

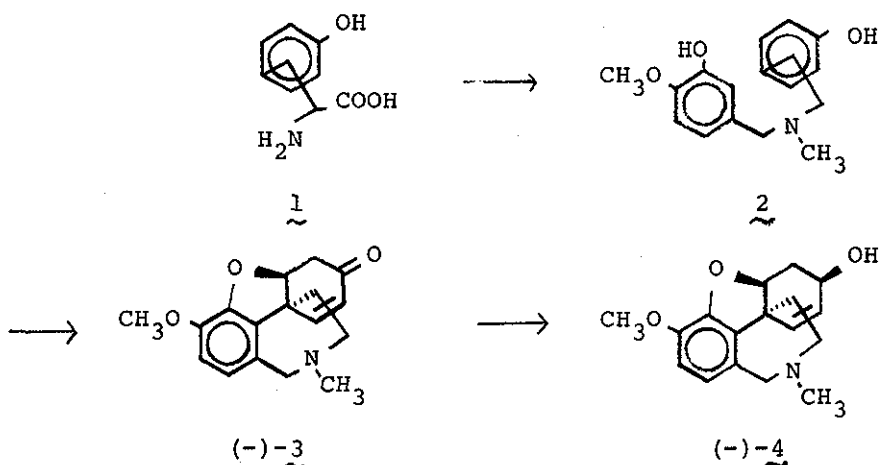
A BIOGENETIC-TYPE ASYMMETRIC SYNTHESIS OF OPTICALLY
ACTIVE AMARYLLIDACEAE ALKALOIDS : (+)- AND
(-)-GALANTHAMINE FROM L-TYROSINE¹⁾

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A biogenetic-type asymmetric synthesis of optically active galanthamine (4) from L-tyrosine (L-1) was achieved via the intramolecular phenolic oxidative coupling of norbelladine derivative (5) followed by asymmetric cyclization. Enantiomeric interconversion of narwedine derivative (7) is also described.

(-)-Galanthamine ((-)-4), one of the representatives of Amaryllidaceae alkaloids, is known to be biosynthesized from tyrosine (1) via (-)-narwedine ((-)-3) by the intramolecular phenolic oxidative coupling of N,O-dimethylnorbelladine (2) at p,o'-positions.²⁾ Total synthesis of galanthamine along this biogenetic route has been reported,³⁾ and Barton and Kirby obtained optically active isomers ((+)- and (-)-4) by

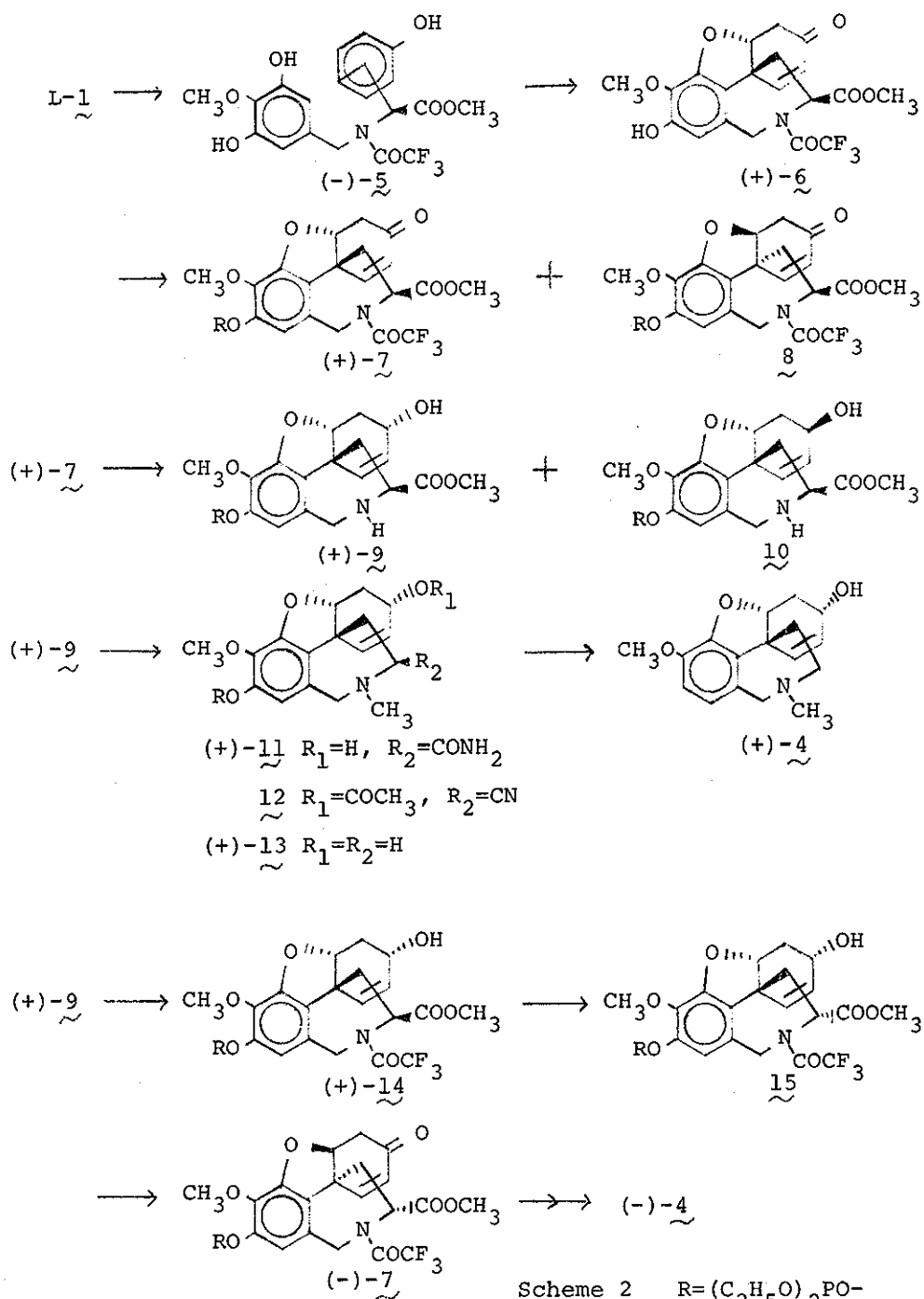


Scheme 1

the resolution of narwedine (3) followed by reduction.^{3a)} As an extension of our previous report on the synthesis of (+)-maritidine,⁴⁾ the present paper describes a biogenetic-type asymmetric synthesis of (+)- and (-)-4 from L-tyrosine (L-1) as shown in Scheme 2. The method involves (i) the use of N-(3,5-dihydroxy-4-methoxy)benzyl derivative ((-)-5) having C₂ symmetry in the aromatic moiety as the substrate for oxidative coupling for the purpose of obtaining the p,o'-coupled product after reductive elimination of the phenolic hydroxyl group⁵⁾ of the resulting (+)-6, (ii) the use of the asymmetric cyclization of (-)-5 to (+)-6 followed by elimination of the original chirality by reductive decyanization,⁶⁾ and (iii) the enantiomeric transformation of (+)-7 to its antipode ((-)-7) by utilizing optical instability of narwedine skeleton.^{3a)}

The norbelladine-type phenol ((-)-5),⁷⁾ prepared from L-1 in 77% overall yield by the modification of the known procedures, was oxidized to the narwedine-type enone ((+)-6),⁷⁾ $[\alpha]_D^{20} +125^\circ$ (c=1.12, CH₃OH), with 5 molar equiv. of manganic tris(acetylacetonate)⁸⁾ (acetonitrile, reflux 5 hr) in 34% yield after chromatographic purification. The other diastereomer was not isolated. The reaction of (+)-6 with diethyl phosphorochloridate in the presence of triethylamine afforded (+)-7,⁷⁾ $[\alpha]_D^{22} +138^\circ$ (c=1.1, CHCl₃) in 81% yield accompanied by a small amount of its diastereomer (8). It was found that diastereomeric equilibrium ((+)-7 : 8 = 13 : 1) could be easily attained with a catalytic amount of triethylamine in chloroform (room temp., overnight).

Sodium borohydride reduction of (+)-7 resulted in the formation of isomeric alcohols, (+)-9,⁷⁾ $[\alpha]_D^{20} +45.1^\circ$ (c=0.82, CHCl₃), and 10 in a ratio of 4 : 1. The modified Eschweiler-Clarke N-methylation of (+)-9 followed by amidation with ammonia afforded carboxamide ((+)-11),⁷⁾ $[\alpha]_D^{20} +40.2^\circ$ (c=1.0, CHCl₃). Acetylation of (+)-11 with acetic anhydride in pyridine followed by dehydration with phosphorous oxychloride yielded the unstable amino nitrile (12).^{7b)} Lithium aluminum hydride reduction of 12 in tetrahydrofuran at 0° gave (+)-10-diethylphosphoroxycalanthamine ((+)-13)⁷⁾ in 37% overall yield from (+)-11. Brief treatment of (+)-13 with excess sodium in liq. ammonia at -78° afforded (+)-galanthamine⁷⁾ ((+)-4) (mp 127-129°, $[\alpha]_D^{26} +116^\circ$ (c=1.0, C₂H₅OH)) in 72% yield.



Scheme 2 $R=(C_2H_5O)_2PO-$

Physical and spectral data of this sample agreed well with those of the authentic natural (-)-galanthamine except the sign of optical rotation.

On the other hand, treatment of (+)-14,⁷⁾ obtained from (+)-9 in 79% overall yield, with lithium diisopropylamide in tetrahydrofuran containing tetramethylethylenediamine and hexamethylphosphoramide at -20° under N₂ afforded the C-6 epimer (15) after chromatographic purification in 11% yield. Oxidation of 15 with pyridinium chlorochromate in methylene chloride afforded (-)-7 as a glass of $[\alpha]_D^{22} -108^\circ$ (c=1.1, CHCl₃) in 72% yield, corresponding to be 78% optically pure. This result means the enantiomeric transformation of (+)-7 to (-)-7, and constitutes the formal total synthesis of (-)-galanthamine having natural configuration from L-tyrosine.

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REFERENCES AND NOTES

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