cyclohexene-1-butanal (20a).

20 **20a**

Ozone was bubbled through a stirred and cooled (-78°C) solution of triethylsilyl ethers **20** (3.04 g, 10.32 mmol) in dry CH_2Cl_2 (50 mL), until just a trace of starting material remained (TLC, silica, 1:3 EtOAc--hexane). Ph_3P (5.41 g, 20.64 mmol) was added and the solution was left at -78°C for 10 min. The cold bath was removed and the mixture was stirred overnight, and then evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), first with 1:19 EtOAc--hexane (to separate triphenylphosphine) and then with 1:3 EtOAc--hexane, gave **20a** (2.41 g, 78.9%) as an oil. [The two components were chromatographically resolvable (TLC, silica, 1:3 EtOAc--hexane).]: IR ($CHCl_3$ cast) 1725, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two diastereoisomers in a ratio of 1:4) δ 0.50--0.70 (m, 6 H), 0.85--1.05 (m, 9 H), 1.60--2.65 (m, 9 H), 4.38--4.45 (dt, J = 8.3, 4.0 Hz, 0.8 H), 4.45--4.55 (dt, J = 6.3, 3.0 Hz, 0.2 H), 5.92--6.08 (m, 1 H), 6.90--7.02 (m, 1 H), 9.76 (t, J = 1.65 Hz, 0.8 H), 9.80 (t, J = 1.5 Hz, 0.2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 4.977, 6.880, 1.928, 25.343, 26.066, 41.359, 53.304, 69.854, 130.163, 150.281, 199.543, 202.555; (minor isomer) δ 5.067,

6.939, 21.604, 25.286, 27.889, 40.395, 51.255, 68.600, 130.236, 150.210, 199.381, 201.851; exact mass, *m/z* calcd for $C_{16}H_{28}O_3Si$ 296.1808, found 296.1808.

(R*,R*)-(±)-2-Oxo-γ-[(triethylsilyl)oxy]-3-cyclohexene-1-butanal (37a).



20 **37a**

The above procedure was followed, using triethylsilyl ethers **20** (5.8364 g, 19.82 mmol), CH_2Cl_2 (100 mL) and Ph_3P (10.39 g, 39.63 mmol). Flash chromatography of the the total reaction product over silica gel (7.5 x 20 cm) with 1:19 EtOAc--hexane (1500 mL), 1:9 EtOAc--hexane (1000 mL), and then with 3:17 EtOAc--hexane, gave **37a** (2.7994 g, 60%) as a homogeneous (TLC, silica, 1:3 EtOAc--hexane) oil, and a mixture of **37a** and the corresponding (*R*,S**)-(±)-isomer [which was the major (89%) component of the mixture] (1.8717 g, 22%) as an oil. Compound **37a** had: IR ($CHCl_3$ cast) 1725, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.61 (q, *J* = 8.0 Hz, 6 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 1.62--1.94 (m, 3 H), 2.18--2.65 (m, 6 H), 4.44 (dt, *J* = 8.5, 4.0 Hz, 1 H), 5.98 (ddd, *J* = 10.0, 3.0, 1.0 Hz, 1 H), 6.95--7.04 (m, 1 H), 9.78 (t, *J* = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 4.99, 6.91, 21.94, 25.30, 26.09, 41.39, 53.32, 69.87, 130.18, 150.30, 199.57,

202.60; exact mass, *m/z* calcd for $C_{16}H_{28}O_3Si$ 296.1808, found 296.1808.

General Procedures for Titanium-mediated Dicarbonyl Coupling. Procedure A. Freshly prepared potassium graphite (C_8K)[42] and $TiCl_3$ were weighed under argon in a dry box and transferred successively to a 100-mL round bottomed flask containing dry DME. The mixture was refluxed for 2 h under argon, and the carbonyl compound in dry DME was added by syringe pump over 10 h to the stirred and refluxing slurry of titanium reagent. Stirring was continued for an additional 3 h. The mixture was cooled to room temp and filtered under argon through a pad of Florisil (3.5 x 5 cm) contained in a sintered funnel that was equipped with an argon inlet near the top. The pad was washed with ether (3 x 50 mL). The combined filtrates were evaporated and the crude product was isolated as described in the individual examples.

Procedure B. Na was added to a stirred solution of naphthalene (1 mol per mol Na) in THF (argon atmosphere). Stirring was continued for 2 h and then $TiCl_4$ (freshly distilled from copper powder) was added over about 10 min while the flask was cooled with a cold-water bath, a small portion of THF being used to rinse all the halide into the reaction vessel. The resulting black mixture was refluxed for 30 min and cooled to room temp. A solution of the carbonyl compound in THF was injected over 10 h at room temp.

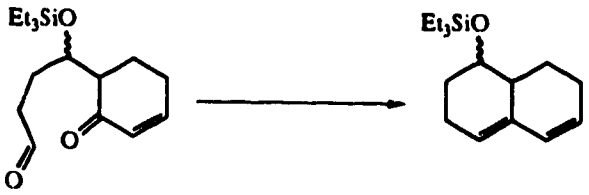
The mixture was then refluxed for 4 h, cooled to room temp and filtered, under argon, through a pad of Florisil, using ether as the wash solvent. The filtrate was evaporated and the product was isolated as described for the individual examples. In some cases the carbonyl compound was added at the reflux temp of THF.

Procedure C. $TiCl_4$ was added dropwise to a stirred suspension of liquid sodium amalgam (39.5% w/w) in DME (or THF) while the flask was cooled with a cold-water bath, a small portion of solvent being used to rinse all the halide into the reaction vessel. The resulting mixture was refluxed with stirring for 5 h and then cooled to room temp. A solution of the carbonyl compound in DME (or THF) was injected over 10 h at room temp. The mixture was then refluxed for 4 h, cooled to room temp and filtered, under argon, through a pad of Florisil, using ether as the wash solvent. The filtrate was evaporated and the product was isolated as described for the individual examples.

Procedure D. $TiCl_4$ was added dropwise to a stirred suspension of liquid sodium-potassium alloy (17% w/w Na) in DME while the flask was cooled with a cold-water bath, a small portion of DME being used to rinse all the halide into the reaction vessel. The resulting mixture was refluxed with stirring for 4 h, and then a solution of the carbonyl compound in DME was injected over 10 h. The mixture was then

refluxed for a further 4 h, cooled to room temp and filtered, under argon, through a pad of Florisil, using ether as the wash solvent. The filtrate was evaporated and the product was isolated as described for the individual examples.

Triethyl[(1,2,3,7,8,8a-hexahydro-1-naphthalenyl)oxy]-silane (20b).

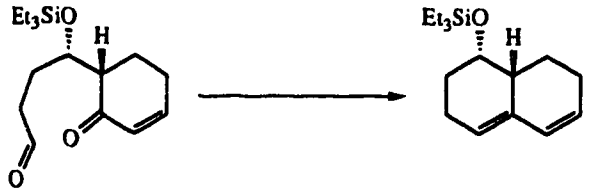


20a **20b**

Procedure A was followed, using $TiCl_3$ (265.3 mg, 1.72 mmol), C_8K (488.3 mg, 3.61 mmol) in DME (25 mL), and **20a** (30.0 mg, 0.101 mmol) in DME (5 mL). Flash chromatography of the crude product over silica gel (1 x 10 cm) with petroleum ether gave **20b** (22.0 mg, 82%) as an apparently homogeneous (TLC, silica, 1:9 ether--petroleum ether) oil: IR ($CHCl_3$ cast) 3020, 2952, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two diastereoisomers in a ratio of 1:4) δ 0.50--0.70 (m, 6 H), 0.90--1.05 (m, 9 H), 1.58--2.48 (m, 9 H), 3.40 (m, 0.2), 4.05 (br s, 0.7 H), 5.38 (br s, 0.2 H), 5.50 (br s, 0.8 H), 5.60--5.75 (m, 1 H), 6.04 (d, J = 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 5.207, 7.061, 21.194, 25.792, 26.058, 30.218, 40.468, 68.698, 122.890, 126.926, 130.187, 134.018; (minor isomer) δ 5.128, 6.985, 25.287, 26.470, 32.398, 43.645, 73.763, 122.548, 127.818, 128.984, 135.518;

exact mass, *m/z* calcd for $C_{16}H_{28}OSi$ 264.1909, found 264.1910. Anal. Calcd for $C_{16}H_{28}OSi$: C, 72.66; H, 10.67. Found: C, 72.94; H, 10.67.

(*R*,S)-(±)-Triethyl[(1,2,3,7,8,8a-hexahydro-1-naphthalenyl)oxy]silane (37b).**



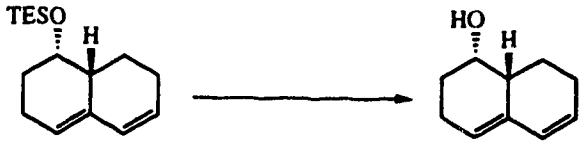
37a **37b**

(a) Procedure C was followed, using Na(Hg) (40%, 890.7 mg, 15.50 mmol), $TiCl_4$ (0.62 mL, 5.64 mmol) in DME (25 mL), and **37a** (98.4 mg, 0.33 mmol) in DME (10 mL). Refluxing was continued for a further 5 h after the addition. Flash chromatography of the crude product over silica gel (1 x 15 cm), first with hexane and then with 1:19 EtOAc--hexane, gave **37b** (75.2 mg, 86%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 3010, 2952, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.61 (q, J = 8.5 Hz, 6 H), 0.95 (t, J = 8.5 Hz, 9 H), 1.55--1.85 (m, 4 H), 1.95--2.45 (m, 5 H), 4.02 (br s, 1 H), 5.48 (br s, 1 H), 5.60--5.70 (m, 1 H), 6.04 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.115, 7.052, 21.173, 25.768, 26.039, 30.201, 40.447, 68.679, 122.891, 126.939, 130.173, 134.012; exact mass, *m/z* calcd for $C_{16}H_{28}OSi$ 264.1909, found 264.1906. Anal. Calcd for $C_{16}H_{28}OSi$: C, 72.66; H, 10.67. Found: C, 72.64; H, 10.63. This

experiment was repeated several times (on different scales); the yield varied between 71 and 86%.

(b) Procedure D was followed, using sodium-potassium alloy (17% w/w Na, 990.6 mg, 28.36 mmol) and $TiCl_4$ (1.13 mL, 10.31 mmol) in DME (40 mL), and **37a** (179.8 mg, 0.61 mmol) in DME (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with hexane gave **37b** (104.4 mg, 65%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil.

Desilylation of compound 37b to give 41.

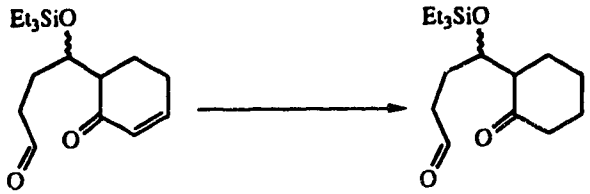


37b **41**

Bu_4NF (1.0 M in THF, 17.5 mL, 19.26 mmol) was added to a stirred solution of compound **22A** (2.0379 g, 7.70 mmol) in THF (100 mL) under argon. The solvent was evaporated after 1 h and flash chromatography of the residue over silica gel (3.0 x.15 cm) with 1:4 EtOAc--hexane followed by recrystallization from CH_2Cl_2--petroleum ether gave **41** (1.1769 g, 100%) as a homogeneous (TLC, silica, 1:4 EtOAc--hexane) white crystal (mp 88--91°C): IR ($CHCl_3$ cast) 3315, 2910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHZ) δ 1.5 (d, J = 7.0 Hz, 1 H), 1.57--1.81 (m, 3 H), 1.91--2.02 (m, 1 H), 2.10--2.44 (m, 5 H), 4.00 (br s, 1 H), 5.52 (dd, J = 0.8, 3.5 Hz, 1 H), 5.67--5.75 (m, 1 H),

6.04 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHZ) δ 20.57, 25.27, 25.75, 29.10, 39.82, 68.41, 122.62, 127.74, 129.78, 133.35; exact mass, *m/z* calcd for $C_{10}H_{14}O$ 150.1045, found 150.1043.

2-Oxo-γ-[(triethylsilyl)oxy]cyclohexanebutanal (38a).



20a **38a**

Compounds **20a**[78] (157.0 mg, 0.53 mmol) in EtOAc (30 mL), together with 5% Pd-C (52.3 mg), were stirred at room temp under hydrogen for 2.5 h. The mixture was filtered through a pad of Florisil and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm) with 1:4 EtOAc--hexane gave **38a** (130.6 mg, 83%) as an oil. [The two components were resolvable by TLC (silica, 4:6 ether--petroleum ether).]: IR ($CHCl_3$ cast) 1724, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.52--0.68 (m, 6 H), 0.95 (t, *J* = 8 Hz, 9 H), 1.50--2.55 (m, 13 H), 4.20--4.30 (two overlapping q, 1 H), 9.74--9.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 5.07, 6.90, 24.52, 27.41, 27.86, 28.36, 39.55, 42.38, 55.04, 68.57, 202.05, 211.59; (minor isomer) δ 4.96, 6.82, 24.86, 25.69, 26.85, 27.25, 40.93, 42.18, 56.66, 69.67, 202.53, 211.26; exact mass, *m/z* calcd for $C_{14}H_{25}O_3Si$ (M - C_2H_5)$^+$ 269.1573, found 269.1567. Anal. Calcd for

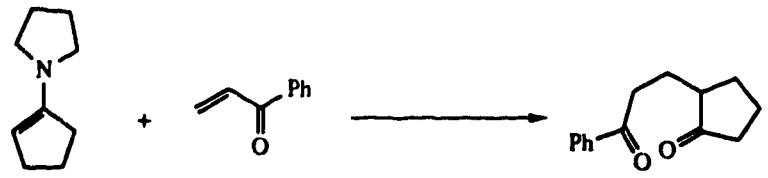
$C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.09; H, 10.15.

Triethyl[(1,2,3,5,7,8,8a-octahydro-1-naphthalenyl)-oxy]silane (38b).

38a **38b**

A slight modification of procedure A was followed, using $TiCl_3$ (269.0 mg, 1.74 mmol) and C_8K (480.0 mg, 3.55 mmol) in DME (25 mL), and **38a** (20.0 mg, 0.067 mmol) in DME (5 mL). Refluxing was continued for a further 30 h after the addition. Flash chromatography of the crude product over silica gel (1 x 10 cm) with petroleum ether gave **38b**, which was almost exclusively [^{1}H NMR (300 MHz)] one isomer, (10.4 mg, 64%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.55 (q, J = 11.0 Hz, 6 H), 0.96 (t, J = 11.0 Hz, 9 H), 1.10--2.20 (m, 13 H), 3.85--3.95 (m, 1 H), 5.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.02, 7.02, 23.52, 26.69, 28.23, 28.74, 28.99, 38.07, 44.53, 70.04, 117.47, 140.82; exact mass, *m/z* calcd for $C_{16}H_{30}OSi$ 266.2065, found 266.2062. In another experiment, using a different batch of **38a**, the product was a mixture of isomers (*ca.* 1:2) and the minor component had: ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.21, 6.98, 23.88, 26.18, 27.62, 28.74, 31.41, 35.17, 46.41, 75.05, 118.53, 139.30.

2-(3-Oxo-3-phenylpropyl)cyclopentanone (31a).



31a

A different method from that reported[79] in the literature was followed. Phenyl vinyl ketone (202.6 mg, 1.53 mmol) was added to a stirred solution of the pyrrolidine enamine of cyclopentanone (209.7 mg, 1.53 mmol) in benzene (15 mL), and the resulting solution was refluxed for 12 h. A mixture of acetic acid (2.5 mL), water (5 mL) and sodium acetate (1.25 g) was then added, and refluxing was continued for 1 h. The mixture was cooled and poured into water (20 mL). The organic layer was separated and the aqueous phase was extracted with ether (3 x 25 mL). The combined organic layers were washed with 1.0 M HCl (2 x 20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with hexane, 1:9 EtOAc--hexane, and then with 1:4 EtOAc--hexane, gave **31a** (263.8 mg, 79%) as an oil: IR ($CHCl_3$ cast) 2880--2835, 1795, 1684 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.50--1.65 (m, 1 H), 1.65--1.90 (m, 2 H), 1.95--2.40 (m, 6 H), 3.05--3.20 (m, 2 H), 7.45--7.65 (m, 3 H), 7.98 (dd, J = 9, 3 Hz, 2 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 21.00, 24.57, 30.18, 36.36, 36.55, 48.52, 128.28, 128.91, 133.25, 137.41, 199.94, 220.68; exact mass, *m/z* calcd for

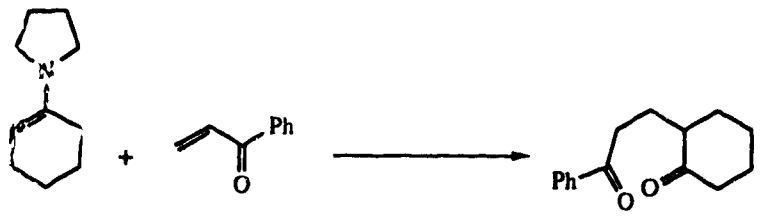
$C_{14}H_{16}O_2$ 216.1150, found 216.1147. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.47. Found: C, 77.50; H, 7.25.

2,3,3a,4,5,6-Hexahydro-1-phenylpentalene (31b).

31a **31b**

Procedure A was followed, using C_8K (1.7390 g, 12.86 mmol) and $TiCl_3$ (0.9427 g, 6.11 mmol) in DME (20 mL), and **31a** (79.5 mg, 0.368 mmol) in DME (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with pentane gave **31b** (58.8 mg, 86%) as a colorless oil: IR ($CHCl_3$ cast) 3080--3010, 2948, 2857, 1494, 759, 691 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.00--1.15 (m, 1 H), 1.40--1.55 (m, 1 H), 1.90--2.20 (m, 4 H), 2.40--2.55 (m, 2 H), 2.90--3.15 (m, 3 H), 7.15--7.50 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 26.26,30.18, 30.78, 32.47, 39.60, 55.72, 126.14, 126.83, 128.52, 128.67,137.80, 151.28; exact mass, *m/z* calcd for $C_{14}H_{16}$ 184.1247, found 184.1247. Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.01; H, 8.97.

2-(3-Oxo-3-phenylpropyl)cyclohexanone (32a).

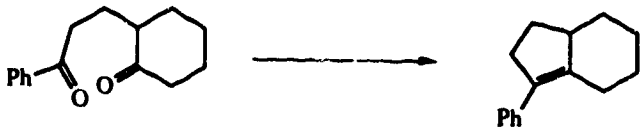


32a

A different method from that reported[79] in the literature was followed. Phenyl vinyl ketone (84.7 mg, 0.64 mmol) was added to a stirred solution of the pyrrolidine enamine of cyclohexanone (97.4 mg, 0.64 mmol) in benzene (10 mL), and the resulting solution was refluxed for 22 h. A mixture of acetic acid (2.5 mL), water (5 mL) and sodium acetate (1.25 g) was then added, and refluxing was continued for 1 h. The mixture was cooled and poured into water (20 mL). The organic layer was separated and the aqueous phase was extracted with ether (3 x 25 mL). The combined organic layers were washed with 1.0 M HCl (2 x 20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with hexane, 1:10 EtOAc--hexane, and then with 1:5 EtOAc--hexane, gave **32a** (127.2 mg, 86%): IR (film) ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.35--1.50 (m, 1 H), 1.55--1.95 (m, 4 H), 2.00--2.20 (m, 3 H), 2.25--2.50 (m, 3 H), 2.90--3.15 (m, 2 H), 7.40--7.60 (m, 3 H), 7.90--8.00 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 24.75, 25.49, 28.[illegible], 34.82, 36.65, 42.55, 50.26, 128.32, 128.87, 133.18, 137.43,

200.28, 212.87; exact mass, *m/z* calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1307.

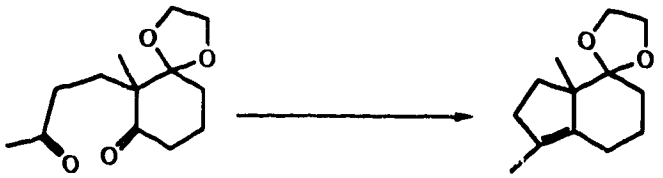
2,4,5,6,7,7a-Hexahydro-3-phenyl-1H-indene (32b).



32a **32b**

Procedure A was followed, using C_8K (2.0544 g, 15.19 mmol) and $TiCl_3$ (1.1193 g, 7.26 mmol) in DME (20 mL), and **32a** (101.6 mg, 0.0.434 mmol) in dry DME (15 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with 1:19 EtOAc--hexane, followed by Kugelrohr distillation (15 mm Hg, 160°C), gave **32b** (81.7 mg, 87%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 3080--3020, 2924, 2848, 1598 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.05--1.30 (m, 2 H), 1.30--1.50 (m, 2 H), 1.70--1.85 (m, 2 H), 1.85--2.20 (m, 3 H), 2.55--2.85 (m, 4 H), 7.15--7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 26.42, 27.37, 27.68, 29.78, 36.13, 36.32, 48.58, 126.47, 128.25, 128.39, 132.39, 145.45; exact mass, *m/z* calcd for $C_{15}H_{18}$ 198.1409, found 198.1411. Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.82; H, 9.34.

2',3',3'a,5',6',7'-Hexahydro-1',3'a-dimethylspiro[1,3-dioxolane-2,4'-[4H]indene] (28b).



28a **28b**

Compound **28b** was prepared a number of times using different procedures (see Table 9).

(a) A slight modification of procedure A was followed, using $TiCl_3$ (524.5 mg, 1.72 mmol), C_8K (942.2 mg, 3.61 mmol) in DME (30 mL), and **28a**[60] (48.0 mg, 0.20 mmol) in DME (5 mL). The carbonyl compound was injected at reflux over 10 h, and the mixture was refluxed for an additional 30 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with 1:19 EtOAc--hexane gave **28b** (31.2 mg, 75%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 2936, 2877, 1170, 1120, 1086, 1058, 1035, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 3 H), 1.35--1.50 (m, 2 H), 1.55--1.92 (m, 7 H), 2.05--2.48 (m, 4 H), 3.96 (s, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.05, 21.62, 23.09, 29.86, 30.36, 35.44, 55.78, 64.66, 65.26, 112.64, 129.24, 136.31; exact mass, *m/z* calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1462.

(b) A slight modification of procedure B was followed, using Na (234.6 mg, 10.20 mmol), naphthalene (1.3200 g, 10.20

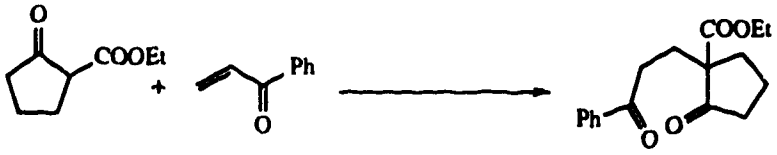
mmol), and $TiCl_4$ (0.42 mL, 3.83 mmol) in THF (38 mL), and **28a**[60] (53.7 mg, 0.22 mmol) in THF (5 mL). The carbonyl compound was injected at reflux over 10 h, and the mixture was refluxed for an additional 30 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with 1:19 EtOAc--hexane gave **28b** (33.0 mg, 70%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil.

(c) A slight modification of procedure C was followed, using $TiCl_4$ (0.71 mL, 6.50 mmol), Na(Hg) (39.5%, 1.0210 g, 17.5 mmol) in DME (40 mL), an initial reflux period of 5 h, and **28a**[60] (91.3 mg, 0.38 mmol) in DME (10 mL). The carbonyl compound was injected at reflux over 10 h, and the mixture was refluxed for an additional 30 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with 1:19 EtOAc--hexane gave **28b** (52.7 mg, 69%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil.

(d) Use of $TiCl_3$-DME complex. Freshly prepared Zn(Cu)[9] (221.0 mg, 3.40 mmol) and $TiCl_3(DME)_2$ (524.5 mg, 3.40 mmol)[70] were weighed under argon in a dry box and transferred successively to a 100-mL round bottomed flask containing dry DME (30 mL). The mixture was refluxed for 2 h under argon. Diketone **28a**[60] (48.0 mg, 0.20 mmol) in dry DME (5 mL) was added over 10 h to the stirred and refluxing slurry of titanium reagent. Stirring was continued for an additional 28 h. The mixture was cooled to room temp and filtered under

argon through a pad of Florisil (3.5 x 5 cm) contained in a sintered funnel that was equipped with an argon inlet near the top. The pad was washed with ether (3 x 50 mL). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (1 x 15 cm) with 1:19 EtOAc--hexane gave **28b** (30.2 mg, 72.6%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil.

Ethyl 2-Oxo-1-(3-oxo-3-phenylpropyl)cyclopentane-carboxylate (33a).



33a

A different method from that reported[80] in the literature was followed. Ethyl 2-cyclopentanonecarboxylate (255.4 mg, 1.64 mmol) was added to a stirred and cooled (0°C) suspension of sodium hydride (60%, 32.7 mg, 0.82 mmol) in THF (10 mL). After 20 min, phenyl vinyl ketone (216.7 mg, 1.64 mmol) in THF (3.0 mL) was added over 40 min. The resulting mixture was then warmed to room temp and the reaction was quenched after a further 2 h by pouring the solution onto cracked ice. The resulting mixture was acidified with 10% v/v aqueous HCl and extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the

residue over silica gel (3 x 15 cm) with 1:4 EtOAc--hexane, followed by Kugelrohr distillation (0.3 mm Hg, 160°C), gave **33a** (381.3 mg, 80%): IR ($CHCl_3$ cast) 3080--3040, 2980, 1748, 1724, 1685, 1449, 1287, 1267, 1242, 1212, 1191, 1180, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 6.6 Hz, 3 H), 1.92--2.18 (m, 4 H), 2.24--2.58 (m, 4 H), 2.96--3.05 (m, 1 H), 3.22--3.32 (m, 1 H), 4.20 (q, J = 6.6 Hz, 2 H), 7.42--7.60 (m, 3 H), 7.94--8.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.13, 19.67, 27.78, 34.09, 34.43, 38.04, 59.24, 61.50, 128.13, 128.61, 133.11, 136.78, 171.49, 199.46, 214.84; exact mass, *m/z* calcd for $C_{17}H_{20}O_4$ 288.1361, found 288.1362. Anal. Calcd for $C_{17}H_{20}O_4$: C,70.81; H, 6.99. Found: C, 70.62; H, 6.77.

Compound **33a** was also prepared as follows: Et_3N (0.06 mL, 0.40 mmol) was added to a stirred mixture of phenyl vinyl ketone (196.5 mg, 1.49 mmol) and ethyl 2-cyclopentanonecarboxylate (0.32 mL, 1.49 mmol) in benzene (5 mL). Stirring was continued at room temp for 38 h and the solution was then evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:4 EtOAc--hexane gave **33a** (388.7 mg, 90%).

Ethyl 2,3,4,5-Tetrahydro-6-phenyl-3a(1H)-pentalene-carboxylate (33b).

33a **33b**

(a) Procedure A was followed, using C_8K (1.8034 g, 13.34 mmol) and $TiCl_3$ (0.9995 g, 6.48 mmol) in DME (20 mL), and **33a** (109.9 mg, 0.38 mmol) in DME (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with 1:9 ether--pentane gave **33b** (59.6 mg, 61%) as a homogeneous (TLC, silica, 1:19 ether--pentane) oil: IR ($CHCl_3$ cast) 3080--3020, 2950, 1720, 1157 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.24 (t, J = 6.6 Hz, 3 H), 1.35--1.48 (m, 1 H), 1.78--1.90 (m, 1 H), 2.00--2.32 (m, 3 H), 2.42--2.64 (m, 3 H), 3.05--3.20 (m, 2 H), 4.10 (q, J 6.6 Hz, 2 H), 7.16--7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.42, 25.78, 28.51, 35.80, 35.94, 38.86, 60.78, 68.44, 127.02, 127.47, 128.56, 132.75, 136.96, 148.11, 176.27; exact mass, *m/z* calcd for $C_{17}H_{20}O_4$ 256.1463, found 256.1462. Anal. Calcd for $C_{17}H_{20}O_2$: C,79.65; H, 7.86. Found: C, 79.57; H, 7.91.

(b) Procedure B was followed, using Na (0.3635 g, 15.81 mmol), naphthalene (2.0267 g, 15.81 mmol), and $TiCl_4$ (0,64 mL, 5.86 mmol) in THF (50.0 mL), and **33a** (99.3 mg, 0.34 mmol) in THF (10 mL). Flash chromatography of the crude product

over silica gel (4 x 15 cm) with hexane (to separate naphthalene), and then with 1:19 ether--petroleum ether, followed by Kugelrohr distillation (0.3 mm Hg, 135°C), gave **33b** (60.5 mg, 69%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil.

(c) Procedure C was followed, using $TiCl_4$ (1.44 mL, 13.13 mmol), sodium amalgam (39.5% w/w, 2.0636 g, 35.46 mmol) in THF (100 mL), and **33a** (222.7 mg, 0.77 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with 1:19 EtOAc--hexane gave **33b** (144.9 mg, 73%) as a homogeneous (TLC, silica, 1:19 EtOAc--hexane) oil.

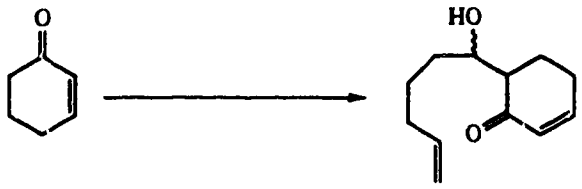
5-Hexenal.

DMSO (4.80 mL, 67.69 mmol) was added over ca 10 min to a cold solution (-78°C) solution of oxylyl chloride (2.95 mL, 33.85 mmol) in CH_2Cl_2 (50 mL). After a further 10 min, a solution of 5-hexenol (2.26 g, 22.6 mmol) in CH_2Cl_2 (20 mL) was added over 30 min. Stirring was continued for an additional 20 min, and Et_3N (15.7 mL, 112.8 mmol) was then added dropwise. After a further 20 min the cold bath was removed and, after 30 min, water (25 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with 10% v/v aqueous HCl (2 x 40 mL), saturated aqueous $NaHCO_3$ (2 x 40 mL) and brine (1 x 40 mL), and dried ($MgSO_4$). The solvent was distilled at 1 atm using a 30 cm

Vigreaux column followed by flash chromatography of the residue over silica gel (4.0 x 15 cm) with 1:19 ether--pentane. The solvent was removed as before and distillation of the residue [bp 122--125°C (1 atm)] afforded 5-hexenal (1.1215 g, 50.7%): IR ($CHCl_3$ cast) 3080--3020, 2920, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHZ) δ 1.70--1.82 (m, 2 H), 2.06--2.18 (m, 2 H), 2.46 (dt, J = 7.5, 1.80, 2 H), 4.96--5.10 (m, 2 H), 5.70--5.85 (m, 1 H), 9.78 (t, J = 1.80, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHZ) δ 21.72, 33.01, 43.16, 115.61, 137.61, 202.49; exact mass, *m/z* 98.0712 (calcd for $C_6H_{10}O$, *m/z* 98.0732).

6-[[1-(Triethylsilyl)oxy]-5-hexenyl]-2-cyclohexen-1-one (26).

(a) 6-(1-Hydroxy-5-hexenyl)-2-cyclohexen-1-one.

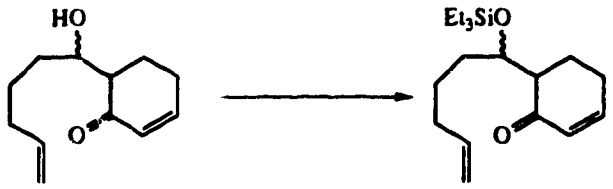


25

n-BuLi (1.6 M in hexanes, 1.78 mL, 2.88 mmol) was added dropwise to a stirred and cooled (0°C) solution of *i*-Pr_2NH (0.48 mL, 3.41 mmol) in dry ether (10 mL). Stirring at 0°C was continued for 10 min and the mixture was then cooled to -78°C. A solution of 2-cyclohexen-1-one (251.9 mg, 2.62 mmol) in ether (2.0 mL) was added over *ca.* 15 min. Stirring at -78°C was continued for 40 min. Then a solution of 5-hexenal (257.2 mg, 2.62 mmol) in ether was added in one portion.

After 10 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was left to warm to room temp, the layers were separated, and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 3:7 EtOAc--hexane gave the product (383.3 mg, 75.3%) as an apparently homogeneous (TLC, silica, 3:7 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 3460 (broad), 3070--3020, 2921, 2860, 1660, 1399, 1220, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two diastereoisomers in a ratio of *ca.* 1:3) δ 1.30--1.80 (m, 5 H), 1.85--2.20 (m, 3 H), 2.25--2.60 (m, 3.25 H), 3.82--3.94 (m, 0.77 H), 4.04--4.12 (d, J = 3 Hz, 0.75 H, exchanges with D_2O), 4.14--4.24 (m, 0.23 H), 4.90--5.08 (m, 2 H), 5.72--5.90 (m, 1 H), 5.98--6.08 (m, 1 H), 6.96--7.08 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 24.14, 25.16, 25.89, 33.08, 33.72, 51.59, 71.61, 114.60, 129.92, 138.81, 150.93, 203.78; (minor isomer) δ 22.52, 25.55, 32.48, 33.58, 51.62, 69.78, 114.63, 130.23, 138.69, 150.83; exact mass, *m/z* calcd for $C_{12}H_{16}O$ $(M - H_2O)^+$ 176.1201, found 176.1201. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.37; H, 9.34.

(b) 6-[[1-(Triethylsilyl)oxy]-5-hexenyl]-2-cyclohexen-1-one (26).

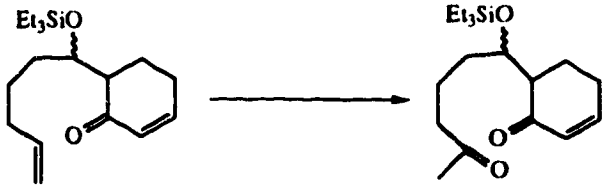


25 **26**

A general procedure[77] for triethylsilylation was used: Et_3SiCl (0.93 mL, 5.52 mmol) was added to a solution of the above aldols (536.2 mg, 2.76 mmol) in dry pyridine (6.0 mL). The solution was heated at 60°C for 2 h, cooled to room temp, diluted with ether (50 mL) and extracted with 10% w/v $CuSO_4.5H_2O$ (4 x 20 mL). The combined aqueous extracts were back-extracted with ether (50 mL) and the combined ether solutions were washed with water (2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm) with 1:9 EtOAc--hexane gave **26** (693.3 mg, 81%) as an apparently homogeneous (TLC, silica, 1:9 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 3080--3030, 2952, 2876, 1677, 1385, 1084, 1006, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two diastereoisomers in a ratio of *ca.* 1:3) δ 0.52--0.68 (m, 6 H), 0.86--1.00 (m, 9 H), 1.25--1.90 (m, 5 H), 1.95--2.55 (m, 6 H), 4.39--4.45 (m, 0.78 H), 4.46--4.52 (m, 0.22 H), 4.88--5.06 (m, 2 H), 5.75--5.88 (m, 1 H), 5.94--6.06 (m, 1 H), 6.92--7.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 5.07, 6.96, 22.05, 25.95, 26.09, 32.56, 33.82, 53.67, 70.53, 114.35, 130.35, 138.95, 149.99, 199.80; (minor

isomer) δ 21.12, 25.18, 25.44, 35.00, 51.01, 69.70, 114.60, 130.53, 138.94, 150.02, 199.79; exact mass, *m/z* calcd for $C_{18}H_{32}O_2Si$ 308.2172, found 308.2170. Anal. Calcd for $C_{18}H_{32}O_2Si$: C,70.07; H, 10.45. Found: C, 70.23; H, 10.51.

6-[5-Oxo-1-[(triethylsilyl)oxy]hexyl]-2-cyclohexen-1-one (26a).[62]



26 **26a**

$PdCl_2$ (12.8 mg, 0.072 mmol) and CuCl (35.[illegible] 0.36 mmol) were added to a stirred mixture of **26** (56.0 mg, 0.18 mmol) (both isomers), water (0.28 mL) and DMSO (2.0 mL). Oxygen was then bubbled through the resulting mixture for 6 min, and stirring was continued for an additional 1.5 h. The mixture was diluted with water (10 mL) and extracted with ether (4 x 6 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm) with 1:4 EtOAc--hexane gave **26a** (44.2 mg, 75%) as an apparently homogeneous (TLC, silica, 1:4 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 2959, 2875, 1716, 1679, 1086, 1004, 742, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two diastereoisomers in a ratio of 1:3) δ 0.50--0.66 (m, 6 H), 0.88--1.00 (m, 9 H), 1.22--1.42 (m, 2 H), 1.46--1.62 (m, 2 H), 1.68--1.86 (m, 2 H),

2.00--2.15 (m, 3 H), 2.15--2.55 (m, 5 H), 4.36--4.44 (m, 0.78 H), 4.44--4.52 (m,0.22 H), 5.94--6.06 (m, 1 H), 6.92--7.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 4.52, 6.38, 20.42, 21.49, 25.54, 29.23, 31.95, 43.09, 52.97, 69.65, 129.73, 149.59, 199.19, 208.42; (minor isomer) δ 19.50, 20.62, 24.86, 29.24, 34.43, 43.08, 50.14, 68.82, 129.90, 149.60, 199.20, 208.44; exact mass, *m/z* calcd for $C_{18}H_{32}O_3Si$ 324.2121, found 324.2123. Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.33; H, 9.99.

Triethyl[2,6,7,8,9,9a-hexahydro-5-methyl-1H-benzocyclohepten-9-yl)oxy]silane (26b).

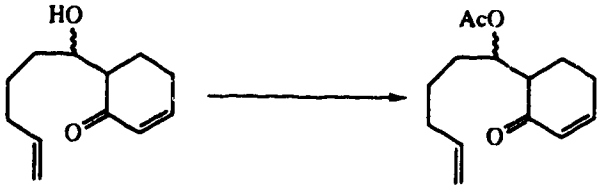
26a **26b**

Procedure A was followed, using C_8K (1.2218 g, 9.04 mmol), $TiCl_3$ (677.1 mg, 4.39 mmol) in DME (25 mL), and **26a** (83.3 mg, 0.258 mmol) in DME (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm) with hexane gave (*R*,S**)-(±)-**26b**[81] (44.5 mg, 59%) as a homogeneous (TLC silica, hexane) oil, and (*R*,R**)-(±)-**26b** (11.4 mg, 15%) as a homogeneous (TLC, silica, hexane) oil. The (*R*,S**)-(±)-isomer had: IR ($CHCl_3$ cast) 3030, 2920, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.55 (q, *J* = 8.0 Hz, 6 H), 0.92 (t, *J* = 8.0 Hz, 9 H), 1.40--2.02 (m, 11 H), 2.20--2.50 (m, 2 H), 2.78 (br

t, 1 H), 88--3.92 (m, 1 H), 5.64--5.72 (m, 1 H), 6.44 (dt, J = 10, 1.80, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ.5.50, 7.04, 20.30, 20.32, 23.22, 29.78, 35.70, 39.48, 41.20, 74.67, 126.21, 126.94, 128.77, 133.36; exact mass, *m/z* calcd for $C_{16}H_{27}O$ $(M - C_2H_5)^+$ 263.1823, found 263.1826.

The (*R**,*R**)-(±)-isomer had: IR ($CHCl_3$ cast) 3030, 2920, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.60 (q, J = 9.0 Hz, 6 H), 0.94 (t, J = 9.0, 9 H), 1.25--2.26 (m, 12 H), 2.52--2.64 (m, 1 H), 2.82 (br s, 1 H), 3.45--3.55 (m, 1 H), 5.72--5.82 (m, 1 H), 6.48 (dd, J = 10.0, 2.0, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.43, 7.06, 19.85, 21.69, 23.14, 23.32, 33.83, 39.92, 42.50, 69.47, 124.80, 127.01, 129.94, 135.00; mass, *m/z* calcd for $C_{18}H_{32}OSi$ 292.2216, found 292.17 ?

6-[1-(Acetoxy)-5-hexe]-2-cyclohexen-1-one (27).



25 **27**

Ac_2O (1.65 mL, 17.5 mmol) was added to a solution of 6-(1-hydroxy-5-hexenyl)-2-cyclohexen-1-one **25** , prepared as described above, (200.0 mg, 1.03 mmol) in dry pyridine (1.74 mL, 21.1 mmol) and the mixture was stirred at room temp for 10 h. The mixture was then diluted with ether (25 mL), and washed with water (2 x 15 mL) and brine (1 x 15 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (3 x 15 cm) with 1:4 EtOAc--hexane gave **27** (215.0 mg, 88%) as an oily mixture of two isomers [*ca.* 94:6; ^{1}H NMR (300 MHz)] that were not separable by chromatography (TLC, silica, 1:4 EtOAc--hexane): IR ($CHCl_3$ cast) 3080--3020, 2930, 1755, 1675, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40--1.70 (m, 5 H), 1.82--2.18 (m, 6 H), 2.28--2.56 (m, 2 H), 2.72 (dt, J = 12, 4.5, 1 H), 4.90--5.10 (m, 2 H), 5.40--5.50 (m, 1 H), 5.70--5.86 (m, 1 H), 5.95--6.05 (m, 1 H), 6.90--7.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 21.22, 23.09, 23.50, 25.26, 25.37, 29.99, 33.43, 49.82, 72.94, 114.80, 130.11, 130.44, 149.50, 149.88, 170.65, 198.40; exact mass, *m/z* calcd for $C_{12}H_{17}O_2$ $(M - CH_3CO)^+$ 193.1229, found 193.1225. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.96; H, 8.42.

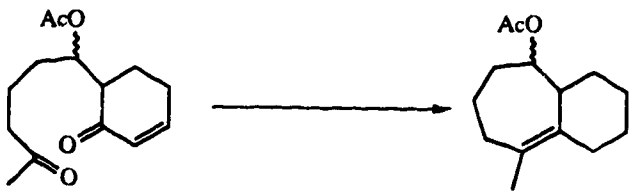
6-[1-(Acetoxy)-5-oxohexyl]-2-cyclohexe-1-one (27a).

27 **27a**

Oxygen was bubbled into a mixture of $PdCl_2$ (30.0 mg, 0.17 mmol), CuCl (83.8 mg, 0.85 mmol), water (0.66 mL) and DMSO (4.70 mL) for 15 min at room temp. Compounds **27** (100.0 mg, 0.42 mmol) were then added. Stirring was continued for an additional 30 min (TLC control, silica, 3:7 EtOAc--hexane), and the mixture was diluted with water (20 mL) and

extracted with ether (4 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 3:7 EtOAc--hexane gave **27a** (92.2 mg, 87%) as as an oily mixture of two isomers (*ca.* 93:7; ^1H NMR (300 MHz)) that were not separable by chromatography (TLC, silica, 3:7 EtOAc--hexane): IR ($CHCl_3$ cast) 2930, 1735, 1715, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40--1.75 (m, 5 H), 1.80--2.20 (m, 7 H), 2.30--2.60 (m, 4 H), 2.75 (dt, *J* = 13.0, 4.5, 1 H), 5.36--5.40 (m, 1 H), 5.95--6.05 (m, 1 H), 6.90--7.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (two isomers) δ (major) 19.91, 21.20, 23.34, 25.46, 29.66, 29.97, 42.88, 49.68, 72.35, 130.04, 149.72, 170.67, 198.39, 208.68; δ (minor) 23.05, 25.09, 31.47, 49.40, 70.68, 129.91, 150.02; exact mass, *m/z* calcd for $C_{14}H_{20}O_4$ 252.1361, found 252.1359. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.85; H, 8.17.

2,6,7,8,9,9a-Hexahydro-5-methyl-1H-benzocyclhepten-9-ol acetate (27b).



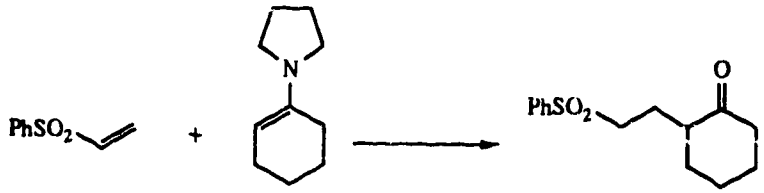
27a **27b**

(a) Procedure B was followed, using Na (315.2 mg, 13.71 mmol), naphthalene (1.7574 g, 13.71 mmol) and $TiCl_4$ (0.56 mL,

5.08 mmol) in THF (50.0 mL), and **27a** (75.0 mg, 0.297 mmol) in THF (10 mL). Flash chromatography of the crude product over silica gel (4 x 15 cm), first with hexane (to separate naphthalene), and then with 1:19 EtOAc--hexane, gave **27b**[82] (38.4 mg, 58%) as white crystals: IR ($CHCl_3$ cast) 3030, 2920, 2830, 1730, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30--1.60 (m, 2 H), 1.65--2.10 (m, 13 H), 2.50 (t, J = 13.0 Hz, 1 H), 2.96 (t, J = 4.5 Hz, 1 H), 5.00 (t, J = 4.0 Hz, 1 H), 5.75 (dt, J = 10.0, 4.0 Hz, 1 H), 6.50 (dt, J = 10.0, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.22, 20.67, 21.53, 22.51, 29.04, 35.27, 35.65, 38.44, 75.77, 126.13, 126.48, 127.85, 134.69, 171.12; exact mass, *m/z* calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1463.

2-[2-(Phenylsulfonyl)-5-hexenyl]cyclohexanone (36).

(a) 2-[2-(Phenylsulfonyl)ethyl]cyclohexanone.[83]



34

A solution of phenyl vinyl sulfone (875.6 mg, 5.20 mmol) in THF (5.0 mL) was added to a stirred solution of the pyrrolidine enamine of cyclohexanone (787.3 mg, 5.20 mmol) in THF (15 mL) at room temp under argon. The resulting mixture was stirred for 2 h, then refluxed for 4 h, cooled to room temp, and diluted with a mixture of water (10 mL) and

saturated aqueous NH_4Cl (5 mL). Stirring was continued overnight at room temp. Water (10 mL) was added and the mixture was extracted with ether (3 x 50 mL). The combined organic extracts were washed with 5% v/v aqueous HCl (1 x 40 mL), and brine (2 x 50 mL), dried ($MgSO_4$), and evaporated. The crude product[83] **34** (1.32 g) was used directly for ketalization.

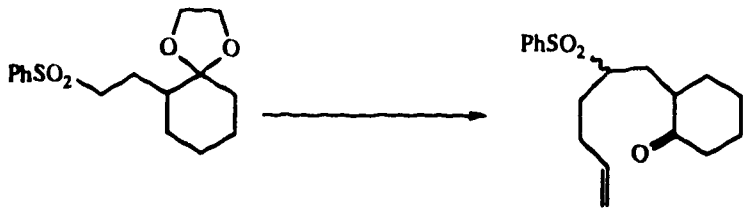
(b) [2-[1,4-Dioxaspiro[4,5]decan-6-yl]ethyl]sulfonyl-benzene.

34 **35**

A solution of the above crude product **34** (1.32 g), ethylene glycol (645.0 mg, 10.40 mmol) and $TsOH.H_2O$ (98.9 mg, 0.52 mmol) in dry benzene (30 mL) was refluxed under an addition funnel packed with 3Å molecular sieves for 3 h, and was then cooled to room temp. Water (20 mL) was added and the resulting mixture was washed with saturated aqueous $NaHCO_3$ (1 x 20 mL), and brine (2 x 40 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 9:10 EtOAc--hexane gave the required ketal (1.4163 g, 87% over the two steps) as a homogeneous (TLC, silica, 9:10 EtOAc--hexane) white solid **35** : mp 59--61°C; IR ($CHCl_3$ cast) 2934, 1305, 1147 cm^{-1}; ^1H NMR ($CDCl_3$,

300 MHz) δ 1.10--1.80 (m, 10 H), 1.90--2.08 (m, 1 H), 3.18 (dd, J = 9.0, 7.5 Hz, 2 H), 3.70--3.96 (m, 4 H), 7.50--7.70 (m, 3 H), 7.85--7.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 22.12, 23.53, 24.64, 29.69, 34.57, 43.16, 55.19, 64.41, 64.66, 110.38, 128.12, 129.19, 133.54, 139.28; exact mass, m/z calcd for $C_{16}H_{22}O_4S$ 310.1238, found 310.1242.

(c) 2-[2-(Phenylsulfonyl)-5-hexenyl]cyclohexanone (36).



35 **36**

n-BuLi (1.47 M in hexanes, 2.45 mL, 3.60 mmol) was added dropwise to a stirred and cooled (-78°C) solution of the above ketal (931.5 mg, 3.00 mmol) in dry THF (20 mL). The solution was stirred at -78°C for 20 min, and 4-bromobutene (0.76 mL, 3.60 mmol) was then added, followed by HMPA (5.0 mL). The resulting mixture was warmed to -30°C and stirred at this temp for 40 min, and then at 0°C for 2 h. Water (30 mL) was added and the mixture was extracted with ether (3 x 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 30 mL) and brine (2 x 40 mL), dried ($MgSO_4$), and evaporated. The crude alkylated product was used directly for deketalization.

A mixture of the crude alkylated product in THF (15 mL) and 5% v/v aqueous HCl (7.5 mL) was stirred overnight at 40°C under argon, and then cooled to room temp. The layers were separated and the aqueous phase was extracted with ether (3 x 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 x 20 mL) and brine (2 x 30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), first with 1:4 EtOAc--hexane and then with 3:7 EtOAc--hexane, gave **36** as a mixture of two isomers. The major isomer amounted to 369.7 mg (38% over the two steps). The sample of the minor isomer amounted to 289.9 mg (30% over the two steps; 68% overall for both isomers, from the ketal sulfone), but the material contained a little [*ca.* 11% (^{1}H NMR)] of the other isomer. The major isomer had: IR ($CHCl_3$ cast) 1707, 1300, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20--1.90 (m, 8 H), 2.00--2.45 (m, 6 H), 2.82--2.95 (m, 1 H), 3.15--3.30 (m, 1 H), 4.95--5.05 (m, 2 H), 5.60--5.75 (m, 1 H), 7.50--7.70 (m, 3 H), 7.80--7.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.26, 28.28, 29.19, 29.46, 30.23, 35.39, 42.38, 48.56, 61.89, 115.84, 128.85, 129.14, 133.64, 136.99, 137.95, 212.82; exact mass, *m/z* calcd for $C_{18}H_{24}O_3S$ 320.1446, found 320.1442. Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55; S, 10.01. Found: C, 67.12; H, 7.39; S, 10.02.

The sample of the minor isomer[84] had: IR ($CHCl_3$ cast) 1706, 1285, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20--2.40 (m, 14 H), 2.60--2.72 (m, 1 H), 3.08--3.26 (m, 1 H), 4.90--

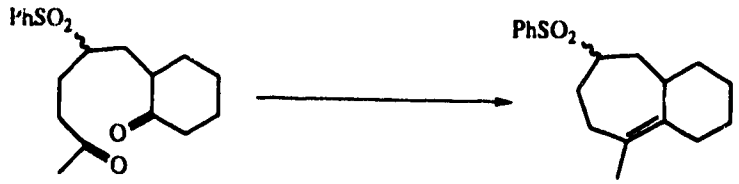
5.06 (m, 2 H), 5.56--5.74 (m, 1 H), 7.50--7.70 (m, 3 H), 7.80--7.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.07, 27.62, 27.94, 28.34, 30.74, 34.42, 42.04, 47.53, 60.56, 116.20, 128.98, 129.12, 133.67, 136.71, 137.68, 219.77; exact mass, *m/z* calcd for $C_{18}H_{24}O_3S$ 320.1446, found 320.1438.

2-[5-Oxo-2-(phenylsulfonyl)hexyl]cyclohexanone (36a).

36 **36a**

The procedure for **27a** was followed using **36** (major isomer) (341.6 mg, 1 07 mmol), and flash chromatography of the crude product over silica gel (3 x 15 cm) with 9:11 EtOAc--hexane gave **36a** (307.5 mg, 85%) as a homogeneous [^1H NMR (300 MHz), TLC, silica, 2:3 EtOAc--hexane)] oil: IR ($CHCl_3$ cast) 1709, 1300, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18--1.34 (m, 1 H), 1.50--2.20 (m, 12 H), 2.30--2.40 (m, 2 H), 2.78 (t, *J* = 6.8 Hz, 2 H), 2.82--2.95 (m, 1 H), 3.08--3.18 (m, 1 H), 7.54--7.72 (m, 3 H), 7.82--7.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 23.43, 25.25, 28.26, 28.58, 30.01, 35.14, 39.54, 42.40, 48.81, 61 54, 128.92, 129.19, 133.77, 137.57, 207.54, 212.05; exact mass, *m/z* calcd for $C_{18}H_{24}O_4S$ [illegible], found 336.1384. Compound **36a** was a single isomer, but its stereochemistry was not determined.

(2,6,7,8,9,9a-Hexahydro-5-methyl-1H-benzocyclhepte- 8-yl)phenylsulfone 36b.

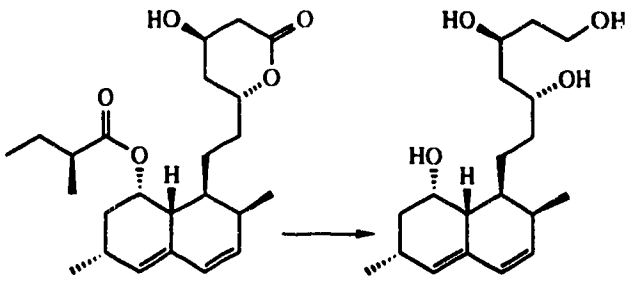


36a **36b**

Procedure B was followed, using Na (216.2 mg, 9.40 mmol), naphthalene (1.2054 g, 9.40 mmol), and $TiCl_4$ (0.38 mL, 3.48 mmol) in THF (40 mL), and **36a** (68.9 mg, 0.205 mmol) in THF (10 mL). Flash chromatography of the crude product over silica gel (3 x 15 cm), first with hexane (to separate naphthalene) and then 3:17 EtOAc--hexane, gave **36b** (24.4 mg, 39%) as a homogeneous (TLC, silica, 15:85 EtOAc--hexane) oil: IR ($CHCl_3$ cast) 2927, 1304, 1145 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30--1.70 (m, 11 H), 1.85--2.10 (m, 4 H), 2.20--2.45 (m, 3 H), 3.15--3.30 (m, 1 H), 7.50--7.70 (m, 3 H), 7.82--7.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 21.22, 23.32, 24.70, 25.26, 27.82, 30.44, 30.66, 33.06, 41.31, 65.20, 127.13, 129.03, 129.09, 133.52, 135.75, 137.70; exact mass. *m/z* calcd for $C_{18}H_{24}O_2S$ 304.1496, found 304.1497. Anal. Calcd for $C_{18}H_{24}O_2S$: C, 71.01; H, 7.95; S, 10.53. Found: C, 71.32; H, 8.05; S, 10.57. Compound **36b** was a single isomer, but its stereochemistry was not determined.

Degradation of Mevinolin

Conversion of mevinolin (1b) into 3.

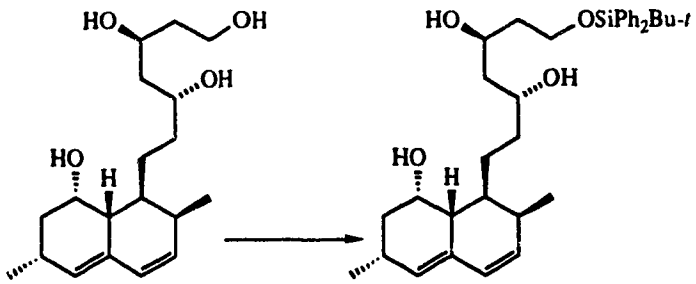


1b **3**

Monacolin K (1.0722 g, 2.65 mmol) in THF (10 mL) was added over 5 min to a stirred and cooled (-5°C) suspension of lithium aluminum hydride (0.60 g, 15.8 mmol) in THF (50 mL). The mixture was stirred and allowed to attain room temperature (with the cold bath left in place) over 4-5 h. The mixture was then cooled to 0°C and water (1.8 mL) was added dropwise with stirring. Stirring was continued for 10 min, and aqueous sodium hydroxide (2 M, 1.8 mL) was then added. Stirring was continued for another 10 min, and then water (1.8 mL) was added as before. The cold bath was removed and the mixture was stirred for an additional 20 min and filtered through a pad (2.5 x 3.5 cm) of Florisil. The pad was washed with acetone (120 mL). The combined filtrates were evaporated. The resulting white solid was dissolved in dichloromethane (150 mL) and the solution was washed with water (1 x 50 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm),

using first 3:7 acetone--chloroform and then 1:1 acetone--chloroform, gave **3** (722.2 mg, 84%) as a homogeneous (TLC, silica, 3:2 acetone--chloroform) white solid: IR ($CHCl_3$ cast) 3340 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 7.5 Hz, 3 H), 1.22--1.38 (m, 2 H), 1.40--1.76 (m, 8 H), 1.80--1.98 (m, 4 H), 2.12--2.20 (m, 1 H), 2.34--2.54 (m, 2 H), 2.62--2.74 (m, 1 H), 3.65--4.35 (m, 5 H), 5.52--5.58 (m, 1 H), 5.78 (dd, J = 9.5, 6.0 Hz, 1 H), 5.98 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.22, 20.07, 23.76, 27.45, 30.75, 33.93, 35.20, 35.61, 38.08, 38.84, 43.29, 61.67, 65.68, 71.46, 73.34, 128.58, 130.05, 131.63, 133.83; exact mass, m/z calcd for $C_{19}H_{30}O_3$ $(M - H_2O)^+$ 306.2195, found 306.2183. For analaysis a sample that was recrystallized from acetone: mp 137.5-139.5°C. Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.01; H, 9.98.

Conversion of 3 into 4.

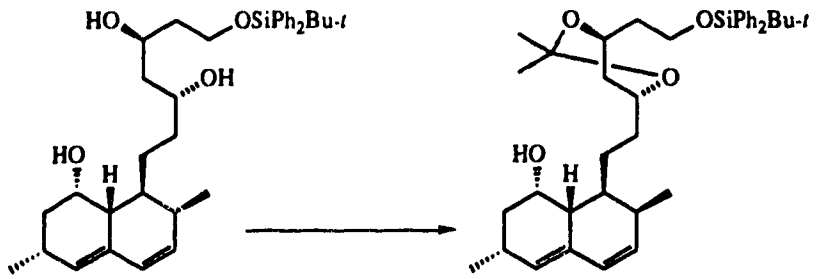


3 **4**

t-Butyldiphenylsilyl chloride (0.64 mL, 2.45 mmol) was added to a stirred solution of tetraol **3** (722.2 mg, 2.23

mmol) and imidazole (378.9 mg, 5.57 mmol) in dry DMF (10 mL) at room temperature. Stirring was continued overnight and the mixture was then diluted with ethyl acetate (100 mL), washed with water (1 x 30 mL), saturated aqueous ammonium chloride (1 x 30 mL) and brine (1 x 30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using first 1:5 ethyl acetate--hexane and then 2:3 ethyl acetate--hexane, gave **4** (1.2656 g, 100%) as a homogeneous (TLC, silica, 2:3 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.20 (d, J = 7.5 Hz, 3 H), 1.24--1.68 (m, 7 H), 1.70--1.82 (m, 1 H), 1.84--1.96 (m, 3 H), 1.98--2.18 (m, 1 H), 2.35--2.50 (m, 3 H), 3.78--3.88 (m, 2 H), 3.94--4.05 (m, 2 H), 4.10--4.24 (m, 2 H), 4.30--4.35 (m, 1 H), 5.52--5.58 (m, 1 H), 5.78 (dd, J = 9.5, 6.0 Hz, 1 H), 5.98 (d, J = 9.5 Hz, 1 H), 7.35--7.50 (m, 6 H), 7.60--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.29, 19.07, 22.42, 23.54, 26.86, 27.69, 30.81, 33.67, 35.23, 35.44, 38.32, 38.92, 43.62, 63.23, 65.46, 71.00, 73.20, 127.88, 128.71, 129.94, 130.14, 131.78, 132.88, 133.64, 135.59; exact mass, *m/z* calcd for $C_{35}H_{48}O_3Si$ $(M - H_2O)^+$ 544.3372, found 544.3382.

Conversion of 4 into 5.

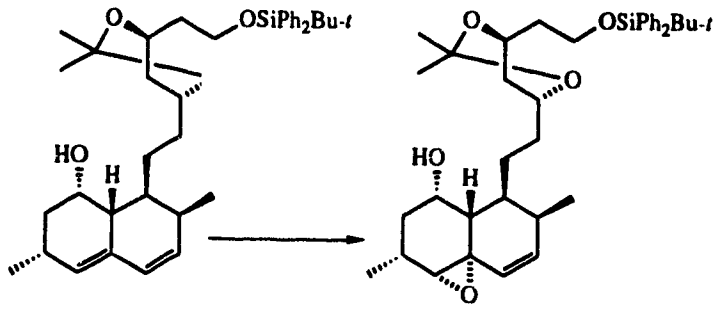


4 **5**

p-Toluenesulfonic acid monohydrate (42 mg, 0.22 mmol) was added to a stirred solution of triol **4** (1.2656 g, 2.25 mmol) in dry acetone (20 mL). Stirring was continued overnight and then solid sodium bicarbonate (*ca.* 55 mg, 0.66 mmol) was added. The mixture was stirred for 10 min and then filtered. The solid was rinsed with dry acetone (*ca.* 5 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using first 1:19 ethyl acetate--hexane and then 1:9 ethyl acetate--hexane, gave alcohol **5** (1.1111 g, 82%) as a homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) glass: IR ($CHCl_3$ cast) 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, J = 7.0 Hz, 3 H), 1.06 (s, 9 H), 1.12--1.50 [m, 14 H, including a doublet at δ 1.20 (J = 7.5 Hz, 3 H) and singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.54--1.85 (m, 5 H), 1.85--1.92 (m, 2 H), 2.08--2.18 (m, 1 H), 2.36--2.50 (m, 2 H), 3.64--3.74 (m, 1 H), 3.78--3.90 (m, 2 H), 4.08--4.18 (m, 1 H), 4.22--4.30 (m, 1 H), 5.52--5.57 (m, 1 H), 5.80 (dd, J = 9.5, 6.0 Hz, 1 H), 5.98 (d, J = 9.5 Hz, 1 H), 7.34--7.46 (m,

6 H), 7.64--7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.07, 19.27, 19.90, 23.44, 23.70, 26.92, 27.62, 30.33, 30.87, 33.20, 35.67, 35.99, 37.59, 38.84, 39.42, 59.75, 65.38, 65.70, 68.71, 90.56, 127.64, 128.56, 129.60, 130.05, 131.61, 133.63, 134.00, 135.61; exact mass, *m/e* calcd for $C_{37}H_{51}O_4Si$ $(M - CH_3)^+$ 587.3556, found 587.3538. Anal. Calcd for $C_{38}H_{54}O_4Si$: C, 75.70; H, 9.03. Found: C, 75.52; H, 8.98.

Conversion of 5 into 8.



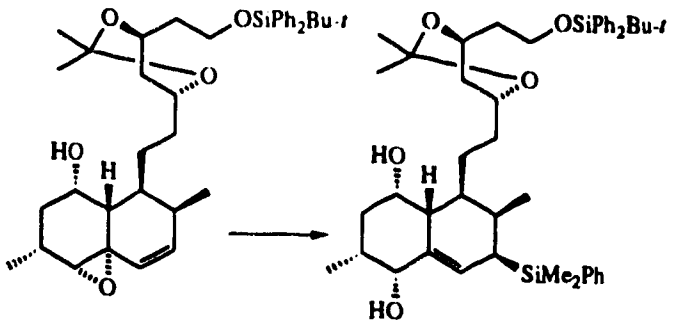
5 **8**

Homoallylic alcohol **5** (180 mg, 0.299 mmol) was added to a stirred mixture of vanadyl acetylacetonate (8 mg, 0.03 mmol) and sodium bicarbonate (30 mg, 0.357 mmol) in dry benzene (8 mL). The mixture was stirred and cooled by a cold-water bath (6°C) and *t*-butylhydroperoxide (4.15 M in benzene, 86 μL, 0.359 mmol) was added dropwise (over *ca.* 1 min). The water bath was allowed to attain room temperature and, after 5 h, during which time the initial purple color faded to a pale yellow, the mixture was evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm),

using first 1:19 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine) and then 1:9 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine), gave epoxide **8** (152.3 mg, 82%) as a homogeneous (TLC, silica gel, 1:4 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.10--1.52 [m, 14 H, including a doublet at δ 1.25 (J = 7.5 Hz, 3 H) and singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.66--1.84 (m, 6 H), 2.05--2.14 (m, 1 H), 2.26--2.38 (m, 1 H), 2.48--2.55 (m, 1 H), 3.28 (dd, J = 3.5, 1.0 Hz, 1 H), 3.58 (d, J = 11.5 Hz, 1 H), 3.66--3.74 (m, 1 H), 3.78--3.90 (m, 2 H), 3.95--4.00 (m, 1 H), 4.10--4.18 (m, 1 H), 5.70 (d, J =9.5 Hz, 1 H), 6.16 (dd, J = 9.5, 5.5 Hz, 1 H), 7.35--7.46 (m, 6 H), 7.64--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.62, 19.22, 19.94, 20.33, 23.52, 25.83, 26.92, 30.36, 31.44, 33.72, 35.75, 36.15, 36.87, 37.54, 39.45, 59.77, 62.27, 65.69, 66.54, 67.17, 69.54, 98.47, 125.20, 127.67, 129.59, 134.05, 135.63, 142.78; exact mass, *m/z* calcd for $C_{37}H_{51}O_5Si$ $(M - CH_3)^+$ 603.3506, found 603.3533; CIMS, *m/z* calcd for $C_{38}H_{54}O_5Si$ 618, found 619 $(M + 1)^+$. Anal. Calcd for $C_{38}H_{54}O_5Si$: C, 73.74; H, 8.79. Found: C, 73.27; H, 8.74.

Compcund **8** is very sensitive to acids; failure to use $NaHCO_3$ and Et_3N, as described above, results in a low yield.

Conversion of 8 into 50.



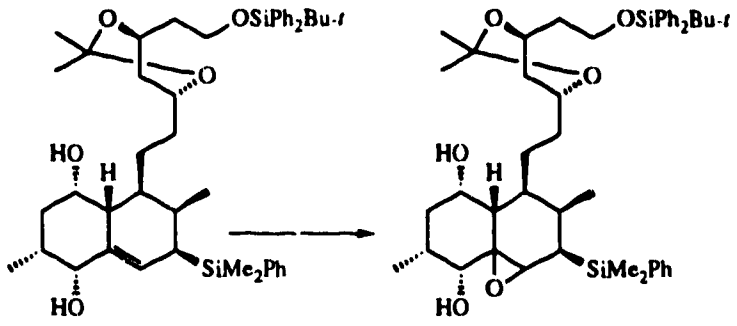
8 **50**

A stock solution of phenyldimethylsilyllithium[29] was prepared by addition of lithium ribbon (111.3 mg, 16.0 mmol), cut into small pieces, to a solution of phenyldimethylsilyl chloride (0.76 mL, 4.58 mmol) in dry THF (15 mL) at 0°C. The mixture was sonicated at 0°C [Branson Sonic Bath, type B-12, 80W] for 30 min and then stirred at 0°C overnight. An aliquot (1 mL) was added to water (10 mL) and the solution was titrated with 0.1 N hydrochloric acid using phenolphthalein as indicator. The average of several runs indicated that the solution of phenyldimethylsilyllithium was 0.311 M. The organometallic was stored in a freezer and could be kept for at least 3 weeks.

Phenyldimethylsilyllithium (0.311 M in THF, 2.35 mL, 0.729 mmol) was added dropwise (over *ca.* 5 min) to a stirred and cooled (-20°C) solution of epoxide **8** (129.0 mg, 0.208 mmol) in THF (10 mL). Stirring was continued for 2 h (TLC control, silica, 1:3 ethyl acetate--hexane) and then water (0.2 mL) was added. The cold bath was removed and the mixture was allowed to attain room temperature (*ca.* 30 min).

The solution was filtered through a pad (2 x 3 cm) of a 2:1:1 mixture of Florisil, sodium bicarbonate and magnesium sulfate. The pad was washed with THF (20 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using first 3:17 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine) and then 1:4 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine), gave **50** (144.5 mg, 89%) as a homogeneous (TLC, silica, 1:3 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.34 (s, 6 H), 0.71 (d, J = 6.5 Hz, 3 H), 0.95--1.32 [m, 15 H, including a singlet at δ 1.05 (9 H)], 1.34--1.78 [m, 13 H, including singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.80--2.15 (m, 5 H), 2.28--2.36 (m, 1 H), 2.44--2.52 (m, 1 H), 3.64--3.80 (m, 3 H), 4.02--4.18 (m, 3 H), 5.86 (s, 1 H), 7.32--7.48 (m, 9 H), 7.50--7.58 (m, 2 H), 7.64--7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -3.41, -3.31, 10.97, 19.21, 19.83, 25 36, 26.85, 29.70, 30.25, 31.43, 32.66, 34.07, 36.74, 37.35, 39.25, 39.36, 41.73, 59.71, 65.68, 66.14, 69.24, 74.19, 98.46, 125.89, 127.59, 127.82, 128.94, 129.55, 133.83, 133.94, 134.00, 135.55, 136.82, 138.69; CIMS, *m/z* calcd for $C_{46}H_{66}O_5Si_2$ 754, found 755 $(M + 1)^+$. Anal. Calcd for $C_{46}H_{66}O_5Si_2$: C, 73.16; H, 8.81. Found: C, 73.36; H, 8.78.

Conversion of 50 into 51.

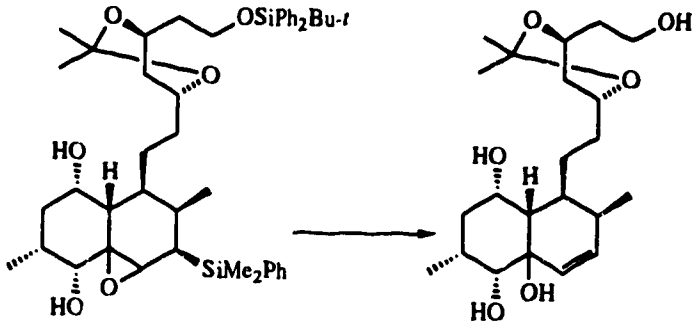


50 **51**

Allylsilane **50** (129 mg, 0.186 mmol) was added to a stirred mixture of vanadyl acetylacetonate (5 mg, 0.0186 mmol) and sodium bicarbonate (30 mg, 0.357 mmol) in dry benzene (6 mL). The mixture was stirred at room temperature and *t*-butylhydroperoxide (4.15 M in benzene, 86 μL, 0.359 mmol) was added dropwise (over *ca.* 1 min). Stirring was continued for 3 h, during which time the initial purple color faded to a pale yellow. The mixture was filtered through a pad (2 x 2 cm) of Florisil and the pad was washed with ethyl acetate (10 mL). The combined filtrate was evaporated and flash chromatography of the residue over silica gel (2 x 15 cm), using first 1:4 ethyl acetate--hexane and then 3:7 ethyl acetate--hexane, gave epoxide **51** (120.5 mg, 84%) as a homogeneous (TLC, silica gel, 1:3 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.38 (s, 3 H), 0.42 (s, 3 H), 0.74 (d, J = 6.5 Hz, 3 H), 1.06 (s, 9 H), 1.08--1.86 [m, 23 H, including a doublet at δ 1.18 (J = 6.5 Hz, 3 H), and singlets at δ 1.36 (3 H) and δ 1.42 (3 H)], 2.05--2.14 (m, 2 H), 2.26--2.38 (m, 1 H), 3.25

(s, 1 H), 3.66--3.82 (m, 4 H), 4.06--4.14 (m, 1 H), 4.16--4.22 (m, 1 H), 7.34--7.45 (m, 9 H), 7.52--7.58 (m, 2 H), 7.65--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ -3.18, -2.93, 12.41, 15.43, 19.19, 19.80, 24.38, 26.84, 28.35, 30.24, 31.32, 34.07, 34.27, 36.55, 37.34, 37.81, 39.34, 40.64, 49.74, 59.69, 62.73, 65.61, 67.49, 69.12, 69.44, 98.44, 127.57, 128.00, 129.21, 129.53, 133.75, 133.99, 135.54, 137.65; CIMS, *m/z* calcd for $C_{46}H_{66}O_6Si_2$ 770, found 771 $(M + 1)^+$. Anal. Calcd for $C_{46}H_{66}O_6Si_2$: C, 71.64; H, 8.63. Found: C, 71.36; H, 8.74.

Conversion of 51 into 52.

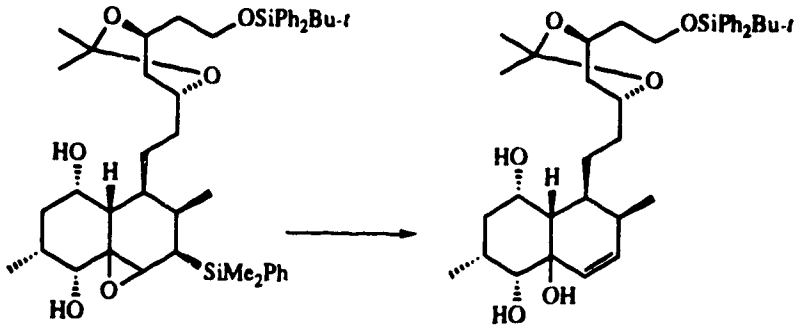


51 **52**

Tetrabutylammonium fluoride (1 M in THF, 0.24 mL, 0.24 mmol) was added to a stirred solution of epoxysilane **51** (45.3 mg, 0.0587 mmol) in THF (2 mL). After 3 h, the solvent was evaporated and flash chromatography of the residue over silica gel (1 x 10 cm) using ethyl acetate gave tetraol **52** (21.5 mg, 91%) as a homogeneous (TLC, silica, ethyl acetate) white solid: IR ($CHCl_3$ cast) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, J = 7.0 Hz, 3 H), 1.22--1.42 [m, 11 H,

including a doublet at δ 1.28 (J = 7.5 Hz, 3 H), and a singlet at δ 1.38 (3 H)], 1.44--1.70 [m, 6 H, including a singlet at δ 1.46 (3 H))], 1.70--1.84 (m, 3 H), 2.02--2.08 (m, 1 H), 2.20--2.34 (m, 2 H), 2.36--2.44 (m, 1 H), 2.52--2.60 (m, 1 H), 2.72 (s, 1 H), 3.42 (d, J = 6.5 Hz, 1 H), 3.45--3.52 (m, 1 H), 3.74--3.84 (m, 2 H), 3.84--3.92 (m, 1 H), 4.08--4.15 (m, 2 H), 5.84 (dd, J = 9.5, 5.0 Hz, 1 H), 6.04 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.76, 16.36, 19.94, 23.10, 30.29, 31.44, 32.11, 32.28, 33.60, 37.03, 37.77, 38.13, 41.45, 60.91, 67.45, 69.09, 69.46, 74.35, 75.16, 98.70, 127.49, 136.55; exact mass, m/z calcd for $C_{21}H_{35}O_6$ $(M - CH_3)^+$ 383.2433, found 383.2433.

Conversion of 51 into 49.



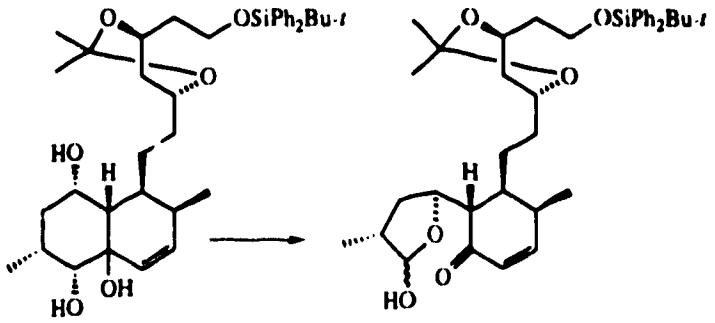
51 **49**

Pyridinium *p*-toluenesulfonate (37.4 mg, 0.149 mmol) was added to a stirred solution of epoxysilane **51** (86.0 mg, 0.115 mmol) in dry THF (10 mL). The mixture was stirred overnight and then solid sodium bicarbonate (*ca.* 30 mg, 0.35 mmol) was added. The suspension was stirred for 15 min and then filtered through a pad (2 x 2 cm) of a 2:1 mixture of

Florisil and sodium bicarbonate. The pad was then washed with ethyl acetate (20 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using first 3:7 ethyl acetate--hexane and then 2:3 ethyl acetate--hexane, gave triol **49** (52.8 mg, 74%) as a homogeneous (TLC, silica, development first with 3:7 ethyl acetate--hexane and then with 1:1 ethyl acetate--hexane) solid: mp 154-156 °C; IR ($CHCl_3$ cast) 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (d, J = 7.0 Hz, 3 H), 0.95--1.20 [m, 10 H, including a singlet at δ 1.06 (9 H)], 1.20--1.54 [m, 13 H, including a doublet at δ 1.28 (J = 7.5 Hz, 3 H), and singlets at δ 1.34 (3 H) and δ 1.44 (3 H)], 1.54--1.92 (m, 5 H), 1.98--2.10 (m, 1 H), 2.15--2.32 (m, 2 H), 2.35--2.45 (m, 1 H), 2.48 [d, J = 9.0 Hz, 1 H (signal disappeared upon exchange with D_2O)], 3.01 [s, 1 H (signal disappeared upon exchange with D_2O)], 3.42--3.54 [m, 2 H, (signal for 1 H disappeared upon exchange with D_2O)], 3.64--3.74 (m, 1 H), 3.78--3.92 (m, 2 H), 4.08--4.20 (m, 2 H), 5.84 (dd, J = 10.0, 5.0 Hz, 1 H), 6.04 (d, J = 10.0 Hz, 1 H), 7.32--7.50 (m, 6 H), 7.58--7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.81, 14.14, 16.32, 19.25, 19.92, 23.06, 26.90, 30.30, 31.48, 31.89, 32.21, 33.56, 37.56, 39.39, 41.43, 59.70, 65.67, 67.50, 69.02, 74.28, 75.10, 98.56, 127.47, 127.62, 127.65, 129.58, 133.97, 134.03, 135.59, 136.63; exact mass, *m/z* calcd for $C_{37}H_{51}O_5Si$ $(M - CH_3 - H_2O)^+$ 603.3506, found 603.3527; CIMS, *m/z* calcd for $C_{38}H_{56}O_6Si$ 636, found 637 $(M + 1)^+$. Anal. Calcd for $C_{38}H_{56}O_6Si$: C, 71.66; H, 8.86. Found: C, 71.56; H,

8.86.

Conversion of 49 into 53.

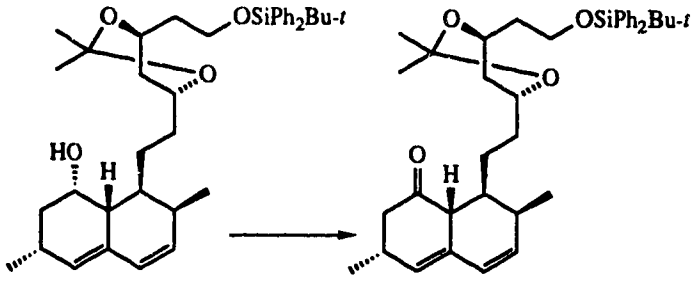


49 **53**

Lead tetraacetate (5.4 mg, 0.011 mmol) was added to a stirred solution of triol **49** (6.7 mg, 0.0105 mmol) in dry dichloromethane (1.5 mL) at room temperature. The suspension was stirred for 45 min and the mixture was then filtered through a pad (0.5 x 4 cm) of silica gel. The pad was washed with dichloromethane (5 mL) and ethyl acetate (10 mL). The combined filtrates were evaporated and flash chromatography of the residue over silica gel (0.5 x 8 cm), using first 3:17 ethyl acetate--chloroform and then 1:4 ethyl acetate--chloroform, gave keto lactols **53** (5.4 mg, 81%) as an apparently homogeneous (TLC, silica, two developments with 1:4 ethyl acetate--chloroform) thick oil: IR ($CHCl_3$ cast) 3420, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (d, J = 7.0 Hz, 3 H), 1.06 (s, 9 H), 1.15 (d, J = 7.5 Hz, 3 H), 1.20--1.52 [m, 11 H, including singlets at δ 1.35 (3 H) and δ 1.40 (3 H))], 1.56--1.74 (m, 5 H), 1.98--2.06 (m, 1 H), 2.22--2.34 (m, 2 H), 2.42--2.48 (m, 0.35 H), 2.52--2.58 (m, 0.65 H),

2.90--3.04 (m, 1 H), 3.65--3.88 (m, 3 H), 4.05--4.14 (m, 1 H), 4.48--4.54 (m, 0.65 H), 4.58--4.62 (m, 0.35 H), 5.04 (d, J = 4.0 Hz, 0.65 H), 5.32 (dd, J = 4.0, 2.0 Hz, 0.35 H), 5.82--6.00 (m, 1 H), 6.56--6.78 (m, 1 H), 7.36--7.46 (m, 6 H), 7.65--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (major isomer) δ 16.58, 17.05, 19.27, 19.90, 22.76, 26.92, 30.33, 31.42, 34.15, 35.87, 37.30, 39.37, 40.71, 42.36, 56.14, 59.71, 65.65, 69.48, 78.27, 98.50, 104.60, 127.69, 128.54, 129.62, 134.03, 135.61, 153.57, 200.77; (minor isomer) 13.04, 22.55, 35.54, 37.21, 42.88, 55.48, 69.56, 99.83, 127.64, 128.35, 134.00, 153.04, 200.02; exact mass, *m/z* calcd for $C_{37}H_{51}O_6Si$ $(M - CH_3)^+$ 619.3454, found 619.3439.

Conversion of 5 into 56.

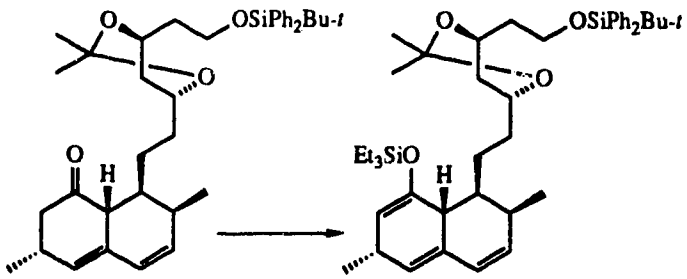


5 **56**

Dry DMSO (32 µL, 0.448 mmol) was added to a stirred and cooled (-78°C) solution of oxalyl chloride (19.5 µL, 0.224 mmol) in dichloromethane (10 mL), and stirring was continued for 10 min. Alcohol **5** (90 mg, 0.149 mmol) in dichloromethane (1 mL plus 1 mL as a rinse) was added dropwise over *ca.* 2 min. Stirring at -78°C was continued for 1 h, and then

triethylamine (103.8 μL, 0.745 mmol) was added. The cold bath was removed 5 min after the end of the addition and stirring was continued for a further 1 h. Water (10 mL) and dichloromethane (10 mL) were added and the layers were separated. The aqueous phase was extracted with dichloromethane (1 x 10 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using first 1:19 ethyl acetate--hexane and then 1:9 ethyl acetate--hexane, gave ketone **56** [78.3 mg, 87%, or 96% corrected for recovered starting alcohol (8.7 mg)] as a homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) oil. IR ($CHCl_3$ cast) 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.15 (d, J = 7.5 Hz, 3 H), 1.22--1.78 [m, 14 H, including singlets at δ 1.38 (3 H) and δ 1.44 (3 H))], 1.92--2.02 (m, 1 H), 2.12 (dd, J = 13.0, 9.5 Hz, 1 H), 2.36--2.48 (m, 1 H), 2.62 (dd, J = 13.0, 6.0 Hz, 1 H), 2.74--2.88 (m, 2 H), 3.65--3.80 (m, 3 H), 4.08--4.18 (m, 1 H), 5.52 (br s, 1 H), 5.80 (dd, J = 9.5, 6.0 Hz, 1 H), 6.04 (d, J = 9.5 Hz, 1 H), 7.35--7.48 (m, 6 H), 7.64--7.74 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.15, 19.21, 19.88, 21.36, 23.79, 25.34, 26.59, 26.87, 28.93, 30.30, 31.60, 32.28, 33.89, 37.36, 38.44, 39.38, 46.97, 48.41, 59.67, 65.58, 69.26, 98.40, 126.27, 127.60, 127.63, 129.48, 129.54, 133.95, 133.99, 134.84, 135.56, 135.90, 212.21. exact mass, m/z calcd for $C_{38}H_{52}O_4Si$ 600.3665 M^+, found 600.3648.

Conversion of 56 into 57.

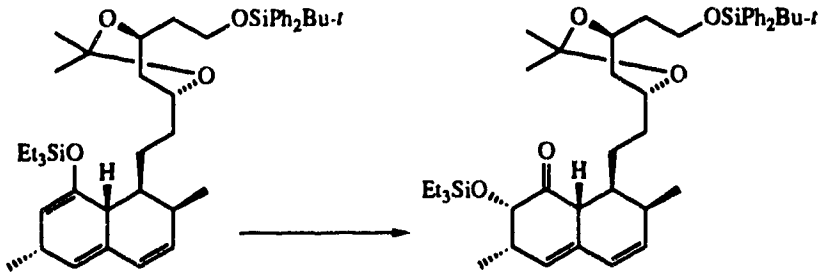


56 **57**

A stock solution of LDA was prepared by adding *n*-butyllithium (1.6 M in hexanes, 0.67 mL, 1.07 mmol) to a stirred and cooled (0°C) solution of diisopropylamine (0.15 mL, 1.07 mmol) in THF (3 mL). Stirring was continued for 10 min and a portion (1.65 mL, 0.462 mmol of LDA) of the above LDA solution was diluted with THF (6 mL) and cooled to -78°C. A solution of ketone **56** (55.5 mg, 0.0924 mmol) in THF (1 mL plus 1 mL as a rinse) was added over *ca.* 2 min with stirring and, after 15 min, 4:1 triethylchlorosilane-triethylamine (58 µL, 0.277 mmol of triethylchlorosilane) was added. Stirring at -78°C was continued for 15 min. At this stage some starting ketone remained (TLC, silica, 1:19 ethyl acetate--hexane) and so more of the stock LDA solution (which had been kept at -78°C) (1.65 mL mL, 0.462 mmol) was added, followed by another portion of the triethylchlorosilane-triethylamine solution (58 µL, 0.277 mmol of triethylchlorosilane). Stirring was continued for 15 min and then saturated aqueous sodium bicarbonate (1 mL) was added. The cooling bath was removed and the mixture was allowed to attain room

temperature (*ca.* 30 min). The mixture was concentrated and the residue was dissolved in dichloromethane (10 mL). The solution was washed with water (1 x 5 mL) and brine (1 x 5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) using 1:9 chloroform--hexane gave silyl enol ether **57** (47.5 mg, 72%) as a homogeneous (TLC, silica, 1:19 ethyl acetate--hexane) thick oil: IR ($CHCl_3$ cast) 2955 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.65 (q, J = 8.0 Hz, 6 H), 0.90--1.28 [m, 27 H, including doublets at δ 0.94 (J = 7.0 Hz, 3 H) and δ 0.98 (J = 7.8 Hz, 3 H), and a singlet at δ 1.04 (9 H)], 1.30--1.60 [m, 8 H, including singlets at δ 1.35 (3 H) and δ 1.40 (3 H)], 1.62--1.88 (m, 4 H), 2.30--2.40 (m, 1 H), 2.56--2.64 (m, 1 H), 2.89--2.95 (m, 1 H), 3.64--3.70 (m, 1 H), 3.72--3.86 (m, 2 H), 4.06--4.14 (m, 1 H), 4.86 (m, 1 H), 5.34 (br s, 1 H), 5.65 (dd, J = 9.5, 5.5 Hz, 1 H), 6.04 (d, J = 9.5 Hz, 1 H), 7.32--7.44 (m, 6 H), 7.62--7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 5.28, 6.97, 13.67, 19.26, 19.82, 23.49, 26.39, 26.69, 30.35, 32.13, 33.81, 34.59, 37.63, 38.81, 39.54, 46.33, 59.77, 65.71, 69.72, 98.42, 108.80, 125.24, 127.66, 127.97, 129.59, 133.98, 134.03, 134.07, 135.61, 136.35, 150.43; CIMS, *m/z* calcd for $C_{44}H_{66}O_4Si_2$ 714, found 715 $(M + 1)^+$.

Conversion of 57 into 58.

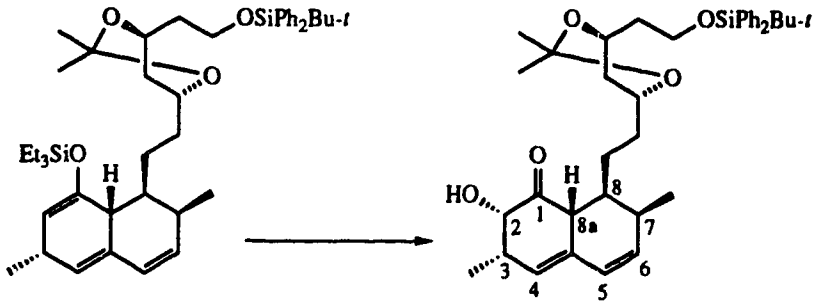


57 **58**

A solution of silyl enol ether **57** (42 mg, 0.0587 mmol) in dichloromethane (1 mL) was added quickly to a stirred and cooled (0°C) solution of *m*-chloroperbenzoic acid (80-85% w/w, 11 mg, *ca*. 0.0528 mmol) in dichloromethane (8 mL). Stirring at 0°C was continued for 80 min, at which stage some starting silyl enol ether still remained (TLC control, silica, development first with 1:19 ethyl acetate--hexane and then with 1:9 ethyl acetate--hexane). More *m*-chloroperbenzoic acid (2 mg, 0.001 mmol) was added and stirring at 0°C was continued for 10 min, by which time the reaction was over (TLC control). Aqueous sodium bisulfite (1 M, 2 mL) was added and the mixture was stirred vigorously for 10 min. The layers were separated and the organic layer was washed with sodium bicarbonate (2 x 5 mL). The combined aqueous phases were extracted with dichloromethane (1 x 15 mL), and the combined organic extracts were washed with brine (1 x 15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using first hexane and then 1:19 ethyl acetate--hexane, gave ketone **58** (20 mg, 47%).

Further elution with 3:17 ethyl acetate--hexane afforded another compound (6.9 mg) which has yet to be identified. Ketone **58** had: IR ($CHCl_3$ cast) 2954, 1795 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (q, J = 8.0 Hz, 6 H), 0.84--1.14 (m, 22 H), 1.14--1.78 (m, 15 H, including singlets at δ 1.38 (3 H) and δ 1.44 (3 H)], 1.84--2.08 (m, 2 H), 2.35--2.48 (m, 1 H), 2.94--3.06 (m, 1 H), 3.10--3.18 (m, 1 H), 3.64--3.94 (m, 3 H), 4.08--4.18 (m, 1 H), 4.68 (d, J = 7.0 Hz, 1 H), 5.38--5.44 (m, 1 H), 5.82 (dd, J = 9.5, 6.0 Hz, 1 H), 5.96 (d, J = 9.5 Hz, 1 H), 7.34--7.48 (m, 6 H), 7.64--7.74 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 4.92, 6.85, 14.68, 14.89, 19.26, 19.68, 24.78, 26.90, 30.14, 33.55, 35.92, 37.45, 39.49, 42.17, 47.12, 59.71, 65.59, 68.21, 76.41, 98.43, 126.05, 127.62, 127.67, 127.86, 128.85, 129.57, 129.60, 134.07, 135.08, 135.61, 208.36; exact mass, *m/z* calcd for $C_{39}H_{55}O_5Si_2$ $(M - CH_3 - t\text{-}Bu)^+$ 659.3588 M^+, found 659.3579.

Conversion of 57 into 59.



57 **59**

A solution of silyl enol ether **57** (33.9 mg, 0.047 mmol) in ethyl acetate (0.5 mL plus 0.5 mL as a rinse) was added

quickly (over *ca.* 1 min) to a stirred and cooled (0°C) mixture of *m*-chloroperbenzoic acid (80-85% w/w, 12.0 mg, *ca.* 0.0569 mmol) and solid sodium bicarbonate (12.0 mg, 0.141 mmol) in ethyl acetate (2 mL). Stirring at 0°C was continued for 1 h (TLC control, silica, 1:9 ethyl acetate—hexane). Aqueous sodium bisulfite (1 M, 0.5 mL) was added and the mixture was stirred vigorously for 10 min. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate (1 x 1.5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:9 ethyl acetate—hexane, gave ketone **59** (20.2 mg, 70%) as a homogeneous (TLC, silica, 1:9 ethyl acetate—hexane) thick oil: IR (CH_2Cl_2 cast) 3500, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 [d, J = 7.0 Hz, 3 H corresponding to C(3)-Me], 0.90 [d, J = 7.0 Hz, 3 H corresponding to C(7)-Me], 1.05 (s, 9 H), 1.10—1.35 (m, 3 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.47—1.66 (m, 2 H), 1.66—1.78 (m, 2 H), 1.92—2.03 [m, 1 H corresponding to C(8)-H], 2.06—2.16 (m, 1 H), 2.37—2.47 [m, 1 H corresponding to C(7)-H], 3.12—3.23 [m, 1 H corresponding to C(3)-H], 3.28 [d, J = 12.5 Hz, 1 H corresponding to C(8a)-H], 3.38 [d, J = 7.0 Hz, 1 H (signal disappeared upon exchange with D_2O)], 3.65—3.90 (m, 3 H), 4.08--4.18 (m, 1 H), 4.71 [t, J = 7.3 Hz, 1 H corresponding to C(2)-H], 5.50 [t, J = 3.8 Hz, 1 H corresponding to C(4)-H], 5.84 [dd, J = 9.5, 6.0 Hz, 1 H corresponding to C(6)-H], 5.96 [d, J = 9.5 Hz, 1 H corresponding to C(5)-H], 7.32--7.45 (m, 6 H), 7.64--7.74 (m,

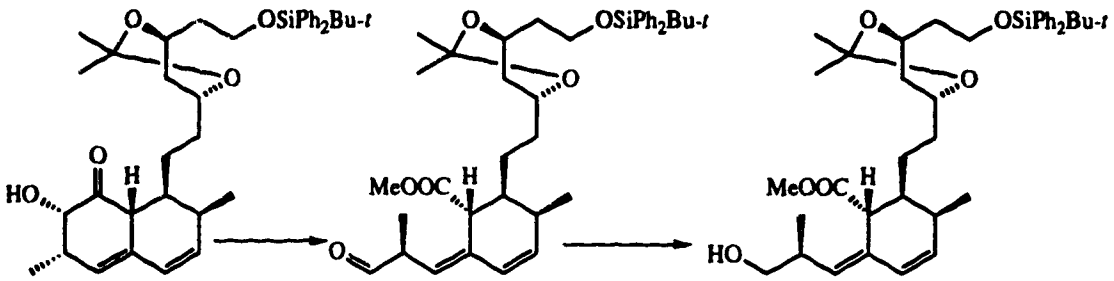
4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.41, 14.69, 19.23, 19.90, 24.55, 26.88, 29.98, 30.32, 33.58, 35.60, 37.41, 39.40, 41.72, 46.42, 59.71, 65.65, 69.44, 74.83, 98.43, 125.96, 127.61, 127.64, 128.09, 129.56, 133.26, 133.96, 134.02, 135.25, 135.58, 210.42; exact mass, *m/z* calcd for $C_{37}H_{49}O_5Si$ $(M - CH_3)^+$ 601.3349, found 601.3352.

The stereochemistry of **59** at C(2) was established by decoupling and NOE ^1H NMR (300 MHz) experiments. Decoupling served to locate the chemical shifts of the signals corresponding to C(2)-H (d, δ 4.71), C(3)-H (m, δ 3.12—3.23), C(7)-H (m, δ 2.37—2.47), .C(8)-H (m, δ 1.92—2.03), C(8a)-H (d, δ 3.28). Irradiation of the C(3)-H signal (δ 3.12—3.23) caused collapse of one of the high field methyl doublets (that centered at δ 0.87) *and* at the same time the olefinic signal due to C(4)-H (δ 0.87) changed to a narrow (J = 3.8 Hz) doublet. The signal due to C(2)-H also changed into a doublet (residual coupling with the hydroxyl hydrogen). These observations allow assignment of the signal at δ 3.12—3.23 to C(3)-H and the signal at δ 4.71 to C(2)-H. Similarly, irradiation of the signal at δ 2.37—2.47 caused collapse of the other high field doublet (that centred at δ 0.90) and at the same time the olefinic signal due to C(6)-H (δ 5.84) changed to a doublet. The olefinic signals corresponding to C(4)-H, C(5)-H, and C(6)-H could be assigned on the basis of their splitting patterns and coupling constants. The signal due to C(4)-H is a doublet of doublets [coupling with C(3)-H and C(8a)-H], that due to C(5)-H is a

doublet [coupling with C(6)-H], and that due to C(6)-H is a doublet of doublets [coupling with C(5)-H and C(7)-H]. Irradiation of the signal due to C(7)-H also caused a change in the signal due to C(8)-H, and so the location of C(8)-H could be found. Irradiation of C(8)-H and of C(4)-H in separate experiments served to locate the signal due to C(8a)-H.

Irradiation of the doublet corresponding to C(8a)-H (centered at δ 3.28) caused a 15% enhancement of the signal at δ 4.71 [corresponding to C(2)-H)]. Hence C(2)-H and C(8a)-H are taken to be *cis*.

Conversion of 59 into 64.



59 **63** **64**

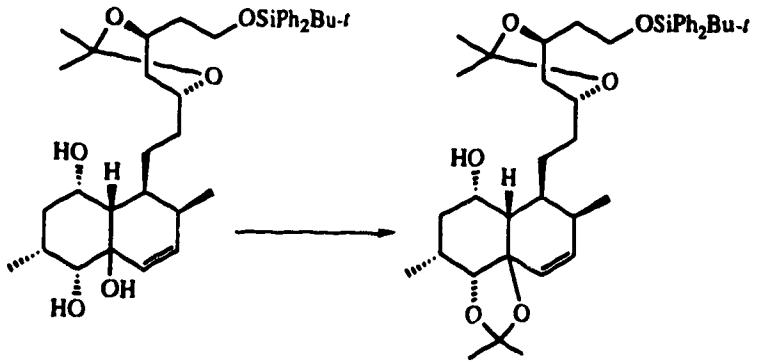
Lead tetraacetate (32.0 mg, 0.0688 mmol) and then acetic acid (30.0 μL, 0.52 mmol) were added to a stirred solution of ketone **59** (40.4 mg, 0.065 mmol) in a mixture (1:1) of benzene and dry methanol (3.0 mL) at room temperature. Stirring was continued for 20 min (TLC control, silica, 15:85 ethyl acetate--hexane). Aqueous sodium bisulfite (1 M, 4.0 mL) was added and the mixture was stirred vigorously for 10 min and

extracted with dichloromethane (2 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (1 x 10 mL), dried ($MgSO_4$) and evaporated to give crude aldehyde ester **63**. The material had: IR ($CHCl_3$ cast) 1725 cm^{-1}; exact mass, *m/z* calcd for $C_{38}H_{51}O_6Si$ $(M - CH_3)^+$ 631.3462, found 631.3441.

The crude material was dissolved in 98% ethanol (2.5 mL) and sodium borohydride (13.5 mg, 0.358 mmol) was added at 0°C (stirring). After 40 min, water (5 drops) and acetic acid (10 drops) were added and the mixture was stirred for 5 min. The solvents were evaporated and the residue was dissolved in dichloromethane (10.0 mL), washed with saturated aqueous sodium bicarbonate (1 x 5.0 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using first 1:4 ethyl acetate--hexane and then 3:7 ethyl acetate--hexane, gave hydroxy ester **64** (5.4 mg, 81%) as a homogeneous (TLC, silica, 3:7 ethyl acetate--hexane) thick oil: IR ($CHCl_3$ cast) 3424, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, J = 6.5 Hz, 3 H), 1.02 (d, J = 7.5 Hz, 3 H), 1.03--1.09 [m, 10 H, including a singlet at δ 1.04 (9 H)], 1.30--1.55 [m, 10 H, including singlets at δ 1.37 (3 H) and δ 1.43 (3 H)], 1.61--1.75 (m, 3 H), 2.18--2.30 (m, 2 H), 2.48--2.68 (m, 2 H), 3.30--3.40 (m, 1 H), 3.47--3.58 (m, 1 H), 3.62--3.88 [m, 7 H, including a singlet at δ 3.69 (3 H)], 4.05--4.17 (m, 1 H), 5.34 (d, J = 10.5 Hz, 2 H), 6.04 (dd, J = 10.5, 3.0 Hz, 1 H), 7.32--7.46 (m, 6 H), 7.60--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 17.397, 17.849,

19.251, 19.877, 21.412, 26.890, 30.303, 31.370, 34.577, 35.909, 37.430, 39.394, 39.546, 44.910, 52.393, 59.735, 65.703, 67.731, 69.466, 98.487, 127.640, 127.661, 129.063, 129.609, 131.735, 131.816, 133.938, 133.992, 135.585, 174.635; exact mass, *m/z* calcd for $C_{38}H_{53}O_6Si$ $(M - CH_3)^+$ 633.3611, found 633.3603; CIMS, *m/z* calcd for $C_{39}H_{56}O_6Si$ 648, found 649 $(M + 1)^+$.

Conversion of 49 into 66.

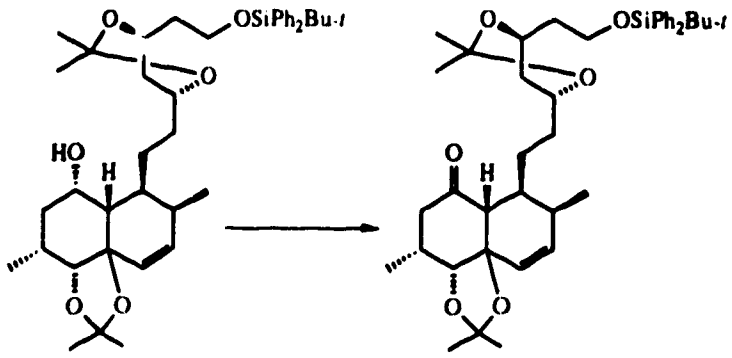


49 **66**

2-Methoxypropene (28 μL, 0.288 mmol) was added to a stirred and cooled (0°C) solution of triol **49** (61.3 mg, 0.096 mmol) and pyridinium *p*-toluenesulfonate (4.8 mg, 0.019 mmol) in dry dichloromethane (5.0 mL). Stirring was continued at 0°C for 4 h (TLC control, silica, 1:9 ethyl acetate--hexane). The mixture was diluted with dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate (1 x 5.0 mL). The aqueous layer was extracted with dichloromethane (1 x 5.0 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over

silica gel (1.5 x 15 cm), using first 1:19 ethyl acetate--hexane and then 1:9 ethyl acetate--hexane, gave alcohol **66** (60.9 mg, 93%) as a homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) foam: IR ($CHCl_3$ cast) 3540 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 1.02--1.34 [m, 12 H, including a singlet at δ 1.05 (9 H)], 1.34--1.75 [m, 19 H, including singlets at δ 1.36 (3 H), δ 1.42 (3 H), δ 1.46 (3 H), and δ 1.52 (3 H)], 1.86--2.00 (m, 1 H), 2.07--2.28 (m, 2 H), 2.40--2.52 (m, 1 H), 3.51 (d, J = 10.5 Hz, 1 H), 3.63--3.73 (m, 1 H), 3.74--3.88 (m, 2 H), 3.97--4.18 (m, 3 H), 5.71 (d, J = 10.0 Hz, 1 H), 5.86 (dd, J = 10.0, 4,5 Hz, 1 H), 7.30--7.46 (m, 6 H), 7.60--7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.697 MHz) δ 12.736, 17.095, 19.249, 19.937, 23.378, 26.879, 27.219, 28.672, 29.475, 30.341, 31.217, 33.679, 33.736, 36.128, 37.525, 37.980, 39.386, 59.676, 65.097, 65.624, 69.596, 81.822, 83.547, 98.425, 107.988, 127.615, 127.653, 129.552, 129.586, 130.346, 133.958, 134.00, 135.585, 135.597, 138.121; exact mass, *m/z* calcd for $C_{40}H_{57}O_6Si$ $(M - CH_3)^+$ 661.3924, found 661.3933.

20Conversion of 66 into 67.

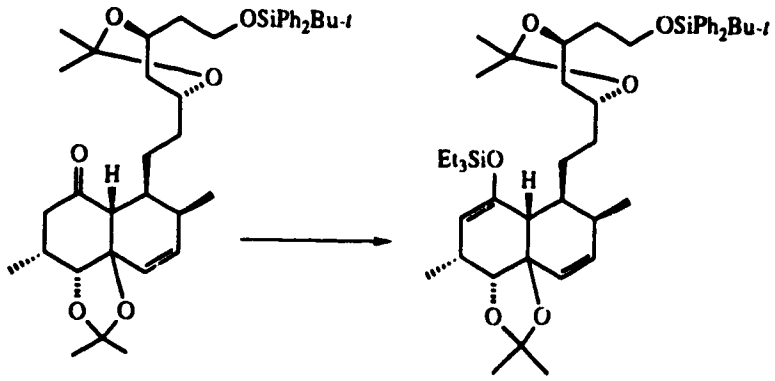


66 **67**

Alcohol **66** (76.8 mg, 0.113 mmol) in dichloromethane (2.0 mL plus 2 x 1.0 mL as rinses) was added at room temperature to a stirred mixture of pyridinium chlorochromate (48.9 mg, 0.227 mmol), sodium acetate (20 mg) and powdered 4Å molecular sieves (54 mg) in dichloromethane (5.0 mL). The mixture was stirred overnight (11 h), at which time the reaction was complete (TLC [silica, (both the sample of the reaction mixture and the sample of the starting material must be applied to the plate as very dilute solutions), 1:9 ethyl acetate--hexane developed twice]. The mixture was diluted with ether (15 mL) and filtered through a pad (2 x 3 cm) of Florisil. The pad was washed with ether (35 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using first 5:95 ethyl acetate--hexane and then 15:85 ethyl acetate--hexane, gave ketone **67** (71.9 mg, 94%) as a homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) foam: IR ($CHCl_3$ cast) 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (d, J = 7.0 Hz, 3 H), 0.97--

1.22 [m, 14 H, including a singlet at δ 1.04 (9 H) and a doublet at δ 1.12 (J = 6.5 Hz, 3 H)], 1.22--1.76 [m, 17 H, including singlets at δ 1.30 (3 H), δ 1.36 (3 H), δ 1.38 (3 H), and δ 1.42 (3 H)], 2.11--2.52 (m, 6 H), 2.64 (d, J = 10.0 Hz, 1 H), 3.62--3.88 (m, 3 H), 4.07--4.18 (m, 2 H), 5.76 (dd, J = 9.5, 1.5 Hz, 1 H), 5.89 (dd, J = 9.5, 4,5 Hz, 1 H), 7.34--7.46 (m, 6 H), 7.63--7.42 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 13.43, 17.10, 19.26, 19.94, 23.33, 26.43, 26.92, 27.52, 30.36, 30.77, 31.02, 32.05, 33.66, 37.60, 39.46, 43.79, 50.09, 59.80, 65.72, 69.70, 82.63, 83.39, 98.42, 108.11, 127.63, 127.67, 128.97, 129.56, 129.59, 134.10, 135.63, 138.61, 209.01; exact mass, m/z calcd for $C_{40}H_{55}O_6Si$ $(M - CH_3)^+$ 659.3768, found 659.3772; CIMS, m/z calcd for $C_{41}H_{58}O_6Si$ 674, found 675 $(M + 1)^+$.

Conversion of 67 into 68.



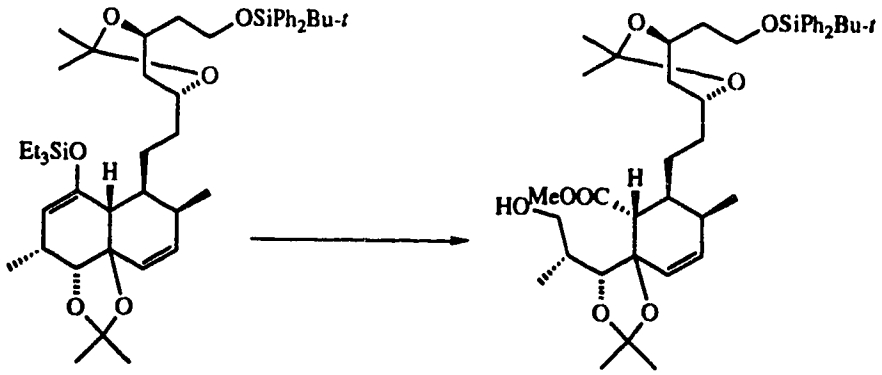
67 **68**

n-Butyllithium (1.6 M in hexane, 0.33 mL, 0.530 mmol) was added to a stirred and cooled (0°C) solution of diisopropylamine (74.2 μL, 0.530 mmol) in THF (5.0 mL).

Stirring was continued for 15 min and the solution was then cooled to -78°C. A solution of ketone **67** (71.5 mg, 0.106 mmol) in THF (2.0 mL plus 2 x 1.0 mL as rinses) was added dropwise (over *ca.* 5 min) with stirring and, after 30 min, another portion of *n*-butyllithium (1.6 M in hexane, 66 μl, 0.106 mmol) was added. Stirring was continued for 15 min and 4:1 chlorotriethylsilane-triethylamine (67.0 μL, 0.318 mmol of chlorotriethylsilane) was added. Stirring was continued for 1 h, the cooling bath was removed, and the mixture was allowed to attain room temperature (*ca.* 40 min). Saturated aqueous sodium bicarbonate (3 drops) was added and stirring was continued for 5 min. The mixture was filtered through a pad (2 x 2 cm) of a 2:1:1 mixture of Florisil, sodium bicarbonate and magnesium sulfate. The pad was washed with ethyl acetate (20 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 5:95 ethyl acetate--hexane, gave silyl enol ether **68** (80.4 mg, 96%) as a homogeneous (TLC, silica, 5:95 ethyl acetate--hexane) thick oil: IR ($CHCl_3$ cast) 2956, 2934, 2875 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (m, 6 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.98 (t, J = 7.5 Hz, 9 H), 1.04 (s, 9 H), 1.08--1.22 [m, 4 H, including a doublet at δ 1.13 (J = 7.0 Hz, 3 H)], 1.24--1.44 [m, 14 H, including singlets at δ 1.33 (3 H), δ 1.37 (3 H), δ 1.41 (3 H), and δ 1.42 (3 H)], 1.44--1.78 (m, 4 H), 2.00--2.10 (m, 2 H), 2.18--2.35 (m, 2 H), 2.42--2.50 (m, 1 H), 3.65--3.88 (m, 3 H), 4.00 (d, J = 2.5 Hz, 1 H), 4.08--4.17 (m, 1 H), 4.39 (t, J = 1.5

Hz, 1 H), 5.76--5.87 (m, 2 H), 7.33--7.45 (m, 6 H), 7.63--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 4.89, 6.88, 14.11, 16.02, 19.27, 19.80, 25.28, 26.90, 29.63, 30.36, 31.30, 33.22, 33.67, 33.77, 37.70, 39.52, 42.21, 59.78, 65.68, 69.92, 84.91, 86.84, 98.40, 103.75, 109.27, 127.64, 127.66, 128.69, 129.60, 134.02, 134.06, 135.61, 136.29, 153.31; Neither FABMS nor CIMS spectra could be obtained.

Conversion of 68 into 69.

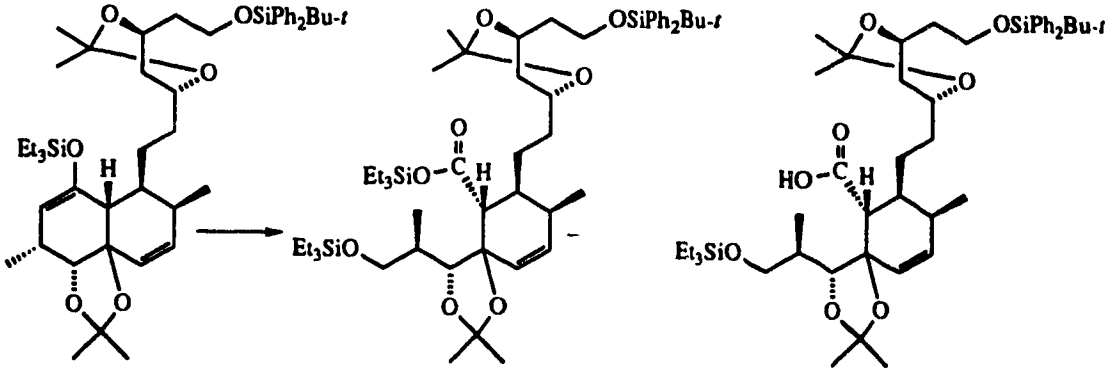


68 **69**

Ozonized oxygen was bubbled from a 50-mL syringe into a stirred and cooled (-78°C) solution of silyl enol ether **68** (18.2 mg, 0.023 mmol) in 1:4 dichloromethane-methanol (2.0 mL) until the starting material disappeared (TLC control, silica, 15:85 ethyl acetate--hexane). Sodium borohydride (0.9 mg, 0.023 mmol) was then added (-78°C) and stirring was continued. After 1 h, another portion of sodium borohydride (0.9 mg, 0.023 mmol) was added, the cooling bath was removed, and the mixture was allowed to attain room temperature (*ca.* 30 min). Stirring was then continued for 3 h, after which

acetic acid (4 drops) was added. The mixture was evaporated and the residue was dissolved in ether (3.0 mL). The organic solution was treated with an excess of diazomethane in ether. After 10 min, acetic acid was added until a colorless solution was formed. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using first 1:4 ethyl acetate--hexane and then 35:65 ethyl acetate--hexane, gave ester **69** (71.9 mg, 94%) as a homogeneous (TLC, silica, 35:65 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 3460, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 7.0 Hz, 3 H), 0.98--1.16 [m, 10 H, including a singlet at δ 1.03 (9 H)], 1.22--1.46 [m, 16 H, including singlets at δ 1.34 (3 H), δ 1.40 (3 H), δ 1.42 (3 H), and δ 1.43 (3 H)], 1.46--1.74 (m, 3 H), 2.18--2.28 (m, 1 H), 2.35--2.43 (m, 1 H), 2.40--2.77 (m, 3 H), 3.54--3.88 [m, 9 H, including a singlet at δ 3.70 (3 H)], 4.08--4.15 (m, 1 H), 5.41 (dd, J = 10.0, 1.0 Hz, 1 H), 5.96 (dd, J = 10.0, 5.5 Hz, 1 H), 7.35--7.45 (m, 6 H), 7.63--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.24, 13.25, 19.27, 19.93, 24.87, 26.12, 26.34, 26.91, 29.78, 30.32, 33.63, 34.22, 35.08, 37.43, 39.40, 46.26, 51.11, 59.70, 65.58, 68.51, 69.12, 80.83, 88.98, 98.45, 108.23, 127.64, 127.68, 129.12, 129.61, 133.99, 134.05, 135.61, 137.28, 172.27; exact mass, *m/z* calcd for $C_{41}H_{59}O_8Si$ $(M - CH_3)^+$ 707.3971, found 707.3998; CIMS, *m/z* calcd for $C_{42}H_{62}O_8Si$ 722, found 723 $(M + 1)^+$.

Conversion of 68 into 72.



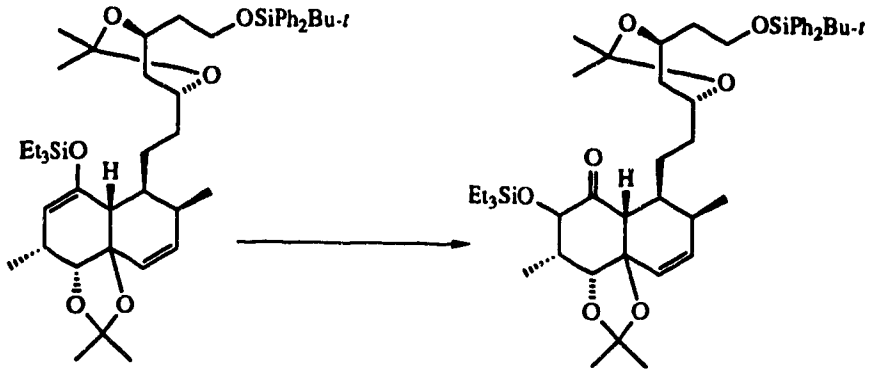
68 **71** **72**

Ozonized oxygen was bubbled from a 50-mL syringe into a stirred and cooled (-78°C) solution of silyl enol ether **68** (77.0 mg, 0.0975 mmol) in 1:4 dichloromethane-methanol (6.0 mL) until the starting material disappeared (TLC control, silica, 15:85 ethyl acetate--hexane). Sodium borohydride (7.0 mg, 0.185 mmol) was then added (-78°C) and stirring was continued. After 1 h, another portion of sodium borohydride (8.0 mg, 0.211 mmol) was added, the cooling bath was removed and the mixture was allowed to attain room temperature (*ca.* 30 min). Stirring was then continued for 3 h, after which acetic acid (6 drops) was added. The mixture was evaporated and the residue was dissolved in dichloromethane (1.0 mL) and filtered through a pad of Florisil (*ca.* 3 cm, contained in a pasteur pipet), and the pad was then washed with ethyl acetate (10.0 mL). The combined filtrates were evaporated and the residue was left on oil pump for *ca.* 30 min to remove traces of solvent. The crude material was dissolved in dry ether and chlorotriethylsilane (65 μL, 0.39 mmol),

triethylamine (68 μL, 0.487 mmol) and DMAP (two crystals) were then added. The mixture was stirred overnight, diluted with ethyl acetate (10 mL) and washed sequentially with water (1 x 10 mL), aqueous hydrochloric acid (1.0 M, 1 x 10 mL), and brine (1 x 10 mL). The solution was dried (Na_2SO_4) and evaporated. The residue was dissolved in 1:9 ethyl acetate--hexane (0.8 mL) and stirred with flash silica gel (0.9 g) for 5 h. The slurry was evaporated and flash chromatography of the residue over silica gel (1.5 x 10 cm), using first 1:9 ethyl acetate--hexane and then 1:4 ethyl acetate--hexane, gave ester **72** (20.9 mg, 26%) as a homogeneous (TLC, silica, 1:4 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.54 (q, J = 8.0 Hz, 6 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.92 (t, J = 8.0 Hz, 9 H), 0.97--1.13 [m, 10 H, including a singlet at δ 1.02 (9 H)], 1.15--1.28(m, 2 H), 1.29--1.58 [m, 15 H, including singlets at δ 1.31 (3 H), δ 1.36 (3 H), δ 1.38 (3 H), and δ 1.40 (3 H)], 1.59--1.68 (m, 2 H), 1.98--2.09 (m, 1 H), 2.18--2.29 (m, 1 H), 2.35--2.44 (m, 1 H), 2.63 (d, J = 12.0 Hz, 1 H), 3.54--3.75 (m, 4 H), 3.76--3.83 (m, 1 H), 3.86 (d, J = 10.0 Hz, 1 H), 4.02--4.11 (m, 1 H), 5.48 (dd, J = 10.0, 1.0 Hz, 1 H), 5.95 (dd, J = 10.0, 5.5 Hz, 1 H), 7.30--7.43 (m, 6 H), 7.59--7.67 (m, 4 H), 9.57--9.86 (br, 1 H, COOH); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 4.48, 6.82, 11.84, 13.47, 19.25, 19.89, 24.88, 25.83, 25.98, 26.90, 30.12, 30.28, 33.63, 34.57, 35.94, 37.44, 39.39, 46.99, 59.67, 64.66, 65.54, 68.95, 80.44, 84.78, 98.50, 108.14, 127.64, 127.67,

129.16, 129.58, 134.00, 135.61, 137.76, 173.85; exact mass, *m/z* calcd for $C_{43}H_{63}O_8Si$ $(M - C_2H_5 - CH_3 - CH_3)^+$ 735.4292, found 735.4319; CIMS, *m/z* calcd for $C_{47}H_{74}O_8Si_2$ 822, found 823 $(M + 1)^+$.

Conversion of 68 into 76.

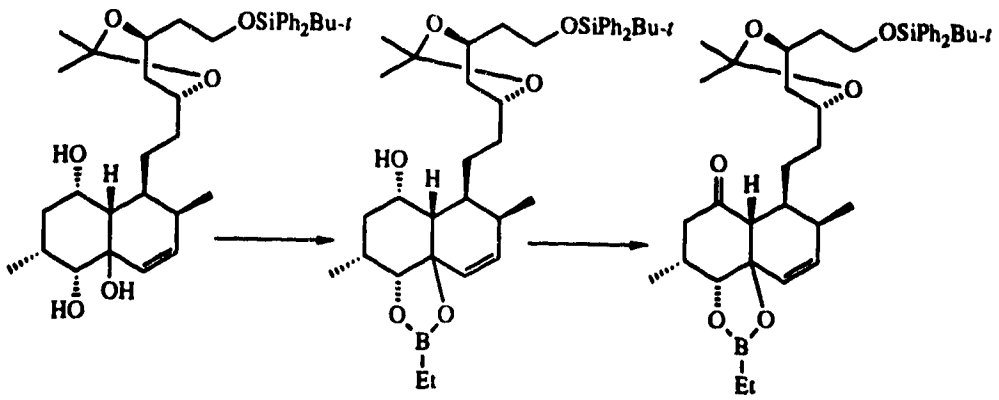


68 **76**

A solution of silyl enol ether **68** (17.0 mg, 0.0215 mmol) in ethyl acetate (1.0 mL plus 2 x 0.5 mL as rinses) was added quickly (over *ca.* 1 min) to a stirred and cooled (0°C) mixture of *m*-chloroperbenzoic acid (80-85% w/w, 6.8 mg, *ca.* 0.0323 mmol) and solid sodium bicarbonate (5.4 mg, 0.0646 mmol) in ethyl acetate (1.5 mL). Stirring was continued for 4 h at 0°C and for 2 h with the cooling bath removed (TLC control, silica, 1:9 ethyl acetate--hexane). The mixture was diluted with ethyl acetate (5.0 mL) and washed with aqueous sodium bisulfite (1 M, 1 x 5.0 mL). The aqueous layer was extracted with ethyl acetate (1 x 5.0 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm),

using first 5:95 ethyl acetate--hexane and then 1:9 ethyl acetate--hexane, gave ketone **76** (30.0 mg, 86%) as a homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 2958, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.52--0.75 (m, 6 H), 0.85--0.99 [m, 12 H, including a doublet at δ 0.89 (J = 7.0 Hz, 3 H)], 1.04 (s, 9 H), 1.08--1.28 [m, 8 H, including a doublet at δ 1.22 (J = 7.0 Hz, 3 H) and a singlet at δ 1.25 (3 H)], 1.28--1.60 [m, 12 H, including singlets at δ 1.32 (3 H), δ 1.34 (3 H), and δ 1.40 (3 H)], 1.62--1.74 (m, 2 H), 2.00--2.17 (m, 2 H), 2.28--2.42 (m, 1 H), 2.42--2.52 (m, 1 H), 2.90 (d, J = 11.0 Hz, 1 H), 3.53 (d, J = 8.5 Hz, 1 H), 3.63--3.88 (m, 3 H), 4.03--4.16 [m, 2 H, including a doublet at δ 4.08 (J = 1.8 Hz, 1 H)], 5.70 (dd, J = 9.5, 1.5 Hz, 1 H), 5.91 (dd, J = 9.5, 5.0 Hz, 1 H), 7.32--7.47 (m, 6 H), 7.62--7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 4.82, 6.78, 13.35, 15.25, 19.26, 19.80, 23.26, 26.08, 26.74, 26.90, 30.33, 30.77, 31.36, 33.42, 37.52, 39.50, 39.61, 47.13, 59.75, 65.70, 69.75, 77.59, 82.23, 82.43, 98.40, 107.84, 127.63, 127.67, 128.68, 129.57, 129.61, 134.05, 135.62, 139.17, 206.61; exact mass, *m/z* calcd for $C_{43}H_{63}O_7Si_2$ $(M - C_4H_9)^+$ 747.4112, found 747.4143.

Conversion of 49 into 86.



49 **80** **86**

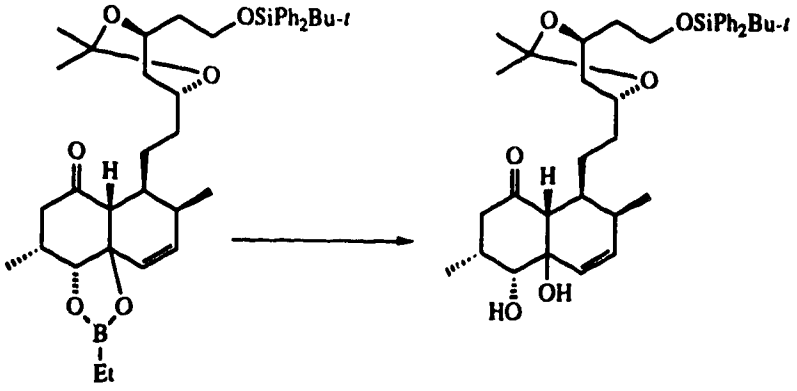
Superhydride (1.0 M in THF, 0.12 mL, 0.12 mmol) was added to a stirred and cooled (0°C) solution of triol **49** (30.6 mg, 0.048 mmol). The cooling bath was removed after 5 min and stirring was continued for 1 h. Water (1 drop) was added and the mixture was stirred for 10 min. The solvents were evaporated and the residue was dissolved in dichloromethane. The solution was filtered through a pad (3 cm, contained in a pasteur pipet) of a 1:1 mixture of $MgSO_4$ and Celite. The pad was washed with dichloromethane (6.0 mL). The combined filtrates were evaporated to give the crude protected alcohol **80** (30.9 mg) as a white foam: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80--0.92 (m, 6 H), 0.93--1.09 [m, 14 H, including a singlet at δ 1.04 (s, 9 H)], 1.08--1.80 [m, 16 H, including singlets at δ 1.36 (3 H) and δ 1.43 (3 H)], 1.88--2.02 (m, 1 H), 2.10--2.25 (m, 2 H), 2.48--2.50 (m, 1 H), 2.58 (d, J = 11.0 Hz,1 H), 3.63--3.88 (m, 3 H), 4.06--4.18 (m, 3 H), 5.48 (d, J = 10.0 Hz, 1 H), 5.89 (d, J = 10.0, 6.0 Hz, 1 H), 7.33--7.48 (m, 6 H), 7.62--7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$,

75.469 MHz) δ 7.85, 12.86, 15.88, 19.27, 19.94, 23.25, 26.91, 29.64, 30.36, 30.90, 33.31, 33.66, 35.97, 36.93, 37.57, 39.43, 59.74, 65.68 (two carbons), 69.44, 82.15, 83.33, 98.48, 127.64, 127.67, 128.22, 129.59, 134.02, 134.07, 135.62, 137.21; exact mass, *m/z* calcd for $C_{39}H_{56}BO_6Si$ $(M - CH_3)^+$ 659.3939, found 659.3938. We forgot to obtain an IR spectrum.

The crude alcohol (30.9 mg) in dichloromethane (2.0 mL) was added to a stirred mixture of pyridinium chlorochromate(31.0 mg, 0.144 mmol), sodium acetate (31 mg) and powdered 4Å molecular sieves (31 mg) in dichloromethane (2.5 mL). Stirring was continued for 4.5 h (TLC control, silica, 4:96 diethyl ether--chloroform). The reaction mixture was diluted with ether (10 mL) and filtered through a pad (2 x 2 cm) of Florisil. The pad was washed with ether (20 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using first pure chloroform and then 4:96 ether--chloroform, gave ketone **86** (27.9 mg, 86%) as a homogeneous (TLC, silica, 4:96 diethyl ether--chloroform) white foam: IR ($CHCl_3$ cast) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.70--1.20 [m, 21 H, including a singlet at δ 1.03 (9 H) and a doublet at δ 1.09 (*J* = 6.5 Hz, 3 H)], 1.24--1.77 [m, 14 H, including singlets at δ 1.35 (3 H) and δ 1.42 (3 H)], 2.20--2.52 (m, 4 H), 2.79 (d, *J* = 11.0 Hz, 1 H), 3.62--4.17 (m, 4 H), 4.30 (d, *J* = 3.0 Hz, 1 H), 5.58 (dd, *J* = 10.0, 1.5 Hz, 1 H), 5.93 (dd, *J* = 10.0, 5.0 Hz, 1 H), 7.33--7.47 (m, 6 H), 7.62--7.73 (m, 4 H); ^{13}C NMR

($CDCl_3$, 75.469 MHz) δ 7.73, 12.56, 13.56, 15.68, 19.27, 19.95, 21.48, 23.59, 26.91, 30.36, 30.55, 31.14, 32.15, 33.69, 37.57, 39.43, 42.10, 48.95, 59.74, 65.68, 69.61, 81.63, 83.56, 98.43, 127.32, 127.64, 127.68, 129.57, 129.61, 134.03, 135.62, 138.00, 208.11; exact mass, *m/z* calcd for $C_{39}H_{54}BO_6Si$ $(M - CH_3)^+$ 657.3782, found 657.3779.

Conversion of 86 into 17.

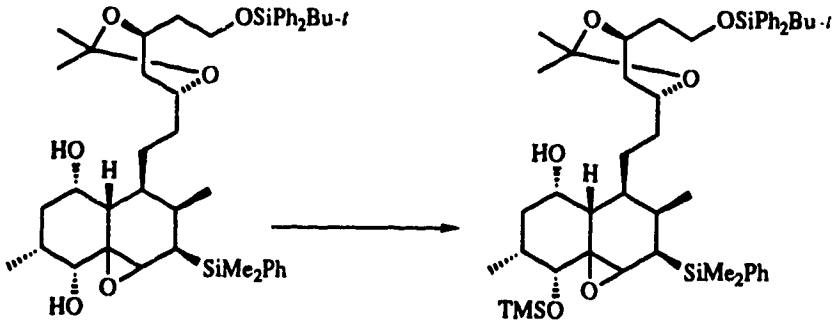


86 **17**

Hydrogen peroxide (30% w/v, 5 drops) was added to a stirred solution of ketone **86** (10.0 mg, 0.0149 mmol) in ethyl acetate (2.0 mL). Stirring was continued for *ca.* 3 h (TLC control, silica, 3:7 ethyl acetate--hexane). The mixture was diluted with ethyl acetate (10 mL) and washed with aqueous sodium thiosulfite (10% w/v, 1 x 5.0 mL) and brine (1 x 5.0 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 15:85, 3:7 and 45:55 ethyl acetate--hexane, gave dihydroxy ketone **17** (4.1 mg, 43%): IR ($CHCl_3$ cast) 3440, 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ a satisfactory integration could not be obtained; ^{13}C

NMR ($CDCl_3$, 100.614 MHz) δ 13.56, 14.05, 14.67, 19.19, 19.87, 23.59, 26.83, 30.27, 31.75, 33.90, 35.09, 37.41, 39.34, 45.78, 51.19, 59.62, 65.53, 69.52, 73.32, 75.99, 98.37, 126.89, 127.57, 129.52, 133.95, 135.55, 136.78, 209.14; exact mass, *m/z* calcd for $C_{37}H_{51}O_6Si$ $(M - CH_3)^+$ 619.3455, found 619.3444

Conversion of 51 into 91.

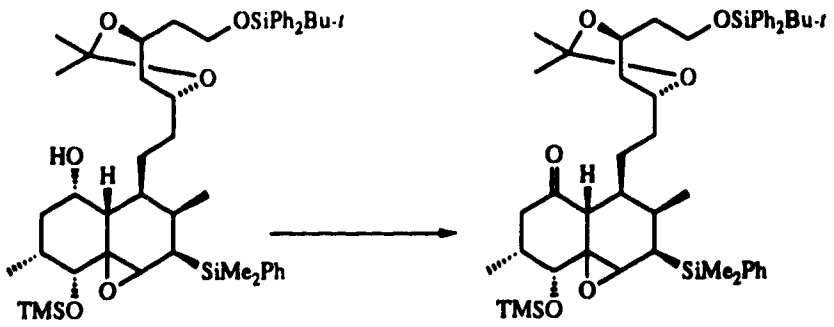


51 **91**

A mixture of chlorotriethylsilane and triethylamine (1:4, 0.20 mL, 0.370 mmol of chlorotriethylsilane) was added to a stirred and cooled (0°C) solution of epoxy silane **51** (158 mg, 0.205 mmol) and 4-dimethylaminopyridine (10 mg, 0.0819 mmol) in dichloromethane (10 mL). Stirring was continued for 20 min (TLC control, silica, 1:4 ethyl acetate--hexane). Water (2.0 mL) was added at 0°C and stirring was continued for 10 min. The mixture was diluted with dichloromethane (10 mL) and washed with water (2 x 5.0 mL). The combined aqueous layers were extracted with dichloromethane (1 x 10 mL). The combined organic phases were washed with aqueous saturated sodium bicarbonate (1 x 10

mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using first 1:9 ethyl acetate--hexane and then 15:85 ethyl acetate--hexane, gave compound **91** (156.8 mg, 91%) as a homogeneous (TLC, silica, 15:85 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 3560 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 9 H), 0.39 (s, 3 H), 0.41 (s, 3 H), 0.71 (d, J = 7.0 Hz, 3 H), 1.07 (s, 9 H), 1.10--1.29 [m, 6 H, including a doublet at δ 1.24 (J = 7.8 Hz, 3 H)], 1.32--1.86 [m, 16 H, including singlets at δ 1.36 (3 H) and δ 1.42 (3 H)], 2.10--2.27 (m, 2 H), 2.50 (br doublet, J = 8.5 Hz, 1 H), 3.20 (s, 1 H), 3.63--3.88 (m, 3 H), 3.93 (d, J = 5.8 Hz, 1 H), 4.04--4.20 (m, 2 H), 7.32--7.47 (m, 9 H), 7.50--7.58 (m, 2 H), 7.63--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -2.91, -2.82, 0.13, 12.55, 16.09, 19.26, 19.89, 24.50, 26.91, 28.38, 30.32, 31.51, 34.47, 35.88, 36.57, 37.42, 38.19, 39.41, 41.61, 49.29, 59.75, 63.39, 65.67, 68.14, 69.34, 70.92, 98.51, 127.64, 127.66, 128.06, 129.25, 129.60, 133.91, 134.00, 134.05, 135.61, 137.70; CIMS, *m/z* calcd for $C_{49}H_{74}O_6Si_3$ 842, found 860 $(M + 18)^+$.

Conversion of 91 into 92.

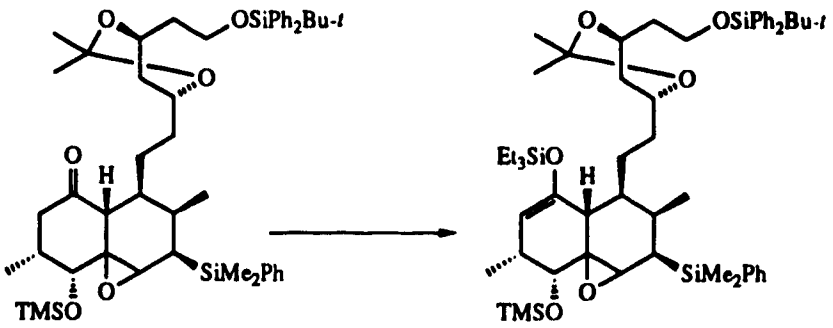


91 **92**

Alcohol **91** (143.0 mg, 0.17 mmol) in dichloromethane (2.0 mL plus 2 x 2.0 mL as rinses) was added to a stirred mixture of pyridinium chlorochromate (73.1 mg, 0.339 mmol), sodium acetate (56 mg, 0.678 mmol) and powdered 4Å molecular sieves (75 mg) in dichloromethane (4.0 mL). The mixture was stirred for 22.5 h (TLC control, silica, 15:85 ethyl acetate--hexane), diluted with ether (40.0 mL), and filtered through a pad (3 x 3 cm) of Florisil. The pad was washed with ether (80 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 15:85 ethyl acetate--hexane, gave ketone **92** (109.5 mg, 77%) as a homogeneous (TLC, silica, 15:85 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 9 H), 0.37 (s, 3 H), 0.39 (s, 3 H), 0.72 (d, J = 6.5 Hz, 3 H), 0.98--1.12 [m, 13 H, including a doublet at δ 1.02 (J = 7.0 Hz, 3 H) and a singlet at δ 1.04 (9 H)], 1.17--1.47 [m, 12 H, including singlets at δ 1.33 (3 H) and δ 1.41 (3 H)], 1.62--1.85 (m, 4 H), 2.27--2.50 (m, 2 H), 2.58--2.78 (m, 2 H), 3.17 (s, 1 H), 3.62--3.76 (m, 2 H),

3.78--3.88 (m, 1 H), 4.03--4.13 (m, 1 H), 4.34 (d, J = 5.0 Hz, 1 H), 7.32--7.47 (m, 9 H), 7.49--7.55 (m, 2 H), 7.62--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -2.89, -2.86, 0.11, 12.69, 13.88, 19.26, 19.95, 25.47, 26.91, 27.75, 30.33, 31.37, 34.50, 35.69, 37.44, 38.44, 39.42, 47.53, 51.06, 51.14, 59.73, 65.48, 65.64, 69.53, 70.24, 98.45, 127.63, 127.67, 128.07, 129.28, 129.58, 133.92, 134.05, 135.61, 137.53, 206.88; FABMS, *m/z* calcd for $C_{49}H_{72}O_6Si_3$ 840, found 841 $(M + 1)^+$ and 863 $(M + 23)^+$.

Conversion of 92 into 93.

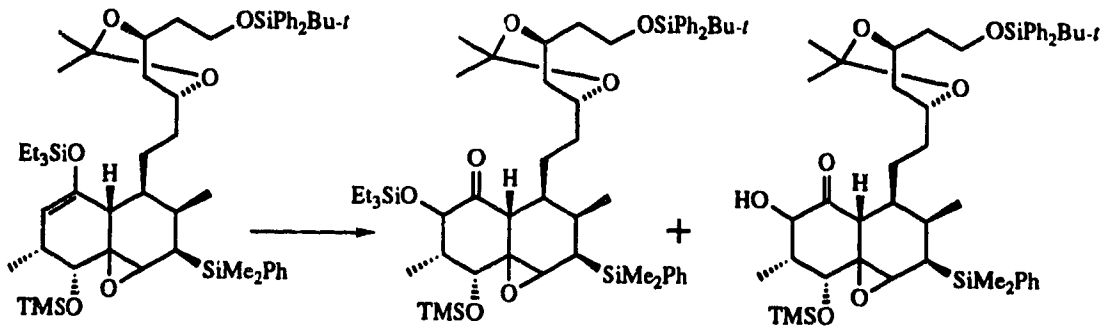


92 **93**

n-Butyllithium (1.6 M in hexane, 0.40 mL, 0.648 mmol) was added to a stirred and cooled (0°C) solution of diisopropylamine (91.0 μL, 0.0.648 mmol) in THF (6.0 mL). Stirring was continued for 10 min and the solution was cooled to -78°C. A solution of ketone **92** (109.1 mg, 0.130 mmol) in THF (4.0 mL plus 2 x 1.0 mL as rinses) was added dropwise (over *ca.* 5 min) with stirring and, after 30 min, 4:1 chlorotriethylsilane-triethylamine (81.0 μL, 0.389 mmol of chlorotriethylsilane) was added. Stirring was continued for

1 h, the cooling bath was removed, and the mixture was allowed to attain room temperature (*ca.* 40 min). Saturated aqueous sodium bicarbonate (3 drops) was added and the mixture was stirred for 5 min. It was then filtered through a pad (2 x 2 cm) of a 2:1:1 mixture of Florisil, sodium bicarbonate and magnesium sulfate. The pad was washed with ethyl acetate (20 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 5:95 ethyl acetate--hexane, gave silyl enol ether **93** (125.0 mg, 100%) as a homogeneous (TLC, silica, 5:95 ethyl acetate--hexane) thick oil: IR (CH_2Cl_2 cast) 2955 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 9 H), 0.40 (s, 3 H), 0.41 (s, 3 H), 0.67--0.80 (m, 9 H), 0.88--1.24 [m, 25 H, including a singlet at δ 1.07 (9 H)], 1.32--1.65 [m, 10 H, including singlets at δ 1.37 (3 H) and δ 1.43 (3 H)], 1.66--1.76(m, 1H), 1.78--1.89 (m, 1 H), 2.12--2.25 (m, 1 H), 2.48--2.62 (m, 2 H), 3.39 (s, 1 H), 3.65--3.77 (m, 2 H), 3.82--3.92 (m, 1), 4.07--4.18 [m, 2 H, including a doublet at δ 4.12 (J = 7.5 Hz, 1 H)], 4.72 (dd, J = 4.0, 1.5 Hz, 1 H), 7.32--7.47 (m, 9 H), 7.51--7.60 (m, 2 H), 7.65--7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ -2.79, -2.75, 0.08, 4.99, 6.82, 12.43, 16.64, 19.20, 19.76, 26.68, 26.81, 29.10, 30.26, 31.59, 34.82, 35.89, 37.53, 38.78, 39.40, 40.42, 52.89, 59.64, 64.40, 65.53, 68.87, 69.76, 98.35, 107.28, 127.59, 127.93, 129.05, 129.56, 133.90, 133.94, 135.54, 137.98, 151.10; FABMS, *m/z* calcd for $C_{55}H_{86}O_6Si_4$ 954, found 955 $(M + 1)^+$.

Conversion of 93 into 94 and 95.



93 **94** **95**

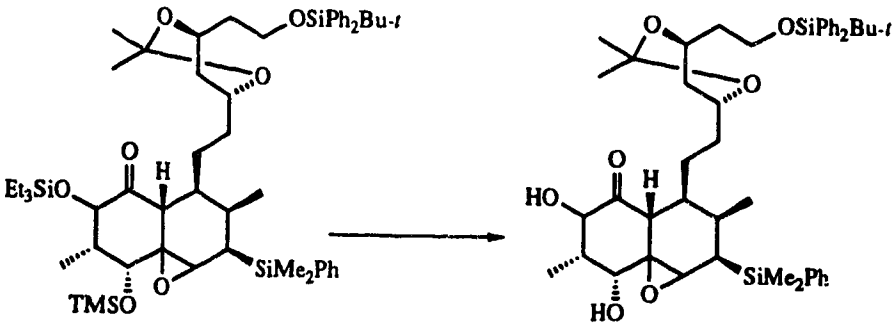
A solution of silyl enol ether **93** (208.0 mg, 0.217 mmol) in ethyl acetate (3.0 mL plus 2 x 2.0 mL as rinses) was added quickly (over *ca.* 2 min) to a stirred and cooled (0°C) mixture of *m*-chloroperbenzoic acid (80-85% w/w, 68.5 mg, *ca.* 0.326 mmol) and solid sodium bicarbonate (55.0 mg, 0.652 mmol) in ethyl acetate (6.0 mL). Stirring was continued for 1.5 h at 0°C (TLC control, silica,1:9 ethyl acetate--hexane). Aqueous sodium bisulfite (10% w/v, 3.0 mL) was added at 0°C and stirring was continued for 5 min. The mixture was then diluted with ethyl acetate (10.0 mL) and washed with water (3 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using successively 5:95 ethyl acetate--hexane, 1:9 ethyl acetate--hexane, and 1:4 ethyl acetate--hexane, gave ketone **94** (193.8 mg, 92%) and ketone **95** (10.8 mg, 6.0%), both as homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) thick oils. Ketone **94** had: IR (CH_2Cl_2 cast) 1792 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 9 H), 0.37 (s, 3 H), 0.39 (s, 3

H), 0.60 (q, J = 8.0 Hz, 6 H), 0.72 (d, J = 7.0 Hz, 3 H), 0.89--0.99 [m, 12 H, including a doublet at δ 0.91 (J = 7.5 Hz, 3 H) and a triplet at δ 0.92 (J = 8.0 Hz, 9 H)], 1.00--1.13 [m, 10 H, including a singlet at δ 1.04 (9 H)], 1.17--1.50 [m, 11 H, including singlets at δ 1.31 (3 H) and δ 1.39 (3 H)], 1.55--1.75 (m, 3 H), 1.75--1.88 (m, 2 H), 2.23--2.36 (m, 1 H), 3.12 (s, 1 H), 3.42 (d, J = 11.0 Hz, 1 H), 3.62--3.75 (m, 2 H), 3.65--3.90 [m, 2 H, including a doublet at δ 3.87 (J = 3.0 Hz, 1 H)], 4.02--4.14 (m, 1 H), 4.63 (d, J = 5.0 Hz, 1 H), 7.31--7.47 (m, 9 H), 7.49--7.57 (m, 2 H), 7.63--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -2.90, -2.86, 0.05, 4.68, 6.73, 10.33, 12.59, 19.25, 19.85, 25.43, 26.89, 27.86, 30.29, 31.46, 34.21, 34.84, 37.41, 39.46, 45.34, 46.45, 51.18, 59.69, 65.61, 65.96, 66.77, 69.48, 80.90, 98.40, 127.62, 127.65, 128.05, 129.25, 129.57, 129.61, 133.91, 134.03, 135.60, 137.56, 207.82; FABMS, m/z calcd for $C_{55}H_{86}O_7Si_4$ 970, found 971 $(M + 1)^+$ and 993 $(M + 23)^+$.

Ketone **95** had: ^{1}H NMR ($CDCl_3$, 300 MHz) (approximate integration) δ 0.12 (s, 9 H), 0.36 (s, 3 H), 0.38 (s, 3 H), 0.74 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.5 Hz, 3 H), 1.00--1.13 [m, 10 H, including a singlet at δ 1.03 (9 H)], 1.17--1.50 [m, 11 H, including singlets at δ 1.33 (3 H) and δ 1.40 (3 H)], 1.60--1.72 (m, 3 H), 1.75--1.85 (m, 2 H), 2.30--2.38 (m, 1 H), 2.45 (br s, 1 H), 3.15 (s, 1 H), 3.24 (d, J = 11.0 Hz, 1 H), 3.62--3.73 (m, 2 H), 3.77--3.85(m, 1 H), 3.96--4.15 (m, 2 H,), 4.57 (d, J = 5.0 Hz, 1 H), 7.31--7.47 (m, 9 H), 7.49--7.57 (m, 2 H), 7.63--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$,

75.469 MHz) δ -3.00, -2.88, 0.03, 10.99, 12.68, 19.19, 19.86, 25.29, 26.83, 28.11, 29.68, 29.97, 30.32, 31.39, 34.33, 35.48, 37.24, 39.32, 44.46, 45.61, 51.55, 59.64, 65.51, 65.58, 66.56, 69.38, 73.24, 79.72, 98.45, 127.58, 127.62, 128.03, 129.25, 129.56, 133.84, 133.99, 135.55, 137.40, 208.71.

Conversion of 94 into 96.

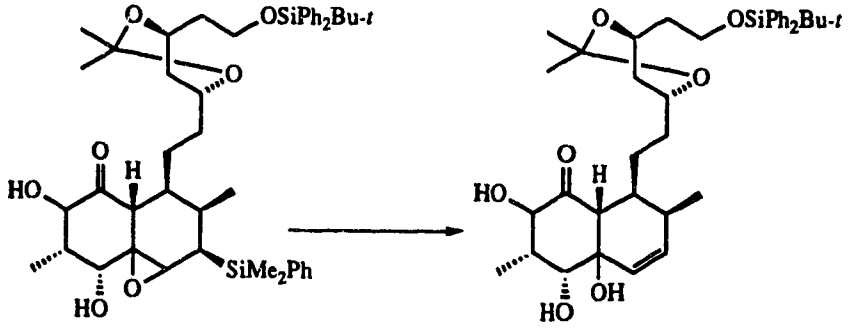


94 **96**

Tetrabutylammonium fluoride (1.0 M in THF, 0.73 mL, 0.728 mmol) was added to a stirred solution of ketone **94** (177.0 mg, 0.182 mmol) and acetic acid (0.20 mL, 3.64 mmol) in THF (8.0 mL). Stirring was continued for 5 h (TLC control, silica, 4:6 ethyl acetate--hexane) and the solvents were evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using first 1:4 ethyl acetate--hexane and then 4:6 ethyl acetate--hexane, gave ketone **96** (122.2 mg, 85%) as a homogeneous (TLC, silica, 4:6 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 3440, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.38 (s, 3 H), 0.41 (s, 3 H), 0.77 (d, J = 7.0 Hz. 3 H), 0.97--1.31 [m, 15 H, including a singlet at δ

1.04 (9 H) and a doublet at δ 1.07 (J = 7.0 Hz, 3 H)], 1.32--1.55 [m, 9 H, including singlets at δ 1.35 (3 H) and δ 1.42 (3 H)], 1.62--2.00 (m, 6 H), 2.27--2.39 (m, 1 H), 2.80--2.97 [m, 2 H, including a doublet at δ 2.92 (J = 10.5 Hz, 1 H)], 3.30 (s, 1 H), 3.66--3.89 (m, 3 H), 3.94 (d, J = 8.5 Hz, 1 H), 4.06--4.18 (m, 1 H), 4.29--4.38 (m, 1 H), 7.30--7.47 (m, 9 H), 7.48--7.57 (m, 2 H), 7.63--7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -3.15, -2.95, 11.13, 12.48, 19.26, 19.91, 25.96, 26.90, 28.44, 30.32, 31.19, 34.43, 37.33, 37.37, 39.40, 40.51, 44.77, 54.05, 59.71, 62.67, 65.63, 66.14, 69.44, 76.47, 98.48, 127.63, 127.66, 128.14, 129.44, 129.59, 133.79, 133.98, 134.04, 135.60, 137.23, 210.19; FABMS, *m/z* calcd for $C_{46}H_{64}O_7Si_2$ 784, found 785 $(M + 1)^+$.

Conversion of 96 into 97.

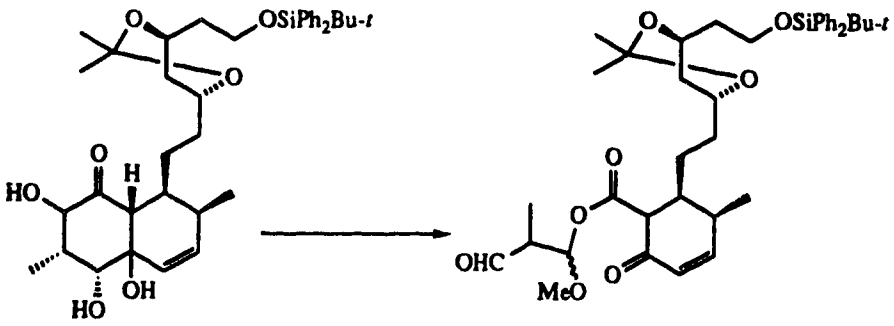


96 **97**

Pyridinium *p*-toluenesulfonate (15.0 mg, 0.0599 mmol) was added to a solution of ketone **96** (47.0 mg, 0.0599 mmol) in absolute ethanol (argon atmosphere). After *ca.* 12 h the ethanol was evaporated and the residue was dissolved in dry acetone (4.0 mL) and left for 5 h. The acetone was then

evaporated, and flash chromatography of the residue over silica gel (1 x 15 cm), using first 1:4 ethyl acetate--hexane and then 1:1 ethyl acetate--hexane, gave ketone **97** (22.2 mg, 57%) as a homogeneous (TLC, silica, 1:1 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 3440, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, J = 7.0 Hz, 3 H), 0.98--1.23 [m, 13 H, including a singlet at δ 1.04 (9 H) and a doublet at δ 1.15 (J = 7.0 Hz, 3 H)], 1.23--1.47 [m, 9 H, including singlets at δ 1.36 (3 H) and δ 1.43 (3 H)], 1.48--1.75 (m, 4 H), 2.10--2.60 (m, 5 H), 2.82 (d, J = 11.5 Hz, 1 H), 2.89--3.03 (m, 1 H), 3.63--4.03 [m, 5 H, including a doublet at δ 4.01 (J = 8.5 Hz, 1 H)], 4.05--4.20 (m, 1 H), 5.86 (dd, J = 10.0, 4.5 Hz, 1 H), 5.96 (dd, J = 10.0, 1.0 Hz, 1 H), 7.32--7.48 (m, 6 H), 7.62--7.73 (m 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 11.93, 13.34, 19.25, 19.93, 23.88, 26.90, 30.33, 31.15, 33.00, 34.11, 37.41, 39.41, 40.70, 47.14, 59.71, 65.64, 69.55, 71.47, 74.62, 76.64, 77.49, 98.47, 126.98, 127.63, 127.67, 129.58, 129.60, 133.98, 134.03, 135.60, 136.78, 211.51; exact mass, m/z calcd for $C_{37}H_{51}O_7Si$ $(M - CH_3)^+$ 635.3404, found 635.3380; FABMS, m/z calcd for $C_{38}H_{54}O_7Si$ 650, found 651 $(M + 1)^+$.

Conversion of 97 into 98.

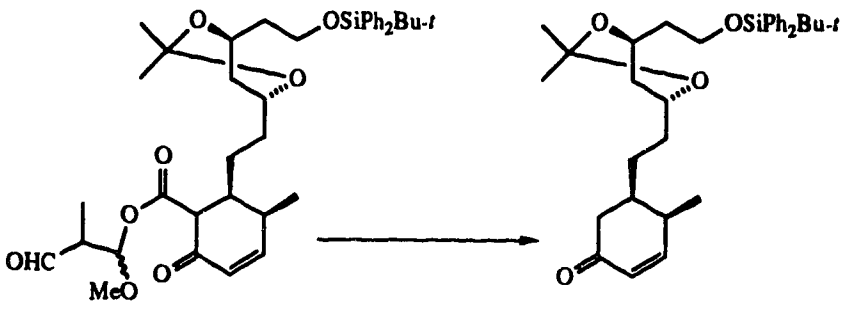


97 **98**

Lead tetraacetate (50.0 mg, 0.113 mmol) was added to a stirred solution of compound **97** (35.0 mg, 0.0538 mmol) in 1:1 benzene-methanol (6.0 mL) at room temperature. Stirring was continued for 1 h. The mixture was then diluted with dichloromethane (15 mL), washed with water (1 x 5 mL), and brine (1 x 10 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:3 ethyl acetate--hexane, gave compound **98** (24.0 mg, 66%) as a viscous oil: IR (CH_2Cl_2 cast) 1710, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 1.05--1.10 [3 H, two sets of doublets at δ 1.07 (J = 7.0 Hz) and δ 1.08 (J = 7.0 Hz)], 1.12--1.20 [3 H, two sets of doublets at δ 1.14 (J = 7.0 Hz) and δ 1.18 (J = 7.0 Hz)], 1.23--1.45 [m, 10 H, including two sets of two singlets (6 H, one set is at δ 1.33 and δ 1.40, and the other set is at δ 1.34 and δ 1.41], 1.47--1.75 (m, 4 H), 2.47--2.85 (m, 1 H), 2.63--2.73 (m, 1 H), 2.73--2.86 (m, 1 H), 3.30--3.40 (m, 1 H), 3.50 (s, 1.11 H), 3.56 (s, 1.89 H), 3.64--3.76 (m, 1 H), 3.72--3.87 (m, 2 H), 4.06--4.17 (m, 1 H), 6.01 (d, J = 10.0 Hz, 1 H), 6.05 (d, J =

5.0 Hz, 0.37 H), 6.13 (d, J = 4.0 Hz, 0.63 H), 7.04 (dd, J = 10.0, 6.0 Hz, 1 H), 7.34--7.47 (m, 6 H), 7.63--7.72 (m, 4 H), 9.75 (d, J = 1.2 Hz, 0.63 H), 9.79 (d, J = 1.5 Hz, 0.37 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 8.57, 9.19, 12.37, 19.26, 19.77, 25.68, 26.90, 29.76, 30.24, 30.95, 32.87, 37.20, 39.25, 39.33, 39.40, 50.39, 50.78, 56.90, 57.03, 57.60, 57.70, 59.66, 65.52, 68.64, 98.55, 99.23, 99.92, 127.04, 127.65, 129.62, 133.94, 134.01, 135.60, 156.26, 170.00, 170.25, 194.04, 200.96, 201.06; exact mass, *m/z* calcd for $C_{34}H_{45}O_6Si$ $(M - C_5H_9O_2)^+$ 577.2992, found 577.2977; FABMS, *m/z* calcd for $C_{39}H_{54}O_8Si$ 678, found 679 $(M + 1)^+$.

Conversion of 98 into 2.



98 **2**

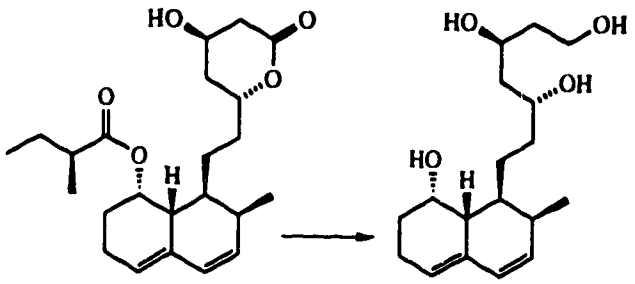
The flask used in this experiment must be washed with chromic acid and then rinsed with water (3-4 times), and with acetone (3-4 times), and finally oven dried (120°C) for 3-4 h or overnight.

A solution of compound **98** (3.0 mg, 0.0042 mmol) in dry dioxane (2.0 mL) was refluxed for 10 h (TLC control, silica, 1:3 ethyl acetate--hexane). The solvent was evaporated, and

flash chromatography of the residue over silica gel (4 cm, contained in a pasteur pipet), using first 5:95 ethyl acetate--nexane and then 15:85 ethyl acetate--hexane, gave the desired enone **2** (2.0 mg, 84%) as a homogeneous (TLC, silica, 1:3 ethyl acetate--hexane) viscous oil: IR (CH_2Cl_2 cast) 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (d, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.12 (q, J = 12.0 Hz, 1 H), 1.21--1.57 [m, 11 H, including singlets at δ 1.37 (3 H) and δ 1.43 (3 H)], 1.62--1.75 (m, 2 H), 2.06--2.20 (m, 1 H), 2.25--2.34 (m, 2 H), 2.47--2.61 (m, 1 H), 3.63--3.89 (m, 3 H), 4.06--4.17 (m, 1 H), 5.94 (d, J = 10.0 Hz, 1 H), 6.95 (dd, J = 10.0, 5.0 Hz, 1 H), 7.33--7.47 (m, 6 H), 7.62--7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.17, 19.27, 19.89, 26.91, 27.52, 30.32, 33.13, 33.64, 37.28, 37.46, 39.38, 39.93, 59.74, 65.72, 69.07, 98.52, 127.65, 128.18, 129.62, 134.01, 135.61, 155.99, 199.93; exact mass, *m/z* calcd for $C_{32}H_{43}O_4Si$ $(M - CH_3)^+$ 519.2931, found 519.2938. Anal. Calcd for $C_{33}H_{46}O_4Si$: C, 74.11; H, 8.67. Found: C, 73.94; H, 8.79. The material was indistinguishable from an authentic sample made[1] by total synthesis.

Degradation of Compactin

Conversion of Compactin (1a) into 99.

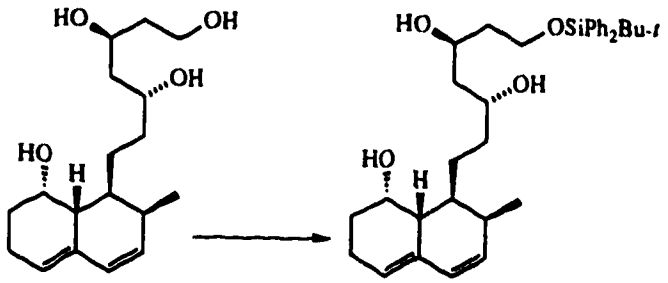


1a 99

Compactin (8.2825 g, 21.21 mmol) in THF (40 mL) was added over 10 min to a stirred and cooled (0°C) suspension of lithium aluminum hydride (3.22 g, 84.83 mmol) in THF (200 mL). Additional rinses of THF (3 x 10 mL) were used to dissolve and transfer the residual compactin. The cold-bath was removed and the mixture was stirred at room temperature for 9 h.(TLC control, silica, 6:4 acetone--chloroform). The mixture was then cooled to 0°C and ethyl acetate (20 mL) was added. Stirring was continued for 30 min and then water (3.5 mL) was added dropwise with stirring. After 15 min aqueous sodium hydroxide (15% w/v, 3.5 mL) was added. Stirring was continued for another 15 min, and then water (10.5 mL) was added as before. The cold bath was removed, the mixture was stirred for an additional 30 min, and then Celite (20 g) was added. Stirring was continued for 30 min and the mixture was then filtered through a pad (9.5 x 6.5 cm) of Florisil. The pad was washed with methanol (750 mL) until no more UV-active components were eluted (TLC). The combined filtrates were

evaporated. The resulting white solid was dissolved in methanol (150 mL) and flash silica gel (60 g) was added to the cloudy solution, which was then evaporated at room temperature. Flash chromatography of the residue over silica gel (5 x 15 cm), using first 3:7 acetone--chloroform and then 7:3 acetone--chloroform, gave **99** (5.34 g, 81%) as a homogeneous (TLC, silica, 6:4 acetone--chloroform) white solid (mp 102-104°C): IR ($CHCl_3$ cast) 3385 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, J = 6.0 Hz, 3 H), 1.20--2.08 (m, 11 H), 2.08--2.45 (m, 4 H), 2.83 [br s, 1 H (signal disappeared upon exchange with D_2O)], 3.41 [br s, 1 H (signal disappeared upon exchange with D_2O)], 3.70--3.90 (m, 2 H), 3.90--4.02 (m, 1 H), 4.03--4.17 (m, 1 H), 4.30 (s, 1 H), 4.38 [br s, 1 H (signal disappeared upon exchange with D_2O)], 4.60 (s, 1 H), 5.57 (s, 1 H), 5.72 (dd, J = 9.5, 6.0 Hz, 1 H), 5.96 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.12, 20.38, 21.95, 28.98, 30.76, 33.61, 35.30, 38.44, 38.64, 43.10, 60.86, 64.74, 71.08, 72.30, 123.69, 128.46, 133.19, 133.65; exact mass, m/z calcd for $C_{18}H_{28}O_3$ $(M - H_2O)^+$ 292.2038, found 292.2041. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.70; H, 10.07.

Conversion of 99 into 100.

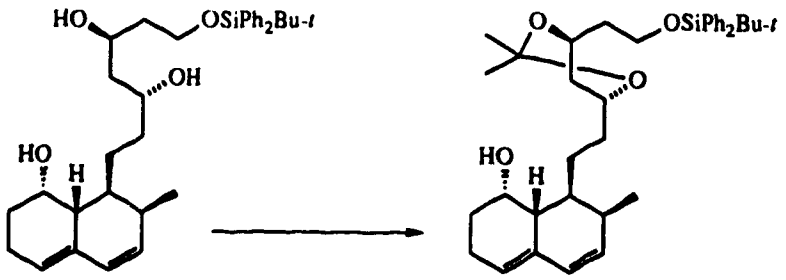


99 **100**

t-Butyldiphenylsilyl chloride (1.39 mL, 5.36 mmol) was added to a stirred and cooled (0°C) solution of tetraol **99** (5.30 g, 17.07 mmol) and imidazole (2.91 g, 42.68 mmol) in dry DMF (30 mL). Stirring was continued for 1 h and the mixture was then diluted with ethyl acetate (450 mL), washed with water (2 x 100 mL) and brine (1 x 100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 x 10 cm), using first 4:6 ethyl acetate--hexane and then 6:4 ethyl acetate--hexane, gave **100** (8.64 g, 92%) as a homogeneous (TLC, silica, 6:4 ethyl acetate--hexane) white foam: IR (CHCl3 cast) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.23--2.23 (m, 13 H), 2.26--2.45 (m, 2 H), 2.71 (br s, 1 H), 3.77--3.91 (m, 2 H), 3.94--4.05 (m, 1 H), 4.05--4.20 (m, 2 H), 4.29 (s, 2 H), 5.57 (s, 1 H), 5.73 (dd, J = 9.5, 6.0 Hz, 1 H), 5.96 (d, J = 9.5 Hz, 1 H), 7.33--7.50 (m, 6 H), 7.60--7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.26, 19.07, 20.55, 22.20, 26.85, 28.97, 30.90, 33.65, 35.37, 38.51, 38.99, 43.55, 63.10, 64.57, 71.00, 72.99, 123.86, 127.85, 128.60, 129.91,

132.91, 132.99, 133.10, 133.81, 135.58; exact mass, *m/z* calcd for $C_{34}H_{44}O_2Si$ $(M - 2\ H_2O)^+$ 512.3111, found 512.3111; FABMS, *m/z* calcd for $C_{34}H_{48}O_4Si$ 548, found 549 $(M + 1)^+$. Anal. Calcd for $C_{34}H_{48}O_4Si$: C, 74.41; H, 8.82. Found: C, 74.32; H, 9.07.

Conversion of 100 into 101.

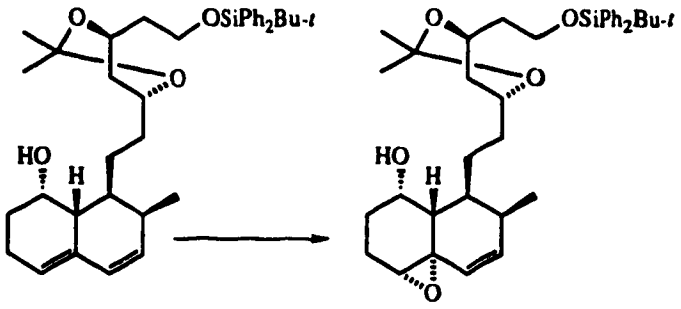


100 **101**

2-Methoxypropene (2.75 mL, 28.64 mmol) was added dropwise (over *ca.* 2 min) to a stirred and cooled (0°) solution of triol **100** 7.86 g, 14.32 mmol) and pyridinium *p*-toluenesulfonate (360 mg, 1.43 mmol) in dichloromethane (200 mL). Stirring was continued for 10 min and saturated aqueous sodium bicarbonate (100 mL) was added. The mixture was diluted with dichloromethane (200 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (1 x 100 mL) and brine (1 x 150 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 x 10 cm), using 1:9 ethyl acetate--hexane, gave alcohol **101** (7.51 g, 89%) as a homogeneous (TLC, silica, 15:85 ethyl acetate--hexane) glass: IR ($CHCl_3$ cast) 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 300

MHz) δ 0.89 (d, J = 7.0 Hz, 3 H), 1.07 (s, 9 H), 1.09--1.52 [m, 10 H, including singlets at δ 1.38 (3 H) and δ 1.43 (3 H)], 1.52--1.88 (m, 7 H), 1.95--2.26 (m, 3 H), 2.26--2.48 (m, 2 H), 3.36--3.77 (m, 1 H), 3.78--3.91 (m, 2 H), 4.05--4.19 (m, 1 H), 4.25 (s, 1 H), 5.56 (s, 1 H), 5.74 (dd, J = 9.5, 7.0 Hz, 1 H), 5.95 (d, J = 9.5 Hz, 1 H), 7.30--7.47 (m, 6 H), 7.60--7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.01, 19.23, 19.89, 20.44, 23.22, 26.88, 29.04, 30.31, 30.90, 33.10, 36.05, 37.56, 38.92, 39.37, 59.70, 64.52, 65.66, 68.69, 98.52, 123.65, 127.61, 127.64, 128.43, 129.57, 133.28, 133.53, 133.94, 134.00, 135.50; exact mass, m/z [illegible]cd for $C_{36}H_{49}O_4Si$ $(M - CH_3)^+$ 573.3400, found 573.3397. [illegible]. Calcd for $C_{37}H_{52}O_4Si$: C, 75.46; H, 8.90. Found: C, [illegible]; H, 8.80.

Conversion of 101 into 102.

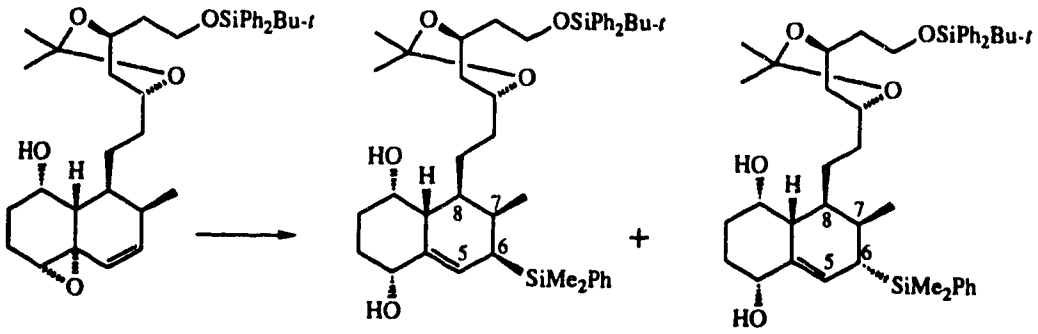


101 **102**

Homoallylic alcohol **101** (3.33 g, 5.65 mmol) was added to a stirred mixture of vanadyl acetylacetonate (150 mg, 0.565 mmol) and sodium bicarbonate (666 mg) in dry benzene (70 mL). The mixture was stirred and cooled by a cold-water bath (6°C)

and *t*-butylhydroperoxide (4.15 M in benzene, 1.90 mL, 7.92 mmol) was added dropwise (over *ca.* 5 min). The water bath was removed and the mixture allowed to attain room temperature. After 2 h, during which time the initial purple color faded to a pale yellow, the mixture was evaporated at room temperature. Flash chromatography of the residue over silica gel (4 x 15 cm), using first 15:85 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine) and then 2:8 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine), gave epoxide **102** (3.04 g, 89%) as a homogeneous (TLC, silica gel, 2:8 ethyl acetate--hexane) white foam: IR ($CHCl_3$ cast) 3480 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, J = 7.5 Hz, 3 H), 1.06 (s, 9 H), 1.09--1.88 [m, 16 H, including singlets at δ 1.37 (3 H) and δ 1.41 (3 H)], 1.90--1.99 (m, 1 H), 2.01--2.25 (m, 3 H), 2.45--2.68 (m, 1 H), 3.30 (d, J = 4.0 Hz, 1 H), 3.53 (d, J = 11.5 Hz, 1 H), 3.64--3.73 (m, 1 H), 3.76--3.88 (m, 2 H), 3.94--4.02 (m, 1 H), 4.08--4.18 (m, 1 H), 5.17 (d, J =9.5 Hz, 1 H), 6.13 (dd, J = 9.5, 5.0 Hz, 1 H), 7.33--7.45 (m, 6 H), 7.64--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 12.45, 19.18, 19.64, 19.85, 23.31, 26.83, 28.38, 29.65, 30.27, 31.45, 33.58, 35.81, 37.48, 39.34, 59.65, 61.94, 62.43, 65.60, 69.45, 98.38, 124.98, 127.55, 127.58, 129.50, 129.52, 133.92, 135.53, 142.79; exact mass, *m/z* calcd for $C_{36}H_{49}O_5Si$ $(M - CH_3)^+$ 589.3349, found 589.3345. Anal. Calcd for $C_{37}H_{52}O_5Si$: C, 73.47; H, 8.66. Found: C, 73.76; H, 8.63.

Treatment of 102 with Phenyldimethylsilyllithium Cuprate



102 **103** **104**

A stock solution of phenyldimethylsilyllithium[28] was prepared at 0°C by addition of lithium ribbon (245.0 mg, 35.31 mmol) cut into small pieces to a solution of phenyldimethylsilyl chloride (1.70 mL, 10.09 mmol) in dry THF (30 mL). The mixture was sonicated at 0°C [Branson Sonic Bath, type B-12, 80W] for 30 min and then stirred at -5°C for 36 h. An aliquot (1 mL) was added to water (10 mL) and the solution was titrated with 0.1 N hydrochloric acid using phenolphthalein as indicator. The average of several runs indicated that the solution of phenyldimethylsilyllithium was 0.337 M. The organometallic was stored in a freezer (in an argon-filled vessel) and could be kept for at least 3 weeks.

In the reaction of epoxide **102** with the silyl cuprate the ratio of **104** to **103** depends on the ratio of phenyldimethylsilyllithium to copper(I) cyanide. Based on ^{1}H-NMR studies, the combined yields and the ratios of **104** to **103** for the different silyl cuprates are[29(b)]: $PhMe_2SiCu(CN)Li$ (93%, 6.0:1), $(PhMe_2Si)_2Cu(CN)Li_2$ (95%, 1:11),

$(PhMe_2Si)_3CuLi_2$ (97%, 1:15). It should be noted that if copper(I) iodide is used instead of copper(I) cyanide only a 1:1 mixture of compounds **104** and **103** is obtained. We decided to use compound **103** for the later operations, based on our impression that compound **103** is more stable than **104**. The preparations of the silyl cuprates were all carried out by the following procedure, varying *only* the ratio of phenyldimethylsilyllithium to copper(I) cyanide.

Phenyldimethylsilyllithium (0.337 M in THF, 9.97 mL, 3.36 mmol) was added dropwise (over *ca.* 6 min) to a stirred and cooled (-23°C) solution of copper(I) cyanide (150.5 mg, 1.68 mmol) in THF (10 mL). Stirring was continued for 30 min and the mixture was then cooled to -78°C. After 10 min, epoxide **102** in THF (3.0 mL plus 2 x 1.0 mL as rinses) was added dropwise (over *ca.* 3 min). Stirring was continued for 4 h and then saturated aqueous ammonium chloride (2.0 mL) was added. The cold-bath was removed and the mixture was allowed to attain room temperature (*ca.* 30 min). The mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous ammonium chloride (1 x 15 mL), water (1 x 20 mL), and brine (1 x 20 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using first 35:65 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine) and then 1:1 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine), gave **103** (460.1 mg, 92%) and **104** (21.9 mg, 4%), both as homogeneous (TLC, silica, 1:1 ethyl

acetate--hexane) white foams. Compound **103** had: IR (CH_2Cl_2 cast) 3360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.36 (s, 6 H), 0.68 (d, J = 8.0 Hz, 3 H), 0.98--1.85 [m, 29 H, including singlets at δ 1.07 (9 H), 1.34 (3 H) and δ 1.45 (3 H)], 1.85--2.00 (m, 3 H), 2.00--2.12 (m, 1 H), 3.66--3.90 (m, 3 H), 3.90--4.04 (m, 2 H), 4.07--4.19 (m, 1 H), 5.87 (s, 1 H), 7.30--7.48 (m, 9 H), 7.53--7.63 (m, 2 H), 7.63--7.76 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ -3.41, -3.32, 10.37, 19.45, 20.02, 26.09, 27.03, 29.23, 30.45, 30.65, 31.27, 31.69, [illegible] 37.74, 39.82, 40.34, 45.21, 60.19, 66.06, 66.96, 69.36, 71.65, 98.72, 118.35, 128.01, 128.14, 129.26, 129.96, 134.30, 134.36, 134.41, 135.92, 138.42, 139.26; exact mass, *m/z* calcd for $C_{44}H_{61}O_5Si_2$ $(M - CH_3)^+$ 725.4058, found 725.4059, *m/z* calcd for $C_{45}H_{62}O_4Si_2$ $(M - H_2O)^+$ 722.4186, found 722.4168; FABMS, *m/z* calcd for $C_{45}H_{[illegible]}Si_2$ 740, found 741 $(M + 1)^+$. Anal. Calcd for $C_{45}H_{6[illegible]}$ C, 72.92; H, 8.70. Found: C, 73.02; H, 8.60.

Compound **104** had: IR (CH_2Cl_2 cast) 3440 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.34 (s, 3 H), 0.38 (s, 3 H), 0.80 (d, J = 7.0 Hz, 3 H), 1.00--1.25 [m, 12 H, including a singlet at δ 1.05 (9 H)], 1.26--160 [m, 13 H, including singlets at δ 1.31 (3 H) and δ 1.40 (3 H)], 1.62--1.90 (m, 7 H), 2.00--2.12 (m, 1 H), 3.64--3.77 (m, 2 H), 3.79--3.96 (m, 3 H), 4.05--4.18 (m, 1 H), 5.92 (d, J = 5.5 Hz, 1 H), 7.30--7.46 (m, 9 H), 7.49--7.56 (m, 2 H), 7.64--7.73 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ -3.25, -2.79, 15.34, 19.44, 20.11, 25.35, 27.02, 28.59, 30.44, 31.27, 34.24, 37.78, 39.83, 44.01,

60.02, 66.02, 69.21, 71.80, 98.70, 120.07, 127.99, 128.16, 129.43, 129.95, 134.38, 134.42, 134.50, 134.91, 135.93, 138.92; exact mass, *m/z* calcd for $C_{44}H_{59}O_4Si_2$ (M - CH_3 - 2 H_2O)$^+$ 707.3951, found 707.3941; FABMS, *m/z* calcd for $C_{45}H_{64}O_5Si_2$ 740, found 741 (M + 1)$^+$. Anal. Calcd for $C_{45}H_{64}O_5Si_2$: C, 72.92; H, 8.70. Found: C, 72.78; H, 8.70.

The stereochemical assignment was made on the basis of ^1H NMR measurements run at 500 MHz. By decoupling measurements and a 2D ^1H-^1H correlation spectrum it was possible to locate the signals due to C(6)-H, C(7)-H, and C(8)-H in both isomers. The data are as follows:

500 MHz NMR data for Compounds 104 and 103

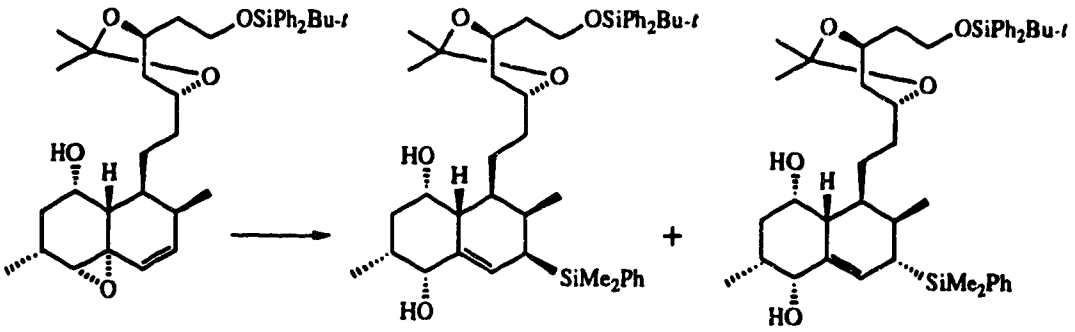
103	**104**
C(7)-Me δ 0.68 (d, *J* = 8.0 Hz)	C(7)-Me δ 0.80 (d, *J* = 7.0 Hz)
	C(8)-H δ 1.46--1.53 [m, 4 H (1 H is due to C(8)-H)]
	C(6)-H δ 1.62--1.74 [m, 4 H (1 H is due to C(6)-H)]
C(7)-H δ 2.00--2.12 (m)	C(7)-H δ 2.00--2.12 (m)
$J_{5,6}$ = 0 Hz	$J_{5,6}$ = 5.5 Hz

For **103**, $J_{5,6}$ = 0 Hz since the C(5)-H signal is a singlet. Irridiation at δ 0.68 [C(7)-Me] causes the

multiplet due to the C(7)-H to collapse to a triplet (J = 3.0 Hz). This implies that $J_{6,7} = J_{7,8}$ and, on this basis, we assume that C(6)-H and C(8)-H adopt a similar angular position relative to C(7)-H. Consequently the hydrogens on C(6), C(7), and C(8) are all *syn*.

For compound **104**, irridiation at δ 1.5 [C(8)-H] causes the signal due to C(7)-H collapse to a quartet. This means that $J_{6,7}$ must be very small or zero. Irridiation at δ 0.8 [C(7)-Me] changes the C(7)-H signal into a doublet. From an inspection of Dreiding models it is not clear why $J_{5,6}$ is as large as 5.5 Hz, and so we regard the assignement to **104** as being tentative; and we have submitted **103** for X-ray analysis.

Treatment of 8 with Phenyldimethylsilyllithium Cuprate



8 **50** **105**

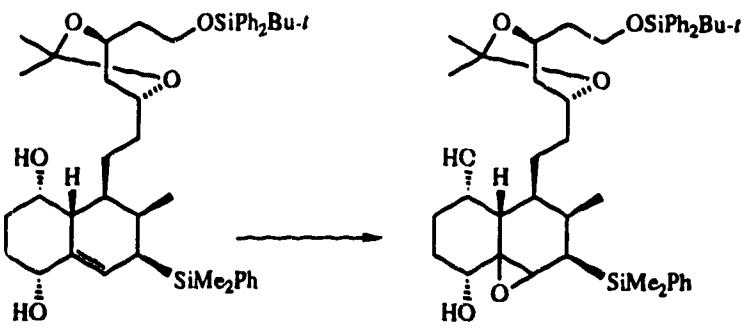
As in the above reaction (**102** → **103** and **104**), the ratio of **50** to **105** (for the mevinolin series) depends on the ratio of phenyldimethylsilyllithium to copper(I) cyanide. Based on ^{1}H-NMR studies, the combined yields and the ratios of **105** to **50** for the different silyl cuprates are:

$PhMe_2SiCu(CN)Li$ (98%, 8.0:1), $(PhMe_2Si)_2Cu(CN)Li_2$ (97%, 1:7.0), $(PhMe_2Si)_3CuLi_2$ (96%, 1:7.1). The preparations of the silyl cuprates were all carried out by the following procedure, varying *only* the ratio of phenyldimethylsilyl-lithium to copper(I) cyanide.

Phenyldimethylsilyllithium (0.337 M in THF, 0.74 mL, 0.249 mmol) was added dropwise (over *ca.* 70 sec) to a stirred and cooled (-23°C) solution of copper(I) cyanide (11.1 mg, 0.124 mmol) in THF (2.0 mL). Stirring was continued for 30 min and the mixture was then cooled to -78°C. After 10 min, epoxide **8** in THF (0.5 mL plus 0.5 mL as a rinse) was added dropwise (over *ca.* 1 min). Stirring was continued for 5 h and then saturated aqueous ammonium chloride (0.5 mL) was added. The cold-bath was removed and the mixture was allowed to attain room temperature (*ca.* 30 min). The mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous ammonium chloride (1 x 3 mL), water (1 x 5 mL), and brine (1 x 5 mL). The organic layer was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using first 2:8 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine) and then 25:75 ethyl acetate--hexane (the mixture containing 1% by volume of triethylamine), gave a mixture of **50** and **105** (35.5 mg, 97%) as pure (TLC, silica, 3:7 ethyl acetate--hexane), white foam. ^{1}H-NMR analysis showed that the ratio of **50** to **105** is 7.0:1. Compound **50** (obtained from silyl cuprate), which was obtained pure by flash chromatography over silica

gel, using 15:85 ethyl acetate--hexane and 2:8 ethyl acetate--hexane, was identical with compound **50** (based on ^{1}H NMR, ^{13}C NMR and combustion analysis), obtained previously by using just phenyldimethylsilyllithium (i.e. not the cuprate). Compound **105** had: IR (CH_2Cl_2 cast) 3480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.36 (s, 3 H), 0.37 (s, 3 H), 0.81 (d, J =6.5 Hz, 3 H), 1.00 [d, J = 6.5 Hz, 3 H), 1.03--1.17 (m, 12 H, including a singlet at δ 1.05 (9 H)], 1.32--1.46 [m, 9 H, including singlets at δ 1.37 (3 H) and δ 1.41 (3 H)], 1.47--1.98 [m, 9 H (1 H signal disappeared upon exchange with D_2O)], 2.03--2.15 (m, 1 H), 2.46 [br s or d depending on the concentration of the NMR sample, 1 H (signal disappeared upon exchange with D_2O)], 3.36--3.76 (m, 2 H), 3.80--3.90 (m, 1 H), 3.90--4.01 (m, 2 H), 4.07--4.18 (m, 1 H), 5.88 (d, J = 4.5 Hz, 1 H), 7.33--7.46 (m, 9 H), 7.48--7.55 (m, 2 H), 7.66--7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ -3.68, -3.49, 15.51, 16.88, 19.23, 19.93, 24.76, 26.87, 28.65, 30.30, 31.39, 33.75, 34.64, 36.12, 36.44, 37.39, 39.39, 41.03, 59.71, 62.58, 65.63, 66.02, 69.00, 74.37, 98.45, 127.62, 127.83, 129.19, 129.36, 129.58, 133.97, 134.19, 135.57, 138.27. A satisfactory mass spectrum could not be obtained. Anal. Calcd for $C_{46}H_{66}O_5Si_2$: C, 73.16; H, 8.81. Found: C, 73.24; H, 9.04.

Conversion of 103 into 106.

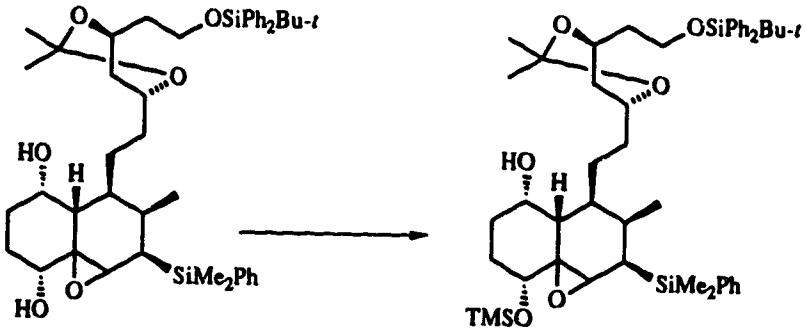


103 **106**

Allylsilane **103** (5.8213 g, 7.85 mmol) was added to a stirred mixture of vanadyl acetylacetonate (208 mg, 0.785 mmol) and sodium bicarbonate (1.1640 g) in dry benzene (100 mL). The mixture was cooled by cold water-bath (8°C) and *t*-butylhydroperoxide (4.15 M in benzene, 2.65 mL, 10.99 mmol) was added dropwise (over *ca.* 4 min). Stirring was continued for 6 h, during which time the initial purple color faded to a pale yellow. The mixture was evaporated and flash chromatography of the residue over silica gel (5.5 x 15 cm), using first 3:7 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine), then 4:6 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine), and finally 6:4 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine), gave epoxide **106** (5.65 g, 95%) as a homogeneous (TLC, silica gel, 4:6 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.38 (s, 3 H), 0.40 (s, 3 H), 0.72 (d, J = 7.0 Hz, 3 H), 0.77 (m, 1 H), 0.97--1.30 [m, 12 H, including a singlet at 1.04 (s, 9 H)], 1.30--1.60 [m, 12 H, including singlets at

δ 1.35 (3 H) and δ 1.40 (3 H)], 1.60--1.89 (m, 5 H), 1.89--2.00 (m, 1 H), 2.00--2.11 (m, 1 H), 2.63 (d, J = 8.5 Hz, 1 H), 3.40 (s, 1 H), 3.62--3.89 (m, 4 H), 4.03--4.18 (m, 2 H), 7.30--7.45 (m, 9 H), 7.50--7.60 (m, 2 H), 7.62--7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ -3.17, -2.89, 12.42, 19.24, 19.86, 24.71, 26.88, 28.02, 28.24, 30.30, 31.40, 31.82, 34.49, 36.87, 37.36, 39.36, 40.73, 52.65, 59.68, 64.14, 65.63, 66.60, 68.28, 69.30, 98.48, 127.63, 127.65, 128.07, 129.30, 129.59, 133.78, 133.92, 133.99, 135.58, 137.62; exact mass, *m/z* calcd for $C_{44}H_{61}O_6Si_2$ $(M - CH_3)^+$ 741.4006, found 741.4020, *m/z* calcd for $C_{45}H_{62}O_5Si_2$ $(M - H_2O)^+$ 738.4131, found 738.4139; FABMS, *m/z* calcd for $C_{45}H_{64}O_6Si2$ 756, found 779 $(M + 23)^+$. Anal. Calcd for $C_{45}H_{64}O_6Si_2$: C, 71.38; H, 8.52. Found: C, 71.16; H, 8.44.

Conversion of 106 into 107.

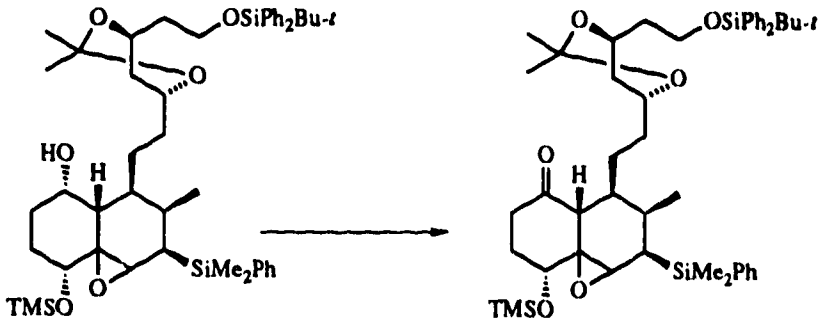


106 **107**

A 1:4 mixture of chlorotriethylsilane-triethylamine (1.44 mL, 2.25 mmol of chlorotriethylsilane) was added to a stirred and cooled (0°C) solution of epoxysilane **106** (1.135 g, 1.50 mmol) and 4-dimethylaminopyridine (73.3 mg, 0.60

mmol) in dichloromethane (30 mL). Stirring was continued for 10 min (TLC control, silica, 2:8 ethyl acetate--hexane). Water (5.0 mL) was added at 0°C and stirring was continued for 10 min. The mixture was diluted with dichloromethane (30 mL) and the organic layer was washed with water (2 x 20.0 mL) and brine (1 x 30 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using first 1:9 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine) and then 15:85 ethyl acetate--hexane (the mixture containing 1% by volume triethylamine), gave compound **107** (1.013 g, 82%) as a homogeneous (TLC, silica, 15:85 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 3540 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.11 (s, 9 H), 0.38 (s, 3 H), 0.39 (s, 3 H), 0.71 (d, J = 7.0 Hz, 3 H), 1.00--1.30 [m, 12 H, including a singlet at δ 1.04 (s, 9 H)], 1.32--1.58 [m, 12 H, including singlets at δ 1.35 (3 H) and δ 1.41 (3 H)], 1.63--2.10 (m, 7 H), 2.94 (d, J = 9.6 Hz, 1 H), 3.32 (s, 1 H), 3.63--3.87 (m, 4 H), 4.05--4.15 (m, 2 H), 7.30--7.44 (m, 9 H), 7.51--7.57 (m, 2 H), 7.62--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ -3.23, -2.94, 0.01, 12.38, 19.16, 19.80, 24.60, 26.81, 27.69, 28.11, 30.23, 31.56, 32.04, 34.48, 36.73, 37.32, 39.30, 41.03, 52.46, 59.62, 64.42, 65.56, 66.93, 69.26, 69.31, 98.39, 127.55, 127.57, 127.98, 129.19, 129.51, 133.75, 133.86, 133.92, 135.51, 137.48; FABMS, *m/z* calcd for $C_{48}H_{72}O_6Si_3$ 828, found 851 $(M + 23)^+$. Anal. Calcd for $C_{48}H_{72}O_6Si_3$: C, 69.52; H, 8.75. Found: C, 69.60; H, 8.62.

Conversion of 107 into 108.

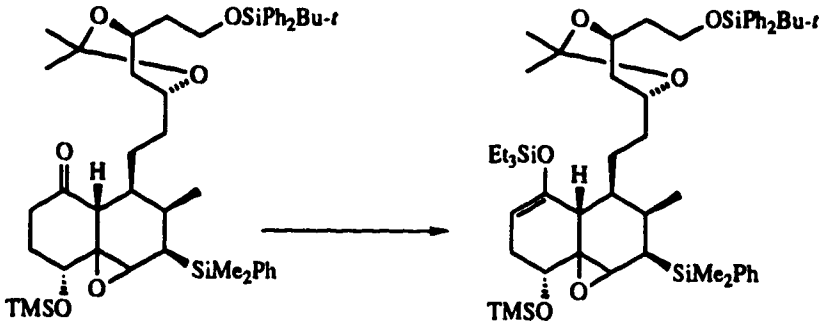


107 **108**

Tetrapropylammonium perruthenate (89 mg, 0.253 mmol) was added in one portion to a stirred and cooled (0°) mixture of alcohol **107**.(2.1000 g, 2.53 mmol), powdered 4Å molecular sieves (1.2660 g, 500 mg/mmol), and 4-methylmorpholine *N*-oxide (593 mg, 5.06 mmol) in dichloromethane (100 mL). The cold-bath was removed and the mixture was stirred under argon for 6 h. The mixture (no evaporation of solvent) was then filtered through silica gel (4.5 x 10 cm), and the pad was washed with 3:7 ethyl acetate--hexanes (the mixture containing 1% by volume triethylamine). Evaporation of the solvents gave ketone **108** (2.04 g, 97%) as a homogeneous (TLC, silica, 2:8 ethyl acetate--hexane) white solid (mp 138-140°C): IR (CH_2Cl_2 cast) 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 9 H), 0.38 (s, 3 H), 0.40 (s, 3 H), 0.73 (d, J = 6.9 Hz, 3 H), 0.98--1.10 [m, 10 H, including a singlet at δ 1.03 (9 H)], 1.20--1.47 [m, 12 H, including singlets at δ 1.28 (3 H) and δ 1.39 (3 H)], 1.63--1.72 (m, 3 H), 1.77--1.92 (m, 2 H), 2.03--2.10 (m, 1 H), 2.33--2.56 (m, 3 H), 3.30 (s, 1 H),

3.65--3.75 (m, 2 H), 3.78--3.85 (m, 1 H), 4.04--4.13 (m, 1 H), 4.24 (dd, J = 11.0, 5.0,Hz, 1 H), 7.33--7.46 (m, 9 H), 7.53--7.58 (m, 2 H), 7.64--7.70 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ -3.07, -2.79, -.0.01, 12.63, 19.44, 20.03, 26.10, 27.02, 28.23, 30.44, 32.12, 32.24, 34.72, 36.35, 37.71, 39.63, 40.15, 51.05, 60.17, 65.96, 66.45, 68.99, 69.62, 98.65, 127.99, 128.02, 128.36, 129.58, 129.94, 129.96, 134.25, 134.40, 134.43, 135.93, 138.09, 207.35; FABMS, *m/z* calcd for $C_{48}H_{70}O_6Si_3$ 826, found 827 $(M + 1)^+$. Anal. Calcd for $C_{48}H_{70}O_6Si_3$: C, 69.68; H, 8.53. Found: C, 69.40; H, 8.66.

Conversion of 108 into 109.



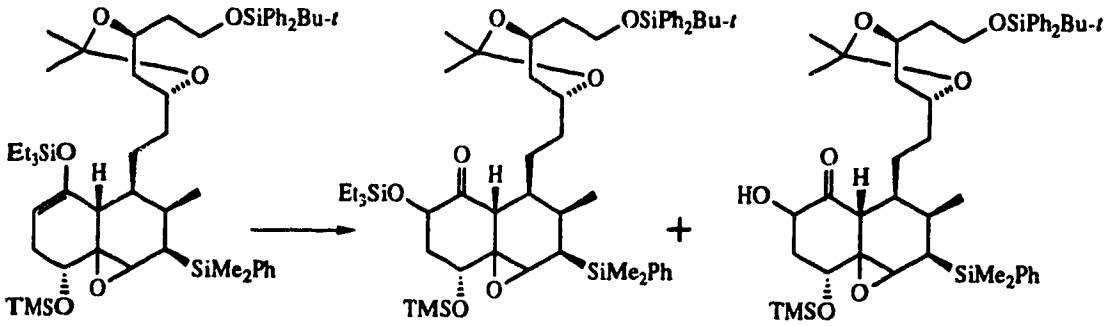
108 **109**

n-Butyllithium (1.6 M in hexane, 0.47 mL, 0.755 mmol) was added to a stirred and cooled (0°C) solution of diisopropylamine (106 µL, 0.755 mmol) in THF (4.5 mL). Stirring was continued for 15 min and the solution was cooled to -78°C. A solution of ketone **108** (125 mg, 0.151 mmol) in THF (1.5 mL plus 2 x 1.5 mL as rinses) was added dropwise (over *ca.* 4 min) with stirring and, after 30 min, 4:1

chlorotriethylsilane-triethylamine (95 μL, 0.453 mmol of chlorotriethylsilane) was added. Stirring was continued for 25 min [close monitoring (every 5 min) by TLC], saturated aqueous ammonium chloride (3.0 mL) was added, the mixture was stirred for 5 min at -78°C, and ethyl acetate (10 mL) was then added. After 5 min, the mixture was poured into a separatory funnel containing ethyl acetate (15 mL) and saturated aqueous sodium bicarbonate (15 mL). The layers was separated and the organic layer was washed with saturated aqueous sodium bicarbonate (1 x 15 mL) and brine (1 x 15 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 15 cm), using 5:95 ethyl acetate--hexane, gave silyl enol ether **109** (113 mg, 79%) as a homogeneous (TLC, silica, 5:95 ethyl acetate--hexane) thick oil: IR (CH_2Cl_2 cast) 2960 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 9 H), 0.38 (s, 3 H), 0.39 (s, 3 H), 0.69 (d, J = 7.5 Hz, 3 H), 0.71 (q, J = 7.9 Hz, 6 H), 0.97 (t, J = 7.9 Hz, 9 H), 1.04 (s, 9 H), 1.12--1.57 [m, 13 H, including singlets at δ 1.29 (3 H) and δ 1.39 (3 H)], 1.66 (q, J = 12.5, 6.5 Hz, 2 H), 1.79--1.86 (m, 1 H), 2.06--2.22 (m, 2 H), 2.24--2.32 (m, 1 H), 2.48 (br d, J = 12.0 Hz, 1 H), 3.42 (s, 1 H), 3.65--3.75 (m, 2 H), 3.78--3.87 (m, 1 H), 4.00--4.14 [m, 2 H, including a double doublet at δ 4.03 (J = 9.0, 6.7 Hz, 1 H)], 4.60--4.67 (m, 1 H), 7.33--7.46 (m, 9 H), 7.55--7.60 (m, 2 H), 7.65--7.77 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ -2.96, -2.67, 0.00, 5.32, 6.99, 12.62, 19.42, 20.00, 27.03, 27.11, 29.46, 30.47, 32.22, 32.32, 35.37, 38.05, 39.67, 39.91,

40.90, 55.75, 60.20, 65.20, 65.96, 67.72, 70.05, 98.66, 100.07, 128.00, 128.30, 129.46, 129.96, 134.27, 134.46, 135.93, 138.60, 153.01; FABMS, *m/z* calcd for $C_{54}H_{84}O_6Si_4$ 940, found 963 $(M + 23)^+$. Anal. Calcd for $C_{54}H_{84}O_6Si_4$: C, 68.88; H, 8.99. Found: C, 69.08; H, 8.94.

Conversion of 109 into 110 and 111.

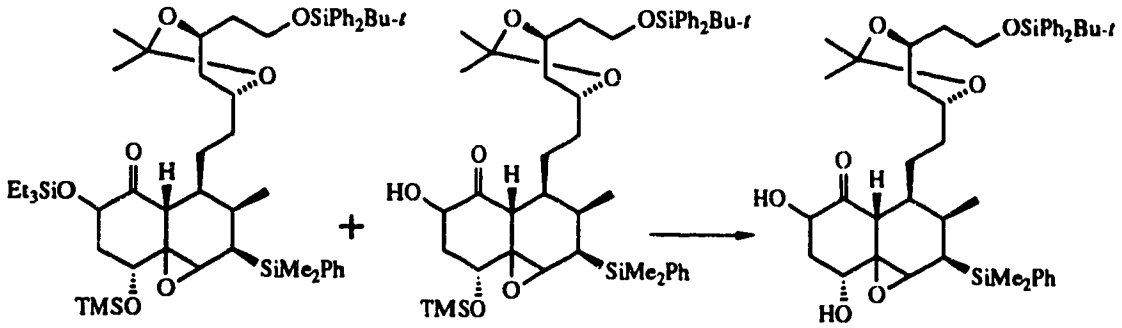


109 **110** **111**

A solution of silyl enol ether **111** (112.0 mg, 0.119 mmol) in hexane (1.5 mL plus 2 x 1.0 mL as rinses) was added quickly (over *ca.* 2 min) to a stirred and cooled (0°C) mixture of *m*-chloroperbenzoic acid (80-85% w/w, 37 mg, *ca.* 0.178 mmol) and solid sodium bicarbonate (30.0 mg, 0.356 mmol) in ethyl acetate (4.5 mL). Stirring was continued for 30 min at 0°C (TLC control, silica,1:9 ethyl acetate--hexane). Direct (no evaporation of the solvent) flash chromatography of the mixture over silica gel (1.5 x 10 cm), using 25:75 ethyl acetate--hexane, gave ketone **110** (72 mg, 63%) and ketone **111** (29 mg, 29%), both as homogeneous (TLC, silica, 1:9 ethyl acetate--hexane) thick oils. These compounds were not characterized but the corresponding

desilylated compound **112** was fully characterized.

Conversion of 110 and 111 into 112.

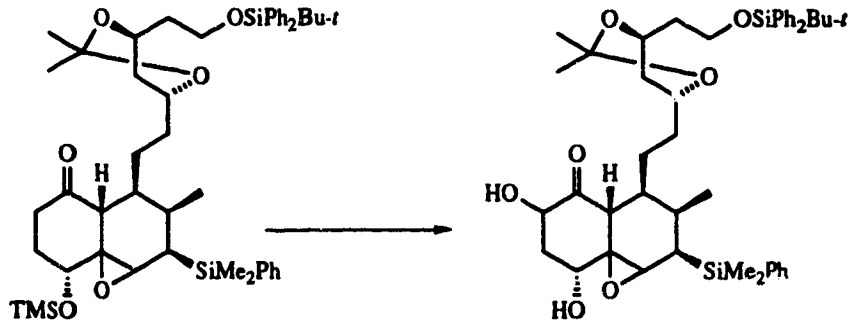


110 **111** **112**

Tetrabutylammonium fluoride (1.0 M in THF, 0.36 mL, 0.36 mmol) was added to a stirred solution of ketones **110** (64.1 mg, 0.067 mmol) and **111** (19.2 mg, 0.023 mmol), and acetic acid (0.1 mL, 1.79 mmol) in THF (4.0 mL). Stirring was continued for 5 h (TLC control, silica, 1:1 ethyl acetate--hexane) and the mixture was diluted with ethyl acetate (15 mL), washed with water (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using first 3:7 ethyl acetate--hexane and then 1:1 ethyl acetate--hexane, gave dihydroxy ketone **112** (50.7 mg, 73%) as a homogeneous (TLC, silica, 4:6 ethyl acetate--hexane) white foam: IR (CH_2Cl_2 cast) 3310, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.38 (s, 3 H), 0.42 (s, 3 H), 0.78 (d, J = 7.0 Hz. 3 H), 1.03 (s, 9 H), 1.09--1.35 [m, 6 H, including a singlet at δ 1.28 (3 H)], 1.36--1.78 [m, 11 H, including singlets at δ 1.39 (3 H)], 1.81--1.90 (m, 2 H), 2.31 (dt, J = 14.0, 5.8 Hz, 1 H), 2.63

[br s, 1 H (signal disappeared upon exchange with D_2O)], 3.11 (d, J = 10.9 Hz, 1 H), 3.38 (s, 1 H), 3.66--3.77 (m, 2 H), 3.78--3.86 (m, 1 H), 4.05--4.12 (m, 1 H), 4.16 (dd, J = 5.8, 3.9 Hz, 1 H), 4.37--4.45 (m, 1 H), 7.33--7.46 (m, 9 H), 7.53--7.60 (m, 2 H), 7.63--7.70 (m, 4 H)); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ -3.16, -2.68, 12.60, 19.45, 20.03, 25.99, 27.03, 28.57, 30.43, 31.84, 34.60, 36.60, 37.64, 39.81, 45.33, 55.68, 60.17, 64.37, 65.60, 65.99, 73.87, 98.73, 128.02, 128.37, 129.64, 129.96, 134.21, 134.39, 134.45, 135.93, 138.01, 209.35; FABMS, *m/z* calcd for $C_{45}H_{62}O_7Si_2$ 770, found 771 $(M + 1)^+$. Anal. Calcd for $C_{45}H_{62}O_7Si_2$: C, 70.09; H, 8.10. Found: C, 70.20; H, 8.28.

Conversion of 108 into 112.

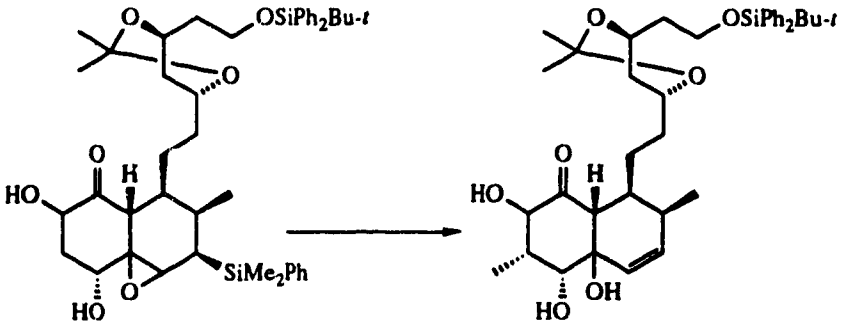


108 **112**

Ketone **108** (2.3595 g, 2.85 mmol) in THF (10 mL plus 2 x 3.0 mL as rinses) was added dropwise (over *ca.* 5 min) to a stirred and cooled (-78°C) solution of potassium bis(triemthylsilyl)amide (0.5 M in toluene, 8.56 mL, 4.28 mmol) in THF (80 mL). Stirring was continued for 30 min, and then 2-(phenylsulfonyl)-3-phenyloxaziridine **90**[23] (1.1180 g,

4.28 mmol) in THF (14 mL) was added over *ca.* 5 min. Stirring was continued for 30 min and then acetic acid (3.26 mL, 57 mmol) was added. The cold-bath was removed and the mixture was allowed to attain room temperature (30-40 min). Tetrabutylammonium fluoride (1.0 M in THF, 11.5 mL, 11.4 mmol) was added and, after 30 min (TLC control, silica, 3:7 ethyl acetate--hexane), the mixture was concentrated at room temperature to 5-10 mL. The residue was dissolved in ethyl acetate (150 mL), washed with saturated aqueous ammonium chloride (1 x 50 mL), water (2 x 50 mL) and brine (1 x 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (4.5 x 15 cm), using first 1:9 ethyl acetate--dichloromethane, then 1:4 ethyl acetate--dichloromethane, and finally 35:65 ethyl acetate--dichloromethane, gave ketone **112** (1.9120 g, 87%) as a homogeneous (TLC, silica, 4:6 ethyl acetate--hexane) white foam. This material was identical with the compound obtained by a the earlier route.

Conversion of 112 into 113.

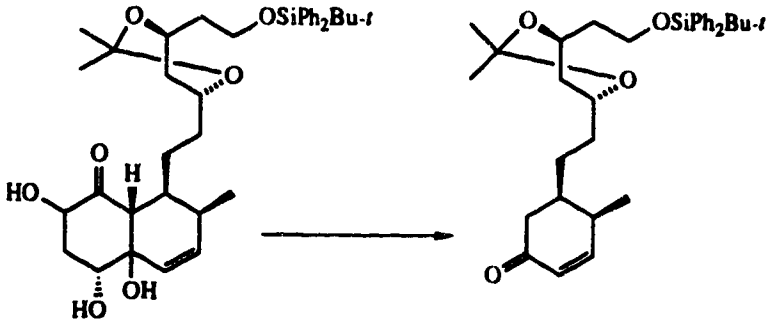


112 **113**

Acetic acid (3.4 mL) was added to a stirred solution of epoxysilane **112** (849 mg, 1.101 mmol) in methanol (20.6 mL). The resulting solution was stirred for 11 h. The solvents were evaporated and as much as possible of the acetic acid was removed at room temperature, using a Rotovapor with a dry ice-acetone condenser. The residue (still smelling faintly of acetic acid) was dissolved in dry acetone (20 mL). Pyridinium *p*-toluenesulfonate (83 mg, 0.33 mmol) was then added and the mixture was stirred for 7.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 x 15 cm), using first 4:6 ethyl acetate--hexane, then 6:4 ethyl acetate--hexane, and finally 8:2 ethyl acetate--hexane, gave ketone **113** (549 mg, 78%) as a homogeneous (TLC, silica, 6:4 ethyl acetate--hexane) slightly yellow foam: IR (CH_2Cl_2 cast) 3410, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, J = 7.1 Hz, 3 H), 1.04 (s, 9 H), 1.08--1.61 [m, 11 H, including singlets at δ 1.36 (3 H) and δ 1.42 (3 H)], 1.65--1.76 (m, 2 H), 1.84 [s, 1 H (signal disappeared upon exchange with D_2O)], 1.90--2.18 [m, 4 H (1 H

signal disappeared upon exchange with D_2O)], 2.26--2.34 (m, 1 H), 2.36--2.45 (m, 1 H), 2.53 [br s, 1 H (signal disappeared upon exchange with D_2O)], 2.76 (d, J = 12.0 Hz, 1 H), 3.69 (dt, J = 10.5, 5.0 Hz, 1 H), 3.74--3.88 (m, 2 H), 4.02--4.17 (m, 3 H), 5.92 (dd, J = 10.0, 5.0 Hz, 1 H), 5.99 (dd, J = 10.0, 1.0 Hz, 1 H), 7.35--7.48 (m, 6 H), 7.62--7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 13.73, 19.43, 20.09, 23.59, 27.02, 30.43, 30.93, 31.09, 34.04, 37.64, 39.04, 39.78, 46.65, 60.12, 65.96, 69.72, 70.30, 75.18, 76.35, 98.79, 126.25, 128.02, 129.96, 134.34, 134.39, 135.69, 135.92, 137.78, 210.24; exact mass, *m/z* calcd for $C_{36}H_{49}O_7Si$ $(M - CH_3)^+$ 621.3247, found 621.3237. Anal. Calcd for $C_{37}H_{52}O_7Si$: C, 69.78; H, 8.23. Found: C, 69.78; H, 8.34.

Conversion of 113 into 2 using Sodium Periodate.

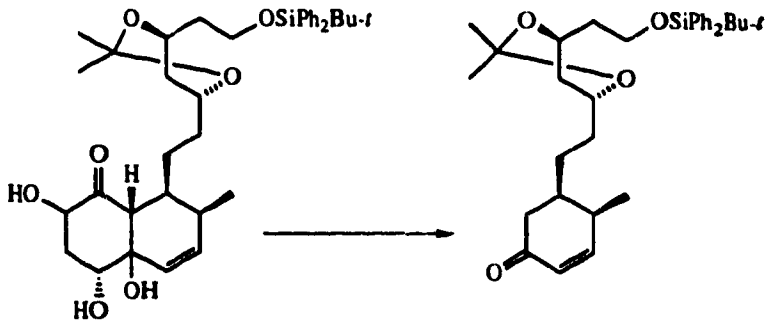


113 **2**

Sodium periodate (543 mg, 2.542 mmol) was added to a stirred solution of triol **113** (323.8 mg, 0.508 mmol) in 3:1 methanol-water. The resulting suspension was stirred at room temperature for 23 h. Methanol (40 mL) was added and the mixture was filtered through a pad (2 x 2.5 cm) of Florisil.

The pad was washed with methanol (40 mL). The combined filtrates were evaporated, water being removed at room temperature using a Rotovapor with a dry ice-acetone condenser. The residue was dissolved in acetone (40 mL), dried (Na_2SO_4), and evaporated. The resulting mixture was dissolved in dry acetone, pyridinium *p*-toluenesulfonate was added, and the mixture was stirred for 2.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.0 x 15 cm), using first 1:9 ethyl acetate--hexane and then 2:8 ethyl acetate--hexane, gave enone **2** (156.5 mg, 57%) as an homogeneous (TLC, silica, 3:7 ethyl acetate--hexane) viscous oil. The material was indistinguishable [^{1}H NMR, ^{13}C NMR, TLC (silica, 3:7 ethyl acetate--hexane)] from an authentic sample made[1] by total synthesis and with the sample made as described above by degradation of natural mevinolin. [We did not prove that the reketalization conditions were necessary, but our impression is that by applying that procedure the TLC spot corresponding to the desired product becomes stronger.]

Conversion of 113 into 2 using Lead Tetraacetate



113 **2**

Lead tetraacetate (42.4 mg, 0.096 mmol) was added to a stirred solution of trihydroxy ketone **113** (29 mg, 0.045 mmol) in 1:1 benzene-methanol (2.0 mL). After 5 min, aqueous sodium bisulfite (10% w/v, 2 drops) was added and the mixture was diluted with dichloromethane (5 mL), and dried (Na_2SO_4). The solution was filtered through a short column (1 x 5 cm) of silica gel. The pad was washed with ethyl acetate (30 mL), and the filtrate was evaporated. The residue was dissolved in dichloromethane (1.5 mL) and silicic acid (450 mg) was added. The resulting slurry was stirred under argon for 13 h, and direct chromatography (no evaporation of solvent) over silica gel (1 x 8 cm), using first 15:85 ethyl acetate--hexane and then 3:7 ethyl acetate--hexane, gave enone **2** (5.7 mg, 23%) as an homogeneous (TLC, silica, 3:7 ethyl acetate--hexane) viscous oil. The material was indistinguishable [^{1}H NMR, ^{13}C NMR, TLC (silica, 3:7 ethyl acetate--hexane)] from an authentic sample made[1] by total synthesis and with the sample made as described above by degradation of natural mevinolin.

References and footnotes

1 Clive, D.L.J.; Keshava Murthy, K.S.; Wee, A.G.H.; Siva Prasad, J.; da Silva, G.V.J.; Majewski, M.; Anderson, P.C.; Evans, C.F; Haugen, R.D.; Heerze, L.D.; Barrie, J.R. *J. Am. Chem. Soc.* **1990**, *112*, 3018.

2 Clive, D.L.J.; Keshava Murthy, K.S.; George, R.; Poznansky, M.J. *J. Chem. Soc., Perkin Trans I* **1990**, 2099.

3 Clive, D.L.J.; Keshava Murthy, K.S.; Zhang, C.; Hayward, W.D.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1990**, 509. Clive, D. L. J.; Zhang, C.; Keshava Murthy, K. S.; Hayward, W. D.; Daigneault, S. *J. Org. Chem.* **1991**,*56*, 6447.

4 DeCamp, A.E.; Verhoeven, T.R.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3207.

5 Kuo, C.H.; Patchett, A. A.; Wendler, N.L. *J. Org. Chem.* **1983**, *48*, 1991.

6 UK Patent Application GB 2 075 013 A (Sankyo Company). There appears to be a printing error on p. 44 of the patent: the mass and analytical data given do not refer to the intended compound.

7 Cambie, R.C.; Read, C.M.; Rutledge, P.S.; Walker, G.J.; Woodgate, P.D.; Hanson, J.R. *J. Chem. Soc., Perkin Trans I* **1980**, 2581. Shoppee, C.W.; Coll, J.C. *J. Chem. Soc.*(C) **1969**, 2157. McMurry, J.E.; Musser, J.H.; Ahmad, M.S.; Blaszczak, L.C. *J. Org. Chem.* **1975**, *40*, 1829.

8 Eur. Pat. Appl. 320052 A2 14 June 1989 (Merck). (*Chem.*

Abstr. **1990**, *111*, 233285x.)

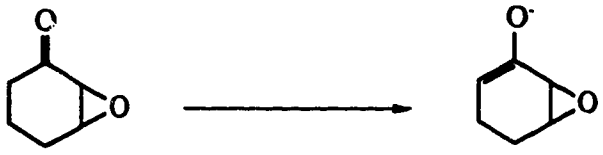
9 (a) Sharpless, K B.; Verhoeven, T.R. *Aldrichimica Acta* **1979**, *12*, 63. (b) Kobayashi, M.; Kurozumi, S.; Toru, T.; Ishimoto, S. *Chemistry Lett.* **1976**, 1341.

10 For monoepoxidation of conjugated dienes see: *Chem. Abstr.* **1989**, *111*, 39670d. *Chem. Abstr.* **1988**, *108*, 74607y. Ogawa, S.; Toyokuni, T.; Ara, M.; Suetsugu, M.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1710.

11 (a) Bartlett, P.A. ; Meadows, J.D.; Brown, E.G.; Morimoto, A.; Jernstedt, K.K. *J. Org. Chem.* **1982**, *47*, 4013. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.

12 Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis* Wiley: New York, 1991; p 83. Cunico, R.F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

13 Efficient deprotonation of a ketone epoxide has been reported (Wender, P.A.; Erhardt, J.M.; Letendre, L.J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.):



In the case of **9→10**, it may be necessary to use a temperature of -100°C and to carry out the deprotonation in the presence of Me_3SiCl (*Cf.* Ireland, R. E.; Norbeck, D.W. *J. Am. Chem. Soc.* **1985**, *107*, 3279). Lithium

tetramethylpiperidide-Me_3SiCl may be an even better choice of reagents (*cf.* Krizan, T.D.; Martin, J.C. *J. Am. Chem. Soc.* **1983**, *105*, 6155).

14 Corey, E.J.; Katzenellenbogen, N.W.; Gilman, S.A.R.; Erickson, B.W. *J. Am. Chem. Soc.* **1968**, *90*, 5618. Knöll, W.; Tamm, C. *Helv. Chim. Acta* **1975**, *58*, 1162.

15 Goldbach, M.; Jäkel, E.; Schneider, M.P. *J. Chem. Soc., Chem. Commun.* **1987**, 1434. Nagarkatti, J.P.; Ashley, K.R. *Tetrahedron Lett.* **1973**, 4599. Evans, D.A.; Williams, J.M. *Tetrahedron Lett.* **1988**, *29*, 5065.

16 Suitable conditions would have to be established when the compound is in hand. *Cf.* (a) Kayser, R.H.; Brault, M.; Pollack, R.M.; Bantia, S.; Sadoff, S.F. *J. Org. Chem.* **1983**, *48*, 4497. (b) Hunter, D.H.; Patel, V.; Perry, R.A. *Can. J. Chem.* **1980**, *58*, 2271.

17 Trost, B.M.; Angle, S.R. *J. Am. Chem. Soc.* **1985**, *107*, 6123. Fujinami, T.; Suzuki, T.; Kamiya, M. *Chem. Lett.* **1985**, 199.

18 The *tert*-butyldiphenylsilyl group survives, for example, exposure to benzyltrimethylammonium hydroxide [see ref 1 and its Supplementary Material, p. 79.] If the group *is* lost, it can be replaced since the resulting hydroxyl is the only primary one present.

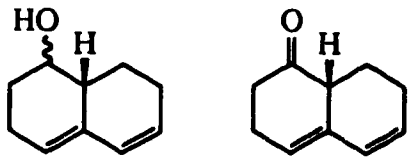
19 This method has been used in the synthesis of **1a** (see ref. 1). The *tert*-butyldiphenylsilyl group remains intact under these conditions.

20 It is unlikely that the C(1) ester in the example of eq

5 plays a role in the reaction shown. During the transformation of **21** into **22** neutral (and definitely not acidic) conditions will have to be maintained in order to preserve the trimethylsilyl group at C(1).

21 *Cf.* Karanewsky, D. *Tetrahedron Lett.* **1991**, *32*, 3911.

22 If the isomers are not separated then a mixture of alcohols **i** is obtained. Swern oxidation gives **ii**. In early experiments the yield in the oxidation was poor (20-43%) and so we did not examine the possibility of treating ketone **ii** with L-Selectride so as to generate only isomer **7**.



i **ii**

23 (a) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774. (b) Davis, F. A.; Chattopadhyay, S. *Tetrahedron Lett.* **1986**, *27*, 5079. (c) Davis, F. A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3243.

24 In those cases where the stereochemistry is known a heavy or dotted line is used to connect a substituent to a ring; where the stereochemistry was not established a line of ordinary thickness is used. A wavey line is used where two isomers are present.

25 Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100.

26 Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

27 The catalyst is made from $Pd(OAc)_2$ and $(i\text{-}PrO)_3P$. See reference 17.

28 Fleming, I.; Marchi Jr., D. *Synthesis* **1981**, 560.

29 (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans I* **1981**, 2522. Sharma, S. (b) Oehlschlager, A. C. *Tetrahedron* **1989**, *45*, 557.

30 Epoxidation [t-BuOOH/$VO(acac)_2$] of allylic silane **50**, followed by treatment with TBAF gave a tetraol (**52**). After selective silylation of the primary hydroxyl, the resulting triol (**49**) could be converted into an acetonide (**66**), as described on page 141. However, epoxidation [t-BuOOH/$VO(acac)_2$] of the isomeric allylic silane (to which we tentatively assign structure **105**), followed by treatment with TBAF gave a tetraol that was different from **52**. However, we did not rigorously establish the structure of this new material; possibly, it could have the angular hydroxyl group [C(4a)] on the upper (β) face. If this is the case then epoxidation of our allylic silanes occurs on different faces of the substrate, depending on the stereochemistry of the C(6) silyl group.

31 *Cf.* Suginome, H.; Yamada, S. *J. Org. Chem.* **1984**, *49*, 3753. de Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem. Int. Edn. Engl.* **1992**, *31*, 772.

32 Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett*

1980, *21*, 1357. Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946. *Cf.* Nitz, T.J.; Paquette, L.A. *Tetrahedron Lett.* **1984**, *25*, 3047.

33 The C(4a) hydroxyl is probably *syn* to that at C(4).

34 Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.*, **1977**, *99*, 6066.

35 DeCamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564.

36 Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* **1987**, *28*, 6207.

37 Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. Okada, K.; Okamoto, K.; Oda, M. *J. Am. Chem. Soc.*, **1988**, *110*, 8736.

38 Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.

39 Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827.

40 Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

41 Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789.

42 Hanessian, S.; Bargiotti, A.; LaRue, M. *Tetrahedron Lett.* **1978**, 737.

43 Lipshutz, B. H.; Morey, M. C. *J. Org. Chem.* **1981**, *46*, 2419.

44 Yankee, E. W.; Axen, U.; Bundy, G. L. *J. Am. Chem. Soc.*,

1974, *96*, 5865. Cooper, E. L.; Yankee, E. W. *J. Am. Chem. Soc.*, **1974**, *96*, 5876.

45 Garlaschelli, L.; Mellerio, G.; Vidari, G. *Tetrahedron Lett.* **1989**, *30*, 597.

46 Larson, G.L; Hernandez, A. *J. Org. Chem.* **1973**, *38*, 3935.

47 Miller, T.C. J. Org. Chem. **1969**, *34*, 3829.

48 Evans, D. A.; Polniaszek, R. P. *Tetrahedron Lett.* **1986**. *27*, 5683.

49 Ferrier, R. J. *Methods Carbohydr. Chem.* **1972**, *VI*, 419.

50 Roush, W.R.; Grover, P.T. *Tetrahedron* **1992**, *48*, 1981.

51 Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206.

52 Morgans, D.J.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1981**, *103*, 462.

53 Terao, S.; Kato, K. *Synthesis* **1979**, 467. Scheidl, F. *Synthesis* **1982**, 728.

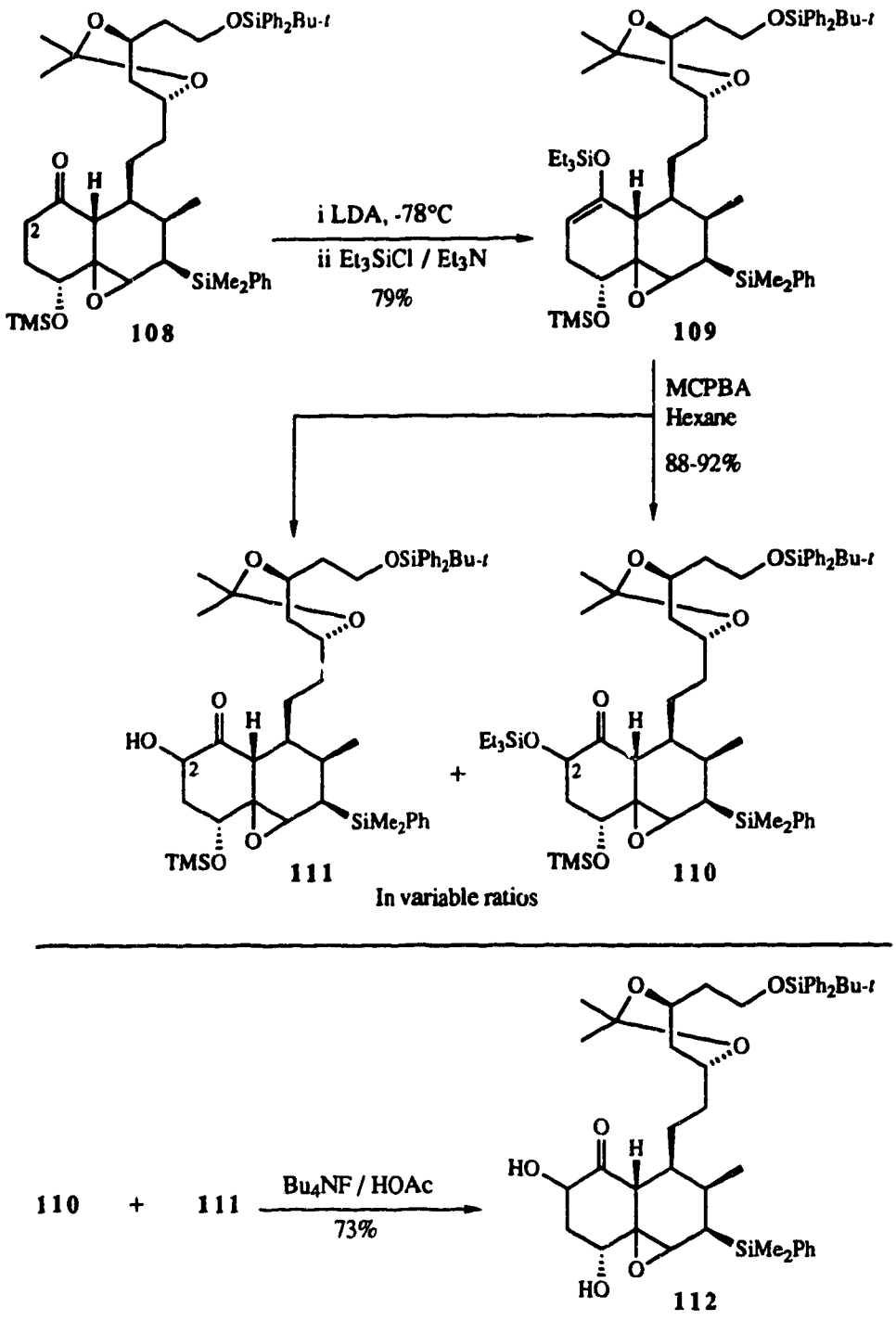
54 Pihlaja, K.; Lampi, A. *Acta Chem. Scand.* **1986**, *B 40*, 196.

55 Griffith, W.P.; Ley, S.V. *Aldrichimica Acta* **1990**, *23*, 13.

56 Epifanio, R. de A.; Camargo, W.; Pinto, A.C. *Tetrahedron* **1988**, *29*, 6403.

(loss of the trimethylsilyl group) than the corresponding mevinolin derivative, **91**, and should be processed rapidly. Oxidation of the C(1) hydroxyl, previously done with pyridinium chlorochromate, initially proved troublesome, but we quickly found that use of NMO and a catalytic amount of Pr_4NRuO_4[55] gave the required ketone **108** in almost quantitative yield.

From this point, our aim was to form the silyl enol ether **109** and to oxygenate it at C(2). The first of these two steps was tried by our original mevinolin procedure (see Scheme 61), which involved warming the reaction mixture to room temperature in order to ensure complete reaction.

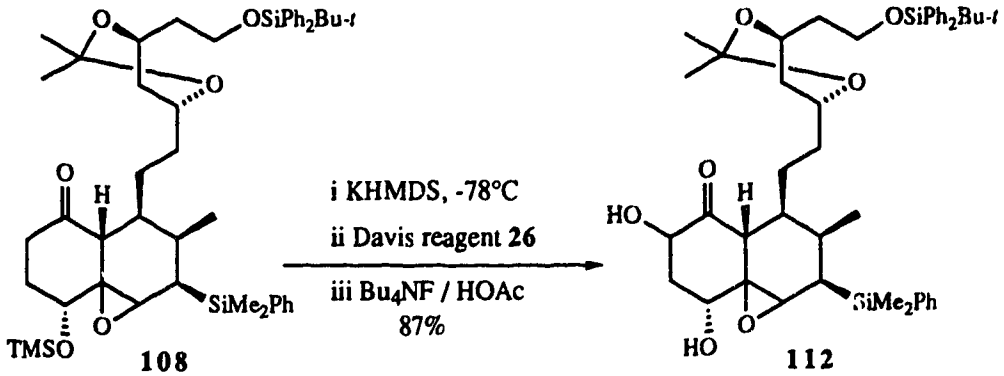


Scheme 61

However, in the present case this method led to decomposition of the desired compound (**109**) into an unidentified material.

We found it best to keep the reaction mixture at -78°C and to work it up after 25 minutes. Even at -78°C some decomposition of **109** takes place and it is necessary to monitor the progress of the reaction very closely. A little starting material (**108**) always remains but the yield is consistently *ca.* 80% on a 120-mg scale. We were not confident enough to try a large scale run and, fortunately, this problem could be bypassed, as described below. With some of the silyl enol ether **109** in hand we examined its response to *m*-chloroperbenzoic acid, and found that the two oxygenated products **110** and **111** are produced in a ratio that varies from run to run. In the mevinolin series the material corresponding to **110** was always by far the major product. The mixture of **110** and **111** could be partially desilylated (**110** + **111**→**112**; Scheme 61) in modest yield.

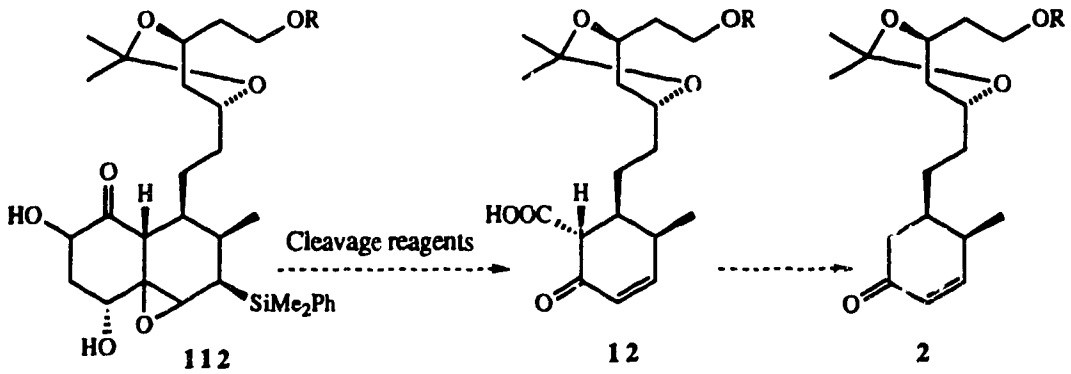
Mainly because of the difficulties in making the silyl enol ether **109** we sought an improved procedure and found it in the treatment of the potassium enolate of ketone **108** with with Davis' reagent **26** (Scheme 62).[23c] The initial product



Scheme 62

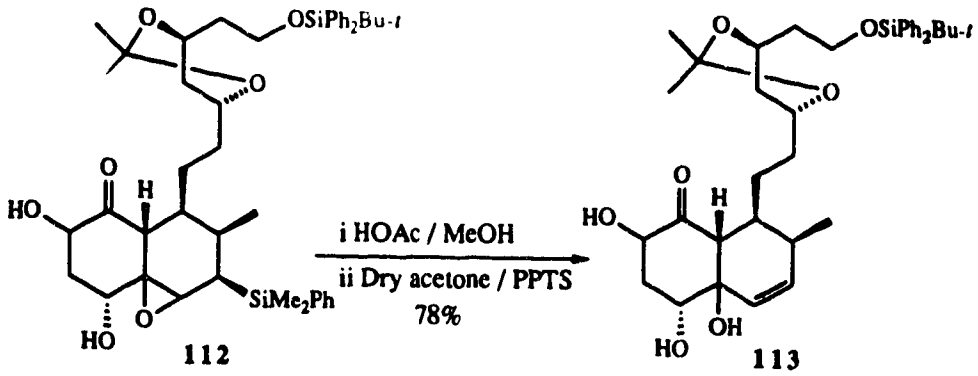
of this α-oxygenation was not easily separable from the components derived from Davis' reagent, but brief treatment with Bu_4NF in the presence of acetic acid served to give the diol **112**, which was easily separated and obtained in high yield.

We recognized that it would have been very convenient if **112** could be cleaved directly (*cf.* Scheme 63) to ketoacid **12**,



Scheme 63

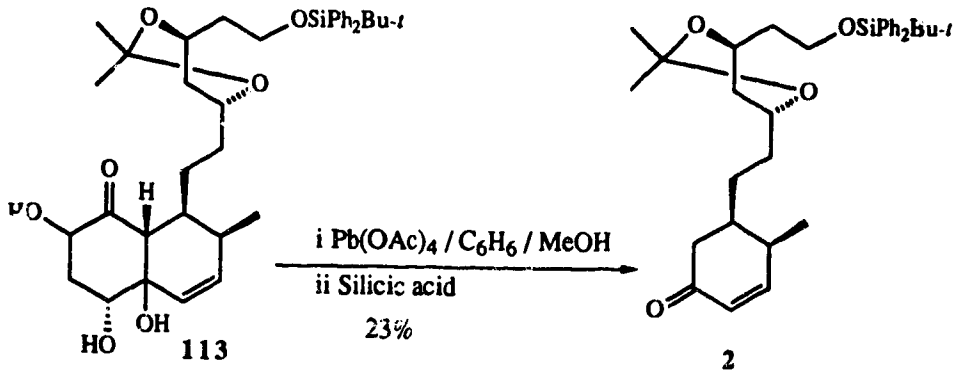
but attempts to do this with $Pb(OAc)_4$, $NaIO_4$, HIO_4, or Jones reagent[56] were unsuccessful; we obtained complex mixtures or observed no reaction (for $NaIO_4$). Consequently, the epoxide **112** was converted into the trihydroxy ketone **113** (see Scheme 64), using a slightly different method from that employed in



Scheme 64

the mevinolin series (*cf.* Scheme 52). The use of acetic acid-methanol[50] had been unsuccessful with mevinolin, but here the reagent worked well.

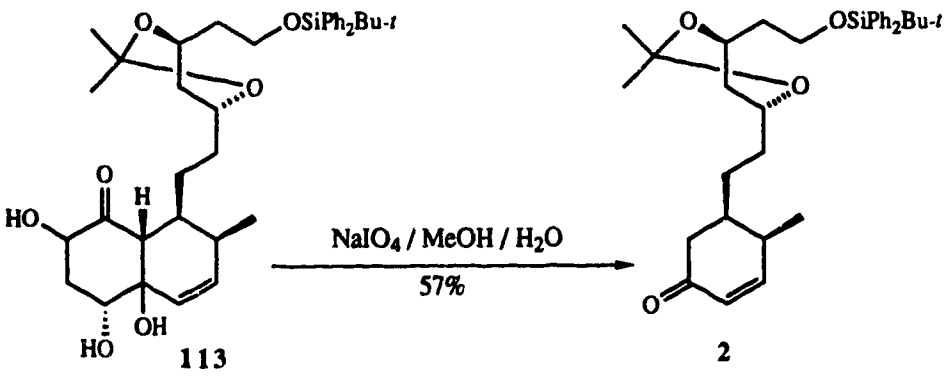
Treatment of the trihydroxy ketone **113** with Pb(OAc)$_4$ in PhH-MeOH, followed by exposure to silicic acid, gave the desired enone **2** in poor yield (Scheme 65), presumably by the same mechanism that operates in the mevinolin series (Schemes 55 and 56). If a small sample of the crude product from the



Scheme 65

Pb(OAc)$_4$ experiment is left on a silica TLC plate (Merck silica gel 60 F-254) for 2 hours and then recovered by

extraction with dichloromethane, the enone **2** is again formed after the dichloromethane solution has stood for *ca*. 12 hours. If the extract from the TLC plate is evaporated and refluxed for 2 hours in dioxane the enone is also obtained, but the reaction is less clean. However, we have found that trihydroxy ketone **113** can be degraded to the enone in one step by prolonged treatment (20-24 hours) with $NaIO_4$ in aqueous methanol — conditions that did not work in the mevinolin series (see Table 4). The enone was isolated in 57% yield (after chromatographic purification) from an experiment run on 320 mg of the starting hydroxy ketone (see Scheme 66). Our impression is that the $Pb(OAc)_4$ procedure

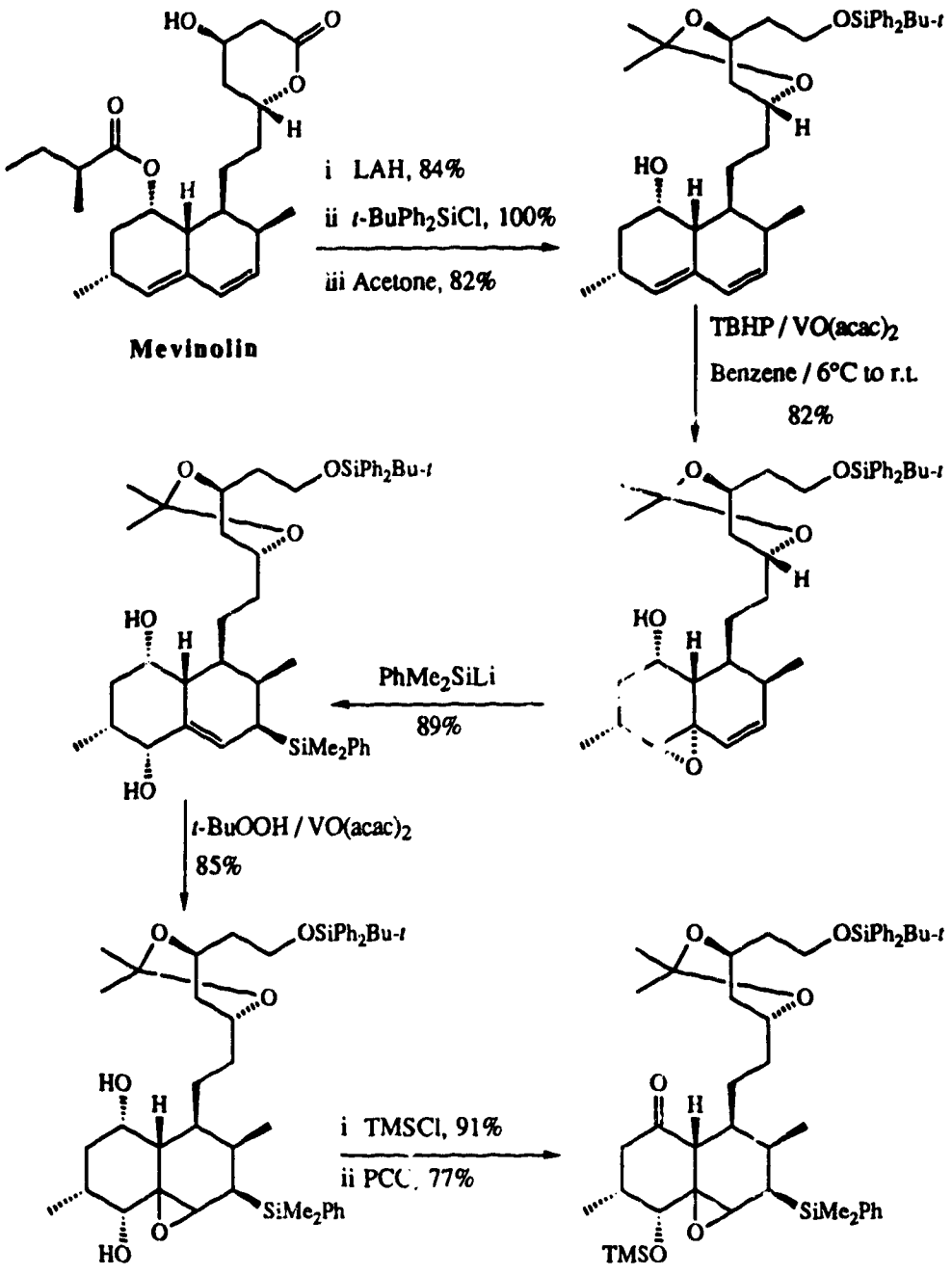


Scheme 66

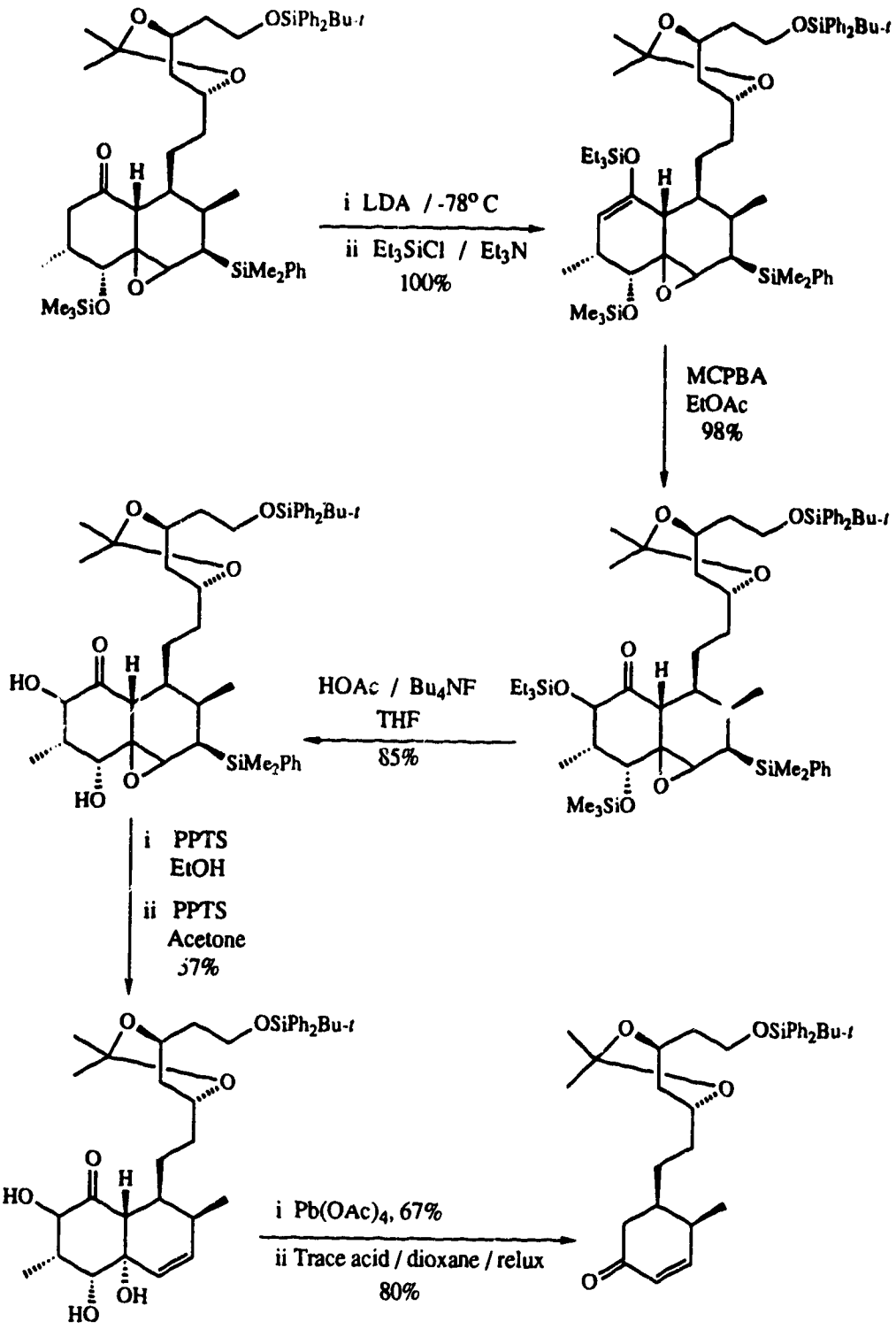
would give slightly purer product if a practical method could be found for hydrolysis of the first intermediate (*cf*. **98**, Scheme 55) to the ketoacid. The latter would spontaneously decarboxylate when stored in dichloromethane, judged by the observation cited above for the experiments with silica TLC plates.

Conclusion

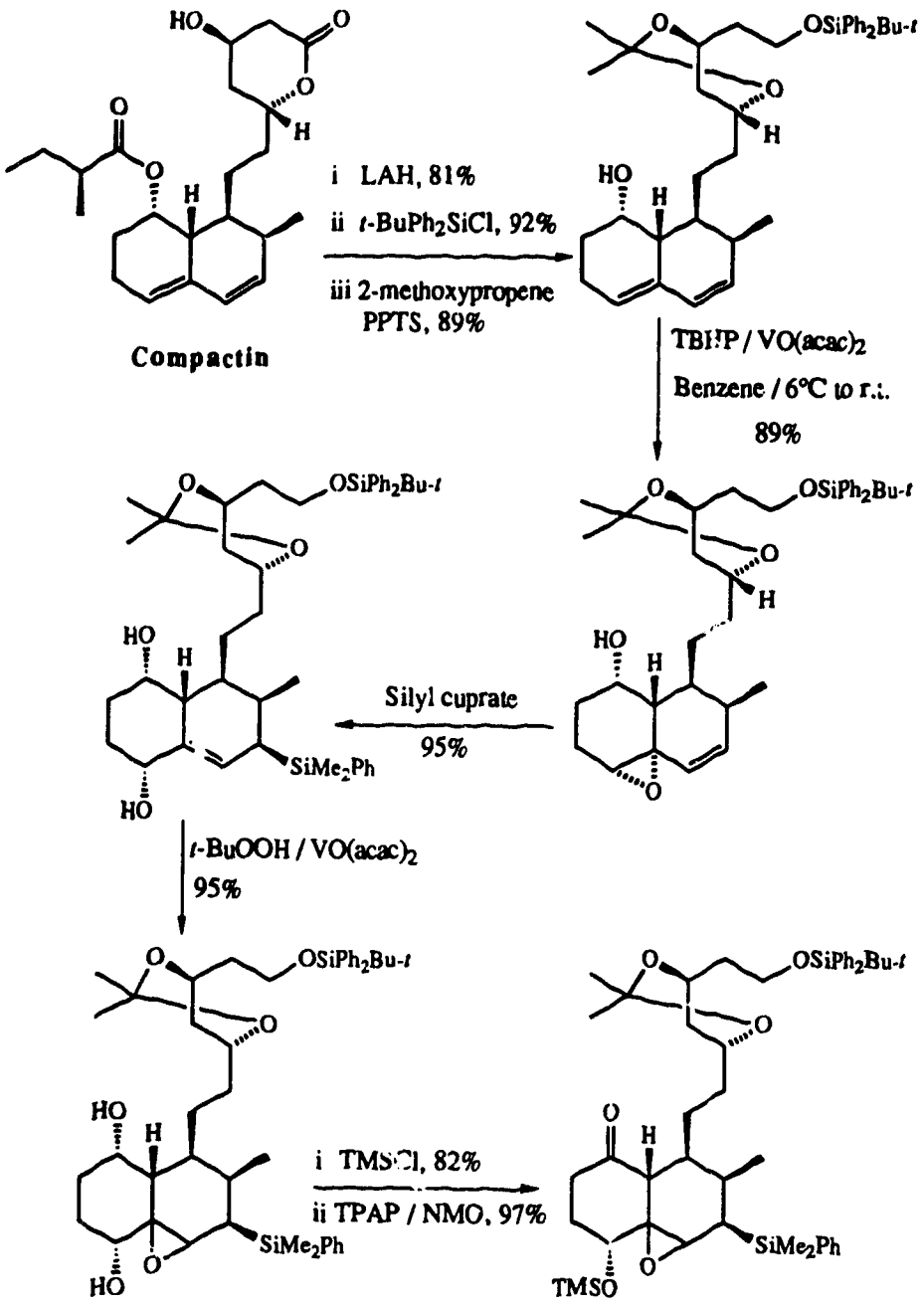
The procedure that had been developed for mevinolin can be applied with some modifications — that also shorten the route — to compactin, and the stage is now set to prepare semisynthetic analogues of the natural compounds. Our degradation of mevinolin (7 % over 14 steps) is summarized in Schemes 67 and 68 and the corresponding sequence for compactin (16.4% over 11 steps) is given by Schemes 69 and 70. It is of interest to note that the synthesis of enone **2** from *S*-malic acid required 22 steps and was accomplished in 0.52% overall yield.


Mevinolin
i LAH, 84%
ii t-BuPh2SiCl, 100%
iii Acetone, 82%
TBHP / VO(acac)2
Benzene / 6°C to r.t.
82%
PhMe2SiLi
89%
t-BuOOH / VO(acac)2
85%
i TMSCl, 91%
ii PCC, 77%
OSiPh2Bu-t
SiMe2Ph
TMSO

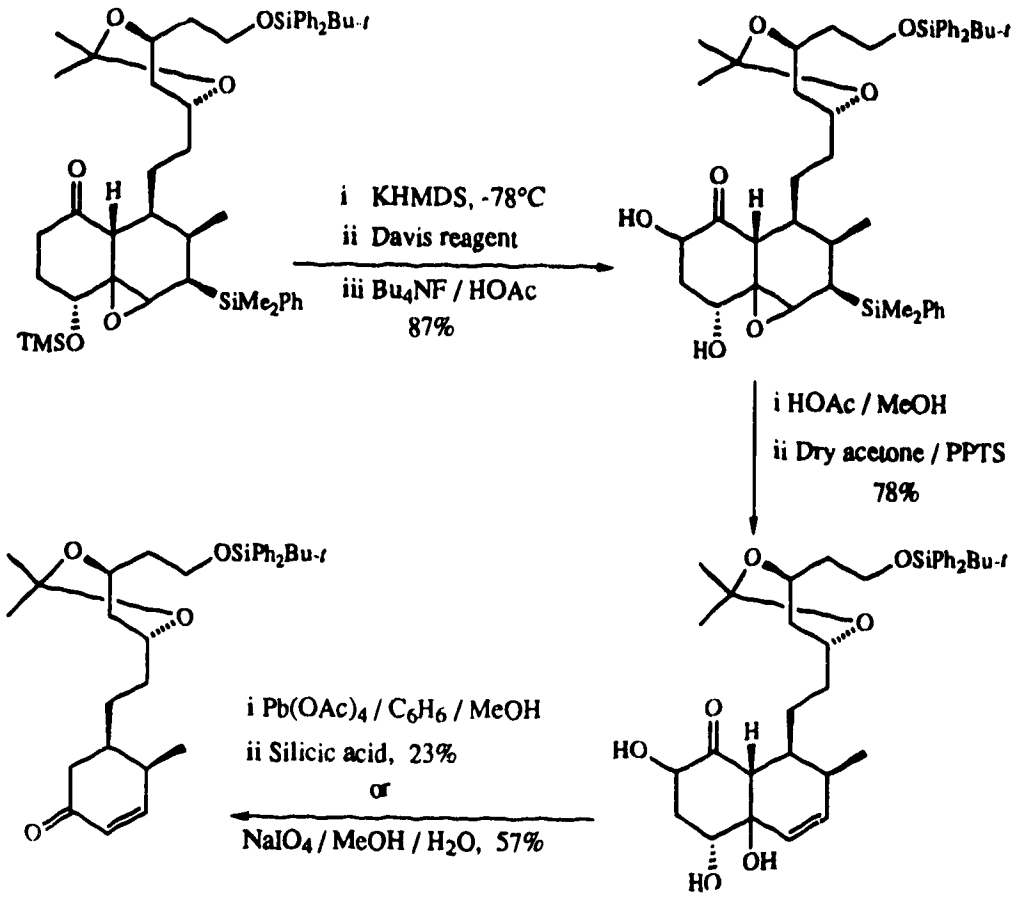
Scheme 67


OSiPh2Bu-t
SiMe2Ph
Me3SiO
i LDA / -78° C
ii Et3SiCl / Et3N
100%
Et3SiO
MCPBA
EtOAc
98%
HO
HOAc / Bu4NF
THF
85%
i PPTS
EtOH
ii PPTS
Acetone
57%
OH
i Pb(OAc)4, 67%
ii Trace acid / dioxane / relux
80%

Scheme 68


Compactin
i LAH, 81%
ii t-BuPh2SiCl, 92%
iii 2-methoxypropene PPTS, 89%
TBHP / VO(acac)2
Benzene / 6°C to r.t.
89%
Silyl cuprate
95%
t-BuOOH / VO(acac)2
95%
i TMSCl, 82%
ii TPAP / NMO, 97%
OSiPh2Bu-t
SiMe2Ph
TMSO

Scheme 69


OSiPh2Bu-t
SiMe2Ph
TMSO
i KHMDS, -78°C
ii Davis reagent
iii Bu4NF / HOAc
87%
HO
i HOAc / MeOH
ii Dry acetone / PPTS
78%
i Pb(OAc)4 / C6H6 / MeOH
ii Silicic acid, 23%
or
NaIO4 / MeOH / H2O, 57%
OH

Scheme 70

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Experimental

General

The same experimental techniques were used as described in the first part of this thesis. The following additional points apply:

Microliter syringes were dried under oil-pump vacuum overnight. Small quantities of moisture-sensitive reagents were dispensed from stock solutions of such strength that the required aliquots could be measured conveniently with a microliter syringe (e.g. 10-20 μL amounts). Viscous starting materials were stored as stock solutions in benzene (which were kept frozen when not in use); aliquots were dispensed as required by syringe. Samples for combustion analysis, whether recrystallized or directly from flash chromatography (by simple evaporation of the solvent), were stored overnight under diffusion pump vacuum before being analyzed. *All evaporations of solvents were done at or below room temperature.*