Efficient Synthesis of Okadaic Acid. 1. Convergent Assembly of the C15−C38 Domain

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Abstract: A convergent synthesis of the C15−C38 domain of the marine natural product okadaic acid is reported. This involved the preparation of intermediates representing the C16−C27 and C28−C38 portions of okadaic acid, their direct coupling, and elaboration to the complete C15−C38 intermediate. A C16−C27 intermediate bearing an aldehyde at C27 was constructed in 14-steps from methyl 3-*O*-benzyl-α-D-altropyranoside. A C28−C38 intermediate with a primary alkyl bromide at C28 was prepared in 10 steps from methyl (*S*)-3-hydroxy-2-methylpropionate. These fragments were then joined in ∼55% yield by conversion of the bromide into an alkylcerium reagent then addition to a sensitive β,γ-unsaturated C27 aldehyde to give a mixture of C27 carbinols (27*R*:27*S* = 2.5:1). The configuration at C27 of the major coupling product was inverted by a simple oxidation−reduction sequence to establish the 27*S*-configuration of okadaic acid. Elaboration into a C15 β-keto phosphonate completed the synthesis of the fully functionalized C15−C38 portion of okadaic acid in 19 linear steps and ∼3% overall yield from methyl 3-*O*-benzyl-α-D-altropyranoside.

Introduction

Okadaic acid (**1**) is a marine natural product originally isolated from the Pacific and Caribbean sponges *Halichondria okadai* and *H. melanodocia*, respectively.[1] Subsequently, it was found to have its biogenetic origins in the marine dinoflagellates *Prorocentrum lima*, *Dinophysis fortii*, and *D. acuminata*.[2,3] Since the complex structures of okadaic acid[1] and the related C9−C10 episulfide acanthifolicin[4] determined by X-ray crystallography were published in 1981, the biomedical and commercial importance of compounds of this class has been well-established and widely recognized. In addition to being one of the chief causative agents of diarrhetic shellfish poisoning,[5,6] okadaic acid has been characterized as a potent nonphorbol ester-type tumor promoter on mouse skin.[7] In contrast to the phorbol ester class of natural products that may perturb intracellular signal transduction pathways by stimulating protein kinase C serine/threonine kinase activity,[8] okadaic acid was found to be a potent inhibitor of protein serine/threonine phosphatases 1 and 2A (PP1 and PP2A, respectively).[9] Okadaic acid's inhibition of PP1- and PP2A-like enzymes may account for the natural product's induction of a diverse array of acute cellular responses, which, depending upon the cell type, may range from mitogenic stimulation[10] to apoptosis.[11−13] A number of structurally diverse natural products have since been identified as okadaic acid type inhibitors of PP1 and PP2A. These include calyculin A,[14] dephosphonocalyculin A,[15] tautomycin,[16] microcystin-LR,[17] motuporin,[18] cantharidin,[19] and thyrsiferyl 23-acetate,[20] all of which have drawn considerable attention from the synthetic community. Okadaic acid itself, however, has remained the most widely used tool for probing the roles of these ubiquitous enzymes in a wide variety of cellular processes.[21−23] Recent X-ray crystal structures of the PP1 catalytic subunit covalently linked with microcystin[24] and complexed with tungstate[25] have provided detailed structural information of the PP1 active site and plausible binding domains for members of the okadaic acid class of inhibitors. These results have been augmented by molecular modeling[26,27] and molecular biology experiments[28,29]

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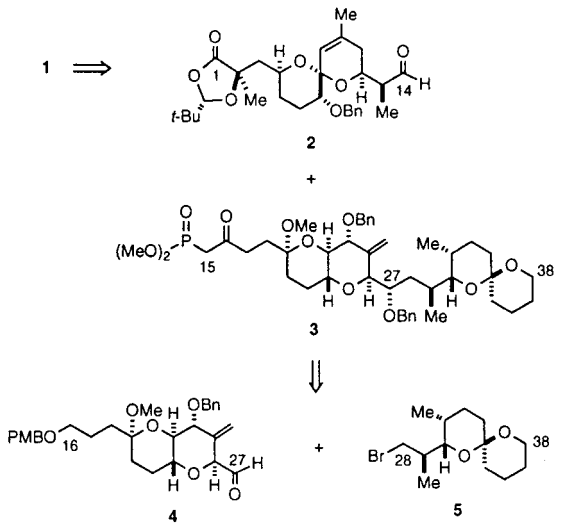
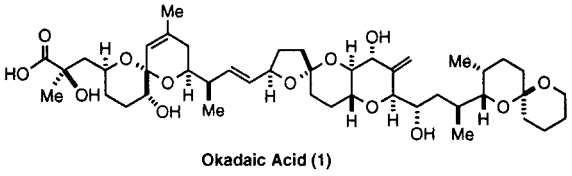
Scheme 1



aimed at illuminating the interactions of okadaic acid type inhibitors with their phosphatase receptors. In addition, earlier work has implicated the importance of several of okadaic acid's functional groups for phosphatase inhibition.[30−33] However, despite substantial synthetic efforts[34−37]that have culminated in a previous total synthesis[34,35] of okadaic acid, comprehensive and definitive studies to determine the structural basis of PP1 and PP2A inhibition by okadaic acid have been limited by a lack of designed structural variants.

As part of a program aimed at understanding the molecular interactions between **1** and its phosphatase receptors, we have recently developed an efficient and flexible total synthesis of okadaic acid from intermediates representing the C1−C14 (**2**) and C15−C38 (**3**) portions of the natural product (Scheme 1).[36] The full details of the synthesis of the advanced okadaic acid intermediate **3** are described here. In an accompanying paper the synthesis of the complementary fragment **2** and its utilization in conjunction with **3** for the total synthesis of **1** are detailed.[37]



Okadaic Acid (1)

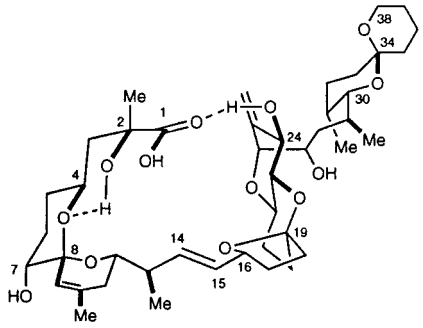


Figure 1. Cyclic conformation of okadaic acid.

Results and Discussion

Synthetic Plan. Okadaic acid is a functionally and topologically complex molecule. The 38 contiguous carbons of its backbone, as well as single carbon branches are believed to arise biosynthetically via a unique polyketide pathway.[38−40] Among okadaic acid's skeleton are 23 functionalized carbons that include 17 stereogenic carbons and 3 spiroketal moieties. Much of this functionality contributes to a cyclic conformation of **1** in solution[41,42] that is similar to the solid-state conformation[1] of the *o*-bromobenzyl ester derivative (Figure 1). This pseudomacrolide allows the hydroxyl group at C24 to form an intramolecular hydrogen bond with the natural product's C1 carboxylate moiety. Additional structural features that may contribute to a rigidified cyclic conformation are the opportunity for another hydrogen bond between the C2 hydroxyl and the C4 oxygen, thermodynamically enforced anomeric configurations at C8 and C19, the C14−C15 *trans*-alkene, and the C19−C26 *trans*-dioxadecalin system.[43] In particular, the C8 and C19 spiroketal carbons define two reinforcing 90° turns in the pseudomacrolide domain. Extending from okadaic acid's cyclic core is a lipophilic domain that terminates in the C30−C38 1,7-dioxaspiro[5.5]undecane system. This degree of structural complexity contributes to the challenge presented for total synthesis and to the unique potential of molecules based upon the conformationally well-defined okadaic acid architecture to delineate the specific structural requirements for phosphatase binding and inhibition.

In the original total synthesis of okadaic acid,[34,35] Isobe and co-workers disconnected **1** into three fragments, representing C1−C14 (**A**), C15−C27 (**B**), and C28−C38 (**C**) of the natural product. Each fragment was assembled independently, then joined sequentially. This resulted in a substantial total synthesis effort that spanned 54 steps in the longest linear sequence.[34,35] This included a 47 linear step preparation from triacetyl D-glucal of a C15−C38 fragment (**B** and **C**) that was coupled to the C1−C14 intermediate (**A**). Although laborious, this landmark synthesis illustrated the utility of several synthetic methods for reliable carbon−carbon bond formation and for cyclic and acyclic stereocontrol. In particular, phenyl sulfone stabilized carbanions were used to form the C14−C15, C18−C19, C27−C28, and C34−C35 bonds;[34,44,45] the C13 and C29 methyl groups were installed stereoselectively using heteroconjugate

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addition chemistry;[45,46] and the C2 stereogenic center was set by a highly stereoselective oxymercuration.[47]

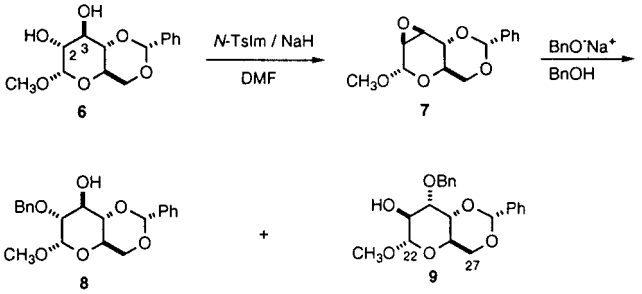
A more flexible and streamlined synthetic entry to the okadaic acid system than that represented by the original synthetic effort was desired for the purpose of rapidly generating a variety of analogues to probe the structural requirements for phosphatase binding and inhibition. Therefore, we designed a new and efficient total synthesis which employed major skeletal disconnections similar to those used in the original synthesis.

Key features of our synthetic plan were to minimize the number of transformations required to prepare each fragment, to install a maximal degree of functionality into each advanced synthetic intermediate so as to minimize the extent of post-coupling transformations, to utilize direct and chemoselective reactions to couple the fragments, and to rely upon thermodynamic equilibration[45,48] to set the configurations of the three spiroketal moieties of **1**.[36] In particular, it was anticipated that the natural configuration at C19 could be established readily at a late stage by intramolecular ketalization of a C16 hydroxyl upon a masked C19 ketone.[49] In contrast to the Isobe synthesis where the C16−C23 spiroketal was constructed prior to C14−C15 bond formation, we chose to defer formation of this central spiroketal moiety until after joining the C1−C14 and C15−C38 fragments. Hence, our initial retrosynthetic dissection involved cleavage of the central C16−C23 spiroketal to afford an allylic alcohol at C16 and a mixed methyl acetal at C19. The C16 carbinol could be derived from the diastereoselective reduction of a C16 ketone, and the *trans*-C14−C15 alkene could be obtained via a Horner−Wadsworth−Emmons coupling of an aldehyde (**2**) and a β-keto phosphonate (**3**, Scheme 1).

The choice of a keto phosphonate−aldehyde pair would allow for mild coupling[50] in the presence of the intact C1 carboxylate resident in **2**, and provide the C14−C15 (*E*)-alkene stereoselectively. Further, the two final coupling partners en route to **1**, C14 aldehyde (**2**) and C15−C38 β-keto phosphonate (**3**), contain all of the functionality present in okadaic acid in appropriately masked form. With C16 at the ketone, rather than the alcohol oxidation state, and just benzyl ether and acetal protecting groups present, only a few transformations would be required to convert **2** and **3** into **1**.

Dissection of intermediate **3** at the C27−C28 carbon−carbon bond and retrosynthetic simplification of the β-keto phosphonate moiety yields the C27 aldehyde **4** and C28 bromide **5**. Ideally, a direct coupling of aldehyde **4** with an unstablized primary carbanion derived from **5** would generate the C27 carbinol with a useful degree of stereoselectivity and without the previous necessity of post coupling removal of a carbanion stabilizing group.[34,35] Of course, β,γ-alkenyl aldehyde **4** is expected to be susceptible to base-induced enolization-conjugation to give the corresponding α,β-unsaturated aldehyde.[44,51] Nevertheless, we anticipated that, if successful, the convergency of adding a primary organometallic species derived from **5** directly to aldehyde **4** to generate the C27 carbinol would provide a substantial gain in synthetic efficiency. Ideally, only protection

Scheme 2



of the C27 hydroxyl and elaboration of the C16 terminus to the keto phosphonate would then be required to complete the assembly of **3**. The synthesis of okadaic acid thus began with the preparation of aldehyde **4** and bromide **5**, and an examination of their direct and convergent coupling.

Synthesis of the C16−C27 Fragment (4). Examination of the central C22−C26 ring of **1** immediately suggested that a D-altropyranoside could provide much of the stereochemistry (C23, C24, and C26) and functionality present in this portion of the natural product. Conversion of D-altropyranose into intermediate **4** (Scheme 1) would entail methylenation at C25, α-selective *C*-glycosidation to form the C21−C22 bond, annulation to construct the functionalized C19−C23 oxane ring, and final functional group transformations to provide the C27 aldehyde (Scheme 2). While commercially available, the high costs of D-altrose and its derivatives precluded the selection of any of these sugars as an actual starting point for the synthesis of **4**. However, it was recognized that inversion of both the C2 and C3 configurations of inexpensive D-glucose would provide D-altrohexose with the correct stereochemistry for C23 and C24, respectively. Therefore, a two-step protocol based upon conversion of methyl 4,6-di-*O*-benzylidene-α-D-glucopyranoside (**6**)[52] into the corresponding 2,3-anhydromannopyranoside (**7**),[53] followed by regioselective opening of the oxirane at C3 with sodium benzoxide was adopted to provide the requisite altropyranoside[54] (Scheme 2). In the event, treatment of **7** with sodium benzoxide in benzyl alcohol gave an approximate 1:4 ratio of gluco (**8**) and altro (**9**) isomers in ~70% combined yield.[54] Altropyranoside **9** could be separated conveniently by fractional crystallization from the minor glucoisomer (**8**), which arose from nucleophilic attack of sodium benzoxide at C2 of **7**. Although the oxirane moiety of **7** distorts the conformation of the parent pyranoside, *trans*-diaxial-like opening still predominates to generate **9**. Hence, ready access was established to large quantities of a chiral building block for the C22−C27 portion of **1** with the correct absolute configurations at C23, C24, and C26.

The next task was to append stereoselectively carbons C16−C21 to the anomeric position of **9**. An obvious approach to accomplish this was via an α-selective *C*-glycosidation. Initially, we examined convergent *C*-glycosidations under Hosami-Sakurai-type conditions[55] using highly functionalized allylic silanes that contained the entire six carbons of the C16−C21 side chain, with C16 and C19 functionalized as masked alcohol and ketone moieties, respectively. However, construction of the C16−C21 side chain three carbons at a time, although less convergent, was more successful. The one-pot procedure of Gray[56] for *C*-glycosidation of methyl glycosides with allyltri-

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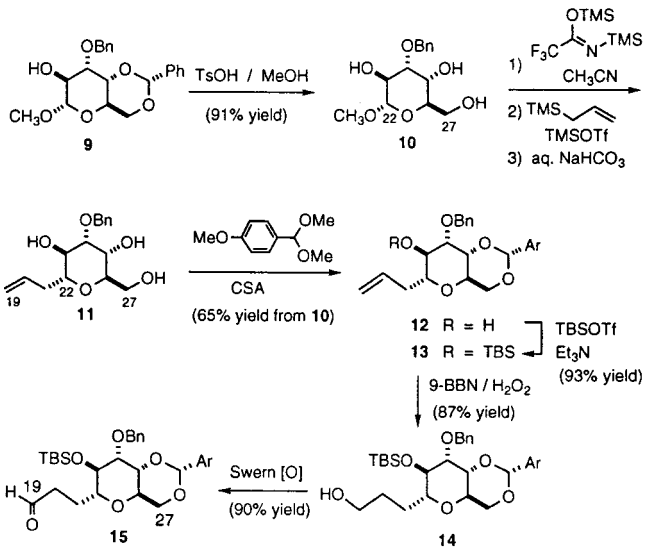
Scheme 3



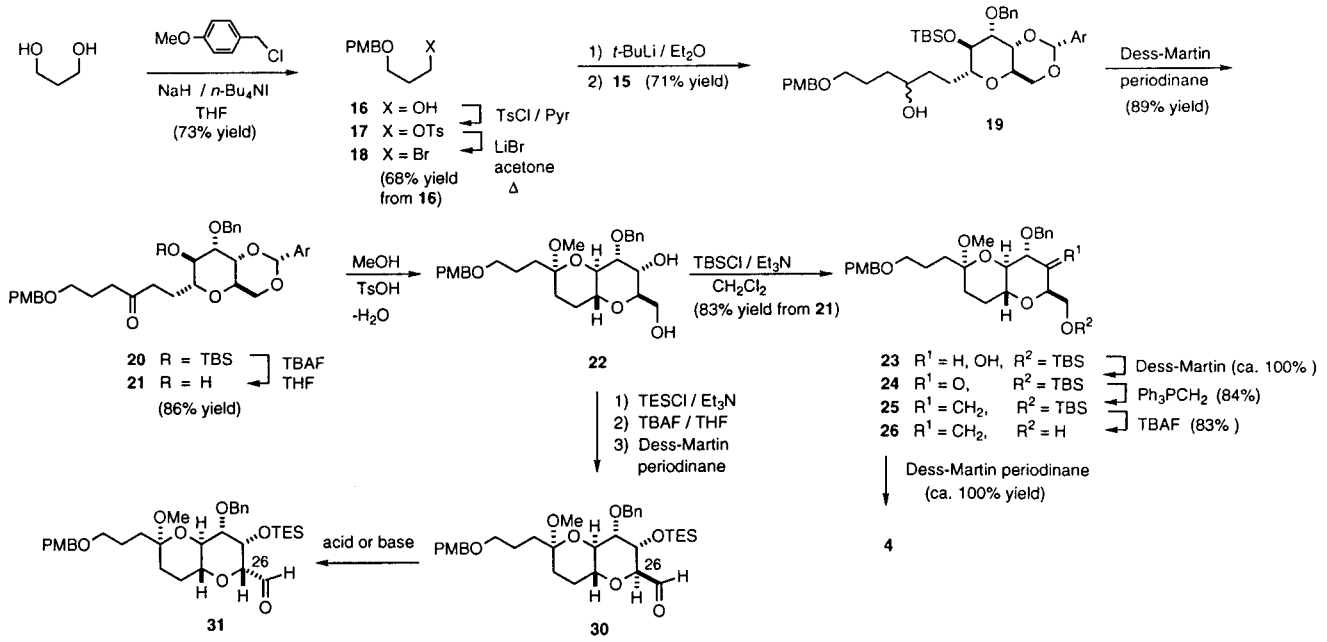
methylsilane provided a convenient and efficient method for installation of carbons 19−21. Acidic methanolysis removed the benzylidene group from **9**. The resultant triol **10** was treated with *N,O*-bis(trimethylsilyl)trifluoroacetamide to generate the tris-TMS ether derivative. Without isolation, the tris-TMS ether was treated with trimethylsilyl trifluoromethanesulfonate and allyltrimethylsilane to produce, after aqueous work up, propenylated product **11** as the major component of a ∼10:1 mixture of α:*β* epimers (Scheme 3). Conversion of crude **11** into the corresponding anisylidene derivative facilitated product purification and yielded the C19−C27 intermediate **12**. Before installing carbons C16−C18, the free C23 hydroxyl group of **12** was strategically capped as a silyl ether to give **13**. A routine hydroboration−oxidation sequence then converted alkene **13** into aldehyde **15**.

The remaining three carbons of the side chain were derived from 1,3-propane diol via bromide **18** (Scheme 4). Conversion of **18** into the corresponding organolithium followed by addition to aldehyde **15** gave a 1:1 diastereomeric mixture of C19 carbinols **19**. Treatment of **19** with Dess−Martin periodinane[57] provided **20** with C19 at the ketone oxidation state required for **1**. The C19 carbon of **20** was to remain at this oxidation state throughout the duration of the synthesis. However, this necessitated masking the carbonyl from nucleophilic attack or premature spiroketalization. A mixed-methyl ketal seemed an ideal choice for this. In addition to providing requisite protection of the ketone, intramolecular mixed ketal formation was expected to provide a rigid and stable *trans*-dioxadecalin system with a well-defined single anomeric configuration. Further, a mixed-methyl acetal would be expected to participate readily in an acid-triggered C16−C23 spiroketalization at the appropriate juncture late in the total synthesis. The targeted mixed-methyl acetal (**22**) could be obtained directly from silyl ether **20** by treatment with TsOH or CSA in methanol. However, silyl ether cleavage was sluggish under these conditions, requiring prolonged reaction times or forcing conditions, both of which led to competitive cleavage of the *p*-methoxybenzyl ether and subsequent C16−C23 spiroketalization. Instead, a two-step process involving cleavage of the silyl ether of **20** by treatment with TBAF, followed by ketalization of the resultant keto alcohol **21** in acidic methanol was favored. The C25−C27 anisylidene group was conveniently dispensed with in the process. Acetal **22** produced under these conditions appeared as only one anomeric isomer by 500-MHz ^{1}H NMR spectroscopy, in analogy to a model of the C16−C23 spiroketal moiety of **1** prepared previously.[44]

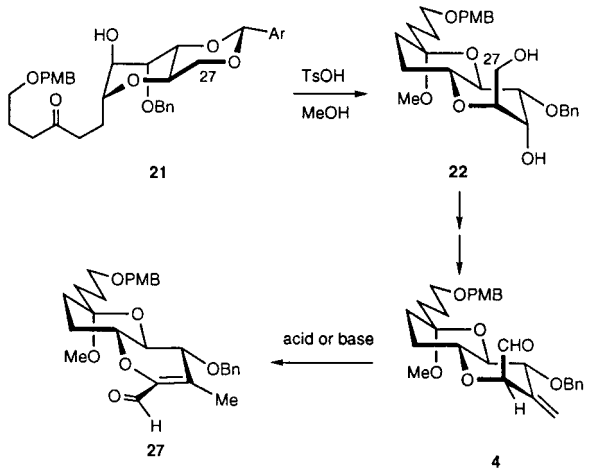
Treatment of **21** with acid under dehydrating conditions but without sufficient methanol present led to formation of the glycal corresponding to **22**. In addition, the mixed methyl acetal was susceptible to hydrolysis to give the corresponding hemiacetal in the presence of acid.[58] However, careful handling allowed the mixed acetal moiety present in **22** to be carried forward throughout the remainder of the synthetic sequence until called upon for end-game spiroketalization.

In the course of converting keto alcohol **21** into methyl acetal **22**, the central pyran ring is allowed to undergo a chair−chair ring flip concomitant with loss of the anisylidene group. Whereas the chair−chair conformation of **22** is buttressed by anomeric stabilization at C19 and equatorial deployment of the C19 alkyl side chain and C24 benzyloxy group, it places the

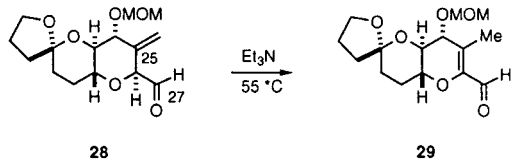
Scheme 4



C27 hydroxymethyl substituent axial with respect to the *trans*-dioxadecalin system. Thus, enolization of a derived C27 aldehyde may either lead to epimerization to place the C27 side chain in an equatorial position, or in the case of β,γ-unsaturated carboxaldehyde (**4**), lead to endocyclic migration of the alkene into conjugation to give **27**.



This latter concern is related to the base-induced conversion of **28** into **29** observed by Isobe and co-workers in model studies associated with the original synthesis of **1**.[51] The reported conjugation of **28** effected with Et_3N at 55 °C raised concerns that the β,γ-alkene might pose problems in a low-temperature coupling of a stabilized carbanion with a β,γ-unsaturated carboxaldehyde such as **28**. Therefore, installation of the C25 alkene was deferred until after C27−C28 bond formation in the Isobe synthesis of **1**. To minimize the extent of postcoupling transformations, however, we were interested in pursuing an alternative sequence.



Although the C26 α-proton of the targeted β,γ-unsaturated carboxaldehyde **4** is both allylic and adjacent to the C27 carbonyl group, the C25 alkene is not expected to contribute much to the kinetic acidity of the C26 proton. This is because the local conformation of the rigid *trans*-dioxadecalin system maintains the C26 carbon−proton σ-bond nearly perpendicular to the π-system of the C25 alkene in **4**. However, once enolized, γ-protonation may readily occur to migrate the alkene into conjugation (**27**). To determine the extent to which the presence of the C25 alkene might complicate a direct coupling between an unstabilized organometallic species and a β,γ-unsaturated carboxaldehyde, we first performed baseline studies with aldehyde derivatives of **22** that lacked the C25 alkene. Thus, routine protecting and functional group manipulations converted **22** into β-silyloxy aldehyde **30** (Scheme 4). Compound **30** did not undergo carbon−carbon bond formation with unstabilized primary organolithium and magnesium species cleanly, even at −78 °C. Instead, the equatorial C27 carboxaldehyde **31**, as well as other products of base-induced side reactions were observed. Hence, there seemed no advantage to attempt to optimize conditions for C27−C28 bond formation before installing the C25 exocyclic methylene group.

C25 was set up for methylenation by selective silylation of the primary alcohol of **22** to give silyl ether **23** (Scheme 4). Treatment of **23** with Dess−Martin periodinane gave ketone **24**, which could be methylenated using either Lombardo−Takai[59] or Wittig conditions to give **25**. Whereas the Lombardo−Takai olefination proceeded cleanly and without detectable epimerization, it required a large excess of reagent which made workup and isolation of **25** difficult. Wittig olefination according to Miljkovic and Glisin[60] was trouble-free. TBAF-induced removal of the silyl group from **25** provided primary alcohol **26**, which was converted into the corresponding aldehyde **4** with Dess−Martin periodinane. As was the case with axial carboxaldehyde **30**, β-methylenated aldehyde **4** was quite prone to isomerization, but in this case, isomerization to the α,β-conjugated carboxaldehyde **27** occurred. The equatorial carboxaldehyde 26-epi-**4** was never observed. Thus, **4** was best prepared from **26** immediately prior to use.

Aldehyde **4** was thus prepared in 14 steps from methyl 3-*O*-benzyl-α-D-altropyranoside **10**. Although preliminary studies aimed at defining useful conditions for C27−C28 bond formation were performed with simple organometallic species, the unique characteristics of carbanions generated from the C28−C38 intermediate **5** dictated that optimization be carried out with the actual synthetic intermediates. Hence, a facile synthesis of the C28−C38 portion of **1** was developed.

Synthesis of the C28−C38 Fragment (5). The C28−C38 domain of okadaic acid contains four stereogenic centers, including a contiguous triad spanning C29−C31, as well as the C34 spiroketal carbon. Because the two chair perhydropyran rings of the C30−C38 spiroketal benefit from mutual anomeric stabilization, while the bulkier C30 substituent adopts an equatorial position in preference to the axially disposed C31 methyl branch, the natural product's configuration at C34 was expected to result preferentially from simple spiroketalization and thermodynamic equilibration of the corresponding δ,δ'-dihydroxy ketone.[61,62] In contrast to the original synthesis of **1** where a phenylsulfonyl group was installed at C28 to stabilize a carbanion for C27−C28 bond formation,[34,35] an unstablized primary carbanion at C28 was planned here to simplify the overall synthetic sequence. Thus, the C28 bromide **5** was selected as a precursor to a range of potential organometallic species that could be used to explore formation of the C27−C28 bond. Because the bromide functionality could be elaborated from the corresponding primary alcohol, acid-induced spiroketalization−equilibration of an acyclic trihydroxy ketone (**32**) was planned (Scheme 5). Ketotriol **32** would derive from the corresponding trisbenzyloxy α,β-unsaturated ketone (**33**), which, in turn, could be obtained by Horner−Emmons coupling of a C33−C38 β-keto phosphonate (**35**) and a C28−C32 aldehyde (**34**). All of the stereochemistry of **5** would derive from the latter. This general approach could also provide synthetic access to the related dinophysistoxin natural products[6,63,64] by simply varying the methyl substitution at C31 and C35 in the aldehyde and keto phosphonate.

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

(58) This was first realized upon dissolving **22** in untreated $CDCl_3$ containing trace amounts of HCl.

(59) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.

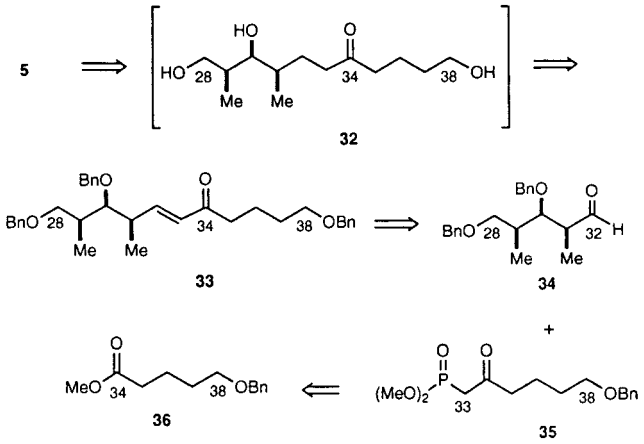
(60) Miljkovic, M.; Glisin, D. *J. Org. Chem.* **1975**, *40*, 3357.

(61) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**, *43*, 4759.

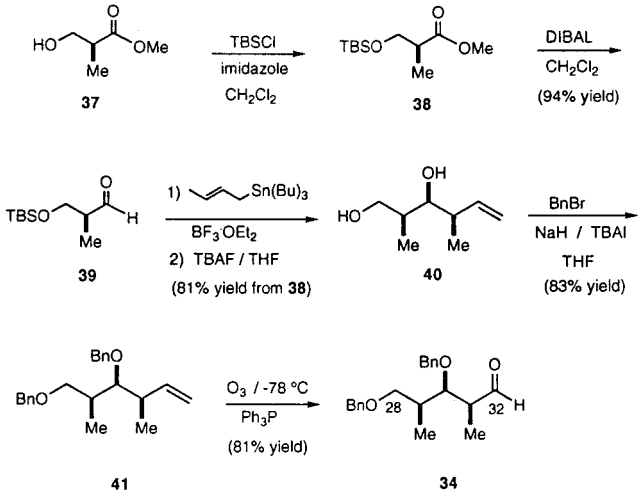
(62) Tsuboi, K.; Ichikawa, Y.; Isobe, M. *Synlett* **1997**, 713.

(63) Hu, T.; Doyle, J.; Jackson, D.; Marr, J.; Nixon, E.; Pleasance, S.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1992**, 39.

Scheme 5



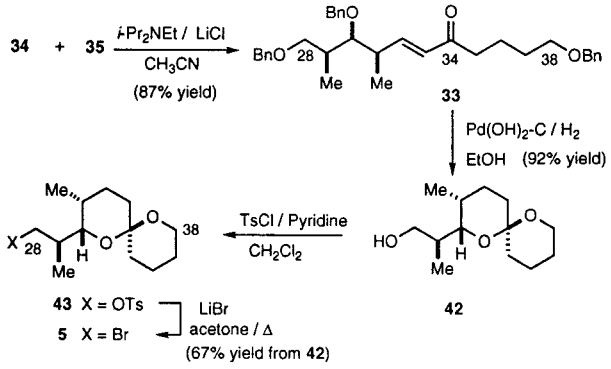
Scheme 6



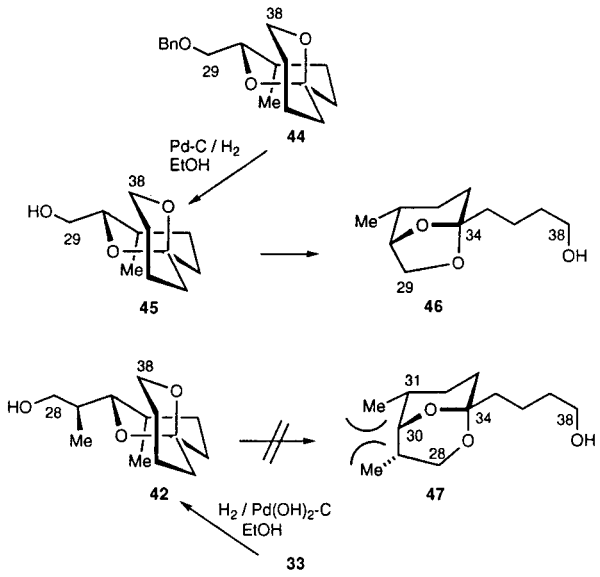
Carbons 34−38 were derived conveniently from δ-valerolactone via methyl ester **36**[65] (Scheme 5). Addition of the lithium anion of dimethyl methyl phosphonate to **36** provided β-keto phosphonate **35**. The stereochemical triad spanning C29−C31 was established in a direct fashion using Keck's crotylstannane methodology. Silylation of commercially available methyl (*S*)-3-hydroxy-2-methylpropionate (**37**), followed by reduction of the resulting ester **38** with DIBAL gave aldehyde **39** (Scheme 6). Keck had shown that the use of a silyl protecting group in aldehydes similar to **39** was required for high syn−syn diastereoselectivity in $BF_3{\cdot}OEt_2$-mediated crotyl stannane additions.[66] However, uniform protection of the hydroxyl groups as benzyl ethers was desired here to facilitate a subsequent reduction−spiroketalization sequence. Thus, the crude product of crotyl addition to **39** was desilylated with TBAF to afford diol **40** in 81% overall yield (~18:1 syn−syn:syn−anti) from **39**. Silyl group removal also facilitated chromatographic isolation of the crotyl addition product. After **40** was converted into dibenzyl ether **41**, ozonolytic cleavage of the alkene and reductive workup gave aldehyde **34**.

Coupling of **34** and **35** under Masamune−Roush conditions[50] provided *trans*-enone **33** without detectable epimerization of the α-aldehyde stereogenic center of **34** (Scheme 7). A two-step conversion of the trisbenzyloxy enone **33** into the spiroketal

Scheme 7



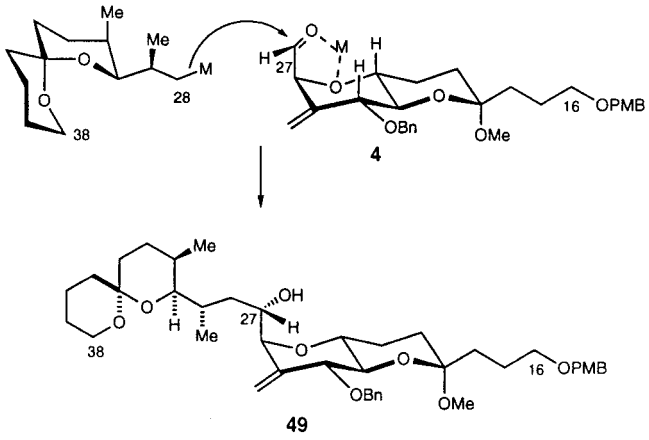
42 was planned. This was to involve reductive cleavage of the benzyl ethers and concomitant saturation of the alkene under Pd-catalyzed hydrogenation conditions, followed by a discrete acid-induced dehydration step. However, vigorous stirring of enone **33** with 20% palladium hydroxide on carbon in absolute ethanol under 1 atm of H_2 not only reduced the alkene and cleaved the three benzyl ethers, but also led directly to spiroketalization to give **42**. This in situ reduction−spiroketalization sequence was not only reproducible, but also stereoselective, giving the expected product of thermodynamic spiroketalization (**42**) in greater than 90% yield. Rather than being promoted by trace acid arising from the solvent,[67] it is likely that the commercially obtained $Pd(OH)_2$ on carbon used in this sequence provides a source of acid that promotes in situ thermodynamic spiroketalization.[68] In the original synthesis of **1**, prolonged exposure of benzyloxy spiroketal **44** to Pd-catalyzed hydrogenation conditions designed to simply cleave the benzyl ether and give **45**, led to competitive formation of the bridged spiroketal ketal isomer **46**.[61] No similar complication was observed with **42**, however, presumably because unfavorable steric interactions would be encountered between a C30 axial isopropyl-like substituent and an adjacent C31 equatorial methyl group on the pyran chair of hypothetical bridged spiroketal **47**. In a recently reported synthesis of the C28−C38 domain of **1**,[62] an alternative ordering of events precludes the possibility of undesired bridged spiroketal formation (cf. **46**).



(64) Sakai, R.; Rinehart, K. *J. Nat. Prod.* **1995**, *58*, 773.
(65) Hoye, T.; Kurth, M.; Lo, V. *Tetrahedron Lett.* **1981**, *22*, 815.
(66) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.
(67) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, *62*, 2678.
(68) Luss, E.; Forsyth, C. J. Unpublished results.

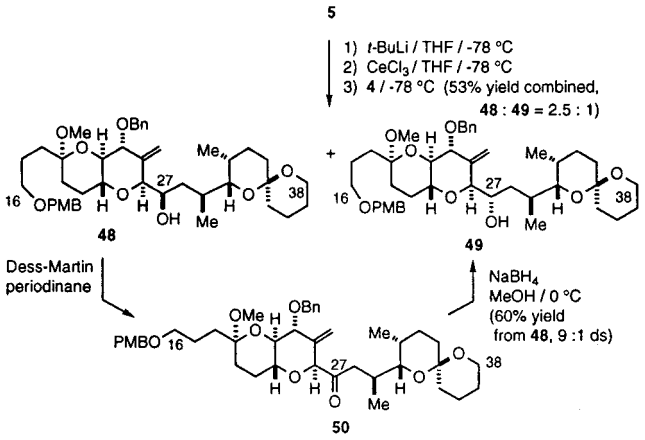
Having successfully constructed the fully functionalized C28−C38 domain of **1** in eight-steps from methyl (*S*)-3-hydroxy-2-methylpropionate, two additional steps were used to convert the primary alcohol **43** into the corresponding bromide **5** (Scheme 7). With multigram quantities of **5** thus available, direct C27−C28 bond formation could be thoroughly examined.

Convergent C27−C28 Bond Formation. The direct addition of an organometallic species derived from bromide **5** to aldehyde **4** would provide the fully functionalized C16−C38 portion of **1**. However, stereochemical control over C27 carbinol formation and the previously established base sensitivity of **4** were two important issues to be addressed. Intramolecular metal chelation involving the C27 aldehyde and the α-pyranyl oxygen would be expected to preferentially reveal the *pro-S* face of the aldehyde to nucleophilic species. Hence, the natural product's 27*S*-configuration might result from a chelation-controlled addition of a C28 nucleophile to the C27 aldehyde.



However, for any nucleophilic species to be useful for C27−C28 bond formation, enolization of the C27 aldehyde would have to be avoided. Preliminary studies revealed that simple Grignard reagents (EtMgBr, $Ph(CH_2)_3MgBr$) could be added cleanly to **4** at low temperature, but with essentially no stereoselectivity (∼1:1 27*R*:27*S*). The simple cuprate (*n*-$Bu)_2CuCNLi$ also added cleanly to **4** to give only a slight excess (<2:1) of the desired 27*S*-configuration. However, attempts to convert **5** into such species were unsuccessful and frustrating. The organolithium derived from **5** by metal−halogen exchange with *tert*-butyllithium was itself short-lived and difficult to handle. THF solutions of the generated organolithium could be maintained at low temperature and added to **4**, in poor yield (30−35%) and nonstereoselectively (1:1 ds). Use of the unmodified organolithium species gave predominantly α,β-unsaturated aldehyde **27**, as well as numerous other byproducts. Attempts to trans-metalate the organolithium derived from **5** at or below −78 °C with $MgBr_2$, CuBr·DMS, CuCN, or $CrCl_3$·THF prior to addition of **4** led to combinations of poor yields, unfavorable diastereoselectivities, and byproduct formation. Similar attempts to trans-metalate at temperatures much above −60 °C were also ineffective, yielding species that were either too basic or insufficiently nucleophilic. In the most stereoselectively favorable case, the use of stoichiometric 2-thienyl-CuCNLi in conjunction with the organolithium derived from **5** by metal−halogen exchange with *tert*-butyllithium appeared to give only the desired (27*S*)-alcohol diastereomer (**49**), but in ∼10% yield and accompanied by **27**, as well as polar byproducts. However, the organocerium species[69] derived from lithium−halogen exchange of **5** followed by addition of a THF suspension of $CeCl_3$[70] to the organolithium at −78 °C added successfully to aldehyde **4** to give the C27 carbinols **48** and **49** (2.5:1 diastereomeric ratio, respectively) in useful yield (Scheme 8).

Scheme 8



Several experiments were performed to assign the configurations at C27 of the chromatographically separable adducts **48** and **49**. First, an oxidation−reduction sequence analogous to that used in the original synthesis of **1** and in the preparation of [27-^{3}H]okadaic acid[71] was performed. Treatment of the major coupling diastereomer **48** with Dess−Martin periodinane gave ketone **50**. With a minimum of handling, the ketone was reduced with $NaBH_4$ at 0 °C to generate a 9:1 mixture of **49** and **48**, respectively. It had been established previously that the major, or exclusive, diastereomers resulting from $NaBH_4$ reduction of ketones similar to **50** have the same 27*S* configuration as **1**.[35,44] Next, carbinol **49** was subjected to the modified Mosher ester analysis.[72] Separate treatment of **49** with either (*R*)- or (*S*)-MTPA chloride and DMAP gave the corresponding (*S*)- and (*R*)-MTPA esters **51** and **52**, respectively. This led to an empirical assignment based upon the measured Δδ values of the C26 methine proton that was in accord with the above 27*S* configurational assignment. Final proof of configuration was, of course, later provided by conversion of **49** into **1**.[36,37]

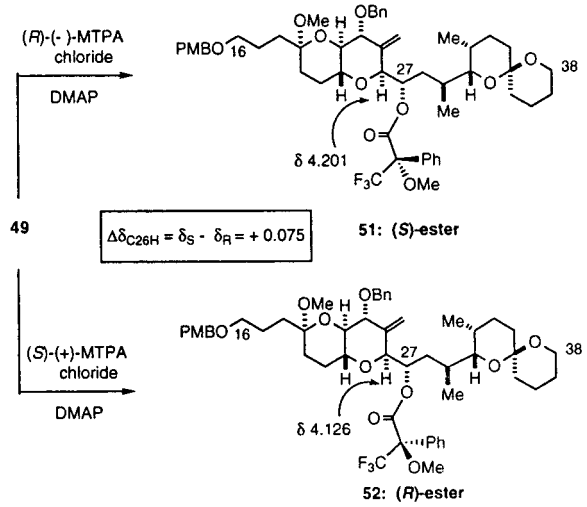
Inversion of the C27 carbinol configuration via the conversion of **48** into **49** via ketone **50** not only supported the stereochemical assignment, but also provided a facile preparative route to overcome the unfavorable coupling diastereoselectivity. Although modest in both yield and diastereoselectivity, this coupling−inversion protocol represented a reliable and useful method for the direct joining of okadaic acid intermediates **4** and **5**. Unfortunately, the use of an organocerium species for the formation of the C27−C28 bond did not provide the desired chelation control outcome to set the C27 stereogenic center. While this methodology is useful for the present purpose, the realization of a direct *and* diastereoselectively favorable coupling between an unstablized C28 carbanion and a base-sensitive aldehyde will require further study.

(69) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171.

(70) Obtained by treatment of commercially available $CeCl_3·7H_2O$ under conditions (see the Experimental Section) expected to generate the monohydrate $CeCl_3·H_2O$: Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.

(71) Levine, L.; Fujiki, H.; Yamada, K.; Ojika, M.; Gjika, H. B.; van Vumakis, H. *Toxicon* **1989**, *26*, 1123.

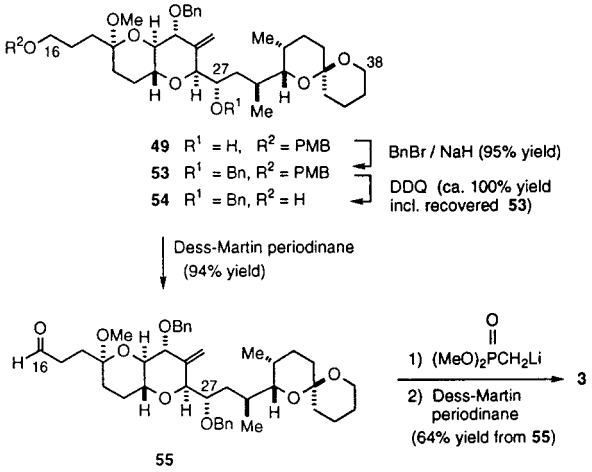
(72) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, *3*, 4092.



The phenyl sulfone carbanion mediated coupling of a C27 aldehyde with a C28−C38 fragment that was used in the original synthesis of **1** reportedly provided the (27*S*)-carbinol in 52% overall yield, after removal of the carbanion stabilizing group and correction of the C27 stereogenic center. Although the efficiency of this sequence is comparable to that of the direct coupling between **4** and **5** before the stereochemical adjustment via oxidation−reduction, having the C25 alkene and an optimal array of protecting groups already installed in **4** expedites the advancement of **49** toward **1**. More careful handling of the ketone **50** and/or a lower temperature reduction[35] than was performed here may further enhance the efficiency of generating **49**.

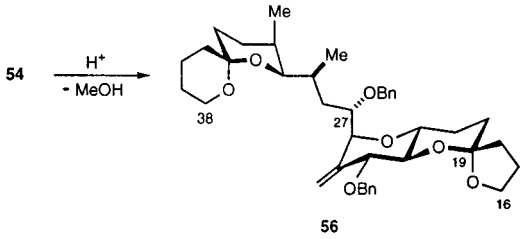
Preparation of a C15−C38 *β*-Keto Phosphonate (3). With the central and C38 terminal fragments of okadaic acid joined, preparation for the attachment of the C1−C14 domain required only elaboration of the C16 terminus into a *β*-keto phosphonate. This was preceded by conversion of the C27 hydroxyl of **49** into the corresponding benzyl ether **53** (Scheme 9). Oxidative

Scheme 9



removal of the *p*-methoxybenzyl group using DDQ[73] liberated the C16 hydroxyl to give **54**. However, unless the DDQ reaction mixture and the alcohol product were protected against low pH, spontaneous formation of the C16−C23 spiroketal occurred to give **56**, which appeared as a single isomer by 500 MHz ^{1}H NMR spectroscopy, by analogy to **22**.

(73) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.



This premature spiroketalization demonstrated the facility with which the C16−C23 1,6-dioxaspiro[4.5]decane ring system is formed from the mixed C19 methyl acetal, but it also diverted useful material. Thus, considerable attention was paid to preventing this side reaction from occurring, for example, by adding Et_3N to the crude product and the chromatography solvents. Oxidation of the primary alcohol of **54** with Dess−Martin periodinane buffered with $NaHCO_3$ gave the aldehyde **55** uneventfully. Thereafter, addition of the lithium anion of dimethyl methylphosphonate followed by a second oxidation with Dess−Martin periodinane delivered the *β*-keto phosphonate **3**.

Conclusions

The present synthesis provides the C15−C38 okadaic acid intermediate **3** in ∼19 linear steps from methyl 3-*O*-benzyl-α-D-altropyranoside **9**. The utilization of a readily available D-altrose derivative[54] for C22−C27, as well as the expeditious assembly of the C28−C38 spiroketal-containing fragment contribute substantially to the overall efficiency of this approach. The direct, convergent coupling of the central and lipophilic domains of **1** illustrated here may allow for the facile preparation of analogues varying in substitution and functionalization in both of these regions. Hence, the dinophysistoxin natural products,[6,63,64] as well as nonnatural derivatives,[62] which may be designed to probe specific interactions with the phosphatase receptors, may be accessed by variations of this synthetic theme. Opportunities to improve upon this route include the correction and enhancement of the stereoselectivity of C27−C28 bond formation, and the development of a more convergent annulation of C15−C21 upon the C22−C27 core. Nonetheless, the current synthesis provides relatively succinct access to the fully functionalized C15−C38 portion of okadaic acid. As described in an accompanying paper, this advanced intermediate (**3**) was elaborated into **1** in only five additional steps.[37]

Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out under an argon or nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa techniques. Benzene, diethyl ether, toluene, and tetrahydrofuran were distilled from sodium or potassium/benzophenone ketyl under N_2 immediately prior to use; dichloromethane, triethylamine, acetonitrile, allyltrimethylsilane, oxalyl chloride, dimethyl sulfoxide, pyridine, and diisopropylethylamine were distilled from CaH_2. DMF was distilled from BaO under vacuum. All other solvents were used as received. $Pd(OH)_2$ on carbon [20% by wt $Pd(OH)_2$] was obtained from Aldrich Chemical Co. LiBr and LiCl were dried by heating at 140 °C for 14 h at ∼0.4 Torr. Silica gel chromatography of **22** and all subsequent intermediates bearing the C19 mixed-methyl acetal was performed with triethylamine (0.5 vol %) present in the chromatography solvents, even if this was not specified in experimental procedures given below. Analytical TLC was performed with 0.25 mm EM silica gel 60 F_{254} plates. NMR spectra are referenced to residual $CHCl_3$ at 7.25 (^{1}H) and 77.0 ppm (^{13}C). The mass spectrometers used show deviations of less than 5 ppm. Melting points are uncorrected. Combustion analyses were performed by M−H−W Laboratories (Phoenix, AZ).

1. Synthesis of the C16−C27 Fragment. 1-Deoxy-1-*C*-(2-propenyl)-α-D-3-*O*-benzyl-4,6-di-*O*-*p*-anisylidenealtropyranoside (12). To a stirred room-temperature solution of **10** (10.8 g, 37.8 mmol) in acetonitrile (150 mL) was added *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (40.2 mL, 151 mmol) under Ar. The resultant solution was heated to 70−80 °C for 2.5 h, and then cooled to room temperature before allyltrimethylsilane (30.0 mL, 189 mmol) and trimethylsilyl trifluoromethanesulfonate (36.4 mL, 189 mmol) were added. After the solution was stirred at room temperature for 12 h, it was cooled to 0 °C and ethyl acetate (800 mL) and saturated aqueous $NaHCO_3$ (200 mL) were added. The separated organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), H_2O (2 × 100 mL), and saturated aqueous NaCl (2 × 100 mL). The aqueous phases were combined and extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was suspended in dichloromethane and gravity-filtered through filter paper, and the filtrate was concentrated. The resultant crude triol (37.8 mmol theor) was dissolved in CH_2Cl_2 (350 mL) and cooled to 0 °C under Ar. *p*-Anisaldehyde dimethyl acetal (6.58 mL, 38.3 mmol), (±)-camphorsulfonic acid (404 mg, 1.74 mmol), and 4 Å molecular sieves (∼50 g) were added, and the resultant mixture was allowed to warm to room temperature and stir for 3.5 h, at which time the TLC showed no remaining triol. Ethyl acetate (120 mL) and saturated aqueous $NaHCO_3$ (25 mL) were added, the mixture was filtered through a fritted glass funnel and the separated organic phase was washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL) and saturated aqueous NaCl (30 mL). The aqueous phases were combined and extracted with ethyl acetate (2 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1−2:1, v/v) of the residue gave **12** (10.1 g, 24.5 mmol, 65% from **10**) as an off-white solid: mp 84−87 °C (hexanes−ethyl acetate); R_f 0.25 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{23}_D$ = +57.9 (*c* 1.14, $CHCl_3$); IR (neat) 3420, 2900, 1639, 1610, 1515, 1450, 1246, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (d, J = 9 Hz, 2H), 7.26−7.38 (m, 5H), 6.91 (d, J = 9 Hz, 2H), 5.79 (m, 1H), 5.55 (s, 1H), 5.12 (m, 1H), 5.10 (m, 1H), 4.93 (d, J = 12.5 Hz, 1H), 4.65 (d, J = 12.5 Hz, 1H), 4.27 (dd, J = 5, 10 Hz, 1H), 4.20 (ddd, J = 5, 9.5, 9.5 Hz, 1H), 4.03 (dd, J = 2.5, 9.5 Hz, 1H), 3.95 (m, 2H), 3.85 (dd, J = 7.5, 7.5 Hz, 1H), 3.82 (s, 3H), 3.73 (dd, J = 10, 10 Hz, 1H), 2.88 (dddd, J = 1.5, 7.8, 7.8, 15.5 Hz, 1H), 2.63 (ddd, J = 7, 7, 14 Hz, 1H), 1.96 (d, J = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1, 138.7, 134.8, 130.3, 128.3, 127.5, 127.4, 117.5, 113.7, 102.4, 79.2, 77.8, 76.3, 73.8, 70.5, 69.7, 60.4, 55.3, 34.1. Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.77; H, 6.69.

1-Deoxy-1-*C*-[(*R*,*S*)-3-hydroxy-6-[(4-methoxybenzyl)oxy]hexanyl]-α-D-3-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-4,6-di-*O*-*p*-anisylidenealtropyranosides (19). To a stirred −78 °C solution of **18** (404 mg, 1.55 mmol) in diethyl ether (7.8 mL) under Ar was added *tert*-butyllithium (1.74 mL of a 1.7 M solution in pentane, 3.0 mmol). The resulting solution was stirred for 20 min before a solution of **15** (423 mg, 780 μmol) in diethyl ether (7.8 mL) was added slowly via cannula. The resultant solution was stirred for an additional 15 min before saturated aqueous NH_4Cl (5 mL) was added. After the mixture was warmed to 0 °C, it was extracted with diethyl ether (25 mL), and the separated organic phase was washed with saturated aqueous NH_4Cl (15 mL), H_2O (2 × 15 mL) and saturated aqueous NaCl solution (2 × 15 mL). The combined aqueous layers were extracted with diethyl ether (2 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 2:1, v/v) of the residue gave **19** (402 mg, 555 μmol, 71%) as a 1:1 diastereomeric mixture and colorless oil: R_f 0.34 (hexanes−ethyl acetate, 2:1, v/v); IR (neat) 3457, 2930, 1614, 1515, 1464, 1249, 1098, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 1:1 diastereomeric mixture) δ 7.43 (d, J = 8.5 Hz, 4H), 7.23−7.34 (m, 10H), 6.89 (d, J = 7.2 Hz, 4H), 6.87 (d, J = 8.2 Hz, 4H), 5.54 (s, 2H), 4.89 (d, J = 12.2 Hz, 1 H), 4.88 (d, J = 12.3 Hz, 1H), 4.61 (d, J = 12.3 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.44 (s, 4H), 4.23 (m, 2H), 4.14 (m, 2H), 4.01 (m, 2H), 3.80 (s, 6H), 3.78 (s, 6H), 3.59−3.76 (m, 10H), 3.47 (t, J = 5.6 Hz, 4H), 2.73 (d, J = 3.8 Hz, 1H), 2.62 (d, J = 4.2 Hz, 1H), 2.29 (m, 2H), 1.50−1.70 (m, 14H), 0.86 (s, 18H), −0.01 (s, 3H), −0.02 (s, 3H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 1:1 diastereomeric mixture) δ 168.0, 160.1, 159.2, 138.8, 130.5, 130.3, 130.2, 129.4, 129.3, 128.6, 128.3, 127.6, 127.56, 114.0, 113.9, 113.6, 102.2, 80.4, 80.1, 76.7, 73.5, 73.4, 72.7, 72.1, 71.6, 71.1, 70.3, 69.9, 59.9, 59.8, 55.3, 55.28, 35.1, 34.8, 34.7, 34.5, 26.4, 26.3, 25.9, 25.8, 25.5, 18.06, −5.00, −5.03. Anal. Calcd for $C_{41}H_{58}O_9Si$: C, 68.11; H, 8.09. Found: C, 68.28; H, 7.96.

Acetal 22. A solution of **21** (170 mg, 280 μmol), benzene (12 mL), anhydrous methanol (5 mL), and *p*-toluenesulfonic acid monohydrate (5.3 mg, 28 μmol) was heated at reflux under a Dean−Stark trap and N_2 for 3.5 h, at which point TLC showed no remaining **21**. The solution was cooled to room temperature, diluted with diethyl ether (50 mL), and washed with 10% aqueous NaOH (5 mL), H_2O (20 mL), and saturated aqueous NaCl (20 mL). The combined aqueous phases were extracted with ethyl acetate (3 × 25 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give crude **22** (143 mg) as a yellow oil. This was used without further purification. Preparative TLC (hexanes−ethyl acetate, 1:5, v/v) provided an analytical sample of **22** as a white solid: mp 56−58 °C (hexanes−ethyl acetate); R_f 0.22 (hexanes−ethyl acetate, 1:5, v/v); $[\alpha]^{23}_D$ = −7.3 (*c* 0.55, $CHCl_3$); IR (neat) 3292, 2956, 1613, 1514, 1454, 1248, 1101, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.86 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.8 Hz, 1H), 4.44 (s, 2H), 4.07 (dd, J = 5, 9 Hz, 1H), 3.95 (m, 1H), 3.79−3.87 (m, 2H), 3.78 (s, 3H), 3.55 (m, 2H), 3.46 (t, J = 6 Hz, 2H), 3.32 (ddd, J = 4.5, 10, 10 Hz, 1H), 3.20 (s, 3H), 2.88 (s, 1H), 2.19 (br s, 1H), 1.78−1.92 (m, 4H), 1.52−1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 138.3, 130.6, 129.2, 128.5, 127.8, 127.6, 113.8, 99.4, 78.3, 76.7, 73.0, 72.6, 71.5, 70.0, 69.6, 68.3, 59.7, 55.3, 47.5, 32.4, 32.3, 25.2, 24.0. Anal. Calcd for $C_{28}H_{38}O_8$: C, 66.91; H, 7.62. Found: C, 66.84; H, 7.82.

C25 Ketone 24. To a stirred room-temperature solution of **23** (225 mg, 365 μmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (2.45 g, 29.1 mmol), followed by the Dess−Martin periodinane reagent [57] (1.24 g, 2.91 mmol). The resultant mixture was allowed to stir for 2 h. Diethyl ether (50 mL), saturated aqueous $NaHCO_3$ (10 mL), and 10% aqueous $Na_2S_2O_3$ (10 mL) were added, and the mixture was stirred until the organic layer became clear. The separated organic phase was washed with H_2O (2 × 10 mL) and saturated aqueous NaCl (2 × 10 mL). The aqueous phases were combined and extracted with diethyl ether (2 × 25 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through a pad of silica gel with hexanes−ethyl acetate (2:1, v/v) and the eluant concentrated to yield crude **24** (223 mg) as an oil. This was used without further purification. Preparative TLC (hexanes−ethyl acetate, 2:1, v/v) provided an analytical sample of **24** as a colorless oil: R_f 0.50 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{22}_D$ = −17.3 (*c* 1.95, $CHCl_3$); IR (neat) 2954, 2857, 1731, 1612, 1513, 1462, 1249, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (d, J = 8.5 Hz, 2H), 7.26−7.30 (m, 5H), 6.88 (d, J = 8.5 Hz, 2H), 5.00 (d, J = 12 Hz, 1H), 4.80 (d, J = 12 Hz, 1H), 4.46 (s, 2H), 4.16 (ddd, J = 6, 10, 10 Hz, 1H), 4.12 (dd, J = 2.5, 2.5 Hz, 1H), 4.05 (d, J = 10.5 Hz, 1H), 3.95 (m, 2H), 3.79 (s, 3H), 3.74 (dd, J = 10, 10 Hz, 1H), 3.47 (t, J = 6 Hz, 2H), 3.21 (s, 3H), 1.80−1.92 (m, 4H), 1.55−1.60 (m, 4H), 0.81 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.8, 159.2, 138.2, 130.6, 129.2, 128.2, 127.7, 127.6, 113.8, 99.0, 83.6, 83.3, 74.5, 74.1, 72.6, 72.1, 70.0, 66.6, 55.3, 47.5, 32.2, 31.9, 25.9, 25.8, 25.5, 24.1, 18.0, −5.7, −5.8. Anal. Calcd for $C_{34}H_{50}O_8Si$: C, 66.42; H, 8.20. Found: C, 66.36; H, 8.12.

C25 Alkene 25. To a room temperature solution of methyltriphenylphosphonium bromide (325 mg, 910 μmol) in toluene (8.5 mL) under N_2 was added potassium hexamethyldisilazide (1.45 mL of a 0.5 M solution in toluene, ∼728 μmol). The resulting deep yellow mixture was heated to 90 °C for 30 min and then cooled to room temperature before a solution of ketone **24** (365 μmol theor) in toluene (2 mL) was added via cannula. The resultant solution was heated to 90 °C for 30 min and then cooled to room temperature before saturated NH_4Cl (4 mL) was added. The toluene was removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate (35 mL). The organic phase was washed with H_2O (2 × 10 mL) and saturated aqueous NaCl (2 × 10 mL). The combined aqueous phases were extracted with ethyl acetate (2 × 25 mL), and the combined

organic extracts were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 8:1−5:1, v/v) of the residue gave **25** (189 mg, 308 μmol, 84% from **23**) as a colorless oil: R_f 0.33 (hexanes−ethyl acetate, 5:1, v/v); $[\alpha]^{25}_D = -11$ (*c* 0.89, $CHCl_3$); IR (neat) 2940, 1737, 1610, 1585, 1510, 1460, 1245, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, $J = 7.5$ Hz, 2H), 7.26−7.34 (m, 5H), 6.88 (d, $J = 7.5$ Hz, 2H), 5.42 (dd, $J = 2$, 2 Hz, 1H), 5.06 (s, 1H), 4.91 (d, $J = 12$ Hz, 1H), 4.79 (d, $J = 12$ Hz, 1H), 4.45 (s, 2H), 4.30 (dd, $J = 5$, 5 Hz, 1H), 4.19 (d, $J = 9.5$ Hz, 1H), 3.80 (s, 3H), 3.78−3.86 (m, 2H), 3.65 (dd, $J = 9$, 16 Hz, 1H), 3.47 (t, $J = 6$ Hz, 2H), 3.40 (dd, $J = 10$, 10 Hz, 1H), 3.21 (s, 3H), 1.77−1.87 (m, 4H), 1.56−1.61 (m, 4H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 143.3, 139.1, 130.6, 129.2, 128.3, 127.5, 127.4, 113.8, 111.8, 99.2, 80.7, 78.2, 73.9, 72.6, 71.0, 70.1, 65.2, 55.3, 47.4, 32.4, 32.3, 25.9, 25.7, 24.1, 18.3, −5.4. Anal. Calcd for $C_{35}H_{52}O_7Si$: C, 68.59; H, 8.55. Found: C, 68.49; H, 8.37.

2. Synthesis of the C28−C38 Fragment. (2*S*,3*S*,4*R*)-2,4-dimethylhex-5-ene-1,3-diol (40).[66,74] To a stirred −98 °C solution of (*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropanal (**39**, 7.546 g, 37.4 mmol) in CH_2Cl_2 (300 mL) under Ar was added borontrifluoride etherate (9.65 mL, 78.4 mmol) via syringe over 5 min. Tri-*n*-butylcrotylstannane[75,76] (15 mL, ∼37 mmol) was added via cannula over 10 min. After 1 h, the solution was allowed to warm to room temperature and stir for an additional 2 h before tetra-*n*-butylammonium fluoride in THF (50 mL of a 1 M solution in THF, 50 mmol) was added. After 1 h, the solution was cooled to 0 °C and diluted with diethyl ether, and saturated aqueous $NaHCO_3$ was added until the aqueous phase was neutral to pH paper. The mixture was filtered, and the separated organic phase was washed with H_2O and saturated aqueous NaCl (150 mL ea) and then concentrated by rotary evaporation. The biphasic residue was extracted with ethyl acetate, and the combined organic extracts were concentrated to a residue that was purified by silica gel column chromatography (hexanes−ethyl acetate, 5:1−1:2, v/v) to give **40** (4.335 g, 30.1 mmol, 81%), as a clear, colorless liquid: R_f 0.21 (hexanes−ethyl acetate, 1:1, v/v); $[\alpha]^{23}_D = +37$ (*c* 0.7, $CHCl_3$); IR (neat) 3312, 2967, 1467, 1325, 1128, 1094, 1037, 992 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.63 (ddd, $J = 8.5$, 10.0, 17.0 Hz, 1H), 5.08 (dd, $J = 1.5$, 17.0 Hz, 1H), 5.00 (dd, $J = 1.5$, 10.0 Hz, 1H), 3.74 (dd, $J = 4.0$, 10.5, Hz, 1H), 3.69 (dd, $J = 5.0$, 10.5, Hz, 1H), 3.58 (dd, $J = 2.5$, 9.0 Hz, 1H), 2.31 (m, 1H), 1.84 (m, 1H), 1.10 (d, $J = 6.5$ Hz, 3H), 0.96 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.7, 114.7, 77.4, 67.9, 42.1, 36.5, 16.9, 8.9; HRMS calcd for $C_8H_{17}O_2$ $[M + H]^+$ 145.1229, found 145.1224.

(2*S*,3*R*,4*S*)-1,3-Bis(benzyloxy)-2,4-dimethylpentanal (34). A stream of O_2/O_3 was bubbled through a solution of **41** (1.280 g, 3.95 mmol) in CH_2Cl_2 (50 mL) at −78 °C until a faint blue color persisted. A stream of N_2 was then bubbled through the solution until it became colorless. Triphenylphosphine (1.553 g, 5.93 mmol) was added, and the mixture was allowed to warm to room temperature and stir for 1.5 h. The solution was concentrated and the residue purified by silica gel column chromatography (hexanes−ethyl acetate, 10:1, v/v) to give **34** (1.041 g, 3.20 mmol, 81%) as a clear, colorless oil: R_f 0.72 (hexanes−ethyl acetate, 5:1, v/v); $[\alpha]^{25}_D = +30$ (*c* 1.95, $CHCl_3$); IR (neat) 3064, 3030, 2971, 1721, 1496, 1454, 1361, 1207, cm^{-1}; ^1H NMR ($CDCl_3$, 500Mz): δ 9.79 (s, 1H), 7.37−7.26 (m, 10H), 4.54 (d, $J =$ 11.0 Hz), 4.49 (d, $J = 11.0$ Hz, 1H), 4.47 (s, 2H), 4.00 (dd, $J = 5.0$, 7.0 Hz, 1H), 3.45 (dd, $J = 7.0$, 9.5 Hz, 1H), 3.36 (dd, $J = 5.0$, 9.0 Hz, 1H), 2.69 (dt, $J = 5.0$, 7.0 Hz, 1H), 2.04 (m, 1H), 1.16 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4, 138.3, 138.2, 128.4, 128.3, 127.7, 127.6, 127.5, 73.9, 73.1, 72.7, 50.0, 36.8, 12.7, 9.4; HRMS calcd for $C_{21}H_{26}O_3$ $[M + H]^+$ 327.1960, found 327.1960.

(2*S*,3*S*,4*R*)-1,3,11-Tris(benzyloxy)-2,4-dimethylundec-5-en-7-one (33). To a mixture of LiCl (381 mg, 8.27 mmol) and **35** (2.360 g, 7.52 mmol) in acetonitrile (90 mL) at room temperature under Ar was added diisopropylethylamine (1.298 mL, 7.52 mmol). The resultant mixture was stirred for 10 min before a solution of **34** (1.686 g, 5.17 mmol) in acetonitrile (10 mL) was added via cannula. After the reaction mixture was stirred for 6 h, it was diluted with ethyl acetate (250 mL), washed with aqueous 5% HCl, H_2O, and saturated aqueous NaCl (100 mL ea). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 10:1−5:1, v/v) to give **33** (2.318 g, 4.51 mmol, 87%) as a clear, colorless oil: R_f 0.39 (hexanes−ethyl acetate, 5:1, v/v); $[\alpha]^{25}_D = +3.2$ (*c* 0.75, $CHCl_3$); IR (neat) 3300, 3030, 2930, 1693, 1454, 1098, 1028, 986 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.27 (m, 15H), 6.78 (d, $J = 8.5$, 16.0 Hz, 1H), 6.11 (d, $J =$ 16.0 Hz, 1H), 4.58 (d, $J = 11.5$ Hz, 1H), 4.52 (d, $J = 11.5$ Hz, 1H), 4.50 (s, 2H), 4.46 (d, $J = 3.5$ Hz, 2H), 3.56 (dd, $J = 3.0$, 7.5 Hz, 1H), 3.49 (t, $J = 6.5$ Hz, 2H), 3.43 (dd, $J = 8.5$, 8.5 Hz, 1H), 3.32 (dd, J = 5.5, 9.5 Hz, 1H), 2.65 (m, 1H), 2.55 (t, $J = 7.5$ Hz, 2H), 1.97 (m, 1H), 1.73−1 64 (m, 4H), 1.15 (d, $J = 6.5$ Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.4, 149.2, 138.6, 138.3, 129.5, 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.3, 82.2, 73.1, 73.0, 72.9, 70.0, 40.4, 39.8, 36.6, 29.3, 20.9, 16.4, 11.0; HRMS calcd for $C_{34}H_{43}O_4$ $[M + H]^+$ 515.3161, found 515.3181, calcd for $C_{34}H_{46}NO_4$ $[M + NH_4]^+$ 532.3427, found 532.3425.

[2*R*(1′*S*),3*R*]-2-[2-Hydroxy-1-methylethyl]-3-methyl-1,7-dioxaspiro-[5.5]undecane (42). A mixture of **33** (2.04 g, 3.97 mmol) and 20% $Pd(OH)_2$ on carbon (0.04 g, 0.3 mmol) in absolute ethanol (40 mL) was stirred vigorously under 1 atm of H_2 for 15 h. The mixture was filtered through Celite with ethyl acetate. The filtrate was concentrated and the residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 4:1, v/v) to give **42** (901 mg, 3.65 mmol, 92%) as a clear, colorless oil: R_f 0.59 (hexanes−ethyl acetate, 1:1, v/v); $[\alpha]^{25}_D$ = +69 (*c* 1.55, $CHCl_3$); IR (neat) 3402, 2936, 2875, 1452, 1383, 1181, 1071, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.68 (m, 1H), 3.65 (dd, $J = 5.0$, 11.0 Hz, 1H), 3.56 (m, 1H), 3.54 (dd, $J = 2.5$, 9.5 Hz, 1H), 3.48 (dd, $J = 6.5$, 11.0 Hz, 1H), 2.03 (dddd, $J = 4.5$, 4.5, 9.0, 9.0, Hz, 1H), 1.19−1.72 (m, 3H), 1.70−1.34 (m, 8H), 1.13 (d, $J = 6.5$ Hz, 3H), 0.94 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 95.7, 72.6, 64.9, 60.4, 37.6, 35.9, 30.3, 28.1, 26.4, 25.4, 18.7, 14.4, 11.4; HRMS calcd for $C_{13}H_{25}O_3$ $[M + H]^+$ 229.1804, found 229.1794, calcd for $C_{13}H_{28}NO_3$ $[M+NH_4]^+$ 246.2069, found 246.2070.

3. Synthesis of the C15−C38 Fragment. C27−C28 Bond Formation [(27*R*)-48 and (27*S*)-49]. $CeCl_3 \cdot 7H_2O$ (714 mg, 1.92 mmol) was magnetically stirred in a 10-mL conical two-necked flask at 150 °C and 0.4 Torr for 18 h. After the $CeCl_3$ was cooled to 0 °C under Ar (1 atm), THF (3.3 mL) was added. The resultant slurry was allowed to warm to room temperature and stir for ∼5 h. Bromide **5** (176 mg, 605 μmol) was azeotropically dried from benzene, dissolved in THF (3.4 mL), and the resulting solution was cooled to −78 °C under Ar. *tert*-Butyllithium (616 μL of a 1.77 M solution in pentane, 1.09 mmol) was added dropwise under Ar. The resultant deep yellow solution was stirred for 45 min, before the $CeCl_3$/THF slurry prepared above was added dropwise via syringe (16 Ga needle), resulting in a brown suspension. After the suspension was stirred for 15 min, a solution of aldehyde **4** (135 μmol theor, azeotropically dried from benzene) in THF (2 mL) was added via cannula. After 30 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was allowed to warm to room temperature. THF (5 mL) was added and the mixture was filtered through Celite, followed by ethyl acetate washes. The organic solvents were removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate (35 mL). The separated organic phase was washed with H_2O (1 × 10 mL) and saturated aqueous NaCl (2 × 10 mL). The aqueous phases were extracted with ethyl acetate, and the organic phases were combined, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes−ethyl acetate, 5:1−2:1, v/v) of the residue gave **48** and **49** (50.4 mg, 71.1 μmol, 53%) as a 2.5:1 mixture on the basis of integration of the 300-MHz ^1H NMR resonances at δ 5.14 and 5.06, respectively. An analytical sample of each diastereomer was obtained as an oil upon further silica gel column chromatography. Data for **48**: R_f 0.35 (hexanes−ethyl acetate, 2:1, v/v); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.41 (m, 7H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.58 (dd, $J = 1.8$, 1.8 Hz, 1H), 5.14 (s, 1H), 4.96 (d, $J = 12$ Hz, 1H), 4.78 (d, $J = 12$ Hz, 1H), 4.45 (s, 2H), 4.13 (m, 1H), 3.96 (m, 1H), 3.89 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 3.69 (ddd, $J = 3$, 11, 11 Hz, 1H), 3.57

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(m, 1H), 3.44 (m, 5H), 3.20 (s, 3H), 1.76−1.99 (m, 8H), 1.48−1.66 (m, 11H), 1.37−1.45 (m, 4H), 1.17 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H); HRFABMS calcd for $C_{41}H_{57}O_8$ $[M - OCH_3]^+$ 677.4053, found 677.4080.

Data for **49**: R_f 0.26 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{23}_D$ = +1.2 (*c* 1.4, $CHCl_3$); IR (neat) 3480, 2930, 1610, 1510, 1450, 1240, 1090, 990 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.39 (m, 7H), 6.88 (d, J = 8.7 Hz, 2H), 5.47 (s, 1H), 5.06 (s, 1H), 4.90 (d, J = 12 Hz, 1H), 4.77 (d, J = 12 Hz, 1H), 4.46 (s, 2H), 4.00 (dd, J = 10, 10 Hz, 1H), 3.90 (m, 2H), 3.80 (s, 3H), 3.69 (ddd J = 3, 11, 11 Hz, 1H), 3.39−3.61 (m, 5H), 3.26 (dd, J = 2, 10 Hz, 1H), 3.21 (s, 3H), 2.47 (s, 1H), 1.77−2.06 (m, 8H), 1.48−1.68 (m, 11H), 1.38−1.45 (m, 3H), 0.97 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 147.0, 141.9, 138.6, 130.6, 129.2, 128.3, 127.6, 113.8, 99.3, 95.6, 85.1, 76.9, 75.1, 73.8, 72.6, 70.1, 69.9, 64.4, 60.4, 55.3, 47.5, 35.9, 35.2, 32.3, 31.0, 30.4, 27.4, 26.4, 25.5, 24.0, 18.8, 16.2, 10.7; HRFABMS calcd for $C_{41}H_{57}O_8$ $[M - OCH_3]^+$ 677.4053, found 677.4003.

Alcohol 54. To a stirred room temperature solution of **53** (27 mg, 34 μmol) in CH_2Cl_2 (2.2 mL) in a 25-mL round-bottom flask was added aqueous phosphate buffer (pH 7, 2.2 mL), *tert*-butyl alcohol (420 μL), and DDQ (23 mg, 0.10 mmol). The flask was immersed and sonicated in a H_2O bath for 15 min then removed from the bath. Triethylamine (100 μL) and diethyl ether (15 mL) were added, and the resulting mixture was washed with saturated aqueous $NaHCO_3$ (2 × 3 mL), H_2O (2 × 3 mL), and saturated aqueous NaCl (2 × 3 mL). The combined aqueous phases were extracted with diethyl ether (2 × 5 mL), and triethylamine (100 μL) was added to the combined organic extracts. Drying over Na_2SO_4, filtration and concentration gave a residue that was purified by silica gel column chromatography (hexanes−ethyl acetate-triethylamine, 5:1:0.3, v/v/v) to give **54** (17 mg, 25 μmol, 75%) and **53** (7.1 mg, 8.9 μmol) as colorless oils. Data for **54**: R_f 0.14 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D$ = +19 (*c* 0.60, $CHCl_3$); IR (neat) 3430 (broad), 2930, 1495, 1450, 1350, 1230, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.38 (m, 10H), 5.44 (dd, J = 1.8, 1.8 Hz, 1H), 5.06 (s, 1H), 4.86 (d, J = 12.3 Hz, 1H), 4.74 (d, J = 12.3 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.58 (d, J = 11.1 Hz, 1H), 4.27 (d, J = 7.8 Hz, 1H), 3.91 (m, 2H), 3.69 (m, 3H), 3.64 (m, 2H), 3.43 (dd, J = 9.6, 9.6 Hz, 1H), 3.24 (s, 3H), 3.22 (m, 1H), 1.79−2.06 (m, 8H), 1.49−1.67 (m, 11H), 1.38−1.45 (m, 3H), 1.26 (s, 1H), 0.94 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5, 138.7, 128.3, 128.2, 127.63, 127.6, 127.5, 127.4, 112.7, 99.3, 95.7, 85.2, 77.3, 77.2, 75.1, 74.4, 73.6, 73.0, 70.6, 63.0, 60.4, 47.4, 35.9, 34.6, 32.3, 32.2, 31.2, 30.4, 27.4, 27.0, 26.3, 25.5, 25.4, 18.8, 16.6, 10.8 HRFABMS calcd for $C_{40}H_{55}O_7$ $[M - OCH_3]^+$ 647.3948, found 647.3906.

Aldehyde 55. To a stirred room-temperature solution of **54** (24 mg, 35 μmol) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (120 mg, 1.40 mmol) followed by the Dess−Martin periodinane reagent[57] (60 mg, 0.14 mmol). This mixture was stirred for 45 min, at which time TLC showed no remaining **54**. Diethyl ether (15 mL), saturated aqueous $NaHCO_3$ (1 mL) and 10% aqueous $Na_2S_2O_3$ (1 mL) were added. This mixture was stirred vigorously until the organic layer became clear (∼20 min). The separated organic phase was washed with H_2O (2 × 3 mL) and saturated aqueous NaCl solution (2 × 3 mL). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through silica gel with hexanes−ethyl acetate (2:1, v/v) and concentrated to yield aldehyde **55** (22 mg, 33 μmol, 94%) as an oil, which was used without further purification: R_f 0.31 (hexanes−ethyl acetate, 2:1, v/v); $[\alpha]^{26}_D$ = +15 (*c* 1.1, $CHCl_3$); IR (neat) 2940, 2870, 2720, 1725, 1495, 1455, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.81 (s, 1H), 7.26−7.36 (m, 10H), 5.44 (s, 1H), 5.06 (s, 1H), 4.82 (d, J = 12.3, 1H), 4.72 (d, J = 12.3 Hz, 1H), 4.71 (d, J = 11 Hz, 1H), 4.58 (d, J = 11 Hz, 1H), 4.26 (d, J = 7.5 Hz, 1H), 3.91 (m, 2H), 3.63−3.69 (m, 3H), 3.40 (dd, J = 9.6, 9.6 Hz, 1H), 3.26 (m, 1H), 3.22 (s, 3H), 2.50 (dd, J = 7.5, 7.5 Hz, 2H), 1.19−2.10 (m, 20H), 0.96 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.3, 143.5, 138.7, 138.6, 128.3, 128.2, 127.6, 127.5, 127.4, 112.7, 98.7, 95.7, 85.0, 77.2, 75.1, 74.7, 73.6, 73.0, 70.5, 60.4, 47.5, 38.7, 35.9, 34.6, 32.2, 31.2, 30.4, 27.6, 27.4, 26.4, 25.5, 25.4, 18.8, 16.7, 10.8; HRFABMS calcd for $C_{40}H_{53}O_7$ $[M - OCH_3]^+$ 645.3791, found 645.3813.

***β*-Keto Phosphonate 3.** To a stirred −78 °C solution of dimethyl methylphosphonate (38 μL, 0.35 mmol) in THF (1.5 mL) under Ar was added *tert*-butyllithium (160 μL of a 1.77 M solution in pentane, 280 μmol) dropwise. The solution was stirred for 45 min before a solution of **55** (22 mg, 33 μmol) in THF (1 mL) was added slowly via cannula. The resultant pale yellow solution was stirred for an additional 45 min, at which time TLC showed no remaining **55**. Saturated aqueous NaCl (1 mL) was added, and the mixture was allowed to warm to room temperature. THF was removed by rotary evaporation and the aqueous residue was extracted with ethyl acetate (15 mL). The separated organic phase was washed with H_2O (2 × 3 mL) and saturated aqueous NaCl (2 × 3 mL). The combined aqueous phases were extracted with ethyl acetate, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through silica gel with hexanes−ethyl acetate−triethylamine (1:5:0.3, v/v) and the filtrate concentrated to yield crude β-hydroxy phosphonate **55a** (29 mg) as an oil, which was used without further purification.

To a stirred room temperature solution of **55a** (33 μmol theor) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (120 mg, 1.4 mmol) and Dess−Martin periodinane reagent[57] (60 mg, 0.14 mmol). The resultant mixture was stirred for 45 min, at which time TLC showed no remaining **55a**. Diethyl ether (15 mL), saturated aqueous $NaHCO_3$ (1 mL), and 10% aqueous $Na_2S_2O_3$ (1 mL) were added, and the mixture was stirred vigorously until the organic layer became clear. The separated organic phase was washed with H_2O (2 × 3 mL) and saturated aqueous NaCl (2 × 3 mL). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes−ethyl acetate, 1:1−1:5, v/v) to give **3** (17 mg, 21 μmol, 64% from **55**) as a pale oil: R_f 0.23 (hexanes−ethyl acetate, 1:5, v/v); $[\alpha]^{26}_D$ = +15 (*c* 1.7, $CHCl_3$); IR (neat) 2950, 1715, 1455, 1315, 1095, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25−7.37 (m, 10H), 5.44 (dd, J = 1.8, 1.8 Hz, 1H), 5.06 (s, 1H), 4.84 (d, J = 12.3 Hz, 1H), 4.73 (d, J = 12.3 Hz, 1H), 4.72 (d, J = 11 Hz, 1H), 4.58 (d, J = 11 Hz, 1H), 4.26 (d, J = 7.8 Hz, 1H), 3.88−3.94 (m, 2H), 3.79 (d, J_{P-H} = 11.4 Hz, 6H), 3.61−3.69 (m, 3H), 3.40 (dd, J = 9.8, 9.8 Hz, 1H), 3.23 (dd, J = 2.1, 10.2 Hz, 1H), 3.20 (s, 3H), 3.12 (d, J_{P-H} = 22.8 Hz, 2H), 2.66 (dd, J = 7.8, 7.8 Hz, 2H), 1.97−2.13 (m, 2H), 1.77−1.90 (m, 7H), 1.47−1.68 (m, 8H), 1.35−1.45 (m, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.0, 143.5, 138.7, 138.6, 128.3, 128.2, 127.6, 127.5, 127.4, 112.7, 98.7, 95.6, 85.1, 77.4, 77.2, 75.1, 74.5, 73.6, 73.0, 70.4, 60.4, 53.0, 47.5, 41.5 (d, J_{C-P} = 127 Hz), 38.6, 35.9, 34.7, 32.2, 31.2, 30.4, 29.0, 27.4, 26.3, 25.5, 25.4, 18.8, 16.6, 10.8; HRFABMS calcd for $C_{43}H_{60}O_{10}P$ $[M - OCH_3]^+$ 767.3924, found 767.3958.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **5**, **9**, **10**, **13**−**18**, **20**, **21**, **23**, **26**, **35**, **41**, **43**, **48**, and **49** via $NaBH_4$ reduction of **50**, and **50**−**53**; photocopies of ^1H NMR spectra for compounds **3**, **4**, **33**−**35**, **40**, **41**, **48**, **49**, and **53**−**55** and of ^{13}C NMR spectra for compounds **3**, **53**−**55** (31 pages). See any current masthead page for ordering and Web access instructions.

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