SILICON-MEDIATED BERBINE SYNTHESIS: SYNTHESIS OF 11,12-METHYLENEDIOXY-2,3-DIMETHOXY-7,8,13,14-TETRAHYDROPROTOBERBERINE

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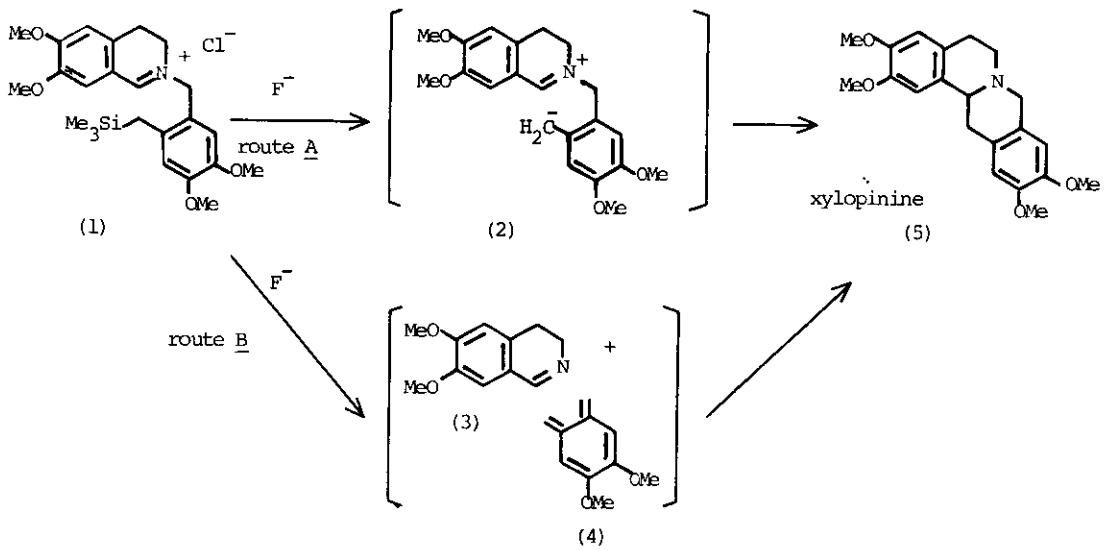
Abstract-----Silicon-mediated synthesis of 11,12-methylenedioxy-2,3-dimethoxy-7,8,13,14-tetrahydroprotoberberine (8) is described.

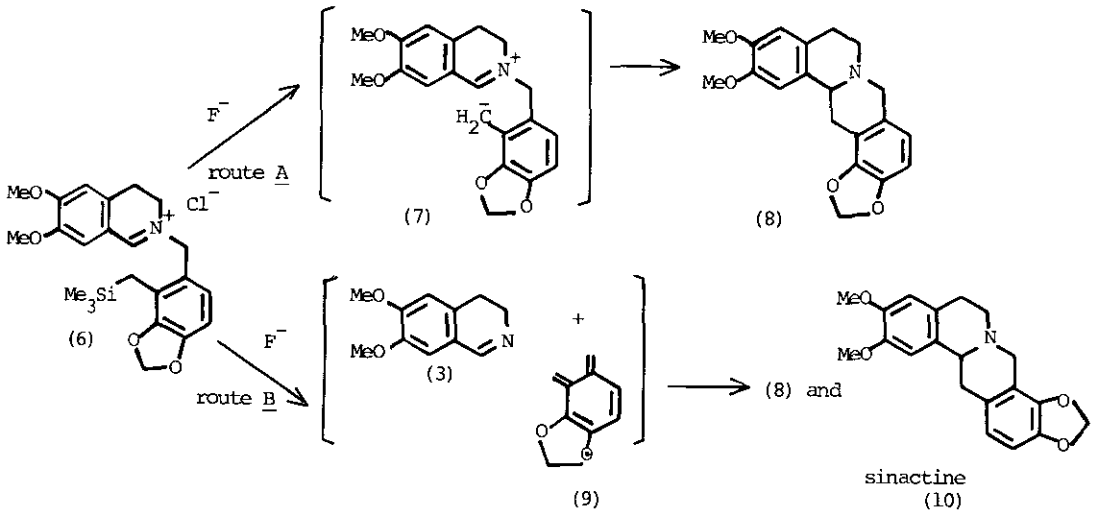
Recently we reported a novel silicon-mediated synthesis of the protoberberine alkaloid xylopinine (5) upon treatment of the 3,4-dihydroisoquinolinium salt (1) with cesium fluoride[1] (Scheme 1). The reaction was presumed to proceed intramolecularly via the betaine intermediate (2) (route A). However an alternative pathway via the elimination-cycloaddition mechanism involving the 3,4-dihydroisoquinoline (3) and the symmetrically substituted o-quinodimethane (4) (route B) could also be conceivable as both the fluoride



Scheme 1

promoted 1,4-elimination of o-[(trimethylsilyl)benzyl]ammonium salts to form o-quinodimethanes[2,3] and the intermolecular cycloaddition of 3,4-dihydroisoquinolines and o-quinodimethanes to form tetrahydroprotoberberines[4] were well-established. In this paper we describe the silicon-mediated synthesis of the

tetrahydroprotoberberine derivative by the reaction of 3,4-dihydro-6,7-dimethoxy-2-(3,4-methylenedioxy-2-trimethylsilylmethyl)benzylisoquinolinium chloride (6) with cesium fluoride in order to establish the reaction mechanism. With the salt (6), the exclusive formation of the single product (8) via the betaine (7) might be expected in the intramolecular pathway (route A), while the formation of two products, (8) and sinactine (10)[5], might be expected in the elimination-cycloaddition pathway (route B) as 3,4-dihydro-6,7-dimethoxyisoquinoline (3) and the unsymmetrically substituted o-quinodimethane (9) would be involved in the latter pathway (Scheme 2).

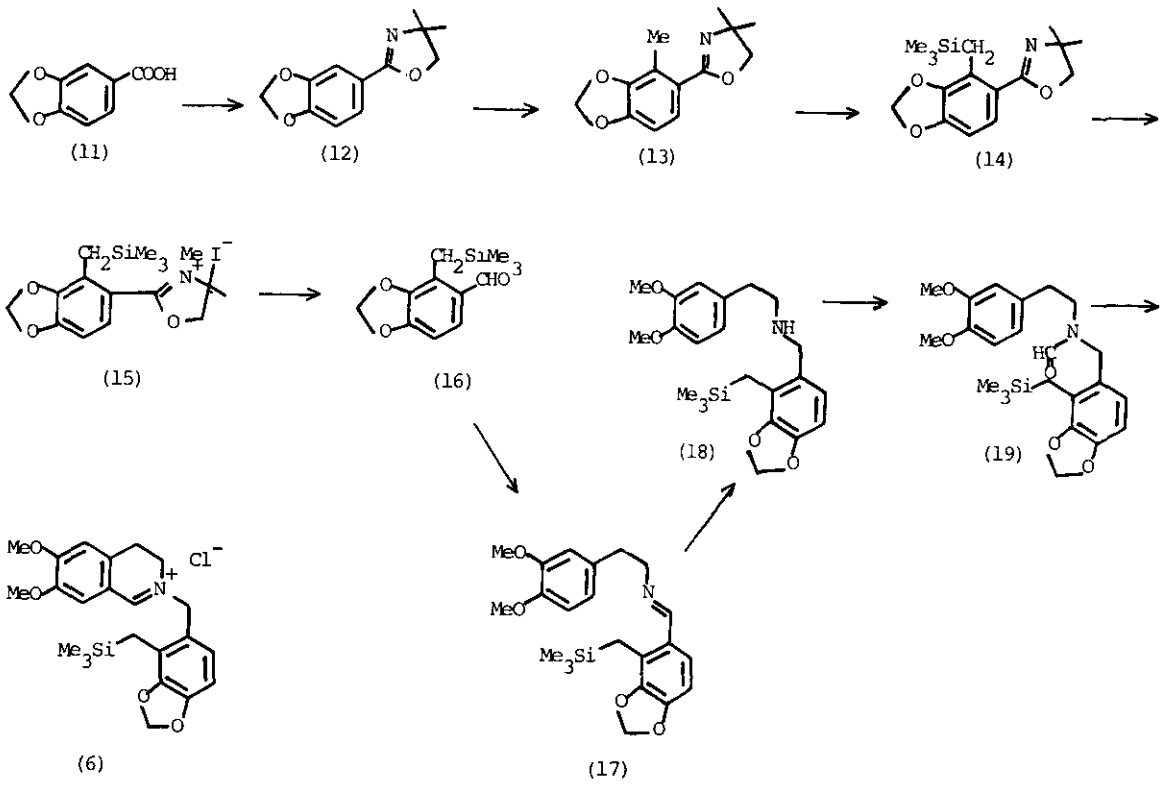


Scheme 2

Piperonic acid (11) was converted into the oxazoline derivative (12), $bp_{0.8}$ 145°C, in 88 % yield employing Meyers' procedure[6,7]. Treatment of (12) with n-butyllithium in ether at -20°C, followed by treatment with methyl iodide at -20°C ∿ room temperature[8] gave the 2-methyl derivative (13), $bp_{0.5}$ 130°C, selectively in 87 % yield. The methyl derivative (13) was then converted into the trimethylsilyl derivative (14), $bp_{0.2}$ 135°C, in 75 % yield on treatment with trimethylchlorosilane in the presence of n-butyllithium in ether at -20°C ∿ room temperature[9]. Treatment of (14) with an excess of methyl iodide at refluxing temperature gave the quaternary salt (15), mp 169-173°C, in 80 % yield, which was transformed to the aldehyde (16), bp_I 150°C, in 82 % yield upon reduction with sodium borohydride in ethanol, followed by treatment with 90 % acetic acid[10].

Condensation of the aldehyde (16) with 2-(3,4-dimethoxyphenyl)ethylamine at 60°C gave the Schiff base (17) which was immediately reduced with sodium borohydride to give the secondary amine (18) as an oil in 93 % overall yield. The amine (18) was converted into the formamide (19) as an oil in 91 % yield on treatment with acetic formic anhydride in pyridine at 80-90°C[11]. Bischler-Napieralski cyclization of the amide (19) using phosphorus oxychloride in benzene at refluxing temperature gave the crude quaternary

salt (6) which could be used for the following reaction without further purification. Thus, the crude salt (6), upon reflux with five equivalents of cesium fluoride in 90 % ethanol for 2 h, afforded the tetrahydroprotoberberine derivative[12] (8) as a glass as a sole isolable product in 77 % overall yield from the amide (19) and no trace of sinactine (10) could be detected in the reaction mixture (Scheme 3). A similar result was obtained by using potassium fluoride in place of cesium fluoride though longer reaction time was required (∿ 48h), but tetrabutylammonium fluoride[1,2] was found to be not effective. Interestingly, the use of cesium, potassium, or tetrabutylammonium fluorides not only in an aprotic solvent such as dimethylformamide, acetonitrile, or tetrahydrofuran, but in a protic solvent such as water and pure ethanol gave no fruitful result.



Scheme 3

On the basis of the above evidence, it would therefore conclude that the exclusive formation of the single product (8) can be explained in terms of the intramolecular pathway (route A), namely, initial generation of the betaine intermediate (7), followed by cyclization (Scheme 2).

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REFERENCES AND NOTES

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7. Satisfactory spectroscopic and analytical data were obtained for all new compounds: [IR ($\nu_{max}cm^{-1}$); NMR($CDCl_3$)ppm; MS(m/e)], (12): [1643; 1.33 (s, 6H), 4.03 (s, 2H), 5,90 (s, 2H) 6.75 (d, 1H), 7.40 (m, 2H); 219 (M^+) 204 (100%)], (13): [1641; 1.33 (s, 6H), 2.41 (s, 3H), 4.00 (s, 2H), 5.90 (s, 2H), 6.60 (d, 1H), 7.30 (d, 1H); 233 (M^+), 190 (100%)], (14): [1635; 1.33 (s, 6H), 2.70 (s, 2H), 4.00 (s, 2H), 5.90 (s, 2H), 6.60 (d, 1H), 7.40 (d, 1H); 305 (M^+), 290 (100%)], (15) [NMR 1.90 (s, 6H), 2.25 (s, 2H), 3.50 (s, 3H), 5.12 (s, 2H), 6.05 (s, 2H), 6.85 (d, 1H), 7.75 (d, 1H)], (16): [1670; 2.70 (s, 2H), 6.00 (s, 2H), 6.77 (d, 1H), 7.40 (d, 1H), 9.95 (s, 1H); 305 (M^+), 236 (100%)], (18): [3300; 1.25 (s, 1H), 2.12 (s, 2H), 2.90 (m, 4H), 3.70 (s, 2H), 3.90 (s, 6H), 5.90 (s, 2H), 6.5-7.0 (m, 5H); 401 (M^+), 221 (100%)], (19): [1650; 2.05 (m, 2H), 2.75 (m, 2H), 3.40 (m, 2H), 3.85 (s. 6H), 4.30 (m, 2H), 5.90 (s, 2H), 6.5-7.0 (m, 5H), 7.95 and 8.20 (s x 2, total (1H); 429 (M^+), 166 (100%)], (8): [2820, 2740; 2.20-3.80 (m, 9H), 3.80 (s, 6H), 5.85 (s, 2H), 6.50-6.70 (m, 4H); 339 (M^+), 148 (100%)].
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