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Synthesis of (+)-Uniflorine A: A Structural Reassignment and a Configurational Assignment†

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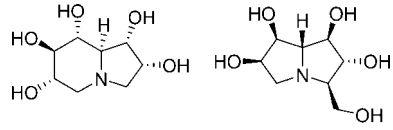
ABSTRACT



Originally proposed structure of (-)-unflorine A

Revised structure of (-)-uniflorine A

The total synthesis of (+)-uniflorine A has allowed for the structural reassignment and the configurational assignment of the alkaloid (−)-uniflorine A from a 1,2,6,7,8-pentahydroxyindolizidine structure to (−)-(1*R*,2*R*,3*R*,6*R*,7*S*,7a*R*)-1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidine (6-*epi*-casuarine).

The alkaloids (−)-uniflorine A and (+)-uniflorine B, along with the known alkaloid (+)-(3α,4α,5β)-1-methylpiperidine-3,4,5-triol, were 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. Uniflorines A and B were found to be inhibitors of the α-glucosidases, rat intestinal maltase (IC_{50} values of 12 and 4.0 μM, respectively), and sucrase (IC_{50} values 3.1 and 1.8 μM, respectively).[1] The structures of uniflorines A and B were deduced from NMR analysis to be that of the pentahydroxyindolizidine structures **1** and **3**, respectively.[1] The proposed structure of uniflorine A is similar to that of castanospermine, except for the stereochemistry at C-1 and the extra hydroxyl substitution at C-2. As part of our program concerned the synthesis of polyhydroxylated indolizidine and pyrrolizidine alkaloids,[4–12] we reported an efficient 9-step synthesis of the purported structure of 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 ^{1}H 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 ^{1}H NMR spectrum, perhaps consistent with the amine salt. The ^{1}H NMR spectrum of the hydrochloride salt of synthetic **1**, however, did not match the literature spectral data either. We therefore concluded that the structure originally assigned to uniflorine A was not correct.[10]

† This paper is dedicated to E. J. Corey on the occasion of his 80th birthday.

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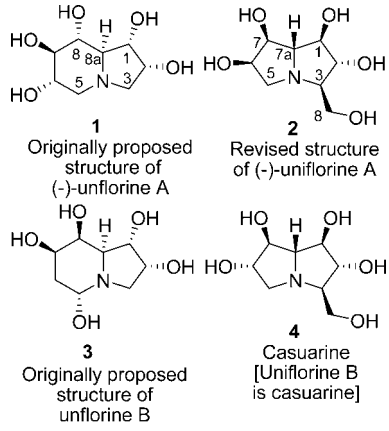
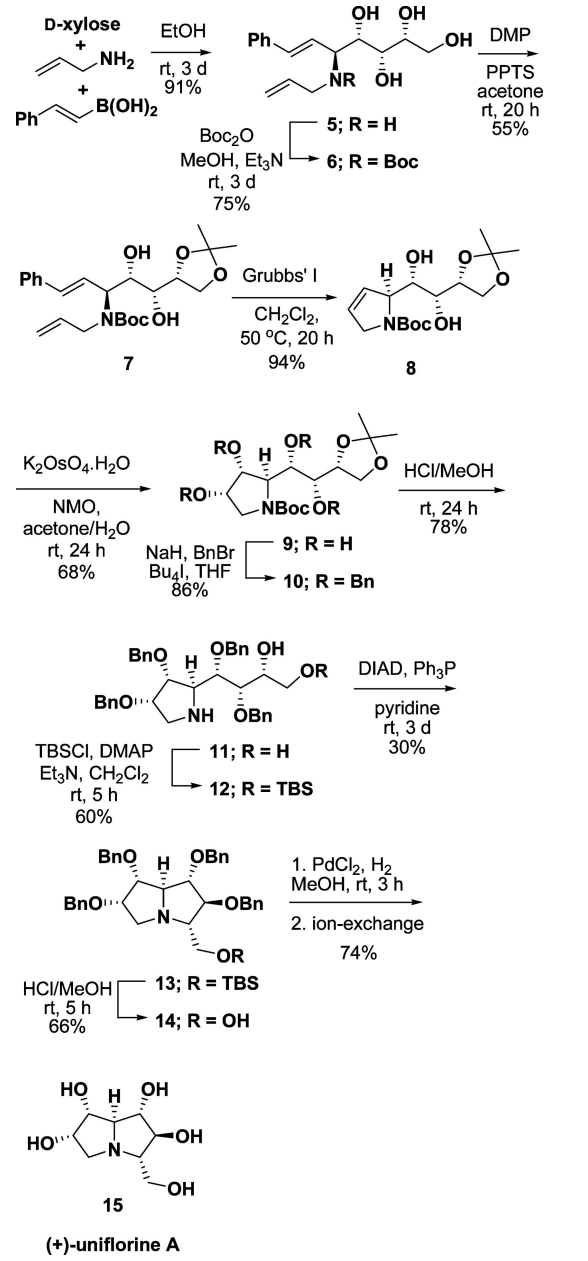


In 2006, Dhavale et al.[13] also reported the synthesis of compound **1**; their sample had NMR spectral data identical to ours. This paper also reported the synthesis of 8a-*epi*-**1** and 1,2,8a-tri*epi*-**1**. In 2005, Mariano[14] reported the synthesis of 1-*epi*-**1**, while that of 1,2-di-*epi*-**1** was reported by Fleet[15] in 1996, before uniflorine A was even isolated, and later by Mariano[14] and by us in 2008.[16] In 2008, we also reported the synthesis of 2-*epi*-**1**.[16] These 1,2,6,7,8-pentahydroxyindolizidine molecules also had NMR spectral data significantly different from that of uniflorine A.

Our analysis of the NMR spectral data for uniflorine B and its optical rotation clearly indicated that uniflorine B was the known alkaloid casuarine **4**, an identified inhibitor of α-glycosidases.[16] The published NMR spectral data for uniflorine A revealed to us that this alkaloid was 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 **4**. From the published NMR data we suggested that uniflorine A was 6-*epi*-casuarine (**2**).[16] We now report here the unequivocal proof that (−)-uniflorine A is 6-*epi*-casuarine from the synthesis of its enantiomer, (+)-uniflorine A, from D-xylose. This synthesis also established the absolute configuration of the natural product to that shown in structure **2**.

The synthesis of (+)-uniflorine A is shown in Scheme 1. The enantiomer of the known tetrol **5**[10] was prepared in one step from the boronic acid−Mannich reaction (Petasis reaction)[10] of D-xylose, allylamine, and (*E*)-styrene boronic acid and then converted to its *N*-Boc derivative **6**.[10] The terminal diol functionality of **6** was selectively protected as the acetonide derivative **7** under standard conditions. A ring-closing metathesis (RCM) reaction of the diene **7** using Grubbs' first-generation ruthenium catalyst provided the 2,5-dihydropyrrole **8** in 94% yield that underwent an osmium-(VIII)-catalyzed *syn*-dihydroxylation (DH) reaction to furnish the tetrol **9** as a single diastereomer in 68% yield. The

Scheme 1



stereochemical outcome of this DH reaction was expected due to the stereodirecting effect of the C-2 pyrrolidine substituent in **8**.[4,5,10,16] The configuration of this diol was established from ROESY NMR studies on the final product **15**. The tetrol **9** was readily converted to its per-*O*-benzyl-protected derivative **10** in 86% yield using standard reaction conditions.[10] Treatment of **10** under acidic conditions (HCl/MeOH) resulted in *N*-Boc and acetonide hydrolysis and gave the aminodiol **11** in 78% yield. Regioselective silylation of **11** with TBSCl/Et_3N/DMAP gave the primary silyl ether **12** which underwent cyclization under Mitsunobu reaction conditions using pyridine[6,17] as the solvent to give a mixture (ca. 4: 1) of the desired pyrrolizidine **13** and an indolizidine product (structure not shown) in a combined yield of 30% after purification of the crude reaction mixture by column

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chromatography. The undesired indolizidine product arose from first base catalyzed *O*-TBS migration to the secondary hydroxyl group in **12** followed by Mitsunobu cyclization onto the primary carbon of the butyl side chain. These cyclized products could be separated by a second, more careful, column chromatographic separation. Acid hydrolysis of **13** gave the primary alcohol **14**, which upon hydrogenolysis using $PdCl_2/H_2$[6,16,18] gave (+)-uniflorine A **15** ($[\alpha]^{22}_D$ +6.6 (*c* 0.35, H_2O) (lit.[1] for (−)-uniflorine A, $[\alpha]_D$ −4.4 (*c* 1.2, H_2O)), in 74% yield after ion-exchange chromatography and in a total of 11 synthetic steps from D-xylose. The ^1H NMR spectral data (D_2O) of **15** and that of the natural product were essentially identical ($\Delta\delta_H = 0.00-0.02$ ppm, see Table 1 of the Supporting Information). The ^{13}C NMR signals of **15** (in D_2O with MeCN as an internal reference at δ 1.47), however, were all consistently 2.1−2.2 ppm upfield of those reported for the natural product (Supporting Information).

We[16] noted earlier that while the ^1H NMR spectral data reported for uniflorine B and casuarine were also essentially identical, the ^{13}C NMR shifts reported for casuarine were all consistently 3.0−3.2 ppm upfield of the corresponding ^{13}C NMR resonances reported for uniflorine B.[1] We suggested that alternative referencing between the two samples accounts for this consistent discrepancy.[16] The ^{13}C NMR spectrum of casuarine was referenced to acetone at δ 29.80 while that of uniflorines A and B were apparently referenced to TMS as an internal standard (a standard not known for its water (D_2O) solubility).[1] Thus, the consistent differences in the ^{13}C NMR chemical shifts between synthetic **15** and that of (−)-uniflorine A can also be ascribed to the differences in referencing between the different samples.[19]

The observed cross-peaks in the ROESY spectrum of **15** were fully consistent with the configurational assignment of **15** as shown in Figure 1. Thus our synthesis of **15**, the

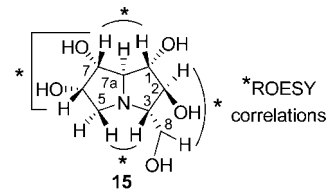

Figure 1. ROESY NMR correlations for **15**.

enantiomer of (−)-uniflorine A, provides unequivocal proof that (−)-uniflorine A is 6-*epi*-casuarine. This synthesis also establishes the absolute configuration of (−)-uniflorine A as that shown in structure **2**. (−)-Uniflorine A therefore represents one of now two known natural product stereoisomers of casuarine.[20]

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Supporting Information Available: Full experimental and spectroscopic details of all compounds shown in Scheme 1. A table of the NMR spectal data of **15** and (−)-uniflorine A and copies of the ^1H, ^{13}C, COSY, and HSQC NMR spectra of **15**. This information is available free of charge via the Internet at http://pubs.acs.org.

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