Tetrahedron Letters, Vol.31, No.20, pp 2883-2884, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

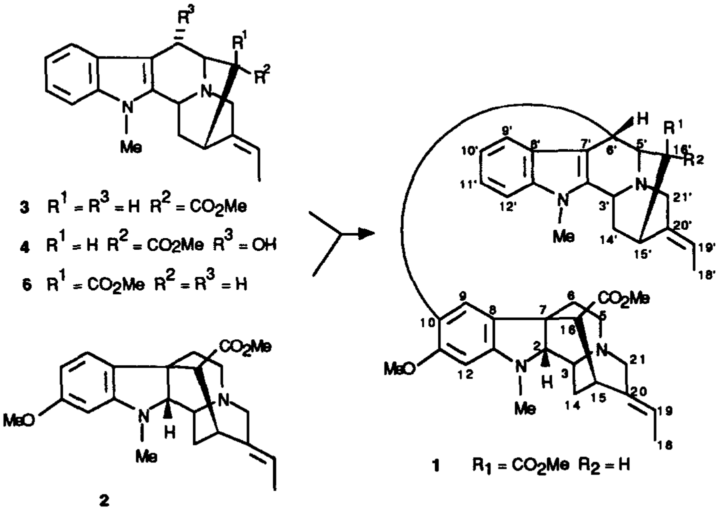
ALTERNATIVE PARTIAL SYNTHESIS OF BISINDOLE ALKALOIDS

G. MASSIOT, J.M. NUZILLARD, B. RICHARD and L. LE MEN-OLIVIER

Laboratoire de Pharmacognosie, U.F.R. de Pharmacie, associé au C.N.R.S.
51 rue Cognacq-Jay, 51096 REIMS

Abstract : Indoline derivatives of the pericyclivine series are oxidized at position 6 with DDQ ; the corresponding alcohols are coupled with nucleophilic indolines under acid conditions to yield dimers similar to undulatine.

Bisindole alkaloids are usually made by condensation of electron rich partners with carbenium ions and these processes commonly involve C-10 of 11-methoxy dihydroindoles as nucleophiles and *inter alia* positions-2, -3 or -16 when a positive charge may receive some sort of stabilization by a nearby nitrogen atom. Recent isolation of undulatine 1, which is a novel bisindole alkaloid with a C-10 to C-6' bond[1], and the known possible generation of carbenium ions at position 6 of indoles by means of DDQ[2], suggested a preparation of 1 (or analogues) using DDQ as a coupling agent.



3 $R^1 = R^3 = H$ $R^2 = CO_2Me$

4 $R^1 = H$ $R^2 = CO_2Me$ $R^3 = OH$

6 $R^1 = CO_2Me$ $R^2 = R^3 = H$

2

1 $R_1 = CO_2Me$ $R_2 = H$

5 $R_1 = H$ $R_2 = CO_2Me$

Initial attempts at inducing a coupling between cabucraline 2 and pericyclivine derivative 3 were thwarted by the aggressive behaviour of DDQ towards both partners of the reaction. Use of the reagent was however made possible, by running the reaction in two steps. Treatment of 3 with a molar equivalent of DDQ in dry THF (30 minutes, room temperature, followed by aqueous work-up) gave the 6-hydroxy derivative 4 (86%), whose structure was determined by high field ^{1}H NMR and mass spectroscopy[3]. Attack of the hydroxyl from the *exo* face is demonstrated by the low value (1.9 Hz) of the H-5 to H-6 vicinal coupling constant, which is quite different from the 8.3 Hz values of the *endo* derivative[4]. Reflux of 4 with cabucraline 2 in 2N ethanolic hydrogen chloride allows isolation of a single bisindole 5 in 38% isolated yield[5]. The mass spectrum of 5 is dominated by a molecular ion at m/z 702, accompanied by a peak at m/z 716 due to transmethylation. The aromatic part of the ^{1}H NMR spectrum of 5 shows signals for six protons, one of them is a singlet at d 6.22 ppm (H-12), and another one appears as two singlets featuring H-9 (d = 6.4 and 6.5 ppm) because of atropoisomerism. The ^{13}C NMR spectrum of 5, totally assigned by means of HMQC[6] and HMBC[7] experiments, fully supports the proposed structure ; worthy of note, in the HMBC experiment, are the correlations observed between protons of one moiety and carbon atoms of the other (i.e. H-9-->C-6' ; H-6'-->C-9 + C-10 + C-11 ; H-5'-->C-10). Proton H-6' appears as a broad singlet at δ 4.18 ppm ($W_{1/2}$ = 2 Hz) indicating attack of the nucleophile from the less hindered α-face.

Preparation of undulatine itself awaits isolation or preparation of the requisite monomer, N-methyl pericyclivine 6. This new scheme for the synthesis of "dimers", somewhat different from existing methodology, opens the way for the preparation of heretofore unknown and intriguing trimeric indole alkaloids.

References and notes

1- Nuzillard, J.M. ; Pinchon, T.M. ; Caron, C. ; Massiot, G. ; Le Men-Olivier, L. *C.R. Acad. Sc. Paris*, Série II, **1989**, *309*, 195-198.

2- Oikawa, Y. ; Yonemitsu, O. *J. Org. Chem.*, **1977**, *42*, 1213-1216.

3- $[\alpha]_D$ = - 38° (c = 0.5, CHCl$_3$) ; mass spectrum (EI, 70 ev) : m/e : 352, 335, 293, 198, 183 ; IR (CHCl$_3$ film) υ cm^{-1} : 3250, 2940, 1745, 1610, 1580, 1560 ; UV λ max (MeOH) nm : 223, 282, 291 ^{1}H NMR (CDCl$_3$, 300 MHz) : δ 1.55 (dt, J = 10, 1.5 Hz, H-14), 1.6 (d, J = 6 Hz, H-18), 1.9 (bt, J = 10 Hz, H-14), 2.3 (d, J = 7 Hz, H-16), 3.15 (s, N-CH$_3$), 3.2 (dd, J = 1, 1.5 Hz, H-15), 3.6 (dd, J = 7.2, 1.9 Hz, H-5), 3.65 (s, H-21), 3.8 (dd, J = 9, 1.5 Hz, H-3), 4.7 (d, J = 1.9 Hz, H-6), 5.3 (q, J = 6 Hz, H-19), 7.1-7.3 (m, 3 H), 7.7 (d, J = 7 Hz, 1 H).

4- Morfaux, A.M. ; Guillaume, D. ; Massiot, G. ; Le Men-Olivier, L. *C.R. Acad. Sc. Paris*, Série II, **1989**, *309*, 33-36.

5- $[\alpha]_D$ = - 31° (c = 0.3, CHCl$_3$) ; MS (EI, 70 ev) : m/e : 716 (M$^+$ + 14), 702 (M$^+$), 349, 335 ; IR (CHCl$_3$ film) : 2980, 1740, 1620 cm^{-1} ; UV λ max (MeOH) : 257, 289 ; ^{1}H NMR (CDCl$_3$, 300 MHz) : 6.5, 6.4 (2s, H-9), 6.22 (s, H-12), 5.48 (q, J = 7 Hz, H-19'), 5.28 (q, J = 7 Hz, H-19'), 4.49 (d, J = 3 Hz, H-3), 3.95 (s, OMe), 3.67 (s, N-Me), 3.66 (s, OMe), 2.95 (s, OMe), 2.7 (s, NMe), 1.55 (d, J = 7 Hz, CH$_3$-18'), 1.4 (d, J = 7 Hz, CH$_3$-18) ; ^{13}C NMR (CDCl$_3$, 75 MHz) : 173 (C-17'), 171 (C-17), 156 (C-11), 151 (C-13), 140 (C-2'), 136.5 (C-13'), 134.5 (C-20'), 130 (C-20), 128.5 (C-8), 127 (C-8'), 124 (C-10 + C-19), 122 (C-9), 120 (C-11'), 118.5 (C-12'), 118 (C-10'), 115 (C-19'), 107.5 (C-9'), 105 (C-7'), 94 (C-12), 77 (C-2), 58.5 (C-5'), 56 (C-21'), 55.5 (OMe), 53 (C-21), 52 (CO$_2$Me), 51 (C-16 + CO$_2$Me), 50 (C-5), 48.5 (C-3'), 48 (C-16'), 47.5 (C-3), 41 (C-7), 38 (C-6'), 34 (N-Me), 33 (C-15), 32 (C-14'), 31 (C-14), 29 (C-15' + N-Me), 27 (C-6), 13 (C-18), 12.5 (C-18').

6- Bax, A. ; Subramanian, S. *J. Magn. Reson.*, **1986**, *67*, 565-566.

7- Bax, A. ; Summers, M.F. *J. Am. Chem. Soc.*, **1986**, *108*, 2093-2094.

(Received in France 6 March 1990)