A Synthesis of (±)-Cularicine

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A synthesis of (±)-cularicine is reported. 2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxyphenylacetic acid was converted in four steps to 6-benzyloxy-2,3-methylenedioxy-10,11-dihydrodibenz[*b*,*f*]oxepin-10(11*H*)-one. A modified Pomeranz–Fritsch reaction was applied to this ketone to add the two carbon atoms and one nitrogen atom required to complete the carbon skeleton of cularicine. The norcularicine derived from this reaction was *N*-methylated with formaldehyde and sodium borohydride.

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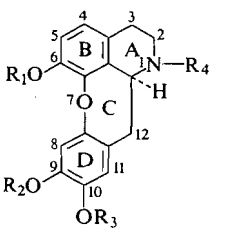
On rapporte une synthèse de la (±)-cularicine. L'acide (benzyloxy-2′ phénoxy)-2 méthylènedioxy-4,5 phénylacétique est transformé en quatre étapes en 11*H*-benzyloxy-6 méthylènedioxy-2,3 dihydro-10,11 dibenz[*b*,*f*]oxepinone-10. On a soumis cette cétone à une forme modifiée de la réaction de Pomeranz–Fritsch. Afin d'ajouter les deux atomes de carbone et l'atome d'azote nécessaire pour compléter le squelette carboné de la cularicine. La norcularicine obtenue par cette réaction a été *N*-méthylée avec de la formaldéhyde et du borohydrure de sodium.

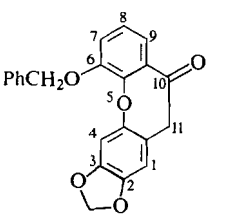
[Traduit par le journal]

(+)-Cularicine (**1**, $C_{18}H_{17}NO_4$), an alkaloid of *Corydalis claviculata* (L.) DC, was isolated by Manske (1, 2), who elucidated its structure (2) by converting it into cularine (**2**), an alkaloid of established structure (3, 4). Besides **1** and **2** only two other alkaloids of this type have been isolated, cularimine (3) and cularidine (4). The absolute configuration of cularine, shown in the accompanying structure, has recently been established by relating it chemically to *S*-laudanosine (5) and by X-ray analysis of its methiodide (6). Since **1**, **3**, and **4** have all been converted to cularine their configuration is also known (3, 4).



1 (cularicine) $R_1 = H$; $R_2 + R_3 = CH_2$; $R_4 = Me$
2 (cularine) $R_1 = R_2 = R_3 = R_4 = Me$
3 (cularimine) $R_1 = R_2 = R_3 = Me$; $R_4 = H$
4 (cularidine) $R_1 = H$; $R_2 = R_3 = R_4 = Me$

Several successful approaches to the synthesis of cularine have been reported. In two of these the diphenyl ether linkage was formed in an Ullmann reaction in the initial stages of the synthetic scheme and rings A and C were subsequently constructed from the appropriately substituted diphenyl ether (7, 8). In another approach, substituted benzylisoquinolines were synthesized and the diphenyl ether linkage was introduced in a late stage of the synthetic scheme either through oxidative coupling (9–11) or through an intramolecular Ullmann reaction (12, 13). Resolution of synthetic (±)-cularine has been effected (14). Initial attempts to synthesize cularidine (15, 16) led only to derivatives that were not convertible into the racemic phenolic base. More recently, however, the intramolecular Ullmann reaction has been applied to the synthesis of cularidine (17) and of cularicine (18). Here we describe another synthesis of (±)-cularicine by a method that should serve equally well for the synthesis of (±)-cularidine.



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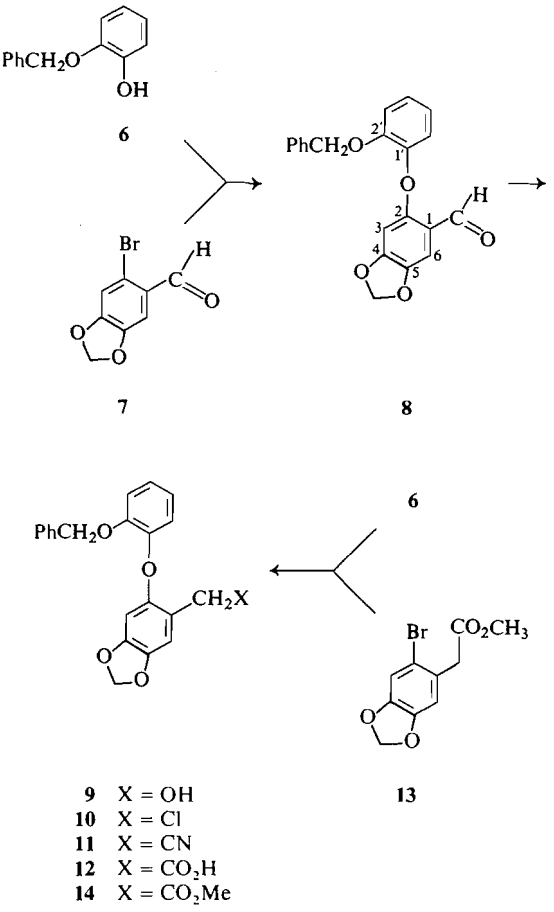
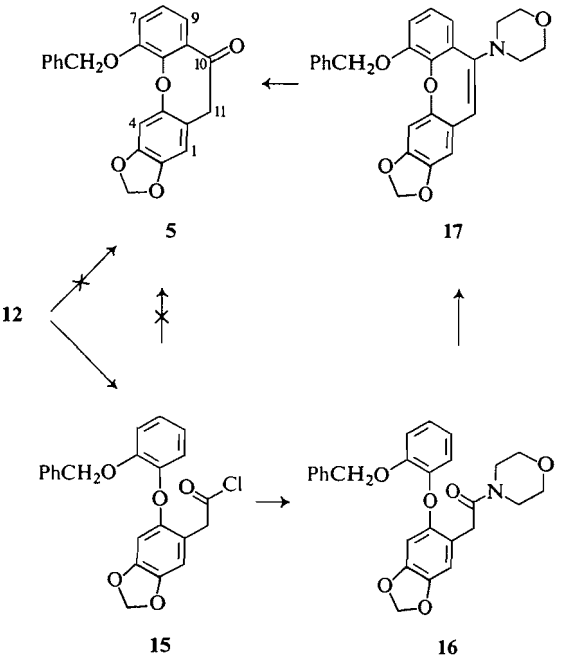


SCHEME 1

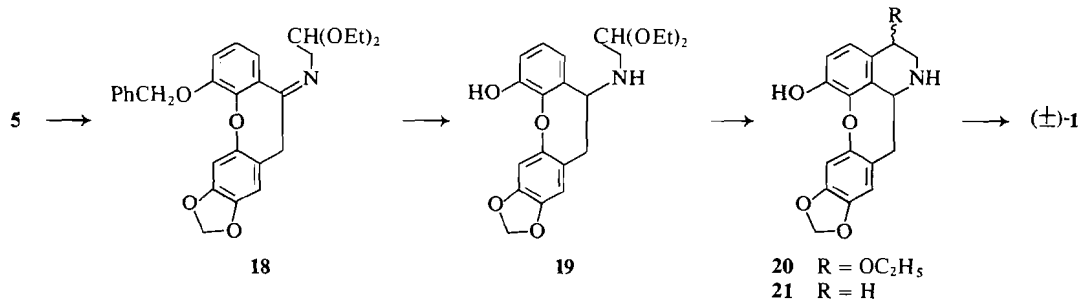
The first objective of our synthesis was the oxepinone (**5**) containing three of the four rings of cularicine with the potential phenolic group at C-6 of cularicine suitably protected. The synthesis of **5** was brought about in the manner shown in Schemes 1 and 2. Ullmann condensation of *o*-benzyloxyphenol (**6**) (19) with 6-bromopiperonal (**7**) (20) in the presence of copper and cupric oxide gave the diphenyl ether (**8**), in 53% yield, which was reduced to the alcohol (**9**) in quantitative yield. Treatment of **9** with thionyl chloride yielded the chloride (**10**) that was converted directly to the cyanide (**11**) with sodium cyanide in methyl ethyl ketone. Base-catalyzed hydrolysis of **11** led to the acid **12** in good yield. Compound **12** was also prepared by fusion of **6** with methyl 6-bromohomopiperonylate (**13**) in the presence of copper and cupric oxide at 140° for 8 h. The methyl ester (**14**) so obtained was hydrolyzed directly to the acid (**12**). These experiments are summarized in Scheme 1. Up to this point our synthetic scheme is analogous to that used in the original synthesis of cularine (7).

Attempts to cyclize **12** in various acidic media led to failure. Similarly, cyclization of the acid chloride (**15**) under a variety of Friedel–Crafts conditions gave uncharacterized products apparently resulting from debenzylation of the ether by the Lewis acid catalysts. At length it was found that the amide (**16**) cyclized to the enamine (**17**) on treatment with phosphoryl chloride in a mixture of benzene and toluene at reflux. To our knowledge this method of cyclization is unique. However, it has an analogy in the Bischler–Napieralski cyclization of phenylethyl amides to dihydroisoquinolines. The general utility of this cyclization for the preparation of ketones will be investigated further. The structure of **17** follows from an examination of its spectroscopic properties and from its hydrolysis to the oxepinone (**5**). The spectroscopic properties of **5** are in accord with the structure assigned. These transformations are outlined in Scheme 2.

The introduction of two carbon atoms and a



SCHEME 2



SCHEME 3

nitrogen atom was now necessary to complete the ring system of cularicine. To bring this about, we turned to the modified Pomeranz–Fritsch procedure developed by Bobbitt *et al.* (21) and eventually worked out satisfactory conditions to prepare a Schiff base and to effect the cyclization of its dihydro derivative (Scheme 3).

The oxepinone (**5**) was condensed with aminoacetaldehyde diethyl acetal to the Schiff base (**18**) which was converted directly to the phenolic amino acetal (**19**). The protecting benzyl group was removed by hydrogenolysis simultaneously with the reduction of the carbon–nitrogen double bond. The acetal (**19**) was converted in 6 *N* ethanolic hydrochloric acid into the cyclized compound (**20**). The formation of an ethoxy rather than the usual hydroxy compound in the Bobbit cyclization appears to be without precedent in the literature (22, and references cited therein). The 3-ethoxynorcularicine (**20**) obtained in this reaction represents one of a pair of racemates but its relative configuration was not established. In an analogous reaction Dalton *et al.* (23) also obtained only one of a pair of possible racemates. The ethoxy group of **20** was removed by hydrogenolysis over Pt in ethanolic hydrochloric acid yielding racemic norcularicine (**21**). Treatment of the mother liquor, remaining after the separation of **20**, with hydrogen over Pt also led to the recovery of (±)-norcularicine.

Finally, *N*-methylation was brought about with formaldehyde and sodium borohydride. The product of this reaction, (±)-cularicine, had spectral properties in solution that were identical with those of a sample of natural (+)-cularicine obtained from Professor R. H. F. Manske. The melting point of our product differs from that reported (18) but the spectral properties agree within experimental error.

Experimental

Apparatus, Methods, and Materials

Infrared spectra were recorded on a Beckmann IR-5 spectrometer in KBr, in liquid film or in solution as stated. The data are reported in $\nu\,cm^{-1}$.

Proton magnetic resonance spectra were recorded on Varian HA-100 or A-60 spectrometers. All spectra were recorded at ambient temperature in solution in the solvent specified with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported relative to TMS = 0.0 δ. The symbols s, d, t, m, refer to singlet, doublet, triplet, and multiplet, respectively.

Mass spectra were determined on a C.E.C. 21-110B mass spectrometer. Samples were introduced through a direct inlet system. Relative intensity data were obtained from low resolution spectra recorded under identical conditions at an ionization voltage of 70 eV, a trap current at 140 μA, and at 200 °C or at the source temperature specified. Relative intensities of individual ions are placed in parenthesis after the *m/e* value.

Melting points are uncorrected.

2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxybenzaldehyde (8)

A mixture of *o*-benzyloxyphenol (19) (**6**, 5.0 g), 6-bromopiperonal (20) (**7**, 5.5 g), potassium carbonate (12.0 g), copper powder (10.0 g), cupric oxide (5.0 g) and pyridine (15 ml) was heated at 110–115° with vigorous stirring for 20 h. The product was extracted with chloroform, and the extract was filtered and washed with 10% HCl and 5% NaOH. It was then dried over potassium carbonate and evaporated to leave a dark syrup. Purification was effected by column chromatography on silica gel using chloroform as eluent to give 2-(2′-benzyloxyphenoxy)-4,5-methylenedioxybenzaldehyde (**8**, 4.6 g, 52.9%) as colorless needles melting at 104–105° after recrystallization from ethanol; i.r. (KBr): 1670 (CO), 935 (OCH_2O), 735, 695 (monosubstituted benzene); p.m.r. ($CDCl_3$): 10.14 (1 H, s, —C*H*O), 7.35–6.92 (10 H, m, Ar—H), 6.25 (1 H, s, H-3), 5.92 (2 H, s, OCH_2O), 5.05 (2 H, s, OCH_2Ph).

Anal. Calcd. for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found: C, 72.52; H, 4.74.

2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxybenzyl Alcohol (9)

Sodium borohydride (10.0 g) was added in portions to a stirred solution of the aldehyde (**8**) (20.0 g) in methanol

(600 ml) at room temperature. After stirring the mixture for a further 2 h, the solvent was removed to leave a colorless viscous residue which was diluted with water and extracted with benzene. The extract gave on evaporation the alcohol (**9**), (19.4 g, 97%) as colorless needles melting at 84–85° after crystallization from chloroform–hexane; i.r. (KBr): 3250 (OH), 935 (OCH_2O), 745, 695 (monosubstituted benzene); p.m.r. ($CDCl_3$): 7.27 (5 H, s, C_6H_5), 7.15–6.90 (4 H, m, Ar—H), 6.85 (1 H, s, H-6), 6.34 (1 H, s, H-3), 5.83 (2 H, s, OCH_2O), 5.02 (2 H, s, OCH_2Ph), 4.58 (2 H, CH_2OH), 2.48 (1 H, broad s, OH).

Anal. Calcd. for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 71.99; H, 5.23.

*2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxybenzyl Cyanide (**11**)*

Thionyl chloride (40 ml) was added dropwise to a stirred solution of alcohol (**9**) (20 g) in benzene (300 ml) at 5–10° and the mixture was then heated under reflux for 1 h. Removal of the solvent yielded the chloride (**10**) which was used in the next step without further purification. The chloride (**10**) in benzene (100 ml) was added dropwise to a stirred mixture of methyl ethyl ketone (500 ml), sodium cyanide (20 g), and sodium iodide (15 g) at room temperature. This mixture was warmed to 60–70° and stirred for a further 8 h at the same temperature. Water (100 ml) was then added to the reaction mixture, and the organic layer was separated, washed with a small amount of water, and dried over potassium carbonate. The extract was worked up to give the crude cyanide (**11**) which crystallized from ethanol to afford colorless needles melting at 108–109°; yield, 19.2 g (93.2% based on **9**); i.r. (KBr): 2255 (weak, CN), 935 (OCH_2O), 735, 695 (monosubstituted benzene); p.m.r. ($CDCl_3$): 7.29 (5 H, broad s, C_6H_5), 6.9–7.2 (4 H, m, Ar—H) 6.88 (1 H, s, H-6), 6.34 (1 H, s, H-3), 5.91 (2 H, s, OCH_2O), 5.04 (2 H, s, OCH_2Ph), 3.67 (2 H, s, CH_2CN).

Anal. Calcd. for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.74; H, 4.81; N, 3.75.

*2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxyphenylacetic Acid (**12**)*

A mixture of the cyanide (**11**) (19.5 g), ethanol (500 ml), potassium hydroxide (40 g), and water (100 ml) was refluxed for 48 h. After removal of solvent from the mixture, the brown residue was diluted with water, washed with ether, and then acidified with hydrochloric acid to afford a precipitate which was extracted with chloroform. The extract was dried over magnesium sulfate, and evaporated to leave a slightly colored syrup which crystallized from chloroform–hexane yielding the acid (**12**) (14.3 g, 70.0%) as colorless needles melting at 128–129°; i.r. (KBr): 3300–2550 (OH), 1720 (CO), 750, 700 (monosubstituted benzene); p.m.r. ($CDCl_3$): 7.30 (5 H, broad s, C_6H_5), 7.15–6.85 (4 H, m, Ar—H), 6.75 (1 H, s, H-6), 6.37 (1 H, s, H-3), 5.90 (2 H, s, OCH_2O), 5.08 (2 H, s, OCH_2Ph), 3.63 (2 H, s, CH_2COOH).

Anal. Calcd. for $C_{22}H_{18}O_6$: C, 69.83; H, 4.80. Found: C, 69.90; H, 4.66.

*Methyl 2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxyphenylacetate (**14**)*

A mixture of methyl 6-bromohomopiperonylate (24) (**13**, 5.6 g), *o*-benzyloxyphenol (**6**, 6.0 g), potassium carbonate (5.6 g), copper powder (6.0 g), cupric oxide (2.0 g), and pyridine (8 ml) was heated at 140° under vigorous stirring for 8 h. The product was exhaustively extracted with chloroform and the extract was filtered to remove suspended material. The chloroform filtrate was then washed with 10% HCl, dried over magnesium sulfate, and evaporated, yielding a dark colored syrup. Purification of the crude product by column chromatography on silica gel using chloroform as eluent gave the diphenyl ether (**14**) (6.7 g, 58.1%) as a slightly colored syrup; i.r. (liquid film): 1730 (CO), 925 (OCH_2O), 745, 680 (monosubstituted benzene); p.m.r. ($CDCl_3$): 7.33 (5 H, broad s, C_6H_5), 7.15–6.85 (4 H, m, Ar—H), 6.77 (1 H, s, H-6), 6.39 (1 H, s, H-3), 5.89 (2 H, s, OCH_2O), 5.08 (2 H, s, OCH_2Ph), 3.63 (2 H, s, $—CH_2COOCH_3$), 3.57 (3 H, s, OCH_3).

*Hydrolysis of **14***

The methyl ester (**14**) (6.5 g) was dissolved in a mixture of ethanol (150 ml) and 20% NaOH (80 ml) and refluxed for 2 h. The residue obtained after removal of solvent was diluted with water, washed with ether, and acidified with hydrochloric acid to afford a colorless precipitate. Extraction of the precipitate with chloroform gave the phenylacetic acid (**12**) (5.4 g, 96.3%) obtained as colorless needles melting at 128–129.5° after crystallization from chloroform–hexane. This compound was identical with the sample prepared above.

*N-[2-(2′-Benzyloxyphenoxy)-4,5-methylenedioxyphenacetyl]morpholine (**16**)*

Thionyl chloride (60 ml) was added dropwise to a cooled solution of the acid (**12**) (20.0 g) in dry benzene (300 ml) and the mixture was gently refluxed for 1.5 h. Removal of the solvent gave the acid chloride (**15**) which was dissolved in 30 ml of chloroform and used in the next reaction without purification.

To a stirred mixture of triethylamine (24 ml), morpholine (36 g), and chloroform (240 ml) the acid chloride solution, prepared above, was added dropwise at 0–10°. The mixture was stirred for 3.5 h at room temperature and was then washed with 10% NaOH and 10% HCl. The chloroform solution was dried over potassium carbonate and evaporated to yield the amide **16**, (21 g, 88.9%) as a slightly colored syrup; i.r. (liquid film): 1660 (CO), 935 (OCH_2O), 750, 700 (monosubstituted benzene); p.m.r. ($CDCl_3$): 7.33 (5 H, broad s, C_6H_5), 7.10–6.80 (4 H, m, Ar—H), 6.90 (1 H, s, H-6), 6.38 (1 H, s, H-3), 5.92 (2 H, s, OCH_2O), 5.08 (2 H, s, OCH_2Ph), 3.63 (2 H, s, CH_2CON ), 3.58–3.23 (8 H, m, morpholine hydrogens).

*10-N-Morpholino-6-benzyloxy-2,3-methylenedioxydibenz[b,f]oxepin (**17**)*

A mixture of the amide (**16**) (20 g), dry toluene (120 ml), dry benzene (60 ml), and phosphoryl chloride (51 ml) was gently refluxed for 3.5 h. The reaction mixture was poured into a large volume of hexane and yielded

a precipitate which was collected by filtration. The crude product was basified by adding it in portions to a stirred mixture of chloroform and aqueous ammonia. The chloroform layer was separated, and worked up in the usual manner to give a dark colored viscous residue. Purification by column chromatography on silica gel using chloroform gave the enamine (**17**) (3.84 g, 20.0%) as yellow prisms melting at 175–177° after recrystallization from ether; i.r. (KBr): 1630 (weak, C=C), 945 (OCH_2O), 745, 695 (monosubstituted benzene); p.m.r. ($CDCl_3$): 7.65–6.95 (8 H, m, Ar—H), 6.82 (1 H, s, H-1), 6.60 (1 H, s, H-4), 5.93 (1 H, s, H-11), 5.90 (2 H, s, OCH_2O), 5.19 (2 H, s, OCH_2Ph), 3.86 (4 H, t, J = 4.0 Hz, CH_2—, O, CH_2—), 2.98 (4 H, t, J = 4.0 Hz, —N(CH_2—)(CH_2—)); mass spectrum: *m/e* 429 (M^+).

Anal. Calcd. for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.26. Found: C, 72.77; H, 5.64; N, 3.26.

*6-Benzyloxy-2,3-methylenedioxy-10,11-dihydrodibenz-[b,f]oxepin-10(11H)-one (**5**)*

A stirred solution of the enamine (**17**) (1.5 g) in tetrahydrofuran (43 ml) was treated dropwise with 1 *M* sulfuric acid (50 ml) and the mixture stirred for 4 h at room temperature. The reaction mixture was extracted with chloroform, the extract dried over magnesium sulfate and potassium carbonate, and evaporated to give a brown syrup. Crystallization from ether gave the dihydrodibenzoxepinone (**5**) (0.91 g, 72.2%) as yellow prisms melting at 131–132°; i.r. (KBr); 1680 (CO), 935 (OCH_2O), 735, 700 (monosubstituted benzene); p.m.r. ($CDCl_3$); 7.69 (1 H, pair of doublets, J = 2.5 and 7.5 Hz, H-7 or H-9), 7.55–7.05 (7 H, m, Ar—H), 6.86 (1 H, s, H-1 or H-4), 6.75 (1 H, s, H-4 or H-1), 5.98 (2 H, s, OCH_2O), 5.26 (2 H, s, OCH_2Ph), 4.02 (2H, s, CO-CH_2); mass spectrum; *m/e* 360 (M^+).

Anal. Calcd. for $C_{22}H_{16}O_5$: C, 73.32; H, 4.48. Found: C, 73.43; H, 4.34.

*10-(2′,2′-Diethoxyethylamino)-6-hydroxy-2,3-methylenedioxy-10,11-dihydrodibenz[b,f]oxepin (**19**)*

A mixture of **5** (1.6 g), dry toluene (50 ml), aminoacetaldehyde diethyl acetal (3.5 ml), and pyridine (6 drops) was allowed to stand at room temperature for 10 h and then refluxed using a Dean–Stark apparatus for 20 h. Most of the solvent was removed, fresh toluene (40 ml) and aminoacetaldehyde diethyl acetal (3.5 ml) were added and reflux was continued for a further 8 h. The solvent was removed leaving the Schiff base **18** as a slightly colored syrup. This residue was dissolved in ethanol (100 ml) and hydrogenated over platinum at 20 p.s.i.g. for 15 h. The filtrate, after removal of catalyst, was hydrogenated again in the presence of 10% palladium-on-charcoal at 40 p.s.i.g. for 20 h. The catalyst was filtered off and the solvent was evaporated to give a pale yellow syrup. The residue, dissolved in ether, was treated with ether saturated with dry hydrogen chloride yielding the hydrochloride of **19** (0.91 g). Attempts to crystallize the hydrochloride from ethanol–ether gave only an amorphous material melting at 118° (dec.); i.r. (KBr): 3200 (OH), 2800–2500 ($\overset{+}{N}H_2$), 930 (OCH_2O). Crude **19** was used in the next reaction without purification.

*Cyclization of **19***

A stirred solution of the hydrochloride of **19** (0.85 g) in ethanol (6 ml) was treated dropwise with 6 *N* ethanolic hydrochloric acid solution (40 ml) at 5–10° and the mixture was stirred for 20 h at room temperature. The colorless precipitate, which separated, was collected by filtration, and recrystallized from ethanol–ether to afford 3-ethoxy-norcularicine (**20**) hydrochloride (0.75 g, 88.1%) as colorless needles melting at 236° (dec.); i.r. (KBr): 3200 (OH), 2450 ($\overset{+}{N}H_2$), 925 (OCH_2O); p.m.r. (DMSO-d_6): 6.96, 6.85 (each 1 H, d, J = 8.2 Hz, H-4 and H-5), 6.95, 6.71 (each 1 H, s, H-8 and H-11), 5.92 (2 H, s, OCH_2O), 4.73–4.40 (2 H, m, H-12a and H-3), 3.60–3.00 (7 H, m, 3 × CH_2 and NH), 0.97 (3 H, t, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd. for $C_{19}H_{19}NO_5 \cdot HCl$: C, 60.40; H, 5.33; N, 3.70. Found: C, 60.50; H, 5.36; N, 3.79.

The free base was liberated from the hydrochloride by ammonia. It melted at 176–178° (dec.) after crystallization from chloroform–hexane; i.r. (KBr): 3290 (NH), 930 (OCH_2O); p.m.r. (DMSO-d_6): 7.01, 6.64 (each 1 H, s, H-8 and H-11), 6.91, 6.71 (each 1 H, d, J = 8.2 Hz, H-4 and H-5), 5.92 (2 H, s, OCH_2O), 4.38 (1 H, pair of doublets, J = 10.0 and 7.0 Hz, H-12a), 4.07 (1 H, m, H-3), 3.46 (2 H, m, CH_2CH_3), 3.08–2.85 (4 H, m, 2 × CH_2), 1.08 (3 H, t, J = 7.0 Hz, CH_2CH_3); mass spectrum *m/e*: 341 (M^+, 100), 324 (7), 311 (7), 294 (41), 283 (33), 278 (13).

The mother liquor from the separation of **20** was treated with hydrogen over platinum at 25 p.s.i.g. for 6 h. The filtrate, after removal of catalyst, was concentrated to 5 ml, cooled with ice, carefully basified with ammonia, and then extracted with chloroform. The extract gave on evaporation a brown gum which was purified by preparative thick-layer chromatography on silica gel (chloroform–benzene–methanol, 1:3:1) to give (±)-*N*-norcularicine (**21**) (72 mg, 7.0% based on **19**) as a glass which crystallized from methanol yielding colorless prisms melting at 99° with softening and some decomposition at 92°. The crystals are probably solvated. Mass spectrum (270°), *m/e*: 297 (M^+, 100), 296 (46), 280 (47), 268 (16), 267 (21), 148.5 (M^{2+}, 7), 147 (20); i.r. (KBr): 3400–3300 (NH and OH), 935 (OCH_2O). Compound **21** was recrystallized from acetone yielding colorless needles melting at 96–99°. These crystals were also solvated; i.r. (KBr): 3400–3300 (NH and OH), 935 (OCH_2O), 1710 (acetone carbonyl); p.m.r. (CD_3OD):[1] 6.92, 6.58 (each 1 H, s, H-8 and H-11), 6.74 (2 H, s, H-4 and H-5), 5.90, 5.88 (each 1 H, d, J = 1.0 Hz, O—CH_2—O), 4.33 (1 H, pair of doublets,

[1]The sample for p.m.r. analysis was prepared in the following manner. The crystals obtained from the crystallization in acetone were dissolved in an excess of methanol, the solution evaporated to dryness, and the residue taken up in CD_3OD.

J = 11.0 and 4.0 Hz, H-12a), 3.25–2.60 (6 H, m, 3 × CH_2). Compound **21** formed a picrate as yellow needles melting at 241° (dec.); i.r. (KBr): 3410 (OH), 1570, 1320 (NO_2), 935 (OCH_2O).

Anal. Calcd. for $C_{17}H_{15}NO_4 \cdot C_6H_3N_3O_7$: C, 52.47; H, 3.45; N, 10.64. Found: C, 52.59; H, 3.65; N, 10.41.

Acid-catalyzed Hydrogenolysis of 20

3-Ethoxynorcularicine hydrochloride (**20**, HCl, 320 mg) was dissolved in 3 *N* ethanolic hydrochloric acid solution (60 ml) and treated with hydrogen over platinum at 25 p.s.i.g. for 15 h. The filtrate, after removal of catalyst, was concentrated to 15 ml, basified with ammonia, and extracted with chloroform. The extract was dried over magnesium sulfate, and evaporated to leave a brown residue. This was purified by preparative thick-layer chromatography on silica gel (chloroform–benzene–methanol, 1:3:1) to give (±)-*N*-norcularicine (**21**, 104 mg, 41%) as a colorless glass which crystallized from methanol to give colorless prisms melting at 101°. The mass spectrum of this sample was the same as that described above for **21**. Recrystallization from acetone gave a sample melting at 97–101°. The i.r. spectrum of this sample was superimposable on that described in the preceding section for the sample of (±)-norcularicine crystallized from acetone.

(±)-Cularicine (1)

A mixture of (±)-*N*-norcularicine (**21**) (60 mg), methanol (6 ml), and 37% formalin (1.0 ml) was warmed at 40–45° for 30 min. The mixture was cooled and sodium borohydride (0.7 g) was then added in portions. The solvent was removed *in vacuo* and the residue obtained was treated with water and extracted with chloroform. The extract, after drying over magnesium sulfate, was evaporated to leave a slightly colored syrup which was purified by preparative thick-layer chromatography on silica gel (chloroform–benzene–methanol, 1:3:1) to give (±)-cularicine (**1**, 45 mg, 71%) as a glass which crystallized from methanol yielding solvated crystals melting at 95–96°; i.r. (KBr): 3150 (OH), 935 (OCH_2O); mass spectrum (270°), *m/e*: 311 (M^+, 100), 310 (16), 294 (58), 282 (10), 267 (9), 161 (18), 155.5 (M^{2+}, 5).

Recrystallization of **1** from acetone gave a colorless crystalline mass melting at 81–82°; i.r. (KBr): 3400 (OH), 935 (OCH_2O), 1710 (acetone carbonyl). The presence of acetone of crystallization was also apparent when the mass spectrum of this sample was recorded.

Compound **1**, obtained from acetone, was dissolved in chloroform and evaporated to dryness yielding a glass that was used to measure the i.r. and p.m.r. spectra; p.m.r. ($CDCl_3$): 6.80 (2 H, s, H-4 and H-5), 6.67, 6.53 (each 1 H, s, H-8 and H-11), 5.91, 5.89 (each 1 H, d, J = 1.3 Hz, OCH_2O), 4.23 (1 H, pair of doublets, J = 10.0 and 4.0 Hz, H-12a), 3.20–3.75 (6 H, m, 3 × CH_2), 2.53 (3 H, s, N—CH_3); i.r. ($CHCl_3$): 3550 (OH), 2820 (N—CH_3), 940 (OCH_2O). The i.r. spectrum in chloroform and the p.m.r. spectrum in deuteriochloroform were identical with those of natural (+)-cularicine. When recrystallized from ether racemic **1** gave colorless needles melting at 155–156°. Mass spectrum (270°), *m/e*: 311 (M^+, 100), 310 (21), 294 (65), 282 (12), 268 (5), 267 (11), 174 (10), 161 (24), 155.5 (M^{2+}, 7); t.l.c. of racemic **1** in a variety of solvent systems showed the same behavior as natural (+)-cularicine.

Compound **1** formed a hydrochloride as colorless needles melting at 255–257° (dec.), (MeOH–Et_2O); i.r. (KBr): 3150 (OH), 2750–2400 ($-\overset{+}{N}H$), 935 (OCH_2O).

Anal. Calcd. for $C_{18}H_{17}NO_4 \cdot HCl$: C, 62.16; H, 5.21; N, 4.02. Found: C, 62.31; H, 5.36; N, 4.02.

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