Stereospecific Transformation of 2,2-Dimethylcyclobutanols into Optically Active 1,2-Cis-Disubstituted Cyclopropanes

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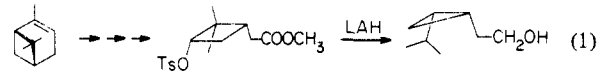
Abstract: Optically active 3-substituted 2,2-dimethylcyclobutanol (+)-**7** and its *p*-toluenesulfonate (−)-**2**, obtained by a stereocontrolled route from (+)-α-pinene (**1**), were shown to undergo facile stereospecific ring contraction under different conditions to yield mainly optically active 1,2-cis-disubstituted cyclopropanes (i.e., (−)-**3**, (−)-**18**, (−)-**20**). The degree of stereospecificity and the absolute configuration of these products are discussed.

Introduction

The cyclopropane unit is present in a large number of natural products[1] and pharmaceutically interesting compounds.[2] Our own interest in sterols from marine sources containing this structural unit in the side chain[3] prompted us to investigate feasible stereospecific routes to optically active cyclopropane-containing compounds which may serve as model compounds and chiral synthones. Our present approach is based on the observation, that the hydride reduction of the optically active cyclobutane tosylate (−)-**2** proceeds mainly with concomitant ring contraction to the optically active cyclopropane derivative (−)-**3**. Since the tosylate (−)-**2** is readily available by a stereocontrolled route from natural (+)-α-pinene (**1**) and the reduction rearrangement to (−)-**3** was found to proceed stereospecifically (eq 1), this ring contraction[4] was further investigated with respect to its stereochemical and mechanistic consequences as well as its probable utility for the synthesis of 1,2-disubstituted cyclopropanes of known absolute configuration.



(+)-1 (−)-2 (−)-3 (1)

Results and Discussion

(i) Synthesis of (1*S*,3*S*)-(−)-Methyl (2,2-Dimethyl-3((*p*-toluenesulfonyl)oxy)cyclobutyl)acetate ((−)-2). The synthesis of the tosylate (−)-**2** was accomplished by the reactions outlined in Scheme I. Oxidation of (+)-α-pinene (**1**) of 92% optical purity[5] by the known procedure of Delepine[6] to (+)-*cis*-pinonic acid (**4**) (98.4% optically pure[7]) followed by esterification with diazomethane to (+)-**5**[7] and subsequent Bayer–Villiger oxidation with *m*-chloroperbenzoic acid leads to the diester (−)-**6** which was partly hydrolyzed to the hydroxy ester (+)-**7**, accompanied by (+)-**8**, and thence transformed into the crystalline tosylate (−)-**2**. Except for the oxidation step **5** → **6**, which is known to proceed with retention of configuration,[8] none of the other reactions were expected to affect the stereocenters C-1 and C-3 of the cyclobutyl ring. Therefore, the absolute configurations 1*S* and 3*S* can be assigned to (−)-**2** with an optical purity corresponding to that of the crystalline intermediate (+)-(**4**).

Scheme I

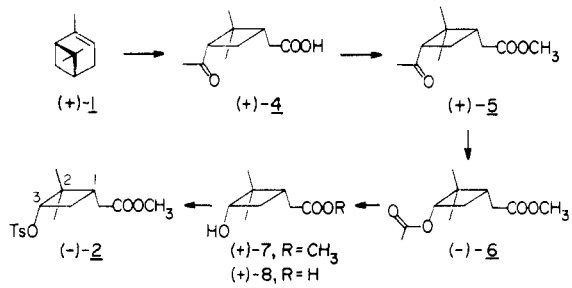
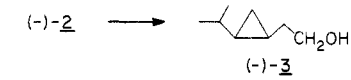


Table I. Product Distribution from Hydride Reductions of the Cyclobutyl Tosylate (−)-2

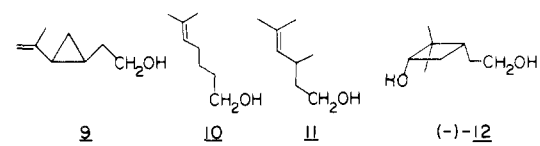
reactn conditns	% yields[a] 3 + 9 + 10 + 11	% yields[a] 12	% compositn[b] of mixtures of 3, 9, 10, and 11[c] 3	9	10	11	$[\alpha]^{20}_D$ of 3, deg
$LiAlH_4$/ether, RT/66 h	64	29	68	2	22	8	−47.9
$NaBH_4$/diglyme, 70 °C/8 days	38	trace[b]	83	4	10	3	−48.5
$NaBH_4$/DME, 85 °C/7 days	31	trace[b]	88	2	5	5	−47.8
$LiEt_3BH$/THF, 65 °C/2 h	50	trace[b]	60	14	20	6	*d*

[a] After short-path distillation. [b] Based on GC analysis. [c] Value for **11** includes amount of accompanying impurity.[12] [d] Not determined.

(ii) Hydride and Deuteride Reductions of Cyclobutyl Tosylate (−)-2. The reduction of the tosylate (−)-**2** with different hydride reagents under the conditions shown in Table I yielded in each case a mixture of the alcohols (−)-**3**, **9**, **10**,[9] and **11** together with the diol (−)-**12** (eq 2). Distillation allowed the separation of the



(−)-2 → (−)-3 (2)



9 10 11 (−)-12

diol **12** from the mixture of the monohydroxy compounds **3**, **9**, **10**, and **11** which then were separated by preparative gas chromatography. The structural assignments are mainly based on the

(1) Beckmann, S.; Geiger, H. *Methoden Org Chem. (Houben-Weyl)* **1971**, *4*, 445-478.
(2) Otto, H.-H. *Dtsch, Apoth.-Ztg.* **1975**, *115*, 89-94.
(3) Tarchini, C.; Rohmer, M.; Djerassi, C. *Helv. Chim. Acta* **1979**, *62*, 1210-1216.
(4) To our knowledge a cyclobutyl–cyclopropane rearrangement of a cyclobutyl tosylate by treatment with lithium aluminum hydride has so far only been reported in one case by: Wiberg, K. B.; Lowry, B. R.; Colby, T. H. *J. Am. Chem. Soc.* **1961**, *83*, 3998-4006.
(5) Calculated with $[\alpha]^{20}_D$ +52.4° for optically pure (+)-α-pinene: Comyns, A. E.; Lucas, H. Y. *J. Am. Chem. Soc.* **1957**, *79*, 4339-4341.
(6) Delepine, M. *Bull. Soc. Chim. Fr.* **1936**, 1369-1382.
(7) Muscio, O. J.; Poulter, C. D. *J. Org. Chem.* **1974**, *39*, 3288-3291.
(8) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 324 and references cited therein.
(9) Johnson, W. S.; Owylang, R. *J. Am. Chem. Soc.* **1964**, *86*, 5593-5598.

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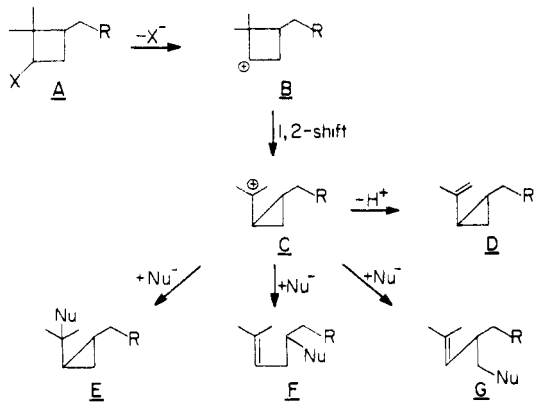
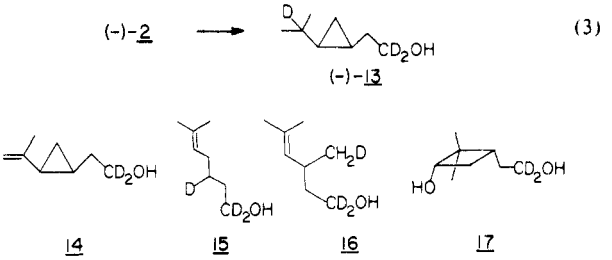
Scheme II



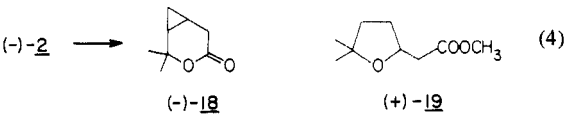
following data. Evidence for the cyclopropyl unit in the main component **3** is provided by the characteristic infrared absorption at 3070 cm^{-1} as well as by the upfield part of the proton NMR spectrum which includes four separated one-proton signals between δ 0.70 and −0.27. The diastereotopic isopropyl methyl groups, giving rise to an unexpected six-proton singlet[10] at a field strength corresponding to 100 MHz, appear as two overlapping three-proton doublets at 360 MHz. Together with the obvious $-CH_2CH_2OH$ substructure and the fact that none of the eight carbon atoms is a quaternary one (based on the off-resonance-decoupled ^{13}C NMR spectrum) the only structure compatible with these data is the 1,2-disubstituted cyclopropane derivative **3**. Furthermore, both the proton chemical shift position and the multiplicity of the cyclopropyl proton signal at δ −0.27 indicate the cis relationship of the two cyclopropyl substitutents.[11] The isopropylidene group of **9**, easily deduced from ^1H NMR and IR data, was hydrogenated by homogeneous catalysis to the isopropyl group of **3** (vide infra) without cleavage of the cyclopropyl ring. The ^1H NMR spectra of the two isomeric olefinic alcohols **10** and **11**,[12] which both show two olefinic methyl signals and one olefinic proton, differ mainly in the fact that **11** features an additional aliphatic methyl doublet caused by the methyl group at C-3 (confirmed by irradiation of the allylic C-3 proton (δ 2.50), which reduces both the olefinic one-proton doublet and the aliphatic methyl doublet to singlets). Diol **12**, the only unrearranged compound found among the products, arises from reductive cleavage of the sulfur oxygen bond in **2**, a well-known side reaction of fairly hindered tosylates.[13]

The isolation of the products **3**, **9**, **10**, and **11** under varying conditions reported in Table I strongly suggests a cyclobutyl–cyclopropylcarbinyl homoallylic type rearrangement for their formation. Although the reaction conditions applied are hardly comparable to solvolytic conditions under which a large number of cyclobutyl tosylate rearrangments have been observed,[14] the nature of the resulting products indicates similar reaction paths as outlined in Scheme II (with R changing from methoxycarbonyl to hydroxymethylene throughout the reaction and X representing the tosyloxy group). Ionization of A (i.e., **2**) to the cyclobutyl cation B and concomitant or subsequent bond shift to the stabilized, tertiary, homoconjugated cyclopropylcarbinyl cation C is followed by loss of a proton to form D (i.e., **9**). Alternatively, attack of the hydride nucleophile at different sites leads either directly to the main product E (i.e., **3**) or indirectly to the "homoallylic" products F (i.e., **10**) and G (i.e., **11**). To test this mechanistic hypothesis, we treated (−)-**2** with lithium aluminum deuteride to give the deuterated analogues (−)-**13** and **14**–**17** (eq 3). The deuterium positions in each compound were easily derived from the characteristic changes of the ^1H NMR spectra and found to be in full agreement with the proposed mechanistic scheme.



(3)

(iii) Hydrolysis of the Tosylate (−)-2. In order to relate the observations described in part ii to the extensive information available on the mechanistic and stereochemical consequences of solvolytic cyclobutyl tosylate rearrangements,[14] we performed the hydrolysis of (−)-*2* in aqueous dimethoxyethane at 80 °C. The optically active δ-lactone (−)-**18** was isolated in 60% yield as the only neutral component. By acidification of the remaining aqueous phase, extraction, and methylation with diazomethane, the tetrahydrofuran derivative (+)-**19** was obtained (eq 4). Consequently the formation of both **18** and **19** can be visualized by the following paths of Scheme II (with R changing from methoxycarbonyl in **2** to the carboxyl functionalities in the final products). Direct attack of the intermediate cyclopropylcarbinyl cation C by water and loss of a proton leads to the nonisolated intermediate E which subsequently lactonizes to (−)-**18** as a consequence of the cis relationship of the cyclopropyl substituents. Similarly the indirect attack of the nucleophile leads to the nonisolated hydroxy acid corresponding to F which upon workup procedures is transformed into 19.



(4)

From these results it can be concluded that both hydride reduction of (−)-**2** under anhydrous conditions and hydrolysis proceed through related intermediates, and therefore the results of the hydride reductions[15] can be interpreted as a border case of the hydrolytic behavior of **2**.

(iv) Dehydration of (1*S*,3*S*)-(+)-Methyl (3-Hydroxy-2,2-dimethylcyclobutyl)acetate ((+)-7) with Phosphorus Oxychloride in Pyridine. Both hydride reduction and hydrolysis of **2** result in mixtures of products due to the different pathways available for the stablization of the cationic intermediate C. This diversity of products detracts from the synthetic utility of this cyclopropane synthesis. Therefore, conditions were sought to favor the formation of a unique product. Since the dehydration of alcohols with phosphorus oxychloride tends to proceed through cationic intermediates,[16] the cyclobutyl alcohol (+)-**7** was subjected to these conditions. In accordance with expectations, the optically active (−)-methyl (2-isopropylidenylcyclopropyl)acetate (**20**) corresponding to elimination path C → D in Scheme II (with R being methoxycarbonyl and X representing the hydroxy group) was obtained in high yield. The cis relationship of the cyclopropyl substituents in **20** is derived from the fact that upon preparative gas chromatography partial conversion to the unsaturated ester **21**[17] occurs. This thermal process, interpreted as a pericyclic homo-[1,5] hydrogen shift, requires a cis relationship of the two cyclopropyl subsitutents. Furthermore, (−)-**20** was chemically related to the main product (−)-**3** of the hydride reduction by lithium aluminum hydride treatment to (−)-**9** (see eq 5) and

(10) Apparently due to the unusually small chemical shift difference between these methyl groups and the vicinal tertiary isopropyl proton.

(11) Wendisch, D. *Method. Org. Chem. (Houben-Weyl)* **1971**, *4*, 28–32 and references cited therein.

(12) Although **11** could not be separated thorougly from an accompanying unknown impurity, the pertinent ^1H NMR data sufficiently support the suggested structure.

(13) Brown, H. C.; Krishnamurthy, S. *J. Org. Chem.* **1976**, *41*, 3064–3066 and references cited therein.

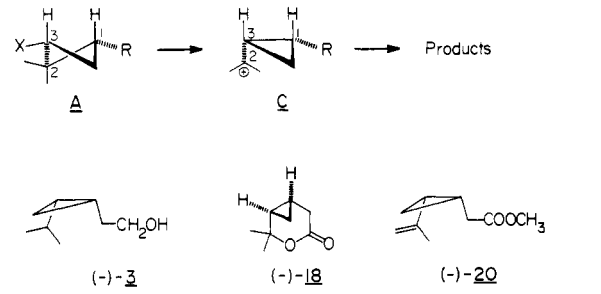
(14) Wiberg, K. B.; Hess, B. A.; Ashe, A. J. In "Carbonium Ions"; Olah, G. A., Schleyer, P. V. R., Eds.; Wiley Interscience: New York, 1972; Vol. III, Chapter 26.

(15) Sodium borohydride reductions of cyclobutyl methanesulfonates under solvolytic conditions are known: Majerski, Z.; Borcic, Z.; Sunko, D. E. *Tetrahedron* **1969**, *25*, 301–313.

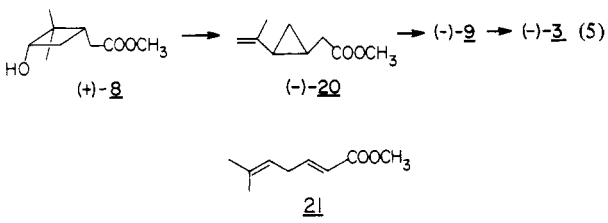
(16) Sauers, R. R.; Landenberg, J. M. *J. Org. Chem.* **1961**, *26*, 964–966.

(17) Beger, J.; Dung, N. X.; Duschek, C.; Hobold, W.; Pritzkow, W.; Schmidt, H. *J. Prakt. Chem.* **1972**, *314*, 863–876.

Scheme III



selective hydrogenation of the double bond to (−)-**3** which showed the same optical rotation as (−)-**3** previously obtained (see Table I).



(v) Stereochemical Consequences of the Cyclobutyl–Cyclopropylcarbinyl Rearrangements. In all the ring contractions reported herein, the cyclopropane-containing products (i.e., (−)-**3**, (−)-**18**, and (−)-**20**) were found to be optically active, suggesting some degree of stereospecificity in their formation. Furthermore, they all represent the thermodynamically less stable cis isomers, thus pointing to kinetic rather than thermodynamic control. The degree of stereospecificity can be estimated in the following manner. The optical rotation of (−)-**3** was found to be independent of the hydride reaction conditions (e.g., hydride source, solvent, temperature, and reaction time). Furthermore, the same rotation was found for (−)-**3** derived from the elimination rearrangement product (−)-**20**. On this basis the assumption of an overall stereospecific ring contraction process (A → C) is very likely. The same assumption is valid for the formation of the lactone (−)-**18**, since a comparable[18] solvolytic reaction of a cyclobutyl methanesulfonate in D-nor steroids has been shown to form only one stereoisomer.

On the basis of literature data[14,18,19] dealing with the stereochemistry of cyclobutyl–cyclopropylcarbinyl rearrangments of related secondary cyclobutyl systems, the correlation shown in Scheme III leads also to absolute configurational assignments of the cyclopropane derivatives, by a process retaining the configuration at carbon atom 1 and inverting it at carbon atom 3.

The obvious tendency of these 3-substituted 2,2-dimethylcyclobutanol systems to undergo preferentially ring contraction can be understood by a concerted ionization rearrangement step (A → C) in which the 1,2-bond cleavage and the backside attack at C-3 is facilitated by the geometry of the favored 1,3-diequatorial conformation of A as shown in Scheme III.

In view of the ready availability of optically active pinene in both enantiomeric forms as a source of chiral cyclobutyl synthons and the fact that both the methoxycarbonyl and the isopropenyl group of **20** can be transformed into other functionalities, the presently described ring contraction sequence may prove to be useful for the synthesis of certain cyclopropanes with defined stereochemistry and high optical purity.

Experimental Section

General Notes. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in a thermostated 1.00-dm microcell. Infrared spectra (IR) were recorded on a Perkin-Elmer 700A spectrometer. ^{1}H Nuclear magnetic resonance spectra (NMR) were obtained on a Varian T-60 (60-MHz), Varian XL-100 (100-MHz), or Bruker HX 360 (360-MHz) spectrometer using tetramethylsilane as internal standard. ^{13}C nuclear magnetic resonance spectra (CMR) were recorded on a Varian XL-100 spectrometer using tetramethylsilane as internal standard: methine, methylene, and methyl carbons were identified by off-resonance decoupling. Low-resolution mass spectra (MS) were obtained on a Varian MAT-44 quadrupole mass spectrometer using a direct inlet system for sample introduction. High-resolution mass spectra (HRMS) were recorded on a Varian MAT-711 double-focusing mass spectrometer using a direct inlet system for sample introduction and a PDP-11/45 computer for data acquisition and reduction. Elemental analyses were determined by Mr. E. Meier of the Stanford Microanalytical Laboratory.

Analytical gas chromatography (GC) was performed on a Hewlett-Packard 402 system with flame ionization detector on a 8-ft × $^1/_8$-in. glass column of 10% Carbowax 20M on gas chrom Q 120/140 (Applied Science). Preparative gas chromatographic separations were done on a Varian Aerograph 2700 with thermal conductivity detector on a 10-ft × $^1/_4$-in. aluminum column of 15% Carbowax 20M or 10% SE-30 on Chromosorb W. Thin-layer chromatography (TLC) was performed on silica gel coated (0.25 mm) glass plates (23 × 85 mm) with UV indicator. UV-inactive spots were made visible by spraying the plates with a 2.5% solution of cerium sulfate in 25% aqueous sulfuric acid and subsequent heating.

The temperatures cited for short-path (bulb to bulb) distillations refer to the maximum temperature attained by the air chamber during the distillation.

(+)-(1*S*,3*S*)-Methyl (3-Acetyl-2,2-dimethylcyclobutyl)acetate (5). To a stirred solution of (+)-*cis*-pinonic acid[6,7] (15.0 g, 81.5 mmol, mp 71–72 °C, $[\alpha]^{20}_D$ +93.5° (*c* 2.2, $CHCl_3$) (lit.[6] mp 68–69 °C, $[\alpha]^{20}_D$ +95.0° ($CHCl_3$))) in 70 mL of ether was added dropwise an ethereal solution of diazomethane[20] until the yellow color persisted. After the mixture was dried over anhydrous $MgSO_4$, the solvent was evaporated to yield 16.0 g (99%) of **5** as a pale yellow oil, which was used without further purification. An analytical sample of **5** was obtained by short-path distillation (180 °C at 18 mm) as a colorless liquid: $[\alpha]^{20}_D$ +84.0° (*c* 2.0, $CHCl_3$); IR (neat) 2950, 1735, 1700, 1435, 1370, 1160 cm^{-1}; NMR (CCl_4, 60 MHz) δ 3.55 (s, 3 H), 2.85 (t, *J* = 8 Hz, 1 H), 2.5–1.5 (m, 5 H), 1.95 (s, 3 H), 1.35 (s, 3 H), 0.9 (s, 3 H); MS *m/z* (relative intensity), 198 (0.4%, M^+), 98 (19%), 96 (23%), 83 (73%), 71 (25%), 69 (100%).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.40; H, 9.09.

(−)-(1*S*,3*S*)-Methyl (3-Acetoxy-2,2-dimethylcyclobutyl)acetate (6). A solution of (+)-**5** (16.0 g, 80.8 mmol) and commercial *m*-chloroperbenzoic acid (ca. 80%, 28.5 g, ca. 132 mmol) in 200 mL of CH_2Cl_2 was stirred at room temperature for 3 days. The white precipitate was filtered and the clear solution treated with a saturated aqueous Na_2SO_3 solution until a negative KI/starch test was obtained. The organic layer was extracted twice with saturated aqueous $NaHCO_3$, four times with cold 5% aqueous NaOH, and then with water, dried over anhydrous $MgSO_4$ and evaporated to yield 17.1 g (99%) of **6** as a pale yellow liquid which was used without further purification. An analytical sample of **6** was obtained by short-path distillation (160 °C at 18mm) as a colorless liquid: $[\alpha]^{20}_D$ −45.9° (*c* 1.1, $CHCl_3$); IR (neat) 2950, 1740, 1440, 1370, 1235, 1190, 1030 cm^{-1}; NMR (CCl_4, 60 MHz) δ 4.55 (t, *J* = Hz, 1 H), 3.6 (s, 3 H), 2.6–1.3 (m, 5 H), 1.9 (s, 3 H), 1.1 (s, 3 H), 0.9 (s, 3 H).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.63; H, 8.58.

(+)-(1*S*,3*S*)-Methyl (3-Hydroxy-2,2-dimethylcyclobutyl)acetate (7) and (+)-(1*S*,3*S*)-(3-Hydroxy-2,2-dimethylcyclobutyl)acetic Acid (8). To a stirred solution of (−)-**6** (9.72 g, 45.4 mmol) in 100 mL of methanol was added at 2 °C 22.2 mL of 2.46 M aqueous KOH solution dropwise without exceeding 6 °C (ca. 15 min). After 1 h of stirring at 2 °C, the solution was neutralized with a few drops of 5 N aqueous HCl and partially evaporated at reduced pressure and 50 °C bath temperture. The remaining aqueous phase was extracted with ether, and the extracts were washed with 5% aqueous NaOH and water, dried over anhydrous $MgSO_4$, filtered, and evaporated to yield after short path distillation (165 °C at 18 mm) 5.75 g (74%) of **7** as a colorless liquid: $[\alpha]^{20}_D$ +5.7° (*c* 1.7, $CHCl_3$); IR (neat) 3420, 2950, 1740, 1440, 1370, 1195 cm^{-1}; NMR (CCl_4, 60 MHz) δ 4.05 (br s, 1 H), 3.65 (t, *J* = 8 Hz, 1 H), 3.6 (s, 3 H), 2.5–1.1 (m, 5 H), 1.05 (s, 3 H), 0.9 (s, 3 H).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.26; H, 9.29.

Acidification of the basic extracts with 5 N aqueous HCl to pH 1 and extraction with ether yielded after drying over anhydrous $MgSO_4$ and evaporation 1.79 g (25%) of **8** as a pale yellow oil which upon recrys-

(18) Meinwald, J.; Taggi, A. J. *J. Am. Chem. Soc.* **1973**, *95*, 7663–7671.
(19) Diaz. A. F.; Miller, R. D. *J. Am. Chem. Soc.* **1978**, *100*, 5905–5910.
(20) Arndt, F. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, pp 165–167.

tallization from CCl_4/ethyl acetate could be obtained as white crystals: mp 88–89 °C; $[\alpha]^{20}_D$ +7.0° (*c* 1.0, $CHCl_3$); IR (neat) 3600–2400, 1710, 1370, 1225, 1125, 1035 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 6.9 (br s, 2 H), 3.8 (t, *J* = 8 Hz, 1 H), 2.6–1.2 (m, 5 H), 1.1 (s, 3 H), 0.95 (s, 3 H).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.89; H, 8.74.

(–)-(1*S*,3*S*)-Methyl (2,2-Dimethyl-3-((*p*-toluenesulfonyl)oxy)cyclobutyl)acetate (2). To a solution of *p*-toluenesulfonyl chloride (12.08 g, 63.3 mmol) in 25 mL of dry pyridine was added at 10 °C with stirring a solution of (+)-**7** (7.27 g, 42.25 mmol) in 25 mL of dry pyridine. After being left standing overnight at 5 °C, the reaction mixture was poured onto ice and extracted with ether, and the combined extracts were washed with cold 5 N aqueous HCl and water, dried over anhydrous $MgSO_4$/K_2CO_3, filtered, and evaporated to yield 13.30 g (96%) of **2** as a pale yellow oil which solidified on standing at −10 °C: mp 40–41 °C; $[\alpha]^{20}_D$ −12.4° (*c* 1.0, $CHCl_3$); IR (neat) 2950, 1735, 1600, 1440, 1360, 1170, 965, 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 7.65 (d, *J* = 8 Hz, 2 H), 7.15 (d, *J* = 8 Hz, 2 H), 4.3 (t, *J* = 8 Hz, 1 H), 3.55 (s, 3 H), 2.4 (s, 3 H), 2.4–1.3 (m, 5 H), 1.0 (s, 3 H), 0.95 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.87, H, 6.79; S, 9.82. Found: C, 58.95; H, 6.86; S, 9.74.

Lithium Aluminum Hydride Reduction of (–)-2. To a slurry of $LiAlH_4$ (0.87 g, 22.9 mmol) in 25 mL of dry ether was added with stirring a solution of (–)-**2** (5.0 g, 15.32 mmol) in 25 mL of dry ether over a period of 20 min, during which time the temperature rose to 30 °C and a new spot with R_f = 0.1 (**2**: R_f = 0.4) appeared on TLC (hexane/ethyl acetate = 80/20). After the mixture was stirred at room temperature for 18 h, an additional portion of $LiAlH_4$ (0.87 g, 22.9 mmol) was added followed by stirring for 48 h during which time the spot at R_f = 0.1 disappeared and the UV-inactive spot of the product mixture at R_f = 0.4 developed. Workup[21] and short-path distillation yielded two fractions. Up to 125 °C at 18 mm 1.26 g of a colorless oil was collected which contained the components **3** (68%), **9** (2%), **10** (22%), and **11** (8%) on the basis of GC analysis (64% yield). By preparative GC (Carbowax 20M, 160 °C) the components were eluted in the order **11**, **3**, **10**, and **9** and isolated as colorless oils. Continued short-path distillation up to 160 °C (18 mm) furnished 0.63 g (29%) of **12** as a pale yellow oil, an analytical, colorless sample of which was obtained by preparative GC (SE-30, 160 °C). Physical and analytical data for these reductions products are listed herewith.

(–)-(1*S*,2*R*)-2-(2-Isopropylcyclopropyl)ethan-1-ol (3): $[\alpha]^{20}_D$ −47.9° (*c* 1.2, $CHCl_3$); IR (neat) 3330, 3070, 2950, 2865, 1465, 1390, 1370, 1055, 1015, 845 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.69 (t, *J* = 7 Hz, 2 H), 1.90–1.80 (m, 1 H), 1.42 (br s, 1 H), 1.30–1.18 (m, 1 H), 1.13–0.97 (m, 1 H), 0.95 (d, *J* = 8 Hz, 3 H), 0.93 (d, *J* = 8 Hz, 3 H), 0.77–0.65 (m, 1 H), 0.57 (dt, J = 5 and 8 Hz, 1 H), 0.49–0.38 (m, 1 H), −0.27 (ddd, all *J* ≈ 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 25.2 MHz) δ 63.22 (t), 31.71 (t), 28.70 (d), 24.01 (d), 23.07 (q), 22.91 (q), 12.82 (d), 9.95 (t); HRMS *m/z* (relative intensity), 128.117 35 (0.2% calcd for $C_8H_{16}O$, 128.120 11), 113.096 52 (0.3%, $C_7H_{13}O$, M − CH_3), 110.109 65 (3%, M − (CH_3 + H_2O)), 95.086 39 (16%, C_7H_{11}), 82.079 31 (23%, C_6H_{10}), 56.071 56 (100%, C_4H_8).

Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.64; H, 12.64.

***cis*-2-(2-Isopropenylcyclopropyl)ethan-1-ol (9)**: IR (neat) 3330, 3070, 2930, 2860, 1645, 1455, 1055, 1015, 870 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 4.84 (s, 1 H), 4.57 (s, 1 H), 3.68 (t, *J* = 7 Hz, 2 H); 1.81 (s, 3 H), 1.70–1.55 (m, 1 H), 1.47–1.25 (m, 3 H), 1.05–0.95 (m, 1 H), 0.78–0.70 (m, 1 H), 0.41 (ddd, all *J* ≈ 5 Hz, 1 H); HRMS *m/z* (relative intensity), 126.10478 (6% calcd for $C_8H_{14}O$, 126.104 46), 111.081 28 (89%, M − CH_3), 93.070 53 (82%, M − (CH_3 + H_2O)), 81.071 88 (55%, C_6H_9), 67.053 88 (82%, C_5H_7), 41 (100%).

6-Methyl-5-hepten-1-ol (10): IR (neat) 3330, 2920, 2855, 1450, 1380, 1055 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 5.11 (t, *J* = 7 Hz, 1 H), 3.64 (q, *J* = 6 Hz, 2 H, reduces to a triplet, *J* = 6 Hz, after D_2O exchange), 1.98 (q, *J* = 7 Hz, 2 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.60–1.50 (m, 2 H), 1.39 (quintet, *J* = 7 Hz, 2 H), 1.22 (t, *J* = 6 Hz, 1 H, exchangeable with D_2O); HRMS *m/z* (relative intensity), 128.12049 (27% calcd for $C_8H_{16}O$, 128.120 11), 113.096 06 (0.5%, M − CH_3), 110.108 69 (6%, M − H_2O), 95.085 46 (46%, M − (CH_3 + H_2O)), 82.077 27 (89%, C_6H_{10}), 69.070 24 (82%, C_5H_9), 67.054 45 (50%, C_5H_7), 41.038 68 (100%, C_3H_5).

Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.52; H, 12.49.

3,5-Dimethyl-4-hepten-1-ol (11): IR (neat) 3320, 2950, 2920, 2860, 1445, 1375, 1040 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 4.92 (dm, *J* = 8 Hz, 1 H), 3.67–3.54 (m, 2 H), 2.56–2.43 (m, 1 H), 1.69 (d, *J* ≈ 1 Hz, 3 H), 1.63 (d, *J* ≈ 1 Hz, 3 H), 1.67–1.38 (m, 2 H), 1.29 (t, *J* = 6 Hz, 1 H), 0.95 (d, *J* = 7 Hz, 3 H) (irradiation at δ 2.50, 4.92 (s), 0.95 (s); separately visible signals of unknown impurity[12] δ 3.73–3.67 (m), 1.05–0.85 (m), 0.52–0.42 (m), 0.30–0.20 (m)); HRMS *m/z* (relative intensity), 128.120 77 (27% calcd for $C_8H_{16}O$; 128.120 11), 113.096 65 (4%, M − CH_3), 110.109 81 (7%, M − H_2O), 95.085 72 (47%, M − (CH_3 + H_2O)), 83.085 69 (100%, C_6H_{11}), 55.054 66 (97%, C_4H_7), 41.039 40 (59%, C_3H_5).

(–)-(1*S*,3*R*)-3-(2-hydroxyethyl)-2,2-dimethylcyclobutan-1-ol (12): $[\alpha]^{20}_D$ −2.9° (*c* 1.2, $CHCl_3$); IR (neat) 3320, 2940, 2870, 1465, 1135, 1055 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.78–3.70 (m, 1 H, after D_2O exchange; 3.74 (t, *J* = 6 Hz)), 3.62–3.52 (m, 2 H), after D_2O exchange; 3.57 (t, *J* = 6 Hz)), 2.40–2.31 (m, 1 H), 1.72–1.62 (m, 1 H), 1.62–1.38 (m, 5 H), 1.17 (t, *J* = 7 Hz, 1 H, exchangeable with D_2O), 1.07 (s, 3 H), 0.96 (s, 3 H); HRMs *m/z* (relative intensity), 126.10411 (1%, M − H_2O, calcd for $C_8H_{14}O$, 126.104 45), 1110.081 28 (8%, M − (H_2O + CH_3)), 100.089 18 (36%, $C_6H_{12}O$), 72.057 82 (59%, C_4H_8O), 69.070 66 (100%, C_5H_9), 57.070 45 (36%, C_4H_9), 57.034 18 (33%, C_6H_5O), 41.038 89 (70%, C_3H_5).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.58; H, 10.89.

Lithium Aluminum Deuteride Reduction of (–)-2. The reaction and workup were carried out in the same way as with lithium aluminum hydride and resulted in the isolation of the deuterated analogues (–)-**13**, **14**, **15**, **16**, and (–)-**17**. Physical and analytical data for these reduction products are listed herewith.

(–)-(1*S*,2*S*)-2-(2-(1-methylethyl-*1-d*)cyclopropyl)ethan-*1,1-d*$_2$-1-ol (13): $[\alpha]^{20}_D$ −47.0° (*c* 1.0, $CHCl_3$); IR (neat) 3330, 3070, 2950, 2865, 2200, 2145, 2090, 1460, 1385, 1365, 1160, 1130, 1095, 960, 830 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.83 (dd, *J* = 14 and 4 Hz, 1 H), 1.41 (s, 1 H, exchangeable with D_2O), 1.22 (dd, *J* = 14 and 9 Hz, 1 H), 0.95 (s, 3 H), 0.93 (s, 3 H), 0.77–0.65 (m, 1 H), 0.57 (dt, *J* = 5 and 8 Hz, 1 H), 0.47–0.39 (m, 1 H), −0.27 (ddd, all *J* ≈ 5 Hz); ^{13}C NMR ($CDCl_3$, 25.2 MHz) δ 31.71 (t), 24.01 (d), 23.07 (2), 22.97 (q), 12.81 (d), 9.95 (t); HRMS *m/z* (relative intensity), 131.141 37 (0.4% calcd for $C_8H_{13}D_3O$, 131.138 94), 116.113 86 (0.4%, M − CH_3), 113.127 64 (3%, M − H_2O), 98.104 32 (11%, M − (CH_3 + H_2O)), 83.084 85 (13%, C_6H_9D), 57.078 49 (100%, C_4H_7D).

***cis*-2-(2-Isopropenylcyclopropyl)ethan-*1,1-d*$_2$-1-ol (14)**: NMR ($CDCl_3$, 360 MHz) δ 4.84 (s, 1 H), 4.57 (s, 1 H), 1.81 (s, 3 H), 1.70–1.60 (m, 1 H), 1.47–1.31 (m, 3 H), 1.05–0.95 (m, 1 H), 0.78–0.70 (m, 1 H), 0.41 (ddd, all *J* ≈ 5 Hz, 1 H); HRMS *m/z* (relative intensity), 128.111 774 (7% calcd for $C_8H_{12}D_2O$, 128.117 01), 113.094 39 (70%, M − CH_3), 95.084 68 (87%, M − (CH_3 + H_2O)), 81.070 15 (51%, C_6H_9), 67.054 89 (59%, C_5H_7), 41.038 70 (100%, C_3H_5).

6-Methyl-5-hepten-*1,1,3-d*$_3$-1-ol (15): IR (neat) 3330, 2960, 2920, 2855, 2190, 2130, 2080, 1445, 1375, 1130, 1100, 955 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 5.11 (t, *J* = 7 Hz, 1 H), 1.98 (t, *J* = 7 Hz, 2 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.60–1.50 (m, 2 H), 1.39 (quintet, *J* = 7 Hz, 1 H), 1.18 (s, 1 H); HRMS *m/z* (relative intensity), 131.137 90 (39% calcd for $C_8H_{13}D_3O$, 131.138 94), 116.114 15 (0.7%, M − CH_3), 113.128 32 (6%, M − H_2O), 98.105 19 (28%, M − (CH_3 + H_2O)), 83.085 77 (81%, C_6H_9D), 69.0699 (90%, C_5H_9), 41.039 54 (100%, C_3H_5).

3-Methyl-*1-d*-5-methyl-4-hexen-*1,1-d*$_2$-1-ol (16): IR (neat) 3320, 2950, 2920, 2860, 2190, 2095, 1445, 1375, 1190, 1130, 1095, 960 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 4.92 (dm, *J* = 8 Hz, H), 2.56–2.43 (m, 1 H), 1.69 (d, *J* = 1 Hz, 3 H), 1.63 (d, *J* = 1 Hz, 3 H), 1.67–1.53 (m, 1 H), 1.43 (dd, *J* = 14 and 8 Hz, 1 H), 1.27 (s, 1 H), 0.95 (dm, *J* = 7 Hz, 2 H) (irradiation at δ 2.50, 4.92 (s), 1.43 (d, *J* = 14 Hz), 0.95 (s)); HRMS *m/z* (relative intensity), 131.13932 (25% calcd for $C_8H_{13}D_3O$, 131.138 94), 116.115 65 (3%, M − CH_3), 115.107 98 (1%, M − CH_2D), 113.128 67 (7%, M − H_2O), 98.105 51 (29%, M − (CH_3 + H_2O)), 84.092 89 (100%, $C_6H_{10}D$).

(–)-(1*S*,3*R*)-3-(2-Hydroxyethyl)-2,2-dimethylcyclobutan-*2,2-d*$_2$-1-ol (17): $[\alpha]^{20}_D$ −2.9° (*c* 1.1, $CHCl_3$); IR (neat) 3320, 2940, 2865, 2180, 2080, 1465, 1110, 1090, 1045, 960 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 3.78–3.70 (m, 1 H), 2.40–2.31 (m, 1 H), 1.69–1.62 (m, 1 H); 1.62–1.38 (m, 4 H), 1.15 (s, 1 H), 1.07 (s, 3 H), 0.96 (s, 3 H); HRMS *m/z* (relative intensity) 128.11655 (0.8% calcd for $C_8H_{12}D_2O$, 128.1 1702, M − H_2O), 113.09 372 (5%, M − (H_2O + CH_3)), 102.101 95 (29%, $C_6H_{10}D_2O$), 72.057 33 (39%, C_4H_8O); 69.070 20 (100%, C_5H_9), 57.078 50 (19%, C_4H_9), 57.043 69 (27%, C_3H_5O).

Sodium Borohydride Reduction of (–)-2. A solution of (–)-**2** (1.0 g, 3.07 mmol) and $NaBH_4$ (0.1 g, 2.6 mmol) in 5 mL of diglyme was stirred at 68–70 °C. After 6 days 0.1 g of $NaBH_4$ was added and the stirring continued at 70–75 °C for 2 days after which time the TLC spot of the product mixture (hexane/ethyl acetate = 80/20) was fully developed. After addition of water and pentane, the organic layer was extracted five times with water to remove diglyme, dried over anhydrous $MgSO_4$, filtered, and evaporated to yield after short-path distillation (120 °C at 15 mm) 149 mg of a colorless oil which contained the components **3** (83%),

(21) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; p 584, reference 4.

9 (4%), **10** (10%), and **11** (3%) on the basis of GC analysis (38% yield). From this mixture, compound **3** was separated by preparative GC (Carbowax 20M, 160 °C): $[\alpha]^{20}_D$ −48.5° (*c* 1.0, $CHCl_3$).

In a similar experiment (−)-**2** (0.5 g, 1.53 mmol) and $NaBH_4$ (0.29 g, 7.63 mmol) were heated in 20 mL of dimethoxyethane at reflux for 7 days, poured onto ice, stirred for 2 h, and extracted twice with ether; the combined extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to yield after short-path distillation (130 °C at 16 mm) 61 mg of a colorless oil which contained the components **3** (88%), **9** (2%), **10** (5%), and **11** (5%) on the basis of GC analysis (31% yield). From this mixture, compound **3** was separated by preparative GC (Carbowax 20M, 160 °C): $[\alpha]^{20}_D$ −47.8° (*c* 1.0, $CHCl_3$).

Lithium Triethyl Borohydride Reduction of (−)-2. To a stirred solution of (−)-**2** (0.33 g, 1.0 mmol) in 4 mL of dry tetrahydrofuran was added with ice cooling 6 mL of ca. 1 M solution of lithium triethyl borohydride in tetrahydrofuran under argon. After 1 h at room temperature, the solution was heated to reflux for 2 h. The addition of 2.4 mL of 15% aqueous NaOH was followed by 2.4 mL of 30% H_2O_2. The warm mixture was cooled to room temperature, the tetrahydrofuran layer separated, and the aqueous layer extracted twice with pentane. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to yield after short-path distillation (140 °C at 18 mm) 64 mg of a colorless oil which contained the components **3** (60%), **9** (14%), **10** (20%), and **11** (6%) based on GC analysis (50% yield).

Hydrolysis of (−)-2. A solution of (−)-**2** (200 mg, 0.61 mmol) and 2.3 mg of $Zn(OAc)_2 \cdot 2H_2O$ in 4 mL of dimethoxyethane and 1 mL of water was stirred at reflux for 21 h. After addition of ether and 4 mL of saturated aqeous $NaHCO_3$, the aqueous layer was extracted with ether, and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to yield after short-path distillation (150 °C at 16 mm) 53 mg (62%) of **(−)-(1*S*,6*S*)-5,5-dimethyl-4-oxabicyclo[4.1.0]heptan-3-one (18)** as colorless crystals: mp 54 °C; $[\alpha]^{20}_D$ −144.4° (*c* 1.1, $CHCl_3$); IR (CCl_4) 3100, 2990, 2960, 1745, 1385, 1375, 1275, 1155, 1085, 970 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.94–2.84 (m, 2 H), 1.49 (s, 3 H), 1.44 (s, 3 H), 1.44–1.05 (m, 2 H), 0.84–0.52 (m, 1 H), 0.40 (ddd, all $J \approx 5$ Hz, 1 H); MS *m/z* (relative intensity), 140 (5%, M), 125 (81%), 96 (50%), 83 (95%), 81 (100%), 54 (60%), 53 (69%). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.60.

Acidification of the aqueous layer with 10% aqueous H_2SO_4, extraction with ether, drying of the combined extracts over anhydrous $MgSO_4$ yielded after filtration and evaporation 29 mg of a slightly yellow oil, which was dissolved in ether and treated with an etheral solution of diazomethane[20] until the yellow color persisted. After evaporation the remaining yellow oil was purified by short-path distillation (150 °C at 15 mm) and preparative GC (Carbowax 20M, 200 °C) to yield (+)-**methyl (5,5-dimethyltetrahydrofuryl)acetate (19)** as a colorless oil: $[\alpha]^{20}_D$ +3.6° (*c* 1.1, $CHCl_3$); IR (neat) 2960, 2875, 1740, 1460, 1440, 1380, 1365, 1300, 1250, 1190, 1170, 1135, 1145 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 4.40–4.20 (m, 1 H), 3.68 (s, 3 H), 2.65 (dd, J = 15 and 6 Hz, 1 H) and 2.44 (dd, J = 15 and 7 Hz, 1 H) AB part of ABX-type pattern, 2.37–1.98 (m, 1 H), 1.92–1.55 (m, 4 H); 1.24 and 1.23 (2 s, together 6 H); MS *m/z* (relative intensity), 172 (2%, M), 157 (44%), 116 (86%), 99 (58%), 81 (56%), 59 (48%), 55 (100%). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.95; H, 9.30.

Dehydration of (+)-7 with Phosphorus Oxychloride in Pyridine. A stirred solution of (+)-**7** (520 mg, 3 mmol) and phosphorus oxychloride (930 mg, 6 mmol) in 6 mL of dry pyridine was heated in an oil bath kept at 90 ± 2 °C for 60 min, poured onto ice, acidified with ca. 15 mL of 5 N aqueous HCl, and extracted twice with ether. The combined extracts were washed with diluted aqueous HCl, dried over anhydrous $MgSO_4$, filtered, and evaporated to yield 449 mg (96%) of **(−)-(1*S*,2*S*)-methyl-(2-isopropenylcyclopropyl)acetate (20)** as a pale yellow oil, which according to analytical GC and NMR analysis contains only traces of impurities. Short-path distillation (160 °C at 95 mm) furnished (−)-**20** as a colorless oil: $[\alpha]^{20}_D$ −35.8° (*c* 1.0, $CHCl_3$); IR (neat) 3080, 2960, 1740, 1650, 1440, 1320, 1260, 1190, 1170, 880 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 4.85 (s, 1 H), 4.58 (s, 1 H), 3.67 (s, 3 H), 2.32 (dd, J = 15 and 6 Hz) and 2.14 (dd, J = 15 and 6 Hz, 1 H) AB-part of an ABX-type pattern, 1.78 (s, 3 H), 1.76-1.10 (m, 2 H), 0.92–0.68 (m, 1 H), 0.48 (ddd, all $J \approx 5$ Hz, 1 H); MS *m/z* (relative intensity) 154 (12%, M), 139 (5%), 111 (14%), 95 (100%), 79 (69%), 67 (53%). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.02; H, 8.93.

Preparative GC (Carbowax 20M) of (−)-**20** in the range of 160–200 °C showed two unresolved peaks whose relative intensities changed with column temperature favoring at high temperatures the second peak which was identified as **methyl 6-methyl-2,5-heptadienoate (21)** by its IR and NMR spectra.[17]

Lithium Aluminum Hydride Reduction of (−)-20. A solution of (−)-**20** (1.33 g, 8.6 mmol) in 20 mL of dry ether was added to a stirred slurry of lithium aluminum hydride (0.65 g) in 30 mL of dry ether over a period of 15 min. After 1 h of stirring, workup,[21] and evaporation of the solvent 0.95 g (87%) of (−)-**9** was isolated as a colorless oil which was used without further purification. An analytical sample of (−)-**9** was obtained by column chromatography (silica gel, hexane/ethyl acetate = 90/10) and subsequent short-path distillation (125 °C at 18 mm): $[\alpha]^{20}_D$ −63.1° (*c* 1.1, $CHCl_3$).

Hydrogenation of (−)-9. A solution of (−)-**9** (134 mg, 1.06 mmol) and tris(triphenylphosphine)rhodium chloride (50 mg) in 1 mL of benzene was degassed 4 times in a pressure vessel and then stirred under a pressure of hydrogen at 14 psi for 20 h. After evaporation of the solvent the residue was taken up in pentane, filtered through Celite, and evaporated to yield 122 mg (90%) of (−)-**3** as a yellow oil. An analytical sample of (−)-**3** was obtained by preparative GC (Carbowax, 160 °C): $[\alpha]^{20}_D$ −48.3° (*c* 1.2, $CHCl_3$).

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