JOC*Note*

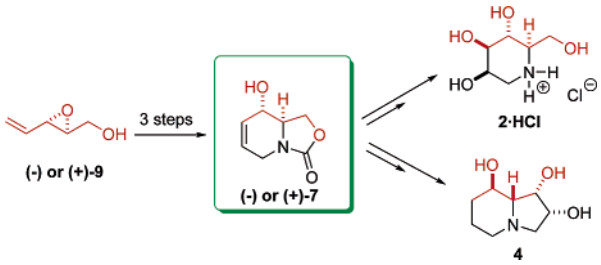
General Approach to Glycosidase Inhibitors. Enantioselective Synthesis of Deoxymannojirimycin and Swainsonine

Rubén Martín, Caterina Murruzzu, Miquel A. Pericàs, and Antoni Riera*

Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Parc Científic de Barcelona, and Departament de Química Orgànica, Universitat de Barcelona, c/Josep Samitier, 1-5, 08028-Barcelona, Spain

ariera@pcb.ub.es

Received October 15, 2004



Deoxymannojirimycin (**2**) and swainsonine (**4**) have been synthesized from each enantiomer of the same bicyclic carbamate precursor **7**. The key intermediate was prepared by a simple and efficient three-step synthesis involving RCM of the diene **8**, which in turn is easily accessible in any configuration from enantiomerically enriched 2,3-epoxy-4-penten-1-ol **9**.

Glycobiology is an emerging research field at the frontier of chemistry, enzymology, and biology. Many important biological processes in which glycosidases play a crucial role are being uncovered, hence opening the possibility of finding new therapeutic targets for the treatment of diseases such as diabetes, AIDS, or cancer.[1] Most glycosidase inhibitors share two common structural features: (i) a basic nitrogen that, at physiological pH, mimics the positive charge formed during the hydrolysis of the glycosidic bond and (ii) an array of hydroxyl groups in a conformationally restricted motif that selectively fit into the enzyme site.[2] Consequently, the structures of many glycosidase inhibitors include polyhydroxylated piperidine, pyrrolidine, or indolizidine rings. Representative examples are deoxynojirimycin (**1**), deoxymannojirimycin (**2**), or deoxygalactostatin (**3**). In these compounds, referred to as 1-deoxy-azasugars, or iminosugars, the hemiacetalic function in the monosacharides has been substituted by an aminomethylenene group. This simple modification usually improves a compound's inhibition of glycosidases,

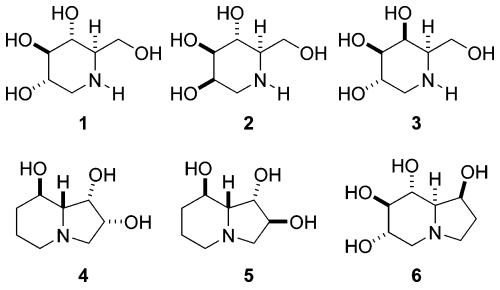


FIGURE 1. Representative glycosidase inhibitors with a polyhydroxylated piperidine or indolizidine structure.

some of them being therapeutically useful substances.[3−6] In addition, bicyclic compounds such as swainsonine (**4**), 2-epi-swainsonine (**5**), and castanospermine (**6**) also exhibit glycosidase inhibitory properties having been tested for the treatment of cancer, HIV, or immunological disorders.[7]

The absolute configuration of the stereogenic centers is obviously crucial for their biological activity, and therefore many stereoselective syntheses of these natural alkaloids have been described to date.[8−10] Moreover, in efforts to increase the biological activity or/and selectivity of these compounds, a great number of derivatives, stereoisomers, and analogues of this family have also been synthesized.[11] Although most of the aforementioned

(1) (a) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999. (b) Elbein, A. D. *FASEB J.* **1991**, *5*, 3055.

(2) Reviews of glycosidase inhibitors: (a) Look, G. C.; Fotsch, C. H.; Wong, C. H. *Acc. Chem. Res.* **1993**, *26*, 182−190. (b) van den Broek, L. A. G. M.; Vermaas, D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A.; Bolscher, J. G. M.; Ploegh, H. L.; van Kemenade, F. J.; de Goede, R. E. Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 82−94. (c) Junge, B.; Matzke, M.; Stoltefuss, J. *Handb. Exp. Pharmacol.* **1996**, *119*, 411−482. (d) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1−8.

(3) Therapeutic utility. (a) Johnston, P. S.; Lebovitz, H. E.; Coniff, R. F.; Simonson, D. C.; Raskin, P.; Munera, C. L. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 1515−1522. (b) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74−76. (c) Tsuruoka, T.; Fukuyasu, H.; Ishii, M.; Usui, T.; Shibahara, S.; Inouye, S. *J. Antibiot.* **1996**, *49*, 155−161.

(4) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *11*, 135−162.

(5) (a)Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977−978. (b) Fuhrmann, U.; Bause, E.; Legler, G.; Ploegh, H. *Nature* **1984**, *307*, 755−758.

(6) Miyake, Y.; Ebata, M. *J. Antibiot.* **1987**, *40*, 122−123.

(7) (a) Oredipe, O. A.; Furbert-Harris, P. M.; Green, W. R.; White, S. L.; Olden, K.; Laniyan, I.; Parish-Gause, D.; Vaughn, T.; Griffin, W. M.; Sridhar, R. *Pharm. Res.* **2003**, *47*, 69−74. (b) Oredipe, O. A.; Furbert-harris, P. M.; Laniyan, I.; Green, W. R.; Griffin, W. M.; Sridhar, R. *Cell. Mol. Biol.* **2003**, *49*, 1089−1099. (c) Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131−5136. (d) Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res.* **1988**, *48*, 1410−1415.

(8) Selected synthesis of 1-deoxymannojirimycin: (a) McDonnell, C.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *J. Org. Chem.* **2004**, *69*, 3565−3568. (b) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387−2391. (c) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281−286. (d) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931−8952. (e) Shirai, M.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 5331−5332. (f) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841−859. (g) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741−746. (h) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175−3185. (i) Park, K. H.; Yoon, Y. J.; Lee, S. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2621−2623. (j) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327−336. (k) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319−326. (l) Pederson, R. L.; Kim, M.-J.; Wong, C.-H. *Tetrahedron Lett.* **1988**, *29*, 4645−4648. (m) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123−1126.

(9) Selected synthesis of 1-deoxynojirimycin: (a) Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839−6841. (b) Lindstrom, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173−7176. (b) Berger, A.; Ebner, M.; Stuetz, A. E. *Tetrahedron Lett.* **1995**, *36*, 4989−4990. (c) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043−2053. (d) Anzeveno, P. B.; Creemer, L. J. *Tetrahedron Lett.* **1990**, *31*, 2085−2088. (e) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337−3342.

10.1021/jo048172s CCC: $30.25
Published on Web 02/17/2005

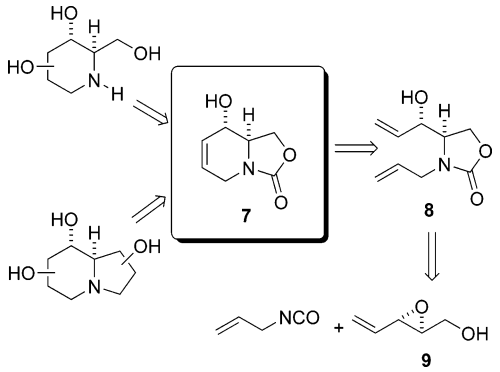


FIGURE 2. General retrosynthetic analysis.

synthetic approaches involve chemical transformations of monosaccharides, efficient syntheses based in asymmetric catalysis have also been described. However, a stereodivergent approach that could lead to different stereoisomers of monocyclic and bicyclic compounds from a common precursor is still lacking.

Some years ago, in a project devoted to the preparation of natural alkaloids using ring-closing metathesis[12] as a key step,[13] we envisaged[14] that oxazolidinylpiperidine **7** could be a key intermediate for the synthesis of many glycosidase inhibitors. The trans stereochemistry between the nitrogen and the secondary hydroxyl is present in many compounds such as deoxynojirimycin, deoxymannojirimycin, or swainsonine. The synthetic potential of carbamate **7** for the construction of glycosidase inhibitors has also been recognized by other groups.[15−18]

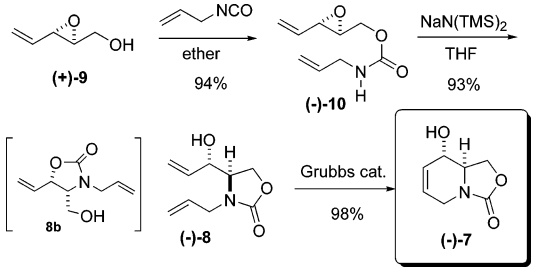
Our synthetic approach was based on the preparation of **7** by RCM of the unsaturated carbamate **8**, the stereochemistry of which would be conveniently set by a nucleophilic C-2 ring-opening of an enantiomerically enriched epoxide. Consequently, we planned to start from the known unsaturated epoxyalcohol **9** and to use allyl isocyanate as a nucleophilic reagent. We describe here full details of the straightforward preparation of intermediate **7** as well as its conversion to 1-deoxymannojirimycin (**2**), swainsonine (**4**), and epi-swainsonine (**5**).

Results and Discussion

Our synthesis started with the preparation of the known epoxy alcohol **9**. This epoxide can be obtained in high enantiomeric purity by Sharpless epoxidation[19] of the readily available (*E*)-2,4-pentadien-1-ol.[20] Although pure (2*S*,3*S*)-2,3-epoxy-4-penten-1-ol (>91% ee) can be obtained by distillation,[21] the crude product from the epoxidation was used to prepare the carbamate. Alternatively, **9** can be obtained in more than 99% ee by Payne rearrangement of (2*R*,3*S*)-1,2-epoxy-4-penten-3-ol, prepared by Sharpless epoxidation of the commercially available bis allylic alcohol.[22]

The crude epoxide **9**, prepared by either way, was treated by allyl isocyanate/Et_3N in ether at reflux to provide allyl carbamate **10** in 94% yield (59% overall yield from 2,4-pentadienol; Scheme 1). The subsequent intramolecular ring opening of **10** required extensive

SCHEME 1



experimentation since the standard conditions (NaH/THF) gave a 1:1 mixture of the desired oxazolidinone **8** and the trans-acylated isomer **8b**.[23] Other bases such as Bu^{t}OK gave only slightly better yields, whereas treatment with Lewis acid catalysts such as $LiClO_4$ or Ti(^{i}PrO)$_4$ led to decomposition of the starting material. Ultimately, the use of sodium bis(trimethylsilyl)amide in ether provided the desired oxazolidinone **8** in 88% yield with no sign of the isomer **8b** in the crude reaction mixture.[24] As expected, ring-closing metathesis on the bis olefinic compound **8** took place cleanly using 5% mol Grubbs's catalyst[25] in dichloromethane at room temperature and afforded the target oxazolidinylpiperidine **7** in

(10) (a) Lindsay, K. B.; Pyne, S. G. *Aust. J. Chem.* **2004**, *57*, 669−672. (b) Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 7284−7293. (c) Buschmann, N.; Rueckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329. (d) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774−7780. (e) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761−1767. (f) Punniyamurthy, T.; Irie, R.; Katsuki, T. *Chirality* **2000**, *12*, 464−468. (g) De Vicente, J.; Arrayas, R. G.; Canada, J.; Carretero, J. C. *Synlett* **2000**, 53−56. (h) Mukai, C.; Sugimoto, Y.-I.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281−6287. (i) Ferreira, F.; Greck, C.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 615−621. (j) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217−7221. (k) Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2599−2604. (l) Kang, S. H.; Kim, G. T. *Tetrahedron Lett.* **1995**, *36*, 5049−5052. (m) Oishi, T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404−406. (n) Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, *36*, 1291−1294. (o) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358−1364.

(11) (a) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. (b) El Memr, A. *Tetrahedron* **2000**, *56*, 8579−8629. (c) Carmona, A. T.; Fuentes, J.; Robina, I.; Rodriguez-García, E.; Demange, R.; Vogel, P.; Winters, A. L. *J. Org. Chem.* **2003**, *68*, 3874−3883.

(12) Reviews on this subject: (a) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (b) Maier, M. E. *Angew. Chem., Int Ed.* **2000**, *39*, 2073−2077. (c) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. (d) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959−968.

(13) (a) Martin, R.; Alcón, M.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896−6901. (b) Ginesta, X.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **2002**, *43*, 779−782.

(14) Preliminary communication: Martín, R.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *1*, 93−95.

(15) Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun.* **1999**, *7*, 41−42.

(16) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105−114.

(17) Shirai, M.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 5331−5332.

(18) Al-Rawi, S.; Hinderlich, S.; Reutter. W.; Giannis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4366−4370.

(19) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (b) Katsuki, T.; Martín, V. S. *Org. React.* **1996**, *48*, 1−299.

(20) Schneider, M. P.; Goldbach, M. *J. Am. Chem. Soc.* **1980**, *102*, 6114−6116.

(21) Wershofen, S.; Scharf, H.-D. *Synthesis* **1988**, 854−858.

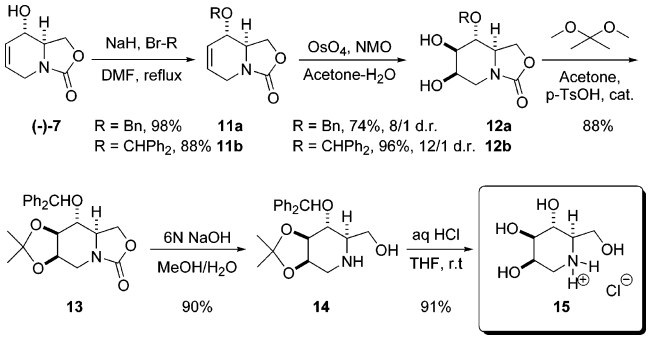
(22) (a) Jäger, V.; Hummer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769−776. (b) Jäger, V.; Stahl, U.; Gracza, T.; Hummer, W. *Synthesis* **1991**, 776−782. (c) Jäger, V.; Schroeter, D.; Koppenhoefer, B. *Tetrahedron* **1991**, *47*, 2195−2210.

(23) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752−3757. This methodology, as Roush already pointed out, has the serious drawback that the base also catalyzes an acyl migration, yielding a mixture of oxazolidinones. Other conditions (TMS−Cl, imidazole DMF) lead to the formation of the carbonate between both alcohols (see ref 14).

98% yield. The metathesis reaction was also performed in supercritical CO_2 (200 bar and 40 °C) providing an 88% yield with only 2 mol % standard Grubbs's catalyst.[26]

Once the key intermediate (−)-**7** was acquired, the study of its transformation into 1-deoxy-azasugars was initiated. Katsumura et al.[15] already described the transformation of **7** into 1-deoxymannojirimycin **2** and to 1-deoxygalactostatin **3** through a *tert*-butyldimethylsilyl ether derivative. In our hands, however, the silyl protective group was too sensitive to the basic hydrolysis conditions necessary for the deprotection of the carbamate group. It was thus decided to use benzyl or benzhydryl groups to protect the secondary hydroxyl functionality. In both cases, the corresponding ethers **11a** and **11b** were obtained in good yield (Scheme 2). The dihydroxylation of both compounds took place in high diastereoselectivity anti to the alkoxy group, but as might be anticipated, the benzhydryl derivative **12b** was obtained in a significantly better diastereomeric ratio (12:1). Protection of the vicinal diol in **12b** as a dimethyl acetal followed by chromatography provided diastereomerically pure **13**, a completely protected form of 1-deoxymannojirimycin **2**. Although in acetal **13** all protecting groups can, in principle, be hydrolyzed by acid treatment to give **2**, all attempts to perform the hydrolysis of all three protecting groups using HCl failed. On the other hand, basic hydrolysis led to clean and selective deprotection of the carbamate, affording **14** in excellent yield. Hydrogenolysis as well as acid hydrolysis of the benzhydryl group in **14** proved to be more difficult than expected. Whereas Pd/C or $Pd(OH)_2$ catalytic hydrogenation only afforded starting material, hydrolysis using HCl/MeOH gave the desired product contaminated by a methyl ether derivative. Ultimately, it was found that hydrolysis in HCl/THF cleaved both groups cleanly, affording the hydrochloride **15** (**2**·HCl) in almost quantitative yield and high purity.

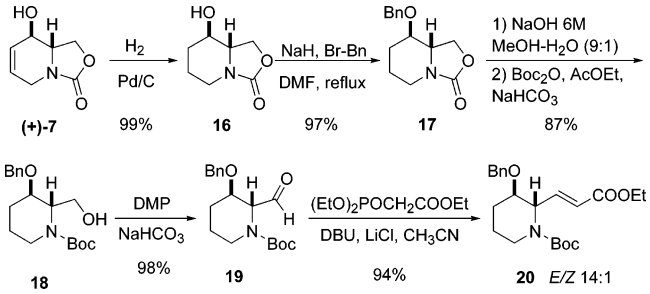
SCHEME 2



The stereogenic centers in the piperidine ring of swainsonine have the opposite configuration of those in mannojirimycin. Consequently, their synthesis requires starting from the enantiomer of the intermediate used in the previously described synthesis. One of the advantages of using Sharpless epoxidation as a source of chirality is that both enantiomers are readily accessible. Therefore, (−)-**9** was prepared by simply changing the configuration of the tartrate in the epoxidation step, and (+)-**7** was synthesized from it following the same reaction sequence. We plan to build up the five-membered ring by introducing an unsaturated ester via olefination of aldehyde **19**, which in turn could be prepared via deprotection of the carbamate and subsequent oxidation of the primary alcohol. The syn dihydroxylation of the unsaturated ester would control the stereochemistry of the diol fragment in the cyclic derivatives. Syn-dihydroxylation of *E*-**20** would lead to a trans diol, whereas syn-dihydroxylation of *Z*-**20** would afford the stereochemistry present in swainsonine **4**.

The synthetic plan employed required the choice of an adequate protecting group for the secondary alcohol after hydrogenation of the double bond in (+)-**7**. The benzyl group was chosen for the case at hand since it is more resistant to hydrolysis than benzhydryl and we hoped that its bulkiness would not be necessary in the diastereoselectivity control of the side chain dihydroxylation. Thus, hydrogenation of (+)-**7** gave alcohol **16** which, after protection as a benzyl ether gave **17** uneventfully (Scheme 3). Basic hydrolysis of the carbamate took place smoothly, and the free amine was protected in situ with a Boc group, yielding hydroxymethylpiperidine **18** in an overall yield of 87% from **17**. Oxidation of the primary alcohol required some experimentation. While Swern oxidation provided aldehyde **19** in only 68% yield, the use of Dess−Martin periodinane (DMP)[27] as an oxidant in basic media afforded **19** in nearly quantitative yield.

SCHEME 3



Horner−Emmons olefination of **19** afforded the unsaturated ester *E*-**20** in good yield and diastereoselectivity (86%, 10:1), although these results were improved using Masamune−Roush conditions[28] (94%, 14:1). On the other hand, the corresponding *Z* isomer was conveniently obtained using bis(trifluoroethoxy)phosphonate under Still conditions,[29] which gave *Z*-**20** as the major isomer (5:1).

Gratifyingly, dihydroxylation using catalytic OsO_4 and NMO as a stoichiometric oxidant[30] of both *Z* and *E*

(24) Other reports using $NaN(TMS)_2$ in the ring opening of epoxycarbamates: (a) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491−5494. (b) Li, Y.-L.; Wu, Y.-L. *Tetrahedron Lett.* **1995**, *36*, 3875−3876.

(25) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−552. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (e) Ivin, K. J. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1−16.

(26) (a) Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000−9006. (b) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2466−2469.

(27) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(28) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *21*, 2183-2186.

(29) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(30) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron. Lett.* **1976**, *23*, 1973−1976.

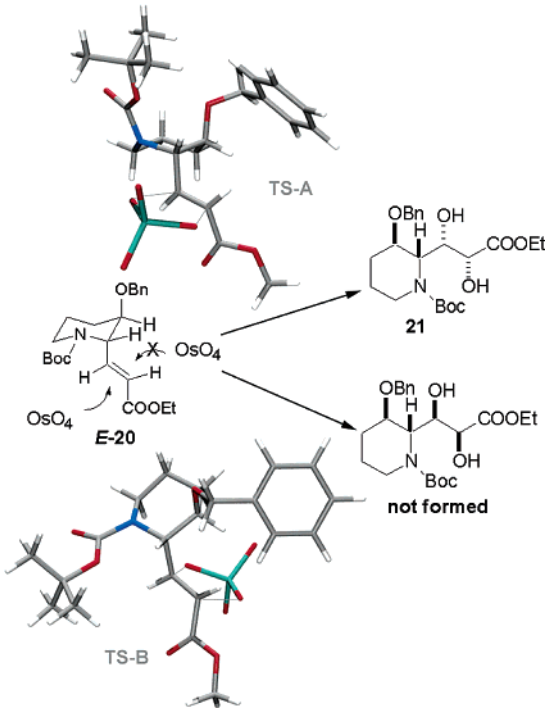
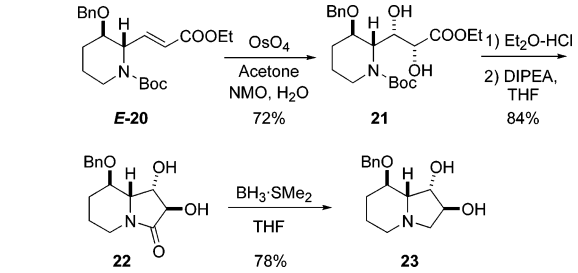


FIGURE 3. Diastereoselectivity of the dihydroxylation of unsaturated ester *E*-**20**.

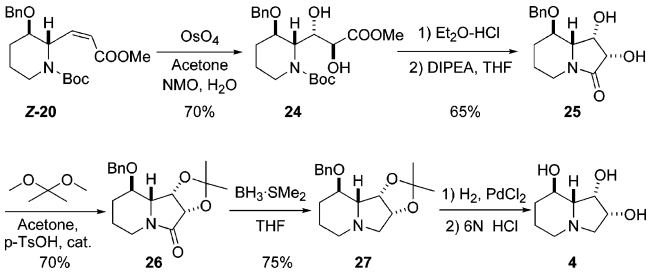
unsaturated esters **20** took place with excellent diastereoselectivity, affording *syn*-diols with 1′*S* configuration. According to geometry optimizations at the ab initio 6-31G* level,[31] in the most stable conformations of *E*-**20** the alkene and benzyloxy are trans-diaxial (ca. 2.5 kcal/mol more stable than the diequatorial). However, within diaxial conformers the energetic difference of the structures arising from rotation of the C2−C1′ bond was too small to justify the observed diastereoselectivity. Thus, we performed a calculation of both transition states (TS-A and TS-B), leading to the osmate intermediates resulting of the OsO_4 attack to each of the two diastereotopic double-bond faces (Figure 3). The geometry of these TSs was optimized at the semiempirical PM3 level, and their corresponding vibrational analysis showed only one imaginary frequency. Gratifyingly, the lowest energy transition state (TS-A, ca. 6 kcal/mol more stable) is the one leading to the 1′*S* configuration, as experimentally observed. In the most stable TS, the approach of OsO_4 takes place to an anti-periplanar conformation between C2−H and C1′−H bonds, whereas in the less stable transition state (TS-B) osmium approaches to a synclinal conformation. As it can be readily seen, the lower energy TS (TS-A) is free of strong steric repulsions because the carbamate can avoid the pathway of the OsO_4. On the other hand, the osmylation by the opposite face encounters the steric repulsion of the C3−H bond as well as the benzyl group. Taking this into account, the sense of the diastereoselectivity can be easily understood, the most stable TS-A being the one in which the attack of osmium is opposite to the benzyloxy group (Figure 3). The same arguments can be used in the understanding of the dihydroxylation of *Z*-**20**.

(31) Spartan 02'; Wavefuction, Inc.; Irvine, CA.

SCHEME 4



SCHEME 5



Thus, starting from *E*-**20**, syn-dihydroxylation with osmium tetroxide afforded diol **21** in good yield and total stereoselectivity (Scheme 4). Careful acid hydrolysis of the *tert*-butyl carbamate, followed by treatment with DIPEA, cleanly afforded the cyclic amide **22**, which was reduced by borane−dimethyl sulfide complex to the protected 2-epi-swainsonine **23** in good yield.

To synthesize swainsonine **4**, a diastereomerically enriched mixture of **20** (Z/E 5/1) was dihydroxylated under the same conditions described above (Scheme 5). Diol **24** was obtained in excellent diastereoselectivity and then cyclized as described above for **21** to give **25**. Both products **24** and **25** were obtained in good yield but accompanied by a small amount of products derived from the *E* isomer that could not be removed by chromatography. Protection with 2,2-dimethoxypropane afforded diastereomerically pure **26** in good yield since the trans stereochemistry of the products derived from *E*-**20** impeded its protection. The cyclic amide **26** was then reduced to obtain the protected swainsonine **27**,[10a,e,k,o] which was spectroscopically identical to that described.[10,e,k,o] Following their procedure, **27** was easily converted into swainsonine **4** by hydrogenation with $PdCl_2$ and HCl hydrolysis.

In summary, we have developed an efficient procedure for the preparation of polyhydroxy piperidine and indolizine alkaloids. The key intermediate **7** was prepared in both enantiomeric forms from unsaturated epoxide **9**, easily obtained by Sharpless epoxidation. The same intermediate **7** was used as a precursor of monocyclic and bicyclic important glycosidase inhibitors, thereby illustrating its high synthetic utility.

Acknowledgment. Financial support from CIRIT (2001SGR-00050) and from DGICIT (BQU2002-02459) is gratefully acknowledged. R.M. and C.M. thank CIRIT (Generalitat de Catalunya) for doctoral fellowships.

Supporting Information Available: General experimental information, preparation of compounds **7**, **8**, and **10**−**27** and ^1H and ^{13}C NMR spectra of compounds *E*-**20**, *Z*-**20**, and **21**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048172S