Tetrahedron Vol. 43, No. 20, pp. 4759 to 4766, 1987
Printed in Great Britain

0040-4020/87 $3.00 + .00
Pergamon Journals Ltd.

SYNTHESIS OF A MARINE POLYETHER TOXIN, OKADAIC ACID (3)[1] -- SYNTHESIS OF SEGMENT C

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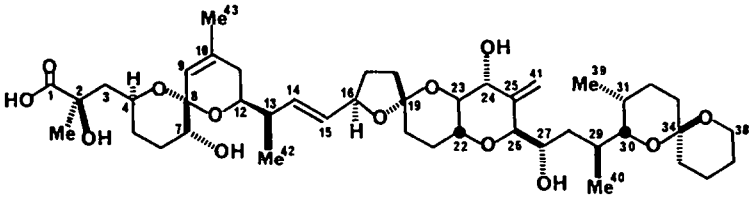
(*Received in UK* 4 *September* 1987)

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. Synthesis of the segment C in the optically active natural form starting from a D-glucose derivatives is described. The key features are stereochemical control which includes a methodology named heteroconjugate addition involving carbon chain extension using carbanion stabilized by phenylsulfonyl group.*

Introduction

Okadaic acid *1* was first isolated as a potent antitumor agent from marine sponges *Halichondria okadai* and *H. melanodocia*.[2] We became interested in the synthesis of this new class of marine natural product. These problems were solved by a new methodology of developed "heteroconjugate addition" exploited during the synthetic studies directed toward okadaic acid.[3] The retrosynthesis of okadaic acid involves two disconnections between the bonds of C-14/15, and C-27/28 to give rise to three synthetic segments A, B and C.

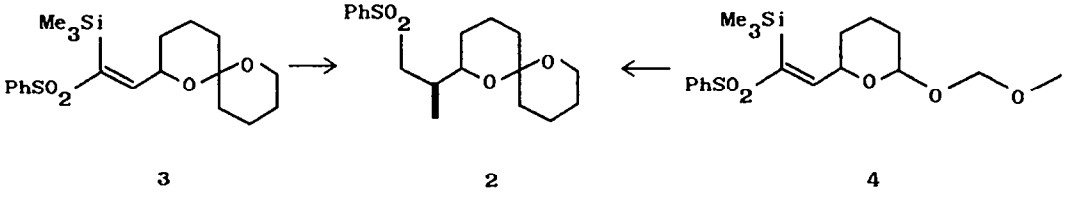


OKADAIC ACID (1) $C_{44}H_{68}O_{13}$

This paper deals with the syntheses of segment C in the optically active form starting from D-glucose derivative as chiral pool.[4] The stereochemical problems to elaborate correct configurations of those asymmetric carbons in the rings are to be solved by predictable stereocontrol on ring system. Especially the asymmetric spiro-carbon C-34 is to be controlled thermodynamically from the corresponding keto-diol under an equilibrium condition, which is understood as stereoelectronic effect.[5] On the other hand, the asymmetric carbon C-29 which locates on acyclic part of this molecule should be controlled under a straightforward tactics in acyclic transition state involving heteroconjugate addition strategy. It has solved not only the elaboration of this asymmetric center but also played a central role for the coupling with other segment B.

Model Studies for the Acyclic Stereocontrol on the vicinity of the Spiro Ether

Introduction of the asymmetric center C-29 was designed to be derived from the asymmetric ether at C-30, which was associated by the presence of the other oxygen atom on the spiro-carbon. The closest experience had already been studied to elaborate such asymmetric center found in the case as *4* which derived from a carbohydrate as optically active source.[6] The *syn*-selective heteroconjugate addition has been developed since it was established in the ansa-macrolactam *maytansine* synthesis in 1979.[7] To ensure the *syn*-selectivity in the current spiro-system the spiro-heteroolefin *3* was prepared from acrolein dimer[8] and examined the stereoselectivity. The result was sufficiently high to introduce the methyl group in the right stereochemistry, which was confirmed from the following two evidences. One was the empirical rule that the *syn*-methyl groups appear in the ^{13}C nmr at around δ14 ppm, while *anti*-methyl groups do at around δ17 ppm. The methyl signal of *2* appeared at 14.9 ppm, thus, the value for the *syn*-stereochemistry. The second evidence is the identification of the product with an authentic sample converted from the authentic *4*. Thus, the racemic model study suggested that the optically active system as shown in Scheme 1 was to be conceivable for the synthesis of the segment C.



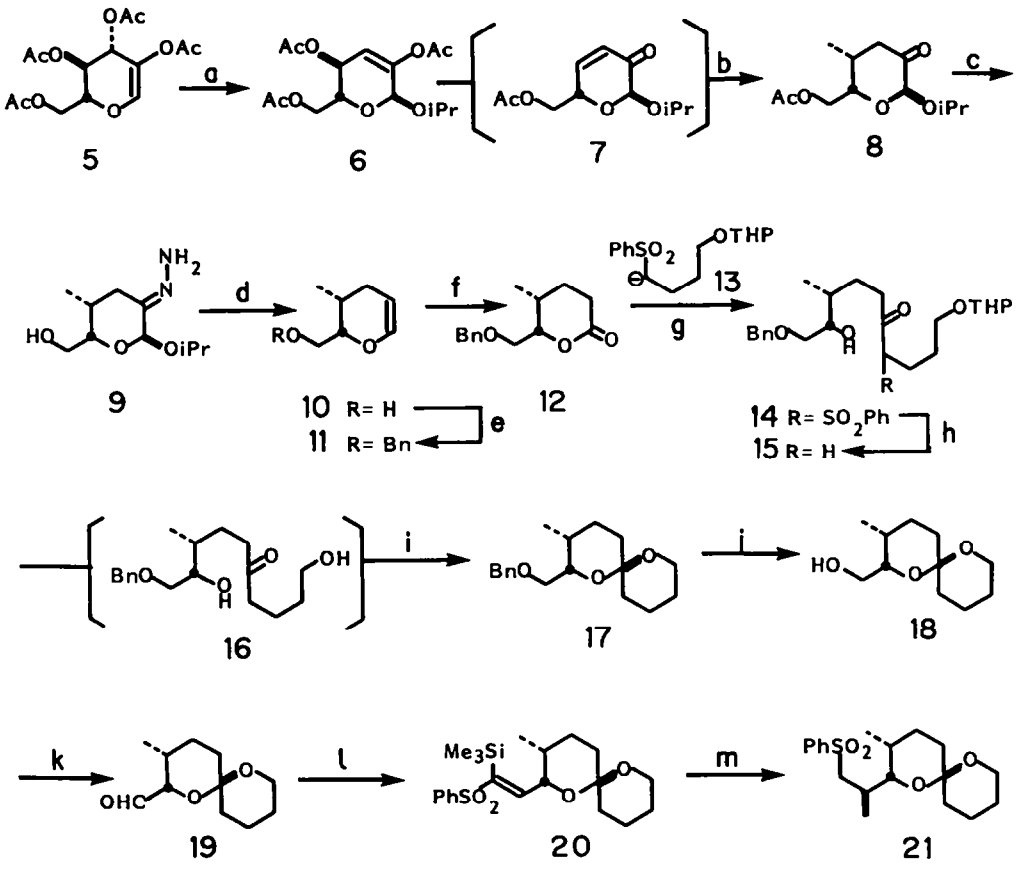
3 2 4

Model Studies in the Spiro-heteroolefin

Synthesis of Segment C

The synthetic goal in this chapter is compound *21* which possesses two methyl groups and two etherial carbons. The methyl group in the ring (C-31) locates in axial orientation and thus it is to be introduced in an axial mode into an α,β-unsaturated ketone. Since the absolute configuration of C-30 is the same as *D*-glucose, we designed the unsaturated ketone *7*, which was derivable from 2-acetoxy-*D*-Glucal *5*. The synthesis is summarized in Scheme 1.

D-Glucose was converted into *5* in three steps involving peracetylation with acetic anhydride in acetic acid, C-1 bromination with HBr and then dehydrobromination with DBU (1,8-diazabicyclo[5,4,0]undec-7-ene).[9] Acidic glycosidation of *5* with 2-propyl alcohol in the presence of BF_3-OEt_2 produced a crystalline and stable 2'-propyl glycoside *6*. Similar glycosides were prepared with methanol, ethanol, n-propanol and t-butanol[10] beside 2-propanol to study the stability of the corresponding glycosides and to compare the stereoselectivity in the introduction of the methyl group at the stage of the α,β-unsaturated system corresponding to *7*. The complete selectivity was observed in the cases with 2-propyl and t-butyl glycosides. In the former case, however, showed a highly (shelf stickball) stable crystals mp 61° C rather than the case in the latter. Addition of Me_2CuLi to *6* first generated the electrophile enone *7* to which conjugate addition occurred to produce the adduct *8*, but the yields were not constant. The same conjugate addition to *6* afforded the best yield of 79 % with Me(CN)CuLi[11] in THF solvent at -20 ° C to give *8* as only the stereoisomer. Stereochemistry that the methyl group stood on axial orientation was proven by its nmr spectrum showing the coupling constants of H-4 $J_{3,4}$= 6Hz, and $J_{3,4}$= 2 Hz.



Scheme 1

a) 2-PrOH/BF_3-OEt_2; b) Me(CN)CuLi; c) N_2H_4/EtOH; d) $NaCH_2S(O)CH_3$; e) $PhCH_2Br$/NaH; f) H_3O^+, Br_2; g) n-BuLi; h) Al-Hg; i) PPTS/EtOH; j) Pd-C/H_2; k) $(COCl)_2$/DMSO/Et_3N; l) $PhS(Me_3Si)_2CLi$, MCPBA; m) MeLi, KF.

Removal of the carbonyl group from *8* directed toward the spiro ether system should be followed by the introduction of the other tetrahydropyranyl fragment. Ordinary Wolff-Kishner reduction requires extremely high temperature of nearly 200° C, which is not suitable all the time. Tosyl hydrazone did not reduce the ketone in high yield under a reported conditionsuch as sodium borohydride[12] , lithium aluminum hydride[13] and catecholborane[14].

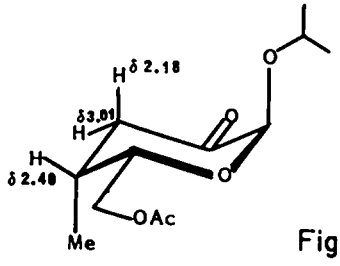


Fig 2

We developed a special Wolff-Kishner reduction which accompanied elimination of the neighbouring alkoxy group. This eliminative reduction of the hydrazone *9* was facilitated with $NaCH_2S(O)CH_3$ in DMSO solvent[15] at room temperature to yield the vinyl ether *10*.

The acetyl protecting group at the 6 position which had been cleaved off during the hydrazone formation, was protected as the corresponding benzyl ether *11* (in 74% overall yield). Hydrolysis of the vinyl ether *11* with dil HCl in aq. THF to the hemi-acetal was followed by oxidation with bromine in N,N-dimethylformamide in the presence of sodium acetate as a buffer[16] to afford the lactone *12* in 52% yield. Addition of lithium carbanion of the butyl sulfone *13* to

12 yielded the keto-sulfone *14* in 86% yield, which was reduced with aluminum amalgam[17] in aq. THF. The product was further treated with pyridinium p-toluenesulfonate[18] in refluxing ethanol in the presence of a small amount of 2,2-dimethoxypropane as a dehydrating agent to give the spiro ether *17* in 80% yield.

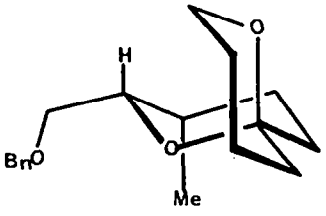


Fig 3

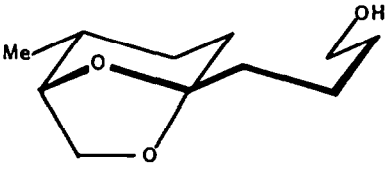


Fig 4

Deprotection of the benzyl ether *17* with 10% palladium-charcoal did not only afford the corresponding spiro-alcohol in Fig 3 but also a bicyclic ether in Fig 4 when the reaction condition was examined for overnight. This re-acetalyzation did not occur when the reaction was interrupted right after the starting benzyl ether compound was hydrogenolyzed. Treatment of *17* with Pd-C for 1.5 hr at room temperature produced the spiro alcohol *18* in high yield. Swern oxiation[19] of this alcohol *18* into the corresponding aldehyde *19* was followed by Peterson olefination with $PhS(Me_3Si)_2CLi$[20] in THF at -40° C and further by oxidation with MCPBA in dichloromethane at 0° C to obtain the spiro heteroolefin *20* in 56% overall yield. The stereochemistry of this compound was confirmed: thus, the olefin being *Z* by the ^1H nmr δ 6.48(1H, d, J= 9Hz)ppm and the spiro ether (C-O bonds) being *axial to each other*, as shown from the value of the δ 96 ppm.

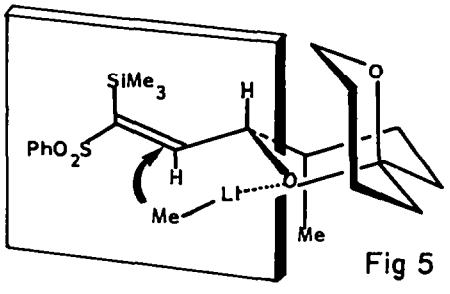


Fig 5

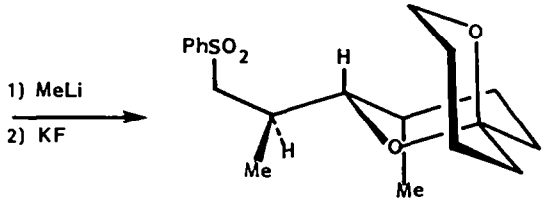


Fig 6

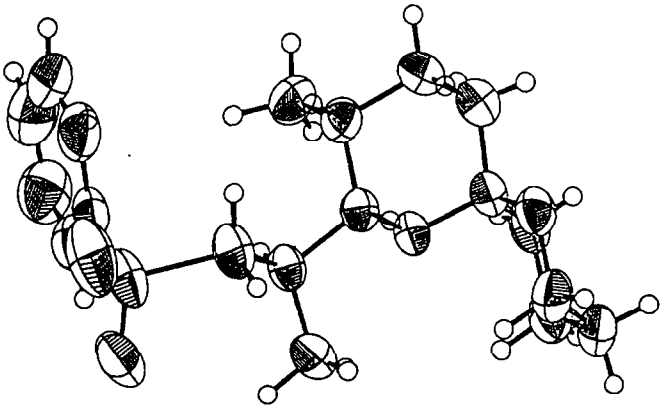


Fig 7

Heteroconjugate addition of methyllithium to *20* at -78° C for 30 min (and at higher temperatures to ensure the completion of the reaction) gave, *via* the chelation control as in Fig 5, the adduct which was further treated with KF in methanol to produce in 89% yield the segment C, *21* as white crystals (mp 82.5° C). The ^{13}C nmr analysis of this adduct showed introduced methyl group at δ17.0 ppm, which suggested the *anti*-stereochemistry instead of the desired *syn*-configuration when judged from the chemical shift empirical rule (see above).[21] It might be ruled out due to the presence of unusual *axial* Me in the ring. The structure of this segment was confirmed by X-ray crystallographic analysis. The ORTEP figure is shown in Fig 7: displacement ellipsoids are drawn at the 50% probability level. The synthesis of Segment C has been accomplished in 16 steps in 6.6 % overall yield from 2-acetoxy-*D*-Glucal. This segment was prepared in multi gram quantity and used for the following coupling process with segment B directed toward the totally chemical synthesis of *okadaic acid*, which will be reported in the following paper.

EXPERIMENTAL

Model Spiroether by Heteroconjugate Addition 2

To a solution of the spiro-heteroolefin *3* (482 mg, 1.3 mmol) dissolved in THF (15 mL) cooled to -78° C under nitrogen atmosphere was added methyllithium (1.5M solution in ether, 2.6 mL, 3.9 mmol) dropwise. The reaction mixture was stirred at -78° C for 30 min and then warmed up to -10° C over 30 min. Addition of saturated aqueous ammonium chloride was followed by three portions of ether. The combined organic layer was washed (H_2O, NaCl), dried (Na_2SO_4) and then concentrated under reduced pressure to afford the adduct (482 mg, 96% yield) as an oil. This oil was dissolved in methanol (15 mL) and then treated with potassium fluoride (0.15 g) overnight. The solvent was removed in vacuum, and the resulting residue was taken up in ether. The ether solution was washed (H_2O, NaCl), dried (Na_2SO_4) and then concentrated under reduced pressure to provide *2* (378 mg, 85% yield): ^1H nmr δ1.06(3H, d, J= 7), 1.0-2.2(12H), 2.90(1H, dd, J= 14, 8), 3.2-3.7(4H), 7.3-7.8(5H); ^{13}C nmr δ14.9, 18.5(x2), 25.2, 26.4, 33.3, 35.3, 35.6, 59.2, 60.4, 71.2, 95.5, 127.9, 129.2, 133.4, 139.9.

Isopropylglycoside 6

To a stirred solution of acetoxy-*D*-glucal *5* (50 g, 0.152 mol) in benzene (200 mL) under nitrogen atmosphere was added boron trifluoride etherate (55 mL, 0.45 mol), 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 *6* as a crude crystal. Recrystallization from ether/hexane afforded the analytical sample (31.5 g, yield 63.1%), m.p. 61° C, $[\alpha]_D$=+93.7° (c=1.00, $CHCl_3$); ^1H nmr δ1.11(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 $C_{15}H_{22}O_8$

Addition of dimethylcopperlithium 8

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 *6* (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 8 (0.61 g, in 82%) as an oil. (In other batchs of larger scales, the yields were 30-40% and not constant, so that we used cyanocuprate, *vide infra*, instead.) 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 *8* 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$_3$, ddd, J=14, 2, 1), 2.40(1H, m), 3.01(1H$_3$, 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 $C_{12}H_{20}O_5$.

Addition of Cyanocuprate to 6 improved method for 8

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 *6* (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 *8* (582 mg, 79%) as an oil.

Reductive Wolff-Kishner Elimination 10

A mixture of the ketone *8* (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 sodium dimsylate 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 *10* (3.1 g, 74% yield) as a dark red oil. This material was used in subsequent experiments without further purification. ^1H nmr (100 MHz) 0.96(, d, J=7), 1.64(, brd, J=16), 1.9-2.5(3H), 3.4-4.1(3H), 4.68(, brs), 6.32(, brd, J=6).

Protection of the alcohol 10 as Benzyl ether 11

The alcohol *10* (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 *11* (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).

Acid hydrolysis of the Vinyl ether 11 and *Bromine oxidation to the Lactone 12*

Vinyl ether *11* (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 (5.07 g) as an oil, which was used for the following reaction without further purification.

The crude lactol (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 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 *12* (2.94 g, 52% three steps from *10*) as a colorless oil. $[\alpha]_D$=+31.4° (c=0.90, $CHCl_3$), ^1H 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 ($CHCl_3$) ν 1735cm^{-1}.

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

Attachment of the 4-carbon fragment, Preparation of 17

To a stirred solution of the sulfone *13* (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 *12* (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 keto-sulfone *14* (7.9 g in 86% yield) as an oil.

Formation of the spiro-ether 17

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 keto-sulfone *14* (14 g, 26.3 mmol) dissolved in THF (500 mL) and water (40 mL) was added aluminum amalgam, prepared above, and stirred vigorously at room temperature for one day. The reaction mixture was filtered through a pad of Super-Cel, 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 *15* 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 *17* (6.2 g in 81% yield). $[\alpha]_D$=+57.7° (c=1.34, $CHCl_3$), ^1H nmr δ0.90(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).

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

Debenzylation 18

To a solution of *17* (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 *18* (4.9 g). This material was used for the subsequent reactions without further purification.

$[\alpha]_D$=+102.4° (c=0.93, $CHCl_3$), ^{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 ($CHCl_3$) ν 3450cm^{-1}.

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

Swern Oxidation the Aldehyde 19

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 *18* (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 *19* (5.06 g). The crude aldehyde was dried azeotropically by evaporation of benzene solution before next step.

$[\alpha]_D$= +42,1° (c=0.65, $CHCl_3$), ^{1}H 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 ($CHCl_3$) ν 2720, 1735 cm^{-1}.

Preparation of the Spiro-Heteroolefin 20

A solution of lithium bis-(trimethylsilyl)-phenylsulfinylmethylid 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 *19* (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 (4.5 g in 56% yield three steps from *18* as an oil).

To a stirred solution of the sulfide (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 *20* (5.0g, in quantitative yield). Recrystallization from a mixture of ether and hexane gave the only pure Z-isomer *20* (3.8 g). m.p. 145° C, $[\alpha]_D$= +4.0° (c=1.09, $CHCl_3$), ^{1}H nmrδ0.34(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).

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

Heteroconjugate addition to the Spiro-heteroolefin to 21

To a solution of the heteroolefin *20* (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. Preparative thin layer chromatography of the residue (1:3 ether/hexane) afforded the vinylsulfone (7 mg in 5.2% yield) and segment C *21* (125 mg in 89% yield) as white crystals. Recrystallization of this material from ether/hexane afforded the analytically pure sample. m. p. 83° C, $[\alpha]_D$= +21.6° (c=1.21, $CHCl_3$), ^{1}H 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.

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

Crystal Structure Analysis

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

Crystallographic Data

Formula Weight	352.493	
Space group	$P2_1$	
a,b,c	11.889, 10.532, 7.725	A°

α, β, γ	90.008, 94.026, 90.013	(degree)
V	964.88	A°
Z	2	
d_{obsd}	1.250	g/cm³
d_{calcd}	1.212	g/cm³
R	0.0496	
$2\theta_{max}$	126	(degree)
NO. of non-zero unique data	1623	
Crystal size	0.15 x 0.15 x 0.75	mm³
λ (CuKα)	1.5418	A°

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 (Cu =1.5418A°). Composition of the complexes and crystallographic data are listed in Table together with experimental results. Crystal structures were solved by the Monte-Carlo direct method[22] using MULTAN 78 program system[23] and were refined on F^2 by the full-matrix least-squares program with the analytical absorption correction.[24] Atomic scattering factors were taken from International Tables for X-ray Crystallography.[25] ORTEP[26] was used for drawing of the molecular and crystal structures. Anisotropic temperature factors were used for the refinement of the non-H atoms. All H atoms were located from difference Fourier maps and were refined with the isotropic temperature factors equivalent to that of the bonded carbon atoms. The final atomic parameters are listed in Table 2. All computations were carried out at the Computation Center of Nagoya University. The complete F_o-F_c data and the anisotropic temperature parameters are deposited as Document No. 8535 at the Office of the Editor of Bull. Chem. Soc. Japan.[27]

Following data have been submitted as supplements with this manuscript.

1. Complete list of refined co-ordinates
2. Table of bond distances
3. Complete crystal data
4. Structure factor table (F_o-F_c table)

References and Notes

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1 For the part (2) see the previous paper of this issue, *Tetrahedron*, 45, 0000 (1987).
2 K. Tachibana, P.J. Scheuer, Y. Tsukitani, H. Kikuchi, D.V. Enger, J. Clardy, Y. Gopichand, F. Schmitz, *J. Am. Chem. Soc.*, 103, 2469 (1981), and see the references cited in the part (1) of this series.
3 For the review of this methodology, see M. Isobe "*Perspectives in the Organic Chemistry of Sulfur*" Ed. B. Zwanenburg et al., p209-229, Elsevier Science Publishers, Amsterdam (1987).
4 S. Hanessian "*Total Synthesis of Natural Products: The 'Chiron' Approach*", Pergamon Press, London (1983).
5 (a) P. Deslongchamps "*Stereoelectronic effects in Organic chemistry*" Pergamon Press, London, (1983). (b) A.J. Kirby "*The Anomeric effect and Related Stereoelectronic effects at Oxygen*, Springer-Verlag, New York (1983).
6 M. Isobe, *Perspectives in the Organic Chemistry of Sulfur*, p209 *Ed.* B. Zwanenburg et al., Elsevier (1987).
7 M. Isobe, M. Kitamura and T. Goto, *J. Am. Chem. Soc.*, 104, 4997 (1982); M. Kitamura, M. Isobe and T. Goto, *J. Org. Chem.*, 49, 3517 (1984); *idem*, *J. Am. Chem. Soc.*, 106, 3252 (1984).
8 M. Isobe, Y. Ichikawa, H. Masaki and T. Goto, *Tetrahedron Lett.*, 25, 3869 (1984).
9 F. Shafizadeh, "*Methods in Carbohydrate Chemistry*", Ed. R.L. Whistler and M.L. Wolfrom, 409 Academic Press Inc., New York (1963).
10 S. Hanessian, P.C. Tyler, Y. Chapleur, *Tetrahedron Lett.*, 22, 4853 (1981).
11 B.H. Lipshutz and R.S. Wilhelm, *J. Am. Chem. Soc.*, 104, 4696 (1982).
12 R. Giovanoli, K. Bernhard and W. Feitknecht, *Helv. Chim. Acta.*, 51, 355 (1968).
13 D. Dollimore and K.H. Tonge, *J. Chem. Soc. B*, 1380 (1967).
14 G.W. Kabalka and J.H. Chandler, *Synthetic Communications*, 9, 275 (1979).
15 (a) R. Greenwald, M. Chaykovsky and E.J. corey, *J. Org. Chem.*, 28, 1128 (1963). (b) D.J. Cram, R. Sahyun and G.R. Knox, *J. Am. Chem. Soc.*, 84, 1734 (1962).
16 M. Rosenberger, D. Andrews, F. DiMaria, A.J. Duggan and G. Saucy, *Helv. Chim. Acta.*, 55, 249 (1972).
17 E.J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1351 (1965).
18 M. Miyashita, A. Yoshikoshi and P.A. Grieco, *J. Org. Chem.*, 42, 3772 (1977).
19 A.J. Mancuso, S.L. Huang and D. Swern, *J. Org. Chem.*, 43, 2480 (1978).
20 (a) B.T. Grobel and D. Seebach, *Chem. Ber.*, 110, 852 (1977). (b) M. Isobe, M. Kitamura and T. Goto, *Tetrahedron Lett.*, 3465 (1979).
21 The rule out of this empirical rule might be attributed to the presence of the extra *axial*-methyl group in the ring, which affected the most stable conformation of the side chain.
22 Furusaki, *Acta Crystalog., Sect. A*, 35, 220 (1979).
23 P. Main, S. E. Hull, L. Lessinger, G. Germain, J.P. Declercq, and M.M. Woolfson, MULTAN, 78, (1978). Univs. of York, England, and Louvain, Belgium.
24 C. Katayama, N. Sakabe and K. Sakabe, *Acta Crystallogr., Sect. A*, 28, S207 (1972).
25 "International Tables for X-ray Crystallography," Kynonch Press, Birmingham (1974), Vol IV
26 C.K. Johnson, ORTEP, (1965). Report ORNL-3794, Oak Ridge National Laboratory, Tennessee.
27 C. Katayama et al., *Bull. Chem. Soc. Jpn.*, 58, 2272 (11985).