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A BIOGENETIC TYPE SYNTHESIS OF S(+)-LAUDANOSINE FROM L(-)-DOPA

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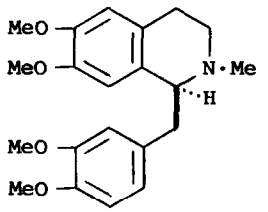
S(+)-Laudanosine[1] (I) is one of the long known 1-benzyltetrahydroisoquinoline alkaloids. Several syntheses of I in its racemic modification have been reported.[1] Asymmetric synthesis of its unnatural form (R) has also recently[2] been attempted with miserable asymmetric induction. The biosynthesis of the isoquinoline alkaloids of this type is well investigated,[1] and L-dihydroxyphenylalanine derivatives have been proved to be precursors.



I

We now wish to report a biogenetic type synthesis of S(+)-laudanosine (I) from L-3,4-dihydroxyphenylalanine derivatives using 1,3-asymmetric induction.[3] The condensation of L(+)-3,4-dihydroxyphenylalanine methyl ester hydrochloride[4] with sodium 3-(3,4-dimethoxyphenyl)-glycidate[5] at pH 4 and 35° gave in 44% yield a diastereoisomeric mixture of the Pictet-Spengler products (II), mp 173-174°, $[\alpha]_D^{21}$ -124.6° (MeOH), and (III), mp 110-112°, $[\alpha]_D^{20}$ -38.4° (MeOH), the separation of which was carried out by a combination of silica-gel column chromatography and

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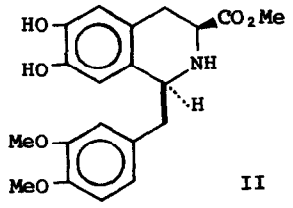
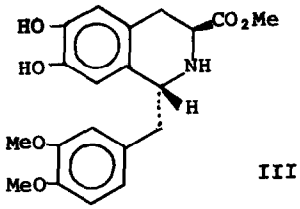
recrystallization. The i.r. and n.m.r. spectra of both compounds support the structural assignment of II (i.r. 1740, 1723 cm^{-1}; n.m.r. (τ) 6.36 (3H, s), 6.28 (3H, s), 6.24 (3H, s)) and III (i.r. 1725 cm^{-1}; n.m.r. (τ) 6.35 (3H, s), 6.23 (6H, s)). The mass spectra of II and III show the intense peak A (m/e 222, R=R'=H, R"=CO_2Me) which is characteristic of 1-benzyl-1,2,3,4-tetrahydroisoquinolines.[6] The product ratio of II to III was found to be ca. 2.4:1. The stereochemistry of the predominant isomer (II) was assumed[3,7] to be 1,3-cis configuration as shown in the Chart, and this was confirmed by the conversion of II to S(+)-I.

Methylation of II with diazomethane gave the amine (IVa),[8] mp 126-128°, $[\alpha]_D^{23}$ -106.8° (MeOH) in 87% yield in company with the N-methyl amine (IVb) as an oil in 5% yield. Treatment of IVa and IVb with methanolic ammonia afforded the amides (Va), mp 196-198°, $[\alpha]_D^{20.5}$ -124.8° ($CHCl_3$), i.r. 1685 cm^{-1}, in 94% yield and (Vb), mp 149-151°, $[\alpha]_D^{20}$ -40.7° ($CHCl_3$), i.r. 1690 cm^{-1}, in 41% yield, respectively. The amide (Vb) was obtained in 97% yield by the reaction of Va with methyl iodide in refluxing methanol in the presence of potassium carbonate. Dehydration of Vb with phosphorus pentoxide in hot pyridine, followed by reductive decyanization[3] with sodium borohydride in ethanol-pyridine at room temperature gave the desired S(+)-laudanosine (I), mp 84-88°, $[\alpha]_D^{21}$ +82.5° (EtOH), Lit.[9] mp 90-91°, $[\alpha]_D^{29}$ +83.4° (EtOH). However, the yield was very poor owing to the instability of the intermediate aminonitrile (VIa). This obstacle has been surmounted by the replacement of the N-methyl group with the N-benzyl group as follows.

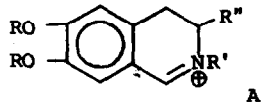
Treatment of the amide (Va) with benzyl chloride and potassium carbonate in refluxing ethanol quantitatively gave the N-benzyl amide (Vc), an oil, picrate: mp 109-111°, which was dehydrated as above to furnish the N-benzyl nitrile (VIb) in 55% yield. The nitrile (VIb) was again labile and reduced with sodium borohydride without purification to give the decyanized product (VIIa) in 87% yield. Catalytic hydrogenation of VIIa with 5% Pd-C in the presence of hydrochloric acid resulted in the formation of S-norlaudanosine (VIIb) hydrochloride, mp 164-167°, $[\alpha]_D^{26}$ +37.4° (H_2O) (Lit.[10] mp 167°, $[\alpha]_D$ +38° (H_2O)) in 66% yield. Reductive methylation of the VIIb hydrochloride occurred smoothly on treatment



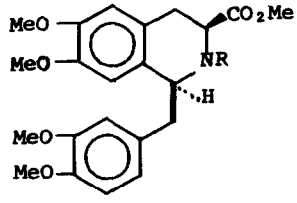
II



III

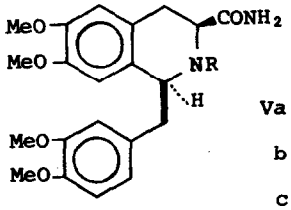


A



IVa : R = H

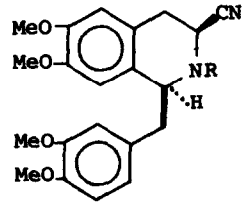
b : R = Me



Va : R = H

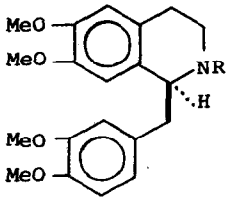
b : R = Me

c : R = CH_2Ph



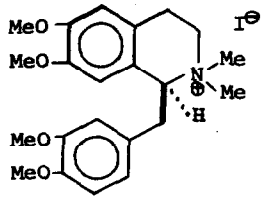
VIa : R = Me

b : R = CH_2Ph



VIIa : R = CH_2Ph

b : R = H



VIII

with sodium borohydride-formalin in methanol to give S(+)-laudanosine (I) in 81% yield. The methiodide (VIII), mp 225-227°, $[\alpha]_D^{20.5}$ +121° (EtOH) (Lit.[10] mp 218-221°, $[\alpha]_D$ +120° (EtOH)) was obtained by the reaction of VIIb with methyl iodide and potassium carbonate.

The successful conversion of L(-)-DOPA to S(+)-laudanosine may promise the asymmetric synthesis of various optically active isoquinoline alkaloids from optically active hydroxyphenylalanine derivatives.

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