Expedient Access to the Okadaic Acid Architecture: A Novel Synthesis of the C1−C27 Domain

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A newly designed synthetic entry to the C1−C27 domain of okadaic acid has been developed. This incorporates substantial improvements in the preparations of the key okadaic acid building blocks representing the C3−C8, C9−C14, and C16−C27 portions. The synthesis of the C3−C8 lactone used (*R*)-glycidol as the origin of the C4 stereogenic center and featured a late-stage optional incorporation of the C7 hydroxyl group. The complementary C9−C14 fragment was synthesized in a concise route from (*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpropanal and propargyl bromide. Assembly of the C3−C14 spiroketal-containing intermediate from the constituent fragments revealed a dramatic effect of C7 functionalization upon spiroketalization efficiency. In contrast, both (9*E*)- and (9*Z*)-enones converged readily to the C8 spiroketal upon treatment with acid. Modifications to the central C16−C27 fragment of okadaic acid included the early replacement of benzylic protecting groups by more suitable functionalities to facilitate both the generation of the C15−C27 intermediate and the deprotection of the final products. These modular building blocks were deployed for the synthesis of the C1−C27 scaffold of 7-deoxyokadaic acid. This work demonstrates improvements in the formation of versatile okadaic acid intermediates, as well as a reordering of fragment couplings. This alternative order of coupling was designed to promote the late stage incorporation of nonnatural lipophilic extensions from the C27 terminus.

The marine natural product okadaic acid (**1**)[1] has attracted significant attention in recent years because of its engaging architecture and its broad range of biological activities. This interest has culminated in three reported total syntheses to date,[2−4] as well as other innovative synthetic approaches.[5] Although first isolated as a potential anticancer agent,[6] okadaic acid has subsequently been characterized as a causative agent of diarrhetic shellfish poisoning,[7] a nonphorbol ester type of tumor promoter,[8] and a potent inhibitor of select serine-threonine phosphatases.[9] Ultimately, inhibition of phosphatases may be the cause of many or all of the observed cellular responses to okadaic acid exposure. Because of the increasing recognition of the vital roles of okadaic acid-sensitive phosphatases in a variety of cellular processes,[10] elucidation of the structural basis of enzyme binding by okadaic acid is an important objective. Previous structure−activity relationship (SAR) studies using naturally occurring analogues and semisynthetic derivatives of okadaic acid[11] have been limited by a lack of designed structural variants. SAR data[11] and computational studies[12] suggest that potent inhibition of PP1 and PP2A by **1** requires the C1 carboxylate, the hydroxyls at C2, C24, and C27, and the terminal lipophilic domain. In contrast, 7-deoxyokadaic acid (**2**) maintains much of the phosphatase inhibitory activity of **1**.[11d] Although it is generally believed that the carboxylate may mimic the phosphate group of endogenous phospho-

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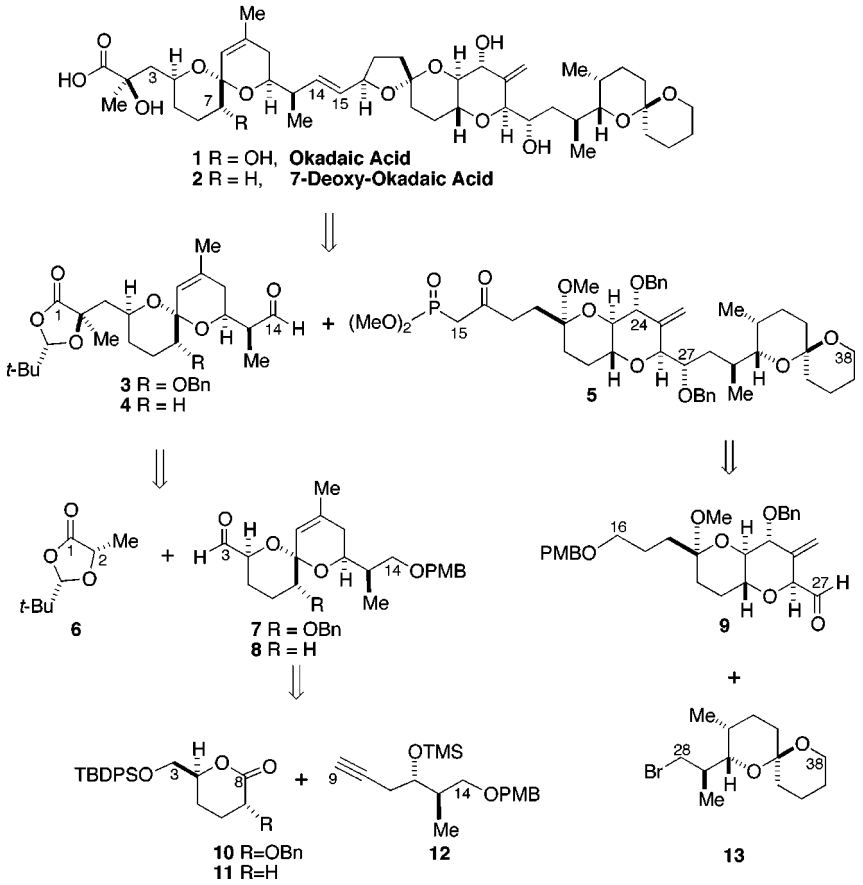
Scheme 1



peptide substrates and the lipophilic domain may contribute positive hydrophobic−hydrophobic interactions between the natural product and the enzymes, a detailed structural basis for binding and inhibition is not known. In particular, the hypothesis that **1** utilizes bimodal carboxylate−liphophilic binding for potent phosphatase inhibition has not been thoroughly evaluated by empirical study. A series of analogues that preserves the C1−C27 core of **1** or **2**, but substitutes unique hydrophobic tails for the natural C28−C38 domain, would be useful for probing the role of the C28−C38 lipophilic portion of okadaic acid in binding to phosphatases.

In the course of adapting the synthesis of **1** to the construction of strategically designed analogues, a number of opportunities for improving the synthetic approach have emerged. We report here the full details of recent modifications in our synthetic route that provide improved access to key okadaic acid intermediates[13,14] as well as expedient access to a C1−C27 okadaic acid scaffold amenable to combinatorial elaboration.

Results and Discussion

Synthetic Design. The synthesis of **1** developed in our laboratories was designed to be directly applicable to the preparation of an array of nonnatural analogues of okadaic acid. Thus, key design features include convergence, flexibility, and minimization of post-coupling transformations. The synthetic strategy employed required an aldehyde (**3**) and a ketophosphonate (**5**) that could be joined under mild conditions[15] to provide the entire carbon skeleton of the natural product, which could be converted to **1** in only four additional steps, including a sensitive final reductive scission of the benzyl ethers at C7, C24, and C27 (Scheme 1).[3] The C1−C14 fragment (**3**) was derived from spiroketal **7**, which was obtained from lactone **10** and alkyne **12** using an approach similar to that used in Isobe's first total synthesis of **1**.[2a] The C15−C38 fragment (**5**) was obtained in several steps after the cerium-mediated coupling of aldehyde **9** with the C28−C38 domain represented by alkyl bromide **13**.

This convergent approach to **1** could be readily applied to the synthesis of designed structural variants of the natural product. However, opportunities to improve upon the original preparation of each of the fragments were recognized. Careful scrutiny of our previously reported synthesis of the C1−C14 domain (**3**) suggested that improvements within the synthesis of this fragment alone might dramatically enhance the overall synthetic access to okadaic acid and its analogues. To this end, more efficient routes to two of the early synthetic intermediates, lactone **10** and alkyne **12**, were sought. Lactone **10** had been previously prepared in eight steps from D-2-acetoxy-triacetylglucal, and alkyne **12** was derived from diethyl L-tartrate in 14 steps.[16] Additionally, improvement upon the modest yield of the acid-catalyzed formation of the C3−C14 spiroketal was also desired.

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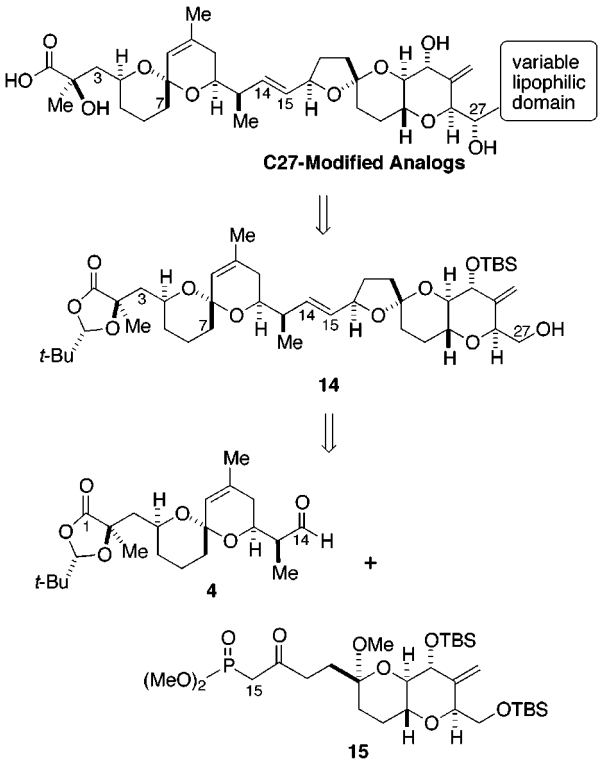
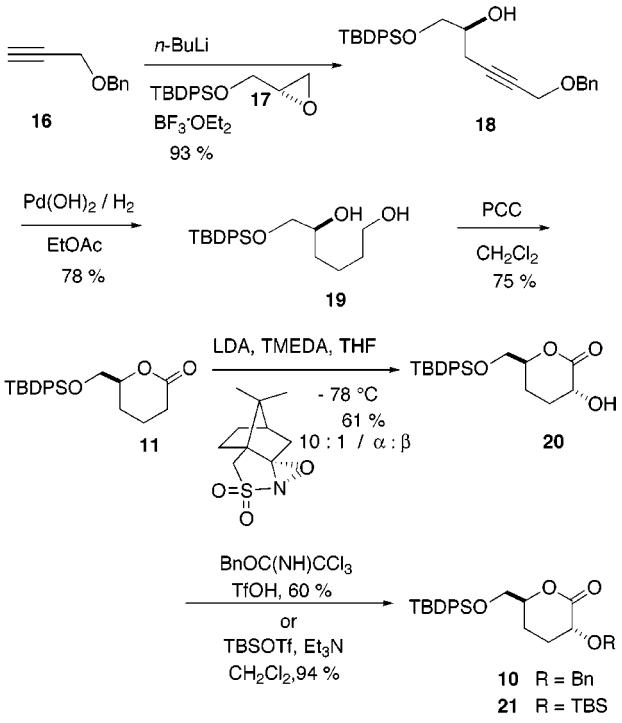
(16) Our syntheses of these intermediates[3] were closely modeled after the seminal work of Isobe and co-workers.[2]

Scheme 2



Scheme 3



Minor modifications in our synthesis of the C15−C27 fragment were also warranted. Specific complications that could conceivably be avoided via reengineering of functional group deployment include the propensity of the C16 hydroxyl group to undergo premature spiroketalization and the problematic final reductive debenzylation.

In addition to the opportunities to modify the preparation of each fragment, an alternative order of fragment coupling would support the facile construction of analogues of okadaic acid bearing unnatural variable extensions at the C27 position.Our original synthesis of **1** relied upon the early coupling of C16−C27 and C28−C38 fragments via a moderate yielding cerium-mediated process. This approach allows for easy late-stage incorporation of C1−C14 domains that may vary in functionalization, as illustrated by the total syntheses of both **1**[3] and its naturally occurring 7-deoxy analogue **2**[13b] (Scheme 1). However, this ordering of fragment coupling and the organocerium methodology are impractical for the efficient incorporation of a library of nonnatural lipophilic domains. Hence, the sequence of events for coupling the three domains has been reversed to allow for elaboration of an aldehyde derived from the C1−C27 alcohol (**14**) near the end of the synthesis, after formation of the C14−C15 bond (Scheme 2). For ease of synthetic access, **14** lacks the C7 hydroxyl group of okadaic acid.[13] Because the C7 alcohol of **1** does not appear to contribute substantially to its biological activity, omission of this functional group is warranted.[11d] In this new synthetic design, it was envisioned that alcohol **14** would be obtained via the mild and stereoselective Horner−Wadsworth−Emmons coupling of the C1−C14 aldehyde **4** with the C15−C27 ketophosphonate **15**.

Synthesis of the C1−C14 Domain. Modified Approach to the C3−C8 Lactone. An improved route to the C1−C14 fragment of **1** began with a novel, abbreviated synthesis of the C3−C8 lactone (Scheme 3).[13a] Epoxide **17** was opened with the acetylide anion derived from benzyl propargyl ether (**16**) under Yamaguchi conditions[17] to provide secondary alcohol **18**. Hydrogenation of **18** gave diol **19**, which was oxidized with PCC to give lactone **11**, the C3−C8 domain for 7-deoxy analogues of **1**. Davis' chiral oxaziridine[18] was employed for the diastereoselective installation of the C7 hydroxyl group. A variety of conditions were surveyed to optimize this oxidation, and ultimately, treatment of the lithium enolate of lactone **11** with (+)-(2*R*,8*S*)-camphorsulfonyloxaziridine[19] in the presence of TMEDA followed by a careful quench with CSA provided α-hydroxy lactone **20** in moderate yield. The hydroxyl group could be protected as a benzyl ether using the corresponding trichloroacetimidate to yield the known okadaic acid intermediate **10** via this abbreviated route. Alternatively, the C7 hydroxyl group could also be masked as a TBS ether (**21**) to avoid the problematic final cleavage of benzyl ethers.[3,4,20] This abbreviated route not only leads to the C3−C8 intermediate in markedly improved overall yield, but the inherent flexibility of this approach also provides for access to 7-deoxy analogues of **1** as well as derivatives that retain the C7 hydroxyl group.

Improved Synthesis of C9−C14 Alkyne. As part of an effort to streamline the synthesis of the C3−C14 fragment of okadaic acid, abbreviated routes to the C9−C14 alkyne (**12**) have also been explored. One new approach to this key intermediate is illustrated in Scheme 4. Silylated propargyl chloride **22**[21] and vinyl stannane **23**[22] underwent palladium-mediated coupling to afford allylic alcohol **24**. This coupling proceeded in

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(18) Davis, F. A.; Kumar, A. *J. Org. Chem.* **1992**, *57*, 3337.
(19) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.
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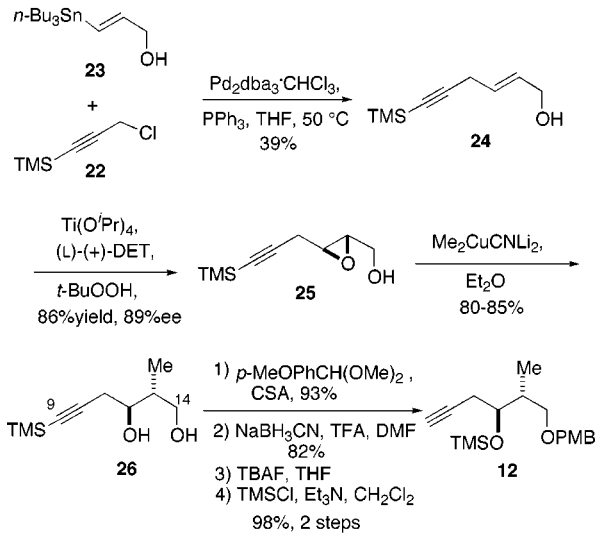
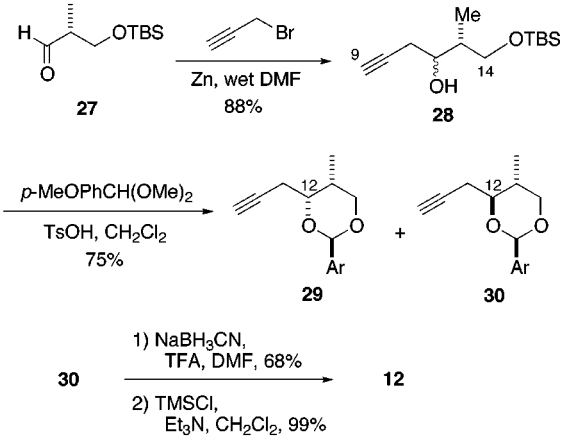
Scheme 4



modest yield when carried out using $Pd_2dba_3{\cdot}CHCl_3$ and PPh_3 in THF at 50 °C. The use of TMS-protected propargyl bromide instead of **22**, DMF rather than THF, and $Pd(PPh_3)_4$ in place of $Pd_2dba_3{\cdot}CHCl_3$ provided no improvement in reaction yield.[23] Sharpless asymmetric epoxidation[24,25] of **24** was followed by hydroxy-directed dimethyl cuprate opening of epoxide **25** to effect the regio- and stereoselective installation of the C13 methyl group.[26] Diol **26** was then protected as an anisylidene acetal, which was treated with trifluoroacetic acid and sodium cyanoborohydride to induce regioselective reductive opening of the anisylidene to the secondary alcohol.[27] The alkyne was cleanly desilylated and the free secondary alcohol was silylated to complete the shortened synthesis of alkyne **12**.[3c]

This alternative route to the C9−C14 alkyne represents an improvement upon our original synthesis of this intermediate, but a more readily scalable route was desired that avoids both the noxious organotin intermediate and the asymmetric epoxidation, which gave variable yields and enantioselectivities in our hands. Therefore, further refinements toward alkyne **12** were explored (Scheme 5). Treatment of readily available aldehyde **27**[3b] with propargyl bromide and zinc provided alcohol **28** (1:1 diastereomeric ratio) along with minor amounts of its allenic isomer (~6:1 alkyne:allene) in excellent combined yield.[28] Reaction of the product mixture with *n*-butyllithium converted the allene into alkyne, increasing the alkyne:allene ratio to ≥ 20:1.[29] Subjection of the mixture of epimeric alcohols (**28**) to anisaldehyde dimethyl acetal and TsOH caused in situ desilylation and acetal formation to give the chromatographically separable anisylidenes (12*R*)-**29** and (12*S*)-**30**.[30,31] Regioselective reductive opening of the desired anisylidene acetal **30**, followed by silylation provided alkyne **12**. In principle, reductive opening of anisylidene acetal **29** followed by inversion of configuration of the C12 secondary alcohol and silylation should allow for efficient conversion of **29** into alkyne **12**. However, preliminary efforts to invert the carbinol stereocenter under Mitsunobu conditions have been unsuccessful due to the competitive elimination of the activated alcohol. Likewise, oxidation to the ketone as a prelude to asymmetric reduction was also problematic. Nevertheless, this approach provides the C9−C14 alkyne intermediate via a remarkably short route that is readily scalable.

Scheme 5



Formation of the C3−C14 Spiroketal. The remaining goal with respect to improving the overall synthesis of the C1−C14 domain was to enhance the yield of spiroketalization. To determine the utility of C7 variants for formation of spiroketals, alkyne **12** was treated with *n*-butyllithium followed by lactone **21** or **11** to generate the corresponding δ-hydroxy ynones, which were converted to silyl ethers **31** or **32**, respectively (Scheme 6). Conjugate addition of dimethylcuprate to **31** or **32** provided nearly quantitative yields of enones **33** or **34**, respectively, each as an approximate 1:1 mixture of (*E*,*Z*)-isomers. TsOH-induced spiroketalization of the (*E*,*Z*)-mixture of **33** generated (8*R*)-spiroketal **35** in 31% yield, comparable to the yield obtained for the analogous transformation in the total synthesis of **1** in which a benzyloxy substituent was present at the C7 position.[3] Similar yields of **35** were obtained by subjecting chromatographically separated samples of (*E*)-**33** and (*Z*)-**33** to the ketalization conditions. However, treatment of the (*E*,*Z*)-mixture of the 7-deoxy enones **34** under the same

(22) Jung, M. W.; Light, L. A. *Tetrahedron Lett.* **1982**, 3851.

(23) The use of ligands that may provide enhanced yields for the Stille coupling has not been explored. See: Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.

(24) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(25) The enantiomeric excess (ee) was determined by formation of the (*R*)-MTPA ester [Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.] under standard conditions [(*S*)-MTPACl, DMAP, CH_2Cl_2] and subsequent analysis. ^{1}H NMR spectroscopic analysis in $CDCl_3$ at 500 MHz showed a diastereomeric pair of doublet of doublets at $\delta = 4.62$ and $\delta = 4.75$, corresponding to the major and minor epoxide products, respectively. Integration of these signals showed an 18:1 ratio, corresponding to 89% ee.

(26) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305. ^{1}H NMR spectroscopy of the crude reaction mixture in $CDCl_3$ at 500 MHz showed an >8:1 ratio of 1,3-diol to 1,2-diol, as determined by the integration of the methyl doublets at $\delta = 0.89$ and $\delta = 0.99$. The mixture of diols was treated with $NaIO_4$ to induce oxidative cleavage of the 1,2-diol in order to facilitate purification of **26**.

(27) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

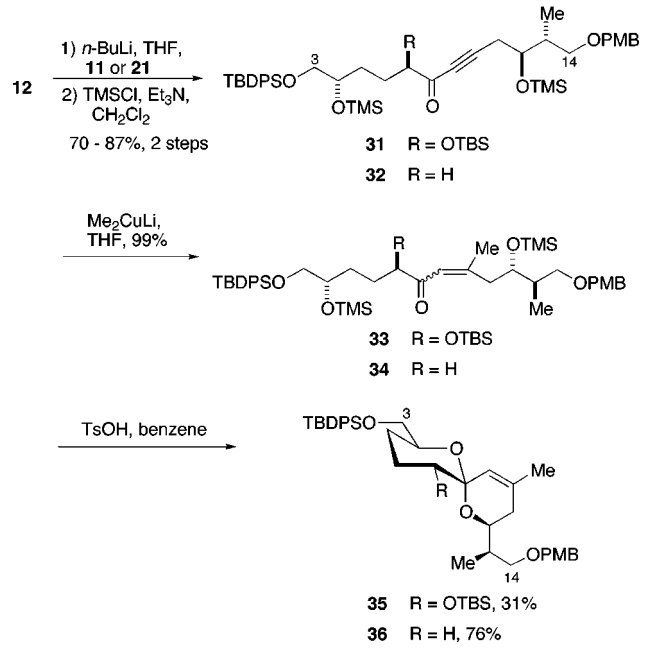
(28) For alternative methods which may provide diastereoselectivity, see: (a) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483. (b) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1992**, *57*, 1242. (c) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696, and references therein.

(29) Isomeric ratio was determined by ^{1}H NMR spectroscopy.

(30) Carbon numbers correspond to the okadaic acid skeleton.

(31) Chromatographic separation of the anisylidene acetals from anisaldehyde, a byproduct of the reaction, was facilitated by treatment of the crude mixture with $NaBH_4$ in MeOH, which reduced anisaldehyde to *p*-methoxybenzyl alcohol.

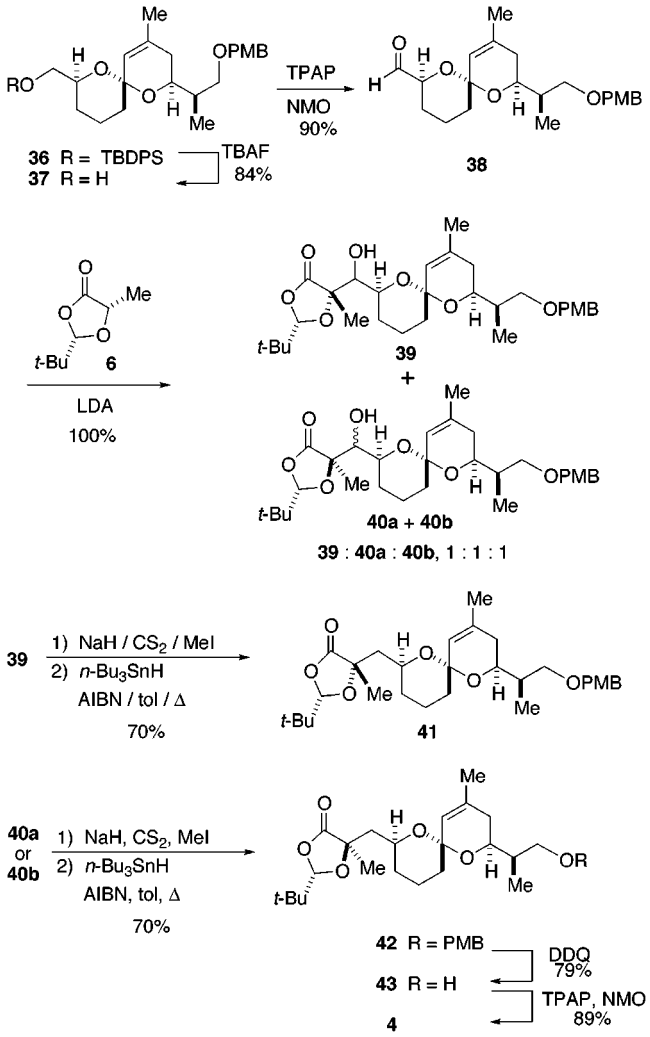
Scheme 6



conditions generated (8*R*)-spiroketal **36** in significantly higher yield (76%). The structure of **36** was confirmed at this stage via correlation with a deoxygenation product obtained from the corresponding (8*R*,7*R*)-7-benzyloxy-spiroketal used in the total synthesis of **1**.[32] This demonstrates that (*E*)-**34** isomerizes to an appreciable extent to the corresponding (*Z*)-isomer en route to **36**. Because the starting enone configuration has little impact on the overall efficiency of bicyclodehydration, the limited yield of spiroketal **35** obtained via the conjugate addition-spiroketalization sequence may largely be attributable to the presence of the substituent at C7. Hence, focusing synthetic efforts toward a novel 7-deoxy C1−C14 intermediate lacking the biologically dispensable[11d] and synthetically cumbersome C7 hydroxyl group of **1** was warranted. This intermediate was useful for the synthesis of 7-deoxyokadaic acid (**2**)[13b] and may serve as well for its analogues.

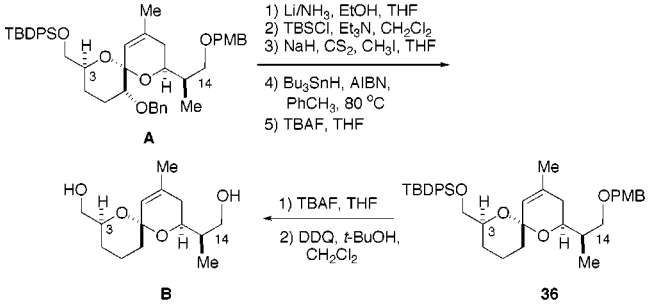
Completion of C1−C14 Domain. Completion of the synthesis of the 7-deoxy-C1−C14 fragment required installation of the protected α-hydroxy-α-methyl carboxylate functionality at the C3 position. Desilylation of **36** with TBAF followed by oxidation of the resultant alcohol with TPAP/NMO[33] gave aldehyde **38** (Scheme 7). Treatment of **38** with the lithium enolate of lactate pivalidene

Scheme 7



6[34] gave an approximately equimolar ratio of three chromatographically separable products, **39**, **40a**, and **40b**. Separate treatment of each of the alcohol products under Barton deoxygenation conditions[35] showed that **40a** and **40b** converged to the single product **42** upon deoxygenation, indicating that they were epimeric at the newly formed C3 stereocenter, whereas **41**, the product of deoxygenation of **39**, was diastereomeric with **42**. At this stage, **40a** and **40b** were assigned the (2*R*)-configuration, based on literature precedent,[3,34] which included the observation that a similar ratio (∼2:1) of (2*R*,2*S*)-isomers was obtained in the synthesis of **1**. The low level of diastereoselectivity in the lactate enolate addition may reflect the dominant effect of the large chiral substituent adjacent to the aldehyde. Oxidative cleavage of the *p*-methoxybenzyl ether of **42** with DDQ in the presence of a phosphate buffer (pH = 7.0) afforded primary alcohol **43**, which was cleanly oxidized to aldehyde **4** using TPAP/NMO. Thus, the synthesis of the 7-deoxy-C1−C14 fragment of okadaic acid was achieved in 15 steps and 8.1% overall yield from commercially available *R*-(+)-glycidol, which represents a significant improvement over our previous synthesis of the corresponding intermediate (cf. **3**, Scheme 1) in 25 steps and 0.6% overall yield from diethyl L-tartrate in the synthesis of **1**.

(32) Spiroketal **A** used in the total synthesis of **1**[3] and spiroketal **36** were both converted to diol **B** (vide infra) to confirm the structure of **36**.

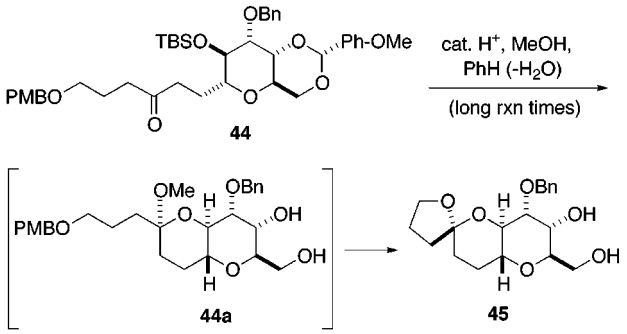


(33) Ley, S.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

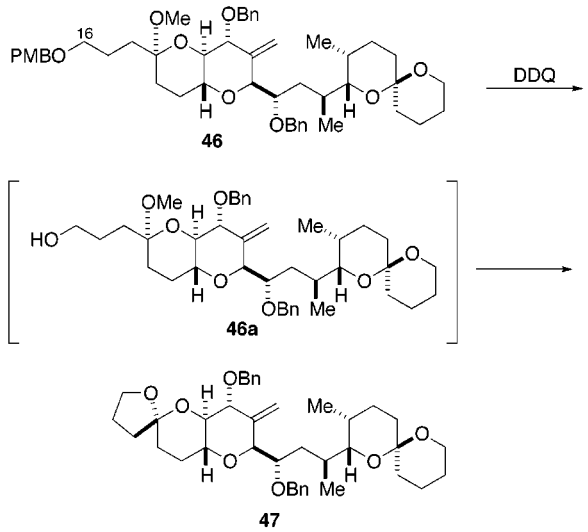
(34) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.

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

Scheme 8



Scheme 9

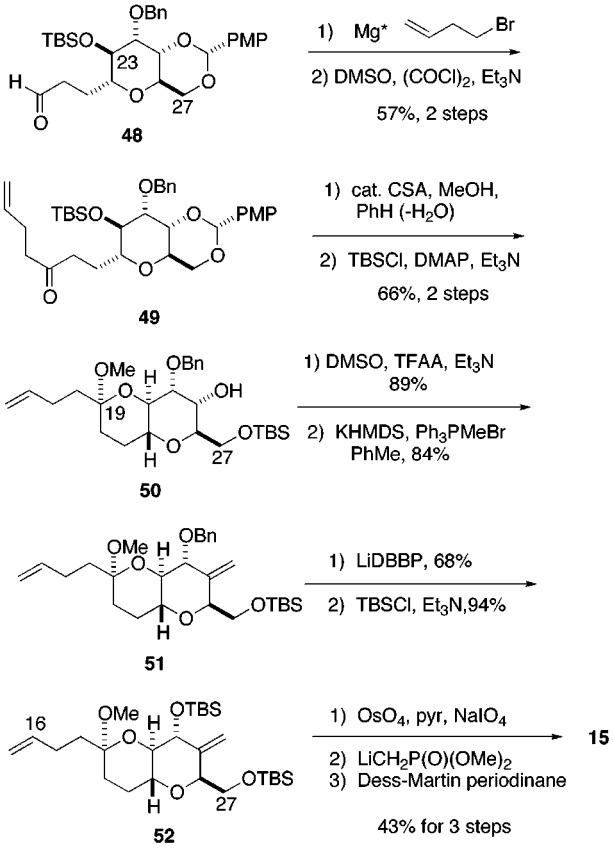


Synthesis of a Modified C16−C27 Central Core. The synthesis and functionalization of the C16−C27 bis-pyran core of okadaic acid and its derivatives have also been altered. One previously reported difficulty was the premature spiroketalization of the C16 oxygen onto the C19 ketal center to form the 1,3-dioxaspiro[4.5]decane system irreversibly.[3b,14] This event occurred both during formation of the mixed methyl ketal (**44** to **44a** to **45** in Scheme 8) as well as during the oxidative removal of the *p*-methoxybenzyl group at C16 (**46** to **46a** to **47** in Scheme 9). Although conditions to prevent this spiroketalization have been identified,[14] use of a different functional group altogether at the C16 position could completely eliminate concerns over premature spiroketalization. To this end, an olefin was selected to replace the *p*-methoxybenzyloxy group at C16, with the aim that oxidative cleavage of the olefin would lead directly to the C16 aldehyde. This new tactic would preclude undesired side reactions associated with the presence of a free C16-primary alcohol at any step in the synthetic sequence.

Final cleavage of benzyl ethers was another difficulty encountered in each of the reported syntheses of **1**.[3,4,20] For this reason, the new synthetic plan called for replacement of the benzyl ethers at the C24 and C27 positions with silyl ethers. The silyl ethers would be labile under much milder conditions, and the steric differentiation between the C24 and C27 positions should favor selective liberation of the C27 alcohol, as required for our targeted C1−C27 intermediate.

The modified synthesis of the C16−C27 core began with aldehyde **48**[3b] (Scheme 10). Treatment of **48** with the Grignard reagent derived from 1-bromo-3-butene

Scheme 10

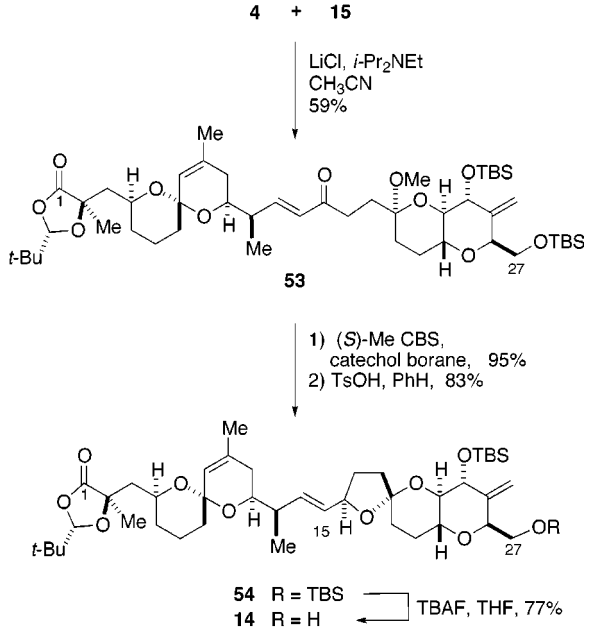


afforded a diastereomeric mixture of alcohols, which were oxidized under Swern conditions[36] to afford ketone **49**. Acidic methanolysis of **49** under Dean−Stark conditions efficiently cleaved both the *tert*-butyldimethylsilyl ether and the anisylidene acetal and provided the mixed methyl ketal at C19 in only one step. Essentially one isomer was generated at the newly formed acetal center (19*R*), as analyzed by ^{1}H NMR spectroscopy. The resultant diol was monoprotected as its primary *tert*-butyldimethylsilyl ether **50** in 66% yield for the two steps. In the initial route, cleavage of the C23 silyl ether was best performed in a separate step prior to assembly of the mixed methyl ketal to bypass formation of spiroketal **45**.[3b] In the present modification, with an olefin at C16, the silyl ether could be removed concomitantly with mixed ketal formation at C19 in reasonable yields. Alcohol **50** was oxidized to the ketone under modified Swern conditions,[36] and subsequent methylenation[37] provided exocyclic olefin **51** in 75% yield for the two steps. Replacement of the C24 benzyl ether with a *tert*-butyldimethylsilyl ether at this stage proved optimal. The debenzylation was effected with lithium di-*tert*-butylbiphenylide (LiDBBP)[38] to give the corresponding secondary alcohol in moderate yield. The free C24 alcohol was cleanly converted into bis-silyl ether **52**, a versatile precursor to a variety of analogues of okadaic acid.

Completion of the synthesis of the C15−C27 intermediate required installation of the β-ketophosphonate functionality. Selective oxidative cleavage of the mono-

(36) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(37) Miljkovic, M.; Glisin, D. *J. Org. Chem.* **1975**, *40*, 3357.
(38) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

Scheme 11



substituted olefin at C16 of **52** in the presence of the C25-disubstituted olefin yielded the C16 aldehyde in moderate yield. Addition of lithiated methyl dimethyl phosphonate to the C16 aldehyde followed by Dess−Martin oxidation[39] gave *β*-ketophosphonate **15** and completed the synthesis of this modified C15−C27 okadaic acid core. The newly developed approach to **52** circumvents several potentially problematic transformations encountered in our total synthesis of **1**.[3] Furthermore, the unique ketophosphonate **15** may be employed for the preparation of novel analogues of the natural product.

Completion of the C1−C27 Domain of 7-Deoxyokadaic Acid. After successful syntheses of the C1−C14 (**4**) and C15−C27 (**15**) domains, completion of the convergent synthesis of the C1−C27 portion simply required formation of the C14−C15 alkene, followed by a few further transformations. Nearly equimolar amounts of aldehyde **4** and *β*-ketophosphonate **15** were subjected to the Masamune−Roush modified conditions[15] of the Horner−Wadsworth−Emmons olefination to provide the C1−C27 enone **53** in moderate yield (Scheme 11). Stereo- and chemoselective reduction of the carbonyl at C16 with the (*S*)-CBS oxazaborolidine reagent and catechol borane[40] at −78 °C provided the desired (16*R*)-alcohol along with the chromatographically separable (16*S*)-alcohol as a minor side product (∼9:1, 16*R*:16*S*). The (16*R*)-alcohol was treated with TsOH in benzene to effect intramolecular trans-ketalization to the bis-TBS-ether **54**, forming the desired C19 spiroketal center with complete stereocontrol.[41] The stereoselectivities observed in this reduction−spiroketalization process suggest that the previously reported minor product of the similar sequence in the synthesis of **1**[3c] resulted from the reduction step, not the subsequent spiroketalization.

The advanced synthetic product representing the C1−C27 core of 7-deoxy okadaic acid (**54**) is a potentially valuable intermediate to probe the relationship between okadaic acid structure and biological activity. Several derivatives of okadaic acid have been assayed previously for their phosphatase inhibitory activity, including compounds representing the C1−C14[11a] and C15−C38[11a,d] portions of **1**. These domains alone do not maintain enzyme inhibitory activity that is comparable to that of the parent compound. However, intact C1−C27 portions of **1** or **2**, or unnatural derivatives bearing variable lipophilic extensions from the C27 position have not been available for comparable studies. Advanced intermediate **54** was designed to be deployed to further advance such empirical investigations via the divergent synthesis of a series of potential phosphatase inhibitors.[42] Toward this end, **54** was selectively deprotected with TBAF to give the primary alcohol **14** due to the differential steric environment about the two silyl ethers.[43] It is anticipated that oxidation of this alcohol to the corresponding aldehyde would provide a useful intermediate for the chemoselective addition of organometallic coupling partners to C27 in the presence of the C1 carboxylate. Indeed, preliminary studies on model systems representing the C16−C27 portion of **1** bearing an aldehyde at C27 indicate that Nozaki-Hiyama-Kishi coupling may provide a reliable method for introducing a variety of lipophilic appendages at C27.[44]

Conclusions

This work summarizes a number of distinct synthetic innovations that support the facile generation of okadaic acid and its analogues. Improvements in the C3−C14 fragment, some of which have been previously communicated,[13] are fully detailed here. These include a versatile new and abbreviated preparation of the C3−C8 lactone intermediate of okadaic acid and its 7-deoxy analogues. This route avoids the extensive manipulations that were previously used[2,3] to obtain this simple building block from carbohydrate starting materials, and allows for either the incorporation or omission of C7 functionalization. The complementary C9−C14 alkynyl coupling partner was similarly obtained in only a few steps from commercially available materials. The joining of these fragments under standard conditions provided ynone Michael acceptors as a prelude to the introduction of the C10 methyl group. Both the (*E*)- and (*Z*)-enones derived from nonstereoselective conjugate addition of dimethylcuprate converged to the C8 spiroketal upon treatment with acid, thus demonstrating that productive (*E*) to (*Z*)

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

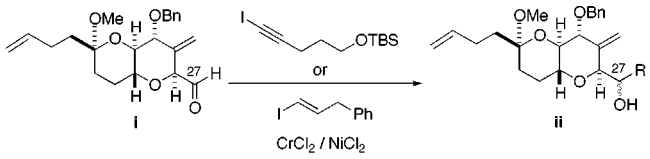
(40) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P. Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(41) The desired stereoisomer was formed with dr >95:5, as only a single product was observed by ^{1}H NMR spectroscopy ($CDCl_3$, 500 MHz).

(42) Wipf, P.; Cunningham, A.; Rice, R. L.; Lazo, J. S. *Bioorg. Med. Chem.* **1997**, *5*, 165.

(43) The regioselectivity of the mono-desilylation of **54** was verified by acetylation of **14** to give monoacetate **55** coupled with extensive NMR spectroscopic studies, which are summarized in the Supporting Information.

(44) Nozaki-Hiyama-Kishi couplings with a C16−C27 model aldehyde (i) and various vinyl and alkynyl iodides have demonstrated that this *C*−*C* bond formation is useful for providing the corresponding secondary alcohols (ii).



isomerization occurs under the spiroketalization reaction conditions. Furthermore, the efficiency of spiroketalization was found to be dramatically affected by substitution at the C7 position. The utility of this approach to the C1−C14 domain for natural product synthesis has been demonstrated by the total synthesis of 7-deoxy-okadaic acid.[13b] The synthesis of the central domain of okadaic acid was similarly revised to both overcome problems encountered in previous total synthesis efforts and to provide ready access to nonnatural products. Early replacement of the benzylic ethers at C16 and C24 with alternative functional groups led to the versatile bispyran intermediate **52**, representing the C16−C27 core of **1** and its analogues. Targeting a C1−C27 truncated form of **2**, **52** was elaborated into the C1−C27 enone using the endgame strategy employed in the total syntheses of **1**[3] and **2**.[13b] Finally, the choice of silyl ethers to protect the C24 and C27 hydroxyls allowed for the selective and mild liberation of the C27 hydroxyl group. Ongoing efforts include the chemoselective functionalization of the C27 position to generate a series of nonnatural products with variable lipophilic side chain extensions. Such compounds may be instrumental for defining the role of the C28−C38 lipophilic domain and exploiting the potential of the bimodal carboxylate−lipophilic binding of okadaic acid-like molecules with their phosphatase receptors.[45]

Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out under an Ar or N_2 atmosphere using oven-dried glassware and standard syringe, cannula, and septa techniques. Diethyl ether, THF, and benzene were distilled from Na/benzophenone under N_2. Toluene was distilled from Na under N_2. CH_2Cl_2, CH_3CN, Et_3N, *i*-Pr_2NEt, *i*-Pr_2NH, TMSCl, and $BF_3{\cdot}OEt_2$ were distilled from CaH_2 under N_2. Toluene solutions of (*S*)-methyl oxazaborolidine were purchased from Strem Chemicals, Newburyport, MA. (2*R*,8*S*)-Camphorsulfonyloxaziridine was prepared from (1*S*)-(+)-camphorsulfonic acid following the procedure by Davis and coworkers.[19] Dess−Martin periodinane was freshly prepared in our laboratory following the original procedure by Dess and Martin.[39] Solutions of *n*-butyllithium in hexanes and methyllithium in diethyl ether (Aldrich) were titrated according to the procedure of Watson and Eastman.[46] Flash chromatography was performed using Baker Flash silica gel 60 (40 μm) or ICN silica gel 32−63 and the solvent systems indicated. Analytical TLC was performed with 0.25 mm or 0.50 mm EM silica gel 60 F_{254} plates that were analyzed by fluorescence upon 254 nm irradiation or by staining upon heating with anisaldehyde reagent (450 mL 95% EtOH, 25 mL concentrated H_2SO_4, 15 mL of acetic acid, and 25 mL of anisaldehyde). High-resolution mass spectrometric data were obtained by the University of Minnesota Mass Spectrometry Laboratory using CI, FAB, and MALDI techniques. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

C3−C8 Lactones. (*2S*)-6-Benzyloxy-1-*tert*-butyldiphenylsilyloxy-4-pentyn-2-ol (18). To a stirred −78 °C solution of benzyl propargyl ether (**16**, 4.70 g, 32.0 mmol) in THF (100 mL) was added *n*-butyllithium (11.7 mL of a 2.60 M solution in hexanes, 30.4 mmol). The resulting solution was stirred for 15 min before being added via cannula to a solution of **17** (5.00 g, 16.0 mmol) in THF (60 mL) at −78 °C. Freshly distilled boron trifluoride diethyl etherate (2.3 mL, 16.0 mmol) was added dropwise, and the resulting solution was stirred at −78 °C for 40 min. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the THF was removed by rotary evaporation. The residue was diluted with ethyl acetate, and the resulting emulsion was filtered under vacuum. The separated aqueous residue was extracted with ethyl acetate (3 × 75 mL), and the combined organic layers were washed with H_2O and saturated aqueous NaCl (75 mL each), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 4:1, v/v) to yield **18** (6.83 g, 14.9 mmol, 93%) as a clear, colorless oil: R_f 0.35 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{26}_D = +3.9$ (*c* 1.27, $CHCl_3$); IR (neat) 3435, 3031, 2930, 2857, 1428, 1360, 1070, 823, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (apparent d, J = 6.0 Hz, 4H), 7.40−7.32 (m, 11H), 4.52 (s, 2H), 4.11 (s, 2H), 3.88 (m, 1H), 3.73 (ddd, J = 14.1, 9.9, 4.2 Hz, 1H), 2.52 (m, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) (overlapping signals in aromatic region) δ 135.7, 133.2, 130.0, 128.6, 128.2, 128.0, 83.0, 78.3, 71.7, 70.5, 66.6, 57.8, 27.0, 23.8, 19.4. Anal. Calcd for $C_{29}H_{34}O_3Si$: C, 75.94; H, 7.47. Found: C, 76.03; H, 7.28.

(*2S*)-1-*tert*-Butyldiphenylsilyloxy-2,6-hexanediol (19). To a stirred solution of **18** (7.0 g, 15 mmol) in ethyl acetate (200 mL) was added $Pd(OH)_2$ on carbon (812 mg of 20% Pd catalyst, 1.52 mmol). The reaction flask was repeatedly evacuated and flushed with H_2. After a H_2 atmosphere (1 atm) was established in the reaction flask, the suspension was vigorously stirred for 6 h and then filtered through Celite with ethyl acetate (300 mL). The filtrate was concentrated, and silica gel column chromatography (hexanes/ethyl acetate, 2:1, v/v) of the residue gave **19** (4.4 g, 12 mmol, 78%) as a clear, colorless oil: R_f 0.15 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{27}_D = +15.2$ (*c* 0.46, $CHCl_3$); IR (neat) 3351, 3048, 2932, 1472, 1461, 1427, 1261, 1112, 824, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (dd, J = 6.5, 1.5 Hz, 4H), 7.47−7.39 (m, 6H), 3.74 (m, 1H), 3.67 (dd, J = 10.5, 3.5 Hz, 1H), 3.62 (t, J = 6.0 Hz, 2H), 3.50 (dd, J = 10.5, 8.0 Hz, 1H), 2.62 (s, 1H), 1.55−1.39 (m, 7H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.6, 132.2, 129.9, 128.0, 71.9, 68.0, 62.7, 32.6, 32.4, 27.0, 21.7, 19.3; HRFABMS calcd for $C_{18}H_{23}O_3Si$ [M − *t*-Bu]$^+$ 315.1416, found 315.1409.

(*5S*)-6-*tert*-Butyldiphenylsilyloxy-5-hydroxyhexanoic Acid δ-Lactone (11). To a stirred rt solution of **19** (4.30 g, 11.5 mmol) in CH_2Cl_2 (125 mL) were added crushed 4 Å molecular sieves (3.0 g). PCC (8.7 g, 40 mmol) was added in two equal portions, allowing a 3 h reaction time between additions. The reaction mixture was allowed to stir for 16 h before being filtered through silica gel with ethyl acetate (350 mL). The filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 4:1, v/v) to yield **11** (3.14 g, 8.6 mmol, 75%) as a clear, colorless oil: R_f 0.45 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{26}_D = +9.8$ (*c* 2.0, $CHCl_3$); IR (neat) 2955, 2931, 2857, 1738, 1240, 1133, 823, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.66 (m, 4H), 7.43 (m, 6H), 4.40 (m, 1H), 3.77 (ddd, J = 15.5, 11.0, 4.5 Hz, 2H), 2.65−2.39 (m, 2H), 1.94−2.00 (m, 2H), 1.75−1.86 (m, 2H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 135.6, 133.1, 130.0, 127.8, 80.2, 65.6, 29.9, 26.8, 24.4, 19.3, 18.3; HRFABMS calcd for $C_{22}H_{29}O_3Si$ [M + H]$^+$ 369.1885, found 369.1862.

Hydroxy Lactone 20. To a stirred −78 °C solution of diisopropylamine (84 μL, 0.60 mmol) in THF (1 mL) under Ar was added *n*-butyllithium (0.23 mL of a 2.4 M solution in hexanes, 0.54 mmol). After 30 min, TMEDA (0.20 mL, 1.4 mmol) was added, followed by **11** (100 mg, 0.27 mmol) in THF (2 mL). After an additional 30 min, a solution of (+)-(2*R*,8*S*)-camphorsulfonyloxaziridine (93 mg, 0.41 mmol) in THF (2 mL) was added. The reaction was warmed to −40 °C and maintained at this temperature for 2 h, before camphorsulfonic acid (126 mg, 0.544 mmol) in THF (2 mL) was added. The reaction mixture was concentrated, and the crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 5:1 to 2:1, v/v). The resulting product was dissolved in ether, and the insoluble residual sulfonimine was removed by filtration. The filtrate was concentrated to provide **20** (64 mg, 0.17 mmol, 61%) as a clear, colorless oil: R_f 0.31 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D = +10.3$ (*c* 3.2, $CHCl_3$); IR (neat) 3450, 3080, 3040, 2920, 2850, 1740, 1475, 1430, 1100, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65 (ddd, J = 8.0, 1.5, 1.5 Hz, 4H),

(45) Takai, A.; Tsuboi, K.; Koyasu, M.; Isobe, M. *Biochem. J.* **2000**, *350*, 81−88.
(46) Watson, S. C.; Eastman, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

7.47−7.38 (m, 6H), 4.45 (dddd, J = 10.5, 4.5, 4.5, 4.5 Hz, 1H), 4.13 (ddd, J = 12.5, 6.5, 1.5 Hz, 1H), 3.81 (dd, J = 11.0, 5.0 Hz, 1H), 3.72 (dd, J = 11.0, 3.5 Hz, 1H), 3.23 (d, J = 1.0 Hz, 1H), 2.38 (m, 1H), 2.06 (m, 2H), 1.87 (dddd, J = 12.0, 12.0 12.0, 4.5 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 135.5, 132.8, 129.8, 127.7, 82.1, 67.8, 65.2, 27.2, 26.7, 24.0, 19.2; HRFABMS calcd for $C_{22}H_{29}SiO_4$ $[M + H]^+$ 385.1835, found 385.1855.

***tert*-Butyldimethylsilyloxy Lactone 21.** To a stirred 0 °C solution of **20** (250 mg, 0.65 mmol) in CH_2Cl_2 (10 mL) under Ar were added 2,6-lutidine (200 μL, 1.9 mmol) and *tert*-butyldimethylsilyltriflate (300 mg, 1.14 mmol). The reaction mixture was warmed to rt. After 1.5 h, saturated aqueous NH_4Cl (5 mL) was added. The separated aqueous phase was washed with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with H_2O and saturated aqueous NaCl (10 mL each), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) to provide **21** (306 mg, 0.61 mmol, 94%) as a clear colorless oil, which was stored in a benzene matrix at −20 °C: R_f 0.70 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{26}_D$ = +21.0 (*c* 2.7, $CHCl_3$); IR (neat) 2955, 2930, 2857, 1755, 1472, 1428, 1253, 1147, 1114, 837, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (m, 4H), 7.45−7.38 (m, 6H), 4.51 (m, 1H), 4.16 (dd, J = 9.0, 6.0 Hz, 1H), 3.75 (d, J = 4.5 Hz, 2H), 2.16 (m, 1H), 2.04 (m, 1H), 1.99−1.91 (m, 2H), 1.07 (s, 9H), 0.92 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 135.8, 133.2, 130.4, 128.0, 80.3, 69.4, 65.8, 29.2, 27.0, 26.0, 23.9, 19.5, 18.5, −4.5, −5.3; HRFABMS calcd for $C_{28}H_{43}O_4$ Si_2Na $[M + Na]^+$ 521.2519, found 521.2548.

C9−C14 Alkyne. Enyne 24. To a round-bottomed flask under Ar containing vinyl stannane **23**[22] (25.1 g, 84.5 mmol) was added a solution of 3-chloro-1-(trimethylsilyl)-1-propyne **22**[21] (13.7 g, 92.9 mmol) in THF (170 mL). This solution was deoxygenated by bubbling a stream of Ar through it for 10 min. To the resultant solution were added $Pd_2(dba)_3{\cdot}CHCl_3$ (890 mg, 845 μmol) and triphenylphosphine (443 mg, 1.69 mmol). This deep burgundy mixture was heated to 50 °C with stirring for 24 h, cooled to rt, and stirred for an additional 36 h. The THF was removed under reduced pressure, and the crude residue was filtered through Celite and rinsed with hexanes. Silica gel column chromatography (hexanes/ethyl acetate, 8:1 to 5:1 to 2:1, v/v) of this residue gave enyne **24** (5.57 g, 33.2 mmol, 39%) as a pale oil: R_f 0.39 (hexanes/ethyl acetate 2:1, v/v); IR (neat) 3300, 2960, 2180, 1415, 1295 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddddd, J = 15.3, 5.7, 5.7, 1.8, 1.8 Hz, 1H), 5.64 (ddddd, J = 15.3, 5.4, 5.4, 1.5, 1.5 Hz, 1H), 4.10 (dddd, J = 5.7, 1.5, 1.5, 1.5 Hz, 2H), 2.98 (dddd, J = 5.4, 1.5, 1.5, 1.5 Hz, 2H), 2.09 (s, 1H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 125.8, 103.5, 86.9, 63.0, 22.8, −0.06; HRCIMS calcd for $C_9H_{20}OSiN$ $[M + NH_4]^+$ 186.1314, found 186.1319.

Epoxide 25.[47] To a stirred solution of (+)-diethyltartrate (1.84 g, 8.90 mmol) in CH_2Cl_2 (160 mL) under Ar was added crushed 4 Å molecular sieves (∼ 10 g). This mixture was cooled to −20 °C, and $Ti(O^iPr)_4$ (2.19 mL, 7.42 mmol) was added, followed by *tert*-butyl hydroperoxide (13.5 mL of a ∼5.5 M solution in decane, ∼74 mmol). The resultant mixture was stirred for 30 min before a solution of allylic alcohol **24** (6.23 g, 37.1 mmol) in CH_2Cl_2 (25 mL) was added dropwise via cannula. The resulting mixture was stirred at −20 °C for an additional 7.5 h, then stored at this temperature without stirring for an additional 14 h. The mixture was warmed to 0 °C, filtered, and slowly poured into a 0 °C solution of $FeSO_4{\cdot}7H_2O$ (12.2 g) and tartaric acid (3.7 g) in H_2O (40 mL). The two-phase mixture was stirred vigorously at rt for 30 min. The separated aqueous layer was extracted with diethyl ether, and the combined organic phases were cooled to 0 °C. A precooled 0 °C solution of 30% NaOH (w/v) in saturated aqueous NaCl (15 mL) was added, and the mixture was stirred vigorously at 0 °C for 20 min. The solution was diluted with H_2O (100 mL), and the phases were separated. The combined organic phases were washed with H_2O and saturated aqueous NaCl (50 mL each). The combined aqueous phases were extracted with diethyl ether, and the organic phases were combined, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 5:1 to 2:1, v/v) yielded epoxide **25** (5.80 g, 31.9 mmol, 86% yield, 89% ee[25]): R_f 0.24 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D$ = −11 (*c* 2.1, $CHCl_3$); IR (neat) 3400, 2950, 2175, 1410, 1245, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (ddd, J = 12.5, 5.5, 2.5 Hz, 1H), 3.68 (ddd, J = 12.5, 7.5, 4.0 Hz, 1H), 3.16 (ddd, J = 5.0, 5.0, 2.0 Hz, 1H), 3.13 (ddd, J = 4.0, 2.5, 2.5 Hz, 1H), 2.67 (dd, J = 17.5, 4.5 Hz, 1H), 2.57 (dd, J = 18.0, 5.0 Hz, 1H), 1.74 (dd, J = 7.5, 5.5 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.4, 87.3, 60.9, 57.7, 52.8, 22.6, −0.15. Anal. Calcd for $C_9H_{16}O_2Si$: C, 58.65; H, 8.75. Found: C, 58.73; H, 8.62.

Diol 26. CuCN (6.56 g, 73.2 mmol) was azeotropically dried with benzene (25 mL) at rt under vacuum and then placed under Ar. Diethyl ether (55 mL) was added, and the resultant mixture was cooled to −78 °C. Methyllithium (74.9 mL of a 1.76 M solution in diethyl ether, 132 mmol) was added dropwise via a pressure-equalizing addition funnel, and the resulting mixture was warmed to −15 °C and stirred vigorously until all of the CuCN dissolved (∼20 min), resulting in a pale green solution. A solution of epoxide **25** (2.22 g, 12.2 mmol) in diethyl ether (6 mL) was added, and the resultant mixture was stirred at −10 to −15 °C for 1 h. Diethyl ether (100 mL) and saturated aqueous NH_4Cl (75 mL) were added. The resultant mixture was warmed to rt and filtered to give a cloudy suspension. The separated organic phase was washed with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl (2 × 50 mL each). The combined aqueous phases were extracted with diethyl ether and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give crude **26** (2.43 g, 12.2 mol, 100%) as an off-white solid. ^{1}H NMR analysis in $CDCl_3$ showed a >8:1 ratio of regioisomeric diols. To this crude material were added THF (70 mL), H_2O (55 mL), and $NaIO_4$ (652 mg, 3.05 mmol) at rt. The resultant solution was stirred for 1 h and then was diluted with diethyl ether (200 mL), and the phases were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL). The combined aqueous phases were extracted with diethyl ether and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 5:1 to 2:1 to 1:1, v/v) of the residue afforded **26** (1.79 g, 8.91 mmol, 73%) as an amorphous white solid: R_f 0.41 (hexanes/ethyl acetate, 1:1, v/v); $[\alpha]^{26}_D$ = −18.0 (*c* 3.0, $CHCl_3$); IR (neat) 3340, 2960, 2170, 1410, 1240, 1020, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (m, 1H), 3.67 (m, 2H), 2.89 (m, 1H), 2.85 (br s, 1H), 2.57 (dd, J = 17.0, 4.0 Hz, 1H), 2.43 (dd, J = 17.0, 7.5 Hz, 1H), 1.84 (m, 1H), 0.90 (d, J = 7.0 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.7, 88.0, 74.9, 67.2, 39.4, 27.3, 13.6, 0.02. Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.76; H, 10.27.

Anisylidene 26a. To a 0 °C solution of diol **26** (2.33 g, 11.7 mmol) in CH_2Cl_2 (120 mL) was added anisaldehyde dimethyl acetal (2.21 mL, 12.9 mol) followed by camphorsulfonic acid (136 mg, 585 μmol). The resulting solution was warmed to rt and stirred for 2 h, diluted with diethyl ether (250 mL) and washed with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl (2 × 75 mL each). The combined aqueous phases were extracted with diethyl ether, and the organic phase was dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 8:1 to 5:1, v/v) yielded anisylidene **26a** (3.51 g, 10.9 mmol, 93%) as a white crystalline solid (hexanes/ethyl acetate): mp 39−40 °C; R_f 0.43 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{26}_D$ = −16 (*c* 1.6, $CHCl_3$); IR (neat) 2950, 2825, 2170, 1610, 1515, 1460, 1240, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.47 (s, 1H), 4.09 (dd, J = 11.4, 4.8 Hz, 1H), 3.80 (s, 3H), 3.58 (m, 1H), 3.50 (dd, J = 11.4, 11.4 Hz, 1H), 2.65 (dd, J = 17.0, 4.8 Hz, 1H), 2.56 (dd, J = 17.0, 5.7 Hz, 1H), 2.03 (m, 1H), 0.86 (d, J = 7.0 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 131.0, 127.4, 113.6, 103.1, 101.1, 86.6, 81.0,

(47) Freshly distilled (+)-diethyltartrate and $Ti(O^iPr)_4$, activated molecular sieves, and efficient stirring were crucial for high yields and enantioselectivities in this reaction.

72.7, 55.3, 33.9, 25.0, 12.4, 0.04. Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.88; H, 8.23. Found: C, 67.87; H, 8.37.

Alcohol 26b. To a 0 °C solution of anisylidene **26a** (3.47 g, 10.8 mmol) in DMF (90 mL) containing 4 Å molecular sieves (~6.5 g) under Ar was $NaBH_3CN$ (6.77 g, 108 mmol) followed by a cannula addition over 30 min of a 0 °C solution of trifluoroacetic acid (16.6 mL, 216 mmol) in DMF (70 mL), which had been dried over 4 Å molecular sieves for ~20 min. The resulting mixture was stirred at 0 °C for an additional 30 min then at rt for 4.5 h, at which time TLC showed almost complete disappearance of **26a**. The mixture was filtered, and the filtrate was cooled to 0 °C before saturated aqueous $NaHCO_3$ (225 mL) was added cautiously. The aqueous phase was extracted with CH_2Cl_2 (6 × 50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl (100 mL each). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel column chromatography (hexanes/ethyl acetate, 5:1, v/v) of the residue gave recovered **26a** (208 mg, 646 μmol), alcohol **26b** (2.87 g, 8.86 mmol, 82%, 88% based on recovered **26a**), and the regioisomeric anisylidene-opening product (408 mg, 1.26 mmol, 12%). Alcohol **26b** was indistinguishable by TLC (R_f 0.30 in hexanes/ethyl acetate, 5:1, v/v) and ^{1}H NMR spectroscopy from an authentic sample.[3c] The observed specific rotation ($[\alpha]^{24}_D$ = + 8.3 (*c* 1.7, $CHCl_3$)) is consistent with an 89% enantiomeric excess obtained in the Sharpless asymmetric epoxidation.

Anisylidene 30. To a stirred rt solution of aldehyde **27** (384 mg, 1.90 mmol) in DMF (25 mL) were added Zn pieces (185 mg, 2.85 mmol), followed by propargyl bromide (254 μL, 2.85 mmol) and water (0.5 mL). The Zn dissolved and the solution became cloudy before completion of the reaction. After 8 h, the reaction mixture was poured into saturated aqueous NH_4Cl (100 mL), extracted with diethyl ether (4 × 75 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude mixture was purified by silica gel flash chromatography (hexanes/ethyl acetate, 6:1, v/v) to give **28** (410 mg) as a 6:1 mixture of alkyne and allene, with an approximately 1:1 mixture of alcohol diastereomers. This mixture was dissolved in THF (200 mL) under Ar, and cooled to −78 °C before *n*-butyllithium in hexanes (2.17 mL of a 2.63 M solution in hexanes, 5.71 mmol) was added. After 3 h at −78 °C, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was warmed to rt. The reaction mixture was extracted with ether (3 × 100 mL), and the combined organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude product was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 4:1, v/v) to give **28** (405 mg, 1.67 mmol, 88%) as a >20:1 mixture of alkyne to allene, as determined by ^{1}H NMR spectroscopy.

To a stirred solution of **28** (360 mg, 1.49 mmol) in CH_2Cl_2 (25 mL) under Ar at rt were added *p*-anisaldehyde dimethyl acetal (383 μL, 2.23 mmol) and *p*-toluenesulfonic acid (71 mg, 0.37 mmol). The solution turned dark violet. After 9 h, triethylamine (~2 mL) was added, and the mixture was concentrated by rotary evaporation. The crude residue was dissolved in methanol (50 mL) and cooled to 0 °C, and $NaBH_4$ (84 mg, 2.2 mmol) was added. After 1 h, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 100 mL). The organic phase was washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude mixture was purified by flash chromatography on silica gel (pentane/Et_2O, 5:1, v/v) to give **29** (164 mg, 666 μmol, 45%) and **30** (137 mg, 556 μmol, 38%). Anisylidene **29** was isolated as a colorless oil: R_f 0.53 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{25}_D$ = +0.94 (*c* 2.4, $CHCl_3$); IR (neat) 3289, 2964, 2853, 2121, 1616, 1588, 1518, 1463, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.48, (s, 1H), 4.15−4.06 (m, 3H), 3.81 (s, 3H), 2.54 (ddd, *J* = 16.8, 5.8, 2.8 Hz, 1H), 2.42 (ddd, *J* = 16.8, 9.5, 2.8 Hz, 1H), 2.01 (t, *J* = 2.8 Hz, 1H), 1.88 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 160.1, 131.1, 128.4, 127.5, 113.7, 101.8, 79.8, 73.6, 70.1, 55.3, 33.1, 22.6, 10.7; HRCIMS calcd for $C_{15}H_{18}O_3$ $[M + H]^+$ 247.1334, found 247.1338. Anisylidene **30** was isolated as a colorless, crystalline solid (pentane/ether): mp 95−97 °C; R_f 0.47 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{25}_D$ = −15.3 (*c* 2.0, $CHCl_3$); IR (neat) 3275, 3066, 2966, 2862, 2122, 1615, 1590, 1518, 1460, 1402, 1371, 1303, 1249, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.50 (s, 1H), 4.10 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.80 (s, 3H), 3.60 (m, 1H), 3.50 (t, *J* = 11.4 Hz, 1H), 2.64 (ddd, *J* = 17.2, 3.9, 2.7 Hz, 1H), 2.53 (ddd, *J* = 17.2, 5.7, 2.7 Hz, 1H), 2.12−2.06 (m, 1H), 2.05 (t, *J* = 2.5 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.0, 142.1, 130.9, 127.5, 113.6, 101.2, 80.9, 72.7, 70.1, 55.3, 33.4, 23.4, 12.4; HRCIMS calcd for $C_{15}H_{18}O_3$ $[M + H]^+$ 247.1334, found 247.1325. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.26; H, 7.10.

Alcohol 30a. To a stirred 0 °C solution of **30** (1.72 g, 6.99 mmol) in DMF (60 mL) over 4 Å molecular sieves under Ar was added $NaBH_3CN$ (4.39 g, 69.9 mmol). A solution of trifluoroacetic acid (10.78 mL, 139.8 mmol) in DMF (50 mL) that had been stirred over 4 Å molecular sieves at 0 °C under Ar for 20 min was added via cannula over 30 min. The reaction mixture was stirred at 0 °C for 30 min, then warmed to rt. After 6 h, the mixture was filtered through a fritted glass funnel and cooled to 0 °C, and saturated aqueous $NaHCO_3$ was added. The crude mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), and saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude mixture was purified by flash column chromatography on silica gel (hexanes/ethyl acetate, 4:1, v/v) to give **30a** (1.18 g, 4.78 mmol, 68%) as a colorless oil, which was indistinguishable from the an authentic sample[3c] by TLC, specific rotation, ^{1}H and ^{13}C NMR, and HRCIMS.

C1−C14 Aldehyde. Ynone 11a. To a stirred −78 °C solution of alkyne **12** (1.0 g, 3.1 mmol) in THF (30 mL) under Ar was added *n*-butyllithium (1.05 mL of a 2.80 M solution in hexanes, 2.94 mmol). After the mixture was stirred for 45 min, a solution of lactone **11** (680 mg, 1.84 mmol) in THF (15 mL) was added via cannula. After 50 min, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was allowed to warm to rt. The mixture was extracted with ethyl acetate (2 × 40 mL), and the combined organic extracts were washed with H_2O and saturated aqueous NaCl (30 mL each). The organic fraction was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) to give **11a** (1.10 g, 1.60 mmol, 87%) as a clear, colorless oil: R_f 0.30 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{26}_D$ = +9.2 (*c* 6.6, $CHCl_3$); IR (neat) 3510, 2950, 2850, 2210, 1675, 1605, 1508, 1455, 1420, 1355, 1295, 1240, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (ddd, *J* = 8.0, 1.5, 1.5 Hz, 4H), 7.42 (m, 6H), 7.27 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 3.91 (m, 2H), 3.80 (s, 3H), 3.73 (m, 1H), 3.66 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.51 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.47 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.36 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.56 (m, 5H), 2.03 (m, 1H), 1.83 (dddd, *J* = 14.0, 14.0, 7.5, 7.5 Hz, 1H), 1.70 (dddd, *J* = 14.5, 14.5, 8.0, 8.0 Hz, 1H), 1.43 (m, 2H), 1.09 (s, 9H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.7, 159,1, 135.6, 133.2, 130.6, 129.9, 129.1, 127.8, 113.8, 92.0, 82.1, 72.7, 72.2, 71.6, 71.5, 68.0, 55.3, 45.3, 39.0, 32.0, 26.9, 25.5, 20.1, 19.3, 13.7, 0.4. Anal. Calcd for $C_{40}H_{56}O_6Si_2$: C, 69.73; H, 8.19. Found: C, 69.97; H, 8.00.

Bis-Trimethylsilyl Ether 32. To a solution of **11a** (460 mg, 669 μmol) in CH_2Cl_2 (15 mL) under Ar at 0 °C was added triethylamine (470 μL, 3.35 mmol), followed by chlorotrimethylsilane (170 μL, 1.34 mmol), and 4-*N*,*N*-(dimethylamino)-pyridine (8 mg, 67 μmol). After the mixture was stirred for 35 min, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was diluted with ethyl acetate (20 mL). The organic phase was separated and washed with H_2O and saturated aqueous NaCl (10 mL each) and then dried over $NaSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) to give **32** (495 mg, 651 μmol, 97%) as a clear, colorless oil: R_f 0.30 (hexanes/ethyl acetate, 8:1, v/v); $[\alpha]^{26}_D$ = +0.5 (*c* 3.1,

$CHCl_3$); IR (neat) 2950, 2850, 2210, 1660, 1600, 1500, 1415, 1235, 1095, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, J = 6.5 Hz, 4H), 7.41 (m, 6 H), 7.26 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.90 (dd, J = 11.5, 5.0 Hz, 1H), 3.812 (s, 3H), 3.70 (m, 1H), 3.58 (dd, J = 5.5, 10.5 Hz, 1H), 3.47 (m, 2H), 3.36 (dd, J = 9.0, 6.0 Hz, 1H), 2.56 (m, 4H), 2.02 (ddd, J = 12.0, 6.0, 6.0 Hz, 1H), 1.75 (m, 1H), 1.68 (m, 2H), 1.41 (m, 1H), 1.06 (s, 9H), 0.95 (d, J = 6.5 Hz, 3H), 0.15 (s, 9H), 0.61 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.8, 159.1, 135.6, 133.6, 133.5, 130.6, 129.7, 129.1, 127.7, 113.8, 91.8, 82.1, 72.7, 72.2, 71.5, 67.9, 55.3, 45.6, 39.0, 33.4, 26.9, 25.5, 20.0, 19.2, 13.8, 0.4, 0.3. Anal. Calcd for $C_{43}H_{64}O_6Si_3$: C, 67.85; H, 8.47. Found: C, 68.22; H, 8.30.

Spiroketal 36. To a −78 °C solution of CuI (860 mg, 4.51 mmol) in THF (15 mL) under Ar was added methyllithium (5.0 mL of a 1.8 M solution in diethyl ether, 9.0 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 **32** (1.0 g, 1.3 mmol) in THF (30 mL) was added via cannula. After 25 min, saturated aqueous NH_4Cl (6 mL) was added, and the mixture was allowed to warm to rt. The mixture was stirred until the aqueous phase became bright blue. The mixture was extracted with ethyl acetate (2 × 30 mL), and the combined organic phases were washed with H_2O and saturated aqueous NaCl (20 mL each), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) of the residue provided a 1:1 mixture of *E* and *Z* isomers **34** (990 mg, 1.28 mmol, 99%) as a clear, colorless oil: R_f 0.28 and 0.30 (hexanes/ethyl acetate, 8:1, v/v).

To a solution of (*E*,*Z*)-**34** (670 mg, 863 μmol) in benzene (25 mL) was added $TsOH\cdot H_2O$ (16 mg, 86 μmol). After the solution was stirred for 2.5 h at rt, saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was diluted with ethyl acetate (15 mL). The organic phase was washed with H_2O and saturated aqueous NaCl (15 mL each), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (hexanes/ethyl acetate, 8:1, v/v) provided **36** (400 mg, 653 μmol, 76%) as a clear, colorless oil: R_f 0.30 (hexanes/ethyl acetate, 8:1, v/v); $[\alpha]^{24}_D = -39.0$ (*c* 2.8, $CHCl_3$); IR (neat) 2930, 2850, 1615, 1508, 1455, 1422, 1240, 1110, 990, 815, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70 (ddd, J = 5.5, 4.0, 1.5 Hz, 4H), 7.38 (m, 6H), 7.28 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.34 (s, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.45 (d, J = 11.0 Hz, 1H), 3.89 (m, 1H), 3.80 (s, 3H), 3.79 (m, 2H), 3.71 (dd, J = 10.5, 5.5 Hz, 1H), 3.52 (dd, J = 10.0, 7.0 Hz, 1H), 3.37 (t, J = 9.0 Hz, 1H), 1.98−1.77 (m, 5H), 1.73 (s, 3H), 1.65 (m, 2H), 1.50 (ddd, J = 14.0, 14.0, 4.5 Hz, 1H), 1.20 (dddd, J = 11.5, 11.5, 11.5, 3.5 Hz, 1H), 1.07 (s, 9H), 1.02 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.0, 135.9, 135.7, 133.9, 130.9, 129.5, 129.2, 127.6, 124.8, 113.7, 94.6, 72.7, 72.3, 70.8, 68.7, 67.8, 55.3, 38.7, 35.2, 33.4, 27.8, 26.9, 23.0, 19.3, 18.7, 14.0; HRFABMS calcd for $C_{38}H_{51}O_5Si$ $[M + H]^+$ 615.3506, found 615.3557. Anal. Calcd for $C_{38}H_{50}O_5Si$: C, 74.46; H, 7.43. Found: C, 74.63; H, 7.55.

Alcohol 37. To a stirred 0 °C solution of **36** (160 mg, 261 μmol) in THF (6 mL) was added TBAF (365 μL of a 1.0 M solution in THF, 365 μmol). The solution was allowed to warm to rt, and after 15 h, saturated aqueous NH_4Cl (1 mL) was added. The mixture was diluted with ethyl acetate (10 mL), and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (hexanes/ethyl acetate, 8:1 to 2:1, v/v) yielded **37** (82 mg, 220 μmol, 84%) as a clear, colorless oil: R_f 0.30 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{26}_D = -18.6$ (*c* 3.4, $CHCl_3$); IR (neat) 3461, 2941, 2865, 1675, 1614, 1516, 1614, 1516, 1455, 1375, 1246, 1094, 1037, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.34 (s, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.78 (m, 2H), 3.63 (dd, J = 9.0, 4.0 Hz, 1H), 3.51 (m, 1H), 3.48 (dd J = 9.0, 6.5 Hz, 1H), 3.44 (m, 1H), 1.95−1.82 (m, 4H), 1.72 (s, 3H), 1.63 (m, 2H), 1.48 (m, 1H), 1.31 (dddd, J = 13.5, 13.5, 13.5, 4.0 Hz), 1.00 (d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 136.3, 130.8, 129.1, 124.5, 113.7, 94.8, 72.7, 72.0, 70.7, 68.4, 66.2, 55.3, 38.6, 35.0, 33.3, 26.3, 23.0, 18.6, 13.9; HRFABMS calcd for $C_{22}H_{33}O_5$ $[M + H]^+$ 377.2328, found 377.2352.

Alcohols 39, 40a, and 40b. To a stirred rt solution of **37** (62 mg, 0.17 mmol) in CH_2Cl_2 (8 mL) were added crushed 4 Å molecular sieves (60 mg) and tetrapropylammonium perruthenate (3.0 mg, 8.3 μmol), followed by 4-methylmorpholine *N*-oxide (49 mg, 0.42 mmol). After 30 min, the reaction mixture was concentrated under a stream of N_2. Filtration through silica gel (hexanes/ethyl acetate, 2:1, v/v) gave **38** (56 mg, 0.15 mmol, 90%) as a clear, colorless oil. This was used directly without further purification: R_f 0.50 (hexanes/ethyl acetate, 2:1, v/v); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.54 (s, 1H), 7.23 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.31 (s, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.16 (dd, J = 12.0, 2.5 Hz, 1H), 3.85 (m, 1H), 3.80 (s, 3H), 3.51 (m, 2H), 1.96−1.65 (m, 6H), 1.74 (s, 3H), 1.55 (ddd, J = 13.0, 13.0, 4.5 Hz, 1H), 1.33 (dddd, J = 12.5, 12.5, 12.5, 4.0 Hz, 1H), 1.28 (t, J = 4.5 Hz, 1H), 1.01 (d, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 159.1, 137.0, 130.6, 129.1, 123.7, 113.7, 95.2, 75.1, 72.8, 71.7, 68.6, 55.3, 38.6, 34.8, 33.2, 25.2, 23.0, 18.3, 13.8.

To a stirred −78 °C solution of diisopropylamine (310 μL, 2.21 mmol) in THF (8 mL) under Ar was added *n*-butyllithium (0.85 mL of a 2.6M solution in hexanes, 2.21 mmol). After 30 min, a solution of *cis*-(*S*)-lactate pivalidene **34** (350 mg, 2.21 mmol) in THF (8 mL) was added via cannula. After 45 min, a solution of **38** (80 mg, 0.22 mmol) in THF (8 mL) was added via cannula. The resulting solution was allowed to stir for 20 min before saturated aqueous NH_4Cl was added. The mixture was allowed to warm to rt and diluted with ethyl acetate (30 mL), washed with H_2O and saturated aqueous NaCl (10 mL each), and dried over Na_2SO_4. The solution was filtered, concentrated, and purified by silica gel column chromatography (hexanes/ethyl acetate, 3:1, v/v) to give a mixture of **39**, **40a**, and **40b** (114 mg, 0.216 mmol, 100%). Further silica gel chromatography (hexanes/ethyl acetate, 10:1 to 3:1, v/v) allowed for separation of the three products: Alcohol **39**: R_f 0.10 (hexanes/ethyl acetate, 4:1, v/v); IR (neat) 3478, 2962, 2935, 1795, 1613, 1514, 1247, 1089, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.32 (s, 1H), 5.15 (s, 1H), 4.46 (s, 2H), 4.00 (m, 1H), 3.78 (m, 2H), 3.78 (s, 3H), 3.71 (ddd, J = 11.0, 7.5, 3.5 Hz, 1H), 3.23 (t, J = 9.0 Hz, 1H), 2.61 (d, J = 4.0 Hz, 1H), 2.01−1.20 (m, 7H), 1.70 (s, 3H), 1.44 (s, 3H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 159.0, 135.8, 131.0, 129.2, 124.4, 113.7, 107.4, 95.1, 81.4, 76.5, 72.7, 72.5, 70.0, 69.1, 55.3, 38.6, 35.1, 34.3, 33.0, 25.8, 23.7, 22.9, 18.4, 15.9, 13.8; HRFABMS calcd for $C_{30}H_{45}O_8$ $[M + H]^+$ 533.3114, found 533.3113. Alcohol **40a**: R_f 0.15 (hexanes/ethyl acetate, 4:1, v/v); IR (neat) 3483, 2936, 1794, 1612, 1513, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.39 (s, 1H), 5.30 (s, 1H), 4.45 (s, 2H), 3.98 (ddd, J = 11.5, 3.0, 3.0 Hz, 1H), 3.89 (t, J = 3.5 Hz, 1H), 3.81 (s, 3H), 3.75 (dd, J = 9.5, 5.0 Hz, 1H), 3.67 (ddd, J = 10.5, 7.0, 3.0 Hz, 1H), 2.68 (t, J = 8.0 Hz, 1H), 2.35 (d, J = 3.5 Hz, 1H), 1.98−1.40 (m, 9H), 1.72 (s, 3H), 1.32 (s, 3H), 1.00 (d, 7.0 Hz, 3H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 159.1, 136.3, 130.7, 129.1, 129.0, 124.2, 113.8, 110.5, 95.4, 81.4, 72.7, 72.2, 69.8, 69.2, 55.3, 38.5, 34.9, 34.5, 33.1, 23.9, 23.3, 22.9, 20.3, 18.2, 14.0; HRFABMS calcd for $C_{30}H_{45}O_8$ $[M + H]^+$ 533.3114, found 533.3138. Alcohol **40b**: R_f 0.20 (hexanes/ethyl acetate, 4:1, v/v); IR (neat) 3542, 2943, 1790, 1613, 1514, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.43 (s, 1H), 5.29 (s, 1H), 4.50 (d, J = 11.0 Hz, 1H), 4.44 (d, J = 11.0 Hz, 1H), 3.90 (ddd, J = 11.0, 3.0, 3.0 Hz), 3.82 (m, 1H), 3.81 (s, 3H), 3.69 (ddd, J = 11.0, 7.5, 3.5 Hz, 1H), 3.51 (dd, J = 6.5, 3.5 Hz, 1H), 3.33 (t, J = 9.0 Hz, 1H), 2.90 (d, J = 8.5 Hz, 1H), 1.96−1.42 (m, 9H), 1.71 (s, 3H), 1.49 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 159.0, 136.0, 131.0, 129.4, 123.9, 113.6, 109.3, 95.1, 80.9, 76.9, 72.6, 72.4, 69.5, 68.6, 55.3, 38.6, 35.0, 34.5, 33.0, 27.5, 23.3, 22.8, 22.0, 18.0, 13.9; HRFABMS calcd for $C_{30}H_{45}O_8$ $[M + H]^+$ 533.3114, found 533.3107.

***p*-Methoxybenzyl Ether 42.** To a stirred 0 °C solution of **40** (10 mg, 19 μmol) in THF (2 mL) under Ar was added NaH (23 mg of 60% NaH in mineral oil, 0.57 mmol). The mixture was allowed to warm to rt over 40 min before freshly distilled CS_2 (53 μL, 0.91 mmol) was added. After 30 min, methyl iodide (35 μL, 0.57 mmol) was added. After 20 min, the solution was cooled to 0 °C, and saturated aqueous NH_4Cl (1 mL) was added. The mixture was warmed to rt, and ethyl acetate (4 mL) was added. The separated organic phase was washed with H_2O and saturated aqueous NaCl (2 mL each), dried over Na_2SO_4, filtered, and concentrated. The residue was azeotropically dried from benzene (2 × 3 mL) and then dissolved in toluene (2 mL). To the solution were added 2,2′-azobisisobutyronitrile (3 mg, 19 μmol) and tri-*n*-butyltin hydride (20 μL, 76 μmol), and Ar was bubbled through the resultant solution for 15 min to remove oxygen. The mixture was then heated to 80 °C under Ar for 1.5 h. After the solution was cooled to rt, it was diluted with ethyl acetate (2 mL), washed with H_2O and saturated aqueous NaCl (2 mL each), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 1:0 to 8:1, v/v) yielded **42** (6.8 mg, 13 μmol, 70%) as a clear, colorless oil: R_f 0.35 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{26}_D = +1.8$ (*c* 1.6, $CHCl_3$); IR (neat) 2960, 2937, 2869, 1793, 1611, 1516, 1455, 1375, 1365, 1249, 1173, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.33 (s, 1H), 5.31 (s, 1H), 4.49 (d, $J = 11.0$ Hz, 1H), 4.44 (d, $J = 11.0$ Hz, 1H), 3.92 (m, 1H), 3.82 (dd, $J = 9.0$, 4.5 Hz, 1H), 3.80 (s, 3H), 3.69 (ddd, $J = 11.5$, 8.0, 3.5 Hz, 1H), 3.32 (t, $J = 8.5$ Hz, 1H), 1.99−1.45 (m, 10H), 1.71 (s, 3H), 1.46 (s, 3H), 1.24 (m, 1H), 1.03 (d, $J = 6.5$ Hz, 3H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 159.0, 135.6, 131.0, 129.3, 124.5, 113.7, 108.2, 94.8, 78.8, 72.7, 72.4, 69.3, 66.2, 55.4, 42.8, 38.6, 34.9, 34.3, 33.1, 31.5, 24.6, 23.4, 22.9, 18.6, 14.0; HRFABMS calcd for $C_{30}H_{45}O_7$ $[M + H]^+$ 517.3165, found 517.3182.

Alcohol 43. To a mixture of **42** (19 mg, 37 μmol), CH_2Cl_2 (5 mL), an aqueous phosphate buffer (pH = 7, 1.0 mL), and *tert*-butyl alcohol (280 μL) was added DDQ (42 mg, 0.185 mmol). The reaction flask was placed in an aqueous bath, sonicated for 1 min, and then assayed by TLC. This process was repeated for a total of 4.5 min of sonication, at which point no starting material remained. (Note: After cleavage of the *p*-methoxybenzyl ether, care must be taken to prevent acid-catalyzed conversion of **43** to an undesired tricyclic product.)[3c] Saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was diluted with ethyl acetate (5 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 1 mL), H_2O, and saturated aqueous NaCl (2 mL each), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (hexanes/ethyl acetate/triethylamine, 4:1:0.004, v/v/v) to give **43** (12 mg, 29 μmol, 79%) as a clear, colorless oil: R_f 0.05 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{26}_D = +4.9$ (*c* 1.5, $CHCl_3$); IR (neat) 3469, 2960, 2930, 2873, 1793, 1000 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.31 (s, 1H), 5.28 (br. s, 1H), 4.08 (dddd, $J = 12.0$, 9.5, 3.0, 3.0 Hz, 1H), 4.03 (ddd, $J = 11.5$, 8.5, 3.5 Hz, 1H), 3.91 (m, 2H), 2.98 (t, $J = 6.0$ Hz, 1H), 1.87 (dd, $J = 15.0$, 9.5 Hz, 1H), 1.81 (m, 2H), 1.70, (m, 1H), 1.60 (m, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.32 (m, 2H), 1.22 (m, 1H), 0.95 (m, 1H), 0.90 (d, $J = 6.5$, 3H), 0.83 (s, 9H); ^{13}C NMR (C_6D_6, 125 MHz) 174.8, 135.0, 124.6, 107.8, 94.8, 78.3, 71.5, 66.0, 65.8, 43.7, 40.1, 34.8, 33.9, 33.6, 31.2, 25.1, 23.1, 22.4, 18.7, 13.1; HRFABMS calcd for $C_{22}H_{37}O_6$ $[M + H]^+$ 397.2590, found 397.2559.

C15−C27 Ketophosphonate. Ketone 49. To a three-necked round-bottom flask containing dry-stirred magnesium (688 mg, 28.3 mmol) under N_2 were added 10 mL of a solution of 4-bromo-1-butene (2.30 mL, 23.0 mmol) and 1,2-dibromoethane (15 μL) in THF (34 mL). This mixture was heated to reflux for 5 min, and then the external heating was removed. The remainder of the bromide solution was added dropwise over 30 min to maintain reflux. The mixture was then externally heated at reflux for an additional 30 min. The Grignard mixture was cooled to rt and added to a solution of aldehyde **48**[3] (3.07 g, 5.66 mmol) in THF (50 mL) at −78 °C dropwise via cannula. After the resulting mixture was stirred for 30 min, saturated aqueous NH_4Cl (6 mL) was added and the mixture was warmed to rt. The THF was removed by rotary evaporation and the aqueous phase was extracted with ethyl acetate. The organic phase was washed successively with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl (50 mL each). The organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give the crude product **48a** (3.14 g, 5.25 mmol, 93%) as a diastereomeric mixture of alcohols. This material was taken to the next step without further purification.

To a −78 °C solution of oxalyl chloride (687 mL, 7.88 mmol) in CH_2Cl_2 (18 mL) under Ar was added a solution of DMSO (1.12 mL, 15.8 mmol) in CH_2Cl_2 (3.6 mL) via cannula. The resultant mixture was stirred for 25 min before a solution of crude **48a** (3.14 g, 5.25 mmol) in CH_2Cl_2 (6 mL) was added via cannula. After the mixture was stirred for an additional 1.5 h at −78 °C, triethylamine (4.79 mL, 34.1 mmol) was added, and the resulting mixture was allowed to warm to 0 °C over 30 min. Saturated aqueous NH_4Cl (50 mL) and ethyl acetate (150 mL) were added. The mixture was warmed to rt, and the separated organic phase was washed with H_2O and saturated aqueous NaCl (100 mL each). The combined aqueous phases were extracted with ethyl acetate, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Silica gel chromatography (hexanes/ethyl acetate, 5:1 to 2:1, v/v) of the residue gave recovered aldehyde **48** (871 mg, 1.61 mmol) and **49** (1.91 g, 3.20 mmol, 79% for 2 steps based on recovered starting material) as a pale oil: R_f 0.38 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{26}_D = -6.1$ (*c* 1.10, $CHCl_3$); IR (neat) 2920, 1720, 1620, 1520, 1470, 1350, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, $J = 9.0$ Hz, 2H), 7.36−7.28 (m, 5H), 6.91 (d, $J = 9.0$ Hz, 2H), 5.76−5.84 (m, 1H), 5.54 (s, 1H), 5.03 (ddd, $J = 17.0$, 2.5, 1.5 Hz, 1H), 4.98 (ddd, $J = 10.0$, 2.8, 1.5 Hz, 1H), 4.90 (d, $J = 12.0$ Hz, 1H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.21 (dd, $J = 10.0$, 5.0 Hz, 1H), 4.06−4.10 (m, 1H), 4.01 (dd, $J = 9.5$, 2.5 Hz, 1H), 3.82 (s, 3H), 3.79 (d, $J = 3.5$ Hz, 1H), 3.75 (m, 1H), 3.72 (dd, $J = 10.0$, 10.0 Hz, 1H), 3.64 (dd, $J = 12.0$, 4.0 Hz, 1H), 2.57 (m, 1H), 2.51 (m, 5H), 2.31 (m, 1H), 1.76 (m, 1H), 0.87 (s, 9H), 0.001 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 160.0, 138.7, 137.1, 130.4, 128.3, 127.6, 127.5, 115.2, 113.6, 102.2, 79.3, 77.8, 76.5, 73.5, 72.4, 69.8, 59.7, 55.3, 42.0, 39.3, 27.8, 25.8, 23.2, 18.0, −5.1 (2C). Anal. Calcd for $C_{34}H_{48}O_7Si$: C, 68.42; H, 8.11. Found: C, 68.64; H, 7.98.

Primary TBS Bispyran 50. A solution of **49** (1.05 g, 1.76 mmol) and camphorsulfonic acid (82 mg, 0.35 mmol) in benzene (20 mL) and methanol (10 mL) was heated at reflux under N_2 for 7 h under a Dean−Stark trap. The solution was cooled to rt and diluted with methanol (50 mL), and triethylamine was added until the solution was neutral or slightly basic to pH paper. The solvents were removed under reduced pressure to yield an orange oil that was used without further purification. To this crude material in CH_2Cl_2 (17 mL) under Ar at rt were added *tert*-butyldimethylsilyl chloride (796 mg, 5.28 mmol), triethylamine (1.47 mL, 10.6 mmol), and 4-*N*,*N*-(dimethylamino)pyridine (cat.). This mixture was stirred for 5 h and then diluted with ethyl acetate (75 mL). The separated organic phase was washed with saturated aqueous NH_4Cl (2 × 25 mL), H_2O (25 mL), and saturated aqueous NaCl (25 mL). The aqueous phases were combined and extracted with ethyl acetate (2 × 25 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 5:1, v/v) of the residue gave silyl ether **50** (573 mg, 1.16 mmol, 66% from ketone **49**) as an off-white solid: mp 66−68 °C; R_f 0.47 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D = -20.8$ (*c* 1.14, $CHCl_3$); IR (neat) 3460, 3030, 2940, 1630, 1455, 1355, 1250, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.26 (m, 5H), 5.92−5.79 (m, 1H), 5.05 (ddd, $J = 17.0$, 1.5, 1.5 Hz, 1H), 4.98 (m, 1H), 4.85 (d, $J = 12.0$ Hz, 1H), 4.75 (d, $J = 12.0$ Hz, 1H), 4.16 (dd, $J = 1.0$, 1.0 Hz, 1H), 3.98 (dd, $J = 5.0$, 5.0 Hz, 1H), 3.88−3.74 (m, 4H), 3.56−3.48 (m, 1H), 3.22 (s, 3H), 2.84 (s, 1H), 2.09−2.02 (m, 2H), 1.92−1.76 (m, 4H), 1.62−1.51 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 138.2, 128.3, 127.6, 127.4, 114.4, 99.1, 78.2, 76.6, 72.4, 71.5, 71.3, 68.8, 63.8, 47.3, 34.8, 32.3, 27.9, 25.8, 25.3, 18.0, −5.6, −5.7. Anal.

Calcd for $C_{27}H_{44}O_6Si$: C, 65.82; H, 9.00. Found: C, 66.02; H, 8.84.

Ketone 50a. To a stirred −78 °C solution of DMSO (255 μL, 3.60 mmol) in CH_2Cl_2 (10 mL) under Ar was added trifluoroacetic anhydride (381 μL, 2.70 mmol) dropwise. The resultant mixture was stirred for 15 min before a solution of alcohol **50** (887 mg, 1.80 mmol) in CH_2Cl_2 (4.5 mL) was added via cannula. After the mixture was stirred for an additional 1.5 h at −78 °C, triethylamine (700 μL, 5.04 mmol) was added, and the resulting mixture was stirred at 0 °C for 30 min. Saturated aqueous NH_4Cl (25 mL) and ethyl acetate (100 mL) were added. The separated organic phase was washed with H_2O and saturated aqueous NaCl (25 mL each). The combined aqueous phases were extracted with ethyl acetate, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 5:1, v/v) of the residue gave ketone **50a** (784 mg, 1.60 mmol, 89%) as a pale oil: R_f 0.39 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{26}_D = -21.3$ (*c* 1.15, $CHCl_3$); IR (neat) 2920, 1725, 1450, 1250, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.43 (m, 2H), 7.35−7.26 (m, 3H), 5.93−5.80 (m, 1H), 5.09−4.98 (m, 2H), 5.02 (d, *J* = 12.3 Hz, 1H), 4.81 (d, *J* = 12.3 Hz, 1H), 4.22−4.16 (m, 1H), 4.12 (dd, *J* = 2.7, 2.7 Hz, 1H), 4.10 (d, *J* = 10.5 Hz, 1H), 3.96 (m, 2H), 3.74 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.23 (s, 3H), 2.10−2.02 (m, 2H), 1.94−1.81 (m, 4H), 1.67−1.53 (m, 2H), 0.81 (s, 9H), 0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 138.1, 138.0, 128.1, 127.6, 127.5, 114.4, 98.7, 83.4, 83.2, 74.3, 73.9, 71.9, 66.5, 47.4, 34.4, 31.8, 27.8, 25.6, 25.3, 17.9, −5.9 (2C). Anal. Calcd for $C_{27}H_{42}O_6Si$: C, 66.09; H, 8.63. Found: C, 65.94; H, 8.77.

Olefin 51. To a stirred rt mixture of methyltriphenylphosphonium bromide (1.41 g, 3.96 mmol) in toluene (35 mL) under N_2 was added potassium bis(trimethylsilyl)amide (7.2 mL of a 0.50 M solution in toluene, ∼3.6 mmol). The deep yellow mixture was heated to 80−90 °C for 30 min, and then the resultant deep orange solution was cooled to rt before a solution of ketone **50a** (784 mg, 1.60 mmol) in toluene (9 mL) was added via cannula. The resultant solution was heated to 80−90 °C for 30 min, then cooled to rt before saturated NH_4Cl (25 mL) was added. The toluene was removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The organic phase was washed with H_2O and saturated aqueous NaCl (2 × 25 mL each). The combined aqueous phases were extracted with ethyl acetate and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 15:1, v/v) of the residue gave olefin **51** (656 mg, 1.34 mmol, 84%) as a colorless oil: R_f 0.48 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{27}_D = -10.2$ (*c* 1.66, $CHCl_3$); IR (neat) 2960, 1635, 1455, 1350, 1250, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43−7.41 (m, 2H), 7.36−7.33 (m, 2H), 7.29−7.26 (m, 1H), 5.91−5.83 (m, 1H), 5.44 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.07 (m, 1H), 5.07 (dd, *J* = 2.0, 2.0 Hz, 1H), 4.99 (m, 1H), 4.92 (d, *J* = 12 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.32 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.21 (m, 1H), 3.88−3.80 (m, 2H), 3.68 (m, 1H), 3.42 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.23 (s, 3H), 2.10−2.06 (m, 2H), 1.93−1.85 (m, 2H), 1.83−1.78 (m, 2H), 1.63−1.54 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.2, 138.9, 138.2, 128.1, 127.4, 127.3, 114.4, 111.6, 98.9, 80.6, 78.0, 76.9, 73.7, 70.9, 65.2, 47.3, 34.7, 32.2, 27.8, 25.8, 25.6, 18.1, −5.53, −5.57. Anal. Calcd for $C_{28}H_{44}O_5Si$: C, 68.81; H, 9.07. Found: C, 69.00; H, 8.83.

Alcohol 51a. To a −60 °C solution of benzyl ether **51** (135 mg, 276 μmol) in THF (3 mL) under Ar was added a solution of lithium di-*tert*-butylbiphenylide[38] (16.2 mL of a 0.17 M solution in THF, ∼2.8 mmol) dropwise. After the mixture was stirred at this temperature for 10 min, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was warmed to rt and diluted with diethyl ether (50 mL). The phases were separated, and the organic phase was washed successively with H_2O and saturated aqueous NaCl (25 mL each). The aqueous washes were extracted with diethyl ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 1:0 to 5:1, v/v) of the residue gave alcohol **51a** (75 mg, 0.19 mmol, 68%) as a white solid: mp 88−90 °C; R_f 0.19 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{27}_D = -17$ (*c* 1.0, $CHCl_3$); IR (neat) 3460, 2930, 1635, 1250, 1090, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.88−5.80 (m, 1H), 5.36 (m, 1H), 5.07 (m, 1H), 5.04 (m, 1H), 4.98 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.39 (m, 1H), 4.32 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.88 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.81 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.65 (m, 1H), 3.21 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.19 (s, 3H), 2.45 (d, *J* = 3.0 Hz, 1H), 2.08−2.03 (m, 2H), 1.94−1.87 (m, 2H), 1.82−1.79 (m, 2H), 1.60−1.51 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.8, 138.0, 114.5, 110.6, 99.2, 80.6, 76.7, 71.0, 70.3, 65.2, 47.4, 34.5, 32.2, 27.8, 25.9, 25.2, 18.3, −5.4, −5.4; HRFABMS calcd for $C_{21}H_{39}O_5Si$ $[M + H]^+$ 399.2567, found 399.2555.

Bis-TBS Ether 52. To a 0 °C solution of alcohol **51a** (150 mg, 377 μmol) in DMF (4 mL) under Ar were added triethylamine (1.05 mL, 7.54 mmol), 4-*N*,*N*-(dimethylamino)pyridine (46 mg, 377 μmol) and *tert*-butyldimethylsilyl chloride (568 mg, 3.77 mmol). This solution was allowed to warm to rt and stirred for 22 h. CH_2Cl_2 (25 mL) was then added, followed by saturated aqueous NH_4Cl (10 mL). The phases were separated, and the organic phase was washed successively with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl (10 mL each). The combined aqueous washes were extracted with CH_2Cl_2, 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, 8:1 to 5:1, v/v) to yield silyl ether **52** (181 mg, 354 μmol, 94%) as a pale oil: R_f 0.50 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{26}_D = -18.4$ (*c* 1.18, $CHCl_3$); IR (neat) 2960, 1635, 1460, 1360, 1250, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.93−5.79 (m, 1H), 5.35 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.06 (m, 1H), 5.04 (m, 1H), 4.99 (m, 1H), 4.40 (m, 1H), 4.33 (dd, *J* = 5.1, 5.1 Hz, 1H), 3.87 (d, *J* = 5.1 Hz, 2H), 3.71 (m, 1H), 3.20 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.21 (s, 3H), 2.12−2.03 (m, 2H), 1.92−1.77 (m, 4H), 1.62−1.51 (m, 2H), 0.97 (s, 9H), 0.93 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H), 0.094 (s, 3H), 0.087 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.8, 138.3, 114.4, 111.3, 99.0, 80.7, 76.5, 72.0, 71.3, 65.7, 47.4, 34.6, 32.3, 28.0, 25.9 (2C), 25.6, 18.4, 18.2, −4.4, −5.0, −5.4, −5.5. Anal. Calcd for $C_{27}H_{52}O_5Si_2$: C, 63.23; H, 10.22. Found: C, 63.37; H, 10.03.

***β*-Ketophosphonate 15.** To a solution of olefin **52** (74 mg, 0.15 mmol) in THF (1 mL) and H_2O (0.5 mL) was added pyridine (5.9 μL, 72 μmol), followed by sodium periodate (94 mg, 0.44 mmol), and osmium tetraoxide (120 μL of a 76 mM solution in *tert*-butyl alcohol, 8.9 μmol). This mixture was stirred vigorously for 2 h. The reaction was diluted with diethyl ether (10 mL) and washed successively with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl (3 mL each). The combined aqueous phases were extracted with diethyl ether, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a crude oil. Silica gel column chromatography (hexanes/ethyl acetate, 1:0 to 5:1, v/v) of the residue afforded recovered olefin **52** (8 mg, 0.02 mmol) and aldehyde **52a** (41 mg, 80 μmol, 55%, 61% based on recovered **52**).

To a stirred −78 °C solution of dimethyl methylphosphonate (120 μL, 1.11 mmol) in THF (2 mL) under Ar was added *n*-butyllithium (400 μL of a 2.4 M solution in hexanes, ∼961 μmol) dropwise. The resultant mixture was stirred for 1 h before a solution of **52a** (38 mg, 74 μmol) in THF (0.5 mL) was added via cannula. The resultant pale yellow solution was stirred for an additional 50 min, at which time saturated aqueous NH_4Cl (1 mL) was added and the mixture was allowed to warm to rt. Diethyl ether (10 mL) was added, and the phases were separated. The organic phase was washed with H_2O and saturated aqueous $NaHCO_3$ (3 mL each). 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 (hexanes/ethyl acetate, 2:1, v/v) to yield the crude β-hydroxy phosphonate as an oil. This material was used without further purification.

To a stirred rt solution of the above alcohols (74 μmol theoretical) in CH_2Cl_2 (1.5 mL) were added $NaHCO_3$ (250 mg, 2.96 mmol) and the Dess−Martin periodinane reagent (250 mg, 591 μmol). The resultant mixture was stirred for 1.5 h

before diethyl ether (20 mL), saturated aqueous $NaHCO_3$ (4 mL), and 10% aqueous $Na_2S_2O_3$ (4 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 and saturated aqueous NaCl (2 × 5 mL each). The aqueous phases were extracted with diethyl ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 1:1 to 1:5, v/v) gave β-ketophosphonate **15** (33 mg, 52 μmol, 70% from **52a**) as a pale oil: R_f 0.29 (hexanes/ethyl acetate, 1:5, v/v); $[\alpha]^{25}_D = -12$ (*c* 1.5, $CHCl_3$); IR (neat) 2930, 1715, 1460, 1250, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.32 (dd, *J* = 2.1, 2.1 Hz, 1H), 5.02 (s, 1H), 4.36 (m, 1H), 4.30 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.84 (d, *J* = 5 Hz, 2H), 3.79 (d, J_{P-H} = 11.4 Hz, 6H), 3.73−3.67 (m, 1H), 3.15 (s, 3H), 3.15 (m, 1H), 3.10 (d, J_{P-H} = 22.8 Hz, 2H), 2.63 (dd, *J* = 8, 8 Hz, 2H), 2.08−1.97 (m, 2H), 1.84−1.44 (m, 4H), 0.93 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.0, 145.7, 111.4, 98.6, 80.7, 76.7, 71.9, 71.1, 65.6, 53.0, 47.4, 41.4 (d, J_{C-P} = 127 Hz), 38.8, 32.3, 28.6, 25.9, 25.5, 18.4, 18.2, −4.3, −5.0, −5.4, −5.5; HRFABMS calcd for $C_{28}H_{54}O_9PSi_2$ $[M - OCH_3]^+$ 605.3095, found 605.3107.

Enone 53. To a stirred rt solution of **43** (9.0 mg, 23 μmol) in CH_2Cl_2 (3 mL) were added crushed 4 Å molecular sieves (20 mg) and tetrapropylammonium perruthenate (0.4 mg, 1 μmol), followed by 4-methylmorpholine *N*-oxide (6 mg, 50 μmol). After 30 min, the reaction mixture was concentrated under a stream of N_2. Filtration through a silica gel column (hexanes/ethyl acetate, 2:1, v/v) gave **4** (8 mg, 20 μmol, 89%) as a white solid. This was used directly without further purification: R_f 0.60 (hexanes/ethyl acetate, 4:1, v/v); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.81 (d, *J* = 6.0 Hz, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 4.16 (ddd, *J* = 19.5, 13.0, 7.0 Hz, 1H), 3.90 (m, 1H), 2.40 (dddd, *J* = 24.0, 11.5, 11.5, 6.0 Hz, 1H), 2.04−1.78 (m, 6H), 1.73 (s, 3H), 1.62−1.46 (m, 3H), 1.48 (s, 3H), 1.25 (m, 1H), 1.16 (d, *J* = 11.5 Hz, 3H), 0.92 (s, 9H).

To a stirred rt solution of **15** (11 mg, 19 μmol) in CH_3CN (2 mL) was added LiCl (10 mg, 0.24 mmol) followed by diisopropylethylamine (25 μL, 0.14 mmol). After the mixture was stirred for 10 min, a solution of **4** (9 mg, 25 μmol) in CH_3CN (1 mL) was added. The resulting mixture was stirred for 36 h. The solvent was removed under a stream of N_2, and the resulting residue was mixture was diluted with ethyl acetate (4 mL), washed with H_2O and saturated aqueous NaCl (1 mL each), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 12:1 to 8:1, v/v) of the residue gave enone **53** (10 mg, 11 μmol, 58%) as a clear, colorless oil: R_f 0.55 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{25}_D = -20.0$ (*c* 2.9, $CHCl_3$); IR (neat) 2950, 2930, 1785, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.97 (dd, *J* = 15.5, 8.5 Hz, 1H), 6.13 (d, *J* = 15.5 Hz, 1H), 5.38 (s, 1H), 5.34 (s, 1H), 5.33 (s, 1H), 5.03 (s, 1H), 4.36 (d, *J* = 9.5 Hz, 1H), 4.31 (t, *J* = 5.0 Hz, 1H), 3.93 (dddd, *J* = 11.0, 2.0, 2.0, 2.0 Hz, 1H), 3.85 (m, 3H), 3.67 (m, 1H), 3.18 (s, 3H), 3.18 (m, 1H), 2.67 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H), 2.57 (ddd, *J* = 17.0, 10.0, 5.0 Hz, 1H), 2.46 (m, 1H), 2.09 (ddd, *J* = 15.5, 10.5, 5.5 Hz, 1H), 1.96−1.74 (m, 10H), 1.71 (s, 3H), 1.61−1.48 (m, 4H), 1.47 (s, 3H), 1.23 (m, 1H), 1.18 (d, *J* = 13.0 Hz, 3H), 0.94 (s, 9H), 0.909 (s, 9H), 0.906 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 175.4, 149.8, 145.7, 135.2, 130.8, 128.4, 124.5, 111.5, 108.4, 99.0, 94.8, 80.8, 78.6, 76.6, 72.0, 71.2, 69.9, 66.1, 65.5, 47.5, 43.8, 42.2, 34.7, 34.2, 34.0, 33.3, 32.4, 31.4, 29.7, 29.1, 25.9, 25.6, 25.4, 23.4, 22.8, 18.4, 18.2, 16.3, −4.3, −4.9, −5.3, −5.5; HRFABMS calcd for $C_{49}H_{84}O_{11}Si_2Na$ $[M + Na]^+$ 927.5450, found 927.5479.

Allylic Alcohol 53a. To a stirred rt solution of **53** (3.0 mg, 3.0 μmol) in toluene (0.5 mL) under Ar was added (*S*)-2-methyl-CBS-oxazaborolidine (26 μL of a 1.0 M solution in toluene, 26 μmol). The mixture was cooled to −78 °C, and catechol borane (2 μL, 0.01 mmol) was added. After 10 min, saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was allowed to warm to rt. Ethyl acetate (2 mL) was added, and the organic phase was washed with H_2O and saturated aqueous NaCl (1 mL each), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 8:1 to 4:1, v/v) provided **53a** (2.9 mg, 2.9 μmol, 95%) as a clear, colorless oil: R_f 0.05 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{26}_D = -12.2$ (*c* 0.77, $CHCl_3$); IR (neat) 3465, 2952, 2933, 2857, 3465, 1789, 1458, 1367, 1253, 831, 774 cm^{-1}; ^1H NMR (C_6H_6, 500 MHz) δ 6.03 (dd, *J* = 15.0, 8.5 Hz, 1H), 5.71 (dd, *J* = 15.0, 6.0 Hz, 1H), 5.53 (t, *J* = 1.5 Hz, 1H), 5.50 (s, 1H), 5.34 (s, 1H), 4.95 (s, 1H), 4.59 (d, *J* = 9.5 Hz, 1H), 4.39 (t, *J* = 4.5 Hz, 1H), 4.13 (m, 2H), 3.83 (m, 3H), 3.77 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.55 (t, *J* = 9.5 Hz, 1H), 3.22 (s, 3H), 2.34 (dddd, *J* = 14.0, 7.0, 7.0, 7.0 Hz, 1H), 2.24 (m, 2H), 1.97−1.58 (m, 10H), 1.61 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 0.96 (s, 9H), 0.85 (s, 9H), 0.36 (s, 6H), 0.29 (s, 3H), 0.19 (s, 3H); HRMALDIMS calcd for $C_{49}H_{86}O_{11}Si_2Na$ $[M + Na]^+$ 929.5606, found 929.5676.

Spiroketal 54. To a stirred rt solution of **53a** (~2.5 mg, 2.6 μmol) in benzene (0.8 mL) was added *p*-toluenesulfonic acid monohydrate (~0.1 mg, 0.5 μmol). After the solution was stirred for 45 min, saturated aqueous $NaHCO_3$ (0.5 mL) was added, and the mixture was diluted with ethyl acetate (1 mL). The organic phase was washed with H_2O and saturated aqueous NaCl (0.8 mL each), dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) of the residue yielded **54** (2.0 mg, 2.4 μmol, 83%) as a clear, colorless oil: R_f 0.40 (hexanes/ethyl acetate, 4:1, v/v); $[\alpha]^{26}_D = +5.0$ (*c* 1.5, $CHCl_3$); IR (neat) 2956, 2930, 2854, 1793, 1466, 1364, 1253, 1120, 1082, 1010, 980, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.73 (dd, *J* = 15.5, 8.5 Hz, 1H), 5.49 (dd, *J* = 15.0, 7.0 Hz, 1H), 5.33 (s, 1H), 5.32 (s, 1H), 5.31 (s, 1H), 5.01 (s, 1H), 4.51 (q, *J* = 7.5 Hz, 1H), 4.31 (m, 2H), 4.00 (m, 1H), 3.86 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.81 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.72 (ddd, *J* = 9.0, 5.5, 3.5 Hz, 1H), 3.63 (m, 1H), 3.41 (t, *J* = 10.0 Hz, 1H), 2.29 (m, 1H), 2.16 (m, 1H), 2.00−1.73 (m, 10H), 1.71 (s, 3H), 1.64−1.54 (m, 3H), 1.47 (s, 3H), 1.32−1.16 (m, 4H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); HRFABMS calcd for $C_{48}H_{83}O_{10}Si_2$ $[M + H]^+$ 875.5524, found 875.5529.

Alcohol 14. To a stirred rt solution of **54** (~1.5 mg, 1.7 μmol) in THF (0.5 mL) was added TBAF (5 μL of a 1.0 M solution in THF, 5 μmol). After 3 h, the reaction mixture was concentrated under a stream of N_2. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 2:1, v/v) to give recovered **54** (0.3 mg, 0.3 μmol) and **14** (~1 mg, 1.3 μmol, 76%, 95% corrected for recovered starting material) as a clear, pale yellow oil: R_f 0.33 (hexanes/ethyl acetate, 2:1, v/v); ^1H NMR ($CDCl_3$ 500 MHz) δ 5.74 (dd, *J* = 15.0, 8.0 Hz, 1H), 5.50 (dd, *J* = 15.5, 7.5 Hz, 1H), 5.37 (t, *J* = 2.0 Hz, 1H), 5.34 (s, 1H), 5.33 (s, 1H), 5.09 (s, 1H), 4.51 (q, *J* = 7.0 Hz, 1H), 4.43 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.15 (d, *J* = 8.5 Hz, 1H), 3.99 (m, 2H), 3.72 (ddd, *J* = 11.0, 5.5, 3.5 Hz, 1H), 3.51−3.44 (m, 3H), 2.29 (q, *J* = 7.0 Hz, 1H), 2.16 (m, 1H), 1.99−1.48 (m, 16H), 1.75 (s, 3H), 1.47 (s, 3H), 1.23 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.91 (s, 9H); HRFABMS calcd for $C_{42}H_{69}O_{10}Si$ $[M + H]^+$ 761.4660, found 761.4658.

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Supporting Information Available: NMR spectral data of all new compounds described in the Experimental Section as well as derivative **55**. This material is available free of charge via the Internet at http://pubs.acs.org.

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