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SYNTHESIS OF A MARINE POLYETHER TOXIN, OKADAIC ACID [4][1] -- TOTAL SYNTHESIS

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Abstract Three segments A, B and C for okadaic acid synthesis were coupled with each other in the order of A+(B+C), the key steps of the twice couplings being between sulfone carbanions and aldehydes. After the B+C coupling, the asymmetric center C-27 was generated by a hydride reduction of the corresponding ketone 16 under electronic control. The second coupling was followed to form the C-14/15 double bond. Oxidation of the α-oxy aldehyde 36 into the carboxylic acid group was achieved with sodium chlorite without C-1/C-2 bond cleavage. The total synthesis of okadaic acid was accomplished in 106 steps from commercially available D-glucose derivatives and butyne-diol.

Introduction

Okadaic acid [*1*] has been divided into three segments according to the retrosynthetic analysis based on a heteroconjugate addition methodology.[2] This methodology has been developed so that one can control the stereochemistry as well as can couple the segments by utilizing the specific reactivity of those heteroatoms. The synthetic studies toward okadaic acid have culminated in the preceeding three papers to obtain all three segments A, B and C,[3] which were synthesized in the optically active form in principle from D-glucose derivatives. The crucial couplings in this paper should involve utilization of the carbanion nucleophile stabilized by phenylsulfonyl group toward aldehyde moiety. The twice couplings of the three segments were thus planned to occur at C-27/28 and then at C-14/15. In the latter case, the coupling should end up with a double bond formation. In the former case, it should assist to generate one asymmetric center at C-27. This paper deals with the total synthesis of okadaic acid along this line.

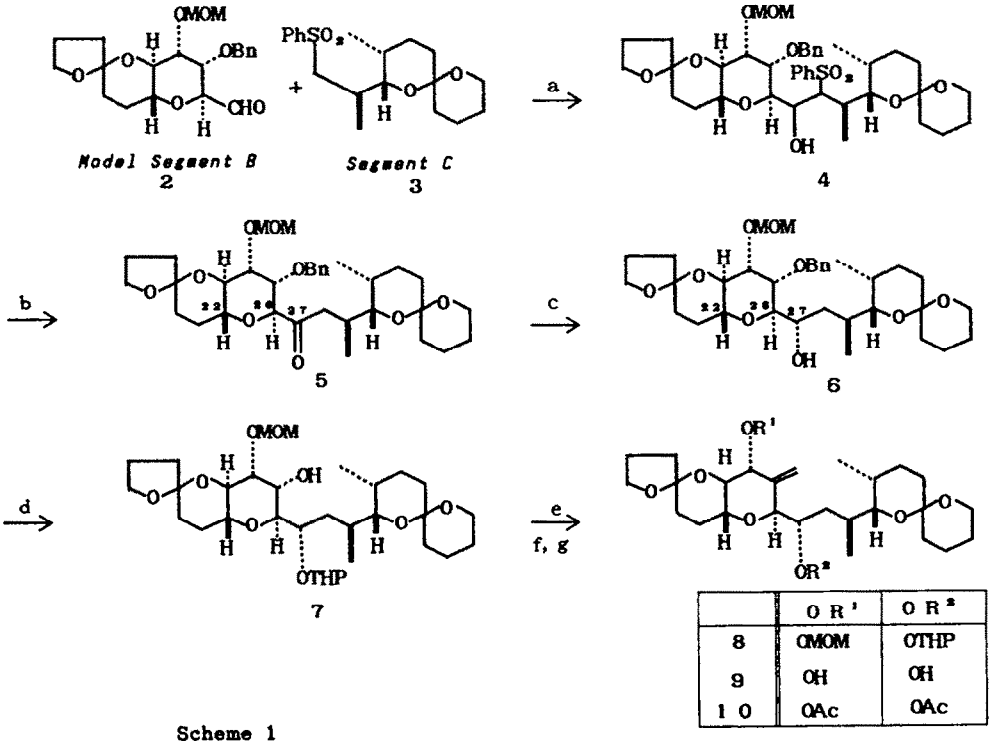
Model Studies for the Coupling of Segments B and C

As had been designed, the sulfone carbanion of segment C should play the nucleophilic role[4] toward the electrophile aldehyde of segment B (such as *2*). Significant question was the stability of the aldehyde which oriented in axial to the tetrahydropyran ring. The second question was the generation of the asymmetric carbon at C-27. These problems were first studied by the model system shown in Scheme 1. The sulfone-carbanion of segment C (*3*) was generated by treatment with n-butyllithium in tetrahydrofuran (THF). The generation was confirmed by a coupling with a simple model aldehyde (*2*) to yield the corresponding adduct. The coupling with the model aldehyde *2* (lacking C-15)[5] in THF as the sole solvent, however, afforded *4* in only ca. 25% yield, although tetrahydropyranyl aldehyde [C_5H_9CHO] reacted in higher yields under the same condition. Such a low reactivity in THF might arise due to the aggregate formation of the segment C anion with the poly-oxygenated moiety in segment B. The aggregates might keep the nucleophile away from the reaction center aldehyde. When the same coupling reaction was carried out at -42° C in a less polar [mixture of diethyl ether and n-hexane (3:2)] solvent, the

adduct *4* was obtained in 66 %. The product was revealed to be a mixture of possible diastereoisomers.

Oxidation of the alcohol with CrO_3-2Py[6] afforded the keto-sulfone, which was reduced first with aluminum amalgam to give *5*. This reduction was studied with a simpler system in Scheme 2, in which *11* was subjected to the amalgam reduction to yield *12*. Prolonged reaction with excess reagents, however, afforded *13*. The ketone 5 was further reduced with sodium borohydride into the alcohol *6*. When examined the ^1H nmr spectra of *5* and *6* about the H-22, the signal at δ 3.6 ppm in the ketone originated from the signal at δ 3.20 ppm in the alcohol. The Δ 0.4 ppm appeared to be due to the anisotropic effect by the carbonyl group; thus, the H-22 and the carbonyl group being both on the upper-side of the tetrahydropyran ring, thus the correct configuration being operated at the C-26.

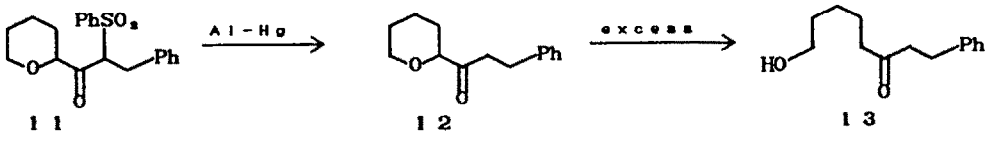
The alcohol *6* was protected as tetrahydropyranyl ether and its benzyl group was deprotected by hydrogenation into *7*. Swern oxidation of the C-25 alcohol and subsequent oxidation to the ketone was followed by Wittig reaction[7] to afford the exomethylene *8*. The methoxymethyl group (MOM) was hydrolyzed with 2.9N HCl in THF at 50° C overnight. The corresponding acetate *10* was compared with natural okadaic acid acetate[8] to show the identical ^1H nmr about the corresponding signals. The stereochemistry at the C-27 was studied in the real system (in Table 1).



	OR'	OR²
8	OMOM	OTHP
9	OH	OH
10	OAc	OAc

Scheme 1

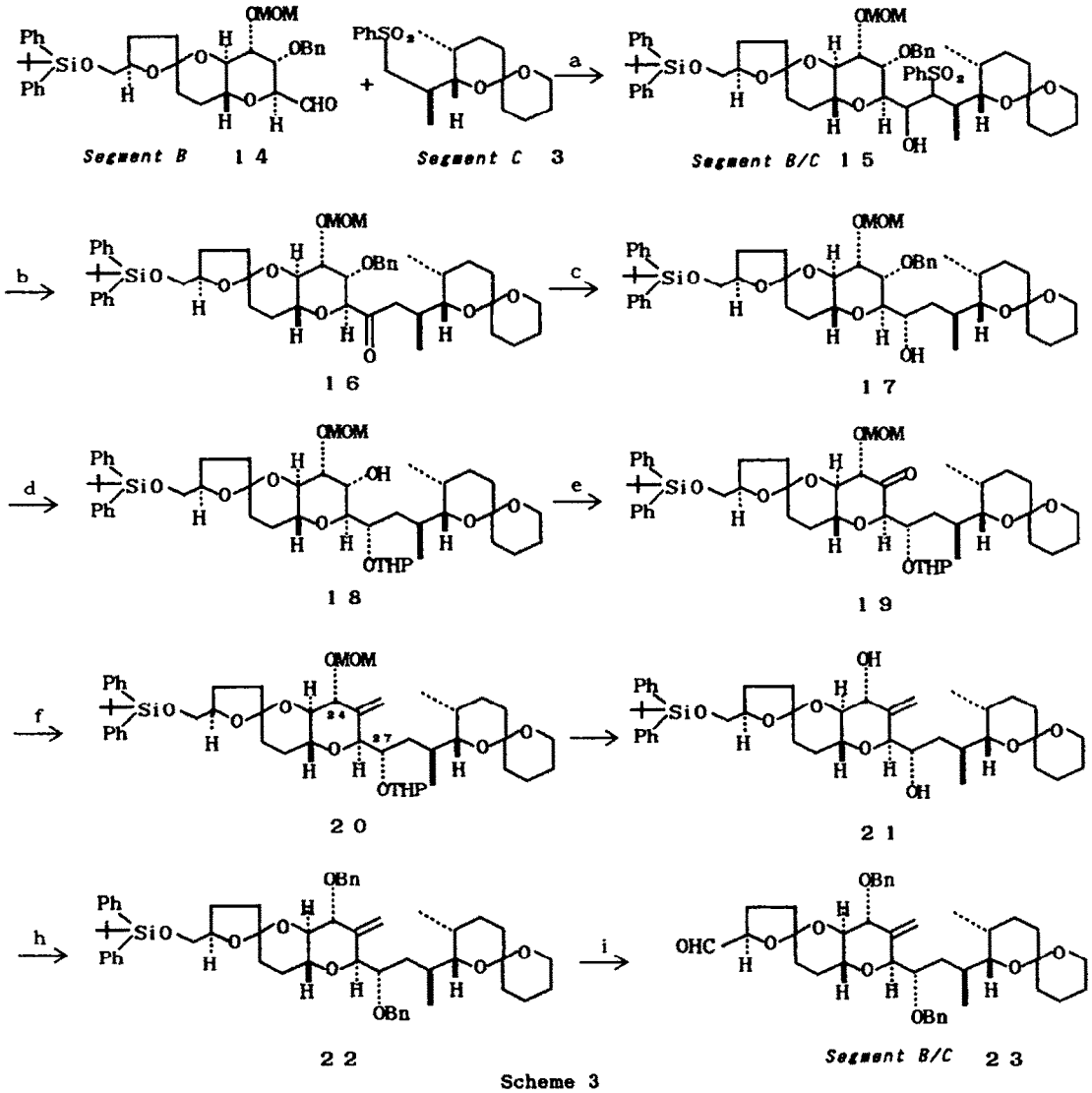
a) n-BuLi; b) CrO_3-2Py, Al-Hg; c) $NaBH_4$; d) DHP/H^+, Pd-C/H_2; e) $(COCl)_2$/DMSO, $Ph_3P{=}CH_2$/THF; f) H_3O^+; g) Ac_2O.



Scheme 2

Coupling of Segment B and Segment C

The aldehyde segment B (*14*) was coupled with the sulfone carbanion which was generated with n-butyllithium from segment C (*3*) at -42° C in a mixture of n-hexane and ether solvents of 5 : 6 ratio. The coupling proceeded smoothly to give *15* in 92% yield as a diastereoisomers. Oxidation of the adducts to a keto-sulfone with CrO_3-2Py was followed by aluminum amalgam reduction to afford the ketone *16*.



Scheme 3

a) n-BuLi; b) CrO_3-2Py, Al-Hg; c) $NaBH_4$; d) DHP/H^+, $Pd(OH)_2$-C/H_2; e) $(COCl)_2$/DMSO; f) $Ph_3P{=}CH_2$/THF; g) Me_3SiBr; h) $PhCH_2Br$/NaH; i)n-Bu_4NF, $(COCl)_2$/DMSO.

Reduction of this ketone with sodium borohydride gave a single alcohol *17*, the stereochemistry of which was assumed to be as *17a*. In the real system, *16* was reduced under the condition shown in Table 1, which indicates complete selectivity with sodium borohydride and lithium aluminum hydride. This selectivity arose by an electronic control of the hydride attack in *anti-periplanar* mode toward the carbonyl group as illustrated in Fig. 1. Entries 3-5 in Table 1 show low or opposite-dominant selectivities (producing *17b*) which were caused by chelative

interaction of the reagent between the two oxygen atoms concerned to allow the attack from less hindered site at the transition state in Fig. 2. The ketone *16* did not epimerize from the *axial* orientation to equatorial under the oxidation conditions, but it was not a stable compound. It did not equilibrate during the following reduction to *17*. This was evident from the fact that reduction products *17a* and *17b* was converted back to *16* by Swern oxidation. When it was treated with a mild base (K_2CO_3) in methanol, an unsaturated ketone *24* (^1H nmr δ5.8 ppm) was produced *via* enolization of the C-27 ketone.

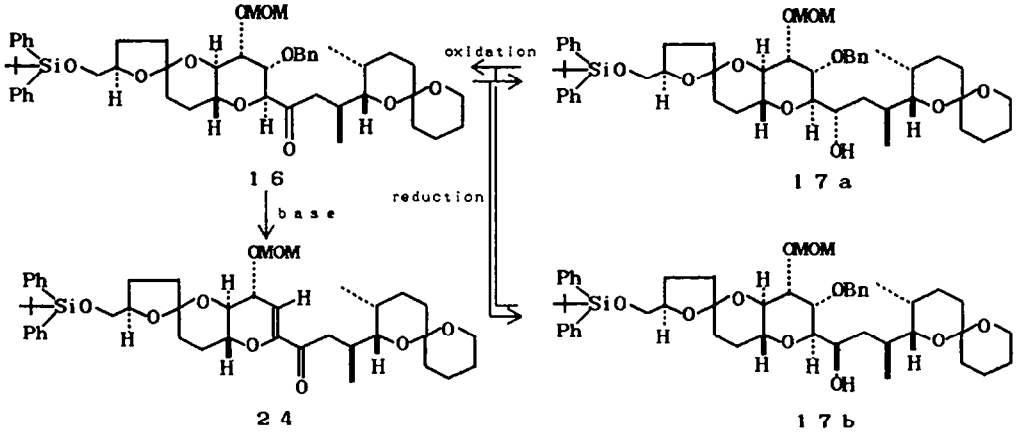
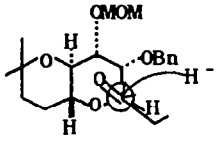


Table 1

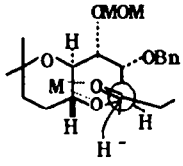
entry	hydride	react temp	17a : 17b
1	$NaBH_4$	0°C	>99 : <1
2	$LiAlH_4$	−78°C	>99 : <1
3	$Zn(BH_4)_2$	0°C	85 : 15
4	DIBAL	−78°C	70 : 30
5	B_2H_6	0°C	40 : 60

Fig 1



anti-periplanar

Fig 2



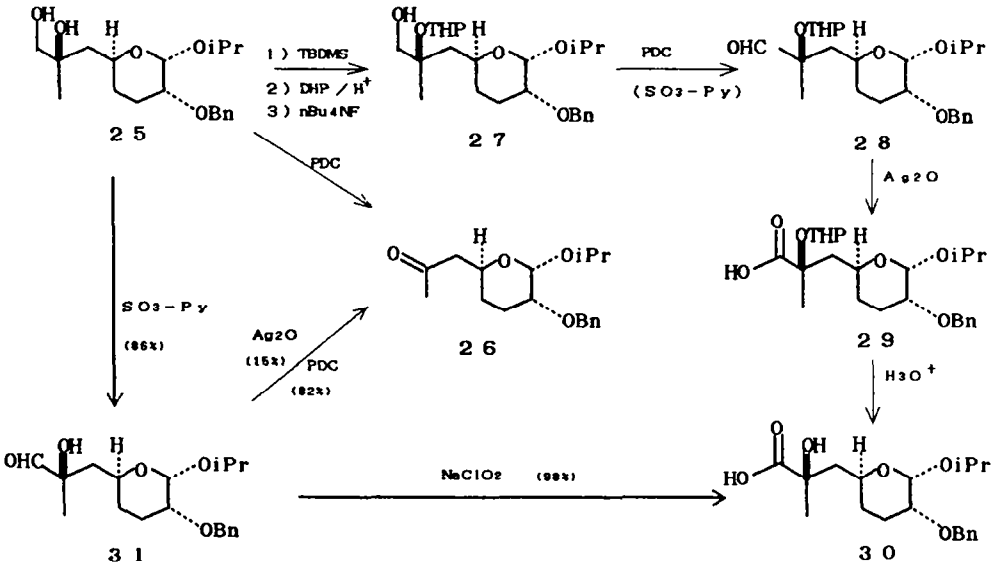
chelation

The same functional group manipulation was followed for the partial completion from C-24 through C-27 for the steps upto *20*. The debenzylation with palladium hydroxide[9] was effected for the conversion of *17* to *18*. The two protective groups at C-24 and C-27 of *20* was hydrolized with trimethylbromosilane[10] and *21* was re-protected as the di-benzyl ether *22*, so that the hydroxy protection will be removed at the very last step of this total synthesis. The silyl protective group of *22* at C-15 was now hydrolyzed with tetra-n-butylammonium fluoride. Swern oxidation of the hydrolysate afforded the corresponding aldehyde *23*, which was prepared right before the following coupling with segment A (*32*).

Coupling of Segment A and Segment B/C

The final section of this total synthesis studies involves (i) coupling of segments A and B/C, (ii) generation of the C-13/14 double bond, (iii) oxidation to the carboxylic acid group and the deprotection of the benzyl groups.

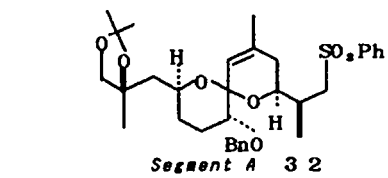
Following model system *25* was studied toward the carboxylic acid (*30*) preparation, for which the basic two process are shown in Scheme 4. The major problem in this oxidation of the 1,2-glycol was to avoid the over reaction cleaving the C-1/C-2 bond and affording *26*. The clockwise process from *25* was first achieved through the protected *tert*-hydroxy group to avoid the C-C bond sission. The counter clockwise process involves two step synthesis of the acid 30 without the protection or sission through the aldehyde *31* by treatment with sodium chlorite, which was used for oxidation of unsaturated aldehyde[13].



Scheme 4

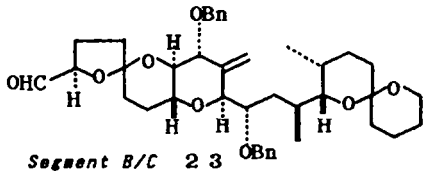
Generation of the carbanion next to the sulfonyl group in segment A (*32*) was rather tricky because the anion turned out to be very unstable under certain conditions. Treatment of segment A with 2 equiv. *tert*-butyllithium in THF and quenching with water did not give back the starting material but gave a decomposed product. The carbanion was cleanly generated by treatment with *sect*-butyllithium in a mixed solvent of THF and n-hexane (1:1) at -78° C for 15 min. Addition of the aldehyde of segment B/C (*23*) in ca. two equivalent into this carbanion solution at -78° C and they were allowed to react to each other for 20 min. [Reaction at a higher temperature in other lot made no great progress for the coupling yield but it lowered the recovery of the aldehyde.] The coupled product was converted into the corresponding *trans*-olefin [olefinic protons at δ5.54 and 5.81ppm J= 15.8 Hz)] in two steps involving acetylation and sodium amalgam reduction and isolated as *34* in 32% yield in three steps. The product was identified with an authentic sample derived in a micro scale from natural okadaic acid.[11]

The acetonide protected the C-1/2 glycol in *34* was removed by heating at 55° C for 24 hr with a weak acid mixture [acetic acid : THF : water = 1 : 2 : 1]. Atempted oxidation of this primary alcohol *35* into the corresponding carboxylic acid *37* were all failed due to the bond sission between C-1 and C-2 until we found the conditions in Scheme 4. The successful oxidation involved two steps involving first oxidation with SO_3-Py[12] into the aldehyde *36*, which was then oxidized into the carboxylic acid *37* with sodium chlorite in the presence of buffer (NaH_2PO_4) and chlorine scavenger (2-methyl-2-butene)[13] in 52% yield. The final removal of the benzyl ether groups was achieved with lithium metal in liquid ammonia and ethanol solvent in 80% yield.



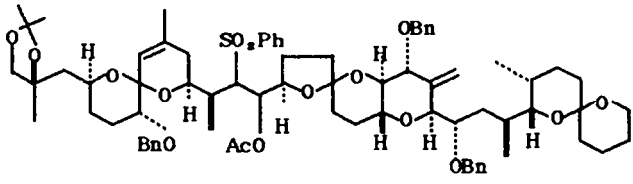
Segment A 3 2

+



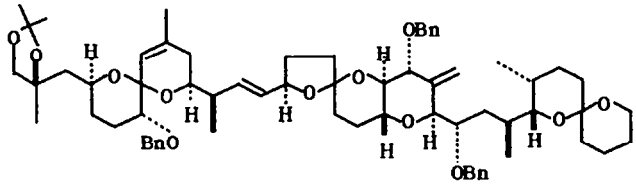
Segment B/C 2 3

a →



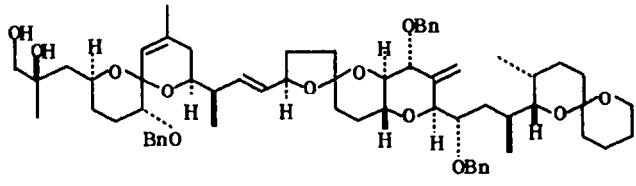
3 3

b →



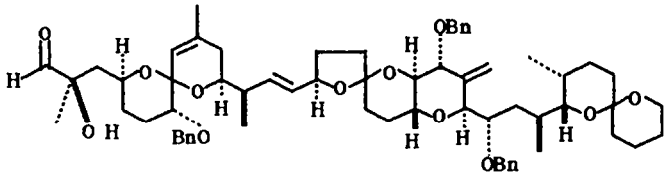
3 4

c →



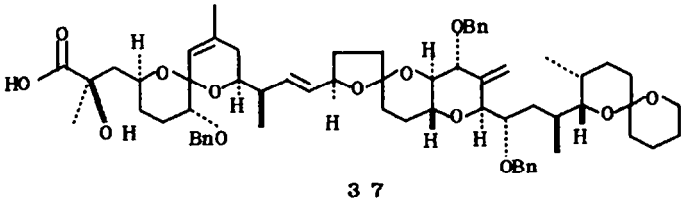
3 5

d →



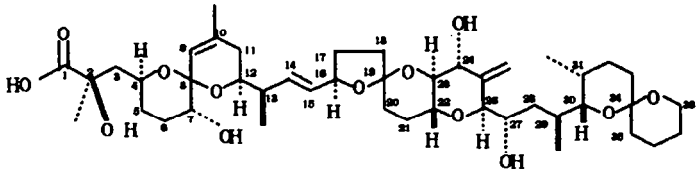
3 6

e →



3 7

f →



OKADAIC ACID 1

Scheme 5

a) *sec*-BuLi, Ac_2O/Py; b) Na-Hg; c) AcOH/THF-H_2O; d) SO_3-Py; e) $NaClO_2$/MeC(Me)=CHEt/NaH_2PO_4; f) Li/liq. NH_3/EtOH

Conclusion of the Total Synthesis of Okadaic Acid

Okadaic acid, marine polyether toxin and antitumor agent, has been successfully synthesized from *D*-glucal tri-acetate and *D*-glucal tetra-acetate through the couplings of the three segments A, B and C. Each segment was prepared from even smaller fragments in the optically active forms. Segment A was constructed in 36 steps, segment B and segment C were done in 35 and 16 steps, respectively. And 19 steps have been required for (and after) the couplings among the segments. Total synthesis was accomplished in 106 overall steps from the *D*-gluccals and butyne-diol. The stereo-selectivity of the asymmetric centers were C-2(91 %), C-7(100 %), C-8(100 %), C-13(91%), C-16(99 %), C-19(100 %), C-22(96 %), C-23(100 %), C-24(100 %), C-27(100 %), C-29(100 %), C-31(100 %) and C-34(100 %); but the unnecessary stereoisomers were separated in the course of the synthesis. Therefore the synthetic okadaic acid as well as the important intermediate *34* showed only the single stereoisomerisms, respectively, which were identified with the natural source-derived authentic material by 500 MHz ^{1}H nmr. The overall chemical yield was in the order of 0.01%. The challenging to such multi-step synthesis have successfully accomplished but also revealed the synthetically impractical problems, which are to be solved in future as well.

The above studies prompted us to generalize the empirical rule on the stereochemical control in the differentiation of the *sp² face* which is dis-symmetrized because of the presence of the neighbouring asymmetric center. The studies have also stimulated the important synthetic subjects of the harmoney of the C-C bond formation with stereochemical control. And these problems have been demonstrated in the developments of heteroconjugate addition methodology involving the switching selectivity.

EXPERIMENTALS

Coupling of Segment B and Segment C

Segment C 3 (0.89 g, 2.53 mmol) was dissolved in ether solvent (15 mL) and cooled to 0° C under nitrogen atmosphere. n-Butyllithium (1.55 M, 1.60 mL, 2.48 mmol) was added to this solution dropwise with stirring. The stirring was continued at 0° C for 10 min and then at -42° C for 15 min with a dry-ice acetonitrile bath. To the mixture were added dry n-hexane (15 mL), and a solution of segment B (the aldehyde prepared immediately before use, 1.050 g, 1.50 mmol) in ether solvent (3 mL) dropwise. After 10 min stirring, sat. ammonium chloride solution was added to this mixture and worked up with ether; thus, involving extraction with ether (x3), washing the extracts with water, NH_4Cl and NaCl, drying over sodium sulfate and concentration *in vacuo*. The crude product was purified by silica gel (55 g) chromatography with a mixture of ether and n-hexane 1:3 (700 mL) and then 1:1 (800 mL) as eluant to afford 15 (1.4 g, 92% yield).

A solution of 15 (2.6 g, 2.6 mmol) in dichloromethane (50 mL) was stirred vigorously with CrO_3-2Py (12 g, 47 mmol) at room temperature for 30 min. Silica gel (10 g) was added to this mixture, which was diluted with ether and decanted. The remaining gum was sonicated with ether and decanted to repeat three times. The combined organic solution was filtered through Super Cel and the filtrate was passed through a short column of silica gel. Concentration of the filtrate gave the keto-sulfone (2.4 g), which was used for the next step.

A mixture of (2.4 g), THF (tetrahydrofuran, 90 mL), water (10 mL) and aluminum amalgam (prepared from aluminum foil 3 g, 2% aq. $HgCl_2$) was stirred overnight at room temperature. Sat. sodium potassium tartrate solution was added to the mixture and worked up with ether to give the ketone 16 (1.8 g) as an oil, which was used for the next step. Part of the sample was purified on silica gel tlc to give the analytically pure sample.

$[\alpha]_D$=+9.7° (c=1.15, $CHCl_3$); ^{1}H nmrδ 0.87(3H, d, J= 6), 0.98(3H, d, J= 6), 1.04(9H, s), 1.3-2.4(22H), 3.05(1H, td, J= 10, 4), 3.39(3H, s), 3.35-3.78(6H), 4.12(1H, t, J= 10), 4.19(1H, d, J= 2), 4.22-4.35(2H), 4.64-4.87(4H), 7.2-7.8(15H). irν 1720 cm^{-1}

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

Reduction of the C-27 Ketone to 17

The C-27 ketone *16* (1.8 g) was dissolved in ethanol (40 mL) and cooled to 0° C. Sodium borohydride (0.3 g) was added portionwise to this mixture with stirring, and the stirring was continued for 1 hr. The mixture was poured into water and extracted with ether to be worked up. The crude product (1.8 g) was chromatographed with silica gel and a mixture of ether and n-hexane (1:1) as eluant to give pure alcohol 17 (1.3 g, 57% overall yield 3 steps from the adduct *15*: $[\alpha]_D$=+15.1° (c=2.15, $CHCl_3$); ^{1}H nmrδ 0.88(3H, d, J= 6), 1.03(3H, d, J= 6), 1.04(9H, s), 1.1-2.3(22H), 3.20(1H, dd, J= 10, 2), 3.38(3H, s), 3.30(3H, s), 3.30-3.80(8H), 3.92(1H, brt, J= 10), 4.17(1H,

t, J= 10), 4.30(1H, td, J= 8, 4), 4.63-4.81(4H), 7.2-7.8(15H).
Found C 70.14, H 8.23; Calcd C 70.15, H 8.31, for $C_{51}H_{72}O_{10}Si$.

Exo-methylene 20

A mixture of the alcohol 17 (1.3 g, 1.49 mmol), dichloromethane (40 mL), PPTS (pyridinium p-toluenesulfonate, 0.05 g) and dihydropyran (1.03 mL, 11.3 mmol) was stirred at room temperature overnight. The reaction mixture was diluted with ether solvent and then poured into sodium bicarbonate solution. Etherial work-up gave the crude tetrahydropyranyl ether (1.7 g), which was used for the next step.

A mixture of the benzyl ether (1.7 g), ethyl acetate (45 mL) and palladium hydroxide on carbon (Pearlman's catalyst,[9] 2.3 g) was vigorously stirred under hydrogen atmosphere for 6 hr. The reaction mixture was filtered through Super Cel and the filtrate was concentrated to give residue, which was chromatographed on silica gel (30 g) with a mixture of ether and n-hexane 1:1 as eluant to give the alcohol 18 (890 mg, 69% overall yield from 17).

Oxalyl chloride (75 microL, 0.86 mmol) was dissolved in dichloromethane (5 mL) and cooled to -78° C under nitrogen atmosphere. DMSO (dimethylsulfoxide 0.15 mL, 2.1 mmol) was added to this over 5 min and then the alcohol 18 (150 mg, 0.17 mmol, dissolved in dichloromethane 1 mL) was introduced slowly over 5 min to the mixture, which was further stirred for 10 min at -78° C. Triethylamine (0.4 mL, 2.9 mmol) was added at this temperature and the stirring was continued for 15 min and then at ambient temperatures by removing the cooling bath to 0° C. The reaction mixture was mixed with water and extracted with a mixture of ether and n-hexane. Subsequent usual work-up gave the ketone 19 (178 mg): irν 1730 cm^{-1}.

To a suspension of methyltriphenylphosphonium bromide (492 mg, 1.38 mmol) in THF (5.5 mL) was added n-butyllithium (1.55 M, 0.78 mmol) at 0° C. The reaction mixture was stirred at room temperature for 30 min to give methylenetriphenylphosphorane and then cooled to -78° C under nitrogen atmosphere. The ketone 19 (178 mg, 0.17 mmol) was added to this mixture at -78° C and then the cooling bath was removed from the reaction vessel, which was then heated to reflux for 2 hr. The reaction mixture was poured into ammonium chloride solution and extracted with ether solvent. Work-up was followed by silica gel (8 g) chromatography with a mixture of ether and n-hexane 1:5 as eluant to give exo-methylene compound 20 (116 mg, 79% overall yield from 18).

To a cold solution of the methoxymethyl ether 20 (142 mg, 0.16 mmol) in dichloromethane (2.5 mL) was added at -78° C a solution of trimethylbromosilane (0.25 mL, 1.9 mmol) in dichloromethane (0.5 mL) with magnetic stirring, which was continued at -78° C for 15 min and at -25° C for 30 min. The reaction mixture was poured into sodium bicarbonate solution and extracted with dichloromethane. Work-up gave the diol 21 (0.12 g), which was used for the next step. Part of the sample was purified with silica gel tlc for analytically pure 21: $[\alpha]_D$=+15.9° (c=1.29, $CHCl_3$); ^1H nmrδ 1.09(3H, d, J= 7), 1.15(9H, s), 1.25(3H, d, J= 6), 1.3-2.7(24H), 3.42(1H, dd, J= 10, 2), 3.45-3.82(6H), 4.00(1H, d, J= 10), 4.06(1H, m), 4.17(1H, t, J= 10), 4.27(1H, d, J= 10), 4.95(1H, s), 5.65(1H, t, J= 1), 7.2-7.9(10H).
Found C 70.40, H 8.51; Calcd C 70.26, H 8.50, for $C_{43}H_{62}O_8Si$.

Protection to the Benzyl Ether 22

Sodium hydride (60% dispersion, 30 mg, 0.75 mmol) was washed with dry n-hexane, suspended in THF (2.2 mL) and cooled to 0° C. A solution of the diol 21 (0.12 g, 0.16 mmol) in THF (2.2 mL), benzyl bromide (0.15 mL, 1.3 mmol) and DMF (N,N-dimethylformamide 0.45 mL) were added at 0° C to this suspension, which was further stirred at room temperature for 16 hr. The reaction mixtrure was poured into ammonium chloride and extracted with ether. The dibenzyl ether 22 (0.24 g, crude), which was used for the next reaction without purification. Part of the sample was purified by silica gel tlc to give pure 22: $[\alpha]_D$=+29.3° (c=1.64, $CHCl_3$); ^1H nmrδ 0.89(3H, d, J= 7), 0.94(3H, d, J= 6), 1.04(9H, s), 1.3-2.25(22H), 3.24(1H, dd, J= 10, 2), 3.5-3.8(6H), 3.85-4.02(2H), 4.22-4.34(2H), 4.55-4.88(4H), 5.05(1H, s), 5.43(1H, t, J= 1), 7.2-7.8(20H).
Found C 74.81 H 8.19; Calcd C 74.80, H 8.15, for $C_{57}H_{74}O_8Si$.

Desilylation of 21

A mixture of the silyl ether 22 (0.24 g, 0.10 mmol), THF (1.5 mL), acetonitrile (1.5 mL) and n-Bu_4NF (1M soln. in THF, 0.5 mL, 0.5 mmol) was stirred at room temperature overnight. The solution was poured into water and extracted with ether. Work-up and purification of the crude product with silica gel tlc afforded pure alcohol (53 mg, 50% overall yield from 20): $[\alpha]_D$=+33.5° (c=1.73, $CHCl_3$); ^1H nmrδ 0.88(3H, d, J= 7), 0.93(3H, d, J= 6), 1.3-2.2(24H), 3.24(1H, dd, J= 10, 2), 3.45-3.82(6H), 3.89-4.01(2H), 4.20-4.33(2H), 4.55-4.86(4H), 5.05(1H, s), 5.43(1H, t, J= 1). irν 3480 cm^{-1}.
Found C 72.77, H 8.44; Calcd C 72.75, H 8.34, for $C_{41}H_{56}O_8$.

Oxidation of the Segment B/C to Aldehyde 23

To a solution of oxalyl chloride (20 uL, 0.11 mmol) dissolved in CH_2Cl_2 (1.0 mL) cooled to -78° C under nitrogen atmosphere was added DMSO (25 uL, 0.35 mmol) dropwise. After stirring for 2 min, the alcohol (15 mg, 0.022 mmol) in CH_2Cl_2 (0.5 mL) was added and the stirring was continued for 15 min. Afte addition of triethylamine (0.05 mL, 0.36 mmol), the reaction mixture was allowed to warm slowly to 0° C and then poured into H_2O. The aq. layer was extracted with ether (x3) and the extracts were washed (sat. NH_4Cl, sat. $NaHCO_3$, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the aldehyde *23* (19 mg). This material was promptly subjected to the subsequent reactions without purification. (When a part of the sample was separated in another lot, the yield was 81%.)

^1H nmr δ0.89(3H, d, J=7), 0.95(3H, d, J=6), 1.1-2.5(22H), 3.24(1H, dd, J=10, 2), 3.55-4.00(4H), 3.85-4.00(2H), 4.28(1H, d, J=8), 4.47(1H, qd, ,J=4, 2), 4.55-4.86(4H), 5.06(1H, s), 5.43(1H, t, J=1), 7.2-

7.4(10H), 9.71(1H, d, J=2).

Coupling of Segment A 32 with Segment B/C 23

To a solution of segment A 32 (83 mg, 0.14 mmol) dissolved in THF (1.5 mL) cooled to -78° C under nitrogen atmosphere was added sec-BuLi (1.35 M hexane, 0.12 ml, 0.16 mmol) dropwise. After stirring for 10 min, the solution was diluted with dry hexane (1.5 mL), and the aldehyde *24* (19 mg) in THF (0.5 mL) was added. After stirring at -78° C for 20 min, the reaction mixture was quenched by the addition of sat. NH_4Cl solution and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the residue.

The resulting residue was dissolved in MeOH (1.5 mL) and then treated with $NaBH_4$ (10 mg) at 0° C for 30 min. The solution was poured into H_2O and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried and concentrated under reduced pressure. Purification of the residue on preparative silica gel TLC gave a mixture of segment A and the coupling product *33a* (9 mg), and the segment B/C alcohol (10 mg).

A solution of the coupling product *33a* and segment A (9 mg) dissolved in a mixture of pyridine (2 mL) and acetic anhydride (1 mL) was heated at 55° C overnight. The solvent was removed in vacuum to afford the residue which was dissolved in a mixture of MeOH (0.4 mL) and ethyl acetate (0.1 mL). To this solution was added sodium amalgam (5%) portionwise until TLC analysis showed the absence of starting material. The solution was poured into H_2O and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O, sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on silia gel TLC gave the trans-olefin 34 (2.2 mg, 32% overall yield from *23*) as an oil.

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

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

Hydrolysis of the Acetonide 34 to the Diol 35

A solution of the acetonide 34 (7 mg, 0.0064 mmol) in a mixture of THF (0.40 mL), AcOH (0.30 mL) and water (0.15 mL) was heated at 55° C for 1.5 day. Solvent was removed in vacuum and chromatography (silica gel 1.5 g) of the residue with 1:1 and 3:1 ether/hexane gave the diol 35 (4.4 mg, 63% yield).

^1H nmr (500 MHz) δ 0.88(3H, d, J= 7), 0.92(3H, d, J= 6), 1.05(3H, d, J= 7), 1.14(3H, s), 1.72(3H, s), 2.37(1H, tq, J= 7.1, 7.0), 3.45-3.52(2H), 3.58-3.7(5H), 3.9-4.0(3H), 4.24(1H, d, J= 8), 4.46(1H, d, J= 13), 4.53(1H), 4.56(1H, d, J= 11), 4.59(1H, d, J= 13), 4.67(1H, brs), 4.74(1H, d, J= 13), 4.74(1H, d, J= 11), 4.86(1H, d, J= 13), 5.03(1H, brs), 5.13(1H, brs), 5.40(1H, t, J= 1), 5.55(1H, dd, J= 15, 8), 5.61(1H, dd, J= 15, 9), 7.2-7.4(15H), 9.30(1H, s).

$[\alpha]_D$=+34.4° (c=0.28, $CHCl_3$)

Oxidation of the Diol 35 to the Aldehyde 36

To a solution of the diol 35 (4.4 mg, 0.0042 mmol) dissolved in a mixture of DMSO (0.20 mL) and triethylamine (0.8 mL) was added sulfur trioxide pyridine complex (15 mg, 0.094 mmol) portionwise. After stirring at room temperature for 30 min, the solution was poured into H_2O and the aq. layer was extracted with ether (x3). The extracts were washed (sat. NH_4Cl x2, sat. $NaHCO_3$, sat. NaCl) and dried (Na_2SO_4). Concentration under reduced pressure gave the aldehyde 36 (4 mg). This material was promptly subjected to the subsequent reaction.

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

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

Sodium Chlorite Oxidation of the α-Oxyaldehyde 37

To a solution of the aldehyde 36 (4 mg), 2-methyl-2-butene (75 uL) and sodium phosphate, monobasic dihydrate (7 mg, 0.045 mmol) dissolved in a mixture of tert-butanol (0.25 mL) and H_2O (50 μL) was added sodium chlorite ($NaClO_2$, 85%, 4 mg, 0.038 mmol) portionwise. After stirring at room temperature for 2.5 hr, sat. $NaHSO_3$ solution was added. The solution was acidified at 0 ° C with 1N HCl and the aq. layer was extracted with CH_2Cl_2 (x3). After being dried (Na_2SO_4), concentration under reduced pressure followed by chromatography (silica gel 1 g) of the residue with 1:1 ether (containing 0.5% of acetic acid)/hexane gave the carboxylic acid 37 (2.6 mg 66% overall yield).

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

$[\alpha]_D$=+50.2° (c=0.22, $CHCl_3$).

Debenzylation to Total Synthesis of Okadaic Acid 1

To a solution of the tribenzyl okadaic acid 37 (2.7 mg) dissolved in EtOH (0.3 mL) and ammonia (distilled from sodium metal) cooled to -78° C was added lithium metal (trace). After stirring at -78° for 30 min, the reaction mixture was allowed to warm to room temperature and to stand at room temperature for 2 hr until ammonia dissolved in EtOH was evaporated. Water was added and the solution was acidified at 0° C with 1N HCl. The aq. layer was extracted with CH_2Cl_2 (x3) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crystalline mass were washed with hexane to give the synthetic okadaic acid as white crystalline (1.7 mg 87% yield).

^1H nmr (500 MHz) δ0.93(3H, d, J=6), 1.02(3H, d, J=7), 1.06(3H, d, J=6), 1.37(3H, s), 1.77(3H, s), 3.29(H-30, dd, J=11, 2), 3.35-3.62(2H), 3.55(H-38, brd, J=11), 3.61(H-22, td, J=10, 4), 3.66(H-38, td, J=11, 3), 3.94(H-26, d, J=10), 4.07(H-4, brt, J=11), 4.09(H-27, t, J=10), 4.12(H-24, d, J=10), 4.54(H-16, td, J=9, 7), 5.06(1H, brs), 5.32(1H, brs), 5.44(1H, t, J=1), 5.48(1H, dd, J=15, 9), 5.67(1H, dd, J=15, 9), 5.78(1H, brs). All other signals are left unsesolved between 1.25-2.40 ppm.

Analytical TLC; Rf-value (solvent system), 0.28 (0.5% acetic acid/ethyl acetate:hexane 1:1), 0.28 (0.5% acetic acid/ether), 0.21 (5% methanol/dichloromethane), 0.49 (acetone/n-hexane 1:1).

m.p. 164.5-166° C.

$[\alpha]_D$=+23.9° (c=0.088, $CHCl_3$).

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