An Efficient Total Synthesis of Okadaic Acid

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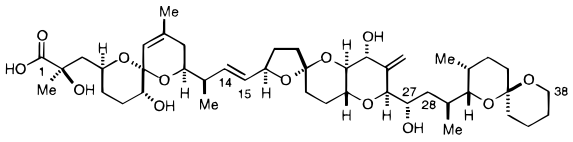
Okadaic acid (**1**)[1] is the archetypal member of a class of structurally diverse natural products that inhibit the protein serine/threonine phosphatases 1 (PP1) and 2A.[2] As such, **1** has become a widely used tool to study the roles of these ubiquitous enzymes.[3−5] Other members of the okadaic acid class of phosphatase inhibitors, including calyculin A,[6] tautomycin,[7] microcystin-LR,[8] motuporin,[9] and cantharidin,[10] have drawn considerable synthetic attention recently. However, little synthetic activity toward **1** or its analogs has been reported since Isobe's original total synthesis in 1986.[11,12] Although several of okadaic acid's structural features have been implicated to be important for phosphatase inhibition[13−15] and an X-ray structure of microcystin covalently bound to PP1 has been determined recently,[16] the structural basis of phosphatase inhibition by **1** remains largely undefined. Practical synthetic access to rationally designed, non-natural analogs of **1** will facilitate further studies aimed at fully defining the structural requirements for phosphatase binding and inhibition. Toward this end, we have developed an efficient and flexible total synthesis of okadaic acid.



Okadaic Acid (1)

With 17 stereogenic carbons and three separate polyether domains, **1** presents a substantial challenge for efficient assembly. This challenge was met by the synthesis and sequential coupling of three fragments, representing C1−C14, C16−C27, and C28−C38 of the natural product. Although disconnections similar to those used in the original synthesis[11] of **1** were employed, the present strategy relied upon the incorporation of maximal functionality into each fragment and the use of direct and chemoselective coupling methods to minimize the number of post-coupling transformations.

The synthesis of the C1−C14 portion of **1** combined an established spiroketalization approach[17] with Seebach's lactate enolate alkylation methodology.[18] Addition of the lithium acetylide of **2**[19] to lactone **3**,[20] followed by trimethylsilylation gave ynone **4** (Scheme 1). Conjugate addition of lithium dimethyl cuprate to **4** provided predominately the (*Z*)-enone **5**,[17,21] which upon treatment with acid generated spiroketal **6**[22] in 31% overall yield from **3**. Attempts to incorporate the C1−C2 moiety of **1** by alkylation of metal enolates of lactate pivalidene **7**[18] with primary tosylate, triflate, or halides obtained from **6** were unproductive. In contrast, the lithium enolate of **7** added smoothly to the aldehyde derived from **6**. The major resultant alcohol **8** was deoxygenated[23] without incident to give **9** (70% yield from **6**). Removal of the *p*-methoxybenzyl (PMB) protecting group[24] at C14 followed by oxidation with Dess−Martin periodinane[25] gave aldehyde **10**, to complete the synthesis of the C1−C14 intermediate in 11 steps and ca. 20% overall yield from lactone **3**.

The synthesis of the central C16−C27 fragment of **1** began with Gray's one-pot *C*-glycosidation[26] of altropyranoside **11**[27] (Scheme 2). Subsequent formation of the anisylidene acetal aided purification and provided α-propenyl-*C*-glycoside **12**. Treatment of the derived aldehyde **13** with organolithium **14**[28] followed by oxidation[25] installed carbons 16−19 with C19 at the ketone oxidation state required for **1**. The ketone was masked as a mixed acetal en route to secondary alcohol **15** (45% yield from **13**). Installation of the C24 exocyclic methylene[29] and the C27 aldehyde were then accomplished routinely to give **16** (ca. 20% yield from **11**).

The sensitive β,γ-unsaturated aldehyde **16** was coupled directly with an intermediate representing the C28−C38 portion of **1**. Addition of freshly prepared **16** to an excess of thermally unstable organolithium **17**[30] yielded the epimeric secondary alcohols **18** and **19**[31] nonstereoselectively and in low yield. Preliminary attempts to enhance the coupling diastereoselectivity

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(20) Lactone **3** was prepared from isopropyl 4,5-dideoxy-α-D-glucopyranoside [Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1985**, *26*, 5199−5202.] as follows: (i) TBDPSCl/Et_3N, (ii) BnBr/NaH, (iii) PhSH/$BF_3{\cdot}OEt_2$, (iv) I_2/aqueous $NaHCO_3$, and (v) PCC.
(21) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851−1852.
(22) Spiroketal **6** was formed as the major isomer of a ca. 2.2:1 ratio of diastereomers.
(23) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574−1585.
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(27) Compound **11** was obtained by hydrolysis of the known benzylidene derivative: Kunz, H.; Weissmueller, J. *Liebigs Ann. Chem.* **1984**, 66−77.
(28) Compound **14** was prepared from 1,3-propanediol as follows: (i) anisaldehyde/TsOH, (ii) $AlCl_3$/$LiAlH_4$/Et_2O, (iii) CBr_4/Ph_3P, and (iv) *t*-BuLi/Et_2O.
(29) Miljkovic, M.; Glisin, D. *J. Org. Chem.* **1975**, *40*, 3357−3359.
(30) Compound **17** was obtained from the corresponding bromide (*t*-BuLi/THF/−78 °C), which in turn was prepared in 10 steps and 35% overall yield from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate as follows: (i) TBSCl/Im, (ii) Dibal/CH_2Cl_2, (iii) tri-*n*-butylcrotylstannane/$BF_3{\cdot}OEt_2$ [Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883−1886.], (iv) TBAF/THF, (v) BnBr/NaH, (vi) O_3/Ph_3P, (vii) dimethyl (2-oxo-6-benzyloxy)hexyl phosphonate/LiCl/*i*-Pr_2NEt, (viii) H_2/$Pd(OH)_2$ (spontaneous spiroketalization occurred), (ix) TsCl/Et_3N, and (x) LiBr/CH_3CN.

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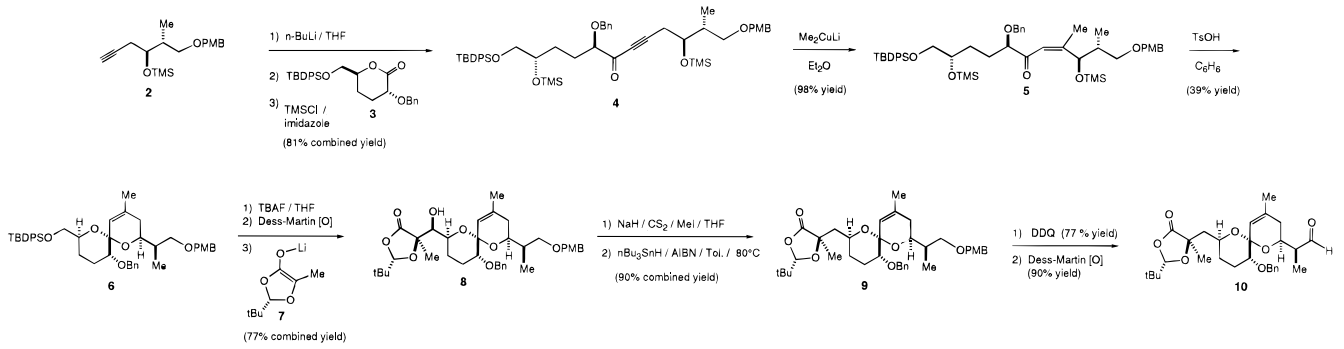
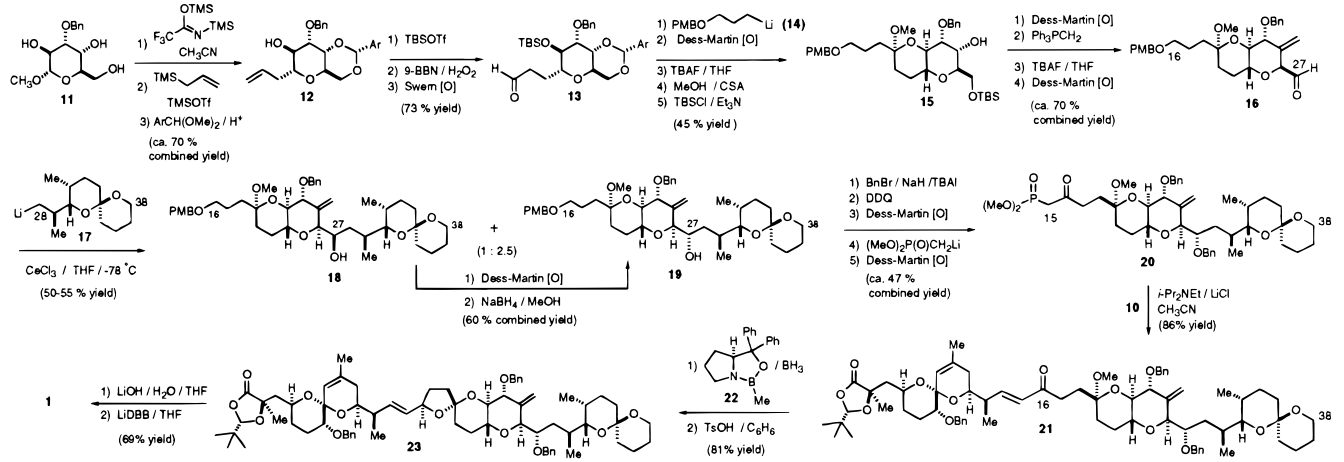
Scheme 1



Scheme 2



using other organometallics derived from **17** were only marginally successful.[32] However, useful yields of coupled products **18** and **19** (2.5:1, 55% yield combined) could be obtained reproducibly using the less basic reagent generated from $CeCl_3$ and **17** in THF at −78 °C. Neither appreciable epimerization at C26 nor conjugation of the alkene occurred under these conditions. A simple two-step oxidation−reduction sequence[33] gave **19** in a 9:1 ratio (**19**:**18**) from **18**. Removal of the PMB group from **19** was accomplished using DDQ in a buffered (pH 7) suspension to avoid premature and irretrievable C16−C19 spiroketalization. Thereafter, the C15−C38 ketophosphonate **20** was obtained uneventfully and in 21 steps and ca. 5% overall yield from altropyranoside **11**.

The complete carbon skeleton of **1** was assembled by joining **10** and **20** (86% yield) under standard conditions.[34] Only four steps were required to convert the resultant enone **21** into okadaic acid. Diastereoselective reduction of **21** using Corey's (*S*)-CBS/BH_3 system (**22**),[35] followed by acid-induced spiroketalization gave **23** (81% yield from **21**).[36] Final deprotection involving LiOH-promoted removal of the pivalidene group and carefully optimized reductive debenzylation[37] using LiDBB in THF[38,39] delivered **1**[40] (ca. 70% yield from **23**) after workup and purification. Thus, the convergent assembly of okadaic acid was accomplished in 26 steps and ca. 3% overall yield in the longest linear sequence from altropyranoside **11**.[41]

In addition to providing an alternative source of **1**, the direct and modular nature of this synthesis makes it amenable to the facile construction of new compounds based upon the okadaic acid architecture. The preparation and exploration of such compounds for selective ligand modulation of protein serine/threonine phosphatase activity is currently underway in our laboratory.

Acknowledgment. This work was dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday. We thank Prof. D. Uemura for providing an authentic sample of **1** isolated from *Halichondria okadai*. Financial support from the NIH (CA62195) and a University of Minnesota McKnight Land-Grant Professorship (C.J.F.) is gratefully acknowledged.

Supporting Information Available: Physical and spectral data for compounds **1**−**6**, **8**−**13**, **15**, **16**, **18**−**21**, and **23** and comparison of ^{1}H NMR spectra of natural and synthetic **1** (50 pages). See any current masthead page for ordering and Internet access instructions.

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(31) The C27 carbinol configuration of **19** was assigned at this stage by Mosher ester analysis.

(32) Use of the following in conjunction with **17** gave low de's and/or low yields: $MgBr_2$, CuBr·DMS, CuCN, 2-thienyl-CuCNLi, or $CrCl_3$·THF.

(33) Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 5049−5052.

(34) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(35) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.

(36) The ratio of diastereomeric spiroketal products was ca. 5:1; the configurations at C16 and C19 of the minor diastereomer were not determined.

(37) As noted previously[11] (Ichikawa, Y.; Isobe, M.; Goto, T. *Agric Biol. Chem.* **1988**, *4*, 975−981), over reduction occurs readily upon debenzylation of 7,24,27-tri-*O*-benzylokadaic acid using Li/NH_3/EtOH; however, overreduction was avoided here using LiDBB in THF at −78 °C.[38,39]

(38) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930.

(39) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854−860.

(40) Synthetic **1** matched (^{1}H NMR, $[\alpha]_D$, HRMS, and TLC; see Supporting Information) an authentic sample of the natural product isolated from *H. okadai* that was kindly provided by Prof. D. Uemura.

(41) Although this total synthesis has not been optimized, it compares favorably in length and efficiency with the original synthesis of **1**,[11,12] which reportedly spanned 54 steps and ca. 0.01% overall yield for the longest linear sequence.