ences in the fine structure of the nmr and ir spectra. Both bridgehead olefins are probably produced by the Hofmann route, and, by analogy with the thermolysis[3c] of 1-bicyclo[4.2.1]nonyltrimethylammonium hydroxide, it is likely that the $\Delta^{1(7)}$ olefin is the major olefin from this reaction. Thus, we conclude that bridgehead olefin **1** is formed in good yield from the thionocarbonate **13** and that both bridgehead olefins **1** and **2** are probably formed in small amounts in thermolysis of quaternary ammonium hydroxide **4**. We are continuing to investigate synthetic routes to **1** and **2** in the hope that we can prepare them under mild conditions and record their spectra.

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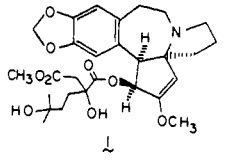
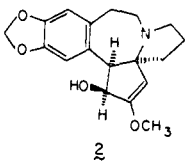
Total Synthesis of Cephalotaxus Alkaloids

Sir:

The harringtonine family of minor alkaloids from *Cephalotaxus harringtonia* (Japanese plum yew) includes active inhibitors against experimental lymphoid leukemia in mice at relatively low dosage levels.[1] The active species are all relatively simple esters [*e.g.*, harringtonine (**1**)] of cephalotaxine (**2**), the major alkaloid of *C. harringtonia*.[2] The unusual 1-azaspiro[4.4]nonene structural feature and the relative scarcity of the natural material attracted our interest in the total synthesis of cephalotaxine. We wish to report a simple, efficient, convergent synthesis of a key intermediate **3**, and successful conversion of **3** to cephalotaxinone (**4**) and cephalotaxine (**2**).



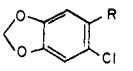
1



2

Cephalotaxinone (**4**), also obtained from *C. harringtonia*,[3] is an obvious relay intermediate as it is known to give cephalotaxine (**2**) by stereospecific hydride reduction.[4] Our synthetic sequence begins with the preparation of the *p*-nitrobenzenesulfonate ester (**5**) of 2-(2-chloro-4,5-methylenedioxophenyl)ethyl alcohol and 1-aza-7-methoxyspiro[4.4]non-6-en-8-one (**6**), which are related to the two sections of cephalotaxinone, as dissected in representation **4**.

Piperonat was converted to 6-chloropiperonylacetic acid (**10**, mp 176.5–177.5°, lit.[5] 174–175°) in 55% overall yield *via* the intermediates **7–9** using minor modifications of known procedures.[5–7] Reduction of **10** with lithium aluminum hydride gave an alcohol (**11**, 96% yield)[8] which was converted to *p*-nitrobenzenesulfonate ester **5** *via* the sodium alkoxide of **11** (from sodium hydride–tetrahydrofuran) and *p*-nitrobenzenesulfonyl chloride (2 equiv) in tetrahydrofuran.[9] The yellow crystalline sulfonate ester (**5**) is obtained in 92% yield, mp 143–144°.



7, R = CH_2OH
8, R = CH_2Cl
9, R = CH_2CN
10, R = CH_2CO_2H
11, R = CH_2CH_2OH

The preparation of the heterospirocycle **6** began with the reaction of 2-ethoxy-1-pyrroline and 3 mol equiv of allylmagnesium bromide in ether at 25° for 18 hr. After hydrolysis of excess Grignard reagent and the magnesium salts with aqueous barium hydroxide, 2,2-diallylpyrrolidine (**12**) was obtained [bp 72–74° (12 Torr); 78% yield; ^{1}H nmr ($CDCl_3$) δ 1.30 (s, NH), 1.5–1.9 (m, CH_2CH_2, in pyrrolidine ring), 2.18 (d, 4 H, $CH_2C{=}C$, J = 7 Hz), 2.95 (br t, 2 H, CH_2N), 4.8–6.3 (typical allyl pattern, 6 H)]. The following sequence of reactions was carried out without purification of the intermediates.[10] Treatment of **12** with *tert*-butoxycarbonyl azide in aqueous tetrahydrofuran containing magnesium oxide (18 hr, 50°) gave the corresponding *N-tert*-butoxycarbonyl derivative of **12** which was exposed to ozone at −78° in methyl alcohol. The crude ozonide was hydrolyzed in 1:1 dioxane–water at 80° for 1.25–1.35 hr and then oxidized with silver oxide–potassium hydroxide. The filtrate was concentrated to dryness at 55° (0.01 Torr) to give a residue which was suspended in refluxing methyl alcohol containing hydrogen chloride (6%) and trimethyl orthoformate (7%). After 14 hr, amino diester **13** was isolated in 61% yield: bp 74–76° (0.01 Torr); ^{1}H nmr ($CDCl_3$) δ 1.7–2.0 (m, 4 H, CH_2CH_2, in pyrrolidine ring), 2.38 (s, NH), 2.70 (s, CH_2CO), 2.9–3.2 (m, 2 H, CH_2N), 3.72 (s, CO_2CH_3).

A series of operations, again without isolation of intermediates, led to the formation of the desired azaspirocycle **6** from **13**. A mixture of excess sodium–potassium alloy, excess chlorotrimethylsilane,[11] and amino diester **13** was stirred under argon in benzene at 25° for 12–20 hr. The solution was filtered through Celite, diluted with an equal volume of methylene chloride, cooled to −78° under argon, and oxidized with bromine.[12] After addition, the system was evacuated (0.01 Torr) and allowed to warm which caused the volatile material (benzene, methylene chloride,

(1) (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); (c) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972).

(2) (a) For the original isolation and partial structural determination of cephalotaxine, see: W. W. Paudler, G. I. Kerley, and J. Mackay, *J. Org. Chem.*, **28**, 2194 (1963); (b) for the crystal structure by X-ray diffraction, see: D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).

(3) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).

(4) Unpublished observations of R. G. Powell and K. L. Mikolajczak, personally communicated by Mr. Powell.

(5) R. G. Niak and R. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).

(6) A. M. B. Orr, R. Robinson, and M. M. Williams, *ibid.*, **111**, 948 (1917).

(7) W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, **23**, 1012 (1958).

(8) Intermediates **3** (X = Cl, Br, I), **5**, **6**, **11**, **12**, and **13** are new compounds and have been characterized by satisfactory analytical and/or spectral data. For certain key intermediates, characteristic spectral features are given.

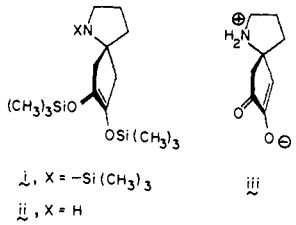
(9) We are grateful to Mr. Thomas Rogerson for his assistance in developing this step.

(10) We are grateful to Mr. Anthony Chong for his assistance in developing this sequence.

(11) (a) K. Ruhlmann and S. Poredda, *J. Prakt. Chem.*, **12**, 18 (1960); (b) U. Schräpler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964). The conversion of **13** → **6** is the first example of the acyloin reaction in the presence of a free NH group, although this distinction is purely formal because the amino group of **13** is probably silylated *in situ* before or during the acyloin reaction.

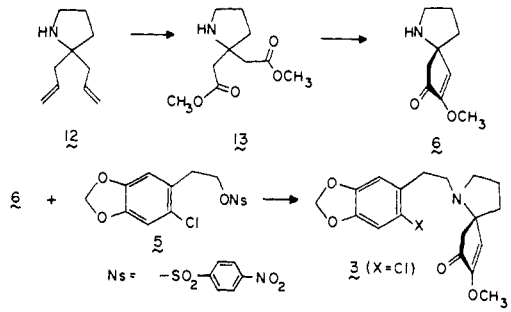
(12) (a) Ruhlmann, *Synthesis*, **2**, 236 (1971); (b) H. G. Heine, *Chem. Ber.*, **104**, 2869 (1971).

bromotrimethylsilane) to distill at low temperature, leaving a tan solid. To the residue dissolved in absolute ethyl alcohol at 0° was added a solution of excess (sixfold) diazomethane in methylene chloride. The crude product was a mixture of **6**, the *N*-methyl derivative of **6** (10:1 ratio, respectively), and products related to chlorotrimethylsilane (^{1}H nmr absorption at δ 0.0–0.2).[13] The crude product (*ca.* 60% yield of **6**)

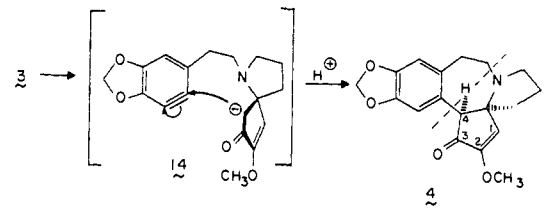


could be used in the next step without loss of efficiency: column chromatography (20% water on neutral alumina) afforded pure **6** in 45–55% yield; ^{1}H nmr ($CDCl_3$) δ 1.7–2.0 (m, CH_2CH_2 in pyrrolidine ring), 2.30 (s, NH), 2.46 (s, CH_2CO), 2.9–3.2 (m, CH_2N), 3.68 (s, CO_2CH_3); ir (neat) 1630, 1725 cm^{-1}; mass spectral mol wt, 157; mp of 3,5-dinitrobenzamide, 236.5–237° dec.

In the presence of diisopropylethylamine in acetonitrile at 55° for 12–15 hr, intermediates **5** and **6** reacted to produce the tertiary amine **3** (X = Cl), in 65–87% yield: mp 109.9–110.7°; ^{1}H nmr ($CDCl_3$) δ 1.8–2.1 (m, CH_2CH_2 in pyrrolidine ring), 2.30 (AB qt, J = 14 Hz, CH_2CO), 2.5–3.1 (br m, 6 H), 3.67 (s, OCH_3), 5.88 (s, OCH_2O), 5.92 (s, C=CH), 6.61 (s, aryl H), 6.72 (s, aryl H); mass spectral mol wt, 349. *Anal.* Found: C, 61.77; H, 5.68; N, 3.96; Cl, 10.32.



Compound **3** (X = Cl) and related derivatives (X = F, Br, I, H) are potentially very versatile intermediates in the synthesis of cephalotaxine (**2**) and cephalotaxinone (**4**). Suitable modification of the functional groups in the cyclopentenone ring of **3** should allow several fundamentally different approaches for the ring closure to give **4** (or **2**). The most direct approach, requiring no functional group protection or modification, is based on the reaction of nucleophiles with benzyne derivatives; this concept has been used with moderate success in numerous simple intramolecular examples[14] but not, to our knowledge, in natural product synthesis. The reaction of **3** (X = Cl) with potassium triphenylmethide (twofold excess) in 1,2-dimethoxyethane at 50° for 2 hr produced (±)-cephalotaxinone (**4**), identical in ir, ^{1}H nmr, and tlc behavior with natural (−)-cephalotaxinone.[15] The yield, after isolation by preparative layer chromatography, was 13–16%. A parallel series of experiments on **3** (X = Br) and **3** (X = I) afforded, at best, similar yields of **4**. The epimer of **4** (at C-4) was not isolated, consistent with inspection of models which indicates that **4** is the more stable isomer and with the expectation that proton exchange at C-4 occurs readily during the reaction and isolation procedures. Even with the present low yield in the ring closure to give **4**, the convergent plan and short sequences allow the preparation of 8–9 g of cephalotaxinone from 100 g of pyrrolidone and from *ca.* 75 g of piperonal.



Reduction of synthetic cephalotaxinone with diisobutylaluminum hydride[16] in benzene for 1 hr at 25° afforded a single product, (±)-cephalotaxine (**2**), identical in ^{1}H nmr, ir, and tlc behavior with (−)-cephalotaxine of natural origin.

Further work is under way to improve the efficiency of the conversion **3** → **4**, so as to provide a truly practical synthesis of cephalotaxine and harringtonine.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (AI-08687).

(13) An alternate series of operations for the conversion **13** → **6** revealed the intermediates. After filtering the crude mixture from the reaction with sodium–potassium alloy, the benzene was removed at reduced pressure to leave a colorless oil containing mainly i (tentatively identified by ^{1}H nmr) which was selectively hydrolyzed with wet ether at 25° to give ii (^{1}H nmr). Addition of bromine to ii in methylene chloride at −78° followed by warming to 25° gave a tan solid, identified as the zwitterion iii by ^{1}H nmr (DMSO-d_6, D_2O) and solubility properties (insoluble in acetonitrile and tetrahydrofuran, soluble in water). Diazomethane reacted with iii to give **6** containing 10% of the *N*-methyl derivative of **6**. The yields are somewhat lower than from the procedure outlined in the discussion, and the operations are more cumbersome.

(14) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(15) We are indebted to Mr. R. G. Powell of the United States Department of Agriculture, Peoria, Ill., for a generous gift of the natural material.

(16) The use of diisobutylaluminum hydride for this reduction was suggested by Professor R. H. Schlessinger (University of Rochester) based on his studies with material of natural origin.

(17) National Institutes of Health Postdoctoral Fellow, 1972.

(18) National Science Foundation Undergraduate Research Participant, 1971.

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^{1}H and ^{31}P Nuclear Magnetic Resonance Evidence for the Existence of 1,2-Diphenyldiphosphine in Equilibrium with Phenylphosphine and Pentaphenylcyclopentaphosphine

Sir:

Compared with the large number of tetrasubstituted derivatives of diphosphine, P_2H_4, which have been isolated in the last 10 years,[1] only a few derivatives bearing

(1) A. H. Cowley, *Chem. Rev.*, **65**, 617 (1965); E. Fluck, "Preparative Inorganic Reactions," Vol. 5, Interscience, New York, N. Y., 1968, pp 103–156.