Strategies for Macrolide Synthesis. A Concise Approach to Protected Seco-Acids of Erythronolides A and B

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Abstract: Concise syntheses of protected derivatives of the seco-acids of erythronolides A and B, **5** and **6**, respectively, have been completed wherein the longest linear sequence requires only 13 chemical steps from 5-ethylfuraldehyde (**15**). The syntheses commenced with the asymmetric aldol condensation of **15** according to the Evans protocol to afford the optically pure *syn*-adduct **16**, thereby establishing the critical stereocenters at C(4) and C(5) of the erythromycin backbone. Reductive removal of the chiral auxiliary from **16** gave the diol **17**, which was converted to the bicyclic enone **18** by an one-pot process involving sequential oxidation of the furan ring and acid-catalyzed bicycloketalization. Stereoselective elaboration of **18** to the tertiary alcohol **19** was achieved in two steps by sequential treatment with lithium dimethylcuprate and methyllithium in the presence of cerium trichloride. Compound **19** underwent facile acid-catalyzed reorganization to the isomeric ketal **21**, which was transformed into **24** by a Swern oxidation and a second asymmetric aldol condensation. However, the necessary refunctionalization of **24** into a ketone that would participate in the requisite aldol reaction to append the C(11)–C(15) segment of the erythronolide backbone could not be induced. On the other hand, transthioketalization of **19** gave the triol **26**, which was converted to **28** by the thermodynamically-controlled formation of an acetonide of the 1,2-diol array. Deprotection of the C(9) ketone function followed by Swern oxidation produced the keto aldehyde **31**, which underwent chemoselective, Lewis acid-mediated addition of tri-*n*-butylcrotylstannane to the aldehyde function to furnish a mixture (4:1) of the homoallylic alcohols **32** and **33**; the major product **32** comprises the C(1)–C(10) subunit common to the seco-acids of both erythronolides A and B. Diastereoselective aldol condensation of the enolate derived from **32** with **40** gave **42** as the major adduct; oxidative processing of the terminal olefin then delivered the erythronolide B seco-acid derivative **46**. The proposed structure of **42** was initially based upon its conversion into the polyol **48**, which was identical to that derived from natural erythronolide B (**49**). Subsequent to this chemical correlation, the X-ray structure of **50**, which was prepared from **42**, unequivocally verified this assignment. In experiments directed toward the preparation of the seco-acid of erythronolide A, the directed aldol reactions of **32** with the aldehydes **59** and **60** were examined. Although the addition of the enolate of **32** to **59** produced none of the requisite adduct, its reaction with **60** gave a mixture (1:5) of **62** and **64**. Stereoselective reduction of the C(9) carbonyl function of **62** followed by oxidative cleavage of the double bond and global deprotection gave the polyol **62**, which was identical with the polyol derived from natural erythromycin A (**1**).

Introduction

The erythromycins A (**1**) and B (**2**), which were originally isolated from *Saccharopolyspora erythraea*, are the archetypal representatives of the family of 14-membered macrolide antibiotics and owe their potent antibiotic activity to their efficient inhibition of ribosomal-dependent protein biosynthesis.[1,2] The combination of the chemotherapeutic value of **1** and the stereochemically complex architecture and dense functionalization on the macrolide backbones of both **1** and **2** has rendered these antibiotics as targets of numerous synthetic efforts. Consequent to these extensive investigations, a number of elegant syntheses of derivatives of the aglycons of **1** and **2** and their respective seco-acids, as well as of erythromycin A itself, have been recorded.[3] A significant fruit of these synthetic endeavors is the development of effective methods and tactics for the stereoselective elaboration of the functionalized skeletal arrays consisting of three or more contiguous and/or alternating stereogenic centers that are common to polyketide-derived natural products. Although genetically engineered actinomycetes that produce novel erythromycin analogues have recently been disclosed,[4] interest in developing synthetic or partially synthetic routes to the erythromycin antibiotics remains intense, since biologically active derivatives that are not otherwise accessible may be thus prepared.

All previous strategies for the synthesis of the erythromycins have followed the basic approach that was devised by nature for the biosynthesis of erythromycin A.[5] Namely, a suitable seco-acid derivative of an erythronolide is first assembled. Following cyclization of this precursor to form the macrolide ring, refunctionalization of the backbone and glycosylation of the hydroxyl residues at C(5) and C(3) with desosamine and cladinose, respectively, lead to the natural antibiotics. The elegant and solitary total synthesis of erythromycin A reported by Woodward and co-workers in 1981 proceeded according to this "biomimetic" strategy.[3e] In pioneering studies, the Woodward group identified a number of structural features that must be incorporated in a seco-acid precursor to ensure successful macrolactonization. For example, dihydro seco-acid derivatives having the 9(*S*)-stereochemistry were found to cyclize more readily than their corresponding 9(*R*)-epimers.[3e] It is also essential to reduce the conformational freedom available to the seco-acid backbone, and several tactics have been invented and exploited to reduce its flexibility, usually in two sections. Rigidification of the fragment spanning C(2) and C(7) has been routinely achieved by forming a cyclic protecting group that incorporates the hydroxyl groups at C(3) and C(5); an alternate approach involves incorporation of a conjugated enone between C(5) and C(7).[3k] Conformational restriction of a second segment of the carbon framework has been most commonly accomplished by constructing a six-membered

⊗ Abstract published in *Advance ACS Abstracts*, April 15, 1994.

(1) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother. (Washington, D. C.)* **1952**, *2*, 281.

(2) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.

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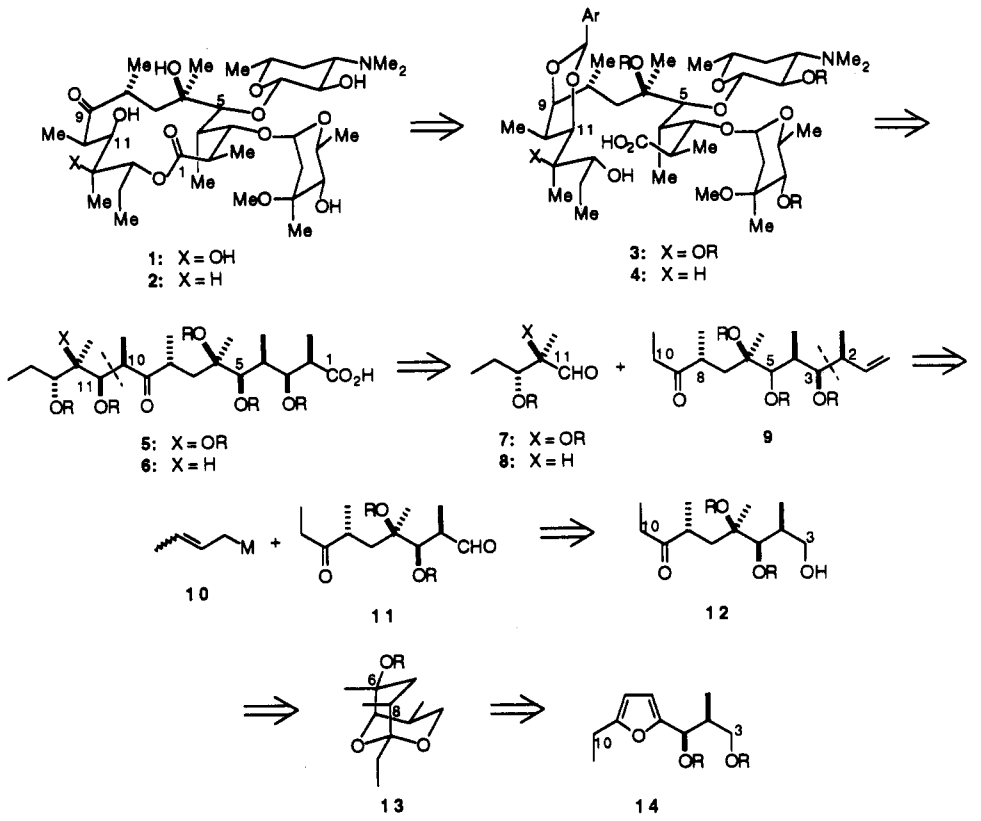
Scheme 1



ring between the functional groups at C(9) and C(11).[3e-i,m-r,w] Other constraints that have been used to restrict the conformational space available to a second section of the backbone include insertion of a double bond at C(7)–C(8),[3v] C(8)–C(9),[3s] C(10)–C(11),[3b,c] or C(11)–C(12).[3k]

In designing our own plan for the synthesis of the erythromycin antibiotics, we elected to explore a unique and adventurous strategy that featured the *macrolactonization of fully glycosylated derivatives of the seco-acids of erythromycins A and B*.[6] Examination of prior art in the erythronolide area led to the formulation of an approach in which **3** and **4** would serve as the substrates for macrolactonization (Scheme 1). The fundamental question was whether the combined presence of the two protected carbohydrate residues at C(3) and C(5) and the conventional cyclic acetal moiety bridging C(9) and C(11) would confer sufficient conformational restraint on the resulting backbone to enable the cyclizations of **3** and **4**. In a significant advance, we validated the key step of this novel strategy by effecting the successful cyclization of a fully glycosylated derivative of the seco-acid of erythromycin B.[6] To our knowledge, the only other account of a macrocyclization of a glycosylated acyclic array is found in the elegant total synthesis of *O*-mycinosyltylonolide by Nicolaou, wherein the critical cyclization was achieved by an intramolecular Wadsworth–Emmons reaction.[7]

Having formulated this novel approach to the erythromycins, it remained to identify a convergent and efficient route to compounds such as **3** and **4**. We reasoned that the seco-acid derivatives **5** and **6** would admirably serve as key intermediates toward this end, and these compounds became the initial targets of our synthetic undertaking.[8] The disconnection of the C(10)–C(11) bond by retroaldolization leads to the ketone **9** and the two

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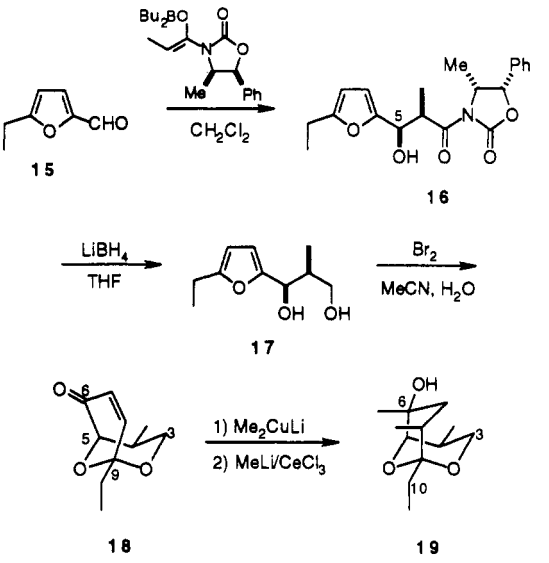
(7) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.

aldehydes **7** and **8**. Selection of an aldol reaction to construct the C(10)–C(11) carbon–carbon bond endows this approach with maximal flexibility, since seco-acid derivatives of both erythronolide A and B can be accessed from the common, advanced intermediate **9**. Significantly, the stereoselective formation of the C(10)–C(11) bond via an aldol reaction was precedented in the elegant synthesis of 6-deoxyerythronolide B recorded by Masamune.[3d,9] Since protected aldehydes of the general type **7** and **8** were known at the outset of our inquiry,[10] the major task before us was the development of a concise and efficient route to the protected ketone **9**. Toward this end, we envisioned that addition of a crotyl organometallic reagent to the aldehyde **11** would form the C(2)–C(3) bond with the correct stereochemistry attending the two newly created stereogenic centers. In this operation, the C(1) carboxyl function would be introduced in masked form as a carbon–carbon double bond. The aldehyde **11** would logically arise from the primary alcohol **12**, which might in turn be obtained upon hydrolysis of the bicyclic ketal **13**. Experience garnered in our successful asymmetric total syntheses of tirandamycin and other highly oxygenated natural products suggested that the bicyclic ketal **13** could be accessed via oxidative transformation of the furan **14** followed by stereoselective introduction of the two requisite methyl groups at C(6) and C(8).[11] We now report the details of our investigations in this area and the successful syntheses of protected derivatives of the seco-acids of erythronolides A and B.

Results and Discussion

The foregoing analysis dictated that the synthesis of the bicyclic ketal **19** would serve as the initial objective in our study. Toward this end, the known aldehyde **15**, which was readily prepared by the Vilsmeier–Haack formylation of 2-ethylfuran, was subjected to a diastereoselective aldol reaction according to the Evans protocol[12] to give the adduct **16** in 81% yield (Scheme 2); no other stereoisomeric adducts were isolated. This key step established the absolute stereochemistry at the two centers C(4) and C(5) that would serve as the critical stereochemical control elements for the subsequent introduction of *all other stereocenters in the C(1)–C(10) subunit*. Reductive removal of the chiral auxiliary with lithium borohydride proceeded in 90% yield to give the diol **17**.[13] When **17** was oxidized with bromine in 15% aqueous acetonitrile,[14] the intermediate dihydroxy enedione formed *in situ* underwent facile acid-catalyzed bicycloketalization to provide **18** in 69% yield. This bicyclic enone embraces two significant design features: Firstly, the hydroxyl functions at C(3) and C(5) together with the ketone function at C(9) are *internally* protected in the form of the bicyclic ketal to minimize the unproductive protection/deprotection steps that would otherwise be required to implement future reactions. Secondly, the conformationally biased skeletal framework in **18** presents sterically well-differentiated faces to incoming nucleophilic

Scheme 2



reagents so attack occurs almost exclusively from the more accessible exo face of the bicyclic array. Thus, the 1,4-addition of lithium dimethylcuprate to **18** gave a single saturated ketone, which then underwent 1,2-addition of methyllithium in the presence of cerium trichloride[15] to furnish **19** in 85% overall yield. Only small quantities, generally less than 5%, of the C(6) epimeric tertiary alcohol were occasionally isolated. If cerium trichloride was omitted during the addition of methyllithium to the ketone function, significant quantities of starting material were recovered; even larger amounts of starting material were recovered when methylmagnesium bromide was used as the nucleophile. Thus, the complete C(3)–C(10) segment of the erythromycin backbone was fashioned with the correct absolute and relative stereochemistry by a concise sequence of only five reactions.

Subsequent elaboration of **19** required dismantling of the bicyclic ketal array to expose those functional groups that would be exploited in subsequent bond constructions. Analysis of selected vicinal proton coupling constants for **19** suggested that the two six-membered rings in **19** existed predominantly in chair conformations despite an unfavorable 1,3-diaxial interaction between the two methyl groups at C(6) and C(8). This conclusion was later verified by single crystal X-ray analysis of a derivative of **19**.[16] We reasoned that the steric strain resulting from this interaction would predispose the bicyclic ketal to undergo an acid-catalyzed reorganization to form a more stable product such as the hydropyran **20**, which maintained protection of the C(9) carbonyl group while releasing the C(3) hydroxyl group for subsequent manipulation (Scheme 3). However, despite numerous attempts, we were unable to induce the superficially straightforward conversion of **19** into any monocyclic product related to **20**. On the other hand, we serendipitously discovered that under carefully controlled conditions **19** underwent a "ketal shuffle" to furnish the isomeric bicyclic ketal **21** in 85% yield; prolonged exposure of **21** to acid led to further reorganization and to the isolation of **22** as the major product. Although **21** was not the intended product, it nevertheless possesses the requisite functionality for chain extension at C(3) while retaining the favorable internal protection of the hydroxyl groups at C(5) and C(6) and the ketone group at C(9). Consequently, we explored the chemistry of **21** to ascertain whether it might be exploited as

(8) For a preliminary report of some of these results, see: Martin, S. F.; Pacofsky, G. J.; Gist, R. P.; Lee, W.-C. *J. Am. Chem. Soc.* **1989**, *111*, 7634.

(9) Consequent both to the report by Masamune and to our preliminary report of the synthesis of a protected analogue of **6**,[8] Kochetkov and coworkers described a similar construction for the preparation of erythronolides A and B.[3t]

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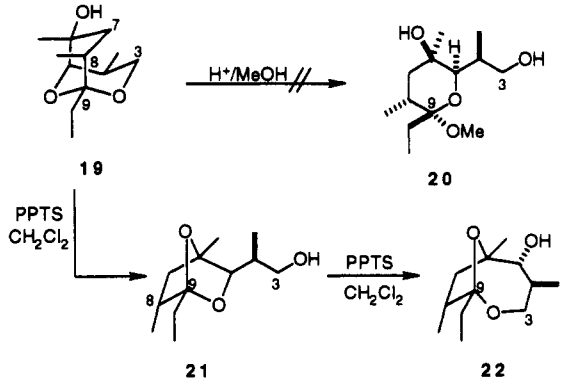
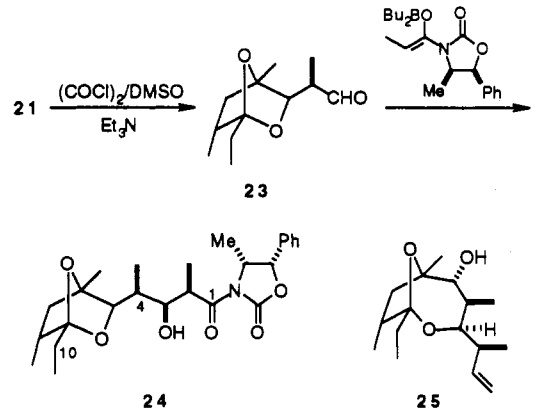
(16) Lynch, V. M.; Lee, W.-C.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1994**, *C44*, in press.

Scheme 3



Scheme 4



a useful intermediate in the syntheses of seco-acid derivatives of the erythronolides.

In the first step toward evaluating this conjecture, **21** was oxidized under Swern conditions[17] to provide the aldehyde **23**, which proved to be relatively unstable, a property that might be attributed to facile β-elimination and subsequent self-destruction. Owing to its fragile nature, **23** was subjected *in situ* to an Evans aldol reaction to give **24** reproducibly in 60–70% yields, *provided* the chiral boron enolate was generated using freshly prepared di-*n*-butylboron triflate (Scheme 4); an adduct epimeric at C(4) of **24** was sometimes isolated as a byproduct. Difficulties were then encountered in removing the chiral auxiliary from **24** as well as its *tert*-butyldimethylsilyl ether derivative, and in the best case (**24**, 4 equiv of LiOBn, THF, −15 to 0 °C, 1.5 h), the reaction proceeded in only 62–72% yield. In some cases products derived from competing nucleophilic attack on the carbonyl of the auxiliary were isolated. In an attempt to circumvent the problems associated with the removal of the chiral auxiliary from **24**, other tactics for introducing the remaining carbons on the C(1)–C(10) subunit were briefly examined. However, reaction of the aldehyde **23** with tri-*n*-butylcrotylstannane[18] in the presence of boron trifluoride etherate did not afford the expected adduct but rather a product that was tentatively identified as **25** on the basis of its NMR spectral characteristics. The lability of the 2,7-dioxabicyclo-[2.2.1]heptane ring system toward acid was again evident. Although one can envision possible scenarios for converting **25** into erythronolide seco-acids, a number of additional protection and deprotection steps would be required, thereby rendering that strategy unacceptable and prompting us to reevaluate our options.

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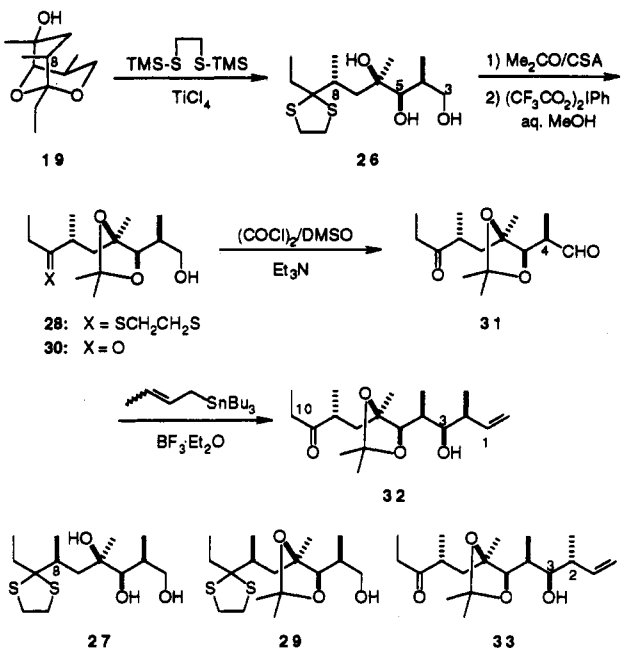
Scheme 5



Selective differentiation of the three hydroxyl groups and the carbonyl group that reside in **19** stood as the principle bulwark to our progress. Given the functional complexity of this small molecule, it is possible to envision a number of possible avenues of approach, but we first queried whether it might be possible to directly convert the ketal function in **19** to a dithioketal moiety while releasing all the hydroxyl groups.[19] After considerable experimentation, we discovered that treating **19** with bis-(trimethylsilyl)ethanedithiol in the presence of titanium tetrachloride at −78 °C gave a mixture (ca. 4:1) of the thioketal **26** (Scheme 5) together with its C(8) epimer **27**. The epimerization at C(8) during this transketalization step appears to be quite facile and difficult to avoid, but we have recently discovered that the use of aluminum trichloride as a catalyst at 0 °C gives primarily **26** contaminated with only small amounts of **27**.[20] Since it was difficult to separate the diastereomers **26** and **27**, this mixture was treated with acetone and camphorsulfonic acid (CSA) under thermodynamically-controlled conditions[21] to produce a separable mixture of the acetonides **28** and **29**. In this fashion, **28** was routinely obtained in >65% overall yield from **19**. Although the 1,3-dioxane derived from acetonide formation between the hydroxyl groups at C(3) and C(5) was formed kinetically, the five-membered ring acetonide from the C(5) and C(6) hydroxyls was virtually the exclusive product at equilibrium. Removal of the dithiolane protecting group from **28** was induced most efficiently using bis(trifluoroacetoxy)iodobenzene to provide **30** in 90% yield.[22] Comparison of the two compounds **19** and **30** suggests the provocative possibility that treatment of **19** with acetone, or an equivalent thereof, in the presence of a suitable acid should furnish **30** by transketalization. However, despite numerous attempts, we were unable to effect this "simple" transformation and were forced to employ the aforementioned three-step sequence.

Oxidation of **30** under Swern conditions gave the keto aldehyde **31** in 92% yield. Ketones are known to be less reactive than

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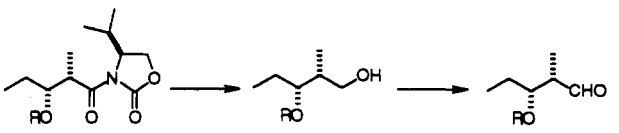
(21) *Cf.*: (a) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949. (b) Tius, M. A.; Fang, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 1035. (c) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111. (d) El Ashry, E. S. H.; El Kilany, Y.; Singab, F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 133.

(22) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

Scheme 6



34: R = H
35: R = TES
36: R = BOM

37: R = TES
38: R = BOM

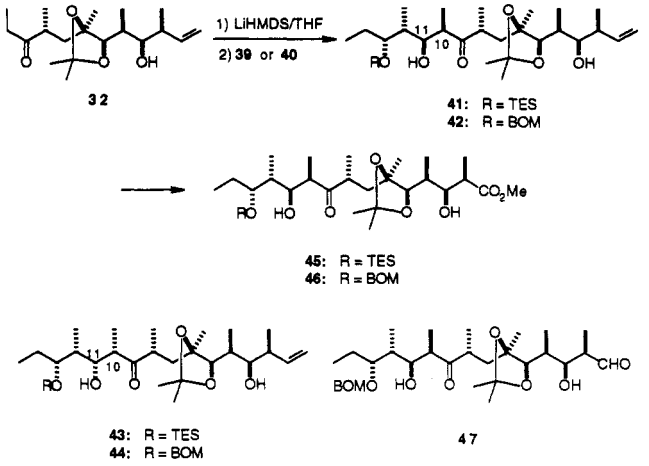
39: R = TES
40: R = BOM

aldehydes toward acid-catalyzed reaction with tri-*n*-butylcrotylstannane,[23] so **31** was treated with tri-*n*-butylcrotylstannane in the presence of $BF_3{\cdot}OEt_2$ at −90 °C to give the *syn*-adduct **32** as the major product in 66% yield together with the *anti*-adduct **33** (16% yield). The structures of both **32** and **33** were confirmed by single crystal X-ray analyses.[24] The formation of such large quantities of the *anti*-adduct is surprising in view of the known propensity of such additions to proceed with significantly higher *syn*-selectivity.[18,25] Although the addition of chiral (*Z*)-crotyl boronates or boranes to **31** might proceed with higher levels of diastereoselectivity,[26] we have not explored this option. An Evans aldol reaction with **31** was also explored to see whether the C(2)–C(3) bond might be formed with higher stereoselectivity, but this reaction was both sluggish and inefficient. At this juncture, the key intermediate ketone **32**, which incorporates C(1)–C(10), is available from **15** by a sequence of only 10 steps; the stage was then set to complete the elaboration of the backbone of the seco-acids of erythronolide A and B by a final aldol construction.

The aldehyde **39** had been previously prepared by Masamune,[3d] but we developed an alternative and more expedient route that commenced with the diastereoselective Evans aldol reaction of propionaldehyde to give the adduct **34** (Scheme 6). Protection of the secondary hydroxyl group with triethylsilyl triflate[27] gave **35** in 78% overall yield. Preliminary experiments to effect the reductive removal of the chiral auxiliary from **35** were unsatisfactory, and consequently the alcohol **37** was prepared from **35** by the two-step sequence involving esterification[28] ($PhCH_2OLi$, THF, 25 °C; 80%) followed by hydride reduction (DIBAL-H, Et_2O, −78 to 0 °C; 93%). Swern oxidation of **37** then provided the aldehyde **39**, the optical rotation of which was identical to that reported by Masamune.[3d]

The critical aldol reaction to establish the complete seco-acid backbone was now at hand. In the event, the *Z*-enolate of the ketone **32**, which was generated with excess lithium hexamethyldisilazide,[29] reacted with the aldehyde **39** (Scheme 7) to give a mixture (3:1) of **41** (59% yield based on recovered starting material) together with a diastereomer that was tentatively identified as being the alternate C(10)–C(11) *syn*-adduct **43** (22% yield based on recovered starting material). The initial assignment of stereochemistry for **41** was founded upon the observed vicinal proton coupling constants of $J_{10,11}$ = 2.0 Hz and $J_{11,12}$ = 9.8 Hz, which are in excellent agreement with values reported by Kochetkov[3t] for structurally similar adducts. Further support

Scheme 7



32

1) LiHMDS/THF
2) **39** or **40**

41: R = TES
42: R = BOM

45: R = TES
46: R = BOM

43: R = TES
44: R = BOM

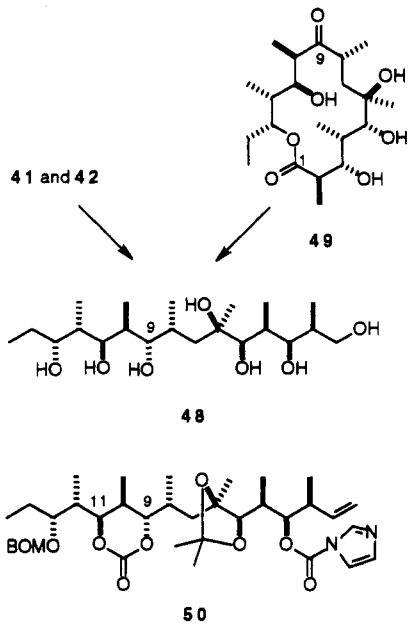
47

for the *syn*-stereochemical relationship between the centers at C(10) and C(11) is the observed resonance for the C(10) methyl group at 7.8 ppm in the ^{13}C NMR spectrum of **41**. Heathcock has noted that the ^{13}C chemical shifts of the α-methyl substituents in *syn*-aldol adducts lie in the range 7.6–12.9 ppm.[30] In the corresponding *anti*-aldol adducts, the chemical shifts for the α-methyl groups may appear between 10.9 and 17.9 ppm, although they are generally in the region 13.7–17.9 ppm for the aldol adducts of ketones and carboxylic acid derivatives; shifts below 13.7 ppm seem typical only of *anti* β-hydroxy-α-methyl aldehydes. The veracity of this preliminary structural assignment for **41** was later confirmed by its conversion into the polyol **48** (*vide infra*). The measured vicinal coupling constants ($J_{10,11}$ = 4.8 Hz and $J_{11,12}$ = 6.0 Hz) for the protons along the C(10)–C(12) segment of **43** did not provide any convincing insights regarding the relative stereochemistry at C(10)–C(12). However, the ^{13}C chemical shift of the methyl group at C(10) of **43** is 8.5 ppm, suggesting that the relative stereochemical relationship at C(10)–C(11) is also *syn*; consequently, **43** must then arise from addition of the *Z*-enolate of **32** to the other diastereotopic face of the aldehyde **39**. No products having the *anti*-stereochemical relationship were isolated.

The modest stereoselectivity in the directed aldol reaction of the *Z*-enolate of **32** with **39** stands in sharp contrast to the high stereoselectivity (17:1) that was observed by Masamune in a closely related coupling.[3d] Kochetkov has recently reported obtaining an adduct having the relative stereochemistry at C(10)–C(12) corresponding to that shown in **41** as the only product of a similar condensation.[3t] The precise factors for the relatively large differences in the observed stereoselectivity in these aldol reactions involving ketone enolates and aldehydes similar to those of the present study remain obscure. After considering a number of tactical options, it occurred to us that higher levels of stereoselectivity should be obtained if addition of the *Z*-enolate of **32** to the aldehyde reaction partner proceeded *via* a tightly organized transition state in which the lithium cation simultaneously coordinated with *both* the aldehyde carbonyl and the protected hydroxyl function on the β-carbon atom. Indeed, Masamune rationalized the stereochemical outcome of a similar process on precisely this basis,[31] although other explanations for such *anti* Felkin–Anh stereoselectivity have been advanced.[32] The use of silyl protecting groups on hydroxyl functions is known to decrease the ability of the oxygen atom to chelate with metal

(23) Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* **1979**, 919.
(24) Lynch, V. M.; Pacofsky, G. J.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1989**, *C45*, 973, 1641.
(25) For a related addition, see: Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645.
(26) See for example: (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (c) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (d) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 3701; **1989**, *54*, 1570. (e) Garcia, J.; Kim, B. M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831. (f) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (g) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348 and references cited therein.
(27) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(28) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. See also ref 13a.
(29) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. See also ref 3d.
(30) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.
(31) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
(32) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.

Scheme 8



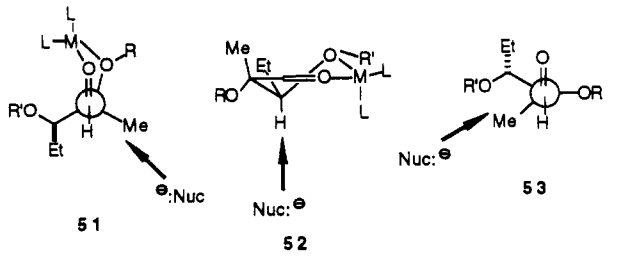
ions,[33] so replacement of the triethylsilyl protecting group on **39** with an alkyl residue would be required to favor nucleophilic addition to the aldehyde carbonyl by a metal-chelated transition state.

Toward this end, the adduct **34** was treated with benzyl chloromethyl ether in the presence of Hünig's base to give **36** in 91% yield (Scheme 6). Removal of the chiral auxiliary using lithium borohydride in the presence of 1 equiv of water provided the alcohol **38**,[13b] which was oxidized under modified Swern conditions using *N*-methylmorpholine to provide the aldehyde **40** in 84% overall yield. The use of triethylamine as the base in the Swern oxidation led to significant epimerization at the carbon α to the aldehyde function—even when the quantity of triethylamine was strictly controlled. When the lithium *Z*-enolate derived from **32** was allowed to react with the aldehyde **40**, a mixture (6:1) of **42** and **44** was produced in 72% yield. The enhanced diastereofacial selectivity in this aldol reaction is consistent with the premise that chelation control plays a more significant role in the addition to **40**. In ancillary investigations, we have examined the effect of metal counterions on the stereoselectivity of some aldol reactions of **40** with enolates related to that derived from **32**.[34] The initial assignment of the relative stereochemistry at C(10)–C(12) in **42** was based upon the measured vicinal coupling constants of $J_{10,11}$ = 2.0 Hz and $J_{11,12}$ = 9.9 Hz, which were virtually identical to those found previously for **41**. The chemical shift of the C(10) methyl group in the ^{13}C NMR spectrum of **42** at 8.2 ppm further supports the *syn*-relationship between the methyl and hydroxyl groups.[30] Although the coupling constants between the protons attached to C(11) and C(12) in **44** could not be determined, the resonance of the C(10) methyl group at 10.1 ppm in the ^{13}C NMR spectrum of **44** is suggestive of *syn* stereochemistry between the newly created centers at C(10) and C(11).

The structural assignments for the aldol adducts **41** and **42** thus rested solely on their NMR spectra and were therefore equivocal. To establish unambiguously the veracity of these assignments, both adducts were converted in parallel sequences of reactions into the polyol **48** (Scheme 8). In the event, stereoselective hydride reduction of **41** and **42** with $Me_4NBH(OAc)_3$, which reduces β-hydroxy ketones to *anti*-1,3-diols,[35] gave the corresponding 9(*S*)-alcohols as the major products. Ozonolysis of the terminal olefin moiety of each of these intermediates followed by treatment of the intermediate ozonides with $LiAlH_4$ and global removal of the hydroxyl protecting groups then gave the synthetic polyol **48** as the sole product of both sequences. An authentic sample of **48** was readily prepared from naturally-derived erythronolide B (**49**)[36] by sequential reduction with sodium borohydride, which gave 9(*S*)-dihydroerythronolide B,[37] and lithium aluminum hydride. The three samples of **48** thus obtained independently were identical by ^{13}C NMR and TLC. The ^1H NMR spectrum of **48** is highly concentration dependent owing to the numerous hydroxyl groups, so comparison by this technique is problematic. Subsequent to completing this chemical correlation, we obtained an X-ray analysis of a single crystal of **50**, which was prepared by sequential reduction of **42** with $Me_4NBH(OAc)_3$ and formation of a cyclic carbonate between the C(9) and C(11) hydroxyl groups with 1,1′-carbonyldiimidazole.[38]

Having assembled the backbone, it remained to convert the terminal olefin functions of **41** and **42** into a carboxylic acid moiety to complete the synthesis of protected derivatives of the seco-acid of erythronolide B. In the first experiments, **41** was treated with ozone in the presence of Sudan III, and the intermediate ozonide was oxidized with either *m*-CPBA or magnesium monoperoxyphthalate (MMPP) to give a carboxylic acid that was esterified by reaction with diazomethane to furnish **45** in 74% yield (Scheme 7). In later experiments, an alternative procedure was developed and applied to the refunctionalization of **42**. Thus, **42** was treated with ozone in methanol in the presence of Sudan III, and the intermediate peroxide was dehydrated with acetic anhydride and triethylamine to deliver the methyl ester **46** directly in 61% yield;[39] the corresponding aldehyde **47** was also obtained in 24% yield. A few attempts to optimize this transformation to produce only **46** were unavailing.

We then turned our attention to the aldol reactions of the enolate of **32** with a suitably protected aldehyde to complete the synthesis of the seco-acid of erythronolide A. The selection of protecting groups for the hydroxyl substituents on the aldehyde partner was guided by consideration of the possible transition states for addition of nucleophiles to α,β-dialkoxy aldehydes. If the nucleophile added to a chelated intermediate in which a metal ion was coordinated to the aldehyde carbonyl group and *either* the α- or the β-hydroxyl oxygen as shown in **51** and **52**, respectively, an adduct having the correct stereochemistry at C(11) would be formed. However, addition *via* the alternate pathway predicted according to the Felkin–Anh model **53** would result in the wrong stereochemistry at C(11) by addition to the opposite face of the carbonyl group. The necessity of inducing the aldol addition via a chelated transition state was thus evident.



Addition of the *Z*-enolate of **32** to an α,β-dialkoxy aldehyde *via* a five-membered ring transition state **51** would be favored by

(33) (a) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (b) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (c) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130.

(34) Martin, S. F.; Lee, W.-C. *Tetrahedron Lett.* **1993**, *34*, 2711.

(35) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

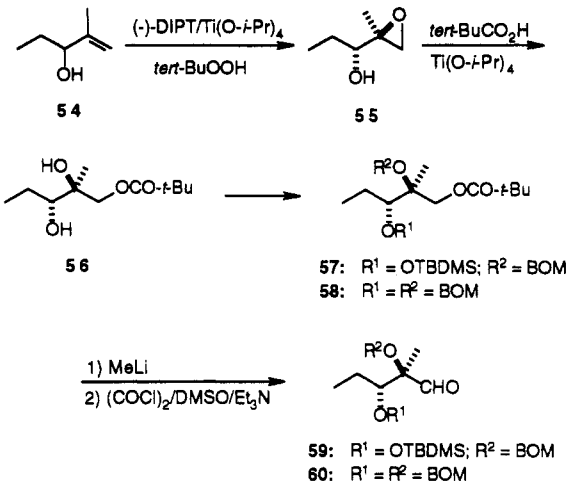
(36) We are grateful to Dr. Paul A. Lartey (Abbott Laboratories) for a generous gift of erythronolide B.

(37) Jones, P. H.; Rowley, E. K. *J. Org. Chem.* **1968**, *33*, 665.

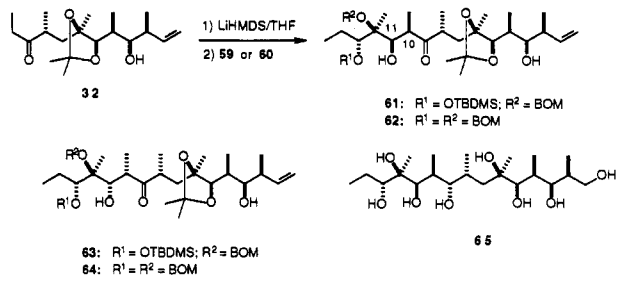
(38) Lynch, V. M.; Lee, W.-C.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1991**, *C47*, 1117.

(39) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

Scheme 9



Scheme 10



placing a silyl ether on the β-hydroxy group of the reacting aldehyde, such as **59**, to suppress chelation via the alternate six-membered ring transition state **52**. Toward this end, the commercially available racemic alcohol **54** was converted into the epoxide **55** in 97% enantiomeric excess by kinetic resolution according to the Sharpless protocol (Scheme 9).[40] Titanium-mediated opening of the epoxide occurred exclusively at the less hindered terminus to afford the pivalate **56** in 36% overall yield.[41] Selective silylation of the secondary alcohol function of **56** ((TBDMS)OTf/2,6-lutidine, CH_2Cl_2, −20 °C) followed by alkylation of the tertiary hydroxyl group with benzyl chloromethyl ether in the presence of Proton Sponge and sodium iodide gave **57** in 68% overall yield.[42] The pivalate ester was cleaved by the action of methyllithium, and Swern oxidation of the intermediate primary alcohol then afforded the requisite aldehyde **59** in 78% overall yield.

The reaction of the *Z*-enolate of **32** with the aldehyde **59** proceeded with excellent (>30:1) diastereoselectivity to provide a mixture of adducts in 49% yield (86% based on recovered **32**) together with unreacted starting material (Scheme 10). Upon the basis of our prior analysis, we optimistically presumed the major product to be the desired adduct **61**. The observed coupling constant $J_{10,11}$ of 1.5 Hz together with the fact that the ^{13}C chemical shift for the methyl group at C(10) was 10.5 ppm suggested that the stereochemical relationship between C(10) and C(11) was *syn*. The relative stereochemistry between C(11) and C(12) could not be determined by NMR spectroscopy because of the quaternary center at C(12). Preliminary attempts to obtain a crystalline derivative of this adduct for verification of the structure were unsuccessful, so it was necessary to establish the structure of this adduct by a chemical correlation similar to that outlined in Scheme 8. In the event, the major aldol adduct was subjected to a sequence of stereoselective reduction of the C(9) carbonyl group with $Me_4NBH(OAc)_3$, ozonolysis of the terminal carbon–carbon double bond followed by reductive workup of the ozonide, and global deprotection of the acetal and ketal protecting groups. As judged by TLC and ^{13}C NMR, however, the synthetic polyol thus obtained was *not* identical with the naturally-derived polyol **65**, which was prepared from erythromycin A according to the protocol previously reported by Chamberlin.[3j,43] We have not rigorously established the structure of the major product of the directed aldol reaction of **32** with **59**, but it now seems reasonable to conclude that it is **63**; the minor product was presumably the desired adduct **61**.

Since the aldol reaction of **32** with **59** did not appear to proceed via a five-membered ring chelate as shown in **51**, we queried whether changing the nature of the protecting group on the secondary hydroxyl group at C(13) to an alkyl residue would allow the addition to the aldehyde function to proceed via a six-membered ring transition state as shown in **52**. Toward this end, we prepared the aldehyde **60** from the diol **56** by a simple modification of the procedure used to prepare **59** (Scheme 9). Reaction of **56** with excess benzyl chloromethyl ether in the presence of NaI and Proton Sponge gave **58** in 84% yield; subsequent removal of the pivalate moiety with methyllithium followed by Swern oxidation of the resulting primary hydroxyl group provided **60** in 79% overall yield. Deprotonation of **32** with lithium hexamethyldisilazide and condensation of the resulting *Z*-enolate with **60** proceeded smoothly to give a mixture (1:5) of isomeric adducts in 41% yield (75% yield based upon recovered starting material). As judged from the ^{13}C chemical shifts for the C(10) methyl groups of the minor (12.2 ppm) and major (10.3 ppm) adducts, each appeared to have the *syn* stereochemical relationship at C(10) and C(11). That the minor product was **62** and in fact possessed the stereochemical relationship at C(10)–C(12) present in erythromycin A was established by its conversion into the known polyol **65** by sequential reduction of the C(9) carbonyl group with $Me_4NBH(OAc)_3$, ozonolysis of the terminal carbon–carbon double bond followed by reductive workup of the ozonide, and global deprotection of the acetal and ketal protecting groups. The synthetic polyol thus obtained was identical by TLC and ^{13}C NMR with the naturally-derived polyol **65**. Since subjection of the major aldol adduct to the same sequence of reactions gave a polyol identical with that previously derived from **63**, the structure of this adduct may be assigned as being **64**.

Although the stereoselectivity of the addition of **32** to the aldehydes **39** and **40** did proceed preferentially with the desired diastereofacial selectivity to give the adducts **41** and **42** as the major products,[44] the corresponding reactions of **32** with the aldehyde **59** and **60** proceeded in the *opposite* stereochemical sense. The preferential Felkin–Anh (Cram) mode of addition of enolates to aldehydes related to **59** and **60** has been previously observed by Heathcock.[45] We were unable to enhance the formation of the desired adduct **62** even in the presence of Lewis acids such as $MgBr_2$, $TiCl_4$, or $ZnBr_2$. After we had completed our own results, Kochetkov described closely related aldol reactions with the aldehydes **59** and **60**; he also observed low diastereofacial selectivity with the undesired adducts related to **63** and **64** being the major products.[3t] The diastereoselectivity in this critical aldol reaction thus stands as a potential chemical "Achilles' heel" impeding our progress toward an efficient, stereoselective ap-

(40) (a) Sharpless, K. B.; Hanson, R. M. *J. Org. Chem.* **1986**, *51*, 1922. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. For the preparation of the antipode of **49**, see: (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

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(42) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269.

(43) We are grateful to Prof. A. R. Chamberlin (The University of California at Irvine) for a generous gift of authentic 3′-de(dimethylamino)-3′,4′-dehydroerythromycin A,[37] which we converted according to the procedure outlined in ref 3j into the natural polyol **65** for comparison with synthetic material.

(44) For an account of some related aldol reactions, see: Martin, S. F.; Lee, W.-C. *Tetrahedron Lett.* **1993**, *34*, 2711.

(45) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.

proach to the erythronolide A skeleton, and we are presently conducting experiments to resolve this stereochemical problem. In this context, it is noteworthy that Hoffmann[3w] recently observed that the additions of chiral crotyl boronates to aldehydes related to **59** and **60** may proceed with the desired diastereofacial selectivity. Alternatively, it may be possible to utilize boron enolates derived from chiral boranes to override the inherent diastereofacial selectivity in this substrate-controlled reaction.[46] We are currently screening a number of tactics to solve this remaining problem.

Conclusions

The syntheses of **46** and **62** conclude a concise route to protected derivatives of the seco-acids of erythronolides B and A, respectively. The longest linear sequence in the synthesis of **46** employs only 13 chemical operations from **15**, and the total number of steps from commercially available starting materials is a mere 18. The Evans asymmetric aldol reaction to give the furfuryl carbinol **16** established the critical stereocenters at C(4) and C(5), and the absolute configuration at this center is then exploited to create all of the stereogenic centers in the C(1)–C(10) subunit **32** of both erythronolide A and B seco-acids via the internally protected and conformationally biased bicyclic template found in **18**. Final assembly of the seco-acid framework is achieved through the agency of a directed aldol reaction of the enolate of **32** with a suitably functionalized aldehyde partner such as **40** or **60**. Although this reaction is highly stereoselective for constructing the backbone of erythronolide B, it is not yet well suited for the synthesis of precursors of erythronolide A, and modifications of this process must be developed prior to launching an assault on erythromycin A. Continued application of this strategy to the syntheses of the erythromycins A and B and other highly oxygenated natural products is the subject of active investigation, the results of which will be described in due course.

Experimental Section

General Procedures. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium/benzophenone ketyl under nitrogen prior to use. *N,N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled under reduced pressure from calcium hydride and stored over 4-Å molecular sieves under argon. Methylene chloride (CH_2Cl_2), triethylamine, diisopropylethylamine, *N*-methylmorpholine, hexamethyldisilazane, and oxalyl chloride were freshly distilled from calcium hydride. Benzyl chloromethyl ether was passed through a column of basic aluminum oxide. Boron trifluoride etherate was distilled from excess Et_2O and calcium hydride and stored under argon at −20 °C, and bromine was distilled from phosphorus pentoxide. All reactions involving organometallic reagents or other moisture-sensitive reactants were executed under an atmosphere of dry nitrogen or argon using oven dried glassware. Flash chromatography was performed using silica gel 60 (230–400 mesh ASTM) with the indicated solvent. Melting points are uncorrected. ^{1}H NMR spectra were recorded at the indicated field strength as solutions in deuteriochloroform ($CDCl_3$), unless otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) (δ = 0.00 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; comp, complex multiplet; br, broad. Coupling constants are given in hertz (Hz). ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS (δ = 0.00 ppm) and are referenced to the deuterated solvent. IR spectra were recorded either as films on sodium chloride plates or as solutions in $CHCl_3$ as indicated and reported in wavenumbers (cm^{-1}).

(46) For examples, see: (a) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (b) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (c) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229. (d) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (e) Paterson, I. *Chem. Ind.* **1988**, 390.

(4*R*,5*S*)-3-[(2′*R*,3′*R*)-3′-(2″-(5″-Ethylfuryl))-3′-hydroxy-2′-methylpropionyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one (16). Di-*n*-butylboron triflate (54.7 mL, 61.3 g, 224 mmol) was added dropwise with stirring to a solution of (4*R*,5*S*)-3-propionyl-4-methyl-5-phenyloxazolidin-2-one[12] (52.1 g, 224 mmol) in CH_2Cl_2 (450 mL) at −78 °C. Triethylamine (37.4 mL, 27.1 g, 268 mmol) was added, and the reaction was stirred for 1 h at −78 °C and then for 1 h at 0 °C. After the mixture was cooled to −78 °C, a solution of 5-ethylfuraldehyde (**15**) (26.99 g, 218 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 1 h, whereupon the reaction was quenched by the addition of 0.25 M aqueous NaH_2PO_4 (pH = 7) (200 mL). MeOH was added until the mixture became homogeneous. The solution was cooled to 0 °C, a mixture (1:1) of MeOH and 30% H_2O_2 (total volume of 460 mL) was added while maintaining the internal temperature <5 °C, and the solution was stirred for 2 h at room temperature. The organic solvents were removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude product as a solid that was recrystallized from hexanes/EtOAc to give 62.9 g (81%) of **16**: mp 116–117 °C; ^{1}H NMR (300 MHz) δ 7.45–7.38 (m, 3 H), 7.37–7.28 (m, 2 H), 6.20 (d, J = 3.1 Hz, 1 H), 5.93 (d, J = 3.1 Hz, 1 H), 5.65 (d, J = 7.2 Hz, 1 H), 5.00 (t, 1 H, J = 4.9 Hz), 4.69 (p, J = 6.6 Hz, 1 H), 4.21 (p, J = 6.8 Hz, 1 H), 2.84 (d, J = 4.5 Hz, 1 H), 2.63 (q, J = 7.6 Hz, 2 H), 1.36 (d, J = 6.8 Hz, 3 H), 1.22 (t, J = 7.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz) δ 175.8, 157.5, 152.5, 152.4, 133.2, 128.8, 128.7, 125.7, 125.6, 107.4, 104.6, 79.0, 69.0, 54.9, 46.7, 42.8, 21.4, 14.3, 12.3, 12.1; IR ($CHCl_3$) ν 3550, 1800, 1710 cm^{-1}; mass spectrum m/z 357.1587 ($C_{20}H_{23}NO_5$ requires 357.1576), 339, 177, 124, 107 (base). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.92; H, 6.52; N, 3.89.

(1*R*,2*S*)-1-[2′-(5′-Ethylfuryl)]-2-methylpropane-1,3-diol (17). A solution of 2.0 M $LiBH_4$ in THF (57.8 mL, 115.7 mmol) was slowly added with stirring to a solution of the aldol adduct **16** (34.4 g, 96.4 mmol) in THF (500 mL) at −45 °C. The reaction was stirred for 1 h at −45 °C and then at 0 °C for 2 h. Most of the THF was removed under reduced pressure, whereupon saturated NH_4Cl (200 mL) and CH_2Cl_2 (200 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and Et_2O (ca. 40 mL) was added to the residue. Hexanes were then added until the solution was cloudy, and the mixture was allowed to stand at room temperature and then at 0 °C; the chiral auxiliary that precipitated (11.0 g) was collected by vacuum filtration. The filtrate was concentrated under reduced pressure to give a mixture of diol **17** and the chiral auxiliary that was separated by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 16.8 g (94%) of the diol together with an additional 5.9 g of the chiral auxiliary. The diol was recrystallized from ethyl acetate/hexanes to give fine colorless needles: mp 52–53 °C; ^{1}H NMR (250 MHz) δ 6.08 (d, J = 3.0 Hz, 1 H), 5.86 (d, J = 3.0 Hz, 1 H), 4.75 (d, J = 4.2 Hz, 1 H), 3.66–3.50 (comp, 3 H), 3.18 (br s, 1 H), 2.57 (q, J = 7.5 Hz, 2 H), 2.17–2.09 (m, 1 H), 1.16 (t, J = 7.5 Hz, 3 H), 0.89 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (90 MHz) δ 157.2, 152.6, 106.1, 103.3, 69.7, 64.8, 38.7, 20.4, 11.1, 10.5; IR ($CHCl_3$) ν 3450 cm^{-1}; mass spectrum m/z 184.1105 ($C_{10}H_{16}O_3$ requires 184.1099), 166, 150, 136, 121 (base). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.50. Found: C, 65.01; H, 8.50.

(1*R*,4*S*,5*R*)-1-Ethyl-4-methyl-2,9-dioxabicyclo[3.3.1]non-7-en-6-one (18). A solution of bromine (1.60 mL, 30.8 mmol) in 15% aqueous MeCN was added rapidly with stirring to a solution of **17** (5.61 g, 30.5 mmol) in 15% aqueous MeCN (150 mL) at −20 °C. The reaction was stirred for 30 min at −20 °C and then 30 min at room temperature. The reaction was quenched by the addition of saturated $NaHCO_3$ until the solution was slightly basic (pH = 8). The mixture was extracted with CH_2Cl_2 (4 × 200 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 3.86 g (69%) of **18** as a colorless oil: ^{1}H NMR (300 MHz) δ 6.53 (d, J = 10.1 Hz, 1 H), 6.29 (d, J = 10.1 Hz, 1 H), 4.07 (d, J = 6.0 Hz, 1 H), 3.75 (dd, J = 12.0, 5.6 Hz, 1 H), 3.48 (t, J = 12.0 Hz, 1 H), 2.45–2.36 (m, 1 H), 1.70 (q, J = 7.6 Hz, 2 H), 0.93 (t, J = 7.6 Hz, 3 H), 0.66 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (20 MHz) δ 195.4, 144.0, 130.6, 94.7, 79.3, 64.8, 32.2, 31.7, 11.7, 6.6; IR ($CHCl_3$) ν 1695, 1465 cm^{-1}; mass spectrum m/z 182.0949 ($C_{10}H_{14}O_3$ requires 182.0943), 112 (base), 97, 83.

(1*R*,4*S*,5*R*,8*R*)-4,8-Dimethyl-1-ethyl-2,9-dioxabicyclo[3.3.1]nonan-6-one. A 1.4 M solution of MeLi in Et_2O (32 mL, 44.8 mmol) was added

dropwise to a suspension of purified CuI (4.27 g, 22.4 mmol) in Et_2O (120 mL) at 0 °C. The resulting solution was then cooled to −78 °C, and a solution of **18** (2.72 g, 14.9 mmol) in Et_2O (50 mL) was added. The mixture was stirred for 15 min at −78 °C and then at −10 °C for 1 h. Saturated NH_4Cl (120 mL) and concentrated NH_4OH (20 mL) were added, and the mixture was stirred for 1 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes/Et_2O (2:1) to give 2.65 g (90%) of the product as a yellow oil: ^1H NMR (360 MHz, C_6D_6) δ 4.10 (d, J = 8.3 Hz, 1 H), 3.99 (dd, J = 11.6, 5.8 Hz, 1 H), 3.48 (dd, J = 11.6, 6.3 Hz, 1 H), 2.80 (dd, J = 16.7, 6.8 Hz, 1 H), 2.53–2.31 (m, 2 H), 2.25 (ddd, 1 H, J = 15.7, 4.1, 1.1 Hz), 1.89–1.53 (m, 2 H), 1.06 (d, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.4 Hz, 3 H), 0.89 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (90 MHz, C_6D_6) δ 208.3, 100.3, 79.5, 64.4, 45.0, 35.1, 33.2, 28.2, 17.7, 13.3, 7.5; IR ($CHCl_3$) ν 1718, 1460 cm^{-1}; mass spectrum m/z 198.1252 ($C_{11}H_{18}O_3$ requires 198.1256), 128, 117, 100, 69, 57 (base).

(1*R*,4*S*,5*R*,6*R*,8*R*)-1-Ethyl-6-hydroxy-4,6,8-trimethyl-2,9-dioxabicyclo-[3.3.1]nonane (19). Cerium(III) chloride heptahydrate (8.02 g, 21.5 mmol) was heated *in vacuo* (0.1 mmHg) for 2 h at 150 °C (oil bath). Argon was bled into the flask, the flask was allowed to cool to room temperature, and THF (100 mL) was added. The resulting suspension was stirred for 2 h at room temperature and then cooled to −78 °C. A 1.4 M solution of MeLi in Et_2O (15.4 mL, 21.5 mmol) was added, and the mixture stirred for 30 min at −78 °C, whereupon a solution of the ketone from the previous experiment (2.24 g, 11.3 mmol) in THF (20 mL) was added. After the mixture was stirred for 1.5 h at −78 °C, the reaction was quenched by the addition of saturated NH_4Cl (25 mL), and the mixture was allowed to warm to room temperature. Water (ca. 10 mL) was added to dissolve the remaining solids, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (1:1) to give 2.28 g (94%) of **19**: ^1H NMR (360 MHz, C_6D_6) δ 3.97 (t, J = 11.1 Hz, 1 H), 3.78 (dd, J = 11.1, 6.5 Hz, 1 H), 3.57 (d, J = 5.3 Hz, 1 H), 2.47 (dddd, J = 11.1, 7.5, 6.5, 5.3 Hz, 1 H), 2.23 (dd, J = 13.8, 7.3 Hz, 1 H), 2.13–2.07 (m, 1 H), 1.82 (s, 1 H), 1.59–1.42 (comp, 3 H), 1.41 (s, 3 H), 1.05 (d, J = 7.5 Hz, 3 H), 1.00 (d, J = 7.6 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (90 MHz, C_6D_6) δ 98.3, 78.3, 71.6, 66.8, 44.4, 35.1, 34.8, 33.2, 31.1, 19.5, 14.5, 7.5; IR ($CHCl_3$) ν 3460 cm^{-1}; mass spectrum m/z 214.1572 ($C_{12}H_{22}O_3$ requires 214.1569), 197, 185, 171, 155, 137, 126, 111, 98 (base), 85.

(1*S*,3*R*,4*R*,6*R*)-1-Ethyl-4,6-dimethyl-3-[(2′*S*)-1′-hydroxy-2′-methyl-eth-2′-yl]-2,7-dioxabicyclo[2.2.1]heptane (21). A slurry containing the tertiary alcohol **19** (427 mg, 2.00 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (100 mg, 0.4 mmol) in dry CH_2Cl_2 (20 mL) was stirred at ca. −15 °C (ice–salt bath) for 1 h. Following the addition of Et_2O (50 mL), the mixture was immediately filtered through a plug (0.2 × 15 cm) of silica gel. The crude product was purified by HPLC, eluting with hexanes/EtOAc (3:1) to afford the primary alcohol **21** (370 mg, 87%) as a colorless oil together with small amounts of the secondary alcohol **22**. **21**: ^1H NMR (360 MHz, C_6D_6) δ 3.67 (d, J = 1.6 Hz, 1 H), 3.53 (dd, J = 10.3, 6.9 Hz, 1 H), 3.44 (dd, J = 10.3, 5.1 Hz, 1 H), 1.97 (m, 1 H), 1.85 (m, 1 H), 1.70 (m, 1 H), 1.60 (t, J = 11.5 Hz, 1 H), 1.49 (m, 1 H), 1.19 (s, 3 H), 1.04 (m, 6 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.91 (m, 1 H); ^{13}C NMR (90 MHz, C_6D_6) δ 111.1, 84.6, 83.1, 66.7, 46.1, 41.7, 37.7, 23.9, 16.4, 15.4, 11.4, 8.7; mass spectrum m/z 214.1574 ($C_{12}H_{22}O_3$ requires 214.1569), 155, 140, 126, 109 (base). **22**: ^1H NMR (360 MHz, C_6D_6) δ 3.56 (m, 1 H), 3.32 (dd, J = 12.2, 3.2 Hz, 1 H), 2.79 (d, J = 9.3 Hz, 1 H), 1.90 (m, 1 H), 1.65–1.79 (m, 2 H), 1.45–1.62 (m, 3 H), 1.29 (s, 3 H), 1.00 (m, 6 H), 0.73 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (90 MHz, C_6D_6) δ 108.2, 84.5, 81.3, 64.2, 41.2, 38.0, 29.2, 27.0, 15.0, 12.9, 8.3; IR (film) ν 3410 cm^{-1}; mass spectrum m/z 214.1564 ($C_{12}H_{22}O_3$ requires 214.1569), 143 (base), 125, 98.

(4*R*,5*S*)-3-{(2′*R*,3′*S*,4′*S*)-3′-Hydroxy-2′,4′-dimethyl-4′-[(1″*S*,3″*R*,4″*R*,6″*R*)-(1″-ethyl-4″,6″-dimethyl-2″,7″-dioxabicyclo[2.2.1]-heptan-3″-yl]-1′-butanoyl}-4-methyl-5-phenyl-1,3-oxazolidin-2-one (24). Triethylamine (0.29 mL, 2.1 mmol) was added to a solution of *freshly prepared* di-*n*-butylboron triflate (0.33 mL, 1.3 mmol) and (4*R*,5*S*)-3-propionyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one[12] (330 mg, 1.4 mmol) in CH_2Cl_2 (7 mL) at −78 °C. The solution was then stirred at −78 °C for 30 min and at 0 °C for 1 h, whereupon the resulting solution of boron enolate was recooled to −78 °C while the aldehyde **23** was prepared in a separate flask.

DMSO (0.27 mL, 3.7 mmol) was added to a solution of freshly distilled oxalyl chloride (0.16 mL, 1.9 mmol) in CH_2Cl_2 (2 mL) at −60 °C, and the stirring was continued for 10 min. A solution of **21** (200 mg, 0.94 mmol) in CH_2Cl_2 (4.5 mL) was added dropwise. After the mixture was stirred for 10 min, triethylamine (0.78 mL, 5.6 mmol) was added, and the bath was allowed to warm slowly over 30 min to 0 °C. The solution of aldehyde **23** thus obtained was then transferred to the solution of boron enolate prepared above. The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 45 min. The reaction was quenched by adding 0.25 M NaH_2PO_4 buffer (15 mL). After the solution was warmed to room temperature, the mixture was diluted with MeOH (ca. 50 mL) to give a single phase, and a solution of 30% aqueous H_2O_2 (2 mL) in MeOH (2 mL) was added. The solution was stirred for 45 min, and the MeOH was evaporated under reduced pressure. The aqueous mixture was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated to an oil under reduced pressure. The crude product was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give **24** (258 mg, 62%) as a white foam: ^1H NMR (360 MHz, C_6D_6) δ 7.00 (m, 3 H), 6.81 (m, 2 H), 4.56 (d, J = 7.3 Hz, 1 H), 4.52 (m, 1 H), 4.47 (m, 1 H), 4.25 (m, 1 H), 3.82 (d, J = 1.7 Hz, 1 H), 3.58 (br s, 1 H), 1.92–1.98 (comp, 2 H), 1.79 (m, 1 H), 1.64 (m, 1 H), 1.62 (d, J = 6.6 Hz, 3 H), 1.55 (t, J = 11.6 Hz, 1 H), 1.41 (d, J = 6.8 Hz, 3 H), 1.28 (s, 3 H), 1.03 (t, J = 7.5 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.88 (dd, J = 11.6, 4.2 Hz, 1 H), 0.53 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz, C_6D_6) δ 176.9, 152.3, 134.1, 128.6, 128.5, 125.8, 111.5, 85.4, 84.8, 78.3, 75.9, 54.5, 46.1, 41.6, 41.1, 37.6, 23.8, 16.3, 15.4, 14.0, 9.0, 8.6; IR (film) ν 3500, 1785, 1690 cm^{-1}; mass spectrum m/z 445.2457 ($C_{25}H_{35}NO_6$ requires 445.2464), 446 (M + 1), 428, 371, 233, 178, 107 (base).

(2*S*,3*R*,4*R*,6*R*)-7,7-(Ethylenedithio)-3,4-(isopropylidenedioxy)-2,4,6-trimethylnonanol (28). A solution of bicyclic ketal **19** (648 mg, 3.03 mmol) in CH_2Cl_2 (60 mL) containing 1,2-bis[(trimethylsilyl)thio]ethane (1.28 g, 6.66 mmol) at −78 °C was treated with $TiCl_4$ (0.67 mL, 6.06 mmol). After it was stirred at −78 °C for 1 h, the reaction mixture was warmed to room temperature over 1.5 h, whereupon saturated $NaHCO_3$ (ca. 2 mL) was added and stirring continued for 1 h. The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes/EtOAc (1:1) as the eluent to provide 771 mg of a mixture of diastereomeric triols **26** and **27** as a colorless glass. This mixture was dissolved in anhydrous acetone (15 mL) and CH_2Cl_2 (15 mL) containing a catalytic amount of camphorsulfonic acid, and the solution was stirred at room temperature for 2 h. Saturated $NaHCO_3$ (ca. 3 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (4:1) to give **28** (682 mg, 65%) as a white solid and 175 mg (17%) of **29** as a colorless oil. **28**: mp 73–74 °C (white needles recrystallized from hexane); ^1H NMR (300 MHz) δ 3.80 (d, J = 7.0 Hz, 1 H), 3.61 (m, 1 H), 3.25–3.14 (comp, 4 H), 2.26 (m, 1 H), 2.07–1.81 (comp, 5 H), 1.56 (dd, J = 14.5, 9.1 Hz, 1 H), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.22 (d, J = 6.5 Hz, 3 H), 1.17 (s, 3 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.07 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 106.2, 82.5, 81.7, 79.8, 65.9, 43.1, 40.0, 39.6, 39.4, 35.9, 34.2, 28.8, 26.8, 24.5, 20.0, 14.0, 10.5; IR (film) ν 3040, 1420 cm^{-1}; mass spectrum (CI) m/z 349, 291, 273, 197 (base), 133. Anal. Calcd for $C_{17}H_{32}O_3S_2$: C, 58.58; H, 9.25. Found: C, 58.77; H, 9.44. **29**: ^1H NMR (300 MHz) δ 3.62 (dd, J = 10.6, 4.5 Hz, 1 H), 3.55 (d, J = 7.9 Hz, 1 H), 3.50 (dd, J = 10.6, 5.8 Hz, 1 H), 3.20–3.11 (comp, 4 H), 2.25–1.36 (comp, 7 H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.17 (d, J = 6.6 Hz, 3 H), 1.12 (s, 3 H), 1.09 (d, J = 6.7 Hz, 3 H), 1.04 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ 106.2, 85.0, 82.5, 79.4, 65.2, 44.0, 40.0, 39.6, 39.2, 35.6, 34.2, 28.6, 26.6, 20.8, 19.1, 14.6, 10.5; IR (film) ν 3400, 1450 cm^{-1}; mass spectrum (CI) m/z 349.1881 [$C_{17}H_{33}O_3S_2$ (M + 1) requires 349.1871], 291, 273, 255, 197, 133 (base).

(4*R*,6*R*,7*R*,8*S*)-9-Hydroxy-6,7-(isopropylidenedioxy)-4,6,8-trimethylnonan-3-one (30). A mixture of dithiolane **28** (604 mg, 1.74 mmol) and bis(trifluoroacetoxy)iodobenzene (1.12 g, 2.60 mmol) in MeOH/H_2O (9:1, 17 mL) was stirred at 0 °C for 10 min. The reaction was quenched with saturated $NaHCO_3$ (ca. 5 mL) and then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic extracts were washed with saturated NaCl (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to provide 422 mg (89%) of ketone **30** as a clear colorless oil: ^1H NMR (300 MHz) δ 3.56–3.52 (comp, 2 H), 3.48 (d, J = 8.2 Hz, 1 H), 2.89 (m, 1 H), 2.52 (q, J = 7.2 Hz, 2 H), 2.18 (dd,

J = 14.2, 9.3 Hz, 1 H), 1.85–1.76 (comp, 2 H), 1.42 (dd, J = 14.2, 2.9 Hz, 1 H), 1.34 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.06 (d, J = 7.1 Hz, 3 H), 1.02 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 215.8, 106.0, 83.6, 81.5, 64.9, 42.8, 41.5, 35.6, 34.5, 28.6, 26.3, 22.2, 19.3, 14.5, 7.8; IR (film) ν 3430, 1725 cm^{-1}; mass spectrum (CI) m/z 273 (M + 1), 197 (base).

(2*R*,3*R*,4*R*,6*R*)-3,4-(Isopropylidenedioxy)-2,4,6-trimethyl-7-oxononanal (31). To a solution of freshly distilled oxalyl chloride (0.16 mL, 1.82 mmol) in CH_2Cl_2 (3 mL) at –60 °C was added DMSO (0.26 mL, 3.65 mmol). After the mixture was stirred at –60 °C for 15 min, a solution of **30** (242 mg, 0.91 mmol) in CH_2Cl_2 (5 mL) was introduced. The reaction mixture was stirred at –60 °C for an additional 15 min and then treated with Et_3N (0.76 mL, 5.47 mmol) and warmed to room temperature over 30 min. The mixture was diluted with Et_2O (ca. 50 mL), and then washed with saturated aqueous $NaHCO_3$ (1 × 10 mL), saturated aqueous $CuSO_4$ (1 × 10 mL), and saturated aqueous NaCl (1 × 10 mL). The resulting solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (3:1) to give 222 mg (92%) of aldehyde **31** as a colorless oil: ^{1}H NMR (300 MHz) δ 9.61 (d, J = 2.9 Hz, 1 H), 3.83 (d, J = 8.7 Hz, 1 H), 2.84 (dqd, J = 9.9, 6.8, 2.6 Hz, 1 H), 2.49 (qd, J = 7.2, 1.6 Hz, 2 H), 2.11 (dd, J = 14.0, 9.9 Hz, 1 H), 1.32 (dd, J = 14.0, 2.6 Hz, 1 H), 1.31 (s, 3 H), 1.21 (d, J = 6.8 Hz, 3 H), 1.20 (s, 3 H), 1.09 (s, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 1.00 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 214.8, 202.0, 106.9, 82.2, 81.4, 47.2, 43.2, 41.4, 34.6, 28.4, 26.1, 22.2, 19.1, 11.8, 7.7; IR (film) ν 1745 cm^{-1}; mass spectrum (CI) m/z 271 (M + 1), 43 (base).

(4*R*,6*R*,7*R*,8*S*,9*R*,10*S*)-9-Hydroxy-6,7-(isopropylidenedioxy)-4,6,8,-10-tetramethyldodec-11-en-3-one (32) and (4*R*,6*R*,7*R*,8*S*,9*R*,10*R*)-9-Hydroxy-6,7-(isopropylidenedioxy)-4,6,8,10-tetramethyldodec-11-en-3-one (33). To a solution of aldehyde **31** (122 mg, 0.45 mmol) in CH_2Cl_2 (4.5 mL) at –90 °C was added boron trifluoride etherate (0.12 mL, 0.95 mmol). After this mixture was stirred at –90 °C for 5 min, tri-*n*-butylcrotylstannane (234 mg, 0.68 mmol) was added. The reaction mixture was stirred at –90 °C for 30 min, quenched with saturated aqueous $NaHCO_3$ (2 mL), and warmed to room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a mixture of adducts that was separated by flash chromatography, eluting with hexanes/Et_2O (2:1) to give 97 mg (66%) of **32** and 24 mg (16%) of **33**, each of which was recrystallized from hexanes to give colorless needles. **32**: mp 113–114 °C; ^{1}H NMR (300 MHz) δ 5.56 (ddd, J = 17.1, 10.2, 9.0 Hz, 1 H), 5.05 (ddd, J = 17.1, 1.3, 0.4 Hz, 1 H), 4.98 (dd, J = 10.2, 1.8 Hz, 1 H), 3.56 (d, J = 8.3 Hz, 1 H), 3.26 (ddd, J = 9.7, 5.1, 1.4 Hz, 1 H), 2.91 (dqd, J = 9.0, 7.1, 2.9 Hz, 1 H), 2.53 (m, 1 H), 2.31 (m, 1 H), 2.24 (d, J = 5.1 Hz, 1 H), 2.23 (dd, J = 14.4, 9.0 Hz, 1 H), 1.90 (m, 1 H), 1.41 (dd, J = 14.4, 2.9 Hz, 1 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.09 (s, 3 H), 1.08 (d, J = 7.1 Hz, 3 H), 1.02 (t, J = 7.2 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 216.0, 140.4, 115.0, 105.6, 83.9, 81.5, 75.3, 42.9, 42.1, 41.5, 35.4, 34.5, 28.5, 26.3, 22.6, 19.4, 17.8, 8.9, 7.7; IR (film) ν 3440, 1700, 1635, 1000, 920 cm^{-1}; mass spectrum (CI) m/z 327.2523 [$C_{19}H_{35}O_4$ (M + 1) requires 327.2535], 311, 269, 251 (base), 213, 195. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.03; H, 10.67. **33**: mp 98–99 °C; ^{1}H NMR (300 MHz) δ 5.67 (m, 1 H), 5.17–5.11 (comp, 2 H), 3.71 (d, J = 9.0 Hz, 1 H), 3.18 (ddd, J = 9.4, 2.0, 2.0 Hz, 1 H), 2.88 (ddq, J = 9.1, 7.1, 3.4 Hz, 1 H), 2.51 (q, J = 7.3 Hz, 2 H), 2.25 (m, 1 H), 2.22 (dd, J = 14.3, 9.1 Hz, 1 H), 1.89 (d, J = 2.5 Hz, 1 H), 1.88 (m, 1 H), 1.42 (dd, J = 14.3, 3.4 Hz, 1 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 1.13 (s, 3 H), 1.06 (d, J = 7.1 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 3 H), 1.01 (t, J = 7.2 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 215.4, 141.6, 116.8, 105.6, 84.2, 81.4, 73.3, 43.4, 42.4, 41.8, 34.3, 34.2, 28.6, 26.3, 21.8, 19.3, 16.2, 9.4, 7.8; IR (film) ν 3460, 1705, 1635, 1000, 925 cm^{-1}; mass spectrum (CI) m/z 327.2516 [$C_{19}H_{35}O_4$ (M + 1) requires 327.2535], 311, 269, 251 (base), 233, 195.

(4*S*)-3-[(2′*S*,3′*R*)-3′-Hydroxy-2′-methylpentanoyl]-4-isopropyl-1,3-oxazolidin-2-one (34). To a solution of (4*S*)-4-isopropyl-3-propionyl-1,3-oxazolidin-2-one (1.01 g, 5.46 mmol) and (*n*-Bu)$_2$BOTf (1.47 mL, 6.00 mmol) in CH_2Cl_2 (18 mL) at –78 °C was added Et_3N (0.95 mL, 6.80 mmol). The reaction mixture was stirred at –78 °C for 30 min, warmed to 0 °C, stirred an additional 1 h, then cooled to –78 °C once again at which time propionaldehyde (0.55 mL, 7.60 mmol) was introduced. The reaction mixture was stirred at –78 °C for 30 min, warmed to 0 °C, stirred an additional 1 h, then quenched with 0.25 M aqueous NaH_2PO_4 (ca. 15 mL) and warmed to room temperature. The mixture was diluted with MeOH (ca. 50 mL) to give a single phase, then cooled to 0 °C and treated with a mixture (1:1) of MeOH (7 mL) and 30% aqueous H_2O_2 (7 mL). The mixture was warmed to room temperature and stirred for 45 min, whereupon the MeOH was removed under reduced pressure. The residual aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give 1.12 g (84%) of **34** as a solid. Recrystallization from hexanes/ether at –20 °C gave colorless plates: mp 37.5–39 °C; ^{1}H NMR (300 MHz) δ 4.47 (dt, J = 8.0, 3.8 Hz, 1 H), 4.28 (t, J = 8.0 Hz, 1 H), 4.21 (dd, J = 8.0, 3.8 Hz, 1 H), 3.84 (ddd, J = 10.9, 5.0, 2.6 Hz, 1 H), 3.78 (dq, J = 7.0, 2.6 Hz, 1 H), 3.00 (d, J = 2.6 Hz, 1 H), 2.34 (m, 1 H), 1.55 (m, 1 H), 1.43 (m, 1 H), 1.23 (d, J = 7.0 Hz, 3 H), 0.96 (t, J = 7.4 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.87 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz) 177.4, 153.4, 72.5, 63.2, 58.1, 41.5, 28.2, 26.5, 17.6, 14.5, 10.6, 10.2; IR ($CHCl_3$) ν 3500, 1795, 1695 cm^{-1}; mass spectrum (CI) m/z 243 (M + 1), 57 (base). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.21; H, 8.73; N, 5.64.

(4*S*)-3-[(2′*S*,3′*S*)-3′-((Triethylsilyl)oxy)-2′-methylpentanoyl]-4-isopropyl-1,3-oxazolidin-2-one (35). To a solution of alcohol **34** (494 mg, 2.03 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMAP (1.49 g, 12.2 mmol) and chlorotriethylsilane (1.36 mL, 8.13 mmol). The reaction mixture was warmed to room temperature over 1 h. Et_2O (75 mL) was then added, and the mixture was washed with H_2O (1 × 10 mL), saturated aqueous $CuSO_4$ (1 × 10 mL), and saturated aqueous NaCl (1 × 10 mL) and dried (Na_2SO_4). The excess solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes/Et_2O (5:1) to give 640 mg (88%) of ether **35** as a colorless oil: ^{1}H NMR (300 MHz) δ 4.37 (ddd, J = 6.8, 3.9, 3.9 Hz, 1 H), 4.24–4.17 (comp, 2 H), 3.97–3.83 (comp, 2 H), 2.37 (m, 1 H), 1.51 (m, 2 H), 1.17 (d, J = 6.7 Hz, 3 H), 0.93 (t, J = 7.8 Hz, 9 H), 0.90 (t, J = 6.4 Hz, 3 H), 0.85 (d, J = 7.2 Hz, 6 H), 0.56 (q, J = 7.8 Hz, 6 H); ^{13}C NMR (75 MHz) δ 175.5, 153.6, 74.1, 63.3, 58.9, 42.6, 28.6, 28.5, 18.0, 14.8, 12.7, 9.3, 6.8, 5.3; IR (film) ν 1800, 1720, 1410, 1260 cm^{-1}; mass spectrum (CI) m/z 358.2407 [$C_{18}H_{36}NO_4Si$ (M + 1) requires 358.2414] (base), 328, 226. Anal. Calcd for $C_{16}H_{35}NO_4Si$: C, 60.46; H, 9.87; N, 3.92. Found: C, 60.19; H, 9.95; N, 3.80.

(2*S*,3*R*)-2-Methyl-3-[(triethylsilyl)oxy]pentanoic Acid Benzyl Ester. To a solution of benzyl alcohol (1.75 mL, 17.0 mmol) in THF (7 mL) at 0 °C was added *n*-butyllithium (5.40 mL, 2.53 M solution in hexanes). After the mixture was stirred at 0 °C for 30 min, a portion (ca. 6 mL) of this solution was transferred to a solution of imide **35** (605 mg, 1.70 mmol) in THF (7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature, and stirred an additional 30 min, whereupon the reaction was quenched with saturated aqueous NH_4Cl (ca. 5 mL). The mixture was diluted with Et_2O (ca. 50 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (20:1) to provide 470 mg (83%) of the ester as an oil: ^{1}H NMR (300 MHz) δ 7.40–7.30 (comp, 5 H), 5.13 (d, J = 12.5 Hz, 1 H), 5.08 (d, J = 12.5 Hz, 1 H), 3.96 (q, J = 5.6 Hz, 1 H), 2.59 (qd, J = 7.0, 5.6 Hz, 1 H), 1.49 (m, 2 H), 1.15 (d, J = 7.0 Hz, 3 H), 0.93 (t, J = 7.8 Hz, 9 H), 0.86 (t, J = 7.5 Hz, 3 H), 0.56 (q, J = 7.8 Hz, 6 H); ^{13}C NMR (75 MHz) δ 174.9, 136.3, 128.4, 128.1, 128.0, 74.6, 66.0, 44.6, 28.1, 11.6, 9.4, 6.8, 5.3; IR (film) ν 3070, 3040, 1745, 1470 cm^{-1}; mass spectrum (CI) m/z 337 (M + 1) (base), 307.1731 [$C_{17}H_{27}O_3Si$ (M – C_2H_5) requires 307.1730], 119.

(2*R*,3*R*)-2-Methyl-3-[(triethylsilyl)oxy]pentanol (37). To a solution of the above ester (410 mg, 1.22 mmol) in Et_2O (12 mL) at –78 °C was added diisobutylaluminum hydride (2.91 mL, 1 M solution in hexanes). After it was stirred at –78 °C for 30 min, the reaction mixture was warmed to 0 °C and stirred for an additional 30 min; MeOH (1.5 mL) was added, and the mixture was allowed to warm to room temperature. The mixture was added to saturated aqueous potassium sodium tartarate (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (4 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (elution with 4:1 pentane/Et_2O) to give 260 mg (92%) of **37** as a clear colorless oil: ^{1}H NMR (300 MHz) δ 3.72–3.64 (comp, 2 H), 3.52 (m, 1 H), 2.72 (m, 1 H), 1.93 (m, 1 H), 1.48 (m, 2 H), 0.95 (t, J = 8.0 Hz, 9 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.80 (d, J = 7.1 Hz, 3 H), 0.60 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (75 MHz) δ 77.1, 66.2, 39.5, 25.9, 11.5, 10.6, 6.8, 5.3; IR (film) ν 3350, 1390, 1255 cm^{-1};

mass spectrum (CI) m/z 233.1932 [$C_{12}H_{29}O_2Si$ (M + 1) requires 233.1937] (base), 203, 133.

(2S,3R)-2-Methyl-3-[(triethylsilyl)oxy]pentanal (39). DMSO (78 μL, 1.10 mmol) was added to a solution of oxalyl chloride (48 μL, 0.55 mmol) in CH_2Cl_2 (0.5 mL) at −60 °C and the solution stirred for 15 min, whereupon a solution of primary alcohol **37** (64 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) was added. After 15 min, triethylamine (0.23 mL, 1.66 mmol) was added, and the reaction was warmed to room temperature over a period of 20 min. The reaction mixture was added to Et_2O (ca. 15 mL), washed with saturated aqueous $NaHCO_3$ (1 × 4 mL), saturated aqueous $CuSO_4$ (1 × 4 mL), and saturated NaCl (1 × 2 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with pentane/Et_2O (20:1) to provide 40 mg (63%) of aldehyde **39** as a colorless oil: ^{1}H NMR (300 MHz) δ 9.75 (d, J = 1.0 Hz, 1 H), 4.03 (td, J = 6.6, 3.7 Hz, 1 H), 2.44 (qdd, J = 6.9, 3.7, 1.0 Hz, 1 H), 1.50 (m, 2 H), 1.03 (d, J = 6.9 Hz, 3 H), 0.91 (t, J = 7.9 Hz, 9 H), 7.5 (t, J = Hz, 3 H), 0.56 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (75 MHz) δ 205.1, 73.6, 51.0, 27.6, 10.0, 7.7, 6.8, 5.2; IR (film) ν 1740, 1400, 1265 cm^{-1}; mass spectrum (CI) m/z 231 (M + 1), 201, 173 (base), 133.

(3R,4R,5S,6R,8R,10R,11R,12S,13R,14S)-5,13-Dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethyl-3-[(triethylsilyl)oxy]hexadec-15-en-7-one (41) and (3R,4R,5R,6S,8R,10R,11R,12S,13R,14S)-5,13-Dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethyl-3-[(triethylsilyl)oxy]hexadec-15-en-7-one (43). To a solution of lithium hexamethyldisilazide (1.01 mmol) in THF (1 mL) at −78 °C was added a solution of ketone **32** (110 mg, 0.34 mmol) in THF (1.5 mL). After the mixture was stirred at −78 °C for 3 h, a solution of the aldehyde **39** (140 mg, 0.61 mmol) in THF (1.5 mL) was added and the mixture was stirred at −78 °C for an additional 30 min. The reaction was quenched at −78 °C with saturated aqueous NH_4Cl (1 mL), and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/acetone (15:1) to afford 46 mg (42%) of recovered **32**, 64 mg (34%, 59% based upon recovered **32**) of desired aldol adduct **41**, and 24 mg (13%, 22% based upon recovered **32**) of the minor adduct **43**, each as colorless oils. **41**: ^{1}H NMR (500 MHz) δ 5.56 (ddd, J = 17.2, 10.3, 8.9 Hz, 1 H), 5.05 (ddd, J = 17.2, 1.7, 0.8 Hz, 1 H), 4.98 (dd, J = 10.3, 1.8 Hz, 1 H), 4.02 (ddd, J = 9.8, 2.0, 1.4 Hz, 1 H), 3.87 (ddd, J = 7.4, 5.7, 2.2 Hz, 1 H), 3.73 (d, J = 1.5 Hz, 1 H), 3.64 (d, J = 8.1 Hz, 1 H), 3.25 (ddd, J = 5.0, 4.9, 1.3 Hz, 1 H), 3.13 (qdd, J = 8.3, 7.2, 3.4 Hz, 1 H), 2.78 (qd, J = 7.0, 2.0 Hz, 1 H), 2.30 (m, 1 H), 2.20 (dd, J = 14.3, 8.3 Hz, 1 H), 1.94 (d, J = 5.1 Hz, 1 H), 1.90 (dqd, J = 8.1, 6.8, 1.5 Hz, 1 H), 1.70 (dqd, J = 9.8, 7.0, 2.3 Hz, 1 H), 1.59–1.50 (comp, 2 H), 1.42 (dd, J = 14.3, 3.4 Hz, 1 H), 1.32 (s, 3 H), 1.23 (s, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.10 (s, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.94 (t, J = 8.0 Hz, 9 H), 0.90 (t, J = 7.4 Hz, 3 H), 0.77 (d, J = 7.0 Hz, 3 H), 0.60 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz) δ 218.3, 140.4, 115.2, 105.8, 84.4, 81.5, 76.3, 75.5, 72.3, 48.0, 43.6, 42.2, 39.5, 39.4, 35.3, 28.6, 26.4, 25.8, 22.3, 19.7, 17.7, 11.4, 11.0, 8.9, 7.8, 6.9, 5.1; IR (film) ν 3450, 1700, 1640, 1380, 1010, 920 cm^{-1}; mass spectrum (CI) m/z 556.4163 ($C_{31}H_{60}O_6Si$ requires 556.4159), 499, 481, 451, 349, 269, 251, 201, 173 (base). **43**: ^{1}H NMR (500 MHz) δ 5.56 (ddd, J = 17.1, 10.2, 8.9 Hz, 1 H), 5.06 (ddd, J = 17.1, 1.7, 0.8 Hz, 1 H), 4.99 (dd, J = 10.2, 1.7 Hz, 1 H), 4.00 (ddd, J = 6.0, 4.8, 2.6 Hz, 1 H), 3.70 (ddd, J = 8.4, 6.0, 2.4 Hz, 1 H), 3.68 (d, J = 8.1 Hz, 1 H), 3.28 (m, 1 H), 3.22 (d, J = 2.6 Hz, 1 H), 3.06 (pd, J = 7.1, 4.0 Hz, 1 H), 3.01 (qd, J = 6.9, 4.8 Hz, 1 H), 2.31 (m, 1 H), 2.25 (dd, J = 14.4, 7.1 Hz, 1 H), 2.01 (d, J = 5.3 Hz, 1 H), 1.91 (dqd, J = 8.1, 6.8, 1.6 Hz, 1 H), 1.65 (qdd, J = 6.9, 6.0, 2.4 Hz, 1 H), 1.58–1.46 (comp, 2 H), 1.37 (dd, J = 14.4, 4.0 Hz, 1 H), 1.34 (s, 3 H), 1.25 (s, 3 H), 1.14 (d, J = 7.1 Hz, 3 H), 1.11 (s, 3 H), 1.10 (d, J = 6.9 Hz, 1 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.96 (t, J = 8.0 Hz, 9 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.81 (t, J = 7.5 Hz, 3 H), 0.60 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz) δ 217.3, 140.2, 115.3, 106.1, 84.4, 81.9, 75.6, 75.2, 73.4, 48.2, 42.2, 42.0, 40.3, 38.1, 35.4, 28.4, 27.2, 26.4, 22.2, 19.9, 17.7, 10.8, 10.3, 8.9, 8.5, 7.0, 5.5; IR (film) ν 3060, 1705, 1640, 1385, 990, 920 cm^{-1}; mass spectrum (CI) m/z 557.4235 [$C_{31}H_{61}O_6Si$ (M + 1) requires 557.4237], 251, 201, 173 (base).

(2R,3S,4S,5R,6R,8R,10R,11S,12R,13R)-13-[(Triethylsilyl)oxy]-3,11-dihydroxy-5,6-(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyl-9-oxopentadecanoic Acid Methyl Ester (45). A solution of **41** (11 mg, 0.02 mmol) and Sudan III (1 mg) in EtOAc (2 mL) at −78 °C was treated with ozone until the dye began to fade, at which time 2,3-dimethyl-2-butene (0.15 mL, 1.3 mmol) was added all in one portion. The reaction mixture was warmed to room temperature over 30 min and then concentrated under reduced pressure. The residue was dissolved in 10% aqueous THF (2 mL), magnesium monoperoxyphthalate (40 mg, 0.08 mmol) was added, and the resulting solution was heated at reflux for 4 h. After it was cooled to room temperature, the mixture was extracted with CH_2Cl_2 (3 × 5 mL); the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 11 mg of the crude acid. The acid was dissolved in Et_2O (1 mL) at 0 °C and treated with excess diazomethane. The solvent was then removed, and the residue was purified by flash chromatography, eluting with hexanes/acetone (7:1) to give 7 mg (60% overall yield) of **45**: ^{1}H NMR (500 MHz) δ 4.05 (d, J = 9.9 Hz, 1 H), 3.88 (s, 1 H), 3.84 (ddd, J = 7.7, 5.5, 2.3 Hz, 1 H), 3.66 (comp, 1 H), 3.65 (s, 3 H), 3.61 (d, J = 8.6 Hz, 1 H), 3.15 (dqd, J = 7.9, 7.0, 3.2, 1 H), 2.76 (qd, J = 6.9, 1.8 Hz, 1 H), 2.63 (dq, J = 9.3, 6.9 Hz, 1 H), 2.36 (d, J = 5.7 Hz, 1 H), 2.22 (dd, J = 14.4, 7.9 Hz, 1 H), 1.70 (comp, 2 H), 1.54 (comp, 2 H), 1.47 (dd, J = 14.4, 3.2 Hz, 1 H), 1.32 (s, 3 H), 1.25 (d, J = 6.9 Hz, 3 H), 1.22 (s, 3 H), 1.13 (d, J = 7.0 Hz, 3 H), 1.11 (s, 3 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.93 (t, J = 7.9 Hz, 9 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.59 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (125 MHz) δ 218.7, 175.4, 105.7, 83.4, 81.5, 72.4, 51.7, 48.1, 43.6, 43.4, 39.6, 39.4, 36.4, 28.6, 26.5, 25.7, 22.0, 19.8, 14.9, 11.5, 11.1, 9.7, 7.8, 6.9, 5.0; IR (film) 3500, 3000, 1750, 1720, 1480, 1400, 1030 cm^{-1}; mass spectrum (CI) m/z 589 (M + 1) (base), 531, 301, 283, 173.

(3S,4R,5S,6R,7R,9R,10S,11S,12R,13R,14R)-14-[(Triethylsilyl)oxy]-6,7-(isopropylidenedioxy)-3,5,7,9,11,13-hexamethylhexadec-1-ene-4,10,-12-triol. A solution of ketone **41** (20.0 mg, 0.04 mmol) in CH_3CN (1 mL) was added to a solution of $Me_4NBH(OAc)_3$ (284 mg, 1.08 mmol) in a mixture of CH_3CN (0.5 mL) and HOAc (0.5 mL) at −40 °C. After the mixture was stirred at −40 °C for 2 h, TLC showed the presence of unreacted **41**, and an additional amount of $Me_4NBH(OAc)_3$ (140 mg, 0.53 mmol) was added. The reaction mixture was stirred at −40 °C for 3 h, quenched with saturated $NaHCO_3$ (ca. 2 mL), and warmed to room temperature. Solid $NaHCO_3$ was added to neutralize excess HOAc, then the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/acetone (7:1) to afford 8.0 mg (40%) of the desired 9(*S*)-alcohol as a colorless oil together with 1.5 mg (7%) of the 9(*R*)-epimer: ^{1}H NMR (500 MHz) δ 5.59 (ddd, J = 17.1, 10.2, 9.0 Hz, 1 H), 5.07 (dd, J = 17.1, 1.6 Hz, 1 H), 4.99 (dd, J = 10.2, 1.6 Hz, 1 H), 4.51 (s, 1 H), 4.08 (d, J = 10.3 Hz, 1 H), 3.88 (d, J = 8.2 Hz, 1 H), 3.75 (d, J = 4.4 Hz, 1 H), 3.72 (comp, 2 H), 3.33 (dd, J = 9.0, 4.4 Hz, 1 H), 3.19 (d, J = 5.1 Hz, 1 H), 2.33 (m, 1 H), 2.14 (m, 1 H), 1.91 (m, 2 H), 1.87 (dd, J = 14.9, 5.3 Hz, 1 H), 1.67 (m, 1 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.15 (s, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 3 H), 0.98 (t, J = 8.0 Hz, 9 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.73 (d, J = 7.1 Hz, 3 H), 0.64 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz) δ 140.6, 114.9, 105.6, 82.7, 80.2, 76.6, 75.0, 73.3, 42.1, 41.8, 40.0, 35.7, 35.6, 32.2, 28.7, 26.9, 23.9, 23.0, 17.9, 16.6, 13.5, 11.5, 10.5, 9.0, 6.8, 4.9; mass spectrum (CI) 559 (M + 1, base).

(2S,3R,4S,5R,6R,8R,9S,10S,11S,12S,13R)-3,5,6,9,11,13-Hexahydroxy-2,4,6,8,10,12-hexamethylpentadecanol (48). A solution of the olefin from the preceding experiment (7 mg, 0.013 mmol) and Sudan III (1 mg) in EtOAc (2 mL) at −78 °C was treated with ozone until the dye began to fade, whereupon 2,3-dimethyl-2-butene (0.15 mL, 1.3 mmol) was added in one portion. The reaction mixture was warmed to room temperature over 30 min and concentrated under reduced pressure. The oily residue was immediately dissolved in THF (2 mL), cooled to 0 °C, and treated with $LiAlH_4$ (10 mg, 0.26 mmol). After it was stirred at 0 °C for 30 min, the reaction mixture was quenched by the successive addition of H_2O (10 μL), 10% aqueous NaOH (10 μL), and H_2O (30 μL) then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/acetone (3:1) to give 3.5 mg of primary alcohol that was dissolved in a mixture (1:1) of MeOH/H_2O (2 mL) that previously had been saturated with NH_2-OH·HCl, and then KH_2PO_4 (40 mg, 0.29 mmol) was added. The resulting solution was heated at reflux for 3 h, cooled to room temperature, and concentrated under reduced pressure. The aqueous residue was neutralized with solid $NaHCO_3$ and extracted with EtOAc (5 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (85:15) to furnish 1.5 mg (60%) of synthetic polyol **48** as an oil; this substance was identical with the sample prepared from natural erythronolide B (**49**) as outlined below: ^{1}H NMR (500

MHz, acetone-d_6) δ 4.11 (m, 1 H), 4.00 (br s, 1 H), 3.96 (br s, 1 H), 3.86 (d, J = 4.1 Hz, 1 H), 3.75 (comp, 3 H), 3.63 (comp, 2 H), 3.52 (comp, 4 H), 1.86 (dd, J = 14.5, 5.6 Hz, 1 H), 1.78 (m, 1 H), 1.71 (comp, 2 H), 1.49 (m, 1 H), 1.42 (comp, 2 H), 1.31 (dd, J = 14.5, 5.6 Hz, 1 H), 1.19 (s, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.74 (d, J = 7.0 Hz, 3 H) (some OH's not detected); ^{13}C NMR (125 MHz, acetone-d_6) δ 81.1, 79.1, 76.9, 75.8, 75.4, 72.7, 65.8, 44.2, 41.0, 39.0, 37.8, 36.3, 31.6, 26.8, 23.5, 16.2, 13.4, 11.6, 10.1, 8.0.

From erythronolide B (**49**): To a solution of **49** (75 mg, 0.19 mmol) in toluene (2.5 mL) and *t*-BuOH (0.5 mL) at 75 °C was added $NaBH_4$ (212 mg, 5.58 mmol) in four portions, and the reaction mixture was heated at 75 °C for 45 min. The mixture was cooled to room temperature and quenched with an ice–pH = 7 buffer mixture (ca. 3 mL). The aqueous mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (20:1) to give 55 mg (73%) of 9(*S*)-dihydroerythronolide B and 3 mg (4%) of 9(*R*)-dihydroerythronolide B, both as oils. 9(*S*)-Dihydroerythronolide B: ^{1}H NMR (300 MHz, acetone-d_6) δ 5.22 (dd, J = 9.4, 4.3 Hz, 1 H), 4.32 (d, J = 2.4 Hz, 1 H), 4.26 (d, J = 3.4 Hz, 1 H), 4.13 (d, J = 5.9 Hz, 1 H), 4.12 (s, 1 H), 3.92 (d, J = 1.5 Hz, 1 H), 3.77 (d, J = 10.2 Hz, 1 H), 3.53 (s, 1 H), 3.48 (m, 1 H), 2.99 (dd, J = 8.7, 2.2 Hz, 1 H), 2.85 (comp, 2 H), 2.71 (dq, J = 10.3, 6.7 Hz, 1 H), 1.93 (m, 1 H), 1.80 (m, 1 H), 1.74 (dd, J = 4.6, 2.5 Hz, 1 H), 1.65 (comp, 2 H), 1.55 (m, 1 H), 1.23 (d, J = 6.4 Hz, 3 H), 1.21 (s, 3 H), 1.20 (d, J = 6.2 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H), 0.80 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 178.0, 82.8, 81.2, 81.0, 76.3, 71.4, 44.6, 41.6, 41.5, 37.1, 34.8, 33.0, 27.2, 26.2, 18.0, 15.0, 10.9, 9.1, 6.4.

To a solution of 9(*S*)-dihydroerythronolide B (27 mg, 0.07 mmol) in THF (4 mL) at 0 °C was added $LiAlH_4$ (254 mg, 6.68 mmol). The reaction mixture was warmed to room temperature over 15 min then heated at reflux for 3.5 h. The suspension was cooled to 0 °C and treated successively with H_2O (254 μL), 10% aqueous NaOH (254 μL), and H_2O (762 μL). The organic mixture was then dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (85:15) to give 15 mg (56%) of natural erythronolide B polyol (**48**) as an oil.

(4*S*,2′*S*,3′*R*)-3-[3′-((Benzyloxy)methoxy)-2′-methylpentanoyl]-4-isopropyl-1,3-oxazolidin-2-one (36). To a solution of secondary alcohol **34** (968 mg, 3.98 mmol) and benzyl chloromethyl ether (1.66 mL, 12.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added *i*-Pr_2NEt (1.38 mL, 7.97 mmol) dropwise. The reaction was stirred at 0 °C for 10 min and then at room temperature for 45 h. The excess solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes/EtOAc (5:1) to provide 1.31 g (91%) of **36** as a white solid: mp 64–64.5 °C; ^{1}H NMR (500 MHz) δ 7.33–7.24 (comp, 5 H), 4.75 (d, J = 7.3 Hz, 1 H), 4.74 (d, J = 7.3 Hz, 1 H), 4.60 (d, J = 11.9 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H), 4.12 (ddd, J = 8.0, 3.8, 2.4 Hz, 1 H), 4.04 (dd, J = 9.0, 2.4 Hz, 1 H), 3.99 (qd, J = 6.8, 4.5 Hz, 1 H), 3.96 (dd, J = 9.0, 8.0 Hz, 1 H), 3.83 (td, J = 6.2, 4.5 Hz, 1 H), 2.32 (dd, J = 7.0, 3.8 Hz, 1 H), 1.64–1.58 (m, 2 H), 1.21 (d, J = 6.8 Hz, 3 H), 0.94 (t, J = 7.5 Hz, 3 H), 0.80 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz) δ 174.9, 153.9, 138.0, 128.3, 127.5, 127.4, 94.5, 80.0, 69.8, 63.1, 58.9, 41.0, 28.2, 25.6, 17.9, 14.5, 11.5, 10.0; IR (film) ν 3080, 3050 1785, 1710 cm^{-1}; mass spectrum (CI) m/z 364.2119 [$C_{20}H_{30}NO_5$ (M + 1) requires 364.2124], 364, 256 (base), 226, 130, 91. Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.18; H, 8.13; N, 3.80.

(2*R*,3*R*)-3-[(Benzyloxy)methoxy]-2-methylpentanol (38). A solution of $LiBH_4$ (3.46 mmol, 1.73 mL of a 2 M solution in THF) was added dropwise to a solution of **36** (1.14 g, 3.15 mmol) in Et_2O (30 mL) containing H_2O (62 μL, 3.47 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The excess hydride was quenched by adding saturated NH_4Cl (ca. 5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the resulting residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to provide 694 mg (92%) of **38** as a colorless oil: ^{1}H NMR (300 MHz) δ 7.34–7.26 (comp, 5 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.67 (d, J = 11.8 Hz, 1 H), 4.62 (d, J = 11.8 Hz, 1 H), 3.63–3.61 (comp, 2 H), 3.52 (ddd, J = 11.2, 7.2, 5.4 Hz, 1 H), 2.56 (dd, J = 7.2, 4.9 Hz, 1 H), 2.02–1.89 (m, 1 H), 1.73–1.43 (m, 2 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz) δ 137.5, 128.5, 127.8, 127.8, 94.5, 81.3, 70.0, 65.4, 37.6, 24.0, 10.8, 10.5; IR (film) ν 3400 cm^{-1}; mass spectrum (CI) m/z 239.1650 [$C_{14}H_{23}O_3$ (M + 1) requires 239.1647], 221, 131 (base), 108, 101.

(2*S*,3*R*)-3-[(Benzyloxy)methoxy]-2-methylpentanal (40). DMSO (0.41 mL, 5.83 mmol) was added to a solution of freshly distilled oxalyl chloride (0.25 mL, 2.92 mmol) in CH_2Cl_2 (12 mL) at –60 °C. After the mixture was stirred for 15 min at –60 °C, a solution of the alcohol **38** (347 mg, 1.46 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred at –60 °C for 15 min. After the mixture was cooled to –70 °C, *N*-methylmorpholine (0.64 mL, 5.83 mmol) was added, and the mixture was allowed to warm to room temperature over a period of 30 min. The resulting white suspension was diluted with Et_2O (ca. 25 mL) and then passed through a plug of silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes/Et_2O (6:1) to give 312 mg (91%) of aldehyde **40** as a clear, colorless oil: ^{1}H NMR (300 MHz) δ 9.78 (s, 1 H), 7.36–7.25 (comp, 5H), 4.80 (d, J = 7.2 Hz, 1 H), 4.75 (d, J = 7.2 Hz, 1 H), 4.58 (d, J = 11.8 Hz, 1 H), 4.53 (d, J = 11.8 Hz, 1 H), 4.01 (ddd, J = 6.8, 6.8, 3.5 Hz, 1 H), 2.56 (qd, J = 7.0, 3.5 Hz, 1 H), 1.80–1.50 (m, 2 H), 1.11 (d, J = 7.0 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 204.2, 137.8, 128.4, 127.8, 127.7, 94.2, 78.8, 69.9, 49.5, 24.9, 10.2, 7.9; IR (film) ν 1740 cm^{-1}; mass spectrum (CI) m/z 237.1490 [$C_{14}H_{21}O_3$ (M + 1) requires 237.1491], 149, 129 (base).

(3*R*,4*R*,5*S*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*,14*S*)-3-[(Benzyloxy)methoxy]-5,-13-dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethylhexadec-15-en-7-one (42) and (3*R*,4*R*,5*R*,6*S*,8*R*,10*R*,11*R*,12*S*,13*R*,14*S*)-3-[(Benzyloxy)methoxy]-5,13-dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethylhexadec-15-en-7-one (44). A solution of ketone **32** (58 mg, 0.18 mmol) in THF (0.6 mL) was added to a solution of lithium hexamethyldisilazide (0.53 mmol) in THF (0.7 mL) at –78 °C. After the mixture was stirred at –78 °C for 2 h, a solution of freshly prepared aldehyde **40** (130 mg, 0.55 mmol) in THF (0.6 mL) was added, and the mixture was stirred at –78 °C for 2 h. The reaction was quenched by adding saturated NH_4Cl (ca. 2 mL), and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 6 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (3:1) to provide 62 mg (62%) of the desired aldol adduct **42** and 10 mg (17%) of the minor product **44** as colorless oils, along with 10 mg (10%) of recovered ketone **32**. **42**: ^{1}H NMR (500 MHz) δ 7.25–7.34 (comp, 5 H), 5.52 (ddd, J = 17.2, 10.2, 9.0 Hz, 1 H), 5.03 (ddd, J = 17.2, 1.7, 0.6 Hz, 1 H), 4.97 (dd, J = 10.3, 1.7 Hz, 1 H), 4.83 (d, J = 6.8 Hz, 1 H), 4.77 (d, J = 6.8 Hz, 1 H), 4.64 (d, J = 11.8 Hz, 1 H), 4.60 (d, J = 11.8 Hz, 1 H), 4.04 (m, 1 H), 3.87 (ddd, J = 8.0, 6.5, 2.1 Hz, 1 H), 3.72 (d, J = 2.6 Hz, 1 H), 3.68 (d, J = 8.4 Hz, 1 H), 3.19 (dd, J = 9.8, 2.6 Hz, 1 H), 3.15 (dqd, J = 7.8, 6.0, 3.8 Hz, 1 H), 2.80 (qd, J = 7.0, 2.0 Hz, 1 H), 2.28 (ddq, J = 9.8, 9.0, 6.6 Hz, 1 H), 2.18 (d, J = 5.0 Hz, 1 H), 2.15 (dd, J = 14.4, 7.8 Hz, 1 H), 1.88 (ddd, J = 8.4, 6.7, 1.5 Hz, 1 H), 1.74 (dqd, J = 9.9, 7.0, 2.1 Hz, 1 H), 1.71 (dqd, J = 13.8, 8.0, 7.4 Hz, 1 H), 1.50 (dqd, J = 13.8, 7.4, 6.5 Hz, 1 H), 1.43 (dd, J = 14.4, 3.8 Hz, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.08 (s, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H), 0.82 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 218.7, 140.3, 137.6, 128.5, 127.9 127.8, 115.2, 105.8, 95.2, 84.2, 81.6, 80.9, 75.4, 72.1, 70.0, 47.5, 43.1, 42.2, 39.4, 38.1, 35.3, 28.6, 26.5, 25.0, 22.4, 19.8, 17.7, 10.8, 10.3, 9.1, 8.2; IR (film) ν 3480, 3100, 3060, 1735, 1670, 920 cm^{-1}; mass spectrum (CI) m/z 563.3958 [$C_{33}H_{55}O_7$ (M + 1) requires 563.3948], 438, 379, 349, 311, 295, 251 (base), 165, 149, 129. **44**: ^{1}H NMR (500 MHz) δ 7.34–7.26 (comp, 5 H), 5.54 (ddd, J = 17.2, 10.2, 8.9 Hz, 1 H), 5.05 (dd, J = 17.2, 1.2 Hz, 1 H), 4.98 (dd, J = 10.2, 1.7 Hz, 1 H), 4.79 (s, 2 H), 4.65 (d, J = 12.0 Hz, 1 H), 4.59 (d, J = 12.0 Hz, 1 H), 4.05 (m, 1 H), 3.68 (d, J = 8.2 Hz, 1 H), 3.55 (td, J = 6.9, 2.3 Hz, 1 H), 3.26–3.24 (comp, 2 H), 3.05 (m, 1 H), 3.03 (qd, J = 6.9, 3.9 Hz, 1 H), 2.30 (m, 1 H), 2.24 (dd, J = 14.4, 7.7 Hz, 1 H), 1.94 (d, J = 1.0 Hz, 1 H), 1.90 (dqd, J = 8.2, 6.7, 1.5 Hz, 1 H), 1.76 (m, 1 H), 1.69 (m, 1 H), 1.54 (m, 1 H), 1.34 (dd, J = 14.4, 3.7 Hz, 1 H), 1.33 (s, 3 H), 1.24 (s, 3 H), 1.09 (d, J = 6.9 Hz, 3 H), 1.09 (s, 3 H), 1.08 (d, J = 7.1 Hz, 3 H), 1.08 (d, J = 7.3 Hz, 3 H,), 1.01 (d, J = 6.9 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 217.8, 140.2, 137.7, 128.4, 127.7, 127.6, 115.3, 106.1, 94.0, 84.4, 82.1, 81.8, 75.6, 72.6, 69.8, 48.0, 42.5, 42.2, 40.3, 37.4, 35.4, 28.4, 26.3, 24.5, 22.1, 19.9, 17.6, 10.5, 10.1, 9.7, 8.9; IR (film) ν 3440, 3060, 3030, 1700, 1645, 990, 920 cm^{-1}; mass spectrum (CI) m/z 563.3947 [$C_{33}H_{55}O_7$ (M + 1) requires 563.3948], 455, 154 (base), 136.

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*S*,12*R*,13*R*)-13-[(Benzyloxy)methoxy]-3,-11-dihydroxy-5,6-(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyl-9-oxopentadecanoic Acid Methyl Ester (46). Ozone was passed over the surface of a solution of olefin **42** (15 mg, 0.027 mmol) in anhydrous MeOH (3 mL) containing a small crystal of Sudan III at −95 °C until the red color began to fade. 2,3-Dimethyl-2-butene (0.15 mL, 1.3 mmol) was immediately added, and the resulting solution was stirred for 20 min at 0 °C. The excess solvents were removed under reduced pressure, and the residue was azotropically dried with benzene (3 × 5 mL). The residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C, and then triethylamine (7.4 μL, 0.053 mmol) and acetic anhydride (7.5 μL, 0.08 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 20 min and at room temperature for 1 h, whereupon saturated $NaHCO_3$ (ca. 3 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to give 9.6 mg (61%) of methyl ester **46** along with 3.4 mg (24%) of the corresponding aldehyde: ^{1}H NMR (500 MHz) δ 7.33–7.25 (comp, 5 H), 4.83 (d, J = 6.8 Hz, 1 H), 4.76 (d, J = 6.8 Hz, 1 H), 4.64 (d, J = 11.9 Hz, 1 H), 4.60 (d, J = 11.9 Hz, 1 H), 4.05 (br d, J = 9.8 Hz, 1 H), 3.86 (ddd, J = 7.4, 6.4, 2.2 Hz, 1 H), 3.74 (br s, 1 H), 3.65 (comp, 1 H), 3.64 (s, 3 H), 3.64 (d, J = 8.4 Hz, 1 H), 3.15 (dqd, J = 7.9, 7.1, 3.7 Hz, 1 H), 2.81 (qd, J = 7.1, 2.0 Hz, 1 H), 2.63 (dq, J = 9.4, 6.8 Hz, 1 H), 2.48 (br s, 1 H,), 2.18 (dd, J = 14.4, 7.9 Hz, 1 H), 1.76 (dqd, J = 9.8, 7.0, 2.2 Hz, 1 H), 1.71 (m, 1 H), 1.67 (dqd, J = 8.4, 6.8, 1.6 Hz, 1 H), 1.51 (m, 1 H), 1.46 (dd, J = 14.4, 3.7 Hz, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.12 (d, J = 7.1 Hz, 3 H), 1.11 (s, 3 H), 1.10 (d, J = 7.1 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H), 0.82 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 218.8, 175.4, 137.6, 128.4, 127.8, 127.7, 105.7, 95.1, 83.4, 81.6, 81.0, 72.4, 72.0, 69.9, 51.7, 47.4, 43.6, 42.8, 39.4, 38.0, 36.4, 28.6, 26.5, 24.9, 22.1, 19.8, 14.9, 10.3, 9.7, 8.2; IR (film) ν 3450, 1735, 1710, 1460, 1380, 1250, 1175 cm^{-1}; mass spectrum (CI) m/z 595.3831 [$C_{33}H_{55}O_9$ (M + 1) requires 595.3846], 429, 411, 289, 248 (base), 221.

(3*S*,4*R*,5*S*,6*R*,7*R*,9*R*,10*S*,11*S*,12*R*,13*R*,14*R*)-14-[(Benzyloxy)methoxy]-6,7-(isopropylidenedioxy)-3,5,7,9,11,13-hexamethylhexadecene-4,10,12-triol. Anhydrous acetic acid (1.3 mL) was slowly added to a solution of $Me_4NBH(OAc)_3$ (340 mg, 1.29 mmol) in CH_3CN (1.3 mL). After it was stirred at room temperature for 40 min, the solution was cooled to −45 °C, and **42** (107 mg, 0.19 mmol) in CH_3CN (1.3 mL) was added. The reaction was then stirred between −40 and −50 °C for 8 h and warmed to 10 °C over a period of 8 h. The reaction mixture was poured into saturated $NaHCO_3$ (20 mL), and the mixture was stirred at room temperature for 30 min. The aqueous mixture was extracted with CH_2Cl_2 (4 × 20 mL), and the combined extracts were washed with saturated NaCl (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/acetone (6:1) to give 97 mg (91%) of the desired 9(*S*)-alcohol as a colorless oil. The structure of this triol was confirmed by its conversion into the synthetic polyol **48** using the same procedure described previously for transforming **41** into **48**: ^{1}H NMR (500 MHz) δ 7.33–7.25 (comp, 5 H), 5.54 (ddd, J = 17.2, 10.3, 8.9 Hz, 1 H), 5.05 (ddd, J = 17.2, 1.6, 0.6 Hz, 1 H), 4.97 (dd, J = 10.3, 1.8 Hz, 1 H), 4.84 (d, J = 6.9 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.70 (d, J = 12.0 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.06 (ddd, J = 10.2, 2.1, 2.1 Hz, 1 H), 3.81 (d, J = 7.9 Hz, 1 H), 3.79–3.74 (comp, 2 H), 3.38 (d, J = 4.0 Hz, 1 H), 3.31 (dd, J = 9.5, 3.3 Hz, 1 H), 2.61 (d, J = 4.0 Hz, 1 H), 2.03 (m, 1 H), 2.09 (m, 1 H), 1.93–1.88 (comp, 2 H), 1.78 (dd, J = 14.8, 6.9 Hz, 1 H), 1.74 (m, 1 H), 1.66 (m, 1 H), 1.53 (dd, J = 14.8, 6.1 Hz, 1 H), 1.53 (m, 1 H), 1.36 (s, 3 H), 1.30 (s, 3 H), 1.13 (s, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H,), 0.87 (d, J = 7.0 Hz, 3 H), 0.78 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 140.4, 137.5, 128.5, 127.8, 127.7, 115.1, 105.8, 94.7, 83.6, 83.0, 82.6, 75.6, 75.2, 72.0, 70.1, 42.5, 42.1, 37.9, 35.9, 35.4, 31.8, 28.7, 26.8, 23.9, 22.2, 17.8, 15.8, 11.5, 11.0, 10.0, 8.9; IR (film) ν 3405, 3080, 3020, 1640, 920 cm^{-1}; mass spectrum (CI) m/z 565.4104 [$C_{33}H_{57}O_7$ (M + 1) requires 565.4104], 457, 399, 381 (base), 297.

(3*S*,4*R*,5*S*,6*R*,7*R*,9*S*,10*S*,11*S*,12*S*,13*S*,14*R*)-14-[(Benzyloxy)methoxy]-10,12-(carbonyldioxy)-3,5,7,9,11,13-hexamethyl-4-[((*N*-imidazolyl)carbonyl)oxy]-6,7-(isopropylidenedioxy)hexadecene (50). A solution of the triol obtained by reduction of **42** (45 mg, 0.08 mmol) and 1,1′-carbonyldiimidazole (65 mg, 0.40 mmol) in benzene (3 mL) was heated at reflux for 20 h. The solvent was evaporated under reduced pressure to afford an oily residue that was purified by flash chromatography, eluting with hexanes/EtOAc (2:1) to afford **50** (53 mg, 98%) as a colorless oil which solidified upon standing in a freezer; **50** was recrystallized from a solution in hexanes/Et_2O by slow evaporation: mp 101–102 °C; ^{1}H NMR (500 MHz) δ 8.11 (s, 1 H), 7.40 (s, 1 H), 7.33–7.24 (comp, 5 H), 7.07 (s, 1 H), 5.64 (ddd, J = 17.1, 10.2, 8.9 Hz, 1 H), 5.18 (dd, J = 17.1, 1.3 Hz, 1 H), 5.12 (dd, J = 10.2, 1.3 Hz, 1 H), 4.91 (dd, J = 10.0, 1.5 Hz, 1 H), 4.78 (s, 2 H), 4.64 (d, J = 12.2 Hz, 1 H), 4.56 (d, J = 12.2 Hz, 1 H), 4.43 (dd, J = 10.4, 2.6 Hz, 1 H), 3.96 (td, J = 7.1, 1.3 Hz, 1 H), 3.86 (dd, J = 8.5, 1.6 Hz, 1 H), 3.52 (d, J = 4.2 Hz, 1 H), 2.66 (ddq, J = 10.0, 8.9, 6.6 Hz, 1 H), 2.28 (qdd, J = 7.4, 2.6, 1.6 Hz, 1 H), 2.06 (qdd, J = 6.8, 4.2, 1.5 Hz, 1 H), 1.96 (m, 1 H), 1.80 (dqd, J = 10.4, 7.0, 1.3 Hz, 1 H), 1.76 (m, 1 H), 1.43 (m, 1 H), 1.39–1.31 (m, 2 H), 1.22 (s, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.04 (s, 3 H), 1.04 (br t, 6 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.00 (s, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 0.81 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 149.9, 149.0, 138.3, 137.9, 137.2, 130.6, 128.4, 127.5, 127.3, 117.2, 117.2, 106.6, 95.2, 89.0, 85.0, 84.7, 82.3, 78.2, 77.9, 69.6, 43.8, 40.3, 36.7, 34.5, 33.0, 29.1, 28.3, 26.4, 25.5, 21.5, 18.5, 17.2, 12.3, 10.3, 8.6, 7.9; IR (film) ν 3600, 3100, 1750, 1650, 910 cm^{-1}; mass spectrum (CI) m/z 685.4063 [$C_{38}H_{57}N_2O_9$ (M + 1) requires 685.4064], 154 (base), 136, 107.

(2*S*,3*R*)-1,2-Epoxy-2-methylpentan-3-ol (55). A suspension of powdered 4-Å molecular sieves (2.80 g), diisopropyl D-tartarate (2.78 mL, 13.1 mmol), and titanium tetraisopropoxide (3.25 mL, 10.9 mmol) in CH_2Cl_2 (220 mL) was stirred at −20 °C for 10 min. *tert*-Butyl hydroperoxide (18.0 mL, 3 M solution in 2,2,4-trimethylpentane) was added, and stirring continued at −20 °C for an additional 30 min, whereupon a solution of 2-methyl-1-penten-3-ol (**48**) (10.9 g, 10.9 mmol) in CH_2Cl_2 (30 mL) was added slowly. The mixture was stirred at −20 °C for 11 h, and triethanolamine (7 mL of a 2.16 M solution in CH_2Cl_2) was then added. The mixture was allowed to warmed to room temperature and stirred for 10 h. The suspension was filtered through a pad of silica gel that was washed with Et_2O (ca. 300 mL). The filtrate was concentrated under reduced pressure, and the residue was partially purified by flash chromatography, eluting with pentane/Et_2O (2:1) to give a mixture of **55** and diisopropyl tartarate. Distillation of this mixture gave 3.07 g (48%) of **55** (bp 80–82 °C, 25 mmHg) as a colorless oil: ^{1}H NMR (300 MHz) δ 3.57 (ddd, J = 8.3, 3.0, 1.7 Hz, 1 H), 2.88 (d, J = 4.8 Hz, 1 H), 2.58 (d, J = 4.8 Hz, 1 H), 2.05 (d, J = 1.1 Hz, 1 H), 1.68 (m, 1 H), 1.41 (m, 1 H), 1.32 (s, 3 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 73.0, 58.9, 50.3, 25.9, 18.0, 9.8; IR (film) ν 3430, 3030, 1240, 870 cm^{-1}; mass spectrum (CI) m/z 117, 99 (base), 87, 81, 71. Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.88; H, 10.08.

2,2-Dimethylpropanoic Acid (2*S*,3*R*)-2,3-Dihydroxy-2-methylpentanyl Ester (56). A solution of pivalic acid (3.83 g, 37.6 mmol) and titanium tetraisopropoxide (8.40 mL, 28.2 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min, whereupon a solution of **55** (1.09 g, 9.4 mmol) in CH_2Cl_2 (9 mL) was added, and the resulting mixture was warmed to room temperature and stirred for 40 h. Triethanolamine (15 mL of a 2.40 M solution in CH_2Cl_2) was added, and the mixture was stirred for 30 min and then filtered through a Celite pad with Et_2O (ca. 300 mL). The organic layer was washed with saturated $NaHCO_3$ (3 × 75 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (1:1) to give 1.29 g (63%) of diol **56** as a solid that was recrystallized from hexanes to give **56** as colorless plates: mp 58–60 °C; ^{1}H NMR (300 MHz) δ 4.22 (d, J = 11.5 Hz, 1 H), 3.98 (d, J = 11.5 Hz, 1 H), 3.32 (m, 1 H), 2.54 (br s, 1 H), 2.29 (br d, J = 4.2 Hz, 1 H), 1.61 (dqd, J = 13.9, 7.4, 2.1 Hz, 1 H), 1.33 (m, 1 H), 1.21 (s, 9 H), 1.16 (s, 3 H), 1.02 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz) δ 178.8, 77.9, 73.9, 68.3, 38.9, 27.1, 23.9, 20.7, 11.3; IR (film) 3500, 1720, 1400 cm^{-1}; mass spectrum (CI) m/z 219 (M + 1), 201 (base), 117, 99, 85. Anal. Calcd for $C_{11}H_{22}O_4$: C, 60.53; H, 10.16. Found: C, 60.68; H, 10.18.

2,2-Dimethylpropanoic Acid (2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-2-methylpentanyl Ester. To a solution of diol **56** (335 mg, 1.54 mmol) in CH_2Cl_2 (8 mL) containing 2,6-lutidine (0.54 mL, 4.60 mmol) at −20 °C was added (TBDMS)OTf (0.42 mL, 1.84 mmol). The reaction mixture was stirred at −20 °C for 1 h, saturated $NaHCO_3$ (ca. 5 mL) was added, and the mixture was allowed to warm to room temperature. Ether (ca. 50 mL) was added, and the layers were separated. The organic layer was washed with saturated $CuSO_4$ (2 × 5 mL) and saturated NaCl (1 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/ether (5:1) to give 407 mg (80%) of the TBDMS ether as an oil: ^{1}H NMR (300 MHz) δ 4.07 (AB q, 2 H, $\Delta\nu_{AB}$ = 24.2 Hz, J = 11.3 Hz), 3.51 (dd, 1 H, J = 7.0, 4.0 Hz), 2.30 (s, 1 H), 1.70 (m, 1 H), 1.42 (m, 1 H), 1.23 (s, 9 H), 1.15 (s, 3 H), 0.97 (t, J = 7.5 Hz, 3 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz)

δ 178.6, 78.4, 74.4, 68.4, 38.9, 27.2, 26.0, 25.3, 20.7, 18.2, 11.5, –3.9, –4.4; IR (film) ν 3520, 2975, 2882, 1775, 1510, 1492, 1431, 1397 cm^{-1}; mass spectrum (CI) *m/z* 333 (M + 1), 315 (base). Anal. Calcd for $C_{17}H_{36}O_4Si$: C, 61.40; H, 10.91. Found: C, 61.54; H, 11.09.

2,2-Dimethylpropanoic Acid (2*S*,3*R*)-2-[(Benzyloxy)methoxy]-2-methyl-3-[(*tert*-butyldimethylsilyl)oxy]pentanyl Ester (57). A mixture of the above alcohol (500 mg, 1.51 mmol), NaI (1.13 g, 7.53 mmol), and Proton Sponge (1.93 g, 9.04 mmol) in DME (15 mL) was stirred at 0 °C until all solids dissolved, whereupon benzyl chloromethyl ether (1.05 mL, 7.53 mmol) was added. The suspension was warmed to room temperature and stirred for 24 h. Ether (50 mL) was added, and the mixture was filtered through a Celite pad by washing with a small volume of ether. The filtrate was washed with saturated aqueous $CuSO_4$ (2 × 50 mL), saturated NaCl (1 × 50 mL), and H_2O (1 × 50 mL). The combined aqueous layers were back-extracted with Et_2O (1 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes/ether (20:1) to give 575 mg (84%) of **57** as an oil: ^{1}H NMR (300 MHz) δ 7.32 (comp, 5H), 4.88 (AB q, $\Delta\nu_{AB}$ = 28.6 Hz, *J* = 7.5 Hz, 2 H), 4.61 (AB q, $\Delta\nu_{AB}$ = 23.3 Hz, *J* = 11.9 Hz, 2 H), 4.14 (AB q, $\Delta\nu_{AB}$ = 131.6 Hz, *J* = 11.9 Hz, 2 H), 1.82 (m, 1 H), 1.42 (m, 1 H), 1.24 (s, 3 H), 1.21 (s, 9 H), 0.99 (t, *J* = 7.5 Hz, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz) δ 178.1, 138.0, 128.3, 127.7, 127.5, 89.6, 79.9, 76.3, 69.6, 66.3, 38.8, 27.3, 26.0, 25.1, 18.3, 15.8, 11.9, –4.0, –4.3; IR (film) ν 2960, 2840, 1751, 1449, 1430, 1308, 1280, 1180 cm^{-1}; mass spectrum (CI) *m/z* 451 (M – 1), 345 (base). Anal. Calcd for $C_{25}H_{44}O_5Si$: C, 66.33; H, 9.80. Found: C, 66.26; H, 9.92.

(2*S*,3*R*)-2-[(Benzyloxy)methoxy]-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpentanol. Methyllithium (0.83 mL, 1.40 M, Et_2O) was added to a solution of ester **57** (210 mg, 0.47 mmol) in Et_2O (4.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and saturated NH_4Cl (ca. 4 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (7:1) to give 148 mg (86%) of the primary alcohol as a colorless oil: ^{1}H NMR (500 MHz) δ 7.35–7.26 (comp, 5 H), 4.88 (d, *J* = 7.5 Hz, 1 H), 4.84 (d, *J* = 7.5 Hz, 1 H), 4.67 (d, *J* = 11.7 Hz, 1 H), 4.61 (d, *J* = 11.7 Hz, 1 H), 3.63 (dd, *J* = 7.4, 3.6 Hz, 1 H), 3.62 (dd, *J* = 12.4, 6.4 Hz, 1 H), 3.55 (dd, *J* = 12.4, 7.0 Hz, 1 H), 3.18 (dd, *J* = 7.0, 6.4 Hz, 1 H), 1.71 (dqd, *J* = 14.1, 7.5, 3.6 Hz, 1 H), 1.40 (m, 1 H), 1.10 (s, 3 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (75 MHz) δ 137.4, 128.5, 127.8, 127.7, 89.1, 81.8, 76.5, 69.9, 65.4, 26.0, 25.2, 18.2, 15.5, 11.8, –4.1, –4.4; IR (film) ν 3460, 3050, 3020, 1380, 1260 cm^{-1}; mass spectrum (CI) *m/z* 369 (M + 1), 261, 215, 173 (base), 149, 129, 91. Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.85. Found: C, 65.06; H, 9.83.

(2*R*,3*R*)-2-[(Benzyloxy)methoxy]-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpentanal (59). DMSO (0.11 mL, 1.58 mmol) was added to a solution of oxalyl chloride (69 μL, 0.79 mmol) in CH_2Cl_2 (2 mL) at –60 °C, and the solution was stirred at –60 °C for 15 min. A solution of the above alcohol (145 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) was added, the resulting mixture was stirred at –60 °C for 15 min, and Et_3N (0.33 mL, 2.36 mmol) was added. The mixture was allowed to warm to room temperature over 45 min, and Et_2O (ca. 50 mL) was added. The resulting mixture was washed with saturated $NaHCO_3$ (1 × 10 mL), saturated $CuSO_4$ (1 × 10 mL), and saturated NaCl (1 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with pentane/Et_2O (20:1) to give 126 mg (87%) of aldehyde **59** as an oil: ^{1}H NMR (300 MHz) δ 9.57 (s, 1 H), 7.32 (comp, 5 H), 4.90 (d, *J* = 7.3 Hz, 1 H), 4.73 (d, *J* = 7.3 Hz, 1 H), 4.66 (d, *J* = 11.9 Hz, 1 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 3.77 (dd, *J* = 7.5, 4.2 Hz, 1 H), 1.67 (dqd, *J* = 14.1, 7.5, 4.2 Hz, 1 H), 1.42 (m, 1 H), 1.30 (s, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz) δ 203.0, 137.5, 128.4, 127.7, 127.6, 90.0, 84.4, 76.9, 69.9, 25.9, 25.4, 18.1, 13.2, 11.1, –4.0, –4.2; IR (film) ν 3080, 3060, 1760, 1410, 1290 cm^{-1}; mass spectrum (CI) *m/z* 366, 245 (base), 239, 193.

(3*R*,4*S*,5*S*,6*S*,8*R*,10*R*,11*R*,12*S*,13*R*,14*S*)-4-[(Benzyloxy)methoxy]-3-[(*tert*-butyldimethylsilyl)oxy]-5,13-dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethylhexadec-15-en-7-one (63). A solution of ketone **32** (50.0 mg, 0.15 mmol) in THF (0.5 mL) was added to a solution of lithium hexamethyldisilazide (0.54 mmol) in THF (0.5 mL) at –78 °C. After the mixture was stirred at –78 °C for 2.5 h, a solution of aldehyde **59** (170 mg, 0.46 mmol) in THF (0.5 mL) was added, and the resulting mixture was stirred at –78 °C for an additional 1 h. Saturated NH_4Cl (2 mL) was added and the reaction warmed to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/acetone (9:1) to afford 22 mg of recovered **32** and 51 mg (48%) of the *syn*-adduct **63** together with 1.5 mg (1%) of a diastereoisomer that was tentatively assigned the structure **61**. For **63**: ^{1}H NMR (500 MHz) δ 7.34–7.25 (comp, 5 H), 5.54 (ddd, *J* = 17.1, 10.3, 8.9 Hz, 1 H), 5.10 (d, *J* = 6.9 Hz, 1 H), 5.05 (ddd, *J* = 17.1, 1.7, 0.7 Hz, 1 H), 4.98 (dd, *J* = 10.3, 1.7 Hz, 1 H), 4.84 (d, *J* = 6.9 Hz, 1 H), 4.70 (d, *J* = 11.9 Hz, 1 H), 4.52 (d, *J* = 11.9 Hz, 1 H), 4.06 (dd, *J* = 4.7, 1.5 Hz, 1 H), 3.71 (d, *J* = 8.4 Hz, 1 H), 3.70 (dd, *J* = 6.4, 3.7 Hz, 1 H), 3.38 (qd, *J* = 7.0, 1.5 Hz, 1 H), 3.24 (dd, *J* = 9.4, 2.8 Hz, 1 H), 3.11 (m, 1 H), 2.75 (d, *J* = 4.7 Hz, 1 H), 2.30 (m, 1 H), 2.25 (dd, *J* = 14.4, 7.8 Hz, 1 H), 2.09 (br d, *J* = 5.0 Hz, 1 H), 1.90 (dqd, *J* = 8.2, 6.8, 1.5 Hz, 1 H), 1.74 (dqd, *J* = 14.4, 7.6, 3.7 Hz, 1 H), 1.50 (m, 1 H), 1.40 (dd, *J* = 14.4, 3.7 Hz, 1 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.25 (s, 3 H), 1.18 (d, *J* = 7.0 Hz, 3 H), 1.11 (d, *J* = 7.1 Hz, 3 H), 1.10 (s, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz) δ 218.5, 140.3, 138.1, 128.4, 127.7, 127.6, 115.2, 106.0, 90.4, 84.1, 82.6, 81.8, 79.0, 75.4, 71.3, 69.8, 46.1, 42.6, 42.2, 39.8, 35.4, 29.7, 28.5, 26.4, 26.1, 25.6, 22.3, 20.1, 18.3, 17.7, 16.9, 11.7, 10.5, 8.9, –3.9, –4.1; IR (film) ν 3450, 1700, 1640, 1385, 1260, 1010 cm^{-1}; mass spectrum (CI) *m/z* 693.4757 [$C_{39}H_{69}O_8Si$ (M + 1) requires 693.4762], 399, 313, 285 (base), 269, 227, 209, 173.

2,2-Dimethylpropanoic Acid (2*S*,3*R*)-2,3-Bis[(benzyloxy)methoxy]-2-methylpentanyl Ester (58). A mixture of diol **56** (100 mg, 0.46 mmol), NaI (344 mg, 2.29 mmol), and Proton Sponge (589 mg, 2.75 mmol) in DME (4.5 mL) was stirred at 0 °C until all solids dissolved, whereupon benzyl chloromethyl ether (0.32 mL, 2.29 mmol) was added. The suspension was stirred at 0 °C for 15 min and then at room temperature for 40 h. The mixture was diluted with Et_2O (35 mL) and filtered through a Celite pad. The filtrate was washed with saturated $CuSO_4$ (2 × 15 mL) and saturated NaCl (1 × 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/ether (7:1) to give 176 mg (84%) of **58** as a colorless oil: ^{1}H NMR (300 MHz) δ 7.32 (comp, 10 H), 4.89 (s, 2 H), 4.83 (s, 2 H), 4.70 (d, *J* = 16.9 Hz, 1 H), 4.62 (s, 2 H), 4.61 (dd, *J* = 14.1, 3.5 Hz, 2 H), 4.20 (AB q, $\Delta\nu_{AB}$ = 76.5 Hz, *J* = 12.4 Hz, 2 H), 3.56 (dd, *J* = 10.6, 3.5 Hz, 1 H), 1.81 (m, 1 H), 1.55 (m, 1 H), 1.39 (s, 3 H), 1.19 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3 H).

(2*S*,3*R*)-2,3-Bis[(benzyloxy)methoxy]-2-methylpentanol. Methyllithium (1.9 mL, 1.40 M solution in Et_2O) was added to a solution of ester **58** (416 mg, 0.91 mmol) in Et_2O (9 mL) at 0 °C. After the mixture was stirred at 0 °C for 30 min, saturated NH_4Cl (ca. 4 mL) was added and the mixture warmed to room temperature. The layers were separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 297 mg (87%) of the primary alcohol as a colorless oil: ^{1}H NMR (300 MHz) δ 7.48–7.28 (comp, 10 H), 4.94 (d, *J* = 7.5 Hz, 1 H), 4.93 (d, *J* = 6.6 Hz, 1 H), 4.87 (d, *J* = 7.5 Hz, 1 H), 4.85 (d, *J* = 6.6 Hz, 1 H,), 4.70 (d, *J* = 11.8 Hz, 1 H), 4.69 (d, *J* = 12.0 Hz, 1 H), 4.65 (d, *J* = 12.0 Hz, 1 H), 11.8 (d, *J* = 4.6 Hz, 1 H), 3.72 (dd, *J* = 12.7, 7.0 Hz, 1 H), 3.65 (br s, 1 H), 3.62 (dd, *J* = 12.7, 7.0 Hz, 1 H), 3.38 (t, *J* = 7.0 Hz, 1 H), 1.79 (m, 1 H), 1.51 (m, 1 H), 1.15 (s, 3 H), 1.05 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 137.6, 137.4, 128.4, 128.3, 127.8, 127.7, 127.6, 96.3, 89.0, 82.6, 81.4, 70.2, 69.9, 65.2, 23.1, 15.7, 11.5; IR (film) ν 3450 cm^{-1}; mass spectrum (CI) *m/z* 375.2169 [$C_{22}H_{31}O_5$ (M + 1) requires 375.2172], 237, 159 (base), 129.

(2*R*,3*R*)-2,3-Bis[(benzyloxy)methoxy]-2-methylpentanal (60). DMSO (108 μL, 1.58 mmol) was added to a solution of oxalyl chloride (66 μL, 0.76 mmol) in CH_2Cl_2 (2 mL) at –60 °C. After the mixture was stirred at –60 °C for 15 min, a solution of the above alcohol (142 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) was introduced and the mixture stirred at –60 °C for 20 min, whereupon Et_3N (0.32 mL, 2.28 mmol) was added. The mixture was warmed to room temperature over 45 min, and Et_2O (ca. 20 mL) was added. The resulting mixture was washed with saturated $NaHCO_3$ (1 × 10 mL), saturated $CuSO_4$ (1 × 10 mL), and saturated NaCl (1 × 10 mL) and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with hexanes/Et_2O (4:1) to furnish 129 mg (91%) of aldehyde **60** as a

clear yellowish oil: ^{1}H NMR (300 MHz) δ 9.64 (s, 1 H), 7.42–7.27 (comp, 10 H), 4.92 (d, J = 7.4 Hz, 1 H), 4.82 (s, 2 H), 4.76 (d, J = 7.4 Hz, 1 H), 4.71 (d, J = 11.9 Hz, 1 H), 4.61 (d, J = 11.9 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 4.55 (d, J = 11.9 Hz, 1 H), 3.76 (dd, J = 8.7, 3.5 Hz, 1 H), 1.74 (dqd, J = 14.5, 7.4, 3.5 Hz, 1 H), 1.57 (m, 1 H), 1.37 (s, 3 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 202.3, 137.6, 137.3, 128.4, 127.7, 95.8, 89.8, 83.9, 82.4, 70.1, 69.9, 23.3, 13.3, 11.0; IR (film) ν 3060, 3025, 1745 cm^{-1}; mass spectrum (CI) m/z 373.2007 [$C_{22}H_{29}O_5$ (M + 1) requires 373.2015], 314, 289, 235 (base), 199, 181.

(3*R*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*,14*S*)-3,4-Bis[(benzyloxy)methoxy]-5,13-dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethylhexadec-15-en-7-one (62) and (3*R*,4*S*,5*S*,6*S*,8*R*,10*R*,11*R*,12*S*,13*R*,14*S*)-3,4-Bis[(benzyloxy)methoxy]-5,13-dihydroxy-10,11-(isopropylidenedioxy)-4,6,8,10,12,14-hexamethylhexadec-15-en-7-one (64). A solution of ketone **32** (33 mg, 0.10 mmol) in THF (0.5 mL) was added to a solution of lithium hexamethyldisilazide (0.30 mmol) in THF (0.4 mL) at –78 °C. After the mixture was stirred at –78 °C for 2.5 h, a solution of aldehyde **60** (67 mg, 0.18 mmol) in THF (0.5 mL) was added, and the mixture was stirred at –78 °C for 30 min. The reaction was quenched at –78 °C by adding saturated NH_4Cl (1 mL), and the resulting mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/Et_2O (6:1) to afford 5 mg (7%) of adduct **62**, 24 mg (34%) of adduct **64**, and 15 mg of recovered ketone **32**. **62**: ^{1}H NMR (500 MHz) δ 7.34–7.25 (comp, 10 H), 5.53 (ddd, J = 17.1, 10.2, 8.9 Hz, 1 H), 5.04 (ddd, J = 17.1, 1.5, 0.6 Hz, 1 H), 4.97 (dd, J = 10.2, 1.7 Hz, 1 H), 4.92 (d, J = 7.5 Hz, 1 H), 4.90 (d, J = 6.7 Hz, 1 H), 4.85 (d, J = 6.7 Hz, 1 H), 4.79 (d, J = 7.5 Hz, 1 H), 4.67 (d, J = 11.9 Hz, 1 H), 4.63 (d, J = 11.9 Hz, 1 H), 4.62 (d, J = 11.8 Hz, 1 H), 4.57 (d, J = 11.8 Hz, 1 H), 4.16 (dd, J = 6.0, 4.5 Hz, 1 H), 3.79 (dd, J = 8.8, 2.3 Hz, 1 H), 3.76 (d, J = 6.0 Hz, 1 H), 3.67 (d, J = 8.3 Hz, 1 H), 3.23 (br d, J = 9.4 Hz, 1 H), 3.08 (m, 1 H), 3.06 (qd, J = 7.0, 4.5 Hz, 1 H), 2.29 (m, 1 H), 2.14 (d, J = 1.7 Hz, 1 H), 2.14 (dd, J = 14.4, 6.6 Hz, 1 H), 1.89 (dqd, J = 8.3, 6.7, 1.5 Hz, 1 H), 1.78 (dqd, J = 14.4, 7.4, 2.3 Hz, 1 H), 1.57 (m, 1 H), 1.41 (dd, J = 14.4, 4.6 Hz, 1 H), 1.34 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 1.21 (d, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 1.10 (s, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 1.02 (t, J = 7.4 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz) δ 217.0, 140.4, 137.7, 137.4, 128.4, 127.8, 127.7, 127.6, 115.2, 105.8, 96.4, 90.0, 84.3, 84.2, 82.5, 81.7, 75.4, 73.8, 70.5, 70.2, 46.2, 42.8, 42.2, 40.0, 35.4, 26.6, 25.6, 23.7, 22.6, 19.6, 17.7, 16.9, 12.2, 11.7, 9.0; IR (film) ν 3460, 3060, 3020, 1705, 1640 cm^{-1}; mass spectrum (CI) m/z 699.4473 [$C_{41}H_{63}O_9$ (M + 1) requires 699.4472], 269, 251 (base), 213, 194, 182. **64**: ^{1}H NMR (500 MHz) δ 7.36–7.25 (comp, 10 H), 5.55 (ddd, J = 17.2, 10.3, 9.1 Hz, 1 H), 5.05 (dd, J = 17.2, 1.3 Hz, 1 H), 5.03 (d, J = 7.1 Hz, 1 H), 4.98 (dd, J = 10.3, 1.6 Hz, 1 H), 4.87 (d, J = 7.1 Hz, 1 H), 4.84 (s, 2 H), 4.68 (d, J = 11.9 Hz, 2 H), 4.60 (d, J = 11.9 Hz, 1 H), 4.55 (d, J = 11.9 Hz, 1 H), 4.13 (dd, J = 4.9, 1.0 Hz, 1 H), 3.70 (d, J = 8.4 Hz, 1 H), 3.57 (dd, J = 8.4, 2.7 Hz, 1 H), 3.34 (qd, J = 7.0, 1.0 Hz, 1 H), 3.29 (m, 1 H), 3.12 (dqd, J = 7.6, 7.1, 3.6 Hz, 1 H), 2.93 (d, J = 4.9 Hz, 1 H), 2.30 (m, 1 H), 2.25 (dd, J = 14.4, 7.6 Hz, 1 H), 1.15 (br d, J = 0.6 Hz, 1 H), 1.91 (m, 1 H), 1.78 (dqd, J = 14.5, 7.4, 2.7 Hz, 1 H), 1.57 (m, 1 H), 1.42 (dd, J = 14.4, 3.6 Hz, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.20 (d, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.1 Hz, 3 H), 1.10 (s, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.03 (t, J = 7.4 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz) δ 218.4, 140.3, 138.0, 137.9, 128.4, 128.3, 127.7, 127.6, 127.5, 115.2, 105.9, 96.4, 90.1, 85.8, 83.9, 82.8, 81.8, 75.3, 71.4, 70.2, 69.9, 46.0, 42.6, 42.2, 39.8, 35.4, 28.5, 26.4, 23.8, 22.3, 20.1, 17.6, 16.4, 11.9, 10.3, 9.0; IR (film) ν 3450, 3060, 3020, 1700, 1640 cm^{-1}; mass spectrum (CI) m/z 698.4376 ($C_{41}H_{62}O_9$ requires 698.4394), 485, 395, 377, 319, 251 (base).

(2*S*,3*R*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5,6,9,11,12,13-Heptahydroxy-2,4,6,8,10,12-hexamethylpentadecanol (65). A solution of ketone **62** (43 mg, 0.06 mmol) in CH_3CN (0.5 mL) was added to a solution of $Me_4NBH(OAc)_3$ (75 mg, 0.29 mmol) in a mixture (1:1) of CH_3CN/HOAc (1.0 mL) at –40 °C. The mixture was stirred at –40 °C for 4 h, saturated $NaHCO_3$ (ca. 1 mL) was added, and the mixture was allowed to warm to room temperature. Solid $NaHCO_3$ was added to neutralize excess HOAc, and the aqueous phase was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then purified by flash chromatograpy, eluting with hexanes/acetone (5:1) to give 4 mg of the 9(*S*)-alcohol as a colorless oil. A solution of the olefinic 9(*S*)-alcohol (4 mg, 0.01 mmol) thus obtained in EtOAc (2 mL) containing Sudan III (ca 0.5 mg) at –78 °C was treated with ozone until the dye began to fade. 2,3-Dimethyl-2-butene (0.15 mL) was added immediately in one portion. The reaction mixture was warmed to room temperature over 30 min and then concentrated under reduced pressure. The oily residue was dissolved in dry THF (2 mL) at 0 °C, and $LiAlH_4$ (10 mg) was added. After it was stirred at 0 °C for 30 min, the reaction mixture was quenched by the successive addition of H_2O (10 μL), 10% aqueous NaOH (10 μL), and H_2O (30 μL). The mixture was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was dissolved in MeOH/H_2O (1:1, 2 mL) that had been previously saturated with $HONH_2$·HCl and KH_2PO_4 (10 mg, 0.07 mmol). The resulting mixture was heated at reflux for 4 h and then cooled to room temperature. The volume of the solvent was reduced to about one-fourth under reduced pressure, solid $NaHCO_3$ was added, and the mixture was extracted with EtOAc (5 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (5:1) to give 1 mg of synthetic polyol **65** as an oil; this material was identical with TLC and ^{13}C NMR results of an authentic sample prepared from 9(*S*)-dihydroerythronolide A:[3j] ^{13}C NMR (125 MHz, acetone-d_6) δ 81.6, 81.0, 78.9, 77.3, 76.3, 76.0, 73.2, 65.7, 43.8, 38.9, 37.1, 36.3, 31.1, 25.1, 23.3, 20.2, 16.0, 13.3, 11.9, 11.8, 8.1; mass spectrum (CI) 425 (M + 1), 85 (base).

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