Silicon-mediated Isoquinoline Alkaloid Synthesis: a Novel Route to (±)-Xylopinine and (±)-Laudanosine

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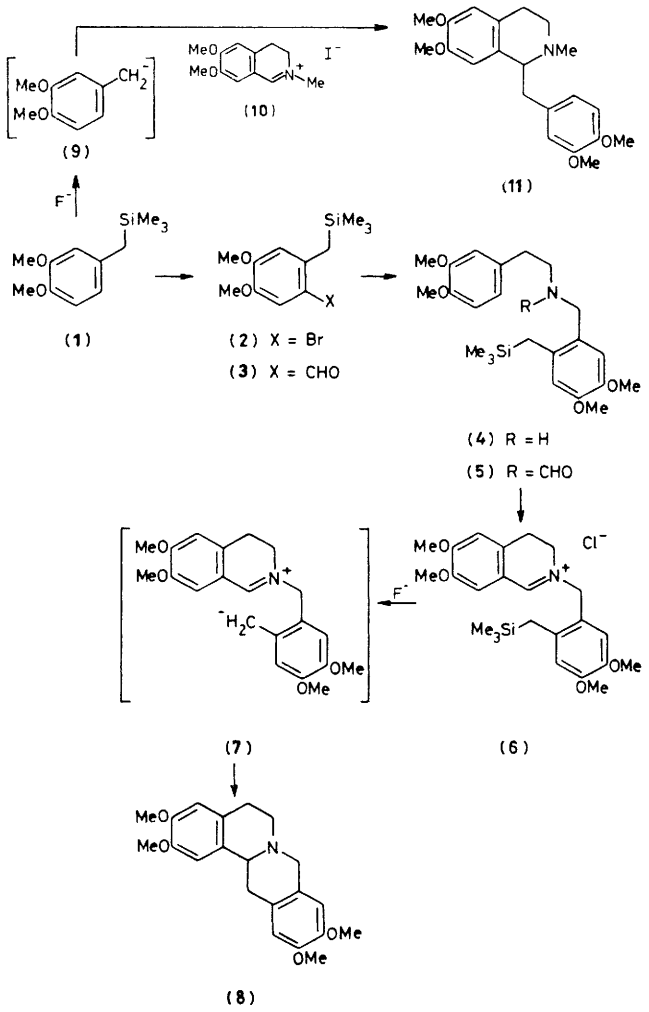
A novel synthesis of the isoquinoline alkaloids, (±)-xylopinine and (±)-laudanosine, has been developed *via* intra- and inter-molecular nucleophilic addition, respectively, of an organosilicon compound to a carbon–nitrogen double bond.

Although recent developments in organosilicon chemistry have produced many synthetically useful reactions,[1] few syntheses which include nucleophilic addition of an organosilicon compound to a carbon–nitrogen double bond have been reported so far.[2] We now describe a novel synthesis of the isoquinoline alkaloids, (±)-xylopinine (**8**) and (±)-laudanosine (**11**), which constitutes a new example of nucleophilic addition of an organosilicon compound to a carbon–nitrogen double bond.

3,4-Dimethoxybenzyltrimethylsilane (**1**),† prepared quantitatively from 3,4-dimethoxybenzyl chloride and trimethylsilyl chloride by Grignard reaction,[3] was brominated (Br_2, 1 mol. equiv.) in CH_2Cl_2 in the presence of aqueous sodium hydrogencarbonate (two phase) at 0 °C to give the 6-bromo-derivative (**2**) in 87% yield. Treatment of (**2**) with n-butyl-

† Satisfactory spectral (i.r., ^{1}H-n.m.r., m.s.) and analytical data have been obtained for all new compounds.



lithium (1 mol. equiv., THF) at −78 °C (THF = tetrahydrofuran), followed by *N*,*N*′-dimethylformamide (DMF) at the same temperature, furnished the benzaldehyde (**3**) in 93% yield. The benzaldehyde (**3**), on treatment with 2-(3,4-dimethoxyphenyl)ethylamine, followed by reduction with sodium borohydride, afforded the secondary amine (**4**) in 91% overall yield. The amine (**4**) was then converted into the formamide (**5**) in quantitative yield by treatment with acetic formic anhydride.[4]

On Bischler–Napieralski reaction ($POCl_3$, benzene, reflux), (**5**) gave the 3,4-dihydroisoquinolinium salt (**6**) quantitatively with the silyl group intact. The trimethylsilyl group was unexpectedly inert to fluoride anion and showed almost no change when (**6**) was subjected to 1,4-elimination reaction conditions (tetrabutylammonium fluoride[5] or caesium fluoride[6] in an aprotic solvent such as CH_2Cl_2, THF, or MeCN). However, it underwent intramolecular cyclisation to give a 70% yield of (±)-xylopinine (**8**),‡§ presumably *via* the betaine intermediate (**7**), upon treatment with an excess of caesium fluoride (5 mol. equiv.)¶ in 90% ethanol at reflux temperature (12 h). No cyclisation occurred in an aprotic solvent such as CH_2Cl_2, THF, or acetonitrile.

An intermolecular version of this silicon-mediated addition also took place and gave a 1-benzylisoquinoline, though in poor yield, under more forcing conditions. Thus, treatment of (**1**) with 3,4-dihydro-7,8-dimethoxy-1-methylisoquinolinium iodide (**10**) in DMF at reflux temperature in the presence of caesium fluoride gave (±)-laudanosine (**11**)‡ in 4% yield. No addition occurred when EtOH replaced DMF as solvent.

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‡ Identical in all respects (t.l.c., i.r., ^{1}H-n.m.r., m.s.) with the authentic material.

§ A compound with a non-natural substitution pattern, 11,12-methylenedioxy-2,3-dimethoxy-7,8,13,14-tetrahydroprotoberberine, could be prepared similarly in comparable yield as a single product from the corresponding precursor. This eliminates an intermolecular cycloaddition mechanism between a 3,4-dihydroisoquinoline and an *o*-xylylene both formed *via* a fluoride-promoted 1,4-elimination: *cf.* T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *J. Org. Chem.*, 1974, **39**, 447.

¶ Potassium fluoride also initiated the intramolecular cyclisation and gave comparable yields, though a longer reaction time was required.