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A Concise Enantioselective Entry to the Synthesis of Deoxy-azasugars

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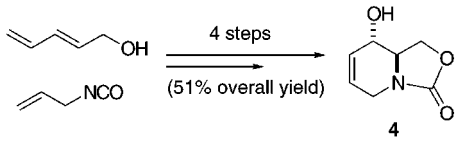
ABSTRACT



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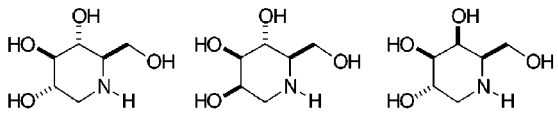
A concise enantioselective preparation of oxazolidinylpiperidine 4, a key intermediate in the synthesis of glycosidase inhibitors such as 1-deoxymannojirimycin or 1-deoxygalactostatin, has been developed. Sharpless catalytic asymmetric epoxidation of (*E*)-2,4-pentadienol followed by treatment with allyl isocyanate afforded epoxy carbamate 8. Regioselective intramolecular ring opening promoted by sodium bis(trimethylsilyl)-amide and ring-closing metathesis provided the bicyclic intermediate 4 in high enantiomeric purity. The four-step sequence takes place in 51% overall yield.

Glycobiology has experienced a major development in recent years uncovering multiple biological processes wherein saccharides play a major role and finding selective inhibitors with therapeutic utility.[1] Among these, glycosidase inhibitors are the most important,[2] being extensively studied in the treatment of metabolic disorders such as diabetes[3] and as antiviral[4] or anticancer agents.[5] Most glycosidase inhibitors are saccharide-like compounds with an easily protonated basic *N*-atom replacing the ring oxygen atom (azasugars) or the anomeric oxygen (aminosugars).[2] Many approaches to their synthesis have been described, but they usually rely on monosaccharide transformations, so that the development of efficient catalytic enantioselective methods for their preparation still constitutes an active area of research. 1-Deoxynojirimycin **1** (Figure 1) is a promising antiviral drug



1 2 3

Figure 1. Naturally occurring glycosidase inhibitors with the 1-deoxy-azasugar structure.

that has served as a precursor for many important glucosidase inhibitors.[6] 1-Deoxymannojirimycin **2** is a specific inhibitor of glucoprotein-processing mannosidase and mammalian α-fucosidase.[7] On the other hand, deoxygalactostatin **3** is a potent galactosidase inhibitor.[8] The therapeutic importance

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of these compounds has stimulated much synthetic effort toward their preparation.[9]

In a project devoted to the enantioselective synthesis of glycosidase inhibitors, we envisaged the preparation of 1-deoxy-azasugars from a common intermediate, oxazolidinylpiperidine **4**, through diastereoselective dihydroxylation of the double bond and/or inversion of the free alcohol. The versatility of the common intermediate **4** has been recently demonstrated by the preparation of **2** and **3** from an adequately protected derivative of **4**.[10,11] The synthesis of **4** has been accomplished so far by three research groups, each involving a considerable number of steps. Katsumura and co-workers prepared the *tert*-butyldimethylsilyl derivative **11** starting from (*R*)-(+)-4-methoxycarbonyloxazolidinone which, in turn, was prepared from glycidol (11 steps overall).[10] Ciufolini et al. prepared the benzyl ether of **4** from a furylglycine derivative in 12 steps,[11] and Sato's group used D-serine as a starting material to prepare **4** again in 12 steps.[12] We describe herein a new entry to the synthesis of glycosidase inhibitors by the preparation of oxazolidinylpiperidine **4** in an extremely straightforward and stereoselective manner using catalytic Sharpless asymmetric epoxidation[13] as the sole source of chirality and catalytic ring-closing metathesis[14] for the construction of the piperidine ring.

Our retrosynthetic analysis of deoxy-azasugars is outlined in Figure 2. The common intermediate **4** would be prepared

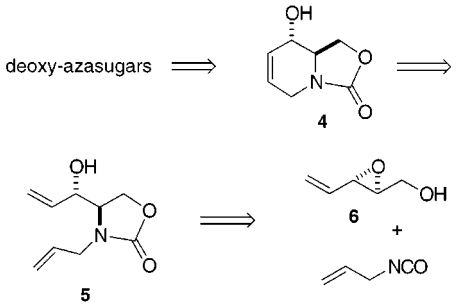


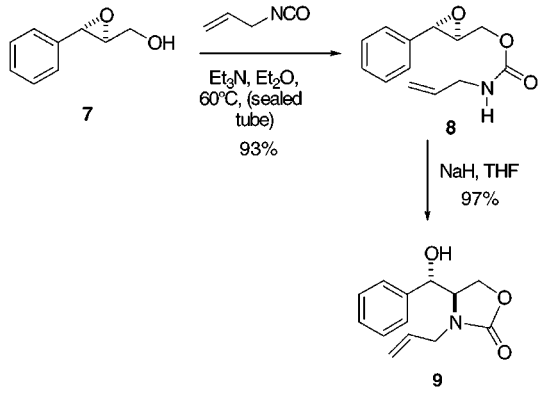
Figure 2. Retrosynthetic analysis.

by ring-closing metathesis[15] of oxazolidinone **5** which, in turn, would come from the regioselective ring opening of enantiomerically enriched epoxy alcohol **6** by allyl isocyanate.

Alkyl isocyanates have been used in some instances as nitrogen nucleophiles to regioselectively attack the C-2 position of epoxy alcohols,[16] but the reaction of allyl isocyanate[17] remains virtually unexplored. To fill this gap, reaction conditions were first optimized using 3-phenyl-2,3-epoxypropan-1-ol **7**[13a] as a model epoxide.

The best reaction conditions found consisted of heating the epoxy alcohol with allyl isocyanate and triethylamine in ether at 60 °C in a sealed tube. In this way, epoxy carbamate **8** was obtained in an excellent 93% yield. The intramolecular regioselective ring opening of this carbamate was induced by exposure to NaH in THF, yielding the cyclic oxazolidinone **9** almost quantitatively (Scheme 1).[18]

Scheme 1



Readily available (*E*)-2,4-pentadien-1-ol[19] was first submitted to Sharpless asymmetric epoxidation. The process went to completion in 2 h at −20 °C, yielding, after treatment with Ph_3P and citric acid, epoxy alcohol **6**.[20] The crude reaction mixture was then treated according to the previously optimized reaction conditions (allyl isocyanate/Et_3N in ether

(9) Selected synthesis of 1-deoxymannojirimycin: (a) 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. (b) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841−859. (c) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741−746. (d) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175−3185. (e) Park, K. H.; Yoon, Y. J.; Lee, S. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2621−2623. (f) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327−336. (g) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319−326. (h) Pederson, R. L.; Kim, M.-J.; Wong, C.-H. *Tetrahedron Lett.* **1988**, *29*, 4645−4648. (i) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123−1126.

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(18) All new compounds gave satisfactory IR, ^1H and ^{13}C NMR, and MS data.

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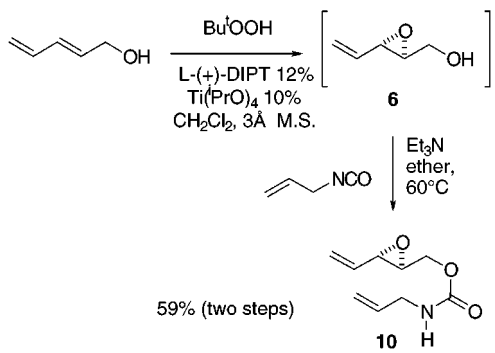
(20) Pure (2*S*,3*S*)-2,3-epoxy-4-penten-1-ol (>91% ee) can be obtained by distilation of the crude reaction mixture. See: Wershofen, S.; Scharf, H.-D. *Synthesis* **1988**, 854−858.

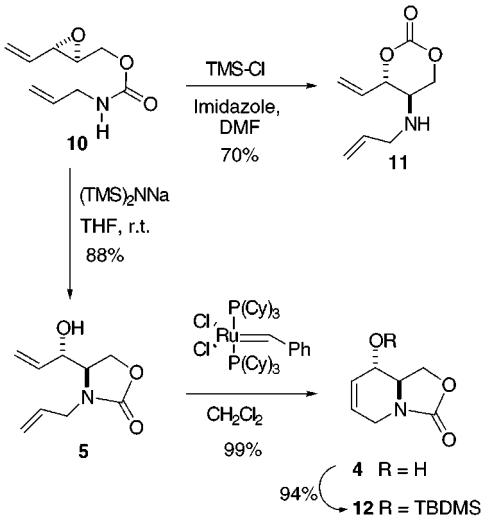
at 60 °C in a pressure tube) to provide allyl carbamate **10** in 59% overall yield from 2,4-pentadienol (Scheme 2).

Scheme 2



The subsequent intramolecular ring opening of **10** required extensive experimentation, since the previously developed conditions (NaH/THF) gave very poor yields of the desired oxazolidinone **5**. Other bases such as Bu^{t}OK gave only sligthly better yields whereas treatment with Lewis acid catalysts such as $LiClO_4$ or Ti(^{i}PrO)$_4$ led to decomposition of the starting material. On the other hand, reaction of **10** with TMS-Cl/imidazole/DMF afforded the cyclic carbonate **11** in 70% yield (Scheme 3).[21] We were finally pleased to find that the use of sodium bis(trimethylsilyl)amide in THF provided the desired oxazolidinone **5** in 88% yield and that under these conditions **11** was not present in the crude reaction mixture. According to our expectations, the ring-closing metathesis reaction on the doubly olefinic compound **5** took place cleanly using 10 mol % of Grubbs' catalyst[14] in dichloromethane at room temperature and afforded the target oxazolidinylpiperidine **4** in quantitative yield. For structural confirmation purposes, **4** was converted into the known *tert*-butyldimethylsilyl derivative **12** (TBDMS-Tf, 2,6-lutidine, CH_2Cl_2). As expected, **12** showed ^{1}H and ^{13}C NMR spectra completely coincident with those described in the literature.[10] Moreover, the specific rotation of **12** ($[\alpha]_D = 24.9$ (*c* 1.0, $CHCl_3$) indicated a 96% ee (lit.[10] $[\alpha]_D = 26.0$ (*c* 1.0, $CHCl_3$)) which corresponds to the enantiomeric purity of epoxide **6** arising from the Sharpless epoxidation.[22]

Scheme 3



In summary, an extremely concise enantioselective synthesis of deoxy-azasugars has been developed. The key intermediate **4** in the synthesis of 1-deoxymannojirimycin **2** and deoxygalactostatin **3** has been prepared in only four steps and 51% overall yield from 2,4-pentadien-1-ol in what constitutes a formal total synthesis of those compounds. The present work is among the most concise enantioselective entries to the synthesis of deoxy-azasugars described up to now.

Acknowledgment. Financial support from DGICYT (PB98-1246 and PB97-0939) and from CIRIT (1998SGR 00005) is gratefully acknowledged.

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(21) Cyclic carbonate **11** can be seen as arising from an acyl migration product of **5**. Treatment of **5** with TMS-Cl/imidazole/DMF afforded a complex mixture of products wherein **11** was present.

(22) Since **4** and **5** are highly crystalline solids, it should be possible to increase the enantiomeric purity of **4** by crystallization.