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

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ABSTRACT
The reaction of cyclic imines (1-pyrrolines and piperideines) with a cyclopropenone leads to pyrrolizidines and indolizidines, respectively, each with a hydroxy group on the carbon atom at 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.

Keywords:
Hyacinthacine
Alexine
Jenamidine
Pyrrolizidine and indolizidine
Cyclopropenone

The pyrrolizidine1 and indolizidine1b,2 heterocycles attract significant attention due to their biological activity, and the synthetic challenges that they present.1,2 Typical compounds, shown in Figure 1, are natural iminosugars such as hyacinthacines A1/A2 (1),3 hyacinthacines B1/B2 (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, lysosomal 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 pyrrolizin-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 Letter 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 B1/B2 (9b) and C (10),11a,14 and the synthetic

Figure 1. Indolizidine and pyrrolizidine natural products.
In this Letter, 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.

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 pyyroloazepine (n = 3) classes, as summarised in Scheme 2.

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.

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 A1/A2 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 hyacinthacine B1/B2 (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 1919 and 2020 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 availability21 and its potential to allow access to polyhydroxylated pyrrolizidines, including hyacinthacine A2 (1) and australine (3) and/or their epimers, after pyrrolidine reduction and benzyl deprotection.

With imines 17–21 synthesised as described17–21 we started to explore their reactivity towards diphenylcyclopropenone (12a; R1 = R2 = Ph), phenylcyclopropenone (12b; R1 = H, R2 = Ph) and cyclopropenone (12c; R1 = R2 = H). Diphenylcyclopropenone is commercially available, whilst phenylcyclopropenone16c,22 and cyclopropenone23 were synthesised as described in the literature. Cyclopropenones have attracted recent interest as all-carbon 1,3-dipole equivalents16c,22 as alkyne precursors in click processes25 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 13C and 1H NMR spectra, the presence of an additional quaternary carbon (13C) and a clear OH in the infra-red and 1H 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 (Fig. 3),28 which confirmed that the structure was that deduced. 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 13 and 14. Similarly, 3-hydroxypyrroles have been shown to undergo photooxidation to give highly reactive hydroperoxides which are easily intercepted in synthetically useful processes, lending further credence to the involvement of species 22/23. We cannot rule out the possibility that cyclopropenones, cyclic enamines or their hydroxyprrole tautomers, behave as photooxidants. Further mechanistic studies on this aspect are underway in our laboratory.

Other imines and cyclopentenones behaved in the same manner and the results are summarised in Table 1. 17, 18 and 19 reacted with phenylcyclopentenone to give compounds 14c, 14d and 14e as single regioisomers (R1 = R2 = Ph); easily identified by HMBC and, presumably due to the attack of the cyclopropenone 12 by the imine at the least hindered carbon, as we previously observed when working with this and other mono-substituted cyclopropenones. With imines 18 and 20, the products 14e-i were isolated as single diastereoisomers. Each of the pyrrolizidines 14g-h showed the CH2OTBDMS 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 imine 21.

Table 1

<table>
<thead>
<tr>
<th>Product</th>
<th>n</th>
<th>Imine</th>
<th>12, R1 and R2</th>
<th>Yield [%]</th>
</tr>
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<tbody>
<tr>
<td>14a</td>
<td>1</td>
<td>17</td>
<td>R1 = R2 = Ph</td>
<td>61</td>
</tr>
<tr>
<td>14b</td>
<td>2</td>
<td>19</td>
<td>R1 = R2 = Ph</td>
<td>84</td>
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<tr>
<td>14c</td>
<td>1</td>
<td>17</td>
<td>R1 = R2 = Ph</td>
<td>26</td>
</tr>
<tr>
<td>14d</td>
<td>2</td>
<td>19</td>
<td>R1 = R2 = Ph</td>
<td>57</td>
</tr>
<tr>
<td>14e</td>
<td>1</td>
<td>18</td>
<td>R1 = R2 = Ph</td>
<td>36</td>
</tr>
<tr>
<td>14f</td>
<td>1</td>
<td>18</td>
<td>R1 = R2 = H</td>
<td>30</td>
</tr>
<tr>
<td>14g</td>
<td>1</td>
<td>18</td>
<td>R1 = R2 = H</td>
<td>37</td>
</tr>
<tr>
<td>14h</td>
<td>2</td>
<td>20</td>
<td>R1 = R2 = H</td>
<td>33</td>
</tr>
<tr>
<td>14i</td>
<td>1</td>
<td>21</td>
<td>R1 = R2 = H</td>
<td>34</td>
</tr>
</tbody>
</table>

Acknowledgments

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References and notes


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was obtained from mixing imine $^{21}$ (0.3710 g, 0.92 mmol) and cyclopropenone $^{12c}$ ($R^*=R^*=H$; 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: $\nu_{max}$ (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$_3$), $\delta$: 3.44–3.47 (1H, dd, J 7.2, 5.9, 4.7, CHN), 3.53 (1H, dd, J 7.2, 9.4, CH$_2$OBn), 3.58 (1H, dd, J 4.7, 9.4, CH$_2$OBn), 3.82 (1H, d, J 6.8, C(OH)CHOBn), 3.89 (1H, br s, OH), 4.17 (1H, dd, J 5.9, 6.8, CH(CH$_2$OBn)$\_2$), 4.49 (1H, d, J 11.7, OCH$_2$Ph), 4.51 (1H, d, J 11.9, OCH$_2$Ph), 4.55 (1H, d, J 11.9, OCH$_2$Ph), 4.61 (1H, d, J 11.7, OCH$_2$Ph), 4.66 (1H, d, J 11.7, OCH$_2$Ph), 4.97 (1H, d, J 11.7, OCH$_2$Ph), 5.23 (1H, d, J 3.7, C=C=C), 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: $\delta$: (125 MHz, CDCl$_3$): 137.18 (C), 137.30 (C), 168.75 (CH), 201.73 (C), 71.58 (CH$_3$), 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); m/z (electrospray) HRMS: calcd for C$_{29}$H$_{29}$NO$_5$ + Na$^+$ * Na* = 494.1938, found: 494.1947 [2 ppm error].

Crystallographic data have 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 or from http://www.ccdc.cam.ac.uk/data_request/cif.


28. We would like to thank the reviewers for useful comments on these aspects of the manuscript.