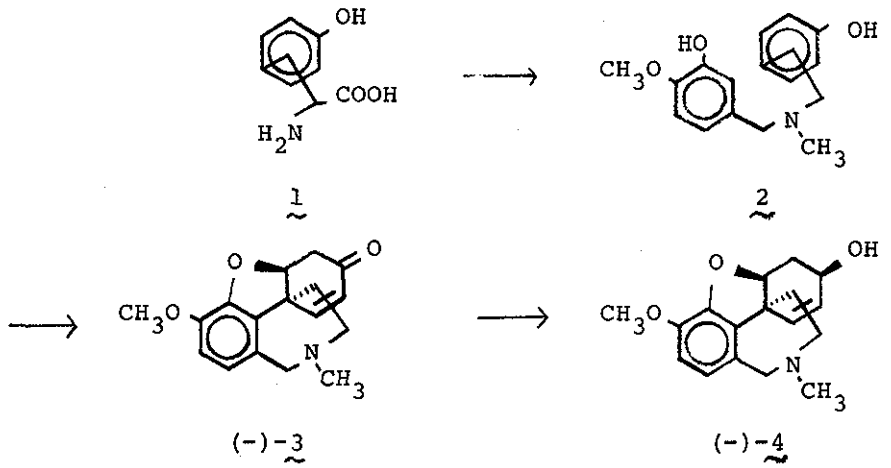
A BIOGENETIC-TYPE ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE AMARYLLIDACEAE ALKALOIDS : (+)- AND (-)-GALANTHAMINE FROM L-TYROSINE[1)]

Kimihiro Shimizu, Kiyoshi Tomioka,
Shun-ichi Yamada, and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo
7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan

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

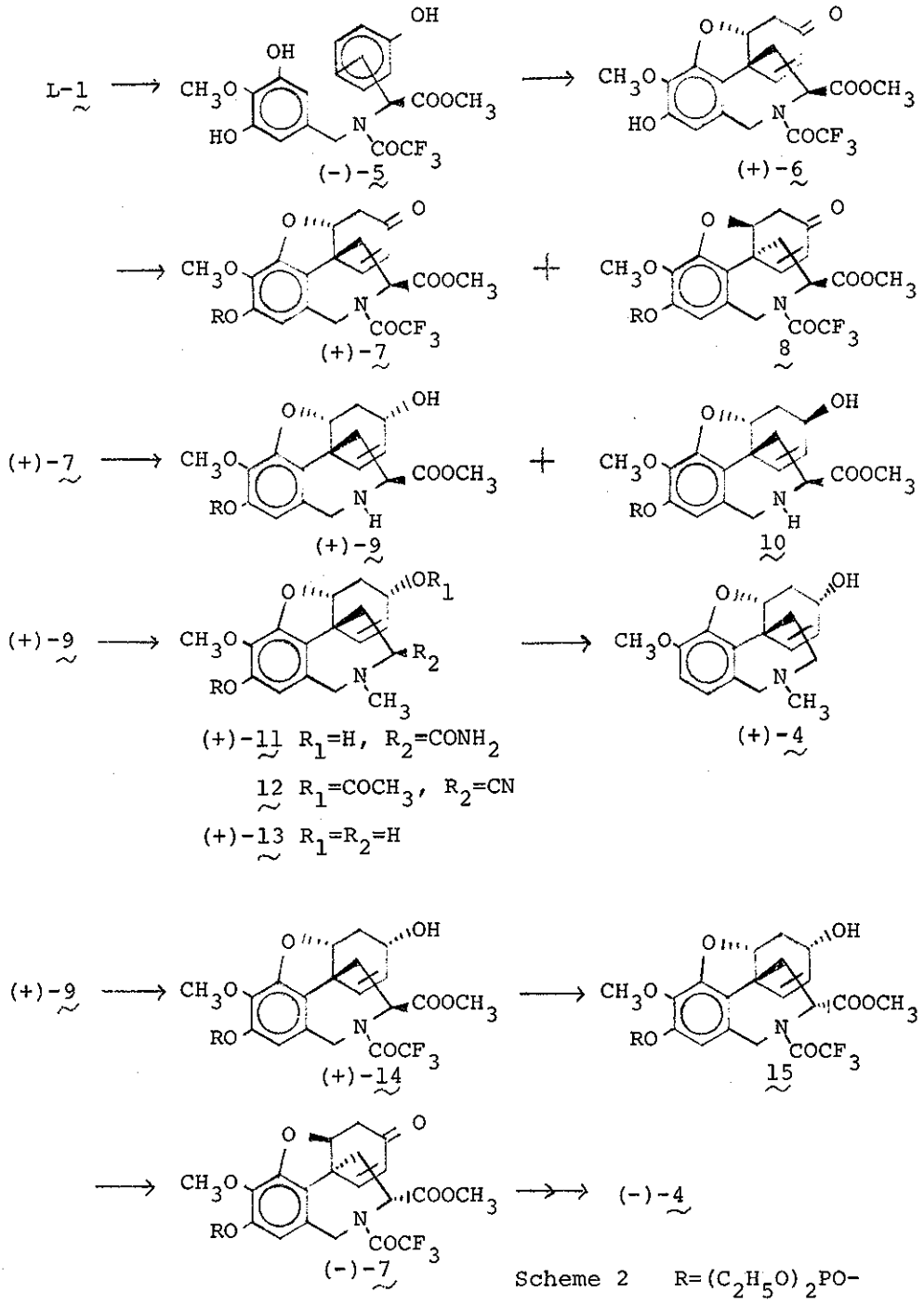


Scheme 1

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 C_2 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 group[5] 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° (c=1.12, CH_3OH), 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° (c=1.1, $CHCl_3$) 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° (c=0.82, $CHCl_3$), 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° (c=1.0, $CHCl_3$). 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-diethylphosphoroxygalanthamine ((+)-13)[7] in 37% overall yield from (+)-11. Brief treatment of (+)-13 with excess sodium in liq. ammonia at -78° afforded (+)-galanthamine[7] ((+)-4) (mp 127-129°, $[\alpha]_D^{26}$ +116° (c=1.0, C_2H_5OH)) 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 N_2 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° (c=1.1, $CHCl_3$) 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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7) Satisfactory elemental analysis was obtained. b) Mass spectrum exhibited molecular ion peak.

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