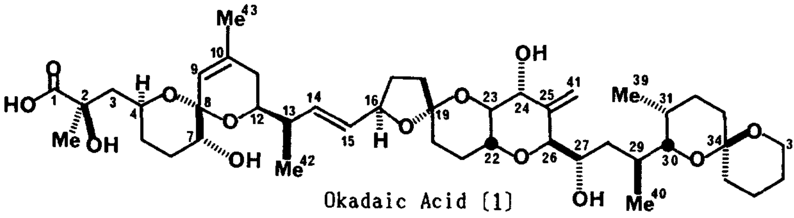
Tetrahedron Letters, Vol.27, No.8, pp 963-966, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain ©1986 Pergamon Press Ltd.

SYNTHETIC STUDIES TOWARD MARINE TOXIC POLYETHERS [5]
THE TOTAL SYNTHESIS OF OKADAIC ACID

Minoru Isobe,* Yoshiyasu Ichikawa and Toshio Goto
Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University
Chikusa, Nagoya 464, JAPAN

Abstract: The total synthesis of okadaic acid has been accomplished through the coupling of all the segments, A, B and C, by means of sulfone-carbanion strategy.

The synthetic studies toward okadaic acid (1)[1] have recently been accumulated to afford the three necessary segments, A, B and C, which were prepared from D-glucose derivatives.[2a-d] The coupling is principally based on the strategy utilizing sulfonyl-carbanion as key reactions. The high acyclic stereoselectivity is attributed to a successful development of switching the syn/anti-diastereoselectivity in the heteroconjugate addition.[2,3] In this paper we describe the first total synthesis of okadaic acid.

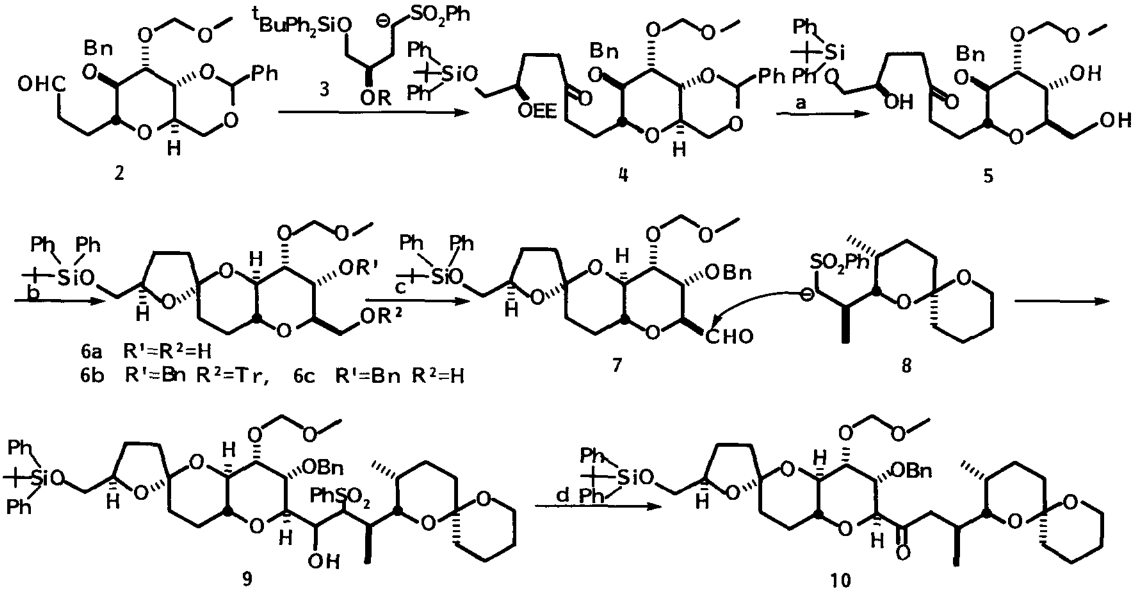


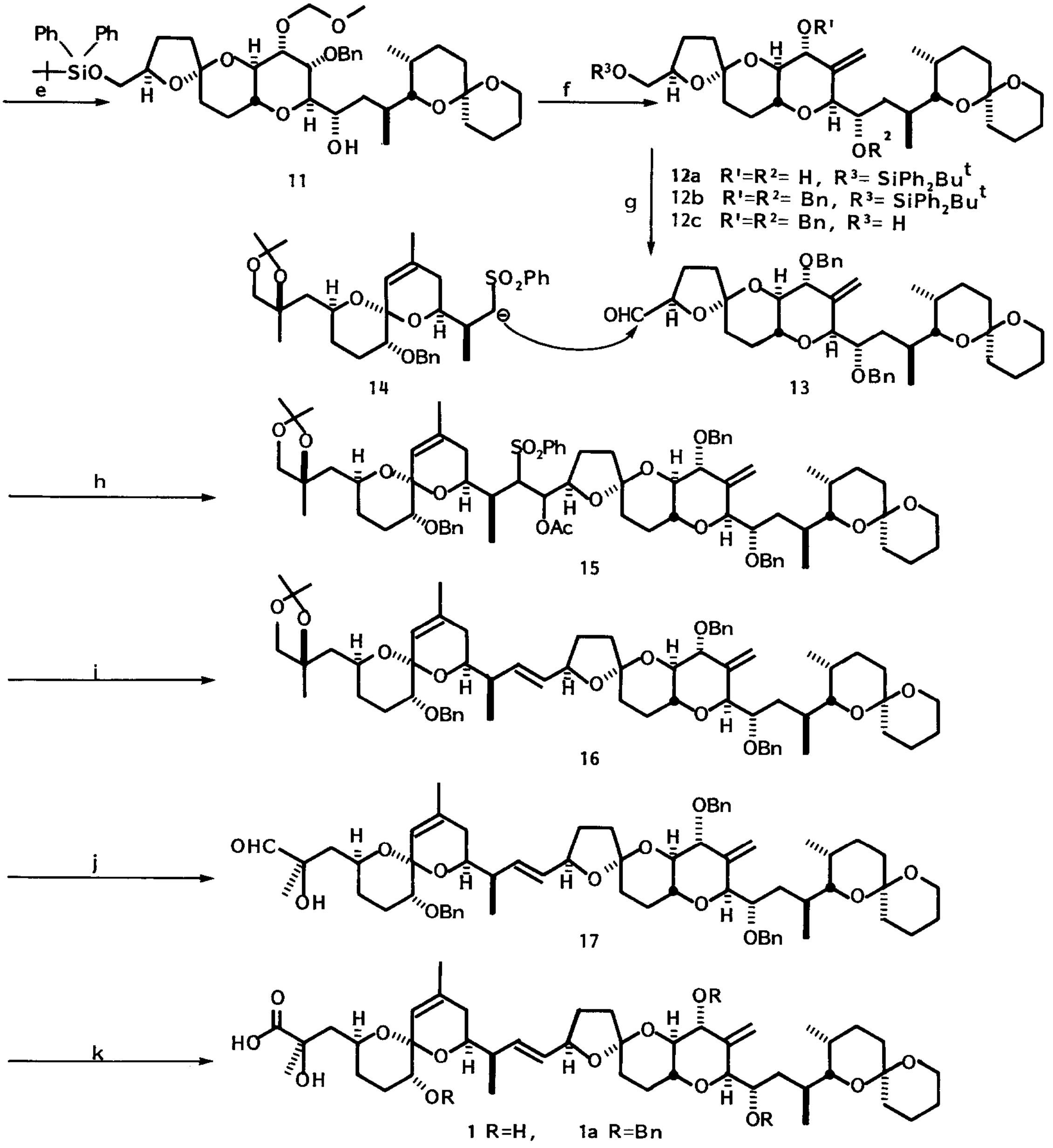
Okadaic Acid [1]

For complete synthesis of segment B 7 (from C-15 to C-27), an additional carbon chain involving one asymmetric center should be added to the previously reported intermediate 2^{2b}; thus, the additional fragment was prepared from R-butan-1,2,4-triol[2d] which was converted into R-1-(benzensulfonyl)-butane-3,4-diol [mp 92°C $[\alpha]_D$ +13.1° (c= 1.04)], and further into the silyl ether 3 [R=H], $[\alpha]_D$ +13.7° (c= 1.51). Introduction of the sulfone-carbanion of 3 [R=CH(Me)OEt] into the previously prepared aldehyde 2^{2b} gave the adduct, which was oxidized by Swern condition and then reduced with Al-Hg into 4. It was further converted into **6a** via the same sequences as were reported.[2b] Selective tritylation was followed by benzylation to produce 6b $[\alpha]_D$ -4.4° (c= 1.68) in 40% overall yield from 2. Trityl group in 6b was quantitatively hydrolyzed with Et_2AlCl^{4a} into the corresponding alcohol 6c $[\alpha]_D$ -8.7° (c= 1.45) in

99% yield. It was oxidized by (Swern) into the aldehyde 7, which was treated with the sulfone-carbanion 8 of the segment C, generated with n-BuLi in a mixture of Et_2O and n-hexane (1:1). The coupled product 9 (in 92% yield) was converted with CrO_3-2Py and Al-Hg to the ketone 10 $[\alpha]_D$ +9.7° (c= 1.15), which was reduced with $NaBH_4$ into the alcohol 11 $[\alpha]_D$ +15.1° (c= 2.15) (57% yield).[5] Tetrahydropyranylation and subsequent de-benzylation[4b] of the hydroxyl groups (78% yield) were followed by Swern oxidation and Wittig olefination (69% yield) and then by hydrolysis with Me_3SiBr[4c] (72% yield) to afford the en-diol 12a $[\alpha]_D$ +15.9° (c= 1.29), which was finally protected as the corresponding di-benzylether 12b $[\alpha]_D$ +29.3° (c= 1.64); ^1H nmr δ 4.17(H-27 t J=10), 4.27(H-24 d J=10), 4.95(H-41 s), 5.65(H-41 t J= 1) in 50% yield. The t-butyldiphenylsilyl group in 12b was hydrolyzed with $n-Bu_4NF$ in $THF-CH_3CN$ (1:1) (96% yield) to give the alcohol 12c $[\alpha]_D$ +33.5° (c= 1.73); ^1H nmr δ 0.88(3H d J=7), 0.93(3H d J=6), 1.3-2.2(24H), 3.24(H-30 dd J=10, 2), 3.45-3.82(6H), 3.89-4.01(H-22, 27), 4.20-4.33(H-16, 26), 4.55-4.86(4H), 5.05(1H s), 5.43(1H t J=1); ir ($CHCl_3$) 3480 cm^{-1}.

The alcohol 12c was subjected to Swern oxidation to afford the aldehyde 13 (δ 9.71 d J=2) in 81% yield. On the other hand, the sulfone-carbanion 14[2d] was generated with t-BuLi in THF and hexane (1:1) at -78°C for 15 min and it was mixed with the aldehyde 13 at -78°C for 2 hr[6] to afford the adduct 15 as a diastereomeric mixture, which was further acetylated (Ac_2O/Py) and then reduced with Na-Hg. The product was isolated and purified with a silica gel tlc to afford in 32% yield (in 3 steps) the trans-olefin 16; $[\alpha]_D$ +31.5° (c= 0.20); ^1H nmr δ Me's at 0.88(d), 0.92(d), 1.06(d), 1.26(s), 1.30(s), 1.37(s), 1.73(s), the trans-olefins at 5.54(H-14 dd J= 15.8, 7), 5.81(H-15 dd J=15.8, 7.5).[7] At this stage, the authentic sample was prepared for comparison from natural okadaic acid (1). It was converted in 4 steps [overall yield 66%; i) diazomethane in MeOH, ii) $LiAlH_4$, iii) $Me_2C(OMe)_2$, iv) $PhCH_2Br$/NaH] into the corresponding





a) H_3O^+; b) Pd-C/H_2, TrCl, $PhCH_2Br$/NaH, Et_2AlCl; c) $(COCl)_2$/DMSO; d) CrO_3-2Py, Al-Hg; e) $NaBH_4$, DHP/PPTS, $Pd(OH)_2$-C/H_2, $(COCl)_2$/DMSO; f) $Ph_3P{=}CH_2$/THF, Me_3SiBr, $PhCH_2Br$, n-Bu_4NF; g) $(COCl)_2$/DMSO; h) Ac_2O/Py; i) Na-Hg; j) H_3O^+, SO_3-Py; k) $NaClO_2$/t-BuOH, Li/NH_3.

tri-benzylether-acetonide **16**; $[\alpha]_D$ +35.6° (c= 0.20). Synthetic **16** was identical to this authentic sample in 500 MHz ^{1}Hnmr both in $CDCl_3$ and in C_6D_6.[7] The acetonide of **16** was hydrolyzed with a mixture of AcOH-THF-H_2O (1:2:1) at 55°C for 1 day into the corresponding diol which was oxidized[8] first with SO_3-Py into **17** and then with $NaClO_2$ at rt for 1 hr in aq t-BuOH (containing NaH_2PO_4 and 2-methyl-2-butene)[9] into the carboxylic acid **1a** in 52% yield. The product was treated with lithium metal in liquid ammonia[10] to afford **1** in 80% yield. ^{1}H Nmr spectra of **1** and its methyl ester **1b** (obtained by diazomethane in MeOH) were identical to the corresponding authentic okadaic acid and its methyl ester. We have concluded the total synthesis of okadaic acid in 28 steps from **2**.

Acknowledgements The authors are indebted to Professors D. Uemura, Y. Hirata, and P. Scheuer and Dr. Tsukitani for their kind furnishing natural okadaic acid and to Dr. T. Kondo for measurement of the 500 MHz ^{1}H nmr spectra. Thanks are due to Foundation for the Promotion of Research on Medicinal Resources, to Ishida Foundation, and to Grant-in-aid for Scientific Research from Ministry of Education, Science and Culture for financial support.

References and Notes

1. a) K. Tachibana, P.J. Scheuer, Y. Tsukitani, H. Kikuchi, D.V. Engen, J. Clardy, Y. Gopichand, F. Schmitz; J. Am. Chem. Soc., 103, 2469 (1981): b) M. Murata, M. Shimatani, H. Sugitani, Y. Oshima, T. Yasumoto; Bull. Japan. Soc. Sci. Fish., 48, 549 (1982).
2. a) M. Isobe, Y. Ichikawa, H. Masaki, T. Goto; Tetrahedron Lett., 25, 3607 (1984): b) Y. Ichikawa, M. Isobe, T. Goto; ibid., 25, 5049 (1984): c) M. Isobe, Y. Ichikawa, D. Bai, T. Goto; ibid., 26, 5199 (1985): d) M. Isobe, Y. Ichikawa, T. Goto; ibid., 26, 5203 (1985).
3. M. Isobe, Y. Ichikawa, Y. Funabashi, S. Mio, T. Goto; Tetrahedron 41, 0000 (1985).
4. a) H. Koster and N.D. Sinha; Tetrahedron Lett., 23, 2641 (1982): b) W.M. Pearlman; ibid., 1663 (1967): c) S. Hanessian, D. Delorme, Y. Dufresne; ibid., 25, 2515 (1984).
5. For stereochemistry of the alcohol 11, see Ref #2b; ^{1}H nmr of 11 δ 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), 3.30-3.80(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).
6. Addition of excess base caused a decomposition of the sulfone-carbanion with a fragmentation; no such side reaction was monitored by tlc under this condition. The coupling reaction was so slow that the starting materials were recovered in ca. 70% which were substracted in the yield calculation and also were used again.
7. Few overlap of the proton signals were observed 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(H-7 dd J=12, 4), 3.41(H-30 dd J=10, 2), 3.61(H-38eq dd J=11, 4), 3.68(H-4 ddd J=11, 7, 3), 3.76(H-38ax ddd J=13, 11, 3), 3.86(H-1 d J=9), ca.3.88(H-22), 4.01(H-27 ddd J=10, 8, 2), 4.05(H-23 t J=10), 4.11(H-1 d J=9), ca.4.1(H-12), 4.21(H-24 d J=10), 4.36(PhCH d J=13), 4.41(H-26 d J=8), 4.49(PhCH d J=13), 4.56(PhCH d J=11), 4.73(H-16 q J=7), 4.84(PhCH d J=11), 4.86(PhCH d J=13), 4.95(PhCH d J=13), 5.01(H-41 s), 5.30(H-9 s), 5.64(H-15 dd J=16, 7), 5.69(H-41 t J=2), 5.95(H-14 dd J=16, 8), 7.1-7.5(15-Ar-H's).
8. The first example of oxy-aldehyde into oxy-carboxylic acid without the C_1-C_2 bond cleavage, which was not avoidable under other condition to give the corresponding methyl ketone [^{1}H nmr at 2.17 ppm studied on a model compound]. E.J. Corey and C.U. Kim reported an oxidation of oxy-ketone without the cleavage; Tetrahedron Lett., 287 (1974).
9. a) G.A. Kraus and M.J. Taschner, J. Org. Chem., 45, 1175 (1980); b) G.A. Kraus and B. Roth, ibid, 45, 4825 (1980); c) B.S. Bal, W.E. Childers, Jr. and H.W. Pinnick, Tetrahedron, 37, 2091 (1981); d) B.O. Lindgren, T. Nilsson, Acta Chem. Scand. 27, 888 (1973).
10. Utilization of excess metal (Li) or no proton source (EtOH) caused a possible hydrogenolysis of the allyl ether (C-16), which was confirmed by the disappearance of H-16 [appearing at 4.48(q J=7)].

All the nmr spectral data were taken in $CDCl_3$ and in 200 MHz with TMS as the internal standard unless otherwise specified. Optical rotations were measured in $CHCl_3$.

(Received in Japan 19 December 1985)