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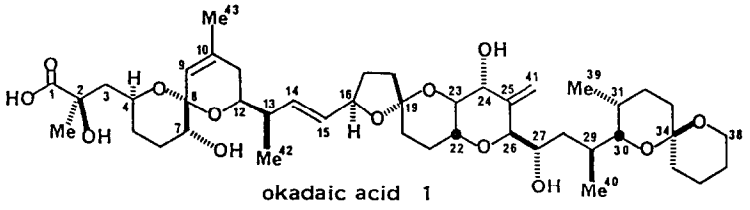
SYNTHETIC STUDIES TOWARD MARINE TOXIC POLYETHERS [3] STEREOCONTROL FOR SEGMENT-A_1 OF OKADAIC ACID BY MEANS OF OXYMERCURATION AND EPOXYDATION

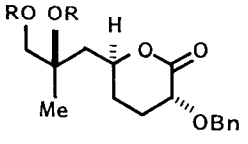
Minoru Isobe,* Yoshiyasu Ichikawa and Toshio Goto
Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University
Chikusa, Nagoya 464, JAPAN

Abstract: Segment-A_1 of okadaic acid was synthesized from glucose via an acyclic stereocontrol for C-2 by means of oxymercuration. The stereochemistry was proven by comparison with S and R epoxides which were synthesized selectively by chelational and stereoelectronic effects, respectively.

Efforts for the total synthesis toward okadaic acid 1[1] have recently led us to obtain the segment-B/C of 1.[2] The continuous studies recently awarded us a success in the synthesis of segment-A which has the carbon chains of C-1 through C-14 containing six asymmetric centers. This segment was prepared by the coupling of segment-A_1 (in the form of 2 or 3) and segment-A_2 4. In this paper are described the syntheses of segment-A_1. The carbons corresponding to C-3 through C-8 were derived from a D-glucose derivative as the chiral starting substance. The crucial acyclic asymmetric induction at C-2 from C-4 was achieved by oxymercuration and the stereochemistry was confirmed through an epoxidation.



okadaic acid 1



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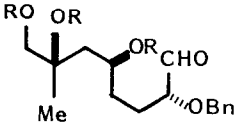

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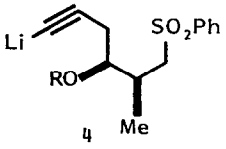

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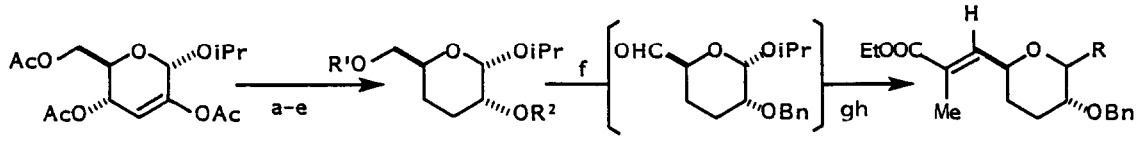
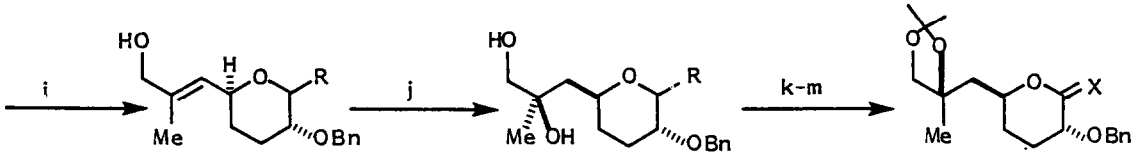
The unsaturated sugar **5**, the common starting substance for the segment-C, was prepared from D-glucose as shelf-stockable crystals (mp 61°C).[2a] Treatment of **5** with $LiAlH_4$ in THF at rt and then with H_2/Pd-C(10%) in AcOEt gave the diol **6a** (96% yield in two steps), which was selectively benzylated to **6c** in 81% yield by the following three successive treatments: 1) TBDMSCl/imidazole in DMF (**6b**), 2) benzyl bromide/NaH in a mixture of DMF and THF and then 3) n-Bu_4NF in a mixture of CH_3CN and THF (1:2) at 60°C for 12 hr. The alcohol **6c** {$[\alpha]_D$ +104.7° (c= 1.49); ^{1}H nmr δ 1.21(3H d, J= 6), 1.27(3H d, J= 6), 4.58(2H AB), 4.96(1H d, J= 3)} was oxidized by oxalyl chloride, DMSO and Et_3N in CH_2Cl_2 into the corresponding aldehyde **7**, to which was further added (in one-pot without isolating **7**) with triphenyl-ethoxycarbonylethyl-phosphorane in CH_2Cl_2 at -20°C to rt to give the unsaturated ester **8** {$[\alpha]_D$ +78.9° (c= 1.64); ^{1}H nmr δ 1.21(3H d, J= 6), 1.27(3H t, J= 7), 1.28(3H d, J= 6), 1.88(3H d, J= 1), 3.50(1H ddd, J= 11, 5, 3), 3.95(1H septet, J= 6), 4.17(2H q, J= 7), 4.96(1H d, J= 3), 6.60(1H ddd, J= 8, 2, 1)} in 83% overall yield, the geometry being pure E. A trans-glycosylation of **8** with 2-chloroethanol by heating at 50°C for 5 hr in the presence of camphorsulfonic acid gave a mixture of alpha and beta 2-chloroethyl glycosides **9a** and **9b** in 6:4 ratio in 76%. The mixture was reduced with DIBAL-H in CH_2Cl_2 at -78°C for 1 hr to the E-tri-substituted olefin **10a** and **10b**,[3] and then subjected to oxymercuration [$Hg(OAc)_2$ in a mixture of THF and H_2O (5:1) at -10 to 0°C for 2 days, and then with $NaBH_4$] to give **11a** [^{1}H nmr δ1.17(3H s)(2-epimer1.21), 4.82(1H d, J= 3), 5.35(1H d, J= 8)] and **11b** [^{1}H nmr δ1.18(3H s)(2-epimer 1.21), 4.38(1H d, J=8), 5.45(1H d, J= 8)] as largely single isomers (in 81% yield and in ca. 90% diastereopurity) at the C-2 position.[3] The mixture of the diol **11a** and **11b** was first protected as its acetonide [2,2-dimethoxypropane and PPTS in CH_2Cl_2] and then heated with $NaSO_2Ph$ and KI in DMF at 105°C for 5 hr to afford the hemiacetal (**12a,b**).[4] The hemiacetal was oxidized with bromine in DMF containing acetate buffer (pH 5.6) at 0°C for 5 min to produce in 70% overall yield from **11** the lactone **12c**, {$[\alpha]_D$ +87.3° (c= 1.04), ^{1}H nmr δ 1.35(6H s), 1.39(3H s), 1.6-2.2(6H), 3.76-3.88(2H AB), 3.95(1H m), 4.63-4.92(2H AB), 4.72(1H m), 7.3-7.4(5H)}.

The transition state in the above oxymercuration may be illustrated as shown in Fig. 1 to have Hg^{++} in a chelation face, since a slow reaction velocity was observed with the protected OH system. The stereochemistry of **12c** was shown to be 2R by comparing it with the authentic 2R and 2S compounds which were separately prepared via 2,3-epoxides **15** and **16**. In an epoxidation of the allylic alcohol **14a**, {$[\alpha]_D$ +129.7° (c= 0.86), ^{1}H nmr δ 1.69(3H s), 4.79(2H AB), 5.29(1H ddd, J= 11, 9, 3), 5.50(1H ddd, J= 9, 3, 1)}, we found an interesting acyclic stereoelectronic effect in the lactone **14a** which showed opposite selectivity to the case effected by chelation control. The results are summarized in Table 1. The transition state might have such a conformation as **13**. The isopropyl derivative **14b** showed rather conceivable asymmetric induction based on the chelation effect; thus, MCPBA afforded S-dominant epoxides (**15b<16b**),[5] but all the Ti(IV) mediated oxidations[6] afforded R-dominant epoxides (**15b>16b**). On the other hand, the lactone **14a** produced R-dominant epoxide **15a** with MCPBA.[7] The less chelational effect and the more electronic effect in the lactone **14a** afforded the more enantioselective epoxidation under the Sharpless's condition[6], particularly L-(+)-DET showed exclusive selectivity to give **15a** {$[\alpha]_D$ +85.7° (c= 1.22), ^{1}H nmrδ1.37(3H s), 3.09(epoxidic H d, J= 8), 4.01(1H dd, J= 8,



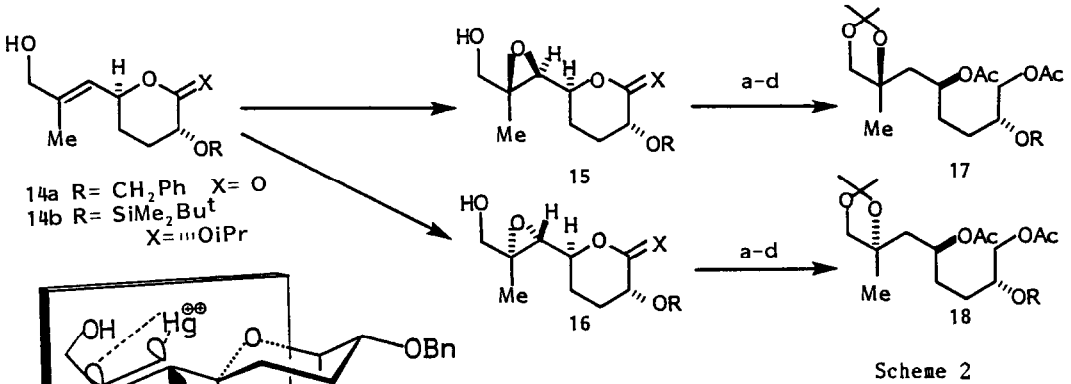
5 6a R¹=R²= H 6b R¹= $SiMe_2Bu^t$ R²= H 6c R¹= H, R²= CH_2Ph 7 8 R=OiPr 9a R=OCH_2CH_2Cl 9b R=OCH_2CH_2Cl



10a R=OCH_2CH_2Cl 10b R=OCH_2CH_2Cl 11a R=OCH_2CH_2Cl 11b R=OCH_2CH_2Cl 12a X= 12b X= 12c X= O

Scheme 1

a) $LiAlH_4$, b) H_2/Pd-C, c) t-$BuMe_2SiCl$, d) $PhCH_2Br$, e) n-Bu_4NF, f) $(COCl)_2$/DMSO/Et_3N, g) Ph_3P=CMeCOOEt, h) $HOCH_2CH_2Cl/H^+$, i) DIBAL-H, j) $Hg(OAc)_2$, $NaBH_4$, k) $Me_2C(OMe)_2/H^+$, l) $PhSO_2Na$, m) Br_2/NaOAc.



14a R= CH_2Ph X= O 14b R= $SiMe_2Bu^t$ X=OiPr 15 16 17 18

Scheme 2

a) DHP/H^+, b) $LiAlH_4$, c) Ac_2O, d) MeOH/$Me_2C(OMe)_2/H^+$

Fig 1

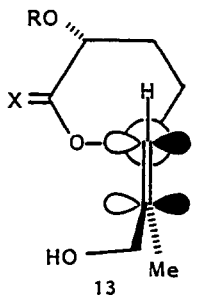


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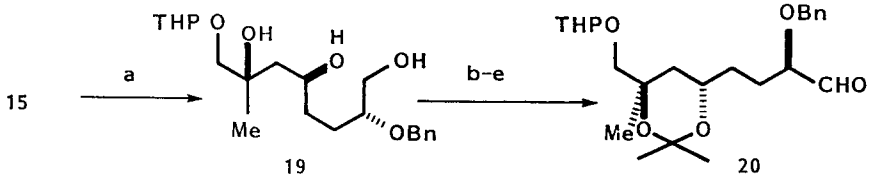
Table 1 Ratio of the epoxides 15 : 16

		14a X=O, R=CH_2 Ph	14b X=H/OiPr, R=$SiMe_2$ Bu^t
1	MCPBA	2 : 1	1 : 5.2
2	TBHP ±	2 : 1	2 : 1
3	TBHP-D	1 : 5.5	1.5 : 1
4	TBHP+L	> 25 : 1	5.2 : 1

TBHP ±, -D and +L indicate Ti(OiPr)₄ with no tartrate, with (D)-DET and with (L)-DET, respectively.

6), 4.36(1H ddd, J= 11, 8, 3), 4.77(2H, AB centered)}, while **16a** showed {[α]$_D$ +118.0° (c= 0.99), ^{1}H nmr δ 1.32(3H s), 3.20(1H d, J= 8), 4.02(1H dd, J= 7, 6), 4.52(1H ddd, J= 11, 8, 4), 4.75(2H, ABq, centered). The stereochemistry of **12c** was confirmed by leading each R- and S-epoxylactone **15a** and **16a** into the diacetylacetonides **17a** [^{1}H nmr δ 1.26(3H s), 1.35(3H s), 1.39(3H s), 2.03(3H s), 2.07(3H s), 3.57(1H m), 3.71(2H ABq), 4.13(2H ABq), 4.58(2H ABq), 5.03(1H m)} and **18a** [^{1}H nmr δ 1.28(3H s), 1.37(3Hx2 s), 2.02(3H s), 2.07(3H s), 3.57(1H m), 3.78(2H ABq), 4.13(2H ABq), 4.58(2H ABq), 5.06(1H m)] in 4 steps. The R-isomer **17a** was identical to the one derived from the oxymercuration product **12c** [via 1) $LiAlH_4$, 2) Ac_2O/Py]. It concluded the R-configuration of C-2 in **11**, and **12**.



Scheme 3

a) dihydropyran/H$^+$, $LiAlH_4$, b) ^{t}BuMe$_2$SiCl/imidazole, c) MeC(OMe)=CH$_2$, d) n-Bu$_4$NF, e) Swern oxidation

Alternatively, the epoxide **15** was first converted into the segment-A via the above open chain intermediates **19** and **20**. Both of the aldehyde **20** and the lactone **12c** are to be used as the segment-A$_1$ **2** and **3** for the synthesis of segment-A for okadaic acid (**1**).

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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) Yoshiyasu Ichikawa, Minoru Isobe, T. Goto; ibid., 25, 5049 (1984).

3. The alpha and beta glycosidic isomers (**10a** and **10b**) were partly separated for an analytical purpose to show [α]$_D$ +66.7° (c= 1.18) ^{1}H nmr δ 1.69(3H s), 3.49(1H ddd, J= 11, 4, 3), 4.84(1H d, J= 3), 5.35(1H d, J= 8); and [α]$_D$ -0.70° (c= 1.13), δ 1.68(3H s), 4.42(1H d, J= 8), 5.45(1H d, J= 8), respectively. The diastereopurity (88% and 91%) in the oxymercuration to **10a** and **10b** was checked as a purity of **11a** and **11b**, respectively, by means of 200 MHz ^{1}H-nmr and HPLC (Develosil 60-5).

4. This non-acidic hydrolysis of glycosides is a modification of the reported conditions: a) M. Isobe, M. Kitamura, T. Goto; J. Am. Chem. Soc., 104, 4997 (1982), b) M. Kitamura, M. Isobe, Y. Ichikawa, T. Goto; ibid, 106, 3252 (1984), c) idem, J. Org. Chem., 49, 3517 (1984).

5. Epoxidation of **14c** (R= CH_2Ph) gave the corresponding ratio of **15a**:**16a**= 1 : 3.5 to show the same tendency.

6. a) M. Isobe, M. Kitamura, S. Mio, T. Goto; Tetrahedron Lett., 23, 221 (1982); b) T. Katsuki, K.B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).

7. This may be consistent with the case in ally alcohol vs allyl acetate in cyclic case; see H.B. Henbest, R.A.L. Wilson, J. Chem. Soc., 1958 (1957).

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