Asymmetric Syntheses of (−)-8-*epi*-Swainsonine Triacetate and (+)-1,2-Di-*epi*-swainsonine. Carbonyl Addition Thwarted by an Unprecedented Aza-Pinacol Rearrangement

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Indolizidines (−)-8-*epi*-swainsonine triacetate and (+)-1,2-di-*epi*-swainsonine were synthesized from the O'Donnell Schiff base ester **1** derived from D-serine. Reductive-alkenylation of **1** with $^{i}Bu_5$-$Al_2H/H_2C{=}CHMgBr$ followed by substrate-directed dihydroxylation of the pendant allylic group with OsO_4, reduction of imine, and cyclization with Ph_3P/CCl_4 gave the polyhydroxylated pyrrolidines **8a** and **8b** as advanced intermediates. Efficient protecting group manipulations converted pyrrolidines **8a** and **8b** to their corresponding partially protected analogues **10a** and **10b**, which upon Swern oxidation and diastereoselective Keck-type allylation with $BF_3{\cdot}Et_2O$ afforded the required three-carbon homologues (**10a**, >20:1 de; **10b**, 3.5:1 de). Use of the chelating Lewis acid $MgBr_2$ instead of $BF_3{\cdot}Et_2O$ with **10a** led to a novel aza-pinacol rearrangement and allylation at the α-carbon to yield amino alcohol **17**, which is similar to a hydride migration in the biosynthetic pathway of indolizidine alkaloids. Subsequent hydroboration, cyclization, and deprotection furnished (−)-8-*epi*-swainsonine triacetate **15a** and (+)-1,2-di-*epi*-swainsonine **16b** in good overall yields (6.3% for **1** → **15a**, 13 steps, and 4.0% for **1** → **16b**, 14 steps).

Introduction

Polyhydroxylated indolizidine alkaloids were initially recognized for their toxic effects on biological organisms. The toxicological focus on indolizidines has since expanded to their use as glycosidase inhibitors[1−4] and their application as tools for the study of glycobiology.[5] Swainsonine, castanospermine, and slaframine (Figure 1) represent a class of glycosidase inhibitors that can be regarded as conformationally constrained bicyclic "aza-sugars" or "nitrogen-in-the-ring" sugar analogues,[6] which may be useful in the treatment of cancer,[7,8] HIV,[9] and immunological disorders.[10] Thus, the efficient chemical synthesis of swainsonine and various analogues has become increasingly important for structure−activity relationship (SAR) and for clinical studies.

Swainsonine is the active agent responsible for the toxicity of plants indigenous to Australia and North America[11] that include *Swainsona* (Darling pea), *Astragalus lentiginosus* (locoweed), and *Oxytropis*,[12] and the ubiquitous mold *Rhizoctonia leguminicola*,[13] where it can also poison diverse human populations.[14] The biogenesis of swainsonine starts with L-lysine, and the early stages of biosynthesis are identical in several other indolizidine alkaloids (e.g., slaframine). (Figure 2) Although enolization of the 1-ketoindolizidine intermediate can occur, hydride migration from the 8a → 1 position appears to be responsible for the biological reduction of the ketone during biosynthesis. Interestingly, a similar Lewis acid-promoted hydride shift has been observed during these studies (vide infra).

Synthetic Strategy. Over the years, various synthetic strategies for swainsonine have been published. D-Maleic

(1) For a review see: Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Vol. 5, pp 1−54; Wiley: New York, 1987.

(2) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29.

(3) (a) Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 5073. (b) Post, C. B.; Karplus, M. *J. Am. Chem. Soc.* **1986**, *108*, 1317.

(4) Tulsiani, D. P. R.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936.

(5) Bock, K.; Sigurskjold, B. W. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman Ed.; Elsevier: Amsterdam, 1990; Vol. 7, pp 29−86.

(6) (a) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999. (b) Nishimura, Y. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 495−583. (c) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

(7) (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1752. (b) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091. (c) Goss, P. E.; Baptiste, J.; Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 1450−1453.

(8) (a) Das, P. C.; Roberts, J. D.; White, S. L.; Olden, K. *Oncol. Res.* **1995**, *7*, 425. (b) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (c) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res.* **1997**, *3*, 1077.

(9) (a) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. (b) Jacob, G. S. *Curr. Biol. Struct. Biol.* **1995**, *5*, 605−611.

(10) (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer. Res.* **1988**, *48*, 1410. (b) White, S. L.; Nagai, T.; Akiyama, S. K.; Reeves, E. J.; Grzegorzewski, K.; Olden, K. *Cancer Commun.* **1991**, *3*, 83.

(11) Martin, C. J. *Agric. Gaz. N. S. Wales* **1897**, *8*, 363.

(12) Molyneux, R. J.; James, L. F. *Handbook of Natural Toxins*; Keeler, R. F., Tu, A. T., Ed.; Marcel Dekker: New York, 1991; Vol. 6, pp 191ff.

(13) (a) Clevenstine, E. C.; Broquist, H. P.; Harris, T. M. *Biochemistry* **1979**, *18*, 3659. (b) Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940−949. (c) Harris, C. M.; Campbell, B. C.; Molyneux, R. J.; Harris, T. M. *Tetrahedron Lett.* **1988**, *29*, 4815−4818. (d) Sim, K. L.; Perry, D. *Glycoconjugate J.* **1997**, *14*, 661.

(14) (a) Cuengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (b) Broquist, H. P. *J. Toxicol., Toxin Rev.* **1986**, *5*, 241−252.

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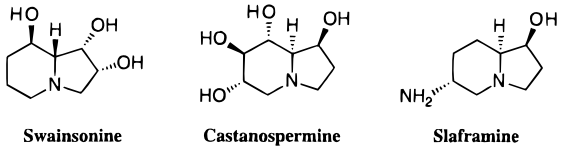


Figure 1. Major indolizidine alkaloids.

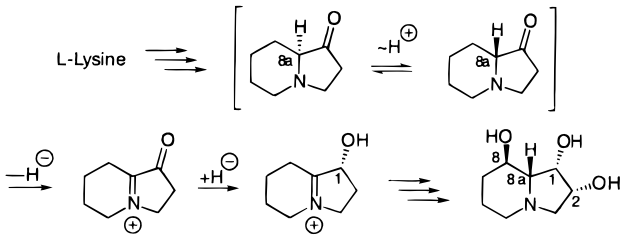


Figure 2. Biosynthesis of swainsonine.

acid[15] and D-tartaric acid[16] have been used as sources of chirality. The fact that the four contiguous chiral centers of swainsonine resemble those of manno- and gluco-sugars has led to the utilization of these carbohydrates as starting materials for a large number of syntheses.[17] However, the preexisting chiral centers can limit the scope of carbohydrate-based methods. In addition, the need for orthogonal protection of the hydroxyl groups confines these methods to arduous and redundant sequences of protecting group manipulations that reduces the efficiency and lengthens this approach. In light of these limitations, the need for non-carbohydrate-based syntheses has become more apparent, and a few asymmetric syntheses, starting from achiral substrates, have been published.[18] In view of the fact that the biosynthetic pathway to swainsonine begins with L-lysine, it is surprising to note that very few approaches to the total synthesis of this compound from an amino acid precursor have been reported.[19]

As part of a program directed at efficient chemical syntheses of enantiomerically pure glycosidase inhibitors such as (−)-swainsonine, we have synthesized (−)-8-*epi*-swainsonine and (+)-1,2-di-*epi*-swainsonine from D-serine. Previous communications describe the synthesis

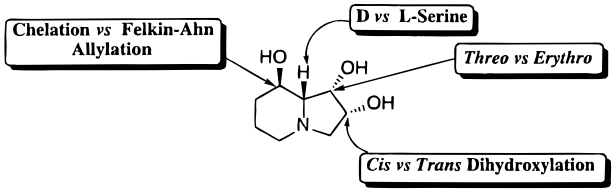


Figure 3. Enantiodivergent approach allows for the synthesis of various indolizidines from common intermediates and starting materials.

of simple *β*-amino alcohols (sphingosines) from their corresponding amino acids in a stereoselective fashion.[20] This method has since been extended to the synthesis of sphingosine analogues,[21] and heterocycles such as *N*-methyl-D-fucosamine, deoxyfuconojirimycin, and iminolyxitols.[22]

In principle, all the stereoisomers of swainsonine can be accessed by an enantiodivergent modification of this amino acid-based approach (Figure 3): (1) Starting with D- vs L-serine inverts the enantiomeric series; (2) the reductive-alkenylation methodology can furnish either the *threo*- or *erythro*-*β*-amino alcohols from the fully protected serine Schiff base; (3) substrate-directed *cis*- vs *trans*-diol formation could alter the hydroxyl configuration in the pyrrolidine ring; and (4) chelation-controlled vs Felkin−Ahn addition of the allyl moiety could, in principle, invert the hydroxyl configuration in the piperidine ring.

Synthesis of the Pyrrolidine Segment. Construction of the aza-furanose skeleton required the addition of a vinyl group to D-serine in a manner that would afford the enantiomerically pure *threo β*-amino alcohol (syn or like product) in good yield.[23] To this end, we relied on the reductive-alkenylation methodology which has previously worked well with more-substituted sp^2-hybridized carbanions.

The starting material **1**, conveniently prepared from D-serine,[21,24] was treated sequentially with *i*-Bu_5Al_2H (1:1 mixture of *i*-Bu_2AlH and *i*-Bu_3Al in hexanes) and vinylmagnesium bromide in THF/CH_2Cl_2 at −78 °C. This provided a chromatographically separable mixture[25] of diastereomers (**2a**:**2b**, 1.7:1) in 76% yield (Scheme 1). We attribute the lack of stereoselectivity to the presence of THF in the reaction mixture, which destroys the five-membered chelation template that is essential for *threo*-selectivity.[20] In fact, the reductive alkenylation methodology has been shown to be *threo*-selective (∼8:1) when the carbanion is prepared in Et_2O, and extremely selec-

(15) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem*. **1994**, *59*, 1358.

(16) Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem*. **1988**, *53*, 6022.

(17) (a) Suami, T.; Tadano, K.; Iimura, Y. *Chem. Lett*. **1984**, 513. (b) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun*. **1984**, 447. (c) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett*. **1984**, *25*, 1853. (d) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett*. **1984**, 1201. (e) Suami, T.; Tadano, K.; Iimura, Y. *Carbohydr. Res*. **1985**, *136*, 67. (f) Ali, M. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res*. **1985**, *136*, 225. (g) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem*. **1985**, *50*, 3948. (h) Bashyai, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. (i) Carpenter, N. M.; Fleet, G. W. J.; diBello, I. C.; Winchester, B.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett*. **1989**, *30*, 7261. (j) Bennett, R. B., III.; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc*. **1989**, *111*, 2580. (k) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett*. **1990**, *31*, 7571. (l) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc*. **1990**, *112*, 8100. (m) Kang, S. H.; Kim, G. T. *Tetrahedron Lett*. **1995**, *36*, 5049. (n) Gonzalez, F. B.; Barba, A. L.; Espina, M. R. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 567.

(18) (a) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem*. **1985**, *50*, 420. (b) Honda, T.; Hoshi, M.; Kanai, K.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2091. (c) Angermann, J.; Homann, K.; Reissig, H.-U.; Zimmer, R. *Synlett* **1995**, 1014. (d) Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2599. (e) Hunt, J. A.; Roush, W. R. *J. Org. Chem*. **1997**, *62*, 1112.

(19) (a) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull*. **1987**, *35*, 2140, (b) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull*. **1990**, *38*, 2712.

(20) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem*. **1992**, *57*, 5469.

(21) Mitchell, S. A.; Oates, B. D.; Razavi, H.; Polt, R. *J. Org. Chem*. **1998**, *63*, 8837.

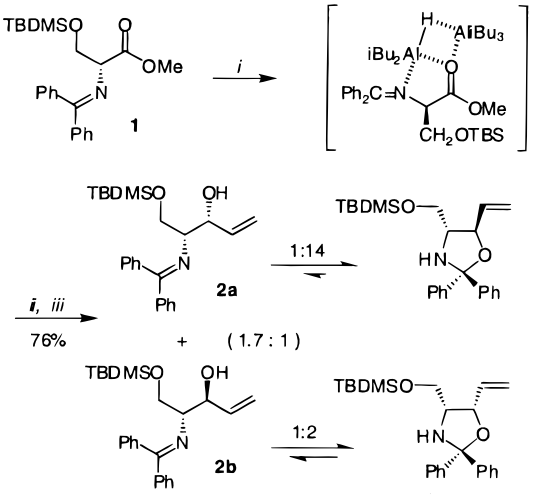
(22) (a) Sames, D.; Polt, R. *J. Org. Chem*. **1994**, *59*, 4596. (b) Sames, D.; Polt, R. *Synlett* **1995**, 552. (c) Razavi, H.; Polt, R. *Tetrahedron Lett*. **1998**, *39*, 3371.

(23) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, H.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem*. **1991**, *56*, 4370−4382. (b) Angle, S. R.; Henry, R. M. *J. Org. Chem*. **1997**, *62*, 8549−8555. (c) Angle, S. R.; Breitenbucher, J. G. *Tetrahedron Lett*. **1993**, *34*, 3985−3988. (d) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc*. **1999**, *121*, 9088−9095. (e) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett*. **1992**, *33*, 1697−700.

(24) (a) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem*. **1982**, *47*, 2663. (b) Polt, R., Chapter 9 in *Amino Acid Derivatives: A Practical Approach*, Barrett, G. C., Ed., Oxford University Press: Oxford, UK, 2000.

(25) Wijayaratne, T.; Collins, N.; Li, Y.; Bruck, M. A.; Polt, R. *Acta Crystallogr*. **1993**, *B49*, 316.

Scheme 1[a]



[a] Reagents: (i) $^{i}Bu_5Al_2H$, (ii) $H_2C{=}CHMgBr$/THF/−78 °C → rt, (iii) $NaHCO_3$ workup.

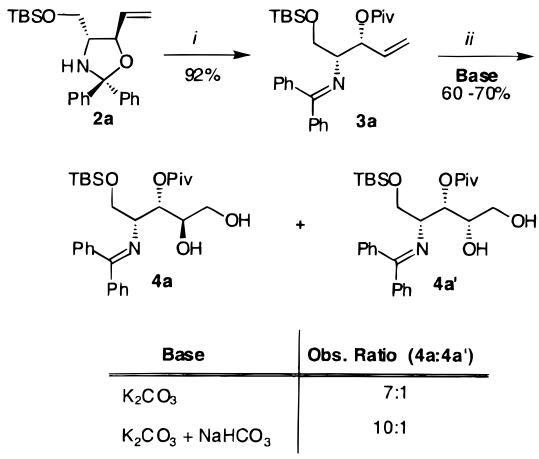
tive (>20:1) in noncoordinating solvents such as toluene or hexanes.[26] The *threo* product **2a** and the *erythro* product **2b** exist as a mixture of oxazolidine−imine tautomers. In each case, the oxazolidine is the major species. Based on the integration of the proton spectra, the ratio of the oxazolidine to the open chain imine was estimated to be ∼14:1 for **2a** and ∼2:1 for **2b** in $CDCl_3$.

Subsequently, the *threo*-hydroxy Schiff base (oxazolidine) **2a** was protected as the corresponding pivalate, and the substrate-directed osmylation[27] of compound **3a** with a catalytic amount of $K_2OsO_2(OH)_4$ and $K_3Fe(CN)_6$ as a reoxidant proceeded cleanly in accordance with the Stork−Kishi[28] rule to afford the desired diol **4a** in 70% yield (10:1 ratio). A reduction in yield (60%) and the diastereomeric ratio (7:1) was observed when K_2CO_3 was solely used in the reaction (pH 12). These results have been attributed to the base-catalyzed migration of the pivalate from its original location to the newly created hydroxyl groups that are less sterically demanding. This migration was significantly suppressed when the aqueous layer was buffered to pH 10 using a 1:1 mixture of K_2CO_3 and $NaHCO_3$ (Scheme 2).

Next, the imine **4a** was reduced with NaH_3BCN to provide the amino diol **5a**, which was cyclized with CCl_4/PPh_3 to give an inseparable mixture of pyrrolidines **6a** and **6a′**.[29] Hydrolysis of the pivaloyl groups of **6a** and **6a′** under basic conditions (Bu_4NOH, H_2O, dioxane) was complicated by the premature removal of the *tert*-butyldimethylsilyl protecting group. The desired transformation was achieved using a modified Zemplèn transesterification procedure (1 equiv of NaOMe, anhydrous MeOH),[30] which provided the silyl-protected pyrrolidine **8a** in quantitative yield (Scheme 3).

Efforts were made to reduce the number of synthetic transformations and purifications required by combining two or more steps into one. One such expedient was the

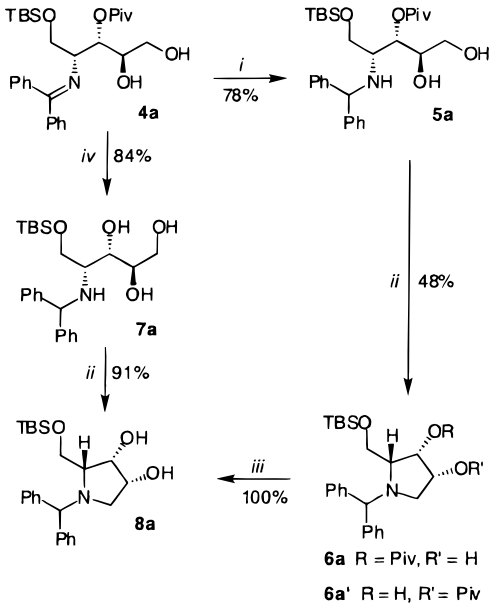
Scheme 2[a]



Base	Obs. Ratio (4a:4a')
K_2CO_3	7:1
$K_2CO_3 + NaHCO_3$	10:1

[a] Reagents: (i) $(CH_3)_3CCOCl$/pyridine/DMAP, (ii) $K_2OsO_2(OH)_4$/$K_3Fe(CN)_6$/tBuOH/H_2O/base (see table).

Scheme 3[a]



[a] Reagents: (i) $NaCNBH_3$/AcOH, CH_3CN 4 Å mol sieves, (ii) $Ph_3P/CCl_4/Et_3N$/DMF, (iii) NaOMe/MeOH, (iv) $LiBH_4$/THF reflux.

reduction of the imine under conditions that also removed the pivaloyl group. The simultaneous reduction of Schiff bases and esters was feasible with $LiAlH_4$; however this reagent can remove silyl ethers, presumably due to the presence of AlH_3.[31] The less-reactive $LiBH_4$ effected the desired tandem reduction in 84% overall yield.[32] Cyclization of the amino triol **7a** was then achieved with CCl_4/PPh_3 as before to give the trihydroxylated pyrrolidine **8a** in much higher yield. A single crystal X-ray analysis of compound **8a** confirmed the absolute configuration (Figure 4).

The hydroxyl groups on the pyrrolidine ring were protected as an acetonide, giving a degree of rigidity to the substrate, which would allow better stereochemical control of the ensuing allylation reaction. After initial

(26) Polt, R.; Sames, D.; Chruma, J. *J. Org. Chem*. **1999**, *64*, 6147.
(27) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.
(28) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett*. **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett*. **1983**, *24*, 3947. (c) Stork, G.; Kahn, M. *Tetrahedron Lett*. **1983**, *24*, 3951.
(29) Chen, Y.; Vogel, P. *Tetrahedron Lett*. **1992**, *33*, 4917.
(30) Szurmai, Z.; Kerekgyarto, J.; Harangi, J.; Liptak, A. *Carbohydr. Res*. **1987**, *164*, 313.
(31) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem*. **1992**, *57*, 1179.
(32) Soai, K.; Ookawa, A. *J. Org. Chem*. **1986**, *51*, 4000.

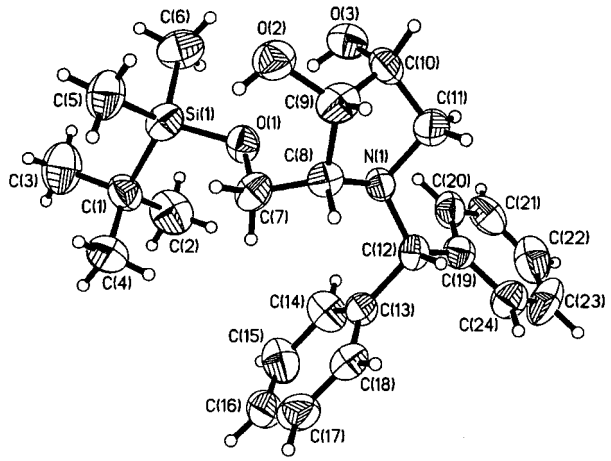
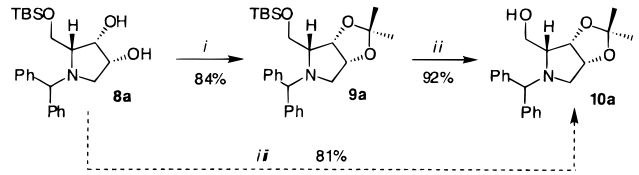


Figure 4. Single-Crystal X-ray Structure of Aza-D-lyxitol, **8a**.

Scheme 4[a]



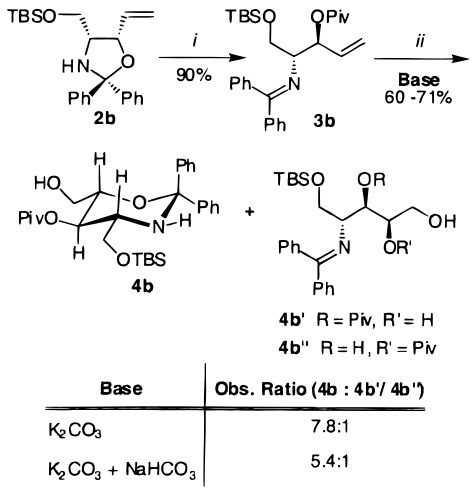
[a] Reagents: (i) $(CH_3)_2C(OCH_3)_2$/cat. CSA/CH_2Cl_2 reflux, (ii) $^nBu_4NF$/THF, (iii) $(CH_3)_2C(OCH_3)_2$/1.45 equiv of CSA/CH_2Cl_2 reflux/72 h.

screening of various methods for ketal formation,[33] the diol portion of **8a** was protected with the aid of 2,2-dimethoxypropane and CSA to provide acetonide **9a**.[34] The pendent silyl group was cleaved with TBAF under standard conditions to yield pyrrolidine **10a** (Scheme 4).[22c,35]

During acetonide formation, the silyl protecting group was removed to some extent, and desilylated compound **10a** was obtained as a minor product. Armed with this knowledge, it was possible to optimize the reaction conditions (1.45 equiv of CSA, refluxing CH_2Cl_2, 72 h) to effect tandem acetonide formation−desilylation to afford the desired product **10a** in 81% yield in one step (Scheme 4).

In a parallel sequence of reactions, the *erythro*-amino alcohol **2b** was converted to the corresponding pyrrolidine **8b.** This sequence provided the biologically interesting aza-sugar 1,4-dideoxy-1,4-imino-D-ribitol.[36] The interest in this *erythro*-series of compounds stemmed primarily from the desire to understand the factors that control the stereochemical outcome of the dihydroxylation reactions of allylic alcohols bearing a homoallylic amine. A secondary interest in the *erythro*-series was to examine the stereochemical influence on the allylation reaction exerted by the acetonide orientation versus the configuration of the α-amino aldehyde bearing the bulky *N*-benzhydryl group (vide infra). The complexation of tertiary

Scheme 5[a]



Base	Obs. Ratio (4b : 4b'/ 4b'')
K_2CO_3	7.8:1
K_2CO_3 + $NaHCO_3$	5.4:1

[a] Reagents: (i) $(CH_3)_3CCOCl$/pyridine/DMAP, (ii) $K_2OsO_2(OH)_4$/$K_3Fe(CN)_6$/tBuOH/H_2O/base (see table).

amines to OsO_4 and their ability to direct and accelerate osmylation reactions has been documented,[37] but the stereochemical influence of the imine nitrogen was expected to be minor.[26] Thus, the *erythro*-amino alcohol **2b** was converted to the corresponding pivalate **3b** and reacted with $K_2OsO_2(OH)_4$/$K_3Fe(CN)_6$ and $CH_3SO_2NH_2$ (Scheme 5).

These experiments indicate that osmylation of compounds **3a** and **3b** proceed with the predicted stereochemical results. That is, the approach of OsO_4 is primarily dictated by the configuration at the oxygen-bearing allylic center, and the chirality at the nitrogen-bearing homoallylic carbon has a negligible effect on the stereochemical outcome of the reaction. Once again, the use of additives had a profound effect on the yield and the selectivity of the osmylation reaction. As expected, the use of a 1:1 mixture of K_2CO_3 and $NaHCO_3$ (pH 10) instead of K_2CO_3 (pH 12) resulted in a marked improvement in the reaction yield (from 60% to 71%), which was identical to the results obtained from the dihydroxylation of the diastereomer **3a**. However, unlike the earlier studies, a *lower* ratio (5.4:1) was observed at pH 10, which seemed inconsistent with the earlier result. Interestingly, the ^{13}C NMR spectrum of the major product showed that **4b** existed entirely as the 1,3-oxazine. It appears that the migration of the pivalate did not occur with the major product **4b** because the hydroxyl group adjacent to the pivalate was immediately protected upon its formation. But, migration of this type did occur in the diastereomeric product **4b′** (e.g., **4b′** → **4b″**). Buffering of the aqueous layer to pH 10 suppressed the migration of the pivalate and enhanced the isolated yield of the minor product **4b′**, which resulted in a lower observed ratio.

Subsequently, compound **4b** was reduced with $NaCNBH_3$ under acidic conditions, and the resulting amino tetrol **5b** was cyclized to give a mixture of pyrrolidines **6b** and **6b′** in 84% yield. Since chromatographic separation of **6b/6b′** was difficult, the mixture was treated with NaOMe (1 equiv) in MeOH, which removed the pivaloyl ester to give the dihydroxylated pyrrolidine **8b** in quantitative yield (Scheme 6).

(33) (a) Evans, M. E.; Parrish, F. W.; Long, L. *Carbohydr. Res.* **1967**, *3*, 453. (b) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495. (c) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

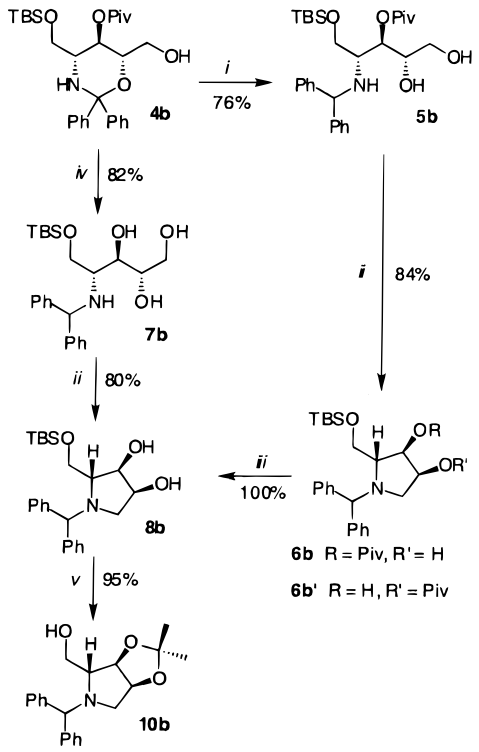
(34) Green, T. W.; Wutz, P. G. M.; *Protective Group in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp 123−127.

(35) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(36) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637.

(37) (a) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941. (b) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413.

Scheme 6[a]



[a] Reagents: (i) $NaCNBH_3$/AcOH, CH_3CN 4 Å mol sieves, (ii) $Ph_3P/CCl_4/Et_3N$/DMF, (iii) 1 equiv of NaOMe/MeOH, *(*iv) $LiBH_4$/THF reflux, (v) $(CH_3)_2C(OCH_3)_2$/1.45 equiv of CSA/CH_2Cl_2 reflux/72 h.

Alternatively, amino alcohol **4b** was subjected to $LiBH_4$, which effected reduction of the imine, followed by treatment of the reaction mixture with MeOH to remove the pivalate in 82% yield. However, contrary to earlier results from the reduction of **4a** with $LiBH_4$, reduction of the imine **4b** proceeded very slowly and was completed only after 4 days at reflux. The resistance of **4b** toward reduction with $LiBH_4$ further illustrates that this compound does not exist as an imine. Cyclization of the newly generated secondary amine to the terminal carbon provided the protected 1,4-dideoxy-1,4-imino-D-ribitol **8b** in good yield.

The hydroxyl groups of compound **8b** were protected as an acetonide. Once again, diol protection and silyl ether hydrolysis proceeded in tandem under mild acidic conditions (1.45 equiv of CSA). This transformation furnished the desired partially protected pyrrolidine **10b**, but more importantly it proved that the two hydroxyl groups on the periphery of the pyrrolidine were positioned on the same face of the ring. Thus, assignment of the stereochemical outcome based on rational mechanistic considerations of the earlier transformations was correct.

Alkylation of the Pyrrolidine Ring. It was envisaged that stereoselective addition of an allylic nucleophile to an aldehyde would ultimately give the indolizidine carbon skeleton. The subsequent functional group transformation, protecting group manipulation, and cyclization would afford the desired indolizidine alkaloid.

An efficient method for construction of the requisite three-carbon adduct is the Hosomi−Sakurai[38] or the

(38) Hosomi, A.; Sakurai, H. *Tetrahedron Lett*. **1976**, 1295.

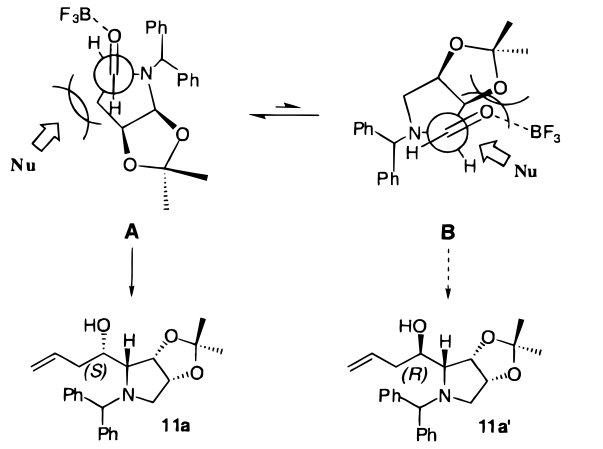


Figure 5. Dioxolane ring cis to the aldehyde moiety prevents normal Felkin−Ahn stereocontrol.

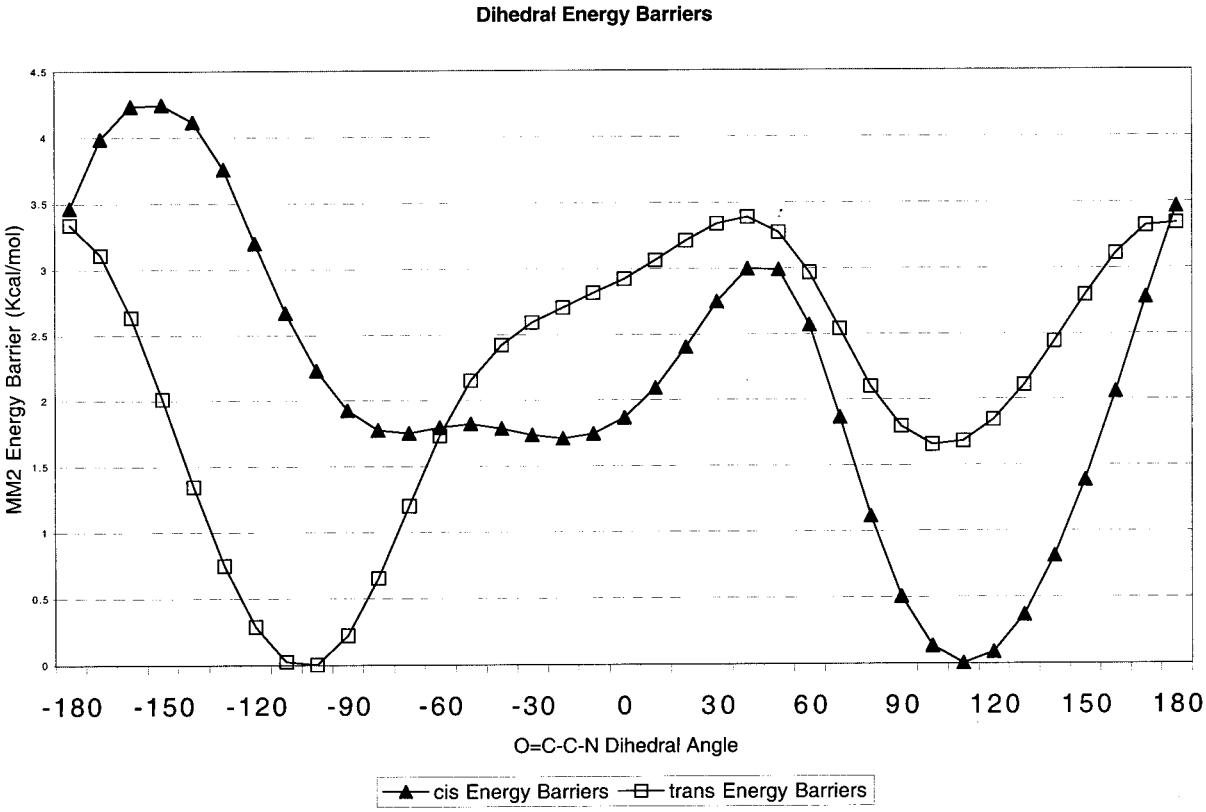
Keck-type[39] allylation. The only concern was the stereochemical outcome of the reaction. We were confident that the stereocontrol at this stage of the construction was attainable, in part because of the preliminary molecular modeling that had indicated a strong inherent steric bias due to the presence of the *N*-benzhydryl protecting group. Added assurance was provided by literature precedent describing the stereoselective allylation of amino aldehydes,[40] as well as the X-ray structure (Figure 4) of the protected alcohol **8a** that indicated the *N*-benzhydryl group would project out to mask one face of the carbonyl.

Thus, Swern oxidation of hydroxy pyrrolidine **10a** under standard conditions furnished the corresponding aldehyde,[41] which was immediately used in the next step without purification due to the well-documented configurational instability of α-amino aldehydes.[42] In an attempt to synthesize the homoallylic alcohol **11a**, $^nBu_3SnCH_2$-$CH{=}CH_2$ and $BF_3{\cdot}OEt_2$ was added to the unpurified amino aldehyde. To our delight, the reaction proceeded at −78 °C to give one stereoisomer in 80% yield (>20:1 diastereomeric ratio). In addition, allylation of the protected aza-lyxose from **10a** with $Sn(CH_2CH{=}CH_2)_4$ (0.3 equiv) in MeOH proceeded at room temperature to afford compound **11a** exclusively (Scheme 5).[43] Reaction with $Me_3SiCH_2CH{=}CH_2$ under the same conditions ($BF_3{\cdot}OEt_2$, −78 °C, 2 h) afforded a much lower (8%) yield of **11a**. A similar lack of reactivity for the allylation of a protected amino aldehyde with $Me_3SiCH_2CH{=}CH_2$ in the presence $BF_3{\cdot}OEt_2$ was reported by Ganem et al. in their synthesis of (+)-castanospermine.[44]

According to the Felkin−Ahn model, nucleophilic additions to aldehydes bearing α-heteroatoms proceed principally via two reactive conformers.[45] The normal application of the Felkin−Ahn model led us to conclude that the homoallylic alcohol would have the *(R)* configuration (Figure 5). However, the configuration at the

(39) Keck, G. E.; Castellino, S. J. *J. Am. Chem. Soc*. **1986**, *108*, 3847.
(40) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem*. **1994**, *59*, 5139.
(41) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480.
(42) Jurczak, J.; Golebiowski, A. *Chem. Rev*. **1989**, *89*, 149.
(43) (a) Cokley, T. M.; Harvey, P. J.; Marshall, R. L.; McCluskey, A.; Young, D. J. *J. Org. Chem*. **1997**, *62*, 1961. (b) Yasuda, M.; Fujibayashi, T.; Baba, A. *J. Org. Chem*. **1998**, *63*, 6401.
(44) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem*. **1987**, *52*, 5492.
(45) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61.

Chart 1. Rotomer Energies for the Amino Aldehydes Derived from 10a and 10b



homoallylic center was shown to be (*S*) based on the correlation of the C-8 configuration of the triacetoxy indolizidine with that of triacetoxy 8-*epi*-swainsonine (vide infra). These results indicated that **A** was the preferred conformer. Other methods, including $^{n}Bu_3SnCH_2CH{=}CH_2/TiCl_4$ and $BrMgCH_2CH{=}CH_2$ also failed to provide the elusive chelation-controlled aldehyde addition product. It appeared that **B** was the higher energy conformer due to the dipole−dipole and/or steric interaction between the carbonyl and the dioxolane groups. In theory, this interaction was avoided in conformer **A**, and the higher energy associated with the approach of the nucleophile along this pathway was still lower than the energy associated with conformer **B**.

To confirm this hypothesis, molecular mechanics calculations[46] (MM2) were undertaken to examine the conformational preferences of the epimeric aldehydes derived from alcohols **10a** and **10b**. The minimum energy calculated for the "cis" aldehyde derived from alcohol **10a** was 27.3 and 25.4 kcal/mol for the corresponding "trans" isomer derived from **10b** (vide infra). After minimization and "bump testing" to ensure that the conformations were at true global minima, a dihedral driving routine was used to rotate each carbonyl in 10° increments, and the compounds were minimized again with the O=C−C−N angle constrained to this angle. To facilitate conformational comparison, the global minima were both set to zero, and the energy *differences* were plotted as a function of dihedral angle for each rotomer. The results are illustrated in Chart 1. While it is not possible to speculate about the population of the rotomer states displayed, it is clear that the preferred dihedral angles for the two aldehydes are quite different, and that the observed energy minima support the transition state suggested in Figure 5 for the "cis" case. Furthermore, this suggested

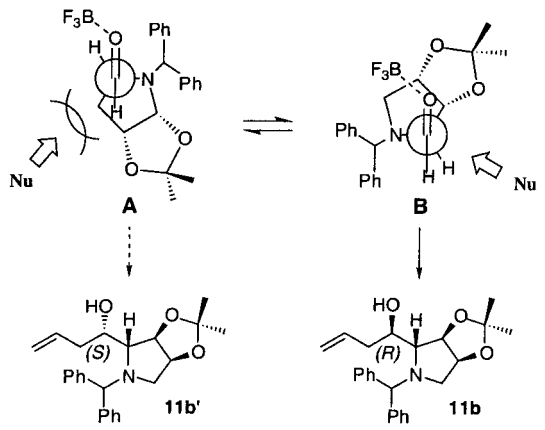


Figure 6. Dioxolane ring trans to the aldehyde moiety allows normal Felkin−Ahn stereocontrol.

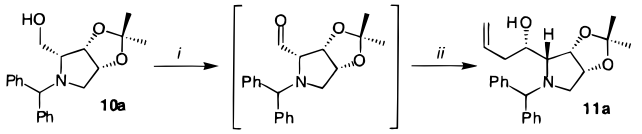
that the epimeric "trans" case should react via a normal Felkin−Ahn transition state (Figure 6, vide infra).

Aza-Pinacol Rearrangement. Remarkably, allylation of the aldehyde derived from **10a** with $^{n}Bu_3SnCH_2CH{=}CH_2$ in the presence of $MgBr_2{\cdot}OEt_2$ at −23 °C, expected to provide the chelation-controlled homoallylic alcohol, instead afforded the α-allylation product **17** as the only isolable product (64%). Apparently, *β*-chelation of the substrate induced a [1,2]-hydride shift to afford the corresponding cyclic iminium ion,[47] which was attacked by the nucleophile from the least-hindered face (opposite to the isopropylidene group) to furnish **17** (Scheme 8). The Mg ion, in addition to aligning the two

(46) Calculations were performed on a Macintosh G4, using Chem-3D Pro, available from CambridgeSoft Corp., http://www.camsoft.com.

(47) For a related mechanism, see: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241−11250.

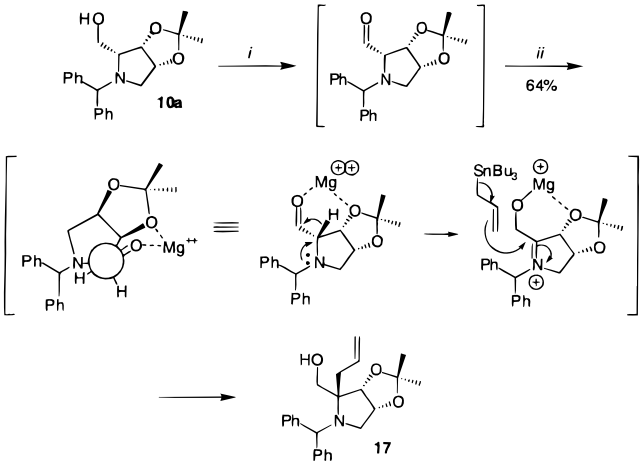
Scheme 7[a]



Entry	Tin Reagent	Lewis Acid	Solvent	Temp(°C)	Ratio(11a:11a')	Yield
1	$SnBu_3$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	-78°	>20:1	80%
2	$_4$(⟋)Sn	None	MeOH	RT	11a Only	66%

[a] Reagents: (i) $(ClCO)_2$,/DMSO/Et_3N/CH_2Cl_2/−60 °C → rt, (ii) (see table).

Scheme 8[a]



[a] Reagents: (i) $(ClCO)_2$,/DMSO/Et_3N/CH_2Cl_2/−60 °C → rt, (ii) $H_2C{=}CHCH_2SnBu_3/MgBr_2{\cdot}Et_2O/CH_2Cl_2$/−20 °C.

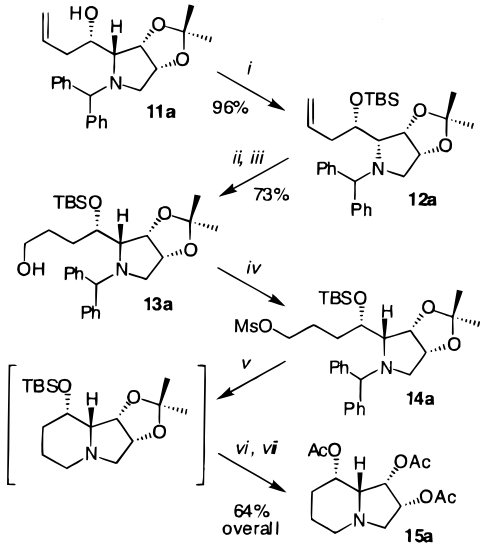
oxygens of the *β*-chelate, polarizes the carbonyl group, which is then perfectly aligned with the migrating hydride, probably assisted by the nitrogen lone pair.[7]

Piperidine Ring Formation. Elaboration of the epimeric Keck product proceeded as expected. Alcohol **11a** was protected as the *t*-butyldimethylsilyl ether (96%),[48] and hydroboration/oxidation[49] of the resulting silyl ether **12a** with 9-BBN provided the corresponding 1° alcohol **13a** in 73% yield (Scheme 9).

Compound **13a** was converted to its corresponding mesylate **14a** under standard conditions,[50] and hydrogenolysis of the *N*-benzhydryl group proceeded with the concomitant piperidine ring formation. The product was then globally deprotected under acidic conditions, and the resulting indolizidine was acetylated in situ to facilitate isolation and characterization (64% yield from **13a**) (Scheme 9). Product **15a** exhibited physical properties identical to those reported in the literature for 8-*epi*-swainsonine triacetate {mp 77−78 °C, $[\alpha]^{22}_D$ −19.3° (*c* 0.73, $CHCl_3$); lit.[51] mp 79−80 °C, $[\alpha]^{19}_D$ −17.1° (*c* 0.35, $CHCl_3$); lit.[52] $[\alpha]^{25}_D$ −17.4° (*c* 0.80, $CHCl_3$)}.

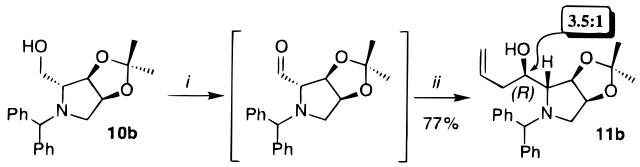
The Keck-type allylation, featured prominently in the synthesis of 8-epimer above, was also utilized in the

Scheme 9[a]



[a] Reagents: (i) TBDMS−OTfl/2,6-lutidine/CH_2Cl_2/0 °C, (ii) 9-BBN/THF/rt, (iii) H_2O_2/EtOH/NaOH, (iv) $MeSO_2Cl/Et_3N/CH_2Cl_2$, (v) H_2/Pd−C/MeOH, (vi) CF_3COOH/H_2O, (vii) Ac_2O/DMAP/pyridine.

Scheme 10[a]



[a] Reagents: (i) $(ClCO)_2$,/DMSO/Et_3N/CH_2Cl_2/−60 °C → rt, (ii) $H_2C{=}CHCH_2SnBu_3/BF_3{\cdot}Et_2O/CH_2Cl_2$/−78 °C.

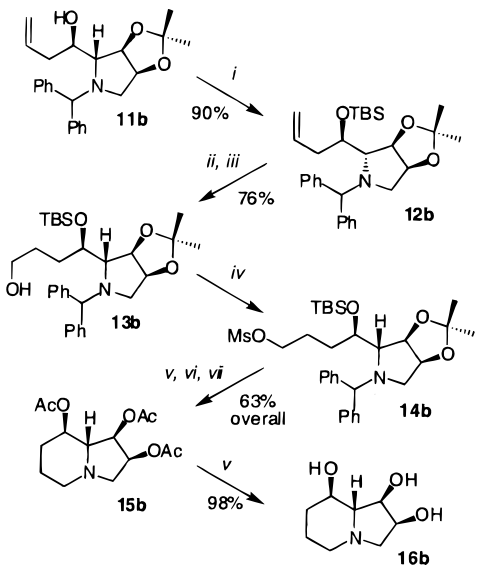
synthesis of 1,2-di-*epi*-swainsonine. On the basis of the MM2 calculations described above, we reasoned that the dipole−dipole and/or steric interactions between the carbonyl and the acetonide groups, which previously thwarted the desired stereochemical outcome of the allylation, would be minimized, since the dioxolane group resided on the opposite face of the pyrrolidine ring. On the basis of the steric inaccessibility of the reactive conformer **A** in the Felkin−Ahn transition state, it was expected that the reaction would proceed through the alternate conformer **B** to give homoallylic alcohol **11b** as the major product (Figure 6). In fact, Swern oxidation of compound **10b** followed by the allylation of the resulting aldehyde afforded a mixture of homoallylic alcohols in 3.5:1 diastereomeric ratio (Scheme 10).

To confirm the configuration at the homoallylic center, the piperidine portion of the indolizidine alkaloid was constructed so that axial/equatorial coupling constants could be observed in the piperidine ring. The homoallylic alcohol **11b** was converted to the triacetate **15b** as before in excellent overall yield (63%; six transformations) (Scheme 11). The final deprotection with NaOMe/MeOH afforded (+)-1,2-di-*epi*-swainsonine **16b**.

To our knowledge, (+)-1,2-di-*epi*-swainsonine has not previously been synthesized. Thus, the identity of indolizidine **16b** was unequivocally established based on the comparison of its physical and spectral data to those from its enantiomer. The spectral data (^1H and ^{13}C) and melting point for synthetic (+)-1,2-di-*epi*-swainsonine were in good agreement with previously published data

(48) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(49) (a) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441. (b) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027.
(50) Furst, A.; Koller, F. *Helv. Chim. Acta* **1947**, *30*, 1454.
(51) Tadano, K.-I.; Iimura, Y.; Hotta, Y.; Fukabori, C.; Suami, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3885.
(52) Blanco, M. J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748.

Scheme 11[a]



[a] Reagents: (i) TBDMS−OTfl/2,6-lutidine/CH_2Cl_2/0 °C, (ii) 9-BBN/THF/rt, (iii) H_2O_2/EtOH/NaOH, (iv) $MeOSO_2Cl/Et_3N/CH_2Cl_2$, (v) H_2/Pd−C/MeOH, (vi) CF_3COOH/H_2O, (vii) Ac_2O/DMAP/pyridine, (viii) cat. NaOMe/MeOH.

for (−)-8,8a-di-*epi*-swainsonine. In addition, the observed optical rotation for **16b** was comparable in magnitude and opposite in sign to the literature values for (−)-8,-8a-di-*epi*-swainsonine {(+)-1,2-di-*epi*-swainsonine: mp 127−128 °C, $[\alpha]^{25}_D$ +16.1° (*c* 1.23, MeOH); (−)-8,8a-di-*epi*-swainsonine: lit.[53] mp 130−131 °C, $[\alpha]^{22}_D$ −21.2° (*c* 0.78, MeOH); lit.[54] mp 129−130 °C, $[\alpha]_D$ −18.7° (*c* 0.55, MeOH); lit.[55] mp 134−135 °C, $[\alpha]^{29}_D$ −13.2° (*c* 0.27, MeOH)}. Furthermore, the ^{1}H NMR analysis of the indolizidine **16b** indicated 8.6 and 7.5 Hz coupling constants for proton 8a (Figure 7), characteristic of fused six-membered ring axial−axial protons.

Conclusions

Syntheses of (−)-8-*epi*-swainsonine triacetate **15a** and (+)-1,2-di-*epi*-swainsonine **16b** from D-serine have been achieved in 6.3% and 4.0% overall yields, respectively. Both the *threo* and *erythro* amino alcohols were synthesized from the O'Donnell's Schiff base of D-serine **1** in good yields (44% and 31%, respectively) and without any detectable racemization of the original chiral center. Substrate-directed dihydroxylation of the resultant *threo* and *erythro* products proceeded with good selectivity (10:1 at pH 10; 7:1 at pH 12 for **3a**; 5.4:1 at pH 10; 7.8:1 at pH 12 for **3b**). The osmylation was primarily directed by the oxygen-bearing allylic center, and the yield of osmylation was enhanced at lower pH regardless of the substrate (70% at pH 10; 60% at pH 12 for **3a**, 71% at pH 10; 60% at pH 12 for **3b**). In addition, hydroxyl protecting group manipulations, typically achieved in a stepwise manner, were accomplished in tandem with great efficiency (81% for **8a** → **10a**, 95% for **8b** → **10b**). The Keck-type allylation of pyrrolidines **10a** and **10b** in the presence of $BF_3{\cdot}OEt_2$ proceeded with high yields and moderate to high selectivities (80% yield; >20:1 dr for **10a** → **11a**, 77% yield; 3.5:1 dr for **10b** → **11b**). Both the dioxolane and the benzhydryl protecting groups can control the stereochemical outcome of the allylation reaction due to dipole−dipole and steric interactions. For the system studied, the Lewis acid induced β-chelation allowed 1,2-hydride migration to compete effectively with allylation of the aldehyde group, resulting in an aza-pinacol-type rearrangement. Obviously, favorable orbital overlap between the carbonyl, the hydride, and the amine lone pair must have been achieved to permit this rearrangement, but it is much less clear if dipole−dipole interactions due to the acetonide oxygens play a role in the rearrangement. This novel reaction may have synthetic utility for the synthesis of sterically hindered β-amino alcohols.

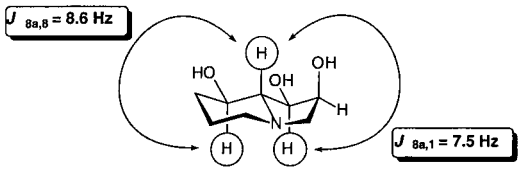


Figure 7. Diaxial coupling constants confirm the configuration of 1,2-di-*epi*-swainsonine.

In conclusion, the attractive feature of the synthetic method offered is the stereocontrolled introduction of functional groups in stepwise fashion. This approach offers greater flexibility in manipulating orthogonal protection schemes than carbohydrate-based approaches and lends itself well to the syntheses of swainsonine epimers.

Experimental Section

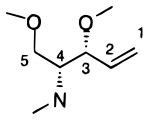
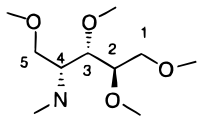
General Methods. ^{1}H NMR spectra were measured at 250 or 500 MHz, and were referenced with internal TMS (0.0 ppm). The attached proton test (APT) ^{13}C spectra were performed at 62.9 MHz and were referenced with $CDCl_3$. COSY and HETCOR spectra were performed at 300 and 75.4 MHz, respectively. IR spectra were recorded in a KBr pellet, neat, or as $CHCl_3$ solutions. Melting points are uncorrected. Optical rotations were taken at the Na_D-line. Thin-layer chromatographic analyses were performed on silica gel TLC plates (UV, 250 μm), and visualization was accomplished using 10% phosphomolybdic acid in EtOH or ninhydrin in a 3% HOAc/n-BuOH solution. Flash chromatography was performed on silica gel 60 (230−400 mesh) as described by Still et al.[56]

Unless stated otherwise, all reactions were carried out in flame-dried glassware under dry argon atmosphere. Pyridine and Et_3N were dried and distilled over KOH. Solvents were dried and purified in the following fashion: toluene was distilled from sodium; Et_2O and THF were distilled from potassium benzophenone ketyl; CH_2Cl_2 was distilled from P_2O_5. DMSO was distilled over CaH_2 under reduced pressure. DMF was dried and distilled from BaO. All other reagents and solvents were used without further purification.

(2*R*,3*R*)-*N*-Diphenylmethylene-1-*O*-*tert*-butyldimethylsilyl-2-amino-4-pentene-1,3-diol (2a), (2*R*,3*S*)-*N*-Diphenylmethylene-1-*O*-*tert*-butyldimethylsilyl-2-amino-4-pentene-1,3-diol (2b). To a solution of Schiff base ester **1** (8.00 g, 20.1 mmol) in 200 mL of dry CH_2Cl_2 was added *i*-Bu_5Al_2H (20.1 mmol, 40.2 mL of 0.5 M 1:1 mixture of DIBAL:TRIBAL in hexanes) over two h via syringe pump at −78 °C, and the yellow solution was stirred for 1 h. Next, vinylmagnesium bromide (60.4 mmol, 60.4 mL 1.0 M solution in THF) was added to the reaction mixture in a dropwise fashion over 90 min while maintaining the internal temperature of the reaction below −70 °C. The resulting bright orange solution was allowed to warm to rt gradually. After 10 h, the reaction

(53) Tadano, K−i.; Morita, M.; Hotta, Y.; Ogawa, S.; Winchester, B.; Cenci di Bello, I. *J. Org. Chem.* **1988**, *53*, 5209.
(54) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083.
(55) Oishi, T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404.
(56) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

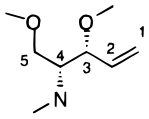
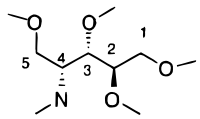
Table 1. ^{1}H NMR Data for Serine Derived Acyclic *Threo* Products (250 MHz, $CDCl_3$)

	2a[a]		**3a**		**4a**		**7a**	
	Chemical Shift (ppm), Multiplicity							
H-1	5.30	ddd	5.21	ddd	3.62	dd	3.65	dd
H-1′	5.16	ddd	5.14	ddd	3.44	dd	3.56	dd
H-2	5.74	ddd	5.75	ddd	3.90	m	3.81	m
H-3	4.40	t	5.41	dt	4.94	dd	3.81	m
H-4	3.01	dt	3.81	m	3.94	m	2.90	dt
H-5	3.71	dd	3.74	m	3.83	dd	3.73	dd
H-5′	3.92	dd	3.74	m	3.83	dd	4.04	dd
Ph_2CH	–	–	–	–	–	–	5.02	s
	Coupling Constants ($J_{H,H}$, Hz)							
$J_{1,1'}$	1.7		1.4		12.0		11.3	
$J_{1,2}$	17.2		17.3		3.0		4.3	
$J_{1',2}$	10.2		10.6		3.9		4.7	
$J_{1,3}$	0.7		1.4		–		–	
$J_{1',3}$	0.6		1.2		–		–	
$J_{2,3}$	7.9		6.2		8.9		–	
$J_{3,4}$	8.0		5.5		3.8		2.8	
$J_{4,5}$	1.4		–		5.1		3.6	
$J_{4,5'}$	3.1		–		7.2		4.0	
$J_{5,5'}$	10.6		–		10.0		10.6	

[a] This compound exists as a mixture of two tautomers. The resonances for the major tautomer (the oxazolidine) are reported in this table.

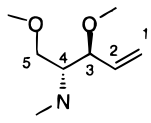
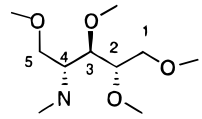
Table 2. ^{13}C NMR Data for Serine-Derived Acyclic *Threo* Products (62.9 MHz, $CDCl_3$)

	chemical shift (ppm)			
carbon no.	**2a**[a]	**3a**	**4a**	**7a**
C-1	117.3	117.3	62.9	64.1
C-2	138.0	134.5	70.8	73.5
C-3	81.0	74.5	71.7	72.4
C-4	65.2	66.3	64.5	56.3
C-5	59.4	64.1	62.6	62.5
Ph_2CH	–	–	–	64.0

[a] This compound exists as a mixture of two tautomers. The resonances for the major tautomer (the oxazolidine) are reported in this table.

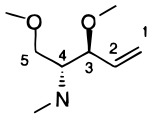
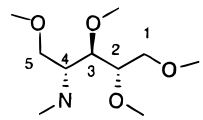
Table 3. ^{1}H NMR Data for Serine-Derived Acyclic *Erythro* Products (250 MHz, $CDCl_3$)

	2b[a]		**3b**		**4b**		**7b**	
	Chemical Shift (ppm), Multiplicity							
H-1	5.26	ddd	5.25	ddd	3.70	dd	3.76	d
H-1′	5.17	ddd	5.22	ddd	3.55	dd	3.76	d
H-2	6.06	ddd	5.91	ddd	3.61	ddd	3.62	dd
H-3	4.38	t	5.42	dddd	4.99	t	3.65	t
H-4	3.37	m	3.84	m	3.04	d	2.75	ddd
H-5	3.78	dd	3.77	m	3.73	dd	3.89	dd
H-5′	3.71	dd	3.77	m	3.64	dd	3.86	dd
Ph_2CH	–	–	–	–	–	–	4.98	s
	Coupling Constants ($J_{H,H}$, Hz)							
$J_{1,1'}$	1.7		1.2		12.5		−3.5	
$J_{1,2}$	17.2		17.3		2.0			
$J_{1',2}$	10.3		10.5		4.3		3.5	
$J_{1,3}$	1.2		1.2		–		–	
$J_{1',3}$	0.9		1.0		–		–	
$J_{2,3}$	7.5		6.7		9.9		8.3	
$J_{3,4}$	7.7		3.9		10.0		7.0	
$J_{4,5}$	4.9		–		2.3		2.6	
$J_{4,5'}$	3.1		–		2.2		3.9	
$J_{5,5'}$	10.5		–		10.0		10.4	

[a] This compound exists as a mixture of two tautomers. The resonances for the major tautomer (the oxazolidine) are reported in this table.

Table 4. ^{13}C NMR Data for Serine Derived Acyclic *Erythro* Products (62.9 MHz, $CDCl_3$)

	chemical shift (ppm)			
carbon no.	**2b**[a]	**3b**	**4b**	**7b**
C-1	116.9	117.6	62.4	63.8
C-2	136.3	134.1	64.9	74.3
C-3	79.6	75.2	73.4	69.1
C-4	62.1	66.2	54.1	59.4
C-5	60.4	64.1	61.0	58.5
Ph_2CH	–	–	–	64.0

[a] This compound exists as a mixture of two tautomers. The resonances for the major tautomer (the oxazolidine) are reported in this table.

mixture was cooled to −10 °C and quenched with saturated $NaHCO_3$. The mixture was poured into ice-cold saturated $NaHCO_3$, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous K_2CO_3, filtered, and concentrated in vacuo. The resulting golden brown oil was purified by flash chromatography (3% → 5% EtOAc/hexanes gradient) to afford 3.52 g of the amino alcohol **2a** and 2.49 g of the diastereomeric product **2b** as colorless oils (76%). Data for **2a**: ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); $[\alpha]^{28}_D$ −88.6° (*c* 4.75, $CHCl_3$); IR (neat) 3307, 3056, 2952, 1663, 1447 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{34}NO_2Si$ (MH^+) 396.2359, found 396.2350. Data for **2b**: ^{1}H NMR (Table 3); ^{13}C NMR (Table 4); $[\alpha]^{26}_D$ −60.7° (*c* 4.01, $CHCl_3$); IR (neat) 3480, 3307, 3065, 2952, 1628, 1455 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{34}NO_2Si$ (MH^+) 396.2359, found 396.2361.

(2*R*,3*R*)-*N*-Diphenylmethylene-1-*O*-*tert*-butyldimethylsilyl-3-*O*-trimethylacetyl-2-amino-4-pentene-1,3-diol (3a). Trimethylacetyl chloride (6.58 mL, 53.4 mmol) was added to a solution of Schiff base-protected amino alcohol **2a** (3.52 g, 8.90 mmol) and DMAP (109 mg, 0.890 mmol) in dry pyridine (36 mL) at 0 °C over 30 min via syringe pump. The resulting mixture was warmed to rt, and the reaction progress was monitored by TLC. After 60 h, the reaction mixture was cooled to 0 °C and poured into a cold saturated $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2. The organic layers were pooled, dried over anhydrous K_2CO_3, filtered through Celite, and concentrated in vacuo. The residue was chromatographed (5% EtOAc/hexanes) to provide 3.93 g of **3a** as a colorless oil (92%). Data for **3a**: ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); $[\alpha]^{28}_D$ +12.8° (*c* 6.16, $CHCl_3$); IR (neat) 3065, 2952, 1732, 1637, 1464 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{42}NO_3Si$ (MH^+) 480.2934, found 480.2941.

(2*R*,3*S*)-*N*-Diphenylmethylene-1-*O*-*tert*-butyldimethylsilyl-3-*O*-trimethylacetyl-2-amino-4-pentene-1,3-diol (3b). Prepared from allylic alcohol **2b** (527 mg, 1.33 mmol), according to the procedure used for the synthesis of **3a**, to afford **3b** as a pale yellow oil (576 mg, 90% yield). Data for **3b**: ^{1}H NMR (Table 3); ^{13}C NMR (Table 4); $[\alpha]^{30}_D$ −37.5° (*c* 0.505, $CHCl_3$); IR (neat) 3079, 2957, 1737, 1632, 1477 cm^{-1}; HRMS (FAB)

calcd for $C_{29}H_{42}NO_3Si$ (MH^+) 480.2934, found 480.2930.

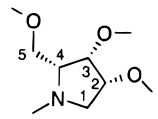
(2*R*,3*S*,4*R*)-*N*-Diphenylmethylene-5-*O*-*tert*-butyldimethylsilyl-3-*O*-trimethylacetyl-4-aminopentane-1,2,3,5-tetrol (4a). The dihydroxylation was performed according to the procedure described by Sharpless et al.[57] A solution of allylic pivalate **3a** (3.93 g, 8.18 mmol) in *t*-BuOH (40 mL) was added to a stirred solution K_2CO_3 (3.39 g, 24.6 mmol), $NaHCO_3$ (2.06 g, 24.6 mmol), $K_3Fe(CN)_6$ (8.08 g, 24.6 mmol), potassium osmate dihydrate (90.5 mg, 0.246 mmol), and methanesulfonamide (778 mg, 8.18 mmol) in H_2O, and the resulting bright yellow biphasic mixture was stirred vigorously at rt for 12 h. The reaction mixture turned dark brown over time, and the periodic TLC analysis indicated that the reaction was proceeding very slowly. Thus, additional K_2CO_3 (3.39 g, 24.6 mmol), $NaHCO_3$ (2.06 g, 24.6 mmol $K_3Fe(CN)_6$ (8.08 g, 24.6 mmol), and potassium osmate dihydrate (30.2 mg, 0.0818 mmol) was added to the reaction mixture, and the vigorous stirring was continued for an additional 24 h. The reaction was quenched with Na_2SO_3 (12.4 g, 98.2 mmol), and the resulting dark green solution was stirred for 45 min. The phases were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (20% → 30% EtOAc/Hexanes gradient) afforded 2.91 g of **4a** as a colorless viscous oil (70%, 10:1 diastereomeric ratio based on ^1H NMR of the crude reaction mixture). Data for **4a**: ^1H NMR (Table 1); ^{13}C NMR (Table 2); $[\alpha]^{25}_D$ −29.9° (*c* 1.47, $CHCl_3$); IR (neat) 3437, 3056, 2961, 1724, 1620, 1464 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{44}NO_5Si$ (MH^+) 514.2989, found 514.2980.

(4*R*,5*R*,6*S*)-4-(*tert*-Butyldimethylsiloxymethyl)-6-hydroxymethyl-5-trimethylacetoxy-2,2-diphenyltetrahydro-1,3-oxazine (4b). Prepared from pivalate **3b** (576 mg, 1.20 mmol), according to the procedure used for the synthesis of **4a**, to give **4b** as a colorless oil (437 mg, 71%, 5.4:1 diastereomeric ratio based on ^1H NMR of the crude reaction mixture). Data for **4b**: ^1H NMR (Table 3); ^{13}C NMR (Table 4); $[\alpha]^{20}_D$ −52.6° (*c* 1.08, $CHCl_3$); IR (neat) 3437, 3065, 2961, 1724, 1456, 1265, 1152 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{44}NO_5Si$ (MH^+) 514.2989, found 514.2969.

(2*R*,3*S*,4*R*)-*N*-Diphenylmethyl-5-*O*-*tert*-butyldimethylsilyl-4-aminopentane-1,2,3,5-tetrol (7a). $LiBH_4$ (472 mg, 21.7 mmol) was added to a solution of diol **4a** (2.78 g, 5.42 mmol) in THF (20 mL). The flask was equipped with a reflux condenser, the resulting mixture was brought to a gentle reflux, and MeOH (880 μL, 21.7 mmol) was added via syringe pump over 2 h. The resulting mixture was refluxed for an additional 8 h, cooled to 0 °C, and quenched by careful addition of H_2O. The mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. The residue was chromatographed (50% → 70% EtOAc/hexanes gradient) to provide 1.96 g of **7a** as a white solid (84%). Data for **7a**: ^1H NMR (Table 1); ^{13}C NMR (Table 2); mp 99−100 °C; $[\alpha]^{29}_D$ −53.0° (*c* 6.04, $CHCl_3$); IR ($CHCl_3$) 3681, 3616, 3470, 3006, 2974, 1518, 1412 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{38}NO_4Si$ (MH^+) 432.2570, found 432.2562.

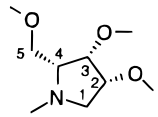
(2*S*,3*R*,4*R*)-*N*-Diphenylmethyl-5-*O*-*tert*-butyldimethylsilyl-4-aminopentane-1,2,3,5-tetrol (7b). A solution of diol **4b** (437 mg, 0.850 mmol) in THF (5 mL) was treated with $LiBH_4$ (74 mg, 3.40 mmol). The resulting mixture was refluxed, and the reaction progress was monitored by TLC. After 4 days, the reduction of imine was deemed complete. Next, MeOH (140 μL, 3.40 mmol) was added in a dropwise manner, and the resulting mixture was refluxed for an additional 8 h. The reaction mixture was cooled to 0 °C, quenched with H_2O, and partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. The residue was purified by flash chromatography (50% EtOAc/hexanes) to give 302 mg of **7b** as an oil (82%). Data for **7b**: ^1H NMR (Table 3); ^{13}C NMR (Table 4); $[\alpha]^{25}_D$ −63.4° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 3411, 3065, 3056, 2918, 2857, 1464, 1256, 1118, 1066 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{38}NO_4Si$ (MH^+) 432.2570, found 432.2582.

Table 5. ^1H NMR Data for D-Iminolyxitol Products (250 MHz, $CDCl_3$)



	8a		9a		10a	
	Chemical Shift (ppm), Multiplicity					
H-1	2.50	dd	2.50	dd	2.06	dd
H-1′	3.03	d	3.53	d	3.13	d
H-2	3.96	t	4.01	t	4.50	dd
H-3	4.26	dd	4.28	dd	4.64	t
H-4	3.09	bs	3.08	m	2.44	ddd
H-5	3.33	dd	3.02	dd	3.75	dd
H-5′	3.51	dd	3.11	dd	3.88	dd
Ph_2CH	4.74	s	4.76	s	5.04	s
	Coupling Constants ($J_{H,H}$, Hz)					
$J_{1,1'}$	10.8		11.2		11.0	
$J_{1,2}$	3.7		4.1		4.4	
$J_{1',2}$	0		0		0	
$J_{2,3}$	4.8		5.0		6.4	
$J_{3,4}$	8.7		8.8		5.0	
$J_{4,5}$	4.0		4.0		3.3	
$J_{4,5'}$	1.3		1.6		6.4	
$J_{5,5'}$	10.4		11.3		11.7	

Table 6. ^{13}C NMR Data for D-Iminolyxitol Products (62.9 MHz, $CDCl_3$)



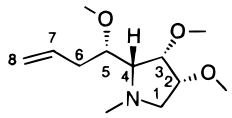
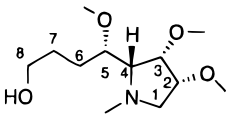
	chemical shift (ppm)		
carbon no.	8a	9a	10a
C-1	56.3	56.3	53.8
C-2	70.8	70.5	77.3
C-3	73.4	73.1	81.4
C-4	62.2	62.8	64.5
C-5	61.6	59.0	60.3
Ph_2CH	72.4	72.6	66.3

5-*O*-*tert*-Butyldimethylsilyl-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-lyxitol (8a). Ph_3P (2.38 g, 9.07 mmol), CCl_4 (880 μL, 9.07 mmol), and Et_3N (1.26 mL, 9.07 mmol) were sequentially added to a solution of aminotetrol **7a** (1.96 g, 4.53 mmol) in anhydrous DMF (15 mL) under argon, and the resulting mixture was stirred in the dark at rt for 17 h. Next, the reaction mixture was quenched by a dropwise addition of anhydrous MeOH (10 mL). The mixture was stirred for 30 min, concentrated in vacuo, and passed through a plug of silica gel. The filtrate was concentrated, and the resulting residue was chromatographed (25% EtOAc/hexanes) to afford 1.70 g of **8a** as a white crystalline solid (90%). A small sample was recrystallized from CH_2Cl_2/pentane to give an analytically pure sample. Data for **8a**: ^1H NMR (Table 5); ^{13}C NMR (Table 6); mp 80−81 °C; $[\alpha]^{31}_D$ +44.4° (*c* 0.570, $CHCl_3$); IR ($CHCl_3$) 3681, 3616, 3006, 2974, 1518, 1420 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{36}NO_3Si$ (MH^+) 414.2464, found 414.2453.

5-O-*tert*-Butyldimethylsilyl-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-ribitol (8b). Aminopolyol **7b** (270 mg, 0.626 mmol) was cyclized according to the procedure used for the synthesis of **8a**, to afford **8b** as an oil (208 mg, 80%). Data for **8b**: ^1H NMR (Table 9); ^{13}C NMR (Table 10); $[\alpha]^{26}_D$ +56.0° (*c* 0.600, $CHCl_3$); IR ($CHCl_3$) 3394, 3065, 3048, 2918, 2857, 1447, 1256, 1100 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{36}NO_3Si$ (MH^+) 414.2464, found 414.2454.

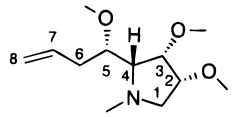
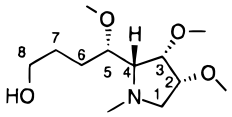
(57) Gobel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329.

Table 7. ^{1}H NMR Data for Imino-L-gulo-octitol Products (250 MHz, $CDCl_3$)

	11a		12a		13a	
	Chemical Shift (ppm), Multiplicity					
H-1	2.22	dd	1.78	dd	1.83	dd
H-1′	3.03	dd	3.04	d	3.07	d
H-2	4.44	dt	4.34	dd	4.37	dd
H-3	4.56	dd	4.48	dd	4.50	dd
H-4	2.65	m	2.40	dd	2.43	dd
H-5	4.03	ddd	4.32	m	4.32	m
H-6	2.37	dt	2.50	ddt	1.69	m
H-6′	2.65	m	2.65	ddd	2.03	m
H-7	5.84	dddd	5.98	dddd	1.69	m
H-8	5.11	d	5.02	d	3.62	t
H-8′	5.11	d	5.01	d	3.62	t
Ph_2CH	5.45	s	5.76	s	5.65	s
	Coupling Constants ($J_{H,H}$, Hz)					
$J_{1,1'}$	11.7		11.2		11.2	
$J_{1,2}$	4.9		4.5		4.5	
$J_{1',2}$	1.5		0		0	
$J_{2,3}$	5.4		6.4		6.4	
$J_{3,4}$	6.5		4.8		4.7	
$J_{4,5}$	3.1		7.6		7.4	
$J_{5,6}$	8.6		1.7		–	
$J_{5,6'}$	6.5		5.2		–	
$J_{6,6'}$	14.4		15.0		–	
$J_{6,7}$	8.6		3.7		–	
$J_{6',7}$	6.2		8.6		–	
$J_{7,8}$	9.7		10.8		6.1	
$J_{7,8'}$	17.9		−16.2		–	
$J_{8,8'}$	0		0		–	

Table 8. ^{13}C NMR Data for Imino-L-gulo-octitol Products (62.9 MHz, $CDCl_3$)

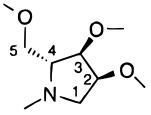



	chemical shift (ppm)		
carbon no.	**11a**	**12a**	**13a**
C-1	52.7	52.5	52.8
C-2	77.8	76.8	76.8
C-3	80.5	80.1	80.5
C-4	66.5	65.1	65.5
C-5	69.9	73.0	73.0
C-6	39.4	39.1	30.1
C-7	135.7	136.2	28.7
C-8	117.6	116.5	63.4
Ph_2CH	66.0	63.5	64.0

2,3-*O*-Isopropylidene-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-lyxitol (10a). Camphorsulfonic acid (621 mg, 2.03 mmol) and 2,2-dimethoxypropane (1.13 mL, 9.21 mmol) were added to a solution of pyrrolidine **8a** (762 mg, 1.84 mmol) in CH_2Cl_2 (30 mL), the resulting mixture was brought to a gentle reflux, and the reaction progress was monitored by TLC. After 72 h, the reaction mixture was poured into aqueous saturated $NaHCO_3$, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered through a pad of Celite, and concentrated in vacuo. The residue was chromatographed (5% → 25% EtOAc/hexanes gradient) to afford 504.7 mg of **10a** as a colorless oil (81%). Data for **10a**: ^{1}H NMR (Table 5); ^{13}C NMR (Table 6); $[\alpha]^{24}_D$ −44.7° (*c* 2.06, $CHCl_3$); IR (neat) 3437, 3056, 3022, 3013, 2926, 1499, 1447, 1369 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{26}NO_3$ (MH^+) 340.1913, found 340.1909.

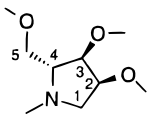
2,3-*O*-Isopropylidene-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-ribitol (10b). Prepared from pyrrolidine **8b** (167 mg, 0.403 mmol), according to the procedure used for the synthesis of **10a**, to afford **10b** as a colorless oil (130 mg, 95%). Data for **10b**: ^{1}H NMR (Table 9); ^{13}C NMR (Table 10); $[\alpha]^{27}_D$ +62.77° (*c* 0.150, $CHCl_3$); IR (neat) 3446, 3065, 3022, 2987, 1490, 1455, 1386 cm-1; HRMS (FAB) calcd for C21H26NO3 (MH+) 340.1913, found 340.1916.

Table 9. ^{1}H NMR Data for D-Iminoribitol Products (500 MHz, $CDCl_3$)



	8b		10b	
	Chemical Shift (ppm), Multiplicity			
H-1	3.17	dd	3.03	dd
H-1′	2.57	dd	2.99	dd
H-2	4.16	q	4.70	ddd
H-3	4.07	t	4.52	dd
H-4	2.94	dt	3.33	dd
H-5	3.26	dd	3.36	dd
H-5′	3.03	dd	3.32	dd
Ph_2CH	4.84	s	5.29	s
	Coupling Constants ($J_{H,H}$, Hz)			
$J_{1,1'}$	11.3		12.9	
$J_{1,2}$	5.0		4.7	
$J_{1',2}$	3.8		2.0	
$J_{2,3}$	4.9		6.2	
$J_{3,4}$	4.9		0	
$J_{4,5}$	8.5		8.9	
$J_{4,5'}$	4.3		5.5	
$J_{5,5'}$	9.8		12.8	

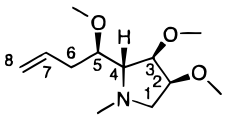
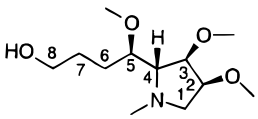
Table 10. ^{13}C NMR Data for D-Iminoribitol Products (62.9 MHz, $CDCl_3$)



	chemical shift (ppm)	
carbon no.	**8b**	**10b**
C-1	57.8	55.7
C-2	70.6	80.7
C-3	77.0	83.6
C-4	67.0	66.4
C-5	66.1	59.9
Ph_2CH	74.3	70.9

2,3-*O*-Isopropylidene-*N*-diphenylmethyl-1,4,6,7,8-pentadeoxy-1,4-imino-L-gulo-oct-7-enitol (11a). Method A: A mixture of oxalyl chloride (60 μL, 0.682 mmol) in CH_2Cl_2 (800 μL) was cooled to −60 °C under anhydrous conditions, treated with DMSO (97 μL, 1.36 mmol), and stirred for 10 min. Next, a solution of alcohol **10a** (210 mg, 0.620 mmol) in CH_2Cl_2 (1.6 mL) was added dropwise via syringe. After 30 min, Et_3N (432 μL, 3.01 mmol) was added; the reaction was allowed to warm to rt at which time it was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with NH_4Cl, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, the solution was concentrated at 0 °C in the dark and used in the next step without purification. The solution of crude aldehyde and tributylallyl tin (211 μL, 0.682 mmol) in CH_2Cl_2 (1.8 mL) was treated with 4 Å molecular sieves and cooled to −78 °C. Next, $BF_3{\cdot}OEt_2$ (105 μL, 0.806 mmol) was added dropwise, and the mixture was stirred for 2 h. Subsequently, a mixture of pentane/ether (1:1, 20 mL) was added, and the reaction was quenched at −78 °C with saturated $NaHCO_3$. The resulting mixture was vigorously stirred at rt for 3 h and extracted with ether. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give a yellow oil which was flash chromatographed (5% → 10% EtOAc/hexanes gradient) to afford 189 mg of **11a** as a colorless oil (80%, >20:1 diastereomeric ratio).

Table 11. ^{1}H NMR Data for Imino-D-allo-octitol Products (500 MHz, $CDCl_3$)

	11b		12b		13b	
	Chemical Shift (ppm), Multiplicity					
H-1	3.15	dd	3.09	dd	3.09	dd
H-1′	2.78	dd	2.88	dd	2.91	d
H-2	4.65	dt	4.64	ddd	4.66	t
H-3	4.76	dd	4.81	d	4.81	d
H-4	3.06	dd	3.27	d	3.24	d
H-5	3.63	ddd	3.84	ddd	3.79	ddd
H-6	2.15	m	2.14	dt	1.38	m
H-6′	2.14	m	2.05	m	1.38	m
H-7	5.60	dddd	4.98	dddd	0.83	m
H-8	5.04	d	4.64	dd	3.24	t
H-8′	5.05	d	4.74	ddd	3.24	t
Ph_2CH	5.12	s	5.09	s	5.09	s
	Coupling Constants ($J_{H,H}$, Hz)					
$J_{1,1'}$	11.4		11.8		11.7	
$J_{1,2}$	5.4		5.0		0	
$J_{1',2}$	2.9		1.0		4.9	
$J_{2,3}$	6.4		6.2		6.2	
$J_{3,4}$	1.8		0		0	
$J_{4,5}$	3.0		1.5		1.0	
$J_{5,6}$	5.8		9.6		9.5	
$J_{5,6'}$	8.2		4.0		2.7	
$J_{6,6'}$	–		14.2		–	
$J_{6,7}$	7.1		7.6		–	
$J_{6',7}$	6.8		6.5		–	
$J_{7,8}$	10.2		10.2		–	
$J_{7,8'}$	17.2		17.1		–	
$J_{8,8'}$	0		3.2		0	

Method B: A solution of oxalyl chloride (13 μL, 0.142 mmol) in CH_2Cl_2 (160 μL) was cooled to −70 °C treated with DMSO (20 μL, 0.283 mmol) and stirred for 5 min. Alcohol **10a** (43.7 mg, 0.129 mmol) in CH_2Cl_2 (340 μL) was added to the reaction mixture in a dropwise manner, and the resulting solution was stirred for 30 min. Next, Et_3N (90 μL, 0.644 mmol) was added at −70 °C, and the mixture was allowed to warm to rt. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were sequentially washed with NH_4Cl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, concentrated at 0 °C in the dark, and used without further purification.

The crude aldehyde was dissolved in MeOH (130 μL) and treated with $Sn(CH_2CH{=}CH_2)_4$ (9 μL, 0.039 mmol). The resulting mixture was stirred at rt, and the reaction progress was monitored by TLC. After 4 days, ether (5 mL) and aqueous KF (1 mL saturated KF; 4 mL H_2O) were added, and the mixture was vigorously stirred at rt for 20 min. Phases were separated, and the aqueous layer was extracted with ether. Organic layers were pooled, extracted with $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil which was purified on silica gel (10% EtOAc/hexanes) to afford 32.1 mg of **11a** as an oil (66%, ≫20:1 diastereomeric ratio). Data for **11a**: ^{1}H NMR (Table 7); ^{13}C NMR (Table 8); $[\alpha]^{27}_D$ −76.9° (*c* 1.08, $CHCl_3$); IR (neat) 3567, 3468, 3061, 2974, 2931, 1641, 1591, 1492 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{30}NO_3$ (MH^+) 380.2226, found 380.2222.

2,3-*O*-Isopropylidene-*N*-diphenylmethyl-1,4,6,7,8-pentadeoxy-1,4-imino-D-*allo*-oct-7-enitol (11b). Prepared from alcohol **10b** (128 mg, 0.376 mmol), according to procedure **A**, to give **11b** as a colorless oil (110 mg, 77%, 3.5:1 diastereomeric ratio). Data for **11b**: ^{1}H NMR (Table 11); ^{13}C NMR (Table 12); $[\alpha]^{30}_D$ +6.71° (*c* 0.830, $CHCl_3$); IR (neat) 3446, 3074, 3030, 2987, 2926, 1455, 1386, 1109 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{30}NO_3$ (MH^+) 380.2226, found 380.2216.

5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-*N*-diphenylmethyl-1,4,6,7,8-pentadeoxy-1,4-imino-L-*gulo*-oct-7-enitol (12a). A solution of homoallylic alcohol **11a** (398 mg, 1.05 mmol) and 2,6-lutidine (305 μL, 2.62 mmol) in CH_2Cl_2 (20 mL) was cooled to −5 °C and treated with *t*-$BuMe_2Si{-}SO_2CF_3$ (289 μL, 1.26 mmol). After 30 min at 0 °C, the reaction mixture was quenched with aqueous saturated $NaHCO_3$, phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction product was chromatographed (2% EtOAc/hexanes) to give 498 mg of **12a** as an oil (96%). Data for **12a**: ^{1}H NMR (Table 7); ^{13}C NMR (Table 8); $[\alpha]^{25}_D$ −63.0° (*c* 0.540, $CHCl_3$); IR (neat) 3061, 3024, 2931, 2851, 1641, 1597, 1492, 1443, 1375 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{44}NO_3Si$ (MH^+) 494.3090, found 494.3076.

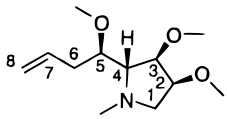
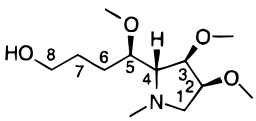
5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-*N*-diphenylmethyl-1,4,6,7,8-pentadeoxy-1,4-imino-D-*allo*-oct-7-enitol (12b). Prepared from homoallylic alcohol **11b** (105 mg, 0.276 mmol), according to the procedure used for the synthesis of **12a**, to give **12b** as a colorless oil (123 mg, 90%). Data for **12b**: ^{1}H NMR (Table 11); ^{13}C NMR (Table 12); $[\alpha]^{25}_D$ +19.4° (*c* 0.720, $CHCl_3$); IR (neat) 3091, 3082, 2926, 2857, 1646, 1602, 1447, 1377, 1248, 1118 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{44}NO_3Si$ (MH^+) 494.3090, found 494.3085.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-*N*-diphenylmethyl-1,4,6,7-tetradeoxy-1,4-imino-L-*gulo*-octitol (13a). A solution of compound **12a** (76.2 mg, 0.154 mmol) in anhydrous THF (1.2 mL) was treated with 9-BBN (0.232 mmol, 463 μL of a 0.5 M solution in THF) and stirred at RT for 20 h. Next, the reaction was cooled to 0 °C and quenched with EtOH (1 mL). The resulting mixture was sequentially treated with NaOH (0.232 mmol, 77.0 μL, 3 M) and H_2O_2 (0.232 mmol, 23.0 μL, 30% solution). After stirring at rt for 3 h, the reaction mixture was diluted with CH_2Cl_2 and washed with brine. The aqueous layer was back-extracted with CH_2Cl_2, and the combined organic layers were washed with saturated NH_4Cl, aqueous saturated $NaHCO_3$, and brine. Subsequently, the organic layer was dried over $MgSO_4$, filtered through a pad of Celite, and concentrated. Chromatography (20% EtOAc/hexanes) afforded 57.2 mg of **13a** (73%). Data for **13a**: ^{1}H NMR (Table 7); ^{13}C NMR (Table 8); $[\alpha]^{22}_D$ −91.1° (*c* 0.640, $CHCl_3$); IR (neat) 3432, 3065, 3021, 2933, 2855, 1597, 1457, 1378 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{46}NO_4Si$ (MH^+) 512.3196, found 512.3196.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-*N*-diphenylmethyl-1,4,6,7-tetradeoxy-1,4-imino-D-*allo*-octitol (13b). Prepared from compound **12b** (120 mg, 0.243 mmol), according to the procedure used for the synthesis of **13a**, to furnish **13b** as an oil (94 mg, 76%). Data for **13b**: ^{1}H NMR (Table 11); ^{13}C NMR (Table 12); $[\alpha]^{28}_D$ −3.30° (*c* 1.01, $CHCl_3$); IR (neat) 3437, 3065, 3030, 2952, 2849, 1455, 1386, 1248, 1049 cm^{-1}; HRMS (FAB) calcd for $C_{30}H_{46}NO_4Si$ (MH^+) 512.3196, found 512.3190.

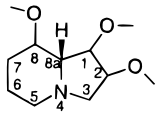
(1*S*,2*R*,8*S*,8a*R*)-1,2,8-Triacetoxyindolizidine [(−)-8-*epi*-swainsonine triacetate] (15a). A solution of alcohol **13a** (321 mg, 0.626 mmol) in CH_2Cl_2 (30 mL) was cooled to −5 °C and

Table 12. ^{13}C NMR Data for Imino-D-allo-octitol Products (62.9 MHz, $CDCl_3$)

	chemical shift (ppm)		
carbon no.	11b	12b	13b
C-1	56.4	57.4	57.4
C-2	79.8	81.7	81.7
C-3	80.9	81.8	81.8
C-4	69.5	68.6	68.9
C-5	68.8	72.9	72.6
C-6	38.5	40.3	31.6
C-7	134.4	133.4	28.2
C-8	117.9	116.8	62.2
Ph_2CH	69.8	71.8	71.7

Table 13. ^{1}H NMR Data for Indolizidine Products (500 MHz, $CDCl_3$)



	15a		15b		16b	
	Chemical Shift (ppm), Multiplicity					
H-1	5.40	t	5.01	t	3.94	t
H-2	5.26	dt	5.20	ddd	4.20	q
H-3	3.27	dd	3.57	dd	3.41	dd
H-3′	2.43	dd	2.33	dd	2.27	dd
H-5ax	2.10	m	2.10	m	2.13	t
H-5eq	3.22	m	2.93	br,d	2.93	br,d
H-6ax	1.54	m	1.63	dddt	1.54	m
H-6eq	2.00	m	1.72	m	1.78	br,d
H-7ax	1.46	m	1.29	m	1.34	dq
H-7eq	1.90	m	2.10	m	2.06	m
H-8	5.36	br,t	4.69	ddd	3.54	dt
H-8a	2.26	dd	2.29	t	1.99	t
	Coupling Constants ($J_{H,H}$, Hz)					
$J_{1,2}$	6.5		7.7		7.5	
$J_{1,8a}$	5.8		7.7		7.5	
$J_{2,3}$	1.8		6.9		7.4	
$J_{2,3'}$	6.8		5.7		6.4	
$J_{3,3'}$	11.2		10.0		9.8	
$J_{5ax,5eq}$	–		10.7		10.2	
$J_{5ax,6eq}$	–		–		1.2	
$J_{5ax,6ax}$	–		–		11.1	
$J_{6ax,5eq}$	–		–		–	
$J_{6eq,5eq}$	–		–		–	
$J_{6ax,6eq}$	–		13.6		13.8	
$J_{6ax,7eq}$	–		–		–	
$J_{6ax,7ax}$	–		–		–	
$J_{6eq,7eq}$	–		–		–	
$J_{6eq,7ax}$	–		–		3.7	
$J_{7eq,7ax}$	–		–		12.4	
$J_{7ax,8}$	–		11.0		9.9	
$J_{7eq,8}$	–		4.6		4.2	
$J_{8,8a}$	1.3		9.2		8.6	

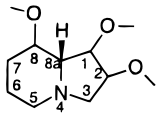
sequentially treated with Et_3N (131 μL, 0.939 mmol) and CH_3SO_2Cl (73 μL, 0.939 mmol). After 30 min, the reaction was quenched with saturated $NaHCO_3$. Next, the organic layer was washed with aqueous saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was used in the next step without purification.

The crude mesylate **14a** was azeotroped with EtOAc and dissolved in MeOH (30 mL). The flask was purged with argon and charged with Pd−C (200 mg, 10%). Subsequently, the reaction vessel was evacuated and charged with H_2 gas three times. The suspension was stirred under an atmosphere of H_2 gas (rubber balloon) for 20 h. Next, the reaction was quenched with 2 mL of CH_2Cl_2, filtered through a pad of Celite, and concentrated to give a yellow oil. The crude indolizidine was dissolved in a mixture of H_2O (5 mL) and TFA (5 mL) and stored at rt. After 72 h, the mixture was concentrated in vacuo at rt, and the resulting residue was azeotroped with toluene to give a waxy solid.

The crude reaction mixture was dissolved in dry pyridine (5 mL) and treated with DMAP (8 mg, 63 μmol). Next, the reaction was cooled to 0 °C, and Ac_2O (540 μL, 5.67 mmol) was added in a dropwise fashion. The reaction mixture was stirred at rt for 14 h, concentrated, dissolved in CH_2Cl_2, and extracted with saturated $NaHCO_3$. Subsequently, the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was flashed chromatographed to give 120 mg of **15a** as a off-white solid (64%). Data for **15a**: ^{1}H NMR (Table 13); ^{13}C NMR (Table 14); mp 77−78 °C, $[\alpha]^{22}_D$ −19.3° (*c* 0.730, $CHCl_3$); IR ($CHCl_3$) 2935, 2857, 1741, 1377, 1248, 1109 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{22}NO_6$ (MH^+) 300.1447, found 300.1458.

(1*R*,2*S*,8*R*,8a*R*)-1,2,8-Triacetoxyindolizidine [(+)-1,2-di-*epi*-swainsonine triacetate] (15b). Prepared from alcohol **13b** (93.4 mg, 0.183 mmol), according to the procedure used for the synthesis of **15a**, to give **15b** as a white solid (34.4 mg, 63%). Data for **15b**: ^{1}H NMR (Table 13); ^{13}C NMR (Table 14); mp 132−134 °C, $[\alpha]^{23}_D$ +61.1° (*c* 2.11, $CHCl_3$); IR ($CHCl_3$) 2952, 2926, 2857, 1750, 1395, 1239, 1109 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{22}NO_6$ (MH^+) 300.1447, found 300.1449.

Table 14. ^{13}C NMR Data for Indolizidine Products (62.9 MHz, $CDCl_3$)



	chemical shift (ppm)		
carbon no.	15a	15b	16b
C-1	71.9	73.9	75.9
C-2	69.8	68.4	69.3
C-3	59.1	58.5	61.6
C-5	53.2	51.2	53.3
C-6	19.6	23.6	25.3
C-7	29.6	30.1	34.9
C-8	66.1	72.9	73.4
C-8a	66.6	67.4	74.2

(1*R*,2*S*,8*R*,8a*R*)-1,2,8-Trihydroxyindolizidine [(+)-1,2-di-*epi*-swainsonine] (16b). A solution of compound **15b** (34 mg, 0.114 mmol) in anhydrous MeOH (1 mL) was treated with NaOMe/MeOH at rt until the solution remained basic, and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was applied to a short column of SiO_2 and eluted with 20% MeOH/CH_2Cl_2 to give 19.4 mg of **16b** as a white crystalline solid (98%). Data for **16b**: ^{1}H NMR (Table 13); ^{13}C NMR (Table 14); mp 127−128 °C, $[\alpha]^{25}_D$ +16.1° (*c* 1.23, MeOH); HRMS (FAB) calcd for $C_8H_{16}NO_3$ (MH^+) 174.1130, found 174.1134.

4-*C*-Allyl-2,3-*O*-isopropylidene-*N*-diphenylmethyl-1,4-dideoxy-1,4-imino-D-lyxitol (17). Swern oxidation was performed on alcohol **10a** (139 mg, 0.411 mmol) as prescribed in procedure **A**. Next, the crude aldehyde was treated with 4A activated molecular sieves (150 mg, powder) and $MgBr_2{\cdot}OEt_2$ (212 mg, 0.822 mmol) in CH_2Cl_2 (6 mL) at −20 °C. The resulting mixture was stirred at −20 °C for 30 min, $Bu_3SnCH_2CH{=}CH_2$ (140 μL, 0.452 mmol) was added, and the reaction mixture was stored at −23 °C. After 20 h, ether (10 mL) and aqueous KF (1 mL saturated KF; 4 mL H_2O) were added, and the mixture was vigorously stirred at rt for 30 min. Phases were separated, and the aqueous layer was extracted with ether. Organic layers were pooled, extracted with $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (10% EtOAc/hexanes) to afford 99.6 mg of **17** as an oil (64%, >20:1 dr). Data for **17**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.15−7.40 (10H, m, Ar), 5.50−5.66 (1H, dddd, J = 17.8, 10.3, 7.6, 7.3 Hz, C*H*=CH$_2$), 5.24 (1H, s, Ph$_2$C*H*), 4.9−5.0 (2H, m, C=C*H*$_2$), 4.58 (1H, s, *H*-C(3)), 4.57 (1H, d, J = 2.0 Hz, *H*-C(2)), 3.61−3.78 (2H, ddd, J = 11.8, 7.0, 5.7 Hz, *H*-C(5)), 3.14 (1H, d, J = 10.8 Hz, *H*-C(1)), 2.83 (1H, dt, J = 10.8, 2.0 Hz, *H*-C(1)), 2.71 (1H, dd, J = 7.0, 5.7 Hz, O-*H*), 2.25 (1H, dd, J = 14.1, 7.7 Hz, C*H*-C=C), 2.10 (1H, dd, J = 14.1, 7.3 Hz, C*H*-C=C), 1.62 (3H, s, Me), 1.31 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 143.1 (Ar), 142.1 (Ar), 134.0 (*C*H=CH$_2$), 129.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 126.9 (Ar), 126.6 (Ar), 118.1 (C=*C*H$_2$), 111.1 (−O-*C*-O-), 85.0 (*C*3), 77.5 (*C*2), 68.5 (*C*4), 65.7 (*C*5), 62.8 (Ph$_2$*C*), 52.7 (*C*1), 36.7 (*C*H$_2$−C=C), 26.2 (*C*H$_3$), 24.3 (*C*H$_3$); HRMS (FAB) calcd for $C_{24}H_{30}NO_3$ (MH^+) 380.2226, found 380.2231.

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Supporting Information Available: Proton and carbon NMR spectra are available for compounds **2a**, **2b**, **7a**, **7b**, **10a**, **10b**, **12a**, **12b**, **15b**, **16b**, and **17**. A complete X-ray structure report is available for compound **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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