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Synthetic Studies on (2*R*,4′*R*,8′*R*)-α-Tocopherol. Facile Syntheses of Optically Active, Saturated, Acyclic Isoprenoids via Stereospecific [3,3] Sigmatropic Rearrangements

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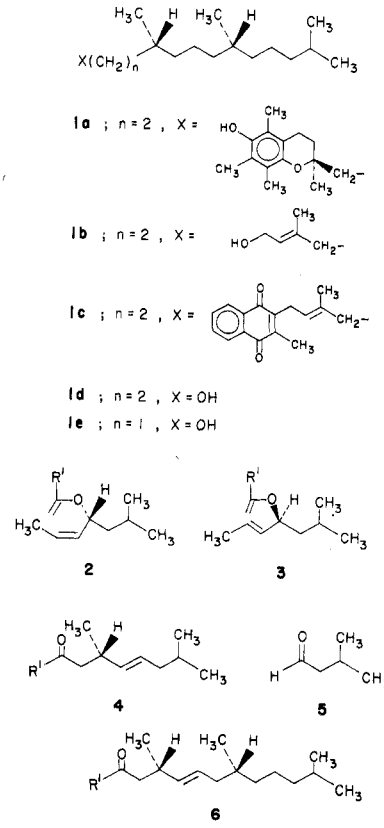
(*R*)-(+)-3,7-Dimethyloctanoic acid (**12b**) was synthesized from isovaleraldehyde (**5**) using a stereospecific, five-carbon homologation process. The key transformations involve [3,3] sigmatropic rearrangements of (*R*)-(+)-(*Z*)-6-methylhept-2-en-4-ol (**10a**) and the (*S*)-(−)-(*E*) isomer **11a** which were prepared from **5** via (±)-6-methylhept-2-yn-4-ol (**7a**). Under a variety of conditions, Claisen rearrangements of **10a** and **11a** were shown to proceed with 97–99% chiral transmission, leading, ultimately, to (*S*)-(+)-(*E*)-3,7-dimethyl-4-octenoic acid [**4b**, 94–96% (*S*)] and **12b**. Repetition of this sequence starting from (*R*)-(+)-3,7-dimethyloctanal (**12a**) produced ethyl (3*S*,7*R*)-3,7,11-trimethyl-4-dodecenoate (**6c**) in a state of high enantiomeric purity [99% (3*S*), 96% (7*R*)]. Ester **6c** was converted to (3*R*,7*R*)-3,7,11-trimethyldodecan-1-ol (**1d**), an important, 15-carbon side chain intermediate in the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**).

The presence of a saturated, aliphatic moiety of the type shown in structure **1**, possessing two chiral, secondary methyl centers, is a feature common to many natural products including the tocopherols, phytol (**1b**), and vitamin K (**1c**, phylloquinone). Because of a particular interest in one of these compounds, namely, (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**),[1] and the lack of efficient, general methods for preparing chiral, acyclic isoprenoids, we recently confronted the problem of producing such species in optically pure form. In this and the following reports,[2,3] we wish to describe our synthetic endeavors aimed at the achievement of this goal.



In the previous syntheses of **1a**,[1,4,5] the key side chain intermediates, alcohols **1d**[4] and **1e**,[5] were produced via degradation of natural phytol (**1b**).[6] Owing to the difficulty of obtaining this natural product in large quantity, it became desirable to develop alternative routes to these intermediates by synthesis starting from simple and readily available starting materials.

One strategy we envisioned was based upon observations reported by several groups indicating that the intramolecular transfer of asymmetry associated with certain [3,3] sigmatropic processes is often substantial.[8-11] Thus, it was our expectation that Claisen rearrangement of the optically active, isomeric allylic alcohol derivatives **2** and **3** should provide, in both cases, the same ten-carbon[12] γ,δ-unsaturated carbonyl compound **4**.[13] Consideration of the mechanism of these rearrangements[14] (Figure 1) led to the conclusion that the chairlike transition states A [derived from the (*R*)-*Z* intermediate **2**] and B [derived from the (*S*)-*E* intermediate **3**] would be favored by virtue of having the smallest number of nonbonded interactions (i.e., pseudoaxial substituents). As can be seen, both A and B yield the same product, **4**, having the (*S*)-*E* stereochemistry.

Since rearrangement substrates **2** and **3** are conceptual

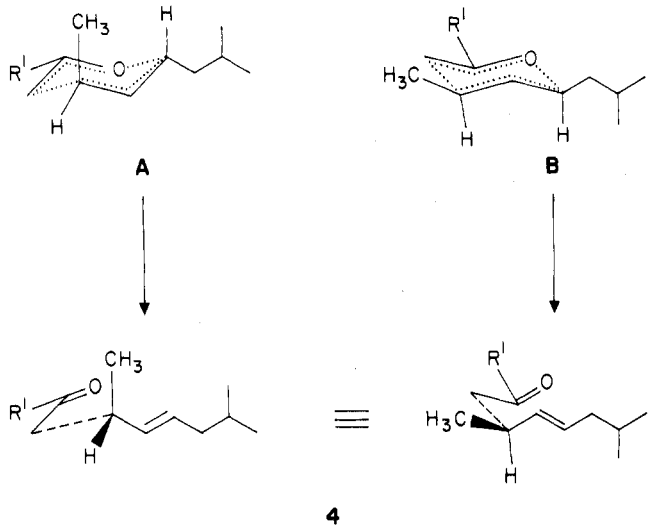


Figure 1.

derivatives of isovaleraldehyde (**5**) (vide infra), their transformation into **4** constitutes a stereospecific, five-carbon homologation process. By repetition of this sequence starting from an aldehyde obtainable from **4** [e.g., (*R*)-(+)-dihydrocitronellal), the ten-carbon synthon could be further homologated, again stereospecifically, to yield a 15-carbon intermediate **6** possessing both of the desired chiral centers. Having **6** in hand, only simple transformations would then be required in order to produce the key alcohol **1d.**

In this report, we wish to present the results of a thorough examination into the extent of chiral transmission in several variants of the Claisen rearrangement, a study which was greatly facilitated by the use of a recently developed, precise technique (HPLC) for measuring the enantiomeric composition of chiral, aliphatic carboxylic acids such as **4** and **6** (R^1 = OH).[15] The application of these rearrangements to the synthesis of **1d** will also be described.

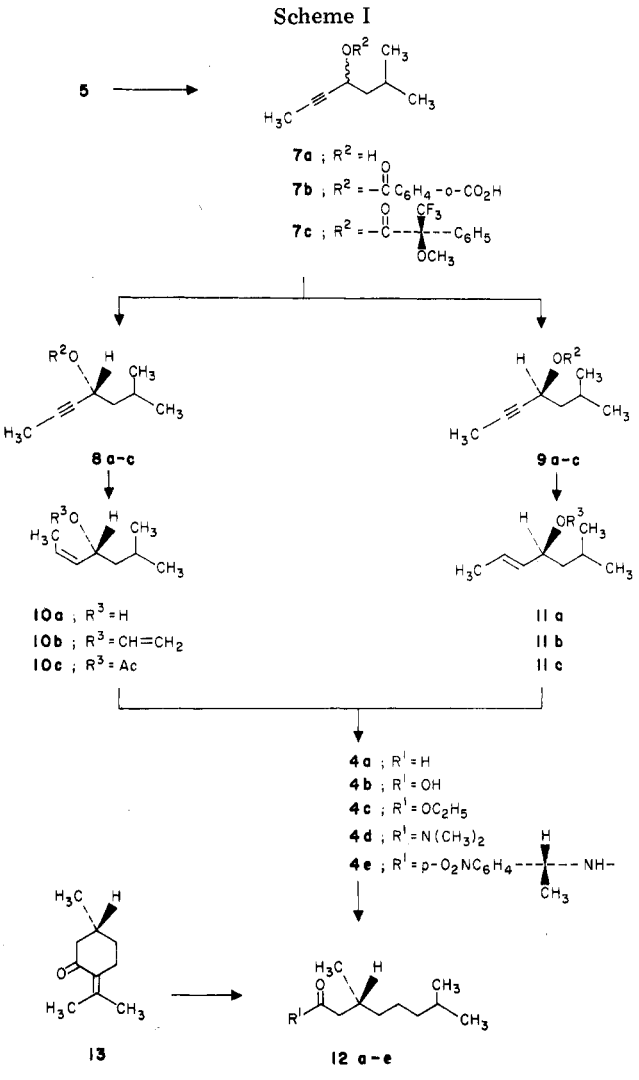
Results

The key Claisen substrates, optically active, allylic alcohols **10a** and **11a,** were prepared starting from isovaleraldehyde (**5**) by, initially, reaction with propynylmagnesium bromide giving the racemic acetylenic carbinol **7a** (Scheme I) in 81.5% yield. This material was resolved via its hemiphthalate **7b** using the enantiomeric α-methylbenzylamines. Thus, (*R*)-(+)-α-methylbenzylamine gave rise to the (*R*)-(+)-hemiphthalate **8b** whereas the antipodal half-acid **9b** was obtained upon resolution with (*S*)-(−)-α-methylbenzylamine. Alkaline hydrolysis of **8b** and **9b** furnished the corresponding acetylenic carbinols **8a** and **9a,** respectively.

The absolute configurations of these carbinols were determined by correlation of **8a** with 2-hydroxy-4-methylpentanoic acid.[16] This was accomplished by partial hydrogenation[17] of **8a** to the allylic alcohol **10a** followed by ozonolysis.[16] The same configurational assignments were arrived at by applying the Horeau method[18] directly to **8a** and **9a.**[19]

Having assigned the absolute configuration of these propynyl carbinols, we next turned our attention to the determination of their enantiomeric purities. This was achieved most expeditiously by GC analysis of the MTPA esters[21] **8c** and **9c** which revealed favorable enantiomeric compositions of 96.5% *R*, 3.5% *S* (±1%) for **8a** and 97.8% *S*, 2.2% *R* (±1%) for **9a.** These antipodes were then selectively reduced to give the desired Claisen substrates. Thus, partial hydrogenation[17] of **8a,** as mentioned above, afforded the (*R*)-*Z*-allylic alcohol **10a** (92%; 98.7% *Z*) whereas reduction of **9a** with sodium in liquid NH_3[22a] yielded the (*S*)-*E* isomer **11a** (81%; 99% *E*).

Scheme I



NMR studies on these alcohols, using chiral shift reagents, indicated that no racemization had occurred during the reduction processes.

With the required substrates in hand, in a state of high, if not absolute, purity, their utility for the production of optically active isoprenoid substances could now be investigated. To this end, alcohols **10a** and **11a** were subjected to four synthetically useful variants of the Claisen rearrangement. In the first, these compounds were treated with ethyl vinyl ether[23] affording the corresponding vinyl ethers **10b** and **11b** (i.e., **2** and **3,** R^1 = H), respectively. Upon refluxing in benzene for 70 h, both of these substrates yielded the expected unsaturated aldehyde (*S*)-*E*-**4a** (100% *E*), which via silver oxide oxidation (→ **4b**) followed by catalytic hydrogenation produced the known (*R*)-(+)-dihydrocitronellic acid **12b** [derived for comparison purposes from (*R*)-(+)-pulegone (**13**)[24]]. Alternatively, treatment of **10a** and **11a,** respectively, with triethyl orthoacetate–propionic acid[25] smoothly yielded the unsaturated (*S*)-*E* ester **4c** (100% *E*) in both cases. These ester samples were converted into **4b** by saponification or to **12c** by hydrogenation. The third Claisen procedure involved the conversion of **10a** and **11a** into the (*S*)-*E* unsaturated amide **4d** (100% *E*) via the agency of 1,1-dimethoxy-1-dimethylaminoethane.[26] Again, **4b** was obtained by alkaline hydrolysis of the initial rearrangement product (**12b** was obtained from **4d** by hydrogenation followed by acidic hydrolysis). Finally, the acetates **10c** and **11c** were converted with lithium diisopropylamide into their enolates which were subsequently quenched with *tert*-butyldimethylchlorosilane at −78 °C.[27] Warming the resultant ketene acetals (i.e., **2** and **3,** R^1 =

Table I. Claisen Rearrangements Leading to 4

Starting alcohol[a]	Method[b]	Initial product	Chemical purity (GC), %	Chemical yield, %	$[\alpha]^{25}D$ of initial product[c]	$[\alpha]^{25}D$ of 4b[c,d]	Enantiomeric composition in 4b[d,e] % S	% R	% transfer of chirality[f]
10a	A	**4a**	87.2	32[h,l]	+30.18	+27.20[m]	94.9	5.1	98.4
11a	A	**4a**	79.4	48[h,l]		+26.46[m]	95.8	4.2	98.0
10a	B	**4c**	97.0	54[i,l]	+18.08	+28.57[n]	94.4	5.6	97.8
11a	B	**4c**	93.5	65[h,l]	+18.42	+27.65[n]	95.4	4.6	97.5
10a	C	**4d**	100	82[h]	+19.36	+26.18[o]	95.9	4.1	99.4
11a	C	**4d**	97.7	92[h,l]	+20.64	+27.11[o]	95.5	4.5	97.6
10a	D	**4b**[g]	100	63[h,j]		+27.21	94.5	5.5	98.0
11a	D	**4b**[g]	98.4	51[h,k,l]		+24.09	94.5	5.5	96.5

[a] Enantiomeric composition of **10a**, 96.5% *R*, 3.5% *S*; for **11a**, 97.8% *S*, 2.2% *R* based on GC analysis of the corresponding MTPA esters, **8c** and **9c** (limits of accuracy ±1%). [b] A, (1) ethyl vinyl ether, (2) 80 °C;[23] B, $CH_3C(OC_2H_5)_3$, propionic acid, 140 °C;[25] C, $CH_3C(OCH_3)_2N(CH_3)_2$, 140 °C;[26] D, (1) Ac_2O, (2) $LiN(i\text{-}C_3H_7)_2$, (3) *t*-$Bu(CH_3)_2SiCl$, (4) Δ, r.t.; (5) H_3O^+.[27] [c] 5% in $CHCl_3$. [d] Essentially pure acid; no detectable *Z* isomer by GC analysis of the Me_3Si derivative. [e] Determined by HPLC analysis[15] of the crude amide, **4e** (limits of accuracy ±1%). [f] Calculated as % major enantiomer in product/% major enantiomer in starting material × 100. [g] The initially formed *tert*-butyldimethylsilyl ester of **4b** was directly hydrolyzed. [h] Yields not optimized. [i] Yields improved to 70–80% in subsequent experiments. [j] Yield based on the acetate, **10c**. [k] Yield based on the acetate, **11c**. [l] Corrected for GC purity. [m] Prepared by silver oxide oxidation of **4a**. [n] Prepared by saponification of **4c**. [o] Prepared by alkaline hydrolysis of **4d**.

$OSiMe_2$-*t*-Bu) to room temperature caused their rearrangement to occur resulting, in both cases, after acidic hydrolysis, in the unsaturated acid, **4b** (100% *E*).

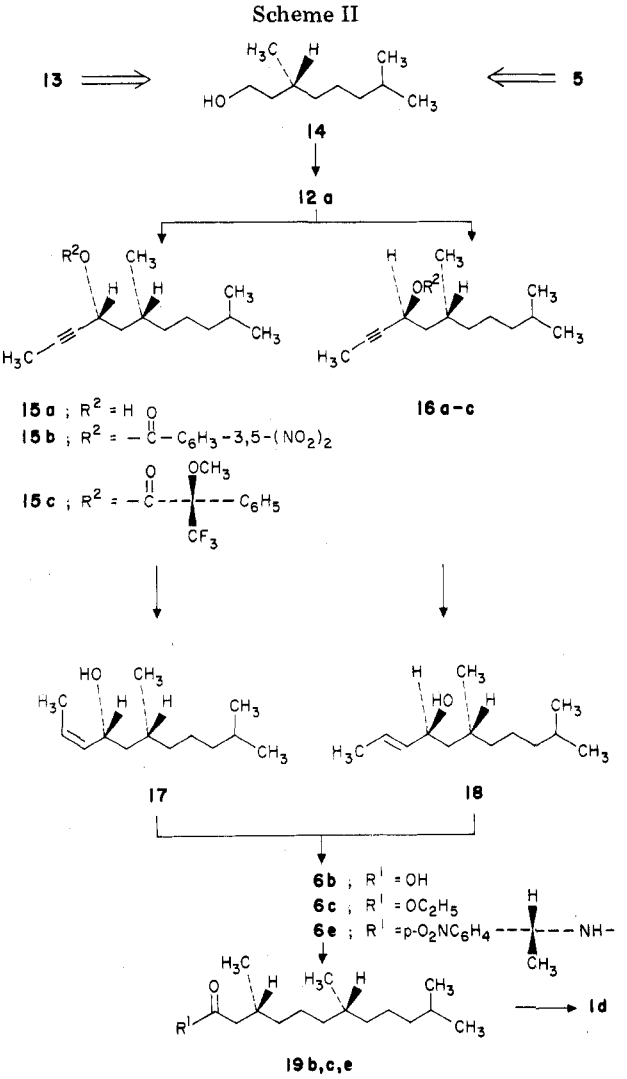
In order to ascertain the degree of chiral transmission in these transformations, samples of the unsaturated acid **4b** from each of the eight rearrangement reactions were converted into the corresponding (*R*)-α-methyl-*p*-nitrobenzylamides **4e** whose enantiomeric compositions were then determined by high-pressure liquid chromatographic analysis.[15] The results are summarized in Table I and clearly demonstrate that Claisen rearrangements of the substrates **2** and **3** proceed with essentially total stereospecificity (97–99 ± 1% chiral transmission) to give the same isoprenoid synthons **4**, possessing the required absolute configuration for natural product synthesis. Of considerable interest is the fact that virtually no difference in chiral transmission is observed among the rearrangements which occur at room temperature[27] and those taking place at 140 °C.[25,26]

An important, practical feature of the conversion of isovaleraldehyde into the ten-carbon intermediates **4** by the above processes should be noted. This involves the consideration that, although a classical resolution is employed to introduce the optical activity initially, both enantiomers of the resolved material (**8** and **9**) can be utilized productively in the synthetic sequence. Thus, the major disadvantage normally associated with such resolutions, namely, the loss of overall efficiency due to the formation of a useless enantiomer, is overcome.

It was found that when the unsaturated substances **4b–d** were hydrogenated over palladium catalysts, racemization of the chiral center occurred to a certain extent.[28] This frustrating problem could be overcome through the use of Raney nickel as the hydrogenation catalyst, which allowed double bond reduction with essentially no accompanying racemization. These results are summarized in Table II.

Having accomplished our initial goal of preparing chiral ten-carbon synthons such as **12b**, in high enantiomeric purity (94–95% *R*), starting from isovaleraldehyde, we next turned our attention to synthesis of **1d** by the route delineated in Scheme II. Oxidation of (*R*)-(+)-dihydrocitronellol (**14**)[29] with freshly prepared silver carbonate on Celite[30] afforded (*R*)-(+)-dihydrocitronellal (**12a**)[7] in 46% yield. Treatment of this aldehyde with propynylmagnesium bromide as described above produced the mixture of carbinols **15a** and **16a** (ca. 1:1) in essentially quantitative yield. This mixture was partially resolved by column chromatography on silica gel to give the

Scheme II



more polar epimer **15a** having a composition of 92% *R*, 8% *S* at C_4 as determined by GC analysis of the MTPA derivative **15c**, whereas the less polar epimer **16a** was isolated having a composition of 96% *S*, 4% *R* at C_4. Final purification of these epimers was effected by recrystallization of the corresponding 3,5-dinitrobenzoate derivatives **15b** and **16b**, which were ob-

Table II. Hydrogenation of 4[a]

Starting compd	Enantiomeric composition[b] % S	% R	Catalyst	$[\alpha]^{25}D$ of initial product 12[c]	$[\alpha]^{25}D$ of derived 12b[c]	Enantiomeric composition[d] % R	% S
(S)-(+)-4b[e]	94.4	5.6	5% Pd/C[j]	+5.61		87.9	12.1
(S)-(+)-4b[e]	94.4	5.6	Ni (Raney)[k]	+7.05		95.4	4.6
(S)-(+)-4c[f]	95.4	4.6	5% Pd/C[k]	+3.29	+6.31[n]	87.9	12.1
(S)-(+)-4c[g]	94.4	5.6	5% Pd/C[l]	+3.23	+6.16[n]	84.7	15.3
(R)-(−)-4c[h]	2.1	97.9	5% Pd/C[k]	−3.31	−5.77[n]	11.0	89.0
(R)-(−)-4c[h]	2.1	97.9	PtO_2[k]	−3.51	−6.29[n]	9.0	91.0
(R)-(−)-4c[h]	2.1	97.9	Ni (Raney)[k]	−3.64	−6.72[n]	5.0	95.0
(S)-(+)-4d[i]	95.9	4.1	5% Pd/C[m]	+1.18	+6.90[o]	93.0	7.0

[a] All hydrogenations carried out at 23 °C and 1 atm and allowed to proceed until essentially 1 molar equiv of H_2 absorbed. [b] Determined by HPLC analysis[15] of the amide derivatives, **4e.** [c] $CHCl_3$, *c* 5; (+)-**12b** having an enantiomeric composition of >99% 3*R* exhibits $[\alpha]^{25}D$ +7.2°.[2] [d] Determined by HPLC analysis of the amide derivatives, **12e.**[15] [e] $[\alpha]^{25}D$ +28.57° (*c* 5, $CHCl_3$). [f] $[\alpha]^{25}D$ +18.42° (*c* 5.03, $CHCl_3$). [g] $[\alpha]^{25}D$ +18.08 (*c* 3.43, $CHCl_3$). [h] Bp 88–89 °C (8 mm); $[\alpha]^{25}D$ −19.02° (*c* 5, $CHCl_3$); prepared by Lindlar hydrogenation[17] of **9a** (giving the *Z* isomer of **11a**) followed by ortho ester Claisen rearrangement,[25] as described for the conversion of **8a** to (*S*)-(+)-**4c.** [i] $[\alpha]^{25}D$ +19.36° (*c* 5, $CHCl_3$). [j] Carried out in ethyl acetate. [k] Carried out in EtOH. [l] Carried out in ethyl acetate with added Et_3N. [m] Carried out in MeOH. [n] Prepared by saponification of **12c.** [o] Prepared by acidic hydrolysis of **12d.**

tained by treatment of the impure carbinols with 3,5-dinitrobenzoic acid–*p*-toluenesulfonyl chloride.[31] Alkaline hydrolysis of the purified esters regenerated the parent carbinols, now found to be essentially enantiomerically pure at C_4. The absolute configurations at C_4 in **15a** (*R*) and **16a** (*S*) were assigned by comparison of their observed optical rotations with those of the homologous carbinols **8a** and **9a.**

Partial hydrogenation[17] of **15a** afforded the (4*R*,6*R*)-*Z*-allylic alcohol **17** (93%) containing approximately 1–2% of the *E* isomer as shown by GC analysis of the Me_3Si derivative. On the other hand, reduction of **16a** with $NaAlH_2(OCH_2CH_2OMe)_2$[22b] gave the (4*S*,6*R*)-*E*-allylic alcohol **18** (84%) free of the *Z* isomer.

Ortho ester Claisen rearrangement[25] of the isomeric alcohols **17** and **18** gave, in both cases, the desired 3*S*,7*R* unsaturated ester **6c** in 92 and 77% yields, respectively. Samples of **6c** from both of these experiments were saponified (→ **6b**) and converted to the amide **6e.** HPLC analysis[15] of these amide samples revealed enantiomeric compositions at C_3 of 99 ± 1% *S*, for the materials derived from both **17** and **18.** Hydrogenation of **6c** over palladium on carbon gave samples of the saturated ester **19c** which were shown to have enantiomeric purities at C_3 of 91–92% based on HPLC analysis of the corresponding amide **19e.**[15,32] Hydride reduction of **19c** furnished the target alcohol **1d,** $[\alpha]^{25}D$ +2.77° ($CHCl_3$),[33] having enantiomeric compositions of approximately 91% *R* at C_3 and 96% *R* at C_7.

Although the amide **19e** was prepared originally for analytical purposes,[15] its use for optical purification of these 15-carbon synthons was briefly investigated and found to be moderately successful. Thus, two recrystallizations of a sample of crude **19e** (91.5% 3*R*, 8.5% 3*S*) from ether–petroleum ether gave material, in 56% yield, now shown to be 97.4% 3*R* and 2.6% 3*S*. On hydrolysis with concentrated HCl the acid **19b,** $[\alpha]^{25}D$ +5.97° ($CHCl_3$),[33] was regenerated, albeit in only 17% yield (83% of the amide was recovered). Nonetheless, from these preliminary results, it would appear that α-methyl-*p*-nitrobenzyl amide derivatives such as **19e** may have considerable potential for the optical purification of certain chiral carboxylic acids.

In conclusion, the studies described above have provided a facile route to optically active, saturated, acyclic isoprenoids having high enantiomeric purity (94–99%). As to the degree of chiral transmission in the various Claisen rearrangements employed, the previous estimate of >90%[10] can now be refined to essentially 100% (within the limits of the analytical methods utilized). This factor in conjunction with the efficient generation and utilization of the Claisen substrates renders the approach delineated herein of wide potential applicability in natural product synthesis.

Experimental Section

Unless otherwise noted, the "usual work-up" procedure involves dilution of the reaction mixture with water or brine followed by three extractions with the specified solvent. The organic extracts were then combined, washed with water and saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under water aspirator pressure, at 30–40 °C, on a rotary evaporator. Melting points were determined on a Reichert micromelting point apparatus and are uncorrected. Column chromatography was performed using Merck (Darmstadt) silica gel, 0.063–0.2 mm. Varian A-60 and HA-100 spectrometers were used to obtain the ^1H NMR spectra ($CDCl_3$ solution). Chemical shifts are reported relative to Me_4Si as an internal standard. Infrared spectra were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Gas–liquid chromatography was performed using Becker 409 or Hewlett-Packard 5700 instruments with flame ionization detector. High-pressure liquid chromatographic separations were carried out under the conditions described previously.[15]

(±)-6-Methyl-2-heptyn-4-ol (7a). Into a refluxing solution of ethylmagnesium bromide [prepared from 78.5 g (3.23 g-atoms) of magnesium and 338 g (3.13 mol) of freshly distilled ethyl bromide in 2000 ml of ether] was bubbled 143 g (3.6 mol) of dried propyne. The nonabsorbed gas was recondensed and recycled a total of six times over a 4-h period. At the end of this time, a greenish viscous oil appeared. The flask was cooled to 0 °C in an ice–salt bath and with rapid stirring, under an argon flow, 221 g (2.58 mol) of distilled isovaleraldehyde was added dropwise over a period of 1 h at such a rate that the internal temperature did not exceed 5 °C. After the addition was complete, stirring was continued for 30 min. The reaction mixture was cautiously poured into a solution of NH_4Cl (400 g) in 2000 ml of water with stirring and worked up in the usual manner with ether. The light-yellow, oily residue was distilled giving 264 g (81.5%) of **7a** as a colorless oil, bp 60 °C (3 mm).

Anal. Calcd for $C_8H_{14}O$: C, 76.15; H, 11.18. Found: C, 75.90; H, 11.01.

(±)-6-Methyl-2-heptyn-4-yl Hemiphthalate (7b). A mixture of 220 g (1.74 mol) of **7a,** 265 g (1.76 mol) of phthalic anhydride, and 220 ml of dry pyridine was refluxed for 4 h. After cooling, the resulting mixture was diluted with ether and extracted, three times, with 1 N NH_4OH. The combined aqueous extracts were washed twice with ether, then acidified with concentrated HCl and worked up with $CHCl_3$ in the usual manner. The light-brown residue was recrystallized from aqueous EtOH to give 428 g (89.5%) of **7b** as colorless crystals, mp 103–105 °C.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.21; H, 6.64.

(*S*)-(−)-6-Methyl-2-heptyn-4-yl Hemiphthalate (9b). To a solution of 202 g (0.736 mol) of **7b** in ether (3000 ml) was added 122 g (1.092 mol) of (*S*)-(−)-α-methylbenzylamine. The mixture was

stirred at 25 °C, under N_2, for 2.0 h. The crystalline material was filtered off and washed with ether, then recrystallized from methanol–ether to constant rotation. There was obtained 102.7 g of the (*S*)-α-methylbenzylamine salt of **9b** as very fine needles, mp 125–136 °C, $[\alpha]^{25}D$ −27.39° (*c* 1.05, $CHCl_3$). A mixture of 102.7 g (0.26 mol) of this salt in 100 ml of ether and 500 ml of 1 N HCl was stirred at 25 °C for 1 h. The ether layer was separated and washed with 1 N HCl, then the combined aqueous phase was again extracted with ether. Processing of the solution in the usual manner gave a light-yellow oil which was crystallized from aqueous EtOH yielding 70.4 g (69.7%) of **9b** as a white powder, mp 103–106 °C, $[\alpha]^{25}D$ −8.54° (*c* 5.4, EtOH).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.17; H, 6.59.

(*R*)-(+)-6-Methyl-2-heptyn-4-yl Hemiphthalate (8b). The mother liquor from the first salt crystallization described in the preceding experiment was treated with 1 N HCl and worked up as described to give a yellow oil. Treatment of this material with 88 g of (*R*)-(+)-α-methylbenzylamine as above gave 88.15 g of the (*R*)-α-methylbenzylamine salt of **8b** as fine needles, mp 128–138 °C, $[\alpha]^{25}D$ +27.06° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{18}O_4 \cdot C_8H_{11}N$: C, 72.89; H, 7.39; N, 3.59. Found: C, 72.98; H, 7.45; N, 3.82.

Treatment of this salt with 1 N HCl as above gave 61.05 g (60.4%) of **8b**, after crystallization from aqueous EtOH, as colorless solid, mp 105–109 °C, $[\alpha]^{25}D$ +8.43° (*c* 4.8, EtOH).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.24; H, 6.57.

(*R*)-(+)-6-Methyl-2-heptyn-4-ol (8a). A 119-g (0.435 mol) sample of hemiphthalate **8b** was stirred and refluxed in 500 ml of 2 N NaOH for 1 h. The reaction mixture was cooled and extracted four times with $CHCl_3$. The combined $CHCl_3$ extracts were washed with 1 N HCl, then processed in the usual manner giving a yellow oil. Distillation afforded 44.65 g (81.5%) of **8a** as a colorless oil, bp 58–59 °C (1 mm), $[\alpha]^{25}D$ +13.48° (*c* 4.9, $CHCl_3$).

Anal. Calcd for $C_8H_{14}O$: C, 76.15; H, 11.18. Found: C, 75.86; H, 11.24.

A sample of this material was converted to the MTPA ester **8c** using the acid chloride derived from (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid as described previously.[21a] GC analysis of this ester revealed a major peak (96.5%, 4*R* isomer), retention time 13.8 min, and a minor peak (3.5%, 4*S* isomer), retention time 15.7 min (1.8 m × 0.2 cm column packed with 10% SP-2300 on GCQ 100/120; 170 °C, N_2, 60 ml/min). GC analysis of the racemic ester **7c** showed the same two peaks in a ratio of approximately 1:1.

Horeau Analysis of 8a. A solution of 28.2 mg (0.223 mmol) of **8a** [$[\alpha]^{25}D$ +13.48° (*c* 4.87, $CHCl_3$)] and 207 mg (0.583 mmol) of (±)-α-phenylbutyric anhydride in 2.5 ml of dry pyridine was stirred for 6.5 h at 23 °C.[18] Water (1 ml) was added and stirring was continued for 6 h. The solution was diluted with ether and washed with water, 5% $NaHCO_3$, and again with water. The combined aqueous extracts were washed with $CHCl_3$, acidified with 1 N H_2SO_4, and worked up with $CHCl_3$ in the usual manner giving 87 mg of pure α-phenylbutyric acid, $[\alpha]^{25}D$ +6.03° (*c* 1.03, C_6H_6).

(*S*)-(−)-6-Methyl-2-heptyn-4-ol (9a). A 120-g (0.438 mol) sample of hemiphthalate **9b** was hydrolyzed as described above for the enantiomer giving 47.1 g (86%) of alcohol **9a** as a colorless oil, bp 54–55 °C (0.3 mm), $[\alpha]^{25}D$ −13.02° (*c* 5.05, $CHCl_3$).

Anal. Calcd for $C_8H_{14}O$: C, 76.15; H, 11.18. Found: C, 76.47; H, 11.32.

A sample of this material was converted to the MPTA ester **9c**.[21a] GC analysis of this ester (same conditions as described above for analysis of **8c**) revealed a composition of 97.8% 4*S* isomer (retention time 15.4 min) and 2.2% 4*R* isomer (retention time 13.6 min).

Horeau Analysis of 9a. A 28.2-mg sample of **9a** was treated with 207 mg of (±)-α-phenylbutyric anhydride as described above for the enantiomer. There was obtained 98 mg of α-phenylbutyric acid, $[\alpha]^{25}D$ −5.03° (*c* 5.1, C_6H_6).

(*R*)-(+)-(*Z*)-6-Methyl-2-hepten-4-ol (10a). A mixture of 25 g (0.195 mol) of carbinol **8a**, 2.5 g of Lindlar catalyst,[17] 1 ml of quinoline, and 300 ml of hexane was stirred in an atmosphere of hydrogen, at 23 °C. After 3.5 h, 5050 ml of H_2 was absorbed. The catalyst was filtered and washed with hexane, then the filtrate and washes were combined and concentrated in vacuo. Distillation of the residue yielded 23.3 g (91.7%) of a colorless oil: bp 48–49 °C (1 mm); $[\alpha]^{25}D$ +21.02° (*c* 5.05, $CHCl_3$); ir (neat) 3350 (OH), 730 cm^{-1} (*Z*-CH=CH); Raman (neat, 5145 Å) 1665 cm^{-1}; NMR δ 5.49 (m, 2, –HC=CH–), 4.55 (q, 1, –CHOH), 1.70 (d, 3, CH_3CH=), 0.96 ppm [d, 6, $(CH_3)_2CH$–]; GC (1.8 m × 2 mm column packed with 10% OV-225 on GCQ 100/120; 50–200 °C at 3 °C/min; N_2, 30 ml/min) 98.7% purity; retention time 15.3 min.

Anal. Calcd for $C_8H_{16}O$: C, 74.95; H, 12.58. Found: C, 74.73; H, 12.28.

(*S*)-(−)-(*E*)-6-Methyl-2-hepten-4-ol (11a). A solution of 11.3 g (0.492 g-atom) of sodium metal in 300 ml of dry, liquid NH_3 was stirred at −78 °C while a solution of 20 g (0.159 mol) of carbinol **9a** in 25 ml of dry ether was added dropwise. After the addition was complete, the cooling bath was removed and the reaction mixture was allowed to reflux (dry ice condensor) for 6 h. NH_4Cl (2 g) was added (blue color discharged) followed by 50 ml of saturated aqueous NH_4Cl. The ammonia was allowed to evaporate, then the residue was worked up with ether in the usual manner (ether extracts additionally washed with 1 N HCl). Distillation of the residual yellow oil yielded 16.36 g (80.5%) of **11a** as a colorless oil: bp 43–44 °C (0.6 mm); $[\alpha]^{25}D$ −9.88° (*c* 5.1, $CHCl_3$); ir (neat) 3400 (OH), 965 cm^{-1}; Raman (neat, 5145 Å) 1670 cm^{-1}; NMR δ 5.73 (m, 2, *E*-HC=CH–), 4.10 (m, 1, –CHOH), 1.75 (d, 3, CH_3CH=), 0.97 ppm [d, 6, $(CH_3)_2CH$–]; GC (9 ft × 0.25 in. column packed with 10% OV-225 on GCQ 100/120; 50–200 °C at 1 °C/min; N_2, 30 ml/min) 99% purity; retention time 55.5 min.

Anal. Calcd for $C_8H_{16}O$: C, 74.95; H, 12.58. Found: C, 75.09; H, 12.85.

(*R*)-(+)-2-Hydroxy-4-methylpentanoic Acid. Ozone was bubbled through a solution of 1.0 g (7.81 mmol) of allylic alcohol **10a** in 15 ml of ethyl acetate, at −78 °C, until the solution became blue (ca. 10 min). Most of the solvent was evaporated, in vacuo and the residue was treated with 25 ml of 10% aqueous Na_2CO_3 and 15 ml of 30% H_2O_2. The mixture was heated at 80 °C with stirring for 3 h, then cooled, acidified with concentrated HCl, and saturated with NaCl. Workup with ether in the usual manner gave 585 mg of an oily residue. Recrystallization from hexane afforded 260 mg (25.2%) of (*R*)-(+)-2-hydroxy-4-methylpentanoic acid, mp 79–81 °C, $[\alpha]^{25}D$ +14.36° (*c* 0.599, H_2O) [lit.[16] for the enantiomer $[\alpha]^{27}D$ −13.1° (*c* 0.6, H_2O)].

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.64; H, 9.26.

(*S*)-(+)-(*E*)-3,7-Dimethyl-4-octenal (4a). A. From 10a. A mixture of 1.5 g (11.7 mmol) of allylic alcohol **10a**, 3.5 g (11.0 mmol) of mercuric acetate, and 15 ml of ethyl vinyl ether were refluxed, under argon, for 21 h. Additional ethyl vinyl ether (5 ml) and benzene (40 ml) were then added and refluxing was continued for 4 h.[23] After cooling to room temperature, 1 ml of glacial HOAc was added, and the solution was stirred at room temperature for 1 h, then taken up in ether and washed with 5% aqueous KOH. After drying (K_2CO_3), the ether solution was concentrated in vacuo and the crude product was evaporatively distilled giving 1.578 g of **10b** as a colorless liquid: bp 30–60 °C (40 mm) (bath temperature); ir (neat) 1610, 1170, 1160 cm^{-1}; NMR δ 6.31 (q, 1, –OCH=), 5.49 (m, 2, =CH), 4.56 (m, 1, –CHO–), 4.23 (d of d, 1, =CH), 3.94 (d of d, 1, =CH), 1.69 (d of d, CH_3CH=), 0.96 ppm [d, $(CH_3)_2CH$–]. This material was dissolved in 100 ml of benzene and the solution was refluxed, under argon, for 120 h. The solvent was removed in vacuo and the residual yellow oil was chromatographed on 25 g of silica gel. Elution with 9:1 petroleum ether (bp 30–60 °C)–ether gave the aldehyde **4a** which was evaporatively distilled yielding 658 mg (32% from **10a** corrected for GC purity) of a colorless oil: bp 36 °C (0.5 mm) (bath temperature); $[\alpha]^{25}D$ +30.18° (*c* 3.57, $CHCl_3$); ir (neat) 2750 (aldehyde CH), 1730 (C=O), 980 cm^{-1}; NMR δ 9.71 (t, 1, –CHO), 5.35 (m, 2, *trans*-CH=CH), 2.75 (m, 1, –CHCH=), 2.35 (m, 2, $-CH_2CHO$), 1.85 (m, $-CH_2CH$=), 1.07 (d, 3, CH_3CH–), 0.87 ppm [d, 6, $(CH_3)_2CH$–]; GC (9 ft × 0.25 in. column packed with 10% OV-101 on GCQ 100/120; 60 °C/20 min then 60–220 °C at 1 °C/min; N_2 30 ml/min) 87.2% purity; retention time 83.1 min.

B. From 11a. A 2.0-g (15.6 mmol) sample of allylic alcohol **11a** was converted into **11b** as described in part A, for the preparation of **10b**. The resulting vinyl ether **11b** [2.94 g, bp 35–70 °C (35 mm) (bath temperature)] was refluxed in 100 ml of benzene, under argon, for 74 h. Solvent removal in vacuo followed by chromatography on silica gel (40 g, eluted with 9:1 petroleum ether–ether) gave 1.45 g (48% corrected for GC purity) of unsaturated aldehyde **4a** of 79.4% purity (GC) which was used without further purification.

(+)-Ethyl (*S*)-(*E*)-3,7-Dimethyl-4-octenoate (4c). A. From 10a. A solution of 3.0 g (23.4 mmol) of allylic alcohol **10a** and 173 mg (2.34 mmol) of propionic acid in 26.4 g (0.163 mol) of triethyl orthoacetate[25] was distilled under argon until no more ethanol was present, then refluxed (142 °C) for 4 h. The excess triethyl orthoacetate was removed under aspirator pressure and the residue was distilled, giving 2.59 g (54% corrected for GC purity) of ester **4c** as a colorless oil: bp 102–105 °C (20 mm); $[\alpha]^{25}D$ +18.08° (*c* 3.43, $CHCl_3$); ir (neat) 1740 (C=O), 970 cm^{-1}; NMR δ 5.50 (m, 2, –CH=CH), 4.21 (q, $-OCH_2CH_3$), 1.30 (t, $-OCH_2CH_3$), 1.08 (d, CH_3CH–), 0.92 ppm [$(CH_3)_2CH$–]; mass spectrum *m/e* 198 (M^+), 110 (base); GC (9 ft × 0.25 in. column packed with 10% OV-101 on GCQ 100/120; 80–260 °C

at 2 °C/min; N_2, 30 ml/min) 97.0% purity; retention time 41.1 min.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.73; H, 11.37.

In a subsequent experiment carried out in a similar manner the ester **4c** was obtained in 82% yield: bp 90 °C (0.5 mm) (bath temperature); $[\alpha]^{25}D$ +16.85° (*c* 5, $CHCl_3$); GC purity 91.3%.

B. From 11a. A 5-g sample of **11a** was transformed into **4c** using the procedure described in part A. The ester **4c** (5.34 g, 65% corrected for GC purity) was obtained as a colorless oil: bp 67–68 °C (0.5 mm); $[\alpha]^{25}D$ +18.42° (*c* 5.03, $CHCl_3$); GC purity 93.5%.

(*S*)-(+)-(*E*)-3,7-Dimethyl-4-octenoic Acid *N,N*-Dimethylamide (4d). A. From 10a. A mixture of 2 g (15.6 mmol) of alcohol **10a,** 4 g of 1-dimethylamino-1,1-dimethoxyethane, and 20 ml of ylene was refluxed for 17 h.[26] The xylene was removed in vacuo and the residue was distilled, giving 2.54 g (82.5%) of amide **4d,** as a pale-yellow oil: bp 115–116 °C (1.5 mm); $[\alpha]^{25}D$ +19.36° (*c* 5.09, $CHCl_3$); ir (neat) 1640 (C=O), 960 cm^{-1}; NMR δ 5.34 (m, 2, *E*-CH=CH), 2.92, 2.99 [2 s, 6, $-N(CH_3)_2$], 1.04 (d, 3, CH_3CH-), 0.85 ppm [d, $(CH_3)_2CH$]; homogeneous on GC analysis (9 ft × 0.25 in. column packed with 10% OV-225 on GCQ 100/120; 60–200 °C at 1 °C/min; N_2, 30 ml/min); retention time 128 min.

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.79; H, 11.61; N, 7.21.

B. From 11a. A 2-g sample of alcohol **11a** was treated as described in part A. There was obtained 2.91 g (92.5% corrected for GC purity) of amide **4d,** as a pale-yellow oil: bp 103–104 °C (0.7 mm); $[\alpha]^{25}D$ +20.64° (*c* 5.03, $CHCl_3$); GC purity 97.7%.

(*R*)-(−)-(*Z*)-6-Methylhept-2-en-4-yl Acetate (10c). A solution of 4 g (31.25 mmol) of allylic alcohol **10a** in 6 ml of acetic anhydride and 6 ml of dry pyridine was kept at 23 °C for 17 h. Workup with ether in the usual manner (the combined ether extracts were additionally washed with 1 N HCl) and distillation of the crude product gave 4.87 g (91.8%) of acetate **10c** as a colorless oil, bp 39 °C (0.5 mm), $[\alpha]^{25}D$ −14.21° (*c* 4.87, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.34; H, 10.63.

(*S*)-(−)-(*E*)-6-Methylhept-2-en-4-yl Acetate (11c). Acetylation of 5 g (39 mmol) of allylic alcohol **11a** as in the preceding experiment gave 6.49 g (97.5%) of acetate **11c** as a colorless oil, bp 94 °C (3 mm), $[\alpha]^{25}D$ −57.45° (*c* 5.02, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.28; H, 10.48.

(*S*)-(+)-(*E*)-3,7-Dimethyl-4-octenoic Acid (4b). A. From Acetate 10c. A 4.67-ml (10.3 mmol) portion of *n*-butyllithium (2.2 M in *n*-hexane) was stirred with ice-bath cooling, under argon, while a solution of 1.78 ml (10.5 mmol) of *N*-isopropylcyclohexylamine (distilled from CaH_2) in 2 ml of anhydrous THF was added dropwise. Hexane was removed from the resulting solution under reduced pressure, then the residual solution was cooled to −78 °C and 3 ml of hexamethylphosphoric triamide (distilled from CaH_2) was added. This was followed by the dropwise addition of 1.70 g (10 mmol) of acetate **10c** in 2 ml of dry THF. After stirring for 10 min, the resulting yellow slurry was treated with 1.65 g (11 mmol) of *tert*-butyldimethylchlorosilane in 2 ml of THF. The reaction mixture was stirred at −78 ° for 10 min and then allowed to warm to 20 °C over a 2-h period.[27] Workup with pentane in the usual manner, followed by evaporative distillation of the crude product, gave 2.77 g of the *tert*-butyldimethylsilyl ester of **4b** as a yellow oil: bp 40–50 °C (0.5 mm) (bath temperature); ir (neat) 1750 (C=O), 1260, 845 cm^{-1}; NMR (CCl_4) δ 5.4 (m, 2, –HC=CH–), 1.0 (s, *t*-Bu), 0.25 ppm [$(CH_3)_2Si-$]. This material was directly hydrolyzed in THF (25 ml) containing 10% HCl (5 ml) for 17 h at 23 °C. The solution was treated with 5% NaOH and extracted with ether. The aqueous, alkaline phase was cooled to 0 °C and acidified with concentrated HCl. Workup with ether in the usual manner followed by evaporative distillation of the crude product yielded 1.06 g (62.7%) of acid **4b** as a colorless oil: bp 55° (0.4 mm) (bath temperature); $[\alpha]^{25}D$ +27.21° (*c* 4.74, $CHCl_3$); ir ($CHCl_3$) 3250–3000 (acid OH), 1700 (C=O), 970 cm^{-1}; NMR δ 5.4 (m, 2, –HC=CH–), 1.1 (d, CH_3CH-), 0.90 ppm [d, $(CH_3)_2CH-$]. The trimethylsilyl derivative of this acid was homogeneous on GC analysis (1.8 m × 2 mm column packed with 10% OV-101 on GCQ 100/120, 80–200 °C at 2 °C/min, N_2, 30 ml/min); retention time 37 min.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.43; H, 10.83.

B. From Acetate 11c. A 1.7-g (10 mmol) sample of acetate **11c** was converted into **4b** in exactly the same manner as described in part A. There was obtained 873 mg (50.5% corrected for GC purity) of acid **4b:** bp 56 °C (0.4 mm) (bath temperature); $[\alpha]^{25}D$ +24.09° (*c* 3.35, $CHCl_3$); GC purity, 98.4% (Me_3Si derivative).

C. From Aldehyde 4a. A mixture of 500 mg (2.83 mmol) of aldehyde **4a,** prepared as described above ($[\alpha]^{25}D$ +30.18°; 87.2% GC purity), 1.1 g (6.5 mmol) of silver nitrate, 10 ml of EtOH, and 20 ml of water was stirred while 2.17 ml (13 mmol) of 6 N aqueous NaOH was added dropwise. The black mixture was stirred at 23 °C for 1.5 h, then the precipitate was filtered and washed with 0.1 N NaOH and water. The filtrate and washes were combined and washed twice with ether, then cooled to 0 °C and acidified with concentrated HCl. Workup with ether as usual followed by evaporative distillation of the crude product gave 375 mg (78%) of acid **4b,** bp 56 °C (0.5 mm) (bath temperature), $[\alpha]^{25}D$ +27.20° (*c* 5.18, $CHCl_3$). The Me_3Si derivative of this material was homogeneous on GC analysis.

D. From Ester 4c. A mixture of 0.8 g (4.04 mmol) of ester **4c** [$[\alpha]^{25}D$ +18.08° (*c* 3.43, $CHCl_3$); prepared as described above from **10a**], 2 ml of 6 N aqueous NaOH, and 5 ml of MeOH was refluxed for 2 h. The resulting solution was diluted with water and extracted twice with ether. The aqueous solution was acidified with concentrated HCl and worked up as usual with ether. Evaporative distillation of the crude product gave 608 mg (88.5%) of acid **4b,** bp 150 °C (30 mm) (bath temperature), $[\alpha]^{25}D$ +28.57° (*c* 5.0, $CHCl_3$). The Me_3Si derivative of this material was homogeneous on GC analysis.

E. From Amide 4d. A mixture of 0.3 g (1.52 mmol) of amide **4d** (prepared from **10a** as described above) and 0.67 g of KOH in 10 ml of 9:1 ethylene glycol–water was stirred and heated at 200 °C for 4 h. After cooling, the resulting solution was diluted with water and processed as in part D giving 84 mg (32.4%) of acid **4b** as a colorless oil, bp 150 °C (20 mm) (bath temperature), $[\alpha]^{25}D$ +26.18° (*c* 2.0, $CHCl_3$).

(*S*)-(*E*)-3,7-Dimethyl-4-octenoic Acid (*R*)-α-Methyl-*p*-nitrobenzylamide (4e). A 100-mg (0.586 mmol) sample of acid **4b** [$[\alpha]^{25}D$ +24.09° (*c* 3.35, $CHCl_3$); preparation from acetate **11c** described above] was converted into the amide **4e** using the procedure described previously.[15] There was obtained 181 mg (97%) of a crystalline solid which was shown by HPLC analysis to have a composition of 94.5% 3*S* and 5.5% 3*R*. The analysis was carried out using the same conditions as described previously for **12e.**[15] The major and less polar 3*S* isomer exhibited $k' = 2.94$ and the minor, more polar 3*R* isomer, $k' = 4.55$ [material with a composition of 97.9% 3*R*, 2.1% 3*S* (prepared by Lindlar hydrogenation of **9a** followed by ortho ester Claisen rearrangement, saponification, and amide formation) exhibited peaks of identical retention volumes]. Recrystallization of this material from aqueous EtOH gave 100 mg of amide **4e,** mp 88–94 °C, $[\alpha]^{25}D$ +73.39° (*c* 2.03, $CHCl_3$). HPLC analysis of this material revealed a composition of 96.7% 3*S* and 3.3% 3*R*.

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.60; H, 8.32; N, 8.41.

(+)-Ethyl (*R*)-3,7-Dimethyloctanoate (12c). A solution of 2.43 g (12.27 mmol) of the unsaturated ester **4c** ($[\alpha]^{25}D$ +18.42°; preparation described above) in 20 ml of EtOH was stirred in the presence of 1 g of 5% palladium on carbon, at 23 °C, in an atmosphere of hydrogen, for 2 h. The catalyst was filtered, the filtrate was concentrate in vacuo, and the residue was evaporatively distilled giving 1.8 g (73.3%) of ester **12c,** as a colorless oil: bp 39–45 °C (0.2 mm); $[\alpha]^{25}D$ +2.39° (*c* 5.03, $CHCl_3$); 98.5% pure by GC analysis (3 m × 4 mm column packed with 10% PEG-20M on GCQ 100/120; 80–220 °C at 2 °C/min; N_2, 30 ml/min). Pure **12c** was obtained by preparative GC, $[\alpha]^{25}D$ +3.29° (*c*, 4.65, $CHCl_3$).

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.07; H, 12.08.

(*R*)-(+)-3,7-Dimethyloctanoic Acid *N,N*-Dimethylamide (12d). A solution of 2 g (10.15 mmol) of the unsaturated amide **4d** ($[\alpha]^{25}D$ +19.36°; preparation described above) in 20 ml of MeOH was stirred in the presence of 100 mg of 5% palladium on carbon, at 22 °C, in an atmosphere of hydrogen. Workup as in the preceding experiment gave 1.89 g (93.6%) of amide **12d** as a pale-yellow oil: bp 60 °C (0.4 mm) (bath temperature); $[\alpha]^{25}D$ +1.18° (*c* 5.1, $CHCl_3$); homogeneous on GC analysis.

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 72.15; H, 12.54; N, 6.99.

(*R*)-(+)-3,7-Dimethyloctanoic Acid (12b). A. From (*R*)-(+)-Pulegone. (*R*)-(+)-Citronellic acid [0.5 g (2.94 mmol); $[\alpha]^{25}D$ +8.56° (neat); prepared from (*R*)-(+)-pulegone (**13**) as described previously[24]] was hydrogenated over 50 mg of 5% palladium on carbon, in 15 ml of ethyl acetate, at 23 °C and atmospheric pressure. Workup as in the preceding experiments yielded 0.485 g (95.8%) of acid **12b,** bp 150 °C (20 mm) (bath temperature), $[\alpha]^{25}D$ +6.85° (*c* 2.8, $CHCl_3$) [lit.[24] $[\alpha]^{25}D$ +5.70° (neat)]. This material was shown to have an enantiomeric composition of 96.6% 3*R* and 3.4% 3*S* by HPLC analysis of the amide derivative **12e.**[15]

B. From Acid 4b. A solution of 224 mg (1.3 mmol) of acid **4b** ($[\alpha]^{25}D$ +28.57°; preparation described above) in 10 ml of EtOH was stirred

at 23 °C, in an atmosphere of hydrogen, in the presence of a small amount of Raney nickel, until gas uptake ceased. Workup as above afforded 200 mg (88.1%) of **12b**, as a colorless liquid, bp 150 °C (30 mm) (bath temperature), $[\alpha]^{25}D$ +7.05° (*c* 2.55, $CHCl_3$). This material was shown to have an enantiomeric composition of 95.4% 3*R* and 4.6% 3*S* by HPLC analysis of the amide derivative **12e**.[15] Hydrogenation of **4b** and related compounds over other catalysts led to racemization as shown in Table II.

C. From Ester 12c. A 0.3-g (1.5 mmol) sample of ester **12c** ($[\alpha]^{25}D$ +3.29°; preparation described above) was saponified as described above for **4c**. This yielded 226 mg (87.6%) of **12b**, bp 54 °C (0.4 mm) (bath temperature), $[\alpha]^{25}D$ +6.31° (*c* 5.07, $CHCl_3$). This material was shown to have an enantiomeric composition of 87.9% 3*R* and 12.1% 3*S* by HPLC analysis of the amide derivative **12e**.[15]

D. From Amide 12d. A mixture of 0.6 g (3.01 mmol) of the amide **12d** ($[\alpha]^{25}D$ +1.18°; preparation described above) and 4 ml of concentrated HCl was stirred and refluxed for 48 h. The reaction mixture was concentrated in vacuo and the residue was worked up with ether in the usual manner. Evaporative distillation of the crude product afforded 0.431 g (83%) of **12b**, bp 66 °C (0.5 mm) (bath temperature), $[\alpha]^{25}D$ +6.90° (*c* 5.03, $CHCl_3$). HPLC analysis of the amide **12e** derived from this acid revealed an enantiomeric composition of 93% 3*R* and 7% 3*S*.

(*R*)-(+)-3,7-Dimethyl-1-octanol (14). A. From (*R*)-(+)-Pulegone. A solution of 68.1 g (0.4 mol) of (*R*)-(+)-citronellic acid [$[\alpha]^{25}D$ +8.56° (neat); prepared from (*R*)-(+)-pulegone (**13**)[24]] in 100 ml of anhydrous ether was added, dropwise, to a precooled (4 °C) solution of 252 ml of sodium bis(2-methoxyethoxy)aluminum hydride (70% in benzene) in 300 ml of dry ether, with stirring and at such a rate that a gentle reflux was maintained. After the addition was complete (ca. 60 min), the resulting solution was stirred at 22 °C for 17 h, then recooled in an ice bath and cautiously decomposed by the dropwise addition of 400 ml of 3 N aqueous H_2SO_4. The organic layer was separated and the aqueous layer was filtered over Celite to remove a white precipitate. The aqueous filtrate was then extracted three times with ether. The combined organic solutions were washed three times with saturated aqueous $NaHCO_3$ and processed in the usual manner. The residue was distilled giving 60.48 g (96.8%) of (*R*)-(+)-citronellol as a colorless oil, bp 68 °C (0.5 mm), $[\alpha]^{25}D$ +5.45° (neat) [lit.[24] $[\alpha]^{20}D$ +5.37° (neat)].

A 31.2-g (0.2 mol) sample of this material, dissolved in 180 ml of ethyl acetate, was stirred, at 23 °C, in an atmosphere of hydrogen, in the presence of 1.5 g of 5% palladium on carbon. After 2 h and 55 min, nearly the theoretical amount of H_2 was absorbed and the catalyst was filtered and washed with ethyl acetate. The filtrate and washes were combined and concentrated in vacuo, then the residue was distilled. This afforded 29.82 g (94.4%) of **14** as a colorless oil, bp 62 °C (0.25 mm), $[\alpha]^{25}D$ +4.65° (neat) [lit.[6] $[\alpha]^{25}D$ +5.23° (neat)].

B. From Totally Synthetic 12b. A 564-mg sample of **12b** ($[\alpha]^{25}D$ +6.77°; 93% 3*R*, 7% 3*S*; prepared from **10a** via **4d** and **12d** as described above) was reduced with $NaAlH_2(OCH_2CH_2OCH_3)_2$ using the procedure described in part A. There was obtained 460 mg (88.9%) of **14** as a colorless oil, bp 50 °C (0.16 mm) (bath temperature), $[\alpha]^{25}D$ +4.10° (*c* 4.0, $CHCl_3$).

(*R*)-(+)-3,7-Dimethyloctanal (12a). A mixture of 280 g of freshly prepared silver carbonate on Celite,[30] 15.8 g (0.1 mol) of **14** (derived from **13**), and 2000 ml of toluene was vigorously stirred, in an argon atmosphere, at reflux, for 14 h, using a Dean-Stark trap. After cooling to room temperature, the mixture was filtered and the dark solids were washed well with pentane. The filtrate and washes were combined and concentrated in vacuo. The residue was rapidly filtered through 150 g of silica gel. Elution with 19:1 petroleum ether–ether gave the aldehyde, which was evaporatively distilled, affording 7.26 g (46.5%) of pure **12a** as a colorless oil of characteristic odor, bp 55–60 °C (0.8 mm) (bath temperature), $[\alpha]^{25}D$ +14.07° (*c* 5.07, $CHCl_3$) [lit.[7a] $[\alpha]^{25}D$ +13.2° (neat)]. Further elution with ether allowed recovery of unreacted **14**.

Mixture of (4*R*,6*R*)- and (4*S*,6*R*)-6,10-Dimethylundec-2-yn-4-ol (15a and 16a). A 26.4-g (0.169 mol) sample of aldehyde **12a** was treated with propynylmagnesium bromide using the procedure described above for similar treatment of **5**. There was obtained 33.1 g (100%) of the crude mixture of carbinols **15a** and **16a** as a pale-yellow oil. Most of this material (32 g) was chromatographed on 3400 g of silica gel (70–230 mesh). Elution with 9:1 petroleum ether–ether gave, first, 8.53 g of, mainly, the 4*S* epimer, **16a**, shown to be 95.9% 4*S* and 4.1% 4*R* by GC analysis of the MTPA ester derivative **16c** [9 ft × 0.25 in. column packed with 10% OV-225 on GCQ 100/120; 215 °C; N_2, 30 ml/min; retention times, 33.5 min (minor) and 35.9 min (major)], prepared from the acid chloride of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid.[21] Further elution yielded 10.1 g of a mixture of **15a** and **16a** followed by 8.37 g of, mainly, the 4*R* epimer, **15a** (91.8% 4*R*, 8.2% 4*S* by GC analysis of the derived ester, **15c**).

(4*S*,6*R*)-(−)-6,10-Dimethylundec-2-yn-4-yl 3,5-Dinitrobenzoate (16b). A solution of *p*-toluenesulfonyl chloride (7.75 g, 40.72 mmol) in 15 ml of dry pyridine was added in portions to a solution of 3,5-dinitrobenzoic acid (4.33 g, 20.36 mmol) in 25 ml of pyridine.[31] The resulting solution was cooled in an ice bath and a solution of 4.0 g (20.36 mmol) of the impure carbinol **16a** from the preceding experiment (95.9% 4*S*) in 15 ml of pyridine was added portionwise, with stirring, at such a rate that the internal temperature did not exceed 6 °C. Stirring was continued at 5 °C for 20 min, then the reaction mixture was poured into ice–water and worked up with $CHCl_3$ in the usual manner (the $CHCl_3$ extracts were additionally washed with 2 N HCl and saturated $NaHCO_3$ solutions). The crude crystalline product was recrystallized from MeOH to give 5.07 g (64%) of pure **16b**, mp 88–90.5 °C, $[\alpha]^{25}D$ −30.33° (*c* 1.02, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.71; H, 6.57; N, 7.23.

(4*S*,6*R*)-(−)-6,10-Dimethylundec-2-yn-4-ol (16a). A solution of 5.4 g (13.8 mmol) of pure ester **16b**, prepared as in the previous experiment, and 54 ml of 6 N aqueous NaOH in 250 ml of MeOH was refluxed for 1.5 h. Most of MeOH was removed in vacuo and the residue was worked up with ether in the usual manner. Evaporative distillation of the crude product gave 2.1 g (77.8%) of essentially pure **16a** as a colorless oil, bp 87 °C (0.175 mm) (bath temperature), $[\alpha]^{25}D$ −10.08° (*c* 2.95, $CHCl_3$). GC analysis of the derived ester **16c** indicated a composition of ca. 99% 4*S*, ca. 1% 4*R*.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.33; H, 12.10.

(4*R*,6*R*)-(+)-6,10-Dimethylundec-2-yn-4-yl 3,5-Dinitrobenzoate (15b). A 4.22-g (21.6 mmol) sample of impure carbinol **15a** (91.8% 4*R*) was esterified as described above for the 4*S* epimer except that the reaction mixture was kept at 4 °C for 3.5 h. One recrystallization of the crude product from MeOH afforded 6.73 g (84.2%) of pure ester **15b**, mp 90–91 °C, $[\alpha]^{25}D$ +20.40° (*c* 1.11, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.70; H, 6.88; N, 7.16.

(4*R*,6*R*)-(+)-6,10-Dimethylundec-2-yn-4-ol (15a). Alkaline hydrolysis of 6.65 g (17.1 mmol) of pure ester **15b** as described above for the 4*S* epimer gave 3.3 g (98.8%) of pure carbinol **15a** as a colorless oil, bp 87 °C (0.2 mm) (bath temperature), $[\alpha]^{25}D$ +10.52° (*c* 3.32, $CHCl_3$). GC analysis of the derived ester **15c** indicated a composition of >99% 4*R*.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.27; H, 12.38.

(4*R*,6*R*)-(+)-(*Z*)-6,10-Dimethylundec-2-en-4-ol (17). A 3.2-g (16.3 mmol) sample of pure carbinol **15a** was partially hydrogenated as described above for the preparation of **10a**. There was obtained 3.0 g (92.8%) of the *Z* allylic alcohol **17** as a colorless oil: bp 102 °C (0.2 mm) (bath temperature); $[\alpha]^{25}D$ +19.65° (*c* 5.01, $CHCl_3$); ir (neat) 3300 (OH), 740 cm^{-1}; NMR δ 5.46 (m, 2, *Z*-CH=CH), 4.56 (m, 1, –CHO–), 1.71 (d, CH_3CH=), 0.90 (d, CH_3CH–), 0.89 ppm [d, $(CH_3)_2(CH$–)]; GC analysis (9 ft × 0.25 in. column packed with 10% OV-225 on GCQ 100/120; 110 °C, N_2, 30 ml/min) revealed a purity of 98–99% (retention time 26.2 min) with ca. 2% of the *E* isomer present (retention time 24 min).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.58; H, 13.00.

(4*S*,6*R*)-(−)-(*E*)-6,10-Dimethylundec-2-en-4-ol (18). To a solution of 1.9 g (9.66 mmol) of pure, acetylenic carbinol **16a** in 75 ml of anhydrous ether was added, dropwise, with stirring, a solution of 3 ml of sodium bis(2-methoxyethoxy)aluminum hydride (70% in benzene) in 60 ml of ether. The resulting solution was stirred and refluxed, under argon, for 20 h, then cooled in an ice bath and cautiously decomposed by the dropwise addition of 20 ml of dilute, aqueous H_2SO_4. Workup with ether in the usual manner (the organic extracts were additionally washed with saturated aqueous $NaHCO_3$) followed by evaporative distillation of the crude product afforded 1.61 g (83.8%) of **18** as a colorless oil: bp 85 °C (0.11 mm) (bath temperature); $[\alpha]^{25}D$ −9.00° (*c* 3.79, $CHCl_3$); ir (neat) 3300 (OH), 960 cm^{-1}; NMR δ 5.55 (m, 2, *E*-CH=CH), 4.09 (m, 1, –CHO–), 1.66 (d, CH_3CH=), 0.88 (d, CH_3CH–), 0.84 ppm [d, $(CH_3)_2CH$–]. GC analysis of the Me_3Si derivative (2.7 m × 4 mm column packed with 10% OV-101 on GCQ 100/120; 100–260 °C at 2.5 °C/min; N_2, 30 ml/min) revealed a purity of >99% (retention time 41.9 min; no *Z* isomer detectable).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.40; H, 13.05.

(+)-Ethyl (3*S*,7*R*)-(*E*)-3,7,11-Trimethyl-4-dodecenoate (6c). A. From 17. A 2.9-g (14.6 mmol) sample of the *Z* allylic alcohol **17** was

treated with triethyl orthoacetate (16.5 g) and propionic acid (57 mg) as described above for the conversion of **10a** and **11a** to **4c**. There was obtained 3.6 g (92%) of unsaturated ester **6c** as a colorless oil: bp 95–101 °C (0.1 mm) (bath temperature); $[\alpha]^{25}D$ +15.19° (*c* 3.77, $CHCl_3$); ir (neat) 1730 (C=O), 970 cm^{-1}; NMR δ 5.36 (m, 2, *E*-CH=CH), 4.10 (q, 2, $-OCH_2CH_3$), 1.2 (d, CH_3CH-), 1.0 (d, CH_3CH-), 0.83 [d, $(CH_3)_2CH-$], 0.81 ppm (t, $-OCH_2CH_3$). This material was homogeneous on GC analysis (same conditions as for **17** except temperature program 80–100 °C at 1 °C/min; retention time 85 min).

Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.03; H, 11.75.

B. From 18. A 1.44-g (7.27 mmol) sample of the *E* allylic alcohol **18** was treated with 9.05 g of triethyl orthoacetate and 34 mg of propionic acid as above giving 1.51 g (77.5%) of ester **6c**: bp 96–105 °C (0.25 mm) (bath temperature); $[\alpha]^{25}D$ +10.39° (*c* 0.49, $CHCl_3$); GC purity 93.3%.

(3*S*,7*R*)-(*E*)-3,7,11-Trimethyl-4-dodecenoic Acid (*R*)-α-Methyl-*p*-nitrobenzylamide (6e). Samples of the unsaturated ester **6c** from parts A and B of the preceding experiment were separately saponified and converted into the amide derivatives, **6e**, in the usual manner. The crude crystalline amides (obtained in 96% yield) were analyzed by HPLC using the conditions described previously for **12e** and **19e**.[15] Both samples showed essentially a single component (3*S*), $k' = 6.82$; mass spectrum *m/e* 388 (M^+). Analysis of material racemic at C_3 showed two peaks of essentially equal intensity, $k' = 6.82$ (3*S*) and $k' = 11.0$ (3*R*).

(+)-Ethyl (3*R*,7*R*)-3,7,11-Trimethyldodecanoate (19c). A 3.53-g (13.17 mmol) sample of unsaturated ester **6c** ($[\alpha]^{25}D$ +15.19°; preparation from **17** described above) was hydrogenated over 360 mg of 5% palladium on carbon[32] in 120 ml of ethyl acetate as described above for the conversion of **4c** to **12c**. This afforded 3.44 g (96.7%) of pure ester **19c**, as a colorless oil, bp 101–107 °C (0.15 mm) (bath temperature), $[\alpha]^{25}D$ +2.24° (*c* 4.99, *n*-octane). This material was homogeneous on GC analysis.

Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67. Found: C, 75.83; H, 12.76.

(3*R*,7*R*)-(+)-3,7,11-Trimethyldodecanoic Acid (19b). A 145-mg (0.537 mmol) sample of ester **19c** from the preceding experiment was saponified as described above for the conversion of **12c** to **12b**. The acid **19b** (101 mg, 77.7%) was obtained as a colorless oil, bp 135–139 °C (0.2 mm) (bath temperature), $[\alpha]^{25}D$ +4.74° (*c* 4.09, $CHCl_3$). HPLC analysis of the amide derivative, **19e**,[15] of this material revealed a composition of 92.3% 3*R* and 7.7% 3*S*.

Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47. Found: C, 74.37; H, 12.79.

Optical Purification of Acid 19b via Amide 19e. A 657-mg sample of the crude, crystalline amide **19e** (prepared[15] from acid **19b**, $[\alpha]^{25}D$ +4.97°), having an enantiomeric composition of 91.5% 3*R* and 8.5% 3*S* as determined by HPLC analysis,[15] was recrystallized twice from 1:2 ether–petroleum ether giving 368 mg (56) of **19e**, mp 63.5–67.5 °C, $[\alpha]^{25}D$ +66.6° (*c* 0.99, $CHCl_3$). This material was shown to have an improved enantiomeric composition of 97.4% 3*R* and 2.6% 3*S* by HPLC analysis.[15]

Anal. Calcd for $C_{23}H_{38}N_2O_3$: C, 70.73; H, 9.81; N, 7.17. Found: C, 70.77; H, 9.81; N, 7.25.

A 200-mg sample of this purified amide was refluxed in 10 ml of 1:1 concentrated HCl–dioxane for 3 days. Workup in the usual manner gave 170 mg of recovered amide and 20 mg of acid **19b**, bp 130 °C (0.15 mm) (bath temperature), $[\alpha]^{25}D$ +5.97° (*c* 1.1, $CHCl_3$).[33]

(3*R*,7*R*)-(+)-3,7,11-Trimethyldodecan-1-ol (1d). A solution of 3.13 g (11.6 mmol) of ester **19c** ($[\alpha]^{25}D$ +2.24°; preparation described above; enantiomeric composition 92.3% 3*R*, 7.7% 3*S*, 96.6% 7*R*, 3.4% 7*S*) in 35 ml of anhydrous ether was added dropwise to a stirred slurry of 2 g of $LiAlH_4$ in 150 ml of ether. The mixture was stirred and refluxed for 2.5 h, then cooled in an ice bath and cautiously decomposed by dropwise addition of water followed by 450 ml of 2 N H_2SO_4. Workup with ether in the usual manner followed by evaporative distillation of the crude product afforded 2.57 g (97.4%) of alcohol **1d** as a colorless oil, bp 104–110 °C (0.1 mm) (bath temperature), $[\alpha]^{25}D$ +2.77° (*c* 4.69, $CHCl_3$)[33] [lit.[4] bp 100–110 °C (0.1 mm) (bath temperature)].

Anal. Calcd for $C_{15}H_{32}O$: C, 78.88; H, 14.12. Found: C, 78.61; H, 13.87.

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Registry No.—**1d,** 54154-26-6; **4a,** 59983-63-0; **4b,** 59983-64-1; **4b** *tert*-butyldimethylsilyl ester, 59983-65-2; **4c,** 59983-66-3; **4d,** 59983-67-4; (3*S*)-**4e,** 59983-68-5; (3*R*)-**4e,** 59983-69-6; **5,** 590-86-3; **6c,** 59983-70-9; **6e,** 59983-71-0; **7a,** 59983-72-1; **7b,** 59983-73-2; **8a,** 60018-69-1; **8b,** 60018-70-4; **8b** (*R*)-α-methylbenzylamine salt, 60018-71-5; **9a,** 60018-72-6; **9b,** 60018-73-7; **9b** (*S*)-α-methylbenzylamine salt, 59983-75-4; **10a,** 59983-76-5; **10b,** 59983-77-6; **10c,** 59983-78-7; **11a,** 59983-79-8; **11b,** 59983-80-1; **11c,** 59983-81-2; **12a,** 60018-13-5; (3*S*)-**12b,** 55509-77-8; (3*R*)-**12b,** 32531-52-5; **12c,** 59983-82-3; **12d,** 59983-83-4; **14,** 1117-60-8; **15a,** 59983-84-5; **15b,** 59983-85-6; **16a,** 59983-86-7; **16b,** 59983-87-8; *E*-**17,** 59983-88-9; *Z*-**17,** 59991-72-9; **18,** 59983-89-0; **19b,** 13955-73-2; **19c,** 59983-90-3; (3*R*)-**19e,** 56994-97-9; (3*S*)-**19e,** 57030-83-8; propyne, 74-99-7; phthalic anhydride, 85-44-9; (*S*)-(−)-α-methylbenzylamine, 2627-86-3; (*R*)-(+)-α-methylbenzylamine, 3886-69-9; (±)-α-phenylbutyric anhydride, 1519-21-7; α-phenylbutyric acid, 90-27-7; (*R*)-(+)-2-hydroxy-4-methylpentanoic acid, 20312-37-2; ethyl vinyl ether, 109-92-2; triethyl orthoacetate, 78-39-7; 1-dimethylamino-1,1-dimethoxyethane, 18871-66-4; acetic anhydride, 108-24-7; (*R*)-(+)-citronellic acid, 18951-85-4; (*R*)-(+)-citronellol, 1117-61-9; 3,5-dinitrobenzoic acid, 99-34-3.

References and Notes

(1) For reviews of the chemistry and synthesis of α-tocopherol and related compounds see (a) H. Mayer and O. Isler in "Methods in Enzymology", Vol. XVIII, Part C, S. P. Colowick and N. O. Kaplan, Ed., Academic Press, New York, N.Y., 1971, pp 241–348, 469–547; (b) P. Schudel, H. Mayer, and O. Isler in "The Vitamins", Vol. V, W. H. Sebrell, Jr., and R. S. Harris, Ed., Academic Press, New York, N.Y., 1972, pp 168–218.

(2) N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, *J. Org. Chem.*, following paper in this issue.

(3) N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, *J. Org. Chem.*, accompanying paper in this issue.

(4) H. Mayer, P. Schudel, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **46,** 650 (1963).

(5) J. W. Scott, F. T. Bizzarro, D. R. Parrish, and G. Saucy, *Helv. Chim. Acta*, **59,** 290 (1976).

(6) A synthesis of optically impure phytol utilizing Kolbe couplings of chiral intermediates has been reported. Natural (+)-citronellal[7] was employed as a starting material: J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, *J. Chem. Soc. C*, 2144 (1966). In this paper, a total synthesis of (*R*)-(+)-dihydrocitronellol (**14**) is also described.

(7) Natural (+)-citronellal has been shown to be only 75–80% optically pure: (a) G. W. O'Donnell and M. D. Sutherland, *Aust. J. Chem.*, **19,** 525 (1966); (b) F. Ciardelli and P. Pino, *Ric. Sci., Sez. A*, **4,** 694 (1964); (c) B. D. Sully and P. L. Williams, *Perfum. Essent. Oil Rec.*, **59,** 365 (1968).

(8) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, p 374, and references cited therein.

(9) J. W. Scott and D. Valentine, Jr., *Science*, **184,** 943 (1974), and references cited therein.

(10) R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.*, **37,** 3737 (1972).

(11) (a) W. Sucrow, P. Caldeira, and M. Slopianka, *Chem. Ber.*, **106,** 2236 (1973); (b) W. Sucrow, B. Schubert, W. Richter, and M. Slopianka, *ibid.*, **104,** 3689 (1971).

(12) The description of intermediates throughout this paper by number of carbon atoms refers only to those carbon atoms destined to form part of the target molecule.

(13) The Claisen rearrangement has been previously applied to the synthesis of isoprenoids. Cf. (a) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50,** 2091 (1967); (b) R. Marbet and G. Saucy, *ibid.*, **50,** 2095 (1967).

(14) (a) S. J. Rhoads and N. R. Raulins, *Org. React.*, **22,** 1 (1975), and references cited therein; (b) D. J. Faulkner and M. R. Peterson, *J. Am. Chem. Soc.*, **95,** 553 (1973); (c) H-J. Hansen and H. Schmid, *Tetrahedron*, **30,** 1959 (1974).

(15) D. Valentine, Jr., K. K. Chan, C. G. Scott, K. K. Johnson, K. Toth, and G. Saucy, *J. Org. Chem.*, **41,** 62 (1976).

(16) (*S*)-(−)-2-Hydroxy-4-methylpentanoic acid exhibits $[\alpha]^{27}D$ −13.1° (*c* 0.6, H_2O): L. Verbit and P. J. Heffron, *Tetrahedron*, **24,** 1231 (1968). We observed $[\alpha]^{25}D$ +14° (*c* 0.6, H_2O) for the (*R*)-(+) enantiomer derived from **8a.**

(17) H. Lindlar and R. Dubuis, *Org. Synth.*, **46,** 89 (1966); (b) H. Lindlar, *Helv. Chim. Acta*, **35,** 446 (1952).

(18) (a) A. Horeau and H. B. Kagan, *Tetrahedron*, **20,** 2431 (1964); (b) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32,** 216 (1967).

(19) It should be noted that when applying the Horeau method to the determination of absolute configuration of such acetylenic carbinols, the alkynyl group must be considered larger than alkyl in a steric as well as nomenclature sense.[20] The recovered α-phenylbutyric acid from the reaction of (+)-**8a** with α-phenylbutyric anhydride[18] exhibited $[\alpha]^{25}D$ +6.03° (*c* 1, C_6H_6) indicating the *R* configuration when the propynyl group is considered the sterically largest substituent. From similar treatment of (−)-**9a,** α-phenylbutyric acid having $[\alpha]^{25}D$ −5.03° was recovered.

(20) R. Pappo, P. Collins, and C. Jung, *Ann. N.Y. Acad. Sci.*, **180,** 64–75

(1971).
(21) (a) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); (b) G. R. Sullivan, J. A. Dale, and H. S. Mosher, *ibid.*, **38**, 2143 (1973).
(22) (a) R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis", Academic Press, New York, N.Y., 1955, p 27. (b) $LiAlH_4$ reduction of acetylenic carbinols is reported to give *E* allylic alcohols. Cf. B. Grant and C. Djerassi, *J. Org. Chem.*, **39**, 968 (1974). In our studies, higher yields of *E* products were obtained using $NaAlH_2(OCH_2CH_2OCH_3)_2$.
(23) W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).
(24) J. Plesek, *Collect. Czech. Chem. Commun.*, **22**, 644 (1957).
(25) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.*, **92**, 741 (1970).
(26) (a) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964); (b) D. Felix, K. G. Steen, A. E. Wick, and A. Eschenmoser, *ibid.*, **52**, 1030 (1969).
(27) (a) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5897 (1972); (b) R. E. Ireland and A. K. Willard, *J. Org. Chem.*, **39**, 421 (1974). We thank Professor Ireland for providing us with detailed experimental procedures.
(28) Racemization most likely occurs via double bond migration during hydrogenation. Cf. P. N. Rylander, "Oganic Synthesis with Noble Metal Catalysts", Academic Press, New York, N.Y., 1973, Chapter 5.
(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**.
(30) M. Fetizon and M. Golfier, *C. R. Acad. Sci., Ser. C*, **267**, 900 (1968).
(31) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).
(32) These experiments were carried out before it was discovered that palladium catalysts caused racemization during hydrogenation of such unsaturated esters. It would be expected that hydrogenation of the 15-carbon ester **6c** over nickel, in analogy with the results obtained for ester **4c**, should provide **19c** without concomitant racemization. Such experiments were not carried out, however.
(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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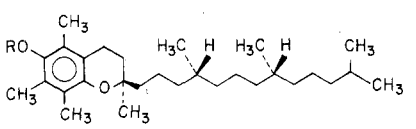
A synthesis of (2*R*,4'*R*,8'*R*)-α-tocopheryl acetate (**1**, R = Ac) is described in which key, optically active side chain synthons are produced starting from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (**6**), itself a readily available enantiomerically homogeneous substance of microbiological origin. 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



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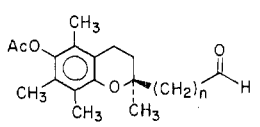
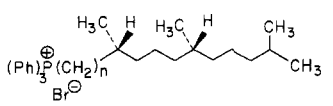
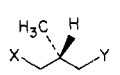


2a; n = 0
2b; n = 1



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



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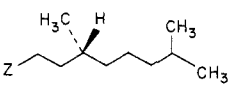

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15-carbon[3] phosphonium salt **3a**. More recently, a related scheme was described by Scott et al.[4] involving coupling of the homologous units, chroman-2-acetaldehyde **2b** and the 14-carbon phosphonium salt **3b**. In both of these approaches, 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-