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

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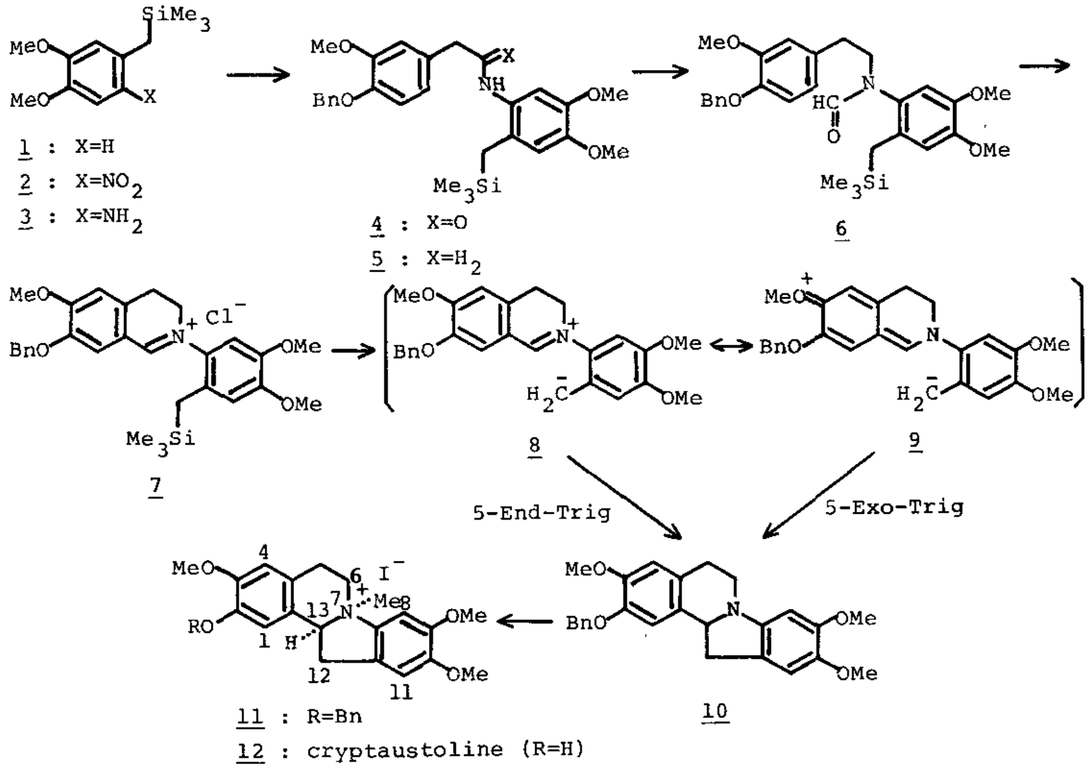
Abstract——A fundamentally new synthesis of the benzopyrrocoline alkaloid (±)-cryptaustoline iodide (12) has been devised by employing the silicon mediated ring closure through a formal 5-*Endo*-*Trigonal* process.

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).
3. Pertinent reviews: (a) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, pp. 169-176; (b) M. Shamma and J. L. Monniot, "Isoquinoline Alkaloids Research 1972-1977", Plenum Press, New York, 1978, pp. 113-116.
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).
5. F. A. Carey and R. M. Giuliano, J. Org. Chem., 46, 1366 (1981).
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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