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Enantiomerically Pure Polyhydroxylated Acyliminium Ions. Synthesis of the Glycosidase Inhibitors (−)-Swainsonine and (+)-Castanospermine

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Abstract: Hydroxylactams, which are useful precursors of acyl iminium ions for cationic cyclization, are most often prepared by hydride reduction of imides. This procedure is not directly applicable, however, to the enantioselective preparation of any highly substituted hydroxy lactam that would be derived from a meso imide, since such a reduction with the usual achiral agents must produce a racemic product. Two enantioselective methods of preparing representative examples of this type of substituted hydroxylactam have therefore been explored. Reduction of a meso imide with a number of enantiomerically pure chiral reducing agents has been found to give up to 56% ee of the corresponding hydroxylactam. Much higher levels of enantiomeric purity are readily obtainable by direct synthesis from monosaccharide lactones derived from either ribose or lyxose, affording either enantiomeric series of hydroxy lactams, (+)-**9**α, **14–16**, and (−)-**9**α, **20–23**, respectively. One such hydroxylactam, **23** has been converted into the mannosidase inhibitor (−)-swainsonine via a synthetic route that features a novel multiple reduction of a vinylogous *N*-acylurethane to establish the correct ring juncture stereochemistry. Extension of the monosaccharide strategy to the enantioselective synthesis of six-membered-ring hydroxylactams also allows a facile preparation of **29**, leading to the glucosidase inhibitor (+)-castanospermine and the new indolizidine alkaloid 1,8a-diepicastanospermine.

Introduction

The bicyclic polyhydroxyindolizidines swainsonine (**1**) and castanospermine (**2**) are potent inhibitors of mannosidases and glucosidases, respectively, enzymes that are essential in the biosynthetic processing of polysaccharides and glycoproteins.[1] Because the removal of specific mannosyl and glucosyl residues from the glycoprotein surface of viral envelopes plays a crucial role in host cell recognition and replication, glycosidase inhibitors show promise for the chemotherapeutic treatment of viral diseases, including AIDS.[2]

One well-established synthetic route to indolizidines and related bicyclic alkaloids relies on cationic cyclization induced by an acyl iminium ion, the precursor of which is normally a hydroxylactam prepared by hydride reduction of an imide.[3] For **1**[4] and **2**,[5] however, this standard route (Figure 1) is doomed to produce only racemic products because in both cases the stereochemistry of the targets leads antithetically to meso starting materials, **5** and **6**. This "meso imide problem" thus was addressed—in the context of the synthesis of (−)-swainsonine and (+)-castanospermine—first by exploring enantioselective methods of reducing the imides **5** and **6**, and ultimately by developing short alternative routes to the required hydroxylactams **3** and **4** that circumvent the problem entirely.[6]

A second important stereochemical issue common to both routes concerns the ring juncture stereochemistry, which is initially established in the cyclization step. There is substantial precedent in OR-directed cyclizations of five-membered ring acyl iminium ions for attack of the internal nucleophile anti to the directing group (Figure 2),[7] which in the case of **1** would give the incorrect ring juncture stereochemistry. Thus, the synthetic plan for **1** needed to incorporate at some point an inversion at this center. For **2** on the other hand, acyl iminium ion cyclization anti to the OR group would give the correct stereochemistry; however, the anti directing effect would be expected to be substantially weaker in this six-membered ring than it is in a five-membered ring.[8] In fact, the diastereoselectivity might well be reversed due to a preference for axial attack in an all-equatorial half-chair, which would give the undesired ring juncture stereochemistry in **2**. Since no good precedent for these competing directing effects was found, this issue was also explored.

Results and Discussion

Solving the "meso imide problem" can in principle be accomplished in at least three ways, including enantioselective reduction of the appropriate meso imide itself, preparation of the hydroxylactam from chiral, nonracemic starting materials by a route that avoids meso intermediates entirely, or utilization of a chiral auxiliary attached at nitrogen to direct the reduction of the correct carbonyl group of the imide. This latter approach has proved to work well,[9] but in the current application we felt that the more

(1) For a good introduction to glycosidase inhibitors, see: Elbein, A. D. *Crit. Rev. Biochem.* **1984**, *16*, 21.

(2) (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229. (b) Montefiori, D. C.; Robinson, W. E., Jr.; Mitchell, W. M. *Ibid.* **1988**, *85*, 9248. (c) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wllson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. *FEBS Lett.* **1988**, *237*, 128.

(3) (a) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 3963. (b) For a review of acyliminium cyclizations in alkaloid synthesis, see: Speckamp, W. N. *Recueil* **1981**, *100*, 345. (c) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235. (d) Chamberlin, A. R.; Chung, J. Y. L. *Ibid.* **1985**, *50*, 4425 and references therein.

(4) For previous synthesis of swainsonine, see: (a) Fleet, G. W. J.; Gough, J. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, 1853. (b) Ali, M. H.; Houg, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447; *Carbohydr. Res.* **1985**, *136*, 225. (c) Suami, T.; Tadano, K.; limura, Y. *Chem. Lett.* **1984**, 513; *Carbohydr. Res.* **1985**, 135, 67. (d) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1984**, 1201. (e) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420. (f) Setoi, H.; Takeno, H.; Hashimoto, M. *Ibid.* **1985**, *50*, 3948. (g) lkota, N.; Hanuki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140. (h) Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022. (i) Bennett, R. B., III; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580.

(5) For previous syntheses of castanospermine, see: (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, 165. (b) Setoi, H.; Takeno, H.; Hashimoto, M. *Ibid.* **1985**, 4617. (c) Hamana, H.; lkota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5494. (d) (±) Castanospermine: Reymond, J.-L.; Vogel, P. *Tetrahedron Lett.* **1989**, 705.

(6) For a clever approach to the asymmetric synthesis of either enantiomer of a hydroxylated indolizidine via a related strategy, as well as pertinent references to related previous work, see: Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.

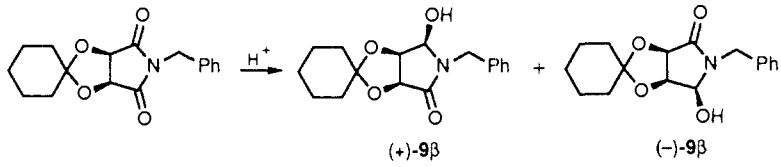
(7) For examples, see: (a) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, 1987. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (c) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.

(8) Relatively little is known about directing effects of ring substituents in six-membered ring acyl iminium ion cyclizations. For an example, see; Kano, S.; Yuasa, Y.; Shibuya, S. *Synthesis* **1984**, 1071. Whether the anti directing effect discussed in the text is purely steric or has an electronic component, it will weaken when the OR group is closer to being in-plane with the π-bond, as it is when OR is pseudo-equatorial in a half-chair acyl iminium ion intermediate (Figure 2).

(9) Miller, S. A.; Chamberlin, A. R. *J. Org. Chem.* **1989**, *54*, 2502.

0002-7863/90/1512-8100$02.50/0

Table 1. Enantioselective Meso Imide Reduction Studies



(+)-9β (−)-9β

entry	reagent	% yield[a]	% ee[b]	major enantiomers[c]
1	potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane	44	9	(+)-9β
2	LAH + (*S*,*S*)-(−)-*N*,*N*′-bis(α-methylbenzyl)sulfamide	40	23[d]	–
3	LAH + (*R*)-(+)-1,1′-bi-2-napthol	no reaction	–	–
4	LAH + chirald (darvon alcohol)	81	7	(+)-9β
5	LAH + *N*-ethylaniline + (1*R*,2*S*)-(−)-*N*-methylephedrine	95	0	–
6	LAH + (*S*,*S*)-*N*,*N*-bis-(2-propanol)-(*S*)-α-benzylamine	52	8	(+)-9β
7	LAH + (*S*)-2-(2,6-xylidinomethyl)pyrrolidine	79	56	(−)-9β
8	LAH + (*S*)-2-[2,6-(diisopropylanilino)methyl]pyrrolidine	70	11	(−)-9β
9	LAH + (*S*)-2-(*m*-anisidinomethyl)pyrrolidine	35	34	(−)-9β
10	LAH + (*S*)-2-[(1-adamantylamino)methyl]pyrrolidine	51	0	–

[a] Yield of unpurified product. [b] ^{1}H NMR of the Mosher ester. [c] Comparison with Mosher ester of authentic material prepared from D-lyxose. [d] ^{1}H NMR of the acetate in the presence of Eu(tfc)$_3$.

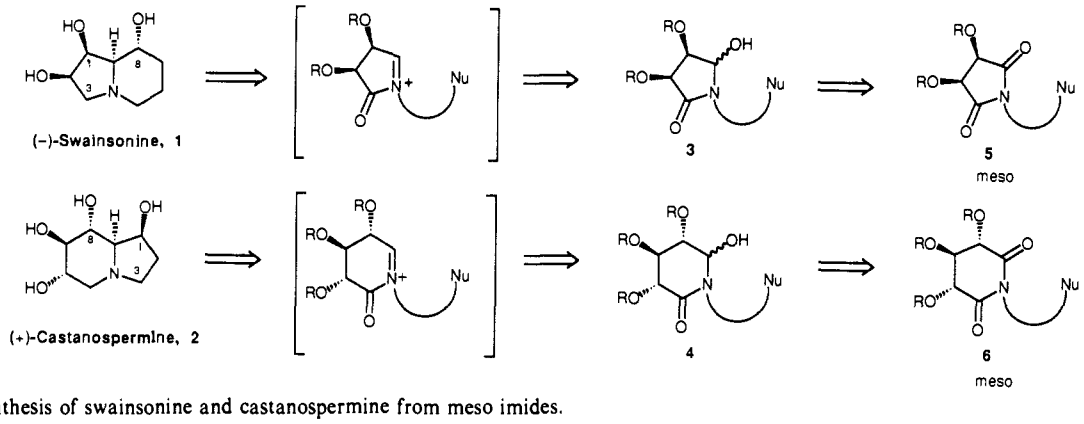


Figure 1. Synthesis of swainsonine and castanospermine from meso imides.

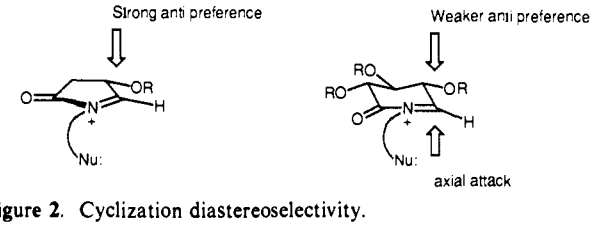


Figure 2. Cyclization diastereoselectivity.

direct methods would be preferable since they would avoid the necessity of replacing the auxiliary with a tether containing the internal nucleophile needed for the cyclization. The first two routes were therefore explored in some detail, as described below.

Synthesis and Reduction Studies of *meso*-Cyclohexylidene-*N*-benzyltartrimide. The first method investigated was the reduction of a meso imide with chiral reagents known to reduce ketones enantioselectively. Although imides, which are comparable to ketones in reactivity toward nucleophiles, have the reputation of being sensitive to overreduction,[10] our experience has been that strong reducing agents at low temperature reduce them cleanly to the corresponding hydroxylactams. The preferred trajectory of hydride reagents would be expected to be from the convex face of the bicyclic ring system, and preferential attack on one of the carbonyl groups—which is possible with chiral reagents since the transition states are diastereomeric—would provide an excess of one hydroxylactam enantiomer. This approach is an appealing one because reduction of the meso imide can in theory give a quantitative yield of one hydroxylactam enantiomer while establishing the absolute stereochemistry at three centers in a single step.[11]

The appropriate meso-imide precursor for (−)-swainsonine is **5**, which upon reduction would give the hydroxylactam **3**. Initial model studies designed to test this reduction were conducted on the *N*-benzylimide **8**. Although various N-protected 3,4-*cis*-dihydroxy imides have been prepared from *meso*-tartaric acid,[12,13] our initial attempts at reproducing these procedures were unsuccessful. Since the relatively high cost of *meso*-tartaric acid[14] makes this approach less than optimal to begin with, an alternative preparation of **8** was developed. Treating maleic anhydride with benzylamine followed by sodium acetate in acetic anhydride gives *N*-benzylmaleimide (**7**)[15] which undergoes catalytic osmylation followed by protection of the resultant cis diol to give the meso imide **8** (eq 1).

In order to verify the assumption that hydride delivery to the imide carbonyl group would occur exclusively from the convex face, **8** was first treated with achiral hydride reducing agents such as $NaBH_4$ or $LiAlH_4$. These reductions give a *single* (racemic) hydroxylactam (±)-9β that undergoes clean conversion to an isomeric product, (±)-9α, by treatment with ethanolic NaOH. This result is consistent with kinetically controlled formation of the β-hydroxylactam followed by epimerization to the thermodynamically more stable α-hydroxy diastereomer, confirming that

(10) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, 1437. (b) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Ibid.* **1978**, 179.

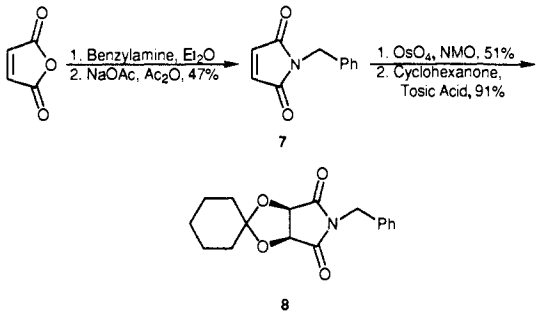
(11) This general strategy—selective functionalization of one "end" of a meso-derivative—has seen a recent surge in popularity. For representative examples, see: (a) Jones, J. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, 330. (b) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255. (c) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (d) Hoye, T. R.; Jenkins, S. A. *Ibid.* **1987**, *109*, 6196.

(12) Meissner, *Chem. Ber.* **1897**, *30*, 1574.

(13) *Beilstein, 4th Ed.* **1953**, *21*, 626.

(14) *meso*-Tartaric acid sells for ca. $3.00 per gram, compared with ca. $0.02 per gram for the L isomer and $0.50 per gram for the D isomer.

(15) Mehta, N. B.; Phillips, A. P.; Fu, F.; Brooks, R. *J. Org. Chem.* **1960**, *25*, 1012.

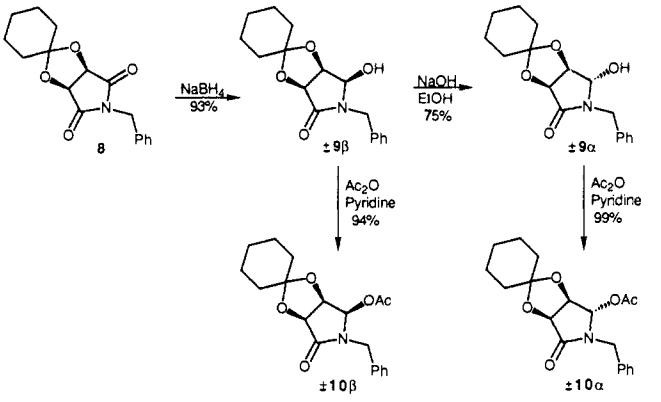


delivery of hydride occurs from the convex face of the heterobicyclo[3.3.0] ring system (Scheme I). Interestingly, the less stable hydroxylactam is not unduly prone to epimerize spontaneously and can be isolated or acetylated without detectable equilibration,[16]

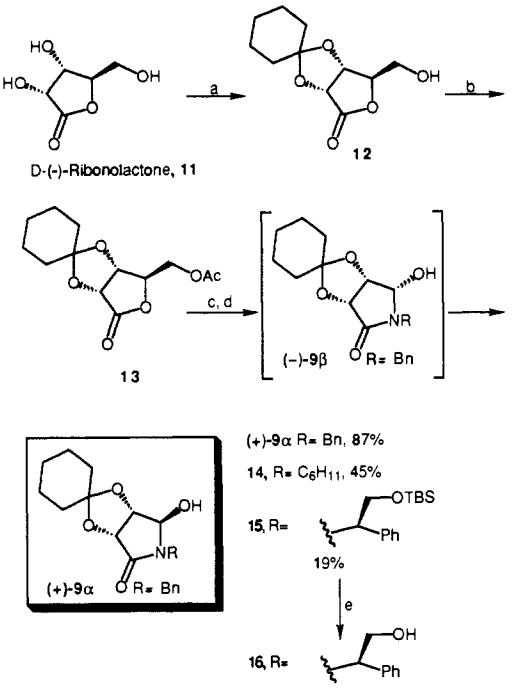
The meso imide **8** was then treated with a variety of known chiral reducing agents (Table I). In order to determine the enantiomeric excess for each reduction, the initially formed hydroxylactam was equilibrated to the more stable diastereomer as described above, acylated with the Mosher acid chloride,[17] and then analyzed by ^{1}H NMR. The absolute stereochemistry was in each case established by comparison with an authentic sample of one enantiomer prepared from lyxose (vide infra). Attempted enzymatic reductions, such as Baker's yeast/HLADH, as well as several boron-based reagents (NB-Enantride and Alpine Borane), resulted in either poor conversion or extensive side reactions. Chiral amine–LAH complexes (entries 2–10) gave consistently better yields, although in most cases the selectivity was poor. In fact, of all the reagents tested, only Mukaiyama's (*S*)-2-(2,6-xylidinomethyl)pyrrolidine complex[18] gave an enantiomeric excess above 50% (entry 7), in this case favoring the enantiomer (−)-**9**β. In an attempt to increase the selectivity we prepared several modified diamines, such as the 2,6-diisopropyl aniline and the adamantylamine analogues, but to no avail. Although this type of reduction is unprecedented for such meso imides, the mediocre selectivity prompted us to focus our further attention on an alternative means of preparing either hydroxylactam enantiomer.

Synthesis of Acyliminium Ion Precursors from D-Lyxose and D-Ribonolactone. In order to determine the enantioselectivity of the reductions unambiguously, it was necessary to prepare an authentic sample of one of the hydroxylactam enantiomers, and monosaccharide lactones appeared to offer a convenient source of starting materials for this purpose. In fact, the preparation of either enantiomer from readily available sugar derivatives proved to be so facile that further reduction studies were abandoned. The preparation of (−)-**9**α begins with the known[19] 2,3-*O*-cyclohexylidene-D-(−)-ribonolactone (**12**) (Scheme II) prepared by treatment of D-ribonolactone (**11**) with 1-methoxycyclohexene and boron trifluoride etherate in tetrahydrofuran. Attempts to induce the reaction of amines with the lactone carbonyl group of **12** proved fruitless, even after heating the reactants in refluxing 2-propanol for 8 days. However, simply protecting the primary alcohol group as the TBS ether or the acetate increases the reaction rate dramatically. In the case of benzylamine, the acetate group is cleaved under the reaction conditions, whereas with cyclohexylamine and (*tert*-butyldimethylsilyl)-phenylglycinol it survives and is removed in situ by the addition of potassium carbonate prior to work up. It is not clear why protecting the alcohol group results in enhanced reactivity; nonetheless, the reaction smoothly gives the amides, which undergo clean diol cleavage (lead tetraacetate

Scheme I



Scheme II[a]



[a] (a) 1-methoxycyclohexene, BF_3OEt_2, THF, 78%; (b) Ac_2O, pyridine, CH_2Cl_2, 93%; (c) H_2NR, MeOH; (d) $Pb(OAc)_4$, CH_3CN, K_2CO_3; (e) $FN(Bu)_4$, THF, 94%.

in the presence of K_2CO_3) to provide the epimers (+)-**9**α, **14**, and **15**, respectively, after ring closure. Yields for the two-step process are clearly dependent on the amine substitution pattern: primary amines invariably give better yields than do more highly substituted examples. It is also possible to cleanly remove the *tert*-butyldimethylsilyl (TBS) group in **15**, which provided the comparison sample for our previously reported chiral auxiliary-directed reductions.[9]

Hydroxylactams in the other enantiomeric series were prepared by protection of D-(−)-lyxose[20] under conditions similar to those employed for 2,3-*O*-cyclohexylidene-D-(−)-ribonolactone (see above) to give the cyclohexylidene ketal **18** (Scheme III), which was oxidized to the lactone with silver carbonate on Celite.[21] The lactone **19** was then treated with benzylamine in methanol, followed by lead tetraacetate in acetonitrile, to give a mixture of the epimers (+)-**9**β and (−)-**9**α. In contrast to the sluggish reaction of **12**, this reaction proceeds smoothly without protecting the primary alcohol group. The greater reactivity of the lactone **19** compared with its counterpart **12** presumably is due to the fact

(16) We have found that the success of silica gel purification of hydroxy lactams is highly structure specific. Hydroxy lactams such as **9a** and **9b** can be easily purified, while **23** and **29** (vide infra) appear to be unstable on silica gel.

(17) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

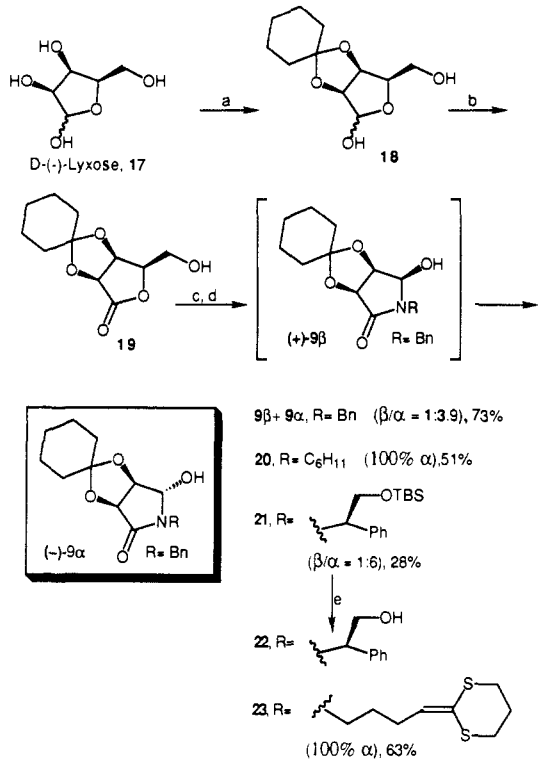
(18) Asami, M.; Mukaiyama, T. *Heterocycles* **1979**, *12*, 499. (b) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869.

(19) Beer, D.; Mewly, R.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2570.

(20) Lyxonolactone is the starting material for a recent synthesis of the α-L-fucosidase inhibitor deoxyfuconojirimycin: Fleet, G. W.; Petursson, S.; Cambell, A. L.; Mueller, R. A.; Behling, J. R.; Babiak, K. A.; Ng, J. S.; Scaros, M. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, *3*, 665.

(21) Fetizon, M.; Golfier, M. *Angew. Chem.* **1969**, *81*, 423.

Scheme III[a]



[a](a) 1-methoxycyclohexene, BF_3OEt_2, THF, 78%; (b) Ag_2CO_3/Celite, C_6H_6 65%; (c) H_2NR, MeOH; (d) $Pb(OAc)_4$, CH_3CN; (e) $FN(Bu)_4$, THF, 96%.

that nucleophilic attack from the convex face along the preferred trajectory is impeded by the *cis*-hydroxymethyl substituent in the 3-position of **12**.[22] While the product diastereomers can either be separated chromatographically or epimerized to (−)-**9α** prior to purification (as in Scheme II), this factor is of no consequence for our purposes since they both would be expected to produce the same acyliminium ion.[23] Several other amines gave similar results. For example, **20** was prepared from cyclohexylamine and authentic[9] **21α** and **21β** from TBS-D-phenylglycinol (Scheme III). Finally, the hydroxylactam intermediate **23** required for the synthesis of (−)-swainsonine was obtained similarly from 2-(4-aminobutylidene)-1,3-dithiane.[24]

Synthesis of (−)-Swainsonine. Having developed an efficient method of preparing the enantiomerically pure acyliminium ion precursor **23** required for the synthesis of (−)-swainsonine, we then proceeded to carry it on to the target. Formation of the indolizidine ring system was accomplished by treatment of **23** with methanesulfonyl chloride and triethylamine in dichloromethane followed by the addition of acetonitrile (which accelerates acyliminium ion formation by increasing the solvent polarity[3d]), resulting in a single diastereomer that was isolated in 60% yield (Scheme IV). Assuming, as discussed above, that this cyclization gives the incorrect stereochemistry at the ring juncture (**24**), the correct diastereomer appeared to be readily accessible by introducing a C-8/C-8a double bond as in **25** and then reducing it from the convex face of the tricyclic ring system. Accordingly, the ketene dithioacetal **24** was converted into the α-bromoester with *N*-bromosuccinimide in ethanol,[25] followed by treatment with DBU in THF to give the unsaturated ester **25**. Catalytic hydrogenation of the tetrasubstituted π-bond in **25**, however, proved to be very inefficient because of competing hydrogenolytic scission of the allylic ether. A variety of direct conjugate reductions of the α,β-unsaturated ester moiety also failed.

Moving away from reductions of the tetrasubstituted carbon–carbon double bond, we attempted to remove the lactam carbonyl group, anticipating that the resultant vinylogous *N*-acylurethane could afterward be reduced (as the iminium ion) with acidic sodium cyanoborohydride—again from the convex face of the tricyclic ring system—to give the desired ring juncture diastereomer. Lactam reduction was thus carried out under standard conditions by treating **25** with Meerwein's reagent followed by $NaBH_3CN$. To our immense delight, the reduction did not stop at **25a** (Scheme V), but instead proceeded directly on to a single fully saturated indolizidine, **26**, in 55% yield (86% based on recovered starting material). Presumably **26** is formed from the expected lactam reduction product **25a** via unanticipated protonation followed by reduction of the resultant iminium ion from the less hindered convex face, as shown. None of the C-8a epi product was detected, nor was any of the thermodynamically less stable C-8 diastereomer.

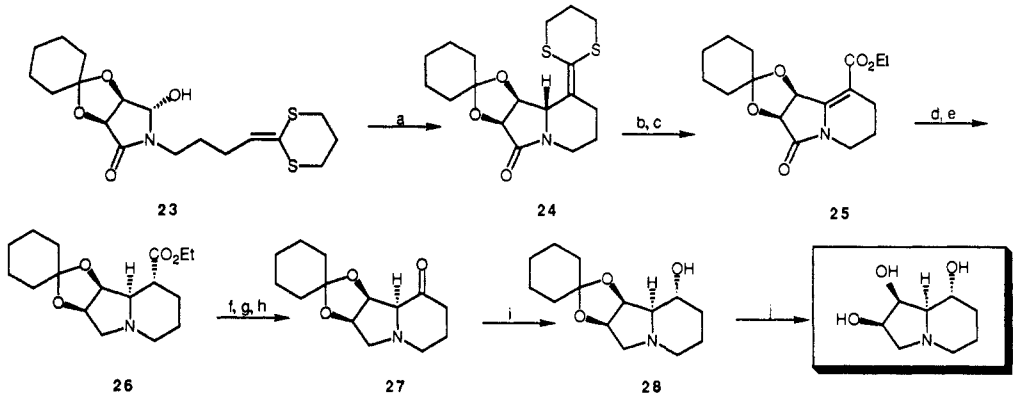
This fortuitous "overreduction" not only establishes the correct C-8a stereochemistry and removes the C-3 lactam carbonyl group, but also leaves a C-8 appendage that if oxidized with retention of configuration would provide the correct C-8 alcohol diastereomer directly. Accordingly, a carboxy inversion reaction[26] of the acid derived from **26** was attempted, but it failed to give the desired (protected) alcohol, as did numerous attempted Baeyer–Villiger reactions of the methyl ketone derived from the ester.

These problems could in principle be circumvented by conversion of the ester into the C-8 ketone, which then would require reduction to the equatorial alcohol. This transformation would not be expected to be trivial from a stereochemical point of view, however, since it requires axial reduction from a very hindered face, i.e., syn to the cyclohexylidene protecting group. Nonetheless, the requisite ketone (**27**) was prepared by α-hydroxylation of the ester **26**,[27] followed by lithium aluminum hydride reduction to the diol and oxidative cleavage with sodium periodate. Reduction of this unstable ketone with sodium borohydride or lithium aluminum hydride under a variety of conditions gave a mixture of epimers at C-8, favoring the axial alcohol (8-episwainsonine), and even Meerwein–Pondorff–Verley reduction of **27** (aluminum isopropoxide/2-propanol) gave primarily the axial alcohol. But treatment of the ketone with Na/NH_3 gave >95% of the desired equatorial alcohol (45% yield for the three step sequence from the α-hydroxy ester). Removal of the cyclohexylidene ketal then uneventfully afforded (−)-swainsonine in 95% yield, which was identical in all respects with an authentic sample.

Synthesis of (+)-Castanospermine. The structurally related glycosidase inhibitor (+)-castanospermine presented the opportunity to test the enantioselective hydroxylactam strategy for a six-membered ring triol. Preparation of the requisite hydroxylactam **29** began with the known 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone,[28] which was treated with 2-[3-aminopropylidene]-1,3-dithiane,[3d] followed by lead tetraacetate oxidation, to afford the expected hydroxylactam **29** (Scheme VI) contaminated with the open-chain aldehyde from which it is formed. Treatment of this mixture with acetic acid cyclized the remaining aldehyde,[29] giving **29** as a mixture of epimers. Without separation or further purification, this mixture was cyclized to the indolizidine ring system by adding methanesulfonyl chloride and triethylamine in dichloromethane (the addition of acetonitrile is not necessary in this case), giving an 84% yield of ring juncture epimers **30** and **31** in approximately a 1:1 ratio (Scheme VI). Variation of solvent and temperature did not affect the stereochemical outcome of this cyclization. Thus, the stereoelectronic preference for axial attack

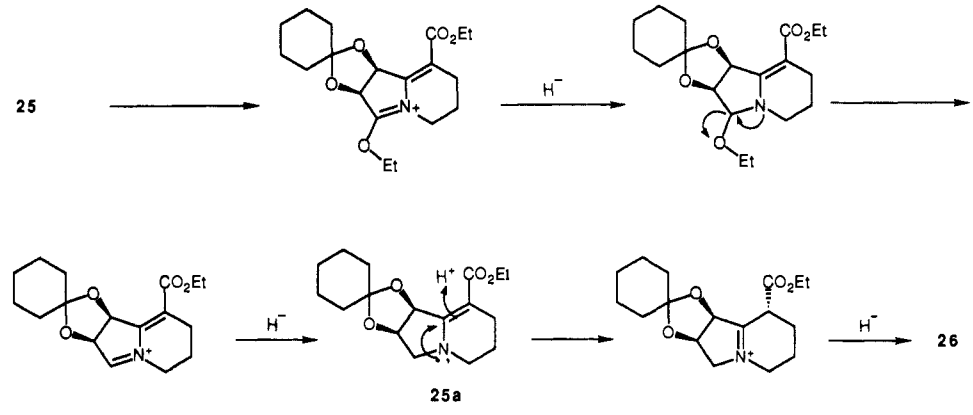
(22) Similar effects have been noted in the attack of nucleophiles on other substituted lactones: Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247.
(23) For example, the mixture of epimers **29** cyclized in 84% yield.
(24) Prepared by a minor modification of the literature procedure. See ref 3d.
(25) Gröbel, B.-T.; Bürstinghaus, R.; Seebach, D. *Synthesis* **1976**, 121.
(26) Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378.
(27) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731.
(28) Horito, S.; Asano, K.; Umemura, K.; Hashimoto, H.; Yoshimura, J. *Carbohydr. Res.* **1983**, *121*, 175.
(29) In contrast to the five-membered ring examples, this aldehyde is often observed after workup. It is sufficiently slow to cyclize to the hydroxylactam that it survives silica gel chromatography.

Scheme IV[a]

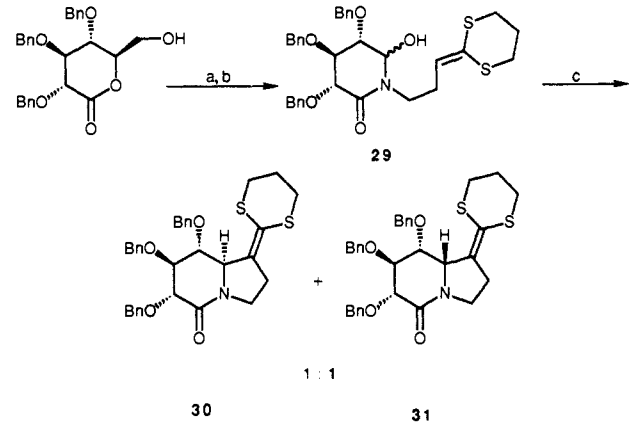


[a](a) Et_3N, MsCl, CH_2Cl_2 then CH_3CN, 60%; (b) NBS, EtOH, CH_3CN; (c) DBU, THF, 71%; (d) $Et_3O^+ {}^-BF_4$, CH_2Cl_2; (e) $NaCNBH_3$, MeOH, 86%; (f) LDA, THF, O_2, 76%; (g) $LiAlH_4$, THF; (h) $NaIO_4$, H_2O; (i) Na/NH_3, H_2O, THF, 45% from f; (j) 6 M HCl, 95%.

Scheme V



Scheme VI[a]



[a](a) 2-(3-aminopropylidene)-1,3-dithiane, MeOH; (b) $Pb(OAc)_4$, CH_3CN, then AcOH, 66%; (c) Et_3N, MsCl, CH_2Cl_2, 84%.

on the all-equatorial acyliminium ion half-chair appears to be counterbalanced exactly by the anti directing effect of the allylic benzyloxy group. Since the 8a-epimer **31** is itself of interest (the synthesis and biological activity of 1,8a-diepicastanospermine have not been reported), the diastereomers were separated chromatographically and carried on separately to the respective targets.

It was anticipated that introduction of the C-1 alcohol group could be carried out with good control of stereochemistry by direct conversion of the ketene dithioacetal group into a ketone, followed by hydride reduction from the less hindered face. Oxidative cleavage of simple ketene dithioacetals to ketones via ozonolysis has been reported by Corey[30] and by Ziegler,[31] and several other groups have carried out this transformation in simple systems with singlet oxygen.[32] For the oxidation of **30**, treatment with singlet oxygen (generated in CCl_4/CH_3OH, sodium lamp) gave an unstable ketone that could not be isolated without substantial decomposition.[33] As a result, all reduction studies were performed on crude reaction mixtures immediately following oxidation.

Lithium tri-*tert*-butoxyaluminum hydride reduction of crude **30** resulted in a 51% yield of a 5:1 mixture of C-1 epimers, favoring the undesired diastereomer. Likewise, treatment with sodium borohydride also produced primarily the incorrect epimer (3:1 ratio, 59% yield). However, L-Selectride gave exclusively the desired epimer **32** in 39% overall yield (Scheme VII). Similarly, the reduction of **31** gave **33** in 42% yield. Thin-layer chromatography of the singlet oxygen reaction indicated only two major products: the expected ketone and dithiocarbonate. By TLC, however, the reduction step resulted in several unidentified minor products (by UV and stain visualization), none of which corresponded to the diastereomeric reduction product. Attempts at ozonolysis of **30** followed by L-Selectride reduction gave a similar yield (34%) of **32**, and other more selective and less reactive reducing agents, such as LS-Selectride and potassium triphenylborohydride, also failed to improve on the overall 40% (two step) yield obtained with L-Selectride.

By having introduced the hydroxy group with the correct C-1 stereochemistry in **32** and **33**, albeit in modest yield, all that remained was to reduce each lactam carbonyl group to the corresponding amine and deprotect the alcohol groups. Treatment of **32** with lithium aluminum hydride in refluxing THF resulted

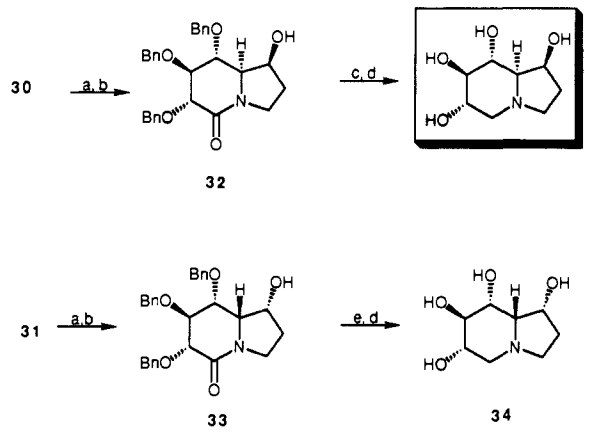
(30) Corey, E. J.; Pan, B.-C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816.

(31) Ziegler, F. E.; Fang, J.-M.; Tam, C. C. *Ibid.* 7174.

(32) (a) Ando, W. *J. Chem. Soc. Chem. Commun.* **1984**, 741. (b) Geller, G. G.; Foote, C. S.; Pechman, D. B. *Tetrahedron Lett.* **1983**, 673. (c) Adam, W.; Arias, L. A.; Schetzow, D. *Ibid.* **1982**, 2835.

(33) The instability of this α-amino ketone is probably due to rapid oxidation, either during workup or during the oxidation itself: cf. Yates, P.; MacLachlan, F. N. *J. Ind. Chem. Soc.* **1978**, *55*, 1116. Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. T.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. We thank a referee for alerting us to these references.

Scheme VII[a]



[a](a) $^1O_2$, CCl_4/MeOH; (b) L-Selectride, THF; (c) BH_3/DMS, THF, 67%; (d) H_2, 10% Pd/C, MeOH/HCl; (e) $LiAlH_4$, THF, 70%.

in extensive decomposition, whereas the 1,8a-diepicastanospermine precursor **33** gave the desired tertiary amine in 70% yield under the same conditions. The reduction of **32** could be accomplished cleanly, however, with borane–dimethyl sulfide complex to give the tertiary amine in 67% yield. Finally, catalytic hydrogenation of each isomer with 10% PdC in methanol/HCl gave (+)-castanospermine (**2**) in 82% yield and 1,8a-diepicastanospermine (**34**) in 79% yield.

In conclusion, the methodology described in this paper allows the preparation of either enantiomer of several highly oxidized hydroxylactams—and hence acyl iminium ion intermediates—from readily available ribonolactone or lyxose precursors. The synthesis of (−)-swainsonine takes advantage of not only this highly satisfactory solution to the "meso imide problem," but also an interesting and potentially general method of inverting the indolizidine ring junction stereochemistry via a novel multiple reduction of a vinylogous *N*-acylurethane. The applicability of similar methodology to polyhydroxylated six-membered-ring hydroxylactams has also been demonstrated in the synthesis of (+)-castanospermine and in the first synthesis of (+)-1,8a-diepicastanospermine, both of which have been prepared in a concise seven-step route from 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone.

Experimental Section

General Methods. Proton and carbon-13 nuclear magnetic resonance (NMR) spectra were measured on a General Electric QE-300 (300 MHz) spectrometer, or where specified on a General Electric GN-500 (500 MHz). Data are reported in ppm from internal tetramethylsilane for ^1H NMR and in ppm from the solvent in ^{13}C NMR, or from 3-(trimethylsilyl)propionic acid, sodium salt (TSP) when using D_2O as solvent, on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant. Infrared (IR) spectra were taken with a Perkin-Elmer Model 283 and a series 1600 FT-IR spectrophotometer and a Nicolet 5DXB FT-IR. Mass spectra (MS) were measured on a Finnegan 9610 spectrometer. High-resolution mass spectra (HRMS) were determined on a VG analytical 7070e spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 MC polarimeter or a JASCO DIP-360 and DIP-370 digital polarimeter. Data are reported in degrees. Combustion analyses were obtained from Galbraith (TN) and Desert Analytical (AZ). Melting points were taken on a Laboratory Devices Mel-Temp apparatus and are reported uncorrected.

Dry tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Unless otherwise noted methylene chloride and ethyl acetate were used without further drying or purification. All inert atmosphere operations were conducted under dry argon in flame-dried glassware. Unless otherwise noted, organic layers from extractive workups were dried over $MgSO_4$ and filtered, and the solvent was removed on a rotary evaporator. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated 60 F_{254} silica gel plates by using radial elution.[34]

Flash chromatography was performed on ICN 200–400-mesh silica gel. Small- and medium-scale purifications (20 mg–1.5 g) were performed by radial chromatography by using a Harrison Research chromatotron on plates of 1-, 2-, or 4-mm thickness made with Merck silica 60 PF_{254} containing gypsum.

***N*-Benzyl-(3*S*,4*R*)-3,4-dihydroxy-2,5-pyrrolidinedione.** By following the procedure by Van Rheenen,[35] to 21 mL of distilled water, 15 mL of acetone, and 4.86 g (41.4 mmol) of *N*-methylmorpholine *N*-oxide (Aldrich, 98%) were added 26.6 mL (0.417 mmol) of a stock solution of osmium textraoxide (1.57×10^{-2} M OsO_4 in *tert*-butyl alcohol) and then 6.00 g (32.1 mmol) of *N*-benzylmaleimide (**7**).[15] The yellow/brown solution was heated in an oil bath at 35 °C overnight and monitored by TLC. After 17 h the solution was cooled to room temperature and 7.24 g of Florisil (Fisher Scientific) and 1.89 g of $NaHSO_4$ (Alfa, ACS) were added, and the slurry was filtered through a sintered glass funnel. After the solution was concentrated on a rotary evaporator and dissolved in water, the aqueous solution was saturated with NaCl and extrracted five times with 35 mL of ethyl acetate. Purification by flash chromatography (silica gel, ether) gave 3.65 g (51%) of colorless crystals: mp 133–134 °C; IR (KBr) 3330 (m), 1780 (w), 1710 (s) cm^{-1}; NMR (Me_2SO-d_6) δ 7.30 (m, 5 H), 6.03 (d, 2 H, J = 5 Hz), 4.55 (s, 2 H), 4.42 (d, 2 H, J = 5 Hz) (Addition of D_2O to the NMR sample causes the doublet at δ 6.03 to disappear and the doublet at δ 4.42 to collapse to a singlet); MS (El, 70 eV) *m/e* (relative intensity) 221 (35.4), 203 (20.4), 91 (100); HRMS (El, 70 eV) calcd for $C_{11}H_{11}NO_4$ 221.0688, found 221.0705.

***N*-Benzyl-(3*S*,4*R*)-3,4-(cyclohexylidenedioxy)-2,5-pyrrolidinedione (8).** To a 25-mL round-bottomed flask with magnetic stirbar, Dean–Stark trap, and condenser were added 0.300 g (1.36 mmol) of *N*-benzyl-(3*S*,4*R*)-3,4-dihydroxy-2,5-pyrrolidinedione 12 mL of benzene (Mallinckrodt, anhydrous), and 2 mL of cyclohexanone (Aldrich, 99.8%). To this solution was then added 0.0026 g (0.0136 mmol) of *p*-toluenesulfonic acid (Aldrich, 99%). The reaction mixture was heated at reflux for 28 h. After a small amount of $NaHCO_3$ (s) was added, the solvent was concentrated on a rotary evaporator. To the residue was added 10 mL of water, and the solution was washed four times with 5 mL of Et_2O. The combined organic layers were dried, filtered, and concentrated on a rotary evaporator to give a yellow oil which was purified by flash chromatography (silica gel, 2:1 hexane/ether) to give 0.359 g (88%) of a colorless powder: IR (KBr) 1795 (w), 1730 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 4.76 (s, 2 H), 4.59 (s, 2 H), 1.65–1.20 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C), 134.5 (C), 128.9 (CH), 128.6 (CH), 128.2 (CH), 116.4 (C), 74.6 (CH), 42.5 (CH_2), 36.3 (CH_2), 35.0 (CH_2), 24.6 (CH_2), 23.6 (CH_2), 23.5 (CH_2); MS (El, 70 eV) *m/e* (relative intensity) 301 (29.7), 272 (19.1), 258 (98.1), 55 (100); HRMS calcd for $C_{12}H_{19}NO_4$ 301.1314, found 301.1294. An analytical sample was prepared by recrystallization from hexane/CH_2Cl_2 to give colorless needles, mp 95–96 °C. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 67.74; H, 6.36; N, 4.65. Found: C, 67.53; H, 6.47; N, 4.57.

(±)-*N*-Benzyl-(3*S*,4*R*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone ((±)-9β). To 7.06 g (23.4 mmol) of **8** in 200 mL of methanol, cooled to −4 °C, was added 8.87 g (23.4 mmol) of $NaBH_4$ (Alpha, 98%) with stirring. After 10 min the reaction was quenched with 150 mL of saturated aqueous $NaHCO_3$, added slowly while stirring. The cloudy solution was extracted with five 100-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried, filtered, and concentrated to give colorless crystals: yield 7.1 g (~100%); IR (KBr) 3340 (br m), 3040 (w), 2940 (s), 2860 (m), 1690 (s), 1430 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.90 (d, 1 H, J = 14.6 Hz), 4.89 (dd, 1 H, J = 11.2, 4.4 Hz), 4.68 (m, 2 H), 4.18 (d, 1 H, J = 14.4 Hz), 3.57 (d, 1 H, J = 11.2 Hz), 1.80–1.30 (m, 10 H) (Decoupling δ 3.57 causes the dd at δ 4.89 to collapse to a doublet. Decoupling δ 4.18 causes the doublet at δ 4.90 to collapse to a singlet. D_2O exchange causes the d at δ 3.57 to disappear and the dd at δ 4.89 to collapse to a doublet.); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 4.90 (dd, 1 H, J = 11.1, 4.7 Hz), 4.89 (d, 1 H, J = 14.3 Hz), 4.69 (m, 2 H), 4.19 (d, 1 H, 14.4 Hz), 3.52 (d, 1 H, J = 11.2 Hz), 1.80–1.30 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 135.9, 129.1, 128.9, 128.0, 114.9, 78.8, 77.4, 72.6, 43.4, 36.7, 35.7, 25.0, 24.1, 23.8; MS (El, 70 eV) *m/e* (relative intensity) 303 (12.8), 274 (6.1), 260 (44.3), 91 (100). An analytical sample was prepared by recrystallization from CH_2Cl_2/hexane to give colorless needles, mp 157–158 °C. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 66.92; H, 7.09; N, 4.52.

(±)-*N*-Benzyl-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone ((±)-9α). To 3.5 g (11.5 mmol) of (±)-9β in 250 mL of ethanol was added 25 mL of 4 M NaOH. After 20 min the ethanol was removed on a rotary evaporator, and the solution was saturated with NaCl and washed with four 50-mL portions of CH_2Cl_2, dried, filtered,

(34) Gadwood, R. C. *J. Chem. Ed.* **1985**, *62*, 820.

(35) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

and concentrated to give 3.5 g (~100%) of a colorless powder: IR ($CDCl_3$) 3350 (br m), 2940 (s), 2860 (w), 1700 (s), 1450 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 4.96 (br s, 1 H), 4.85 (d, 1 H, J = 14.9 Hz), 4.82 (d, 1 H, H = 5.7 Hz), 4.72 (br s, 1 H), 4.50 (d, 1 H, J = 5.7 Hz), 4.18 (d, 1 H, J = 14.9 Hz), 1.70–1.30 (m, 10 H) [Peaks at δ 4.96–4.72 varied with sample concentration [e.g., 4.97 (d, 1 H, J = 7.7 Hz), 4.88 (d, 1 H, J = 5.6 Hz), 4.82 (d, J = 14.9 Hz), 4.61 (d, 1 H (OH), J = 7.7 Hz)]]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 135.4, 129.0, 128.4, 128.0, 114.0, 84.6, 79.4, 76.9, 43.8, 37.0, 35.5, 25.0, 24.0, 23.9; MS (EI, 70 eV) m/e (relative intensity) 304 (4), 303 (28), 274 (12), 260 (58), 188 (12), 91 (100). An analytical sample was prepared by recrystallization from CH_2Cl_2/hexane to give 2.62 g (75%) colorless needles, mp 153–154 °C. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.00; H, 7.05; N, 4.54.

(±)-*N*-Benzyl-(3*S*,4*R*,5*R*)-3,4-(cyclohexylidenedioxy)-5-acetoxy-2-pyrrolidinone ((±)-10β) and (±)-*N*-Benzyl-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-acetoxy-2-pyrrolidinone ((±)-10α). The racemic hydroxylactam (±)-9β (0.015 g, 0.049 mmol) was dissolved in 1 mL of acetic anhydride and 10 drops of pyridine. After 6 h of stirring the solution was dissolved in 5 mL of water and washed with ethyl acetate. The organic layers were washed with 5% HCl and saturated aqueous $NaHCO_3$. After drying, filtering, and concentrating, 0.016 g (94%) of the acetate ±10β was isolated as a cloudy oil: NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.79 (d, 1 H, J = 5.3 Hz), 4.89 (d, 1 H, J = 14.6 Hz), 4.81 (dd, 1 H, J = 6.6, 5.3 Hz), 4.68 (d, 1 H, J = 6.7 Hz), 4.10 (d, 1 H, J = 14.6 Hz), 2.07 (s, 3 H), 1.80–1.30 (m, 10 H); IR (CCl_4) 3040 (w), 2940 (s), 2860 (m), 1730 (br s) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 345 (11), 316 (13), 302 (64), 91 (100); HRMS (EI, 35 eV), calcd for $C_{19}H_{23}NO_5$ 345.1576, found 345.1586. Likewise ±10α was obtained in 99% yield from ±9α as an oil: NMR ($CDCl_3$) δ 7.28 (m, 5 H), 5.97 (s, 1 H), 4.86 (d, 1 H, J = 5.5 Hz), 4.72 (d, 1 H, J = 14.8 Hz), 4.49 (d, 1 H, J = 5,6 Hz), 4.24 (d, 1 H, J = 14.8 Hz), 1.91 (s, 3 H), 1.70–1.20 (m, 10 H); IR (neat) 2937 (m), 2862 (w), 1746 (m), 1725 (s) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 345 (4), 230 (21), 188 (42), 91 (100); HRMS (EI, 35 eV) calcd for $C_{19}H_{23}NO_5$ 345.1576, found 345.1563.

General Reduction Procedure. Reduction of 8 with $LiAlH_4$ and (*S*)-2-(2,6-Xylidinomethyl)pyrrolidine. By following the procedure of Mukaiyama,[18] to a 10-mL round-bottomed flask equipped with magnetic stirbar were added 16 mg (0.415 mmol) of $LiAlH_4$ (weighed out in a glove bag) and 2 mL of Et_2O. To this suspension was added (*S*)-2-(2,6-xylidinomethyl)pyrrolidine (102 mg, 0.498 mmol) in 0.8 mL of Et_2O via a cannula at room temperature. The flask and cannula were rinsed with 0.4 mL of Et_2O, and the resulting white cloudy solution was stirred for 1–1.5 h. The imide **8** was finely pulverized to facilitate solubility in Et_2O, and 50 mg (0.166 mmol) in 2 mL of Et_2O was then added to the chiral reducing agent at −109 °C (liquid N_2, THF bath), and flask and cannula were rinsed with another 2 mL of Et_2O. Upon addition the reaction solution turned a deep pink/red color. The reaction mixture was monitored by TLC. Water (2 mL) was added after 6 h at −78 °C, and the reaction was warmed to room temperature. Note: quenching with water gives the thermodynamic epimer 9α. The kinetic hydroxylactam 9β could be obtained by quenching with 10% acetic acid in THF. The layers were separated, and the aqueous phase was washed with two 5-mL portions of Et_2O. The organic phases were washed with four 2.5-mL aliquots of 5% HCl and one 2.5-mL portion of saturated aqueous $NaHCO_3$. Drying, filtering, and concentrating gave **9b** as a white powder; 39.8 mg (79%) 56% ee (see below).

Enantiomeric Excess Determination of 9b Obtained by Reduction. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (Aldrich) was converted to the acid chloride by standard procedure.[17] The reduced imide 9α (29.0 mg, 0.0956 mmol), obtained by the reduction of **8** using $LiAlH_4$ and (*S*)-2-(2,6-xylidinomethyl)pyrrolidine at −109 °C, was added to 36.0 mg (0.143 mmol) of the MTPA-Cl and 1 mL of dry pyridine in a 5-mL round-bottomed flask and stirred for 5 h. In this case equilibration to the thermodynamic product, prior to the ester synthesis, was not necessary. However, if the kinetic product, or a mixture of epimers, was isolated from the reduction, epimerization was necessary in order to give a clean product for NMR analysis. Addition of 10 mL of Et_2O, extraction with 3 × 5 mL of 5% HCl and 5 mL of saturated $NaHCO_3$, drying, filtering, and concentrating gave an oil: 49.6 mg, 97%. The sample was analyzed by 500 MHz NMR. The protons on the five-membered ring were split into two pairs, one for each diastereomer: NMR ($CDCl_3$) δ 7.53–7.00 (m, 10 H), 6.00 (s, 0.22 H), 5.98 (s, 0.78 H), 5.00 (d, 0.78 H, 14.3 Hz), 4.97 (d, 0.22 H, 13.6 Hz), 4.85 (d, 1 H, J = 5.9 Hz), 4.53 (d, 0.22 H, J = 5.6 Hz), 4.46 (d, 0.78 H, J = 5.6 Hz), 3.84 (d, 0.78 H, J = 14.8 Hz), 3.70 (d, 0.22 H, J = 14.7 Hz), 3.51 (s, 0.66 H), 3.50 (s, 2.34 H), 1.6–1.2 (m, 10 H); 56% ee based on the integration of the doublets at 4.46, and 4.38, 3.76 and 3.62. Comparison of the NMR with the Mosher ester prepared from hydroxylactam (−)-9α (vide infra) indicates that the selectivity favors (+)-9α.

2,3-*O*-Cyclohexylidene-D-ribonolactone 12. In a flame-dried round-bottomed flask with a magnetic stirbar under Ar gas was placed 10.0 g (67.5 mmol) of D-ribonolactone (U.S. Biochemical), 200 mL of THF, 12.27 g (109 mmol) of 1-methoxycyclohexene[36] and 0.373 mL (0.575 g, 4.05 mmol) BF_3/OEt_2 (freshly distilled from CaH_2). After 30 min all the ribonolactone had dissolved. The reaction was stirred at room temperature and quenched with 3 mL of Et_3N after 7 h. Purification by flash chromatography (silica gel, 2% to 5% THF/CH_2Cl_2) gave 10.3 g (67%) as a colorless solid: mp 129–130 °C (lit.[19] mp 128–129 °C); $[\alpha]^{28}_D$ −62.2, $[\alpha]^{28}_{577}$ −57.1, $[\alpha]^{28}_{546}$ −64.4, $[\alpha]^{28}_{435}$ −122.1, $[\alpha]^{28}_{405}$ −148.7 (*c* 1.045 EtOH), lit.,[19] $[\alpha]_D$ −54.6 (*c* neat). ^{1}NMR data was in agreement with the literature.

Acetate of 2,3-*O*-Cyclohexylidene-D-ribonolactone, 13. To 6 mL of CH_2Cl_2 was added 3.00 g (13.1 mmol) **12** and 3.19 mL (3.12 g, 39.4 mmol) of pyridine. After several minutes of stirring the solution became homogeneous and 1.86 mL (2.01 g, 19.7 mmol) of acetic anhydride was added. The solution was stirred overnight and then washed with 5% HCl and saturated $NaHCO_3$, dried, filtered, and concentrated to give a colorless powder: 3.29 g (93%); mp 124.5–125 °C; $[\alpha]^{28}_D$ −37.0, $[\alpha]^{28}_{577}$ −30.1, $[\alpha]^{28}_{546}$ −34.2, $[\alpha]^{28}_{435}$ −69.3, $[\alpha]^{28}_{405}$ −86.5 (*c* 1.02, EtOH); ^1H NMR ($CDCl_3$) δ 4.79 (d, 1 H, J = 5.5 Hz), 4.78 (d, 1 H, J = 2.4 Hz), 4.39 (dd, 1 H, J = 12.4, 2.8 Hz), 4.25 (dd, 1 H, J = 12.4, 2.4 Hz), 2.08 (s, 3 H), 1.75–1.30 (m, 10 H); IR ($CHCl_3$) 2950 (m), 1798 (s), 1755 (s), 1230 (s) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 270 (M^+, 5), 241 (7), 227 (32), 69 (15), 55 (100); HRMS (EI, 35 eV) calcd for $C_{13}H_{18}O_6$ 270.1103, found 270.1109.

***N*-Benzyl-(3*R*,4*S*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (+)-9α.** To 9 mL of methanol were added 1.00 g (3.70 mmol) of the protected ribonolactone **12** and 0.793 g (0.81 mL, 7.40 mmol) of benzylamine. The solution was heated at reflux for 6 h and the solvent removed on a rotary evaporator. The residue was dissolved in ethyl acetate and washed with 5% HCl and then with saturated $NaHCO_3$. The organic phase was dried, filtered, and concentrated to give 1.39 g of the crude product. NMR and IR confirm the absence of the acetate group: ^1H NMR δ 7.30 (m, 5 H), 5.14 (d, 1 H, J = 2.9 Hz), 4.69 (d, 1 H, J = 7.3 Hz), 4.51 (apparent t overlapping m at δ 4.49, 2 H, J = 5.8 Hz), 4.49 (m, 1 H), 4.40 (dd, 1 H, J = 9.2, 7.4 Hz), 3.85 (m, 1 H), 3.66 (m, 2 H), 2.38 (br t, 1 H, J = 5.9 Hz), 1.8–1.3 (m, 10 H); IR (neat) 3400 (br s), 1660 (s) cm^{-1}.

To the crude amide–diol (0.722 g, 2.15 mmol) in 45 mL of acetonitrile, at 0 °C, was added 1.05 g (2.37 mmol) of $Pb(OAc)_4$ in 13 mL of acetonitrile in 2-mL increments every 5 min and the progress of the reaction monitored by TLC. Upon complete addition the solution was stirred for 20 min. To the reaction were then added 2.16 g of $NaHCO_3$ and 0.100 g of K_2CO_3, and the solvent was removed on a rotary evaporator. The yellow solid was washed with ethyl acetate, filtered through silica gel, and concentrated. The crude product was purified by radial chromatography (2-mm plate, 5% THF/CH_2Cl_2) to give 0.566 g (87%) of (+)-9α as a colorless powder. An analytical sample was prepared by recrystallization from hexanes/CH_2Cl_2: mp 152–153 °C; $[\alpha]^{26}_D$ +85.2, $[\alpha]^{26}_{577}$ +89.2, $[\alpha]^{26}_{546}$ +104.0, $[\alpha]^{26}_{435}$ +197.0, $[\alpha]^{26}_{365}$ +357.2 (*c* 1.03, EtOH). Spectral data are identical with (±)-9α. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 7.13; N, 4.62. Found: C, 67.19; H, 6.95; N, 4.57.

***N*-Cyclohexyl-(3*R*,4*S*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (14).** To 0.200 g (0.74 mmol) of **13** in 1.5 mL of methanol was added 0.17 mL (0.147 g, 1.5 mmol) of benzylamine, and the solution was heated at 40 °C. After 5 h 10 mg of K_2CO_3 was added and the solution stirred for an additional 10 min. The solvent was removed on a rotary evaporator while warming and the residual oil dissolved in Et_2O, washed twice with 5% HCl and once with saturated $NaHCO_3$, dried, filtered, and concentrated. The crude product, in 15 mL of CH_3CN, was treated with 0.361 g (0.81 mmol) of $Pb(OAc)_4$ in 5 mL of CH_3CN as described for the preparation of (+)-9α. Addition of 0.74 g of $NaHCO_3$ and 0.030 g of K_2CO_3 and work up and purification as for (+)-9α afforded 0.098 g (45%) of **14** as a colorless oil/foam which crystallized upon standing. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexanes to give clear colorless rhomboids: mp 156.5–157 °C; $[\alpha]^{28}_D$ −55.7, $[\alpha]^{28}_{577}$ −57.1, $[\alpha]^{28}_{546}$ −61.7, $[\alpha]^{28}_{435}$ −103.2, $[\alpha]^{28}_{365}$ −117.5 (*c* 1.1, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (br d, 1 H, J = 7.4 Hz), 5.14 (br d, 1 H, J = 7.8 Hz), 4.87 (d, 1 H, J = 5.4 Hz), 4.48 (d, 1 H, J = 5.4 Hz), 3.74 (dddd (apparent tt), 1 H, J = 12.0, 12.0, 3.7, 3.7 Hz), 1.91 (br d, 1 H, J = 12.4 Hz), 1.82 (br d, 1 H, J = 13.3 Hz), 1.78 (br d, 1 H, J = 13.2 Hz), 1.70–1.30 (m, 15 H), 1.30 (apparent qt, 1 H, J = 13.0, 3.3 Hz), 1.15 (apparent qt, 1 H, J = 13.0, 3.4 Hz) (Position of d at δ 5.14 was dependent on concentration as was the multiplicity of d at δ 5.23 and apparent tt at δ 3.74); ^{13}C NMR (125

(36) Prepared by the method of Lindsay and Reese: Lindsay, D. G.; Reese, C. B. *Tetrahedron* **1965**, *21*, 1673.

MHz, $CDCl_3$) δ 172.3, 113.5, 83.8, 79.6, 77.4, 52.2, 37.1, 35.6, 31.7, 29.6, 25.8, 25.6, 25.4, 24.9, 23.9, 23.7; IR (thin film) 3321 (br w), 2934 (s), 2855 (m), 1675 (s), 1449 (m), 1116 (m), 1063 (m) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 295 (8), 266 (7), 252 (28), 180 (16), 99 (21), 98 (64), 83 (22), 81 (22), 55 (100); HRMS (EI, 35 eV) calcd for $C_{16}H_{25}NO_4$ 295.1783, found 295.1792. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.04; H, 8.54; N, 4.74. Found: C, 65.01; H, 8.63; N, 4.53.

***N*-(2*R*)-[2-Phenyl-1-(*tert*-butyldimethylsiloxy)ethyl]-(3*R*,4*S*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (15).** To 6 mL of methanol was added 1.00 g (3.70 mmol) of **13** and 1.11 g (4.44 mmol) of TBS-phenylglycinol.[37] The heterogeneous solution was stirred for 2 days during which time the ribonolactone dissolved. The reaction was heated at reflux for 2 h and then allowed to stir another 12 h at room temperature. To this solution was then added 1.02 g (7.40 mmol) of K_2CO_3 and 10 drops of water and stirred another 30 min. The methanol was removed on a rotary evaporator, the oil dissolved in ethyl acetate and the K_2CO_3 removed by filtration. The ethyl acetate was washed with 10% HCl, saturated $NaHCO_3$, dried, filtered, and concentrated to give 1.50 g (87%) of a yellow oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.86 (br d, 1 H, *J* = 7.6 Hz), 7.30 (m, 5 H), 5.01 (m, 1 H), 5.00 (br s, 1 H), 4.67 (d, 1 H, *J* = 7.3 Hz), 4.39 (dd, 1 H, *J* = 9.5, 7.4 Hz), 3.96 (dd, 1 H, *J* = 10.2, 3.7 Hz), 3.79 (dt, 2 H, *J* = 10.4, 3.5 Hz), 3.63 (dd, 1 H, *J* = 11.4, 5.5 Hz), 3.42 (m, 1 H), 1.80–1.30 (m, 10 H).

To the crude amide–diol 1.49 g (3.21 mmol) in 25 mL CH_3CN at −10 °C was added 0.100 g K_2CO_3 followed by 1.71 g (3.86 mmol) of $Pb(OAc)_4$ in 65 mL CH_3CN. Purification by radial chromatography (4-mm plate, 1% THF/CH_2Cl_2) gave 0.324 g (22%) of **15** as a colorless powder. Spectral data has been reported in the supplementary material of ref 9. Anal. Calcd for $C_{24}H_{37}NO_5Si$: C, 64.40; H, 8.33; N, 3.13. Found: C, 64.28; H, 8.32; N, 3.11.

***N*-(2*R*)-(2-Phenyl-1-hydroxyethyl)-(3*R*,4*S*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (16).** Under the same conditions as for the desilylation of **21α** (vide infra), **16** was isolated in 94% yield. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexane to give a colorless fluffy powder: mp 166–167 °C; $[\alpha]^{29}_D$ −19.0, $[\alpha]^{29}_{577}$ −18.1, $[\alpha]^{29}_{546}$ −18.4, $[\alpha]^{29}_{435}$ −26.0, $[\alpha]^{29}_{405}$ −28.9 (*c* 0.815, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.05 (d, 1 H, *J* = 5.4 Hz), 4.84 (d, 1 H, *J* = 5.6 Hz), 4.74 (dd, 1 H, *J* = 8.4, 3.8 Hz), 4.49 (d, 1 H, *J* = 5.6 Hz), 4.40 (m, 1 H), 4.36 (m, 1 H), 4.00 (m, 1 H), 3.80 (br s, 1 H), 1.8–1.3 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 136.1, 128.8, 128.2, 127.5, 113.9, 85.5, 78.7, 76.9, 62.5, 60.7, 36.7, 35.2, 24.8, 23.8, 23.6; IR (thin film) 3200 (br m), 2950 (m), 1683 (s), 1447 (m), 1070 (s) cm^{-1}; HRMS (CI, 50 eV) calcd for $C_{18}H_{26}NO_5$ (M^+ + 1) 334.1654, found 334.1655. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.72; H, 6.79; N, 4.16.

2,3-*O*-Cyclohexylidene-D-(−)-lyxose (18). According to the procedure described for the preparation of **12** (14.81 g, 98.6 mmol) of D-(−)-lyxose (U.S. Biochemical) was treated with 17.93 g (159.8 mmol) of 1-methoxycyclohexene and 0.546 mL (0.841 g, 5.92 mmol) of BF_3/OEt_2. Purification by flash column (silica gel, Et_2O) gave **18** as a colorless oil: 16.3 g (72%); $[\alpha]^{26}_D$ +10.9, $[\alpha]^{26}_{577}$ +16.5, $[\alpha]^{27}_{546}$ +18.2, $[\alpha]^{27}_{435}$ +22.7, $[\alpha]^{27}_{405}$ +25.8 (*c* 1.36, EtOH); ^1H NMR ($CDCl_3$) δ 5.43 (s, 1 H), 4.78 (dd, 1 H, *J* = 5.8, 3.8 Hz), 4.70 (br s, 1 H), 4.60 (d, 1 H, *J* = 5.9 Hz), 4.26 (m, 1 H), 3.90 (br m, 2 H), 2.75 (br s, 1 H), 1.8–1.3 (m, 10 H); IR (neat) 3370 (br s), 2937 (s), 2862 (m), 1105 (s), 1058 (s) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 230 (M^+, 6), 201 (8), 187 (37), 115 (6), 99 (16), 98 (10), 97 (16), 81 (16), 69 (24), 55 (100); HRMS (EI, 70 eV) calcd for $C_{11}H_{18}O_5$ 230.1154, found 230.1147.

2,3-*O*-Cyclohexylidene-D-(−)-lyxonolactone (19). According to the procedure of Morgenlie[38] 16.30 g (70.8 mmol) of **18** was placed in a 1-L round-bottomed flask equipped with a Dean–Stark trap and condenser (to remove any residual water in the Ag_2CO_3/Celite) along with 400 mL of benzene and 121.06 g (ca. 212.4 mmol) of Ag_2CO_3/Celite.[22] After 5 min the solution turned brown and upon heating at reflux the solution turned black. The reaction was monitored by TLC and more Ag_2CO_3/Celite added with time. The total amount of Ag_2CO_3/Celite used was 289.36 g (507.6 mmol), the total reflux time was 73.5 h. After cooling to room temperature the slurry was filtered through Celite with ethyl acetate. The solvent was removed on a rotary evaporator and the brown oil purified by flash chromatography (silica gel, 8% THF/CH_2Cl_2) to give a pale yellow oil which crystallized with time: yield 10.5 g (65%); ^1H NMR ($CDCl_3$) δ 4.89 (d, 2 H, *J* = 1.7 Hz), 4.62 (m, 1 H), 4.01 (m, 2 H), 2.75 (br s, 1 H), 1.75–1.30 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 173.7, 115.2, 79.3, 75.9, 75.7, 61.0, 36.2, 35.2, 24.6, 23.8, 23.6; IR (neat, taken before crystallization) 3700–3100 (m), 2940 (s), 2860 (m), 1790 (s); MS (EI, 70 eV) *m/e* (relative intensity) 228 (M^+, 8), 199 (12), 185 (53), 83 (36), 69 (16), 55 (100); HRMS (EI, 35 eV) calcd for $C_{11}H_{16}O_5$ 228.0998, found 228.0994. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexanes to give colorless needles which turned opaque upon exposure to vacuum: mp 62.5–63.5 °C; $[\alpha]^{28}_D$ +61.0, $[\alpha]^{28}_{577}$ +62.3, $[\alpha]^{28}_{546}$ +75.7, $[\alpha]^{28}_{435}$ +129.6, $[\alpha]^{28}_{405}$ +164.5 (*c* 1.04, CH_2Cl_2). Analytical samples showed consistently a 2.5–3% H_2O content (e.g., Anal. Calcd for $C_{11}H_{16}O_5$ C, 57.88; H, 7.06. Found C, 56.62; H, 7.20).

***N*-Benzyl-(3*S*,4*R*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone ((+)-9β) and *N*-Benzyl-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone ((−)-9α).** According to the procedure described for the preparation of (+)-**9α**, 0.440 g of **19** (1.93 mmol) in 20 mL of methanol was reacted with 0.32 mL (0.31 g, 2.89 mmol) of benzylamine to give a colorless oil (0.572 g (88%)) which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 7.05 (br t, 1 H, *J* = 5.7 Hz), 4.64 (d, 1 H, *J* = 7.9 Hz), 4.48 (apparent d, 2 H, *J* = 4.9 Hz), 4.06 (br m, 1 H), 3.77 (br m, 1 H), 3.67 (br m, 1 H), 3.18 (br m, 1 H), 2.80 (br m, 1 H), 1.80–1.30 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 138.0, 129.1, 127.95, 128.01, 111.0, 77.9, 75.9, 69.4, 65.0, 43.4, 36.6, 34.1, 25.3, 24.4, 23.9; IR (neat) 3700–3240 (s), 3040 (w), 2940 (s), 2860 (m), 1720 (s) cm^{-1}.

As described for the preparation of (+)-**9α** the crude amide–diol was treated with a stock solution of $Pb(OAc)_4$ (1.16 g, 2.62 mmol in 15 mL acetonitrile). Upon completion of the reaction 2.4 g of $NaHCO_3$ was added and the solvent removed on a rotary evaporator. The yellow solid was washed with ethyl acetate, filtered through silica gel, and concentrated. Purification by radial chromatography (silica gel, 5% THF/CH_2Cl_2) gave two fractions (+)-**9β** (higher R_f) (0.1225 g) and (−)-**9α** (0.476 g) for a combined yield of 0.598 g (83%). Analytical samples were prepared by recrystallization from CH_2Cl_2/hexane.

***N*-Benzyl-(3*S*,4*R*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone ((+)-9β):** Colorless needles; mp 157–158 °C; $[\alpha]^{22}_D$ +95.8, $[\alpha]^{23}_{578}$ +101.8, $[\alpha]^{24}_{546}$ +117.8, $[\alpha]^{24}_{435}$ +312.4, $[\alpha]^{24}_{365}$ +375.1 (*c* 1.020, EtOH); spectral data are identical with (±)-**9β**; HRMS (EI, 28 eV) calcd for $C_{17}H_{21}NO_4$ 303.1470, found 303.1456.

***N*-Benzyl-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone ((−)-9α):** Colorless needles; mp 153–154 °C; $[\alpha]^{26}_D$ −81.5, $[\alpha]^{27}_{578}$ −85.6, $[\alpha]^{27}_{546}$ −99.3, $[\alpha]^{27}_{435}$ −190.8, $[\alpha]^{24}_{365}$ −345.1 (*c* 1.015, EtOH); spectral data are identical to (±)-**9α**; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1470, found 303.1459. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 7.13; N, 4.62. Found: C, 67.45; H, 7.13; N, 4.50.

Preparation of the Mosher Ester of (−)-9α. The Mosher ester was prepared as described for **9α** in 87% yield: ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 5 H), 7.31 (m, 3 H), 7.18 (m, 2 H), 6.00 (s, 1 H), 4.97 (d, 1 H, *J* = 14.5 Hz), 4.85 (dd, 1 H, *J* = 5.5, 1.0 Hz), 4.53 (d, 1 H, *J* = 5.5 Hz), 3.70 (d, 1 H, *J* = 14.7 Hz), 3.50 (d, 1 H, *J* = 1.1 Hz), 1.70–1.30 (m, 10 H).

***N*-Cyclohexyl-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (20).** According to the procedure described for the preparation of **14**, 0.500 g (2.19 mmol) of **19** was converted to 0.328 g (51%) of **20**. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexanes to give clear colorless rhomboids: mp 156.5–157 °C; $[\alpha]^{27}_D$ +49.3, $[\alpha]^{27}_{577}$ +49.0, $[\alpha]^{27}_{546}$ +57.1, $[\alpha]^{27}_{435}$ +92.0, $[\alpha]^{27}_{365}$ +113.6 (*c* 0.95, CH_2Cl_2). Spectral data are identical with **14**. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.04; H, 8.54; N, 4.74. Found: C, 64.97; H, 8.48; N, 4.68.

***N*-(2*R*)-[2-Phenyl-1-(*tert*-butyldimethylsiloxy)ethyl]-(3*S*,4*R*,5*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (21β) and *N*-(2*R*)-[2-Phenyl-1-(*tert*-butyldimethylsiloxy)ethyl]-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (21α).** To 0.50 g (2.19 mmol) **19** in 6 mL of methanol was added 1.10 g (4.38 mmol) TBS-*D*-(−)-2-phenylglycinol and the solution stirred at room temperature for 2 days. The methanol was then removed and the oil dissolved in ethyl acetate and washed with 5% HCl, dried, filtered, and concentrated. Purification of the yellow oil by radial chromatography (4-mm plate, 10% THF/CH_2Cl_2) gave a pale yellow oil: 1.02 g (100%); ^1H NMR ($CDCl_3$) δ 7.67 (br d, 1 H, *J* = 8.3 Hz), 7.28 (m, 5 H), 5.05 (apparent m, 1 H), 4.62 (d, 1 H, *J* = 7.7 Hz), 4.46 (dd, 1 H, *J* = 7.7, 4.1 Hz), 4.08 (apparent q, 1 H, *J* = 4 Hz), 3.94 (dd, 1 H, *J* = 10.2, 3.7 Hz), 3.80 (m, 2 H), 3.65 (dd, 1 H, *J* = 11.3, 5.5 Hz), 2.80 (br s, 2 H), 1.90–1.40 (m, 10 H), 0.83 (s, 9 H), −0.07 (s, 3 H), −0.11 (s, 3 H).

The amide (0.98 g, 2.11 mmol) was treated with a $Pb(OAc)_4$ solution (1.12 g, 2.54 mmol in 15 mL CH_3CN) as described for **15**, with the exception that no K_2CO_3 was added. The crude oil was purified via radial chromatography (4-mm plate, CH_2Cl_2) to give two products **21β** (higher R_f) (0.0312 g) **21α** (0.188 g) and a mixture of the two (0.048 g) for a total yield of 0.267 g (28%).

21β. Pale yellow solid. Attempts at recrystallization resulted in desilylation. Further purification was not attempted: ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 2 H), 7.29 (m, 3 H), 5.31 (dd, 1 H, *J* = 11.2,

(37) See the supplementary material of ref 9.
(38) Morgenlie, S. *Acta Chem. Scand.* **1972**, *26*, 2518.

4.9 Hz), 4.95 (dd, 1 H, J = 9.8, 5.0 Hz), 4.71 (dd, 1 H, J = 6.2, 4.9 Hz), 4.65 (d, 1 H, J = 6.1 Hz), 4.53 (dd, 1 H, J = 10.7, 10.0 Hz), 4.03 (dd, 1 H, J = 10.8, 5.0 Hz), 3.62 (d, 1 H, J = 11.2 Hz), 1.70–1.30 (m, 10 H), 0.86 (s, 9 H), 0.056 (s, 3 H), 0.039 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 138.3, 128.8, 128.6, 128.2, 129.0, 114.6, 79.8, 73.1, 62.2, 59.2, 36.8, 35.9, 26.1, 25.98, 25.0, 24.1, 23.9, 18.4, -5.1, -5.2; IR ($CHCl_3$) 3600–3300 (w), 3005 (w), 2940 (m), 1705 (s) cm^{-1}; MS (CI, isobutane) m/e 448 (MH^+), 430 ($MH^+ - H_2O$); MS (EI, 70 eV) m/e (relative intensity) 390 (18), 302 (4), 270 (46), 177 (46), 75 (100); HRMS (EI, 28 eV) calcd for $C_{23}H_{34}NO_5Si$ (M = CH_3) 432.2206, found 432.2195.

21α. An analytical sample was recrystallized from hexane to give colorless crystals: mp 163–164 °C; $[\alpha]^{22}_D$ −33.5, $[\alpha]^{22}_{578}$ −34.3, $[\alpha]^{23}_{546}$ −40.1, $[\alpha]^{23}_{435}$ −81.0, $[\alpha]^{23}_{365}$ −156.2 (c 1.00, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (apparent d, 3 H, J = 4.4 Hz), 7.29 (m, 2 H), 5.38 (dd, 1 H, J = 5.4, 3.5 Hz), 5.26 (d, 1 H, J = 1.3 Hz), 5.22 (d, 1 H, J = 1.2 Hz), 4.90 (d, 1 H, J = 5.2 Hz), 4.52 (d, 1 H, J = 5.2 Hz), 4.24 (dd, 1 H, J = 11.6, 5.6 Hz), 4.05 (dd, 1 H, J = 11.6, 3.5 Hz), 1.65–1.30 (m, 10 H), 0.90 (s, 9 H), 0.14 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 136.2, 128.6, 127.6, 127.4, 113.6, 81.7, 78.0, 76.6, 64.1, 55.6, 37.7, 35.4, 25.8, 25.6, 24.8, 23.73, 23.66, 18.1, -5.6, -5.7; IR ($CHCl_3$) 3700–3200 (m), 3005 (m), 2950 (s), 1708 (s) cm^{-1}; MS (CI, isobutane) m/e 448 (MH^+), 430 ($MH^+ - H_2O$); MS (EI, 70 eV) m/e (relative intensity) 390 (31), 302 (5), 270 (10), 177 (41), 75 (100); HRMS (EI, 28 eV) calcd for $C_{23}H_{34}NO_5Si$ ($M - CH_3$) 432.2206, found 432.2212. Anal. Calcd for $C_{24}H_{37}NO_5Si$: C, 64.40; H, 8.33; N, 3.13. Found: C, 64.78; H, 8.26; N, 3.10.

***N*-(2*R*)-(2-Phenyl-1-hydroxyethyl)-(3*S*,4*R*,5*S*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (22).** Hydroxylactam **21α** (0.060 g, 0.134 mmol) was added to 0.500 mL of tetra-*n*-butylammonium fluoride (Aldrich, 1.0 M in THF, was azeotroped twice with benzene and the salt dissolved in 1.0 mL of freshly distilled THF). The reaction was quenched after 15 min with 10 mL of water and 5 mL of ethyl acetate. The aqueous phase was saturated with NaCl, the layers were separated, and the aqueous phase was washed twice with 5 mL of ethyl acetate. The combined organic phases were washed (5 × 5 mL 10% HCl), dried, filtered, and concentrated to give colorless crystals which were placed on a vacuum pump overnight: yield 0.0429 g (96%). Spectral data has been reported in the supplementary material of ref 9.

Synthesis of *N*-[4-(1,3-Dithian-2-ylidene)butyl]phthalimide. The ketene dithioacetal was prepared from δ-valerolactone as previously described[39] with the following modifications. All glassware used in the workup was base washed. The reaction was quenched by slow addition of saturated aqueous sodium carbonate. The ether suspension was dried over K_2CO_3. *Note*: It is imperative that all glassware used in the workup be base washed and whenever the solution was concentrated there be a large excess of potassium carbonate present to prevent cyclization of the alcohol.

The ketene dithioacetal was transfered with a pipet to a base-washed, flame-dried, 500-mL, round-bottomed flask containing 33.8 g (129 mmol) of triphenylphosphine (Aldrich, 98%), 14.7 g (100 mmol) of phthalimide (Aldrich), and 100 mL of dry THF. To this solution was added dropwise 20.3 mL (129 mmol, 22.47 g) of diethyl azodicarboxylate in 48 mL of dry THF by use of an addition funnel. The solution was stirred overnight at room temperature. To the brown/black solution was added silica gel and the solvent removed on a rotary evaporator. The silica gel was rinsed once with methylene chloride and the solvent removed again. The solvent-free silica gel was then applied to a packed column (silica gel, 3:1 hexane/ether) and the product isolated as a hydroscopic white granular solid: 21.1 g (66%); mp 72–75 °C (Further purification was not attempted); ^{1}H NMR (300 MHz) δ 7.85 (m, 2 H), 7.70 (m, 2 H), 5.94 (t, 1 H, J = 7.3 Hz), 3.70 (apparent t, 2 H, J = 7.3 Hz), 2.84 (m, 4 H), 2.29 (AB q, 2 H, υ_A = 2.31, υ_B = 2.26, J_{AB} = 7.3 Hz), 2.14 (m, 2 H), 1.79 (apparent m, 2 H); IR (neat) 2935 (w), 1709 (s), 1396 (s), 720 (s) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 321 (0.31), 320 (0.57), 319 (M^+, 3.2), 230 (7.0), 172 (12.7), 160 (54.7), 145 (95.9), 133 (53.9), 119 (85.3), 77 (48.0), 71 (100); HRMS (EI, 70 eV) calcd for $C_{16}H_{17}NO_2S_2$ 319.07011, found 319.0696.

2-[4-Aminobutylidene]-1,3-dithiane. According to the procedure of Mitsunobu,[40] the phthalimide ketene dithioacetal (24.0 g, 75.1 mmol) was combined with 14.6 mL (15.03 g, 300 mmol) of hydrazine hydrate and 150 mL of benzene and heated at reflux. After the solution was heated for 2 h TLC showed the presence of a large amount of starting material so another 14 mL of hydrazine hydrate was added and the solution refluxed until no starting material was present (1 h). Frequently more hydrazine hydrate had to be added to complete the reaction. The solution was filtered through Celite and the solvent removed, yield 13.9 g (98%). The yellow oil was used immediately without further purification: ^{1}H NMR (300 MHz) δ 5.94 (t, 1 H, J = 7.4 Hz), 2.85 (apparent m, 4 H), 2.69 (t, 2 H, J = 7.0 Hz), 2.26 (AB q, 2 H, υ_A = 2.29, υ_B = 2.25, J_{AB} = 7.4 Hz), 2.16 (m, 2 H), 1.52 (quintet, 2 H, J = 7.2 Hz); IR (neat) 3300 (br m), 2925 (s), 2860 (s), 1670 (m), 1590 (m), 1420 (m), 1280 (m), 685 (s) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 189 (M^+, 4.2), 172 (15.9), 145 (14.2), 115 (31.8), 98 (51.6), 82 (67.2), 71 (base).

***N*-[4-(1,3-Dithian-2-ylidene)butyl]-(3*S*,4*R*)-3,4-(cyclohexylidenedioxy)-5-hydroxy-2-pyrrolidinone (23).** In a 100-mL round-bottomed flask were placed 2.00 g (8.8 mmol) of cyclohexylidenelyxonolactone, 20 mL of methanol, and 2.49 g (13.1 mmol) of 2-[4-aminobutylidene]-1,3-dithiane. The lyxonolactone dissolved after about 5 min, and the reaction was stirred overnight at room temperature. The solvent was removed under vacuum and the crude material carried on to the next step without purification.

In a flame-dried 500-mL round-bottomed flask was placed the diol, 3.03 g (21.9 mmol) of potasslum carbonate, and 150 mL of CH_3CN. To the cooled solution (0 °C) was then added a solution of 4.27 g of $Pb(OAc)_4$ (9.6 mmol, in 60 mL of CH_3CN, kept dark) in 10-mL increments. After complete addition the reaction was allowed to stir for 30 min and 8.8 g of sodium bicarbonate was added and the solvent removed on a rotary evaporator. The crude reaction mixture was taken up in ethyl acetate and filtered through silica gel and purified by flash column (silica gel, 5% THF/CH_2Cl_2), yield 2.14 g (63%), pale yellow oily solid. Due to rapid decomposition an analytical sample could not be prepared. Yields of the following step were generally much better when the hydroxylactam was used immediately following chromatography: ^{1}H NMR (500 MHz) δ 5.91 (t, 1 H, J = 7.3 Hz), 5.12 (d, 1 H, J = 8.1 Hz), 4.89 (d, 1 H, J = 8.2 Hz), 4.81 (d, 1 H, J = 5.7 Hz), 4.52 (d, 1 H, J = 5.7 Hz), 3.45 (dt, 1 H, J = 13.8, 7.7 Hz), 3.18 (dt, 1 H, J = 13.8, 8 Hz), 2.86 (m, 4 H), 2.23 (m, 2 H), 2.15 (m, 2 H), 1.7–1.3 (m, 12 H); ^{13}C (125 MHz) δ 172.1, 132.5, 126.9, 113.7, 85.0, 79.1, 76.6, 39.8, 36.7, 35.2, 30.2, 29.5, 26.6, 26.3, 25.1, 24.8, 23.8, 23.6; IR (KBr) 3200 (br s), 2935 (s), 2861 (m), 1684 (s), 1450 (m), 1220 (s), 790 (m) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 385 (M^+, 2.0), 171 (21.4), 119 (base), 97 (31.9); HRMS (EI, 26 eV) calcd for $C_{18}H_{27}NO_4S_2$ 385.1381, found 385,1362.

(1*S*,2*R*)-1,2-(Cyclohexylidenedioxy)-8-[2-(1,3-dithianylidene)]indolizidin-3-one (24). The hydroxylactam (6.13 g, 15.9 mmol) was placed in a 100-mL flame-dried round-bottomed flask with 4.4 mL of triethylamine (31.8 mmol, freshly distilled from CaH_2) and 15 mL of CH_2Cl_2. The solution was cooled to 0 °C and 1.5 mL of methanesulfonyl chloride (19.1 mmol, distilled from CaH_2) was added dropwise with a syringe. The solution was warmed to room temperature, and after 30 min 8 mL of dry acetonitrile (distilled from CaH_2) was added and the cloudy orange solution was stirred overnight at room temperature. The solvent was removed under vacuum and the mixture purified by flash column (silica gel, 1% THF/CH_2Cl_2) to give a pale yellow foam: yield 3.5 g (60%); $[\alpha]^{29}_D$ 156.3, $[\alpha]^{29}_{577}$ 171.1, $[\alpha]^{29}_{546}$ 197.2, $[\alpha]^{29}_{435}$ 354.0, $[\alpha]^{29}_{405}$ 423.3 (c 1.015, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 4.62 (d, 1 H, J = 6.7 Hz), 4.55 (d overlapping d at δ 4.53, 1 H, J = 8.9 Hz), 4.53 (d, 1 H, J = 6.7 Hz), 4.12 (ddd, 1 H, J = 13.6, 10.5, 6.3 Hz), 3.02 (m, 2 H), 2.92 (m, 4 H), 2.18 (quintet, 2 H, J = 6.2 Hz), 2.01 (m, 1 H), 1.74–1.55 (m, 10 H), 1.45 (m, 1 H), 1.30 (m, 1 H); ^{13}C (125 MHz) δ 171.0, 135.7, 124.3, 113.4, 77.8, 76.9, 64.8, 36.3, 36.0, 35.1, 29.41, 29.35, 25.0, 24.9, 24.3, 23.8, 23.6, 21.4; IR (KBr) 2940 (s), 2860 (m), 1700 (br s), 1435 (s), 1210 (s), 920 (m), 730 (m) cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 367 (M^+, 0.2), 342 (3.2), 269 (1.5), 136 (23.9), 55 (base); HRMS (EI, 22 eV) calcd for $C_{18}H_{25}NO_3S_2$ 367.1276, found 367.1255.

(1*S*,2*R*)-1,2-(Cyclohexylidenedioxy)-8-(ethoxycarbonyl)indolizid-8-en-3-one (25). The freshly prepared ketene dithioacetal **24** (3.5 g, 9.5 mmol) was added dropwise in 15 mL of THF to a solution of 8.475 g (47.6 mmol) of recrystallized *N*-bromosuccinimide, 45 mL of ethanol, and 45 mL of acetonitrile in a 250-mL round-bottomed flask. The reaction solution turned dark orange immediately upon addition and lightened gradually. After 15 min of stirring 45 mL of H_2O was added and the solution stirred for 2 h. The organic solvent was removed on a rotary evaporator, the aqueous layer diluted with 50 mL of H_2O, washed with CH_2Cl_2, dried, filtered, and concentrated.

The crude product was transferred to a flame-dried 250-mL round-bottomed flask under argon in 100 mL THF. To this solution was added 5.9 mL (6.00 g, 39.4 mmol) of 1,8-diazabicyclo[5,4,0]undec-7-ene and the cloudy brown solution heated at reflux for 1 h. Upon cooling to room temperature the solution was filtered through silica gel with THF and concentrated on a rotary evaporator. Purification by flash column gave a colorless pale yellow viscous oil: yield 2.17 g (71%); $[\alpha]^{26}_D$ −169.5, $[\alpha]^{26}_{577}$ −175.8, $[\alpha]^{26}_{546}$ −203.9, $[\alpha]^{26}_{435}$ −405.6, $[\alpha]^{26}_{405}$ −525.6 (c 0.955, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 5.75 (d, 1 H, J = 6.5 Hz), 4.69 (d, 1 H, J = 6.5 Hz), 4.26 (m, 2 H), 3.67 (ddd, 1 H, J = 16.4, 6.3, 4.6 Hz),

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(40) Mitsunobu, O. *Synthesis*, **1981**, 1.

3.44 (ddd, 1 H, J = 13.2, 8.8, 4.0 Hz), 2.49 (m, 2 H), 1.90 (m, 1 H), 1.75 (m, 2 H), 1.62 (m, 8 H), 1.47 (m, 1 H), 1.33 (t, 3 H, J = 7.1 Hz); ^{13}C (125 MHz, DEPT assignments) δ 171.1 (C), 166.1 (C), 145.9 (C), 114.3 (C), 107.5 (C), 75.0 (CH), 73.2 (CH), 60.5 (CH_2), 39.1 (CH_2), 36.3 (CH_2), 34.8 (CH_2), 24.9 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.5 (CH_2), 19.4 (CH_2), 14.2 (CH_3); IR (neat) 2940 (s), 2860 (m), 1740 (s), 1690 (s), 1645 (s), 1260 (s), 1110 (s) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 321 (M^+, 31.5), 292 (18.9), 276 (base), 224 (44.1), 207 (25.9), 178 (69.6), 134 (64.3); HRMS (EI, 60 eV) calcd for $C_{17}H_{23}NO_5$ 321.1576, found 321.1563.

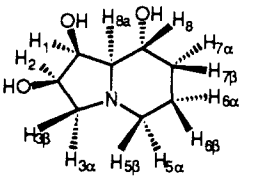
(1*S*,2*R*,8*R*,8a*R*)-1,2-(Cyclohexylidenedioxy)-8-(ethoxycarbonyl)-indolizidine (26). In a flame-dried 25-mL round-bottomed flask was placed 1.005 g (3.13 mmol) of the unsaturated ester–lactam **25** in 2 mL of CH_2Cl_2. The solution was cooled to 0 °C and 5.63 mL (5.63 mmol) of triethyloxonium tetrafluoroborate (Aldrich, 1 M solution in CH_2Cl_2) was added via syringe. Upon addition the solution turned to a dark orange color. The solution was allowed to warm to room temperature and stirred overnight (10–12 h). The solvent was removed under vacuum, the brown oil was dissolved in 3 mL of methanol (distilled from CaH_2 and stored over 3-Å sieves overnight), and 0.630 g (10.00 mmol) of sodium cyanoborohydride was added dropwise via a cannula in 3 mL of dry methanol at 0 °C. The cannula and flask were rinsed with 2 mL of methanol and the reaction warmed to room temperature and stirred for 1 h. The solvent was removed on a rotary evaporator, the residual salts were washed with CH_2Cl_2, and the organic solution was filtered and concentrated. Purification by radial chromatography (4-mm plate, silica gel, 5 to 10 to 20 to 30% EtOAc/CH_2Cl_2) gave 0.365 g of starting material and 0.533 g of the product as a viscous pale yellow oil (55%, 86% based on recovered starting material): $[\alpha]^{24}_D$ −170.9, $[\alpha]^{24}_{577}$ −172.1, $[\alpha]^{24}_{546}$ −193.5, $[\alpha]^{24}_{435}$ −302.3, $[\alpha]^{24}_{405}$ −354.8 (*c* 0.61, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 4.67 (dd, 1 H, J = 6.2, 4.5 Hz), 4.56 (dd, 1 H, J = 6.2, 4.2 Hz), 4.16 (q, 2 H, J = 7.1 Hz), 3.12 (d, 1 H, J = 10.7 Hz), 3.06 (br dt, 1 H, J = 10.8, 2.8 Hz), 2.67 (ddd, 1 H, J = 13.2, 9.5, 3.9 Hz), 2.12 (m, 1 H), 2.08 (dd, 1 H, J = 10.8, 4.2 Hz), 1.90 (m, 2 H), 1.72 (m, 2 H), 1.66 (m, 2 H), 1.60 (m, 2 H), 1.52 (m, 4 H), 1.36 (m, 2 H), 1.33 (m, 1 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C (125 MHz) δ 174.3, 111.6, 79.4, 77.5, 68.2, 60.1, 59.95, 51.9, 41.8, 35.5, 34.3, 28.3, 25.2, 24.7, 24.1, 23.8, 14.2; HETCOR and COSY spectra (500 MHz) are consistent with the assigned structure;[41] IR (thin film) 2937 (s), 2860 (m), 2790 (w), 1730 (s), 1140 (m) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 309 (M^+, 3.3), 280 (2), 264 (5), 194 (66.2), 120 (58.5), 96 (base), 82 (52.3); HRMS (EI, 70 eV) calcd for $C_{17}H_{27}NO_4$ 309.1940, found 309.1923.

1,2-(Cyclohexylidenedioxy)-8-(ethoxycarbonyl)-8-hydroxyindolizidine. According to the procedure of Wasserman and Lipshutz,[27] the ester (0.303, 0.979 mmol) in 1 mL of THF was added dropwise to a freshly prepared solution of LDA (prepared from 0.274 mL, 1.96 mmol diisopropyl amine and 0.75 mL (1.96 mmol) of a 2.6 M solution of *n*-BuLi in hexane) in 1 mL of THF at −78 °C. The cannula was rinsed twice with 0.5 mL of THF and after 10 min the black reaction solution was warmed to 0 °C and stirred for 2 h. Oxygen was then bubbled through the solution with a needle for 15 min at −78 °C and 15 min at room temperature. The solvent was then removed on a rotary evaporator and the orange residue diluted with 25% Na_2SO_3, saturated with NaCl, and washed with ethyl acetate and methylene chloride. The combined organic phases were dried over K_2CO_3, filtered, and concentrated. Purification by radial chromatography (2-mm plate, 7.5% THF/CH_2Cl_2) gave 0.230 g of the α-hydroxy ester as an inseparable mixture of diasteriomers (a yellow oil) and 0.013 g of recovered starting material, 72% (76% based on recovered starting material). Spectral data are for the mixture of diasteriomers, the NMR peaks of the major diasteriomer are reported: ^{1}H NMR (500 MHz) δ 4.69 (dd, 1 H, J = 6.2, 4.4 Hz), 4.54 (dd, J = 6.2, 4.5 Hz), 4.47 (dq, 1 H, J = 10.7, 7.1 Hz), 4.08 (dq, 1 H, J = 10.7, 7.2 Hz), 3.30 (d, 1 H, J = 10.8 Hz), 3.15 (br dd, 1 H, J = 10.7, 2.6 Hz), 2.22 (qt, 1 H, J = 13.5, 4.5 Hz), 1.96 (dd, 1 H, J = 10.8, 4.5 Hz), 1.91 (br d, 1 H, J = 13 Hz), 1.87–1.77 (m, 2 H), 1.70–1.34 (m, 13 H), 1.32 (t, 3 H, J = 7.1 Hz); peaks of the minor diastereomer can be seen at δ 4.74 (dd), 4.59 (dd), 4.26 (m), 3.22 (d); ^{13}C (125 MHz) δ 175.2, 111.6, 77.3, 76.7, 75.2, 71.5, 61.4, 60.3, 52.5, 39.6, 34.8, 33.1, 25.0, 23.9, 23.4, 22.9, 14.1; IR (neat) 3487 (br w), 2936 (s), 2862 (m), 2789 (w), 1715 (s) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 325 (0.4), 296 (0.5), 252 (0.6), 223 (1.8), 210 (2.8), 196 (3.3), 192 (6.6), 164 (1.8), 83 (100); HRMS (EI, 65 eV) calcd for $C_{17}H_{27}NO_5$ 325.1889, found 325.1873.

(1*S*,2*R*,8*R*,8*S*,8a*R*)-1,2-(Cyclohexylidenedioxy)-8-(hydroxymethyl)-8-hydroxyindolizidine. To 0.057 g (1.50 mmol) of $LiAlH_4$ in 1 mL of THF at 0 °C was added 0.247 g (0.759 mmol) of the α-hydroxy ester in 2 mL of THF dropwise via a cannula. The cannula and flask were rinsed twice with 1 mL of THF. After 10 min the solution was warmed to room temperature and stirred for 1 h. After cooling back to 0 °C the reaction was quenched with saturated NaCl. The layers were separated, and the aqueous phase was washed with THF and then CH_2Cl_2. The organic layers were dried over K_2CO_3, filtered, and concentrated to give 0.226 g of the crude diol as a colorless viscous oil. This product was carried on without further purification. An analytical sample was prepared by radial chromatography purification (1-mm plate, 40% EtOAc/CH_2Cl_2 then 10% MeOH/CH_2Cl_2): ^{1}H NMR (500 MHz) δ 4.73 (dd, 1 H, J = 6.2, 4.0 Hz), 4.65 (apparent t, 1 H, J = 6.2 Hz), 4.30 (br m overlapping d at δ 4.28, 1 H), 4.28 (d, 1 H, J = 11.5 Hz), 3.75 (br m, 1 H), 3.22 (d overlapping d at δ 3.19, 1 H, J = ~10 Hz), 3.19 (d, 1 H, J = ~10 Hz), 3.09 (d, 1 H, J = 10.9 Hz), 2.06 (dd, 1 H, J = 10.9, 5.0 Hz), 1.78 (m, 4 H), 1.68 (m, 2 H), 1.60–1.48 (m, 8 H), 1.40 (m, 2 H); Peaks of the minor diasteriomer can be seen at δ 4.85 (dd), 4.59 (dd), and 2.00 (dd); ^{13}C (125 MHz) (DEPT results) δ 111.8 (C), 78.4 (CH), 77.3 (CH), 75.1 (CH), 70.1 (C), 64.2 (CH_2), 60.1 (CH_2), 53.4 (CH_2), 38.6 (CH_2), 35.1 (CH_2), 33.6 (CH_2), 24.9 (CH_2), 24.0 (CH_2), 23.6 (CH_2), 22.1 (CH_2); IR (neat) 3440 (br s), 2936 (s), 2861 (m), 2787 (m) cm^{-1}; MS (EI, 22 eV) *m/e* (relative intensity) 283 (3.7), 281 (1.0), 266 (0.9), 252 (1.8), 196 (24.9), 168 (36.0), 150 (61.2), 112 (100); HRMS (EI, 35 eV) calcd for $C_{15}H_{25}NO_4$ 283.1783, found 283.1781.

(1*S*,2*R*,8*R*,8a*R*)-1,2-(Cyclohexylidenedioxy)-8-hydroxyindolizidine (28). The crude diol (0.0506 g, 0.178 mmol) was placed in a 5-mL pear-shaped flask with 0.6 mL of H_2O and 0.1 mL of methanol, and the turbid solution was stirred at room temperature. Sodium periodate (0.0458 g, 0.214 mmol) was added in two portions, 10 min between additions. The reaction was stirred for 30 min after the final addition of sodium periodate and was then diluted with 6 mL of THF and 0.2 mL of methanol. The heterogeneous solution was added via a syringe pump dropwise to 0.665 g (28.9 mmol) of sodium in 20 mL liquid ammonia and 8 mL THF at −78 °C. After the addition the reaction was stirred for 30 min at −78 °C and quenched with 1 mL of water. Upon evaporation of the ammonia the aqueous phase was saturated with NaCl, the layers were separated, and the aqueous phase was washed repeatedly with THF. The combined organic layers were dried over K_2CO_3, filtered, and concentrated. Purification by radial chromatography (1-mm plate, prewashed with 5% THF/CH_2Cl_2 containing 0.5% Et_3N and eluted with 5% THF/CH_2Cl_2) gave 0.0202 g (45% from the α-hydroxy ester) of the product as a colorless powder: ^{1}H NMR (500 MHz) δ 4.70 (dd, 1 H, J = 6.1, 4.7 Hz), 4.61 (dd, 1 H, J = 6.2, 4.2 Hz), 3.85 (br m, 1 H), 3.16 (d, 1 H, J = 10.7 Hz), 2.99 (br dt, 1 H, J = 10.5, 2.9 Hz), 2.12 (dd, 1 H, J = 10.7, 4.2 Hz), 2.05 (apparent dq, 1 H, J = 12.2, 3.6 Hz), 1.96 (br s, 1 H), 1.85 (td, 1 H, J = 10.7, 4.0 Hz), 1.80–1.30 (m, 13 H), 1.24 (m, 1 H); ^{1}H NMR (500 MHz) of a more concentrated sample shows the following differences 3.85 (ddd, 1 H, J = 12.2, 7.7, 4.5 Hz) and no brand singlet at δ 1.96, ^{13}C (125 Mhz) δ 112.0, 78.7, 77.8, 73.9, 67.6, 59.9, 51.6, 35.5, 34.3, 32.8, 25.2, 24.1, 24.0, 23.8; IR (thin film) 3250 (br m), 2935 (s), 2857 (m), 2790 (m), 801 (s) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 254 (0.9), 253 (M^+, 7.2), 210 (6.6), 196 (4.6), 138 (100), 120 (28.2), 113 (53.4), 96 (40.7), 71 (36.6), 55 (60.3); HRMS (EI, 70 eV) calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.1694. An analytical sample was prepared by recrystallization from CH_2Cl_2/CCl_4/hexane to give colorless needles: mp 133.5–134.5; $[\alpha]^{27}_D$ −75.3, $[\alpha]^{27}_{577}$ −80.0, $[\alpha]^{27}_{546}$ −87.0, $[\alpha]^{27}_{435}$ −142.8, $[\alpha]^{27}_{405}$ −162.0 (*c* 0.82, CH_2Cl_2).

(1*S*,2*R*,8*R*,8a*R*)-1,2,8-Trihydroxyindolizidine ((−)-Swainsonine, 1). In a 5-mL pear-shaped flask was placed 0.031 g (0.122 mmol) of cyclohexylidene **28** and 1 mL of 6 M HCl. After the solid had dissolved, the solution was heated in an oil bath at 65–70 °C for 30 min. The solvent was removed on a rotary evaporator with heating and the brown residue purified by ion-exchange chromatography (Amberlite 1RA-400-(OH)). The fractions were spotted by TLC (eluted with 20:3:0.2 $CHCl_3$/MeOH/concentrated NH_4Cl and visualized with ninhydrin) and lyophilized. Crystallization from Et_2O gave 0.0201 g (95%) of swainsonine as an off-white powder. Further purification was achieved by sublimation: mp 138–140 °C dec (lit.[3h] mp 134–136 °C dec, lit.[42] mp 144–145 °C dec); $[\alpha]^{27}_D$ −85.2, $[\alpha]^{27}_{577}$ −91.0, $[\alpha]^{27}_{546}$ −94.2, $[\alpha]^{27}_{435}$ −164.1, $[\alpha]^{27}_{405}$ −181.6 (*c* 0.50, MeOH) (lit.[42] $[\alpha]^{25}_D$ −87.2 (*c* 2.1, MeOH));



(41) See supplementary material.

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

^{1}H NMR (500 MHz, D_2O, 3-(trimethylsilyl)propionic acid, sodium salt) δ 4.35 (overlapping ddd, 1 H (H-2), J = 8.0, 5.9, 2.5 Hz), 4.26 (dd, 1 H (H-1), J = 6.0, 3.7 Hz), 3.81 (ddd, 1 H (H-8), J = 12.6, 8.0, 4.6 Hz), 2.91 (d br t overlapping with dd δ 2.88, 1 H (H-5$_\beta$), J = 10, 2 Hz), 2.88 (dd, 1 H (H-3$_\beta$), J = 11.0, 2.4 Hz), 2.55 (dd, 1 H (H-3$_\alpha$), J = 11.0, 7.9 Hz), 2.06 (overlapping dq, 1 H (H-7$_\beta$), J = 12.3, 3.7 Hz), 1.96 (dt overlapping dd δ 1.92, 1 H (H-5$_\alpha$), J = 11.4, 2.9 Hz), 1.92 (dd, 1 H (H-8a), J = 9.5, 3.7 Hz), 1.72 (apparent d quintets, 1 H (H-6$_\alpha$), J = 13.9, 2.4 Hz), 1.52 (qt, 1 H (H-6$_\beta$), J = 13.5, 4.2 Hz), 1.24 (qd, 1 H (H-7$_\alpha$), J = 12.3, 4.5 Hz); HRMS (EI, 60 eV) calcd for $C_8H_{15}NO_3$ 173.1052, found 173.1050. ^{1}H, ^{13}C NMR, and TLC were identical with authentic swainsonine.

***N*-[3-(1,3-Dithian-2-ylidene)propyl]phthalimide.** According to the procedure described for the preparation of *N*-[4-(1,3-dithian-2-ylidene)butyl]phthalimide 11.3 g (64 mmol) of the ketene dithioacetal derived from butyrolactone[39] was converted to the title compound. Purification by column chromatography (silica gel, 2:1 hexane/ether) gave 15.14 g (77%) of a colorless granular solid, mp 78–83 °C, which was used without further purification: ^{1}H NMR (300 MHz) δ 7.85 (m, 2 H), 7.72 (m, 2 H), 5.90 (t, 1 H, J = 7.4 Hz), 3.76 (t, 2 H, J = 7.0 Hz), 2.79 (apparent t, 2 H, J = 6 Hz), 2.72 (apparent t, 2 H, J = 6 Hz), 2.61 (ABq, 2 H, υ_A = 2.60, υ_B = 2.24, J_{AB} = 7 Hz), 2.07 (m, 2 H); IR (thin film) 2935 (w), 1771 (m), 1713 (s), 1395 (s), 1359 (m), 720 (s) cm^{-1}; MS (EI, 70 eV) *m/e* (relative intensity) 305 (4), 160 (10), 158 (8), 145 (100), 111 (16), 77 (15), 76 (12), 71 (60); HRMS (EI, 33 eV) calcd for $C_{15}H_{15}NO_2S_2$ 305.0544, found 305.0561.

2-[3-Aminopropylidene]-1,3-dithiane. The phthalimide ketene dithioacetal was converted to the free amine in quantitative yield as described for 2-(4-aminobutylidene)-1,3-dithiane. NMR agrees with the literature.[39]

***N*-[3-(1,3-Dithian-2-ylidene)propyl]-(3*R*,4*S*,5*S*,6*RS*)-3,4,5-tris(benzyloxy)-6-hydroxy-2-piperidinone (29).** A solution of 10.76 g (21.8 mmol) of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone[28] in 15 mL of methanol was treated with 4.26 g (26.1 mmol) of 2-[3-aminopropylidene]-1,3-dithiane overnight at room temperature. After the addition of 0.30 g of K_2CO_3, the solution was concentrated and the orange oil dissolved in 275 mL CH_3CN. The solution was cooled to 0 °C, 3.0 g (21.7 mmol) of K_2CO_3 was added, and 10.61 g (23.9 mmol) of $Pb(OAc)_4$ in 130 mL of CH_3CN was poured into the reaction solution. After 30 min the reaction was warmed to room temperature and concentrated. The salts were washed with ethyl acetate, filtered through silica gel and concentrated. The crude product was dissolved in CH_2Cl_2 and 1 mL of acetic acid was added and the yellow solution was stirred at room temperature overnight. The solution was concentrated and purified by flash chromatography (silica gel, 20% acetone/hexane, sample applied to column by using CCl_4[43]) to give 7.163 g of the hydroxylactam as a mixture of epimers and 4.42 g of the ring-opened aldehyde (identified by aldehyde proton in ^{1}H NMR δ 9.77, and carbon ^{13}C NMR δ 200.0). The aldehyde fractions were combined, dissolved in 25 mL of CH_2Cl_2, and treated with 0.5 mL of acetic acid until TLC indicated complete conversion (overnight). Purification by flash column, as above, gave 1.35 g of the hydroxylactam as a mixture of epimers for a total yield of 8.51 g (66%). The viscous, yellow oil was used without further purification. The ratio of epimers varied from reaction to reaction. Spectral data are for the major epimer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.20 (m, 15 H), 5.92 (t, 1 H, J = 7.5 Hz), 5.09 (d, 1 H, J = 11.6 Hz), 4.86 (br s, 1 H), 4.72 (d, 1 H, J = 11.6 Hz), 4.67 (d, 1 H, J = 11.6 Hz), 4.54 (ABq, 2 H, υ_A = 4.57, υ_B = 4.51, J_{AB} = 11.9 Hz), 4.54 (d between ABq, 1 H, J = 11.6 Hz), 4.27 (d, 1 H, J = 6.7 Hz), 3.84 (dd, 1 H, J = 6.6, 3.8 Hz), 3.77 (apparent t, 1 H, J = 3.6 Hz), 3.72 (br s, 1 H), 3.55 (apparent quintet, 1 H, J = 7 Hz), 3.41 (apparent quintet, 1 H, J = 7 Hz), 2.80 (apparent t, 4 H, J = 6 Hz), 2.51 (apparent octet, 2 H, J = 7 Hz), 2.09 (m, 2 H); Minor epimer protons were most clearly visible at δ 5.89 (t) and 5.13 (d); ^{13}C NMR (125 MHz, $CDCl_3$) 169.1 (C), 138.0 (C), 137.44 (C), 137.38 (C), 129.5 (CH), 128.7 (C), 128.4 (CH), 128.3 (CH), 128,2 (CH), 128.0 (CH), 127.83 (CH), 127.81 (CH), 127.7 (CH), 127.6 (CH), 83.2 (CH), 79.8 (CH), 87.5 (CH), 77.3 (CH), 74.0 (CH_2), 73.2 (CH_2), 71.8 (CH_2), 44.9 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 24.8 (CH_2); IR (thin film) 3350 (br m), 3062 (w), 3030 (w), 2910 (m), 1651 (s), 1453 (m), 1080 (s), 786 (m), 736 (m), 697 (m) cm^{-1}; MS (Cl, isobutane) *m/e* (relative intensity) 592 (1), 574 (2), 147 (22), 107 (100), 92 (35); HRMS (EI, 35 eV) calcd for $C_{33}H_{37}NO_5S_2$ 591.2113, found 591.2116.

(6*R*,7*S*,8*R*,8a*R*)-1-[2-(1,3-Dithianylidene)]-6,7,8-tris(benzyloxy)-indolizidin-5-one (30) and (6*R*,7*S*,8*R*,8a*S*)-1-[2-(1,3-Dithianylidene)]-6,7,8-tris(benzyloxy)indolizidin-5-one (31). In a flame-dried 100-mL round-bottomed flask, under argon, was placed 7.10 g (12.0 mmol) of the hydroxylactam **29** (mixture of epimers) and 50 mL of CH_2Cl_2. After the solution was cooled to 0 °C, 3.51 mL (2.55 g, 25.2 mmol) of triethylamine was added with a syringe, followed by the dropwise addition of 1.11 mL (1.65 g, 14.4 mmol) of methane sulfonylchloride. After 5 min, the reaction was placed in a freezer at −20 °C for 2 days (usually the reaction was allowed to stir at room temperature overnight). The brown reaction solution was washed twice with 5% HCl and once with brine, dried, filtered, and concentrated on a rotary evaporator. Purification by chromatography (silica gel, CH_2Cl_2) gave 2.58 g of **30** (the higher R_f band) and 3.21 g of a mixture of **30** and **31** for a combined yield of 5.79 g (84%). ^{1}H NMR before purification indicates and approximate 1:1 ratio of diastereomers. Analytical samples were prepared by careful repurification by radial chromatography (separation of **30** and **31** was not necessary at this stage and could be more easily accomplished in the next step). **30**: colorless, highly viscous oil; $[\alpha]^{26}_D$ −89.9, $[\alpha]^{26}_{577}$ −93.9, $[\alpha]^{26}_{546}$ −105.3, $[\alpha]^{26}_{435}$ −187.3, $[\alpha]^{26}_{405}$ −226.7 (*c* 1.23, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.15 (m, 15 H), 4.87 (d, 1 H, J = 10.1 Hz), 4.75 (d, 1 H, J = 12.0 Hz), 4.60 (d, 1 H, J = 12.0 Hz), 4.56 (s, 2 H), 4.52 (d, 1 H, J = 11.5 Hz), 4.40 (d, 1 H, J = 11.5 Hz), 4.06 (dd, 1 H, J = 11.2, 9.4 Hz), 4.03 (d, 1 H, J = 1.6 Hz), 3.96 (dd, 1 H, J = 5.5, 1.7 Hz), 3.10 (td, 1 H, J = 11.4, 6.9 Hz), 3.0–2.85 (m, 4 H), 2.63 (dt, J = 13.5, 4.4 Hz), 2.17 (m, 2 H), 2.06 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 137.6, 137.4, 137.34, 137.32, 128.7, 128.3, 128.1, 128.0, 127.97, 127.81, 127.78, 127.6, 125.0, 84.0, 82.5, 79.0, 73.2, 72.0, 71.6, 58.6, 44.1, 29.78, 29.74, 28.8, 24.4. IR (thin film) 3056 (w), 3029 (w), 2902 (m), 1668 (s), 1434 (m), 1072 (m), 737 (m), 698 (m); cm^{-1} λ_{max}(MeOH) 258.2 nm (ϵ = 11 306) 210.7 nm (ϵ = 25 039); MS (EI, 70 eV) *m/e* (relative intensity) 574 (0.2), 573 (0.6), 482 (1), 242 (9), 186 (5), 91 (100); HRMS calcd for $C_{33}H_{35}NO_4S_2$ 573.2007, found 573.2009. **31**: low R_f band, pale yellow oil which crystallizes on standing. Recrystallization from hexane gives colorless needles: mp 74–75 °C; $[\alpha]^{26}_D$ +144.5, $[\alpha]^{26}_{577}$ +151.6, $[\alpha]^{26}_{546}$ +176.0, $[\alpha]^{26}_{435}$ +302.4, $[\alpha]^{26}_{405}$ +371.8 (*c* 1.05, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5–7.1 (m, 15 H), 5.10 (d, 1 H, J = 11.8), 4.70 (d, 1 H, J = 11.8 Hz), 4.60 (s, 1 H), 4.57 (ABq, 2 H, υ_A = 4.59, υ_B = 4.55, J_{AB} = 11.7 Hz), 4.40 (d, 1 H, J = 12.2 Hz), 4.26 (d, 1 H, J = 12.2 Hz), 4.15 (dt, 1 H, J = 10.7, 2.2 Hz), 4,03 (d, 1 H, J = 6.2 Hz), 4.01 (d, 1 H, J = 0.7 Hz), 3.75 (d, 1 H, J = 6.1 Hz), 3.28 (apparent q, 1 H, J = 8.7 Hz), 2.96 (m, 1 H), 2.92–2.80 (m, 3 H), 2.66 (dt, 1 H, = 13.4, 5.3 Hz), 2.51 (dddd, 1 H, J = 16.2, 9.7, 9.7, 1.9 Hz), 2.14 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 139.7, 138.0, 137.8, 137.5, 128.4, 128.3, 128.24, 128.19, 127.9, 127.72, 127.66, 127.58, 120.1, 81.8, 79.9, 77.4, 73.1, 72.1, 71.2, 60.7, 44.2, 30.2, 29.5, 29.4, 24.4; IR (neat) 3062 (w), 3029 (w), 2907 (m), 1682 (s), 1454 (m), 1427 (w), 1074 (s), 735 (s), 698 (s) cm^{-1}; λ_{max}(MeOH) 260.0 nm (ϵ = 9478) 210.7 nm (ϵ = 24 723); MS (EI, 70 eV) *m/e* (relative intensity) 575 (0.2), 574 (0.9), 573 (3), 482 (3), 242 (14), 186 (9), 91 (100); HRMS calcd for $C_{33}H_{35}NO_4S_2$ 573.2007, found 573.2013. Anal. Calcd for $C_{33}H_{35}NO_4S_2$: C, 69.08; H, 6.15; N, 2.44. Found: C, 68.86; H, 5.98; N, 2.44.

(1*S*,6*R*,7*S*,8*R*,8a*R*)-1-Hydroxy-6,7,8-tris(benzyloxy)indolizidin-5-one (32). A solution of 0.106 g (0.18 mmol) of **30**, 0.002 g of rose bengal, bis(triethyl ammonium) salt (Aldrich), 2 mL of CCl_4, and just enough methanol to dissolve the dye (0.2 mL) was irradiated with a sodium lamp while bubbling oxygen through the solution with a syringe needle. The reaction was monitored by TLC, and upon completion (11.5 h) the solution was transferred to a flame-dried round-bottomed flask and concentrated, and 5 mL of benzene added, and the solution concentrated again. The oil was dissolved in 8 mL of THF, the solution cooled to −78 °C, and 0.28 mL of L-Selectride (0.28 mmol, Aldrich 1 M solution in THF) added with a syringe. After 30 min 4 mL of brine was added and the solution warmed to room temperature. The layers were separated, and the aqueous phase was washed with ethyl acetate. The combined organic layers were dried, filtered, and concentrated. Purification by radial chromatography (1-mm plate, 2% THF/CH_2Cl_2 then 5% and finally 10% THF/CH_2Cl_2) gave 0.034 g (39%) of **32** as a colorless oil. Note: the rate of this reaction was highly dependent on the power of the lamp used. In this case the reaction vessel was placed next to a sodium lamp in a polarimeter. Subsequent reactions were run with use of a 400-W high-pressure sodium lamp (average reaction time 30 min at 0 °C, and yields ranged from 30 to 37% for the two steps): $[\alpha]^{27}_D$ +127.0, $[\alpha]^{27}_{577}$ +131.4, $[\alpha]^{27}_{546}$ +151.9, $[\alpha]^{27}_{435}$ +263.5, $[\alpha]^{27}_{405}$ +323.3 (*c* 1.31, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.25 (m, 15 H), 5.16 (d, 1 H, J = 11.1 Hz), 4.84 (d, 1 H, J = 11.4 Hz), 4.82 (s, 1 H), 4.79 (d, 1 H, J = 8.7 Hz), 4.76 (d, 1 H, J = 8.9 Hz), 4.71 (d, 1 H, J = 11.6 Hz), 4.26 (br s, 1 H), 4.03 (d, 1 H, J = 7.1 Hz), 3.94 (dd, 1 H, J = 8.9, 7.2 Hz), 3.76 (apparent t, 1 H, J = 9.3 Hz), 3.59 (dt, 1 H, J = 11.4, 9.3 Hz), 3,48 (m, 1 H), 3.43 (dd, 1 H, J = 9.5, 2.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 138.1, 137.8, 128.7, 128.4, 128.34, 128.3, 127.9, 127.7, 83.7, 80.2, 74.5, 74.4, 74.2, 73.7, 70.1, 63.8, 43.2, 31.4; IR (neat) 3385 (br m), 3067 (w), 3030 (w), 2933 (m), 2882 (m), 1640 (s), 1454 (m), 1070 (s), 736 (m), 698 (s) cm^{-1}; MS (Cl, isobutane) *m/e* (relative in-

(43) Pivnitsky, K. K. *Aldrichimica Acta* **1989**, *22*(2), 30.

tensity) 474 (8), 147 (9), 107 (100), 92 (18), 91 (10); HRMS (CI, isobutane) calcd for $C_{29}H_{32}NO_5$ ($M-H^+$) 474.2280, found 474.2256.

(1*R*,6*R*,7*S*,8*R*,8a*R*)-1-Hydroxy-6,7,8-tris(benzyloxy)indolizidin-5-one (35). A solution of 0.072 g (0.125 mmol) of **30**, 0.001 g rose bengal, bis(triethyl ammonium) salt in 10 mL CCl_4, and 1 mL of methanol was irradiated with a 400-W high-pressure sodium lamp while bubbling oxygen through the solution with a syringe needle. After 20 min the reaction was concentrated, dissolved in benzene, and concentrated again. To the oil was added 8 mL of THF under argon and the solution cooled to −78 °C and 0.12 mL (0.125 mmol, Aldrich 1 M in THF) of lithium tris-*tert*-butoxyaluminohydride was added with a syringe. After 20 min the reaction was warmed to −15 °C for 5 min and quenched with 3 mL of saturated aqueous sodium tartrate. The layers were separated, and the aqueous phase was washed with ethyl acetate. The combined organic phases were dried, filtered, and concentrated. Purification by radial chromatography gave 0.0051 g of **32** and 0.0248 g of the C-1 epimer **35** as a colorless oil for a total yield of 0.030 g (51%). Spectral data of the minor product is identical with that obtained by L-Selectride reduction. Spectral data of **35**: $[\alpha]^{26}_D$ +103.4, $[\alpha]^{26}_{577}$ +103.4, $[\alpha]^{26}_{546}$ +123.8, $[\alpha]^{26}_{435}$ +219.6, $[\alpha]^{26}_{405}$ +275.2 (*c* 0.82, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.25 (m, 15 H), 5.02 (d, 1 H, *J* = 11.4 Hz), 4.84 (d, 1 H, *J* = 11.5 Hz), 4.74 (ABq, 2 H, υ_A = 4.75, υ_B = 4.73, J_{AB} = 6.5 Hz), 4.62 (d overlapping d at 4.61, 1 H, *J* = 11.2), 4.61 (d overlapping d at 4.62, 1 H, *J* = 11.5 Hz), 4.04 (d, 1 H, *J* = 5.0 Hz), 3.94 (m overlapping dd at 3.93, 1 H), 3.93 (dd overlapping m at 3.94, 1 H, *J* = 7.5, 5.1), 3.51 (m, 3 H), 3.41 (dd, 1 H, *J* = 9.7, 6.5), 2.25 (d, 1 H, *J* = 2.2 Hz), 2.12 (m, 1 H), 1.80 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 137.6, 137.5, 137.46, 128.8, 128.4, 128.38, 128.35, 128.3, 128.2, 128.1, 127.93, 127.89, 83.6, 81.3, 80.0, 75.7, 73.5, 73,4, 63.0, 42.2, 30.5; IR (neat) 3380 (br w), 3029 (w), 2887 (w), 1650 (s), 1454 (m), 1096 (s), 1072 (s), 737 (m), 698 (s) cm^{-1}; MS (CI isobutane) *m/e* (relative intensity) 474 (15), 147 (10), 92 (19), 107 (100); HRMS (CI, isobutane) calcd for $C_2\infty9H_{32}NO_5$ (MH^+) 474.2280, found 474.2287.

(1*S*,6*R*,7*S*,8*R*,8a*S*)-1-Hydroxy-6,7,8-tris(benzyloxy)indolizidin-5-one (33). To 1.01 g (1.76 mmol) of **31** in 50 mL of CCl_4 and 3 mL of methanol was added 0.004 g of rose bengal and bis(triethyl ammonium) salt. The solution was cooled in an ice bath (clear pyrex crystallizing dish) and irradiated with a 400-W high-pressure sodium lamp while bubbling oxygen through the solution with a syringe needle. After 35 min, irradiation was stopped and the solvent removed on a rotary evaporator. The oil was dissolved in 10 mL of benzene and reconcentrated. After the solution was purged with argon, 20 mL of THF and 20 mL of Et_2O was added and the solution cooled to −109 °C and 1.76 mL (1.76 mmol) of L-Selectride (Aldrich, 1 M in THF) added. After 10 min the reaction was warmed to 0 °C, and 7 mL of 10% aqueous KOH, followed by 5 mL 30% H_2O_2, was added, and the solution was stirred at 0 °C for 10 min. The solution was saturated with NaCl, the layers were separated, and the aqueous phase was washed with ethyl acetate. The combined organic layers were washed once with brine, twice with saturated aqueous $NaHSO_3$, and twice with brine, dried, filtered, and concentrated. Purification by radial chromatography (4-mm plate, 2% to 5% to 10% THF/CH_2Cl_2) gave 0.350 g (42%) which crystallizes upon standing. Recrystallization from CH_2Cl_2/hexane gave clear colorless needles: mp 114–115.5 °C, $[\alpha]^{27}_D$ +42.8, $[\alpha]^{27}_{577}$ +43.2, $[\alpha]^{27}_{546}$ +51.0, $[\alpha]^{27}_{546}$ +51.0, $[\alpha]^{27}_{435}$ +82.0, $[\alpha]^{27}_{405}$ +98.6 (*c* 1.48, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.15 (m, 15 H), 5.13 (d, 1 H, *J* = 11.7 Hz) 4.78 (d, 1 H, *J* = 11.7 Hz), 4.66 (d, 1 H, *J* = 11.2 Hz), 4.62 (d, 1 H, *J* = 11.6 Hz), 4.50 (m, 1 H), 4.49 (d, 1 H, *J* = 11.6 Hz), 4.37 (d, 1 H, *J* = 11.2 Hz), 4.08 (m, 1 H), 3.97 (d, 1 H, *J* = 1.5 Hz), 3.85 (d, 1 H, *J* = 5.4 Hz), 3.83 (apparent dd overlapping d at 3.85, 1 H, *J* = 4.6, 3.7 Hz), 3.79 (dd, 1 H, *J* = 4.7, 3.0 Hz), 3.42 (ddd, 1 H, *J* = 11.9, 7.8, 4.3 Hz), 1.91 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 137.9, 137.3, 136.2, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 78.1, 77.5, 75.6, 73.9, 73.2, 72.4, 71.2, 58.7, 42.9, 32.6; IR (neat) 3405 (br m), 3062 (w), 3029 (w), 2880 (w), 1658 (s), 1454 (m), 1107 (s), 737 (m), 698 (s) cm^{-1} MS (CI, isobutane) *m/e* (relative intensity) 474 (100), 107 (2); HRMS (CI, isobutane) calcd for $C_{29}H_{32}NO_5$ ($M-H^+$) 474.2280, found 474.2275,

(1*R*,6*S*,7*S*,8*R*,8a*R*)-1-Hydroxy-6,7,8-tris(benzyloxy)indolizidine. To 0.156 g (0.329 mmol) of **32** in 4 mL of THF was added 0.20 mL (1.97 mmol) of BH_3/DMS (10 M in BH_3, Aldrich) at 0 °C. The clear colorless solution was warmed to room temperature and, after 20 min, heated at reflux for an additional 30 min at which point no starting material was visible by TLC. After the solution was cooled in an ice bath, 0.33 mL (1.97 mmol) of 6 M HCl was added slowly while stirring. The reaction was then heated at reflux, allowing the solvent to evaporate. Once all the solvent had boiled off (about 30 min) the flask was cooled to room temperature, and 2 mL of 4 M NaOH was added. The aqueous solution was saturated with K_2CO_3 and washed with EtOAc. The combined organic layers were dried over K_2CO_3, filtered, and concentrated. Purification by radial chromatography (1-mm plate, 5% THF/CH_2Cl_2) gave 0.101 g (67%) as a colorless oil: $[\alpha]^{26}_D$ +36.4, $[\alpha]^{26}_{577}$ +37.9, $[\alpha]^{26}_{546}$ +44.3, $[\alpha]^{26}_{435}$ +72.3, $[\alpha]^{26}_{405}$ +90.4 (*c* 1.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 15 H), 4.98 (d, 1 H, *J* = 10.9 Hz), 4.87 (d, 1 H, *J* = 10.9 Hz), 4.84 (ABq, 2 H, υ_A = 4.86, υ_B = 4.81, J_{AB} = 11.3 Hz), 4.68 (ABq, 2 H, υ_A = 4.70, υ_B = 4.66, J_{AB} = 11.6 Hz), 4.23 (m, 1 H), 3.69 (m, 1 H), 3.67 (apparent t, 1 H, *J* = 9.3 Hz), 3.56 (apparent t, 1 H, *J* = 9.0 Hz), 2,99 (dd, 1 H, *J* = 10.5, 5,0 Hz), 3.09 (dt, 1 H, *J* = 9, 2 Hz), 2.21–2.08 (m, 2 H), 2.00 (apparent t, 1 H, *J* = 10.4 Hz), 1.94 (dd, 1 H, *J* = 9,5, 3.6 Hz), 1.72 (m, 1 H), 1.52 (d, 1 H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (C), 139,0 (C), 138.6 (C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 87.4 (CH), 79.4 (CH), 76.6 (CH), 75,6 (CH), 74.3 (CH_2), 73.0 (CH_2), 71.9 (CH_2), 72.0 (CH), 70.9 (CH), 54.4 (CH_2), 51.7 (CH_2), 33.8 (CH_2); IR (thin film) 3436 (br w), 3067 (w), 3029 (w), 2910 (m), 2810 (m), 1453 (m), 1096 (s), 1068 (s), 734 (s), 696 (s) cm^{-1} MS (EI, 70 eV) *m/e* (relative intensity) 368 (1), 262 (0.9), 246 (3), 91 (100); MS (CI, isobutane) *m/e* (relative intensity) 460 (4), 352 (7), 147 (17), 107 (100), 92 (32); HRMS (CI, Methane) calcd for $C_{29}H_{34}NO_4$ (MH^+) 460.2487, found 460.2478.

(1*R*,6*S*,7*S*,8*R*,8a*S*)-1-Hydroxy-6,7,8-tris(benzyloxy)indolizidine. To 0.0684 g (0.144 mmol) of **33** in 3 mL of THF was added 0.011 g (0.284 mmol) of lithium aluminum hydride, and the solution was heated at reflux for 1.5 h. Upon cooling to room temperature the reaction was quenched with 3 mL of saturated aqueous sodium tartrate, The layers were separated, and the aqueous phase was washed with EtOAc, The combined organic layers were dried over K_2CO_3, filtered, and concentrated. Purification by radial chromatography (1-mm plate, 15% THF/CH_2Cl_2) gave 0.0463 g (70%) of the product as a pale yellow oil. An analytical sample was prepared by repurification by radial chromatography using 10% THF/CH_2Cl_2 to give a colorless oil: $[\alpha]^{27}_D$ +6.9, $[\alpha]^{27}_{577}$ +5.1, $[\alpha]^{27}_{546}$ +9.5, $[\alpha]^{27}_{435}$ +13.3, $[\alpha]^{27}_{405}$ +22.0 (*c* 0.82, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (m, 15 H), 4.65 (d, 1 H, *J* = 11.4 Hz), 4.58 (ABq, 2 H, υ_A = 4.59, υ_B = 4.57, J_{AB} = 12.7 Hz), 4.52 (d, 1 H, *J* = 11.4 Hz), 4.49 (d, 1 H, *J* = 12.0 Hz), 4,42 (d overlapping a m, 1 H, *J* = 12.0 Hz), 4.42 (m, 1 H), 4.01 (br s, 1 H), 4,01 (apparent t, 1 H, *J* = 3.2 Hz), 3,74 (apparent t, 1 H, *J* = 3.7 Hz), 3.54 (apparent q, 1 H, = 3.4 Hz), 3.20 (dd, 1 H, *J* = 11.8, 3.8 Hz), 3.17 (apparent t, 1 H, *J* = 8 Hz), 2,42 (m, 2 H), 2.12 (m, 2 H), 1.85 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4 (C), 137.9 (C), 137,1 (C), 128,5 (CH), 128,42 (CH), 128,41 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127,7 (CH), 127,6 (CH), 74.4 (CH), 73.8 (CH), 73.5 (CH), 72,5 (CH_2), 72,4 (CH_2), 71.6 (CH_2), 64.3 (CH), 53.5 (CH_2), 53,2, (CH_2) 34.1 (CH_2); IR (thin film) 3432 (br w), 3067 (w), 3030 (w), 2920 (m), 2869 (m), 1454 (m), 1114 (s), 1071 (s), 1027 (m), 735 (m), 697 (s) cm^{-11}; MS (EI, 70 eV) *m/e* (relative intensity) 368 (3), 262 (2), 246 (6), 160 (3), 91 (100); MS (CI, isobutane) *m/e* (relative intensity) 460 (1), 107 (100), 92 (50); HRMS (CI, isobutane) calcd for $C_{29}H_{34}NO_4$ (MH^+) 460.2487, found 460.2463,

(1*S*,6*S*,7*S*,8*R*,8a*R*)-1,6,7,8-Tetrahydroxyindolizidine ((+)-Castanospermine, 1). TO 0,012 g of 10% Pd/C was added 0.0587 g (0.128 mmol) of (1*S*,6*S*,7*S*,8*R*,8a*R*)-1-hydroxy-6,7,8-tris(benzyloxy)indolizidine in 4 mL of methanol, followed by 5 drops of concentrated HCl. The solution was placed on a Parr medium-pressure hydrogenation apparatus under 50 psi of H_2, After 6 h TLC indicated absence of starting material, 1 g of Amberlite (Amberlite IRA-400(OH)) was added, and, after 5 min, the solution was filtered through Celite and concentrated, The light brown solid was purified by radial chromatography (1-mm plate, 70:26:2:2 $CHCl_3$/MeOH/H_2O/NH_4OH, under argon to give 0.022 g of a colorless solid which was dissolved in 2 mL of H_2O and treated with 0.5 g of Amberlite resin for 2 h (to ensure complete conversion of the free base), Filtration followed by lyophilization gave 0.0199 g (82%) of a colorless solid. Note: Frequently more catalyst had to be added in order for the reaction to go to completion, An analytical sample was prepared by recrystallization from EtOH; mp 213.5–215 °C dec (lit.[44] mp 212–215 °C), $[\alpha]^{27}_D$ +74,1, $[\alpha]^{27}_{577}$ +73,6, $[\alpha]^{27}_{546}$ +104.6, $[\alpha]^{27}_{435}$ +173.5, $[\alpha]^{27}_{405}$ +236,1 (*c* 0.3, H_2O) (lit. $[\alpha]^{25}_D$ +79.7 (*c* 0.93, H_2O),[44] $[\alpha]_D$ +71 (*c* 0.27, H_2O)[44a]); ^1H NMR (500 MHz, D_2O, TSP) δ 4.41 (ddd, 1 H (H_1), *J* = 6,8, 4,6, 1.5 Hz), 3.61 (m, 1 H(H_6)), 3,60 (apparent t, 1 H (H_8), *J* = 9,6 Hz), 3,32 (apparent t, 1 H (H_7), 9.1 Hz), 3.18 (dd, 1 H ($H_{5\beta}$), *J* = 10.8, 5.1 Hz), 3.08 (td, 1 H ($H_{3\beta}$), *J* = 9.1, 2,1 Hz), 2.33 (dddd, 1 H ($H_{2\alpha}$), *J* = 14.8, 8.1, 7.3, 2.2 Hz), 2.21 (apparent q, 1 H ($H_{3\alpha}$), *J* = 9.2 Hz), 2,06 (apparent t, 1 H ($H_{5\alpha}$), *J* = 10,7 Hz), 2.02 (dd, 1 H (H_{8a}), *J* = 9,8, 4,4 Hz), 1,71 (dddd, 1 H ($H_{2\beta}$), *J* = 14.2, 8.7, 8.7, 1.8 Hz); DEPT (125 MHz, D_2O, TSP) δ 81.8 (CH), 74.2 (CH), 72,8 (CH), 72.3 (CH), 71.7 (CH), 58.1 (CH_2), 54.3 (CH_2), 35,5 (CH_2); IR (thin film) 3345 (br s), 2920 (m), 2813 (w), 1122 (m), 1090 (m), 1006

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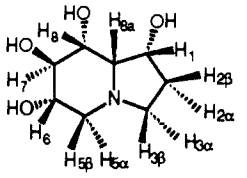
(m) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_8H_{15}NO_4$ 189.1001, found 189.1008. ^1H and ^{13}C NMR, and TLC (multiple solvents) were identical with an authentic sample (Sigma).

(1*R*,6*S*,7*S*,8*R*,8a*S*)-1,6,7,8-Tetrahydroxyindolizidine ((+)-1, 8a-Diepicastanospermine, 34). A solution of 0.165 g (0.359 mmol) of (1*R*,6*S*,7*S*,8*R*,8a*S*)-1-hydroxy-6,7,8-tris(benzyloxy)indolizidine and 0.020 g of 10% Pd/C in 4 mL of methanol and 8 drops of concentrated HCl was hydrogenated and purified as for **1** (the second treatment with Amberlite resin was not necessary for this compound), yield 0.054 g (79%), pale yellow oil which crystallizes upon standing at room temperature



NMR assignments are based on ^1H–^1H and ^1H–^{13}C COSY spectra:[41] ^1H NMR (500 MHz, D_2O, TSP) δ 4.59 (ddd, 1 H (H_1), J = 7.4, 5.0, 2.5 Hz), 4.18 (apparent t, 1 H (H_8), J = 4.3 Hz), 3.92 (apparent t, 1 H (H_7), J = 5.1 Hz), 3.74 (apparent q, 1 H (H_6), J = 5.1 Hz), 3.08 (m overlapping dd at 3.06, 1 H ($H_{3\alpha}$), 3.06 (dd, 1 H ($H_{5\alpha}$), J = 11.6, 5.3 Hz), 2.64 (dd, 1 H ($H_{5\beta}$), J = 11.9, 3.1 Hz), 2.55 (apparent t, 1 H (H_{8a}), J = 4.3 Hz), 2.40 (apparent q, 1 H ($H_{3\beta}$), J = 9.4 Hz), 2.30 (dddd, 1 H ($H_{2\beta}$), J = 14.1, 8.0, 7.4, 2.1 Hz), 1.79 (dddd, 1 H ($H_{2\alpha}$), J = 14.1, 9.0, 9.0, 2.5 Hz); DEPT (125 MHz, D_2O, TSP) δ 75.7 (C_1), 73.5 (C_8), 73.4 (C_7), 72.4 (C_6), 67.3 (C_{8a}), 56.8 (C_5), 54.8 (C_3), 35.2 (C_2); IR (thin film) 3354 (br s) 2932 (m), 2813 (m), 1115 (m), 1062 (m) cm^{-1} MS (EI, 70 eV) *m/e* (relative intensity) 189 (1.5), 171 (1.6), 154 (1.2), 145 (21), 128 (8), 116 (7), 100 (14), 98 (14), 86 (100), 82 (38), 72 (23), 68 (19), 58 (55); HRMS (EI, 70 eV) calcd for $C_8H^{15}NO_4$ 189.1001, found 189.1012. An analytical sample was prepared by recrystallization from acetone/hexane to give clear colorless needles; mp 140–141 °C; $[\alpha]^{28}_D$ −8.8, $[\alpha]^{27}_{577}$ −3.4, $[\alpha]^{27}_{546}$ +7.4, $[\alpha]^{27}_{435}$ +5.6, $[\alpha]^{27}_{405}$ +26.6 (*c* 0.46, CH_3OH). Anal. Calcd for $C_8H^{15}NO_4$: C, 50.77; H, 7.99; N, 7.40. Found c, 50.58; H, 8.08; N, 7.22.

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Supplementary Material Available: Experimental and spectral data for the preparation of the chiral diamines and reduction procedures listed in Table I, ^1H–^1H COSY spectrum for **1**, ^1H–^1H COSY and ^1H–^{13}C COSY spectra for **26** and **34**, DNOE data for **34** (10 pages). Ordering information is given on any current masthead page.

Expansolides A and B: Tetracyclic Sesquiterpene Lactones from *Penicillium expansum*

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Abstract: Two isomeric sesquiterpene lactones, expansolides A and B, have been isolated from a culture of the fungus *Penicillium expansum* and their structures elucidated from a spectroscopic study including IR, MS, NMR, and X-ray crystallography.

Introduction

Penicillium expansum ranks as one of the most common *Penicillium* species on various rotting substrates and is a widely distributed soil fungus.[1] It displays an antagonistic activity in vitro toward various bacteria and fungi.[2] As part of our interest in investigating fungi with antagonistic properties as a source of antifungal products, we examined an isolate of *P. expansum* collected on a fruit. From the ethyl acetate extract of the culture filtrate, we isolated in addition to the known patuline,[3-5] which was responsible for the antifungal properties, a mixture of two new compounds for which we suggest the names expansolides A and B. Each of them, obtained as a pure compound by column chromatography, spontaneously gave rise to a mixture, in various proportions, of both compounds when kept in solution.

Results and Discussion

The molecular formula of expansolide A, **1**, was determined from the HR-MS spectrum as $C_{17}H_{22}O_5$; the CI-MS showed the pseudomolecular $[M + H]^+$ ion at m/z = 307. The loss of a molecule of acetic acid leading to the ion m/z = 246 suggested the involvement of an acetyl group. Its IR spectrum was indicative of two ester carbonyls, as strong absorptions were observed at 1778 and 1743 cm^{-1}. The ^{13}C NMR spectrum exhibited 17 carbon atoms (Table I). Deshielded ^{13}C NMR resonances at δ 113.8 (C), 170.3, and 178.9 indicated the presence of a ketal and two ester functionalities, respectively. A ^{13}C NMR *J*-modulated experiment revealed 12 carbons attached to a total of 22 hydrogen atoms. From the ^1H–^1H COSY and ^1H–^1H LR COSY spectra, the protons could be classified into three spin-relaying groups: (i) CH_3CHCH_2–, (ii) >CCH_2CCH_2O–, (iii) –$CHCH_2CHCH_2CH$-(OAc)C=CH_2. Connectivities between these substructures were established by a 2D-INADEQUATE experiment in the range δ_C 10–80 and resulted in the determination of the plane structure of the

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