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SYNTHESIS OF A MARINE POLYETHER TOXIN, OKADAIC ACID (2)[1] -- SYNTHESIS OF SEGMENT B

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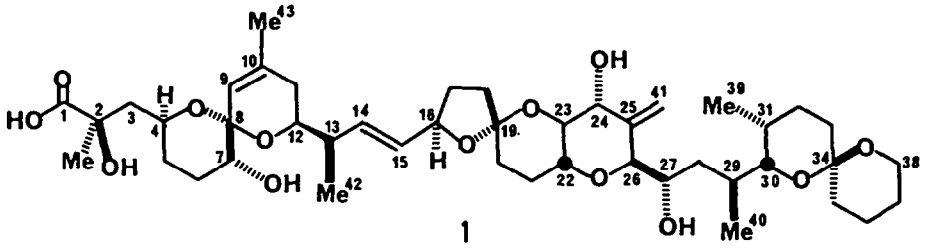
Abstract *The central synthetic segment B for okadaic acid comprises the carbons from 15 through 27 including 6 asymmetric carbons. Its synthesis started from a D-Glucose derivative, whose carbon was extended twice for the six and five membered etherial ring formation. The original conformation of the sugar was inverted when the spiro-ether was formed to eventuate the axial aldehyde formation in 35 overall steps.*

Introduction

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 paper deals with the syntheses of segment B comprising of C-15 through C-27 in the optically active form starting from a *D*-glucose derivative and a malic acid derivative. The stereochemical problems to elaborate correct configurations of asymmetric carbons are to be solved largely by predictable stereocontrol on ring system. Especially the asymmetric spiro-carbon C-19 is to be controlled thermodynamically from the corresponding keto-diols under an equilibrium condition.[2]



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The synthetic goal in this chapter is compound 2 which possesses six necessary asymmetric carbons. Notable thing is that the aldehyde group of C-27 is oriented to be *axial* to the tetrahydropyran ring. The configuration of C-26 is the same as the one of C-5 in D-glucose derivative despite of its conformation, when segment B of okadaic acid is to be synthesized from a glucose derivative 4 as illustrated in Fig 1. The one of the synthetic tactics should involve rational conformational inversion of the pyranoside carbohydrate derivative into unnatural sugar conformation. It should be first examined with a proper model system whether the aldehyde group might tend to *axial*, which might be helped due to an extended anomeric effect[2] without epimerization or not. The hypothetical intermediate 3 would be synthesized in the conformation equivalent to compound 5, conformation of which is now to be inverted into the one such as in 6 in Fig. 2.

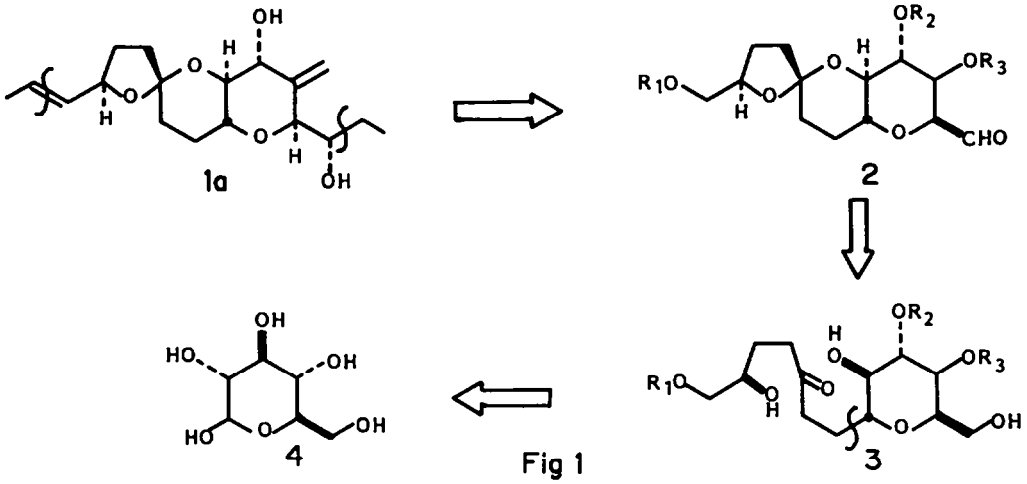


Fig 1

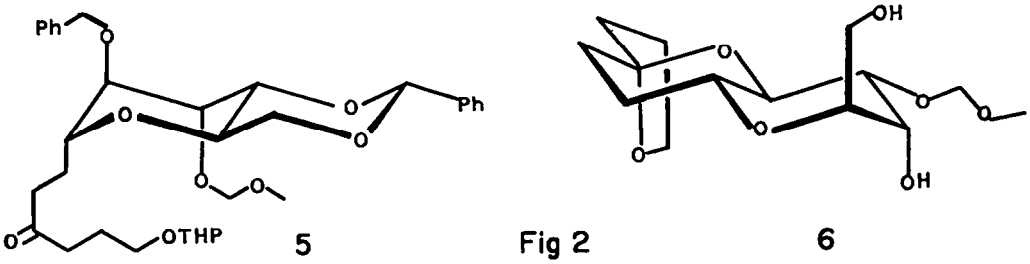
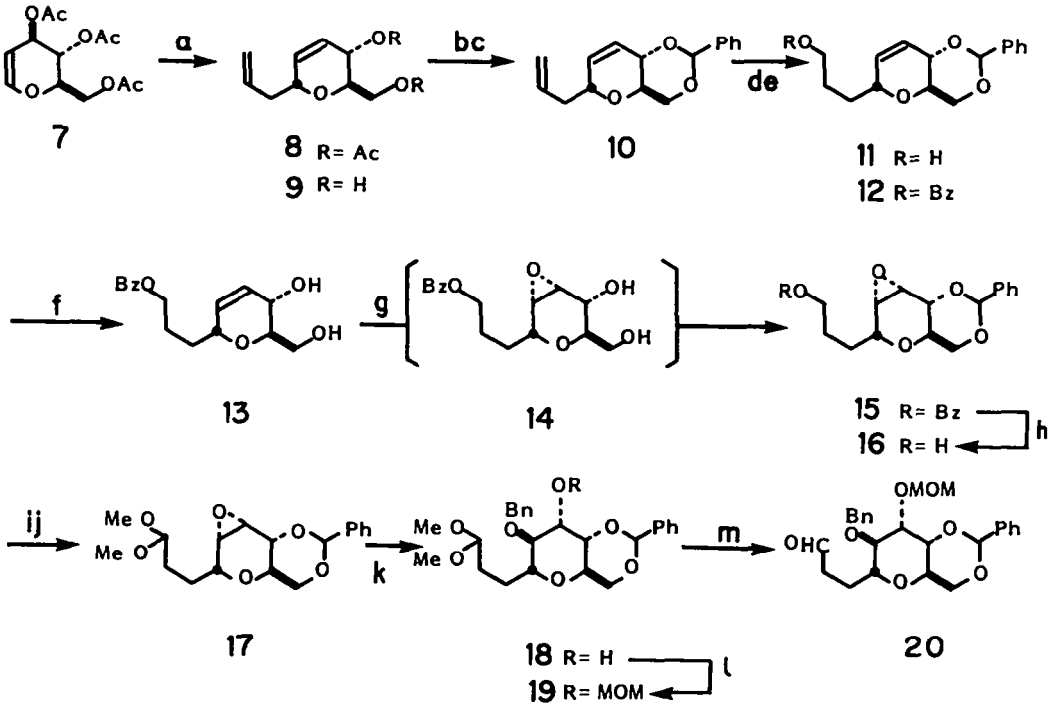


Fig 2

Synthesis of the Major Fragment from C-19 through C-27

Tri-*O*-acetyl-D-glucal 7 was employed as the starting material for this segment synthesis. The first step was the carbon chain extension corresponding to the carbons from C-19 through C-21 for the bicyclic ether. Hosomi-Sakurai reaction[3] was employed for trimethylallylsilane to 8 in the presence of BF_3-OEt_2 at -50° C to produce the corresponding α,β-mixture (ca. 16:1) of the adducts. The HPLC-separated minor isomer with the same procedure was already reported to have the β-stereochemistry by Danishefsky et al.[4]. We have converted the mixture into the crystalline benzilidene derivative 10 in two steps involving hydrolysis of the acetyl groups with Et_3N in aq. MeOH and treatment the diol with benzaldehyde dimethylacetal in the presence of CSA (*d,l*-10-camphorsulfonic acid). Recrystallization from a mixture of ether and n-hexane afforded the pure isomer of benzilidene 10, mp 63° C in 80% overall yield in a 100g-scale. Incidentally, the pure α-isomer of 8 was obtained in two steps involving hydrolysis of the acetal and acetylation of the hydroxy groups without any chromatographic separation to show $[\alpha]_D$= +62.3° .[5] The terminal olefin of pure 10 was hydroborated with B_2H_6 in THF at -25° C for 4.5 hr to give the alcohol 11 as crystals mp 81° C. This alcohol was protected as the benzoate (mp 84° C) and the benzylidene group was hydrolyzed with acidic resin, Dowex 50W (H^+) in methanol to produce the crystalline diol 13, mp 99° C. The free hydroxy group on the allylic position was necessary to have the subsequent epoxidation highly stereoselective.[6] Usual epoxidation with MCPBA in dichloromethane at 0° C (14) was followed by the benzylidene formation with benzaldehyde dimethyl acetal[7] in the presence of CSA to afford the epoxide 15, the purified epoxide being crystalline mp 125° C. The benzoyloxymethyl group was converted into the corresponding aldehyde dimethyl acetal 17 by the following two steps, which involved first hydrolysis with NaOMe at 0° C to give the epoxy alcohol 16 (mp 124° C), and second oxidation with DMSO and $(COCl)_2$. The aldehyde was protected as its dimethyl acetal 17 (mp 110° C). The benzylidene group had played an important role to make the product crystalline, and it further played an additional role of fixing the conformation of the pyranosyl ring. Such fixation facilitated the

subsequent stereoselective opening of the epoxide ring with sodium benzyloxide. The product alcohol 18 (mp 89° C, appeared to be less polar than the original epoxide on a silica gel tlc) was protected as methoxymethyl ether 19. The aldehyde 20 was re-generated by dil. HCl hydrolysis when the counterpart fragment became ready to introduce the tetrahydrofuryl moiety.



Scheme 1

a) $CH_2=CHCH_2SiMe_3/BF_3\text{-}OEt_2$; b) $Et_3N/MeOH$; c) $PhCH(OMe)_2/CSA$; d) B_2H_6/THF; e) BzCl/Py; f) H_3O^+; g) MCPBA, $PhCH(OMe)_2/CSA$; h) NaOMe; i) $(COCl)_2/DMSO$; j) $HC(OMe)_3/H^+$; k) $PhCH_2ONa$; l) CH_3OCH_2Cl; m) H_3O^+.

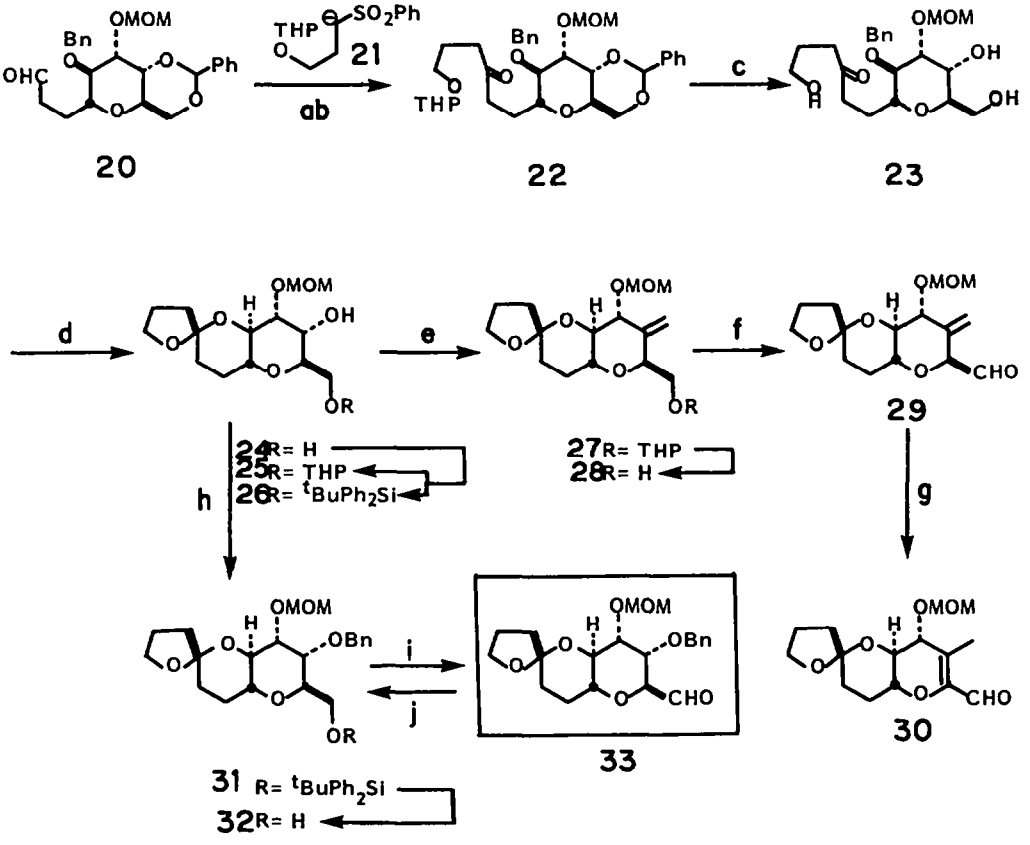
Model Studies for Selection of Segment B

Since the nature of a hypothetical segment B unsaturated aldehyde such as 29 was not known, a model system was designed to examine whether the β,γ-(exo)-unsaturated aldehyde could survive or not under a basic condition predictable in case of the coupling reaction with the sulfone carbanion of segment C.[8] For this purpose a tentative three-carbon fragment γ-oxypropylsulfone derivative 21 was employed for the construction of the model system. The sulfone carbanion was added to the aldehyde 20, and then the adduct alcohol was oxidized[9] into the keto-sulfone, which was subsequently reduced with aluminum amalgam[10] into the ketone 22. The benzylidene group in 22 was hydrolyzed by heating in a mixture of methanol and acetic acid (4:1) for 22 hr. The benzyl group in 23 was further deprotected quantitatively with palladium black in methanol containing 5% acetic acid under hydrogen atmosphere. The product was isolated as the spiro-ether diol 24.

A selective protection of the primary hydroxy group with diphenyl-t-butylchlorosilane[11] gave the silyl ether 26. After oxidation of the secondary hydroxy group to the ketone, attempted Wittig reaction with $Ph_3P=CH_2$ produced the corresponding exo-olefin only in low yield, although the starting material was consumed. A silicon group migration was suspected after the first addition of the ylide to the ketone to produce the betaine from which subsequent elimination of the phosphine oxide was blocked by the silyl migration. Another selective protection of the primary hydroxy group with THP was followed by the oxidation, and successful Wittig reaction afforded

the β,γ-(exo)-unsaturated aldehyde 29 in 59% yield. On the other hand, an alternative segment B was prepared from the silyl ether 26 by subsequent benzylation to yield 31, from which silyl group was removed by treatment with n-Bu_4NF. Swern oxidation afforded the alternative aldehyde 33 in 81% yield.

Treatment of the β,γ-unsaturated aldehyde 29 with triethylamine at 55° C, however, became a complex mixture which might start by equilibration into the α,β-(exo)-unsaturated aldehyde 30 judging from the disappearance of the *exo*-methylene signal in nmr. Therefore, we concluded the saturated aldehyde 33 to be the candidate which might survive under the basic coupling condition with segment C. Reduction product of this aldehyde with sodium borohydride was identical with the original alcohol to prove no epimerization at the C-26 position.

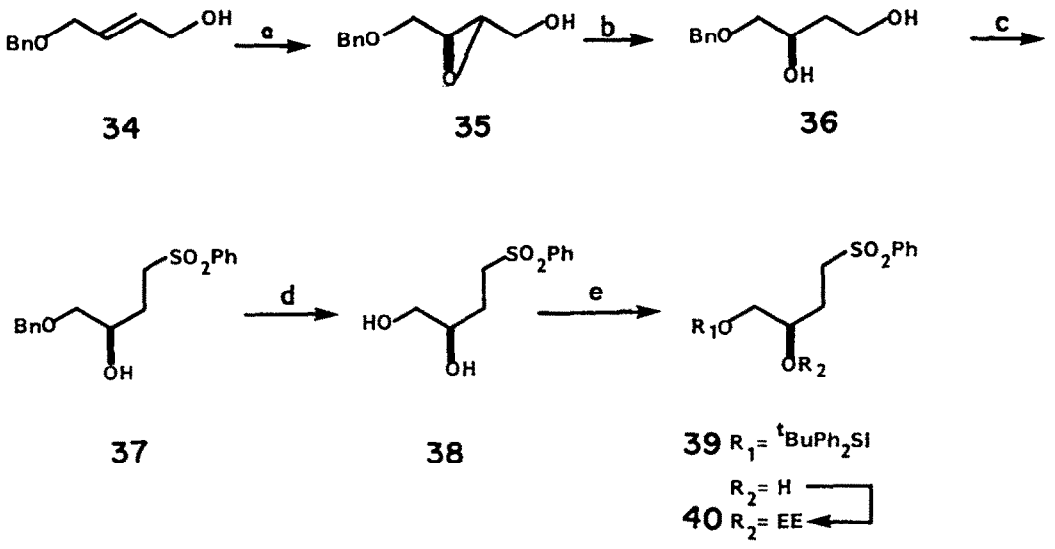


Scheme 2

a) in THF; b) PCC, Al-Hg; c) H^+; d) Pd/H_2; e) DHP/H^+, Swern, $Ph_3P{=}CH_2$; f) H_3O^+, CrO_3-2Py; g) Et_3N; h) DHP/H^+, $^tBuPh_2SiCl$/imidazole, BnBr/NaH; i) n-Bu_4NF, Swern; j) $NaBH_4$.

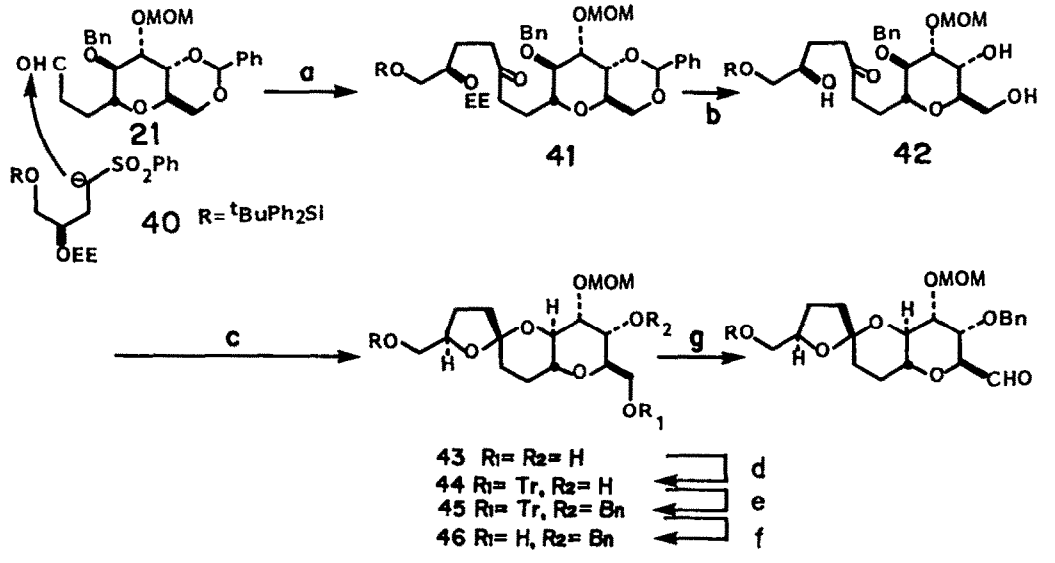
Synthesis of Segment B

The dioxybutylsulfone derivative 41 was synthesized for the introduction of the four-carbon fragment corresponding to the tetrahydrofuran (C-15 to C-18). The sulfone was prepared by the following five-steps in the optically active form from the known *R*-1,2,4-trihydroxybutane 1-benzyl ether[12] (Scheme 3). Mono tosylation of the primary hydroxy group and subsequent displacement with phenylthio group was followed by oxidation into the corresponding sulfone 37. After hydrogenolytic debenzylation, two hydroxy groups in 38 were protected by selective silylation 39 and ethoxyethylation of the primary and secondary hydroxy groups, respectively. The



Scheme 3

a) L-(+)-DET, TBHP, $Ti(OPr)_4$; b) $[(CH_3OCH_2CH_2O)_2AlH_2]Na$; c) TsCl, PhSNa, MCPBA; d) Pd-C/H_2; e) $^tBuPh_2SiCl$/imidazole, CH_2=CHOEt/H^+.



Scheme 4

a) n-BuLi, Swern oxidation, Al-Hg/aq. THF; b) H_3O^+; c) Pd-C/H_2; d) TrCl; e) $PhCH_2Br$/NaH; f) Et_2AlCl; g) $(COCl)_2$/DMSO;

protected sulfone compound 40 was converted into its lithium carbanion which was introduced into the aldehyde 21 in THF at -78° C to give the coupled product in 86% yield. After the oxidation of the hydroxy group with dimethyl sulfoxide (DMSO) and $(COCl)_2$ into the corresponding ketone, the sulfonyl group was removed under reduction condition with Al-Hg in aq. THF to give 42. Simultaneous deprotection of the benzylidene and ethoxyethyl groups was effected in refluxing ethanol containing acetic acid (8 %) for the period of 3 days to afford the triol benzyl ether 43. It was further treated with palladium on charcoal in ethanol containing acetic acid (3

%) at room temperature, the corresponding tetraol ketone was allowed to react in 15 hr into the spiro ether **43**. Selective tritylation and subsequent benzylation of the primary and secondary hydroxy groups gave a compound in which all the hydroxy groups were protected **45**. Dissolving this compound in cold CH_2Cl_2 and stirring with Et_2AlCl[13] for 20 min at -78° C gave mono-ol **46**, in which only trityl group was removed.

Oxidation of the hydroxy group under Swern condition afforded the corresponding aldehyde **47**, which is the segment B 2. This oxidation should be carried out right before use for the following coupling process with segment C, since the aldehyde might not be so stable.

The couplings between the segments are described in the following paper.[14]

EXPERIMENTAL

C-Glycosidation of D-Glucal triacetate with Allyltrimethylsilane, Hosomi-Sakurai-Danishefsky Method 8

A solution of *D*-glucal triacetate *7* (400 g) was dissolved in dichloromethane (4.5 L) and cooled to -50° C, to which was added BF_3-OEt_2 (190 mL) dropwise over a period of 30 min. The reaction mixture was stirred at -50° C for 1 hr and then at 0° C for 2.5 hr. The reaction mixture was poured into sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried over sodium sulfate and concentrated under reduced pressure. Since the product (475.2 g) was a mixture of α,β-isomers in 16 : 1 ratio, this material was used for the subsequent experiments without further purification.

Purification method without chromatography afforded pure α-isomer *8*: $[\alpha]_D$=+62.3° (c=1.03, $CHCl_3$); ^{1}H nmrδ2.09(3Hx2, 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). ^{13}C nmrδ20.7, 20.9, 37.8, 62.8, 64.9, 69.7, 71.2, 117.2, 123.7, 132.5, 133.9, 169.8, 170.1ppm. irν 1740 cm^{-1}.

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

Hydrolysis of the acetate and Benzylidenation 9, 10

A mixture of the diacetate *8* (475.2 g), methanol (3.2 L), triethylamine (650 mL) and water (550 mL) was stirred at room temperature two overnights. The reaction mixture was concentrated under reduced pressure to give the crude diol *9* (225.4 g, 89% yield in two steps from 7).

$[\alpha]_D$=-35.1° (c=0.85, $CHCl_3$); ^{1}H nmrδ2.2-2.55(2H), 2.8(1H, br, OH), 3.1(1H, br, OH), 3.5(1H, m), 3.7-3.9(2H), 4.10(1H, brd, J= 8), 4.23(1H, brt, J= 7), 5.05-5.2(2H), 5.7-5.95(3H).

Found C 63.49, H 8.33; Calcd. C 63.51, H 8.29, for $C_9H_{14}O_3$.

To a solution of the diol *9* (99.6 g, 0.585 mol) in dichloromethane (1.2 L) were added *d,l*-camphorsulfonic acid (10 g) and benzaldehyde dimethyl acetal (170 mL, 1.01 mol). The mixture was stirred at room temperature overnight. The reaction mixture was heated to concentrate into 80-90% volume while no starting material was detected on tlc analysis. The reaction mixture was cooled down to room temperature and poured into ice cold sodium bicarbonate solution. The separated organic layer was collected, dried over sodium sulfate and then passed through a short column containing silica gel. Concentration afforded the crude crystals (251.1 g), which was re-crystallized from a mixture of ether and hexane to give white needles of pure benzylidene *10* (121 g, 80% yield): m.p.63.0° C, $[\alpha]_D$=+26.7° (c=1.25, $CHCl_3$); ^{1}H nmrδ2.25-2.6(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). The pure material, when hydrolyzed and acetylated, afforded the pure sample depicted above.

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

Hydroboration of the terminal olefin 11

The diene *10* (180 g, 0.647 mol) was dissolved in THF (2.1 L) and cooled to -25° C. Diborane (1M, solution in THF, 260 mL) was added to this mixture, after 7.5 hr an additional amount of diborane (80 mL) was added. The reaction mixture was kept at this temperature for 4.5 hr. To this reaction mixture were successively added the following agents: ethanol (90 mL, carefully dropwise), 2N NaOH (360 mL) and 30% H_2O_2 (240 mL) at this temperature. The cooling bath was removed from the reaction vessel, which was then kept at room temperature overnight. Saturated $NaHSO_3$ was added portionwise, while potassium iodide/starch test paper became negative. The resultant mixture was extracted with ether and the usual work-up gave crude crystals (186.3 g), which was used for the following reaction. Part of the sample was recrystallized from a mixture of ether and hexane to give analytically pure *11*: m.p.81° C, $[\alpha]_D$=+31.0° (c=1.05, $CHCl_3$); ^{1}H nmrδ 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).

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

Benzoylation of the alcohol 12

A solution of the alcohol *11* (186.3 g) in pyridine (2 L) was stirred with benzoyl chloride (88 mL, 0.76 mol) at room temperature overnight. The reaction mixture was diluted with chloroform (2 L) and washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give solids (281.2 g), which was washed with a mixture of ether and n-hexane (20:1) to give crystalline benzoate *12* (237.3 g), which was used for the following reaction. Part of the sample

was recrystallized from a mixture of n-hexane and ethyl acetate to afford analytically pure crystals: m.p.84° C, $[\alpha]_D$=+11.7° (c=1.58, $CHCl_3$); ^1H nmrδ 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). irν 1715 cm^{-1}

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

Hydrolysis of the benzylidene group to the Diol 13

A solution of the benzoate *12* (232.3 g) in methanol (2.5 L) was stirred vigorously in the presence of Dowex 50W (H^+)(35 g) at room temperature for 9.5 hr. The reaction mixture was filtered to remove the resin. Pyridine (3 mL) was added to the filtrate, which was then concentrated under a reduced pressure to give white solid *13* (264.2 g). This solid was used for the following reaction without further purification. Part of the sample was recrystallized from a mixture of ethyl acetate and n-hexane to provide analytically pure sample: m.p.99° C, $[\alpha]_D$=-23.5° (c=1.04, $CHCl_3$); ^1H nmrδ 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).

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

Epoxidation of the olefin and benzylidene formation 14, 15

MCPBA (80%, 150 g) was added to a solution of the diol *13* (264.2 g) in chloroform (2.6 L) at 0° C and the mixture was stirred at 5° C overnight. To this reaction mixture were added benzaldehyde dimethylacetal (150 mL) and *d,l*-10-camphorsulfonic acid (1.0 g). The reaction mixture was heated to remove the solvent, while no starting material became detectable by tlc analysis. After cooling the mixture, it was poured into sodium bicarbonate and extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to afford the epoxide *15* as solid (402.6 g). This was used without further purification. Recrystallization of part of the sample from a mixture of ethyl acetate and n-hexane gave crystals: m.p.125° C, $[\alpha]_D$=+37.8° (c=1.08, $CHCl_3$); ^1H nmrδ 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). irν 1715 cm^{-1}

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

Hydrolysis of the Benzoate 16

The benzoate *15* (402.6 g) was dissolved in a mixture of THF (1.5 L) and methanol (750 mL) and cooled to 0° C. Sodium methoxide (1.16 M in methanol, 100 mL) was added at this temperature and the mixture was stirred at 5° C overnight. Neutralization by addition of dry ice was followed by evaporation to remove most of the solvent. The residue was diluted with water and then extracted with ether. After washing and drying the organic layer, evaporation of the solvent afforded crude solid (311 g). Crystallization of this solid from a mixture of ether and n-hexane gave the alcohol *16* as pure white crystals (122.1 g, 65% overall yield in 6 steps from *10*): m.p.124° C, $[\alpha]_D$=+49.2° (c=0.95, $CHCl_3$); ^1H nmrδ 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).

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

Oxidation to Aldehyde and Protection to the Dimethyl Acetal 17

To a solution of oxalyl chloride (11 mL, 0.13 mol) in dichloromethane (380 mL) were added with stirring at -78° C under nitrogen atmosphere DMSO (22 mL, 0.3 mol, distilled from CaH_2) dropwise over 5 min, (after 2 min) a solution of the alcohol *16* (20.0 g, 68.4 mmol) in dichloromethane (20 mL), and (after further 10 min) triethylamine (66 mL). The stirring was continued at -78° C for 10 min and then the dry-ice cooling bath was replaced to an ice bath. After 15 min, water was added to the reaction mixture and it was extracted with ether to give the aldehyde (21.8 g) as an oil, which was dissolved in dichloromethane (400 mL) and successively treated with trimethyl orthoformate (120 mL) and PPTS (3 g) at room temperature overnight. Pouring into sodium bicarbonate, the reaction mixture was extracted with dichloromethane and worked up to afford the dimethyl acetal *17*, which was used for the following reaction. Part of the sample was purified by recrystallization from a mixture of n-hexane and ether: m.p.110° C, $[\alpha]_D$=+44.6° (c=0.98, $CHCl_3$); ^1H nmrδ 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).

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

Opening of the Epoxide 18

Sodium hydride (60% in mineral oil, 35 g, 0.875 mol) was placed in a 2 L-flask, washed with n-hexane, and then suspended in DMF (N,N-dimethylformamide, 750 mL) at 0° C, to which was added dropwise benzyl alcohol (140 mL). The mixture was stand overnight at 5° C and the supernatant solution (650 mL) was added to a solution of the epoxide *17* (29.1 g) in DMF (50 mL), which was then heated at 70° C for 3.5 hr under nitrogen atmosphere. The solution was cooled to room temperature and poured into sat. ammonium chloride solution (800 mL). The product was worked-up with ether to give crude benzyl ether, which was purified by silica gel (250 g) chromatography with a mixture of ether and n-hexane 1:3 as eluant. The produced *18* (15.5 g, 51% overall yield from *16*) as white solid was used for the next step. A small portion of this solid was recrystallized to give the analytically pure sample: m.p.89° C, $[\alpha]_D$=+26.7° (c=1.17, $CHCl_3$); ^1H nmrδ 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), 3.88-4.15(3H, m), 4.20-4.33(2H, m), 4.38(1H, t, J= 6), 4.53-4.67(2H, AB), 5.64(1H, s), 7.25-7.55(10H).

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

Protection of the Alcohol 18 as the Methoxymethyl Ether 19

Potassium hydride (35% in mineral oil, 14.2 g, 124 mmol) was washed with n-hexane, suspended in DMF (380 mL) and mixed with the alcohol *18* (15.5 g, 28.9 mmol in 20 mL of DMF). After stirring at room temperature for 10 min, the reaction mixture was reacted with chloromethyl methyl ether (7 mL, 92.6 mmol), while slight exothermic nature was observed. The mixture was stirred further 30 min at room temperature and poured into water. Etherial work-up gave the product *19* (16.9 g, quantitative yield): $[\alpha]_D$=-6.8° (c=1.66, $CHCl_3$); ^1H nmrδ 1.4-1.85(3H, m), 2.25(1H, m), 3.30(3H, s), 3.31(3Hx2, s), 3.50(1H, d, J= 3), 3.7-4.3(6H), 4.38(1H, t, J= 6), 4.62(2H, s), 4.62-4.79(2H, AB), 5.58(1H, s), 7.2-7.5(10H).

Found C 66.36, H 7.43; Calcd C 66.37, H 7.43, for $C_{27}H_{36}O_8$.

Hydrolysis of the Acetal to the Aldehyde 20

A mixture of the acetal 4-16 (2.4 g) and THF (70 mL) and 0.5 N HCl (20 mL) was stirred at room temperature for 3 hr and poured into sodium bicarbonate solution. Etherial work-up afforded the aldehyde 4-17 (2.14 g, 98% yield): $[\alpha]_D$=-6.4° (c=3.02, $CHCl_3$); ^1H nmrδ 1.72(1H, m), 2.4-2.75(3H), 3,30(3H, s), 3.51(1H, d, J= 3), 3.72(1H, m), 3.85-4.3(5H), 4.62(2H, s), 4.62-4.79(2H, AB), 5.56(1H, s), 7.2-7.5(10H), 9.78(1H, s); irν 2750, 1720 cm^{-1}

Model Studies without C-14

A solution of the diol *24* (127 mg, 0.42 mmol) and dihydropyran (0.30 mL, 3.2 mmol) dissolved in dichloromethane (9 mL) in the presence of pyridinium p-toluenesulfonate (PPTS, 10 m) was stirred at -20° C for two days. The reaction mixture was poured into aq. sodium bicarbonate and the separated aqueous layer was extracted with a portion of dichloromethane. The combined organic layer was dried (Na_2SO_4) and then concentrated under reduced pressure to afford the oil (0.21 g). Purification of this oil by silica gel (4 g) chromatography with ether as eluant provided the tetrahydropyranyl ether *25* (81 mg, 50% yield) as diastereo mixtures. Swern oxidation of this alcohol (81 mg, 0.21 mmol) under the usual conditions (oxalyl chloride 0.10 mL, DMSO 0.20 mL, Et_3N 0.60 mL) in 75% yield. *28*: ^1H nmrδ 1.6-2.1(8H), 3.43(3H, s), 3.49-3.60(3H), 3.88-4.05(3H), 4.22(1H, m), 4.43(1H, dd, J=10, 4), 4.68-4.94(2H, AB), 5.12(1H, brs), 5.34(1H, dd, J=3, 2).

To a slurry of methyltriphenylphosphonium bromide (294 mg, 0.82 mmol) in tetrahydrofuran (4.5 mL) cooled to 0° C was added n-butyllithium (1.65 M solution in hexane, 0.50 mL, 0.83 mmol) dropwise. The solution was stirred at room temperature for 30 min, and then cooled to -78° C. A solution of the ketone (61 mg) in tetrahydrofuran (0.5 mL) was introduced to this solution of methylenetriphenylphosphorane, and the cooling bath was removed. This reaction mixture was heated under reflux overnight, and usual etherial work-up gave the crude oil (132 mg), which was purified by silica gel chromatography with ether:hexane:1 as eluant to provide the exomethylene product (36 mg, 59% yield).

This product (36 mg, 0.094 mmol) was dissolved in methanol (1.5 mL) and then heated at 50 ° C for 3 hr in the presence of PPTS (4 mg). The solution was poured into aq. sodium bicarbonate solution and then extracted with three portions of ether. The combined organic layer was washed with water and saturated aq. NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting oil was purified by silica gel (0.68 g) chromatography with ether:hexane=3:1 as eluant to afford *30* (27 mg, 96% yield).

Preparation of the model compound 33 was initiated from the coupling of the aldehyde 20 with γ-THP-oxypropylsulfone lithium salt. Four steps equivalent to the following synthetic scheme with the case having C-14 led us to have the mono-ol 26, which was benzylated to 31: $[\alpha]_D$=-5.5° (c=1.59, $CHCl_3$); ^1H nmrδ 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).

Desilylation of 31 (283 mg, 0.45 mmol) was effected with n-Bu_4NF (1M solution in THF, 0.90 mL, 0.90 mmol) in a mixture of THF (3 mL) and acetonitrile (3 mL) at room temperature for 1 hr. Etherial work up and silica gel purification gave the primary alcohol 32 (177 mg, quantitative yield): $[\alpha]_D$=-40.1° (c=1.30, $CHCl_3$); ^1H nmrδ 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).

Oxidation of the alcohol 32 (32 mg, 0.082 mmol) with oxalyl chloride (40 μL), DMSO (0.1 mL), dichloromethane (0.8 mL) and triethylamine (0.23 mL) into 33 (30 mg, 94% yield):^1H nmrδ 1.6-2.1(8H), 3.2-3.4(2H), 3.34(3H, s), 3.48(1H, dd, J=10, 3), 3.8-4.0(2H), 4.06(1H, t, J=10), 4.18(1H, dd, J=3, 2), 4.30(1H, d, J=2), 4.5-4.9(4H), 7.2-7.4(5H), 9.78(1H, s).

The above aldehyde was reduced with sodium borohydride to give the alcohol *32* and identified.

Preparation of the Diol-sulfone 38

R-Butane triol mono-benzyl ether *36* (24.1g, 0.12 mol) was dissolved in a mixture of triethylamine (300 mL) and dichloromethane (700 mL) and cooled to 5° C. p-Toluenesulfonyl chloride (27 g, 0.14 mol) was added portionwise over a period of 2 days with occasional tlc analysis. The reaction mixture was poured into water and the organic layer was washed with dil. HCl, water, sat. $NaHCO_3$ and sat. NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to yield the mono-tosylate as oil. Sodium hydride (8 g, 0.2 mol) was washed with n-hexane and suspended in a mixture of THF (tetrahydrofuran, 500 mL) and DMF (400 mL), to which thiophenol (22 mL, 0.2 mol) was added dropwise. After the evolution of hydrogen ceased, the solution of the above mono-tosylate dissolved in DMF (100 mL) was reacted with the sodium sulfide solution at room temperature for 1 hr. Etherial work-up gave the crude sulfide (52.4 g), which was dissolved in dichloromethane (1 L). MCPBA (90 g) was added to this solution and stirred for 1 hr at 0° C. The solution was washed with sat. $NaHSO_3$, sat. $NaHCO_3$, water and sat. NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude oil (59.2 g), which was purified with silica gel (700 g) chromatography. After washing the silica gel column with a mixture of ether and n-hexane 1:3, the sulfone 37 was eluted with the same mixture of 3:1 ratio to give 26.7 g (70%

yield) as oil.

The benzyl ether *37* (31.6 g, 99 mmol) was dissolved in a mixture of acetic acid (58 mL) and ethanol (580 mL) and the solution was vigorously stirred with palladium (25% on charcoal, 7 g) under hydrogen atmosphere at room temperature for 5 hr. Filtration through Super Cel and subsequent concentration afforded crystals of the diol *38* (22.7 g, quantitative), which was recrystallized from a mixture of ethyl acetate and n-hexane to yield the first crystals (9.2 g, 40%), mp 92° C; $[\alpha]_D$=+13.1° (c=1.04, $CHCl_3$); ^1H nmrδ(CD_3OD) 1.55-2.0(2H), 3.2-3.5(2H), 3.6(1H, m), 7.6-8.0(5H).

Found C 52.20, H 6.16; Calcd C 52.17, H 6.13, for $C_{16}H_{14}O_4S$.

Protection into the silyl ether 39

A mixture of the diol *38* (8.7 g, 37.8 mmol), imidazole (12 g, 0.18 mol), DMF (100 mL) and tert-butylchlorodiphenylsilane (10 mL, 38.9 mmol) was stirred at room temperature for 2 hr. Etherial work-up gave the crude oil (20.0 g), which was used for the following step. Part of the sample was purified with silica gel tlc to afford pure *39*: $[\alpha]_D$=+13.7° (c=1.51, $CHCl_3$); ^1H nmrδ 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).

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

Ethoxyethyl Ether 40

A mixture of the silyl ether *39* (20 g, crude), PPTS (5 g), dichloromethane (50 mL) and ethyl vinyl ether (30 mL) was stirred overnight at room temperature overnight. The mixture was poured into sat. $NaHCO_3$ and extracted with dichloromethane to give crude oil, which was separated by silica gel (500 g) chromatography. After washing with a mixture of ether and n-hexane 1:4 (4 L) and 1:3 (4L), the pure ethoxyethyl ether *40* was eluted with a mixture of ether and hexane (1:1, 1 L) to give 18.4 g (90% overall yield from *38*).

The sulfone *40* (6.9 g, 12.8 mmol) was dissolved in THF (140 mL) and cooled to -78° C, to which was added n-butyllithium (1.6 M solution in n-hexane, 7.6 mL, 12.1 mmol) with stirring to generate the corresponding sulfone-carbanion in 30 min. This anion was used for the following coupling.

Coupling of the Fragment 40 with the Aldehyde 21 into the Spiro-ether 43

A solution of the aldehyde *21* (3.0 g, 5.2 mmol) in THF (10 mL) was added into the cold solution of the sulfone-carbanion (prepared in above experiment) at -78° C. After stirring for 30 min, the mixture was poured into water and etherial work-up gave the crude oil, which was separated with silica gel (100 g) chromatography. Washing with a mixture of ether and n-hexane 1:3 ratio, the coupling product was eluted with the mixture 3:1 to give the sulfone (4.8 g, 86% yield). To a solution of oxalyl chloride (1.8 mL, 20.6 mmol) in dichloromethane (150 mL) was added dropwise at -78° C DMSO (3.6 mL, 50.8 mmol). After 2 min, a solution of the coupling product (4.8 g, 4.46 mmol) in dichloromethane (10 mL) was added to this mixture and it was stirred for 15 min. Triethylamine (11 mL, 79.1 mmol) was added and the mixture was allowed to warm to 0° C. Etherial work-up gave the keto-sulfone as oil, which was successively treated in a mixture of THF (210 mL) and water (20 mL). Aluminum foil (5.0 g) was cut into stripes and immersed into a 2% $HgCl_2$ solution for 30 sec and rinsed with methanol and then with ether. These stripes were cut into smaller pieces and introduced into the above solution of the keto-sulfone. The mixture was stirred at 60° C overnight and diluted with sat. sodium potassium tartrate solution. Extraction with ethyl acetate and subsequent washing and evaporation of the organic layer afforded the crude oil (4.3 g), which was purified with silica gel (90 g) chromatography as a mixture of ether and n-hexane as eluant to give the ketone *41* (3.1 g, 75 % yield in 2 steps).

A mixture of the ketone *41* (4.1 g) in ethanol (100 mL) and acetic acid (8 mL) was heated under reflux for 3 days. The etherial work-up followed by silica gel (40 g) chromatography [ether/hexane 1:1 250 mL, ether 250 mL and then ethyl acetate 200 mL] gave the unreacted starting material, which was re-cycled, and the triol *42* (1.8 g in total, 60% combined yield).

The triol *42* (4.1 g, 6.03 mmol) was dissolved in ethanol (130 mL) and acetic acid (4 mL) and the solution was stirred with palladium on charcoal (25%, 4 g) under hydrogen atmosphere at room temperature for 15 hr. The reaction mixture was diluted with dichloromethane (200 mL) and then filtered through Super Cel. The filtrate was mixed with pyridine (250 mL) and triethylamine (2 mL) and then concentrated at ca. 10° C to give the tricyclic compound *43*, which was used without further purification. Part of this sample was purified for analysis: $[\alpha]_D$=+2.9° (c=1.49, $CHCl_3$); ^1H nmrδ 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).

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

Tritylation 44

A mixture of the diol *43* (crude oil ca. 6 mmol), pyridine (600 mL) and trityl chloride (3.5 g, 12.6 mmol) was heated to 65° C overnight. Etherial work-up and silica gel (140 g) chromatography with a mixture of ether and n-hexane 1:2 and 1:1 as eluant afforded the trityl ether *44* (3.9 g, 79% overall yield from *42*): $[\alpha]_D$=+0.5° (c=1.99, $CHCl_3$); ^1H nmrδ 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).

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

Benzyl Ether 45

Sodium hydride (60% mineral oil dispersion, 1 g, 24 mmol) was washed with n-hexane and suspended in THF (100 mL). The trityl ether *44* (4.9 g, 6.02 mmol) in THF (25 mL) was added to this suspension. After 5 min benzyl bromide (1.3 mL, 11 mmol) and DMF (25 mL) was added to

this mixture, which was stirred at room temperature for 3.5 hr. Etherial work-up afforded the benzyl ether *45* (6.28 g, crude), which was used for the next step. Part of the sample was purified with tlc: $[\alpha]_D$=-4.4° (c=1.68, $CHCl_3$); ^1H nmrδ 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).

Found C 75.65, H 7.20; Calcd C 75.63, H 7.13, for $C_{57}H_{64}O_6Si$.

Desilylation to the Alcohol 46

A mixture of the trityl ether *45* (6.2 g, 6.02 mmol), dichloromethane (150 mL), diethylaluminum chloride (1.8 M solution in toluene, 18 mL, 32.4 mmol) was stirred at -78° C for 20 min. To this mixture was added sodium bicarbonate solution and the cooling bath was removed. Sodium potassium tartrate (45 g) was added and the stirring was continued until the layers were clearly separated. The aqueous layer was extracted with dichloromethane and the organic layers were combined. Usual work-up and silica gel (50 g) chromatography with a mixture of ether and n-hexane (400 mL 1:3; then ether 500 mL) afforded the alcohol *46* (3.3 g, 83% overall yield from *44*): $[\alpha]_D$=-8.7° (c=1.45, $CHCl_3$); ^1H nmrδ 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).

Found C 68.86, H 7.55; Calcd C 68.85, H 7.60, for $C_{38}H_{50}O_6Si$.

The Aldehyde as Segment B 47

To a cold (-78° C) solution of oxalyl chloride (0.26 mL, 3.0 mmol) in dichloromethane (20 mL) were added under nitrogen atmosphere DMSO (0.55 mL, 7.8 mmol), (in 5 min), a solution of the above alcohol *46* (998 mg, 1.50 mmol) in dichloromethane (5 mL) and (after stirring for 10 minutes), triethylamine (1.3 mL, 9.3 mmol). Stirring was continued at -78° C for 15 min and at temperatures until it reaches up to 0° C. The solution was diluted with a mixture of ether and n-hexane 1:1 and then washed with ammonium chloride (x3), sodium bicarbonate (x1), sodium chloride (x1). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to give the aldehyde *47* (1.05 g crude), which was used without storage for the next coupling reaction.

^1H nmrδ 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).

References and Notes

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