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Ferricyanide-promoted biogenetic-type phenolic oxidative coupling of an 8,3'-dihydroxytetrahydrobenzylisoquinoline **19a** afforded the isomeric phenolic cularines **5** and **21**. Vanadium oxytrifluoride oxidation of the *N*-borane complex of **19a** afforded, regioselectively, the *para*-coupled product **21**. Moreover, when this reagent was used on the monophenolic tetrahydrobenzylisoquinoline **19b** protected as its *N*-borane complex, cularine **1** was regioselectively obtained in good yield. Other structural modifications and reagents were not successful.

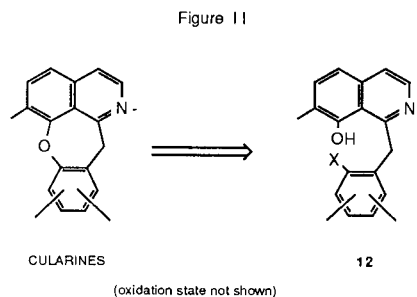
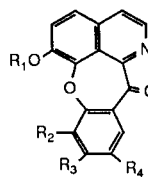
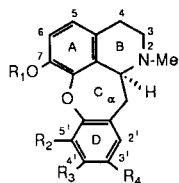
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The cularine group of isoquinoline alkaloids [3] is a fast growing class of natural products. Most of them, like cularine **1** [3], celtine **2** [4] and celtisine **3** [4] possess a 7,3',4'-substitution pattern, although those having 7,4',5'-substitution constitute a rapidly expanding subgroup. Members of this so-called isocularine [5] or cancentre-type [6] subgroup are sarcocapnine **4** [6a], sarcocapnine **5** [6b] and claviculine **6** [6c].

Ideally, it would be desirable to develop suitable synthetic approaches to each (or both) subgroups of cularines which also permitted the synthesis of the highly oxidized members of the group, such as the oxocularines namely: oxocularine **7** [7] and oxocompostelline **8** [7], and the oxoisocularines namely: oxosarcocapnine **9** [6a], oxosarcocapnine **10** [6b] and oxosarcophylline **11** [6c]. In this series of articles [8] we give a full account of our recent work [9], which has partially achieved this goal.

bond have all met with low yields in the Pomeranz-Fritsch [11] or Bischler-Napieralski [12] cyclization steps, and syntheses with late formation of the diaryl ether bond are characterized by low yields in the construction of the required 8-hydroxybenzylisoquinoline [13] or in the cyclization step using phenolic oxidative coupling [5,14]. An Ullmann reaction as the last step generally gives good yields [13,15], but a set of protection-deprotection steps are necessary. Retrosynthetic analysis of the cularine skeleton led us to consider phenolic isoquinoline **12** as the most attractive intermediate. An adequate choice of substituents, oxidation state and reaction type would in principle allow us to achieve our planned goals.

Figure 1



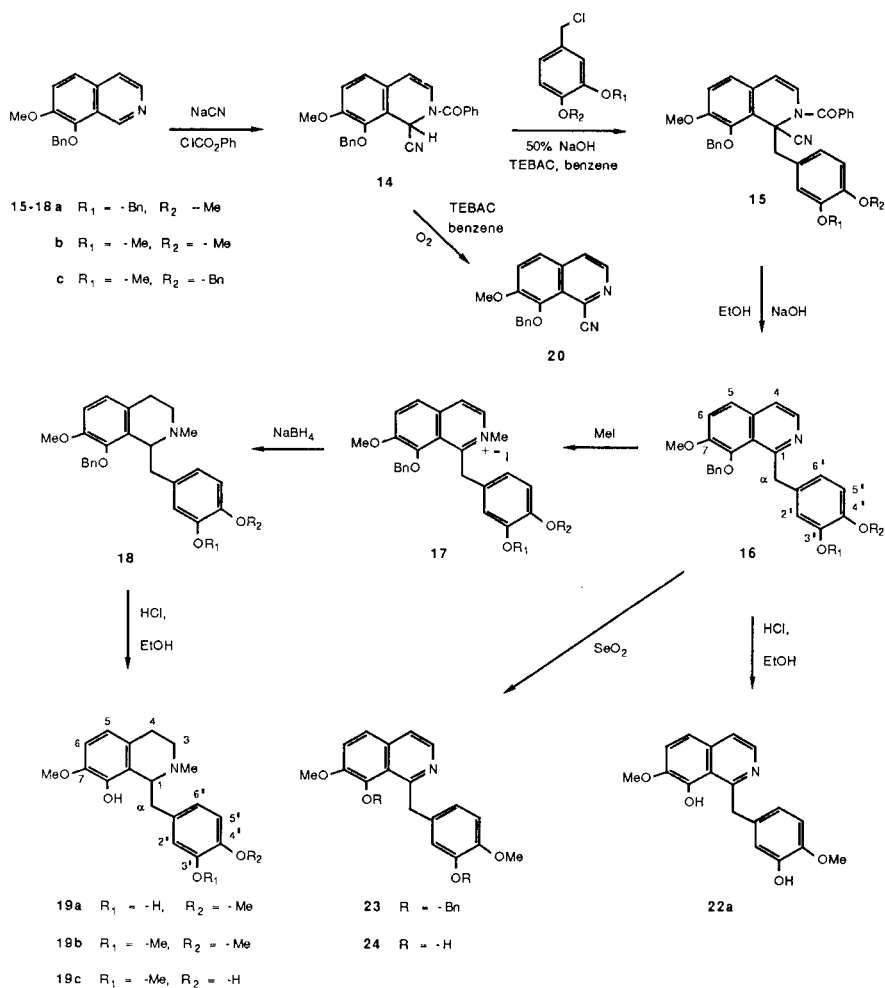
Although much work has been done on phenolic oxidative cyclization to cularines we felt further work in the field was still needed in order to clarify some erratic experiments [5,14] and to improve early results. The first phenolic coupling to be considered was the contradictory [5,14] potassium ferricyanide-promoted oxidative coupling of diphenolic tetrahydrobenzylisoquinoline **19a**. Two syntheses of this compound have been reported [5,14] and we selected that based on the alkylation of a Reissert compound **14** prepared from isoquinoline **13** [14,16] under the conditions recommended by Schwartz [17].

Ferricyanide treatment of compound **19a** as reported by Kametani [5] and Jackson [14] yielded a crude product from which isocularine **5** (6% yield) and cularine **21** (2.5% yield) were separated chromatographically (see Figure I).

At the outset, we knew of the difficulties earlier workers had met in their efforts to synthesize cularines [10]. Thus syntheses with earlier formation of the key diaryl ether

	R ₁	R ₂	R ₃	R ₄		R ₁	R ₂	R ₃	R ₄
1	-Me	-H	-OMe	-OMe	7	-Me	-H	-OMe	-OMe
2	-Me	-H	-OH	-OMe	8	-Me	-H	-OCH ₂ O-	
3	-H	-H	-OH	-OMe	9	-Me	-OMe	-OMe	-H
4	-Me	-OMe	-OMe	-H	10	-Me	-OH	-OMe	-H
5	-Me	-OH	-OMe	-H	11	-H	-OMe	-OMe	-H
6	-H	-OH	-OMe	-H					
21	-Me	-H	-OMe	-OH					

Figure III



Both *ortho* **5** and *para* **21** cyclized products were found to be identical to those described [5] by Kametani thus settling the question as to whether the *ortho* compound is [5] or is not [14] produced.

With regard to the biogenesis of these compounds, *Corydalis claviculata* (L.) D. C. has been found [6b] to contain both the tetrahydrobenzylisoquinoline **19a** (crassifoline) and the isoscularine **5** (sarcocapnidine), and both these and the coularine **21** have been isolated from *Sarcocapnos crassifolia* (Desf.) D. C. [6b,18]. Moreover, Blaschke's group [19] has reported the incorporation of tritium into coularine **1** after feeding *Corydalis claviculata* with labelled crassifoline **19a**. These results strongly suggest that direct oxidative coupling [20] of crassifoline **19a** is the main, if not the unique, biogenetic route to coularines.

Attempts to improve yields and/or regioselectivity by using the cuprous chloride/oxygen/pyridine complex model for laccase [22] produced a complex mixture in which isoscularine **5** (see Figure I) was detected as a very minor component. The use of the tyrosinase [23] model Co(II) (salen)-

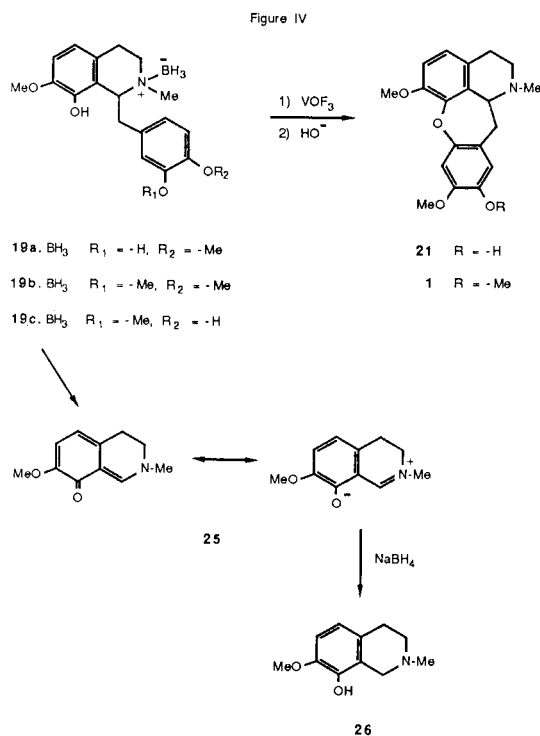
oxygen yielded unaltered starting material **19a**, and the same result was obtained using the soluble reagent tetrabutylammonium ferricyanide [24] in chloroform or methanol.

We also tried to get a simple entry to the highly oxidized members of the coularine family *via* direct oxidative coupling in the benzoylisoquinoline **24**, which was obtained by acid deprotection of **23** produced by selenium dioxide oxidation [25] of the benzylisoquinoline **16a** (see Figure III). However, no oxocoularines could be detected in the complex mixture of highly coloured compounds produced by ferricyanide oxidation of **24**, whatever the conditions tried.

Faced with these disappointing results, we next tried to circumvent the problems intrinsic to ferricyanide oxidation (mainly high concentration of oxidant and dilution of substrate) by using a stoichiometric oxidant such as vanadium oxytrifluoride or vanadium oxytrichloride. These

compounds have been shown to react with a phenol yielding substitution products of the general type VOX(OAr)_2 or VO(OAr)_3 [26]. We selected monophenolic [27] tetrahydrobenzylisoquinoline **19b** as the most interesting substrate for vanadium oxytrifluoride oxidation. This compound was synthesized following the same schemes [14] used for the parent compound **19a** (see Figure III). However, an improvement has been achieved in the Reissert alkylation step. Under sodium hydride/dimethylformamide conditions [14], besides the condensation product **15**, a variable amount of 8-benzyloxy-7-methoxyisoquinoline-1-carbonitrile **20** was obtained. It was found that phase-transfer-catalyzed alkylation is in fact the best method only if careful deoxygenation of solvents is carried out prior to alkylation [28]. The scheme is completed with the basic hydrolysis [14] of **15b**, followed by standard *N*-methylation [29], sodium borohydride reduction [29] and debenzoylation [29], yielding the required tetrahydrobenzylisoquinoline **19b** (see Figure III).

Addition of vanadium oxytrifluoride in ethyl acetate/trifluoroacetic acid/trifluoroacetic anhydride to a solution of the *N*-borane complex [27] of **19b** in methylene chloride/trifluoroacetic acid/trifluoroacetic anhydride at -10° and the usual work-up yielded, after 20 minutes stirring, racemic cularine **1** in 56% yield (70% allowing for recovered starting material). Worthy of note is the fact that the reaction was found to be highly regioselective, the isocularine analogue **4** not being detected.



In order to further establish the generality of the above vanadium-promoted synthesis of cularines, we decided to

subject the *N*-protected tetrahydrobenzylisoquinoline **19a** to the same process, obtaining 3'-*O*-demethylcularine **21** (see Figure I) as the major product in 35% yield (40% allowing for recovered starting material). With the isomeric tetrahydrobenzylisoquinoline **19c** [29] adequately protected we have not obtained procularines (as in the case of ferricyanide oxidation) [29]. Instead, we obtained compound **25** in 45% yield (identified by sodium borohydride reduction to the known [30] tetrahydroisoquinoline **26**), which constitutes further proof of the improbability of **19c** mediating in the biogenesis of cularine compounds. Attempts to extend the vanadium oxytrifluoride reaction to the direct synthesis of oxocularines starting from *N*-protected benzylisoquinoline **22a** met with failure (see Figure III).

To sum up, the vanadium oxytrifluoride-promoted oxidative coupling of appropriately substituted tetrahydrobenzylisoquinolines gave the corresponding *para*-coupled cularines in moderate to good yields. No isocularines (*ortho*-coupled products) have been detected.

EXPERIMENTAL

Materials and Techniques.

Melting points were determined on a Büchi apparatus and are uncorrected. Infrared spectra were taken in potassium bromide pellets with a Pye Unicam SP-1100 spectrometer. Ultraviolet-visible spectra were determined in ethanol solution on a Pye Unicam SP-1700 spectrophotometer. The nmr spectra were recorded on either a Varian CFT-20 or a Bruker WM-250 spectrometer; chemical shifts are reported in parts per million (ppm) downfield (δ) from internal tetramethylsilane; the solvent for nmr spectra was deuteriochloroform unless otherwise stated. The nmr multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; J = coupling constant (Hertz). Routine mass spectra were obtained using a Kratos MS-25 instrument operating at 70 eV. Combustion analyses were performed with a Perkin-Elmer model 240 B at the Inorganic Chemistry Department.

All reactions were monitored by thin-layer chromatography (tlc) carried out on 0.2-mm silica gel 60 GF-254 (Merck) plates using uv light and iodine vapour as the developing agent. Preparative-layer chromatography was performed on 0.5 mm \times 20 mm \times 20 mm silica gel 60 GF-254 (Merck) plates. Column chromatography was conducted with silica gel 60 (Merck) or neutral aluminium oxide Activity grade I (Woelm).

Reactions sensitive to air or moisture were conducted in oven-dried glassware under an atmosphere of dry nitrogen or argon using dry freshly distilled solvents. Methylene chloride and ethyl acetate were distilled under nitrogen from calcium hydride. Benzene was dried and distilled under nitrogen from sodium benzophenone ketyl.

All the starting materials and reagents used in this work were either commercially available with 98% or higher purity and were used without further purification or prepared by standard literature procedures. Benzyl chlorides were prepared as usual from the corresponding commercial aldehydes by sodium borohydride reduction [31] and treatment with thionyl chloride [31].

2-Benzoyl-8-benzyloxy-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**14**).

In a two-neck, round-bottomed flask provided with an addition funnel, nitrogen inlet and magnetic stirring bar, 0.696 g of sodium cyanide (14.2 mmoles) was dissolved in 2 ml of water and 4.0 g (15.09 mmoles) of iso-

quinoline **13** [14] in 15 ml of methylene chloride was added. From the addition funnel was slowly added (2.5 hours) a solution of 1.996 g (14.2 mmoles) of benzoyl chloride in 20 ml of methylene chloride. After stirring for a further 2 hours, silica tlc in 10% ether-benzene showed that about 50% of **13** remained. More sodium cyanide (0.696 g) in water (2 ml) and dropwise benzoyl chloride (0.5 g) in methylene chloride (5 ml) were added, and the resulting solution was stirred overnight. The organic layer was separated and washed with water (3 × 50 ml), 2*N* hydrochloric acid (50 ml) and water again (2 × 50 ml). Drying (sodium sulfate), filtration and evaporation gave the Reissert derivative as a brown crystalline solid (6.49 g). It was recrystallized from methanol as pale yellow crystals (4.2 g). An additional 1.17 g were obtained from the mother liquors, mp 132-134° (lit 132-134°) [14], total yield = 90%.

The physical and spectroscopic data of compounds **15a-19a** and **15c-19c** (obtained as per refs [14] and [29] respectively) coincided with published data [14,29].

8-Benzyloxy-*N*-benzoyl-1-(3',4'-dimethoxybenzyl)-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (**15b**).

A solution of 2.52 mmoles of the Reissert compound **14**, 3.28 mmoles of 3,4-dimethoxybenzyl chloride and 0.014 g of tetrabutylammonium-chloride in 6 ml of dry benzene was deoxygenated by gentle heating with simultaneous entry of an inert gas for at least two hours. Through a septum 1.5 ml of 50% sodium hydroxide was then added and stirring was maintained for a further 6 hours. Water (100 ml) and benzene (100 ml) were then added and the layers separated. Benzene extractions (2 × 50 ml) of the aqueous layer followed by drying of the organic extracts (sodium sulfate) and final evaporation yielded an oil which crystallized from ethanol, mp 138-140°, yield 85%; ¹H-nmr: 3.48, 3.76 and 3.93 (ss, each 3H, 3 × -OMe), 3.71 (d, J = 13.3 Hz, -CH₂Ar), 4.31 (d, J = 13.3 Hz, -CH₂Ar), 4.96 (d, J = 8.0 Hz, H_A), 5.43 (d, J = 8.1 Hz, -OCH₂Ar), 5.56 (d, J = 8.0 Hz, -OCH₂Ar), 6.00-7.74 (m, 16 H, ArH); ms: m/e (%) 546 (M⁺, 3), 520 (37), 429 (22), 428 (33), 416 (44), 415 (71), 414 (35), 397 (78), 396 (100), 395 (88), 105 (75), 91 (54).

Anal. Calcd. for C₂₄H₃₀N₂O₅: C, 74.72; H, 5.49; N, 5.12. Found: C, 74.60; H, 5.50; N, 5.10.

Without solvent deoxygenation, variable amounts of 8-benzyloxy-7-methoxyisoquinoline-1-carbonitrile (**20**) were obtained. This compound crystallized from methanol as a gummy yellow solid, mp 89-91°; ¹H-nmr: 4.04 (s, 3H, -OMe), 5.36 (s, 2H, -OCH₂OAr-), 7.29-7.64 (m, 7H, ArH), 7.74 (d, J = 5.6 Hz, H_A), 8.50 (d, J = 5.6 Hz, H_B); ms: m/e (%) 327 (M⁺, 100), 199 (45), 142 (44), 130 (68), 91 (95).

Anal. Calcd. for C₁₈H₁₄N₂O₂: C, 74.48; H, 4.82; N, 9.65. Found: C, 74.29; H, 4.74; N, 9.27.

8-Benzyloxy-1-(3',4'-dimethoxybenzyl)-7-methoxyisoquinoline (**16b**).

A mixture of 0.36 mmole of **15b**, 10 ml of ethanol and 5 ml of 50% sodium hydroxide was refluxed under an inert atmosphere for 2 hours and 30 minutes. On cooling, the aqueous layer separated from the organic layer, which was decanted and collected. Water (50 ml) was added to the alkaline layer and this was extracted with benzene (50 ml). The organic extracts were combined and evaporated. The resulting oil was redissolved in benzene (100 ml) and washed with water (2 × 70 ml). The dried (sodium sulfate) extracts were evaporated to dryness to afford the benzyloisoquinoline **16b**, which crystallized from ethanol, mp 115-117°, yield 95%; ¹H-nmr: 3.58, 3.76 and 3.96 (ss, each 3 H, 3 × -OMe), 4.81 and 4.99 (ss, each 2 H, 2 × -CH₂Ar), 6.54-7.56 (m, 11 H, ArH), 8.35 (d, J = 5.6 Hz, H_B); ms: m/e (%) 415 (M⁺, 18), 400 (7), 324 (50), 308 (14), 294 (11), 266 (11), 251 (9), 227 (9), 91 (100).

Anal. Calcd. for C₂₆H₂₈N₂O₄: C, 75.18; H, 6.02; N, 3.37. Found: C, 74.77; H, 6.20; N, 2.96.

8-Benzyloxy-1-(3',4'-dimethoxybenzyl)-7-methoxy-*N*-methylisoquinolinium Iodide (**17b**).

Compound **16b** (0.24 mole) was dissolved in 1 ml of neat methyl iodide and the solution was left under inert gas for 15 hours. The 1-benzyloisoquinolinium iodide formed as a bright yellow precipitate and was filtered

and dried. It was recrystallized from acetone, mp 168-170°; yield 82%; ¹H-nmr: 3.68, 3.80 and 4.07 (ss, each 3 H, 3 × -OMe), 4.54 (s, 3 H, -N⁺Me), 5.02 and 5.35 (ss, each 2 H, 2 × -CH₂Ar), 6.03 (dd, J_{AX} = 8.3 Hz, J_{BX} = 1.7 Hz, H_C), 6.53 (d, J = 1.7 Hz, H₂), 6.65 (d, J = 8.1 Hz, 1 H, H₅), 7.14-7.34 (m, 5 H, ArH), 7.93 (d, J = 9.0 Hz, 1 H, H_D), 8.08 (d, J = 9.2 Hz, 1 H, H₅), 8.30 (d, J = 6.8 Hz, 1 H, H_A), 8.82 (d, J = 6.8 Hz, 1 H, H₃); ms: m/e (%) 429 (4), 428 (3), 325 (18), 310 (11), 254 (100), 142 (82), 141 (44), 127 (66) and 91 (44).

Anal. Calcd. for C₂₇H₂₈INO₄: C, 58.16; H, 5.02; N, 2.51. Found: C, 58.21; H, 5.06; N, 2.63.

8-Benzyloxy-1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline (**18b**).

To a stirred suspension of methiodide **17b** (3.94 mmoles) in 125 ml of methanol and 2.5 ml of water, sodium borohydride (65.78 mmoles) was added in small portions over 90 minutes at room temperature. Stirring was maintained for two hours more, the solvent was removed under vacuum and ice was added to destroy the boron complex. The product was extracted into benzene (2 × 200 ml) and the dried extracts (sodium sulfate) were evaporated to dryness, leaving an oil in quantitative yield that could not be crystallized and was used for the next step without further purification. An attempt to purify a sample by sublimation resulted in decomposition; ¹H-nmr: 2.20 (s, 3H, -NMe), 2.60-3.31 (m, 6H, 3 × -CH₂), 3.65, 3.82 and 3.88 (ss, each 3 H, 3 × -OMe), 4.94 (d, J = 11.1 Hz, 1 H, -OCH₂Ar), 5.21 (d, J = 11.1 Hz, 1 H, -OCH₂Ar), 6.61-7.35 (m, 10H, ArH).

1,2,3,4-Tetrahydro-1-(3',4'-dimethoxybenzyl)-7-methoxy-*N*-methylisoquinoline-8-ol (**19b**).

The foregoing tetrahydrobenzyloisoquinoline (0.93 mmole) in ethanol (7 ml) was treated with concentrated hydrochloric acid (7 ml) under inert gas and the solution was refluxed for one hour. The mixture was diluted with water (30 ml) and extracted with ether (2 × 30 ml). After neutralization with sodium bicarbonate the phenolic compound was extracted into methylene chloride (4 × 50 ml) and dried (sodium sulfate). Solvent was removed under vacuum giving the phenolic tetrahydrobenzyloisoquinoline **19b** in nearly quantitative yield as a non-crystalline solid of mp 68-70° which since it could not be recrystallized due to its instability was used without purification; ¹H-nmr: 2.38 (s, 3H, NMe), 2.48-3.00 (m, 6 H, 3 × -CH₂-), 3.79, 3.83 and 3.84 (ss, each 3 H, 3 × -OMe), 4.10 (dd, J_{AX} = 7.1 Hz, J_{BX} = 4.2 Hz, 1 H, H₁), 6.61-6.87 (m, 5 H, ArH); ms: m/e (%) 344 (M⁺ + 1, 12), 342 (4), 193 (79), 192 (100), 191 (50), 190 (50), 177 (67).

8-Benzyloxy-1-(3'-benzyloxy-4'-methoxybenzyl)-7-methoxyisoquinoline (**23**).

A mixture of 0.1 mmole of benzyloisoquinoline **16a** and 0.36 mmole of selenium dioxide was dissolved in dioxane-water (10 ml:3 ml) and refluxed during 7 hours until tlc showed that no starting material remained. Solvent was removed under vacuum and water (30 ml) and 10% sodium hydroxide (5 ml) were added. Selenium was filtered off and the aqueous layer was extracted with methylene chloride (3 × 50 ml). The dried (sodium sulfate) extracts were concentrated to dryness, affording a dark oil which was separated from colloidal selenium by filtration through a silica column. Pure **23** was obtained and recrystallized from ethanol, mp 164-166°, yield 78%; ir: 1660 (C=O) cm⁻¹; ¹H-nmr: 3.84 and 3.95 (ss, each 3 H, 2 × -OMe), 4.89 and 4.93 (ss, each 2 H, 2 × -CH₂Ar), 6.67 (d, J = 8.5 Hz, 1 H, H₅), 7.01 (dd, J_{AX} = 8.4 Hz, J_{BX} = 1.9 Hz, 1 H, H₆), 7.24-7.72 (m, 13 H, ArH), 7.72 (d, J = 9.0 Hz, 1 H, H₃), 8.45 (d, J = 5.8 Hz, 1 H, H₂); ms: m/e (%) 505 (M⁺, 33), 415 (35), 414 (39), 324 (35), 151 (28), 92 (78), 91 (100).

Anal. Calcd for C₃₂H₂₇NO₄: C, 76.04; H, 5.34; N, 2.77. Found: C, 75.64; H, 5.30; N, 2.91.

1-(3'-Hydroxy-4'-methoxybenzyl)-7-methoxyisoquinoline-8-ol (**24**).

Debenzylation of **23** was performed under the conditions described for the conversion of **18b** into **19b**. The unstable product so obtained crystallized from ethanol, mp 220-222° and could be used without further purification, yield 90%; ¹H-nmr (deuteriochloroform + perdeuterio-

methanol): 3.89 and 3.93 (ss, each 3 H, $2 \times$ -OMe), 6.78 (d, $J = 8.5$ Hz, 1 H, H₅), 7.15 (dd, $J_{AX} = 8.5$ Hz, $J_{BX} = 2.0$ Hz, 1H, H₆), 7.42 (d, $J = 2.0$ Hz, H₂), 7.48 (s, 2H, ArH), 7.65 (d, $J = 5.8$ Hz, 1 H, H₄), 8.31 (d, $J = 5.8$ Hz, 1H, H₃); ms: m/e (%) 325 (M⁺, 48), 296 (16), 202 (24), 201 (20), 186 (20), 151 (100), 130 (26), 108 (56).

Anal. Calcd. for C₁₈H₁₅NO₅: C, 66.46; H, 4.61; N, 4.30. Found: C, 66.14; H, 4.72; N, 4.41.

Ferricyanide Oxidation of Diphenolic Tetrahydrobenzylisoquinoline (19a).

A solution of **19a** (0.5 g, 1.52 mmole) in chloroform (42 ml) was added to a mixture of potassium ferricyanide (2 g, 6 mmole), 1*N* ammonium acetate (100 ml) and chloroform (22 ml) with stirring at room temperature over 30 minutes, and the resulting mixture was stirred vigorously for 3.5 hours. The organic layer was separated, washed with brine, dried (sodium sulfate) and evaporated to leave a dark brown residue (0.38 g) which was chromatographed on silica gel (8 g) using chloroform:methanol (99:1 v/v) as eluent. The first eluted product was identified as isocularine **5** (0.035 g, 6% yield), which was crystallized from ethanol, mp 125-127° (lit [5] 128-129°); ¹H-nmr: 2.61 (s, 3H, -NMe), 2.77-3.40 (m, 6 H, $3 \times$ -CH₂), 3.86 (s, 3H, -OMe), 3.87 (s, 3H, -OMe), 4.51 (dd, $J_{AX} = 11.8$ Hz, $J_{BX} = 4.8$ Hz, 1H, H₁), 6.57 (s, 2H, H₂ and H₅), 6.74 (d, $J = 8.5$ Hz, 1H, H₆), 6.92 (d, $J = 8.5$, 1H, H₃), ms: m/e (%) 327 (M⁺, 100), 312 (51), 310 (29), 296 (20), 281 (35), 174 (40).

The second product was identified as cularine **21** (0.015 g, 2.5% yield) by comparison of its spectroscopic data with those published [5] for **21**. After crystallization from ethanol, mp 209-211°, a good elemental analysis could be obtained; ¹H-nmr: 2.57 (s, 3H, -NMe), 2.75-3.17 (m, 6H, $3 \times$ -CH₂), 3.84 (s, 3H, -OMe), 3.86 (s, 3H, -OMe), 4.00-4.40 (broad s, 1H, -OH), 4.46 (dd, $J_{AX} = 11.4$ Hz, $J_{BX} = 4.2$ Hz, 1H, H₁), 6.57 (s, 1H, H₅), 6.74 (d, $J = 8.4$ Hz, 1H, H₆), 6.81 (s, 1H, H₂), 6.88 (d, $J = 8.5$ Hz, 1H, H₃); ms: m/e (%) 327 (M⁺, 100), 312 (64), 310 (32), 284 (11), 192 (23), 174 (25).

Anal. Calcd. for C₁₉H₂₁NO₄: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.74; H, 6.65; N, 3.89.

Preparation of the Borane Complex of 19a.

A solution of 0.3 g (0.92 mmole) of **19a** in 8 ml of anhydrous methylene chloride was treated with 1 ml of a 1*M* solution of diborane in tetrahydrofuran and the reaction was stirred for 15 minutes at room temperature. The solvent was evaporated and the residue was subjected to column silica gel chromatography with methylene chloride as eluent to obtain 0.18 g of an amorphous solid, mp 163-165°, yield 58%; ms: m/e (%) 343 (M⁺, 0.8), 340 (0.8), 328 (2), 192 (100).

Preparation of the Borane Complex of 19b.

To a solution of 0.22 g (0.67 mmole) of **19b** in 6 ml of anhydrous methylene chloride was added 1.1 ml of a 1*M* solution of diborane in tetrahydrofuran. Stirring for 15 minutes and treatment of the residue as above afforded an amorphous solid, mp 68-70°, in quantitative yield; ms: m/e (%) 357 (M⁺, 0.2), 342 (0.6), 192 (100).

Preparation of the Borane Complex of 19c.

This compound was obtained in the same conditions and yield described for its isomeric compound derived from **19a**. The final product was an oil; ms: m/e 343 (M⁺, 1), 328 (3), 192 (100).

Vanadium Oxytrifluoride Oxidation. General Procedure.

In a typical experiment, a cooled (-10°) solution of 0.53 mmole of the substrate in 10 ml of anhydrous methylene chloride containing 2.2 ml of trifluoroacetic acid:trifluoroacetic anhydride (20:1 by wt) was treated under an argon atmosphere with a solution of vanadium oxytrifluoride (0.16 g, 2.5 mole-equivalents) in 1 ml of ethyl acetate and 1 ml of trifluoroacetic acid:trifluoroacetic anhydride (20:1 by wt). The resulting dark blue solution was stirred for various lengths of time at -10°. The reaction was quenched with a 10% citric acid solution and the pH adjusted to 7.5 with 28% ammonium hydroxide. The aqueous solution was extracted

with methylene chloride (3 × 50 ml) and the organic extracts were washed with brine, dried (sodium sulfate) and evaporated under reduced pressure to give the crude product. This residue was taken up in 30 ml of methanol and refluxed under inert gas with 0.25 g of anhydrous sodium carbonate for 2 hours. The solid was filtered and the solution evaporated to give a brown residue, which was chromatographed on preparative silica gel plates.

Vanadium Oxytrifluoride Oxidation of the Borane Complex of 19a.

Starting from 0.18 g (0.53 mmole) of *N*-borane complex of **19a** and with 45 minutes stirring at -10°, a final residue was obtained which yielded 0.06 g (35% yield) of **21** and 0.02 g of recovered **19a**.

Vanadium Oxytrifluoride Oxidation of the Borane Complex of 19b.

From 0.15 g (0.42 mmole) of starting material and with 15 minutes stirring, we obtained 0.08 g (56% yield) of cularine **1** and 0.03 g of recovered **19b**. The (±)-cularine **1** so obtained crystallized from ethanol as brown crystals, mp 130-132° (lit [5] 125-126°, from ether).

Vanadium Oxytrifluoride Oxidation of the Borane Complex of 19c.

Starting from 0.18 g (0.53 mmole) of the *N*-borane complex of **19c** and with 45 minutes stirring, compound **25** (0.45 g, 45% yield) was obtained as a red solid. It crystallized from ethanol-ether, mp 174-176°; ir: 1602 and 1630 cm⁻¹; uv (ethanol): λ max 230 sh, 255, 326 and 458; uv (ethanol + H⁺): λ max 226 sh, 238 sh, 310 and 398 nm; ¹H-nmr: 2.81 (m, 2H, -CH₂), 3.34 (s, 3H, -NMe), 3.47 (m, 2H, -CH₂), 3.74 (s, 3H, -OMe), 5.80 and 6.40 (ABq, $J = 7.2$ Hz, 2H, H₅ and H₆), 8.42 (broad s, 1H, H₁), ¹H-nmr (deuteriochloroform + deuteriotrifluoroacetic acid): 3.11 (t, 2H, -CH₂), 3.78 (s, 3H, -N⁺-Me), 3.88 (s, 3H, -OMe), 6.74 (d, $J = 8.0$ Hz, 1H, H₆), 7.10 (d, $J = 8.0$ Hz, 1H, H₃), 9.05 (s, 1H, H₁); ms: m/e (%) 193 (M⁺+2, 13), 192 (M⁺+1, 30), 191 (M⁺, 100), 190 (91).

This was reduced to 1,2,3,4-tetrahydro-7-methoxy-*N*-methylisoquinoline-8-ol **26** [30] by the same procedure as used in the conversion of **17b** to **18b**. Its picrate melted at 177-179° (lit [30b] 180°); ¹H-nmr: 2.45 (s, 3H, -NMe), 2.63-2.83 (m, 4H, $2 \times$ -CH₂), 3.57 (s, 2H, -CH₂-N), 3.57 (s, 3H, -OMe), 6.19 (broad s, -OH), 6.54 (d, $J = 8.1$ Hz, H₆), 6.66 (d, $J = 8.4$ Hz, 1H, H₃); ms: m/e (%) 193 (M⁺, 49), 192 (47), 178 (15), 150 (100), 135 (38) and 107 (23).

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