Synthetic Studies on (2*R*,4′*R*,8′*R*)-α-Tocopherol. An Alternative Synthesis of (2*R*,6*R*)-(+)-2,6,10-Trimethylundecan-1-ol, a Key Side Chain Synthon

Noal Cohen,* Wayne F. Eichel, Rocco J. Lopresti, Christian Neukom, and Gabriel Saucy

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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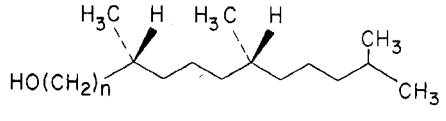
Ortho ester Claisen rearrangement of both (2*R*,4*S*)-(*Z*)-1-*tert*-butoxy-2-methylhept-5-en-4-ol (**10**) and its (2*R*,4*R*)-(*E*) isomer, **11**, gave ethyl (3*R*,7*R*)-(*E*)-8-*tert*-butoxy-3,7-dimethyl-4-octenoate (**12**) having an enantiomeric composition of 87–89% 3*R* and >99% 7*R*. The allylic alcohol substrates were prepared starting from (*S*)-(+)-3-*tert*-butoxy-2-methyl-1-propanol *p*-toluenesulfonate (**3**) or (*S*)-(+)-3-*tert*-butoxy-2-methyl-1-bromopropane (**6**), both intermediates of microbiological origin. Coupling of the tosylate **17** (prepared from **12** via **13** and **16**) with 2-methyl-1-propylmagnesium bromide followed by trifluoroacetic acid treatment of the resultant ether **18** gave the desired, 14-carbon alcohol, **1**.

The homologous, optically active alcohols **1** and **2** are key intermediates in the existing total syntheses of (2*R*,4′*R*,8′*R*)-α-tocopherol.[1-4] Although these compounds can be obtained by degradation of naturally occurring (7*R*,11*R*)-phytol,[1,2] they have recently been made accessible by synthesis as well.[3,4] Whereas the 14-carbon alcohol **1** was constructed from small, microbiologically derived synthons,[3] the homologue **2** was obtained, starting from isovaleraldehyde, by a



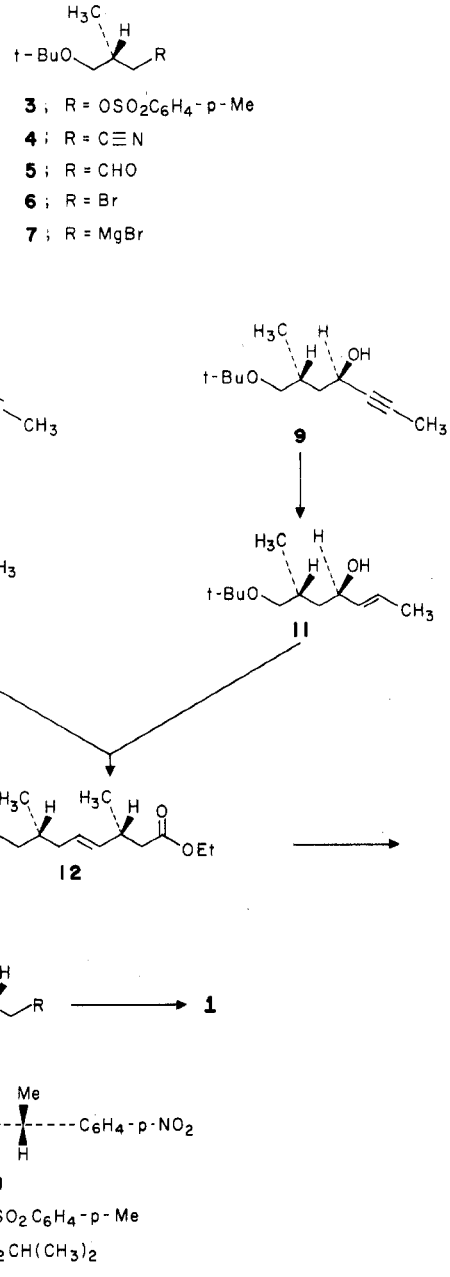
1; n = 1
2; n = 2

process utilizing stereoselective Claisen homologations.[4] In the present report, we wish to describe yet another method for preparing the alcohol **1** which combines key elements of both of these schemes. Our plan envisaged the asymmetric center at C_2 as arising from our four-carbon synthons of microbiological origin and the C_6 center being introduced subsequently via the Claisen sequence.

Results

The required Claisen substrates, allylic alcohols **10** and **11**, were prepared via the epimeric propynyl carbinols **8** and **9** which were themselves obtained by two routes. In the first, the tosylate **3**[3] was homologated with sodium cyanide giving the nitrile **4** (92%). Reduction with diisobutylaluminum hydride then furnished the aldehyde **5** (70%) which yielded the mixture of **8** and **9** (approximately 1:1, 83%) upon reaction with propynyllithium. Alternatively, the same alcohol mixture could be obtained in 60% yield from the bromo ether **6**[3] via interaction of the corresponding Grignard reagent **7**[3] with but-2-yn-1-al.[5]

Attempts to effect the crucial separation of the epimers **8** and **9** using column or preparative thin layer chromatographic techniques were consistently unrewarding. Subsequently, the separation of this mixture was achieved using high-pressure liquid chromatography by which method gram quantities of both epimers could be obtained in essentially pure form. A sample of the less polar epimer was subjected to the Horeau analysis[6] the results of which[7] led to its being assigned the 2*R*,4*S* configuration, **8**. On the basis of this assignment, compound **8** was hydrogenated over Lindlar catalyst[8] giving one of the two required Claisen substrates,[9] (2*R*,4*S*) cis allylic alcohol **10**. The other useful isomer, (2*R*,4*R*) trans alcohol **11**, was obtained by sodium–ammonia reduction of the more polar propynyl carbinol **9**.



3; R = $OSO_2C_6H_4$-p-Me
4; R = C≡N
5; R = CHO
6; R = Br
7; R = MgBr

8
9
10
11
12
13; R = CO_2Et
14; R = CO_2H
15; R = CONH-(Me)-C_6H_4-p-NO_2
16; R = CH_2OH
17; R = $CH_2OSO_2C_6H_4$-p-Me
18; R = $(CH_2)_2CH(CH_3)_2$

Claisen rearrangement, using the ortho ester variation,[4,10] of both allylic alcohols **10** and **11** led to essentially the same product mixture, containing predominantly the desired 3*R*,7*R* unsaturated ester **12**. Samples of this ester derived from both

10 and 11 were separately hydrogenated over Raney nickel[11] giving the saturated 3S,7R ester 13 contaminated with minor amounts of the 3R epimer (see below). The enantiomeric compositions at the newly introduced chiral center were determined by saponification of the saturated ester samples and conversion of the acid 14 to the amide derivative 15. Analysis of the amide samples by high-pressure liquid chromatography[12] revealed a composition at C_3 in the sample derived from 10 of 89% S and 11% R whereas the material derived from 11 exhibited a C_3 composition of 87% S and 13% R. These ratios would be expected to be highly representative of the C_3 composition in the initially formed Claisen product 12, direct analysis of which was not carried out. The transfer of chirality observed upon rearrangement of 10 and 11 is, therefore, of approximately the same magnitude as that exhibited with similar substrates.[4]

It was interesting to note that the major peak observed upon HPLC analysis of the amide 15 was the one of greater elution volume. This result indicated that the major product had the desired 3S configuration by analogy with previous observations.[13] For reference purposes, a sample of racemic 15 was prepared[14] and found to exhibit two peaks of equal intensity on HPLC analysis, identical in retention volume with the two peaks exhibited by the amide samples 15 derived from 12.

Transformation of the ester 13 into the target alcohol 1 was carried out by a sequence in which the final four carbon atoms were introduced using the Fouquet–Schlosser coupling procedure.[16] Thus hydride reduction of 13 gave the alcohol 16 (89%), the tosylate derivative of which (17) was treated with isobutylmagnesium bromide in the presence of dilithium tetrachlorocuprate.[16,17] This produced mainly the desired 14-carbon ether 18[3] along with a minor impurity of similar chromatographic properties. Since this mixture could not be easily separated, it was subjected to trifluoroacetic acid treatment which gave the corresponding alcohol mixture, now readily resolved by column chromatography, affording pure 1 (53% from 17), having an enantiomeric composition of >99% R at C_2 and 87–89% R at C_6.

Experimental Section

All reactions, except hydrogenations, were carried out under an atmosphere of argon. The "usual workup" consists of treatment of the reaction mixture with saturated brine followed by three extractions with the indicated solvent. The organic extracts were then combined, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under water aspirator pressure using a rotary evaporator. The residue was dried to constant weight under high vacuum or aspirator pressure in the case of volatile materials. Column chromatography was performed using Merck (Darmstadt) silica gel 0.063–0.2 mm. The progress of reactions was usually monitored by thin layer chromatography (TLC) which was performed using Merck (Darmstadt) silica gel 60 F-254 plates. Plates were developed with 1:1 hexane–ether as the mobile phase. Spots were detected with phosphomolybdic acid spray followed by heating. Varian A-60, HA-100, or Jeolco C-60H spectrometers were used to obtain the ^1H NMR spectra (in $CDCl_3$ solution). Chemical shifts are reported relative to Me_4Si as an internal standard. Unless otherwise noted, infrared spectra were recorded in $CHCl_3$ solution. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Tetrahydrofuran (THF) was dried by slurrying over Woelm grade I neutral alumina just prior to use.

(R)-(+)-4-*tert*-Butoxy-3-methylbutyronitrile (4). A mixture of 6.4 g (0.021 mol) of the tosylate 3[3] and 2.09 g (0.043 mol) of sodium cyanide in 63 ml of EtOH and 7 ml of water was stirred and refluxed for 11 h. After cooling, the reaction mixture was diluted with ice–water and worked up by extraction with CH_2Cl_2 in the usual manner. The crude product (3.7 g) was chromatographed on 125 g of silica gel. Elution with 4:1 hexane–ether gave 2.98 g (91.7%) of the pure (TLC) nitrile 4 as a colorless liquid. In another run, the chromatographed nitrile was evaporatively distilled yielding a colorless liquid: bp 88–90 °C (bath temperature) (11 mm); $[\alpha]^{25}D$ +7.41° (c 1.8, C_6H_6); ir (neat) 2225 cm^{-1} (C≡N).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.32; H, 11.06; N, 8.72.

(R)-4-*tert*-Butoxy-3-methylbutanal (5). A solution of 4.18 g (0.027 mol) of nitrile 4 in 250 ml of hexane was stirred and cooled to −70 °C and then treated with 19.4 ml (0.0297 mol) of a 25% solution of diisobutylaluminum hydride in toluene, dropwise, over a 20-min period. After the addition was complete, the reaction mixture was stirred at −70 °C for 30 min and then at room temperature for 4 h before being decomposed by the addition of 2.5 ml of ethyl acetate followed by aqueous NH_4Cl and finally 1 N aqueous H_2SO_4. The organic phase was separated and the aqueous phase was extracted with ether. The organic solutions were combined and washed with aqueous $NaHCO_3$ and workup was completed in the usual manner yielding 3.95 g of a yellow oil. This material was evaporatively distilled giving 2.92 g (70%) of the aldehyde 5 as a colorless liquid: bp 81–85 °C (bath temperature) (11 mm); ir 2725 (aldehyde CH), 1715 cm^{-1} (aldehyde C=O); NMR δ 9.67 (m, 1, HC=O), 3.26 (m, 2, $-OCH_2-$), 2.38 (m, 3, > $CHCH_2CHO$), 1.23 (s, 9, $-O-t-C_4H_9$), 1.07 ppm (d, 3, J = 7 Hz, $CH_3CH<$).

Mixture of (2R,4S)- and (2R,4R)-1-*tert*-Butoxy-2-methylhept-5-yn-4-ol (8 and 9). A. From Aldehyde 5. To a stirred solution of 9.8 ml of n-butyllithium (2 M in hexane) in 75 ml of anhydrous THF, at −70 °C, was added 15 ml of liquefied propyne. The cooling bath was removed and the mixture was stirred at 8–15 °C for 1 h. After being recooled to 0 °C, the reaction mixture was treated with a solution of 1.58 g (10 mmol) of aldehyde 5 in 25 ml of dry THF and stirring was continued for an additional 1 h at room temperature. The resulting mixture was treated with aqueous NH_4Cl solution and worked up with ether in the usual manner giving 2.1 g of a pale-yellow oil. This material was chromatographed on 100 g of silica gel. Elution with 2:1 and 1:1 hexane–ether afforded the carbinol mixture (8 and 9) which was evaporatively distilled yielding a colorless liquid (1.98 g, 83%): bp 73–76 °C (bath temperature) (0.1 mm); ir 3600, 3300 cm^{-1} (OH); Raman (5145 Å, neat) 2250 cm^{-1} (C≡C); NMR δ 4.28 (m, 2, >CHO– and –OH), 3.23 (m, 2, $-CH_2O-$), 1.78 (d, J = 2 Hz, $CH_3C{\equiv}C-$), 1.15 (s, 9, $-O-t-C_4H_9$), 0.95 ppm (d, 3, J = 7 Hz, $CH_3CH<$). Gas chromatographic analysis indicated an approximately 1:1 mixture of two components. Samples of material prepared in this way sometimes contained up to 10% of the corresponding homologous carbinol mixture derived from addition of lithium acetylide (arising from the presence of acetylene as a contaminant in the starting propyne) to the aldehyde 5. This impurity was evidenced by a peak in the Raman spectra at 2140 cm^{-1} and by GC analysis. GC conditions: Hewlett-Packard 5710A; 2.7 m × 4 mm (i.d.) column; 10% OV-225 on GCQ 100/120; N_2 carrier gas flow rate 30 ml/min; 120 °C; flame ionization detector; retention times 94 (8) and 98 min (9).

B. From Bromide 6. a solution of the Grignard reagent 7 was prepared from 2.09 g (10 mmol) of the bromide 6 and 0.267 g (11 mg-atoms) of magnesium powder in a total of 22 ml of THF, as described previously.[3] At room temperature, this solution was stirred and treated dropwise with a solution of 0.748 g (11 mmol) of but-2-yn-1-al[5] in 10 ml of THF. The resulting mixture was stirred for 45 min, then kept at room temperature overnight. The reaction mixture was treated with saturated, aqueous NH_4Cl solution and worked up in the usual manner with ether. The crude product (1.78 g) was chromatographed on 50 g of silica gel. Elution with 2:1 and 1:1 hexane–ether followed by evaporative distillation gave 1.17 g (59.1%) of the acetylenic carbinol mixture as a colorless liquid, bp 88–90 °C (bath temperature) (0.2 mm). This material was identical with that produced as in part A, above, by GC, TLC, and spectral comparison.

Separation of 8 and 9. A 9.5-g sample of the ~1:1 carbinol mixture prepared as in part A of the preceding experiment (containing 8.4% of the homologous mixture of acetylene adducts by GC analysis) was separated by preparative high-pressure liquid chromatography. A 4 ft × 21 mm (i.d.) column of silica gel (20–44 μ) was employed with a carrier solvent of 10:1 heptane–ethyl acetate, at a flow rate of 40 ml/min and a pressure drop across the column of 800 psi, at room temperature. The sample was injected in 1.5-g portions. The less polar 4S epimer 8 was isolated after one pass (3.55 g) and was found to be 90% pure (GC). A 0.208-g sample of this material was further purified by dissolution in ether and stirring the resulting solution at room temperature for 3.5 h with 10% aqueous silver nitrate solution. The ether solution was separated and processed in the usual manner, then the residue was evaporatively distilled giving >99% pure 8 (0.189 g) as a colorless oil, bp 88–94 °C (bath temperature) (0.15 mm), $[\alpha]^{25}D$ −3.10° (c 2, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.44; H, 11.36.

The more polar 4R epimer 9 required three passes after which there was obtained 2.71 g. Evaporative distillation gave a colorless liquid, bp 84–88 °C (bath temperature) (0.2 mm). This material was purified

by treatment with $AgNO_3$ as above followed by redistillation yielding 2.46 g of colorless oil. A 0.5-g sample of this material was chromatographed on 25 g of silica gel. Elution with 2:1 and 1:1 hexane–ether followed by evaporative distillation afforded 0.474 g of pure **9** as a colorless oil, bp 64–68 °C (bath temperature) (0.05 mm), $[\alpha]^{25}D$ + 29.74° (*c* 2, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.51; H, 11.07.

Horeau Analysis of 8. A solution of 279 mg (0.9 mmol) of (±)-α-phenylbutyric anhydride and 59.5 mg (0.3 mmol) of carbinol **8** in 3.5 ml of pyridine was kept at room temperature for 20 h.[6] Water (1.5 ml) was added and the mixture was kept at room temperature for 6 h, then extracted with ether. The ether extracts were then washed with 5% $NaHCO_3$ solution and water. The combined aqueous washes were extracted once with $CHCl_3$, then acidified with 1 N H_2SO_4. The recovered acid was isolated by extraction with $CHCl_3$ in the usual manner giving 138 mg of a yellow oil, $[\alpha]^{25}D$ −5.85° (*c* 5.16, C_6H_6).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.26; H, 7.60.

(2*R*,4*S*)-(*Z*)-1-*tert*-Butoxy-2-methylhept-5-en-4-ol (10). A mixture of 1.04 g (5.26 mmol) of carbinol **8**, 0.2 g of Lindlar catalyst,[8] 0.05 g of quinoline, and 50 ml of hexane was stirred in an atmosphere of H_2 for 35 min at the end of which time H_2 uptake (131 ml total) had ceased. The catalyst was filtered and the filtrate was washed with 1 N aqueous HCl, water, aqueous $NaHCO_3$, and brine, then dried, filtered, and concentrated in vacuo. The residue was evaporatively distilled giving 1.0 g of allylic alcohol **10** as a colorless oil: bp 86–89 °C (bath temperature) (0.15 mm); $[\alpha]^{25}D$ −10.99° (*c* 2, $CHCl_3$); Raman (5145 Å, neat) 1675 cm^{-1} (*Z*-CH=CH–). GC analysis (same conditions as for **8** and **9**) indicated a purity of 93.9%. This material was used without further purification.

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.89; H, 12.19.

(2*R*,4*R*)-(*E*)-1-*tert*-Butoxy-2-methylhept-5-en-4-ol (11). A solution of 0.358 g (0.0155 g-atom) of sodium metal in 50 ml of anhydrous liquid ammonia (distilled from sodium) was stirred at −78 °C while a solution of 1.0 g (5.02 mmol) of the carbinol **9** in 5 ml of anhydrous ether was added dropwise over a 10-min period. The resulting blue solution was stirred at reflux for 6 h, then decomposed by the addition of 0.5 g of NH_4Cl. Ether and saturated aqueous NH_4Cl solution were then added and the ammonia was evaporated. Workup with ether in the usual manner (the combined ether extracts were additionally washed with 1 N aqueous HCl and saturated aqueous $NaHCO_3$) afforded 1.05 g of oily product. Evaporative distillation gave 0.975 g of allylic alcohol **11** as a colorless liquid: bp 75–79 °C (bath temperature) (0.15 mm); Raman (5145 Å, neat) 1690 (*E*-CH=CH–), 3300 cm^{-1} (OH). GC analysis indicated the presence of ~10% starting acetylenic alcohol. This material was used without further purification.

(3*R*,7*R*)-(*E*)-Ethyl 8-*tert*-Butoxy-3,7-dimethyl-4-octenoate (12). A. From 10. A mixture of 0.895 g (4.47 mmol) of allylic alcohol **10** (GC purity 94%), 31 mg of propionic acid, and 8.72 g (54 mmol) of triethyl orthoacetate was heated until distillation began. Distillation was continued until the head temperature reached 120 °C, then the distillation head was replaced by a reflux condensor and the solution was stirred at reflux for 3 h (internal temperature 144 °C). After cooling, the reaction mixture was treated with aqueous $NaHCO_3$ and worked up with ether in the usual manner. The crude product was chromatographed on 50 g of silica gel. The ester **12** was eluted with 9:1 and 4:1 hexane–ether and evaporatively distilled giving 0.992 g (82.2%) of a colorless oil: bp 74–78 °C (bath temperature) (0.2 mm); ir (neat) 1750 cm^{-1} (ester C=O); NMR δ 5.36 (m, 2, –CH=CH–), 4.11 (q, 2, *J* = 7 Hz, $-OCH_2CH_3$), 3.13 (d, 2, *J* = 6 Hz, *t*-$BuOCH_2$–), 2.26 (m, 2, $-CH_2C$=O), 1.20 ppm (s, 9, –O-*t*-Bu); GC [1.2 m × 4 mm (i.d.); 20% Carbowax 20M on Chromosorb W 80/100; 200 °C]: 91% (retention time ~5 min).

B. From 11. A 0.96-g (4.8 mmol) sample of the allylic alcohol **11** (GC purity 90%) was rearranged as in part A except that the reaction time was reduced to 1.5 h. Chromatographic purification of the crude product gave 1.03 g (79.5%) of ester **12** which was essentially identical by ir, GC, and TLC comparison with the material prepared as described in part A above.

(3*S*,7*R*)-Ethyl 8-*tert*-Butoxy-3,7-dimethyloctanoate (13). A. A mixture of 1.104 g (4.08 mmol) of unsaturated ester **12** (derived from ortho ester Claisen rearrangement of **10**), a small amount of Raney nickel, and 30 ml of ethyl acetate was stirred in an atmosphere of hydrogen, at room temperature, for 2 h, during which time approximately 1 equiv of hydrogen was taken up. The catalyst was filtered off and washed with ethyl acetate. Concentration of the combined filtrate and washes in vacuo followed by evaporative distillation afforded 1.045 g (95%) of saturated ester **13** as a colorless oil, bp 80–83 °C (bath temperature) (0.15 mm).

B. In a similar manner, a 1.018-g (3.76 mmol) sample of **12** (derived from rearrangement of **11**) was hydrogenated giving **13** (0.957 g, 93.3%) as a colorless oil: bp 81–85 °C (bath temperature) (0.15 mm); GC [1.8 m × 2 mm (i.d.); 10% Carbowax 20M on High Performance Chromosorb W 80/100; 200 °C]: 92% purity (retention time 8.5 min).

(3*S*,7*R*)-8-*tert*-Butoxy-3,7-dimethyloctanoic Acid (14). A. A solution of 0.108 g (0.397 mmol) of ester **13** (from part A of the preceding experiment) in 2.5 ml of MeOH and 1.5 ml of 6 N aqueous NaOH was refluxed for 3 h. The resulting solution was cooled, diluted with water, and extracted with ether. (The ether extract was discarded.) The aqueous solution was then acidified with 6 N aqueous HCl and worked up with ether in the usual manner yielding 0.082 g (85%) of the oily acid **14**, $[\alpha]^{25}D$ +4.26°C (*c* 2, C_6H_6).

Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.55; H, 11.61.

B. A 0.944-g (3.47 mmol) sample of ester **13** (from part B of the preceding experiment) was saponified as above. There was obtained 0.796 g (94%) of acid **14** as a colorless oil, $[\alpha]^{25}D$ +4.74° (*c* 2, C_6H_6).

Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.96; H, 11.31.

(±)-8-*tert*-Butoxy-3,7-dimethyloctanoic Acid [(±)-14]. To a mixture of 5 g (24 mmol) of ethyl 7-formyl-3-methyl-2,4,6-octatrienoate[15] and 115 ml of EtOH was added a solution of 0.239 g (6.3 mmol) of $NaBH_4$ in 25 ml of EtOH at −5 to −10 °C dropwise, with stirring. The resulting solution was stirred at 0 °C for 3 h, then treated with 1 N HCl (→pH 5). Most of the EtOH was removed in vacuo and the residue was worked up with ether in the usual manner giving 4.5 g (89.3%) of ethyl 3,7-dimethyl-8-hydroxy-2,4,6-octatrienoate as an orange oil which solidified upon storage at 0 °C: ir (neat) 3400 (OH), 1715 (ester C=O), 1610 cm^{-1} (C=C). This material was used without further purification.

A mixture of 3.3 g (15.7 mmol) of this hydroxy ester, 1 g of 5% palladium on carbon, and 500 ml of ethyl acetate was stirred in an atmosphere of H_2. After 905 ml of H_2 had been absorbed, the hydrogenation essentially stopped. The catalyst was filtered and the filtrate was concentrated in vacuo. The residue was then dissolved in 500 ml of EtOH and stirred in an H_2 atmosphere in the presence of 0.2 g of platinum oxide until H_2 uptake ceased. The catalyst was filtered and the filtrate was concentrated in vacuo. The residue (3.2 g) was chromatographed on 150 g of silica gel. Elution with 4:1 and 2:1 benzene–ether gave 2.0 g (59%) of ethyl 3,7-dimethyl-8-hydroxyoctanoate as a colorless oil: ir (neat) 3400 (OH), 1740 cm^{-1} (ester C=O).

To a stirred solution of this saturated hydroxy ester (9.25 mmol) and 8 ml of liquid isobutylene in 15 ml of CH_2Cl_2, at −72 °C, was added 0.17 ml of anhydrous phosphoric acid (prepared by dissolving 5 g of P_2O_5 in 11 ml of 85% H_3PO_4) followed by 0.39 ml of boron trifluoride etherate. The resulting mixture was stirred at −72 °C for 2.5 h and at 0–5 °C for 16 h before being decomposed with ice–water followed by $NaHCO_3$. Workup with CH_2Cl_2 in the usual manner gave 2.2 g of oily product which was chromatographed on 125 g of silica gel. Elution with 19:1 benzene–ether gave 0.734 g (29.2%) of ethyl 8-*tert*-butoxy-3,7-dimethyloctanoate as a colorless oil, ir (neat) 1745 cm^{-1} (ester C=O). This material was saponified as described above for the optically active modification giving 0.61 g (93.4%) of **(±)-14** as a pale-yellow oil. The ir and ^1H NMR spectra were identical with those of the optically active modification.

Enantiomeric Purity of Acid 14. A. A 49-mg (0.2 mmol) sample of acid **14** (derived from allylic alcohol **10**) was converted into the amide **15** using the previously described procedure.[12] The crude product was chromatographed on 4 g of silica gel. Elution with ether gave 61 mg of **15** as a yellow oil. Analysis of this amide sample by HPLC[12] revealed a composition of 89.1% *R*,3*S*,7*R* (capacity ratio *k'* = 3.3) and 10.9% *R*,3*R*,7*R* (*k'* = 2.9) (α = 1.14).

B. A 47-mg (0.193 mmol) sample of acid **14** (derived from allylic alcohol **11**) was transformed into the amide **15** as in part A, giving 66 mg of a yellow oil. Analysis of this sample by HPLC[12] revealed a composition of 87% *R*,3*S*,7*R* and 13% *R*,3*R*,7*R*.

C. A 0.60-g (2.47 mmol) sample of **(±)-14** was converted into the amide derivative corresponding to **15**, as above.[12] This material (colorless oil, 0.752 g) was analyzed by HPLC[12] and exhibited two peaks of equal intensity, *k'* = 4.0 (*R*,3*S*,7*R*,*S*) and *k'* = 3.5 (*R*,3*R*,7*R*,*S*) (α = 1.14). Coinjection of this material with that from part A caused enhancement of the peak of longer retention volume. No new peaks were apparent.

(2*R*,6*R*)-(+)-2,6,10-Trimethylundecan-1-ol (1). A slurry of 125 mg (3.28 mmol) of $LiAlH_4$ in 25 ml of ether was stirred and cooled in an ice bath while a solution of 893 mg (3.28 mmol) of ester **13** in 25 ml of ether was added dropwise. After the addition was complete, the

reaction mixture was stirred at room temperature for 4 h, then cooled to 0 °C and cautiously decomposed with 0.45 ml of saturated aqueous Na_2SO_4 solution. After stirring at room temperature for 19 h, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was chromatographed on 30 g of silica gel. Elution with 2:1 and 1:1 hexane–ether gave 669 mg (89%) of the desired alcohol **16** as a colorless oil.

To a stirred solution of 640 mg (2.78 mmol) of this alcohol in 12 ml of pyridine at 0 °C was added 1.057 g (5.56 mmol) of *p*-toluenesulfonyl chloride. The resulting mixture was kept at 0 °C for 17 h, then treated with ice water and stirred for 30 min. The precipitated oil was extracted with ether and the ether extracts were washed with cold 1 N aqueous HCl, saturated aqueous $NaHCO_3$, water, and saturated brine, then dried. Filtration and solvent removal afforded 1.017 g (95%) of the tosylate **17** as a yellow oil which was used without further purification.

A solution of 437 mg (1.14 mmol) of tosylate **17** in 2.5 ml of THF was stirred at −78 °C while 1.42 ml (1.42 mmol) of 1 M 2-methyl-1-propylmagnesium bromide solution in THF was added dropwise followed by 0.058 ml of 0.1 M dilithium tetrachlorocuprate solution in THF.[16,17] The resulting mixture was stirred at −78 °C for 10 min, then allowed to warm to room temperature over a 2-h period and stirred for an additional 18 h. Upon treatment with 1 N aqueous H_2SO_4, the organic materials were isolated by ether extraction in the usual manner giving 339 mg of crude product which was chromatographed on 15 g of silica gel. Elution with 19:1 and 9:1 hexane–ether afforded 237 mg of an oil composed of, mainly, the desired ether **18**[3] (major) but containing a minor impurity. These components were separable only by GC [6 ft × 0.25 in. (o.d.); 20% Carbowax 20M on Chromosorb W 80/100; 200 °C]: retention time 1.3 (**18**) and 3.1 min.

This material was stirred at 0 °C and treated with 4 ml of trifluoroacetic acid. The resulting solution was kept at 0 °C for 17 h, after which time the trifluoroacetic acid was evaporated at reduced pressure. The residue was made alkaline with 20% methanolic KOH, then neutralized with 6 N aqueous HCl. The product was isolated by ether extraction in the usual manner giving 181 mg of crude, oily product. GC analysis (conditions as for the ether precursor) revealed a composition of 79.2% **1** (retention time 4 min) and 18.9% of a more polar impurity, retention time 10.6 min. This material was chromatographed on 10 g of silica gel. Elution with 7:3 and 6:4 hexane–ether gave 130 mg (53.3% based on tosylate **17**) of pure alcohol **1** as a colorless oil, $[\alpha]^{25}D$ +8.16° (*c* 2, hexane). This material was essentially identical with an authentic sample of **1**[2,3] by ir, ^1H NMR, and GC comparison [lit.[2] $[\alpha]^{25}D$ + 9.36° (*c* 2, hexane)].

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Registry No.—**1,** 54154-25-5; **3,** 59965-12-7; **4,** 59983-25-4; **5,** 59983-26-5; **6,** 59965-13-8; **8,** 59983-27-6; **9,** 59983-28-7; **10,** 59983-29-8; **11,** 59983-30-1; **12,** 59991-68-3; **13,** 59983-31-2; **14,** 59991-69-4; **16,** 59991-70-7; **17,** 59991-71-8; **18,** 59965-16-1; propyne, 74-99-7; but-2-yn-1-al, 764-01-2; (±)-α-phenylbutyric anhydride, 40348-94-5; (±)-α-phenylbutyric acid, 7782-29-8; ethyl 7-formyl-3-methyl-2,4,6-octatrienoate, 55646-04-3; ethyl 3,7-dimethyl-8-hydroxy-2,4,6-octatrienoate, 58626-75-8; ethyl 3,7-dimethyl-8-hydroxyoctanoate, 59983-32-3; isobutylene, 115-11-7; ethyl 8-*tert*-butoxy-3,7-dimethyloctanoate, 59983-33-4; *p*-toluenesulfonyl chloride, 98-59-9; 2-methyl-1-propyl bromide, 78-77-3.

References and Notes

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(5) This material was prepared by hydrolysis of the commercially available diethyl acetal (Farchan Co.) using the procedure of L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971, p 170.
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(7) The recovered α-phenylbutyric acid exhibited $[\alpha]^{25}D$ −5.85° (*c* 5.17, C_6H_6) indicating the *S* configuration at the alcohol center by analogy with previous results with related propynyl carbinols.[4]
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(9) Since the direction of construction of compound **1** in the present approach (i.e., "left to right") is opposite to that employed in the previous work leading to **2**,[4] the opposite combination of absolute stereochemistry (at the hydroxyl center) and double bond geometry is required in the Claisen substrates (relative to the previous substrates[4]) in order to produce intermediates (i.e., **12**) having the "natural" configuration at the newly introduced chiral center.
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(13) In the HPLC analysis of amides derived from (*R*)-α-methyl *p*-nitrobenzylamine and 3-methylcarboxylic acids of the type **14** (e.g., citronellic acid, dihydrocitronellic acid, etc.), the *R,3S* diastereomer is generally the one eluted last; see ref 12.
(14) This material (actually a mixture of two racemates) was prepared starting from ethyl 7-formyl-3-methyl-2,4,6-octatrienoate[15] by a sequence involving (1) selective $NaBH_4$ reduction; (2) exhaustive hydrogenation; (3) *tert*-butylation; (4) saponification; (5) conversion to the acid chloride, and (6) reaction with (*R*)-α-methyl-*p*-nitrobenzylamine; see Experimental Section. The presence of an additional, relatively remote enantiomeric mixture at C_7 did not complicate the HPLC analysis.
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