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TOTAL SYNTHESIS OF BISBENZYLISOQUINOLINE ALKALOIDS, TRILOBINE AND OBABERINE

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Bisbenzylisoquinoline alkaloids are usually classified by the number of the diphenyl ether linkage in the molecule. Synthesis of alkaloids containing one or two diphenyl ether linkages has been found in the literature but that of the alkaloid possessing three diphenyl ether linkages, to which trilobine (1)[1] belongs, has not been presented.

In the design of synthetic schemes for trilobine, the following aspects were considered. Thus, the major problem is the construction of the dibenzo-p-dioxin nucleus. This nucleus can be constructed by a dual Ullmann condensation reaction but the yield of this type of reaction is usually very poor. Another problems are that trilobine possesses two asymmetric centers and two different nitrogen functions, thus one is an N-CH_3 group and the other an NH group. Taking these problems into account, syntheses of trilobine (1) as well as obaberine (2)[2] have now been achieved.

dl-O-Benzyl-8-bromo-N-norarmepavine (3:dl-form)[3],*1 was synthesized from p-benzyloxyphenylacetic acid[4] and 3-bromo-4,5-dimethoxyphenethylamine[5] through an established route. The dl-compound was resolved via its N-acetyl-L-leucine salt and the absolute configuration and optical purity of the resolved free base[3: mp 122°, $[\alpha]_D$ +22.2° ($CHCl_3$), 16% yield] were confirmed by conversion into (S)-armepavine [4: mp 140-142°, $[\alpha]_D$ +96° ($CHCl_3$)] of established absolute configuration.[6]

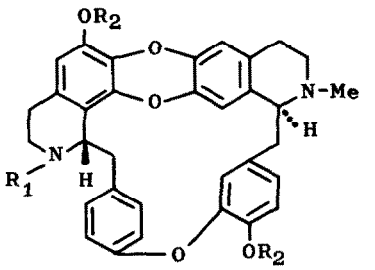
The resolved free base (3) was derived to the N-benzoyl compound [5: mp 120-122°, $[\alpha]_D$ +162° ($CHCl_3$)] which was condensed with N-t-butoxycarbonyl-3-

methoxy-4-hydroxy-β-phenethylamine[7] to give the diphenyl ether (6: amorphous, 48% yield). Hydrogenolysis of the compound (6) on Pd-C catalyst gave the phenol [7: amorphous, $[\alpha]_D$ +99.9° ($CHCl_3$), 94% yield]. Ullmann condensation of the phenol (7) with methyl-3-bromo-4-methoxyphenylacetate[8] under argon atmosphere afforded the diphenyl ether [8: amorphous, $[\alpha]_D$ +71.6° ($CHCl_3$), 34% yield]. Alkaline hydrolysis of the diphenyl ether (8), followed by esterification with p-nitrophenol in the presence of DCC and removal of the N-t-BOC group with CF_3COOH gave the phenethylammonium trifluoroacetate (9). The trifluoroacetate (9) was then cyclized to the amide [10: amorphous, $[\alpha]_D$ +95.0° ($CHCl_3$), 36% yield from 8] by adding dropwise a solution of the compound (9) in anhydrous DMF to pyridine at 70°. Bischler-Napieralski cyclization of the amide (10) yielded the imine [11: amorphous, $[\alpha]_D$ -6.7° ($CHCl_3$), 78% yield]. Reduction of the imine (11) with $NaBH_4$, followed by N-methylation with $H{\cdot}CHO\text{-}NaBH_4$ and preparative thin layer chromatography on Al_2O_3 gave N-benzoyldihydroepistephanine-A [12: amorphous, $[\alpha]_D$ +101.3° ($CHCl_3$) and the antipode [13: amorphous, $[\alpha]_D$ -127° ($CHCl_3$)] of N-benzoyldihydroepistephanine-B derived from epistaphanine[9], respectively, in a 2:5 ratio.

Successive treatments of the compound (12) with $LiAlH_4\text{-}AlCl_3$[*2], hydrogen on Pd catalyst and $H{\cdot}CHO\text{-}NaBH_4$ afforded obaberine (O-methyloxyacanthine)[2: mp 142-144°, $[\alpha]_D$ +240° ($CHCl_3$), 22% yield from 12], a sample of which was identical with an authentic sample of natural obaberine in all respects including its optical rotation. Thus, the absolute configuration of an asymmetric center at the right-hand isoquinoline moiety of the compound (12) was established.

On the other hand, $LiAlH_4\text{-}AlCl_3$ reduction of the compound (13) gave the N-benzyl base [14: mp 139-141°, $[\alpha]_D$ -88.5° ($CHCl_3$), 55% yield] which in CH_2Cl_2 was treated with BBr_3 at 0° to give the O-demethylated derivative. This compound in a saturated aqueous HBr solution was heated in a sealed tube at 135-140° for 3 hr[10] to provide the phenol (15). On methylation with diazomethane, the phenol gave N-benzyltrilobine [16: amorphous, $[\alpha]_D$ +203° ($CHCl_3$), 1.5% yield from 14]. Finally, hydrogenolysis of N-benzyltrilobine (16) on Pd-C catalyst afforded trilobine [1: mp 244-246°, $[\alpha]_D$ +304.5° ($CHCl_3$)

34% yield], a sample of which was identical with an authentic sample of natural trilobine in all respects including its optical rotation. Moreover, the present synthesis amounts to synthesis of isotrilobine because trilobine was derived to isotrilobine by N-methylation.[11]

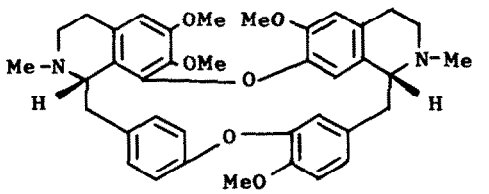


(1) $R_1 = H$, $R_2 = Me$

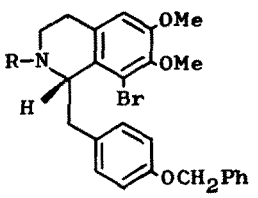
(15) $R_1 = PhCH_2$, $R_2 = H$

(16) $R_1 = PhCH_2$, $R_2 = Me$

(17) $R_1 = R_2 = Me$

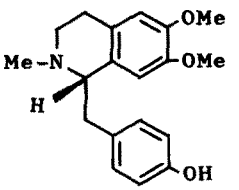


(2)

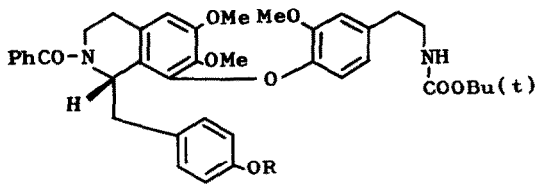


(3) R = H

(5) R = COPh

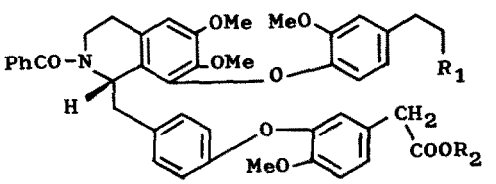


(4)



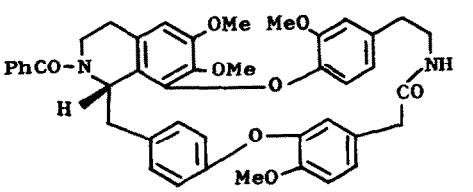
(6) R = CH_2Ph

(7) R = H

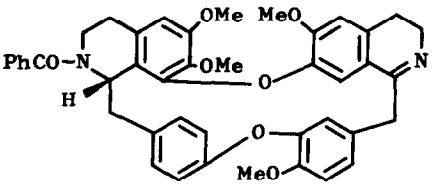


(8) R_1=NHCOOBu(t), R_2 = Me

(9) $R_1 = NH_3^+CF_3COO^-$, $R_2 = C_6H_4NO_2$



(10)



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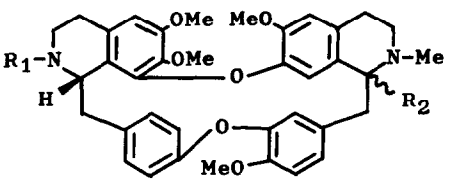

(12) R_1 = PhCO, R_2 = βH
(13) R_1 = PhCO, R_2 = αH
(14) R_1 = $PhCH_2$, R_2 = αH

Footnotes and References

*1 Satisfactory IR (in $CHCl_3$) and NMR (in $CDCl_3$) spectral data were obtained on chromatographically homogeneous samples of each new compound reported herein.

*2 Reduction with $LiAlH_4$ gave no satisfactory result.

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