SILICON-MEDIATED ISOQUINOLINE ALKALOID SYNTHESIS: A NEW ROUTE TO THE DIBENZOPYRROCOLINE ALKALOID (±)-CRYPTAUSTOLINE

Seiichi Takano,* Shigeki Satoh, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

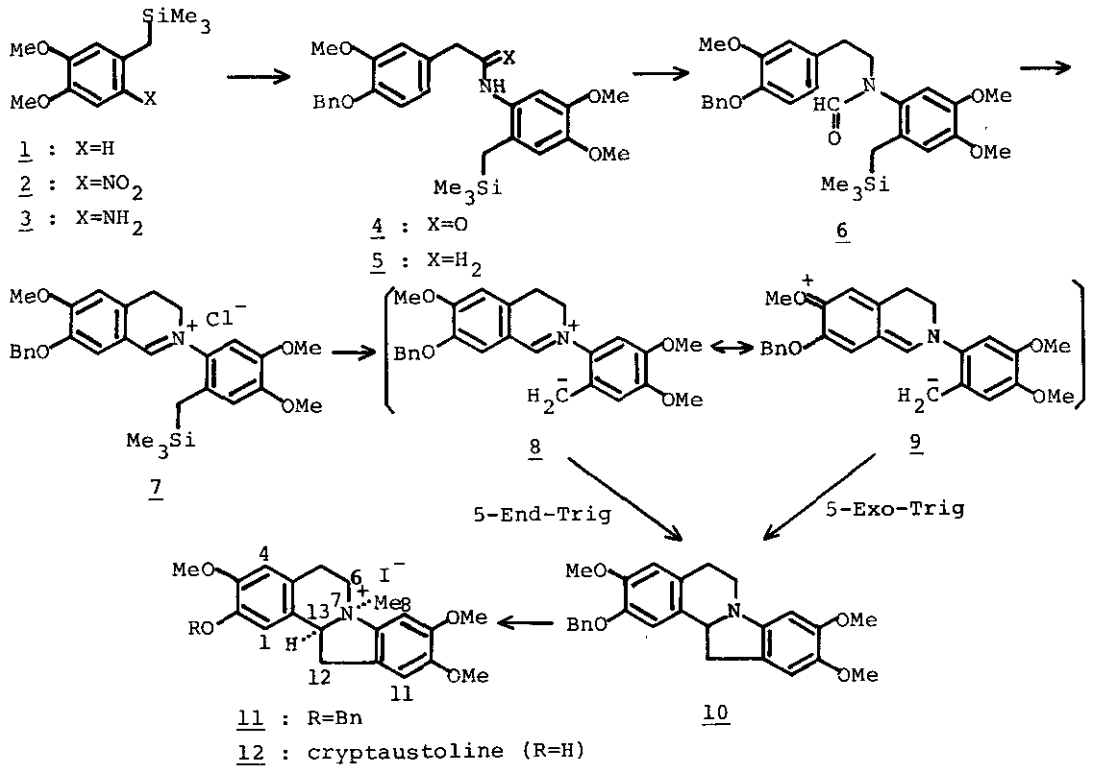
Abstract———A fundamentally new synthesis of the benzopyrrocoline alkaloid (±)-cryptaustoline iodide (12) has been devised by employing the silicon mediated ring closure through a formal 5-Endo-Trigonal process.

Recently, we developed a novel route to the protoberberine type isoquinoline alkaloids via intramolecular nucleophilic addition of a benzylsilane derivative to a carbon-nitrogen double bond through a favorable 6-Endo-Trigonal process.[1,2] We report here an extension of this method for the construction of a dibenzopyrrocoline framework intending to develop a new route to the dibenzopyrrocoline alkaloids.[3] Although some synthetic routes to the benzopyrrocoline alkaloids have been already developed by several workers,[4] the methodologies employed were fundamentally based on the same principle involving the bond construction between 7-nitrogen and aromatic 7a-position at the key step. The present method involves the bond formation between 12 and 13 carbons at the key step employing the silicon-mediated method.

The key intermediate (7) was prepared from the known 4,5-dimethoxybenzylsilane[1] (1) via a 6 step-sequence of reactions. Nitration of 1 with cupric nitrate in acetic anhydride[5] gave the 6-nitroderivative (2) in 43% yield. Hydrogenation (H_2, 10% Pd-C, EtOH) of 2 followed by condensation with 4-benzyloxy-3-methoxyphenylacetyl chloride yielded the anilide (4) (93% overall) via the amine (3). Reduction of 4 with a 3:1 mixture of lithium aluminum hydride and aluminum chloride gave the secondary amine (5) which was sequentially treated with acetic formic anhydride to give the formamide (6) (89% overall). Treatment of 6 with

phosphorus oxychloride in boiling benzene underwent cyclization to give the desired isoquinolinium base (7) in quantitative yield.

Treatment of 7 with two equivalent of tetra-n-butylammonium fluoride[6] in boiling tetrahydrofuran allowed smooth ring closure to give rise to the known dibenzopyrrocoline[7] (10) in 60% yield. Employing the established three step sequence of reactions[4] 10 was converted into the dibenzopyrrocoline alkaloid, (±)-cryptaustoline iodide[7] (12) in 44% overall yield. Two diastereomeric products may be formed at the quaternization stage with regard to the 7-nitrogen center, however, a single diastereomer with natural cis configuration[8] was selectively obtained as has been confirmed.[4c] Although the key cyclization seem to proceed via the betaine (8) formally through a disfavorable 5-Endo-Trigonal process, the observed facile ring closure may be the result of contribution from the quinonoid structure (9) which permits the favored 5-Exo-Trigonal mode of cyclization.[9]



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2. More recently a similar silicon mediated reaction was also reported, see: G. Dai-Ho, A. J. Y. Lan, and P. S. Mariano, Tetrahedron Lett., 26, 5867 (1985).

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4. (a) T. Kametani and K. Ogasawara, J. Chem. Soc. C, 2208 (1967); (b) F. Benington and R. D. Morin, J. Org. Chem., 32, 1050 (1967); (c) T. Kametani, K. Fukumoto, and T. Nakano, J. Heterocyclic Chem., 9, 1363 (1972); (d) I. W. Elliott, Jr., J. Org. Chem., 47, 5398 (1982).

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6. Interestingly, the cyclization did not take place with cesium fluoride under the same conditions which brought the 6-Endo-Trigonal cyclization.[1]

7. Identical in all respects with an authentic material obtained by the benzyne route.[4a] All new isolable compounds described showed satisfactory spectral (IR, ^{1}H-NMR, Mass) and analytical (combustion and high resolution Ms) data.

8. The configuration of the alkaloids has not yet been determined to date, see: S. Takano, S. Satoh, Y. Oshima, and K. Ogasawara, accompanied paper.

9. (a) J. E. Baldwin, J. Chem. Soc., Chem. Commun., 734 (1976); (b) J. E. Baldwin, J. Cutting, W. Dupont, L. I. Kruse, L. Silberman, and R. C. Thomas, ibid., 736 (1976).

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