I^- guest as depicted in Scheme I since the I^----I^- distance in $4{\cdot}I_2^{2-}$ (3.969 (1) Å) is shorter than the corresponding van der Waals distance (4.30 Å).

The host–guest chemistry of $4{\cdot}I_2Li_2$ has been investigated. The reaction of $4{\cdot}I_2Li_2$ with AgOAc in EtOH proceeded quantitatively to yield yellow AgI and a THF-soluble white solid **5**,[19] which has ^1H, ^{13}C, and ^{11}B NMR spectra similar to those of $4{\cdot}X_n^{n-}$ (X = Cl, n = 1; X = I, n = 1 or 2).[9-11] The ^1H and ^{13}C NMR spectra of **5** proved that **5** does not contain OAc^- ion. The ^{199}Hg NMR spectrum of **5** has a unique resonance at −1309 ppm in 50% THF-d_8, compared with those for $4{\cdot}I_2Li_2$ at −716 ppm, 4·ILi at −809 ppm, and 4·ClLi at −1077 ppm. A ^{199}Hg NMR experiment demonstrated that 4·ILi and $4{\cdot}I_2Li_2$ were formed upon the addition of 1 and 2 equiv of n-Bu_4NI, respectively, to **5** in acetone/THF solution, as shown in eq 2. Similar results were obtained when $AgNO_3$ was employed to remove the halide ions from the host.

$$4{\cdot}I_n^{n-} \underset{nI^-}{\overset{nAg^+}{\rightleftharpoons}} \mathbf{5} + n\mathrm{AgI}\downarrow \qquad n = 1,2 \qquad (2)$$

A ^{199}Hg NMR experiment also established that $4{\cdot}Cl^-$ was converted to $4{\cdot}I_2^{2-}$ by the addition of n-Bu_4NI to an acetone solution of 4·ClLi.[9] These data strongly suggest that **5** is actually the host **4**. Determination of the equilibrium constants for the complexation of **4** to halide ions and a study of the catalytic potential of **4** are under active investigation.

Acknowledgment. We are grateful to the National Science Foundation (DMR-9014487) for support of this work and to Mr. Albert Calleros for the illustrations.

Supplementary Material Available: Tables of position and thermal parameters, bond lengths and angles, and crystallographic data (15 pages); listing of observed and calculated structure factors (35 pages). Ordering information is given on any current masthead page.

(19) Spectroscopic data for **5**: ^1H NMR (360 MHz, THF-d_6, 25 °C) δ = 1.0–3.6 ppm; ^{13}C NMR (90 MHz, THF-d_8, 25 °C, decoupled) δ = 94.5 ppm; ^{11}B NMR (160 MHz, THF, 25 °C, $BF_3{\cdot}Et_2O$ external, decoupled) δ = 1.4, −5.5 −8.5 ppm (2:2:6); ^{199}Hg NMR (89.6 MHz, 50% THF-d_8 25 °C, 1.0 M PhHgCl in DMSO-d_6 as an external reference[20] at 1187 ppm upfield from neat Me_2Hg, decoupled) δ = −1309 ppm; IR (KBr) ν (cm^{-1}) = 2560 (B–H).

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Biomimetic Synthesis of the Pentacyclic Alkaloid (±)-Nirurine and Possible Biogenetic Rearrangement of a Precursor into (±)-Norsecurinine

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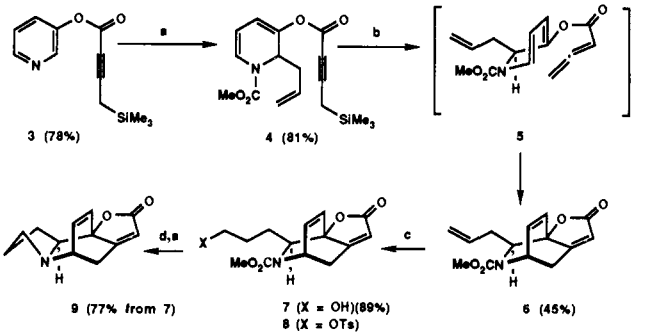
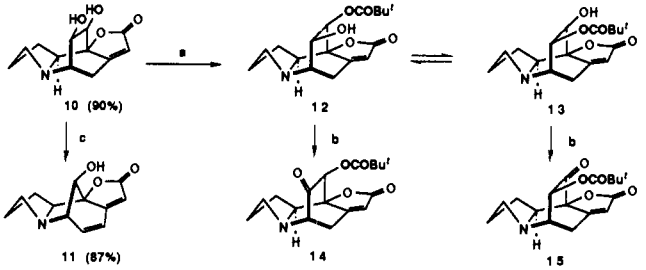
(+)-Nirurine (**1**) was isolated from *Phyllanthus niruri* L. and its pentacyclic structure elucidated by X-ray crystallography.[1] It appears that **1** is biogenetically related to norsecurinine (**2**) (also isolated from *Phyllanthus*). **2** has been synthesized;[2] however, there are no reported synthetic studies on **1**, nor is there a possible structural relationship between the two alkaloid skeleta.

Scheme I[a]



[a] (a) $ClCO_2Me/CH_2{=}CHCH_2SnBu_3$ (81%). (b) $KF{\cdot}2H_2O$/MeOH/AcOH (45%). (c) Diisoamylborane/THF/−23 to 25 °C, $NaOH/H_2O_2$ (89%). (d) TsCl/py. (e) 30% HBr/AcOH/cyclohexene (77%).

Scheme II[a]



[a] (a) $Bu^tCOCl/DMAP/Et_3N/CH_2Cl_2$ (100%). (b) DMSO/$(ClCO)_2/Et_3N$. (c) Mitsunubo conditions (87%).

The strategy we have used to construct the azabicyclo-[2.2.2]octane (isoquinuclidine) core depends upon the generation of aza diene **5** and stereospecific intramolecular trapping by an allenyl ester to produce the core skeleton and the fused butenolide **6** in a single step, Scheme I.[3] Thus, 3-hydroxypyridine was treated with 4-(trimethylsilyl)-2-butynoic acid/DCC/CH_2Cl_2 to give the labile ester **3** (78%), which was immediately converted into **4** (81%).[4] Desilylation of **4** gave the azabicyclo[2.2.2]octane **6** (45%) as a single stereoisomer, presumably via the intermediate aza diene **5**. The structure and relative stereochemistry of **6** were established by single-crystal X-ray crystallography of a derivative of **6**.[5] Hydroboration of **6** gave, after oxidative workup, **7** (89%). The derived tosylate **8** was converted into **9** in 77% yield, Scheme I.

The disubstituted double bond in **9** proved to be extremely reluctant to undergo electrophilic addition, presumably because of the strongly inductively electron withdrawing allylic N and O substituents. The only useful functionalization was achieved by treatment of **9** with OsO_4(cat.)/NMNO/acetone–water to give the *cis*-diol **10** (90%).[6] Unfortunately, this compound has the

† Indiana University.

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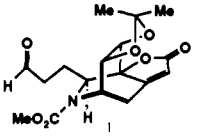
(5) The stereochemistry of **6** was determined by X-ray crystallographic analysis of the derivative i.



i

(6) Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *tetrahedron Lett.* **1976**, 1973.

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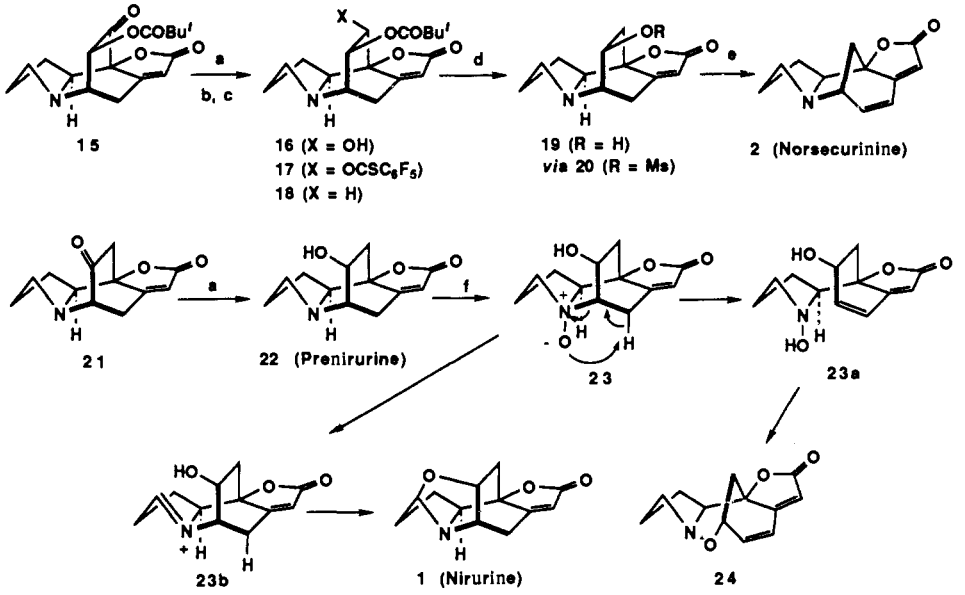
Scheme III[a]



[a] (a) $NaBH_4$/MeOH (64% from **12**/**13**). (b) $C_6F_5OCSCl/DMAP/CH_2Cl_2$ molecular sieves (100%). (c) *n*-Bu_3SnH/AIBN/benzene, reflux 15 min (100%). (d) NaOMe/MeOH (82% from **19**). (e) $MsCl/Et_3N/DMAP/CH_2Cl_2$, 25 °C for 15 min (91%). (f) MCPBA/MeOH.

incorrect configuration at C-4, and consequently we were faced with the daunting task of inverting at C-4 in a molecule where S_N2 chemistry is obviously sterically encumbered, combined with the problem of differentiating between the two secondary hydroxyl groups, Scheme II. Attempts to invert at C-4 in **10** interestingly led to the rearranged product **11** (87%), which now has the norsecurinine skeleton.[7]

Pivaloylation of the diol **10** gave a mixture of monopivaloates **12** and **13** (1:2) (100%). If a mixture of **12** and **13** is allowed to stand in methanol for a few minutes, the ^1H NMR spectrum shows that rapid equilibration takes place to give predominantly **13**. Swern-Moffatt oxidation of the mixture of **12** and **13** gave **15**, along with a small amount of the isomer **14**. Evidently **13** is more rapidly oxidized than **12**. Consequently, while pivaloylation of **10** is not regiospecific, the subsequent equilibration allows the ketone **15** to be made without any separation from isomeric compounds, Scheme II. Reduction of **15** gave the inverted alcohol **16** (64% overall from **12**/**13**), which was converted into its pentafluorophenol thiono ester derivative **17** (100%) and deoxygenated to give **18** (100%).[8]

The alcohol **19** (94%) cleanly rearranged to norsecurinine (**2**) (91%, overall yield of 10.5% through 13 steps from 3-hydroxypyridine) on exposure to standard mesylation conditions. Swern-Moffatt oxidation of **19** gave the ketone **21**, which was reduced to give prenirurine (**22**) (82% overall from **19**), the speculated biogenetic precursor to nirurine (**1**).[1] Treatment of **22** with *m*-chloroperoxy benzoic acid in methanol gave the unstable *N*-oxide **23**, which rapidly rearranged to **24**, presumably via the Cope elimination product **23a**.[7] The *N*-oxide **23** is more stable in dichloromethane, and treatment with trifluoroacetic anhydride gave small amounts of **1** (ca. 10%), but largely **24**, Scheme III.[9] In view of the low yield of **1** because of the competing rearrangement, it seems likely that **22** is not the biogenetic precursor to **1**, and that aminal formation (oxidation adjacent to nitrogen) takes place at an earlier stage.

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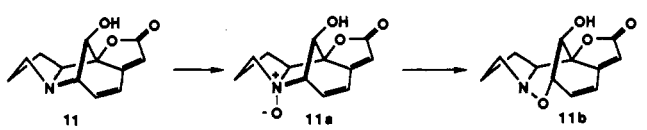
Supplementary Material Available: General spectral details for compounds **6**, **7**, **9**, **10**, **16**-**19**, and **22**, details of the X-ray structure determination of **11**, and tables of fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond lengths, and bond angles for **11** (15 pages); listing of observed and calculated structure factors for **11** (5 pages). Ordering information is given on any current masthead page.

(7) Treatment of **11** with MCPBA gave the *N*-oxide **11a**, which on heating (xylene at reflux) rearranged to the derivative **11b** (see ref 1).



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(9) Treatment of prenirurine (**22**) with a range of oxidizing agents [$Hg(OAc)_2$, $Hg(OTFA)_2$, $Pb(OAc)_4/I_2$, Br_2/HgO] did not give any detectable amounts of nirurine.

Total Synthesis of (±)-FR-900482

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FR-900482 (**1**) was recently isolated from a culture broth of *Streptomyces sandaensis* No. 6897 at Fujisawa Pharmaceutical Co. in Japan.[1] This unique antibiotic exists as a mixture of tautomers, **1a** and **1b**, and has been shown to exhibit exceptionally potent antitumor activities. Preliminary biological testings against experimental tumors have indicated that FR-900482 is at least as active as mitomycin C (**2**)[2] and is also active against mitomycin C- and vincristine-resistant P388 cells. Furthermore, FR-900482 appears to be less toxic than mitomycin C, a clinically used cancer

† On leave from Fujisawa Pharmaceutical Co., Ltd., Japan (1988-1989).

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