# Synthetic Studies toward the Total Synthesis of Swinholide. 1. Stereoselective Construction of the $C_{19}$−$C_{35}$ Subunit

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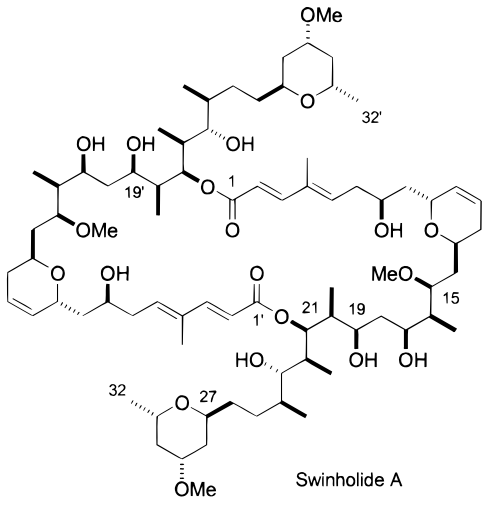
The development of an approach directed at the total synthesis of the complex cytotoxic marine macrodiolide swinholide is described. The present study focuses on the development of a synthetic route for the preparation of the $C_{19}$−$C_{35}$ segment of the structure, which is composed of a trisubstituted pyran moiety with a contrathermodynamic anti arrangement of the $C_2$ and $C_6$ pyran substituents (swinholide $C_{27}$ and $C_{31}$) which is joined by an ethano linker to an acyclic array containing five contiguous stereocenters. The pyran subunit was constructed using a stereoselective allylation of a $\beta$-alkoxy aldehyde with 1,3-asymmetric induction and a second stereoselective allylation to prepare the C-glycosidic type of linkage. Use of the Hafner−Duthaler reagent was investigated as a potential means of constructing the anti vicinal hydroxyl−methyl relationships found in the $C_{19}$−$C_{24}$ segment but was found not to be practical in this instance. The Evans bis propionate methodology was used to introduce a four-carbon unit, and a Mukaiyama aldol was used for chain extension to incorporate the remaining two carbons and two stereocenters of this segment. Attempted use of the Hanessian benzylidene acetal fragmentation reaction in this sequence was thwarted by neighboring group participation of an oxazolidinone in one case and an unexpected regiochemical outcome in another. The approach developed affords the $C_{19}$−$C_{35}$ substructure in 18 steps overall from ethyl acetoacetate and in adequate quantities (10% overall yield) to support the projected total synthesis.

## Introduction

Swinholide A, a potent cytotoxic macrolide, was first isolated from Okinawan marine sponges of genus *Theonella swinhoei* by Carmely and Koshman in 1985.[1] Although originally assigned as monomeric,[2] FABMS[3] and X-ray crystallography[4−6] have shown that swinholide A is a dimer containing a 44-membered dilactone ring which exists in the solid phase in the shape of a twisted saddle. Swinholide A possesses in vitro antifungal activity and exhibits high cytotoxic activity for L1210 ($IC_{50}$ = 0.03 $\mu$g/mL) and KB ($IC_{50}$ = 0.04 $\mu$g/mL) tumor cells.[3,4] Recently it has been shown that swinholide A dimerizes actin and disrupts the actin skeleton.[7] It is because of this potent activity and unique structure that we undertook the asymmetric total synthesis of swinholide A.




Swinholide A

Swinholide A has attracted much interest in the field of synthetic organic chemistry. Paterson[8] and Nicolaou[9] have each completed the synthesis of this large marine macrolide while Nakata[10] has synthesized the monomer preswinholide A and Mulzer[11] has synthesized the $C_{25}$−$C_{32}$ tetrapyran subunit.

**Synthetic Plan.** Our approach to swinholide A is similar to that of Paterson and Nicolaou in that the molecule is first broken down into its monomer **1** and

(1) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511.
(2) Tanaka, J.-I.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963.
(3) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629.
(4) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.-I.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710.
(5) Kobayashi, M.; Tanako, J.-I.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409.
(6) Rotem, M.; Kashman, Y. *Magn. Reson. Chem.* **1986**, *24*, 343.
(7) Bubb, M. R.; Spector, I.; Bershadsky, A. D.; Korn, E. D. *J. Biol. Chem.* **1995**, *270*, 3463.
(8) (a) Paterson, I.; Cumming, J. *Tetrahedron Lett.* **1992**, *33*, 2847. (b) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261. (c) Paterson, I.; Yeung, K. *Tetrahedron Lett.* **1993**, *34*, 5347. (d) Paterson, I.; Smith, J. D. *Tetrahedron Lett.* **1993**, *34*, 5354. (e) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 3405. (f) Paterson, I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 2615. (g) Paterson, I.; Yeung, K.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (h) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (i) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (j) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K. *Tetrahedron* **1995**, *51*, 9437. (k) Paterson, I.; Yeung, K.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9467.
(9) (a) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1147. (b) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P.; Nicolaou, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1151. (c) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059.
(10) (a) Nakata, T.; Komatsu, T.; Nagasawa, K. *Chem. Rev. Bull.* **1994**, *42*, 2403. (b) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 8225. (c) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6881. (d) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6885.

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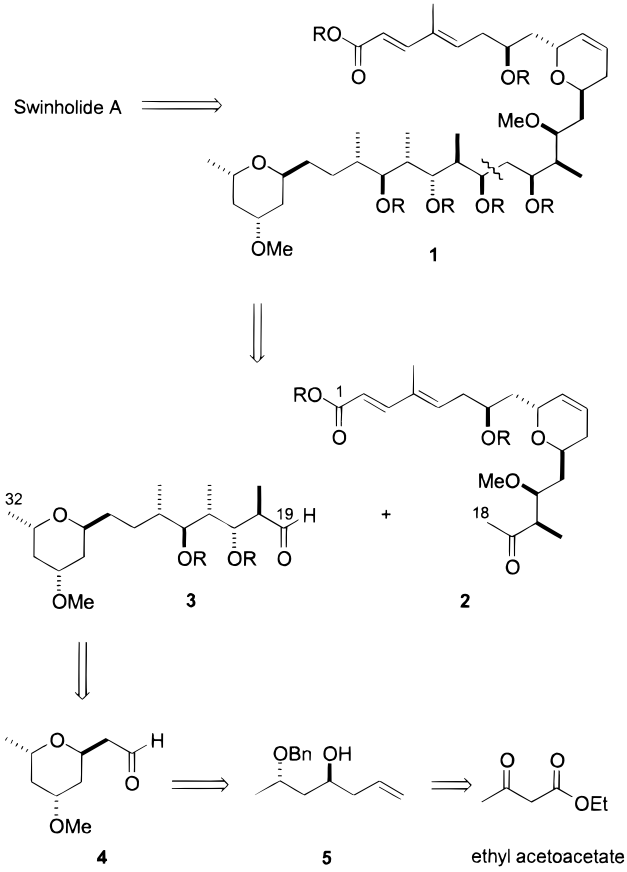
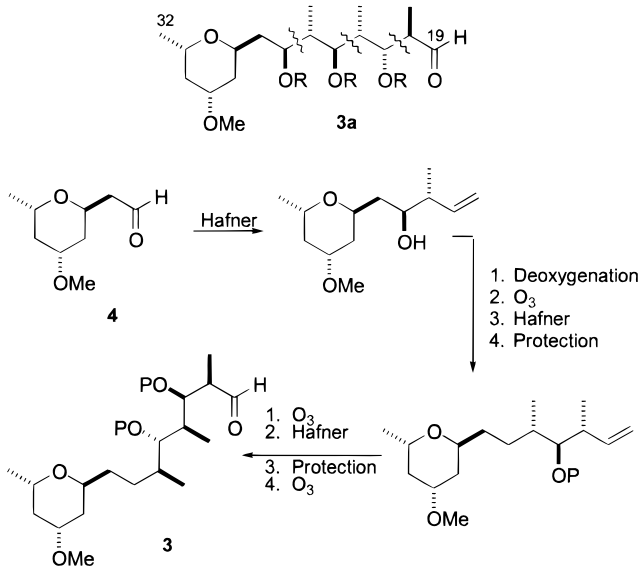
further disconnected into the $C_1-C_{18}$ (**2**) and $C_{19}-C_{32}$ (**3**) pyran subunits, which we planned to couple together using a Mukaiyama aldol reaction. The focus of this discussion will be on the synthesis of **3**.




The original plan for assembling **3** involved a series of iterative polypropionate additions to pyran aldehyde **4** which could be made from homoallylic alcohol **5** and, ultimately, from ethyl acetoacetate through a series of highly selective reagent- and substrate-controlled reactions. This approach (outlined above) describes the overall basis of our plan. More specifically, if one introduces an additional hydroxyl substituent at $C_{25}$, then a reasonable means for coupling of the pyran subunit with the $C_{19}-C_{24}$ acyclic segment can be envisioned by nucleophilic addition to **4**. Moreover, if this hydroxyl is of $\beta$ orientation, then it can be seen that three iterative disconnections of anti vicinal hydroxyl−methyl units can be envisioned, as indicated below in structure **3a**. We hoped to accomplish these anti bond construction events through the use of the Hafner−Duthaler reagent (vide infra). Thus the plan becomes one of iterative chain extension from pyran aldehyde **4** involving anti bond constructions under "reagent control". Crotyl addition to aldehyde **4** should give the desired *anti*-homoallylic alcohol using the appropriate Hafner reagent. After deoxygenation and aldehyde formation, a second crotyl addition would be performed. Finally, conversion of the terminal olefin to the aldehyde, a third crotyl addition, and protection and aldehyde formation would give the desired $C_{19}-C_{32}$ segment **14**. The pyran aldehyde **4** itself was to be prepared by two sequential allylstannane additions previously studied in our laboratories.

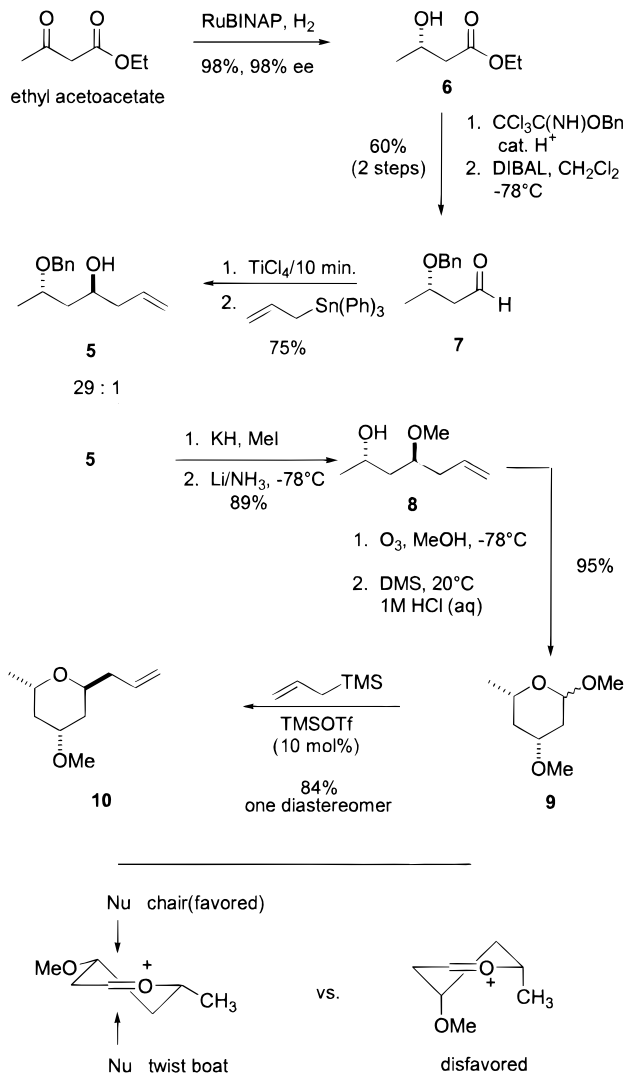
**Construction of the Dihydropyran Unit and Investigation of the Iterative Approach.** Ethyl acetoacetate was reduced using Noyori conditions[12] to provide the $\beta$-hydroxy ester **6** in 98% yield and 98% ee. After benzyl protection[13] and a low-temperature half-reduction using DIBAL, aldehyde **7** was subjected to a chelation-controlled allylstannane addition. This allylation process, previously developed in our laboratories and used in the synthesis of (−)-colletol,[14] produced **5** in 75% yield and with 29:1 anti:syn diastereoselectivity.



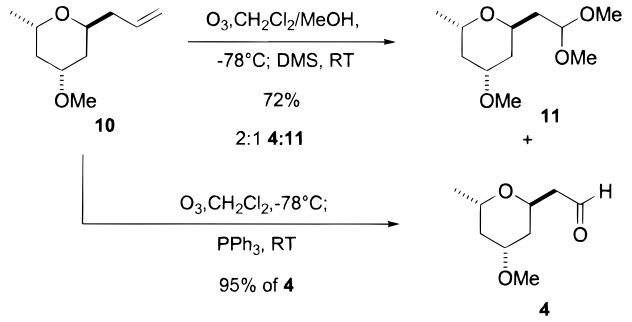

After conversion of the hydroxyl group to the methyl ether using KH/MeI and removal of the benzyl group using dissolving metal conditions, **8** was treated with ozone and worked up with DMS followed by acidic methanol to give tetrahydropyran **9**. This material was isolated as a 3:1 mixture of anomers which did not require separation, since the planned installation of the allyl side chain utilized conditions which would allow kinetically controlled axial attack on the oxonium ion derived from either anomer of **9**.

This was first attempted using a variety of conditions with allyltributylstannane as the three-carbon nucleophile which should produce a surrogate of the desired aldehyde intermediate **4**. A quick survey of Lewis acids ($Bu_3SnOTf$, TMSOTf, $BF_3{\cdot}OEt_2$) and solvents ($CH_3CN$, $CH_2Cl_2$) provided the desired allylpyran **10** but with only moderate levels of diastereoselectivity. At the same time this work was in progress, the Paterson group published their synthesis of the $C_{19}-C_{32}$ segment of swinholide A and reported the use of allyltrimethylsilane and TMSOTf for this conversion.[3a] These conditions gave the desired product **10** as one diastereomer with a yield greater than 90%, perhaps due to a later transition state for nucleophilic addition with the less reactive allylsilane. Thus we decided, for the sake of time and resources, to use these conditions in our synthesis. Ozonolysis of **10** gave aldehyde **4** in 95% yield. Interestingly, ozonolysis of **10** in $CH_2Cl_2$/MeOH and workup with DMS gave a 30% yield of the pyran aldehyde dimethyl acetal **11**. The formation

(11) Mulzer, J.; Meyer, F.; Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503.
(12) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumbayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
(13) (a) Iverson, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240. (b) Wessel, H.-P.; Iverson, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247. (c) Widmer, J. *Synthesis* **1987**, 568. (d) Clizbe, A.; Overman, L. E. *Org. Synth.* **1978**, *8*, 4.
(14) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606.

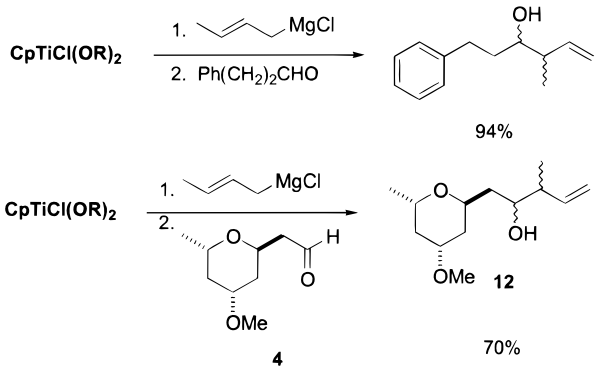



of this undesired side product was easily quelled by omitting MeOH and working up the reaction with $PPh_3$. Unfortunately, the workup and chromatography are somewhat more tedious using the latter method.

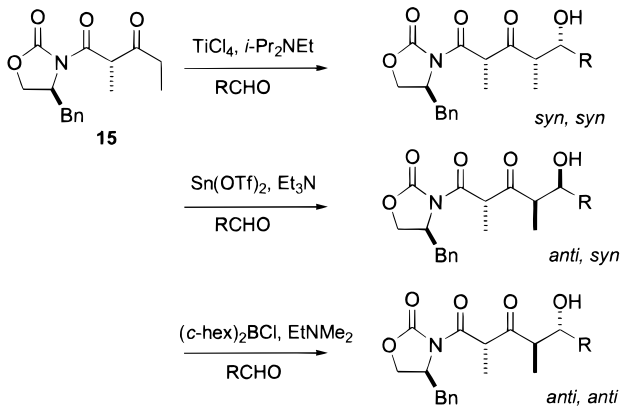



With aldehyde **4** in hand, we were ready to extend the pyran side chain using a series of anti-selective crotyl additions with the Hafner−Duthaler reagent. In 1992, Hafner and Duthaler reported[16] the use of a new tartrate-derived titanium reagent, prepared using an allyl or crotyl Grignard reagent, in the allylation or crotylation of prochiral and chiral aldehydes. Generally, the yields and selectivities reported for these reactions were extremely high with the anti bond construction product formed preferentially.

Examination of this synthetic pathway began by ensuring the Hafner−Duthaler reaction would work in our hands. After working out the intricacies of this reaction (there were many), we were able to successfully repeat the crotyl addition to hydrocinnamaldehyde as reported in the original paper. Unfortunately, translation of this method to pyran aldehyde **4** proved to be futile. In small-scale (25−50 mg) reactions, addition product **12** could be obtained in 70% yield as a single diastereomer. However, these results could not be reliably repeated, and increasing the scale of the reaction required several equivalents of the titanium reagent. The low yields obtained on scale-up, the large amounts of auxiliary required, and the overalll technical difficulty of the reaction (the crotyl Grignard reagent must be freshly prepared and titrated prior to use and the magnesium salts had to be filtered off by running the Grignard reagent directly into the reaction mixture through oven-dried pipets packed with Celite) led us to reexamine our synthetic route.



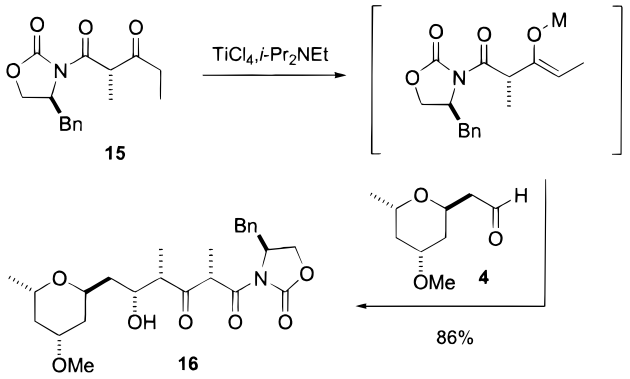

**Construction of the Acyclic Segment Using the Evans Bis Propionate Synthon.** In 1990 Evans and co-workers[17] reported that the readily available $\beta$-ketoimide **15** could be used in aldol reactions to provide a variety of diastereomeric aldol products. The product stereochemistry was shown to depend on the type of Lewis acid and amine base used. Treatment of **15** with $TiCl_4$ and Hünig's base and reaction of the resulting enolate with a variety of aldehydes provide syn,syn aldol products. Likewise, the use of $Sn(OTf)_2$/triethylamine or ($c$-hex)$_2$BCl/EtNMe$_2$ gives predominantly anti,syn and anti,anti aldol products, respectively.



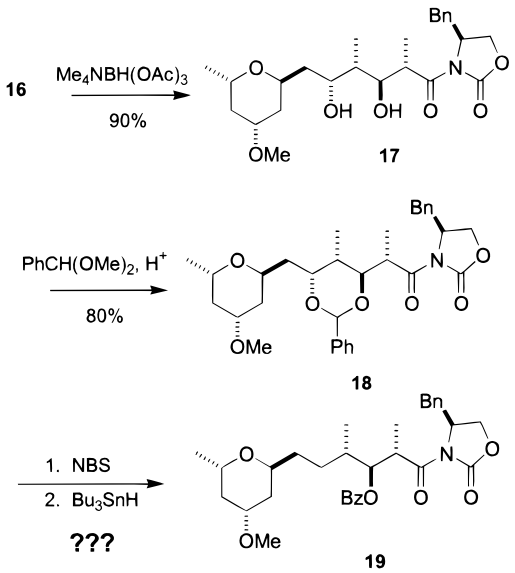

Looking at the $C_{19}-C_{32}$ segment it becomes obvious that the $TiCl_4$/Hünig's base reaction conditions will give

(15) (a) Wiley, M. Ph.D. Thesis, University of Utah, 1988. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478.

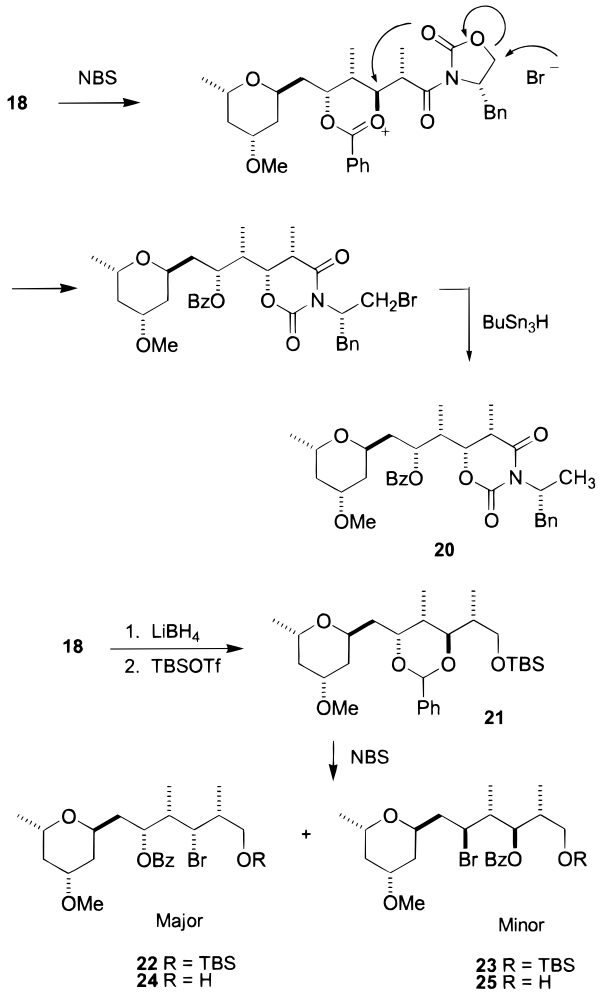
the desired 1,3-syn relationship between the two methyl substituents. The configuration of the resulting hydroxyl group is relatively inconsequential, since it must ultimately be removed. When **4** was subjected to these reaction conditions, aldol product **16** was obtained in 86% yield as a single diastereomer. Moreover, this reaction was reproducible and could be done on a large scale with no compromise in diastereoselectivity and only a slight decrease in yield (80% using 750 mg of aldehyde).




The seemingly extraneous hydroxyl group could now be used as a handle to selectively reduce the ketone to give an anti 1,3-diol. This was accomplished using $Me_4NBH(OAc)_3$[18] which provided **17** exclusively. Diol **17** was then protected as the benzylidene acetal with the intention of using this acetal as a means of removing the $C_{25}$ oxygen functionality. Hannesian has shown,[19] primarily in the context of carbohydrate chemistry, that treatment of a benzylidine acetal with NBS provides a labile intermediate (in which bromine is positioned at the acetal carbon) from free radical bromination. Upon in situ solvolysis of the benzylic bromide, the dioxolane ring is opened, with bromide attacking at the less sterically encumbered carbon. The resulting bromobenzoate can, of course, be reduced with $Bu_3SnH$ which would lead to, in our case, the desired deoxygenated product **19**.



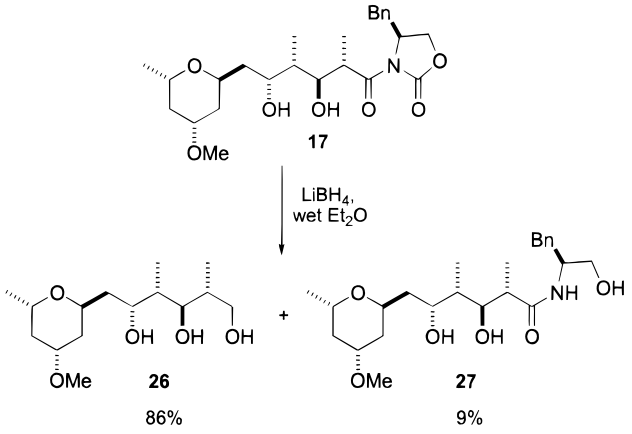

Treatment of **18** under these conditions proceeded very smoothly; however, the product obtained was not the desired deoxygenated compound **19** but was, in fact, **20**. This product can be envisioned to arise as indicated from attack of the oxazolidinone at the $C_{23}$ position with bromide ultimately relieving the resulting positive charge on the oxazolidinone. While this was an interesting result, it obviously did not help to meet the final synthetic goal. In an attempt to rectify this problem, the oxazolidinone was removed with $LiBH_4$ and the resulting alcohol was protected as the TBS ether. Subjecting **21** to the same reaction conditions led to a mixture of TBS-protected compounds **22** and **23** along with the deprotected compounds **24** and **25**. Unfortunately, the major compounds present in these mixtures were the products arising from bromide attack at the seemingly less accessible position, between the two methyl-bearing carbons.




Because these variations of the Hannesian reaction did not work, it became clear that other options had to be examined. It was decided that the triol unit would have to be differentially protected to allow for deoxygenation at $C_{25}$. Initial attempts toward accomplishing this goal using the Tischenko–Evans reaction[20] ($SmI_2$, RCHO) on **16** did not succeed and led to a complex mixture of

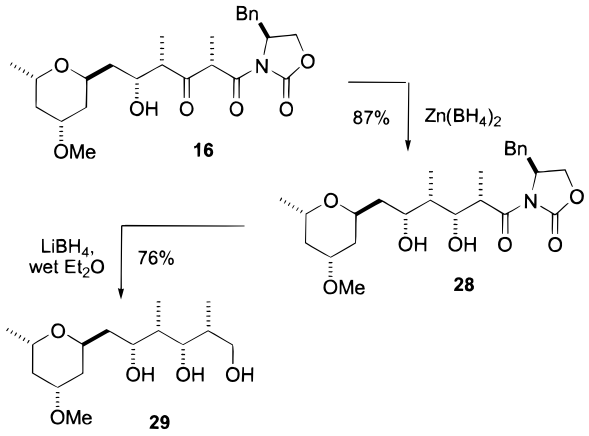
(16) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.
(17) Evans, D. A.; Clark, J. S.; Matternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.
(18) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(19) Hannesian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035, 1045, 1053.
(20) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

products. Therefore, the oxazolidinone of **17** was removed using $LiBH_4$ to give triol **26** as a solid which could be recrystallized from 5% ethyl acetate/hexanes. Although this is a seemingly straightforward reaction, it was discovered that the outcome of the reaction was extremely sensitive to the conditions employed. Large amounts of the side product **27**, in which the oxazolidinone carbonyl had been removed, were produced using Evans' published method of $LiBH_4$ in THF/MeOH. It was found that the yield of this side product could be significantly reduced by excluding MeOH and using wet THF or $Et_2O$.

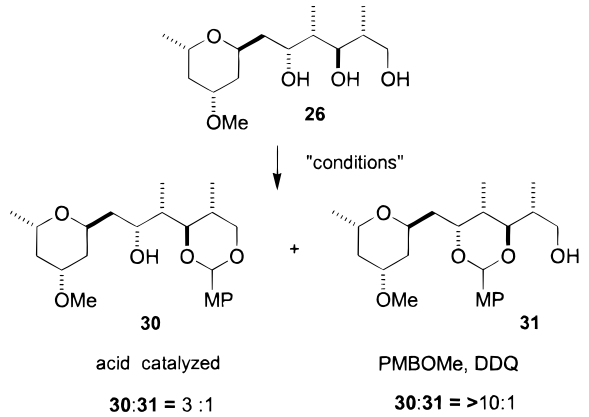



As larger amounts of triol **26** were brought through the synthesis, a concern arose regarding the $Me_4NBH(OAc)_3$ reduction of **16**. The $^1H$ NMR of **26** began to show significant amounts of a previously unnoticed "side product" which would occasionally disappear after silica gel chromatography and which disappeared entirely after the $LiBH_4$ reaction. It was feared that either a large amount of the syn 1,3-diol was produced in the $Me_4NBH(OAc)_3$ reaction and then removed upon chromatography or the product could be epimerizing upon silica gel chromatography. It should be pointed out that the yield for the two-step sequence, $Me_4NBH(OAc)_3$ followed by $LiBH_4$, was quite high (81% on a l g scale) and very clean (one diastereomer). To gain insight into this problem, a known method for making syn 1,3-diols was used. Thus, **16** was treated with $Zn(BH_4)_2$ which presumably provided syn diol **28**. The NMR spectrum obtained for this diol did not match either set of $^1H$ NMR signals observed in the $Me_4NBH(OAc)_3$ reaction and gave, itself, a very clean set of signals. Diol **28** was further reduced to triol **29** using $LiBH_4$, which gave a completely different set of NMR signals than those seen for **26** and, again, was very clean. We now felt confident that **17** was indeed the desired anti diol and that the extra NMR signals observed on occasion were a result of our inability to completely remove some sort of inorganic material from the triol. As a result, we carried the material through to **26** without purification.

Differentiation of the two secondary alcohols was still a concern, and the problem was addressed as follows. Triol **26** was treated with PMPCHO or $PMPCH(OMe)_2$ under a variety of acid-catalyzed acetalization conditions; however, it was generally found that, although the desired "external" acetal **30** was formed preferentially over the "internal" acetal **31**, this occurred in approximately a 3:1 ratio. Subjection of **26** to PMBOMe and




DDQ,[21] though, led to a >10:1 ratio of **30** to **31**, and the remaining alcohol was free for deoxygenation.



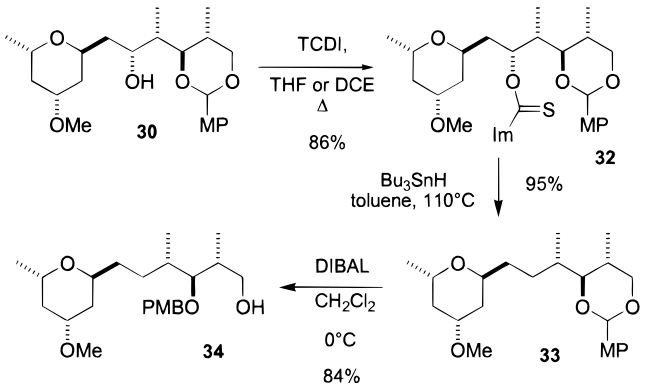

Previously, during the investigation of the Hafner–Duthaler methodology, deoxygenation of the crotyl addition product **12** was attempted via hydride reductions of the corresponding mesylate and phosphoroamidate derivatives. Because these reactions did not succeed, it was decided to use standard radical conditions to remove the hydroxyl substituent in **30**. Initially, thiocarbamate **32** was formed using TCDI and DMAP in dichloroethane at reflux,[22] and then **32** was treated with $Bu_3SnH$ and AIBN in toluene at 110 °C. These two reactions appeared to proceed reasonably well, and the product **33** was taken onto the next reaction; however, regioselective reductive ring opening of **33** using DIBAL[23] at 0 °C gave <50% yield (three steps) of alcohol **34** with no detection of any other products and complete consumption of **33**. Because the TCDI and DIBAL reactions were so clean, the $Bu_3SnH$ reaction was investigated more thoroughly. Paterson reported in his synthesis of the $C_{19}$–$C_{32}$ segment that difficulties were encountered in the deoxygenation of a very similar intermediate. They found that a side product was produced in which the radical intermediate abstracted hydrogen from the $C_{29}$ position, scrambling that center. To overcome this problem, excess $Bu_3SnH$ (10 equiv) was added by syringe to a solution of the radical precursor in toluene at reflux, and the desired deoxy-

(21) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037.

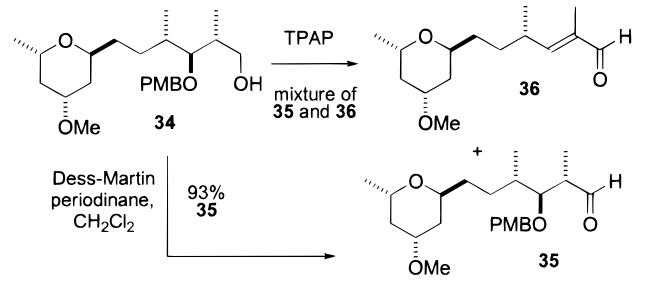
(22) (a) Rasmussen, J. R.; Slinger, C. J..; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843. (b) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(23) Takano, S.; Akiyan, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

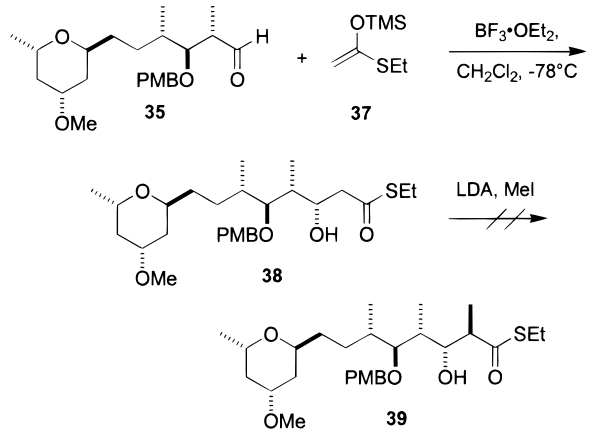
genated product was produced in high yield. When **32** was subjected to the same conditions (notice the absence of a radical initiator) using a freshly opened bottle of $Bu_3SnH$, **33** was isolated in 95% yield and the ensuing DIBAL reaction worked very well (84%).




Oxidation of the primary alcohol to aldehyde **35** with TPAP[24] seemed, at first, to be quite straightforward, with only a small amount of an unidentified side product observed in the reaction. As this reaction was repeated, this side product occasionally became more prevalent and ultimately was identified as the elimination product **36**. It appeared that the amount of **36** formed depended largely on the amount of TPAP used in the reaction. At this late stage in the synthesis it was very difficult to measure the precise amount of a catalytic reagent such as TPAP, and alternative reagents were investigated. Fortunately, the Dess−Martin periodinane[25] oxidation proceeded quite well with none of the elimination product detected. Although this reaction required 10 equiv of periodinane, an aqueous workup, and a chromatography (all of which are unnecessary when TPAP is used), it was deemed the superior procedure for this transformation.



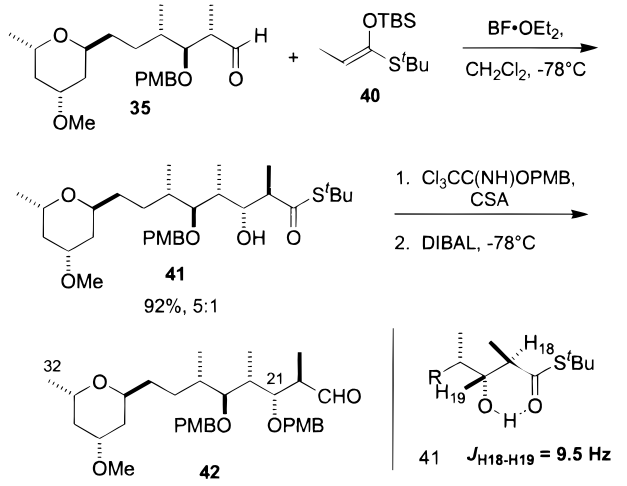

With sufficient quantities of aldehyde **35** in hand, the final three carbons and two stereocenters could be installed. Initially this was attempted in a two-step process using well-known, seemingly reliable chemistry with the idea of then working out a one-step procedure. Thus, aldehyde **35** was treated with thiosilylketene acetal **37** in the presence of $BF_3{\cdot}OEt_2$ and $\beta$-hydroxy thiolester **38** was formed in good yield and high diastereoselectivity.[26] Unfortunately, the following reaction, an attempted Frater-type alkylation of the dianion of **38** with MeI,[27] did not give any of the alkylation product **39**. It is not clear whether this was a result of the small-scale synthesis using strongly basic reagents or was due to the presence of a thiolester in place of a "normal" ester; alkylations of this type of thiolester are not well precedented in the literature. In any event the two-step process was not successful, and attention was turned to the one-step method.




Gennari has reported that aldol reactions between **40** and various aldehydes proceed with moderate selectivity for the anti product independent of the *E* to *Z* ratio of **40**.[28] The Woodward group has also reported the use of this type of chemistry in the synthesis of erythromycin with very high diastereoselectivity.[29] Using the conditions set forth by Gennari, **35** and **40** (1.5 equiv) were stirred in $CH_2Cl_2$ at −78 °C and $BF_3{\cdot}OEt_2$ (2 equiv) was added dropwise to the solution. This led to a 5:1 mixture of diastereomers by $^1H$ NMR which have thus far proven inseparable by chromatography. The major component of this mixture has been characterized with a fair degree of certainty as the desired product **41**. Homonuclear decoupling experiments revealed a $J_{H18-H19}$ coupling constant of 9.5 Hz, which would lead one to believe $H_{18}$ and $H_{19}$ were anti to one another (assuming **41** exists largely in the hydrogen-bonded conformation shown). This would be consistent with the NMR data reported by Gennari for the anti products but not with the coupling constants found for the syn products. While the absolute stereochemistry of this reaction has not yet been proven, the structure will ultimately be confirmed by the completion of the synthesis of preswinholide A. Finally, **41** has been protected as the PMB ether[30] and the thiolester reduced to aldehyde **42** with DIBAL at −78 °C. Aldehyde **42** has been produced on a very small scale (ca. 5 mg) so as not to deplete the resources on hand. Thus, a yield for this step is not meaningful, although, in accord with our previous experiences with the DIBAL reduction of thiolesters, this reaction was very clean. Alcohol **41** was deemed a suitable storage point for material in this portion of the route on the basis that it still allows for variations in strategy should the proposed coupling reaction not proceed as planned.

In summary, the $C_{19}-C_{32}$ segment of swinholide A (in the form of aldehyde **42**) has been made in 16 steps from the known compound **5** (20 steps from ethyl acetoacetate).

(24) Ley, S. V.; Norman, J.; Griffith, W. P.; Mardsen, S. P. *Synthesis* **1994**, 639.
(25) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(26) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(27) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825.
(28) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.
(29) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210.
(30) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.




Excluding the final two steps of this synthesis (yields for these transformations have not been determined), **41** was synthesized from ethyl acetoacetate in 18 steps. The overall yield of **41** was 10% with 98% ee and 62% ds. Our synthesis provides **41** in sufficient quantity to support the overall synthesis and allow for coupling studies at a later time.

## Experimental Section

**General.** Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin and Armarego, Pergamon: Oxford, 1966). Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed on Merck Kieselgel 60 $F_{254}$ plates eluting with the solvent indicated, visualized with a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid or *p*-anisaldehyde. Flash column chromatography was performed with Davisil 62 silica gel slurry packed with the solvents indicated. Nuclear magnetic resonance spectra were acquired at 300 MHz for $^1$H and 75 MHz for $^{13}$C. The abbreviations s, d, t, q, m, and br stand for singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Melting points were obtained on a Mel-Temp electrochemical melting point apparatus and are uncorrected. Optical rotations were obtained (Na D line) using a microcell with a 1 dm path length. Analytical C and H analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Glassware for all reactions was oven-dried at 125 °C and cooled in a desiccator prior to use. Liquid reagents and solvents were introduced by oven-dried syringes through septa-sealed flasks under a nitrogen atmosphere.

**Preparation of (4*S*,6*S*)-4-(Methoxy)-6-(benzyloxy)-1-heptene.** Into a 250 mL round-bottom flask with stirbar was placed potassium hydride (2.48 g, 21.8 mmol, 35% oil dispersion) washed with hexanes (3 × 20 mL) followed by dry THF (100 mL). The stirring solution was cooled to 0 °C, and **5** (2.40 g, 10.9 mmol), dissolved in THF (6 mL), was added dropwise via cannula. After 20 min, MeI (4.64 g, 32.7 mmol) was added to the solution via syringe. This solution was warmed to room temperature, allowed to stir for 1 h, and then quenched by cautious addition of a saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated and the aqueous layer extracted twice with $CH_2Cl_2$ (50 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ solution (75 mL) and brine (75 mL), dried over $Na_2SO_4$, filtered, concentrated, and purified by chromatography over a 4 × 15 cm silica gel column (slurry packed with hexanes) eluting with a solvent gradient from hexanes through 12% ethyl acetate/hexanes. The product-containing fractions were concentrated to yield 2.37 g (93% yield) of a clear, colorless oil: $[\alpha]_D$ +72.1° (*c* 2.60, $CHCl_3$); $R_f$ = 0.47 (20% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.2−7.4 (m, 5H), 5.80 (ddt, *J* = 7.1, 10.4, 16.9 Hz, 1H), 5.1−5.0 (m, 2H), 4.60 (d, $J_{AB}$ = 11.7 Hz, 1H), 4.41 (d, $J_{AB}$ = 11.7 Hz, 1H), 3.74 (dqd, *J* = 3.3, 6.2, 9.0 Hz, 1H), 3.48 (m, 1H), 3.27 (s, 3H), 2.3−2.2 (m, 2H), 1.64 (ddd, *J* = 3.2, 9.4, 14.5 Hz, 1H), 1.51 (ddd, *J* = 3.3, 9.5, 14.5 Hz, 1H), 1.20 (d, *J* = 6.2 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 138.9, 134.4, 128.3(2), 127.8(2), 127.4, 117.1, 76.8, 71.6, 70.6, 56.8, 42.4, 37.9, 20.0. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: 77.02; H, 9.41.

**Preparation of (4*S*,6*S*)-4-(Methoxy)-6-hydroxy-1-heptene (8).** To a 500 mL, three-necked flask equipped with a mechanical stirrer, Dewar condenser, and an ammonia inlet was added (4*S*,6*S*)-4-(methoxy)-6-(benzyloxy)-1-heptene (2.00 g, 8.53 mmol) dissolved in dry THF (75 mL). The flask was cooled to −78 °C, and ammonia was condensed until a final volume of 150 mL was achieved. Small pieces of lithium wire were added to the solution until a deep blue color persisted. At this time, solid ammonium chloride was added until the solution was white. The solution was allowed to warm to room temperature over a period of 4 h and then diluted with $Et_2O$ (75 mL) and $H_2O$ (75 mL). The organic layer was separated and the aqueous layer extracted two times with $CH_2Cl_2$ (75 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ solution (100 mL), then dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by chromatography over a 3.8 × 19 cm silica gel column (slurry packed with hexanes) eluting with 30% ethyl acetate/hexanes. The product-containing fractions were concentrated to yield **8** (1.18 g, 96% yield) as a clear volatile liquid: $[\alpha]_D$ +40.7° (*c* 0.425, $CHCl_3$); $R_f$ = 0.29 (35% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 5.79 (ddt, *J* = 7.0, 10.2, 17.1 Hz, 1H), 5.12 (dd, *J* = 2.1, 10.2 Hz, 1H), 5.07 (dd, *J* = 2.1, 17.1 Hz, 1H), 4.10 (m, 1H), 3.56 (m, 1H), 3.38 (s, 3H), 2.74 (d, *J* = 3.9 Hz, 1H), 2.5−2.2 (m, 2H), 1.7−1.6 (m, 2H), 1.20 (d, *J* = 6.3 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 134.3, 117.3, 78.6, 64.8, 56.8, 41.1, 37.4, 23.7; IR (neat) 3420 (br) cm$^{-1}$. Anal. Calcd for $C_8H_{16}O$: C, 66.63; H, 11.18. Found: C, 66.62; H, 11.14.

**Preparation of (4*R*,6*S*)-2,4-(Dimethoxy)-6-methyltetrahydropyran (9).** To a stirring solution of **8** (0.800 g, 5.55 mmol) in MeOH (35 mL) at −78 °C was bubbled in ozone until a light blue color persisted. Oxygen was then bubbled in until the solution turned clear. DMS (10 mL) was added, and the solution was allowed to warm to room temperature. After a period of 12 h, 1 M aqueous HCl (10 mL) was added. The resulting solution was allowed to stir for 4 h, then quenched with saturated aqueous $NaHCO_3$ solution, and diluted with $CH_2Cl_2$ (30 mL). The organic layer was separated and the aqueous layer extracted three times with $CH_2Cl_2$ (25 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated in vacuo. The resulting oil was purified by chromatography over a 3.5 × 21 cm silica gel column (slurry packed with pentanes), eluting with a solvent gradient from pentanes through 30% ether/pentanes. The product-containing fractions were combined and concentrated to yield **9** (0.844 g, 95% yield) as a colorless volatile liquid.

**Preparation of (2*R*,4*R*,6*S*)-4-(Methoxy)-6-methyl-2-(prop-1-enyl)tetrahydropyran (10).** To a stirring solution of **9** (0.890 g, 55.6 mmol) and allyltrimethylsilane (1.27 g, 11.1 mmol) in acetonitrile (50 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (0.103 g, 0.556 mmol). After being stirred for 15 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (30 mL) and diluted with $CH_2Cl_2$ (30 mL) and $H_2O$ (30 mL). The organic layer was separated and the aqueous layer extracted three times with $CH_2Cl_2$ (50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by chromatography over a 3.5 × 17.5 cm silica gel column (slurry packed with pentanes), eluting with 30% ether/pentanes. The product-containing fractions were combined and concentrated to yield 0.803 g (84%) of **10** as a colorless volatile liquid: $[\alpha]_D$ −59.5° (*c* 2.91, $CHCl_3$); $R_f$ = 0.49 (35% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 5.79 (ddt, *J* = 7.0, 10.2, 17.1 Hz, 1H), 5.09 (dd, *J* = 1.8, 10.2 Hz, 1H), 5.04 (dd, *J* = 1.8, 17.1 Hz, 1H), 4.08 (m, 1H), 3.76 (dqd, *J* = 2.9, 6.2, 9.7 Hz, 1H), 3.53 (m, 1H), 3.33 (s, 3H), 2.5−2.2 (m, 2H), 1.98 (m, 1H), 1.86

(m, 1H), 1.55 (ddd, $J$ = 5.4, 10.1, 12.9 Hz, 1H), 1.21 (buried m, 1H), 1.20 (d, $J$ = 6.2 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 135.0, 116.7, 73.0, 71.5, 65.1, 55.3, 38.5, 36.8, 33.8, 21.7. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.68. Found: C, 70.43; H, 10.68.

**Preparation of (2*R*,4*R*,6*S*)-2-(Ethan-1-al)-4-(methoxy)-6-methyltetrahydropyran (4).** To a stirring solution of **10** (0.612 g, 3.59 mmol) in $CH_2Cl_2$ (40 mL) at −78 °C was bubbled in $O_3$ until a light blue color persisted. Oxygen was then bubbled in until the solution turned clear. $PPh_3$ (1.85 g, 7.05 mmol) was added, and the solution was allowed to warm to room temperature. After a period of 2.5 h, the solution was concentrated in vacuo. The resulting oil was purified by chromatography over a 3.6 × 20 cm silica gel column (slurry packed with 10% acetone/hexanes), eluting with 10% acetone/hexanes (500 mL) and 25% acetone/hexanes (200 mL) and collected in 9 mL fractions. The product-containing fractions (43−77) were combined and concentrated to yield 0.591 g (95%) of **4** as a colorless oil: $[\alpha]_D$ −28.9° (*c* 1.06, $CHCl_3$); $R_f$ = 0.33 (25% acetone/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 9.75 (dd, $J$ = 3.4, 1.6 Hz, 1H), 4.70 (dt, $J$ = 5.2, 9.2 Hz, 1H), 3.78 (dqd, $J$ = 9.4, 6.4, 3.1 Hz, 1H), 3.52 (m, 1H), 3.34 (s, 3H), 2.82 (ddd, $J$ = 3.4, 9.3, 15.9 Hz, 1H), 2.50 (ddd, $J$ = 1.6, 5.3, 15.9 Hz, 1H), 1.99 (m, 1H), 1.82 (m, 1H), 1.70 (ddd, $J$ = 5.3, 9.4, 13.1 Hz, 1H), 1.27 (buried m, 1H), 1.23 (d, $J$ = 6.4 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 200.5, 72.6, 66.3, 65.8, 55.3, 46.4, 37.5, 34.4, 21.1; IR (neat) 2970, 2935, 2825, 2730, 1725 cm$^{-1}$. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.80; H, 9.35.

**Preparation of (4*S*)-4-Benzyl-3-[(2*S*,4*S*,5*R*)-2,4-dimethyl-5-hydroxy-6-((2*S*,4*R*, 6*S*)-4-(methoxy)-6-methyltetrahydropyran-2-yl)-3-oxohexanoyl]-2-oxazolidinone (16).** To a solution of **15**[17] (0.218 g, 0.755 mmol) in $CH_2Cl_2$ (1 mL) at −5 °C was added titanium tetrachloride (0.150 g, 0.790 mmol, 0.087 mL) dropwise by syringe. After 5 min, diisopropylethylamine (0.113 g, 0.871 mmol, 0.152 mL) was added dropwise to the yellow solution, resulting in a deep red color. The solution was allowed to stir at −5 °C for 1 h and then cooled to −78 °C. A solution of aldehyde **4** (0.100 g, 0.581 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise by cannula and rinsed over with an additional 0.5 mL of $CH_2Cl_2$. After a period of 2.5 h, the solution was warmed to −40 °C and allowed to stir for an additional 1.5 h. The solution was allowed to warm to 0 °C and was quenched with pH 7 phosphate buffer. The mixture was diluted with $CH_2Cl_2$ (2 mL) and $H_2O$ (2 mL). The organic layer was separated and the aqueous layer extracted three times with $CH_2Cl_2$ (5 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by chromatography over a 2 × 17 cm silica gel column (slurry packed with 30% ethyl acetate/hexanes), eluting with a solvent gradient of 30%−50% ethyl acetate/hexanes. The product-containing fractions were combined and concentrated to yield 0.231 g (86%) of **16** as a foam: $[\alpha]_D$ +54.3° (*c* 0.910, $CHCl_3$); $R_f$ = 0.17 (50% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.3−7.1 (m, 5H), 4.92 (q, $J$ = 7.3 Hz, 1H), 4.73 (m, 1H), 4.3−4.1 (m, 4H), 3.87 (m, 1H), 3.53 (m, 1H), 3.54 (d, $J$ = 2.1 Hz, 1H), 3.31 (s, 3H), 3.27 (dd, $J$ = 3.2, 13.4 Hz, 1H), 2.93 (dq, $J$ = 4.0, 7.1 Hz, 1H), 2.77 (dd, $J$ = 9.5, 13.4 Hz, 1H), 2.0−1.9 (m, 2H), 1.78 (m, 1H), 1.61 (ddd, $J$ = 5.2, 9.5, 13.1 Hz, 1H), 1.47 (d, $J$ = 7.3 Hz, 3H), 1.44 (m, 1H), 1.22 (m, 1H), 1.21 (d, $J$ = 6.2 Hz, 3H), 1.12 (d, $J$ = 7.1 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 210.1, 170.4, 153.6, 134.9, 129.2(2), 128.8(2), 127.2, 72.7, 71.1, 70.7, 66.3, 65.6, 55.3, 55.2, 51.7, 48.5, 37.7, 37.6, 35.0(2), 21.3, 13.0, 10.5; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.3, 21.3, 13.0, 10.5; $CH_2$ $\delta$ 66.3, 37.7, 37.6, 35.0(2); CH $\delta$ 72.7, 71.1, 70.7, 65.6, 55.2, 51.7, 48.5; IR ($CHCl_3$) 3555 (br), 1780, 1715, 1700 cm$^{-1}$. Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64; N, 3.03. Found: C, 64.91; H, 7.62; N, 3.05.

**Preparation of (2*R*,3*S*,4*S*,5*R*)-2,4-Dimethyl-6-((2*S*,4*R*,6*S*)-4-(methoxy)-6-methyltetrahydropyran-2-yl)hexane-1,3,5-triol (26).** Tetramethylammonium triacetoxyborohydride (8.98 g, 34.1 mmol) was added to acetic acid (34 mL), and the resulting solution was stirred for 1 h. Ketone **16** (1.05 g, 2.27 mmol) was dissolved in 40 mL of acetonitrile (20 mL rinse) and added via cannula. After 45 h, $H_2O$ (16 mL) was added rapidly followed by MeOH (60 mL), and the solution was concentrated. This was repeated four times. The resulting residue was quenched carefully by the addition of 5% aqueous $NaHCO_3$ solution (120 mL) and extracted three times with $CH_2Cl_2$ (80 mL). The combined organic phases were dried over $MgSO_4$, filtered through Celite, and concentrated to yield **17** as a foam which was used without further purification.

To a stirring solution of **17** in wet $Et_2O$ (23 mL) at 0 °C was added 2.3 mL of lithium borohydride (2.0 M in THF) dropwise via syringe. After 1 h the cloudy white solution was quenched with 0.5 N Rochelle salts (10 mL) and stirred for 1 h. This solution was poured into brine (50 mL) and extracted four times with $CH_2Cl_2$ (75 mL). The combined organic phases were dried over $MgSO_4$, filtered through Celite, and concentrated. The resulting oil was purified by chromatography over a 5 × 13 cm silica gel column (slurry packed with 3% MeOH/$CHCl_3$) eluting with 500 mL portions of 3% and 5% MeOH/$CHCl_3$ and collected in 25 mL fractions. The product-containing fractions (22−33) were combined and concentrated to yield 0.533 g (81%, two steps) of **26** as a colorless solid. This solid could be recrystallized from 5% ethyl acetate/hexanes (mp = 73 °C) but was generally used without further purification. $[\alpha]_D$ −27.8° (*c* 0.670, $CHCl_3$); $R_f$ = 0.33 (10% MeOH/$CHCl_3$); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 4.3−4.2 (m, 2H), 4.0−3.5 (br s, 3H), 3.97 (m, 1H), 3.80 (dd, $J$ = 3.3, 11.0 Hz, 1H), 3.66 (dd, $J$ = 7.3, 11.0 Hz, 1H), 3.59 (m, 1H), 3.54 (dd, $J$ = 4.6, 7.8 Hz, 1H), 3.35 (s, 3H), 2.05 (ddd, $J$ = 9.8, 11.2, 14.4 Hz, 1H), 2.0−1.9 (m, 2H), 1.85 (m, 1H), 1.8−1.6 (m, 2H), 1.40 (ddd, $J$ = 7.8, 7.8, 13.2 Hz, 1H), 1.28 (buried m, 1H), 1.28 (d, $J$ = 6.6 Hz, 3H), 1.03 (d, $J$ = 7.1 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 82.7, 73.2, 72.8, 71.0, 68.0, 66.2, 55.5, 37.5, 37.2, 36.3, 35.7, 35.5, 21.1, 14.0, 11.6; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.5, 21.1, 14.0, 11.6; $CH_2$ $\delta$ 68.0, 36.3, 35.7, 35.5; CH $\delta$ 82.7, 73.2, 72.8, 71.0, 66.2, 37.5, 37.2; IR ($CHCl_3$) 3500 (br), 3130 cm$^{-1}$. Anal. Calcd for $C_{15}H_{30}O_5$: C, 62.04; H, 10.41. Found: C, 62.11; H, 10.32.

**Preparation of 18.** To a stirring solution of **17** (0.157 g, 0.339 mmol) and $PhCH(OMe)_2$ (0.254 mL, 0.258 g, 1.69 mmol) in *N*,*N*-dimethylformamide (7 mL) was added $HBF_4$ (0.462 mL, 3.39 mmol, 54% solution in $Et_2O$). After 3 d, the solution was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and diluted with $H_2O$ (10 mL) and $Et_2O$ (10 mL), and the aqueous layer extracted three times with $Et_2O$ (25 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, concentrated, and purified using radial chromatography (2 mm plate, 30% ethyl acetate/hexanes). The product-containing fractions were combined and concentrated to yield 0.187 g (78%) of **18** as a colorless oil: $R_f$ = 0.52 (50% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.4−7.2 (m, 10H), 5.86 (s, 1H), 5.00 (m, 1H), 4.61 (m, 1H), 4.24 (d, $J$ = 11.0 Hz, 1H), 4.2−4.1 (m, 2H), 4.12 (dd, $J$ = 2.3, 11.0 Hz, 1H), 3.97 (dd, $J$ = 7.8, 7.8 Hz, 1H), 3.80 (m, 1H), 3.55 (m, 1H), 3.34 (s, 3H), 3.28 (dd, $J$ = 3.2, 13.3 Hz, 1H), 2.77 (dd, $J$ = 9.8, 13.3 Hz, 1H), 2.18 (ddd, $J$ = 5.8, 11.2, 14.3 Hz, 1H), 2.0−1.8 (m, 3H), 1.64 (ddd, $J$ = 5.6, 10.3, 12.9 Hz, 1H), 1.54 (ddd, $J$ = 4.9, 11.0, 13.9 Hz, 1H), 1.31 (d, $J$ = 7.1 Hz, 3H), 1.3−1.2 (buried m, 1H), 1.25 (d, $J$ = 6.5 Hz, 3H), 1.24 (d, $J$ = 5.9 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 175.6, 153.5, 138.7, 135.1, 129.3-(2), 128.9(3), 128.2(2), 127.3, 126.1(2), 96.7, 82.9, 73.1, 71.8, 67.7, 66.2, 65.3, 55.7, 55.4, 38.4, 37.8, 36.0, 34.8, 33.9, 28.6, 21.7, 14.5, 13.1. Anal. Calcd for $C_{32}H_{41}NO_7$: C, 69.67; H, 7.49; N, 2.54. Found: C, 69.40; H, 7.41; N, 2.62.

**Preparation of 20.** A stirring solution of **18** (0.054 g, 0.098 mmol), barium carbonate (0.435 g, 0.220 mmol), and *N*-bromosuccinimide (0.020 g, 0.113 mmol) in $CH_2Cl_2$ (1 mL) was heated to reflux. After 2.5 h the solution was cooled to room temperature, diluted with $CH_2Cl_2$ (5 mL) and a saturated aqueous $NaHCO_3$ solution (5 mL), and filtered. The aqueous layer was extracted three times with $CH_2Cl_2$ (10 mL), and the combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated to yield 0.059 g (95%) of a slightly yellow foam which was used without further purification: $R_f$ = 0.29 (35% ethyl acetate/hexanes); 300-MHz $^1$H NMR

($CDCl_3$) $\delta$ 8.0−7.9 (m, 2H), 7.64 (m, 1H), 7.5−7.4 (m, 2H), 7.1−7.0 (m, 5H), 6.71 (m, 1H), 5.18 (m, 1H), 5.06 (m, 1H), 4.1−4.0 (buried m, 1H), 4.09 (dd, $J$ = 10.0, 10.0 Hz, 1H), 3.89 (m, 1H), 3.63 (dd, $J$ = 5.6, 10.2 Hz, 1H), 3.6−3.4 (m, 2H), 3.31 (s, 3H), 3.11 (m, 1H), 2.72 (dq, $J$ = 2.4, 7.4 Hz, 1H), 2.31 (ddd, $J$ = 4.9, 12.3, 13.9 Hz, 1H), 2.20 (ddd, $J$ = 1.5, 6.7, 10.2 Hz, 1H), 2.01 (m, 1H), 1.79 (m, 1H), 1.7−1.5 (m, 2H), 1.24 (d, $J$ = 6.8 Hz, 3H), 1.19 (d, $J$ = 6.2 Hz, 3H), 1.19 (buried d, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 172.2, 165.4, 150.6, 136.6, 133.4, 129.6, 129.5(2), 128.8(2), 128.4(2), 128.2(2), 126.7, 78.3, 72.7, 69.6, 68.4, 65.2, 55.3, 38.4, 38.0, 36.0, 34.7, 33.8, 32.2, 21.7, 9.7, 9.2.

A deoxygenated solution of this yellow foam (0.135 g, 0.214 mmol), tributyltin hydride (0.115 mL, 0.125 g, 0.428 mmol), and AIBN (0.007 g, 0.043 mmol) in benzene (2 mL) was heated to reflux. After 2 h, this solution was cooled to room temperature, concentrated, and purified using radial chromatography (2 mm plate, 30% ethyl acetate/hexanes). The product-containing fractions were combined and concentrated to yield 0.114 g (97%) of **20** as a glass: $R_f$ = 0.28 (35% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 8.0−7.9 (m, 2H), 7.65 (m, 1H), 7.6−7.5 (m, 2H), 7.1−7.0 (m, 5H), 6.76 (m, 1H), 5.07 (ddd, $J$ = 1.7, 5.1, 9.7 Hz, 1H), 4.95 (m, 1H), 4.11 (m, 1H), 3.88 (m, 1H), 3.51 (m, 1H), 3.32 (s, 3H), 3.18 (dd, $J$ = 10.7, 13.7 Hz, 1H), 2.96 (dd, $J$ = 6.4, 13.7 Hz, 1H), 2.67 (dq, $J$ = 2.4, 7.4 Hz, 1H), 2.31 (ddd, $J$ = 4.9, 12.2, 13.9 Hz, 1H), 2.16 (m, 1H), 2.02 (m, 1H), 1.80 (m, 1H), 1.7−1.5 (m, 3H), 1.47 (d, $J$ = 6.8 Hz, 3H), 1.21 (d, $J$ = 6.6 Hz, 3H), 1.96 (d, $J$ = 6.1 Hz, 3H), 1.15 (d, $J$ = 7.4 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 172.5, 165.3, 150.5, 138.2, 133.4, 129.6, 129.5(2), 128.8(2), 128.4(2), 128.1(2), 126.2, 78.0, 72.7, 69.6, 68.4, 65.2, 55.3, 50.2, 38.6, 38.5, 38.0, 34.7, 33.8, 32.3, 21.7, 18.1, 9.6, 9.1.

**Preparation of (2*R*,3*S*,4*S*,5*R*)-2,4-Dimethyl-1,3-(*p*-methoxybenzylidenedioxy)-6-((2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydropyran-2-yl)hexan-5-ol (30).** To a stirring solution of **26** (0.270 g, 0.930 mmol) and 4-methoxybenzyl methyl ether (0.566 g, 3.72 mmol) in $CH_2Cl_2$ (9.5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.464 g, 2.05 mmol). After being stirred for 40 min, the cloudy brown solution was filtered through Celite, concentrated, and diluted with $CH_2Cl_2$ (20 mL). The organic layer was washed with a 5% aqueous $NaHCO_3$ solution (30 mL) and the aqueous layer extracted two times with $CH_2Cl_2$ (30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated to yield a slightly yellow solid. This yellow solid was recrystallized from 10% ethyl acetate/hexanes (10 mL) to yield 0.234 g of **30** (64%) as colorless needles (mp = 111 °C). The mother liquor was purified by chromatography over a 3 × 14 cm silica gel column (slurry packed with 10% acetone/hexanes) eluting with 200 mL each of 10% and 25% acetone/hexanes and 100 mL of 50% acetone/hexanes, collected in 9 mL fractions. The product-containing fractions (31−38) were combined and concentrated to yield an additional 0.062 g (16%) of a white solid: $[\alpha]_D$ −17.5° (*c* 0.800, $CHCl_3$); $R_f$ = 0.56 (50% acetone/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.4−7.3 (m, 2H), 6.9−6.8 (m, 2H), 5.40 (s, 1H), 4.22 (dd, $J$ = 6.5, 8.0 Hz, 1H), 4.15 (dd, $J$ = 4.6, 11.2 Hz, 1H), 4.12 (m, 1H), 3.80 (m, 1H), 3.80 (s, 3H), 3.6−3.5 (m, 2H), 3.51 (dd, $J$ = 11.2, 11.2 Hz, 1H), 3.35 (s, 3H), 3.23 (br s, 1H), 2.27 (m, 1H), 2.13 (ddd, $J$ = 5.9, 11.2, 14.2 Hz, 1H), 2.1−2.0 (m, 2H), 1.85 (m, 1H), 1.62 (ddd, $J$ = 5.6, 10.4, 12.8 Hz, 1H), 1.43 (ddd, $J$ = 4.6, 8.8, 13.8 Hz, 1H), 1.20 (d, $J$ = 6.1 Hz, 3H), 1.19 (ddd, $J$ = 10.3, 10.3, 12.5 Hz, 1H), 1.10 (d, $J$ = 7.1 Hz, 3H), 0.82 (d, $J$ = 6.6 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 159.9, 130.7, 127.1(2), 113.6(2), 101.9, 89.2, 73.1, 73.0, 69.1, 66.9, 64.9, 55.3, 55.2, 38.6, 35.3, 34.8, 34.4, 31.0, 21.7, 12.1, 10.6; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.3, 55.2, 21.7, 12.1, 10.6; $CH_2$ $\delta$ 73.1, 38.6, 35.3, 34.8; CH $\delta$ 101.9, 89.2, 73.0, 69.1, 66.9, 64.9, 34.4, 31.0; IR ($CHCl_3$) 3470 (br) cm$^{-1}$. Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.47; H, 8.95.

**Preparation of 32.** A stirring solution of **30** (0.075 g, 0.184 mmol) and 1,1′-thiocarbonyldiimidazole (0.065 g, 0.367 mmol) in THF was heated at reflux for 40 h. The solution was cooled to room temperature, concentrated, purified by chromatography over a 2.5 × 14 cm silica gel column (slurry packed with 20% acetone/hexanes) eluting with 20% acetone/hexanes, and collected in 9 mL fractions. The product-containing fractions (19−31) were concentrated to yield 0.082 g (86%) of **32** as a foam: $[\alpha]_D$ −52.3° (*c* 0.555, $CHCl_3$); $R_f$ = 0.38 (50% acetone/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 8.17 (s, 1H), 7.39 (dd, $J$ = 1.5, 1.5 Hz, 1H), 7.1−7.0 (m, 2H), 6.82 (dd, $J$ = 0.9, 1.5 Hz, 1H), 6.7−6.6 (m, 2H), 6.10 (br dd, $J$ = 4.8, 10.2 Hz, 1H), 5.28 (s, 1H), 4.20 (m, 1H), 4.10 (dd, $J$ = 4.5, 11.4 Hz, 1H), 4.05 (m, 1H), 3.76 (s, 3H), 3.53 (m, 1H), 3.44 (dd, $J$ = 11.1, 11.1 Hz, 1H), 3.5−3.4 (buried m, 1H), 3.34 (s, 3H), 2.48 (ddd, $J$ = 4.9, 12.4, 13.9 Hz, 1H), 2.38 (m, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 1.7−1.6 (m, 2H), 1.3−1.1 (buried m, 1H), 1.28 (d, $J$ = 7.1 Hz, 3H), 1.23 (d, $J$ = 6.4 Hz, 3H), 0.83 (d, $J$ = 6.6 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 183.7, 159.6, 136.8, 130.8, 130.0, 126.8(2), 117.7, 113.2(2), 102.1, 86.8, 79.7, 72.9, 72.9, 69.0, 65.4, 55.3, 55.2, 38.8, 34.7, 33.8, 32.3, 31.1, 21.5, 12.0, 11.9; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.3, 55.2, 21.5, 12.0, 11.9; $CH_2$ $\delta$ 72.9, 38.8, 34.7, 32.3; CH $\delta$ 102.1, 86.8, 79.7, 72.9, 69.0, 65.4, 33.8, 31.1; Anal. Calcd for $C_{27}H_{38}N_2O_6S$: C, 62.52; H, 7.38; N, 5.40; S, 6.18. Found: C, 62.39; H, 7.43; N, 5.29; S, 6.10.

**Preparation of (2*R*,3*S*,4*S*)-2,4-Dimethyl-1,3-(*p*-methoxybenzylidenedioxy)-6-((2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydropyran-2-yl)hexane (33).** To a deoxygenated solution of **32** (0.070 g, 0.135 mmol) in toluene (2 mL) at reflux was added tributyltin hydride (0.363 mL, 0.393 g, 1.35 mmol) via syringe. After 30 min the solution was cooled to room temperature, concentrated, purified by chromatography over a 2.5 × 13 cm silica gel column (slurry packed with 5% ethyl acetate/hexanes), eluting with 100 mL each of hexanes and 15%, 15%, 25%, and 25% ethyl acetate/hexanes, and collected in 8 mL fractions. The product-containing fractions (42−49) were collected and concentrated to yield 0.053 g (100%) of **33** as a colorless oil: $[\alpha]_D$ −34.8° (*c* 2.48, $CHCl_3$); $R_f$ = 0.34 (35% ethyl acetate/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.4−7.3 (m, 2H), 6.9−6.8 (m, 2H), 5.42 (s, 1H), 4.09 (dd, $J$ = 4.8, 11.2 Hz, 1H), 4.01 (m, 1H), 3.80 (s, 3H), 3.71 (dddd, $J$ = 2.7, 6.3, 12.7, 16.1 Hz, 1H), 3.52 (m, 1H), 3.48 (dd, $J$ = 11.2, 11.2 Hz, 1H), 3.35 (dd, $J$ = 2.0, 9.8 Hz, 1H), 3.34 (s, 3H), 2.09 (m, 1H), 2.0−1.8 (m, 4H), 1.60 (ddd, $J$ = 5.6, 10.3, 12.7 Hz, 1H), 1.6−1.2 (m, 3H), 1.2−1.1 (buried m, 1H), 1.21 (d, $J$ = 6.4 Hz, 3H), 1.06 (d, $J$ = 6.8 Hz, 3H), 0.78 (d, $J$ = 6.6 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 159.6, 131.6, 127.2(2), 113.4(2), 101.1, 87.7, 73.2, 73.1, 71.5, 64.5, 55.2(2), 38.6, 34.9, 32.8, 30.6, 29.1, 25.5, 21.7, 16.9, 12.2; 75-MHz DEPT NMR $CH_3$ $\delta$ 55.2(2), 21.7, 16.9, 12.2; $CH_2$ $\delta$ 73.1, 38.6, 34.9, 29.1, 25.5; CH $\delta$ 101.1, 87.7, 73.2, 71.5, 64.5, 32.8, 30.6; Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.22; H, 9.24.

**Preparation of (2*R*,3*S*,4*S*)-2,4-Dimethyl-3-(*p*-methoxybenzyloxy)-6-((2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydropyran-2-yl)hexanol (34).** To a stirring solution of **33** (0.041 g, 0.104 mmol) in $CH_2Cl_2$ (1.5 mL) at 0 °C was added DIBAL (0.210 mL, 0.313 mmol, 1.5 M solution in toluene). After 1.5 h, a saturated solution of Rochelle salts (3 mL) was added and the solution stirred for 5 h. The mixture was diluted with $CH_2Cl_2$ (5 mL) and $H_2O$ (5 mL) and the aqueous layer extracted three times with $CH_2Cl_2$ (10 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated. The resulting oil was purified by chromatography over a 2.5 × 13 cm silica gel column (slurry packed with 20% acetone/hexanes) eluting with 20% acetone/hexanes and collected in 9 mL fractions. The product-containing fractions (11−19) were combined and concentrated to yield 0.038 g (91%) of **34** as a colorless oil: $[\alpha]_D$ −18.9° (*c* 1.48, $CHCl_3$); $R_f$ = 0.51 (50% acetone/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.3−7.2 (m, 2H), 6.9−6.8 (m, 2H), 4.58 (d, $J_{AB}$ = 10.5 Hz, 1H), 4.50 (d, $J_{AB}$ = 10.5 Hz, 1H), 3.99 (m, 1H), 3.80 (s, 3H), 3.71 (dd, $J$ = 3.4, 11.0 Hz, 1H), 3.70 (m, 1H), 3.59 (dd, $J$ = 5.7, 11.0 Hz, 1H), 3.51 (m, 1H), 3.33 (s, 3H), 3.22 (dd, $J$ = 5.2, 6.1 Hz, 1H), 2.84 (br s, 1H), 2.0−1.8 (m, 5H), 1.59 (ddd, $J$ = 5.3, 10.0, 12.8 Hz, 1H), 1.59 (m, 1H), 1.4−1.1 (m, 3H), 1.21 (d, $J$ = 6.2 Hz, 3H), 1.02 (d, $J$ = 7.1 Hz, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 154.2, 130.4, 129.3(2), 113.8(2), 89.4, 74.8, 73.2, 71.8, 66.1, 64.8, 55.3, 55.2, 38.5, 36.9, 35.7, 34.8, 29.7, 28.1, 21.7, 16.9, 15.8; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.3, 55.2, 21.7, 16.9, 15.8; $CH_2$ $\delta$ 74.8, 66.1,

38.5, 34.8, 29.7, 28.1; CH $\delta$ 89.4, 73.2, 71.8, 64.7, 36.9, 35.6; IR (neat) 3380 (br) $cm^{-1}$. Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.02; H, 9.71. Found: C, 69.88; H, 9.63.

**Preparation of (2*R*,3*S*,4*S*)-2,4-Dimethyl-3-(*p*-methoxybenzyloxy)-6-((2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydropyran-2-yl)hexanal (35).** To a stirring solution of **34** (0.190 g, 0.482 mmol) in $CH_2Cl_2$ (10 mL) was added the Dess−Martin periodinane (2.00 g, 4.82 mmol). After 45 min the solution was diluted with $Et_2O$ (25 mL) and poured into a 1:1 mixture of saturated aqueous $NaHCO_3$/$Na_2S_2O_3$ (50 mL). This solution was stirred for 20 min and the aqueous layer extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL) and dried over $MgSO_4$. The solution was filtered through Celite and concentrated. The resulting oil was purified by chromatography over a 2.5 × 13 cm silica gel column (slurry packed with 15% acetone/hexanes) eluting with 15% acetone/hexanes and collected in 9 mL fractions. The product-containing fractions (12−17) were combined and concentrated to yield 0.176 g (93%) of **38** as a colorless oil: $[\alpha]_D$ −5.8° (*c* 1.54, $CHCl_3$); $R_f$ = 0.33 (20% acetone/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 9.78 (d, $J$ = 2.4 Hz, 1H), 7.3−7.2 (m, 2H), 6.9−6.8 (m, 2H), 4.53 (d, $J_{AB}$ = 10.9 Hz, 1H), 4.47 (d, $J_{AB}$ = 10.9 Hz, 1H), 3.98 (m, 1H), 3.80 (s, 3H), 3.68 (dddd, $J$ = 2.9, 6.2, 12.6, 15.6 Hz, 1H), 3.50 (m, 1H), 3.48 (dd, $J$ = 5.4, 5.4 Hz, 1H), 3.33 (s, 3H), 2.70 (m, 1H), 2.0−1.8 (m, 4H), 1.59 (ddd, $J$ = 5.6, 10.3, 12.9 Hz, 1H), 1.56 (m, 1H), 1.4−1.2 (m, 2H), 1.21 (d, $J$ = 6.1 Hz, 3H), 1.13 (d, $J$ = 7.1 Hz, 3H), 0.94 (d, $J$ = 6.8 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 204.7, 159.2, 130.3, 129.2(2), 113.7(2), 85.0, 73.4, 73.2, 71.7, 64.7, 55.3, 55.2, 48.5, 38.5, 35.2, 34.8, 29.4, 28.3, 21.7, 16.1, 11.5; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.3, 55.2, 21.7, 16.1, 11.5; $CH_2$ $\delta$ 73.4, 38.5, 34.8, 29.4, 28.3; CH $\delta$ 85.0, 73.2, 71.7, 64.7, 48.5, 35.2; IR (neat) 2940, 2870, 2725, 1720 $cm^{-1}$. Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 69.83; H, 9.21.

**Preparation of 41.** To a stirring solution of **35** (0.023 g, 0.059 mmol) and **40**[28] (0.023 g, 0.088 mmol) in $CH_2Cl_2$ (1.2 mL) at −78 °C was added $BF_3$·$OEt_2$ (0.014 mL, 0.017 g, 0.117 mmol) dropwise via syringe. After 45 min the solution was quenched with pH 7 phosphate buffer (0.5 mL), warmed to room temperature, and diluted with $CH_2Cl_2$ (5 mL) and $H_2O$ (5 mL). The aqueous layer was extracted three times with $CH_2Cl_2$ (10 mL), and the combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated. The resulting oil was purified by chromatography over a 2.5 × 13 cm silica gel column (slurry packed with 20% acetone/hexanes) eluting with 20% acetone/hexanes and collected in 7 mL fractions. The product-containing fractions (9−13) were combined and concentrated to yield 0.029 g (92%) of **44** as a colorless oil and a 5:1 ratio of inseparable diastereomers. Major diastereomer: $R_f$ = 0.52 (35% acetone/hexanes); 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.3−7.2 (m, 2H), 6.9−6.8 (m, 2H), 4.54 (s, 2H), 4.20 (d, $J$ = 9.8 Hz, 1H), 4.0−3.9 (m, 1H), 3.79 (s, 3H), 3.7−3.6 (m, 1H), 3.6−3.5 (m, 1H), 3.58 (br s, 1H), 3.34 (s, 3H), 3.24 (dd, $J$ = 2.9, 8.3 Hz, 1H), 2.66 (m, 1H), 2.0−1.5 (m, 8H), 1.47 (s, 9H), 1.4−1.1 (buried m, 2H), 1.21 (d, $J$ = 6.1 Hz, 3H), 1.06 (d, $J$ = 7.1 Hz, 3H), 1.03 (d, $J$ = 7.1 Hz, 3H), 0.90 (d, $J$ = 6.6 Hz, 3H); 75-MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 204.0, 159.2, 130.0, 129.4(2), 113.7(2), 90.0, 75.9, 73.1, 72.3, 72.2, 64.8, 55.3, 55.2, 55.2, 47.9, 38.6, 35.8, 34.6, 34.4, 29.7(4), 29.2, 21.8, 16.3, 14.5, 11.3; 75-MHz DEPT NMR ($CDCl_3$) $CH_3$ $\delta$ 55.3, 55.2, 29.7(3), 21.8, 16.3, 14.5, 11.3; $CH_2$ $\delta$ 75.9, 38.6, 34.6, 29.7, 29.2; CH $\delta$ 90.0, 73.1, 72.3, 72.2, 64.8, 52.2, 35.8, 34.4.

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