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(29) This material was obtained by reduction of **12b** with $NaAlH_2(O-CH_2CH_2OMe)_2$. For convenience, the studies shown in Scheme II were carried out using **14** derived from (*R*)-(+)-pulegone (**13**). Thus, **13** was converted to (*R*)-(+)-citronellic acid as described by Plesek.[24] Catalytic hydrogenation then gave **12b** having an enantiomeric composition of 96.4% *R*, 3.6% *S*.[15] Alternatively, the citronellic acid was first reduced with hydride to (*R*)-(+)-citronellol which was then hydrogenated to give **14**.
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(33) A sample of **1d** derived from natural (7*R*,11*R*)-phytol[1,4,5] exhibited $[\alpha]^{25}D$ +3.16° ($CHCl_3$). This alcohol was converted into the acid **19b**, $[\alpha]^{25}D$ +5.43° ($CHCl_3$), shown to be 99+% 3*R* by HPLC analysis[15] of the corresponding amide **19e**.

Synthetic Studies on (2*R*,4'*R*,8'*R*)-α-Tocopherol. An Approach Utilizing Side Chain Synthons of Microbiological Origin

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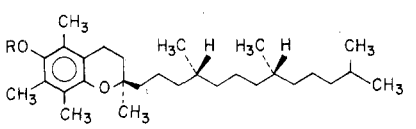
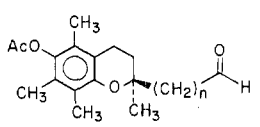
A synthesis of (2*R*,4'*R*,8'*R*)-α-tocopheryl acetate (**1**, R = Ac) is described in which key, optically active side chain synthons are produced starting from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**6**), itself a readily available enantiomerically homogeneous substance of microbiological origin. In the most expeditious approach, (*S*)-(+)-3-*tert*-butoxy-2-methyl-1-propanol *p*-toluenesulfonate (**13**, produced in three steps from **6**) is coupled with (*R*)-3,7-dimethyl-1-octylmagnesium bromide [**33**; derived from (*R*)-(+)-pulegone] giving (2*R*,6*R*)-(+)-1-*tert*-butoxy-2,6,10-trimethylundecane (**20**). The derived 14-carbon Grignard reagent, **22**, is then coupled with (*S*)-(+)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol *p*-toluenesulfonate (**36**) giving (2*R*,4'*R*,8'*R*)-α-tocopheryl benzyl ether and subsequently **1**, R = Ac. The ten-carbon synthons (i.e., **33**) could also be prepared from **13** via (*R*)-(+)-3,7-dimethyloctanoic acid (**28**) thus providing an approach in which both chiral centers as well as eight carbon atoms of the tocopherol side chain are derived from the acid **6**.

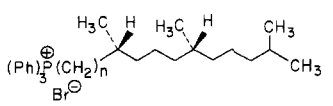
The first formal total synthesis synthesis of (2*R*,4'*R*,8'*R*)-α-tocopherol (**1**, R = H) was reported by Mayer and Isler and co-workers in 1963.[1,2] This group utilized a convergent approach in which the molecule was assembled via a Wittig coupling between the chroman-2-carboxaldehyde **2a** and the



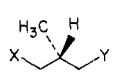
1



2a; n = 0
2b; n = 1



3a; n = 2
3b; n = 1



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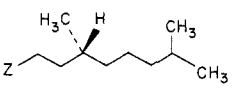


5

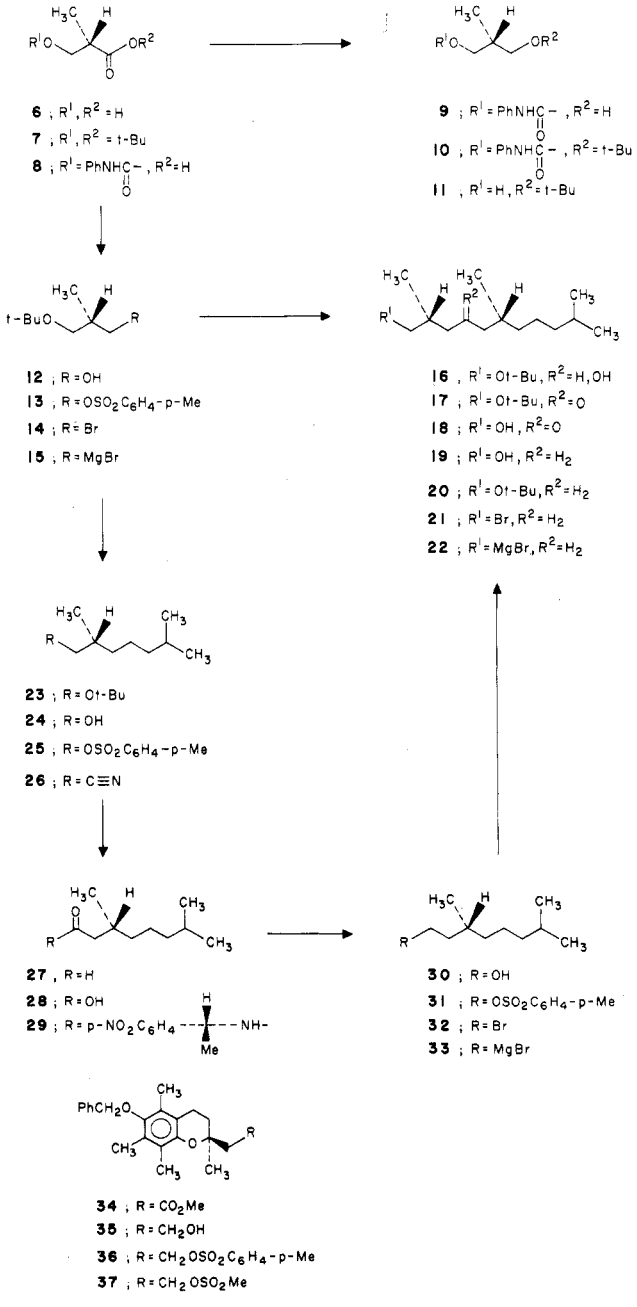
15-carbon[3] phosphonium salt **3a**. More recently, a related scheme was described by Scott et al.[4] involving coupling of the homologous units, chroman-2-acetaldehyde **2b** and the 14-carbon phosphonium salt **3b**. In both of these approaches, the side chain intermediates were derived from natural, (7*R*,11*R*)-phytol, a total synthesis of which had been previously achieved.[5] In the preceding paper, an approach to the synthesis of optically active 15-carbon side chain synthons utilizing stereospecific Claisen rearrangements is delineated.[6] In this report, we wish to describe the preparation, starting from small, microbiologically derived, chiral compounds, of 14-carbon side chain intermediates[4] and their conversion into optically pure (2*R*,4'*R*,8'*R*)-α-tocopheryl acetate (**1**, R = Ac).

Our strategy was based upon the use of a four-carbon intermediate of the type **4** in which the group Y represents a reactive function capable of coupling with a ten-carbon species such as **5** and X, a protected function which would allow subsequent elaboration into a species such as **3b**. It was envisioned that the ten-carbon intermediate **5** could be derived either from natural products or by total synthesis starting from **4**. By reversing the latent and reactive properties of X and Y (i.e., by preparing compounds of opposite chirality) one could employ an alternative sequence in which the four-carbon connective unit was attached first to the chroman portion and the remaining ten carbon atoms added at the end of the synthetic route. It was expected that schemes such as these would be especially well suited for the production of optically pure α-tocopherol in that the crucial carbon–carbon linking operations could be achieved without affecting the integrity of the chiral centers present in the enantiomerically homogeneous starting synthons. This consideration had practical significance since the detection and removal of ra-

cemic or diastereomeric impurities present in the final α-tocopherol molecule (especially materials isomeric at the side chain centers) loomed as a formidable problem which we hoped to avoid.

Results

While searching for potential optically active starting materials from which synthons of the type **4** could be obtained, we were intrigued by a report of Goodhue and Schaeffer[7] indicating that (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**6**) was readily available via the bacterial oxidation of isobutyric acid. Compound **6** possesses not only the desired number of carbon atoms but also two easily distinguishable functional groups. Thus, given the absolute configuration of **6**, it appeared that one need only protect the hydroxyl group in this substance and perform relatively straightforward transformations on the carboxyl moiety in order to obtain intermediates of the type **4** and eventually **3b**. To this end, acid **6** was prepared as described[7] and treated with isobutylene–phosphoric acid–boron trifluoride etherate[8,9] giving the *tert*-butyl ether ester **7** in 79% yield. Lithium aluminum hydride reduction of the latter compound then afforded the (*R*)-hydroxy ether **12** (89%).



The enantiomeric, (*S*)-hydroxy ether **11** was also readily available from **6** by propitious manipulation of protecting groups. Thus, reaction of **6** with phenyl isocyanate gave the urethane acid **8**[7] which was selectively reduced with borane–methyl sulfide complex[10] yielding the hydroxy urethane **9**. *tert*-Butylation[8,9] of the latter substance produced the ether **10** which upon alkaline hydrolysis afforded **11** in 64% overall yield.

Before proceeding with the synthetic scheme, it was deemed necessary to ascertain the enantiomeric composition of these four-carbon intermediates as we lacked assurance first, that the starting acid **6** was enantiomerically pure,[11] and secondly, that racemization had been avoided in the sequences leading from **6** to **11** and **12**. Examination of the ^{1}H NMR spectrum of the ester **7** in the presence of the chiral lanthanide shift reagent Eu(hfbc)$_3$[13] revealed only singlet resonance signals due to the *tert*-butyl groups thus indicating that this material was essentially enantiomerically homogeneous. In contrast, racemic **7**[14] exhibited two singlets of equal intensity separated by 1.5 Hz for each of the *tert*-butyl resonances.[16] A similar analysis could be carried out on the hydroxy ethers **11** and **12**. In the case of the racemic modification,[14] resolutions of 3.0 Hz for the *tert*-butyl protons and 8.0 Hz for the secondary CH_3 protons were observed thus giving rise to two singlets and two doublets, respectively, in the Eu(hfbc)$_3$ shifted spectrum. Because **11** and **12** exhibited shifted spectra in which such resolutions could not be detected, these materials were considered to be essentially enantiomerically pure. On the basis of these results, the starting acid **6**[7] must also be enantiomerically homogeneous since enantiomeric fractionation was not carried out during its conversion into **11** and **12**. Further confirmation of these ^{1}H NMR results is provided below.

Our initial studies aimed at the synthesis of 14-carbon intermediates starting from **6** involved the utilization of ten-carbon species derived from natural products. To this end, the bromide **14** was prepared from **12** by treatment of the latter compound with *N*-bromosuccinimide–triphenylphosphine.[17] The corresponding Grignard reagent **15** (i.e., **4**, X = *t*-BuO; Y = MgBr) was formed in THF and reacted with (*R*)-dihydrocitronellal [**27**, prepared from (*R*)-pulegone[6,18]] giving the adduct **16** as a mixture of hydroxyl epimers, in 61% yield.[19] Direct removal of the hydroxyl group in compounds such as **16** was found, in model studies, to be complicated by side reactions.[20] Therefore, this carbinol mixture was first oxidized[21] to the ketone **17** (84%) which upon treatment with trifluoroacetic acid yielded the ketol **18** quantitatively. Wolff–Kishner reduction[22] of the latter material then provided the desired, optically pure (2*R*,6*R*)-alcohol **19**[4] in 60% yield.

A considerably more expeditious route to **19** was subsequently developed utilizing the coupling procedure of Fouquet and Schlosser[23] by which saturated carbon–carbon linkages can be formed directly and with high efficiency. In this manner, the Grignard reagent **15** upon reaction with tosylate **31** [derived from (*R*)-pulegone via (*R*)-dihydrocitronellol (**30**)[6,18]] in the presence of dilithium tetrachlorocuprate[24] gave the 14-carbon ether **20** in 69% yield. The alternative mode of coupling involving the tosylate **13** and the Grignard reagent **33**[25] furnished **20** in 71% yield. Exposure of the latter compound to trifluoroacetic acid liberated the desired alcohol **19** which was now quite easily accessible from **6**. Finally, the key bromide **21**[4] was obtained either by treatment of **19** with *N*-bromosuccinimide–triphenylphosphine[17] or, more directly, by exposure of the ether **20** to refluxing 48% hydrobromic acid.

The ready availability of our optically pure four-carbon intermediates prompted us to investigate their conversion into the ten-carbon synthons **30**–**33** (i.e., **5**) originally obtained

from natural products. Such an approach, based on the results described above, would provide a route to α-tocopherol in which both asymmetric centers as well as eight carbon atoms of the side chain are derived from the acid **6**. This goal was readily accomplished. Reaction of the tosylate **13** with 3-methyl-1-butylmagnesium bromide in the presence of dilithium tetrachlorocuprate[23,24] gave the nine-carbon ether **23** in 83% yield. A straightforward sequence including *tert*-butyl ether cleavage (→ **24**,[26] CF_3CO_2H), tosylation (→ **25**, *p*-toluenesulfonyl chloride–pyridine), one-carbon homologation (→ **26**,[27] NaCN), and alkaline hydrolysis then produced (*R*)-dihydrocitronellic acid (**28**)[6,18] in 80% overall yield. The enantiomeric composition of this material was determined by high-pressure liquid chromatographic analysis of the corresponding (*R*)-α-methyl-*p*-nitrobenzyl amide derivative **29**[28] and found to consist of essentially only (>99%) the *R* antipode, in confirmation of the aforementioned ^1H NMR shift studies carried out on the four-carbon precursors **7** and **12**. Hydride reduction of **28** led to (*R*)-dihydrocitronellol (**30**)[5,6] thus providing access to optically pure ten-carbon synthons of the type **5**.

Having the 14-carbon bromide **21** (and its precursors) in hand via several routes, all that remained was its coupling with an appropriate chroman unit to form the α-tocopherol molecule. Again, the Fouquet–Schlosser procedure[23] was found to be advantageous. Thus, the required 2-chromanethyl tosylate **36** was prepared starting from the known,[4] (*S*)-(−)-ester **34** via the hydroxy ether **35**, and reacted with the Grignard reagent **22**, in the presence of dilithium tetrachlorocuprate.[24] This procedure afforded (2*R*,4'*R*,8'*R*)-α-tocopheryl benzyl ether (**1**, R = $CH_2C_6H_5$) in 93% yield. Removal of the benzyl protecting group was accomplished by catalytic hydrogenolysis and the resulting α-tocopherol (**1**, R = H) was immediately acetylated. The physical, spectral, and chromatographic properties of the acetate (**1**, R = Ac) so obtained were in excellent agreement with those of natural α-tocopheryl acetate.[2,29] The crucial coupling reaction with **22** was also carried out using the mesylate **37**. In this case, however, the desired product (**1**, R = $CH_2C_6H_5$) was obtained in only 14% yield.

In summary, we have achieved a synthesis of (2*R*,4'*R*,8'*R*)-α-tocopheryl acetate by means of a strategy in which three chiral units of total or near total enantiomeric purity are sequentially coupled. Whereas the asymmetry in the chroman synthon is introduced via a resolution procedure,[4] either one ($C_{4'}$) or both of the chiral centers in the side chain have been derived from the acid **6** via the key four-carbon synthon **12** and related substances. It is anticipated that relatively simple and readily available intermediates such as **12** (and its enantiomer **11**) will have utility in the synthesis of other natural products containing chiral, secondary methyl centers.

Experimental Section

Unless otherwise noted, all reactions were carried out under an atmosphere of argon. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The "usual workup" consists of dilution 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 one of the following mobile phase solvent systems: A, 1:1 benzene–ethyl acetate; B, 1:1 hexane–ether; C, 19:1 hexane–ether. Spots were detected with uv light, or 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. Infrared spectra ($CHCl_3$ solution) were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. The ultraviolet spectra (95% EtOH solution) were recorded on a Cary 14M spectrophotometer. Low-resolution mass spectra were measured on CEC21-110 or JMS-01SG instruments. Tetrahydrofuran (THF) and pyridine were dried by slurrying over Woelm grade I, neutral alumina just prior to use. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. For GC conditions, see paragraph at end of paper regarding supplementary material.

(*S*)-(+)-3-Hydroxy-2-methylpropanoic Acid (6). This material was prepared by bacterial oxidation of isobutyric acid essentially as described by Goodhue and Schaeffer.[7] The crude acidic residue was pumped free of isobutyric acid at 50 °C (0.05 mm) using a rotary evaporator. This gave the hydroxy acid **6**, as a viscous, reddish oil having a GC purity of 87–99% which was not further purified. A sample having a GC purity of >99% exhibited $[\alpha]^{25}D$ +12.72° (*c* 12.5, EtOH) [lit.[12b] $[\alpha]_{578}^{20}$ +4.4° (*c* 11.5, EtOH); lit.[12b] for the enantiomer $[\alpha]_{578}^{20}$ −7.57° (*c* 11.95, EtOH)]; ir 3600–3400 (OH), 1705 cm^{-1} (C=O); NMR δ 7.66 (s, 2, CO_2H, OH), 3.74 (d, 2, *J* = 6 Hz, $-CH_2O-$), 2.69 (sx, 1, >CHCH$_3$), 1.16 ppm (d, 3, *J* = 7 Hz, CH_3).

(*S*)-(+)-*tert*-Butyl 3-*tert*-Butoxy-2-methylpropanoate (7). A solution of 8.7 g (0.074 mol, 89% pure by GC analysis) of acid **6** in 140 ml of CH_2Cl_2 was stirred and cooled to −72 °C (dry ice–acetone bath) whereupon 70 ml of liquefied isobutylene was added rapidly. To the resulting mixture was added with stirring, at −72 °C a mixture of 1.6 ml of phosphoric acid (prepared by dissolving 5 g of P_2O_5 in 11 ml of 85% H_3PO_4) in 10 ml of CH_2Cl_2, dropwise followed by 3.5 ml of boron trifluoride etherate also dropwise. The resulting mixture was stirred at −72 °C for 2 h and at 0–5 °C (ice bath) for 20 h, then treated with ice–water followed by a solution of 19 g of $NaHCO_3$ in 200 ml of water. Workup with CH_2Cl_2 in the usual manner gave 23.3 g of crude product as a yellow oil. This material was chromatographed on 200 g of silica gel. Elution with 19:1 and 9:1 hexane–ether gave the desired product (TLC, system C) which was distilled yielding 12.7 g (79%) of the ether ester **7** as a colorless liquid, bp 99 °C (22 mm), $[\alpha]^{25}D$ +19.52° (*c* 4.25, CH_3OH). The analytical sample was obtained from another, similar preparation as a colorless liquid: bp 77–79.5 °C (10 mm); $[\alpha]^{25}D$ +19.74° (*c* 4, CH_3OH); ir 1715 cm^{-1} (ester C=O); NMR δ 3.38 (m, 2, $-CH_2O-$), 2.50 (sx, 1, *J* = 6 Hz, >CHCH$_3$), 1.44 (s, 9, $-CO_2$-*t*-C_4H_9), 1.14 (s, 9, $-CH_2O$-*t*-C_4H_9), 1.07 ppm (d, 3, *J* = 7 Hz, $CH_3CH<$). [No resolutions of the *tert*-butyl resonances were detectable when the spectrum was run in the presence of Eu(hfbc)$_3$].

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.95; H, 11.33.

(*R*)-(+)-3-*tert*-Butoxy-2-methyl-1-propanol (12). A slurry of 11.2 g (0.295 mol) of lithium aluminum hydride in 470 ml of anhydrous ether was stirred with ice-bath cooling while a solution of 31.9 g (0.1475 mol) of ester **7** in 470 ml of anhydrous ether was added dropwise over 70 min. After stirring at 0–5 °C for 0.5 h and at room temperature for 3 h, the reaction mixture was again chilled and cautiously decomposed by the dropwise addition of 22.4 ml of water and 17.9 ml of 10% aqueous NaOH solution. The resulting mixture was stirred at room temperature for 16 h, then the solids were filtered and washed thoroughly with ether. The filtrate and washes were combined and concentrated at aspirator pressure. Distillation of the residue afforded 19.3 g (89.3%) of hydroxy ether **12** as a colorless liquid, bp 76 °C (13 mm), $[\alpha]^{25}D$ +0.47° (*c* 4.06, CH_3OH). An analytical specimen was obtained from another preparation after purification by chromatography on silica gel (eluted with 2:1 and 1:1 hexane–ether) followed by evaporative distillation, as a colorless liquid: bp 62–67 °C (bath temperature) (10 mm); $[\alpha]^{25}D$ +0.49° (*c* 4, CH_3OH); ir 3625, 3475 cm^{-1} (OH); NMR δ 3.40 (m, 4, $-OCH_2-$), 1.95 (m, 2, $CH_3CH<$ and −OH), 1.20 (s, 9, $-O$-*t*-C_4H_9), 0.86 ppm (d, 3, *J* = 7 Hz, $CH_3CH<$). [No resolutions of the *tert*-butyl or methyl resonances were detectable when the spectrum was run in the presence of Eu(hfbc)$_3$].

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.53; H, 12.18.

(±)-3-Hydroxy-2-methylpropanoic Acid [(±)-6]. Benzyl alcohol (108 g, 1 mol) was stirred and treated with 0.3 g of 50% sodium hydride–mineral oil dispersion. To the resulting solution was added dropwise 415 ml (335 g, 5 mol) of methacrylonitrile over a 40-min period, at room temperature. The reaction mixture was heated at 60–65 °C for 5 , then cooled, acidified with 1 N H_2SO_4, and diluted with ether. The ether solution was worked up in the usual manner. Distillation of the residue gave, after removal of low-boiling materials, 149.3 g (85%) of (±)-3-benzyloxy-2-methylpropionitrile as a colorless liquid, bp 90–93 °C (0.02 mm). An analytical sample was obtained from another, similar run in which the crude product was chromatographed on silica gel. Elution with 19:1 and 9:1 benzene–ethyl acetate followed by evaporative distillation under high vacuum gave pure nitrile, ir 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.07; H, 7.68; N, 8.09.

A solution of 50 g (0.286 mol) of this nitrile in 250 ml of methanol was cooled in an ice–salt bath and stirred while HCl gas was passed in. After the solution had become saturated with HCl, it was refluxed for 2.25 h, then concentrated under aspirator pressure. The residue was treated with aqueous K_2CO_3 and the resulting alkaline mixture was worked up by ether extraction in the usual manner giving 52.2 g of an oil. This material was distilled under reduced pressure yielding 32 g (53.8%) of (±)-methyl 3-benzyloxy-2-methylpropanoate as a colorless liquid, bp 88–90 °C (0.03 mm). In another experiment, the crude product was first chromatographed on silica gel (eluted with 9:1 and 4:1 hexane–ether), then evaporatively distilled under high vacuum giving an analytically pure sample, ir 1735 cm^{-1} (ester C=O).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.64.

A solution of 3.2 g (0.0154 mol) of this ester in 35 ml of CH_3OH was stirred at 0 °C while 15.4 ml of 1 N aqueous NaOH was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, then at room temperature for 2 h. An additional 1.5 ml of 1 N aqueous NaOH was then added and stirring was continued for 1.5 h at room temperature. The resulting solution was diluted with water, some NaCl was added, and the mixture was extracted with ether. The aqueous solution was acidified with 3 N aqueous HCl and the liberated acid was isolated by ether extraction in the usual manner giving 2.5 g (84%) of (±)-3-benzyloxy-2-methylpropanoic acid as an oil. A sample of this material was evaporatively distilled giving a colorless oil, bp 95–100 °C (bath temperature) (0.02 mm), ir 3500–2500 (CO_2H), 1715 cm^{-1} (acid C=O).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.29.

A mixture of 2 g (0.0103 mol) of this acid, 0.5 g of 5% palladium on carbon, and 20 ml of anhydrous THF was stirred in an atmosphere of hydrogen until 1 molar equiv of hydrogen was taken up. The catalyst was filtered and washed with CH_2Cl_2, then the filtrate and washes were combined and concentrated under reduced pressure. The residue was evaporatively distilled giving 0.88 g (82%) of hydroxy acid (±)-**6**[15] as a viscous, colorles oil, bp 105–110 °C (bath temperature) (0.275 mm).The ir and NMR spectra were essentially identical with those of the (*S*)-(+) form.

(±)-*tert*-Butyl 3-*tert*-Butoxy-2-methylpropanoate [(±)-7]. This material was prepared from (±)-**6** as described for the (*S*)-(+) modification. There was obtained a colorless liquid, bp 81–87 °C (bath temperature) (10 mm), in 81.2% yield. This material was identical with (*S*)-(+)-**7** by ir, NMR, GC, and TLC comparisons. When the ^1H NMR spectrum was run in the presence of Eu(hfbc)$_3$, both *tert*-butyl singlet resonances were resolved into two singlets of equal intensity, each with a separation of 1.5 Hz [60 mg of ester + 50 mg of Eu(hfbc)$_3$].

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.53; H, 11.25.

(±)-3-*tert*-Butoxy-2-methyl-1-propanol [(±)-12]. Reduction of the ester (±)-**7** was carried out as described above for the optically active form. The resulting hydroxy ether was obtained in 88% yield as a colorless liquid, bp 70–72 °C (10 mm). This material was identical by ir, NMR, GC, and TLC comparisons with (*R*)-(+)-**12**. When the ^1H NMR spectrum was run in the presence of Eu(hfbc)$_3$ (100 mg/66 mg hydroxy ether), the *tert*-butyl singlet resonance was resolved into two singlets, of equal intensity, separated by 3 Hz whereas the CH_3 doublet was resolved into two doublets, of equal intensity, separated by 8 Hz.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.96; H, 12.64.

(*S*)-(+)-3-*N*-Phenylcarbamoyloxy-2-methylpropanoic Acid (8). A mixture of 106.2 g (0.935 mol) of acid **6** (91.5% purity by GC analysis) and 1380 ml of benzene was stirred efficiently at room temperature while 102 ml (111 g, 0.935 mol) of phenyl isocyanate was added dropwise over a 45-min period. The reaction was mildly exothermic and a clear, orange solution was obtained at the end of the addition period. Crystallization soon began and a very dense slurry formed which was stirred at room temperature for 22 h. The resulting mixture was filtered with suction and the solid was washed with benzene and then hexane. The damp solid was then slurried in hexane, refiltered, and washed with fresh hexane. After drying on a rotary evaporator first at aspirator pressure and then under high vacuum [40 °C (0.4 mm)] there was obtained 159.1 g (76.3%) of the urethane acid **8** as a slightly off-white solid, mp 108–110.5 °C, $[\alpha]^{25}D$ +16.79° (*c* 2.8, CH_3OH) [lit.[7] $[\alpha]^{23}D$ +17.9° (*c* 2.8, CH_3OH), lit[12a] for the enantiomer mp 108–110 °C, $[\alpha]^{23}D$ −17.9° (*c* 2.8, CH_3OH)].

The benzene and hexane filtrates and washes were combined, concentrated under aspirator pressure, and dried under high vacuum giving 58.0 g of impure acid **8** as an orange semisolid which could be separately transformed into the hydroxy ether **11** as described below for the pure material.

(*R*)-3-Hydroxy-2-methyl-1-propyl Carbanilate (9). To a stirred solution of 53 g (0.237 mol) of urethane acid **8** in 177 ml of dry THF was added 24.1 ml (19.3 g, 0.25 mol) of borane–dimethyl sulfide complex[10] dropwise, keeping the temperature between 25 and 30 °C with occasional ice-bath cooling. After the addition was complete and the exotherm had subsided, the reaction mixture was stirred at room temperature for 17 h, then cooled in an ice bath and decomposed by the dropwise addition of 80 ml of MeOH. After stirring at 0–5 °C for 0.75 h and at room temperature for 15 min, the reaction mixture was concentrated under aspirator pressure. The residue was dissolved in ether and the resulting solution was washed with 250-ml portions of saturated aqueous $NaHCO_3$ then worked up in the usual manner yielding 49.6 g of the hydroxy urethane **9** as a yellow oil which was used without further purification (TLC system A).

In a separate experiment, the crude product was chromatographed on silica gel. Elution with 2:1 and 1:1 benzene–ether yielded the pure product as an oil which was evaporatively distilled, bp 110–120 °C (bath temperature) (0.05 mm). A sample of the distillate (which had solidified) was recrystallized from ether–petroleum ether giving colorless solid: mp 59–60 °C; $[\alpha]^{25}D$ +6.00° (*c* 2.00, C_6H_6); $[\alpha]^{25}D$ −4.22° (*c* 2.01, CH_3OH); ir 3650 (OH), 3450 (NH), 1725 (C=O), 1605 cm^{-1}; NMR δ 7.25 (m, 6, C_6H_5, NH), 4.13 (d, 2, J = 5 Hz, $-CO_2CH_2-$), 3.52 (t, 2, J = 5 Hz, $-CH_2OH$), 3.02 (m, 1, –OH), 2.00 (m, 1, $-CHCH_3$), 0.93 ppm (d, 3, J = 7 Hz, CH_3CH-); uv max 235 nm (ϵ 18 420).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.29; H, 7.14; N, 6.85.

(*R*)-(−)-3-*tert*-Butoxy-2-methyl-1-propyl Carbanilate (10). The hydroxy urethane **9** (49.6 g, 0.237 mol) from the preceding experiment was *tert*-butylated using the procedure described above for the conversion of **6** to **7**. The crude product (66 g) was used without further purification. In a separate experiment, a 1-g sample of the crude product was chromatographed on 100 g of silica gel. Elution with 4:1 hexane–ether gave pure **10** (0.793 g) as a viscous, colorless oil: $[\alpha]^{25}D$ −4.89° (*c* 2.04, $CHCl_3$); ir 3440 (NH), 1735 (C=O), 1605 cm^{-1}; NMR δ 7.20 (m, 5, C_6H_5), 6.75 (m, 1, NH), 4.06 (d of d, 2, J = 1, 6 Hz, $-CO_2CH_2-$) 3.22 (d, 2, J = 6 Hz, $-CH_2O$-*t*-Bu), 1.96 (m, 1, $-CHCH_3$), 1.12 (s, 9, –O-*t*-Bu), 0.87 ppm (d, 3, J = 7 Hz, $-CHCH_3$); uv max 235 nm (ϵ 17 450).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.95; H, 8.92; N, 5.33.

(*S*)-(−)-3-*tert*-Butoxy-2-methyl-1-propanol (1). A solution of the crude urethane ether **10** from the preceding experiment and 79.7 g (1.42 mol) of KOH in 915 ml of EtOH was stirred and refluxed for 1.5 h. The resulting slurry was then cooled and concentrated to approximately one-half its original volume on a rotary evaporator. The residue was chilled in an ice bath, treated with ether, and cautiously acidified with 3 N aqueous HCl (gas evolution). The ether layer was separated and the aqueous layer was extracted three times with ether. The combined ether layers were washed twice with 3 N HCl, saturated $NaHCO_3$, and brine, then dried, filtered, and concentrated in vacuo. The residual mixture of oil and solid was distilled at water aspirator pressure using a 5-in. Vigreux column. After removal of a small amount of forerun, the hydroxy ether **11** was obtained as a colorless liquid, bp 78–80 °C (14 mm) (22.2 g, 64.1% overall yield based on acid **8**). GC analysis of this material indicated a purity of 98%.

In a separate experiment, the crude hydrolysis product (11.1 g) was chromatographed on 500 g of silica gel. Elution with 2:1 and 1:1 hexane–ether afforded 5.9 g of the hydroxy ether **11** which was distilled giving 5.1 g of a colorless liquid, bp 77 °C (15 mm), $[\alpha]^{25}D$ −0.35° (*c* 3.96, CH_3OH). The ir and ^1H NMR spectra, GC retention time, and TLC mobility (system B) of this material were identical with those of the (*R*)-(+) enantiomer. No resolutions of the *tert*-butyl or methyl resonances were detectable when the ^1H NMR spectrum was run in the presence of Eu(hfbc)$_3$.

Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.51; H, 12.23.

(*S*)-(+)-3-*tert*-Butoxy-2-methyl-1-bromopropane (14). A solution of 25.8 g (0.176 mol) of hydroxy ether **12** and 50.5 g (0.193 mol) of triphenylphosphine in 105 ml of CH_2Cl_2 was stirred while 32.8 g (0.184 mol) of *N*-bromosuccinimide was added in portions, keeping the temperature below 30 °C with occasional ice-bath cooling. The resulting solution was stirred at room temperature for 1 h, then most of the solvent was distilled under water aspirator pressure using a Vigreux column. The product was distilled from the residue using a short distilling head giving 0.7 g of forerun, bp 58–62 °C (23 mm), and then the main fraction (31.1 g), bp 62–69 °C (14–18 mm). The total

distillate (31.8 g) was chromatographed on 450 g of silica gel. Elution with 19:1 and 9:1 hexane–ether yielded the pure bromo ether **14** which was distilled giving 26 g (70.6%) of colorless liquid, bp 71 °C (16 mm), $[\alpha]^{25}D$ +23.32° (*c* 4.23, C_6H_6). An analytical sample was obtained from another similar preparation as a colorless liquid: bp 56–57 °C (10 mm); $[\alpha]^{25}D$ +22.34° (*c* 4.09, C_6H_6); NMR δ 3.50 (d, 2, *J* = 5 Hz, $-CH_2-$), 3.27 (d, 2, *J* = 6 Hz, $-CH_2-$), 2.06 (m, 1, >CHCH$_3$), 1.20 (s, 9, –O-*t*-C_4H_9), 1.01 ppm (d, 3, *J* =7 Hz, $CH_3CH<$).

Anal. Calcd for $C_8H_{17}BrO$: C, 45.95; H, 8.19; Br, 38.21. Found: C, 46.13; H, 8.36; Br, 38.45.

Mixture of (2*R*,4*R*,6*R*)- and (2*R*,4*S*,6*R*)-1-*tert*-Butoxy-2,6,10-trimethylundecan-4-ol (16). To a stirred mixture of 1.01 g (0.0421 g-atom) of powdered magnesium in 10 ml of anhydrous THF were added a crystal of iodine and a few drops of a solution of 7.35 g (0.0351 mol) of bromide **14** in 14 ml of dry THF. The mixture was brought to reflux and after reaction had begun, the remainder of the bromide solution was added dropwise to the refluxing mixture. After the addition was complete, the reaction mixture was stirred at reflux for an additional 1 h, then cooled to 0–5 °C, whereupon a solution of 5.48 g (0.0351 mol) of (*R*)-(+)-dihydrocitronellal (**27**)[6] in 27 ml of dry THF was added dropwise keeping the temperature at 4–8 °C. The reaction mixture was stirred for 3 h at room temperature, then treated with water and saturated aqueous NH_4Cl solution. The product (9.5 g) was isolated by ether extraction using the usual workup procedure and then chromatographed on 450 g of silica gel. Elution with 4:1 and 2:1 hexane–ether gave the desired product (TLC, system B) which was distilled under high vacuum. There was obtained 6.1 g (61%) of the carbinol mixture **16** as a colorless oil, bp 98–114 °C (0.05 mm). Gas chromatographic analysis indicated the presence of two components in a ratio of 1.45:1. In another, similar experiment, an analytical specimen of **16** was obtained as a colorless oil: bp 75–85 °C (bath temperature) (0.05 mm); $[\alpha]^{25}D$ +2.42° (*c* 2.07, CH_3OH); ir 3375 cm^{-1} (OH).

Anal. Calcd for $C_{18}H_{38}O_2$: C, 75.45; H, 13.37. Found: C, 75.13; H, 13.38.

(2*R*,6*R*)-(+)-1-*tert*-Butoxy-2,6,10-trimethylundecan-4-one (17). A solution of 6 g (0.021 mol) of the hydroxy ether mixture **16** in 90 ml of acetone was stirred with ice bath cooling while 6 ml (0.024 mol of 4 M aqueous H_2CrO_4 solution[21]) was added dropwise, over a 12-min period. The reaction mixture was treated with 12% aqueous $NaHSO_3$ solution and water and the product was isolated by ether extraction in the usual way giving 5.9 g of a colorless oil. This material was chromatographed on 300 g of silica gel. Elution with 19:1 hexane–ether gave the desired keto ether **17** which was distilled under high vacuum yielding 5.0 g (83.8%) of a colorless oil: bp 87–95 °C (0.03 mm); $[\alpha]^{25}D$ +6.62° (*c* 2.03, CH_3OH); ir 1700 cm^{-1} (ketone C=O). The analytical specimen obtained from another experiment exhibited $[\alpha]^{25}D$ +7.04° (*c* 2.02, CH_3OH).

Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76. Found: C, 76.04; H, 12.86.

(2*R*,6*R*)-1-Hydroxy-2,6,10-trimethylundecan-4-one (18). A 5-g (0.0176 mol) sample of keto ether **17** was stirred at 0 °C while 62.5 m of cold trifluoroacetic acid was added dropwise over 0.5 h. The resulting solution was kept at 0 °C for 4.5 h, then poured onto a mixture of ice and excess 10% aqueous NaOH. The product was isolated by ether extraction in the usual manner giving 3.98 g (99%) of the ketol **18** as a pale-yellow oil: ir (neat) 3400 (OH), 1700 cm^{-1} (ketone C=O).

(2*R*,6*R*)-(+)-2,6,10-Trimethylundecan-1-ol (19) from Ketol 18. A mixture of 3.98 g (0.0174 mol) of ketol **18**, 108 ml of diethylene glycol, 25 g of KOH, and 43.5 ml of hydrazine hydrate was stirred and heated until distillation began. Distillation was then continued until the internal temperature of the reaction mixture reached 195 °C, then the mixture was maintained at reflux for 4 h. After cooling, the resulting mixture was treated with ice and 3 N aqueous HCl and worked up by ether extraction in the usual manner giving 2.9 g of a pale-yellow oil. This material was chromatographed on 180 g of silica gel. Elution with 4:1 hexane–ether yielded the desired product, alcohol **19**,[4] which was evaporatively distilled affording 2.22 g (59.7%) of a colorless oil, bp 90–105 °C (bath temperature) (0.2 mm), $[\alpha]^{25}D$ +9.44° (*c* 2.04, hexane) [lit.[4] $[\alpha]^{25}D$ +9.36° (*c* 2.02 hexane), bp 76–78 °C (0.05 mm)]. GC analysis indicated a purity of >99%.

(*R*)-(+)-3,7-Dimethyl-1-octanol *p*-Toluenesulfonate (31). To a solution of 14.2 g (0.09 mol) of (*R*)-(+)-dihydrocitronellol (**30**[6,18]) in 250 ml of anhydrous pyridine at 0 °C was added 34.4 g (0.18 mol) of *p*-toluenesulfonyl chloride in portions. The resulting mixture was kept at 0 °C for 22 h, then treated with ice water. The precipitated oil was extracted with ether and the ether extracts were combined, washed with cold 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and water, then dried over anhydrous K_2CO_3–Na_2SO_4. After filtration and removal of the solvent in vacuo, there was obtained 27.9 g (99.3%) of the tosylate **31** as a yellow oil. This material was used without further purification: ir (neat) 1585, 1180, 1170 cm^{-1}.

(*S*)-(+)-3-*tert*-Butoxy-2-methyl-1-propanol *p*-Toluenesulfonate (13). Using the procedure of the previous experiment, the hydroxy ether **12** was converted into the tosylate **13** in quantitative yield. The tosylate was obtained as a colorless liquid which was used without further purification: $[\alpha]^{25}D$ +8.18° (*c* 4.22, C_6H_6); ir 1595, 1360, 1180, 1170 cm^{-1}.

(*R*)-(−)-1-Bromo-3,7-dimethyloctane (32). To a solution of 10 g (0.0633 mol) of **30** and 18.1 g (0.069 mol) of triphenylphosphine in 38 ml of CH_2Cl_2 was added 11.8 g (0.0663 mol) of *N*-bromosuccinimide[17] in portions, with occasional ice-bath cooling, keeping the temperature below 30 °C. After stirring at room temperaure for 1 h, the solvent was removed in vacuo (aspirator). The residue was treated with hexane and filtered and the solids were washed thoroughly with hexane. Concentration of the combined hexane extracts left 15 g of crude bromide which was chromatographed on 300 g of silica gel. Elution with hexane and 49:1 hexane–ether gave the pure bromide **32** which was distilled, affording 11.5 g (82.3%) of a colorless liquid, bp 105–108 °C (18 mm), $[\alpha]^{25}D$ −5.7° (neat) [lit.[25] bp 102–107 °C (15 mm), $[\alpha]^{20}D$ −4.6° (neat)].

(2*R*,6*R*)-(+)-1-*tert*-Butoxy-2,6,10-trimethylundecane (20) from 15 and 31. A solution of the Grignard reagent **15** was prepared from 3.34 g (0.016 mol) of the bromo ether **14** and 0.42 g (0.0176 g-atom) of magnesium powder in a total of 14 ml of dry THF as described above. To a stirring solution of 2 g (6.4 mmol) of the tosylate **31** in 6 ml of dry THF cooled to −78 °C[23a] was added 7 ml (~8 mmol) of this Grignard solution dropwise followed by 0.33 ml of an 0.1 M Li_2CuCl_4[24] solution in dry THF. The resulting mixture was stirred at −78 °C for 10 min, then in an ice bath (0–5 °C) for 2 h, and finally at room temperature for 16.5 h. The reaction mixture was treated with 1 N aqueous H_2SO_4 and the product was isolated by extraction with ether in the usual manner. Chromatography of the crude product (1.7 g) on silica gel (50 parts) afforded pure ether **20** (eluted with 49:1 hexane–ether). Evaporative distillation gave 1.19 g (68.8%) of colorless oil: bp 75–80 °C (bath temperature) (0.05 mm); $[\alpha]^{25}D$ +1.29° (*c* 2.01, hexane); mass spectrum *m/e* 270 (M^+).

Anal. Calcd for $C_{18}H_{38}O$: C, 79.93; H, 14.16. Found: C, 80.14; H, 14.32.

(2*R*,6*R*)-(+)-1-*tert*-Butoxy-2,6,10-trimethylundecane (20) from 13 and 33. A mixture of 2.33 g (0.097 g-atom) of powdered magnesium and a few iodine crystals in 23 ml of dry THF was stirred at reflux temperature while a solution of 17.9 g (0.08 mol) of bromide **32** in 51 ml of dry THF was added dropwise over 1 h. The mixture was stirred at reflux for an additional 1 h, then cooled to room temperature. To a solution of 19.5 g (0.065 mol) of tosylate **13** in 56 ml of dry THF, stirring at −78 °C, was added the Grignard solution (**33**) dropwise, followed by 3.3 ml of a 0.1 M Li_2CuCl_4 solution in dry THF. The resulting mixture was stirred at −78 °C for 10 min, for 2 h in an ice bath, and finally for 18 h at room temperature. At the end of this time, the reaction mixture was treated with 1 N aqueous H_2SO_4 and workup was carried out by extraction with ether in the usual manner. The crude product was chromatographed on 450 g of silica gel. Elution with 19:1 hexane–ether gave the desired product, which was distilled under high vacuum yielding 12.5 g (71.4%) of **20** as a colorless oil, bp 91–95 °C (0.3 mm), $[\alpha]^{25}D$ +0.94° (*c* 2.01, hexane). This material was virtually identical with that prepared in the preceding experiment by spectral, TLC (systems B and C), and GC comparison. GC analysis indicated a purity of 98.3%.

(2*R*,6*R*)-(+)-2,6,10-Trimethylundecan-1-ol (19) from Ether 20. A 16.9-g (0.0626 mol) sample of ether **20** was treated dropwise with cold trifluoroacetic acid (226 ml) at 0 °C. The resulting solution was kept at 0 °C for 4 h, then concentrated at water aspirator pressure. To the residue was added 400 ml of 5% methanolic NaOH solution. After stirring at room temperature for 15 min, the alkaline mixture was diluted with water and extracted with ether. The crude product (13.5 g) isolated from the ether extracts in the usual manner was chromatographed on 500 g of silica gel. The alcohol **19**[4] was eluted with 4:1 hexane–ether and distilled under high vacuum, giving 12.2 g (91%) of colorless oil, bp 96–99 °C (0.4 mm), $[\alpha]^{25}D$ +9.13° (*c* 2.17, hexane). GC analysis indicated a purity of >99%.

(2*R*,6*R*)-(−)-1-Bromo-2,6,10-trimethylundecane (21) from Alcohol 19. A 12.1-g (0.0565 mol) sample of alcohol **19** from the preceding experiment was treated with *N*-bromosuccinimide (10.65 g, 0.0598 mol) and triphenylphosphine (16.5 g, 0.063 mol) in CH_2Cl_2 (40 ml) using the procedure described above for preparation of **32**. After purification by column chromatography and distillation, there was obtained 13.7 g (88.4%) of bromide **21**[4] as a colorless oil, bp 90–93 °C (0.4 mm), $[\alpha]^{25}D$ −1.152° (neat) [lit.[4] bp 94–95 °C (0.25 mm), $[\alpha]^{25}D$

−0.73° (c 1.92, hexane)].

(2R,6R)-(−)-1-Bromo-2,6,10-trimethylundecane (21) from Ether 20. A mixture of 1 g (3.7 mmol) of ether **20** and 10 ml of 48% aqueous HBr was stirred and heated at reflux for 5.75 h. The resulting mixture was cooled and worked up by ether extraction in the usual manner giving 0.9 g of crude product. This material was chromatographed on 30 g of silica gel. Elution with 49:1 hexane–ether gave the pure bromide **21** which was evaporatively distilled yielding 0.748 g (73.4%) of a colorless oil, bp 83–85 °C (bath temperature) (0.15 mm). GC analysis indicated a purity of 96.9%.

(R)-(+)-1-*tert*-Butoxy-2,6-dimethylheptane (23). A solution of the tosylate **13** (8.6 g, 0.0286 mol) in 30 ml of dry THF was stirred at −70 °C while 21 ml of 3-methyl-1-butylmagnesium bromide solution [prepared from 10.82 g (0.07 mol) of 1-bromo-3-methylbutane and 2.06 g (0.086 g-atom) of magnesium powder in a total of 40 ml of THF] was added dropwise followed by 1.47 ml of 0.1 M Li_2CuCl_4 solution in THF. The resulting mixture was stirred at −70 °C for 10 min, in an ice bath for 2 h, and at room temperature for 18 h, then treated with 1 N aqueous H_2SO_4 and worked up by ether extraction in the usual manner. The crude, oily product (8.0 g) was chromatographed on 250 g of silica gel. Elution with 9:1 hexane–ether afforded 4.72 g (82.7%) of pure ether **23.** A sample prepared in this way was distilled, giving a colorless liquid, bp 94–96 °C (20 mm), $[\alpha]^{25}D$ +9.91° (c 1.22, C_6H_6).

Anal. Calcd for $C_{13}H_{28}O$: C, 77.93; H, 14.08. Found: C, 78.08; H, 14.40.

(R)-(+)-2,6-Dimethylheptan-1-ol (24). Treatment of the ether **23** with trifluoroacetic acid using the procedure described above for conversion of **20** to **19** gave the alcohol **24**,[26] in 90% yield, as a colorless liquid: bp 92–95 °C (bath temperature) (16 mm); $[\alpha]^{25}D$ +10.14° (c 2.01, C_6H_6); ir ($CHCl_3$) 3625 cm^{-1} (OH).

Anal. Calcd for $C_9H_{20}O$: C, 74.93; H. 13.97. Found: C, 74.68; H, 14.08.

(R)-(−)-3,7-Dimethyloctanenitrile (26). Treatment of the alcohol **24** (3.37 g, 0.0234 mol) with *p*-toluenesulfonyl chloride (8.89 g, 0.0468 mol) in 75 ml of pyridine, using the procedure described above for preparation of **31**, gave the tosylate **25** (6.91 g), as a pale-yellow oil. Without further purification, this material was dissolved in 72 ml of EtOH and treated with a solution of 2.27 g (0.0463 mol) of NaCN in 8 ml of water. The resulting mixture was stirred and refluxed for 16 h, then cooled and poured into ice water. Workup with CH_2Cl_2, in the usual manner, gave 3.57 g of crude nitrile **26** as a yellow oil which was used without further purification. In a separate experiment, a sample of the crude nitrile was chromatographed on silica gel (30 parts). Elution with 19:1 and 9:1 hexane–ether, followed by evaporative distillation, furnished pure (Tlc, system B) **26** as a colorless liquid: bp 106–108 °C (bath temperature) (20 mm); $[\alpha]^{25}D$ −3.51° (c 2.08, C_6H_6); ir 2250 cm^{-1} (C≡N) [lit.[27] bp 120–122 °C (35 mm); $[\alpha]^{23}D$ −4.6° (neat)].

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.49; N, 9.14. Found: C, 78.50; H, 12.61; N, 9.08.

(R)-(+)-3,7-Dimethyloctanoic Acid (28). A solution of the crude nitrile from the preceding experiment (3.57 g) in 81 ml of ethylene glycol was treated with a solution of 10 g of KOH in 9 ml of water and the resulting mixture was stirred and refluxed for 17 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ether (the ether extract was discarded). The aqueous, alkaline solution was then acidified with 6 N HCl and worked up with ether in the usual manner. The residue was evaporatively distilled giving 3.54 g (88% based on **24**) of pure (TLC, system B) acid **28**[6,18] as a colorless oil, bp 86–88 °C (bath temperature) (0.10 mm), $[\alpha]^{25}D$ +7.49° (c 5, $CHCl_3$) [lit.[18] bp 109° (3 mm), $[\alpha]^{20}D$ + 5.70° (neat)].

Enantiomeric Purity of Acid 28. A 108-mg (0.63 mmol) sample of acid **28** prepared as described above [a mixture of two lots having $[\alpha]^{25}D$ +7.25 and +7.42° (c 5, $CHCl_3$)] was converted into the amide **29,** a yellow solid (183 mg, 97.3%), using the previously described procedure.[28] Analysis of this amide sample by HPLC[28] revealed a composition of 99.1 ± 0.05% *R*,3*R* (capacity ratio k' = 6.8) and 0.9 ± 0.05% *R*,3*S* (k' = 8.5).

(R)-(+)-3,7-Dimethyloctan-1-ol (30). A solution of 3.33 g (0.0194 mol) of acid **28** (prepared as described above, starting from **12**) in 100 ml of benzene was treated with 16.3 ml of 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene. The resulting mixture was stirred and refluxed for 2 h, then cooled and cautiously poured into 1 N HCl. Workup with ether in the usual manner (the combined ether extracts were additionally washed with aqueous $NaHCO_3$) afforded a yellow oil which was evaporatively distilled. There was obtained 2.97 g (97%) of **30** (GC purity >99%), as a colorless liquid, bp 98–100 °C (bath temperature) (8 mm), $[\alpha]^{25}D$ +4.20° (c 5, $CHCl_3$) [lit.[5] bp 92 °C (0.4 mm), $[\alpha]^{22.5}D$ + 5.23° (neat)].

(S)-(−)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol (35). A 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (35 ml) was stirred with ice-bath cooling while a solution of 20.55 g (0.0558 mol) of ester **34**[4] in 50 ml of benzene was added dropwise over 80 min keeping the temperature below 20 °C. The resulting solution was stirred at room temperature for 2 h, then cautiously poured onto a mixture of ice and 1 N aqueous NaOH. Workup by means of ether extraction in the usual manner afforded 19.8 g of a viscous, colorless oil. This material was triturated with petroleum ether (bp 30–60 °C) and the resulting solid was filtered, washed with petroleum ether, and dried under high vacuum, giving 14.95 g (78.7%) of chromanethanol **35** as a colorless solid: mp 55–56 °C; $[\alpha]^{25}D$ −16.21° (c 2.03, $CHCl_3$); ir 3550 cm^{-1} (OH).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.16; H, 8.20.

An additional 3.26 g (17.2%) of **35** was obtained from the petroleum ether mother liquor.

(S)-(+)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol *p*-Toluenesulfonate (36). Using the procedure described above for preparation of **31**, the chromanethanol **35** was converted into the tosylate **36** which was obtained in essentially quantitative yield as a pale-yellow glass, $[\alpha]^{25}D$ +8.40° (c 1.13, C_6H_6).

Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.39; H, 7.07.

(S)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ethanol Methanesulfonate (37). Treatment of the alcohol **35** (0.5 g, 1.47 mmol) with methanesulfonyl chloride (0.37 g, 3.2 mmol) in pyridine (5 ml), using the procedure described above for preparation of **31**, gave 0.587 g (95.6%) of the mesylate **37** as a colorless solid, mp 81–83 °C, $[\alpha]^{25}D$ −0.36° (c 0.82, C_6H_6).

Anal. Calcd for $C_{23}H_{30}O_5S$: C, 66.00; H, 7.22. Found: C, 66.15; H, 7.25.

(2R,4′R,8′R)-α-Tocopheryl Benzyl Ether (1, R = $CH_2C_6H_5$) from the Mesylate 37. A mixture of 0.216 g (9 mg-atom) of magnesium powder and a crystal of iodine in 2.1 ml of anhydrous THF was stirred and treated with a few drops of a solution of 2.07 g (7.5 mmol) of bromide **21** in 4.9 ml of dry THF. The mixture was brought to reflux and after reaction had begun, the remainder of the bromide solution was added dropwise at reflux. After the addition was complete, the mixture was stirred at reflux for an additional 1 h, then cooled to room temperature. This solution, containing the Grignard reagent **22,** was then added dropwise to a stirring mixture of the mesylate **37** (2.4 g, 5.7 mmol) in 4.7 ml of dry THF, cooled to −72 °C. After the addition of 0.27 ml of 0.1 M Li_2CuCl_4 solution in THF, the reaction mixture was stirred for 10 min at −72 °C, then for 2 h in an ice bath, and finally for 24 h at room temperature. After treatment with aqueous 1 N H_2SO_4, the mixture was worked up by ether extraction in the usual manner, giving 3.6 g of the crude product as a yellow oil. This material was chromatographed on 200 g of silica gel. Fractions eluted with hexane gave 1.0 g of oily material rich in the desired product (TLC, system C). This material was further purified by rechromatography and by preparative thin layer chromatography (silica gel, 19:1 hexane–ether) yielding 0.34 g (14.4%) of pure ether (1, R = $CH_2C_6H_5$) as a pale yellow oil: $[\alpha]^{25}D$ +0.72° (c 1.95, C_6H_6); NMR δ 7.34 (m, 5, C_6H_5–), 4.62 (s, 2, $C_6H_5CH_2$–), 2.56 (t, 2, J = 7 Hz, $ArCH_2$–), 2.18 (s, 3, $ArCH_3$), 2.13 (s, 3, $ArCH_3$), 2.08 (s, 3, $ArCH_3$), 1.76 (t, 2, J = 7 Hz, $ArCH_2CH_2$–), 1.21 (s, CH_3CO–), 0.84 ppm [overlapping d's, 12, >$CHCH_3$ and $(CH_3)_2CH$–]; mass spectrum *m/e* 520 (M^+).

Anal. Calcd for $C_{36}H_{56}O_2$: C, 83.02; H, 10.84. Found: C, 83.22; H, 10.90.

(2R,4′R,8′R)-α-Tocopheryl Benzyl Ether (1, R = $CH_2C_6H_5$) from the Tosylate 36. A solution of the Grignard reagent **22** was prepared as described in the preceding experiment, from 2.68 g (9.7 mmol) of the bromide **21** and 0.28 g (11.7 mg-atoms) of magnesium powder in a total of 8.9 ml of dry THF. This Grignard solution was then added dropwise with stirring to a solution of 3.63 g (7.35 mmol) of the tosylate **36** in 6.3 ml of dry THF, cooled to −78 °C. After the addition of 0.36 ml of 0.1 M Li_2CuCl_4 solution in THF, the reaction mixture was stirred for 10 min at −78 °C, then for 2 h in an ice bath, and finally at room temperature for 19 h. Treatment with 1 N aqueous H_2SO_4 was followed by workup by ether extraction in the usual manner giving 4.3 g of crude product. This material was chromatographed on 200 g of silica gel. Elution with 19:1 hexane–ether afforded 3.55 g (93%) of ether 1 (R = $CH_2C_6H_5$) as a viscous, colorless oil. This material was virtually identical by spectral and TLC comparison with that prepared in the preceding experiment.

(2R,4′R,8′R)-α-Tocopheryl Acetate (1, R = Ac). A solution of the benzyl ether from the preceding experiment (3.55 g, 6.83 mmol) in 63 ml of ethyl acetate was stirred in an atmosphere of hydrogen in the presence of 1.77 g of 5% palladium on carbon catalyst. After hy-

drogen uptake ceased, the catalyst was filtered and the filtrate was concentrated in vacuo yielding 2.90 g of (2R,4'R,8'R)-α-tocopherol (1, R = H) as a colorless oil. A solution of this material in 18 ml of dry pyridine and 14.5 ml of acetic anhydride was kept at room temperature for 20 h, then concentrated under high vacuum. The residue was worked up with hexane in the usual manner, giving a viscous oil which was chromatographed on silica gel (250 g). Elution with 9:1 hexane–ether afforded 2.5 g (78.7%) of pure (TLC, system C) acetate (1, R = Ac) as a colorless oil. A 2.4-g sample of this material was evaporatively distilled yielding 2.37 g of a colorless oil: bp 180–200 °C (bath temperature) (0.7 μ); $[\alpha]^{25}D$ +3.03° (c 5.1, EtOH); uv max 278 mm (ε 1770), 284 (2000), infl 287 (1960); NMR δ 2.56 (t, 2, J = 7 Hz, $ArCH_2$–), 2.27 (s, 3, $-OCOCH_3$), 2.07 (s, 3, $ArCH_3$), 1.99 (s, 3, $ArCH_3$), 1.95 (s, 3, $ArCH_3$), 1.75 (t, 2, J = 7 Hz, $ArCH_2$–), 1.21 (s, CH_3CO), 0.85 ppm [overlapping d's, 12, $CH_3CH<$ and $(CH_3)_2CH$–]; mass spectrum m/e 472 (M^+), 430 (base) [lit.[2b] $[\alpha]^{25}D$ +3.2° (EtOH)]. This material was identical with an authentic sample of d-α-tocopheryl acetate by GC and TLC comparison.

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Registry No.—1 (R = $CH_2C_6H_5$), 59965-06-9; 1 (R = H), 59-02-9; 1 (R Ac), 58-95-7; (S)-(+)-6, 26543-05-5; (+)-6, 44520-17-4; (S)-(+)-7, 59965-07-0; (±)-7, 60018-10-2; 8, 59965-08-1; 9, 59965-09-2; 10, 59965-10-5; 11, 59965-11-6; (R)-(+)-12, 59982-04-6; (±)-12, 60018-11-3; 13, 59965-12-7; 14, 59965-13-8; (2R,4R,6R)-16, 59965-14-9; (2R,4S,6R)-16, 60018-12-4; 17, 59965-15-0; 18, 59982-05-7; 19, 54154-25-5; 20, 59965-16-1; 21, 54154-27-7; 23, 59965-17-2; 24, 59983-44-7; 25, 59965-18-3; 26, 33885-93-7; 27, 60018-13-5; 28, 32531-52-5; 30, 1117-60-8; 31, 59965-19-4; 32, 59965-20-7; 34, 58846-72-3; 35, 60018-14-6; 36, 59965-21-8; 37, 59965-22-9; isobutylene, 115-11-7; benzyl alcohol, 100-51-6; methacrylonitrile, 126-98-7; (±)-3-benzyloxy-2-methylpropionitrile, 59965-23-0; (±)-methyl 3-benzyloxy-2-methylpropanoate, 59965-24-1; (±)-3-benzyloxy-2-methylpropanoic acid, 59965-25-2; phenyl isocyanate, 103-71-9; N-bromosuccinimide, 128-08-5; p-toluenesulfonyl chloride, 98-59-9; 3-methyl-1-butyl bromide, 107-82-4; methanesulfonyl chloride, 124-63-0.

Supplementary Material Available. A table containing the gas chromatographic analytical data pertaining to many of the compounds described above (1 page). Ordering information is given on any current masthead page.

References and Notes

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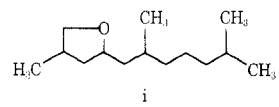

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