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Attempts to find the correct structure of uniflorine A

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

Doctor of Philosophy
from
University of Wollongong



Andrew Stewart Davis

B. Sc (Hons)

School of Chemistry

May, 2008

Declaration

I, Andrew Stewart Davis, 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.

Andrew Stewart Davis

May, 2008

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List of Abbreviations

[α] _D	specific rotation
Ac	acetyl
Ar	aromatic
ax	axial
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br	broad
Bz	benzoyl
CI	chemical ionisation
Cy	cyclohexyl
d	doublet
δ	NMR chemical shift
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	<i>N,N</i> -Dimethyl-4-aminopyridine
DMF	dimethylformamide
EI	Electron impact Ionisation
eq	equatorial
ESI+	electrospray ionisation (positive ion mode)
FCC	flash column chromatography
gCOSY	gradient Correlated Spectroscopy
gHSQC	gradient Heteronuclear Single Quantum Correlation
gHMBC	gradient Heteronuclear Multiple Bond Correlation
HR	high resolution
Hz	Hertz
LR	low resolution
MS	mass spectrometry
m	multiplet
m.p.	melting point
[M ⁺]	molecular ion
<i>m/z</i>	mass/charge ratio
NMR	nuclear magnetic resonance
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
petrol	petroleum spirit bp 40-60 °C

ppm	parts per million
pyr	pyridine
q	quartet
R_f	relative mobility
rt	room temperature
s	singlet
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tr	trityl, triphenylmethyl
Troc	(2,2,2-trichloroethoxy)carbonyl

ABSTRACT

The alkaloid uniflorine A was isolated in 2000 from the leaves of the tree *Eugenia uniflora* L, together with two other water soluble alkaloids, uniflorine B and the known alkaloid (+)-(3 α ,4 α ,5 β)-1-methylpiperidine-3,4,5-triol piperidine. Uniflorine A was found to be an inhibitor of the α -glucosidases, rat intestinal maltase and sucrase, with IC₅₀ values of 12 and 3.1 μ M, respectively, and its structure was deduced from NMR analysis to be structure **1**. Uniflorine B was also found to be an inhibitor of the above α -glucosidases and its structure was determined from NMR analysis to be structure **2**.

The initial goal of this study was to complete the total synthesis of **1** and determine the validity of its proposed structure. In the event, an efficient 9-step diastereoselective synthesis of **1** was achieved by using the Petasis borono-Mannich reaction, ring-closing metathesis and stereoselective *cis*-dihydroxylation as key steps. The structure of our synthetic **1** was unequivocally established by a single-crystal X-ray crystallographic study of its pentaacetate derivative. However, the ¹H and ¹³C NMR data for synthetic **1** did not match with those reported for uniflorine A; the latter showed many more downfield peaks in the ¹H NMR, perhaps consistent with the amine salt. The ¹H NMR of the hydrochloride salt of synthetic **1**, however, did not match the literature spectroscopic data either. We therefore concluded that the structure assigned to uniflorine A was not correct. We also found that the coupling constant $J_{1,8a}$ of 4.5 Hz for uniflorine A, was more consistent with the relative *syn*-H-8a, H-1 configuration, suggesting that uniflorine A, if it was an indolizidine alkaloid, had the same H-1 configuration as castanospermine. Our attempts to prepare 2-*epi*-**1** and 1,2-di-*epi*-**1** were unsuccessful due to unexpected competing side-reactions.

In addition, the diastereoselective synthesis of the C-1, C-2 di-epimer of **1** was achieved. This synthesis employed a novel pyrrolo[1,2-*c*]oxazin-1-one precursor to allow for the reversal of π -facial diastereoselectivity in an osmium(VIII)-catalysed *syn*-dihydroxylation (DH) reaction. The NMR spectroscopic data of this epimeric compound and that of related isomers did not match that of the natural product. From a comparison of the NMR data of uniflorine A and uniflorine B with that of casuarine and the known synthetic 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine isomers we concluded unequivocally that uniflorine B is the known alkaloid casuarine. Although we cannot unequivocally prove the structure of uniflorine A, without access to the original material and data, the published data suggest that the natural product is also a 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine with the same relative C-7-C-7a-C-1-C-2-C-3 configuration as casuarine. We thus suggest that uniflorine A is 6-*epi*-casuarine.

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Publications arising from this thesis

1. Davis, Andrew S.; Ritthiwigrom, Thunwadee; Pyne, Stephen G. 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(21), 4868-4879.
2. Pyne, Stephen G.; Au, Christopher W. G.; Davis, Andrew S.; Morgan, Ian R.; Ritthiwigrom, Thunwadee; Yazici, Arife. Exploiting the borono-Mannich reaction in bioactive alkaloid synthesis. *Pure Appl. Chem.* **2008**, 80(4), 751-762.
3. Machan, Theeraphan; Davis, Andrew S.; Liawruangrath, Boonsom; Pyne, Stephen G. Synthesis of castanospermine. *Tetrahedron*. **2008**, 64(12), 2725-2732.
4. Pyne, Stephen G.; Davis, Andrew S.; Gates, Nicole J.; Hartley, Joseph P.; Lindsay, Karl B.; Machan, Theeraphan; Tang, Minyan. Asymmetric synthesis of polyfunctionalized pyrrolidines and related alkaloids. *Synlett*. **2004**, 15, 2670-2680.
5. Davis, Andrew S.; Pyne, Stephen G.; Skelton, Brian W.; White, Allan H. Synthesis of Putative Uniflorine A. *J. Org. Chem.* **2004**, 69(9), 3139-3143.
6. Davis, Andrew S.; Gates, Nicole J.; Lindsay, Karl B.; Tang, Minyan; Pyne, Stephen G. A new strategy for the diastereoselective synthesis of polyfunctionalized pyrrolidines. *Synlett*. **2004**, 1, 49-52.