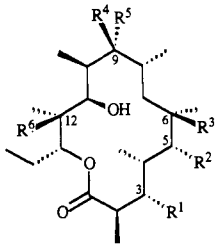
Enantioselective Total Synthesis of 9S-Dihydroerythronolide A Seco Acid

A. Richard Chamberlin,* Milana Dezube, Siegfried H. Reich, and Daniel J. Sall

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received October 21, 1988*

Abstract: A concise and enantioselective total synthesis of 9S-dihydroerythronolide A seco acid (**8**) is described. The functionalized γ-lactones **9** and **10**, which serve as chiral building blocks for the C3–C7 and C9–C15 segments of the seco acid **8**, were readily prepared from the optically active β-hydroxy esters **11** and **12**. The lactones **9** and **10** were elaborated into the vinylstannane **20** and the aldehyde **27**, respectively, which in turn were coupled to afford, after oxidation, the key intermediate **13**. Successive stereoselective reductions of the enone group established the correct stereochemistry at both C8 and C9, and the remaining C1–C2 fragment was introduced via a diastereoselective aldol condensation.

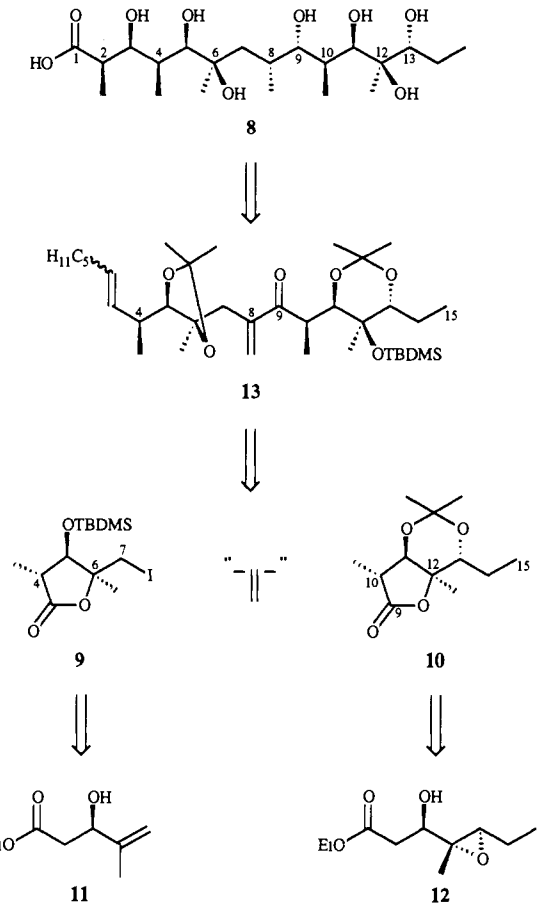
Erythromycin A (**1**), one of the most active and important macrolide antibiotics,[1] was first isolated from cultures of *Streptomyces erythraeus* in 1952.[2] Its structure, unambiguously established first through chemical degradation[3] and later by X-ray crystallographic analysis,[4] was shown to consist of a 14-membered lactone ring with two appended sugars, L-cladinose at C3 and D-desosamine at C5. Erythromycin's potent antibiotic activity, a result of efficient inhibition of bacterial protein biosynthesis,[1b] has led to its widespread use in the treatment of infectious diseases.



1, R^1=L-cladinosyl, R^2=D-desosaminyl, R^3=R^6=OH, R^4=R^5=O
2, R^1=L-cladinosyl, R^2=D-desosaminyl, R^3=OH, R^4=R^5=O, R^6=H
3, R^1=R^2=R^3=R^6=OH, R^4=R^5=O
4, R^1=R^2=R^3=R^4=R^6=OH, R^5=H
5, R^1=R^2=R^3=OH, R^4=R^5=O, R^6=H
6, R^1=R^2=OH, R^3=R^6=H, R^4=R^5=OH

Erythromycin A, as well as the closely related erythromycin B (**2**), has long been a formidable synthetic target because of its challenging macrocyclic stereochemical array. Testimony to the synthetic complexity of the erythromycins is the fact that only one total synthesis, that of erythromycin A by Woodward et al. in 1981,[5] has been accomplished. Other synthetic work has focussed mainly on the aglycon, resulting in several interesting approaches to erythronolide derivatives: erythronolide A (**3**),[6] 9S-dihydroerythronolide A (**4**),[7] erythronolide B (**5**),[8] and 6-deoxyerythronolide B (**6**).[9] The development of effective ma-

Scheme I. Retrosynthetic Analysis



8

13

9 **10**

11 **12**

(1) (a) For a general review of macrolide antibiotics, including erythromycin A, see: Omura, S. *Macrolide Antibiotics: Chemistry, Biology and Practice*; Academic Press: Orlando, FL, 1984. (b) For a review of the biological activity of erythromycin A, see: *Ibid.* p 231.

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

(3) Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V., Jr.; Weaver, O.; Quarck, U. C.; Chauvette, R. R.; Monahan, R. *J. Am. Chem. Soc.* **1957**, *79*, 6062.

(4) Harris, D. R.; McGeachin, S. G.; Mills, H. H. *Tetrahedron Lett.* **1965**, 679.

(5) (a) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. a.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (b) *Ibid.* 3213. (c) *Ibid.* 3215.

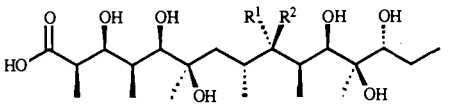
(6) (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (b) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219. (c) *Ibid.* 2223. (d) Kinoshita, M.; Arai, M.; Tomooka, K.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1811. (e) Kinoshita, M.; Arai, M.; Ohsawa, N.; Nakata, M. *Ibid.* 1815.

(7) (a) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564. (b) *Ibid.* 1565. (c) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569.

(8) (a) Corey, E. J.; Trybulski, E. J.; Melvin, L. S., Jr.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618. (b) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *Ibid.* 4620. (c) Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. K. *Tetrahedron Lett.* **1987**, *28*, 3835. (d) *Ibid.* 3839.

0002-7863/89/1511-6247$01.50/0

crolactonization techniques, pioneered by Corey,[10a] Masamune,[10b] and Mukaiyama,[10c] has simplified the once intimidating task of macrolide antibiotic synthesis and has diverted synthetic efforts to the construction of highly oxygenated acyclic precursors of erythronolides A and B (seco acid derivatives). In this regard, the groups of Hanessian,[11] Deslongchamps,[12] Stork,[13] and Nakata[14] have all accomplished stereoselective total syntheses of protected derivatives of erythronolide A seco acid (**7**). In addition, the preparation of a variety of fragments of the carbocyclic backbone of both erythronolide A and erythronolide B have been published.[15]

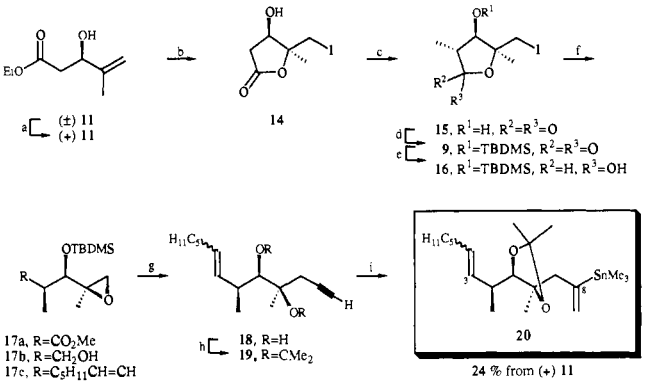


7, $R^1=R^2=O$
8, $R^1=OH$, $R^2=H$

Our interest in the macrolide antibiotics lies in studying the relationship between the conformation of various seco acids and the corresponding macrolactonization efficacy. Pioneering studies by Woodward et al.[5b] have shown that a protected 9*S*-dihydro seco acid related to **7** lactonizes in much higher yield than a related 9*R* epimer, suggesting that a very minor structural change in the seco acid cyclization precursor can have a large effect on the success of macrolactonization. In order to study this effect systematically, i.e., to correlate seco acid conformation with the rate of lactonization, we have set out to prepare a series of diastereomeric erythronolide A seco acids. As a prelude to that endeavor we report a concise and highly efficient synthesis of the parent 9*S*-dihydroerythronolide A seco acid **8**. This approach demonstrates that it is possible to obtain either diastereomer with high stereochemical control at several asymmetric centers and suggests ways of doing the same at a number of others.

We planned a convergent route (Scheme I) to the seco acid **8** that would take advantage of the fact that the C4–C6 and C10–C12 segments are substituted identically and thus might be prepared by closely related synthetic sequences. The two similarly substituted γ-lactones **9** and **10**, embodying these two segments, would serve as the principle chiral building blocks of the seco acid **8** since they contain seven of the eleven stereogenic centers to be constructed. The lactones **9** and **10**, in turn, would be derived from the enantiomerically pure β-hydroxy esters **11** and **12**, respectively, which are readily available using the kinetic resolution methodology of Sharpless et al.[16,17] Coupling of the lactones **9** and **10** by linking C7 and C9 with a suitable vinyl dianion equivalent would provide the enone **13** in which the stereochemistry at C8 and at C9 would be introduced by sequential stereoselective reductions. Finally, unmasking the latent terminal aldehyde and appending the C1–C2 fragment via a stereoselective aldol condensation would introduce the remaining two centers, completing this convergent approach to the seco acid **8**. On the basis of this retrosynthetic analysis, we have carried out the concise, enantioselective total synthesis of 9*S*-dihydroerythronolide A seco acid (**8**) described below.

Scheme II. Preparation of the C3–C8 Fragment (**20**)[a]



[a] Reagents and conditions: (a) Ti(*i*-PrO)$_4$ (1.2 equiv), (+)-DIT (1.5 equiv), *t*-BuOOH (3 equiv), CH_2Cl_2, −25 °C; (b) 1 N aqueous NaOH (3 equiv), THF/Et_2O, reflux; 1 N aqueous HCl (pH 8–9), I_2 (3 equiv), Et_2O, 0 °C; (c) LDA (5 equiv), THF, −78 °C; MeI (10 equiv), THF, −78 °C; (d) *t*-BuMe_2SiOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 25 °C; (e) DIBAL (1.5 equiv), Et_2O, −78 °C; (f) *n*-hexyltriphenylphosphonium bromide (4 equiv), n-BuLi (4 equiv), toluene, 25 °C; (g) $HCCLiH_2NCH_2CH_2NH_2$ (10 equiv), DMSO, 25 °C; (h) acetone, TosOH (3 equiv), 25 °C; (i) Me_6Sn_2 (5 equiv), MeLi (5 equiv), Me_2S·CuBr (5 equiv), MeOH (50 equiv), THF, −65 °C.

Results and Discussion

Preparation of the C3–C8 Fragment (Scheme II). Sharpless kinetic resolution[16] of racemic ethyl 3-hydroxy-4-methyl-4-pentenoate (±)-**11**[18] gives multigram quantities of the β-hydroxy ester (+)-**11**, in >95% ee as determined by ^1H NMR analysis with chiral shift reagents. Saponification of (+)-**11**, followed in situ by kinetically controlled iodolactonization[19] of the corresponding carboxylate gave the chiral iodolactone **14**. Stereoselective introduction of the C2 methyl group was effected by hydroxyl-directed methylation[20] to afford the white crystalline iodolactone **15** (72% from (+)-**11**). While iodolactonization and α-methylation gave diastereomeric ratios of 20:1 and 13:1, respectively, the very minor diastereomers were not easily separable at this stage. Subsequent protection, however, with *tert*-butyldimethylsilyltriflate[21] afforded the silyl derivative **9** (93%), which could be purified by flash chromatography to stereochemical homogeneity, devoid of the diastereomers produced in the preceding iodolactonization and methylation reactions. It is noteworthy that the use of 2,6-di-*tert*-butylpyridine as base effected clean protection of the β-hydroxy group, while 2,6-lutidine, the conventional base for protections employing *tert*-butyldimethylsilyltriflate,[20] gave the corresponding α,β-unsaturated lactone as the major product.

Having established the correct absolute configuration of all the requisite centers of the C3–C8 segment, we were faced with transforming the lactone into a form suitable for coupling with the C9–C15 fragment, via the aforementioned vinyl dianion

(9) Masamune, S.; Hirama, M.; Sachio, M.; Asrof Ali, S.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(10) (a) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654. (b) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S.; *J. Am. Chem. Soc.* **1975**, *97*, 3512. (c) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

(11) Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843.

(12) (a) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810. (b) *Ibid.* 2814. (c) *Ibid.* 2818.

(13) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686.

(14) (a) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219. (b) *Ibid.* 2223.

(15) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095. (b) Hoagland, S.; Morita, Y.; Bai, D. L.; Marki, H.-P.; Kees, K.; Brown, L.; Heathcock, C. H. *Ibid.* **1988**, *53*, 4730. (c) Mulzer, J.; Autenrieth-Ansorge, L.; Kirstein, H.; Matsuoka, T.; Munch, W. *Ibid.* **1987**, *52*, 3784. (d) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S. *Tetrahedron Lett.* **1981**, *22*, 4315. (e) *Ibid.* 4319. (f) Paterson, I.; Patel, S. K.; Porter, J. R. *Ibid.* **1983**, *24*, 3395. (g) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Ibid.* **1983**, *24*, 3635. (h) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V. *Ibid.* **1984**, *25*, 1605. (i) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Ibid.* **1988**, *29*, 1461. (j) Kinoshita, M.; Ohsawa, N.; Gomi, S. *Carbohydr. Res.* **1982**, *109*, 5. (k) Hanessian, S.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 111. (l) Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127. (m) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Sato, F. *Ibid.* **1985**, *107*, 5541.

(16) Kinetic resolution: Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589.

(17) Asymmetric epoxidation: Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

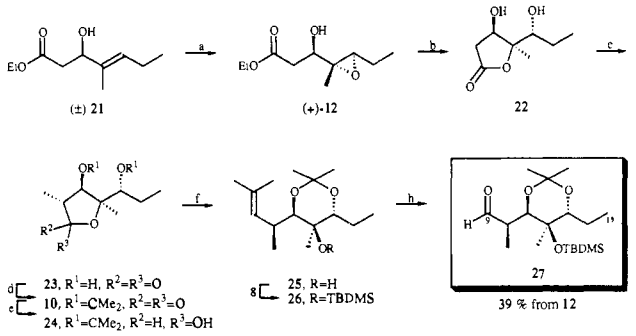
(18) β-Hydroxy ester (±)-**11** was prepared by aldol coupling of ethyl lithioacetate and methacrolein as described in the Experimental Section.

(19) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.

(20) Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, *23*, 3055.

(21) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

Scheme III. Preparation of the C9–C15 Fragment (**27**)[a]



[a] Reagents and conditions: (a) Ti(*i*-PrO)$_4$ (1 equiv), (−)-DET (1.5 equiv), *t*-BuOOH (0.7 equiv), CH_2Cl_2, −25 °C; (b) HCl (1.3 equiv), EtOH, NaI (2 equiv), 0 °C → 25 °C; (c) LDA (10 equiv), THF, −78 °C; MeI (20 equiv), THF, −78 °C; (d) acetone, TosOH (3 equiv), 25 °C; (e) DIBAL (1.5 equiv), Et_2O, −78 °C; (f) i-propyltriphenylphosphonium bromide (5 equiv), *n*-BuLi (5 equiv), toluene, reflux; (g) t-BuMe$_2$SiOTf (1.5 equiv), 2,6-lutidine, CH_2Cl_2, 25 °C; (h) O_3 (1 equiv), CH_2Cl_2, −78 °C; Me_2S, −78 °C.

equivalent. Toward that end, **9** was converted into an epoxide by methanolysis to give **17a**, or with $LiAlH_4$ to give **17b**, but the addition of appropriately substituted vinyl anions (e.g., vinyl cuprates) to either of these epoxides was unsuccessful. We then opted for the well-precedented reaction of phosphorus ylides with γ-lactols[22] as a means of generating a securely protected aldehyde while concurrently forming the desired terminal epoxide. Thus, treatment of the crude lactol **16**, obtained from diisobutylaluminum hydride (DIBAL) reduction of the silylated lactone **9**,[23] with 4 equiv of hexylidenetriphenylphosphorane afforded the protected epoxide **17c** as an *E*:*Z* mixture of geometrical isomers (64% from the lactone **9**). The addition of Wittig reagents (i.e., methylenetriphenylphosphorane) that would give a single alkene isomer resulted in either poor yields of the corresponding olefinic epoxides or inefficient unmasking of the latent aldehyde later in the synthesis.

Once the protected epoxide **17c** was in hand, an effective vinyl dianion equivalent was sought, and the facile two-step conversion of terminal alkynes into 2-lithioalkenes[24] suggested that lithium acetylide should serve this purpose well. The epoxide **17c** was therefore treated with excess lithium acetylide–ethylenediamine complex in DMSO (25 °C, 6 d) to afford the alkynediol **18** in 92% isolated yield. Protection of the alkynediol **18** as the acetonide **19**[25] followed by treatment with trimethylstannylcopper/methanol[23b] afforded the vinylstannane **20** in 92% yield for the two steps. Only the 2-stannyl regioisomer was produced, with no indication (by ^{1}H NMR) of the typical 5–10%[23b] of the 1-stannyl regioisomer. This sequence completes the preparation of **20** in 36% overall yield from the β-hydroxy ester (+)-**11**. This vinylstannane comprises the C3–C8 segment of seco acid **8** and is appropriately functionalized to couple with the C9–C15 fragment whose synthesis is described next.

Preparation of the C9-C15 Fragment (Scheme III). Since the stereochemistry of C10–C12 is identical with C4–C6, the lactone **10** was prepared by a route that is analogous to that employed for **9**. Thus, multigram quantities of the epoxy ester (+)-**12** were prepared by once again applying the kinetic resolution methodology of Sharpless et al.[16] to racemic ethyl 3-hydroxy-4-methyl-4-heptenoate [(±)-**21**][26] but in the opposite sense; i.e., in this case the enantiomerically enriched *epoxy alcohol* was isolated. This epoxide, which is stereochemically analogous to the iodonium ion (or π-complex) intermediate in the iodolactonization leading to the C3–C7 lactone **9**, was then treated with dilute ethanolic HCl/NaI at 0 °C to effect clean conversion into the enantiomerically pure dihydroxy lactone **22**. To the limits of proton nuclear magnetic resonance spectroscopy and high pressure liquid chromatography, **22** is a single diastereomer.

This reaction proceeds in good yield only in the presence of added iodide, presumably because the better nucleophile (I^-) accelerates deethylation of an intermediate oxonium ion. Hydroxyl-directed methylation,[19] as described above, then afforded the chiral lactone **23** (9:1 mixture of diastereomers at the α-carbon) which possesses the four requisite asymmetric centers present in the C9–C15 segment of the seco acid **8**. Acetonide formation[24] provided the protected lactone **10**, which could be purified by flash chromatography to afford a single diastereomer in 69% isolated yield from **12**.

Coupling of the C3–C8 and C9–C15 Segments. With seven of the 11 asymmetric centers of the parent seco acid **8** established in the C3–C7 (**20**) and the C9–C15 (**10**) segments, coupling of the two pieces was attempted. The initial strategy for uniting the lactone **10** with the C3–C8 fragment entailed direct nucleophilic ring opening of the lactone by the vinyllithium derived from the stannane **20**. Despite ample precedent for the reaction of butyrolactones with strong nucleophiles to give ketones,[27] the highly functionalized lactone **10** showed absolutely no tendency to do so. Likewise, the unprotected lactone **23** proved completely resistant to nucleophilic attack at the carbonyl group by organolithium reagents and instead suffered α-deprotonation and subsequent C-2 epimerization. The resistance of these lactones to nucleophilic attack is attributed to obstruction of the preferred trajectory of the incoming nucleophile by the high degree of substitution opposite the carbonyl group. For this reason, an alternative strategy was adopted; namely, conversion of **10** into the corresponding lactol, a procedure that had been effective for ring opening of the lactone **9**. Thus, **10** was reduced with DIBAL,[22] and the intermediate aluminum alkoxide[28] treated in situ with model nucleophiles. The expected addition to the open-chain aldehyde, however, also failed, thus precluding the use of this direct strategy for the coupling of the C3–C8 and the C9–C15 fragments.

The difficulty experienced in effecting ring opening of lactone **10** was finally resolved by temporarily protecting the open-chain aldehyde form of the lactol as an alkene. Thus, the lactol **24** (prepared from DIBAL reduction[22] of the lactone **10** and readily purified by silica gel chromatography) underwent smooth Wittig isopropenylation in refluxing toluene to afford the olefin **25**. Subsequent protection using *tert*-butyldimethylsilyltriflate/2,6-lutidine[20] gave the silyl ether **26** in 60% yield from **10**, and careful ozonolysis of the protected olefin afforded the aldehyde **27** in 39% overall yield from the epoxy ester **12**. Although this scheme is somewhat more circuitous than the original plan, it is efficient and simple to carry out.

With a workable strategy finally in hand, the actual coupling proceeded uneventfully. Transmetalation of the vinylstannane **20** with MeLi at −15 °C (Scheme IV) and subsequent treatment with a THF solution of the aldehyde **27** gave the desired coupling product **28** in 91% isolated yield. Swern oxidation[29] of allylic alcohol **28** afforded the desired enone **13** (92% yield). Successfully joining the two halves of the target in excellent yield sets the stage for studies on controlling the stereochemistry of the C8 methyl and C9 alcohol substituents via reduction of an enone centrally located in an acyclic chain with seven adjacent stereogenic centers.

(22) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363.

(23) Schmidlin, J.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 2799.

(24) (a) Via hydroboration: Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (b) Via hydrostannylation: Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934.

(25) Hampton, A. *J. Am. Chem. Soc.* **1961**, *83*, 3640.

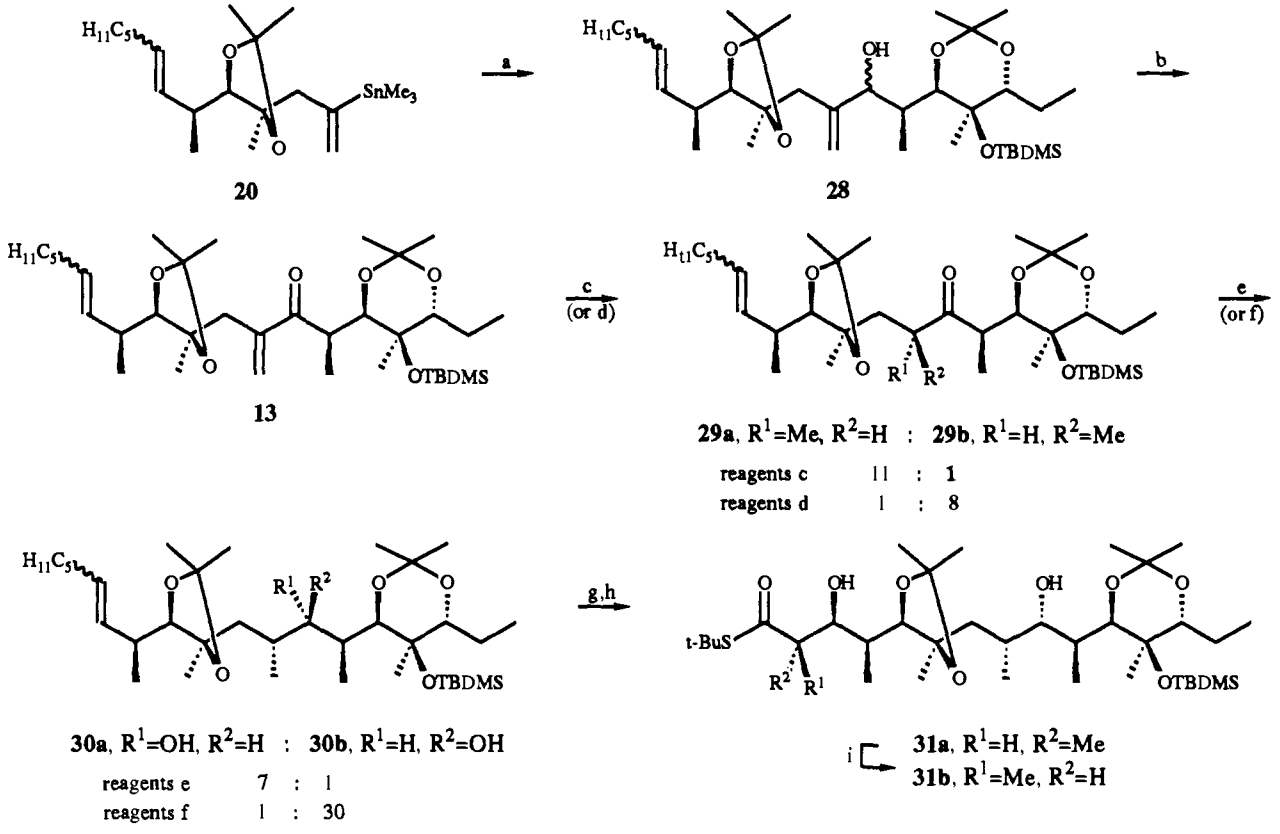
(26) Racemic β-hydroxy ester (±)-**21** was prepared by aldol coupling of ethyl lithioacetate and 2-methyl-2-pentenal as discussed in the Experimental Section.

(27) In contrast to esters, lactones undergo clean monoaddition of organolithium reagents: (a) Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246. (b) Uusvuori, R.; Hase, T. A. *Synth. Commun.* **1982**, *12*, 1081. For example, model studies show that 2-lithio-1-octene adds to γ-butyrolactone to give the corresponding enone alcohol in 85% yield. The reaction must be conducted in ether and quenched with trimethylsilyl chloride then water to achieve clean monoaddition.

(28) Boland, W.; Ney, P.; Jaenicke, L. *Synthesis* **1980**, 1015.

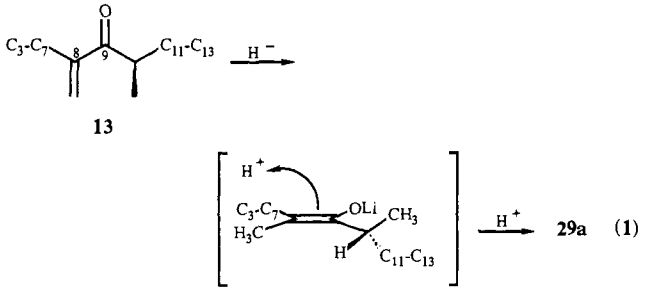
(29) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

Scheme IV. Coupling of the C3–C8 (**20**) and C9–C15 (**27**) Segments[a]



[a] Reagents and conditions: (a) MeLi (1 equiv), THF, −15 °C; **27** (1 equiv), THF, −15 °C → 25 °C; (b) DMSO (18 equiv), $(COCl)_2$ (8 equiv), $(Et)_3N$ (36 equiv), CH_2Cl_2, −65 °C → 25 °C; (c) $NiCl_2{\cdot}6H_2O$ (0.3 equiv), $NaBH_4$ (57 equiv), MeOH, 25 °C; (d) L-selectride (2 equiv), Et_2O, −78 °C; 2,6-di-*tert*-butylpyridinium hydrochloride (3.5 equiv), Et_2O, −120 °C; (e) L-selectride (3 equiv), toluene, −10 °C; (f) $LiAlH_4$ (6 equiv), toluene, −92 °C; (g) O_3, CH_2Cl_2, −78 °C; Me_2S, −78 °C; (h) *t*-$BuSCOC_2H_5$ (33 equiv), LDA (33 equiv), THF, −78 °C; AcOH (40 equiv), THF, −107 °C; (i) *t*-BuLi (45 equiv), TMEDA (106 equiv), THF, −110 °C; AcOH (90 equiv), THF, −110 °C.

The original plan to control the stereochemistry at C8 was to make use of stereoselective enolate generation via conjugate reduction of the enone **13**, followed by kinetic protonation to afford the 8*R* ketone **29a** (R^1 = Me). Initially, the stereoselectivity of 1,4-reduction of the enone was in question, but model studies showed that conjugate reduction of related enones proceeds with high selectivity in the desired direction: there is an excellent correlation between the s-cis/s-trans ground-state ratios of acyclic enones and the *E*/*Z* ratio of the enolates derived from them by conjugate reduction.[30] It was therefore anticipated that the enolate generated from the enone **13** would exist predominately as the desired *Z*-isomer, and kinetic protonation from the (apparently) less sterically hindered re face would afford the desired 8*R* epimer **29a** (eq 1).



(1)

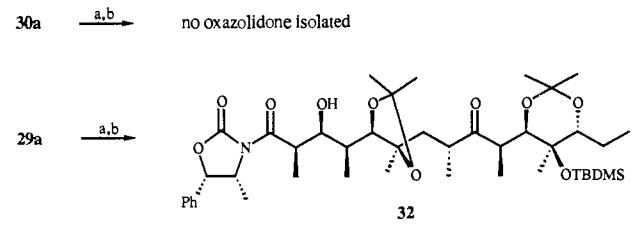
In the complex synthetic intermediate **13**, however, treatment with L-selectride at −78 °C followed by kinetic protonation at −110 °C with 2,6-di-*tert*-butylpyridinium hydrochloride afforded, in 82% yield, an 8:1 ratio of stereoisomers favoring the unnatural 8*S* epimer **29b** (R^2 = Me), contrary to our predictions and extensive model studies. Thus, either the (*E*)-enolate is formed preferentially and protonated from the predicted face or the expected (*Z*)-enolate undergoes protonation from the si face. Fortunately, after a number of attempts, the 8*R* configuration was established with good stereoselectivity by conjugate reduction with $NiCl_2{\cdot}6H_2O/NaBH_4$,[31] which afforded in 90% yield a 10:1 mixture of ketones **29a**/**29b** favoring the 8*R* epimer (**29a**; R^1 = Me). At present, the origin of the stereoselectivity of either reduction is not understood, but these results emphasize that stereocontrol in complex acyclic molecules such as **13** may depend on *overall* conformation and cannot be reliably predicted based on a myopic view of a single α-stereogenic center.

In spite of this quandary, we were next confronted with the necessity of reducing the C9 carbonyl group in a stereocontrolled fashion. Initially it was the 9*S* epimer that was sought, based on Woodward's result that a protected derivative of the 9*S* seco acid **8** lactonizes in a much higher yield than does the corresponding 9*R* diastereomer.[5b] Following chromatographic separation of the ketone mixture **29a**/**29b** prepared above, the 8*R* epimer (**29a**) was stereoselectively reduced with $LiAlH_4$ in toluene at −92 °C to afford a 90% yield of a 30:1 mixture favoring the 9*R* epimeric alcohol **30b** (R^2 = OH) which could be readily separated from the 9*S* derivative by simple chromatography. If the ketone **29a** is instead reduced with L-selectride in toluene at 0 °C, the stereoselectivity of the reaction is reversed, and the 9*S* epimer (**30a**; R^1 = OH) is favored by 7:1 (97% yield). Once again, this stereoselectivity is difficult to rationalize, but it is noteworthy that the last two reactions (conjugate reduction of the enone **13** and reduction of the resulting ketone **29a**) make it possible to obtain, at will, *either* C8 epimer of the 9-keto derivative and *either*

(30) Chamberlin, A. R.; Reich, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 1440.

(31) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.

Scheme V. Preparation of Oxazolidone **31**[a]



32

[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C; Me_2S, −78 °C → 25 °C; (b) (4*R*,5*R*)-4-methyl-5-phenyl-*N*-propionyl-2-oxazolidone (20 equiv), $(n\text{-Bu})_2BOTf$ (22 equiv), $(i\text{-Pr})_2EtN$ (24 equiv), CH_2Cl_2, −78 °C → 25 °C.

C-9 alcohol with the natural stereochemistry at C8. It should also be mentioned that reduction of the 8*S* ketone (**29b**) with $LiAlH_4$ provides a single C9 epimer, but the stereochemistry has yet to be determined.

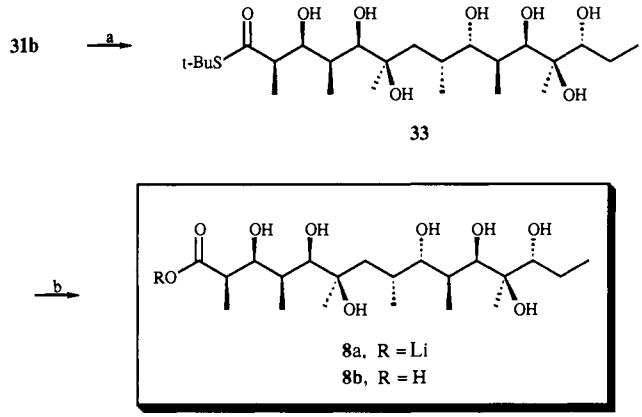
With nine of the 11 stereogenic centers of the seco acid **8** in place, the remaining two centers were readily introduced using the methodology of Woodward et al.[5a] Ozonolysis of **30a** afforded the corresponding aldehyde, which underwent stereoselective aldol coupling with the enolate of *S*-*tert*-butyl thiopropionate[32] to give the expected Cram product **31a** (R^2 = Me)[33] as a 13:1 mixture favoring the epimer with the unnatural *S*-configuration at C2 (81% from **30a**). After separation of the 2*R* and 2*S* stereoisomers by radial chromatography (for analytical purposes), epimerization of the 2*S* to the desired 2*R* configuration was readily effected by enolate generation at −78 °C followed by kinetic protonation at −110 °C to afford **31b** (R^1 = Me; 93% based on recovered **31a**). Interestingly, the intermediate aldehyde from the ozonolysis of **30a** is susceptible to acid-catalyzed (SiO_2) α-epimerization without undergoing significant β-elimination. In the present study, this has proven to be a minor nuisance, yet in the future will provide a means of preparing the C4 diastereomer of the seco acid **8**.

As an alternative to the thio ester enolate conditions of Woodward et al.,[5a] we also attempted the well-precedented asymmetric aldol methodology of Evans et al.[34] which would introduce, in a single step, the C1–C2 fragment with the correct stereochemistry at C2 and C3. In addition, this route would provide greater flexibility in that the other C2/C3 diastereomer could be readily obtained by merely utilizing a different chiral auxiliary. However, no aldol coupling products were detected when the boron enolate of (4*R*,5*R*)-4-methyl-5-phenyl-*N*-propionyl-2-oxazolidone[33] was added to the aldehyde derived from ozonolysis of alcohol **30a** (Scheme V). In direct contrast, the aforementioned chiral boron enolate did readily add to the aldehyde prepared from ozonolysis of the ketone **29a** to afford the oxazolidone **32**. Not surprisingly, however, selective reduction the C9 ketone in the presence of the oxazolidine functionality failed. Although this problem forced us to abandon this synthetic route to the seco acid **8**, we were able to utilize the oxazolidone **32** in correlation studies to support the stereochemical assignment at C2 and C3 of thio ester **31b** (vide infra).

Preparation of the thio ester **31b** marks the completion of the entire backbone of the seco acid **8** with all the requisite stereogenic centers intact, leaving only what appeared to be a delicate deprotection sequence remaining. After some experimentation, selective removal of both acetonide protecting groups as well as the silyl ether was accomplished in one step with a 1:1 solution of H_2O/MeOH saturated with $NH_2OH{\cdot}HCl$[5b] to afford polyol-thio ester **33** in 84% yield (Scheme VI). Finally, hydrolysis of the thioester **33** to the target 9*S*-dihydroerythronolide A seco acid (**8**) was effected, in 98% yield, with lithium hydroxide in aqueous THF. Because of the inherent instability of the free acid, its presence was confirmed by infrared spectroscopy, but detailed

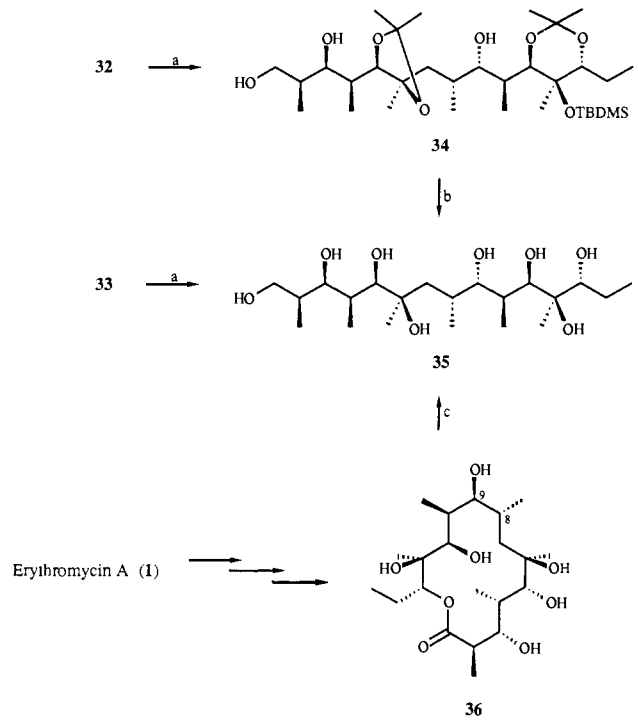
(32) Wemple, J. *Tetrahedron Lett.* **1975**, 3255.
(33) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(34) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23 and references cited therein.

Scheme VI. Deprotection of Thio Ester **31b** to Seco Acid **7**[a]



[a] Reagents and conditions: (a) 1:1 MeOH/H_2O saturated with $NH_2OH{\cdot}HCl$, KH_2PO_4, reflux; (b) LiOH (1 equiv), 1:1 THF/H_2O, 25 °C.

Scheme VII. Correlation Studies[a]



[a] Reagents and conditions: (a) $LiAlH_4$ (40 equiv), THF, 0 °C; (b) 1:1 MeOH/H_2O saturated with $NH_2OH{\cdot}HCl$ KH_2PO_4, reflux; (c) $LiAlH_4$ (48 equiv), THF, 50 °C.

spectral characterization was carried out on the corresponding lithium carboxylate.

Correlation Studies. Preliminary evidence supporting the stereochemical assignment at C2 and C3 in thio ester **31b** was obtained through chemical correlation with the Evans aldol product **32** (Scheme VII). Reduction of the oxazolidone **32** with $LiAlH_4$ gave the expected triol **34**, which upon deprotection afforded the corresponding polyol **35**. For comparison, a sample of **35** was also obtained by $LiAlH_4$ reduction of the thio ester **33**. The polyols (**35**) derived from the oxazolidone **32** and the thio ester **33** shared identical spectroscopic and chromatographic properties, thus supporting the 2*R*,3*S* configuration assigned to the thio ester **31b**.

Ultimate verification of the stereochemistry of **33** (and **32**) was obtained by careful comparison of **35** with a sample of the same polyol prepared by chemical degradation of natural erythromycin A. Jones and Rowly[35] have reported the degradative conversion

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

of erythromycin A into the 9S-dihydroerythronolide A aglycon (**36**), which upon $LiAlH_4$ reduction supplied the polyol **35**. The spectral properties and chromatographic elution profiles in various solvents of the synthetic polyol **35** were identical with those of the polyol prepared through chemical degradation of erythromycin A.

In summary, an efficient enantioselective synthesis of 9S-dihydroerythronolide A seco acid (**8**) starting from the readily available chiral β-hydroxy esters **11** and **12** has been accomplished. The synthesis reported here is convergent and quite efficient, in addition to allowing either diastereomer at C2, C4, C8, and C9 in synthetic intermediates to be readily prepared with good stereoselectivity. Because these centers are established late in the synthetic sequence, it should be possible to produce a variety of diastereomers of seco acid **8** starting from a single key intermediate, namely the enone **13**. During the course of this work, we have developed methodologies for stereoselective, kinetically controlled iodolactonization[18] as well hydroxyl-directed methylation,[19] two synthetic tools that have proven to be generally applicable in the stereoselective preparation of highly functionalized γ-lactones. In addition, the synthesis spawned a regio- and stereoselective method of generating highly substituted enolates that are unobtainable by conventional means.[29] Studies are currently underway to prepare various protected diastereomers of seco acid **8** based on the synthetic route described above.

Experimental Section

Ethyl (±)-3-Hydroxy-4-methyl-4-pentenoate [(±)-11]. To a solution of lithium diisopropylamide (197 mmol, prepared from 28.8 mL (205 mmol) of diisopropylamine and 73.2 mL (197 mmol) of a 2.69 M solution of *n*-BuLi in hexanes) in 300 mL of anhydrous THF at −78 °C was added ethyl acetate (13.3 g, 151 mmol). After stirring at −78 °C for 0.5 h, the mixture was treated with freshly distilled methacrolein (10.6 g, 151 mmol). The reaction was allowed to stir at −78 °C for 1 h and was then quenched with a solution of glacial acetic acid (23.6 g, 394 mmol) in 200 mL of THF. After warming to ambient temperature, the reaction was diluted with 200 mL of saturated aqueous $NaHCO_3$, the aqueous and organic layers were separated, and the former was extracted with either (3 × 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to afford 25.4 g of a yellow oil which was subjected to fractional distillation (60–63 °C, 1 mmHg) to afford 13.2 g (55%) of (±)-**11** as a clear oil [R_f 0.63 (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3 H), 1.72 (s, 3 H), 2.52 (d, J = 8.4 Hz, 2 H), 2.52 (br s, 1 H, OH), 4.14 (q, J = 7.1 Hz, 2 H), 4.40 (t, J = 5.3 Hz, 1 H), 4.84 (s, 1 H), 4.99 (s, 1 H)]. (±)-**11** was shown to be a mixture of enantiomers using ^1H NMR and a chiral shift reagent as follows: a sample of (±)-**11** (10 mg/mL of $CDCl_3$) displayed a single methylene quartet for the ethyl ester (4.17 ppm, J = 7.1 Hz), while an identical sample containing 2.4 mg of tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorato]europium(III) displayed two methylene quartets (4.25 ppm, J = 7.1 Hz and 4.28 ppm, J = 7.1 Hz) arising from the ethyl esters of each enantiomer: IR (CCl_4) 3480, 2980, 2940, 1730 cm^{-1}; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 13.8, 17.6, 40.0, 60.3, 71.2, 110.9, 145.5, 172.0; EIMS, m/z (rel intensity) 158 (M^+ 2), 143 (4), 141 (0.3), 88 (11), 70 (100); HRMS, exact mass calcd for $C_8H_{14}O_3$: M^+ requires 158.0943, found 158.0917.

Ethyl (3*R*)-3-Hydroxy-4-methyl-4-pentenoate [(+)-11]. Alcohol (±)-**11** was resolved according to the method of Sharpless et al.[16a] as follows. A solution of (+)-diisopropyl tartrate (42 g, 179 mmol) in 1 L of anhydrous CH_2Cl_2 at −25 °C was treated with freshly distilled titanium(IV) isopropoxide (40.8 g, 143 mmol). After 15 min, racemic allylic alcohol (±)-**11** (18.9 g, 119 mmol) was added, and the mixture was stirred for an additional 15 min. *tert*-Butyl hydroperoxide (358 mmol, 125 mL of a 2.86 M solution in 1,2-dichloroethane[36]) was added slowly, and the reaction temperature was maintained at −25 °C for 96 h (reaction shown to be 57% complete by GC analysis). The reaction was poured into a stirred solution of 50 mL of H_2O in 2 L of acetone at −50 °C, and after being allowed to reach ambient temperature was filtered through Celite. Removal of the solvents in vacuo followed by fractional distillation (60–65 °C, 1 mmHg) gave a mixture of chiral allylic alcohol (+)-**11** and the corresponding epoxy ester, which was separated by flash chromatography (SiO_2, 2:1 hexanes/Et_2O) to afford 2.95 g (16% based on racemic starting material) of (+)-**11** as a clear oil: $[\alpha]_D^{25}$ +14.6° (c 2.31, EtOH). Addition of tris[3-[(trifluoromethyl)hydroxymethylene]-(+)-camphorato]europium(III) to a ^1H NMR sample of (+)-**11** showed no evidence of the (5,*R*)-enantiomer. The R_f, ^1H NMR, ^{13}C NMR, IR, and mass spectra were identical with those obtained for (±)-**11**.

(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-5-methyl-2(3*H*)-furanone (14). Lactone **14** was prepared by a modification of the previously reported procedure.[18] A solution of β-hydroxy ester (+)-**11** (482 mg, 3 mmol) in 3 mL of a 2:1 THF/Et_2O mixture was treated with NaOH (9 mmol, 6 mL of a 1 N aqueous solution) and heated to reflux. After 2.5 h, the reaction was cooled to 0 °C and was brought to pH 8–9 with 1 N aqueous HCl. The resulting solution was treated with a 0 °C solution of I_2 (2.3 g, 9.0 mmol) in 9 mL of Et_2O, protected from light, and stirred for 3 h at 0 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, the resulting two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to yield 738 mg (96% crude) of a yellow oil which was homogeneous by TLC. HPLC analysis showed lactone **14** to exist as a 20:1 mixture of diastereomers which was used as such in the next reaction. An analytically pure sample of **14** was obtained by flash chromatography (SiO_2, 1:3 hexanes/Et_2O): R_f 0.28 (Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 3 H), 2.65 (apparent dd, J = 18.0, 1.5 Hz, 1 H), 2.99 (apparent dd, J = 18.0, 5.5 Hz, 1 H), 2.89 (d, J = 4.8 Hz, 1 H, OH), 3.49 (ABq, $\Delta\nu_{AB}$ = 25.0, J_{AB} = 10.3 Hz, 2 H), 4.39 (ddd, J = 5.5, 4.8, 1.5 Hz, 1 H); IR ($CDCl_3$) 3450, 2980, 2940, 1780, 1380, 1160, 1080, 910 cm^{-1}; EIMS, m/z (rel intensity) 256 (M^+, 14), 228 (43), 185 (100), 129 (M^+ − I, 9), 127 (I, 70); Anal. Calcd for $C_6H_9O_3I$: C, 28.13; H, 3.54; I, 49.58. Found: C, 28.23; H, 3.64; I, 49.36.

(3*R*,4*R*,5*S*)-Dihydro-3,5-dimethyl-4-hydroxy-5-(iodomethyl)-2-(3*H*)-furanone (15). Lactone **14** was stereoselectively methylated as previously described.[19] A solution of iodolactone **14** (1.59 g, 6.2 mmol) in 6 mL of anhydrous THF was added dropwise to a solution of lithium diisopropylamide (31 mmol, prepared from 4.5 mL (32 mmol) of diisopropylamine and 20.7 mL (31 mmol) of a 1.5 M solution of *n*-BuLi in hexane) in 30 mL of anhydrous THF at −78 °C. After stirring for 1 h, the reaction mixture was transferred by cannula to a −78 °C solution of MeI (8.94 g, 63 mmol) in 40 mL of THF. After 2 h, the reaction was quenched with a solution of glacial acetic acid (6.29 g, 105 mmol) in 20 mL of THF, allowed to reach ambient temperature, and diluted with 100 mL of saturated aqueous $NaHCO_3$. The two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford 2.32 g of an oil which was subjected to flash chromatography (SiO_2, 1:6 hexanes/Et_2O) to afford 180 mg of starting lactone and 1.26 g (85% based on recovered lactone **14**) of methylated lactone **15**. HPLC analysis showed lactone **15** to exist as a 15:1 mixture of diastereomers which was used as such in the ensuing reaction: R_f 0.44 (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J = 7.2 Hz, 3 H), 1.62 (s, 3 H), 2.87 (apparent quartet, J = 7.3 Hz, 1 H), 2.93 (d, J = 5.4 Hz, 1 H, OH), 3.44 (d, J = 3.0 Hz, 2 H), 4.09 (dd, J = 8.4, 5.4 Hz, 1 H); IR ($CHCl_3$) 3450, 2990, 1760, 1095 cm^{-1}; EIMS, m/z (rel intensity) 270 (M^+, 34), 242 (100), 185 (68), 143 (23); HRMS, exact mass calcd for $C_7H_{11}IO_3$: M^+ requires 269.9753, found 269.9739.

(3*R*,4*R*,5*S*)-Dihydro-4-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethyl-5-(iodomethyl)-2(3*H*)-furanone (9). To a solution of iodolactone **15** (1.27 g, 4.7 mmol) in 30 mL of anhydrous CH_2Cl_2 at 0 °C was added 2,6-di-*tert*-butylpyridine (1.8 g, 9.4 mmol) followed by *tert*-butyldimethylsilyltriflate (1.87 g, 7.1 mmol).[20] The reaction was stirred at 0 °C for 45 min and was then poured into 15 mL of MeOH at 0 °C. After adding H_2O (30 mL), the aqueous and organic layers were separated and the former was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give 2.15 g of an oil which was purified by flash chromatography (Florisil, 8:1 hexanes/Et_2O) to afford 1.68 g (93%) of protected lactone **9** which HPLC analysis showed to exist as a single diastereomer: mp 89–90 °C; R_f 0.57 (2:1 Et_2O/hexanes), $[\alpha]_D^{27}$ +32.6° (c 1.53, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.14 (s, 6 H), 0.93 (s, 9 H), 1.31 (d, J = 7.2 Hz, 3 H), 1.56 (s, 3 H), 2.81 (dq, J = 9.0, 7.2 Hz, 1 H), 3.40 (ABq, $\Delta\nu_{AB}$ = 27.4, J_{AB} = 11.4 Hz, 2 H), 3.99 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ −4.3, −4.0, 10.0, 13.7, 18.0, 25.9, 26.9, 43.0, 81.5, 83.1, 175.2; IR (CCl_4) 2960, 2935, 2860, 1790, 1130 cm^{-1}; EIMS, m/z (rel intensity) 385 (MH^+, 0.1), 327 (M^+ − C_4H_9, 47), 283 (19), 271 (38), 185 (64), 155 (70), 115 (100); HRMS, exact mass calcd for $C_{16}H_{25}IO_3Si$: MH^+ − I requires 385.0696, found 385.0725.

(3*R*,4*R*,5*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3,5-dimethyl-2(*R*/*S*)-hydroxy-5-(iodomethyl)-2,3,4,5-tetrahydrofuran (16). To a suspension of lactone **9** (3.19 g, 8.3 mmol) in 200 mL of anhydrous Et_2O at −78 °C was added dropwise DIBAL (12.5 mmol, 8.3 mL of a 1.5 M solution in toluene). The reaction was stirred at −78 °C for 1 h and was then quenched with 50 mL of MeOH. Saturated aqueous sodium tartrate

(36) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.
(37) Schleppnik, A. A.; Zienty, F. B. *J. Org. Chem.* **1964**, *29*, 1910.

(200 mL) and Et_2O (100 mL) were added, and the two layers were separated. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo yielding 3.35 g of crude lactol **16** as a viscous oil which was used in the next reaction without further purification: R_f 0.17 (5:1 hexanes/Et_2O): ^1H NMR (250 MHz, $CDCl_3$, anomer mixture) δ 0.10 and 0.09 (2s, 3 H), 0.12 and 0.11 (2s, 3 H), 0.91 (s, 9 H), 1.08 and 1.17 (2d, J = 7 Hz, 3 H), 2.17–2.38 (m, 1 H), 3.20 (m, 2 H), 3.34 and 3.36 (2s, 3 H), 3.76 and 4.09 (2d, J = 9.9 and 7.4 Hz, respectively, 1 H), 5.02 and 5.27 (apparent t, J = 4.2 Hz, d, J = 4.7 Hz, 1 H); IR (CCl_4) 3620, 3450, 2940, 2860, 1260, 1030, 1010, 985, 810 cm^{-1}; CIMS, m/z (rel intensity) 387 (MH^+, 0.4), 369 ($MH^+ - H_2O$, 93), 243 (11), 185 (10), 71 (100).

(2*S*,3*R*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-1,2-epoxy-5(*E*/*Z*)-(1-hexylidene)pentane (17c). A slurry of *n*-hexyltriphenylphosphonium bromide (14.2 g, 33.2 mmol) in 60 mL of anhydrous toluene at room temperature was treated with *n*-BuLi (33.2 mmol, 21.8 mL of a 1.52 M solution in hexanes). After stirring for 30 min, a solution of crude lactol **16** (3.35 g, 8.3 mmol) in 20 mL of dry toluene was added dropwise to the red ylide solution. After stirring for 1 h, the reaction was quenched by adding 30 mL of H_2O. After adding 50 mL of Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave 3.35 g of an oil which was purified by flash chromatography (SiO_2, 70:1 hexanes/Et_2O) to afford 1.73 g (64% from lactone **9**) of epoxide **17c** as an *E*:*Z* mixture of geometrical isomers. See Supplementary Material for spectral data.

(4*R*,5*R*,6*S*)-4,5-Dihydroxy-4,6-dimethyl-7(*E*/*Z*)-(1-hexylidene)-hept-1-yne (18). To a suspension of epoxide **17c** (1.63 g, 4.99 mmol) in 10 mL of anhydrous DMSO was added lithium acetylide–ethylenediamine complex (3.0 g, 33 mmol) with rapid stirring. The slurry was stirred for 3 days at which time an additional 3.0 g (33 mmol) of the acetylide reagent was added. After a total of 6 days, the reaction was cooled to 0 °C and was carefully quenched with 10 mL of H_2O. After adding 20 mL of Et_2O, the two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 1.9 g of a viscous oil which was subjected to flash chromatography (SiO_2, 2:1 hexanes/Et_2O) to afford 1.10 g (92%) of alkynediol **18** which crystallized on standing. See Supplementary Material for spectral data.

(4*R*,5*R*,6*S*)-4,6-Dimethyl-7(*E*/*Z*)-(1-hexylidene)-4,5-(isopropylidenedioxy)hept-1-yne (19). A solution of alkynediol **18** (1.0 g, 4.2 mmol) in 150 mL of anhydrous acetone was treated with *p*-toluenesulfonic acid (12.6 mmol, 2.40 g of the acid monohydrate azeotropically dried with benzene, 3 × 3 mL). After stirring for 1 h, the reaction was poured into 300 mL of a saturated aqueous $NaHCO_3$/ice mixture with vigorous stirring and was diluted with 200 mL of Et_2O. The aqueous and organic layers were separated, and the former was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give 1.17 g of an oily solid which was subjected to flash chromatography (SiO_2, 15:1 hexanes/Et_2O) to afford 1.12 g (96%) of acetonide **19** as an *E*:*Z* mixture of geometrical isomers. See Supplementary Material for spectral data.

(4*R*,5*R*,6*S*)-4,6-Dimethyl-7(*E*/*Z*)-(1-hexylidene)-4,5-(isopropylidenedioxy)-2-(trimethylstannyl)hept-1-ene (20).[23b] To a stirred solution of hexamethylditin (7.85 g, 24.0 mmol) in 25 mL of anhydrous THF at −20 °C was added dropwise MeLi (22.7 mmol, 19.4 mL of a 1.17 M solution in Et_2O). After stirring for 0.5 h at −20 °C, the solution was cooled to −50 °C, and CuBr·Me_2S (4.90 g, 24.0 mmol) was added, in two portions, to produce a deep red color. The mixture was stirred at −50 °C for 1 h and a solution of alkyne **19** (1.15 g, 4.13 mmol) in 10 mL of dry THF was added dropwise followed by anhydrous MeOH (8.0 g, 250 mmol). The reaction mixture was kept at ca. −65 °C for 16 h and was then quenched by adding 10 mL of saturated aqueous NH_4Cl. The two layers were separated, and the aqueous phase was extracted with hexanes (3 × 30 mL). The organic layers were combined, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded 3.59 g of a clear oil which was subjected to flash chromatography (SiO_2, 70:1 hexanes/Et_2O) to yield 0.25 g of starting alkyne **19** and 1.38 mg (96% based on recovered alkyne **19**) of vinylstannane **20**. See Supplementary Material for spectral data.

Ethyl (±)-3-Hydroxy-4-methyl-4-heptenoate [(±)-21]. To a solution of lithioethyl acetate (262 mmol; prepared as in the synthesis of (±)-**11**) in 450 mL of THF at −78 °C was added dropwise freshly distilled 2-methyl-2-pentenal (25.7 g, 262 mmol). The reaction was stirred at −78 °C for 1 h and was quenched with glacial acetic acid (34.5 g, 570 mmol) in 200 mL of THF. The mixture was warmed to ambient temperature, was diluted with 150 mL of saturated aqueous $NaHCO_3$, and finally extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 82.4 g of an oil which was fractionally distilled (65–70 °C, 0.4 mmHg) to afford 40.6 g (83%) of allylic alcohol (±)-**21** as a clear viscous oil: R_f 0.38 (2:1 hexanes/Et_2O); ^1H NMR (300 MHz, $CDCl_3$ δ 0.95 (t, J = 7.6 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.63 (d, J = 1.1 Hz, 3 H), 2.03 (apparent quintet, J = 7.0 Hz, 2 H), 2.55 (dd, J = 8.0 Hz, 2 H), 2.89 (br s, 1 H, OH), 4.26 (q, J = 7.1 Hz, 2 H), 4.41 (dd, J = 9.0 and 3.6 Hz, 1 H) 5.45 (dt, J = 7.1, 0.7 Hz, 1 H); IR (CCl_4) 3500, 2970, 1715, 1620, 1170, 1030 cm^{-1}; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 13.6, 13.9, 20.5, 40.1, 60.4, 61.9, 72.0, 73.2, 128.3, 134.5, 172.3; EIMS, m/z (rel intensity) 186 (M^+, 16), 168 (40), 157 (61), 98 (100), 88 (12).

Ethyl (3*R*,4*S*,5*S*)-4,5-Epoxy-3-hydroxy-4-methylheptanoate (12). Chiral epoxide **12** was prepared from (±)-**21** by using the methodology of Sharpless et al.[16b] A solution of (−)-diethyl tartrate (10.0 g, 48.5 mmol) in 300 mL of anhydrous CH_2Cl_2 at −25 °C was treated with freshly distilled titanium(IV) isopropoxide (9.2 g, 32.3 mmol). After 15 min, allylic alcohol (±)-**21** (6.0 g, 32.2 mmol) was added, and the mixture stirred for an additional 15 min at which time *tert*-butyl hydroperoxide (22.6 mmol, 7.1 mL of a 3.2 M solution in dichloroethane[35]) was added dropwise. After 25 min (reaction 29% complete by GC), the reaction was poured into a −50 °C solution of 10 mL of H_2O in 600 mL of acetone. The reaction mixture was worked up as with β-hydroxy ester (+)-**11** to yield 16 g of a crude product which was subjected to filtration through SiO_2 to afford 1.42 g of an epoxide/olefin mixture which was used in the next reaction without further purification. An analytical sample of epoxide **12** was obtained by flash chromatography (SiO_2, 4:3 hexanes/Et_2O): R_f 0.51 (Et_2O); $[\alpha]_D^{20}$ +17.6° (*c* 1.52, EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 1.02 (t, J = 6.8 Hz, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.29 (s, 3 H), 1.58 (dq, J = 6.7, 7.3 Hz, 2 H), 2.45 (ABX, $\Delta\nu_{AB}$ = 38.6, J_{AB} = 15.6, J_{AX} = 10.4, J_{BX} = 3.5 Hz, 2 H), 2.83 (d, J = 2.5 Hz, 1 H, OH), 2.95 (t, J = 6.7 Hz, 1 H), 3.80 (dt, J = 10.4, 2.5 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H); IR (neat) 3510, 2970, 2940, 1725, 1455, 1370, 1175, 1020 cm^{-1}; CIMS, m/z (rel intensity) 203 (MH^+, 4), 185 (3), 175 (100), 157 (26), 139 (14); HRMS, exact mass calcd for $C_{10}H_{18}O_4$: MH^+ requires 203.1283, found 203.1276.

(4*R*,5*R*,6*R*)-Dihydro-4-hydroxy-5-(1-hydroxypropyl)-5-methyl-2-(3*H*)-furanone (22). A solution of the olefin/epoxide mixture prepared above (10.3 g, 51 mmol as determined by GC analysis) in 500 mL of anhydrous EtOH at 0 °C was treated with HCl (67 mmol, 67 mL of a 1 M solution in EtOH). After 15 min at 0 °C, NaI (15.4 g, 102 mmol) was added, and the resulting mixture was stirred at ambient temperature for 12 h at which time it was quenched by the addition of 30 mL of saturated aqueous $NaHCO_3$ followed by 50 mL of saturated aqueous Na_2SO_3. The resulting solution was extracted exhaustively with ethyl acetate (8 × 150 mL) and CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to afford 32 g of an oily solid which was purified by flash chromatography (SiO_2, gradient eluent system of 100% Et_2O → 1:1 Et_2O/ethyl acetate → 100% ethyl acetate) to afford 7.0 g (79%) of lactone **22**: R_f 0.18 (Et_2O); $[\alpha]_D^{25}$ +25.4° (*c* 0.66, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, J = 7.6 Hz, 3 H), 1.24 (s, 3 H), 1.51–1.62 (m, 3 H), 2.53 (dd, J = 18.2 and 1.3 Hz, 1 H), 2.93 (dd, J = 18.3, 6.1 Hz, 1 H), 3.26 (d, J = 4.4 Hz, 1 H, OH), 3.83 (dd, J = 18.3, 6.1 Hz, 1 H), 4.16 (d, J = 4.1 Hz, 1 H, OH), 4.26 (dd, J = 6.1 and 1.2 Hz, 1 H); IR (CCl_4) 3400 (br), 2960, 2930, 2870, 1755, 1060, 965 cm^{-1}; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 10.6, 18.4, 23.9, 38.1, 73.4, 74.0, 89.8, 176.2; CIMS, m/z (rel intensity) 175 (MH^+, 100), 157 ($MH^+ - H_2O$, 25), 139 ($MH^+ - 2H_2O$, 13), 89 (14); HRMS, exact mass calcd for $C_8H_{14}O_4$: MH^+ requires 175.0970, found 175.0969.

(3*R*,4*R*,5*R*,6*R*)-Dihydro-3,5-dimethyl-4-hydroxy-5-(1-hydroxypropyl)-2(3*H*)-furanone (23). Lactone **22** was stereoselectively methylated as previously described.[19] A solution of dihydroxy lactone **22** (2.19 g, 12.6 mmol) in 10 mL of anhydrous THF was slowly added to a −78 °C solution of lithium diisopropylamide (126 mmol, prepared from 17.7 mL (126 mmol) of diisopropylamine and 50.4 mL (126 mmol) of 2.5 M *n*-BuLi) in 130 mL of anhydrous THF. The solution was stirred for 1 h and was added via cannula to a −78 °C solution of MeI (35.8 g, 252 mmol) in 100 mL of THF. After stirring at −78 °C for 2 h, the reaction was quenched with a solution of glacial acetic acid (15.7 g, 267 mmol) in 50 mL of THF. After warming to room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 1:3 hexanes/Et_2O) afforded 1.02 g (5.87 mmol) of starting lactone **22** and 1.18 g (93% based on returned starting material) of the desired methylated lactone **23**. On the basis of ^1H NMR analysis, lactone **23** existed as an 88:12 mixture of diastereomers which was used as such in the ensuing reaction: R_f 0.35 (Et_2O); ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.04 (t, J = 7.4 Hz, 3 H), 1.33 (d, J = 7.4 Hz, 3 H), 1.43 (s, 3 H), 1.48–1.78 (m, 2 H), 2.83 (apparent quintet,

J = 7.4 Hz, 1 H), 3.72 (br s, 1 H, OH), 3.82 (dd, J = 10.4 Hz, 1 H), 3.98 (d, J = 7.4 Hz, 1 H), 4.46 (br s, 1 H, OH); IR (CCl_4) 3420, 2990, 2940, 2870, 1770, 1460, 1390, 1320, 1100, 980 cm^{-1}; CIMS, m/z (rel intensity) 189 (MH^+, 100), 171 ($MH^+ - H_2O$, 18), 153 ($MH^+ - 2H_2O$, 15), 103 (6); HRMS, exact mass calcd for $C_9H_{16}O_4$: MH^+ requires 189.1127, found 189.1109.

(3*R*,4*R*,5*R*,6*R*)-Dihydro-3,5-dimethyl-4-hydroxy-5-(1-hydroxypropyl)-4,6-*O*-isopropylidene-2(3*H*)-furanone (10). To a solution of dihydroxy lactone **23** (190 mg, 1.0 mmol) in 30 mL of anhydrous acetone was added *p*-toluenesulfonic acid (3 mmol, 570 mg of the acid monohydrate azeotropically dried with benzene, 3 × 1 mL) at ambient temperature. After stirring overnight the reaction was poured into 50 mL of a saturated aqueous $NaHCO_3$/ice mixture with stirring. The solution was diluted with Et_2O (50 mL), the two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting crude oil was subjected to flash chromatography (SiO_2, 4:1 hexanes/Et_2O) to yield 215 mg (94%) of lactone **10** as a single diastereomer: mp 57–58 °C; R_f 0.70 (Et_2O); $[\alpha]_D^{25}$ +31.7° (c 0.52, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3 H), 1.31 (s, 3 H), 1.33 (s, 3 H), 1.35 (s, 3 H), 1.41 (d, J = 8.1 Hz, 3 H), 1.55–1.63 (m, 2 H), 2.68 (dq, J = 8.1 and 1.1 Hz, 2 H), 3.57 (dd, J = 9.9 and 3.4 Hz, 1 H), 3.77 (d, J = 1.1 Hz, 1 H); IR (CCl_4) 2990, 2940, 2880, 1785, 1460, 1380, 1225, 1170, 1050, 950 cm^{-1}; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 10.2, 16.5, 19.1, 21.5, 23.3, 24.8, 42.2, 73.5, 79.1, 85.4, 100.9, 178.6; CIMS, m/z (rel intensity) 229 (MH^+, 100), 171 ($MH^+ - C_3H_6O$, 17), 153 (7), 112 (16); HRMS, exact mass calcd for $C_{12}H_{20}O_4$: MH^+ requires 229.1439, found 229.1446.

(3*R*,4*R*,5*R*,6*R*)-2(*R*/*S*),4-Dihydroxy-3,5-dimethyl-5-(1-hydroxypropyl)-4,6-*O*-isopropylidene-2,3,4,5-tetrahydrofuran (24). A solution of lactone **10** (1.11 g, 4.8 mmol) in 15 mL of Et_2O at −78 °C was treated with DIBAL (7.3 mmol, 4.9 mL of a 1.5 M solution in toluene). The reaction was stirred at −78 °C for 1 h and was quenched by the careful addition of 10 mL of MeOH. The mixture was warmed to room temperature and was diluted with 200 mL of Et_2O and 300 mL of saturated aqueous sodium tartrate. The two layers were separated, and the aqueous phase was extracted with Et_2O (5 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo yielding 1.19 g (106%) of crude lactol **24** as a white solid which was used in the subsequent reaction without further purification: mp 70–72 °C; R_f 0.31 (1:1 hexanes/Et_2O); ^1H NMR (250 MHz, $CDCl_3$, anomer mixture) δ 0.97 and 0.99 (2t, J = 7.3 Hz, 3 H), 1.16 and 1.13 (2d, J = 7.5 Hz, 3 H), 1.21 (s, 3 H), 1.34 and 1.31 (2s, 3 H), 1.37 and 1.36 (2s, 3 H), 1.39–1.71 (m, 2 H), 2.28–2.39 (m, 1 H), 2.85 (d, J = 4.6 Hz, 1 H), 3.60 and 3.42 (2dd, J = 10.1 and 3.1 Hz, 1 H), 3.69 (t, J = 4.6 Hz, 1 H), 5.46 (t, J = 4.6 Hz, 0.5 H), 5.08 (d, J = 10.2 Hz, 0.5 H); IR (CCl_4) 3630, 3430, 2990, 2950, 1385, 1230, 1180, 1100, 1050, 990 cm^{-1}; CIMS, m/z (rel intensity) 231 (MH^+, 2), 213 ($MH^+ - H_2O$, 65), 173 (5), 155 (31), 114 (22), 97 (100); HRMS, exact mass calcd for $C_{12}H_{22}O_4$: M^+ requires 230.1518, found 230.1554.

(2*S*,3*R*,4*R*,5*R*)-2,4-Dimethyl-4-hydroxy-1-isopropylidene-3,5-(isopropylidenedioxy)heptane (25). A slurry of isopropyltriphenylphosphonium bromide (4.23 g, 10.9 mmol) in 15 mL of anhydrous toluene was treated with *n*-BuLi (10.9 mmol, 7.2 mL of a 1.52 M solution in hexanes), and the resulting mixture was stirred at ambient temperature for 0.5 h. A solution of crude lactol **24** (500 mg, 2.19 mmol) in 6 mL of dry toluene was added to the red ylide suspension, and the resultant mixture was heated at reflux for 3 h. The reaction was cooled to room temperature and was treated with 5 mL of H_2O and 20 mL of Et_2O. The two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 1.61 g of a viscous yellow oil which was subjected to flash chromatography (SiO_2, gradient eluent system of 10:1 → 2:1 hexanes/Et_2O) to afford 87 mg of starting lactol **24** and 321 mg (70% based on unrecovered starting lactol) of olefin **25** as a clear oil: R_f 0.56 (1:1 hexanes/Et_2O); $[\alpha]_D^{25}$ −27.1° (c 0.034, EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 1.09 (s, 3 H), 1.30 (s, 3 H), 1.35 (s, 3 H), 1.40–1.61 (m, 2 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 2.62–2.77 (m, 1 H), 3.20 (d, J = 9.3 Hz, 1 H), 3.39 (dd, J = 10.5, 2.4 Hz, 1 H), 5.07 (d, J = 10.4 Hz, 1 H); IR (CCl_4) 3600, 2990, 2950, 2890, 1460, 1380, 1230, 1180, 1050 cm^{-1}; ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.1, 17.9, 18.9, 21.4, 21.5, 23.5, 24.5, 26.0, 33.8, 76.0, 76.5, 80.1, 100.8, 128.8, 131.5; CIMS, m/z (rel intensity) 257 (MH^+, 0.3), 199 ($MH^+ - C_3H_6O$, 69), 181 (89), 141 (30), 123 (15), 113 (30), 83 (100); HRMS, exact mass calcd for $C_{15}H_{28}O_3$: $M^+ - C_3H_6O$ requires 198.1619, found 198.1606.

(2*S*,3*R*,4*R*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-1-isopropylidene-3,5-(isopropylidenedioxy)heptane (26). To a solution of hydroxy olefin **25** (376 mg, 1.5 mmol) in 2 mL of anhydrous CH_2Cl_2 was added 2,6-lutidine (321 mg, 3 mmol) and *tert*-butyldimethylsilyltriflate (580 mg, 2.2 mmol)[20] at room temperature with stirring. After 48 h, the reaction was quenched with 2 mL of MeOH. The mixture was diluted with 5 mL of Et_2O and 10 mL of saturated aqueous $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 50:1 hexanes/Et_2O) afforded 519 mg (95%) of protected olefin **26** as a clear oil: R_f 0.62 (5:1 hexanes/Et_2O); $[\alpha]_D^{25}$ −13.7° (c 0.044, EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.13 (s, 3 H), 0.90 (s, 9 H), 0.96 (t, J = 7.1 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 1.12 (s, 3 H), 1.29 (s, 3 H), 1.36 (s, 3 H), 1.59 (s, 2 H), 1.63 (d, J = 0.6 Hz, 3 H), 1.67 (d, J = 0.6 Hz, 3 H), 2.63–2.79 (m, 1 H), 3.25 (d, J = 5.1 Hz, 1 H), 3.43 (dd, J = 11.1 and 1.3 Hz, 1 H), 5.15 (br d, J = 10.3 Hz, 1 H); IR (CCl_4) 2970, 2940, 2860, 1385, 1235, 1160, 1120, 1060 cm^{-1}; ^{13}C NMR (62.8 MHz, $CDCl_3$) δ −1.9, −1.2, 11.0, 17.2, 18.1, 18.5, 20.8, 21.4, 23.5, 24.0, 26.2, 31.1, 78.0, 79.9, 80.5, 100.5, 128.8, 130.3; CIMS, m/z (rel intensity) 371 (MH^+, 0.1), 355 ($M^+ - CH_3$, 0.2), 314 ($MH^+ - C_4H_9$, 15), 313 ($MH^+ - C_3H_6O$, 18), 181 (100), 83 (31); HRmS, exact mass calcd for $C_{21}H_{42}O_3Si$: $M^+ - CH_3$ requires 355.2668, found 355.2649.

(2*R*,3*R*,4*R*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-3,5-(isopropylidenedioxy)heptan-1-al (27). A stream of an ozone/oxygen mixture, in which the ozone content had been determined by "titration" with cyclohexene, was bubbled through a solution of protected olefin **26** (1.77 g, 4.77 mmol) in 150 mL of CH_2Cl_2 at −78 °C until just 1 equiv of ozone had been introduced. Methyl sulfide (0.4 mL, 5.5 mmol) was carefully added, and the reaction was allowed to stir at −78 °C for 0.5 h. The mixture was evaporated in vacuo to give 2.1 g of a crude oil which was subjected to flash chromatography (Florisil, 30:1 hexanes/Et_2O) to afford 1.56 g (95%) of aldehyde **27** as a clear oil: R_f 0.42 (5:1 hexanes/Et_2O); $[\alpha]_D^{25}$ +14.0° (c 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.15 (s, 3 H), 0.89 (s, 9 H), 0.97 (t, J = 7.2 Hz, 3 H), 1.10 (s, 3 H), 1.19 (d, J = 7.2 Hz, 3 H), 1.30 (s, 3 H), 1.35 (s, 3 H), 1.52–1.70 (m, 2 H)8 2.72 (ddq, J = 7.2, 5.6, and 1.7 Hz, 1 H), 3.46 (dd, J = 10.9 and 1.2 Hz, 1 H), 3.78 (d, J = 5.6 Hz, 1 H), 9.77 (d, J = 1.7 Hz, 1 H); IR (CCl_4) 2920, 2850, 1720, 1460, 1375, 1140, 1050 cm^{-1}; ^{13}C NMR (62.8 MHz, $CDCl_3$) δ −1.4, −1.1, 10.9, 11.0, 18.8, 20.9, 21.6, 23.8, 24.2, 26.4, 46.3, 76.4, 77.9, 80.0, 101.1, 204.0; EIMS (22 eV), m/z (rel intensity) 329 ($M^+ - CH_3$, 0.1), 229 (10), 201 (11), 199 (79), 171 (100), 143 (70); HRMS, exact mass calcd for $C_{18}H_{36}O_4Si$: $M^+ - CH_3$ requires 329.2148, found 329.2141.

(2*S*,3*R*,4*R*,8*S*,9*R*,10*R*,11*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-1-(*E*/*Z*)-(1-hexylidene)-7(*R*/*S*)-hydroxy-3,4:9,11-bis(isopropylidenedioxy)-2,4,8,10-tetramethyl-6-methylidenetridecane (28). To vinylstannane **20** (650 mg, 1.47 mmol) in 5.0 mL of anhydrous THF at −15 °C was added dropwise MeLi (1.47 mmol, 1.47 mL of a 1.0 M solution of MeLi·LiBr complex in Et_2O). The solution was stirred for 15 min, and a −15 °C solution of aldehyde **27** (458 mg, 1.30 mmol) in 3 mL of dry THF was added dropwise. The reaction was stirred for 0.5 h at −15 °C and 1 h at room temperature before quenching with a solution of glacial acetic acid (630 mg, 10.5 mmol) in 5 mL of Et_2O. Saturated aqueous $NaHCO_3$ (5 mL) was added, the two layers were separated, and the aqueous phase was extracted with Et_2O (4 × 5 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (SiO_2, 10:1 hexanes/Et_2O) of the resulting oil afforded 739 mg (91% based on aldehyde **27**) of allylic alcohol **28** as a clear, viscous syrup. See Supplementary Material for spectral data.

(2*S*,3*R*,4*R*,8*R*,9*R*,10*R*,11*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-1-(*E*/*Z*)-(1-hexylidene)-3,4:9,11-bis(isopropylidenedioxy)-2,4,8,10-tetramethyl-6-methylidene-7-oxotridecane (13). Allylic alcohol **28** was oxidized to enone **13** according to the conditions of Omura and Swern.[28] A solution of oxalyl chloride (160 mg, 1.27 mmol) in 2.8 mL of anhydrous CH_2Cl_2 at −65 °C was treated with a solution of DMSO (220 mg, 2.82 mmol) in 0.58 mL of dry CH_2Cl_2. The mixture was stirred for 15 min and a −65 °C solution of alcohol **28** (100 mg, 0.16 mmol) in 0.3 mL of anhydrous CH_2Cl_2 was added dropwise. After 15 min, triethylamine (0.8 mL, 5.7 mmol) was carefully added, and the reaction was stirred at −65 °C for 10 min. The reaction was allowed to reach room temperature at which time it was diluted with 2 mL of H_2O. The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 210 mg of a yellow oil which was purified by radial chromatography (SiO_2, 20:1 hexanes/Et_2O) to afford 92 mg (92%) of enone **13** as an E/Z mixture of geometrical isomers. See Supplementary Material for spectral data.

(2*S*,3*R*,4*R*,6*R*,8*R*,9*R*,10*R*,11*R*)-10-((*tert*-Butyldmethylsilyl)oxy)-1(*E*/*Z*)-(1-hexylidene)-3,4:9,11-bis(isopropylidenedioxy)-2,4,6,8,10-pentamethyl-7-oxotridecane (29a). A solution of enone **13** (20 mg, 0.03 mmol) and $NiCl_2·6H_2O$ (1.7 mg, 0.01 mmol) in 10 mL of

anhydrous methanol was treated over 8 days with $NaBH_4$ (64 mg, 32 × 2 mg, 1.7 mmol) after which the reaction was quenched with 20 mL of H_2O. After dilution with 20 mL of CH_2Cl_2, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 23 mg of a yellow oil. Flash chromatography (SiO_2, 30:1 hexanes/Et_2O) afforded 15.5 mg (77%) of the (8*R*)-epimer, **29a**, 1.5 mg (6%) of the (8*S*)-epimer, **29b**, and 1.0 mg (6%) of starting enone **13** as clear viscous oils. See Supplementary Material for spectral data.

(2*S*,3*R*,4*R*,6*S*,8*R*,9*R*,10*R*,11*R*)-10-((*tert*-Butyldimethylsilyl)oxy]-1(*E*/*Z*)-(1-hexylidene)-3,4:9,11-bis(isopropylidenedioxy)-2,4,6,8,10-pentamethyl-7-oxotridecane (29b). To a solution of enone **13** (70 mg, 0.11 mmol) in 1 mL of anhydrous Et_2O at −78 °C was added L-selectride (0.2 mmol, 0.2 mL of a 1 M solution in THF). After stirring for 40 min at −78 °C, the reaction was cooled to −120 °C and was treated, via cannula, with a −120 °C suspension of 2,6-di-*tert*-butylpyridinium hydrochloride (91 mg, 0.40 mmol) in 1 mL of dry Et_2O. The reaction was stirred at −120 °C for 0.5 h and was allowed to reach −30 °C over 2 h. The mixture was diluted with 1 mL of saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 2 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 149 mg of a viscous oil. Flash chromatography (SiO_2, 20:1 hexanes/Et_2O) afforded 47 mg (73%) of the (8*S*)-epimer, **29b**, and 6 mg (9%) of the corresponding (8*R*)-epimer, **29a**, as clear oils. See Supplementary Material for spectral data.

(2*S*,3*R*,4*R*,6*R*,7*S*,8*S*,9*R*,10*R*,11*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-1(*E*/*Z*)-(1-hexylidene)-7-hydroxy-3,4:9,11-bis(isopropylidenedioxy)-2,4,6,8,10-pentamethyltridecane (30a). A solution of ketone **29a** (100 mg, 0.16 mmol) in 25 mL of anhydrous toluene at −10 °C was treated with L-selectride (0.5 mmol, 0.5 mL of a 1 M solution in THF). The reaction mixture was kept at −10 °C for 20 h at which time it was quenched by the addition of 1 mL of H_2O. After being warmed to room temperature, the two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 248 mg of a yellow oil which was purified by radial chromatography (SiO_2, 15:1 hexanes/Et_2O) to afford 82 mg (82%) of the (9*S*)-epimeric alcohol, **30a**, and 15 mg (12%) of the corresponding (9*R*)-epimer, **30b**, as clear oils. See Supplementary Material for spectral data.

(2*S*,3*R*,4*R*,6*R*,7*R*,8*S*,9*R*,10*R*,11*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-1(*E*/*Z*)-(1-hexylidene)-7-hydroxy-3,4:9,11-bis(isopropylidenedioxy)-2,4,6,8,10-pentamethyltridecane (30b). A solution of ketone **29a** (60 mg, 0.1 mmol) in 25 mL of anhydrous toluene at −91 °C was treated with $LiAlH_4$ (0.15 mmol, 0.15 mL of a 1 M solution in THF). The reaction was stirred at −91 °C for 5 min at which time it was quenched by the addition of 0.2 mL of H_2O. After warming to room temperature, the two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 68 mg of a clear oil which was purified by radial chromatography (SiO_2, 10:1 hexanes/Et_2O) to afford 58.0 mg (93%) of the (9*R*)-epimer, **30b**, and 2.0 mg (3%) of the (9*S*)-epimer, **30a**, as clear oils. See Supplementary Material for spectral data.

***S*-(*tert*-Butyl) (2*S*,3*S*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-12-((*tert*-Butyldimethylsilyl)oxy)-3,9-dihydroxy-5,6:11,13-bis(isopropylidenedioxy)-2,4,6,8,10,12-hexamethylpentadecanoate (31a).** A solution of olefin **30a** (110 mg, 0.175 mmol) in 4 mL of CH_2Cl_2 at −78 °C was treated with a flow of an ozone/oxygen mixture until a faint blue color appeared. The reaction was quenched immediately by the addition of 0.3 mL of methyl sulfide, and the resulting mixture was stirred at −78 °C for 0.5 h. Evaporation of the volatiles gave 29 mg (104% crude) of an oil which was used immediately in the preparation of thio ester **31a** as follows.

A −78 °C solution of *S*-*tert*-butyl thiopropionate (850 mg, 5.81 mmol)[37] in 1.0 mL of anhydrous THF was added dropwise to a solution of lithium diisopropylamide (5.81 mmol, prepared from 0.88 mL (6.28 mmol) of diisopropylamine and 2.2 mL (5.81 mmol) of a 2.69 M solution of *n*-BuLi in hexanes) in 5.0 mL of anhydrous THF at −78 °C. The mixture was stirred for 0.5 h and was cooled to −107 °C. A solution of the crude aldehyde prepared above (0.175 mmol assuming 100% from preceeding ozonolysis) in 1.0 mL of dry THF at −107 °C was added dropwise to the enolate solution, and the mixture was stirred for 1.5 h. The reaction was quenched at −107 °C by the addition of a solution of glacial acetic acid (420 mg, 7.0 mmol) in 2.0 mL of anhydrous THF. The mixture was allowed to warm and at 0 °C was neutralized with saturated aqueous $NaHCO_3$. Once at room temperature, the two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 155 mg of a yellow oil which was purified by radial chromatography (SiO_2, 3:1 hexanes/Et_2O) to afford 92 mg (75%) of the (2*S*)-epimer, **31a**, and 10 mg (6.0%) of the (2*R*)-epimer, **31b**, as clear oils. See Supplementary Material for spectral data.

***S*-(*tert*-Butyl) (2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-12-((*tert*-Butyldimethylsilyl)oxy)-3,9-dihydroxy-5,6:11,13-bis(isopropylidenedioxy)-2,4,6,8,10,12-hexamethylpentadecanoate (31b).** A solution of the 2*R* epimeric thio ester **31a** (120 mg, 0.17 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2.1 g, 18.1 mmol) in 6 mL of anhydrous THF at −110 °C was treated with *t*-BuLi (7.72 mmol, 5.4 mL of a 1.43 M solution in pentane). The mixture was stirred for 2 h and was quenched with a −110 °C solution of glacial acetic acid (945 mg, 15.7 mmol) in 3 mL of anhydrous THF. The mixture was stirred at −110 °C for 0.5 h and was then allowed to warm. At −10 °C the mixture was neutralized with 4 mL of saturated aqueous sodium bicarbonate. Once at room temperature, the two layers were separated, and the aqueous phase was extracted with Et_2O (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 205 mg of a yellow oil which was subjected to radial chromatography (SiO_2, 3:1 hexanes/Et_2O) to afford 98 mg (82%) of the desired (2*R*)-epimer, **31b**, and 15 mg of the starting (2*S*)-epimer, **31a**. See Supplementary Material for spectral data.

9S-Dihydroerythronolide A Seco Acid, *S*-*tert*-Butyl Thio Ester (33). The protected polyol **31b** (20.0 mg, 0.03 mmol) was dissolved in 5 mL of a solution of 1:1 MeOH/H_2O saturated with hydroxylamine hydrochloride. Potassium phosphate monobasic (150 mg, 1.10 mmol) was added, and the mixture was heated at reflux for 48 h. The reaction was evaporated to 1/2 volume and was extracted with Et_2O (5 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo to give 14 mg of a clear oil which was purified by radial chromatography (SiO_2, gradient eluent system of 5% → 10% → 25% isopropyl alcohol in CH_2Cl_2) to afford 12.0 mg (84%) of the deprotected thio ester **33** as a clear oil: R_f 0.28 (9:1 CH_2Cl_2/MeOH); $[\alpha]_D^{27}$ −6.7° (*c* 0.18, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3 H), 1.01–1.06 (m, 11 H), 1.11 (s, 3 H), 1.16 (s, 3 H), 1.23–1.27 (m, 6 H), 1.45 (s, 9 H), 1.37–1.50 (m, 2 H), 1.58–1.70 (m, 1 H), 1.82–1.93 (m, 4 H), 1.99–2.08 (m, 1 H), 2.70–2.77 (m, 1 H), 3.35 (d, *J* = 10.6 Hz, 1 H)8, 3.50 (br s, 1 H), 3.72 (d, *J* = 3.3 Hz, 1 H), 3.73 (d, *J* = 3.4 Hz, 1 H), 3.84 (dd, *J* = 9.2 and 1.3 Hz, 1 H), 4.21 (br s, 1 H); chemical shifts in the ^1H NMR depend greatly on sample and solvent purity as well as sample concentration and therefore can change slightly from sample to sample; IR (film) 3410, 2970, 2930, 1670, 1457, 1360, 1265, 1140, 1090, 960 cm^{-1}; ^{13}C NMR (125.8 MHz, $CDCl_3$) 6.2, 11.6, 12.1, 15.2, 15.8, 20.4, 21.5, 24.8, 29.6, 29.7, 30.6, 35.6, 36.5, 42.5, 48.2, 52.0, 72.9, 75.3, 75.5, 76.3, 79.2, 82.2, 203.9; CIMS, *m*/*z* (rel intensity) 511 (MH^+, 1), 493 ($MH^+ - H_2O$, 0.7), 475 ($MH^+ - 2H_2O$), 457 ($MH^+ - 3H_2O$, 0.8), 439 ($MH^+ - 4H_2O$, 0.9), 421 ($MH^+ - 5H_2O$, 0.9), 403 ($MH^+ - 6H_2O$, 0.8), 349 (3), 241 (24), 223 (18), 147 (26), 91 (100); HRMS, exact mass calcd for $C_{25}H_{50}O_8S$: MH^+ requires 511.3306, found 511.3310.

9S-Dihydroerythronolide A Seco Acid (8). A solution of thio ester **33** (7.0 mg, 0.014 mmol) in 0.2 mL of freshly distilled THF was treated with LiOH (0.14 mmol, 0.15 mL of a 0.9 M aqueous solution). The reaction was stirred at room temperature for 40 h and was evaporated in vacuo to give 8 mg of a yellow solid which was washed with anhydrous Et_2O (3 × 2 mL) to give 6 mg (98%) of lithium 9*S*-dihydroerythronolide A seco acid carboxylate (**8a**) as a white solid. A sample of **8a** (2 mg) was dissolved in 0.2 mL of H_2O and was acidified with solid CO_2. The aqueous solution was extracted with Et_2O (5 × 0.2 mL) and ethyl acetate (5 × 0.2 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent in vacuo gave a sample of **8b** as a clear oil which was rapidly characterized by IR. **8b**: IR (film) 3411 (br), 2956, 2927, 1717 (C=O dimer), 1458, 1379, 1263, 1101, 1059, 1039 cm^{-1}. The remaining sample of **8a** was subjected to spectral characterization. **8a**: ^1H NMR (500 MHz, DMSO-d_6) δ 0.87–0.90 (m, 2 H), 0.91–0.95 (m, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H), 0.98–1.04 (m, 6 H), 1.06 (d, *J* = 6.5 Hz, 2 H), 1.09 (d, *J* = 7.0 Hz, 1 H), 1.14 (s, 3 H), 1.19–1.23 (m, 2 H), 1.32–1.40 (m, 1 H), 1.68–1.77 (m, 3 H), 1.80–1.85 (m, 1 H), 1.86–1.92 (m, 1 H), 1.94–1.99 (m, 1 H)8 2.03–2.12 (m, 1 H), 2.17–2.25 (m, 1 H), 3.38–3.42 (m, 1 H)8, 3.58 (br s, 1 H)8 3.63 (br s, 1 H), 3.68–3.73 (m, 1 H), 4.09–4.19 (m, 2 H), 4.46 (br s, 1 H), 4.88 (br s, 1 H), 4.92 (br s, 1 H), 6.28 (br, 1 H); IR (KBr) 3425 (br), 2974, 2930, 1578 (asymmetrical stretching, CO_2^-), 1458, 1407 (symmetrical stretching, CO_2^-), 1385, 1040, 983 cm^{-1}; MS (negative ion FAB), *m*/*z* (rel intensity) 437 (M^-, 45), 419 (5), 401 (4); HRMS, exact mass calcd for $C_{21}H_{42}O_9$: M−H requires 437.2741, found 437.2750.

Ketooxazolidone 32. A solution of olefin **29a** (40 mg, 0.064 mmol) in 3 mL of CH_2Cl_2 at −78 °C was treated with a flow of an ozone/oxygen mixture until a faint blue color appeared. The reaction was quenched immediately by the addition of 0.6 mL of methyl sulfide, and the resulting mixture was stirred at −78 °C for 0.5 h. The reaction mixture was slowly warmed to room temperature and evaporated in vacuo to give 36 mg (101% crude) of an oil which was used immediately in the preparation of ketooxazolidone **32** as follows.

To a stirred solution of (4*R*,5*R*)-4-methyl-5-phenyl-*N*-propionyl-2-oxazolidone (147 mg, 0.63 mmol)[33] in 0.8 mL of anhydrous CH_2Cl_2 at 0 °C was added freshly distilled di-*n*-butylboron triflate (173 mg, 0.63 mmol) and diisopropylethylamine (97 mg, 0.75 mmol). The mixture was stirred for 0.5 h at 0 °C and cooled to −78 °C, and the crude aldehyde (0.064 mmol assuming 100% from the previous ozonolysis) in 0.6 mL of dry CH_2Cl_2 was added dropwise. After stirring at −78 °C for 0.5 h, the reaction mixture was warmed to room temperature and concentrated to 1/3 volume using a rapid Ar flow. The mixture was stirred for an additional 1.5 h, quenched with 0.5 mL of pH 7 phosphate buffer, and extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with brine and concentrated in vacuo to give a crude mixture which was purified by analytical preparitive TLC (SiO_2, 1:2 hexanes/Et_2O, double elution) to afford 36 mg (73% from **29a**) aldol product **32**: R_f 0.63 (Et_2O); ^1H NMR (250 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.15 (s, 3 H), 0.90 (s, 9 H), 0.96 (t, *J* = 7.0 Hz, 3 H)8 1.05 (d, *J* = 6.8 Hz, 3 H), 1.10 (s, 3 H), 1.17 (d, 7.0, 3 H), 1.21–1.40 (m, 23 H)8 1.48–1.70 (m, 2 H), 1.79 (apparent quintet, *J* = 7.4 Hz, 1 H), 2.30 (dd, *J* = 14.3, 8.5 Hz, 1 H), 2.43 (d, *J* = 5.6 Hz, 1 H), 2.9 (q, *J* = 7.2 Hz, 1 H), 3.11–3.25 (m, 3 H), 3.44 (br d, *J* = 10.2 Hz, 1 H), 3.64 (d, *J* = 8.8 Hz, 1 H), 3.94–4.18 (m, 3 H), 4.74 (apparent quintet, *J* = 6.6 Hz, 1 H), 5.67 (d, *J* = 7.1 Hz, 1 H), 7.28–7.46 (m, 5 H); IR ($CHCl_3$) 3400–3600 (br), 2990, 2950, 2870, 1800, 1700, 1465, 1390, 1350, 1200, 1125, 1055, 1000, 915 cm^{-1}.

(2*S*,3*R*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-12-((*tert*-Butyldimethylsilyl)oxy)-3,9-dihydroxy-5,6:11,13-bis(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyl-1-pentadecanol (Triol 34). To a solution of the ketooxazolidone **32** (5 mg, 6 μmol) in 3 mL of anhydrous THF was added $LiAlH_4$ (30 mg, 0.75 mmol) at −5 °C with stirring. After 1 h, the reaction mixture was transferred to a −5 °C solution of 1:1 ethyl acetate/Et_2O with stirring. Brine (1 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford 5 mg of a crude product which was purified by gravity chromatography (SiO_2, gradient eluent system of 1:1 → 1:2 hexanes/Et_2O) to afford 1.5 mg (42%) of triol **34** and 2 mg (56%) of the corresponding (9*R*)-epimer. **34**: R_f 0.34 (Et_2O); $[\alpha]_D^{25}$ +9.35° (*c* 0.02, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.12 (s, 3 H), 0.82–0.99 (m, 12 H), 0.87 (s, 9 H), 1.04–1.12 (m, 12 H) 1.17 (s, 3 H), 1.25 (s, 3 H), 1.32 (s, 3 H), 1.33 (s, 3 H), 1.36 (s, 3 H), 1.52–2.05 (m, 6 H), 3.40 (d, *J* = 9.8 Hz, 1 H), 3.60–3.68 (m, 3 H), 3.77 (d, *J* = 6.4 Hz, 1 H), 3.92 (br s, 1 H); IR (film) 3395, 2950, 2930, 1455, 1375, 1235, 1225, 1180, 985, 830 cm^{-1}; ^{13}C NMR (75 MHz) δ −1.4, −0.6, 10.3, 11.5, 11.9, 13.7, 14.2, 18.9, 20.5, 21.0, 21.5, 23.8, 24.7, 26.6, 27.3, 28.9, 30.6, 34.6, 35.8, 38.5, 43.4, 66.2, 72.7, 75.0, 75.8, 78.2, 80.8, 83.2, 84.8, 100.8, 106.5; CIMS, *m/z* (rel intensity) 619 (MH^+, 9), 485 (7), 467 (17), 429 (6), 411 (14), 371 (25), 353 (57), 335 (100), 201 (31), 133 (85).

(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-hexamethyl-1-pentadecanol (Polyol 35). (*A*) **From Deprotection of Triol 34.** Triol **34** (1.5 mg, 0.002 mmol) was dissolved in 1 mL of 1:1 MeOH/H_2O saturated with NH_2OH·HCl. Potassium phosphate monobasic (30 mg, 0.22 mmol) was added, and the mixture was heated at reflux for 6 h. The reaction was cooled to room temperature and was quenched with solid $NaHCO_3$. The mixture was concentrated to 1/2 volume, brine (1 mL) was added, and the mixture was extracted with ethyl acetate (4 × 1 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated in vacuo to give 1.2 mg of an oil which was purified by analytical preparative TLC (SiO_2, 15% MeOH in CH_2Cl_2) to afford 1.0 mg (96%) of polyol **35**: R_f 0.10 (15% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$ +13.6° (*c* 0.004, EtOH); ^1H NMR (500 MHz, DMSO-d_6, 9 mg of sample in 0.35 mL of solvent) δ 0.89 (d, *J* = 7.0 Hz, 3 H), 0.92–0.97 (m, 6 H), 0.98–1.06 (m, 9 H), 1.16 (s, 3 H), 1.23–1.38 (m, 3 H), 1.65–1.97 (m, 4 H)8 3.32–3.54 (m, 4 H), 3.68–3.77 (m, 3 H), 3.83 (s, 1 H), 3.94 (s, 1 H), 4.04 (d, *J* = 6.3 Hz, 1 H), 4.14–4.18 (m, 2 H), 4.28 (d, *J* = 5.4 Hz, 1 H)8, 4.30 (d, *J* = 5.3 Hz, 1 H), 4.45 (t, *J* = 5.0 Hz, 1 H), 4.51 (d, *J* = 6.2 Hz, 1 H); ^{13}C NMR (125.8 MHz, DMSO-d_6, 9 mg of sample in 0.35 mL of solvent) δ 9.4, 11.0, 11.8 (3), 11.8 (7), 14.5, 18.7, 23.4, 25.2, 29.5, 35.6, 36.4, 37.6, 43.3, 64.6, 67.1, 71.1, 74.9, 75.3, 75.6, 76.6, 78.0; chemical shifts in both the ^1H and ^{13}C NMR depend greatly on sample and solvent purity as well as sample concentration and therefore can change slightly from sample to sample; IR (film) 3360, 2980, 2890, 1640, 1455, 1385, 1060, 975 cm^{-1}; CIMS, *m/z* (rel intensity) 425 (M^+, 9), 407 ($M^+ - H_2O$, 9), 389 ($M^+ - 2H_2O$, 4), 371 ($M^+ - 3H_2O$, 7), 353 ($M^+ - 4H_2O$, 15), 335 ($M^+ - 5H_2O$, 11) 295 (32), 277 (100), 209 (15), 173 (10), 103 (18); HRMS, exact mass calcd for $C_{21}H_{44}O_8$: MH^+ requires 425.3114, found 425.3104.

(*B*) **From Reduction of Thio Ester 33.** A sample of polyol-thio ester **33** was reduced with $LiAlH_4$ according to the conditions used in the case of ketooxazolidone **32** to obtain a sample of **35** for spectroscopic analysis. The sample of polyol **35** obtained in this way was identical with that obtained from oxazolidone **32**.

(*C*) **From Reduction of 9*S*-Dihydroerythronolide A Aglycon (36).** 9*S*-Dihydroerythronolide A aglycon (**36**, 20 mg, 0.05 mmol), prepared according to the procedure of Jones and Rowley,[34] in 3 mL of anhydrous THF was added to a suspension of $LiAlH_4$ (244 mg, 6.42 mmol) in 6 mL of dry THF at 0 °C. The cold bath was removed, and the reaction was heated at 50 °C for 8 h. The reaction was cooled to room temperature and was added via cannula to a −10 °C mixture of 1:1 ethyl acetate/Et_2O. Brine (5 mL) was added, the two layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo to give 24 mg of an oil which was subjected to flash chromatography (SiO_2, 12% MeOH in CH_2Cl_2) to afford 11 mg (60%) of natural polyol **35** as a clear oil: R_f 0.10 (15% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$ +14.7° (*c* 0.006, EtOH); ^1H NMR (500 MHz, DMSO-d_6, 13 mg of sample in 0.5 mL of solvent) δ 0.91 (d, *J* = 6.8 Hz, 3 H) 0.93–0.97 (m, 6 H), 0.99–1.06 (m, 9 H), 1.17 (s, 3 H) 1.25–1.39 (m, 3 H), 1.68–2.10 (m, 4 H), 3.34–3.53 (m, 4 H), 3.72–3.75 (m, 3 H), 3.81 (s, 1 H), 3.90–3.95 (m, 1 H), 4.06 (d, *J* = 6.2 Hz, 1 H), 4.12–4.18 (m, 2 H), 4.25 (d, *J* = 5.4 Hz, 1 H), 4.27 (d, *J* = 5.2 Hz, 1 H), 4.42 (t, *J* = 5.2 Hz, 1 H), 4.49 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, DMSO-d_6, 13 mg of sample in 0.5 mL of solvent) δ 9.4, 10.9, 11.8 (3), 11.8 (8), 14.5, 18.7, 23.4, 25.2, 29.4, 35.6, 36.4, 37.6, 43.3, 64.6, 67.1, 71.1, 74.9, 75.3, 75.6, 76.6, 78.0; chemical shifts in both the ^1H and ^{13}C NMR depend greatly on sample and solvent purity as well as sample concentration and therefore can change slightly from sample to sample; IR (KBr) 3100–3600 (br), 2930, 1050, 970 cm^{-1}; CIMS, *m/z* (rel intensity) 425 (MH^+, 30), 407 ($MH^+ - H_2O$, 17), 389 ($MH^+ - 2H_2O$, 4), 371 ($MH^+ - 3H_2O$, 3), 353 ($MH^+ - 4H_2O$, 9), 335 ($MH^+ - 5H_2O$, 8), 295 (34), 277 (100), 173 (8), 103 (18). HRMS, exact mass calcd for $C_{21}H_{44}O_8$: MH^+ requires 425.3114, found 425.3100.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE 8713080) for support of this project.

Supplementary Material Available: General experimental information and spectral data (R_f, ^1H NMR, IR, CIMS, and HRMS) for compounds **13**, **17–20**, and **28–31b** (7 pages). Ordering information is given on any current masthead page.