Total Synthesis of the *Cephalotaxus* Alkaloids. Cephalotaxine, Cephalotaxinone, and Demethylcephalotaxinone

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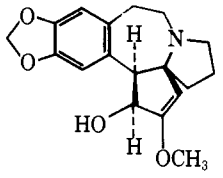
Abstract: Cephalotaxine (**1**), the major alkaloid produced by several species of *Cephalotaxus* (plum-yews), has been synthesized as its racemate in eight steps from 1-prolinol (**4**) and 3,4-methylenedioxyphenylacetyl chloride (**3**). Cephalotaxinone (**22**) and demethylcephalotaxinone (**19**), minor alkaloids which normally occur with cephalotaxine, have been prepared as intermediates in this synthesis.

The genus *Cephalotaxus* (plum-yews) produces a small group of structurally unique alkaloids. The major alkaloid of this group, cephalotaxine, has been studied by a number of investigators and assigned the absolute stereostructure **1**



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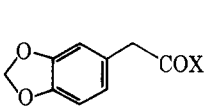
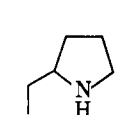
on the basis of chemical, spectral, and X-ray diffraction data.[1] The harringtonines, a collection of four minor alkaloids which occur with cephalotaxine, have been shown to be esters of cephalotaxine and several simple alkyl malic and tartaric acids.[2] Because of the promising antitumor activity of the harringtonines,[3] there has been keen interest in the *Cephalotaxus* alkaloids, especially in their synthesis.[2b,4,5] We recently described in preliminary form a total synthesis of racemic cephalotaxine,[4a] and we now present a detailed description of this work. Two minor alkaloids, cephalotaxinone and demethylcephalotaxinone are intermediates, and thus this work also constitutes their total synthesis.

Treatment of 3,4-methylenedioxyphenylacetic acid (**2**) with thionyl chloride produced the corresponding acid chloride **3**. Without isolation or purification, **3** was treated with 1-prolinol (**4**) in acetonitrile at −20° in the presence of anhydrous potassium carbonate to give alcohol **5**, contaminated with a small amount of N,O-diacylated product. Compound **5** was most easily purified by briefly heating the crude product with aqueous potassium carbonate in order to selectively saponify the *O*-acyl product. This method produced pure **5** in 82% yield as a colorless oil. Oxidation of alcohol **5** with a combination of dimethyl sulfoxide, dicyclohexylcarbodiimide, and dichloroacetic acid[8] gave aldehyde **6** in 67% yield after silica gel chromatography.



2, X = OH
3, X = Cl



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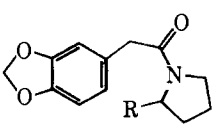
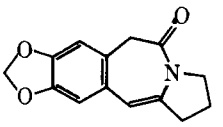


5, R = CH_2OH
6, R = CHO

Aldehyde **6** was smoothly cyclized to the crystalline tetracyclic enamide **7** upon stirring at room temperature in chloroform containing boron trifluoride etherate (87% yield). The intermediate carbinol in this cyclization was never observed, nor was any of the ortho cyclization product detected. Reduction of enamide **7** with lithium aluminum hydride in tetrahydrofuran gave tetracyclic enamine **8** in quantitative yield. The assigned structure for **8** was supported by its NMR spectrum which showed a vinyl singlet at δ 4.83 (vs. δ 5.96 for the vinyl proton in **7**). Enamine **8** can be purified by recrystallization to afford a white solid which decomposes at room temperature over several days but is considerably more stable upon refrigeration. It decomposes very rapidly upon contact with chlorinated solvents.



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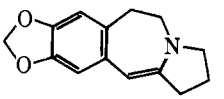

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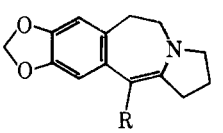
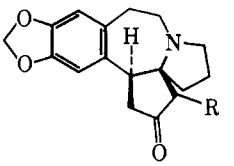
The next phase of the synthesis was concerned with formation of the final five-membered ring of cephalotaxine. Initial approaches attempted utilization of the "endocyclic enamine annelation."[9] Thus, alkylation of **8** with propargyl bromide gave acetylene **9**, which on mercury(II)-catalyzed hydration gave ketone **10**. Treatment of **10** with a wide variety of acid catalysts gave no pentacyclic ketone **13**, nor any other cyclopentanone-containing product. These results are in contrast to the report of Dolby in this area.[4c] In a similar vein, enamine **8** was alkylated with methyl 4-bromo-3-methoxycrotonate, giving compound **11**. A number of attempts were made to convert **11** to **14** but without success. One additional approach was made in an attempt at an analogous acid-catalyzed cyclization of vinyl bromide **12**, prepared by alkylation of enamine **8** with 2,3-dibromopropene. Again, no cyclopentanone-containing product could be detected.



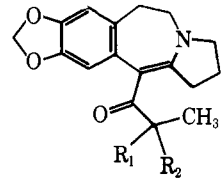
9, R = $CH_2C{\equiv}CH$
10, R = CH_2COCH_3
11, R = $CH_2C(OCH_3){=}CHCOOCH_3$
12, R = $CH_2C(Br){=}CH_2$



13, R = H
14, R = $COOCH_3$

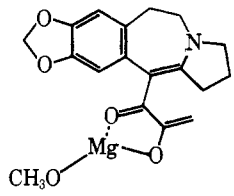
In view of these discouraging results, a different approach was taken to annelate enamine **8**. Acylation of **8** with 2-acetoxypropionyl chloride[10] in acetonitrile produced compound **15** (75%). Hydrolysis of **15** with aqueous potassium carbonate gave the crystalline alcohol **16** (100%). A number of oxidizing agents (e.g., MnO_2, Ag_2CO_3–Celite, cupric acetate, ferric chloride, selenium dioxide) were tried unsuccessfully in an attempt to convert **16** to dicarbonyl

compound **17**. Finally, it was found that lead dioxide[11] would produce **17**, but yields were not reliably reproducible. In addition, dicarbonyl **17** produced by this method could not be crystallized.



15, $R_1 = OCOCH_3$; $R_2 = H$
16, $R_1 = OH$; $R_2 = H$
17, $R_1, R_2 = O$

However, a preferable route to dicarbonyl compound **17** was discovered utilizing the mixed anhydride prepared from pyruvic acid and ethyl chloroformate[12] to acylate enamine **8** in 73% yield. Compound **17** prepared by this method was a stable crystalline orange solid.



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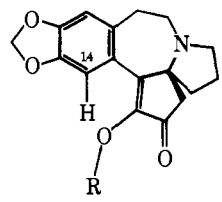
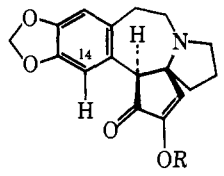


19, R = H
20, R = CH_3



21, R = H
22, R = CH_3

Dicarbonyl compound **17** was then cyclized in an intramolecular Michael reaction using conditions developed by Muxfeldt et al.[13] (magnesium methoxide–methanol), affording demethylcephalotaxinone (**19**)[14] (58%). This cyclization probably proceeds through the intermediate chelated, conformationally rigid magnesium enolate **18**. As might be expected,[13] treatment of compound **17** with nonchelating bases (e.g., sodium hydroxide–methanol) produced a complex mixture of products. Direct comparison of the infrared, NMR, and TLC of our synthetic compound with the natural product[14,15] proved their identity.

Demethylcephalotaxinone, as seen by NMR analysis, exists entirely as the tautomer shown in structure **19**. This conclusion is based on the absence of any vinyl protons and the presence of a two-hydrogen singlet at δ 2.60 due to the protons adjacent to the cyclopentenone carbonyl. None of the tautomer **21** can be detected. It is apparent from molecular models that it is difficult for the cyclopentenone ring and the benzene ring of **19** to achieve coplanarity, thus precluding full overlap of the π orbitals of the α,β-unsaturated carbonyl system with the orbitals of the aromatic ring. It is also apparent that a severe steric interaction is also present between the C-14 aromatic hydrogen and the hydroxyl of the cyclopentenone ring in **19**. The corresponding interaction in **21** between the C-14 hydrogen and the cyclopentenone carbonyl does not seem as severe and certainly does not appear to be worse. In spite of this analysis, tautomer **19** is actually the more stable isomer.

However, we rationalized that methylation of demethylcephalotaxinone (**19**) to give **20** would worsen the aforementioned steric interaction and would tend to twist the α,β-unsaturated carbonyl system even farther from planarity. Methylation of tautomer **21** would add only slight steric strain in cephalotaxinone (**22**). We envisioned that the relative stabilities of tautomeric forms **19** and **21** might be reversed upon methylation, allowing preparation of the desired cephalotaxinone (**22**).

To our chagrin, treatment of demethylcephalotaxinone (**19**) with ethereal diazomethane produced only the unnatural isocephalotaxinone (**20**). However, this is probably a kinetically controlled methylation and does not reflect the relative stabilities of **20** and **22**.

In an attempt to find equilibrating conditions, demethylcephalotaxinone (**19**) was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid for 17 hr. Chromatography of the crude product afforded 45% of desired cephalotaxinone (**22**) and only 15% of isocephalotaxinone (**20**).[19] Cephalotaxinone produced by this method was found to be identical in ir, NMR, and TLC with natural material.[15,16]

To complete the synthesis, cephalotaxinone (**22**) was reduced with sodium borohydride in methanol in a completely stereospecific manner giving racemic cephalotaxine (**1**) (85%).[14a,15] No *epi*-cephalotaxine could be detected in this reaction.

Experimental Section

Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Melting points were determined on a Fisher-Johns hot stage apparatus and are uncorrected. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Infrared spectra were measured on Perkin-Elmer Model 137 and 337 spectrometers. Nuclear magnetic resonance spectra were measured on Varian A-60, A-60A, and XL-100 instruments. Low-resolution mass spectra were determined on a CEC 21-104 instrument using the direct inlet. High-resolution mass spectra were performed at Battelle's Columbus Laboratories on an AEI MS-9 instrument. Brinkman silica gel PF_{254} was used for both analytical and preparative TLC.

***N*-(3,4-Methylenedioxyphenylacetyl)prolinol (5).** A mixture of 18 g (0.10 mol) of 3,4-methylenedioxyphenylacetic acid (**2**)[6] and 20 ml of thionyl chloride was stirred at ambient temperature for 3 hr, and the resulting dark solution was evaporated in vacuo. To a solution of 12 g (0.12 mol) of l-prolinol (**4**)[7] in 125 ml of acetonitrile was added 40 g of anhydrous potassium carbonate, and the mixture was stirred vigorously and cooled in a carbon tetrachloride–Dry Ice bath (−20°). To this mixture was added dropwise the crude acid chloride in 50 ml of acetonitrile. The reaction mixture was stirred an additional 30 min at −20°, diluted with water, and extracted with chloroform. The organic layer was washed with water and 10% hydrochloric acid, dried with magnesium sulfate, and evaporated in vacuo to an oil. Infrared analysis showed a small amount of ester carbonyl to be present.

Purification was best effected by the following procedure. The above oil was dissolved in a mixture of 150 ml of methanol, 13 g of potassium carbonate, and 50 ml of water and was heated at reflux for 1 hr. The mixture was evaporated to a small volume, diluted with water, and extracted with chloroform. The organic extracts were dried ($MgSO_4$) and evaporated in vacuo to 21.5 g (82%) of a colorless oil which appeared homogeneous by TLC (5% methanol–chloroform): ir (max) (film) 3350 and 1630 cm^{-1}; NMR ($CDCl_3$) δ 6.8 (3 H, m), 5.98 (2 H, s), 4.9 (1 H, broad, OH), 4.2 (1 H, m), 3.6 (6 H, m), 1.8 (4 H, m); *m/e* measured 263.1149, calcd 263.1158; uv (max) (CH_3OH) 236 nm (ϵ 3680), 288 (3360).

***N*-(3,4-Methylenedioxyphenylacetyl)prolinal (6).** A mixture containing 21.5 g (0.082 mol) of alcohol **5**, 55 g (0.266 mol) of dicyclohexylcarbodiimide, 6.2 g (0.048 mol) of dichloroacetic acid, and 200 ml of dimethyl sulfoxide[8] was stirred at ambient temperature for 3 hr. Oxalic acid (25 g) was added slowly and cautiously, and the mixture was filtered. The filtrate was diluted with chloroform and washed with water, dilute sodium bicarbonate solution, and water again. The organic extract was dried ($MgSO_4$) and evaporated in vacuo affording a yellow oil. This oil was chromatographed on 150 g of 0.05–0.20 mm of silica gel in ethyl acetate, giving 14 g (67%) of oily, pale-yellow aldehyde which appeared homogeneous by TLC: ir (max) (film) 1720 and 1650 cm^{-1}; NMR

(CCl_4) δ 9.50 (1 H, d, J = 1.5 Hz), 6.8 (3 H, m), 5.92 (2 H, s), 4.3 (1 H, m), 3.5 (4 H, m), 1.9 (4 H, m); uv (max) (CH_3OH) 235 nm (ε 4420), 287 (4030).

5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*][3]-benzazepin-6-one (7). To a solution of 29.4 g (0.113 mol) of aldehyde **6** in 700 ml of chloroform was added 150 ml of boron trifluoride etherate. The reaction mixture was stirred at ambient temperature for 18 hr and washed with water and then with dilute sodium carbonate solution. After drying with magnesium sulfate, the organic layer was evaporated to dryness, affording yellow crystals. This material was filtered through a short column of 0.05-0.20 mm of silica gel in ethyl acetate giving 24.0 g (87%) of pale-yellow crystals, mp 122–126°. An analytical sample was recrystallized from ethyl acetate–hexane, mp 122–123°: ir (max) ($CHCl_3$) 1650 cm^{-1}; NMR ($CDCl_3$) δ 6.65 (1 H, s), 6.52 (1 H, s), 5.96 (1 H, s), 5.90 (2 H, s), 3.68 (2 H, t, J = 3 Hz), 3.26 (2 H, s), 2.74 (2 H, t, J = 3 Hz), 1.90 (2 H, m); uv (max) (C_2H_5OH) 213 nm (ε 26,400), 230 (15,900), 288 (8000), 313 (9000).[18]

5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]-benzazepine (8). A solution of 2.43 g (0.010 mol) of enamide **7** in 90 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was treated with 1.516 g (0.040 mol) of lithium aluminum hydride. The mixture was heated at reflux for 1.25 hr, cooled, and diluted with ether. A solution of 1.5 ml of water in 10 ml of tetrahydrofuran was added slowly, followed by 1.5 ml of 15% sodium hydroxide. The granular precipitate was removed by filtration, and the filtrate was evaporated to afford 2.3 g (100%) of tan solid. An analytical sample recrystallized from ether–hexane had mp 82–83°: ir (max) ($CHCl_3$) 1625 and 1580 cm^{-1}; NMR (C_6D_6) δ 6.62 (1 H, s), 6.44 (1 H, s), 5.45 (2 H, s), 5.00 (1 H, s), 3.1 (2 H, m), 2.8 (4 H, m), 2.45 (2 H, t, J = 4 Hz), 1.5 (2 H, m); uv (max) (CH_3OH) 227 nm (ε 10,000), 323 (15,700); (CH_3OH–HCl) 230 nm (ε 13,800), 285 (13,900).[18]

1-(5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-11-yl)-2-propyne (9). Enamine **8** (176 mg, 0.77 mmol) and 138 mg (1.16 mmol) of propargyl bromide in 6 ml of acetonitrile were heated at reflux for 2.5 hr, and the mixture was evaporated to dryness in vacuo. To the residue was added chloroform and dilute sodium bicarbonate solution. The organic portion was washed with water and saturated sodium chloride, dried with magnesium sulfate, and evaporated to a dark oil. This material was passed through a 1-g column of alumina in ethyl acetate, giving 192 mg (93%) of an unstable oil which appeared homogeneous by TLC and NMR: ir (max) (film) 3300, 2100, and 1625 cm^{-1}; NMR (film) δ 1.2–1.8 (2 H, m), 1.75 (1 H, t, J = 3 Hz), 2.4–3.3 (10 H, m), 5.50 (2 H, s), 6.45 (1 H, s), 7.34 (1 H, s).

1-(5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-11-yl)-2-propanone (10). Acetylene **9** (555 mg, 2.1 mmol) was dissolved in 60 ml of methanol, and 900 mg (4.2 mmol) of red mercuric oxide, along with 1.60 g (10.5 mmol) of boron trifluoride etherate, was added. After stirring at room temperature for 18 hr, the mixture was saturated with gaseous hydrogen sulfide, filtered through Celite, and concentrated in vacuo. The residue was basified with sodium hydroxide and was taken up in chloroform. The organic fraction was washed successively with water and saturated sodium chloride, dried with magnesium sulfate, and evaporated to give 545 mg of an oil. This material was passed through a column of ca. 1 g of alumina in methylene chloride, affording 464 mg (78%) of an oil which was homogeneous by TLC and NMR: ir (max) (film) 1700, 1625, and 1600 cm^{-1}; NMR (C_6D_6) δ 1.2–1.5 (2 H, m), 1.72 (3 H, s), 2.1–3.2 (8 H, m), 3.25 (2 H, s), 5.46 (2 H, s), 6.45 (1 H, s), 6.80 (1 H, s).[4c]

2-Bromo-3-(5,8,9,10-tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo-[2,1-*b*][3]benzazepin-11-yl)-1-propene (12). A solution containing 174 mg (0.76 mmol) of enamine **8** and 228 mg (1.14 mmol) of 2,3-dibromopropene in 10 ml of acetonitrile was heated at reflux for 2.5 hr. The solution was evaporated in vacuo and the residue dissolved in chloroform. The chloroform solution was washed with potassium carbonate solution, water, and saturated sodium chloride, dried with magnesium sulfate, and evaporated. The resulting material was passed through a column of ca. 1 g of alumina in benzene, affording 216 mg (82%) of oily product: ir (max) (film) 1625 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.1 (2 H, m), 2.5–3.7 (10 H, m), 5.47 (1 H, m), 5.75 (1 H, m), 5.88 (2 H, s), 6.52 (1 H, s), 6.75 (1 H, s).

Methyl 4-Bromo-3-methoxycrotonate. A solution of 13.0 g (0.1 mol) of methyl 3-methoxycrotonate,[17] 19.58 g (0.11 mol) of *N*-bromosuccinimide, and 0.2 g of benzoyl peroxide in 100 ml of carbon tetrachloride was heated at reflux and irradiated with a 150-W floodlamp for 0.75 hr. The mixture was filtered and distilled, affording 16.3 g (78%) of clear liquid, bp 66–70° (0.5 Torr): ir (max) (film) 1710, 1640 cm^{-1}; NMR (CCl_4) δ 3.68 (3 H, s), 3.74 (3 H, s), 4.51 (2 H, s), 5.16 (1 H, s).[18]

Methyl 4-(5,8,9,10-Tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo-[2,1-*b*][3]benzazepin-11-yl)-3-methoxy-2-butenoate (11). A solution of 334 mg (1.46 mmol) of enamine **8** and 455 mg (2.19 mmol) of methyl 4-bromo-3-methoxycrotonate in 15 ml of acetonitrile was heated at reflux for 16 hr. The mixture was evaporated to dryness in vacuo, and the residue was dissolved in chloroform. The chloroform solution was washed with potassium carbonate solution, water, and saturated sodium chloride solution, dried with magnesium sulfate, and evaporated in vacuo. The residual oil was chromatographed on silica gel in chloroform, yielding 250 mg (48%) of a pale-yellow oil: ir (max) (film) 1700 and 1600 cm^{-1}; NMR (C_6D_6) δ 0.8–1.2 (2 H, m), 1.9–3.0 (8 H, m), 2.45 (3 H, s), 3.00 (3 H, s), 3.70 (2 H, s), 4.45 (1 H, s), 4.92 (2 H, s), 5.92 (1 H, s), 6.62 (1 H, s). This compound was found by TLC to be homogenous.

2-Hydroxy-1-(5,8,9,10-tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-11-yl)-1-propanone Acetate (15). A mixture of 2.3 g (10 mmol) of enamine **8** and 8.40 g (0.1 mol) of sodium bicarbonate in 70 ml of acetonitrile was treated with 3.01 g (20 mmol) of 2-acetoxypropionyl chloride,[10] and the reaction mixture was stirred for 17 hr. After diluting with saturated sodium chloride solution, the mixture was extracted thoroughly with chloroform. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The resulting oil (4.05 g) was chromatographed on 0.05–0.20 mm of silica gel in ethyl acetate to give 2.68 g (75%) of pure crystalline product. An analytical sample was recrystallized from ethyl acetate–hexane, mp 132–133°: ir (max) ($CHCl_3$) 1740 and 1650 cm^{-1}; NMR ($CDCl_3$) δ 7.05 (1 H, s), 6.60 (1 H, s), 5.94 (2 H, s), 5.60 (1 H, q, J = 7 Hz), 2.8–3.7 (8 H, m), 2.09 (3 H, s), 1.9 (2 H, m), 1.12 (3 H, d, J = 7 Hz); uv (max) (CH_3OH) 232 nm (ε 9030), 268 (7430), 285 (7910), 310 (11,500), 340 (16,900).[18]

2-Hydroxy-1-(5,8,9,10-tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-11-yl)-1-propanone (16). To a solution of 1.56 g (4.55 mmol) of acetate **15** in 30 ml of methanol was added a solution of 3 g (21.5 mmol) of potassium carbonate in 30 ml of water. The resulting mixture was stirred for 3.25 hr at room temperature and was diluted with chloroform. Anhydrous magnesium sulfate (30 g) was added, and the mixture was filtered and evaporated in vacuo to afford 1.37 g (100%) of a solid. A sample was recrystallized from ethyl acetate–hexane for analysis, mp 139–141°: ir (max) ($CHCl_3$) 3300 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 6.56 (2 H, s), 5.90 (2 H, s), 4.75 (1 H, q, J = 7 Hz), 4.1 (1 H, OH), 2.8–3.7 (8 H, m), 2.0 (2, m), 0.85 (3 H, d, J = 7 Hz); uv (max) (CH_3OH) 232 nm (ε 10,900), 254 (9200), 286 (10,200), 312 (15,000), 337 (20,900).[18]

2-Oxo-1-(5,8,9,10-tetrahydro-6*H*-1,3-dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-11-yl)-1-propanone (17). A. From Enamine 8. A mixture of 3.08 g (35 mmol) of pyruvic acid and 8.5 g (0.1 mol) of anhydrous sodium bicarbonate in 20 ml of dry acetonitrile was stirred at room temperature for 30 min. The mixture was cooled in ice, 3.76 g (35 mmol) of ethyl chloroformate was added,[12] and the mixture was stirred in an ice bath. After 2 hr, 3.97 g (18.3 mmol) of freshly prepared enamine **8** was added, and the resultant mixture was stirred at ice-bath temperature for 30 min. Solid material was removed by filtration and washed thoroughly with chloroform. The organic solutions were combined and evaporated to dryness in vacuo. The residue was dissolved in chloroform, washed with water and saturated sodium bicarbonate solution, and dried with magnesium sulfate. The solution was evaporated to a brown solid which was filtered through a short column of silica gel in ethyl acetate. The total eluate was evaporated, and the resulting solid was recrystallized from ethyl acetate–hexane, 3.9 g (73%). An analytical sample was recrystallized from ethyl acetate–hexane, mp 155°: ir (max) ($CHCl_3$) 1690 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.0 (2 H, m), 2.20 (3 H, s), 2.9–3.8 (8 H, m), 5.85 (2 H, s), 6.48 (1 H, s), 6.55 (1 H, s); uv (max) (CH_3OH) 234 nm (ε 7600), 257 (4700), 298 (7900), 354 (8500).[18]

B. From Alcohol 16. A solution of 35 mg (0.115 mmol) of alcohol **16** in 10 ml of benzene was treated with 250 mg of red lead oxide.[11] After stirring for 24 hr at room temperature, it was evi-

dent by TLC that no reaction had occurred. The benzene was removed and replaced by toluene. After heating at reflux for 1 hr, the mixture was filtered through Celite and was evaporated to dryness in vacuo. The residue was filtered through a column of silica gel (ca. 1 g) in acetone, affording 20 mg (57%) of yellow oil upon evaporation of solvent. This material has spectra as described above in part A (*m/e* measured 299.1142, calcd 299.1158).

(*RS*)-5,6,8,9-Tetrahydro-1-hydroxy-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-2(3*H*)-one (Racemic Demethylcephalotaxinone) (19). A solution of magnesium methoxide was prepared by dissolving 0.7 g (0.033 g-atom) of magnesium turnings in 33 ml of boiling methanol.[13] The solution was cooled in ice and 1.00 g (3.33 mmol) of α-dicarbonyl compound **17** in 20 ml of methanol was added. The ice bath was removed, and the mixture was stirred for 1.5 hr at room temperature. The mixture was acidified with 3.4 g of 96% sulfuric acid,[19] excess solid sodium bicarbonate was then carefully added, and the mixture was filtered through Celite and evaporated in vacuo. The resulting solid was extracted continuously in a Soxhlet apparatus for 21 hr with chloroform. Evaporation of the extract in vacuo provided 579 mg (58%) of racemic demethylcephalotaxinone. A sample recrystallized from methanol had mp 104–107°: ir (max) ($CHCl_3$) 3475, 3300, 1700, and 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (4 H, m), 2.60 (2 H, s), 2.9–3.6 (6 H, m), 5.10 (1 H, br s, OH), 6.00 (2 H, s), 6.75 (1 H, s), 7.00 (1 H, s); uv (max) (C_2H_5OH–HCl) 232 nm (ϵ 7800), 262 (8500), 324 (8700); uv (max) (C_2H_5OH–KOH) 341 nm (ϵ 13,100); *m/e* measured 299.1155, calcd 299.1158.[15]

Racemic Cephalotaxinone (22) and Isocephalotaxinone (20). A. A Dean-Stark trap was connected to a flask containing 1.050 g (3.5 mmol) of demethylcephalotaxinone (**19**), 2.660 g (14 mmol) of *p*-toluenesulfonic acid monohydrate, 70 ml of methanol, 70 ml of dioxane, and 70 ml of 2,2-dimethoxypropane.[19] The mixture was slowly heated at such a rate that 100 ml of distillate was collected in the trap over 17 hr. The mixture was evaporated to dryness, dissolved in chloroform, and filtered. The filtrate was chromatographed on 125 g of silica gel, eluting with 3% methanol–chloroform. Fractions were combined which contained mixtures of **22** and **20** (1.005 g total). This material was rechromatographed on a column of silica gel PF_{254} (95 g) in 3% methanol–chloroform, affording 494 mg (45%) of racemic cephalotaxinone (**22**) and 166 mg (15%) of isocephalotaxinone (**20**).

Racemic cephalotaxinone was recrystallized from ethyl acetate, mp 178–180°. Direct comparison of the spectra of this material with those of natural product showed them to be identical.[15]

Isocephalotaxinone was recrystallized from ether–hexane: mp 130.5–132°; ir (max) (film) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (2 H, m), 2.52 (2 H, s), 2.8–3.4 (6 H, m), 5.95 (2 H, s), 6.65 (1 H, s), 6.75 (1 H, s); uv (max) (CH_3OH) 237 nm (ϵ 8670), 251 (sh) (8200), 295 (sh) (8200), 314 (8950); *m/e* measured 313.1301, calcd 313.1314.[18]

B. A solution of 50 mg of demethylcephalotaxinone (**19**) in methylene chloride after treatment with an ethereal solution of diazomethane (from nitrosomethylurea) was stirred at room temperature for 18 hr. The solution was evaporated to dryness, and the residue was purified by preparative TLC on a silica gel PF_{254} plate in 5% methanol–chloroform, affording 31 mg (59%) of isocephalotaxinone having spectra identical with those of material prepared as described above. No cephalotaxinone (**22**) was detected in this preparation.

Racemic Cephalotaxine (1). A solution of 682 mg (2.1 mmol) of cephalotaxinone (**22**) in 50 ml of absolute methanol was treated with 2 g (54 mmol) of sodium borohydride over 1 min. The reaction mixture was allowed to stand at room temperature for 30 min, evaporated to dryness in vacuo, diluted with saturated sodium chloride solution, and extracted with chloroform five times and with ethyl acetate once. The organic extracts were combined and dried with magnesium sulfate. Evaporation of the solvent in vacuo left 579 mg (85%) of essentially pure racemic cephalotaxine (**1**). A sample was recrystallized from ether, mp 116–118°. Spectra and TLC of natural and synthetic cephalotaxine were indistinguishable.[15]

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References and Notes

(1) (a) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963); (b) W. W. Paudler and J. McKay, *ibid.*, **38**, 2110 (1973); (c) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (d) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *ibid.*, 4085 (1969); (e) S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, **39**, 1269 (1974); (f) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).

(2) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *Tetrahedron Lett.*, 815 (1970); (b) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972); (c) S. Brandange, S. Josephson, and S. Vallen, *Acta Chem. Scand., Ser. B*, **28**, 153 (1974); (d) T. Ipaktchi and S. M. Weinreb, *Tetrahedron Lett.*, 3895 (1973).

(3) R. G. Powell, D. Weisleder, and C. R. Smith, Jr., *J. Pharm. Sci.*, **61**, 1227 (1972).

(4) Cephalotaxine synthesis: (a) J. Auerbach and S. M. Weinreb, *J. Am. Chem. Soc.*, **94**, 7172 (1972); (b) M. F. Semmelhack, B. P. Chong, and L. D. Jones, *ibid.*, **94**, 8629 (1972); (c) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, **37**, 3691 (1972); (d) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973).

(5) Harringtonine synthesis: (a) J. Auerbach, T. Ipaktchi, and S. M. Weinreb, *Tetrahedron Lett.*, 4561 (1973); (b) T. R. Kelly, J. C. McKenna, and P. A. Christenson, *ibid.*, 3501 (1973); (c) K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *ibid.*, 283 (1974).

(6) E. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

(7) O. Vogl and M. Pohm, *Monatsh. Chem.*, **83**, 541 (1952).

(8) J. G. Moffatt in "Oxidation", Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N.Y., 1971, Chapter 1.

(9) (a) R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *J. Chem. Soc., Chem. Commun.*, 877 (1969); (b) F. C. Tahk and S. L. Keely, Jr., *J. Am. Chem. Soc.*, **90**, 5584 (1968).

(10) E. B. Reid and G. Denny, Jr., *J. Am. Chem. Soc.*, **81**, 4632 (1959).

(11) H. H. Inhoffen, K. Radscheit, U. Stache, and V. Koppe, *Justus Liebigs Ann. Chem.*, **684**, 24 (1965).

(12) Cf. E. W. Colvin, J. Martin, W. Parker, R. A. Raphael, B. Shroot, and M. Doyle, *J. Chem. Soc., Perkin Trans. 1*, 860 (1972).

(13) H. Muxfeldt, M. Weigele, and V. Van Rheenen, *J. Org. Chem.*, **30**, 3573 (1965).

(14) (a) R. G. Powell and K. L. Mikolajczak, *Phytochemistry*, **12**, 2987 (1973); (b) S. Asada, *Yakugaku Zasshi*, **93**, 916 (1973).

(15) We are greatly indebted to Mr. R. G. Powell, USDA, Peoria, Ill., for comparison samples, spectral data, and unpublished information.

(16) Only the more stable cis-fused ring product **22** was formed. 4-*epi*-Cephalotaxinone has never been observed by us or by other workers.

(17) E. E. Smissman and A. N. Voldeng, *J. Org. Chem.*, **29**, 3161 (1964).

(18) A correct combustion analysis was obtained for this compound.

(19) Merck Sharp & Dohme Research Laboratories under Contract NIH-72-2002 from the National Cancer Institute has repeated our total synthesis of cephalotaxine and has increased our overall yield of 4.5 to 10.4%. This improvement is due primarily to increased yield in two steps: (a) conversion of **17** to demethylcephalotaxinone (**19**) was increased to 84% yield by allowing the acidified reaction mixture to stand for 1 hr before work-up; (b) demethylcephalotaxinone (**19**) could be converted in *quantitative yield* to cephalotaxinone (**22**) by deleting methanol from the reaction mixture. *No* isocephalotaxinone (**20**) was detected using these conditions. We are grateful to Dr. R. D. Babson of Merck for informing us of these results.