aqueous sodium hydroxide (3 × 50 mL) and with water (5 × 70 mL), dried (Na_2SO_4), and evaporated at 1 atm using a simple Claisen head and an oil bath. The residual liquid was distilled under water-pump vacuum to give **16** (3.10 g, 81%) as a colorless, homogeneous (TLC, silica gel, 3:7 ethyl acetate–hexane) liquid: bp 108–110 °C (water-pump), $[\alpha]_D$ −23.84° (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.60 (m, 2 H, H-3, H-4), 3.58 (m, 2 H, -CH_2OH), 2.34–1.50 (m, 7 H, H-1, H_2-2, H_2-5, H-6, OH), 0.89 (d, 3 H, J = 6.8 Hz, CH_3); exact mass, m/z 126.1044 (calcd for $C_8H_{14}O$, m/z 126.1044). NMR measurements on derivatives[12,13] (see text) showed the material to be optically pure.

(1*R*,6*S*)-6-Methyl-3-cyclohexenecarboxylic Acid (4). Jones reagent[34] was added dropwise to a stirred and cooled (0 °C) solution of alcohol **16** (126.3 mg, 1.00 mmol) in acetone (3 mL). Each drop of reagent was added only after the yellow color of the reaction mixture had changed to green and sufficient reagent was introduced to produce a persistent (30 min) yellow coloration. Excess reagent was then destroyed with 2-propanol and the reaction mixture was diluted with diethyl ether (40 mL) and water (20 mL). The green precipitate initially present dissolved. The phases were separated and the aqueous layer was extracted with diethyl ether (20 mL). The combined extracts were washed with 10% w/v aqueous sodium hydroxide (1 × 40 mL, 1 × 20 mL). The alkaline solution was washed with diethyl ether (1 × 20 mL), acidified with 1 N HCl, and extracted with diethyl ether (2 × 40 mL). This last ethereal extract was dried (Na_2SO_4) and evaporated (water-pump vacuum, 20 °C). Kugelrohr distillation [70–75 °C, 0.05 mm] of the residue gave **4** (84.3 mg, 60%) as a colorless liquid $[\alpha]_D$ −31.77° (*c* 1.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 12 (br, 1 H, COOH), 5.66 (br s, 2 H, H-3, H-4), 2.80–2.66 (m, 1 H, H-6), 2.50–2.12 (m, 4 H, H_2-2, H_2-5), 2.02–1.82 (m, 1 H, H-1), 0.98 (d, 3 H, J = 7.2 Hz, CH_3); exact mass, m/z 140.0836 (calcd for $C_8H_{12}O_2$, m/z 140.0837). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 69.04; H, 8.71. Examination of the derived methyl ester (diazomethane) by VPC (Carbowax 20M on Chromosorb W, 6 ft, 190 °C) showed the mixture to be free of trans isomer.

(34) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 142.

Acknowledgment of financial support is made to the Alberta Heart Foundation, the Natural Sciences and Engineering Research Council of Canada, and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil) (G.V.J.d.S.)

Registry No. 1 (R = H), 73573-88-3; **4**, 102629-35-6; **8**, 23339-15-3; **8** (dipivolate), 102586-32-3; **9**, 102574-24-3; **10**, 102574-25-4; **11**, 102574-26-5; **12**, 86646-59-5; **13**, 102574-27-6; **14**, 102574-28-7; **15**, 102574-29-8; **16**, 102629-34-5; 2,2-dimethylpropanoyl chloride, 3282-30-2; butadiene, 106-99-0; benzene-1,2-dithiol, 17534-15-5.

Homochiral Ketals in Organic Synthesis. Enantioselective Synthesis of (*R*)-Muscone

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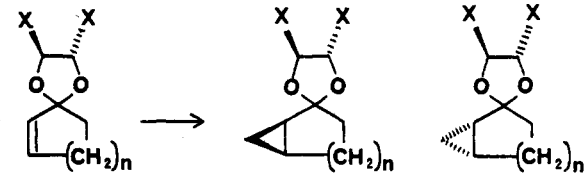
An efficient, enantioselective preparation of (*R*)-muscone employing a diastereoselective Simmons–Smith cyclopropanation is described. Cyclopropanation is directed via chelation control by a homochiral ketal protecting group derived from unnatural tartaric acid. The overall yield of (*R*)-muscone (>95% *R*) from commercially available cyclopentadecanone is 60% over seven steps.

(*R*)-Muscone (1) (Scheme I) is an odoriferous principle isolated from the male musk deer *Moschus moschiferus*. Since the natural supply is severely limited, a number of muscone syntheses have appeared in the literature[1] and several have addressed the problem of enantioselectivity.[2] However, each of the published enantioselective syntheses suffers from one or more of the following: excessive length, low chemical and optical yields, and scarcity of starting materials.

Recently we reported a novel diastereoselective cyclopropanation process involving homochiral ketals **2**.[3] Good diastereoselectivity was observed for conformationally restricted small ring systems, while lower diastereoselectivity was observed for acyclic systems.[4] Intuitively, larger rings (e.g., **2**, n = 11) might be expected to display intermediate diastereoselectivity. However, recent work by Still and Novack has dramatically shown that diastereoselectivity can be observed in conformationally biased large ring systems.[5] Since a number of natural products, including muscone, contain large rings, we decided to test the ap-



(1) For recent syntheses of (±)-muscone, see: (a) Cantoni, G.; Galli, C.; Mandolini, L. *J. Org. Chem.* **1980**, *45*, 1906–1908. (b) Fliri, H. G.; Scholz, D.; Stutz, A. *Montash Chem.* **1979**, *110*, 245–247 and references cited therein.

(2) For enantioselective syntheses of muscone, see: (a) Stallberg-Stenhagen, S. *Arkiv. Kemi* **1951**, *3*, 517–524. (b) Mamdapur, V. R.; Pai, P. P.; Chakravarti, K. K.; Nayak, U. G.; Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 2601–2604. (c) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, 925–944. (d) Utimoto, K.; Tanaka, M.; Kitai, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2301–2304. (e) Abad, A.; Arno, M.; Pardo, A.; Pedro, J. R.; Seoane, E. *Chem. Ind. (London)* **1985**, 29–30.

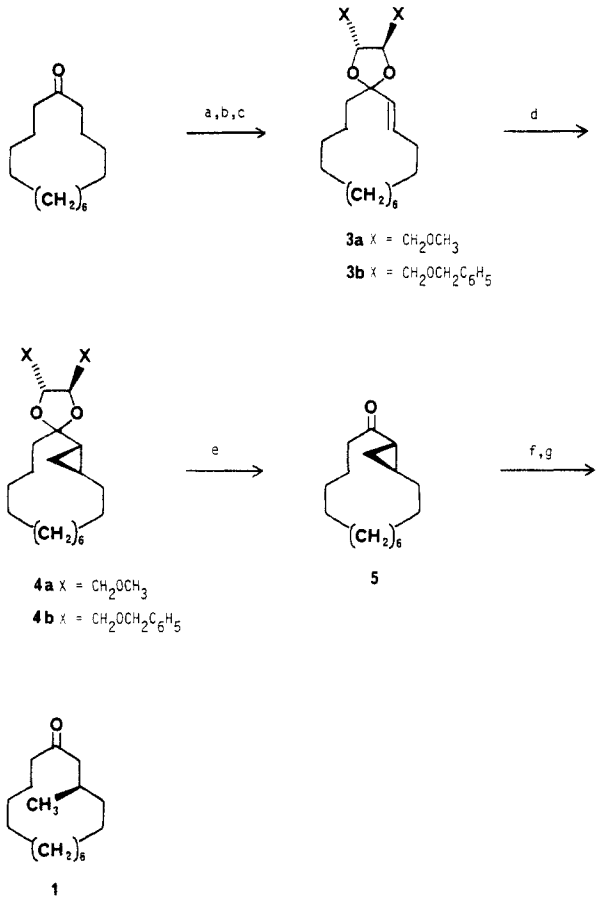
(3) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256–8258.

(4) However, Arai, et al. have described conditions under which related acyclic acetals are cyclopropanated with good diastereoselectivity. See: Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254–8256.

(5) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148–1149. For additional examples of diastereoselective additions to large ring systems, see references cited therein.

0022-3263/86/1951-2721$01.50/0

Scheme I[a]



[a] (a) Br_2, MeOH; (b) 1,4-di-*O*-alkyl-D-threitol, TsOH, C_6H_6, heat; (c) NaOMe, Me_2SO; (d) Zn–Cu, CH_2I_2, ether, heat; (e) 10% HCl, MeOH; (f) Li, *t*-BuOH, NH_3(l), ether; (g) pyridinium dichromate, CH_2Cl_2.

plicability of our method on one such system. An efficient, enantioselective synthesis of (*R*)-muscone was the result (Scheme I).[6]

Bromination of commercially available cyclopentadecanone[7] gave 2-bromocyclopentadecanone in essentially quantitative yield. Ketalization using 1,4-di-*O*-methyl-D-threitol[8] as the diol component (C_6H_6, TsOH, reflux, 68 h), followed by elimination ($NaOCH_3$, Me_2SO, room temperature, 21 h) gave (*E*)-α,β-unsaturated ketal **3a** in 78% yield. Treatment of **3a** with an excess of the Simmons–Smith reagent[9] in refluxing diethyl ether gave, after 4 h and in 95% chemical yield, a single cyclopropane ketal diastereomer as determined by 62.9-MHz ^{13}C NMR spectroscopy (limit of detection 20:1).[10] This diastereomer was assigned structure **4a** on the basis of its conversion to (*R*)-muscone as follows.

Hydrolysis of **4a** (aqueous HCl, methanol, room temperature, 2 h) gave bicyclic ketone **5**, a pleasantly aromatic low-melting solid, in 94% yield. Reductive opening of the cyclopropane ring (Li, *t*-BuOH, liquid NH_3) was accompanied by reduction of the ketone. Oxidation of the crude product alcohol (PDC, CH_2Cl_2, room temperature, 27 h) gave (*R*)-muscone (**1**), $[\alpha]^{25}_D$ −10.6° (*c* 1.10, CH_3OH), lit. $[\alpha]_D$ −11.7° (*c* 0.80, CH_3OH),[2c] in 86% yield from **5**. The yield of (*R*)-muscone from cyclopentadecanone over seven steps was 60%.

Since the dimethylthreitol derivative was not easily recoverable, a second route to **5** was developed by employing 1,4-di-*O*-benzyl-D-threitol.[11] Ketalization (C_6H_6, TsOH, reflux, 47 h), followed by elimination ($NaOCH_3$, Me_2SO, room temperature, 94 h) gave (*E*)-α,β-unsaturated ketal **3b** in 56% yield. Cyclopropanation as above gave, in 88% chemical yield, a single cyclopropane ketal diastereomer.[12] This ketal was assigned structure **4b** based upon its hydrolysis to **5** in 88% yield. 1,4-Di-*O*-benzyl-D-threitol was also recovered from this hydrolysis (86% recovery).

The procedures described herein make available either enantiomer of muscone from the corresponding tartrate derivative. Cyclopropyl ketone **5**, which might itself be of value to the fragrance industry, could also be converted to muscone derivatives functionalized at the methyl appendage.[13]

Reasons for the remarkable diastereoselectivity observed for the cyclopropanations of **3a** and **3b** remain unclear. Most probably, chelation of zinc[14] by appendage and dioxolane oxygens of the ketal protecting group results in preferential delivery of the Simmons–Smith reagent to one face of the alkene.[3,4] In the cases at hand, this may be reinforced by conformationally controlled exposure of this face of the alkene to the ring exterior, making it more accessible to the reagent.[5] Work is in progress to confirm and define the factors responsible for diastereoselection.

Further uses of these and other homochiral protecting groups will be reported in future papers.[15]

Experimental Section

Benzene was distilled from calcium hydride and diethyl ether was distilled from phosphorus pentoxide or sodium benzophenone

(6) For previous syntheses of (±)-muscone from cyclopentadecanone, see: (a) Mookherjee, B. D.; Patel, R. R.; Ledig, W. O. *J. Org. Chem.* **1971**, *36*, 4124–4125. (b) Ruzicka, L.; Stoll, M. *Helv. Chim. Acta* **1934**, *17*, 1308–1318.

(7) From Aldrich Chemical Company.

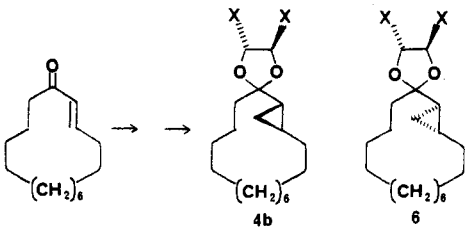
(8) Prepared from unnatural tartaric acid by the method of Schmidt et al. who prepared the L enantiomer from natural tartaric acid: $[\alpha]^{25}_D$ +2.15° (*c* 2.0, CH_3OH) for the D enantiomer; lit. $[\alpha]_D$ −2.5° (*c* 1.9, CH_3OH) for the L enantiomer. Schmidt, M.; Amstutz, R.; Crass, G.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1691–1707.

(9) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825–1826.

(10) For previous examples of the use of ^{13}C NMR in the measurement of diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183–2186.

(11) Prepared from unnatural tartaric acid by the method of Ando et al. who prepared the L enantiomer from natural tartaric acid: $[\alpha]^{25}_D$ +6.2° (*c* 3.8, $CHCl_3$) for the D enantiomer; lit. $[\alpha]_D$ −5.5° (*c* 5.0, $CHCl_3$) for the L enantiomer. Ando, N.; Yamamoto, Y.; Oda, J.; Inouye, Y. *Synthesis* **1978**, 688–690.

(12) An authentic diastereomeric mixture of cyclopropane ketals **4b** and **6** was prepared for spectral comparison by ketalization of racemic bicyclo[13.1.0]hexadecan-2-one with 1,4-di-*O*-benzyl-D-threitol. See Experimental Section.



(13) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412–2414 and references cited therein.

(14) For previous examples of chelation-controlled delivery of the Simmons–Smith reagent, see: (a) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892–6894. (b) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 4290–4291. (c) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React. (N.Y.)* **1972**, *20*, 1–131.

(15) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Partial support of this research by Research Corporation and The American Cancer Society is gratefully acknowledged.

ketyl under an inert atmosphere. Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over 3 Å molecular sieves. Liquid ammonia was distilled from lithium immediately before use. Cyclopentadecanone was purchased from Aldrich Chemical Company and used as received. Zinc–copper couple was prepared according to the method of Shank and Shechter[9] immediately before use. Proton magnetic resonance spectra were recorded at 250 MHz on a Bruker WM-250 NMR spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) from tetramethylsilane. Carbon-13 magnetic resonance spectra were recorded at 62.9 MHz on Bruker WM-250 or AM-250 NMR spectrometers. Chemical shifts are reported as δ values in parts per million (ppm) from the center line of the chloroform-*d* triplet (77.0 ppm). Mass spectral determinations were performed at The Midwest Center for Mass Spectrometry, an NSF Regional Instrumentation Facility (Grant CHE-0211164). Elemental analyses were performed by MicAnal Laboratories, Tucson, AZ. Infrared spectra were recorded on a Perkin–Elmer Model 983 infrared spectrophotometer. Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70–230 mesh ASTM). Merck silica gel 60 (70–230 mesh ASTM) was used for column chromatography.

(*E*)-Cyclopentadec-2-en-1-one 1,4-Di-*O*-methyl-D-threitol Ketal (3a). To a well-stirred solution of cyclopentadecanone (1.36 g, 6.07 mmol) in MeOH (8 mL) at 15–20 °C was added Br_2 dropwise until TLC analysis (10% EtOAc/hexanes) showed the complete consumption of starting material. The solution was poured into a well-stirred suspension of Na_2CO_3 (1.6 g) in pentane (3 mL). Water (8 mL) was added, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo, leaving crude 2-bromocyclopentadecan-1-one as a colorless oil.

A solution of the crude 2-bromocyclopentadecanone from above, 1,4-di-*O*-methyl-D-threitol[8] (185 mg, 1.23 mmol), and *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) in benzene (20 mL) was heated to reflux under argon. Water was removed azeotropically using a Dean–Stark trap. Progress of the reaction was monitored by TLC (5% MeOH/CH_2Cl_2). After 68 h the solution was cooled, diluted with ether (60 mL), washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, then dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (100 g) eluted with 10% EtOAc/hexanes gave 2-bromocyclopentadecan-1-one (1.45 g, 4.78 mmol) and then a mixture of diastereomeric 2-bromocyclopentadecan-1-one 1,4-di-*O*-methyl-D-threitol ketals as a pale yellow oil homogeneous by TLC (R_f 0.23, 10% EtOAc/hexanes): yield 465 mg, 1.07 mmol, 87%; ^1H NMR ($CDCl_3$) δ 1.15–2.00 (26, m), 3.38–4.44 (6, m), 3.48–3.62 (3, m), 3.66–3.78 (1, m), and 4.04–4.29 (3, m).

To a well-stirred solution of the above ketals (3.343 g, 7.678 mmol) in dimethyl sulfoxide (11 mL) at 15–20 °C was added sodium methoxide (1.24 g, 23.0 mmol), and the mixture was warmed to room temperature. Progress of the reaction was monitored by TLC (10% EtOAc/hexanes, two developments). After 21 h the orange slurry was poured into saturated aqueous NaCl (100 mL), and the mixture was extracted with hexanes (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the crude product on silica gel 60 (300 g) eluted with 10% EtOAc/hexanes gave the desired *E* isomer **3a** as a pale yellow oil homogeneous by TLC (R_f 0.31, 10% EtOAc/hexanes, two developments): $[\alpha]^{25}_D$ −2.65° (*c* 3.96, $CHCl_3$); yield 2.458 g, 6.934 mmol, 90%; IR ($CHCl_3$) cm^{-1} 3011, 2929, 2857, 1458, 1239, 1194, 1135, 1101, 975, and 670; ^1H NMR ($CDCl_3$) δ 1.15–1.55 (20, m), 1.65–1.77 (2, m), 2.03–2.16 (2, m), 3.38 (3, s), 3.41 (3, s), 3.48–3.61 (4, m), 3.85–3.98 (2, m), 5.45 (1, dt, $^4J_{HH}$ = 1.3 Hz, $^3J_{HH}$ = 15.6 Hz), and 5.76 (1, dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 15.6 Hz); mass spectrum (70 eV), *m/z* (rel intensity) 355 (3), 354 (13), 325 (2), 313 (4), 309 (15), 297 (3), 283 (3), 271 (7), 257 (8), 223 (7), 214 (7), 213 (49), 200 (15), 187 (21), 116 (6), 115 (100), 85 (13), 81 (10), 69 (11); exact mass calcd for $C_{21}H_{38}O_4$ 354.2770, obsd 354.2769.

Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.42; H, 10.95.

A small amount of the *Z* isomer was also obtained as a colorless oil homogeneous by TLC (R_f 0.37, 10% EtOAc/hexanes, two developments): $[\alpha]^{25}_D$ −4.16° (*c* 3.36, $CHCl_3$); yield 0.265 g, 0.748 mmol, 10%; IR ($CHCl_3$) cm^{-1} 3011, 2929, 2858, 1459, 1240, 1195, 1135, 1099, 960, and 669; ^1H NMR ($CDCl_3$) δ 1.15–1.56 (20, m), 1.68–1.83 (2, m), 2.18–2.35 (2, m), 3.37 (3, s), 3.41 (3, s), 3.49–3.61 (4, m), 3.81–3.97 (2, m), and 5.32–5.49 (2, m); mass spectrum (70 eV), *m/z* (rel intensity) 355 (3), 354 (11), 325 (1), 313 (5), 311 (7), 309 (7), 297 (2), 283 (3), 271 (6), 257 (7), 223 (6), 214 (5), 213 (38), 200 (14), 187 (20), 116 (6), 115 (100), 85 (14), 81 (10), 69 (12); exact mass calcd for $C_{21}H_{38}O_4$ 354.2770, obsd 354.2773.

(*E*)-Cyclopentadec-2-en-1-one 1,4-Di-*O*-benzyl-D-threitol Ketal (3b). In a similar manner, ketal **3b** was prepared from cyclopentadecanone and 1,4-di-*O*-benzyl-D-threitol[11] (470 mg, 1.55 mmol). Chromatography on silica gel 60 (200 g) eluted with 5% EtOAc/hexanes gave (*E*)-cyclopentadec-2-en-1-one 1,4-di-*O*-benzyl-D-threitol ketal (**3b**) as a pale yellow oil homogeneous by TLC (R_f 0.29, 10% EtOAc/hexanes): $[\alpha]^{25}_D$ +2.07° (*c* 7.64, $CHCl_3$); yield 442 mg, 0.872 mmol, 56%; IR ($CHCl_3$) cm^{-1} 3005, 2931, 2851, 1451, 1367, 1097, 973, 907, and 696; ^1H NMR ($CDCl_3$) δ 1.05–1.52 (20, m), 1.64–1.79 (2, m), 1.96–2.11 (2, m), 3.47–3.70 (4, m), 3.92–4.08 (2, m), 4.49–4.65 (4, m), 5.42 (1, br d, J_{HH} = 15.5 Hz), 5.73 (1, dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 15.6 Hz), and 7.21–7.40 (10, m); mass spectrum (100 eV), *m/z* (rel intensity) 506 (13), 423 (4), 409 (5), 385 (7), 365 (8), 352 (7), 339 (4), 283 (4), 223 (4), 181 (5), 105 (5), 92 (9), 91 (100), 81 (4), 69 (7); exact mass calcd for $C_{33}H_{46}O_4$ 506.3396, obsd 506.3386.

(*Z*)-Cyclopentadecen-1-one 1,4-di-*O*-benzyl-D-threitol was also obtained as a colorless oil homogeneous by TLC (R_f 0.33, 10% EtOAc/hexanes): $[\alpha]^{25}_D$ +2.77° (*c* 2.05, $CHCl_3$); yield 116 mg, 0.229 mmol, 15%; IR ($CHCl_3$) cm^{-1} 3013, 2929, 2858, 1453, 1366, 1207, 1097, and 699; ^1H NMR ($CDCl_3$) δ 1.05–1.56 (20, m), 1.71–1.85 (2, m), 2.15–2.40 (2, m), 3.46–3.71 (4, m), 3.91–4.05 (1, m), 4.15–4.32 (1, m), 4.48–4.68 (4, m), 5.27–5.47 (2, m), and 7.20–7.44 (10, m); mass spectrum (70 eV), *m/z* (rel intensity) 507 (2), 506 (4), 465 (1), 423 (1), 385 (1), 365 (2), 352 (2), 339 (2), 223 (2), 181 (3), 175 (1), 109 (1), 107 (1), 105 (3), 97 (2), 95 (2), 92 (8), 91 (100), 81 (3), 69 (5); exact mass calcd for $C_{33}H_{46}O_4$ 506.3396, obsd 506.3409.

(1*S*,15*S*)-Bicyclo[13.1.0]hexadecan-2-one 1,4-Di-*O*-methyl-D-threitol Ketal (4a). To a well-stirred suspension of freshly prepared Zn–Cu couple (2.08 g) and anhydrous K_2CO_3 (2.17 g) in ether (8 mL) were added a large crystal of I_2 and CH_2I_2 (5.0 g, 19 mmol). After 30 min at reflux (external heating), (*E*)-cyclopentadec-2-en-1-one 1,4-di-*O*-methyl-D-threitol ketal (**3a**) (2.137 g, 6.028 mmol) was added as a solution in ether (2 mL). Progress of the reaction was monitored by TLC (1% CH_3OH/CH_2Cl_2). After 4 h the mixture was cooled to 0 °C and quenched with saturated aqueous K_2CO_3 (1.3 mL). After stirring at room temperature for 30 min, the gray-black precipitate was removed by centrifugation and washed well with ether. The combined organic extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product as a pale yellow oil. Chromatography on silica gel 60 (50 g) eluted with 20% EtOAc/hexanes gave (1*S*,15*S*)-bicyclo-[13.1.0]hexadecan-2-one 1,4-di-*O*-methyl-D-threitol ketal (**4a**) as a colorless oil homogeneous by TLC (R_f 0.30, 1% MeOH/CH_2Cl_2): $[\alpha]^{25}_D$ −0.60° (*c* 3.68, $CHCl_3$); yield 2.118 g, 5.746 mmol, 95%; IR ($CHCl_3$) cm^{-1} 3011, 2926, 2857, 1459, 1403, 1344, 1222, 1195, 1138, 1102, 1082, 959, 909, and 669; ^1H NMR ($CDCl_3$) δ 0.18–0.27 (1, m), 0.54–0.62 (1, m), 0.65–0.96 (3, m), 1.10–1.57 (20, m), 1.65–1.82 (3, m), 3.37 (3, s), 3.40 (3, s), 3.43–3.60 (4, m), 3.71–3.81 (1, m), and 3.86–3.96 (1, m); ^{13}C NMR ($CDCl_3$) δ 8.8 (CH_2), 16.4 (CH), 22.3 (CH_2), 25.6 (CH), 25.9 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 27.1 (CH_2), 27.3 (CH_2), 27.5 (CH_2), 29.0 (CH_2), 33.7 (CH_2), 40.3 (CH_2), 59.3 (CH_3), 73.6 (CH_2), 77.1 (CH), 78.5 (CH), and 111.8 (C); mass spectrum (70 eV), *m/z* (rel intensity) 369 (1), 368 (5), 339 (3), 326 (3), 325 (15), 323 (6), 313 (2), 311 (5), 297 (3), 283 (3), 269 (3), 255 (5), 243 (3), 237 (7), 214 (7), 213 (5), 188 (8), 187 (74), 174 (19), 144 (5), 116 (6), 115 (100), 112 (5), 95 (8), 85 (16), 84 (20), 69 (11), 67 (14); exact mass calcd for $C_{22}H_{40}O_4$ 368.2926, obsd 368.2923.

Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.70; H, 10.94. Found: C, 71.67; H, 11.01.

(1*S*,15*S*)-Bicyclo[13.1.0]hexadecan-2-one 1,4-Di-*O*-benzyl-D-threitol Ketal (4b). In a similar manner, ketal **4b** was prepared from (*E*)-cyclopentadec-2-en-1-one 1,4-di-*O*-methyl-D-

threitol ketal (**3b**) (358 mg, 0.706 mmol). Chromatography on silica gel 60 (30 g) eluted with 10% EtOAc/hexanes gave (1*S*,15*R*)-bicyclo[13.1.0]hexadecan-2-one 1,4-di-*O*-benzyl-D-threitol ketal (**4b**) as a pale yellow oil homogeneous by TLC (R_f 0.34, 10% EtOAc/hexanes): $[\alpha]^{25}_D$ +0.18° (*c* 7.34, $CHCl_3$); yield 325 mg, 0.624 mmol, 88%; IR ($CHCl_3$) cm^{-1} 3005, 2925, 2851, 1451, 1361, 1137, 1087, and 697; ^1H NMR ($CDCl_3$) δ 0.14–0.24 (1, m), 0.52–0.62 (1, m), 0.66–0.95 (2, m), 1.10–1.82 (24, m), 3.51–3.70 (4, m), 3.79–3.90 (1, m), 3.96–4.07 (1, m), 4.54 (2, s), 4.57 (2, s), and 7.20–7.39 (10, m); ^{13}C NMR ($CDCl_3$) δ 8.8 (CH_2), 16.4 (CH), 22.2 (CH_2), 25.6 (CH), 25.8 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 26.9 (CH_2), 27.0 (CH_2), 27.2 (CH_2), 27.4 (CH_2), 29.0 (CH_2), 33.6 (CH_2), 40.2 (CH_2), 70.7 (CH_2), 70.8 (CH_2), 73.4 (CH_2), 73.4 (CH_2), 77.1 (CH), 78.7 (CH), 111.7 (C), 127.5 (CH), 127.6 (CH), 128.3 (CH), and 138.1 (C); mass spectrum (70 eV), *m/z* (rel intensity) 520 (2), 477 (2), 399 (1), 340 (2), 339 (7), 237 (2), 181 (3), 175 (3), 158 (2), 130 (2), 105 (6), 99 (2), 92 (9), 91 (100), 69 (4); exact mass calcd for $C_{34}H_{48}O_4$ 520.3552, obsd 520.3544.

(1*S*,15*S*)-Bicyclo[13.1.0]hexadecan-2-one (5). From 4a. To a solution of (1*S*,15*S*)-bicyclo[13.1.0]hexadecan-2-one 1,4-di-*O*-methyl-D-threitol ketal (**4a**) (1.075 g, 2.916 mmol) in CH_3OH (14.5 mL) at room temperature was added slowly 2.7 M aqueous HCl (0.9 mL). Progress of the reaction was monitored by TLC (10% EtOAc/hexanes). After 2 h the solution was poured into saturated aqueous $NaHCO_3$ (60 mL) and the mixture was extracted with pentane (3 × 30 mL). The combined pentane extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo (bath temperature <30 °C at ca. 25 mmHg) to give the crude product ketone as a pale yellow oil. Chromatography on silica gel 60 (200 g) eluted with 5% ether/pentane afforded (1*S*,15*S*)-bicyclo[13.1.0]hexadecan-2-one (**5**) as a white solid homogeneous by TLC (R_f 0.49, 10% EtOAc/hexanes): $[\alpha]^{25}_D$ +6.00° (*c* 4.33, $CHCl_3$); yield 0.647 g, 2.737 mmol, 94%; IR ($CHCl_3$) cm^{-1} 3015, 2929, 2857, 1683, 1458, 1441, 1405, 1361, 1105, 1080, and 669; ^1H NMR ($CDCl_3$) δ 0.68–0.91 (3, m), 1.08–1.60 (20, m), 1.67–1.77 (1, m), 1.78–2.00 (2, m), 2.38 (1, ddd, J_{HH} = 4.9 Hz, J_{HH} = 7.3 Hz, J_{HH} = 16.1 Hz), and 2.71 (1, ddd, J_{HH} = 4.8 Hz, J_{HH} = 8.8 Hz, J_{HH} = 16.0 Hz); ^{13}C NMR ($CDCl_3$) δ 17.4 (CH_2), 23.4 (CH_2), 25.6 (CH_2), 26.0 (CH), 26.3 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.4 (CH_2), 27.7 (CH_2), 28.9 (CH_2), 29.3 (CH), 32.9 (CH_2), 42.4 (CH_2), and 210.4 (C); mass spectrum (70 eV), *m/z* (rel intensity) 237 (3), 236 (15), 207 (6), 193 (6), 179 (3), 178 (7), 165 (4), 163 (4), 151 (4), 149 (8), 136 (8), 135 (15), 125 (9), 123 (11), 122 (10), 121 (15), 111 (20), 109 (22), 98 (34), 97 (37), 96 (31), 95 (46), 94 (20), 82 (43), 81 (62), 71 (40), 69 (58), 67 (58), 55 (100); exact mass calcd for $C_{16}H_{28}O$ 236.2140, obsd 236.2139.

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.13; H, 11.88.

From 4b. (1*S*,15*S*)-Bicyclo[13.1.0]hexadecan-2-one 1,4-di-*O*-benzyl-D-threitol ketal (**4b**) (732 mg, 1.41 mmol) was hydrolyzed in a similar manner, providing crude cyclopropyl ketone **5** as a pale yellow oil contaminated with 1,4-di-*O*-benzyl-D-threitol. Chromatography on silica gel 60 (15 g) eluted with 5% ether/pentane afforded **5**; yield 292 mg, 1.24 mmol, 88%.

1,4-Di-*O*-benzyl-D-threitol was recovered from the silica gel column by elution with 50% EtOAc/hexanes; yield 367 mg, 1.22 mmol, 86%.

(3*R*)-3-Methylcyclopentadecan-1-one (1). To a well-stirred solution of Li metal (56 mg, 8.1 mmol) in liquid ammonia (6 mL) at −78 °C was added a solution of *t*-BuOH (244 mg, 3.29 mmol) and (1*S*,15*S*)-bicyclo[13.1.0]hexadecan-2-one (**5**) (385 mg, 1.62 mmol) in ether (3 mL). The cold bath was removed and the mixture allowed to reflux (−33 °C). Progress of the reaction was monitored by TLC (10% EtOAc/hexanes). After 0.5 h the mixture was cooled to −78 °C, quenched with solid NH_4Cl (380 mg, 7.1 mmol), diluted with ether (6 mL), and warmed to room temperature, and the ammonia was allowed to evaporate. The mixture was filtered and concentrated in vacuo (bath temperature <30 °C at ca. 25 mmHg), leaving a yellow oil which was a mixture of (3*R*)-3-methylcyclopentadecan-1-ol and (3*R*)-3-methylcyclopentadecan-1-one.

To a well-stirred solution of the above oil in CH_2Cl_2 (4.5 mL) was added pyridinium dichromate (2.455 g, 6.522 mmol) at room temperature. Progress of the reaction was monitored by TLC (10% EtOAc/hexanes). After 27.5 h, the mixture was diluted with ether (10 mL) and filtered through a short plug of silica gel 60. The eluent was concentrated in vacuo (bath temperature <25 °C at ca. 25 mmHg) to give crude (3*R*)-muscone (**1**) as a pale yellow oil. Chromatography on silica gel 60 (400 g) eluted with 5% ether/pentane afforded (3*R*)-muscone (**1**) as a pale yellow oil homogeneous by TLC (R_f 0.33, 5% EtOAc/hexanes): $[\alpha]^{25}_D$ −10.6° (*c* 1.10, CH_3OH), lit. $[\alpha]_D$ −11.7° (*c* 0.80, CH_3OH);[2c] yield 334 mg, 1.40 mmol, 86%; IR (neat) cm^{-1} 2921, 2856, 1711, 1458, 1408, 1366, 1275, 1128, 1057, and 717; ^1H NMR ($CDCl_3$) δ 0.94 (3, d, $^3J_{HH}$ = 6.7 Hz), 1.14–1.48 (20, m), 1.50–1.78 (2, m), 1.95–2.12 (1, m), 2.18 (1, dd, J_{HH} = 5.2 Hz, J_{HH} = 15.0 Hz), and 2.36–2.50 (3, m); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3), 23.0 (CH_2), 25.1 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (2 × CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 29.0 (CH), 35.6 (CH_2), 42.1 (CH_2), 50.4 (CH_2), and 211.6 (C); mass spectrum (100 eV), *m/z* (rel intensity) 239 (18), 238 (25), 223 (10), 209 (14), 125 (29), 112 (11), 111 (19), 110 (14), 109 (11), 98 (19), 97 (44), 96 (28), 95 (21), 94 (13), 85 (93), 84 (39), 83 (29), 82 (31), 81 (24), 71 (64), 70 (18), 69 (68), 68 (26), 67 (22), 59 (32), 58 (49), 57 (27), 56 (30), 55 (100); exact mass calcd for $C_{16}H_{30}O$ 238.2297, obsd 238.2272.

Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.98; H, 13.00.

(1*S*,15*S*)-Bicyclo[13.1.0]hexadecan-2-one and (1*R*,15*R*)-Bicyclo[13.1.0]hexadecan-2-one 1,4-Di-*O*-benzyl-D-threitol Ketals (4b and 6). To a well-stirred suspension of freshly prepared Zn–Cu couple (97 mg) and anhydrous K_2CO_3 in ether (0.25 mL) were added a small crystal of I_2 and CH_2I_2 (110 mg, 0.41 mmol). After 30 min at reflux (external heating), (*E*)-cyclopentadec-2-en-1-one[6a] (30 mg, 0.13 mmol) was added as a solution in ether (0.2 mL). Progress of the reaction was monitored by TLC (10% EtOAc/hexanes). After 1.25 h the mixture was cooled to 0 °C and quenched with saturated aqueous K_2CO_3 (35 μL). After stirring at room temperature for 30 min, the gray-black precipitate was removed by centrifugation and washed well with ether. The combined organic extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude product as a pale yellow oil. Chromatography on silica gel 60 (5 g) eluted with 10% EtOAc/hexanes gave racemic bicyclo[13.1.0]hexadecan-2-one (**5**) as a colorless oil homogeneous by TLC (R_f 0.43, 10% EtOAc/hexanes); yield 25 mg, 0.11 mmol, 77%.

A solution of racemic bicyclo[13.1.0]hexadecan-2-one (**5**) (40 mg, 0.17 mmol), 1,4-di-*O*-benzyl-D-threitol (104 mg, 0.344 mmol), and pyridinium *p*-toluenesulfonate (25 mg, 0.10 mmol) in benzene (4 mL) was heated to reflux under argon. Water was removed azeotropically by using a Dean–Stark trap. Progress of the reaction was monitored by TLC (10% EtOAc/hexanes). After 108 h the mixture was worked up as previously described and the crude product purified by chromatography on silica gel 60 (50 g) eluted with 5% EtOAc/hexanes. A 1:1 mixture of bicyclic ketals **4b** and **6** was obtained as a pale yellow oil homogeneous by TLC (R_f 0.33, 10% EtOAc/hexanes): yield 40 mg, 0.08 mmol, 45%; ^{13}C NMR ($CDCl_3$) δ 8.0 and 8.8 (CH_2), 16.4 and 16.5 (CH), 22.2 (CH_2), 25.1 and 25.6 (CH), 25.7 and 25.8 (CH_2), 25.9 and 26.1 (CH_2), 26.0 and 26.3 (CH_2), 26.4 (CH_2), 26.6 and 26.9 (CH_2), 27.0 and 27.1 (CH_2), 27.2 (CH_2), 27.4 (CH_2), 29.0 and 29.1 (CH_2), 33.5 and 33.7 (CH_2), 40.3 and 40.4 (CH_2), 70.1 and 70.5 (CH_2), 70.8 (CH_2), 73.4 and 73.5 (CH_2), 77.1 and 77.7 (CH), 77.9 and 78.8 (CH), 111.2 and 111.8 (C), 127.6 (CH), 128.3 (CH), and 138.1 (C).

Registry No. 1, 10403-00-6; (*E*)-**3a**, 102521-14-2; (*Z*)-**3a**, 102572-87-2; (*E*)-**3b**, 102521-15-3; (*Z*)-**3b**, 102572-88-3; **4a**, 102521-16-4; **4b**, 102521-17-5; **5**, 102521-18-6; (±)-**5**, 102572-89-4; **6**, 102572-90-7; cyclopentadecanone, 502-72-7; 2-bromocyclopentadecanone, 102521-13-1; 1,4-di-*O*-methyl-D-threitol, 33507-82-3; 1,4-di-*O*-benzyl-D-threitol, 91604-41-0; (*S*)-2-bromocyclopentadecan-1-one 1,4-di-*O*-methyl-D-threitol ketal, 102535-18-2; (*R*)-2-bromocyclopentadecan-1-one 1,4-di-*O*-methyl-D-threitol ketal, 102628-47-7; 3-methylcyclopentadecan-1-ol, 62151-56-8; (*E*)-cyclopentadec-2-en-1-one, 56345-01-8.