was added and the solution was refluxed for 2 h. The solvent was evaporated under reduced pressure followed by high vacuum (0.1 Torr, 45 min) to afford a brown oil. The crude residue was flash chromatographed on silica gel (4:1 benzene–ethyl acetate) to give the carbapenam **6** (18 mg, 30%) as a pale yellow oil: R_f 0.33 (4:1 benzene–ethyl acetate); IR (thin film) 2970, 2880, 1760 (br) cm^{-1}, (CCl_4) 1775, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7.4), 1.86–2.05 (m, 2 H), 2.44 (dd, 1 H, J = 7.6, 18.9), 2.90 (ddd, 1 H, J = 0.69, 6.9, 18.9), 3.12 (ddd, 1 H, J = 2.0, 6.9, 8.1), 3.80 (s, 3 H), 3.90 (ddd, 1 H, J = 2.0, 7.0, 7.5), 4.69 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.53, 22.17, 41.41, 53.11, 53.85, 62.59, 64.00, 165.70, 174.85, 207.40; EIMS m/z 211, 179, 151, 141, 114, 96, 69; HRMS calcd for $C_{10}H_{13}NO_4$ 211.0844, found 211.0842.

Acknowledgment. We gratefully acknowledge financial support of this research from the NIH and Eli Lilly and Company. We also thank Dr. Bruce Plashko for obtaining the mass spectral data.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for **3**, **3a**, **3b**, **4**, **4a**, **4b**, **5**, **6**, **19a**, **19b**, **22**, **25**, and **26** (27 pages). Ordering information is given on any current masthead page.

A Friedel–Crafts Cyclization Approach toward Cephalotaxine

Chin-Kang Sha,* Jenn-Jong Young, Chun-Pong Yeh, Shang-Chia Chang, and Sue-Lein Wang

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30043, Republic of China

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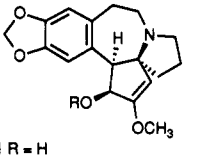
The 1-azaspiro[4.4]nonane portion **11** of cephalotaxine was prepared via an intramolecular S_N2' substitution reaction followed by ozonolysis; condensation of **11** with the aromatic portion **13** gave compound **15**; a Friedel–Crafts cyclization of **15** in polyphosphoric acid smoothly afforded the cephalotaxine skeleton **16**. A single-crystal X-ray analysis of the HCl salt of **16** confirmed the structure of **16**.

Cephalotaxine (**1**), the major alkaloid of *C. harringtonia*, has a unique skeleton with an unusual 1-azaspiro[4.4]nonane moiety fused to a benzazepine system.[1] The simple ester derivatives of **1** including harringtonine (**2**), homoharringtonine (**3**), isoharringtonine (**4**), and deoxyharringtonine (**5**) were shown to exhibit significant antileukemia activity.[2] Due to this potential pharmacological activity and its unique structural features, cephalotaxine (**1**) has been a target of many synthetic efforts. Among them several elegant total syntheses of **1** have been achieved.[3] Recently many novel synthetic entries[4] to the cephalotaxine alkaloid have been reported which prompted us to disclose our efforts aimed at a practical route for cephalotaxine ring synthesis. In this paper, we report our efficient approach to the cephalotaxine skeleton **16** via an intramolecular Friedel–Crafts cyclization reaction.



1 R = H
(-)-Cephalotaxine

2 R = $(CH_3)_2C(OH)CH_2CH_2C(OH)(CH_2CO_2CH_3)CO$-
(-)-Harringtonine

3 R = $(CH_3)_2C(OH)CH_2CH_2CH_2C(OH)(CH_2CO_2CH_3)CO$-
(-)-Homoharringtonine

4 R = $(CH_3)_2CHCH_2CH_2$-C(OH)-CO-
$CH(OH)CO_2CH_3$
(-)-Isoharringtonine

5 R = $(CH_3)_2CHCH_2CH_2C(OH)(CH_2CO_2CH_3)CO$-
(-)-Deoxyharringtonine

The bicyclic lactam **6**, prepared previously in our laboratory,[5] was treated with di-*tert*-butyl dicarbonate, triethylamine, and 4-(dimethylamino)pyridine[6] to give the protected lactam **7** (94%). Reaction of **7** with 2.2 equiv of methyllithium gave the carbinol **8**. Crude **8** was then treated with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane at room temperature to afford the spiro compound **9** (75% overall yield from **7**) via an intramolecular S_N2' substitution reaction (5-*exo*-*trig*[7]). Cleavage of the exo-cyclic double bond of **9** by ozonolysis gave **10** (96%). Removal of the *tert*-butoxycarbonyl group of **10** by trifluoroacetic acid produced **11**. Reaction of crude **11** immediately with *p*-(nitrophenyl)sulfonyl ester **12** afforded **14** (72%). Attempted Friedel–Crafts cyclization of **14** with various acid catalysts to close the seven-membered ring failed. Therefore, the spiroamino ketone **11** was then condensed with the *p*-nitrophenylsulfonyl ester **13** with a dimethoxyphenyl group to give compound

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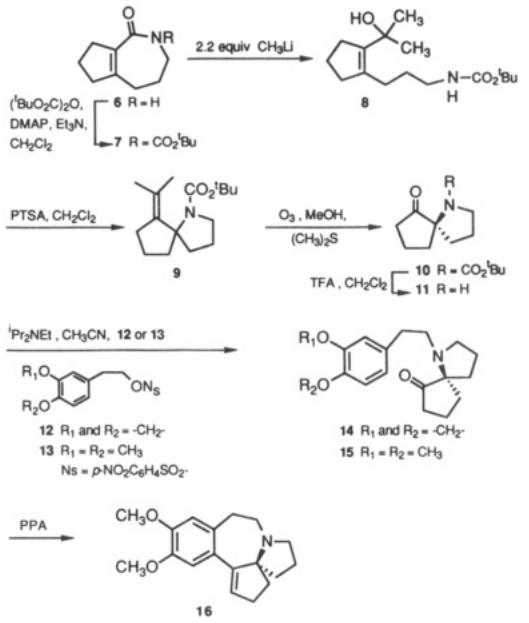
Scheme I



15 (79%). Compound 15, to our surprise, cyclized smoothly in polyphosphoric acid to afford 16 (56%) and some recovered starting material 15 (24%) whereas under the same reaction conditions compound 14 gave no cyclized product, (Scheme I).

We attributed this dramatic difference in reactivity[8] between 14 and 15 to the stereoelectronic effect.[9] In compound 15 lone pairs of electrons of the two methoxy groups could have a good orbital overlap with the π-system of the phenyl ring as a result of their free rotation. However, in compound 14 the rigid methylenedioxy substituent on the phenyl ring does not allow a complete orbital overlap between oxygen lone pairs of electrons and the π-system of the phenyl group (Figure 1). Due to the stereoelectronic effect, the phenyl ring of 15 is of higher electron density and therefore more reactive toward an electrophilic reaction than that of 14.

The structure of the product 16 was confirmed by a single-crystal X-ray analysis of the HCl salt of 16. A molecular drawing of the HCl salt of 16 is shown in Figure 2.

In summary, we have synthesized the cephalotaxine skeleton 16 by a novel approach in which the intramolecular S_N2' cyclization of 8 to 9 and the Friedel–Crafts cyclization of 15 to 16 are the key steps. Application of this approach for the total synthesis of (±)-cephalotaxine needs further investigation.

Experimental Section

General. Melting points were determined with a Yanaco micro melting point apparatus. ^{1}H NMR spectra were recorded on a Varian EM-390, a JEOL HX-100, or a Bruker AM-400 spectrometer. ^{13}C NMR spectra were recorded on a JEOL HX-100 or a Bruker AM-400 spectrometer. Mass spectra refer to the electron impact mass spectra and were recorded on a JEOL TMS-D-100 mass spectrometer. High-resolution mass spectra

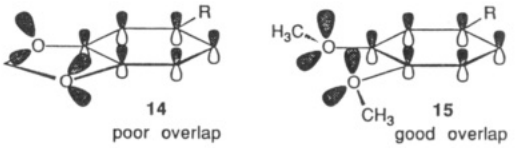


Figure 1. The orientation of lone pairs of electrons of oxygen atoms in compounds 14 and 15.

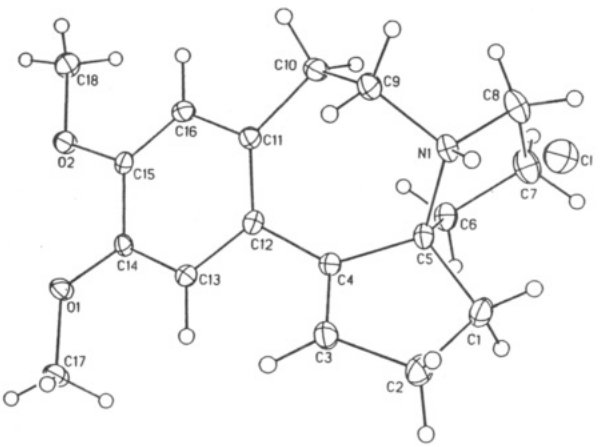


Figure 2. Molecular drawing of the HCl salt of 16 generated by SHELXTL PLUS.

were taken on a JEOL HX-110 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 781 spectrometer, and UV spectra were recorded on a Perkin-Elmer Lambda 5 UV–vis spectrometer. Single-crystal X-ray analysis was performed on a Nicolet R3/V diffractometer. Solvents were distilled before use and were dried, as necessary, according to literature procedures. All reactions were conducted under a nitrogen atmosphere. Elemental analyses were performed by the Microanalytical Laboratory of the NSC Regional Instrumentation Center operated by Department of Chemistry, National Cheng Kung University, Tainan, Taiwan.

2-(*tert*-Butoxycarbonyl)-3,4,5,6,7,8-hexahydrocyclopent-[*c*]azepin-1(2*H*)-one (7). To a solution of 6 (243 mg, 1.61 mmol) in dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (1.4 g, 6.44 mmol), triethylamine (0.23 mL, 167 mg, 1.61 mmol), and 4-(dimethylamino)pyridine (196 mg, 1.61 mmol). The reaction mixture was heated to reflux for 16 h. The mixture was washed with ice-cold 5% hydrochloric acid solution, saturated sodium carbonate solution, and brine. The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 1:6) gave 7 (380 mg, 94%) as a yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 1.70–2.10 (m, 4 H), 2.26–2.86 (m, 6 H), 3.71 (t, 2 H, J = 6.0 Hz); MS m/z (relative intensity) 251 (M^+, 5), 196 (37), 195 (100), 151 (56), 84 (41), 57 (45); IR (neat) 2960, 2935, 1710, 1695, 1452, 1370, 1289, 1148 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1524.

1-[3-[(*tert*-Butoxycarbonyl)amino]propyl]-2-(2-hydroxyisopropyl)cyclopentene (8). To a solution of 7 (174 mg, 0.69 mmol) in anhydrous tetrahydrofuran (5 mL) was added 1.5 N methyllithium in hexane (2.3 mL, 3.45 mmol) dropwise at −78 °C. After being stirred at −78 °C for 0.5 h, the reaction was quenched with water. Then the reaction mixture was extracted with ether. The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated to give 8 (180 mg). The crude product 8 was used in the next reaction without further purification: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 1.41 (s, 9 H), 1.52–2.70 (m, 11 H), 3.10 (q, 2 H, J = 7 Hz), 5.01 (br s, 1 H); MS m/z (relative intensity) 283 (M^+), 265 (23), 209 (100), 148 (77), 122 (79); IR (neat) 3400, 1700, 1610 cm^{-1}.

1-Aza-1-(*tert*-butoxycarbonyl)-6-isopropylidenespiro-[4.4]nonane (9). To a solution of 8 (232 mg, 0.82 mmol) in anhydrous benzene (8 mL) was added *p*-toluenesulfonic acid (20 mg). The reaction mixture was stirred at room temperature for 3 h and then neutralized with saturated sodium carbonate solution. The mixture was extracted with ether. The organic layer was dried

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(8) In two reported Friedel–Craft cyclization methods toward cephalotaxine, we found that the compound with dimethoxyphenyl ring underwent Friedel–Crafts cyclization smoothly, whereas the compound with (methyhenedioxy)phenyl ring gave only the rearranged product and failed to cyclize; see ref 3d and Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.

(9) Deslongchamps, P. *Stereoelectronic Effect in Organic Chemistry*; Pergamon Press: Oxford, 1983; Chapter 8, p 319.

with anhydrous magnesium sulfate, filtered, and concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 1:6) gave **9** (169 mg, 89%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 1.54 (s, 3 H), 1.62 (s, 3 H), 1.38–2.52 (m, 10 H), 3.30–3.77 (m, 2 H); ^{13}C NMR (25.4 MHz, $CDCl_3$) δ 19.0 (q), 22.6 (q), 22.6 (t), 22.7 (t), 28.5 (q), 31.3 (t), 39.1 (t), 39.4 (t), 47.1 (t), 70.1 (s), 78.2 (s), 121.5 (s), 137.7 (s), 153.5 (s); MS m/z (relative intensity) 265 (M^+, 10), 209 (100), 148 (31), 122 (52); IR (neat) 2950, 2870, 1690, 1392, 1250, 1175, 1135, 1100, 935, 870, 775; HRMS calcd for $C_{16}H_{27}NO_2$ 265.2042, found 265.2037.

1-Aza-1-(*tert*-butoxycarbonyl)spiro[4.4]nonan-6-one (10). To a solution of **9** (159 mg, 0.6 mmol) in methanol (8 mL) was bubbled with ozone at 0 °C. The reaction was followed by thin-layer chromatography until the starting material disappeared. The reaction was then quenched with dimethyl sulfide (1 mL). The reaction mixture was stirred at room temperature for 5 min and then concentrated. The residue was purified by silica gel flash column chromatography (ethyl acetate–hexane, 1:6) to give **10** (137 mg, 96%) as a colorless oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.61–2.69 (m, 10 H), 3.33–3.73 (m, 2 H); MS m/z (relative intensity) 239 (M^+, 29), 211 (21), 183 (38), 166 (13), 155 (38), 127 (100); IR (neat) 2965, 2870, 1745, 1685, 1389, 1175, 1145, 1098. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.50; H, 9.12; N, 5.73.

1-Aza-1-[2-[3,4-(methylenedioxy)phenyl]ethyl]spiro[4.4]nonan-6-one (14). To a solution of **10** (900 mg, 3.76 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 0.5 h. After neutralization with saturated sodium carbonate solution at 0 °C, the mixture was extracted with dichloromethane. The combined organic layer was dried with anhydrous magnesium sulfate and concentrated. The residue was then dissolved in acetonitrile (10 mL). To the solution was added a solution of **12** (2 g, 5.6 mmol) and diisopropylethylamine (2 mL, 1.46 g, 11.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 3 days. The solvent was then removed by a rotary evaperator. The residue was taken into dichloromethane solution. The organic layer was dried with anhydrous magnesium sulfate and then concentrated. Silica gel flash column chromatography (ethyl acetate–hexane, 1:1) gave **14** (778 mg, 2.71 mmol, 72%) as a yellow oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.50–2.30 (m, 10 H), 2.44–2.76 (m, 4 H), 2.80–3.24 (m, 2 H), 5.89 (s, 2 H), 6.48–6.77 (m, 2 H); ^{13}C NMR (25.4 MHz, $CDCl_3$) δ 18.2 (t), 21.8 (t), 32.1 (t), 35.6 (t), 35.9 (t), 37.3 (t), 51.7 (t), 68.3 (t), 73.6 (t), 100.4 (t), 107.7 (d), 108.8 (d), 121.0 (d), 133.8 (s), 145.3 (s), 147.0 (s), 221.5 (s); MS m/z (relative intensity) 287 (M^+, 15), 259 (100), 231 (15), 166 (23), 152 (35), 148 (46), 124 (69); IR (neat) 2960, 2880, 1735, 1622, 1495, 1445, 1247, 1180, 1100, 1045 935, 812, 733 cm^{-1}.

1-Aza-1-[2-(3,4-dimethoxyphenyl)ethyl]spiro[4.4]nonan-6-one (15). The same procedure as that for **14** was used. Compound **10** (195 mg, 0.76 mmol), **13** (100 mg, 1.9 mmol), and diisopropylethylamine (3 mL, 2.23 g, 17 mmol) reacted for 3 days to give **15** as a yellow oil (182 mg, 79%): ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.48–2.52 (m, 10 H), 2.52–2.88 (m, 4 H), 2.92–3.28 (m, 2 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 6.24–6.92 (m, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9 (t), 21.5 (t), 31.6 (t), 35.3 (t), 35.5 (t), 36.9 (t), 51.4 (t), 51.5 (t), 55.3 (q), 73.4 (s), 110.7 (d), 111.6 (d), 120.0 (d), 132.6 (s), 146.8 (s), 148.2 (s), 221.6 (s); DEPT technique was used to determine the multiplicity; MS m/z (relative intensity) 303 (M^+, 10), 275 (78), 247 (14), 182 (14), 164 (100), 152 (29), 124 (50); IR (neat) 2950, 2825, 1730, 1600, 1511, 1460, 1425, 1260, 1234, 1138, 1030, 810, 768; HRMS calcd for $C_{18}H_{25}NO_3$ 303.1835, found 303.1841.

(*RS*)-2,3,5,6,8,9-Hexahydro-11,12-dimethoxy-4*H*-cyclopenta[*a*]pyrrolo[2,1-*b*][3]benzazepine (16). A mixture of **15** (504 mg, 1.66 mmol) and polyphosphoric acid (4 g) was stirred and heated at 60 °C for 20 h. The reaction mixture was then poured into a cold saturated sodium carbonate solution. The solution was then adjusted to basic (pH = 10) by sodium hydroxide solution and extracted with dichloromethane (3 × 40 mL). The organic layer was dried with anhydrous magnesium sulfate and concentrated. Silica gel flash column chromatography (dichloromethane–methanol, 9:1) gave the recovered starting material **15** (122 mg, 24%) and product **16** (240 mg, 56%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.45 (m, 1 H), 1.57–1.78 (m, 3 H), 1.82–1.95 (m, 2 H), 2.08–2.22 (m, 1 H), 2.27–2.40 (m, 1 H), 2.69–3.00 (m, 4 H), 3.18–3.35 (m, 1 H), 3.35–3.48 (m, 1 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 5.65 (t, 1 H, J = 2.4 Hz), 6.51 (s, 1 H), 6.58 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.0 (t), 29.0 (t), 32.1 (t), 35.2 (t), 40.8 (t), 43.5 (t) 48.9 (t), 55.5 (q), 55.6 (q), 78.6 (s), 112.2 (d), 113.0 (d), 127.4 (s), 128.2 (d), 129.1 (s), 146.4 (s), 147.8 (s), 150.0 (s); MS m/z (relative intensity) 285 (M^+, 100), 270 (20); IR (neat) 2900, 1600, 1514, 1462, 1240, 1210, 1145, 1150, 1030 cm^{-1}; HRMS calcd for $C_{18}C_{23}NO_3$ 285.1729, found 285.1710. For the single-crystal X-ray analysis, a crystal of the HCl salt of **16** was obtained from recrystallization in ethyl acetate and dichloromethane and subjected to X-ray analysis. Crystal data of **16**, $[C_{18}H_{23}O_2NH]^+Cl^-$: M = 321.88, monoclinic, space group $P2_1/c$, a = 8.070 (2) Å, b = 8.3761 Å, c = 24.211 (6) Å, β = 92.49 (2)°, Z = 4, D_c = 1.31 g/cm^3. A total of 2521 independent reflections were measured of which 1870 were considered observed [$I > 2.5\sigma(I)$]. The structure was solved by the direct method to an R value 0.0466. All calculations were performed on a Micro Vax II based Nicolet SHELXTL PLUS system.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support.

Supplementary Material Available: X-ray data of the HCl salt of **16**, ^{1}H NMR spectra of compounds **7**, **8**, **9**, **10**, **14**, **15**, and **16**, and ^{13}C NMR spectra of compounds **9**, **14**, **15**, and **16** (17 pages). Ordering information is given on any current masthead page.

Total Syntheses of Tubotaiwine and 19,20-Dihydro-20-*epi*-akuammicine

Martin E. Kuehne,* Deborah A. Frasier, and Timothy D. Spitzer

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

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Starting from the indoloazepine **9**, the title products **2** and **7** were synthesized in seven steps in 27 and 22% overall yields, respectively.

Introduction

Synthetic efforts leading to pentacyclic *Strychnos* alkaloids, represented by akuammicine (**1**) and tubotaiwine (**2**), have received less attention than those directed at other classes of indole or indoline alkaloids.[1,2] Nearly all of the studies that culminated in the former ring system utilized an oxidative cyclization of a stemmadenine-type

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