Acyclic Stereoselection. 43. Stereoselective Synthesis of the C-8 to C-15 Moiety of Erythronolide A[1]

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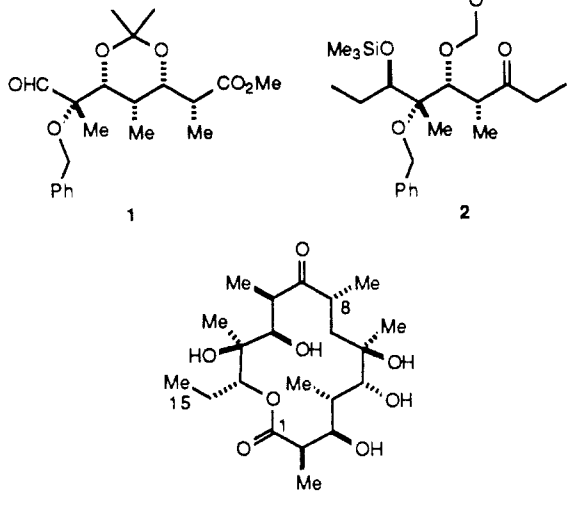
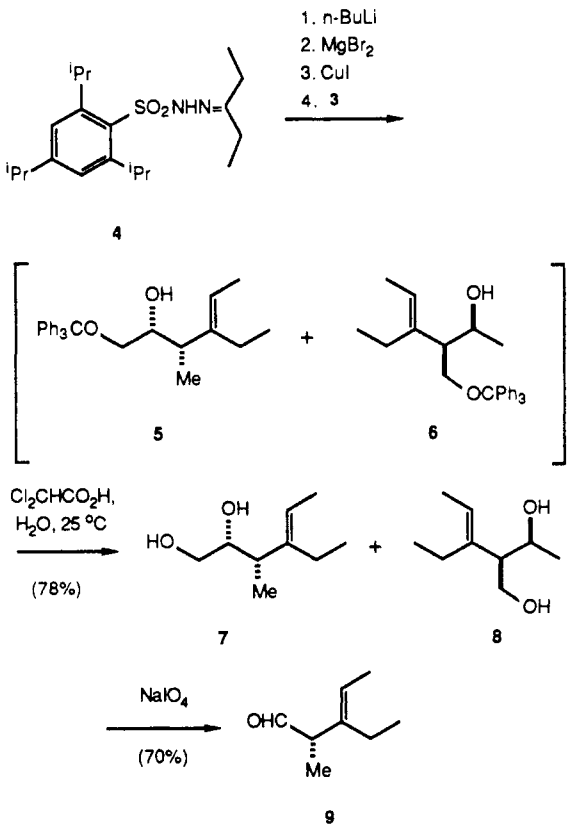
Enantiomerically pure ketone **2**, corresponding to the C-8, C-15 segment of erythronolide A, has been prepared by a 12-step route with crotyl alcohol as starting material in 5–6% overall yield. The synthesis starts with trisylhydrazone **4**, which is converted by the Bond procedure into (*Z*)-3-lithio-2-pentene. The vinyllithium reagent is converted in situ into a Grignard reagent, which is employed to open epoxide **3** with copper(I) catalysis. The resulting mixture of regioisomeric diol monoethers (**5** and **6**) is hydrolyzed to diols **7** and **8**, which are obtained in a 7:1 ratio. Treatment of the mixture with $NaIO_4$ provides optically pure aldehyde **9**. This material is treated with the lithium enolate of BHT *O*-benzyllactate (**10**) to obtain a single stereoisomeric aldol, **11**. Reduction of the derived (benzyloxy)methyl ether **12** provides primary alcohol **13**, which is subjected to Swern oxidation to obtain aldehyde **15**. The remaining stereocenter is established by reaction of **15** with dimethylsulfoxonium methylide; the resulting mixture of diastereomeric epoxides is treated with MeMgBr and CuI to obtain secondary alcohols **17** and **18** in a ratio of 4:1. The synthesis of **2** is completed by silylation of the hydroxy group and ozonolysis of the double bond. The *re* diastereofacial selectivity seen in the reaction of the ylide with aldehyde **15** is not general, as the related aldehyde **20** shows 4.5:1 *si* diastereofacial selectivity in its reaction with ethyllithium. Ethyl ketone **23** also shows *re* diastereofacial preference in reduction by $Li(t\text{-}BuO)_3AlH$. The product of this reaction, alcohol **21**, can be converted into ketone **24**, the C-7 diastereomer of **2**.

In an earlier paper in this series,[3] we described the synthesis of **1**, the C-1 to C-7 moiety of the macrolide antibiotic erythromycin A. In this paper, we report the synthesis of ketone **2**, a substance that corresponds to the C-8 to C-15 segment of the antibiotic aglycone erythronolide A. As in the synthesis of **1**, the synthesis of **2** employs BHT *O*-benzyllactate[4] as a key reagent.[5]



erythronolide A

Scheme I



The synthesis begins with **3**,[6] which was prepared by Sharpless epoxidation of crotyl alcohol (eq 1). Although

(1) For part 42, see: Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.

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(3) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095.

(4) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H.-P.; Montgomery, S. *J. Am. Chem. Soc.* **1984**, *106*, 8161.

(5) In a paper presented by C.H.H. at the Nobel Symposium *Asymmetric Organic Synthesis*; Karlskoga, Sweden, 2–7 September 1984, we reported a synthesis of compound **2** [Heathcock, C. H.; Hagen, J. P.; Young, S. D.; Pilli, R.; Bai, D. L.; Märki, H.-P.; Kees, K.; Badertscher, U. *Scrip. Chim.* **1985**, *25*, 39]. Subsequently, it was shown by L.B. that the material prepared by the route reported in this article has the 7*S*, rather than the indicated 7*R* configuration. The chemistry upon which this determination was made is summarized in the supplementary material. The current synthesis was developed from the earlier route by S.H. and Y.M.

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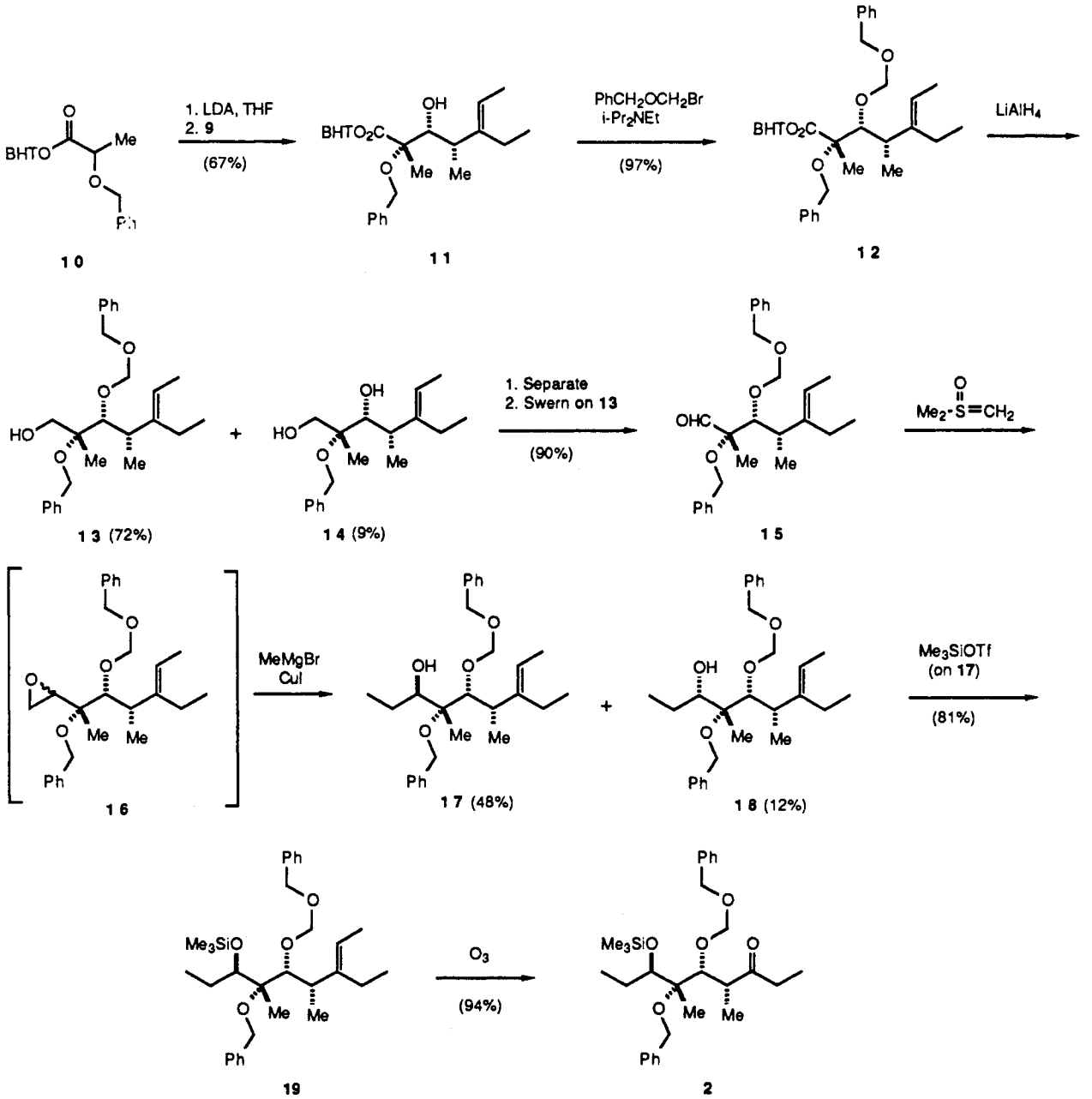
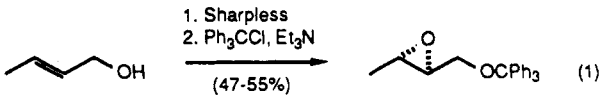
Scheme II



crotyl alcohol gives an epoxy alcohol of only about 95% ee in the Sharpless epoxidation,[7] trityl ether **3** is nicely crystalline; optically pure material is obtained by two recrystallizations. As shown in Scheme I, trisylhydrazone



(1)

3

4[8] is treated sequentially with *n*-butyllithium, magnesium bromide, copper(I) iodide, and epoxide **3**. The resulting mixture of regioisomeric diol monoethers (**5** and **6**) is hydrolyzed by treatment with aqueous dichloroacetic acid at room temperature; diols **7** and **8** are obtained as a 7:1 mixture in 78% yield. Although the diol monoethers **5** and **6** can be separated by chromatography, it is more convenient to oxidize the mixture of **7** and **8** with sodium periodate to obtain aldehyde **9**, which is obtained in 56% overall yield from epoxide **3**. The optical purity of **9** was established by reducing a specimen with lithium aluminum hydride to the corresponding alcohol, which was assayed by the method of Mosher.[9] However, the compound does epimerize with ease. Therefore, it should be distilled and must be used shortly after its preparation.

It is interesting and very convenient that the Bond reaction on trisylhydrazone **4** provides only the *Z* vinyllithium reagent, since unsaturated aldehyde **9** is thereby formed as the pure *E* diastereomer. In our previous work,[5] aldehyde **9** had been obtained as a mixture of *E* and *Z* isomers, favoring the latter. Consequently all of the succeeding intermediates in our earlier work were mixtures of double bond isomers.

(6) Kobayashi, Y.; Kitano, Y.; Taketa, Y.; Sato, F. *Tetrahedron* **1986**, *42*, 2937.
(7) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.
(8) Chamberlin, A. R.; Stemke, J. E.; Bond, F. F. *J. Org. Chem.* **1978**, *43*, 147.
(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

The utilization of β,γ-unsaturated aldehyde **9** for elaboration of intermediate **2** is summarized in Scheme II. The lithium enolate of BHT *O*-benzyllactate (**10**)[4] reacts with aldehyde **9** to provide a single stereoisomeric aldol (**11**) in 67% yield. After protection of the hydroxy group as the (benzyloxy)methyl ether, the ester function of **12** is reduced with lithium aluminum hydride to obtain alcohol **13**, accompanied by a small amount of diol **14**. The conditions for reduction of **12** had to be carefully optimized, since hydrogenolysis of the benzyl ether is fairly facile after the BHT ester has been reduced.

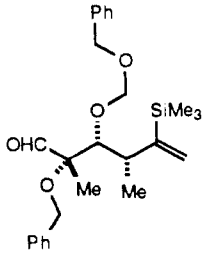
Swern oxidation of primary alcohol **13** affords aldehyde **15**, which reacts with dimethylsulfoxonium methylide to give a diastereomeric mixture of epoxides (**16**). Epoxides **16** are quite unstable but react smoothly with methylmagnesium bromide in the presence of copper(I) iodide to provide a separable, 4:1 mixture of diastereomeric secondary alcohols **17** and **18** in 60% yield. The synthesis of **2** is completed by silylation of the secondary hydroxy group and ozonization of the double bond, using the dye solvent red no. 23 as an indicator.[10]

The *re* diastereofacial preference shown by aldehyde **15** in its reaction with dimethylsulfoxonium methylide is not general, as is shown in Scheme III. In our earlier work[5] we prepared aldehyde **20**, a mixture of *E* and *Z* double bond isomers, slightly favoring the latter. This aldehyde reacts with ethyllithium to give alcohols **21** and **22** in a ratio of 4.5:1. Thus, the diastereofacial preference in the ethyllithium addition is *si*.[11] Oxidation of the mixture of **21** and **22** provides ethyl ketone **23**, which is reduced by lithium tri-*tert*-butoxyaluminum hydride to give essentially pure **21**. The diastereofacial preference in reduction of **23**, is, therefore, *re*. Protection of the hydroxy group in **21** and ozonolysis of the double bond affords **24**, diastereomeric at C-7 with **2**.

In summary, the complete synthesis of ketone **2** requires 12 operations from crotyl alcohol and delivers enantiomerically homogeneous material in 5–6% overall yield. The stereochemical yield is 80%, with the only loss coming in the methylenation of aldehyde **15**. The relative stereostructure of ketone **2** is rigorously established as described in the supplementary material. The absolute configuration follows from the known stereochemistry of the Sharpless epoxidation that was used to obtain the starting epoxide **3**.[7] In a subsequent paper, we will report the synthesis of a scalemic[12] version of aldehyde ester **1**, the union of **1** and **2**, and our efforts to convert the resulting seco acid into erythronolide A.

(10) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

(11) A referee raised the question of whether the facial selectivity observed in reactions of ethyllithium with aldehyde **15** might be related to the stereochemistry of the double bond, since we observed *si* preference with a mixture of *E* and *Z* isomers and *re* selectivity with the pure *E* isomer. We do not believe that the structure in this region of the molecule affects the facial preference of the aldehyde, since a nearly identical 4.5:1 *si*/*re* ratio is obtained in addition of ethyllithium to aldehyde **32** (see the supplementary material for details).



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(12) For a definition of scalemic, see ref 1, footnote 8.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether, tetrahydrofuran (THF), and benzene were distilled from sodium/benzophenone immediately prior to use. Methylene chloride, triethylamine, and diisopropylamine were distilled from calcium hydride prior to use. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Upon workup, solvents were evaporated with a Büchi rotary evaporator. ^{1}H NMR spectra were measured in $CDCl_3$ solution. Data for AB systems are reported in the manner suggested by Jackman and Sternhell.[13]

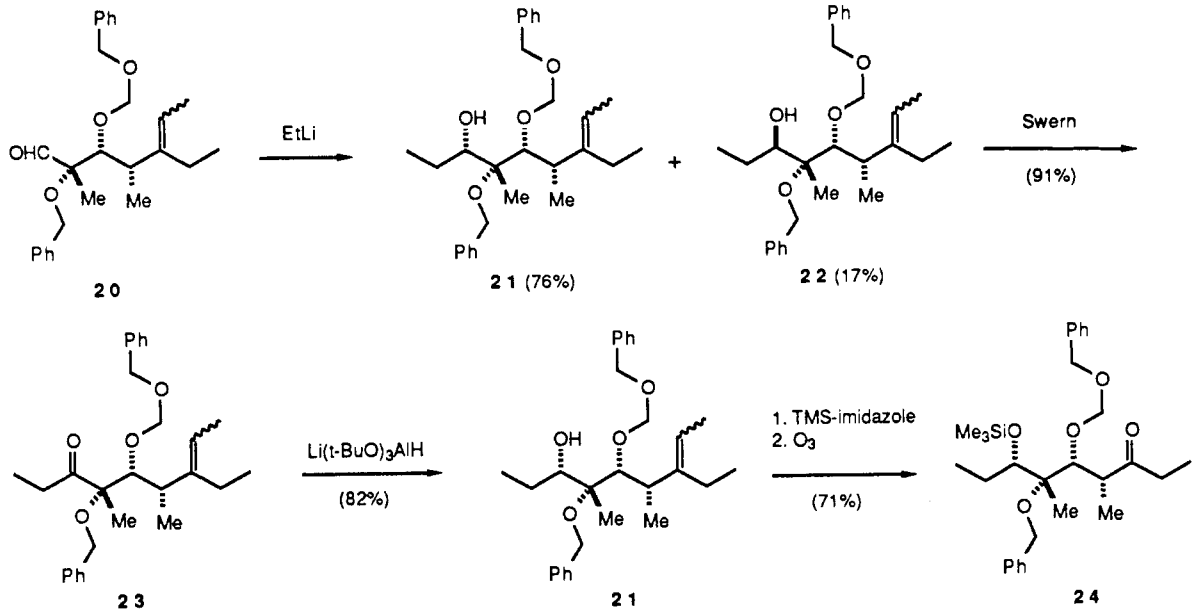
(2*S*,3*S*)-2-[(Triphenylmethoxy)methyl]-3-methyloxirane (3). A 1-L round-bottomed flask containing a magnetic stirring bar and 10 g of previously dried 3-Å molecular sieves was flushed with nitrogen. The flask was charged with 250 mL of CH_2Cl_2 and 3.0 mL (10.0 mmol) of titanium tetraisopropoxide. The contents of the flask were stirred and cooled to −40 °C with a dry ice/acetone cold bath. The following reagents were added in order: (+)-diisopropyl tartrate (2.8 g, 12.0 mmol), after 15 min, crotyl alcohol (17.0 mL, 0.200 mol), and *tert*-butyl hydroperoxide (84.0 mL of a 2.73 M solution in toluene, 0.230 mol).[14] The reaction flask was left to stand in the refrigerator overnight (8 °C) and then removed and placed in an ice bath the next morning. Dimethyl sulfide (2.0 mL, 27.0 mmol) was added to quench unreacted hydroperoxide. After 30 min, triethylamine (56.0 mL, 0.400 mol) and triphenylmethyl (trityl) chloride (61.3 g, 0.220 mol) were added. The tritylation was allowed to proceed at room temperature overnight. The resulting brown suspension was poured into 1.5 L of ether and washed with 250 mL of saturated aqueous Na_2SO_4, water (three times), saturated aqueous $CuSO_4$ (twice), water, and brine. The aqueous and organic layers required at least 15 min to fully separate. The cloudy organic mixture was dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to afford an amber oil (which crystallizes on standing). The crude material (before solidification) was chromatographed on 300 g of silica gel with 1:100 to 1:10 ether/hexane as eluant. Concentration of the eluant using a rotary evaporator provided semipure trityl epoxide **3**, which was recrystallized twice by evaporative crystallization from 400 mL of 1:3 CH_2Cl_2/hexane to give 31–36 g (47–55%) of pure material, mp 123.5–125.0 °C. R_f (1:20 EtOAc/hexane): 0.37. $[\alpha]^{20}_D$: −3.1° (*c* = 0.050, $CHCl_3$). IR (0.08 M, $CHCl_3$): 1500, 1460, 1230, 1070, 1050, 940, 760, 690 cm^{-1}. ^{1}H NMR: δ 1.31 (d, 3, *J* = 4.9), 2.92 (m, 2), 3.17 (dd, 1, *J* = 4.5, 11.9), 3.26 (dd, 1, *J* = 7.1, 11.9), 7.20–7.36 (m, 10), 7.44–7.52 (m, 5). ^{13}C NMR: δ 17.30, 52.13, 58.03, 64.20, 86.51, 126.88, 127.69, 128.50, 143.71. Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.89; H, 6.79.

(*E*,2*R*,3*S*)-4-Ethyl-3-methylhex-4-ene-1,2-diol (7). Trisylhydrazone **4** (27.5 g, 75.0 mmol) was dissolved in 75 mL of dry THF in a 500-mL round-bottomed flask containing a magnetic stirring bar and fitted with a rubber septum. The solution was cooled to −70 °C in a dry ice/acetone cooling bath, and *n*-butyllithium (90.5 mL of a 1.68 M solution in hexanes, 152 mmol) was added dropwise via cannula. The reaction mixture turned orange. The temperature of the reaction mixture was allowed to rise to −10 °C, during which time nitrogen was evolved and the vinyllithium reagent precipitated to form an orange suspension. The contents of the reaction flask were transferred via cannula to a stirring suspension of anhydrous $MgBr_2$ (13.8 g, 75.0 mmol) in 75 mL of THF at 0 °C. The Grignard reagent was allowed to form for 15 min during which time the mixture became homogeneous. Solid CuI (0.57 g, 3.00 mmol) was added, and the solution turned brown. After an additional period of 15 min, epoxide **3** (16.5 g, 50.0 mmol) in 50 mL of THF was added dropwise via cannula. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 days, and then quenched with 50 mL of saturated aqueous NH_4Cl. The resulting mixture

(13) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: New York, 1969; p 129.

(14) *tert*-Butyl hydroperoxide in toluene was prepared according to the procedure of Sharpless and Hill. Sharpless, K. B.; Hill, J. G. In *Organic Syntheses*; Saucy, G., Ed.; Wiley: New York, 1984; Vol. 63, p 66 (see Note 5, p 69).

Scheme III



was diluted with 50 mL of water and extracted with 100 mL of ether in a 1-L separatory funnel. The blue aqueous layer was discarded. The organic layer was washed with 100 mL of 10% aqueous NaOH, and the mixture was separated into three layers. The lower two layers were removed, diluted with 50 mL of brine, and extracted with three 100-mL portions of ether. The combined organic extracts were washed with 50 mL of 1 N aqueous HCl, dilute NH_4OH, and brine and were concentrated with a rotary evaporator to give the crude addition product, a 7:1 mixture of diol monoethers **5** and **6**.

The crude mixture of regioisomers was converted directly to diols **7** and **8** by treatment with 50 mL of dichloroacetic acid and 50 mL of H_2O for 90 min at ambient temperature. The resulting suspension was cooled to 0 °C, and excess acid was quenched with 15% aqueous NaOH (approximately 140 mL). The reaction mixture was filtered, and the solids were washed with 50 mL of water and 50 mL of petroleum ether. The filtrate was extracted with four 250-mL portions of ether. The ether extracts were dried over $MgSO_4$ and concentrated with a rotary evaporator to obtain 16.643 g of a viscous oil. This crude product was chromatographed on 160 g of silica gel with 1:5 to 1:2 EtOAc/hexane as eluant to afford 6.20 g (78%) of a 7:1 mixture of **7** and regioisomer **8**. This material was transformed to aldehyde **9** without further purification.[15]

An analytical sample of diol **7** was obtained by separation of the Grignard addition products **5** and **6** prior to deprotection. Chromatography of the mixture of regioisomers on silica gel using 50:1 loading and 1:30 EtOAc/hexane as eluant afforded semipure **5** free of isomer **6** but containing an impurity tentatively identified as the compound resulting from butyllithium addition to epoxide **3**. Detritylation of **5** and treatment of the resulting diol **7** with acetone and catalytic *p*-toluenesulfonic acid (*p*-TsOH) afforded a crude acetonide,[16] which was purified by chromatography and deprotected to recover diol **7**. This material was chromatographed to provide pure **7**. $[\alpha]^{20}_D$: −18.6° (*c* 0.0665, $CHCl_3$). IR (film): 3440, 1655, 1470, 1380, 1070 cm^{-1}. ^1H NMR: δ 0.98 (t, 3, *J* = 7.5), 1.08 (d, 3, *J* = 7.0), 1.62 (d, 3, *J* = 6.8), 1.84–2.04 (m, 3), 2.04–2.24 (overlapping m, 2), 3.48–3.58 (m, 1), 3.58–3.66 (m, 2), 5.27 (q, 1, *J* = 6.8). ^{13}C NMR: δ 12.87, 13.24, 15.95, 22.48, 43.28, 65.37, 74.68, 119.49, 143.46. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 67.99; H, 11.73.

(*E*,2*S*)-3-Ethyl-2-methylpent-3-enal (9). Diol mixture **7** and **8** (6.33 g, 40.0 mmol) was dissolved in 120 mL of 95% EtOH and cooled to 0 °C. A solution of $NaIO_4$ (17.1 g, 80.0 mmol) in 240 mL of water was added in one portion. The mixture turned cloudy, and a thick white suspension rapidly formed. The suspension was stirred for 30 min and poured into 350 mL of water. The aldehyde was extracted with three 250-mL portions of pentane, and the combined extracts were dried over $MgSO_4$. The pentane solution was filtered and concentrated with a rotary evaporator to afford 3.50 g (70%) of semipure aldehyde **9**. The aldehyde was diluted with 20 mL of dry THF and stored over sieves momentarily before use in the subsequent aldol reaction. ^1H NMR: δ 0.98 (t, 3, *J* = 6), 1.17 (d, 3, *J* = 7), 1.68 (d, 3, *J* = 7), 2.10 (q, 2, *J* = 6), 3.00 (q, 1, *J* = 6), 5.32 (q, 1, *J* = 7), 9.49 (d, 1, *J* = 2). The optical purity of aldehyde **9** prepared in the foregoing manner was determined by reduction of a small portion with $LiAlH_4$ to the corresponding alcohol, which was converted into the (+)-MTPA ester. ^1H and ^{19}F NMR revealed that aldehyde **9** was ≥95% optically pure.

In our early work, we purified aldehyde **9** by distillation, bp 65 °C (21–24 mm). However, this treatment, or prolonged storage of aldehyde **9** at room temperature, led to parital epimerization. IR (film): 2875, 2800, 1725, 1675 cm^{-1}. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.92; H, 10.97.

2′,6′-Di-*tert*-butyl-4′-methylphenyl (*E*,2*S*,3*R*,4*S*)-2-(Benzyloxy)-5-ethyl-3-hydroxy-2,4-dimethylhept-5-enoate (11). To a 250-mL round-bottomed flask, containing a magnetic stirring bar and fitted for removal of solvent by vacuum transfer was added *n*-butyllithium (16.5 mL of a 1.68 M solution in hexanes, 27.7 mmol). The hexanes were removed by vacuum transfer, and the flask was cooled to −30 °C. Tetrahydrofuran (30 mL) was added, and then diisopropylamine (4.06 mL, 29.0 mmol) was slowly added. The LDA solution was cooled to −100 °C with a THF/liquid nitrogen bath and the ester **10**[4] (10.08 g, 26.4 mmol) in 25 mL of THF was added dropwise with a syringe. The syringe was rinsed with 5 mL of THF, and the enolate was allowed to form for 30 min at −70 °C. Freshly prepared aldehyde **9**[17] in 20 mL of THF was added dropwise over a period of 20 min, and the reaction mixture was allowed to stir for another 20-min period. The reaction was quenched with 10 mL of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with 50 mL of ether. The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration with a rotary evaporator afforded 14.419 g of a mixture of starting ester **10** and a single aldol adduct, **11**. The crude mixture was chromatographed on silica gel (1:60 loading, 1:100 → 1:40 EtOAc/hexane as eluant) to afford 9.07 g (67%) of β-hydroxy ester **11**. $[\alpha]^{23}_D$: −7.1° (*c* 0.050, $CHCl_3$). IR (film): 3580,

(15) This mixture of products coelutes upon attempted chromatographic separation on silica gel. The undesired diol **8** does not react in the oxidative cleavage step (**7** → **9**) and is discarded in the workup of aldehyde **9**.

(16) ^1H NMR spectral data and satisfactory combustion analysis were obtained for the acetonide.

(17) Prepared from 6.33 g (40 mmol) of a 7:1 mixture of **7** and **8** affording 3.50 g (approx 28 mmol) of semipure aldehyde **9** (80% based on **7**).

2230, 1760, 1600, 920, 745 cm^{-1}. ^1H NMR: δ 1.00 (t, 3, J = 7.5), 1.09 (d, 3, J = 7.0), 1.36 (s, 9), 1.38 (s, 9), 1.61 (d, 3, J = 6.7), 1.82 (s, 3), 1.95–2.12 (m, 1), 2.15–2.30 (m, 1), 2.31 (s, 3), 2.68 (m, 1), 2.77 (d, 1, J = 9.5), 4.23 (dd, 1, J = 2, 10.3), 4.81 (AB, 2, J = 11.9, σ_{AB} = 60.8), 5.35 (q, 1, J = 6.7), 7.15 (s, 2), 7.24–7.42 (m, 5). ^{13}C NMR: δ 13.10, 13.36, 14.12, 19.37, 21.19, 22.55, 31.23, 31.46, 35.15, 39.90, 66.36, 75.15, 82.88, 119.94, 127.01, 127.12, 127.40, 127.77, 128.07, 135.31, 137.85, 142.07, 145.35, 146.35, 173.02. Anal. Calcd for $C_{33}H_{48}O_4$: C, 77.91; H, 9.51. Found: C, 77.68; H, 9.28.

2′,6′-Di-*tert*-butyl-4′-methylphenyl (*E*,2*S*,3*R*,4*S*)-2-(Benzyloxy)-3-[(benzyloxy)methoxy]-5-ethyl-2,4-dimethylhept-5-enoate (12). Aldol adduct **11** (5.00 g, 9.83 mmol) and ethyldiisopropylamine (5.23 mL, 30.0 mmol) were dissolved in 20 mL of CH_2Cl_2 at ambient temperature. Benzyl bromomethyl ether (3.50 mL, 20.0 mmol) was added in one portion (exothermic reaction), and the mixture was heated at reflux for 12 h. Because the reaction conditions also decompose benzyl bromomethyl ether, additional amine base and BOMBr (5.23 mL and 3.50 mL, respectively) were added and heating was continued for 18 h. The reaction mixture was allowed to cool to ambient temperature and partitioned between 150 mL of ether and 35 mL of 1 N HCl. The aqueous layer was extracted with 75 mL of ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration with a rotary evaporator afforded 6.632 g of crude **12**. Chromatography on 250 g of silica gel using 1:50 EtOAc/hexane as eluant afforded 6.007 g (97%) of pure ester **12**, $[\alpha]^{23}_D$ −10.4° (c 0.0724, $CHCl_3$). IR (film): 1755, 1605, 1465, 1430, 1180, 745, 710 cm^{-1}. ^1H NMR: δ 0.90 (t, 3, J = 7.3), 1.18 (d, 3, J = 6.4), 1.31 (s, 9), 1.39 (s, 9), 1.50 (d, 3, J = 7.2), 1.87 (s, 3), 2.02 (m, 1), 2.17 (m, 1), 2.30 (s, 3), 2.89 (m, 1), 4.13 (d, 1, J = 3.2), 4.64 (AB, 2, J = 11.9, σ_{AB} = 24.9), 4.86 (AB, 2, J = 11.8, σ_{AB} = 6.0), 4.94 (AB, 2, J = 10.3, σ_{AB} = 47.4), 5.33 (q, 1, J = 7.2), 7.13 (s, 2), 7.03–7.42 (m, 10). ^{13}C NMR: δ 13.08, 13.45, 15.90, 19.23, 21.28, 22.64, 31.42, 35.21, 35.29, 39.62, 66.26, 70.34, 83.85, 84.27, 97.63, 118.57, 126.88, 126.93, 127.13, 127.25, 127.36, 127.51, 127.87, 127.91, 128.10, 128.15, 134.38, 138.03, 138.35, 141.90, 142.54, 146.04, 146.24, 172.43. Anal. Calcd for $C_{41}H_{56}O_5$: C, 78.30; H, 8.97. Found: C, 77.98; H, 9.10.

(*E*,2*R*,3*R*,4*S*)-2-(Benzyloxy)-3-[(benzyloxy)methoxy]-5-ethyl-2,4-dimethylhept-5-en-1-ol (13). Into a 100-mL round-bottomed flask, equipped with a magnetic stirring bar, were placed 0.911 g of $LiAlH_4$ (24.0 mmol) and 12 mL of ether. The flask was fitted with a pressure-equalizing dropping funnel and placed under a nitrogen atmosphere. A solution of 2.96 g (4.71 mmol) of ester **12** in 12 mL of ether was added dropwise to the $LiAlH_4$ suspension through the addition funnel. The addition funnel was replaced with a reflux condenser, and the mixture was heated at reflux for 9 h. The reduction reaction was worked up by quenching with 0.9 mL of water, 0.9 mL of 15% aqueous NaOH solution, and 2.7 mL of water. The gray suspension of aluminum salts was left to stir overnight, and the resulting white solids were removed by filtration. The aluminum salts were extracted in refluxing EtOAc for 5 h and once again removed by filtration. The EtOAc and ether extracts were combined and concentrated with a rotary evaporator, providing 2.743 g of crude material. The impure alcohol was chromatographed on 110 g of flash silica gel with 1:15 → 1:1 EtOAc/hexane as eluant to yield 1.405 g of alcohol **13** (72%) and 0.124 g of diol **14** (9%).

Alcohol 13. $[\alpha]^{22}_D$: −63.5° (c 0.0496, $CHCl_3$). IR (film): 3480, 1610, 1505, 1460, 1050, 1035 cm^{-1}. ^1H NMR: δ −0.95 (t, 3, J = 7.5), 1.15 (d, 3, J = 7.1), 1.36 (s, 3), 1.56 (d, 3, J = 6.8), 1.80–1.95 (m, 1), 2.15–2.30 (m, 1), 2.64 (m, 1), 2.94 (m, 1), 3.60 (dd, 1, J = 8.7, 11.0), 3.75 (dd, 1, J = 2.9), 3.88 (dd, 1, J = 7.9, 11.0), 4.56 (s, 2), 4.68 (AB, 2, J = 11.7, σ_{AB} = 45.5), 4.79 (AB, 2, J = 6.6, σ_{AB} = 20.1), 5.27 (q, 1, J = 6.8), 7.20–7.37 (m, 10). ^{13}C NMR: δ 13.04, 14.82, 18.69, 23.00, 38.59, 64.47, 65.21, 70.38, 80.40, 83.66, 96.84, 118.36, 127.04, 127.59, 128.09, 128.29, 137.33, 139.16, 145.48. Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.57; H, 8.93.

Diol 14. $[\alpha]^{22}_D$: −2.3° (c 0.0321, $CHCl_3$). IR (film): 3425, 1460, 1380, 1055, 745,705 cm^{-1}. ^1H NMR: δ 1.00 (t, 3, J = 7.5), 1.12 (d, 3, J = 7.0), 1.23 (s, 3), 1.62 (d, 3, J = 6.7), 1.99 (m, 1), 2.17 (m, 1), 2.47 (m, 1), 2.56 (m, 1), 2.86 (br s, 1), 3.60–3.85 (m, 3), 4.56 (AB, 2, J = 11.0, σ_{AB} = 6.8), 5.31 (q, 1, J = 6.7), 7.33 (m, 5). ^{13}C NMR: δ 13.06, 13.35, 14.68, 16.85, 22.93, 40.77, 64.17, 66.44, 76.27, 79.47, 119.02, 127.26, 128.20, 138.73, 145.37. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.77; H, 9.68.

(*E*,2*S*,3*R*,4*S*)-2-(Benzyloxy)-3-[(benzyloxy)methoxy]-5-ethyl-2,4-dimethylhept-5-enal (15). To a two-necked round-bottomed flask fitted with an addition funnel and rubber septum and charged with 5 mL of dry CH_2Cl_2 was added oxalyl chloride (0.138 mL, 1.58 mmol). The solution was cooled to −70 °C, and DMSO (0.246 mL) was added dropwise over a period of 5 min. The mixture was stirred for 10 min. Alcohol **13** (0.594 g, 1.44 mmol) in 3 mL of CH_2Cl_2 was added dropwise through the addition funnel. After 15 min, the base ethyldiisopropylamine (1.25 mL) was added dropwise. The reaction mixture was allowed to warm to −10 °C and was partitioned between 75 mL of ether and 10 mL of 1 N HCl. The ether layer was washed with 10 mL of water and dried over $MgSO_4$. Concentration with a rotary evaporator afforded 0.605 g of an oil. The crude aldehyde was chromatographed on 24 g of silica gel with 1:40 EtOAc/hexane as eluant to obtain 0.529 g (90%) of pure material, $[\alpha]^{22}_D$ −7.6° (c 0.0312, $CHCl_3$). IR (film) 1740, 1505, 1460, 1390, 1035, 745, 705 cm^{-1}. ^1H NMR: δ 0.95 (t, 3, J = 7.5), 1.16 (d, 3, J = 7.0), 1.40 (s, 3), 1.55 (d, 3, J = 6.8), 1.74 (m, 1), 2.13 (m, 1), 2.44 (quintet, 1), 3.86 (d, 1, J = 6.6), 4.43 (AB, 2, J = 11.4, σ_{AB} = 31.9), 4.62 (AB, 2, J = 10.2, σ_{AB} = 7.5), 4.90 (AB, 2, J = 6.8, σ_{AB} = 32.0), 5.31 (q, 1, J = 6.8), 7.31 (m, 10), 9.44 (s, 1). ^{13}C NMR: δ 12.95, 13.59, 17.17, 23.61, 39.91, 66.15, 70.36, 84.20, 85.65, 96.88, 121.40, 126.98, 127.12, 127.21, 127.33, 127.42, 127.47, 127.54, 127.65, 127.80, 127.85, 127.88, 128.14, 128.18, 137.70, 138.18, 143.23, 199.13. Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 76.07; H, 8.52.

(*E*,3*R*,4*R*,5*R*,6*S*)- and (*E*,3*S*,4*R*,5*R*,6*S*)-4-(Benzyloxy)-5-[(benzyloxy)methoxy]-7-ethyl-4,6-dimethylnon-7-en-3-ol (17 and 18). To a 10-mL round-bottomed flask equipped with a magnetic stirring bar was added sodium hydride (0.062 g of a 60% dispersion in oil, 1.55 mmol). The oil was removed with successive petroleum ether washes. Residual petroleum ether was evaporated with a stream of nitrogen, and 0.341 (1.55 mmol) of trimethylsulfoxonium iodide was added. The flask was sealed with a rubber septum, and 2.60 mL of DMSO was added dropwise. After 30 min, the reaction mixture was cooled to 0 °C and a solution of 0.529 g (1.29 mmol) of aldehyde **15** in 3 mL of THF was added dropwise. The resulting mixture was stirred for 13 h during which time it warmed to room temperature. The reaction was quenched with 2.60 mL of water, and the resulting mixture was extracted with 75 mL of ether. The ether extract was washed with 5 mL of brine and dried over $MgSO_4$. The dried solution was concentrated with a rotary evaporator to obtain 0.679 g of crude epoxides **16**. This material was immediately dissolved in 1.5 mL of THF and cooled to 0 °C. Solid CuI (15 mg, 6 mol %) was added, and methylmagnesium bromide (1.00 mL of a 3.0 M solution in ether, 3.00 mmol) was added dropwise. The epoxide opening was allowed to proceed for 3 h and then quenched with saturated aqueous NH_4Cl. The aqueous layer was diluted with water and extracted with ether. The combined organic layers were washed with 1 N HCl, dilute NH_4OH, and brine and dried over $MgSO_4$. Filtration and concentration with a rotary evaporator afforded 0.589 g of an oil. The crude material was chromatographed on 30 g of silica gel with 1:30 EtOAc/hexane as eluant to afford 0.343 g (60%) of alcohols **17** and **18** in a ratio of 4:1. More careful chromatography (1:60 loading, 1:50 EtOAc/hexane eluant) afforded pure samples of the two isomers.

Major alcohol, 17. $[\alpha]^{22}_D$: −56.2° (c 0.0495, $CHCl_3$). IR (film): 3510, 1610, 1505, 1460, 1380, 740, 705 cm^{-1}. ^1H NMR: δ 0.92 (t, 3, J = 6.5), 1.02 (t, 3, J = 7.3), 1.15 (d, 3, J = 7.1), 1.27 (s, 3), 1.37–1.44 (m, 1), 1.56 (d, 3, J = 6.7), 1.66–1.78 (m, 1), 1.78–1.86 (m, 1), 2.15–2.23 (m, 1), 2.74 (m, 1), 3.82 (dd, 1, J = 4.1, 1.1), 3.89 (d, 1, J = 2.8), 4.00 (ddd, 1, J = 10.2, 4.0, 1.3), 4.58 (AB, 2, J = 11, σ_{AB} = 52.8), 4.68 (AB, 2, J = 11.9, σ_{AB} = 54.6), 4.77 (AB, 2, J = 6.8, σ_{AB} = 36.6), 5.26 (q, 1, J = 6.7), 7.20–7.40 (m, 10). ^{13}C NMR: δ 11.42, 13.10, 14.91, 17.27, 23.16, 38.24, 65.10, 70.74, 73.30, 81.16, 85.43, 97.20, 118.38, 126.95, 127.01, 127.68, 127.83, 128.07, 128.39, 136.93, 139.23, 145.84. Anal. Calcd for $C_{28}H_{40}O_4$: C, 76.33; H, 9.15. Found: C, 76.15; H, 9.23.

Minor alcohol, 18. IR (film): 3520, 1605, 1500, 1460, 740, 705 cm^{-1}. ^1H NMR: δ 0.93 (t, 3, J = 7.5), 1.03 (t, 3, J = 6.6), 1.13 (d, 3, J = 7.1), 1.29 (s, 3), 1.30–1.50 (m, 1), 1.55 (d, 3, J = 6.7), 1.66–1.85 (m, 1), 1.85–1.98 (m, 1), 2.12–2.30 (m, 1), 2.67 (m, 1), 3.76–3.94 (overlapping m, 2), 3.83 (d, 1, J = 2.8), 4.56–4.93 (overlapping dd, 6), 5.33 (q, 1, J = 6.7), 7.23–7.44 (m, 10). ^{13}C NMR: δ 11.24, 13.10, 15.06, 16.29, 22.93, 24.38, 29.92, 32.19, 38.92,

65.30, 70.36, 74.56, 82.70, 83.25, 96.91, 118.39, 127.02, 127.04, 127.46, 127.66, 128.18, 128.22, 137.72, 138.96, 145.85. Anal. Calcd for $C_{28}H_{40}O_4$: C, 76.33; H, 9.15. Found: C, 76.05; H, 9.19.

(*E*,3*R*,4*S*,5*R*,6*S*)-4-(Benzyloxy)-5-[(benzyloxy)methoxy]-7-ethyl-4,6-dimethyl-3-[(trimethylsilyl)oxy]non-7-ene (19). To a 10-mL two-necked flask equipped with a magnetic stirring bar, 10-mL addition funnel, and rubber septum was added 1.50 mL of CH_2Cl_2 and pyridine (0.140 mL, 1.70 mmol). The solution was cooled to −70 °C, and trimethylsilyl triflate (0.164 mL, 0.85 mmol) was added dropwise with a syringe. A white solid precipitated. After 10 min, the alcohol **17** (0.318 g, 0.72 mmol) in 1.50 mL of CH_2Cl_2 was added to the suspension through the addition funnel. The reaction mixture was allowed to stir for 1 h and poured into 50 mL of pentane. The pentane mixture was washed with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with pentane, and the combined pentane extracts were dried over $MgSO_4$ and concentrated with a rotary evaporator to afford 0.382 g of crude silyl ether **19**. Chromatography of this residue on 20 g of flash silica gel with 1:30 EtOAc/hexane as eluant provided 0.300 g (81%) of silyl ether **19**, $[\alpha]^{22}_D$ +28.3° (*c* 0.0313, $CHCl_3$). IR (film): 1605, 1460, 1380, 1260 cm^{-1}. ^1H NMR: δ 0.15 (s, 9), 0.94 (overlapping t, 6), 1.15 (d, 3, J = 7.1), 1.35 (s, 3), 1.56 (d, 3, J = 6.8), 1.60 (m, 2), 2.00 (m, 1), 2.23 (m, 1), 2.35 (m, 1), 3.72 (m, 2), 4.59 (AB, 2, J = 12, σ_{AB} = 38.2), 4.70 (AB, 2, J = 12, σ_{AB} = 9.9), 4.83 (AB, 2, J = 7.5, σ_{AB} = 29), 7.28 (m, 10). ^{13}C NMR: δ 0.84, 11.49, 13.21, 13.62, 15.29, 22.21, 24.90, 40.99, 65.77, 70.12, 79.24, 83.18, 84.12, 97.49, 119.17, 126.57, 127.09, 127.17, 127.40, 127.92, 128.09, 133.33, 140.27, 145.42. Satisfactory elemental analysis could not be obtained on this material.

(4*R*,5*R*,6*S*,7*R*)-6-(Benzyloxy)-5-[(benzyloxy)methoxy]-4,6-dimethyl-7-[(trimethylsilyl)oxy]nonan-3-one (2). Alkene **19** (0.168 g, 0.328 mmol) was dissolved in 2 mL of 1:1 MeOH/CH_2Cl_2 in a two-necked flask fitted with a drying tube and gas inlet bubbler tube. Several crystals of solid K_2CO_3 buffer were added. Four drops of solvent red no. 23 (0.1% solution in 1:2 EtOH/CH_2Cl_2) indicator were added, and the resulting pale red solution was cooled to −70 °C. Ozone was bubbled through the solution until the indicator turned colorless. The system was purged with nitrogen. Dimethyl sulfide (36 μL) was added, and the temperature was allowed to rise to room temperature. Concentration with a rotary evaporator afforded 0.193 g of crude ketone. The impure material was chromatographed on 10 g of flash silica gel with 1:20 EtOAc/hexane as eluant to afford 0.155 g (94%) of pure ketone **2**, $[\alpha]^{23}_D$ +3.3° (*c* 0.0345, $CHCl_3$). IR (film): 1715, 1460, 1255 cm^{-1}. ^1H NMR: δ 0.17 (s, 9), 0.81 (t, 3, J = 7.2), 0.99 (t, 3, J = 7.5), 1.12 (d, 3, J = 7.2), 1.37 (s, 3), 1.61–1.75 (m, 2), 2.34 (m, 2), 3.01 (m, 1), 3.76 (dd, 1, J = 8.6, 3.1), 4.20 (d, 1, J = 5.8), 4.55 (AB, 2, J = 11.2, σ_{AB} = 69.1), 4.60 (s, 2), 4.71 (AB, 2, J = 6.5, σ_{AB} = 16.9), 7.22–7.38 (m, 10). ^{13}C NMR: δ 0.79, 7.42, 11.78, 13.13, 18.89, 25.54, 34.14, 46.86, 65.61, 70.21, 78.90, 81.87, 83.41, 96.99, 126.88, 127.36, 127.44, 127.52, 127.94, 128.17, 137.84, 139.42, 212.86. Anal. Calcd for $C_{29}H_{44}O_5Si$: C, 69.56; H, 8.86. Found: C, 69.92; H, 9.08.

(*E*,*Z*)-(3*S*,4*R*,5*R*,6*S*)- and (*E*,*Z*)-(3*R*,4*R*,5*R*,6*S*)-4-(Benzyloxy)-5-[(benzyloxy)methoxy]-4,6-dimethyl-7-ethylnon-7-en-3-ols (21 and 22). Method A. To a stirring solution of 520 mg (1.27 mmol) of aldehyde **20** in 7 mL of THF under an argon atmosphere at −78 °C was added 6.5 mL (4.2 mmol) of 0.64 M ethyllithium in ether. The reaction solution was stirred at −78 °C for 15 min and then quenched by addition of 5 mL of aqueous NH_4Cl. The mixture was extracted with ether (2 × 25 mL); the combined ether layers were washed with water and dried over $MgSO_4$. Removal of the solvent in vacuo afforded 520 mg (93%) of alcohols **21** and **22** in a ratio of 4.5:1 (^1H NMR). This mixture of alcohols was used directly for formation of ketone **23**.

Method B. To a solution of 1.27 g (4.98 mmol) of lithium tri-*tert*-butoxyaluminum hydride in 5 mL of THF was added 730 mg (1.66 mmol) of ketone **23** (vide infra) in 5 mL of THF at room temperature. After the mixture was stirred overnight, the reaction was quenched by addition of water. The solid was filtered by suction and washed with ether. The residue obtained after removal of filtrate and washings was passed through a short pad of silica gel, with 5:1 hexanes/ether as eluant. Evaporation of the eluate in vacuo gave 600 mg (82%) of alcohol **21**, contaminated by a trace of isomer **22**. A sample was further purified by preparative TLC (5:1 hexanes/ether) for analysis. IR (film): 3570 cm^{-1}. ^1H NMR: δ 0.90–1.06 (m, 6), 1.09–1.16 (2 d, 3, J = 7), 1.23 and 1.29 (2 s, 3), 1.33 (m, 1), 1.55 and 1.62 (2 d, 3, J = 7), 2.07 (d, 2, J = 7), 1.85–2.25 (m, 1, J = 7), 2.31 and 2.41 (2 d, 1, J = 5), 2.67 and 3.27 (2 m, 1, J = 7), 3.75–3.88 (complex m, 2), 4.61–4.90 (complex m, 6), 5.19 and 5.30 (2 q, 1, J = 7), 7.23–7.34 (m, 10). Anal. Calcd for $C_{28}H_{40}O_4$: C, 76.32; H, 9.15. Found: C, 76.18; H, 9.14.

(*E*,*Z*)-(4*S*,5*R*,6*S*)-4-(Benzyloxy)-5-[(benzyloxy)methoxy]-4,6-dimethyl-7-ethylnon-7-en-3-ones (23): To a solution of 0.56 mL (6.45 mmol) of oxalyl chloride in 15 mL of CH_2Cl_2 was added dropwise 0.92 mL (12.9 mmol) of DMSO at −50 °C. After the mixture was stirred for 5 min, 1.29 g (2.93 mmol) of the mixed alcohols **21** and **22** (vide supra) in 5 mL of CH_2Cl_2 was added. Stirring was continued for an additional 20 min while the bath temperature was warmed from −55 °C to −30 °C. After the addition of 4.1 mL (29.3 mmol) of triethylamine, the mixture was warmed to room temperature over a period of 10 min. Dilution with 15 mL of water, extraction with ether (35, 15, and 15 mL), washing with water, drying over $MgSO_4$, and evaporation of the solvents under reduced pressure afforded 1.28 g of residue. This material was passed through a dry column (11 g of silica gel, 2:1 hexane/ether) giving 1.17 g (91%) of ketone **23**. IR (film): 1710 cm^{-1}. ^1H NMR: δ 0.90–1.03 (2 t, 6, J = 7), 1.07 (d, 3, J = 7), 1.41–1.56 (m, 6), 1.82–2.00 (m, 2), 2.25–2.84 (m, 3), 3.93 (d, 1, minor isomer, J = 4), 3.97 (d, 1, major isomer, J = 6), 4.15–5.15 (various AB patterns, 6), 5.12 (q, 1, J = 7, major isomer), 5.24 (q, 1, J = 7, minor isomer), 7.26–7.37 (m, 10). Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 76.55; H, 8.69.

(4*R*,5*R*,6*S*,7*S*)-6-(Benzyloxy)-5-[(benzyloxy)methoxy]-4,6-dimethyl-7-[(trimethylsilyl)oxy]nonan-3-one (24). To a solution of 570 mg (1.29 mmol) of alcohol **21** in 10 mL of CH_2Cl_2 was added 0.25 mL (1.7 mmol) of *N*-(trimethylsilyl)imidazole. The mixture was stirred at room temperature for 4.5 h and then evaporated in vacuo. The resulting residue was passed through a short pad of silica gel, eluting with 5:1 hexanes/ether. Evaporation of the eluate in vacuo gave 660 mg (100%) of the silyl ether of alcohol **21**. ^1H NMR: δ 0.09 and 0.10 (2 s, 9), 0.89–0.97 (m, 6), 1.04 and 1.08 (2 d, 3, J = 7), 1.35–1.38 (m, 4), 1.52 and 1.60 (2 d, 3, J = 7), 1.86 (m, 1, J = 7), 2.08 (m, 2), 2.83 and 3.48 (2 m, 1), 3.69–3.77 (complex m, 2), 4.46–4.88 (complex m, 6), 5.12 and 5.32 (2 q, 1, J = 7), 7.26–7.32 (m, 10). Anal. Calcd for $C_{31}H_{48}O_4Si$: C, 72.61; H, 9.43. Found: C, 72.70; H, 9.41.

Into a 25-mL round-bottomed flask containing 32 mg (0.062 mmol) of olefin and a stirring bar were placed 5.0 mL of CH_2Cl_2 and 50 μL of a solution of solvent red no. 23 (0.1% solution in 2:1 CH_2Cl_2/ethanol). This solution was cooled to −78 °C, and ozone was bubbled through until the red color faded completely. After the addition of 100 μL (0.58 mmol) of triethyl phosphite, the solvent was removed in vacuo, and the residue was chromatographed on a TLC plate with 10:1 hexanes/ether as eluant to give 22 mg (71%) of ketone **24**, $[\alpha]^{24}_D$ −13.42° (c, 0.025, $CHCl_3$). IR (film): 1710 cm^{-1}. ^1H NMR: δ 0.096 (s, 9), 0.832 (t, 3, J = 7.22), 0.947 (t, 3, J = 7.38), 1.126 (d, 3, J = 7.18), 1.252–1.345 (m, 1), 1.363 (s, 3), 1.900 (ddq, 1, J = 1.95, 13.95, 7.38), 2.429 (q, 2, J = 7.22), 3.122 (dq, 1, J = 4.93, 7.18), 3.702 (dd, 1, J = 10.02, 1.95), 4.227 (d, 1, J = 4.93), 4.387 (d, 1, J = 11.22), 4.452 (d, 1, J = 11.22), 4.564 (d, 1, J = 12.03), 4.608 (d, 1, J = 12.03), 4.780 (d, 1, J = 6.47), 4.821 (d, 1, J = 6.47), 7.272–7.331 (m, 10). Anal. Calcd for $C_{29}H_{44}O_5Si$: C, 69.56; H, 8.86. Found: C, 69.45; H, 8.95.

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Supplementary Material Available: A description of work done to prove the relative stereostructure of a racemic version of ketone **24** (Schemes IV–VII, experimental procedures for the preparation of **15** compounds not described in the main paper, and data on the X-ray analysis of an intermediate that has been related to ketones **2** and **24**) (19 pages). Ordering information is given on any current masthead page.