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Synthetic and spectroscopic studies on the structures of uniflorines A and B: structural revision to 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine alkaloids

Andrew S. Davis, Thunwadee Ritthiwigrom, Stephen G. Pyne*

School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia

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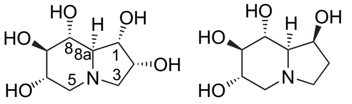
Abstract

The diastereoselective synthesis of the C-2 epimer and the C-1, C-2 di-epimers of the putative structure of the alkaloid uniflorine A has been achieved. The synthesis of the latter di-epimers employed a novel pyrrolo[1,2-*c*]oxazin-1-one precursor to allow for the reversal of π-facial diastereoselectivity in an osmium(VIII)-catalyzed *syn*-dihydroxylation (DH) reaction. The NMR spectral data of these epimeric compounds and that of related isomers did not match that of the natural product. From a comparison of the NMR data of uniflorines A and 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 stereochemistry as casuarine. We thus suggest that uniflorine A is 6-*epi*-casuarine.

1. Introduction

The alkaloid uniflorine A was isolated in 2000 from the leaves of the tree *Eugenia uniflora* L.[1–3] The water-soluble extract of these leaves has been used as an antidiabetic agent in Paraguayan traditional medicine. Uniflorine A was found to be an inhibitor of the α-glucosidases, rat intestinal maltase and sucrase, with IC_{50} values of 12 and 3.1 μM, respectively. The structure of uniflorine A was deduced from NMR analysis to be that shown as structure **1**.[1] The proposed structure of uniflorine A is similar to that of castanospermine **2**, except for the stereochemistry at C-1 and the extra hydroxyl substitution at C-2 (Fig. 1).



1 **2**

Figure 1. Proposed structure of uniflorine A (**1**) and the structure of castanospermine (**2**).

As part of our program concerned with the synthesis of polyhydroxylated indolizidine and pyrrolizidine alkaloids[4–11] we reported an efficient nine-step synthesis of purported uniflorine A from L-xylose.[10] The structure of our synthetic **1** was unequivocally established by a single-crystal X-ray crystallographic study of its pentaacetate derivative.[10] The ^1H and ^{13}C NMR spectral data for synthetic **1**, however, did not match with those reported for uniflorine A; the latter showed many more downfield peaks in the ^1H NMR spectrum, perhaps consistent with the amine salt. The ^1H NMR spectrum of the hydrochloride salt of synthetic **1**, however, did not match the literature spectral data either. We therefore concluded that the structure assigned to uniflorine A was not correct.[10] We also indicated 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 stereochemistry, suggesting that uniflorine A, if it was an indolizidine alkaloid, had the same H-1 stereochemistry as castanospermine **2**.

In 2006, Dhavale et al.[12] also reported the synthesis of compound **1**; their sample had NMR spectral data identical

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* Corresponding author. Fax: +61 242 214287.
E-mail address: spyne@uow.edu.au (S.G. Pyne).

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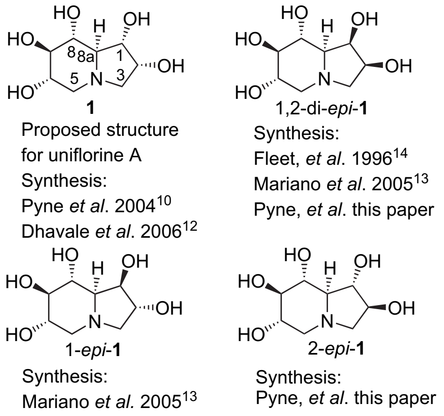
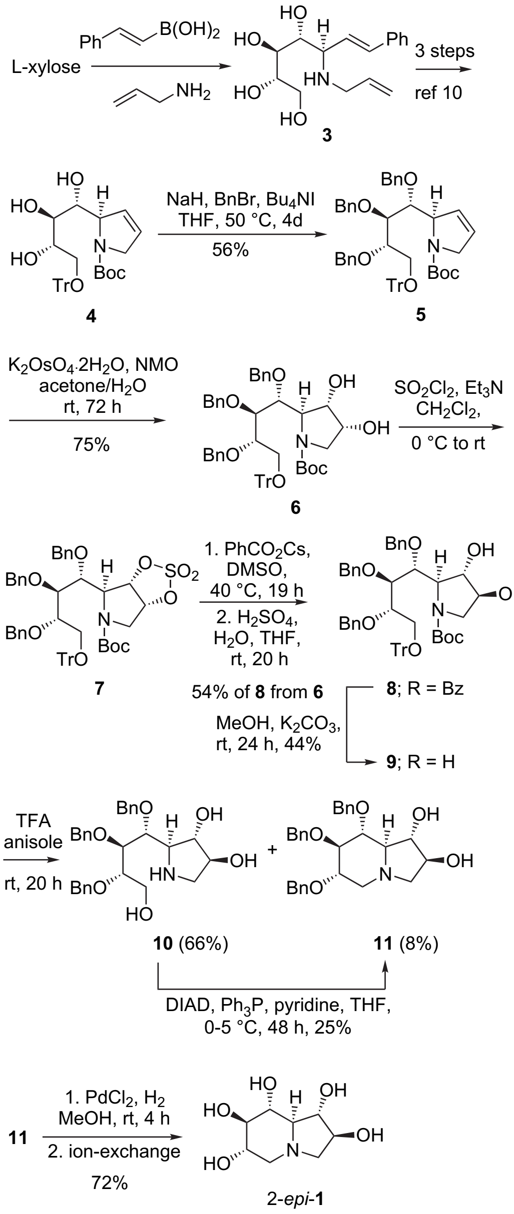


Figure 2.

to ours. This paper also reported the synthesis of 1,2,8a-tri-*epi*-**1** and 8a-*epi*-**1**; these compounds also had NMR spectral data significantly different from that of uniflorine A. In 2005, Mariano et al.[13] reported the synthesis of 1-*epi*-**1**, while 1,2-di-*epi*-**1** was reported by Fleet et al.[14] in 1996 (Fig. 2), before uniflorine was even isolated These indolizidine molecules also had NMR spectral data different from that of uniflorine A. Thus if uniflorine A was epimeric at C-1 and/or C-2 with compound **1** then the only remaining possible structure for the natural product was 2-*epi*-**1**. Thus we report here the diastereoselective synthesis of 2-*epi*-**1** and a comparison of its NMR spectral data with that of uniflorine A. We also report the synthesis of 1,2-di-*epi*-**1** to demonstrate the versatility and flexibility of our earlier synthetic strategy for preparing 1,2,6,7,8-pentahydroxyindolizidines.[10]

2. Results and discussion

2.1. Synthesis of 2-*epi*-**1**



Scheme 1.

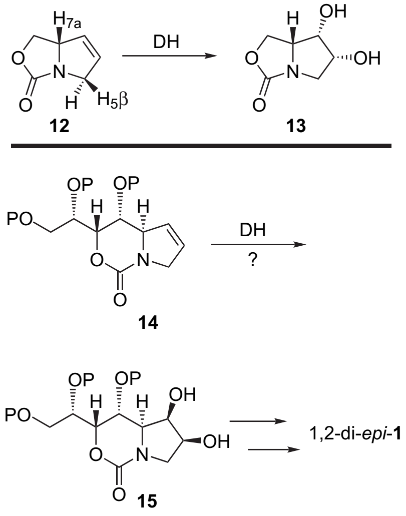
The amino-tetraol **3**, obtained from the boronic acid-Mannich reaction (Petasis reaction)[10] of L-xylose, allylamine, and (*E*)-styrene boronic acid, was converted in three steps to the 2,5-dihydropyrrole **4**, the precursor we used earlier in our synthesis of **1** (Scheme 1).[10] The triol **4** was readily converted to its tri-*O*-benzyl derivative **5** in 56% yield under standard conditions.[15] The relatively low yield for this step was in part due to the competitive formation of the corresponding *O*-dibenzyl-oxazolidin-2-one **20** (3%) and oxazin-2-one **21** (9%) (Scheme 3). Osmium(VIII)-catalyzed *syn*-dihydroxylation (DH) of **5** furnished the diol **6** as a single diastereomer in 75% yield. The stereochemical outcome of this DH reaction was expected due to the stereodirecting effect of the C-2 pyrrolidine substituent in **5**.[4,5,10] The diol **6** was then converted directly to the cyclic sulfate **7** using sulfuryl chloride under basic conditions (SO_2Cl_2, Et_3N).[16] This method was more efficient than the two-step method involving first formation of the corresponding cyclic sulfite ($SOCl_2$, Et_3N) followed by oxidation with catalytic ruthenium tetraoxide ($RuCl_2$, $NaIO_4$).[8,16] The cyclic sulfate **7** was found to be sensitive to purification on silica gel and was thus taken through the next step without purification. Treatment of **7** with cesium benzoate in DMSO at 40 °C for 19 h followed by acid hydrolysis of the resulting adduct gave the benzoate **8** in 54% yield from the diol **6**.[8,16] The benzoate **8** resulted from the regioselective nucleophilic ring opening of the cyclic sulfate **7** at the less hindered C-4 pyrrolidine position giving rise to inversion of stereochemistry at C-4. This reaction also produced a small amount (7%) of the corresponding *O*-trityl deprotected analog of **8** (see Section 4 for details), formed under the acidic hydrolysis conditions. The benzoate group of **8** was removed by methanolysis to give the diol **9**. Selective liberation of the secondary amino and primary hydroxyl groups of **9** was achieved by exposure of **9** to TFA in the presence of anisole, as a cation scavenger, at rt.[17] This reaction gave a mixture of the desired amino-alcohol **10** (66%) and the indolizidine **11** (8%) (Scheme 1). We observed the formation of products related to **10** and **11** from the TFA/anisole deprotection reaction on 1,2-*O*-dibenzyl-2-*epi*-**9** during our synthesis of **1**.[10] The amino-alcohol **10** underwent cyclization under Mitsunobu reaction conditions in THF/pyridine as solvent to give the same indolizidine **11** in a modest yield of 25%.[6,18] The use of the Appel cyclization reaction conditions ($Ph_3P/CBr_4/Et_3N$),[19] that worked well for the cyclization of 1,2-*O*-dibenzyl-2-*epi*-**9**, gave a complex mixture of products. Only the Mitsunobu reaction using pyridine as the solvent gave the desired product. Debenzylation of **11** under hydrogenolysis conditions using $PdCl_2/H_2$[20] gave 2-*epi*-**1** ($[\alpha]_D^{25}$ −9.2 (*c* 0.17, H_2O)) in 72% yield after ion-exchange chromatography in a total of 11 synthetic steps from L-xylose. The ^1H and ^{13}C NMR spectral data for 2-*epi*-**1**, however, did not match with those reported for uniflorine A (Table 1). This data will be discussed further in Section 2.3.

2.2. Synthesis of 1,2-di-epi-**1**

The synthesis of 1,2-di-*epi*-**1** required a method of reversing the stereochemical outcome of the *syn*-DH reaction, as demonstrated in the diastereoselective synthesis of the 3α,4α-diol **6** from the DH reaction of **5** (Scheme 1). We have previously shown by converting substrates like **5** into their corresponding pyrrolo[1,2-*c*]oxazol-3-ones that the DH reaction occurs with the opposite stereochemical outcome to give mainly β-DH.[6,8,9,21] Parsons demonstrated that the unsubstituted pyrrolo[1,2-*c*]oxazol-3-one **12** underwent a photochemical [2+2]-cycloaddition of the alkene group to the unexpected *endo*-face of the bicyclic system.[22] Our group[21] and that of Parsons[23] demonstrated that the DH reaction of **12** was also highly diastereoselective and gave the diol **13**, resulting from attack of OsO_4 from the concave (*endo*) face of **12** (Scheme 2). To explain this stereochemical outcome we suggested that the β-face would be sterically hindered to attack by OsO_4 by the *pseudo*-axial protons H-7a and H-5β.[6,7,9,21] A similar stereochemical argument has been used to explain the stereochemical preference of the DH reactions of 1,2-didehydroindolizidines.[5] Parsons has performed semi-empirical calculations (6-31G*) on **12**, which suggested that the HOMO of **12** is not symmetric about the alkene moiety but has more electron density on the *endo*-face of the molecule.[23] This may be the major reason for the high *endo*-selectivity of reactions on **12**. Whatever the reasons for the π-facial selectivity of **12**, this compound and its substituted derivatives have been successfully used by our group,[6–9,21] and that of Parsons,[23,24] to diastereoselectively prepare polyhydroxylated indolizidine and pyrrolizidine alkaloids and their epimers. When planning our synthesis of 1,2-di-*epi*-**1** we were interested in employing a pyrrolo[1,2-*c*]oxazin-1-one similar to **14** as a precursor and examining the diastereoselectivity of its DH reactions (Scheme 2). To the best of our knowledge such substrates have not been employed in natural product synthesis.

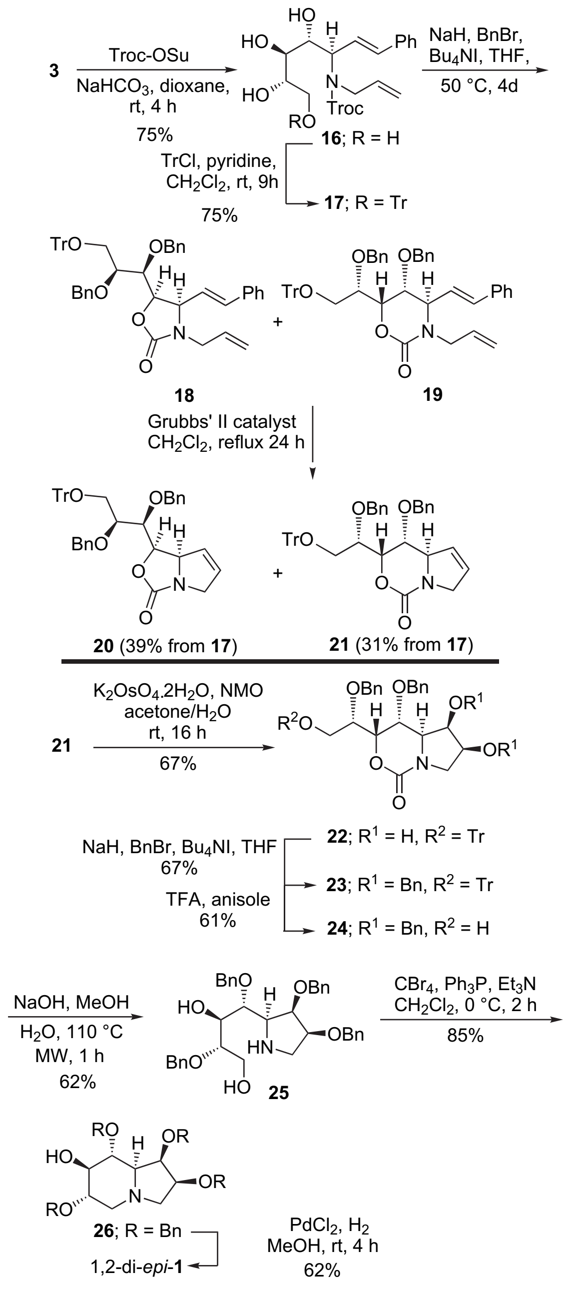
Table 1
^1H NMR spectroscopic data (D_2O) for uniflorine A and epimeric 1,2,6,7,8-pentahydroxyindolizidines

	Uniflorine A[1]	**1**[10]	1-*epi*-**1**[13]	1-2-di-*epi*-**1**[14]	2-*epi*-**1**
Chemical shifts (ppm)					
H-1	4.18	3.82	4.08	4.06	3.96
H-2	4.35	4.11	4.25	4.24	4.14
H-3	2.98	3.26	2.63	2.54	2.76
H-3	3.04	2.20	2.88	2.71	2.87
H-5	3.61	3.01	2.96	2.95	3.11
H-5	3.76	2.09	1.91	1.91	2.16
H-6	2.76	3.46	3.42	3.42	3.64
H-7	3.81	3.20	3.13	3.12	3.29
H-8	3.94	3.25	3.48	3.47	3.47
H-8a	3.14	2.08	2.01	2.01	2.11
Coupling constants (Hz)					
$J_{1,2}$	4.5	7.3	0	5.8	2.5
$J_{1,8a}$	4.5	7.5	6.3	3.5	7.5
$J_{2,3}$	5.1	6.8	6.3	8.1	6.7
$J_{2,3}$	5.1	6.8	4.4	2.6	<1
$J_{3,3}$	12.1	10.7	10.3	10.9	10.9
$J_{5,5}$	11.8	10.5	10.9	10.7	10.8
$J_{5,6}$	6.4	10.9	9.1	10.7	10.4
$J_{5,6}$	3.8	5.5	5.2	5.3	5.3
$J_{6,7}$	9.0	9.0	9.1	9.9	9.0
$J_{7,8}$	7.7	9.0	9.1	9.4	9.0
$J_{8,8a}$	7.7	9.2	10.2	9.5	9.0



Scheme 2.

With the aim of preparing specifically the pyrrolo[1,2-*c*]oxazin-1-one **21** (Scheme 3) and using this compound as a precursor for the synthesis of 1,2-di-*epi*-**1**, the amino-tetraol **3** was converted to its *N*-Troc derivative **16** (75% yield) using trichloroethyl succinimidyl carbonate (Troc-OSu).[25] The primary alcohol of **16** was then regioselectively protected as its *O*-trityl compound **17** (75% yield) (Scheme 3). Treatment of **17** with sodium hydride and benzyl bromide gave a mixture of tri-*O*-benzylated **17** (structure not shown) and the oxazol-2-one **18** and the oxazin-2-one **19**. These compounds were difficult to separate by column chromatography but NMR analysis suggested that the cyclic derivatives, **18** and **19**, were the major products. Because separation was difficult and not efficient the mixture was treated with Grubbs' second-generation ruthenium catalyst[21] to provide three readily separable products. The major bicyclic derivatives, the



Scheme 3.

pyrrolo[1,2-*c*]oxazol-3-one **20** and the pyrrolo[1,2-*c*]oxazin-1-one **21**, were obtained in yields of 39 and 31%, respectively, from the mono-cyclic, *N*-Troc analog of **5** that was not characterized (Scheme 3). Osmium(VIII)-catalyzed *syn*-DH of **21** furnished the diol **22** as a single diastereomer in 67% yield. The diol functionality of **21** was *O*-benzylated (67% yield) and the trityl group was removed by acid hydrolysis to give the primary alcohol **24** (61% yield). Base catalyzed hydrolysis of the oxazinone ring of **24** under microwave irradiation conditions gave the pyrrolidine **25** in 62% yield. The amino-alcohol **25** underwent smooth cyclization to give the indolizidine **26** using $Ph_3P/CBr_4/Et_3N$ in 85% yield.[19] Debenzylation of **26** under hydrogenolysis conditions using $PdCl_2/H_2$[20] gave 1,2-di-*epi*-**1** in 62% yield after ion-exchange chromatography and then recrystallization from ethanol/water. The ^{1}H and ^{13}C NMR spectral data of this compound matched closely ($\Delta\delta$ 0.2−0.6 ppm and $\Delta\delta$ 0.0−0.2 ppm, respectively; ^{1}H NMR coupling constants very also very similar) to that reported in the literature for this compound.[14] The optical rotation of this compound ($[\alpha]_D^{23}$ +21 (*c* 1.5, H_2O), lit.[14] $[\alpha]_D^{23}$ +66.5 (*c* 1.33, H_2O)) was of the same sign but of a significantly different magnitude to that reported. The hydroscopic nature of this compound may explain this difference.[14]

2.3. Proposed structure of uniflorine A and the revised structure of uniflorine B

Table 1 lists the ^{1}H NMR spectral data for uniflorine A,[1] compound **1**,[10] and its three epimers, 1-*epi*-**1**,[13] 2-*epi*-**1**, and 1,2-di-*epi*-**1**.[14] The ^{1}H and ^{13}C NMR spectral data for these compounds do not match with those reported for uniflorine A; the synthetic compounds show many more upfield peaks in their ^{1}H NMR spectra. The newly synthesized 2-*epi*-**1** showed $J_{1,8a}$ (7.5 Hz) and $J_{1,2}$ (2.5 Hz) values consistent with its proposed stereochemistry and the 1,2-diaxial like arrangement of H-8a and H-1 and the 1,2-diequatorial like trans-relationship between H1 and H2.[26]

Uniflorine A was originally isolated along with uniflorine B, which was assigned the structure **27** (Fig. 3).[1] Our analysis of the NMR spectral data for this compound and its optical rotation indicated that uniflorine B is the known 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine alkaloid casuarine **28**.[27] Fleet has also noticed this structural missassignment.[28] The optical rotation and ^{1}H NMR spectral data of both compounds match very closely; the $^{3}J_{HH}$ values for the two samples were in very close accord as were their ^{1}H NMR chemical shifts (Table 2).

The ^{13}C NMR shifts reported for uniflorine B, however, were consistently 3.0–3.2 ppm downfield of the corresponding ^{13}C NMR resonances for casuarine **28**. Alternative referencing between the two samples could account for this consistent discrepancy. Both ^{13}C NMR spectra were determined at 125 MHz in D_2O. The ^{13}C NMR spectrum of casuarine **28** was referenced to acetone at δ 29.80[27] while that of uniflorine B was apparently referenced to TMS (a standard not known for its water (D_2O) solubility) as an internal standard.[1]

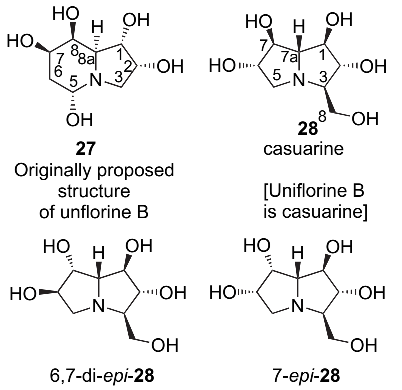


Figure 3.

Table 2
NMR (D_2O) and optical rotation data for casuarine **28** and that reported for uniflorine B

Chemical shifts (ppm)			Coupling constants (Hz)		
Nucleus	Casuarine[27]	Uniflorine B[1]		Casuarine[27]	Uniflorine B[1]
H-1	4.16	4.17 (H-8)[b]	$J_{1,2}$	8.0	8.1 ($J_{7,8}$)[b]
H-2	3.80	3.79 (H-7)	$J_{1,7a}$	8.0	8.1 ($J_{8,8a}$)
H-3	3.04	3.04 (H-5)	$J_{2,3}$	8.0	Multiplet
H-5α	2.91	2.92 (H-3)	$J_{3,8}$	3.8	3.7 ($J_{5,6}$)
H-5β	3.27	3.26 (H-3)	$J_{3,8'}$	6.6	6.8 ($J_{6,7}$)
H-6	4.21	4.22 (H-2)	$J_{5\alpha,6}$	4.0	3.9 ($J_{2,3}$)
H-7	4.19	4.19 (H-1)	$J_{5\beta,6}$	4.7	4.5 ($J_{2,3'}$)
H-7a	3.07	3.06 (H-8a)	$J_{6,7}$	[a]	4.5 ($J_{1,2}$)
H-8	3.77	3.78 (H-6)	$J_{7,7a}$	3.5	3.2 ($J_{1,8a}$)
H-8′	3.61	3.61 (H-6)	$J_{8,8'}$	11.9	11.3 ($J_{6,6''}$)
			$J_{5,5'}$	12.2	12.2 ($J_{3,3'}$)

Chemical shifts (ppm)					
Nucleus	Casuarine[27]	Uniflorine B[1]	Δδ (ppm)	Optical rotation	
C-1	77.8	80.9 (C-8)[b]	3.1	Casuarine[27]	$[\alpha]_D^{24}$ +16.9 (*c* 0.8, H_2O)
C-2	76.6	79.8 (C-7)	3.2		
C-3	70.0	73.0 (C-5)	3.0		
C-5	58.0	61.1 (C-3)[c]	3.1	Uniflorine B[1]	$[\alpha]_D$ +16.3 (*c* 1.1, H_2O)
C-6	77.4	80.6 (C-2)	3.2		
C-7	78.8	81.9 (C-1)	3.1		
C-7a	72.1	75.2 (C-8a)	3.1		
C-8	62.2	65.5 (C-3)[c]	3.1		

[a] Could not be determined due to peak overlap.
[b] Original assignment based on an indolizidine structure.[1]
[c] Both signals were assigned as C-3 in the original paper.[1]

Further support for these compounds being the same was the fact that both casuarine and uniflorine B inhibit the α-glycosidase, rat intestinal maltase with low μM activities. The reported IC_{50} values for uniflorine B and casuarine were 0.7[29] and 4.0 μM,[1] respectively, from experiments in different laboratories.

The ^{13}C NMR chemical shifts of the methylene carbons reported for uniflorine A at δ 65.3 and 60.0 correspond more closely to C-3 and C-5, respectively, of a 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine (cf. casuarine C-3 (δ 70.0) and C-5 (δ 58.0), Table 2) than to C-3 and C-5 of a 1,2,6,7,8-pentahydroxyindolizidine (the methylene resonances in **1** are at C-3 (δ 59.2) and C-5 (δ 55.4)). Thus it would be reasonable to assume that uniflorine A, like uniflorine B, is also a 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine alkaloid. On this assumption we have reassigned the published ^1H NMR data for uniflorine A as shown in Table 3 by analogy with the known chemical shifts, coupling constants and assignments for casuarine **28**.[27] A comparison of this reassigned NMR data for uniflorine A with that of casuarine **28** and its known synthetic diastereomers, 7-*epi*-**28**[30] and 6,7-di-*epi*-**28**[30,31] (Fig. 3), indicated that these three compounds were clearly different. However, their ^1H NMR spectral data showed a much better correlation than that between the reported data for uniflorine A and the epimeric 1,2,6,7,8-pentahydroxyindolizidines shown in Table 1. This NMR reassignment required the numbering of uniflorine A to be transposed to that indicated in brackets in Table 3.

Table 3
The ^1H NMR chemical shifts (ppm, D_2O) for casuarine **28**,[27] 6,7-di-*epi*-**28**,[30] and 7-*epi*-**28**[30] and that reported for uniflorine A[1]

Nucleus	Casuarine **28**	6,7-di-*epi*-**28**	7-*epi*-**28**	Uniflorine A
H-1	4.16	4.23	4.29	3.94 (H-8)[a]
H-2	3.80	3.86	3.75	3.81 (H-7)
H-3	3.04	2.67	2.73	2.76 (H-6)
H-5	2.91	2.85	2.54	2.98 (H-3β)
H-5′	3.27	3.00	3.18	3.04 (H-3α)
H-6	4.21	4.15	4.15	4.35 (H-2)
H-7	4.19	4.08	4.07	4.18 (H-1)
H-7a	3.07	3.36	3.16	3.14 (H-8a)
H-8	3.77	3.55	3.50	3.61 (H-5α)
H-8′	3.61	3.73	3.70	3.76 (H-5β)

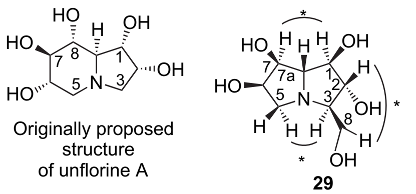
[a] Original assignments based on an indolizidine structure.[1]

A comparison of the coupling constants for the protons in casuarine **28**, 6,7-di-*epi*-**28**, and 7-*epi*-**28** with those observed for uniflorine A revealed a strong correlation between several nuclei (Table 4). Specifically, the originally assigned $J_{8,8a}$ value for uniflorine A was consistent with the $J_{1,7a}$ values of **28**, 7-*epi*-**28**, and 6,7-di-*epi*-**28**. Similarly, the originally assigned $J_{7,8}$ value of uniflorine A was consistent with the $J_{1,2}$ values of **28**, 7-*epi*-**28**, and 6,7-di-*epi*-**28**, while the originally assigned $J_{6,7}$ value of uniflorine A was also consistent with the $J_{2,3}$ values of **28**, 7-*epi*-**28**, and 6,7-di-*epi*-**28**. These high $^3J_{H,H}$ values (7.9–9.6 Hz) describe a trans-diaxial configuration between the contiguous protons (Table 4).[26] On this basis, we propose that uniflorine A has the same C-7a–C-1–C-2–C-3 relative configuration as casuarine **28**, 7-*epi*-**28**, and 6,7-di-*epi*-**28**. A comparison of the last four rows of coupling constants in Table 4 revealed a poorer correlation between the four compounds. Clearly $J_{7,7a}$ was relatively insensitive to the stereochemistry at C-7 since this coupling constant ranged from 3.5 to 4.5 Hz in **28**, 7-*epi*-**28**, and 6,7-di-*epi*-**28**. However, care must be taken in such an analysis as the change of configuration at one or more stereogenic centers can significantly change the conformation of the molecule making stereochemical predictions difficult.[26] The pH of the NMR sample can also influence the chemical shifts and thus a comparison of the above compounds under identical sample and referencing conditions would be required before further conclusions can be drawn. Although we cannot unequivocally prove the structure of uniflorine A, without access to the original material and data, the published data suggests that the natural product is 6-*epi*-casuarine **29** (Fig. 4).[32]

Table 4
J values (Hz) for casuarine diastereomers and that reported for uniflorine A

	Casuarine **28**	6,7-di-*epi*-**28**	7-*epi*-**28**	Uniflorine A
$J_{1,7a}$	8.0	7.2	7.6	7.7 ($J_{8,8a}$)[b]
$J_{1,2}$	8.0	8.1	7.9	7.7 ($J_{7,8}$)
$J_{2,3}$	8.0	9.6	9.6	9.0 ($J_{6,7}$)
$J_{5,6}$	4.0	4.2	9.6	5.1 ($J_{2,3\beta}$)
$J_{5',6}$	4.7	1.8	6.4	5.1 ($J_{2,3\alpha}$)
$J_{6,7}$	[a]	2.3	3.8	4.5 ($J_{1,2}$)
$J_{7,7a}$	3.5	4.5	4.2	4.5 ($J_{1,8a}$)

[a] Could not be determined due to peak overlap.
[b] Original assignments based on an indolizidine structure.[1]



Originally proposed structure of unflorine A

29
6-*epi*-casuarine
Our proposed structure of uniflorine A
*reported NOE correlations

Figure 4. Our proposed structure for uniflorine A.

Further support for this structure came from the results of the reported NOE studies and ^{13}C NMR data of uniflorine A.[1] The original paper reported NOE correlations for uniflorine A between H-1 and H-8, H-3 and H-6, and H-5 and H-7. This would correspond to NOE correlations between H-7 and H-1, H5 and H-3, and H-8 and H-2 in the proposed structure **29** (Fig. 4). These NOE correlations are consistent with the proposed relative stereochemistries at C-1, C-2, C-3, and C-7 in **29**. However, they do not provide information on the relative stereochemistry of H-6 and H-7a, although the later is inferred from the magnitude of $J_{1,7a}$.

Analysis of the ^{13}C NMR chemical shifts for casuarine **28**,[27] 7-*epi*-**28**,[30] and 6,7-di-*epi*-**28**[31] and that reported for uniflorine A[1] (Table 5) indicated that casuarine **28** and uniflorine A had the closest matching chemical shifts. If one assumes that the ^{13}C NMR spectrum of uniflorine A was also incorrectly referenced by 3 ppm then the chemical shifts of these compounds are even more similar, except for the chemical shift of C-6 (δ 77.4 for **28** and δ 74.2−3=71.2) for uniflorine A, again consistent with uniflorine A being 6-*epi*-casuarine **29**.

Table 5
^{13}C NMR (D_2O) chemical shifts (ppm) for casuarine and its epimers and uniflorine A

	Casuarine **28**[27]	6,7-di-*epi*-**28**[31]	7-*epi*-**28**[30]	Uniflorine A[1]	Uniflorine A—3 ppm
C-1	77.8	74.4	73.9	81.2 (C-8)[a]	78.2
C-2	76.6	80.1	78.6	79.9 (C-7)	76.9
C-3	70.0	73.0	71.7	72.5 (C-6)	69.5
C-5	58.0	60.6	56.8	60.0 (C-3)	57.0
C-6	77.4	79.3	75.5	74.2 (C-2)	71.2
C-7	78.8	75.5	70.6	78.1 (C-1)	75.9
C-7a	72.1	71.7	69.1	73.6 (C-8a)	70.6
C-8	62.2	63.0	63.2	65.3 (C-5)	62.3

[a] Original assignments based on an indolizidine structure.[1]

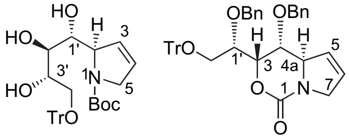
3. Conclusions

We have successfully developed a diastereoselective synthesis of the C-2 (2-*epi*-**1**) and C-1, C-2 (1,2-di-*epi*-**1**) epimers of the putative structure of the alkaloid uniflorine A. The synthesis of the latter epimer employed a novel pyrrolo[1,2-*c*]-oxazin-1-one (**21**) to allow for the reversal of π-facial diastereoselectivity in an osmium(VIII)-catalyzed *syn*-DH reaction. The NMR spectral data of these compounds and that of **1** and 2-*epi*-**1** 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 **28** and its synthetic epimers, we have concluded unequivocally that uniflorine B is the known alkaloid casuarine (**28**). 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 as casuarine **28**. We suggest that uniflorine A is 6-*epi*-casuarine (**29**). This structure is also consistent with the published NOE and our re-referenced ^{13}C NMR data.[1]

4. Experimental

4.1. General

General methods were as described previously.[5,6] All ^{1}H NMR spectra were performed at 500 MHz and all ^{13}C NMR (DEPT) spectra at 125 MHz in $CDCl_3$ solution, unless otherwise noted. NMR assignments are based on COSY, DEPT and HSQC NMR experiments and sometimes HMBC and NOESY experiments. The ^{13}C NMR spectra of 2-*epi*-**1** and 1,2-di-*epi*-**1** in D_2O were referenced to internal acetonitrile at δ 1.47. IR spectra were determined as neat samples. Petrol refers to petroleum spirit, bp 40–60 °C. Compounds are numbered as shown below.



4.1.1. *tert-Butyl (2R)-2-[(1R,2R,3R)-1,2,3-tris(benzyloxy)-4-triphenylmethyloxybutyl]-2,5-dihydro-1H-pyrrole-1-carboxylate* (**5**)

To a solution of **4**[10] (12.41 g, 23.37 mmol) in dry THF (240 mL) at 0 °C was added NaH (3.702 g, 77.12 mmol, 50% in mineral oil). After H_2 evolution had ceased (10 min), BnBr (16.68 mL, 140.2 mmol) and *n*-Bu_4NI (863 mg, 2.337 mmol) were added. The reaction mixture was stirred at rt for 3 days, then treated with MeOH (20 mL) followed by evaporation of all volatiles in vacuo. The residue was dissolved in Et_2O and filtered through Celite, followed by further washings of the solids with Et_2O. The solvent was evaporated and the residue was purified by flash column chromatography (5–30% EtOAc/petrol) to give **5** as a brown oil (10.48 g, 56%), **20** (0.45 g, 3%) as a brown oil, and **21** (1.34 g, 9%) as a brown oil. Compound **5**: R_f 0.46 (20% EtOAc/petrol). $[\alpha]_D^{29}$ +73 (*c* 4.6, $CHCl_3$). MS (ESI+) *m*/*z* 824 (M+Na$^+$, 100%). HRMS (ESI+) calcd for $C_{53}H_{55}NO_6Na$ (M+Na$^+$) 824.3926, found 824.3925. IR ν_{max} (cm^{-1}): 1700, 1449, 1110, 1060. ^{1}H NMR (300 MHz) δ 7.46–7.05 (m, 30H, Ar), 5.84–5.80 (m, 1H, H-4), 5.76–5.74 (m, 1H, H-3), 4.84 (d, 1H, *J* 11.4 Hz, Bn), 4.73 (d, 1H, *J* 11.4 Hz, Bn), 4.66 (d, 1H, *J* 11.4 Hz, Bn), 4.59 (d, 1H, *J* 11.4 Hz, Bn), 4.49–4.46 (m, 1H, H-2), 4.33 (d, 1H, J 11.0 Hz, Bn), 4.21 (d, 1H, J 11.0 Hz, Bn), 4.09 (dq, 1H, J 1.8, 15.3 Hz, H-5), 4.01–3.97 (m, 1H, H-1′), 3.96–3.91 (m, 2H, H-3′, H-5), 3.66 (t, 1H, J 5.4 Hz, H-2′), 3.47 (dd, 1H, J 3.9, 10.2 Hz, H-4′), 3.39 (dd, 1H, J 5.3, 10.4 Hz, H-4′), 1.45 (s, 9H, *t*-Bu). ^{13}C NMR (75 MHz) δ 153.9 (CO), 144.0, 138.7, 138.5, 138.2 (q Ar), 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2 (Ar), 126.9 (C-4), 126.5 (C-3), 86.9 (q C Tr), 80.9 (C-2′), 80.3 (C-1′), 79.7 (q C, Boc), 79.3 (C-3′), 74.8, 74.6, 73.4 (Bn), 67.0 (C-2), 63.8 (C-4′), 53.5 (C-5), 28.4 (CH_3).

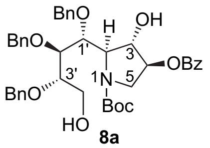
*4.1.2. tert-Butyl (2R,3S,4R)-3,4-dihydroxy-2-[(1R,2S,3S)-1,2,3-tris(benzyloxy)-4-triphenylmethyloxybutyl]-pyrrolidine-1-carboxylate (**6**)*

To a solution of **5** (3.43 g, 4.28 mmol) in acetone (20 mL) and water (20 mL) were added potassium osmate·dihydrate (78.7 mg, 0.214 mmol) and 4-morpholine-*N*-oxide (1.051 g, 8.985 mmol). The reaction mixture was stirred for 3 days at rt and evaporated to give a black oil, which was purified by flash column chromatography (30–50% EtOAc/petrol) to give **6** as a brown foamy solid (2.69 g, 75%). R_f 0.50 (40% EtOAc/petrol). $[\alpha]_D^{25}$ +34 (*c* 0.50, $CHCl_3$). MS (ESI+) *m*/*z* 858 (M+Na$^+$, 25%), 243 (Tr$^+$, 100%). HRMS (ESI+) calcd for $C_{53}H_{57}NO_8Na$ (M+Na$^+$) 858.3981, found 858.3991. IR ν_{max} (cm^{-1}): 3400, 1690, 1395, 1090, 1075. ^{1}H NMR (300 MHz) δ 7.46–7.05 (m, 30H, Ar), 4.86 (d, 1H, J 11.4 Hz, Bn), 4.70 (d, 1H, J 11.4 Hz, Bn), 4.62 (d, 1H, J 11.4 Hz, Bn), 4.53 (d, 1H, J 11.4 Hz, Bn), 4.38 (d, 1H, J 10.8 Hz, Bn), 4.26–4.21 (m, 3H, Bn, H-1′, H-4), 4.12–4.04 (m, 2H, H-3, H-3′), 3.83 (t, 1H, H-2′), 3.72 (m, 1H, H-2), 3.62–3.54 (m, 2H, H-4, H-4′), 3.43–3.40 (m, 1H, H-5), 3.22–3.19 (m, 1H, H-5), 1.43 (s, 9H, *t*-Bu). ^{13}C NMR (75 MHz) δ 154.5 (CO), 143.9, 138.5, 137.9, 137.8 (q Ar), 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 126.9 (Ar), 87.0 (q C, Tr), 81.2 (C-2′), 79.3 (q C, Boc), 79.0 (C-3′), 78.0 (C-1′), 75.2, 74.0, 73.7 (Bn), 71.2 (C-4), 70.4 (C-3), 65.1 (C-2), 64.5 (C-4′), 51.7 (C-5), 28.4 (CH_3).

*4.1.3. tert-Butyl (3aS,4S,6aR)-4-[(1R,2S,3S)-1,2,3-tris-(benzyloxy)-4-triphenylmethyloxybutyl]tetrahydro-5H-[1,3,2]dioxathiolo[4,5-c]pyrrole-5-carboxylate 2,2-dioxide (**7**)*

To a solution of **6** (301 mg, 0.361 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (0.755 mL, 5.42 mmol) followed by sulfuryl chloride (0.145 mL, 1.81 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C under an atmosphere of N_2 and then warmed up to rt for 1 h. The residue was suspended in water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 10 mL) and washed with brine. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a brown oil that was used in the next step without further purification (**7**): R_f 0.36 (20% EtOAc/petrol). MS (ESI+) *m*/*z* 920 (M+Na$^+$, 50%), 243 (Tr$^+$, 100%). HRMS (ESI+) calcd for $C_{53}H_{55}NO_{10}SNa$ (M+Na$^+$) 920.3444, found 920.3439. IR ν_{max} (cm^{-1}): 1700, 1395, 1210, 1160, 1070. ^{1}H NMR δ 7.42–6.93 (m, 30H, Ar), 5.44 (d, 1H, J 5.0 Hz, H-3), 5.07 (m, 1H, H-4), 4.76 (d, 1H, J 11.5 Hz, Bn), 4.69 (d, 1H, J 11.0 Hz, Bn), 4.57 (d, 1H, J 12.0 Hz, Bn), 4.50 (d, 1H, J 11.5 Hz, Bn), 4.45 (d, 1H, J 11.5 Hz, Bn), 4.41 (br s, 1H, H-2), 4.18 (d, 1H, J 11.0 Hz, Bn), 4.13 (m, 1H, H-2′), 4.04 (br d, 1H, J 6.5 Hz H-1′), 3.89–3.86 (m, 1H, H-3′), 3.73–3.68 (m, 1H, H-5), 3.59–3.55 (m, 1H, H-4′), 3.46 (dd, 1H, J 4.0, 10.5 Hz, H-4′), 3.39 (dd, 1H, J 6.3, 13.3 Hz, H-5), 1.44 (s, 9H, *t*-Bu). ^{13}C NMR δ 152.8 (CO), 143.9, 138.2, 137.6, 137.4 (q Ar), 128.7, 128.5, 128.3, 127.9, 127.8, 127.7, 127.5, 127.2, 127.0 (Ar), 87.1 (q C Tr), 84.4 (C-3), 83.5 (C-4), 80.8 (q C, Boc), 79.6 (C-1′), 79.3 (C-2′), 77.7 (C-3′), 75.4, 74.2, 73.7 (Bn), 64.4 (C-2), 63.3 (C-4′), 51.3 (C-5), 28.4 (CH_3).

*4.1.4. tert-Butyl (2R,3S,4S)-3-hydroxy-4-phenylcarbonyl-oxy-2-[(2S,3S)-1,2,3-tris(benzyloxy)-4-triphenylmethyl-oxybutyl]pyrrolidine-1-carboxylate (**8**) and tert-butyl (2R,3S,4S)-3-hydroxy-4-phenylcarbonyloxy-2-[(2S,3S)-4-hydroxy-1,2,3-tris(benzyloxy)-butyl]pyrrolidine-1-carboxylate (**8a**)*



8a

The crude cyclic sulfate **7** obtained from the above reaction was dissolved in DMSO (0.5 mL), and benzoic acid (0.221 g, 1.81 mmol) and cesium carbonate (0.647 g, 1.97 mmol) were added and the solution was stirred under an atmosphere of N_2 for 20 h at 40 °C. The reaction was suspended in THF (4 mL). Water (1.5 mL) then concentrated sulfuric acid (0.8 mL) were added and the reaction mixture was stirred at rt for 20 h, then poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude products were purified by flash column chromatography (15–50% EtOAc/petrol) to give **8** (183.3 mg, 54% from **6**), **8a** (18.4 mg, 7% from **6**), and **6** (37.2 mg, 16%). Compound **8**: R_f 0.48 (30% EtOAc/petrol). $[\alpha]_D^{24}$ +36 (*c* 1.0, $CHCl_3$). MS (ESI+) *m*/*z* 961.9 (M+Na$^+$, 62%). HRMS (ESI+) calcd for $C_{60}H_{61}NO_9Na$ (M+Na$^+$) 962.4244, found 962.4247. IR ν_{max} (cm^{-1}): 3385, 1730, 1696, 1271, 1110, 1070, 1027. ^{1}H NMR δ 7.99 (d, 2H, J 7.5 Hz, H-*o*-Bz), 7.55 (t, 1H, J 7.5 Hz, H-*p*-Bz), 7.42–7.07 (m, 32H, Ar), 5.10 (dd, 1H, J 14.5, 8.0 Hz, H-4), 4.79 (d, 1H, J 12.0 Hz, Bn), 4.75 (d, 1H, J 11.5 Hz, Bn), 4.72 (br t, 2H, J 5.5 Hz, H-3, Bn), 4.54 (m, 1H, Bn), 4.53 (m, 1H, Bn), 4.44 (br s, 2H, H-1′, Bn), 4.28 (br s, 1H, OH), 4.20 (br s, 1H, H-5), 4.11 (dd, 1H, J 14.0, 7.0 Hz, H-3′), 3.89 (br s, 1H, H-2′), 3.85 (br s, 1H, H-2), 3.46 (br s, 2H, H-4′, H-4′), 3.15 (br s, 1H, H-5), 1.44 (s, 9H, *t*-Bu). ^{13}C NMR δ 166.9, 153.5 (CO), 143.9, 138.1, 137.7 (q Ar), 133.3, 129.8, 129.4, 128.7, 128.3, 128.29, 128.22, 128.16, 128.13, 127.7, 127.69, 127.61, 127.2, 126.8 (Ar), 86.9 (q C Tr), 80.5 (C-2′), 79.7 (C-4), 79.3 (q C, Boc), 78.7 (C-3′), 78.2 (C-1′), 75.0, 74.2, 73.5 (Bn), 73.2 (C-3), 64.8 (C-2), 63.6 (C-4′), 49.2 (C-5), 28.3 (CH_3).

Compound **8a**: R_f 0.29 (40% EtOAc/petrol). MS (ESI+) *m/z* 697.8 (M+H$^+$, 30%). HRMS (ESI+) calcd for $C_{41}H_{47}NO_9$ (M+H$^+$) 698.3329, found 698.3340. IR ν_{max} (cm^{-1}): 3436, 1700, 1403, 1265, 1110, 1069. ^{1}H NMR δ 8.00 (d, 2H, *J* 7.5 Hz, H-*o*-Bz), 7.53 (t, 1H, *J* 7.5 Hz, H-*p*-Bz), 7.40 (t, 2H, *J* 7.5 Hz, H-*m*-Bz), 7.37–7.18 (m, 15H, Ar), 5.14 (dd, 1H, *J* 14.0, 8.0 Hz, H-4), 4.83–4.44 (m, 6H, 4Bn, H-3, H-1′), 4.30–4.10 (m, 3H, H-5, Bn, H-2), 4.00–3.86 (m, 2H, H-4′, H-4′), 3.84–3.76 (m, 3H, H-2′, H-3′, Bn), 3.24–3.12 (m, 1H, H-5), 1.46 (s, 9H, *t*-Bu). ^{13}C NMR δ 166.7, 154.0 (CO), 143.8, 138.6, 137.5, 134.4 (q Ar), 133.3, 129.8, 129.4, 128.7, 128.5, 128.4, 128.3, 128.29, 128.21, 128.16, 128.0, 127.8, 127.6, 127.3, 126.9 (Ar), 81.0 (C-2′), 80.3 (q C, Boc), 78.8 (C-4), 78.2 (C-3′), 78.1 (C-1′), 75.6, 74.3 (C-3), 74.2, 72.7 (Bn), 64.5 (C-2), 60.7 (C-4′), 49.9 (C-5), 28.7 (CH$_3$).

*4.1.5. tert-Butyl (2R,3S,4S)-3,4-dihydroxy-2-[(1R,2S,3S)-1,2,3-tris(benzyloxy)-4-triphenylmethyloxybutyl]-pyrrolidine-1-carboxylate (**9**)*

To a solution of **8** (34.9 mg, 0.037 mmol) in MeOH (1 mL) was added K_2CO_3 (0.010 g, 0.075 mmol). After stirring at rt for 1 day, the mixture was evaporated and dissolved in $CHCl_3$ then washed with water. The aqueous layer was extracted with $CHCl_3$ and the combined $CHCl_3$ extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by PTLC (30% EtOAc/petrol) to give **9** as a colorless oil (13.5 mg, 44%). R_f 0.16 (30% EtOAc/petrol). $[\alpha]_D^{22}$ +10.5 (*c* 0.7, CHCl$_3$). MS (ESI+) *m/z* 858 (M+Na$^+$, 62%), 243 (Tr$^+$, 100%). HRMS (ESI+) calcd for $C_{53}H_{57}NO_8Na$ (M+Na$^+$) 858.3982, found 858.3970. IR ν_{max} (cm^{-1}): 3400, 1691, 1392, 1163, 1073. ^{1}H NMR δ 7.48–7.11 (m, 30H, Ar), 4.85 (d, 1H, *J* 11.5 Hz, Bn), 4.68 (d, 1H, *J* 11.5 Hz, Bn), 4.61–4.47 (m, 3H, Bn), 4.40 (d, 1H, *J* 11.5 Hz, Bn), 4.24 (d, 1H, *J* 8.5 Hz, H-1′), 4.01 (m, 1H, H-3′), 3.78–3.76 (m, 2H, H-3, H-4), 3.72–3.62 (m, 4H, H-4′, H-2′, H-4′, H-2), 3.48 (dd, 1H, *J* 12.0, 4.5 Hz, H-5), 3.24 (d, 1H, *J* 11.5 Hz, H-5), 1.26 (s, 9H, *t*-Bu). ^{13}C NMR δ 154.5 (CO), 143.9, 137.4, 137.1, 137.08 (q Ar), 128.8, 128.7, 128.5, 128.3, 127.9, 127.8, 127.7, 127.1, 127.0 (Ar), 87.0 (q C Tr), 81.6 (C-2′), 80.0 (q C, Boc), 79.2 (C-1′), 77.4 (C-3′), 77.4, 77.2, 77.1 (Bn), 77.2 (C-4), 73.7 (Bn), 73.3 (C-3), 67.9 (C-2), 63.8 (C-4′), 54.5 (C-5), 29.7 (CH$_3$).

*4.1.6. (2S,3S,4R)-4-[(2R,3S,4S)-3,4-Dihydroxypyrrolidin-2-yl]-2,3,4-tribenzyloxybutan-1-ol (**10**) and (1S,2S,6S,7R,8R,8aR)-1,2-dihydroxy- 6,7,8-tribenzyloxyoctahydro-indolizine (**11**)*

To a solution of **9** (237 mg, 0.284 mmol) in anhydrous CH_2Cl_2 (2.8 mL) were added anisole (0.289 mL, 2.841 mmol) and TFA (2.19 mL, 28.41 mmol). The reaction mixture was stirred under an atmosphere of N_2 at rt for 20 h, followed by the evaporation of all volatiles in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with saturated Na_2CO_3 solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined CH_2Cl_2 layers were dried (Na_2CO_3) and evaporated to give a brown oil, which was purified by flash column chromatography (50–100% EtOAc/petrol and 15% MeOH/EtOAc) to give **11** as a pale yellow solid (11 mg, 8%) and the amino-alcohol **10** (92.3 mg, 66%) as a brown foamy solid. Compound **10**: R_f 0.45 (1:19:80 NH$_4$OH/MeOH/CHCl$_3$). $[\alpha]_D^{21}$ −14.0 (*c* 0.35, MeOH). MS (ESI+) *m/z* 494 (M+H$^+$, 100%). HRMS (ESI+) calcd for $C_{29}H_{35}NO_6$ (M+H$^+$) 494.2543, found 494.2531. IR ν_{max} (cm^{-1}): 3411, 3283, 1454, 1126, 1058, 1044. ^{1}H NMR δ 7.37–7.25 (m, 15H, Ar), 4.86 (d, 1H, *J* 11.0 Hz, Bn), 4.71 (d, 1H, *J* 11.0 Hz, Bn), 4.68 (d, 1H, *J* 11.5 Hz, Bn), 4.65 (d, 1H, *J* 11.0 Hz, Bn), 4.63 (d, 1H, *J* 11.5 Hz, Bn), 4.57 (d, 1H, *J* 11.5 Hz, Bn), 4.00 (br s, 1H, H-3), 3.90–3.88 (m, 1H, H-4), 3.84 (m, 2H, H-1′, H-4′), 3.79 (m, 2H, H-2′, H-4′), 3.74 (m, 1H, H-3′), 3.14 (br s, 1H, H-2), 3.00 (dd, 1H, *J* 11.5, 4.5 Hz, H-5), 2.81 (br d, 1H, *J* 11.5 Hz, H-5). ^{13}C NMR δ 137.6, 137.4, 137.3 (q Ar), 128.7, 128.6, 128.5, 128.3, 128.2, 128.1 (Ar), 80.9 (C-2′), 80.3 (C-1′), 79.5 (C-3), 78.6 (C-3′), 75.5, 74.2, 72.9 (Bn), 66.8 (C-2), 60.8 (C-4′), 52.3 (C-5).

*Synthesis of **11** from **10***: to a solution of **10** (37.0 mg, 0.075 mmol) in pyridine (1 mL) was added triphenylphosphine (39.4 mg, 0.150 mmol) and diisopropyl azodicarboxylate (0.030 mL, 0.150 mmol) at 0 °C. The reaction mixture was stirred under an atmosphere of N_2 at 0 °C for 8 h, and at 0–5 °C for 40 h, then warm up to rt for 48 h. The volatiles were removed in vacuo then 1 M HCl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (2×10 mL). The combined CH_2Cl_2 extracts were washed with water dried ($MgSO_4$), filtered, and then evaporated to give a brown oil. Purification by flash column chromatography (2% MeOH/CHCl$_3$–1:4:95% NH$_4$OH/MeOH/CHCl$_3$) gave **11** (9.0 mg, 25%) as a pale yellow solid. Compound **11**: R_f 0.31 (100% EtOAc). $[\alpha]_D^{23}$ +34 (*c* 0.26, CHCl$_3$). MS (ESI+) *m/z* 476 (M+H$^+$, 100%). HRMS (ESI+) calcd for $C_{29}H_{33}NO_5$ (M+H$^+$) 476.2437, found 476.2327. IR ν_{max} (cm^{-1}): 3293, 1460, 1103, 1071. ^{1}H NMR δ 7.38–7.27 (m, 15H, Ar), 5.00 (d, 1H, *J* 10.5 Hz, Bn), 4.94 (d, 1H, *J* 11.0 Hz, Bn), 4.82 (d, 1H, *J* 11.0 Hz, Bn), 4.70 (d, 1H, *J* 11.5 Hz, Bn), 4.67 (d, 1H, *J* 12.5 Hz, Bn), 4.64 (d, 1H, *J* 11.5 Hz, Bn), 4.04 (dd, 1H, *J* 5.0, 2.0 Hz, H-2), 3.73 (dd, 1H, *J* 6.5, 2.0 Hz, H-1), 3.69 (m, 1H, H-6), 3.53 (m, 1H, H-7), 3.52 (m, 1H, H-8), 3.18 (dd, 1H, *J* 10.5, 5.5 Hz, H-5), 2.85 (d, 1H, *J* 10.5 Hz, H-3), 2.61 (dd, 1H, *J* 10.5, 6.5 Hz, H-3), 2.04 (t, 1H, *J* 10.5 Hz, H-5), 1.96 (dd, 1H, *J* 9.0, 7.0 Hz, H-8a). ^{13}C NMR δ 138.6, 138.2, 138.1 (q Ar), 128.7, 128.43, 128.41, 128.19, 128.14, 127.9, 127.8, 127.7, 127.6 (Ar), 87.3 (C-7), 84.1 (C-1), 81.6 (C-8), 79.4 (C-6), 78.0 (C-2), 75.5, 74.8, 72.9 (Bn), 72.6 (C-8a), 60.4 (C-3), 54.1 (C-5).

*4.1.7. (1S,2S,6S,7R,8R,8aR)-Octahydroindolizine-1,2,6,7,8-pentol (2-epi-**1**)*

To a solution of **11** (11.0 mg, 0.023 mmol) in EtOAc (0.5 mL) and MeOH (0.5 mL) was added PdCl$_2$ (6.16 mg, 0.035 mmol). The reaction mixture was stirred at rt under an atmosphere of H_2 (balloon) for 4 h. The mixture was filtered through a Celite pad and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo and the residue was dissolved in water and applied to a column of Amberlyst (OH$^-$) A-26 resin. Elution with water followed by evaporation in vacuo gave compound **4** (3.4 mg, 72%) as a pale yellow, foamy solid. $[\alpha]_D^{25}$ −9.2 (*c* 0.17, H_2O). MS (ESI+) *m*/*z* 206 ($M+H^+$, 100%). HRMS (ESI+) calcd for $C_8H_{15}NO_5$ ($M+H^+$) 206.1028, found 206.0990. IR ν_{max} (cm^{-1}): 3308, 1073, 1043. ^1H NMR (D_2O) δ 4.14 (br d, 1H, $J_{2,3\beta}$ 7.0 Hz, H-2), 3.96 (dd, 1H, $J_{1,8a}$ 7.0, $J_{1,2}$ 2.5 Hz, H-1), 3.64 (ddd, 1H, $J_{5\beta,6}$ 10.0, $J_{6,7}$ 9.0, $J_{5\alpha,6}$ 5.3 Hz, H-6), 3.47 (t, 1H, $J_{7,8}$=$J_{8,8a}$ 9.0 Hz, H-8), 3.29 (t, 1H, $J_{6,7}$=$J_{7,8}$ 9.0 Hz, H-7), 3.11 (dd, 1H, $J_{5\alpha,5\beta}$ 10.8, $J_{5\alpha,6}$ 5.3 Hz, H-5α), 2.87 (br d, 1H, $J_{3\alpha,3\beta}$ 11.0 Hz, H-3α), 2.76 (dd, 1H, $J_{3\alpha,3\beta}$ 10.8, $J_{2,3\beta}$ 6.3 Hz, H-3β), 2.16 (t, 1H, $J_{5\alpha,5\beta}$=$J_{5\beta,6}$ 10.8 Hz, H-5β), 2.11 (dd, 1H, $J_{8,8a}$ 9.0, $J_{1,8a}$ 8.0 Hz, H-8a). ^{13}C NMR (D_2O) δ 82.7 (C-1), 79.2 (C-7), 78.1 (C-2), 74.1 (C-8), 72.1 (C-8a), 70.3 (C-6), 59.7 (C-3), 55.6 (C-5).

4.1.8. *(6E)-5-{Allyl[(2,2,2-trichloroethoxy)carbonyl]amino}-5,6,7-trideoxy-7-phenyl-D-gluco-hept-6-enitol (**16**)*

To a solution of **3**[10] (4.94 g, 16.9 mmol) in 1,4-dioxane (50 mL) were added $NaHCO_3$ solution (34 mL, 2 M) and succinimidyl-2,2,2-trichloroethyl carbonate (4.90 g, 16.9 mmol). The reaction mixture was stirred at rt for 5 h then diluted with water (100 mL) and extracted with EtOAc (2×100 mL). The combined EtOAc extracts were washed with 10% HCl (2×100 mL) and brine (100 mL) before being dried ($MgSO_4$) and evaporated, giving a clear oil. The residue was purified by flash column chromatography (100% EtOAc) to give **16** as a clear oil (5.75 g, 75%). R_f 0.30 (100% EtOAc). $[\alpha]_D^{22}$ −35 (*c* 2.0, $CHCl_3$). MS (ESI+) *m*/*z* 490 ($M+Na^+$, 60%), 243 (Tr^+, 100%). HRMS (ESI+) calcd for $C_{19}H_{24}Cl_3NO_6Na$ ($M+Na^+$) 490.0567, found 490.0566. IR ν_{max} (cm^{-1}): 3400, 1697, 1412, 1244, 1141, 1050. ^1H NMR δ 7.39–7.22 (m, 5H, Ar), 6.62 (d, 1H, *J* 16.2 Hz, H-7), 6.45 (dd, 1H, *J* 7.8, 15.9 Hz, H-6), 5.86 (dddd, 1H, *J* 2.7, 7.1, 10.2, 17.0 Hz, H-2′), 5.22 (d, 1H, *J* 17.4 Hz, H-3′), 5.16 (d, 1H, *J* 10.2 Hz, H-3′), 4.83 (d, 1H, *J* 12.0 Hz, CH_2CCl_3), 4.74 (d, 1H, *J* 12.0 Hz, CH_2CCl_3), 4.42 (t, 1H, *J* 7.7 Hz, H-5), 4.13 (m, 1H, H-4), 4.00 (m, 2H, H-1′, H-1′), 3.86 (q, 1H, *J* 4.2 Hz, H-2), 3.72 (m, 2H, H-1, H-1), 3.65 (m, 1H, H-3). ^{13}C NMR δ 154.8 (CO), 136.3 (q Ar), 135.1 (C-7), 133.7 (C-2′), 128.5, 127.9, 126.5 (Ar), 124.1 (C-6), 118.1 (C-3′), 95.3 (CCl_3), 75.0 (CH_2CCl_3), 73.2 (C-2), 72.2 (C-4), 70.0 (C-3), 63.9 (C-1), 61.6 (C-5), 49.7 (C-1′).

4.1.9. *(6E)-5-{Allyl[(2,2,2-trichloroethoxy)carbonyl]amino}-1-O-triphenylmethyl-5,6,7-trideoxy-7-phenyl-D-gluco-hept-6-enitol (**17**)*

To a solution of **16** (15.0 g, 32.1 mmol) in dry CH_2Cl_2 (150 mL) were added dry pyridine (2.85 mL, 35.3 mmol) and TrCl (9.04 g, 32.4 mmol). The reaction mixture was stirred at rt for 9 h, then poured into water (150 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by flash column chromatography (40% EtOAc/petrol) to give **17** (17.15 g, 75%) as a clear oil. R_f 0.60 (20% EtOAc/petrol). $[\alpha]_D^{25}$ −8 (*c* 1.0, $CHCl_3$). MS (ESI+) *m*/*z* 732 ($M+Na^+$, 100%). HRMS (ESI+) calcd for $C_{38}H_{38}Cl_3NO_6Na$ ($M+Na^+$) 732.1662, found 732.1631. ^1H NMR (major rotamer inter alia) δ 7.44–7.21 (m, 20H, Ar), 6.59 (d, 1H, *J* 16.2 Hz, H-7), 6.44 (dd, 1H, *J* 7.5, 15.8 Hz, H-6), 5.83 (dddd, 1H, *J* 6.2, 6.2, 10.8, 16.5 Hz, H-2′), 5.17 (d, 1H, *J* 17.1 Hz, H-3′), 5.10 (d, 1H, *J* 10.5 Hz, H-3′), 4.77 (d, 1H, *J* 11.7 Hz, CH_2CCl_3), 4.70 (d, 1H, *J* 11.7 Hz, CH_2CCl_3), 4.37 (t, 1H, *J* 7.8 Hz, H-5), 4.07 (m, 1H, H-4), 3.96 (m, 2H, H-1′, H-1′), 3.91 (m, 1H, H-2), 3.71 (m, 1H, H-3), 3.34 (dd, 1H, *J* 4.8, 9.6 Hz, H-1), 3.24 (dd, 1H, *J* 5.7, 9.6 Hz, H-1). ^{13}C NMR δ 154.9 (CO), 143.6 (q Ar), 136.2 (C-7), 135.0 (C-2′), 133.7 (q Ar), 128.6, 127.9, 127.1, 126.6 (Ar), 123.9 (C-6), 118.1 (C-3′), 95.3 (CCl_3), 86.9 (q C, Tr), 75.1 (CH_2CCl_3), 73.0 (C-4), 72.4 (C-2), 69.5 (C-3), 64.6 (C-1), 62.1 (C-5), 50.0 (C-1′).

4.1.10. *(1R,7aR)-1-[(1R,2S)-1,2-Bis(benzyloxy)-3-triphenylmethyloxypropyl]-5,7a-dihydro-1H-pyrrolo[1,2-c][1,3]oxazol-3-one (**20**) and (3S,4R,4aR)-3-[(1S)-1-(benzyloxy)-2-triphenylmethyloxyethyl]-4-(benzyloxy)-3,4,4a,7-tetrahydropyrrolo[1,2-c][1,3]oxazin-1-one (**21**)*

To a solution of triol **17** (14.0 g, 19.74 mmol) in dry THF (200 mL) were added *n*-Bu_4NI (730 mg, 1.974 mmol) and BnBr (14.10 mL, 118.48 mmol). The reaction mixture was stirred at rt for 10 min then cooled to 0 °C before the addition of NaH (7.3 g, 78.98 mmol, 30% dispersion in mineral oil). The mixture was then warmed to rt and stirred for 1 h before the addition of MeOH (2 mL). After stirring for 10 min, the mixture was filtered through Celite followed by the washing of the solids with CH_2Cl_2. The filtrate was evaporated. Oxazolidinone **18** and oxazinanone **19** were obtained as a mixture (12.0 g) and separated from tri-O-benzylated **17** (which was not isolated) by flash column chromatography (25% EtOAc/petrol). The mixture of **18** and **19** was dissolved in dry CH_2Cl_2 (900 mL) and Grubbs II catalyst (687 mg, 0.81 mmol) was added and the reaction mixture was stirred and heated at reflux for 24 h, then cooled to rt and evaporated. The residue was purified by flash column chromatography (40% EtOAc) to give oxazolone **20** (4.85 g 39%) and oxazinone **21** (3.85 g, 31%) as oils.

Compounds **20**: R_f 0.51 (40% EtOAc/petrol). $[\alpha]_D^{25}$ +13 (*c* 4.5, $CHCl_3$). MS (ESI+) *m*/*z* 660 ($M+Na^+$, 43%). HRMS (ESI+) calcd for $C_{42}H_{39}NO_5Na$ ($M+Na^+$) 660.2726, found 660.2712. ^1H NMR δ 7.47–7.15 (m, 25H, Ar), 5.86 (dq, 1H, *J* 2.0, 5.9 Hz, H-7), 5.69 (dq, 1H, *J* 2.0, 5.9 Hz, H-6), 4.81 (dd, 1H, *J* 5.7, 8.1 Hz, H-1), 4.74 (d, 1H, *J* 12.0 Hz, Bn), 4.68 (d, 1H, *J* 11.1 Hz, Bn), 4.61 (d, 1H, *J* 11.1 Hz, Bn), 4.39 (d, 1H, *J* 11.1 Hz, Bn), 4.27 (ddt, 1H, *J* 2.1, 3.6, 15.5 Hz, H-5), 4.09–4.03 (m, 1H, H-7a), 3.73–3.67 (m, 2H, H-1′, H-2′), 3.63 (dddd, 1H, *J* 1.5, 2.7, 4.8, 15.6 Hz, H-5), 3.56 (dd, 1H, *J* 4.8, 10.2, H-3′), 3.47 (dd, 1H, *J* 4.8, 10.2 Hz, H-3′). ^{13}C NMR δ 162.2 (C-3), 144.0, 138.2, 138.1 (q Ar), 131.7 (C-7), 128.53, 128.49, 128.5, 128.1, 128.0, 127.9, 127.6, 127.3, 127.2 (Ar), 125.8 (C-6), 87.4 (q C, Tr), 79.0 (C-1), 78.3, 77.1 (C-1′ or C-2′), 74.6, 72.6 (Bn), 67.0 (C-7a), 62.5 (C-3′), 54.7 (C-5).

Compound **21**: R_f 0.20 (40% EtOAc/petrol). $[\alpha]_D^{25}$ +80 (*c* 7.8, $CHCl_3$). MS (ESI+) *m*/*z* 660 ($M+Na^+$, 45%), 243 (Tr^+, 100%). HRMS (ESI+) calcd for $C_{42}H_{39}NO_5Na$ 660.2726, found 660.2710. ^{1}H NMR δ 7.44–7.16 (m, 25H, Ar), 5.82 (s, 2H, H-5, H-6), 4.603 (dd, 1H, *J* 1.3, 6.3 Hz, H-3), 4.601 (d, 1H, *J* 11.5 Hz, Bn), 4.59 (d, 1H, *J* 11.8 Hz, Bn), 4.56 (d, 1H, *J* 11.8 Hz, Bn), 4.52 (dd, 1H, *J* 1.2, 9.5 Hz, H-4a), 4.45 (d, 1H, *J* 11.8 Hz, Bn), 4.39 (dd, 1H, *J* 4.8, 15.3 Hz, H-7), 4.01 (dd, 1H, *J* 5.3, 15.5 Hz, H-7), 3.86 (ddd, 1H, *J* 1.5, 6.3, 7.3 Hz, H-1′), 3.60 (dd, 1H, *J* 6.0, 10.0 Hz, H-4), 3.54 (dd, 1H, *J* 6.0, 10.0 Hz, H-2′), 3.51 (dd, 1H, *J* 7.0, 10.0 Hz, H-2′). ^{13}C NMR δ 151.7 (C-1), 143.8, 138.0, 136.9 (q Ar), 128.59 (C-5 or C-6), 128.55, 128.2, 128.1 (Ar), 127.8 (C-5 or C-6), 127.7, 127.6, 127.4, 127.3, 127.1, 127.0 (Ar), 87.4 (q C, Tr), 75.2 (C-1′), 75.0 (C-3), 73.9 (C-4), 72.7, 72.2 (Bn), 62.8 (C-2′), 62.7 (C-4a), 55.1 (C-7).

*4.1.11. (3S,4R,4aR,5R,6S)-4-Benzyloxy-3-[(1S)-1-(benzyloxy)-2-triphenylmethyloxyethyl]-5,6-dihydroxy-hexahydropyrrolo[1,2-c][1,3]oxazin-1-one (**22**)*

To a solution of **21** (3.43 g, 5.38 mmol) in acetone (20 mL) and water (20 mL) were added potassium osmate·dihydrate (99 mg, 0.269 mmol) and 4-morpholine-*N*-oxide (1.32 g, 11.30 mmol). The reaction mixture was stirred for 16 h at rt and evaporated to give a black oil, which was purified by flash column chromatography (60% EtOAc/petrol) to give **22** as a brown foamy solid (2.4 g, 67%). R_f 0.10 (60% EtOAc/petrol). $[\alpha]_D^{24}$ +75 (*c* 2.8, $CHCl_3$). MS (ESI+) *m/z* 672 (M+H$^+$, 100%). HRMS (ESI+) calcd for $C_{42}H_{42}NO_7$ (M+H$^+$) 672.2961, found 672.2941. ^{1}H NMR δ 7.45–7.17 (m, 25H, Ar), 4.70 (d, 1H, *J* 11.5 Hz, Bn), 4.581 (d, 1H, Bn), 4.579 (dd, 1H, *J* 1.5, 6.0 Hz, H-3), 4.51 (d, 1H, *J* 12.0 Hz, Bn), 4.33 (d, 1H, *J* 11.5 Hz, Bn), 4.06 (dd, 1H, *J* 5.8, 9.3 Hz, H-4), 3.97 (dt, 1H, *J* 3.9, 8.1 Hz, H-6), 3.88 (q, 1H, *J* 3.5 Hz, H-5), 3.84 (dt, 1H, *J* 1.5, 6.3 Hz, H-1′), 3.54 (dd, 1H, *J* 6.0, 10.0 Hz, H-2′), 3.52–3.48 (m, 3H, H-2′, H-7, H-4a), 3.22 (dd, 1H, *J* 8.3, 11.3 Hz, H-7). ^{13}C NMR δ 152.5 (C-1), 143.8, 138.1, 137.5 (q Ar), 128.6, 128.5, 128.2, 128.1, 127.84, 127.77, 127.5, 127.1, 126.9 (Ar), 87.3 (q C, Tr), 75.7 (C-1′), 75.5 (C-3), 72.5 (Bn), 72.4 (Bn), 70.9 (C-5), 69.9 (C-6), 67.6 (C-4), 62.7 (C-2′), 60.3 (C-4a), 50.3 (C-7).

*4.1.12. (3S,4R,4aR,5R,6S)-4,5,6-Tris(benzyloxy)-3-[(1S)-1-(benzyloxy)-2-triphenylmethyloxyethyl]-hexahydropyrrolo[1,2-c][1,3]oxazin-1-one (**23**)*

To a solution of **22** (2.24 g, 3.34 mmol) in dry THF (20 mL) at 0 °C was added NaH (353 mg, 7.35 mmol, 50% in mineral oil). After H_2 evolution had ceased (10 min), BnBr (1.6 mL, 13.36 mmol) and *n*-BuNI (123 mg, 0.334 mmol) were added. The mixture was brought to 50 °C and stirred for 18 h, then cooled to rt and treated with MeOH (5 mL) and Et_3N (3 mL), and stirred for 10 min. After evaporating all volatiles, the residue was dissolved in Et_2O and filtered through Celite, followed by further washings of the solids with Et_2O. The solvent was evaporated and the residue was purified by flash column chromatography (30% EtOAc/petrol) to give **23** as a yellow oil (1.9 g, 67%). R_f 0.19 (30% EtOAc/petrol). $[\alpha]_D^{24}$ +64 (*c* 2.77, $CHCl_3$). MS (ESI+) *m/z* 874 (M+Na$^+$, 100%). HRMS (ESI+) calcd for $C_{56}H_{53}NO_7Na$ (M+Na$^+$) 874.3719, found 874.3720. IR ν_{max} (cm^{-1}): 1680, 1449, 1091, 1060, 1024. ^{1}H NMR δ 7.42–7.08 (m, 35H, ArH), 4.96 (d, 1H, *J* 11.4 Hz, Bn), 4.65 (d, 1H, *J* 11.7 Hz, Bn), 4.56 (dt, *J* 1.2, 6.0 Hz, H-3), 4.50 (d, 1H, *J* 12.0 Hz, Bn), 4.48 (s, 2H, Bn×2), 4.44 (d, 1H, *J* 11.7 Hz, Bn), 4.37 (d, 1H, *J* 11.4 Hz, Bn), 4.21 (d, 1H, *J* 11.7 Hz, Bn), 4.14 (ddd, 1H, *J* 1.2, 5.9, 9.6 Hz, H-4), 3.94 (dt, 1H, *J* 1.0, 3.0 Hz, H-5), 3.77 (dt, 1H, *J* 1.2, 3.5 Hz, H-1′), 3.65 (ddd, 1H, *J* 3.0, 6.8, 10.2 Hz, H-6), 3.54 (dd, 1H, *J* 7.5, 10.0 Hz, H-7), 3.51 (m, 4H, H-2′, H-2′, H-4a, H-7). ^{13}C NMR δ 151.7 (C-1), 143.9, 138.23, 138.18, 137.4, 137.2 (q Ar), 128.6, 128.5, 128.45, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.74, 127.67, 127.4, 127.3, 127.1, 126.6 (Ar), 87.5 (q C, Tr), 78.0 (C-6), 76.0 (C-5), 75.6 (C-1′), 74.6 (C-3), 73.4, 72.4, 72.2, 72.1 (Bn), 67.7 (C-4), 62.7 (C-2′), 59.4 (C-4a), 48.0 (C-7).

*4.1.13. (3S,4R,4aR,5R,6S)-4,5,6-Tris(benzyloxy)-3-[(1S)-1-(benzyloxy)-2-hydroxyethyl]-hexahydropyrrolo[1,2-c]-[1,3]oxazin-1-one (**24**)*

To a solution of **23** (1.88 g, 2.21 mmol) in dry CH_2Cl_2 (20 mL) was added anisole (2.41 mL, 22.1 mmol) and the mixture was cooled to 0 °C before the addition of TFA (1.7 mL, 22.1 mmol). The reaction mixture was stirred for 1 h at 0 °C, then poured into saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (2×50 mL). The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash column chromatography (60% EtOAc/petrol) to give **24** (820 mg, 61%) as a yellow oil. R_f 0.17 (60% EtOAc/petrol). $[\alpha]_D^{25}$ +120 (*c* 1.5, $CHCl_3$). MS (ESI+) *m/z* 633 (M+Na$^+$, 100%). HRMS (ESI+) calcd for $C_{37}H_{39}NO_7$ (M+Na$^+$) 633.2702, found 633.2690. ^{1}H NMR δ 7.38–7.26 (m, 16H, Ar H), 7.21–7.17 (m, 4H, Ar H), 4.97 (d, 1H, *J* 11.4 Hz, Bn), 4.79 (d, 1H, *J* 12.0 Hz, Bn), 4.58 (dd, 1H, *J* 2.0, 5.6 Hz, Bn), 4.53 (d, 1H, *J* 11.1 Hz, Bn), 4.52 (d, 1H, *J* 11.7 Hz, Bn), 4.51 (s, 2H, Bn×2), 4.49 (d, 1H, *J* 12.3 Hz, Bn), 4.40 (d, 1H, *J* 11.1 Hz, Bn), 4.17 (dd, 1H, *J* 5.7, 9.3 Hz, H-4), 4.01 (t, 1H, *J* 3.0 Hz, H-5), 3.92 (ddd, 1H, *J* 1.5, 5.4, 7.1 Hz, H-1′), 3.84 (ddd, 1H, *J* 1.2, 5.7, 10.2 Hz, H-2′), 3.79 (m, 1H, H-2′), 3.74 (dd, 1H, *J* 3.2, 7.8 Hz, H-6), 3.61 (dd, 1H, *J* 2.9, 9.5 Hz, H-4a), 3.58 (dd, 1H, *J* 7.8, 10.2 Hz, H-7), 3.50 (t, 1H, *J* 9.9 Hz, H-7). ^{13}C NMR δ 152.4 (C-1), 138.1, 138.0, 137.3, 137.0 (q Ar), 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 126.8 (Ar), 77.8 (C-6), 77.6 (C-1′), 77.3 (C-5), 75.7 (C-3), 73.4, 72.5, 72.2, 72.1 (Bn), 67.7 (C-4), 60.6 (C-2′), 59.4 (C-4a), 48.0 (C-7).

*4.1.14. (2S,3S,4R)-4-[(2S,3R,4S)-3,4-Dibenzyloxypyrrolidin-2-yl]-2,4-dibenzyloxybutane-l,3-diol (**25**)*

To a solution of **24** (30 mg, 49.18 μmol) in MeOH (1 mL) were added NaOH (20 mg, 0.5 mmol) and H_2O (0.5 mL) in a 10 mL sealed microwave reactor tube. The reaction mixture was stirred and irradiated with microwaves in a CEM microwave reactor for 1 h at 110 °C using a maximum applied power of 500 W. After cooling, the mixture was poured into water and the product was extracted with EtOAc (2×5 mL). The combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (100% EtOAc and 10% MeOH/EtOAc) to give a clear oil (18 mg, 62%). R_f 0.32 (20% MeOH/EtOAc). $[\alpha]_D^{21}$ +75 (*c* 0.85, $CHCl_3$). MS (ESI+) *m*/*z* 584 ($M+H^+$, 100%). HRMS (ESI+) calcd for $C_{36}H_{42}NO_6$ 584.3012 ($M+H^+$), found 584.3023. ^1H NMR δ 7.35–7.14 (m, 20H, Ar), 5.02 (d, 1H, *J* 11.5 Hz, Bn), 4.75 (d, 1H, *J* 10.5 Hz, Bn), 4.52 (s, 2H, Bn×2), 4.50 (d, 1H, *J* 11.5 Hz, Bn), 4.43 (d, 1H, *J* 10.5 Hz, Bn), 4.42 (s, 2H, Bn×2), 4.11 (t, 1H, *J* 3.3 Hz, H-3), 4.08 (t, 1H, *J* 4.0 Hz, H-3′), 4.02 (dd, 1H, *J* 3.5, 9.5 Hz, H-4), 3.96 (m, 1H, H-1), 3.73–3.66 (m, 3H, H-1, H-2, H-4′), 3.57 (dd, 1H, *J* 4.8, 9.3 Hz, H-2′), 2.90 (dd, 1H, *J* 9.3, 10.8 Hz, H-5′), 2.77 (dd, 1H, *J* 6.8, 10.8 Hz, H-5′). ^{13}C NMR δ 138.7, 138.3, 138.04, 138.0 (q Ar), 128.43, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.3 (Ar), 80.9 (C-2 or C-4′), 77.4 (C-3′), 76.9 (C-2 or C-4′), 74.6 (C-4), 73.3 (C-3), 73.2, 72.11, 72.10, 71.7 (Bn), 62.7 (C-1), 61.1 (C-2′), 46.4 (C-5′).

4.1.15. (1*R*,2*S*,6*S*,7*R*,8*R*,8a*R*)-1,2,6,8-Tetrabenzyloxy-octahydroindolizin-7-ol (**26**)

To a solution of amino-alcohol **25** (290 mg, 0.497 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C were added Et_3N (2.77 mL, 19.88 mmol), PPh_3 (326 mg, 1.24 mmol), and CBr_4 (410 mg, 1.24 mmol). The reaction mixture was stirred for 2 h at 0 °C and poured into water (20 mL). The water layer was extracted with CH_2Cl_2 (2×20 mL). The combined CH_2Cl_2 extracts were washed with brine, dried (K_2CO_3), and evaporated. The residue was purified by flash column chromatography (50% EtOAc/petrol) to give **26** as a yellow oil (240 mg, 85%). R_f 0.69 (40% EtOAc/petrol). MS (ESI+) *m*/*z* 566 ($M+H^+$, 100%). HRMS (ESI+) calcd for $C_{36}H_{40}NO_5$ ($M+H^+$) 566.2906, found 566.2922. ^1H NMR δ 7.37–7.20 (m, 20H, Ar), 4.95 (d, 1H, *J* 11.1 Hz, Bn), 4.88 (d, 1H, *J* 11.4 Hz, Bn), 4.65 (d, 1H, *J* 11.7 Hz, Bn), 4.58 (d, 1H, *J* 12.0 Hz, Bn), 4.56 (d, 1H, *J* 11.7 Hz, Bn), 4.54 (d, 1H, *J* 12.0 Hz, Bn), 4.52 (d, 1H, *J* 11.1 Hz, Bn), 4.50 (d, 1H, *J* 12.0 Hz, Bn), 4.19 (dd, 1H, *J* 3.5, 5.3 Hz, H-1), 4.14 (ddd, 1H, *J* 3.6, 5.6, 8.0 Hz, H-2), 3.84 (t, 1H, *J* 9.2 Hz, H-8), 3.59 (m, 1H, H-6), 3.57 (m, 1H, H-7), 3.24 (dd, 1H, *J* 4.2, 10.2 Hz, H-5), 3.20 (dd, 1H, *J* 3.3, 9.9 Hz, H-3), 2.47 (dd, 1H, *J* 8.0, 10.1 Hz, H-3), 2.17 (dd, 1H, *J* 3.5, 9.2 Hz, H-8a), 1.94 (t, 1H, *J* 10.1 Hz, H-5). ^{13}C NMR δ 139.1, 138.4, 138.1, 138.0 (q Ar), 128.5, 128.32, 128.3, 128.2, 128.1, 127.9, 127.6, 127.5, 127.4, 127.3 (Ar), 79.2 (C-7), 78.5 (C-2), 78.2 (C-6), 77.4 (C-1), 77.0 (C-8), 74.2, 73.8, 72.4, 72.2 (Bn), 69.2 (C-8a), 57.3 (C-3), 53.4 (C-5).

4.1.16. (1*R*,2*S*,6*S*,7*R*,8*R*,8a*R*)-Octahydroindolizine-1,2,6,7,8-pentol (1,2-di-*epi*-**1**)

To a solution of **26** (168 mg, 0.297 mmol) in MeOH (3 mL) was added $PdCl_2$ (79 mg, 0.446 mmol). The reaction mixture was stirred at rt under a H_2 atmosphere (balloon) for 18 h. The mixture was filtered through Celite and the solids were washed with MeOH. The combined filtrates were evaporated and the residue was dissolved in H_2O and applied to a column of Amberlyst (OH^-) A-26 resin. Elution with H_2O followed by evaporation resulted in a cloudy white residue that was recrystallized from boiling EtOH with a few drops of H_2O to give 1,2-di-*epi*-**1** (38 mg, 62%) as transparent micro-crystals. $[\alpha]_D^{23}$ +21 (*c* 1.5, H_2O) [lit. $[\alpha]_D^{23}$ +66.5 (*c* 1.33, H_2O)] MS (ESI+) *m*/*z* 206 ($M+H^+$, 100%). HRMS (ESI+) calcd for $C_8H_{16}NO_5$ ($M+H^+$) 206.1028, found 206.1036. IR ν_{max} (cm^{-1}): 3344, 1618, 1294. ^1H NMR (D_2O) δ 4.29 (ddd, 1H, $J_{2,3\beta}$ 2.8, $J_{1,2}$ 5.8, $J_{2,3\alpha}$ 8.5 Hz, H-2), 4.12 (dd, 1H, $J_{1,8a}$ 3.8, $J_{1,2}$ 6.3 Hz, H-1), 3.53 (t, 1H, $J_{7,8}$=$J_{8,8a}$ 9.5 Hz, H-8), 3.48 (ddd, 1H, $J_{5\alpha,6}$ 5.5, $J_{6,7}$ 9.0, $J_{5\beta,6}$ 10.5 Hz, H-6), 3.18 (t, 1H, $J_{6,7}$=$J_{7,8}$ 9.3 Hz, H-7), 3.00 (t, 1H, $J_{5\alpha,6}$ 5.0, $J_{5\alpha,5\beta}$ 11.0 Hz, H-5α), 2.76 (dd, 1H, $J_{2,3\beta}$ 2.8, $J_{3\alpha,3\beta}$ 10.8 Hz, H-3β), 2.50 (dd, 1H, $J_{2,3\alpha}$ 8.3, $J_{3\alpha,3\beta}$ 10.8 Hz, H-3α), 2.04 (dd, 1H, $J_{1,8a}$ 3.5, $J_{8,8a}$ 9.5 Hz, H-8a), 1.95 (t, 1H, $J_{5\alpha,5\beta}$=$J_{5\beta,6}$ 10.5 Hz, H-5β). ^{13}C NMR (D_2O) δ 79.3 (C-7), 70.7 (C-8a), 70.4 (C-6), 70.2 (C-2), 69.7 (C-1), 69.3 (C-8), 59.9 (C-3), 55.7 (C-5).

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References and notes

1. Matsumura, T.; Kasai, M.; Hayashi, T.; Arisawa, M.; Momose, Y.; Arai, I.; Amagaya, S.; Komatsu, Y. *Pharm. Biol.* **2000**, *38*, 302–307.
2. Arisawa, M.; Hayashi, T.; Momose, Y. *Food Style* **2001**, *21*, 69–73.
3. Momose, Y. Jpn. Kokai Tokkyo Koho 2000, 7 pp (JP 2000072770, CAN 132:203147).
4. Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731–734.
5. Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774–7780.
6. Tang, M.; Pyne, S. G. *J. Org. Chem.* **2003**, *68*, 7818–7824.
7. Lindsay, K. B.; Pyne, S. G. *Aust. J. Chem.* **2004**, *57*, 669–672.
8. Tang, M.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 5759–5767.
9. Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670–2680.
10. Davis, A. S.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139–3143.
11. Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097–7099.
12. Karanjule, N. S.; Markad, S. D.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 6273–6276.
13. Zhao, Z.; Song, L.; Mariano, P. S. *Tetrahedron* **2005**, *61*, 8888–8894.
14. Bell, A. W.; Pickering, L.; Watson, A. A.; Nash, R. J.; Griffiths, R. C.; Jones, M. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8561–8564.
15. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535–3536.
16. Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051–7091.
17. Medeiros, E. F. D.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2725–2730.
18. (a) Mulzer, J.; Dehmlow, H. *J. Org. Chem.* **1992**, *57*, 3194–3202; (b) Casiraghi, G.; Ulgheri, F.; Spanu, P.; Rassu, G.; Pinna, L.; Gasparri, F. G.; Belicchi, F. M.; Pelosi, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2991–2997; (c) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358–1364.
19. Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487–2496.
20. Zhao, H.; Hans, S.; Chemg, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761–1767; Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, *36*, 1291–1294.
21. Davis, A. S.; Gates, N. J.; Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2004**, 49–52.
22. Greenwood, E. S.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **2003**, *59*, 3307–3314.

23. Murray, A. J.; Parsons, P. J.; Greenwood, E. S.; Viseux, E. M. E. *Synlett* **2004**, 1589–1591.
24. Murray, A. J.; Parsons, P. J.; Hitchcock, P. B. *Tetrahedron* **2007**, *63*, 6485–6492.
25. Lapatsanis, L.; Milias, G.; Froussios, K.; Kolovos, M. *Synthesis* **1983**, 671–673.
26. Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549–2558.
27. Nash, R. J.; Thomas, P. I.; Waigh, R. D.; Fleet, G. W. J.; Wormald, M. R.; de Q. Lilley, P. M.; Watkin, D. J. *Tetrahedron Lett.* **1994**, *35*, 7849–7852.
28. Personal e-mail communication with George W. J. Fleet (Oxford University).
29. Kato, A.; Kano, E.; Adachi, I.; Molyneux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. R.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 325–331.
30. Bell, A. D.; Pickering, L.; Watson, A. A.; Nash, R. J.; Pan, Y. T.; Elbein, A. D.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 5869–5872.
31. Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron* **2005**, *61*, 6527–6533.
32. Unfortunately we have not been able to obtain a copy of the NMR spectra of uniflorine A for comparison purposes from the original authors.[1]