Stereoisomeric Sugar-Derived Indolizines as Versatile Building Blocks: Synthesis of Enantiopure Di- and Tetrahydroxyindolizidines†

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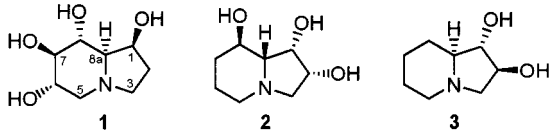
The synthesis of the sugar-derived (1*S*,2*R*,8a*R*)-1,2-di-*O*-isopropylidene-1,2,3,5,6,8a-hexahydro-5-oxoindolizine (**8**) and by analogy of the corresponding stereoisomers *ent*-**8** and *ent*-**7**, an epimer at C_2 of *ent*-**8**, has been accomplished in a straightforward manner. The carbon−carbon double bond and the carbonyl functionalities on the six-membered ring make these nitrogen-containing heterocycles useful building blocks for the efficient preparation of a variety of enantiopure polyhydroxylated indolizidines of interest for their glycosidase inhibitory activity. We report here the synthesis of 2,8a-diepilentiginosine **12** from **8** and the preparation of stereoisomeric 1,2,7,8-tetrahydroxyindolizidines **9**−**11** performed by OsO_4-catalyzed double bond syn dihydroxylation of **7** and **8**, followed by deoxygenation of the amide group.

Introduction

Polyhydroxylated indolizidines such as castanospermine[1] (**1**, Chart 1, isolated from the Australian legume *Castanospermun australe*),[1a] swainsonine[2] (**2**, found in the seeds of *Swainsona canence*), and lentiginosine[3] (**3**, recently extracted from *Austragalus lentiginosus*) are interesting and challenging targets for the synthetic organic chemist. Because of their biological activity, mainly as glycosidase inhibitors,[4−6] these compounds are regarded as potential antiviral, antitumor, and immunomodulating agents.[7] The specificity toward their molecular target remains, however, to be optimized,[8] and new methodologies to generate structural analogues are needed. This is further reinforced by the observation that even small structural modifications may induce very

Chart 1



1 **2** **3**

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† Dedicated to the memory of Professor Antonino Fava.

(1) (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Price, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811. Castanospermine (**1**) from dried pods of *Alexa leiopetala*: (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403. More recent synthesis of **1**: (c) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046. (d) Kang, S. H.; Kim, J. S. *J. Chem. Soc., Chem. Commun.* **1998**, 1353. (e) Zhao, H.; Mootoo, D. R. *J. Org. Chem.* **1996**, *61*, 6762. (f) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, 2335.

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(5) Swainsonine (**2**) as an α-mannosidase inhibitor: (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletiers, S. W., Ed.; Wiley: New York, 1997; p 1. (b) Kotai, K.; Jennings, C.; Winchester, B. G.; Dorling, P. *J. Cell. Biochem.* **1983**, *21*, 107. (c) See ref 2c. (d) Fleet, G. W. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E. *J. Chem. Soc., Chem. Commun.* **1984**, 1240. (e) Tulsiani, D. R. P.; Broquist, H. P.; Touster, O. *Arch. Biochem. Biophys.* **1985**, *236*, 427. (f) Tadano, K. I.; Morita, M.; Hotta, Y.; Ogawa, S.; Winchester, B. G.; Cenci di Bello, I. *J. Org. Chem.* **1988**, *53*, 5209. (g) Elbein, A. D.; Tropez, J. E.; Mitchell, M.; Kansal, G. P. *J. Biol. Chem.* **1990**, *265*, 15599. (h) Fairbanks, A. J.; Fleet, G. W. J.; Jones, H. A.; Bruce, I.; Al Daher, S.; Cenci di Bello, I.; Winchester, B. G. *Tetrahedron* **1991**, *47*, 131. (i) Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett.* **1993**, *1*, 1. (j) Winchester, B. G.; Al Daher, S.; Carpenter, N. C.; Cenci di Bello, I.; Choi, S. S.; Fairbanks, A. J.; Fleet, G. W. J. *Biochem J.* **1993**, *290*, 743. (k) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5537. (l) Molyneux, R. J.; Roitman, J. N.; Dunnheim, G.; Szumilo, T.; Elbein, A. D. *Arch. Biochem. Biophys.* **1997**, *251*, 450. (m) Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936. (n) See ref 4h.

(6) Lentiginosine (**3**) as an amyloglucosidase inhibitor (a) See ref 3a. (b) Molyneux, R. J.; Pan, Y. T.; Tropea, J. E.; Benson, M.; Kaushal, G. P.; Elbein, A. D. *Biochemistry* **1991**, *30*, 9981. (c) See ref 3b,c.

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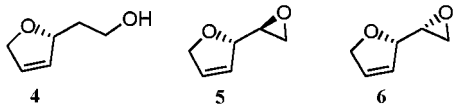
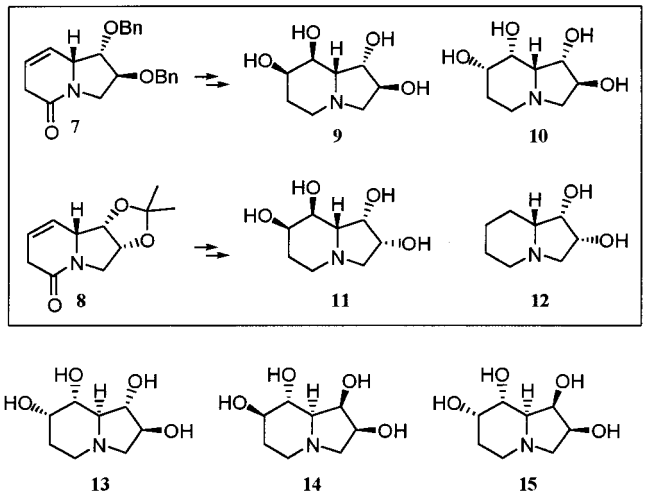
Chart 2



significant changes in terms of inhibiting potency and selectivity on the glycosidase enzymes.[9] On the basis of these considerations, ready access to the unnatural epimers of polyhydroxylated indolizidines **1**−**3** has received much attention.[10−12]

We have previously reported the preparation of chiral building blocks **4**−**6** (Chart 2) from D-mannitol or D-sorbitol and their use for the syntheses of several enantiopure insect pheromones[13a,b] as well as the Geissman−Waiss lactone,[14] developing the "chiral pool approach".[26] More recently, we have shown how chiral synthons such as **4**−**6** can be used to prepare a dihydroxyindolizidine such as (−)-8a-epilentiginosine in high enantiomeric purity.[12c]

Chart 3



In this paper, we report the application of our methodology to the novel optically pure polyhydroxylated indolizidines **9**−**12** (Chart 3) via 5-oxohexahydroindolizines **7** and **8**. To the best of our knowledge, 1,2,7,8-tetrahydroxyindolizines do not occur naturally, and tetraol **13** has been prepared by diethylaminosulfur trifluoride (DAST)-induced rearrangement of 1,6,7-tri-*O*-benzoylcastanospermine,[15] while **14** and **15** have been obtained from D-glucoheptonic γ-lactone.[11k]

Result and Discussion

Preparation of Oxoindolizine 8 and Formal Synthesis of Its Stereoisomers *ent*-8 and *ent*-7. To extend the methodology initiated with our synthesis of (−)-8a-epilentiginosine[12c] via derivative **7**, we first prepared amide **8** as depicted in Scheme 1. Pyrrolidine **17**, obtained from the epoxide **6**[12c] via dihydrofuran derivative **16**, was deprotected with Me_3SiI[16] and converted to 3-butenoyl derivative **20**. The diene moiety of **20** was then submitted to a ruthenium-catalyzed ring-closing metathesis[17] to give the desired bicyclic product **8** with a 78% overall yield from **17**.

The same synthetic sequence may be used to prepare *ent*-**8** starting from building block *ent*-**6**, readily available from L-sorbitol[18] though L-isosorbide[27a,b] (Chart 4). The fourth and last stereoisomer in this series,[19] *ent*-**7**, could be prepared likewise from L-mannitol, although this is

(7) (a) Elbein, A. D. *FASEB J.* **1991**, *5*, 3055. (b) Cenci di Bello, I.; Fleet, G. W. J.; Namgoong, S. K.; Tadano, K. I.; Winchester, B. G. *Biochem. J.* **1989**, *259*, 855. (c) Kino, I.; Inamura, N.; Klakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1985**, *38*, 936. (d) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (e) Das, P. C.; Robert, J. D.; White, S. L.; Olden, K. *Oncol. Res.* **1995**, *7*, 425. (f) Elbein, A. D.; Molyneux, R. J. In *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999, pp 216−251 and references therein.

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(9) (a) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. (b) See refs 4g, 5j, and 7b.

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(12) Synthesis and biological activity of lentiginosine close analogues: (a) Colegate, S. M.; Dorling, R. R.; Huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503. (b) See ref 3b,c. (c) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415. (d) Heitz, M. P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2951.

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(14) Paolucci, C.; Venturelli, F.; Fava, A. *Tetrahedron Lett.* **1995**, *36*, 8127.

(15) Forneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Teyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1995**, *51*, 12611.

(16) Lott, R. S.; Chanhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495.

(17) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. Our catalyst was a commercial sample purchased from Strem Chemicals.

(18) Synthesis of L-sobitol from commercially available D-gulonic acid γ-lactone: Wolfrom, M. L.; Thompson, A. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press, Inc.: New York, 1962; Vol. II, pp 66−67 and references therein.

(19) Only four of the eight possible stereoisomers can be synthesized by this way because the bridgehead carbon configuration, C_{8a}, is fixed by the stereochemistry at C_1, as a consequence of the synthetic protocol used.[12c]

(20) *ent*-Lentiginosine: (a) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, 8871. (b) See ref 3b,g. 2,8a-Diepilentiginosine: (c) Harris, T. M.; Harris, C. M.; Hill, J. E.; Ungemach, F. S. *J. Org. Chem.* **1987**, *52*, 3094. (d) Pearson, W. H.; Lin, K. C. *Tetrahedron Lett.* **1990**, *31*, 7571. 2-Epilentiginosine: (e) See ref 20b. (f) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1992**, *3*, 999. (g) Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591. 1,8a-Diepilentiginosine: (h) See ref 20e. 8a-Epilentiginosine: (i) See ref 12c. 1-Epilentiginosine: (l) See ref 3e.

(21) Performed as implemented in *Chem3D Pro*, Ser. 495965; CambridgeSoft: Cambridge, MA.

(22) (a) Wilson, C. W. *Org. React.* **1957**, *9*, 332. (b) Woodward, R. B.; Brutche, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.

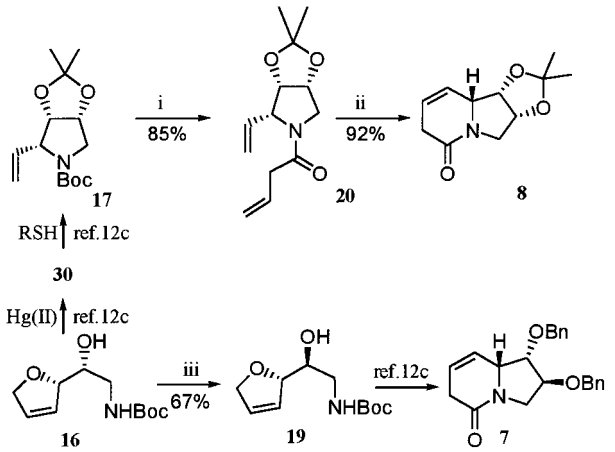
(23) (a) Cambie, R. C.; Hayward, R. C.; Robert, J. L.; Ritledge, P. S. *J. Chem. Soc., Perkin Trans 1* **1974**, 1858. (b) Seebach, D.; Liesmer, M.; Wilka, E. M. *Org. Synth.* **1980**, *59*, 169.

(24) Because of the slow rotation of the N−C(O) bond in the NMR time scale, the amide **32** gives rise to broad or split signals at the spectrometer temperature (22 °C). When this is the case, the signals of both conformers (3:1* ratio) are reported as separated by a dash.

(25) Benzyl alcohol (39 mg, 40% yield) was isolated as a byproduct.

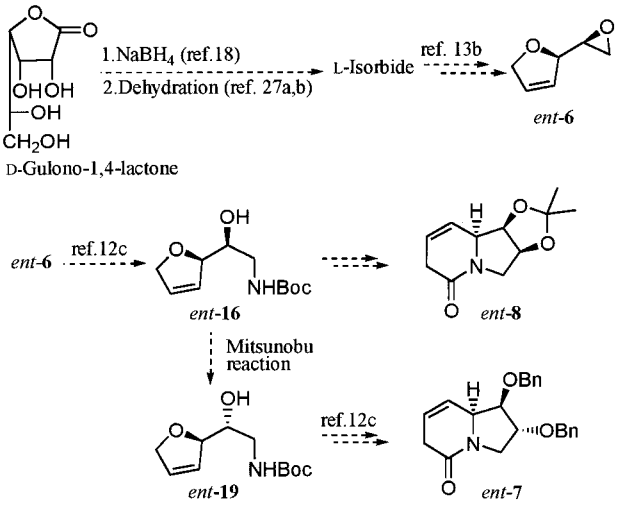
(26) Hanessian, S. In *Total Synthesis of Natural Products: The "Chiron" Approach*; Baldwing, J. E., FRS, Ed.; Organic Chemistry Series; Pergamon Press Ltd.: Elmsford, New York, 1983; Vol. 3.

Scheme 1[a]



[a] Reagents: (i) (a) TMSI, acetone; (b) CH_2=$CHCH_2COCl$, Et_3N, CH_2Cl_2. (ii) $(Cl)_2(Cy_3P)_2RuCHPh$ (1 mol %), C_6H_6, rt to reflux. (iii) (a) PPh_3, $PhCO_2H$, DEAD, THF, rt (75%). (b) K_2CO_3, MeOH−H_2O (90%).

Chart 4



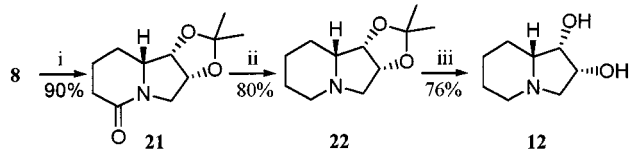
not a convenient starting material because of its elevated cost. The feasibility of diastereodivergent synthesis starting from L-sorbitol was therefore evaluated via an inversion of configuration at the hydroxylated carbon adjacent to the dihydrofuranic ring on *ent*-**16** (Chart 4).

When submitted to Mitsunobu's conditions in the presence of benzoic acid, urethane **16** gave benzoic ester **18**, which after alkaline hydrolysis afforded urethane **19** in 67% overall yield (Scheme 1). Consequently, both stereoisomers, *ent*-**7** and *ent*-**8**, could be obtained from L-sorbitol, which demonstrate the high flexibility of our methodology. Moreover, *ent*-**7** opens a way to the 1,2-diepilentiginosine, the only unknown lentiginosine stereoisomer,[20] by applying the same synthetic protocol used to obtain the 8a-epilentiginosine from **7**.[12c]

Synthesis of Dihydroxyindolizidine 12. Naturally occurring lentiginosine (**3**) was found to be a potent and selective inhibitor of amyloglucosidase,[6a−c] and its synthesis,[3b−f] as well as those of its stereoisomers, has been the subject of several reports,[20] including our own preparation of 8a-epilentiginosine from D-mannitol via epoxide

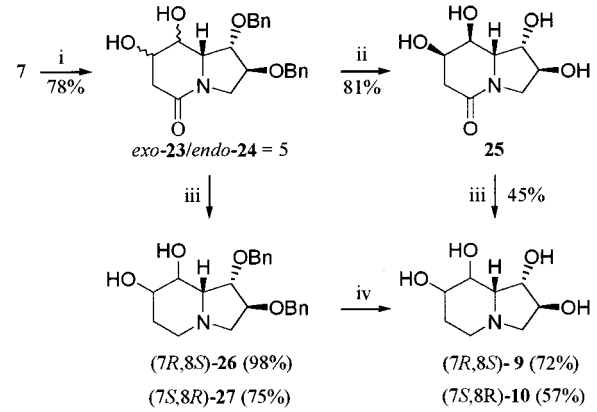
(27) (a) Montgomery, R.; Wiggins, L. F. *J. Chem. Soc.* **1946**, 390. (b) Hockett, R. C.; Fletcher, H. G., Jr.; Sheffield, E. L.; Goepp, R. M., Jr. *J. Am. Chem. Soc.* **1946**, *68*, 1946.

Scheme 2[a]



[a] Reagents: (i) H_2−Pd/C. (ii) (a) BH_3·Me_2S/THF, rt to reflux. (b) EtOH, reflux. (iii) HCl (2 M), 60 °C.

Scheme 3[a]



[a] Reagents: (i) OsO_4 catalyst, NMO, acetone−water. (ii) H_2−Pd/C. (iii) (a) BH_3·Me_2S/THF, rt to reflux. (b) EtOH, reflux. (iv) H_2Pd (black), EtOH/HCl concentration (10:1).

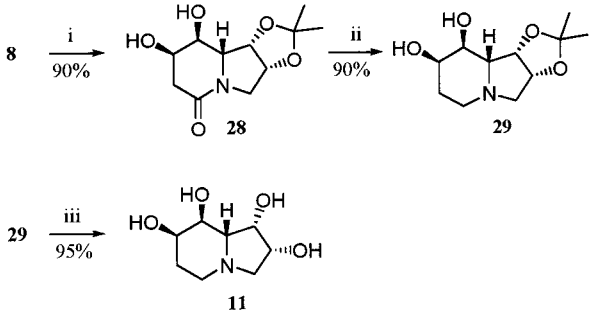
5.[12c] An interesting stereoisomer of **3** is 2,8-diepilentiginosine **12**, which was previously obtained as a di-*O*-acetate derivative by a regioselective dehydroxylation of 1,2-di-*O*-isopropylidene swainsonine.[20c] Interestingly, **12** can be efficiently converted into swainsonine (**2**) by *Rhizoctonia leguminicola*.[20c] Another efficient preparation of **12** starting from 2,3-di-*O*-isopropylidene-D-erythrose has been reported by Pearson.[20d] Scheme 2 illustrates our approach to indolizidine **12**, which consists of catalytic hydrogenation of indolizine **8** to saturated amide **21**, a borane reduction of the carbonyl to amine **22**, and finally a deprotection of the diol to the desired target **12**.

Synthesis of Tetrahydroxyindolizidines 9−11. The presence of a carbonyl and a nonconjugated double bond in the six-member ring adds versatility to chiral building blocks **7** and **8**. Reactions at the double bond were examined first, and when the β,γ-unsaturated amide derivative **7** was submitted to syn-dihydroxylation catalyzed with osmium tetroxide, two isomeric diols (**23** and **24**) were obtained in a 5:1 ratio Scheme 3.[28]

After chromatographic separation, the main isomer (*exo*-**23**) could be converted to the desired tetrahydroxylated indolizidine **9** by a Pd(0)/C-catalyzed debenzylation followed by borane reduction of the carbonyl. The low yield (45%) of last step is probably due to low solubility of intermediate **25**. By reversing the two steps, tetraol **9** was obtained in 70% overall yield from **23** (Scheme 3).

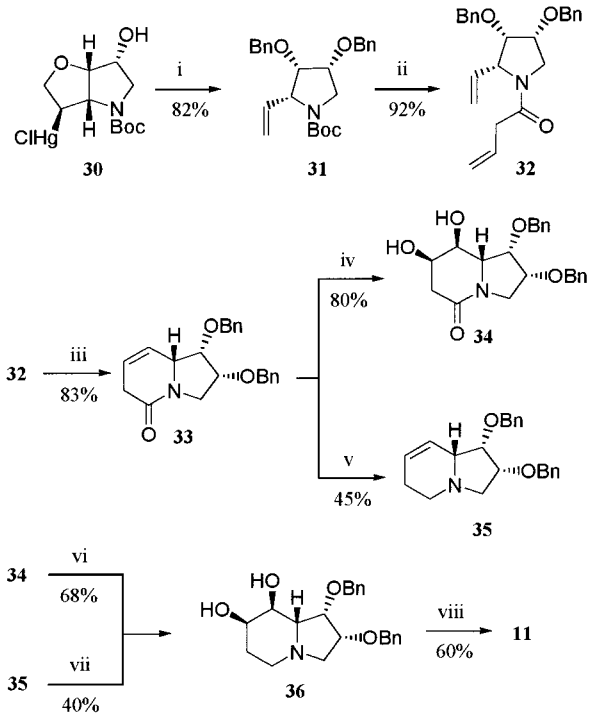
(28) The exo-configuration of the newly formed diol was unambiguously assigned to the major isomer **23**, by means of ^{1}H NMR analysis on the corresponding reduction products **26** and **9**. The coupling constants between H_{8a} (hydrogen on the bridgehead carbon, see **1** in Chart 1) and H_8 were 9.7 Hz for **26** and 9.4 Hz for **9**, typical values for the 1,2-di-axial relationship between H_{8a} and H_8; otherwise, the reduction products **27** and **10**, derived from the minor isomer **24**, showed J_{8a-8} of 5.7 and 4.9 Hz, respectively, typical values for the equatorial−axial relationship between H_8 and H_{8a} (see Abraham, R. J.; Fisher, J.; Loftus, R. *Introduction to NMR Spectroscopy*; John Wiley & Sons: Chichester, 1988; Chapter 3.).

Scheme 4[a]



[a] Reagents: (i) OsO_4 catalyst, NMO, acetone−water. (ii) (a) BH_3·Me_2S/THF, rt to reflux. (b) EtOH, reflux. (iii) 2 M HCl, 60 °C.

Scheme 5[a]



[a] Reagents: (i) (a) *n*-$C_{12}H_{25}SH$, MeOH (deg). (b) NaH, BnBr, THF−DMF. (ii) (a) TFA, CH_2Cl_2. (b) CH_2=$CHCH_2COCl$, Et_3N, CH_2Cl_2. (iii) $(Cl)_2(Cy_3P)_2RuCHPh$, C_6H_6, rt to reflux. (iv) OsO_4 catalyst, NMO, acetone−water. (v) LAH, THF. (vi) (a) BH_3·Me_2S/THF, rt to reflux. (b) EtOH, reflux. (vii) OsO_4 catalyst, NMO, AcOH (3 equiv), acetone−water. (viii) H_2−Pd (black), EtOH/HCl concentration (10:1).

Isomeric tetraol **10** was prepared with a similar reaction sequence with a 42% overall yield from the minor dihydroxyl amide *endo*-**24**.

The OsO_4-catalyzed syn-dihydroxylation of amide **8**, on the other hand, showed an exclusive exo-selectivity providing diol **28** as the sole product[29] (Scheme 4). Borane-mediated carbonyl reduction to amine **29**, followed by diol deprotection, furnished the desired tetraol **11**, enantiomeric to **15**[11k] (Chart 3).

The high exo-diastereofacial selectivity in the OsO_4-catalyzed dihydroxylation of **8** precluded the preparation of the 7,8-diepitetrahydroxyindolizidine isomer of **11** (the counterpart of **10** in Scheme 3). This remains a rather puzzling result since both Dreiding models and MM2 calculations[21] show that the endo face of **8** is not particularly more sterically hindered when compared to epimeric dibenzyl derivative **7**. In an attempt to elucidate this point (Scheme 5), our general methodology was applied to bicyclic derivative **30**[12c] to afford amide **33**, the corresponding di-*O*-benzyl derivative of **8**. Again, when **33** was submitted to OsO_4-catalyzed dihydroxylation, diol **34** was obtained as a single diastereomer. Alternatively, amine **35**, obtained by LAH carbonyl reduction of **33**, resisted OsO_4-catalyzed oxidation and was recovered unreacted after 5 days. The addition of small amounts of acetic acid to the same reaction mixture allowed the dihydroxylation to proceed, generating the diastereoisomer **36** as a single product. This product was revealed to be identical to the that obtained by borane reduction of **34** (Scheme 5). Acetic acid probably reactivates the catalytic cycle by displacing the osmium from amine complexation. When **36** was submitted to diol, deprotection furnished the tetraol **11**,[29] and this fact confirmed the exo-selectivity of double bond dihydroxylation of **33** and **35** (Scheme 5).

A final attempt at an endo-selective dihydroxylation **33** was performed under Prévost conditions using AgOAc/I_2[22] in acetic acid as well as its Cambie modification with TlOAc,[23] but only an amide decomposition was observed.

Conclusions

In conclusion, this work, completing a previous one,[12c] provides a straightforward approach to prepare enantiopure stereoisomeric 5-oxohexahydroindolizines **7** and **8**, starting from the sugar-derived epoxides **5** and **6,** already shown to be important and useful precursors in synthesis.[13a,b] Moreover, a route is depicted to prepare the corresponding enantiomers *ent*-**7** and *ent*-**8** by a stereodivergent synthesis from *ent*-**6**, achievable from D-gulono-1,4-lactone. From these hydroxylated nitrogen-containing bicycles, sets of stereoisomeric indolizidines can be obtained in enantiopure form and in an efficient manner. The preparation of two sets of these interesting compounds (**12** and **9**−**11**) is reported here as an example of the method. Our efforts are aimed to give a contribution in gaining more insights about the mechanism by which these substances act on glycosidase enzymes.

Experimental Section

General. Bulb to bulb distillations were done on a Büchi GRK-50 Kugelrohr apparatus; boiling points refer to air-bath temperatures and are uncorrected. Melting points were obtained with a Büchi apparatus and are uncorrected. Yields are for isolated compounds. Unless otherwise specified, ^1H and ^{13}C spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as solvent. Chemical shifts are in ppm downfield of TMS as an internal standard. Electron impact mass spectra were obtained with a VG 7070 instrument at 70 eV. For optical rotation measurements, a Perkin-Elmer 341 was used. Preparative flash chromatographic separations were performed using Merck silica gel 60 (70−230 mesh ASTM). For TLC, Merck precoated glass plates (silica gel 60 GF_{254}, 0.25 mm) were used. Dry solvents and reagents were obtained prior to use as follows: THF was distilled from benzophenone ketyl; MeCN, CH_2Cl_2, benzene, Et_3N, and DMF were distilled from CaH_2; acetone was from K_2CO_3; and Me_3SiCl was on magnesium turnings. NaI was dried at 100 °C under reduced pressure (0.1 mm) for 4 h.

(29) The exo-configuration of the diol moiety was confirmed from the enantiomeric relationship between the tetraol **11**, derived from **28** (Scheme 4), and the tetraol **15** in Chart 4 (see Experimental Section). Moreover, **11** showed a coupling constant between H_{8a} and H_8 of 10.2 Hz (see ref 28).

(2*R*,3*S*,4*R*)-(−)-*N*-Vinylacetyl-3,4-di-*O*-isopropylidene-2-vinylpyrrolidine (20). To a dried NaI (1.5 g, 10 mmol) solution in anhyd MeCN (10 mL), Me_3SiCl (0.734 mL, 10 mmol) was added dropwise under nitrogen at 0−5 °C. After 5 min, the orange suspension was allowed to warm to ambient temperature and maintained for 30 min. The stirring was stopped, and the decanted Me_3SiI solution (7 mL, ∼7 mmol) was transferred, by syringe, into an oven-dried flask under nitrogen, and then a solution of N-Boc derivative **17**[12c] (1 g, 3.7 mmol) in acetone (15 mL) was added. The resulting mixture was stirred at rt for 45 min and then warmed to 45 °C. The progress of the reaction was monitored by TLC (20% Et_2O/petroleum ether). After 30 min at 45 °C, the starting material disappeared. The reaction mixture was cooled to 0 °C and quenched with 1 mL of NaOMe (3 M solution in methanol, 3 mmol) followed by CH_2Cl_2 (30 mL) addition. The insoluble solid was filtered off, solvents were removed under reduced pressure, and the residue was treated with CH_2Cl_2 (30 mL) and refiltered to completely remove the insoluble salt. Solvent evaporation furnished 1 g of amine (R_f = 0.15, 20% MeOH/EtOAc), which then dissolved in 4 mL of $CHCl_3$ (filtered through neutral alumina) cooled at −10 °C, and Et_3N (0.733 mL, 5.5 mmol) was added. To the resulting mixture, vinylacetyl chloride (0.338 mL, 4 mmol) was slowly added by syringe. The reaction was followed by TLC (20% MeOH/EtOAc), and after 1 h at −10 °C, Et_2O (40 mL) was added. The reaction mixture was then washed twice with water (3 mL) and dried on $MgSO_4$. After the solvent evaporated, the crude product was flash chromatographed on silica gel to furnish 0.811 g (92% yield) of diene **20** as a colorless oil. Bulb to bulb distillation at 0.05 mm (bp 145 °C) furnished 0.75 g (85%) of colorless oil: $[\alpha]^{28}_D = -23.6°$ (*c* 0.64, $CHCl_3$). ^{1}H NMR (*T* = 55 °C): δ 6.04−5.80 (m, 2H), 5.33−5.08 (m, 4H), 4.86−4.76 (m, 2H), 4.57 (bs, 1H), 4.05 (bs, 1H), 3.57−3.48 (m, 1H), 3.12−3.06 (m, 2H), 1.52 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (*T* = 55 °C): δ 170.11, 134.12 (br), 131.25, 117.58, 116.16, 113.29, 80.79, 77.68, 62.22, 49.92 (br), 39.26, 26.07, 25.08. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.01; H, 8.09, N, 5.89.

(1*S*,2*R*,8a*R*)-(+)-1,2-Di-*O*-isopropylidene-1,2,3,5,6,8a-hexahydro-5-oxoindolizine (8). An oven-dried, 250-mL, three-necked, round-bottomed flask, equipped with a reflux condenser and an argon inlet, was charged with $(Cl)_2(Cy_3P)_2$-Ru=CHPh (56 mg, 1 mol %) and degassed dry benzene (100 mL). The distilled diene **20** (1.6 g, 6.8 mmol) was added under Ar into the purple solution, and the mixture was slowly brought to reflux at which time the color changed to orange-brown and after 50 min changed to green. The residue, after the solvent evaporated, was supported on silica gel and purified by flash chromatography (75% EtOAc/petroleum ether, 1% MeOH/CH_2Cl_2) to give 1.32 g (92%) of **13** as a light brown waxy solid: mp 64−65 °C (crystallized from *n*-hexane); $[\alpha]^{23}_D = +84.8°$ (*c* 1.05, $CHCl_3$). ^{1}H NMR: δ 5.96−5.89 (m, 1H), 5.88−5.81 (m, 1H), 4.80−4.75 (m, 1H), 4.71 (dd, *J* = 5.8, 4.0 Hz, 1H), 4.43 (d, *J* = 13.5 Hz, 1H), 4.08−4.01 (m, 1H), 3.04 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.99−2.94 (m, 2H), 1.35 (s, 3H), 1.31 (s, 3H). ^{13}C NMR: δ 166.15, 124.14, 119.49, 111.66, 80.21, 77.79, 62.05, 49.51, 31.67, 26.22, 24.54. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.22; N, 6.70.

(2*S*,1′*S*)-(−)-*N*-*tert*-Butoxycarbonyl-2-(2′-amino-1′-*O*-benzoyl)-2,5-dihydrofuran (18). Diethylazodicarboxylate (1.73 mL, 10.63 mmol) was added to an ice-cooled solution of PPh_3 (2.88 g, 11 mmol), $PhCO_2H$ (1.34 g, 11 mmol), and the alcohol derivative **16**[12c] (1.14 g, 5 mmol) in dry THF (60 mL) under nitrogen. The reaction mixture was stirred at rt and monitored on TLC (50% EtOAc/petroleum ether). After 18 h, the reaction was quenched with MeOH (0.3 mL), stirred for 1 h, and diluted with Et_2O (60 mL), and the solid was filtered. The solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography (50% Et_2O/petroleum ether) to give 1.35 g of benzoate derivative **18**. Bulb to bulb distillation at 0.1 mm (bp 150 °C) afforded 1.25 g (75% yield) of product as a colorless oil: $[\alpha]^{21}_D = -124.9°$ (*c* 2.06, $CHCl_3$). ^{1}H NMR: δ 8.10−7.99 (m, 2H), 7.61−7.51 (m, 1H), 7.47−7.39 (m, 2H), 5.98−5.91 (m, 1H), 5.84−5.77 (m, 1H), 5.31−5.24 (m, 1H), 5.18−5.00 (m, 2H), 4.77−4.54 (m, 2H), 3.66−3.40 (m, 2H), 1.39 (s, 9H). ^{13}C NMR: δ 165.91, 155.81, 132.92, 129.82, 129.58, 128.76, 128.20, 125.56, 85.65, 79.22, 75.70, 73.87, 41.30, 28.16. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.87; H, 6.95; N, 4.20.

(2*S*,1′*S*)-(−)-*N*-*tert*-Butoxycarbonyl-2-(2′-amino-1′-hydroxyethyl)-2,5-dihydrofuran (19). A solution of benzoate **18** (0.87 g, 2.61 mmol) in MeOH/water 95:5 (6 mL) was treated with solid K_2CO_3 (0.481 g, 3.48 mmol). After 12 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and the inorganic salt was filtered. After the solvent evaporated, the crude product was purified by flash chromatography (Et_2O) to give 0.538 (90% yield) of alcohol **19** as a colorless oil: $[\alpha]^{22}_D = -93.6$ (*c* 1.06, $CHCl_3$) [lit[12c] −94.5° (*c* 1.31, $CHCl_3$)]. ^{1}H and ^{13}C NMR spectra coincided with those of the literature.[12c]

(1*S*,2*R*,8a*R*)-(+)-1,2-Di-*O*-isopropylidene-5-oxoindolizidine (21). A mixture of lactam **8** (0.67 g, 3.2 mmol), 10% Pd on carbon (67 mg), and MeOH (30 mL) was treated with hydrogen (3.3 bar). TLC monitoring (EtOAc) indicated that the reaction was complete in 1 h. After filtration through Celite and flash chromatography (5% MeOH/EtOAc), the title compound **21** was isolated and distilled (bulb to bulb at 150 °C/01 mm) to give 0.608 g (90% yield) of white solid: mp 63−65 °C; $[\alpha]^{22}_D = +61.1°$ (*c* 1.16, $CHCl_3$). ^{1}H NMR (200 MHz): δ 4.78−4.70 (m, 1H), 4.62 (dd, *J* = 6.0, 4.1 Hz, 1H), 4.22 (d, *J* = 13.5 Hz, 1H), 3.42 (m, 1H), 3.10 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.50−2.19 (m, 2H), 2.08−1.62 (m, 4H), 1.41 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (50 MHz): δ 169.31, 111.75, 81.08, 77.60, 61.18, 50.24, 31.22, 26.45, 24.75, 22.50, 20.92. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.53; H, 8.12; N, 6.63.

(1*S*,2*R*,8a*R*)-(−)-1,2-Di-*O*-isopropylidenindolizidine (22). To a solution of lactam **21** (0.23 g, 1.09 mmol) in dry THF (10 mL), a solution of $Me_2S{\cdot}BH_3$ (2 M in THF, 2.5 mL, 5 mmol) was added under Ar, and the reaction mixture was kept at rt for 2 h and refluxed for 1 h. The excess of reducing agent was quenched by careful addition of EtOH (2 mL) at −5 °C. After the solvent evaporated, the residue was dissolved in EtOH (2 mL) and heated to reflux for 2 h and then cooled to rt and concentrated under reduced pressure. The residue was purified by flash chromatography (2% MeOH/EtOAc) to give 0.172 g (80%) of amine **22** as a white solid: mp 89−91 °C; $[\alpha]^{23}_D = -38.0°$ (*c* 0.95, CH_3OH). ^{1}H and ^{13}C NMR spectra were identical to those previously reported.[20c]

(1*S*,2*R*,8a*R*)-(−)-1,2-Dihydroxyindolizidine (12). Acetonide **22** (0.18 g, 0.91 mmol) was treated with 2 M HCl (5 mL) for 18 h at 60 °C. The solvent was evaporated, and the residue was basified with saturated aqueous KOH (1 mL) and extracted with THF (10 mL). The organic phase was dried (K_2CO_3) and concentrated under reduced pressure. The purification of the residue by flash chromatography (10% MeOH/CH_2Cl_2) gave 0.109 g (76% yield) of amine **12** as a white solid: mp 109−111 °C (crystallized from *n*-hexane); $[\alpha]^{24}_D = -37.1°$ (*c* 0.55, CH_3OH). ^{1}H NMR: δ 4.27−4.17 (m, 1H), 3.98 (dd, *J* = 6.1, 4.2 Hz, 1H), 3.65 (bs, 2H, (2OH)), 3.10−3.00 (m, 1H), 2.96 (d, *J* = 10.7 Hz, 1H), 2.31 (dd, *J* = 10.7, 7.1 Hz, 1H), 1.98−1.47 (m, 7H), 1.33−1.13 (m, 1H). ^{13}C NMR: δ 72.37, 69.48, 68.19, 62.57, 53.28, 24.95, 24.84, 23.80. HRMS (*m*/*z*): (M^+) calcd for $C_8H_{15}NO_2$, 157.1104; found, 157.1103. MS *m*/*z*: 157 (16), 140 (11), 97 (100), 84 (24), 69 (23).

(1*S*,2*S*,7*R*,8*S*,8a*R*)-(−)- (23) and (1*S*,2*S*,7*S*,8*R*,8a*R*)-(−)-1,2-Dibenzyloxy-7,8-dihydroxy-5-oxoindolizidine (24). To a solution of *N*-methylmorpholine *N*-oxide (0.78 g, 1.5 equiv) in water (0.5 mL) was added, in succession, a solution of 0.19 M OsO_4 (0.9 mL, 0.04 equiv) and the unsaturated amide **7** (1.5 g, 4.29 mmol) dissolved in acetone (3 mL). The solution was stirred at rt and monitored by TLC (1% MeOH/EtOAc). After 36 h, saturated aqueous sodium hydrosulfite (0.5 mL) was added, and after 30 min, the resulting reaction mixture was filtered through Celite and rinsed with acetone. The solvents were evaporated, and the dark oil was purified by flash chromatography (2−5% MeOH/CH_2Cl_2) to give the isomeric amides **23** (1.07 g, 65% yield) and **24** (0.214 g, 13% yield) as colorless oils. Amide **23**: $[\alpha]^{22}_D = -49.1°$ (*c* 1.01, $CHCl_3$). ^{1}H NMR: δ 7.40−7.22 (m, 10H), 4.58 (AB q, $\delta\nu$ = 14.1 Hz, *J* =

11.8 Hz, 2H), 4.45 (AB q, $\delta\nu = 15.1$ Hz, $J = 12.0$ Hz, 2H), 4.18−4.08 (m, 2H), 4.02−3.94 (m, 3H), 3.78 (dd, $J = 13.5$, 5.1 Hz, 1H), 3.56 (bs, 1H (OH)), 3.52 (d, $J = 13.5$ Hz, 1H), 3.23 (bs, 1H (OH)), 2.62 (m, 2H). ^{13}C NMR: δ 167.96 137.65, 137.29, 128.46, 127.96, 127.87, 127.74, 127.66, 127.61, 80.02, 77.12, 72.25, 71.12, 68.14, 66.64, 59.66, 50.48, 38.35. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.71; H, 6.59; N, 3.66. Amide **24**: $[\alpha]^{22}_D = -42.6°$ (*c* 0.97, $CHCl_3$). ^{1}H NMR: δ 7.41−7.22 (m, 10H), 4.57 (AB q, $\delta\nu = 47.4$ Hz, $J = 11.7$ Hz, 2H), 4.51 (AB q, $\delta\nu = 35.3$ Hz, $J = 11.9$ Hz, 2H), 4.39−4.36 (m, 1H), 4.27−4.23 (m, 2H, (1OH)), 4.06−4.02 (m, 1H), 4.00−3.87 (m, 1H), 3.83−3.72 (m, 2H), 3.63 (d, $J = 13.4$ Hz, 1H), 2.75 (dd, $J = 17.4$, 7.0 Hz, 1H), 2.73 (bs, 1H, (OH)), 2.54 (dd, $J = 17.4$, 10.1 Hz, 1H). ^{13}C NMR: δ 168.29, 137.00, 136.01, 128.93, 128.70, 128.66, 128.21, 127.96, 127.74, 83.73, 76.53, 72.24, 71.47, 68.92, 68.29, 58.91, 48.83, 36.69. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.19; H, 6.55; N, 6.88.

(1*S*,2*S*,7*R*,8*S*,8a*R*)-(−)-1,2,7,8-Tetrahydroxy-5-oxoindolizidine (25). A mixture of lactam **23** (0.386 g, 1.01 mmol), 10% Pd on carbon (50 mg), MeOH (20 mL), and 6 M HCl (1 mL) was treated with hydrogen at 2 bar. TLC monitoring (5% MeOH/CH_2Cl_2) indicated that the reaction was complete in 3 h. After filtration through Celite, an aqueous solution of NaOH (3 M, 2.2 mL) was added, and the solvents were evaporated under reduced pressure. The crude material was adsorbed on silica gel and column chromatographed (30% MeOH/CH_2Cl_2). The title compound **25** was obtained (0.165 g, 81% yield) as a white solid, highly hygroscopic: $[\alpha]^{20}_D = -64.5°$ (*c* 0.97, CH_3OH). ^{1}H NMR (D_2O): δ 4.33−4.22 (m, 3H), 3.98 (dd, $J = 9.9$, 2.1 Hz, 1H) 3.92 (dd, $J = 10.1$, 2.3 Hz, 1H), 3.81 (dd, $J = 13.7$, 4.7 Hz, 1H), 3.36 (d, $J = 13.7$ Hz, 1H), 2.72 (dd, $J = 18.7$, 3.8 Hz, 1H), 2.53 (dd, $J = 18.7$, 1.9 Hz, 1H). ^{13}C NMR (MeOH as initial standard): δ 170.52, 74.70, 72.54, 68.00, 65.92, 59.26, 52.49, 38.06. Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.35; H, 6.43; N, 6.88.

(1*S*,2*S*,7*R*,8*S*,8a*R*)-(−)-1,2-Dibenzyloxy-7,8-dihydroxyindolizidine (26). A solution of lactam **23** (0.48 g, 1.25 mmol) in dry THF (30 mL) was treated with $Me_2S{\cdot}BH_3$ (2 M in THF, 3.5 mL, 7 mmol) using conditions described for **21**. After the solvent evaporated, the crude product was flash chromatographed (6% MeOH/CH_2Cl_2) to give 0.453 g (98% yield) of amine **26** as a white semisolid material: $[\alpha]^{22}_D = -62.7°$ (*c* 1.30, $CHCl_3$). ^{1}H NMR: δ 7.43−7.25 (m, 10H), 4.59 (AB q, $\delta\nu = 60$ Hz, $J = 12.1$ Hz, 2H), 4.45 (AB q, $\delta\nu = 15.2$ Hz, $J = 11.6$ Hz, 2H), 4.10−4.03 (m, 2H), 3.98 (dd, $J = 5.2$, 1.1 Hz, 1H), 3.89 (dd, $J = 9.7$, 3.2 Hz, 1H), 3.53 (dd, $J = 9.4$, 6.9 Hz, 1H), 2.78−2.69 (m, 1H), 2.55 (dd, $J = 9.7$, 5.2 Hz, 1H), 2.40−2.30 (m, 1H), 2.24 (dd, $J = 9.4$, 6.2 Hz, 1H), 2.20 (bs, 2H, (2 OH)), 1.90−1.73 (m, 2H). ^{13}C NMR: δ 138.15, 137.78, 128.53, 128.45, 128.00, 127.89, 127.82, 127.71, 82.29, 82.24, 71.63, 71.22, 68.72, 67.67, 64.82, 59.56, 46.08, 30.61. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C,71.31; H, 7.39; N, 3.80.

(1*S*,2*S*,7*R*,8*S*,8a*R*)-(−)-1,2,7,8-Tetrahydroxyindolizidine (9) from 26. A suspension of palladium black (75 mg) in 95% EtOH (3 mL) and HCl (concentrated, 1 mL) was prehydrogenated in a Parr hydrogenator under 3 bar of hydrogen for 15 min, a solution of amine **26** (0.15 g, 0.406 mmol) in 95% EtOH (8 mL) was added, and the suspension was shaken under 3 bar of hydrogen for 8 h. The reaction mixture was basified by aqueous solution of NaOH addition (3 M, 4.5 mL) and filtered on Celite. The crude product dissolved in 5 mL of water was purified through a Dowex 50WX8-100 (H^+) ion-exchange column (5 g) washed with water (2×, 50 mL) and eluted with 2 M NH_4OH (4×, 50 mL) to give the amine **9**. After the solvent evaporated, under reduced pressure, the crude material was adsorbed on silica gel and column chromatographed (0−5% NH_4OH concentrated/MeOH) to give the amine **9** as a white solid: 56 mg (72% yield); mp 184−185 °C (crystallized from *i*-PrOH); $[\alpha]^{23}_D = -68.3°$ (*c* 0.95, H_2O). ^{1}H NMR (D_2O, MeOH as an internal standard): δ 4.25−4.16 (m, 3H), 3.84 (dd, $J = 10.3$, 3.2 Hz, 1H), 3.57 (dd, $J = 10.3$, 7.1 Hz, 1H), 2.85 (ddd, $J = 11.3$, 4.8, 2.2 Hz, 1H), 2.61 (dd, $J = 10.3$, 4.4 Hz, 1H), 2.42 (m, 1H), 2.20 (dd, $J = 10.3$, 5.9 Hz, 1H), 2.00−1.91 (m, 1H), 1.90−1.77 (m, 1H). ^{13}C NMR (D_2O, MeOH as an internal standard): δ 78.24, 77.62, 68.88, 68.64, 65.48, 61.32, 46.62, 31.14. HRMS (*m*/*z*): (M^+) calcd for $C_8H_{15}NO_4$, 189.10018; found, 189.10011. MS *m*/*z*: 189 (20), 172 (14), 154 (6), 129 (100), 116 (26).

9 from 25. The lactam **25** (50 mg, 0.25 mmol) was submitted to $Me_2S{\cdot}BH_3$ reduction according to the procedure described for **26** synthesis. After concentration, ∼3 mL of the mixture was purified on a Dowex 50WX8-100 (H^+) ion-exchange column; after being washed with 20% MeOH/water (50 mL), the unreacted lactam **25** was recovered (20 mg, 40% yield, after flash chromatography purification), and then with 2 M NH_4OH (3×, 30 mL), the amine **9** was isolated, and purification as described above led to the recovery of 21 mg (45% yield) of **9** as a white solid.

(1*S*,2*S*,7*S*,8*R*,8a*R*)-(−)-1,2-Dibenzyloxy-7,8-dihydroxyindolizidine (27). The lactam **24** (0.154 g, 0.4 mmol) was reduced with $Me_2S{\cdot}BH_3$ (2 M in THF, 1.2 mL, 2.4 mmol) as described for the reduction of **21**. After solvent evaporation and flash chromatography purification (5% MeOH/CH_2Cl_2), 0.111 g (75% yield) of amine **27** was obtained as a white waxy material: mp 72−73 °C (crystallized from *n*-hexane); $[\alpha]^{21}_D = -29.7°$ (*c* 1.11, $CHCl_3$). ^{1}H NMR: δ 7.40−7.25 (m, 10H), 4.56 (AB q, $\delta\nu = 50.7$ Hz, $J = 11.7$ Hz, 2H), 4.48 (AB q, $\delta\nu = 22.9$ Hz, $J = 11.6$ Hz, 2H), 4.19−4.11 (m, 3H), 4.08 (bs, 1H (OH)), 3.61−3.37 (m, 2H), 3.10−3.00 (m, 1H), 2.63 (bs, 1H (OH)), 2.19 (dd, $J = 5.7$, 1.1 Hz, 1H), 2.07 (dd, $J = 9.3$, 2.5 Hz, 1H), 2.05−1.89 (m, 2H), 1.85−1.70 (m, 1H). ^{13}C NMR: δ 137.47, 136.84, 128.60, 128.49, 128.15, 128.05, 127.99, 127.84, 86.32, 82.75, 71.75, 71.45, 70.90, 68.40, 67.20, 58.79, 50.43, 28.70. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.34; H, 7.39; N, 3.78.

(1*S*,2*S*,7*S*,8*R*,8a*R*)-(−)-1,2,7,8-Tetrahydroxyindolizidine (10). Benzyl ether hydrogenolysis of amine derivative **27** (0.103 g, 0.28 mmol) was performed using the condition described above for **26**. The crude product, a light brown oil, was purified through a Dowex 50WX8-100 (H^+) ion-exchange column (4 g), washed with water (50 mL), and eluted with 2 M NH_4OH (3×, 50 mL) to give the amine **10**. After water evaporation under reduced pressure with a water bath temperature below 35 °C, the amine was stored in a desiccator under vacuum in the presence of $CaCl_2$ overnight to give 30 mg (57% yield) of amine **10** as a white solid: mp 174−175 °C (crystallized from EtOH); $[\alpha]^{24}_D = -18.5°$ (*c* 0.53, H_2O). ^{1}H NMR (D_2O, MeOH as an internal standard): δ 4.48−4.43 (m, 1H), 4.37 (dd, $J = 4.9$, 1.5 HZ, 1H), 4.35−4.29 (m, 1H), 3.88 (ddd, $J = 11.7$, 4.9, 2.9 Hz, 1H), 3.63 (dd, $J = 10.4$, 7.0 Hz, 1H), 3.28−3.19 (m, 1H), 2.63 (d, $J = 4.9$ Hz, 1H), 2.48−2.36 (m, 1H), 2.24 (dd, $J = 10.4$, 6.0 Hz, 1H), 2.14−1.98 (m, 1H), 1.94−1.83 (m, 1H). ^{13}C NMR (D_2O, MeOH initial standard): δ 79.78, 77.20, 70.13, 68.76, 66.12, 58.97, 49.93, 26.49. HRMS (*m*/*z*): (M^+) calcd for $C_8H_{15}NO_4$, 189.10047; found, 189.10011. MS *m*/*z*: 189 (17), 172 (15), 154 (7), 129 (100), 116 (28).

(1*S*,2*R*,7*R*,8*S*,8a*R*)-(−)-1,2-Di-*O*-isopropylidene-7,8-dihydroxy-5-oxoindolizidine (28). To a solution of *N*-methylmorpholine *N*-oxide (0.63 g, 4.65 mmol) in water (0.3 mL) was added, in succession, a solution of OsO_4 (0.19 M, 0.63 mL, 0.12 mmol) and the unsaturated amide **8** (0.65 g, 3.1 mmol) dissolved in acetone (1.5 mL). The solution was stirred for 43 h at rt and monitored by TLC (5% MeOH/EtOAc). After addition of saturated aqueous sodium hydrosulfite (0.4 mL), the reaction mixture was filtered through Celite and rinsed with acetone. The solvents were evaporated, and the dark oil was purified by flash chromatography (1−10% MeOH/CH_2Cl_2) to give 0.679 g (90% yield) of lactam **28** as a white solid: mp 145−146 °C (crystallized from *n*-hexane/*i*-PrOH 5:1); $[\alpha]^{26}_D = -29.2°$ (*c* 1.09, $CHCl_3$). ^{1}H NMR: δ 4.83 (dd, $J = 5.9$, 4.3 Hz, 1H), 4.78−4.73 (m, 1H), 4.25−4.20 (m, 1H), 4.15−4.05 (m, 2H), 4.10 (bs, 1H (OH)), 3.90 (bs, 1H (OH)), 3.63 (dd, $J = 8.8$, 4.3 Hz, 1H), 3.15 (dd, $J = 13.6$, 4.9 Hz, 1H), 2.60−2.55 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H). ^{13}C NMR: δ 167.69, 111.74, 79.57, 72.28, 68.32, 66.91, 60.83, 50.76, 37.79, 26.33, 24.49. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.40; H, 7.03; N, 5.77.

(1*S*,2*R*,7*R*,8*S*,8a*R*)-(−)-1,2-Di-*O*-isopropylidene-7,8-dihydroxyindolizidine (29). Lactam **28** (0.5 g, 2.05 mmol) reduction with $Me_2S{\cdot}BH_3$ was performed according to the procedure described for **21**. Purification by flash chromatography (10% MeOH/CH_2Cl_2) afforded 0.423 g (90% yield) of amine **29** as white solid material: mp 114−116 °C (crystallized from *n*-hexane); $[\alpha]^{24}_D = -68.0°$ (*c* 1.03, $CHCl_3$). ^{1}H NMR: δ 4.68 (dd, J = 6.3, 4.4 Hz, 1H), 4.63 (dd, J = 6.3, 4.1 Hz, 1H), 4.09 (m, 1H), 3.89 (dd, J = 9.7, 3.2 Hz, 1H), 3.16 (d, J = 10.7 Hz, 1H), 2.83−2.70 (m, 3H (2 OH)), 2.33−2.23 (m, 1H), 2.22−2.14 (m, 2H), 1.92−1.81 (m, 2H), 1.51 (s, 3H), 1.34 (s, 3H). ^{13}C NMR: δ 111.18, 79.28, 78.25, 68.99, 67.92, 66.20, 59.69, 45.71, 30.83, 25.84, 24.69. HRMS (*m*/*z*): (M^+) calcd for $C_{11}H_{15}NO_4$, 229.13119; found, 229.13141. MS *m*/*z*: 229 (43), 214 (15), 171 (13), 154 (56), 129 (100).

(1*S*,2*R*,7*R*,8*S*,8a*R*)-(−)-1,2,7,8-Tetrahydroxyindolizidine (11) from 29. A solution of **29** (0.22 g, 0.96 mmol) in MeOH (7.5 mmol) was treated with HCl (concentrated, 2.5 mL), and the resulting mixture was stirred at 60 °C for 24 h. The crude product, obtained after solvent evaporation under reduced pressure, was purified on Dowex 50WX8-100 (H^+) column (5 g) washing with water (2×, 50 mL) and eluting with 2 M NH_4OH (3×, 50 mL). From solvent evaporation, 0.173 g (95% yield) of tetraol **11** was obtained: mp 179−181 °C (crystallized from *i*-PrOH); $[\alpha]^{25}_D = -103.9°$ (*c* 0.40, H_2O) [its enantiomer **15**:[11k] $[\alpha]^{25}_D = +22.0°$ (*c* 0.05, H_2O)]. ^{1}H and ^{13}C NMR spectra were identical to those previously reported.[11k] HRMS (*m*/*z*): (M^+) calcd for $C_8H_{15}NO_4$, 189.099 74; found, 189.100 11. MS *m*/*z*: 189 (21), 172 (14), 154 (8), 129 (100), 116 (17).

11 from 36. The dibenzyl derivative **36** (75 mg, 0.0203 mmol) was hydrogenated in the presence of palladium black (40 mg) following the procedure described previously for its C-2 epimer, **26**. After purification, 23 mg (60% yield) of tetraol **11** was obtained as a white solid.

(2*R*,3*S*,4*R*)-(+)-*N*-*tert*-Butoxycarbonyl-2-vinyl-3,4-dibenzyloxypyrrolidine (31). To a solution of chloromercury derivative **30**[12c] (4.04 g, 8.7 mmol) in degassed MeOH (300 mL), dodecane-1-thiol (2.15 g, 10.44 mmol) was added at rt under Ar. The mixture was protected from light, and the reaction course was followed on TLC (60% EtOAc/petroleum ether). After 6 h, the mixture was filtered on paper, and the solid was washed with MeOH. The solvent was removed under reduced pressure, and the residue was dried under high vacuum. The crude diol so obtained was dissolved in dry DMF (20.2 mL) and added dropwise under Ar to a suspension of NaH (0.905 g, 22.62 mmol, washed with *n*-hexane) in dry THF (20.2 mL) and cooled at −10 °C. The temperature was allowed to rise to rt under stirring, and benzyl bromide (2.83 mL, 23.46 mmol) was added dropwise. The mixture was stirred at rt until the diol was not detectable on TLC (5% MeOH/CH_2Cl_2). After 5 h, the reaction was quenched by careful addition of water (0.5 mL) at −10 °C, and the resulting mixture was poured onto EtOAc:benzene 1:1 (40 mL) and then dried ($MgSO_4$). The residue, after solvent evaporation, was flash chromatographed (15% EtOAc/petroleum ether) to give **31** as a colorless oil: 2.92 g (82% yield); bp 210 °C/0.01 mm; $[\alpha]^{22}_D = -29.3°$ (*c* 1.67, $CHCl_3$). ^{1}H NMR (T = 55 °C): δ 7.36−7.22 (m, 10H), 6.13 (ddd, J = 17.2, 10.1, 8.4 Hz, 1H), 5.38−5.08 (m, 2H), 4.73−4.53 (m, 4H), 4.34 (bs, 1H), 4.06−3.99 (m, 1H), 3.95 (dd, J = 7.1, 4.1 Hz, 1H), 3.63−3.48 (m, 1H), 3.45 (dd, J = 12.1, 4.9 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (T = 55 °C; *broad signals): δ 154.50*, 138.36, 137.98, 135.63*, 128.27, 128.23, 127.59, 127.52 (2 C's), 127.44, 117.26*, 79.89*, 79.51, 76.13*, 72.09, 71.98, 61.23*, 49.35*, 28.41. Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.12; H, 7.65; N, 3.43.

(2*R*,3*S*,4*R*)-(+)-*N*-(Vinylacetyl)-2-vinyl-3,4-dibenzyloxypyrrolidine (32). The dibenzyloxypyrrolidine **31** (2.6 g, 6.34 mmol), dissolved in CH_2Cl_2 (7 mL), was treated with TFA (7 mL) at rt and stirred for 30 min. The residue, after solvent and TFA evaporation at reduced pressure, was dissolved in THF:MeOH 5:1 (6 mL), and $NaHCO_3$ (0.5 g) was added. The suspension was stirred for 15 min, diluted with CH_2Cl_2 (30 mL), and filtered. Evaporation of the solvent left a light brown oil (R_f = 0.5, 10% MeOH/CH_2Cl_2). To this crude material dissolved in CH_2Cl_2 (10 mL) containing Et_3N (1.34 mL, 9.48 mmol) and cooled at −10 °C, vinylacetyl chloride (0.806 g, 7.7 mmol) was added dropwise. The mixture was stirred at 0 °C, and the reaction was followed on TLC (8% MeOH/CH_2Cl_2). After 4 h, Et_2O (70 mL) was added, and the solid material was filtered off on paper. Solvent evaporation gave a crude product that was flash chromatographed (35% EtOAc/petroleum ether) to give 2.2 g (92% yield) of diene **32** as a colorless oil: bp 220 °C/0.05 mm; $[\alpha]^{23}_D = +32.7°$ (*c* 1.11, $CHCl_3$). ^{1}H NMR:[24] δ 7.38−7.24 (m, 10H), 6.24−6.04 (m, 1H), 6.02−5.86 (m, 1H), 5.41−5.20 (m, 2H), 5.17−5.04 (m, 2H), [4.81−4.53 (m)/4.41−4.34 (m), 5H], 4.13−4.04 (m, 1H), 4.00−3.91 (m, 1H), [3.77 (d, J = 13.5 Hz)/3.63* (dd, J = 11.3, 2.2 Hz), 1H], [3.56−3.51 (m)/3.51−3.46* (m), 1H], [3.17−3.02 (m)/3.01−2.94* (m), 2H]. ^{13}C NMR:[24] δ 170.85/169.94*, 138.08*/137.94, 137.65*/137.49, 135.52/134.05*, 131.55/131.01*, 128.46, 128.42, 128.37, 127.92, 127.69, 127.62, 118.78*/118.37, 117.96*/117.80, 79.90/78.78*, 77.03*/74.49, 72.51*/71.89, 72.04*/71.76, 61.87/60.42*, 50.50*/49.32, 39.66*/39.48. Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.61; H, 7.19; N, 3.70.

(1*S*,2*R*,8a*R*)-(+)-1,2-Dibenzyloxy-1,2,3,5,6,8a-hexahydro-5-oxoindolizine (33). The diene **32** (2 g, 5.3 mmol) was submitted to ring-closing metathesis in the presence of $(Cl)_2(Cy_3P)_2Ru{=}CHPh$ (44 mg, 1 mol %) as described previously for the corresponding acetonide derivative **20**. The crude product was chromatographed (EtOAc) to give the unsaturated lactam **33** (1.57 g, 83% yield) as a light brown oil: bp 220 °C/0.05 mm; $[\alpha]^{23}_D = +24.7°$ (*c* 1.17, $CHCl_3$). ^{1}H NMR: δ 7.40−7.22 (m, 10 H), 5.91−5.83 (m, 1H), 5.80−5.73 (m, 1H), 4.78 (AB q, $\delta\nu$ = 42.0 Hz, J = 12.2 Hz, 2H), 4.59 (AB q, $\delta\nu$ = 14.6 Hz, J = 12.2 Hz, 2H), 4.19−4.09 (m, 2H), 4.06−4.03 (m, 1H), 3.76−3.69 (m, 2H), 3.02−2.82 (m, 2H). ^{13}C NMR: δ 166.90, 138.28, 137.56, 128.49, 128.28, 127.89, 127.78, 127.64, 127.52, 124.73, 121.66, 77.85, 76.69, 73.08, 72.15, 61.42, 46.75, 32.47. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N 4.01. Found: C, 75.83; H, 6.64; N, 4.04.

(1*S*,2*R*,7*R*,8*S*,8a*R*)-(−)-1,2-Dibenzyloxy-7,8-dihydroxy-5-oxoindolizidine (34). The unsaturated lactam **33** (0.15 g, 0.39 mmol) was submitted to OsO_4-catalyzed dihydroxylation according to the procedure described previously for **7**. The crude product was supported on silica gel and flash chromatographed (5% MeOH/CH_2Cl_2, R_f = 0.18) to give 0.12 g (80% yield) of titled diol **34** as a white solid (insoluble in $CHCl_3$ and low solubility in CH_3OH): mp 188−189 °C (crystallized from *i*-PrOH); $[\alpha]^{26}_D = -29.5°$ (*c* 0.83, 1,4-dioxane:H_2O 9:1). ^{1}H NMR (CD_3OD): δ 7.34−7.18 (m, 10H), 4.75 (AB q, $\delta\nu$ = 35.2 Hz, J = 11.3 Hz, 2H), 4.51 (AB q, $\delta\nu$ = 17.2 Hz, J = 11.8 Hz, 2H), 4.26−4.17 (m, 2H), 4.07−4.02 (m, 1H), 3.93 (dd, J = 9.5, 2.2 Hz, 1H), 3.75 (bd, J = 9.5 Hz, 1H), 3.68−3.59 (m, 1H), 3.38−3.28 (m, 1H), 2.52 (dd, J = 18.3, 3.9 Hz, 1H), 2.35 (dd, J = 18.3, 1.9 Hz, 1H). ^{13}C NMR (CD_3OD): δ 169.67, 139.89, 139.33, 129.43, 129.27, 129.08, 128.83, 128.80, 128.66, 79.31, 77.71, 74.96, 73.47, 69.14, 67.52, 61.48, 48.72, 39.30. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.98; H, 6.58; N, 3.66.

(1*S*,2*R*,8a*R*)-(+)-1,2-Dibenzyloxy-1,2,3,5,6,8a-hexahydroindolizine (35). The unsaturated lactam **33** (0.16 g, 0.458 mmol), dissolved in dry THF (2.5 mL), was added to a suspension of $LiAlH_4$ (23 mg, 0.6 mmol) in dry THF (5 mL) under nitrogen. The reaction was maintained for 1 h at rt and then refluxed. After 4 h, the reaction mixture was cooled at −10 °C and quenched with a THF solution of triethanolamine (90 mg, 0.6 mmol) followed by 5% aqueous NH_4Cl (0.2 mL). The solid was removed by filtration and rinsed with EtOAc (10 mL), and the organic solution was dried ($MgSO_4$). The crude material was purified by flash chromatography (1−5% MeOH/CH_2Cl_2) to give the title product **35** (69 mg, 45%)[25] as a colorless oil: $[\alpha]^{26}_D = +71.9°$ (*c* 0,86 $CHCl_3$). ^{1}H NMR: δ 7.42−7.21 (m, 10H), 5.98−5.89 (m, 1H), 5.84−5.76 (m, 1H), 4.70 (AB q, $\delta\nu$ = 23.9 Hz, J = 12.3 Hz, 2H), 4.56 (AB q, $\delta\nu$ = 16.9 Hz, J = 12.1 Hz, 2H), 4.14−4.06 (m, 1H), 4.00−3.95 (m, 1H), 3.58−3.50 (m, 1H), 3.22 (dd, J = 10 Hz, 7.2 Hz, 1H), 3.05−2.85 (m, 3H), 2.33−2.29 (m, 1H), 2.13−1.98 (m, H). ^{13}C NMR: δ 138.54, 138.21, 128.30, 128.22, 127.68, 127.61, 127.58, 127.47, 126.69, 124.28, 78.54, 78.04, 72.87, 72.16, 60.53, 55.40,

47.35, 22.42. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 79.07; H, 7.53; N, 4.18.

(1*S*,2*R*,7*R*,8*S*,8a*R*)-(−)-1,2-Dibenzyloxy-7,8-dihydroxyindolizidine (36) from 35. To a solution of *N*-methylmorpholine *N*-oxide (28 mg, 0.23 mmol) in water (0.24 mL) was added, in succession, a 0.19 M solution of OsO_4 (32 μL, 5 mol %) and unsaturated amine **35** (40 mg, 0.12 mmol) dissolved in a 0.3 M solution of AcOH in acetone (1.2 mL, 3 equiv of AcOH) at rt and stirred for 56 h. The oxidant was quenched with a saturated aqueous sodium hydrosulfite (50 μL) and stirred for 30 min. The reaction mixture was supported on silica gel and purified by flash chromatography (6% MeOH/CH_2Cl_2, $R_f = 0.8$) to give the diol **36** (18 mg, 40%) as a colorless oil: $[\alpha]^{24}_D = -99.3°$ (*c* 1.75, $CDCl_3$). ^{1}H NMR: δ 7.54−7.20 (m, 10H), 4.72 (AB q, $\delta\nu = 106.1$ Hz, $J = 11.9$ Hz, 2H), 4.56 (AB q, $\delta\nu = 32.8$ Hz, $J = 12.1$ Hz, 2H), 4.13−4.01 (m, 3H), 3.96 (dd, $J = 9.6$, 3.1 Hz, 1H), 3.20 (dd, $J = 10.2$, 4.5 Hz, 1H), 2.69 (ddd, $J = 11.4$, 4.7, 2.3 Hz, 1H), 2.50 (dd, $J = 10.2$, 7.0 Hz, 1H), 2.39 (dd, $J = 9.6$, 4.5 Hz, 1H), 2.34 (dd, $J = 11.4$, 3.7 Hz, 1H), 2.10 (bs, 2H (2 OH)), 1.93−1.73 (m, 2H). ^{13}C NMR: δ 138.64, 138.20, 128.50, 128.31, 128.27, 127.85, 127.71, 127.60, 77.20, 77.10, 73.56, 72.03, 68.43, 67.73, 64.64, 57.74, 45.43, 29.74. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.79; H, 7.39; N, 3.78.

36 from 34. The lactam **34** (0.132 g, 0.377 mmol) was dissolved in warm THF (10 mL) under Ar and then cooled at ca. 15 °C before the addition of 2 M $Me_2S{\cdot}BH_3$ in THF (1.5 mL, 3 mmol). After 2 h at rt, the reaction mixture was refluxed for an additional 2 h and then cooled at −5 °C, and MeOH was added until effervescence ceased (≅300 μL). The solvent was removed under reduced pressure, the crude product was dissolved in MeOH (5 mL), and the resulting solution was refluxed for 36 h. After solvent evaporation, the crude product was dissolved in MeOH (3×, 5 mL) and supported on silica gel. From flash chromatography purification, 95.8 mg (68% yield) of diol **36** was obtained as a colorless oil.

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Supporting Information Available: ^{1}H and ^{13}C (including DEPT) spectra of **8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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