# Efficient Synthesis of Okadaic Acid. 2. Synthesis of the C1−C14 Domain and Completion of the Total Synthesis

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**Abstract:** Described here are the full details of the preparation of a synthetic intermediate representing carbons 1−14 (C1−C14) of the marine natural product okadaic acid (**1**), the coupling of this fragment with the previously prepared C15−C38 domain, and the completion of an efficient total synthesis of **1**. The C1−C14 intermediate was prepared in 11 steps and ∼20% overall yield from a functionalized δ-valerolactone derivative representing C3−C8 of **1**. This featured a classic spiroketalization strategy to construct the highly substituted 1,7-dioxaspiro-[5.5]undec-4-ene system, followed by incorporation of the intact C1−C2 α-hydroxyl, α-methyl carboxylate moiety using *cis*-(*S*)-lactate pivalidene enolate. The complete C1−C14 intermediate was converted into **1** in five additional steps. Coupling of the C1−C14 fragment with the C15−C38 domain of **1** via C14 aldehyde and C15 β-keto phosphonate moieties provided the complete carbon skeleton of **1** bearing a ketone at C16 and a mixed-methyl acetal at C19. Reduction of the C16 ketone using Corey's (*S*)-CBS/$BH_3$ system and subsequent acid-triggered spiroketalization formed the central 1,6-dioxaspiro[4.5]decane ring system. Saponification of the C1−C2 pivalidene group and final reductive cleavage of the three benzyl ethers using lithium di-*tert*-butylbiphenylide in THF provided **1** in 48% yield from the C1−C14 aldehyde, and in 26 steps and ∼2% overall yield in the longest linear sequence from the C22−C27 synthon methyl 3-*O*-benzyl-α-D-altropyranoside.

## Introduction

Okadaic acid (**1**) is a marine natural product with a rich modern history. Originally isolated from the Pacific sponge *Halichondria okadai* in the 1970s as a potential anticancer agent,[1] **1** was subsequently identified as a diarrhetic toxin that accumulates in shellfish,[2,3] and a potent inhibitor of protein serine/threonine phosphatases 1 and 2A (PP1 and PP2A, respectively).[4] Thus, **1** has emerged as both a contemporary public health concern and a valuable tool in modern biomedical research.[5−7] Okadaic acid has also become the focus of renewed synthetic interest[8−11] since Isobe's original total synthesis was reported in 1986.[12,13] This is due to its unique and challenging polyether structure,[14] as well as the potential of compounds based upon the okadaic acid architecture to contribute further to our understanding of the structural basis of protein phosphatase inhibition. A number of additional and structurally diverse natural products potently inhibit PP1 and PP2A by competitive binding to the okadaic acid receptor.[15] Members of this okadaic acid class of phosphatase inhibitors have been the objects of several recent total syntheses. These include calyculin A,[16] tautomycin,[17−19] microcystin-LA,[20] and motuporin.[21]

As the archetypal member of this varied array of natural products, okadaic acid, as well as its analogues hold considerable, if not unique, potential for delineating the precise structural requirements for selective phosphatase binding and inhibition. This is due to okadaic acid's combination of dense functionalization, well-defined molecular topology,[22,23,14] and preferential inhibition of PP2A ($K_i$ = 32 pM) over PP1 ($K_i$ = 147 ± 34 nM).[24] Among the naturally occurring inhibitors of these enzymes, okadaic acid displays the highest degree of differential inhibition.[15] As detailed structural information of the active site and possible ligand binding domains of the serine/threonine

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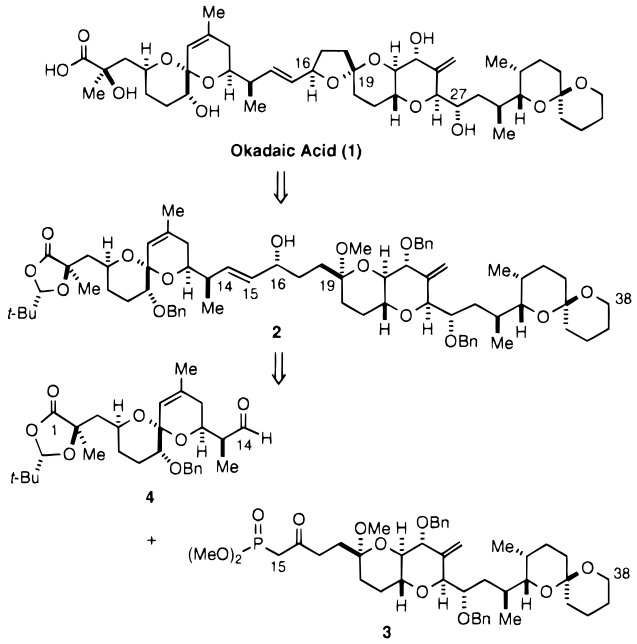
phosphatases becomes available,[25,26] the relevance, utility, and availability of ligands designed to probe and take advantage of these features take on greater importance. In this context, we have designed and recently executed an efficient and flexible total synthesis of okadaic acid.[9]

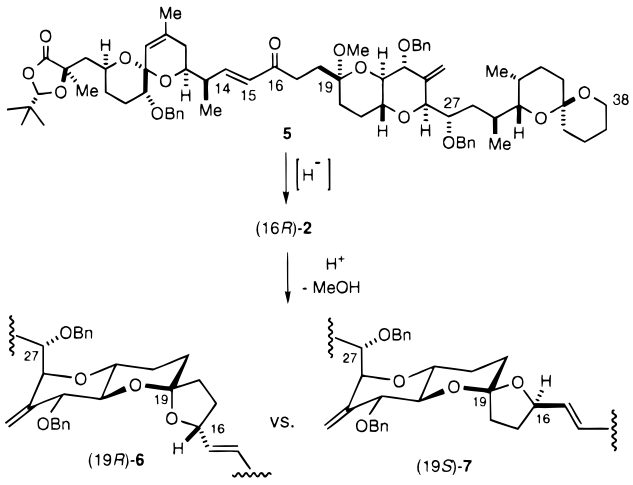
A major goal of this work has been to develop a modular and convergent approach to access the okadaic acid architecture to allow for the facile generation of analogues incorporating specific structural modifications. Using logical skeletal disconnections,[12] **1** was divided into three fragments, corresponding to C1−C14, C16−C27, and C28−C38 of the natural product. The full details of the convergent assembly of the C15−C38 domain (**3**) from the respective fragments was reported in a previous paper.[27] The preparation of the complementary C1−C14 domain (**4**) and its utilization in conjunction with **3** for an efficient total synthesis of okadaic acid are described here.




## Results and Discussion

**Overall Synthetic Plan.** The strategy for a facile assembly of **1** relied upon several key elements, chief among these was to incorporate a maximal degree of functionalization into each advanced synthetic intermediate so as to minimize the extent of postcoupling transformations required to complete the synthesis. It was anticipated that the 19*R*-configuration of the central C19−C23 spiroketal could be established near the end of the synthesis by an acid-triggered spiroketalization of a C16 hydroxyl upon a masked ketone at C19. Thus, the first retrosynthetic disconnection was to open the C16−C19 tetrahydrofuran of **1** to yield the $\gamma$-hydroxy mixed-methyl acetal **2**. Only acetal and benzyl ether protecting groups were chosen to differentiate **2** from **1**. Thus, the end-game strategy relied upon a stereoselective spiroketalization of **2** followed by final hydroxyl and carboxylate deblocking.

The *trans*-C14−C15 alkene of **2** was to be obtained by coupling **3**[27] and **4** under conditions sufficiently mild[28] to allow the C1 carboxylate to be incorporated in **4**. The expected product (*E*)-enone **5** would then serve as a substrate for diastereoselective ketone reduction to provide the natural product's 16*R*-configuration. Because the C16 carbonyl of **5** would be in an acyclic region of the carbon skeleton and insulated from the nearest stereogenic center by several carbons, reagent-based control would be required. Subsequent intramolecular ketalization under equilibrating conditions was then expected to provide predominately the required 19*R* configuration in the 1,6-dioxaspiro[4.5]decane ring system of **6**. Previous studies on simpler compounds indicated that the natural product's thermodynamically favored[29] 19*R* configuration would predominate upon acid-induced ketalization.[27,30] The chair−chair conformation of the C19−C26 *trans*-dioxadecalin system in concert with the anomeric stabilization afforded by an axial ketal oxygen at C19 should favor the formation of **6** over the alternative 19*S* epimer **7**.[31,32] In addition to being a source of local instability, the 19*S* configuration of contra-thermodynamic ketal **7** would likely impose a severe distortion from the native cyclic conformation[14,22] of **1**. It was expected that a late stage spiroketalization−equilibration could avoid this complication.




**Synthetic Design for the C1−C14 Domain.** A convergent assembly of enone **5** required synthetic access to aldehyde **4** and keto phosphonate **3**. Combined, these two advanced synthetic intermediates embody all of the functionality required for **1**. Whereas the synthesis of keto phosphonate **3** was detailed in a preceding paper,[27] the strategy used for the preparation of **4** is outlined in Scheme 1. The intact C1−C2 α-hydroxyl, α-methyl carboxylate moiety would be installed by diastereoselective alkylation of Seebach's lactate pivalidene **8** with a C3−C14 spiroketal-bearing fragment (**9**). Facial selectivity in the alkylation of **8** to set the C2 stereogenic center of **1** was expected to be high on the basis of ample literature precedent,[33] although previous alkylations of **8** have all involved electrophiles that were considerably simpler in structure than **9**. The electrophilic C3 carbon of **9** would bear an α-stereogenic center and be

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(30) Only one isomer was reportedly observed upon C16−C19 spiroketalization in the original synthesis of **1**: Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 5049.
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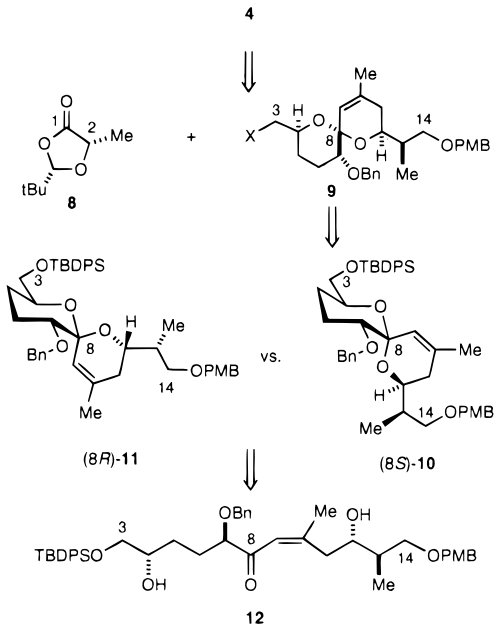
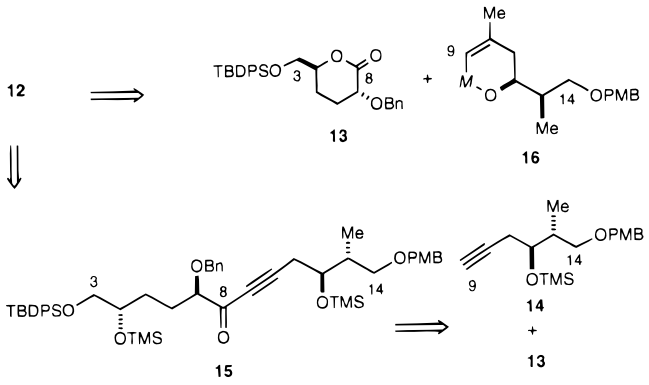
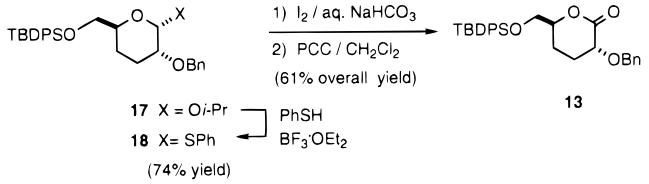
**Scheme 1**



**Scheme 2**



**Scheme 3**



equatorially disposed on the C4−C8 oxane ring of the 1,7-dioxaspiro[5.5]undec-4-ene system. Hence, potential complications arising from steric hindrance and double diastereoselective matching[34] could be anticipated. However, the expediency of incorporating the fully functionalized, stereochemically correct, and appropriately masked C1−C2 moiety in such a direct fashion would avoid reliance upon alternative multistep sequences[12,13] to incorporate the biologically essential[35] α-hydroxyl carboxylate moiety. Once installed, the protected α-hydroxyl carboxylate moiety would be subjected to only a few mild transformations en route to **1**. Whereas the pivalidene group would be expected to resist premature cleavage during late-stage C16−C23 spiroketalization catalyzed by mildly acidic conditions, it could be removed readily by saponification at the penultimate step in the total synthesis.

A hydroxyl group at C3 could act as a versatile precursor to a variety of potential leaving groups in **9** for lactate addition. Differential protection of the latent hydroxyl at C14 from those at C2, C3, and C7 would facilitate final installation of the C14 aldehyde. Hence, the (8*S*)-spiroketal **10** was targeted as a key intermediate in the preparation of **4** (Scheme 1). Thermodynamic equilibration would be relied upon to generate preferentially the natural product's 8*S* configuration in **10** versus the alternative (8*R*)-**11** diastereomer upon acid-catalyzed dehydration of *δ*,*δ*′-dihydroxy enone **12**.[36] The partially flattened conformation of the C8−C12 dihydropyran ring may diminish the benefit of positioning the C4 oxygen axially with respect to the C8−C12 ring, but the 8*S*-configuration in **10** should confer full anomeric stabilization to the C4−C8 chair oxane ring to strongly favor formation of the natural configuration.[31] Hanessian's application of a similar strategy to form the substituted 1,7-dioxaspiro[5.5]undec-4-ene system of the avermectins was quite successful.[37] However, in the context of the previous okadaic acid synthesis Isobe had reported that the yield of the desired and anticipated major diastereomer obtained via acid-catalyzed spiroketalization to form a similar fragment was limited to ∼30−40%.[38] This indicated a need to explore potential improvements for the formation of the targeted okadaic acid intermediate **10**.

Two synthetic approaches to (*Z*)-enone **12** were considered. A direct assembly of the desired spiroketal **10** via (*Z*)-enone **12** might involve the monoaddition of a (*Z*)-vinyl nucleophile (**16**) to the lactone **13** (Scheme 2). For this, the homopropargylic alcohol of an alkyne (cf. **14**) might be used to anchor a net *trans*-methyl metalation[39,40] to provide oxavinyl metallocycle **16**. By analogy to Collum's direct annulation approach to the synthesis of the phyllanthocin spiroketal,[41] the addition of **16** to **13**, followed by acidic workup could result in the direct formation of **10**. A reliable alternative route to the (*Z*)-enone **12** would involve methyl cuprate addition upon the corresponding ynone (**15**),[38,42] which, in turn, could be obtained from the monoaddition of alkyne **14** to lactone **13**.[43] Subsequent acid-catalyzed spiroketalization would complete the synthesis of **10**. The projected synthesis of the C1−C14 domain of **1** was thus focused on three stages: the formation of (*Z*)-enone **12** from lactone and alkyne precursors, thermodynamic spiroketalization to provide **10**, and installation of the α-hydroxyl, α-methyl carboxylate moiety using lactate **8**.

**Synthesis of the C1−C14 Aldehyde (4).** Lactone **13**, representing carbons 3−8 of **1**, was obtained from the known[44] isopropyl glycoside **17** (Scheme 3). To avoid cleavage of the silyl ether of **17**, the anomeric hydroxyl was liberated in two steps. Trans-glycosidation with thiophenol and $BF_3{\cdot}OEt_2$ yielded the α-thiophenyl glycoside **18**. Oxidative cleavage of the thioglycoside was effected cleanly using a heterogeneous

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(41) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496.
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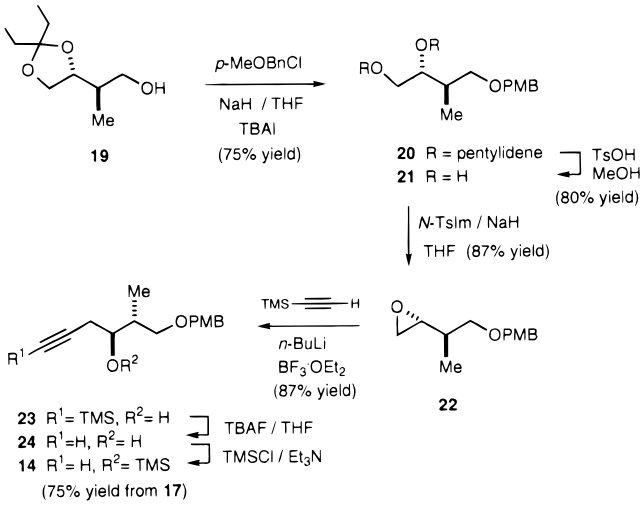
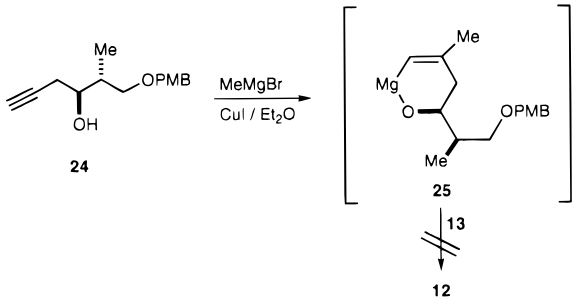
(44) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1985**, *26*, 5199.

**Scheme 4**




mixture of $I_2$, acetone, and aqueous $NaHCO_3$.[45] The resultant lactol was oxidized cleanly to **13** using PCC.[46]

Carbons 11−14 of **1** were derived from the known[47] pentylidene protected triol **19** (Scheme 4). Conversion of the free alcohol into the *p*-methoxybenzyl ether **20**, followed by methanolytic removal of the pentylidene group yielded diol **21**. The vicinal diol was transformed into oxirane **22** in one pot by treatment with *N*-*p*-toluenesulfonyl imidazole and NaH.[48] $BF_3$-assisted nucleophilic opening[49] of **22** with lithium trimethylsilylacetylide proceeded smoothly to give secondary alcohol **23**. A two-step transposition of the trimethylsilyl group from the alkyne terminus to the newly formed secondary hydroxyl then provided terminal alkyne **14**.

The direct addition of a (*Z*)-vinyl metallic species bearing a free homoallylic alkoxide group (**16**) to lactone **13** was investigated as a potentially expedient approach to the bicyclic ketal **10**. Because dihydroxy (*Z*)-enone **12** would result from monoaddition of **16** to **13**, the product could be dehydratively ketalized with a minimum of handling. This would avoid the necessity of an intervening hydroxyl group deprotection step and minimize the exposure of the isomerizable (*Z*)-enone **12** to acidic conditions. Encouraged by literature precedents for effecting the net *trans*-carbometalation of propargylic alcohols using simple Grignard reagents and catalytic CuI,[39,40] an attempt to extend this methodology to the homopropargylic alcohol **24** was made. However, *trans*-carbometalation of **24** could not be effected with MeMgBr/10% CuI. Attempts to generate[39,40] magnesium metallocycle **25** and add the resultant nucleophile to lactone **13** or an aldehyde were unsuccessful. No evidence for alternative electrophilic trapping of an in situ generated vinyl nucleophile was observed.

Because preliminary attempts to form and add (*Z*)-vinyl nucleophilic species derived from **24** to lactone **13** were unsuccessful, installation of the C10 methyl group of okadaic acid was deferred until after C8−C9 bond formation. Acetylide addition to lactone **13**[43] followed by conjugate addition of dimethylcuprate to the resultant ynone was expected to give selectively the corresponding (*Z*)-enone.[38,42] Among the potential complications that may limit the utility of this route for the assembly of **10** are competitive formation of the (*E*)-enone; generation of the kinetic spiroketal **11**; epimerization of the C7 stereogenic center; and premature loss of the C3 hydroxyl protecting group, which might lead to formation of a bridged ketal (cf. **30**, Scheme 5) involving the C3 and C4 hydroxyls. Therefore, minimal protection of the secondary hydroxyls, as well as stable protection of the latent primary alcohols of intermediates leading to **10** was desired to minimize some of these possible side reactions.

A brief survey was made to define useful protecting groups for the C4 and C12 hydroxyls for each of the three discrete steps: acetylide addition to **13**, cuprate addition to the derived ynone, and deprotection−spiroketalization. The lithium acetylide dianion derived from **24**, bearing no protecting group at the homopropargylic hydroxyl, added effectively to **13**. However, the resultant dihydroxy ynone **26** was a poor substrate for dimethylcuprate addition.

Capping the C4 and C12 hydroxyls as *tert*-butyldimethylsilyl (TBS) ethers at the ynone stage allowed for near quantitative yield in the conjugate addition step, but subsequent one-pot, acid-induced TBS removal and bicyclodehydration was unsatisfactory. An improved sequence involved blocking of both the C4 and C12 hydroxyls as trimethylsilyl (TMS) ethers, which could be removed rapidly upon acid treatment in the deprotection−spiroketalization step. In the event, addition of the lithium acetylide derived from **14** to lactone **13** gave ynone **27** (Scheme 5). Without purification of **27**, the newly formed hydroxyl at C4 was silylated to provide bis-TMS ether **15**. Conjugate addition of dimethylcuprate led to the $\beta$-methyl enone **28**, which, without purification, was treated with $TsOH \cdot H_2O$ in benzene at room temperature to remove the TMS groups and promote spiroketalization. Although TLC indicated rapid loss of the TMS groups to generate **12**, subsequent spiroketalization appeared to be relatively slow, and only modest yields of the spiroketal **10** were obtained. The 8*S* configuration of **10** was confirmed at this stage by the observation of reciprocal NOE enhancements between the C7 methine and C9 vinyl protons.

Although the overall yield of **10** from **15** was only moderate, no direct evidence for loss of the C3-hydroxyl protecting group was observed. The stable *tert*-butyldiphenylsilyl (TBDPS) ether was specifically chosen to prevent the primary alcohol of the hypothetical triol **29** from participating in an acid-catalyzed ketalization process (Scheme 5).[50] Instead, it is likely that the yield of **10** reflects an unfavorable *Z*−*E* selectivity in the generation of enone **28** via the conjugate addition of dimethylcuprate upon ynone **15**.[51] While the present route provides reasonable access to **10**, continuing studies are aimed at improving this sequence.

Completion of the synthesis of the C1−C14 intermediate **4** required elaboration of the 1,7-dioxaspiro[5.5]undec-4-ene **10** to incorporate the C1−C2 α-hydroxyl, α-methyl carboxylate

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(46) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
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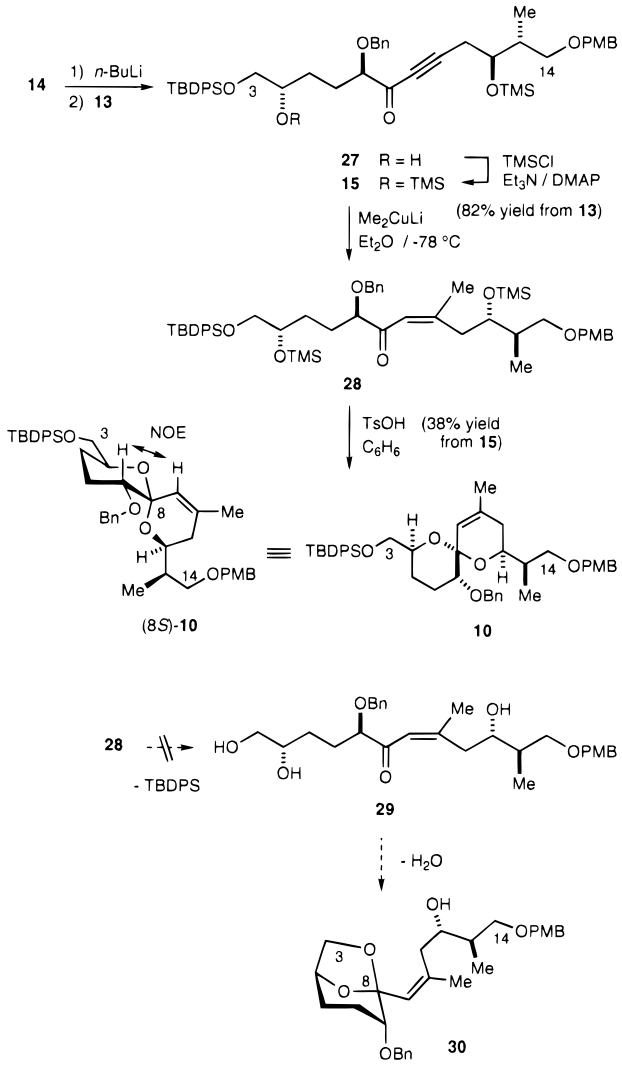
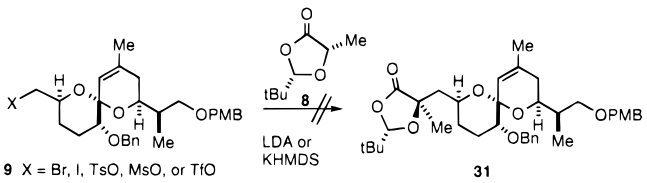
**Scheme 5**

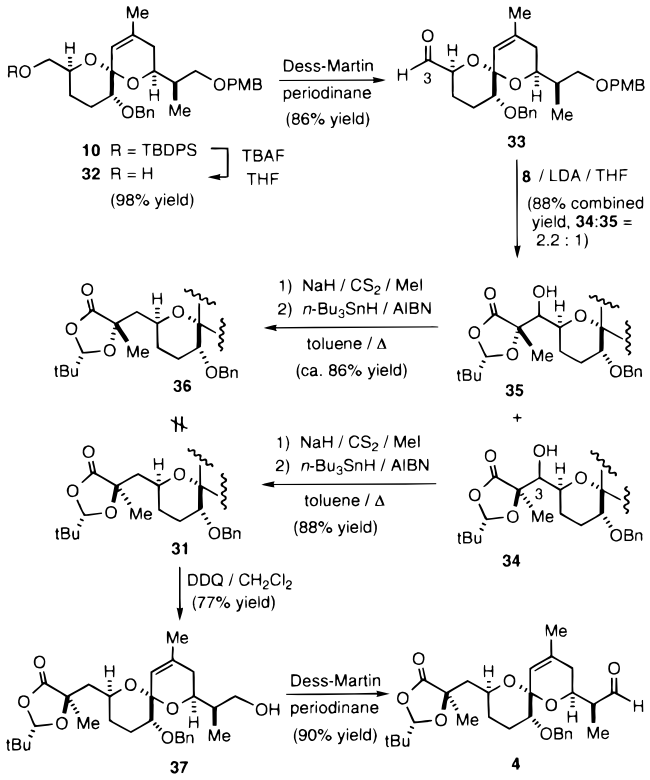


and C14 aldehyde moieties. Cleavage of the C3-silyl ether of **10** with TBAF yielded primary alcohol **32**, which served as a precursor to a variety of potential leaving groups (Scheme 6). Numerous attempts to displace potential halide and sulfonate leaving groups derived from **32** with enolates arising from lactate pivalidene **8** were unsuccessful. Instead of the desired alkylation product **31**, unreacted electrophilic species (**9**) were generally recovered. This may well reflect the crowded steric environment about the C3 carbon of **9**.



In contrast to primary halides and sulfonates, the aldehyde (**33**) obtained by treatment of **32** with Dess−Martin periodinane[52] participated readily in carbon−carbon bond formation. Addition of **33** to an excess of the preformed lithium enolate derived from (*S*)-lactate pivalidene **8** gave alkylation products **34** and **35** in good combined yield. However, the facial

**Scheme 6**



selectivity of lactate alkylation was much lower (2.2:1.0) than originally anticipated. That **34** and **35** were diastereomeric at C2 was confirmed by removal of the C3 stereogenic center via Barton deoxygenation.[53] Although it was clear that the resultant 3-deoxy derivatives **36** and **31** (Scheme 6) were diastereomeric to one another, the configuration at C2 of the latter was only tentatively assigned to be *R*, in accordance with the expectation that lactate alkylation would occur predominately anti to the *tert*-butyl substituent of **8**. No definitive NOE results could be obtained to secure the C2-configurational assignment at the stage of **31**. Deeming it unlikely that a complete reversal from the anticipated sense of diastereoselectivity would have occurred, **31** was selected for advancement toward **1**. This ultimately demonstrated that **31** and the natural product share the same 2*R*-configuration. The unexpected modest level of stereoselectivity in the addition of the lithium enolate obtained from **8** to aldehyde **33** may be due to unfavorable double diastereoselection between the mismatched pair **8** and **33**. In particular, secondary steric interactions in the transition state leading to **31** may serve to erode the degree of facial selectivity expected on the basis of the *tert*-butyl substituent alone.

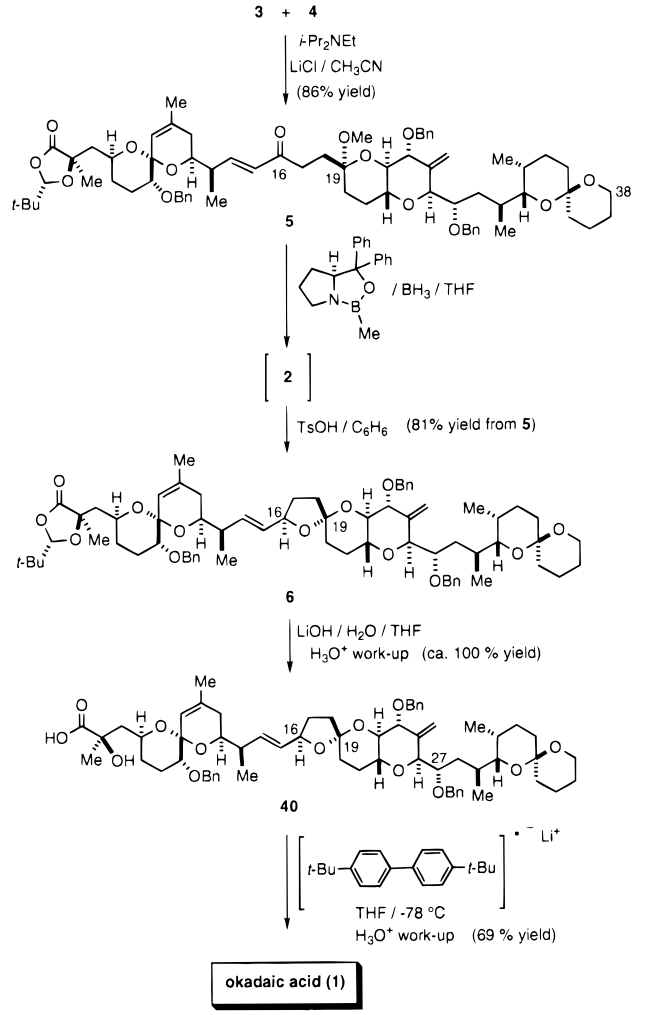
With the installation of C1−C2 successfully completed, only conversion of C14 into an aldehyde remained to complete the synthesis of **4**. This seemingly straightforward task was accompanied by an unexpected acid-catalyzed isomerization. Oxidative cleavage of the *p*-methoxybenzyl ether of **31** using DDQ predictably gave primary alcohol **37**, which could be oxidized efficiently to aldehyde **4** with $NaHCO_3$-buffered Dess−Martin periodinane (Scheme 6). However, exposure of **37** to acidic chloroform revealed the propensity of the $\delta$-alkenyl alcohol to undergo intramolecular addition of the alcohol across the alkene to irretrievably generate tricyclic ether **38**. This presumably involves activation of the latent Michael acceptor by protonation of a spiroketal oxygen followed by 1,4-addition

(51) Dounay, A. B.; Forsyth, C. J. Unpublished results.

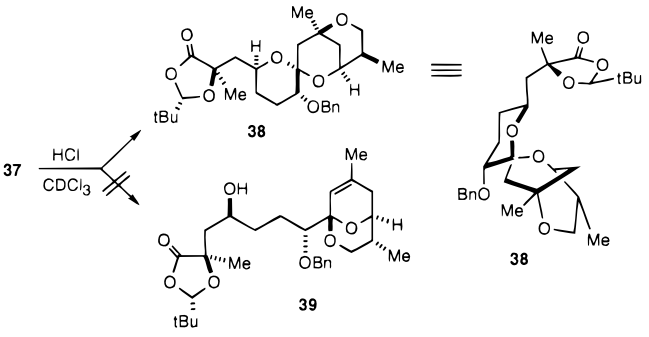
(52) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(53) Barton, D. H. R.; McCombie, S. W. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

**Scheme 7**




of the proximal C14 hydroxyl group to C10 of the allylically stabilized oxonium species. No evidence for formation of the alternative ketal (**39**) was observed. Formation of the trioxatricycle **38** was prevented by simply avoiding exposure of **31** to acidic conditions. Hence, the C1−C14 intermediate **4** could be prepared in 11 steps and ∼20% overall yield from lactone **13**.




**Total Synthesis of Okadaic Acid.** The complete carbon skeleton of okadaic acid was assembled by joining aldehyde **4** with keto phosphonate **3**[27] under Masamune−Roush conditions (Scheme 7).[28] This mildly basic Horner−Wadsworth−Emmons reaction allowed the fully functionalized coupling partners to be joined reliably to give (*E*)-enone **5**. In addition to conjoining all of the functionality required for **1** that is resident in **3** and **4**, this convergent coupling cleanly provided the *trans*-C14−C15 alkene stereoselectively.[54] Only assembly of the central C16−C23 spiroketal and deprotection remained as the final synthetic tasks. Diastereoselective reduction of the C16 carbonyl was a necessary prelude to spiroketal formation. Corey's CBS reagent system[55] seemed ideal for the diastereoselective reduction of enone **5**, given that the ketone was flanked by unbranched aliphatic carbons on one side and an (*E*)-alkene on the other. Thus, regio- and stereoselective reduction of **5** was accomplished using the (*S*)-CBS/$BH_3$ combination to give the (16*R*)-allylic alcohol **2**.[56] Because partial spiroketalization occurred upon acidic work up of the CBS reaction, **2** was not fully characterized. Instead, the reduction product mixture was subjected directly to acid-catalyzed spiroketalization without rigorous prior purification. This provided spiroketal **6** in 81% yield from **5**. As noted previously,[9] a minor spiroketal stereoisomer was generated along with **6** in this two-step sequence. Although it has not been confirmed, it seems likely that this minor diastereomer arises from the ketone reduction step, rather than spiroketalization process, because the latter has been demonstrated to be stereospecific in earlier synthetic intermediates.[27]

Only removal of the carboxylate and hydroxyl protecting groups was required to complete the synthesis of **1**. After the C1−C2 pivalidene protecting group withstood the previous coupling, reduction, and acid-induced spiroketalization reactions, it was easily detached from **6** by mild aqueous base-induced saponification to free both the C2 hydroxyl and C1 carboxylate moieties. Hence, the present synthesis intercepts the previous one[12,13] at the stage of 7,24,27-tri-*O*-benzyl okadaic acid (**40**). Saponification prior to dissolving metal cleavage of the benzyl ethers allowed the carboxylate to be protected from reduction as its carboxylate salt. Benzyl ethers were selected early in the synthetic planning as useful protecting groups for the C7, C24, and C27 hydroxyls. However, Isobe and co-workers reported that the reductive cleavage of the same protecting groups in the final step of the original synthesis of **1** was complicated by overreduction using lithium in liquid ammonia.[12,13,57] Similar difficulties were encountered in the present effort upon treatment of **40** with lithium in ammonia−ethanol. In contrast, the use of lithium di-*tert*-butylbiphenylide[58] (LiDBB) solutions in THF for controlled debenzylation[59] was far less problematic. The final deprotection could be carefully optimized even on small scale using stock solutions of known concentration of LiDBB. Thus, the three benzyl ethers of **40** were reductively cleaved without substantial complications from the other potentially sensitive functional groups to deliver **1** reproducibly in ∼70% yield after isolation and purification. The synthetic okadaic acid obtained in this fashion was chromatographically and spectroscopically indistinguishable from a sample of **1** that was isolated from *Halichondria okadai*. Aside from the initial difficulties associated with liberating the three secondary hydroxyl groups of **1**, the end-game strategy for a rapid completion of the total synthesis played out splendidly.

## Conclusion

An efficient total synthesis of the potent protein serine-threonine phosphatase inhibitor okadaic acid has been developed

(54) Wadsworth, D. H.; Schupp, O. E.; Seus, E. J.; Ford, J. A. J. *J. Org. Chem.* **1965**, *30*, 0, 680.
(55) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(56) The use of stoichiometric amounts of the CBS reagent was effective and convenient for small-scale reductions, although catalytic amounts may suffice for preparative-scale reduction of **5**.
(57) Ichikawa, Y.; Isobe, M.; Goto, T. *Agric. Biol. Chem.* **1988**, *52*, 975.
(58) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
(59) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

and executed on the basis of a direct and convergent synthetic strategy. This involved the individual syntheses and sequential coupling of fragments representing carbons 28−38, 16−27, and 1−14 of the natural product. As detailed in the preceding paper, the C28−C38 fragment was prepared in 10 steps from methyl (*S*)-3-hydroxy-2-methylpropionate, and its C16−C27 coupling partner was assembled from readily available methyl 3-*O*-benzyl-α-D-altropyranoside in 14 steps.[27] Their direct coupling and subsequent elaboration to form a fully functionalized C16−C38 synthetic intermediate (**3**) spanned an additional 5−7 steps.[27] The complementary C1−C14 intermediate (**4**) was prepared in 11 steps from functionalized δ-valerolactone (**13**) and alkyne (**14**) intermediates representing carbons 3−8 and 9−14, respectively. The incorporation of a maximal degree of functionalization into each advanced intermediate allowed a rapid completion of the total synthesis, which was effected in 5 steps and 48% yield from **3** and **4**. This featured a highly stereoselective 2-step construction of the central 1,6-dioxaspiro-[4.5]decane system by the tandem use of Corey's CBS reduction[55] and an acid-triggered trans-ketalization. In addition to delivering the natural product and highlighting a number of useful synthetic tactics and methods, the present work is notable because minor variations of the synthetic route will provide access to previously unavailable analogues of okadaic acid. Such compounds will be valuable for probing the structural basis of protein serine-threonine phosphatase inhibition.

## Experimental Section[27]

**1. Synthesis of the C1−C14 Fragment. (2*R*,3*S*,8*R*,11*S*)-8-*O*-Benzyl-12-*O*-(*tert*-butyldiphenylsilyl)-1-*O*-(4-methoxybenzyl)-2-methyl-3,11-bis-*O*-(trimethylsilyl)-7-oxo-5-undecyne-1,3,8,11,12-pentaol (15).** To a stirred −78 °C solution of **14** (1.268 g, 3.96 mmol) in THF (40 mL) under $N_2$ was added *n*-butyllithium (1.427 mL of a 2.50 M solution in hexanes, 3.57 mmol). After the mixture was stirred for 20 min, a solution of **13** (1.030 g, 2.17 mmol) in THF (10 mL) was added via cannula. After 40 min, saturated aqueous $NH_4Cl$ (5 mL) was added, followed by $H_2O$ (25 mL), and the mixture allowed to warm to room temperature. The mixture was extracted with diethyl ether (2 × 150 mL) and the combined organic extracts were washed with $H_2O$ and saturated aqueous NaCl. The organic fraction was dried over $Na_2SO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (hexanes−ethyl acetate, 6:1) and the resultant **27** was dissolved in $CH_2Cl_2$ (40 mL). To this solution was added chlorotrimethylsilane (300 μL, 2.39 mmol) followed by imidazole (259 mg, 4.34 mmol). After stirring for 45 min, the mixture was diluted with diethyl ether (100 mL) and washed with $H_2O$ and saturated aqueous NaCl (15 mL ea). The organic phase was dried over over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 10:1 then 3:1, v/v) to give **15** (1.529 g, 1.77 mmol, 82%) as a clear, colorless oil: $R_f$ 0.32 (hexanes−ethyl acetate, 5:1, v/v); $[\alpha]^{25}_D = +16$ (*c* 0.5, $CHCl_3$); IR (neat) 2958, 2210, 1674, 1515, 1423 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.68−7.66 (m, 4H), 7.44−7.24 (m, 13H), 6.87 (m, 2H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 3.89 (m, 2H), 3.80 (s, 3H), 3.69 (m, 1H), 3.55 (dd, *J* = 5.5, 10.5 Hz, 1H), 3.45 (dd, *J* = 6.0, 9.5 Hz, 1H), 3.43 (dd, *J* = 6.0, 10.5 Hz, 1H), 3.33 (dd, *J* = 5.5, 9.0 Hz, 1H), 2.62 (dd, *J* = 5.5, 17.5 Hz, 1H), 2.52 (dd, *J* = 7.0, 17.5 Hz, 1H), 2.04−1.89 (m, 3H), 1.70 (m, 1H), 1.42 (m, 1H), 1.05 (s, 9H), 0.92 (d, *J* = 12.0 Hz, 3H), 0.13 (s, 9H), 0.03 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 189.3, 159.0, 137.6, 135.6, 135.5, 133.6, 133.5, 130.6, 129.6, 129.1, 128.4, 127.9, 127.8, 127.7, 113.7, 95.4, 85.2, 80.4, 72.8, 72.7, 72.3, 72.1, 71.4, 67.9, 55.3, 38.9, 30.1, 28.4, 26.8, 25.8, 19.2, 13.8, 0.33, 0.28; HRMS calcd for $C_{50}H_{70}O_7Si_3$ $[M + H]^+$ 867.4508, found 867.4459.

**Spiroketal 10.** To a −78 °C supension of CuI (205 mg, 1.08 mmol) in diethyl ether (8 mL) under $N_2$ was added methyllithium (1.54 mL of a 1.40 M solution in diethyl ether, 2.16 mmol). The mixture was allowed to warm slowly to ∼−40 °C until a clear and colorless solution formed. The solution was cooled to −78 °C, and a solution of **15** (234 mg, 270 μmol) in diethyl ether (2 mL) was added via cannula. After 2.5 h, saturated aqueous $NH_4Cl$ (3 mL) was added and the mixture allowed to warm to room temperature and stir until the aqueous phase became bright blue. The solution was extracted with diethyl ether (3 × 25 mL) and the combined organic phases were washed with $H_2O$ and saturated aqueous NaCl (10 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. The residue was filtered through silica gel with hexanes−ethyl acetate (4:1, v/v) and the filtrate concentrated to give crude enone **28** (234 mg, 265 μmol). This was dissolved in benzene (10 mL), and *p*-toluenesulfonic acid monohydrate (2.5 mg, 13 μmol) was added. After the solution was stirred at room temperature for 11 h, it was diluted with diethyl ether (30 mL), washed with $H_2O$ and saturated aqueous NaCl (5 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 10:1, v/v) of the residue gave **10** (74 mg, 103 μmol, 38% from **15**) as a clear, colorless oil: $R_f$ 0.38 (hexanes−ethyl acetate, 5:1, v/v); $[\alpha]^{25}_D = -21$ (*c* 0.4, $CHCl_3$); IR (neat) 2929, 1512, 1427 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.70−7.64 (m, 4H), 7.45−7.23 (m, 11H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.19 (s, 1H), 4.65 (d, *J* = 12.5 Hz, 1H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 3.89−3.80 (m, 2H), 3.79 (s, 3H), 3.77 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.68 (dd, *J* = 5.5, 10.0 Hz, 1H), 3.48 (dd, *J* = 6.5, 10.0 Hz, 1H), 3.43 (dd, *J* = 8.0, 8.5 Hz, 1H), 3.29 (dd, *J* = 4.5, 11.5 Hz, 1H), 2.12−2.02 (m, 2H), 2.01−1.82 (m, 4H), 1.76 (s, 3H), 1.30 (m, 1H), 1.05 (s, 9H), 1.02 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 159.0, 138.9, 137.5, 135.7, 133.7, 130.9, 129.5, 129.2, 129.1, 128.3, 128.1, 127.6, 127.5, 123.0, 113.6, 95.9, 79.0, 72.6, 72.1, 71.4, 69.8, 69.2, 67.1, 55.2, 38.3, 33.2, 28.2, 26.9, 24.1, 23.1, 19.3, 13.9; HRMS calcd for $C_{45}H_{56}O_6Si$ $[M + H]^+$ 721.3925, found 721.3939.

**(2*R*)-Carboxylate 34 and (2*S*)-Carboxylate 35.** To a stirred −78 °C solution of diisopropylamine (102 μL, 733 μmol) in THF (8 mL) under $N_2$ was added *n*-butyllithium (261 μL of a 2.30 M solution in hexanes, 600 μmol). After 20 min, a solution of (*S*)-lactate pivalidene **8**[33] (105 mg, 667 μmol) in THF (1 mL) was added via cannula. After 20 min, a solution of **33** (32 mg, 67 μmol) in THF (1 mL) was added via cannula. The resulting solution was allowed to stir for 15 min before saturated aqueous $NH_4Cl$ was added. The mixture was allowed to warm to room temperature, and diluted with diethyl ether (30 mL), washed with $H_2O$ and saturated aqueous NaCl (5 mL ea), and dried over $Na_2SO_4$. Filtration and concentration gave a residue that was purified by silica gel column chromatography (hexanes−ethyl acetate, 10:1 to 7:1, v/v) to give **34** (26 mg, 41 μmol, 60%) and **35** (12 mg, 19 μmol, 28%) as clear, colorless oils. Data for **34**: $R_f$ 0.58 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D = +9.5$ (*c* 1.2, $CHCl_3$); IR (neat) 3469, 2962, 1797, 1515 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.32−7.27 (m, 7H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.40 (s, 1H), 5.16 (s, 1H), 4.61 (d, *J* = 12.5, 1H), 4.49 (d, *J* = 9.5 Hz, 1H), 4.47 (d, *J* = 9.5 Hz, 1H), 4.42 (d, *J* = 12.5 Hz, 1H), 3.87 (ddd, *J* = 3.0, 5.0, 11.5 Hz, 1H), 3.84 (dd, *J* = 5.0, 9.5 Hz, 1H), 3.71 (ddd, *J* = 3.5, 8.0, 11.5 Hz, 1H), 3.48 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.36 (dd, *J* = 8.5, 8.5 Hz, 1H) 3.23 (dd, *J* = 4.5, 11.5 Hz, 1H), 2.71 (d, *J* = 9.5 Hz, 1H), 2.10−2.04 (m, 2H), 1.93 (m, 1H), 1.83 (m, 2H), 1.76 (s, 3H), 1.63 (m, 1H), 1.49 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 173.6, 158.9, 138.8, 137.9, 131.1, 129.3, 128.2, 127.7, 127.4, 121.9, 113.6, 109.3, 96.4, 80.8, 78.3, 76.1, 72.6, 72.3, 71.3, 70.2, 67.9, 55.3, 38.3, 34.4, 32.8, 27.8, 23.5, 23.3, 23.0, 22.2, 13.9; HRMS calcd for $C_{37}H_{50}O_9$ $[M + H]^+$ 639.3534, found 639.3546.

**3-Deoxy-34 (31).** To a stirred 0 °C solution of **34** (26 mg, 41 μmol) in THF (2.5 mL) under $N_2$ was added NaH (29 mg, 1.2 mmol). The stirred mixture was allowed to warm to room temperature over 30 min before $CS_2$ (73 μL, 1.2 mmol) was added. After 10 min, methyl iodide (76 μL, 1.2 mmol) was added and the solution became yellow. After another 10 min, the yellow color dissipated and the solution was cooled to 0 °C. Saturated aqueous $NH_4Cl$ (0.3 mL), diethyl ether (5 mL), and $H_2O$ (1.5 mL) were added. The separated aqueous phase was extracted with diethyl ether (3 mL) and the combined organic phases were washed with saturated aqueous NaCl (2 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was azeotropically dried from benzene (5 mL) and then dissolved in toluene (5 mL). After the resultant solution was deoxygenated with a stream of Ar for 15 min,

2,2′-azobisisobutyronitrile (27 mg, 0.16 mmol) and tri-*n*-butyltin hydride (88 $\mu$L, 0.33 $\mu$mol) were added, and the mixture was heated at 80 °C for 2 h under Ar. After the solution was cooled to room temperature, it was diluted with ethyl acetate (5 mL), washed with $H_2O$ and saturated aqueous NaCl (2 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 1:0 to 7:1, v/v) of the residue gave **31** (22 mg, 35 $\mu$mol, 88%) as a clear, colorless oil: $R_f$ 0.74 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D = +11$ (*c* 0.2, $CHCl_3$); IR (neat) 2926, 1738, 1549 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.31 (d, $J = 9.0$ Hz, 2H), 7.30−7.25 (m, 5H), 6.86 (d, $J = 9.0$ Hz, 2H), 5.28 (s, 1H), 5.18 (s, 1H), 4.61 (d, $J = 12.5$ Hz, 1H), 4.48 (d, $J = 12.5$ Hz, 1H), 4.47 (d, $J = 11.0$ Hz, 1H), 4.42 (d, $J = 11.0$ Hz, 1H), 3.91−3.87 (m, 1H), 3.86 (dd, $J = 4.5$, 9.0 Hz, 1H), 3.80 (s, 3H), 3.70 (ddd, $J = 3.5$, 8.0, 11.5 Hz, 1H), 3.35 (dd, $J = 8.5$, 9.0 Hz, 1H), 3.27 (dd, $J = 4.5$, 11.5 Hz, 1H), 2.12−2.02 (m, 2H), 2.01−1.60 (m, 6H), 1.75 (s, 3H), 1.44 (s, 3H), 1.31 (m, 1H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 175.3, 157.1, 138.8, 137.5, 131.0, 129.2, 128.2, 127.8, 127.4, 122.5, 119.1, 113.6, 108.2, 96.1, 78.3, 72.6, 72.4, 71.3, 70.0, 68.2, 65.4, 55.3, 42.0, 38.3, 34.2, 32.9, 32.0, 25.2, 24.5, 23.3, 14.0; HRMS calcd for $C_{37}H_{50}O_8$ $[M + H]^+$ 623.3585, found 623.3624.; HRMS (MALDI) calcd for $C_{37}H_{50}O_8Na$ $[M + Na]^+$ 645.3404, found 645.3407.

**C14 Alcohol 37.** To a mixture of **31** (27 mg, 43 $\mu$mol), $CH_2Cl_2$ (3.5 mL), an aqueous $Na_2PO_4$ buffer (pH = 7, 2.0 mL), and *tert*-butyl alcohol (0.35 mL) was added dichlorodicyanoquinone (49 mg, 0.22 mmol). The reaction flask was placed in a aqueous bath and sonicated for 1 min and then assayed for disappearance of **31** by TLC. This process was repeated for a total of three 1-min sonications, at which point no **31** remained. The mixture was diluted with diethyl ether (8 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with diethyl ether (2 × 2 mL) and the combined organic phases were washed with $H_2O$ and saturated aqueous NaCl (1.5 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 5:1 to 3:2, v/v) to give **37** (17 mg, 34 $\mu$mol, 77%) as a clear, colorless oil: $R_f$ 0.26 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D$ +9.7 (c 0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.28−7.15 (m, 5H), 5.34 (s, 1H), 5.25 (s, 1H), 4.44 (d, $J = 12.5$ Hz, 1H), 4.31 (d, $J = 12.5$ Hz, 1H), 4.13−4.07 (m, 2H), 4.02 (m, 1H), 3.88 (m, 1H), 3.17 (dd, $J = 5.0$, 12.0 Hz, 1H), 2.01−1.94 (m, 2H), 1.85−1.77 (m, 2H), 1.68 (m, 1H), 1.66−1.56 (m, 4H), 1.55 (s, 3H), 1.46 (s, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 0.86 (s, 9H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 175.4, 139.9, 137.5, 128.9, 128.9, 128.8, 128.7, 128.4, 128.1, 127.9, 123.4, 108.5, 96.6, 79.1, 72.6, 71.6, 65.9, 65.8, 43.5, 40.8, 34.6, 33.9, 32.3, 25.7, 25.0, 23.8, 23.3, 14.5; HRMS calcd for $C_{29}H_{42}O_7$ $[M + H]^+$ 503.3010, found 503.3033.

**Aldehyde 4.** To a stirred room-temperature solution of **37** (10 mg, 20 $\mu$mol) in $CH_2Cl_2$ (1.5 mL) was added $NaHCO_3$ (25 mg, 0.30 mmol) followed by the Dess−Martin periodinane reagent[52] (25 mg, 60 $\mu$mol). The mixture was stirred for 30 min before diethyl ether (4 mL) and 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (0.5 mL ea) were added. The mixture was stirred until the organic phase became clear and colorless. The separated aqueous phase was extracted with diethyl ether (2 × 0.5 mL), and the combined organic fractions were washed with $H_2O$ and saturated aqueous NaCl (1 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) of the residue gave **4** (9 mg, ∼0.18 $\mu$mol, 90%) as a white crystalline solid: mp 125−126 °C (hexanes−ethyl acetate); $R_f$ 0.57 (hexanes−ethyl acetate, 2:1, v/v); $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 10.13 (d, $J = 3.0$ Hz, 1H), 7.33−7.15 (m, 5H), 5.36 (s, 1H), 5.30 (s, 1H), 4.51 (d, $J = 12.5$ Hz, 1H), 4.36 (d, $J = 12.5$ Hz, 1H), 4.35 (ddd, $J = 3.5$, 7.5, 11.0 Hz, 1H), 4.04 (ddt, $J = 3.5$, 9.5, 12.0 Hz, 1H), 3.23 (dd, $J = 4.5$, 12.0 Hz, 1H), 2.45 (ddq, $J = 3.0$, 7.0, 7.0 Hz, 1H), 2.04 (m, 1H), 1.86 (m, 2H), 1.71−1.60 (m, 2H), 1.56 (s, 3H), 1.54−1.45 (m, 2H), 1.43 (s, sH), 1.31 (m, 1H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H).

**2. Synthesis of Okadaic Acid. C14−C16 Enone 5.** To a stirred room-temperature solution of **3**[27] (12 mg, 15 $\mu$mol) in $CH_3CN$ (0.5 mL) was added LiCl (3 mg, 0.07 mmol) followed by diisopropylethylamine (4 $\mu$L, 0.02 mmol). After stirring for 10 min, a solution of **4** (6 mg, ∼12 $\mu$mol) in $CH_3CN$ (0.6 mL) was added. The resulting mixture became turbid after 10 min and was stirred for an additional 20 h. The mixture was diluted with diethyl ether (5 mL), washed with $H_2O$ and saturated aqueous NaCl (0.5 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1, v/v) of the residue gave **5** (12 mg, 10 $\mu$mol, ∼86%) as a clear, colorless oil: $R_f$ 0.54 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D = +7$ (*c* 0.2, $CHCl_3$); IR (neat) 2948, 1788, 1682 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.37−7.24 (m, 15H), 7.04 (dd, $J = 8.5$, 16.0 Hz, 1H), 6.19 (d, $J = 16.0$ Hz, 1H), 5.45 (s, 1H), 5.35 (s, 1H), 5.19 (s, 1H), 5.05 (s, 1H), 4.87 (d, $J = 12.0$ Hz, 1H), 4.76 (d, $J = 12.0$ Hz, 1H), 4.73 (d, $J = 11.0$ Hz, 1H), 4.60 (d, $J = 12.5$ Hz, 1H), 4.57 (d, $J = 11.0$ Hz, 1H), 4.45 (d, $J = 12.5$ Hz, 1H), 4.26 (d, $J = 8.0$ Hz, 1H), 3.94−3.81 (m, 4H), 3.71−3.60 (m, 3H), 3.41 (dd, $J = 10.0$, 10.0 Hz, 1H), 3.27 (dd, $J = 4.5$, 11.5 Hz, 1H), 3.23 (dd, $J = 2.0$, 10.0 Hz, 1H), 3.21 (s, 3H), 2.70 (ddd, $J = 6.5$, 10.5, 16.5 Hz, 1H), 2.61−2.55 (m, 2H), 2.06−1.98 (m, 2H), 1.92−1.77 (m, 11H), 1.75 (s, 3H), 1.70−1.36 (m, 13H), 1.44 (s, 3H), 1.29 (m, 1H), 1.17 (d, $J = 6.5$ Hz, 3H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.89 (s, 9H), 0.88 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 199.9, 175.1, 150.1, 143.5, 138.6, 137.0, 130.9, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 122.6, 112.7, 108.5, 102.8, 99.1, 96.0, 95.7, 85.3, 85.3, 78.6, 78.1, 77.2, 75.1, 74.4, 73.6, 73.1, 71.1, 70.7, 70.5, 65.4, 60.4, 47.5, 43.2, 42.0, 35.9, 34.7, 34.1, 33.6, 32.3, 31.2, 30.4, 29.2, 27.4, 26.3, 25.5, 25.4, 23.7, 23.4, 22.9, 18.8, 16.6, 16.0, 10.8; HRMS (MALDI) calcd for $C_{71}H_{96}NaO_{14}$ $[M+ Na]^+$ 1195.6701, found 1195.6660.

**1,2-Di-*O*-(*S*)-pivalidene-7,24,27-tri-*O*-benzylokadaic Acid (6).** To a stirred solution of (*S*)-2-methyl-CBS-oxazaborolidine[55] (136 $\mu$L of a 1.3 M solution in toluene, 0.18 mmol) in THF (0.6 mL) at 0 °C and under $N_2$ was added borane-tetrahydrofuran complex (120 $\mu$L of a 1 M solution in THF, 120 $\mu$mol) followed by a solution of **5** (13.6 mg, 11.6 $\mu$mol) in THF (0.35 mL). After 5 min, $H_2O$ (∼200 $\mu$L) was added and the mixture was allowed to warm to room temperature. Diethyl ether (2 mL) was added and the mixture was washed with 5% aqueous HCl. The aqueous phase was extracted with diethyl ether (2 × 0.5 mL), and the combined organic phases were washed with $H_2O$ and saturated aqueous NaCl (0.5 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. The crude allylic alcohol **2** ($R_f$ 0.28; hexanes−ethyl aceatate, 2:1, v/v) was filtered through silica gel with ethyl acetate, the filtrate was concentrated and then diluted with benzene (1 mL). *p*-Toluenesulfonic acid monohydrate (1 mg, 5 $\mu$mol) was added and the mixture stirred at room temperature for 2 h. Triethylamine (∼300 $\mu$L) was added, the mixture was filtered through silica gel, and the filtrate was concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 12:1, v/v) of the residue gave **6** (10.7 mg, 9.4 $\mu$mol, 81%) as a clear, colorless oil: $R_f$ 0.70 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D = +18$ (*c* 0.2, $CHCl_3$); IR (neat) 2934, 2874, 1792, 1728, 1664 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.39−7.23 (m, 15H), 5.78 (dd, $J = 8.5$, 10.5 Hz, 1H), 5.60 (dd, $J = 7.5$, 10.5 Hz, 1H), 5.41 (s, 1H), 5.33 (s, 1H), 5.19 (s, 1H), 5.01 (s, 1H), 4.85 (d, $J = 13.0$ Hz, 1H), 4.76 (d, $J = 13.0$ Hz, 1H), 4.75 (d, $J = 11.0$ Hz, 1H), 4.62 (d, $J = 12.5$ Hz, 1H), 4.58 (m, 1H), 4.56 (d, $J = 12.5$ Hz, 1H), 4.47 (d, $J = 12.5$ Hz, 1H), 4.24 (d, $J = 8.0$ Hz, 1H), 4.02 (m, 1H), 3.91 (m, 2H), 3.72−3.61 (m, 5H), 3.28 (dd, $J = 4.0$, 12.0 Hz, 1H), 3.22 (dd, $J = 2.5$, 10.5 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 2.09−1.93 (m, 5H), 1.87−1.77 (m, 10H), 1.75 (s, 3H), 1.69−1.36 (m, 13H), 1.45 (s, 3H), 1.30 (m, 1H), 1.08 (d, $J = 7.0$ Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H), 0.89 (s,9H), 0.87 (d, $J = 7.5$ Hz, 3H); HRMS (MALDI) calcd for $C_{70}H_{94}O_{13}Na$ $[M + Na]^+$ 1165.6595, found 1165.6569.

**7,24,27-Tri-*O*-benzylokadaic acid (40).**[12] To a solution of **6** (4.8 mg, 4.2 $\mu$mol) in THF (1 mL) was added 1 M aqueous LiOH (100 $\mu$L, 100 $\mu$mol). After the mixture was stirred for 48 h at room temperature, the THF was removed under a stream of $N_2$. The resulting aqueous mixture was diluted with $H_2O$ (0.4 mL) and acidified to pH 5 with 0.5 M aqueous HCl. The mixture was extracted with diethyl ether (4 × 2 mL), and the combined ether extracts were washed with $H_2O$ and saturated aqueous NaCl (0.5 mL ea), dried over $Na_2SO_4$, filtered, and concentrated. The crude residue was filtered through a pad of silica gel using hexanes−ethyl acetate−acetic acid (1:1:0.05, v/v/v) and the filtrate was concentrated to give **40** (4.5 mg, ∼4.2 $\mu$mol) as an oil: $R_f$ 0.69 (hexanes−ethyl acetate-acetic acid, 1:1:0.05, v/v/v); $^1H$ NMR ($CDCl_3$, 500 MHz) matched previously reported data [lit.[13] $^1H$ NMR

(500 MHz) $\delta$ 7.2−7.4 (15H), 5.74 (1H, dd, $J$ = 15, 8 Hz), 5.61 (1H, dd, $J$ = 15, 8 Hz), 5.35 (1H, t, $J$ = 1 Hz), 5.17 (1H, brs), 5.14 (1H, brs), 5.02 (1H, brs), 4.89 (1H, d, $J$ = 13 Hz), 4.77 (1H, d, $J$ = 13), 4.73 (1H, d, $J$ = 8 Hz), 4.61 (1H), 4.60 (1H, d, $J$ = 13 Hz), 4.56 (1H, d, $J$ = 11 Hz), 4.48 (1H, d, $J$ = 13 Hz), 4.24 (1H, d, $J$ = 8 Hz), 4.02 (1H, tt, $J$ = 11, 2 Hz), 3.88−3.95 (2H), 3.55−3.7 (5H), 3.24 (1H, dd, $J$ = 12, 4 Hz), 3.22 (1H, dd, $J$ = dd, 11, 2 Hz), 2.42 (1H, qt, $J$ = 7, 7 Hz), 2.23 (1H), 2.13 (1H, dd, $J$ = 14, 2 Hz), 1.73 (3H, s), 1.36 (3H, s), 1.05 (3H, d, $J$ = 7 Hz), 0.91 (3H, d, $J$ = 7 Hz), 0.87 (3H, d, $J$ = 7 Hz)]; HRMS (MALDI) calcd for $C_{65}H_{86}O_{13}Na$ $[M + Na]^+$ 1097.5967, found 1097.6010, calcd for $C_{65}H_{85}O_{13}Na_2$ $[M + 2Na - H]^+$ 1119.5787, found 1119.5837.

**Okadaic Acid (1).** To a stirred −78 °C solution of **40** (2.5 mg, 2.3 $\mu$mol) in THF (0.2 mL) under $N_2$ was added a solution of lithium di-*tert*-butylbiphenylide[59] (0.2 mL of 0.15 M solution in THF, ∼0.03 mmol). After stirring for 15 min, $H_2O$ (0.2 mL) was added to the deep blue-green solution and the resulting colorless mixture was allowed to warm to room temperature. The THF was removed under a stream of $N_2$, and the residue was diluted with $H_2O$ (0.2 mL) and washed with hexanes (3 × 1 mL). The aqueous phase was acidified to pH 5 with 0.5 M aqueous HCl, and extracted with diethyl ether (4 × 1 mL). The combined ether extracts were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate-acetic acid, 1:1:0.05, v/v/v) to give **1** (1.3 mg, 1.6 $\mu$mol, 69%) as a white solid: $[\alpha]^{25}_D$ +30.0 (*c* 1.3, $CHCl_3$) [*H. okadai* isolate lit.[14] $[\alpha]^{20}_D$ = +21 (*c* 0.33, $CHCl_3$), *H. melanodocia* isolate lit.[14] $[\alpha]^{25}_D$ = +25.4 (*c* 0.24, $CHCl_3$), *Prorocentrum lima* isolate lit.[22] $[\alpha]_D$ = +16.8 (*c* 0.83, $CHCl_3$)]; TLC (Baker 7011-4 Si-HPF TLC), indistinguishably cochromatographed with naturally occurring **1** isolated from *H. okadai*: $R_f$ 0.27 (hexanes−ethyl acetate−acetic acid, 1:1:0.05, v/v), 0.26 (dichloromethane−methanol, 19:1, v/v), 0.17 (diethyl ether−acetic acid, 99.5:0.05), 0.15 (hexanes−acetone, 1:1), 0.50 (*tert*-butyl methyl ether−chloroform−methanol−acetic acid, 9:1:0.5:0.05); indistinguishable (Baker 7011-4 Si-HPF TLC) from naturally occurring **1** (*H. okadai*) upon multiple elutions in hexanes−ethyl acetate−acetic acid (1:1:0.05), and hexanes−ethyl acetate−chloroform−acetic acid (1:1:0.5:0.05); $^1$H NMR ($CDCl_3$, 500 MHz) matched naturally occurring **1** isolated from *H. okadai*, and previously reported data;[14,22] photocopies of spectra are included in the Supporting Information; HRMS (MALDI) calcd for $C_{44}H_{67}O_{13}Na_2$ $[M + 2Na - H]^+$ 849.4377, found 849.4352.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **18**, **13**, **14**, **20**−**24**, **32**, and **33**; photocopies of $^1$H NMR spectra for synthetic and natural **1** and synthetic intermediates **4**−**6**, **10**, **13**−**15**, **18**−**24**, **31**−**34**, **37**, and **40** and of $^{13}$C NMR spectra for compounds **4**, **5**, **10**, **31**, and **34** (34 pages). See any current masthead page for ordering and Web access instructions.

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