J = 7.8, 2 H), 2.23 (quart of d, J = 7.0, 1.6, 2 H), 2.83 (sept, J = 6.9, 1 H), 6.16 (dt, J = 15.8, 1.5, 1 H), 6.88 (dt, J = 15.8, 7.0, 1 H); mass spectrum, M^+ at m/e 154.

Conjugate Reduction of 1-Phenyl-2-heptyn-1-one (3). The reaction was carried out as described above, using 1.00 mmol of **3**. The crude product obtained after workup was purified by PLC [silica gel, benzene–chloroform (10:1, v/v) as eluent] to give two fractions. The front fraction gave (*Z*)-1-phenyl-2-hepten-1-one [(*Z*)-**11**]: 97 mg (51%); IR (liquid film, cm^{-1}) 1680, 1615; ^1H NMR (400 MHz, $CDCl_3$) 0.91 (t, J = 7.2, 3 H), 1.37 (sext, J = 7.4, 2 H), 1.47 (quint, J = 7.5, 2 H), 2.63 (quart of d, J = 7.4, 1.7, 2 H), 6.33 (dt, J = 11.6, 7.4, 1 H), 6.80 (dt, J = 11.6, 1.8, 1 H), 7.40–8.00 (m, 5 H); mass spectrum, m/e (relative intensity) 81 (21), 91 (12), 105 (100), 120 (12), 131 (18), 134 (15), 145 (58), 159 (106), 188 (M^+, 46). The rear fraction gave (*E*)-1-phenyl-2-hepten-1-one [(*E*)-**11**]:[17] 76 mg (41%); IR (liquid film, cm^{-1}) 1670, 1620; ^1H NMR (400 MHz, $CDCl_3$) 0.94 (t, J = 7.3, 3 H), 1.39 (sext, J = 7.5, 2 H), 1.52 (quint, J = 7.7, 2 H), 2.33 (quart of d, J = 7.0, 1.3, 2 H), 6.88 (dt, J = 15.4, 1.5, 1 H), 7.07 (dt, J = 15.4, 6.9, 1 H), 7.4–8.0 (m, 5 H); mass spectrum, m/e (relative intensity) 81 (6), 91 (2), 105 (100), 120 (7), 131 (2), 134 (2), 145 (9), 159 (5), 188 (M^+, 7).

Conjugate Reduction of 2-Methyl-4,10-dodecadiyn-3-one (4). The reaction was carried out as described above, using 0.72 mmol of **4**. The crude product obtained after workup was purified by PLC [silica gel; hexane–ethyl acetate (8:1, v/v) as eluent] to give two fractions. The front fraction gave (*Z*)-2-methyl-2-dodecen-10-yn-3-one [(*Z*)-**12**]: 52 mg (37%); IR (liquid film, cm^{-1}) 2050, 1685, 1610; ^1H NMR (400 MHz, $CDCl_3$) 1.10 (d, J = 7.0, 6 H), 1.45–1.55 (m, 4 H), 1.77 (t, J = 2.6, 3 H), 2.1–2.2 (m, 2 H), 2.62 (sept, J = 7.0, 1 H), 2.63 (quart, J = 7.1, 2 H), 6.11 (dt, J = 11.5, 7.1, 1 H), 6.21 (dt, J = 11.5, 1.5, 1 H); mass spectrum, m/e (relative intensity) 55 (31), 57 (20), 71 (67), 79 (57), 93 (100), 107 (32), 121 (46), 135 (30), 149 (40), 163 (58), 177 (57), 192 (M^+, 1.5). The rear fraction gave (*E*)-2-methyl-2-dodecen-10-yn-3-one [(*E*)-**12**]: 36 mg (26%); ^1H NMR (400 MHz, $CDCl_3$) 1.11 (d, J = 6.8, 6 H), 1.45–1.65 (m, 4 H), 1.78 (t, J = 2.6, 3 H), 2.1–2.2 (m, 2 H), 2.24 (quart of d, J = 7.1, 1.3, 2 H), 2.83 (sept, J = 6.9, 1 H), 6.18 (dt, J = 15.8, 1.5, 1 H), 6.85 (dt, J = 15.8, 6.9, 1 H); mass spectrum, m/e (relative intensity) 55 (31), 57 (26), 71 (8), 79 (63), 93 (100), 107 (14), 121 (34), 135 (7), 149 (35), 163 (20), 177 (39), 192 (M^+, 0.90).

Reaction of the (α-Carbomethoxyvinyl)aluminum Intermediate with 3-Bromocyclohexene. To a stirred solution of THF (5 mL) and HMPA (0.522 mL, 3.00 mmol) cooled to 0 °C was added a hexane solution of DIBAH (1.50 mmol). After 0.5 h, methyl propiolate (0.089 mL, 1.00 mmol) was added. The reaction mixture was stirred for 1 h, and then 3-bromocyclohexene (0.244 mL, 2.10 mmol) was added. The mixture was allowed to warm to room temperature, stirred for 15 h, treated with 3 mL of 1 N HCl solution, and extracted with 15 mL of ether. The organic layer was washed three times with 3 mL of 1 N HCl solution, 3 mL of saturated $NaHCO_3$ solution, and 3 mL of water. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by PLC [silica gel; hexane–ether (1:1, v/v) as eluent] to give methyl 2-(2-cyclohexenyl)propenoate (**21**): 132 mg (79%); IR (liquid film, cm^{-1}) 1730, 1625, 950, 730; ^1H NMR (60 MHz, $CDCl_3$) 1.3–1.8 (m, 4 H), 1.8–2.3 (m, 2 H), 3.33 (m, 1 H), 3.73 (s, 3 H), 5.3–6.3 (m, 4 H); mass spectrum, M^+ at m/e 166. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.86; H, 8.60.

Other allylation products **17–20** were similarly obtained and identified as follows. Compound **17**: IR (liquid film, cm^{-1}) 1720, 1625, 995, 940, 915; ^1H NMR (60 MHz, $CDCl_3$) 3.07 (d, 2 H), 3.76 (s, 3 H), 4.8–5.3 (m, 2 H), 5.57 (s, 1 H), 5.6–6.0 (m, 1 H), 6.20 (s, 1 H); mass spectrum, M^+ at m/e 126. Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.67; H, 8.14. Compound **18**: IR (liquid film, cm^{-1}) 1725, 1630, 970, 945; ^1H NMR (60 MHz, $CDCl_3$) 1.5–1.8 (m, 3 H), 2.98 (d, 2 H), 3.75 (s, 3 H), 5.3–5.6 (m, 2 H), 5.55 (s, 1 H), 6.16 (s, 1 H); mass spectrum, M^+ at m/e 140. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.74; H, 8.81. Compound **19**: IR (liquid film, cm^{-1}) 1720, 1625, 990, 945, 915; ^1H NMR (60 MHz, $CDCl_3$) 1.20 (d, 3 H), 3.1–3.7 (m, 1 H), 3.76 (s, 3 H), 4.8–5.3 (m, 2 H), 5.55 (s, 1 H), 5.5–6.1 (m, 1 H), 6.19 (s, 1 H); mass spectrum, M^+ at m/e 140. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.67; H, 8.81. Compound **20**: IR (liquid film, cm^{-1}) 1730, 1635, 950; ^1H NMR (60 MHz, $CDCl_3$) 1.64 (s, 3 H), 1.74 (s, 3 H), 3.00 (d, 2 H), 3.76 (s, 3 H), 4.9–5.3 (m, 1 H), 5.54 (s, 1 H), 6.14 (s, 1 H); mass spectrum, M^+ at m/e 154. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.88; H, 9.23.

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A Short Synthesis of (*S*)-(+)-Tylophorine

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Tylophorine (**6**) is one of a group of selectively toxic alkaloids whose structures represent the fusion of a polymethoxyphenanthrene or -stilbene with indolizidine or quinolizidine.[2] Tylophorine has been synthesized in racemic form through a number of approaches,[3] and one optically active preparation has recently been reported.[4]

We describe here a short enantiospecific synthesis of tylophorine illustrative of yet another alternative route to preparation of β-arylalkylamines based on Friedel–Crafts acylations with *N*-(trifluoroacetyl)-α-amino acid chlorides and anhydrides.[5]

Results and Discussion

The reaction sequence employed is outlined in Scheme I. The key step was the first, wherein 2,3,6,7-tetramethoxyphenanthrene (**1**)[6] was acylated with 1.2 equiv of (*S*)-*N*-(trifluoroacetyl)prolyl chloride (**2**) in boiling CH_2Cl_2.[5a,b] Crystalline ketone **3** was obtained in 51% yield after flash chromatographic separation from residual **1**, *N*-(trifluoroacetyl)proline (from hydrolysis of excess **2**), and an unidentified minor byproduct. The regiochemistry was anticipated from a preliminary demonstration that acetylation of **1** takes place cleanly at the 9-position. The

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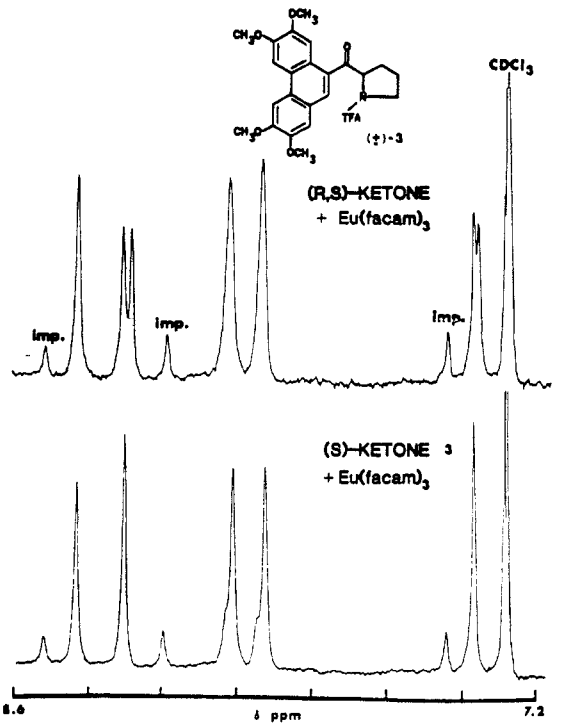
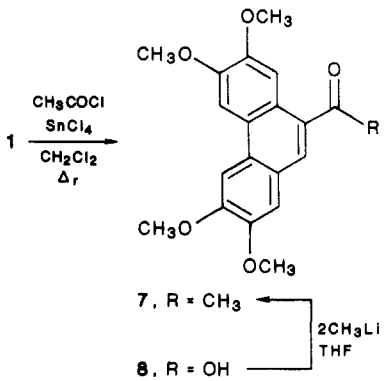


Figure 1. Eu(facam)$_3$-dispersed, 200-MHz ^{1}H NMR spectra of *S* ketone **3** and *R,S* ketone **3**.

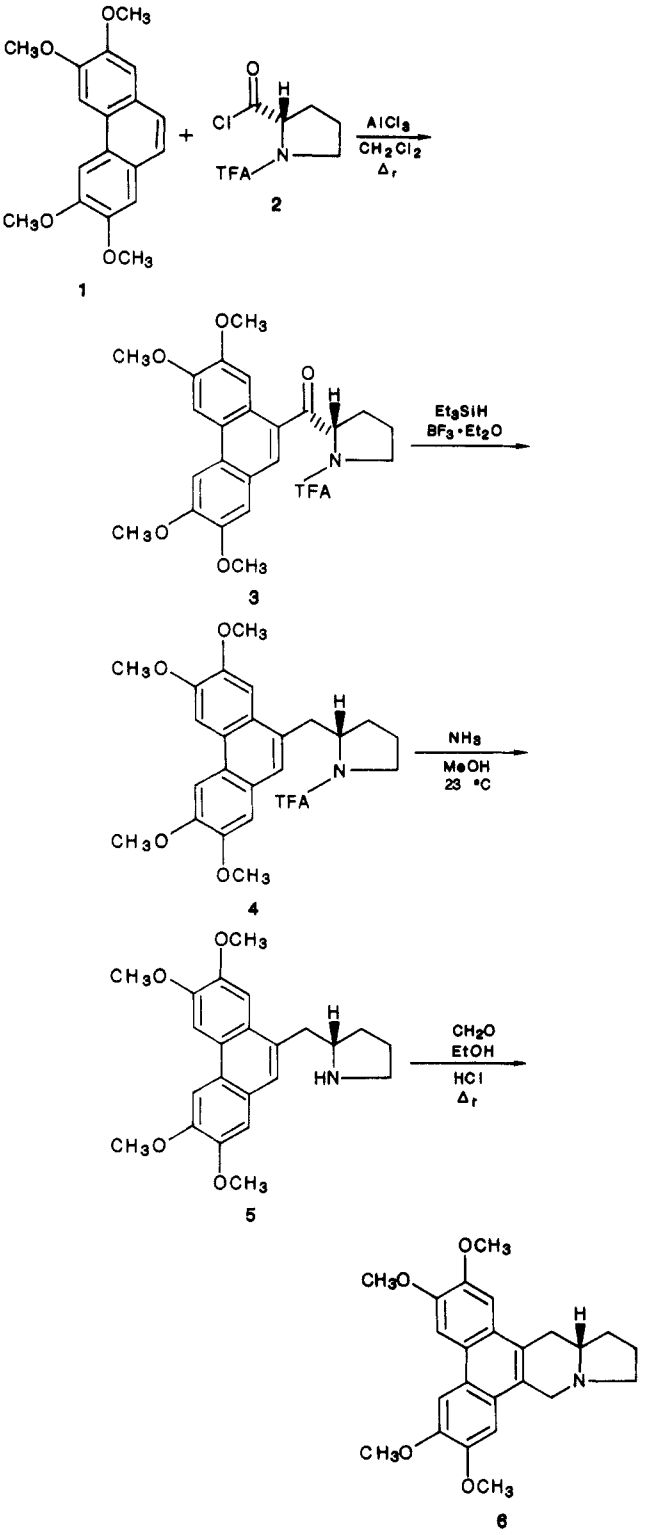
structure of the resultant ketone, **7**, was ascertained by independent synthesis from known carboxylic acid **8**.[3e]



Crude ketone **3** was determined to be of >98% enantiomeric purity by comparison of its 200-MHz ^{1}H NMR spectrum in the presence of chiral chemical shift reagent Eu(facam)$_3$[5b,7] with the corresponding spectrum of the racemic ketone (see Figure 1). The *S* ketone (Scheme I) gave rise as expected to five well-separated singlets in the aromatic region from δ 7.3 to 8.5. In the Eu(facam)$_3$-dispersed spectrum of the racemic ketone two of these absorptions appeared as distinct doublets, evincing the presence of diastereomeric complexes. The doublet signals are evidently those of the C-8 and C-10 protons, most proximate to the ketone function, on the basis of the comparatively large shifts induced by the Eu(facam)$_3$ reagent. Control experiments established that 2% of the *R* ketone is detectable in admixture with the *S* enantiomer by this method.

Deketonization of **3** was effected in 64% yield by treatment with Et_3SiH in neat BF_3·Et_2O[5,8] at room temperature. Deacylation of the resultant trifluoroacetamide, **4**, proceeded optimally in saturated methanolic ammonia[9] to furnish the tetracyclic amine **5** in 71% yield. The enantiomeric composition of **5** was measured by 200-MHz ^{1}H NMR spectroscopy with added chiral shift reagent Eu(dcm)$_3$.[7] This reagent gave rise to a clean doubling of one of the aromatic proton singlets and two of the methoxy singlets in the spectrum of the separately prepared racemic amine. Intermediate **5** under the same conditions exhibited a strong and a weak peak for each of these pairs of

Scheme I



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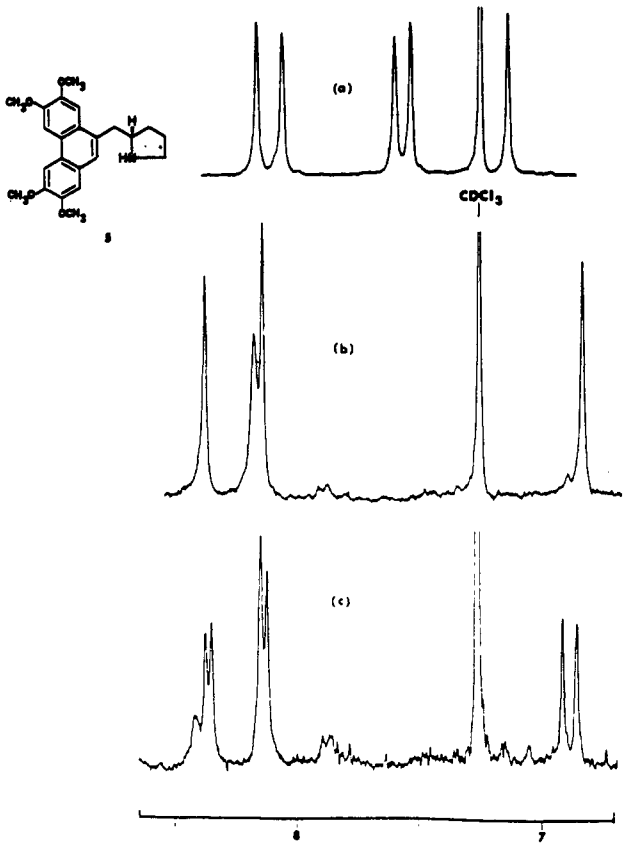

Figure 2. 200-MHz ^1H NMR spectra of (a) *S* amine **5**, (b) *S* amine **5** with $Eu(dcm)_3$, (c) *R,S* amine **5** with $Eu(dcm)_3$.

signals with a common intensity ratio of 32.3:1, corresponding to an enantiomeric purity of 97% (see Figure 2).

Pictet–Spengler cyclomethylenation[5a] of amine **5** by reaction with formaldehyde in boiling acidic aqueous ethanol completed the synthesis. (*S*)-Tylophorine (**6**) was isolated in 53% yield after recrystallization from $CHCl_3$/MeOH. The product had mp 284–286 °C dec, closely similar to literature values for both the optically active[2a,4] and racemic substance.[3d] The constitution of **6** was secured by matching its ^1H NMR,[3c] IR,[3c,d] UV,[2a,3c,d] and mass spectra[3c,i,4] with those published for the natural and synthetic compound by previous investigators.

The literature has been inconsistent on the optical activity of tylophorine. For their synthetic *S* enantiomer Buckley and Rapoport[4] recorded $[\alpha]^{23}_D$ +15° (*c* 0.7, $CHCl_3$), agreeing fairly well in magnitude but disagreeing in sign with the values reported earlier by Govindachari et al.[2a,3a] and by Gellert et al.[10] for the natural product deduced to have the same configuration.[11] We found this measurement difficult because of the instability of tylophorine in solution, as others have noted;[12] decomposition with yellowing sets in promptly, accompanied by decreasing rotatory strength. By working rapidly we found for our synthetic *S* enantiomer $[\alpha]^{21}_D$ +73° (*c* 0.7, $CHCl_3$), a markedly higher value than those from all preceding groups, conforming in sign with that of Buckley and Rapoport.[4] After standing for 3 days, the same sample (now deep yellow) had $[\alpha]^{21}_D$ +51° and exhibited a ^1H NMR spectrum of greatly increased complexity.

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Experimental Section

General. Melting points in capillary tubes were obtained on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-8 or IR-10 spectrophotometer. ^1H NMR spectra were recorded at 200 MHz on a Varian XL-200 Fourier-transform spectrometer using $CDCl_3$ as solvent unless otherwise indicated and Me_4Si as internal standard. ^{13}C NMR spectra were recorded at 25.4 MHz on the same spectrometer using Me_2CO-d_6 for internal lock. Optical rotations were measured with a Perkin-Elmer Model 141 electronic polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

2,3,6,7-Tetramethoxyphenanthrene (1). In a procedure similar to that described by Govindachari,[6] a magnetically stirred mixture of 4.3 g (12.5 mmol) of 2,3,6,7-tetramethoxyphenanthrene-9-carboxylic acid[3e] (**8**) and 4.3 g of anhydrous $CuSO_4$ in 130 mL of distilled quinoline under N_2 was boiled under reflux for 1 h, cooled, and poured into excess 4 N aqueous HCl. The product was extracted into 3 × 500 mL of benzene. The benzene solution was washed with dilute NaOH and H_2O and dried over $MgSO_4$. The solvent was removed by rotary evaporation to afford a brown solid, which was recrystallized from toluene/hexane to give 2.1 g (7.10 mmol, 57%) of **1** as white crystals: mp 180–181 °C (lit. mp 178 °C,[6] 180–181 °C[13]); ^1H NMR δ 3.97 and 4.03 (s, 6 H each, OCH_3), 7.25, 7.56, and 7.75 (s, 2 H each, ArH); (Me_2CO-d_6) δ 3.96 and 4.04 (s, 6 H each, OCH_3), 7.36, 7.58, and 8.06 (s, 2 H each, Ar H); ^{13}C NMR (Me_2CO-d_6) δ 56.40 and 56.85 (OCH_3), 104.95, 109.90, 125.85, 126.30, 128.10, 150.35, and 150.80 (Ar).

(*S*)-*N*-(Trifluoroacetyl)prolyl Chloride (2). To a magnetically stirred solution of 0.43 g (2.01 mmol) of (*S*)-*N*-(trifluoroacetyl)proline[5a,b] in 40 mL of benzene under N_2 at 0 °C was added 3 drops of dry pyridine and 565 μL of oxalyl chloride (Aldrich) in one portion. The reaction mixture was allowed to warm to room temperature and was then boiled under reflux for 1 h. After concentration of the mixture by rotary evaporation an amber yellow oil was obtained: ^1H NMR δ 1.80–2.73 (m, 4 H, CH_2CH_2), 3.54–4.00 (m, 2 H, CH_2N), 4.85 (dd, 1 H, COCHN); $[\alpha]^{22}_D$ −94.7° (*c* 2.5, $CHCl_3$).

(*S*)-*N*-(Trifluoroacetyl)-2,3,6,7-tetramethoxy-9-prolylphenanthrene (3). To a magnetically stirred, ice-bath cooled solution of acid chloride **2** from 0.43 g (0.21 mmol) of (*S*)-*N*-(trifluoroacetyl)proline in 80 mL of CH_2Cl_2 containing 0.27 g (2.00 mmol) of suspended fresh anhydrous $AlCl_3$ under N_2 was added 0.50 g (1.68 mmol) of tetramethoxyphenanthrene **1**. The mixture was boiled under reflux for 54 h and cooled to room temperature, and 20 mL of cold 1 M aqueous HCl was added. The phases were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with H_2O, dried over $MgSO_4$, and concentrated by rotary evaporation. The residue was subjected to flash chromatography on a silica gel column. Elution with ether furnished first some unreacted tetramethoxyphenanthrene, next an unidentified minor product, and then cleanly the desired ketone, **3**, in 51% yield. *N*-(Trifluoroacetyl)proline was subsequently eluted by using EtOAc. Recrystallization of the **3** from Et_2O between 36 and 0 °C afforded a light yellow powder: mp 198–200 °C; IR (Nujol) 1685, 1620, 1520, 1200 cm^{-1}; ^1H NMR δ 1.90–2.43 (br m, 4 H, $-CH_2CH_2-$), 3.67–3.93 (br t, 2 H, NCH_2), 4.03 (s, 6 H, OCH_3), 4.12 (s, 3 H, OCH_3), 4.14 (s, 3 H, OCH_3), 5.71 (br t, 1 H, COCHN), 7.29, 7.77, 7.82, 8.19, and 8.22 (s, 1 H each, Ar H). Analysis by ^1H NMR spectrometry using chiral shift reagent tris[3-(trifluoroacetyl)-(+)-camphorato]europium ($Eu(facam)_3$)[7] (Aldrich) indicated the configurational purity to be >98% *S*; see text. Anal. Calcd for $C_{25}H_{24}F_3NO_6$: C, 61.10; H, 4.92; N, 2.85. Found: C, 61.25; H, 4.99; N, 2.80.

(*S*)-*N*-(Trifluoroacetyl)-2-[(2,3,6,7-tetramethoxyphenanthren-9-yl)methyl]pyrrolidine (4). Triethylsilane (0.26 mL, 1.62 mmol) was added to a solution of 0.2 g (0.41 mmol) of ketone **3** in 1.0 mL (1.15 g, 8.13 mmol) of freshly distilled BF_3·Et_2O under N_2. The mixture was stirred magnetically for 48 h at 23 °C and then treated with 10 mL of saturated NaCl solution. The

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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

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