TOTAL SYNTHESIS OF OKADAIC ACID

A thesis presented

by

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Special thanks are expressed to all the members of our laboratory for their infailing friendships.

Abbreviations

AcOEt	ethyl acetate
AcOH	acetic acid
Al-Hg	aluminum amalgam
Bz	benzoyl
BF_3OEt_2	boron trifluoride etherate
Bn	benzyl
n-BuLi	n-buthyllithium
sec-BuLi	sec-butyllithium
tert-BuLi	tert-butyllithium
$n\text{-}Bu_4NF$	tetrabutylammonium fluoride
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CH_2N_2	diazomethane
CrO_3-2Py	Collins reagent
DIBAL	diisobutylaluminum hydride
DMF	N,N-dimetylformamide
DMSO	dimethyl sulfoxide
EE	ethoxy ethyl
Et_2AlCl	diethylaluminum chloride
Et_2O	diethyl ether
EtOH	ethanol
HCl	hydrochloric acid

KF	potassium fluoride
KOH	potassium hydroxide
LAH	lithium aluminum hydride
MCPBA	3-chloroperbenzoic acid
MeMgBr	methylmagnesium bromide
MeOH	methnol
N_2	nitrogen
$NaBH_4$	sodium borohydride
NaH	sodium hydride
sat.$NaHCO_3$	saturated aqueous sodium hydrogen carbonate solution
sat. Na_2SO_3	saturated aqueous sodium sulfite solution
sat. NH_4Cl	saturated aqueous ammonium chloride solution
Na_2SO_4	anhydrous sodium sulfate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PPTS	pyridinium p-toluenesulfonate
SO_3-Py	sulfur trioxide pyridine complex
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSBr	trimethylsilyl bromide

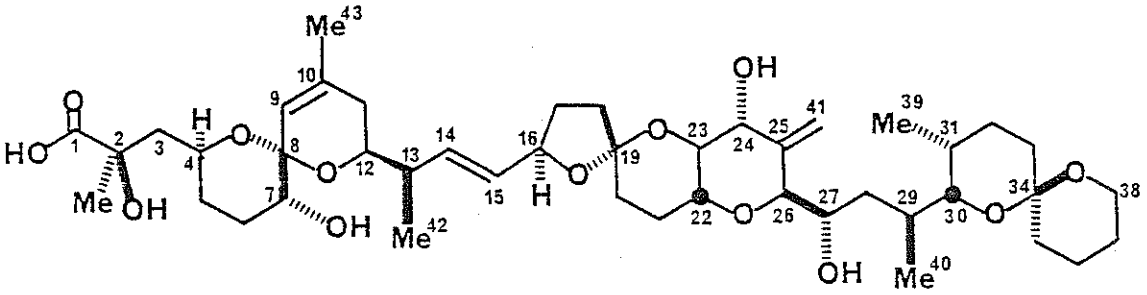
Index

CHAPTER I

Introduction

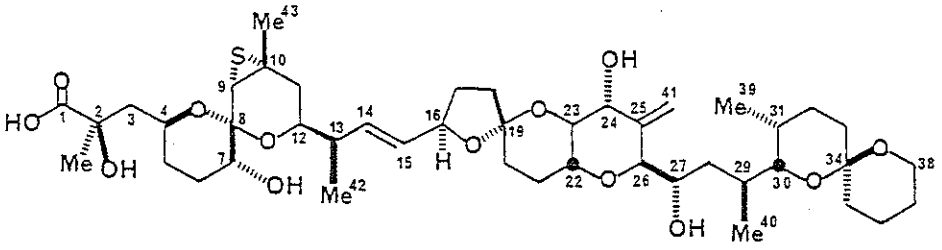
Okadaic acid was isolated from two kinds of sponges, Halicondria okadai, found along the Pacific coast of Japan, and Halicondria melanodocia, collected in Florida Keys.[1] Its structure was eluciated to be 1-1 as shown in Fig 1-1 by X-ray crystallographic analysis on the o-bromobenzyl ester. Okadaic acid was later identified as a major toxic component isolated from a benthic marine dinoflagellate Prorocentrum lima collected in French Polynesia.[2] A highly cytotoxic compound, acanthifolicin 1-2 was isolated from a sponge, Pandaros acanthifolium collected around the U. S. Virgin Islands.[3] X-Ray analysis of this compound revealed acanthifolicin 1-2 to be an 9S/10R episulfide of okadaic acid as shown in Fig 1-2.

Recently, okadaic acid 1-1 and dinophysistoxin-1 was identified with the diarrhetic shellfish poisoning. I would like to mention it briefly. A series of food poisonings resulting from eating mussels and scallops harvested in Tohoku district occurred in late June of both 1975 and 1977.[4] A total of 164 persons were officially documented to have suffered severe vomiting and diarrhea. Toxicity studies revealed the presence of an unknown fat-soluble toxin in the hepatopancreas of the shellfish. General aspects of the poisoning such as regionality in distribution of toxic shellfish and the periodic occurrence strongly suggest that this poisoning is associated with a toxic

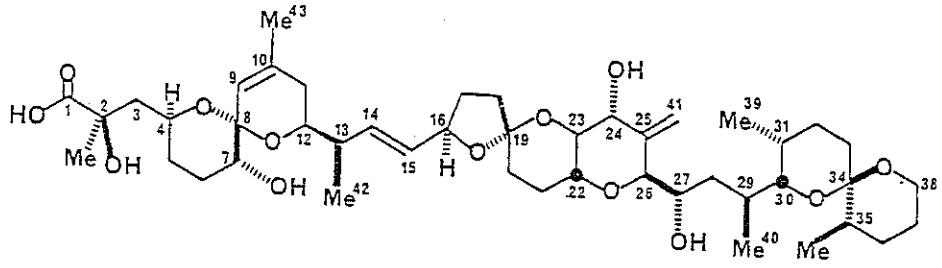


Okadaic Acid 1-1

Fig 1-1



Acanthifolicin 1-2



Dinophysistoxin-1 1-3

Fig 1-2

dietary plankton as in the case of paralytic shellfish poisoning.[5] A search was made for a plankton which transmit a fat-soluble toxin to shellfish and thus lead to a new type of shellfish poisoning. Dinoflagellate Dinophysis fortee was identified as the organism which would transmit the toxin to shellfish.[6] It was proposed to name the toxin dinophysistoxin and the poisoning diarrhetic shellfish poisoning. The major toxin involved in the diarrhetic shellfish poisoning was isolated from the hepatopancreas of the mussel Mytilus edulis and was named dinophysistoxin-1.[7] It was also established that Dinophysis fortii was the progenitor of this dinophysistoxin-1. Comparison of the toxin by various spectrometries with okadaic acid established that dinophysistoxin-1 1-3 is 35S-metyl okadaic acid as shown in Fig 1-2. In addition to this identified Dinophysis fortii, Dinophysis acumina was newly suggested as a source of toxins.[8] Toxic scallops or mussels were collected in April when Dinophysis fortii was scarce in the sea and Dinophysis acumina was present in the sea. And okadaic acid was isolated from the toxic scallops or mussels, so that this result strongly suggests the implication of okadaic acid in diarrhetic shellfish poisoning.

We became interested in the synthesis of this complex molecule, and started synthetic studies in 1982.

CHAPTER II

Synthetic Strategy of Okadaic Acid

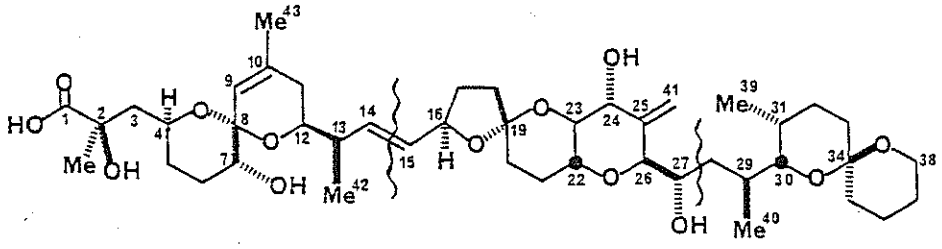
Okadaic acid 1-1 is a polyether carboxylic acid which contains 38 carbon atoms backbone, 17 asymmetric centers, 4 hydroxy groups, 6 methyl groups and three olefins. Among reported polyethers,[9] okadaic acid 1-1 has a unique structures. For example, it has two spiro fused six memberd ketal ring systems and a trans fused tetrahydropyran rings which containes spiro fused ketal ring system with tetrahydrofuran ring.

Synthetic analysis of okadaic acid lead us to the following synthetic strategies.

1) Three asymmetric centers of the spiro ketal moiety at C8, C19 and C34 should be derived from the corresponding keto-diol under a thermodynamically controlled condition (anomeric effect).[10]

2) Pyranose sugar is to be chosen as starting materials for the construction of the tetrahydropyran ring system in an optically active form.

3) On its acyclic part of okadaic acid molecule are there 4 asymmetric centers which should collect special attentions for designing the synthesis of okadaic acid. Asymmetric centers at C2, C13, C27 and C29 on the acyclic part are to be induced from the asymmetric carbons at C4, C12, C26 and C30 on the pyranose ring system, respectively. This is a character of our carbohydrate based synthesis, thus asymmetric centers on the



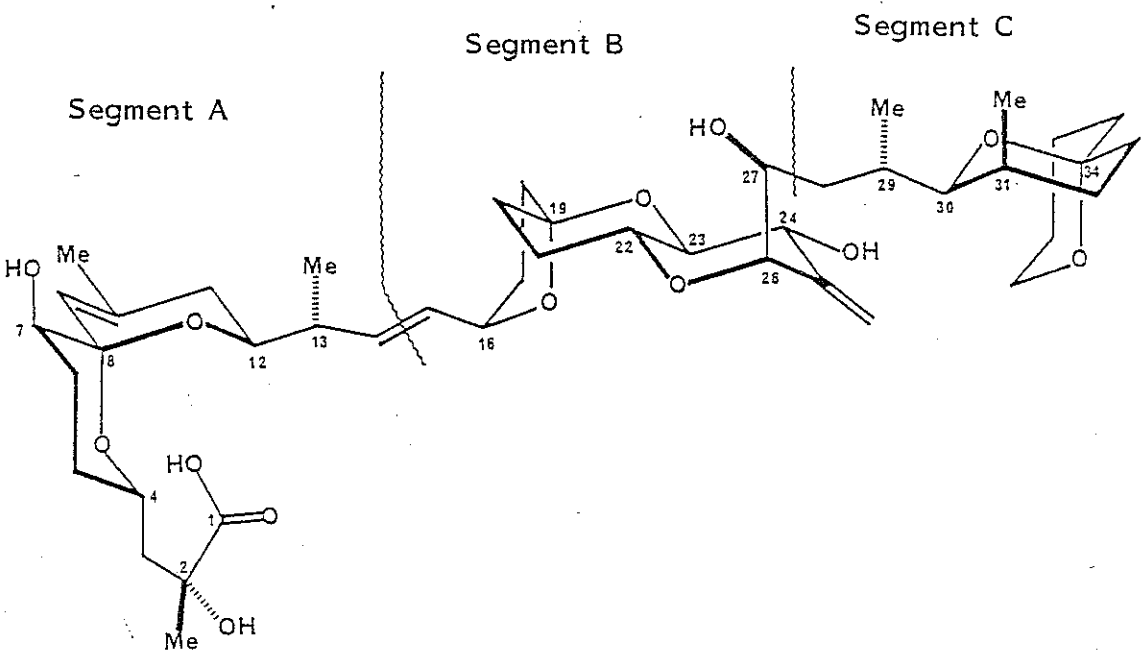


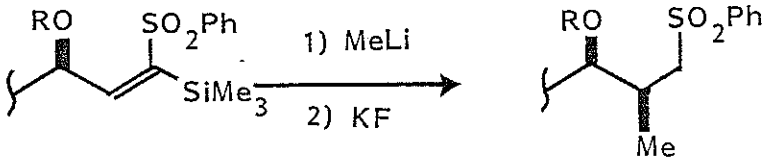
Fig 2-1

acyclic side chain are to be diastereomerically induced from the asymmetric centers on the carbohydrarte ring system.[11] If we apply heteroconjugate addition methodology to the synthesis of okadaic acid, stereocontrol of the asymmetric center bearing methyl group at the C29 position would be achieved by syn-selective heteroconjugate addition as shown in Scheme 2-1.[12] Stereocontrol at C13, however, demands a new methodology, thus, anti-selective heteroconjugate addition.

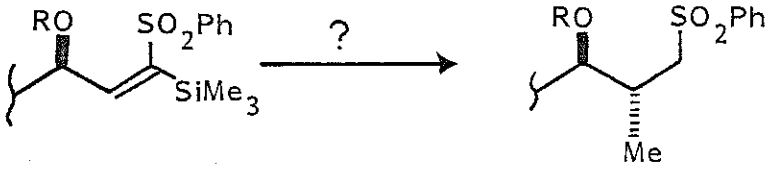
5) These considerations lead us to the disconnection of okadaic acid molecule at C14/15 and C27/28 carbon-carbon bond to result in three hypothetical segment A ,B, and C as illrstrated in Fig 2-1.

6) It was planned that segment A,B, C were synthesized in an opticaly active form and that they are coupled in the sequence C with B, and then with A. We choose the reaction of sulfone carbanion with aldehyde for the coupling reactions, since it is a very useful carbon carbon-bond formation reaction.[13] The basic plan is depicted in Scheme 2-2 involving; i) coupling of the segment B (aldehyde) 2-2 and segment C (sulfone) 2-3, ii) transformation of the product 2-4 to the alcohol 2-5 corresponding to C27, iii) preparation of the segment B/C (aldehyde) 2-7 and coupling with segment A (sulfone) 2-6, iv) conversion of the product 2-8 to the trans olefin 2-9 corre-

Heteroconjugate Addition

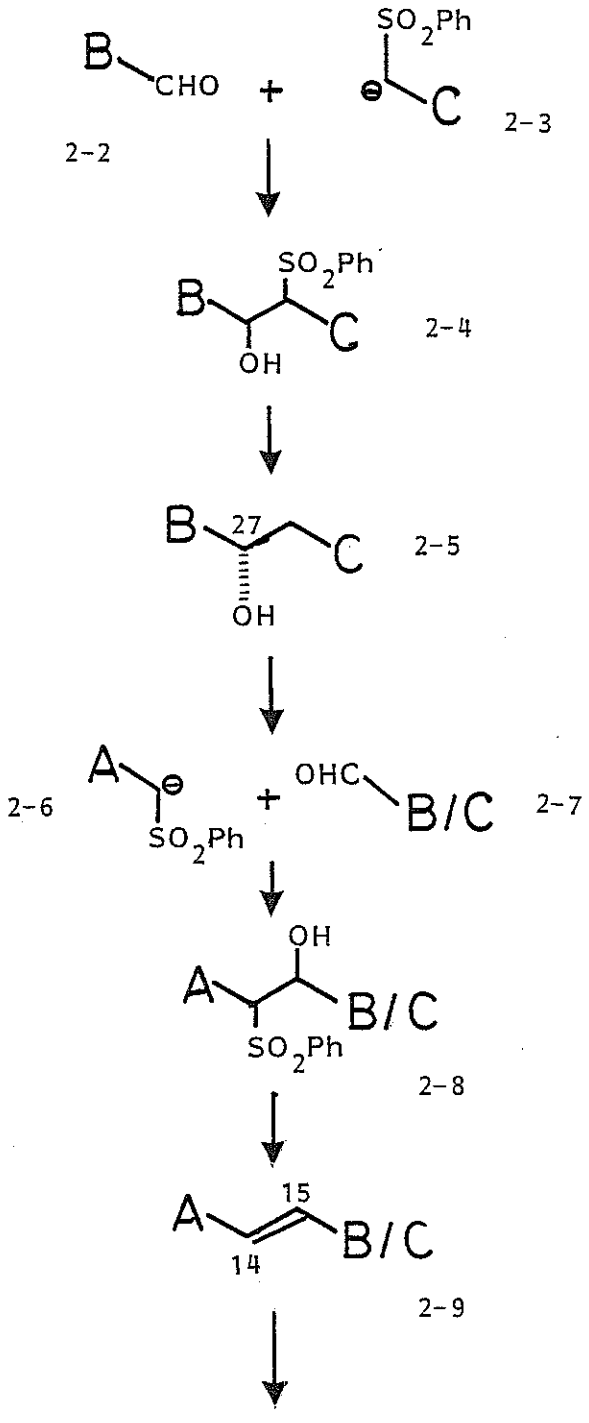


syn



anti

Scheme 2-1


B
CHO
+
SO2Ph
C
2-2
2-3
SO2Ph
B
C
OH
2-4
B
27
C
OH
2-5
2-6
A
SO2Ph
+
OHC
B/C
2-7
OH
A
B/C
SO2Ph
2-8
15
A
B/C
14
2-9
Okadaic acid

Scheme 2-2

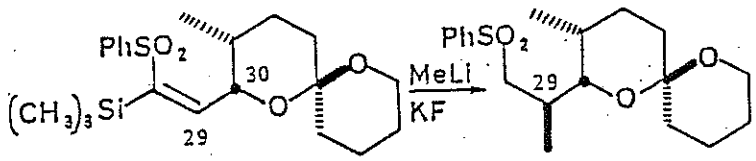
sponding to C16 and $C17^{14}$ and v) transformation of 2-9 to okadaic acid.

CHAPTER III

Synthesis of Segment C

SYNTHETIC PLAN OF SEGMENT C

The segment C has the carbon backbone comprising C28 through C38 which involves four asymmetric centers at C29, 30, 31 and 34 of okadaic acid. On the basis of the discussion in chapter II, these asymmetric centers would be controlled as follows; i) the asymmetric center of the spiro ketal moiety at C34 will be derived from the corresponding keto-diol under thermodynamically controlled condition due to the anomeric effect, ii) the asymmetric center at C30 and C31 would be derived from pyranose sugar and iii) crucial synthetic step is stereocontrol for the asymmetric carbon at C29 on the acyclic part. The metyl group on C29 will be induced by syn-selective heteroconjugate addition to the heteroolefin 3-1 as shown in Fig 3-1. The most stable conformation of the heteroolefin 3-1 could be expected that the bulky heteroolefin moiety of 3-1 will exist in the eclipsed form to the C30-H. And methyl lithium would rapidly locate near the oxygen atom by a chelation effect through a lithium cation, so that methyl lithium would attack the heteroolefin from only one face in which the oxygen exists. The product must be the desired syn-isomer 3-2.


PhSO2
(CH3)3Si
30
29
O
MeLi
KF
PhSO2
29
O
O

3-1 3-2

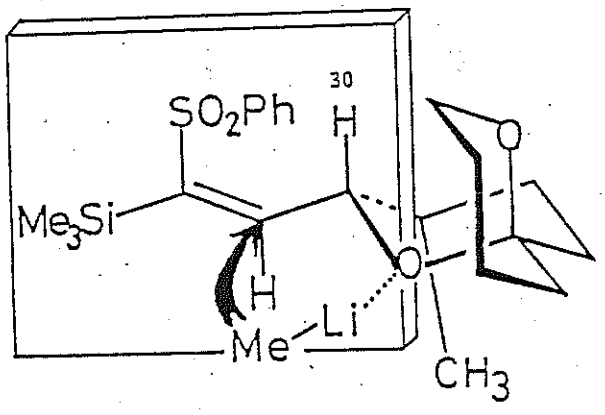

SO2Ph
30
H
Me3Si
O
H
Me
Li
CH3

Fig 3-1

SYNTHESIS OF SEGMENT C

We started the synthesis of segment C 3-2 from 2-acetoxy-D-glucal 3-3 to use its tetrahydropyrane ring for one of the rings in segment C (Scheme 3-1). O-Glycosidation of 3-3 with 2-propanol in the presence of boron trifluoride etherate at room temperature afforded the crystalline compound 3-4. Treatment of 3-4 with Me(CN)CuLi[15] in tetrahydrofuran directly gave the ketone 3-6.[16] This reaction mechanism may involve the following sequences; i) cleavage of the enol acetate ester of 3-4, ii) β-elimination of the acetoxy moiety to give the α,β-unsaturated ketone 3-5 and

iii) conjugate addition of Me(CN)CuLi in axial orientation to 3-5.

Attempts to reduce the tosylhydrazone of the ketone 3-6 under a variety of conditions including sodium borohydride,[17] lithium aluminum hydride[18] and catecholborane[19] were fruitless, thus, in each case, the reduced product was obtained only in low yield. Usual Wolff-Kishner reduction of the ketone 3-6 such as heating at 160°C with potassium hydroxide afforded a mixture of the vinyl ether 3-8 and the corresponding reduced product.[20] But we found that the reaction of the hydrazone 3-7 with methylsulfinyl carbanion ($NaCH_2SOCH_3$) in DMSO[21] proceeded quite

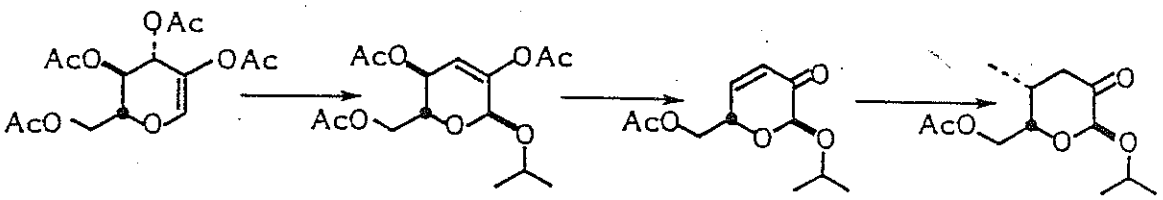
smoothly at room temperature to afford only the vinyl ether 3-8 in 74% yield.[22]

The hydroxy group in 3-8 was protected as its benzyl ether 3-9. The vinyl ether moiety in 3-9 was hydrolized with a mixture of 0.3N HCl/THF (1:5) at 55°C for 6 hr to give the lactol 3-10, which was subsequently oxidized with bromine[23] to afford the lactone 3-11 in 52% overall yield from 3-8. Alkylation of the lactone 3-11 with sulfone carbanion 3-12 in THF at -78°C produced the keto-sulfone 3-12 in 86% yield. Reduction of the keto-sulfone 3-13 with aluminum amalgum in aq. THF gave the ketone 3-14,[24] which was treated with pyridinium p-toluenesulfonate[25] in refluxing ethanol to afford the spiro compound 3-15 in 81% overall yield from 3-14. The stereochemistry of the spiro center of 3-15 was expected to be the same as that of okadaic acid due to the anomeric effect.[26] Hydrogenolysis of the benzyl group of 3-15 with H_2/palladium on carbon (10%) gave the alcohol 3-16, which was converted into the heteroolefin 3-1 as follows; i) Swern oxidation of the alcohol 3-16,[27] ii) condensation of the aldehyde 3-17 with bis-(trimethylsilyl)-thiophenylmethyllithium [$PhS(Me_3Si)_3CLi$] and iii) m-chloroperbenzoic acid oxidation of the vinyl sulfide 3-18 afforded the heteroolefin 3-1. The heteroolefin 3-1 was obtained in 56% overall yield from 3-16.

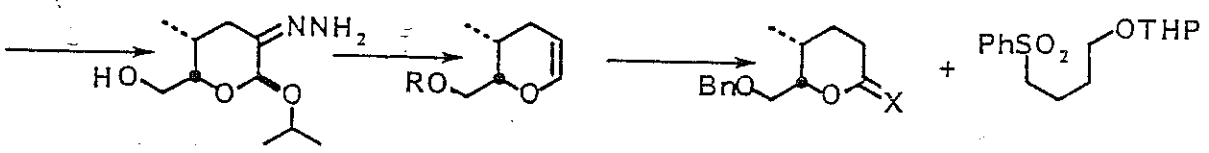
The heteroconjugate addition of methyl lithium to the spiro-

heteroolefin 3-1 gave the methyl adduct which was successively treated with potassium fluoride in methanol to yield the syn-adduct 3-2 in 89% yield. ^{1}H Nmr (200 MHz) analysis and HPLC analysis showed the absence of the anti-diastereoisomer at C29. There is an empirical rule that the ^{13}C nmr chemical shift of the induced methyl group appeares in a range between δ 13.4 and 15.7 ppm for syn-isomer and in a range between δ 16.7 and 17.4 ppm for anti-isomer.[28] The ^{13}C nmr chemical shift of the introduced methyl group of 3-2 appeared at δ 17.0 ppm. The stereochemistry of the induced methyl group in 3-1 should be syn-isomer on the basis of the reaction mechanism discussed above. However, the ^{13}C nmr chemical shift of the introduced methyl group in 3-1 is corresponding to that of anti-isomer. This may be attributed to the interaction with ring methyl group to cause the down field shift of its chemical shift. The stereochemistry of 3-2 was finally confirmed as syn-isomer by X-ray crystallographic analysis as shown in Fig 3-2.

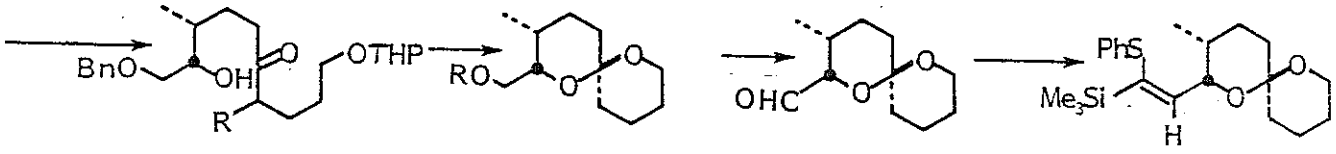
The segment C 3-2 for okadaic acid synthesis was achieved in 16 steps in 6.6% overall yield from 2-acetoxy-D-glucal 3-3.



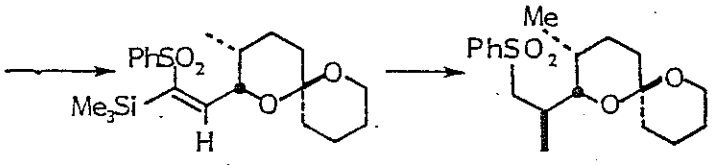
3-3 3-4 3-5 3-6



3-7 3-8; R= H
3-9; R= Bn
3-10; X= OH, H
3-11; X= O
3-12

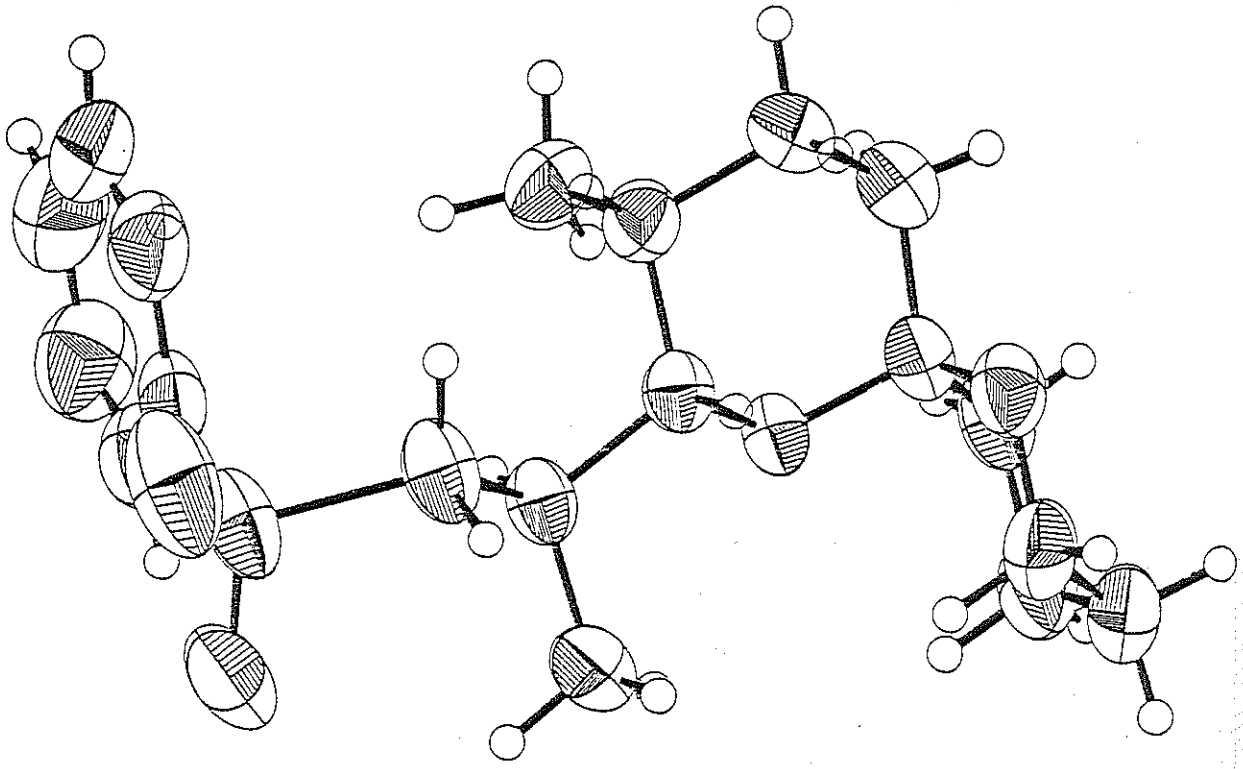


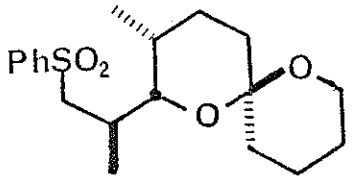
3-13; R= SO_2Ph
3-14; R= H
3-15; R= Bn
3-16; R= H
3-17 3-18



3-1 3-2

Scheme 3-1





Segment C

Fig 3-2

CHAPTER IV

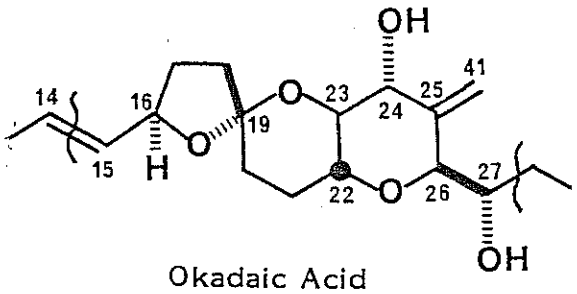
Synthesis of Segment B

SYNTHETIC PLAN OF SEGMENT B

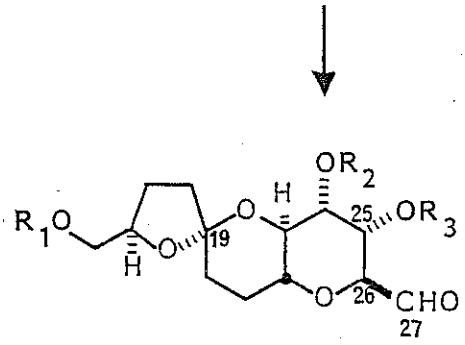
As was discussed in chpter II, the segment B in the okadaic acid synthesis should have a carbonyl center at C27 in order to receive the attack of a sulfone carbanion of segment C. Thus, an aldehydic carbonyl center can be a candidate as the electrophile at this center (see Scheme 4-1). A question arises that γ,δ-unsaturated aldehyde moiety would exist without isomerization into α,β-conjugare system or not. It will also lead us to another question when the exo-olefin at C25 position should be prepared ; namely, before or after this coupling process. We , therefore, determined that the C25-olefination should be carried out after the coupling reaction . Above retrosynthetic analysis concluded the aldehyde 4-1 as an equivalent of segment B.

The right hand pyranosyl ring in segment B contains five asymmetric centers. It is recognized as an equivalent to the C-glycosidation product 4-2 which will be prepared from a D-glucal derivative 4-3. Indeed, the synthesis of segment B was commenced from D-glucose 4-4.

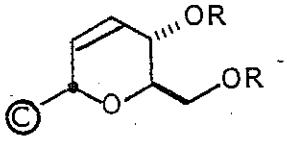
The stereochemistry of the spiroketal carbon at C19 is to be thermodynamically controlled from the corresponding keto-diol due to an anommeric effect as the case in segment C.



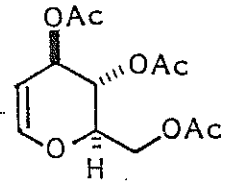
Okadaic Acid



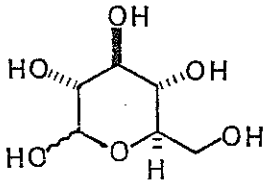
4-1



4-2



4-3



D-Glucose 4-4

Scheme 4-1

SYNTHESIS OF MODEL COMPOUND OF SEGMENT B

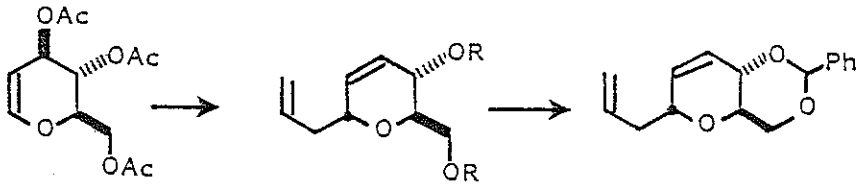
We started the synthesis of segment B from commercially available D-glucal triacetate 4-3 (Scheme 4-2). C-Glycosidation of D-glucal triacetate 4-3 with allyltrimemthylsilane and boron trifluoride etherate gave a mixture of 4-5 and its isomer in 16:1 ratio as an oil,[29] which was hydrolized with triethylamine and water to afford the diol 4-6 in 89% overall yield from 4-3. This mixture was separated in two steps, first by transformation into the benzylidine derivative 4-7, and secondaly by crystallization and re-crystallization in 80% yield. Selective hydroboraton of the terminal olefin of 4-7 with diborane gave the alcohol 4-8 which was protected as the benzoate 4-9. Its benzylidene group was selectively hydrolyzed with Dowex 50W (H^+) to give the diol 4-10 in 70% yield. The diol 4-10 was epoxidized with m-chloroperoxybenzoic acid in chloroform at $5^{\circ}C$ in stereoselective manner according to Henvest rule.[30] The product was again benzylidenated with benzaldehyde dimethylacetal in the presence of dl-camphorsulfonic acid to affrd 4-11. This benzylidene group played an important role to fix such conformation of the tetrahydropyran ring of 4-11 that renders the diaxial opening of the epoxide ring at C23 with alkoxide.

The benzoyl group was hydrolized with sodium methoxide to afford the alcohol 4-12 in 65% overall yield from 4-7. Swern oxidation of this alcohol 4-12 gave the aldehyde 4-13 which was converteed into the dimethyl acetal 4-14 with methyl orthoformate in the presence of pyridinium p-toluenesulfonate. The diaxial opening of the epoxide 4-14 with sodium benzyl alkoxide in N,N-dimethyl-formamide at 70°C gave the corresponding alcohol 4-15, which was protected as methoxymethyl (MOM) ether 4-16 in 51% overall yield from 4-12. The dimethyl acetal 4-16 was selectively hydrolized in a mixture of 0.5N HCl-THF (2:7) at room temperature to afford the aldehyde 4-17 in 98% yield.

A model compound 4-27 of segment B involving C16 through C27 was prepared as follows (Scheme 4-3). The three carbon unit 4-18 was prepared from 3-chloro-propanol via i) tetrahydro-pyranylation with dihydropyran in the presence of pyridinium p-toluenesulfonate, ii) S_N2 displacement of the chloride with sodium benzene-sulfinate in the presence of sodium iodide in N, N-dimethylformamide as solvent.

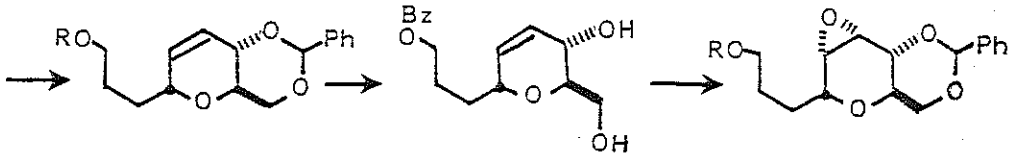
The sulfone stabilized carbanion of 4-18 was added to the aldehyde 4-17, and the adduct 4-19 was oxidized with pyridinium chlorochromate into the keto-sulfone 4-20.[31] It was reduced with aluminum amalgam in a mixture of tetrahydrofuran and water (10:1) at 70°C for 7.5 hr to afford the ketone 4-21. The tetrahydro-

pyranyl and benzylidene group of 4-21 was hydrolized in a refluxing mixture of methanol and acetic acid (4:1) to afford the triol 4-22 in 85% overall yield from 4-17. A solution of this product 4-22 was dissolved in methanol containing 5% acetic acid, and it was stirred under hydrogen atmosphere in the presence of palladium on carbon (25%) to afford the tricyclic compound 4-23. It was converted into 4-23 through protection-deprotection and oxidation procedure involving i) selective protection of the primary hydroxy group of 4-23 with t-butyldiphenylchlorosilane (70% overall yield from 4-23),[32] ii) benzylation of the secondary hydroxy group of 4-24 in 81% yield, iii) desilylation of 4-25 with tetra-n-butylammonium fluoride in tetrahydrofuran gave the alcohol 4-26 (quantitatively),[33] and iv) Swern Oxidation of 4-26 afforded the aldehyde 4-27 in 94% yield (Scheme 4-3).



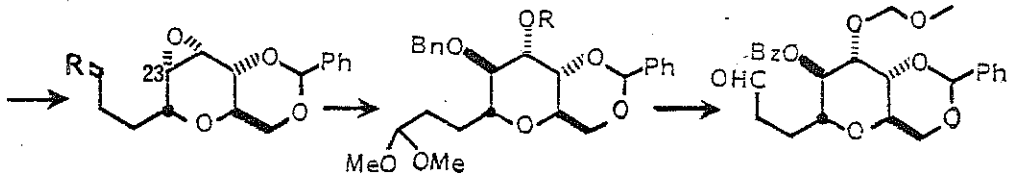
4-3 4-5; R= Ac 4-7

4-6; R= H



4-8; R= H 4-10 4-11; R= Bz

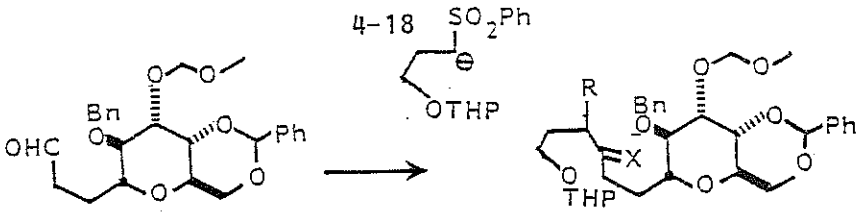
4-9; R= Bz 4-12; R= H



4-13; R= O 4-15; R= H 4-17

4-14; R= $(OMe)_2$ 4-16; R= MOM

Scheme 4-2

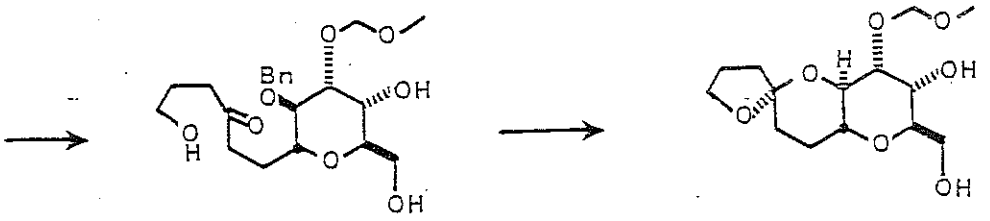


4-17

4-19; R= SO_2Ph, X= H, OH

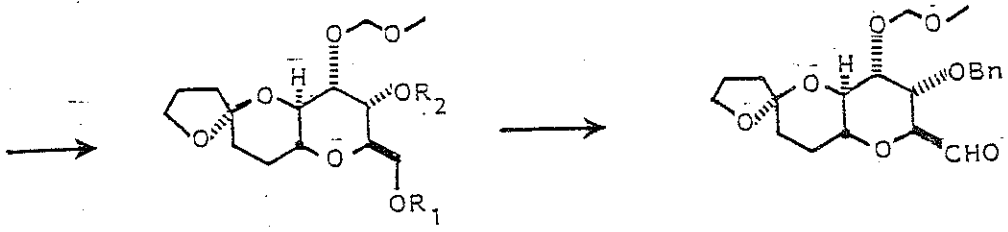
4-20; R= SO_2Ph, X= O

4-21; R= H, X= O



4-22

4-23



4-24; R_1= $^tBuPh_2Si$, R_2= H

4-25; R_1= $^tBuPh_2Si$, R_2= Bn

4-26; R_1= H, R_2= Bn

4-27

Scheme 4-3

SYNTHESIS OF SEGMENT B

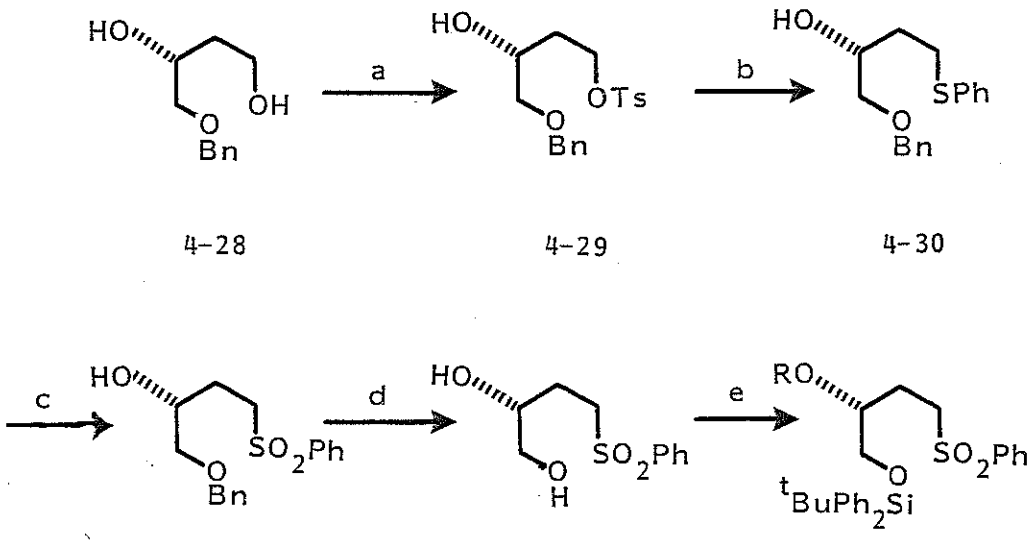
In addition to the model system 4-27, the real segment B system involving C15 through C27 requires an additional fragment carbon at C15 with one asymmetric center at C16. Therefore, it is necessary to synthesis a sulfone which has correct asymmetric center at C15 and the five carbon fragment of C15 through C18. Such a sulfone was prepared from R-butane-1,2,4-triol derivative 4-28 as shown in Scheme 4-4.[34] The diol 4-28 was converted into R-1-(benzene-sulonyl)-butane-3,4-diol 4-32 via the following sequence; i) mono-tosylation of the primary hydoxy group of 4-28, ii) S_N2 displacement of the tosylate 4-29 with sodium thiophenoxide, iii) m-chloroperbenzoic acid oxidation of the sulfide 4-30 into the sulfone 4-31, and iv) hydrogenolysis of the benzyl group of 4-31 yielded the diol 4-32. Protection of the primary hydroxy group of 4-32 as tert-butyldiphenylsilyl ether was followed by another protection of the secondary hydroxy group of 4-33 as ethoxy ethyl ether to give the sulfone 4-34.

Segment B aldehyde 4-43 was synthesized from this sulfone 4-34 and aldehyde 4-17 as shown in Scheme 4-5. Addition of the sulfone carbanion 4-34 to the aldehyde 4-17 gave the adduct 4-35 in 86% yield, and it was oxidized by Swern oxidation into the keto-sulfone 4-37 which was reduced with aluminum amalgum into

the ketone 4-37 in 75% overall yield from 4-35. Tetrahydropyranyl and benzylidene group in 4-37 was hydrolized in a refluxing mixture of ethanol and acetic acid (25:2) to afford the triol 4-38 in 60% yield. Hydrogenolysis of the benzyl group of 4-38 with H_2/palladium on carbon (25%) in a mixture of ethanol and acetic acid afforded the tricyclic compound 4-39, which was succesively treated with trityl chloride to afford the trityl ether 4-40 in 79% overall yield from 4-38. Benzylation was followed by removal of trityl group with diethylaluminum chloride to give the alcohol 4-42 in 83% overall yield from 4-40.[35]

Swern oxidation of the alcohol 4-42 provided the aldehyde 4-43 as segment B.

Synthesis of the segment B 4-43 was now accomplished in 22 steps (longest linear sequence) in 4.1% overall yield from tri-O-acetyl-D-glucal 4-3.

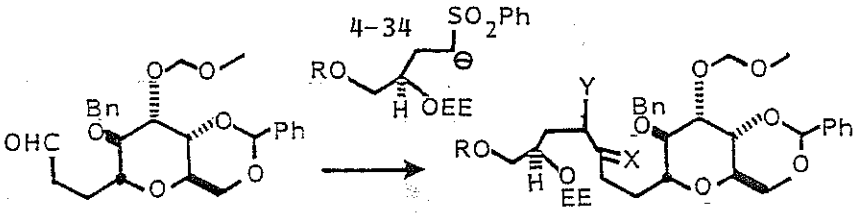


4-28 4-29 4-30

4-31 4-32 4-33, R= H
4-34, R= EE

a) TsCl/Py; b) PhSNa; c) MCPBA; d) H_2/Pd-C; e) $^tBuPh_2SiCl$, ethyl vinyl ether/PPTS

Schme 4-4

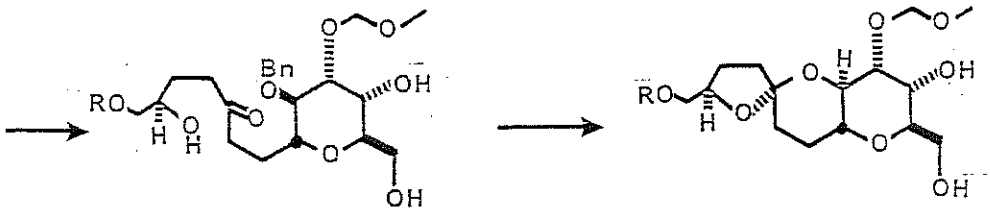


4-17

4-35; Y= SO_2Ph, X= H, OH

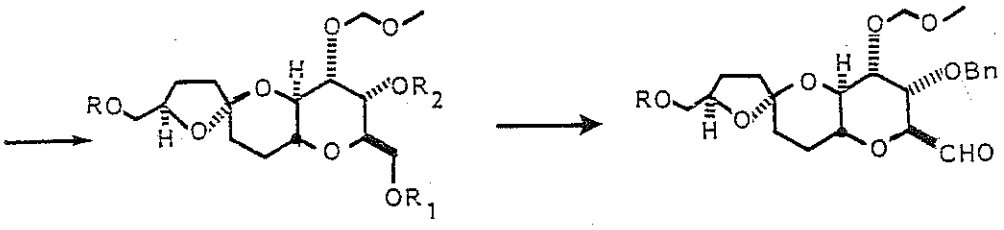
4-36; Y= SO_2Ph, X= O

4-37; Y= H, X= O



4-38

4-39



4-40; R_1= Tr, R_2= H

4-41; R_1= Tr, R_2= Bn

4-42; R_1= H, R_2= Bn

4-43

R= $^tBuPh_2Si$

Scheme 4-5

CHAPTER V

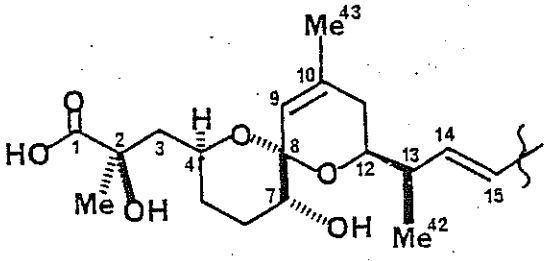
Synthesis of Segment A

SYNTHETIC PLAN OF SEGMENT A

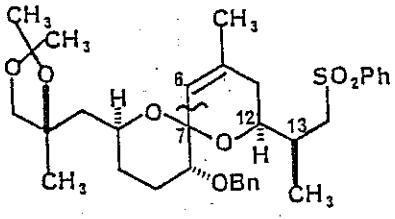
The segment A has the carbon backbone comprising C1 through C14 of okadaic acid, in which 6 asymmetric centers and Z-tri-substituted olefin exist. Retrosynthetic analysis of segment A 5-1 led us to the two components, segment A1 5-2 and segment A2 5-4 as shown in Scheme 5-1. Our basic plan for the synthesis of segment A is the coupling between aldehyde 5-2 (segment A1) and lithium acetylide derived from acetylene 5-4 (segment A2) followed by introduction of Z-tri-substitutured olefin moiety.

The segment A1 will be derived from the E-ally-alchol 5-3. The asymmetric center at C2 would be introduced from that at C4 via 1,3-asymmetric induction. The tri-substituted E-allyl-alcohol moiety in 5-3 seems to be the best choice for this asymmetric induction. Tetrahydropyran ring system of 5-3 will be derived from the common intermediate 3-4 prepared for the synthesis of segment C.

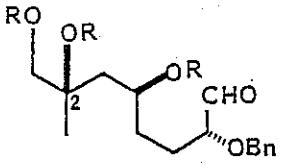
When we apply the methodology of heteroconjugate addition to the synthesis of segment A2 (5-4), we should develop new selectivity, anti-selective heteorconjugate addition, for the introduction of methyl group at C13.



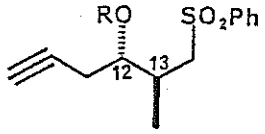
Okadaic Acid



Segment A 5-1

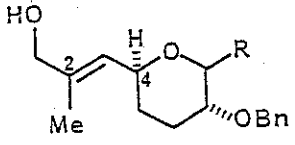


Segment A1 5-2

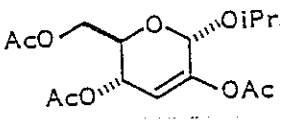


Segment A2 5-4

anti-selective heteroconjugate addition



5-3



3-4

Scheme 5-1

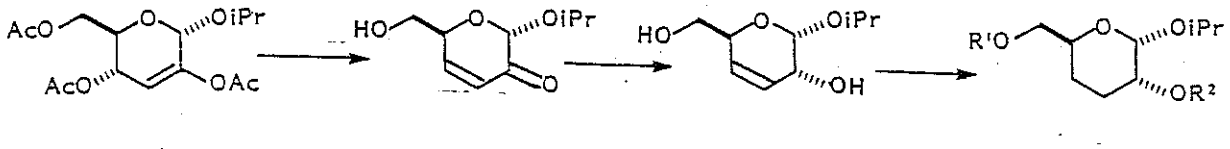
SYNTHESIS OF SEGMENT A1

We started the synthesis of segment A1 from the common intermediate 3-4 as shown in Scheme 5-2. Treatment of the enol acetate 3-4 with lithium aluminum hydride in tetrahydrofuran directly afforded the allyl-alcohol 5-6. The mechanism of this reaction is the same as that disussed in chapter III, which involves, i) cleavage of the enol acetate ester of 3-4, ii) production of the α,β-unsaturated ketone 5-5 and iii) lithium aluminum hydrdride reduction of the ketone 5-5 to afford the allyl-alcohol 5-6. The hydride attacked the ketone 5-5 from the less hindered side due to the steric repulsion to the isopropyl glycoside moiety affording the equatrial isomer 5-6. Hydrogenation of the allyl-alcohol 5-6 with H_2/palladium on carbon (10%) gave the diol 5-7, which was converted into 5-10 in 83% overall yield from 5-6 by the following sequences; i) protection of the primary hydroxy group with tert-butyldimetylsilyl chloride and imidazole, ii) benzylation of 5-8 with benzyl bromide and sodium hydride and iii) desilylation of 5-9 with tetra-n-butylammonium fluoride into 5-10. Swern oxidation of the alcohol 5-10 gave the aldehyde 5-11 which was successively treated with triphenyl-ethoxycarbonylethyl-phosphorane without isolation of the aldehyde 5-10 to afford the ester 5-12 in 83% yield.[36,37] The ester 5-12

was reduced with diisobutylaluminum hydride to afford E-allyl-alcohol 5-15.

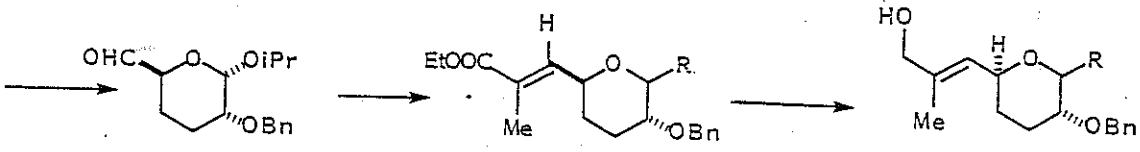
At this stage, we explored stereoselective introduction of a hydroxy group at C2, that is, the synthesis of the diol 5-18. We chose oxymercuration-demercuration procedure for the introduction of a hydroxy group at C2 position to this E-allyl-alcohol 5-15.[38] We envisioned that this reaction is regio- and stereospecific to provide the desired isomer 5-18 as shown in Fig 5-1. Oxymercuration reaction may proceed such a way, that is, i) olefin moiety of 5-15 should exist in the most stable conformation making the bulky E-trisubstituted olefin in the eclipsed form to the C4-H, ii) the mercuric ion come to a near position to this E-tri-substituted olefin by a chelation effect with the oxygen in the tetrahydropyran, iii) trans addition of water and mercuric ion to this olefin , and iv) demercuration with sodium borohydride should afford the desired diol 5-18. In fact, oxymercuration-demercuration of the E-tri-substituted olefin 5-15 with mercuric acetate in a mixture of tetrahydorfuran and water and then with sodium borohydride afforded the diol 5-18 stereospecifically in 86:14 ratio.

At this stage, we faced two problems. One was hydrolysis of isopropyl glycoside moiety and the other was determination of stereochemistry at C2. Hydrolysis of the isopropyl glycoside 5-



3-4 5-5 5-6

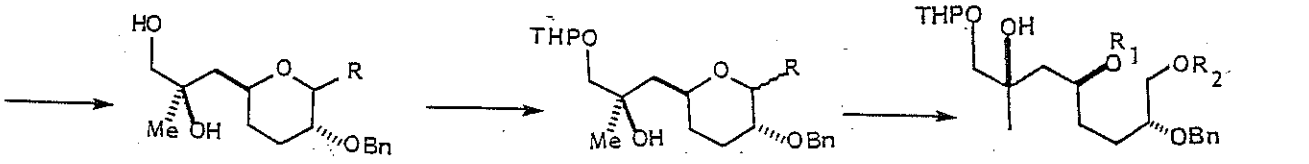
5-7; R_1= H, R_2= H
5-8; R_1= ^{t}BuMe$_2$Si, R_2= H
5-9; R_1= ^{t}BuMe$_2$Si, R_2= Bn
5-10; R1= H, R_2= Bn



5-11

5-12; R= ⋯OiPr
5-13; R= ⋯OCH$_2$CH$_2$Cl
5-14; R= —OCH$_2$CH$_2$Cl

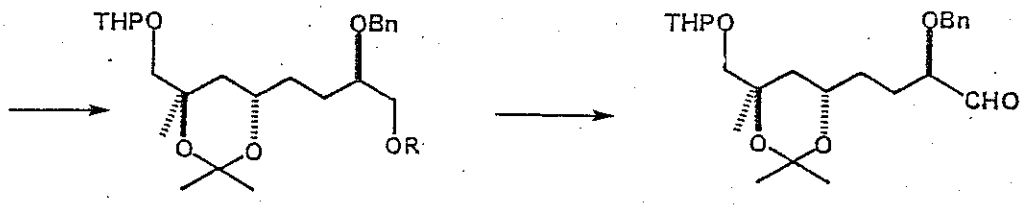
5-15; R= ⋯OiPr
5-16; R= ⋯OCH$_2$CH$_2$Cl
5-17; R= —OCH$_2$CH$_2$Cl



5-18; R= ⋯OiPr
5-19; R= ⋯OCH$_2$CH$_2$Cl
5-20; R= —OCH$_2$CH$_2$Cl

5-21; R= OCH$_2$CH$_2$Cl
5-22; R= OCH$_2$CH$_2$SO$_2$Ph
5-23; R= OH

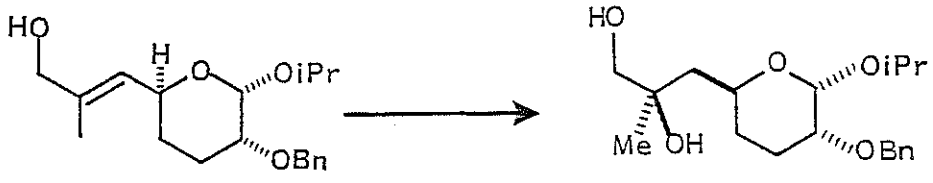
5-24; R_1= H, R_2= H
5-25; R_1= H, R_2= ^{t}BuMe$_2$Si



5-26; R= ^{t}BuMe$_2$Si
5-27; R= H

5-28

Scheme 5-2



5-15 5-18

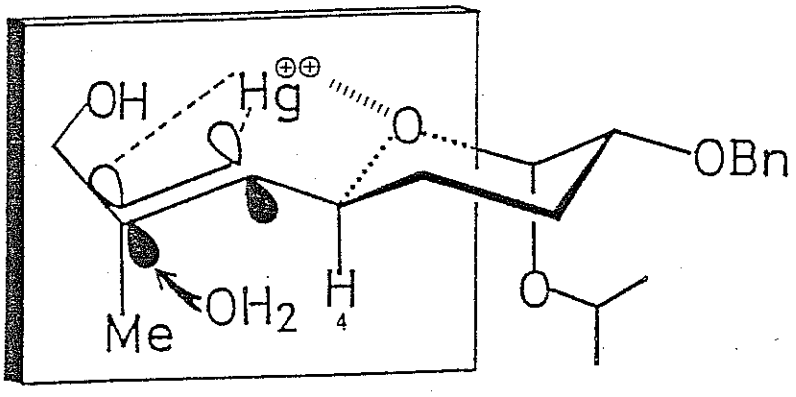


Fig 5-1

18 under aqueous acidic conditions proved to be difficult. This may be attributed to the presence of the acid labile moiety of tert-alcohol at C2. So, it is necessary to convert the isopropyl glycoside moiety to some glycosidic moiety which will be removed under a mild condition after oxymercuration step. This problem was solved by exchanging the isopropyl glycoside group for the chloroethyl glycoside group. This chloroethyl glycoside group can be removed under a basic condition.[39] Trans-glycosidation of 5-12 in 2-chloroethanol in the presence dl-camphorsulfonic acid gave a mixture of α- and β-chloroethyl glycoside 5-13 and 5-14 (55:45), which were reduced with diisobutylaluminum hydride to afford a mixture of E-allyl-alcohol 5-13 and 5-14 in 79% yield. A portion of this mixture was separated by HPLC, and each isomer, 5-16 and 5-17, was subjected to the oxymercuration-demercuration procedure. The corresponding diol 5-19 and 5-20 was obtained in 91% and 100% yield, respectively. The diastereoselectivity was found to be enough to use this reaction, that is, 88% and 91% diastereoselectivity to 5-19 and 5-20. Exchange of the glycosidic moiety did not cause the decrease in the selectivity of this oxymercuration reaction.

In order to confirm the stereochemistry at C2, we must prepare the authentic sample which has the known absolute configuration, and compare the authentic sample with the

derivative of this oxymercuration reacton product.

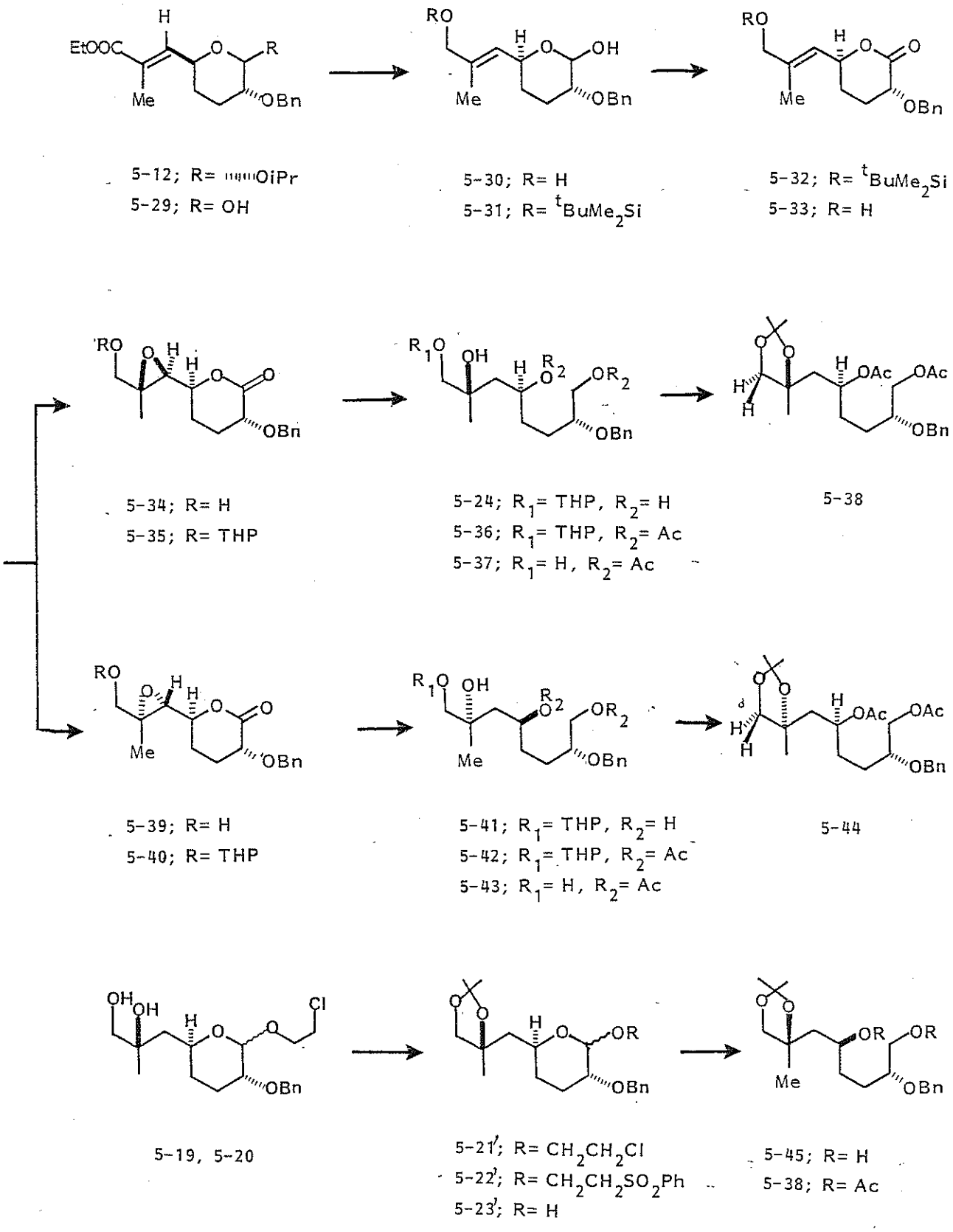
The authentic 2R-5-38 and 2S-compound 5-24 were prepared via 2,3-epoxides 5-34 and 5-39, respectively as shown in Scheme 5-3. Hydrolysis of the isopropyl glycoside 5-12 with acetic acid and water gave the lactol 5-29 which was reduced with diisobutyl-aluminum hydride to afford the allyl-alcohol 5-30. Protection of the alcohol 5-30 with tert-butyldimethylsilyl chloride followed by Swern oxidation afforded the lactone 5-32. Deprotection of the silyl group with tetra-n-butylammonium fluoride afforded the E-tri-substituted olefin 5-33. It was epoxidized under Sharpless asymmetric epoxidation using titanium(IV) isopropoxide [$Ti(Oi\text{-}Pr)_4$], L-(+)-diethyl tartrate and tert-butyl hydroperoxide to afford the β-epoxide 5-34 exclusively.[40] Tetrahydropyranylation of 5-34 with dihydropyran in the presence of pyridinium p-toluenesulfonate followed by lithium aluminum hydride reduction gave the triol 5-24. Acetylation of this triol 5-24 with acetic anhydride and pyridine gave the diacetate 5-36. Tetrahydropyranyl ether of 5-36 was hydrolized with pyridinium p-toluenesulfonate in methanol to afford the diol 5-37. Treatment of this diol 5-37 with 2,2-dimethoxypropane in the presence of pyridinium p-toluenesulfonate gave the 2R-compound 5-38.

Sharpless asymmetric epoxidation of 5-33 using D-(-)-diethyl tartrate afforded the α-epoxide (5-39) and β-epoxide (5-34) in

11:2 ratio. The low selectivity in the case of D-(-)-diethyl tartarate would be attributed to the preferred anti-periplanar attack to the syn-periplanar attack of the reagent to the olefin (Felkin-Nguen transition state model).[41] The α-epoxide 5-39 was converted into the 2S-compound 5-44 using the same procedure described above for the preparation of 2R-compound 5-38.

The oxymercuration product (a mixture of 5-19 and 5-20) was treated with 2,2-dimethoxypropane in the presence of pyridinium p-toluenesulfonate gave the acetonide 5-21'. The chloroethyl glycoside moiety of 5-21' was converted into the sulfonylethyl glycoside moiety with potassium iodide and benzene sulfinic acid sodium salt to afford 5-22'. Treatment of 5-22' with potassium carbonate gave the lactol 5-23', which was reduced with lithium aluminum hydride to give the diol 5-45. Acetylation of this diol 5-45 with acetic anhydride and pyridine gave the diacetate. The major component of this diacetate was identical to the 2R-compound 5-38. This result confirmed the stereochemistry of the oxymercuration product as to be expected one. Since three asymmetric centers of segment A1 were prepared, the oxymercuration product was converted into segment A1.

The primary alcohol of 5-19 and 5-20 (mixture) was protected with dihydropyrane in the presence of pyridinium p-toluene-sulfonate to afford the tetrahydropyranyl ether 5-21 (scheme 5-



5-12; R= OiPr
5-29; R= OH

5-30; R= H
5-31; R= $^{t}BuMe_2Si$

5-32; R= $^{t}BuMe_2Si$
5-33; R= H

5-34; R= H
5-35; R= THP

5-24; R_1= THP, R_2= H
5-36; R_1= THP, R_2= Ac
5-37; R_1= H, R_2= Ac

5-38

5-39; R= H
5-40; R= THP

5-41; R_1= THP, R_2= H
5-42; R_1= THP, R_2= Ac
5-43; R_1= H, R_2= Ac

5-44

5-19, 5-20

5-21; R= CH_2CH_2Cl
5-22; R= $CH_2CH_2SO_2Ph$
5-23; R= H

5-45; R= H
5-38; R= Ac

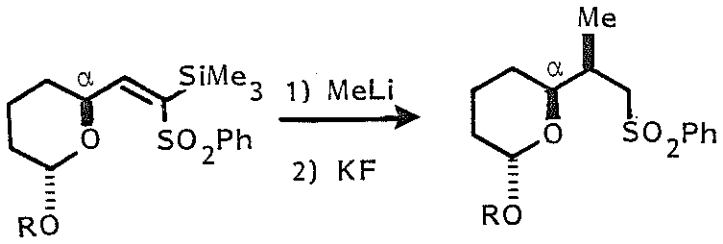
Scheme 5-3

2). Treatment of 5-21 with potassium iodide and benzenesulfinic acid sodium salt followed by sodium borohydride reduction gave the triol 5-24. Protection of the primary alcohol of 5-24 with tert-butyldimethylsilyl chloride followed by protection of the diol 5-25 with 2,2-dimethoxypropane gave the acetonide 5-26 in 47% overall yield from the diol (a mixture of 5-19 and 5-20). Removal of the silyl group of 5-26 with tetra-n-butylammonium fluoride followed by Swern oxidation provided the segment A1 aldehyde 5-28 in 72% overall yield from 5-26.

The segment A1 aldehyde 5-28 was synthesized in 16 steps in 17% overall yield from 3-4.

SYNTHESIS OF SEGMENT A2

The reaction of a heteroolefin such as 5-46 with methyllithium always provides the syn-isomer such as 5-47.[42] This selectivity can be explained by a transition state model as shown in Fig 5-2 which is the same as that disussed in chapter III in Fig 3-1. In this reaction, a chelation effect of the oxygen at α-position determines this selectivity. We envisioned that if we synthesized a heteroolefin 5-48 which has a substitute X at the β-position, we could achieve an anti-diastereoselectivity (Fig 5-3). When a substitute X has stronger chelation effect than that of the oxygen at α-position, methyllithium would attack the heteroolefin 5-48 from the side in which a substitute X exists as shown in Fig 5-3. Therefore, the product would be the anti-isomer 5-49. We envisioned that free hydroxy group has a stronger chelation effect than that of the oxygen on tetrahydropyran ring. In order to test this hypothesis, several kinds of heteroolefins with free hydroxy groups at β-positions were prepared from D-glucal 4-3. Funabashi et. al. reported that reaction of the β-hydroxy heteroolefin 5-50 with methyllithium gave the anti- and syn-isomer in 48:50 ratio.[43] Usually, such a heteroolefin with no hydroxy group at β-position always affords syn-isomer as major product. Therefore this selectivity suggests



5-46 syn 5-47

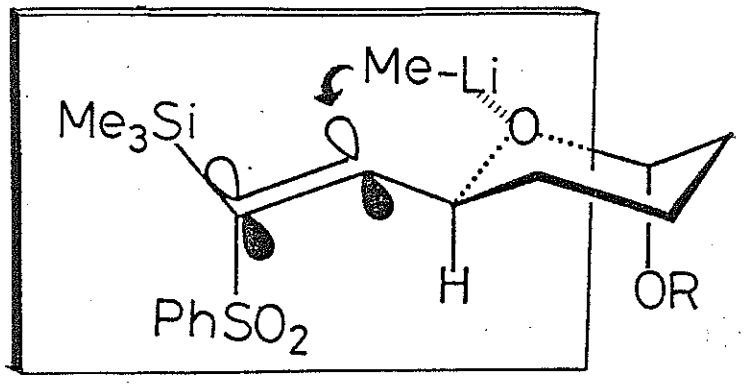
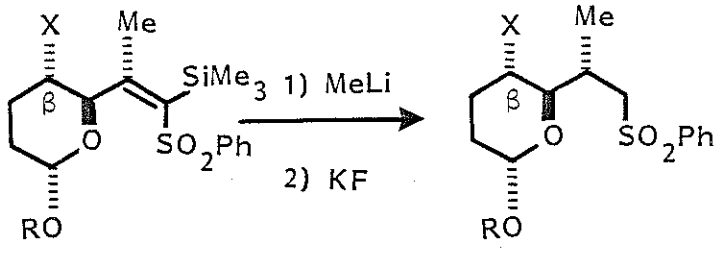


Fig 5-2



5-48 anti 5-49

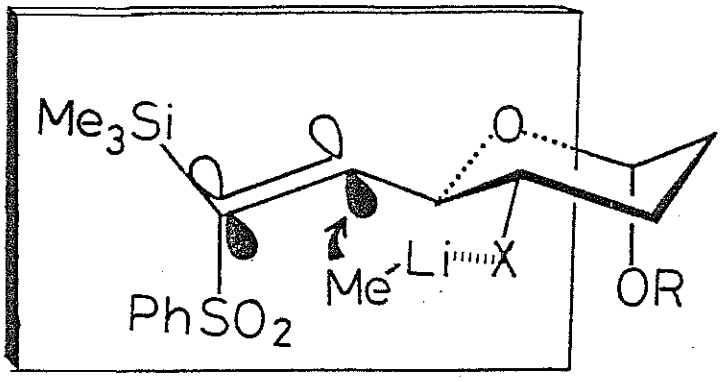
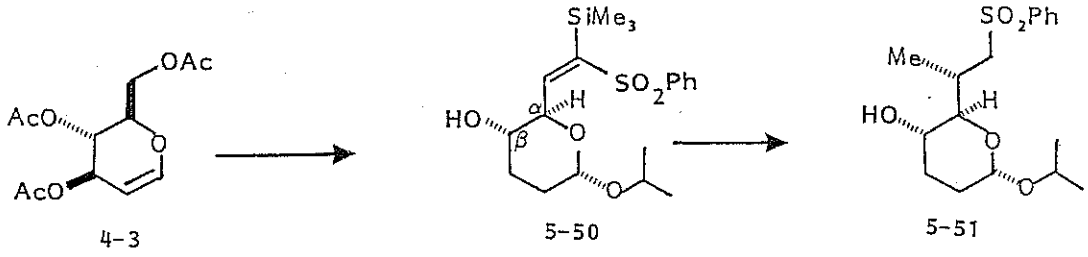
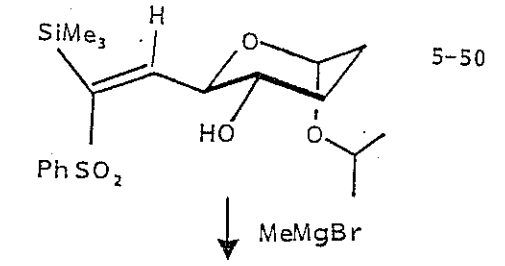
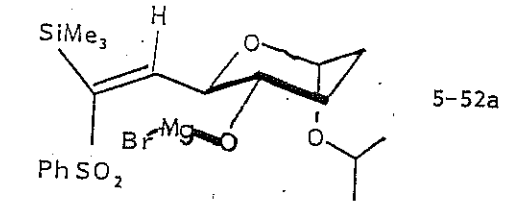


Fig 5-3

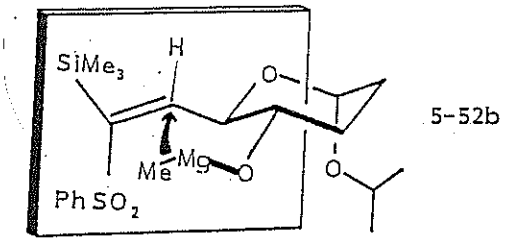




MeMgBr



- MeMgBr + MeMgBr



KF

anti-isomer 5-51

Fig 5-4 (Funabashi[43])

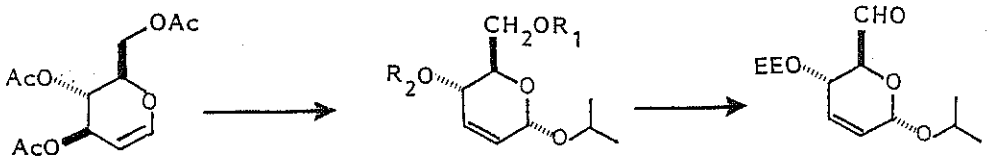
that β-chelation effect indeed exists. But this selectivity was not enough to use this heteroolefin 5-51 as a synthetic tool. Fortunately, an exchange of the nucleophile increased this selectivity. Heteroconjugate addition of methylmagnesium bromide to this heteroolefin 5-50 afforded the anti-isomer 5-51 as a major product in 95:5 ratio. Such a high selectivity by methylmagnesium bromide could be explained by the equilibrium as shown in Fig 5-4. Reaction of one equivalent of methylmagnesium bromide with the heteroolefin 5-50 gave the magnesium alkoxide 5-52a. Second equivalent of methylmagnesium bromide would cause equilibrium between 5-52a and 5-52b. And heteroconjugate addition would proceed intramolecularly through such a species as shown in 5-52b to give the anti-isomer 5-51. The reaction velocity of α-hydroxy heteroolefin with methylmagnesium bromide was reported to be very slow even at high temperature; for example, 23% yield at 18°C for 12 hr.[44] In the case of this β-hydroxy-heteroolefin 5-50 with methylmagnesium bromide, the reaction proceeds even at low temperature, that is, at -20°C for 2.4 hr. The difference of reactivity between α-oxy and β-hydroxy-heteroolefin would suggest such a mechanism and species discussed above.

We applied this methodology to the synthesis of segment A1 as shown in Scheme 5-4. O-Glycosidation of D-glucal 4-3 with 2-

propanol and boron trifluoride etherate gave the isopropyl glycoside 5-53. Acetyl group of 5-53 were hydrolized with triethylamine, water and methanol to afford the diol 5-54 in 81% yield. The diol 5-54 was converted into the alcohol 5-57 as follows; i) monobenzoylation with benzoyl chloride in pyridine, ii) protection of the allyl- alcohol 5-54 with ethyl vinyl ether,[45] and iii) removal of the benzoyl group of 5-56 with potassium hydroxide gave the alcohol 5-57 in 52% overall yield from 5-54. Swern oxidation of 5-57 followed by Peterson olefination of the aldehyde 5-58 gave the vinylsulfide 5-59 in 52% overall yield form 5-57. The vinylsulfide 5-59 was oxidized to the heteroolefin 5-60 with m-chloroperbenzoic acid in the presence of aq. sodium hydrogen carbonate solution. Careful hydrolysis of ethoxyethyl ether of 5-60 with pyridinium p-toluenesulfonate in a mixture of dichloromethane and 2-propanol afforded the β-hydroxy-heteroolefin 5-61. Heteroconjugate addition of methylmagnesium bromide to 5-61 followed by treatment with potassium fluoride afforded the anti-isomer 5-62 in high 91% selectivity. At this stage, it was difficult to separate the anti-isomer 5-62 from the corresponding syn-isomer in a multi-gram scale, purification procedure was avoided until the synthesis of 5-71. Acetylation of 5-62 with acetic anhydride and pyridine gave the acetate 5-63 in 63% overall yield from 5-59.

Hydrolysis of 5-63 in a mixture of acetic acid and water followed by pyridinium dichromate oxidation of the lactol 5-64 gave the lactone 5-65 in 63% overall yield from 5-63.[46] Reductive deconjugation of 5-65 with zinc-copper couple yielded the β-γ-unsaturated lactone 5-66 in 63% yield.[47] Ozonolysis of the olefin 5-66 followed by a work-up with sodium borohydride gave the diol 5-67. This diol 5-67 was successively treated with p-toluenesulfonyl chloride and triethylamine to afford a mixture of the tosylate 5-68 and the epoxide 5-69. Treatment of the tosylate 5-68 with potassium tert-butoxide gave the epoxide 5-69 in 40% overall yield from 5-66. The epoxide ring of 5-69 was opened with lithium trimethylsilyl acetylide in the presence of boron trifluoride etherate yielded the alcohol 5-70,[48] which was treated with tetra-n-butylammonium floride to afford the acetylene 5-71 in 95% overall yield from 5-69. Purification of this acetylene with HPLC followed by protection with ethyl vinyl ether gave the segment A2 (5-72).

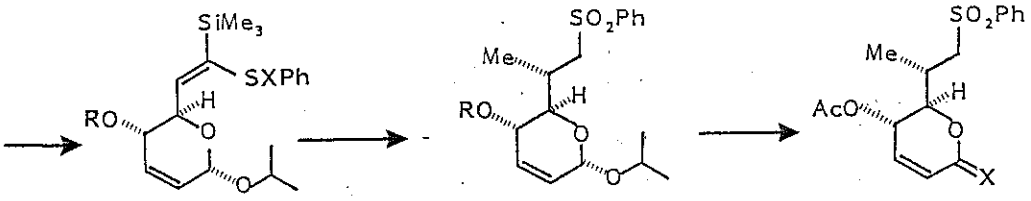
Segmetnt A2 (5-72) was synthesized in 20 steps in 2.1% overall yield from tri-O-acetyl-D-glucal 4-3.



4-3

5-53; R_1= R_2= Ac
5-54; R_1= R_2= H
5-55; R_1= Bz, R_2= H
5-56; R_1= Bz, R_2= EE
5-57; R_1= H, R_2= EE

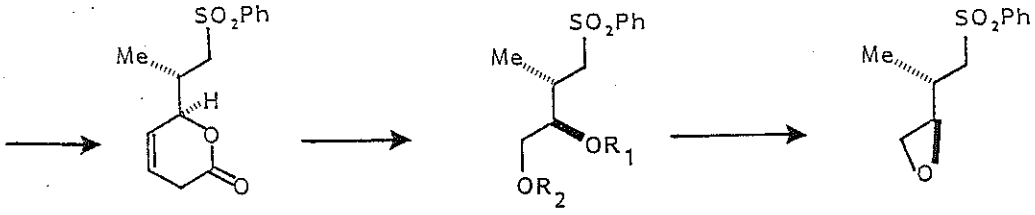
5-58



5-59; R= EE, X= none
5-60; R= EE, X= O_2
5-61; R= H, X= O_2

5-62; R= H
5-63; R= Ac

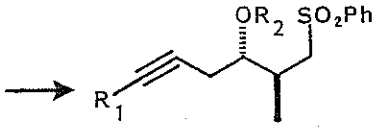
5-64; X= H, OH
5-65; X= O



5-66

5-67; R_1= R_2= H
5-68; R_1= H, R_2= Ts

5-69



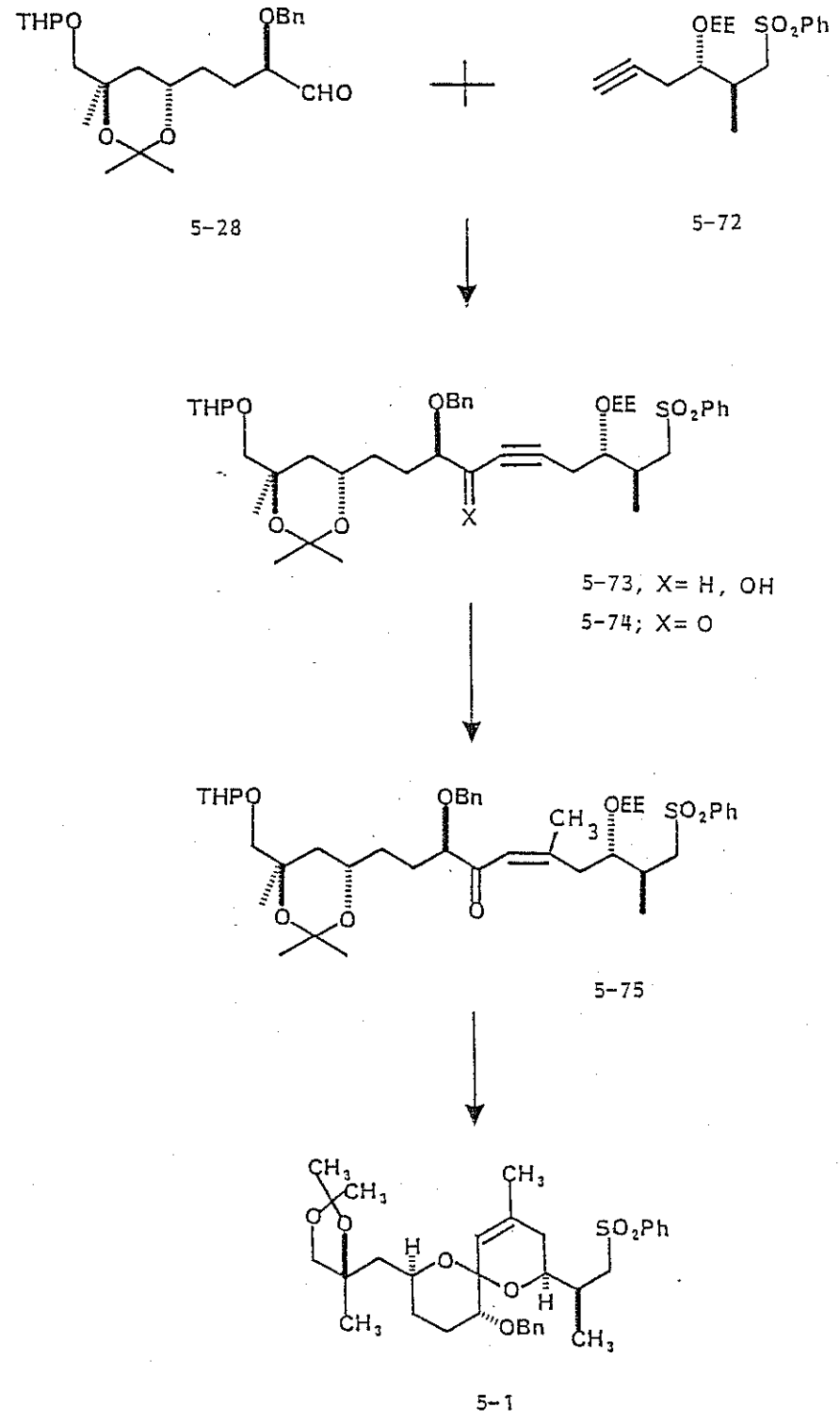
5-70; R_1= TMS, R_2= H
5-71; R_1= H, R_2= H
5-72; R_1= H, R_2= EE

Scheme 5-4

SYNTHESIS OF SEGMENT A

Treatment of the segment A2 (5-72) with 1 equivalent of n-butyllithium genarated the corresponding acetylide, which was reacted with segment A1 (5-28) to afford the coupling product 5-73 in 48% yield as shown in Scheme 5-5. Oxidation of 5-73 with active manganese(IV) oxide provided the acetylene-ketone 5-74 in 80% yield. Addition of lithium dimethyl cuprate (Me_2CuLi) to this acetylene ketone 5-74 in ether at -78°C afforded the Z-olefin 5-75 in 95% yield. The purity of this geometry could not be determined at this stage due to the presence of four possible diastereomixtures in both tetrahydropyranyl and ethoxy ethyl groups. However, additon of lithium dimethyl cuprate (Me_2CuLi) to such an acetylenic ketone or ester usually provides Z-olefin,[49] and this was confirmed previously by a model study of this reaction. Acidic spiroketalization with pyridinium p-toluenesulfonate in methanol, and acetonidation with 2,2-dimethoxypropane yielded the segment A (5-1) in 43% yield.

The synthesis of segment A was accomplished in 5 steps in 16% overall yield from segment A1 5-28.



Scheme 5-5

CHPATER VI

Coupling Reaction

COUPLING REACTION BETWEEN SEGMENT C AND MODEL COMPOUND SEGMENT B

As discussed in chapter II, we started on coupling reaction between segment B and segment C to form the carbon-carbon bond between C27 and C28 of okadaic acid. At first, we examined the coupling reaction between segment C (3-2) and model compound of segmet B (4-47) as shown in scheme 6-1.

Since the aldehyde moiety of segment B 4-27 is axially oriented, epimerization at C26 is to be worried to afford the more stable equatorial isomer. Therefore, we must confirm that no epimerization at C26 occurred during Swern oxidation step before trying the coupling reaction. Reduction of the aldehyde 4-27 with sodium borohydride gave the alcohol 4-26, which was identified as its acetate 4-28. This experiments showed that the condition of Swern oxidation did not cause epimerization at C26. And sodium borohydride reduction step is equivalent to the attack of nucleophile to the axially oriented aldehyde of segment B. Therefore it could be expected that nucleophile of sulfone carbanion of segment C would not cause epimerization at C26 of segment B.

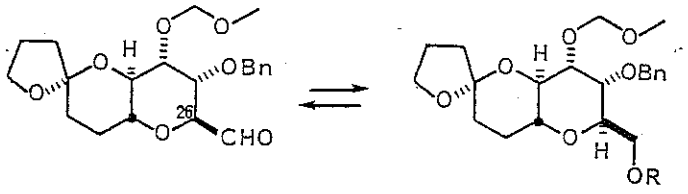
Segment C (3-2) was treated with 1 equivalent of n-butyl-lithium to result in the formation of its sulfone carbanion. Reaction of this segmet C (3-2) with segment B (4-27) in tetra-

hydrofuran at -78°C gave the coupling product 6-1 in low yield (24%). After many experiments to maximize the yield, it was found that the coupling reaction smoothly proceed in a less polar solvent. The coupling reaction in a mixture of ether and hexane (3:2) gave 6-1 in a modest yield (66%).

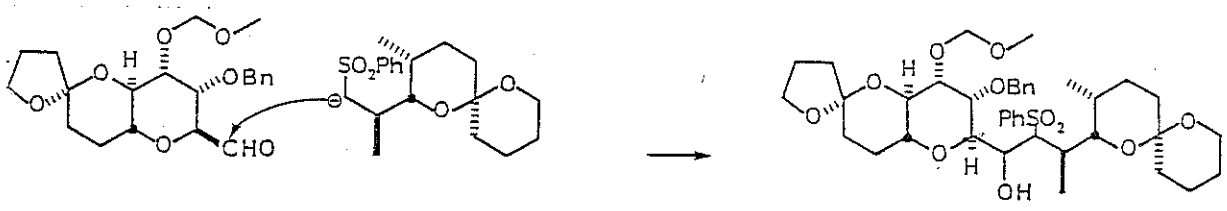
The next stage of segment B/C synthesis had two problems. One was induction of the asymmetric center at C27, and the other was preparation of the exo-methylene moiety at C25.

Oxidation of the alcohol 6-1 proved to be difficult. Both Swern oxidation and pyridinium chlorochromate were unsuccessful; in each case, the starting material was recovered. Though pyridinium dichromate oxidation gave the keto-sulfone, this reaction condition caused epimirization of the axial substituent at C26. Only Collins reagent (CrO_3-2Py) oxidation was successful without epimerization at C26 to afford the keto-sulfone 6-2 in 69% yield.[50] The keto-sulfone 6-2 was reduced with aluminum amalgam in aq. THF to the ketone 6-3 without carbon oxygen bond cleavage at C26 in 74% yield.

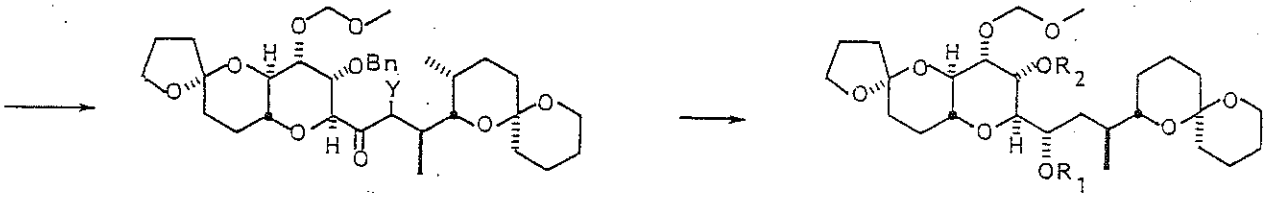
The stereochemistry in the hydride reduction of the keton 6-3 can be expected by Felkin-Nguen transition state model.[41] The attack of hydride to the ketone 6-3 can be postulated to occurr from a conformation as shown in Fig 6-1. The nucleophile hydride attacks the ketone 6-3 in an antiperiplanar arrangement with the



4-27 4-26; R= H
4-28; R= Ac

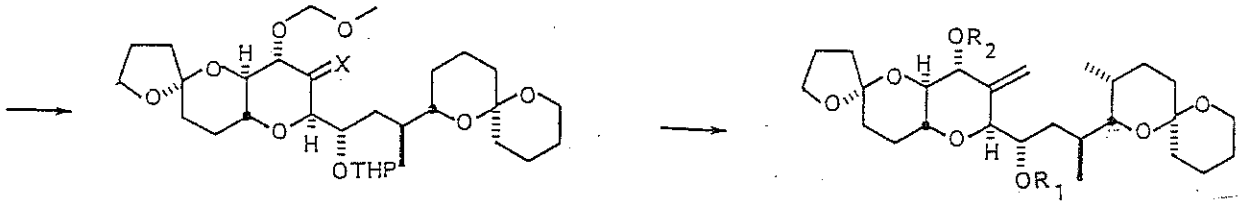


4-27 3-2 6-1



6-2; Y= SO_2Ph
6-3; Y= H

6-4; R_1= H, R_2= Bn
6-5; R_1= THP, R_2= Bn
6-6; R_1= THP, R_2= H



6-7; X= O
6-8; X= CH_2

6-9; R_1= H, R_2= MOM
6-10; R_1= H, R_2= H
6-11; R_1= Ac, R_2= Ac

Scheme 6-1

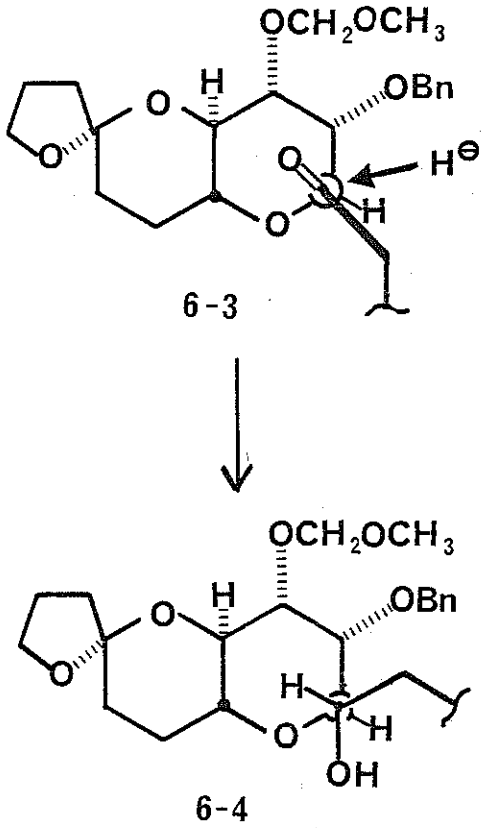


Fig 6-1

most electronegative group (in this case, oxygen) at the adjacent chiral center (C26). Thus, the stereochemistry of the product can be expected to be desired one (6-4). Indeed, reduction of the ketone 6-3 with sodium borohydride in ethanol at $0^{o}C$ for 2 hr gave the only one isolable alcohol 6-4. The stereochemistry of this alcohol was tentaively assigned to be 6-4. The alochol 6-4 was protected as tetrahydropyranyl ether with dihydropyran in the presence of pyridinium p-toluenesulfonate. Deprotection of the benzyl group at C25 with H_2/palladium on carbon (25%) gave the alcohol 6-6 in 76% overall yield from 6-3. Swern oxidation of 6-6 followed by Wittig olefination of the ketone 6-7 with methylenetriphenylphosphorane in tetrahydrofuran gave the exo-methylene 6-8.[51] Deprotection of the tetrahydropyranyl and methoxymethyl ether groups with pyridinium p-toluenesulfonate and 10% HCl afforded the diol 6-10. This diol 6-10 was acetylated with acetic anhydride and pyridine to afford the diacetate 6-11 in 14% overall yield from 6-6.

The chemical shift and coupling constant of each proton at C27 and C26 of this synthetic substance 6-11 was found to be identical to that of natural okadaic acid tetra-acetate methyl ester (see Fig 6-2 and 6-3). The stereochemistry of the induced C27 position of 6-11 was assigned to be the same as that of okadaic acid based on this 500 MHz ^{1}H nmr spectra, and was

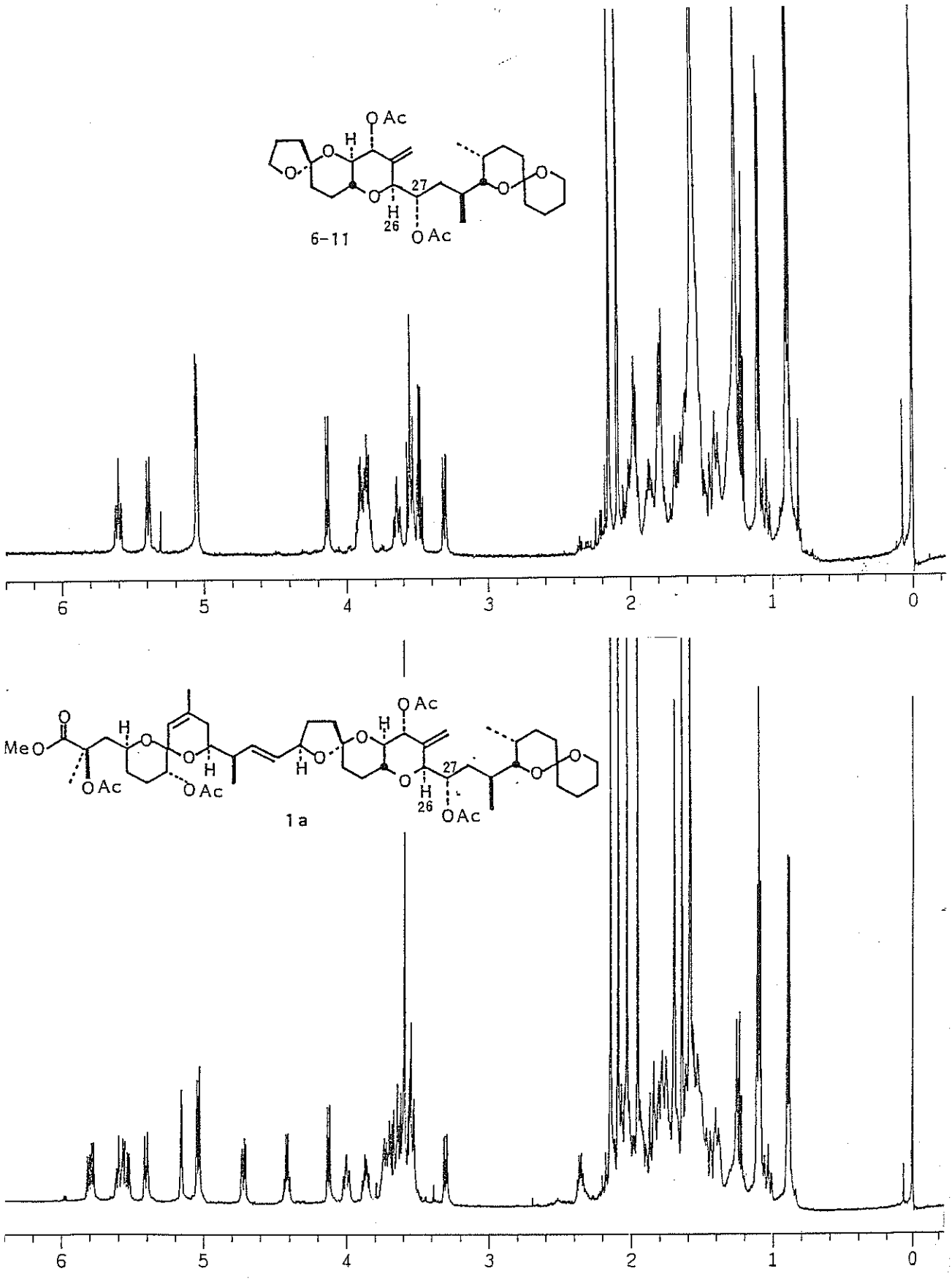


Fig 6-2

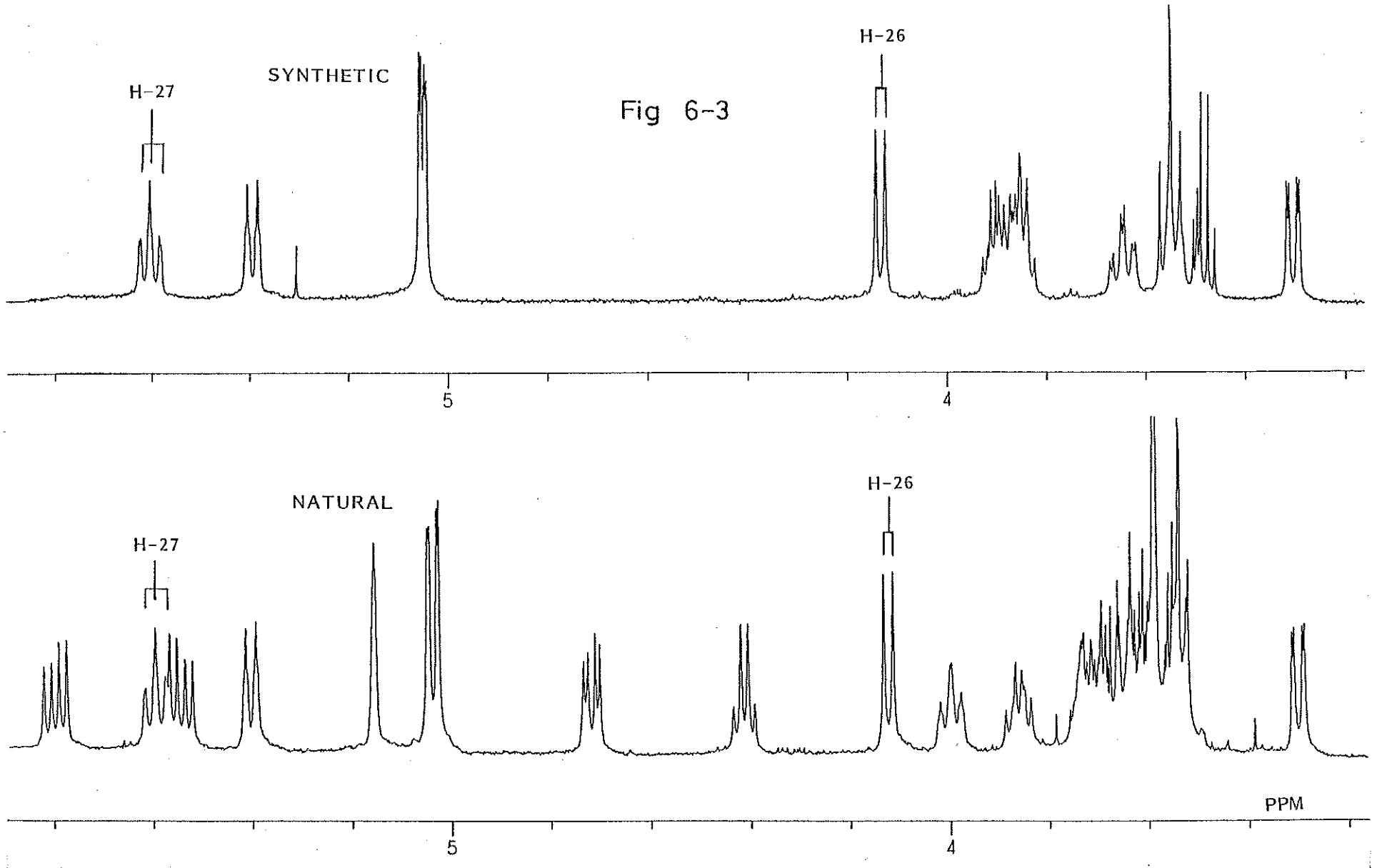


Fig 6-3

finally confirmed by the total synthesis of okadaic acid.

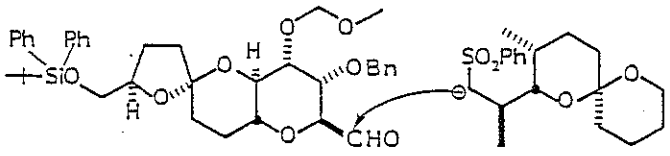
We synthesized segment B/C 6-11 involving C-16 through C38 in 11 steps in 3.5% overall yield from the model compound 4-27 of segment B.

SYNTHESIS OF SEGMENT B/C

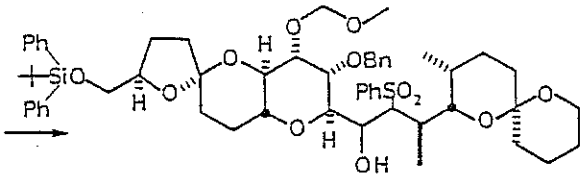
Since we have established the synthetic method of segment B/C using model compound 4-27 of segment B, we applied this method to the synthesis of segment B/C involving C14 through C38 of okadaic acid as shown in Scheme 6-2.

Segment B 4-43 was reacted with segment C under the condition identical to that of model compound 4-27 to afford the coupling product 6-12 in good yield (92%). Collins reagent (CrO_3-2Py) oxidation of 6-12 followed by reduction of the keto-sulfone 6-13 with aluminum amalgam gave the ketone 6-14. The ketone 6-14 was reduced with sodium borohydride in ethanol at $0^{o}C$ for 1 hr afforded the alcohol 6-15 in 57% overall yield from 6-12. The alcohol 6-15 was protected as tetrahydropyranyl ether with dihydropyran in the presence of pyridinium p-toluene-sulfonate. The benzyl group of 6-16 was removed by hydrogenolysis with H_2/palladium hydroxide on carbon (Pearlman's catalyst[52]) to afford the alcohol 6-17 in 69% overall yield from 6-15. Swern oxidation of the alcohol 6-17 followed by Wittig olefination with methylenetriphenylphosphorane in tetrahydrofuran gave the exo-methylene 6-19 in 79% overall yield from 6-15.

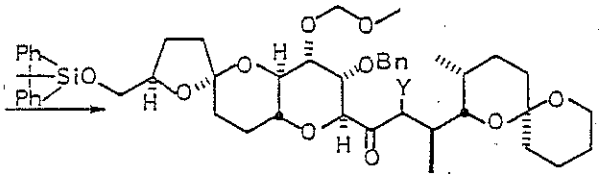
At this stage, we had the best chance to exchange the



4-43 3-2

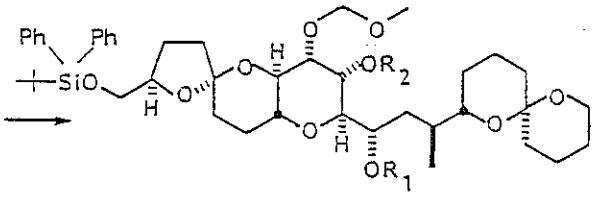


6-12



6-13; Y= SO_2Ph

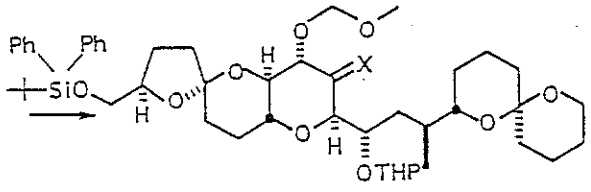
6-14; Y= H



6-15; R_1= H, R_2= Bn

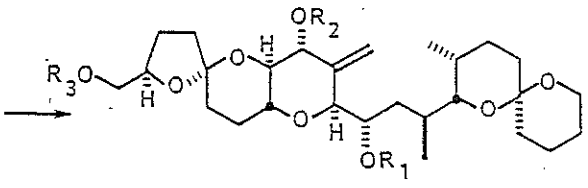
6-16; R_1= THP, R_2= Bn

6-17; R_1= THP, R_2= H



6-18; X= O

6-19; X= CH_2

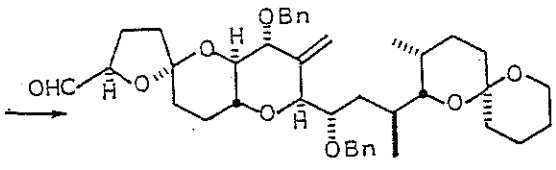


6-20; R_1= H, R_2= MOM, R_3= $^tBuPh_2Si$

6-21; R_1= H, R_2= H, R_3= $^tBuPh_2Si$

6-22; R_1= Bn; R_2= Bn; R_3= $^tBuPh_2Si$

6-23; R_1= Bn, R_2= Bn, R_3= H



6-24

Scheme 6-2

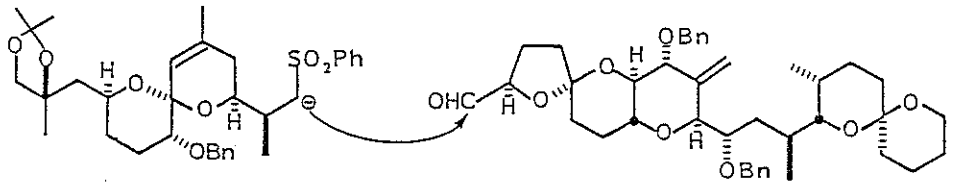
protecting groups at C24 and C27 for the protecting groups which could easily be removed under a mild condition at the final stage of okadaic acid synthesis. We chose benzyl group for this purpose. The reason of this choice will be discussed in chapter VII. Both tetrahydropyranyl and methoxymethyl ether group of 6-19 were removed at a time with trimethylsilyl bromide at $-20^{\circ}C$ in dichloromethane,[53] and the resulting two hydroxyl groups of 6-21 were re-protected with benzyl bromide and sodium hydride to afford the di-benzyl ether 6-22.

Removal of the tert-butyldiphenylsilyl group of 6-22 with tetra-n-butylammonium fluoride gave the alcohol 6-23 in 50% overall yield from 6-19. Swern oxidation of the alcohol 6-23 afforded the B/C segment aldehyde 6-24 which was immediately used in the next coupling reaction with segment A.

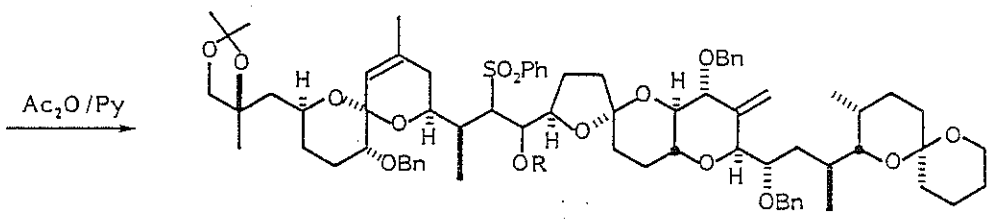
Segment B/C 6-24 was synthesized in 11 steps in 14.3% overall yield from segment B (4-23).

COUPLING REACTION BETWEEN SEGMENT B/C AND SEGMENT A

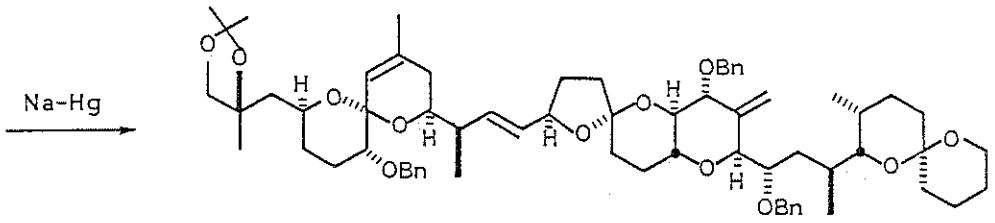
The species used in the second coupling reaction are sufone carbanion 5-1 and aldehyde 6-24, both of which are the same species as that used in the first coupling reaction (sulfone carbanion 3-2 and aldehyde 4-43). Therefore, condition which was used in the first coupling reaction was applied to the second coupling reaction (Scheme 6-3). Sulfone carbanion of segment A generated with n-butyllithium did not react with segment B/C aldehyde 6-24. Utilization of strong base, either sec- or tert-butyllithium, was necessary for the generation of segment A sulfone carbanion which reacts with segment B/C aldehyde. The sulfone carbanion of segment A (5-1) generated with sec-butyl-lithium was mixed with segment B/C (aldehyde 6-24) in a mixture of tetrahydrofuran and hexane (1:1) at -78^{o}C for 20 min to afford the coupling product 6-25 as diastereomixtures. The yield of this coupling reaction could not correctly be estimated, because separation of the product 6-25 from segment A (5-1) was very difficult due to the similar Rf value on TLC. In this coupling reaction, we utilized 6 equivalents of segment A to segment B/C. But segment B/C remained unchanged and 67% of segment B/C was recoverd from the reaction mixture. We envisioned that it could



5-1 6-24



6-25; R= H
6-26; R= Ac



6-27

Scheme 6-3

be attributed to the low reactivity of the segment A sulfone carbanion. To increase the reactivity of segment A sulfone carbanion, we used two equivalents of t-butyllithium to generate the dianion of segment A.[54] However, elimination of the benzyl group or fragmentation of the ring system occurred, and we could not increase the reactivity of segment A. This coupling reaction step has now been under investigation.

The alcohol **6-25** was acetylated in a mixture of acetic anhydride and pyridine at 55°C overnight to afford the acetae **6-26**. This acetate **6-25** was successively treated with sodium-amalgam in a mixture of ethyl acetate and methanol to afford the trans-olefin **6-27** in 25% overall yield from **6-23**. This synthetic compound **6-27** was found to be identical with that derived from natural okadaic acid in comparison with spectroscopic (500 MHz nmr) and TLC data. The 500 MHz ^{1}H nmr spectra of synthetic and natural compound **6-27** measured in C_6D_6 are illustrated in Fig 6-4 and 6-5 [δ 1.00(3H, d, J=7), 1.02(3H, d, J=7), 1.13(3H, d, J=7), 1.43(3H, s), 1.49(3H, s), 1.52(3H, s), 1.53(3H, s), 3.27(H-7, dd, J=12, 4), 3.41(H-30, dd, J=10, 2), 3.61(H-38, dd, J=11, 4), 3.68(H-4, ddd, J=11, 7, 3), 3.76(H-38, ddd, J=13, 11, 3), 3.86(H-1, d, J=9), 3.88(H-22), 4.01(H-27, ddd, J=10, 8, 2), 4.05(H-23, t, J=10), 4.11(H-1, d, J=9), 4.1(H-12), 4.21(H-24, d, J=10), 4.36(1H, d, J=13), 4.41(H-26, d, J=8), 4.49(1H, d, J=13),

4.56(1H, d, J=11), 4.73(H-16, q, J=7), 4.84(1H, d, J=11), 4.86(1H, d, J=13), 4.95(1H, d, J=13), 5.01(1H, brs), 5.30(H-9, brs), 5.64(1H, dd, J=16, 7), 5.69(1H, t, J=2), 5.95(1H, dd, J=16, 8)].

At this stage, we succeeded in the synthesis of the molecule 6-27 which has 17 asymmetric centers and 38 carbon backbone identical to that of okadaic acid.

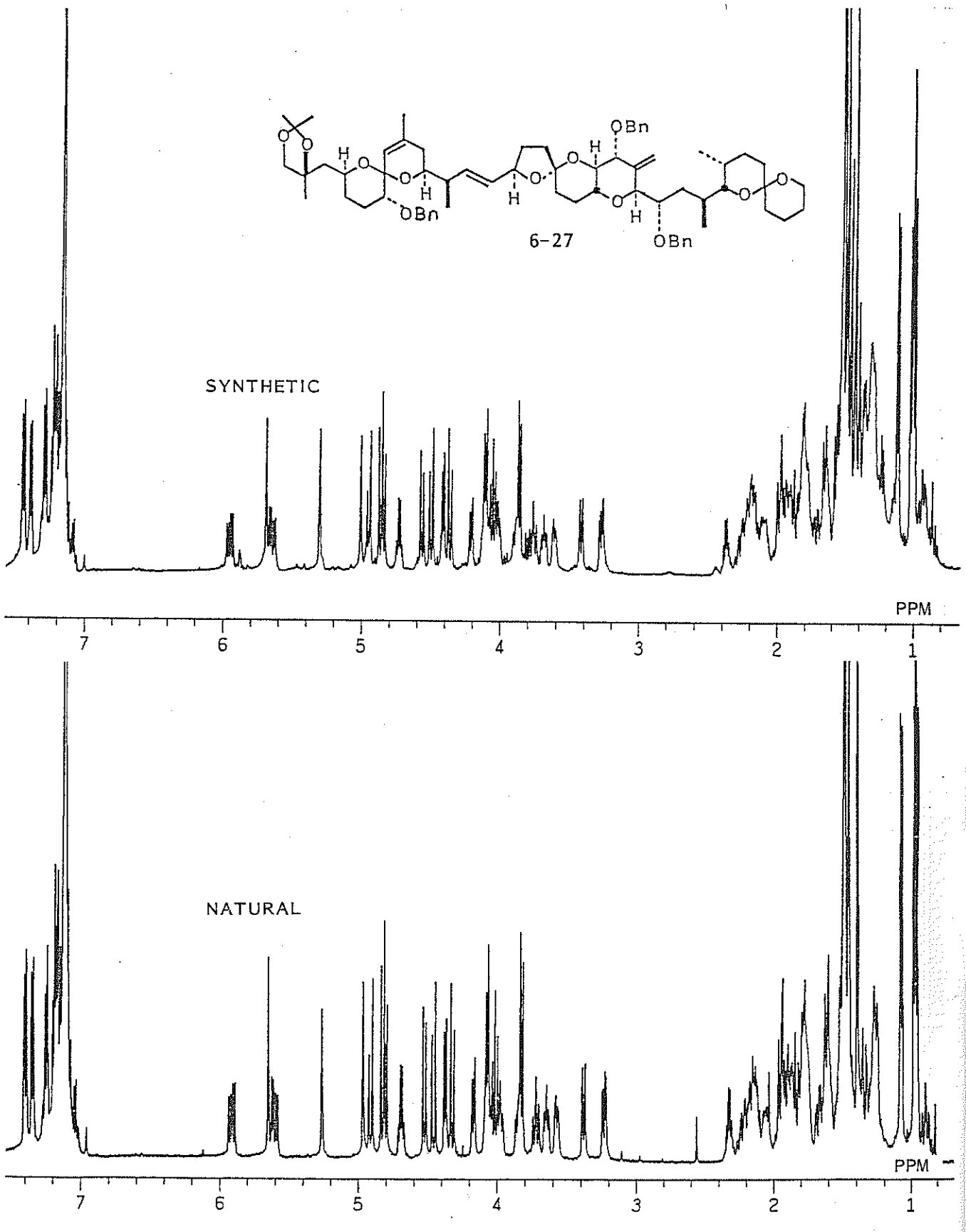
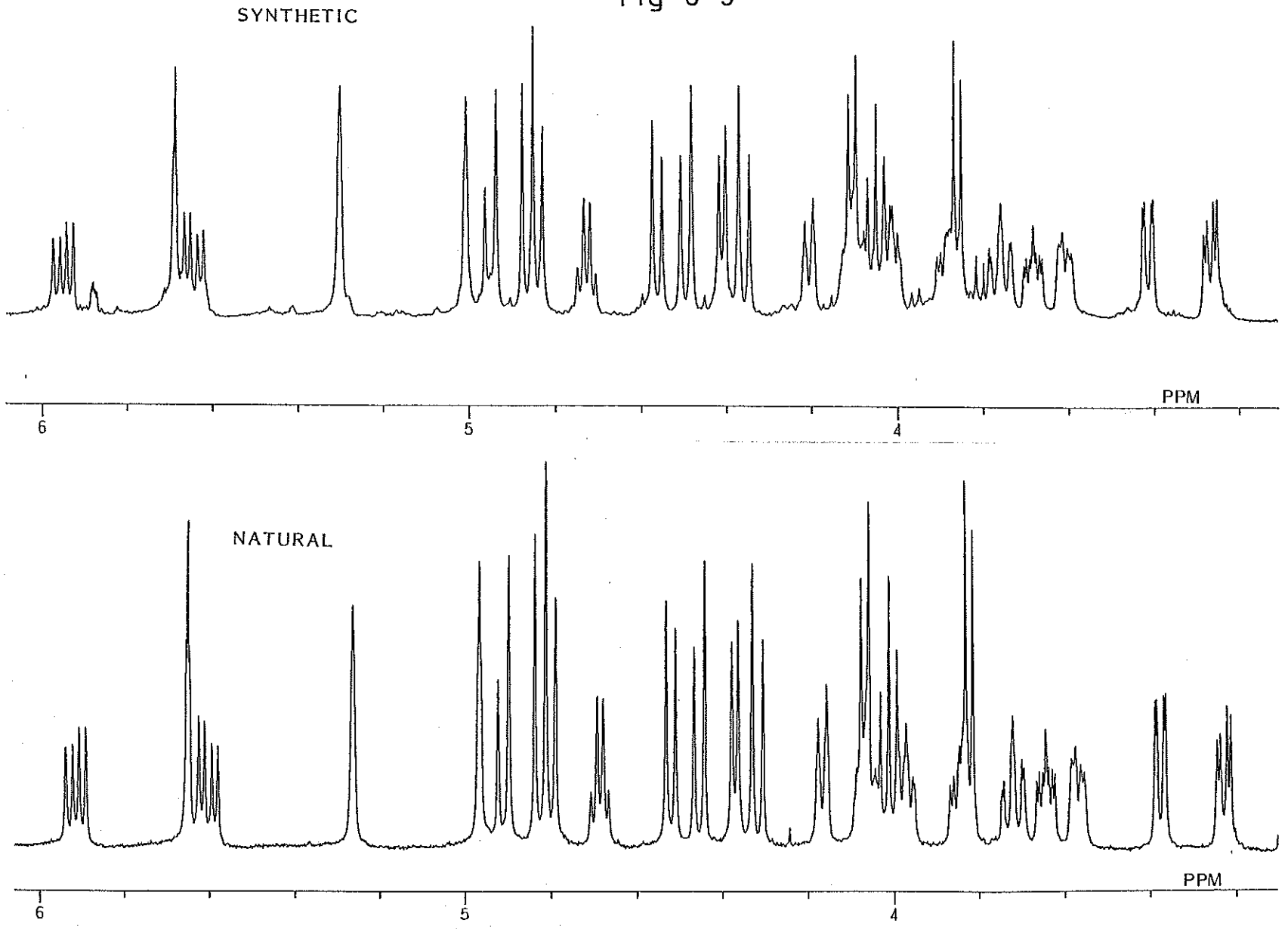

OBn
H
O
H
OBn
6-27
OBn
SYNTHETIC
PPM
7
6
5
4
3
2
1
NATURAL
PPM
7
6
5
4
3
2
1

Fig 6-4

Fig 6-5



CHAPTER VII

Total Synthesis of Okadaic Acid

As described in chpater VI, we succeeded in the coupling reactions and obtained the molecule **6-27** with 17 asymmetric centers and 38 carbon backbone identical to that of okadaic acid. Thus, only two problems remained for the total synthesis of okadaic acid. One is removal of protecting group and the other is conversion of the 1,2-diol to the α-hydroxy-carboxylic acid moiety.

At the final stage of natural product synthesis, we are often confronted with some difficulties in removing protective groups. Therefore, it is necessary to choose such a protective group that can be removed under a mild condition. Since benzyl group is stable to a variety of acidic or basic conditions and can be easily removed with lithim metal or sodium metal in liquid ammonia, we chose the benzyl group as protecting group. This protective group will be removed with lithium metal in liquid ammonia at the final stage of okadaic acid synthesis.

Okadaic acid has four carbon atoms, each of which attaches both oxygen atom and double bond, and such a moiety is often hydrogenolized with lithium metal. Therefore, we must confirm such a condition of debenzylation without undesirable hydrogenolysis of okadaic acid molecule. For this purpose, natural okadaic acid derivatives which have benzyl groups were synthesized and the condition of debenzylation was examined as

shown in Scheme 7-2.

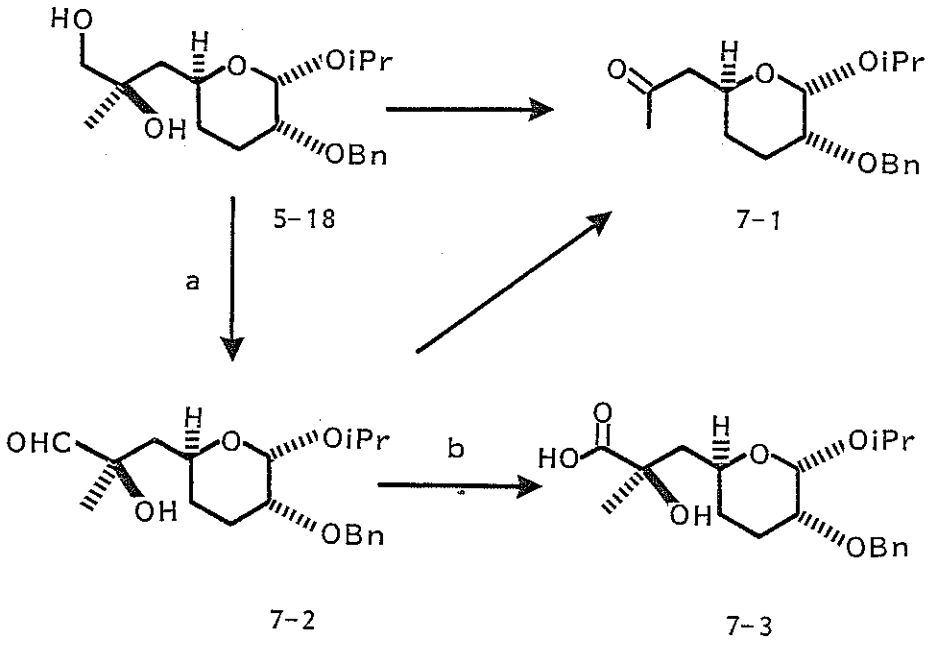
Benzylation of natural okadaic acid (1-1) with benzyl bromide and sodium hydride gave the tribenzyl okadaic acid 7-6. Treatment of 7-6 with diazomethane in methanol afforded the methyl ester 7-6 which was reduced with lithium aluminum hydride to afford the diol 7-4. The diol 7-4 was converted into the tribenzyl acetonide derivative 6-27 with 2,2-dimethoxypropane and pyridinium p-toluenesulfonate. We examined the condition of debenzylation on 6-27 and 7-6 with lithium metal in liquid ammonia. Indeed, the use of excess lithium metal caused the cleavage of the C-O bond at C16. We must use a limited amount of lithium metal for debenzylation. Indeed, treatment of either 6-27 or 7-6 with a limited amount of lithium in a mixture of liquid ammonia and ethanol (7:3) at $-78^{\circ}C$ gave the debenzylated product 6-27 or 1-1 without carbon-oxygen bond cleavage at C16. So, we chose the benzyl group for the protection of hydroxy groups at the final stage of okadaic acid synthesis. As described in chapter V and VI, three hydroxyl groups at C7, 24 and 27 were protected or re-protected as benzyl ether.

The final problem for okadaic acid synthesis is conversion of the 1,2-diol into α-hydroxy-carboxylic acid. At first, oxidation of the model compound 5-18 was examined (scheme 7-1). It is well known that oxidation of the diol, such as 5-18, caused

carbon-carbon bond cleavage to afford the keton 7-1.[55] Indeed, a variety of chromium oxidation reagent, such as pyridinium dichromate, Jones oxidation or pyridinium chlorochromate gave only ketone 7-1.[56] Corey reported the synthesis of α-hydroxy ketone without carbon-carbon bond cleavage with N-chloro-succinimide and thioanisole that is a modification of DMSO oxidation.[57] Therefore, we tried a variety of DMSO oxidations and found that DMSO oxidation using sulfur trioxide pyridine complex gave only α-hydroxy-aldehyde 7-2.[58]

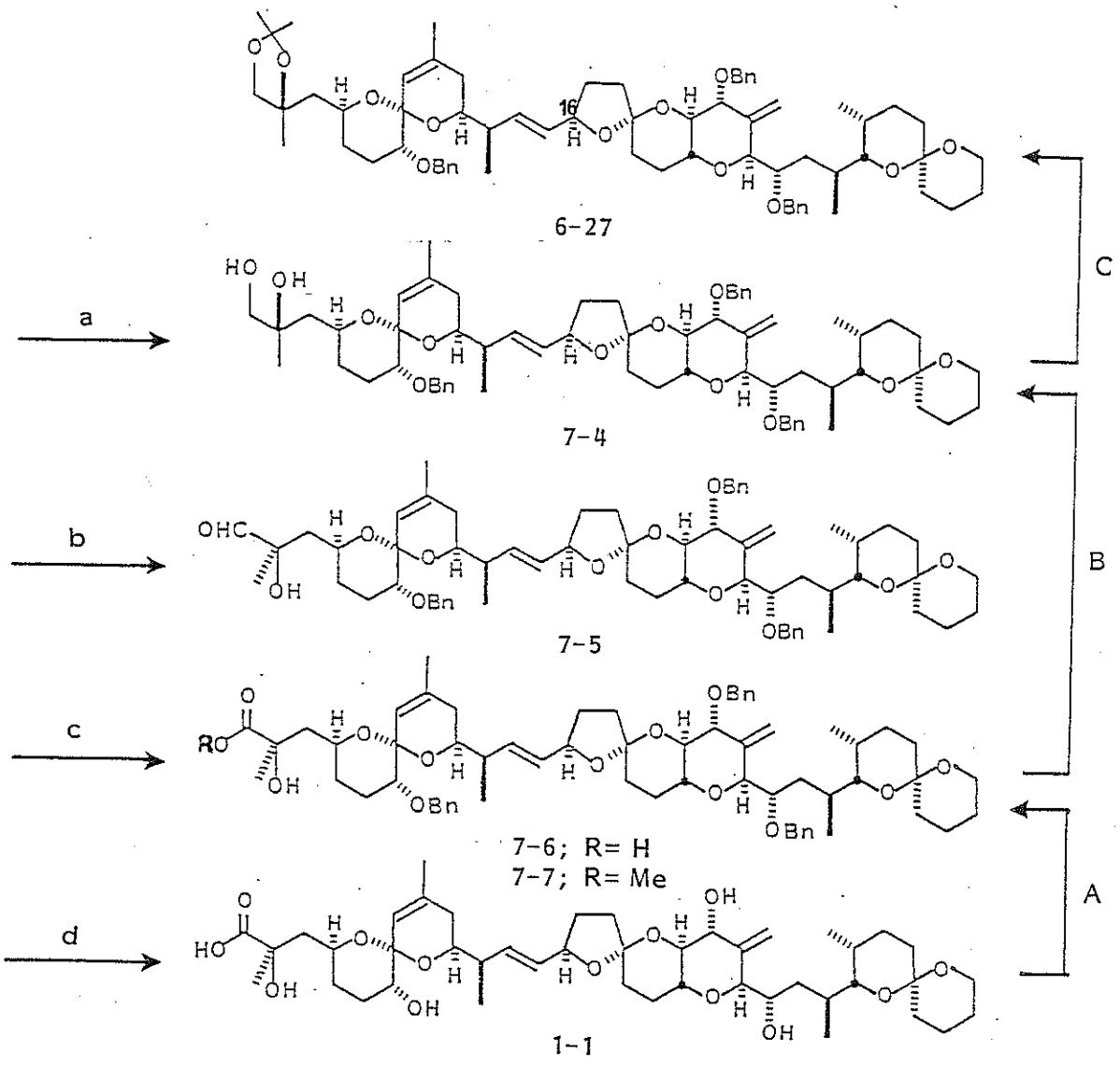
And now one more step of oxidation is necessary. At this time, such an example to oxidize α-hydroxy-aldehyde to the α-hydroxy-carboxylic acid had not been known. We tried the mildest oxidizing reagent, such as silver oxide.[59] But the yield of this oxidation reaction was very low (less than 20%), and the major reaction was conversion of the aldehyde 7-2 to the ketone 7-1. After many unsuccessful experiments, it was found that sodium chlorite ($NaClO_2$) oxidation of the aldehyde 7-2 gave only α-hydroxy-carboxylic acid 7-3 without carbon-carbon bond cleavage.[60] This is the first example of a direct α-hydroxy-carboxylic acid synthesis from the 1,2-diol without protection.

Application of these reaction conditions to the diol 6-27 (scheme 7-2) led us to the first total synthesis of okadaic acid. The acetonide 6-27 was hydrolized in a mixture of acetic acid and



a) SO_3-Py/DMSO; b) $NaClO_2$

Scheme 7-1



a) AcOH/THF/H_2O; b) SO_3-Py; c) $NaClO_2$; d) Li/NH_3/EtOH
A) $PhCH_2Br$/NaH, CH_2N_2/MeOH; B) $LiAlH_4$; C) $Me_2C(OMe)_2$/PPTS

Scheme 7-2

water at 55°C for 1.5 day to give the diol 7-4 in 63% yield. DMSO oxidation of the diol 7-4 to the aldehyde 7-5 with sulfur trioxide pyridine complex followed by sodium chlorite oxidation gave the carboxylic acid 7-6 in 66% yield. Deprotection of the benzyl ether 7-6 with litium metal in a mixture of liquid ammonia solvent and ethanol as proton source (7:3) at -78°C afforded the totally synthetic okadaic acid (1-1) in 87% yield. 500 MHz ^{1}H nmr of this synthetic material measured in $CDCl_3$ was completely identical with that of natural okadaic acid as shown in Fig 7-1 [δ 0.93(3H, d, J=6), 1.02(3H, d, J=7), 1.06(3H, d, J=6), 1.37(3H, s), 1.77(3H, s), 3.29(H-30, dd, J=11, 2), 3.35-3.62(2H), 3.55(H-38, brt, J=11), 3.61(H-22, td, J=10, 4), 3.66(H-38, td, J=11, 3), 3.94(H-26, d, J=10), 4.07(H-4, brt, J=11), 4.09(H-27, t, J=10), 4.12(H-24, d, J=10), 4.54(H-16, td, J=9, 7), 5.06(1H, brs), 5.32(H-9, brs), 5.44(1H, t, J=1), 5.48(1H, dd, J=15, 9), 5.67(1H, dd, J=15, 9), 5.78(1H, brs). .

Total synthesis of okadaic acid was achieved in 4 steps in 36% overall yield from 6-27.

We could obtain 1.7 mg of totally synthetic okadaic acid in totally 98 steps.

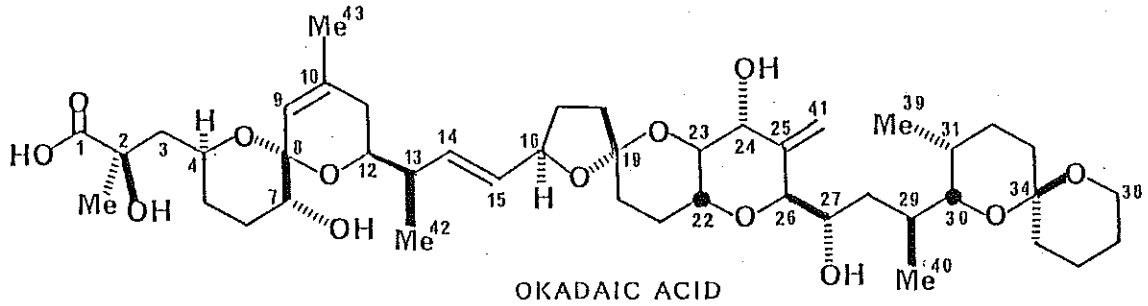


Fig 7-1

CHPATER VIII

Conclusion

The first total synthesis of okadaic acid has finally been accomplished in about 100 steps in total since we planned it four years ago. During these studies were cultivated several synthetic concepts and methodologies which are to be mentioned below.

We used D-glucose as an only starting material for the construction of tetrahydropyran ring system of okadaic acid. Our policy of carbohydrate-based synthesis has demonstrated that asymmetric centers on acyclic parts are to be induced from the asymmetric centers on the carbohydrote ring system. Indeed, four asymmetric centers on acyclic parts were induced from the asymmetric center at C-5 positon of pyranose sugar. For this purpose, we could develop the following new methodologies; spiro-heteroolefin, anti-selective heteroconjugate addition and stereoselective oxymercuration of E-allyl-alcohol. We could also indicate the importance of Felkin-Nguen transition state model and chelation model. This was very important when we have designed and predicted selectivity of reaction in acyclic systems.

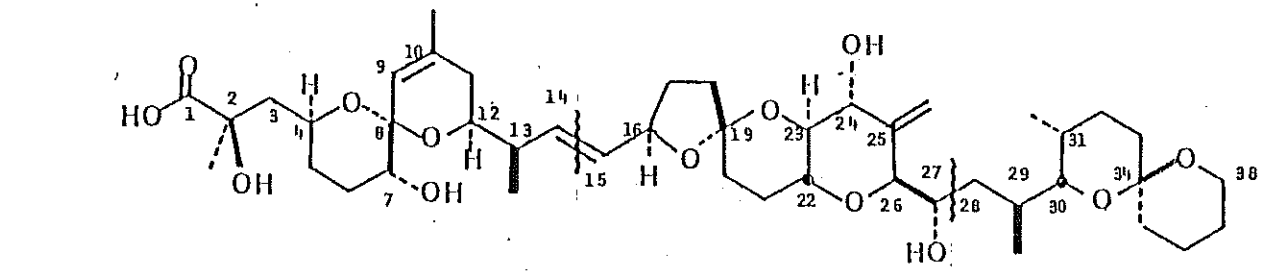
In Fig 8-1 we summarized the carbon-carbon bond formation reactions which were used in the okadaic acid synthesis. The key was the coupling reactions of each segment to construct a long C-38 carbon backbone of okadaic acid. The reaction between sulfone

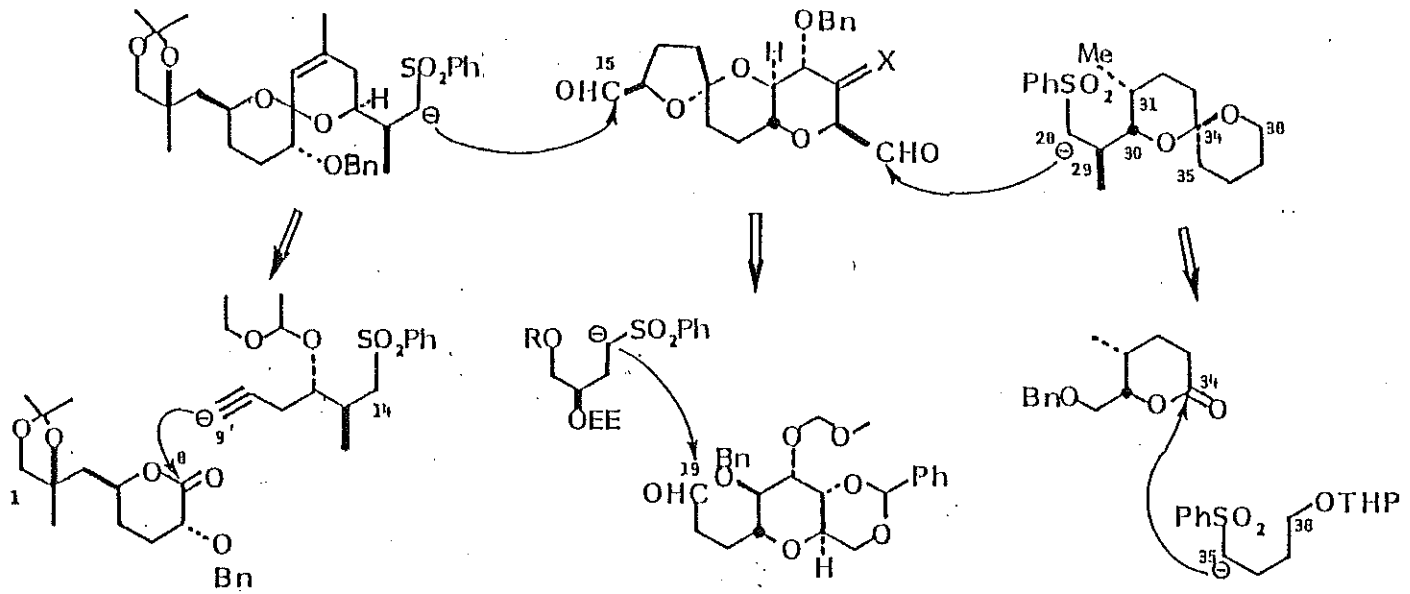
carbanion and aldehyde led us to the success in this key reaction. Including coupling reactions, we tried 8 times of carbon-carbon bond forming reaction among which sulfone carbanion was used for five different coupling steps.

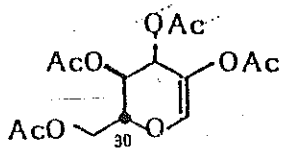
At the final stage of okadaic acid synthesis (chapter VII), we confronted a problem, that is, transformation of 1,2-diol to α-hydroxy carboxylic acid. Such a transformation usually required protection of hydroxy group. This protection procedure requires 5 steps for transformation. Eventually, we developed a direct carboxylic acid synthesis and transformed 1,2-diol to α-hydroxy carboxylic acid in only 2 steps.

Recently, two classes of new polyethers were isolated, for expample, Brevetoxin B (8-1) and Norhalicondrin A (8-2) which contain the common partial structures found in that of okadaic acid as shown in Fig 8-2.[61, 62] Methodologies used in our synthesis could be extensively applicable to the synthesis of these molecules.

Organic chemists will continue their efforts toward the syntheses of natural products.







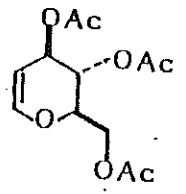
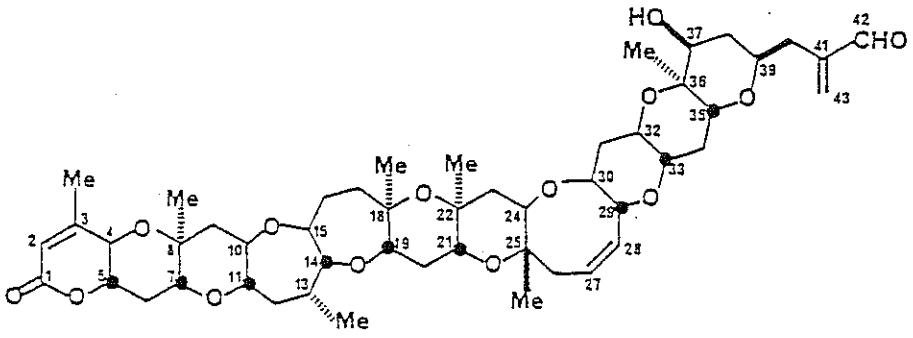
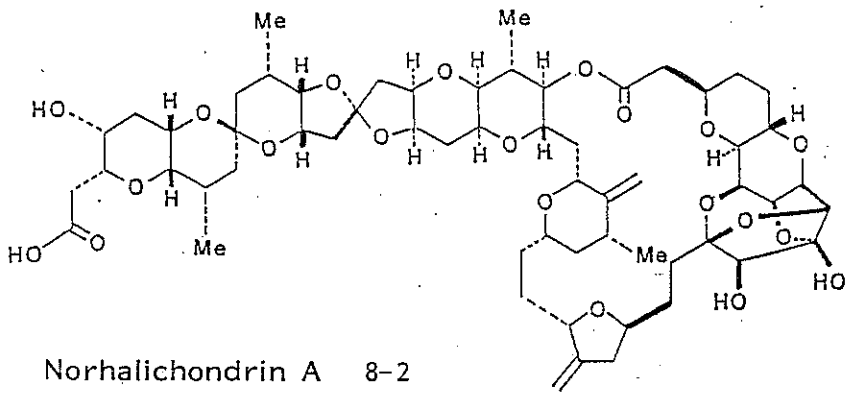


Fig 8-1



Brevetoxin B 8-1



Norhalichondrin A 8-2

Fig 8-2

CHAPTER IX

Experimental Section

NOTES

Melting points were determined on a hot stage melting point apparatus. All melting points and boiling points were uncorrected.

Infrared (IR) spectra were recorded on JASCO A-3 and are repoted in wave numver (cm^{-1}).

Proton nuclear magnitic resonance spectra were recorded on a JEOL FX-100, FX-200 or FX-500 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (0.0) as an internal standard. All samples were dissolved in $CDCl_3$ and recorded on JEOL FX-200 unless described otherwise. Data are reported as follows: chemical shift (intergrated intensity, multiplicity, coupling constatns). Following abbreviation are used for spin multiplicity: s=singlet, d=doublet, t-triplit, q=quartet and m=multiplet. Coupling constats are reported as J in Hz.

Carbon nuclear magnetic resonance (CMR) spectra were recorded on JEOL FX-100 or FX-200 spectrometer. Chemical shift are reported as values in parts per milllion relative to tetrametylsilane (0.0) as an internal standard.

Optical rotations were measured in 1-dm cells of 2 and 8 ml capacity by using a JASCO MODEL DIP-4 polarimeter.

The x-ray diffraction data were collected by use of an automated four-circle diffractometer, Rigaku AFC-5, set on a rotating anode x-ray generator, Rigaku RU-200, with a graphite monochromated Cu radiation. ORTEP was used for drawing of the molecular and crystal sturctures.

Elemental analyses were performed by Analytical Laboratories at Faculty of Agriculture, Nagoya University to which the author gratefully acknowledge.

Analytical thin-layer chromatography (TLC) was conducted on 0.25mm pre-coated silica gel plates manufactured by E. Merck (Art # 57515) and M. Nagel (Art.-Nr. 809 023). Column chromatography were performed on silica gel supplied by E. Merck (Art # 7734) and Fuji Davison (BW-820MH). Preparative TLC separation were made on plates perpared with a 2mm layer of silica gel PF_{254} obtained from E. Merck (Art # 7747), or on plates with 0.5mm pre-coated silica gel PF_{254} obtained from E. Merck (Art # 5744).

Reactions were run under an atmosphere of nitrogen or argon when the reactions were sensitive to moisture or oxygen.

"Dry" solvents were dried under the following method.

ether: dried over sodium wire .

tetrahydrofuran: distilled from potassium.

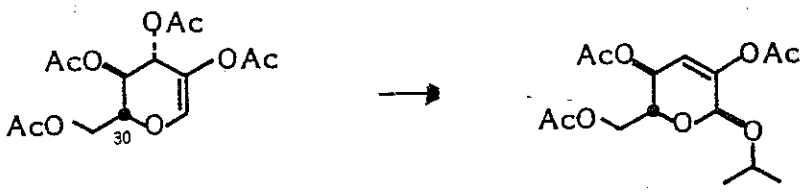
benzene: dried over sodium wire.

chloroform: dried over alumina.

methylene chloride: dried over alumina.

All other reactants and solvents were "reagent grade" unless described wtherwise.

HPLC separation was performed on JASCO Finepak-STL using a High Pressure Liquid Chromatography JASCO Twincle.



3-3 3-4

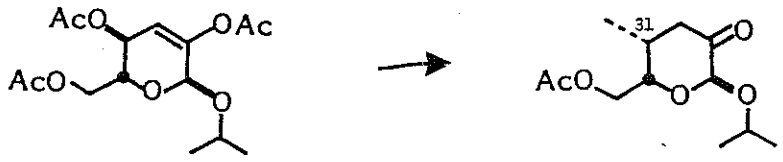
To a stirred solution of acetoxy-glucal 3-3 (50 g, 0.152 mol) in benzene (200 mL) under nitrogen atmosphere was added boron trifluoride etherate (55 mL, 0.45 mL), and the resulting reaction mixture was stirred at room temperature for 10 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution. The aqueous solution was extracted with ether, and the combined organic extracts were washed brine and then dried with Na_2SO_4. Removal of the solvent at reduced pressure gave the enol ether 3-4 as a crude crystal. Recrystallization from ether/hexane afforded the analytical sample (31.5 g, yield 63.1%).

^1H nmr δ 1.11(3H, d, J=6.0), 1.18(3H, d, J=6.0), 2.02(9H, s), 3.76(1H, m), 4.00-4.32(3H, m), 5.10(1H, s), 5.28-5.48(1H, m), 5.65(1H, d, J=2.0).

$[\alpha]_D$=+93.7° (c=1.00, $CHCl_3$).

Found C 54.64, H 6.68; Calcd C 54.50, H 6.67, for $C_{15}H_{22}O_8$

m. p. 60-61°C.



3-4 3-6

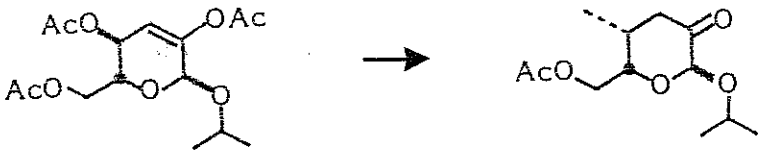
To a stirred slurry of cuprous iodide (2.3 g, 12.1 mmol) in THF (20 mL) cooled to -20°C (CCl_4/dry ice bath) under nitrogen atmosphere was added methyllithium (1.3 M, 18.6 mL). After 10 min, a solution of 3-4(1.0 g, 3.0 mmol) in THF (5 mL) was added dropwise over 5 min to this rapidly stirred solution of dimethylcopperlithium at -40°C. The reaction mixture was quenched after 30 min by the addition of saturated aqueous NH_4Cl solution. The layers were separated, and the aqueous layer (blue) was extracted with ether. After the combined organic layers were dried over Na_2SO_4, concentration under reduced pressure afforded the ketone 3-6 (0.61 g, in 82%) as an oil. Chromatography of a portion of this oil on 12 g of silica gel with 1:5 ether/hexane afforded the analytical sample of the ketone 3-6 as a colorless oil.

^1H nmr δ 0.98(3H, d, J=7), 1.18(3H, d, J=6), 1.29(3H, d, J=6), 2.09(3H, s), 2.18(1H, ddd, J=14, 2, 1), 2.40(1H, m), 3.01(1H, dd, J=14, 6), 4.01(1H, tt, J=6, 6), 4.1-4.2(2H, m), 4.60(1H, ddd, J=7, 5, 2), 4.69(1H, s).

IR ($CHCl_3$) 1735cm^{-1}.

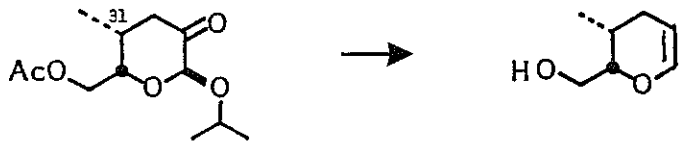
$[\alpha]_D$=+1577° (c=1.03, $CHCl_3$).

Found C 58.94, H 8.19; Calcd C 59.02, H 8.20, for $C_{12}H_{20}O_5$.



3-4 3-6

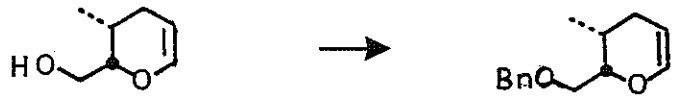
To a stirred suspension of cuprous cyanide (2.25 g, 25.1 mmol) in THF (13.5 mL) at -20°C under nitrogen was added methyllithium (17.5 mL, 1.25 M, LiBr complex in ether) dropwise. After 30 min, a solution of the enol acetate 3-4(1.00 g, 3.0 mmol) in THF (5 mL) was added into the reaction mixture. After being stirred at -20°C for 3 hr, the reaction mixture was poured into saturated aqueous NH_4Cl solution, and then extracted with ether. The combined organic layers were washed with water and brine, and then dried over Na_2SO_4. Removal of the solvent at reduced pressure gave the ketone 3-6(582 mg, 78.8%) as an oil.



3-6 3-8

A mixture of the ketone **3-6**(8.00 g), hydrazine monohydrate (9.0 mL, 0.18 mol) and triethylamine (15.4 mL) in ethanol (160 mL) was heated at 55°C overnight. Concentration under reduced pressure followed by azeotropic removal of hydrazine monohydrate with toluene afforded the crude hydrazine as an oil. This material was used without further purification. A solution of methylsulfinylmethylsodium was prepared from sodium hydride (9.1 g, 0.23 mol) and DMSO (142 mL) according to the procedure by Corey.[21] To this solution was added the hydrazine in DMSO (28 mL) dropwise at room temperature to evolve nitrogen. After stirring for 1.5 hr, the resulting dark red solution was diluted with saturated aqueous NH_4Cl solution, and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and passed through a short column of silica gel. Evaporation of the solvent under reduced pressure afforded the vinyl ether **3-8** (3.1 g) as a dark red oil. This material was used in subsequent experiments without further purification.

^1H nmr (100 MHz) δ 0.96(d, 3H, J=7), 1.64(brd, 1H, J=16), 1.9-2.5(3H), 3.4-4.1(3H), 4.68(brs, 1H), 6.32(brd, 1H, J=6).



3-8 3-9

The alcohol 3-8 (2.83 g, 22 mmol) dissolved in THF (32 mL) was added to a suspension of sodium hydride (60% in mineral oil, 2.4 g, washed with hexane before use) in THF (73 mL) and DMF (53 mL). After stirring at room temperature for 20 min, benzyl bromide (5.0 mL, 1.9 equiv.) was added dropwise. After being stirred for 20 h, the reaction mixture was poured into saturated aqueous NH_4Cl. The aqueous solution was extracted with ether, and the combined organic extracts were washed with brine and then dried over Na_2SO_4. Removal of the solvent at reduced pressure gave the benzyl ether 3-9 (5.8 g) as an oil which was used directly without further purification.

^1H nmr δ 0.92(3H, d, J=7), 1.64(1H, m), 2.04(1H, brm), 1.28(1H, ddt, J=17,6, 2), 3.46(1H, dd, J=10, 4), 3.52(1H, dd, J=10, 7), 4.08(1H, ddd, J=7, 4, 2), 4.5-4.7(3H), 6.54(1H, dt, J=6, 2), 7.3(5H).

3-9 3-10

Vinylether 3-9(5.5 g, 25.2 mmol) was heated at 55°C in a mixture of THF (240 mL), water (32 mL) and 1N HCl (14.0 mL) for five hours. After the heating, the solution was extracted with ether. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and then dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the lactol 3-10(5.07 g) as an oil, which was used for the following reaction without further purification.

3-10 3-11

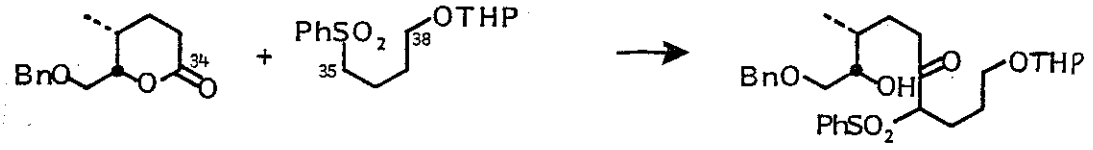
The crude lactol **3-10** (5.07g) was dissolved in DMF (54 mL) and aqueous sodium acetate buffer (72 mL). The solution was cooled in an ice bath and then mixed with bromine (1.8 mL). After removing the ice bath, the reaction mixture was stirred for about three hours at room temperature. Solid sodium hydrosulfite was added to decompose excess bromine until purple color of the reaction mixture was disappeared. The reaction mixture was diluted with water and then extracted with ether. The combined organic layers were washed with water, saturated aqueous sodium-bicarbonate and saturated aqueous NaCl, and then dried over anhydrous sodium sulfate. The combined extracts were concentrated under reduced pressure, and chromatography of the residue (4.8 g) on silica gel (100 g) with 1:1 ether/hexane afforded the lactone (2.94 g, 52% three steps from **3-8**) as a colorless oil.

^{1}H nmr δ 0.96(3H, d, J=6), 1.6-2.1(2H, m), 2.2(1H, m), 2.5(2H), 3.5-3.7(2H), 4.4-4.6(3H), 8.2-8.4(5H).

IR ($CHCl_3$) 1735cm^{-1}.

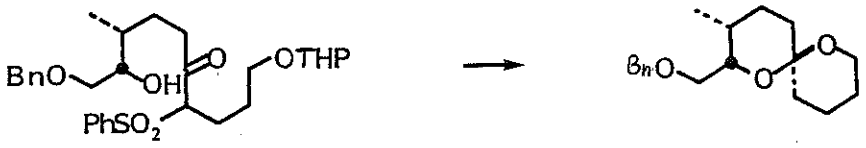
$[\alpha]_D$=+31.4^o (c=0.90, $CHCl_3$).

Found C 71.76, H 7.70; Calcd C 71.77, H 7.74, for $C_{14}H_{18}O_3$.



3-11 3-12 3-13

To a stirred solution of the sulfone 3-12(16.5 g, 55.3 mmol) in THF (200 mL) cooled to -78°C was added n-butyllithium (37 mL, 57.4 mmol, 1.55 M soln in hexane), and the reaction mixture was stirred at this temperature for 10 min and then at 0°C for 15 min. The lactone 3-11 (4.04 g, 17.3 mmol) in THF (20 min) was added to the solution of the sulfone carbanion, prepared above. After being stirred for 1 hr at -78°C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution, and extracted with ether. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of this residue on silica gel (200 g) with 1:3 (3 L), 1:1 (3 L) ether/hexane and then ether (1.5 L) afforded the ketosulfone 3-13 (7.9 g in 86% yield) as an oil.



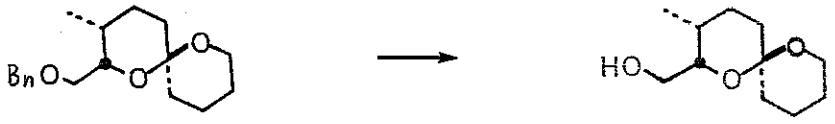
3-13 3-15

Aluminum foil (28 g) was cut into strips, and immersed all at once into a 2% aqueous solution of mercuric chloride for 30 sec. The strips were rinsed with methanol and then with ether, and cut immediately with scissors. To a solution of the ketosulfone 3-13 (14 g, 26.3 mmol) dissolved in THF (500 mL) and water was added aluminum amalgum, prepared above, and stirred vigorously at room temperature for one day. The reaction mixture was filtered through a pad of Super Cell, and the filter cake was washed with ether. The filtrate was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give the ketone 3-14 as an oil. The resulting oil (9.4 g) dissolved in ethanol (200 mL) and 2,2-dimethoxypropane (20 mL) was refluxed in the presence of a catalytic amount of PPTS (1.0 g) overnight. About half of the volume of the solvent was removed by evaporation. The resulting reaction mixture was diluted with ether, washed with water, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (8.4 g) with silica gel (100 g) with 1:15 ether/hexane afforded the spiroketal 3-15 (6.2 g in 81% yield).

^1H nmr δ 0.90(3H, d, J=7), 1.2-2.0(10H), 2.10(1H, tt, J=13, 5), 3.4-3.9(4H), 4.05(1H, ddd, J=7,6,2), 4.6(2H, AB), 7.3(5H).

$[\alpha]_D$=+57.7° (c=1.34, $CHCl_3$).

Found C 74.61, H 9.01; Calcd C 74.44, H 9.03, for $C_{18}H_{26}O_3$.



3-15 3-16

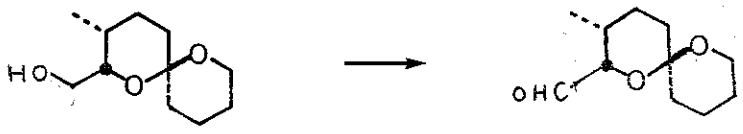
To a solution of **3-15** (ca. 6.2 g, 21.4 mmol) in ethanol (200 mL) was added palladium on carbon (10%, supplied from Nihon Engelhalt Company, 0.688g). The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 1.5 h. The catalyst was then removed by filtration and washed with dichloromethane. Removal of the solvent from the combined filtrates gave the crude alcohol **3-16** (4.9 g). This material was used for the subsequent reactions without further purification.

^{1}H nmr δ 0.90(3H, d, J=7), 1.2-2.2(10H), 2.10(1H, tt, J=12, 5), 3.4-3.8(4H), 3.92(1H, ddd, J=9, 4, 2).

IR ($CHCl_3$) 3450cm^{-1}.

$[\alpha]_D$=+102.4° (c=0.93, $CHCl_3$).

Found C 66.03, H 10.06; Calcd C 65.97, H 10.07, for $C_{11}H_{20}O_3$.



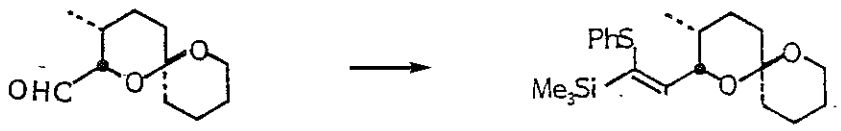
3-16 3-17

To a stirred solution of oxalyl chloride (5.5 mL, 155 mmol) in dichloromethane (270 mL) was added DMSO (11 mL, 155 mmol) at -78°C (in a dry ice-methanol bath). The reaction mixture was stirred for 1 min and the alcohol **3-16** (4.9 g, ca. 21.4 mmol diluted in 30 mL of dichloromethane) was added within 5 min; stirring was continued for an additional 15 min. Triethylamine (28 mL, 201 mmol) was added and the reaction mixture was stirred for 10 min and then allowed to warm to -20°C. Aqueous ammonium chloride solution was then added and the aqueous layer was extracted with ether. The organic layer were combined, washed successively with aqueous saturated ammonium chloride (four times), aqueous saturated sodium bicarbonate and aqueous saturated sodium chloride solution, and then dried over anhydrous Na_2SO_4. The filtered solution was evaporated to dryness to give the crude aldehyde **3-17** (5.06 g). The crude aldehyde was dried azeotropically by evaporation of benzene solution before next step.

^1H nmr δ 0.98(3H, d, J=7), 1.0-2.2(11H), 3.5-3.7(2H), 4.16(1H, d, J=3), 9.60(1H, s).

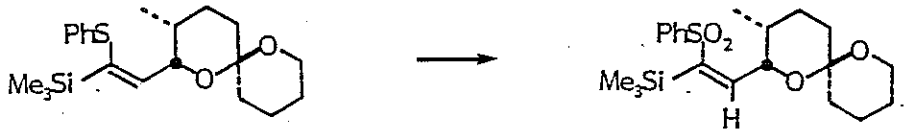
IR ($CHCl_3$) 2720, 1735 cm^{-1}.

$[\alpha]_D$= +42,1° (c=0.65, $CHCl_3$).



3-17 3-18

A solution of lithium bis-(trimethylsilyl)-phenylsulfinyl-methylid was prepared in the following manner. A 500 mL round bottom flask was fitted with a gas-inlet tubing connected to an argon cylinder and the apparatus was kept under a positive pressure of argon and carefully protected from moisture through the reaction. The flask was charged with bis-(trimethylsilyl)-phenylsulfinylmethane (13 mL, 46.3 mmol) and THF (250 mL), and was cooled to -78°C. A solution of n-butyllithium (30 mL, 1.55 M solution in hexane) was introduced into the flask over 5 min. The reaction mixture was allowed to warm to -45°C in three hours, stirred for 1 h at -45°C and then warmed up to -25°C in 1.5 h to give the yellow solution. To this solution, prepared above, was added the aldehyde 3-17 (5.06 g, 21.4 mmol, crude oil) dissolved in THF (20 mL) at -40°C. After being stirred for 30 min at -40°C, the reaction mixture was allowed to warm to 0°C, was diluted with saturated aqueous NH_4Cl solution, and was extracted with ether. The combined extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on silica gel (160 g) with 1:120 ether/hexane gave the excess reagent. Further elution with 1:10 ether/hexane afforded a 10:1 (by NMR) mixture of the Z- and E-vinylsulfide 3-18 (4.5 g in 56% yield three steps from 3-16) as an oil.



3-18 3-1

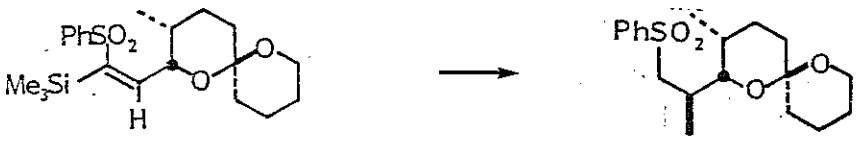
To a stirred solution of the sulfide **3-18** (4.5 g, 12.0 mmol) in dichloromethane (150 mL) cooled to 0°C (ice bath) was added MCPBA (5.7 g, 26.4 mmol) portionwise. After 30 min at 0°C, the reaction mixture was allowed to warm to room temperature and then stirred for 30 min. The reaction mixture was diluted with saturated aqueous $NaHSO_3$ and extracted with ether. The combined extracts were washed with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride and then dried over sodium sulfate. Evaporation of the solvent afforded the heteroolefin 3-1 (5.0g, in quantitative yield). Recrystallization from a mixture of ether and hexane gave the only pure Z-isomer **3-1** (3.8 g).

^1H nmr δ 0.34(9H, s), 0.90(3H, d, J=7), 2.2-2.9(9H), 2.02(1H, tt, J=13, 4), 3.00(1H, td, J=11, 3), 3.26(1H, ddd, J=11, 4, 2), 4.88(1H, dd, J=9,3), 6.48(1H, d, J=9), 7.2-7.4(3H), 7.8-7.9(2H).

$[\alpha]_D = +4.0^\circ$ (c=1.09, $CHCl_3$).

Found C 61.77, H 7.86; Calcd C 61.74, H 7.89, for $C_{21}H_{32}O_4SSi$.

m.p. 143-145°C.



3-1 3-2

To a solution of the heteroolefin 3-1 (150 mg, 0.40 mmol) in THF (4 mL) cooled to -78°C under nitrogen atmosphere was added methyllithium (0.80 mL, 1.5 M solution in ether as LiBr complex) dropwise. The reaction mixture was stirred at -78°C for 30 min, warmed up to -30°C in 5.5 h, and then at 0°C for 10 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The solution of the residue (151 mg) in methanol (5 mL) was treated with potassium fluoride (0.12 g) at room temperature for 3 h. The solvent was removed under reduced pressure, and the resulting residue was taken up in ether. The organic layer was washed with water and saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. Prepatative thin layer chromatography of the residue (1:3 ether/hexane) affrded the vinylsulfone (7 mg in 5.2% yield) and segment C 3-2 (125 mg in 89% yield) as white crystalls. Recrystallization of this material from ether/hexane afforded the analytically pure sample.

^1H nmr δ 0.68(3H, d, J=7), 1.26(3H, d, J=7), 1.3-2.2(12H), 2.84(1H, dd, J=14, 10), 3.20(1H, dd, J=14, 2), 3.38(1H, dd, J=10, 2), 3.5-3.6(2H), 7.6(3H), 7.9(2H).

^{13}C nmr δ 10.7, 17.0, 18.7, 25.3, 26.4, 27.5, 30.1, 31.4, 35.7, 58.9, 60.5, 73.2, 95.9, 128.0, 129.3, 133.6, 139.8.

$[\alpha]_D = +21.6^\circ$ (c=1.21, $CHCl_3$).

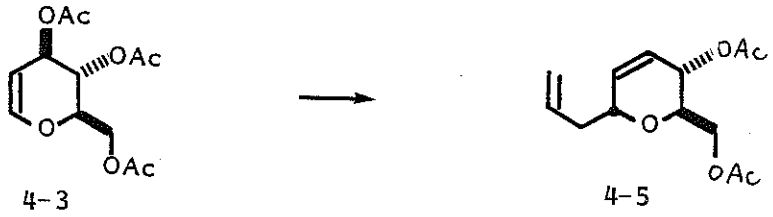
Found C 64.89, H 7.99; Calcd C 64.75, H 8.01, for $C_{19}H_{28}O_4S$.

m. p. 81.5-82.5°C.

Crystallization of this segment C from hexane and ether gave the suitable crystals for x-ray analysis.

Crystallographic Data

Space group	$P2_1$
a,b,c	11.889, 10.532, 7.725
α , β , γ	90.008, 94.026, 90.013
V	964.88
Z	2
d_{obsd}	1.250
d_{clcd}	1.212
R	0.0496
2^{o}_{max}	126
NO. of non-zero unique data	1623
Crystal size	0.15 x 0.15 x 0.75
CuK_{α}	1.5418



4-3 4-5

To a solution of D-glucal 4-3 (400 g) and allyltrimethylsilane (370 mL) in CH_2Cl_2 (4.5 L) at -50°C was added boron trifluoride etherate (190 mL) dropwise over 30 min. After being stirred at -50°C for 1h, the reaction mixture was allowed to warm to 0°C over 2.5 hr. The reaction mixture was then poured into aqueous $NaHCO_3$, and then extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the diacetate 4-5 and its isomer (475.2 g, ration 16:1) as an oil. This material was used for the subsequent experiments without further purification.

^1H nmr δ 2.09(3H x 2, s), 2.2- 2.6(2H), 3.95(1H, td, J=6, 4), 4.1-4.25(2H, AB), 4.29(1H, m), 5.05-5.2(3H), 5.75-6.0(3H).

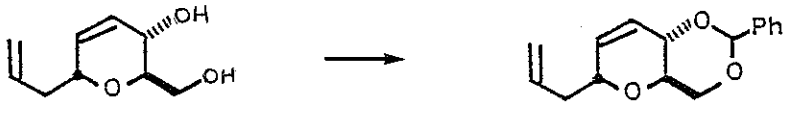
IR ($CHCl_3$) 1740 cm^{-1}.

$[\alpha]_D$= +62.3° (c=1.03, $CHCl_3$).

Found C 61.40, H 7.21; Calcd C 61.40, H 7.14, for $C_{13}H_{18}O_5$.

4-5 4-6

To a solution of the diacetate **4-5** (475.2g) in methanol (3.2L) was added triethylamine (650 mL) and water (550 mL), and the resulting solution was stirred at room temperature two overnights. The solvent was removed under reduced pressure to give the crude diol **4-6** (225.4 g, yield 89%, 2 steps) which was used directly without further purification.



4-6 4-7

To a solution of the diol **4-6** (99.6 g, 0.585 mol) and dl-camphorsulfonic acid (10 g) in dichloroethane (1.2 L) was added benzaldehyde dimethyl acetal (170 mL, 1.01 mmol) dropwise and the reaction mixture was stirred at room temperature overnight. Solvent (120 mL) was removed by heating until TLC analysis showed the absence of starting material. The resulting reaction mixture was cooled to room temperature and then poured into sat. $NaHCO_3$ solution. The separated organic layer was dried (Na_2SO_4), and passed through a short column of silica gel. Concentration under reduced pressure afforded the crude crystals (251.1g).

Recrystallization of this solid from ether and hexane gave the benzylidene **4-7** (121 g, yield 80%) as white crystals (needles).

^1H nmr δ 2.25-2.60(2H), 3.62(1H, ddd, J=10, 8, 4), 3.77(1H, t, J=10), 4.14(1H, dq, J=8, 2), 4.23-4.38(2H), 5.09(1H, brs), 5.16(1H, dq, J=8, 1), 5.59(1H, s), 5.76(1H, dt, J=10, 2), 5.75-5.94(1H, m), 6.01(1H, brd, J=10), 7.3-7.6(5H).

$[\alpha]_D = +26.7^\circ$ (c=1.25, $CHCl_3$).

Found C 74.37, H 7.03; Calcd C 74.39, H 7.02, for $C_{16}H_{18}O_3$.

4-7 4-8

To a stirred solution of the diene **4-7** (180 g, 0.647mol) in THF (2.1 L) colled to -25°C under nitrogen atomosphere was added borane (1M solution in THF, 260 mL) dropwise over 20 min. After 7.5 hr at -25°C, additional borane (80 mL) was added and then the temperature was kept at -25°C for 4.5 hr.

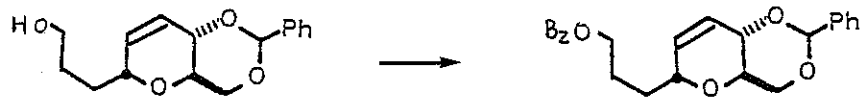
The reaction mixture was quenched by the slow, cautious addition of ethanol (90 mL), 2N NaOH aq. solution (360 mL) and 30% aq. H_2O_2 solution (240 mL). The resulting mixture was allowed to warm to room temperature and then stirred overnight. Saturated aq. $NaHSO_3$ solution was added until KI-starch paper indicated negative result. The aq. layer was extracted with ether (x3), and the combined extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4), and concentrated under reduced pressure to give the alcohol **4-8** as crude crystals (186.3 g). This material was successively used without further purification. recrystallization of a portion of this crude crystals from ether and hexane gave the analytically pure sample.

^1H nmr δ 1.5-1.9(4H), 3.45-3.73(3H), 3.78(1H, t, J=10), 4.15(1H, dq, J=8, 2), 4.22-4.34(2H), 5.59(1H, s), 5.72(1H, dt, J=10, 2), 5.98(1H, d, J=10), 7.3-7.6(5H).

$[\alpha]_D$= +31.0° (c=1.05, $CHCl_3$).

Found C 69.62, H 7.35; Calcd C 69.54, H 7.30, for $C_{16}H_{20}O_4$.

m. p. 80-81°C.



4-8 4-9

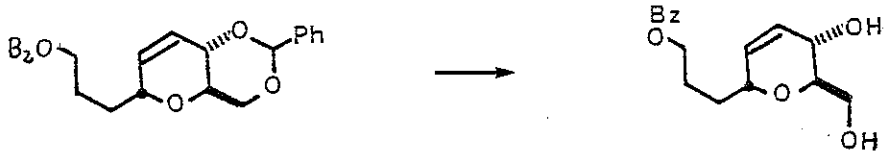
To a stirred solution of the alcohol **4-8** (186.3 g) in pyridine (2 L) was added benzoyl chloride (88 mL, 0.76 mol) dropwise. After being stirred at room temperature overnight, the reaction mixture was diluted with $CHCl_3$ (2 L), washed with water and dried (Na_2SO_4). Removal of the solvents gave the crude solids (281.2 g), which was washed with 20:1 ether/hexane to give the benzoate **4-9** as crude crystals (237.3 g). This material was washed in subsequent experiments without further purification. Recrystallization of a portion of this material from hexane/ethyl acetate afforded the analytically pure sample as a white solid.

^1H nmr δ 1.5-2.1(4H), 3.59(1H, ddd, J=8, 4, 2), 3.77(1H, t, J=10), 4.15(1H, ddd, J=8, 4, 2), 4.2-4.45(4H), 5.59(1H, s), 5.73(1H, dt, J=10, 2), 5.99(1H, d, J=10), 7.3-7.6(8H), 8.0-8.1(2H).

$[\alpha]_D = +11.7^\circ$ (c=1.58, $CHCl_3$).

Found C 72.68, H 6.45; Calcd C 72.61, H 6.36, for $C_{23}H_{24}O_5$.

m. p. 83-84°C.



4-9 4-10

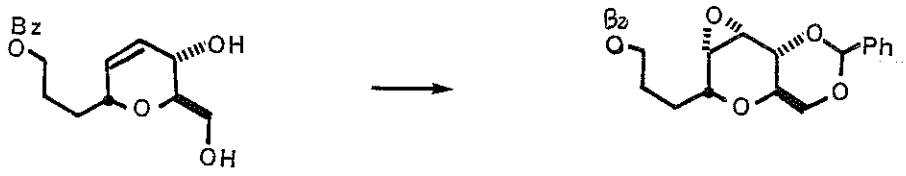
A solution of the benzoate 4-9 (232.3 g) in MeOH (2.5 L) was stirred vigorously in the presence of Dowex 50W (H^+) (35 g) at room temperature. After stirring for 9.5 hr, the resin was removed by filtration. The filtrate was treated with pyridine (3 mL), and the concentrated under reduced pressure to give the diol 4-10 as white solid (264.2 g). This material was used without further purification. Recrystallization of a portion of this solid from ethyl acetate/hexane provided the analytically pure sample.

^1H nmr δ 1.5-2.1(4H), 2.2-2.5(2H, br), 3.53(1H, dt, J=8, 5), 3.82(2H, d, J=5), 4.12(1H, brd, J=7), 4.18-4.29(1H, m), 4.37(2H, t, J=7), 5.74-5.89(2H, AB), 7.4-7.6(3H), 8.0-8.1(2H).

$[\alpha]_D$=-23.5° (c=1.04, $CHCl_3$).

Found C 65.74, H 6.97; Calcd C 65.74, H 6.90, for $C_{16}H_{20}O_5$.

m. p. 98-99°C.



4-10 4-11

To a cold solution of the diol 4-10 (264.2 g) dissolved in $CHCl_3$ (2.6 L) was added MCPBA (80%, 150 g) portionwise at 0°C and the solution was stirred at 5oC overnight. To this reaction mixture was added benzaldehyde dimethylacetal (150 mL) and dl-10-camphorsulfonic acid (1.0 g), and the solvent (1.2L) was removed by heating until the TLC analysis showed absence of the epoxy-diol. The reaction mixture was cooled to room temperature, washed with sat. aq. $NaHCO_3$, and then dried (Na_2SO_4). Concentration under reduced pressure afforded the crude epoxide 4-11 as solid (402.6 g). This material was used without further purification. The analytical sample was prepared by recrystallization from ethyl acetate/hexane.

^1H nmr δ 1.7-2.1(4H), 3.42(1H, dd, J=5, 3), 3.59(1H, brd, J=4), 3.67(1H, d, J=10), 3.85(1H, td, J=9, 5), 4.02(1H, dd, J=9, 1), 4.07-4.18(1H, m), 4.19(1H, dd, J=10, 5), 4.30-4.50(2H, AB), 5.57(1H, s), 7.3-7.6(8H), 8.0-8.1(2H).

$[\alpha]_D$= +37.8° (c=1.08, $CHCl_3$).

Found C 69.50, H 6.11; Calcd C 69.68, H 6.10, for $C_{23}H_{24}O_6$.

m. p. 123-125°C.

4-11 4-12

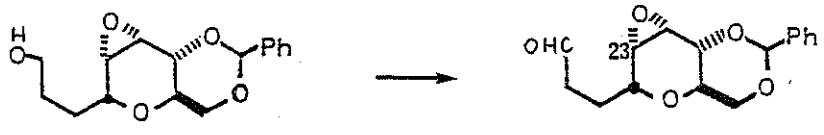
To a solution of the benzoate 4-11 (402.6 g) dissolved in THF (1.5 L) and MeOH (750 mL) cooled to 0°C was added NaOMe solution (100 mL, 1.16M solution in MeOH) dropwise, and the reaction mixture was stirred at 5°C overnight. Addition of dry ice and removal of the solvent afforded the residue. This residue was dissolved in H_2O and the aq. layer was extracted with ether (x3). The combined extracts were dried (Na_2SO_4), and concentrated under reduced pressure to give the crude solid (311.1 g). Recrystallization of this solid from ether/hexane gave the alcohol 4-12 as pure white crystals (122.1 g, overall yield 65% from 4-7).

^1H nmr δ 1.6-2.0(4H), 3.40(1H, dd, J=5, 3), 3.57(1H, d, J=5), 3.62-3.74(3H), 3.83(1H, td, J=10, 5), 4.00(1H, dd, J=9,1), 4.04-4.13(1H, m), 4.18(1H, dd, J=10, 5), 4.57(1H, s), 7.3-7.6(5H).

$[\alpha]_D$= +49.2° (c=0.95, $CHCl_3$).

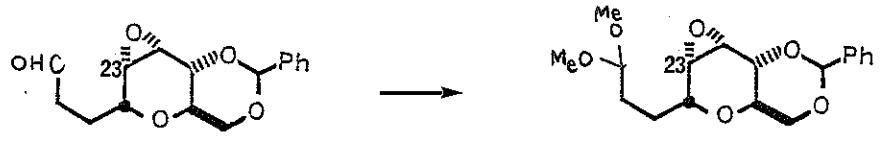
Found C 65.65, H 6.88; Calcd C 65.74, H 6.90, for $C_{16}H_{20}O_5$.

m. p. 123-124°C.



4-12 4-13

To a stirred solution of oxalyl chloride (11 mL, 0.13 mol) in CH_2Cl_2 (380 mL) cooled to -78°C (dry ice/MeOH) under nitrogen atmosphere was added DMSO (22 mL, 0.3 mol, distilled from CaH_2) dropwise over 5 min. After 2 min, the alcohol 4-12 (20.0 g, 68.4 mmol) in CH_2Cl_2 (20 mL) was added to the resulting solution. After 10 min at -78oC, triethylamine was added dropwise. After being stirred for 10 min, the reaction mixture was allowed to warm slowly to 0°C. Water was added, and the separated aq. layer was extracted with ether (x3). The combined organic layers were washed (sat.NH_4Cl, sat. NaCl), dried (Na_2SO_4), and concentrated under reduced pressure to give the aldehyde 4-13 (21.8 g) as an oil. This material was used to subsequent experiments without further purification.



4-13 4-14

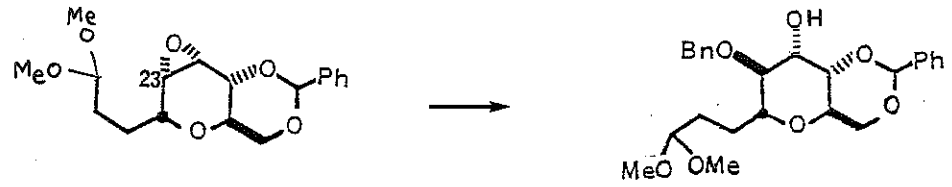
A solution of the aldehyde 4-13 (21.8 g), $(MeO)_3CH$ (120 mL) and PPTS (3 g) in CH_2Cl_2 (400 mL) was stirred at room temperature overnight. The resulting mixture was poured into sat. $NaHCO_3$ solution and the separated aq. phase was extracted with CH_2Cl_2 (x2). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude dimethylacetal 4-14 (29.1 g) as solids. This material was used without further purification. Recrystallization of a portion of these solids from hexane/ether afforded the analytically pure sample.

^1H nmr δ 1.6-2.0(4H), 3.33(3H, s), 3.34(3H, s), 3.38(1H, dd, J=5, 3), 3.56(1H, brd, J=5), 3.65(1H, d, J=10), 3.82(1H, td, J=9, 5), 3.99(1H, dd, J=9, 1), 4.01-4.11(1H, m), 4.17(1H, dd, J=10, 5), 4.41(1H, t, J=5), 5.56(1H, s), 7.3-7.6(5H).

$[\alpha]_D = +44.6^\circ$ (c=0.98, $CHCl_3$).

Found C 64.04, H 7.14; Calcd C 64.27, H 7.19, for $C_{18}H_{24}O_6$.

m. p. 108-110°C.



4-14 4-15

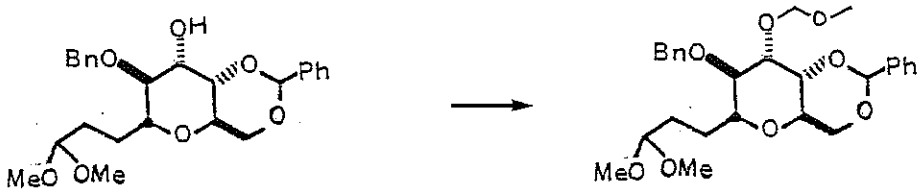
To a suspension of NaH (60 % dispersion in mineral oil, 35 g, 0.875 mol) in DMF (750 mL) cooled to 0°C was added benzyl alcohol (140 mL) dropwise. The mixture was stirred at room temperature until the evolution of hydrogen ceased and then stand still at 5°C overnight. To the supernatant of the benzyl alkoxide solution (650 mL), prepared above, was added the epoxide 4-14 (29.1 g) in DMF (50 mL), and the resulting reaction mixture was heated at 70°C under nitrogen atmosphere for 3.5 hr. The solution was cooled to room temperature and then poured into sat. NH_4Cl solution (800 mL). The aq. phase was extracted with ether (x3). The combined extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4), and concentrated under reduced pressure. Removal of the excess benzyl alcohol under high vacuum afforded the curde oil. Chromatography of this oil on silica gel (250 g) with 1:3 ether/hexane afforded the product 4-15 (15.5 g, 51% overall yield from 4-12) as a white solid. Recrystallization of a portion of this solid from ether/hexane provided the analytically pure sample.

^1H nmr δ 1.5-1.8(4H, m), 2.2-2.4(1H, m), 3.11(6H, s), 3.55(1H, d, J=3), 3.77(1H, t, J=10), 388-4.15(3H, m), 4.20-4.33(2H, m), 4.38(1H, t, J=6), 4.38(1H, t, J=6), 4.53-4.67(2H, AB), 5.64(1H, s), 7.25-7.55(10H).

$[\alpha]_D = +26.7^\circ$ (c=1.17, $CHCl_3$).

Found C 67.55, H 7.11; Calcd C 67.55, H 7.26, for $C_{25}H_{32}O_7$.

m. p. 88-89°C.

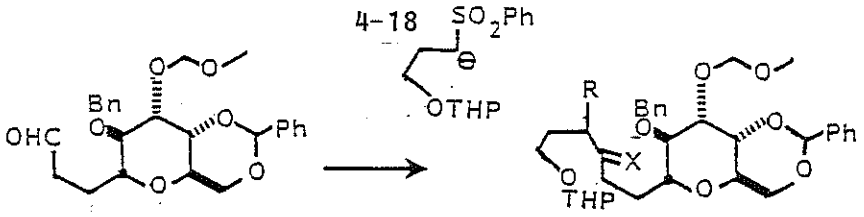


4-15 4-16

To a suspension of potassium hydride (35%, dispersion in mineral oil, 14.2 g, 124 mmol, washed with hexane before use) in DMF (380 mL) was added the alcohol **4-15** (15.5 g, 28.9 mmol) in DMF (20 mL) dropwise over 5 min. After being stirred at room temperature for 10 min, chloromethyl methyl ether (7.0 mL, 92.6 mmol) was added dropwise. A slight exothermic reaction was observed. The reaction mixture was stirred at room temperature for 30 min, poured into H_2O, and then extracted with ether (x3). The combined organic layers were washed (H_2O, sat. NaCl), dried (Na_2SO_4), and then concentrated under reduced pressure to afford the methoxymethyl ether **4-16** (16.9 g, quantitatively) as an oil.

4-16 4-17

A solution of the dimethyl acetal **4-16** (2.4 g) dissolved in a mixture of THF (70 mL) and 0.5N HCl (20 mL) was stirred at room temperature for 3 hr. The solution was poured into sat. $NaHCO_3$ solution, and then extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the aldehyde **4-17** (2.14 g, yield 98%) as an oil. This material was promptly subjected to subsequent reactions without further purification.



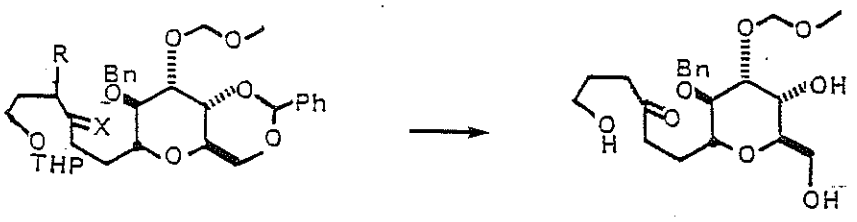
4-17

4-19; R= SO_2Ph, X= H, OH

4-20; R= SO_2Ph, X= O

1) To a solition of the sulfone 4-18 (3.00 g, 11 mmol) in THF (70 mL) cooled to -78°C under nitrogen atmosphere was added n-BuLi (1.6 M solution in hexane, 5.4 ml, 8.6 mmol) dropwise. After stirring at -78°C for 30 min, the aldehyde 4-17 (2.14 g, 4.1 mmol) in THF (7 mL) was added, and the stirring was continued for 30 min. Saturated NH_4Cl solution was added and the separated aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the residue (5.3 g).

2) This residue was dissolved in CH_2Cl_2 (90 mL), and sodium acetate (2.5 g) and PCC (3.3 g) was added. After stirring at room temperature for 2 hr, the reaction mixture was diluted with ether and then filtered through a pad of Super Cell. The filtrate was washed (sat. $NaHCO_3$, H_2O, sat. NaCl), dried (Na_2SO_4), passed through a short column of silica gel to remove the trace of chronium species. Concentration under reduced pressure gave the keto-sulfone 4-20 (4.9 g). This material was used without purification.



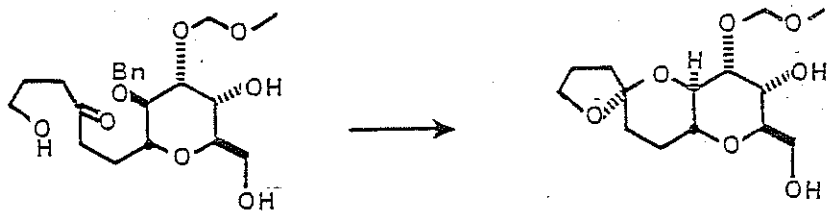
4-20; R= SO_2Ph, X= O

4-21; R= H, X= O

4-22

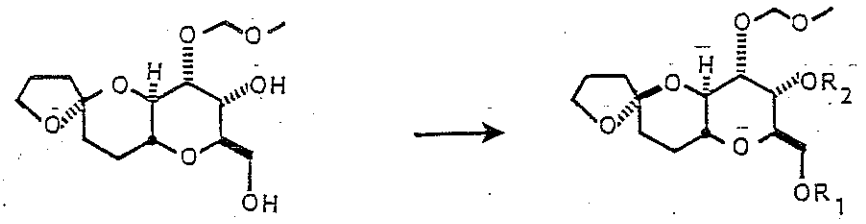
1) To a solution of the keto-sulfone 4-20 (crude 4.9 g, 4.1 mmol) in a mixture of THF (150 mL) and H_2O (15 mL) was added Al-Hg (prepared from aluminium foil 4.4g according to the procedure described before). After stirring at 70°C for 7 hr, the solition was diluted with ether and filtered through a pad of Super Cell. The filtrate was washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the residue (3.8 g).

2) The residue was dissolved in a mixture of MeOH (60 mL) and AcOH (15 mL), and refluxed for 3 days. Concentration under reduced pressure followed by chromatography (silica gel 30 g) of the residue with 1:1 ether/hexane (120 mL), ether (480 mL) and 10% MeOH in CH_2Cl_2 affored the triol 4-22 (1.44 g, overall yield 85% from 4-17).



4-22 4-23

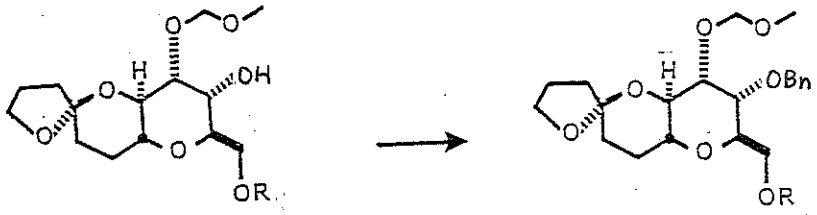
A solution of the triol **4-22** (1.37 g, 3.3 mmol) in MeOH (40 mL) and AcOH (2 mL) was stirred vigorously under a hydrogen atmosphere in the presence of palladium (25% on the carbon, 1.0 g). After stirring for 5 hr, the reaction mixture was filtered through a pad of Super Cell and concentrated under reduced pressure to give the diol **4-23** (1.19 g). This material was used without purification.



4-23

4-24; $R_1 = {}^{t}BuPh_2Si$, $R_2 = H$

To a solution of the diol4-23 (0.70 g, 2.3 mmol) and imidazole (0.55 g, 8.1 mmol) dissolved in DMF (20 ml) was added tert-butyldiphenyl silylchloride (1.1 mL, 4.0 mol) dropwise over 4hr. After stirring at room temperature for 5 hr, the reaction mixture was poured into H_2O, and the separated aq. layer was extracted with ether (x3). The extracs were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 20 g) of the residue with 1:3 and 3:1 ether/hexane gave the silyl ether 4-24 (0.87 g, yield 70%).



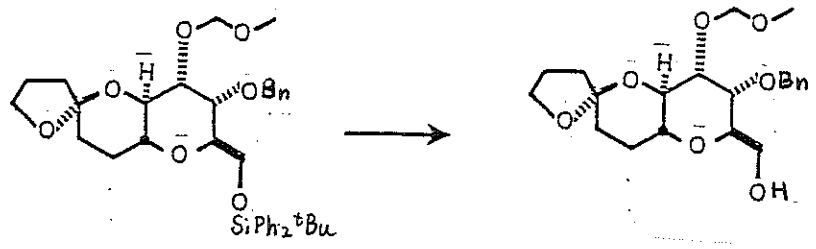
4-24 4-25

R= $SiPh_2Bu^t$

To a solution of the alcohol 4-24(0.30 g, 0.55 mmol) in THF (10 mL) was aded NaH (60% oil dispersion, 50 mg, 1.25 mmol) portionwise. After stirring at room temperature for 5 min, benzyl bromide (0.15 mL, 1.26 mmol) and DMF (1 mL) was added and the stirring was continued for 3 hr. The solution was poured into sat. NH_4Cl solution and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 10 g) of the residue with 1:15 and 1:3 ether/hexane afforded the benzyl ether 4-25 (283 mg, yield 81%).

^1H nmr δ 1.00(9H, s), 1.5-2.0(8H), 3.21(1H, td, J=10, 4), 3.7-4.2(9H), 4.60-4.82(2H, AB), 4.76(2H, s), 7.2-7.7(15H).

$[\alpha]_D = -5.5^\circ$ (c=1.59, $CHCl_3$).

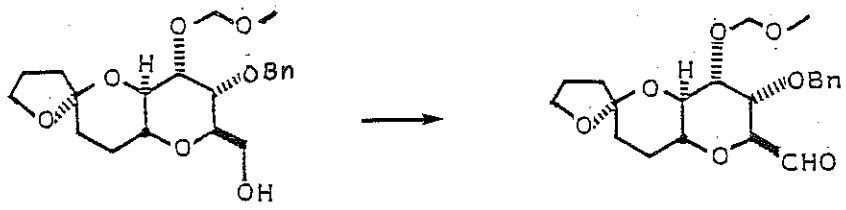


4-25 4-26

To a solution of the silyl ether 4-25 (283 mg, 0.45 mmol) dissolved in a mixture of THF (3 mL) and CH_3CN (3 mL) was added n-Bu_4NF (1M solution in THF, 0.90 mL, 0.90 mmol) dropwise. After stirring at room temperature for 1 hr, the solution was poured into H_2O. The aq. layer was extracted with ether (x3), and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and then concentrated under reduced pressure. Chromatography (silica gel 8 g) of this residue with 1:3 ether/hexane afforded the alcohol 4-26 (177 mg, quantitatively).

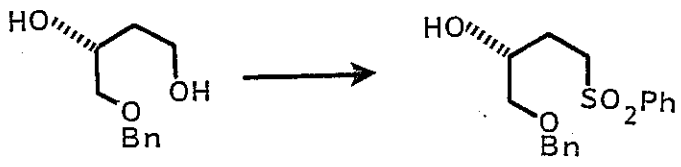
^1H nmr δ 1.6-2.0(8H), 2.25(1H, br), 3.34(3H, s), 3.49(1H, dd, J=10, 5), 3.65-4.15(9H), 4.59-4.80(2H, AB), 4.73(2H, s), 7.2-7.4(5H),

$[\alpha]_D = -40.1^\circ$ (c=1.30, $CHCl_3$).



4-26 4-27

To a solution of oxalyl chloride (40 μL, 0.46 mmol) in CH_2Cl_2 (2.2 mL) cooled to -78°C was added DMSO (0.10 mL, 1.4 mmol) dropwise. After 2 min, the alcohol 4-26 (32 mg, 0.082 mmol) in CH_2Cl_2 (0.8 mL) was added, and the stirring was continued for 15 min. Triethylamine (0.23 mL, 1.7 mmol) was added and after 20 min, the reaction mixture was allowed to warm to -20°C. The reaction mixture was diluted with sat. NH_4Cl and the aqueous layer was extracted with ether (x3). The extracts were washed (sat. NH_4Cl x3, sat. $NaHCO_3$, sat. NaCl) dried (Na_2SO_4) and concentrated under reduced pressure to afford the aldehyde 4-27 (30 mg, 94% yield) as an oil. This material was subjected to the subsequent reaction without purification.

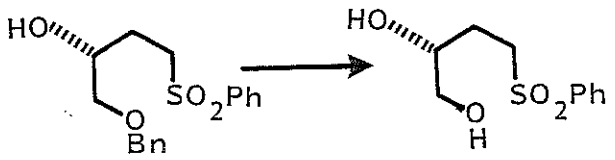


4-28 4-31

1) To a solution of the diol 4-28 dissolved in a mixture of triethylamine (300 mL) and CH_2Cl_2 (700 mL) cooled to 5°C was added p-toluenesulfonyl chloride (27 g, 0.14 mol) portionwise over 2 days. After stirring at 5°C for 2 days, the reaction mixture was poured into H_2O. The separated organic layer was washed (diluted HCl, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the tosylate 4-29 as an oil.

2) A suspension of NaH (8 g, 0.2 mol, washed with hexane before use) in THF (500 mL) and DMF (400 mL) was added thiophenol (22 mL, 0.2 mol) dropwise. After evolution of hydrogen ceased, the crude oil in DMF (100 mL) was introduced into this solution. After stirring for 1 hr, the reaction mixture was poured into water, and the separated aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude sulfide 4-30 (52.4 g) as an oil.

3) This oil was dissolved in CH_2Cl_2 (1 L) and treated with MCPBA (90 g). After stirring for 1 hr, the solution was washed (sat. $NaHSO_3$, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude oil (59.2 g). Chromatography (silica gel 700 g) of this oil with 1:3 and 3:1 ether/hexane afforded the sulfone 4-31 (26.7 g, yield 70%) as an oil.



4-31 4-32

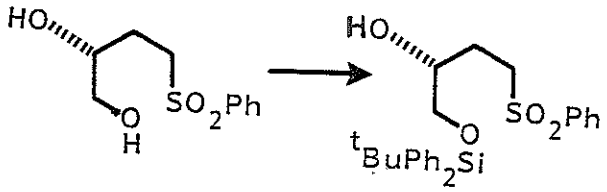
A solution of the benzyl ether 4-31(31.6 g, 99 mmol) dissolved in a mixture of AcOH (58 mL) and ethanol (580 mL) was stirred vigorously under a hydrogen atmosphere in the presence of palladium (25% on the carbon, 7 g). After stirring for 5 hr, the reaction mixture was filtered through a pad of Super Cell. Concentration of the filtrate afforded the diol 4-32 (22.7 g, quantitatively) as an oil, which was purified by recrystallization from AcOEt and hexane to afford the analytically pure sample (9.2 g, yield 40%).

sulfone 4-32

^{1}H nmr δ (in CD_3OD); 1.55-2.0(2H), 3.2-3.5(2H), 3.6(1H, m), 7.6-8.0(5H).

$[\alpha]_D = +13.1^\circ$ (c=1.04, $CHCl_3$).

Found C 52.20, H 6.16; Calcd C 52.17, H 6.13, for $C_{10}H_{14}O_4S$.



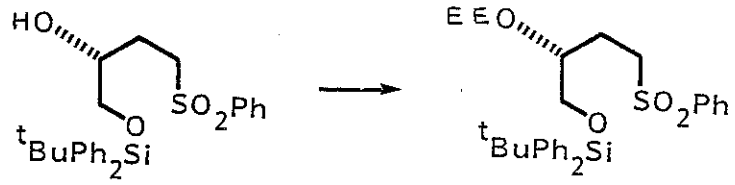
4-32 4-33

To a solution of the diol 4-32 (8.7 g, 37.8 mmol) and imidazole (12 g, 0.18 mol) in DMF (100 mL) was added tert-butyldiphenylsily chloride (10 mL, 38.9 mmol) dropwise. After stirring at room temperature for 2 hr, the mixture was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the silyl ether 4-33 as crude oil (20.0 g). This oil was used for the subsequent reactions without purification. A portion of this oil was purified on preparative silica gels TLC to afford the analytically pure sample.

^1H nmr δ 1.02(9H, s), 1.65-2.0(2H), 2.48(1H, d, J=4), 3.05-3.4(2H, AB), 3.41-3.65(2H, AB), 3.75(1H, br), 7.3-8.0(15H).

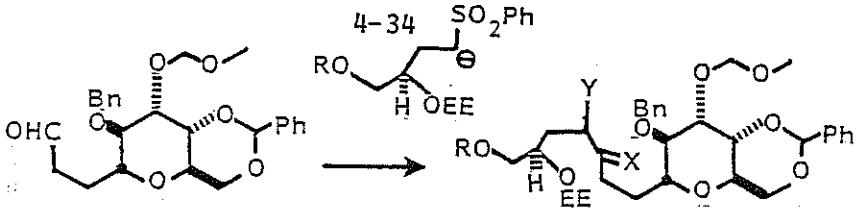
$[\alpha]_D = +13.7^{\circ}$ (c=1.51, $CHCl_3$).

Found C 66.63, H 6.87; Calcd C 66.63, H 6.88, for $C_{26}H_{32}O_4SSi$.



4-33 4-34

To a solution of the silyl ether 4-33 (20g, crude) and PPTS (5 g) dissolved in CH_2Cl_2 (50 mL) was added ethyl vinyl ether (30 mL) dropwise. After stirring overnight, the reaction mixture was poured into sat. $NaHCO_3$ solution and the aq. layer was extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the residue. Purification of the residue by chromatography on silica gel (500 g) with 1:4 (4 L), 1:3 (4 L) and 1:1 (1 L) ether/hexane afforded the sulufone 4-34 (18.4 g, overall yield 90% from 4-32).



4-17 4-35; Y= SO_2Ph, X= H, OH

To a solution of the sulfone 4-34 (6.9 g, 12.8 mmol) dissolved in THF (140 mL) cooled to -78°C was added n-BuLi (1.6M solution in hexane, 7.6 mL, 12.1mmol) dropwise. After stirring for 30 min, the aldehyde 4-17 (3.0 g, 5.2 mmol) in THF (10 mL) was added and stirring was continued at -78°C for 30 min. The reaction mixture was poured into sat. NH_4Cl solution and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O x3, sat. NaCl), dried (Na_2SO_4), concentrated and chromatographed on silica gel(100 g) with 1:3 and 3:1 ether/hexane affording the product 4-35 (4.8 g, yield 86%).

4-35; Y= SO_2Ph, X= H, OH

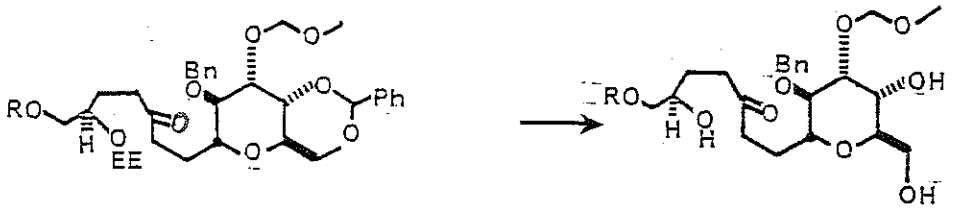
4-36; Y= SO_2Ph, X=O

4-37

R= $SiPh_2Bu^t$

1) To a solution of oxalyl chloride (1.8 mL, 20.6 mol) dissolved in CH_2Cl_2 (150 mL) cooled to -78°C was added DMSO (3.6 mL, 50.8 mmol) dropwise. After stirring for 2 min, the alcohol **4-35** (4.8 g, 4.46 mol) in CH_2Cl_2 (10 mL) was added, and the stirring was continued for 15 min. After addition of triethylamine (11 mL, 79.1 mol), the solution was allowed to warm to 0°C, diluted with H_2O and then extracted with ether (x3). The extracts were washed (sat. NH_4Cl x3, sat. $NaHCO_3$ x1, sat. NaCl x1), dried (Na_2SO_4) and then concentrated to furnish the ketosulfone **4-36** as an oil.

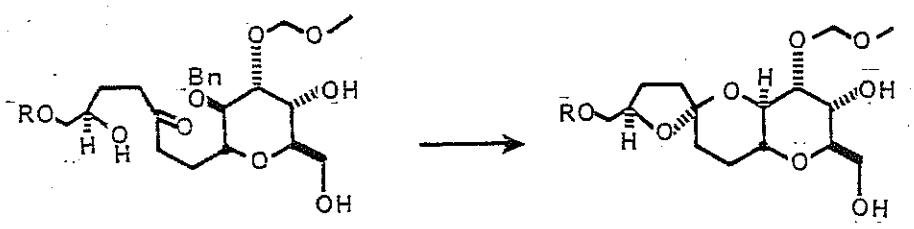
2) This ketosulfone **4-36** was dissolved in THF (210 mL) and water (20 mL). To this solution was added Al-Hg (prepared from aluminum foil 5.0 g according to the procedure described before). After stirring at 60°C overnight, the reaction mixture was diluted with sat. aq. sodium potassium tatrate solution. The aqueous layer was extracted with AcOEt (x3), and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4), and concentrated under reduced pressure to give the crude oil (4.3 g). Chromatography of this oil on silica gel (90 g) with 1:1 ether/hexane afforded the ketone **4-37** (3.1 g, 75% yield in 2 steps).



4-37 4-38

R= $SiPh_2Bu^t$

A solution of the ketone 4-37 (4.1 g) in EtOH (100 mL) and AcOH (8 mL) was refluxed for 3 days. Concentration of the reaction mixture under reduced pressure followed by chromatography of the residue on silica gel (40 g) with 1:1 ether/hexane (250 mL), ether (250 mL) and AcOEt (200 mL) afforded recovered starting material and the triol 4-38 (1.0 g 33% yield). According to the same procedure described above, the additional triol 4-38 (0.8 g, 27%) was obtained from the recovered starting material (combined yield 60%).



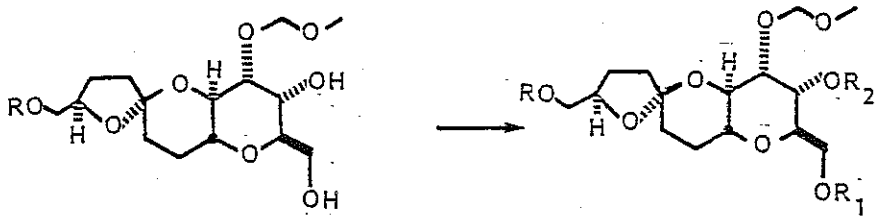
4-38 R= $SiPh_2Bu^t$ 4-39

A solution of the triol **4-38** (4.1 g, 6.03 mol) dissolved in EtOH (130 mL) and AcOH (4 mL) was stirred under hydrogen atmosphere at room temperature for 15 hr in the presence of palladium on carbon (25%, 4 g). The reaction mixtrure was diluted with CH_2Cl_2 (200 mL) and then filtered through a pad of Super Cell. The filtrate was mixed with pyridine (250 mL) and triethylamine (2 mL) and concentrated at about $10^{\circ}C$ to give the tricyclic compound **4-39** as crude oil. A portion of this oil was purified on preparative tlc to afford the analytically pure sample.

^1H nmr δ 1.05(9H, s), 1.7-2.3(9H), 2.80(1H, brs), 3.32-3.47(1H), 3.41(3H, s), 3.55-4.17(8H), 4.22(1H, m), 4.70-4.88(2H, AB), 7.3-7.8(10H).

$[\alpha]_D = +2.9^{\circ}$ (c=1.49, $CHCl_3$).

Found C 65.01, H 7.81; Calcd C 65.00, H 7.74, for $C_{31}H_{44}O_8Si$.



4-39 4-40; R_1= Tr, R_2= H

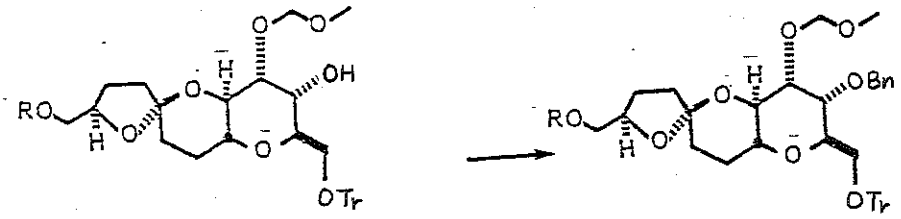
R= $SiPh_2Bu^t$

To a solution of the diol 4-39 (crude oil about 6.03 mol) dissolved in pyridine (600 mL) was added trityl chloride (3.5 g, 12.6 mmol) portionwise at room temperature. After heating at 65°C overnight, the reaction mixture was poured into H_2O. The separated aq. layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to provide the residue. Chromatography (silica gel 140 g) of the residue with 1:2 and 1:1 ether/hexane provided the trityl ether 4-40 (3.9 g, 79% overall yield).

^1H nmr δ 1.06(9H, s), 1.6-2.2(8H), 2.66(1H, d, J=1), 3.15-3.49(3H), 3.36(3H, s), 3.58-3.79(3H), 4.01(1H, t, J=10), 4.08(1H, brs), 4.13-4.31(2H), 4.64-4.81(2H, AB), 7.2-7.8(25H).

$[\alpha]_D$= +0.5° (c=1.99, $CHCl_3$).

Found C 73.67, H 7.17; Calcd C 73.68, H 7.17, for $C_{50}H_{58}O_8Si$.



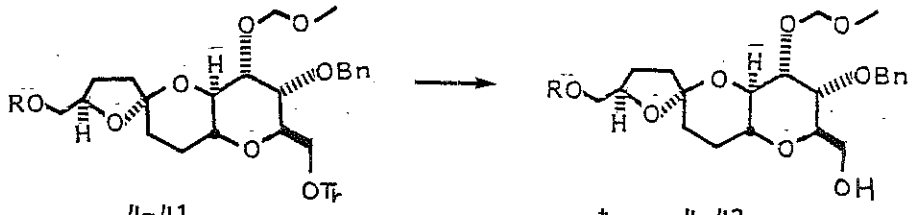
4-40 R= $SiPh_2Bu^t$ 4-41

To a suspension of NaH (60% dispersion in mineral oil, 1 g, 24 mmol, washed with hexane before use) in THF (100 mL) was added the trityl ether 4-40 (4.9 g, 6.02 mmol) in THF (25 mL) dropwise. After stirring at room temperature for 5 min, benzyl bromide (1.3 mL, 11 mmol) and DMF (25 mL) was added. After being stirred at room temperature for 3.5 hr, the reaction mixture was poured into H_2O and the separated aq. layer was extracted with ether (x3). The extracxts were washed (H_2Ox2, sat. NaCl), dried (Na_2SO_4) and concentrated to give the benzyl ether 4-41 (6.28 g, crude). A portion of this oil was purified on preparative silica gel tlc to afford the analytically pure sample.

^1H nmr δ 1.04(9H, s), 1.6-2.2(8H), 3.02-3.42(3H), 3.31(3H, s), 3.57-3.78(3H), 3.90(1H, d, J=2), 4.12(1H, t, J=10), 4.20-4.34(2H), 4.56-4.80(4H), 7.2-7.8(30H).

$[\alpha]_D = -4.4^o$ (c=1.68, $CHCl_3$).

Found C 75.65, H 7.20; Calcd C 75.63, H 7.13, for $C_{57}H_{64}O_8Si$.



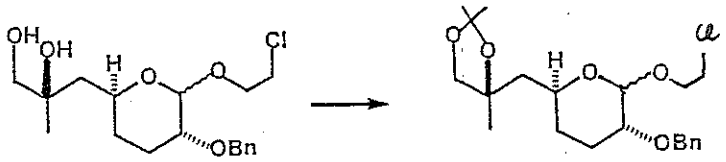
4-41 R= $SiPh_2Bu^t$ 4-42

To a solution of the trityl ether 4-41 (6.2 g, 6.02 mol) in CH_2Cl_2 (150 mL) cooled to -78°C was added Et_2AlCl 1.8 M solution in toluene, 18 mL, 32.4 mmol) dropwise. After stirring at -78oC for 20 min, sat. $NaHCO_3$ solution was added and the cooling bath was removed. Sodium potassium tartrate (45 g) was added and the stirring was continued until the aq. layer was separated. The separated aq. layer was extracted with CH_2Cl_2 (x2), and the extracts were dried (Na_2SO_4), concentrated and chromatographed on silica gel (50 g), with 1:3 ether/hexan (400 mL) and ether (500 mL) to afford the alcohol 4-42 (3.3 g 83% overall yield from 4-40).

^1H nmr δ 1.04(9H, s), 1.7-2.2(8H), 3.25-3.78(6H), 3.86(1H, t, J=10), 4.05-4.20(2H), 4.29(1H, td, J= 8, 4), 4.60-4.28(2H, AB), 4.73(2H, s), 7.2-7.8(15H).

$[\alpha]_D = -8.7^\circ$ (c=1.45, $CHCl_3$).

Found C 68.86, H 7.55; Calcd C 68.85, H 7.60, for $C_{38}H_{50}O_8Si$.



5-19
5-20

5-21'

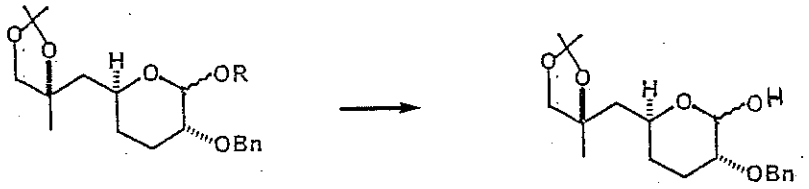
To a solution of the diol (a mixture of 5-19 and 5-20, 1.8 g, 5.0 mmol) and PPTS (0.15 g) in CH_2Cl_2 (36 mL) was added 2,2-dimethoxypropane (3.5 mL) dropwise. After stirring at room temperature overnight, the solution was poured into sat. $NaHCO_3$ solution and the aq. layer was extracted with CH_2Cl_2 (x2). After being dried (Na_2SO_4), the combined organic layer was concentrated under reduced pressure to afford the acetonide 5-21' (1.6 g, 80% yield).

5-21′

5-22′; R= $CH_2CH_2SO_2Ph$

5-23′; R= H

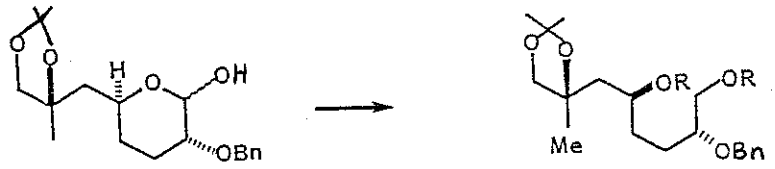
A solution of the chloroethyl glycoside **5-21** (482 mg, 1.2 mmol), benzenesulfinic acid, sodioum salt, dihydrate (1.3 g, 6.5 mmol) and sodium iodide (1.3 g, 8.7 mmol) dissolved in DMF (18 mL) under nitrogen atmosphere was heated at 100°C for 5 hr. The solution was poured into H_2 and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of lactol **5-23′** and sulfonyl ethyl glycoside **5-22′** (543 mg). This material was used to subsequent reactions without further purification.



5-22′; R= $CH_2CH_2SO_2Ph$
5-23′; R= H

5-23′

A solution of a mixture of lactol 5-23′ and sulfonyl ethyl glycoside 5-22′ (181 mg, 0.4 mmol) and potassium carbonate (0.28 g, 2.0 mmol) dissolved in DMF (4 mL) under nitrogen atmosphere was heated at 80°C for 5 hr. The solution was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (H_2 sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue (131 mg) on preparative silica gel tlc gave the lactol 5-23′ (61 mg, 45% overall yield).



5-23′

5-45; R= H

5-38; R= Ac

1) To a solution of the lactol 5-23′ (21 mg, 0.0625 mmol) in THF (1 ml) was added $LiAlH_4$ (10 mg) portionwise. After stirring at room temperature for 2 hr, H_2O (40 mL), 15% NaOH (10 mL) and hexane (0.7 mL) was added. The solution was filtered on a pad of Super Cell and the filtrate cake was washed with AcOEt. Concentration of the filtrate under reduced pressure gave the diol 5-45 (24 mg).

2) The diol 5-45 was dissolved in a mixture of pyridine (1 mL) and acetic anhydride (0.5 mL). After stirring at 30°C overnight, concentration of the solution followed by passing the residue through a short column of silica gel with ether gave the diacetate 5-38 (27 mg, quantitatively).

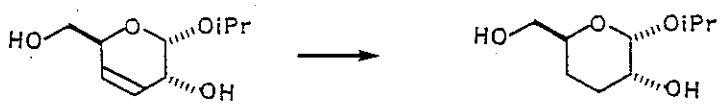
^1H Nmr analysis showed that the product ratio of α-/β epoxide was 1/7.

3-4 5-6

To a solution of LAH (29 g, 0.76 mol) in THF (1.8 L) cooled to 0°C was added enol acetate **3-4** (90 g, 0.27) in THF (200 mL) dropwise over 1 hr. After stirring at 0° for 1 hr, AcOEt (20 mL), H_2O (30 mL), hexane (1.2 L), 15% NaOH (30 mL) and H_2O (90 mL) was added in this sequence. After being stirred at room temperature overnight, the reaction mixture was filtered through a pad of Super Cell, and the filter cake was washed with AcOEt (2 L). Concentration of the filtrate under reduced pressure gave the diol **5-6** (51.7 g, quantitative yield) as an oil. Chromatography of a portion of this oil gave the analytically pure sample.

^1H nmr δ 1.21(3H, d, J=6), 1.26(3H, d, J=6), 2.25-2.45(2H), 3.5-3.8(2H), 4.01(1H, septet, J=6), 4.1-4.3(2H), 5.10(1H, d, J=4), 5.65-5.82(2H).

$[\alpha]_D = +40.9^\circ$ (c=2.71, $CHCl_3$).

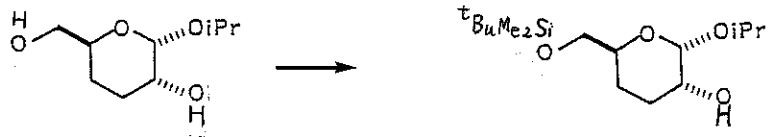


5-6 5-7

A vigorously stirred solution of the olefin 5-6 (50 g, 0.27 mmol) in AcOEt (1.5 L) was hydrogenated under a hydrogen atmosphere at room temperature in the presence of palladium (10% on the carbon, 5 g) for 1 day. The reaction mixture was filtered through a pad of Super Cell and the filter cake was washed with AcOEt. Concentration of the filterate under reduced pressure gave the diol 5-7 (47.9 g, 96% yield) as an oil. A portion of this oil was purified by chromatography to afford the analytically pure sample.

^{1}H nmr δ 1.18(3H, d, J=6), 1.26(3H, d, J=6), 1.3-2.2(6H), 3.4-3.65(3H), 3.83(1H, m), 3.96(1H, septet, J=6), 4.89(1H, d, J=4).

$[\alpha]_D$= +137.2° (c=0.68, $CHCl_3$).



5-7 5-8

To a solution of the diol 5-7 (40 g, 0.21 mol) and imidazole (65 g, 0.96 mol) in DMF (1.2 L) cooled to 0°C was added t-butyldimethylchlorosilane (30 g, 0.20 mol) portionwise. After stirring at room temperature overnight, the solution was poured into H_2O, and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the silyl ether 5-8 as an oil. This oil was used without further purification. A portion of this oil was purified by chromatography (silica gel) to afford the analytically pure sample.

^1H nmr δ 0.06(6H, s), 0.89(H, s), 1.17(3H, d, J=6), 1.25(3H, d, J=6), 1.2-1.95(5H), 2.45-2.66(3H), 3.45-3.66(3H), 3.76(1H, dddd, J=11, 5, 5, 2), 3.96(1H, septet, J=6), 4.86(1H, d, J=4).

$[\alpha]_D = +82.4^\circ$ (c=1.74, $CHCl_3$).

Found C 59.17, H 10.58; Calcd C 59.17, H 10.59, for $C_{15}H_{32}O_4Si$.

5-8 5-9

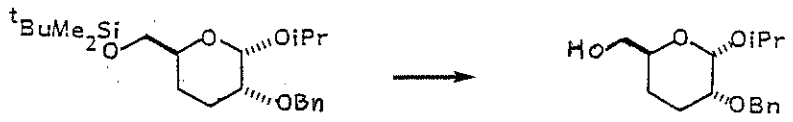
R = $^{t}BuMe_2Si$

To a stirred slurry of NaH (60% oil dispersion, 12 g, 0.3 mol) in THF (900 mL) was added the alcohol 5-8 (0.21 mol) in THF (100 mL) dropwise. After stirring at room temperature for 5 min, benzyl bromide (30 mL, 0.25 mol) and DMF (240 mL) was added and the stirring was continued for 6.5 hr. The solution was poured into H_2O and the separated aq. layer was extracted with ether (x3). The combined organic layers were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the benzyl ether 5-9 (85.6 g) as an oil. This material was used without purification. A portion of this material was purified on preparative silica gel tlc to afford the analytically pure sample.

^1H nmr δ 0.05(6H, s), 0.89(9H, s), 1.19(3H, d, J=6), 1.27(3H, d, J=6), 1.3-2.0(4H), 3.4-3.6(3H), 3.82(1H, dddd, J=11, 6, 6, 2), 3.96(1H, septet, J=6), 4.57(2H, s), 4.96(1H, d, J=4), 7.2-7.4(5H).

$[\alpha]_D = +74.2^{\circ}$ (c=1.10, $CHCl_3$).

Found C 67.14, H 9.66; Calcd C 66.96, H 9.71, for $C_{22}H_{38}O_4Si$.



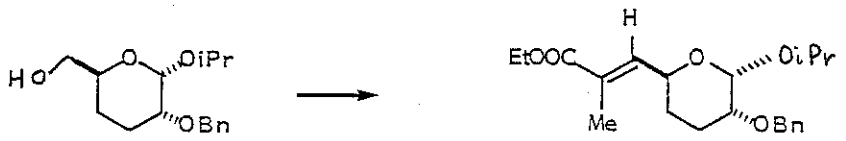
5-9 5-10

To a solution of the silyl ether **5-9** (82.5 g, 0.21 mL) in a mixture of THF (800 mL) and CH_3CN (400 mL) was added n-Bu_4NF (1M solution in THF, 200 mL, 0.2 mol) dropwise. After stirring at room temperature overnight, the solution was poured into H_2O and the aq. layers was extracted with ether (x3). The combined organic layer were washed (H_2O x2, sat. NaCl) and dried (Na_2SO_4). Concentration under reduced pressure followed by chromatography (silica gel 600 g) with 1:3 and 1:1 ether/hexane as eluant afforded the alcohol **5-10** (47 g, 80% overall yield from **5-7**).

^1H nmr δ 1.21(3H, d, J=6), 1.27(3H, d, J=6), 1.35-2.1(4H), 3.35-3.65(3H), 3.8-4.0(2H), 4.5-4.65(2H, AB), 4.96(1H, d, J=3), 7.2-7.4(5H).

$[\alpha]_D = +104.7^o$ (c=1.49, $CHCl_3$).

Found C 68.45, H 8.58; Calcd C 68.54, H 8.63, for $C_{16}H_{24}O_4$.



5-10 5-12

To a solution of oxalyl chloride (15 mL, 0.17 mol) in CH_2Cl_2 (480 mL) cooled to -78oC under N_2 atmosphere was added DMSO (30 mL, 0.42 mol) over 5 min. After 5 min, the alcohol **5-10** (15.2 g, 0.054 mol) in CH_2Cl_2 (20 mL) was added to the resulting solution over 5 min. After stirring at -78oC for 15 min, triethylamine (75 mL, 0.54 mol) was added. After stirring at -78°C for 15 min, the reaction mixtrure was allowed to warm slowly to 0°C and then recooled to -20°C. Triphenylethoxycarbonylethyl-phosphorane (24.2 g, 0.067 mol) was added, and then the solution was warmed up to room temperature. The solution was poured into H_2O and the aqueous layer was extracted with 1:3 ether/hexane. The extracts were washed (sat. NH_4Cl, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 250 g) of the residue (26.9 g) with 1:10 ether/hexane gave the α,β-unsaturakted ester **5-12**(16.3 g, 83% yield).

^1H nmr δ 1.21(3H, d, J=6), 1.27(3H, t, J=7), 1.28(3H, d, J=6), 1.4-2.1(4H), 1.88(3H, d, J=1), 3.50(1H, ddd, J=11, 5, 3), 3.95(1H, septet, J=6), 4.17(2H, q, J=7), 4.5-4.7(2H), 4.96(1H, d, J=3), 6.60(1H, ddd, J=8, 2, 1), 7.2-7.4(5H).

IR ($CHCl_3$) 1710 cm^{-1}.

$[\alpha]_D$= +78.9° (c=1.64, $CHCl_3$).

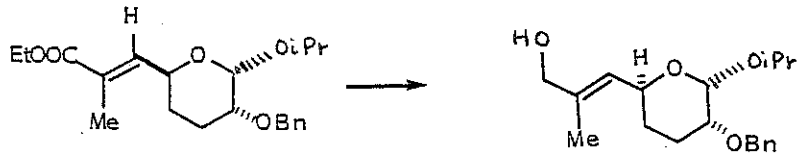
Found C 69.57, H 8.35; Calcd C 69.58, H 8.34, for $C_{21}H_{30}O_5$.

5-12

5-13; R= $\cdots\!\!\cdots OCH_2CH_2Cl$

5-14; R= $\text{—}OCH_2CH_2Cl$

A solution of the isopropyl glycoside 5-12 (45 g, 0.12 mol) and CSA (0.31 g) in 2-chloroethanol (475 mL) was heated at 50°C overnight. The solution was poured into sat. $NaHCO_3$ solution and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of α- and β-chloroethyl glycosides (5-13 and 5-14) in 6:4 ratio (36.3 g, 79% yield).



5-12 5-15

To a solution of the ester **5-12** (3.0 g, 8.3 mmol) dissolved in CH_2Cl_2 (40 mL) cooled to -78 °C under N_2 atmosphere was added DIBAL (1.07 M solution in toluene, 60 mL, 64 mmol) dropwise. After stirring at -78°C for 30 min, aq. saturated tartaric acid solutuin was added. The seaprated aq. layer was extracted with ether (x3). The combined organic layer was washed (sat, $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the allyl alcohol **5-15** (2.7 g, quantitatively).

^1H nmr δ 1.20 (3H, d, J=6), 1.30(3H, d, J=6), 1.70(3H, d, J=1), 1.35-2.10(4H), 3.48(1H, ddd, J=11, 5, 3), 3.73(1H, m), 3.88-4.03(2H, AB), 4.50-4.65(2H, AB), 4.94(1H, d, J=3), 5.37(1H, ddd, J=9, 3, 1), 7.2-7.4(5H).

5-13; R= ⁄⁄⁄⁄OCH$_2$CH$_2$Cl
5-14; R= ▬OCH$_2$CH$_2$Cl

5-16; R= ⁄⁄⁄⁄OCH$_2$CH$_2$Cl
5-17; R= ▬OCH$_2$CH$_2$Cl

To a solution of the α,β-unsaturated ester (a mixture of 5-13 and 5-14, 34g, 88.9 mol) in CH_2Cl_2 (680 mL) cooled to -78°C under nitrogen atmosphere was added diisobutylaluminum hydride (1.5 M solution in toluene, 142 mL, 214 mmol) dropwise. After stirring at -78°C for 1 hr, H_2O (600 mL) and tartaric acid (90 g) was added and the separated aq. layer was extracted with CH_2Cl_2 (x2). The extracts were washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated under reduced pressure to afford the chloroethyl glycoside (a mixture of 5-16 and 5-17, 32.5 g, quantitatively). A portion of this mixture was seaprated by HPLC to afford the pure α- 5-16 and β-chloroethyl glycoside 5-17.

α-chloroethyl glycoside 5-16

^{1}H nmr δ 1.35-2.1(4H), 1.69(3H, s), 3.49(1H, ddd, J=11, 4, 3), 3.6-4.0(6H), 4.5-4.7(3H), 4.84(1H, d, J=3), 5.35(1H, d, J=8), 7.2-7.4(5H).

$[\alpha]_D$= +66.7° (c=1.18, $CHCl_3$).

Found C 63.41, H 7.47; Calcd C 63.43, H 7.39, for $C_{18}H_{25}O_4Cl$.

β-chloroethyl glycoside 5-17

^{1}H nmr δ 1.3-2.2(4H), 1.68(3H, s), 3.25(1H, m), 3.6-3.85(3H), 3.95(2H, brs), 4.05-4.25(2H), 4.42(1H, d, J=8) 4.62-4.90(2H, AB), 5.45(1H, d, J=8), 7.4-7.8(5H).

$[\alpha]_D$= -0.70° (c=1.13 $CHCl_3$).

Found C 63.32, H 7.45; Calcd C 63.43, H 7.39, for $C_{18}H_{25}O_4Cl$.

5-15 5-18

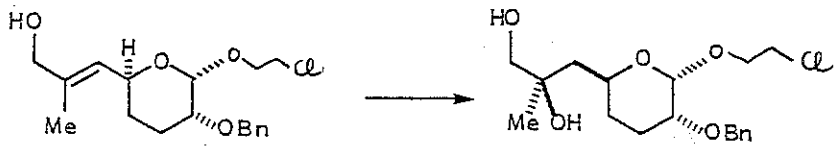
To a solution of the allyl alcohol **5-15** (2.7 g, 8.3 mmol) dissolved in a mixture of THF (50 mL) and H_2O (10 mL) was added mercuric acetate (3.0 g, 12.6 mmol) portionwise. After stirring at room temperature for 1 day, the reactio mixture was cooled to 0^oC, and $NaBH_4$ (6.0g) was added cautiously portionwise. After stirring at room temperature for 1 hr, the reaction mixture was poured into H_2O, and the aqueous layer was extracted with AcOEt(x3). The combined organic layer was washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the diol **5-18** (3.0 g, quantitatively). H1 Nmr analysis showed the stereoselectivity of this oxymercuration reaction to be 86:14.

^1H nmr δ 1.17(3H, s), 1.21(3H, d, J=6), 1.29(3H, d, J=6), 1.3-2.1(6H), 2.56(1H, br), 3.3-3.6(4H), 3.90(1H, septet), 4.06(1H, ddt, J=11, 9, 3), 4.50-4.63(2H, AB), 4.91(1H, d, J=3), 7.2-7.4(5H).

5-16; R= $\cdots\cdots OCH_2CH_2Cl$
5-17; R= $\blacksquare\!\!\blacksquare OCH_2CH_2Cl$

5-19; R= $\cdots\cdots OCH_2CH_2Cl$
5-20; R= $\blacksquare\!\!\blacksquare OCH_2CH_2Cl$

To a solution of the allyl alcohol (a mixture of 5-16 and 5-17, 2.0 g, 5.9 mmol) in a mixture of THF (33 ml) and H_2O (6.6 mL) cooled to 0oC was added mercuric acetate (2.7 g, 8.5 mmol) portionwise. After stirring at 0°C for 1.5 day, $NaBH_4$ (3.0 g) was added at 0oC portionwise, and the stirring was continued at room temperature for 1 hr. The separated aq. layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl) and dried (Na_2SO_4). Concentration under reduced pressure gave the diol (a mixture of 5-19 and 5-20, 1.8 g, 81% yield).



5-16 5-19

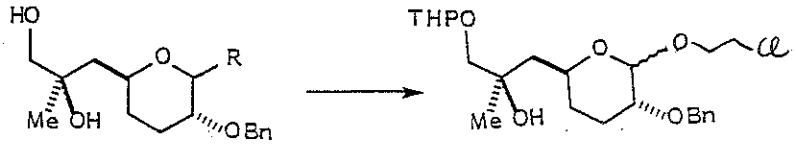
To a solution of the α-glycoside allyl alcohol 5-16 (210mg, 0.62 mol) in a mixture of THF (3.1 mL) and H_2O (0.6 mL) cooled to -20oC was added mercuric acetate (280 mg, 0.88 mmol) portionwise. After stirring at -20°C for 4 days, $NaBH_4$ (250 mg) was added portionwise. The aqueous layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the diol 5-19 (221 mg, quantitatively).

^1H nmr δ 1.17(3H, s), 1.3-2.1(6H), 3.2-4.2(8H), 4.50-4.65(2H, AB), 4.82(1H, d, J=3), 7.2-7.4(5H).

5-17 5-20

By the procedure described before, the β-glycoside allyl alcohol **5-17** (159 mg, 0.46 mmol) with mercuric acetate (210 mg, 0.60 mmol) and $NaBH_4$ (200 mg) in a mixture of THF (2.4 mL) and H_2O (0.5 mL) afforded the diol **5-20** (150 mg, 91% yield).

^1H nmr δ 1.18(3H, s), 1.3-2.2(6H), 3.15-3.85(7H), 4.16(1H, m), 4.38(1H, d, J=8), 4.62-4.89(2H, AB), 7.2-7.4(5H).

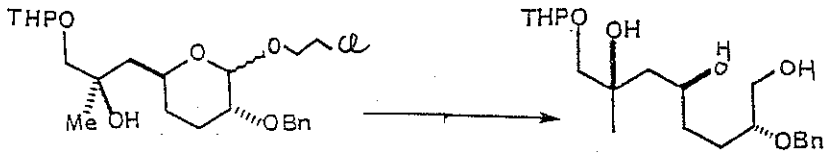


5-19; R= OCH_2CH_2Cl

5-20; R= OCH_2CH_2Cl

5-21

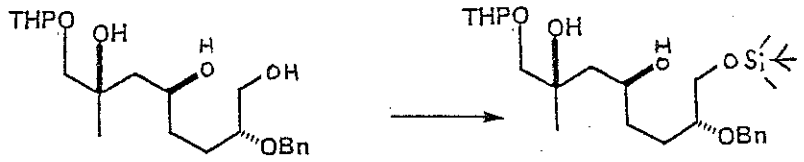
To a solution of the diol (a mixture of **5-19** and **5-20**, 7.1 g, 19.8 mol) and PPTS (0.50 g) dissolved in CH_2Cl_2 (120 mL) was added dihydropyrane (3.0 mL, 40 mmol) dropwise. After stirring at room temperature overnight, the solution was poured into sat. $NaHCO_3$ solution and the aqueous layer was extracted with ether. The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the tetrahydropyranyl ether **5-21** (10.1 g). This material was used to subsequent reactions without purification.



5-21 5-24

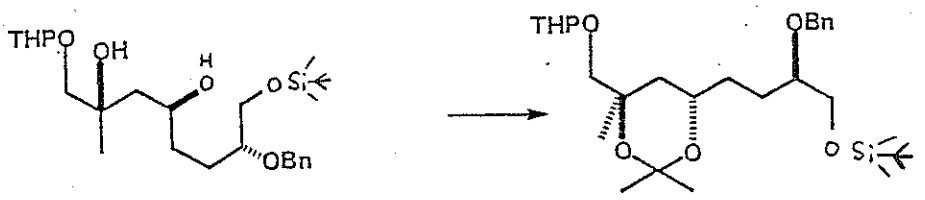
1) To a solution of the chloroethyl glycoside 5-21 (10.1 g. 19.8 mmol) dissolved in DMF (220 mL) was added benzenesulfinic acid sodium salt (18.6 g, 93 mmol) and potassium iodide (27.6g, 166 mmol) portionwise. The solution was heated at 100°C for 6 hr under nitrogen atmosphere and then poured into H_2O. The aqueous layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl) and dried (Na_2SO_4). Concentration under reduced pressure gave the oil (11.1 g).

2) To a solution of the oil (11.1 g) dissolved in isopropanol (240 mL) was added $NaBH_4$ (2.4 g) portionwise. The solution was heated at 70oC for 2 hr under nitrogen atmosphere and then concentrated under reduced pressure. The resulting residue was dissolved in H_2O (115 mL) and the aq. layer was washed with 1:5 ether/hexane (x3) to removed the non-polar by-products. The aqueous layer was extracted with CH_2Cl_2 and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the triol 5-24 (7.9 g). This material was used to subsequent reactions without purification.



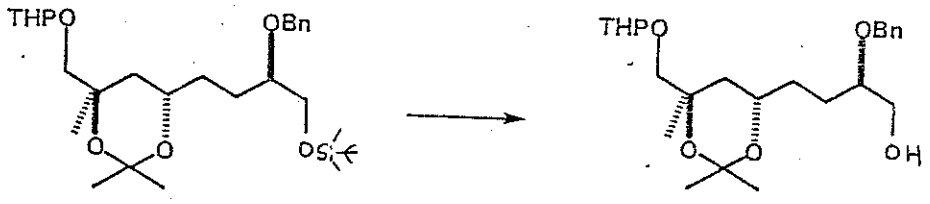
5-24 5-25

To a solution of the triol **5-24** (7.9 g, less than 21 mmol) and imidazole (3.5 g, 51 mmol) in DMF (200 mL) was added tert-butyldimethylsilyl chloride (3.5 g, 12.8 mmol) portionwise. After stirring at room temperature for three hours, the solution was poured into H_2O. The aq. layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the silyl ether **5-25** (10.0 g). This material was used to the subsequent reaction without purification.



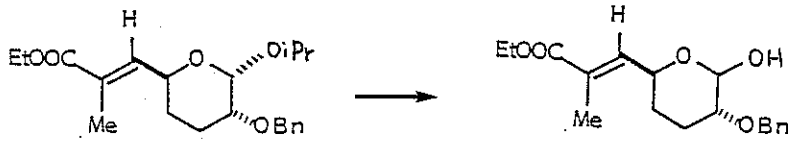
5-25 5-26

To a solution of the diol **5-25** (10.0 g) and PPTS (0.3 g) in CH_2Cl_2 (200 mL) cooled to 0^oC was added 2-methoxypropene (3.7 mL, 38.7 mmol) dropwise. After stirring at 0oC for 30 min, the solution was poured into $NaHCO_3$ solution and the aq. layer was extracted with CH_2Cl_2 (x2). After being dried (Na_2SO_4), concentration of the combined organic layers under reduced pressure, followed by chromatography (silica gel 100 g) of the residue (11.4 g) with 1:5 ether/hexane gave the acetonide **5-26** (5.3 g, 47% overall yield from a mixture of **5-19** and **5-20**).



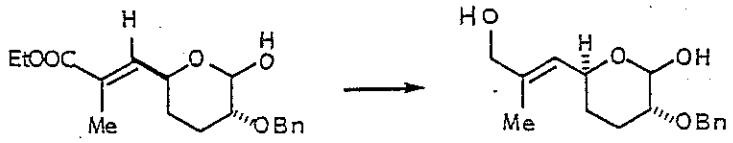
5-26 5-27

To a solution of the silyl ether **5-26** (5.3 g, 9.9 mmol) dissolved in THF (120 mL) was added n-Bu_4NF (1M solution in THF, 10 mL, 10 mmol) dropwise. After stirring at room temperature for 3 hr, the solution was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 80 g) of the residue (4.8 g) with 2:1 ether/hexane gave the alcohol **5-27** (3.1 g 74% yield) as an oil.



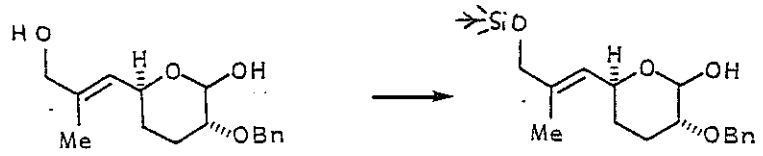
5-12 5-29

A solution of the isopropyl glycoside 5-12 (1.41 g, 4.4 mmol) in a mixture of acetic acid (30 mL) and H_2O (20 mL) was refluxed for 6 hr. The solution was diluted with H_2O (200 mL) and then extracted with ether (x3). The extracts were washed (H_2O, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the lactol 5-29 (1.3 g, quantitatively).



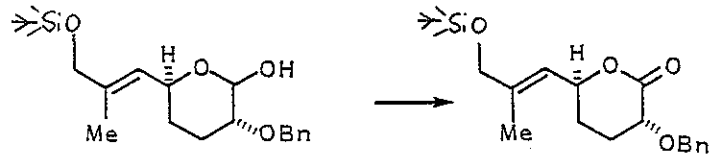
5-29 5-30

To a solution of the α,β-unsaturated ester 5-29 (1.3 g, 4.1 mmol) dissolved in CH_2Cl_2 (40 mL) cooled to -78°C under nitrogen atmosphere was added diisobutylaluminum hydride (1.07 M solution in toluene, 25 mL, 27 mmol) dropwise. After stirring at -78°C for 1 hr, H_2O (50 mL) and tartaric acid (3 g) was added and the stirring was continued at room temperature until the solution became clear. The aq. layer was extraced with CH_2Cl (x2) and the extracts were washed (sat. $NaHCO_3$) and dried (Na_2SO_4). Concentration under reduced pressure gave the E-allyl alcohol 5-30 (1.09 g, 96% yield) as an oil.



5-30 5-31

To a solution of the allyl alcohol **5-30** (9.7 g, 30.5 mmol) and imidazole (5.2 g, 76.4 mmol) in DMF (500 mL) was added tert-butyldimethylsilyl chloride (6.5 g, 24 mmol) portionwise. After stirring at room temperature for 1 hr, the solution was poured into H_2O. The aq. layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the silyl ether **5-31** (11.4 g, 87% yield).



5-31 5-32

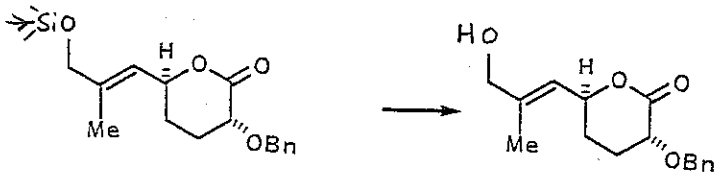
To a solution of oxalyl chloride (5.6 mL, 64 mmol) dissolved in CH_2Cl_2 (230 mL) cooled to -78°C was added DMSO (11 mL, 155mmol) dropwise. After stirring for 2 min, the lactol **5-31** (11.4 g, 26 mmol) in CH_2Cl_2 (20 mL) was added and the stirrng was continued at -78°C for 15 min. Triethylamine (30 mL, 0.22 mol) was added and the reaction mixture was allowed to warm slowly to 0°C. The solution was poured into H_2O and the aqueous layer was extracted with ether. The extracts were washed (sat. NH_4Cl, x2, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the lactone **5-32** (11.7g).

^1H nmr δ 0.06(6H, s), 0.90(9H, s), 1.65(3H, s), 1.7-2.3(4H), 3.95-4.05(3H), 4.64-4.96(2H, AB), 5.30(1H, ddd, J=10, 9, 4), 5.56(1H, ddd, J=9, 3, 1), 7.3-7.5(5H).

IR ($CHCl_3$) 1740 cm^{-1}.

$[\alpha]_D$= +96.1° (c=1.83, $CHCl_3$).

Found C 67.74, H 8.77; Calcd C 67.65, H 8.77, for $C_{22}H_{34}O_4Si$.



5-32 5-33

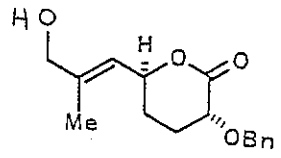
To a solution of the silyl ether 5-32 (3.5 g, 8.1 mol) in a mixture of THF (30 mL) and CH_3CN (5 mL) coolded 0°C was added n-Bu_4NF (1M solution in THF, 8 mL, 8 mol) dropwise. The cooling bath was removed and, after stirring overnight, the solution was poured into H_2O. The aq. layer was extracted with ether (x3), and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrataed under reduced pressure to afford the allyl alcohol 5-33 (2.06 g, 92% yield).

^1H nmr δ 1.69(3H, s), 1.7-2.3(4H), 3.95-4.05(3H), 4.63-4.95(2H, AB), 5.29(1H, ddd, J=11, 9, 3), 5.50(1H, ddd, J=9, 3, 1), 7.3-7.5(5H).

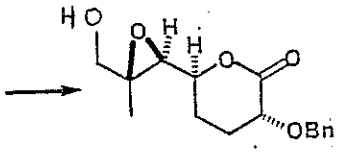
IR ($CHCl_3$) 3450, 1740 cm^{-1}.

$[\alpha]_D$= +129.7° (c=0.86, $CHCl_3$).

Found C 69.57, H 7.45; Calcd C 69.54, H 7.30, for $C_{16}H_{20}O_4$.



5-33



5-34

To a solution of the allyl alcohol **5-33** (25 mg, 0.090 mmol) and (+)-DET (40 mL, 0.23 mmol) in CH_2Cl_2 (1 mL) cooled to -20°C was added titanium(IV) isopropoxide (50 mL, 0.168 mmol). After stirring for 20 min, tert-butyl hydroperoxide (3.3 M in 1,2-dichloroethane, 0.15 mL, 0.50 mmol) was added and the stirring was continued at -20°C for 1 day. The solution was poured into sat. tartaric acid solution and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue (55 mg) on prepatative silica gel TLC gave the β-epoxide **5-34** (12 mg, 46% yield).

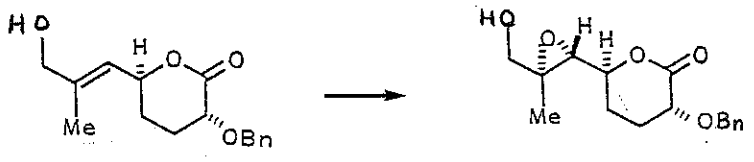
^1H Nmr analysis of the residue [a mixture of (+)-DET and epoxide] showed the absence of α-epoxide.

^1H nmr δ 1.37(3H, s), 1.6-2.3(5H), 3.09(1H, d, J=8), 3.55-3.80(2H), 4.01(1H, dd, J=8, 6)4.36(1H, ddd, J=11, 8, 3), 4.64-4.93(2H, AB), 7.3-7.4(5H).

IR ($CHCl_3$) 3500, 1750 cm^{-1}.

$[\alpha]_D$= +85.7° (c=1.22, $CHCl_3$).

Found C 65.81, H 6.99; Calcd C 65.74, H 6.90, for $C_{16}H_{20}O_5$.



5-33 5-39

To a solution of the allyl alcohol **5-33** (86 mg, 0.31 mmol) and (-)-DET (0.10 mL, 0.59 mmol) in CH_2Cl_2 (4 mL) cooled to -20°C was added titanium(IV) isopropoxide (0.11 mL, 0.37 mmol) dropwise. After stirring for 15 min, the solution became slightly yellow. To this solution was added tert-butyl hydroperoxide (3.3 M in 1,2-dichloroethane, 0.40 mL, 1.32 mmol) and the stirring was continued for 2 days. The solution was poured into sat. tartaric acid solution and the aqueous layer was extracted with ehter (x3). The extracts were washed (sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on preparative silica gel TLC gave the α-epoxide **5-39** (39 mg, 43% yield) and β-epoxide **5-34** (10 mg, 10%).

^{1}H Nmr analysis of the crude product [a mixture of (+)-DET, α- and β-epoxide] showed that the product ratio of α- and β-epoxide is a 11:2 ratio.

^{1}H nmr δ 1.32(3H, s), 1.7-2.3(5H), 3.20(1H, d, J=8), 3.53-3.77(2H), 4.02(1H, dd, J=7, 6), 4.52(1H, ddd, J=11, 8, 4), 4.60-4.91(2H, AB), 7.3-7.4(5H).

IR ($CHCl_3$) 3500, 1750 cm^{-1}.

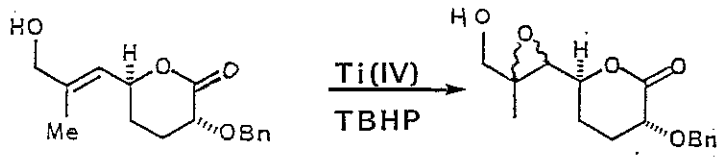
$[\alpha]_D$= +118.0° (c=0.99, $CHCl_3$).

Found C 65.74, H 6.94; Calcd C 65.74, H 6.90, for $C_{16}H_{20}O_5$.

5-33 5-34
5-39

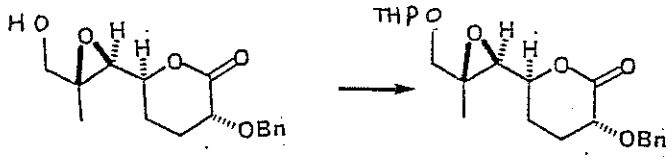
To a solution of the allyl alcohol 5-33 (5 mg, 0.018 mmol) dissolved in CH_2Cl_2 (0.2 mL) cooled to 0°C was added MCPBA (80%, 5 mg, 0.023 mmol) portionwise. After stirring at 0oC for 2.5 hr, the reaction mixture was poured into sat. $NaHCO_3$ solution. The aq. layer was extracted with ether and the extracts were washed (sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of starting material, α - 5-39 and β -epoxide 5-34 (4mg).

^1H nmr analysis of this crude mixture showed the product ratio of α -/β -epoxide being 1/2.



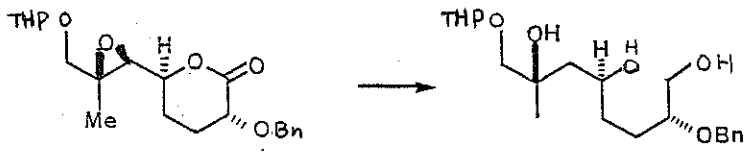
5-33 5-34
5-39

To a solution of the allyl alcohol **5-33** (18 mg, 0.065 mmol) and titanium(IV) isopropoxide (50 µL, 0.16 mol) dissolved in CH_2Cl_2 (1 mL) cooled to -20°C was added tert-butyl hydroperoxide (3.3 M solution in 1,2-dichloroethane, 0.1 mL, 0.33 mmol) dropwise. After stirring at -20°C overnight, the solution was poured into sat. tartaric acid solution. The aqueous solution was extracted with water (x3) and the extracts were washed (sat. $NaHSO_3$, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of epoxide (21 mg). ^1H Nmr analysis showed the product ratio of α/β epoxide being 1/2.



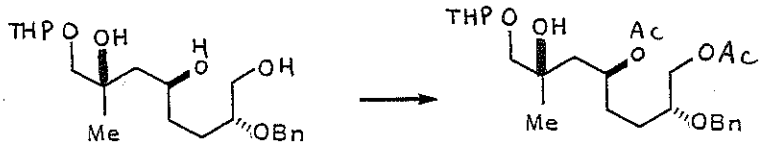
5-34 5-35

To a solution of the alcohol **5-34** (216 mg, 0.79 mmol) and PPTS (20 mg) in CH_2Cl_2 (7 mL) was added dihydropyrane (0.20 mL, 2.2 mmol) dropwise. After stirring at room temperature for 5 hr, the reaction mixture was poured into sat. $NaHCO_3$, and the aq. layer was extracted with CH_2Cl_2 (x2). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure to afford the tetrahydropyranyl ether **5-35** (300 mg).



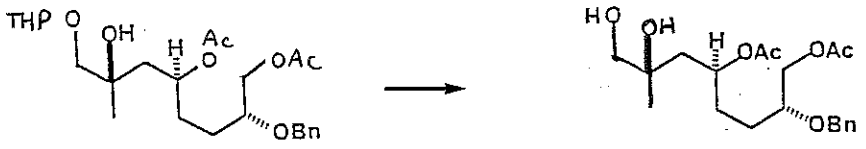
5-35 5-24

To a solution of the tetrahydropyranyl ether **5-35** (355 mg, 0.94 mmol) in THF (10 mL) at room temperature was added $LiAlH_4$ (0.20 g, 5.3 mmol) portionwise. After stirring for 2 hr, H_2O (0.8 mL), 15% NaOH (0.2 mL) and hexane (7 mL) was added. The solution was filtered on a pad of Super Cell and the filtrate cake was throughly washed with AcOEt. Concentration of the filtrate gave the triol **5-24** (305 mg, 85% yield).



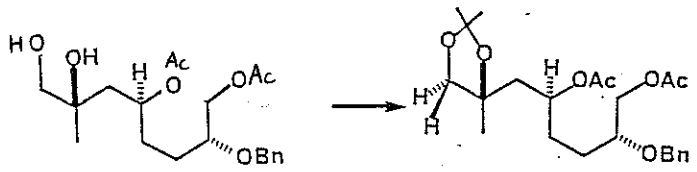
5-24 5-36

A solution of the triol **5-24** (12 mg) in a mixture of pyridine (0.5 mL) and acetic anhydride (0.25 mL) was stirred at room temperature overnight. Concentration under reduced pressure followed by purification of the residue on preparative silica gel tlc gave the diacetata **5-36** (14 mg, 96% yield).



5-36 5-37

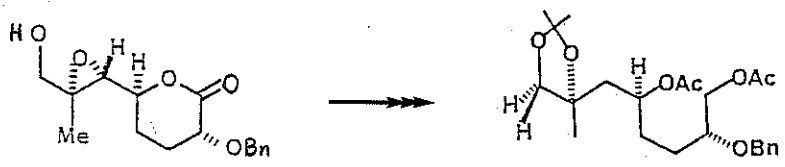
A solution of the tetrahydropyranyl ether 5-36 (14 mg, 0.030 mmol) and PPTS (ca. 2 mg) in MeOH (0.4 mL) was stirred at 50°C for 1.5 hr. The solution was poured into sat. $NaHCO_3$ and the aq. layer was extracted with CH_2Cl_2 (x3). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the diol 5-37 (11 mg, 96% yield).



5-37 5-38

To a solution of the diol **5-37** (11 mg, 0.029 mmol) and PPTS (2 mg) in a mixture of acetone (0.3 mL) and CH_2Cl_2 (0.3 mL) was added a few drops of 2,2-dimetoxypropane. After stirring at room temperature for 2 hr, the solution was poured into sat. $NaHCO_3$ and the aq. layer was extracted with ether (x3). The combined organic layer was washed (sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the acetonide **5-38** (10 mg, 82% yield).

^1H nmr δ 1.26(3H, s), 1.35(3H, s), 1.39(3H, s), 1.5-1.8(4H), 2.03(3H, s), 2.07(3H, s), 3.57(1H, m), 3.63-3.79(2H, AB), 4.02-4.23(2H, AB), 4.50-4.67(2H, AB), 5.03(1H, m), 7.2-7.4(5H).



5-39 5-44

1) To a solution of the alcohol 5-39 (30 mg) and PPTS (5 mg) in CH_2Cl_2 (1.5 mL) was added dihjydropyran (0.05 mL) dropwise. After stirring at room temperature for 2 hr, the solution was poured into sat. $NaHCO_3$ and the aq. layer was extracted with CH_2Cl_2 (x2). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the tetrahydropyranyl ether 5-40(44 mg).

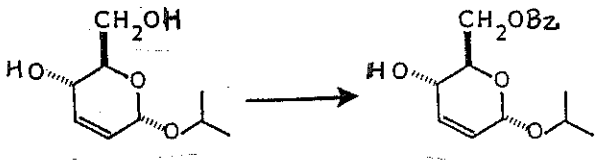
2) To a solution of the tetrahydropyranyl ether 5-40(44 mg) in THF was added $LiAlH_4$ (30 mg) portionwise. After stirring at room temperature overnight, H_2O (0.2 mL), 15% NaOH (50 mL) and hexane was added. The solution was filtered through a pad of Super Cell and the filter cake was washed with AcOEt. Concentration of the filtrate gave the triol 5-41(46 mg).

3) A solution of the triol 5-41(46 mg) in a mixture of pyridine (1 mL) and acetic anhydride (0.5 mL) was stirred at 30°C overnight. Concentration of the solution under reduced pressure gave the diacetate 5-42.

4) The diacetate 5-42 was dissolved in MeOH (1 mL) and PPTS (5 mg) was added to this solution. After stirring at 50°C for 4 hr, the solution was poured into sat. $NaHCO_3$ solution. The aq. layer was extracted with CH_2Cl_2 (x3) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the diol 5-43(35 mg).

5) To a solution of the diol 5-43 (35 mg) in a mixture of CH_2Cl_2 (1 mL) and 2,2-dimethoxypropane (0.1 mL) was added PPTS (5 mg) portionwise. After stirring at room temperature for 2 hr, the solution was poured into sat. $NaHCO_3$ solution. The aq. layer was extracted with CH_2Cl_2 (x2) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on preparative silica gel tlc afforded the diacetate 5-44 (5 mg, 12% overall yield from 5-39).

^{1}H nmr δ 1.28(3H, s), 1.37(3H, 3H, s), 1.5-2.0(4H), 2.02(3H, s), 2.07(3H, s), 3.57(1H, m), 3.66-3.90(2H, AB), 4.03-4.22(2H, AB), 4.50-4.67(2H, AB), 5.06(1H, brm).



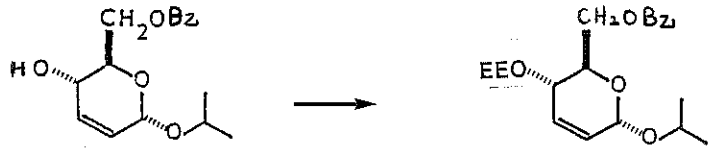
5-54 5-55

To a solution of the diol 5-54 (61.5 g, 0.327 mmol) in a mixture of CH_2Cl_2 (1.5 L) and pyridine (500 mL) cooled to 0°C was added benzoyl chloride (38 mL, 0.33 mmol) dropwise over 1 hr. The reaction mixture was allowed to warm to room temperature and then stirred two overnights. The solution was poured into ice-water and neutralized with HCl (12N HCl, 500 mL). The oraganic layer was washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated under reduced pressure to give the benzoate 5-55 (85.8 g) as an oil.

^{1}H nmr δ 1.15(3H, d, J=6), 1.21(3H, d, J=6), 3.07(1H, br), 3.9-4.2(2H), 4.5-4.7(2H, AB), 5.10(1H, brs), 5.72(1H, dt, J=10, 3), 5.98(1H, d, J=10), 7.4-7.6(3H), 8.0-8.2(2H).

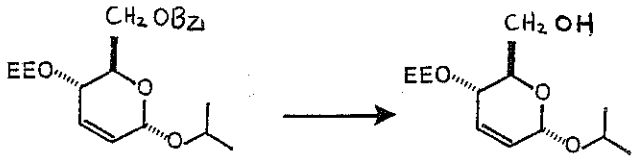
$[\alpha]_D = +8.9^\circ$ (c=1.18, $CHCl_3$).

Found C 65.74, H 6.98; Calcd C 65.74, H 6.90, for $C_{16}H_{20}O_5$.



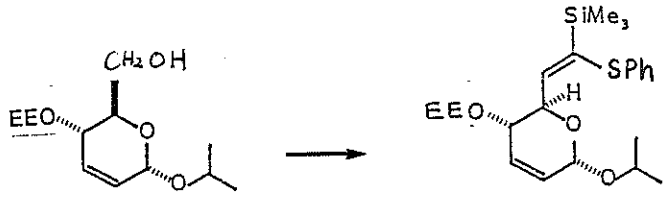
5-55 5-56

To a solution of the alcohol **5-55** (82.8 g) and PPTS (2 g) in CH_2Cl_2 (1.4 L) was added ethyl vinyl ether (80 mL) dropwise. After stirring at room temperature for 3 days, the solution was poured into $NaHCO_3$ and the separated organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the ethoxyethyl ether **5-56** (104.9 g).



5-56 5-57

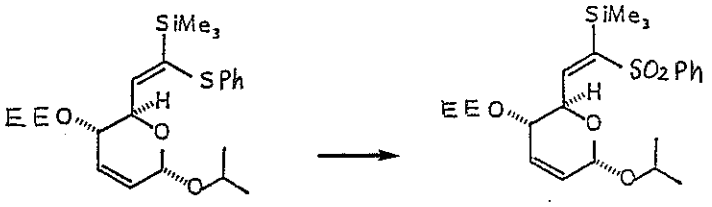
To a solution of the benzoate (104.9 g) in MeOH (1.5 L) was added KOH (85%, 54 g, 0.82 mol) portionwise. After stirring at room temperature overnight, addition of dry ice followed by concentration under reduced pressure gave the residue. Water was added and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 700g) of the residue (76.8 g) with 1:3 (3 L) and 2:1 (4.5 L) ether/hexane gave the alcohol **5-57** as diastereomixture (33.3 g, 52% overall yield from **5-54**).



5-57 5-59

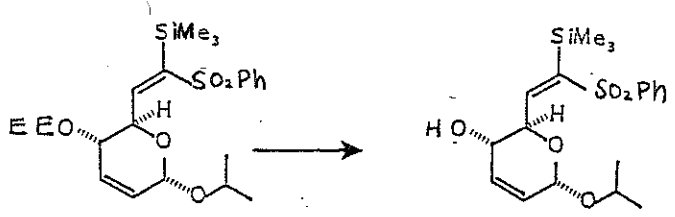
1) To a solution of oxalyl chloride (3.7 mL, 42.4 mmol) in CH_2Cl_2 (280 mL) cooled to -78°C under nitrogen atmosphere was added DMSO (7.4 mL, 106 mmol) dropwise. After stirring for 2 min, the alcohol **5-57** (10.0 g, 38.5 mmol) in CH_2Cl_2 (20 mL) was added and then the stirring was continued for 15 min. Triethylamine (21 mL, 151 mmol) was added and, after 1 hr, the reaction mixture was allowed to warm gradually to -30°C. The reaction was quenched by the addition of sat. NH_4Cl solution and the separated aq. layer was extracted with 1:1 ether/hexane. The extracts were washed (sat. NH_4Cl, x2, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure of afford the aldehyde **5-58** (10.5 g). This material was immediately subjected to subsequent reactions without further purification.

2) To a solution of lithium bis-(trimethylsilyl)-phenylsulfinylmethylid [prepared by addition of n-BuLi (1.55M solution in hexane, 33 mL, 51.2 mmol) to a solution of bis-(trimethylsilyl)-phenylsulfinylmethane (14 mL, 50.0 mmol) in THF (280 mL) according to the procedure described before] cooled to -78°C under argon atmosphere was added aldehyde **5-58** (10.0 g, 38.5 mmol) in THF (20 mL). After stirring at -78°C for 20 min, the reaction mixture was allowed to warm to room temperature and then poured into sat. NH_4Cl solution. The separated aq. layer was extracted with 1:3 ether/hexane (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 200 g) of the residue with hexane and 1:5 ether/hexane afforded the vinylsulfide **5-59** (8.7 g, 52% yield).



5-59 5-60

To a solution of the vinylsulfide **5-59** (12.4 g, 28.4 mmol) in a mixture of CH_2Cl_2 (350 mL) and sat. $NaHCO_3$ solution cooled to 0°C was added MCPBA (80%, 12.3 g, 57.0 mmol) portionwise. After stirring at 0°C for 1 hr, sat. $NaHSO_3$ solution was added until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the hetero-olefin **5-60** (13.9 g).



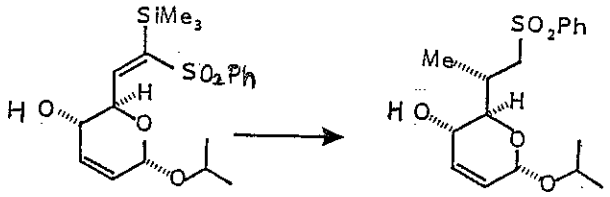
5-60 5-61

A solution of the ethoxyethyl ether **5-60** (13.9 g) and PPTS (1.4 g) in a mixture of CH_2Cl_2 (300 mL) and 2-propanol (50 mL) was heated at 40oC for 1 hr. The solution was poured into sat. $NaHCO_3$ and the separated aq. layer was extracted with CH_2Cl_2 (x2). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the allyl alcohol **5-61** (14.1 g). This material was used without purification. A portion of this material was purified on preparative silica gel TLC afford the Z-olefin.

^{1}H nmr δ 0.23(9H, s), 1.06(3H, d, J=6), 1.13(3H, d, J=6), 1.47(1H, d, J=8), 1.8-2.1(2H), 5.04(1H, brs), 5.31(1H, t, J=9), 5.64(1H, dt, J=10, 1), 6.06(1H, d, J=10), 6.51(1H, d, J=9), 7.4-8.0(5H).

$[\alpha]_D = -82.5^\circ$ (c=0.81, $CHCl_3$).

Found C 57.55, H 7.06; Calcd C 57.55, H 7.12, for $C_{19}H_{28}O_5SiS$.

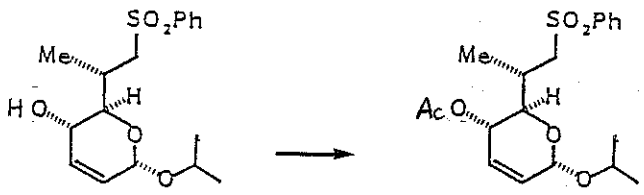


5-61 5-62

1) To a solution of the heteroolefin 5-61 (14.1 g, crude) dissolved in THF (300 mL) cooled to -20°C was added MeMgBr [1M solution in ether] dropwise. After stirring at -20°C for 1.5 day, the solution was poured into sat. NH_4Cl and the separated aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give an oil (13.6 g).

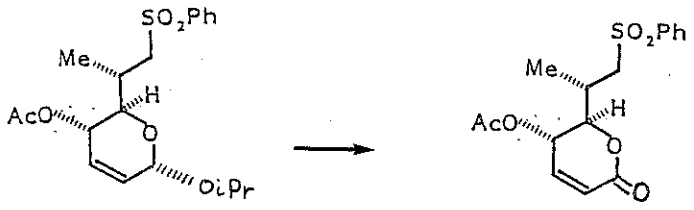
2) This oil was dissolved in MeOH (250 mL), and KF (4 g) was added to this solution. After stirring at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure to give the residue which was taken up in ether. The organic layer was washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the anti-isomer 5-62 (9.3 g) as an oil. This material was used for subsequent reactions without further purification.

^1H nmr δ 1.13(3H, d, J=6), 1.18(6H, d x 2, J=6), 2.65(1H, m), 2.92(1H, dd, J=14, 7), 3.44(1H, dd, J=14, 3), 3.63(1H, dd, J=10, 2), 3.8-4.1(2H), 4.98(1H, s), 5.63(1H, dt, J=10, 2), 5.93(1H, d, J=10), 7.5-7.7(3H), 7.9-8.0(2H).



5-62 5-63

A solution of the allyl alcohol 5-62 (9.3 g) in a mixture of CH_2Cl_2 (100 mL), pyridine (30 mL) and acetic anhydride (15 mL) was stirred at room temperature overnight. Concentration under reduced pressure followed by chromatography (silica gel, 180 g) with 1:3 ether/hexane afforded the acetate 5-63 (6.5 g, 63% overall yield from 5-59).

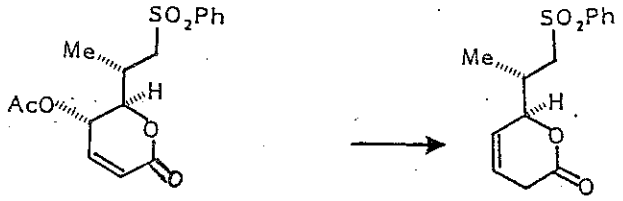


5-63 5-65

1) A solution of the isopropyl glycoside **5-63** (6.5 g) in a mixture of AcOH (120 mL) and H_2O (50 mL) was heated at 40°C for 12 hr. The solution was diluted with CH_2Cl_2 (400 mL) and then washed (H_2O, x3, sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated under reduced pressure to give the lactol **5-64** (5.5 g).

2) To a solution of this lactol **5-64** (5.5 g) dissolved in CH_2Cl_2 (200 mL) was added PDC (32 g) portionwise. After stirring at room temperature overnight, the solution was diluted with ether and then filterd through a pad of Super Cell. The filtrate was passed thuough a short column of silica gel and then concentrated under reduced pressure. Chromatography (silica gel 70 g) of the residue (5.2 g) with 1:1 and 3:1 ether/hexane gave the unchanged starting material **5-63** (1.1 g) and the lactone **5-65** (3.0 g, 63% yield).

^1H nmr δ 1.36(3H, d, J=7), 2.13(3H, s), 2.57(1H, m), 3.03(1H, dd, J=14, 9), 3.39(1H, dd, J=14, 3), 4.38(1H, dd, J=9, 4), 5.45(1H, dt, J=9, 2), 6.02(1H, dd, J=10, 2), 6.77(1H, dd, J=10, 3), 7.5-7.7(3H), 7.85-7.95(2H).



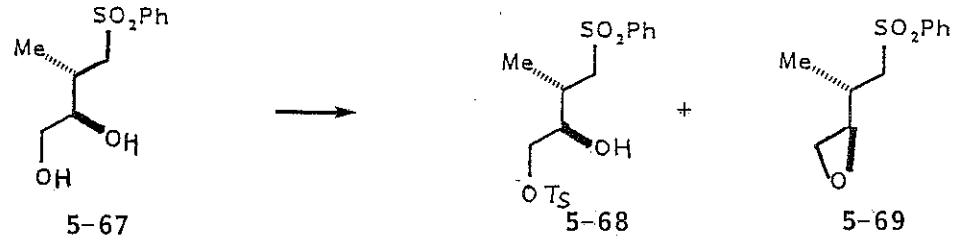
5-65 5-66

To a solution of the α,β-unsaturated lactone 5-65 (3.0 g) and sodium acetate trihydrate (50 g) in a mixture of acetic acid (50 mL) and H_2O (50 mL) cooled to $0^{\circ}C$ was added zinc powder (8 g) and copper(II) sulfate pentahydrate (1.0 g). The reaction mixture was allowed to warm to room temperature, stirred for 5 hr, and filtered through a pad of Super Cell. The filtrate was extracted with ether (x3) and the extracts were washed (H_2O, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the β,γ-unsaturated lactone 5-66 (1.6 g, 64% yield).

^1H nmr δ 1.25(3H, d, J=7), 2.5(1H, m), 2.9-3.1(3H), 3.21(1H, dd, J=14, 3), 4.97(1H, brs), 5.7-6.05(2H, AB), 7.5-7.7(3H), 7.85-7.95(2H).

5-66 5-67

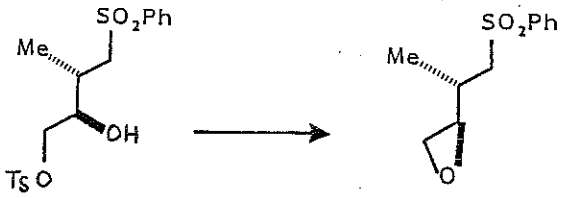
Ozone was passed into a solution of the unsaturated lactone 5-66 (2.2 g, 7.9 mmol) in a mixture of CH_2Cl_2 (35 mL) and MeOH (30 mL) colled to -78oC until the solution became blue. After purging with oxygen, $NaBH_4$ (1.0 g) in MeOH (5 mL) was added and the reaction mixture was allowed to warm to room temperature. The solution was concentrated under reduced pressure and the residue was diluted with H_2O (10 mL). The aq. layer was extracted with CH_2Cl_2 (x20), and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the diol 5-67 (2.2 g). This material was used to subsequent reactions without further purification.



5-67 5-68 5-69

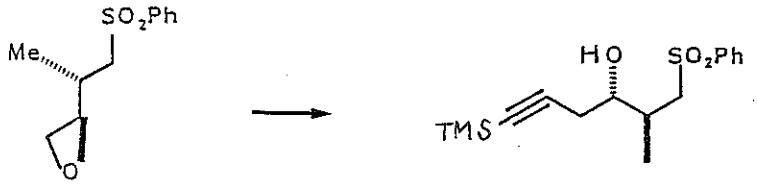
To a solution of the diol **5-67** (2.2 g) in a mixture of CH_2Cl_2 (40 mL) and triethylamine (8 mL) was added p-toluenesulfonyl chloride portionwise until TLC analysis showed the absence of starting material [total 1.0 g (5.2 mmol) of p-toluenesulfonyl chloride was added]. The solution was diluted with ether, washed (1N HCl, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatograhy (silica gel 60 g) of the residue (1.9 g) with 2:1 ether/hexane afforded the epoxide **5-69** (0.29 g) and the tosylate **5-68** (0.8 g) [41% overall yield from **5-66**].

^1H nmr δ 1.08(3H, d, J=7), 2.15(1H, m), 2.45(3H, s), 2.85-3.0(2H), 3.45(1H, dd, J=14, 3), 3.65(1H, m), 3.90-4.15(2H), 7.2-7.8(9H).



5-68 5-69

To a solution of the tosylate 5-68 (o.85 g, 2.1 mmol) in THF (30 mL) cooled to 0°C was added potassium tert-butoxide (1.28 M solution in tert-butanol, 2.0 mL, 2.6 mmol) dropwise. After stirring at 0°C for 30 min, the solution was poured into sat. NH_4Cl solution. The aqueous layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the epoxide 5-69 (463 mg, 98% yield).



5-69 5-70

To a solution of (trimethylsilyl)acetylene (1.7 ml, 12.1 mmol) in THF (35 mL) cooled to -78°C under nitrogen atmosphere was added n-BuLi (1.55M solution in hexane, 6.5 mL, 10.0 mmol) dropwise. After stirring for 20 min, $BF_3 \cdot OEt_2$ (1.0 mL, 8.1 mmol) was added and the stirring was continued for 15 min. To this solution was added the epoxide **5-69** (757 mg, 3.35 mmol) in THF (5 mL) dropwise. After stirring at -78°C for 1 hr, the reaction mixture was poured into sat. $NaHCO_3$ solution and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the alcohol **5-70** (1.03 g, 95% yield).

5-70 5-71

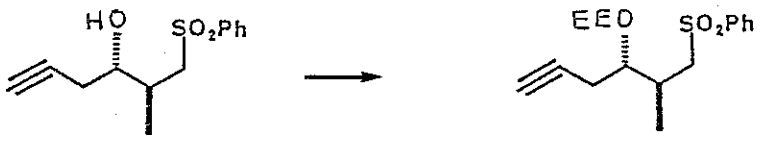
To a solution of the trimethylsilylacetylene **5-70** (1.03 g, 9.2 mmol) in THF (30 mL) was added n-BuNF (1M solution in THF, 3.5 ml, 3.5 mmol) dropwise. After stirring at room temperature for 2 hr, the reaction mixture was poured into H_2O and the separated aq. layer was extracted with ehter (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the acetylane **5-71** (0.82 g, quantitatively).

^1H nmr δ 1.15(3H, d, J=7), 2.04(1H, t, J=2), 2.2-2.6(3H), 2.96(1H, dd, J=14, 7), 3.45-3.52(2H), 7.5-7.7(3H), 7.8-8.0(2H).

IR ($CHCl_3$) 3550, 3320, 2140 cm^{-1}.

$[\alpha]_D = +28.3^{\circ}$ (c=1.49, $CHCl_3$).

Found C 61.64, H 6.58; Calcd C 61.89, H 6.39, for $C_{13}H_{16}O_3S$.

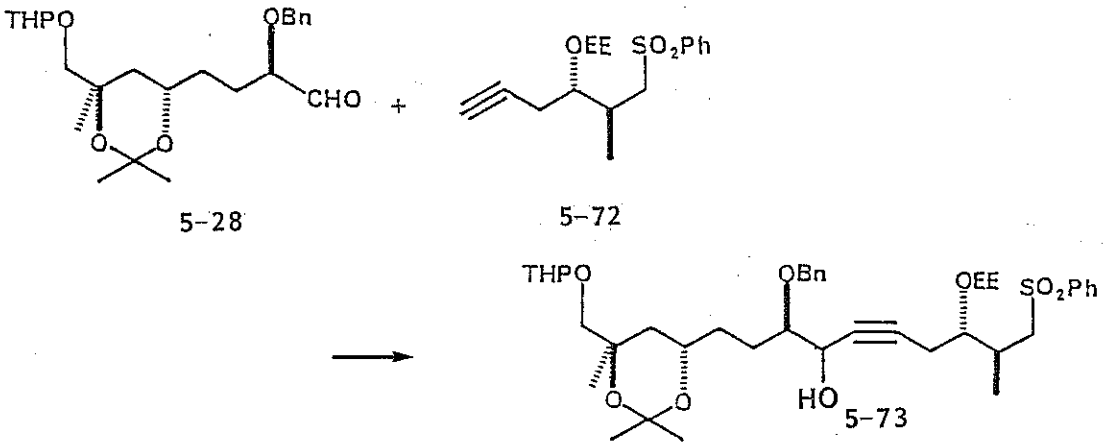


5-71 5-72

To a solution of the alcohol **5-71** (1.00 g, 4.0 mmol) and PPTS (0.10 g) in CH_2Cl_2 was added ethyl vinyl ether (5 mL) dropwise. After stirring at room temperature for 2 hr, the reaction mixture was poured into sat. $NaHCO_3$ solution. The aq. layer was extracted with CH_2Cl_2 (x2) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the ethoxyethyl ether **5-72** (1.37 g, quantitatively) as diastereoisomers.

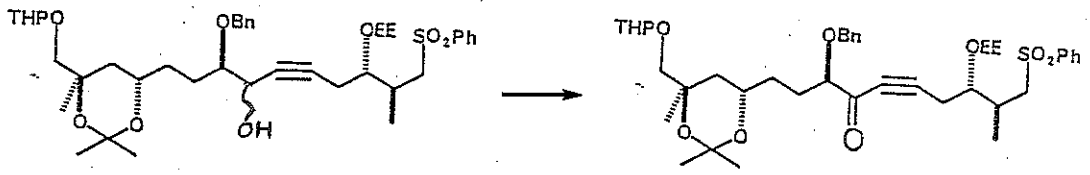
5-27 5-28

To a solution of oxalyl chloride (3.25 mL, 2.9mL) in CH_2Cl_2 (18 mL) cooled to -78oC under nitrogen atmosphere was added DMSO (3.50 mL, 7.1 mmol) dropwise. After stirring for 2 min, the alcohol 5-27 (675 mg) in CH_2Cl_2 (2 mL) was added and the stirring was continued for 15 min. After addition of triethylamine (1.3 mL, 9.3 mmol), the reaction mixture was allowed to warm to 0°C and poured into sat. NH_4Cl solution. The aqueous layer was extracted wilth 1:5 ether/hexane (x3) and the extracts were washed (sat. NH_4Cl x2, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the aldehyde 5-28 (656 mg, 97%).



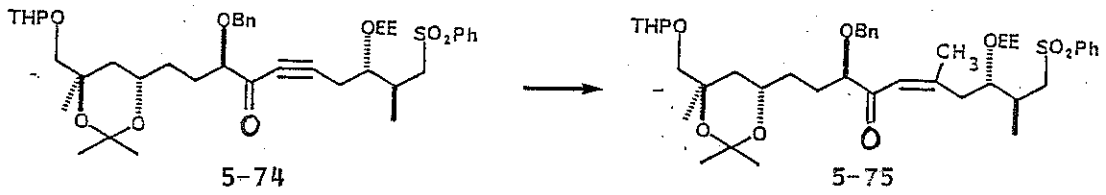
5-28 5-72 5-73

To a solution of the acetylene 5-72 (650 mg, 2.0 mmol) in THF (20 mL) cooled to -78°C under nitrogen atmosphere was added n-BuLi (1.55 M solution in hexane, 1.3 mL, 2.0 mmol) dropwise. After stirring for 15 min, the aldehyde 5-28 (656 mg, 1.6 mmol) in THF (2 mL) was added, and the stirring was continued for 15 min. Saturated aq. NH_4Cl solution was added and the separated aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel) of the residue with 1:3 and 2:1 ether/hexane gave the coupling compound 5-73 (0.57 g, yield 48%).

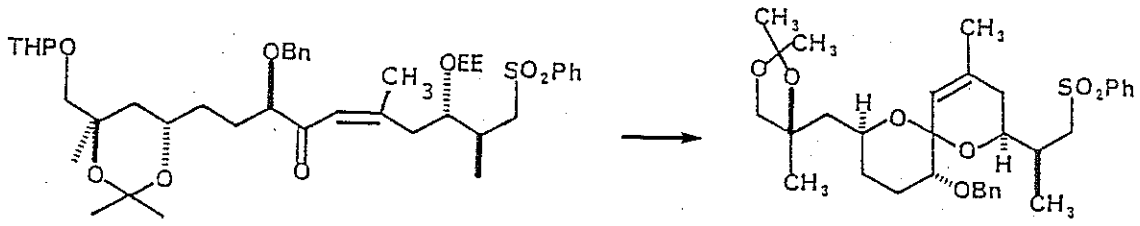


5-73 5-74

To a solution of the alcohol 5-73 (85 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) was added manganese (IV) oxide (activated, 0.40 g) portionwise. After stirring at room temperature for 2 hr, the solution was filtered on a pad of Super Cell, and the filtrate cake was washed with ehter. Concentration of the filtrate under reduced pressure gave the acetylene ketone 5-74 (68 mg, yield 80%).



To a stirred slurry of CuI (10 mg, 0.55 mmol) in ether (3 mL) cooled to $0^{\circ}C$ under nitrogen atmosphere was added MeLi (1.5 M solution in ether, 0.65 mL, 0.98 mmol) dropwise. After stirring at $0^{\circ}C$ for 20 min, the solution was cooled to $-78^{\circ}C$ and the acetylene ketone **5-74** (68 mg, 0.092 mmol) in ether (0.5 mL) was added. After stirring at $-78^{\circ}C$ for 15 min, the reaction mixture was quenched by the addition of sat. NH_4Cl solution. The aqueous layer was extracted with ether (x3) and the extracts were washed (H_2O, sat NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the Z-olefin **5-75** (66 mg, yield 95%).



5-75 5-1

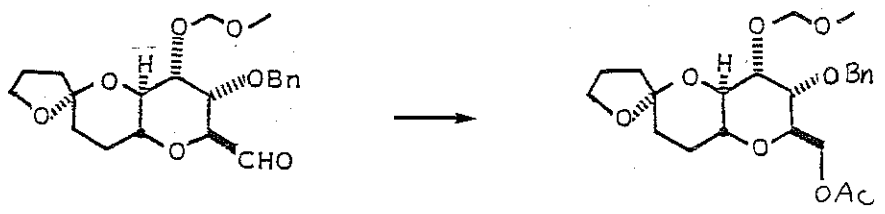
A solition of the ketone 5-75 (66 mg, 0.087 mmol) and PPTS (7 mg) in MeOH (1.5 mL) was stirred at 45°C for 3 hr. The reaction mixture was poured into sat. $NaHCO_3$ and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat.NaCl) and dried (Na_2SO_4). Concentration under reduced pressure gave the residue (51 mg).

A solution of this residue and PPTS (10 mg) in a mixture of CH_2Cl_2 (2 mL) and 2,2-dimethoxypropane (0.2 mL) was stirred at room temperature overnight. The solution was poured into sat. $NaHCO_3$ and the aqueous layer was extracted with ether(x3). The extracts were washed (H_2O, sat. NaCl), dried Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on preparative silica gel TLC gave the segment A 5-1 (22 mg, yield 43%).

^1H nmr δ 1.23(3H, s), 1.24(3H, d, J=7), 1.30(3H, s), 1.37(3H, s), 1.70(3H, s), 1.6-1.9(8H), 2.25(1H, brm), 3.55-3.90(5H), 4.36-4.55(2H, AB), 5.14(1H, s). 7.2-7.4(5H), 7.5-7.7(3H), 7.9-8.0(2H).

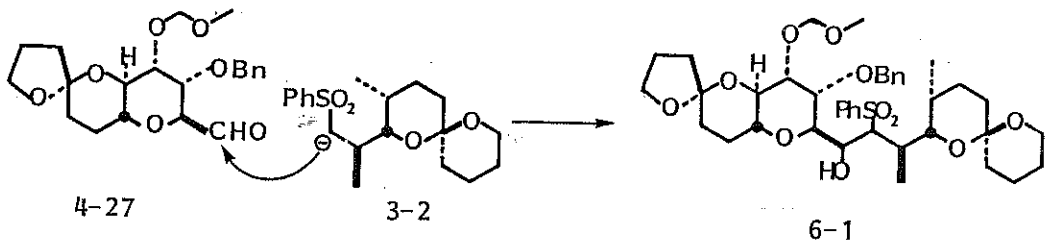
$[\alpha]_D = +11.4^\circ$ (c=1.16, $CHCl_3$).

Found C 67.78, H 7.76; Calcd C 67.79, H 7.59, for $C_{33}H_{44}O_7S$.



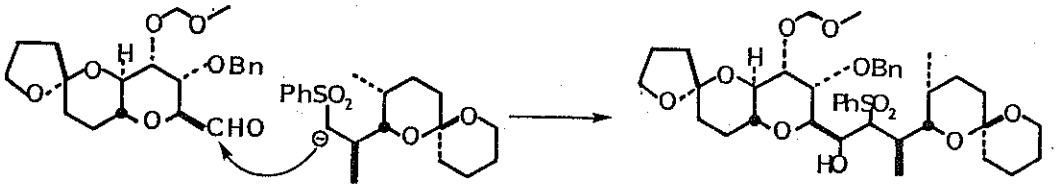
4-27 4-28

A solution of the aldehyde 4-27 (1.5 mg) in EtOH (0.1 mL) cooled to $0^{o}C$ was added $NaBH_4$ (5 mg) portionwise. After stirring at 0oC for 15 min, the solution was poured into H_2O and the aq. layer was extracted with Et_2O (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the oil. This oil was dissolved in a mixture of pyridine (0.2 mL) and acetic anhydride (0.2 mL) and heated at $55^{o}C$ overnight. The solvent was removed in vacuum and the residue was purified on silica gel tlc to afford the acetate 4-28. ^{1}H Nmr analysis showed that this product was identical to the corresponding acetate derived from 4-26. The result of this experiment shows that no epimerization at C26 position of the aldehyde 4-27 occurred.



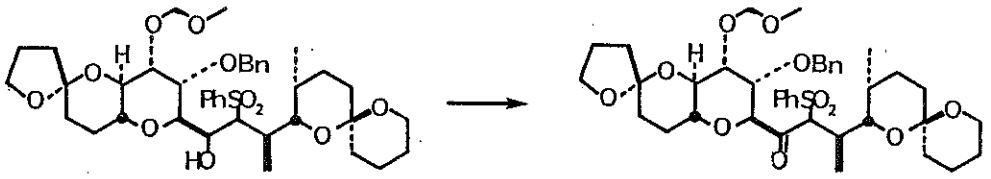
4-27 3-2 6-1

To a solution of the segment C 3-2 (48 mg, 0.130 mmol) in THF (2.5 mL) cooled to -78°C under nitrogen atmosphere was added n-BuLi (1.65 M solution in hexane, 0.09 mL, 0.15 mmol) dropwise. After stirring at -78°C for 20 min, the aldehyde 4-27 (30 mg, 0.077 mmol) in THF (0.5 mL) was added and the stirring was continued for 10 min. The solution was allowed to warm to 0°C and then poured into sat. NH_4Cl solution. The separated aq. layer was extracted with ether (x3), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 2 g) of the residue (74 mg) with 1:1 and 2:1 ether/hexane gave the coupling product 6-1 (14 mg, 24% yield) as diastereomixtures.



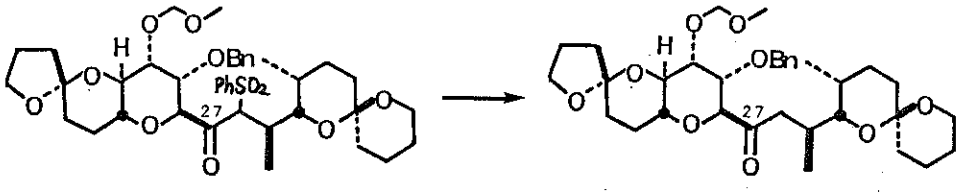
4-27 3-2 6-1

To a solution of the segment C (93 mg, 0.26 mmol) in a mixture of ether (3 mL) and hexane (2 mL) cooled to $0^{\circ}C$ under nitrogen atmosphere was added n-BuLi (1.55M solution in hexane, 0.16 mL, 0.25 mmol) dropwise. After stirring at $0^{\circ}C$ for 5 min, the solution was cooled to $-42^{\circ}C$ (dry ice/CH_2Cl_2) and the aldehyde **4-27** (49 mg, 0.12 mmol) in 1:1 ether/hexane (1 mL) was added. After 10 min, the reaction mixture was quenched by the addition of sat. NH_4Cl solution. The separated aq. layer was extracted with ether (x3), and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue (139 mg) on preparative silica gel tlc afforded the coupling product **6-1** (59 mg, 66% yield) as diastereomixtures.



6-1 6-2

To a solution of the alcohol 6-1 (58 mg, 0.078 mmol) in CH_2Cl_2 (2.5 mL) was added CrO_3-2Py (0.57 g, 2.1 mmol) portionwise. After vigorous stirring at toom temperature for 20 min, the solution was diluted with ether and decanted. The remaining gum of chromium species was washed throughly with ether. The combined organic solution was passed through a short column of silica gel, and the filtrate was concentrated under reduced pressure to afford the residue (62 mg). Purification of this residue on preparative silica gel tlc gave the keto-sulfone 6-2 (40 mg, 69% yield).



6-2 6-3

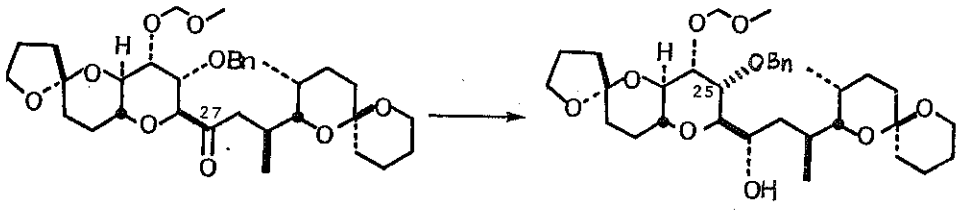
To a solution of the keto-sulfone **6-2** (40 mg, 0.054 mmol) in a mixture of THF (2 mL) and water (0.2 mL) was added Al-Hg (prepared from aluminum foil 30 mg according to the procedure described before) portionwise. After stirring at room temperature for 8 hr, saturated sodium potassium tartrate solution was added and the separated aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to provide the residue (38 mg). Chromatography (silica gel 7 g) of this residue with 1:2 ether/hexane afforded the keton **6-3** (24 mg, 74% yield).

^1H nmr δ 0.88(3H, d, J=7), 0.98(3H, d, J=7). 1.3-2.2(19H), 2.3-2.4(2H), 3.06(1H, ddd, J=10, 10, 5), 3.37(1H, dd, J=10, 2), 3.39(3H, s). 3.52-3.70(3H), 3.86-4.00(2H), 4.08(1H, t, J=10), 4.19(1H, d, J=2). 4.29(1H,dd, J=4, 2), 4.63-4.90(4H), 7.2-7.5f(5H).

IR ($CHCl_3$) 1720 cm^{-1}.

$[\alpha]_D$= +2.8° (c=1.20, $CHCl_3$).

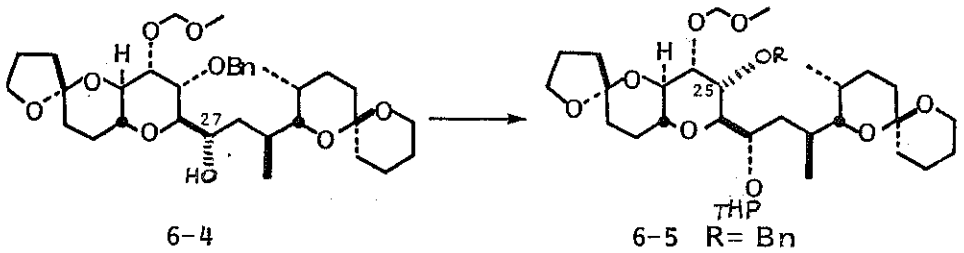
Found C 67.52, H 8.56; Calcd C 67.75, H 8.36, for $C_{34}H_{50}O_9$.



6-3 6-4

To a solution of the ketone 6-3 (4 mg, 0.0066 mmol) in EtOH (0.6 mL) cooled to 0°C was added $NaBH_4$ (3 mg) portionwise. After stirring at 0oC for 2 hr, H_2O was added and the aq. layer was extracted with ether (x3). The combined extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the alcohol 6-4 (3 mg).

^1H nmr δ 0.86(3H, d, J=7), 1.02(3H, d, J=6), 1.1-2.2(22H), 2.40(1H, brs), 3.18(1H, dd, J=10, 2), 3.34(3H, s), 3.5-4.0(9H), 4.10(1H, t, J=10), 4.6-4.9(4H), 7.2-7.5(5H).

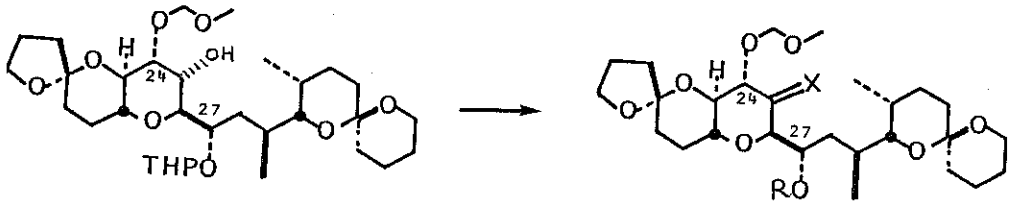


6-4

6-5 R= Bn
6-6 R= H

1) To a solution of the alcohol 6-4 and PPTS (1 mg) in CH_2Cl_2 (0.5 mL) was added dihydropyran (5 drops) and the stirring was continued at room temperature overnight. The solution was poured into sat. $NaHCO_3$ and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the tetrahydropyranyl ether 6-5 as diastereomixture.

2) A solution of this oil was stirred vigorously under a hydrogen atmosphere in the presence of palladium (25% on charcoal 10 mg) and solid $NaHCO_3$ (3 mg). After stirring at room temperature for 1 day, the solution was filtered on a pad of Super Cell. Concentration of the filtrate under reduced pressure followed by chromatography (silica gel 0.8 g) of the residue with 1:3 ether/hexane and ether afforded the alcohol 6-6 (3.1 mg, 76% overall yield from 6-3).



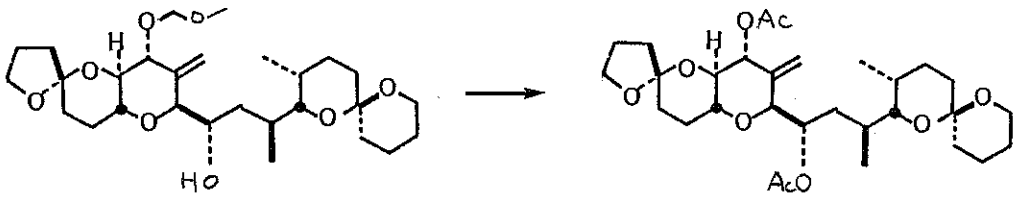
6-6

6-7 X= O R=THP
6-8 X=CH_2 R=THP
6-9 X=CH_2 R=H

1) A solution of oxalyl chloride (50 mL, 0.57 mmol) in CH_2Cl_2 (0.9 mL) cooled to -78°C under nitrogen atmosphere was added DMSO (0.10 mL, 1.4 mmol) dropwise. After 2 min, the alcohol 6-6 (3 mg, 0.005 mmol) in CH_2Cl_2 (0.3 mL) was added and the stirring was continued for 15 min. Triethyhlamine (0.25 mL, 1.8 mmol) was added and the reaction mixture was allowed to warm to 0°C. The solution was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (sat. NH_4Cl x3, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the ketone 6-7.

2) To a solution of methylenetriphenylphosphorane [0.19M, 0.7 mL, prepared by addition of n-BuLi (1.55 M in hexane 0.37 mL) to a stirred slurry of methyltriphenylphosphonium bromide (222 mg, 0.02 mmol) in THF (3 mL) at 0°C, followed by stirring at room temperature for 30 min] cooled -78°C under nitrogen atmosphere was added the ketone 6-7 (0.005 mmol) in THF (0.3 mL) dropwise. After stirring at -78°C for 5 min, the reaction mixture was allowed to warm slowly to room temperature and then refluxed for 2.5 hr. The solution was poured into sat. NH_4Cl solution and the aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the exo-methylene 6-8 as an oil.

3) A solution of this oil and PPTS (one crystal) dissolved in EtOH was heated at 60°C for 1 hr. The solution was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on tlc afforded the alcohol 6-9.



6-9 6-11

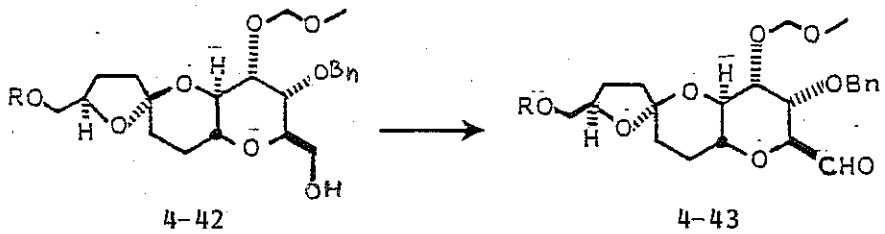
A solution of the alcohol 6-9 (about 0.005mmol) in a mixture of THF (0.3 mL) and 10% HCl (50 mL) was heated at 50°C overnight. Solvent was removed in vacuum to afford the diol 6-10 which was azeotropically dried with benzene. This diol 6-10 was dissolved in a mixture of pyridine (0.2 mL) and acetic anhydride (0.1 mL), and the solution was stirred at room temperature overnight. The solvent was removed in vacuum and tlc purification of the residue afforded the diacetate 6-11 (399 ug, 14% overall yield from 6-6).

diol 6-10

^{1}H nmr δ 0.97(3H, d, J=7), 1.10(3H, d, J=6), 1.2-2.6(22H), 3.32(1H, dd, J=10, 2), 3.45(1H, t, J=10), 3.5-3.7(3H), 3.9-4.0(3H), 4.11(1H, brt, J=10), 4.18(1H, d, J=10), 5.10(1H, brs), 5.43(1H, dd, J=2, 1).

diacetate 6-11

^{1}H nmr (500 MHz); δ 0.89(3H, d, J=7), 1.09(3H, d, J=6), 2.09(3H, s), 2.15(3H, s), 3.31(1H, dd, J=10, 2), 3.53-3.57(2H), 3.65(1H, td, J=11, 3), 3.82-3.93(3H), 4.14(1H, d, J=9), 5.04-5.06(2H), 5.4(1H, dt, J=11, 2), 5.60(1H, ddd, J=12, 9, 2).

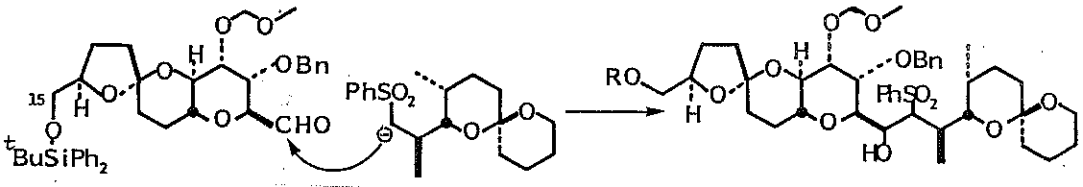


4-42 4-43

R= $SiPh_2Bu^t$

To a stirred solution of oxalyl chloride (0.26 mL, 3.0 mmol) in CH_2Cl_2 (20 mL) cooled to -78°C under N_2 atmosphere was added DMSO (0.55 mL, 7.8 mmol) over 5 min. After 5 min, the alcohol 4-42 (998 mg, 1.50 mmol) in CH_2Cl_2 (5 mL) was added to the resulting solution over 5 min. After stirring at -78oC for 10 min, triethylamine (1.3 mL, 9.3 mmol) was added, and, after15 min, the reaction mixture was allowed to warm slowly to 0°C. The solution was diluted with a 1:1 mixture of ether/hexane, washed (sat. NH_4Cl x 3, sat. $NaHCO_3$ x1, sat. NaCl x1), and then dried (Na_2SO_4). Concentration under reduced pressure gave the aldehyde 4-43 (1.05 g, crude) as an oil. This material was promptly subjected to the subsequent reactions without purification.

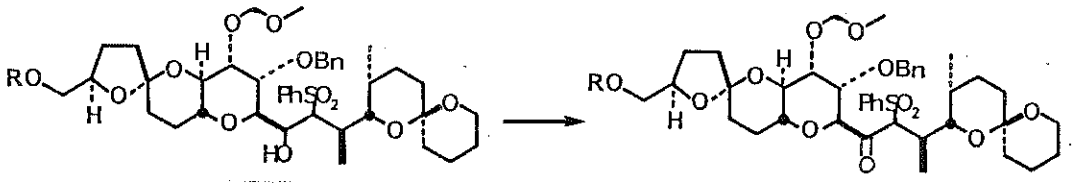
^1H nmr δ 1.05(9H, s), 1.7-2.2(8H), 2.9-3.5(2H), 3.36(3H, s), 3.50(1H, dd, J=10, 3), 3.6-3.8(2H, AB), 4.14(1H, t, J=10), 4.21(1H, dd, J=4, 2), 4.3(1H), 4.6-4.85(4H), 7.2-7.8(15H), 9.81(1H, s).



4-43 3-2 6-12

R= $SiPh_2Bu^t$

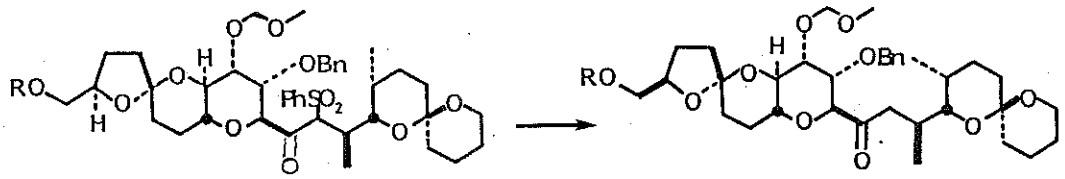
To a solution of the segment C 3-2 (0.89 g, 2.53 mmol) in ether (15 mL) cooled to 0^oC under nitrogen atmosphere was added n-BuLi (1.55M solution in hexane, 1.60 mL, 2.48 mmol) dropwise. After stirring at 0^oC for 10 min, the solution was cooled to -42^o (dry ice/CH_3CN) and diluted with dry hexane (15 mL). To this solution was added the segment B aldehyde 4-43 (1.050 g, 1.50 mmol) in ether (3 mL) dropwise. After stirring at -42^oC for 10 min, sat. NH_4Cl solution was added and the separated aq. layer was extracted with ether (x3). The extrtacts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 55 g) of the residue with ether/hexane (1:3 700 mL, then 1:1 800 mL) afforded the coupling product 6-12 (1.4 g, 92% yield) as diastereomers.



6-12 6-13

R= $SiPh_2Bu^t$

To a vigorously stirred solution of the alcohol 6-12 (2.6 g, 2.6 mmol) in CH_2Cl_2 (50 mL) was added CrO_3-2Py (12 g, 47 mmol). After stirring at room temperature for 30 min, silica gel (10 g) was added. The reaction mixture was diluted with ether and decanted. The remaining residue gum was thoroughly washed with ether (x3). The combined organic solution was filtered through a pad of Super Cell and the filtrate was passed through a short column of silica gel to remove the last traces of chromium species. Concentration under reduced pressure gave the keto-sulfone 6-13 (2.4 g).



6-13 6-14

R= $SiPh_2Bu^t$

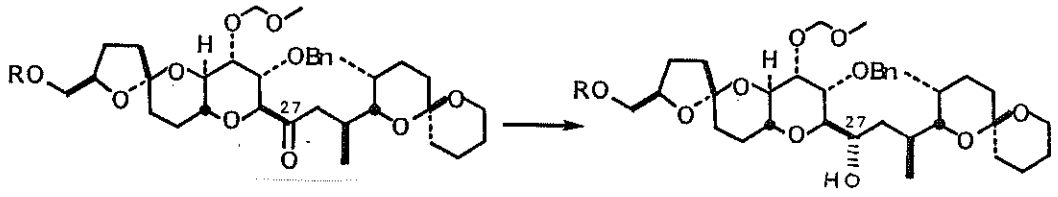
To a solution of the keto-sulfone 6-13 (2.4 g) in a mixture of THF (90 mL) and H_2O (10 mL) was added Al-Hg [prepared from aluminum foil (3 g) according to the procedure described before]. After stirring at room temperature overnight, saturated aq. sodium potassium tartrate solution was added, and the separated aq. layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the ketone 6-14 (1.8 g) as an oil. This ketone was promptly subjected to the subsequent reactions without purification. A portion of this ketone was purified on preparative silica gel tlc to afford the analytically pure sample.

^1H nmr δ 0.87(3H, d, J=6), 0.98(3H, d, J=6), 1.04(9H, s), 1.3-2.4(22H), 3.05(1H, td, J=10, 4), 3.39(3H, s), 3.35-3.78(6H), 4.12(1H, t, J=10), 4.19(1H, d, J=2), 4.22-4.35(2H), 4.64-4.87(4H), 7.2-7.8(15H).

IR ($CHCl_3$) 1720 cm^{-1}.

$[\alpha]_D$= +9.7° (c=1.15, $CHCl_3$).

Found C 70.54, H 8.13; Calcd C 70.31, H 8.09, for $C_{51}H_{70}O_{10}Si$.



6-14 6-15

R= $SiPh_2Bu^t$

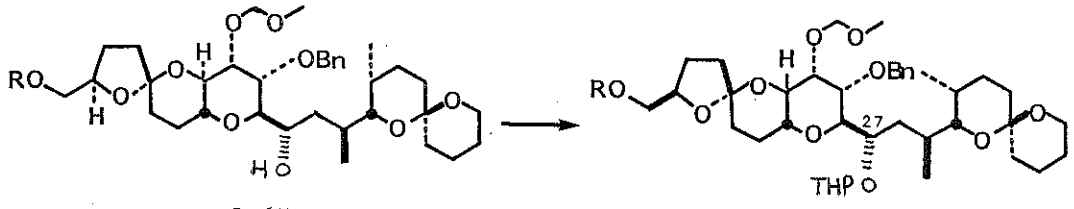
To a solution of the ketone 6-14 (1.8 g) in EtOH (40 mL) cooled to 0°C was added $NaBH_4$ (0.30 g) portionwise. After stirring at 0oC for 1 hr, the reaction mixture was poured into H_2O and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the residue (1.8 g). Chromatography of this residue with 1:3 followed by 1:1 ether/hexane afforded the alcohol 6-15 (1.3 g, 57% overall yield 3 steps from 6-12).

^1H nmr δ 0.88(3H, d, J=6), 1.03(3H, d, J=6), 1.04(9H, s), 1.1-2.3(22H), 3.20(1H, dd, J=10, 2), 3.38(3H, s), 3.30-3.80(8H), 3.92(1H, brt, J=10), 4.17(1H, t, J=10), 4.30(1H, td, J=8, 4), 4.63-4.81(4H), 7.2-7.8(15H).

IR ($CHCl_3$) 3550 cm^{-1}.

$[\alpha]_D$= +15.1° (c=2.15, $CHCl_3$).

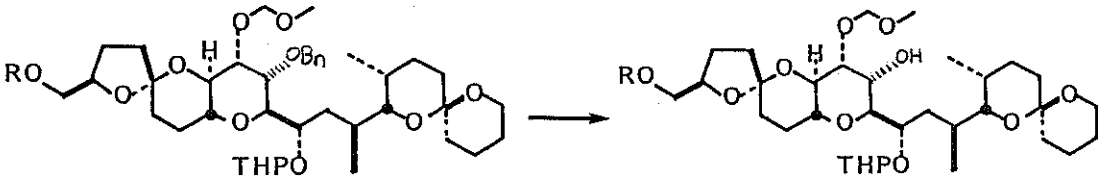
Found C 70.14, H 8.23; Calcd C 70.15, H 8.31, for $C_{51}H_{72}O_{10}Si$.



6-15 6-16

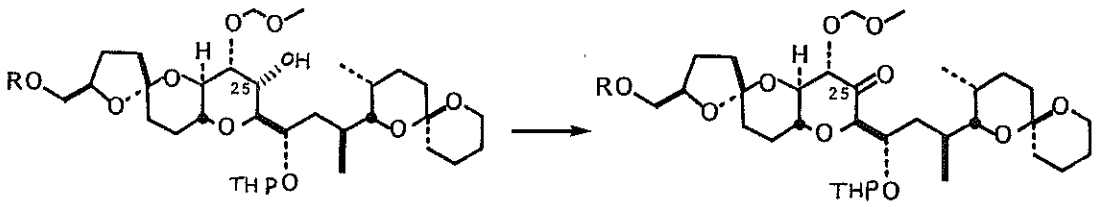
R= $SiPh_2Bu^t$

To a solution of the alcohol 6-15 (1.3 g, 1.49 mmol) and PPTS (0.05 g) in CH_2Cl_2 (40 mL) was added dihydropyran (1.03 mL, 11.3 mmol) dropwise. After stirring at room temperature overnight, the reaction mixture was diluted with ether and then poured into sat. $NaHCO_3$ solution. The aq. layer was extracted with ether (x3) and the combined organic layers were washed (H_2O, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the tetrahydropyranyl ether 6-16 (1.7 g) as diastereomixtures. This material was used without further purification.



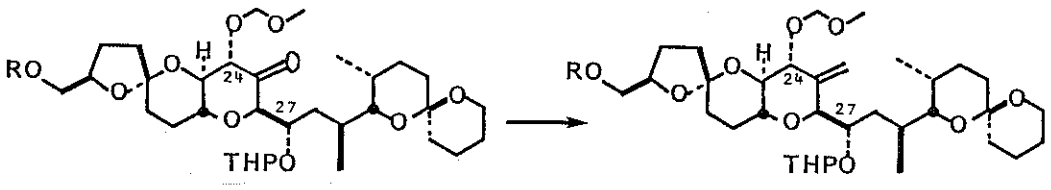
6-16 R= $SiPh_2Bu^t$ 6-17

A solution of the benzyl ether 6-16 (1.7 g) in AcOEt (45 mL) was vigorously stirred under a hydrogen atmosphere in the presence of paladium hydroxide on carbon (Pearlsman's catlayst 2.3g) for 6 hr. The reaction mixture was filtered on Super Cell and the filtrate was concentrated under reduced pressure. Chromatography (silica gel 30 g) of the residue with 1:3 and 1:1 ether/hexane as eluent afforded the alcohol 6-17 (890 mg, 69% overall yield from 6-15).



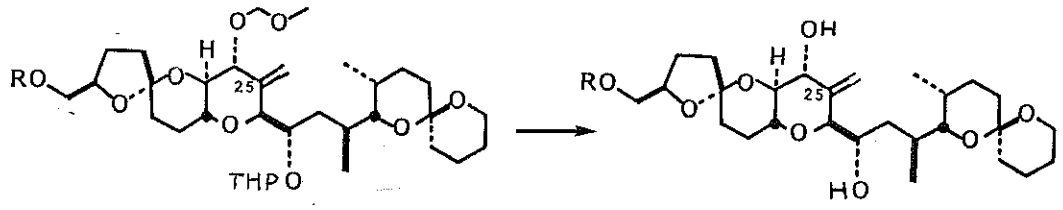
To a solution of oxalyl chloride (75 mL, 0.86 mmol) in CH_2Cl_2 (5 mL) cooled to -78° under N_2 atmosphere was added DMSO (0.15 mL, 2.1 mmol) over 5 min. After 2 min, the alcohol **6-17** (150 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added to the resulting solution over 5 min. After stirring at -78oC for 10 min, triethylamine (0.40 mL, 2.9 mmol) was added. After stirring for 15 min, the reaction mixture was allowed to warm to 0°C. Water was added and the aq. layer was extracted with a 1:1 mixture of ether/hexane. The combined organic layers were washed (sat. NH_4Cl x3, sat. $NaHCO_3$ x1, sat. NaCl x1), dried (Na_2SO_4) concentrated under reduced pressure to afford the ketone **6-18** (178 mg) as an oil. This ketone **6-18** was promptly subjected to the subsequent reactions without purification.

IR ($CHCl_3$) 1730 cm^{-1}.



6-18 R= $SiPh_2Bu^t$ 6-19

To a solution of methylenetriphenylphosphorane in THF [prepared by addition of n-BuLi (1.55M solution in hexane, 0.78 mmol) to a stirring slurry of methyltriphenylphosphonium bromide (492 mg, 1.38 mmol) in THF (5.5 mL) at 0°C, followed by stirring at room temperature for 30 min] cooled to -78°C under nitrogen atmosphere was added the ketone **6-18** (178 mg, 0.17 mmol) in THF (2 mL) dropwise. After stirring at -78°C for 5 min, the reaction mixture was allowed to warm to room temperature and then heated at refluxing temperature for 2 hr. The solution was poured into sat. NH_4Cl solution and the aq. layer was extracted with ether (x3). The combined organic layers were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (silica gel 8 g) of the residue with 1:15 and 1:5 ether/hexane afforded the exo-methylene **6-19** (116 mg, 79% overall yield from **6-17**) as an oil.



6-19 6-21

R= $SiPh_2Bu^t$

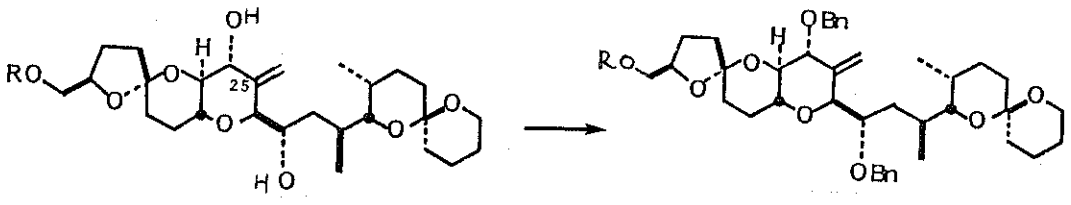
To a solution of the methoxymethyl ether 6-19 (142 mg, 0.16 mmol) dissolved in CH_2Cl_2 (2.5 mL) cooled to -78°C was added TMSBr (0.25 mL, 1.9 mmol) in CH_2Cl_2 (0.5 mL) dropwise. After stirring at -78oC for 15 min, the reaction mixture was allowed to warm to -25°C. After stirring at -25°C for 30 min, sat. $NaHCO_3$ solution was added. The aq. layer was extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the diol 6-21 (0.12 g). This material was subjected to the subsequent reactions without purification. A portion of this oil was purified on preparative silica gel tlc to afford the analytically pure sample.

^1H nmr δ 1.09(3H, d, J=7), 1.15(9H, s), 1.25(3H, d, J=6), 1.3-2.7(24H), 3.42(1H, dd, J=10, 2), 3.45-3.82(6H), 4.00(1H, d, J=10), 4.06(1H, m), 4.17(1H, t, J=10), 4.27(1H, d, J=10), 4.95(1H, s), 5.65(1H, t, J=1), 7.2-7.9(10H).

IR ($CHCl_3$) 3600 cm^{-1}.

$[\alpha]_D$= +15.9° (c=1.29, $CHCl_3$).

Found C 70.40, H 8.51; Calcd C 70.26, H 8.50, for $C_{43}H_{62}O_8Si$.



6-21 6-22

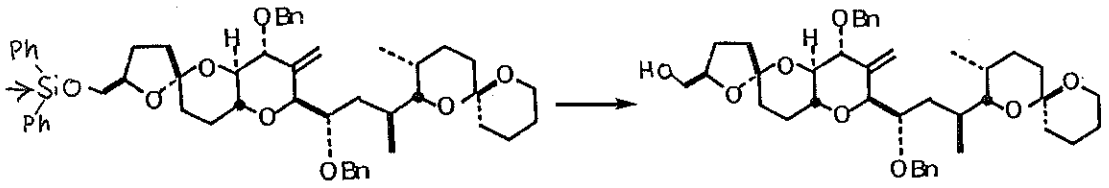
R= $SiPh_2Bu^t$

To a solution of the diol **6-21** (0.12 g, 0.16 mmol) and benzyl bromide (0.15 mL, 1.3 mmol) in THF (2.2 mL) cooled to 0°C was added NaH (60% dispersion in mineral oil, 30 mg, 0.75 mmol) portionwise. After stirring for 5 min, DMF (0.45 mL) was added and the cooling bath was removed. After stirring at room temperature for 16 hr, the solution was poured into sat. NH_4Cl solution. The aq. layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the dibenzyl ether **6-22** (0.24 g, crude). This product is subjected to the subsequent reaction without purification. Purification of a portion of this product on preparative tlc gave the analytically pure sample.

^1H nmr δ 0.89(3H, d, J=7), 0.94(3H, d, J=6), 1.04(9H, s), 1.3-2.25(22H), 3.24(1H, dd, J=10, 2), 3.5-3.8(6H), 3.85-4.02(2H), 4.22-4.34(2H), 4.55-4.88(4H), 5.05(1H, s), 5.43(1H, t, J=1), 7.2-7.8(20H).

$[\alpha]_D$= +29.3° (c=1.64, $CHCl_3$).

Found C 74.81, H 8.19; Calcd C 74.80, H 8.15, for $C_{57}H_{74}O_8Si$.



6-22 6-23

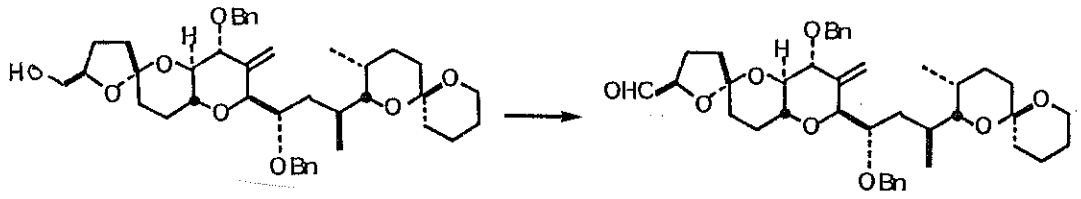
To a solution of the silyl ether 6-22 (0.24 g, 0.10 mmol) in a mixture of THF (1.5 mL) and CH_3CN (1.5 mL) was added n-Bu_4NF (1M solution in THF, 0.5 mL, 0.5 mmol) dropwise. After stirring at room temperature overnight, the solution was poured into H_2O. The separated aq. layer was extracted with ether (x3) and the extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reeduced pressure. Purification of the residue on preparative silica gel tlc afforded the analytically pure sample 6-23 (53 mg, 50% overall yield from 6-19).

^1H nmr δ 0.88(3H, d, J=7), 0.93(3H, d, J=6), 1.3-2.2(24H), 3.24(1H, dd, J=10, 2), 3.45-3.82(6H), 3.89-4.01(2H,), 4.20-4.33(2H), 4.55-4.86(4H), 5.05(1H, s), 5.43(1H, t, J=1).

IR ($CHCl_3$) 3480 cm^{-1}.

$[\alpha]_D = +33.5^o$ (c=1.73, $CHCl_3$).

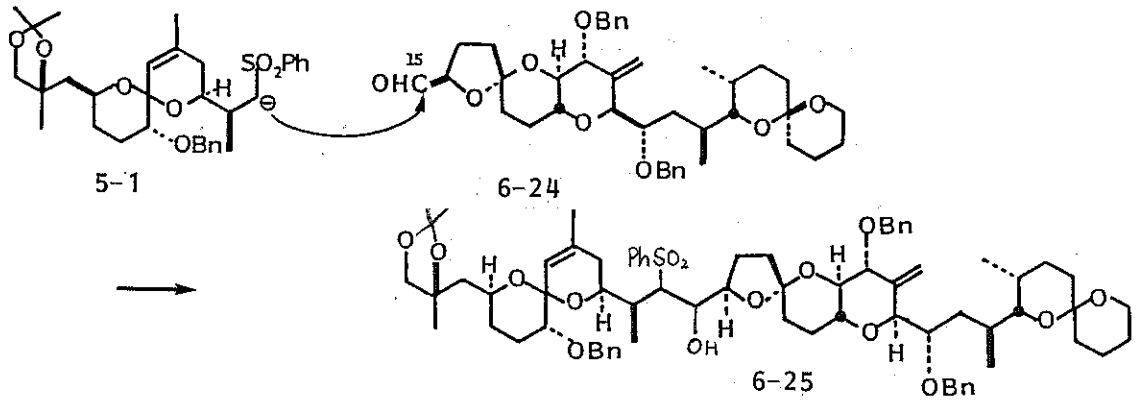
Found C 72.77, H 8.44; Calcd C 72.75, H 8.34, for $C_{41}H_{56}O_8$.



6-23 6-24

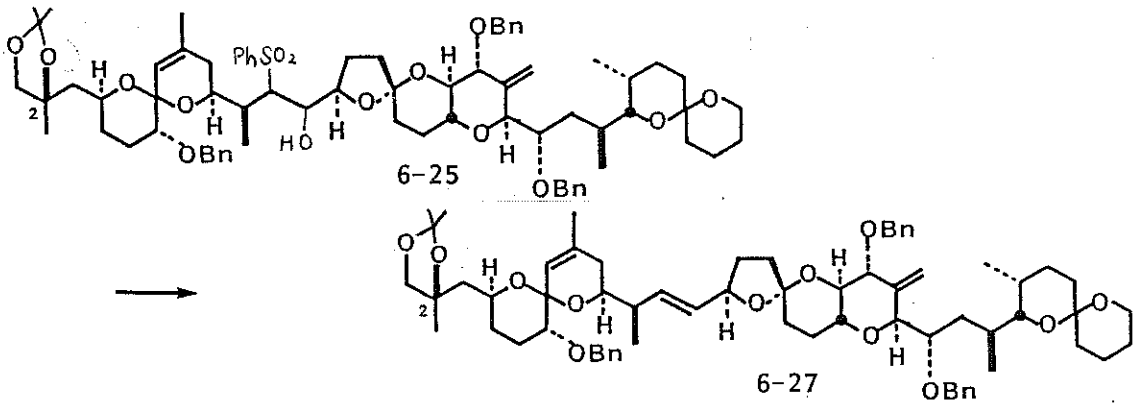
To a solution of oxalyl chloride (20 uL, 0.11 mmol) dissolved in CH_2Cl_2 (1.0 mL) cooled to -78°C under nitrogen atmosphere was added DMSO (25 uL, 0.35 mmol) dropwise. After stirring for 2 min, the alcohol **6-23** (15 mg, 0.022 mmol) in CH_2Cl_2 (0.5 mL) was added and the stirring was continued for 15 min. Afte addition of triethylamine (0.05 mL, 0.36 mmol), the reaction mixture was allowed to warm slowly to 0°C and then poured into H_2O. The aq. layer was extracted with ether (x3) and the extracts were washed (sat. NH_4Cl, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the aldehyde **6-24** (19 mg). This material was promptly subjected to the subsequent reactions without purification.

^1H nmr δ 0.89(3H, d, J=7), 0.95(3H, d, J=6), 1.1-2.5(22H), 3.24(1H, dd, J=10, 2), 3.55-4.00(4H), 3.85-4.00(2H), 4.28(1H, d, J=8), 4.47(1H, qd, ,J=4, 2), 4.55-4.86(4H), 5.06(1H, s), 5.43(1H, t, J=1), 7.2-7.4(10H), 9.71(1H, d, J=2).



To a solution of segment A 5-1 (83 mg, 0.14 mmol) dissolved in THF (1.5 mL) cooled to -78°C under nitrogen atmosphere was added sec-BuLi (1.35 M hexane, 0.12 ml, 0.16 mmol) dropwise. After stirring for 10 min, the solution was diluted with dry hexane (1.5 mL), and the aldehyde 6-24 (19 mg) in THF (0.5 mL) was added. After stirring at -78°C for 20 min, the reaction mixture was quenched by the addition of sat. NH_4Cl solution and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the residue.

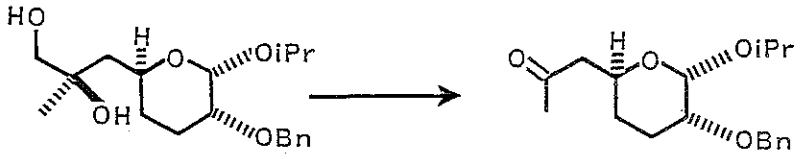
The resulting residue was dissolved in MeOH (1.5 mL) and then treated with $NaBH_4$ (10 mg) at 0°C for 30 min. The solution was poured into H_2O and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried and concentrated under reduced pressure. Purification of the residue on preparative silica gel TLC gave a mixture of segment A and the coupling product 6-25 (9 mg), and the segment B/C alcohol (10 mg).



1) A solution of the coupling product **6-25** and segment A (9 mg) dissolved in a mixture of pyridine (2 mL) and acetic anhydride (1 mL) was heated at 55°C overnight. The solvent was removed in vacuum to afford the residue which was dissolved in a mixture of MeOH (0.4 mL) and ethyl acetate (0.1 mL). To this solution was added sodium amalgam (5%) portionwise until TLC analysis showed the absence of starting material. The solution was poured into H_2O and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on silia gel TLC gave the trans-olefin **6-27** (2.2 mg, 25% overall yield 25% from **6-24**) as an oil.

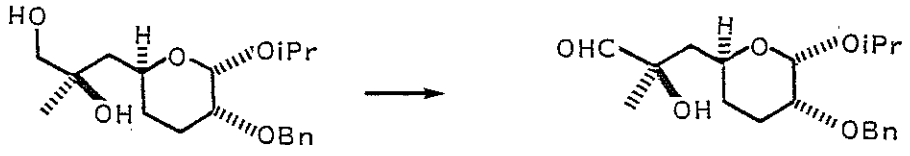
^{1}H nmr (500 MHz, in C_6D_6) δ 1.00(3H, d, J=7), 1.02(3H, d, J=7), 1.13(3H, d, J=7), 1.2-2.4(31H), 1.43(3H, s), 1.49(3H, s), 1.52(3H, s), 1.53(3H, s), 3.27(1H, dd, J=12, 4), 3.41(1H, dd, J=10, 2), 3.61(1H, dd, J=11, 4), 3.68(1H, ddd, J=11, 7, 3), 3.76(1H, ddd, J=13, 11, 3), 3.86(1H, d, J=9), 3.88(1H), 4.01(1H, ddd, J=10, 8, 2), 4.05(1H, t, J=10), 4.11(1H, d, J=9), 4.1(1H), 4.21(1H, d, J=10), 4.36(1H, d, J=13), 4.41(1H, d, J=8), 4.49(1H, d, J=13), 4.56(1H, d, J=11), 4.73(1H, q, J=7), 4.84(1H, d, J=11), 4.86(1H, d, J=13), 4.95(1H, d, J=13), 5.01(1H, s), 5.30(1H, s), 5.64(1H, dd, J=16, 7), 5.69(1H, t, J=2), 5.95(1H, dd, J=16, 8), 7.1-7.5(15H).

$[\alpha]_D$= +31.5° (c=0.20, $CHCl_3$).



5-18 7-1

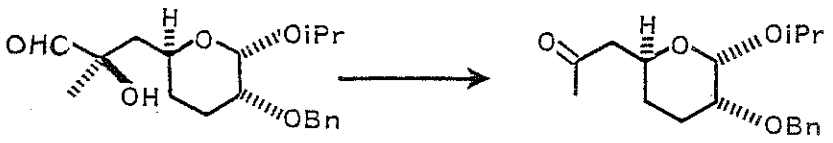
To a solution of the diol **5-18** (35 mg, 0.10 mmol) dissolved in DMF (0.5 mL) was added PDC (0.20 g, 0.50 mmol) portionwise. After stirring at room temperature for 2 hr, TLC analysis showed that the only detectable product was the ketone **7-1**.



5-18 7-2

To a solution of the 1,2-diol 5-18 (109 mg, 0.32 mmol) dissolved in a mixture of DMSO (1.8 mL) and triethylamine (0.7 mL) was added SO_3Py (0.41 g, 2.6 mmol) portionwise. After stirring at room temperature for 20 min, the reaction mixture was poured into H_2O, and the aqueous layer was washed (sat. NH_4Cl x2, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the residue. Purification of this residue on preparative silica gel TLC gave the aldehyde 7-2 (94 mg, yield 86%).

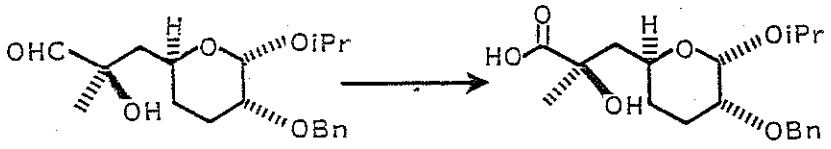
^1H nmr δ 1.19(3H, d, J=6), 1.22(3H, s), 1.24(3H, d, J=6), 1.3-2.0(6H), 3.40(1H, ddd, J=11, 5, 4), 3.84(1H, septet, J=6), 3.99(1H, tt, J=10, 2), 4.5-4.6(3H) 4.90(1H, d, J=3), 9.71(1H, s).



7-2 7-1

To a solition of the aldehyde 7-2 (12 mg, 0.036 mmol) dissolved in DMF (0.10 mL) was added PDC (0.40 g) portionwise. After stirring at room temperature for 2 hr, the reaction mixture was poured into H_2O and the aq. layer was extracted with ether (x3). The combined organic layer was washed (H_2O, sat. NaCl), dried (Na_2SO_4) and passed through a short column of silica gel. Concentration of the filtrate under reduced pressure gave the ketone 7-1 (9 mg, yield 82%).

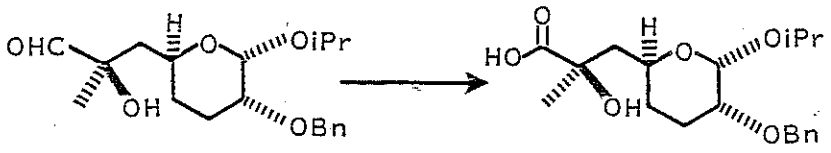
^1H nmr δ 1.18(3H, d, J=6), 1.30(3H, d, J=6), 1.6-2.1(4H) 2.17(3H, s), 2.3-2.7(2H), 3.24(1H, ddd, J=12, 4, 3), 3.96(1H, septet, J=6), 4.28(1H, m), 4.58(2H, s), 4.90(1H, d, J=3), 7.2-7.4(5H).



7-2 7-3

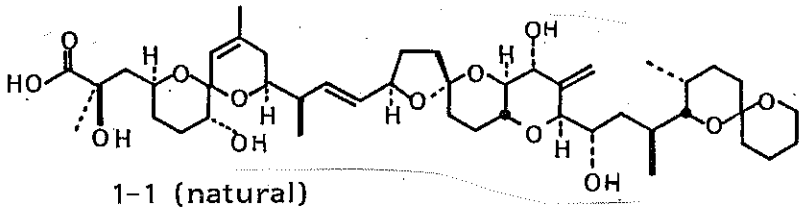
To a solution of the aldehyde 7-2 (14 mg, 0.042 mmol), 2-methyl-2-butene (2 drops), sodium phosphate, monobasic dihydrate (10 mg) dissolved in a mixture of tert-butanol (0.4 mL) and H_2O (0.1 mL) was added sodium chlorite ($NaClO_2$, abt. 85%, 10 mg, 0.094 mmol) portionwise. After stirring at room temperature for 1 hr, sat. $NaHSO_3$ solution was added. The solition was acidified at 0oC with 1N HCl, and the aq. layer was extracted with CH_2Cl_2 (x3). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford the carboxylic acid 7-3 (14 mg, quantitatively).

^1H nmr δ 1.19(3H, d, J=6), 1.26(3H, d, J=6), 1.42(3H, s), 1.4-2.25(6H), 3.41(1H, ddd, J=11, 5, 3), 3.86(1H, septet, J=6), 4.08(1H, tt, J=11, 2), 4.50-4.68(2H, AB), 4.92(1H, d, J=3), 5.3(1H, br), 7.2-7.4(5H).

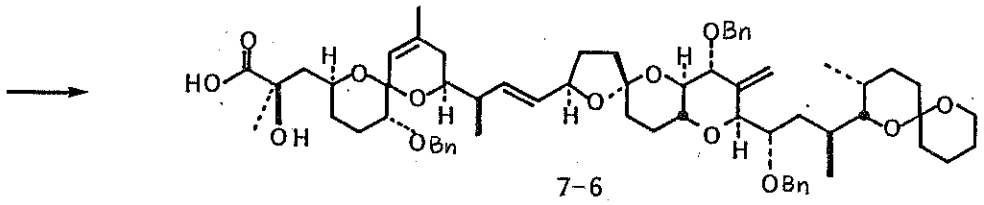


7-2 7-3

To a solution of silver nitrate ($AgNO_3$, 90 mg, 0.53 mmol) in H_2O (0.23 mL) was added aq. KOH (1.8 M solution, 0.60 mL) dropwise. After stirring at room temperature for 10 min, the solution became a balck semi-solid mixture. To this heterogeneous solution cooled to 0°C was added the aldehyde 7-2 in EtOH (0.2 mL) dropwise. After stirring at room temperature for 2 hr, the solution was filtrated on a pad of Super Cell. The filtrate was acidified with 1N HCl and then extracted with CH_2Cl_2 (x3). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the residue (23 mg). 1H Nmr analysis showed that this residue contained the carboxylic acid 7- (estimated yield 15%).



1-1 (natural)



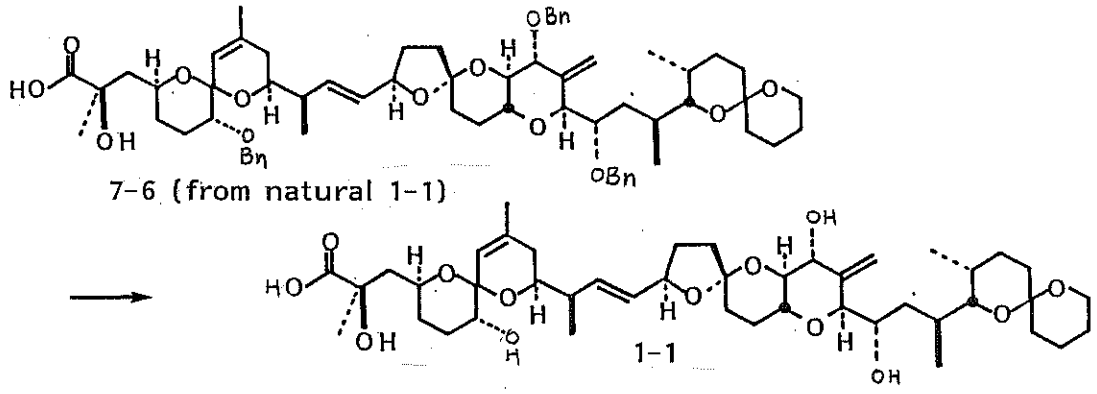
7-6

To a solution of natural okadaic acid (62 mg, 0.077 mmol) dissolved in a mixture of THF (3.5 mL) and DMF (0.9 mL) was added NaH (60% oil dispersion, 10 mg, 250 mmol) portionwise. After stirring at room temperature for 10 min, benzyl bromide (100 uL, 0.84 mmol) was added, and the stirring was continued overnight. The reaction mixture was poured into ice-water and then acidified with 1N HCl. The aq. layer was extracted with CH_2Cl_2 (x4). The combined extracts were dried (Na_2SO_4), and concentrated under reduced pressure to afford the tribenzyl okadaic acid **7-6** as an oil. This material was uded for the subsequent reactions without purification. A portion of this oil was purified with tlc to give an analytically pure sample.

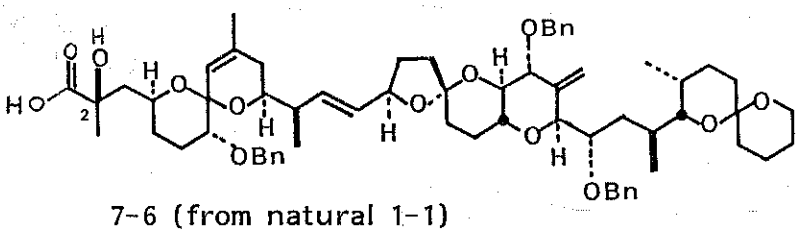
^{1}H nmr δ 0.87(3H, d, J=7), 0.91(3H, d, J=7), 1.05(3H, d, J=7), 1.36(3H, s), 1.73(3H, s), 2.13(1H, dd, J=14, 2), 2.23(1H), 2.42(1H, qt, J=7, 7), 3.22(1H, dd, J=11, 2), 3.24(1H, dd, J=12, 4), 3.55-3.7(5H), 3.88-3.95(2H), 4.02(1H, tt, J=11, 2), 4.24(1H, d, J=8), 4.48(1H, d, J=13), 4.56(1H, d, J=11), 4.60(1H, d, J=13), 4.61(1H), 4.73(1H, d, J=11), 4.77(1H, d, J=13), 4.89(1H, d, J=13), 5.02(1H, brs), 5.14(1H, brs), 5.17(1H, brs), 5.35(1H, t, J=1), 5.61(1H, dd, J=15, 8), 5.74(1H, dd, J=15, 8), 7.2-7.4(15H), (500 MHz).

All other signals are left unresolved between 1.25-2.40 ppm.

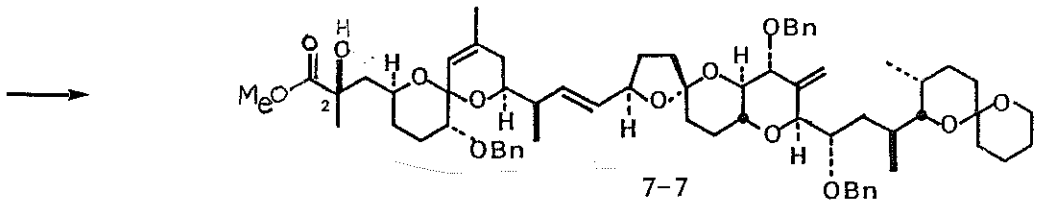
$[\alpha]_D$=+48.1^o (c=0.31, $CHCl_3$).



To a solution of natural tribenzyl okadaic acid 7-6 (3 mg) dissolved in EtOH (0.3 ml) and ammonia (0.7 mL) cooled to -78°C was added lithium metal(trace). After stirring at -78°C for 30 min, the reaction mixture was allowed to warm to room temperature and to stand for 2 hr until ammonia was evaporated. Water was added and the solution was acidified at 0°C with 1N HCl. The aq. layer was extracted with CH_2Cl_2 (x3), and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford the residue. This residue was dissolved in MeOH (0.4 mL) and treated with diazomethane (ether solution) at 0°C until TLC analysis showed the absence of okadaic acid. Cnocentration of the solvent followed by TLC purification gave the okadaic acid methyl ester (1.8 mg, yield 80%).

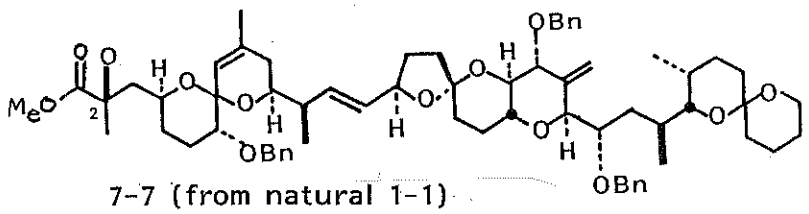


7-6 (from natural 1-1)

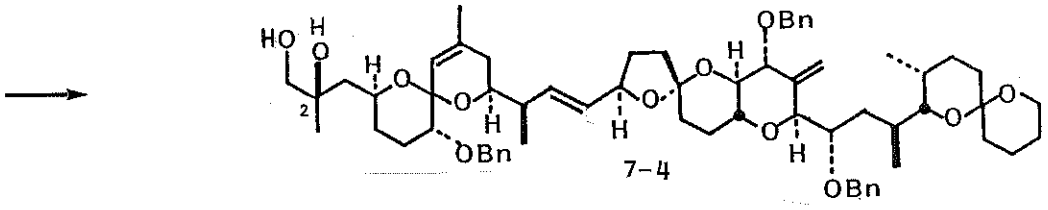


7-7

To a solution of crude tribenzyl okadaic acid 7-6 (0.77 mmol) dissolved in MeOH (2.5 mL) cooled to 0°C was added diazomethane (ether solution) until TLC analysis showed the absence of starting material. Concentration of the solvent gave the residue. Purification of this residue by chromatography on silica gel (3 g) with 1:1 ether/hexane provided the okadaic acid tribenzyl methyl ester 7-7 as an oil (42 mg, overall yield 51% from 1-1).



7-7 (from natural 1-1)



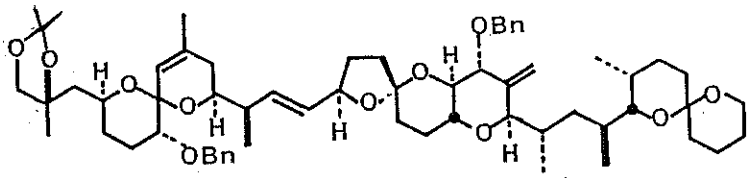
7-4

To a solution of okadaic acid tribenzyl methyl ester 7-7 (42 mg, 0.039 mmol) dissolved in THF (3 mL) cooled to -78°C under N_2 atmosphere was added $LiAlH_4$ (1.2 M solution in THF, 0.2 mL, 0.24 mmol) dropwise. After stirring at -78oC for 30 min, the reaction mixture was gradually warmed up to 0°C. To this solution was added 15% NaOH (2 drops), H_2O (2 drops) and hexane (2 mL). The solution was filtered on a pad of Super Cell and the filtrate cake was washed throughly with AcOEt. Concentration of the filtrate gave the crude oil (39 mg) which was purified by chromatography on silica gel with 1:1 and 2:1 ether /hexane to afford the diol 7-4 (25 mg, yield 60%).

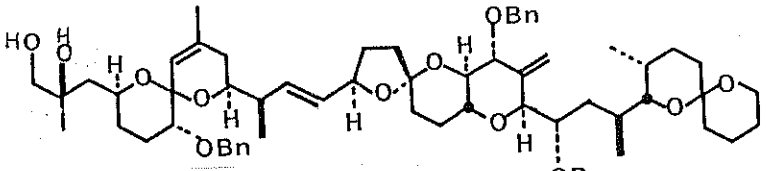
^1H nmr δ 0.87(3H, d, J=7), 0.90(3H, d, J=6), 1.04(3H, d, J=7), 1.13(3H, s), 1.73(3H, s), 2.47(1H, qt, J=7, 7), 3.22(1H, dd, J=10, 2), 3.24(1H, dd, J=12, 4), 3.38-3.5(3H), 3.52(1H, ddd, J=11, 9, 3), 3.58-3.7(5H), 3.88-3.93(2H), , 4.10(1H, tt, J=11, 2), 4.23(1H, d, J=8), 4.47(1H, d, J=13), 4.55(1H, d, J=11), 4.58(1H), 4.61(1H, d, J=13), 4.72(1H, d, J=11), 4.73(1H, d, J=13), 4.82(1H, d, J=13), 5.02(1H, brs), 5.14(1H, brs), 5.40(1H, t, J=2), 5.60(1H, dd, J=16, 7), 5.85(1H, dd, J=16, 7). 7.2-7.5(15H), (500 MHz),

All other signals are left unresolved between 1.25-2.40 ppm.

$[\alpha]_D$=+34.1° (c=0.29, $CHCl_3$).



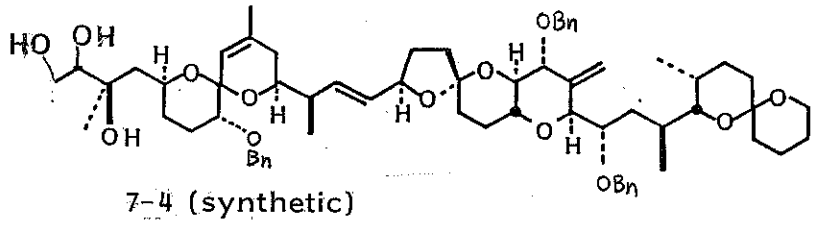
6-27 (synthetic)



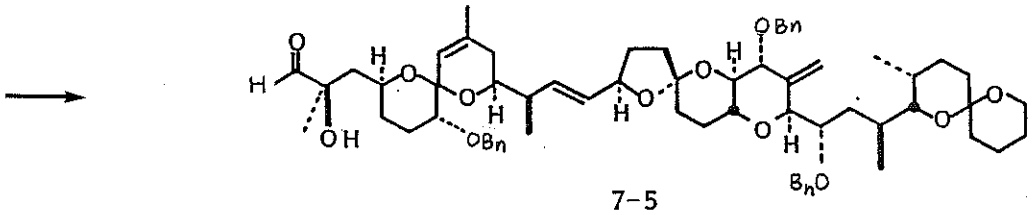
7-4

A solution of the acetonide **6-27** (7 mg, 0.0064 mol) in a mixture of THF (0.40 mL), AcOH (0.30 mL) and water (0.15 mL) was heated at 55°C for 1.5 day. Solvent was removed in vacuum and chromatography (silica gel 1.5 g) of the residue with 1:1 and 3:1 ether/hexane gave the diol **7-4** (4.4 mg, 63% yield).

$[\alpha]_D = +34.4^{\circ}$ (c=0.28, $CHCl_3$).



7-4 (synthetic)

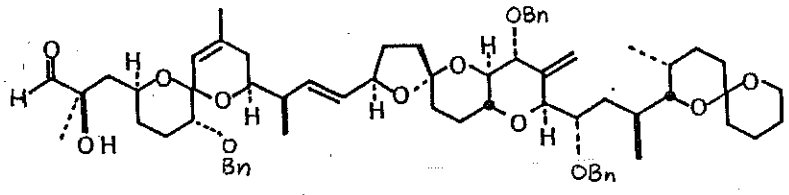


7-5

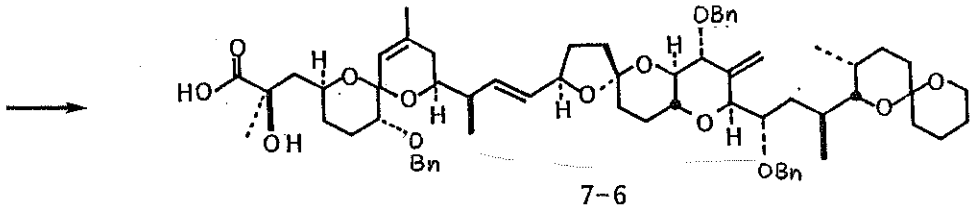
To a solution of the diol **7-4** (4.4 mg, 0.0042 mmol) dissolved in a mixture of DMSO (0.20 mL) and triethylamine (0.8 mL) was added sulfur trioxide pyridine complex (15 mg, 0.094 mmol) portionwise. After stirring at room temperature for 30 min, the solution was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (sat. NH_4Cl x2, sat. $NaHCO_3$, sat. NaCl) and dried (Na_2SO_4). Concentration under reduced pressure gave the aldehyde **7-5** (4 mg). This material was promptly subjected to the subsequent reaction.

^1H nmr δ 0.88(3H, d, J=7), 0.92(3H, d, J=6), 1.05(3H, d, J=7), 1.14(3H, s), 1.72(3H, s), 2.37(1H, tq, J=7, 7), 3.45-3.52(2H), 3.58-3.7(5H), 3.9-4.0(3H), 4.24(1H, d, J=8), 4.46(1H, d, J=13), 4.53(1H), 4.56(1H, d, J=11), 4.59(1H, d, J=13), 4.67(1H, brs), 4.74(1H, d, J=13), 4.74(1H, d, J=11), 4.86(1H, d, J=13), 5.03(1H, brs), 5.13(1H, brs), 5.40(1H, t, J=1), 5.55(1H, dd, J=15, 8), 5.61(1H, dd, J=15, 9), 7.2-7.4(15H), 9.30(1H, s), (500MHz).

All other signals are left unresolved between 1.25-2.40 ppm.



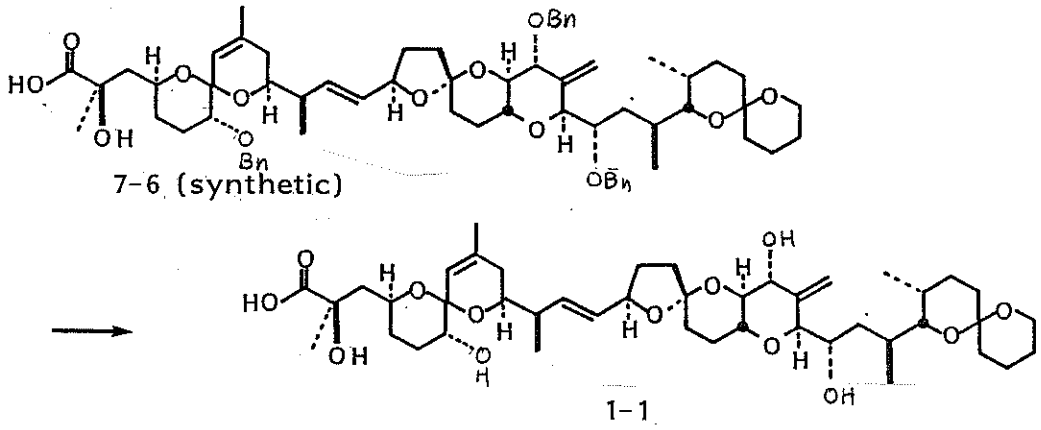
7-5 (synthetic)



7-6

To a solution of the aldehyde 7-5 (4 mg), 2-methyl-2-butene (75 uL) and sodium phosphate, monobasic dihydrate (7 mg, 0.045 mmol) dissolved in a mixture of tert-butanol (0.25 mL) and H_2O (50 mL) was added sodium chlorite ($NaClO_2$, 85%, 4 mg, 0.038 mmol) portionwise. After stirring at room temperature for 2.5 hr, sat. $NaHSO_3$ solution was added. The solution was acidified at $0^{\circ}C$ with 1N HCl and the aq. layer was extracted with CH_2Cl_2 (x3). After being dried (Na_2SO_4), concentration under reduced pressure followed by chromatography (silica gel 1 g) of the residue with 1:1 ether (containing 0.5% of acetic acid)/hexane gave the carboxylic acid 7-6 (2.6 mg 66% overall yield).

$[\alpha]_D = +50.2^{\circ}$ (c=0.22, $CHCl_3$).



7-6 (synthetic)

1-1

To a solution of the tribenzyl okadaic acid 7-6 (2.7 mg) dissolved in EtOH (0.3 mL) and ammonia (distilled from sodium metal) cooled to -78°C was added lithium metal (trace). After stirring at -78° for 30 min, the reaction mixture was allowed to warm to room temperature and to stand at room temperature for 2 hr until ammonia dissolved in EtOH was evaporated. Water was added and the solution was acidified at 0°C with 1N HCl. The aq. layer was extracted with CH_2Cl_2 (x3) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crystalline mass were washed with hexane to give the synthetic okadaic acid as white crystalline (1.7 mg 87% yield).

^{1}H nmr δ 0.93(3H, d, J=6), 1.02(3H, d, J=7), 1.06(3H, d, J=6), 1.37(3H, s), 1.77(3H, s), 3.29(H-30, dd, J=11, 2), 3.35-3.62(2H), 3.55(H-38, brd, J=11), 3.61(H-22, td, J=10, 4), 3.66(H-38, td, J=11, 3), 3.94(H-26, d, J=10), 4.07(H-4, brt, J=11), 4.09(H-27, t, J=10), 4.12(H-24, d, J=10), 4.54(H-16, td, J=9, 7), 5.06(1H, brs), 5.32(1H, brs), 5.44(1H, t, J=1), 5.48(1H, dd, J=15, 9), 5.67(1H, dd, J=15, 9), 5.78(1H, brs). (500MHz)

All other signals are left unsesolved between 1.25-2.40 ppm.

Analytical TLC; R_f value	Solvent
0.28	AcOEt (0.5% AcOH)/hexane 1:1
0.28	Ether (0.5% AcOH)
0.21	CH_2Cl_2/MeOH (5%)
0.49	acetone/hexane 1:1

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