Pergamon

Tetrahedron Letters 39 (1998) 3371–3374

TETRAHEDRON LETTERS

Syntheses of Iminolyxitols *via* Tandem Reduction-Alkenylation of O'Donnell's Schiff Bases.

Hossein Razavi and *Robin Polt

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received 14 January 1998; revised 23 February 1998; accepted 25 February 1998

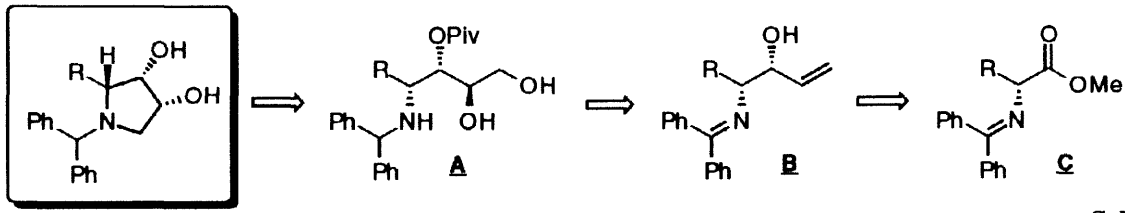
Abstract: *The concise enantioselective synthesis of iminolyxitol glycosidase inhibitors starting from benzophenone imines of D-serine and L-alanine esters is very efficient. The reductive-alkenylation of the Schiff bases followed by substrate-directed dihydroxylation and amino dehydration gave the polyhydroxylated pyrrolidines in excellent overall yields (19.6% for 3 —> 8, 9.9% for 9 —> 13.)*

The inhibition of glycoconjugate processing enzymes (*e.g.* glycosidases, glycosyltransferases) is an effective method for modulating cell-surface glycosylation and attendant cellular functions such as recognition and metabolism.[1] Polyhydroxylated pyrrolidines have been shown to be potent inhibitors of various glycosidases and strong synergistic inhibitors of glycosyltransferases.[2] In particular, 1,4-*dideoxy*-1,4-imino-D-lyxitol (**1**)[3] and 1,4,5-*trideoxy*-1,4-imino-L-lyxitol (**2**)[4] have been shown to be reversible inhibitors of α-galactosidase from green coffee beans and α-fucosidase from bovine kidney, respectively. (**Figure 1**) Recently a number of both carbohydrate[5] and non-carbohydrate[6] based syntheses of furanose-derived azasugars has been reported. In our effort to develop new methodology for the efficient synthesis of these biologically interesting compounds we have adapted amino acid-based approaches used for the synthesis of glycosphingolipids,[7] sphingosines[8] and amino sugars[9] to the pyrrolidine polyols **1** and **2**.

1 **2**

Figure 1

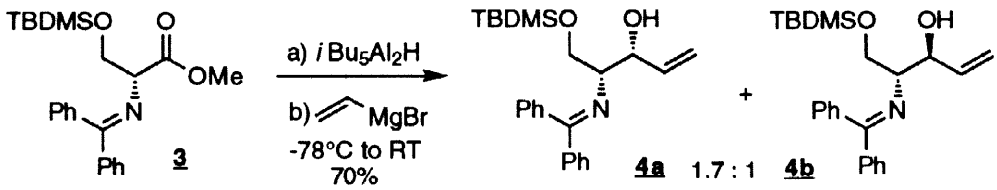
Our retrosynthetic strategy depended on the closure of diols such as **A** which can be synthesized from the corresponding allylic alcohols **B** *via* diastereoselective dihydroxylation. The β-amino alcohols **B** are readily prepared from tandem reduction-alkenylation of fully protected amino acids **C**. (**Scheme 1**) Reduction of the Schiff base moieties provide 2° benzhydrylamines which readily cyclize with the terminal carbon under a number of "dehydrating conditions," and which can be easily removed following cyclization and/or any subsequent manipulations.



Scheme 1

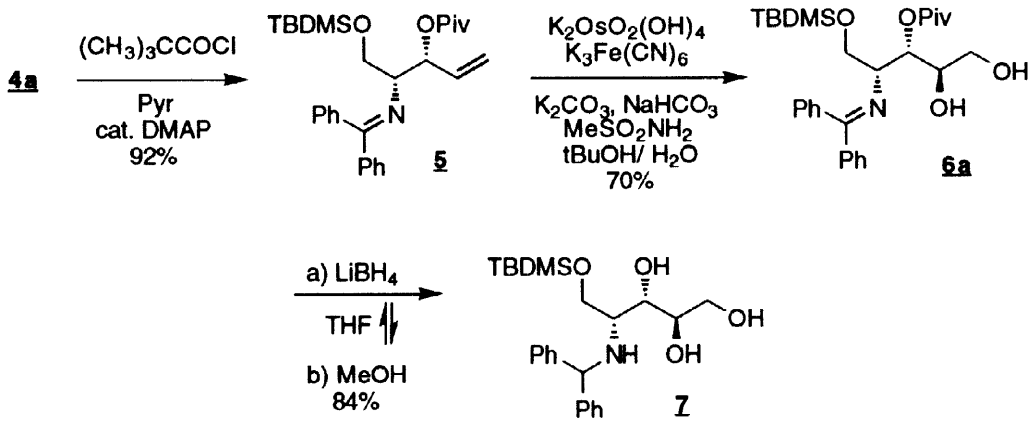
PII: S0040-4039(98)00495-X

For the synthesis of azasugar **1** , compound **3**, conveniently prepared from D-serine,[10] was sequentially treated with iBu$_5$Al$_2$H (1:1 mixture of i Bu$_2$AlH and i Bu$_3$Al) followed by vinyl magnesium bromide in THF at -78°C to give an easily separable mixture of diastereomers **4a** and **4b** (1.7:1) in 70% yield. (**Scheme 2**)[8,11] We have previously shown this method to be *threo* selective (>20:1) when non-coordinating solvents such as hexane, hexane/CH_2Cl_2 or toluene have been used,[9] however, the stereoselectivity drops significantly in ethereal solvents. In our attempts to reverse the selectivity of this reaction, vinyl magnesium bromide in a strongly coordinating solvent was used (commercially available as a 1 M solution in THF) which enabled us to obtain substantial amounts of the epimeric *erythro* product.[12] Racemization of the original chiral center has not been observed in either case.



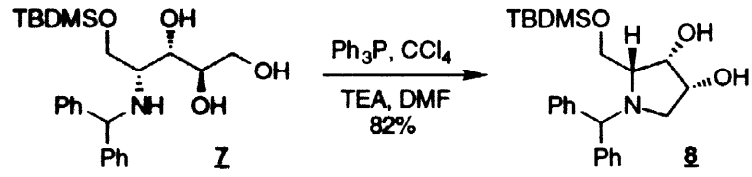
Scheme 2

Next, the *threo* amino alcohol **4a** was acylated using pivaloylchloride in 92% yield followed by substrate-directed osmylation of the resulting pivalate **5** with catalytic amount of $K_2OsO_2(OH)_4$ and $K_3Fe(CN)_6$ to afford a mixture of diols **6** in good yield (70% isolated yield of **6a**) and selectivity (ratio of **6a**:**6b** 7:1).[13] Whereas the use of $CH_3SO_2NH_2$ increased the turnover of the catalyst as described by Sharpless,[13] the addition of amine bases (e.g. pyridine) to the reaction mixtures was unnecessary (presumably due to the presence of the imine nitrogen) and actually resulted in decreased yields. Subsequently, the major product **6a** was treated with $LiBH_4$ under reflux in THF:MeOH, which simultaneously reduced the imine and cleaved the pivalate protecting group to provide the amino triol **7** in 84% yield.[14] (**Scheme3**).



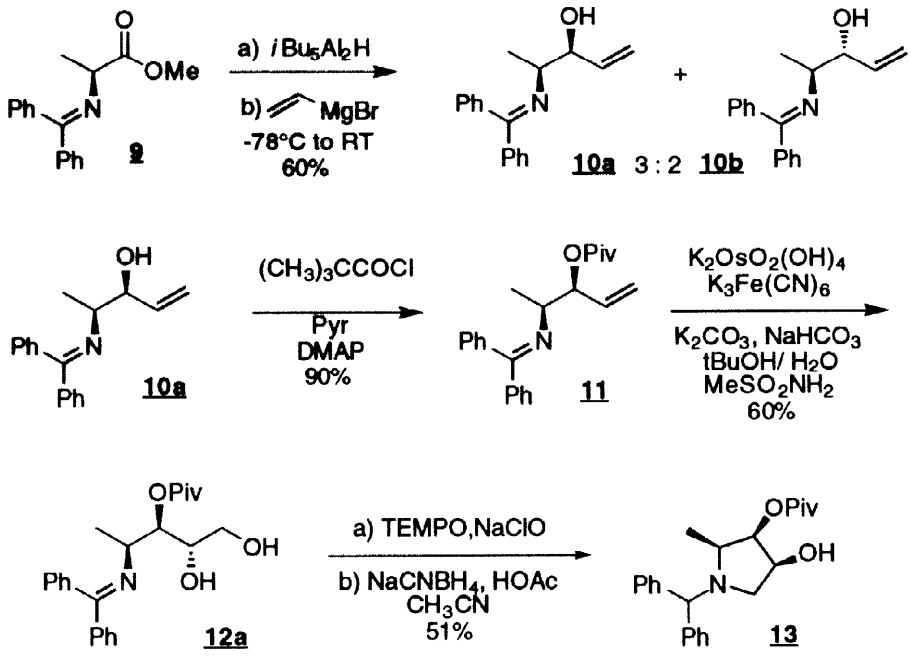
Scheme 3

The cyclization of compound **7** was accomplished in 82% yield in the presence of Ph_3P, CCl_4 and triethyl amine in DMF to afford the protected D-iminolyxitol **8**.[15] (**Scheme 4**) The structure of **8** was confirmed by single crystal X-ray analysis.[16]



Scheme 4

O'Donnell's Schiff base of L-alanine methyl ester was utilized for the synthesis of polyhydroxylated pyrrolidine **2**. The reductive-alkenylation of the Schiff base amino ester **9**, followed by protection of the resulting alcohol **10a** as the pivalate **11** and dihydroxylation as before (6:1 ratio of **12a**:**12b**) gave the requisite protected triol in excellent overall yield (60% yield of isolated **12a**). Selective TEMPO-catalyzed oxidation[17] of the primary alcohol using NaOCl as a primary oxidant, followed by reductive-amination of the crude aldehyde with $NaCNBH_3$ in the presence of acetic acid (pH 5) provided the corresponding pyrrolidine **13** in 51% yield for both steps.[9b] (**Scheme 5**)



Scheme 5

Cleavage of the N-benzhydryl protection is easily accomplished with H_2/Pd-C, and the pivalate esters are cleanly saponified with 3 equiv. Bu_4NOH in aqueous dioxane In conclusion, the efficient synthesis of iminolyxitols **8** (19.6% overall from **3**) and **13** (9.9% overall from **9**) was achieved from readily available crystalline Schiff bases. This methodology is currently being applied to the synthesis of (-)-swainsonine and some related analogs.

Acknowledgements. We are grateful to the NSF for support (CHE-9526909). H.R. would like to thank the University of Arizona Graduate College for a Dean's Fellowship.

References and Notes:

1 a) Provencher, L.; Steensma, D. H.; Wong, C.-H. *Bioorg. Med. Chem.* **1994**, *2*, 1179, b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

2 a) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182, b) Wong, C.-H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefsky, S. J.; Weston, B. W.; Lowe, J. B. *J. Am. Chem. Soc.* **1992**, *114*, 7321.

3 a) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127, b) Bashyal, B. P.; Fleet, G. W. J.; Gough, M.J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083.

4 Wong, C.-H.; Provencher, L.; Porco, J. A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492.

5 a) Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125, b) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685, c) Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P.W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095, d) Buchanan, J. G.; Edgar, A. R.; Hewitt, B. D. *J.C.S. Perkin Trans. 1.* **1987**, 2371, e) Han, S.-Y.; Liddell, P. A.; Joullie, M. M. *Synth. Commun.* **1988**, *18*, 275, f) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637, g) Fleet, G. W. J.; Son, J. C.; Green, D. St. C.; di Bello, I. C.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649, h) Wehner, V.; Jager, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169, i) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asym.* **1990**, *1*, 119, j) Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc. Perkin Trans. 1* **1990**, 699, k) Meng, Q.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 445, l) Moss, W. O.; Bradbury, R. H.; Hales, N. J.; Gallagher, T. *J.C.S. Perkin Trans. 1* **1992**, 1901, m) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827, n) Schumacher-Wandersleb, M. H. M. G.; Peterson, S.; Peter, M. G. *Liebigs Ann. Chem.* **1994**, 555, o) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175, p) Park, K. H. *Heterocycles* **1995**, *41*, 1715, q) Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103.

6 a) Kahl, J.-U.; Wieland, T. *Liebigs Ann. Chem.* **1981**, 1445, b) DeShong, P.; Sidler, D. R.; Kell, D. A.; Aronson, N. N. *Tetrahedron Lett.* **1985**, *26*, 3747, c) Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 716, d) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533, e) Jager, V.; Hummer, W. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1171, f) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240, g) Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678, h) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron: Asym.* **1992**, *3*, 681, i) Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem.* **1993**, *58*, 985, j) Wang, Y.-F.; Dumas, D. P.; Wong, C.-H. *Tetrahedron Lett.* **1993**, *34*, 403, k) Hassner, A.; Falb, E.; Nudelman, A.; Albeck, A.; Gottlieb, H. E. *Tetrahedron Lett.* **1994**, *35*, 2397, l) Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 2889, m) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099, n) Blanco, M. J.; Sardina, F. J. *Tetrahedron Lett.* **1994**, *35*, 8493, o) Zhi-cai, S.; Chun-min, Z.; Guo-qiang, L. *Heterocycles* **1995**, *41*, 277, p) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621, q) Meyers, A. I.; Andres, C. J.; Resek, J. E.; McLaughlin, M. A.; Woodall, C. C.; Lee, P. H. *J. Org. Chem.* **1996**, *61*, 2586, r) Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372.

7 Peterson, M. A.; Polt, R. *J. Org. Chem.* **1993**, *58*, 4309.

8 a) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469. For an interesting example of this method applied to synthesize a pyrrolidine, see : b) McGrane, P.L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485.

9 a) Sames, D.; Polt, R. *J. Org. Chem.* **1994**, *59*, 4596, b) Sames, D.; Polt, R. *Synlett* **1995**, 552.

10 O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

11 The yield of this reaction is highly dependant on the purity of the vinyl magnesium bromide.

12 1,4-dideoxy-1,4-imino-D-ribitol was synthesized from the *erythro* product **4b** *via* the same methodology. Thus, the stereochemistry of the osmylation is controlled primarily by the oxygen-bearing allylic center and is not influenced by the nitrogen-bearing homoallyic center.

13 Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

14 Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.

15 a) Chen, Y.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 4917, b) A solution of amino triol **7** (1.82g, 4.22 mmol) in anhydrous DMF (14 ml) was treated with triphenylphosphine (2.21g, 8.44 mmol), CCl_4 (814 µl, 8.44 mmol) and triethylamine (1.18 ml, 8.44 mmol) sequentially under argon and the resulting mixture was stirred at RT in the dark overnight. After 15 hours, the reaction was quenched with MeOH (10 ml) in a dropwise fashion, the mixture was concentrated in the *vacuo* and the residue was chromatographed with 25% EtOAc/Hexanes on SiO_2 to give **8** as a white solid (1.43g, 82%).

16 Carducci, M.; Razavi, H.; Polt, R. Preliminary isotropic refinement: R = 4.5%. The complete structural data for **8** will be published upon complete refinement.

17 TEMPO (2,2,6,6-tetramethypiperidinyl-1-oxide) has been shown to be useful in the selective oxidation of 1° alcohols and amino alcohols: a) Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177, b) Leanna,M.R.; Sowin, T.J.; Morton, H.E. *Tetrahedron Lett.* **1992**, *33*, 5029.