aqueous layer was extracted twice with CH_2Cl_2, the CH_2Cl_2 layers were combined and dried ($MgSO_4$), and the volatiles were removed by rotary evaporation. The resulting light yellow solid was recrystallized from toluene/heptane to give 0.12 g (0.25 mmol, 64%) of crystalline trifluoroacetamide **4**: mp 141–143 °C; IR (Nujol) 1695, 1620, 1510, 1200 cm^{-1}; ^1H NMR δ 1.32–2.32 (br m, 4 H, $-CH_2CH_2-$), 2.52 (d, J = 4 Hz, 2 H, ArCH_2, 3.71 (br t, 2 H, NCH_2), 3.95 (s, 3 H, OCH_3), 4.03 (s, 6 H, OCH_3), 4.10 (s, 3 H, OCH_3), 7.03, 7.31, 7.68, 7.73, and 8.08 (s, 1 H each, Ar H). Anal. Calcd for $C_{25}H_{26}F_3NO_5$: C, 62.89; H, 5.49; N, 2.93. Found: C, 62.96; H, 5.52; N, 2.75.

(*S*)-2-[(2,3,6,7-Tetramethoxyphenanthren-9-yl)methyl]-pyrrolidine (5). Trifluoroacetamide **5** (0.12 g, 0.27 mmol) was dissolved in 15 mL of saturated methanolic ammonia. After 36 h of stirring, the solvent was removed by rotary evaporation to afford a white semisolid residue. To this was added 15 mL of 2 N H_2SO_4, and the mixture was stirred for 15 min. The acid layer was extracted with CH_2Cl_2 and then cooled and made alkaline with aqueous NaOH, and the basic solution was extracted with $CHCl_3$. The organic solution was dried with $MgSO_4$ and concentrated by rotary evaporation to yield 0.85 g (22.3 mmol, 82%) of the desired pyrrolidine, **5**, as a light yellow oil: ^1H NMR δ 136–2.30 (m, 4 H, $-CH_2CH_2-$), 2.40 (d, J = 5 Hz, 2 H, ArCH_2), 3.30 (br t, 2 H, NCH_2), 3.47 (m, 1 H, CH_2CHN), 3.94 and 3.96 (s, 3 H each, OCH_3), 4.04 (s, 6 H, OCH_3), 7.09, 7.35, 7.38, 7.69, and 7.74 (s, 1 H each, Ar H). ^1H NMR analysis using chiral shift reagent tris(di-(+)-camphorylmethanato)europium (Eu(dcm)$_3$)[7] (Alfa) indicated the configurational purity to be 97% *S*; see text.

***S*-(+)-Tylophorine (6).** A solution of 72 mg (0.19 mmol) of amine **5**, 500 μL of EtOH, and 500 μL of 37% formaldehyde was acidified with 40 μL of concentrated aqueous HCl and boiled under reflux for 12 h in the dark. The volatiles were removed by rotary evaporation, and the residue was treated with 20 mL of 10% HCl. The aqueous layer was washed with $CHCl_3$, basified with 28% aqueous ammonia, and extracted with $CHCl_3$. The dried ($MgSO_4$) solution was subjected to rotary evaporation, and the residual solid was recrystallized from $CHCl_3$/MeOH to give 39.6 mg (10 mmol, 53%) of pure **6** as light tan crystals that showed one spot on silica gel TLC using a $CHCl_3$–MeOH (95:5) solvent system: mp 284–286 °C dec when introduced into the melting apparatus preheated to 250 °C (lit. mp 282–284 °C,[4,10] 284–285 °C[12]); IR 1620, 1515, 1210, 1150, 1020, 840 cm^{-1}; ^1H NMR δ 1.40–2.34 (br m, 4 H, $-CH_2CH_2-$), 2.38–2.58 (br m, 2 H, ArCH_2CH), 2.91 (t, 1 H, J = 16 Hz), 3.34 (d, 1 H, J = 16 Hz), 3.43 (t, 1 H, CH_2CHN, J = 7 Hz), 4.03 (s, 6 H, OCH_3), 4.10 (s, 6 H, OCH_3), 4.16 (dd, apparent $\Delta\delta$ = 0.97, J = 14.5 Hz, 2 H, ArCH_2N), 7.14 and 7.29 (s, 1 H each, Ar H), 7.83 (s, 2 H, Ar H); $[\alpha]^{21}_D$ +73° (c 0.7, $CHCl_3$) (see text); UV (Gilford Response, EtOH) λ_{max} (log ϵ) 257 (4.70), 286 (4.42), 339 (3.28), 356 nm (3.19); mass spectrum (Kratos AE1 MS 30, double-focusing, 70 eV), m/z 393.192 (M^+) ($C_{24}H_{27}NO_4$ requires 393.194), 324.107 (retro-Diels–Alder fragmentation).

9-Acetyl-2,3,6,7-tetramethoxyphenanthrene (7). Tetramethoxyphenanthrene **1** (0.10 g, 0.34 mmol) was dissolved in 10 mL of CH_2Cl_2, and 0.030 g (24 μL, 0.33 mmol) of acetyl chloride and 170 μL of $SnCl_4$ were added. The solution was boiled under reflux under N_2 for 4 h, cooled, and treated with 4 N HCl. The organic layer was separated and washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine, and then dried over $MgSO_4$. The CH_2Cl_2 was rotary evaporated to give a brown residue that after recrystallization from CH_2Cl_2/hexane and then Et_2O afforded 0.10 g (0.29 mmol, 85%) of methyl ketone **7** as a white crystalline solid: mp 212–213 °C; IR 1670, 1610, 1050 cm^{-1}; ^1H NMR δ 2.77 (s, 3 H, CH_3CO), 4.02 (s, 6 H, OCH_3), 4.05 and 4.07 (s, 3 H each, OCH_3), 7.18, 7.67, 7.71, 8.12, and 8.48 (s, 5 H each, Ar H). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.21; H, 5.94.

Methyl ketone **7** was synthesized independently by the following method. An ethereal solution of methyllithium (834 μL of a 1.54 M solution) was added dropwise to a vigorously stirred solution of 0.20 g (0.60 mmol) of carboxylic acid **8** in 15 mL of THF at 0 °C for 0.5 h and at room temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution. The aqueous layer was separated and extracted with 3 × 30 mL of CH_2Cl_2. The combined CH_2Cl_2 solution was washed with 5% $NaHCO_3$ and H_2O and then dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent provided a white solid, which was recrystallized from CH_2Cl_2/hexane to afford 0.14 g (0.40 mmol, 67%) of the pure methyl ketone, **7**. The melting point and ^1H NMR spectrum of this ketone were identical with those of the ketone from Friedel–Crafts acetylation of **1**.

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Optical Resolution of 3-Methyl-*N*-phenylglutaramic Acid and Synthesis of Optically Active Muscone

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Several syntheses of racemic muscone have been reported.[1] However, few reports on the successful synthesis of optically active muscone have appeared.[2]

In this paper we describe the resolution of 3-methyl-*N*-phenylglutaramic acid (**1**) and the synthesis of optically active (*R*)-(−)-muscone starting from both *S* and *R* enantiomers of **1**.

Racemic **1** was prepared in a good yield from aniline and 3-methylpentanedioic anhydride,[3] which was obtained in four steps starting from ethyl cyanoacetate (Scheme I).

In preliminary experiments on the resolution of **1**, using synthetic resolving agents such as α-methylbenzylamine (MBA), 1-naphthylethylamine, 1-phenyl-2-*p*-tolylethylamine, and *cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine, it was noted that MBA was the most effective.

Compound **1** is asymmetric only by differentiation of the carboxymethyl groups around the central carbon atom which suggested the possibility of applying the "meso trick" technique[4] to the preparation of (−)-muscone from optically active **1**.

The synthesis of (*R*)-(+)-diethyl 3-methylhexadecadioate (**12**), one of the key compound for the preparation of (*R*)-(−)-muscone, was carried out by the two routes depicted in Scheme II.

Dieckmann cyclization of (+)-**12** followed by decarboxylation afforded (*R*)-(−)-muscone in 32% yield. The spectral data and the value and the sign of rotation of (−)-muscone obtained were in good agreement with those of the literature.[2b]

Experimental Section

General Methods. Melting points and boiling points were uncorrected. The IR spectra were recorded on a JASCO IR-2A spectrometer. The NMR spectra were determined with JEOL FX90Q and JEOL 60Si spectrometers by using Me_4Si as the internal standard. The optical rotations were measured with a JASCO DIP-360 polarimeter. 3-Methylpentanedioic acid was

(1) (a) Tsuji, J.; Yamada, T.; Shimizu, I. *J. Org. Chem.* **1980**, *45*, 5209. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (c) Taechachoonhakit, S.; Ratananukul, P. *Chem. Lett.* **1986**, 911.

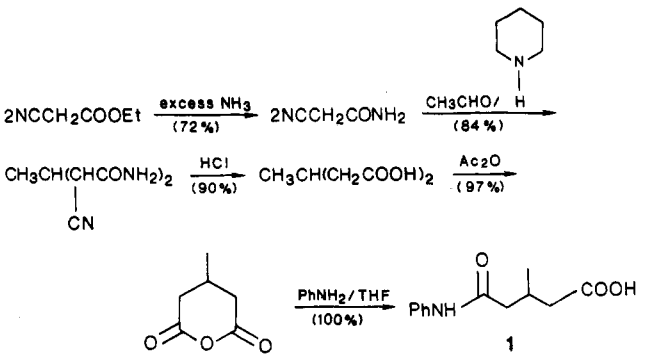
(2) (a) Uchimoto, K.; Tanaka, M.; Kita, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2301. (b) Branca, Q.; Fischli, A.; *Helv. Chim. Acta* **1977**, *60*, 925. (c) Stallberg-Stenhangen, S. *Arkiv Kemi* **1951**, *3*, 517.

(3) (a) Cason, J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 630. (b) Kent, R. E.; McElvain, S. M. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 591.

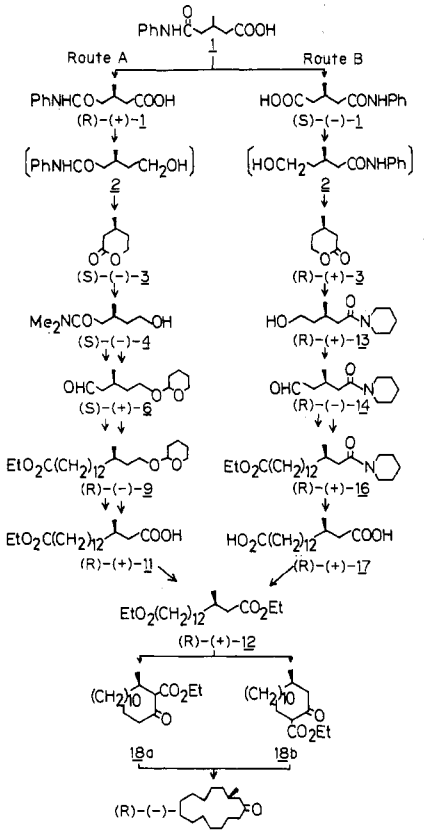
(4) Seebach, D.; Hangerbuhler, E. *Modern Synthetic Methods* **1980**; Salle and Sauerlander: Frankfurt and Main.

0022-3263/87/1952-1630$01.50/0

Scheme I



Scheme II



prepared from ethyl cyanoacetate by a slightly modified procedure described in *Organic Syntheses*[3] (overall yield 53%).

3-Methyl-*N*-phenylglutaramic Acid (1). To a solution of 3-methylpentanedioic anhydride (68.6 g, 0.54 mol) in dry THF (85 mL) was added aniline (74.9 g, 0.80 mol) in THF (50 mL) dropwise over a period of 1 h with stirring. External cooling was required at the beginning of the addition. The mixture was stirred for 1 h at room temperature. After the evaporation of the solvent, 2 M NaOH (300 mL) was added to the residue, and the unreacted aniline was extracted with benzene (50 mL × 2). The solution was acidified with 6 M HCl (150 mL) and then extracted with ethyl acetate (100 mL × 3). The combined extracts were dried (Na_2SO_4); removal of the solvent gave 118 g (99.7%) of crude 1. Recrystallization of 1 (80.7 g) from mixed solvent (benzene/hexane 1:5) (900 mL) gave 1 (73.4 g): yield, 91%; mp 120–121 °C; IR (KBr) 3300, 1700, 1650, 1540 cm^{-1}; NMR ($CDCl_3$) δ 1.1–1.4 (d, 3 H, CH_3), 2.2–2.7 (m, 5 H, CH, CH_2), 6.8–8.3 (m, 7 H, Ph, NH, OH).

Optical Resolution of 1. A mixture of (±)-1 (10.0 g, 0.0452 mol) and (+)-MBA (5.47 g, 0.0452 mol) in water (15 mL) was refluxed until the solution was clear. The solution was allowed to stand at room temperature for 10–15 h. The precipitated salt was collected by filtration and dried (P_2O_5). Recrystallization of the salt from water was repeated 3 times. The diastereomeric salt was obtained in 13% yield: mp 127.5–128.5 °C; $[\alpha]_D$ −0.38° (*c* 1, MeOH). Treatment of the salt with 4 M HCl and extraction with ether gave (+)-1 in a quantitative yield: mp 105.5 °C; $[\alpha]_D$ +8.6° (*c* 1, MeOH).

In a manner similar to that described above, (−)-1 was obtained in 7.3% yield by using (−)-MBA as a resolving agent: mp 105–106 °C; $[\alpha]_D$ −8.4° (*c* 1, MeOH).

(*S*)-(−)-3-Methyl-5-pentanolide (3). To the mixture of (+)-1 (4.42 g, 20 mmol) and Et_3N (2.5 g, 25 mmol) in dry THF (30 mL) was added a solution of ethyl chloroformate (4.3 g, 40 mmol) in dry THF (5 mL) for 20 min with external cooling.[5] The mixture was stirred for 15 min at room temperature. A white precipitate was filtered off and washed with THF (5 mL × 2). The combined filtrate and washings were added to a mixture of $NaBH_4$ (2.3 g, 66 mmol) in water (20 mL) over a period of 1 h, with external cooling. The mixture was stirred for 1.5 h at room temperature. The solution was acidified carefully with 1 M HCl. The mixture was extracted with ether (10 mL × 3), and the combined extracts were washed with water (20 mL × 2), 2 M NaOH (20 mL × 2), and water (20 mL × 2) and dried (Na_2SO_4). Removal of the solvent gave 3.1 g of **2**. A solution of KOH (6.4 g, 0.11 mol) in water (25 mL) was added to the solution of **2** in ethanol (30 mL), and the mixture was refluxed for 14 h with stirring. The ethanol was evaporated, and the solution was diluted with water (30 mL). The liberated aniline was extracted with ether (10 mL × 2). The aqueous layer was acidified with 6 M HCl and extracted with $CHCl_3$ (20 mL × 3). The combined extracts were dried (Na_2SO_4). Evaporation and distillation gave 1.4 g of (*S*)-(−)-**3**:[6] yield 62%; $[\alpha]_D$ −27.0° (*c* 1, $CHCl_3$).

In a manner similar to that described above, (*R*)-(+)-**3** was obtained from (−)-1 in 66% yield: $[\alpha]_D$ +27.1° (*c* 1, $CHCl_3$); lit.[5] $[\alpha]_D$ +27.15° (*c* 2.3, $CHCl_3$).

(3*S*)-(−)-*N*,*N*-Dimethyl-5-hydroxy-3-methylpentanamide (4). Aqueous dimethylamine (45.0 g of 50% solution, 0.5 mol) was added to (*S*)-(−)-**3** (3.6 g, 32 mmol). The solution was maintained for 3 h at 50 °C with stirring. After evaporation of excess dimethylamine and water, benzene was added to the residue, and the solution was dried (Na_2SO_4). Evaporation and distillation gave (3*S*)-(−)-**4**: yield 6.3 g (95%); bp 122–124 °C/0.16 Torr; $[\alpha]_D$ −12.7° (*c* 1, $CHCl_3$); IR (neat) 3250, 2800, 1600 cm^{-1}; NMr (CCl_4) δ 0.75–1.05 (m, 3 H, CH_3), 1.3–1.7 (m, 2 H, CH_2), 2.2 (m, 3 H, CH, C(=O)CH_2), 2.85, 2.95 (two s, 6 H, NCH_3), 3.43 (t, 2 H, OCH_2), 3.6 (s, 1 H, OH).

(3*S*)-(+)-*N*,*N*-Dimethyl-3-methyl-5-[(2-tetrahydropyranyl)oxy]pentanamide (5). To a solution of (3*S*)-(−)-**4** (5.3 g, 34 mmol) in dry benzene (20 mL) was added 2,3-dihydropyran (3.7 g, 44 mmol). After the addition of $POCl_3$ (0.4 mL), the mixture was stirred for 3 h at room temperature. The reaction mixture was washed with 0.1 M NaOH (10 mL × 2) and water (10 mL) and then dried (Na_2SO_4). Evaporation and distillation gave (3*S*)-(+)-**5**: yield 6.3 g (75%); bp 130–134 °C/0.2 Torr; $[\alpha]_D$ +2.9° (*c* 1.1, $CHCl_3$); IR (neat) 2850, 1620 cm^{-1}; NMR (CCl_4) δ 0.8–1.0 (m, 3 H, CH_3), 1.2–1.8 (br s, 8 H, $-CH_2-$), 1.8–2.3 (m, 3 H, C(=O)CH_2, CH), 2.7–3.0 (two s, 6 H, NCH_3), 3.0–4.0 (m, 4 H, OCH_2), 4.45 (br s, 1 H, OCH).

(3*S*)-(+)-3-Methyl-5-[(2-tetrahydropyranyl)oxy]pentanal (6). To a solution of (3*S*)-(+)-**5** (1.0 g, 4.1 mmol) in dry ether (10 mL) was added a solution of an equimolar amount of $LiAl(OEt)_3H$ (30 mL of 0.14 M etheral solution) by using a syringe under the dry nitrogen atmosphere at 0 °C. After stirring for 25 min at 0 °C, water (15 mL) was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ether (10 mL × 2). The combined organic layer and the extracts were washed with 5% $NaHCO_3$ (15 mL × 2) and water (15 mL) and then dried (Na_2SO_4). Evaporation and distillation gave (*S*)-(+)-**6**: yield 0.68 g (83%); bp 85–90 °C/0.16 Torr; $[\alpha]_D$ +2.9° (*c* 1.1, $CHCl_3$); IR (neat) 2850, 1700, 1620 cm^{-1}; NMR (CCl_4) δ 0.7–1.0 (d, 3 H, CH_3), 1.1–1.8 (br s, 8 H, CH_2), 1.8–2.2 (m, 3 H, C(=O)CH_2, C H), 2.8–3.8 (m, 4 H, CH_2O), 4.25 (s, 1 H, OCH), 9.25 (t, 1 H, CHO).

(14*S*)-(+)-Ethyl 14-Methyl-16-[(2-tetrahydropyranyl)oxy]-11-hexadecenoate (8). [10-(Ethoxycarbonyl)decyl]tri-

(5) Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1968**, *16*, 492.

(6) (a) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556. (b) Yabuta, G.; Mori, K. *Nippon Nogeikagaku kaishi* **1982**, *56*, 1121.

phenylphosphonium iodide (7)[7] (17.1 g, 28.3 mmol) was added to a solution of EtONa (1.9 g, 28.3 mmol) in freshly distilled DMF (80 mL) under a dry nitrogen atmosphere at 0 °C. A solution of (3*S*)-(+)-**6** (2.27 g, 11.4 mmol) in DMF (20 mL) was added to the reaction mixture, and it was stirred for 61 h at room temperature. After the complete evaporation of DMF, ether was added to the residue, and the precipitated triphenylphosphine oxide was filtered off. Evaporation and purification of column chromatography (silica gel, hexane/dichloromethane 2:1) gave (*S*)-(+)-**8**. Although the product consisted of a mixture of cis and trans isomers of **8**, no attempt was made to separate them: yield 3.7 g (83%); $[\alpha]_D$ +1.5° (*c* 1, $CHCl_3$); IR (neat) 2800, 1720 cm^{-1}; NMR (CCl_4) δ 0.85 (d, 3 H, CH_3), 1.0–2.3 (m, 32 H, CH_2, CH), 3.0–3.7 (m, 4 H, OCH_2), 3.85 (q, 2 H, OCH_2Me), 4.32 (br s, 1 H, OCH), 5.15 (t, 2 H, =CH).

(14*R*)-(−)-Ethyl 14-Methyl-16-[(2-tetrahydropyranyl)-oxy]hexadecanoate (9). Hydrogenation reaction of (+)-**8** (3.67 g, 9.31 mmol) was carried out in ethanol (30 mL) in the presence of Pd/C (0.55 g) for 17 h. After the catalyst was filtered off, evaporation of the solvent gave (*R*)-(−)-**9**: yield 3.67 g (99.5%); $[\alpha]_D$ −2.1° (*c* 1, $CHCl_3$); IR (neat) 2850, 1740 cm^{-1}; NMR (CCl_4) δ 0.85 (d, 3 H, CH_3), 1.1–1.9 (m, 34 H, CH_2, CH_3, CH), 2.15 (t, 2 H, $C(=O)CH_2$), 3.0–3.7 (m, 4 H, OCH_2Me), 4.35 (br s, 1 H, OCH).

(14*R*)-(+)-Ethyl 16-Hydroxy-14-methylhexadecanoate (10). A solution of (14*R*)-(−)-**9** (3.67 g, 9.29 mmol) in absolute ethanol (30 mL) was refluxed in the presence of strong acid ion-exchange resin (Amberlite IR-120B) (5.0 g) for 3 h with stirring. After the resin was filtered off, evaporation of the solvent gave (*R*)-(+)-**10**: yield 2.91 g (100%); $[\alpha]_D$ +1.4° (*c* 4.2, $CHCl_3$); IR (neat) 3300, 2850, 1730 cm^{-1}; NMR (CCl_4) δ 0.90 (d, 3 H, CH_3), 1.1–1.3 (m, 28 H, CH, CH_2, CH_3), 2.25 (t, 2 H, $C(=O)CH_2$), 2.70 (s, 1 H, OH), 3.50 (t, 2 H, OCH_2), 4.05 (q, 2 H, OCH_2Me).

(*R*)-(+)-1-Ethyl Hydrogen 14-Methylhexadecanedioate (11). A solution of (*R*)-(+)-**10** (2.91 g, 9.27 mmol) in acetic acid (90 mL) was added to a mixture of chromium oxide (3.02 g, 30.2 mmol) in an aqueous acetic acid (30 mL of 80% solution) for 10 min, and the mixture was stirred for 14 h at room temperature. Water (90 mL) was added to the mixture, and the reaction mixture was extracted with benzene (30 mL × 3). The combined extracts were washed with water (50 mL) and dried (Na_2SO_4). Evaporation of the solvent gave (*R*)-(+)-**11**: yield 2.90 g (95.4%); $[\alpha]_D$ +5.0° (*c* 5, $CHCl_3$); IR (neat) 2950, 1740 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, CH_3), 1.0–1.8 (m, 26 H, CH, CH_2, CH_3), 1.9–2.3 (m, 4 H, $C(=O)CH_2$), 3.95 (q, 2 H, OCH_2), 11.0 (s, 1 H, OH).

(*R*)-(+)-Diethyl 3-Methylhexadecanedioate (12). A solution of (*R*)-(+)-**11** (2.90 g, 8.84 mmol) in absolute ethanol (20 mL) was refluxed for 3 h in the presence of $POCl_3$ (0.4 g). After evaporation of the solvent, ether (50 mL) was added to the residue and the solution was washed with saturated $NaHCO_3$ (15 mL × 2) and water (15 mL). The solution was dried (Na_2SO_4). Evaporation and distillation gave (*R*)-(+)-**12**: yield 2.38 g (76%); bp 170–172 °C/0.2 Torr; $[\alpha]_D$ +1.95° (*c* 10, $CHCl_3$); IR (neat) 2900, 1750 cm^{-1}; NMr (CCl_4) δ 0.90 (d, 3 H, CH_3), 1.0–1.9 (m, 29 H, CH, CH_2, CH_3), 1.9–2.3 (m, 4 H, C(=O)CH), 4.00 (q, 4 H, OCH_2).

(*R*)-(+)-1-(5-Hydroxy-3-methylpentanoyl)piperidine (13). Piperidine (2.99 g, 35.1 mmol) was added to a solution of (*R*)-(+)-**3** (2.00 g, 17.5 mmol) in dry benzene (6 mL). The mixture was refluxed overnight with stirring. Evaporation and distillation gave (*R*)-(+)-**13**: yield 2.87 g (82%); bp 142 °C/0.2 Torr; $[\alpha]_D$ +7.9° (*c* 3, $CHCl_3$); IR (neat) 3400, 2900, 1620 cm^{-1}; NMR (CCl_4) δ 0.8–1.1 (m, 3 H, CH_3), 1.1–1.9 (m, 8 H, CH_2), 1.9–2.4 (m, 3 H, $C(=O)CH_2$, CH), 3.2–3.7 (m, 7 H, OH, OCH_2, NH_2). Anal. Calcd for $C_{11}H_{21}NO_2$: N, 7.03. Found: N, 6.96.

(*R*)-(−)-1-(4-Formyl-3-methylbutanoyl)piperidine (14). A solution of (*R*)-(+)-**13** in $CHCl_3$ (5 mL) was added to a mixture of chromium oxide (4.40 g, 44 mmol), pyridine (20 mL), and dry $CHCl_3$ (110 mL). The mixture was stirred for 15 min at room temperature. The supernatant liquid was separated by decantation, and the residue was washed with 5% HCl (100 mL), 5% $NaHCO_3$ (100 mL), and saturated NaCl (200 mL). The solution was dried over Na_2SO_4. Removal of the solvent gave (*R*)-**14**: yield 1.13 g (78%); $[\alpha]_D$ 0° (*c* 3, $CHCl_3$); IR (neat) 2900, 1720, 1629 cm^{-1}; NMR (CCl_4) δ 1.0 (d, 3 H, CH_3), 1.3–1.8 (br s, 6 H, CH_2), 1.9–2.9 (m, 5 H, CH, $C(=O)CH_2$), 3.1–3.7 (m, 4 H, NCH_2)8 9.65 (t, 1 H, CHO).

(*R*)-(+)-1-[15-(Ethoxycarbonyl)-3-methyl-5-pentadecenoyl]piperidine (15). (*R*)-(+)-**15** was obtained, in a manner similar to that described in the preparation of **8**, by Wittig reaction of (*R*)-**14** (1.13 g, 5.73 mmol) with 2 molar equiv of **7** in 58% (1.30 g) yield: $[\alpha]_D$ +5.5° (*c* 5.68 $CHCl_3$); IR (neat) 2900, 1730, 1650, 1430 cm^{-1}; NMR (CCl_4) δ 0.8–1.0 (m, 3 H, CH_3), 1.15 (t, 3 H, CH_3), 1.2–1.7 (m, 20 H, CH_2), 1.7–2.4 (m, 9 H, $C(=O)CH_2$, $=CCH_2$, CH), 3.2–3.6 (m, 4 H, NCH_2), 4.05 (q, 2 H, OCH_2), 5.2–5.4 (m, 2 H, =CH). Anal. Calcd for $C_{24}H_{43}NO_3$: N, 3.56. Found: N, 3.43.

(*R*)-(+)-1-[15-(Ethoxycarbonyl)-3-methylpentadecanoyl]piperidine (16). Hydrogenation of (*R*)-(+)-**15** (1.30 g, 3.30 mmol) in ethanol (15 mL) in the presence of 5% Pd/C (0.2 g) gave 1.27 g (97%) of (*R*)-(+)-**16**: $[\alpha]_D$ +2.0° (*c* 5, $CHCl_3$); IR (neat) 2900, 1730, 1640 cm^{-1}; NMr (CCl_4) δ 0.8–1.0 (m, 3 H, CH_3), 1.25 (t, 3 H, CH_3), 1.2–1.8 (m, 28 H, CH_2), 1.8–2.3 (m, 5 H, $C(=O)CH_2$, CH), 3.2–3.7 (m, 4 H, NCH_2), 4.0 (q, 2 H, OCH_2).

(*R*)-(+)-3-Methylhexadecanedioic Acid (17). A solution of (*R*)-(+)-**16** (1.27 g, 3.21 mol) in acetic acid (8 mL) and 48% hydrobromic acid (16 mL) was refluxed for 24 h. The solution was extracted with benzene (10 mL × 4). The solvent was evaporated as completely as possible. The crude (*R*)-(+)-**17** was treated with activated charcoal in hot benzene (20 mL). After the charcoal was filtered off, the solvent was evaporated: yield 0.87 g (90%); mp 73–75 °C; $[\alpha]_D$ +3.5° (*c* 4, $CHCl_3$); IR (KBr) 3100, 2700, 1700 cm^{-1}; NMR ($CCCl_4$) δ 0.97 (d, 3 H, CH_3), 1.3 (s, 22 H, CH_2), 2.1–2.5 (m, 5 H, CH, $C(C=O)CH_2$).

(*R*)-(+)-Diethyl 3-Methylhexadecanoate (12). Esterification of (*R*)-(+)-**17** (0.87 g, 2.90 mmol) was carried out in a manner similar to that described in route A. (*R*)-(+)-**12** was obtained in 88% (0.91 g) yield: $[\alpha]_D$ +1.8° (*c* 5, $CHCl_3$).

Dieckmann Cyclization[8] of (*R*)-(+)-12. The Dieckmann cyclization of (*R*)-(+)-**12** was carried out under a nitrogen atmosphere by using a high-dilution method in the presence of $[(Me_3Si)_2NNa]$. A modified version of the apparatus of Leonard et al.[8] was employed.

A solution of (*R*)-(+)-**12** (300 mg, 0.84 mmol) in dry THF (120 mL) was added to a gently refluxing solution of $[(Me_3Si)_2NNa]$ (1.98 g, 10.8 mmol) in dry THF (160 mL) over a period of 8 h, with vigorous stirring under a nitrogen atmosphere. After the addition was complete, the mixture was refluxed for an additional 30 min. Acetic acid (15 mL) was added to the mixture, and the solution was washed with water (40 mL × 4) and then dried (Na_2SO_4). Evaporation and isolation of the products with TLC (benzene/methanol 99:1) afforded a mixture of **18a** and **18b**; yield 143 mg.

(*R*)-(−)-Muscone. A mixture of **18** (459 mg, 1.5 mmol), Me_2SO (1.2 mL), and water (53 μL) was maintained for 4 h under a nitrogen atmosphere at 165 °C with stirring.[9] After cooling, water (3 mL) was added to the mixture and the mixture was extracted with pentane (7 mL × 4). The combined extracts were dried (Na_2SO_4). Evaporation and distillation gave (*R*)-(−)-muscone in 59% (209 mg) yield: bp 145 °C/0.9 Torr; $[\alpha]_D$ −11.6° (*c* 1, MeOH) [lit. $[\alpha]_D$ −11.7° (*c* 0.8, MeOH)];[2b] IR (neat) 2700, 1750, 1460 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, CH_3), 1.20 (s, 22 H, CH_2), 2.1–2.5 (m, 5 H, $C(=O)CH_2$, CH).

(7) House, H. O.; Babad, H. *J. Org. Chem.* **1963**, *28*, 90.

(8) (a) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 390. (b) Leonard, N. J.; Sentz, R. C. *J. Am. Chem. Soc.* **1952**, *74*, 1704.

(9) (a) Krapcho, A. P.; Jahngen, E. G. E., Jr.; Lovey, A. J. *Tetrahedron Lett.* **1974**, 1091. (b) Krapcho, A. P.; Lovey, A. J. *Ibid.* **1973**, 957.