(19) From a preliminary kinetic study for the $PdCl_2$–LiCl catalyst system, the formation rates of (*E*) and (*Z*) codimers and cotrimer ($R_{E\ codimer}$, $R_{Z\ codimer}$, and $R_{cotrimer}$) were obeyed as follows: $R_{E\ codimer} \propto [PdCl_2][CH{\equiv}CH]^2[CH_2{=}CHCH_2Cl]$; $R_{Z\ codimer} \propto [PdCl_2][CH{\equiv}CH]^2[CH_2{=}CHCH_2Cl]$; $R_{cotrimer} \propto [PdCl_2][CH{\equiv}CH]^3[CH_2{=}CHCH_2Cl]$. Both $R_{E\ codimer}$ and $R_{cotrimer}$ increase with increasing LiCl concentration while $R_{Z\ codimer}$ decreases with increasing LiCl concentration.
(20) G. P. Chiusoli and L. Cassar, *Angew. Chem., Int. Ed. Engl.*, **6**, 124 (1967).
(21) The stereochemistry of addition of [Pd–X] across double or triple bonds is not absolute and rather depends on subtle factors; cis addition is favored in low polarity solvent when an excess of halide is absent while use of polar solvent and the presence of excess halide lead to trans addition, but even in low polarity solvent such as benzene, trans addition occurs with cyclic olefins. In retrospect the fact that addition of lithium chloride and use of polar solvent increased yields of (*E*) codimer and cotrimer agrees with the above phenomena: ref 16 Vol. 2, p 150; G. Wiger, G. Albero, and M. F. Rettig, *J. Chem. Soc., Dalton Trans.*, 2242 (1974); W. T. Wipke and G. L. Goeke, *J. Am. Chem. Soc.* **96**, 4244 (1974).
(22) A similar σ-butadienyl complex can be isolated: B. E. Mann, P. M. Bailey, and P. M. Maitlis, *J. Am. Chem. Soc.*, **97**, 1275 (1975).
(23) The codimerization of acetylenes and olefin free from halogen to 1,3-dienes contains the β-hydrogen elimination by palladium, ref 14.
(24) The ^{13}C chemical shifts of acetylenic carbons were as follows. Phenylacetylene C^α 83.3, C^β 77.7 ppm (ref 24a); 1-hexyne C^α 83.0, C^β 66.0 ppm (ref 24a); propargylic acid C^α 73.9, C^β 78.5 ppm (ref 24b); methoxycarbonylacetylene C^α 74.5, C^β 75.6 ppm (ref 24b): (a) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 71; (b) our unpublished results.
(25) For examples concerning carbon–carbon bond formations by using transition metal complexes, see: E. J. Corey and G. H. Poner, *J. Am. Chem. Soc.*, **89**, 3911 (1967); G. M. Whitesides, E. F. Fisher, J. S. Filoppo, R. W. Bashe, and H. O. House, *ibid.*, **91**, 4871 (1969); K. Tamao, K. Sumitani, and M. Kumada, *ibid.*, **94**, 4374 (1972); M. Yamamura, I. Moritani, and S. I. Murahashi, *J. Organomet. Chem.*, **91**, C 39 (1975); Y. Tamaru, Y. Yamada, and Z. Yoshida, *Tetrahedron Lett.*, 3365 (1977).
(26) M. S. Kharash, R. C. Seyler, and F. R. Mayo, *J. Am. Chem. Soc.*, **60**, 882 (1938).
(27) T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, and G. Wilkinson, *J. Chem. Soc.*, 3632 (1965).
(28) A. A. Grinberg and L. K. Simonova, *Zh. Prikl. Khim. (Leningrad)*, **26**, 880 (1953).
(29) J. Chatt and F. G. Mann, *J. Chem. Soc.*, 1622 (1939).
(30) W. T. Dent, R. Long, and A. J. Wilkinson, *J. Chem. Soc.*, 1585 (1964).
(31) D. M. Adams, P. J. Chandler, and R. G. Churchill, *J. Chem. Soc. A*, 1272 (1967).
(32) S. Oae and C. A. V. Werf, *J. Am. Chem. Soc.*, **75**, 2724 (1953).
(33) E. A. Bried and G. F. Hennion, *J. Am. Chem. Soc.*, **59**, 1310 (1937).
(34) T. H. Vaughn, G. F. Hennion, R. R. Vogt, and J. A. Nieuwland *J. Org. Chem.*, **2**, 1 (1937).
(35) I. A. Zakharova, *Zh. Obshch. Khim.*, **20**, 1572 (1950).
(36) A. C. Cope, D. S. Smith, and R. J. Cotter, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 377.

Preparation of Harringtonine from Cephalotaxine

T. Ross Kelly,* [1a] Robert W. McNutt, Jr., Michel Montury, and Nicholas P. Tosches

Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167

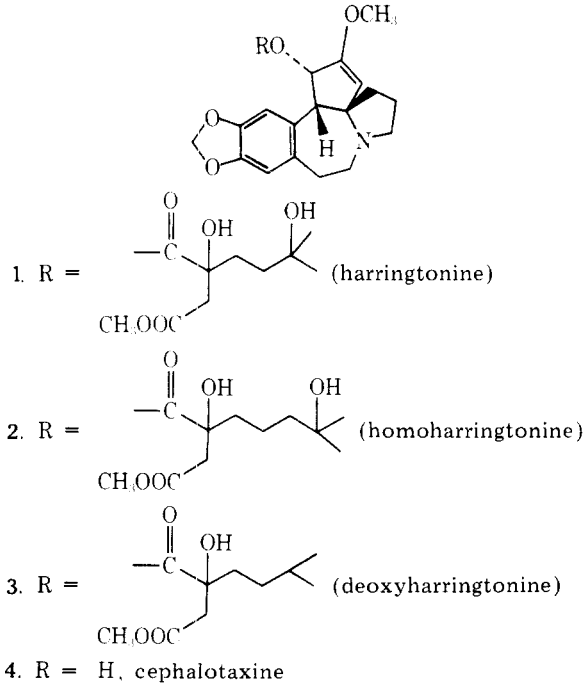
K. L. Mikolajczak, C. R. Smith, Jr., and D. Weisleder

Northern Regional Research Center,[1b] Peoria, Illinois 61604

Received September 11, 1978

Use of racemic **5** as a side-chain synthon provides a three-step conversion of *l*-cephalotaxine (**4**) into a readily separable, ~1:1 mixture of the clinically useful anticancer drug harringtonine (**1**) and its side-chain epimer. The synthesis of **5** is described.

Harringtonine (**1**) and its congeners were first characterized approximately 10 years ago and shown to exhibit anticancer activity in in vivo systems.[2-4] More recently, workers in the People's Republic of China have established that harringtonine and its homologue homoharringtonine (**2**) are efficacious in the treatment of human cancers.[5,6]



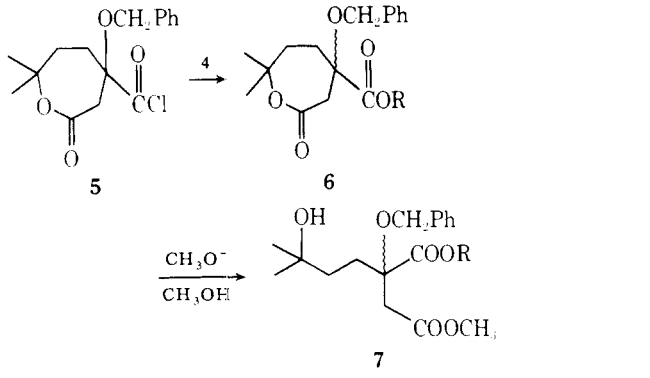
The parent alkaloid, cephalotaxine (**4**), was first synthesized in 1972[4,7] and is now relatively accessible by either isolation or total synthesis.[8] Harringtonine (**1**) and its natural homologue **2** are much less available, however, and clinical evaluation of these esters has not been undertaken in the United States due to lack of material. Numerous groups have attempted to prepare **1** from **4**, but no satisfactory solution has yet been achieved.[9,10] We now report a conversion of cephalotaxine (**4**) into harringtonine (**1**) which is a substantial improvement over existing methods[10b] and offers a potential means of alleviating the present scarcity of **1**. The approach utilizes **5** as a side-chain synthon.[11]

Use of racemic **5** provides a three-step conversion of *l*-cephalotaxine into a readily separable (LC, C_{18} μ-Bondapac column)[12] 1:1 mixture of harringtonine (**1**) and its side-chain epimer (**1a**) in an overall, incompletely optimized yield of approximately 35% (Scheme I).[13] Since the conversion of **4** into the mixture of **1** and its epimer is unaccompanied by asymmetric induction, use of the appropriate antipode (vide infra) of **5** should provide pure **1** in similar overall yield.

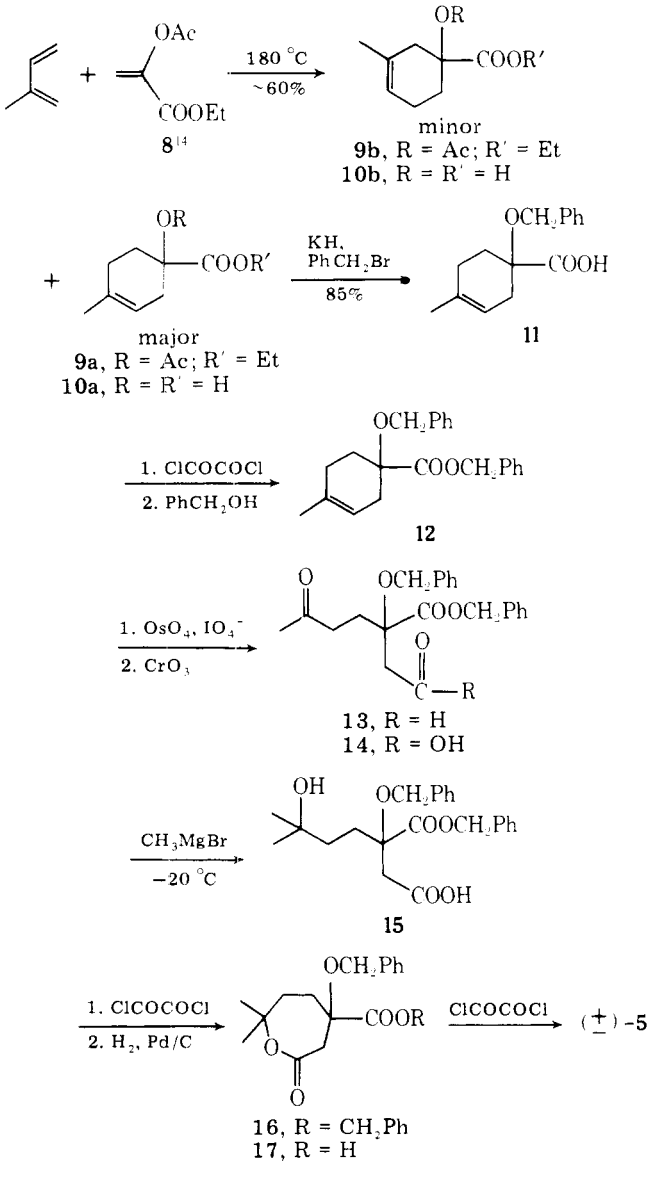
Lactone acid chloride **5** is available by the operationally straightforward sequence outlined in Scheme II. The minor, undesired Diels–Alder adduct **9b** is removed most easily by fractional crystallization[15] after saponification of **9** to the mixture of hydroxy acids **10**.[16] The conversion of **11** to **16** is most conveniently conducted without purification of intermediates and proceeds in 37% overall yield. The selective

0022-3263/79/1944-0063$01.00/0

Scheme I



Scheme II



hydrogenolysis of benzyl ester **16** (95% yield), although not unanticipated,[17] appears to be the first example of the hydrogenolysis of a benzyl ester in a molecule which also contains a benzyl ether.

With the successful demonstration of the viability of **5** as a side-chain synthon for the synthesis of harringtonine, it was necessary only to obtain the appropriate enantiomer of **5** to complete the project. A formal solution to this last problem has now been achieved with the obtention of the levorotatory antipode of **10a** by resolution via the *l*-ephedrine salt.[18]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 421 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with an Hitachi Perkin-Elmer Model R-24 instrument. The 90-MHz NMR spectra were obtained with a Bruker WH-90 fourier transform spectrometer. Chemical shifts are reported in ppm downfield from internal tetramethylsilane. Vapor phase chromatography analyses were performed on a Varian Aerograph, Series 1700, with a column of 20% SE-30 on 80/100 mesh Chromosorb W (6 ft × ¼ in.). Low-resolution mass spectra were determined on an Hitachi Perkin-Elmer Model RMS-3 instrument. High-resolution mass-spectral analyses were done on a Nuclide 12-90G instrument. Brinkmann Polygram Sil G/UV 254 plates, 0.25 mm (Machery-Nagel Co.), were used for analytical thin-layer chromatography (TLC), and preparative TLC separations were performed with Brinkmann Silica Gel PF-254 (EM Reagents). LC separations were accomplished with a Waters Associates M-6000 liquid chromatograph. Melting points (Pyrex capillary) and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc.

Ethyl 1-Acetoxy-4-methylcyclohex-3-enecarboxylate (9a). To a stainless steel bomb (capacity 500 mL) was added 150 g (0.950 mol) of ethyl 2-acetoxypropenoate (**8**),[14] 195 mL (1.95 mol) of isoprene, and a trace amount of hydroquinone. The sealed bomb was immersed in an oil bath at 180 °C for 16 h. Distillation at 5 mm removed isoprene dimer (bp ≤ 80 °C), whereupon the pressure was lowered to 1.0 mm and the product distilled (bp 97–100°) to give 110–135 g (52–62%) of colorless liquid: NMR ($CDCl_3$) δ 1.26 (t, 3 H, $J \sim 7$ Hz), 1.70 (broad s, 3 H), 2.07 (s over m, 7 H), 2.50 (m, 2 H), 4.22 (q, 2 H, $J \sim 7$ Hz), 5.30 (m, 1 H); IR ($CHCl_3$) ν_{max} 1735, 1275, 1200 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.95; H, 7.98. The product was homogeneous by VPC and TLC, but the NMR spectrum showed a shoulder (δ 5.45) on the olefinic proton peak that was assumed to represent 20–25% of the 3-methyl regioisomer **9b**.

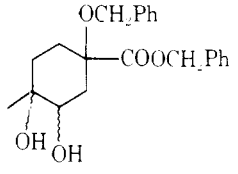
1-Hydroxy-4-methylcyclohex-3-enecarboxylic Acid (10a).[15] Diester **9a** (containing ca. 20% **9b**) (47.1 g, 0.208 mol) was added to a solution of 30 mL of water, 80 mL of 95% ethanol, and 20 g of sodium hydroxide. The mixture was stirred at room temperature until homogeneous and adjusted to pH 8–9 with 6 N hydrochloric acid. Ethanol was removed under vacuum at a temperature below 60 °C until the sodium salt began to precipitate out of solution. Crystallization was completed by chilling for 2 h and the resulting product was recrystallized from the minimum volume of hot water. The collected salt was redissolved in water, acidified with 3 M sulfuric acid, extracted with methylene chloride, and dried over sodium sulfate. Removal of solvent and recrystallization from 1:1 benzene/cyclohexane gave 8.4 g (26%) of colorless powdery crystals: mp 104–5 °C; NMR ($CDCl_3$) δ 1.75 (broad s, 3 H), 1.70–2.85 (m, 6 H), 5.40 (m, 1 H); IR ($CHCl_3$) 1730 cm^{-1}. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.34; H, 7.73.

1-Benzyloxy-4-methylcyclohex-3-enecarboxylic Acid (11). Hydroxy acid **10a** (3.0 g, 19.5 mmol) was added slowly to 10.0 g (0.055 mol, 3 equiv) of 22.7% potassium hydride oil dispersion in 75 mL of dry tetrahydrofuran under nitrogen and refluxed for 30 min. The reaction was cooled to room temperature, 8.2 g (0.048 mol, 2.5 equiv) of benzyl bromide was added, and the reaction was refluxed for 1 h. After cooling, 3 mL of MeOH were added *cautiously* and the reaction mixture was poured into 75 mL of water and extracted with two portions of ether. The ether extracts were combined and back-extracted with 5% aqueous sodium hydroxide. All aqueous phases were combined and acidified with 1 N hydrochloric acid, followed by extraction with three 40-mL portions of chloroform. The organic extracts were dried over sodium sulfate and the solvent was removed to give a colorless crystalline residue. Recrystallization from 9:1 ligroine/methylene chloride gave 3.5 g (85%) of prisms (mp 120–22 °C): NMR ($CDCl_3$) δ 1.70 (broad s, 3 H), 2.10 (broad s, 4 H), 2.50 (m, 2 H), 4.49 (s, 2 H), 5.25 (m, 1 H), 7.29 (s, 5 H); IR ($CHCl_3$) 1712 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.98; H, 7.25.

Benzyl 1-Benzyloxy-4-methylcyclohex-3-enecarboxylate (12). Benzyloxy acid **11** (5.00 g, 20.3 mmol) was dissolved in 20 mL of oxalyl chloride under nitrogen and stirred overnight at room temperature, at which point the NMR spectrum of the reaction solution indicated that formation of the acid chloride was complete: NMR (ClCOCOCl/Me_4Si) δ 1.65 (3 H, br s), 2.08 (4 H, br s), 2.48 (2 H, v br s), 4.42 (2 H, s), 4.21 (2 H, v br s), 7.20 (5 H, s). Excess oxalyl chloride was removed under vacuum below 40 °C and the crude acid chloride was

immediately dissolved in 60 mL of dry tetrahydrofuran under nitrogen. Benzyl alcohol (2.41 g, 22.3 mmol) and triethylamine (5.7 mL, 41 mmol) were added and the mixture was stirred overnight. The reaction was diluted with 100 mL of ether and washed successively with 50 mL of 1 N hydrochloric acid, two 50-mL portions of 5% aqueous sodium bicarbonate, and 50 mL of saturated salt solution. The ethereal layer was dried over sodium sulfate and the solvent removed to give 7.28 g (quantitative crude yield) of an oil whose NMR spectrum showed no impurities other than a small amount of excess benzyl alcohol: NMR ($CDCl_3$) δ 1.62 (broad s, 3 H), 2.05 (broad s, 4 H), 2.50 (m, 2 H), 4.45 (s, 2 H), 5.17 (s, 2 H), 5.30 (m, 1 H), 7.28 (s, 5 H), 7.33 (s, 5 H); IR ($CHCl_3$) 1728 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.63; H, 7.22.

Benzyl 2-Benzyloxy-5-oxo-2-(2-oxoethyl)hexanoate (13) and Benzyl 1-Benzyloxy-3,4-dihydroxy-4-methylcyclohexanecarboxylate (18). A catalytic amount of osmium tetroxide (254 mg, 1.00 mmol) was added to a solution of 7.28 g (20.0 mmol) of crude benzyl ester **12** in 230 mL of tetrahydrofuran and 58 mL of water. Sodium *m*-periodate (13.0 g, 60.8 mmol) was added to the dark solution and stirred overnight. The resulting yellow-white mixture was poured into 400 mL of water and extracted with three 100-mL portions of ether. The ether extract was washed quickly with 100 mL of 0.05 M aqueous sodium sulfide and 100 mL of saturated salt solution and dried over sodium sulfate, and the solvent was removed to give 7.20 g of oil containing a small amount of the crystalline cis-diol intermediate **18**. An analytical sample of **13** was obtained by preparative TLC with chloroform: NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.1–2.6 (m, 4 H), 2.88 (d,



18

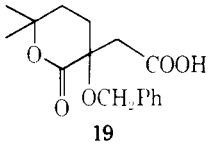
2 H, $J \sim 2$ Hz), 4.48 (s, 2 H), 5.20 (s, 2 H), 7.28 (s, 5 H), 7.33 (s, 5 H), 9.75 (t, 1 H, $J \sim 2$ Hz); IR ($CHCl_3$) 1723 cm^{-1} with shoulders at 1715 and 1738 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.47; H, 6.47.

A sample of the crystalline diol (**18**) was removed from the oily keto aldehyde and recrystallized three times from cold ether to give fluffy white needles; soften 107, 115 °C, mp 123–5 °C; NMR ($CDCl_3$) δ 1.24 (s, 3 H), 1.6–2.3 (m, 6 H), 3.65 (m, 1 H), 4.38 (s, 2 H), 5.16 (s, 2 H), 7.28 (s, 5 H), 7.33 (s, 5 H); IR ($CHCl_3$) 3570, 3450, 1725, 1740 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.75; H, 7.02.

3-Benzyloxy-3-benzyloxycarbonyl-6-oxoheptanoic Acid (14). Jones oxidation of keto aldehyde **13** was performed by dissolving 7.20 g (19 mmol) of the crude (containing **18**) substrate in 240 mL of acetone with 60 mL of water and 13 mL of 2.67 M chromic acid in aqueous sulfuric acid.[19] The solution was stirred overnight and 5 mL of 2-propanol was added to destroy excess oxidant. Saturated salt solution (100 mL) was added, the product extracted with two 200-mL portions of ether and dried over sodium sulfate, and the solvent removed in vacuo. The crude product was redissolved in 75 mL of ether and extracted with five 50-mL portions of 5% aqueous sodium bicarbonate. Acidification with 2 N aqueous hydrochloric acid was followed by extraction with three 75-mL portions of methylene chloride which were dried over sodium sulfate and evaporated to give 5.70 g of a viscous oil (78% from keto aldehyde **13**, 73% overall from benzyloxy acid **11**). The product was greater than 95% pure by NMR and TLC. An analytical sample was obtained by preparative TLC in ether–hexane–acetic acid (55:45:2): NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.40 (broad s, 4 H), 2.99 (s, 2 H), 4.57 (s, 2 H), 5.20 (s, 2 H), 7.28 (s, 5 H), 7.33 (s, 5 H); IR ($CHCl_3$) 1712, 1722, 1740 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.64; H, 6.33.

3-Benzyloxy-3-benzyloxycarbonyl-6-hydroxy-6-methylheptanoic Acid (15). Keto acid **14** (3.74 g, 9.74 mmol) was dissolved in 165 mL of dry tetrahydrofuran under nitrogen and cooled to −30 °C in a dry ice/acetone bath. Addition of 35 mL of 1.9 M methyl magnesium bromide in THF/benzene (67 mmol) over 1 min was exothermic, and simultaneous cooling with additional dry ice was necessary to maintain the reaction temperature at −25 to −30 °C. (The reaction temperature rose briefly to −15 °C before additional cooling reversed the temperature increase. At this point the acetone bath temperature was −45 °C.) After stirring for 6.0 min the cold reaction was *immediately* quenched in 300 mL of 10% aqueous tartaric acid and extracted with three 100-mL portions of ether. The ether extracts were washed with saturated salt solution and dried over sodium sulfate and the solvent was removed to give an oil which was redissolved in 50 mL of ether, filtered from tartaric acid crystals, and extracted with six 50-mL portions of 5% aqueous sodium bicarbonate. The aqueous solution was acidified with tartaric acid and extracted with three 50-mL portions of methylene chloride which were dried over sodium sulfate and evaporated to give 3.50 g (89%) of viscous oil which was essentially pure (by NMR) and used without further purification. An analytical sample was obtained by preparative TLC with ether–hexane–acetic acid (55:45:2): NMR ($CDCl_3$) δ 1.15 (s, 6 H), 1.20–1.70 (m, 2 H), 1.95–2.30 (m, 2 H), 2.98 (s, 2 H), 4.53 (s, 2 H), 5.22 (s, 2 H), 7.26 (s, 5 H), 7.32 (s, 5 H); IR ($CHCl_3$) 1742, 1730, 1715 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.71; H, 7.03.

In some reactions (especially when low temperatures were not carefully maintained) varying amounts of the δ-lactone acid **19** were



19

also produced. An analytical sample of **19**, mp 122–3 °C, was obtained by preparative TLC with ether–hexane–acetic acid (55:45:2) and recrystallization from benzene/hexane: NMR ($CDCl_3$) δ 1.41 (s, 6 H), 1.85–2.50 (m, 4 H), 2.53, 2.81, 3.22, 3.50 (AB q, 2 H, J = 17 Hz), 4.29, 4.48, 4.51, 4.70 (AB q, 2 H, $J \sim 11$ Hz), 7.26 (s, 5 H); IR ($CHCl_3$) 1714 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.82; H, 6.85.

Benzyl 4-Benzyloxy-7,7-dimethyl-2-oxo-1-oxacycloheptane-4-carboxylate (16). Crude hydroxy half acid **15** (325 mg, 0.811 mmol) was dissolved in 10 mL of dry benzene under nitrogen and cooled in an ice-water bath. Oxalyl chloride (0.85 mL, 12 equiv) was added to the solution, the ice bath was removed, and the reaction solution was stirred for 2 h. After quenching in saturated aqueous sodium bicarbonate, the product was washed with four 10-mL portions of 5% aqueous sodium bicarbonate and 10 mL of saturated salt solution. The organic phase was dried over sodium sulfate and the solvent removed to give 228 mg of a viscous oil. Preparative TLC in ether–hexane–acetic acid (55:45:2) gave 173 mg (56%) of **16** as a colorless oil: NMR ($CDCl_3$) 1.37 (s, 3 H), 1.44 (s, 3 H), 2.20 (m, 4 H), 3.04, 3.29, 3.37, 3.62 (AB q, 2 H, $J \sim 15$ Hz), 4.25, 4.42, 4.62, 4.79 (AB q, 2 H, $J \sim 10$ Hz), 5.21 (s, 2 H), 7.27 (s, 5 H), 7.34 (s, 5 H); IR ($CHCl_3$) 1725 cm^{-1}. Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.13; H, 6.94.

4-Benzyloxy-7,7-dimethyl-2-oxo-1-oxacycloheptane-4-carboxylic Acid (17). Benzyl ester **16** (422 mg, 1.05 mmol) was dissolved in 15 mL of glacial acetic acid with 50 mg of 5% palladium on carbon and hydrogenated at 1 atm. Hydrogenolysis was limited to the ester benzyl group by plotting hydrogen consumption (mL) vs. reaction time (min) and interrupting the hydrogenation when the reaction rate showed a negative deviation from linearity. This occurred after 24 min with consumption of 26.5 mL (1.02 equiv) of hydrogen. The reaction solution was diluted with methylene chloride and filtered through Celite, followed by removal of solvent in vacuo at room temperature. The residue was redissolved in methylene chloride and washed with 2% aqueous tartaric acid to remove the last traces of acetic acid. After drying over sodium sulfate the solvent was removed to give 291 mg (95%) of colorless foam whose NMR spectrum showed excellent purity. The product underwent thermal isomerization to δ-lactone acid **19** upon heating or upon standing at room temperature for several days. However, it could be crystallized at room temperature in excellent purity by dissolving in ether–benzene, evaporating the ether under a stream of nitrogen, and adding hexane to give colorless prisms: mp 119–22 °C (TLC analysis showed that substantial isomerization occurred during the melting point determination); NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.50 (s, 3 H), 2.0–2.4 (m, 4 H), 3.09, 3.34, 3.41, 3.66 (AB q, 2 H, J = 15 Hz), 4.37, 4.53, 4.67, 4.83 (AB q, 2 H, $J \sim 10$ Hz), 7.27 (s, 5 H); IR ($CHCl_3$) 1715 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.65; H, 6.89.

4-Benzyloxy-7,7-dimethyl-2-oxo-1-oxacycloheptane-4-carboxylic Acid Cephalotaxine Ester (6) (1:1 Mixture of Epimers at C-4). The acid chloride of ϵ-lactone acid **17** was prepared by dissolving 135 mg (0.46 mmol) of the acid in 2 mL of oxalyl chloride under nitrogen and stirring 24 h at room temperature. Excess oxalyl chloride was removed under vacuum to leave the crude acid chloride whose NMR spectrum [in $CDCl_3$, δ 1.50 (3 H, s), 1.60 (3 H, s), 1.7–2.5 (4 H, m), 3.21 (1 H, d, J = 15 Hz), 3.55 (1 H, d, J = 15 Hz), 4.49 (1 H, d, J = 10 Hz), 4.88 (1 H, d, J = 10 Hz), 7.33 (5 H, s)] showed that it was of good purity. *l*-Cephalotaxine (93 mg, 0.295 mmol, 0.64 equiv) in 0.5 mL of dry (stored over 4A molecular sieves) pyridine was added to the acid chloride and stirred under nitrogen for 48 h. The reaction mixture was concentrated in vacuo and the residue dissolved in a

mixture of benzene, methanol, and ammonium hydroxide (80:20:0.5 by volume) and chromatographed on 10 g of silica gel (Woelm dry column silica gel). Elution with the same solvent system gave 162 mg of **6** [88% based on (−)-**4**] as a gum which, although dark, was judged to be of good purity by TLC and NMR: NMR ($CDCl_3$) δ 1.40 (4 overlapping s, 6 H), 1.50–3.50 (m, 16 H), 3.65 and 3.69 (two s, total 3 H), 3.85 (d, 1 H, J = 9 Hz), 4.08, 4.30, 4.45, 4.67 and 4.12, 4.34, 4.50, 4.72 (overlapping AB q's, 2 H), 5.08 (s, 1 H), 5.52–6.05 (m, 3 H), 6.60 (s, 2 H), 7.28 (s, 5 H); IR ($CHCl_3$) 1715 (broad), 1655, 1502, 1485 cm^{-1}. An acceptable microanalysis could not be obtained for this compound.

Methyl 3-Benzyloxy-3-carboxy-6-hydroxy-6-methylheptanoate Cephalotaxine Ester (7) (Mixture of Epimers at C-3 of Side Chain). Cephalotaxine lactone ester **6** (152 mg, 0.234 mmol) was dissolved in 20 mL of dry methanol under nitrogen with 15.5 mg (1.1 equiv) of sodium methoxide. The reaction was stirred 4 h at room temperature then quenched by adding 20 mg of tartaric acid. After diluting with 25 mL of chloroform, the reaction solution was washed with two 20-mL portions of 5% aqueous sodium bicarbonate and dried over sodium sulfate and the solvent was removed to give 120 mg of gum, which was used in the next reaction without further purification. Analytically pure material was obtained by preparative TLC with benzene–methanol–ammonium hydroxide (80:20:1.0): NMR ($CDCl_3$) δ 1.15 and 1.02 (s, 6 H), 1.30–3.40 (m, 16 H), 3.59 (s, 3 H), 3.66 (s, 3 H), 3.85 (d, 1 H, $J \sim 9$ Hz), 3.87, 4.02, 4.03, 4.18 (AB q, 2 H, $J \sim 9$ Hz), 5.04 (s, 1 H), 5.60 and 5.74 (2 s, total 2 H), 5.92 and 5.99 (d, 1 H, $J \sim 9$ Hz), 6.51 and 6.59 (2 s, total 2H), 7.27 (s, 5 H); IR ($CHCl_3$) 1730, 1650, 1502, 1482 cm^{-1}. Anal. Calcd for $C_{35}H_{43}NO_9$: C, 67.62; H, 6.97. Found: C, 67.57; H, 7.02.

Harringtonine and *epi*-harringtonine (1 + 1a) (1:1 Mixture of Epimers at C-3 of Heptanoate Side Chain). Benzyl ether **7** (100 mg, 0.17 mmol) was dissolved in 5 mL of acetic acid with 100 mg of 5% palladium on carbon and hydrogenated at 1 atm. The progress of the reaction was monitored by TLC (C_6H_6, CH_3OH, NH_4OH, 80:20:0.5, detection by iodoplatinic acid) and stopped after 10 h. The reaction solution was diluted with 10 mL of acetic acid and filtered through Celite, rinsing with 10 mL of acetic acid. The acetic acid was removed under high vacuum and the residue was redissolved in 15 mL of H_2O, washed with two 10-mL portions of methylene chloride, made basic with 5% aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were combined and dried over sodium sulfate and the solvent removed to give 50 mg of oil (58%), which was a single spot on TLC with an R_f identical to that of authentic1: NMR ($CDCl_3$) δ 1.10, 1.17 (s, 6 H), 1.3–3.3 (m, 16 H), 3.59 and (broad) 3.66 (2 s, total 6 H), 3.80 (d, 1 H, $J \sim 9$ Hz), 5.02, 5.06 (s, 1 H), 5.85 (s, 2 H), 6.02 (d, 1 H, $J \sim 9$ Hz), 6.54, 6.61 (s, br s, total 2 H); IR ($CHCl_3$) 3525, 1730, 1650, 1485 cm^{-1}; MS m/e (rel intensity) 535 (10, M^+), 500 (2), 473 (2), 315 (20), 314 (10), 299 (30), 298 (100).

Separation of a Harringtonine–*epi*-Harringtonine Mixture (1 + 1a). The 1:1 mixture of epimers (80 mg), dissolved in methanol, was separated by liquid chromatography of 5-mg injections onto a reversed phase C_{18} μ-Bondapac column (Waters Associates, 0.78 × 30 cm). Base-line resolution between harringtonine (30 mg), which eluted first, and *epi*-harringtonine (24 mg) was achieved by using a water–methanol–diethylamine (55:45:0.05) solvent system. The samples of 1 and 1a so obtained were virtually pure, as judged by NMR and TLC analysis, but were contaminated by a small amount of hydrocarbon-type material (presumably washed from the LC column). Further purification was obtained by preparative TLC with methanol–chloroform (1:9) followed by column chromatography on neutral alumina (Woelm, grade III) with methanol–chloroform (1:9). NMR (90 MHz, $CDCl_3$) of 1: δ 1.14, 1.16 (2 s, total 6 H), 1.3–3.3 (m, 14 H), 1.81, 1.99, 2.22, 2.40 (AB q, 2 H, J = 18 Hz), 3.58, 3.70 (2 s, total 6 H), 3.79 (d, 1 H, J = 11 Hz), 5.06 (s, 1 H), 5.87 (s, 2 H), 5.99 (d, 1 H, J = 11 Hz), and 6.55, 6.61 (2 s, total 2 H). Anal. Calcd for $C_{28}H_{37}NO_9$: 531.2468. Found: M^+ 531.2452. NMR (90 MHz, $CDCl_3$) of **1a:** δ 1.09, 1.11 (2 s, total 6 H), 1.3–3.3 (m, 14 H), 2.40, 2.58, 2.61, 2.79 (AB q, intensity of outer lines about 10% that of inner lines, 2 H, J = 18 Hz), 3.65, 3.67 (2 s, total 6 H), 3.80 (d, 1 H, J = 11 Hz), 5.04 (s, 1 H), 5.85, 5.89 (2 d, total 2 H, J = 1.6 Hz), 5.87 (d, 1 Hz, J = 11 Hz), and 6.62 (br s, 2 H). Anal. Calcd for $C_{28}H_{37}NO_9$: 531.2468. Found: M^+ 531.2471.

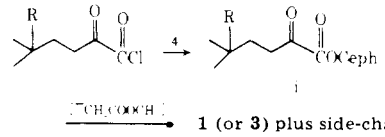
Resolution of Hydroxy Acid 11. Ten grams of hydroxy acid **10a** (64.0 mmol) was dissolved in the minimum volume of ethyl acetate on a steam bath and 10.4 g (1.0 equiv) of *l*-ephedrine (Aldrich Chemicals) was added. The amine salt precipitated after several minutes of continued warming. The salt was collected and recrystallized ten times to a constant melting point of 176–177.5 °C. The first five recrystallizations were performed in ethyl acetate containing 2–5% methanol to improve solubility and thereby avoid unnecessarily large volumes. Pure ethyl acetate was used for the remaining recrystallizations. The yield of amine salt was 1.50 g, $[\alpha]^D_{25}$ −38° (*c* 7.5, methanol). Hydrolysis of the amine salt was accomplished by dissolving it in 0.5 M hydrochloric acid and extracting continuously with chloroform to obtain the levorotatory isomer of the very water-soluble hydroxy acid **11**, $[\alpha]^D_{25}$ −32° (*c* 5.1, methanol).

Acknowledgments. Support of this project at Boston College by a grant (CA 14014) from the National Institutes of Health is gratefully acknowledged. We also wish to thank Dr. John Douros of the National Cancer Institute for providing generous samples of (+)- and (−)-cephalotaxine, Dr. Robert E. Perdue, Jr. (USDA, Beltsville, MD) for plant material, and Dr. W. K. Rohwedder (Northern Regional Research Center) for high-resolution mass-spectral analysis. Grateful appreciation is also extended to George Perdrizet, Barbara Prazak, Regina Mancini, Fletcher Anderson, Daryl Douglas, and Joseph Magee for technical assistance in times of need. Thanks are also due the Harringtonine Study Group of the Chinese Academy of Medical Science (Peking) for exchange of information.

Registry No.—**1**, 26833-85-2; **1a**, 67938-56-1; **4**, 24316-19-6; **5**, 68423-50-7; **6** isomer 1, 68423-51-8; **6** isomer 2, 68474-29-3; **7** isomer 1, 68423-52-9; **7** isomer 2, 68423-53-0; **8**, 22807-79-0; **9a**, 68423-54-1; **9b**, 68423-55-2; **10a**, 68423-56-3; (±)-**10a**, 68423-57-4; **10a** ephedrine salt, 68423-58-5; **11**, 68423-59-6; **11** acid chloride, 68423-67-6; **12**, 68423-60-9; **13**, 68423-61-0; **14**, 68423-61-2; **15**, 68437-42-3; **16**, 68423-63-2; **17**, 68423-64-3; **18**, 68423-65-4; **19**, 68423-66-5; isoprene, 78-79-5; methyl bromide, 74-83-9.

References and Notes

(1) (a) Recipient of a Research Career Development Award (CA-00040) from the National Cancer Institute; (b) Federal Research, Science and Education Administration, U.S. Department of Agriculture.
(2) For the initial structure determinations see: (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (b) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *ibid.*, 815 (1970); and (c) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972). (d) Cephalotaxine had been isolated earlier by workers at Ohio University but not completely characterized: J. McKay, Ph.D. Dissertation, Ohio University (1966); W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963); W. W. Paudler and J. McKay, *ibid.*, **38**, 2110 (1973).
(3) For crystallographic studies see: D. J. Abraham, R. D. Rosenstein and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969); S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, **39**, 1269 (1974); S. K. Arora, R. B. Bates, R. A. Grady, G. Germain, J. P. Declercq, and R. G. Powell, *ibid.*, **41**, 551 (1976).
(4) For a review, see S. M. Weinreb and M. F. Semmelhack, *Acc. Chem. Res.*, **8**, 158 (1975).
(5) (a) Cephalotaxus Research Coordinating Group, *Chin. Med. J.*, **2**, 263 (1976); (b) Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences, *ibid.*, **3**, 131 (1977).
(6) For a discussion of semisynthetic, less-active derivatives of **4** see: K. L. Mikolajczak, C. R. Smith, Jr., and D. Weisleder, *J. Med. Chem.*, **20**, 328 (1977), and references therein.
(7) For full papers see: (a) S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, **97**, 2503 (1975); (b) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, **97**, 2507 (1975). For additional routes to an intermediate in the Weinreb-Auerbach synthesis see: (c) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, **37**, 3691 (1972); (d) B. Weinstein and A. R. Craig, *ibid.*, **41**, 875 (1976); (e) I. Tse and V. Snieckus, *J. Chem. Soc., Chem. Commun.*, 505 (1976).
(8) A large-scale preparation of cephalotaxine (**4**) has been carried out by chemists at Merck (see ref 7a, footnote 19). Synthetic cephalotaxine has been resolved.
(9) For preparations of the appropriate side-chain half acids see: (a) ref 2c; (b) T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 3501 (1973); (c) J. Auerbach, T. Ipaktchi, and S. M. Weinreb, *ibid.*, 4561 (1973); (d) T. Ipaktchi and S. M. Weinreb, *ibid.*, 3895 (1973); (e) see also R. B. Bates, R. S. Cutler, and R. M. Freeman, *J. Org. Chem.*, **42**, 4162 (1977).
(10) (a) Attempts to acylate cephalotaxine with half acids corresponding to the natural esters of **4** have been totally unsuccessful in a number of laboratories, including those at Boston College (unpublished nonresults of T. R. Kelly and J. C. McKenna, 1973), the Northern Regional Research Center,[2c] and Fordham University.[9c] For a recent, related, unsuccessful effort see ref 9e. (b) Two syntheses of deoxyharringtonine[10c,d] and two of harringtonine[10e,f] have been reported. All four employ the same basic approach (eq i) and suffer from two serious complications which severely limit, if not preclude, their use in large-scale preparation: (i) the conversion of i



to **1** (or **3**) produces an approximately equal amount of the undesired (and difficultly separable) side-chain diastereomer, and (ii) the overall yield for the conversion of i to **1** (or **3**) is, in all four cases, ≤5%. (c) K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 283 (1974); (d) S.-W. Li and J.-Y. Dai, *Hua Hsueh Hsueh Pao*, **33**, 75 (1975) [*Chem. Abstr.*, **84**, 150812q (1976)]; W.-K. Huang, Y.-L. Li, and S.-F. Pan, *K'o Hsueh T'ung Pao*, **21**, 178 (1976) [*Chem. Abstr.*, **85**, 63208 (1976)]; (e) Institute of Pharmacology, *ibid.*, **20**, 437 (1975); **21**, 509, 512 (1976) [*Chem. Abstr.*, **86**, 171690e (1977)]; (f) K. L. Mikolajczak and C. R. Smith, Jr., Abstracts of the 175th American Chemical Society National Meeting, March 1978, Anaheim, Abstract MEDI 023.

(11) The selection of **5** as the precursor to the side chain was influenced by the following considerations: (a) the limiting substrate in the preparation of **1** will be, almost certainly, **4**; consequently the side-chain synthon should be as fully elaborated as possible and require a minimum of further transformations once attached to **4**; (b) generation of the chiral center in the acyl moiety should precede esterification to cephalotaxine in order to avoid diastereomeric difficulties;[10b] (c) the acyl synthon should be sufficiently stable to survive the relatively vigorous conditions (vide infra) required to acylate **4**.

We submit that previous unsuccessful attempts[10a] to prepare **1** and **3** are a consequence of (a) steric hindrance (in both **4** and the acylating agents) and (b) the suspected instability of activated derivatives of the appropriate fully elaborated half acids corresponding to the natural esters of **4**. The absence in the literature of physical or spectral characterizations of any activated side-chain synthons[10a] would appear to support the latter hypothesis.

It was envisaged that constraining the two alkyl substituents in the acyl group into a lactone ring would not only reduce steric hindrance problems but also attenuate the potential for destructive intramolecular interactions between the various functional groups in putative side-chain precursors.

(12) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

(13) As anticipated from the studies of R. Huisgen and H. Ott [*Tetrahedron*, **6**, 253 (1959)], cleavage of the acyl linkage to cephalotaxine is less facile than methanolysis of the lactone ring in **6**. The olefinic double bond in cephalotaxine has been shown[2d] to be highly resistant to catalytic hydrogenation.

(14) J. Monnin, *Helv. Chim. Acta*, **39**, 1721 (1956).

(15) The procedure described in the Experimental Section for the obtention of pure **10a** from the mixture of **9a** and **9b** was developed by Professor R. J. Parry and Dr. Richard Dufresne at Brandeis University and is a distinct improvement over methods previously used by us. In particular, recrystallization of the sodium salt of **10a** provides material of higher purity than can be obtained by recrystallization of the acid itself. We thank Professor Parry for advising us of this procedure.

(16) Cursory attempts to enhance the regioselectivity of the reaction between isoprene and **6** by employing Lewis acid catalysis ($AlCl_3$) were unfruitful (unpublished results of T. R. Kelly and B. K. Prazak). The possibility of preparing **12** directly by Diels–Alder reaction of isoprene with $CH_2{=}CH(OCH_2Ph)COOCH_2Ph$ (ii) was not investigated (nor was ii prepared) because it was anticipated [S. M. McElvain, H. I. Anthes, and S. H. Shapiro, *J. Am. Chem. Soc.*, **64**, 2525 (1942)] that ii would undergo a Claisen rearrangement in preference to cycloaddition.

(17) M. Freifelder, "Practical Catalytic Hydrogenation", Wiley, New York, N.Y., 1971, p 429.

(18) While it remains to be determined whether the absolute configuration of (−)-**10a** corresponds to that found in **1**, since both enantiomers of ephedrine are available, resolution of **10a** with the other enantiomer of ephedrine will, if necessary, provide (+)-**10a**. At present the yield of the resolution is approximately 20% of theory. Efforts to improve the resolution step are in progress.

(19) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

6-Aminoalkyl Catechol Estrogens: Models of Steroidal Biogenic Amines[1]

Akira Takadate[2] and Jack Fishman*

The Rockefeller University, New York, New York 10021

Received August 14, 1978

Reaction of 2,3-dibenzyloxy-17β-acetoxyestra-1,3,5(10)-trien-6-one (IIc) with trimethylsilyl cyanide gave as the sole product the 6β-cyano-6α-(trimethylsilyloxy) derivative IIIa. Subsequent reductive elaboration of IIIa afforded 6β-(aminomethyl)estra-1,3,5(10)-triene-2,3,6α,17β-tetrol (IIIe) which combines the structural features of the centrally active catechol estrogens and the biogenic catecholamines. The synthesis of the related 6α- and 6β-(2-acetaminoethyl)estra-1,3,5(10)-triene-2,3,17β-triol triacetates (VIe and VIf) was attained via Wittig reaction of the 6-ketone IIc with diethyl cyanomethylphosphonate and subsequent reduction.

The catechol estrogens (2,3-dihydroxyestrogens) have been identified as the major metabolites of estradiol in man and other species.[3,4] The principal site of their formation is in the liver but the presence of this biotransformation has also been demonstrated in the CNS[5,6] where the concentration of the catecholestrogens has been reported to be disproportionately high.[7] The formation and presence of the catechol estrogens within CNS assumes particular significance because of the unusual nature of their biological activity. The major catechol estrogen, 2-hydroxyestrone (Ia), is unique among the estrogens in that it exhibits central[8,9] but not peripheral hormonal activity[10] and hence its in situ biosynthesis in the brain may have important physiological consequences. The neuroendocrine action of the catechol estrogens could be mediated by their competitive inhibition of the O-methylation of the biogenic catecholamines by catechol-*O*-methyl transferase,[11] or possibly by other interactions with catecholaminergic mechanisms. These as well as other considerations suggested that compounds which combine the structural features of the catechol estrogens and of the catecholamines may exhibit novel pharmacological properties. Additional interest in such compounds derives from their structural relationship to morphine and related opiates which would imply a potential for analgetic activity in these substances. Because of the inherent symmetry of the 2,3-dihydroxyestrogen structure the desired catechol ethylamine feature could be generated by the insertion of an amino group at carbons 7, 8, and 11, or of an aminomethyl group at positions 6 and 9. Because of relative accessibility and because of the opportunity for greater structural versatility in an amino group located on a primary carbon, we elected to construct the structures initially by the introduction of the 6-aminomethyl group at the C-6 position.

Functionalization of the 6-keto intermediate which is readily accessible via benzylic oxidation of a suitably protected catechol estrogen represented a convenient route to these compounds. Reaction of 2,3,17β-trihydroxyestra-1,3,5(10)-triene triacetate (Ib) with chromic anhydride in acetic acid[12] yielded the corresponding 6-keto derivative IIa in over 30% yield. Attempts to obtain a cyanohydrin from the C-6 ketone in IIa by conventional procedures failed to yield any product. Similarly, an attempt to generate the cyanohydrin by the reaction of the intermediate tosylhydrazone with potassium cyanide in ethanol provided only the regenerated ketone IIa. Modification of the phenolic protection groups was then sought in the hope of affecting the reactivity of the benzylic ketone. Hydrolysis of the acetates at C-2 and C-3 and their replacement by benzyl ethers was accomplished at the same

0022-3263/79/1944-0067$01.00/0