Synthesis of Naucléfine, Angustidine, Angustine, and (±)-13b,14-Dihydroangustine

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2,9-Bis-(trimethylsilyl)-3,4-dihydropyrido[3,4-*b*]indolium trifluoromethanesulphonate reacts with the lithio derivatives of 3-cyano-4-methylpyridines to generate pentacyclic amidines which, upon hydrolysis and oxidation, produce naucléfine, angustine, and angustidine.

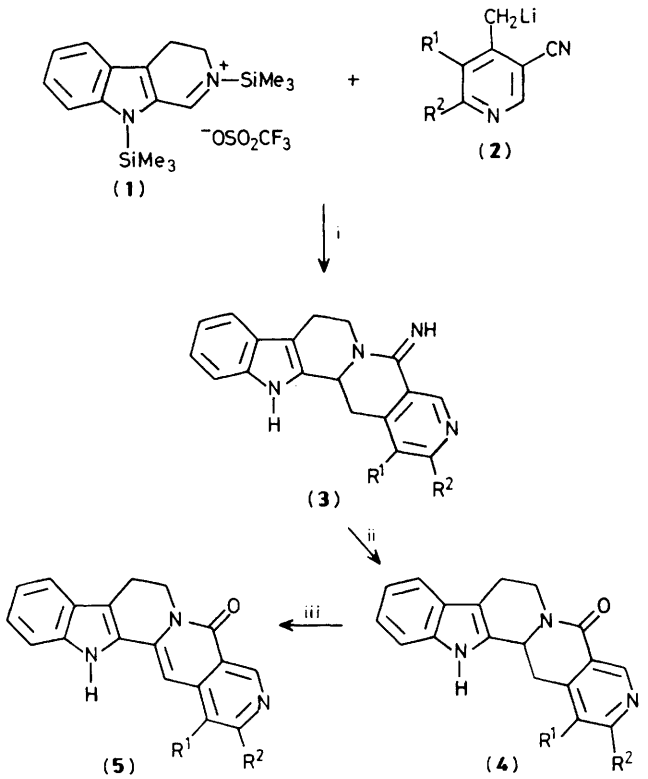
Species of the genera *Strychnos* L., *Nauclea* L., *Mitragyna* Korth, and *Uncaria* Schreb have proven to be rich sources of alkaloids.[1,2] Among the structural subtypes, the indolo-[2′:3′,3:4]pyrido[1,2-*b*]naphthyridine system is an attractive target for synthesis. A number of difficulties have been encountered in previous preparations of naucléfine (**5a**)[3—5] and angustine (**5b**)[4,6] including lengthy, low-yield syntheses, an inability to obtain the 13b,14-dihydro compounds directly, and the lack of regiospecficity with regard to the pyridine nitrogen.

We have previously demonstrated the production of oxoberbines by condensation of lithiated toluamides and cyclic imines,[7] and the utility of trimethylsilyl iminium trifluoromethanesulphonates (triflate) for the synthesis of the Alangium alkaloids, alamaridine,[8] alangimaridine, and alangimarine.[9] The application of this latter methodology to the synthesis of the *N*-benzyl derivatives of 13b,14-dihydroangustine and 13b,14-dihydronaucléfine has also been reported.[9,10] However, removal of the benzyl protecting group under conditions which would not compromise the integrity of the molecules could not be accomplished.[11] Neither the parent 3,4-dihydro-β-carboline, nor its 9-lithio derivative, would undergo condensation with lithiated 3-cyano-4-methylpyridine (**2a**) or lithiated 3-cyano-4-methyl-5-vinylpyridine (**2b**).[10]

These problems have been overcome through the use of the bis-trimethylsilyl species (**1**). Thus, treatment of 3,4-dihydro-β-carboline at low temperature first with n-butyl-lithium (1 equiv.), then with trimethylsilyl trifluoromethane sulphonate (2 equiv.) generated the Me_3Si-protected, triflate-activated imine (**1**). Addition of a cold (−65 °C) solution of the red [(**2b**)] or yellow [(**2a** or **c**)] lithio species to a suspension of (**1**) led to a rapid decolourization, which, when followed by aqueous work-up, gave the de-protected pentacyclic amidines (**3a—c**). Hydrolysis of (**3b**) produced the natural product 13b,14-dihydroangustine (**4b**).[2†] The three lactams (**4a—c**) were then oxidised to the alkaloids naucléfine (**5a**), angustine (**5b**), and angustidine (**5c**), respectively,† using iodine in refluxing methanol.[9]

The amidine (**3c**) was obtained in low yield (11%). This can probably be attributed to equally favourable complexation of lithium with the 6-methyl group in (**2c**) as well as with the 4-methyl group. Indeed, quenching of the lithio derivative of 3-cyano-4,6-dimethyl-pyridine with D_2O produced a 1:1 mixture of the 4- and 6-deuteriomethyl isomers. This behav-

† N.m.r. and mass spectral data for (**4b**) and (**5a—c**) were identical to those reported in the literature.



a; $R^1 = R^2 = H$
b; $R^1 = CH{=}CH_2$, $R^2 = H$
c; $R^1 = H$, $R^2 = Me$

Scheme 1. *Reagents and conditions*: i, tetrahydrofuran, −65 °C, 5 min; ii, 20% KOH, H_2O–dioxane, reflux, 24—48 h; iii, I_2, MeOH, reflux, 15 h. (**3a**) m.p. 264—266 °C, 78%; (**3b**) m.p. 282—284 °C, 63%; (**3c**) m.p. 247—248 °C, 11%; (**4a**) m.p. 266—268 °C, 89%; (**4b**) m.p. 305—306 °C, 93%; (**4c**) m.p. 288—289 °C, 88%; (**5a**) m.p. 288—292 °C (lit.,[4] m.p. 285—290 °C), 91%; (**5b**) softens at 290 °C, m.p. >350 °C (lit.,[4] m.p. >300 °C, lit.,[1b] m.p. 283—284 °C, lit.,[1c] m.p. >340 °C), 94%; (**5c**) m.p. >350 °C. (lit.,[1c] m.p. 309—311 °C, lit.,[6] m.p. 300 °C), 95%.

iour has been previously noted upon metallation of 2,4-lutidine and its derivatives.[12]

This reaction sequence provides regiochemical control with respect to the pyridine nitrogen and offers flexibility with regard to the position and type of functionality which could be introduced on the pyridine or indole rings.

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References

1 (a) R. F. Raffauf, 'A Handbook of Alkaloids and Alkaloid-containing Plants,' Wiley, New York, 1970; (b) J. D. Phillipson, S. R. Hemingway, N. G. Bisset, P. J. Houghton, and E. J. Shellard, *Phytochemistry*, 1974, **13**, 973; (c) T. Y. Au, H. T. Cheung, and S. Sternhell, *J. Chem. Soc., Perkin Trans. 1*, 1973, 13; (d) F. Hotellier, P. Delaveau, and J.-L. Pousset, *Phytochemistry*, 1975, **14**, 1407; (e) M. Sainsbury and B. Webb, *ibid.*, 2691.
2 M. Zeches, B. Richard, L. Gueye-M'Bahia, L. Le Men-Olivier, and C. DeLaude, *J. Natural Prod.*, 1985, **48**, 42.
3 M. Sainsbury and N. L. Uttley, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2416; M. Sainsbury and N. L. Uttley, *ibid.*, 1977, 2109.
4 T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1976, **41**, 2542.
5 M. J. Wanner, G. J. Koomen, and U. K. Pandit, *Tetrahedron*, 1983, **39**, 3673; T. Naito, O. Miyata, and I. Ninomiya, *J. Chem. Soc., Chem. Commun.*, 1979, 517.
6 A. Shafiee and E. Winterfeldt, *Chem. Ber.*, 1974, **107**, 966.
7 R. D. Clark, *Heterocycles*, 1985, **23**, 825; R. D. Clark and Jahangir, *J. Org. Chem.*, 1987, **52**, 5378.
8 Jahangir, D. B. MacLean, and H. L. Holland, *Can. J. Chem.*, 1987, **65**, 727.
9 Jahangir, D. B. MacLean, M. A. Brook, and H. L. Holland, *J. Chem. Soc., Chem. Commun.*, 1986, 1608.
10 Jahangir, M. A. Brook, D. B. MacLean, and H. L. Holland, *Tetrahedron*, 1988, in the press.
11 D. B. Repke, unpublished results.
12 R. Levine, D. A. Dimmig, and W. M. Kadunce, *J. Org. Chem.*, 1974, **39**, 3834; E. M. Kaiser, G. J. Bartlung, W. R. Thomas, S. B. Nichols, and D. R. Nash, *ibid.*, 1973, **38**, 71; O. Compagnon and P.-L. Compagnon, *Bull. Soc. Chim. Fr.*, 1973, 3381.