The synthesis of hydroxy-pyrrolizidines and indolizidines from cyclopropenones: towards hyacinthacines, australines and jenamidines

Vishnu V. R. Kondakal, M. Ilyas Qamar, Karl Hemming*

Institute for Materials, Medicines and Molecular Sciences, Division of Chemistry, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, West Yorkshire, HD1 3DH, United Kingdom

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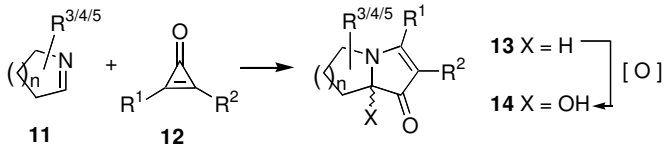
ABSTRACT

The reaction of cyclic imines (1-pyrrolines and piperidines) with a cyclopropenone leads to pyrrolizidines and indolizidines, respectively, each with a hydroxy group on the carbon atom of the bridgehead. The cyclopropenone functions as an all-carbon 1,3-dipole equivalent towards the cyclic imine in this reaction, and the cyclic imines used include polyhydroxylated systems, thus allowing access to australine, alexine and hyacinthacine type compounds. The pyrrolizidine products contain the core of the jenamidine and bohemamine natural products which are of interest as cell-proliferation inhibitors and cell-cell adhesion inhibitors.

The pyrrolizidine[1] and indolizidine[1b,2] heterocycles attract significant attention due to their biological activity, and synthetic challenges that they present.[1,2] Typical compounds, shown in Figure 1, are natural iminosugars such as hyacinthacines A_1/A_2 (**1**),[3] hyacinthacines B_1/B_2 (**2**),[4] australine (**3**) (and its bridgehead epimer alexine),[5] and castanospermine (**4**),[6] which have attracted interest as glycosidase inhibitors. Glycosidases play important roles in a number of diseases including many cancers, lysomal storage disorders such as Gaucher's disease, and type II diabetes.[7] Iminosugars have also gained interest as antiviral compounds and antibiotics.[7] Also of importance are indolizidine alkaloids with alkyl substituents, such as the amphibian derived indolizidine 195B (**5**),[8] and related systems.[1b,9] These continue to attract interest as, for example, inhibitors of nicotinic receptor-channels and neuromuscular transmission. Of particular interest to our work are pyrrolizidines such as bohemamine (**6**)[10] and the related de-epoxidised NP25302,[11] a rare pyrrolizidin-1-one sub-class isolated from *Actinosporangium* sp. and from marine *Streptomyces* sp., members of which have shown significant cell-cell adhesion inhibitory activity. The structurally related fungal derived pyrrolizin-1-ols, epohelmins A and B (**7**)[12] are lanosterol synthase inhibitors. Of great relevance to the work reported in this paper are systems that have a hydroxy group on the carbon atom at the bridgehead such as the antitumour, antibiotic, and antiviral clazamycins A and B (**8**),[13] jenamidines B_1/B_2 (**9b**) and C (**10**),[11a,14] and the synthetic 8a-hydroxy-indolizidines.[15] Jenamidine A_1/A_2 (**9a**) inhibits proliferation of leukemia cell line K-562 with a reported GI_{50} of 1.9 μg/mL.[11a,14]

In this paper, we describe a new synthesis of bridgehead (7a- and 8a-) hydroxy-substituted pyrrolizidines and indolizidines (**14**) (see Scheme 1) from the reaction of cyclic imines (**11**, n = 1 or 2) with cyclopropenones (**12**), a process that we believe proceeds through the rapid aerial oxidation of a transient intermediate (**13**).



Scheme 1: Synthesis of hydroxy-pyrrolizidines and indolizidines

* Corresponding author. Tel.: +0-44-1484-472188; fax: +0-44-1484-472182; e-mail: k.hemming@hud.ac.uk

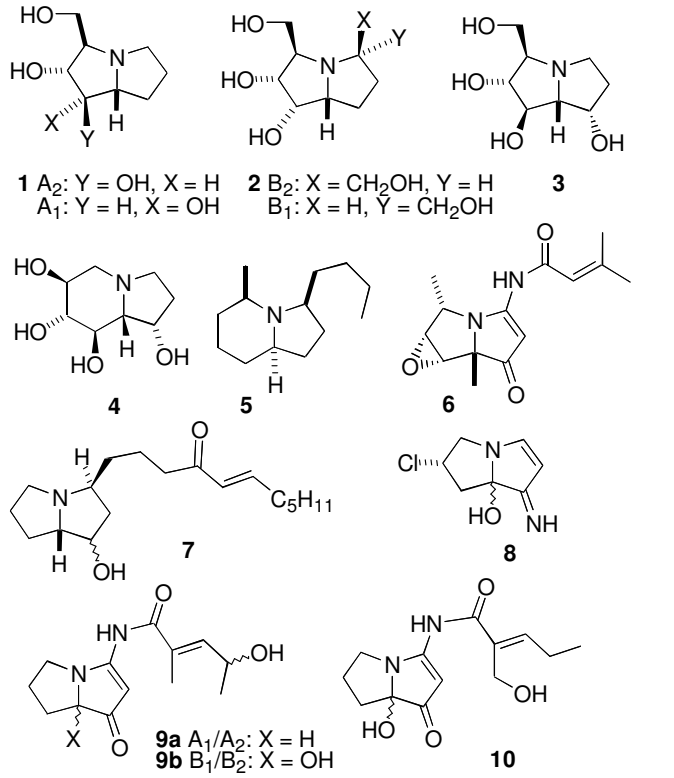
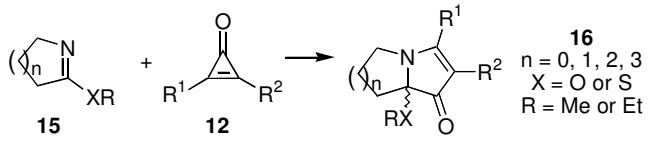


Figure 1: Indolizidine and pyrrolizidine natural products

The reaction of cyclic imines with cyclopropenones is a process that we have studied previously using cyclic imines (**15**) that are 2-substituted (X = O, S; R = Me, Et),[16] and we have shown that a range of alkoxy- and alkylthio-substituted cyclic imines react to give bicyclic systems (**16**) in the azetidinopyrrole (n = 0), pyrrolizidine (n = 1), indolizidine (n = 2) and pyrroloazepine (n = 3) classes, as summarized in Scheme 2.



Scheme 2: The use of 2-substituted cyclic imines

In order to produce compounds with a bridgehead hydrogen, a feature common to natural products (**1**)-(**5**), (**7**) and (**9a**), we sought to explore the reactions of 2-unsubstituted cyclic imines with cyclopropenones, and report the results of this study herein. We began our study with the synthesis of the imines (**17**)-(**21**) shown in Figure 2, with the ultimate goal of natural product syntheses.

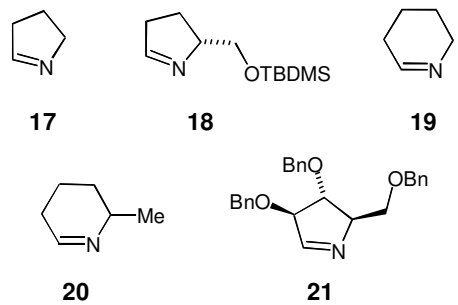
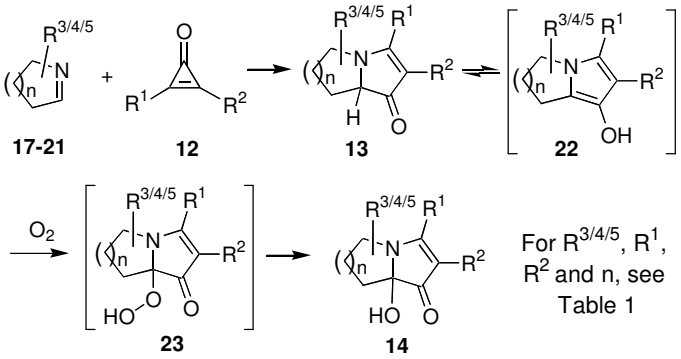


Figure 2: Cyclic imines selected for study

Imine (**17**) was selected to allow, after reaction with an appropriate cyclopropenone, direct access to analogues (**13**) (see Scheme 1) of the jenamidines (**9a**) and, after manipulation of the enone functionality and/or side-chains, access to jenamidines A_1/A_2 themselves. Imine (**17**) was accessed by cyclisation of 4-aminobutyraldehyde diethyl acetal which was stabilised as its zinc iodide complex.[17] Imine (**18**) was chosen ultimately to explore access to hyacinthacines B_1/B_2 (**2**), but also to a range of potentially interesting hydroxymethyl pyrrolizidines, and we synthesised it as a single enantiomer using an aza-Wittig based route starting from L-glutamic acid exactly as described by Banfi *et al*.[18] Imines (**19**)[19] and (**20**)[20] were chosen as they offer a potential route into indolizidines such as (**5**) and analogues, and these imines were made by an adaptation of reported *N*-chlorination-dehydrochlorination sequences.[19,20] Imine (**21**) was chosen due to its ready availablity[21] and its potential to allow access to polyhydroxylated pyrrolizidines, including hyacinthacine A_2 (**1**) and australine (**3**) and/or their epimers, after pyrrolidinone reduction and benzyl deprotection.

With imines (**17**)-(**21**) synthesised as described,[17-21] we started to explore their reactivity towards diphenylcyclopropenone (**12a**; $R^1 = R^2 = Ph$), phenylcyclopropenone (**12b**; $R^1 = H$, $R^2 = Ph$) and cyclopropenone (**12c**; $R^1 = R^2 = H$). Diphenylcyclopropenone is commercially available, whilst phenylcyclopropenone[16c,22] and cyclopropenone[23] were synthesised as described in the literature. Cyclopropenones have attracted recent interest as all-carbon 1,3-dipole equivalents,[16,24] as alkyne precursors in click processes,[25] and as novel catalytic platforms.[26] The first cyclopropenone reactions performed in our current study, as shown in Scheme 3, were those of imines (**17**) and (**20**) (the most readily available) with commercially available diphenylcyclopropenone (**12a**). These two reactions occurred extremely smoothly, but we were surprised to discover an extra 16 mass units in the mass spectra of the products. This, together with the absence of a C-H signal (the expected bridgehead C-H) in each of the ^{13}C and ^{1}H-NMR spectra, the presence of an additional quaternary carbon (^{13}C) and a clear OH in the infra-red and ^{1}H-NMR spectra, led us to believe that the products that had formed were the alcohols (**14a**) and (**14b**), rather than the expected compounds (**13a**) and (**13b**).[27] Alcohols (**14a**) and (**14b**) were isolated in 61% and 84% yields, respectively. Compound (**14a**) was crystalline and found to be suitable for study by X-ray crystallography (Figure 3),[28] which confirmed that the structure was that predicted. We assume that the expected adducts (**13**), via their enol tautomers (**22**), are unusually susceptible to aerial oxidation, and that the initial product of oxidation, the hydroperoxide (**23**) (Scheme 3), undergoes O-O cleavage to form the isolated alcohols (**14**). It is known that enols and their derivatives can undergo easy oxidation to α-hydroxy ketones[29] even in the absence of catalyst, photosensitisor or photoinducer.[30] Similarly, 3-hydroxypyrroles have been shown to undergo photooxidation to give highly reactive hydroperoxides which are easily intercepted in synthetically useful processes,[31] lending further credence to the involvement of species (**22**) / (**23**). We cannot rule out the possibility that cyclopropenones, cyclic enaminones or their hydroxypyrrole tautomers, behave as photosensitisors or photoinducers. In other catalyst-free aerobic oxidation systems involving enols, it has been noted that free-radical traps fail to halt the reaction or give ESR signals, and that intermediate peroxides can be detected.[30] It is also possible that intermediate (**23**) acts as an oxidising agent towards compound (**22**) in order to produce the final product (**14**).[32] Further mechanistic studies are underway in our laboratory.



Scheme 3: Synthesis of 7a- / 8a-hydroxy-indolizidines and pyrrolizidines

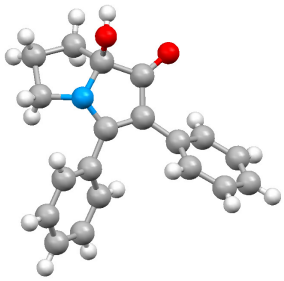


Figure 3: X-ray crystallographic structure of compound (**14a**)

Other imines and cyclopropenones behaved in the same manner and the results are summarised in Table 1.[27] Imines (**17**), (**18**) and (**19**) reacted with phenylcyclopropenone to give compounds (**14c**), (**14d**) and (**14e**) as single regioisomers (R^1 = H, R^2 = Ph; easily identified by HMBC), presumably due to the attack of the cyclopropenone (**12**) by the imine at the least hindered carbon, as we observed when working with this and other mono-substituted cyclopropenones before.[16] With imines (**18**), (**20**) and (**21**), the products (**14e-i**) were isolated as single diastereoisomers. Each of the pyrrolizidines (**14e-g**) showed the $CH_2OTBDMS$ and OH groups to be *cis* to each other (nOesy). We were unable to determine the relative stereochemistry in indolizidine (**14h**), but by analogy to that observed in compounds (**14e-g**), we have tentatively assigned the OH and Me groups as *cis* to each other. Pyrrolizidine (**14i**) was formed from the chiral pool derived enantiopure[21] imine (**21**). The stereochemistry of the new stereocentre – the bridgehead OH – was established by nOesy which showed the OH to be *cis* to the adjacent OBn and *cis* to the CH_2OBn group, and also confirmed the relative stereochemistry of the other chiral centres. In the case of compound (**14i**), the enol (**22**) was the initial isolated product but underwent quantitative conversion ($CDCl_3$, NMR tube) into the 7a-hydroxypyrrolizidine (**14i**) over 24 hours. Whilst this is significant in terms of the proposed mechanism in Scheme 3, this was the only system where we were able to observe enol formation. The use of imine (**21**) has allowed us to produce systems that are closely related to the hyacinthacine, australine and alexine natural products (**1**)-(**3**). The 7a-hydroxypyrrolizidines (**14**, n = 1) produced from the pyrrolines (**17**), (**18**) and (**21**) have a core structure that is closely related to the 7a-hydroxypyrrolizidine natural products (**8**), (**9b**) and (**10**). It is of note that natural product (**9a**) has a hydrogen at the bridgehead position and this presents the intriguing possibility that the jenamidine B_1/B_2 (**9b**) may arise from jenamidine A_1/A_2 (**9a**) through the type of mechanism presented in Scheme 3. Natural products (**8**) and (**10**) may have similar origins,[32] and we are actively pursuing this possibility.

Current studies in our laboratory are focusing upon the synthesis of hyacinthacine, australine, alexine and castanospermine (and their epimers), and their 7a-/8a-hydroxy analogues. A programme of study focused on the synthesis of 8a-hydroxy analogues of the alkylated indolizidines (such as compound **5**) is also underway alongside our continuing studies on the jenamidines.

Table 1: 7a-/ 8a-Hydroxy-indolizidines and pyrrolizidines from cyclopropenones (**12**) and imines (**17**)-(**21**)[27]

Product	n	Imine	**12**, R^1 and R^2	Yield (%)
14a	1	**17**	$R^1 = R^2 =$ Ph	61
14b	2	**19**	$R^1 = R^2 =$ Ph	84
14c	1	**17**	$R^1 =$ H, $R^2 =$ Ph	26
14d	2	**19**	$R^1 =$ H, $R^2 =$ Ph	57
14e	1	**18**	$R^1 =$ H, $R^2 =$ Ph	36
14f	1	**18**	$R^1 = R^2 =$ H	30
14g	1	**18**	$R^1 = R^2 =$ Ph	37
14h	2	**20**	$R^1 = R^2 =$ H	33
14i	1	**21**	$R^1 = R^2 =$ H	34

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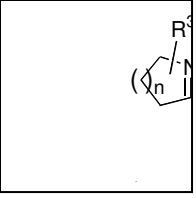

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27. Products (**14a–i**) reported in Table 1 all gave satisfactory spectroscopic data (^{1}H and ^{13}C-NMR, IR, mass spectra and HRMS). Typical procedure: A solution of the cyclopropenone (**12**) in dry MeCN was added dropwise over 1 min. to an equimolar amount of the imine (**17**) **–** (**21**)[17-21] in the same solvent at room temperature (commercial diphenylcyclopropenone and phenylcyclopropenone[16c,22]) or at 0 °C (cyclopropenone[23]). The mixture was stirred at room temperature for 4 h or overnight until IR showed the absence of the distinctive cyclopropenone absorbance at ~1840 cm^{-1}. The solvent was removed by rotary evaporation and the residual oil was purified by silica gel column chromatography (typically using hexane: EtOAc 4: 6). As an example, compound (**14i**) (0.1480 g) was obtained from mixing imine (**21**)[21] (0.3710 g, 0.92 mmol) and cyclopropenone (**12c**)[23] ($R^1 = R^2 = H$; 0.050 g, 0.92 mmol) in MeCN (10 mL) at 0 °C for 1 h and then warming to room temperature over 4 h. Compound (**14i**): IR: υ_{max} (neat, cm^{-1}): 3359 (b, m), 3062 (w), 3031 (m), 2926 (m), 2867 (m), 1688 (s), 1538 (s), 1454 (m), 1362 (m), 1206 (m), 1111 (s), 738 (m), 699 (m); ^{1}H NMR (500 MHz, $CDCl_3$), δ_H: 3.44 – 3.47 (1H, ddd, *J* 7.2, 5.9, 4.7, C*H*N), 3.53 (1H, dd, *J* 7.2, 9.4, CHC*H*$_2$OBn), 3.58 (1H, dd, *J* 4.7, 9.4, CHC*H*$_2$OBn), 3.82 (1H, d, *J* 6.8, C(OH)C*H*OBn), 3.89 (1H, br s, OH), 4.17 (1H, dd, *J* 5.9, 6.8, C*H*(CHOBn)$_2$), 4.49 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.51 (1H, d, *J* 11.9, OC*H*$_2$Ph), 4.55 (1H, d, *J* 11.9, OC*H*$_2$Ph), 4.61 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.66 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.97 (1H, d, *J* 11.7, OC*H*$_2$Ph), 5.23 (1H, d, *J* 3.7, C=C*H*), 7.17 – 7.19 (2H, m, ArH), 7.28 – 7.37 (13H, m, ArH), 7.76 (1H, d, *J* 3.7, *H*C=C); ^{13}C NMR: δ_c (125 MHz, $CDCl_3$): 62.90 (CH), 71.58 (CH_2), 72.50 (CH_2), 73.06 (CH_2), 73.28 (CH_2), 82.00 (CH), 87.07 (CH), 92.02 (C), 102.24 (CH), 127.36 (CH), 127.47 (CH), 127.51 (CH), 127.57 (CH), 127. 75 (CH), 128.05 (CH), 128.07 (CH), 128.13 (CH), 128.14 (CH), 136.68 (C), 137.18 (C), 137.30 (C), 168.75 (CH), 201.73 (C=O); *m/z* (electrospray) HRMS: calcd for $C_{29}H_{29}NO_5$ + Na^+ = 494.1938, found: 494.1947 [2 ppm error].
28. Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre as a CIF deposition with file number CCDC 873002. Copies of these data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK at www.ccdc.cam.ac.uk/data_request/cif.
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