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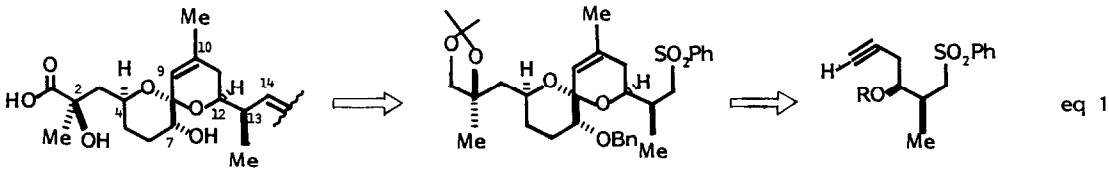
SYNTHETIC STUDIES TOWARD MARINE TOXIC POLYETHERS (4)
SYNTHESIS OF SEGMENT-A OF OKADAIC ACID VIA ANTI-SELECTIVITY BY HETEROCONJUGATE ADDITION[1]

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

Abstract: Segment-A of okadaic acid was synthesized in an optically active form by coupling the lithium acetylide (segment-A_2) and the previously prepared segment-A_1. The key step was the preparation of anti-diastereoisomer for C-12/13 asymmetric center by means of heteroconjugate addition involving Mitsunobu inversion of syn-isomer or direct formation of anti-isomer by beta-chelation effect.

Synthetic studies on okadaic acid (1) involves the syntheses of three segments A, B and C and their coupling.[2] In our previous paper, we have prepared segment-A_1 as a left half of segment-A 2 for okadaic acid in the form of the lactone 20 and the aldehyde 23.[1] The counter nucleophilic segment-A_2 to these synthetic intermediates should have the anti-configuration corresponding to 12S/13S with an additional geometric control for the Z-olefin at C-9/10 stereochemistry. Retrosynthetic analysis in eq. 1 led us to choose the acetylene 3 as the best candidate for this purpose. It was prepared via two independent routes shown in Scheme 1 and Scheme 2. The key reactions in these routes involve two different heteroconjugate addition for production of the anti-diasteroisomer.

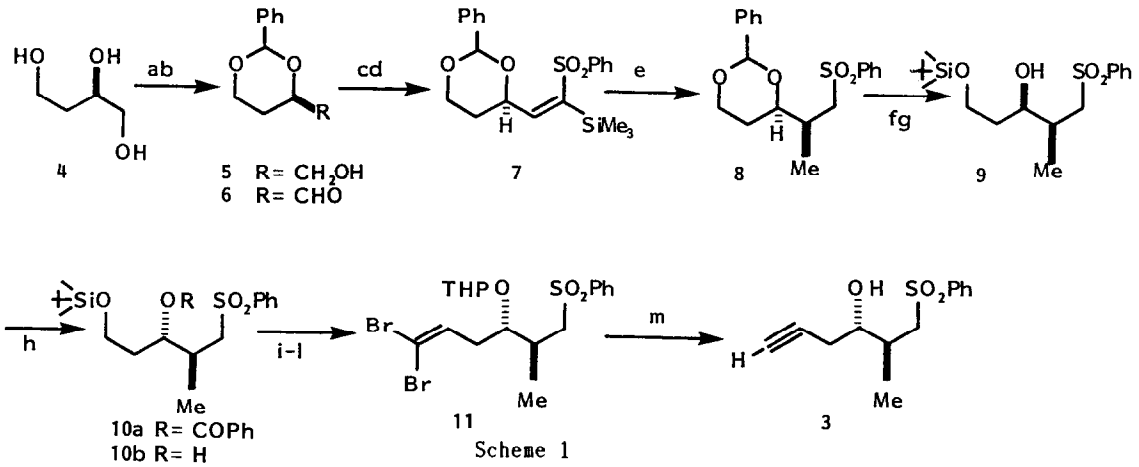


1 2 3 eq 1

The acyclic stereoselection in Scheme 1 involves first elaboration of the syn-diastereoisomer by the normal (alpha chelation) heteroconjugate addition, which was followed by inversion of configuration at the original asymmetric center (C-12) by Mitsunobu reaction.[3] The heteroolefin 7 was prepared by a Peterson olefination to the aldehyde 6, (prepared from 2-R-propanetriol[4] 4 via its benzylidene derivative 5), which was followed by MCPBA-oxidation to afford 7 [as a mixture of geometric isomer; ^{1}H nmr {Z-isomer δ 6.59(1H d, J=8)}; {E-iso-

mer δ7.26(1H d, J= 8)}. An addition of MeLi to 7 in THF at -78°C (work-up with KF) underwent non-stereospecifically to afford a mixture of the syn- and anti-diastereoisomer in a ratio of 2:1. When MeLi was added to 7 in a mixture of THF and hexane (1:3) solvent[5] at 0°C the ratio was improved to 10:1 to give the syn-adduct 8 [^{1}H nmr δ1.16(3H d, J= 7)]. After ejecting the benzylidene group with Pd-C under H_2 atmosphere, the primary OH was protected as TBDM-silyl ether 9 {[α]$_D$ -10.3° (c= 1.87); ^{1}H nmr δ1.06(3H d, J= 7), 2.96(1H dd, J= 14, 8), 3.42(1H dd, J= 14, 4); ^{13}C nmr δ14.1(Me)[6] }(29% yield from 4). Mitsunobu inversion of the alcohol 9 was carried out with diethylazodicarboxylate (DAD), Ph_3P and PhCOOH in THF at 5°C to produce the inverted benzoate 10a {[α]$_D$ -6.6° (c= 1.66); ^{1}H nmr δ-0.02(6H s), 0.84(9H s), 1.20(3H d, J= 7), 3.01(1H dd, J= 14, 9), 3.36(1H dd, J= 14, 2), 3.61(2H t, J= 6), 5.20(1H dt, J= 8, 5)}, which was further hydrolyzed with NaOMe in MeOH to give the anti-alcohol 10b (in 86% overall yield from 9) {[α]$_D$ +17.8° (c= 1.60); ^{1}H nmr δ1.15(3H d, J= 7), 2.91(1H dd, J= 14, 9), 3.57(1H dd, J= 14, 3); ^{13}C nmr δ17.0(Me)[6] }. After the secondary OH in 10b was protected as THP, the primary OH was deprotected with n-Bu_4NF and oxidized to the corresponding aldehyde, which was coupled with $Ph_3P{=}CBr_2$[7] to give 11 in 83% yield. Treatment of the dibromide with n-BuLi at -100°C gave in 58% yield the acetylene 3: {[α]$_D$ +28.3° (c= 1.49); ^{1}H nmr δ1.15(3H d, J= 7), 2.04(1H t, J= 2), 2.96(1H dd, J= 14, 7)}.

Alternatively, a direct anti-selection was achieved by means of a "beta-chelation effect"[8] (Fig. 1) in the heteroconjugate addition to 4-hydroxypyranosylheteroolefin 14. It was prepared from D-glucal[8] via 12 and the corresponding aldehyde 13 by Peterson olefination and MCPBA oxidation, as shown in Scheme 2. Addition of MeMgBr to 14 at -20°C and desilylation with KF gave the anti-adduct 15 [^{1}H nmr δ 1.13(3H d, J= 6), 1.18(6H dx2, J= 6), 2.92(1H ddd, J= 14, 7), 3.44(1H dd, J= 14, 3), 3.63(1H dd, J= 10, 2), 4.98(1H s), 5.63(1H dt, J= 10, 2), 5.93(1H d, J= 10)] in 80% yield; the selectivity being 91%.[8] The adduct was converted in



Scheme 1

a) PhCH(OMe)$_2$/H$^+$, b) SO_3-Py, c) PhSCLi(SiMe$_3$)$_2$, d) MCPBA, e) MeLi(THF:Hex=1:3, 0°C/KF), f) H_2/Pd-C, g) TBDMSCl, h) PhCOOH/Ph_3P/EtOOCN=NCOOEt, NaOMe, i) THP/H$^+$, j) n-Bu_4NF, k) (COCl)$_2$/DMSO/Et_3N, l) $Ph_3P{=}CBr_2$, m) n-BuLi/H$^+$

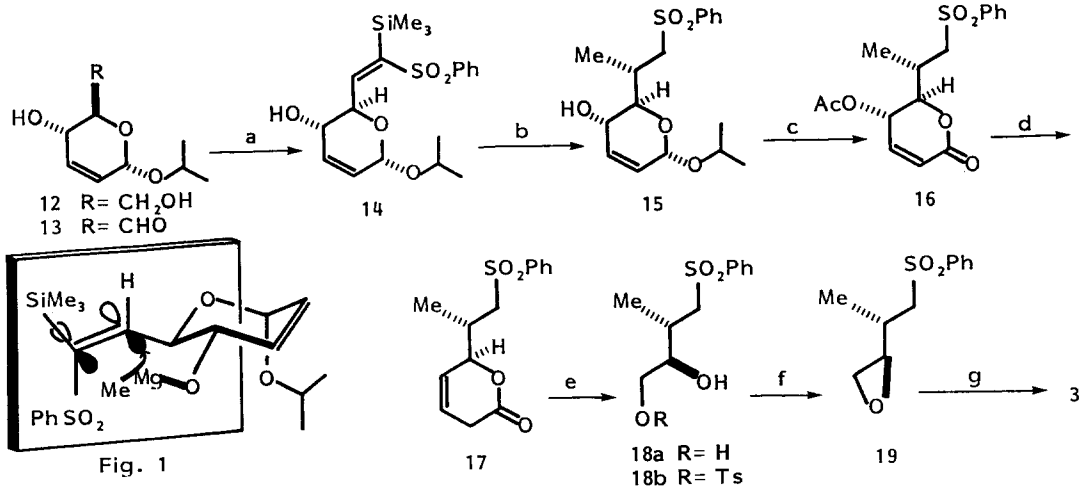
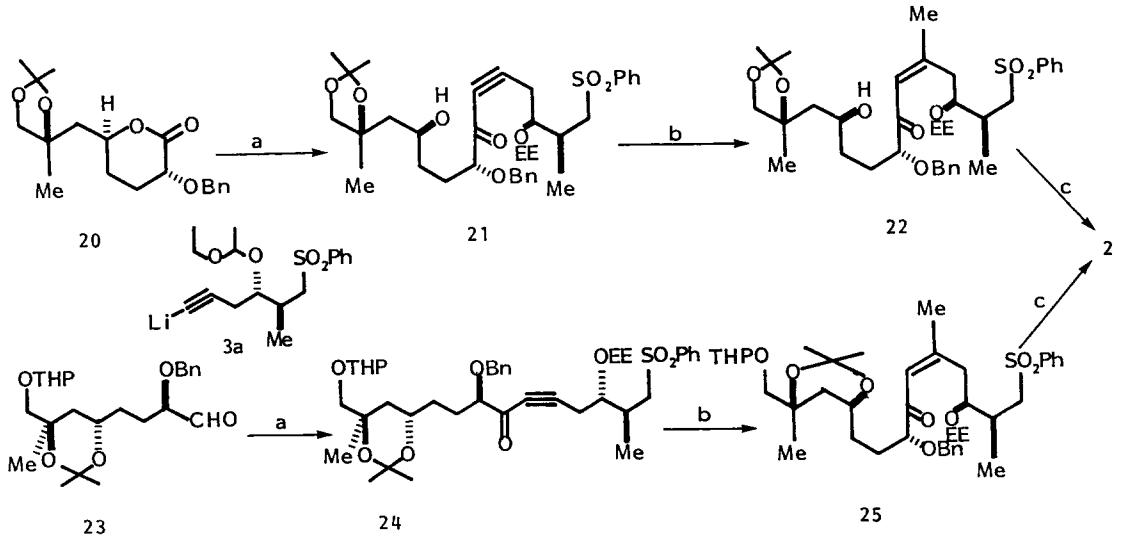


Fig. 1

Scheme 2

a) $PhSCLi(SiMe_3)_2$, MCPBA, H^+ b) MeMgBr 0°C/KF, c) Ac_2O/Py, H^+, PDC, d) Zn-Cu, e) O_3, $NaBH_4$, p-TsCl/Py, f) t-BuOK, g) $Me_3SiC{\equiv}CLi$, n-Bu_4NF



Scheme 3

a) in THF, b) Me_2CuLi, c) PPTS, $Me_2C(OMe)_2/H^+$

three steps [1) acetylation of the 4-OH, 2) hydrolysis of the isopropyl glycoside with heating in a mixture of AcOH and H_2O (7:3) at 40°C for 12 hr and 3) oxidation with PDC] into the lactone **16** (in 63% overall yield): ^{1}H nmr δ 1.36(3H d, J= 7), 2.13(3H s), 3.03(1H dd, J=14, 9), 3.39(1H dd, J= 14,3), 4.38(1H dd, J= 9, 4), 5.45(1H dt, J= 9, 2), 6.02(1H dd, J= 10, 2), 6.77(1H dd, J= 10). Reductive deconjugation of **16** with zinc-copper couple yielded the beta-gamma unsaturated lactone **17** [^{1}H nmr δ 1.25(3H d, J= 7), 3.21(1H dd, J= 14, 3), 4.97(1H brs)] in 64% yield. Ozonolysis of the olefin **17** was followed by the three successive treatments: 1) work-up with $NaBH_4$ [**18a**], 2) selective tosylation with p-TsCl/Py [**18b**, 41% overall yield] and then 3) epoxidation with t-BuOK to produce **19** (99%). Treatment of **19** with the lithium trimethylsilylacetylide in the presence of BF_3-Et_2O[9] at -78°C and then with n-Bu_4NF quantitatively yielded **3**.

The hydroxy group of **3** was protected as its ethoxyethylether and then activated with n-BuLi into the acetylide **3a**, which was added to segment-A_1 (**Scheme 3**). First the coupling with the lactone **20** afforded the adduct **21** (80% yield) existing largely in an open chain unsaturated ketone (ν 2200, 1675 cm^{-1}), which received the conjugate addition with Me_2CuLi to give Z-unsaturated ketone **22**.[10] Treatment of **22** with PPTS afforded the spiro-substances:[11] **2** {[α]$_D$ +11.4° (c= 1.16), ^{1}H nmr δ 1.23(3H s), 1.24(3H d, J= 7), 1.30(3H s), 1.37(3H, s), 1.70(3H s), 4.46(2H AB), 5.14(1H s)} in 30% yield. An alternative segment-A_1 in the form of aldehyde **23** was converted by coupling with **3a** (48 %) followed by MnO_2 oxidation (91 %) into **24** (ν 2230, 1680 cm^{-1}), which was treated with Me_2CuLi in Et_2O solvent to afford **25** (98 %). Acidic spiroketalization with PPTS in MeOH and ketalization with 2,2-dimethoxypropane gave **2** in 43 % yield.

The synthesis of segment-A **2** will be used for the final coupling with segment-B/C to accomplish the total synthesis of okadaic acid (**1**).

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References and Notes

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5. A higher syn-selectivity in less polar solvent may be due to the stronger chelation effect; see M. Isobe, Y. Funabashi, Y. Ichikawa, S. Mio, T. Goto, Tetrahedron Lett., 25, 2021 (1984).
6. In the ^{13}C nmr, syn-isomers empirically exhibited at ca. 14 ppm, whereas anti-isomers do at 17 ppm.
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11. Since the acetonide was partially hydrolyzed to the corresponding diol, it was re-acetonized to produce a single product.

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