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Biogenetic-Type Synthesis of Cularine

T. KAMETANI,[1] K. FUKUMOTO, AND M. FUJIHARA

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan, and Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., 2-2-5, Kawagishi, Toda, Saitama, Japan

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The phenolic oxidation of 1,2,3,4-tetrahydro-8-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7-methoxy-2-methylisoquinoline (**2**) with alkaline ferricyanide gave a demethylcularine (**4**) and its isomer (**5**). The former was converted into cularine (**1**). Furthermore, diphenolic isoquinoline (**7**) gave a mixture of two isomeric dienones (**8A** and **8B**) which were separated.

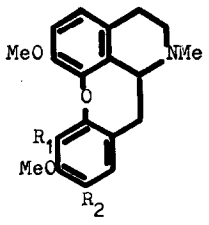
Cularine, an alkaloid isolated from a number of the *Dicentra* species and from *Corydalis claviculata*, was assigned by Manske (*1*) the structure (**1**), on the basis of chemical degradation. This structure was proved to be correct by total synthesis (*2–4*). Cularine and its related alkaloids are characterized by the presence of an unusual 7,8-dioxygenated pattern and of a dihydrodibenzoxepine ring system. The biogenesis of this group of alkaloids would simply involve the appropriate C–O oxidative coupling of the diphenolic base (**2**) (*1*). Until recently, no 1-benzylisoquinoline having the 7,8-oxygenation pattern was known, but now petaline (**3**) (*5*) fills this gap. Here, *para*-coupling of a base (**2**) would afford a product (**4**) requiring only *O*-methylation for the generation of cularine (**1**). Similarly, *ortho*-coupling of (**2**) would afford a product (**5**) which, by further modification, could give rise to cancentrine (**6**), isolated recently from *Dicentra canadense* (*6*). Moreover, the second diphenolic isoquinoline (**7**) could undergo oxidative coupling to the dienone (**8**), whose dienone–phenol rearrangement, followed by *O*-methylation, might afford cularine (**1**) (*7*).

This paper describes the total, biogenetically patterned synthesis of cularine (**1**) from the proposed intermediate, as the most synthetically useful route to the cularine ring system.

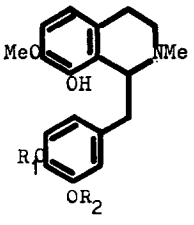
There are many examples of the synthesis of the 6,7-dioxygenated 1-benzylisoquinolines (**9**) from 3,4-dialkoxyphenethylamines (**10**) by the Bischler–Napieralski reaction and the Pictet–Spengler reaction. However, these methods were not useful for the synthesis of the 7,8-dioxygenated 1-benzylisoquinolines (**11**) as the cyclization occurs preferentially at the position *para* to the oxygenation function (*8*). Many chemists made several unsuccessful attempts to obtain the 7,8-dioxygenated 1-benzylisoquinolines (**11**) by the foregoing methods (*8–10*). Consequently, certain of our efforts were directed toward the synthesis of the 7,8-dioxygenated isoquinolines (**2** and **7**), which were the hypothetical precursors of cularine (**1**).

One of the authors (*10*) subjected the β-phenethylamine (**12**), whose *para* cyclization site was protected by a bromine atom, to the Pictet–Spengler reaction, in order to obtain 7,8-dioxygenated isoquinoline (**13**). This reaction resulted in failure. However, we presumed that the cyclization at the *ortho*-position to the hydroxy-group would proceed smoothly if the reactivity of the benzene nucleus were increased by the presence

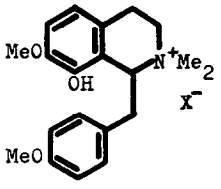
[1] Communications concerning this paper should be directed to Professor T. Kametani.



(1) R_1=H, R_2=OMe
(4) R_1=H, R_2=OH
(5) R_1=OH, R_2=H
(20) R_1=OMe, R_2=H



(2) R_1=Me, R_2=H
(7) R_1=H, R_2=Me



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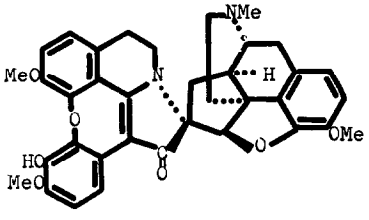

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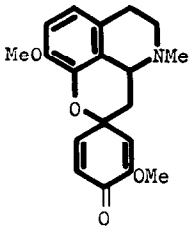

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CHART 1.

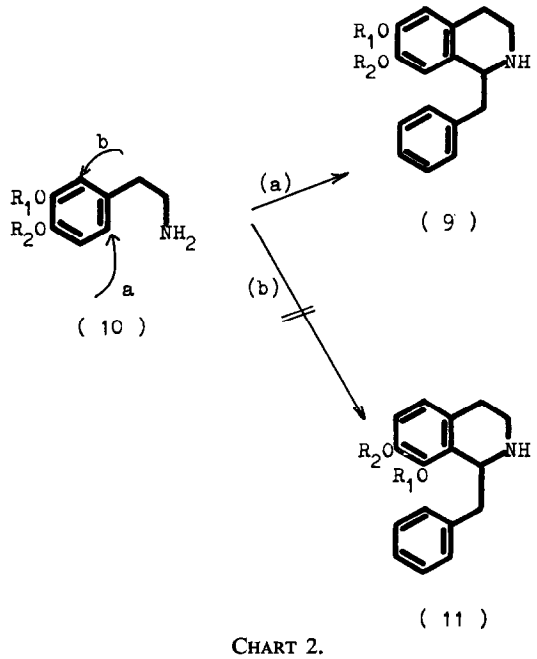

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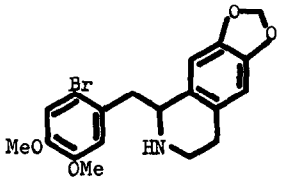
CHART 2.

of a phenolic hydroxyl group in the amine (**12**). Therefore, we investigated the cyclization of the phenolic amine (**14**) (*11*).

The phenolic amine (**14**) hydrochloride was subjected to the Pictet–Spengler reaction with the sodium bisulfite adduct of 4-benzyloxy-3-methoxyphenylacetaldehyde (**15A**) (*12*) in boiling alcohol in the presence of ammonia (*13*) to give the expected 1,2,3,4-tetrahydroisoquinoline (**16A**) in good yield. This compound was also obtained by the Pictet–Spengler reaction of the phenolic amine (**14**) hydrochloride with sodium 3-(4-benzyloxy-3-methoxyphenyl)glycidate (**17A**) in boiling ethanol at pH 2.4 (*14*) or by



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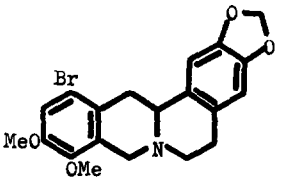

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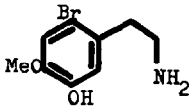

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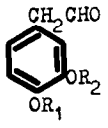
CHART 3.

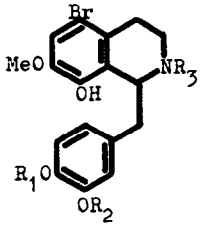
phenolic cyclization (*11*) of (**14**) with 4-benzyloxy-3-methoxyphenylacetaldehyde (**15A**). The structure of (**16A**) was elucidated by spectroscopic methods. The ir spectrum showed the phenolic hydroxyl and the secondary amino functions. The uv spectrum showed the substance to be a 1,2,3,4-tetrahydroisoquinoline, which result was supported by the mass spectrometry [M^+: 483 and 485, base peak at *m/e* 256 and 258 (**18**)]. The ions (**18**) also indicated this isoquinoline to have a bromine atom in the isoquinoline ring. The nmr spectrum showed the C_1-methine proton at 5.62 τ as a distorted quartet, thus revealing the 8-oxygenated 1,2,3,4-tetrahydroisoquinoline system (*15*), in addition to two *O*-methyls, four aromatic protons and a *O*-benzyl-resonances.

N-Methylation of the 5-bromo-1,2,3,4-tetrahydroisoquinoline (**16A**) with formalin and sodium borohydride gave the 2-methylisoquinoline (**19A**), which was hydrogenolyzed on 10% palladium–charcoal in the presence of sodium acetate to afford the diphenolic isoquinoline (**7**), characterized easily as the oxalate.



(15A) R_1=CH_2Ph, R_2=Me

(15B) R_1=Me, R_2=CH_2Ph

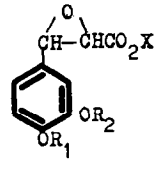


(16A) R_1=CH_2Ph, R_2=Me, R_3=H

(16B) R_1=Me, R_2=CH_2Ph, R_3=H

(19A) R_1=CH_2Ph, R_2=R_3=Me

(19B) R_1=R_3=Me, R_2=CH_2Ph



(17A) R_1=CH_2Ph, R_2=Me, X=Na

(17B) R_1=Me, R_2=CH_2Ph, X=Me

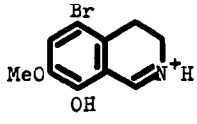


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CHART 4.

Another diphenolic isoquinoline (**2**) was synthesized in the same method from 3-benzyloxy-4-methoxyphenylacetaldehyde (**15B**), which was obtained by decomposition of glycidate (**17B**) followed by treatment with sodium bisulfite. The latter compound (**17B**) was derived from benzylisovanillin and methyl chloroacetate by a Darzens reaction. Condensation of **15B** with the phenolic amine (**14**) hydrochloride gave the *N*-methyl derivative (**19B**), by way of the 1,2,3,4-tetrahydroisoquinoline (**16B**).

The phenolic oxidation of the diphenolic isoquinoline (**7**) has been studied under a wide variety of conditions, both in aqueous media and in organic solvents, using several oxidation methods. However, although polymeric products were often obtained, in one system we did obtain the dienone type compound (**8A** and **8B**), viz., aqueous potassium ferricyanide buffered with 1*N* ammonium acetate in chloroform. The dienones were separated by silica-gel-column chromatography into the dienone A (**8A**) (2.5% yield) and dienone B (**8B**) (3.85% yield), which differed in configuration at the spiro-center (*16*).

The dienone A (**8A**), $C_{19}H_{21}O_4N$ (M^+, *m/e* 327) showed a typical α-methoxylated cross-conjugated dienone system in the ir (ν_{max} 1680, 1645, and 1620 cm^{-1}) and uv (λ_{max} 236.5 nm, log ε 4.11) spectra. This assignment was supported by the nmr spectrum, showing three olefinic protons resonances at 3.98 as a doublet (*J* 3 Hz), 3.73 as a doublet

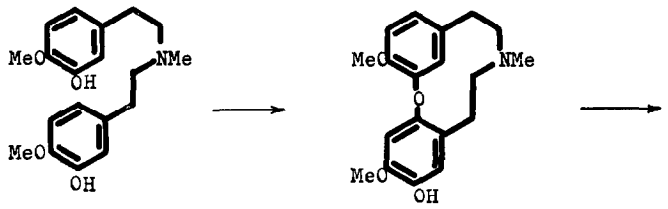
(*J* 10 Hz), and 3.03 as a quartet (*J* 3 and 10 Hz). The dienone B (**8B**), $C_{19}H_{21}O_4N$ (M^+, *m/e* 327) was similar to dienone A (**8A**) in the uv (λ_{max} 236.5 nm, logϵ 4.32), ir (ν_{max} 1680, 1650, and 1620 cm^{-1}) and mass spectra; but there was a small difference in the chemical shift of the olefinic protons in its nmr spectrum (4.17, d, *J* 3 Hz; 3.77, d, *J* 10 Hz; and 2.84, q).

Both dienones (**8A** and **8B**) were subjected to dienone–phenol rearrangement under several conditions, but we could not obtain the expected cularine-type compounds. Other rearrangement conditions are under examination.

Secondly, we investigated the direct route from the diphenolic isoquinoline (**2**). The oxidation of 2 was effected with potassium ferricyanide in a way similar to the previously described phenol oxidation to furnish the cularine system (**5**) in 5% yield and *O*-demethylcularine (**4**) in 2.5% yield. The former (**5**), $C_{19}H_{21}O_4N$ (M^+, *m/e* 327), showed a methine proton on the C_{5a} position at 5.49 τ as X part in ABX pattern and two pairs of *ortho*-coupling aromatic protons at 3.48, 3.37, 3.25, and 3.07 τ in its nmr spectrum. This fact clearly showed this product to be an *ortho*-coupled product (**5**).

The second compound, $C_{19}H_{21}O_4N$ (M^+, *m/e* 327), revealed also a methine proton at 5.55 τ as quartet in the nmr spectrum, but four aromatic protons appeared at 3.42 and 3.19 as singlets in addition to *ortho*-coupled protons at 3.25 and 3.12 which showed that this was *O*-demethylcularine (**4**) coupled at the *para*-position to the hydroxyl group. (See Figs. 1 and 2.)

Both products (**4** and **5**) were methylated by diazomethane to yield (±)-cularine (**1**) and the cancentrine type compound (**20**), named tentatively as "isocularine," respectively. The former was identical with an authentic sample, on the basis of spectroscopic and chromatographic comparisons. Thus, the biogenetic type synthesis of cularine has been accomplished.



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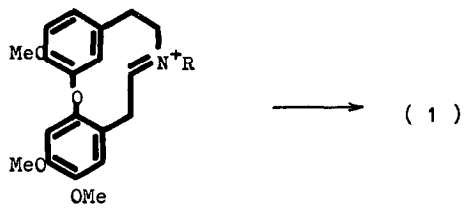

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(22)

CHART 5.

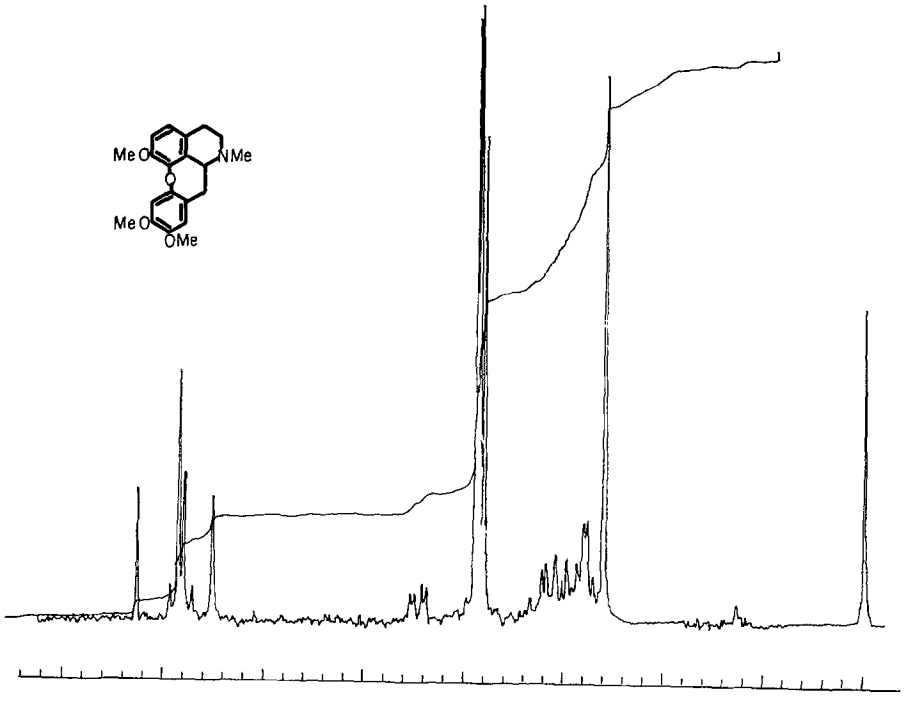

FIG. 1.

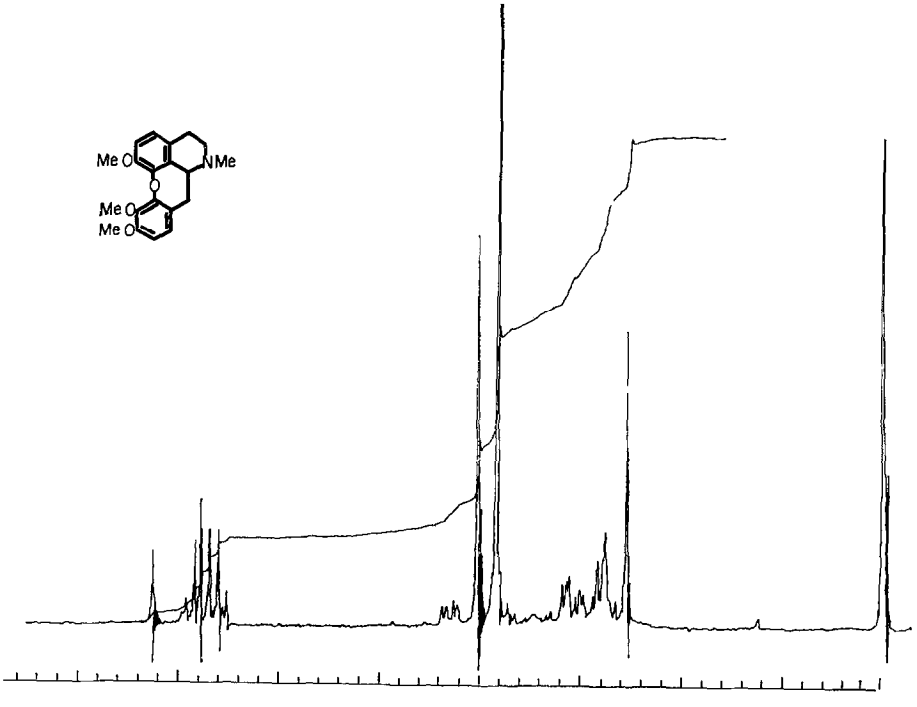

FIG. 2.

A further possible route starts from the bisphenethylamine (**21**), whose phenol oxidation, followed by biological oxidation to the imine (**22**), could precede the final ring closure to cularine. The variation analogous to the above, involving a dienone–phenol rearrangement, could also operate for this route. A decision among these various possible methods will depend upon critical tracer experiments.

EXPERIMENTAL SECTION

The ir and uv spectra were recorded on type EPI-3 and EPS-3 Hitachi recording spectrometer, respectively. Mass spectra were measured with Hitachi RMS-4 and Hitachi RMU-7 mass spectrometers. Nuclear magnetic resonance spectra were taken with JNM-60, JNM-4H-100, and Hitachi R-20 spectrometers with tetramethylsilane as an internal standard.

Methyl 3-(3-benzyloxy-4-methoxy)phenylglycidate (**17B**). A solution of 3-benzyloxy-4-methoxybenzaldehyde (100 g) and methyl chloroacetate (70 g) in anhydrous methanol (17 ml) was added dropwise to sodium methoxide solution (prepared from sodium (16 g) and anhydrous methanol (270 ml)) with cooling (−8 to ~−10°C) and stirring. Stirring was continued at −5 to ~0°C for 2 hr, and at room temperature for an additional 2 hr. The reaction mixture was then poured onto crushed ice and acidified with acetic acid (6 ml). The separated solid was collected and dissolved in chloroform (500 ml). The organic layer was washed with water, dried on sodium sulfate, and the solvent was removed *in vacuo*. The oily residue was crystallized from ether (300 ml) to give glycidate (**17B**) (94 g, 76.8%) as colorless needles, mp 93–95°C. Recrystallization from methanol afforded colorless needles, mp 95–96.5°C, ν_{max} ($CHCl_3$) 1730 cm^{-1}, τ ($CDCl_3$) 6.58 (1H, d, $J_{\alpha\beta}$ 2.0 Hz, C_β-*H*), 6.22 (3H, s, OMe), 6.15 (3H, s, OMe), 6.0 (1H, d, $J_{\alpha\beta}$ 2.0 Hz, C_α-*H*), 4.90 (2H, s, OCH_2Ph), 3.1–3.25 (3H, m, 3 × ArH), 2.5–2.75 (5H, broad s, $OCH_2C_6H_5$). *Anal.* Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.61; H, 5.89.

3-Benzyloxy-4-methoxyphenylacetaldehyde (**15B**). To a mixture of the foregoing glycidate (**17B**) (55 g) in dry benzene (335 ml), sodium methoxide (prepared from sodium (4.45 g) and anhydrous methanol (63 ml)) was added dropwise with cooling (5°C) and stirring, and then water (3.9 ml) was added. After stirring for 10 min, ether (300 ml) was added and the solution was stirred for additional 3 hr to separate the corresponding sodium glycidate, which was collected, washed with ether, and dried to furnish a colorless powder (54 g). The sodium glycidate was heated in benzene (500 ml) and acetic acid (10.7 g) for 2 hr. After cooling, the benzene solution was washed with water, dried over sodium sulfate, and evaporated. The oily residue was stirred with a mixture of sodium bisulfite (20 g), water (40 ml) and ether (300 ml) at room temperature for 10 hr to give the adduct (48 g, 81.0%) of the aldehyde (**15B**) with bisulfite. The semicarbazone of the aldehyde gave colorless prisms, mp 142–143.5°C (*17*) (from ethanol).

1-(4-Benzyloxy-3-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline (**16A**). (a) To a solution of 3-(4-benzyloxy-3-methoxyphenyl)glycidate (**17A**) (*12*) (1.26 g) in water (40 ml) was added a solution of 2-bromo-5-hydroxy-4-methoxyphenethylamine (**14**) (*11*) hydrochloride (1·0 g) in ethanol (40 ml) and the resulting solution was adjusted to pH 2.4 by an addition of a mixture of 10% hydrochloric acid (1.8 ml) and glacial acetic acid (1.0 ml). This was refluxed for 72 hr, and the solvent was distilled off *in vacuo* to leave a brown oil, which was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried on sodium sulfate, and evaporated to dryness under reduced pressure to give the tetrahydroisoquinoline (**16A**) (348 mg, 20.3%) as colorless needles, mp 179–180°C (from

ethyl acetate), λ_{max} (EtOH) 284 nm ($\log\epsilon$ 3.84), ν_{max} ($CHCl_3$) 3560 cm^{-1}; τ(CF_3CO_2H) 6.0–7.1 (6H, m, 3 × CH_2), 6.07 (3H, s, OMe), 6.00 (3H, s, OMe), 5.62 (1H, distorted q, *J* 4 and 11 Hz, C_1-*H*), 4.80 (2H, s, OCH_2Ph), 2.8–3.1 (3H, m, C_2'-*H*, C_5'-*H*, and C_6'-*H*), 2.67 (1H, s, C_6-*H*), and 2.55 (5H, s, $OCH_2C_6H_5$), *m/e* 485 and 483 (M^+), 258 and 256 (**18**) (base peak). *Anal.* Calcd for $C_{25}H_{26}O_4NBr$: C, 61.99; H, 5.41; N, 2.89; Br,16.50. Found: C, 61.68; H, 5.47; N, 3.06; Br, 16.38.

(b) To a solution of the phenethylamine (**14**) (250 mg) in ethanol (40 ml) was added 4-benzyloxy-3-methoxyphenylacetaldehyde (**15A**) (*12*) (290 mg), and the mixture was refluxed for 19 hr. Solvent was removed by distillation *in vacuo* to give the tetrahydroisoquinoline (**16A**) (95 mg, 18.0%), mp 177–179°C (from ethyl acetate).

(c) To a suspension of sodium bisulfite adduct (7.0 g) of 4-benzyloxy-3-methoxyphenylacetaldehyde (**15A**) in ethanol (150 ml) was added the phenethylamine (**14**) hydrochloride (5.0 g), and the mixture was basified with concentrated ammonia (20 ml). This was refluxed for 3 hr and then set aside overnight at room temperature. After evaporation of the solvent under reduced pressure, the residue was extracted with chloroform, and the extract was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo* to afford the tetrahydroisoquinoline (**16A**) (4.2 g, 49.0%), mp 178–180°C (from ethyl acetate).

1-(3-Benzyloxy-4-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline (**16B**). A mixture of the phenethylamine (**14**) hydrochloride (6.0 g), sodium bisulfite adduct (8 g) of 3-benzyloxy-4-methoxyphenylacetaldehyde (**15B**), and ethanol (140 ml) was made basic (pH >11) with concentrated ammonia (24 ml) and the resulting alkaline mixture was heated under reflux for 4 hr. The separated inorganic material was filtered off and the filtrate was allowed to stand at room temperature overnight. The precipitate was collected by filtration and recrystallized from ethyl acetate to give the tetrahydroisoquinoline (**16B**) (2.83 g, 27.5%) as colorless prisms, mp 163–164.5°C, λ_{max} (EtOH) 284.5 nm ($\log\epsilon$ 3.76); ν_{max} ($CHCl_3$) 3560 (OH) and 3350 (NH) cm^{-1}; τ (CF_3CO_2H) 7.6–6.7 (6H, m, 3 × CH_2), 6.30 (3H, s, OMe), 6.14 (3H, s, OMe), 5.74 (1H, distorted q, *J* 5 and 12 Hz, C_1-*H*), 4.88 (2H, s, OCH_2Ph), 3.3–3.0 (4H, m, ArH) and 2.4–2.19 (5H, broad signal, $OCH_2C_6H_5$); *m/e* 485 and 483 (M^+), 258 and 256 (**18**) (base peak). *Anal.* Calcd for $C_{25}H_{26}O_4NBr$: C, 61.99; H, 5.41; N, 2.89; Br, 16.50. Found: C, 61.64; H, 5.37; N, 2.87; Br, 16.09.

1-(4-Benzyloxy-3-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline (**19A**). To a suspension of the 1,2,3,4-tetrahydroisoquinoline (**16A**) (7.5 g) in methanol (450 ml) was added 37% formalin (2.73 ml) at 5°C and the mixture was stirred for 5 hr at this temperature. Sodium borohydride (2.57 g) was added in portions to the resulting clear solution with stirring at 2–5°C during 1 hr, and the stirring was further continued for 2 hr at the same temperature as above. After being set aside overnight at room temperature, methanol was distilled off under reduced pressure, and the residue was treated with 10% ammonium chloride solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to leave 2-methylisoquinoline (**19A**) as a pale brown viscous syrup, ν_{max} ($CHCl_3$) 3560 cm^{-1}; τ ($CDCl_3$) 7.69 (3H, s, NMe), 6.6–7.8 (6H, m, 3 × CH_2), 6.21 (3H, s, OMe), 6.19 (3H, s, OMe), 5.92 (1H, q, *J* 4.5 and 7.5 Hz, C_1-*H*), 4.91 (2H, s, OCH_2Ph), 3.16–3.24 (3H, m, C_2'-*H*, C_3'-*H* and C_6'-*H*), 3.02 (1H, s, C_6-*H*) and 2.5–2.8 (5H, m, $OCH_2C_6H_5$); *m/e* 499 and 497 (M^+), 272 and 270 (base peak). This was characterized as its oxalate (8.50 g, 93.4%), mp 129–131°C (dec) (from methanol), λ_{max} (EtOH) 285 nm ($\log\epsilon$ 3.65). *Anal.* Calcd for $C_{26}H_{28}O_4NBr \cdot C_2H_2O_4 \cdot H_2O$: C, 55.45; H, 5.32; N, 2.32; Br, 13.18. Found: C, 55.69; H, 5.55; N, 2.38; Br, 13.15.

1-(3-Benzyloxy-4-methoxybenzyl)-5-bromo-1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline (**19B**). To a suspension of 5-bromo-1,2,3,4-tetrahydroisoquinoline (**16B**) (6.0 g) in methanol (450 ml) was added 37% formalin (2.19 ml), and the mixture was stirred at room temperature for 4 hr. To the resulting clear solution was added in small portions sodium borohydride (2.16 g) at 5°C during 1 hr with stirring, and the mixture was stirred at 5°C for 2 hr and then allowed to stand overnight at room temperature. After removal of the solvent by distillation, the residue was decomposed by 10% ammonium chloride solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave a pale brown viscous syrup, which crystallized on trituration with methanol. Recrystallization from methanol afforded the isoquinoline (**19B**) (4.23 g, 68.5%) as pale brown prisms, mp 121–122.5°C, λ_{max} (EtOH) 284.5 nm (logϵ 3.76); ν_{max} ($CHCl_3$) 3560 cm^{-1}; τ ($CDCl_3$) 7.74 (3H, s, NMe), 6.8–7.7 (6H, m, 3 × CH_2), 6.15 (6H, s, 2 × OMe), 5.96 (1H, q, *J* 4.5 and 8 Hz, C_1-*H*), 4.86 (2H, s, OCH_2Ph), 3.25–3.05 (3H, m, $C_{2'}$-*H*, $C_{3'}$-*H* and $C_{6'}$-*H*), 2.99 (1H, s, C_6-*H*), and 2.8–2.35 (5H, broad signal, $OCH_2C_6H_5$), *m/e* 499 and 497 (M^+), 272 and 270 (base peak). *Anal.* Calcd for $C_{26}H_{28}O_4NBr$: C, 62.65; H, 5.67; N, 2.81; Br, 16.03. Found: C, 62.78; H, 5.73; N, 2.84; Br, 15.71.

1,2,3,4-Tetrahydro-8-hydroxy-1-(4-hydroxy-3-methoxybenzyl)-7-methoxy-2-methylisoquinoline (**7**). A mixture of the 2-methylisoquinoline (**19A**) oxalate (1.0 g), sodium acetate (170 mg), water (6 ml), and ethanol (50 ml) was shaken at room temperature and atmospheric pressure on 10% palladium–charcoal (100 mg) in a current of hydrogen. After absorption of the calculated amount of hydrogen, the reaction mixture was basified with 10% ammonia and the catalyst was filtered off. The filtrate was concentrated to dryness under reduced pressure to leave a pale brown syrup, which was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to afford the diphenolic isoquinoline (**7**) (640 mg, 97.0%) as a pale brown viscous syrup, ν_{max} ($CHCl_3$) 3560 cm^{-1}; τ ($CDCl_3$) 7.64 (3H, s, NMe), 7.8–6.5 (6H, m, 3 × CH_2), 6.22 (3H, s, OMe), 6.15 (3H, s, OMe), 5.90 (1H, q, *J* 4.5 and 8.0 Hz, C_1-*H*), 4.2–5.2 (2H, broad signal, 2 × OH), 3.43 (1H, d, *J* 8.5 Hz, C_6-*H*), 3.24 (1H, d, *J* 8.5 Hz, C_5-*H*) and 3.25 (3H, s, $C_{2'}$-*H*, $C_{3'}$-*H* and $C_{6'}$-*H*); *m/e* 329 (M^+), 192 (base peak). This oil was characterized as oxalate to give colorless prisms (610 mg, 85.5%), mp 187–189°C (dec) (from ethanol), λ_{max} (EtOH) 285 nm (logϵ 3.73). *Anal.* Calcd for $C_{19}H_{23}O_4N \cdot C_2H_2O_4$: C, 60.13; H, 6.01; N, 3.34. Found: C, 59.90; H, 5.90; N, 3.51.

1,2,3,4-Tetrahydro-8-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7-methoxy-2-methylisoquinoline (**2**). A mixture of the above bromoisoquinoline (**19B**) (2.3 g), sodium acetate (580 mg), water (10 ml) and ethanol (50 ml) was shaken at room temperature and low pressure (45 lb) by using Parr Pressure Reaction Apparatus on 10% palladium–charcoal (500 mg) in a current of hydrogen. After absorption of a calculated amount of hydrogen, the catalyst was filtered off and the solvent was evaporated. The residue was basified with ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave the crystals, which were recrystallized from a mixture of benzene and *n*-hexane to afford the dihydroxy-1,2,3,4-tetrahydroisoquinoline (**2**) (1.31 g, 86.2%) as colorless prisms, mp 119–120°C, λ_{max} (EtOH) 284 (logϵ 3.72); ν_{max} ($CHCl_3$) 3560 cm^{-1}; τ ($CDCl_3$) 7.65 (3H, s, NMe), 7.6–6.8 (6H, m, 3 × CH_2), 6.22 (3H, s, OMe), 6.18 (3H, s, OMe), 5.97 (1H, q, *J* 4.0 and 9.0 Hz, C_1-*H*), 3.45 (1H, d, *J* 9.0 Hz, C_6-*H*), 3.30 (1H, d, *J* 9.0 Hz, C_5-*H*), and 3.05–3.25 (3H, m, $C_{2'}$-*H*, $C_{3'}$-*H* and $C_{6'}$-*H*); *m/e* 329 (M^+), 192 (base peak). *Anal.* Calcd for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.34; H, 7.07; N, 4.28.

Phenol oxidation of **7**. A solution of the diphenolic isoquinoline (**7**) oxalate (4.0 g)

in 1*N* ammonium acetate (400 ml) was added dropwise to a mixture of potassium ferricyanide (16 g), 1*N* ammonium acetate (1000 ml) and chloroform (400 ml) with stirring at room temperature within 4 hr, and the mixture was stirred for further 3 hr. The organic layer was separated, and the aqueous layer was extracted with chloroform. The combined organic solution was washed with water, dried over sodium sulfate, and distilled off *in vacuo* to leave a red-brown gum (3.4 g), which was chromatographed on silica gel (50 g) eluting with chloroform [fractions (100 ml) 1–15, monitored by ir and uv spectra), chloroform–methanol (99:1 v/v; fractions (100 ml) 16–19], and chloroform–methanol (98:2 v/v; fractions (40 ml) 20–37]. Fractions 20–23 were combined to give a pale brown oil (383 mg) which was rechromatographed on alumina (7 g) using chloroform as eluant to afford the dienone A (**8A**) (77 mg, 2.5%) as pale yellow fine needles, mp 132–133°C (from ethyl acetate), λ_{max} (EtOH) 236.5 and 284.0 nm ($\log\epsilon$ 4.11 and 3.56); ν_{max} ($CHCl_3$) 1680, 1645 and 1620 cm^{-1}; τ ($CDCl_3$) 7.59 (3H, s, NMe), 6.34 (3H, s, OMe), 6.18 (3H, s, OMe), 3.98 (1H, d, *J* 3.0 Hz, O═C—C(—OMe)═C*H*—), 3.73 (1H, d, *J* 10.0 Hz, O═C—C*H*═CH—), 3.25 (2H, s, ArH), and 3.03 (1H, q, *J* 10.0 and 3.0 Hz, O═C—CH═C*H*), *m/e* 327 (M^+), 191 (base peak). *Anal.* Calcd for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; M, 4.28. Found: C, 69.45; H, 6.58; N, 4.23.

The fractions 24–33 gave a reddish-brown viscous syrup (459 mg), which was purified by alumina (13 g) chromatography using chloroform as an eluant to furnish the dienone B (**8B**) (120 mg, 3.85%), mp 137–138.5°C, as pale brown prisms (from ethyl acetate), λ_{max} (EtOH) 236.5 and 286.0 nm ($\log\epsilon$ 4.32 and 3.65); ν_{max} ($CHCl_3$) 1680, 1650 and 1620 cm^{-1}; τ ($CDCl_3$) 7.61 (3H, s, NMe), 6.30 (3H, s, OMe), 6.20 (3H, s, OMe), 4.17 (1H, d, *J* 3.0 Hz, O═C—C(—OMe)═C*H*), 3.77 (1H, d, *J* 10.0 Hz, O═C—C*H*═CH), 3.25 (2H, s, ArH), and 2.84 (1H, q, *J* 10.0 and 3.0 Hz, O═C—CH═C*H*—), *m/e* 327 (M^+) and 191 (base peak). *Anal.* Calcd for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.44; H, 6.59; N, 4.24.

Phenol oxidation of diphenolic isoquinoline (**2**). A solution of diphenolic isoquinoline (**2**) (3.55 g) in chloroform (300 ml) was added dropwise to a mixture of potassium ferricyanide (14.2 g), 1*N* ammonium acetate (700 ml) and chloroform (150 ml) with stirring at room temperature during 30 min, and the mixture was stirred vigorously at room temperature for 3.5 hr. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and distilled off to leave a dark brown gum (2.76 g), which was chromatographed on silica gel (55 g). The elution was separated by fraction collector by Toyo SF-160 K (Rectangular Balance Operated Fraction Collector). The first chloroform–methanol (99:1 v/v) eluate gave 5,5a,6,7,8-pentahydro-1-hydroxy-2,11-dimethoxy-6-methylbenzo[b]oxepino[7,6,5-ij]isoquinoline (**5**) (177 mg, 5.0%) as colorless needles, mp 128–129°C (from ether), λ_{max} (EtOH) 276^{sh} and 283 nm ($\log\epsilon$ 3.77 and 3.78); ν_{max} ($CHCl_3$) 3480 cm^{-1}; τ ($CDCl_3$) 7.41 (3H, s, NMe), 6.13 (6H, s, 2 × OMe), 5.49 (1H, q, *J* 4.5 and 12.0 Hz, C_{5a}-*H*), 3.48 (1H, d, *J* 8.5 Hz, C_3-*H*), 3.37 (1H, d, *J* 8.5 Hz, C_4-*H*), 3.25 (1H, d, *J* 8.5 Hz, C_{10}-*H*), 3.07 (1H, d, *J* 8.5 Hz, C_9-*H*) and 2.85 (1H, O*H*), *m/e* 327 (M^+, base peak). *Anal.* Calcd for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.52; H, 6.33; N, 4.29.

The second chloroform–methanol (99:1 v/v) eluant gave a pale yellow syrup (131 mg), which was subjected to silica gel (2 g) chromatography. Elution with chloroform–methanol (99:1 v/v) afforded 3-hydroxy-2,11-dimethoxy-6-methyl-5,5a,6,7,8-pentahydrobenzo[b]oxepino[7,6,5-ij]isoquinoline (**4**) (88 mg, 2.5%) as a pale yellow viscous syrup, ν_{max} ($CHCl_3$) 3560 cm^{-1}; τ ($CDCl_3$) 7.42 (3H, s, NMe), 6.15 (3H, s, OMe), 6.14 (3H, s, OMe), 5.55 (1H, q, *J* 12.0 and 4.5 Hz, C_{5a}-*H*), 5.0–5.6 (1H, O*H*), 3.42 (1H, s, C_1-*H*), 3.25 (1H, d, *J* 8.5 Hz, C_{10}-*H*), 3.19 (1H, s, C_4-*H*), and 3.12 (1H, d, *J* 8.5 Hz, C_9-*H*); *m/e* 327 (M^+, base peak).

1,2,11 - Trimethoxy - 6 - methyl - 5,5a,6,7,8 - pentahydrobenzo[b]*oxepino*[*7,6,5* - ij]*iso - quinoline* (**20**). To a solution of the monophenolic isoquinoline (**5**) (42 mg) in methanol (4 ml) was added an excess of diazomethane [prepared from nitrosomethylurea (2 g)] in ether (20 ml), and the mixture was set aside for 3 hr at 0–5°C and then overnight at room temperature. The solvent was distilled off and the residue was extracted with chloroform, washed with water, dried over potassium carbonate, and distilled to leave the trimethoxy compound (**20**) (40 mg), which was subjected to silica gel (1.2 g) chromatography. Elution with chloroform–methanol (99:1 v/v) gave the trimethoxy compound (**20**) (28 mg) as a pale yellow viscous syrup, τ ($CDCl_3$) 7.44 (3H, s, NMe), 6.09 (6H, s, 2 × OMe), 5.95 (3H, s, OMe), 5.68 (1H, q, J 11.5 and 4.5 Hz, C_{5a}-*H*), 3.42 (1H, d, J 8.5 Hz, C_3-*H*), 3.24 (1H, d, J 8.5 Hz, C_4-*H*), 3.24 (1H, d, J 8.5 Hz, C_{10}-*H*), and 3.11 (1H, d, J 8.5 Hz, C_9-*H*), *m/e* 341 (M^+, base peak). This was characterized as its oxalate (25 mg, 45.2%), mp 197.5–199°C (dec) (from methanol–ether), λ_{max} (EtOH) 2.80^{sh} and 284 nm (log ϵ 3.50 and 3.52). *Anal.* Calcd for $C_{20}H_{23}O_4N \cdot C_2H_2O_4 \cdot 1/4H_2O$: C, 60.61; H, 5.78; N, 3.21. Found: C, 60.67; H, 5.81; N, 3.28.

(±)-*Cularine* (**1**). A solution of diazomethane [prepared by usual way from nitrosomethylurea (2 g)] in ether (20 ml) was added to a solution of (**4**) (40 mg) in methanol (5 ml). The same treatment as described in the case of (**20**) yielded cularine (**1**) (25 mg) as pale yellow prisms, mp 125–126° (from ether). The ir ($CHCl_3$) and nmr ($CDCl_3$) spectra of this compound were completely identical with those of the natural product.

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