JOC*Article*

Synthesis of Putative Uniflorine A

Andrew S. Davis,[†] Stephen G. Pyne,*[,†] Brian W. Skelton,[‡] and Allan H. White[‡]

Department of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia, and Department of Chemistry, University of Western Australia, Crawley, Western Australia, 6009, Australia

spyne@uow.edu.au

Received February 2, 2004

A diastereoselective synthesis of the putative structure of the natural product uniflorine A has been achieved by using the Petasis borono−Mannich reaction and ring-closing metathesis as key steps. The NMR data of the synthetic material did not match that reported for the natural product. The structure of the final synthetic product was unequivocally determined by single-crystal X-ray study of its pentaacetate derivative. Thus it was concluded that the proposed structure of uniflorine A is incorrect.

The polyhydroxylindolizidine 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 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. As part of our program concerned with the synthesis of polyhydroxylated indolizidine and pyrrolizidine alkloids[4−6] we have developed a short and efficient synthesis of **1**, which is reported here.

Our retrosynthetic analysis of **1** (Scheme 1) suggested that the target compound could be acquired from the precursor **3** using a ring-closing metathesis (RCM) reaction[7−9] and *N*-alkylation to prepare the five- and six-membered rings of **1**, respectively. The 1,2-anti amino alcohol **3** would be expected to be readily obtained from the boronic acid−Mannich reaction (Petasis reaction)[10] of L-xylose, allylamine, and (*E*)-styrene boronic acid, followed by chemo- and regioselective *N*- and *O*-protection reactions.

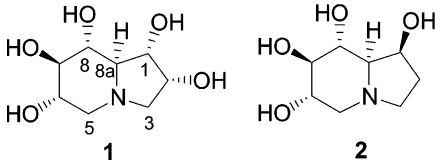
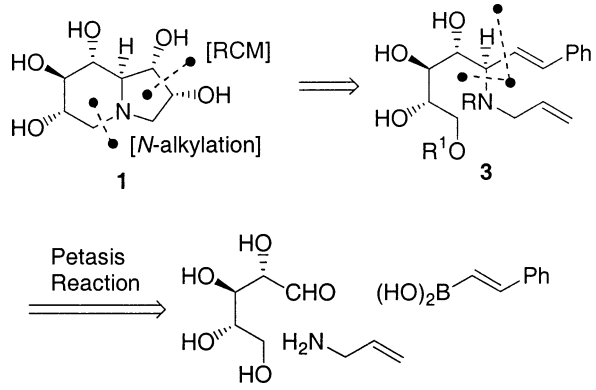


FIGURE 1. Proposed structure of uniflorine A (**1**) and the structure of castanospermine (**2**).

SCHEME 1. Retrosynthetic Analysis of 1



[†] University of Wollongong.

[‡] University of Western Australia.

(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* 21 **2001**, *5*, 69−73.

(3) Momose, Y. Japanese 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.

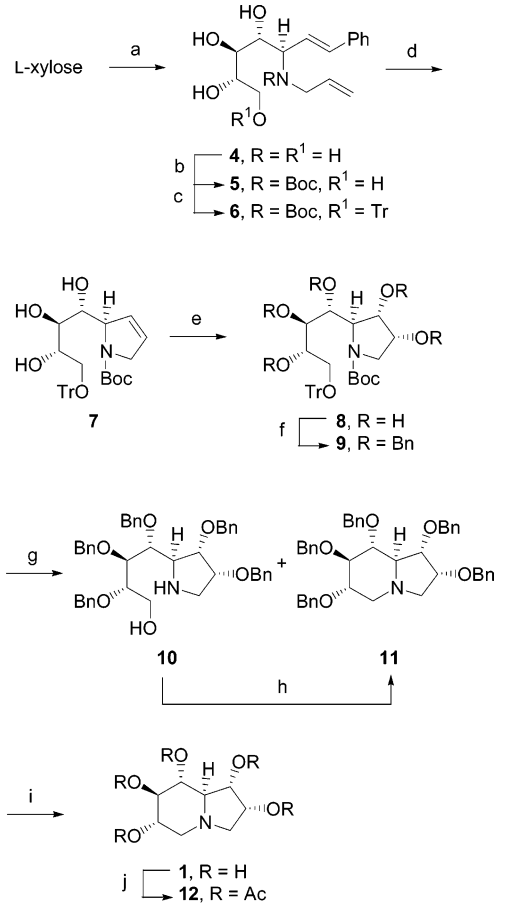
(7) For the application of the ring-closing metathesis reaction to the synthesis of aza-sugars see refs 4−6 and: (a) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621−1624. (b) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547−550. (c) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61−67. (d) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360. (e) Lindstrom, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173−7176. (f) Ovaa, H.; Stragies, R.; van der Marcel, G. A.; van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501−1502. (g) Subramanian, T.; Lin, C.-C.; Lin, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4079−4082. (h) Klitze, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605−5608. (i) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630−4633. (j) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329.

(8) For the application of the ring-closing metathesis reaction to the synthesis of 2,5-dihydropyrroles from dienes see: (a) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376−2378. (b) Furstner, A.; Fursterner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315−1316. (c) Cerezo, S.; Cortes, J.; Moreno-Manas, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14869−14884. (d) Furstner, A.; Ackermann, L. *Chem. Commun.* **1999**, 95−96. (e) Bujard, M.; Briot, A.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8795−8788. (f) Furstner, A.; Liebl, M.; Hill, A. F.; Wilton-Ely, J. D. E. T. *Chem. Commun.* **1999**, 601−602. (g) Ackermann, L.; Furstner, A.; Weskamp, T.; Kohl, F. J.; Hermann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787−4790. (h) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657−8662. (i) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929−1931. (j) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771−1772.

(9) For RCM reactions on related acyclic *N*-protected dienes see: (a) Huwe, C. M.; Kiehl, O. C.; Blechert, S. *Synlett* **1996**, 67−8. (b) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113−4116. (c) Martín, R.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 93−95. (d) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393−5401. (e) Fustero, S.; Navarro, A.; Pina, B.; Soler, Juan G.; Bartolome, A.; Asensio, A.; Simon, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621−2624.

10.1021/jo049806y CCC: $27.50
Published on Web 04/02/2004

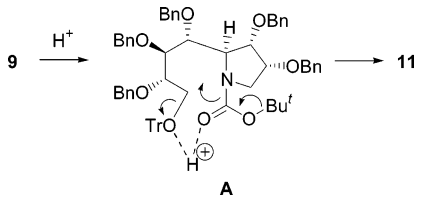
SCHEME 2[a]



[a] Reagents and conditions: (a) (*E*) $PhCH{=}CHB(OH)_2$, allylamine, EtOH, rt, 16 h; ion exchange, 73%; (b) $(Boc)_2O$, Et_3N, MeCN, DMF, 0 °C (4 h) then rt (14 h), 51%; (c) TrCl, pyridine, rt, 18 h, 68%; (d) Grubbs' catalyst, DCM, reflux, 18 h, 86%; (e) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone/water, rt, 30 h, 88%; (f) NaH, BnBr, *n*-Bu_4NI, THF, 50 °C, 3 d, 76%; (g) TFA, anisole, DCM, 0 °C, 2 h, **10** (37%) and **11** (54%); (h) PPh_3, CBr_4, NEt_3, CH_2Cl_2, 0 °C, 2 h, 54%; (i) $PdCl_2$, H_2 (1 atm), MeOH, rt, 2 h; ion exchange then recrystallization, 63% (j) Ac_2O, pyridine, rt, 4 h, 88%.

In the event, the requisite Petasis reaction gave the desired amino-tetraol **4** in 73% yield as a single diastereomer after purification by ion-exchange chromatography (Scheme 2). The amino-tetraol **4** was converted to its *N*-Boc derivative **5** (51% yield) and then the primary alcohol was regioselectively protected as its *O*-trityl compound **6** (68% yield). A RCM reaction of **6** with Grubbs' first generation catalyst (benzylidene bis(tricyclohexylphosphine)dichlororuthenium, 10 mol %) smoothly gave the 2,5-dihydropyrrole **7** in 86% yield. Osmium-(VIII)-catalyzed *syn*-dihydroxylation (DH) of **7** furnished the pentaol **8** as a single diastereomer in 88% yield. The stereochemical outcome of this DH reaction was expected due to the stereodirecting effect of the C-2 substituent in **7**[4,5] and was later confirmed from the single-crystal X-ray analysis of the pentaacetate derivative of **1** (**12**, see Supporting Information**)**. The pentaol **8** was readily converted to its penta-*O*-benzyl derivative **9** in 76% yield under standard conditions.[11] Selective liberation of the

SCHEME 3



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 room temperature.[12] Surprisingly, this reaction gave a mixture of the desired amino-alcohol **10** (37%) and the indolizidine **11** (54%) (Scheme 2). When this reaction was performed at 0 °C a mixture of **10** and the monodeprotected trityl derivative of **9** was obtained. Treatment of this compound or **10** with TFA/anisole at room temperature gave only a very poor yield (<5% from ^1H NMR analysis) of **11** after 2 days. We suggest that **11** arises by cyclization of an incipient amide anion **A** with activation of the *O*-trityl group by protonation by TFA, as shown in Scheme 3. The amino-alcohol **10** underwent smooth cyclization to give the same indolizidine **11**, using $Ph_3P/CBr_4/Et_3N$ (54%).[13] Debenzylation of **11** under hydrogenolysis conditions with $PdCl_2/H_2$[14] gave **1** in 63% after ion-exchange chromatography and then recrystallization in a total of eight synthetic steps from L-xylose. The structure of **1** was unequivocally established by single-crystal X-ray study of its pentaacetate derivative **12** (see the Supporting Information). The ^1H and ^{13}C NMR data for synthetic **1**, however, did not match those reported for uniflorine A (Table 1); 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 spectral data either. Most significantly, the ^1H NMR of synthetic **1** showed H8a had the expected coupling for $J_{1,8a}$ of 7.7 Hz and for $J_{8,8a}$ of 9.0 Hz, consistent with their *anti*-H-8a, H-1 and *anti*-H-8, H-8a stereochemical relationship (1,2-*trans*-diaxial like couplings[15]), whereas in uniflorine A, the coupling constant $J_{1,8a}$ is 4.5 Hz, more consistent with the relative *syn*-H-8a, H-1 stereochemistry, suggesting that uniflorine A, if it is an indolizidine alkaloid, has the same H-1 stereochemistry as castanospermine **2**. We therefore conclude that the structure assigned to uniflorine A is not correct.[1,16]

(10) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798−11799.

(11) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535−3536.

(12) Medeiros, E. F. D.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2725−2730.

(13) (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. Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1538−1364. (c) This experiment was performed on the enantiomer of **10** only.

(14) 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.

(15) (a) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487−2496. (b) Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1015−1027. (c) Razavi, H.; Polt, R. *J. Org. Chem.* **2000**, *65*, 5693−5706.

(16) 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]

TABLE 1. Physical and Spectral Data for 1 and Uniflorine A[1]

	uniflorine A[1]	synthetic **1**
physical appearance	colorless microcrystals	colorless microcrystals
optical rotation	$[\alpha]_D$ −4.4 (*c* 1.2, H_2O)	$[\alpha]^{25}_D$ −6 (*c* 5.0, H_2O)
melting point	174−178 °C	170−172 °C
mass spectrometry	ISMS *m*/*z* 206 ($M + H^+$)	CI + ve *m*/*z* 206 ($M + H^+$, 100%)
^1H NMR[a]	500 MHz, D_2O	500 MHz, D_2O
	2.76 (1H, m, $J_{5\alpha,6} = 6.4$, $J_{5\beta,6} = 3.8$, $J_{6,7} = 9.0$, H6)	2.08 (dd, 1H, $J_{1,8a} = 7.5$, $J_{8,8a} = 9.3$, H8a)
	2.98 (1H, m, $J_{2,3\beta} = 5.1$, $J_{3\alpha,3\beta} = 12.1$, H3$\beta$)	2.09 (t, 1H, $J_{5\alpha,5\beta} = J_{5\alpha,6} = 10.8$, H5α)
	3.04 (1H, dd, $J_{2,3\alpha} = 5.1$, $J_{3\alpha,3\beta} = 12.1$, H3α)	2.20 (dd, 1H, $J_{2,3\beta} = 6.5$, $J_{3\alpha,3\beta} = 10.5$, H3$\beta$)
	3.14 (1H, dd, $J_{8,8a} = 7.7$, $J_{8a,1} = 4.5$, H8a)	3.01 (dd, 1H, $J_{5\beta,6} = 5.5$, $J_{5\alpha,5\beta} = 10.5$, 5$\beta$)
	3.61 (1H, dd, $J_{5\alpha,6} = 6.4$, $J_{5\alpha,5\beta} = 11.8$, H5α)	3.20 (t, 1H, $J_{6,7} = J_{7,8} = 9.0$, H7)
	3.76 (1H, dd, $J_{5\beta,6} = 3.8$, $J_{5\alpha,5\beta} = 11.8$, H5$\beta$)	3.25 (t, 1H, $J_{7,8} = J_{8,8a} = 9.0$, H8)
	3.81 (1H, dd, $J_{6,7} = 9.0$, $J_{7,8} = 7.7$, H7)	3.26 (dd, 1H, $J_{2,3\alpha} = 6.5$, $J_{3\alpha,\beta} = 10.5$, H3α)
	3.94 (1H, t, $J_{7,8} = J_{8,8a} = 7.7$, H8)	3.46 (ddd, 1H, $J_{5\beta,6} = 5.5$, $J_{6,7} = 9.0$, $J_{5\alpha,6} = 11.0$, H6)
	4.18 (1H, t, $J_{8a,1} = J_{1,2} = 4.5$, H1)	3.82 (t, 1H, $J_{1,2} = J_{1,8a} = 7.5$, H1)
	4.35 (1H, m, H2)	4.11 (q, 1H, $J_{1,2} = J_{2,3\alpha} = J_{2,3\beta} = 7.0$, H2)

[a] *J* values in hertz.

In conclusion, we have developed an efficient 8-step synthesis of purported uniflorine A from L-xylose. While others have developed syntheses of other 1,2,6,7,8-pentahydroxyindolizidines,[15a,b,17] our synthetic strategy is more versatile and is sufficiently flexible to allow the synthesis of other analogues of **1** for future structure−biological activity studies and to unequivocally determine the correct structure of uniflorine A.

Experimental Section

General methods were as described previously.[5,6] All ^1H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted.

(6*E*)-5-(Allylamino)-5,6,7-trideoxy-7-phenyl-D-*gluco*-hept-6-enitol (4). To a mixture of L-xylose (5 g, 33.3 mmol) and *trans*-2-phenylvinyl boronic acid (4.928 g, 33.3 mmol) was added absolute ethanol (65 mL) and allylamine (2.5 mL, 33.3 mmol). The mixture was stirred at room temperature for 16 h, followed by the evaporation of all volatiles in vacuo. The residue was dissolved in a 50:50 mixture of HCl (1 M) and MeOH (ca. 15 mL), applied to a column of DOWEX resin (H^+ form), and washed with distilled H_2O (800 mL). The product was eluted with 7 M NH_4OH (500 mL) and 14 M NH_4OH (500 mL). The fractions containing the product were combined and concentrated to a brown foamy solid (7.147 g, 73%). $[\alpha]^{25}_D$ +27 (*c* 0.06, MeOH); MS (CI + ve) *m*/*z* 294 ($M + H^+$, 100%); HRMS (CI + ve) calcd for $C_{16}H_{24}NO_4$ ($M + H^+$) 294.1705, found 294.1713. ^1H NMR (300 MHz, CD_3OD) δ 7.44−7.29 (m, 5H, Ar), 6.56 (d, 1H, $J = 16.2$ Hz, H7), 6.17 (dd, 1H, $J = 16.1$, 9.2 Hz, H6), 5.29 (dddd, 1H, $J = 17.0$, 9.9, 6.6, 5.7 Hz, H2′), 5.20 (dq, 1H, $J = 17.1$, 1.5 Hz, H3′), 5.12 (dq, 1H, $J = 9.9$, 1.4 Hz, H3′), 3.85 (t, 1H, *J* 4.8 Hz, H4), 3.76 (ddd, 1H, $J = 6.3$, 5.1, 3.0 Hz, H2), 3.69 (dd, 1H, $J = 5.1$, 3.2 Hz, H3), 3.62 (d, 1H, *J* = 5.1 Hz, H1), 3.61 (d, 1H, $J = 6.2$ Hz, H1), 3.50 (dd, 1H, $J = 9.0$, 4.8 Hz, H5), 3.34 (ddt, 1H, $J = 13.8$, 5.6, 1.5 Hz, H1′), 3.17 (ddt, 1H, $J = 13.5$, 6.6, 1.5 Hz, H1′); ^{13}C NMR (CD_3OD) δ 137.9 (C), 136.3 (CH), 135.8 (CH), 129.5 (2 × CH), 128.7 (CH), 127.4 (2 × CH), 117.9 (CH), 74.4 (CH), 73.1 (CH), 72.8 (CH), 64.4 (CH_2), 63.4 (CH), 50.0 (CH_2).

(6*E*)-5-[Allyl(*tert*-butylcarbonyl)amino]-5,6,7-trideoxy-7-phenyl-D-*gluco*-hept-6-enitol (5). To a solution of the amino alcohol **4** (3.8 g, 12.97 mmol) in anhydrous CH_3CN (20 mL) and anhydrous DMF (4 mL) was added anhydrous triethylamine (2.0 mL, 14.37 mmol). The mixture was cooled to 0 °C and a solution of di-*tert*-butyldicarbonate (3.110 g, 14.27 mmol) in anhydrous CH_3CN (10 mL) was added dropwise over 1 h. The reaction was stirred at 0 °C for 4 h then at room temperature for 14 h, followed by the evaporation of all volatiles in vacuo at 60 °C for 20 min. The residue was purified by column chromatography (60−100% EtOAc/petrol) to give compound **5** (2.6 g, 51%) as a brown oil. R_f 0.40 (100% EtOAc); $[\alpha]^{25}_D$ −50 (*c* 3.0, $CDCl_3$); MS (CI + ve) *m*/*z* 394 ($M + H^+$, 30%); HRMS (CI + ve) calcd for $C_{21}H_{32}NO_6$ ($M + H^+$) 394.2230, found 394.2229. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.17 (m, 5H, Ar), 6.56 (d, 1H, $J = 15.9$ Hz, H7), 6.40 (dd, 1H, $J = 15.9$, 6.6 Hz, H6), 5.82−5.76 (m, 1H, H2′), 5.13−5.05 (m, 2H, H3′), 4.50−4.43 (m, 1H, H5), 4.41−4.35 (m, 1H, OH), 4.34−4.27 (m, 1H, OH), 4.15−4.08 (m, 1H, OH), 4.04−3.95 (m, 1H, H4), 3.89−3.84 (m, 1H, H2), 3.78−3.69 (m, 4H, H1α, H1β, H1′), 3.59−3.54 (m, 1H, H3), 1.44 (s, 9H, *t*Bu); ^{13}C NMR δ 156.4 (CO), 136.6 (C), 134.7 (CH), 134.4 (CH), 128.4 (2 × CH), 127.6 (CH), 126.4 (CH), 125.1 (CH), 116.9 (CH_2), 80.8 (C), 73.0 (CH), 72.4 (CH), 70.2 (CH), 63.8 (CH_2), 60.2 (CH), 48.9 (CH_2), 28.3 (CH_3).

(6*E*)-5-[Allyl(*tert*-butylcarbonyl)amino]-1-*O*-triphenylmethyl-5,6,7-trideoxy-7-phenyl-D-*gluco*-hept-6-enitol (6). To a solution of the primary alcohol **5** (2.6 g, 6.616 mmol) in anhydrous pyridine (20 mL) was added trityl chloride (2.767 g, 9.924 mmol). The mixture was stirred for 18 h at room temperature, diluted with water (50 mL), and extracted with diethyl ether (2 × 50 mL). The combined ether portions were washed with saturated Cu_2SO_4 solution (3 × 80 mL) and brine (80 mL), dried ($MgSO_4$), and evaporated to give a brown oil that was purified by column chromatography (20−40% EtOAc/petrol) to give compound **6** as a white foamy solid (2.66 g, 68%). R_f 0.45 (40% EtOAc/petrol); $[\alpha]^{26}_D$ −24 (*c* 1.5, $CHCl_3$); MS (ES + ve) *m*/*z* 658 ($M + Na^+$, 43%); HRMS (ES + ve) calcd for $C_{40}H_{45}NO_6Na$ ($M + Na^+$) 658.3145, found 658.3144. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.19 (m, 20H, Ar), 6.57 (d, 1H, $J = 15.9$ Hz, H7), 6.36 (dd, 1H, $J = 15.9$, 6.9 Hz, H6), 5.83−5.68 (m, 1H, H2′), 5.10−5.01 (m, 2H, H3′), 4.48 (br s, 1H, H5), 3.95−3.90 (m, 1H, H2), 3.89−3.79 (m, 2H, H4, H3), 3.78−3.69 (m, 2H, H1′), 3.37 (dd, 1H, $J = 9.3$, 2.7 Hz, H1), 3.23−3.13 (m, 1H, H1), 1.43 (s, 9H, *t*Bu); ^{13}C NMR δ 156.4 (CO), 143.7 (C), 136.5 (C), 134.8 (CH), 134.5 (CH), 128.6 (3 × CH), 128.5 (2 × CH), 127.8 (3 × CH), 127.7 (2 × CH), 127.0 (CH), 126.5 (CH), 124.9 (CH), 116.9 (CH_2), 86.9 (C), 80.9 (C), 73.2 (CH), 72.2 (CH), 69.3 (CH), 64.0 (CH_2), 60.4 (CH), 48.8 (CH_2), 28.3 (CH_3).

***tert*-Butyl (2*R*)-2-[(2*S*,3*S*)-4-(Triphenylmethyloxy)-1,2,3-trihydroxybutyl]-2,5-dihydro-1*H*-pyrrole-1-carboxylate (7).** To a solution of the diene **6** (840 mg, 1.323 mmol) in anhydrous DCM (200 mL) was added Grubbs' I catalyst (109 mg, 0.132 mmol). The reaction was stirred and heated at reflux for 18 h under N_2 followed by the removal of all volatiles in vacuo. The residue was purified by column chromatography (40−60% EtOAc/petrol) to give compound **7** as a white foamy solid (605 mg, 86%). R_f 0.25 (40% EtOAc/petrol); $[\alpha]^{25}_D$ +74 (*c* 0.72, $CHCl_3$), MS (ES + ve) *m*/*z* 554 ($M + Na^+$, 60%); HRMS

(17) Bell, A. D.; Pickering, L.; Watson, A. A.; Nash, R. J.; Griffiths, R. C.; Jones, M. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8561−8564.

(ES + ve) calcd for $C_{32}H_{37}NO_6Na$ (M + Na^+) 554.2519, found 554.2524. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.20 (m, 15H, Ar), 5.87 (dd, 1H, J = 6.4, 1.8 Hz, H4), 5.81 (d, 1H, J = 6.6 Hz, H3), 4.70−4.62 (m, 1H, H2), 4.22 (dd, 1H, J = 15.9, 1.5 Hz, H5), 3.98 (dd, 1H, J = 15.6, 3.0 Hz, H5), 3.86−3.83 (m, 1H, H3′), 3.81−3.78 (m, 1H, H2′), 3.53 (br s, 1H, H1′), 3.33 (dd, 1H, J = 9.6, 4.8 Hz, H4′), 3.15 (dd, 1H, J = 9.6, 4.8 Hz, H4′), 1.47 (s, 9H, *t*Bu); ^{13}C NMR δ 157.0 (CO), 143.8 (C), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.0 (CH), 126.4 (CH), 86.6 (C), 80.8 (C), 75.3 (CH), 72.5 (CH), 69.5 (CH), 67.2 (CH), 64.3 (CH_2), 54.3 (CH_2), 28.4 (CH_3).

***tert*-Butyl (2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-[(2*S*,3*S*)-1,2,3-trihydroxy-4-triphenylmethyloxybutyl]pyrrolidine-1-carboxylate (8).** To a solution of the olefin **7** (1.56 g, 2.932 mmol) in acetone (15 mL) and water (15 mL) was added potassium osmate dihydrate (54 mg, 0.147 mmol) and *N*-morpholine-*N*-oxide (721 mg, 6.158 mmol). The reaction was stirred for 30 h at room temperature and evaporated to give a black oil that was purified by column chromatography (80−100% EtOAc/petrol) to give compound **8** as a white foamy solid (1.46 g, 88%). R_f 0.07 (50% EtOAc/petrol); $[\alpha]^{25}_D$ +20 (*c* 4.6, $CHCl_3$). MS (ES + ve) *m*/*z* 588 (M + Na^+, 26%); HRMS (ES + ve) calcd for $C_{32}H_{39}NO_8Na$ (M + Na^+) 588.2541, found 588.2545. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.38 (m, 15H, Ar), 4.27−4.20 (m, 1H, H4), 4.16−4.07 (m, 1H, H3), 3.88−3.83 (m, 1H, H2′) 3.81−3.76 (m, 1H, H3′), 3.74−3.69 (m, 1H, H1′), 3.37−3.29 (m, 3H, H2, H4′, H5), 3.10−3.05 (m, 1H, H5), 1.39 (s, 9H, *t*Bu); ^{13}C NMR δ 157.3 (CO), 143.7 (C), 128.6 (2 × CH), 127.8 (2 × CH), 127.0 (CH), 86.5 (C), 81.0 (C), 73.3 (CH), 72.6 (CH), 72.5 (CH), 69.9 (CH), 69.0 (CH), 65.1 (CH), 63.9 (CH_2), 51.2 (CH_2), 28.3 (CH_3).

***tert*-Butyl (2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-[(2*R*,3*R*)-1,2,3-tris(benzyloxy)-4-triphenylmethyloxybutyl]pyrrolidine-1-carboxylate (9).** To a solution of the pentaol **8** (2.25 g, 3.989 mmol) in anhydrous THF (20 mL) at 0 °C was added 50% NaH in mineral oil (1.053 g, 21.94 mmol). After H_2 evolution had ceased (10 min), benzyl bromide (4.75 mL, 39.89 mmol) and tetrabutylammonium iodide (147 mg, 0.399 mmol) were added. The mixture was brought to 50 °C and stirred for 3 d, then cooled to room temperature, treated with methanol (5 mL) and triethylamine (3 mL), and stirred for 10 min. All volatiles were removed in vacuo and the residue was dissolved in diethyl ether, filtered through Celite, followed by further washings of the solids with diethyl ether. The solvent was removed in vacuo and the residue was purified by column chromatography (5−30% EtOAc/petrol) to give compound **9** as a brown oil (3.08 g, 76%). R_f 0.65 (10% EtOAc/petrol); $[\alpha]^{23}_D$ +14 (*c* 3.5, $CHCl_3$); MS (ES + ve) *m*/*z* 1016 (M + H^+, 33%); HRMS (ES + ve) calcd for $C_{67}H_{70}NO_8$ (M + H^+) 1016.5101, found 1016.5113. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−6.69 (m, 40H, Ar), 4.80−4.40 (m, 10H, CH_2Ph), 4.40−3.26 (m, 10H, H2−H5, H1′-H4′), 1.43 (s, 9H, *t*Bu); ^{13}C NMR (125 MHz) δ (major rotamer) 154.3 (CO), 143.9 (C), 138.7 (C), 138.6 (C), 138.3 (C), 138.0 (C), 137.8 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.14 (CH), 128.10 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 86.9 (C), 80.0 (C), 79.9 (CH), 79.1 (CH), 78.0 (CH), 77.4 (CH), 76.9 (CH), 75.7 (CH), 75.1 (CH), 74.6 (CH_2), 73.7 (CH_2), 72.5 (CH_2), 71.7 (CH_2), 64.0 (CH), 63.8 (CH_2), 48.7 (CH_2).

(2*S*,3*S*)-4-[(2*R*,3*S*,4*R*)-3,4-Dibenzyloxypyrrolidin-2-yl]-2,3,4-tribenzyloxybutan-1-ol (10) and (1*S*,2*R*,6*S*,7*R*,8*R*,-8a*R*)-1,2,6,7,8-Pentabenyloxyoctahydroindolizine (11). To a solution of **9** (774 mg, 0.763 mmol) in anhydrous DCM (7 mL) at 0 °C was added anisole (0.83 mL, 7.626 mmol) and trifluoroacetic acid (5.87 mL, 76.26 mmol). The mixture was stirred at 0 °C for 2 h, followed by the evaporation of all volatiles in vacuo. The residue was dissolved in DCM (15 mL) and washed with saturated Na_2CO_3 solution (20 mL). The aqueous layer was extracted with DCM (2 × 15 mL). The combined DCM layers were dried ($MgSO_4$) and evaporated to give a brown oil that was purified by column chromatography (40−100% EtOAc/petrol and 20% MeOH/EtOAc) to give compound **11** (270 mg, 54%) as a white solid and the amino alcohol **10** (190 mg, 37%) as a brown oil. **10**: $[\alpha]^{22}_D$ −21 (*c* 1.34, $CHCl_3$); MS (CI + ve) *m*/*z* 674 (M + H^+, 2%); HRMS (ES + ve) calcd for $C_{43}H_{48}NO_6$ (M + H^+) 674.3481, found 674.3504. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 25H, Ar), 4.82 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.72 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.68 (d, 1H, J = 11.1 Hz, CH_2Ph), 4.64 (d, 1H, J = 11.7 Hz, CH_2Ph), 4.60 (d, 1H, J = 11.1 Hz, CH_2Ph), 4.57 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.54 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.46 (d, 1H, J = 12.0, CH_2Ph), 4.41 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.02 (dd, 1H, J = 5.7, 5.1 Hz, H3), 3.90−3.85 (m, 1H, H4), 3.83−3.79 (m, 1H, H1′), 3.78−3.73 (m, 1H, H3′), 3.72−3.69 (m, 1H, H4′), 3.69−3.66 (m, 1H, H2′), 3.65−3.61 (m, 1H, H4′), 3.39 (dd, 1H, J = 5.4, 4.8 Hz, H2), 2.98 (dd, 1H, J = 12.0, 4.5 Hz, H5), 2.90 (dd, 1H, J = 12.0, 4.5 Hz, H5); ^{13}C NMR δ 138.6 (C), 138.2 (C), 138.11 (C), 138.06 (C), 138.0 (C), 128.3 (CH), 128.25 (CH), 128.23 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.64 (CH), 127.60 (CH), 127.4 (CH), 80.6 (CH), 80.2 (CH), 79.7 (CH), 78.6 (CH), 77.6 (CH), 74.8 (CH_2), 74.3 (CH_2), 72.1 (CH_2), 71.9 (CH_2), 71.4 (CH_2), 62.1 (CH), 61.2 (CH_2), 48.9 (CH_2). **11**: R_f 0.60 (30% EtOAc/petrol); $[\alpha]^{22}_D$ −11 (*c* 0.7, $CHCl_3$); MS (CI + ve) *m*/*z* 656 (M + H^+, 5%); HRMS (ES + ve) calcd for $C_{43}H_{46}NO_5$ (M + H^+) 656.3375, found 656.3367. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.20 (m, 25H, Ar), 4.93 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.89 (d, 1H, J = 11.7 Hz, CH_2Ph), 4.81 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.72 (d, 1H, J = 11.1 Hz, CH_2Ph), 4.66−4.51 (m, 6H, CH_2Ph), 3.99 (app. q, 1H, J = 7.2 Hz, H2), 3.80 (dd, 1H, J = 6.9, 5.7 Hz, H1), 3.65−3.60 (m, 1H, H6), 3.58 3.53 (m, 1H, H7), 3.35 (dd, 1H, J = 9.3, 8.4 Hz, H8), 3.22−3.18 (m, 1H, H3), 3.17−3.13 (m, 1H, H5), 2.57−2.54 (m, 1H, H8a), 2.53−2.49 (m, 1H, H3), 2.20 (t, 1H, J = 10.2 Hz, H5); ^{13}C NMR δ 138.7 (C), 138.5 (C), 138.3 (C), 138.2 (C), 138.0 (C), 128.4 (CH), 128.3 (2 × CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (3 × CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 87.1 (CH), 81.6 (CH), 80.2 (CH), 79.0 (CH), 76.0 (CH), 75.7 (CH_2), 74.3 (CH_2), 72.8 (CH_2), 72.2 (CH_2), 72.0 (CH_2), 70.3 (CH), 57.1 (CH_2), 53.5 (CH_2).

(1*S*,2*R*,6*S*,7*R*,8*R*,8a*R*)-Octahydroindolizine-1,2,6,7,8-pentol (1). To a solution of **11** (460 mg, 0.702 mmol) in EtOAc (4 mL) and MeOH (3 mL) was added palladium chloride (187 mg, 1.053 mmol). The mixture was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 18 h. The mixture was filtered through Celite and the solids were washed with methanol. 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 resulted in a cloudy white residue that was recrystallized from boiling EtOH with a few drops of H_2O to give compound **1** (90 mg, 63%) as colorless microcrystals, mp 170−172 °C. $[\alpha]^{25}_D$ −10 (*c* 0.67, MeOH); $[\alpha]^{25}_D$ −6 (*c* 5.0, H_2O); MS (CI + ve) *m*/*z* 206 (M + H^+, 100%); HRMS (CI + ve) calcd for $C_8H_{15}NO_5$ 205.0950, found 205.0947; ^{1}H NMR refer to Table 1; ^{13}C NMR (D_2O) δ 79.1 (CH), 74.1 (CH), 73.9 (CH), 70.5 (CH), 70.4 (CH), 68.6 (CH), 59.2 (CH_2), 55.4 (CH_2).

(1*S*,2*R*,6*S*,7*R*,8*R*,8a*R*)-Octahydroindolizine-1,2,6,7,8-pentylpentaacetate (12). To a solution of **1** (38 mg, 0.185 mmol) in anhydrous pyridine (0.75 mL, 9.268 mmol) was added acetic anhydride (0.87 mL, 9.268 mmol) and *N*,*N*-(dimethylamino)pyridine (ca.. 2 crystals). The mixture was stirred at room temperature for 4 h followed by the evaporation of all volatiles in vacuo. The oily residue was purified by column chromatography (40−60% EtOAc/petrol and 100% EtOAc) and recrystallized (boiling petrol with a few drops of EtOAc) to give the pentaacetate **12** (68 mg, 88%) as colorless crystals, mp 142 °C. R_f 0.34 (40% EtOAc/petrol); $[\alpha]^{21}_D$ −15 (*c* 1.36, $CHCl_3$); MS (CI + ve) *m*/*z* 416 (M + H^+, 87%); HRMS (ES + ve) calcd for $C_{18}H_{26}NO_{10}$ 416.1557, found 416.1573. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (q, 1H, $J_{1,2}$ = $J_{2,3\alpha}$ = $J_{2,3\beta}$ = 6.3 Hz, H2), 5.11 (t, 1H, $J_{6,7}$ = $J_{7,8}$ = 9.3 Hz, H7), 5.02 (t, 1H, $J_{1,2}$ = $J_{1,8a}$ = 7.3 Hz, H1), 4.97 (dd, 1H, $J_{5\beta,6}$ = 5.8 Hz, $J_{5\alpha,6}$ = 9.8 Hz, H6), 4.96 (t,

1H, $J_{7,8} = J_{8,8a} = 9.3$ Hz, H8), 3.57 (dd, 1H, $J_{2,3\beta} = 6.8$ Hz, $J_{3\alpha,3\beta} = 10.3$ Hz, H3β), 3.28 (dd, 1H, $J_{5\beta,6} = 5.5$ Hz, $J_{5\alpha,5\beta} = 10.5$ Hz, H5β), 2.60 (t, 1H, $J_{1,8a} = J_{8,8a} = 8.5$ Hz, H8a), 2.42 (dd, 1H, $J_{2,3\alpha} = 5.0$ Hz, $J_{3\alpha,3\beta} = 10.0$ Hz, H3α), 2.27 (t, 1H, $J_{5\alpha,5\beta} = J_{5\alpha,6} = 10.3$ Hz, H5α), 2.04 (s, 3H, Ac), 2.028 (s, 3H, Ac), 2.025 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.01 (s, 3H, Ac); ^{13}C NMR δ 170.3 (CO), 169.9 (CO), 169.8 (CO), 169.6 (CO), 168.9 (CO), 73.9 (CH), 73.7 (CH), 72.0 (CH), 69.9 (CH), 69.3 (CH), 65.7 (CH), 57.3 (CH_2), 52.0 (CH_2), 20.74 (CH_3), 20.67 (CH_3), 20.60 (2 $\times$ CH_3), 20.2 (CH_3).

Acknowledgment. We thank the Australian Research Council for financial support and the University of Wollongong for a Ph.D. scholarship to A.S.D.

Supporting Information Available: Full spectral details and assignments and copies of the ^{1}H and ^{13}C NMR spectra of compounds **1** and **4**−**12** and the ORTEP plot of **12** (CCDC deposition no. 226165). This material is available free of charge via the Internet at http://pubs.acs.org.

JO049806Y