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The structure of Uniflorines A and B and the total synthesis of Casuarine, Australine and their epimers

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The Structure of Uniflorines A and B and
The Total Synthesis of Casuarine, Australine
and their epimers

A thesis submitted in fulfilment of the requirements
for the award of the degree of

Doctor of Philosophy
from
University of Wollongong

Thunwadee Ritthiwigrom
MSc

School of Chemistry

February, 2010
FOR MUM AND DAD
DECLARATION

I, Thunwadee Ritthiwigrom, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless due reference is provided. This document has not been submitted for qualifications at any other academic institution.

Thunwadee Ritthiwigrom

February, 2010
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<table>
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<th>Description</th>
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<tbody>
<tr>
<td>$[\alpha]_D$</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>$\text{tert}$-butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>deutero-chloroform</td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>chloroform</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR)</td>
</tr>
<tr>
<td>d</td>
<td>day (s)</td>
</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift (NMR)</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethylazodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer</td>
</tr>
<tr>
<td>DMAP</td>
<td>$N,N$-Dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>DMDP</td>
<td>2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionisation</td>
</tr>
<tr>
<td>eq.</td>
<td>equatorial</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>electrospray ionisation mass spectrometry</td>
</tr>
<tr>
<td>FCC</td>
<td>flash column chromatography</td>
</tr>
<tr>
<td>gCOSY</td>
<td>gradient Correlated Spectroscopy</td>
</tr>
<tr>
<td>gHSQC</td>
<td>gradient Heteronuclear Single Quantum Correlation</td>
</tr>
<tr>
<td>gHMBC</td>
<td>gradient Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HR</td>
<td>high resolution</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>LR</td>
<td>low resolution</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
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</table>
[M+]  molecular ion
m/z  mass/charge ratio
NMR  nuclear magnetic resonance
NMO  N-methylmorpholine-N-oxide
petrol  petroleum spirit bp 40-60 °C
ppm  parts per million
py  pyridine
q  quartet
Rf  relative mobility
rt  room temperature
s  singlet
t  triplet
TBAF  tetra-n-butylammonium fluoride
TBDPS  tert-butyldiphenylsilyl
TBS  tert-butyldimethylsilyl
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TPAP  tetrapropylammonium perruthenate
Tr  trityl, triphenylmethyl
ABSTRACT

The polyhydroxylated alkaloids uniflorines A and B were isolated in 2000 from the leaves of the tree *Eugenia uniflora* L. The common name for this tree is Surinam Cherry and the water soluble extracts of its leaves have been used as an antidiabetic agent in Paraguayan traditional medicine. Uniflorines A and B showed moderate activity in inhibiting the $\alpha$-glucosidases, rat intestinal maltase (IC$_{50}$ values of 12 and 4.0 $\mu$M, respectively) and sucrase (IC$_{50}$ values of 3.1 and 1.8 $\mu$M, respectively). Uniflorines A and B were deduced from NMR analysis to have pentahydroxyindolizidine structures. In 2004 Davis and Pyne reported the synthesis of the proposed structure of uniflorine A. Unfortunately, the NMR spectroscopic data of this synthetic material did not match with those of natural uniflorine A. Davis and Pyne then assumed that the structure of uniflorine A must be a diastereomer of the initially proposed structure. Several other diastereomers of the proposed structure, that were epimeric in the A-ring, have been synthesised by other researchers. One remaining A-ring diastereomer was the C-2 epimer of the proposed structure. In Chapter 2 of this thesis we report the synthesis of this compound in 11 synthetic steps and in 0.5% overall yield from L-xylose. However the NMR spectroscopic data for this synthetic compound did not match with those of the natural product. We then re-examined the NMR spectroscopic data of the natural product and revised the structures of uniflorines A and B from initially proposed pentahydroxyindolizidines to 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidines. Uniflorine B was the known alkaloid casuarine, while uniflorine A was tentatively assigned as 6-epi-casuarine. This was confirmed by the synthesis of the enantiomer of 6-epi-casuarine and then 6-epi-casuarine itself. These syntheses are reported in Chapters 2.2 and 2.3. The total synthesis of uniflorine A (6-epi-casuarine) was achieved in 11 steps and in 13% overall yield from L-xylose. The NMR spectroscopic data of this synthetic compound matched with those of the natural product uniflorine A. Thus we had successfully determined the correct structures of uniflorines A and B. Glycosidase inhibitor testing of uniflorine A at 143 $\mu$M showed it had 94-97% inhibition against the $\alpha$-D-glucosidases of *Saccharomyces cerevisiae* and *Bacillus sterothemophilus* and the amyloglucosidase of *Aspergillus niger*. The IC$_{50}$ values
were only determined for the two aforementioned α-D-glucosidases and were found to be modest at 34 and 28 µM, respectively.

In addition, we describe a flexible method for the diastereoselective total synthesis of several natural and unnatural polyhydroxylated indolizidines and pyrrolizidines from a common precursor.

The synthesis of the alkaloid casuarine, which was obtained in total of 13 synthetic steps and in 8% overall yield from L-xylose, is described in Chapter 3. A key step in this synthesis was a regioselective epoxide ring-opening reaction with hydrogensulfate ion. This reaction secured the correct configurations at C-6 and C-7 of the target molecule.

In Chapter 4 we describe the successful synthesis of australine in a total of 14 steps and 6% overall yield from L-xylose. Key steps in this synthesis were a regioselective epoxide ring-opening reaction with LiAlH₄ followed by a Mitsunobu reaction that secured the correct configuration C-7 of the target molecule.

The synthesis of the natural product 3-epi-casuarine was completed in 13 steps and in 0.4% overall yield. This synthesis required an inversion of configuration at C-3’ of the butyl side chain which was achieved using the Mitsunobu reaction. The low overall yield was due to a low yielding epoxide ring-opening reaction due to a competing intramolecular epoxide ring-opening reactions involving the 3-α-hydroxymethyl substituent.

Natural 3-epi-australine was obtained in total of 14 synthetic steps and in 2% overall yield, all from L-xylose. This synthesis required an inversion of configuration at C-3’ of the butyl side chain which was achieved using the Mitsunobu reaction. Key steps in this synthesis were a regioselective epoxide ring-opening reaction with LiAlH₄ followed by a Mitsunobu reaction that secured the correct configuration C-7 of the target molecule.

From this work a number of novel unnatural indolizidine and pyrrolizidine compounds were also obtained as side products. Some of these compounds were screened against 10 different glycosidases at 800 µg/mL. Unfortunately, none showed strong inhibition with only four compounds showing approximately 40-50% inhibition at this relative high concentration.
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PUBLICATIONS ARISING FROM THIS THESIS


3. Andrew S. Davis; Thunwadee Ritthiwigrom; Stephen G. Pyne. Synthetic and spectroscopic studies on the structures of uniflorines A and B: structural revision to 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine alkaloids. Tetrahedron. 2008, 64, 4868-4879.