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Synthesis of the *Securinega* Alkaloids (±)-Norsecurinine and (±)-Nirurine from 3-Hydroxypyridine.

Philip Magnus*, Julian Ródriguez-López, Keith Mulholland and Ian Matthews†.

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712.

†Department of Chemistry, Indiana University, Bloomington, Indiana 47405.

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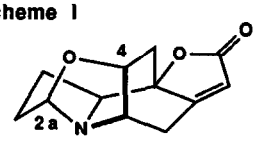
Dedicated to Derek H. R. Barton on the occasion of his 75th birthday

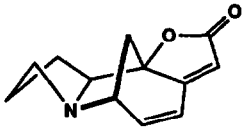
Abstract: Treatment of the dihydropyridine **5** with fluoride anion resulted in *in situ* formation of the allenyldiene **4** which cyclized to the azabicyclo[2.2.2]octene **9**. Subsequent elaboration to the alcohol **24** and rearrangement gave norsecurinine **2**. The intermediate diol **16** was converted into prenirurine **34** which upon conversion into an N-oxide rapidly rearranged to give traces of nirurine **1** and norphyllanthine **38**.

(+)-Nirurine **1** was isolated from *Phyllanthus niruri* L., and its pentacyclic structure elucidated by X-ray crystallography.[1] Nirurine **1** is biogenetically related to norsecurinine **2** (also isolated from *Phyllanthus*). Norsecurinine **2** has been synthesized,[2] however there are no reported synthetic studies on nirurine **1**, nor any structural relationships established between the azabicyclo[2.2.2]octane core of nirurine and the azabicyclo[3.2.1]octane core of norsecurinine.

Scheme I



1 (Nirurine)

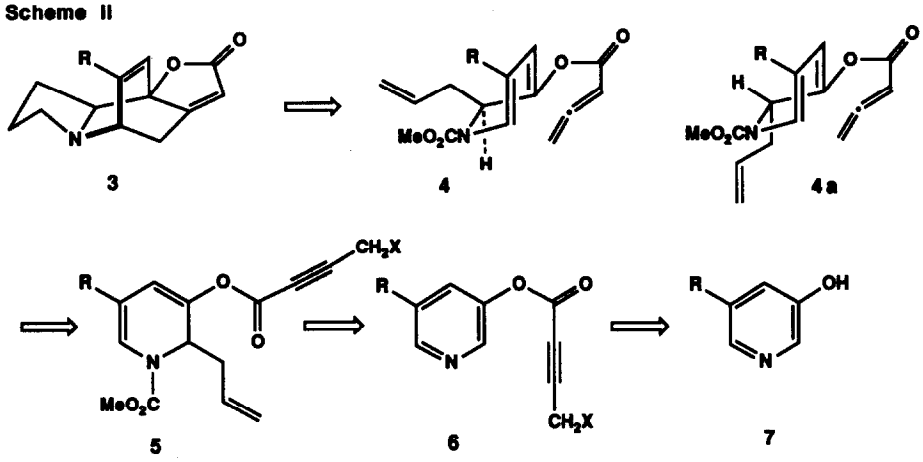


2 (Norsecurinine)

The strategy we have developed to construct the azabicyclo[2.2.2]octane (isoquinuclidine) core of nirurine depends upon the generation of the diene **4/4a**, and its stereospecific intramolecular trapping by an allenyl ester to produce the core skeleton and the fused butenolide **3** in a single step, **Scheme II**.[3] In turn, we envisioned that the allenyl ester could be generated *in situ* from the propargylic ester **5** by treatment with fluoride anion. The stereochemical outcome of the intramolecular 2+4 cycloaddition to give **3**, requires that the allyl side chain occupy the face opposite that of the allenyl substituent. This appears to be the more favorable situation (steric hindrance), and it was anticipated that **4**, rather than **4a**, would determine the correct stereochemistry required for the eventual pyrrolidine ring. The 1,2-dihydro-2-allylpyridine **5** should be readily available from **6**, which is the simple propargylation product of the 3-hydroxypyridine **7**. While we initially

examined the successful prototype situation where R = H, leading to **3** (R = H), there remains the somewhat difficult problem of selectively introducing the required oxygen functionality in a regiospecific manner on the bridging C=C double bond, where both ends have inductively electron withdrawing substituents. The only difference between the ends of the double bond is the degree of steric hindrance.

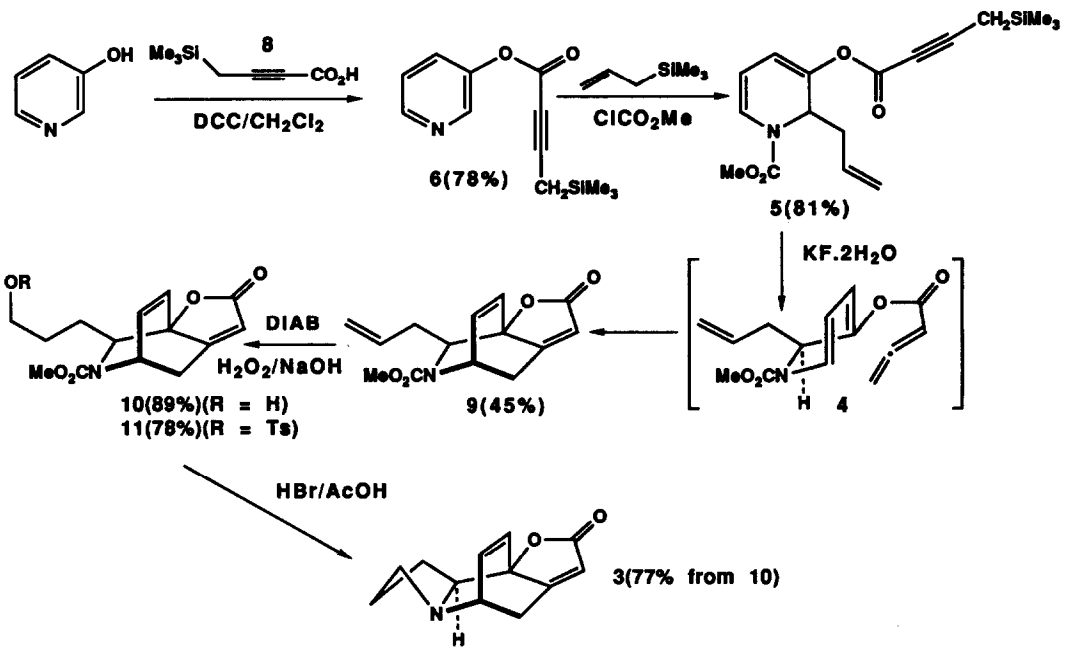
Scheme II



3-Hydroxy-5-methoxypyridine **7** (R = OMe) was converted into the ester **6** (R = OMe, X = $SiMe_3$), and treated with methyl chloroformate/allyl tri-*n*-butyl stannane to give the adduct **5** as a mixture containing other allyl regioisomers. Treatment of the mixture with fluoride anion did not give **3** (R = OMe). The only identifiable product was the starting pyridine **7**. Consequently, we were restricted to the prototype series (R = H).

4-Trimethylsilyl-2-butynoic acid **8** was prepared by deprotonation of 2-butynoic acid with *n*-BuLi/TMEDA/-78 °C, followed by the addition of trimethylsilyl chloride. The acid **8** is rather sensitive, and is best stored in a freezer and used within a few days. 3-Hydroxypyridine was treated with 4-trimethylsilyl-2-butynoic acid DCC/CH_2Cl_2 to give the labile ester **6** (78%). Immediate exposure of **6** to the Yamaguchi allylation conditions[4] ($ClCO_2Me$/allyltri-*n*-butylstannane/0-25 °C gave the 2-allyl-1,2-dihydropyridine adduct **5** (81%). No other regioisomers could be detected (^1H NMR). Fluoride ion induced desilylation of **5** (KF. $2H_2O$/MeOH/AcOH) gave the azabicyclo[2.2.2]octane **9** (45%) as a single stereoisomer, presumably *via* the intermediate allenyl-diene **4**. We could not detect any stereoisomer that would arise from the *endo*-allyl intermediate **4a**. The only significant by-product was protodesilylation of **5** (replacement of $SiMe_3$ by H). If an anhydrous fluoride source was used (CsF or *n*-$Bu_4N^+F^-$) none of the required product **9** could be isolated, only extensive decomposition was observed. Consequently, we were restricted to the protic system with the limitation of competing protodesilylation. The complete sequence of transformations from **6** to **9** can be carried out without purification of the intermediates, **Scheme III**.

Scheme III



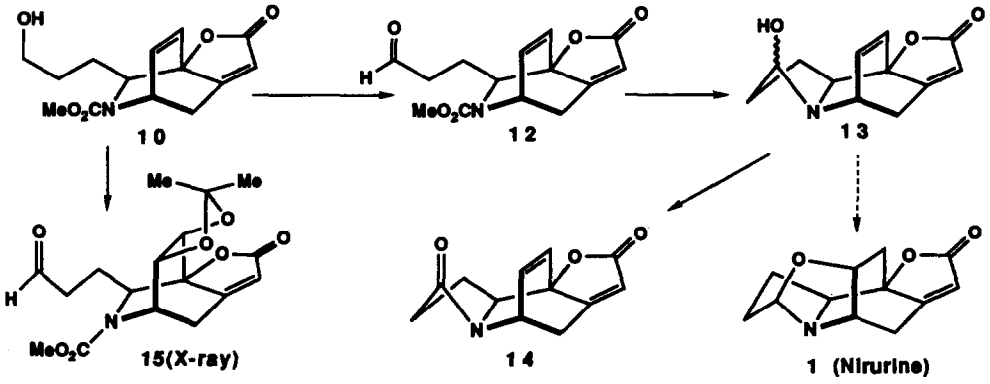
Selective hydroboration (1° vs 2°) of the vinyl functionality in **9** was readily achieved by exposure of **9** to diisoamylborane/THF/-23 °C followed by oxidative work-up to give the alcohol **10** (89%). The allylically disubstituted double bond showed no inclination towards competitive hydroboration. Attempted deprotection of the carbamate **10** using trimethylsilyliodide resulted in decomposition. Whereas, conversion of **10** into its derived *p*-toluenesulfonyl ester **11**, followed by treatment with hydrogen bromide in acetic acid containing a bromine scavenger (cyclohexene) gave the core structure **3** (77%).

Our initial plan (which failed) is worth mentioning if only for the fact that it reemphasizes the inertness of the allylically disubstituted double bond in **3** (and similar structures) towards electrophilic addition chemistry. Oxidation of **10** using the Swern-Moffatt procedure gave the aldehyde **12**. Treatment of the aldehyde with hydrogen bromide in acetic acid gave the unstable carbanolamine **13** as an anomeric mixture (^{1}H NMR). The derived methyl ether is a single epimer. All attempts [$HgO/Br_2/CCl_4$, PhSeCl, PhSeBr, NBS, NIS, Br_2, $Hg(OCOCF_3)_2$, KI/I_2, I_2/AgOAc/AcOH, MCPBA etc, and photolysis] failed to induce direct cyclization of **13** into nirurine **1**. The only product that could be isolated from these cyclization attempts was the amide **14** (40%, from the NBS reaction). Thus, this direct and simple route, could not be realized, **Scheme IV**.

In the course of this part of the research it was found that the only addition reaction to the unconjugated C=C double bond in **10** could be achieved by osmylation using OsO_4(cat)/NMNO/*t*-BuOH/THF-water[5] to give a *cis*-diol (at this stage of unspecified stereochemistry). The *cis*-diol was converted into its acetonide derivative and oxidized to give the crystalline aldehyde **15** (X-ray). This structure

confirmed the stereochemistry of the osmylation (approach from the trigonal butenolide side), and the stereochemistry of the aldehyde side chain (allyl, **4** into **9**, Scheme III).

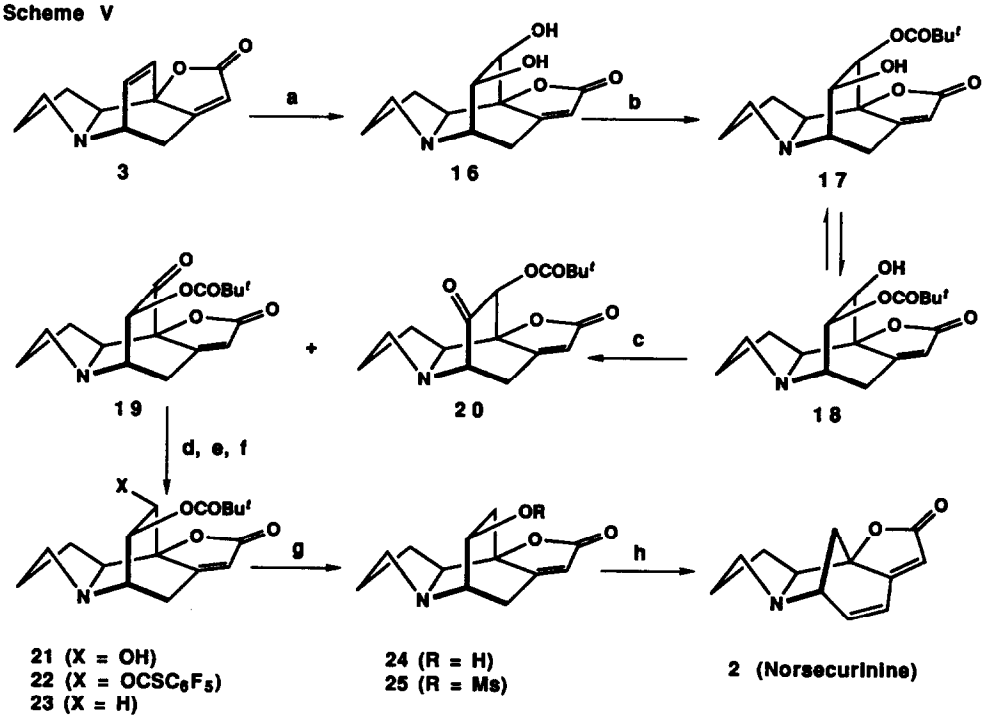
Scheme IV



As emphasized above, the disubstituted double bond in **3** 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 **3** with OsO_4(cat)/NMNO/acetone-water to give the *cis*-diol **16** (90%). Unfortunately, this is the incorrect configuration at C-4, and consequently we were faced with the difficult task of inverting at C-4 in a molecule where SN2 chemistry is obviously sterically encumbered, combined with the problem of differentiating between the two secondary hydroxyl groups.

After considerable experimentation it was found that pivaloylation of the diol **16** gave a mixture of monopivaloates **17** and **18** (1 : 2) (100%). If a mixture of **17** and **18** is allowed to stand in methanol for a few minutes the ^1H NMR spectrum indicated that rapid equilibration takes place to give predominantly **18**. Swern-Moffatt oxidation of the mixture of **17** and **18** gave **19**, along with a small amount of the isomer **20**. Evidently **18** is more rapidly oxidized than **17**. Consequently while pivaloylation of **16** is not regiospecific, the subsequent equilibration allows the ketone **19** to be made without any separation from isomeric compounds. Reduction of **19** gave the inverted alcohol **21** (64% overall from **17**/**18**). Deoxygenation of **21** using the Barton procedure[6] *via* the pentafluorophenolthiono ester derivative **22** (100%) and subsequent treatment with *n*-Bu_3SnH/AIBN gave **23** (100%). Treatment of the ester **23** with NaOMe/MeOH gave the alcohol **24** (94%). The alcohol **24** (94%) cleanly rearranged to norsecurinine **2** (91%, overall yield of 10.5% through 13 steps from 3-hydroxypyridine) on exposure to standard mesylation conditions, Scheme V.

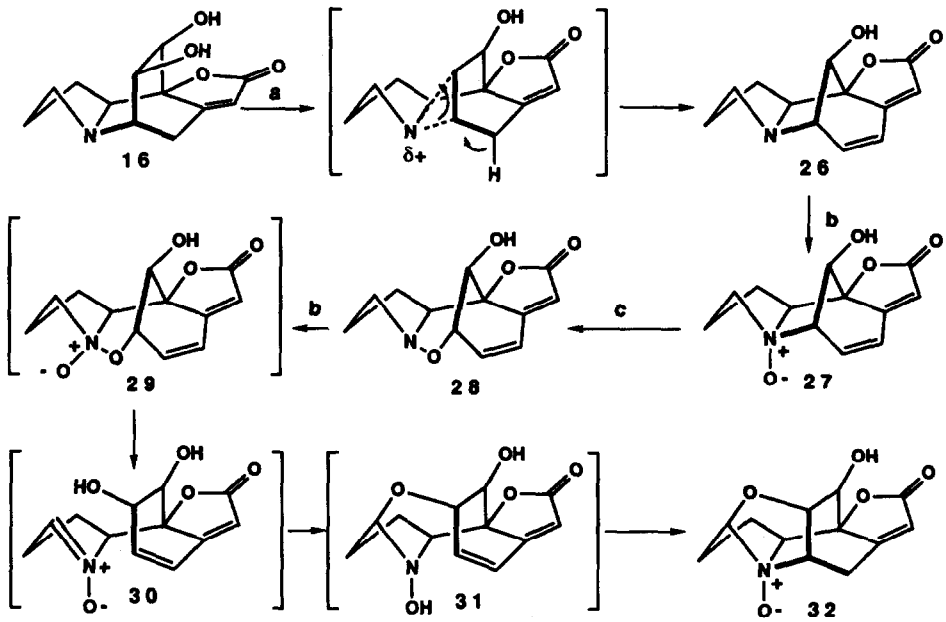
Scheme V



a) OsO_4 (cat)/N-methylmorpholine-N-oxide/acetone, water (90%). b) Bu^tCOCl/DMAP, Et_3N/CH_2Cl_2 (100%). c) DMSO/$(ClCO)_2$/Et_3N. d) $NaBH_4$/MeOH (64% from **16**). e) C_6F_5OCSCl/DMAP/CH_2Cl_2 (100%). f) *n*-Bu_3SnH/AIBN/PhH reflux (100%). g) NaOMe/MeOH (94%). h) $MeSO_2Cl$/CH_2Cl_2/Et_3N (91%).

The rearrangement of the seco-nirurine skeleton **24** into the norsecurinine skeleton **2** may have possible biogenetic relevance since both alkaloids occur in the same plant. This same type of rearrangement can be conducted on the diol **16**. Treatment of **16** with the Mitsunobu reagent $PPh_3/EtO_2CN{=}NCO_2Et$/THF did not give the desired inverted alcohol, but instead the rearranged 8-hydroxynorsecurinine **26** (87%) was formed (structure by X-ray). We considered the possibility that the derived N-oxide **27** would undergo rearrangement into the O-alkylhydroxylamine **28**, which could be oxidized to **29**, and eliminated to the nitrone **30**.[1] The nitrone **30** should cyclize to **31**, and undergo conjugate addition to give the N-oxide of hydroxynirurine **32**. Treatment of 8-hydroxynorsecurinine **26** with *m*-chloroperoxy benzoic acid gave the N-oxide **27** (100%), which cleanly rearranged to the required O-alkyl hydroxylamine **28** (99%) when heated in xylene at reflux. When **28** was treated with *m*-chloroperoxybenzoic acid an unstable polar material was formed, which upon heating gave a complex mixture that did not contain (^1H NMR, carbanolamine CH) any of the rearranged product **32**, **Scheme VI**.

Scheme VI



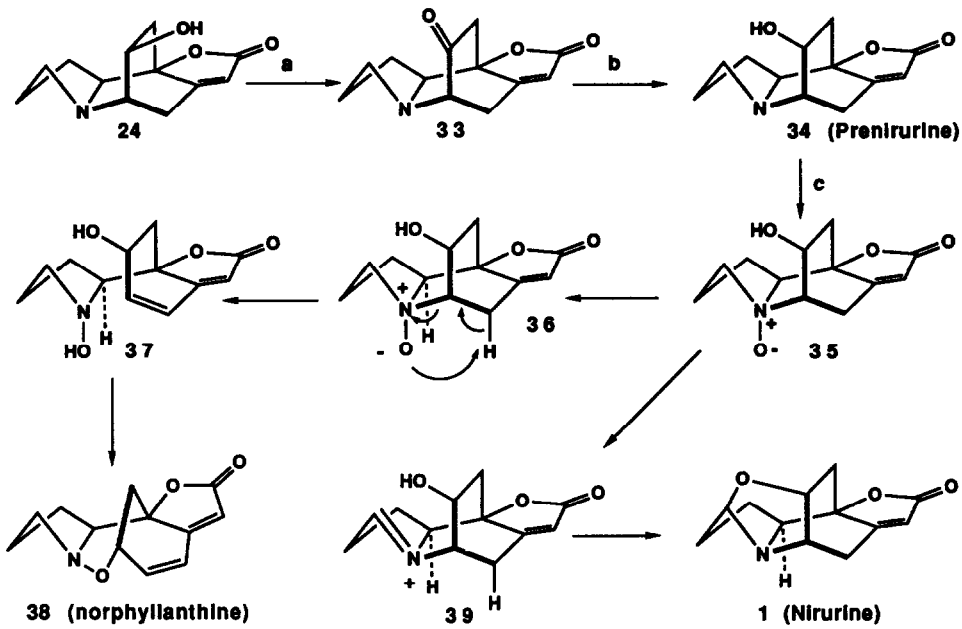
a) Mitsunobu conditions (87%). b) *m*-$ClC_6H_4CO_3H$/MeOH (100%). c) Xylene reflux (99%).

Oxidation of **24** using the Swern-Moffatt conditions gave the ketone **33**, which was directly reduced with sodium borohydride to give the inverted alcohol **34** (82%, from **24**). Treatment of **34** with a variety of oxidizing agents [NBS, NIS, $Hg(OCOCF_3)_2$, $Hg(OAc)_2$, $Pb(OAc)_4$ etc] either destroyed **34** to give numerous products none of which were **1** or **34**, or was recovered unchanged. It was found that treatment of **34** with *m*-chloroperoxybenzoic acid in methanol gave the unstable N-oxide **35**, which rapidly rearranged to **38**, presumably *via* the Cope elimination product **36/37**. The N-oxide **35** is more stable in dichloromethane, and treatment with trifluoroacetic anhydride gave small amounts of nirurine **1** (ca.10%), but largely **38**. In view of the low yield of **1**, because of the competing rearrangement, it seems likely that **34** is not the biogenetic precursor to **1**, and that aminal formation (oxidation adjacent to nitrogen) takes place at an earlier stage.

Summary

The simple strategy depicted in **Scheme II** provides a short route to azabicyclo[2.2.2]octane skeleton **3**. While the subsequent elaboration of **3** to give norsecurinine **2** was straightforward, the conversion of **3** into nirurine was extremely inefficient because of the difficulty experienced during attempts to oxidize prenirurine **34** to the iminium ion **39**. This perhaps illustrates the paucity of methods that are available that directly dehydrogenate amines to iminium species in a controlled manner. We are currently developing a new method based upon hypervalent iodine chemistry to address this specific problem.

Scheme VII



a) DMSO/$(ClCO)_2$/Et_3N. b) $NaBH_4$/MeOH (82% from **24**). c) *m*-$ClC_6H_4CO_3H/CH_2Cl_2$.

Experimental Section

4-Trimethylsilyl-2-Butynoic acid 8. A stirred solution of tetramethyl ethylenediamine (4.82 ml, 31.9 mmol) in dry pentane (100ml) under argon was treated with a 2.5 M solution of *n*-BuLi in hexanes (18.4 ml, 46.0 mmol) at 25 °C. After 1 h, the reaction mixture was cooled to -78 °C, and a solution of 2-butynoic acid (1.75 g, 20.8 mmol) in THF (25 ml) was added *via* cannula. After 2 h, the resulting yellow suspension was treated with trimethylsilyl chloride (10.6 ml, 85.4 mmol). After a further 1.5 h at -78 °C, the mixture was allowed to warm to room temperature. The reaction mixture was poured into 10% aqueous HCl (90 ml), and extracted with Et_2O (2x50 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. Kugelrohr distillation provided the acid **8** (3.175 g, 98%) as a colorless oil, which solidified on storage in the freezer, B.p. 123 °C/0.45 mm Hg. IR (film) 3000 (br), 2951, 2219, 1678, 1408, 1286, 1251, 844 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 9.4 (1H, br s), 1.12 (2H, s), -0.14 (9H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 158.66, 92.19, 73.09, 7.38, -2.34. CIMS, m/e 157 (MH^+, base), 139, 113. HRMS, m/e calcd. for $C_7H_{13}O_2Si$ 157.0685. Found 157.0704.

Azabicyclo[2.2.2]octane Diels-Alder adduct 9. A stirred suspension of 3-hydroxypyridine (0.717 g, 7.54 mmol) in dry CH_2Cl_2 (45 ml) under argon was treated with a solution of dicyclohexylcarbodiimide (1.556 g, 7.54 mmol) in dry CH_2Cl_2 (20 ml), followed by a solution of 4-trimethylsilyl-2-butynoic acid **8** (1.178 g,

7.54 mmol) in dry CH_2Cl_2 (20 ml). After 10 min, the mixture was treated with saturated aqueous $NaHCO_3$, and diluted with CH_2Cl_2 (20 ml). The organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to give a brown oil which was rapidly purified by silica gel chromatography (10:1 dichloromethane: ethyl acetate) to provide the ester **6** as a yellow oil (1.373 g, 78%). It was used immediately in the next reaction to avoid decomposition.

The ester **6** from the above sequence was dissolved in dry CH_2Cl_2 (20 ml), cooled to 0 °C, and treated with methyl chloroformate (0.546 ml, 7.07 mmol), followed by allyltri-*n*-butylstannane (1.82 ml, 5.46 mmol). The resulting yellow solution was allowed to warm to 25 °C, and was stirred under argon for 3 h. The mixture was concentrated *in vacuo*, and the residue purified by silica gel chromatography eluting with hexane followed by dichloromethane to provide the carbamate **5**, (1.478 g, 81%), as a yellow oil. It was used immediately in the next sequence to avoid decomposition.

The carbamate **5** was dissolved, with stirring, in methanol (300 ml), and treated with potassium fluoride dihydrate (4.18 g, 44.40 mmol), followed by acetic acid (0.266 ml, 4.44 mmol). After 17 h, the mixture was concentrated *in vacuo* , and the residue partitioned between CH_2Cl_2 (20 ml) and water (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2x20 ml), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil, which was purified by silica gel chromatography to give the desired adduct **9** (0.517 g, 45%) as a pale yellow oil. IR (CH_2Cl_2) 2920, 1760, 1695, 1659 cm^{-1}. ^1H NMR (CD_3SOCD_3, 500 MHz at 70 °C) δ 6.61 (1H, dd, J = 8.4, 6.4 Hz), 6.47 (1H, d, J = 8.4 Hz), 5.97 (1H, t, J = 1.9 Hz), 5.82 (1H, m), 4.95-5.03 (3H, m), 3.63 (3H, s), 3.48 (1H, t, J = 6.0 Hz), 2.92 (1H, dt, J = 18.6, 1.9 Hz), 2.32-2.53 (3H, m). ^{13}C NMR (125 MHz, C_6D_6 at 70 °C) δ 172.07 (s), 168.94 (s), 155.19 (s), 135.29 (d), 131.41 (d), 131.18 (d), 116.44 (t), 112.25 (d), 86.89 (s), 61.51 (d), 52.31 (q), 49.07 (d), 37.21 (t), 31.55 (t). CIMS, m/e 262 (MH+), 220 (base), 192, 154, 128, 96. HRMS, m/e calcd for $C_{14}H_{15}NO_4$ 262.1080. Found 262.1068.

Hydroboration of 9. A solution of BH_3.THF (1.0 M in THF, 17.8 ml, 17.8 mmol) at 0° C under argon was treated 2-methyl-2-butene (2.0 M in THF, 17.8 ml, 35.6 mmol) and the resulting solution left at 0 °C for 1 h. This solution was added *via* cannula to a stirred solution of the alkene **9** (0.930 g, 3.56 mmol) in dry THF (50 ml) at -23 °C under argon. After 2.5 h, the reaction mixture was allowed to warm to room temperature, and 30% aqueous H_2O_2 (15 ml), and 2 M aqueous NaOH (15 ml) were carefully added. After a further 0.5 h, the reaction mixture was treated with 2M aqueous Na_2SO_3. When effervescence had ceased, the mixture was extracted with EtOAc (3x20 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a colorless oil. Purification by silica gel chromatography, eluting with ethyl acetate gave the alcohol **10** as a colorless oil (0.893 g, 89%). IR (CH_2Cl_2) 3620, 3500, 2930, 1770, 1690, 1670 cm^{-1}. ^1H NMR (500 MHz, CD_3SOCD_3 at 80 °C) δ 6.58 (1H, dd, J = 8.4 and 6.3 Hz), 6.45 (1H, d, J = 8.4 Hz), 5.93 (1H, s), 4.98-5.06 (1H, m), 4.05 (1H, br s), 3.60 (3H, s), 3.50-3.32 (3H, m), 2.88 (1H, d, J = 18.9 Hz), 2.47 (1H, d, J = 18.9 Hz), 1.70-1.40 (4H, m). ^{13}C NMR (75 MHz, CD_3SOCD_3 at 80 °C) δ 172.08 (s), 170.29 (s), 154.54 (s), 131.53 (d), 129.94 (d), 110.83 (d), 86.71 (s), 60.53 (t), 60.36 (d), 51.95 (q), 48.28 (d), 31.24 (t), 29.16 (t), 28.69 (t). CIMS m/e 280 (MH^+), 262, 220, 192, 154, 134, 106 (base).

HRMS, m/e calcd for $C_{14}H_{18}NO_5$ 280.1185. Found 280.1192.

Desoxadehydronirurine 3. A stirred solution of the alcohol **10** (1.97 g, 7.06 mmol) in dry CH_2Cl_2 (107 ml) was treated with triethylamine (1.08 ml, 7.77 mmol), followed by 4-dimethylaminopyridine (947 mg, 7.77 mmol) and *p*-toluenesulphonyl chloride (1.48 g, 7.77 mmol). After 5 h, the reaction mixture was diluted with CH_2Cl_2 (100 ml) and washed with 5% aqueous HCl, and water. The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to give the crude tosylate **11** as colorless foam. The crude tosylate was used directly in the next stage. Rf = 0.65 (silica gel, EtOAc).

The crude tosylate **11** from the above sequence was suspended in cyclohexene (26 ml) and treated with 30% HBr in acetic acid (107 ml) under argon. After 17 h, the mixture was added slowly to an excess of saturated aqueous Na_2CO_3 (50 ml), and the resulting cloudy suspension extracted with dichloromethane (5x20 ml). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to give a pale yellow oil, which was purified by silica gel chromatography (EtOAc/MeOH 10:1, then 7:3) to give the amine **3** as a colorless solid (1.10 g, 77% overall). M.p. 57-59 °C. IR (film) 2965, and 1760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (1H, dd, J = 8.5, 5.1 Hz), 6.31 (1H, d, J = 8.5 Hz), 5.70 (1H, t, J = 1.8 Hz), 3.95 (1H, dd, J = 4.6, 1.6 Hz), 3.14 (2H, m), 3.00-2.93 (1H, dt, J = 18.4, 1.9 Hz), 2.62-2.53 (1H, m), 2.46-2.38 (1H, dt, J = 18.4, 2.0 Hz), 1.94-1.90 (1H, m), 1.77-1.54 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.26 (s), 171.35 (s), 135.14 (d), 128.22 (d), 109.72 (d), 88.46 (s), 66.23 (d), 54.30 (d), 53.83 (t), 30.73 (t), 27.93 (t), 24.81 (t). EIMS, m/e 203 (M^+), 134, 106, 78, 70 (base). HRMS calcd. for $C_{12}H_{13}NO_2$ 203.0939, found 203.0946. Anal calcd.for $C_{12}H_{13}NO_2$. C, 70.91; H, 6.45; N, 6.89. Found C, 70.78; H, 6.34; N, 6.85%.

Dihydroxynirurine 16. A stirred solution of the alkene **3** (0.040 g, 0.196 mmol) in acetone/water (5:2) (2 ml) was treated with 4-methylmorpholine-N-oxide [0.058 g, 0.490 mmol, followed by osmium tetroxide (2.5 wt % in *t*-BuOH) (0.040 ml, 0.0039 mmol]. After 4 h, the reaction mixture was treated with saturated aqueous Na_2SO_3, and stirred at room temperature for a further 0.5 h. The reaction mixture was diluted with water and extracted with *n*-BuOH (3x20 ml), dried, (Na_2SO_4), and evaporated to give an off white solid, which was purified by silica gel chromatography, eluting with CH_2Cl_2/MeOH (10:1) to give the diol **16** (0.042 g, 90%) as a colorless oil, which crystallized on standing. M.p 152-162 °C (dec). IR (KBr) 3600-2500 br, 1761 cm^{-1}. ^1H NMR (300 MHz, CD_3SOCD_3) δ 5.85 (1H, s), 5.09 (1H, d, J = 4.6 Hz), 4.85 (1H, d, J = 5.1 Hz), 4.25-4.12 (2H, m), 2.99-2.82 (5H, m), 2.70 (1H, d, J = 18.2 Hz), 1.88-1.70 (3H, m), 1.63-1.50 (1H, m). ^{13} C NMR (75 MHz, CD_3OD) δ 176.21, 173.20, 114.16, 88.44, 65.54, 64.87, 62.71, 57.66, 52.27, 27.96, 27.89, 26.59. CIMS m/e 238 (MH+, base), 220. HRMS calcd. for $C_{12}H_{15}NO_4$ 237.1001. Found 237.1013. Anal calcd.for $C_{12}H_{15}NO_4$. C, 60.75; H, 6.37; N, 5.90. Found C, 60.73; H, 6.35; N, 5.68%. Further characterized as its diacetate and cyclic carbonate respectively. M.p. 143-145 (dec.). IR (KBr) 1762, 1737, 1653 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.7-2.1 (4H, m), 1.96 (3H, s, OCH_3), 1.99 (3H, s, OCH_3), 2.9-3.0 (3H, m), 3.1-3.2 (3H, m), 5.44 (1H, dd, J = 3.0, 8.5 Hz), 5.55 (1H, d, J = 8.5 Hz), 5.83 (1H, t, J = 1.7 Hz). CIMS, m/e 322 (MH^+, 44), 321 (M^+, 10), 280 (2), 262 (100), 221 (3), 202 (4), 177 (4), 154 (7). HRMS, m/e calcd. for $C_{16}H_{19}NO_6$ 321.1212, found 321.1205. Analysis, calcd. for $C_{16}H_{19}NO_6$. C, 59.81, H, 5.96, N, 4.36. Found C, 59.73, H 5.90, N, 4.09%.

M.p. decomposed between 170 and 235 °C. IR (KBr) 1817, 1771, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.8-2.0 (3H, m), 2.0-2.1 (1H, m), 2.8-3.0 (1H, m), 3.04 (2H, d, J = 2.4 Hz), 3.1-3.3 (2H, m), 3.53 (1H, s), 5.17 (2H, s), 5.94 (1H, t, J = 2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 165.5, 153.3, 115.5, 83.8, 72.0, 70.7, 62.0, 51.9, 51.4, 27.3, 27.1, 25.7.
CIMS, m/e 264 (MH^+, 100), 248 (12), 220, (18), 177 (4). HRMS, m/e calcd. for $C_{13}H_{13}NO_5$ 263.0794, found 263.0769. Analysis, calcd. for $C_{13}H_{13}NO_5$. C, 59.31, H, 4.98, N, 5.32. Found C, 59.02, H, 4.91, N, 5.00%.

Aldehyde 15. The alcohol **10** was converted into aldehyde acetonide **15** by catalytic osmylation (95%) (as above), acetonide formation (acetone/2,2-dimethoxy propane/HClO4, 90%) and oxidation (DMSO/oxalylchloride/Et_3N, 89%) to give **15**, M.p 147°-149°C (from EtOAc). IR ($CHCl_3$) 2997, 1778, 1707, 1447, 1386, 1070 and 909 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (1H, s), 5.84 (1H, s), 4.79 (1H, d, J = 7.6 Hz), 4.63-4.39 (1H, bs), 4.52 (1H, dd, J's = 7.6 and 1.5 Hz), 3.72 (3H, s), 3.61-3.50 (1H, bs), 3.10-2.92 (1H, dd, J's = 8.9 and 1.5 Hz), 2.89-2.66 (3H, m), 2.30-2.14 (1H, bs), 2.10-1.90 (1H, bs), 1.39 (3H, s), 1.35 (3H, s). ^{13} C NMR (75 MHz, $CDCl_3$) δ 200.71 (s), 171.92 (s), 167.50 (s), 155.94 (s), 114.58 (d), 111.30 (s), 85.53 (s), 72.57 (d), 71.36 (d), 58.65 (d), 53.29 (q), 49.63 (d), 41.17 (t), 26.59 (t), 25.59 (q), 24.26 (q), 24.06 (t). Anal calcd.for $C_{17}H_{21}NO_7$. C, 58.11; H, 6.03; N, 3.99. Found C, 57.94; H, 5.96; N, 3.90%. Crystals suitable for X-ray crystallographic analysis were grown from ethyl acetate.

Conversion of 16 into the alcohol 21. To a stirred solution of the diol **16** (250 mg, 1.05 mmol), DMAP (141 mg, 1.15 mmol) and Et_3N (0.16 ml, 1.15 mmol) in CH_2Cl_2 (20 ml) under argon was added trimethylacetylchloride (0.14 ml,1.10 mmol) dropwise. After 10 min the solvent was evaporated and the residues purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to give a mixture of monoesters **17** and **18** (ratio 2:1) as a white solid (337 mg, 100%). Rfs = 0.38 and 0.45 (silica gel, 10:1 CH_2Cl_2/MeOH).

Oxalyl chloride (10.28 ml of 2M solution in CH_2Cl_2, 20.56 mmol) and molecular sieves (4 Å) in dry CH_2Cl_2 (20 ml) were cooled to -78 °C under argon. DMSO (2.91 ml, 41.12 mmol) was then added dropwise so as to maintain an internal temperature below -60 °C. After 10 min a solution of the alcohols **17** and **18** (1.32 g, 4.11 mmol) in CH_2Cl_2 (12 ml) was added slowly. After 45 min, dry Et_3N (11.44 ml, 82.24 mmol) was added and the mixture stirred for a further 45 min. The cooling bath was removed and water added at room temperature. Stirring was continued for 10 min and the organic layer separated. The aqueous layer was extracted twice with CH_2Cl_2 (2x10 ml) and the combined organic layers dried ($MgSO_4$) before being concentrated *in vacuo*.

The crude ketones **19** and **20** from the above sequence were then dissolved in methanol (35 ml), cooled to 0 °C, and $NaBH_4$ (468 mg, 12.33 mmol) was added in small portions. The mixture was stirred for 15 min. Saturated NH_4Cl was added before neutralizing with 10% HCl. The methanol was evaporated *in vacuo*, and the aqueous phase extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were dried ($MgSO_4$) before being concentrated. The crude product was purified by chromatography on silica gel (EtOAc) to give the desired product **21** as a white solid

(847 mg, 64% overall from **16**). Rf = 0.43 (silica gel, EtOAc). M.p. 164-165 °C (dec.) (EtOAc/hexanes). IR (KBr): 3300-3100, 1773, 1725, 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (9H, s), 1.6-1.8 (1H, m), 1.85-2.10 (2H, m), 2.60-2.75 (1H, m), 2.83 (1H, dt, J = 19.2, 2.1 Hz), 2.95-3.20 (4H, m), 3.25-3.28 (1H, m), 3.45 (1H, br s), 3.63 (1H, br), 5.06 (1H, br s), 5.78 (1H, t, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 173.2, 172.0, 112.0, 86.2, 76.3, 73.8, 61.5, 53.1, 51.4, 38.6, 28.4, 28.0, 27.0, 25.7. CIMS, m/e 322 (MH^+, 100), 321 (M^+, 28), 304 (5), 248 (5), 220 (83), 177 (9), 149 (2). HRMS, m/e calcd for $C_{17}H_{23}NO_5$ 322.1654. Found 322.1654.

Pentafluorophenylthiono ester 22. To a stirred solution of the alcohol **21** (150 mg, 0.467 mmol), DMAP (125 mg, 1.028 mmol) and molecular sieves (4 Å) in CH_2Cl_2 (5 ml) under argon was added pentafluorophenyl chlorothionoformate (0.15 ml, 0.935 mmol). After 30 min the solvent was evaporated and the residues purified by chromatography on silica gel (EtOAc/hexanes, 1:1, then 4:1) to give the thionoester **22** as a pale yellow oil (256 mg, 100%). Rf = 0.47 (silica gel, 4:1 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (9H, s), 1.7-1.9 (1H, m), 2.00-2.15 (2H, m), 2.35-2.47 (1H, m), 2.95 (1H, dt, J = 19.5, 2.1 Hz), 3.04-3.36 (5H, m), 5.42-5.46 (2H, m), 5.93 (1H, t, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 176.8, 172.1, 169.4, 113.5, 86.3, 84.5, 69.8, 61.2, 53.4, 51.5, 38.5, 28.5, 27.8, 26.8, 25.5. CIMS, m/e 548 (MH^+, 11), 446 (48), 364 (10), 322 (5), 304 (54), 276 (16), 220 (5), 213 (24), 185 (100), 184 (85), 147 (5), 129 (9), 117 (9), 102 (17). HRMS, m/e calcd for $C_{24}H_{23}NO_6F_5S$ 548.1166. Found 548.1168.

Pivaloyloxynirurine 23. A stirred solution of the thionoester **22** (175 mg, 0.32 mmol), *n*-Bu_3SnH (0.26 ml, 0.96 mmol) and AIBN (8 mg) in benzene (8 ml) under argon was heated to reflux temperature for 15 min. The solvent was evaporated *in vacuo* and the residues purified by chromatography over silica gel (EtOAc-hexanes 1:1, then EtOAc) to give the desired product as a colorless oil (97 mg, 100%). Rf = 0.26 (silica gel, 4:1 EtOAc/hexanes). IR ($CHCl_3$) 1760, 1732, 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (9H, s), 1.25-1.40 (1H, m), 1.7-2.0 (4H, m), 2.81-3.13 (6H, m), 3.23 (1H, dd, J = 6.0, 2.7 Hz), 5.19-5.25 (1H, m), 5.73 (1H, t, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 173.6, 173.2, 110.9, 83.5, 63.7, 62.1, 52.8, 51.2, 38.5, 31.5, 27.8, 27.1, 26.9, 25.5. CIMS, m/e 306 (MH^+, 100), 305 (M^+, 46), 291 (13), 269 (8), 235 (5), 233 (16), 213 (5), 204 (34), 184 (24), 177 (6), 135 (6), 111 (5), 103 (14). HRMS, m/e calcd for $C_{17}H_{23}NO_4$ 305.1627. Found 305.1628.

Hydroxynirurine 24. A solution of the ester **23** (92 mg, 0.287 mmol) and NaOMe (23 mg, 0.43 mmol) in methanol (3 ml) was stirred under argon at room temperature. After 5 h the solvent was evaporated and the residues purified by chromatography over silica gel (CH_2Cl_2:MeOH, 10:1) to give the corresponding alcohol **24** as a white solid (59 mg, 94%). Rf = 0.30 (silica gel, 10:1 CH_2Cl_2/MeOH). M.p. 153-155 °C (dec.). IR (KBr) 3097, 1758, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (1H, m), 1.7-2.0 (4H, m), 2.44 (1H, br s), 2.71-3.10 (6H, m), 3.23 (1H, dt, J = 19.2, 2.1 Hz), 4.37-4.42 (1H, m), 5.67 (1H, t, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 174.0, 110.3, 84.3, 62.0, 61.5, 55.7, 51.2, 34.1, 27.3, 27.2, 25.6. CIMS, m/e 222 (MH^+, 100), 192 (25), 177 (6), 160 (14), 149 (34), 126 (8), 120 (35), 112 (53), 109 (6).

HRMS, m/e calcd for $C_{12}H_{15}NO_3$ 221.1052. Found 221.1055.

Norsecurinine 2. To a stirred solution of the alcohol **24** (5 mg, 0.023 mmol), Et_3N (7 µl, 0.05 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (1 ml) under argon was added $MeSO_2Cl$ (3.5 µl, 0.045 mmol). After 15 min the solvent was evaporated and the residues purified by chromatography over silica gel (CH_2Cl_2/MeOH, 10:1) to give **2** as a white solid (4.2 mg, 91%). IR ($CHCl_3$) 1749, 1634 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (1H, d, J = 11 Hz), 1.7-1.9 (2H, m), 1.98 (2H, m), 2.5-2.6 (2H, m), 3.21 (1H, t, J = 7.5 Hz) 3.28-3.33 (1H, m), 3.63 (1H, t, J = 5.5 Hz), 5.65 (1H, s), 6.48 (1H, d, J = 9.0 Hz), 6.74 (1H, dd, J = 9.0, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 168.2, 143.5, 120.6, 108.0, 91.6, 65.1, 59.8, 55.3, 35.8, 29.3, 26.8. EIMS, m/e 203 (M^+, 5), 134 (12), 106 (25), 78 (52), 70 (100), 61 (21), 55 (3), 51 (10), 43 (22). HRMS, m/e calcd for $C_{12}H_{13}NO_2$ 203.0946. Found 203.0957. The spectra were compared with an authentic sample of norsecurinine, kindly supplied by Dr. Peter Jacobi, and they were identical.

8-Hydroxynorsecurinine 26. A stirred solution of the diol **16** (300 mg, 1.27 mmol) in dry dioxane (10 ml) and molecular sieves (4 Å) under argon, was treated with a solution of Ph_3P (498 mg, 1.90 mmol) in dry THF (6 ml), followed by a solution of DEAD (331 mg, 1.90 mmol) in THF (6 ml). The mixture was stirred for 15 min at room temperature, and then warmed to 70-75 °C and stirred overnight at that temperature. The reaction mixture was diluted with methanol and the molecular sieves were filtered. The solvent was evaporated *in vacuo* and the residue purified by chromatography over silica gel (diethyl ether/methanol, 2:1) to give 8-hydroxy norsecurinine **26** (240 mg, 87%) as a white solid. M.p. decomposed above 165 °C. IR (KBr): 3500-3400, 1740, 1636 cm^{-1}. ^1H NMR (300 MHz, d_4-methanol) δ 1.65-2.10 (4H, m), 2.71-2.80 (1H, m), 3.23 (2H, dt), 3.60 (1H, t, J = 5.5 Hz), 4.71 (1H, d, J = 4.8 Hz), 5.81 (1H, s), 6.60 (1H, dd, J = 6.3, 9.0 Hz), 6.73 (1H, d, J = 9.3 Hz). ^{13}C NMR (75 MHz, d_6-DMSO) δ 172.6, 166.6, 140.7, 121.0, 108.5, 92.4, 70.8, 62.9, 61.7, 54.6, 29.2, 26.6. CIMS, m/e 220 (MH^+, 100), 219 (M^+, 13), 202 (M-17, 18), 179 (7), 151 (2). Analysis, calcd. for $C_{12}H_{13}NO_3$. C, 65.74, H, 5.98, N, 6.39. Found C, 65.59, H, 5.91, N, 6.09%.

8-Hydroxynorsecurinine-N-oxide 27. To a stirred suspension of 8-hydroxynorsecurinine **26** (219 mg, 1 mmol) in methanol (15 ml) *m*-chloroperoxy benzoic acid was added (259 mg, 1.5 mmol). Immediately, the mixture became homogeneous. After 5 min. at room temperature the solvent was evaporated *in vacuo* and the residue purified by chromatography over silica gel (MeOH/CH_2Cl_2 2:1, then MeOH) to give the N-oxide **27** (235 mg, 100%) as a white solid. M.p. decomposed between 155 and 178 °C. IR (KBr) 3608, 3450-3100, 1758, 1640 cm^{-1}. ^1H NMR (300 MHz, d_4-methanol) δ 2.10-2.50 (4H, m), 3.68 (2H, m), 3.82 (1H, m), 4.62 (1H, dd, J = 6.3, 4.5 Hz), 4.82 (1H, d, J = 4.5 Hz), 6.04 (1H, s), 6.43 (1H, dd, J = 9.0, 6.3 Hz), 7.05 (1H, d, J = 9.0 Hz). ^{13}C NMR (75 MHz, d_4-methanol) δ 173.4, 165.1, 135.0, 126.8, 113.2, 88.9, 84.7, 74.3, 74.2, 72.8, 29.7, 25.8. CIMS, m/e 236 (MH^+, 100), 235 (M^+, 7), 220 (21), 218 (M-17, 27), 202 (6), 179 (9), 171 (4), 151 (5), 133 (7).

Rearrangement of 8-Hydroxynorsecurinine-N-oxide 27 into 28. A stirred suspension of 8-hydroxynorsecurinine N-oxide **27** (235 mg, 1 mmol) in xylenes (50 ml) was heated at reflux until all the solid was dissolved (approx. 30 min). The solvent was evaporated *in vacuo* and the residue purified by chromatography over silica gel (CH_2Cl_2/MeOH, 10:1) to give the desired product **28** (233 mg, 99%) as a white solid. M.p. decomposed between 165-199 °C (melt at 198-199 °C). IR (KBr): 3265, 1751, 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-2.20 (4H, m), 2.81-2.92 (1H, m), 3.13 (1H, t, J = 8.7 Hz), 3.30-3.38 (1H, m), 4.49 (1H, t, J = 4.5 Hz), 4.62 (1H, t), 5.91 (1H, s), 6.22 (1H, dd, J = 9.3, 5.7 Hz), 7.03 (1H, d, J = 9.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 163.9, 131.1, 127.1, 114.1, 85.5, 74.4, 72.4, 67.78, 57.0, 24.6, 23.5. CIMS, m/e 236 (MH^+, 100), 235 (M^+, 14), 218 (46), 190 (12), 179 (50), 172 (9), 151 (47), 133 (85). Analysis, calcd. for $C_{12}H_{13}NO_4$. C, 61.27, H, 5.57, N, 5.95. Found C, 61.12, H, 5.51, N, 5.70%.

Prenirurine 34. The procedure adopted for the Swern oxidation was similar to that described previously. The crude ketone **33** obtained was reduced with $NaBH_4$ at 0 °C for 15 min. After evaporating the solvent the crude product was directly purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to give the desired product **34** as a white solid (82% overall). Rf = 0.18 (silica gel, 10:1 CH_2Cl_2/MeOH). M.p. 146-148 °C (dec). IR (KBr) 3129, 1767, 1654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.80 (1H, m), 1.85-2.01 (2H, m), 2.04-2.22 (2H, m), 2.35 (1H, dd, J = 13.5, 4.5 Hz) 2.46 (1H, br s), 2.65 (1H, dt, J = 19.2, 2.1 Hz), 2.98 (1H, br s), 3.05-3.15 (2H, m), 3.32 (1H, s), 3.65-3.74 (1H, m), 4.22 (1H, dd, J = 10.5, 4.5 Hz), 5.74 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 173.7, 111.6, 84.6, 72.2, 63.2, 56.2, 52.7, 33.1, 31.2, 26.9, 25.6. CIMS, m/e 222 (MH^+, 100), 221 (M^+, 9), 206 (2), 185 (15), 171 (4), 157 (15), 153 (4), 129 (6), 127 (6), 125 (37), 111 (12). HRMS, m/e calcd for $C_{12}H_{15}NO_3$ 221.1052. Found 221.1054.

Oxidation of Prenirurine. To a solution of **34** (2.5 mg) in dichloromethane (1.0 ml) at 25 °C was added *m*-chloroperoxybenzoic acid (3 mg), and the mixture stirred for 1 h. The solution was treated with trifluroacetic anhydride (3 μl) and stirring continued for 15 h. The solution was diluted with dichloromethane (3 ml), washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to give a mixture (1.5 mg). The ^1H NMR of the mixture was complex, but characteristic signals at 5.94 (1H, s), 6.28 (1H, dd, J = 9.3, 5.7 Hz) and 6.60 (1H, d, J = 9.3 Hz) indicated the presence of **38** (major component), and a diagnostic signal at 4.96 (1H, d, J = 2.8 Hz, H_{2a}) for nirurine **1** (<10%).

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