Regioselective Syntheses of the Indolopyridine Alkaloids Nauclefine, Angustine, Dihydroangustine and Naucletine from a Common Intermediate

Rodolfo Lavilla,* Francisco Gullón and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain

A short, flexible route for the synthesis of the title indolopyridine alkaloids consisting of the cyclization of enamide **3**, followed by introduction of the requisite pyridine substituent by Pd^0-catalysed reactions from the resulting pentacyclic bromo intermediate **4** is reported.

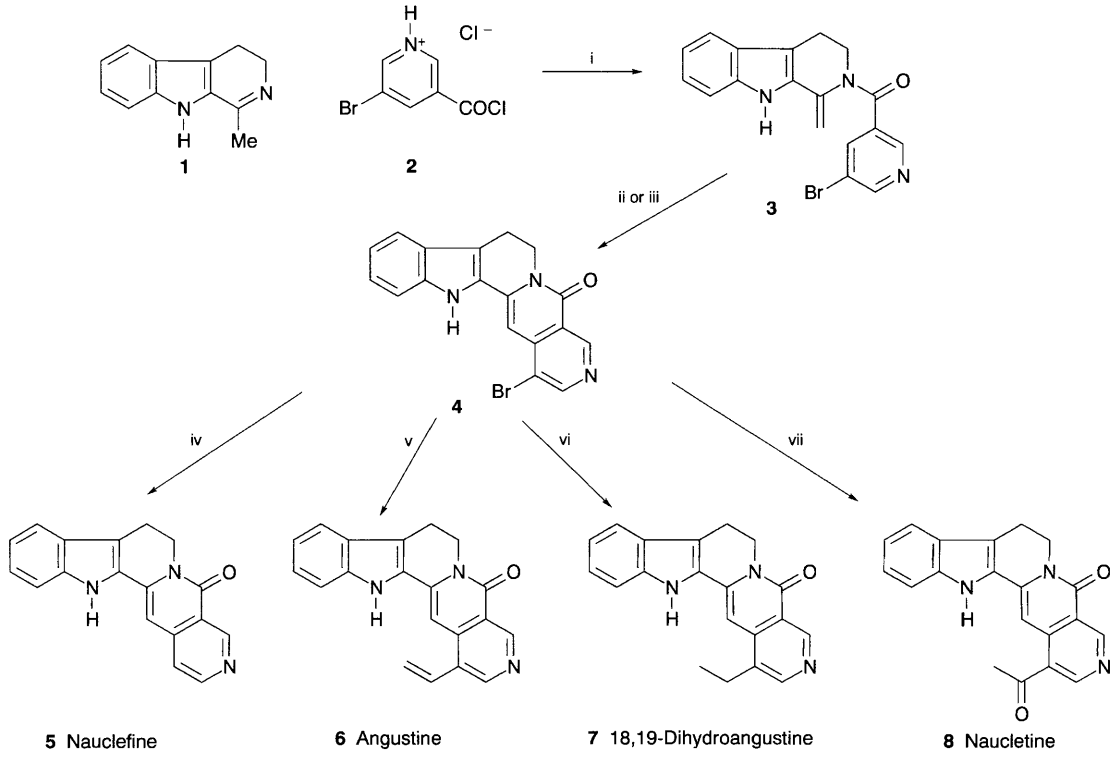
Nauclefine **5**, angustine **6** and naucletine **8** belong to the Vallesiachotaman class of monoterpenoid indole alkaloids,[1] and their biogenesis seems to involve the intermediacy of strictosidine and strictosamide.[2] 18,19-Dihydroangustine **7** is a synthetic product prepared in the context of the structural elucidation of angustine.[3]

Continuing our studies on nucleophilic additions to *N*-acylpyridinium salts,[4] we present herein a new and general synthetic entry to this group of indolopyridine alkaloids, which involves the cyclization of a pyridine-enamide and subsequent transformations of a common pentacyclic intermediate **4**. Thus, condensation of harmalan **1** with 3-bromonicotinoyl chloride hydrochloride **2** (prepared from the corresponding acid by oxalyl chloride treatment) afforded enamide **3**† in good yield. Treatment of this compound with acetyl chloride gave **4**‡ directly in 42% yield through a sequence involving an intramolecular nucleophilic addition of the enamide moiety of the γ-position of the *in situ* formed *N*-acyl-3,5-disubstituted pyridinium cation,[5] followed by oxidation of the resulting 1,4-dihydropyridine. Photochemical, acid, or TFAA induced cyclizations were ineffective,[6] but thermal cyclization improved the yield to 83%. Note that the above cyclizations are highly regioselective; the undesired regioisomer arising from reaction at the pyridine α-position was not detected.

The bromine atom in **4** was replaced by a hydrogen atom by a chemoselective, catalytic, palladium-mediated reduction using sodium methoxide as the hydrogen donor (Helquist method).[7] In this manner, nauclefine **5**[8,9] was obtained regioselectively from a more substituted pyridine precursor. The preparation of angustine **6**[3,10] from **4** was effected by a Stille coupling with tributylvinyltin catalysed by palladium(0).[11] The synthesis of 18,19-dihydroangustine **7**[12] was performed in a similar way using tetraethyltin. Finally, naucletine **8**[8,13]§ was prepared in 23% yield through a palladium-catalysed carbonylative coupling of bromide **4** with tetramethyltin[14] in 23% yield. This also constitutes a formal synthesis of (±)-angustoline.[13] The natural products prepared here showed spectroscopic data in accordance with those reported in the literature, and a direct, confirmatory comparison (TLC behaviour and NMR spectra) with authentic samples was made with angustine and nauclefine. The above results show the usefulness of this approach and expand the scope of the nucleophilic additions to pyridinium salts. Further studies on the synthesis of more complex indolopyridine alkaloids using this flexible route are under way.

We are grateful to Dr D. B. Repke (Syntex) for samples of angustine and nauclefine. Professor J. M. Moretó (CSIC, Barcelona) is thanked for the use of equipment and useful comments. Financial support from the DGICYT, Spain (project PB91-0800) and the 'Commissionat per a Universitats i Recerca' (Generalitat de Catalunya) through grant GRQ93-1.059 is gratefully acknowledged.

Received, 13th June 1995; Com. 5/03827H



Scheme 1 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, reflux, 84%; ii, MeCOCl, CH_2Cl_2, reflux, 5 h, 42%; iii, 180 °C, 0.1 mmHg, 15 min, 83%; iv, NaOMe, $Pd(PPh_3)_4$, DMF, 100 °C, 96%; v, CH_2=CH-$SnBu_3$, $Pd(PPh_3)_4$, toluene, DMF, 100 °C, 95%; vi, Et_4Sn, $Pd(PPh_3)_4$, HMPA, 100 °C, 87%; vii, CO (80 psi), Me_4Sn, $Pd(PPh_3)_4$, HMPA, LiCl, 75 °C, 23%

Footnotes

† All new compounds gave satisfactory analytical and spectral data. All yields are from material purified by flash chromatography.

‡ *Selected sepctral data* for **4**: ^{1}H NMR [$(CD_3)_2SO$, 300 MHz; *J*/Hz] δ 12.00 (s, 1H), 9.22 (s, 1H), 8.86 (s, 1H), 7.63 (d, *J* 8.0, 1H), 7.46 (d, *J* 8.2, 1H), 7.27 (m, *J* 8.2, 8.0, 1.2, 1H), 7.13 (s, 1H), 7.09 (m, *J* 8.2, 8.0, 1.0, 1H), 4.39 (t, *J* 6.7, 2H), 3.12 (t, *J* 6.7, 2H); ^{13}C NMR [$(CD_3)_2SO$, 75.5 MHz) δ 160.5, 152.3, 149.6, 141.1, 138.9, 138.7, 127.4, 125.3, 124.9, 120.6, 120.1, 120.0, 116.9, 115.8, 112.2, 95.4, 40.7, 38.9.

§ *Selected spectral data* for **8**: ^{1}H NMR [$(CD_3)_2SO$, 300 MHz; *J*/Hz] δ 11.9 (s, 1H), 9.41 (s, 1H), 9.21 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J* 8.0, 1H), 7.45 (d, *J* 8.1, 1H), 7.23 (m, 1H), 7.07 (m, 1H), 4.39 (t, *J* 6.9, 2H), 3.12 (t, *J* 6.9, 2H), 2.71 (s, 3H).

References

1 M. V. Kisakürek, A. J. M. Leeuwenberg and M. Hesse, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Wiley, New York, 1983, vol. 1, ch. 5.

2 M. Lounasmaa and A. Tolvanen, in *Indoles, Monoterpenoid Indole Alkaloids*, ed. J. E. Saxton, in *The Chemistry of Heterocyclic Compounds, ed. E. C. Taylor, Wiley, Chichester, 1994, vol. 25, suppl. to part 4, ch. 3.*

3 T. Y. Au, H. T. Cheung and S. Sternhell, *J. Chem. Soc., Perkin Trans. 1*, 1973, 13.

4 R. Lavilla, T. Gotsens, M. Guerrero and J. Bosch, *Synthesis,* 1995, 382.

5 For nucleophilic additions to 3,5-disubstituted pyridinium salts, see: R. Lavilla, T. Gotsens, S. Rodríguez and J. Bosch, *Tetrahedron*, 1992, **48**, 6445.

6 J. Laronze, J. Y. Laronze, M. Garnier, C. Trentesaux and J. Lévy, *Bull. Soc. Chim. Fr.*, 1992, **129**, 303 and references cited therein.

7 A. Zask and P. Helquist, *J. Org. Chem.*, 1978, **43**, 1619.

8 F. Hotellier, P. Delaveau and J.-L. Pousset, *Phytochemistry*, 1975, **14**, 1407.

9 For previous syntheses of this alkaloid, see: R. Vohra and D. B. MacLean, *Heterocycles*, 1994, **39**, 445 and references cited therein.

10 D. B. Repke, Jahangir, R. D. Clark, J. T. Nelson and D. B. MacLean, *Tetrahedron*, 1989, **45**, 2541.

11 D. R. McKean, G. Parrinello, A. F. Renaldo and J. K. Stille, *J. Org. Chem.*, 1987, **52**, 422.

12 For a previous synthesis, see: A. Shafiee and E. Winterfeldt, *Synthesis*, 1974, 185.

13 For a previous synthesis, see: I. Ninomiya, T. Naito and H. Takasugi, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1865.

14 G. T. Crisp, W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1984, **106**, 7500.