Pergamon

Tetrahedron Letters 39 (1998) 679–680

TETRAHEDRON LETTERS

Synthesis of Isobatzelline B

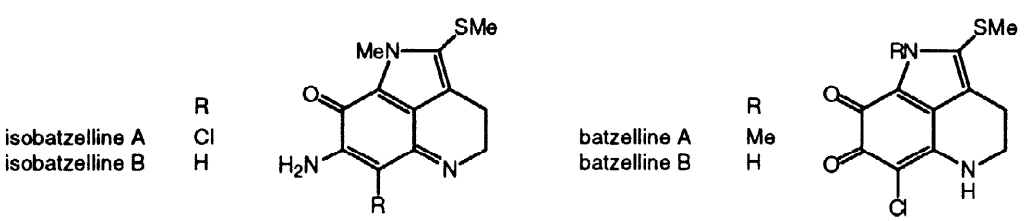
Mercedes Alvarez,[a]* M. Antonieta Bros,[a] and John A. Joule[b]*

a Laboratorio de Química Orgánica, Facultad de Farmacia, Universidad de Barcelona, 08028 Barcelona, Spain.
b Chemistry Department, University of Manchester, Manchester M13 9PL, U. K.

Received 31 October 1997; accepted 7 November 1997

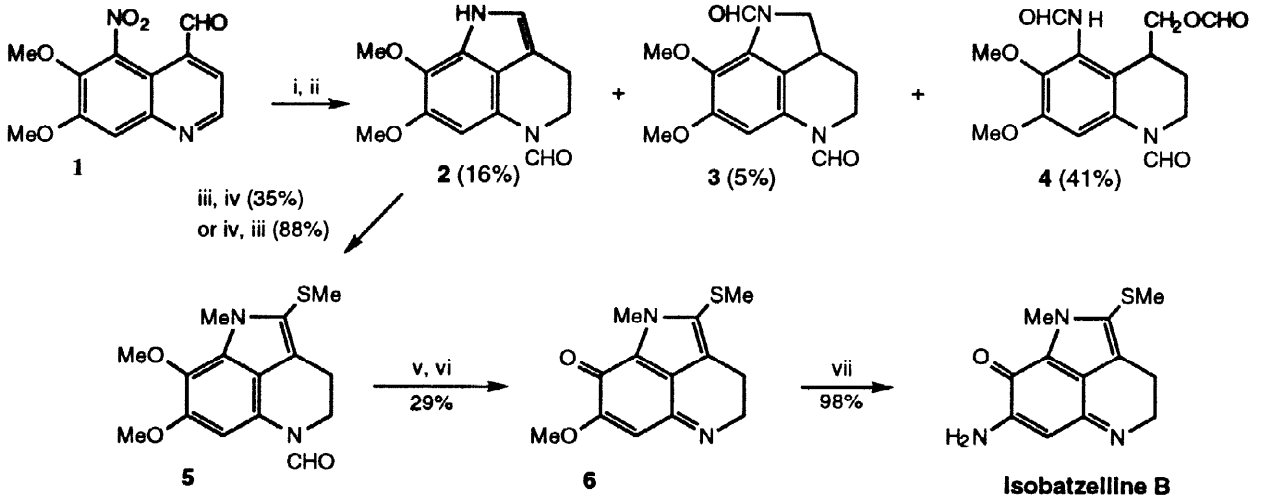
Abstract: **6,7-Dimethoxy-4-methylquinoline has been converted in nine steps into the sulfur-containing pyrrolo[4,3,2-*de*]quinoline marine alkaloid isobatzelline B. This constitutes the first total synthesis of an alkaloid of the group which contains a methylthio substituent.**

A group of marine alkaloids – batzellines,[1] isobatzellines,[2] damirones,[3] wakayin,[4] and the makaluvamines[5] – share a common 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus, and many possess biological activity.[5,6] A small subset of the tetrahydropyrrolo[4,3,2-*de*]quinoline alkaloids contain sulfur substituents on the pyrrole ring: batzellines A and B and isobatzellines A and B. We have developed[7] a synthetic approach to compounds containing the nucleus which is based on the manipulation of simple quinoline starting materials and here describe its use for the first total synthesis of one of the group which contains a sulfur substituent.



We have described the low temperature, selective 5-mononitration of 6,7-dimethoxy-4-methylquinoline and the oxidation of the product to the 4-aldehyde **1**.[7] Exposure of this to a large excess of a combination of sodium borohydride and nickel(II) chloride gave three products, the desired tricyclic formamide **2** together with over-reduced **3** and the tetrahydroquinoline **4**. The key step in the synthesis of isobatzelline B was the formation of **5**[8] by introduction of the methylthio group regioselectively at the pyrrole α-position *i.e.* not on the electron-rich benzene ring. For this we used $MeSSMe/SO_2Cl_2$, a combination which generates MeSCl *in situ* for the electrophilic substitution of the indole.[9] This step could be carried out either before or after indole-*N*-methylation. Hydrolysis of the formamide and then ceric ammonium nitrate (CAN) oxidation gave the quinone-imine **6**[10] and replacement of the methoxyl with amino was achieved quantitatively with ammonium chloride in methanol in a sealed tube at 50 °C to give material with spectroscopic properties identical to those reported.[2]

0040-4039/98/$19.00
PII: S0040-4039(97)10591-3



Reagents: i, 80xNaBH$_4$, 13xNiCl$_2$.6H$_2$O, MeOH, rt; ii, HCO$_2$H, Ac$_2$O, rt; iii, MeSSMe, SO$_2$Cl$_2$, CH$_2$Cl$_2$, 0 °C to rt; iv, NaH, MeI, THF, rt; v, 2.5M aq.NaOH, reflux; vi, CAN, MeCN, H$_2$O, rt; vii, NH$_4$Cl, MeOH, 50 °C, sealed tube.

ACKNOWLEDGEMENTS

We thank for generous support CIRIT (Generalitat de Catalunya) (Grant QFN 95-4701), Comissionat per a Universitats i Recerca (Generalitat de Catalunya) (Grant 95-SGR00429), and CIRIT for a fellowship (AB).

REFERENCES AND SPECTROSCOPIC DATA

1 Sakemi, S.; Sun, H. H.; Jefford, C. W.; Bernadinelli, G., *Tetrahedron Lett.*, **1989**, *30*, 2517.

2 Sun, H. H.; Sakemi, S.; Burres, N.; McCarthy, P., *J. Org. Chem.*, **1990**, *55*, 4964.

3 Stierle, D. B.; Faulkner, D. J., *J. Nat. Prod.*, **1991**, *54*, 1131.

4 Copp, B. R.; Ireland, C. M.; Barrows, L. R., *J. Org. Chem.*, **1991**, *56*, 4596.

5 Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M., *J. Am. Chem. Soc.*, **1993**, *115*, 1632; Barrows, L. R.; Radisky, D. C.; Copp, B. R.; Swaffer, D. S.; Kramer, R. A.; Warters, R. C.; Ireland, C. M., *Anti-Cancer Drug Design*, **1993**, *8*, 333.

6 Wang, H.; Al-Said, N. H.; Lown, J. W., *Tetrahedron Lett.*, **1994**, *35*, 4085.

7 Roberts, D; Joule, J. A.; Bros, M. A.; Alvarez, M., *J. Org. Chem.*, **1997**, *62*, 568.

8 Spectroscopic data for **5**: IR (film): 1679 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 200 MHz): 2.27 (s, 3H); 2.88 and 2.96 (2xt, *J*= 5.8 Hz, 2H); 3.92 and 3.93 (2xs, 3H); 3.93 and 3.94 (2xs, 3H); 4.01 (s, 3H); 4.05 (t, *J*= 5.8Hz, 2H); 6.58 and 6.60 (2xs, 1H); 8.87 and 8.89 (2xs, 1H); ^{13}C-RMN (CDCl$_3$, 75MHz): 20.0 (q); 31.4 (q); 39.8 and 40.2 (2xt); 46.6 and 47.2 (2xt); 57.6 and 58.2 (2xq); 61.9 (q); 94.1 and 94.6 (2xd); 115.1 (s); 116.2 (s); 125.9 (s); 126.7 (s); 130.0 (s); 133.1 (s); 149.9 (s); 160.1 and 161.6 (2xd); EIMS: 306 (M$^+$, 100); 291 (91); 279 (41); Found M$^+$ 306.1039. $C_{15}H_{18}N_2O_3S$ requires *M* 306.1038.

9 Tupper, D. E.; Pullar, I. A. ; Clemens, J. A.; Fairhurst, J.; Risius, F. C.; Timms, G. H.; Wedley, S., *J. Med. Chem.*, **1993**, *36*, 912.

10 Spectroscopic data for **6**: IR (film): 1674, 1644 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz): 2.39 (s, 3H); 3.10 (t, *J*= 8.0 Hz, 2H); 4.00 (s, 3H); 4.04 (s, 3H); 4.19 (t, *J*= 8.0 Hz, 2H); 6.61 (s, 1H); ^{13}C-NMR (CDCl$_3$, 50 MHz): 17.4 (t,); 17.7 (q); 32.5 (q); 43.4 (t); 57.5 (q); 96.7 (d); 104.5 (s); 110.8 (s); 112.5 (s); 121.6 (s); 141.3 (s); 163.5 (s); 169.4 (s); EIMS: 262 (M$^+$, 15); 249 (13); 231 (10); 219 (10); Found M$^+$ 262.0765. $C_{13}H_{14}N_2O_2S$ requires *M* 262.0776.