APPROACHES TO THE BIOGENETIC-TYPE ASYMMETRIC SYNTHESIS OF SOME AMARYLLIDACEAE ALKALOIDS

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It is well recognized that natural products having chiral structures are optically active in almost all cases, and that biological activities of chiral compounds are highly dependent on their configurations. At the syntheses of these chiral compounds, therefore, the targets should be optically active compounds having the desired absolute configurations.

Amaryllidaceae alkaloids[1] are known to be biosynthesized via intramolecular phenolic oxidative coupling of 2 as shown in Chart 1,[2] and many biogenetic-type syntheses have been reported in racemic forms.[1] The present report describes the approaches to the biogenetic-type asymmetric synthesis of maritidine and galanthamine in optically active forms starting from L-tyrosine (1), via intramolecular oxidative coupling of 7 and 16 similar to 2. The chiral center of 1 was used as the chiral source in the asymmetric cyclization, and was later removed by reductive decyanization.[3]

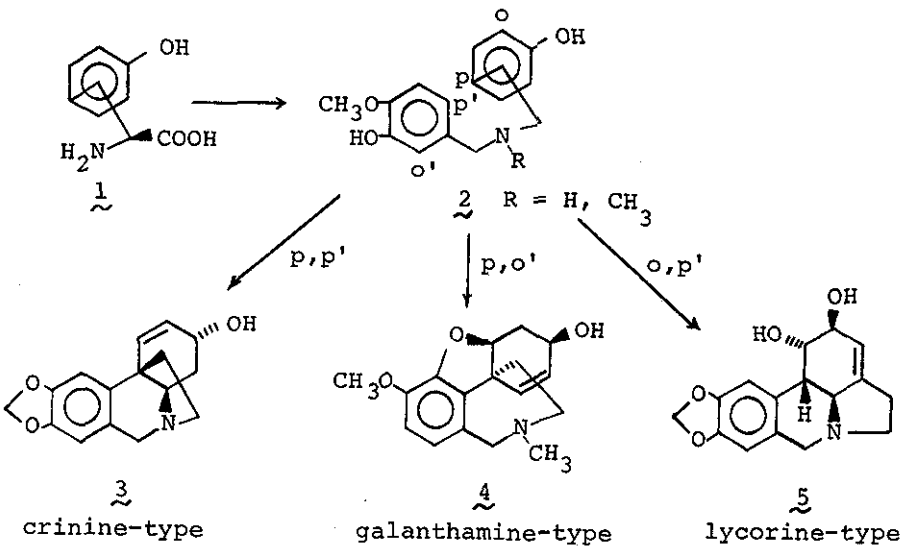

Chart 1

Synthesis of (+)-Maritidine (15)[4]

Oxidative coupling of the amide (7) at p-p' position, a key step in the construction of maritidine skeleton, was effected in 66.5% yield. The enone (10) was obtained in 41% yield by the Michael-type cyclization of 9, but the other possible diastereomer (11) could not be isolated. This highly specific asymmetric cyclization could be explained by the severe steric interactions between amide group and methylene group in 11, while no such interactions in 10.

Decyanization of 13 was not successful with $NaBH_4$,[3] probably due to the effect known as Bredt's rule, but was successful with sodium in liquid ammonia. Epimerization at C-3 of epimaritidine (14) by the reported method[5] afforded (+)-maritidine, identical with the natural material in all respects.

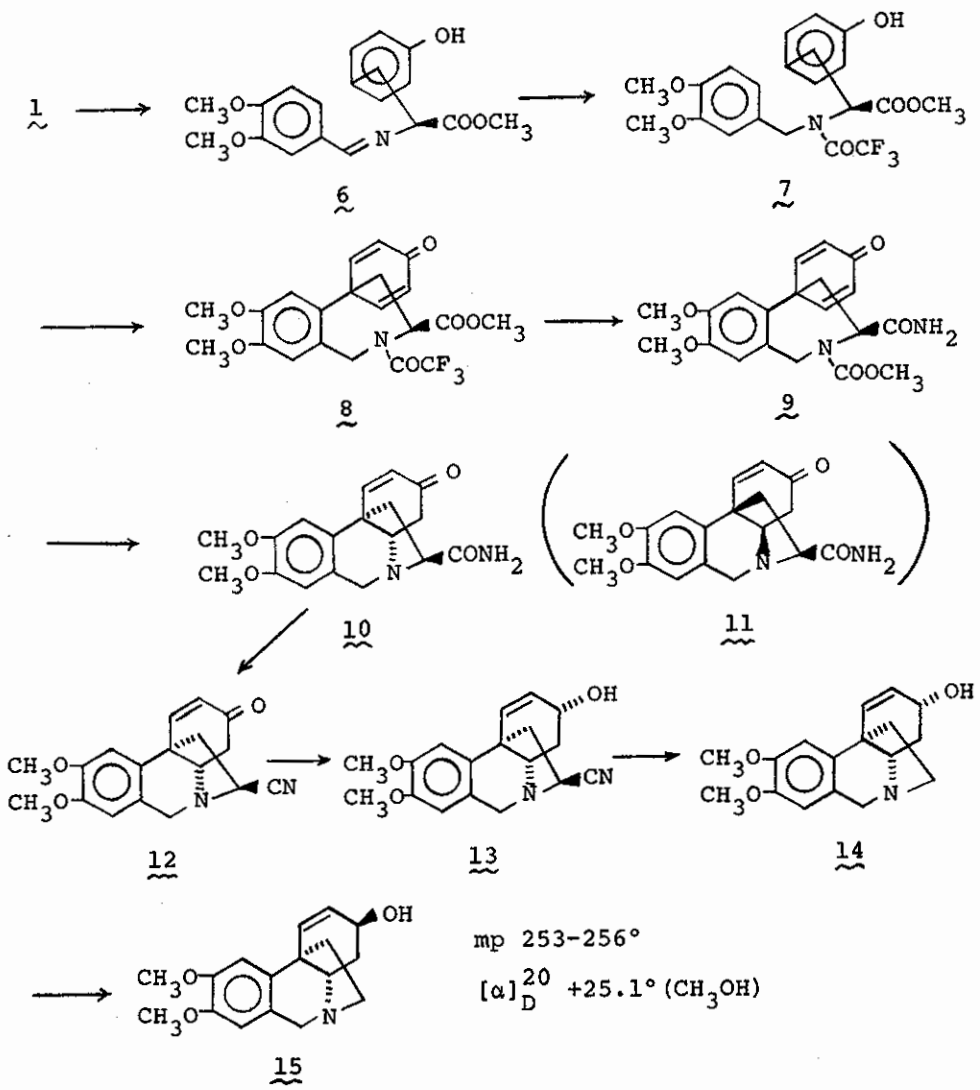

Chart 2

Synthesis of (+)-Galanthamine (22)

The amide (16) was chosen as a substrate for oxidative coupling because 17 is considered to be a p,o'-coupling product after reductive elimination of the phenolic hydroxyl group.[6,7]

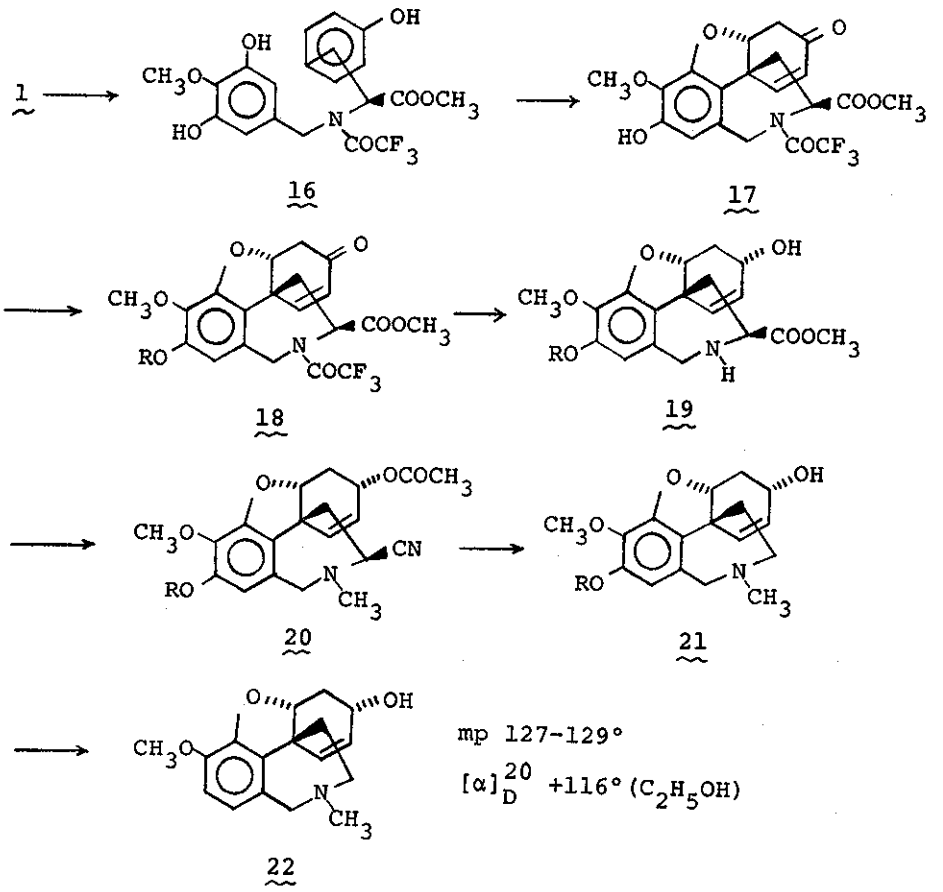

Chart 3 R = $(C_2H_5O)_2PO$

Asymmetric cyclization was again found to be highly specific, but galanthamine (22) obtained was found to be antipodal to the natural material.

Configurational interconversion of 19 to its antipode via the corresponding enone[8] is a matter of current investigation.

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