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Homologation of Large Rings[‡]

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Abstract: *Free radical-promoted, one-carbon, ring expansion of twelve, fourteen-, and fifteen-membered cyclic β-keto esters is described. The method is then extended to include a three-carbon ring expansion of cyclododecanone, the targets being (±)-muscone and naturally occurring (R)-(–)muscone.*

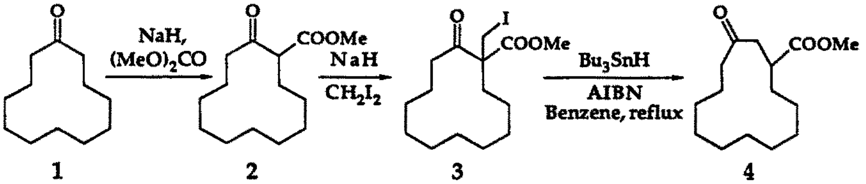
Introduction

Construction of large rings with appropriately situated functional groups affords a synthetic challenge of substantial utility. Methods employed in the past include direct condensation of open chain precursors, usually conducted under conditions of high dilution. The advent of readily available twelve-membered rings provides an attractive starting point for ring expansion or ring contraction to gain access to larger or smaller rings.[1] Our experiments are aimed at development of convenient free radical methods for ring enlargement.[2]

The general strategy is straightforward; it involves alkylation of readily available β-keto esters with dihaloalkanes of variable chain length followed by free radical promoted ring expansion.[2,3]

Ring Expansion

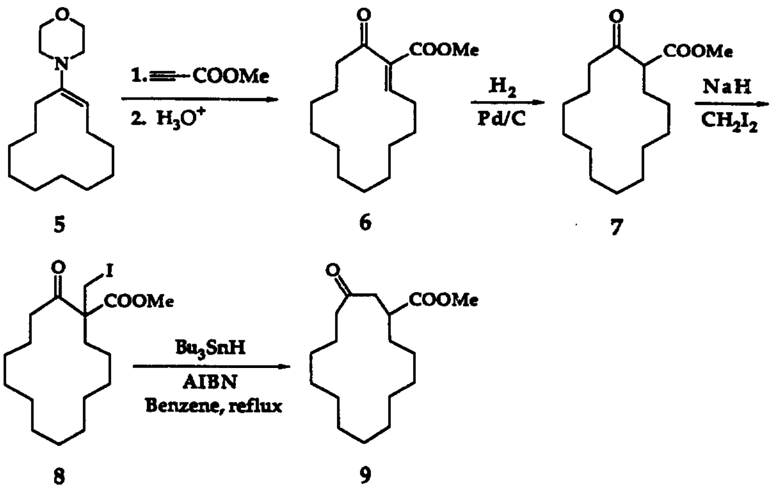
With this strategy, one-carbon ring expansion of twelve-, fourteen- and fifteen-membered rings leads to the next higher homolog in the series. As an illustration, cyclododecanone (1) was carboxymethylated under standard conditions yielding **2**, then **2** was alkylated with methylene iodide. The resulting iodomethyl adduct **3** was treated with tri-*n*-butyltin hydride[4] and underwent smooth transformation (79%) to the thirteen-membered γ-keto ester **4** (eq 1).



(1)

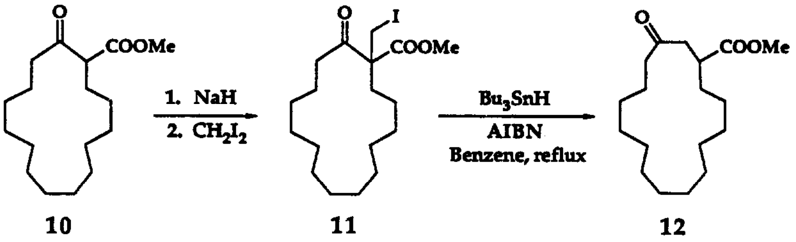
[‡] Dedicated with best wishes to Professor Gabor Fodor on the occasion of his 75th birthday.

In a second example, the fourteen-membered ring β-keto ester 7 was prepared by cycloaddition of methyl propiolate to the morpholine enamine[5] 5 of cyclododecanone, followed by catalytic hydrogenation of the adduct (eq 2). Alkylation of the keto ester 7 with methylene iodide



(2)

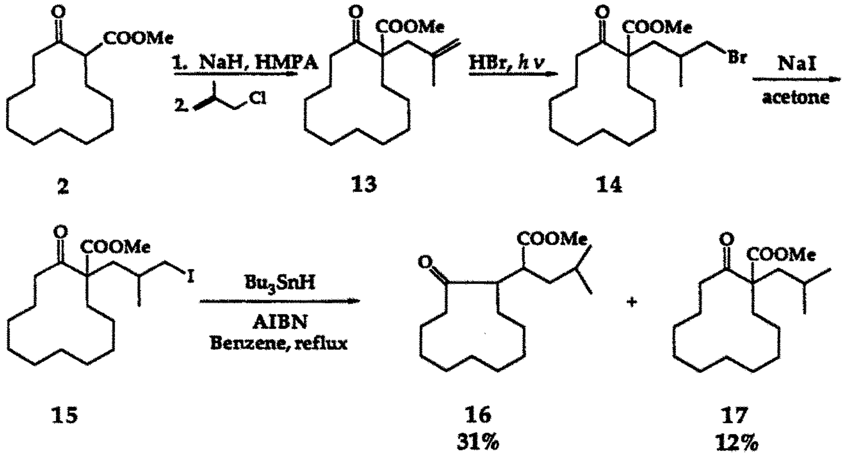
yielded 8. Tri-*n*-butyltin hydride promoted ring expansion of 8 led to the desired fifteen-membered ring γ-keto ester 9. In similar fashion, the sixteen-membered cyclic γ-keto ester 12 was obtained following ring expansion of the iodomethylated cyclopentadecanone β-keto ester 11 (eq 3).



(3)

Muscone Synthesis

The three-carbon ring expansion of a twelve- to a fifteen-membered ring was used to explore the extension of this method to larger increments. For this purpose, muscone was chosen as a target molecule.[6] First, methyl cyclododecanone-2-carboxylate (2) was alkylated with 3-chloro-2-methylpropene. The resulting adduct 13 was hydrobrominated under free radical conditions yielding the terminal bromide **14**, which was then converted to the iodide **15** in a

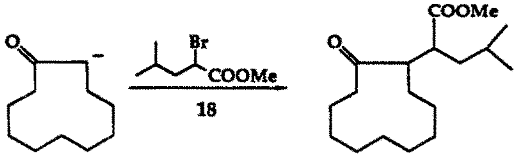


2 **13** **14** (4)

15 **16** 31% **17** 12%

Finklestein displacement reaction. The iodide **15** was treated with tri-*n*-butyltin hydride but did not yield the desired fifteen-membered γ-keto ester. Instead, ring contraction occurred yielding the eleven-membered keto ester **16** together with the product **17** of direct reduction (eq 4).

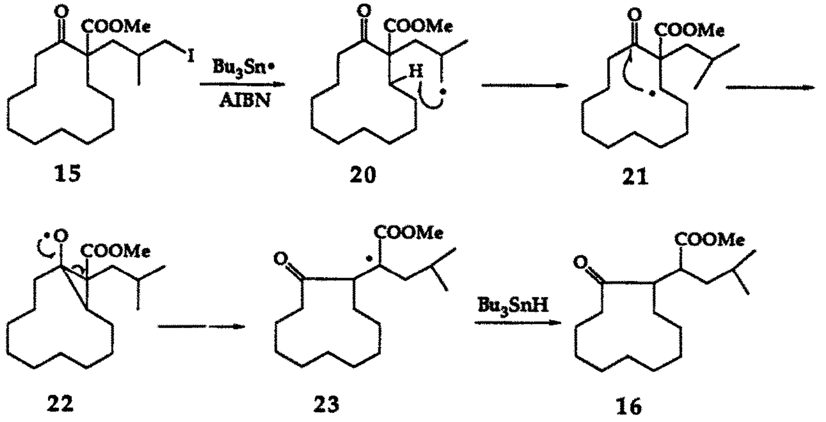
Authentic samples of both ring contracted and reduced products, **16** and **17**, were prepared for direct comparison with the reaction products. Thus, catalytic hydrogenation of the starting alkene **13** gave a product whose spectral properties were identical to those of **17**. An authentic sample of the ring contracted product **16** was obtained by the sequence shown in eq 5. Methyl 2-bromo-4-methylpentanoate (**18**), prepared from the corresponding acid under Hell-



19 **16** (5)

Volhard-Zelinsky conditions, was added to the enolate **19** of cycloundecanone. The product **16** consisted of a pair of diastereomers (eq 5), which were separated by column chromatography. The spectroscopic properties of the individual diastereomers of **16** were in good agreement with those of the diastereomeric products from the tri-*n*-butyltin hydride-promoted rearrangement of **15** to **16** (eq 4).

We suggest that the initially formed primary radical **20** may preferentially abstract a hydrogen atom from the ring β-methylene group. If the resulting secondary radical **21** then adds to the ketone carbonyl group, an oxy radical **22** will be generated that can fragment in the direction of the ester (eq 6). The ester stabilized radical **23** can then undergo hydrogen chain transfer with the tin hydride reagent.

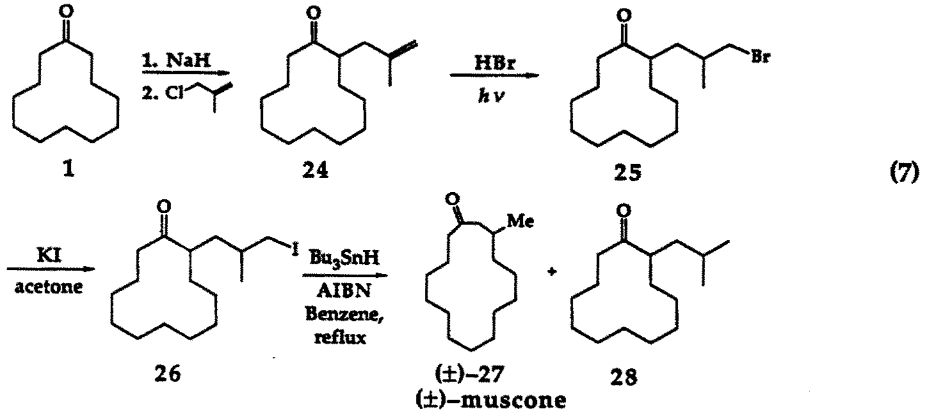


(6)

Among the many conformations available to the twelve-membered ring some will place the side chain radical in a favorable position for hydrogen abstraction. Attempts at molecular modelling reveal many thermally accessible conformations.[7] As a consequence, attempts to define specifically the key conformational contributors were not fruitful.

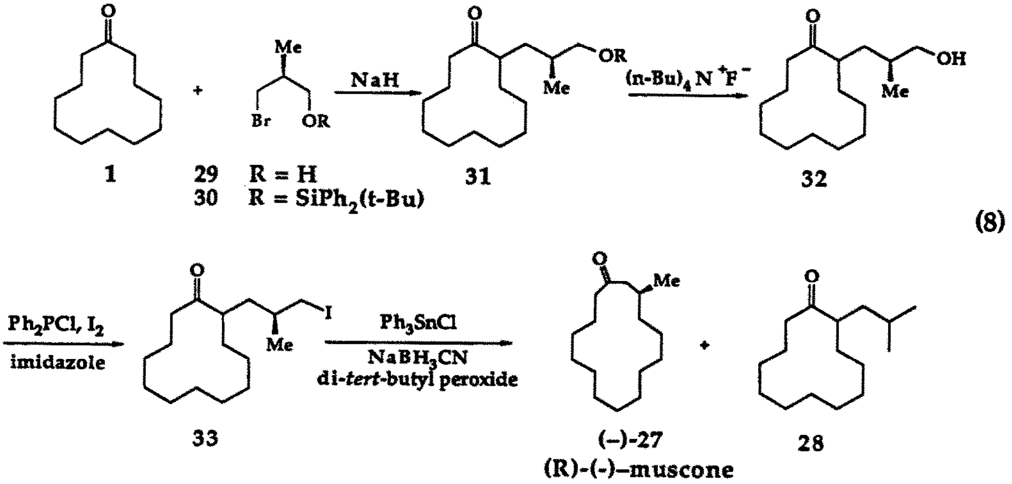
The ester plays an important role in the free radical-based ring enlargement reactions. The β-keto ester grouping facilitates alkylation with the designated alkyl halide and acts as a radical stabilizing group to facilitate the ring expansion. It is also possible that the ester makes the ring carbonyl group more susceptible to nucleophilic radical attack. In spite of these advantages, the ring contraction described in eq 4 made it essential to explore the possibility of ring expansion in the absence of the ester.

Accordingly, the enolate anion of cyclododecanone (1) was alkylated with 3-chloro-2-methylpropene in the presence of iodide ion and yielded the adduct **24** (54%). Hydrogen bromide was added to the double bond of **24** under free radical conditions leading to **25**. The primary bromide in **25** was displaced by iodide ion in a Finkelstein reaction. The resulting iodide **26** was treated with tri-*n*-butyltin hydride and rearranged to (±)-muscone ((±)-**27**) (15%) together with the product of direct reduction **28** (eq 7). Even under conditions of high dilution, free radical directed ring expansion and direct reduction occur with significant advantage to the direct reduction product **28**.



(7)

Although the yield of muscone (27) was low, this route is highly expeditious. That aspect of the sequence encouraged exploration of a direct synthesis of the naturally occurring levorotatory enantiomer of muscone.[8] Thus, the readily available S-(+)-3-bromo-2-methylpropanol (29) was protected as its t-butyldiphenylsilyl ether 30, and the latter was used to alkylate cyclododecanone (1) yielding 31. The silyl group was removed with fluoride ion and the resulting alcohol 32 was converted to the iodide 33 with chlorodiphenylphosphine and iodine. The iodide 33 was treated with triphenyltin hydride under modified Stork[9] conditions and yielded, after workup and chromatographic separation, pure R-(-)-muscone ((–)-27), with spectral and optical properties in excellent agreement with those of an authentic sample.



(8)

Experimental Section

A. One-Carbon Ring Expansion of Twelve-, Fourteen-, and Fifteen-Membered Cyclic β-Keto Esters

Methyl 2-Oxocyclododecanoate (2). A solution of 1.36 g (7.5 mmoles) of cyclododecanone (1) (Aldrich) in 5 mL of benzene was added dropwise over 3.5 hr to a refluxing slurry of 0.720 g (15.0 mmoles) of NaH (60% dispersion in mineral oil) and 1.26 mL (15.0 mmoles) of dimethyl carbonate in 20 mL of benzene. After further heating at reflux for 1 hr, the reaction mixture was cooled to room temperature, and cautiously quenched with a solution of 1.5 mL of acetic acid in 4 mL of ice water. The product was extracted with benzene (3 x 4 mL), washed with cold water (3 x 10 mL), dried over K_2CO_3, and evaporated *in vacuo*; to give 1.75 g of a brown oil. Distillation under reduced pressure gave 1.53 g (85%) of 2 as a colorless oil, bp 140-145 °C (0.3 mm Hg). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.70 (s, 3 H), 3.63 (dd, J_{AB} = 11.5, 3.5 Hz, 1 H), 2.66 (ddd, J = 15.7, 10.9, 3.5 Hz, 1 H), 2.56 (ddd, J = 15.7, 6.5, 3.3 Hz, 1 H), 2.24-2.08 (m, 1 H), 1.19-1.15 (m, 17 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 13 lines at δ: 205.9 (s), 170.0 (s), 56.8 (d, J = 130.1 Hz), 51.9 (q, J = 149.0 Hz), 38.2 (t, J = 126.3 Hz), 26.6, 25.2, 24.9, 24.1, 23.9, 22.8, 22.1, 21.8. The IR spectrum (neat) showed bands at: 2930 (s), 2861 (s), 1746 (vs), 1711 (vs), 1470 (s), 1437 (s), 1240 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 240 (M^+, 3.7) and 209 (M^+-OMe, 6.5). Exact mass calc'd for $C_{14}H_{24}O_3$ (M^+): 240.1725. Found: 240.1725.

Methyl 1-Iodomethyl-2-oxocyclododecanoate (3). A solution of 1.2 g (5.0 mmoles) of methyl 2-oxocyclododecanoate (2) in 5 mL of dry tetrahydrofuran (THF) was added slowly to a suspension of 0.240 g (6.0 mmoles, 60% suspension in mineral oil) of NaH in 30 mL of THF containing 3.5 mL (20 mmoles) of HMPA at room temperature under argon. The mixture was stirred at room temperature for 0.5 hr, followed by addition of 0.8 mL (10.0 mmoles) of diiodomethane. The reaction was then heated at reflux for 24 hr, cooled to room temperature and poured into 150 mL of ether. The organic layer was washed with water (5 x 5 mL), dried over K_2CO_3, filtered and concentrated *in vacuo* affording 3.0 g of a brown oil. Column chromatography on 80 g of silica gel (elution with 3:2 dichloromethane-*n*-hexane) gave 0.645 g (34%) of 3 as a colorless oil, R_f 0.55 (3:2 dichloromethane-*n*-hexane). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.77 (s, 3 H), 3.62 (d, J_{AB} = 10.5 Hz, 1 H), 3.49 (d, J_{AB} = 10.5 Hz, 1 H), 3.05 (m, 1 H), 2.19-2.01 (m, 5 H), 1.57-1.21 (m, 14 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 15 lines at δ: 204.5 (s), 170.8 (s), 64.5 (s), 52.9 (q, J = 148.4 Hz), 34.8 (t, J = 124 Hz), 29.9 (t, J = 129.4 Hz), 26.2, 26.1, 23.3, 22.5, 21.8, 21.7, 21.5, 18.1 (t, J = 123.5 Hz), and 7.8 (t, J = 149.5 Hz, -CH_2I). The IR spectrum (neat) showed bands at: 2930 (vs), 2858 (vs), 1748 (vs, CO, ester), 1711 (vs, CO, ketone) and 1468 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 349

(M^+-OMe, 5), 253 (M^+-I, 100). Exact mass calc'd for $C_{14}H_{22}IO_2$ (M^+-OMe): 349.0665. Found: 349.0666.

Reaction of Methyl 1-Iodomethyl-2-oxocyclododecanoate (3) with Tri-*n*-butyltin Hydride and Azobisisobutyronitile (AIBN). A solution of tri-*n*-butyltin hydride (0.081 mL, 0.3 mmoles) and AIBN (0.010 g, 0.058 mmoles) in 7 mL of benzene was added dropwise over 1 hr to a refluxing solution of methyl 1-iodomethyl-2-oxocyclododecanoate (3) (0.076 g, 0.2 mmoles) in 12 mL of benzene. After heating at reflux for an additional 4 hr, the reaction mixture was cooled to room temperature and concentrated *in vacuo* yielding an oil. The crude product was dissolved in 25 ml of dichloromethane and washed with 10% potassium fluoride solution (5 x 1 mL). The organic layer was dried over K_2CO_3, filtered and concentrated. The resulting oil was taken up in 25 mL of acetonitrile, washed with *n*-hexane (4 x 5 mL), and concentrated *in vacuo*. Column chromatography (elution with 10:1 *n*-hexane-ethyl acetate) of the crude product on 2 g of silica gel afforded 0.040 g (79 %) of the rearrangement product, methyl 3-oxocyclotridecanoate (4) as a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) of 4 showed peaks at δ: 3.68 (s, 3 H), 2.96 (m, 1 H), 2.84 (dd, J_{AB} = 16.7, J_{AX} = 8.7 Hz, 1 H), 2.73 (dd, J_{AB} = 16.7, J_{BX} = 3.3 Hz, 1 H), 2.54 (m, 1 H), 2.34 (m, 1 H), 1.85-1.15 (m, 18 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 15 lines at δ: 210.0 (s), 175.6 (s), 51.8 (q, J = 146.9 Hz), 43.4 (t, J = 125.4 Hz), 42.3 (t, J = 127.1 Hz), 39.5 (d, J = 130.3 Hz), 29.4 (t, J = 128.5 Hz), 26.1, 26.01 (overlapped), 25.4, 24.5, 24.2, 23.6, 23.5. The IR spectrum (neat) showed bands at: 2932 (vs), 2861 (vs), 1736 (vs, CO, ester), 1711 (vs, CO, ketone), 1435 (m), 1265 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 254 (M^+ 20) and 222 (M^+-CH_3OH, 27). Exact mass calc'd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1882.

Methyl 2-Oxocyclotetradec-14-enoate (6). A solution of 4.55 g (25 mmoles) of cyclododecanone (1), 2.6 g (30 mmoles) of morpholine, and 0.046 g of *p*-toluenesulfonic acid in 5 mL of toluene was heated at reflux for 16 hr while the water generated was separated using a Dean-Stark apparatus. At this point, the proton nmr spectrum indicated that only about half of the starting material had been converted into the desired enamine. Accordingly, 2.6 g (30 mmoles) of morpholine and 0.1 g of *p*-toluenesulfonic acid were added, and heating at reflux was continued for an additional 24 hr. The reaction was evaporated *in vacuo* to give 5.2 g of a brown oil, which was composed of the starting material 1 and the desired enamine 5 in a ratio of 35:65 according to ^1H nmr. The mixture was used in the next step without further purification.

The crude enamine 5 (2.05 g, 65% pure, 5.3 mmoles) was taken up in 20 mL of benzene and heated to reflux. A solution of methyl propiolate (0.690 g, 8.2 mmoles) in 5 mL of benzene was added dropwise over 15 min, and the reaction was heated at reflux for 35 hr. The reaction was cooled to room temperature, and concentrated *in vacuo* to a brown oil. The resulting oil was added to a solution of 0.8 mL of concentrated HCl in 1.6 mL of water. After it was warmed on the steam bath for 30 min, the hydrolysis mixture was cooled and extracted with ether (4 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to 1.78 g of a brown oil. Column chromatography on 80 g of silica gel (10 :1 *n*-hexane-ethyl acetate) provided 0.348 g (27%) of the fast moving isomer of the title compound **6**, 0.121 g (9%) of the mixture of two isomers of **6**, and 0.195 g (14%) of the slow moving isomer of **6** as an oil, with R_f 0.31 and 0.21 (10:1 *n*-hexane-ethyl acetate), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the fast moving isomer of **6** showed peaks at δ: 6.89 (t, J = 8.1 Hz, 1 H), 3.77 (s, 3 H), 2.71 (t, J = 6.7 Hz, 2 H), 2.19 (q, J = 7.8 Hz, 2 H), 1.74-1.63 (m, 3 H), 1.49-1.15 (m, 15 H). The IR spectrum (neat) showed bands at: 2930 (vs), 2857 (s), 1732 (s), 1709 (s), 1637 (w), 1437 (m), 1246 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 266 (M^+, 8.7), 234 (M^+-MeOH, 21), 206 (M^+-MeOH-CO, 6.3). Exact mass calc'd for $C_{16}H_{26}O_3$ (M^+): 266.1882. Found: 266.1882.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the slow moving isomer of **6** showed peaks at δ: 6.83 (t, J = 7.9 Hz, 1 H), 3.82 (s, 3 H), 2.64 (t, J = 6.9 Hz, 2 H), 2.46-2.40 (m, 2 H), 1.68-1.57 (m, 3 H), 1.42-1.10 (m, 15 H). The IR spectrum (neat) showed bands at: 2930 (vs), 2859 (s), 1736 (vs), 1694 (s), 1670 (s), 1636 (w), 1437 (m), 1217 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 266 (M^+, 8.7), 234 (M^+-MeOH, 21), 206 (M^+-MeOH-CO, 6.3). Exact mass calc'd for $C_{16}H_{26}O_3$ (M^+): 266.1882. Found: 266.1882.

Methyl 2-Oxocyclotetradecanoate (7). The mixture of isomers of methyl 2-oxocyclotetradec-14-enoate (**6**) (0.579 g, 2.189 mmoles) and 0.12 g of 10% palladium on carbon in 100 mL of methanol was stirred at room temperature under an atmosphere of hydrogen for 24 hr. The mixture was filtered to remove the catalyst, and the filtrate was concentrated *in vacuo* to give 0.539 g (94%) of the title compound **7** as a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.63 (s, 3 H), 3.50 (dd, J = 10.1, 4.9 Hz, 1 H), 2.52 (sextet, J = 3.3 Hz, 2 H), 2.15-1.94 (m, 1 H), 1.80-1.07 (m, 21 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 15 lines at δ: 205.6 (s), 169.9 (s), 57.1 (d, J = 130.6 Hz), 51.9 (q, J = 146.9 Hz), 39.7 (t, J = 124.5 Hz), 27.7, 25.9, 25.7, 25.3, 25.1, 24.6, 24.5, 24.4, 24.2, 21.5. The IR spectrum (neat) showed bands at: 2930 (vs), 2859 (m), 1745 (s), 1713 (s), 1462 (m), 1246 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 268 (M^+, 9.9), 237 (M^+-MeO, 8.9), 208 (M^+-MeOH-CO, 3.2), 98 (100). Exact mass calc'd for $C_{16}H_{28}O_3$ (M^+): 268.2038. Found: 268.2038.

Methyl 1-Iodomethyl-2-oxocyclotetradecanoate (8). A solution of 0.456 g (1.7 mmoles) of methyl 2-oxocyclotetradecanoate (**7**) in 4.5 mL of dry THF was added slowly to a suspension of 0.082 g of NaH (2.0 mmoles, 60% suspension in mineral oil) in 4.5 mL of THF containing 1.2 mL (6.8 mmoles) of HMPA at room temperature under argon. The reaction mixture was stirred at room temperature for 1 hr, followed by addition of 0.273 mL (3.4 mmoles) of diiodomethane. The reaction mixture was heated at reflux for 24 hr and then cooled to room temperature. After standard aqueous workup, column chromatography of the resulting crude product on 80 g of silica gel (elution with 10:1 *n*-hexane-ethyl acetate) gave 0.228 g (33%) of **8** as a colorless oil, R_f 0.58 (10:1 *n*-hexane-ethyl acetate). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.76 (s, 3 H), 3.72 (d, J_{AB} = 10.6 Hz, 1 H), 3.45 (d, J_{AB} = 10.5 Hz, 1 H), 2.75 (m, 1 H), 2.25-2.00 (m, 4 H), 1.57-1.21 (m, 17 H). The IR spectrum (neat) showed bands at: 2930 (vs), 2860 (s), 1746 (vs, CO, ester), 1712 (vs, CO, ketone), and 1462 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 377 (M^+-OMe, 1), 281 (M^+-I, 9), 249 (M^+-I-MeOH, 10). Exact mass calc'd for $C_{16}H_{26}IO_2$ (M^+-OMe): 377.0978. Found: 377.0977.

Reaction of Methyl 1-Iodomethyl-2-oxocyclotetradecanoate (8) with Tri-*n*-butyltin Hydride and AIBN. A solution of tri-*n*-butyltin hydride (0.148 mL, 0.53 mmoles) and AIBN (0.020 g, 0.116 mmoles) in 25 mL of benzene was added dropwise over 5 hr to a refluxing solution of methyl 1-iodomethyl-2-oxocyclotetradecanoate (**8**) (0.123 g, 0.296 mmoles) in 50 mL of benzene. After heating at reflux for an additional 5 hr, the reaction was cooled to room temperature and concentrated. Following standard aqueous workup, flash column chromatography (elution with 10:1 *n*-hexane-ethyl acetate) of the crude product on a 0.7" x 6" column of silica gel afforded 0.042 g (50%) of the ring expansion product, methyl 3-oxocyclopentadecanoate (**9**) as a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) of **9** showed peaks at δ: 3.68 (s, 3 H), 2.96-2.90 (m, 1 H), 2.80 (dd, J_{AB} = 17.7, J_{AX} = 5.4 Hz, 1 H), 2.72 (dd, J_{AB} = 17.7, J_{BX} = 6.8 Hz, 1 H), 2.56-2.47 (m, 1 H), 2.39-2.30 (m, 1 H), 1.74-1.27 (m, 22 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 14 lines at δ: 209.4 (s), 175.6 (s), 51.5 (q, J = 145.5 Hz), 43.1 (t, J = 126.0 Hz), 41.8 (t, J = 125.3 Hz), 38.7 (d, J = 129.8 Hz), 30.1 (t, J = 128.5 Hz), 27.5, 26.6 (overlapped), 26.4 (overlapped), 26.1, 25.8, 24.8, 23.5. The IR spectrum (neat) showed bands at: 2928 (vs), 2857 (vs), 1738 (vs, CO, ester), 1715 (vs, CO, ketone), 1435 (m), 1262 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 282 (M^+ 0), 250 (M^+-CH_3OH, 9), and 222 (M^+-MeOH-CO, 6). Exact mass calc'd for $C_{17}H_{30}O_3$ (M^+): 282.2195. Found: 282.2193.

Methyl 2-Oxocyclopentadecanoate (10). A solution of 1.68 g (7.5 mmoles) of cyclopentadecanone (Aldrich) in 5 mL of benzene was added dropwise over 4 hr to a refluxing slurry of 0.720 g (15.0 mmoles) of NaH (60% dispersion in mineral oil) and 1.26 mL (15.0 mmoles) of dimethyl carbonate in 20 mL of benzene. After further heating at reflux for 1 hr, the reaction mixture was cooled to room temperature. After standard aqueous workup, flash column chromatography of 1.75 g of the crude product on 4.5" x 6" column of silica gel (10:1 *n*-hexane-ethyl acetate) gave 0.824 g (39%) of **10** as a colorless oil, R_f 0.35 (10:1 *n*-hexane-ethyl acetate). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.70 (s, 3 H), 3.54 (dd, J = 9.2, 4.4 Hz, 1 H), 2.55 (t, J = 7.0 Hz, 2 H), 2.00-1.60 (m, 5 H), 1.45-1.18 (m, 19 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 13 lines at δ: 205.5 (s), 169.5 (s), 57.4 (d, J = 129.0 Hz), 51.6 (q, J = 153.7 Hz), 41.0 (t, J = 124.5 Hz), 27.5, 26.9, 26.6, 26.4, 26.1, 25.9, 25.7, 22.2 (t, J = 126.0 Hz). The IR spectrum (neat) showed bands at: 2928 (vs), 2857 (s), 1750 (vs), 1713 (vs), 1460 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 282 (M^+, 3.8), 251 (M^+-OMe, 3.1), 224 (M^+-MeOH-CO, 2.0), 134 (100). Exact mass calc'd for $C_{17}H_{30}O_3$ (M^+): 282.2195. Found: 282.2195.

Methyl 1-Iodomethyl-2-oxocyclopentadecanoate (11). A solution of 0.282 g (1.0 mmoles) of methyl 2-oxocyclopentadecanoate (10) in 5 mL of dry THF was added slowly to a suspension of 0.048 g of NaH (1.2 mmoles, 60% suspension in mineral oil) in 30 mL of THF containing 0.7 mL (4.0 mmoles) of HMPA at room temperature under argon. The reaction mixture was stirred at room temperature for 3 hr, followed by addition of 0.53 g (2.0 mmoles) of diiodomethane. The reaction mixture was heated at reflux for 28 hr and cooled to room temperature. After standard aqueous workup, column chromatography (elution with 3:2 dichloromethane-*n*-hexane) of the crude product on a 1" x 6" flash column gave 0.088 g (21%) of the title compound **11** as a colorless oil, R_f 0.55 (3:2 dichloromethane-*n*-hexane). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.77 (s, 3 H), 3.64 (d, J_{AB} = 10.5 Hz, 1 H), 3.50 (d, J_{AB} = 10.5 Hz, 1 H), 2.71-2.62 (m, 1 H), 2.31-2.20 (m, 1 H), 2.10-2.00 (m, 2 H), 1.78-1.67 (m, 2 H), 1.56-1.08 (m, 22 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 16 lines at δ: 204.9 (s), 170.9 (s), 64.4(s), 52.9 (q, J = 146.3 Hz), 38.3 (t, J = 124.5 Hz), 32.4 (t, J = 128.5 Hz), 27.7, 27.2 (overlapped), 26.9, 26.4, 26.1, 25.9, 25.8, 22.6 (t, J = 125.3 Hz), 21.5 (t, J = 126 Hz), and 7.8 (t, J = 155.3 Hz, -CH_2I). The IR spectrum (neat) showed bands at: 2927 (vs), 2856 (vs), 1748 (s, CO, ester), 1712 (vs, CO, ketone), and 1252 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 391 (M^+-OMe, 4.5), 295 (M^+-I, 40), 263 (M^+-I-MeOH, 80). Exact mass calc'd for $C_{17}H_{28}IO_2$ (M^+-OMe): 391.1134. Found: 391.1135.

Reaction of Methyl 1-Iodomethyl-2-oxocyclopentadecanoate (11) with Tri-*n*-butyltin Hydride and AIBN. A solution of tri-*n*-butyltin hydride (0.034 mL, 0.3 mmoles) and AIBN (0.005 g, 0.029 mmoles) in 6 mL of benzene was added dropwise over 6 hr to a refluxing solution of methyl 1-iodomethyl-2-oxocyclopentadecanoate (11) (0.029 g, 0.063 mmoles) in 7 mL of benzene. After heating at reflux for an additional 16 hr, the reaction was cooled to room temperature and concentrated. Following standard aqueous workup, column chromatography (elution with 6:1 *n*-hexane-ethyl acetate) of the crude product on 2 g of silica gel afforded 0.012 g (67%) of the rearrangement product, methyl 3-oxocyclohexadecanoate (12) as a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) of **12** showed peaks at δ: 3.68 (s, 3 H), 2.99-2.91 (m, 1 H), 2.78 (dd, J_{AB} = 17.6, J_{AX} = 5.9 Hz, 1 H), 2.69 (dd, J_{AB} = 17.6, J_{BX} = 7.2 Hz, 1 H), 2.56-2.46 (m, 1 H), 2.39-2.30 (m, 1 H), 1.77-1.06 (m, 27 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 15 lines at δ: 209.4 (s), 175.9 (s), 51.8 (q, J = 145.5 Hz), 43.2 (t, J = 122.3 Hz), 42.2 (t, J = 125.3 Hz), 39.0 (d, J = 127.5 Hz), 30.4 (t, J = 127.5 Hz), 27.5, 27.1, 26.9, 26.8, 26.7, 26.5, 26.4, 25.29, 23.7 (t, J = 126.8 Hz). The IR spectrum (neat) showed bands at: 2929 (vs), 2858 (vs), 1738 (vs, CO, ester), 1714 (vs, CO, ketone), 1461 (m), 1261 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 296 (M^+, 13), 264

(M^+-CH_3OH, 28), 237 (M^+-COOMe, 7). Exact mass calc'd for $C_{18}H_{32}O_3$ (M^+): 296.2351. Found: 296.2351.

B. Application of Three-Carbon Ring-Expansion of Cyclododecanone to the Synthesis of Muscone

Approach A: From 2-Methoxycarbonylcyclododecanone

Methyl 1-(2'-Methyl-2'-propenyl)-2-oxocyclododecanoate (13). A solution of 0.120 g (0.5 mmoles) of methyl 2-oxocyclododecanoate (2) in 3 mL of dry THF was added dropwise over 30 min to a suspension of 0.02 g of NaH (0.5 mmoles, 60% suspension in mineral oil) in 10 mL of THF containing 0.043 mL (0.5 mmoles) of HMPA at room temperature under argon. The reaction mixture was stirred at room temperature for 1 hr, then 0.091 g (1.0 mmoles) of 3-chloro-2-methylpropene was added. The reaction mixture was heated at reflux for 12 hr, cooled to room temperature and poured into 200 mL of ether. The organic layer was washed sequentially with 5% sodium thiosulfate (20 mL) and water (5 x 25 mL), dried over K_2CO_3, filtered, and concentrated to 0.220 g of a brown oil. Flash column chromatography on a 0.8" x 6" column of silica gel (elution with 10:1 *n*-hexane-ethyl acetate) gave 0.111 g (75%) of 13. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 4.82 (s, 1 H), 4.70 (s, 1 H), 3.71 (s, 3 H), 2.96-2.86 (m, 1 H), 2.62 (s, 2 H), 2.16-2.02 (m, 3 H), 1.91-1.79 (m, 1 H), 1.63 (s, 3 H), 1.51-1.10 (m, 15 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 18 lines at δ: 206.3 (s), 173.7 (s), 141.4 (s), 114.7 (t, J = 154.6 Hz), 62.9 (s), 52.1 (q, J = 147.0 Hz), 38.2 (t, J = 127.6 Hz), 33.9 (t, J = 124.0 Hz), 29.3, 26.7, 26.4, 23.5, 23.2, 22.7, 22.2, 22.1, 21.5, 19.2. The IR spectrum (neat) showed bands at: 2932 (m), 2865 (m), 1742 (w), 1732 (w), 1711 (vs), 1470 (w), and 1242 (w). The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 294 (M^+, 30), 262 (M^+-MeOH, 20), 234 (M^+-MeOH-CO_2, 48), 141 (100) cm^{-1}. Exact mass calc'd for $C_{18}H_{30}O_3$ (M^+): 294.2195. Found: 294.2195.

Methyl 1-(3'-Bromo-2'-methylpropyl)-2-oxocyclododecanoate (14). A solution of methyl 1-(2'-methyl-2'-propenyl)-2-oxocyclododecanoate (13) (0.170 g, 0.578 mmoles) in 390 mL of pentane was placed in a photochemical reaction vessel fitted with a quartz, immersion-well and flushed with argon for 5 min. Gaseous HBr was passed through the solution for 15 min, while the solution was irradiated with light from a Hanovia 450-W medium-pressure mercury lamp. During the irradiation, the reaction temperature was kept at around 0 °C by circulating ice-water through the immersion-wall. The resulting light brown reaction mixture was flushed with argon to remove most of the HBr. The organic layer was washed with 5% $Na_2S_2O_3$ (3 x 5 mL), dried over K_2CO_3, filtered, and concentrated *in vacuo* to 0.80 g of a dark brown oil. Flash column chromatography of the crude product on a 0.8" x 6" column of silica gel (elution with 10:1 *n*-hexane-ethyl acetate) afforded 0.036 g (17%) of the fast moving diastereomer of the title compound 14 and 0.079 g (37%) of a mixture of two diastereomers of 14. The 300 MHz proton nmr spectrum ($CDCl_3$) of the fast moving diastereomer of 14 showed peaks at δ: 3.73 (s, 3 H), 3.35

(dd, J = 9.8, 3.5 Hz, 1 H), 3.21 (dd, J = 9.8, 5.9 Hz, 1 H), 2.95-2.80 (m, 1 H), 2.26-1.64 (m, 8 H), 1.45-1.10 (m, 14 H), 1.04 (d, J = 6.3 Hz, 3 H). The IR spectrum (neat) showed bands at: 2932 (s), 2865 (m), 1734 (m), 1711 (vs), 1469 (m), and 1229 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 374, 372 (M^+, 2), 343, 341 (M^+-MeO, 1.5), 315, 313 (M^+-CO_2Me, 1.7), 295 (M^+-Br, 60).

Methyl 1-(3'-Iodo-2'-methylpropyl)-2-oxocyclododecanoate (15). A solution of methyl 1-(3'-bromo-2'-methylpropyl)-2-oxocyclododecanoate (14) (0.370 g, 0.98 mmoles) and 0.325 g (2.16 mmoles) of sodium iodide in 2.5 mL of acetone was heated at reflux for 17 hr. The precipitate of sodium bromide was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The resulting dark brown oil was treated with 100 mL of ether, washed with 5% sodium thiosulfate (3 x 5 mL), dried over anhydrous potassium carbonate and filtered. The filtrate was concentrated to 0.298 g of a light brown oil. Flash column chromatography on a 0.8" x 6" column of silica gel (elution with 2:3 *n*-hexane-ethyl acetate) afforded 0.213 g (50%) of the mixture of the fast and slow moving diastereomers **15** and 0.322 g (8%) of the pure, slow moving diastereomer of **15**. The 300 MHz proton nmr spectrum ($CDCl_3$) of the slow moving diastereomer of **15** showed peaks at δ: 3.72 (s, 3 H), 3.16 (dd, J = 9.7, 5.3 Hz, 1 H), 3.11 (dd, J = 9.7, 6.2 Hz, 1 H), 2.96-2.84 (m, 1 H), 2.19-2.04 (m, 4 H), 1.88-1.71 (m, 3 H), 1.50-1.06 (m, 15 H), 0.88 (d, J = 6.3 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 18 lines at δ: 206.1 (s), 174.2 (s), 62.2 (s), 52.3 (q, J = 147.8 Hz), 36.6 (t, J = 130.4 Hz), 33.7 (t, J = 125.7 Hz), 31.3 (d, J = 124.3 Hz), 29.2 (t, J = 125.8 Hz), 26.7, 26.4, 23.5, 22.7, 22.1, 21.9, 21.5, 20.3, 19.3, 17.8 (t, J = 140.3 Hz). The IR spectrum (neat) showed bands at: 2934 (s), 2865 (m), 1740 (m), 1711 (vs), 1470 (m), and 1223 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 422 (M^+, 11), 391 (M^+-MeO, 2), 363 (M^+-CO_2Me, 2.5), 295 (M^+-I, 100). Exact mass calc'd for $C_{18}H_{31}IO_3$ (M^+): 422.1318. Found: 422.1320.

Reaction of Methyl 1-(3'-Iodo-2'-methylpropyl)-2-oxocyclododecanoate (15) with Tri-*n*-butyltin Hydride and AlBN. Formation of the Ring-Contraction Product, 2-(1'-Methoxycarbonyl-3'-methylbutyl)cyclo-undecanone (16). A solution of tri-*n*-butyltin hydride (0.280 mL, 1.034 mmoles) and AlBN (0.02 g) in 30 mL of benzene was added dropwise over 17 hr to a refluxing solution of methyl 1-(3'-iodo-2'-methylpropyl)-2-oxocyclododecanoate (15) (0.196 g, 0.47 mmoles) in 90 ml of benzene. After further heating at reflux for 1 hr, the reaction was cooled to room temperature and concentrated *in vacuo*. Following standard aqueous workup, flash column chromatography (elution with 10:1 *n*-hexane-ethyl acetate) of the crude product on a 0.7" x 6" column afforded 0.017 g (12%) of the reduced product, methyl 1-(2'-methylpropyl)-2-oxocyclododecanoate (17), 0.032 g (23%) of a mixture of **17** and the fast moving diastereomer of **16** in a ratio of 16:36, 0.016 g (11%) of a mixture of the fast and slow moving diastereomers of **16** , and 0.011 g (8%) of the pure, slow moving diastereomer of **16**. Rechromatography of 0.032 g of the contaminated fast moving diastereomer on 2 g of silica gel (elution with 10:1 *n*-hexane-ethyl acetate) provided 0.0164 g of the pure fast moving diastereomer of **16**. The ^{1}H nmr, ^{13}C nmr, IR, and mass spectra of the reduced product **17** and the two diastereomers of the one-carbon ring-contracted compound **16** were in good agreement with those of authentic samples (*vide infra*).

Preparation of Authentic Samples

(a) Authentic Reduced Product; Methyl 1-(2'-Methylpropyl)-2-oxocyclododecanoate

Methyl 1-(2'-Methylpropyl)-2-oxocyclododecanoate (17). A mixture of methyl 1-(2'-methyl-2'-propenyl)-2-oxocyclododecanoate (**13**) (0.06 g, 0.20 mmoles) and 0.01 g of 10% palladium on carbon in 20 mL of methanol was stirred under an atmosphere of hydrogen at room temperature for 17 hr. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to 0.058 g (96%) of **17**, a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.69 (s, 3 H), 2.94-2.85 (m, 1 H), 2.13-2.02 (m, 4 H), 1.96-1.81 (m, 3 H), 1.73-1.49 (m, 2 H), 1.44-1.03 (m, 13 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.76 (d, J = 6.4 Hz, 3 H). The IR spectrum (neat) showed bands at: 2950 (s), 2868 (w), 1742 (w), 1712 (vs), 1470 (w), and 1220 (w) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 296 (M^+, 0.5), 265 (M^+-MeO, 1.3), 264 (M^+-MeOH, 1.5), 240 (M^+-isobutene, 100). Exact mass calc'd for $C_{18}H_{32}O_3$ (M^+): 296.2351. Found: 296.2356.

(b) Authentic Ring-Contraction Product; 2-(1'-Methoxy-carbonyl-3'-methylbutyl)cycloundecanone (16)

Methyl 2-Bromo-4-methylpentanoate (18). To a mixture of 2.32 g (20 mmoles) of 4-methylpentanoic acid (Aldrich) and 1.95 mL (21 mmoles) of phosphorus tribromide, dry bromine (2.1 mL, 40 mmoles) was added dropwise over 10 min. The reaction was heated to 80 °C for 1.5 hr. An additional 0.5 mL (9.5 mmoles) of bromine was added and heating at 80 °C was continued for 18 hr. The reaction was cooled to room temperature; 8 mL (200 mmoles) of methanol was added dropwise over 15 min at such a rate that the exothermic reaction was controlled. The resulting pale-orange reaction mixture was heated at reflux for 30 min, cooled, and diluted with 20 mL of ice water. The product was extracted with ether (4 x 20 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo* to 4.2 g (96%) of **18**. This crude product was used in the next step without further purification. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 4.28 (t, J = 7.6 Hz, 1 H), 3.78 (s, 3 H), 1.91 (dt, J = 7.6, 7.5 Hz, 2 H), 1.83-1.71 (m, 1 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H). The IR spectrum (neat) showed bands at: 2960 (s), 2873 (m), 1746 (vs), 1438 (m), and 1282 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 177, 179 (M^+-MeO, 2.5), 165, 167 (M^+-$CHMe_2$, 6.2), 152, 154 (M^+-isobutene, 100). Exact mass calc'd for $C_6H_{10}{}^{79}BrO$ (M^+-MeO): 176.9915. Found: 176.9911.

2-(1'-Methoxycarbonyl-3'-methylbutyl)cycloundecanone (16). A solution of 0.336 g (2 mmoles) of cycloundecanone (Aldrich) in 2 mL of THF was added dropwise over 15 min to a solution of lithium diisopropylamide (LDA) (1.5 M in *n*-hexane) (1.7 mL, 2.6 mmoles) in 2.0 mL of THF at -78 °C under argon. The resulting solution was stirred for 1.5 hr, then a solution of methyl 2-bromo-4-methylpentanoate (**18**) (0.624 g, 3.0 mmoles) and HMPA (0.160 mL) in 2 mL of THF was added. The reaction mixture was allowed to warm to room temperature over 3 hr then stirred at room temperature for 12 hr. The reaction mixture was poured into 100 mL of ether, washed with water (5 x 10 mL), dried over K_2CO_3, filtered, and evaporated *in vacuo* to 0.650 g of a brown oil. Flash column chromatography (elution with 6:1 *n*-hexane-ether) of the crude product on a 1.5" x 6" flash column afforded 0.057 g of the mixture of the starting bromoester **18** and the fast moving diastereomer of the title compound **16** in a ratio of 1:1 together with 0.117 g of the mixture of the starting ketone and the fast moving diastereomer of **16** in a ratio of 2:1, and finally 0.092 g (8%) of the mixture of the starting ketone and the slow moving diastereomer of **16** in a ratio of 3:4. Rechromatography on 2 g of silica gel (elution with 7:1 *n*-hexane-ether) of 0.080 g of the fast moving diastereomer of **16** contaminated with the starting ketone afforded 0.003 g of pure, fast moving diastereomer of **16** along with 0.059 g of impure, fast moving diastereomer of **16**. Rechromatography on 2 g of silica gel (elution with 10:1 *n*-hexane-ether) of 0.092 g of the slow moving diastereomer of **16** contaminated, with the starting ketone, afforded 0.010 g of the the pure, slow moving diastereomer of **16**, along with 0.055 g of impure, slow moving diastereomer of **16**.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the fast moving diastereomer of **16** showed peaks at δ: 3.69 (s, 3 H), 2.88-2.70 (m, 3 H), 2.34 (ddd, J = 16.6, 7.5, 3.3 Hz, 1 H), 1.96-1.76 (m, 1 H), 1.76-1.23 (m, 19 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 16 lines at δ: 214.8 (s), 175.6 (s), 55.1 (d, J = 132.1 Hz), 51.5 (q, J = 146.5 Hz), 46.6 (d, J = 135.7 Hz), 42.7 (t, J = 124.7 Hz), 40.4 (t, J = 126.3 Hz), 28.5, 26.6, 25.5, 25.3, 24.7, 24.5, 23.7, 22.0, 21.2. The IR spectrum (neat) showed bands at: 2935 (s), 2870 (m), 1737 (vs), 1708 (s), 1471 (w), 1440 (w), and 1163 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 296 (M^+, 4), 265 (M^+-MeO, 16), 264 (M^+-MeOH, 20), 237 (M^+-COOMe, 7.5), 168 (M^+-$Me_2CHCH_2CH_2COOMe$, 80). Exact mass calc'd for $C_{18}H_{32}O_3$ (M^+): 296.2351. Found: 296.2357.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the slow moving diastereomer of **16** showed peaks at δ: 3.64 (s, 3 H), 2.90-2.86 (m, 1 H), 2.83-2.70 (m, 2 H), 2.28 (ddd, J = 16.6, 7.4, 3.0 Hz, 1 H), 1.91-1.86 (m, 1 H), 1.76-1.26 (m, 19 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 18 lines at δ: 215.4 (s), 176.6 (s), 54.5 (d, J = 130.8 Hz), 51.6 (q, J = 147.3 Hz), 43.8 (d, J = 134.0 Hz), 41.7 (t, J = 124.6 Hz), 39.1 (t, J = 123.4 Hz), 26.1, 26.0, 25.8, 25.7, 25.4, 25.2, 23.9, 23.6, 23.1, 22.2, 21.3. The IR spectrum (neat) showed bands at: 2930 (vs), 2869 (s), 1732 (vs), 1709 (vs), 1470 (m) and 1170 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 296 (M^+, 8), 265 (M^+-MeO, 21), 264 (M^+-MeOH, 24), 237 (M^+-COOMe, 9), 168 (M^+-$Me_2CHCH_2CH_2COOMe$, 88). Exact mass calc'd for $C_{18}H_{32}O_3$ (M^+): 296.2351. Found: 296.2357.

Approach B. From Cyclododecanone

(A) Synthesis of (±)-Muscone

1-(2'-Methyl-2'-propenyl)cyclododecanone (24). A solution of 1.32 g (7.5 mmoles) of cyclododecanone (1) in 30 mL of dry THF was added dropwise over 30 min to a suspension of 0.36 g of NaH (9.0 mmoles, 60% suspension in mineral oil) in 90 mL of THF containing 0.73 mL (9 mmoles) of HMPA at room temperature under argon. The reaction mixture was heated at reflux for 20 min, then 1.4 mL (15.0 mmoles) of 3-chloro-2-methylpropene and 3.6 g (24 mmoles) of dry sodium iodide were added. The reaction mixture was heated at reflux for 4 hr and poured into 200 mL of ether. The organic layer was washed sequentially with 5% sodium thiosulfate (20 mL) and water (5 x 15 mL), dried over K_2CO_3, filtered, and concentrated to 1.5 g of a brown oil. Flash column chromatography on a 3.5" x 6" column of silica gel (elution with 10:1 dichloromethane-*n*-hexane) gave 0.964 g (54%) of **24**. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 4.75 (s, 1 H, vinyl H), 4.67 (s, 1 H, vinyl H), 2.77 (m, 1 H), 2.6-2.4 (m, 2 H), 2.31 (dd, J = 14.2, 7.7 Hz, 1 H), 2.08 (dd, J = 14.2, 7.2 Hz, 1 H), 1.7 (s, 3 H, Me), 1.82-1.15 (m, 21 H). The IR spectrum (neat) showed bands at: 2932 (vs), 2864 (vs), 1705 (s, CO, ketone), and 1469 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 236 ($M^{+\cdot}$ 55) and 181 (M^{+}-CH_2=CH(Me)CH_2, 10). Exact mass calc'd for $C_{16}H_{28}O$ ($M^{+\cdot}$ 55): 236.2140. Found: 236.2140.

1-(3'-Bromo-2'-methylpropyl)cyclododecanone (25). A solution of 1-(2'-methyl-2'-propenyl)cyclododecanone (24) (0.777 g, 3.29 mmoles) in 700 mL of pentane was placed in a quartz, immersion-well, photochemical reaction vessel and flushed with argon for 5 min. Then, gaseous HBr was passed through the solution for 5 min, while it was irradiated with the light from a Hanovia 450-W medium-pressure mercury lamp. During irradiation, the reaction temperature was kept around 0 °C by circulating ice-water through the immersion-well jacket. The resulting light brown reaction mixture was flushed with argon to remove the remaining HBr.

The organic layer was washed with 5% $Na_2S_2O_3$ (3 x 5 mL), dried over K_2CO_3, filtered and concentrated to 1.067 g of a dark brown oil. Column chromatography of the crude product on 60 g of silica gel (elution with 2:3 *n*-hexane-dichloromethane) afforded 0.803 g (77%) of **25**. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.36-3.32 (m, 2 H, -CH_2Br), 2.7-2.4 (m, 2 H), 2.0-1.15 (m, 24 H), 1.00 (d, J = 6.52 Hz, 3 H), 0.99 (d, J = 6.54 Hz, 3 H). The IR spectrum (neat) showed bands at: 2935 (vs), 2928 (vs), 2864 (vs), 1709 (s, CO, ketone), 1704 (s, CO, ketone), and 1469 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 318, 316 (M^+ 10) and 237 (M^+-Br, 100). Exact mass calc'd for $C_{16}H_{29}O^{79}Br$ (M^+): 316.1402. Found: 316.1401.

1-(3'-Iodo-2'-methylpropyl)cyclododecanone (26). A solution of 1-(3'-bromo-2'-methylpropyl)cyclododecanone (25) (0.717 g, 2.26 mmoles) and 0.975 g (6.48 mmoles) of sodium iodide in 7.5 mL of acetone was heated at reflux for 5 hr. The precipitate of sodium bromide was filtered, and the filtrate was concentrated under vacuum to dryness. The residue was treated with 100 mL of ether, washed with 5% sodium thiosulfate (3 x 5 mL), dried over anhydrous potassium carbonate and filtered. The filtrate was concentrated to 0.797 g of a light brown oil. Column chromatography of the crude product on 60 g of silica gel (elution with 2:3 *n*-hexane-dichloromethane) afforded 0.616 g (75%) of **26** as a light brown oil. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.23-3.12 (m, 2 H, -CH_2I), 2.7-2.35 (m, 3 H), 1.9-1.15 (m, 21 H), 0.95 (d, J = 6.1 Hz, 3 H), 0.93 (d, J = 5.9 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 23 lines at δ: 213 (s), 49.3 (d, J = 127.5), 49.2 (d, J = 127.5), 37.5, 36.8, 36.3, 31.9, 29.6, 29.2, 25.9, 25.6, 25.5, 23.7, 23.2, 23.1, 22.9, 22.8, 22.2, 21.9, 21.5, 20.7, 20.3, 17.3 (t, J = 150.2 Hz, -CH_2I). The IR spectrum (neat) showed bands at: 2930 (vs), 2864 (m), 1705 (s, CO, ketone), and 1468 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 364 (M^+ 17.2), 336 (M^+-CO, 1.6), and 237 (M^+-I, 100). Exact mass calc'd for $C_{16}H_{29}OI$ (M^+): 364.1263. Found: 364.1263.

(±)-Muscone: Reaction of 1-(3'-Iodo-2'-methylpropyl)-cyclododecanone (26) with Tri-*n*-butyltin Hydride and AIBN. A solution of tri-*n*-butyltin hydride (0.106 mL, 0.39 mmoles) and AIBN (0.012 g, 0.07 mmoles) in 30 mL of *tert*-butylbenzene was added dropwise over 3 hr to a refluxing solution of 1-(3'-iodo-2'-methylpropyl)cyclododecanone (**26**) (0.110 g, 0.302 mmoles) in 160 mL of *tert*-butylbenzene. After heating at reflux for an additional 1 hr, the reaction was cooled to room temperature and concentrated under high vacuum. Following standard aqueous workup, flash column chromatography (elution with 10:1 *n*-hexane-ether) of the crude product on a 0.7" x 6" column of silica gel afforded 0.0091 g (14%) of (±)-muscone ((±)-**27**) and 0.0412 g (63%) of the reduced product, 1-(2'-methylpropyl)cyclododecanone (**28**) as colorless oils of R_f 0.42 and 0.53 (10:1 *n*-hexane-ether), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of (±)-muscone ((±)-**27**) showed peaks at δ: 2.45-2.38 (m, 3 H), 2.18 (dd, J_{AB} = 15.0, 5.1 Hz, 1 H), 2.04 (m, 1 H), 1.60 (m, 2 H), 1.50-1.10 (m, 20 H), 0.94 (d, J = 6.7 Hz, -$CHCH_3$, 3 H), in good agreement with the reported spectrum[1]. The IR spectrum (neat) showed bands at 2926 (vs), 2855 (s), 1713 (m, CO, ketone), and 1462 (m) cm^{-1}: The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 238 (M^+ 22), 223, 209, 195, 182, 125, 55. Exact mass calc'd for $C_{16}H_{30}O$ (M^+): 238.2297. Found: 238.2297.

The spectral properties (^1H nmr, IR, and mass) of the reduced product were identical to those of an authentic sample (*vide infra*).

1-(2'-Methylpropyl)cyclododecanone (28). A mixture of 1-(2'-methylpropenyl)cyclododecanone (**24**) (0.065 g, 0.28 mmoles) and Pd/C (10%, 0.010 g) in 20 mL of methanol was stirred under an atmosphere of hydrogen at room temperature for 12 hr. The reaction mixture was filtered through celite and the filtrate was concentrated to 0.035 g (53%) of **28**, a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 2.57-2.7 (m, 1 H), 2.48 (t, J = 6.0 Hz, 2 H), 1.9-1.1 (m, 21 H), 0.88 (d, J = 5.9 Hz, 3 H), 0.86 (d, J = 5.9 Hz, 3 H). The IR spectrum (neat) showed bands at: 2928 (vs), 2864 (m), 2851 (vs), 1704 (s, CO, ketone) and 1469 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 238 (M$^+$, 10), 182 (M$^+$-CH_2=CMe_2, 1.6). Exact mass calc'd for $C_{16}H_{30}O$ (M$^+$): 238.2297. Found: 238.2296.

(B) Synthesis of Naturally Occurring (R)-(-)-Muscone ((-)-27)

(S)-(+)-3-Bromo-2-methyl-1-*tert*-butyldiphenylsilyoxypropane (30). Imidazole (4.8 g, 65.3 mmoles) was added to a solution of (S)-(+)-3-bromo-2-methylpropanol (29) (Aldrich) (5 g, 32.7 mmoles) and *tert*-butylchlorodiphenylsilane (19.6 g, 65.3 mmoles) in 100 mL of dimethylformamide (DMF) at room temperature under argon. The reaction mixture was stirred for 24 hr, poured into 200 mL of ether, washed with brine (3 x 10 mL) and water (3 x 10 mL), dried over anhydrous potassium carbonate, filtered, and evaporated *in vacuo* to 23.2 g of a colorless oil. Flash column chromatography on a 4" x 6" column of silica gel (elution with 5:1 *n*-hexane-ether) provided 14.1 g of 30 as a colorless oil, R$_f$ 0.95 (5:1 *n*-hexane-ether). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 7.72-7.61 (m, 4 H), 7.47-7.35 (m, 6 H), 3.71-3.47 (m, 4 H), 2.11-1.97 (m, 1 H), 1.06 (s, 9 H), 0.99 (d, J = 7.2 Hz, 3 H). The IR spectrum (neat) showed bands at: 3071 (m), 2960 (s), 2858 (s), 1589 (w), 1463 (s), 1427(s), and 1111 (vs) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 333 (M$^+$-*t*-Bu, 20), 263 (50), and 199 (100). Exact mass calc'd for $C_{16}H_{18}OSi^{79}Br$ (M$^+$-*t*-Bu): 333.0312. Found: 333.0317.

2-(3'-*tert*-Butyldiphenylsilyoxy-2'R-methyl-1'-propyl)cyclododecan-one (31). To a suspension of 0.714 g of NaH (18 mmoles, 60 % suspension in mineral oil) in 50 mL of dry THF containing 1.43 mL (18 mmoles) of HMPA at room temperature under argon, a solution of 2.71 g (15.0 mmoles) of cyclododecanone (1) in 40 mL of THF was added dropwise over 1 hr. The reaction mixture was heated at reflux for 20 min, then 6.97 g (18.0 mmoles) of (S)-(+)-3-Bromo-2-methyl-1-*tert*-butyldiphenylsilyoxypropane (30) and 2.68 g of sodium iodide were added. After further heating at reflux for 28 hr, the reaction mixture was cooled to room temperature and poured into 200 mL of ether. The organic layer was washed with water (3 x 10 mL), dried over K_2CO_3, filtered and concentrated *in vacuo*, affording 8.5 g of a brown oil. Flash column chromatography on a 2.0" x 6" column of silica gel (elution with 28:1 *n*-hexane-ether) gave 4.27 g (57%) of the title compound 31 as a colorless oil, consisting of a mixture of epimers R$_f$ 0.42 (28:1 *n*-hexane-ether). The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 7.66-7.63 (m), 7.45-7.28 (m), 3.48-3.42 (m), 2.62-2.34 (m), 1.84-1.09 (m), 1.05 (s, 9 H), 0.91 (d, J = 6.7 Hz, 3 H, from one epimer), 0.90 (d, J = 6.6 Hz, 3 H, from the other epimer). The ^{13}C nmr spectrum ($CDCl_3$) showed 35 lines at δ: 214.7 (s), 214.6 (s), 135.4 (d, J = 164.0 Hz), 133.6 (s), 129.4 (d, J = 158.6 Hz), 127.5 (d, J = 157.5 Hz), 68.5 (t, J = 141.0 Hz), 50.2 (d, J = 129.8 Hz), 49.3 (d, J = 127.3 Hz), 37.02 (t, J = 124.4 Hz), 36.0 (t, J = 123.3 Hz), 35.3, 34.4, 33.8, 33.7, 30.5, 29.4, 26.9, 26.3, 26.2, 25.9, 25.8, 24.1, 23.8, 23.6, 23.5, 23.3, 23.02, 22.5, 22.2, 21.9, 21.8, 19.3, 17.2 (q, J = 124.5 Hz), 16.9 (q, J = 125.1 Hz). The IR spectrum (neat) showed bands at: 3050 (w), 2939 (vs), 2930 (vs), 2862 (vs), 1705 (s), 1470 (m), and 1111 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 492 (M$^+$, 0.13) and 435 (M$^+$-*t*-Bu, 100). Exact mass calc'd for $C_{32}H_{48}O_2Si$ (M$^+$-*t*-Bu): 435.2719. Found: 435.2719.

2-(3'-Hydroxy-2'*R*-methyl-1'-propyl)cyclododecanone (32). A solution of 2-(3'-*tert*-Butyldiphenylsilyoxy-2'*R*-methyl-1'-propyl)cyclododecanone (31) (1.82 g, 3.7 mmoles) in 7.4 mL of a 1 M solution of *n*-Bu_4NF in THF was stirred at room temperature for 3 hr. Thin-layer chromatography indicated that the reaction was complete. The reaction was poured into 200 mL of ether, washed with brine (3 x 10 mL), dried over anhydrous potassium carbonate, filtered, and evaporated to a light pinkish oil. Flash column chromatography on a 2" x 6" column of silica gel (3:2 ether-*n*-hexane) provided 0.325 g (36%) of the impure fast moving diastereomer of 32, 0.028 g (3%) of a mixture of two diastereomers of 32, and 0.192 g (21%) of the slow moving diastereomer of 32 as a colorless oil, R_f 0.3 (2:3 ether-*n*-hexane). The 300 MHz proton nmr spectrum ($CDCl_3$) of the slow moving diastereomer of 32 showed peaks at δ: 3.61 (d, J = 5.5 Hz, 1 H), 3.43 (t, J = 5.5 Hz, 2 H), 2.71-2.57 (m, 2 H), 2.47-2.38 (m, 1 H), 1.73-1.55 (m, 7 H), 1.54-1.04 (m, 13 H), 0.89 (d, J = 7.3 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 16 lines at δ: 215.4 (s), 67.6 (t, J = 141.6 Hz), 49.3 (d, J = 127.4 Hz), 36.7 (t, J = 124.0 Hz), 34.0 (t, J = 125.5 Hz), 33.5 (d, J = 126.9 Hz), 29.3 (t, J = 124.6 Hz), 26.0, 25.7, 23.9, 23.5, 23.1, 22.3, 22.1, 21.8, 16.7 (q, J = 124.6 Hz). The IR spectrum (neat) showed bands at: 3426 (br OH), 2936 (vs), 1703 (s), 1459 (m), and 1041 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 254 (M$^+$, 18), 236 (M$^+$-H_2O, 38), 435 (M$^+$-C_4H_8O, 20). Exact mass calc'd for $C_{16}H_{30}O_2$ (M$^+$): 254.2286. Found: 254.2286.

2-(3'-Iodo-2'*R*-methyl-1'-propyl)cyclododecanone (33). A solution of iodine (0.115 g, 0.46 mmoles) in 4 mL of toluene was added dropwise over 4 min to a stirring solution of 2-(3'-hydroxy-2'*R*-methyl-1'-propyl)cyclododecanone (32) (0.089 g, 0.35 mmoles), chlorodiphenylphosphine (0.081 mL, 0.46 mmoles), and imidazole (0.053 g, 0.77 mmoles) in 2 mL of toluene at room temperature under argon was added dropwise. The reaction was stirred for 5 min. Saturated $NaHCO_3$ (15 mL) was added followed by iodine until the color of the reaction became pink. Then, the organic layer was separated, washed with 10 mL of 5% $Na_2S_2O_3$ and water (10 mL), dried over Na_2SO_4, filtered, and evaporate to a solid. Column chromatography on 2 g of silica gel (elution with 1:1 dichloromethane-n-hexane) provided 0.057 g (45%) 33 as a colorless oil. The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ: 3.20 (dd, J_{AB} = 10.0, J_{AX} = 4.6 Hz, 1 H, $-CH_2I$), 3.16 (dd, J_{AB} = 10.0, J_{BX} = 5.4 Hz, 1 H, $-CH_2I$), 2.66-2.51 (m, 2 H), 2.50-2.37 (m, 1 H), 1.80-1.10 (m, 21 H), 0.95 (d, J = 6.1 Hz, $-CHCH_3$, 3 H). The IR spectrum (neat) showed bands at: 2930 (vs), 2864 (m), 1705 (s, CO, ketone), and 1468 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 364 (M$^+$, 17.2), 336 (M$^+$-CO, 1.6), and 237 (M$^+$-I, 100). Exact mass calc'd for $C_{16}H_{29}OI$ (M$^+$): 364.1263. Found: 364.1263.

R-(-)-Muscone ((–)-27): Reaction of 2-(3'-Iodo-2'*R*-methyl-1'-propyl)cyclododecanone (33) with Triphenyltin Chloride in the Presence of Sodium Cyanoborohydride and *tert*-Butyl Peroxide. Following a modification of Stork's protocol[2], a mixture of 2-(3'-Iodo-2'*R*-methyl-1'-propyl)cyclododecanone (33) (0.340 g, 0.934 mmoles), triphenyltin chloride (0.0018 g, 4.6 x 10^{-3} mmoles), sodium cyanoborohydride (0.121 g, 3.8 mmoles) and *tert*-butyl peroxide in 186 mL of *n*-pentanol was degassed by evacuating and flushing with argon, and the reaction mixture was heated at reflux for 3 hr. At this point, thin-layer chromatographic analysis showed the reaction was not complete. Thus, additional triphenyltin chloride (0.0054 g, 0.014 or 1.4 x 10^{-2} mmoles), sodium cyanoborohydride (0.121 g, 3.8 mmoles) and *tert*-butyl peroxide were added and the reaction was further heated at reflux for 12 hr. Thin-layer chromatographic indicated that all the starting material was consumed at this point. The reaction was concentrated under high vacuum and the resulting crude product was purified by flash column chromatography (2" x 6" column of silica gel, elution with 10:1 *n*-hexane-ether) affording 0.034 g (15 %) of *R*-(-)-muscone ((–)-27) of $[\alpha]_D^{21}$ -10.9 (c 0.0063, CH_3OH), lit. $[\alpha]_D^{25}$ -10.6° (c 1.10, CH_3OH)[3] and -11.7° (c 0.80, CH_3OH)[4]. The spectral properties (^1H nmr, IR, and mass) of *R*-(-)-muscone were identical to those of racemic muscone.

Some (0.135 g, 61%) of the reduced product, 1-(2'-methylpropyl)-cyclododecanone (28) was obtained as a colorless oil, whose spectral properties (^1H nmr, IR, and mass) were identical to those of authentic reduced product **28.**

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