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SYNTHETIC STUDIES TOWARD MARINE TOXIC POLYETHERS (2)

SYNTHESIS OF THE B-SEGMENT OF OKADAIC ACID AND COUPLING WITH THE C-SEGMENT

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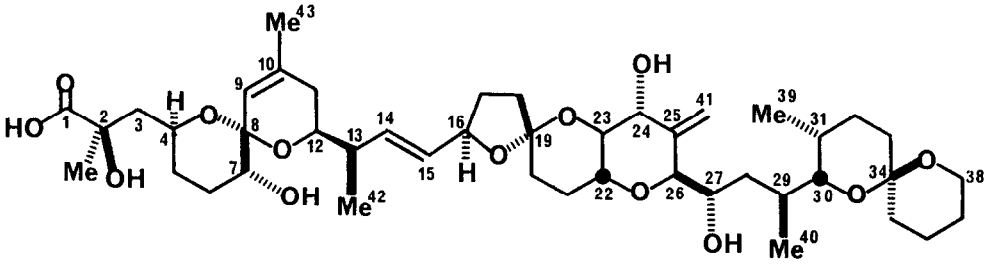
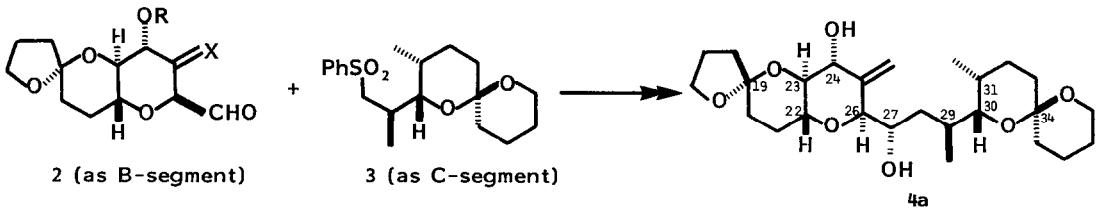
Abstract: Part of okadaic acid **1a** was synthesized stereoselectively in the form of **4a** (involving C-16 through C-38 with 10 asymmetric carbons), by coupling the equivalents of **2** and **3** as the synthetic segments B and C (Scheme 1), the former being prepared via **12** and **6** from a D-glucopyranose derivative (Scheme 2).

We have been studying the total synthesis toward okadaic acid (1)[1], and recently reported the stereocontrolled synthesis of its C-segment (**3** containing C-28 through C-38).[2] Continuation of our project provided a success in the synthesis of the B-segment (equivalent of **2**), which contains a chain with 12 carbons (C-16 through C-27) with five asymmetric centers at C-19, 22, 23, 24 and 26. Crucial synthetic step is the coupling of B and C segments and the stereocontrol for the asymmetric carbon (C-27); the principle being illustrated in Scheme 1.



1a R= H Okadaic Acid 1b R= Ac



2 (as B-segment) 3 (as C-segment) 4a

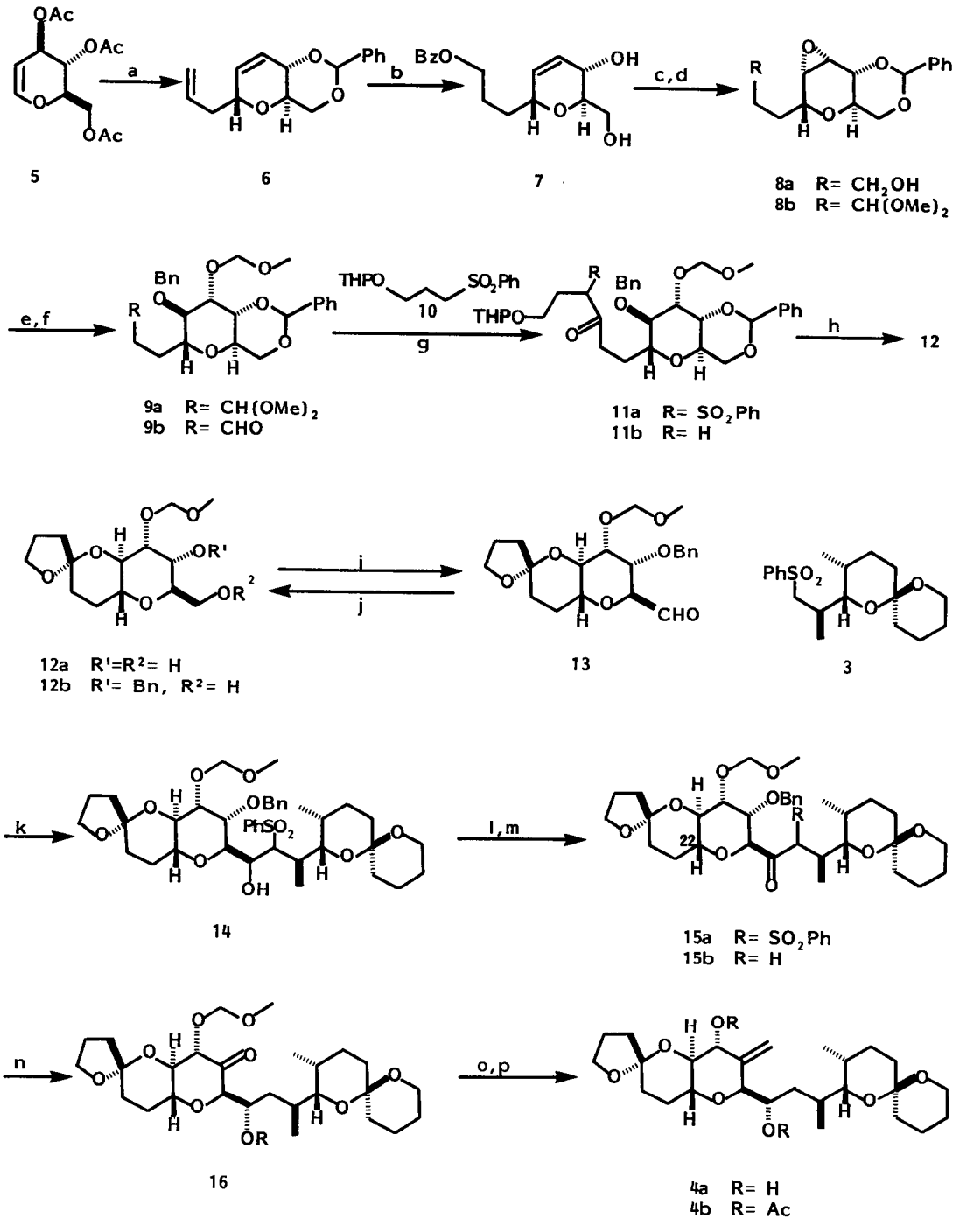
Scheme 1

D-Glucal triacetate (5) was C-glycosylated with allyltrimethylsilane[3] and BF_3-Et_2O [in CH_2Cl_2 first the temp. being kept at -50°C for 1.5 hr and then allowed to raise upto 0°C under N_2] to give

a mixturte (94% yield) of the alpha and beta C-glycosides in 16:1 ratio which was used for the next step without purification. The mixture was hydrolyzed with Et_3N in aq.-MeOH at rt overnight to obtain the corresponding diol, and then treated with $PhCH(OMe)_2$ [in 1,2-dichloroethane containing CSA (d,l-10-camphorsulfonic acid)] to give **6** which was purified by recrystallization [mp 63°C, $[\alpha]_D$= +26.7° (c= 1.25, $CHCl_3$) (80% yield)]. The terminal olefin of **6** was hydroborated with diborane in THF at -20°C for 6 hr (worked-up with H_2O_2 and 6 N NaOH at 60°C for 1 hr) to give a benzylidene-alcohol [mp 81°C, $[\alpha]_D$= +31.0° (c= 1.05)], which was protected as benzoate and treated with Dowex 50W(H^+) in MeOH to give the diol **7** (70% yield) [mp 99°C, $[\alpha]_D$= -23.5° (c= 1.04)]. The ring-olefin of **7** was epoxidized in 100%-alpha orientation with MCPBA in $CHCl_3$ at 5°C, and the product was treated with $PhCH(OMe)_2$ and CSA in refluxing $CHCl_3$ and then with NaOMe at 5°C to give **8a** (70%) [mp 124°C, $[\alpha]_D$= +49.2° (c= 0.95)], which was quantitatively converted into the dimethyl acetal **8b** [mp 110°C, $[\alpha]_D$= +44.6° (c= 0.98)] with $(COCl)_2$/DMSO and then $(MeO)_3CH/H^+$. The epoxide ring of **8b** was cleaved by addition of $NaOCH_2Ph$ in DMF at 70°C to give the corresponding alcohol [mp 89°C, $[\alpha]_D$= 26.7° (c= 1.17)],[4] which was protected as methoxymethyl (MOM) ether **9a** [48% yield]. The dimethyl ketal was selectively hydrolyzed in a mixture of 0.5 N HCl-THF (2:7) at rt for 3 hr to give **9b** (δ 9.80, s) in 98% yield. To this aldehyde was added the carbanion of the sulfone **10** [prepared from 3-chloropropanol by treatment with (i) DHP/CSA (ii) $NaSO_2Ph$, and (iii) n-BuLi/THF] at -78°C for 0.5 hr and the adduct was oxidized with PCC into the keto-sulfone **11a**, which was then reduced with Al-Hg in a mixture of THF-water (10:1) at 70°C for 7.5 hr. The product **11b** (85% yield) was heated in refluxing mixture of MeOH-AcOH (4:1) for 22 hr, and the hydrolysate (after purification with SiO_2) was stirred with Pd-black under H_2 atmosphere at rt for 2.5 hr in MeOH containing 5% AcOH to give in quantitative yield **12a**. The spiro-tricyclic compound **12a** was prepared in 18 steps from D-glucal triacetate (**5**) in 14 % overall yield.

The key aldehyde **13** was prepared from **12a** via the following functional group manipulation involving (i) selective protection of the primary hydroxyl group of **12a** with diphenyl-t-butylchloro-silane [70 %, $[\alpha]_D$= +8.2° (c= 1.29)], (ii) benzylation of the secondary hydroxyl group [$[\alpha]_D$= -5.5° (c= 1.59)], (iii) desilylation with n-Bu_4NF in THF (rt for 1.5 hr) (**12b**)$[\alpha]_D$= -40.1° (c= 1.30)], and (iv) Swern oxidation to the aldehyde **13** (81 %) [δ 3.9(H-16,m), 4.07(H-23, t, J= 10), 4.19(H-25, dd, J= 3.5, 2.5), 4.39(H-26, d, J= 2), 9.78(H-27)] (57 % overall yield). The fact that no epimerization of **13** at C-26 would take place during the oxidation was proven by reducing **13** back to **12b** with $NaBH_4$ and by identification as the corresponding acetate. On the other hand, β,γ-unsaturated aldehyde **2** (X= CH_2) was prepared from **12** (R^1=R^2=H) by the following reaction sequences involving (i) 1 equiv. DHP/PPTS, (ii) $(COCl)_2$/DMSO, (iii) $Ph_3P{=}CH_2$, (iv) H_3O^+ and (v) CrO_3-2Py (21 % overall yield). The aldehyde **2** [(X= CH_2, δ 5.20(brs), 5.58(brs), 9.67(s)], however, tended to isomerize into the conjugated form (e.g. Et_3N, at 55°C, 2 hr), which was useless; and thus, this olefination should be carried out after the coupling step.

To **13** was added two fold excess of the nucleophile **3** of the C-segment [prepared separately from D-glucose[2] and generated as the carbanion by treatment with 1 equiv. of n-BuLi and recovered after the reaction] in a mixture of Et_2O-hex (3:2) at -40°C to give **14** (66% yield based on **13**) as a mixture of diastereoisomers.[5] Oxidation of the alcohol **14** with CrO_3-2Py in CH_2Cl_2 gave the keto-sulfone **15a**, which was subsequently reduced with Al-Hg in aq. THF to the ketone **15b** (51% yield) [$[\alpha]_D$= +2.8° (c= 1.20)].[6] The ketone was selectively reduced with $NaBH_4$ in MeOH at 0°C into a single alcohol,[7] which was protected as THP, and the benzyl ether at C-25 was deprotected with Pd-



Scheme 2

(a) CH_2=$CHCH_2SiMe_3/BF_3$-Et_2O, Et_3N/aq-MeOH, $PhCH(OMe)_2$/CSA; (b) B_2H_6/H_2O_2, BzCl, H_3O^+; (c) MCPBA, $PhCH(OMe)_2$/CSA, NaOMe; (d) $(COCl)_2$/DMSO, $HC(OMe)_3/H^+$; (e) $PhCH_2ONa$, CH_3OCH_2Cl; (f) H_3O^+; (g) **10**/n-BuLi, PCC, Al-Hg; (h) H_3O^+, Pd-C/H_2; (i) $(COCl)_2$/DMSO; (j) $NaBH_4$; (k) **3**/n-BuLi; (l) CrO_3-2Py; (m) Al-Hg; (n) $NaBH_4$, DHP/PPTS, Pd-C/H_2, $(COCl)_2$/DMSO; (o) Ph_3P=CH_2/THF, H_3O^+; (p) Ac_2O/Py.

C/H_2 and then oxidized (Swern) to yield **16** (60 %). Wittig olefination of **16** with $Ph_3P{=}CH_2$ in THF was followed by deprotection of both hydroxy groups at C-24 and C-27 positions with 2.9 N HCl/THF [at 50°C overnight] to give **4a** (60 %). The pmr of the **4b** [δ 0.89(3H, d, J= 6), 1.09(3H, d, J=6), 2.08(3H, s), 2.14(3H, s), 3.30(H-30, dd, J= 10, 2), 3.54(H-23, t, J=10), 3.5(H-38), 3.9(H-22, H-16, 2Hm), 4.13(H-26, d, J= 10), 5.04(H-41, brs), 5.39(H-24, brd, J= 10), 5.60(H-27, brt, J= 10)] in 200 MHz was exactly the same with respects to the signals corresponding to those of the natural okadaic acid tri-acetate **1b**.[1a]

The stereocontrolled synthesis of the B-segment and its coupling with those of the C-segment was achieved to give **4** (13% in 10 steps from **12a**), chiral carbons of which were identical with the natural okadaic acid.

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References and Notes

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2. M. Isobe, Y. Ichikawa, H. Masaki, T. Goto; Tetrahedron Lett., **25**, 0000 (1984).
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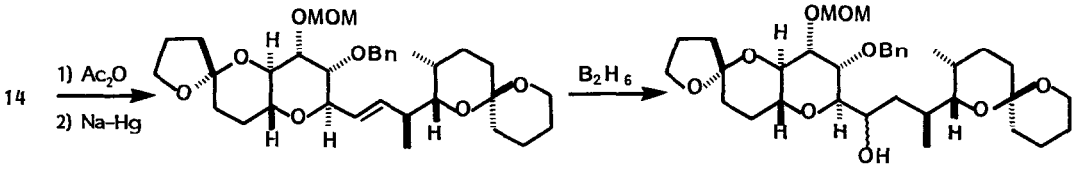
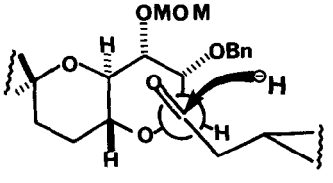
4. Interestingly, this alcohol showed the less polarity on silica gel tlc with a mixture of Et_2O-hex (2:1) [Rf shifted from 0.4 to 0.5].
5. The coupling underwent the more cleanly in the less polar solvent. When the diastereomixture of **14** was acetylated with Ac_2O/Py and then reduced with Na-Hg/MeOH, they were converted into the olefin **17** [δ 5.5(1H, dd, J= 16, 8), 5.6(1H, dd, J= 16, 5), 0.88 (d, J= 7Hz)] which was hydroborated into a mixture of regioisomers (27-OH and 28-OH in 4:1 ratio); the major isomer being identified by oxidation (Swern) into **15b**.



17 18

6. The pmr signal of H-23 of **15b** appeared at a higher field [δ 3.2 ppm] by the anisotropic effect of C-27 carbonyl group relative to the case in the corresponding alcohol [**18**, δ 3.6 ppm]. This fact indicates that the carbonyl locates cis to H-23; thus, no epimerization at C-26 took place during Al-Hg reduction.
7. The selectivity may be explained by the Felkin's transition state model in the following figure [see M. Cherest, H. Felkin, Tetrahedron Lett., 2199 (1968); and P. Deslongchamps, chapter 6 in "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, Oxford (1983)].



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