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# Studies in Macrolide Synthesis: A Stereocontrolled Synthesis of Oleandolide Employing Reagent- and Substrate-Controlled Aldol Reactions of (*S*)-1-(Benzyloxy)-2-methylpentan-3-one

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**Abstract:** A highly stereocontrolled total synthesis of oleandolide (**2**), the aglycon of the macrolide antibiotic oleandomycin (**1**), has been completed in 8% overall yield (20 steps longest linear sequence, 26 steps in total) with 90% overall diastereoselectivity. Initially, reagent-controlled *syn* aldol reactions of (*S*)-1-(benzyloxy)-2-methylpentan-3-one ((*S*)-**8**) were employed to prepare adducts **6** (*SS*) and **7** (*SA*), which were elaborated to provide the two advanced fragments **33** and **27**, respectively. Coupling of these fragments followed by functional group manipulation and macrolactonization gave the macrocyclic ketone **42**, possessing *S* configuration at $C_9$. Elaboration of **42** to oleandolide, however, proved troublesome. Substrate-controlled *syn* and *anti* aldol reactions of ketone (*S*)-**8**, meanwhile, provided the adducts **6** (*SS*) and **7** (*AA*), which enabled synthesis, *via* fragments **64** and **60**, of the key macrocyclic ketone intermediate **69**, having *R* configuration at $C_9$. Stereoselective epoxidation of ketone **69**, by reaction with dimethylsulfonium methylide under macrocyclic stereocontrol, provided the (8*R*)-epoxide **83**; subsequent elaboration then gave oleandolide (**2**).

## Introduction

Oleandomycin (**1**) is a 14-membered macrolide antibiotic[1] produced by the actinomycete *Streptomyces antibioticus* and originally reported by Sobin *et al.* in 1954.[2] It was first chemically characterized in 1958, by Celmer and co-workers,[3a] as "*a polyhydroxy, epoxy, polymethyl ketolactone of the macrolide type, containing glycosidically bound desosamine and L-oleandrose*," and a partial structure was proposed at that time. The complete structure of oleandomycin was published in 1960 by Celmer, Woodward, and co-workers,[3b] while the absolute configuration was established in 1965 by Celmer,[3c] and later confirmed by X-ray analysis of the 11,4″-bis[*O*-(*p*-bromobenzoyl)] derivative by Ogura *et al.*[3d]

Oleandomycin shows moderately broad antibacterial activity, having a bacteriostatic rather than a bactericidal action. In common with several other macrolides, it inhibits bacterial RNA-dependent protein synthesis—by binding to the 50-S ribosomal subunit and blocking either transpeptidation and/or translocation reactions—but does not affect bacterial nucleic acid synthesis.[4] Oleandomycin is active against Gram-positive and some Gram-negative bacteria and is used widely in both clinical[5a] and veterinary[5b] fields, principally as its triacetate (troleandomycin) but also as its phosphate derivative, as a treatment for bacterial infections. It has also been used as a feed additive to promote growth in poultry.[5b]

A synthesis of oleandomycin which employs a carbohydrate-based approach to construct the aglycon oleandolide (**2**) has recently been completed by Tatsuta *et al.*[6b,7] The glycosidation of oleandolide to provide the natural product has also been accomplished by Tatsuta's group,[6a] and thus a synthesis of **2** constitutes a formal total synthesis of oleandomycin. We now describe our successful efforts to synthesize this macrolide antibiotic,[8,9] which inspired our development of new stereoselective methods for the construction of polypropionate-derived natural products.[10]

## Retrosynthetic Analysis

Oleandomycin, in common with the other macrolide antibiotics, presents a 3-fold challenge to the synthetic chemist:[11] firstly, the *construction of a 14-membered lactone*, in which the success or otherwise of any ring-closing reaction will depend critically on the conformations available to the seco-acid; secondly, the *stereoselective construction* of the 10 stereogenic centers of the macrolide ring; and thirdly, *glycosidation*—the stereo- and

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(1) *Macrolide Antibiotics, Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.

(2) Sobin, B. A.; English, A. R.; Celmer, W. D. *Antibiot. Annu.* **1955**, 827.

(3) (a) Els, H.; Celmer, W. D.; Murai, K. *J. Am. Chem. Soc.* **1958**, *80*, 3777. (b) Hochstein, F. A.; Els, H.; Celmer, W. D.; Shapiro, B. L.; Woodward, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 3225. (c) Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1797. (d) Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* **1978**, *100*, 6733.

(4) For a review of the mode of action of macrolide antibiotics, see: Corcoran, J. W. In ref 1.

(5) For a review of macrolides in (a) clinical practice, see: Nakayama, I. In ref 1. For (b) veterinary practice, see: Wilson, R. C. In ref 1.

(6) (a) Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975. (b) Tatsuta, K.; Ishiyama, T.; Tajima, S.; Koguchi, Y.; Gunji, H. *Tetrahedron Lett.* **1990**, *31*, 709.

(7) Other synthetic studies: (a) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S. *Tetrahedron Lett.* **1981**, *22*, 4315, 4319. (b) Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 1311. (c) Costa, S. S.; Olesker, A.; Thang, T. T.; Lukacs, G, *J. Org. Chem.* **1984**, *49*, 2338. (d) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Sato, F. *J. Am. Chem. Soc.* **1985**, *107*, 5541. (e) Paterson, I.; Arya, P. *Tetrahedron* **1988**, *44*, 253. (f) Kochetkov, N. K.; Yashunsky, D. V.; Sviridov, A. F.; Ermolenko, M. S. *Carbohydr. Res.* **1990**, *200*, 209. (g) Sviridov, A. F.; Yashunsky, D. V.; Kuz'min, A. S.; Kochetkov, N. K. *Mendeleev Commun.* **1991**, 4. (h) Sviridov, F. S.; Yashunsky, D. V.; Kuz'min, A. S.; Kochetkov, N. K. *Mendeleev Commun.* **1992**, 65.

(8) For preliminary communications of this work, see: (a) Paterson, I.; Lister, M. A.; Norcross, R. D. *Tetrahedron Lett.* **1992**, *33*, 1767. (b) Paterson, I.; Ward, R. A.; Romea, P.; Norcross, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 3623.

(9) For a different (less effective) aldol-based approach to oleandolide synthesis, see: Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229.

(10) (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (b) ref 9. (c) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (d) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (e) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. S.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (f) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821. (g) Paterson, I. Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (h) Paterson, I. Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.

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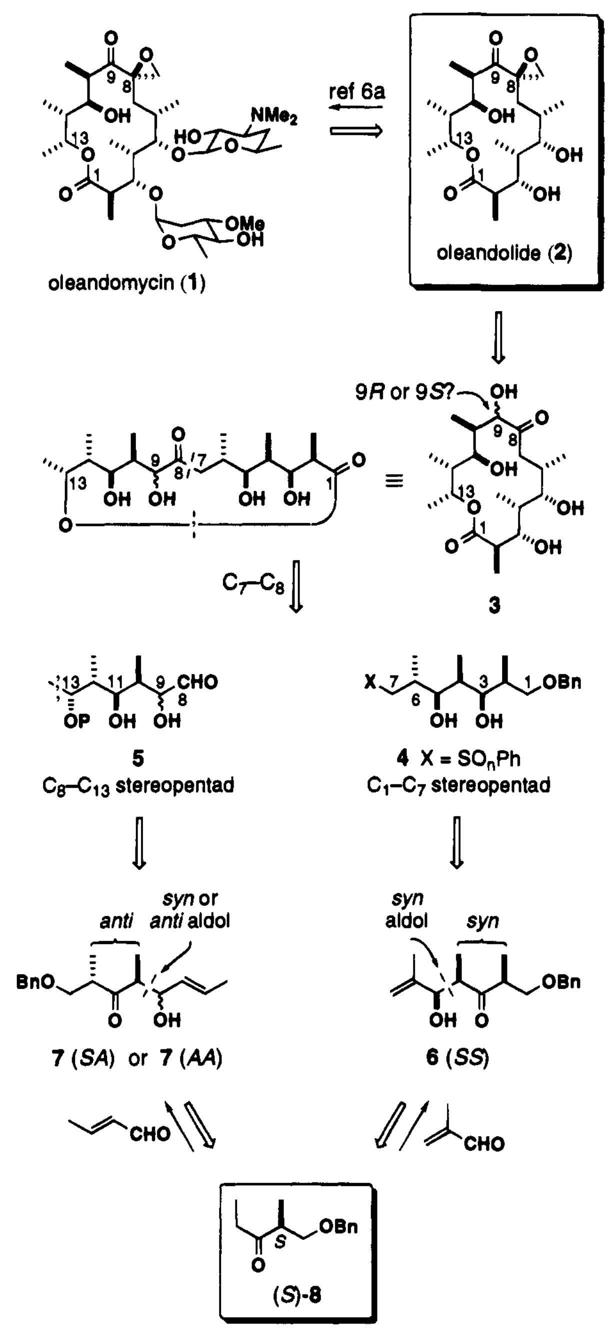
Scheme 1



regiocontrolled attachment of the sugars L-oleandrose (at $C_3$) and D-desosamine (at $C_5$). It was the fulfillment of the first and second challenges with which the work described in this paper was primarily concerned.

Our retrosynthetic analysis for oleandomycin is outlined in Scheme 1. The exocyclic epoxide at $C_8$ of **2** is a unique structural feature of oleandolide, not found in any of the other known macrolide antibiotics,[1] and it was envisaged that this sensitive functionality might be introduced late in the synthesis by manipulation of the $C_8$ ketone in macrolide **3**, possibly by using a sulfur ylide reagent. Alternatively, the $C_8$ ketone of **3** might first be transformed to an exocyclic alkene which could then be epoxidized. The possibility of macrocyclic stereocontrol would be an important issue in these reactions.

Macrolide **3** was therefore identified as a pivotal synthetic target. The absolute configuration at $C_9$ of **3** is not specified in Scheme 1. Work on the related macrolide antibiotic erythromycin has shown[12] that the stereochemistry at $C_9$ is critically important in determining the efficiency of macrolactonization reactions[11c] used to close the 14-membered ring: changing the configuration at $C_9$ has a profound effect on the conformations available to the seco-acid and hence on the success, or otherwise, of the macrolactonization. The choice of stereochemistry at $C_9$ might also be important in allowing a hydroxyl-directed epoxidation of an exocyclic alkene at $C_8$. Ideally, a strategy was desired that could construct **3** with *either* *R* or *S* stereochemistry at $C_9$, in order that the effect of the configuration of this stereogenic center might be further investigated.

Disconnection of macrolide **3** to $C_1$–$C_7$ and $C_8$–$C_{13}$ stereopentad fragments **4** and **5** was considered attractive, since this would divide the molecule into two approximately equal segments thus constituting a highly convergent approach. The critical $C_7$–$C_8$ coupling and ring-forming reactions were planned to be nucleophilic addition of an anion of **4** (generated at $C_7$, α to a suitable charge-stabilizing sulfur substituent) to the $C_8$ aldehyde **5**, followed by macrolactonization.

The array of alternating methyl and oxygenated functionalities around the lactone of **2** reveals the polyketide-derived biosynthetic origin of oleandomycin,[13] and suggested to us that *asymmetric aldol methodology*[14] might be applied to achieve a highly stereoselective synthesis. According to this strategy, fragments **4** and **5** should be available from β-hydroxyketones **6** (*SS*) and **7** (*SA* or *AA*), respectively.[15] Diol **4** would require a stereoselective hydroboration of **6** (*SS*) to introduce the $C_6$ stereogenic center, and a stereoselective ketone reduction to construct the $C_3$ stereocenter. Meanwhile, another stereoselective ketone reduction was envisaged to set up the $C_{11}$ stereocenter of **5** from **7**, and a Cram-controlled addition of a methyl nucleophile onto an aldehyde was proposed to establish the $C_{13}$ stereocenter. The choice of either a *syn* or an *anti* aldol for the $C_8$–$C_{13}$ fragment (*i.e.*, **7** (*SA* or *AA*)) would enable either the 9*S* or the 9*R* stereochemistry of macrolide **3** to be generated, respectively.

Since aldol products **6** (*SS*) and **7** (*SA* or *AA*) should all originate from our dipropionate reagent ethyl ketone (*S*)-**8**,[10c,d,h] this plan represented a particularly concise and highly convergent approach in which *six* of the ten stereocenters of macrolide **3** were to be constructed by two aldol reactions of the *same* ketone precursor.

## Results and Discussion

**Synthesis of the Dipropionate Reagent: Chiral Ethyl Ketone (*S*)-8.** Ketone (*S*)-**8** was readily prepared by the

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[11] General reviews on macrolide synthesis: (a) Masamune, S.; McCarthy, P. A. In ref 1. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (c) Bartra, M.; Urpí, F.; Vilarassa, J. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Kukacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2.

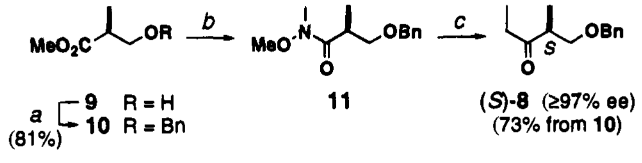
[12] Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chêneveret, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garrat, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; 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, 3213, 3215.

[13] Grisebach, H.; Hofheinz, W. *J. R. Inst. Chem.* **1964**, *88*, 332.

[14] For a review of asymmetric aldol methodology, see: (a) Heathcock, C. H.; Moon Kim, B.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2. (b) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.*, in press.

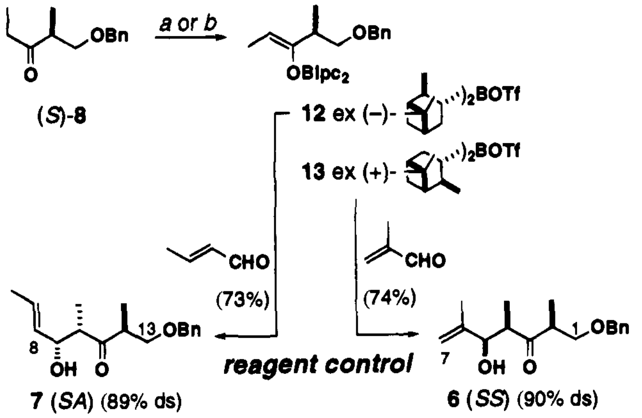
[15] In our nomenclature system for aldol diastereomers, such as **7** (*SA*), the first descriptor (in this case *S* for *syn*) refers to the relative stereochemistry of the aldol bond construction and the second descriptor (here *A* for *anti*) defines the relative stereochemistry of the two methyl substituents flanking the carbonyl.

**Scheme 2**[a]



[a] (a) $Cl_3CC(=NH)OBn$, catalytic TfOH, cyclohexane/$CH_2Cl_2$, 20 °C, 16 h; (b) Me(MeO)NH·HCl, $AlMe_3$, PhMe, 80 °C, 2 h; (c) EtMgBr, THF, 0 °C, 1 h.

**Scheme 3**[a]



[a] (a) (−)-$(Ipc)_2BOTf$, $^{i}Pr_2NEt$, $CH_2Cl_2$, 20 °C, 2 h; (*E*)-MeCH=CHCHO, 0 °C, 16 h; $H_2O_2$, MeOH/pH 7 buffer, 20 °C, 2 h; (b) (+)-$(Ipc)_2BOTf$, $^{i}Pr_2NEt$, $CH_2Cl_2$, 20 °C, 2 h; $H_2C=C(Me)CHO$, 0 °C, 16 h; $H_2O_2$, MeOH/pH 7 buffer, 20 °C, 2 h.

sequence of reactions depicted in Scheme 2. Thus, methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**9**) (Aldrich, ≥97% enantiomeric excess (ee)) was benzylated in good yield (81%) using benzyl 2,2,2-trichloroacetimidate as the benzylating agent[16a] and triflic acid as the catalyst, with no loss of configurational purity at the stereogenic center α to the carbonyl.[16b] Ester **10** was then converted into *N*-methoxy-*N*-methylamide **11**,[17a] which was reacted with ethylmagnesium bromide[17b] to provide the desired chiral ethyl ketone (*S*)-**8** (73% yield from **10**, $[\alpha]^{20}_{D} = +25.8°$ (*c* 8.2, $CHCl_3$), ≥97% ee[18] ).

**Synthesis of a Macrolide with 9*S* Configuration. Reagent-Controlled *Syn*-Selective Aldol Reactions of Ethyl Ketone (*S*)-8.** We elected first to direct our efforts toward a synthesis of the macrolide **3** bearing *S* configuration at $C_9$. Inspection of Scheme 1 reveals that this requires access to the two *syn* aldol adducts **6** (*SS*) (for the $C_1$−$C_7$ segment) and **7** (*SA*) (for the $C_8$−$C_{13}$ segment), which we envisaged being obtained from the (*Z*)-enol borinate of ketone (*S*)-**8**.

Initially, the aldol reaction of (*S*)-**8** using an *achiral* boron reagent was examined in order to ascertain whether there was any significant enolization stereoselectivity and/or enolate π-face diastereoselectivity arising from the ketone stereogenic center. By employing the sterically encumbered base diisopropylethylamine in the $^{n}Bu_2BOTf$-mediated aldol reaction[19] of ketone (*S*)-**8** and methacrolein, selective (*Z*)-enol borinate formation and hence good *syn* diastereoselectivity could be obtained (*syn*:*anti* = 89:11).[10c,20] The *syn* aldol adducts were formed in almost equal amounts (*SS*:*SA* = 54:46) which established that the (*Z*)-enol borinate of ketone (*S*)-**8** bearing *achiral* ligands on the boron displays insignificant π-face selectivity in its aldol reactions; *i.e.*, the influence of the α stereogenic center is negligible, and thus there is very low *substrate control*. This finding was important since it suggested that, in principle, the use of *chiral* ligands should allow *reagent control* of asymmetric induction in the boron-mediated aldol reactions of ketone (*S*)-**8**.

Employing the chiral boron reagent (−)-diisopinocampheylboron triflate ((−)-$(Ipc)_2BOTf$)[21] and $^{i}Pr_2NEt$ to enolize ethyl ketone (*S*)-**8** gave the corresponding (*Z*)-enol diisopinocampheylborinate **12** (Scheme 3). Addition of crotonaldehyde then provided the *syn*−*anti* aldol diastereomer **7** (*SA*), required for the $C_8$−$C_{13}$ fragment, with 89% diastereoselectivity and 73% yield. The *syn*−*syn* aldol diastereomer **7** (*SS*) was produced as the minor isomer, and ≤3% *anti* aldol diastereomers were observed. Similarly, the *syn*−*syn* aldol adduct **6** (*SS*), required for the $C_1$−$C_7$ fragment, was prepared in 74% yield and with 90% diastereoselectivity *via* (+)-$(Ipc)_2BOTf$-mediated enolization of (*S*)-**8**, giving the (*Z*)-enol diisopinocampheylborinate **13**, followed in this case by addition of methacrolein. The *syn*−*anti* aldol adduct **6** (*SA*) was now the minor diastereomer. In both cases, high-performance liquid chromatography (HPLC) on silica allowed separation of the aldol diastereomers. The high levels of asymmetric induction obtained in these reactions demonstrate the considerable degree of control obtainable with the chiral diisopinocampheylboron triflate reagents.

These results were as expected from the $(Ipc)_2BOTf$-mediated aldol reactions of *achiral* ethyl ketones with prochiral aldehydes. For the reactions of diethyl ketone and methacrolein or crotonaldehyde, for example, the *syn* aldol adducts are obtained with enantiomeric excesses of 86−91% when using the diisopinocampheylboron reagents (Scheme 4).[10a,e] The sense of asymmetric induction is the same as that observed for ketone (*S*)-**8**. Thus, *syn* aldol adduct **14** is afforded by use of the (−)-$(Ipc)_2BOTf$ reagent, *via* the (*Z*)-enol borinate **15**. Similarly, its enantiomer **16** is provided by the (+)-$(Ipc)_2BOTf$-derived (*Z*)-enol borinate **17**.

A rationale for the sense of asymmetric induction in these $(Ipc)_2BOTf$-mediated aldol reactions has been provided by a computational study using transition state (TS) modeling.[22] The calculated transition structures for the aldol reaction of the (*Z*)-enol diisopinocampheylborinate **18** of butanone with acetaldehyde are shown in Scheme 5 ($R^1 = R^2 =$ Me). TS **19** was the lowest energy structure found for reaction on the *si* face of the aldehyde, whereas TS **20** was the lowest energy structure found for *re*-face attack.[23] This latter TS is disfavored (+1.4 kcal $mol^{-1}$ relative to **19**), due largely to a steric interaction between the methyl group adjacent to the boron on the pseudoaxial Ipc ligand and the $R^1$ group of the enolate. Thus, reaction preferentially occurs *via* TS **19**, in which the same methyl group is orientated more favorably toward the aldehyde hydrogen, *i.e.*, away from the $R^1$ group of the enolate. This would account

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(16) (a) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240. (b) Widmer, U. *Synthesis* **1987**, 568.

(17) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(18) The enantiomeric purity of (*S*)-**8** was determined by debenzylation ($H_2$, 10% Pd/C, 20 °C, 3 h) to give an 89% yield of the corresponding hydroxyketone which chiral shift $^1H$ NMR studies at 250 MHz using $Eu(hfc)_3$ indicated had ≥97% ee.

(19) For leading references on dialkylboron triflate mediated *syn* aldol reactions of ethyl ketones, see: (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 153. (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (d) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (e) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (f) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, *19*, 1665. (g) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2225. (h) Van Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, *24*, 2295. (i) Hirama, M.; Garvey, D. S.; Lu, L. D. L.; Masamune, S. *Tetrahedron Lett.* **1979**, *41*, 3937.

(20) In contrast, enolization of (*S*)-**8** using the less-hindered base triethylamine leads to a marked preference for (*E*)-enol borinate formation, giving almost entirely *anti* aldol adducts in the reaction with methacrolein (*syn*:*anti* = 6:94; see ref 10c).

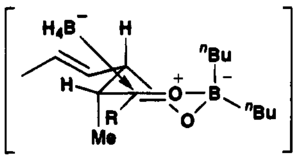
(21) Prepared in two steps from (+)-α-pinene: see ref 10e.

(22) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471.

for the experimental observation of predominantly *si*-face attack when using the (−)-enantiomer of the reagent.

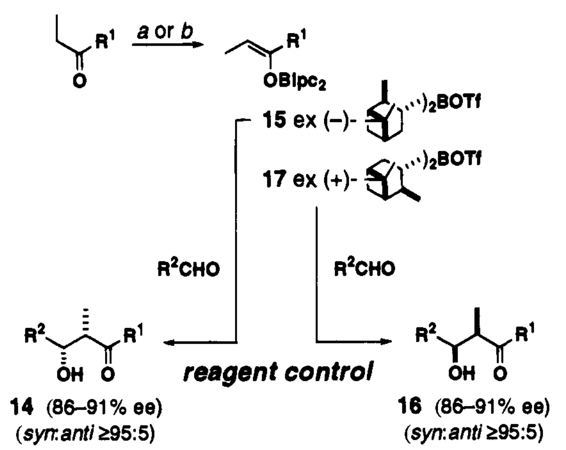
In TSs **19** and **20**, the Ipc ligands hold the same relative orientation. A second TS was found for *si*-face attack (**21** in Scheme 5), in which the two ligands hold a different relative orientation. However, this conformation was of significantly higher energy (+2.3 kcal $mol^{-1}$ relative to **19**). From this we conclude that the pseudoequatorial Ipc ligand is not merely acting as a bulky group, but is serving to lock the pseudoaxial ligand in position in low-energy forms for both *re*- and *si*-face attack (*i.e.*, TSs **19** and **20**). Thus, both the pseudoaxial and the pseudoequatorial chiral ligands are important in determining $\pi$-face selectivity of the enol borinate.

**Synthesis of the (9*S*)-$C_8$−$C_{13}$ Fragment.** The (−)-$(Ipc)_2BOTf$-mediated asymmetric aldol methodology supplied $\beta$-hydroxyketone **7** (*SA*) with three stereocenters ($C_9$, $C_{10}$, and $C_{12}$) correctly in place for the (9*S*)-$C_8$−$C_{13}$ fragment of oleandolide. The next transformation required was introduction of the $C_{11}$ stereocenter by directed reduction of the carbonyl group of **7** (*SA*), *i.e.*, **7** (*SA*) → $C_9$,$C_{11}$ *syn*-diol **22** in Scheme 6. This was accomplished with ≥97% diastereoselectivity (ds) (single diastereomer by 250 MHz $^1H$ NMR) and good yield (89%) by employing a modification (using the more reactive $LiBH_4$ in place of $NaBH_4$) of the Narasaka reduction protocol.[25] Thus, the dibutylboron aldolate **23**, derived from reaction of **7** (*SA*) with di-*n*-butylmethoxyborane, was reduced *in situ* by treatment with lithium borohydride at −78 °C; oxidative workup (hydrogen peroxide/pH 7 buffer) then gave the desired $C_9$,$C_{11}$ *syn*-diol **22**.[26,27] The high diastereoselectivity obtained on reduction may be rationalized by stereoelectronically favored axial attack of borohydride preferentially on the less-hindered face of aldolate **23**, which reacts in the most energetically favorable chair conformation shown. Attack on the lower face of **23** (as drawn) is impeded by the methyl and propenyl substituents.



**23**

**Scheme 4**[a]



$R^1$ = Et; $R^2$ = $H_2C{=}C(Me)$-, $MeCH{=}CH$-.

[a] (a) (−)-$(Ipc)_2BOTf$, $^iPr_2NEt$, $CH_2Cl_2$, −78 °C, 2 h; $R^2CHO$, −20 °C, 16 h; $H_2O_2$, MeOH/pH 7 buffer, 20 °C, 2 h; (b) (+)-$(Ipc)_2BOTf$, $^iPr_2NEt$, $CH_2Cl_2$, −78 °C, 2 h; $R^2CHO$, −20 °C, 16 h; $H_2O_2$, MeOH/pH 7 buffer, 20 °C, 2 h.

Following uneventful protection of the two secondary hydroxyls of **22** as their *tert*-butyldimethylsilyl (TBS) ethers, to provide **24** in high yield (86%), the next synthetic challenge was the stereoselective introduction of a methyl substituent at $C_{13}$. This we envisaged *via* addition to aldehyde **25**. Such a plan required debenzylation of **24** and oxidation of the resulting $C_{13}$ primary alcohol to provide the desired aldehyde. The presence of the double bond in **24** precluded hydrogenolysis of the benzyl ether. Debenzylation using a dissolving metal reduction (lithium in liquid ammonia/THF at −78 °C) was attempted, but unfortunately, under the polar reaction conditions, migration of TBS from the $C_{11}$ oxygen to the newly formed $C_{13}$ alkoxide was found to be a significant side reaction. Quantitative cleavage of the benzyl ether of **24** was effected *without* any accompanying TBS migration, however, by employing the lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB) radical anion reagent[28] in THF at −78 °C. Swern oxidation[29] then gave the desired $C_{13}$ aldehyde **25** in readiness for stereoselective methyl addition. During the oxidation, after addition of triethylamine at −78 °C, the reaction was allowed to warm only to −23 °C before quenching in order to prevent $\beta$-elimination of the siloxy substituent, which was a significant problem at higher temperatures.

The (9*S*)-$C_8$−$C_{13}$ fragment of oleandolide required the Felkin−Cram[30,31] product of methyl addition to aldehyde **25**, and of a number of reagents screened, methylmagnesium chloride gave both the highest yield and highest stereoselectivity. Thus, addition of MeMgCl to **25** at low temperature (−100 °C) gave the desired (13*R*)-alcohol **26** with 88% diastereoselectivity and in 73% yield over the three steps from **24**.[32] HPLC allowed separation of **26** from the minor epimer. This completed the construction of the $C_9$−$C_{13}$ stereopentad in six steps from (*S*)-**8**.

Protection of the $C_{13}$ hydroxyl in **26** as the (benzyloxy)methyl (BOM) ether and subsequent ozonolysis with a reductive workup provided the $C_8$ aldehyde **27** (92% yield over the two steps) in readiness for coupling with a nucleophilic $C_1$−$C_7$ fragment. The (9*S*)-$C_8$−$C_{13}$ fragment **27** had been obtained in eight steps from ethyl ketone (*S*)-**8** in 30% yield and with 76% overall diastereoselectivity.

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(23) Note that TSs **19** and **20** both possess a chair conformation. Boat TSs were found to be significantly higher in energy, thus accounting for the experimental observation of essentially complete *syn* diastereoselectivity for (*Z*)-enol borinates **15** and **17**.

(24) In **21** the methyl groups adjacent to the boron on the two Ipc ligands are on *opposite* sides, whereas in **19** and **20** these methyl groups are on the *same* side.

(25) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233; (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

(26) *In situ* reduction of the diisopinocampheylboron aldolate formed during the aldol reaction used to prepare **7** (*SA*) was also attempted, thus saving a synthetic step. Unfortunately, it proved difficult to separate the resulting diol **22** from the isopinocampheol produced on oxidative workup. However, the strategy of *in situ* reduction of the aldolate resulting from an aldol reaction was later successfully applied in our synthesis of the marine natural product denticulatin (see: Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801), and also in our synthesis of the $\delta$-lactone subunit of the marine natural product discodermolide (see: Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1790).

(27) The $C_9$,$C_{11}$-*syn* relative stereochemistry of **22** was confirmed by formation of its acetonide ($(MeO)_2CMe_2$, PPTS, $CH_2Cl_2$, 20 °C, 1 h; 88% yield) which had $^{13}C$ NMR resonances at $\delta$ 98.9, 30.0, and 19.7, consistent with the indicated stereochemistry. See: (a) Rychnovsky, S. D.; Skalitsky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

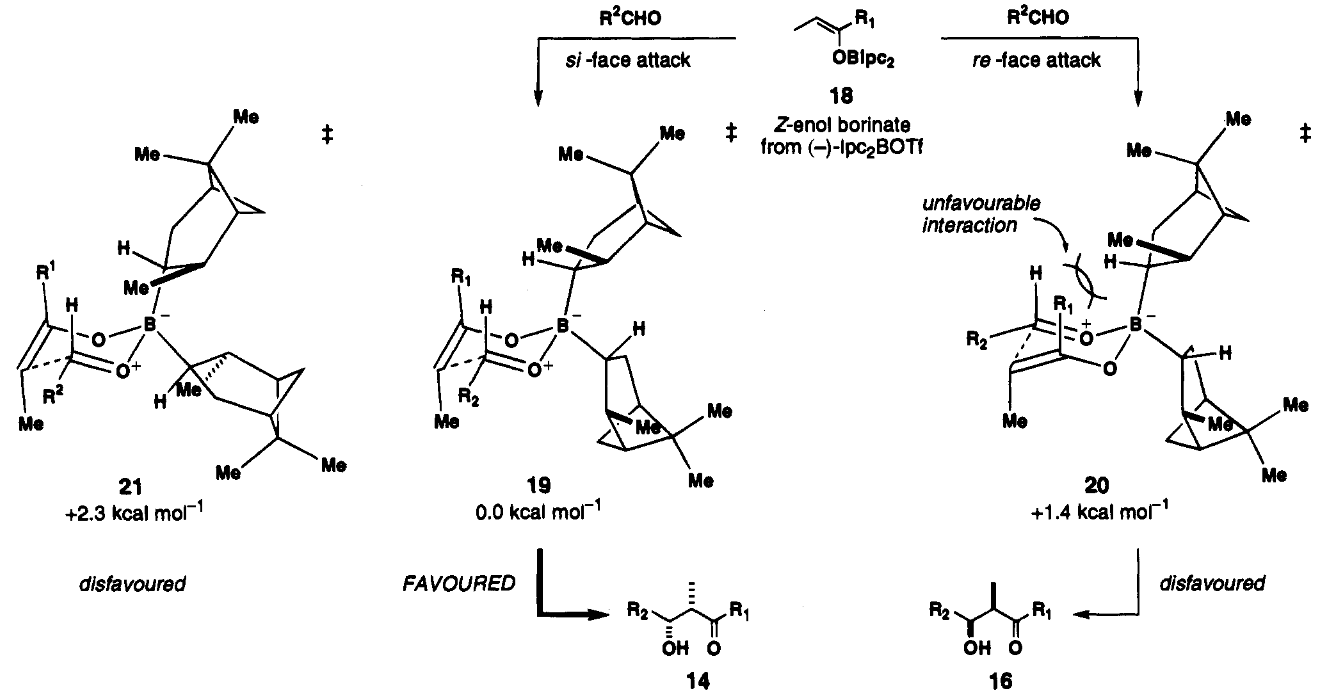
(28) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854 and references cited therein.

(29) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, 43, 2480.

(30) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

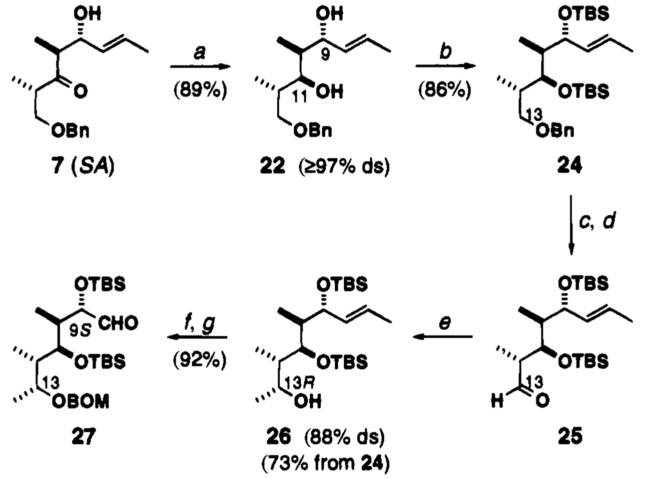
(31) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (c) Anh, N. T.; Thanh, B. T. *Nouv. J. Chim.* **1986**, *10*, 681.

Scheme 5



**Synthesis of the $C_1$–$C_7$ Fragment.** Having obtained $\beta$-hydroxyketone **6** (*SS*) *via* (+)-(Ipc)$_2$BOTf-mediated aldol reaction of ketone (*S*)-**8**, with three stereocenters ($C_2$, $C_4$, and $C_5$) correctly assembled for the $C_1$–$C_7$ fragment of oleandolide, a stereoselective ketone reduction and a stereoselective alkene hydroboration were required next to set the $C_3$ and $C_6$ centers, respectively, *i.e.*, **6** (*SS*) → **28** in Scheme 7. It was anticipated that this should be possible in a *one-pot* reaction of **6** (*SS*) with the sterically demanding borane (Ipc)$_2$BH.[34] Thus, treatment of **6** (*SS*) with (+)-(Ipc)$_2$BH (3 equiv) in ether at 0 → 20 °C, followed by oxidative workup with *m*-CPBA, gave three out of the four possible triols by HPLC analysis. These were the desired triol **28**, a minor product epimeric at $C_6$ (6-*epi*-**28**), and another minor product epimeric at $C_3$ (3-*epi*-**28**) in a ratio of 90:5:5 and in a total yield of 69%. By increasing the amount of borane used from 3 to 5 equiv, triol **28** was obtained in an improved yield of 76% after chromatography. The stereochemical configuration of **28** was confirmed by conversion into trihydroxytosylate **29**, the spectral analysis of which correlated with material synthesized during our earlier approach to oleandomycin.[7b]

Scheme 6[a]



[a] (a) $^n$Bu$_2$BOMe, THF/MeOH (5:1), −78 °C, 15 min; LiBH$_4$, −78 °C, 1 h; H$_2$O$_2$, MeOH/pH 7 buffer, 20 °C, 1 h; (b) $^t$BuMe$_2$SiOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78 °C, 1 h; (c) LiDBB, THF, −78 °C, 1 h; (d) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, 1 h; Et$_3$N, −23 °C, 30 min; aqueous NH$_4$Cl; (e) MeMgCl, THF, −100 °C, 1 h; (f) BnOCl, $^i$Pr$_2$NEt, CH$_2$Cl$_2$, 20 °C, 48 h; (g) O$_3$, CH$_2$Cl$_2$/Et$_2$O, −78 °C, 15 min; Me$_2$S, 20 °C, 15 min.

Reaction of $\beta$-hydroxyketone **6** (*SS*) with the opposite chirality of the borane, *i.e.*, (−)-(Ipc)$_2$BH, still led to formation of triol **28** as the major product, but with reduced stereoselectivity (63% ds) and with 6-*epi*-**28** as the next most abundant product (26%). This indicated that in the one-pot alkene hydroboration/ketone reduction of $\beta$-hydroxyketone **6** (*SS*) there is a significant degree of *substrate control* of asymmetric induction. In the case of (+)-(Ipc)$_2$BH, the asymmetric influences of the substrate and reagent are *matched*; in the *mis-*

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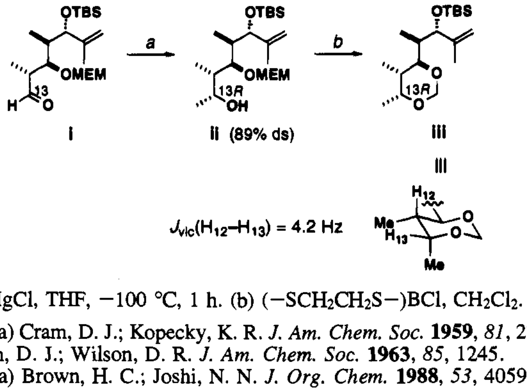
(32) The $C_{13}$ configuration of alcohol **26** was assigned by analogy with the known sterochemical outcome of Grignard addition to aldehyde i, structurally similar to **25**, which provided the (13*R*)-alcohol ii with 89% ds as part of our earlier synthetic efforts directed at oleandomycin (see ref 7b). The configuration at $C_{13}$ of ii was established by preparation of the dioxane iii. The vicinal coupling between $C_{12}H$ and $C_{13}H$ (4.2 Hz) of iii was typical of that expected for an axial–equatorial relationship. Note that the $C_{13}$ configuration of ii is opposite to that originally reported (ref 7b), and Cram-chelate control (ref 33) in the Grignard addition to aldehyde i may be occurring.

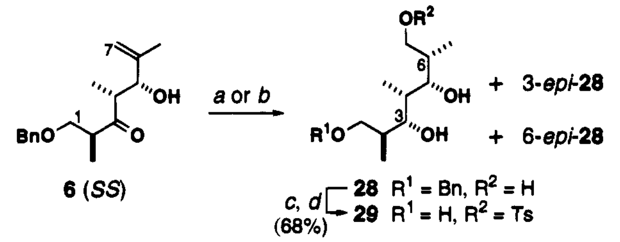


(a) MeMgCl, THF, −100 °C, 1 h. (b) (−SCH$_2$CH$_2$S−)BCl, CH$_2$Cl$_2$.

(33) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.

(34) (a) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059. (b) For a review, see: Brown, H. C.; Jadhav, P. K.; Singaram, B. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4.

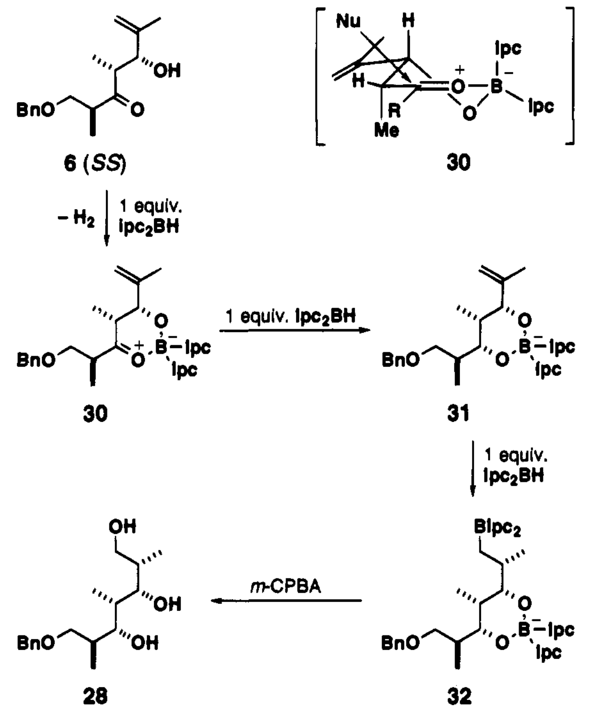
**Scheme 7**[a]



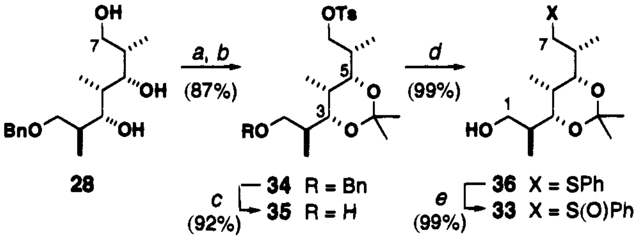
| reagent | product distribution[b] (**28**:6-*epi*-**28**:3-*epi*-**28**) | yield[c] (%) |
|---|---|---|
| a | 90:5:5 | 69 |
| b | 63:26:11 | 64 |

[a] (a) (+)-(Ipc)$_2$BH (3 equiv), Et$_2$O, 0 → 20 °C, 2 h; *m*-CPBA, 1 h, 20 °C; (b) (−)-(Ipc)$_2$BH (3 equiv), Et$_2$O, 0 → 20 °C, 2 h; *m*-CPBA, 1 h, 20 °C; (c) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 20 °C, 1 h; (d) H$_2$, 10% Pd/C, $^i$Pr$_2$O, 20 °C, 2 h. [b] Ratio of isolated yields after chromatography. [c] Combined yield of all isomers.

**Scheme 8**



**Scheme 9**[a]



[a] (a) TsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 20 °C, 1.5 h; (b) (MeO)$_2$CMe$_2$, PPTS, CH$_2$Cl$_2$, 20 °C, 15 h; (c) H$_2$, 10% Pd/C, $^i$Pr$_2$O, 20 °C, 2 h; (d) PhSLi, THF, 80 °C, 3 h; (e) NaIO$_4$, MeOH/H$_2$O, 20 °C, 21 h.

*matched* situation, using the antipodal reagent, substrate control dominates over reagent control and the Ipc groups are to a large extent merely acting as bulky ligands.

The sense of stereochemical control due to the substrate may be rationalized according to existing models. On the basis of the experimental observation of gas evolution upon addition of the substrate to a solution of (Ipc)$_2$BH, we hypothesize that, in the reaction using 3 equiv of the borane, the first equivalent of reagent discharges hydrogen from β-hydroxyketone **6** (*SS*) to form the boron aldolate **30** (Scheme 8). The formation of this aldolate should activate the carbonyl to reduction by a second equivalent of borane, with attack occurring preferentially from the less-hindered upper face (as drawn) of the six-membered chelate to provide borate **31**, and may account for the extremely high level of diastereoselectivity observed for the ketone reduction.[35] Reaction with a third equivalent of reagent then leads to hydroboration of the alkene (in the stereochemical sense predicted by Still[36]) to provide **32**, which upon oxidative workup yields triol **28**. We have, however, been unable to establish unambiguously that ketone reduction precedes alkene hydroboration, and the two processes may well occur competitively. The scope of our hydroboration/reduction protocol has been extended to the preparation of other stereopentad systems.[10g]

With the preparation of triol **28** accomplished, all of the five contiguous stereogenic centers spanning C$_2$−C$_6$ in oleandolide had now been constructed, in only *two* steps from ethyl ketone (*S*)-**8**. On the basis of our previous studies,[7b] we elected to convert **28** into the known phenyl sulfoxides **33** (Scheme 9) in readiness for coupling to aldehyde **27**. Thus, selective tosylation of the C$_7$ primary hydroxyl of **28** and subsequent protection of the two secondary hydroxyls as an acetonide provided **34** in 87% yield over the two steps. The use of a cyclic protecting group for the C$_3$ and C$_5$ hydroxyls was intended to introduce a degree of conformational rigidity to the seco-acid, which we anticipated would promote an efficient macrolactonization (*vide infra*).[11] Hydrogenolysis of the C$_1$ benzyl ether of **34** gave **35** in 92% yield. Introduction of sulfur, which was needed to direct deprotonation at C$_7$ in the subsequent coupling reactions, was then accomplished by thiophenolate ion displacement of the tosyl group of **35**, affording the phenyl sulfide **36** in 99% yield. Compound **36** was identical in all respects with material synthesized during our earlier approach to oleandomycin.[7b] An uneventful periodate oxidation of **36** then gave a mixture of the diastereomeric sulfoxides **33**, which were not separated, again in 99% yield. The C$_1$−C$_7$ fragment **33** had thus been synthesized in seven steps from ethyl ketone (*S*)-**8** in an overall yield of 40% and with 81% diastereoselectivity.

**Fragment Coupling and Macrolactonization.** Optimum conditions for the coupling of the C$_1$−C$_7$ and C$_8$−C$_{13}$ fragments involved lithiation of sulfoxides **33** with LDA (2.2 equiv) in DME at −78 °C, followed by addition of aldehyde **27** (0.6 equiv) at the same temperature (Scheme 10). This led to a complex mixture of adducts **37** in 88% yield (80% conversion of aldehyde), which were not separated. The excess sulfoxide used in the reaction could be recovered unchanged, after flash chromatography, and used in future reactions.

Desulfurization of adducts **37** was effected in 65% yield by treatment with W-2 Raney nickel in ether at room temperature.[37] The combined mixture of isomeric diols resulting from the Raney nickel treatment (**38** + suspected C$_8$ OTBS regioisomers) was then subjected to a two-step oxidation procedure involving initial Swern oxidation,[29] to give the corresponding ketoaldehydes, followed by further oxidation to the C$_1$ carboxylic acid **39** and its C$_8$ OTBS regioisomer using Masamune's neutral

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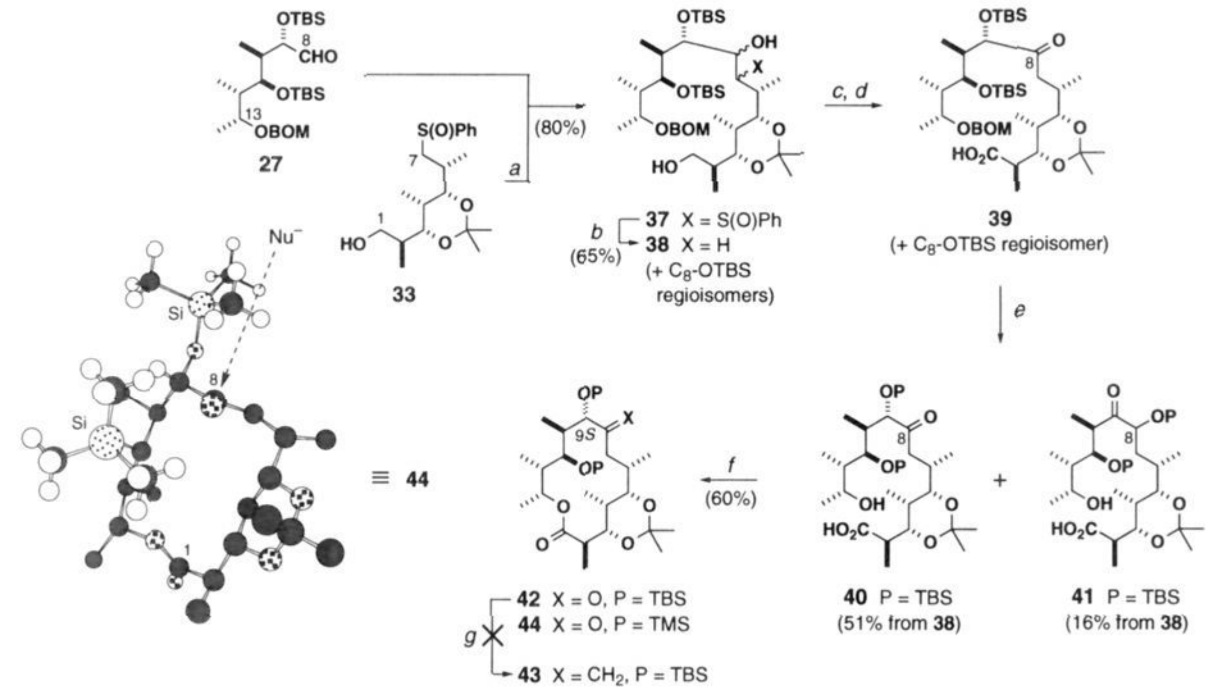
[35] A similar mechanism has been proposed by Evans for reduction of β-hydroxyketones using catecholborane. See: Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

[36] Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

[37] *Four* isomeric products were obtained, however, instead of the two epimers **38** expected. It was suspected that the two additional products arose from migration of TBS from the C$_9$ oxygen to the C$_8$ hydroxyl (a conceivably less sterically hindered environment) which could have occurred during either the coupling or subsequent desulfoxidation steps.

**Scheme 10**[a]



[a] (a) LDA (2.2 equiv), DME, −78 °C, 15 min; **27**, −78 °C, 5 min; (b) W-2 Raney Ni, $Et_2O$, 20 °C, 90 min; (c) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 1 h; $Et_3N$, −23 °C, 30 min; aqueous $NH_4Cl$; (d) $KMnO_4$, ${}^tBuOH$/pH 7 buffer, 20 °C, 30 min; (e) $H_2$, Pd/C, EtOH, 20 °C, 90 min; (f) 2,4,6-$Cl_3(C_6H_2)COCl$, $Et_3N$, THF, 20 °C, 2 h; add to DMAP, PhMe, 80 °C, 3 h; (g) $Ph_3MeP^+Br^-$, KHMDS, PhMe, 100 °C, 16 h.

conditions of buffered potassium permanganate.[38] Finally, hydrogenolysis of the $C_{13}$ (benzyloxy)methyl ether provided two hydroxy acids, separable by flash chromatography, in a ratio of 3.3:1 and in 67% overall yield from **38**. The major product was confirmed as the desired seco-acid **40**.[39]

With seco-acid **40** thus in hand, albeit in a yield reduced by unwanted TBS migration, the critical macrolactonization step could be attempted. The conditions chosen for macrolactonization were those developed by Yamaguchi *et al.*,[40] which had been used with notable success in our earlier synthesis of (9*S*)-dihydroerythronolide A (91% macrolactonization yield).[41] Accordingly, the mixed anhydride of seco-acid **40** was prepared by treatment with 2,4,6-trichlorobenzoyl chloride and triethylamine in THF (2 h, 20 °C), and then added slowly (3 h) by syringe pump as a dilute solution in toluene to a solution of DMAP in toluene at 80 °C. Gratifyingly, a 60% yield of macrolide **42** was obtained for this key reaction.

**Attempted Olefination of Macrolide 44 and Related Modeling Studies.** We envisaged that the exocyclic epoxide at $C_8$ of oleandolide might be introduced *via* epoxidation of the alkene **43**, which could conceivably be prepared by Wittig olefination of the macrolide **42** using triphenylphosphonium methylide ($Ph_3P{=}CH_2$). Unfortunately, macrolide **42** proved resistant to attack by the phosphorus ylide, even at temperatures as high as 100 °C, and only unchanged starting material was recovered from the reaction. The failure of **42** to undergo nucleophilic attack at $C_8$ was rationalized by molecular modeling of the related macrolide **44** using MacroModel.[42] In the lowest energy conformer of **44** (Scheme 10), attack on the *re* face of the $C_8$ ketone is blocked by the OTMS group on $C_9$ (dashed arrow), whereas *si*-face attack is obstructed by the macrocyclic ring structure. Higher energy conformations (considered significant up to 8 kJ $mol^{-1}$ above the ground state) showed a similar local conformation about the $C_8$ ketone.

At this stage, we resolved to further examine the conformational requirements for olefination of macrolides possessing a ketone at $C_8$, with a view to introduction of the $C_8$ exocyclic epoxide needed for oleandolide, by investigating the 9*R* epimer of **42**, *i.e.*, macrolide **45** (Scheme 11). Our initial retrosynthetic analysis (Scheme 1) revealed that the synthesis of a macrolide bearing *R* configuration at $C_9$ was indeed an option (*vide infra*). However, for the model studies, macrolide **45** was obtained by the sequence of reactions depicted in Scheme 11. Degradation of oleandomycin according to the procedure of Tatsuta *et al.* provided tetrol **46**,[6a] which was selectively protected as its $C_3$,$C_5$-acetonide **47** in 78% yield. Subjection of **47** to standard silylation conditions (TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C) gave only monosilylation. Bis-TBS protection of **47** required forcing conditions (8 equiv of reagent, minimum use of solvent and extended reaction times at room temperature), implying that there was a considerable degree of steric crowding in the product **48**, but could be achieved in 69% yield. Ozonolysis of **48** then provided the macrolide **45** (84% yield) in readiness for the olefination model studies.

Subjection of ketone **45** to a range of nucleophilic reagents ($Zn/CH_2I_2/TiCl_4$,[43] $Cp_2TiCH_2ClAlMe_2$,[44] $TMSCH_2Li/CeCl_3$,[45] $Me_2S{=}CH_2$,[46] $Me_2S(O){=}CH_2$,[46] $CH_2N_2$, $Ph_3P{=}CH_2$ at ≤70 °C,

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(38) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

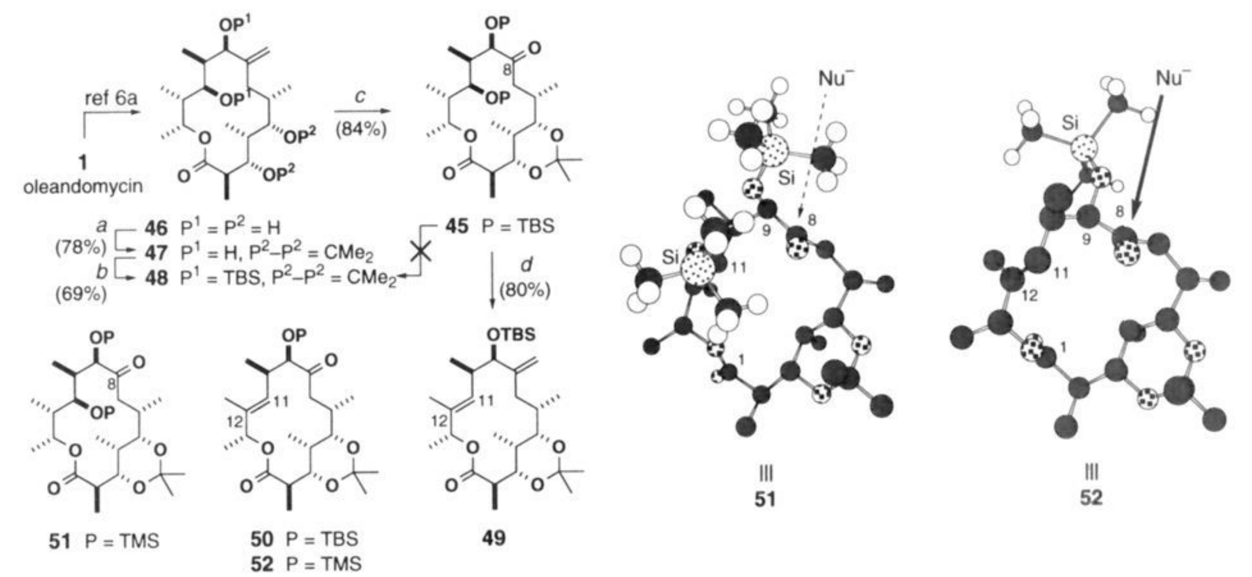
(39) The 400 MHz $^1H$ NMR spectrum of the major product had characteristic signals due to the two geminally coupled protons at $C_7$ [$\delta$ 2.74 (1H, dd, $J$ = 17.6, 2.5 Hz), 2.22 (1H, dd, $J$ = 17.6, 9.0 Hz)] of **40**. Such signals were absent in the proton NMR spectrum of the minor product, which was thus tentatively assigned the structure **41** wherein TBS migration had taken place. The configuration at $C_8$ of **41** was not determined.

(40) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(41) (a) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461. (b) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463.

(42) We used the MM2 force field in MacroModel, v 3.5: Mohamedi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Scheme 11[a]



[a] (a) $(MeO)_2CMe_2$, PPTS, $CH_2Cl_2$, 20 °C, 3 h; (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$ (1:1:1 by volume), 20 °C, 84 h; (c) $O_3$, EtOAc, −78 °C, 90 min; $Me_2S$, 20 °C, 30 min; (d) $Ph_3MeP^+Br^-$, KHMDS, PhMe, 90 °C, 8 h.

$NaBH_4$, MeLi, and MeMgCl), however, led only to reisolation of starting material. It thus appeared that the $C_8$ carbonyl group of macrolide **45**, as in the 9*S* macrolide **42**, was simply too sterically hindered to react with nucleophiles. However, upon heating to a high enough temperature (≥80 °C), macrolide **45** *did* react with the ylide generated from methyltriphenylphosphonium bromide by treatment with potassium hexamethydisilazide (KHMDS), to afford a product having the required $C_8$ *exo*-methylene group. Unfortunately, this product also possessed another double bond and contained only one TBS group. It was apparent that there had been an elimination of TBSOH across $C_{11}-C_{12}$ during the course of the reaction, and the product was accordingly identified as macrolide **49**.[47] In no case was the product of $C_8$ methylenation before $C_{11}-C_{12}$ elimination (*i.e.*, the desired **48**) ever observed. Reaction at lower temperatures (≤70 °C) led only to recovery of starting material and no product formation.

It was thus hypothesized that although the $C_8$ carbonyl group of macrolide **45** was too sterically hindered to react with nucleophiles (especially bulky phosphorus ylides), when **45** was heated to a high enough temperature (>80 °C) under the conditions of the Wittig reaction, elimination of TBSOH across $C_{11}-C_{12}$ occurred to give alkene **50**, the conformation of which was sufficiently different to allow access of nucleophiles to the $C_8$ carbonyl group. At 80 °C the Wittig olefination of **50** was thus facile and occurred immediately to give the isolated product **49**. This hypothesis was supported by computer modeling using MacroModel.[42] The lowest energy conformation calculated for **51** (in which the TBS groups of **45** have been replaced by TMS groups to simplify the computation) is shown in Scheme 11.[48] Attack on the *si* face of the ketone is obstructed by the macrocyclic ring structure, while the ketone is shielded from *re*-face attack (dashed arrow) by the $C_9$ OTMS group, which is locked in position by the $C_{11}$ OTMS group. In the real system (*i.e.*, **45**), the sterically more-demanding OTBS group would be expected to have an even greater blocking effect. In contrast, in the lowest energy conformer calculated for **52**, the product of $C_{11}-C_{12}$ elimination from **51**, the $C_8$ ketone is now exposed to attack on its *re* face (solid arrow) as the silyl ether at $C_9$ can rotate out of the way, thus explaining why **50** undergoes methylenation with phosphorus ylide reagents.

At this stage of the research it was apparent that although a short and highly stereoselective synthesis of the (9*S*)-macrolide **42** had been developed (5% yield over 14 steps from ketone (*S*)-**8** with 62% overall ds), the elaboration of this intermediate to complete a synthesis of oleandolide was likely to be problematical due to the difficulties encountered in introducing further functionality at the sterically encumbered $C_8$ position. For similar reasons, it appeared that if a macrolide having 9*R* configuration was to be synthesized *de novo*, the TBS group (as in **45**) was an unacceptable choice of protecting group for the $C_9$ (and $C_{11}$) hydroxyls. In addition, the loss of material during the coupling and/or desulfoxidation steps in the synthesis of macrolide **42**, due to migration of the TBS protecting group

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(43) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417. (b) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (c) Hibino, J; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

(44) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733. (c) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.

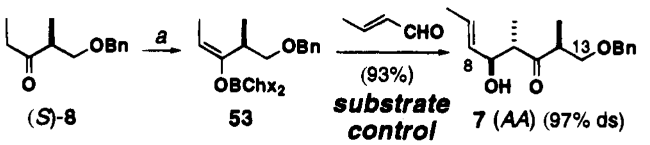
(45) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

(46) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Gololobov, Yu. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskful, I. E. *Tetrahedron* **1987**, *43*, 2609.

(47) **49** had 400 MHz $^1H$ NMR resonances at $\delta$ 5.31 (1H, br s) and 5.11 (1H, br s) for the exocyclic olefinic protons and an additional resonance at $\delta$ 5.47 (1H, br d, $J = 8.5$ Hz) for the endocyclic olefin. Subsequent computer modeling (*vide infra*) of the two possible $C_{11}-C_{12}$ elimination products from **51** (in which the TBS groups of **45** have been replaced by TMS groups to simplify the computation) suggested that formation of the 11*E* double-bond isomer **52** was more likely (despite requiring a *syn* elimination of TBSOH) than production of the 11*Z* isomer (which was calculated to be 2.6 kJ mol$^{-1}$ higher in energy than the 11*E* isomer, and which required an *anti* elimination process necessitating approach of base from a direction blocked by the macrolide ring structure; the distance was too great to postulate that such deprotonation at $C_{12}$ could occur by transannular attack of an enolate anion formed at $C_7$). Hence, the product from the Wittig reaction of ketone **45** was tentatively assigned the 11*E* structure **49**. The alternative possibilities of elimination of TBSOH across $C_9-C_{10}$ or $C_{10}-C_{11}$ could be easily ruled out, since the resultant structures were incompatible with the recorded $^1H$ NMR spectrum.

(48) Evidence for the applicability of this conformation was provided by NOE difference NMR experiments on **45**. Irradiation of the $C_9$ hydrogen resulted in NOE signal enhancements for the hydrogens on both $C_7$ (4.2%) and $C_{10}$ (6.8%), and a transannular NOE was observed from the hydrogen on $C_3$ to one of the methyl groups of the OTMS substituent on $C_{11}$ (2.7%). Both observations are consistent with the conformation of **51** depicted in Scheme 11.

**Scheme 12**[a]



[a] (a) $(Chx)_2BCl$, $Et_3N$, $Et_2O$, −78 °C, 2 h; (*E*)-MeCH=CHCHO, 0 °C, 16 h; $H_2O_2$, MeOH/pH 7 buffer, 20 °C, 2 h.

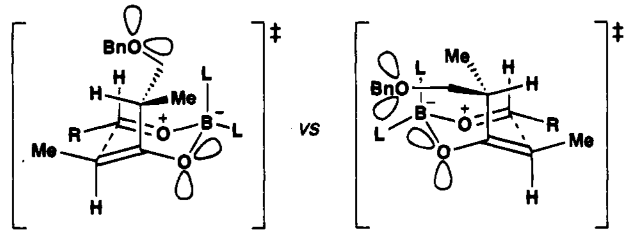
from $C_9$ to $C_8$, was undesirable. In an attempt to achieve a more efficient synthesis, we therefore elected to employ a *cyclic* group to protect the $C_9$ and $C_{11}$ hydroxyls, since this should eliminate the problem of protecting group migration. Such a choice of protecting group necessitated the synthesis of a macrolide having *R* configuration at $C_9$. An additional requirement was that the protecting group used should not significantly hinder nucleophilic attack at $C_8$ of the macrolide. Computer modeling studies (*vide infra*) indicated that acetal protecting groups should satisfy such criteria; accordingly, the synthesis of a macrolide so-protected was now attempted.

**Synthesis of a Macrolide with 9*R* Configuration. Substrate-Controlled *Anti*-Selective Aldol Reaction of Ethyl Ketone (*S*)-8.** Inspection of the retrosynthesis for oleandolide (Scheme 1) reveals that access to a macrolide (**3**) having 9*R* configuration requires the stereoselective synthesis of the *anti* aldol adduct **7** (*AA*). This in turn requires the selective generation of the (*E*)-enol borinate of ketone (*S*)-**8**, and control over the π-face diastereoselectivity of its aldol addition to crotonaldehyde.

Brown has described the use of the achiral reagent dicyclohexylboron chloride ($(Chx)_2BCl$) for the selective *E* enolization of diethylketone.[49] Optimum selectivity is obtained by using the less-hindered base triethylamine (rather than the sterically more-demanding $^{i}Pr_2NEt$), and by employing ether as the solvent. The boron chloride reagent is readily available *via* hydroboration of cyclohexene with monochloroborane.[49b] We were gratified to discover that, on applying Brown's enolization protocol to ethyl ketone (*S*)-**8** (at a temperature of −78 °C), followed by addition of crotonaldehyde and buffered oxidative ($H_2O_2$) workup, essentially a *single* aldol isomer was produced, in excellent yield (Scheme 12).[10d] The diastereoselectivity of this extraordinary reaction was judged by HPLC and 400 MHz $^1H$ NMR analysis to be at least 97%.[50] The major aldol adduct was determined to be **7** (*AA*),[51] the isomer required for oleandolide synthesis.

In the analogous *syn* aldol reaction of (*S*)-**8** mediated by the achiral reagent $^{n}Bu_2BOTf$, with $^{i}Pr_2NEt$ as base, the corresponding *SA*:*SS* ratio was close to unity (*vide supra*). Thus, *whereas a (Z)-enol borinate of ketone (S)-8 possessing achiral ligands displays negligible π-face selectivity, the corresponding (E)-enol borinate displays marked π-face selectivity in its reaction with achiral aldehydes.* In the $(Chx)_2BCl$-mediated aldol reaction of ethyl ketone (*S*)-**8** there is thus a substantial degree of *substrate control* of asymmetric induction.

The remarkably high level of diastereoselectivity operating in the $(Chx)_2BCl$-mediated aldol reaction of ketone (*S*)-**8** can be traced to the relative steric and electronic properties of the three substituents—H, Me, and $CH_2OBn$—at the α stereogenic center of the (*E*)-enol borinate **53**. Computational transition state modeling of the reaction has identified **54** as the lowest energy TS conformer.[52] This chairlike structure minimizes the A(1,3) allylic strain[53] with the (*E*)-enol methyl substituent, and has the methyl group pointing outward and the (benzyloxy)-methyl substituent directed in toward the aldehyde. The apparent contrasteric preference for TS **54** (*re*-face attack) over TS **55** (*si*-face attack) is considered to have an electronic origin.[10f,52,54,55] It is conceivable that TS **55** is destabilized by lone-pair repulsion[56] between the oxygen atoms.



**54**
*re*-face attack
FAVOURED

**55**
*si*-face attack

A model to account for the considerable difference in enolization selectivity of the $(Ipc)_2BOTf/^{i}Pr_2NEt$ system (→ (*Z*)-enol borinate **12**) compared to the $(Chx)_2BCl/Et_3N$ system (→ (*E*)-enol borinate **53**) has recently been proposed.[57]

**Synthesis of the (9*R*)-$C_8$–$C_{13}$ Fragment.** Having synthesized the *anti* aldol adduct **7** (*AA*), the next transformation required in the route to the (9*R*)-$C_8$–$C_{13}$ fragment of oleandolide was introduction of the $C_{11}$ stereocenter. In view of the inverted configuration at $C_9$ (*i.e.*, 9*R* rather than 9*S*), a directed ketone reduction of **7** (*AA*) giving the $C_9$,$C_{11}$ *anti*-diol was now required. This was accomplished in 92% yield and with ≥97% ds (single diastereomer by 400 MHz $^1H$ NMR)[58] by employing the tetramethylammonium triacetoxyborohydride reducing agent introduced by Evans (Scheme 13).[59]

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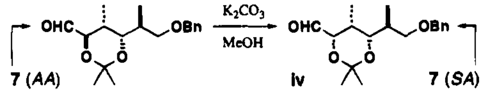
[49] (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441; (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499; (c) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716. (d) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1992**, *57*, 3767. (e) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147. (f) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 7162.

[50] Some selectivity in *anti* aldol product formation had already been noted for the $^{n}Bu_2BOTf/Et_3N$-mediated aldol reaction of ketone (*S*)-**8** (*anti*:*syn* = 94:6, *AA*:*AS* = 88:12; see ref 10c). The greater π-face selectivity obtained with $(Chx)_2BCl$ is consistent with the greater steric bulk of the cyclohexyl ligand compared to *n*-butyl.

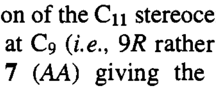
[51] The configuration of the major aldol adduct (**7** (*AA*)) was deduced by synthesis of aldehyde **iv** and chemical correlation with material synthesized independently from the known aldol adduct **7** (*SA*) (see supplementary material and ref 10d).



[52] Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685.

[53] For a review of A(1,3) allylic strain, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

[54] This is supported by the results of the $(Chx)_2BCl/Et_3N$-mediated *anti* aldol reaction of ketone **v**, where a $CH_2$ group replaces the benzyl ether oxygen in (*R*)-**8**.



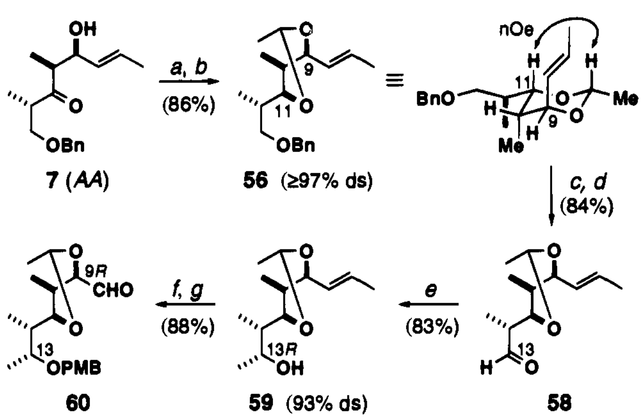
A dramatic erosion of π-face selectivity in aldol addition to methacrolein was observed, giving 72:28 (*si*:*re* or *re*:*si*) for **v** compared to 98:2 (*si*:*re*) for (*R*)-**8** itself. See: Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182.

[55] For *contrasting* stereoselectivities in the *anti* aldol reactions of some other chiral ethyl ketones, see ref 46 and (a) Paterson, I.; Hulme, A. N.; Wallace, D. J. *Tetrahedron Lett.* **1991**, 32, 7601. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

[56] Lone-pair repulsion has been invoked by Roush to rationalize the asymmetric induction occurring in tartrate-mediated allylboration reactions. Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

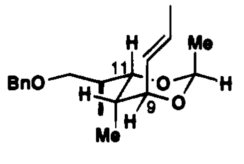
[57] (a) Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219. (b) Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7213.

**Scheme 13**[a]



[a] (a) $Me_4NBH(OAc)_3$, AcOH/MeCN, −20 °C, 48 h; (b) $(MeO)_2CHMe$, $CH_2Cl_2$, catalytic p-TsOH, 20 °C, 70 h; (c) LiDBB, THF, −78 °C, 1 h; (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 1 h; $Et_3N$, −23 °C, 30 min; aqueous $NH_4Cl$; (e) MeMgCl, $CH_2Cl_2$, −100 °C, 1 h; (f) PMBCl, KH, THF, 0 → 20 °C, 90 min; (g) $OsO_4$, NMO, $^tBuOH/THF-H_2O$, 20 °C, 15 h; $NaIO_4$, pH 7 buffer, 20 °C, 25 min.

On the basis of our molecular modeling studies (*vide infra*) we elected to protect the $C_9$,$C_{11}$ *anti*-diol as its ethylidene acetal. However, the use of such an acetal introduces an additional stereogenic center. Note that the macrolide modeling studies suggested that only one acetal configuration would permit the correspondingly protected seco-acid to undergo macrolactonization.[60] The required acetal stereochemistry was that of **56** (Scheme 13). Molecular modeling using MM2[42] predicted that the desired acetal **56** should, however, be thermodynamically preferred over its epimer **57** by >99:1. Accordingly, thermodynamically controlled acetalization of the $C_9$,$C_{11}$ *anti*-diol with acetaldehyde dimethyl acetal using p-toluenesulfonic acid as catalyst gave, after 24 h, the desired **56** as a single isomer in 86% yield over the two steps from **7** (*AA*). Shorter reaction times (<24 h) or weaker acids (pyridinium p-toluenesulfonate) led to a mixture of **56** and **57**. The stereochemistry of **56** was confirmed by NOE experiments, in which irradiation of the acetal hydrogen led to enhancement of the olefinic (8.5%) and $C_{11}$ hydrogen (11.6%) resonances.



**57**

Acetal **56** was elaborated to a (9*R*)-$C_8$−$C_{13}$ fragment suitable for coupling by a sequence of reactions analogous to that used earlier in the 9*S* route. Thus, cleavage of the $C_{13}$ benzyl ether of **56** was achieved in 97% yield by use of the LiDBB radical anion reagent[28] in THF at −78 °C. Swern oxidation[29] (warming only to −23 °C after addition of triethylamine, as before, in order to prevent elimination of the β-alkoxy substituent) then gave the $C_{13}$ aldehyde **58** in 87% yield. Stereoselective introduction of a methyl substituent at $C_{13}$ of **58** was expected to be achieved by addition of a methyl Grignard reagent at low temperature. As in the 9*S* route, the product of Felkin−Cram addition[30,31] was required, but the use of the ethylidene protecting group provided the possibility of chelation control.[33] In the event, addition of MeMgCl to a solution of aldehyde **58** in dichloromethane at −100 °C gave 93% diastereoselectivity in favor of the desired (13*R*)-alcohol **59**,[61] and a yield of 89%; the minor epimer could now be removed by flash chromatography on silica gel. Grignard addition in either THF or ether gave similar levels of diastereoselectivity, but lower yields. After protection of alcohol **59** as its p-methoxybenzyl (PMB) ether, oxidative cleavage of the double bond (dihydroxylation using osmium tetroxide, followed by *in situ*[62] cleavage by sodium periodate[63,64]) then gave the (9*R*)-$C_8$−$C_{13}$ aldehyde **60** in 88% yield over the two steps.

The (9*R*)-$C_8$−$C_{13}$ fragment had been prepared in an overall yield of 48% over the eight steps from ethyl ketone (*S*)-**8** and with 90% ds (*cf.* 30% yield and 76% ds for the earlier 9*S* fragment). The improved efficiency of the latest route was a direct consequence of the remarkably high diastereoselectivity (97%) achieved in the substrate-controlled $(Chx)_2BCl$-mediated *anti* aldol reaction of (*S*)-**8**, together with the high diastereoselectivity (93%) obtained in Grignard addition to aldehyde **58**.

**Substrate-Controlled *Syn*-Selective Aldol Reaction of Ethyl Ketone (*S*)-8.** Encouraged by the success of the substrate-controlled *anti* aldol reaction providing **7** (*AA*), we decided to investigate whether substrate control might also be used to afford improved diastereoselectivity in the *syn* aldol reaction generating **6** (*SS*) for the $C_1$−$C_7$ fragment, which had previously been performed under reagent control (*vide supra*).

The (*Z*)-enol di-n-butylborinate of ketone (*S*)-**8**, which reacts through a nonchelated chair transition state, had already been shown to display insignificant π-face selectivity in its aldol addition to methacrolein (*SS*:*SA* = 54:46). It was conceivable that asymmetric induction from the α stereogenic center of ketone (*S*)-**8** might be magnified by reaction through a conformationally restricted enolate. Such an enolate might be obtained by the use of a Lewis acidic metal capable of internally chelating the benzyl ether oxygen. Following the report by Evans of a procedure for the direct formation of chlorotitanium (*Z*)-enolates ($TiCl_4$, $^iPr_2NEt$),[65] the titanium-mediated aldol addition of ketone (*S*)-**8** to methacrolein was examined. An excellent yield of the *syn* aldol adducts was obtained (93%, *syn*:*anti* ≥ 98:2), but the observed π-face stereoselectivity for this reaction, although higher than in the dibutylboron-mediated case, was still low (*SS*:*SA* = 62:38), implying that the reaction was not proceeding through a chelated transition state.

Mukaiyama[66a] has introduced tin(II) enolates[66] for the *syn*-selective aldol reactions of simple ketones. When ketone (*S*)-**8** was enolized under modified Mukaiyama conditions ($Sn(OTf)_2$, $Et_3N$ in $CH_2Cl_2$ at −78 °C for 2 h), followed by addition of methacrolein, an excellent yield (90%) of aldol adducts was obtained (Scheme 14).[67] A high level of *syn* diastereoselectivity

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[58] The $C_9$,$C_{11}$ *anti* relative stereochemistry of the product diol was confirmed by formation of its acetonide ($(MeO)_2CMe_2$, PPTS, $CH_2Cl_2$, 20 °C, 18 h; 88% yield) which had $^{13}C$ NMR resonances at δ 100.8, 24.6, and 24.1, consistent with the desired stereochemistry (ref 27).

[59] (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939; (b) Evans D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

[60] For a similar observation of the effect of $C_9$,$C_{11}$ acetal stereochemistry in macrolactonizations of erythronolide seco-acids, see: Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565.

[61] The $C_{13}$ configuration of **59** was confirmed by synthesis of a correlation compound, and comparison with material derived from the known alcohol **26** (see supplementary material for details).

[62] Attempts to isolate the intermediate diol led to reduced yields.

[63] Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958.

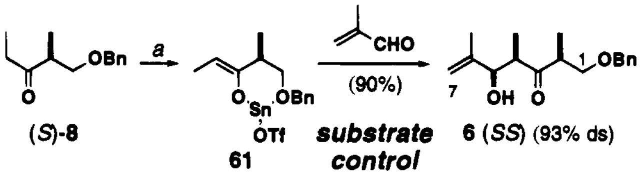
[64] Ozonolysis of the double bond led to a reduced yield of **60** (52%) together with a number of degradation products arising from reaction of the acetal protecting group.

[65] Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.

[66] For aldol reactions using tin(II) enolates, see *inter alia*: (a) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. (b) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. (c) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476. (d) ref 63.

[67] Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.

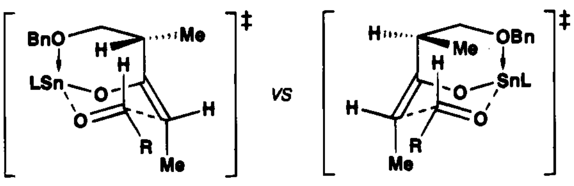
**Scheme 14**$^{a}$



$^{a}$ (a) Sn(OTf)$_2$, Et$_3$N, CH$_2$Cl$_2$, −78 °C, 2 h; H$_2$C=C(Me)CHO, −78 °C, 1 h.

was observed for the reaction (*syn*:*anti* $\geq$ 99:1), consistent with selective formation of the tin(II) (*Z*)-enolate **61**[68] and addition to the aldehyde *via* a chair transition state. Moreover, the required isomer **6** (*SS*) was formed with a selectivity (*SS*:*SA* = 93:7) superior to that previously achieved using the chiral boron triflate reagent (+)-(Ipc)$_2$BOTf.[10c] The tin-mediated aldol reaction has the additional advantage, compared to its boron analogue, that an oxidative workup is not required.

The sense of $\pi$-face diastereoselectivity obtained from the tin(II) enolate **61** may be rationalized by reaction occurring preferentially through the internally chelated chair transition state **62** (*re*-face attack), in which the small (*i.e.*, hydrogen) substituent on the $\alpha$ stereogenic center of the enolate is orientated toward the center, rather than the more sterically congested transition state **63** (*si*-face attack), in which the methyl substituent is pointing in toward the aldehyde.



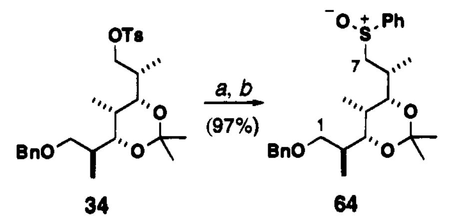
**62** *re*-face attack FAVOURED

**63** *si*-face attack

The substrate-controlled, Sn(OTf)$_2$-mediated, aldol reaction of ketone (*S*)-**8** has been successfully extended to include a range of both prochiral and chiral $\alpha$-branched aldehydes.[67] The latter substrates, in particular, gave poor yields and stereoselectivities in our previous (Ipc)$_2$BOTf-mediated, reagent-controlled procedure.[10e]

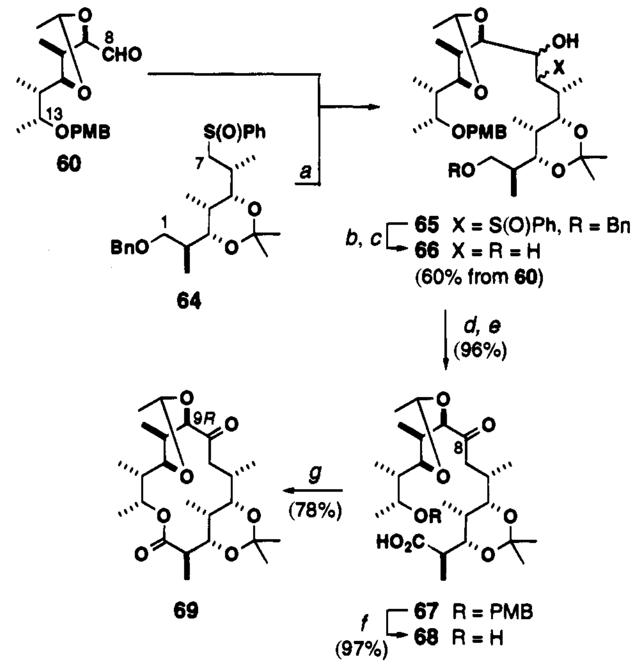
**Synthesis of a Modified C$_1$−C$_7$ Fragment.** In order to achieve a fragment coupling reaction of minimum complexity, and hence maximum reliability, we decided that the C$_1$ hydroxyl in the C$_1$−C$_7$ fragment **33** should remain protected as its benzyl ether. This option required selective cleavage of the C$_1$ benzyl ether *after coupling*, which was now possible (*vide infra*) because of the choice of a *p*-methoxybenzyl ether, rather than a (benzyloxy)methyl ether, as the protecting group for the C$_{13}$ hydroxyl of the (9*R*)-C$_8$−C$_{13}$ fragment **60**. Accordingly, the tosylate **34**, derived from **6** (*SS*) as previously, was subjected directly to the thiophenolate displacement reaction (Scheme 15). The resulting sulfide was then oxidized to provide the modified C$_1$−C$_7$ fragment **64** in 97% yield over the two steps from **34**, and in an overall yield of 54% and with 84% ds in six steps from the ethyl ketone (*S*)-**8**. The increased efficiency with which a C$_1$−C$_7$ fragment was now obtained was due principally to the development of the substrate-controlled aldol reaction for **6** (*SS*).

**Scheme 15**$^{a}$



$^{a}$ (a) PhSLi, THF, 80 °C, 3 h; (b) NaIO$_4$, MeOH/H$_2$O, 20 °C, 21 h.

**Scheme 16**$^{a}$



$^{a}$ (a) LiNEt$_2$ (1.7 equiv), THF, −20 °C, 15 min; **60**, −78 → −20 °C, 30 min; (b) W-2 Raney Ni, Et$_2$O, 20 °C, 3 h; (c) W-2 Raney Ni, H$_2$, EtOH, 20 °C, 18 h; (d) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, 1 h; Et$_3$N, −23 °C, 30 min; aqueous NH$_4$Cl; (e) NaClO$_2$, NaH$_2$PO$_4$, $^t$BuOH/H$_2$O, 20 °C, 30 min; (f) H$_2$, Pd/C, EtOH, 20 °C, 18 h; (g) 2,4,6-Cl$_3$(C$_6$H$_2$)COCl, Et$_3$N, THF, 20 °C, 2 h; add to DMAP, PhMe, 60 °C, 3 h.

**Fragment Coupling.** Optimized conditions for the coupling of the C$_1$−C$_7$ and C$_8$−C$_{13}$ fragments involved $\alpha$-lithiation of the sulfoxides **64**[69] with the less-hindered base lithium diethylamide (1.05 equiv), rather than LDA, in THF at −20 °C, followed by addition of aldehyde **60** (0.63 equiv) at −78 °C and subsequent warming to −20 °C (Scheme 16). Desulfoxidation of the resulting mixture of adducts **65** was accomplished, after chromatographic separation of the excess sulfoxides **64**, by using W-2 Raney nickel in diethyl ether. This was followed by selective[70] hydrogenolysis of the C$_1$ benzyl ether using W-2 Raney nickel in ethanol,[71] to give the two epimeric diols **66** in 60% yield over the three steps from aldehyde **60**. Swern oxidation[29] of **66** to the ketoaldehyde and immediate further oxidation with sodium chlorite provided the acid **67** in 96% overall yield. Hydrogenolysis of the C$_{13}$ *p*-methoxybenzyl ether then gave the seco-acid **68** in 97% yield in readiness for macrolactonization.

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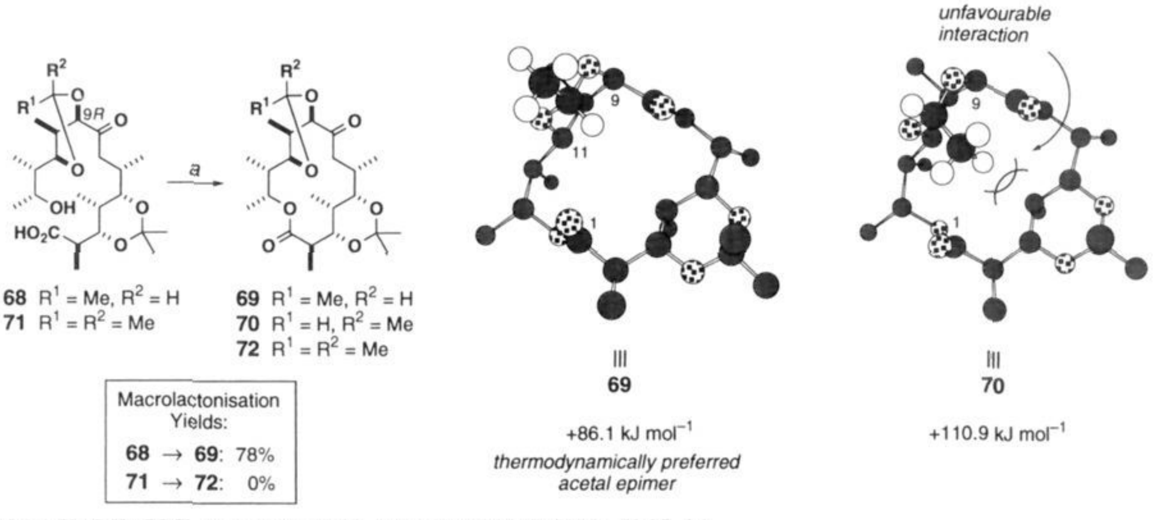
(68) For simplicity, the structure of the intermediate tin(II) enolate **61** is shown here as a monomer, assuming that there is one triflate still attached to the metal center. However, such tin(II) enolates may well be oligomeric, possibly with associated triethylamine.

(69) The use of the sulfoxides **33**, as in the previous route, led to reduced yields in the coupling reaction with aldehyde **60**. Employing the sulfoxides **64**, however, led to a much less capricious coupling reaction.

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

(71) The debenzylation reaction required ethanol as solvent, whereas the desulfoxidation reaction had to be performed in ether: use of ethanol as solvent in the desulfoxidation reaction led to cleavage of the C$_7$−C$_8$ bond.

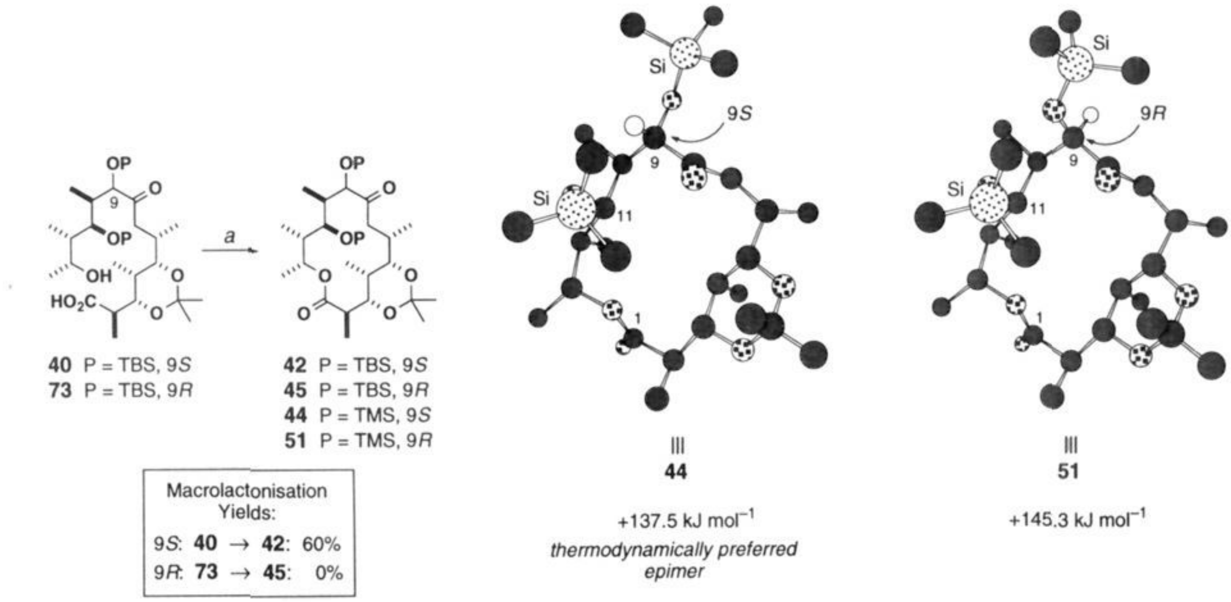
**Scheme 17**[a]



Macrolactonisation Yields:
**68** → **69**: 78%
**71** → **72**: 0%

[a] (a) 2,4,6-$Cl_3(C_6H_2)COCl$, $Et_3N$, THF, 20 °C, 2 h; add to DMAP, PhMe, 60 °C, 3 h.

**Scheme 18**[a]



Macrolactonisation Yields:
9*S*: **40** → **42**: 60%
9*R*: **73** → **45**: 0%

[a] (a) 2,4,6-$Cl_3(C_6H_2)COCl$, $Et_3N$, THF, 20 °C, 2 h; add to DMAP, PhMe, 80 °C, 3 h.

**Macrolactonization and Modeling Studies.** Cyclization of **68** to the macrolide **69** was achieved in good yield (78%) using Yamaguchi's procedure (2,4,6-$Cl_3(C_6H_2)COCl$, DMAP).[40] Crucial to the success of this reaction is the use of the ethylidene protecting group with the correct acetal stereochemistry. Molecular modeling[42] indicated that macrolide **69** was thermodynamically preferred by 24.8 kJ mol$^{-1}$ over its ethylidene acetal epimer **70**, in which there is an unfavorable steric interaction of the acetal methyl group and the macrocycle (Scheme 17). A similar interaction presumably accounts for the observed failure of the seco-acid **71** with acetonide protection at $C_9-C_{11}$ to cyclize (→ macrolide **72**) under the Yamaguchi conditions.[60,72]

The seco-acid **73**[72] with *tert*-butyldimethylsilyl ether protection at $C_9$ and $C_{11}$ also failed to cyclize under the Yamaguchi conditions (Scheme 18). This is in marked contrast to the behavior of its $C_9$ epimer, seco-acid **40**, which was successfully cyclized in 60% yield (*vide supra*).[73] Molecular modeling[42] of the corresponding macrolides **44** and **51** (wherein the TBS groups were replaced by TMS groups in order to simplify the computation) revealed that the 9*S* epimer **44** is thermodynamically preferred by 7.8 kJ mol$^{-1}$ over the 9*R* epimer **51**, in which the silyl groups at $C_9$ and $C_{11}$ are necessarily closer and as a consequence suffer the greatest steric interaction. Thus, it appears that a sterically demanding protecting group at $C_9$ and $C_{11}$ (*e.g.*, TBS) is advantageous in the seco-acid of 9*S* configuration, but undesirable in the seco-acid of 9*R* configuration.

**Completing a Synthesis of Oleandolide. Epoxidation of $C_8$ Alkene.** The elaboration of macrolide **69** to oleandolide requires stereoselective introduction of an exocyclic epoxide at $C_8$. Initially, we examined accomplishing such a transformation *via* the exocyclic alkene. Accordingly macrolide **74** was prepared, in 92% yield, by a straightforward Wittig methylena-

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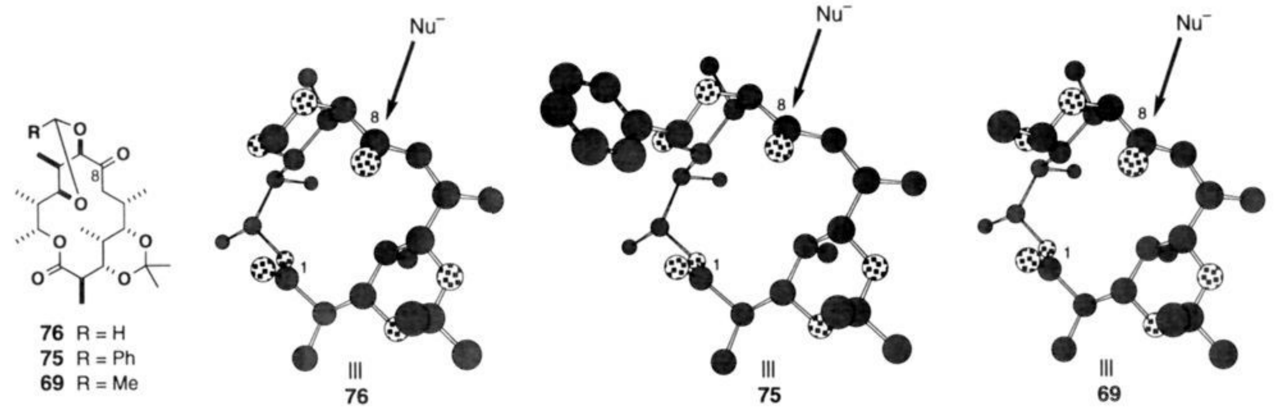
(72) The seco-acids **71** and **73** were each prepared by a route analagous to that used to synthesize **68**. For details see the supplementary material.

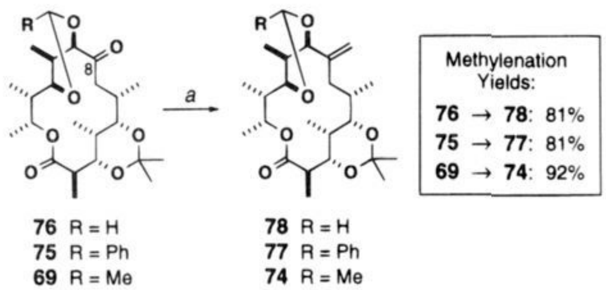
(73) A similar, albeit less dramatic, difference in macrolactonization yields for seco-acids epimeric at $C_9$ was noted by Masamune *et al.* in their synthesis of 6-deoxyerythronolide B. See: Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.



re-face of $C_8$ ketone exposed to attack

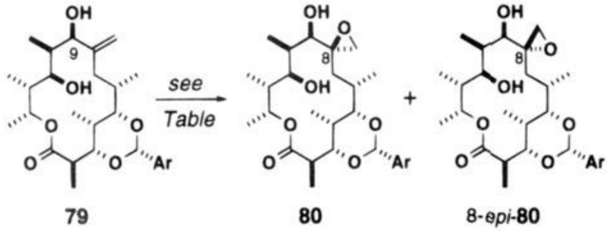
**Figure 1.**

**Scheme 19**[a]



[a] (a) $Ph_3MeP^+Br^-$, KHMDS, PhMe, 60−90 °C, 1−16 h.

**Table 1**

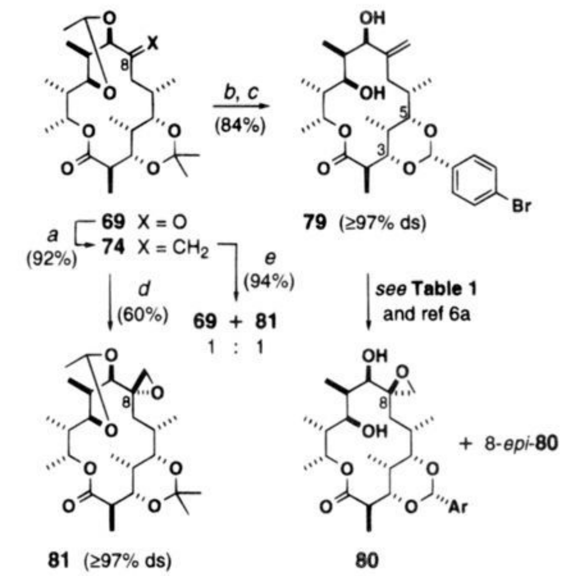


| reagent | solvent | **80**:8-*epi*-**80**[a] | yield[b] % |
|---|---|---|---|
| *m*-CPBA | $CCl_4$ | 50:50 | 82 |
| *m*-CPBA | $CH_2Cl_2$ | 50:50 | 73 |
| *m*-CPBA | PhMe | 64:36 | 80 |
| *m*-CPBA | $Et_2O$ | 33:66 | 65 |
| $CF_3CO_3H/NaHCO_3$ | $CH_2Cl_2$ | 5:95 | 50 |
| dimethyldioxirane | $Me_2CO$ | 0:100 | 70 |
| $PhCN/H_2O_2/KHCO_3$ | MeOH | 0:100 | 60 |

[a] Ratio determined by $^1$H NMR. [b] Isolated yield after chromatography.

tion of macrolide **69** using methyltriphenylphosphonium bromide and potassium hexamethyldisilazide in THF at 60 °C (Scheme 19). The $C_9$,$C_{11}$ benzylidene and $C_9$,$C_{11}$ methylene acetal-protected macrolides **75** and **76**[74] similarly underwent ready methylenation (→ **77** and **78**, respectively) under these reaction conditions. This is in marked contrast to the macrolides **42** and **45** which were inert under the same reaction conditions (*vide supra*). Molecular modeling[42] of the macrolides **69**, **75**, and **76** suggested that although the *si* face of the $C_8$ ketone was blocked by the macrocycle, the *re* face was readily accessible to attack by nucleophilic reagents (Figure 1). Thus, the employment of an acetal protecting group, rather than a *tert*-butyldimethylsilyl ether, at $C_9$ and $C_{11}$ not only permitted high yielding macrolactonization in the 9*R* series, but also enabled subsequent nucleophilic addition at $C_8$ of the macrocycle.

**Scheme 20**[a]



[a] (a) $Ph_3MeP^+Br^-$, KHMDS, PhMe, 60 °C, 1 h; (b) 2 M HCl(aq), THF, 50 °C, 2 h; (c) $p$-$Br(C_6H_4)CH(OMe)_2$, CSA, $CH_2Cl_2$, 20 °C, 45 min; (d) *m*-CPBA, $CH_2Cl_2$, 20 °C, 14 h; (e) $O_3$, $CH_2Cl_2$, −78 °C, 15 min; $Ph_3P$, −78 → +20 °C, 15 min.

Alkene **74** was converted, by means of initial acetal deprotection at $C_3$,$C_5$ and $C_9$,$C_{11}$ and subsequent selective reprotection as the $C_3$,$C_5$ *p*-bromobenzylidene acetal, to the known[6a] alkene **79** (84% yield over the two steps, Scheme 20). At this stage, since **79** had already been converted by Tatsuta *et al.* to oleandomycin,[6a] this completed a formal synthesis of the natural product. Stereoselective epoxidation of **79** using *m*-chloroperbenzoic acid (*m*-CPBA) in $CCl_4$, directed by the $C_9$ hydroxyl, was reported to provide exclusively the required exocyclic (8*R*)-epoxide **80**.[6a] Upon detailed examination of this reaction, however (Table 1), we identified the presence of the epimeric (8*S*)-epoxide 8-*epi*-**80**. In $CCl_4$, a 1:1 mixture of **80** and 8-*epi*-**80** was produced. Up to 64% diastereoselectivity in favor of **80** could be obtained, by performing the reaction in toluene; in ether, the selectivity of the reaction was turned over, with 8-*epi*-**80** now being obtained with modest (66%) diastereoselectivity. In light of our modeling studies (*vide supra*), the lack of stereoselectivity obtained on epoxidation of **79** is not surprising.

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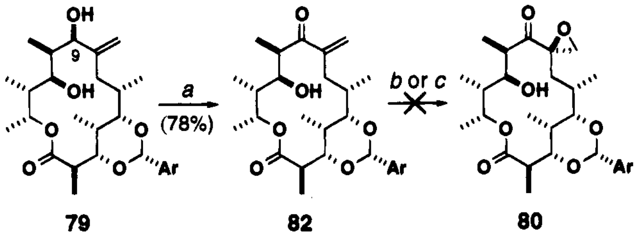
(74) **75** and **76** were prepared during studies to identify the optimum acetal protecting group for $C_9$ and $C_{11}$. For details see the supplementary material.

**Scheme 21**[a]



[a] (a) $MnO_2$, $CH_2Cl_2$, 20 °C, 18 h; (b) ${}^tBuOOH$, ${}^nBuLi$, THF, $-78 \rightarrow 0$ °C, 1 h; (c) ${}^tBuOOH$, KH, THF, $-78 \rightarrow 0$ °C, 1 h.

Alkene **79** should be conformationally very similar to the modeled ketone **69**, and so epoxide 8-*epi*-**80** is the epimer expected to be favored by macrocyclic stereocontrol (*re*-face attack), whereas **80** requires direction of the reagent onto the more hindered *si* face of the $C_8$ alkene. The use of a noncoordinating solvent (such as toluene) thus favors formation of the hydroxyl-directed product; employing a coordinating solvent (ether) favors formation of the product of macrocyclic stereocontrol. The use of other epoxidizing agents ($CF_3CO_3H$/$NaHCO_3$, dimethyldioxirane, or $PhCN/H_2O_2/KHCO_3$[75]) in place of *m*-CPBA led to near-exclusive formation of the undesired epimer 8-*epi*-**80**.

Further evidence for the participation of macrocyclic stereocontrol, in the sense predicted by the modeling studies, was provided by epoxidation of the $C_9$-protected macrolide **74**. In this case hydroxyl-directed epoxidation is not possible, and when using *m*-CPBA only **81**, the product of *re*-face attack, was isolated, in 60% yield (Scheme 20).[76] We were intrigued to discover at this point that ozonolysis of alkene **74** besides providing the expected ketone **69** also afforded an equal amount of the epoxide **81**, which presumably arose from an alternative breakdown of the initial molozonide through loss of bimolecular oxygen.

In an attempt to obtain the required epoxide stereochemistry with greater diastereoselectivity, the enone **82** was prepared by selective allylic oxidation of macrolide **79** using manganese(IV) oxide (Scheme 21). However, all attempts to epoxidize **82** using *tert*-butyl hydroperoxide under standard conditions proved unsuccessful, and this strategy was abandoned.

**Introduction of the Epoxide *via* the $C_8$ Ketone.** The molecular modeling studies had predicted that good levels of *re*-face selectivity were to be expected in additions to the $C_8$ ketone of macrolide **69**, since the *si* face of the ketone was blocked by the macrocycle. Attack of a sulfur ylide, therefore, should occur preferentially in the sense providing the (8*R*)-epoxide **83** required for oleandolide. In the event, reaction of **69** with dimethylsulfonium methylide[46] gave exclusively (single diastereoisomer by 400 MHz $^1H$ NMR) the desired epoxide **83** in 83% yield (Scheme 22).[77] Attempts to remove the acetonide and ethylidene protecting groups from **83** under acidic conditions proved difficult, and so the reactive epoxide was temporarily converted to the more robust iodohydrin **84** (87% yield),[78] a strategy which had been successfully employed in our previous degradative studies on oleandomycin.[7e] Attempted direct conversion of ketone **69** to the iodohydrin **84**, by iodomethylenation using diiodomethane and samarium(II) iodide,[79] only resulted in deoxygenation at $C_9$ and formation of **85** in 79% yield. Treatment of **84** with hydrochloric acid in THF gave the labile pentol, which was immediately protected as its $C_3$,$C_5$ *p*-bromobenzylidene derivative and worked up with sodium hydrogen carbonate to provide **80** in 72% yield. Selective oxidation at $C_9$ was best accomplished using pyridinium chlorochromate (PCC) on alumina,[80] which gave the ketone **86** in 78% yield (89% based on recovered **80**). Finally, hydrogenolysis of the *p*-bromobenzylidene acetal gave a 95% yield of oleandolide (**2**), $[\alpha]^{20}_D = -14.3°$ (*c* 1.05, $CHCl_3$) [*cf.* lit.[6a] $[\alpha]^{20}_D = -13.0°$ (*c* 1.0, $CHCl_3$)], obtained as a mixture of the keto- and 5,9-hemiacetal forms. This had physical and spectroscopic data identical with those of material derived from oleandomycin. The 400 MHz $^1H$ NMR spectra of **2** ($CDCl_3$, $CD_3OD$) matched exactly the spectra of oleandolide kindly provided by Professor Tatsuta. As an additional verification of structure, peracetylation provided the known triacetate **87**, $[\alpha]^{20}_D = +39.7°$ (*c* 0.61, $CHCl_3$) [*cf.* lit.[6a] $[\alpha]^{20}_D = +43.0°$ (*c* 1.0, $CHCl_3$)], which also had spectroscopic data in agreement with authentic spectra.

## Conclusions

In conclusion, a novel and expedient synthesis of oleandolide has been completed (8% overall yield, 20 steps longest linear sequence with 90% overall ds, 26 steps in total), which is summarized in Scheme 23. Since the two sugar units have been previously introduced onto oleandolide by the Tatsuta group,[6a] this work also constitutes a formal total synthesis of oleandomycin itself. Key features of the synthesis include short, highly stereocontrolled syntheses of the coupling fragments **60** and **64** from the same starting ketone (*S*)-**8**, and introduction of the required (8*R*)-epoxide using macrocyclic stereocontrol. In addition, further insight has been gained into the conformational requirements for successful macrolactonization of 13-carbon seco-acids, and the range of protecting groups which can be successfully utilized has been identified. Several new methods for acyclic stereocontrol were developed during the evolution of this work in response to problems encountered by the stereochemical complexity and high level of oxygenation of oleandomycin. Of particular value is the stereocontrolled aldol chemistry of (*S*)-1-(benzyloxy)-2-methylpentan-3-one (and its enantiomer),[10c,d,f–h] which should see general use in the concise synthesis of other polypropionate-derived natural products.

## Experimental Section

**General Procedures.** See supplementary material for details of instrumentation, purification of reagents and solvents, and chromatography. All nonaqueous reactions were performed under an atmosphere of argon using oven-dried apparatus and employing standard techniques for handling air-sensitive materials.

**Methyl (*S*)-3-(Benzyloxy)-2-methylpropanoate (10).** To a stirred solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (**9**) (7.76 mL, 70.0 mmol) in $CH_2Cl_2$ (250 mL) was added by cannula a solution of benzyl 2,2,2-trichloroacetimidate (14.3 mL, 77.0 mmol) in cyclohexane (500 mL). Triflic acid (2.48 mL, 28.0 mmol) was added dropwise, whereupon a white solid (trichloroacetamide) precipitated. After stirring at room temperature for 16 h, the precipitate was allowed to settle and the supernatant liquor decanted into a separating funnel. The white crystalline residue was washed with hexanes (2 × 50 mL), and the

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(75) (a) Payne, G. B.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 651. (b) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659.

(76) The stereochemistry of the epoxide in **81** was established by NOE difference NMR experiments. Thus, irradiation of the ethylidene methine resulted in an NOE signal enhancement (8.1%) for the epoxide hydrogens, which is consistent with *S* configuration at $C_8$. In addition, a transannular NOE (7.4%) was observed from the ethylidene methine to the hydrogen on $C_5$, which is consistent with a macrolide conformation similar to that predicted for ketone **69** by the molecular modeling studies (Figure 1).

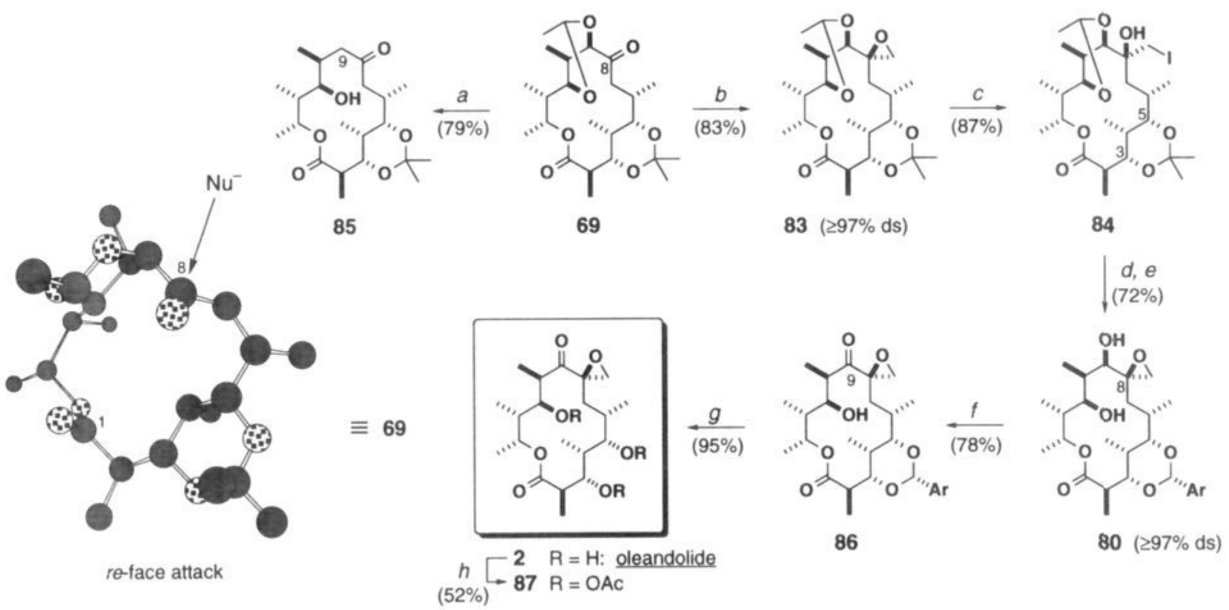
(77) Use of the less-reactive sulfur ylide dimethylsulfoxonium methylide (ref 46) gave lower yields of oxirane **83**.

(78) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021.

(79) Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243. (b) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3891.

(80) Cheng, Y.-S.; Liu, W.-L.; Chen, S. *Synthesis* **1980**, 223.

**Scheme 22**[a]



[a] (a) SmI$_2$, CH$_2$I$_2$, THF, 20 °C, 2 min; (b) Me$_3$S$^+$I$^-$, NaH, DMSO, THF, 0 → 20 °C, 5 h; (c) LiI, AcOH, THF, 20 °C, 18 h; (d) 2 M HCl, THF, 55 °C, 1 h; (e) *p*-Br(C$_6$H$_4$)CH(OMe)$_2$, CSA, CH$_2$Cl$_2$, 20 °C, 1 h; aqueous NaHCO$_3$, 20 °C, 10 min; (f) PCC/alumina, PhMe, 20 °C, 18 h; (g) H$_2$, 10% Pd/C, NaHCO$_3$, EtOAc, 30 min; (h) Ac$_2$O, py, DMAP, 20 °C, 40 h.

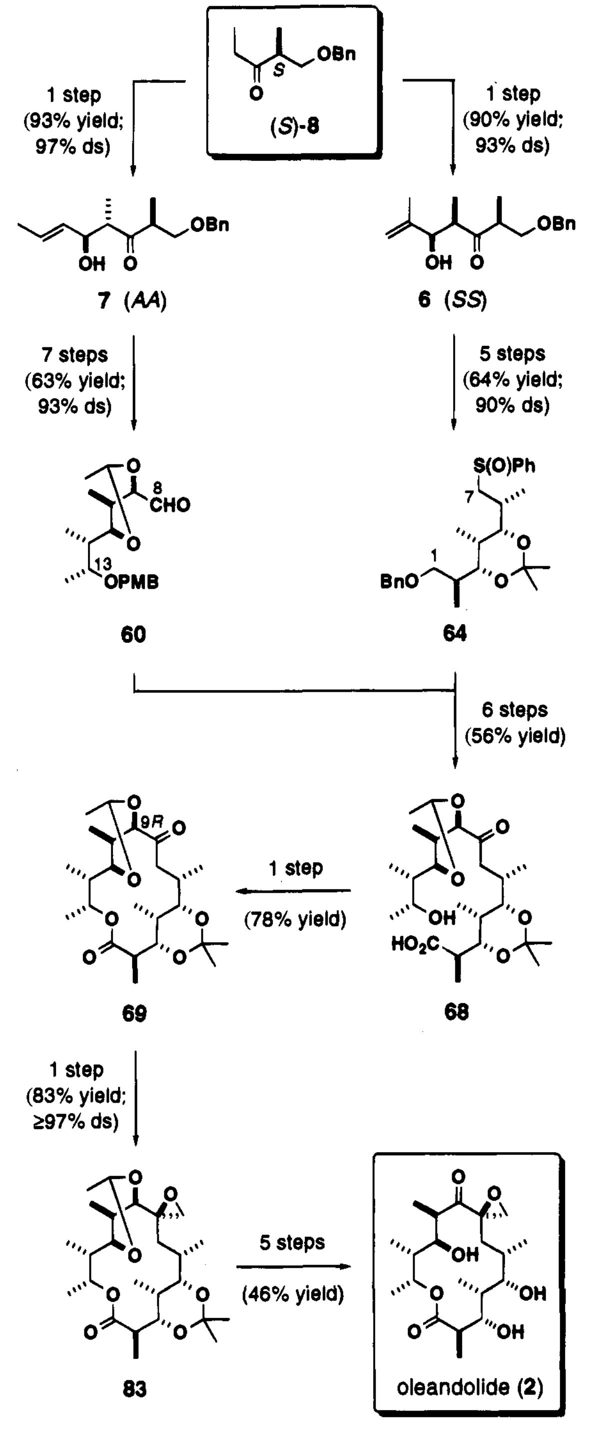
washings were combined with the supernatant liquor. The combined organic extracts were washed with sodium bicarbonate solution (100 mL; saturated, aqueous) and then brine (100 mL; saturated), before being dried (MgSO$_4$). The solvent was evaporated *in vacuo* and the residue, which still contained some trichloroacetamide, rerinsed with hexanes (2 × 150 mL) whereupon the remaining trichloroacetamide precipitated. The combined washings, which contained some dibenzyl ether, were then concentrated *in vacuo*, and the crude product was purified by flash chromatography (15% EtOAc/hexanes) to yield 11.83 g (81%) of **10** as a colorless oil: $[\alpha]^{20}_{D} = +12.1°$ (*c* 10.0, CHCl$_3$) [*cf.* lit.[16b] $[\alpha]^{20}_{D} = +11.6°$ (*c* 1.0, CHCl$_3$) for 95% ee material]; TLC (15% EtOAc/hexanes) $R_f = 0.30$; IR (thin film) 1730 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 7.34–7.25 (5H, m, Ar*H*), 4.52 (2H, s, C*H*$_2$Ph), 3.69 (3H, s, OC*H*$_3$), 3.65 (1H, dd, $J$ = 9.0, 7.3 Hz, one of C*H*$_2$OBn), 3.49 (1H, dd, $J$ = 9.0, 5.9 Hz, one of C*H*$_2$OBn), 2.79 (1H, dqd, $J$ = 7.3, 7.1, 5.9 Hz, C*H*CH$_3$), 1.18 (3H, d, $J$ = 7.1 Hz, CHC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 175.3, 138.1, 128.4, 127.6, 73.1, 71.9, 51.7, 40.2, 14.0; HRMS (CI, NH$_3$) calcd for C$_{12}$H$_{20}$NO$_3$ ([M + NH$_4$]$^+$) 226.1443, found 226.1450; *m/z* 226 (100, [M + NH$_4$]$^+$), 209 (11, [M + H]$^+$), 108 (4), 91 (3).

**(*S*)-3-(Benzyloxy)-*N*-methoxy-*N*,2-dimethylpropanamide (11).** To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (3.00 g, 30.8 mmol) in toluene (30 mL) at 0 °C was added *cautiously* by syringe trimethylaluminum (15.4 mL, 30.8 mmol; 2 M solution in toluene). During the addition the reaction flask was vented through a mineral oil bubbler to allow methane gas produced in the reaction to escape. After addition (30 min), the reaction mixture was allowed to warm to room temperature for 15 min, then recooled to 0 °C, and diluted with more toluene (40 mL), followed by addition by cannula of a solution of ester **10** (3.20 g, 15.4 mmol) in toluene (50 mL + 10 mL washings). The mixture was heated at 70–80 °C for 2 h and then cannulated into tartaric acid solution (100 mL; 1 M aqueous). This mixture was stirred vigorously for 1 h, the layers were separated, and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 70 mL). The combined organic extracts were washed with brine (100 mL; saturated), dried (MgSO$_4$), and concentrated *in vacuo*. The crude product was eluted through a short column of silica gel with diethyl ether and used in the next step without further purification: $[\alpha]^{20}_{D} = +5.0°$ (*c* 3.9, CHCl$_3$); TLC (10% diethyl ether/CH$_2$Cl$_2$) $R_f = 0.32$; IR (thin film) 1650 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 7.33–7.25 (5H, m, Ar*H*), 4.55 (1H, d, $J$ = 12.1 Hz, one of C*H*$_2$Ph), 4.46 (1H, d, $J$ = 12.1 Hz, one of C*H*$_2$Ph), 3.70 (1H, dd, $J$ = 8.7, 8.7 Hz, one of C*H*$_2$OBn), 3.68 (3H, s, OC*H*$_3$), 3.42 (1H, dd, $J$ = 8.7, 5.7 Hz, one of C*H*$_2$OBn), 3.23 (1H, buried m, C*H*CH$_3$), 3.20 (3H, s, NC*H*$_3$), 1.10 (3H, d, $J$ = 6.9 Hz, CHC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 175.9, 138.4, 128.3, 127.5, 127.5, 73.2, 72.6, 61.5, 35.6, 32.1, 14.2; HRMS (CI, NH$_3$) calcd for C$_{13}$H$_{20}$NO$_3$ ([M + H]$^+$) 238.1443, found 238.1448; *m/z* 238 (100, [M + H]$^+$), 208 (15), 148 (11), 118 (4), 108 (4), 91 (2).

**(*S*)-1-(Benzyloxy)-2-methylpentan-3-one ((*S*)-8).** To a stirred solution of amide **11** prepared above (semicrude; 3.65 g, 15.4 mmol) in THF (120 mL) at 0 °C was added dropwise a THF solution of ethylmagnesium bromide (15.4 mL, 30.8 mmol; 2 M). The reaction was complete within 1 h and was quenched by cannulation into a vigorously stirred solution of ammonium chloride (30 mL; saturated, aqueous). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (5% diethyl ether/CH$_2$Cl$_2$) provided 2.31 g (73% over two steps) of (*S*)-**8** as a colorless oil: $[\alpha]^{20}_{D} = +25.8°$ (*c* 8.2, CHCl$_3$); TLC (5% diethyl ether/CH$_2$Cl$_2$) $R_f = 0.55$; IR (thin film) 1705 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 7.37–7.23 (5H, m, Ar*H*), 4.50 (1H, d, $J$ = 12.3 Hz, one of C*H*$_2$Ph), 4.45 (1H, d, $J$ = 12.3 Hz, one of C*H*$_2$Ph), 3.62 (1H, dd, $J$ = 9.0, 7.9 Hz, one of C*H*$_2$OBn), 3.45 (1H, dd, $J$ = 9.0, 5.5 Hz, one of C*H*$_2$OBn), 2.88 (1H, dqd, $J$ = 7.9, 7.1, 5.5 Hz, C*H*CH$_3$), 2.51 (2H, q, $J$ = 7.3 Hz, C*H*$_2$Me), 1.07 (3H, d, $J$ = 7.1 Hz, CHC*H*$_3$), 1.04 (3H, t, $J$ = 7.3 Hz, CH$_2$C*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 213.8, 138.1, 128.4, 127.6, 127.5, 73.2, 72.4, 46.2, 35.3, 13.6, 7.5; HRMS (CI, NH$_3$) calcd for C$_{13}$H$_{22}$NO$_2$ ([M + NH$_4$]$^+$) 224.1651, found 224.1659; *m/z* 224 (100, [M + NH$_4$]$^+$), 207 (85, [M + H]$^+$), 129 (20), 91 (100), 57 (20). Anal. Calcd for C$_{13}$H$_{18}$O$_2$: C, 75.69; H, 8.79. Found C, 75.74; H, 8.89.

**(2*S*,4*S*,5*R*,6*E*)-1-(Benzyloxy)-5-hydroxy-2,4-dimethyl-6-octen-3-one (7 (*SA*)).** To a stirred solution of (−)-(Ipc)$_2$BOTf[10e] (1.09 mL, 0.65 mmol; ~0.6 M in hexane) in CH$_2$Cl$_2$ (2 mL) at room temperature was added dropwise diisopropylethylamine (228 μL, 1.31 mmol) followed by addition *via* cannula of a solution of ketone (*S*)-**8** (90 mg, 0.44 mmol) in CH$_2$Cl$_2$ (1 mL + 1 mL washings). Following 3 h of enolization at room temperature, the reaction mixture was cooled to 0 °C and freshly distilled crotonaldehyde (108 μL, 1.31 mmol) added dropwise. The reaction mixture was stirred at 0 °C for a further 1 h, before being left in the refrigerator (−4 °C) for 16 h. The reaction mixture was then partitioned between diethyl ether (3 × 20 mL) and pH 7 buffer solution (20 mL), and the combined organic extracts were concentrated *in vacuo*; the residue was resuspended in methanol (4 mL) and pH 7 buffer (1 mL) and cooled to 0 °C. Hydrogen peroxide solution (2 mL; 30% aqueous) was added dropwise and stirring

**Scheme 23**



continued at room temperature for 1−2 h. The mixture was then poured into distilled water (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were washed in turn with sodium bicarbonate solution (15 mL; 5% aqueous) and brine (10 mL; saturated), dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Flash chromatography (10% diethyl ether/$CH_2Cl_2$) allowed separation of the aldol products from isopinocampheol; HPLC purification (10% diethyl ether/$CH_2Cl_2$) provided 1.0 mg of the *anti−syn* aldol product **7** (*AS*), 9.4 mg of the *syn−syn* aldol product **7** (*SS*), and 78.1 mg of the desired *syn−anti* aldol product **7** (*SA*), contaminated by a very small amount (~2%) of the remaining *anti−anti* aldol product **7** (*AA*), as colorless oils in a total yield of 73%. Data for major diastereomer **7** (*SA*): $[\alpha]^{20}_D$ = +26.2° (*c* 5.0, $CHCl_3$); TLC (10% diethyl ether/$CH_2Cl_2$) $R_f = 0.39$; HPLC (10% diethyl ether/$CH_2Cl_2$) $R_t$ = 17.5 min; IR (thin film) 3450 (br), 1690 (s), 1600 (w) $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 7.36−7.23 (5H, m, Ar*H*), 5.68 (1H, dqd, $J$ = 15.3, 6.3, 1.1 Hz, $H_3CC\mathit{H}{=}CH$), 5.44 (1H, ddq, $J$ = 15.3, 6.2, 1.3 Hz, $H_3CCH{=}C\mathit{H}$), 4.48, 4.46 (2H, ABq, $J$ = 12.1 Hz, $C\mathit{H}_2Ph$), 4.33 (1H, ddd, $J$ = 6.2, 4.0, 1.1 Hz, $C\mathit{H}OH$), 3.64 (1H, dd, $J$ = 8.7, 8.7 Hz, one of $C\mathit{H}_2OBn$), 3.43 (1H, dd, $J$ = 8.7, 5.2 Hz, one of $C\mathit{H}_2OBn$), 3.08 (1H, dqd, $J$ = 8.7, 7.1, 5.2 Hz, $H_3CC\mathit{H}CH_2OBn$), 2.78 (1H, qd, $J$ = 7.1, 4.0 Hz, $H_3CC\mathit{H}CHOH$), 1.68 (3H, dd, $J$ = 6.3, 1.3 Hz, $\mathit{H}_3CCH{=}CH$), 1.12 (3H, d, $J$ = 7.1 Hz, $C\mathit{H}_3$), 1.04 (3H, d, $J$ = 7.1 Hz, $C\mathit{H}_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 217.5, 137.8, 130.7, 128.3, 127.8, 127.6, 127.5, 73.3, 72.7, 72.2, 50.6, 45.8, 17.6, 13.4, 10.2; HRMS (CI, $NH_3$) calcd for $C_{17}H_{28}NO_3$ ($[M + NH_4]^+$) 294.2069, found 294.2069; *m/z* 294 (11, $[M + NH_4]^+$), 259 (100), 224 (18), 207 (30), 108 (60), 91 (11). Data for minor diastereomers (2*S*,4*R*,5*S*,6*E*)-1-(benzyloxy)-5-hydroxy-2,4-dimethyl-6-octen-3-one (**7** (*SS*)) and (2*S*,4*R*,5*R*,6*E*)-1-(benzyloxy)-5-hydroxy-2,4-dimethyl-6-octen-3-one (**7** (*AS*)): see supplementary material.

**(2*S*,4*R*,5*R*)-1-(Benzyloxy)-5-hydroxy-2,4,6-trimethyl-6-hepten-3-one (6 (*SS*)).** To a stirred solution of (+)-$(Ipc)_2BOTf^{10e}$ (1.31 mL, 0.78 mmol; ~0.6 M in hexane) in $CH_2Cl_2$ (2 mL) at room temperature was added dropwise diisopropylethylamine (275 $\mu$L, 1.58 mmol) followed by addition *via* cannula of a solution of ketone (*S*)-**8** (109 mg, 0.53 mmol) in $CH_2Cl_2$ (1 mL + 1 mL washings). Following 3 h of enolization at room temperature, the reaction mixture was cooled to 0 °C and freshly distilled methacrolein (131 $\mu$L, 1.58 mmol) added dropwise. The reaction mixture was stirred at 0 °C for a further 1 h, before being left in the refrigerator (−4 °C) for 16 h. Oxidative workup ($H_2O_2$) as for **7** (*SA*) (*vide supra*), followed by HPLC purification (10% diethyl ether/$CH_2Cl_2$), provided 10.8 mg of the *syn−anti* aldol product **6** (*SA*) and 97.6 mg of the desired *syn−syn* aldol product **6** (*SS*) as colorless oils in a total yield of 74%. Data for major diastereomer **6** (*SS*): $[\alpha]^{20}_D$ = +43.6° (*c* 2.1, $CHCl_3$); TLC (10% diethyl ether/$CH_2Cl_2$) $R_f$ = 0.45; HPLC (10% diethyl ether/$CH_2Cl_2$) $R_t$ = 13.5 min; IR (thin film) 3480 (br), 1700 (s), 1650 (w) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.25 (5H, m, Ar*H*), 5.10 (1H, m, one of $C{=}C\mathit{H}_2$), 4.94 (1H, m, one of $C{=}C\mathit{H}_2$), 4.52 (1H, m, $C\mathit{H}OH$), 4.49 and 4.47 (2H, ABq, $J$ = 12.1 Hz, $C\mathit{H}_2Ph$), 3.63 (1H, dd, $J$ = 8.8, 8.8 Hz, one of $C\mathit{H}_2OBn$), 3.49 (1H, dd, $J$ = 8.8, 5.0 Hz, one of $C\mathit{H}_2OBn$), 3.22 (1H, d, $J$ = 2.7 Hz, $O\mathit{H}$), 3.19 (1H, dqd, $J$ = 8.8, 6.9, 5.0 Hz, $H_3CC\mathit{H}CH_2OBn$), 2.88 (1H, qd, $J$ = 7.2, 2.4 Hz, $H_3CC\mathit{H}CHOH$), 1.63 (3H, br s, $\mathit{H}_3CC{=}C$), 1.05 (3H, d, $J$ = 6.9 Hz, $\mathit{H}_3CCHCH_2OBn$), 1.01 (3H, d, $J$ = 7.2 Hz, $\mathit{H}_3CCHCHOH$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 218.1, 143.3, 137.5, 128.4, 127.8, 127.7, 111.4, 73.4, 73.1, 72.6, 48.4, 44.6, 19.6, 13.5, 8.2; HRMS (CI, $NH_3$) calcd for $C_{17}H_{28}NO_3$ ($[M + NH_4]^+$) 294.2069, found 294.2069; *m/z* 294 (30, $[M + NH_4]^+$), 277 (10, $[M + H]^+$), 259 (28), 224 (32), 207 (100), 108 (30), 91 (30). Data for minor diastereomer (2*S*,4*S*,5*S*)-1-(benzyloxy)-5-hydroxy-2,4,6-trimethyl-6-hepten-3-one (**6** (*SA*)): see supplementary material.

**(2*S*,3*S*,4*S*,5*R*,6*E*)-1-(Benzyloxy)-2,4-dimethyl-6-octene-3,5-diol (22).** To a two-necked flask equipped with a septum inlet and reflux condenser, and containing a stirrer bead and two or three crystals of pivalic acid (catalytic), was added by syringe at room temperature tributylborane (3.76 mL, 15.4 mmol). Methanol (0.50 mL, 12.3 mmol) was added dropwise, whereupon evolution of butane gas was observed; the contents of the flask became very warm and started to reflux. The reaction was over in minutes and allowed to cool. The solution of di-*n*-butylmethoxyborane (12.3 mmol in 4.26 mL; ~2.9 M) was cannulated into a fresh flask and stored in the freezer (−20 °C). It was quite stable at this temperature over a period of several weeks.

To a cooled (−78 °C) stirred solution of $\beta$-hydroxyketone **7** (*SA*) (1.11 g, 4.02 mmol) in THF (50 mL) and methanol (10 mL) was added di-*n*-butylmethoxyborane (1.8 mL, 5.2 mmol; ~2.9 M). After stirring at this temperature for 15 min, lithium borohydride solution (5.0 mL, 10.0 mmol; 2 M in THF) was added and stirring continued for a further 1 h. The reaction was quenched at −78 °C by addition of pH 7 buffer solution (15 mL) and methanol (15 mL), then hydrogen peroxide solution (4 mL; 30% aqueous) was added, and the reaction mixture was allowed to warm to room temperature and stirred for a further 1 h. The mixture was then heated under reflux for 15 min to destroy any remaining peroxide, before being partitioned between EtOAc (3 × 100 mL) and distilled water (100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (10% diethyl ether/$CH_2Cl_2$) provided 999 mg (89%) of the desired *syn*-1,3-diol **22** (single isomer by 250 MHz $^1H$ NMR) as a colorless oil: $[\alpha]^{20}_D$ = +49.9° (*c* 4.2, $CHCl_3$); TLC (10% diethyl ether/CH$_2$Cl$_2$) *R*$_f$ = 0.28; IR (thin film) 3400 (br), 1660 (w) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.40−7.27 (5H, m, Ar*H*), 5.70 (1H, dqd, *J* = 15.3, 6.3, 0.9 Hz, H$_3$CC*H*=CH), 5.51 (1H, ddq, *J* = 15.3, 6.0, 1.3 Hz, H$_3$CCH=C*H*), 4.52 (2H, s, C*H*$_2$Ph), 4.32 (1H, br d, *J* = 6.0 Hz, H$_3$CCH=CHC*H*OH), 3.76 (1H, dd, *J* = 9.2, 2.0 Hz, C*H*OH(CHCH$_3$)$_2$), 3.60 (1H, dd, *J* = 9.0, 4.2 Hz, one of C*H*$_2$OBn), 3.48 (1H, dd, *J* = 9.0, 8.9 Hz, one of C*H*$_2$OBn), 1.99 (1H, m, H$_3$CC*H*CH$_2$OBn), 1.69 (3H, br d, *J* = 6.3 Hz, *H*$_3$CCH=CH), 1.60 (1H, qdd, *J* = 7.0, 2.0, 1.5 Hz, H$_3$CC*H*(CHOH)$_2$), 0.92 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.75 (3H, d, *J* = 6.9 Hz, C*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 137.4, 132.6, 128.5, 127.9, 127.7, 126.0, 81.8, 77.1, 76.7, 73.6, 39.6, 35.9, 17.7, 13.0, 4.6; HRMS (CI, NH$_3$) calcd for $C_{17}H_{27}O_3$ ([M + H]$^+$) 279.1960, found 279.1953; *m*/*z* 279 (9, [M + H]$^+$), 261 (11), 243 (8), 207 (11), 196 (100), 179 (18), 108 (26), 99 (12), 91 (9).

**(2*E*,4*R*,5*S*,6*S*,7*S*)-8-(Benzyloxy)-4,6-bis(*tert*-butyldimethylsiloxy)-5,7-dimethyl-2-octene (24).** To a cooled (−78 °C) stirred solution of diol **22** (352 mg, 1.27 mmol) in CH$_2$Cl$_2$ (10 mL) was added 2,6-lutidine (1.18 mL, 10.1 mmol) followed by *tert*-butyldimethylsilyl triflate (1.16 mL, 5.06 mmol). After stirring for 45 min at this temperature, the reaction was quenched by addition of ammonium chloride solution (50 mL; saturated, aqueous). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with pH 7 buffer solution (2 × 25 mL), dried (MgSO$_4$), and concentrated *in vacuo*. Flash chromatography (5% diethyl ether/hexanes) gave 554 mg (86%) of the desired silyl ether **24** as a colorless oil: $[\alpha]^{20}_{D}$ = −10.7° (*c* 1.1, CHCl$_3$); TLC (5% diethyl ether/hexanes) *R*$_f$ = 0.48; IR (thin film) 1660 (w), 1250 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.33−7.25 (5H, m, Ar*H*), 5.48 (1H, dq, *J* = 15.4, 6.2 Hz, H$_3$CC*H*=CH), 5.33 (1H, ddq, *J* = 15.4, 7.2, 1.1 Hz, H$_3$CCH=C*H*), 4.47 and 4.46 (2H, ABq, *J* = 12.0 Hz, C*H*$_2$Ph), 3.91 (1H, dd, *J* = 7.2, 7.2 Hz, H$_3$CCH=CHC*H*O(TBS)), 3.68 (1H, dd, *J* = 4.0, 4.0 Hz, C*H*O(TBS)(CHCH$_3$)$_2$), 3.52 (1H, dd, *J* = 9.1, 5.1 Hz, one of C*H*$_2$OBn), 3.22 (1H, dd, *J* = 9.1, 7.9 Hz, one of C*H*$_2$OBn), 2.00 (1H, m, H$_3$CC*H*CH$_2$OBn), 1.63 (3H, dd, *J* = 6.2, 1.1 Hz, *H*$_3$CCH=CH), 1.63 (1H, buried m, H$_3$CC*H*(CHO(TBS))$_2$), 0.96 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.89 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 0.87 (9H, s, C(C*H*$_3$)$_3$), 0.86 (9H, s, C(C*H*$_3$)$_3$), 0.03 (3H, s, SiC*H*$_3$), 0.01 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), −0.03 (3H, s, SiC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 138.8, 134.1, 128.2, 127.4, 127.3, 126.6, 75.0, 73.5, 73.0, 72.9, 42.7, 39.2, 26.1, 25.9, 18.5, 18.2, 17.6, 14.7, 11.3, −3.0, −3.7, −3.8, −4.7; HRMS (CI, NH$_3$) calcd for $C_{29}H_{58}NO_3Si_2$ ([M + NH$_4$]$^+$) 524.3955, found 524.3955; *m*/*z* 524 (1, [M + NH$_4$]$^+$), 507 (1, [M + H]$^+$), 310 (5), 293 (100), 243 (28), 227 (56), 185 (43), 132 (46), 108 (48), 99 (50), 91 (52).

**(2*S*,3*S*,4*S*,5*R*,6*E*)-3,5-Bis(*tert*-butyldimethylsiloxy)-2,4-dimethyl-6-octen-1-ol.** To a stirred solution of 4,4′-di-*tert*-butylbiphenyl (4.88 g, 18.3 mmol) in THF (75 mL) at room temperature was added lithium metal (254 mg, 36.6 mmol) which had been washed in petroleum ether under argon. This mixture was stirred vigorously at room temperature for 5 min and then ultrasonicated at room temperature for 30 min during which time the dark green color of the radical anion rapidly developed. The air- and moisture-sensitive dark green solution (75 mL; ~0.24 M) was further ultrasonicated for 3 h at 0−5 °C before being cooled to −78 °C and used immediately.

To a cooled (−78 °C) stirred solution of alkene **24** (981 mg, 1.94 mmol) in THF (30 mL) was added dropwise the LiDBB radical anion solution in portions (2 mL at a time), with a few minutes stirring between each addition, until a green color persisted in the reaction mixture and TLC analysis indicated complete consumption of starting material. The green solution was then stirred for a further 30 min at −78 °C, before being quenched by careful addition of ammonium chloride solution (25 mL; saturated, aqueous), and the now colorless mixture extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (gradient elution: 0−20% EtOAc/hexanes) gave recovered 4,4′-di-*tert*-butylbiphenyl crystals (which could be reused in subsequent reactions) and 806 mg (quantitative) of the desired alcohol as a colorless oil: $[\alpha]^{20}_{D}$ = +3.5° (*c* 8.5, CHCl$_3$); TLC (20% EtOAc/hexanes) *R*$_f$ = 0.37; IR (thin film) 3400 (br), 1670 (w), 1260 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.53 (1H, dq, *J* = 15.4, 6.2 Hz, H$_3$CC*H*C=CH), 5.38 (1H, ddq, *J* = 15.4, 7.1, 1.1 Hz, H$_3$CCH=C*H*), 3.98 (1H, dd, *J* = 7.1, 5.3 Hz, H$_3$CCH=CHC*H*O(TBS)), 3.81 (1H, dd, *J* = 4.1, 4.1 Hz, C*H*O(TBS)(CHCH$_3$)$_2$), 3.67 (1H, dd, *J* = 11.3, 4.7 Hz, one of C*H*$_2$OH), 3.51 (1H, dd, *J* = 11.3, 6.6 Hz, one of C*H*$_2$OH), 2.60 (1H, br s, O*H*), 1.89 (1H, m, H$_3$CC*H*CH$_2$OH), 1.77 (1H, qdd, *J* = 7.0, 5.3, 4.1 Hz, H$_3$CC*H*(CHO(TBS))$_2$), 1.68 (3H, br d, *J* = 6.2 Hz, *H*$_3$CCH=CH), 0.93 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.90 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.89 (9H, s, C(C*H*$_3$)$_3$), 0.87 (9H, s, C(C*H*$_3$)$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$), 0.02 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 132.8, 126.9, 76.5, 74.6, 65.3, 42.6, 39.9, 26.1, 26.0, 18.3, 18.3, 17.7, 13.9, 12.1, −3.7, −4.0, −4.0, −4.7; HRMS (CI, NH$_3$) calcd for $C_{22}H_{49}O_3Si_2$ ([M + H]$^+$) 417.3220, found 417.3214; *m*/*z* 417 (27, [M + H]$^+$), 302 (100), 285 (50), 220 (58), 203 (21), 185 (33), 153 (52), 132 (23), 88 (18).

**(2*R*,3*R*,4*S*,5*R*,6*E*)-3,5-Bis(*tert*-butyldimethylsiloxy)-2,4-dimethyl-6-octenal (25).** To a cooled (−78 °C) stirred solution of freshly distilled oxalyl chloride (123 $\mu$L, 1.41 mmol) in CH$_2$Cl$_2$ (25 mL) was added dropwise DMSO (200 $\mu$L, 2.82 mmol), and the mixture was stirred for 10 min to ensure complete formation of the chlorosulfur complex. The alcohol prepared above (235 mg, 0.56 mmol) was added in solution in CH$_2$Cl$_2$ (10 mL + 5 mL washings) *via* cannula and the reaction mixture stirred for a further 1 h at −78 °C. Triethylamine (589 $\mu$L, 4.23 mmol) was added at −78 °C and the reaction mixture allowed to warm *to −23 °C only* until no alcohol was evident by TLC (*ca.* 30 min). The reaction was immediately quenched by addition of ammonium chloride solution (50 mL; saturated, aqueous), the layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. The crude aldehyde **25** was eluted through a short column of silica gel with diethyl ether, and the oil remaining after evaporation *in vacuo* was taken on to the next reaction within 24 h, without further purification: $[\alpha]^{20}_{D}$ = −27.5° (*c* 4.4, CHCl$_3$); TLC (6% diethyl ether/hexanes) *R*$_f$ = 0.34; IR (thin film) 2720 (w), 2700 (w), 1730 (s), 1670 (w), 1250 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 9.76 (1H, d, *J* = 2.0 Hz, C*H*O), 5.55 (1H, dq, *J* = 15.4, 6.3 Hz, H$_3$CC*H*=CH), 5.39 (1H, ddq, *J* = 15.4, 6.9, 1.2 Hz, H$_3$CCH=C*H*), 4.02 (1H, dd, *J* = 6.9, 6.2 Hz, H$_3$CCH=CHC*H*O(TBS)), 3.95 (1H, dd, *J* = 4.6, 4.6 Hz, C*H*O(TBS)(CHCH$_3$)$_2$), 2.68 (1H, qdd, *J* = 7.0, 4.6, 2.0 Hz, H$_3$CC*H*CHO), 1.72 (1H, buried m, H$_3$CC*H*(CHO(TBS)$_2$), 1.69 (3H, dd, *J* = 6.3, 1.2 Hz, *H*$_3$CCH=CH), 1.05 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.94 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 0.86 (9H, s, C(C*H*$_3$)$_3$), 0.86 (9H, s, C(C*H*$_3$)$_3$), 0.06 (3H, s, SiC*H*$_3$), 0.03 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), −0.02 (3H, s, SiC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 205.0, 133.1, 127.2, 75.2, 74.0, 51.5, 44.3, 26.0, 25.9, 18.4, 18.2, 17.7, 11.5, 11.4, −3.8, −3.8, −4.0, −4.8; HRMS (CI, NH$_3$) calcd for $C_{16}H_{34}NO_2Si$ ([M + NH$_4$ − (TBS)OH]$^+$) 300.2359, found 300.2353; *m*/*z* 300 (1, [M + NH$_4$ − (TBS)OH]$^+$), 283 (26), 225 (25), 201 (86), 185 (100), 151 (20), 143 (40), 132 (30), 86 (14).

**(2*R*,3*S*,4*S*,5*S*,6*R*,7*E*)-4,6-Bis(*tert*-butyldimethylsiloxy)-3,5-dimethyl-7-nonen-2-ol (26).** To a cooled (−100 °C) stirred solution of aldehyde **25** prepared above (semicrude; theoretically 0.56 mmol) in THF (15 mL) was added dropwise by syringe a THF solution of methylmagnesium chloride (1.3 mL, 2.26 mmol; 1.74 M). The reaction mixture was stirred for 40 min, then quenched by dropwise addition of ammonium chloride solution (10 mL; saturated, aqueous), and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. HPLC purification (15% EtOAc/hexanes) gave 25 mg of the 13*S* product epimer 13-*epi*-**26** and 177 mg of the desired 13*R* product epimer **26** as colorless oils in a total yield of 83% over two steps. Data for major diastereomer **26**: $[\alpha]^{20}_{D}$ = +5.3° (*c* 3.6, CHCl$_3$); TLC (15% EtOAc/hexanes) *R*$_f$ = 0.43; HPLC (15% EtOAc/hexanes) *R*$_t$ = 10.5 min; IR (thin film) 3500 (br), 1670 (w), 1260 (s) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.51 (1H, dq, *J* = 15.5, 6.0 Hz, H$_3$CC*H*C=CH), 5.38 (1H, ddq, *J* = 15.5, 6.8, 1.5 Hz, H$_3$CCH=C*H*), 4.27 (1H, qd, *J* = 6.4, 1.8 Hz, H$_3$CC*H*OH), 3.96 (1H, dd, *J* = 6.8, 5.0 Hz, H$_3$CCH=CHC*H*O(TBS)), 3.72 (1H, dd, *J* = 6.7, 2.0 Hz, C*H*O(TBS)(CHCH$_3$)$_2$), 3.50 (1H, s, O*H*), 1.84 (1H, qdd, *J* = 7.1, 6.7, 5.0 Hz, H$_3$CC*H*(CHO(TBS))$_2$), 1.68 (3H, br d, *J* = 6.0 Hz, *H*$_3$CCH=CH), 1.59 (1H, qdd, *J* = 7.1, 2.0, 1.8 Hz, H$_3$CC*H*CHOH), 1.11 (3H, d, *J* = 6.4 Hz, *H*$_3$CCHOH), 0.99 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 0.95 (3H, d, *J* = 7.1 Hz, C*H*$_3$), 0.90 (9H, s, C(C*H*$_3$)$_3$), 0.86 (9H, s, C(C*H*$_3$)$_3$), 0.09 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), −0.01 (3H, s, SiC*H*$_3$), −0.03 (3H, s, SiC*H*$_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 133.2, 126.6, 79.3, 75.8, 66.6, 43.7, 41.2, 26.2, 25.9, 20.9, 18.4, 18.2, 17.6, 12.1, 11.4, −3.5, −3.6, −3.8, −4.9; HRMS (CI, $NH_3$) calcd for $C_{23}H_{51}O_3Si_2$ ([M + H]$^+$) 431.3377, found 431.3375; *m/z* 431 (22, [M + H]$^+$), 299 (72), 234 (25), 199 (25), 185 (100), 167 (55). Data for minor diastereomer (2*S*,3*S*,4*S*,5*S*,6*R*,7*E*)-4,6-bis(*tert*-butyldimethylsiloxy)-3,5-dimethyl-7-nonen-2-ol (13-*epi*-**26**): see supplementary material.

**(2*E*,4*R*,5*S*,6*S*,7*S*,8*R*)-8-[(Benzyloxy)methoxy]-4,6-bis(*tert*-butyldimethylsiloxy)-5,7-dimethyl-2-nonene.** To a stirred solution of alcohol **26** (384 mg, 0.89 mmol) in $CH_2Cl_2$ (10 mL) at room temperature were added diisopropylethylamine (1.70 mL, 9.80 mmol) and (benzyloxy)methoxy chloride (1.24 mL, 8.90 mmol), and the reaction mixture was left stirring for 48 h. It was then partitioned between hydrochloric acid solution (20 mL; 1 M aqueous) and diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5% EtOAc/hexanes) afforded 454 mg (92%) of the desired (benzyloxy)methyl ether as a colorless oil: $[\alpha]^{20}_D = -4.5°$ (*c* 4.4, $CHCl_3$); TLC (5% EtOAc/hexanes) $R_f = 0.31$; IR (thin film) 1670 (w), 1260 (s) cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 7.35−7.29 (5H, m, Ar*H*), 5.53 (1H, dq, *J* = 15.4, 6.3 Hz, $H_3CCH{=}CH$), 5.33 (1H, ddq, *J* = 15.4, 8.0, 1.3 Hz, $H_3CCH{=}CH$), 4.82 (1H, d, *J* = 7.0 Hz, one of $OCH_2OBn$), 4.72 (1H, d, *J* = 7.0 Hz, one of $OCH_2OBn$), 4.62 and 4.62 (2H, ABq, *J* = 12.1 Hz, $CH_2Ph$), 3.86−3.77 (2H, m, 2 × *CH*O(TBS)), 3.58 (1H, dq, *J* = 7.3, 6.2 Hz, $H_3CCHO$(BOM)), 1.67 (3H, dd, *J* = 6.3, 1.3 Hz, $H_3CCH{=}CH$), 1.62 (1H, m, $CHCH_3$), 1.59 (1H, m, $CHCH_3$), 1.21 (3H, d, *J* = 6.2 Hz, $H_3CCHO$(BOM)), 1.01 (3H, d, *J* = 7.0 Hz, $CH_3$), 0.93 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.90 (9H, s, $C(CH_3)_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.05 (6H, s, 2 × $SiCH_3$), 0.02 (3H, s, $SiCH_3$), −0.02 (3H, s, $SiCH_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 138.1, 134.2, 128.4, 127.8, 127.6, 127.1, 93.5, 77.0, 75.5, 71.4, 69.4, 47.0, 41.8, 26.0, 26.0, 19.4, 18.4, 18.3, 17.6, 11.7, 11.6, −3.7, −3.9, −4.2, −4.6; HRMS (CI, $NH_3$) calcd for $C_{31}H_{59}O_4Si_2$ ([M + H]$^+$) 551.3952, found 551.3946; *m/z* 551 (32, [M + H]$^+$), 419 (94), 354 (64), 299 (38), 185 (100), 132 (71), 108 (37).

**(2*S*,3*R*,4*S*,5*S*,6*R*)-6-[(Benzyloxy)methoxy]-2,4-bis(*tert*-butyldimethylsiloxy)-3,5-dimethylheptanal (27).** Ozone was bubbled through a cooled (−78 °C) stirred solution of the alkene prepared above (60 mg, 0.11 mmol) in diethyl ether (1.5 mL) and $CH_2Cl_2$ (1.5 mL) until no starting material was evident by TLC (*ca.* 15 min). Dimethyl sulfide (0.2 mL, large excess) was then added and the solution allowed to warm to room temperature. After stirring for a further 15 min, the solution was concentrated *in vacuo*; flash chromatography (20% EtOAc/hexanes) provided 58 mg (quantitative) of the desired aldehyde **27** as a colorless oil: $[\alpha]^{20}_D = -1.9°$ (*c* 9.0, $CHCl_3$); TLC (20% EtOAc/hexanes) $R_f = 0.46$; IR (thin film) 1740 (s), 1260 (s) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.51 (1H, d, *J* = 2.9 Hz, *CH*O), 7.36−7.30 (5H, m, Ar*H*), 4.83 (1H, d, *J* = 7.0 Hz, one of $OCH_2OBn$), 4.74 (1H, d, *J* = 7.0 Hz, one of $OCH_2OBn$), 4.64 and 4.62 (2H, ABq, *J* = 11.8 Hz, $CH_2Ph$), 3.95 (1H, dd, *J* = 5.0, 2.2 Hz, *CH*O(TBS)$(CHCH_3)_2$), 3.83 (1H, dd, *J* = 7.3, 2.9 Hz, *CH*O(TBS)CHO), 3.63 (1H, dq, *J* = 6.3, 6.3 Hz, $H_3CCHO$(BOM)), 2.04 (1H, dqd, *J* = 7.3, 6.6, 2.2 Hz, $H_3CCH(CHO(TBS))_2$), 1.77 (1H, qdd, *J* = 6.4, 6.3, 5.0 Hz, $H_3CCHCHO$(BOM)), 1.24 (3H, d, *J* = 6.3 Hz, $H_3CCHO$(BOM)), 1.03 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.02 (3H, d, *J* = 6.4 Hz, $CH_3$), 0.92 (9H, s, $C(CH_3)_3$), 0.91 (9H, s, $C(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 202.8, 137.9, 128.4, 127.8, 127.6, 93.6, 79.6, 75.5, 70.6, 69.6, 45.5, 39.2, 26.1, 25.8, 19.3, 18.4, 18.2, 11.8, 10.8, −3.6, −4.2, −4.5, −4.9; HRMS (CI, $NH_3$) calcd for $C_{29}H_{58}NO_5Si_2$ ([M + $NH_4$]$^+$) 556.3854, found 556.3854; *m/z* 556 (1, [M + $NH_4$]$^+$), 431 (18), 401 (20), 299 (40), 271 (42), 257 (43), 137 (92), 108 (100), 91 (81).

**(2*S*,3*S*,4*R*,5*R*,6*S*)-7-(Benzyloxy)-2,4,6-trimethyl-1,3,5-heptanetriol (28).** (+)-$(Ipc)_2BH$ (435 mg, 1.52 mmol) was placed in a tared flask under nitrogen by means of a glovebag and weighed accurately. The flask was then flushed with argon, diethyl ether (4 mL) added, and the resulting suspension cooled to 0 °C followed by addition *via* cannula of a solution of $\beta$-hydroxyketone **6** (*SS*) (134 mg, 0.45 mmol) in diethyl ether (2 mL + 1 mL washings). The effervescing reaction mixture was allowed to warm to room temperature and stirred for 2 h, before being recooled to 0 °C, *m*-CPBA (524 mg, 3.04 mmol; ∼99% purity[81]) added in small portions, and stirring continued for a further 1 h at room temperature. This was followed by addition of dimethyl sulfide (1 mL, excess) to destroy any remaining peracid and subsequent stirring for 30 min. The reaction mixture was then poured into sodium hydroxide solution (10 mL; 10% aqueous) and the aqueous phase saturated with sodium chloride and extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*; flash chromatography (8% isopropyl alcohol/$CH_2Cl_2$) provided 90.1 mg of the desired triol **28**, 5.1 mg of the minor isomer 6-*epi*-**28** and 4.9 mg of the minor isomer 3-*epi*-**28**, in a total yield of 69%. Data for major diastereomer **28**: needles; mp 67−69 °C (from hexane); $[\alpha]^{20}_D = +9.3°$ (*c* 2.3, $CHCl_3$); TLC (8% isopropyl alcohol/$CH_2Cl_2$) $R_f = 0.21$; IR (thin film) 3600 (br), 3430 (br) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.26 (5H, m, Ar*H*), 4.50 and 4.48 (2H, ABq, *J* = 12.0 Hz, $CH_2Ph$), 3.80 (1H, dd, *J* = 6.5, 3.1 Hz, *CH*OH), 3.70 (1H, dd, *J* = 9.4, 1.8 Hz, *CH*OH), 3.70 (1H, dd, *J* = 10.7, 3.9 Hz, one of $CH_2OH$), 3.65 (1H, dd, *J* = 10.7, 8.3 Hz, one of $CH_2OH$), 3.46 (1H, dd, *J* = 9.2, 4.7 Hz, one of $CH_2OBn$), 3.43 (1H, dd, *J* = 9.2, 5.0 Hz, one of $CH_2OBn$), 1.98 (1H, qddd, *J* = 6.9, 6.5, 5.0, 4.7 Hz, $H_3CCHCH_2OBn$), 1.88 (1H, ddqd, *J* = 9.4, 8.3, 6.9, 3.9 Hz, $H_3CCHCH_2OH$), 1.80 (1H, qdd, *J* = 7.0, 3.1, 1.8 Hz, $H_3CCH(CHOH)_2$), 1.07 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.96 (3H, d, *J* = 7.0 Hz, $CH_3$), 0.72 (3H, d, *J* = 6.9 Hz, $CH_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 138.1, 128.4, 127.6, 127.5, 82.6, 79.4, 74.1, 73.3, 69.1, 37.2, 36.8, 36.3, 13.4, 13.2, 5.5; HRMS (CI, $NH_3$) calcd for $C_{17}H_{29}O_4$ ([M + H]$^+$) 297.2066, found 297.2071; *m/z* 297 (100, [M + H]$^+$), 279 (4), 261 (6), 207 (9), 108 (7), 91 (5). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.64; H, 9.55. Data for minor diastereomers (2*R*,3*S*,4*R*,5*R*,6*S*)-7-(benzyloxy)-2,4,6-trimethyl-1,3,5-heptanetriol (6-*epi*-**28**) and (2*S*,3*S*,4*R*,5*S*,6*S*)-7-(benzyloxy)-2,4,6-trimethyl-1,3,5-heptanetriol (3-*epi*-**28**): see supplementary material.

Use of (+)-$(Ipc)_2BH$ (2.07g, 7.24 mmol) and **6** (*SS*) (400 mg, 1.45 mmol) gave 319 mg (76%) of the desired triol **28**. Use of (−)-$(Ipc)_2BH$ (428 mg, 1.50 mmol) and **6** (*SS*) (135 mg, 0.49 mmol) gave 58.6 mg of the desired triol **28**, 24.2 mg of the minor isomer 6-*epi*-**28**, and 10.2 mg of the minor isomer 3-*epi*-**28**, in a total yield of 64%.

**(2*S*,3*S*,4*S*,5*R*,6*S*)-7-(Benzyloxy)-3,5-dihydroxy-2,4,6-trimethylheptyl *p*-Toluenesulfonate.** To a stirred solution of triol **28** (360 mg, 1.21 mmol) in $CH_2Cl_2$ (10 mL) at room temperature were added triethylamine (0.85 mL, 6.10 mmol) and a few crystals of DMAP (catalytic). A solution of *p*-toluenesulfonyl chloride (280 mg, 1.45 mmol) in $CH_2Cl_2$ (5 mL) was added *via* cannula and the reaction mixture stirred for 1.5 h. The solvent was then removed *in vacuo* and the mixture purified by flash chromatography (20% diethyl ether/$CH_2Cl_2$), yielding 518 mg (95%) of the desired tosylate as a colorless oil: $[\alpha]^{20}_D = -4.3°$ (*c* 9.2, diethyl ether); TLC (20% diethyl ether/$CH_2Cl_2$) $R_f = 0.25$; IR (thin film) 3440 (br), 1590 (m), 1490 (m) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (2H, d, *J* = 8.2 Hz, Ar*H* $\alpha$ to $CSO_2$), 7.36−7.26 (7H, m, Ar*H*), 4.48 and 4.47 (2H, ABq, *J* = 12.4 Hz, $CH_2Ph$), 4.19 (1H, dd, *J* = 9.5, 5.3 Hz, one of $CH_2OTs$), 4.09 (1H, dd, *J* = 9.5, 3.2 Hz, one of $CH_2OTs$), 3.75 (1H, ddd, *J* = 6.6, 3.4, 3.4 Hz, *CH*OH), 3.56 (1H, ddd, *J* = 9.8, 2.7, 2.7 Hz, *CH*OH), 3.45 (1H, dd, *J* = 9.3, 4.8 Hz, one of $CH_2OBn$), 3.41 (1H, dd, *J* = 9.3, 5.2 Hz, one of $CH_2OBn$), 3.23 (1H, d, *J* = 2.7 Hz, O*H*), 2.90 (1H, d, *J* = 3.4 Hz, O*H*), 2.44 (3H, s, $ArCH_3$), 1.94 (1H, m, $CHCH_3$), 1.85 (1H, m, $CHCH_3$), 1.79 (1H, m, $CHCH_3$), 1.04 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.88 (3H, d, *J* = 7.1 Hz, $CH_3$), 0.86 (3H, d, *J* = 7.1 Hz, $CH_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 144.7, 138.0, 132.9, 129.8, 128.4, 127.9, 127.7, 127.5, 79.2, 76.1, 74.2, 73.4, 73.2, 36.8, 36.5, 35.7, 21.6, 13.3, 13.1, 5.3; HRMS (CI, $NH_3$) calcd for $C_{24}H_{38}NO_6S$ ([M + $NH_4$]$^+$) 468.2420, found 468.2424; *m/z* 468 (100, [M + $NH_4$]$^+$), 451 (14, [M + H]$^+$), 386 (2), 296 (2).

**(2*S*,3*S*,4*S*,5*R*,6*S*)-7-(Benzyloxy)-3,5-(isopropylidenedioxy)-2,4,6-trimethylheptyl *p*-Toluenesulfonate (34).** To a solution of the tosylate prepared above (518 mg, 1.15 mmol) in $CH_2Cl_2$ (8 mL) and 2,2-dimethoxypropane (8 mL) at room temperature were added a few crystals of PPTS (catalytic). After 15 h of stirring, removal of the solvent *in vacuo* and subsequent flash chromatography (20% EtOAc/hexanes) provided 522 mg (92%) of the desired acetonide **34** as a colorless oil: $[\alpha]^{20}_D = +6.7°$ (*c* 3.8, diethyl ether); TLC (20% EtOAc/hexanes) $R_f = 0.29$; IR (thin film) 1590 (m), 1485 (m) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (2H, d, *J* = 8.2 Hz, Ar*H* $\alpha$ to $CSO_2$), 7.35−

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[81] *m*-CPBA (55−60% purity) was purchased from Lancaster Synthesis and purified by washing with pH 7.4 buffer: Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1988; p 123.

7.26 (7H, m, Ar$H$), 4.51 (1H, d, $J$ = 12.2 Hz, one of C$H_2$Ph), 4.43 (1H, d, $J$ = 12.2 Hz, one of C$H_2$Ph), 4.13 (1H, dd, $J$ = 8.9, 5.0 Hz, one of C$H_2$OTs), 4.04 (1H, dd, $J$ = 8.9, 2.8 Hz, one of C$H_2$OTs), 3.61 (1H, dd, $J$ = 6.2, 2.0 Hz, C$H$OC(CH$_3$)$_2$), 3.58 (1H, dd, $J$ = 6.8, 2.0 Hz, C$H$OC(CH$_3$)$_2$), 3.33 (2H, d, $J$ = 4.6 Hz, C$H_2$OBn), 2.44 (3H, s, ArC$H_3$), 1.89−1.79 (2H, m, 2 × C$H$CH$_3$), 1.49 (1H, qdd, $J$ = 6.7, 2.0, 2.0 Hz, H$_3$CC$H$(CHOC(CH$_3$)$_2$)$_2$), 1.29 (3H, s, $H_3$CCCH$_3$), 1.27 (3H, s, H$_3$CCC$H_3$), 1.03 (3H, d, $J$ = 6.6 Hz, C$H_3$), 0.84 (3H, d, $J$ = 6.9 Hz, C$H_3$), 0.77 (3H, d, $J$ = 6.7 Hz, C$H_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 144.5, 138.3, 133.0, 129.6, 128.2, 127.8, 127.5, 127.4, 98.9, 75.8, 73.1, 72.8, 72.3, 71.4, 34.9, 34.4, 30.4, 29.7, 21.5, 19.4, 14.6, 11.7, 4.7; HRMS (CI, NH$_3$) calcd for C$_{27}$H$_{39}$O$_6$S ([M + H]$^+$) 491.2467, found 491.2503; $m/z$ 491 (91, [M + H]$^+$), 450 (100), 415 (60), 342 (52), 279 (34), 261 (40), 196 (38), 171 (51), 108 (37).

**(2*S*,3*S*,4*S*,5*R*,6*S*)-7-Hydroxy-3,5-(isopropylidenedioxy)-2,4,6-trimethylheptyl *p*-Toluenesulfonate (35).** To a solution of *p*-toluenesulfonate **34** (234 mg, 0.48 mmol) in diisopropyl ether (8 mL) under an argon atmosphere was added palladium on activated charcoal (232 mg, 10% Pd content). The reaction mixture was stirred while hydrogen (from a hydrogen-filled double balloon) replaced the argon. After 2 h, the catalyst was removed by elution with diethyl ether through a short column of Celite. Flash chromatography (20% diethyl ether/CH$_2$Cl$_2$) afforded 176 mg (92%) of the desired alcohol **35** as colorless oil: $[\alpha]^{20}_{D}$ = −3.5° ($c$ 5.0, CHCl$_3$); TLC (15% diethyl ether/CH$_2$Cl$_2$) $R_f$ = 0.28; IR (thin film) 3400 (br) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.76 (2H, br d, $J$ = 8.3 Hz, Ar$H$ α to CSO$_2$), 7.32 (2H, br d, $J$ = 8.3 Hz, Ar$H$ α to CCH$_3$), 4.11 (1H, dd, $J$ = 8.9, 4.9 Hz, one of C$H_2$OTs), 4.01 (1H, dd, $J$ = 8.9, 2.8 Hz, one of C$H_2$OTs), 3.62−3.44 (4H, m, C$H_2$OH, 2 × C$H$OC(CH$_3$)$_2$), 2.43 (3H, s, ArC$H_3$), 1.89−1.72 (2H, m, 2 × C$H$CH$_3$), 1.54 (1H, qdd, $J$ = 6.8, 2.0, 2.0 Hz, H$_3$CC$H$(CHOC(CH$_3$)$_2$)$_2$), 1.27 (3H, s, $H_3$CCCH$_3$), 1.25 (3H, s, H$_3$CCC$H_3$), 0.99 (3H, d, $J$ = 6.7 Hz, C$H_3$), 0.85 (3H, d, $J$ = 6.9 Hz, C$H_3$), 0.79 (3H, d, $J$ = 6.8 Hz, C$H_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 144.6, 133.0, 129.7, 127.9, 99.0, 75.5, 72.8, 72.3, 64.1, 36.7, 34.5, 30.5, 29.7, 21.6, 19.4, 13.8, 11.8, 4.8; HRMS (CI, NH$_3$) calcd for C$_{20}$H$_{36}$NO$_6$S ([M + NH$_4$]$^+$) 418.2263, found 418.2267; $m/z$ 418 (100, [M + NH$_4$]$^+$), 401 (17, [M + H]$^+$), 360 (13), 342 (7), 264 (8), 247 (9), 52 (22).

**(2*S*,3*R*,4*S*,5*R*,6*R*)-3,5-(Isopropylidenedioxy)-2,4,6-trimethyl-7-(phenylthio)heptan-1-ol (36).** To a stirred solution of thiophenol (0.92 mL, 8.96 mmol) in THF (11.3 mL) at room temperature was added dropwise *n*-butyllithium solution (5.00 mL, 8.15 mmol; 1.63 M in hexanes) to give a colorless solution of lithium thiophenolate which was used immediately (total volume 16.3 mL; ~0.5 M).

To a stirred solution of the *p*-toluenesulfonate **35** (380 mg, 0.95 mmol) in THF (20 mL), at room temperature in a flask equipped with a reflux condenser, was added a THF solution of lithium thiophenolate (9.49 mL, 4.75 mmol; ~0.5 M). The colorless reaction mixture was heated under reflux for 3 h and then partitioned between sodium hydroxide solution (50 mL; 10% aqueous) and diethyl ether (3 × 50 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (20% diethyl ether/CH$_2$Cl$_2$) provided 320 mg (quantitative) of the desired sulfide **36** as a colorless oil: $[\alpha]^{20}_{D}$ = −13.3° ($c$ 2.2, CHCl$_3$); TLC (20% diethyl ether/CH$_2$Cl$_2$) $R_f$ = 0.46; IR (thin film) 3400 (br) cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.37−7.07 (5H, m, Ar$H$), 3.67−3.59 (3H, m, one of C$H_2$OH, 2 × C$H$OC(CH$_3$)$_2$), 3.53 (1H, dd, $J$ = 10.8, 5.3 Hz, one of C$H_2$OH), 3.38 (1H, dd, $J$ = 12.8, 2.6 Hz, one of C$H_2$SPh), 2.70 (1H, dd, $J$ = 12.8, 8.3 Hz, one of C$H_2$SPh), 1.93 (1H, m, C$H$CH$_3$), 1.80 (1H, m, C$H$CH$_3$), 1.61 (1H, qdd, $J$ = 6.8, 2.1, 2.1 Hz, H$_3$CC$H$(CHOC(CH$_3$)$_2$)$_2$), 1.39 (3H, s, $H_3$CCCH$_3$), 1.35 (3H, s, H$_3$CCC$H_3$), 1.02 (3H, d, $J$ = 6.7 Hz, C$H_3$), 0.94 (3H, d, $J$ = 6.8 Hz, C$H_3$), 0.83 (3H, d, $J$ = 6.8 Hz, C$H_3$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 137.9, 128.7, 127.9, 125.1, 99.0, 76.2, 75.6, 64.1, 37.0, 36.7, 35.0, 31.1, 29.9, 19.5, 14.0, 14.0, 5.1; HRMS (CI, NH$_3$) calcd for C$_{19}$H$_{31}$O$_3$S ([M + H]$^+$) 339.1994, found 339.1998; $m/z$ 339 (100, [M + H]$^+$), 298 (20), 281 (76), 263 (46).

**(*SRS*,2*S*,3*R*,4*S*,5*R*,6*R*)-3,5-(Isopropylidenedioxy)-2,4,6-trimethyl-7-(phenylsulfinyl)heptan-1-ol (33).** To a stirred solution of sulfide **36** (223 mg, 0.66 mmol) in methanol (10 mL) at room temperature were added sodium periodate (155 mg, 0.73 mmol) and distilled water (1 mL), and the reaction mixture was left stirring for 21 h. It was then partitioned between CH$_2$Cl$_2$ (3 × 20 mL) and distilled water (20 mL). The organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. Elution with diethyl ether through a short column of silica gel gave 233 mg (quantitative) of two diastereomeric sulfoxides **33** in a 2:3 ratio, as a colorless oil. These were not separated: TLC (diethyl ether) $R_f$ = 0.18; IR (thin film) 3400 (br) cm$^{-1}$; $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.66−7.62 (2H, m, Ar$H$ $o$-$H$), 7.53−7.51 (3H, m, Ar$H$ $m$- and $p$-$H$), 3.64−3.44 (4H, m, C$H_2$OH, 2 × C$H$OC(CH$_3$)$_2$), 3.11 (2/5 × 1H, dd, $J$ = 13.0, 3.9 Hz, one of C$H_2$S(O)Ph), 2.95 (3/5 × 1H, dd, $J$ = 13.2, 4.7 Hz, one of C$H_2$S(O)Ph), 2.64 (3/5 × 1H, dd, $J$ = 13.2, 7.2 Hz, one of C$H_2$S(O)Ph), 2.47 (1H, br s, O$H$), 2.43 (2/5 × 1H, dd, $J$ = 13.0, 8.8 Hz, one of C$H_2$S(O)Ph), 2.20−2.00 (1H, m, C$H$CH$_3$), 1.78−1.63 (2H, m, 2 × C$H$CH$_3$), 1.36 (2/5 × 6H, s, $H_3$CCC$H_3$), 1.34 (3/5 × 3H, s, $H_3$CCCH$_3$), 1.33 (3/5 × 3H, s, H$_3$CCC$H_3$), 1.05 (2/5 × 3H, d, $J$ = 7.3 Hz, C$H_3$), 1.03 (3/5 × 3H, d, $J$ = 7.2 Hz, C$H_3$), 1.00 (2/5 × 3H, d, $J$ = 6.6 Hz, C$H_3$), 0.99 (3/5 × 3H, d, $J$ = 6.6 Hz, C$H_3$), 0.83 (3H, d, $J$ = 6.8 Hz, C$H_3$); $^{13}$C NMR (100.6 MHz, CD$_2$Cl$_2$) $\delta$ 145.8, 145.1, 131.0, 130.9, 129.4, 129.3, 124.3, 124.2, 99.3, 99.2, 77.5, 76.9, 75.8, 37.0, 32.2, 31.2, 31.2, 30.9, 29.8, 19.6, 19.6, 15.3, 14.5, 14.0, 5.0, 4.9; HRMS (CI, NH$_3$) calcd for C$_{19}$H$_{31}$O$_4$S ([M + H]$^+$) 355.1943, found 355.1940; $m/z$ 355 (100, [M + H]$^+$), 297 (38).

**(2*S*,3*R*,4*R*,5*S*,6*S*,8*RS*,9*S*,10*R*,11*S*,12*S*,13*R*)-13-[(Benzyloxy)methoxy]-9,11-bis(*tert*-butyldimethylsiloxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12-pentamethyltetradecane-1,8-diol (38).** To a cooled (−78 °C) stirred solution of sulfoxides **33** (60.0 mg, 0.17 mmol) in dry DME (8 mL) was added dropwise a solution of LDA−mono-THF complex (225 $\mu$L, 0.34 mmol; 1.5 M in cyclohexane). The resulting yellow solution was stirred at −78 °C for 15 min followed by addition *via* cannula of a solution of aldehyde **27** (50.0 mg, 92.8 $\mu$mol) in DME (1.0 mL + 0.5 mL washings). The reaction was quenched after 5 min by addition of ammonium chloride solution (2 mL; saturated, aqueous) at −78 °C. The mixture was warmed to room temperature and partitioned between ammonium chloride solution (20 mL; saturated, aqueous) and diethyl ether (3 × 25 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (gradient elution: 40−100% EtOAc/hexanes) provided 30.1 mg of recovered sulfoxides **33** as well as 66.2 mg (80% conversion, 88% based on unrecovered sulfoxides) of a mixture of several adducts **37**, each as a colorless oil.

To a vigorously stirred solution of the mixture of adducts prepared above (66.2 mg, 74.1 $\mu$mol) in diethyl ether (6 mL) at room temperature was added a spatula end of a slurry of W-2 Raney nickel in ethanol.[82] After 1.5 h of stirring, the Raney nickel was removed by elution through a short column of Celite with diethyl ether, taking care that the Raney nickel was not allowed to become dry. The solvent was removed *in vacuo*; subsequent flash chromatography (30% EtOAc/hexanes) afforded 37.2 mg (65%) of a mixture of diastereomers and C$_8$ OTBS regioisomers, comprising two major and two minor components, as a colorless oil. Data for the major high R$_f$ component: TLC (30% EtOAc/hexanes) $R_f$ = 0.47; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.32−7.25 (5H, m, Ar$H$), 4.82 (1H, d, $J$ = 7.0 Hz, one of C$H_2$OBn), 4.75 (1H, d, $J$ = 7.0 Hz, one of C$H_2$OBn), 4.66 (1H, d, $J$ = 11.8 Hz, one of C$H_2$Ph), 4.56 (1H, d, $J$ = 11.8 Hz, one of C$H_2$Ph), 3.93 (1H, br d, $J$ = 7.0 Hz, α to O), 3.80−3.43 (6H, m, α to O), 3.36 (1H, br d, $J$ = 11.2 Hz, α to O), 1.98−1.60 (7H, m, 5 × C$H$CH$_3$, C$H_2$CHOH), 1.36 (6H, s, $H_3$CCC$H_3$), 1.26 (3H, d, $J$ = 6.3 Hz, $H_3$CCHO(BOM)), 1.02 (3H, d, $J$ = 6.4 Hz, C$H_3$), 1.00 (3H, d, $J$ = 7.1 Hz, C$H_3$), 0.91 (9H, s, C(C$H_3$)$_3$), 0.90 (9H, s, C(C$H_3$)$_3$), 0.91−0.87 (6H, buried, 2 × C$H_3$), 0.83 (3H, d, $J$ = 6.6 Hz, C$H_3$), 0.08 (3H, s, SiC$H_3$), 0.06 (6H, s, 2 × SiC$H_3$), 0.05 (3H, s, SiC$H_3$). Data for the major low R$_f$ component: TLC (30% EtOAc/hexanes) $R_f$ = 0.39; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.32−7.26 (5H, m, Ar$H$), 4.82 (1H, d, $J$ = 7.0 Hz, one of C$H_2$OBn), 4.75 (1H, d, $J$ = 7.0 Hz, one of C$H_2$OBn), 4.66 (1H, d, $J$ = 11.9 Hz, one of C$H_2$Ph), 4.57 (1H, d, $J$ = 11.9 Hz, one of C$H_2$Ph), 3.79−3.41 (7H, m, α to O), 3.30 (1H, br d, $J$ = 11.6 Hz, α to O), 1.72−1.51 (7H, m, 5 × C$H$CH$_3$, C$H_2$CHOH), 1.33 (6H, s, $H_3$CCC$H_3$), 1.27 (3H, d, $J$ = 6.2 Hz, $H_3$CCHO(BOM)), 1.03 (3H, d, $J$ = 7.0 Hz, C$H_3$), 1.02 (3H, d, $J$ = 6.6 Hz, C$H_3$), 0.89 (18H, s, 2 × C(C$H_3$)$_3$), 0.89 (3H, buried d, C$H_3$), 0.82 (3H, d, $J$ = 6.6 Hz, C$H_3$), 0.80 (3H, d, $J$ = 6.6 Hz, C$H_3$), 0.10 (3H, s, SiC$H_3$), 0.09 (6H, s, 2 × SiC$H_3$), 0.06 (3H, s, SiC$H_3$).

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(82) Mozingo, R. *Organic Syntheses;* Wiley: New York, 1955; Collect. Vol. III, p 181.

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*S*,10*R*,11*S*,12*S*,13*R*)-9,11-Bis(*tert*-butyldimethylsiloxy)-13-hydroxy-3,5-(isopropylidenedioxy)-2,4,6,10,12-pentamethyl-8-oxotetradecanoic Acid (40).** To a cooled (−78 °C) stirred solution of oxalyl chloride (84 μL, 0.96 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise DMSO (103 μL, 1.45 mmol), and the mixture was stirred for 5 min to ensure complete formation of the chlorosulfur complex. A solution of the mixture of diols from the Raney Ni reaction above (*i.e.*, **38** + $C_8$ OTBS regioisomers; 37.2 mg total, 48.4 μmol) in $CH_2Cl_2$ (1.5 mL + 0.5 mL washings) was then added *via* cannula and the reaction mixture stirred for a further 30 min at −78 °C. Triethylamine (236 μL, 1.69 mmol) was added at −78 °C and the reaction mixture allowed to warm *to −23 °C only* until no starting material was evident by TLC (*ca.* 20 min). The reaction was immediately quenched by addition of ammonium chloride solution (3 mL; saturated, aqueous), the layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude ketoaldehyde was eluted through a short column of silica gel with diethyl ether, and the oil remaining after evaporation *in vacuo* was taken on to the next reaction, without further purification.

To a vigorously stirred solution of the product from the above Swern reaction (theoretically 48.4 μmol) in *tert*-butyl alcohol (2 mL) and pH 7 buffer (2 mL) at room temperature was added dropwise potassium permanganate solution (0.5 mL; 1 M aqueous). The reaction mixture was stirred for 30 min and then diluted with brine (10 mL; saturated). The aqueous layer was saturated with sodium chloride and acidified to pH 3 by dropwise addition of hydrochloric acid solution (1 M aqueous) and then extracted with diethyl ether (3 × 20 mL) followed by ethyl acetate (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Elution through a short column of silica gel with ethyl acetate (containing a few drops of acetic acid), followed by removal of the solvent *in vacuo*, gave reasonably pure acid (two regioisomers) as a colorless oil which was taken on to the next reaction without further purification.

To a solution of the mixture of acids prepared above (theoretically 48.4 μmol) in ethanol (4 mL) under an argon atmosphere was added palladium on activated charcoal (spatula end, 10% Pd content). The reaction mixture was stirred while hydrogen (from a hydrogen-filled double balloon) replaced the argon. After 1.5 h the catalyst was removed by elution with diethyl ether through a short column of Celite. Flash chromatography (40% EtOAc/hexanes), on a column of silica gel prewashed with solvent containing a few drops of acetic acid, afforded 5.0 mg (16% over three steps) of an undesired $C_8$ OTBS regioisomer (**41**) and 16.4 mg (51% over three steps) of the desired seco-acid **40**, both as colorless oils, in a total yield of 67% over three steps. Data for seco-acid **40**: TLC (40% EtOAc/hexanes) $R_f = 0.21$; $^1$H NMR (400 MHz, $CDCl_3$) δ 4.34 (1H, qd, *J* = 6.8, 1.1 Hz, C*H*OH), 3.98 (1H, d, *J* = 4.5 Hz, (TBS)OC*H*C=O), 3.84 (1H, dd, *J* = 9.3, 1.6 Hz, α to O), 3.67 (1H, dd, *J* = 7.3, 2.1 Hz, α to O), 3.49 (1H, dd, *J* = 9.6, 2.0 Hz, $CH(OC(CH_3)_2)CHCO_2H$), 2.74 (1H, dd, *J* = 17.6, 2.5 Hz, one of $CH_2C{=}O$), 2.65 (1H, dq, *J* = 9.6, 7.0 Hz, $H_3CCHCO_2H$), 2.22 (1H, dd, *J* = 17.6, 9.0 Hz, one of $CH_2C{=}O$), 2.22 (1H, buried m, $CHCH_3$), 2.07 (1H, m, $CHCH_3$), 1.66−1.58 (2H, m, 2 × $CHCH_3$), 1.37 (3H, s, $H_3CCCH_3$), 1.35 (3H, s, $H_3CCCH_3$), 1.24 (3H, d, *J* = 6.8 Hz, $H_3CCHOH$), 1.14 (3H, d, *J* = 6.4 Hz, $CH_3$), 1.01 (3H, d, *J* = 7.0 Hz, $CH_3$), 0.91 (9H, s, $C(CH_3)_3$), 0.90 (9H, s, $C(CH_3)_3$), 0.88 (3H, d, *J* = 7.2 Hz, $CH_3$), 0.87 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.81 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 211.5, 178.7, 99.4, 79.8, 78.8, 76.4, 74.9, 66.4, 41.8, 41.5, 40.2, 31.1, 30.2, 29.8, 26.2, 25.8, 25.6, 21.1, 19.6, 18.4, 18.3, 15.0, 14.7, 11.4, 11.2, 4.8, −3.5, −3.5, −4.2, −4.8; HRMS (CI, $NH_3$) calcd for $C_{34}H_{67}O_7Si_2$ ($[M + H - H_2O]^+$) 643.4425; found 643.4440; *m/z* 643 (51, $[M + H - H_2O]^+$), 290 (31), 257 (30), 245 (82), 215 (38), 201 (24), 132 (54), 92 (40), 72 (30), 58 (71), 52 (100). Data for minor component (2*R*,3*S*,4*R*,5*S*,6*S*,8*?*,10*R*,11*S*,12*S*,13*R*)-8,11-bis(*tert*-butyldimethylsiloxy)-13-hydroxy-3,5-(isopropylidenedioxy)-2,4,6,10,12-pentamethyl-9-oxotetradecanoic acid (**41**): see supplementary material.

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*S*,10*R*,11*S*,12*S*,13*R*)-9,11-Bis(*tert*-butyldimethylsiloxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-oxotetradecanolide (42).** To a stirred solution of seco-acid **40** (16.4 mg, 24.8 μmol) in dry THF (1 mL) at room temperature was added dropwise triethylamine (5.2 μL, 37.2 μmol) followed by 2,4,6-trichlorobenzoyl chloride (4.3 μL, 27.5 μmol). The reaction mixture was stirred for 2 h, during which time it became cloudy. The reaction mixture was then filtered through a pad of glass wool, to remove precipitated triethylamine hydrochloride. The filtrate, kept under argon as much as possible, was then diluted with dry toluene to give 10 mL of a solution of mixed anhydride.

To a heated (80 °C) solution of DMAP (16.5 mg, 135 μmol) in dry toluene (3 mL), in a flask equipped with a reflux condenser and septum inlet, was slowly added (over 3 h, by syringe pump) the solution of the mixed anhydride prepared above (10 mL of solution in toluene, theoretically 24.8 μmol). After addition the reaction mixture was stirred for a further 30 min at 80 °C, before being cooled to room temperature and concentrated *in vacuo*. Flash chromatography (40% $CH_2Cl_2$/petroleum ether) afforded 9.6 mg (60%) of the desired macrolactone **42** as a colorless oil: $[\alpha]^{20}_D = -3.8°$ (*c* 0.3, $CHCl_3$); TLC (40% $CH_2Cl_2$/petroleum ether) $R_f = 0.36$; IR ($CHCl_3$ solution) 1700 (s), 1250 (s) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.19 (1H, q, *J* = 6.4 Hz, $C_{13}H$), 4.47 (1H, br d, *J* = 4.4 Hz, $C_5H$), 3.82 (1H, d, *J* = 10.6 Hz, $C_9H$), 3.56 (1H, br d, *J* = 10.8 Hz, $C_3H$), 3.14 (1H, d, *J* = 8.7 Hz, $C_{11}H$), 3.00 (1H, m, one of $C_7H_2$), 2.65 (1H, dq, *J* = 10.8, 6.6 Hz, $C_2H$), 2.54−2.40 (2H, m, $C_6H$ and one of $C_7H_2$), 1.96 (1H, dq, *J* = 10.6, 6.6 Hz, $C_{10}H$), 1.60−1.50 (2H, m, $C_4H$ and $C_{12}H$), 1.41 (3H, s, $H_3CCCH_3$), 1.41 (3H, s, $H_3CCCH_3$), 1.22 (3H, d, *J* = 6.4 Hz, $C_{13}CH_3$), 1.08 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.02 (6H, d, *J* = 6.7 Hz, $CH_3$), 0.97 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.94 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.91 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.90 (9H, s, $C(CH_3)_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.19 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$), −0.03 (3H, s, $SiCH_3$); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 212.5, 173.8, 99.7, 81.7, 75.6, 72.0, 71.4, 71.4, 43.7, 40.2, 40.1, 38.6, 32.8, 30.5, 29.7, 26.3, 25.7, 19.5, 18.8, 18.4, 18.0, 15.6, 12.4, 10.1, 8.7, 7.7, −2.8, −4.9, −5.0, −5.7; HRMS (CI, $NH_3$) calcd for $C_{34}H_{70}NO_7Si_2$ ($[M + NH_4]^+$) 660.4690, found 660.4692; *m/z* 660 (10, $[M + NH_4]^+$), 602 (26), 585 (45), 453 (57), 323 (38), 199 (32), 132 (40), 109 (100), 92 (45), 58 (65).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*R*,12*R*,13*R*)-3,5,9,11-Tetrahydroxy-2,4,6,10,12,13-hexamethyl-8-methylenetetradecanolide (46).** **46** was prepared according to the procedure published by Tatsuta *et al.*:[6a] $[\alpha]^{20}_D = +28.6°$ (*c* 0.7, $CHCl_3$); TLC (70% EtOAc in hexane) $R_f = 0.31$; IR ($CHCl_3$ solution) 3480 (br), 1700 (s) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, br s, one of $C{=}CH_2$), 5.34 (1H, qd, *J* = 6.6, 1.2 Hz, $HCOC{=}O$), 5.05 (1H, br s, one of $C{=}CH_2$), 4.32 (1H, br s, C*H*OH), 3.94 (1H, br d, *J* = 10.0 Hz, C*H*OH), 3.76 (1H, d, *J* = 10.4 Hz, C*H*OH), 3.71 (1H, d, *J* = 10.0 Hz, O*H*), 3.65 (1H, d, *J* = 5.0 Hz, O*H*), 3.16 (1H, ddd, *J* = 10.5, 5.0, 2.5 Hz, C*H*OH), 2.91 (1H, br s, O*H*), 2.66 (1H, dq, *J* = 10.4, 6.7 Hz, $H_3CCHCO_2R$), 2.42 (1H, m, $H_3CCHCH_2C{=}CH_2$), 2.10 (1H, br s, O*H*), 2.06 (1H, m, $CHCH_3$), 1.92 (1H, dd, *J* = 18.5, 1.8 Hz, one of $CH_2C{=}CH_2$), 1.81 (1H, dd, *J* = 18.5, 9.2 Hz, one of $CH_2C{=}CH_2$), 1.64−1.55 (2H, m, 2 × $CHCH_3$), 1.28 (3H, d, *J* = 6.6 Hz, $H_3CCHOC{=}O$), 1.25 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.11 (6H, d, *J* = 7.1 Hz, 2 × $CH_3$), 1.00 (3H, d, *J* = 7.0 Hz, $CH_3$), 0.81 (3H, d, *J* = 7.0 Hz, $CH_3$); COSY (400 MHz, $CDCl_3$) correlations between δ 0.81 and 1.64, 1.00 and 1.55, 1.11 and 2.06, 1.11 and 2.42, 1.25 and 2.66, 1.28 and 5.34, 1.64 and 3.16, 1.81 and 1.92, 2.66 and 3.76, 5.05 and 5.50; $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ 177.2, 147.8, 108.9, 79.0, 78.4, 76.6, 71.7, 69.2, 43.9, 42.2, 37.0, 35.3, 34.3, 34.2, 18.4, 17.3, 14.6, 9.2, 8.4, 6.7; HRMS (CI, $NH_3$) calcd for $C_{20}H_{37}O_6$ ($[M + H]^+$) 373.2590, found 373.2590; *m/z* 373 (40, $[M + H]^+$), 355 (31), 178 (72), 162 (38), 146 (41), 130 (100), 113 (29), 95 (21). The spectroscopic data are in agreement with data kindly provided by Prof. K. Tatsuta.[6a]

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*R*,12*R*,13*R*)-9,11-Dihydroxy-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-methylenetetradecanolide (47).** To a solution of tetrol **46** (687 mg, 1.84 mmol) in $CH_2Cl_2$ (15 mL) and 2,2-dimethoxypropane (15 mL) at room temperature were added a few crystals of PPTS (catalytic). After 3 h of stirring, removal of the solvent *in vacuo* and subsequent flash chromatography (40% EtOAc/hexanes) provided 591 mg (78%) of the desired $C_3$,$C_5$ monoacetonide product **47** and 123 mg (15%) of the $C_3$,$C_5$:$C_9$,$C_{11}$ bisacetonide product, both as colorless oils. Data for monoacetonide product **47**: $[\alpha]^{20}_D = +22.9°$ (*c* 1.4, $CHCl_3$); TLC (40% EtOAc/hexanes) $R_f = 0.30$; IR ($CHCl_3$ solution) 3507 (br), 1713 (s) cm$^{-1}$; $^1$H

NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 5.48 (1H, br s, one of $\mathrm{C{=}C}H_2$), 5.46 (1H, q, $J$ = 6.6 Hz, *H*COC=O), 5.09 (1H, br s, one of $\mathrm{C{=}C}H_2$), 4.33 (1H, d, $J$ = 6.1 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 4.01 (1H, br d, $J$ = 5.8 Hz, C*H*OH), 3.63 (1H, br d, $J$ = 9.8 Hz, C*H*OH), 3.47 (1H, br d, $J$ = 10.7 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 3.31 (1H, d, $J$ = 7.9 Hz, O*H*), 3.03 (1H, d, $J$ = 3.5 Hz, O*H*), 2.65 (1H, dq, $J$ = 10.7, 6.6 Hz, $\mathrm{H_3CC}H\mathrm{CO_2R}$), 2.50 (1H, m, $\mathrm{H_3CC}H\mathrm{CH_2C{=}CH_2}$), 2.03 (1H, m, $\mathrm{C}H\mathrm{CH_3}$), 1.98 (1H, br d, $J$ = 18.2 Hz, one of $\mathrm{C}H_2\mathrm{C{=}CH_2}$), 1.83 (1H, dd, $J$ = 18.2, 11.3 Hz, one of $\mathrm{C}H_2\mathrm{C{=}CH_2}$), 1.60−1.50 (2H, m, 2 × $\mathrm{C}H\mathrm{CH_3}$), 1.44 (6H, s, $H_3\mathrm{CCC}H_3$), 1.26 (3H, d, $J$ = 6.6 Hz, $H_3\mathrm{CCHOC{=}O}$), 1.13 (6H, d, $J$ = 6.8 Hz, 2 × $\mathrm{C}H_3$), 1.04 (3H, d, $J$ = 7.3 Hz, $\mathrm{C}H_3$), 0.98 (3H, d, $J$ = 6.6 Hz, $\mathrm{C}H_3$), 0.86 (3H, d, $J$ = 7.1 Hz, $\mathrm{C}H_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 175.7, 147.5, 109.1, 100.5, 79.0, 77.6, 72.4, 71.9, 69.5, 42.6, 41.5, 35.2, 34.5, 32.3, 32.0, 29.7, 19.9, 18.6, 16.2, 13.2, 9.5, 8.7, 7.6; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{23}H_{41}O_6}$ ($[\mathrm{M + H}]^+$) 413.2903, found 413.2903; *m*/*z* 430 (13, $[\mathrm{M + NH_4}]^+$), 413 (78, $[\mathrm{M + H}]^+$), 372 (60), 355 (100), 337 (60). Data for bis-acetonide product (2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-3,5:9,11-bis(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-methylenetetradecanolide: TLC (40% EtOAc/hexanes) $R_f$ = 0.65; IR (thin film) 1725 (s) cm$^{-1}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 5.56 (1H, br s, one of $\mathrm{C{=}C}H_2$), 5.42 (1H, q, $J$ = 6.6 Hz, *H*COC=O), 5.16 (1H, br s, one of $\mathrm{C{=}C}H_2$), 4.19 (1H, br s, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 4.13 (1H, d, $J$ = 5.3 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 3.51 (1H, d, $J$ = 10.7 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 3.37 (1H, d, $J$ = 9.6 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 2.62 (1H, dq, $J$ = 10.7, 6.6 Hz, $\mathrm{H_3CC}H\mathrm{CO_2R}$), 2.47 (1H, m, $\mathrm{H_3CC}H\mathrm{CH_2C{=}CH_2}$), 2.05 (1H, q, $J$ = 6.7 Hz, $\mathrm{C}H\mathrm{CH_3}$), 1.93−1.86 (2H, m, $\mathrm{C}H_2\mathrm{C{=}CH_2}$), 1.63 (1H, q, $J$ = 6.6 Hz, $\mathrm{C}H\mathrm{CH_3}$), 1.45 (1H, m, $\mathrm{C}H\mathrm{CH_3}$), 1.39 (3H, s, $H_3\mathrm{CCCH_3}$), 1.38 (3H, s, $\mathrm{H_3CCC}H_3$), 1.35 (3H, s, $H_3\mathrm{CCCH_3}$), 1.24 (3H, s, $\mathrm{H_3CCC}H_3$), 1.16 (3H, d, $J$ = 6.6 Hz, $H_3\mathrm{CCHOC{=}O}$), 1.07 (3H, d, $J$ = 6.7 Hz, $\mathrm{C}H_3$), 1.04 (3H, d, $J$ = 6.6 Hz, $\mathrm{C}H_3$), 1.02 (3H, d, $J$ = 7.2 Hz, $\mathrm{C}H_3$), 0.98 (3H, d, $J$ = 6.6 Hz, $\mathrm{C}H_3$), 0.87 (3H, d, $J$ = 7.3 Hz, $\mathrm{C}H_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 173.8, 144.7, 113.8, 100.7, 100.0, 80.6, 76.9, 71.7, 69.4, 68.4, 40.9, 40.1, 33.6, 32.4, 32.3, 30.9, 29.6, 28.9, 26.7, 19.6, 18.5, 16.1, 12.8, 11.6, 7.7, 7.3; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{26}H_{45}O_6}$ ($[\mathrm{M + H}]^+$) 453.3216, found 453.3216; *m*/*z* 453 (20, $[\mathrm{M + H}]^+$), 395 (38), 337 (100), 319 (39), 226 (40), 209 (42), 193 (36), 149 (100).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-Bis(*tert*-butyldimethylsiloxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-methylenetetradecanolide (48).** To a *gently* stirred solution of diol **47** (231 mg, 0.56 mmol) in dry $\mathrm{CH_2Cl_2}$ (0.5 mL) at room temperature was added 2,6-lutidine (0.52 mL, 4.46 mmol) followed by *tert*-butyldimethylsilyl triflate (0.51 mL, 2.23 mmol). After stirring for 84 h, the reaction mixture was eluted through a short column of silica gel with $\mathrm{CH_2Cl_2}$ and concentrated *in vacuo*. Flash chromatography (30% $\mathrm{CH_2Cl_2}$/petroleum ether) gave 246 mg (69%) of the desired bis(silyl ether) **48** as a colorless oil: TLC (30% $\mathrm{CH_2Cl_2}$/petroleum ether) $R_f$ = 0.24; IR ($\mathrm{CHCl_3}$ solution) 1710 (s), 1250 (s) cm$^{-1}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 5.45 (1H, br s, one of $\mathrm{C{=}C}H_2$), 5.19 (1H, q, $J$ = 6.4 Hz, *H*COC=O), 5.13 (1H, br s, one of $\mathrm{C{=}C}H_2$), 4.31 (1H, dd, $J$ = 6.6, 1.6 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 4.06 (1H, d, $J$ = 4.3 Hz, C*H*O(TBS)), 3.55 (1H, dd, $J$ = 11.0, 1.6 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 3.55 (1H, d, $J$ = 8.0 Hz, C*H*O(TBS)), 2.66 (1H, dq, $J$ = 11.0, 6.7 Hz, $\mathrm{H_3CC}H\mathrm{CO_2R}$), 2.48 (1H, m, $\mathrm{H_3CC}H\mathrm{CH_2C{=}CH_2}$), 2.00−1.83 (3H, m, $\mathrm{C}H_2\mathrm{C{=}CH_2}$, $\mathrm{C}H\mathrm{CH_3}$), 1.78 (1H, q, $J$ = 6.6 Hz, $\mathrm{C}H\mathrm{CH_3}$), 1.47 (1H, m, $\mathrm{C}H\mathrm{CH_3}$), 1.43 (3H, s, $H_3\mathrm{CCCH_3}$), 1.40 (3H, s, $\mathrm{H_3CCC}H_3$), 1.21 (3H, d, $J$ = 6.4 Hz, $H_3\mathrm{CCHOC{=}O}$), 1.09 (3H, d, $J$ = 6.6 Hz, $\mathrm{C}H_3$), 1.08 (3H, d, $J$ = 7.3 Hz, $\mathrm{C}H_3$), 1.01 (3H, d, $J$ = 6.7 Hz, $\mathrm{C}H_3$), 0.99 (3H, d, $J$ = 6.6 Hz, $\mathrm{C}H_3$), 0.90 (3H, d, $J$ = 6.8 Hz, $\mathrm{C}H_3$), 0.89 (9H, s, $(\mathrm{C}H_3)_3$), 0.88 (9H, s, $(\mathrm{C}H_3)_3$), 0.17 (3H, s, $\mathrm{SiC}H_3$), 0.07 (3H, s, $\mathrm{SiC}H_3$), 0.05 (3H, s, $\mathrm{SiC}H_3$), −0.02 (3H, s, $\mathrm{SiC}H_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 173.6, 148.0, 109.7, 99.6, 80.6, 76.1, 72.2, 72.1, 71.9, 44.9, 40.1, 37.4, 36.4, 33.0, 32.6, 29.8, 26.5, 26.3, 19.5, 19.1, 19.1, 18.8, 16.8, 12.3, 10.6, 10.5, 7.8, −1.6, −4.1, −4.6, −5.0; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{35}H_{69}O_6Si_2}$ ($[\mathrm{M + H}]^+$) 641.4633, found 641.4633; *m*/*z* 641 (1, $[\mathrm{M + H}]^+$), 583 (5), 509 (11), 451 (42), 319 (48), 273 (30), 199 (100), 132 (18).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-Bis(*tert*-butyldimethylsiloxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-oxotetradecanolide (45).** Ozone was bubbled through a cooled (−78 °C) stirred solution of alkene **48** (200 mg, 0.31 mmol) in ethyl acetate (10 mL), until no starting material was evident by TLC (*ca.* 90 min). Dimethyl sulfide (2 mL, large excess) was then added and the solution allowed to warm to room temperature. After stirring for a further 30 min, the solution was concentrated *in vacuo*; flash chromatography (40% $\mathrm{CH_2Cl_2}$/petroleum ether) provided 169 mg (84%) of the desired ketone **45** as a colorless oil: $[\alpha]^{20}_{\mathrm{D}} = -4.2°$ ($c$ 2.4, $\mathrm{CHCl_3}$); TLC (40% $\mathrm{CH_2Cl_2}$/petroleum ether) $R_f$ = 0.18; IR ($\mathrm{CHCl_3}$ solution) 1700 (s), 1250 (s) cm$^{-1}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 5.16 (1H, q, $J$ = 6.4 Hz, $\mathrm{C_{13}}H$), 4.45 (1H, d, $J$ = 4.5 Hz, $\mathrm{C_9}H$), 4.41 (1H, br d, $J$ = 4.8 Hz, $\mathrm{C_5}H$), 3.59 (1H, dd, $J$ = 10.8, 1.6 Hz, $\mathrm{C_3}H$), 3.28 (1H, d, $J$ = 8.9 Hz, $\mathrm{C_{11}}H$), 2.65 (1H, dq, $J$ = 10.8, 6.7 Hz, $\mathrm{C_2}H$), 2.60 (1H, br d, $J$ = 17.5 Hz, one of $\mathrm{C_7}H_2$), 2.57 (1H, m, $\mathrm{C_6}H$), 2.35 (1H, d, $J$ = 17.5 Hz, one of $\mathrm{C_7}H_2$), 2.28 (1H, qd, $J$ = 6.7, 4.5 Hz, $\mathrm{C_{10}}H$), 1.70 (1H, qdd, $J$ = 6.7, 1.6, 1.6 Hz, $\mathrm{C_4}H$), 1.47 (1H, m, $\mathrm{C_{12}}H$), 1.42 (3H, s, $H_3\mathrm{CCCH_3}$), 1.41 (3H, s, $\mathrm{H_3CCC}H_3$), 1.23 (3H, d, $J$ = 6.4 Hz, $\mathrm{C_{13}C}H_3$), 1.07 (3H, d, $J$ = 6.7 Hz, $\mathrm{C_2C}H_3$), 1.03 (6H, d, $J$ = 6.7 Hz, $\mathrm{C_6C}H_3$, $\mathrm{C_{10}C}H_3$), 0.97 (3H, d, $J$ = 6.7 Hz, $\mathrm{C_4C}H_3$), 0.90 (3H, d, $J$ = 7.4 Hz, $\mathrm{C_{12}C}H_3$), 0.87 (18H, s, 2 × $(\mathrm{C}H_3)_3$), 0.24 (3H, s, $\mathrm{C_{11}OSiC}H_3$), 0.12 (3H, s, $\mathrm{C_9OSiC}H_3$), −0.02 (3H, s, $\mathrm{C_9OSiC}H_3$), −0.05 (3H, s, $\mathrm{C_{11}OSiC}H_3$); COSY (400 MHz, $\mathrm{CDCl_3}$) correlations between $\delta$ 0.90 and 1.47, 0.97 and 1.70, 1.03 and 2.28, 1.03 and 2.57, 1.07 and 2.65, 1.23 and 5.16, 1.47 and 3.28, 2.28 and 4.45, 2.35 and 2.60, 2.57 and 2.60, 2.57 and 4.41, 2.65 and 3.59; long-range COSY $\delta$ (400 MHz, $\mathrm{CDCl_3}$) additional correlations between $\delta$ 1.70 and 3.59, 1.70 and 4.41; NOE difference experiment (400 MHz, $\mathrm{CDCl_3}$) irradiation at 4.45 gave enhancements at $\delta$ (%) 2.35 (4.2), 2.28 (6.8), 0.12 (3.0), −0.02 (3.3); irradiation at 3.59 gave enhancements at $\delta$ (%) 4.41 (9.7), 2.65 (2.1), 1.70 (4.5), 1.42 (9.0), 1.07 (4.2), −0.05 (2.7); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 208.5, 173.6, 99.7, 82.6, 75.2, 72.6, 71.6, 71.4, 44.9, 43.6, 40.0, 38.3, 32.9, 31.0, 29.7, 26.5, 26.1, 19.7, 19.1, 19.0, 18.6, 15.6, 12.3, 10.7, 9.9, 7.8, −1.7, −4.3, −5.3, −5.4; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{34}H_{70}NO_7Si_2}$ ($[\mathrm{M + NH_4}]^+$) 660.4691, found 660.4691; *m*/*z* 660 (3, $[\mathrm{M + NH_4}]^+$), 585 (6), 453 (91), 341 (22), 321 (100), 227 (18), 199 (61), 132 (19), 90 (17).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*E*,13*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-methylene-11-tetradecenolide (49).** To a stirred suspension of methyltriphenylphosphonium bromide (40.0 mg, 0.11 mmol) in dry toluene (1 mL), at room temperature in a flask equipped with a reflux condenser, was added dropwise KHMDS solution (187 µL, 93.5 µmol; 0.5 M in toluene) whereupon the mixture rapidly became bright yellow, indicating formation of a phosphorus ylide. The reaction mixture was heated at 90 °C for 1 h to ensure complete formation of the ylide, before being cooled to room temperature, and a solution of macrolide ketone **45** (6.0 mg, 9.3 µmol) in toluene (0.5 mL + 0.5 mL washings) added *via* cannula. After heating at 90 °C for 8 h, the reaction mixture was partitioned between distilled water (10 mL) and diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine (15 mL; saturated), dried ($\mathrm{MgSO_4}$), and concentrated *in vacuo*; flash chromatography ($\mathrm{CH_2Cl_2}$) gave 3.8 mg (80%) of alkene **49** as a colorless oil: TLC ($\mathrm{CH_2Cl_2}$) $R_f$ = 0.45; $^{1}$H NMR (250 MHz, $\mathrm{CDCl_3}$) $\delta$ 5.47 (1H, br d, $J$ = 8.5 Hz, $H\mathrm{C{=}CCH_3}$), 5.31 (1H, br s, one of $\mathrm{C{=}C}H_2$), 5.11 (1H, br s, one of $\mathrm{C{=}C}H_2$), 5.07 (1H, qd, $J$ = 6.5, 1.8 Hz, *H*COC=O), 4.37 (1H, d, $J$ = 10.2 Hz, C*H*O(TBS)), 4.01 (1H, dd, $J$ = 6.5, 1.6 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 3.67 (1H, br d, $J$ = 10.7 Hz, $\mathrm{C}H\mathrm{OC(CH_3)_2}$), 2.78−2.56 (3H, m, $\mathrm{C}H\mathrm{CH_3}$, $\mathrm{C}H_2\mathrm{C{=}CH_2}$), 2.27 (1H, m, $\mathrm{C}H\mathrm{CH_3}$), 2.00 (1H, br q, $J$ = 6.7 Hz, $\mathrm{C}H\mathrm{CH_3}$), 1.78 (3H, br s, $\mathrm{HC{=}CC}H_3$), 1.65 (1H, m, $\mathrm{C}H\mathrm{CH_3}$), 1.43 (3H, s, $H_3\mathrm{CCCH_3}$), 1.41 (3H, s, $\mathrm{H_3CCC}H_3$), 1.25 (3H, d, $J$ = 6.5 Hz, $H_3\mathrm{CCHOC{=}O}$), 1.14 (3H, d, $J$ = 6.7 Hz, $\mathrm{C}H_3$), 1.05 (3H, d, $J$ = 7.0 Hz, $\mathrm{C}H_3$), 0.98 (3H, d, $J$ = 6.7 Hz, $\mathrm{C}H_3$), 0.94 (3H, d, $J$ = 7.4 Hz, $\mathrm{C}H_3$), 0.90 (9H, s, $(\mathrm{C}H_3)_3$), 0.04 (3H, s, $\mathrm{SiC}H_3$), −0.04 (3H, s, $\mathrm{SiC}H_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 174.7, 153.3, 133.5, 128.4, 110.7, 100.2, 77.2, 74.0, 73.5, 69.3, 43.5, 41.1, 36.7, 32.9, 32.1, 29.7, 25.9, 19.9, 18.2, 17.4, 16.0, 15.4, 13.5, 13.0, 7.6, −4.1, −5.0; MS (CI, $\mathrm{NH_3}$) *m*/*z* 509 (2, $[\mathrm{M + H}]^+$), 451 (91), 413 (12), 393 (12), 337 (20), 319 (100), 279 (39), 263 (18), 199 (26), 163 (40), 149 (12), 91 (18).

**(2*S*,4*S*,5*S*,6*E*)-1-(Benzyloxy)-5-hydroxy-2,4-dimethyl-6-octen-3-one (7 (*AA*)).** To a solution of cyclohexene (16.0 mL, 158 mmol) in diethyl ether (50 mL) at room temperature was added dropwise by syringe monochloroborane−methyl sulfide complex (8.7 mL, 75 mmol). The mildly exothermic reaction was controlled by the rate of addition and the flask maintained at 20−25 °C by immersion in a water bath. The reaction mixture was stirred for 2 h at room temperature, over which time it gradually became clear, before the solvent was removed *in vacuo* (room temperature at ~10 mmHg, vacuum line). Distillation under reduced pressure afforded pure $\mathrm{(Chx)_2BCl}$ as a colorless oil (bp 80–90 °C at 0.3 mmHg; *d* 0.981). The chloroborane could be stored under argon at −20 °C for several months without significant loss of activity.

To a cooled (−78 °C) stirred solution of $\mathrm{(Chx)_2BCl}$ (5.00 mL, 23.0 mmol) in diethyl ether (30 mL) was added dropwise triethylamine (4.22 mL, 30.3 mmol) followed by addition *via* cannula of a solution of ketone (*S*)-**8** (3.90 g, 18.9 mmol) in diethyl ether (10 mL + 10 mL washings), whereupon a white precipitate formed instantaneously. Following 3 h of enolization at −78 °C, freshly distilled crotonaldehyde (3.13 mL, 37.8 mmol) was added dropwise, and the reaction mixture was stirred at −78 °C for a further 3 h, before being left in the freezer (−20 °C) for 16 h. The reaction mixture was then partitioned between diethyl ether (3 × 200 mL) and pH 7 buffer solution (200 mL), and the combined organic extracts were concentrated *in vacuo*; the residue was resuspended in methanol (50 mL) and pH 7 buffer (10 mL) and cooled to 0 °C. Hydrogen peroxide solution (20 mL; 30% aqueous) was added dropwise and stirring continued at room temperature for 1–2 h. The mixture was then poured into distilled water (200 mL) and extracted with $\mathrm{CH_2Cl_2}$ (3 × 200 mL). The combined organic extracts were washed in turn with sodium bicarbonate solution (150 mL; 5% aqueous) and brine (150 mL; saturated), dried ($\mathrm{MgSO_4}$), and concentrated *in vacuo* to afford a yellow oil. Flash chromatography (10% diethyl ether/$\mathrm{CH_2Cl_2}$) provided 4.86 g (93%) of the desired *anti*–*anti* aldol product **7** (*AA*) as a colorless oil: $[\alpha]^{20}_{\mathrm{D}} = +17.1^\circ$ (*c* 4.3, $\mathrm{CHCl_3}$); TLC (10% diethyl ether/$\mathrm{CH_2Cl_2}$) $R_f = 0.39$; IR (thin film) 3440 (br), 1700 (s) $\mathrm{cm^{-1}}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 7.33–7.25 (5H, m, $\mathrm{Ar}\mathit{H}$), 5.71 (1H, dqd, $J = 15.3$, 6.4, 0.9 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{{=}CH}$), 5.43 (1H, ddq, $J = 15.3$, 7.7, 1.6 Hz, $\mathrm{H_3CCH{=}C}\mathit{H}$), 4.49 and 4.47 (2H, ABq, $J = 12.0$ Hz, $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 4.16 (1H, dd, $J = 7.7$, 7.7 Hz, $\mathrm{C}\mathit{H}\mathrm{OH}$), 3.67 (1H, dd, $J = 8.8$, 8.7 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OBn}$), 3.44 (1H, dd, $J = 8.8$, 5.0 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OBn}$), 3.07 (1H, dqd, $J = 8.7$, 7.0, 5.0 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{CH_2OBn}$), 2.81 (1H, br s, $\mathrm{O}\mathit{H}$), 2.75 (1H, dq, $J = 7.7$, 7.1 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{CHOH}$), 1.70 (3H, br d, $J = 6.4$ Hz, $\mathit{H}_3\mathrm{CCH{=}CH}$), 1.05 (3H, d, $J = 7.0$ Hz, $\mathrm{C}\mathit{H}_3$), 1.04 (3H, d, $J = 7.1$ Hz, $\mathrm{C}\mathit{H}_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 217.4, 137.7, 131.4, 128.6, 128.3, 127.6, 127.5, 75.0, 73.2, 72.1, 51.8, 45.8, 17.7, 13.5, 13.4; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{17}H_{28}NO_3}$ ($\mathrm{[M + NH_4]^+}$) 294.2069, found 294.2069; *m/z* 294 (70, $\mathrm{[M + NH_4]^+}$), 259 (78), 224 (93), 207 (100), 108 (39), 91 (18).

The $\mathrm{(Chx)_2BCl}$-mediated asymmetric aldol reaction between ethyl ketone (*S*)-**8** and crotonaldehyde was also performed on a smaller scale (113 mg of ketone, 0.55 mmol), and the products were analyzed by HPLC (7% diethyl ether/$\mathrm{CH_2Cl_2}$): 131.2 mg of the desired *anti*–*anti* aldol product **7** (*AA*) (HPLC $R_t = 20$ min) and 1.4 mg of the *anti*–*syn* aldol product **7** (*AS*) (HPLC $R_t = 17$ min) were isolated in a ratio of 99:1 and total yield of 87%; <1% *syn* aldol products was isolated.

**(2*S*,3*S*,4*S*,5*S*,6*E*)-1-(Benzyloxy)-2,4-dimethyl-6-octene-3,5-diol.** To a stirred solution of $\mathrm{Me_4NHB(OAc)_3}$ (11.0 g, 41.6 mmol) in dry acetonitrile (25 mL) at room temperature was added glacial acetic acid (25 mL), with resulting mild effervescence, and the reaction mixture was stirred for 1 h at room temperature before being cooled to −30 °C. A solution of $\beta$-hydroxyketone **7** (*AA*) (1.44 g, 5.19 mmol) in acetonitrile (12 mL + 5 mL washings) was then added *via* cannula and the mixture stirred at −30 °C for 2.5 h, before being left in the freezer (−20 °C) for 48 h. The reaction was then quenched at 0 °C by careful addition ($\uparrow\mathrm{H_2}$) of potassium sodium tartrate solution (75 mL; 0.5 M aqueous), and vigorous stirring maintained for 1 h at room temperature. The reaction mixture was then diluted with $\mathrm{CH_2Cl_2}$ (100 mL) and washed with sodium bicarbonate solution (100 mL; saturated, aqueous). The layers were separated, and the aqueous phase was extracted with $\mathrm{CH_2Cl_2}$ (6 × 75 mL). The combined organic extracts were then washed with more sodium bicarbonate solution (3 × 75 mL; saturated, aqueous), dried ($\mathrm{MgSO_4}$), and concentrated *in vacuo*. Flash chromatography (15% diethyl ether/$\mathrm{CH_2Cl_2}$) gave 1.34 g (92%) of the desired *anti*-1,3-diol as a colorless oil: $[\alpha]^{20}_{\mathrm{D}} = +4.0^\circ$ (*c* 2.5, $\mathrm{CHCl_3}$); TLC (15% diethyl ether/$\mathrm{CH_2Cl_2}$) $R_f = 0.30$; IR (thin film) 3420 (br), 1660 (w) $\mathrm{cm^{-1}}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 7.33–7.25 (5H, m, $\mathrm{Ar}\mathit{H}$), 5.72 (1H, dqd, $J = 15.3$, 6.5, 1.0 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{{=}CH}$), 5.56 (1H, ddq, $J = 15.3$, 6.6, 1.5 Hz, $\mathrm{H_3CCH{=}C}\mathit{H}$), 4.54 and 4.52 (2H, ABq, $J = 11.8$ Hz, $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 4.07 (1H, dd, $J = 6.6$, 6.0 Hz, $\mathrm{H_3CCH{=}CHC}\mathit{H}\mathrm{OH}$), 3.91 (1H, dd, $J = 9.4$, 2.1 Hz, $\mathrm{C}\mathit{H}\mathrm{OH(CHCH_3)_2}$), 3.60 (1H, dd, $J = 9.0$, 4.3 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OBn}$), 3.52 (1H, dd, $J = 9.0$, 9.0 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OBn}$), 3.39 (2H, br s, 2 × $\mathrm{O}\mathit{H}$), 2.43 (1H, m, $\mathrm{H_3CC}\mathit{H}\mathrm{CH_2OBn}$), 1.73 (3H, dd, $J = 6.5$, 1.5 Hz, $\mathit{H}_3\mathrm{CHC{=}CH}$), 1.62 (1H, qdd, $J = 7.0$, 6.0, 2.1 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{(CHOH)_2}$), 0.98 (3H, d, $J = 7.0$ Hz, $\mathrm{C}\mathit{H}_3$), 0.75 (3H, d, $J = 6.9$ Hz, $\mathrm{C}\mathit{H}_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 137.5, 133.5, 128.5, 127.8, 127.7, 126.7, 76.8, 76.3, 76.1, 73.5, 39.4, 35.8, 17.8, 12.9, 9.8; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{17}H_{27}O_3}$ ($\mathrm{[M + H]^+}$) 279.1960, found 279.1960; *m/z* 296 (5, $\mathrm{[M + NH_4]^+}$), 279 (40, $\mathrm{[M + H]^+}$), 261 (38), 243 (20), 196 (100), 178 (16), 99 (15).

**(2*E*,4*S*,5*S*,6*S*,7*S*)-8-(Benzyloxy)-4,6-(*R*)-(ethylidenedioxy)-5,7-dimethyl-2-octene (56).** To a solution of the diol prepared above (1.34 g, 4.80 mmol) in $\mathrm{CH_2Cl_2}$ (50 mL) and 1,1-dimethoxyethane (50 mL) at room temperature was added *p*-TsOH (179.5 mg, 0.94 mmol). After 70 h of stirring the reaction mixture was partitioned between sodium bicarbonate solution (150 mL; saturated, aqueous) and $\mathrm{CH_2Cl_2}$ (3 × 250 mL). The combined organic extracts were dried ($\mathrm{MgSO_4}$) and concentrated *in vacuo*. Flash chromatography (20% diethyl ether/hexanes) provided 1.36 g (93%) of the desired acetal product **56** as a colorless oil: $[\alpha]^{20}_{\mathrm{D}} = -75.1^\circ$ (*c* 8.0, $\mathrm{CHCl_3}$); TLC (20% diethyl ether/hexanes) $R_f = 0.35$; IR ($\mathrm{CCl_4}$ solution) 1670 (w) $\mathrm{cm^{-1}}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 7.25–7.35 (5H, m, $\mathrm{Ar}\mathit{H}$), 5.76 (1H, ddq, $J = 15.6$, 5.4, 1.3 Hz, $\mathrm{H_3CCH{=}C}\mathit{H}$), 5.67 (1H, dqd, $J = 15.6$, 6.2, 1.5 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{{=}CH}$), 4.93 (1H, q, $J = 5.0$ Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{O_2}$), 4.57 (1H, d, $J = 12.3$ Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 4.43 (1H, d, $J = 12.3$ Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{Ph}$), 4.22 (1H, m, $\mathrm{H_3CCH{=}CHC}\mathit{H}\mathrm{OCHCH_3}$), 3.66 (1H, dd, $J = 10.3$, 2.1 Hz, $\mathrm{H_3CCHOC}\mathit{H}\mathrm{(CHCH_3)_2}$), 3.54 (1H, dd, $J = 8.8$, 3.0 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OBn}$), 3.44 (1H, dd, $J = 8.8$, 6.2 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OBn}$), 1.90–1.80 (1H, m, $\mathrm{H_3CC}\mathit{H}\mathrm{CH_2OBn}$), 1.75 (3H, br d, $J = 6.2$ Hz, $\mathit{H}_3\mathrm{CCH{=}CH}$), 1.60 (1H, qdd, $J = 6.9$, 2.1, 1.2 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{(CHOCHCH_3)_2}$), 1.23 (3H, d, $J = 5.0$ Hz, $\mathit{H}_3\mathrm{CCHO_2}$), 1.13 (3H, d, $J = 6.9$ Hz, $\mathit{H}_3\mathrm{CCH(CHOCHCH_3)_2}$), 0.91 (3H, d, $J = 6.9$ Hz, $\mathit{H}_3\mathrm{CCHCH_2OBn}$); NOE difference experiment (400 MHz, $\mathrm{CDCl_3}$) irradiation at 4.93 gave enhancements at $\delta$ (%) 5.76 and 5.67 (8.5), 3.66 (11.6), 1.23 (8.3); irradiation at 4.22 gave enhancements at $\delta$ (%) 5.76 and 5.67 (7.1), 1.60 (9.2), 1.13 (8.0); irradiation at 3.66 gave enhancements at $\delta$ (%) 5.76 and 5.67 (7.6), 4.93 (12.9), 1.60 (5.4), 0.91 (2.4); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 138.9, 129.7, 128.7, 128.2, 127.5, 127.3, 93.0, 79.5, 75.1, 73.0, 71.7, 35.2, 32.3, 21.1, 18.1, 12.5, 12.3; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{19}H_{29}O_3}$ ($\mathrm{[M + H]^+}$) 305.2117, found 305.2120; *m/z* 305 (14, $\mathrm{[M + H]^+}$), 261 (25), 196 (100), 179 (26), 136 (22), 108 (29), 99 (30), 91 (65), 82 (30).

**(2*S*,3*S*,4*S*,5*S*,6*E*)-3,5-(*R*)-(Ethylidenedioxy)-2,4-dimethyl-6-octen-1-ol.** To a cooled (−78 °C) stirred solution of alkene **56** (1.35 g, 4.43 mmol) in THF (18 mL) was added dropwise LiDBB solution (~0.40 M) in portions (10 mL at a time), with a few minutes of stirring between each addition, until a green color persisted in the reaction mixture and TLC analysis indicated complete consumption of starting material. The green solution was then stirred for a further 30 min at −78 °C, before being quenched by careful addition of ammonium chloride solution (150 mL; saturated, aqueous), and the now colorless mixture extracted with diethyl ether (3 × 150 mL). The combined organic extracts were dried ($\mathrm{MgSO_4}$) and concentrated *in vacuo*. Flash chromatography (gradient elution: 0–40% EtOAc/hexanes) gave recovered 4,4′-di-*tert*-butylbiphenyl crystals and 921 mg (97%) of the desired alcohol as a colorless oil: $[\alpha]^{20}_{\mathrm{D}} = -62.4^\circ$ (*c* 5.15, $\mathrm{CHCl_3}$); TLC (40% EtOAc/hexanes) $R_f = 0.35$; IR (thin film) 3420 (br), 1660 (w) $\mathrm{cm^{-1}}$; $^{1}$H NMR (400 MHz, $\mathrm{CDCl_3}$) $\delta$ 5.75–5.60 (2H, m, $\mathrm{H_3CC}\mathit{H}\mathrm{{=}C}\mathit{H}$), 5.02 (1H, q, $J = 5.0$ Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{O_2}$), 4.20 (1H, m, $\mathrm{H_3CCH{=}CHC}\mathit{H}\mathrm{OCHCH_3}$), 3.70 (1H, dd, $J = 10.0$, 2.0 Hz, $\mathrm{H_3CCHOC}\mathit{H}\mathrm{(CHCH_3)_2}$), 3.61 (1H, dd, $J = 10.8$, 7.6 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OH}$), 3.53 (1H, dd, $J = 10.8$, 3.5 Hz, one of $\mathrm{C}\mathit{H}_2\mathrm{OH}$), 3.0 (1H, br s, $\mathrm{O}\mathit{H}$), 1.90–1.80 (1H, m, $\mathrm{H_3CC}\mathit{H}\mathrm{CH_2OH}$), 1.72–1.70 (3H, m, $\mathit{H}_3\mathrm{CCH{=}CH}$), 1.58 (1H, qdd, $J = 7.0$, 2.0, 1.2 Hz, $\mathrm{H_3CC}\mathit{H}\mathrm{(CHOCHCH_3)_2}$), 1.24 (3H, d, $J = 5.0$ Hz, $\mathit{H}_3\mathrm{CCHO_2}$), 1.14 (3H, d, $J = 7.0$ Hz, $\mathrm{C}\mathit{H}_3$), 0.72 (3H, d, $J = 7.0$ Hz, $\mathrm{C}\mathit{H}_3$); $^{13}$C NMR (100.6 MHz, $\mathrm{CDCl_3}$) $\delta$ 129.3, 129.0, 92.8, 80.2, 79.3, 68.2, 36.2, 32.5, 21.1, 18.0, 12.4, 11.8; HRMS (CI, $\mathrm{NH_3}$) calcd for $\mathrm{C_{12}H_{23}O_3}$ ($\mathrm{[M + H]^+}$) 215.1647, found 215.1647; *m/z* 215 (28, $\mathrm{[M + H]^+}$), 171 (68), 153 (42), 106 (100), 100 (40), 88 (40), 82 (33), 44 (32).

**(2*R*,3*R*,4*S*,5*S*,6*E*)-3,5-(*R*)-(Ethylidenedioxy)-2,4-dimethyl-6-octenal (58).** To a cooled (−78 °C), stirred solution of freshly distilled oxalyl chloride (0.83 mL, 9.52 mmol) in dry $\mathrm{CH_2Cl_2}$ (120 mL) was added dropwise DMSO (1.35 mL, 19.0 mmol), and the mixture was stirred for 15 min to ensure complete formation of the chlorosulfur complex. The alcohol prepared above (817 mg, 3.81 mmol) was added in solution in $CH_2Cl_2$ (40 mL + 10 mL washings) *via* cannula and the reaction mixture stirred for a further 1 h at −78 °C. Triethylamine (4.00 mL, 29.0 mmol) was added at −78 °C and the reaction mixture allowed to warm *to −23 °C only* until no alcohol was evident by TLC (*ca.* 30 min). The reaction was immediately quenched by addition of ammonium chloride solution (100 mL; saturated, aqueous), the layers were separated, and the aqueous phase was extracted with hexane (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5% diethyl ether/$CH_2Cl_2$) afforded 709 mg (87%) of the desired aldehyde **58** as a colorless oil: $[\alpha]^{20}_{D} = -118.8°$ (*c* 4.4, $CHCl_3$); TLC (5% diethyl ether/$CH_2Cl_2$) $R_f = 0.42$; IR (thin film) 1720 (s), 1660 (w) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.73 (1H, d, $J$ = 2.5 Hz, $CHO$), 5.75−5.60 (2H, m, $H_3CCH{=}CH$), 5.01 (1H, q, $J$ = 5.0 Hz, $H_3CCHO_2$), 4.24 (1H, m, $H_3CCH{=}CHCHOCHCH_3$), 4.01 (1H, dd, $J$ = 10.5, 2.2 Hz, $H_3CCHOCH(CHCH_3)_2$), 2.51 (1H, dqd, $J$ = 10.5, 7.1, 2.5 Hz, $H_3CCHCHO$), 1.73 (3H, br d, $J$ = 6.2 Hz, $H_3CCH{=}CH$), 1.58 (1H, qdd, $J$ = 7.0, 2.2, 1.2 Hz, $H_3CCH(CHOCHCH_3)_2$), 1.22 (3H, d, $J$ = 5.0 Hz, $H_3CCHO_2$), 1.16 (3H, d, $J$ = 7.0 Hz, $H_3CCH(CHOCHCH_3)_2$), 0.90 (3H, d, $J$ = 7.1 Hz, $H_3CCHCHO$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 204.7, 129.2 (2C), 92.9, 79.1, 75.2, 47.3, 31.9, 21.0, 18.0, 12.2, 8.9; MS (CI, $NH_3$) $[M + H]^+$ not found; *m/z* 246 (50), 202 (100), 185 (68), 169 (77), 151 (94), 123 (55), 111 (34).

**(2*R*,3*S*,4*S*,5*S*,6*S*,7*E*)-4,6-(*R*)-(Ethylidenedioxy)-3,5-dimethyl-7-nonen-2-ol (59).** To a cooled (−100 °C) stirred solution of aldehyde **58** (309 mg, 1.46 mmol) in $CH_2Cl_2$ (75 mL) was added dropwise by syringe a THF solution of methylmagnesium chloride (1.60 mL, 4.80 mmol; 3.0 M in THF). The reaction mixture was stirred for 15 min, then quenched by dropwise addition of ammonium chloride solution (50 mL; satuated, aqueous), and poured into a mixture of $CH_2Cl_2$ (25 mL) and distilled water (25 mL). The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 50 mL); the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. HPLC (25% diethyl ether/$CH_2Cl_2$) provided 279 mg of the desired 13*R* product epimer **59** and 18.0 mg of the 13*S* product epimer 13-*epi*-**59** as colorless oils in a total yield of 89%. Data for major diastereomer **59**: $[\alpha]^{20}_{D} = -66.5°$ (*c* 4.3, $CHCl_3$); TLC (15% diethyl ether/$CH_2Cl_2$) $R_f = 0.33$; HPLC (25% diethyl ether/$CH_2Cl_2$) $R_t$ = 17.5 min; IR (thin film) 3450 (br), 1660 (w) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.80−5.60 (2H, m, $H_3CCH{=}CH$), 5.02 (1H, q, $J$ = 5.0 Hz, $H_3CCHO_2$), 4.22 (1H, m, $H_3CCH{=}CHCHOCHCH_3$), 3.91 (1H, qd, $J$ = 6.5, 2.3 Hz, $H_3CCHOH$), 3.85 (1H, dd, $J$ = 10.4, 2.1 Hz, $H_3CCHOCH(CHCH_3)_2$), 2.55 (1H, br s, $OH$), 1.85 (1H, dqd, $J$ = 10.4, 7.1, 2.3 Hz, $H_3CCHCHOH$), 1.73 (3H, br d, $J$ = 6.2 Hz, $H_3CCH{=}CH$), 1.55 (1H, qdd, $J$ = 7.0, 2.1,1.2 Hz, $H_3CCH(CHOCHCH_3)_2$), 1.26 (3H, d, $J$ = 5.0 Hz, $H_3CCHO_2$), 1.15 (3H, d, $J$ = 6.5 Hz, $H_3CCHOH$), 1.14 (3H, d, $J$ = 7.0 Hz, $H_3CCH(CHOCHCH_3)_2$), 0.71 (3H, d, $J$ = 7.1 Hz, $H_3CCHCHOH$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 129.4, 129.0, 92.7, 79.5, 76.0, 69.3, 39.1, 32.4, 21.2, 18.9, 18.0, 12.4, 10.3; HRMS (CI, $NH_3$) calcd for $C_{13}H_{25}O_3$ ($[M + H]^+$) 229.1804, found 229.1804; *m/z* 229 (65, $[M + H]^+$), 211 (100), 185 (78), 167 (83), 120 (100), 102 (45), 82 (40). Data for minor diastereomer (2*S*,3*S*,4*S*,5*S*,6*S*,7*E*)-4,6-(*R*)-(ethylidenedioxy)-3,5-dimethyl-7-nonen-2-ol (13-*epi*-**59**): see supplementary material.

**(2*E*,4*S*,5*S*,6*S*,7*S*,8*R*)-4,6-(*R*)-(Ethylidenedioxy)-8-[(*p*-methoxybenzyl)oxy]-5,7-dimethyl-2-nonene.** An argon-flushed flask was charged with potassium hydride (438 mg, ~8.3 mmol; ~35% dispersion in oil). Hexane (10 mL) was added, the mixture stirred vigorously for 5 min and then allowed to stand, and the supernatant removed by syringe without allowing the potassium hydride to become dry; this procedure was repeated twice with hexane and once with THF. Finally, THF (5 mL) was added and the resulting suspension cooled to 0 °C. A solution of alcohol **59** (93.1 mg, 0.41 mmol) in dry THF (3 mL + 1 mL washings) was added *via* cannula, the mixture stirred vigorously for 5 min, and *p*-methoxybenzyl chloride (190 $\mu$L, 1.40 mmol) then added. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h before being recooled to 0 °C. Methanol (1 mL) was added carefully, followed, some minutes later, by addition of ammonium chloride solution (5 mL; saturated, aqueous). The mixture was partitioned between $CH_2Cl_2$ (50 mL) and ammonium chloride (50 mL; saturated, aqueous), the layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (gradient elution: 0−2% diethyl ether/$CH_2Cl_2$) provided 138 mg (97%) of the desired *p*-methoxybenzyl ether as a colorless oil: $[\alpha]^{20}_{D} = -82.0°$ (*c* 2.2, $CHCl_3$); TLC (2% diethyl ether/$CH_2Cl_2$) $R_f = 0.17$; IR (thin film) 1660 (w) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (2H, d, $J$ = 8.7 Hz, Ar$H$), 6.86 (2H, d, $J$ = 8.7 Hz, Ar$H$), 5.75−5.60 (2H, m, $H_3CCH{=}CH$), 4.63 (1H, q, $J$ = 5.0 Hz, $H_3CCHO_2$), 4.54 (1H, d, $J$ = 11.8 Hz, one of Ar$CH_2O$), 4.26 (1H, d, $J$ = 11.8 Hz, one of Ar$CH_2O$), 4.18 (1H, m, $H_3CCH{=}CHCHOCHCH_3$), 3.90 (1H, qd, $J$ = 6.4, 1.8 Hz, $H_3CCHO$(PMB)), 3.79 (3H, s, Ar$OCH_3$), 3.72 (1H, dd, $J$ = 10.2, 2.1 Hz, $H_3CCHOCH(CHCH_3)_2$), 1.78 (3H, br d, $J$ = 6.2 Hz, $H_3CCH{=}CH$), 1.56 (1H, qdd, $J$ = 6.9, 2.1, 1.2 Hz, $H_3CCH(CHOCHCH_3)_2$), 1.43 (1H, dqd, $J$ = 10.2, 7.1, 1.8 Hz, $H_3CCHCHO$(PMB)), 1.14 (3H, d, $J$ = 6.4 Hz, $H_3CCHO$(PMB)), 1.13 (3H, d, $J$ = 5.0 Hz, $H_3CCHO_2$), 1.08 (3H, d, $J$ = 6.9 Hz, $H_3CCH(CHOCHCH_3)_2$), 0.77 (3H, d, $J$ = 7.1 Hz, $H_3CCHCHO$(PMB)); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 159.0, 131.4, 129.8, 129.5, 128.5, 113.5, 92.9, 79.5, 74.5, 70.5, 70.3, 55.2, 40.2, 32.3, 21.1, 18.1, 17.0, 12.1, 7.1; HRMS (CI, $NH_3$) calcd for $C_{21}H_{33}O_4$ ($[M + H]^+$) 349.2379, found 349.2379; *m/z* 349 (8, $[M + H]^+$), 211 (34), 197 (35), 121 (100).

**(2*R*,3*R*,4*S*,5*S*,6*R*)-2,4-(*S*)-(Ethylidenedioxy)-6-[(*p*-methoxybenzyl)oxy]-3,5-dimethylheptanal (60).** To a stirred solution of the *p*-methoxybenzyl ether prepared above (72.4 mg, 208 $\mu$mol) and *N*-methylmorpholine *N*-oxide (51.4 mg, 424 $\mu$mol) in *tert*-butyl alcohol/THF/water (2 mL; 10:3:1) at room temperature was added an aqueous solution of osmium tetraoxide (31.0 $\mu$L, 3.10 $\mu$mol; ~0.1 M), whereupon a pale yellow solution resulted. After stirring for 15 h, pH 7 buffer solution (2 mL) and solid sodium periodate (222 mg, 1.04 mmol) were added, resulting in fast precipitation of a white solid. Vigorous stirring was continued for a further 25 min, and then sodium sulfite solution (6 mL; saturated, aqueous) was added. After 5 min the mixture was partitioned between sodium sulfite solution (50 mL; saturated, aqueous) and hexanes (50 mL), the layers were separated, and the aqueous phase was extracted with hexanes (4 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (30% diethyl ether/hexanes) afforded 63.6 mg (91%) of the desired aldehyde **60** as a colorless oil: $[\alpha]^{20}_{D} = -118.5°$ (*c* 3.2, $CHCl_3$); TLC (30% diethyl ether/hexanes) $R_f = 0.15$; IR ($CHCl_3$ solution) 1730 (s); $cm^{-1}$ $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.85 (1H, s, $CHO$), 7.16 (2H, d, $J$ = 8.5 Hz, Ar$H$), 6.84 (2H, d, $J$ = 8.5 Hz, Ar$H$), 4.49 (1H, d, $J$ = 12.0 Hz, one of Ar$CH_2O$), 4.45 (1H, q, $J$ = 5.0 Hz, $H_3CCHO_2$), 4.17 (1H, d, $J$ = 12.0 Hz, one of Ar$CH_2O$), 4.02 (1H, br s, $H_3CCH{=}CHCHOCHCH_3$), 3.80 (1H, qd, $J$ = 6.4, 1.8 Hz, $H_3CCHO$(PMB)), 3.79 (3H, s, Ar$OCH_3$), 3.28 (1H, dd, $J$ = 10.1, 2.1 Hz, $H_3CCHOCH(CHCH_3)_2$), 2.20−2.10 (1H, m, $H_3CCH(CHOCHCH_3)_2$), 1.40 (1H, dqd, $J$ = 10.1, 7.0, 1.8 Hz, $H_3CCHCHO$(PMB)), 1.19 (3H, d, $J$ = 5.0 Hz, $H_3CCHO_2$), 1.12 (3H, d, $J$ = 6.4 Hz, $H_3CCHO$(PMB)), 1.09 (3H, d, $J$ = 7.0 Hz, $CH_3$), 0.78 (3H, d, $J$ = 7.0 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 204.0, 159.0, 131.2, 129.6, 113.5, 96.9, 85.0, 76.7, 70.0, 69.8, 55.2, 40.1, 28.9, 21.0, 16.8, 11.2, 7.0; HRMS (CI, $NH_3$) calcd for $C_{19}H_{32}NO_5$ ($[M + NH_4]^+$) 354.2280, found 354.2280; *m/z* 354 (15, $[M + NH_4]^+$), 337 (85, $[M + H]^+$), 309 (50), 295 (20), 280 (95%), 263 (100), 121 (100).

**(2*S*,4*R*,5*R*)-1-(Benzyloxy)-5-hydroxy-2,4,6-trimethyl-6-hepten-3-one (6 (*SS*)).** Anhydrous tin(II) chloride (1.23 g, 6.49 mmol) was placed in a tared flask under argon by means of a glovebag and weighed accurately. Triflic acid (10.0 mL) was added and the mixture heated to 80−85 °C for 24 h. The resulting precipitate of $Sn(OTf)_2$ was filtered under argon, washed with dry diethyl ether (10 × 10 mL), and then dried *in vacuo* (~0.1 mmHg) for 12 h, yielding a white solid (~1.5 g, 80%).

$Sn(OTf)_2$ (734 mg, 1.76 mmol) was placed in a tared flask under argon by means of a glovebag and weighed accurately. $CH_2Cl_2$ (15 mL) was added and the resulting suspension stirred at room temperature while triethylamine (300 $\mu$L, 2.15 mmol) was added, whereupon a pale yellow color developed. The mixture was cooled immediately to −78 °C and a solution of ketone (*S*)-**8** (277 mg, 1.34 mmol) in dry $CH_2Cl_2$ (2 mL + 1 mL washings) added *via* cannula. After 2 h of enolization at −78 °C, a solution of freshly distilled methacrolein (250 $\mu$L, 3.00 mmol) in dry $CH_2Cl_2$ (2 mL) was added *via* cannula and the reaction mixture stirred for a further 1 h, before being quenched by pouring into pH 7 buffer solution (125 mL) and extracted with $CH_2Cl_2$ (4 × 100 mL). The combined organic extracts were washed with pH 7 buffer solution (2 × 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (15% diethyl ether/$CH_2Cl_2$) followed by HPLC (33% diethyl ether/hexanes) afforded 310 mg of the desired *syn–syn* aldol product **6** (*SS*), 21.4 mg of the *syn–anti* aldol product **6** (*SA*), and 5.3 mg of an *anti* aldol diastereomer, as colorless oils in a total yield of 90%. The major diastereomer **6** (*SS*) and minor diastereomer **6** (*SA*) had spectral data identical to those of material prepared by the (+)-$(Ipc)_2BOTf$-mediated aldol reaction of ketone (*S*)-**8** and methacrolein (*vide supra*).

**(2*S*,3*R*,4*S*,5*R*,6*R*)-*O*-Benzyl-3,5-(isopropylidenedioxy)-2,4,6-trimethyl-7-(phenylthio)heptan-1-ol.** To a stirred solution of thiophenol (0.16 mL, 1.56 mmol) in THF (2 mL) at room temperature was added dropwise *n*-butyllithium solution (0.93 mL, 1.35 mmol; 1.45 M in hexanes) to give a colorless solution of lithium thiophenolate which was used immediately (total volume 3.0 mL; ~0.45 M).

To a stirred solution of *p*-toluenesulfonate **34** (131 mg, 0.27 mmol) in dry THF (3 mL), at room temperature in a flask equipped with a reflux condenser, was added *via* cannula THF solution of lithium thiophenolate (3.00 mL, 1.35 mmol; ~0.45 M). The colorless reaction mixture was heated under reflux for 3.5 h and then partitioned between sodium hydroxide solution (50 mL; 10% aqueous) and diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (gradient elution: 0–3% diethyl ether/$CH_2Cl_2$) provided 114 mg (99%) of the desired sulfide as a colorless oil: $[\alpha]^{20}_D = -13.9°$ (*c* 5.6, $CHCl_3$); TLC (3% diethyl ether/$CH_2Cl_2$) $R_f = 0.55$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.25 (9H, m, $OCH_2ArH$ and SAr*H* *o-H* and *m-H*), 7.15–7.10 (1H, m, SAr*H* *p-H*), 4.54 (1H, d, *J* = 12.2 Hz, one of $CH_2Ph$), 4.45 (1H, d, *J* = 12.2 Hz, one of $CH_2Ph$), 3.65 (1H, dd, *J* = 9.6, 1.9 Hz, $CHOC(CH_3)_2$), 3.59 (1H, dd, *J* = 9.9, 2.0 Hz, $CHOC(CH_3)_2$), 3.42 (1H, dd, *J* = 12.8, 2.6 Hz, one of $CH_2SPh$), 3.36 (2H, d, *J* = 4.65 Hz, $CH_2OBn$), 2.72 (1H, dd *J* = 12.8, 8.3 Hz, one of $CH_2SPh$), 2.00–1.85 (2H, m, 2 × $CHCH_3$), 1.57 (1H, qdd *J* = 6.8, 2.0, 1.9 Hz, $H_3CCH(CHOC(CH_3)_2)_2$), 1.42 (3H, s, $H_3CCCH_3$), 1.38 (3H, s, $H_3CCCH_3$), 1.07 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.93 (3H, d, *J* = 6.8 Hz, $CH_3$), 0.82 (3H, d, *J* = 6.7 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 138.4, 137.9, 128.7, 128.3, 127.8, 127.5 (two C), 125.0, 99.0, 76.3, 76.0, 73.1, 71.5, 37.0, 35.0, 34.9, 31.1, 29.9, 19.6, 14.8, 14.0, 5.0; HRMS (CI, $NH_3$) calcd for $C_{26}H_{36}O_3S$ ($M^+$) 428.2385, found 428.2385; *m/z* 429 ($[M + H]^+$, 13), 428 (27, $M^+$), 371 (100), 353 (52), 263 (59), 91 (25).

**(*SRS*,2*S*,3*R*,4*S*,5*R*,6*R*)-*O*-Benzyl-3,5-(isopropylidenedioxy)-2,4,6-trimethyl-7-(phenylsulfinyl)heptan-1-ol (64).** To a stirred solution of the sulfide prepared above (359 mg, 0.84 mmol) in methanol (12 mL) at room temperature were added sodium periodate (213 mg, 1.00 mmol) and distilled water (1.5 mL), and the reaction mixture was left stirring for 24 h. It was then partitioned between $CH_2Cl_2$ (3 × 100 mL) and distilled water (100 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Elution with diethyl ether through a short column of silica gel gave 362 mg (97%) of two diastereomeric sulfoxides **64** in a 2:3 ratio, as a colorless viscous oil. HPLC (80% diethyl ether/$CH_2Cl_2$) provided a sample of each diastereomer for analysis, but in general, the unseparated mixture was used in synthetic reactions. Data for the major epimer: TLC (diethyl ether) $R_f = 0.40$; HPLC (80% diethyl ether/$CH_2Cl_2$) $R_t = 28.0$ min; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (2H, dd, m, S(O)Ar*H* *o-H*), 7.51–7.45 (3H, m, S(O)Ar*H* *m-H* and *p-H*), 7.35–7.25 (5H, m, $OCH_2ArH$), 4.49 (1H, d, *J* = 12.2 Hz, one of $CH_2Ph$), 4.41 (1H, d, *J* = 12.2 Hz, one of $CH_2Ph$), 3.58 (1H, dd, *J* = 9.6, 2.0 Hz, $CHOC(CH_3)_2$), 3.48 (1H, dd, *J* = 9.9, 2.1 Hz, $CHOC(CH_3)_2$), 3.32 (2H, d, *J* = 4.6 Hz, $CH_2OBn$), 2.96 (1H, dd, *J* = 13.2, 4.6 Hz, one of $CH_2S(O)Ph$), 2.06 (1H, dd, *J* = 13.2, 7.4 Hz, one of $CH_2S(O)Ph$), 2.15 (1H, m, $H_3CCHCH_2S(O)Ph$), 1.85 (1H, dqt, *J* = 9.6, 6.7, 4.6 Hz, $H_3CCHCH_2OBn$), 1.56 (1H, qdd, J = 6.8, 2.1, 2.0 Hz, $H_3CCH(CHOC(CH_3)_2)_2$), 1.34 (3H, s, $H_3CCCH_3$), 1.33 (3H, s, $H_3CCCH_3$), 1.02 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.01 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.78 (3H, d, *J* = 6.8 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 145.3, 138.4, 130.8, 129.2, 128.3, 127.5 (two C), 124.0, 99.1, 77.3, 75.9, 73.2, 71.4, 63.0, 34.9, 32.1, 30.7, 29.9, 19.7, 15.0, 14.8, 4.8; HRMS (CI, $NH_3$) calcd for $C_{26}H_{37}O_4S$ ($[M + H]^+$) 445.2413, found 445.2413; *m/z* 445 (100, $[M + H]^+$), 387 (60), 217 (93), 108 (37), 91 (48). Data for the minor epimer: TLC (diethyl ether) $R_f = 0.35$; HPLC (80% diethyl ether/$CH_2Cl_2$) $R_t = 36.0$ min; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67–7.64 (2H, m, S(O)Ar*H* *o-H*), 7.52–7.46 (3H, m, S(O)Ar*H* *m-H* and *p-H*), 7.35–7.25 (5H, m, $OCH_2ArH$), 4.50 (1H, d, *J* = 12.2 Hz, one of $CH_2Ph$), 4.42 (1H, d, *J* = 12.2 Hz, one of $CH_2Ph$), 3.61 (1H, dd, *J* = 9.6, 1.9 Hz, $CHOC(CH_3)_2$), 3.58 (1H, dd, *J* = 9.9, 2.1 Hz, $CHOC(CH_3)_2$), 3.33 (2H, m, $CH_2OBn$), 3.14 (1H, dd, *J* = 13.0, 4.4 Hz, one of $CH_2S(O)Ph$), 2.48 (1H, dd, *J* = 13.0, 8.0 Hz, one of $CH_2S(O)Ph$), 2.07 (1H, m, $H_3CCHCH_2S(O)Ph$), 1.86 (1H, dqt, *J* = 9.6, 6.7, 4.9 Hz, $H_3CCHCH_2OBn$), 1.56 (1H, qdd, J = 6.8, 2.1, 1.9 Hz, $H_3CCH(CHOC(CH_3)_2)_2$), 1.36 (3H, s, $H_3CCCH_3$), 1.35 (3H, s, $H_3CCCH_3$), 1.03 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.01 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.77 (3H, d, *J* = 6.8 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 144.6, 138.4, 130.7, 129.1, 128.3, 127.5 (2C), 124.2, 99.1, 76.8, 75.9, 73.2, 71.4, 63.3, 35.0, 31.1, 30.9, 29.9, 19.6, 14.7 (2C), 5.0.

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*RS*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-(*S*)-(Ethylidenedioxy)-8-hydroxy-3,5-(isopropylidenedioxy)-13-[(*p*-methoxybenzyl)oxy]-2,4,6,10,12-pentamethyltetradecan-1-ol (66).** To a cooled (−20 °C) stirred solution of diethylamine (89.0 μL, 0.86 mmol) in THF (2 mL) was added dropwise *n*-butyllithium solution (0.54 mL, 0.84 mmol; 1.56 M in hexanes). The resulting colorless solution was stirred at this temperature for 15 min, before being cooled to −78 °C. A solution of sulfoxide **64** (350 mg, 0.79 mmol) in THF (5 mL) was then added dropwise *via* cannula and the mixture stirred at this temperature for 15 min before dropwise addition *via* cannula of a solution of aldehyde **60** (170 mg, 0.51 mmol) in THF (4 mL + 2 mL washings). After 30 min the reaction mixture was quenched by addition of ammonium chloride solution (30 mL; saturated, aqueous) and allowed to warm to room temperature before being extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (gradient elution: 20–50% EtOAc/hexanes) followed by HPLC (40% EtOAc/hexanes) provided 412 mg of the crude product **65** as a mixture of stereoisomers and 100 mg of recovered sulfoxides **64**.

To a vigorously stirred solution of the mixture of adducts prepared above in diethyl ether (30 mL) under an argon atmosphere at room temperature was added a slurry of W-2 Raney nickel in ethanol (approximately 3 g of catalyst).[82] The mixture was stirred at room temperature for 3 h before removal of the Raney nickel by elution through a short column of Celite with ethanol, taking care that the Raney nickel was not allowed to become dry, and the solvent removed *in vacuo* to give a yellow oil. The oil was then dissolved in ethanol (30 mL), fresh Raney nickel (approximately 3 g of catalyst) added, and the mixture stirred vigorously under a hydrogen atmosphere overnight. The Raney nickel was then removed by elution through a short column of Celite with ethanol, again taking care that the Raney nickel was not allowed to become dry, and the solvent removed *in vacuo*. Flash chromatography (50% EtOAc/hexanes) provided 171 mg (60% over three steps from **60**) of the desired epimeric diols **66**. HPLC (60% EtOAc/hexanes) of an analytical sample provided samples of the two $C_8$ epimers for characterization. Data for the major epimer: $[\alpha]^{20}_D = -30.1°$ (*c* 2.2, $CHCl_3$); TLC (50% EtOAc/hexanes) $R_f = 0.29$; IR (thin film) 3420 (br) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (2H, *J* = 8.6 Hz, Ar*H*), 6.83 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.52 (1H, d, *J* = 12.0 Hz, one of $CH_2Ar$), 4.37 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 4.24 (1H, d, *J* = 12.0 Hz, one of $CH_2Ar$), 3.99 (1H, m, $C_8H$), 3.89 (1H, qd, *J* = 6.4, 1.6 Hz, $C_{13}H$), 3.77 (3H, s, $ArOCH_3$), 3.73 (1H, dd, *J* = 10.1, 2.0 Hz, $C_{11}H$), 3.64 (1H, dd, *J* = 9.4, 1.7 Hz, $C_5H$)), 3.60 (1H, dd, *J* = 10.8, 3.9 Hz, one of $C_1H$), 3.53 (1H, dd, *J* =10.7, 5.2 Hz, one of $C_1H$), 3.44 (1H, dd, *J* = 9.6, 1.7 Hz, $C_3H$), 3.18 (1H, d, *J* = 9.7 Hz, $C_9H$), 2.00 (1H, qd, *J* = 7.1, 1.3 Hz, $C_{11}H$), 1.84–1.72 (2H, m, $C_2H$, $C_6H$), 1.68 (1H, m, $C_4H$), 1.41 (3H, s, $H_3CCCH_3$), 1.40 (3H, s, $H_3CCCH_3$), 1.13 (3H, d, *J* = 6.4 Hz, $C_{14}H$), 1.08 (3H, d, *J* = 5.0 Hz, $CH_3CHO_2$), 1.05 (3H, d, *J* = 7.0 Hz, $C_{10}CH_3$), 1.01 (3H, d, *J* = 7.6 Hz, $C_2CH_3$), 0.93 (3H, d, *J* = 6.8 Hz, $C_6CH_3$), 0.89 (3H, d, *J* = 6.7 Hz, $C_4CH_3$), 0.79 (3H, d, *J* = 7.0 Hz, $C_{12}CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 159.0, 131.6, 129.6, 113.5, 99.5, 93.6, 83.6, 79.4, 75.6, 74.8, 70.6, 70.3, 67.4, 64.0, 55.2, 40.3, 40.2, 36.6, 33.0, 31.5, 29.8, 27.3, 21.5, 19.6, 17.4, 17.1, 14.0, 12.8, 7.2, 5.1; HRMS (CI, $NH_3$) calcd for $C_{32}H_{51}O_9$ ($[M + H]^+$) 567.3897, found 567.3900; *m/z* 567 (5, $[M + H]^+$), 509 (10), 383 (10), 309 (10), 241 (25), 183 (15), 121 (100). Data for the minor epimer: $[\alpha]^{20}_D = -10.6°$ (*c* 2.0, $CHCl_3$); TLC (50% EtOAc/hexanes) $R_f = 0.25$; IR (thin film) 3415 (br) $cm^{-1}$; $^1H$ NMR (400 MHz,

$CDCl_3$) δ 7.20 (2H, *J* = 8.6 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.66 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 4.50 (1H, d, *J* = 11.9 Hz, one of $CH_2Ar$), 4.24 (1H, d, *J* = 11.9 Hz, one of $CH_2Ar$), 4.18 (1H, ddd, *J* = 9.7, 7.9, 3.5 Hz, $C_8H$), 3.88 (1H, qd, *J* = 6.4, 1.7 Hz, $C_{13}H$), 3.78 (3H, s, $ArOCH_3$), 3.63 (1H, dd, *J* = 8.6, 2.0 Hz, $C_{11}H$), 3.61 (1H, dd, *J* = 8.0, 1.9 Hz, $C_5H$)), 3.59 (1H, dd, *J* = 10.8, 1.9 Hz, one of $C_1H$), 3.51 (1H, dd, *J* =10.8, 5.3 Hz, one of $C_1H$), 3.44 (1H, dd, *J* = 9.7, 1.8 Hz, $C_3H$), 3.29 (1H, d, *J* = 9.6 Hz, $C_9H$), 2.80 (1H, br s, O*H*), 1.78 (1H, m, $C_{11}H$), 1.62−1.58 (2H, m, $C_2H$ and $C_6H$), 1.44 (1H, m, $C_4H$), 1.35 (3H, s, $H_3CCCH_3$), 1.34 (3H, s, $H_3CCCH_3$), 1.15 (3H, d, *J* = 5.0 Hz, $CH_3CHO_2$), 1.12 (3H, d, *J* = 6.4 Hz, $C_{14}H$), 1.06 (3H, d, *J* = 6.9 Hz, $C_{10}CH_3$), 1.00 (3H, d, *J* = 6.7 Hz, $C_2CH_3$), 0.90 (3H, d, *J* = 6.9 Hz, $C_6CH_3$), 0.86 (3H, d, *J* = 6.8 Hz, $C_4CH_3$), 0.77 (3H, d, *J* = 7.0 Hz, $C_{12}CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 159.1, 131.4, 129.4, 113.6, 98.9, 93.4, 84.2, 78.8, 75.7, 75.2, 70.2, 67.0, 64.1, 55.3, 40.1, 39.4, 36.7, 31.8, 30.0, 28.4, 21.2, 19.6, 17.0, 16.5, 14.0, 12.9, 7.2, 5.1; HRMS (CI, $NH_3$) calcd for $C_{32}H_{51}O_9$ ($[M + H]^+$) 567.3897, found 567.3900; *m/z* 567 (5, $[M + H]^+$), 241 (15), 183 (10), 121 (100).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-(*S*)-(Ethylidenedioxy)-3,5-(isopropylidenedioxy)-13-[(*p*-methoxybenzyl)oxy]-2,4,6,10,12-pentamethyl-8-oxotetradecanoic Acid (67).** To a cooled (−78 °C) stirred solution of oxalyl chloride (0.48 mL, 0.96 mmol; 2.0 M in $CH_2Cl_2$) in $CH_2Cl_2$ (10 mL) was added dropwise DMSO (137 μL, 1.93 mmol), and the mixture was stirred for 10 min to ensure complete formation of the chlorosulfur complex. A solution of the mixture of diols **66** (109 mg, 0.19 mmol) in $CH_2Cl_2$ (6 mL + 3 mL washings) was then added *via* cannula and the reaction mixture stirred for a further 1 h at −78 °C. Triethylamine (0.40 mL, 2.89 mmol) was added at −78 °C and the reaction mixture allowed to warm *to −23 °C only* until no starting material was evident by TLC (*ca.* 45 min). The reaction was quenched by addition of ammonium chloride solution (25 mL; saturated, aqueous) and allowed to warm to room temperature before extracting with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was triturated with pentane (3 × 10 mL) and then filtered through Celite to remove the solid residue ($Et_3NH^+Cl^-$); concentration of the filtrate *in vacuo* then gave the desired ketoaldehyde (TLC (50% EtOAc/hexanes) $R_f$ = 0.65). This was used immediately in the next reaction.

To a stirred solution of the ketoaldehyde from the above Swern reaction in *tert*-butyl alcohol (9 mL) at room temperature was added 2-methyl-2-butene (170 μL). A solution of sodium chlorite (254 mg, 2.79 mmol) and sodium dihydrogen orthophosphate (339 mg, 2.20 mmol) in distilled water (9 mL) was added dropwise over 2 min. The reaction mixture was stirred for 30 min before diluting with brine (50 mL; saturated) and extracting with diethyl ether (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (1% AcOH/15% diethyl ether/$CH_2Cl_2$) followed by azeotropic removal of acetic acid with toluene on a rotary evaporator afforded 106 mg (96% over two steps) of the desired acid **67** as a viscous oil: $[\alpha]^{20}_D = -38.6°$ (*c* 2.2, $CHCl_3$); TLC (1% AcOH/30% diethyl ether/$CH_2Cl_2$) $R_f$ = 0.50; IR ($CHCl_3$ solution) 1745 (s), 1712 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.82 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.48 (1H, d, *J* = 11.9 Hz, one of $CH_2Ar$), 4.29 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 4.19 (1H, d, *J* = 11.9 Hz, one of $CH_2Ar$), 4.00 (1H, d, *J* = 1.0 Hz, $C_9H$), 3.84 (1H, dd, *J* = 9.6, 2.0 Hz, α to O), 3.81 (1H, qd, *J* = 6.4, 1.8 Hz, $C_{13}H$), 3.78 (3H, s, $ArOCH_3$), 3.44 (1H, dd, *J* = 10.0, 2.0 Hz, α to O), 3.37 (1H, dd, *J* = 10.2, 2.1 Hz, α to O), 2.86 (1H, dd, *J* = 16.3, 5.3 Hz, one of $C_7H_2$), 2.66 (1H, dq, *J* = 9.6, 6.9 Hz, $C_2H$), 2.30−2.20 (2H, m, 2 × $CHCH_3$), 2.08 (1H, dd, *J* = 16.3, 7.0 Hz, one of $C_7H_2$), 1.65 (1H, qt, *J* = 6.9. 2.1 Hz, $CHCH_3$), 1.45−1.35 (1H, m, $CHCH_3$), 1.37 (3H, s, $H_3CCCH_3$), 1.31 (3H, s, $H_3CCCH_3$), 1.25 (3H, d, *J* = 7.1 Hz, $CH_3$), 1.16 (3H, d, *J* = 5.0 Hz, $H_3CCHO_2$), 1.12 (3H, *J* = 6.4 Hz, $CH_3$), 1.06 (3H, d, *J* = 7.1 Hz, $CH_3$), 0.88 (3H, d, *J* = 7.0 Hz, $CH_3$), 0.86 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.81 (3H, d, *J* = 7.0 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 210.5, 179.2, 158.9, 131.3, 129.5, 113.5, 99.3, 96.5, 85.1, 77.3, 76.5, 74.8, 70.1, 70.0, 55.2, 43.2, 41.8, 40.1, 31.2 (2C), 27.9, 21.0, 19.5, 16.9, 15.5, 14.8, 14.1, 11.5, 7.1, 4.9; HRMS (FAB, NOBA) calcd for $C_{32}H_{51}O_9$ ($[M + H]^+$ 579.3478, found 579.3490; *m/z* 579 (8, $[M + H]^+$), 339 (15), 269 (13), 237 (25), 171 (25), 149 (80), 125 (80), 109 (100).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-(*S*)-(Ethylidenedioxy)-13-hydroxy-3,5-(isopropylidenedioxy)-2,4,6,10,12-pentamethyl-8-oxotetradecanoic Acid (68).** To a solution of acid **67** (106 mg, 183 μmol) in ethanol (25 mL) under an argon atmosphere was added palladium on activated charcoal (approximately 50 mg, 10% Pd content). The reaction mixture was stirred while hydrogen (from a hydrogen-filled double balloon) replaced the argon. After stirring for 18 h, the catalyst was removed by elution with ethanol through a short column of Celite. Concentration *in vacuo* afforded the crude product as a yellow oil. Flash chromatography (1% AcOH/25% diethyl ether/$CH_2Cl_2$) afforded 80.6 mg (97%) of the desired seco-acid **68** as a colorless oil: $[\alpha]^{20}_D = -15.8°$ (*c* 0.9, $CHCl_3$); TLC (1% AcOH/30% diethyl ether/$CH_2Cl_2$) $R_f$ = 0.20; IR ($CHCl_3$ solution) 1743 (m), 1710 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.70 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 4.06 (1H, br s, $C_9H$), 3.89 (1H, qd, *J* = 6.6, 2.2 Hz, $C_{13}H$), 3.86 (1H, dd, *J* = 9.5, 2.0 Hz, α to O), 3.59 (1H, dd, *J* = 10.4, 2.0 Hz, α to O), 3.47 (1H, dd, *J* = 9.8, 2.0 Hz, α to O), 2.88 (1H, dd, *J* = 16.3, 5.4 Hz, one of $C_7H_2$), 2.66 (1H, dq, *J* = 9.5, 7.1 Hz, $C_2H$), 2.30−2.20 (2H, m, 2 × $CHCH_3$), 2.16 (1H, dd, *J* = 16.3, 6.7 Hz, one of $C_7H_2$), 1.90−1.80 (1H, m, $CHCH_3$), 1.70−1.60 (1H, m, $CHCH_3$), 1.38 (3H, s, $H_3CCCH_3$), 1.35 (3H, d, *J* = 5.0 Hz, $H_3CCHO_2$), 1.31 (3H, s, $H_3CCCH_3$), 1.24 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.14 (3H, *J* = 7.1 Hz, $CH_3$), 1.11 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.87 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.85 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.76 (3H, d, *J* = 7.1 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 210.6, 178.8, 99.3, 96.4, 84.9, 78.0, 77.3, 74.8, 69.7, 43.3, 41.9, 39.0, 31.3, 31.1, 29.7, 27.7, 21.3, 19.5, 18.7, 15.5, 14.8, 11.7, 10.5, 4.9; HRMS (CI, $NH_3$) calcd for $C_{24}H_{43}O_8$ ($[M + H]^+$) 459.2958, found 459.2958; *m/z* 459 (15, $[M + H]^+$), 441 (15), 415 (20), 401 (50), 383 (60), 357 (100), 339 (90), 321 (20), 171 (30), 125 (50).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-(*S*)-(Ethylidenedioxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-oxotetradecanolide (69).** To a stirred solution of seco-acid **68** (80.0 mg, 175 μmol) in THF (6 mL) at room temperature was added triethylamine (28.0 μL, 201 μmol) followed by 2,4,6-trichlorobenzoyl chloride (29.0 μL, 183 μmol). The reaction mixture was stirred for 2.5 h, during which time it became slightly cloudy. The mixture was then diluted with toluene to give a final volume of 40 mL.

To a heated (60 °C) solution of DMAP (172 mg, 1.40 mmol) in toluene (60 mL), in a flask equipped with a reflux condenser and septum inlet, was slowly added (over 2.5 h by syringe pump) the solution of the mixed anhydride prepared above. After addition, the reaction mixture was stirred for a further 30 min at 60 °C, before being cooled to room temperature and concentrated *in vacuo*. Flash chromatography (20% EtOAc/hexanes) afforded 59.4 mg (78%) of the desired macrolactone **69** as a colorless oil: $[\alpha]^{20}_D = -46.8°$ (*c* 2.7, $CHCl_3$); TLC (40% EtOAc/hexanes) $R_f$ = 0.50; IR ($CHCl_3$ solution) 1719 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.53 (1H, qd, *J* = 6.7, 1.0 Hz, $C_{13}H$), 4.95 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 4.34 (1H, br d, α to O), 4.15 (1H, br s, $C_9H$), 3.66 (1H, dd, *J* = 10.7, 1.5 Hz, α to O), 3.10 (1H, dd, *J* = 9.8, 1.6 Hz, α to O), 2.62 (1H, dq, *J* = 10.7, 6.6 Hz, $C_2H$), 2.70−2.60 (2H, m, $CHCH_3$, one of $C_7H_2$), 2.31 (1H, d, *J* = 16.7 Hz, one of $C_7H_2$), 2.25−2.15 (1H, m, $CHCH_3$), 1.55 (1H, dqd, *J* = 9.7, 7.2, 1.1 Hz, $CHCH_3$), 1.45 (3H, s, $H_3CCCH_3$), 1.41 (3H, s, $H_3CCCH_3$), 1.35 (3H, d, *J* = 5.0 Hz, $H_3CCHO_2$), 1.30−1.25 (1H, buried m, $CHCH_3$), 1.23 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.21 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.11 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.99 (3H, br d, *J* ≈ 8 Hz, $CH_3$), 0.97 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.89 (3H, d, *J* = 7.2 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 206.6, 174.7, 100.4, 97.0, 84.8, 77.2, 76.8, 71.4, 69.2, 41.7, 41.4, 39.9, 32.7, 32.2, 30.6, 20.9, 20.0, 18.3, 14.9, 14.1, 13.4, 11.5, 7.6, 7.2; HRMS (CI, $NH_3$) calcd for $C_{24}H_{41}O_7$ ($[M + H]^+$) 441.2852, found 441.2852; *m/z* 441 (5, $[M + H]^+$), 400 (21), 383 (100), 365 (15), 339 (42), 321 (15), 125 (10).

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-(*S*)-(Ethylidenedioxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-methylenetetradecanolide (74).** To a suspension of methyltriphenylphosphonium bromide (415 mg, 1.16 mmol) in toluene (2 mL) was added potassium hexamethyldisilazide solution (2.18 mL, 1.09 mmol; ~0.5 M in toluene), and the mixture was heated to 60 °C for 30 min to ensure complete ylide formation. After cooling to room temperature, a solution of ketone **69** (32.0 mg, 72.6 μmol) in toluene (1 mL + 0.5 mL washings) was added *via* cannula and the mixture again heated to reflux for 1 h. After cooling to room temperature, the reaction was quenched by addition of saturated ammonium chloride solution (15 mL) followed by extraction with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (10% EtOAc/hexanes) afforded 29.3 mg (92%) of the desired exocyclic alkene **74** as a colorless oil: $[\alpha]^{20}_D = -10.2°$ (*c* 1.3, $CHCl_3$); TLC (30% EtOAc/hexanes) $R_f = 0.57$; IR ($CHCl_3$ solution) 1718 (s), 1647 (w) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.56 (1H, qd, *J* = 6.7, 1.0 Hz, $C_{13}H$), 5.33 (1H, br s, one of $C{=}CH_2$), 5.17 (1H, br s, one of $C{=}CH_2$), 4.99 (1H, q, *J* = 5.1 Hz, $H_3CCHO_2$), 4.21 (1H, dd, *J* = 6.7, 1.7 Hz, α to O), 4.19 (1H, br s, $C_9H$), 3.63 (1H, dd, *J* = 10.7, 1.5 Hz, α to O), 3.23 (1H, dd, *J* = 9.9, 1.6 Hz, α to O), 2.65 (1H, dq, *J* = 10.7, 6.6 Hz, $C_2H$), 2.55−2.45 (1H, m, $CHCH_3$), 1.99 (1H, qt, *J* = 6.7, 1.4 Hz, $CHCH_3$), 1.95 (1H, m, one of $C_7H_2$), 1.84 (1H, dd, *J* = 18.2, 11.4 Hz, one of $C_7H_2$), 1.60−1.50 (2H, m, 2 × $CHCH_3$), 1.43 (3H, s, $H_3CCCH_3$), 1.42 (3H, s, $H_3CCCH_3$), 1.33 (3H, d, *J* = 5.1 Hz, $H_3CCHO_2$), 1.21 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.17 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.11 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.04 (3H, d, *J* = 7.2 Hz, $CH_3$), 0.99 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.87 (3H, d, *J* = 7.2 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 174.8, 141.7, 111.8, 100.3, 94.4, 81.1, 77.4, 75.6, 71.8, 69.4, 41.4, 40.0, 33.9, 32.0, 31.9, 29.7, 29.0, 20.9, 19.9, 18.5, 16.1, 13.3, 11.9, 7.6, 7.1; HRMS (CI, $NH_3$) calcd for $C_{25}H_{43}O_6$ ($[M + H]^+$) 439.3060, found 439.3060; *m/z* 439 (5, $[M + H]^+$), 381 (73), 339 (100), 337 (100), 319 (36), 149 (100).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*9*R*,10*R*,11*S*,12*S*,13*R*)-8,8-(Epoxymethano)-9,-11-(*S*)-(ethylidenedioxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyltetradecanolide (81).** To a solution of alkene **74** (10.0 mg, 22.8 μmol) in $CH_2Cl_2$ (1 mL) was added *m*-chloroperbenzoic acid (24.0 mg, 0.137 mmol; ~99% purity[81]), and the reaction mixture was stirred at room temperature for 18 h. A solution of sodium thiosulfate (0.50 g) in sodium bicarbonate solution (15 mL, saturated, aqueous) was then added and the mixture stirred at room temperature for 1 h. The mixture was then separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (20% EtOAc/hexanes) afforded 6.2 mg (60%) of the desired epoxide **81** as a colorless oil: $[\alpha]^{20}_D = -6.6°$ (*c* 2.1, $CHCl_3$); TLC (20% EtOAc/hexanes) $R_f = 0.39$; IR ($CHCl_3$ solution) 1727 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, q, *J* = 6.6, $C_{13}H$), 4.64 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 3.92 (2H, m, $C_9H$, $C_{11}H$), 3.64 (1H, d, *J* = 10.7 Hz, $C_3H$), 3.31 (1H, d, *J* = 10.0 Hz, $C_5H$), 2.96 (2H, ABq, *J* = 5.0 Hz, $C_8CH_2$), 2.69 (1H, dq, *J* = 10.7, 6.6 Hz, $C_2H$), 1.99 (1H, br q, *J* = 6.8 Hz, $C_4H$), 1.90−1.70 (4H, m, $C_7H_2$, $C_{10}H$, $C_{12}H$), 1.56 (1H, dq, *J* = 9.7, 7.2 Hz, $C_6H$), 1.41 (3H, s, $H_3CCCH_3$), 1.40 (3H, s, $H_3CCCH_3$), 1.28 (3H, d, *J* = 5.0 Hz, $H_3CCHO_2$), 1.22 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.13 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.12 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.00 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.94 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.91 (3H, d, *J* = 7.2 Hz, $CH_3$); NOE difference experiment (400 MHz, $CDCl_3$) irradiation at 4.64 gave enhancements at δ (%) 3.92 (1.1), 3.31 (7.4), 2.96 (8.1), 1.28 (9.5); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 174.8, 100.5, 96.5, 81.3, 77.4, 76.6, 74.1, 69.5, 57.4, 54.2, 41.4, 39.3, 33.3, 32.2, 30.5, 30.2, 29.6, 20.8, 19.8, 18.5, 16.4, 12.9, 12.0, 7.6, 7.2; HRMS (CI, $NH_3$) calcd for $C_{25}H_{43}O_6$ ($[M + H]^+$) 455.3009, found 455.3009; *m/z* 455 (5, $[M + H]^+$), 414 (15), 397 (50), 353 (100), 335 (20), 283 (15), 239 (15), 125 (20).

**Ozonolysis of Exocyclic Alkene 74.** Ozone was bubbled through a cooled (−78 °C) stirred solution of alkene **74** (124 mg, 0.28 mmol) in $CH_2Cl_2$ (10 mL) until the solution turned blue and no starting material was evident by TLC (*ca.* 15 min). Triphenylphosphine (297 mg, 1.31 mmol) was then added and the solution allowed to warm to room temperature before concentration *in vacuo;* flash chromatography (10% EtOAc/hexane) provided 60.0 mg of ketone **69** (48%) and 61.0 mg of epoxide **81** (48%). The spectroscopic data for **69** and **81** were identical to those recorded above.

**Acid Hydrolysis of Protected Exocyclic Alkene 74 To Give Tetrol 46.** To a solution of macrolide **74** (20.2 mg, 46.1 μmol) in THF (1.5 mL) was added hydrochloric acid (1 mL; 2 M aqueous), and the mixture was heated to 50 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of sodium bicarbonate solution (10 mL; saturated, aqueous) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (70% EtOAc/hexanes) afforded 16.1 mg (94%) of the desired tetrol **46** as a colorless oil. The spectroscopic data were identical to those recorded above.

**(2*R*,3*S*,4*R*,5*S*,6*S*,9*R*,10*R*,11*R*,12*R*,13*R*)-3,5-[(*p*-Bromobenzylidene)dioxy]-9,11-dihydroxy-2,4,6,10,12,13-hexamethyl-8-methylenetetradecanolide (79).** To a solution of tetrol **46** (300 mg, 0.81 mmol) and *p*-bromobenzaldehyde dimethyl acetal (0.42 mL, 2.42 mmol) in $CH_2Cl_2$ (8 mL) was added camphorsulfonic acid (*ca.* 5 mg), and the mixture was stirred at room temperature for 45 min. Addition of sodium bicarbonate solution (20 mL, saturated, aqueous) and extraction with $CH_2Cl_2$ (3 × 15 mL), followed by drying ($MgSO_4$) and concentration *in vacuo*, then gave the crude product. Flash chromatography (25% EtOAc/hexanes) afforded 387 mg (89%) of the desired product **79** as a colorless oil: $[\alpha]^{20}_D = +14.2°$ (*c* 1.3, $CHCl_3$); TLC (50% EtOAc/hexanes) $R_f = 0.25$; IR ($CHCl_3$ solution) 3420 (br), 1715 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.40 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.57 (1H, s, $O_2CHAr$), 5.49 (1H, br s, one of $C{=}CH_2$), 5.47 (1H, qd, *J* = 6.7, 1.0 Hz, $C_{13}H$), 5.12 (1H, br s, one of $C{=}CH_2$), 4.30 (1H, dd, *J* = 7.2, 1.1 Hz, $C_5H$), 4.02 (1H, br d, *J* = 5.8 Hz, $C_9H$), 3.64 (1H, dd, *J* = 10.8, 1.2 Hz, $C_3H$), 3.47 (1H, br d, *J* = 9.8 Hz, $C_{11}H$), 3.29 (1H, br d, *J* = 7.6 Hz, O*H*), 3.06 (1H, br d, *J* = 3.5 Hz, O*H*), 2.78 (1H, dq, *J* = 10.7, 6.7 Hz, $C_2H$), 2.70 (1H, m, $CHCH_3$), 2.08−1.85 (3H, m, $CHCH_3$, $C_7H_2$), 1.72 (1H, m, $CHCH_3$), 1.57 (1H, m, $CHCH_3$), 1.26 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.20 (3H, d, *J* = 6.5 Hz, $CH_3$), 1.13 (3H, d, *J* = 7.1 Hz, $CH_3$), 1.11 (3H, d, *J* = 7.5 Hz, $CH_3$), 1.10 (3H, d, *J* = 6.9 Hz, $CH_3$), 0.88 (3H, d, *J* = 7.1 Hz, $CH_3$), $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 175.1, 147.5, 137.6, 131.3, 127.9, 122.8, 109.2, 101.9, 84.6, 80.2, 79.0, 71.9, 69.8, 42.6, 41.5, 35.2, 34.6, 32.3, 18.7, 16.5, 13.2, 9.6, 6.8, 6.7; HRMS (CI, $NH_3$) calcd for $C_{27}H_{40}{}^{79}BrO_6$ ($[M + H]^+$) 539.2008, found 539.2010; *m/z* 541 (30), 439 (30, $[M + H]^+$), 523 (15), 521 (15), 372 (20), 355 (100), 339 (85), 319 (10), 241 (25), 199 (20).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,9*R*,10*R*,11*R*,12*R*,13*R*)-3,5-[(*p*-Bromobenzylidene)dioxy]-8,8-(epoxymethano)-9,11-dihydroxy-2,4,6,10,12,13-hexamethyltetradecanolide (80) and (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*R*,10*R*,-11*R*,12*R*,13*R*)-3,5-[(*p*-Bromobenzylidene)dioxy]-8,8-(epoxymethano)-9,11-dihydroxy-2,4,6,10,12,13-hexamethyltetradecanolide (8-*epi*-80).** To a stirred solution of alkene **79** (78.0 mg, 0.15 mmol) in carbon tetrachloride (3 mL) at room temperature was added *m*-CPBA (74.0 mg, 0.43 mmol; ~99% purity[81]), and the reaction mixture was stirred for 14 h. Dimethyl sulfide (0.5 mL, excess) was then added and the reaction stirred for a further 30 min followed by addition of sodium bicarbonate solution (15 mL; saturated, aqueous). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL), and the combined organic phases were dried and concentrated *in vacuo*. Flash chromatography (50% EtOAc/hexanes) followed by HPLC (50% EtOAc/hexanes) afforded 33 mg (41%) of the epoxide **80** and 33 mg (41%) of the epimeric epoxide 8-*epi*-**80**. Data for (8*S*)-epoxide **80**: $[\alpha]^{20}_D = +3.8°$ (*c* 1.1, $CHCl_3$); TLC (50% EtOAc/hexanes) $R_f = 0.38$; HPLC (50% EtOAc/hexanes) $R_t = 15.8$ min; IR ($CHCl_3$ solution) 3450 (br), 1710 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.38 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.57 (1H, qd, *J* = 6.5, 0.9 Hz, $C_{13}H$), 5.55 (1H, s, $O_2CHAr$), 4.04 (1H, d, *J* = 7.2 Hz, O*H*), 3.96 (1H, d, J = 10.2 Hz, α to O), 3.74 (1H, d, J =10.7 Hz, α to O), 3.72 (1H, dd, *J* = 10.0, 3.2 Hz, α to O), 3.61 (1H, d, *J* = 10.7 Hz, α to O), 3.23 (1H, br s, O*H*), 3.09 (1H, d, *J* = 5.1 Hz, one of $C_8CH_2$), 2.81 (1H, dq, *J* = 10.8, 6.6 Hz, $C_2H$), 2.67 (1H, d, *J* = 5.1 Hz, one of $C_8CH_2$), 2.19 (2H, m, 2 × $CHCH_3$), 2.00 (1H, br q, *J* = 6.5 Hz, $C_4H$), 1.89 (1H, dd, *J* = 15.5, 11.5 Hz, one of $C_7H_2$), 1.81 (1H, dd, *J* = 15.5, 3.6 Hz, $C_7H_2$), 1.62 (1H, dq, *J* = 10.1, 7.0 Hz, $C_{10}H$), 1.28 (3H, d, *J* = 6.8 Hz, $CH_3$), 1.23 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.10 (3H, d, *J* = 7.1 Hz, $CH_3$), 1.08 (3H, d, *J* = 6.8 Hz, $CH_3$), 1.03 (3H, d, *J* = 7.2 Hz, $CH_3$), 0.91 (3H, d, *J* = 7.1 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 176.0, 137.9, 131.5, 128.1, 122.9, 102.2, 84.8, 80.9, 74.7, 72.3, 69.7, 61.0, 43.4, 42.5, 42.1, 33.7, 32.3, 32.2, 29.8, 18.7, 16.2, 13.5, 9.8, 8.8; HRMS (CI, $NH_3$) calcd for $C_{27}H_{40}{}^{79}BrO_7$ ($[M + H]^+$) 555.1957, found 555.1960; *m/z* 557 (10, $[M + H]^+$), 555 (10, $[M + H]^+$), 539 (10), 537 (10), 371 (40), 353 (100), 335 (40), 239 (30), 125 (80). Data for (8*R*)-epoxide 8-*epi*-**80**: $[\alpha]^{20}_D = +14.3°$ (*c* 1.4, $CHCl_3$); TLC (50% EtOAc/hexanes) $R_f = 0.34$; HPLC (50% EtOAc/hexanes) $R_t = 18.3$ min; IR ($CHCl_3$ solution) 3380 (br), 1725 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.36 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.53 (1H, q, *J* = 6.5 Hz, $C_{13}H$), 5.52 (1H, s, $O_2CHAr$), 3.99 (1H, d, *J* = 8.0 Hz, $C_5H$), 3.86

(1H, d, *J* = 2.6 Hz, $C_9H$), 3.65 (1H, d, *J* = 10.6 Hz, $C_3H$), 3.65 (1H, d, *J* = 8.9 Hz, $C_{11}H$), 3.18 (1H, d, *J* = 3.2 Hz, one of $C_8CH_2$), 3.17 (1H, br s, O*H*), 2.92 (1H, d, *J* = 3.2 Hz, one of $C_8CH_2$), 2.80 (1H, dq, *J* = 10.6, 6.6 Hz, $C_2H$), 2.58 (1H, br s, O*H*), 2.27 (1H, m, $C_6H$), 2.05–1.95 (2H, m, one of $C_7H_2$, $C_{12}H$), 1.87 (1H, br q, *J* = 6.5 Hz, $C_4H$), 1.82 (1H, br d, *J* = 16.2 Hz, one of $C_7H_2$), 1.57 (1H, dq, *J* = 8.9, 7.2 Hz, $C_{10}H$), 1.26 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.21 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.14 (3H, d, *J* = 6.9 Hz, $CH_3$), 1.12 (3H, d, *J* = 7.8 Hz, $CH_3$), 1.05 (3H, d, *J* = 7.4 Hz, $CH_3$), 0.93 (3H, d, *J* = 7.2 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 173.8, 137.3, 131.2, 127.8, 122.8, 101.7, 84.2, 81.6, 76.5, 72.1, 70.8, 59.9, 48.9, 42.5, 41.3, 34.4, 32.6, 32.4, 29.2, 18.0, 16.9, 12.9, 9.7, 8.7; HRMS (CI, $NH_3$) calcd for $C_{27}H_{40}{}^{79}BrO_7$ ([M + H]$^+$) 555.1957, found 555.1960; *m/z* 557 (10, [M + H]$^+$), 555 (10, [M + H]$^+$), 539 (5), 537 (5), 371 (30), 353 (100), 335 (25), 257 (20), 239 (15), 125 (45).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,10*R*,11*R*,12*R*,13*R*)-3,5-[(*p*-Bromobenzylidene)dioxy]-8,8-(epoxymethano)-9,11-dihydroxy-2,4,6,10,12,13-hexamethyltetradecanolide (82).** To a stirred solution of the allylic alcohol **79** (31.0 mg, 57.5 μmol) in $CH_2Cl_2$ (2 mL) at room temperature was added freshly prepared activated manganese dioxide (200 mg, excess),[83] and the mixture was stirred for 18 h before filtering through Celite and concentrating *in vacuo*. Flash chromatography (30% EtOAc/hexanes) afforded 28 mg (78%) of the desired enone **82** as a colorless oil: TLC (50% EtOAc/hexanes) $R_f$ = 0.40; $^1H$ NMR (250 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.39 (2H, d, *J* = 8.5 Hz, Ar*H*), 5.97 (1H, br s, one of $C_8CH_2$), 5.63 (1H, qd, *J* = 6.6, 1.0 Hz, $C_{13}H$), 5.55 (1H, s, $ArCHO_2$), 5.38 (1H, br s, one of $C_8CH_2$), 4.07 (1H, dd, *J* = 6.4, 1.0 Hz, $C_5H$), 3.65 (1H, dd, *J* = 10.8, 0.9 Hz, $C_3H$), 3.64 (1H, m, $C_{11}H$), 3.18 (1H, br q, *J* = 6.7 Hz, $C_{10}H$), 2.84 (1H, dq, *J* = 10.8, 6.6 Hz, $C_2H$), 2.68 (1H, m, $C_6H$), 2.38 (2H, m, $C_7H_2$), 1.83 (1H, m, $C_{12}H$), 1.67 (1H, m, $C_4H$), 1.30 (3H, *J* = 6.6 Hz, $CH_3$), 1.25–1.15 (9H, m, 3 × $CH_3$), 1.04 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.01 (3H, d, *J* = 7.1 Hz, $CH_3$).

**(2*R*,3*S*,4*R*,5*S*,6*S*,10*R*,11*S*,12*S*,13*R*)-11-Hydroxy-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyl-8-oxotetradecanolide (85).** To a solution of ketone **69** (20.0 mg, 45.4 μmol) and diiodomethane (24.3 mg, 90.8 μmol) in THF (2 mL) at room temperature was added samarium diiodide solution (1.13 mL, ~113 μmol; ~0.1 M in THF). After stirring for 2 min, the reaction mixture was quenched with ammonium chloride solution (10 mL; saturated, aqueous). Extraction with diethyl ether (3 × 10 mL), drying ($MgSO_4$), and concentration *in vacuo* gave the crude product. Flash chromatography (20% EtOAc/hexanes) afforded 16.3 mg (79%) of the product **85** as a colorless oil: TLC (20% EtOAc/hexanes) $R_f$ = 0.19; IR ($CHCl_3$ solution) 1715 (s) cm$^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.59 (1H, q, *J* = 6.5 Hz, $C_{13}H$), 4.34 (1H, d, *J* = 6.7 Hz, $C_5H$), 3.65 (1H, d, J = 10.7 Hz, $C_3H$), 3.04 (1H, d, *J* = 9.9 Hz, $C_{11}H$), 2.70–2.20 (7H, m, $C_2H$, $C_6H$, $C_7H_2$, $C_9H_2$, $C_{10}H$), 1.58 (1H, m, $C_{12}H$), 1.44 (3H, s, $H_3CCCH_3$), 1.41 (3H, s, $H_3CCCH_3$), 1.28 (1H, m, $C_4H$), 1.25 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.11 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.97 (3H, d, *J* = 7.3 Hz, $CH_3$), 0.96 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.91 (6H, d, *J* = 6.9 Hz, 2 × $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 210.2, 175.7, 100.5, 76.9, 71.9, 71.5, 70.2, 49.2, 44.4, 42.0, 41.5, 32.7, 31.1, 29.7, 20.0, 18.5, 14.9, 13.3, 12.1, 8.8, 7.6; HRMS (CI, $NH_3$) calcd for $C_{22}H_{42}NO_6$ ([M + $NH_4$]$^+$) 416.3012, found 416.3012; *m/z* 416 (25, [M + H]$^+$), 341 (70), 323 (100).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*R*,10*R*,11*S*,12*S*,13*R*)-8,8-(Epoxymethano)-9,11-(*S*)-(ethylidenedioxy)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyltetradecanolide (83).** In an argon-flushed flask, sodium hydride (100 mg, 60% dispersion in mineral oil) was washed with dry hexane (3 × 10 mL) and the supernatant removed *via* cannula. DMSO (5 mL) was then added and the mixture heated at 60 °C until gas evolution stopped (*ca.* 1 h), before cooling to room temperature. The dark solution of base was assumed to be 0.5 M in concentration.

To a solution of trimethylsulfonium iodide (28.0 mg, 0.14 mmol) in DMSO (0.5 mL) and THF (0.75 mL) at 0 °C was added an aliquot of the previously prepared base (0.27 mL, ~0.14 mmol), and the mixture was stirred for 5 min to complete ylide formation. A solution of ketone **69** (20 mg, 45.4 μmol) in THF (0.5 mL + 0.5 mL washings) was then added *via* cannula and the reaction mixture allowed to warm to room temperature over 1 h. Stirring was continued for a further 4 h, after which time the reaction mixture was quenched by addition of ammonium chloride solution (10 mL; saturated, aqueous) and extracted with diethyl ether (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (15% EtOAc/hexanes) afforded 17.1 mg (83%) of the desired epoxide **83** as a colorless oil: $[\alpha]^{20}_D$ = +3.9° (*c* 3.1, $CHCl_3$); TLC (20% EtOAc/hexanes) $R_f$ = 0.38; IR ($CHCl_3$ solution) 1728 (s) cm$^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.53 (1H, q, *J* = 6.6, $C_{13}H$), 5.50 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 4.23 (1H, d, *J* = 6.9 Hz, $C_{11}H$), 3.84 (1H, s, $C_9H$), 3.77 (1H, d, *J* = 10.7 Hz, $C_3H$), 3.66 (1H, d, *J* = 9.4 Hz, $C_5H$), 2.84 (1H, d, *J* = 5.3 Hz, one of $C_8CH_2$), 2.66 (1H, dq, *J* = 10.7, 6.6 Hz, $C_2H$), 2.64 (1H, d, *J* = 5.3 Hz, one of $C_8CH_2$), 2.11 (1H, q, *J* = 6.5 Hz, $C_4H$), 1.98 (1H, dd, *J* = 14.3, 12.3 Hz, one of $C_7H_2$), 1.91 (1H, m, $C_6H$), 1.75 (1H, dd, *J* = 14.3, 0.8 Hz, one of $C_7H_2$), 1.73 (1H, m, $C_{10}H$), 1.52 (1H, m, $C_{12}H$), 1.41 (3H, s, $H_3CCCH_3$), 1.40 (3H, s, $H_3CCCH_3$), 1.23 (3H, d, *J* = 6.7 Hz, $CH_3$), 1.19 (3H, d, *J* = 5.0 Hz, $H_3CCHO_2$), 1.16 (3H, d, *J* = 6.5 Hz, $CH_3$), 1.15 (3H, d, *J* = 6.5 Hz, $CH_3$), 1.02 (3H, d, *J* = 6.6 Hz, $CH_3$), 0.96 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.95 (3H, d, *J* = 7.3 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 174.8, 100.3, 97.1, 77.2, 76.8, 75.2, 73.1, 70.2, 59.5, 43.1, 41.6, 40.5, 32.6, 32.3, 31.3, 29.8, 29.0, 21.5, 20.1, 18.7, 16.0, 13.5, 12.1, 7.9, 7.4; HRMS (CI, $NH_3$) calcd for $C_{25}H_{43}O_6$ ([M + H]$^+$) 455.3009, found 455.3009; *m/z* 455 (10, [M + H]$^+$), 414 (20), 397 (100), 353 (100), 335 (32), 283 (15), 239 (25), 125 (15).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,9*R*,10*R*,11*S*,12*S*,13*R*)-9,11-(*S*)-(Ethylidenedioxy)-8-hydroxy-8-(iodomethyl)-3,5-(isopropylidenedioxy)-2,4,6,10,12,13-hexamethyltetradecanolide (84).** To a solution of epoxide **83** (19.0 mg, 41.8 μmol) in THF (0.5 mL) was added lithium iodide (18.0 mg, 133 μmol) followed by acetic acid (7.2 μL, 125.4 μmol). The mixture was then stirred at room temperature for 18 h before being partitioned between pH 7 buffer solution (10 mL) and diethyl ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give 21.2 mg (87%) of the desired iodohydrin **84** as a pale yellow oil: $[\alpha]^{20}_D$ = −2.5° (*c* 1.6, $CHCl_3$); TLC (40% EtOAc/hexanes) $R_f$ = 0.48; IR ($CHCl_3$ solution) 3486 (s) cm$^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.54 (1H, q, *J* = 5.0 Hz, $H_3CCHO_2$), 5.50 (1H, q, *J* = 6.6, $C_{13}H$), 4.38 (1H, d, *J* = 7.1 Hz, $C_{11}H$), 3.85 (1H, d, *J* = 8.1 Hz, $C_5H$), 3.83 (1H, br s, $C_9H$), 3.67 (1H, d, *J* = 10.7 Hz, $C_3H$), 3.46 (1H, d, *J* = 10.0 Hz, one of $C_8CH_2$), 3.36 (1H, d, *J* = 10.0 Hz, one of $C_8CH_2$), 2.68 (1H, dq, *J* = 10.0, 6.6 Hz, $C_2H$), 2.20 (1H, m, $C_6H$), 2.05 (1H, q, *J* = 6.7 Hz, $C_4H$), 1.97 (1H, dd, *J* = 15.1, 7.1 Hz, one of $C_7H_2$), 1.89 (1H, br q, *J* = 6.5 Hz, $C_{10}H$), 1.68 (1H, br d, *J* = 15.1 Hz, one of $C_7H_2$), 1.50 (1H, m, $C_{12}H$), 1.42 (3H, s, $H_3CCCH_3$), 1.41 (3H, s, $H_3CCCH_3$), 1.31 (3H, d, *J* = 5.0 Hz, $H_3CCHO_2$), 1.23 (3H, d, *J* = 6.6 Hz, $CH_3$), 1.13 (6H, d, *J* = 6.6 Hz, 2 × $CH_3$), 1.02 (3H, d, *J* = 7.4 Hz, $CH_3$), 0.99 (3H, d, *J* = 6.7 Hz, $CH_3$), 0.94 (3H, d, *J* = 7.3 Hz, $CH_3$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 174.9, 100.5, 97.3, 80.0, 77.4, 74.4, 74.0, 70.4, 41.8, 40.4, 36.6, 32.6, 31.9, 29.8, 28.6, 22.1, 20.1, 18.8, 16.8, 16.0, 13.3, 12.6, 7.7, 7.4; HRMS (CI, $NH_3$) calcd for $C_{25}H_{44}IO_6$ ([M + H]$^+$) 583.2131, found 583.2130; *m/z* 583 (5, [M + H]$^+$), 525 (60), 481 (100), 463 (80), 397 (45), 353 (70), 335 (45), 239 (30), 171 (30), 125 (65).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,9*R*,10*R*,11*R*,12*R*,13*R*)-3,5-[(*p*-Bromobenzylidene)dioxy]-8,8-(epoxymethano)-9,11-dihydroxy-2,4,6,10,12,13-hexamethyltetradecanolide (80).** To a solution of iodohydrin **84** (21.0 mg, 36.04 μmol) in THF (1 mL) was added hydrochloric acid (1 mL; 2 M aqueous), and the mixture was heated at 55 °C for 1 h. The mixture was allowed to cool before diluting with water (5 mL) and extracting with diethyl ether (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude pentol as a pale yellow oil which was used immediately in the next reaction.

To a solution of the crude pentol prepared above in $CH_2Cl_2$ (2 mL) was added *p*-bromobenzaldehyde dimethyl acetal (9.0 μL, 51.0 μmol) followed by camphorsulfonic acid (1 crystal), and the mixture was stirred at room temperature for 1 h. Sodium bicarbonate solution (2 mL, saturated, aqueous) was then added and the mixture stirred vigorously at room temperature for 20 min before being extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (50% EtOAc/hexanes) afforded 14.5 mg (72%) of the desired product **80** as

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[83] Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

a colorless oil. Spectroscopic properties are in accordance with those reported for **80** prepared earlier from **79**.

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,10*R*,11*R*,12*R*,13*R*)-3,5-[(*p*-Bromobenzylidene-)dioxy]-8,8-(epoxymethano)-11-hydroxy-2,4,6,10,12,13-hexamethyl-9-oxotetradecanolide (86).** To a stirred solution of epoxide **80** (13.0 mg, 23.4 $\mu$mol) in toluene (1 mL) was added PCC on alumina (70.0 mg, 70.0 $\mu$mol),[76] and the mixture was stirred at room temperature for 18 h. The reaction mixture was then eluted through a Celite plug with toluene and concentrated *in vacuo*. Flash chromatography (25% EtOAc/hexanes) provided 1.6 mg of recovered starting material and 10.1 mg (78%, 89% based on recovered starting material) of the desired ketone **86** as a colorless oil: $[\alpha]^{20}{}_{D} = -48.0°$ (*c* 1.0, $CHCl_3$); TLC (50% EtOAc/hexanes) $R_f = 0.60$; IR ($CHCl_3$ solution) 3500 (br), 1705 (s) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.49 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.39 (2H, d, $J = 8.4$ Hz, Ar*H*), 5.76 (1H, qd, $J = 6.6$, 1.1 Hz, $C_{13}H$), 5.52 (1H, s, $O_2CH$Ar), 4.36 (1H, br d, $J = 9.9$ Hz, $C_{11}H$), 4.02 (1H, d, $J = 7.0$ Hz, $C_5H$), 3.75 (1H, d, $J = 10.9$ Hz, $C_3H$), 3.12 (1H, d, $J = 4.1$ Hz, one of $C_8H_2$), 3.04 (1H, qd, $J = 6.7$, 1.7 Hz, $C_{10}H$), 2.98 (1H, d, $J = 4.1$ Hz, one of $C_8H_2$), 2.87 (1H, dq, $J = 10.9$, 6.6 Hz, $C_2H$), 2.41 (1H, br d, $J = 4.3$ Hz, O*H*), 2.31 (1H, dd, $J = 15.0$, 12.0 Hz, one of $C_7H_2$), 2.20 (2H, m, $C_4H$, $C_6H$), 2.08 (1H, dd, $J = 15.0$, 2.0 Hz, one of $C_7H_2$), 1.65 (1H, dq, $J = 10.0$, 6.9 Hz, $C_{12}H$), 1.29 (3H, d, $J = 6.6$ Hz, $CH_3$), 1.23 (3H, d, $J = 6.6$ Hz, $CH_3$), 1.18 (3H, d, $J = 6.7$ Hz, $CH_3$), 1.10 (3H, d, $J = 7.0$ Hz, $CH_3$), 1.05 (3H, d, $J = 6.6$ Hz, $CH_3$), 1.02 (3H, d, $J = 7.1$ Hz, $CH_3$), $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 205.9, 174.4, 137.7, 131.3, 127.9, 122.8, 101.7, 84.0, 80.3, 70.1, 69.8, 63.3, 46.8, 46.7, 41.4, 41.3, 32.7, 32.1, 31.4, 18.5, 16.2, 13.0, 9.2, 8.7, 6.0; HRMS (CI, $NH_3$) calcd for $C_{27}H_{40}{}^{79}BrO_7$ ($[M + H]^+$) 553.1801, found 553.1800; *m/z* 572 (15, $[M + NH_4]^+$), 570 (15, $[M + NH_4]^+$), 553 (40, $[M + H]^+$), 551 (40 $[M + H]^+$), 369 (100), 351 (85).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,10*R*,11*R*,12*R*,13*R*)-8,8-(Epoxymethano)-3,5,-11-trihydroxy-2,4,6,10,12,13-hexamethyl-9-oxotetradecanolide, Oleandolide (2).** To a solution of acetal **86** (10.6 mg, 19.2 $\mu$mol) in ethyl acetate (2 mL) was added solid sodium bicarbonate (50 mg, excess) followed by palladium on charcoal (10% Pd content, 50 mg), and the mixture was stirred under a hydrogen atmosphere for 30 min. Filtration through a plug of Celite followed by evaporation gave the *crude* product. Rapid flash chromatography (49% EtOAc/1% $Et_3N$/hexanes) then gave 7.0 mg (95%) of oleandolide as a colorless oil: $[\alpha]^{20}{}_{D} = -14.3$ (*c* 1.05 $CHCl_3$) [*cf.* lit[6a] $[\alpha]^{20}{}_{D} = -13.0$ (*c* 1.0 $CHCl_3$)]; TLC (70% EtOAc/hexanes) $R_f = 0.20$; IR (thin film) 3500 (br), 1725 (s) $cm^{-1}$; $^1H$ NMR (400 MHz,$CDCl_3$) (5,9-hemiacetal form) $\delta$ 4.99 (1H, qd, $J = 6.4$, 2.2 Hz, $C_{13}H$), 4.02 (2H, m, $C_5H$, $C_{11}H$), 3.34 (1H, dd, $J = 10.3$, 1.8 Hz, $C_3H$), 2.97 (1H, d, $J = 4.6$ Hz, one of $C_8CH_2$), 2.71 (1H, d, $J = 4.6$ Hz, one of $C_8CH_2$), 2.53 (1H, qd, $J = 7.2$, 0.9 Hz, $C_2H$), 2.26 (1H, q, $J = 6.9$ Hz, $C_{13}H$), 2.10 (1H, m, $C_4H$), 1.92 (1H, dd, $J = 14.0$, 12.3 Hz, one of $C_7H_2$), 1.69 (2H, m, $C_6H$, $C_{12}H$), 1.41 (1H, dd, $J = 14.0$, 4.2 Hz, one of $C_7H_2$), 1.32 (3H, d, $J = 6.5$ Hz, $CH_3$), 1.13 (3H, d, $J = 7.1$ Hz, $CH_3$), 1.01 (3H, d, $J = 6.9$ Hz, $CH_3$), 0.99 (3H, d, $J = 7.3$ Hz, $CH_3$), 0.94 (3H, d, $J = 6.9$ Hz, $CH_3$), 0.83 (3H, d, $J = 6.6$ Hz, $CH_3$); 9-keto form (minor tautomer, some peaks obscured) $\delta$ 5.65 (1H, qd, $J = 6.7$, 1.3 Hz, $C_{13}H$), 3.88 (1H, dd, $J = 10.4$, 1.8 Hz, $C_3H$), 3.79 (2H, m, $C_5H$, $C_{11}H$), 3.05 (1H, d, $J = 4.5$ Hz, one of $C_8CH_2$), 3.03 (1H, qd, $J = 6.7$, 1.8 Hz, $C_{10}H$), 2.77 (1H, d, $J = 4.5$ Hz, one of $C_8CH_2$), 2.72 (1H, m, $C_2H$); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) (5,9-hemiacetal form) $\delta$ 177.8, 98.9, 76.0, 71.1, 70.0, 58.5, 52.2, 43.7, 43.5, 40.2, 36.5, 34.6, 29.9, 17.8, 16.6, 9.7, 9.0, 8.9, 8.65; (9-keto form) (minor tautomer) $\delta$ 207.0, 176.1, 77.3, 76.4, 69.8, 69.2, 62.2, 52.2, 45.0, 43.9, 41.7, 39.1, 32.2, 31.0, 18.6, 18.5, 14.3, 8.9, 7.5, 6.4; HRMS (CI, $NH_3$) calcd for $C_{20}H_{35}O_7$ ($[M + H]^+$) 387.2383, found 387.2383; *m/z* 404 (55, $[M + NH_4]^+$), 387 (50, $[M + H]^+$), 369 (100), 351 (40), 226 (40), 138 (70), 124 (45), 104 (50).

**(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,10*R*,11*R*,12*R*,13*R*)-3,5,11-Triacetoxy-8,8-(epoxymethano)-2,4,6,10,12,13-hexamethyl-9-oxotetradecanolide, Triacetyloleandolide (87).** To a solution of synthetic oleandolide **2** (24 mg, 62.1 $\mu$mol) in dry pyridine (0.5 mL) at room temperature were added acetic anhydride (59.0 $\mu$L, 0.62 mmol) and a crystal of DMAP (*ca.* 5 mg), and the mixture was stirred for 48 h. The solvent was then removed *in vacuo* and the mixture purified by flash chromatography (50% EtOAc/hexanes) followed by HPLC (50% EtOAc/hexanes) to give 17.5 mg (55%) of oleandolide triacetate as a colorless oil: $[\alpha]^{20}{}_{D} = +39.7$ (*c* 0.61 $CHCl_3$), [*cf.* lit[6a] $[\alpha]^{20}{}_{D} = +43$ (*c* 1.0 $CHCl_3$)]; TLC (70% EtOAc/hexanes) $R_f = 0.43$; HPLC (50% EtOAc/hexanes) $R_t = 18.3$ min; IR (thin film) 1737 (s) $cm^{-1}$; $^1H$ NMR (400 MHz,$CDCl_3$) $\delta$ 5.22 (1H, dd, $J = 10.0$, 1.6 Hz, $C_3H$), 5.19 (1H, qd, $J = 6.6$, 1.0 Hz, $C_{13}H$), 4.99 (1H, dd, $J = 9.8$, 1.4 Hz, $C_{11}H$), 4.74 (1H, d, $J = 4.9$ Hz, $C_5H$), 3.18 (1H, qd, $J = 5.0$, 1.5 Hz, $C_{10}H$), 2.75 (1H, dq, $J = 10.0$, 6.8 Hz, $C_2H$), 2.62 (1H, ABq, $J = 5.7$ Hz, one of $C_8CH_2$), 2.59 (2H, obscured m, $C_4H$, $C_6H$), 2.57 (1H, ABq, $J = 5.7$ Hz, one of $C_8CH_2$), 2.31 (1H, m, $C_{12}H$), 2.08 (6H, s, 2 × $H_3CCOO$), 2.03 (3H, s, $H_3CCOO$), 1.86 (1H, m, one of $C_7H_2$), 1.36 (1H, dd, $J = 15.0$, 11.9 Hz, one of $C_7H_2$), 1.25 (3H, d, $J = 6.5$ Hz, $CH_3$), 1.08−0.98 (15H, m, 5 × $CH_3$, all overlapping); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 206.2, 172.4, 170.7, 170.1, 170.0, 78.1, 74.1, 70.4, 68.8, 63.6, 51.2, 42.2, 41.7, 39.8, 39.4, 35.1, 31.5, 20.8, 20.7, 20.6, 18.8, 18.3, 13.5, 9.7, 9.0; HRMS (CI, $NH_3$) calcd for $C_{26}H_{44}NO_{10}$ ($[M + NH_4]^+$) 530.2964, found 530.2970; *m/z* 530 (100, $[M + NH_4]^+$), 514 (10), 453 (10), 393 (10), 96 (10).

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**Supplementary Material Available:** Text giving the details of the experimental procedure for the preparation of seco-acids **71** and **73**, the preparation of protected macrolides **75** and **76**, and the proof of the absolute configurations of the aldol adduct **7** (*AA*) and the (13*R*)-alcohols **59**, **93**, and **100**, details of instrumentation, purification of reagents and solvents, and chromatography, and spectroscopic data for minor diastereomers produced in the aldol, hydroboration, and Grignard addition reactions (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.