Transformation of a Marine Toxic Polyether, Okadaic Acid

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Natural okadaic acid **1** was transformed into the 7,24,27-tri-*O*-benzyl-1,2-acetonide derivative (**4**) in a 66% overall yield. The corresponding synthetic derivative (**4**) was identified with this authentic sample.

In 1981, okadaic acid was isolated from two kinds of sponges, *Halicondria okadai* along the Pacific coast of Japan, and *Halilcondria melanodocia* in the Florida Keys.¹⁾ The structure of okadaic acid was elucidated by Tachibana *et al.*¹⁾ as (**1**) through X-ray crystallographic analysis of an *o*-bromobenzyl derivative. This molecule comprised a backbone with 38-carbon atoms, 17 asymmetric centers, 4 hydroxy groups, 6 methyl groups and 3 types of olefins. Yasumoto *et al.* disclosed that okadaic acid was identified to be a diarrhetic shellfish toxin in 1982.²⁾ The first total synthesis of this toxin was reported from this laboratory in 1986.³⁾ In this synthesis, we confronted the problem of protection and deprotection of the hydroxy groups.⁴⁾

Benzyl ethers were chosen for protecting the hydroxy groups at the C-7, C-24, and C-27 positions, the corresponding tri-benzyl ethers (**4**), (**5**), (**6**) and (**7**) having been from natural okadaic acid.³⁾ Tribenzyl okadaic acid (**5**) was subjected to a debenzylating condition such as

lithium metal in liquid ammonia. Although it had been planned to remove the benzyl protection by the alkali metal, the removal was accompanied by serious over-reduction products in the synthetic study. These were considered to be a mixture of reduction at the C2-OH next to carboxylic acid and at the allyl ethers at the C-8, C-16, C-24 and C-26 positions. When the tri-benzyl **4** was reduced with lithium in liquid ammonia at -78°C , the product was isolated, but showed absence of the peak corresponding to the allylic H-16 proton at around $\delta 4.5$ in the $^1\text{H-NMR}$ spectrum. This result revealed that the hydrogenolysis took place at the allylic C16-O bond. Systematic studies on debenzylation were necessary to find a kinetic condition in which the velocity of hydrogenolysis could be made even less than that of debenzylation. This paper deals with studies to solve these problems by the transformation of natural okadaic acid, which was only obtained in a limited amount.

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Preparation of the tri-benzylether of okadaic acid and debenzylation

Three hydroxy groups at the C-7, C-24 and C-27 positions of okadaic acid (**1**) were protected as its benzyl ether by treating with benzyl bromide and sodium hydride in a mixture of tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF). This condition allowed no benzylation at the tertiary C2-OH, and furnished tribenzyl okadaic acid (**5**) in a 47% yield.

We attempted to remove the benzyl groups with **5** but this was accompanied by overhydrogenolysis (*vide supra*). This problem was finally solved by introducing a small amount of lithium metal into **5** at -78°C . Stirring the mixture for 30 min provided okadaic acid (**1**).⁵⁾ The product was converted into the methyl ester with diazomethane in methanol, purified on TLC (in an 80% yield from **4**), and then identified with the authentic okadaic acid methyl ester.

Debenzylation of tribenzyl okadaic acid (**5**) gave crystalline okadaic acid (**1**) from hot hexane.⁶⁾ Both of the okadaic acids were com-

pletely identical from their 500 MHz ^1H -NMR spectra.

*Preparation of the tribenzyl acetonide (**4**) and confirmation of its stereochemistry*

Okadaic acid (**1**) has 4 asymmetric centers on acyclic parts at the C-2, C-13, C-27 and C-29 positions. ^1H -NMR spectroscopic analysis had already confirmed the stereochemistry of the synthetic intermediates at C-2, C-13 and C-29.⁷⁾ The asymmetric center at C-27 was to be confirmed, since it was induced by reduction of the corresponding ketone. The stereochemistry has been assumed on the basis of a mechanism controlled by steric and electronic effects,⁸⁾ and a direct comparison of the synthetic and natural specimens was necessary. A closer comparable specimen was synthesized by converting natural okadaic acid (**1**) to the tetraacetate methyl ester with acetic anhydride in pyridine, and then with diazomethane in methanol.⁹⁾ This compound from the natural source was compared with the synthetic model compound (**2**) prepared from D-glucose derivatives in 37 steps.¹⁰⁾ The chemical shift and

coupling constant of the hydrogen at C-27 of okadaate (3) (δ 5.59, ddd, $J=11, 9, 2$; see Fig. 2 (δ 5.60, ddd, $J=12, 9, 2$ Hz) was identical to that of methyl 2,7,24,27-tetra-*O*-acetyl- Such a comparison was also examined on

SCHEME 1.

FIG. 1. ^1H -NMR Spectra (in CDCl_3 at 500 MHz) of Tetra-acetyl Okadaic Acid Methyl Ester 3 (Lower) and the Diacetate of B/C-Segment 2 (Upper).

the tri-benzyl acetone (4) with 38 carbon atoms and 17 asymmetric centers, which had been synthesized from D-glucose.³⁾ The authentic compound (4) was prepared as de-

scribed in Scheme 1, and the stereochemistry including the C-27 position was unambiguously confirmed. The crucial step of this transformation involved i) selective protection of the

FIG. 2. ^1H NMR Spectra (in C_6D_6 at 500 MHz) of Synthetic (Lower) and Natural (Upper) Okadaic Acid.

three hydroxy groups at C-7, C-24 and C-27 into the benzyl ether, and ii) transformation of the α -hydroxy carboxylic group into the corresponding 1,2-diol and subsequent protection as its acetonide. Okadaic acid was benzylated with benzyl bromide and sodium hydride into the tribenzyl derivative (**5**). This was successively treated with diazomethane and then purified with chromatography to afford the tribenzyl methyl ester (**6**) in a 48% yield from okadaic acid. The ester moiety of **6** was reduced with lithium aluminum hydride (THF, -78°C to 0°C) to provide the tribenzyl diol (**7**) in a 60% yield.¹¹ This glycol was protected as its acetonide by treating with 2,2-dimethoxy propane in the presence of PPTS (pyridinium *p*-toluenesulfonate).¹² The tribenzyl acetonide (**4**) was obtained quantitatively. The overall yield through this sequence was only 29% from natural okadaic acid (**1**).

Since the preceding process was unsatisfactory in yield, the sequence in Scheme 2 was explored with a 66% overall yield. Okadaic acid was first treated with diazomethane (methanol, 0°C) to provide the methyl ester (**8**). Reduction of the methyl ester with lithium aluminum hydride in tetrahydrofuran furnished the corresponding pentaol. The 1,2-diol moiety of this pentaol was protected with 2,2-dimethoxy propane in the presence of PPTS to afford only the acetonide triol (**9**). Finally, the triol (**9**) was protected as its benzyl ether (**4**) with sodium hydride and benzyl bromide in a mixture of tetrahydrofuran and *N,N*-dimethylformamide.¹¹ This tribenzyl acetonide (**4**) derived from natural okadaic acid was identical in all respects with those of the specimen that was synthesized in 102 steps from D-glucose [500 MHz ^1H -NMR spectra measured in CDCl_3 and C_6D_6 , $[\alpha]_{\text{D}} = +31.5^{\circ}$ ($c=0.20$, CHCl_3 , synthetic); $[\alpha]_{\text{D}} = +35.6^{\circ}$ ($c=0.20$, natural)]. This molecule possessed 17 asymmetric centers, which were examined by the 500 MHz ^1H -NMR spectrum measured in C_6D_6 (Fig. 2). All of the protons attached to the asymmetric centers were observed and assigned (see EXPERIMENTAL section). This result completely confirmed the

stereochemistry at the C-27 position ($\delta 4.01$ ppm, ddd, $J=10$, 2 Hz) of the synthetic material.

The investigation of the transformation of okadaic acid just described supported our efforts that lead to the first total synthesis of okadaic acid in 106 steps from D-glucose.³⁾

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were recorded on a JEOL GX-500 spectrometer. Chemical shifts are reported as values in parts per million relative to tetramethylsilane (0.0 ppm) as an internal standard. All samples were dissolved in CDCl_3 and recorded, unless otherwise described. Optical rotations were measured in 1-dm cells of 2 ml capacity by either JASCO MODEL DIP-4 polarimeter or a JASCO DIP-181 digital polarimeter. Separation by TLC was made on plates with 0.5 mm precoated silica gel PF₂₅₄ obtained from E. Merck (Art #5744). Column chromatography was performed on silica gel supplied by Fuji Davison (BW-820 MH).

Tribenzyl okadaic acid (5). NaH (60% oil dispersion, 5 mg) was added to a solution of okadaic acid (**1**) (8 mg, 0.010 mmol) and BnBr (18 μl , 0.15 mmol) dissolved in a mixture of THF (0.6 ml) and DMF (0.1 ml), and the resulting mixture was stirred over night. A portion of water was added and the mixture was acidified with 1 N HCl. The separated aqueous layer was extracted with CH_2Cl_2 , and the combined organic layer was dried over Na_2SO_4 . Evaporation of the solvent followed by purification on TLC gave the tribenzyl okadaic acid (**5**) (5 mg, 47% yield). $[\alpha]_{\text{D}} = +48.1^{\circ}$ ($c=0.31$, CHCl_3); ^1H -NMR δ : 0.87 (3H, d, $J=7$), 0.91 (3H, d, $J=7$), 1.05 (3H, d, $J=7$), 1.36 (3H, s), 1.73 (3H, s), 2.13 (1H, dd, $J=14$, 2), 2.23 (1H), 2.42 (1H, qt, $J=7$, 7), 3.22 (1H, dd, $J=11$, 2), 3.24 (1H, dd, $J=12$, 4), 3.55~3.7 (5H), 3.88~3.95 (2H), 4.02 (1H, tt, $J=11$, 2), 4.24 (1H, d, $J=8$), 4.48 (1H, d, $J=13$), 4.56 (1H, d, $J=11$), 4.60 (1H, d, $J=13$), 4.61 (1H), 4.73 (1H, d, $J=11$), 4.77 (1H, d, $J=13$), 4.89 (1H, d, $J=13$), 5.02 (1H, br. s), 5.14 (1H, br. s), 5.17 (1H, br. s), 5.35 (1H, t, $J=1$), 5.61 (1H, dd, $J=15$, 8), 5.74 (1H, dd, $J=15$, 8). All other signals were left unresolved between 1.25~2.40 ppm.

Debenzylation of tribenzyl okadaic acid (5). A solution of tribenzyl okadaic acid (**5**, 3 mg) in EtOH (0.6 ml) and ammonia (0.7 ml) was cooled to -78°C , and then Li metal (less than 1 mg) was added. After vigorous stirring at -78°C for 30 min, the cooling bath was removed, and the ammonia was allowed to evaporate. Water (2 ml) was added, and the solution was then acidified with 1 N HCl. The aqueous layer was extracted with CH_2Cl_2 , and the combined organic layer was dried over Na_2SO_4 . Evaporation of the solvent gave the crude okadaic acid.

This was dissolved in MeOH (0.4 ml), and then treated with a solution of diazomethane prepared according to the procedure described by Fieser.¹³ Purification of the resulting product on TLC provided okadaic acid methyl ester (1.82 mg, 80% yield), which was characterized by 500 MHz ¹H-NMR.

Debenzylation of tribenzyl acetonide (4). To a solution of the tribenzyl acetonide derivative (**4** 1 mg) in a mixture of EtOH (0.3 ml) and ammonia (0.6 ml, distilled from Na metal before use) that had been cooled to -78°C was added Li metal (1.37 mg), the solution being stirred vigorously. After stirring at -78°C for 30 min, the cooling bath was removed, and the ammonia was allowed to evaporate. Water was added, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was dried over Na_2SO_4 , and then evaporated to afford the triol (**9**), (1 mg) which was characterized by 500 MHz ¹H-NMR.

Tribenzyl okadaic acid methyl ester (6). Okadaic acid (**1** 11 mg, 0.014 mmol) was converted into tribenzyl okadaic acid (**5**) with benzyl bromide (20 μl , 0.017 mmol), NaH (60% oil dispersion, 7 mg), THF (0.6 ml) and DMF (0.15 ml). The resulting tribenzyl okadaic acid was dissolved in MeOH (0.4 ml) without purification. To this solution was added a solution of CH_2N_2 at 0°C until TLC analysis showed the absence of the starting material.¹³ Concentration of the solvent followed by chromatographic purification on SiO_2 with ether-hexane (1:3 and 1:1) provided the tribenzyl okadaic acid methyl ester (**6** 7 mg, 48% yield). $[\alpha]_{\text{D}}^{25} = +43.8^{\circ}$ ($c = 0.36$, CHCl_3); ¹H-NMR δ : 0.88 (3H, d, $J = 7$), 0.91 (3H, d, $J = 7$), 1.07 (3H, d, $J = 7$), 1.36 (3H, s), 1.71 (3H, s), 3.2~3.27 (2H), 3.57~3.75 (5H), 3.70 (3H, s), 3.87~3.99 (3H), 4.24 (1H, d, $J = 8$), 4.47 (1H, d, $J = 12$), 4.55 (1H, q, $J = 7$), 4.55~4.61 (2H), 4.74~4.84 (4H), 5.02 (1H, br. s), 5.15 (1H, br. s), 5.41 (1H, t, $J = 1$), 5.56 (1H, dd, $J = 15$, 7), 5.73 (1H, dd, $J = 15$, 8), 7.1~7.5 (15H). All the other signals were left unresolved between 1.25~2.40 ppm.

Tribenzyl diol (7). A solution of tribenzyl okadaic acid methyl ester (**5**) (21 mg, 0.020 mmol) dissolved in THF (1.5 ml) was cooled to -78°C in an N_2 atmosphere, and then LiAlH_4 in THF (1.2 M solution, 0.1 ml, 0.12 mmol) was added dropwise. After stirring at -78°C for 10 min, the reaction mixture was gradually warmed up to 0°C , before water (1 drop), 15% aq. NaOH (1 drop) and hexane (1 ml) were added in this sequence. The solution was filtered and the filtrate cake was washed with EtOAc. Evaporation of the filtrate gave an oil (20 mg), which was successively purified by chromatography on SiO_2 with ether-hexane (2:1) as the eluant to provide the tribenzyl diol (**7**) (12 mg, 60% yield). $[\alpha]_{\text{D}}^{25} = +34.1^{\circ}$ ($c = 0.29$, CHCl_3); ¹H-NMR δ : 0.87 (3H, d, $J = 7$), 0.90 (3H, d, $J = 6$), 1.04 (1H, d, $J = 7$), 1.13 (3H, s), 1.73 (3H, s), 2.47

(1H, qt, $J = 7$, 7), 3.22 (1H, dd, $J = 10$, 2), 3.24 (1H, dd, $J = 12$, 4), 3.38~3.5 (3H), 3.52 (1H, ddd, $J = 11$, 9, 3), 3.58~3.7 (5H), 3.88~3.93 (2H), 4.10 (1H, tt, $J = 11$, 2), 4.23 (1H, d, $J = 8$), 4.47 (1H, d, $J = 13$), 4.55 (1H, d, $J = 11$), 4.58 (1H), 4.61 (1H, d, $J = 13$), 4.72 (1H, d, $J = 11$), 4.73 (1H, d, $J = 13$), 4.82 (1H, d, $J = 13$), 5.02 (1H, br. s), 5.14 (1H, br. s), 5.40 (1H, t, $J = 2$), 5.60 (1H, dd, $J = 16.7$), 5.85 (1H, dd, $J = 16$, 7), 7.2~7.4 (15H).

Tribenzyl acetonide (4) from 7. To a solution of the diol (**7** 2 mg) and PPTS (ca. 2 mg) in a mixture of $\text{Me}_2\text{C}=\text{O}$ (0.1 ml) and CH_2Cl_2 (0.3 ml) was added $\text{Me}_2\text{C}(\text{OMe})_2$ (500 μl) dropwise. After stirring at room temperature for two hours, the solution was poured into aq. NaHCO_3 , and the aqueous layer was extracted with ether. The combined organic layer was washed with water and saturated aq. NaCl, and dried over Na_2SO_4 . Evaporation of the solvent gave the tribenzyl acetonide (**4**, 2 mg, quantitatively). $[\alpha]_{\text{D}}^{25} = +35.6^{\circ}$ ($c = 0.20$, CHCl_3); ¹H-NMR (measured in C_6D_6) δ : 1.00 (3H, d, $J = 7$), 1.02 (3H, d, $J = 7$), 1.13 (3H, d, $J = 7$), 1.43 (3H, s), 1.49 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 3.27 (1H, dd, $J = 12$, 4, H-7), 3.41 (1H, dd, $J = 10$, 2, H-30), 3.61 (1H, dd, $J = 11$, 4, H-38), 3.68 (1H, ddd, $J = 11$, 7, 3, H-4), 3.76 (1H, ddd, $J = 13$, 11, 3, H-38), 3.86 (1H, d, $J = 9$, H-1), 3.88 (1H, H-22), 4.01 (1H, ddd, $J = 10$, 8, 2, H-27), 4.05 (1H, t, $J = 10$, H-23), 4.11 (1H, d, $J = 9$, H-1), 4.1 (1H, H-12), 4.21 (1H, d, $J = 10$, H-24), 4.36 (1H, d, $J = 13$), 4.41 (1H, d, $J = 8$, H-26), 4.49 (1H, d, $J = 13$), 4.56 (1H, d, $J = 11$), 4.73 (1H, q, $J = 7$, H-16), 4.84 (1H, d, $J = 11$), 4.86 (1H, d, $J = 13$), 4.95 (1H, d, $J = 13$), 5.01 (1H, br. s, H-41), 5.30 (1H, br. s, H-9), 5.64 (1H, dd, $J = 16$, 7, H-15), 5.69 (1H, t, $J = 2$, H-41), 5.95 (1H, dd, $J = 16$, 8, H-14), 7.1~7.5 (15H). All the other signals were left unresolved between 1.2~2.4 ppm.

Okadaic acid methyl ester (8). To a solution of okadaic acid (**1**) (10 mg) dissolved in MeOH (1 ml) that had been cooled to 0°C was added CH_2N_2 (ether solution) dropwise until TLC analysis showed the absence of the starting material. The cooling bath was removed, and evaporation of the solvent provided the okadaic acid methyl ester (**8**, 10 mg). This ester was used for subsequent reaction without further purification: $[\alpha]_{\text{D}}^{25} = +27.2^{\circ}$ ($c = 0.10$, CHCl_3); ¹H-NMR δ : 0.93 (3H, d, $J = 7$), 1.03 (3H, d, $J = 7$), 1.07 (3H, d, $J = 7$), 1.36 (3H, s), 1.73 (3H, s), 3.29 (1H, dd, $J = 10$, 2), 3.42 (1H, t, $J = 9$), 3.35~3.65 (4H), 3.67 (1H, td, $J = 11$, 3), 3.82 (3H, s), 3.95 (1H, d, $J = 9$), 3.95 (1H, br. t, $J = 11$), 4.09 (1H, t, $J = 10$), 4.1~4.15 (1H), 4.48 (1H, td, $J = 8$, 7), 4.95 (1H, s), 5.07 (1H, br. s), 5.33 (1H, q, $J = 1$), 5.41 (1H, t, $J = 1$), 5.47~5.57 (2H).

7,24,27-Triol-1,2-acetonide (9). To a solution of okadaic acid methyl ester (**5**, 10 mg) dissolved in THF (1 ml) that had been cooled to -78°C in an N_2 atmosphere was added a solution of LiAlH_4 in THF (1.2 M solution, 0.30 ml, 0.36 mmol) dropwise. The reaction mixture was gradually warmed up to 0°C , and then water (2 drops),

15% aq. NaOH (2 drops) and hexane (0.7 ml) were added in this sequence. After stirring for 2 hr at room temperature, Na₂SO₄ was added. The solution was filtered, and the filtrate cake was washed with EtOAc. The combined filtrate was concentrated under reduced pressure to afford the corresponding pentaol (10 mg) as an oil. This pentaol was dissolved in Me₂C=O (2 ml), and Me₂C(OMe)₂ (0.3 ml) and PPTS (2 crystals) were added. The reaction mixture was stirred at room temperature for 2 hr, and then poured into saturated aq. NaHCO₃. The aqueous layer was extracted with CH₂Cl₂, and the combined organic layer was dried over Na₂SO₄. Evaporation of the solvent under reduced pressure gave the acetone triol (**9**, 9 mg), which was used for subsequent reactions without further purification: $[\alpha]_D^{25} = +5.3^\circ$ ($c = 0.076$, CHCl₃); ¹H-NMR δ : 0.93 (3H, d, $J = 7$), 1.06 (3H, d, $J = 7$), 1.09 (3H, d, $J = 7$), 1.29 (3H, s), 1.33 (3H, s), 1.39 (3H, s), 1.75 (3H, s), 3.29 (1H, dd, $J = 10, 2$), 3.39 (1H, dd, $J = 11, 4$), 3.46 (1H, t, $J = 10$), 3.53~3.61 (2H), 3.62~3.70 (2H), 3.69 (1H, d, $J = 9$), 3.84 (1H, d, $J = 9$), 3.8~3.85 (1H), 3.94 (1H, d, $J = 10$), 4.08 (1H, br. t, $J = 10$), 4.16 (1H, br. d, $J = 10$), 4.48 (1H, q, $J = 7$), 5.08 (1H, br. s), 5.31 (1H, br. s), 5.41 (1H, t, $J = 1$), 5.52 (1H, dd, $J = 16, 7$), 5.75 (1H, dd, $J = 16, 8$).

Tribenzyl acetone triol (4) from 9. To a suspension of NaH (5 mg, washed with hexane before use) in THF (0.7 ml) was added a solution of acetone triol (**9**) in THF (0.2 ml) dropwise. After stirring at room temperature for 30 min, BnBr (20 μ l) and DMF (0.2 ml) were added, and stirring was continued for 30 hr. The reaction mixture was poured into water and the separated aqueous layer was extracted with ether. The combined organic layer was washed with water and saturated aq. NaCl, and dried over Na₂SO₄. Evaporation of the solvent gave an oil, which was successively purified by chromatography on silica gel (**4**) with ether-hexane (1:2) as the eluant to provide tribenzyl acetone triol (**4**, 9 mg) in a 66% overall yield starting from okadaic acid (4 steps).

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