JOC*Note*

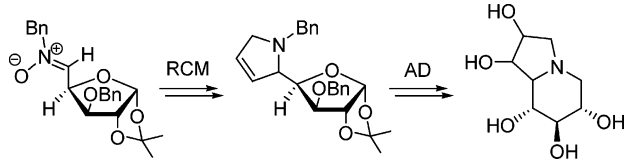
Synthesis of Pentahydroxy Indolizidine Alkaloids Using Ring Closing Metathesis: Attempts To Find the Correct Structure of Uniflorine A

Narayan S. Karanjule, Shankar D. Markad, and Dilip D. Dhavale*

Garware Research Centre, Department of Chemistry, University of Pune, Pune-411 007, India

ddd@chem.unipune.ernet.in

Received April 19, 2006



Ring closing metathesis of D-glucose derived diene-substrate containing nitrogen functionality followed by asymmetric dihydroxylation afforded sugar substituted dihydroxylated pyrrolidines **8a**−**c** which on 1,2-acetonide deprotection and reductive amination afforded putative uniflorine A **2a** and its analogues **2b**−**c**, respectively.

Ring closing metathesis (RCM) of diene-substrate containing nitrogen functionality followed by asymmetric dihydroxylation has found wide applicability in the synthesis of nitrogen heterocycles, alkaloids, peptides, and peptidomimetics.[1] The utility of this approach with sugar substrates wherein the presence of the hydroxylated carbon framework and feasibility to manipulate the functional groups into the required diene-functionality, containing a nitrogen atom, give an easy access toward the synthesis of azasugars.[2] Among azasugars, castanospermine **1** (Figure 1) has attracted considerable attention because of its promising glycosidase inhibitory activity.[3] In the last two decades, a number of castanospermine analogues, with variation of position and number of hydroxyl groups have been synthesized[4] and evaluated for glycosidase inhibition in the treatment of various diseases such as diabetes, cancer, and multiple scelerosis as well as viral infections including AIDS, hepatitis C, and HSV-1.[5] In this respect, M. Arisawa and co-workers have recently isolated uniflorine A **2a**, from leaves of the tree *Eugenia uniflora* L,[6a] which was found to be a promising inhibitor of maltase and sucrase, with IC_{50} values of 12 and 3.1 μM, respectively.

In 2004, Pyne and co-workers[7] have reported the first total synthesis of uniflorine A wherein the pentahydroxy indolizidine ring structure **2a** was confirmed by the X-ray crystallographic data of its peracetyl derivative; however, the authors have noticed a considerable difference in the ^{1}H and ^{13}C NMR data

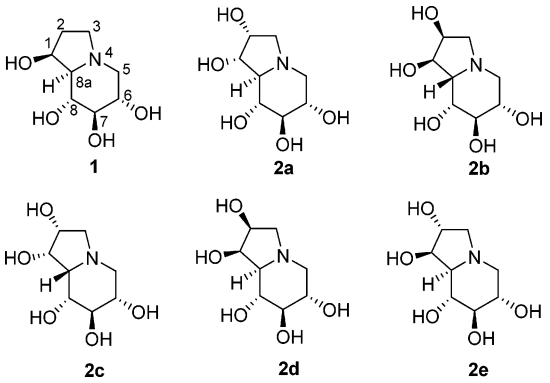


FIGURE 1. Indolizidine alkaloids.

of synthetic and naturally isolated product. In another report, Mariano and co-workers[8b] have reported a photochemical ring rearrangement reaction for the synthesis of castanospermine **1** and pentahydroxy indolizidine alkaloids **2d**[8] and **2e** which also showed deviation in the spectral data from that of the isolated uniflorine A. As a part of our continuing interest in the synthesis

(1) For recent reviews, see (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (c) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124−2145. (d) Fuerstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37−72. (e) Armstrong, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (g) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. (h) Fuerstner, A. *Angew. Chem.* **2000**, *112*, 3140−7172; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (i) Larry, Y. *Chem. Rev.* **2000**, *100*, 2963−3008.

(2) For the application of the ring closing metathesis reaction to the synthesis of azasugars, see the following: (a) Ovaa, H.; Stragies, R.; Van der Marel, G. A.; Van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501−1502. (b) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621−1624. (c) Overkleeft, H. S.; Pandit, U. K. *Teterahedron Lett.* **1996**, *37*, 547−550. (d) Verhelst, S. H. L.; Martinez, B. P.; Timmer, S. M.; Lodder, G.; Van der Marel, G. A.; Overkleeft, H. S.; Van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598−9603. (e) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61−67. (f) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360. (g) Lindstrom, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173−7176. (h) Ovaa, H.; Stragies, R.; Van Der Marel, G. A.; Van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501−1502. (i) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971−3974. (j) Subramanian, T.; Lin, C. C. *Tetrahedron Lett.* **2001**, *42*, 4079−4082. (k) Klitze, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605−5608. (l) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630−4633. (m) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774−7780. (n) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329. (o) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471−2474.

(3) (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives;* Pelletier, S. W., ed.; Wiley-Interscience: New York, 1987; Vol. 5. (b) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 2001; Vol. 55, pp 91−258. (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603−626.

(4) For selected syntheses see the following: (a) Tyler, P. C.; Winchester, B. G. In *Iminosugars as Glycosidase Inhibitors*; Stuetz, A., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1999; pp 125−156. (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625−649. (c) Somfai, P.; Marchand, P.; Torsell, S.; Lindstrom, U. M. *Tetrahedron* **2003**, *59*, 1293−1299. (d) Zhao, H.; Mootoo, D. R. *J. Org. Chem.* **1996**, *61*, 6762−6763. (e) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887−2896.

(5) (a) Nojima, H.; Kimura, I.; Chen, F.-J.; Sugihara, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397−400. (b) Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55*, 2920−2926. (c) Walter, S.; Fassbender, K.; Gulbins, E.; Liu, Y.; Rieschel, M.; Herten, M.; Bertsch, T.; Engelhardt, B. *J. Neuroimmunol.* **2002**, *132*, 1−2.

(6) (a) Matsumura, T.; Kasai, M.; Hayashi, T.; Arisawa, M.; Momose, Y.; Arai, I.; Amagaya, S.; Komatsu, Y. *Pharm. Biol.* **2000**, *38*, 302−307. (b) Arisawa, M.; Hayashi, T.; Momose, Y. *Food Style 21* **2001**, *5*, 69−73. (c) Momose, Y. Japanese Kokai Tokkyo Koho 2000, 7 pp (JP2000072770, CAN 32: 203147).

(7) Davis, A. S.; Pyne, S, G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139−3143.

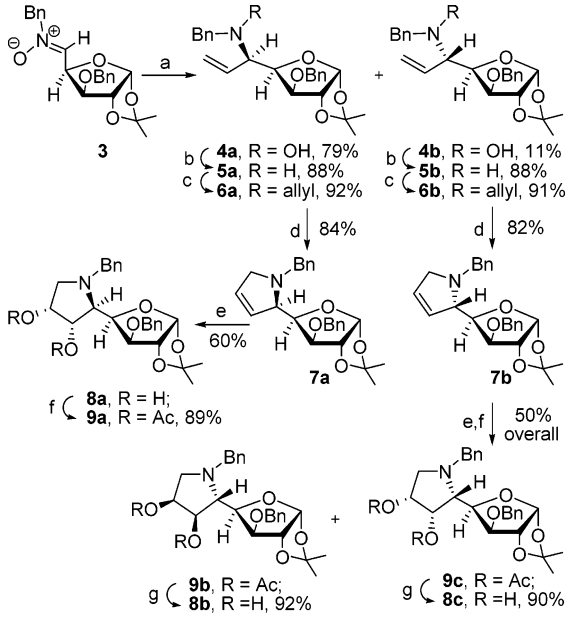
(8) (a) Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Griffiths, R. C.; Jones, M. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8561−8564. (b) Zhao, Z.; Song, L.; Mariano, P. *Tetrahedron*. **2005**, *61*, 8888−8894.

10.1021/jo060823s CCC: $33.50
Published on Web 07/14/2006

of iminosugars,[9] we have now studied the RCM of dienes **6a** and **6b** to provide sugar substituted dihydropyrrolidine ring systems **7a** and **7b**, respectively, that could be elaborated to provide 1,2,6,7,8-pentahydroxylated indolizidine alkaloids to decide whether the naturally isolated product was one of these isomers. Our visualization relies on the fact that the trihydroxylated piperidine ring skeleton of naturally isolated and synthetic uniflorine A is identical. We assume that the same piperidine ring skeleton could be obtained from D-glucose derived nitrone **3** by the π-facial stereoselective 1,3-addition of vinylmagnesium bromide. This will give an access for the bicyclic skeleton with different stereochemistry at the ring junction while *syn*/*anti* dihydroxylation in the pyrrolidine ring will afford the dihydroxylated pyrrolidines, and all the isomers, if obtained, could be converted to the compounds with structures analogous to uniflorine A. Although there are few reports for the synthesis of pentahydroxy indolizidine alkaloids,[10] only a single report describes the synthesis of **2a,**[7] whereas the synthesis of **2b** and **2c** has not been reported so far.

Reaction of vinylmagnesium bromide (3.0 equiv) with nitrone **3**, in the presence of TMSOTf (1 equiv) at −78 °C, afforded a mixture of D-*gluco*- and L-*ido*- configurated *N*-benzylhydroxylamines **4a** and **4b** in the ratio of 87:13 reported earlier by us (Scheme 1).[11,12] The individual treatment of **4a**/**4b** with zinc in acetic acid−water afforded N−O bond reductive cleavage products **5a**/**5b** that on reaction with allyl bromide and potassium carbonate in dry DMF afforded corresponding *N*-allyl aminosugars **6a** and **6b** in good yield. The RCM of **6a** and **6b** using Grubbs catalyst (1st generation) afforded sugar substituted dihydropyrrolidine **7a** and **7b** in high yield, respectively.[13] Osmylation of **7a** under homogeneous reaction conditions using potassium osmate and NMO in acetone−water was unsuccessful; however, the dihydroxylation in biphasic reaction condition using potassium osmate, potassium ferricyanate, methane sulfonamide, and potassium carbonate in *t*-BuOH−H_2O at 0 °C afforded a single α-dihydroxylated product **8a** in good yield

SCHEME 1. Dihydroxylation of 7a and 7b[a]



[a] Reaction conditions: (a) vinylmagnesium bromide, TMSOTf, THF, −78 °C, 2 h, 90%; (b) Zn, $Cu(OAc)_2$, AcOH, 80 °C, 1 h; (c) K_2CO_3, allyl bromide, DMF, rt, 12 h; (d) Grubb's catalyst (1st generation), CH_2Cl_2, rt, 12 h. (e) $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_4 \cdot 2H_2O$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 12 h; (f) Ac_2O, DMAP, pyridine, 0 to 25 °C, 6 h; (g) NaOMe, 0 °C, 2 h.

TABLE 1. Dihydroxylation of 7a and 7b

no.	ligand	substrate	product	dr[a]	% yield[b]
1	no ligand	**7a**	**8a**	100:0[c]	60
2	$(DHQ)_2PHAL$	**7a**	**8a**	100:0[c]	64
3	$(DHQD)_2PHAL$	**7a**	**8a**	100:0[c]	61
4	no ligand	**7b**	**8b/8c**	10:90	60
5	$(DHQ)_2PHAL$	**7b**	**8b/8c**	20:80	59
6	$(DHQD)_2PHAL$	**7b**	**8b/8c**	0:100[c]	62

[a] Determined by ^1H NMR of the crude product. [b] After purification. [c] No corresponding peak for minor isomer was observed.

(Table 1, entry 1)[14] which was further characterized as its diacetate derivative **9a**. Asymmetric dihydroxylation of **7a** using either AD-mix-α or AD-mix-β afforded **8a** as the only isolable diastereomer in good yield (entries 2, 3). Osmylation of **7b** under similar reaction conditions afforded an inseparable mixture of diols **8b** and **8c** in the ratio 1:9 as evident from the ^1H NMR analysis of the crude reaction mixture (entry 4). An inseparable mixture of diols **8b**,**c** was subjected to acetylation and purified to give diacetyl derivatives **9b** and **9c** that on individual treatment with sodium methoxide (catalytic) in methanol afforded pure diols **8b** and **8c**, respectively. Dihydroxylation of **7b** using AD-mix-α afforded **8b** and **8c** in the ratio 2:8 (entry 5), while AD-mix-β gave **8c** as a single isolable diastereomer in good yield (entry 6). Our attempts for epoxidation of **7a**,**b** using *m*-CPBA as well as 1,2-*syn*/*anti* dihydroxylation under Woodward−Prevost conditions were unsuccessful.[15]

The absolute configuration at the newly generated C6 and C7 stereo centers in **9a**−**c** was assigned on the basis of ^1H NMR studies and coupling constant information obtained by decoupling experiments. Thus, the appearance of a doublet of doublet

(9) (a) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065−1074. (b) Karanjule, N. S.; Markad, S. D.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2005**, *70*, 1356−1363. (b) Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; PrakashaReddy, J. *J. Org. Chem.* **2004**, *69*, 4760−4766 and references therein.

(10) (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) Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett*. **1994**, *1*, 1−8. (d) Chen, Y.; Vogel, P. *Tetrahedron Lett*. **1992**, *33*, 4917−4920.

(11) These results are consistent with our earlier studies on the 1,3-addition of methyl-and allyl-magnesium bromide as well as silyl ketene acetal of ethyl acetate to nitrone **3**, in the presence of TMSOTf (1 equiv) at −78 °C in THF, that afforded a good diastereoselectivity in the favor of D-gluco isomer (∼de 75%). (a) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, 57, 39−46. (b) Dhavale, D. D.; Jachak, S. M.; Karche, N. P.; Trombini, C. *Synlett* **2004**, 1549−1552. (c) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475−1486.

(12) Pedro Merino et al. reported the reaction of vinylmagnesium bromide with nitrone **3** using Et_2AlCl as a Lewis acid in which **4a** and **4b** were obtained in the ratio 77:23. Merino, P.; Anoro, S.; Franco, S.; Gascon, J. M.; Martin, V.; Merchan, F. L.; Revuelta, J.; Tejero, T.; Tunon, V. *Synth. Commun.* **2000**, 2989−3021.

(13) For the application of the ring closing metathesis reaction to the synthesis of 2,5-dihydropyrrolidines from dienes see (a) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2376−2378. (b) Fuerstner, A.; Fursterner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem Commun.* **1998**, 1315−1316. (c) Fuerstner, A.; Ackermann, L. *Chem. Commun*. **1999**, 95−96. (d) Bujard, M.; Briot, A.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8795−8788. (e) Fuerstner, A.; Liebl, M.; Hill, A. F.; Wilton-Ely, J. D. E. T. *Chem. Commun*. **1999**, 601−602. (f) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771−1772.

(14) For reviews on dihydroxylation see (a) Masaya, S.; Yoshihiko, I. *Chem. Rev.* **1992**, *92*, 857−871. (b) Corey, E. J.; Noe, M. C.; Sarshar S. *J. Am. Chem. Soc*. **1993**, *115*, 3828−3829. (c) Kolb, H. C.; Van Nieuwenhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

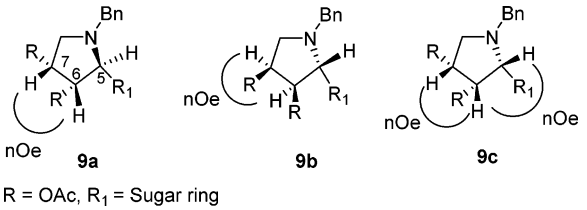


FIGURE 2. NOE experiments.

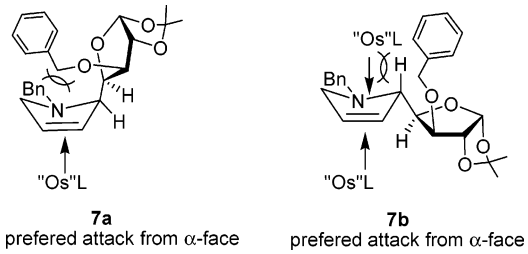


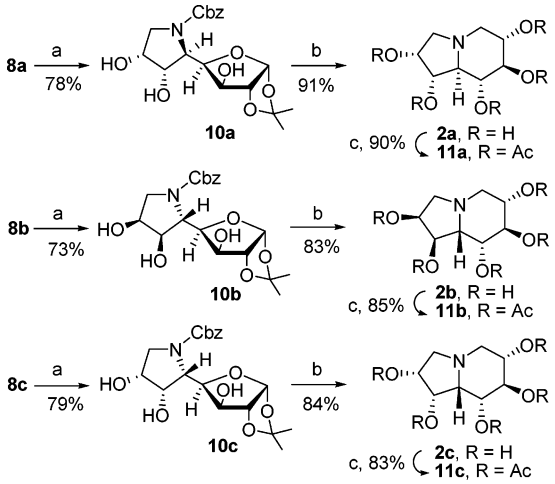
FIGURE 3. Explanation for observed stereoselectivity.

for H-6 in **9a** ($J_{6,7} = 4.2$; $J_{5,6} = 1.2$ Hz) and **9b** ($J_{6,7} = 5.8$; $J_{5,6} = 2.7$ Hz) with a small coupling constant value with H-5 indicated *anti* relationship of H-6 and H-5 in **9a**/**9b**, while appearance of triplet for H-6 in **9c** ($J = 5.2$ Hz) showed *syn* relationship of H-6 with both H-5 and H-7. This observation was supported by 1D NOESY experiments (Figure 2), wherein irradiation of the H-6 in **9a** and **9b** showed nOe with the H-7 while in **9c**, nOe was observed with both the H-7 and H-5 thus establishing the relative stereochemistry (6*S*, 7*R*) for **9a**/**9c** and (6*R*, 7*S*) for **9b**.[16] The stereochemical outcome of the reaction could be explained by the fact that in **7a** the addition of bulky osmium reagent from the α-face of the molecule is preferred over the β-face attack, since the β-face attack is sterically hindered by furanose ring and C3−OBn functionality. In **7b** the β-face attack is hindered by C3−OBn and pseudoaxial H-5 (Figure 3).[17]

In the subsequent step, treatment of **8a** (D-*gluco*-configuration at C-5) with ammonium formate and 10% Pd/C in dry methanol at reflux afforded amino alcohol which was directly subjected to selective amine protection using benzyl chloroformate in the presence of $NaHCO_3$ in methanol−water to give *N*-Cbz protected triol **10a** (Scheme 2).

In the final step, cleavage of 1,2-acetonide functionality in **10a** using TFA-H_2O (3:2) followed by cyclic reductive amination (H_2, 10% Pd/C) afforded **2a** as a white solid. The spectral and analytical data of **2a** was found to be in consonance with that of the synthetically reported uniflorine A[7] and is different from that of the natural product[6a] [mp 171−173 °C, lit.[7] mp 170−172° C; $[\alpha]^{25}_D = -5.2$ (*c* 0.40, H_2O), lit.[7] $[\alpha]^{25}_D = -6.0$ (*c* 5.0, H_2O); lit.[6a] $[\alpha]_D = -4.4$ (*c* 1.2, H_2O)]. Treatment of **2a** with acetic anhydride in pyiridine afforded per-acetate derivative **11a** which showed identical spectral and analytical data with that reported[7] [mp 141−142 °C, lit.[7] mp 142 °C; $[\alpha]^{25}_D = -17$ (*c* 0.90, $CHCl_3$), lit.[7] $[\alpha]^{25}_D = -15$ (*c* 1.56, $CHCl_3$)]. A similar reaction sequence, individually, with **8b**,**c** (L-*ido*-configuration at C-5) afforded 2(*S*)-hydroxy-8a-*epi*-castanospermine **2b**, 2(*R*)-hydroxy-1,8a-di-*epi*-castanospermine **2c** and corresponding pentaacetate derivatives **11b**,**c**. The target molecules **2b**,**c**, *N*-Cbz protected triols **10b**,**c**, and pentaacetates **11b**,**c** were characterized by spectral and analytical techniques, and the data was found to be in agreement with the structures. The spectral properties of **2b**,**c** were different from those of the natural product.

SCHEME 2. Synthesis of Indolizidines 2a−c[a]



[a] Reaction conditions: (a) (i) $HCOONH_4$, 10% Pd/C, MeOH, 80 °C, 1 h; (ii) CbzCl, $NaHCO_3$, MeOH/H_2O (5:1), 2 h; (b) (i) TFA−H_2O (3:2), 25 °C, 2.5 h; (ii) 10% Pd/C, MeOH, 80 psi, 12 h; (c) Ac_2O, DMAP, pyridine, 0 °C to rt,12 h.

In conclusion, RCM methodology with aminosugar derived diene coupled with the substrate directed asymmetric dihydroxylation gave an easy access to the synthesis of three analogues of pentahydroxy indolizidine alkaloids **2a**−**c**. The ^1H and ^{13}C NMR data of known **2a** and newly synthesized **2b**,**c** were found to be different from that of the naturally isolated uniflorine A. Our results are helpful for further study to determine the correct structure of natural uniflorine A.

Experimental Section

3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetra-deoxy-5,8-(*N*-benzylamino)-α-D-*gluco*-6-eno-octa-1,4-furanose (7a). The compound **6a** (1.4 g, 3.2 mmol) was dissolved in dry CH_2Cl_2 (20 mL); benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.26 g, 0.32 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. Solvent was removed in vacuo to give oil which on purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded **7a** (1.10 g, 82%) as a thick liquid: $R_f = 0.63$ (*n*-hexane/ethyl acetate = 8/2); $[\alpha]^{25}_D = -3.3$ (*c* 0.60, $CHCl_3$). IR (Neat): 1607, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.64 (s, 3H), 3.25 (bd, $J = 15.0$ Hz, 1H), 3.62 (d, $J = 14.1$ Hz, 1H), 3.76 (bd, $J = 15.0$ Hz, 1H), 4.03 (dd, $J = 7.5$, 3.0 Hz, 1H), 4.10 (d, $J = 14.1$ Hz, 1H), 4.14 (d, $J = 3.0$ Hz, 1H), 4.17−4.26 (m, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.67 (d, $J = 4.2$ Hz, 1H), 5.69 (d, $J = 11.7$ Hz, 1H), 5.82 (bdd, $J = 6.3$, 1.8 Hz, 1H), 5.97 (d, $J = 4.2$ Hz, 1H), 5.95−6.20 (m, 1H), 7.20−7.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.7, 60.2, 61.0, 68.8, 71.3, 81.3, 82.0, 84.5, 104.8, 111.5, 126.7, 126.8, 127.5(s), 127.6, 127.8(s), 128.1(s), 128.2(s), 128.4(s), 129.8, 137.2. Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17. Found: C, 73.60; H, 7.25.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetra-deoxy-5,8-(*N*-benzylamino)-β-L-*ido*-6-eno-octa-1,4-furanose (7b). The reaction of **6b** (2.1 g, 4.8 mmol) with benzylidene-bis-tricyclohexylphosphine-dichlororuthenium (0.39 g, 0.48 mmol) in dry CH_2Cl_2 (25 mL) was performed under the same reaction conditions described for synthesis of **7a**. Purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded **7b** (1.65 g, 84%) as a thick

(15) (a) Woodward, R. B.; Brutcher, F. V., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209. (b) Brimble, M. A.; Nairn, M. R. *J. Org. Chem.* **1996**, *61*, 4801−4805.

(16) In this experiment, weak nOe was also observed between the H-6 and the H-5 in **9a** and **9b**. Similar observation was also noticed in pyrrolidine derivatives; see Kim, J. H.; Curtis-Long, M. J.; Seo, W. D.; Ryu, Y. B.; Yang, M. S.; Park K. H. *J. Org. Chem.* **2005**, *70*, 4082−4087.

(17) Mukai, C.; Sugimoto, Y.-i.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281−6287.

liquid: $R_f = 0.56$ (*n*-hexane/ethyl acetate = 8/2); $[\alpha]^{25}_D = -51.2$ (*c* 0.63, $CHCl_3$). IR (Neat): 1606, 1452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.56 (s, 3H), 3.32 (bd, $J = 15.2$ Hz, 1H), 3.55-3.78 (m, 2H), 3.97 (d, $J = 2.1$ Hz, 1H), 4.60−4.27 (m, 2H), 4.47 (d, $J = 13.2$ Hz, 1H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.68 (d, $J = 3.9$ Hz, 1H), 4.75 (d, $J = 11.7$ Hz, 1H), 5.41 (bd, $J = 6.0$ Hz, 1H), 5.80 (bd, $J = 6.0$ Hz, 1H), 6.05 (d, $J = 3.9$ Hz, 1H), 7.20−7.52 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 26.7, 59.7, 60.4, 69.6, 71.5, 81.4, 82.6, 85.0, 105.1, 111.3, 126.6, 125.3, 127.9(s), 128.0, 128.1(s), 128.4(s), 128.8(s), 129.3, 137.1, 140.1. Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17. Found: C, 73.82; H, 7.32.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5,8-dideoxy-5,8-(*N*-benzylamino)-6(*S*),7(*R*)-Dihydroxy-α-D-*erythro*-D-*gluco*-oct-1,4-furanose (8a). $K_3Fe(CN)_6$ (1.94 g, 5.8 mmol) and K_2CO_3 (0.80 g, 5.8 mmol) were dissolved in water (6 mL) and *tert*-butyl alcohol (2 mL), and then the mixture was cooled to 0 °C. Methanesulfonamide (0.18 g, 1.9 mmol), catalytic potasium osmate, and alkene **7a** (0.8 g, 1.9 mmol) dissolved in *tert*-butyl alcohol (4 mL) were added, and the mixture was stirred at 0 °C for 10 h. Sodium sulfite (2 g) was added, and the mixture was stirred at room temperature for 1 h. All volatiles were removed in vacuo, and residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with 2 N KOH (5 mL) followed by water (10 mL) and dried over Na_2SO_4, filtered, and evaporated in vacuo to give oil. Purification by column chromatography (*n*-hexane/ethyl acetate = 60/40) gave **8a** (0.52 g, 60%) as a thick liquid: $R_f = 0.44$ (*n*-hexane/ethyl acetate = 1/1); $[\alpha]^{25}_D = -7.4$ (*c* 0.27, $CHCl_3$). IR (Neat): 3550−3200, 1632, 1458 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.51 (s, 3H), 1.60−2.10 (bs, 2H, exchanges with D_2O), 2.56 (dd, $J = 10.8$, 2.0 Hz, 1H), 3.18 (dd, $J = 10.8$, 4.8 Hz, 1H), 3.18−3.30 (m, 1H), 3.62 (d, $J = 13.2$ Hz, 1H), 3.94 (d, $J = 13.2$ Hz, 1H), 3.97 (d, $J = 3.0$ Hz, 1H), 4.12−4.32 (m, 3H), 4.45 (d, $J = 11.4$ Hz, 1H), 4.67 (d, $J = 3.9$ Hz, 1H), 4.70 (d, $J = 11.4$ Hz, 1H), 5.94 (d, $J = 3.9$ Hz, 1H), 7.20−7.42 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 26.8, 58.0, 60.5, 66.8, 70.7, 71.7, 73.9, 81.4, 81.7, 82.5, 104.5, 111.8, 127.0, 128.0(s), 128.3(s), 128.6(s), 128.7(s) 136.5, 139.1. Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08. Found: C, 68.15; H, 7.20.

3-*O*-Benzyl-1,2-*O*-isopropylidene-6(*R*),7(*S*)-diacetoxy-5,8-dideoxy-5,8-(*N*-benzylimino)-α-L-*erythro*-L-*ido*-oct-1,4-furanose (9b) and 3-*O*-Benzyl-1,2-*O*-isopropylidene-6(*S*),7(*R*)-diacetoxy-5,8-dideoxy-5,8-(*N*-benzylimino)-α-D-*erythro*-L-*ido*-oct-1,4-furanose (9c). The reaction of $K_3Fe(CN)_6$ (3.9 g, 11.6 mmol), K_2CO_3 (1.6 g, 11.6 mmol), methanesulfonamide (0.36 g, 3.8 mmol), and catalytic potasium osmate with alkene **7a** (1.6 g, 3.8 mmol) was performed under similar reaction conditions as described for **8a** followed by purification by column chromatography (*n*-hexane/ethyl acetate = 60/40) which gave a mixture of **8b**,**c** (1.1 g, 62%) as a thick liquid. The mixture (1.0 g, 2.26 mmol) was dissolved in pyridine (2.93 g, 36.2 mmol) and cooled to 0 °C. Acetic anhydride (8.2 g, 81.3 mmol) and catalytic DMAP were added, and the mixture was stirred at room temperature for 6 h. The usual workup followed by separation by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded diacetate **9b** (0.12 g, 10%) as a thick liquid: $R_f = 0.61$ (*n*-hexane/ethyl acetate 3/1); $[\alpha]^{25}_D = -19.0$ (*c* 0.52, $CHCl_3$). IR (Neat): 1750, 1615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.50 (s, 3H), 1.88 (s, 3H), 1.98 (s, 3H), 2.54 (t, $J = 9.0$ Hz, 1H), 3.11 (d, $J = 9.0$, 8.5 Hz, 1H), 3.39 (dd, $J = 8.3$, 2.2 Hz, 1H), 3.57 (d, $J = 13.2$ Hz, 1H), 4.01 (d, $J = 3.3$ Hz, 1H), 4.17 (dd, $J = 8.3$, 3.3 Hz, 1H), 4.26 (d, $J = 13.2$ Hz, 1H), 4.46 (d, $J = 11.8$ Hz, 1H), 4.60 (d, $J = 3.9$ Hz, 1H), 4.67 (d, $J = 11.8$ Hz, 1H), 5.21 (dt, $J = 9.4$, 5.8 Hz, 1H), 5.33 (dd, $J = 5.8$, 2.7 Hz, 1H), 5.97 (d, $J = 3.9$ Hz, 1H), 7.18-7.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 20.6, 26.2, 26.7, 54.2, 59.9, 66.3, 70.1, 71.5, 73.2, 77.2, 81.2, 82.6, 105.1, 111.6, 127.1, 127.3-(s), 127.7, 128.2, 128.4(s), 129.1, 137.3, 139.0, 169.6, 169.7. Anal. Calcd for $C_{29}H_{35}NO_8$: C, 66.27; H, 6.71. Found: C, 66.42; H, 6.87. Further elution with (*n*-hexane/ethyl acetate = 90/10) afforded **9c** (0.88 g, 73%) as a thick liquid: $R_f = 0.58$ (*n*-hexane/ethyl acetate 3/1); $[\alpha]^{25}_D = -28.5$ (*c* 0.35, $CHCl_3$). IR (Neat): 1743, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.54 (s, 3H), 1.98 (s, 3H), 2.08 (s, 3H), 2.77 (dd, $J = 10.5$, 2.0 Hz, 1H), 2.98 (dd, $J = 10.5$, 5.4 Hz, 1H), 3.34 (dd, $J = 7.7$, 5.2 Hz, 1H), 3.56 (d, $J = 13.0$ Hz, 1H), 3.88 (d, $J = 3.0$ Hz, 1H), 4.39 (d, $J = 13.0$ Hz, 1H), 4.45 (d, $J = 11.0$ Hz, 1H), 4.45−4.55 (m, 1H), 4.60 (d, $J = 3.9$ Hz, 1H), 4.61 (d, $J = 11.0$ Hz, 1H), 5.17 (bdd, $J = 12.0$, 5.4 Hz, 1H), 5.51 (t, $J = 5.2$ Hz, 1H), 5.99 (d, $J = 3.9$ Hz, 1H), 7.18−7.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.7, 26.3, 26.7, 55.1, 59.1, 62.9, 70.3, 71.8, 72.9, 81.1, 81.8, 83.2, 104.7, 111.4, 126.9, 127.8(s), 128.0, 128.1(s), 128.5(s), 129.3, 137.0, 138.4, 170 0.0, 170.1. Anal. Calcd for $C_{29}H_{35}NO_8$: C, 66.27; H, 6.71. Found: C, 66.38; H, 6.79.

(1*S*,2*R*,6*S*,7*R*,8*R*,8*aR*)-1,2,6,7,8-Pentahydroxy-indolizidine (2a). Compound **10a** (0.30 g, 0.76 mmol) in TFA−H_2O (6.0 mL, 2:1) was stirred at 25 °C for 2.5 h. Trifluroacetic acid was coevaporated with benzene to furnish thick liquid. To a solution of above product in methanol (10.0 mL) was added 10% Pd/C (0.05 g) and the solution was hydrogenated at 80 psi for 12 h. The catalyst was filtered and washed with methanol, and the filtrate was concentrated to afford thick liquid. Purification by column chromatography (chloroform/methanol = 50/50) afforded **2a** (0.14 g, 91%) as a white solid: mp 171−173 °C (lit.[6a] 174−178 °C); $R_f = 0.44$ (MeOH); $[\alpha]^{25}_D = -5.2$ (*c* 0.40, H_2O) [lit.[6a] $[\alpha]_D = -4.4$ (*c* 1.2, H_2O)]. IR (Nujol): 3600−3200 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ 2.18-2.41 (m, 2H), 2.35 (dd, $J = 10.5$, 6.3 Hz, 1H), 3.14 (dd, $J = 10.8$, 5.3 Hz, 1H), 3.32 (t, $J = 9.3$ Hz, 1H), 3.38 (t, $J = 9.3$ Hz, 1H), 3.40 (dd, $J = 10.5$, 6.6 Hz, 1H), 3.58 (ddd, $J = 10.8$, 9.6, 5.1 Hz, 1H), 3.95 (t, $J = 7.6$ Hz, 1H), 4.24 (q, $J = 6.6$ Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 54.6, 58.5, 68.0, 69.6, 69.8, 73.2, 73.3, 78.3. Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37. Found: C, 46.84; H, 7.49.

(1*R*,2*S*,6*S*,7*R*,8*R*,8*aS*)-1,2,6,7,8-Pentahydroxy-indolizidine (2b). The reaction of **10b** (0.07 g, 0.16 mmol) with TFA−H_2O (2 mL, 2:1) followed by 10% Pd/C (0.02 g) in methanol (4 mL) is performed under similar reaction conditions as described for **2a**. Purification by column chromatography (chloroform/methanol = 40/60) afforded **2b** (0.03 g, 83%) as a thick liquid: $R_f = 0.25$ (methanol); $[\alpha]^{25}_D = +217.0$ (*c* 0.35, H_2O). IR (neat): 3600−3200 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ 2.67 (dd, $J = 11.3$, 3.6 Hz, 1H), 2.90−3.07 (m, 2H), 3.21 (dd, $J = 12.6$, 2.0 Hz, 1H), 3.68 (dd, $J = 11.3$, 6.3 Hz, 1H), 3.95 (bs, 1H), 4.02 (t, $J = 3.0$ Hz, 1H), 4.05 (bd, $J = 3.0$ Hz, 1H), 4.17 (dd, $J = 9.4$, 6.4 Hz, 1H), 4.29 (dt, $J = 6.4$, 4.7 Hz, 1H). ^{13}C NMR (75 MHz, D_2O): δ 54.1, 60.1, 64.6, 66.6, 67.4, 68.5, 68.6(s). Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37. Found: C, 46.989; H, 7.48.

(1*S*,2*R*,6*S*,7*R*,8*R*,8*aS*)-1,2,6,7,8-Pentahydroxy-indolizidine (2c). The reaction of **10c** (0.16 g, 0.40 mmol) with TFA−H_2O (3 mL, 2:1) followed by 10% Pd/C (0.03 g) in methanol (5 mL) is performed under similar reaction conditions as described for **2a**. Purification by column chromatography (chloroform/methanol = 20/80) afforded **2c** (0.07 g, 84%) as a thick liquid: $R_f = 0.20$ (methanol); $[\alpha]^{25}_D = -12.0$ (*c* 0.50, H_2O). IR (neat): 3600−3200 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ 3.20 (dd, $J = 12.4$, 3.0 Hz, 1H), 3.25 (dd, J = 13.5, 2.7 Hz, 1H), 3.31−3.48 (m, 3H), 3.80−3.90 (m, 1H), 4.01 (t, $J = 4.9$ Hz, 1H), 4.25 (t, $J = 4.9$ Hz, 1H), 4.50−4.58 (m, 2H). ^{13}C NMR (75 MHz, D_2O): δ 54.6, 58.9, 63.9, 67.9, 68.8, 69.2, 69.6, 71.1. Anal. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37. Found: C, 46.96; H, 7.44.

Acknowledgment. We are grateful to Prof. M. S. Wadia for helpful discussion. We are thankful to CSIR, New Delhi, for the Senior Research Fellowships to N.S.K. and S.D.M. and for the financial assistance (Project No. 01(1906)/03/EMR-II).

Supporting Information Available: General experimental methods, experimental procedures, analytical data for **6a**,**b**, **8b**,**c**, **9a**, **10a**−**c**, and **11a**−**c** and copies of ^1H and ^{13}C NMR spectra of compounds **6a**,**b**, **7a**,**b**, **8a**−**c**, **9a**−**c**, **10a**−**c**, **11a**−**c**, and **2a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060823S