# Synthesis of Stereopentad Subunits of Zincophorin and Rifamycin-S through Use of Chiral Allenyltin Reagents

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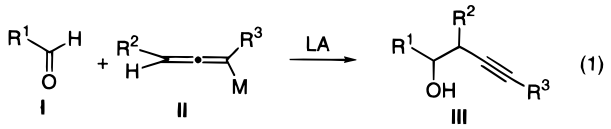
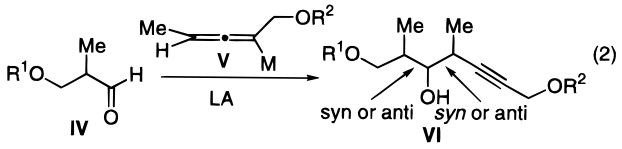
The anti,anti adduct **3**, from addition of the allenic stannane (*P*)-**2** to the α-methyl-*β*-OBn aldehyde (*S*)-**1** promoted by $SnCl_4$, was converted to the stereopentad **6** by a sequence involving reduction to the (*E*)-allylic alcohol with Red-Al, Sharpless asymmetric epoxidation, and addition of the higher-order methyl cyanocuprate to the derived epoxide **5**. Stereopentad **6** was converted to the acetonide acetal **15**, an intermediate in Danishefsky's synthesis of zincophorin. By a similar sequence, adduct *ent*-**4** was converted, via diol **19**, to stereopentad **22**, an intermediate in Kishi's synthesis of rifamycin-S. An alternative route to diol **19** was achieved from the MOM-protected derivative **28** of epoxy diol **18**.

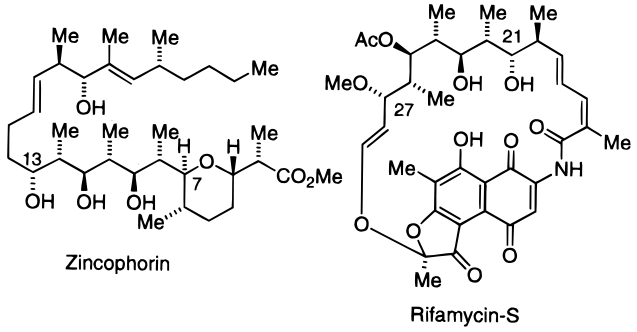
$S_E2'$ additions of chiral allenylmetal compounds to aldehydes give rise to homopropargylic alcohols with the creation of two contiguous stereocenters (eq 1).[1] Though little studied to date, such reactions have the potential for widespread applications in the synthesis of natural products, such as polypropionates, containing multiple proximal stereocenters.[2] Ideally, the allenylmetal reagent would be available in either enantiomeric form and would be configurationally stable under the reaction conditions.



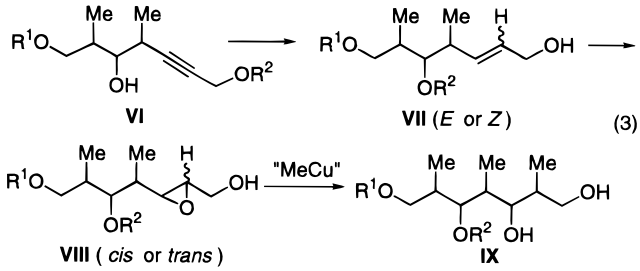

We have found that allenylstannanes and, to a lesser extent, allenylindium halides fulfill these conditions in reactions with aldehydes.[3,4] With chiral α-methyl-*β*-oxygenated aldehydes such as **IV** and the allenyl reagents **V**, it is possible to produce any of the four isomeric stereotriads **VI**[5] and the enantiomers through appropriate matching of substrate and reagent stereogenicity and proper choice of reaction conditions (eq 2).[3]




Our current efforts are concerned with the further elaboration of stereotriads **VI** to stereopentad subunits of polypropionate natural products. The present study deals with the conversion of the enantiomeric anti,anti isomers of **VI** to subunits of zincophorin[6] and rifamycin-S.[7]




In his pioneering studies on polypropionate synthesis, Kishi devised a reiterative epoxidation−methyl cuprate sequence to transform allylic alcohols to syn or anti triad units.[7] This approach seemed well suited to our present objectives, provided the intermediate allylic alcohols **VII** could be epoxidized with acceptable diastereoselectivity and the derived epoxy alcohols **VIII** could be induced to undergo efficient regioselective addition of methylcopper reagents (eq 3).




The anti,anti,anti,anti stereopentad **6** is relatively difficult to access by aldol methodology.[8] However, it was

(1) Yamamoto, H. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.3.
(2) Cf. Boeckman, R. K., Jr.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1988; Vol. 7, Chapter 1.
(3) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.
(4) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001. Marshall, J. A.; Lu, Z. H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.
(5) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.
(6) Cf. Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103.
(7) Cf. Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965 and preceding papers. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637.

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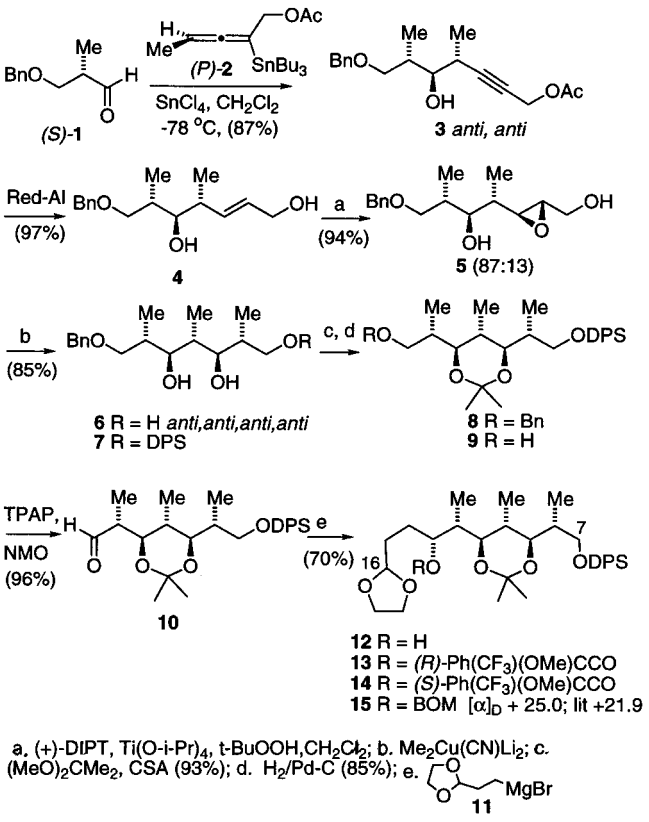
**Scheme 1**




envisioned that this steric array should be readily available by the proposed sequence (eq 3), and we therefore selected triol **6**, a potential C7−C13 subunit of zincophorin, as the initial target of these investigations. The anti,anti precursor **3** was readily obtained through addition of the allenylstannane (*P*)-**2** to the aldehyde (*S*)-**1** in the presence of 1 equiv of $SnCl_4$, as previously described (Scheme 1).[3] Treatment with Red-Al in THF effected removal of the acetate and reduction of the triple bond to provide the (*E*)-allylic alcohol **4**. Substrate-directed epoxidation of **4** with *m*-CPBA yielded a 1:1 mixture of diastereomeric epoxides. The use of $VO(acac)_2$ and *t*-BuOOH gave a somewhat better, but still unacceptable, 1.5:1 mixture of diastereomers.[10] However, reagent controlled epoxidation by the Sharpless methodology, with (+)-diisopropyl tartrate as the chiral ligand, produced the desired $\beta$-epoxide **5** as the major component of an 87:13 mixture.[9]

Epoxy alcohol **5** proved relatively unreactive toward cuprates. Exposure to 10 equiv of the Gilman $Me_2CuLi$ reagent afforded triol **6** in 70% yield after 30 h at 0 °C. The higher-order cyanocuprate proved more serviceable as it provided **6** in 85% yield under comparable conditions.[11] The relative stereochemistry of this adduct was confirmed by single-crystal X-ray analysis.

It was of interest to demonstrate the potential utility of triol **6** by conversion to the acetal acetonide **15**, a key compound in Danishefsky's synthesis of zincophorin.[6] This was achieved through protection as the primary diphenyl-*tert*-butylsilyl (DPS) ether **7**, formation of acetonide **8**, and hydrogenolysis of the benzyl ether. The resulting alcohol **9** was oxidized to aldehyde **10** with tetrapropylammonium perruthenate and 4-methylmorpholine *N*-oxide in excellent yield.[12] In contrast, Swern oxidation of **9** gave only products of decomposition.[13]

Addition of the dioxolanyl Grignard reagent **11** to aldehyde **10** afforded a single adduct in 70% yield.[14] It was found that a large excess of the Grignard reagent was required, presumably the consequence of multiple basic oxygen centers in aldehyde **10**. We had expected the stereochemistry of the alcohol adduct **12** to be as depicted based on a chelated transition state for the addition. Support for this assignment was secured from $^1H$ NMR analysis of the (*R*)- and (*S*)-Mosher esters **13** and **14**.[15] Additional confirmation of stereochemistry was provided by comparison of spectral data and optical rotation of the benzyloxymethyl (BOM) ether **15** with the published values.[6]

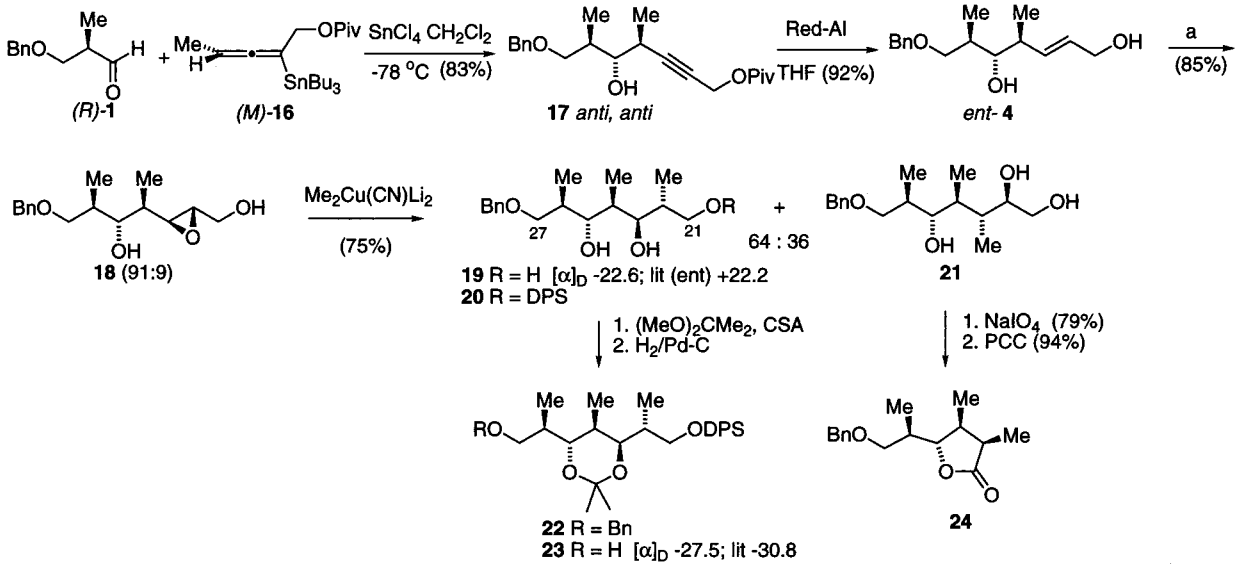
As a second target of this synthetic methodology we selected triol **19**, a potential C21−C27 subunit of rifamycin-S.[7] The precursor, anti,anti stereotriad **17**, was prepared as before but starting with the enantiomeric aldehyde (*R*)-**1** and stannane (*M*)-**16** (Scheme 2). The derived allylic alcohol *ent*-**4** was epoxidized by the same Sharpless protocol to afford the $\beta$-epoxide **18** as the major isomer of a 91:9 mixture. Evidently, allylic alcohol **4** (*ent*-**4**) exhibits only modest facial preferences in these directed epoxidations, thus allowing significant reagent control. Surprisingly, epoxide **18** afforded a 64:36 mixture of 1,3-diol **19** and 1,2-diol **21** upon treatment with the higher-order cyanocuprate. The enantiomer of diol **19**, an anti,anti,syn,anti stereopentad, has previously been prepared by an aldol route.[16] The reported rotation is nearly equal and opposite in sign to that of **19**. The structure of diol **21** was confirmed by its cleavage with $NaIO_4$ to an epimeric mixture of lactols, which afforded the $\gamma$-lactone **24** upon further oxidation.

Stereopentad **19** was converted to the acetonide alcohol **23** through hydrogenolysis of the DPS benzyl ether **22**. The spectra and optical rotation of **23** were in accord with the reported values.[7]

The formation of diol **21** from attack of the cyanocuprate at what we perceived as the more hindered epoxide center was unexpected. None of the analogous product was detected in the related displacement on the stereoisomeric epoxide **5**. A closer inspection of epoxide **18** with the aid of molecular modeling showed that both of the hydroxyl groups are well positioned to direct a coordinated cuprate to the backside of the epoxide (Figure 1). Thus, we postulated that the secondary alcohol moiety might be responsible for the formation of the 1,2-diol **21**. We therefore decided to protect this alcohol as the MOM ether **28**. This was done by starting from the known propargylic derivative **25**,[3] prepared along the lines of the pivalate analogue **17** (Scheme 3). The choice of pivalate or acetate in these systems is somewhat arbitrary. In this case a supply of the acetate intermediate happened to be on hand, whereas **17** was depleted.

(8) Cf. Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629.
(9) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(10) Marino, J. P.; de la Pradilla, R. F.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.
(11) Lipshutz, B. H.; Parker D.; Kozlowski, J. A.; Miller, R. D. *J. Org. Chem.* **1983**, *48*, 3334.
(12) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(13) Omurka, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(14) Buchi, G.; West, H. *J. Org. Chem.* **1969**, *34*, 1122.
(15) Ohtani, I.; Kusumi, T.; Kashman, K.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(16) Paterson, I.; Cannan, J. A. *Tetrahedron Lett.* **1992**, *33*, 797.

**Scheme 2**[a]




[a] Key: (a) (+)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, $CH_2Cl_2$.

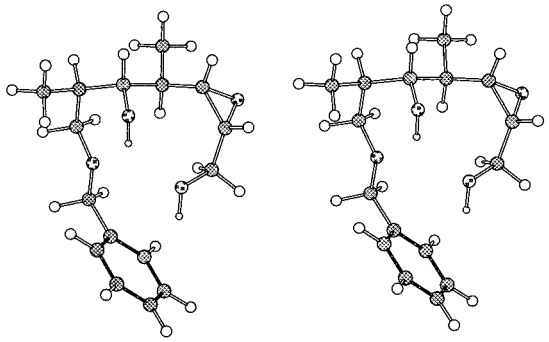
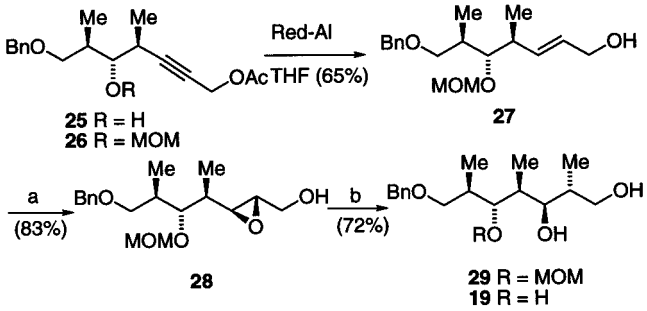


**Figure 1.** Chem 3D representation of a minimized structure (Macromodel 4.5)[17] of epoxy diol **18** illustrating the possible involvement of the hydroxyl groups in the cuprate displacement leading to diols **19** and **21**.

**Scheme 3**[a]




[a] Key: (a) (+)-DIPT, Ti(O-*i*-Pe)$_4$, *t*-BuOOH, $CH_2Cl_2$; (b) $Me_2Cu(CN)Li_2$.

Following a sequence parallel to that of Scheme 2, we prepared the epoxy alcohol **28**. In this case a single diastereomer was formed in the epoxidation step. Treatment with the higher order cyanocuprate effected conversion of epoxy alcohol **28** to the 1,3-diol **29** as the sole product. Confirmation of structure was achieved through cleavage of the MOM ether to give triol **19**.

The foregoing syntheses illustrate the potential of chiral allenic stannane methodology for the preparation of polypropionate segments containing the anti,anti stereotriad array. This work, and our previous studies based on the anti,syn triad,[4] suggest that the allene methodology can compliment more well-established routes to such intermediates. Major advantages of the present approach include the ease of preparing the chiral reagents and the use of all structural features of the adducts for further structural and stereochemical elaborations. The disposal of tin byproducts is perceived as a possible problem. For that reason, alternative chiral allenylmetal reagents are currently under investigation.[18]

## Experimental Section

$^1$H NMR and $^{13}$C NMR spectra were measured at 300 and 75 MHz in $CDCl_3$.

**(2*S*,3*R*,4*R*)-(−)-1-(Benzyloxy)-2,4-dimethyl-7-acetoxy-5-heptyn-3-ol (3).** To a solution of allenic stannane (*P*)-**2** (3.5 g, 8.5 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C was added $SnCl_4$ (8.5 mL, 8.5 mmol). After 40 min, the reaction was cooled to −78 °C, and aldehyde (*S*)-**1** (1.3 g, 7.1 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise. After 4.5 h, the reaction was quenched with 10% HCl (20 mL) and extracted with ether. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$, and triethylamine (3 mL) was added. The resulting slurry was stirred at 0 °C for 30 min and filtered through Celite with ether. The filtrate was concentrated under reduced pressure to give the crude alcohol contaminated with tin byproducts. This material was chromatographed twice on silica gel (eluting first with 35% ether in hexanes and then with 35% ethyl acetate in hexanes) to give 1.9 g (87%) of alcohol **3**[3] as an inseparable 97:3 mixture of diastereomers: $[\alpha]_D$ −1.4 (*c* 1.6, $CHCl_3$); $^1$H NMR $\delta$ 7.32 (m, 5H), 4.68 (d, $J$ = 1.8 Hz, 2H), 4.52 (s, 2H), 3.58 (m, 2H), 3.35 (dd, $J$ = 8.4, 2.9 Hz, 1H), 2.73 (m, 1H), 2.09 (m, 1H), 2.07 (s, 3H), 1.28 (d, $J$ = 7.0 Hz, 3H), 0.91 (d, $J$ = 7.0 Hz, 3H).

**(2*S*,3*R*,4*R*)-(+)-1-(Benzyloxy)-2,4-dimethyl-5-heptene-3,7-diol (4).** To a solution of alcohol **3** (1.84 g, 6.05 mmol) in THF (70 mL) at 0 °C was added Red-Al (19.0 mL, 69.7 mmol). The mixture was allowed to warm to room temperature, and after 48 h, the reaction was quenched with a saturated solution of sodium potassium tartrate and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried

(17) Mohamadi, 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.

(18) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976.

over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (50% ethyl acetate in hexanes) to give 1.55 g (97%) of diol **4** as a clear oil: $[\alpha]_D$ +13.0 (*c* 1.6, $CHCl_3$); IR (neat) 3439 $cm^{-1}$; $^1H$ NMR $\delta$ 7.41−7.20 (m, 5H), 5.84−5.60 (m, 2H), 4.51 (t, $J$ = 12.8 Hz, 2H), 4.12 (d, $J$ = 5.5 Hz, 2H), 3.55 (m, 2H), 3.37 (dd, $J$ = 8.1, 3.7 Hz, 1H), 2.38 (m, 1H), 1.91 (m, 1H), 1.10 (d, $J$ = 6.9 Hz, 3H), 0.88 (d, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR $\delta$ 138.4, 133.8, 130.6, 128.9, 128.2, 128.1, 79.9, 75.3, 74.0, 63.8, 39.7, 36.8, 18.4, 14.7. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.75; H, 9.14.

**(2*S*,3*S*,4*S*,5*S*,6*R*)-(+)-1-(Benzyloxy)-2,4-dimethyl-5,6-epoxy-3,7-heptanediol (5)**. To a solution of (+)-diisopropyl tartrate (0.086 mL, 0.411 mmol) in $CH_2Cl_2$ (25 mL) at −25 °C was added Ti(O-*i*-Pr)$_4$ (0.102 mL, 0.342 mmol). After 10 min, *tert*-butyl hydroperoxide (2.5 mL, 13.7 mmol) was added dropwise. After 30 min, allylic alcohol **4** (1.81 g, 6.85 mmol) in $CH_2Cl_2$ (3 mL) was added dropwise. After 18 h, the reaction was quenched with water (20 mL) and stirred at 0 °C. After 1 h, brine (10 mL) and a saturated solution of NaOH (10 mL) were added, and the mixture was stirred at room temperature. After 1 h, the mixture was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (60% ethyl acetate in hexanes) to give 1.81 g (94%) of epoxide **5** as a separable 87:13 mixture of diastereomers: $[\alpha]_D$ = +10.8 (*c* 1.57, $CHCl_3$); IR (neat) 3431 $cm^{-1}$; $^1H$ NMR $\delta$ 7.39−7.23 (m, 5H), 4.53 (s, 2H), 4.00−3.86 (m, 1H), 3.67−3.56 (m, 2H), 3.53−3.43 (m, 2H), 3.17 (dd, $J$ = 7.7, 2.6 Hz, 1H), 2.92, (m, 1H), 2.21 (m, 1H), 1.61 (m, 2H), 1.03 (d, $J$ = 6.9 Hz, 3H), 0.90 (d, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR $\delta$ 138.2, 129.0, 128.3, 128.2, 80.4, 76.0, 74.0, 62.8, 57.3, 56.9, 38.8, 36.6, 14.7, 14.6. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.20; H, 8.60.

**(2*S*,3*S*,4*R*,5*R*,6*R*)-(−)-1-(Benzyloxy)-2,4,6-trimethyl-3,5,7-heptanetriol (6).** To a suspension of CuCN (0.66 g, 7.4 mmol) in THF (0.25 mL) at −78 °C was added MeLi (11 mL, 15 mmol), and the mixture was allowed to warm to 0 °C. After 30 min, epoxide **5** (0.10 g, 0.37 mmol) was added dropwise. After 36 h, the reaction was quenched with a 9:1 saturated $NH_4Cl/NH_4OH$ solution (200 mL) and stirred at room temperature until a blue color persisted. The mixture was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (50% ethyl acetate in hexanes) to give 0.093 g (85%) of triol **6** as a white solid: mp 85.5−87 °C; $[\alpha]_D$ −7.5 (*c* 4.61, $CHCl_3$); IR (neat) 3383 $cm^{-1}$; $^1H$ NMR $\delta$ 7.41−7.24 (m, 5H), 4.52 (dd, $J$ = 13.6, 12.5 Hz, 2H), 3.91 (dd, $J$ = 11.0, 2.6 Hz, 1H), 3.75 (dd, $J$ = 9.5, 3.7 Hz, 1H), 3.64−3.44 (m, 4H), 2.08 (m, 1H), 1.89 (m, 2H), 1.14 (d, $J$ = 7.3 Hz, 6H), 0.79 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR $\delta$ 138.2, 129.0, 128.4, 128.2, 83.2, 82.6, 74.1, 73.0, 65.4, 39.5, 36.5, 35.7, 16.2, 15.8, 15.1. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.04; H, 9.56.

**(2*S*,3*S*,4*S*,5*R*,6*R*)-(−)-1-[(*tert*-Butyldiphenylsilyl)oxy]-7-(benzyloxy)-2,4,6-trimethyl-3,5-heptanediol (7).** To a solution of triol **6** (0.572 g, 1.93 mmol) in DMF (5 mL) at 0 °C were added imidazole (0.180 g, 2.70 mmol) and DPSCl (0.60 mL, 2.32 mmol), and the mixture was allowed to warm to room temperature. After 18 h, the reaction was quenched with water (10 mL) and extracted with ethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (25% ethyl acetate in hexanes) to give 0.974 g (94%) of diol **7** as a colorless oil: $[\alpha]_D$ −12.0 (*c* 1.36, $CHCl_3$); IR (neat) 3423 $cm^{-1}$; $^1H$ NMR $\delta$ 7.74−7.60 (m, 5H), 7.48−7.19 (m, 10H), 4.46 (s, 2H), 3.76 (dq, $J$ = 10.3, 9.9 Hz, 2H), 3.56 (m, 4H), 2.15−1.82 (m, 3H), 1.13 (d, $J$ = 7.3 Hz, 3H), 1.10 (d, $J$ = 7.0 Hz, 3H), 1.05 (s, 9H), 0.77 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR $\delta$ 136.2, 136.1, 133.6, 130.4, 129.0, 128.4, 128.2, 128.1, 82.2, 81.9, 74.0, 73.0, 66.7, 39.9, 37.5, 36.0, 27.4, 19.7, 16.5, 16.2, 15.1. Anal. Calcd for $C_{32}H_{44}O_4Si$: C, 73.80; H, 8.52. Found: C, 73.77; H, 8.56.

**(2*S*,3*S*,4*S*,5*R*,6*R*)-(−)-1-[(*tert*-Butyldiphenylsilyl)oxy]-7-(benzyloxy)-2,4,6-trimethylheptane-3,5-triol 3,5-Acetonide (8)**. To a solution of diol **7** (0.941 g, 1.76 mmol) in 2,2-dimethoxypropane (5 mL) at room temperature was added CSA (0.041 g, 0.176 mmol). After 3 h, the reaction was quenched with water (10 mL) and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (3% ethyl acetate in hexanes) to give 0.938 g (93%) of acetal **8** as a colorless oil: $[\alpha]_D$ −14.6 (*c* 2.06, $CHCl_3$); $^1H$ NMR $\delta$ 7.74−7.60 (m, 5H), 7.47−7.17 (m, 10H), 4.34 (q, $J$ = 16.8, 11.7 Hz, 2H), 3.87 (dd, $J$ = 10.3, 6.6 Hz, 1H), 3.56 (dd, $J$ = 9.2, 4.8 Hz, 1H), 3.44 (dd, $J$ = 10.3, 6.6 Hz, 1H), 3.33 (m, 2H), 3.24 (t, $J$ = 8.8 Hz, 1H), 2.06 (m, 2H), 1.89 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.03 (s, 9H), 1.01 (d, $J$ = 7.0 Hz, 3H), 0.94 (d, $J$ = 6.9 Hz, 3H), 0.72 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR $\delta$ 139.5, 136.2, 134.6, 134.5, 130.1, 128.8, 128.2, 128.0, 98.4, 78.7, 78.4, 73.6, 72.1, 65.2, 37.0, 34.8, 33.8, 30.6, 27.5, 19.8, 19.7, 16.6, 16.2, 12.6. Anal. Calcd for $C_{36}H_{50}O_4Si$: C, 75.22; H, 8.77. Found: C, 75.29; H, 8.81.

**(2*S*,3*S*,4*S*,5*R*,6*R*)-(−)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2,4,6-trimethylheptane-3,5,7-triol 3,5-Acetonide (9).** A solution of acetal **8** (0.93 g, 1.6 mmol) in ethyl acetate (10 mL) was stirred with 5% Pd/C (1.1 g) under an atmosphere of hydrogen for 17 h. The mixture was filtered through Celite with ether and concentrated under reduced pressure. The crude product was chromatographed on silica gel (15% ethyl acetate in hexanes) to give 0.66 g (85%) of alcohol **9** as a colorless oil: $[\alpha]_D$ −2.1 (*c* 1.71, $CHCl_3$); IR (neat) 3487 $cm^{-1}$; $^1H$ NMR $\delta$ 7.74−7.63 (m, 4H), 7.49−7.32 (m, 6H), 3.86 (m, 2H), 3.42 (m, 4H), 2.05 (m, 1H), 1.94 (m, 1H), 1.81 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.11 (d, $J$ = 7.0 Hz, 3H), 1.04 (s, 9H), 0.94 (d, $J$ = 7.0 Hz, 3H), 0.68 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR $\delta$ 136.2, 134.4, 130.1, 128.2, 98.8, 81.2, 78.1, 65.0, 64.1, 37.0, 34.8, 34.3, 30.7, 27.4, 19.7, 19.3, 16.1, 16.0, 12.5. Anal. Calcd for $C_{29}H_{44}O_4Si$: C, 71.86; H, 9.15. Found: C, 71.78; H, 9.18.

**(2*R*,3*R*,4*R*,5*R*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-2,4,6-trimethyl-3,5-dihydroxyheptanal 3,5-Acetonide (10).** To a solution of alcohol **9** (100 mg, 0.21 mmol) in $CH_2Cl_2$ (2 mL) were added NMO (0.036 g, 0.31 mmol) and crushed 4 Å molecular sieves (0.10 g). After 15 min, TPAP (0.004 g, 0.01 mmol) was added. After 5 min, the mixture was diluted with hexanes (10 mL), filtered through Celite with ether, and concentrated under reduced pressure to give 96 mg (96%) of aldehyde **10**, which was used in the next step without further purification: $^1H$ NMR $\delta$ 9.71 (d, $J$ = 1.95 Hz, 1H), 7.78−7.59 (m, 4H), 7.48−7.29 (m, 6H), 3.85 (dd, $J$ = 10.3, 6.8 Hz, 1H), 3.61 (dd, $J$ = 10.7, 1.9 Hz, 1H), 3.42 (m, 2H), 2.51 (m, 1H), 2.03 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.13 (d, $J$ = 6.4 Hz, 3H), 1.04 (s, 9H), 0.93 (d, $J$ = 6.8 Hz, 3H), 0.74 (d, $J$ = 6.8 Hz, 3H).

**Hydroxy Acetal 12.** To a suspension of Mg turnings (0.12 g, 4.92 mmol) in THF (3 mL) at room temperature was added 2-(2-bromoethyl)-1,3-dioxolane (0.50 mL, 4.28 mmol). After 1 h, the mixture was cooled to 0 °C, and aldehyde **10** (0.10 g, 0.214 mmol) in THF (0.20 mL) was added. After 20 min, the reaction was quenched with saturated $NH_4Cl$ (5 mL) and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (20% ethyl acetate in hexanes) to give 0.088 g (70%) of the alcohol **12** as a colorless oil: $[\alpha]_D$ +0.60 (*c* 5.65, $CHCl_3$); IR (neat) 3519 $cm^{-1}$; $^1H$ NMR $\delta$ 7.76−7.60 (m, 4H), 7.48−7.27 (m, 6H), 4.85 (t, $J$ = 4.4 Hz, 1H), 3.98−3.73 (m, 6H), 3.51−3.33 (m, 3H), 2.06 (m, 2H), 1.87−1.43 (m, 5H), 1.34 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H), 1.00 (d, $J$ = 7.0 Hz, 3H), 0.93 (d, $J$ = 7.0 Hz, 3H), 0.68 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR $\delta$ 136.1, 134.2, 130.0, 128.2, 105.1, 98.9, 82.0, 78.1, 70.1, 65.3, 64.9, 36.9, 36.5, 33.7, 31.2, 30.6, 29.7, 27.4, 19.6, 19.3, 16.0, 12.3, 11.5. Anal. Calcd for $C_{34}H_{52}O_6Si$: C, 69.82; H, 8.96. Found: C, 69.85; H, 9.03.

**Standard Procedure for Formation of Mosher Esters. (*R*)-Mosher Ester 13.** To a solution of alcohol **12** (17.0 mg, 0.029 mmol) in $CH_2Cl_2$ (0.5 mL) at room temperature were added (*R*)-MPTA (68.0 mg, 0.29 mmol), DCC (60.0 mg, 0.299 mmol) and DMAP (35.0 mg, 0.29 mmol). After 24 h, the

reaction was quenched with water (1 mL) and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatogrpahed on silica gel (15% ethyl acetate in hexanes) to give 19.1 mg (82%) of Mosher ester **13**: $^1$H NMR $\delta$ 7.75−7.65 (m, 4H), 7.63−7.56 (m, 2H), 7.45−7.30 (m, 9H), 5.46 (m, 1H), **4.75** (t, $J$ = 4.4 Hz, 1H),[19] 3.95−3.70 (m, 6H), 3.55 (s, 3H), 3.47 (dd, $J$ = 10.3, 6.6 Hz, 1H), 3.36 (dd, $J$ = 9.9, 2.2 Hz, 1H), 3.27 (dd, $J$ = 10.3, 2.9 Hz, 1H), 2.02 (m, 1H), 1.95−1.39 (m, 6H), 1.30 (s, 3H), 1.21 (s, 3H), 1.05 (s, 9H), 0.99 (d, $J$ = 7.0 Hz, 3H), 0.95 (d, $J$ = 7.0 Hz, 3H), **0.68** (d, $J$ = 6.6 Hz, 3H).[19]

**(*S*)-Mosher Derivative 14.** The standard procedure was followed with alcohol **12** (10.9 mg, 0.019 mmol), (*S*)-MPTA (0.045 g, 0.19 mmol), DCC (0.039 g, 0.19 mmol), and DMAP (0.023 g, 0.19 mmol) in $CH_2Cl_2$ (0.5 mL) at room temperature for 26 h to give 3.5 mg of recovered alcohol and 9.5 mg (91%; based on recovered starting material) of Mosher ester **14**: $^1$H NMR[19] $\delta$ 7.74−7.63 (m, 4H), 7.61−7.51 (m, 2H), 7.45−7.28 (m, 9H), 5.43 (m, 1H), **4.82** (t, $J$ = 4.0 Hz, 1H),[17] 3.95−3.71 (m, 6H), 3.50 (s, 3H), 3.32 (m, 1H), 3.20 (dd, $J$ = 9.9, 4.0 Hz, 1H), 2.00 (m, 1H), 1.90−1.57 (m, 6H), 1.27 (s, 3H), 1.14 (s, 3H), 1.04 (s, 9H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.91 (d, $J$ = 7.3 Hz, 3H), **0.62** (d, $J$ = 6.6 Hz, 3H).[19]

**BOM Ether 15.** To a solution of alcohol **12** (19.0 mg, 0.032 mmol) in diisopropylethylamine (0.17 mL, 0.96 mmol) was added BOMCl (0.19 mL, 0.96 mmol). After 6 days, the reaction was quenched with water (1 mL) and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed multiple times (5% ethyl acetate in hexanes) to remove impurities present from the BOMCl to afford 10.0 mg (44%) of the known BOM ether **15**[6] as a colorless oil: $[\alpha]_D$ +25.0 (*c* 0.60, $CHCl_3$) (lit.[6] $[\alpha]_D$ +21.9 (*c* 1.83, $CHCl_3$)); $^1$H NMR $\delta$ 7.73−7.60 (m, 4H), 7.44−7.19 (m, 11H), 4.83 (s, 1H), 4.77 (q, $J$ = 38.8, 6.9 Hz, 2H), 4.60 (q, $J$ = 57.2, 11.7 Hz, 2H), 3.94−3.67 (m, 6H), 3.46 (dd, $J$ = 10.3, 6.9 Hz, 1H), 3.38−3.27 (m, 2H), 2.00 (m, 1H), 1.86−1.57 (m, 6H), 1.31 (s, 3H), 1.28 (s, 3H), 1.03 (s, 9H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.95 (d, $J$ = 6.9 Hz, 3H), 0.67 (d, $J$ = 6.2 Hz, 3H).

(19) The boldface signals are diagnostic for the absolute configuration of the alcohol. The signals at 0.62 and 0.68 ppm are assigned to one of the methyl groups on either C8, C10, or C12. The signals at 4.82 and 4.75 ppm are assigned to the proton on carbon 16.[15]

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**Supporting Information Available:** Experimental procedures for **17**, *ent*-**4**, **18**, **19**, **23**, **24**, **28**, and **29**, $^1$H NMR spectra of key intermediates, a Chem3D representation of the chelated transition state leading to alcohol **12**, and an ORTEP representation for triol **6** (30 pages). This material is contained in 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.

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