Synthesis of Intermediates for the Lactone Moiety of Mevinic Acids *via* Tellurium Chemistry

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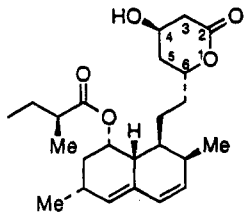
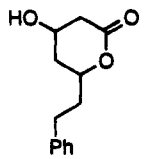
Treatment of *p*-toluenesulfonates of epoxides of specific primary allylic alcohols with telluride ion, prepared *in situ* by reduction of relatively nontoxic elemental tellurium, installs the two key secondary alcohol functions that occur in the lactone part of the cholesterol-lowering drugs, compactin, mevinolin, and lovastatin. Since the epoxides of the primary allylic alcohol starting materials can be synthesized in optically active form by the Sharpless–Katsuki asymmetric epoxidation (SAE) process, the stereospecific telluride transposition can give optically active secondary allylic alcohols configured for maximum inhibition of cholesterol formation.

Introduction

Mevinolin (**1**) (compactin, lovastatin) is a specific inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and is effective in lowering blood plasma cholesterol levels.[1] The key structural feature in HMG-CoA reductase inhibitors is the β-hydroxy-δ-lactone moiety that is characteristic of the class of compounds known as mevinic acids which also contain a functionalized hexalin or octalin connected to the lactone *via* an ethylene bridge.[2,3] The lactone functionality in its (4*R*,6*R*) configuration[4] is essential for inhibition because it closely resembles the HMG portion of the enzyme.[2] The synthesis of this lactone part of compactin has been achieved in a number of ways.[2a,3,5] The synthesis of two enantiomers of **2** by Johnson and Senanayake is noteworthy with respect to yield and high optical purity.[5a]

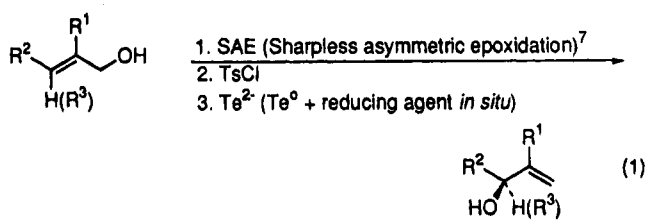


1



2

The construction of the lactone ring system of **3**, or a precursor to it, and introduction of the two secondary carbinol sites and fixation of their stereochemistry would demonstrate the usefulness and enlarge the scope of our recently described tellurium-induced nucleophilic reduction procedure (eq 1).[6] This process in conjunction with



(1)

the Sharpless–Katsuki asymmetric epoxidation (SAE)[7] allows optically active secondary (and also tertiary) allylic alcohols to be obtained without the necessity of a resolution. Either enantiomer may be obtained depending on the chirality of the tartrate ester in the SAE. Manipulation of the terminal vinyl group of the product of the telluride transposition can be used for extension of the

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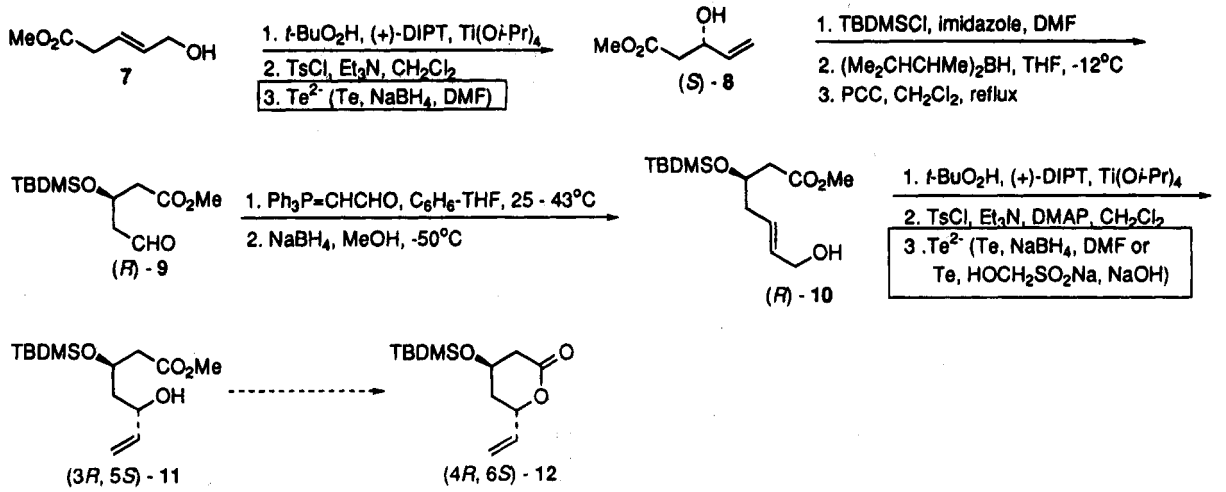
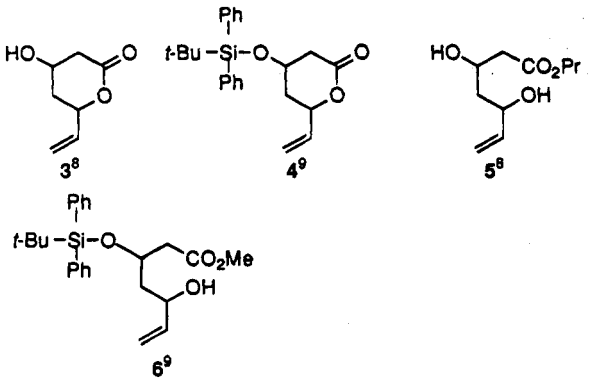
0022-3263/94/1959-4760$04.50/0

Scheme 1



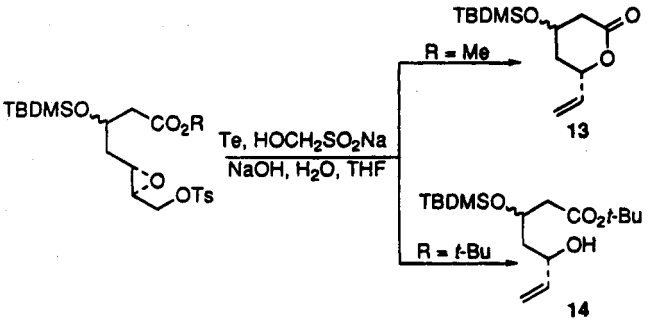
chain. Various precursors, isomers, and derivatives of lactone **3** have been reported[2a,3,5,8-11] and are exemplified by **4**–**6**.



Results and Discussion

Scheme 1 shows the overall process for the synthesis of **3** in the configuration shown in **1**. The synthesis incorporates two telluride-induced transposition steps that preserve the stereochemistry introduced by the SAE. Configurations are assigned according to the rules for SAE.[7] The extension of the chain by Wittig reagents (e.g., **9** → **10**) has ample precedent.[5lm,12] Determination of the compatibility of an ester substituent with the conditions for the Te-transposition of glycidyl sulfonates is important for the success of Scheme 1. Previous examples of the transposition did not involve compounds with an ester functional group.[6] (Results of telluride reactions with glycidyl acetates, in which the acetate function is the leaving group, have been reported recently.)[13] Sodium telluride and sodium hydrogen telluride have been used to deprotect β-haloalkyl, methyl, ethyl, phenacyl, and allyl esters to yield the carboxylic acid.[14]

To test the effect of the ester group on the Te-transposition, a mixture of isomers of **10** (obtained from racemic **8**)[15] was examined as being more convenient to study than **7** due to the difficulty of preparation of the latter. The telluride step was successful, and lactonization occurred spontaneously to give **13**. Although the characterization of diastereomeric **13** was somewhat hampered by its instability, the ^{1}H NMR spectrum was essentially identical with that reported for **4**,[9] except for the differences between the *tert*-butyldimethylsilyl and the *tert*-butyldiphenylsilyl groups. If the *tert*-butyl ester analog of **10** was used, spontaneous lactonization did not occur. Because the chirality of the β-hydroxy group was not fixed, the products consist principally of two diastereomers.



Installation of the desired configuration at the β-hydroxy site in **8** required as starting material the β,γ-unsaturated δ-hydroxy ester, **7**, recently reported by Trost and Granja.[16] The SAE of *trans*-**7** was complicated

(8) Mohr, P. *Tetrahedron Lett.* **1992**, *33*, 2455–2458.
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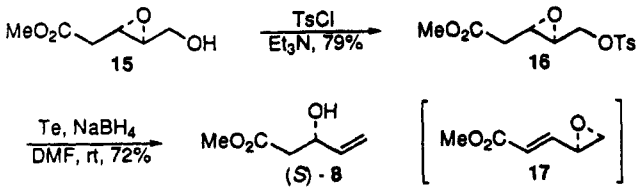
(14) (a) Chen, J.; Zhou, X.-J. *Synth. Commun.* **1987**, *17*, 161–164. (b) Huang, Z.-Z.; Zhou, X.-J. *Synthesis* **1990**, 633–634. (c) Chen, J.; Zhou, X.-J. *Synthesis* **1987**, 586–587. (d) Huang, Z.; Xie, L.; Huang, X. *Synth. Commun.* **1988**, *18*, 1167–1170. (e) Shobana, N.; Shanmugam, P. *Indian J. Chem.* **1985**, *24B*, 690. (f) Suzuki, H.; Padmanabhan, S.; Ogawa, T. *Chem. Lett.* **1989**, 1017–1020. (g) Zhou, X.-J.; Huang, Z.-Z. *Synth. Commun.* **1989**, *19*, 1347–1349.
(15) Racemic **8** was obtained by condensation of the anion of methyl acetate with propenal: Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717–4719. Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedron Lett.* **1981**, *22*, 4611–4614. Compound **8** also has been prepared *via* addition of the dilithio salt of acetic acid to propenal followed by esterification with diazomethane: Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III. *J. Org. Chem.* **1987**, *52*, 4191–4202. *tert*-Butyl esters have been obtained in the same way.
(16) Trost, B. M.; Granja, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 1044–1046. We thank Professor Trost for providing details of the preparation.

by the presence of some of the *cis* isomer that could not be separated. Therefore, the *ee* of glycidol **15** was only 77% ± 5% and that of (*S*)-**8**, was 79% ± 5%. The acidity of the α-protons of the ester required that bases, DMAP and hydroxide ion, be omitted in the tosylation and tellurium transposition steps, respectively. Otherwise, migration of the double bond into conjugation with the carbonyl group and hydrolysis of the ester occur. Replacement of the aqueous, basic Te–rongalite–sodium hydroxide reagent by Te–$NaBH_4$–DMF[6] proved satisfactory, whereas the Te–$LiEt_3BH$–THF reagent[6] gave a considerable amount of **17** possibly originating *via* a rearrangement catalyzed by triethylborane, a byproduct in the reduction of tellurium. In the reduction by $NaBH_4$–DMF, the borane or diborane byproduct is rendered less active by reaction with DMF to give the known dimethylamine–borane complex.[17] Its presence in the reaction mixture was confirmed by ^1H, ^{13}C NMR, and IR spectroscopy and by GC analysis. Intermediate (*S*)-**8** of greater optical purity (94% ee) was obtained by a Sharpless–Katsuki kinetic resolution of (±)-**8**. The synthesis was completed as described from racemic **8**. The synthesis of (*R*)-(−)-**9** by a different route has been described previously.[5m]



Experimental Section

Procedures for SKR, SAE,[7,18] the preparation of tosylates,[6] the tellurium transpositions,[6] and other general information[6] were described previously. In the workup of the products of asymmetric epoxidation the simplified procedure of Roush and Brown is preferred.[19]

(±)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-4-formylbutanoate [(±)-9]. (±)-Methyl 3-hydroxy-4-pentenoate, (±)-**8**[15] (4.00 g, 30.4 mmol), was treated with *tert*-butyldimethylsilyl chloride (5.50 g, 36.5 mmol) and imidazole (5.20 g, 76.0 mmol) in THF (180 mL) to give the silyl ether (6.60 g, 27.0 mmol, 89%) as a colorless oil after purification by flash chromatography (11:1 hexanes/ethyl acetate): ^1H NMR δ 0.05 (s, 3), 0.06 (s, 3), 0.88 (s, 9), 2.41–2.58 (m, 2), 3.67 (s, 3), 4.57–4.60 (m, 1), 5.05–5.26 (m, 2), 5.80–5.90 (m, 1); ^{13}C NMR δ −5.18, −4.43, 18.05, 25.68, 43.53, 51.49, 70.85, 114.6, 140.2, 171.5. This silyl ether of (±)-**8** (3.00 g, 12.3 mmol) was subjected to hydroboration with freshly prepared disiamylborane [19 mL of BH_3·THF (1 M), 19 mL of 2-methyl-2-butene in THF (2 M)] followed by treatment with pyridinium chlorochromate (PCC) (22.0 g, 102 mmol) according to the procedure of Brown *et al.*[20] Purification of crude (±)-**9** by flash chromatography (5:1 hexanes/ethyl acetate) gave a pale yellow oil (2.2 g, 8.4 mmol, 70%): ^1H NMR δ 0.07 (s, 3), 0.08 (s, 3), 0.85 (s, 9), 2.55–2.58 (m, 2), 2.64–2.68 (m, 2), 3.68 (s, 3), 4.60–4.70 (m, 1), 9.80 (t, 1); ^{13}C NMR δ −4.85 (overlapping absorptions), 17.84, 25.59, 42.39, 50.85, 51.64, 64.94, 171.2, 200.9; IR (film) 2720 (w), 1738 (s), 1256 (s), 1169 (m), 1090 (s), 1005 (m), 837 (s), 779 (s) cm.$^{-1}$ (*R*)-(−)-**9** has been prepared *via* ozonolysis of methyl (3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-5-hexenoate.[5m] The (*tert*-butyldiphenylsilyl)oxy aldehyde of the propyl ester has been obtained likewise.[5o]

(±)-(*E*)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy-7-hydroxy-5-heptenoate [(±)-10]. A solution of (±)-**9** (1.80 g, 6.92 mmol) in dry THF (5 mL) was added to a vigorously stirred solution of (formylmethylene)triphenylphosphorane (2.50 g, 8.30 mmol) in benzene (50 mL) at 0 °C. The reaction mixture was warmed to room temperature and refluxed until TLC indicated completion. The solvents were removed on a rotary evaporator, and crude homologated aldehyde was purified by flash chromatography (4:1 hexanes–ethyl acetate) to give a clear, yellow oil (1.60 g, 5.59 mmol, 81%): ^1H NMR δ 0.06 (s, 3), 0.08 (s, 3), 0.89 (s, 9), 2.40–2.67 (m, 4), 3.68 (s, 3), 4.31–4.40 (m, 1), 6.12–6.21 (dd, 1, J = 8.0, 15.5 Hz), 6.80–6.90 (dt, 1, J = 7.8, 15.5 Hz), 9.50 (d, 1, J = 8.0 Hz); ^{13}C NMR δ −4.96, −4.71, 17.85, 25.58, 40.44, 42.03, 51.57, 67.88, 135.3, 154.5, 171.3, 193.5; IR (neat) 2955 (s), 2932 (s), 2859 (s), 1738 (s), 1698 (s), 1169 (m), 1088 (s), 1007 (m), 988 (m), 837 (s), 777 (s) cm.$^{-1}$ The aldehyde (0.08 g, 0.28 mmol) in MeOH (5 mL) at −50 °C was rapidly reduced by $NaBH_4$ (0.012 g, 0.31 mmol). The reaction mixture was quenched with H_2O (1–2 mL), and the methanol was removed and the crude product chromatographed (2:1 hexanes/ethyl acetate) to give (±)-**10** as a colorless oil (0.06 g, 0.20 mmol, 74%): ^1H NMR δ 0.03 (s, 3), 0.05 (s, 3), 0.85 (s, 9), 1.52 (br s, 1), 2.26 (t, 2), 2.43 (d, 2, J = 6.3 Hz), 3.65 (s, 3), 4.10 (d, 2, J = 3.4 Hz), 4.13–4.22 (m, 1), 5.69 (m, 2); ^{13}C NMR δ −4.95, −4.53, 17.96, 25.69, 40.48, 42.05, 51.48, 63.56, 69.02, 127.9, 132.3, 172.1; IR (neat) 3407 (s), 1736 (s), 1250 (s), 1156 (m), 1083 (s), 1005 (m), 973 (m), 832 (s), 774 (s) cm.$^{-1}$

(2*S*,3*S*)-3-[2-[(*tert*-Butyldimethylsilyl)oxy]-3-(methoxycarbonyl)propyl]oxiranemethanol. The SAE [(+)-DIPT catalyst] was performed on (±)-**10** (0.684 g, 2.37 mmol) according to the general procedure. Workup[18] gave crude glycidol which was purified by flash chromatography (2:1 hexanes/ethyl acetate) to a pale yellow oil (0.49 g, 1.6 mmol, 68%): $[\alpha]^{25}_D$ −24.4° (*c* 1.7, $CHCl_3$); ^1H NMR δ 0.05 (s, 3), 0.07 (s, 3), 0.85 (s, 9), 1.65–1.90 (m, 2), 1.98 (br s, 1), 2.52 (d, 1), 2.58 (dd, 1), 2.92 (m, 1), 3.10 (m, 1), 3.67 (s, 3), 3.60–3.70 (m, 1), 3.89–3.93 (dd, 1), 4.3–4.4 (m, 1); ^{13}C NMR δ −5.00, −4.90, −4.80, −4.74, 17.88, 25.65, 25.75, 39.29, 39.65, 42.04, 42.79, 51.56, 52.32, 52.75, 57.92, 58.67, 61.47, 67.31, 171.6, 171.9 [shows overlapping absorptions of two diastereomers, (2*S*,3*S*,β*S*) and (2*S*,3*S*,β*R*]; IR (neat) 3442 (br, m), 1734 (s), 1084 (s), 836 (s), 776 (s) cm.$^{-1}$

4-[(*tert*-Butyldimethylsilyl)oxy]-6-(1-ethenyl)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (13). The above glycidol [(2*S*,3*S*)-3-[2-[(*tert*-butyldimethylsilyl)oxy]-3-(methoxycarbonyl)propyl]-oxiranemethanol] (0.30 g, 1.0 mmol) was converted (room temperature) to the tosylate, obtained as a colorless oil (0.35 g, 0.76 mmol, 76%) after purification by flash chromatography (3:1 hexanes/ethyl acetate): $[\alpha]^{25}_D$ −30.0° (*c* 2.1, $CHCl_3$); ^1H NMR δ 0.05 (s, 3), 0.07 (s, 3), 0.85 (s, 9), 1.52–1.89 (m, 2), 2.48 (s, 3), 2.45–2.55 (m, 2), 2.9–3.0 (m, 2), 3.67 (s, 3), 3.94–4.01 (m, 1), 4.21 (dd, 1), 4.35 (m, 1), 7.33 (d, 2, J = 8.2 Hz), 7.80 (d, 2, J = 8.2 Hz); ^{13}C NMR (overlapping absorptions of diastereomers) δ −5.05, −4.94, −4.88, −4.79, 17.82, 21.59, 25.60, 38.91, 39.25, 41.80, 42.60, 51.49, 52.94, 53.37, 53.99, 54.81, 67.03, 69.72, 69.82, 127.9, 129.9, 132.6, 145.0, 171.5, 171.6; IR (neat) 1734 (s), 1185 (s), 1175 (s), 832 (s), 774 (s), 664 (s) cm.$^{-1}$ This tosylate (0.27 g, 0.59 mmol) was treated with the Te–rongalite reagent. The lactone **13** was obtained as a pale yellow oil (0.12 g, 0.47 mmol, 80%) that decomposed on standing: ^1H NMR δ 0.12 (s, 3), 0.13 (s, 3), 0.90 (s, 9), 1.78 (m, 2), 2.64 (d, 2), 4.30–4.48 (m, 2), 5.10–5.30 (m, 2), 5.81–5.92 (m, 1) [lit.[9,11] ^1H NMR of 4-[(*tert*-butyldiphenylsilyl)oxy] analog **4** δ 1.09 (s, 9), 1.55–1.7 (m, 1), 1.80–2.0 (m, 1), 2.4–2.7 (m, 2), 4.28 (m, 1), 5.15–5.35 (m, 3), 5.7–5.9 (m, 1), 7.35–7.5 (m, 6), 7.6–7.7 (m, 4)].

5(*S*)-*tert*-Butyl 3-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-6-heptenoate (14). The procedure used for the synthesis of lactone **13** was followed. (±)-*tert*-Butyl 3-hydroxy-4-pentenoate[15] (7.3 g, 42.4 mmol) was converted to the TBDMS derivative (11.6 g, 40.4 mmol, 96%), purified by flash chromatography (25:1 hexanes–ethyl acetate): ^1H NMR δ 0.04 (s, 3), 0.06 (s, 3), 0.88 (s, 9), 1.44 (s, 9), 2.3–2.5 (m, 2), 4.5–4.6 (m, 1), 5.0–5.2 (m, 2), 5.8–5.9 (m, 1); ^{13}C NMR δ −4.98, −4.38, 18.11, 25.80, 28.13, 44.76, 70.86, 80.40, 114.4, 140.5, 170.3.

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The TBDMS-protected compound (5.30 g, 12.5 mmol) was subjected to the hydroboration–oxidation procedure[20] to give the *tert*-butyl ester analog of **9** [*tert*-butyl 3-[(*tert*-butyldimethylsilyl)oxy]-4-formylpentanoate] (2.50 g, 8.25 mmol, 66%) after purification by flash chromatography (25:1 hexanes–ethyl acetate): ^{1}H NMR δ 0.09 (s, 3), 0.12 (s, 3), 0.87 (s, 9), 1.44 (s, 9), 2.40–2.50 (m, 2), 2.61–2.69 (m, 2), 4.52–4.61 (m, 1), 9.8 (m, 1); ^{13}C NMR δ −4.85, −4.66, 17.88, 25.66, 28.09, 43.60, 50.72, 64.99, 80.89, 170.0, 201.3. The aldehyde (2.30 g, 7.58 mmol) was treated with (formylmethylene) triphenylphosphorane to give the chain-extended product [^{1}H NMR δ 0.08, (s, 3), 0.09 (s, 3), 0.89 (s, 9), 1.46 (s, 9), 2.30–2.60 (m, 4), 4.26–4.33 (m, 1), 6.10–6.20 (dd, 1, J = 8.0, 15.0 Hz), 6.81–6.92 (dt, 1, J = 7.7, 15.9 Hz), 9.52 (d, 1, J = 7.7 Hz)]. Without purification this aldehyde product (2.0 g, 6.1 mmol) of the Wittig reaction was reduced by $NaBH_4$ to the *tert*-butyl ester analog of **10** [*tert*-butyl 3-[(*tert*-butyldimethylsilyl)oxy]-7-hydroxy-5-heptenoate] (1.30 g, 3.92 mmol, 52% for two steps): ^{1}H NMR δ 0.06 (s, 3), 0.07 (s, 3), 0.87 (s, 9), 1.44 (s, 9), 2.27 (m, 2), 2.35 (d, 2, J = 6.2 Hz), 4.10 (d, 2), 4.15 (m, 1), 5.68 (t, 2); ^{13}C NMR δ −4.76, −4.53, 18.02, 25.79, 28.13, 40.25, 43.28, 63.66, 68.87, 80.38, 128.4, 132.1, 170.9.

The allylic alcohol (*tert*-butyl ester analog of **10**) (1.00 g, 3.00 mmol) was subjected to SAE [(+)-DIPT]. The epoxide was purified by flash chromatography (3:1 hexanes–ethyl acetate) to give a mixture of diastereomers of (2*S*,3*S*)-3-[(2-*tert*-butyldimethylsilyl)oxy]-3-(*tert*-butoxycarbonyl)propyl]oxiranemethanol as a colorless oil (0.400 g, 1.15 mmol, 38%): ^{1}H NMR δ 0.09 (s, 3), 0.10 (s, 3), 0.88 (s, 9), 1.44 (s, 9), 1.70–1.80 (m, 2), 2.40–2.50 (m, 2), 2.91–2.96 (m, 1), 3.02–3.10 (m, 1), 3.70–3.95 (m, 2), 4.22–4.31 (m, 1); ^{13}C NMR δ −4.76, −4.63, 17.95, 25.78, 28.14, 40.15, 43.48, 52.53, 58.35, 63.70, 66.86, 79.37, 171.23. This glycidol (0.14 g, 0.40 mmol) was converted to the tosylate, obtained as a yellow oil (0.13 g, 0.26 mmol, 65%) after purification by flash chromatography (4:1 hexanes–ethyl acetate): ^{1}H NMR δ 0.06 (s, 3), 0.07 (s, 3), 0.86 (s, 9), 1.43 (s, 9), 1.56–1.82 (m, 2), 2.39 (m, 2), 2.45 (s, 3), 2.88–2.98 (m, 2), 3.92–3.98 (dd, 1, J = 5.9, 11.4 Hz), 4.19–4.24 (dd, 1, J = 3.8, 11.2 Hz), 4.20–4.24 (m, 1), 7.33–7.36 (d, 2, J = 8.2 Hz), 7.78–7.81 (d, 2, J = 8.2 Hz).

Treatment of the tosylate (0.115 g, 0.230 mmol) with the Te–rongalite reagent gave **14**, a mixture of diastereomers, as a pale yellow oil after flash chromatography (5:1 hexanes/ethyl acetate): $[\alpha]^{23}_D$ −1.5° (*c* 0.75, $CHCl_3$); ^{1}H NMR δ 0.12 (s, 3), 0.14 (s, 3), 0.89 (s, 9), 1.43 (s, 9), 1.70–1.77 (m, 2), 2.53 (m, 2), 3.05 (br s, 1), 4.38 −4.44 (m, 2), 5.06–5.31 (m, 2), 5.80–5.91 (m, 1) [lit.[9] ^{1}H NMR for 3-[(tert-butyldiphenylsilyl)oxy] methyl ester analog **6**: δ 1.06 (s, 9), 1.6–1.8 (m, 2), 2.1 (m, 1), 2.55 (d, 2), 3.55 (s, 3), 4.25 (m, 1), 4.38 (m, 1), 4.95–5.15 (m, 2), 5.6–5.8 (m, 1), 7.3–7.9 (m, 10); lit.[8,21] ^{1}H NMR for *n*-propyl 3,5-dihydroxy-6-heptenoate (**5**):[8] δ 0.88 (t, 3), 1.56–1.66 (m, 4), 2.46 (d, 2), 4.00 (t, 3), 4.30 (m, 2), 5.05–5.25 (m, 2), 5.74–5.87 (m, 1)]; ^{13}C NMR δ −4.85, −4.74, 17.96, 25.75, 28.08, 42.44, 42.97, 68.02, 69.58, 80.70, 114.0, 141.0, 170.4.

(3*S*)-Methyl 3-Hydroxy-4-pentenoate [(*S*)-8]. Methyl 5-hydroxy-3-pentenoate (**7**)[16] (0.57 g, 4.4 mmol), contaminated with the cis isomer, was subjected to the SAE procedure [(+)-DIPT, CH_2Cl_2, −23 °C]. Workup[19] and purification of the epoxide by flash chromatography (2:1 → 1:1, hexanes/ethyl acetate) gave the epoxide **15** as a colorless oil (0.40 g, 2.7 mmol, 63%), 77% *ee* via NMR of MTPA ester). The low ee is due to the presence of the epoxide from contaminating *cis*-**7**: $[\alpha]^{23}_D$ −26.3° (*c* 3.15, $CHCl_3$); ^{1}H NMR δ 2.05 (br s, 1), 2.61 (d, 2, J = 5.86 Hz), 3.0 (m, 1), 3.30–3.34 (dt, 1, J = 2.2, 5.83 Hz), 3.68–3.7 (dd, 1, J = 4.2, 12.7 Hz), 3.71 (s, 3), 3.89–3.94 (dd, 1, J = 2.60, 12.7 Hz); ^{13}C NMR δ 36.94, 51.22, 51.99, 58.08, 61.17, 170.7. The epoxide undergoes ring opening via an elimination reaction to give methyl 4,5-dihydroxy-2-pentenoate[22] on long exposure to silica gel. MTPA ester of (−)-**15**: ^{1}H NMR δ 1.92–2.08 (m, 1.78), 2.18–2.25 (m, 0.22), 2.37–2.42 (m, 0.89), 2.44–2.48 (m, 0.11), 2.76–2.81 (m, 0.89), 2.82–2.87 (m, 0.11), 3.23 (s, 3), 3.42 (s, 3), 3.60 (dd, 0.11), 3.73 (dd, 0.89), 4.00 (dd, 0.89), 4.16 (dd, 0.11). MTPA ester of (±)-**15**: ^{1}H NMR δ 1.92–2.08 (m, 1), 2.18–2.25 (m, 1), 2.37–2.42 (m, 0.5), 2.44–2.48 (m, 0.5), 2.76–2.81 (m, 0.5), 2.82–2.87 (m, 0.5), 3.21 (s, 1.5), 3.22 (s, 1.5), 3.42 (s, 1.5), 3.43 (s, 1.5), 3.6 (dd, 0.5), 3.73 (dd, 0.5), 4.00 (dd, 0.5), 4.16 (dd, 0.5).

The epoxy alcohol **15** (0.337 g, 2.31 mmol) was converted to the tosylate (CH_2Cl_2, −20 °C → rt) according to the general procedure with the exception that DMAP was omitted. Purification by flash chromatography (2:1 → 1:1 hexanes–ether) gave the tosylate **16** as a white solid (0.55 g, 1.8 mmol, 79%): mp 29–30 °C; ^{1}H NMR δ 2.44 (s, 3), 2.56–2.58 (dd, 2, J = 3.5, 6.2 Hz), 3.06–3.09 (m, 1), 3.16–3.20 (dt, 1, J = 2.0, 5.7 Hz), 3.71 (s, 3), 3.95–4.01 (dd, 1, J = 5.9, 11.6 Hz), 4.21–4.26 (dd, 1, J = 3.6, 11.5 Hz), 7.35 (d, 2, J = 8.2 Hz), 7.80 (d, 2, J = 8.3 Hz); ^{13}C NMR δ 21.61, 36.64, 51.92, 52.02, 54.33, 69.41, 127.92, 129.91, 132.51, 145.13, 170.08. Two minor products produced by elimination reactions were observed.

The transposition of **16** to (*S*)-**8** failed with the Te–rongalite and the Te–$LiEt_3BH$ reagents. Although starting material was consumed, hydrolysis and rearrangement products appeared to be present. The preferred reagent was Te–$NaBH_4$–DMF (purple) (0.061 g, 0.48 mmol; 0.037 g, 0.96 mmol; 2.2 mL) which reacted with **16** (0.079 g, 0.26 mmol) to give **8** (0.025 g, 0.19 mmol, 72% by GC analysis, 69% by ^{1}H NMR analysis) contaminated with the complex $Me_2NH{\cdot}BH_3$, whose spectra were identical with those previously reported[17] and with those of authentic commercial material. The *ee* of (*S*)-**8** was 80% due to the presence of the *cis* isomer of **7** noted above.

Optically purer (*S*)-**8** (94% *ee*) was obtained by performing two sequential kinetic resolutions (SKR) on (±)-**8**. The first SKR applied to (±)-**8** (10.0 g, 76.9 mmol) utilized (−)-DIPT as the chiral ligand and proceeded for 15 days at −20 to −30 °C. Workup[19] included distillation (25 °C, 1.0 Torr, Kugelrohr) to separate the tartrate ester instead of hydrolysis with NaOH–NaCl in order to keep intact the ester group of **8**. Purification by chromatography (3:1 → 2:1, hexanes/ether) gave (−)-**8** (3.70 g, 28.5 mmol, 37%, 64% ee): $[\alpha]^{23}_D$ −4.22° (*c* 5.21, $CHCl_3$). A second SKR [(−)-DIPT] performed on this product (3.60 g, 27.7 mmol) gave (*S*)-(−)-**8** (2.75 g, 21.1 mmol, 76%, 94.3% *ee*): bp 40–45 °C (0.25–0.30 Torr); $[\alpha]^{23}_D$ −6.18° (*c* 5.24, $CHCl_3$); ^{1}H NMR δ 2.54–2.59 (m, 2), 2.91 (d, 1, J = 4.7 Hz), 3.71 (s, 3), 4.53–4.56 (br m, 1), 5.15–5.36 (m, 2), 5.84–5.95 (m, 1); ^{13}C NMR δ 40.92, 51.82, 68.91, 115.5, 138.7, 172.6; IR (neat) 3438 (s), 3086 (w), 2984 (w), 2956 (m), 1737 (s), 1644 (w), 1440 (s), 1357 (m), 1274 (m), 1168 (m), 1126 (m),1043 (m), 992 (s), 927 (s) cm.$^{-1}$ MTPA ester of (*S*)-(−)-**8**: ^{1}H NMR (C_6D_6) δ 2.05–2.11 (m, 1), 2.32–2.42 (dd, 1), 3.23 (s, 3), 3.46 (s, 3), 4.82–4.87 (d, 1), 5.02–5.08 (d, 1), 5.33–5.45 (m, 1), 5.83–5.92 (m, 1). MTPA ester of (±)-**8**: ^{1}H NMR (C_6D_6) δ 2.05–2.14 (m, 1), 2.34–2.44 (m, 1), 3.19 (s, 1.5), 3.22 (s, 1.5), 3.46 (s, 1.5), 3.45 (s, 1.5), 4.82–4.86 (d, 0.5), 4.87–4.90 (d, 0.5), 5.02–5.08 (d, 0.5), 5.11–5.17 (d, 0.5) 5.33–5.45 (m, 0.5), 5.45–5.56 (m, 0.5), 5.84–5.94 (m, 1).

(3*R*)-(−)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-4-formylbutanoate [(*R*)-9]. (*S*)-(−)-**8** (1.99 g, 15.3 mmol) was converted to its TBDMS derivative (3.50 g, 14.3 mmol, 93.7%) as described previously except that DMF was used as the solvent and flash chromatography was performed with a 25:1 mixture of hexanes–ether: $[\alpha]^{23}_D$ −7.41° (*c* 5.29, $CHCl_3$); ^{1}H NMR and ^{13}C NMR spectra were identical with those reported above for the racemic derivative; IR(neat) 3081 (w), 1746 (s), 1251 (s), 1176 (m), 1128 (m), 1087 (m), 836 (s), 778 (s) cm.$^{-1}$ Conversion of the TBDMS derivative of (*S*)-**8** (3.25 g, 13.3 mmol) to (*R*)-**9** (2.04 g, 7.84 mmol, 59%) was done as described for the synthesis of (±)-**9**: $[\alpha]^{22}_D$ −9.83° (*c* 5.38, $CHCl_3$) [lit.[5m] $[\alpha]_D$ −9.6° (*c* 1.2, $CHCl_3$)]; ^{1}H NMR, ^{13}C NMR, and IR spectra were identical with those for (±)-**9**.

(3*R*)-(−)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-7-hydroxy-5-heptenoate [(*R*)-10]. Homologation of (*R*)-**9** (1.56 g, 6.00 mmol) by treatment with (formylmethylene)triphenylphosphorane (2.26 g, 7.21 (mmol) was done as described for the synthesis of (±)-**10** to give (3*R*)-(−)-methyl 3-[(*tert*-butyldimethylsilyl)oxy]-6-formyl-5-pentenoate (1.15 g, 4.02 mmol, 67%): $[\alpha]^{23}_D$ −34.5° (*c* 1.59, $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and IR spectra were essentially the same as those for the racemic derivative reported above. The aldehyde (1.15 g, 4.00 mmol)

(21) Mohr, P., personal communication. We thank Dr. Mohr for supplying us with NMR spectra.

(22) Wee, A. G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1363–1364.

was reduced to the alcohol, (*R*)-**10** (0.90 g, 3.12 mmol, 78%), in the same manner as described for the synthesis of (±)-**10**: $[\alpha]^{23}_D$ − 29.0° (*c* 2.1, $CHCl_3$); ^1H NMR, ^{13}C NMR, and IR spectra were identical with those for (±)-**10**.

(3*R*,5*S*)-(+)-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-6-heptenoate [(3*R*,5*S*)-11]. Epoxidation of (*R*)-**10** (0.727 g, 2.52 mmol) by the SAE procedure [(+)-DIPT] gave after workup[19] the oxiranemethanol (0.305 g, 1.00 mmol, 40%): $[\alpha]^{25}_D$ −38.35° (*c* 2.56, $CHCl_3$); ^1H NMR δ 0.05 (s, 3), 0.07 (s, 3), 0.87 (s, 9), 1.65 (br s, 1), 1.68−1.88 (br m, 2), 2.51−2.64 (m, 2), 2.91 (m, 1), 3.10 (m, 1), 3.60 (dd, 1), 3.67 (s, 3), 3.9 (dd, 1, *J* = 2.2, 12.6 Hz), 4.35 (m, 1); ^{13}C NMR δ −4.98, −4.73, 17.90, 25.66, 39.30, 42.06, 51.57, 52.30, 57.84, 61.43, 67.30, 171.8; IR spectrum was identical with that reported above for the (2*S*,3*S*)-oxiranemethanol from (±)-**10**. Conversion of the (−)-oxiranemethanol (0.142 g, 0.460 mmol) to the tosylate (oil, 0.160 g, 3.50 mmol, 75%) followed the standard procedure: $[\alpha]^{24}_D$ −37.8° (*c* 1.33, $CHCl_3$); ^1H NMR δ 0.03 (s, 3), 0.04 (s, 3), 0.85 (s, 9), 1.60−1.66 (m, 1), 1.80−1.88 (m, 1) 2.45 (s, 3), 2.46−2.60 (m, 2), 2.94 (m, 2), 3.66 (s, 3), 3.93−3.99 (dd, 1, *J* = 5.7, 11.2 Hz), 4.17−4.22 (dd, 1, *J* = 3.4, 11.2 Hz), 4.27−4.35 (m, 1), 7.33−7.36 (d, 2, *J* = 8.1 Hz), 7.78−7.80 (d, 2, *J* = 8.2 Hz); ^{13}C NMR δ −5.01, −4.75, 17.86, 21.64, 25.64, 38.95, 41.84, 51.56, 53.00, 54.04, 67.07, 69.85, 128.0, 129.9, 132.7, 145.1, 171.7; IR spectrum was identical with that reported in the description of the synthesis of **13**.

The (−)-tosylate (0.079 g, 0.17 mmol) was treated with the Te−$NaBH_4$−DMF reagent (0.044 g, 0.345 mmol; 0.030 g, 0.78 mmol; 0.7 mL) according to the general procedure.[6] The reaction was rapid at room temperature. DMF was removed by distillation (Kugelrohr), and flash chromatography (8:1 → 5:1, hexanes/ether) gave (3*R*,5*S*)-**11** as a colorless oil: $[\alpha]^{25}_D$ +5.0° (*c* 0.3, $CDCl_3$), +6.15° (*c* 0.39, $CHCl_3$); ^1H NMR δ 0.08 (s, 3), 0.11 (s, 3), 0.88 (s, 9), 1.58 (br s, 1), 1.70−1.80 (m, 2), 2.56 (d, 2, *J* = 6.3 Hz), 3.67 (s, 3), 4.26−4.38 (m, 2), 5.08−5.29 (m, 2), 5.81−5.92 (m, 1); ^{13}C NMR δ −4.70, −4.61, 17.85, 25.70, 42.74, 43.88, 51.60, 68.40, 70.74, 114.4, 140.6, 171.8; IR(neat) 3456 (m), 3080 (w), 2925 (s), 2857 (s), 1738 (s), 1646 (w), 1439 (m), 1255 (m), 1086 (s), 1013 (m), 835 (s), 777 (s) cm^{-1}. The ^1H NMR spectrum was essentially identical, except for phenyl absorptions and diamagnetic shielding, with that of the (*tert*-butyldiphenylsilyl)oxy analog[9] and is very similar to that of the unsilylated *n*-propyl ester analog.[8,21]

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Supplementary Material Available: ^1H and ^{13}C NMR spectra (24 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.