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SYNTHESIS OF A MARINE POLYETHER TOXIN, OKADAIC ACID [1][1] --- STRATEGY AND SYNTHESIS OF SEGMENT A

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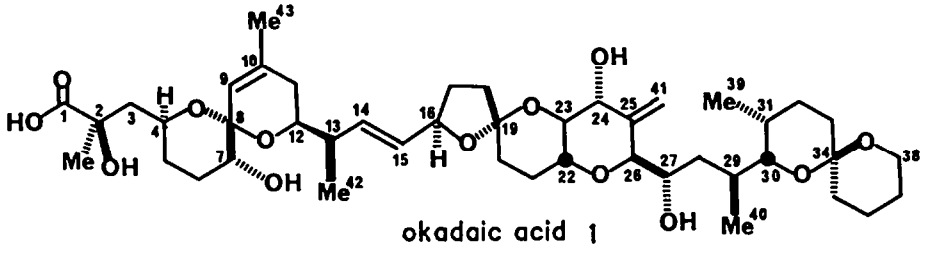
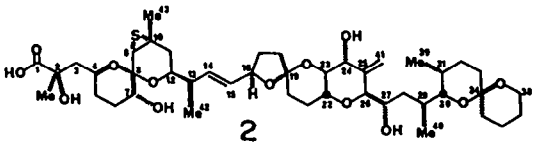
Abstract *The title compound was divided into three retrosynthetic segments A, B and C, by disconnecting two C-C bonds at C-14/15 and C-27/28. Segment A for okadaic acid synthesis comprises the carbon skeleton from C-1 through C-14, which was further disconnected at the bonds between C-8 and C-9 into two fragments A_1 and A_2. Each fragment was synthesized in the optically active form from D-glucose derivatives. Key steps are the oxymercuration and anti-selective heteroconjugate addition to elaborate the asymmetric carbons on acyclic parts of these fragments. The coupling was facilitated between the acetylenic carbanion and the lactone carbonyl of the respective fragments. The segment A was synthesized in 36 steps.*

Introduction

During the course of a search for chemotherapies of marine sources, Okadaic acid *1* was first isolated as a potent antitumor agent from two sponges *Halichondria okadai* and *H. melanodocia*. The structure *1* was elucidated in 1981 by Scheuer and his colleagues with X-ray crystallographic method.[2] In 1982 Yasumoto et al. identified as the major diarrhetic shellfish toxin found in mussel, *Mytilus edulis*. They considered that okadaic acid accumulated from an original producer dinoflagellate, *Dinophysis fortii*.[3] Okadaic acid has commonly been found in various classes of organisms and its structure possesses the basic framework among the other congeners such as acanthifolicin[4] *2* and dinophysistoxin[5] *3*. We became interested in the synthesis of this new class of marine natural product from the following points of view.



okadaic acid 1



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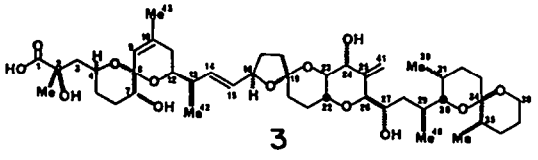

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Retrosynthesis of Okadaic Acid

Okadaic acid has unique structural features as a polyether carboxylic acid containing 38 contiguous carbon atoms of its backbone, 17 asymmetric carbons, 7 etherial rings, 5 methyl side-chains, 4 hydroxy groups, 3 olefins and 3 spiroketals. The retrosynthesis of okadaic acid *1* involves two disconnections between the bonds of C-14/C-15, and C-27/C-28 to give rise to three synthetic segments A, B and C. This is shown in Fig 1. [The wavelines indicate the retrosynthetic disconnection into the three Segments A, B and C.] This paper deals with the synthesis of segment A in the optically active form starting from two glucose derivatives as chiral pool. Segment A comprises the carbon skeleton from C-1 through C-14 and it contains three methyl side chains and six asymmetric carbons, two of which situate on the flexible acyclic part of the molecule. Some devices are necessary for achieving these stereocontrol capable to render at the acyclic transition states. The asymmetric centers, C-2 and C-13, would be induced from the neighbouring tetrahydropyranyl rings, respectively. The stereochemical subjects and the coupling processes of smaller fragments into the larger segments are the substantial problems in the total synthesis of this toxin. These problems are to be solved by a new methodology "heteroconjugate addition" exploited during the synthetic studies directed toward okadaic acid.[6]

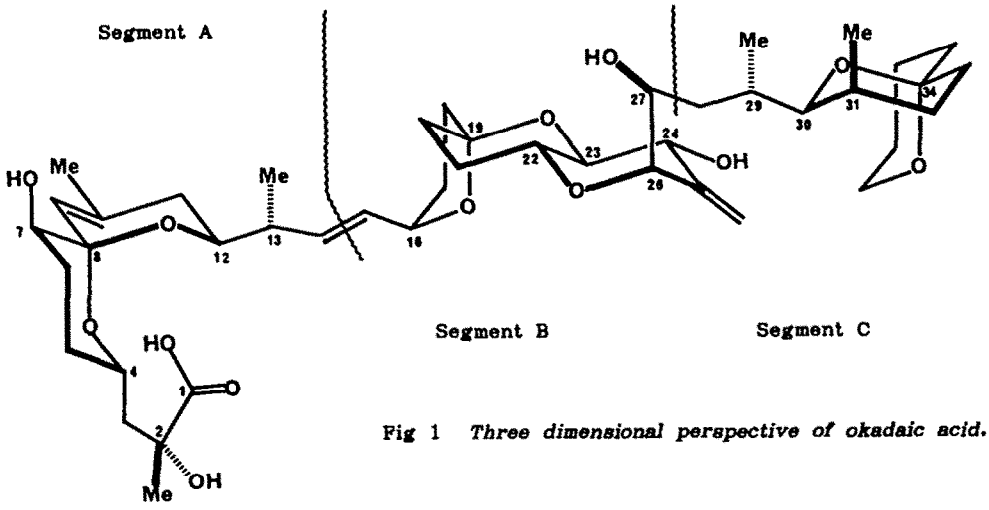


Fig 1 *Three dimensional perspective of okadaic acid.*

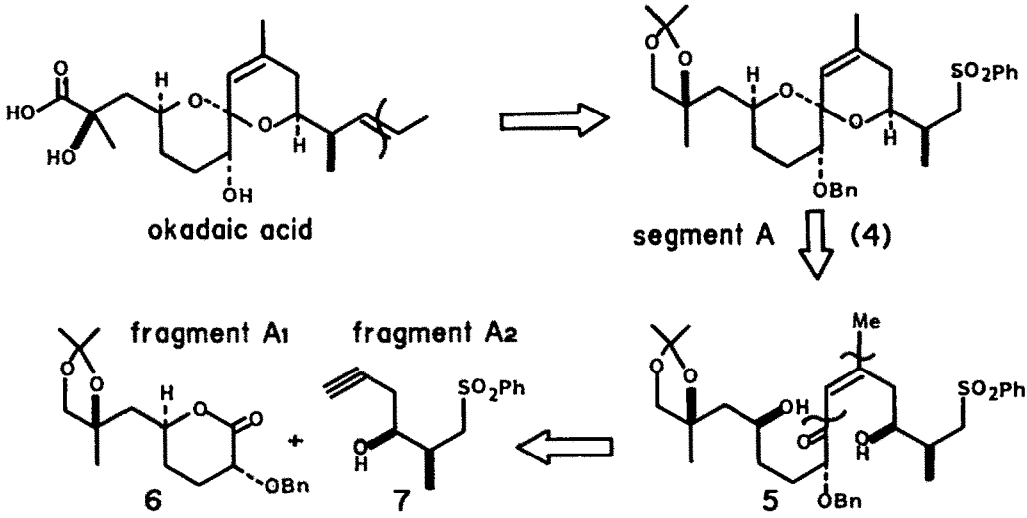
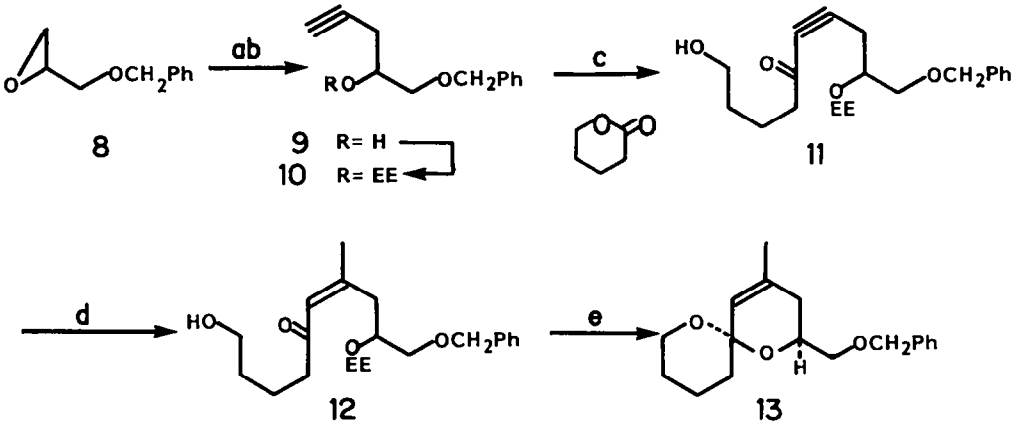


Fig 2 *Retrosynthetic analysis of Segment A*

Model Studies for Retrosynthetic Analysis of Segment A into Fragment A_1 and A_2

Segment A is to be separated into two small fragments, A_1 and A_2 as illustrated in Fig 2. The validity of this retrosynthetic disconnection was first confirmed by a model study as shown in Scheme 1. It involves twice couplings between lithium acetylides deriving from lithium (trimethylsilyl)acetylide with protected glycidol *8*, and the other one being the product *10* with δ-valerolactone. The adduct was the ynone *11*, which received the attack of dimethylcopper-lithium to give the *Z*-enone *12* as only the product.[7] Acidic treatment with pyridinium p-toluenesulfonate in methanol solvent hydrolyzed the ethoxyethyl protection to form the ketodiol intermediate which spontaneously cyclized to the *spiro*-derivative *13* in 72% yield.



Scheme 1

a) $Me_3Si-C\equiv C-Li/BF_3-OEt_2$, KF/MeOH; b) $CH_2=CHOEt$/PPTS;
c) n-BuLi, δ-valerolactone; d) Me_2CuLi/Et_2O; e) PPTS.

Synthesis of Fragment A_2

Above model study suggests that acetylene group of fragment A_2 (*7*) is usuable twice as the nucleophile and also as the precursor of the *Z*-tri-substituted olefin. The *anti*-diastereo relationship between the two asymmetric carbons at C-12 and C-13 and the following coupling steps recalled us to develop the heteroconjugate addition methodology,[8] although this methodology had given only *syn*-diastereoisomers when we started this study. We have developed a new method switchable in *syn/anti*-selectivity along the okadaic acid synthesis. We then concluded that the best candidate will be the sulfone *7* for segment A_2.

The synthetic goal *7* in this chapter will be reached by the coupling of A_1 and A_2. The *anti* diastereomeric relationship between the two asymmetric carbons C-12 and C-13 was scheduled to be derived from a newly developed method; thus, β-chelation controll in the heteroconjugate addition.[8b)] The principle of these retrosynthetic analysis is summarized in Fig 3. It indicates that the precursor of the acetylene is to be a dihydropyran derivative such as *14*. The latter had been developed mainly because of solving the *anti* stereochemical problem; thus, the *anti* addition to the heteroolefin *15* can be controlled *via* the β-chelation effect.[8] This effect was found significant in the heteroconjugate addition in case of Grignard reagents nucleophile *vs.* free alkoxide attached to the β-carbon atom.[8]

The heteroolefin *15* in Scheme 2 was prepared from a D-glucose derivative *16* and it afforded *anti*-adduct *14* by treatment with methyl magnesium bromide in tetrahydrofuran solvent. Acetylation to *18*, deglycosidation[9] and oxidation[10] afforded the conjugated lactone *19*. Zinc-copper couple reduction gave the deconjugated product of β,γ-unsaturated lactone *20*.[11] The double bond was cleaved by ozonolysis to form an ozonide, which was reduced with sodium borohydride into the diol *21*. Monotosylation of the primary hydroxy group *22* and subsequent treatment with

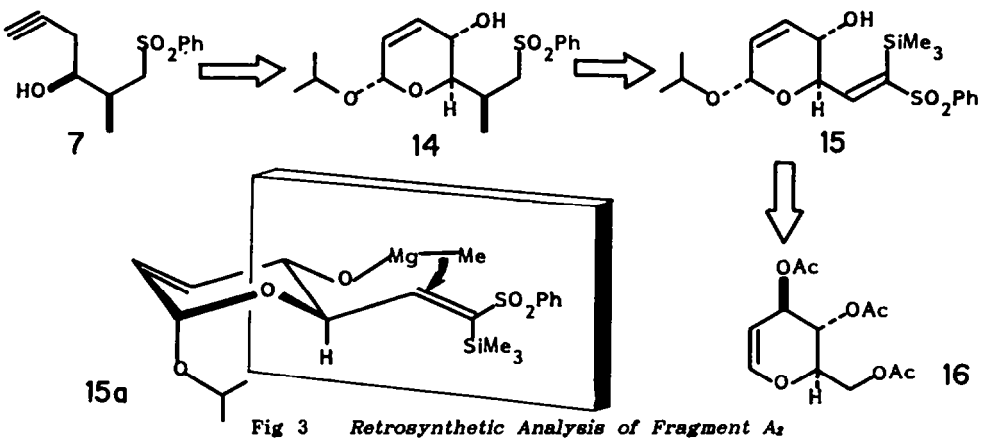
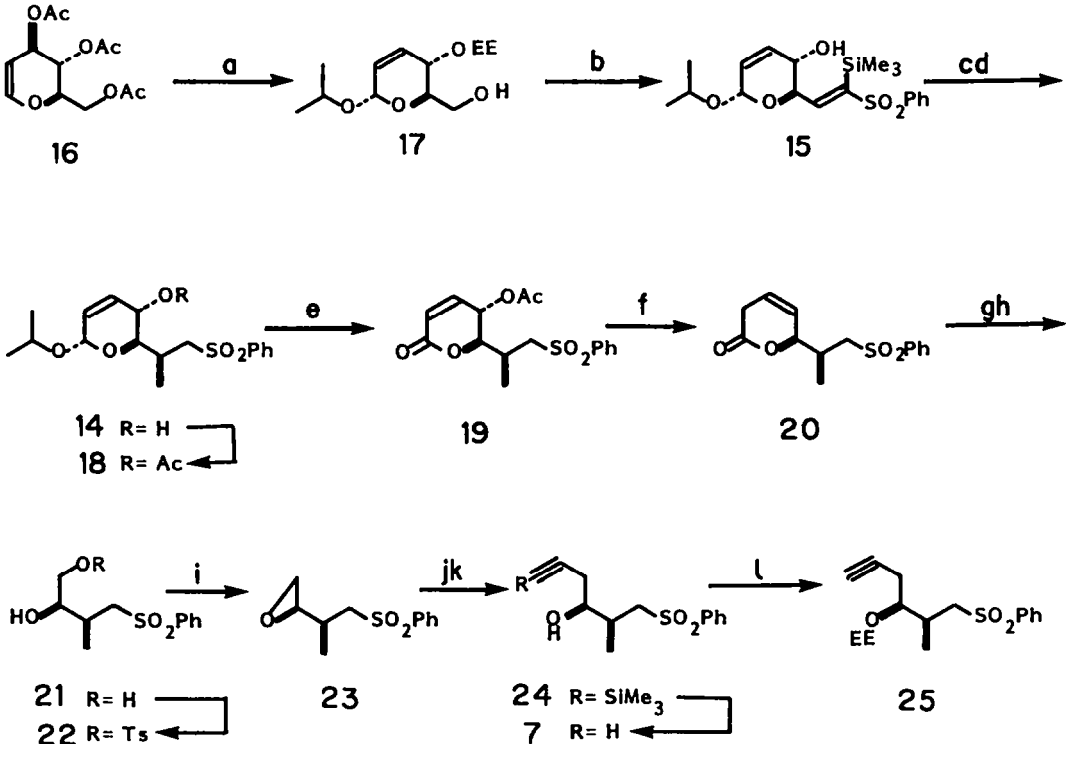


Fig 3 *Retrosynthetic Analysis of Fragment A₂*

t-BuOK yielded the epoxide *23*. Addition of lithium trimethylsilylacetylide in the presence of boron trifluoride-etherate[12] to give *24*, which was treated with n-Bu_4NF to produce the acetylene *7*. The hydroxy group was protected as the ethoxyethyl ether *25*, which was used for the coupling. The overall yield in Scheme 2 was 2.1 % yield in 20 steps, while the diastereomerical purity was 91 %.



Scheme 2

a) 2-PrOH/BF_3, Et_3N, BzCl, $EtOCH{=}CH_2$, KOH; b) Swern, $PhS(Me_3Si)_2CLi$, MCPBA, H_3O^+; c) MeMgBr, 0° C/KF; d) Ac_2O/Py; e) H_3O^+, PDC; f) Zn-Cu; g) O_3, $NaBH_4$; h) p-TsCl/Et_3N; i) ^{t}BuOK; j) $Me_3SiC{\equiv}CLi/BF_3{-}OEt_2$; k) n-$Bu_4NF$; l) $CH_2{=}CHOEt/H^+$.

Synthesis of the Fragment A_1

Fragment A_1 should contain a carboxylic acid group, which has to be generated from the corresponding hydroxy group in a last stage of the total synthesis. The 1,2-acetonide group was employed to protect both of the hydroxy groups at the C-1 and C-2 position; thus, the frag-

ment A_1 was designed as *6*. The asymmetric carbon C-2 will be derived by a selective oxidation or hydration from the corresponding Δ_2 olefin (for example *26*), which will be derived from a glucose derivative (see Fig. 4). The retrosynthesis of Fragment A_1 was analyzed so that the starting material will be connected to a glucose derivative, if possible, a common starting material for the other fragment(s). The precursor of the asymmetric center at C-2 might be elaborated from the olefin *26*, since the sp^2 orbital will have different reactivity due to the presence of adjacent asymmetric center. This is the common strategy in the acyclic asymmetric control in the current synthetic studies.

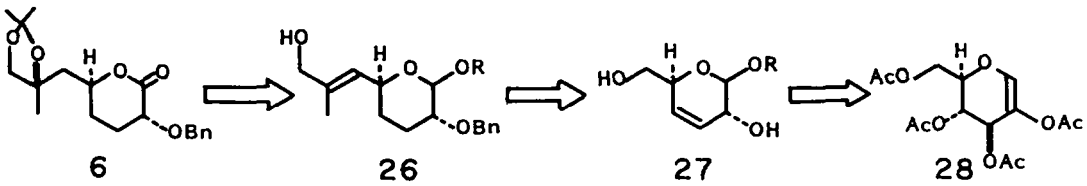
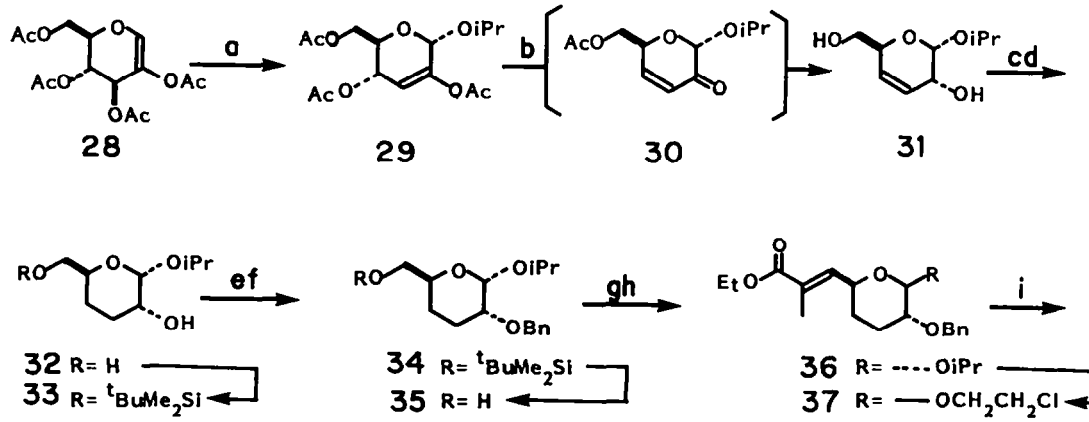
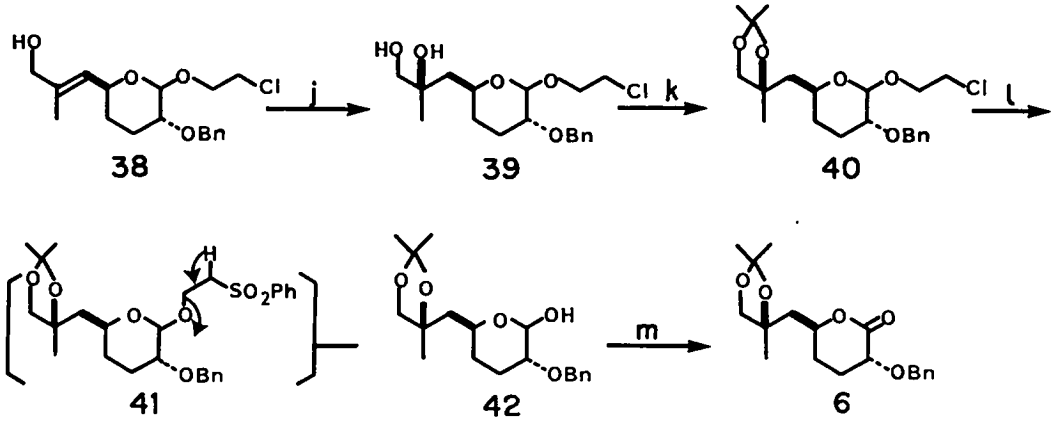


Fig 4 *Retrosynthetic Analysis of Fragment A_1*

The stable 2'-propyl glycoside *29* was employed for the starting material of this fragment, since *29* is preparable from 2-acetoxy glucal *28* commonly used for the Segment C as well.[13] The enol acetate *29*, when treated with lithium aluminum hydride, was first decomposed into the enone *30* due to the basic nature of this reagent, and the enone was subsequently reduced into the 2-α-alcohol *31*. The reduction was highly stereoselective because the reagent approached away from the axially orienting 2'-propyl group. After reduction of the Δ_3-olefin with palladium under hydrogen atmosphere, the two hydroxy groups in *32* were selectively protected first with dimethy-t-butylchlorosilane *33* and then with benzyl bromide to afford *34*. Selective deprotection of the silyl group with n-Bu_4NF, the primary hydroxy group in *35* was oxidized with DMSO/$(COCl)_2$ into the corresponding aldehyde, to which was added the phosphorane Ph_3P=CMeCOOEt[14] without isolating the aldehyde intermediate.[15] The product unsaturated ester *36* was heated with 2-chloroethanol in the presence of camphorsulfonic acid to give a mixture of two anomers of chloroethylglycosides, *37*. Reduction of the ester group with DIBAL-H in dichloromethane at -78° C gave the allylic alcohol *38*. Oxymercuration[16] of this olefin with mercuric acetate and subsequent reductive work-up with sodium borohydride in aq. THF (tetrahydrofuran) afforded the diol *39* in 91% yield. After protecting the diol as the corresponding acetonide, it was heated at 105° C with sodium sulfinate ($PhSO_2Na$) and NaI in DMF (N,N-dimethylformamide) solvent to cleave the chloroethyl glycoside *via* a sulfonylethyl group as shown in *41*. The cyclic hemiacetal *42* was oxidized with bromine-water[17] into the lactone, segment A_1 (*6*).



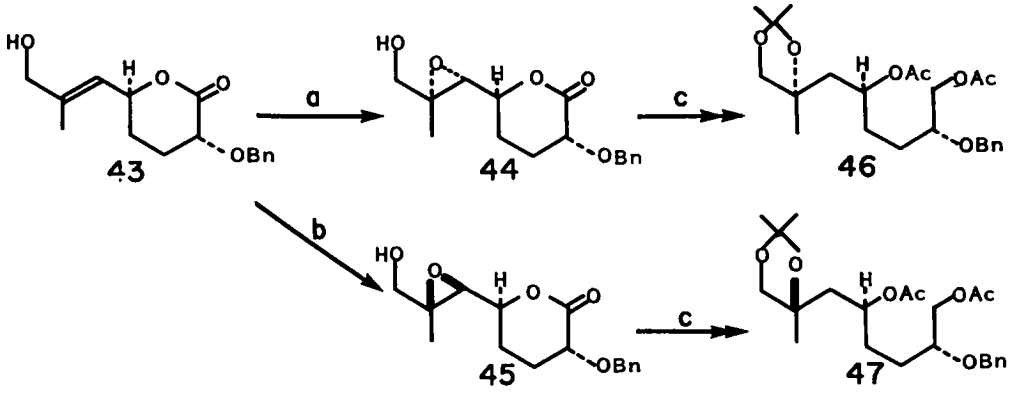


Scheme 3

a) 2-PrOH/BF_3-OEt_2; b) $LiAlH_4$; c) H_2/Pd-C; d) $Me_2{}^tBuSiCl$/imidazole; e) $PhCH_2Br$/NaH; f) n-Bu_4NF; g) $(COCl)_2$/DMSO/Et_3N, Ph_3P=CMeCOOEt; h) $HOCH_2CH_2Cl/H^+$; i) DIBAL-H; j) $Hg(OAc)_2$, $NaBH_4$; k) $Me_2C(OMe)_2/H^+$; l) $PhSO_2Na$, KI/DMF; m) Br_2/NaOAc.

Proof of the Stereochemistry at C-2

The stereochemistry of the product alcohol *3* in the oxymercuration was expected to be the desired 2-*R* isomer. This was assumed from the following consideration and the result was confirmed by the following experimental evidences. Stereochemical authentic samples were prepared *via* established Sharpless's epoxidation[18] to *43*. Two diastereomeric epoxides *44* and *45* were converted into the acetonide acetates *46* and *47*, one of which was identical to the sample derived from *42* by $LiAlH_4$ reduction and acetylation.



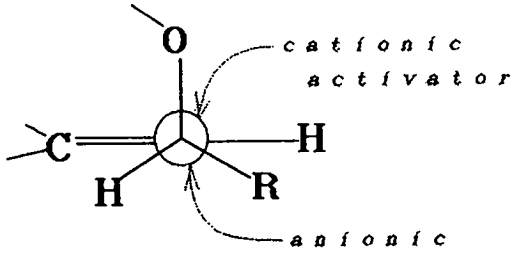


Fig 5

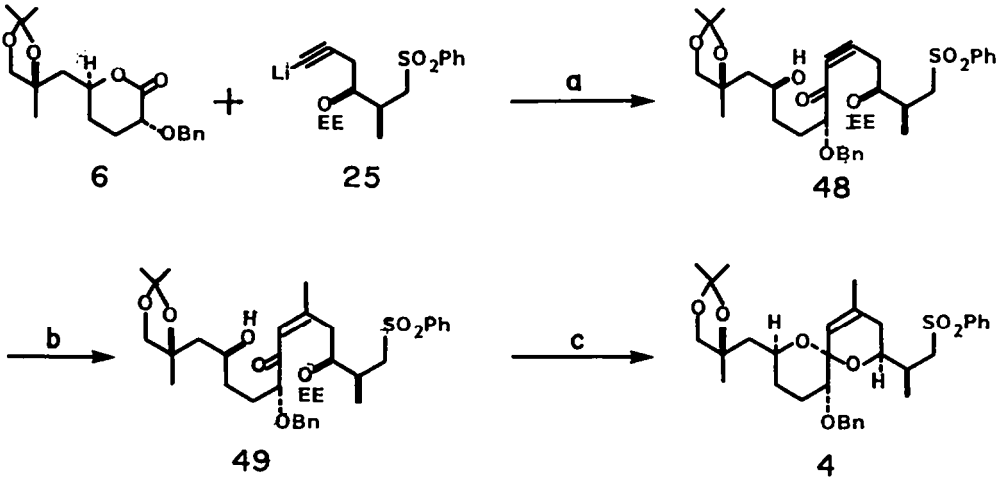
Scheme 4

a) Diethyl (-)-tartrate, TBHP, Ti(IV); b) Diethyl (+)-tartrate, TBHP, Ti(IV); c) dihydropyran/H^+, $LiAlH_4$, Ac_2O/Py, MeOH/H^+, $(MeO)_2CMe_2$/PPTS.

The stereoselection discussed here is the differentiation of the two faces of such an olefin that has a neighbouring asymmetric center involving secondary hydroxy group equivalent. Since *Felkin rule*[19] can predict the major stereoisomer and *Nguen*[20] *rule* can rationalize the result, we would like to apply the rule in a different way.[21] Namely, the anionic nucleophiles such as hydrides, Grignard reagents, alkyl lithiums approaches to the olefin and attacks away from the most polarized C–O bond. The major factor of selection in nucleophile approach is electrostatic interaction; namely, anionic nucleophile attacks away from the C–O due to an repulsive electrostatic interaction, while cationic electrophile attacks favoured to the C–O bond because of the attractive electro static interaction.[22] In case of the above oxymercuration, the reaction will be initiated by the partition of mercurium cation to the olefin; thus the activation with mercury cation occurs at the oxygen face, which eventuates the attack of water *anti* to the Hg^{++} (Fig 5). The generalization will be described elsewhere.

Coupling of fragments A_1 and A_2

The ethoxyethyl ether *25* of fragment A_2 *7* was treated with n-butyllithium to convert it into the lithium acetylide, which was added to the lactone of fragment A_1 *6* in THF at -78° C to afford the adduct *48* in 80% yield. As was studied in the model study, this adduct was largely existed as an open chain unsaturated ketone rather than the hemiacetal, the former being important for the introduction of the methyl group via conjugate addition with Me_2CuLi in ether solvent. The stereochemistry of the trisubstituted olefin in *49* was controlled in the trans protonation to the intermediate allenyl-enolate to produce *Z*-olefin selectively.[8] The geometry was confirmed by the fact that *49* was converted into the spiro ether *4* by treatment with pyridinium p-toluenesulfonate. Part of the acetonide was cleaved off and it was re-acetonized by addition of 2,2-dimethoxypropane at the end of this reaction. The stereochemistry of the spiro moiety was confirmed with its ^{13}C nmr spectrum; thus, the spiro carbon appeared at 94.5 ppm.



Scheme 5

a) n-BuLi/THF; b) Me_2CuLi; c) PPTS.

This segment A was used for the coupling with the rest part, B/C segment of the target okadaic acid. The chemistry is described in the following papers.

EXPERIMENTAL

Model Studies, Pentyne Diol derivatives 9

Sodium hydride (1.4 g, 34 mmol) was placed in a 100 mL-flask and washed with n-hexane three times. To this suspension was introduced at 0° C a solution of glycidol (2 mL, 31.5 mmol) and benzyl bromide (3.0 mL, 26 mmol) in a mixture of solvents, THF (20 mL) and DMF (10 mL). After stirring at 0° C for 30 min, the reaction mixture was further stirred at room temperature for 6 hr. The reaction mixture was poured into water, and the aqueous layer was extracted three times with ether solvent and the combined etherial layers were washed with water and sat. NaCl, dried over sodium sulfate and concentrated under reduced pressure. Kuhgelrohr distillation of the resulting oil at 140° C *in vacuo* (20 mmHg) provided the benzyl ether *8* (3.18 g, 75 % yield). ^{1}H nmrδ 2.4-2.5(2H), 3.1(1H, m), 3.2-3.7(2H), 4.44(2H, s), 7.1-7.2(5H).

A solution of trimethylsilylacetylene (3.3 mL, 31.7 mmol) in THF (tetrahydrofuran) (80 mL) was cooled to -78° C, to which was added with stirring n-BuLi (1.55M in hexane, 22.5 mL, 34.9 mmol). After 20 min, BF_3-OEt_2 (2.9 mL, 23.6 mmol) was added and the stirring was continued further 15 min. The epoxide *8* (3.18 g, 19.4 mmol) was dissolved in THF (5 mL) and added dropwise into the above mixture at -78° C. The reaction was continued at this temperature for 1 hr and then interrupted by pouring the mixture into sat. sodium bicarbonate solution. The product was taken by ether extraction and the crude product (5.5 g) was dissolved in methanol (80 mL) containing KF (4.5 g). The mixture was heated to reflux for 1 hr and then concentrated. The residual oil was dissolved in ether. The etherial solution was washed with water and NaCl, dried over Na_2SO_4 and concentrated to give oil, which was distilled at 120° C *in vacuo* (5 mmHg) to give the acetylene *9* (3.04 g, 82% yield): ^{1}H nmrδ 2.01(1H, t, J= 3), 2.40-2.47(2H), 3.63(1H), 3.45-3.63(2H, AB), 3.96(1H, br), 4.55(2H, s), 7.2-7.4(5H). irν 3600, 3320, 2130cm^{-1}

Found C 75.72, H 7.44; Calcd C 75.76, H7.42, for $C_{12}H_{14}O_2$.

Model Studies, Synthesis of the Spiro-ether 13

The acetylene alcohol *9* (3.04 g, 16 mmol) was dissolved in dichloromethane (20 mL) and stirred with ethyl vinyl ether (5 mL) in the presence of PPTS (pyridinium p-toluenesulfonate, 0.20 g) at room temperature for 3.5 hr. The reaction mixture was poured into sodium bicarbonate and extracted with dichloromethane to give the crude product (3.97 g), which was purified with silica gel (60 g) chromatography to give pure ethoxyethyl ether *10* (2.8 g, 67% yield). n-BuLi was added to a solution of this acetylene to form the acetylide, to which was introduced a solution of valerolactone, part of which (150 mg) was dissolved in ether (1 mL) and introduced into the following cold (-78° C) mixture. Methyllithium (1.5 M, 4.3 mL, 6.5 mmol) was added at 0° C to a slurry of CuI (0.62 g, 3.2 mmol) in ether (6 mL); the mixture being stirred at 0° C for 20 min. The mixture with the unsaturated acetylene was stirred at -78° C for 15 min and then poured into a sat. NH_4Cl. Etherial work-up gave the *Z*-olefin *12* (147 mg, 95% yield): irν 3500, 2220, 1670 cm^{-1}.

The *Z*-enone *12* (147 mg, 0.39 mmol) was dissolved in methanol (3 mL) and stirred with PPTS (10 mg) at room temperature overnight. The normal etherial work-up afforded the spiro ether *13* (85 mg, 72% yield): ^{1}H nmrδ 1.4-2.1(8H), 1.71(3H, s), 3.5-3.7(3H), 3.90(1H, td, J= 12, 3), 4.16(1H, m), 4.64(2H, s), 5.35(1H, d, J= 1), 7.2-7.4(5H).

Found C 75.11, H 8.44; Calcd C 74.97, H 8.39, for $C_{18}H_{24}O_3$.

Fragment A, from β-Chelation Heteroconjugate Addition, Acetylation of the anti-Adduct 18

The *anti*-adduct *14* [8] (9.3 g) selectively produced from a heteroolefin derived from a glucose derivative was dissolved in dichloromethane (100 mL), and it was stirred with pyridine (30 mL) and acetic anhydride (15 mL) at room temperature overnight. Concentration of the reaction mixture *in vacuo* and purification of the residue with silica gel (180 g) chromatography with a mixture of ether and hexane 1:3 yielded the acetate *18* (6.5 g, 63% overall yield from *15*). $[\alpha]_D$= +108.1° (c=1.13, $CHCl_3$); ^{1}H nmrδ 1.15(3H, d, J= 6), 1.20(3H, d, J= 6), 1.32(3H, d, J= 7), 1.99(3H, s), 2.33(1H, m), 2.97(1H, dd, J= 14, 10), 3.33(1H, dd, J= 14, 2), 3.84(1H, dd, J= 10, 2), 3.95(1H, sept, J= 6), 5.0-5.1(2H), 5.65-5.85(2H), 7.5-7.7(3H), 7.9-8.0(2H). irν 1745 cm^{-1}.

Found C 59.40, H 6.82; Calcd C 59.67, H 6.85, for $C_{19}H_{26}O_6S$.

The α,β-Unsaturated lactone 19

The 2'-propyl glycoside *18* (6.5 g) was dissolved in a mixture of acetic acid (120 mL) and water (50 mL) and heated at 40° C for 12 hr. The solution was diluted with dichloromethane (400 mL) and then washed with water and sodium bicarbonate, dried over sodium sulfate and concentrated to give the lactol (5.5 g). This lactol was dissolved in dichloromethane (dried over alumina, 200 mL) and stirred overnight with pyridinium dichlorochromate (32 g, 0.016 mmol) at rom temperature. The mixture was diluted with ether solvent and then filtered through Super Cel. The filtrate was further filtered through a short silica gel column and concentrated to give residue (5.2 g), which was separated with a mixture of ether and n-hexane 1:1 and then 3:1 to give the starting material *18* (1.1 g) and the lactone (ca. 91% purity) *19* (3.0 g, 63% yield). $[\alpha]_D$= +74.1° (c=1.03, $CHCl_3$); ^{1}H nmrδ 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). irν 1740 cm^{-1}.

Deconjugation and Ozonolysis of the Unsaturated Lactone 20

The conjugated lactone *19* (3.0 g) was mixed in a mixture of acetic acid (50 mL) and water (50 mL) with zinc powder (8 g) and copper(II)-sulfate pentahydrate (1.0 g) in the presence of sodium acetate trihydrate (50 g) at 0° C and reacted at room temperature for 5 hr. After filtration of the reaction mixture through Super Cel, it was extracted with ether and the etherial layers were combined, washed with water, NaCl and $NaHCO_3$, dried over Na_2SO_4 and concentrated

to give the de-donjugated lactone *20* (1.6 g, 64% yield). ^{1}H nmrδ1.25(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). ir($CHCl_3$) ν1740cm^{-1}.

Ozone was introduced at -78° C into a solution of the deconjugated lactone *20* (2.2 g, 7.9 mmol) in a mixture of dichloromethane (35 mL) and methanol (30 mL) until the blue color persisted. Perging the ozone with oxygen, the reaction mixture was stirred with sodium borohydride (1.0 g) at room temperature. The mixture was concentrated under reduced pressure and then extracted with dichloromethane ca. 20 times. The organic layers were combined and dried over sodium sulfate and concentrated to give the diol *21* (2.2 g). This material was used for the subsequent reaction without further purification.

Preparation of the Fragment A:

p-Toluenesulfonyl chloride (1.0 g, 5.2 mmol) was added to a solution of the diol *21* (2.2 g) in a mixture of dichloromethane (40 mL) and triethylamine (8 mL)at room temperature. After no starting material was detectable with tlc analysis, the mixture was diluted with ether solvent and washed successively with 1N HCl, sat. $NaHCO_3$ and sat. NaCl, and dried over Na_2SO_4. Concentration of the solvent was followed by purification with silica gel (60 g, ether/n-hexane 2:1 as eluant) chromatography to give the epoxide *23* (1.9g) and the tosylate *22* (0.8 g) in 41% overall yield from *20*. The tosylate showed the ^{1}H nmrδ1.08(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).

The tosylate (0.85 g, 2.1 mmol) was dissolved in THF (30 mL), cooled down to 0° C and then mixed with potassium *tert*-butoxide (1.28M in *tert*-butanol, 2.0 mL, 2.6 mmol) dropwise. After stirring for 30 min, the reaction mixture was poured into sat. NH_4Cl solution. Etherial work-up gave the epoxide *23* (463 mg, 98% yield), which was combined with the above sample (757 mg, 3,35 mmol) and used for the following reaction.

To a solution of trimethylsilylacetylene (1.7 mL, 12.1 mmol) in THF (35 mL) was added at -78° C under nitrogen atmosphere n-butyllithium (1.55 M solution in n-hexane, 6.5 mL, 10.0 mmol) dropwise and then (after 20 min) borontrifluoride etherate (1.0 mL, 8.1 mmol). After stirring for 15 min, a solution of the epoxide *23* (757 mg) in THF (5 mL) was added into this mixture. And the stirring was continued for 1 hr at -78° C. Etherial work-up afforded the alcohol *24* (1.03 g, 9.2 mmol, 95% yield). This product was dissolved in THF (30 mL) and further treated with n-Bu_4NF (1M solution in THF, 3.5 mL, 3.5 mmol) at room temperature for 2 hr. The mixture was poured into water. The etherial work-up afforded the acetylene *7* (0.82 g, quantitative yield): [α]$_D$= +28.3° (c=1.49, $CHCl_3$); ^{1}H nmrδ1.15(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 ($CHCl_3$) ν3550, 3320, 2140 cm^{-1}.

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

Isopropylglycoside 29

To a stirred solution of acetoxy-glucal *28* (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 *29* as a crude crystal. Recrystallization from ether/hexane afforded the analytical sample (31.5 g, yield 63.1%), m.p. 60-61° C, [α]$_D$=+93.7° (c=1.00, $CHCl_3$); ^{1}H 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).

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

Lithium Aluminum Hydride Reduction of the Glycoside 31

A solution of the isopropylglycoside *29* (90 g, 0.27 mol) in THF (200 mL) was introduced dropwise with stirring into a cold (0° C) solution of $LiAlH_4$ (29 g, 0.76 mol) in THF (1.8 L) over a period of 1 hr. The stirring was continued at 0° C for further 1 hr. Following reagents were successively added to this mixture for work-up; thus, ethyl acetate (20 mL), water (30 mL), n-hexane (1.2 L), 15% NaOH (30 mL) and water (90 mL). The mixture was stirred at room temperature overnight and then filtered through a cake of Super Cel, which was washed with ethyl acetate (2 L). The organic solution was concentrated *in vacuo* to yield *31* (51.7 g) quantitatively; [α]$_D$=+40.9° (c=2.71, $CHCl_3$); ^{1}H nmr δ1.21(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).

Hydrogenation and Protection of the Endiol 31

The olefin *31* (50 g, 0.27 mol) was dissolved in ethyl acetate solvent (1.5 L) and it was vigorously stirred with a catalyst palladium on charcoal (10%; 5 g) under hydrogen atmosphere for one day. After removing the catalyst by filtration through a pad of Super Cel, the reaction mixture was concentrated under a reduced pressure to produce the hydrogenated diol *32* (47.9 g, 96% yield); [α]$_D$= +137.2° (c=0.68, $CHCl_3$); ^{1}H nmr 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, sep, J= 6), 4.89(1H, d, J= 4).

To a solution of the diol *32* (40 g, 0.21 mol) in DMF (N,N-dimethylformamide) (1.2 L) was added imidazole (65 g, 0.96 mol) and t-butyldimethylchlorosilane (30 g, 0.20 mol) at 0° C and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and extracted with ether. The extracts were combined, washed with water and aq. NaCl, dried over sodium sulfate and concentrated to give the silyl ether *33* as an oil. This oil was used without further purification. Part of the sample was purified with silica gel chromatography for analyses. [α]$_D$= +82.4° (c=1.74, $CHCl_3$); ^{1}H nmr δ0.06(6H, s), 0.89(9H, 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, sep, J= 6), 4.86(1H, d, J= 4).

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

Benzylation of the Alcohol 33

Sodium hydride (60% in mineral oil, 12 g, 0.3 mol) was placed in a flask and washed with hexane and it was suspended in THF (tetrahydrofuran, 900 mL). A solution of *33* (0.21 mol) in THF (100 mL) was added dropwise at room temperature to the suspension, to which were added benzyl bromide (30 mL, 0.25 mol) and DMF (240 mL). After stirring 6.5 hr, the reaction mixture was poured into water and extracted with ether. The work-up afforded the benzyl ether *35* (85.6 g) as an oil, which was used for the following step without purification. A portion of this material was purified on silica gel tlc for analyses. $[\alpha]_D$= +74.2° (c=1.10, $CHCl_3$); ^1H nmrδ 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, sep, J= 6), 4.57(2H, s), 4.96(1H, d, J= 4), 7.2-7.4(5H).

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

Desilylation of 34

To a solution of the silyl ether *34* (82.5 g, 0.21 mol) in a mixture of THF (800 mL) and acetonitrile (400 mL) was added a solution of n-Bu_4NF (1M solution in THF, 200 mL, 0.2 mol) and the mixture was stirred overnight. The reaction mixture was poured into water and extracted with ether. The work-up gave crude oil, which was purified with silica gel column chromatography (SiO_2 600 g, a mixture of ether-hexane 1:1 as eluant) to produce the mono-ol (*35*) (47 g, 80% overall yield from *32*). $[\alpha]_D$= +104.7° (c=1.49, $CHCl_3$); ^1H nmrδ 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).

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

Unsaturated Ester 36

Dimethyl sulfoxide (30 mL, 0.42 mol) was added dropwise into a cold (-78° C) solution of oxalyl chloride (15 mL, 0.17 mol) in dichloromethane (480 mL) with stirring. After 5 min, the alcohol *35* (15.2 g, 0.054 mol) in dichloromethane (20 mL) was slowly introduced over a period of 5 min. The stirring was continued for further 15 min at -78° C. Triethylamine (75 mL, 0.54 mol) was added to this mixture, which was further stirred at -78° C for 15 min, at 0° C for a few minutes and then at -20° C. Without isolating the corresponding aldehyde product at this point, the reaction mixture was further reacted by addition of triphenylethoxycarbonylethylphosphorane [Ph_3P=C(Me)COOEt] (24.2 g, 0.067 mol) to this mixture at -20° C, and the cooling bath was removed. When the mixture became warmed to the room temperature, it was poured into water and extracted with a mixture of ether and n-hexane 1:3. The extracts were combined, washed with aq. NH_4Cl, aq. $NaHCO_3$, and NaCl, dried over Na_2SO_4 and concentrated to give residue (26.9 g), which was purified with silica gel (250 g) chromatography with a mixture of ether and hexane 1:10 as eluant. The pure product α,β-unsaturated ester *36* (16.3 g) in 83% yield. $[\alpha]_D$= +78.9° (c=1.64, $CHCl_3$); ^1H nmrδ 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, sep, 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 ($CHCl_3$) ν 1710cm^{-1}.

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

Transglycosidation with β-Chloroethanol and Reduction into the Allylic Alcohol 38

The 2'-propyl glycoside *36* (45 g, 0.12 mol) was heated in 2-chloroethanol (475 mL) in the presence of CSA [(±)-10-camphorsulfonic acid] at 50° C overnight. The reaction mixture was poured into sat. sodium bicarbonate and extracted with ether. Usual work-up afforded a mixture of α- and β-chloroethyl glycosides *37-α* and *37-β* in 6:4 ratio (36.3 g, 79% yield).

This mixture *37* (34 g, 88.9 mmol) was dissolved in dichloromethane (680 mL) and then cooled to -78° C. DIBAL-H (diisobutylaluminum, hydride, 1.5 M, solution in toluene, 142 mL, 214 mmol) was introduced dropwise to this mixture solution and it was stirred at -78° C for 1 hr. Tartaric acid (90 g) and water (600 mL) was added and the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed, dried and concentrated under reduced pressure to give the pure α- and β-allylic alcohol *38* (32.5 g, quant. yield).

α-Allylic alcohol *38α*: $[\alpha]_D$= +66.7° (c=1.18, $CHCl_3$); ^1H nmrδ 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).

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

β-Allylic alcohol *38β*: $[\alpha]_D$= -0.70° (c=1.13, $CHCl_3$); ^1H nmrδ 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).

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

Oxymercuration of the Allylic Alcohols 38 into the Diol 39

The mixture of the allyl alcohols *38* (2.0 g, 5.9 mmol) was dissolved in a mixture of THF (33 mL) and water (6.6 mL) and cooled to 0° C. Mercuric acetate (2.7 g, 8.5 mmol) was added to this solution in portions with stirring. The stirring was continued at 0° C for 1.5 days. Sodium borohydride (3.0 g) was added to this mixture at this temperature. After stirring at room temperature for further 1 hr, the reaction mixture was extracted with ether. The etherial layers were combined, washed with water and aq. NaCl, dried and concentrated to give 1.8 g of the mixture *39* in 81% yield.

The purified *38-α* (210 mg, 0.62 mmol) was similarly reacted with $Hg(OAc)_2$ (280 mg, 0.88 mmol) at -20° C for 4 days. Work-up with $NaBH_4$ (250 mg) afforded the compound *39-α* (221 mg) in quantitative yield. ^1H nmrδ 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).

The purified *38-β* (159 mg, 0.46 mmol) and $Hg(OAc)_2$ (210 mg, 0.6 mmol) under the same reaction condition and the same work-up with $NaBH_4$ (200 mg) gave *39-β* (150 mg) in 91%

yield.

^{1}H nmrδ 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).

Preparation of Fragment A_1 6

The diol *39* (0.90 g, 2.49 mmol) was dissolved in dichloromethane (10 mL) and reacted with 2,2-dimethoxypropane (2 mL) in the presence of pyridinium p-toluenesulfonate (5 mg) at room temperature for 5 hr. Etherial work-up gave the acetonide *40* (0.90 g) in 91% yield.

Sodium benzenesulfinate $C_6H_5SO_2Na$ (0.6 g, 3 mmol) and potassium iodide (1.0 g, 6 mmol) was added to the solution of the chloroethyl glycoside (248 mg, 0.62 mmol) dissolved in DMF (N,N-dimethylformamide) solvent (8 mL). The mixture was heated at 100° C for 10 hr. The reaction mixture was poured into water, and worked-up with ether. Preparative tlc separation gave the hemi-acetal *42* (150 mg) in 72% yield.

A solution of the hemi-acetal *42* (150 mg, 0.45 mmol) was dissolved in a mixture of DMF (2 mL) and sodium acetate/acetic acid buffer (3 mL). Bromine (100 microL, 3.9 mmol) was added dropwise and the mixture was stirred for 30 min at 0° C. Sodium hydrogen sulfide was added to this mixture to decompose excess bromine. Etherial work-up and purification of the crude product with tlc gave the lactone *6* (81 mg) in 54% yield. *6*, purity 91%, $[\alpha]_D$=+87.3° (c=1.04, $CHCl_3$); ^{1}H nmrδ 1.35(6H, sx2), 1.39(3H, s), 1.6-2.2(6H), 3.76-3.88(2H, AB), 3.95(1H, m), 4.63-4.92(2H, AB), 4.72(1H, m), 7.3-7.4(5H); irν 1745 cm^{-1}.

Found C 68.21, H 7.78; Calcd C 68.24, H 7.84, for $C_{19}H_{26}O_5$.

Proof of the Stereochemistry, 2-S-Synthesis

Preparation of the R-Epoxide 45

To a cold solution of the allyl alcohol *43* (25 mg, 0.090 mmol) and diethyl (+)-tartrate (40μL, 0.23 mmol) in dichloromethane (1 mL) was added at -20° C titanium(IV) tetra-2-propoxide (50 μL, 0.168 mmol) with stirring and, after 20 min, tert-butyl hydroperoxide (3.3 M in 1,2-dichloroethane, 0.15 mL, 0.50 mmol). The stirring was continued at -20° C for 1 day. The solution was poured into sat. tartaric acid solution and the aqueous layer was extracted with ether and worked-up. The crude product was purified with preparative tlc to give 12 mg (in 46% yield) of the β-epoxide *45*: $[\alpha]_D$=+85.7° (c=1.22, $CHCl_3$); ^{1}H nmrδ 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). irν 3500, 1750 cm^{-1}.

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

Transformation into the comparable compound, Acetonide 47

A mixture of the epoxy alcohol *45* (216 mg, 0.79 mmol), PPTS (20 mg) and dihydropyrane (0.20 mL, 2.2 mmol) in dichloromethane (7 mL) was stirred for 5 hr and poured into sat. sodium bicarbonate. Crude compound was taken into dichloromethane to afford the THP ether (300 mg). This was combined with another lot (total 355 mg, 0.94 mmol) and was further reacted with lithium aluminum hydride (0.2 g, 5.3 mmol) in THF (10 mL) at room temperature for 2 hr. Successive addition of water (0.8 mL), 15% NaOH (0.2 mL) and hexane (7 mL) to the reaction mixture was followed by filtration through Super Cel. The filtrate was concentrated to give the corresponding triol (305 mg, 85% yield). The triol (12 mg) was dissolved in pyridine (0.5 mL) and acetic anahydride (0.25 mL) and the mixture was stirred for overnight at room temperature. Evaporation of the volatile reagents and purification on tlc gave the diacetate (14 mg, 96% yield). The tetrahydropyranyl group in this diacetate (14 mg, 0.03 mmol) was heated in methanol (0.4 mL) containing PPTS (2 mg) at 50° C for 1.5 hr. The work-up with dichloromethane produced the diol (11 mg, 96% yield). It was successively treated with 2,2-dimethoxypropane (a few drops) in a mixture of acetone (0.3 mL) and dichloromethane (0.3 mL) in the presence of PPTS (2 mg) at room temperature for 2 hr. The mixture was poured into sodium bicarbonate and etherial work-up gave the acetonide *47* (10 mg, 82% yield): $[\alpha]_D$=+14.7° (c=0.52, $CHCl_3$); ^{1}H nmrδ 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); ir ν 1735 cm^{-1}.

Proof of the Stereochemistry, 2-S-Synthesis

Preparation of the S-Epoxide 44

A solution of the allyl alcohol *43* (86 mg, 0.31 mmol) in dichlromethane (4 mL) was reacted with diethyl (-)-tartrate (0.10 mL, 0.59 mmol), $Ti(OiPr)_4$ (0.11 mL, 0.37 mmol) and TBHP (3.3M, 0.4 mL, 1.32 mmol) under the similar reaction condition except the reaction period for 2 days at -20° C. The same work-up afforded the α-epoxide *44* (39 mg) in 43% yield and the β-epoxide (10 mg) in 10% yield. ^{1}H Nmr analysis showed the ratio of the two epoxides was 11 : 2. The isolated α-epoxide *44* showed the following data: $[\alpha]_D$=+118.0° (c=0.99, $CHCl_3$); ^{1}H nmrδ 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); irν 3500, 1750 cm^{-1}.

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

The acetonide *46*: $[\alpha]_D$=+8.5K(c=0.28, $CHCl_3$); ^{1}H nmrδ 1.28(3H, s), 1.37(3Hx2, 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, m), 7.2-7.4(5H); ir ν 1735 cm^{-1}.

Coupling of Fragment A_1 and A_2

The acetylene alcohol *7* (1.00 g, 4.0 mmol) was dissolved in dichloromethane (30 mL) and stirred with ethyl vinyl ether (5 mL) in the presence of pyridinium p-toluenesulfonate (0.10 g) at room temperature for 2 hr. The reaction mixture was poured into sat. $NaHCO_3$ and extracted with ether to give the ethoxyethyl ether *25* (1.37 g, quantitative yield).

Above acetylene 117 mg, 0.35 mmol) was dissolved in THF (4 mL), cooled to -78° C and then mixed with n-butyllithium (1.55 M, 0.35 mL, 0.54 mmol) under nitrogen atmosphere with a magnetic stirrer. After stirring was continued for 15 min, a THF solution the fragment A_1 lactone *6* (117 mg, 0.35 mmol/1 mL) was added to this mixture. Further 15 min stirring was followed by pouring this mixture into aq. NH_4Cl. Etherial work-up and purification on tlc gave the ketone *48* (185 mg) in 80% yield.

To a slurry of CuI (128 mg, 0.67 mmol) in ether solvent (3 mL) was added with stirring methyllithium (1.5 M soln in ether, 0.80 mL, 1.2 mmol) dropwise at 0° C under nitrogen atmosphere. After 20 min stirring, the reaction mixture was cooled to -78° C. The keto-acetylene 48 (91 mg, 0.14 mmol) in ether (1 mL) was added to this mixture, which was further stirred for additional 15 min at this temperature. Etherial work-up gave Z-olefin *49* (80 mg) in 87% yield.

The olefin (141 mg, 0.21 mmol) was dissolved in methanol (3 mL) and the solution was stirred with PPTS (10 mg) at room temperature for 2.5 hr. The reaction mixture was once worked-up with ether to afford oil, which was dissolved in dichloromethane (2 mL). This solution was stirred with 2,2-dimethoxypropane (0.3 mL) and PPTS (10 mg) at room temperature overnight. The mixture was poured into sat. $NaHCO_3$ and worked up with ether. The resultant oil was purified with preparative silica gel tlc to afford the Segment A (36 mg) in 29% yield. $[\alpha]_D$=+11.4° (c=1.16, $CHCl_3$); ^1H nmrδ1.23(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). ^{13}C nmrδ17.4, 95.8, 122.9 ppm.

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

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