Synthesis of the Alkaloid Natural Products (+)-Plicane and (−)-Obliqueine, Using Polymer-Supported Reagents and Scavengers

Ian R. Baxendale and Steven V. Ley*
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

Two new naturally occurring amaryllidaceae alkaloids have been synthesized, using a divergent approach facilitated by the use of polymer-supported reagents and scavengers.

Introduction

The amaryllidaceae alkaloids have been the recipients of considerable synthetic interest, because of their extensive structural diversity and broad biological activity.1,2 Our group has already reported on the synthesis of a selection of these compounds that have been prepared using a suite of solid-supported reagents,3–5 to facilitate more-efficient synthesis.6 We were particularly interested in the molecular architecture of (+)-plicamine (1) (Figure 1), which is the first member of a new bis-nitrogen-containing family of alkaloids to be isolated7 from extracts of the Turkish Galanthus plicatus (subsp. Byzantinus).8 Following our synthesis of this molecule,9,10 we became aware of a subsequent study by the same group in which a structurally related alkaloid (+)-plicane (2) was characterized.3 In addition, an investigation into a related amaryllidaceae Cyrtanthus obliquus,10 which is indigenous to the Cape and KwaZulu Natal provinces of South Africa, provided a third member of the series, namely, (−)-obliqueine (3).11 It would appear from the structural similarities that the compounds of the plicamine subgroup can exhibit both configurations at C-3. We anticipated that the synthetic pathway in our original synthesis of plicamine6b,c would allow us to access these two new natural products and also permit the preparation of their two epimeric derivatives (4 and 5) in a rapid and divergent fashion. This would also assist structural assignment, because ambiguity could easily exist in the series and in addition to providing new molecules for biological screening.

Therefore, starting from the common intermediate6,8,9,10,12 two parallel pathways were followed (Scheme 1). Route A involved the initial conversion of the C-3 alcohol to the resulting mesylate, followed by stereocontrolled nucleophilic inversion with methanol to yield 7 in high yield. Alternatively, route B furnished the C-3 methoxy epimer 8 via methylation using trimethylsilyl diazomethane (TMS–CHN₂) and an immobilized sulfonic acid catalyst also in excellent yield. The trifluoroacetate groups from both compounds 7 and 8 could be efficiently cleaved under basic conditions when facilitated by flash microwave heating13,14 to give the corresponding amines 9 and 10, respectively. Direct oxidation of amine 9 with cerium ammonium nitrate absorbed on silica then gave a clean transformation to the imine, (+)-plicane (2). In an identical manner, 3-epi-plicane (4) could be prepared from the matching amine 10, using the same reagent.

Experimental Section

1H NMR spectra were recorded on a Bruker Advance DPX-400 spectrometer, with residual chloroform as the internal reference.
internal reference ($\delta_H = 7.26$ ppm). $^{13}$C NMR spectra were recorded in CDCl$_3$ on the same spectrometers, with the central peak of chloroform as the internal reference ($\delta_C = 77.0$ ppm). DEPT 135 was used to aid in the assignment of signals in the $^{13}$C NMR spectra.

Plicane (2). Rf 2.530, MS 327.1 (MH$^+$). $\left[\alpha\right]_D^285.9$ ($c = 0.15$ in MeOH); IR(neat), $\nu_{\text{max}}$: 3450, 2932, 2850, 1696, 1644, 1609, 1599, 1488, 1386, 1315, 1260, 1186, 1167, 1090, 1028, 987, 837, 820, 815 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.20$ (1 H, s, H-8), 6.85 (1 H, s, H-12),
1H NMR (400 MHz, CDCl3): δ = 7.10 (2 H, d, J = 1.7 Hz, H-9, 10), 6.75 (2 H, d, J = 8.2 Hz, H-10, 20), 6.67 (2 H, m, H-11), 5.98 (2 H, s, OCH2O), 5.90 (2 H, s, OCH2O), 3.66 (1 H, s, H-4a), 3.48 (3 H, s, OMe), 3.35 (1 H, m, H-4b), 1.88 (1 H, m, H-4a). 13C NMR (100 MHz, CDCl3): δ = 157.2 (C-6), 156.8 (C-8), 151.1 (C-11), 146.9 and 146.2 (C-10), 138.1 (C-12), 130.6 (C-13), 128.9 (C-14), 128.6 (C-15), 119.7 (C-16), 119.5 (C-17), 119.0 (C-18), 112.0 (C-19), 108.3 (C-20), 101.3 (C-15), 98.7 (C-14), 95.2 (C-4a), 93.5 (C-8a), 83.7 (C-6a), 74.7 (C-1), 68.6 (C-2), 66.1 (C-3), 64.1 (C-4a), 56.9 (OMe), 50.7 (C-8), 30.8 (NMe). HR-MS Calcd for C26H28N2O5Na: 471.1892. Found: 471.1894.

Acknowledgment

We gratefully acknowledge the financial support from the R.S. Wolfson Fellowship (to I.R.B. and S.V.L.) and the BP Endowment and the Novartis Research Fellowship (to S.V.L.). We wish to thank J. E. Davies for determining the crystal structure of racemic epi-plicane. We also thank the EPSRC for their financial contribution toward the purchase of the diffractometer.

Literature Cited


Received for review December 4, 2004
Revised manuscript received March 10, 2005
Accepted March 10, 2005

IE048822I