Tetrahedron Letters No. 1, pp 57 - 60, 1976. Pergamon Press. Printed in Great Britain.

A BIOGENETIC-TYPE ASYMMETRIC SYNTHESIS OF NATURAL (+)-MARITIDINE FROM L-TYROSINE[1]

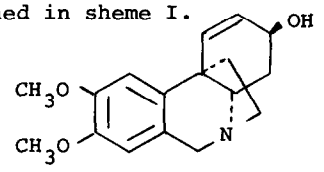
Shun-ichi Yamada,* Kiyoshi Tomioka, and Kenji Koga

Faculty of Pharmaceutical Sciences, University of Tokyo

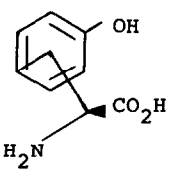
Hongo, Bunkyo-ku, Tokyo 113, Japan

(Received in Japan 20 October 1975; received in UK for publication 24 November 1975)

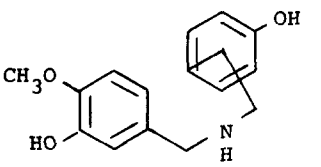
(+)-Maritidine (1) is a representative of the 5-10b ethanophenanthridine class of Amaryllidaceae alkaloids.[2] Many radioactive tracer experiments have verified that alkaloids of this type are biosynthesized from L-tyrosine (2) as a precursor via the phenolic oxidative cyclization of O-methylnorbelladine (3).[3] Although several syntheses of 1 in its racemic modification have been reported,[4] resolution is necessary to obtain an optically active objective. We now wish to report the first, biogenetic-type, asymmetric synthesis of (+)-maritidine (1) from L-tyrosine (2) using asymmetric cyclization.[5] The synthetic route is outlined in sheme I.



1



2



3

The Schiff base (4), prepared from L-tyrosine methyl ester and isovanillin, was reduced with sodium borohydride in methanol to give the amine (5), mp 124.5-125.5°, $[\alpha]_D^{20}$+3.89°(MeOH), in 85% yield. Treatment of 5 with trifluoroacetic anhydride in pyridine followed by aqueous work-up afforded a 71% yield of the N-trifluoroacetyl derivative (6), glass, $[\alpha]_D^{20}$-75.6°(MeOH). Oxidation of 6 with ferric chloride-DMF complex[4b] (10 hr at reflux in Et_2O-water) gave, after column chromatography, the para-para coupled spiro dienone (7), glass, $[\alpha]_D^{20}$+146°(MeOH), ir 1753, 1692, 1667 cm^{-1}, m/e 425, uv (MeOH) 213, 236, 280 nm, in

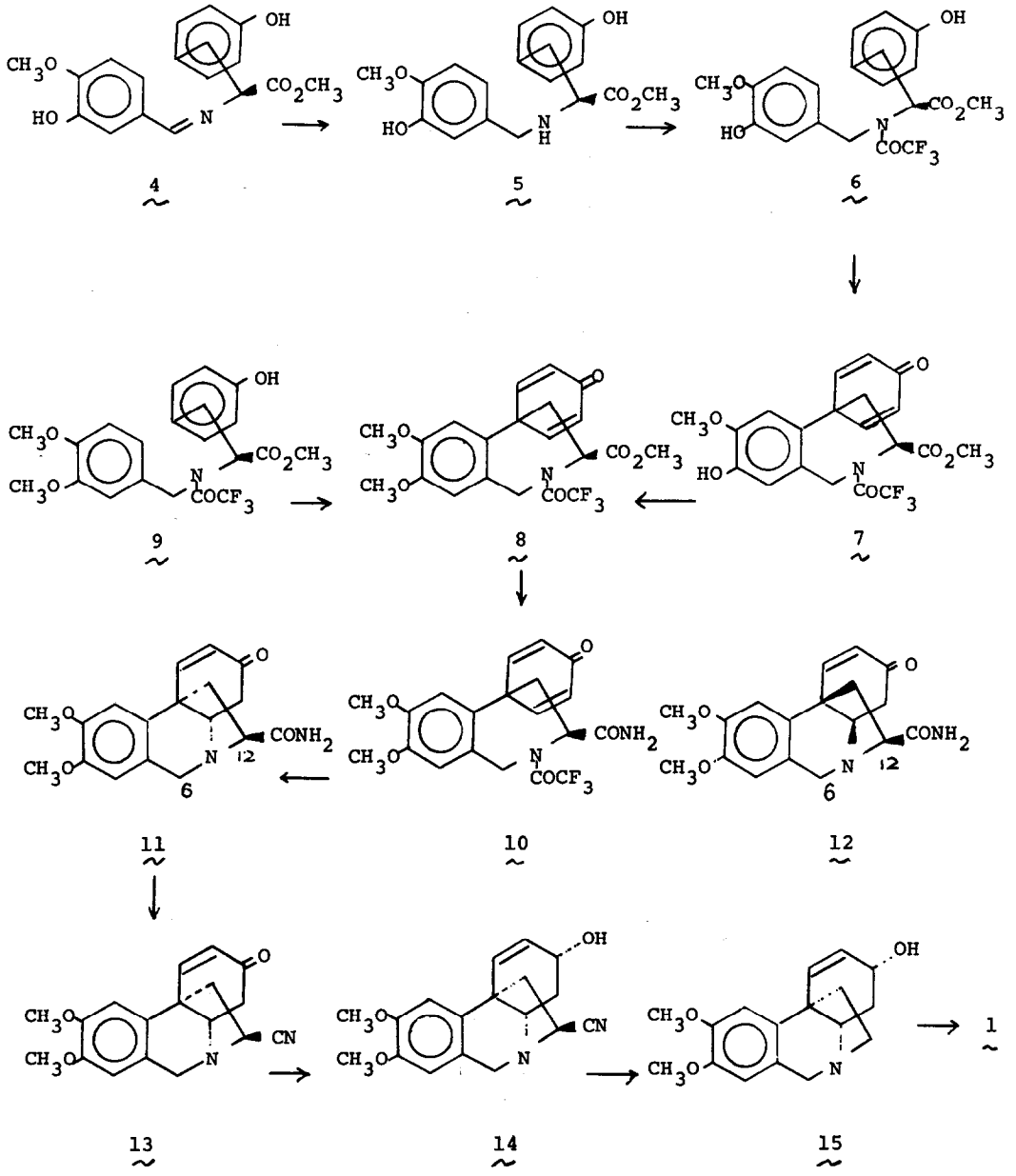
14% yield. The dienone (7) was methylated with MeI and t-BuOK in DMF to give O,O-dimethyl dienone (8), mp 175.5-176.5°, $[\alpha]_D^{20}$+213° (MeOH), ir 1750, 1695, 1665 cm^{-1}, nmr 3.69, 3.75, 3.84 (three s, three OMe), molecular ion at m/e 439.1224(calcd 439.1242), in 25% yield. The dienone (8) was also prepared in another way. Oxidation of 9, glass, $[\alpha]_D^{20}$-65.9° (MeOH), prepared from L-tyrosine methyl ester and veratraldehyde by the same procedure as with 6, using thallium(III) trifluoroacetate[6] in acetonitrile containing a small amount of trifluoroacetic acid (3 hr at -23°, 21 hr at 25°) gave the spiro dienone (8) in 67% yield. A decreased yield of oxidation was observed with methylene chloride as a solvent.

Amidation of 8 with ammonia in methanol afforded the amide (10), mp 226-229° (dec.), $[\alpha]_D^{20}$+198° (MeOH), ir 1695, 1685, 1665 cm^{-1}, m/e 424, in 79% yield. Removal of the N-trifluoroacetyl group from 10 (sodium hydroxide in aqueous methanol at room temperature) resulted in spontaneous cyclization to give the enone (11), mp 114-115°, $[\alpha]_D^{20}$+98.6° (MeOH), ir 1680 cm^{-1}, nmr 4.21(d, J=16 Hz, H-6), 6.05 (d, J=10 Hz, H-2), 6.49 (s, H-7), 6.89 (s, H-10), 7.55 (d, J=10 Hz, H-1), molecular ion at m/e 328.1436 (calcd 328.1423), in 41% yield. The stereochemistry of 11 was confirmed by the conversion of 11 to (+)-maritidine.[2c,4a] The diastereomer (12) was not obtained. This asymmetric cyclization is highly specific due to the difference in steric effects between the methylene group at C-6 and the amide group at C-12 in 11 and 12.

Dehydration of the amide (11) with phosphorus oxychloride in chloroform and pyridine (under reflux for 20 min) afforded the nitrile (13), viscous oil, $[\alpha]_D^{20}$+45.0° (MeOH), ir 2230, 1680 cm^{-1}, m/e 310, in 62% yield. Reduction of 13 with sodium borohydride in methanol at -20° for 1 hr gave allyl alcohol (14), glass, $[\alpha]_D^{20}$+27.4° (MeOH), nmr ca. 4.4 (m, H-3), 5.86 (d, J=10 Hz, H-2), 6.37 (dd, J=10 and 2 Hz, H-1), 6.46 (s, H-7), 6.76 (s, H-10), m/e 312, in 67% yield. Reductive decyanization of 14 was accomplished with sodium in liquid ammonia-THF at -78° for 15 min[7] to give (+)-epimaritidine (15), mp 235.5-236.5°, $[\alpha]_D^{20}$+136° (MeOH), nmr 3.79, 3.85 (two s, two OMe), ca. 4.4 (m, H-3), 4.40(d, J=17 Hz, H-6), 5.76 (d, J=10 Hz, H-2), 6.43 (dd, J=10 and 2 Hz, H-1), 6.47 (s, H-7), 6.75 (s, H-10), molecular ion at m/e 287.1511 (calcd 287.1521), in 58% yield.

Epimerization[4a] at C-3 of (+)-epimaritidine was accomplished by refluxing 15 for 1 hr in 10% hydrochloric acid to give, after preparative tlc on alumina, (+)-maritidine (1), mp 253-256°, $[\alpha]_D^{20}$+25.1° (MeOH), nmr (DMSO-d_6) 3.67, 3.72

Scheme I



(two s, two OMe), 4.24 (d, J=17 Hz, H-6), ca. 4.6 (m, H-3), 5.75 (dd, J=10 and 2 Hz, H-2), 6.56 (s, H-7), 6.62 (d, J=10 Hz, H-1), 6.88 (s, H-10), molecular ion at m/e 287.1500 (calcd 287.1521), in 17% yield.

The melting point, optical rotation, and ir spectra (KBr) of this synthetic (+)-maritidine agreed well with those reported[2a,b] for the natural material. Its tlc behavior and nmr spectra were also shown to be identical with those of (±)-maritidine.[8]

The first successful conversion of L-tyrosine to (+)-maritidine holds promise for the asymmetric syntheses of various optically active Amaryllidaceae alkaloids from optically active hydroxy phenylalanine derivatives.

REFERENCES

(1) Satisfactory elemental analyses have been obtained for all compounds for which the melting point values are given. Nmr spectra were obtained at 100 MHz (in $CDCl_3$ unless otherwise specified). Chemical shift values are expressed in δ values. Ir spectra were obtained in $CHCl_3$ unless otherwise specified.

(2) (a) R. H. F. Manske, "The Alkaloids", Vol. XI, Academic Press, New York, 1968, pp 356. (b) F. Sandberg and K. H. Michel, Lloydia, 26, 78 (1963). (c) G. G. DeAngelis and W. C. Wildman, Tetrahedron Letters, 729 (1969).

(3) (a) W. C. Wildman, H. M. Fales, and A. R. Battersby, J. Am. Chem. Soc., 84, 681 (1962). (b) D. H. R. Barton, G. W. Kirby, J. B. Taylor, and G. M. Thmas, J. Chem. Soc., 4545 (1963).

(4) (a) M. A. Schwartz and R. A. Holton, J. Am. Chem. Soc., 92, 1090 (1970). (b) E. Kotani, N. Takeuchi, and S. Tobinaga, Tetrahedron Letters, 2735 (1973). (c) T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, Tetrahedron, 27, 5441 (1971). (d) E. Kotani, N. Takeuchi, and S. Tobinaga, Chem. Comm., 551 (1973)

(5) S. Yamada, M. Konda, and T. Shioiri, Tetrahedron Letters, 2215 (1972).

(6) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, J. Am. Chem. Soc., 95, 612 (1973).

(7) S. Yamada, K. Tomioka, and K. Koga, Tetrahedron Letters, accompanying paper.

(8) (±)-maritidine was prepared according to the reported method. See 4a.