(176 mg, 55%) and **1** (62 mg, 20%) from the cathodic compartment. The spectral data of **5** were consistent with those of an authentic sample.[15]

Reaction of 1 and 4 with XeF_2-TFA. A mixture of **1** (78 mg, 1 mmol) and TFA (0.23 mL, 3 mmol) in CH_2Cl_2 (2 mL) was added to XeF_2 (254 mg, 1.5 mmol) and then stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure. The organic residue was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane-AcOEt), recovering **1** (55 mg, 70%). By the same procedure, **4** was converted to **5** (202 mg, 65%).

Intramolecular Diels-Alder Approach to Cadinane and Amorphane Sesquiterpenes

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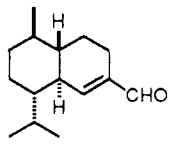
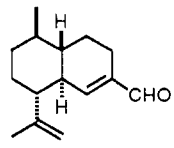
A synthetic route to both cadinane and amorphane type sesquiterpenes is described. Successful implementation of this route showed the structures previously considered for cadinenal (**1**) and dehydrocadinenal (**2**) to be incorrect, but confirmed both the relative and absolute configurations proposed for pernetic acid C (**3**) and pernetic acid B (**4**).

Plant metabolites have often been postulated to provide defense against herbivores. Numerous essential oils have been found to contain terpenes which exhibit insect-repellent activity.[1] The essential oil from the grass *Vetiveria zizanoides* (L.) Nash, known largely because of its use in perfumery, is purportedly repellent to insects. Bioassays using Javanese oil of vetiver showed that the potent topical irritant activity of this oil on flies and cockroaches was attributable to its carbonyl-containing components.[2] Among the minor carbonyl components from this oil, two new sesquiterpene aldehydes, cadinenal (**1**) and dehydrocadinenal (**2**), have been tentatively assigned cadinane-based structures containing four contiguous asymmetric centers, largely on the basis of spectroscopic data.[3]



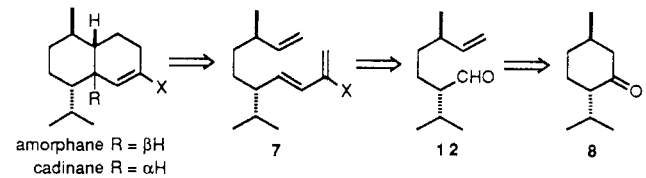
1

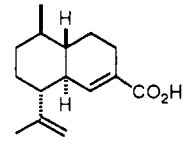


2

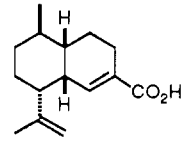
In addition, fruit of the Chilean plant *Pernettya furens* has yielded pernetic acid C (**3**) and pernetic acid B (**4**), which have been assigned structures based on the cadinane and closely related amorphane system, respectively.[4] This fruit, called *hysh-hued* or *hierba-loca*, is toxic to humans and is reported to cause mental confusion and madness.[5] During the characterization of these compounds, both acids were partially hydrogenated over Wilkinson's catalyst to form the corresponding dihydropernetic acids C and B, formulated as **5** and **6**. We have undertaken syntheses of compounds **1**, **5**, and **6** in order to confirm the structural and stereochemical assignments.

Scheme I

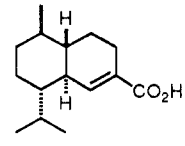




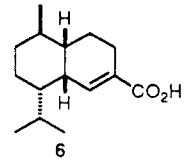
3



4



5



6

Results and Discussion

We sought to establish the four contiguous stereogenic centers in the target compounds by an intramolecular Diels-Alder reaction[6] of an appropriate acyclic triene, as outlined in Scheme I, where X is a suitable precursor to the aldehyde and carboxylic acid functionalities. Consideration of molecular models showed the likelihood of forming both cadinane and amorphane ring systems. We felt that triene **7** could be prepared from aldehyde **12**, which could in turn be formed from (-)-menthone (**8**). This approach would establish the relative stereochemistry of the isopropyl and methyl groups early in the synthesis and would also provide a method by which to determine or confirm the absolute configurations of the natural products.

(1) (a) Sarena, B. P.; Opender, K. In *Cultivation and Utilization of Aromatic Plants*; Atal, C. K., Kapur, B. M., Eds.; Regional Research Laboratory Council on Scientific and Industrial Research: Jammu-Tawi, 1982; p 766. (b) Gilbert, B. In *Natural Products and the Production of Plants*; Marini Bettolo, G. B., Ed.; Elsevier Scientific Publishing: Amsterdam, 1977; p 231.

(2) Jain, S. C.; Nowicki, S.; Eisner, T.; Meinwald, J. *Tetrahdron Lett.* **1982**, 4639.

(3) Plavcan, K. A. Ph.D. Thesis, Cornell University, August, 1985.

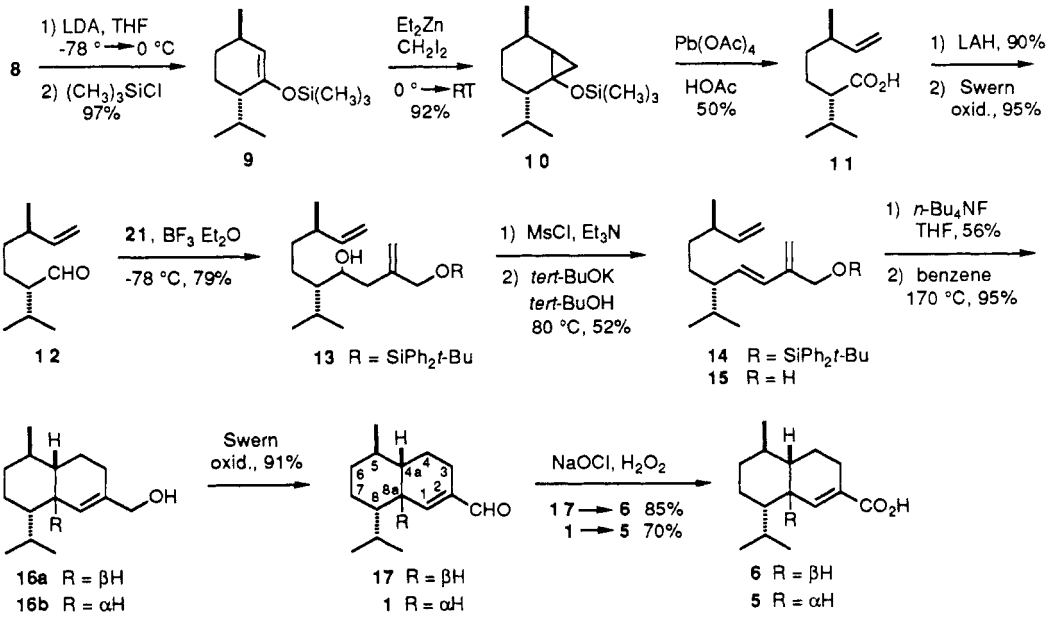
(4) Hosozawa, S.; Miura, I.; Kido, M.; Munoz, O.; Castillo, M. *Phytochemistry* **1985**, *24*, 2317.

(5) Lewis, W. H. *Medical Botany—Plants Affecting Man's Health*; Wiley: New York, 1977.

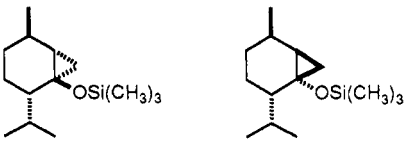
(6) Ciganek, E. *Org. React.* **1984**, *34*, 1.

0022-3263/90/1955-3912$02.50/0

Scheme II



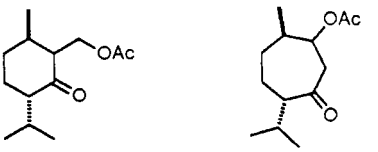
The synthetic route is shown in Scheme II. Treatment of (−)-menthone with lithium diisopropylamide in tetrahydrofuran afforded regioselectively the kinetic enolate, which upon trapping with chlorotrimethylsilane gave silyl enol ether **9**. The ozonolysis of **9** to produce an aldehyde–acid intermediate,[7] which could then be methylenated, proved troublesome, producing unsatisfactory yields. An alternate route was therefore devised, using methodology described by Rubottom et al. which involves the oxidative two-bond cleavage of 1-((trimethylsilyl)oxy)bicyclo[*n*.1.0]alkanes with lead(IV) acetate in acetic acid to form acyclic olefin–acids.[8] Treatment of enol ether **9** with diethylzinc and diiodomethane in hexane[9] provided (silyloxy)cyclopropane **10** as a 3.5:1 mixture of diastereomeric compounds **10a** and **10b** in excellent yield. Difference



10a **10b**

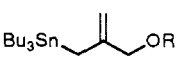
nuclear Overhauser effect experiments (NOE) indicated that the cyclopropane ring was syn to the isopropyl group in the major product (**10a**). Consideration of molecular models suggested that the lowest energy conformation of enol ether **9** should be one in which the trimethylsilyloxy group is anti to the isopropyl group. This would place the bulky group in a position blocking access to the β-face of the enol ether double bond. This hypothesis is consistent with the observed ratio of products. MMX calculations support this predicted conformation as the thermodynamically most stable.

Treatment of **10** with lead(IV) acetate in acetic acid gave a 50% yield of **11** as the single acidic product. The addition of a small amount of ethylene glycol to the completed reaction eliminated problems associated with the formation of insoluble lead dioxide during hydrolysis by reducing unreacted lead(IV) acetate to lead(II) acetate. Byproducts were tentatively identified as **18** and **19**. Lithium aluminum hydride reduction of **11** afforded an alcohol which was oxidized under Swern conditions[10] to give aldehyde **12**.



18 **19**

The construction of the diene functionality was accomplished using a modification of chemistry recently reported by Trost et al.[11] Hydroxymethyl stannane **20** was prepared as described, and then protected as its *tert*-butyldiphenylsilyl ether (**21**) by treatment with *tert*-butylchlorodiphenylsilane and imidazole in *N*,*N*-dimethylformamide. This compound (**21**) was found to be relatively unstable. The coupling reaction between aldehyde **12** and **21**, with 1.5 equiv of boron trifluoride etherate, gave desired homoallylic alcohol **13** in 79% yield. The dehydration of **13** to give the 1,3-diene was carried out using a two-step procedure consisting of mesylation of the secondary alcohol followed by elimination with potassium *tert*-butoxide in *tert*-butyl alcohol at 80–90 °C. Triene **14** was obtained in a 52% yield from alcohol **13**.



20 R = H
21 R = SiPh2t-Bu

Diels–Alder reactions were carried out both on triene **14** and on deprotected triene **15**, formed by treatment of **14** with tetrabutylammonium fluoride.[12] In each case, the Diels–Alder reaction was quite sluggish and occurred at an appreciable rate only when the starting material was heated to 170 °C in a sealed tube. After approximately

(7) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, 2027.
(8) (a) Rubottom, G. E.; Marrero, R.; Krueger, D. S.; Schreiner, J. L. *Tetrahedron Lett.* **1977**, 4013. (b) Rubottom, G. E.; Beedle, E. C.; Kim, C.-W.; Mott, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4230.
(9) Furukawa, J.; Kawabatu, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (b) Ryu, I.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1977**, 4611.
(10) (a) Oumura, K.; Swern, D. *Tetrahedron* **1978**, 1651. (b) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
(11) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778.
(12) Hanessian, S.; Lavellee, P. *Can. J. Chem.* **1975**, *53*, 2975.

2 days, the starting material was ca. 95% consumed, with concurrent formation of two diastereomeric products. The ratio of products could be determined by integration of the olefinic proton signals in the ^1H NMR spectrum. The reaction of triene **14** gave a 2:1 ratio of diastereomeric products, while that of triene **15** produced a 1.6:1 ratio of products **16a** and **16b**. Swern oxidation of **16**, as a mixture of allylic alcohols, provided two α,β-unsaturated aldehydes. Semipreparative reverse-phase HPLC allowed the separation of the two compounds as a colorless oil and a colorless solid.

A comparison of the ^1H NMR spectra of each of the oxidation products with that of cadinenal, from vetiver oil, clearly indicated that neither was the natural product. This finding could result from either a synthetic route which did not in fact produce the desired target structure, or from an incorrect assignment of the cadinenal structure. In order to distinguish between these possibilities, the structures and stereochemistries of the synthetic products were firmly established.

Due to the complexity of the ^1H NMR spectra of these compounds, the disposition of the ring junction protons was not immediately clear. A two-dimensional COSY study of the major compound allowed the assignment of all of the proton signals. The lack of large splitting in the signal observed for the allylic ring junction proton H8a indicates that this compound does not have neighboring protons in a diaxial relationship as required for a trans ring junction stereochemistry. It suggests instead the cis orientation of the ring junction protons as in structure **17**.

This hypothesis was confirmed using an NOE experiment. When allylic ring junction proton H8a in compound **17** was irradiated, an enhancement was observed for both the neighboring ring junction proton H4a and the methine proton H8, which is adjacent to the isopropyl group. This result is consistent with a cis orientation of the ring junction and indicates that both of these protons lie on the β-face of the molecule. The observation of a long-range coupling between H8aβ and H7β, in the COSY spectrum and in double resonance decoupling experiments, suggests a W-shaped 1,3-diequatorial relationship between these protons. This orientation is possible only for the amorphane type ring system.

A 2D COSY experiment on the minor compound allowed assignment of most of the signals in the spectrum. The signal assigned to proton H8a does exhibit several large couplings, which is consistent with a diaxial relationship between the ring junction protons H4a and H8a, and with the adjacent methine proton H8. Recrystallization of this compound from methanol produced crystals suitable for X-ray diffraction analysis. The ORTEP drawing[13] (Figure 1) clearly shows the trans-trans–trans relationship between protons H5, H8a, and H8, allowing us to unambiguously assign structure **1** to this compound.

Oxidation of aldehydes **1** and **17** with sodium chlorite[14] gave acids **5** and **6** in 70% and 85% isolated yields, respectively. The ^1H NMR spectra of these compounds matched the spectral data reported previously, confirming the relative configurations of the structures proposed by Hosozawa et al.[4,16] The absolute configurations of these

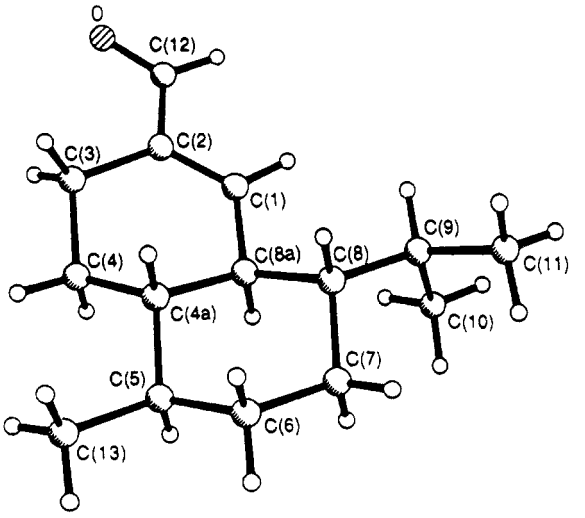


Figure 1. ORTEP representation of compound **1**.

acids are also confirmed by comparing the CD spectra of the naturally derived compounds with those of our synthetic material. As reported, the CD spectrum recorded for dihydropernetic acid B (**5**) exhibits an inverse Cotton effect relative to dihydropernetic acid C (**6**).

In summary, we have developed a convenient synthetic route to the cadinane and amorphane sesquiterpene ring systems. The structures previously proposed for cadinenal (**1**) and dehydrocadinenal (**2**) were shown to be incorrect; however, the relative and absolute configurations of pernetic acid B (**6**) and C (**5**) were confirmed by preparing their dihydro derivatives and making comparisons with the reported data.

Experimental Section

Two dimensional (2D) NMR, DEPT, and NOE experiments were recorded on a Varian XL-400 instrument. Samples for NOE experiments were degassed (freeze, pump, thaw, ×5) and sealed under vacuum. All NMR spectra were recorded in 99.8% deuteriochloroform ($CDCl_3$) unless otherwise stated. Electron-impact spectra (EIMS) were recorded at 70 eV, and chemical ionization spectra (CIMS) were recorded using methane as the reagent gas. Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 polarimeter.

Gas chromatography was performed using a Quadrex Corp. 1.0 μm coated methyl silicone fused silica capillary column, 25 m × 0.63 mm (100–200 °C at 6 deg/min) with helium as the carrier gas. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Reverse-phase HPLC was performed on a Supelco semiprep (5 μm, 10 mm × 25 cm) LC-18 octadecyldimethylsilyl column eluted with methanol–water (88:12). The purity of all title compounds was judged to be ≥90%[15] by GC analysis and/or NMR determinations.

(3*R*,6*S*)-3-Isopropyl-6-methyl-1-((trimethylsilyl)oxy)-cyclohexene (9). To a solution of *n*-butyllithium (0.05 mol, 1.6 M in hexane) in dry tetrahydrofuran (THF, 50 mL) was added diisopropylamine (7.0 mL, 0.05 mol) at 0 °C under nitrogen. The solution was stirred for 10 min, and then the temperature was lowered to −78 °C. To the LDA solution was added dropwise (−)-menthone (**8**) (0.039 mol), the mixture was stirred for 30 min, and then the temperature was raised to 0 °C. Chlorotrimethylsilane (0.05 mol) was then added, and the reaction mixture was stirred for 1 h, at which time it was diluted with pentane and extracted with ice-cold saturated sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated, giving the crude product as a yellow oil. Bulb-to-bulb distillation (115 °C, 1.0 atm)

(13) All crystallographic calculations were done on a Micro VAX II computer using the SHELXTL program package by G. M. Sheldrick, SHELXTL Crystallographic computing System, Nicolet Instruments Division, Madison, WI, 1986.

(14) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

(15) Compound **15** proved difficult to purify and was therefore subjected to the Diels–Alder conditions at approximately 70% purity. The impurities included *tert*-butyldiphenylsilyl fluoride, resulting from the deprotection of **14**, and a small amount of two additional byproducts, none of which interfere with the desired intramolecular reaction.

(16) A direct comparison between the ^1H NMR spectra of the dihydropernetic acids and synthetic compounds **5** and **6** was not possible because neither authentic samples or ^1H NMR spectra were available from authors Hozosawa et al. (ref 4).

gave pure **9** (8.7 g, 0.038 mol, 97%) as a colorless oil: IR (film) 2960, 2875, 2845, 1638, 1455, 1370, 1255, 1220, 1185, 950, 910, 875, 850 cm^{-1}; ^1H NMR δ (300 MHz) 4.67 (s, 1 H), 2.15 (m, 1 H), 2.02 (m, 1 H), 1.87–1.6 (m, 3 H), 1.3 (m, 1 H), 1.02 (m, 1 H), 0.90 (d, 3 H, J = 6.9 Hz), 0.87 (d, 3 H, J = 7.1 Hz), 0.74 (d, 3 H, J = 6.9 Hz) 0.16 (s, 9 H); ^{13}C NMR δ (100 MHz) 152.12, 112.11, 44.32, 31.59, 30.12, 27.27, 22.87, 22.45, 20.17, 16.80, 0.24; EIMS m/z (rel intensity) 226 (M^+, 4), 211 (24), 184 (14), 183 (12), 156 (28), 75 (49), 73 (100), 45 (41), 43 (44), 41 (39); CIMS m/z (rel intensity) 227 (M^+ + 1, 100), 226 (29), 211 (70), 153 (33); HRMS calculated for $C_{13}H_{26}OSi$ 226.1753, found 226.1769.

(1*R*,2*S*,5*R*,6*S*)- and (1*R*,2*S*,5*R*,6*R*)-2-Isopropyl-5-methyl-1-((trimethylsilyl)oxy)bicyclo[4.1.0]heptane (10a and 10b). To a solution of enol ether **9** (1.00 g, 4.4 mmol) and diethylzinc (8.8 mmol, 1.1 M in hexane) in dry hexane (2 mL) was added dropwise diiodomethane (0.65 mL, 8.8 mmol) at 0 °C under nitrogen. After 20 min, air, which was passed through a calcium chloride drying tube, was blown across the reaction surface, initiating the formation of a white precipitate. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 3 h. The reaction mixture was then diluted with hexane, extracted with cold saturated ammonium chloride (×2), cold saturated sodium bicarbonate, and water, and dried ($MgSO_4$). Evaporation of the solvent gave a 3.5:1 diastereomeric mixture of (silyloxy)cyclopropanes **10a** and **10b** (0.96 g, 4.0 mmol, 92%) as a colorless oil. **10a**: $[\alpha]_D$ +9.6° (*c* 0.23, hexane); IR (film) 3005, 2955, 2930, 2870, 1520, 1385, 1368, 1260, 1250, 1213, 1180, 1060, 940, 910, 880, 855, 840 cm^{-1}; ^1H NMR δ (400 MHz) 2.09 (m, 1 H), 1.73 (ddd, 1 H, J = 12.2, 11.8, 4.9 Hz), 1.5–1.6 (m, 2 H), 1.36 (m, 1 H), 1.08 (d, 3 H, J = 6.8 Hz), 0.96 (d, 3 H, J = 6.9 Hz), 0.89 (m, 1 H), 0.86 (d, 3 H, J = 6.9 Hz), 0.83 (dd, 1 H, J = 9.6, 5.8 Hz), 0.70 (m, 1 H), 0.65 (ddd, 1 H, J = 10.7, 5.8, 1.7 Hz), 0.64 (dq, 1 H, J = 11.8, 2.9 Hz), 0.35 (t, 1 H, J = 5.8 Hz), 0.11 (s, 9 H); ^{13}C NMR δ (100 MHz) 60.02 (s), 46.48 (d), 33.47 (d), 32.87 (t), 28.67 (d), 22.24 (d), 22.65 (q), 22.04 (q), 21.90 (t), 18.28 (t), 18.10 (q), 1.54 (q); EIMS m/z (rel intensity) 240 (M^+, 1), 225 (5), 107 (10), 75 (27), 73 (100), 55 (16), 45 (27), 43 (19), 41 (24); CIMS m/z (rel intensity) 225 (M^+ – 15, 22), 151 (100), 109 (11), 95 (74), 81 (31); HRMS calculated for $C_{14}H_{28}OSi$ 240.1909, found 240.1921. **10b**: $[\alpha]_D$ +26.3° (*c* 0.30, hexane); IR (film) 3000, 2960, 2935, 2870, 1460, 1385, 1367, 1263, 1252, 1230, 1205, 1193, 1035, 1010, 995, 940, 905, 868, 840 cm^{-1}; ^1H NMR δ (400 MHz) 2.07 (m, 1 H), 1.93 (m, 1 H), 1.53 (td, 1 H, J = 11.7, 4.8 Hz), 1.44–1.32 (m, 2 H), 1.14 (ddd, 1 H, J = 11.1, 10.7, 6.8 Hz), 1.02 (m, 1 H), 0.95 (d, 3 H, J = 6.9 Hz), 0.88 (d, 3 H, J = 6.9 Hz), 0.87 (d, 3 H, J = 6.2 Hz), 0.60 (dd, 1 H, J = 10.7, 5.5 Hz), 0.47 (d, 1 H, J = 11.7, 2.8 Hz), 0.16 (t, 1 H, J = 6.0 Hz), 0.09 (s, 9 H); ^{13}C NMR δ (100 MHz) 58.78, 47.19, 28.72, 28.45, 28.12, 23.20, 22.65, 20.88, 18.64, 16.22, 1.32; EIMS m/z (rel intensity) 225 (M^+ – 15, 10), 151 (21), 109 (12), 95 (62), 83 (17), 73 (100), 69 (60), 57 (46), 55 (50), 43 (65), 41 (50); CIMS m/z (rel intensity) 241 (M^+ + 1, 1), 240 (1), 239 (2), 225 (21), 151 (97), 117 (43), 109 (20), 95 (100), 81 (38); HRMS calculated for $C_{14}H_{28}OSi$ 240.1909, found 240.1922.

(2*S*,5*R*)-2-Isopropyl-5-methylhept-6-enoic Acid (11). A mixture of (silyloxy)cyclopropane **10** (1.40 g, 5.9 mmol), lead(IV) acetate (2.60 g, 5.9 mmol), and acetic acid (20 mL) was stirred for 8 h at room temperature, at which time ethylene glycol (20 drops) was added and stirring was continued for 3 h. Water (20 mL) was then added to the reaction mixtures, and after 30 min the mixture was further diluted with water and extracted with pentane (×3). The organic phase was extracted with 10% sodium hydroxide (×4). The resulting basic aqueous solution was acidified with concentrated hydrochloric acid to pH 1, and the acidic solution was extracted with diethyl ether (×4). The combined organic layers were dried ($MgSO_4$) and concentrated to give a colorless oil (0.54 g, 2.9 mmol, 50%): IR (film) 3080, 2965, 2935, 2875, 1710, 1640, 1460, 1420, 1390, 1370, 1290, 1230, 1000, 910 cm^{-1}; ^1H NMR δ (300 MHz) 10.9 (br s, 1 H), 5.63 (ddd, 1 H, J = 16.9, 10.3, 7.7 Hz), 4.95 (ddd, 1 H, J = 16.9, 3.0, 1.7 Hz), 4.90 (dt, 1 H, J = 10.3, 1.7), 2.12 (m, 2 H), 1.87 (d of septets, 1 H, J = 10.4, 6.7 Hz), 1.7–1.45 (m, 2 H), 1.35–1.2 (m, 2 H), 0.96 (d, 3 H, J = 7.4 Hz), 0.94 (d, 3 H, J = 6.7 Hz), 0.93 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ (100 MHz) 182.16, 144.12, 112.96, 52.48, 37.75, 34.34, 30.40, 26.91, 20.49, 20.44, 20.08; EIMS m/z (rel intensity) 184 (M^+, 2), 169 (9), 141 (11), 123 (10), 115 (7), 113 (7), 102 (22), 95 (14), 87 (92), 83 (90), 82 (22), 81 (12), 73 (14), 70 (33), 69 (31), 68 (12), 67 (25), 55 (100), 43 (43), 41 (95); CIMS m/z (rel intensity) 185 (M^+ + 1, 100), 168 (11), 167 (79), 139 (18), 83 (70), 69 (15); HRMS calculated for $C_{11}H_{20}O_2$ 184.1463, found 184.1467.

(2*S*,5*R*)-2-Isopropyl-5-methylhept-6-en-1-ol. To a slurry of lithium aluminum hydride (369 mg, 9.7 mmol) in anhydrous diethyl ether (40 mL) was added dropwise a solution of **12** (894 mg, 4.9 mmol) in anhydrous diethyl ether (10 mL) at room temperature under nitrogen. After stirring for 30 min the reaction was quenched by successive additions of water (0.4 mL), 10% sodium hydroxide (0.4 mL), and water (0.8 mL). The mixture was stirred for an additional 15 min, and then the resulting precipitate was removed by filtration and washed with diethyl ether. The organic solution was dried ($MgSO_4$) and concentrated to give the desired alcohol (748 mg, 4.4 mmol, 90%) as a colorless oil: IR (film) 3350, 2960, 2930, 2870, 1640, 1460, 1390, 1050, 910 cm^{-1}; ^1H NMR δ (300 MHz) 5.66 (ddd, 1 H, J = 17.1, 9.9, 7.5 Hz), 4.96 (ddd, 1 H, J = 15.7, 1.7, 1.1 Hz), 4.88 (dt, 1 H, J = 10.0, 1.7 Hz), 3.56 (m, 1 H), 2.12 (m, 1 H), 1.87 (d of septets, 1 H, J = 10.4, 6.7 Hz), 1.25 (m, 5 H), 0.97 (d, 3 H, J = 6.6 Hz), 0.87 (d, 3 H, J = 6.9 Hz), 0.86 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ (100 MHz) 144.65, 112.63, 63.67, 46.63, 38.19, 34.68, 27.85, 25.18, 20.36, 19.80, 19.22; EIMS m/z (rel intensity) 170 (M^+, 0.4), 137 (6), 123 (11), 109 (26), 97 (20), 96 (16), 95 (14), 85 (16), 83 (23), 82 (31), 81 (23), 71 (16), 70 (14), 69 (44), 68 (34), 67 (36), 57 (22), 55 (100), 43 (39), 41 (62); CIMS m/z (rel intensity) 171 (M^+ + 1, 14), 151 (7), 137 (7), 111 (12), 97 (100), 95 (16), 83 (75), 71 (31), 69 (29); HRMS calculated for $C_{11}H_{22}O$ 170.1671, found 170.1690.

(2*S*,5*R*)-2-Isopropyl-5-methylhept-6-enal (12). To a slurry of oxalyl chloride (0.74 mmol, 63 μL) in dry dichloromethane (3 mL) at −78 °C under nitrogen was added dimethyl sulfoxide (1.03 mmol, 73 μL). After 15 min a solution of alcohol (100 mg, 0.59 mmol) in dichloromethane (2 mL) was added by cannula, and the reaction mixture was stirred for 30 min. To the reaction mixture was added triethylamine (2.94 mmol, 0.41 mL), stirring was continued for 15 min, and then the reaction was allowed to warm to room temperture for 1 h. The solvent was removed, and the residue was diluted with diethyl ether. The organic solution was washed with saturated ammonium chloride (×2), water, and brine and dried ($MgSO_4$). Evaporation of the solvent afforded **12** (94 mg, 0.56 mmol, 95%) as a pale yellow oil: IR (film) 3090, 2960, 2870, 2700, 1728, 1640, 1465, 1420, 1390, 1370, 995, 910 cm^{-1}; ^1H NMR δ (300 MHz), 9.57 (d, 1 H, J = 3.4 Hz), 5.62 (ddd, 1 H, J = 17.5, 10.3, 7.9 Hz), 4.95 (ddd, 1 H, J = 17.5, 1.7, 1.1 Hz), 4.91 (dt, 1 H, J = 10.3, 1.7 Hz), 2.11 (m, 1 H), 1.98 (m, 2 H), 1.60 (m, 1 H), 1.45 (m, 1 H), 1.24 (m, 2 H), 0.96 (d, 3 H, J = 6.9 Hz), 0.94 (d, 6 H, J = 6.6 Hz); ^{13}C NMR δ (100 MHz) 206.01, 144.03, 113.10, 58.28, 37.93, 34.23, 28.26, 23.68, 20.40, 20.32, 19.77; EIMS m/z (rel intensity) 168 (1), 153 (6), 139 (6), 126 (10), 111 (12), 107 (14), 98 (11), 97 (18), 95 (26), 93 (11), 86 (23), 83 (56), 82 (62), 81 (26), 71 (64), 70 (40), 69 (61), 68 (40), 67 (59), 57 (23), 56 (19), 55 (100), 53 (17), 43 (30), 41 (38), 39 (15); CIMS m/z (rel intensity) 169 (M^+ + 1, 7), 151 (49), 109 (12), 95 (100), 83 (28), 81 (34), 71 (18), 69 (19); HRMS calculated for $C_{11}H_{20}O$ 168.1514, found 168.1513.

(5*S*,8*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-5-isopropyl-8-methyl-2-methylene-9-decene-1,4-diol (13). Imidazole (215 mg, 1.58 mmol), *tert*-butylchlorodiphenylsilane (0.41 mL, 1.58 mmol), and *N*,*N*-dimethylformamide (10 mL) were stirred for 15 min at room temperature under nitrogen. To the solution was added, by cannula, a solution of **20** (517 mg, 1.43 mmol) in *N*,*N*-dimethylformamide (3 mL), and the mixture was stirred for 2 h. The reaction was then diluted with diethyl ether until a white precipitate formed. The organic solution was washed with saturated ammonium chloride (×2), water, and brine and dried ($MgSO_4$). Evaporation of the solvents gave the crude product as a colorless oil, which was then diluted with dichloromethane (1.5 mL), and to this solution was added boron trifluoride etherate (0.22 mL, 1.78 mmol) at −78 °C under nitrogen. The reaction mixture was immediately added, by cannula, to a solution of aldehyde **12** (200 mg, 1.19 mmol) in dichloromethane (2.5 mL). After stirring for 1 h at −78 °C, the reaction mixture was poured into saturated ammonium chloride and diluted with diethyl ether. The resulting organic layer was washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (petroleum ether–ethyl acetate, 95:5) to give a 3.5:1 mixture of diastereomers as a colorless oil (448 mg, 0.94 mmol, 79%): IR (film) 3450, 3070, 2960, 2920,

2860, 1669, 1640, 1480, 1470, 1430, 1390, 1370, 1130, 1000, 910, 825, 710 cm^{-1}; ^1H NMR δ (400 MHz) 7.66 (d, 4 H, J = 6.4 Hz), 7.39 (m, 6 H), 5.67 (ddd, J = 17.5, 10.3, 7.0 Hz), 5.21 (s, 1 H), 4.95 (s, 1 H), 4.93 (ddd, 1 H, J = 17.5, 1.7, 1.1 Hz), 4.90 (dt, 1 H, J = 10.3, 1.7 Hz), 4.12 (d, 1 H, J = 12.7 Hz), 4.07 (d, 1 H, J = 12.7 Hz), 3.74 (m, 1 H), 2.17 (d, 2 H, J = 6.7 Hz, major diastereomer), 2.06, (m, 1 H), 2.17 (d, 2 H, J = 3.2 Hz, minor diastereomer), 1.45–1.20 (m, 5 H), 1.05 (s, 9 H), 0.97 (d, 3 H, J = 6.5 Hz), 0.89 (d, 3 H, J = 6.8 Hz), 0.84 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ (100 MHz) 145.55 (s), 144.85 (d), 135.52 (d), 133.22 (s), 129.76 (d), 127.71 (d), 112.83 (t), 112.46 (t), 70.41 (d), 66.72 (t), 49.27 (d), 40.19 (t), 38.40 (d), 36.68 (t), 28.85 (d), 26.77 (q), 23.89 (t), 20.57 (q), 20.17 (q), 20.08 (q), 19.21 (s); EIMS m/z (rel intensity) 199 (27), 139 (25), 109 (27), 95 (46), 83 (32), 81 (45), 69 (60), 57 (39), 55 (100), 43 (64), 41 (66); CIMS m/z (rel intensity) 479 (M^+ + 1, 1), 223 (2), 205 (20), 179 (19), 149 (40), 135 (21), 125 (22), 111 (26), 109 (56), 95 (100), 83 (20), 81 (44); HRMS calculated for $C_{31}H_{46}O_2Si$ 478.3267, found 478.3273.

(5*S*,8*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-5-isopropyl-8-methyl-2-methylene-3,9-decadien-1-ol (14). To a mixture of alcohol **13** (100 mg, 0.21 mmol) and triethylamine (88 μL, 0.63 mmol) in dichloromethane (2 mL) was added mesyl chloride (32 μL, 0.42 mmol) at −6 °C under nitrogen. After 1 h the reaction was diluted with diethyl ether, extracted with saturated sodium bicarbonate (×2), water, and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a crude product which was diluted with *tert*-butyl alcohol (1 mL). To this solution was added 0.1 M potassium *tert*-butoxide in *tert*-butyl alcohol (4 mL), and the reaction was stirred at 80–90 °C for 45 h. The reaction was diluted with diethyl ether, extracted with saturated sodium bicarbonate (×2), water, and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a crude product which was chromatographed on silica gel (petroleum ether–ethyl acetate, 99:1). The desired triene **14** was obtained as a colorless oil (50 mg, 0.11 mmol, 52% from alcohol): IR (film) 3080, 2960, 2850, 1470, 1460, 1340, 1320, 1120, 1000, 960, 920, 825, 740, 700 cm^{-1}; ^1H NMR δ (400 MHz) 7.68 (m, 4 H), 7.39 (m, 6 H), 5.94 (d, 1 H, J = 15.9 Hz), 5.58 (ddd, 1 H, J = 17.5, 10.2, 7.6 Hz), 5.30 (dd, 1 H, J = 15.9, 9.3 Hz), 5.25 (s, 1 H), 5.01 (s, 1 H), 4.86 (dd, 1 H, J = 17.3, 2.1 Hz), 4.84 (dd, 1 H, J = 10.0, 2.1 Hz), 4.32 (s, 2 H), 2.01 (m, 1 H), 1.67 (m, 1 H), 1.51 (m, 1 H), 1.40–1.05 (m, 3 H), 1.04 (s, 9 H), 0.91 (d, 3 H, J = 6.7 Hz), 0.85 (m, 1 H), 0.79 (d, 3 H, J = 6.7 Hz), 0.73 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ (100 MHz) 144.78, 144.49, 135.52, 133.62, 132.55, 130.41, 129.61, 127.65, 112.55, 112.42, 63.81, 50.12, 37.90, 34.55, 32.00, 29.82, 26.77, 20.78, 20.46, 19.26, 19.18; EIMS m/s (rel intensity) 265 (4), 251 (4), 199 (100), 135 (20), 109 (24), 95 (26), 81 (25), 69 (35), 67 (28), 57 (38), 55 (76), 43 (66), 41 (75); CIMS m/z (rel intensity) 461 (73), 403 (54), 383 (66), 205 (100), 179 (73); HRMS calculated for $C_{31}H_{44}OSi$ 460.3161, found 460.3166.

(5*S*,8*R*)-5-Isopropyl-8-methyl-2-methylene-3,9-decadien-1-ol (15). To a solution of **14** (204 mg, 0.44 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (0.89 mmol, 1.0 M in THF) at room temperature under nitrogen. After 2 h the reaction mixture was diluted with diethyl ether, extracted with water and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a crude product which was chromatographed on silica gel (petroleum ether–ethyl acetate, 9:1), giving a colorless oil which was 70% pure by GC (55 mg, 0.25 mmol, 56%): IR (CCl_4) 3620, 3160, 2970, 2930, 2880, 1640, 1470, 1340, 1325, 1060, 1025, 1000, 980, 920, 700 cm^{-1}; ^1H NMR δ (400 MHz), 5.98 (d, 1 H, J = 16.0 Hz), 5.63 (ddd, 1 H, J = 17.6, 9.1, 7.6 Hz), 5.45 (dd, 1 H, J = 16.0, 9.5 Hz), 5.12 (s, 1 H), 5.01 (s, 1 H), 4.91 (ddd, 1 H, J = 17.6, 1.7, 1.1 Hz), 4.88 (dt, 1 H, J = 9.1, 1.7 Hz), 4.29 (s, 2 H), 2.05 (m, 1 H), 1.74 (m, 1 H), 1.58 (m, 1 H), 1.40 (m, 1 H), 1.30 (m, 3 H), 0.94 (d, 3 H, J = 6.8 Hz), 0.84 (d, 3 H, J = 6.7 Hz), 0.79 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ (100 MHz), 145.16 (s), 144.71 (d), 133.41 (d), 130.15 (d), 112.85 (t), 112.50 (t), 63.25 (t), 49.96 (d), 37.88 (d), 34.58 (t), 32.01 (d), 29.82 (t), 20.80 (q), 20.46 (q), 19.11 (q); EIMS m/z (rel intensity) 161 (5), 95 (36), 81 (41), 69 (31), 67 (37), 55 (82), 43 (54), 41 (100); CIMS m/z (rel intensity) 205 (M^+ − 17, 6), 179 (8), 149 (38), 135 (30), 123 (30), 121 (30), 111 (36), 109 (82), 107 (28), 97 (40), 95 (100), 93 (25), 83 (48), 81 (57), 69 (43); HRMS calculated for $C_{15}H_{26}O$ 222.1984, found 222.1984.

(4a*S*,5*R*,8*S*,8a*R*)- and (4a*S*,5*R*,8*S*,8a*S*)-8-Isopropyl-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenemethanol (16a and 16b). Triene **15** (approximately 70% pure) in benzene was heated in a sealed tube at 170–180 °C for 46 h. ^1H NMR and GC showed the reaction to be approximately 95% complete based on consumption of starting material. Evaporation of the solvent gave two diastereomeric products **16a** and **16b**, which were used as a mixture in the next reactions. Analytical samples of both of these compounds were prepared by hydrolysis of the corresponding purified *p*-bromobenzoates with 1% sodium hydroxide in methyl alcohol. **16a**: ^1H NMR δ (200 MHz) 5.53 (br s, 1 H), 3.96 (br s, 2 H), 2.54 (br s, 1 H), 2.01–1.95 (m, 3 H), 1.67–1.50 (m, 5 H), 1.38 (m, 1 H), 1.22 (m, 1 H), ~0.95 (m, 1 H), 0.91 (d, 3 H, J = 7.1 Hz), 0.88 (d, 3 H, J = 7.1 Hz), 0.85 (d, 3 H, J = 5.3 Hz); EIMS m/z (rel intensity) 222 (M^+, 9), 191 (41), 179 (62), 161 (66), 135 (67), 107 (66), 105 (59), 95 (86), 93 (54), 91 (68), 81 (100), 79 (80), 69 (53), 67 (67), 55 (65), 41 (78); CIMS m/z (rel intensity) 221 (19), 205 (100), 149 (21); HRMS calculated for $C_{15}H_{26}O$ 222.1984, found 222.1991. **16b**: ^1H NMR δ (200 MHz) 5.80 (br s, 1 H), 3.99 (br s, 2 H), 2.15 (d of septets, 1 H, J = 6.8, 2.6 Hz), 2.1–1.95 (m, 3 H), 1.73 (m, 1 H), 1.65–1.55 (m, 2 H), 1.25 (m, 1 H), 1.15–0.9 (m, 4 H), 0.88 (d, 6 H, J = 6.0 Hz), ~0.80 (m, 1 H), 0.74 (d, 3 H, J = 6.8 Hz); EIMS m/z (rel. intensity) 222 (M^+, 7), 191 (28), 179 (61), 161 (67), 135 (68), 107 (67), 105 (59), 95 (84), 93 (55), 91 (62), 81 (98), 79 (78), 67 (85), 55 (81), 41 (100); CIMS m/z (rel intensity) 222 (4), 221 (22), 205 (100); HRMS calculated for $C_{15}H_{26}O$ 222.1984, found 222.1988.

(4a*S*,5*R*,8*S*,8a*R*)- and (4a*S*,5*R*,8*S*,8a*S*)-8-Isopropyl-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenecarboxaldehyde (17 and 1). To a slurry of oxalyl chloride (0.34 mmol, 29 μL) in dry dichloromethane (1.5 mL) at −78 °C under nitrogen was added dimethyl sulfoxide (0.45 mmol, 32 μL), and the mixture was stirred for 15 min. To the reaction mixture was added a solution of crude **17** (68 mg, 0.31 mmol, 1.6:1 mixture of diastereomers) in dry dichloromethane (1.5 mL), and stirring was continued for 30 min. Triethylamine (1.30 mmol, 0.18 mL) was added, and after 5 min the reaction mixture was allowed to warm to room temperature. After 30 min the solvent was removed and the residue was diluted in diethyl ether. The organic solution was washed with saturated ammonium bicarbonate (×2), water, and brine and dried ($MgSO_4$). Evaporation of the solvent gave a crude product as a colorless oil (62 mg, 0.28 mmol, 91%). GC indicated complete conversion of the starting material into a 1.25:1 mixture of diasteriomeric aldehydes. Semipreparative reverse-phase HPLC (solvent methanol–water, 88:12) yielded pure samples of **17** (1.6 mg) and **1** (5.1 mg). Significant losses incurred during isolation of the purified products was most likely due to volatility of these compounds during the removal of the solvent. **17**: $[\alpha]_D$ +3.6° (*c* 0.11, hexane); IR (CCl_4) 2970, 2920, 2870, 2800, 2700, 1680, 1630, 1475, 1450, 1430, 1190, 1170, 1160, 1100, 790, 770, 710 cm^{-1}; ^1H NMR δ (400 MHz) 9.38 (s, 1 H) 6.70 (br s, 1 H), 2.77 (m, 1 H), 2.26 (ddd, 1 H, J = 17.2, 6.3, 2.6 Hz), 2.06 (m, 1 H), 2.04 (m, 1 H), 1.77 (qdd, 1 H, J = 12.8, 3.2, 1.8 Hz), 1.72–1.62 (m, 2 H), 1.49 (m, 1 H), 1.37 (m, 1 H), 1.23 (m, 1 H), 1.10 (dddd, 1 H, J = 12.8, 10.1, 4.8, 3.2 Hz), 0.96 (d, 3 H, J = 6.6 Hz), 0.94 (d, 3 H, J = 6.6 Hz), 0.91 (m, 1 H), 0.86 (d, 3 H, J = 6.4 Hz), 0.80 (qd, 1 H, J = 12.6, 3.1 Hz); ^{13}C NMR δ (100 MHz) 194.49 (s), 152.23 (d), 142.53 (s), 47.90 (d), 41.95 (d), 40.00 (d), 35.38 (t), 28.85 (d), 28.60 (d), 27.53 (t), 24.45 (t), 21.56 (q), 20.71 (q), 19.58 (q), 18.05 (t); EIMS m/z (rel intensity) 220 (M^+, 31), 205 (17), 177 (30), 159 (22), 150 (100), 149 (29), 135 (25), 107 (28), 105 (16), 95 (21), 93 (21), 86 (38), 84 (55), 81 (40), 79 (28), 77 (19), 67 (20), 55 (26), 51 (26), 49 (77), 41 (38); CIMS m/z (rel intensity) 221 (M^+ + 1, 100), 203 (87), 177 (36), 150 (29); HRMS calculated for $C_{15}H_{24}O$ 220.1827, found 220.1849. **1**: $[\alpha]_D$ −8.8° (*c* 0.16, hexane); IR (CCl_4) 2980, 2940, 2870, 2820, 2720, 1680, 1640, 1470, 1460, 1340, 1320, 1190, 1120, 780, 760, 710 cm^{-1}; ^1H NMR δ (400 MHz) 9.40 (s, 1 H), 6.87 (br s, 1 H), 2.35 (ddd, 1 H, J = 17.1, 5.9, 2.9 Hz), 2.17 (d of septets, 1 H, J = 6.9, 3.0 Hz), 2.07 (m, 1 H), 1.99 (m, 1 H), 1.82 (m, 1 H), 1.73 (qd, 1 H, J = 12.5, 3.2 Hz), 1.66 (qd, 1 H, J = 12.0, 3.2 Hz), 1.20–0.92 (m, 5 H), 0.90 (d, 3 H, J = 6.9 Hz), 0.88 (d, 3 H, J = 6.4 Hz), 0.82 (m, 1 H), 0.77 (d, 3 H, J = 6.9 Hz); ^{13}C NMR δ (100 MHz) 194.82 (s), 152.31 (d), 141.52 (s), 46.41 (d), 45.47 (d), 44.58 (d), 36.80 (d), 35.44 (t), 26.43 (d), 25.42 (t), 24.56 (t), 21.97 (t), 21.29 (q), 19.86 (q), 15.16 (q); EIMS m/z (rel intensity) 220 (M^+, 30), 205 (10), 177 (26), 159 (20), 150 (100), 149 (23), 135 (19), 107 (27), 95 (21), 93 (21), 91 (23), 86 (38), 84 (60), 81 (36), 79 (26), 77 (16), 69 (47), 67 (19), 55 (23), 51 (30), 49 (95), 41 (38); CIMS m/z (rel intensity) 221 (M^+ + 1, 100), 203 (34), 187 (15),

177 (17); HRMS calculated for $C_{15}H_{24}O$ 220.1827, found 220.1824.

X-ray Analysis of 1. A crystal of compound 1 measuring approximately 0.40 × 0.45 × 0.65 mm^3 was selected and aligned on a Nicolet R3m/V diffractometer system. Preliminary X-ray photographs displayed orthorhombic symmetry, and accurate lattice constants of a = 6.320 (1), b = 8.252 (2), and c 26.413 (7) Å were determined from a least-squares fit of 25 diffractometer-measured $2q$ values. The empirical formula was $C_{15}H_{24}O$. The crystal density, 1.062 g/cm^3, indicated that four molecules of 1 made up the unit cell. Systematic extinctions were consistent with space group $P2_12_12_1$ (with four molecules per unit cell). All unique diffraction maxima with $2q < 112°$ were collected using variable speed 1° $2q$–q scans and graphite monochromated Cu Kα radiation (1.541 84 Å). Of the 1046 reflections collected, 997 (95%) were judged observed ($|F_o| > 3s(F_o)$) after correction for Lorentz, polarization, and background effects. All non-hydrogen atoms were located by DF-synthesis. Full-matrix least-squares refinements with anisotropic nonhydrogen atoms converged to a crystallographic residual of 0.042 (R_w = 0.053) for the observed data.

(4a*S*,5*R*,8*S*,8a*R*)-8-Isopropyl-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenecarboxylic Acid (6). To a solution of aldehyde **17** (1.12 mg, 0.005 mmol) in acetonitrile (0.1 mL) was added an aqueous solution of sodium phosphate monobasic (0.6 mM, 10 μL) which had been adjusted to pH 1 with concentrated hydrochloric acid, hydrogen peroxide (30%, 10 μL), and aqueous sodium chlorite (0.1 mL, 1.0 mM). After being stirred for 2 h at room temperature, the reaction mixture was diluted with water and extracted with hexane (×6). The organic solution was dried ($MgSO_4$) and concentrated, yielding **6** (1.03 mg, 0.0044 mmol, 85%) as a white solid: IR (CCl_4) 3075, 2970, 2930, 2880, 1730, 1685, 1640, 1485, 1280 cm^{-1}; ^{1}H NMR δ (200 MHz) 7.02 (br s, 1 H), 2.65 (br s, 1 H), 2.30 (dm, 1 H, J = 17.2 Hz), 2.15 (m, 1 H), 2.04 (m, 1 H), 1.74–1.42 (m, 4 H), 1.37–1.2 (m, 2 H), 1.1–0.9 (m, 2 H), 0.94 (d, 3 H, J = 6.0 Hz), 0.90 (d, 3 H, J = 6.6 Hz), 0.86 (d, 3 H, J = 6.0 Hz), 0.80 (m, 1 H); EIMS m/z (rel intensity) 236 (M$^+$, 10), 193 (56), 150 (40), 147 (83), 137 (36), 107 (50), 105 (53), 95 (76), 93 (42), 91 (74), 81 (93), 79 (86), 77 (60), 41 (100); CIMS m/z (rel intensity) 237 (M$^+$ + 1, 100), 219 (39); HRMS calculated for $C_{15}H_{24}O_2$ 236.1776, found 236.1786.

(4a*S*,5*R*,8*S*,8a*S*)-8-Isopropyl-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2-naphthalenecarboxylic Acid (5). To a solution of aldehyde 1 (2.35 mg, 0.011 mmol) in acetonitrile (0.2 mL) was added an aqueous solution of sodium phosphate monobasic (0.6 mM, 20 μL) which had been adjusted to pH 1 with concentrated hydrochloric acid, hydrogen peroxide (30%, 20 μL), and aqueous sodium chlorite (0.2 mL, 1.0 mM). After being stirred for 3 h at room temperature the reaction mixture was diluted with water and extracted with hexane (×6). The organic solution was dried ($MgSO_4$) and concentrated, yielding a crude product which contained 10% starting material. Chromatography on silica gel (hexane–ethyl acetate, 92:8) gave **5** (1.77 mg, 7.5 mmol, 70%) as a white solid: IR (CCl_4) 3100, 2975, 2940, 2870, 1730, 1680, 1645, 1435, 1280 cm^{-1}; ^{1}H NMR: δ (200 MHz) 7.22 (br s, 1 H), 2.41 (dm, 1 H, J = 17.7 Hz), 2.22–2.06 (m, 3 H), 1.77–1.66 (m, 3 H), 1.20–0.92 (m, 5 H), 0.91 (d, 6 H, J = 6.5 Hz), 0.85 (m, 1 H), 0.77 (d, 3 H, J = 6.8 Hz); EIMS m/z (rel intensity) 236 (M$^+$, 11), 193 (45), 147 (66), 137 (32), 107 (47), 105 (46), 91 (68), 81 (100), 69 (48), 67 (55), 55 (78), 41 (98); CIMS m/z (rel intensity) 237 (M$^+$ + 1, 100), 219 (31); HRMS calculated for $C_{15}H_{24}O_2$ 236.1776, found 236.1775.

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Registry No. **1**, 126580-54-9; **2**, 126580-64-1; **3**, 100019-20-3; **4**, 99957-14-9; **5**, 126642-62-4; **6**, 126580-56-1; **8**, 14073-97-3; **9**, 74185-00-5; **10a**, 126580-57-2; **10b**, 126642-63-5; **11**, 126580-58-3; **12**, 126580-59-4; **12** (alcohol), 126580-55-0; **13** (isomer 1), 126580-60-7; **13** (isomer 2), 126642-66-8; **14**, 126580-61-8; **15**, 126580-62-9; **16a**, 126580-63-0; **16b**, 126642-64-6; **17**, 126642-65-7; **21**, 126580-65-2; CH_2I_2, 75-11-6.

Supplementary Material Available: Tables of atomic coordinates, interatomic angles and distances for **1**, ^{13}C NMR spectra for compounds **9**, **10a,b**, **11–14**, and ^{1}H NMR spectra for compounds **1**, **5**, **6**, **15**, **16a,b**, and **17** (18 pages). Ordering information is given on any current masthead page.

Asymmetric Reduction of Aliphatic Short- to Long-Chain β-Keto Acids by Use of Fermenting Bakers' Yeast

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Eleven β-keto acids, ranging from 3-oxobutanoic to 3-oxooctanoic acids, were reduced with fermenting bakers' yeast to the corresponding optically active β-hydroxy acids, which were isolated as the methyl esters. In all cases, the (*R*)-hydroxy acids were obtained in ≥98% ee, except for 3-oxobutanoic acid, which afforded the (*S*)-hydroxy acid in 86% ee. Inhibition of fermentation was observed for 3-oxoundecanoic to 3-oxotetradecanoic acids, leading to no reduction. Lowering of the substrate concentration was found to be appreciably effective in avoiding inhibition.

In a recent communication,[1] we reported that 3-oxooctadecanoic acid (**1k**) was reduced with fermenting bakers' yeast to optically pure (*R*)-3-hydroxyoctadecanoic acid (**2k**), which was transformed to (+)-corynomycolic acid (**4**), known as a cord factor.[2] Other naturally occurring long-chain 3-hydroxyalkanoic acids include (−)-3-hydroxydecanoic acid (found in a secretion by the leaf-cutting ant),[3] (*R*)-3-hydroxytetradecanoic acid (**2i**) (a constituent of lipid A in endotoxin),[4] (*S*)-3-hydroxyhexadecanoic acid (in the fish toxin, pahutoxin (**3**)),[5] and

(1) Utaka, M.; Higashi, H.; Takeda, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1368.

(2) Lederer, E.; Adam, A.; Ciorbaru, R.; Petit, J.-F.; Wietzerbin, J. *Mol. Cell. Biochem.* **1975**, *7*, 87. Lederer, E. *J. Med. Chem.* **1980**, *23*, 819.

(3) Schildknecht, H.; Koob, K. *Angew. Chem.* **1971**, *83*, 110.

(4) Galanos, C.; Luderitz, O.; Rietschel, E. T.; Westphal, O. In *International Review of Biochemistry, Biochemistry of Lipids, II*; Goodwin, T. W., Ed.; University Park Press: Baltimore, 1977; Vol. 14, p 239. Imoto, M.; Kusumoto, S.; Shiba, T.; Naoki, H.; Iwasaki, T.; Rietschel, E. T.; Wollenweber, H.-W.; Galanos, C.; Luderitz, O. *Tetrahedron Lett.* **1983**, *24*, 4017.

0022-3263/90/1955-3917$02.50/0