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A Short Synthesis of Azasugars via Aldol Reaction of Chelated Amino Acid Ester Enolates

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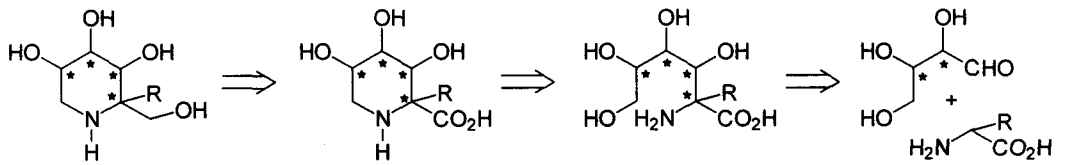
Abstract: Aldol reactions of chelated amino acid ester enolates with chiral aldehydes gives rise to polyhydroxylated amino acids in a highly stereoselective fashion. These oxygenated amino acids can be converted into polyhydroxylated pipecolinic acids and azasugars by cyclization using the Mitsunobu reaction. A interesting epimerization was observed during the cyclization. © 1997 Elsevier Science Ltd.

Based on their structural relationship to sugars, polyhydroxylated piperidines (azasugars) and pipecolinic acid derivatives are interesting candidates for the inhibition of various glycosidases. Protonated azasugars act as transition state analogues of these enzymes.[1] Deoxynojirimycin,[2] isolated from *Bacillus* strains,[3] and deoxymannojirimycin,[4] from *Lonchocarpus sp.*,[5] are specific inhibitors of glucosidases,[2] mannosidases[6] and fucosidases.[7] (2*S*,3*R*,4*R*,5*S*)-Trihydroxy pipecolinic acid,[8] isolated from *Baphia racemosa*,[9] acts as a glucoronidase and fucosidase inhibitor.[10] This biological activity is important for the therapy of diabetes,[11] cancer[12] and viral infections.[13]

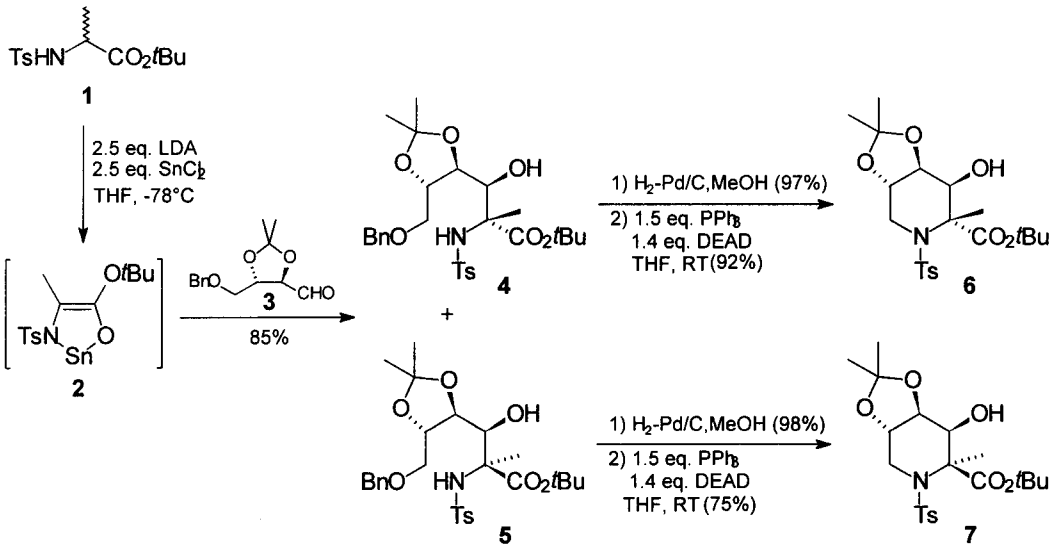
In the meanwhile, several interesting syntheses of natural as well as synthetical deoxyazasugars[14] and related pipecolinic acid derivatives[15] were described. The interesting properties of these compounds encouraged us to develop our own approach to their syntheses, based on asymmetric aldol reactions of chelated ester enolates. The retrosynthetical analysis of the azasugars (scheme 1) leads to the corresponding pipecolinic acid derivatives, which can be obtained from acyclic polyhydroxylated amino acids. These should be accessible via aldol reaction of amino acid ester enolates and chiral polyhydroxylated aldehydes.



Scheme 1

For some time our group has been interested in reactions of metal chelated enolates of *N*-protected amino acid esters. Depending on the metal ion used, these chelated enolates show higher stability than the corresponding lithium enolates. In addition, because of the fixed enolate geometry, their reactions are more selective than those of the lithium enolates. Besides chelate enolate Claisen rearrangements,[16] particulary aldol reactions give very good results.[17] Herein the application of an asymmetric version of this reaction to the synthesis of polyhydroxylated amino acids and azasugars is described.

Deprotonation of alanine ester **1** with an excess of LDA and subsequent transmetalation with tin chloride, probably results in the formation of chelated enolate **2** (Scheme 2). Addition of chiral aldehyde **3**[18] gave rise to the aldol products **4** and **5** in a 4:1 ratio and excellent yield. The induced diastereoselectivity (config. of β-OH) was 95% for the major diastereomer **4**. Diastereomerically pure **4** could be obtained by a single crystallization step (55% yield from **1**). The pure minor diastereomer **5** could be obtained by flash chromatography. After cleavage of the benzyl ether and subsequent cyclization under Mitsunobu conditions,[19] the α-methylated pipecolinic acid derivatives **6** and **7** respectively could be obtained in high yields.[20]



Scheme 2

These cyclic derivatives could also be used to determine the configuration of the two stereogenic centers formed in the aldol reaction. Fig.1 shows the coupling constants and the NOE's observed. Irradiation into the α-methyl group of **6** gave only one NOE to the vicinal β-H, while, in the same experiment, **7** shows three NOE's. This can be explained by an axial orientation of the methyl group in **7**, whereas in **6** the methyl group is oriented in the equatorial position. The axial orientation of the β-OH group is confirmed by a small coupling constant (~ 2.5 Hz) between the β-H and the axial γ-H.

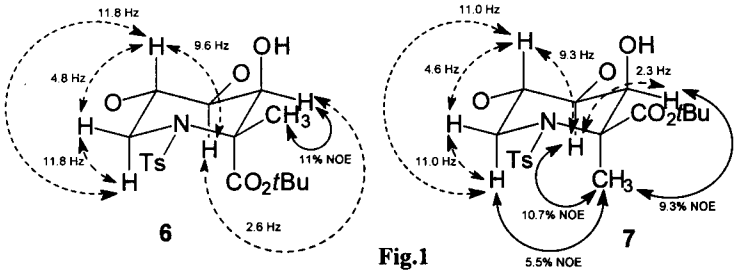
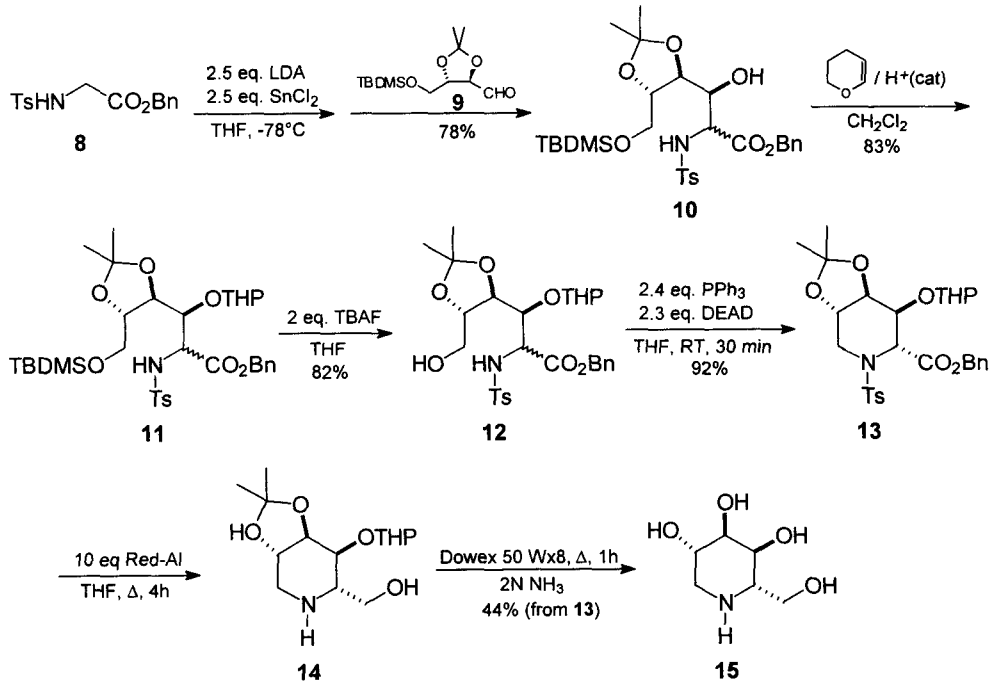


Fig.1

For the synthesis of α-unsubstituted pipecolinic acids, glycine ester **8** was reacted with chiral aldehyde **9**[21] under the conditions described (Scheme 3). In this case the induced diastereoselectivity (β-C) was also very high (> 95% ds) while the α-center gave a 1:1 epimeric mixture. Obviously, this position is configurationally labile and epimerization occurs under the reaction conditions used. Nevertheless, the aldol product **10** was directly used for the following azasugar synthesis. Protection of the β-OH group was necessary in this case to avoid their elimination during the Mitsunobu reaction. The THP protecting group was especially suitable for this purpose. Cleavage of the silyl protecting group and cyclization in the presence of an excess of Mitsunobu reagents gave only one diastereomer of the pipecolinic acid derivative **13**.[20] Addition of an excess Red-Al resulted in a simultaneous cleavage of the *N*-Tosyl protecting group and reduction of the ester moiety. Removal of the acid labile protecting groups gave rise to 1-deoxyaltronojirimycin (**15**).[20]



Scheme 3

The repeated epimerization of the α-chiral center was surprising and obviously occurred before the cyclization and only in the presence of an excess of Mitsunobu reagents. Cyclization of the separated (by chromatography) epimers of **12** with a stoichiometrical amount of PPh_3/DEAD gave the corresponding pipecolinic acid derivatives **13** and 1-*epi*-**13** respectively, without epimerization.[20] Although no epimerization was observed by treating **13** with an excess of Mitsunobu reagents. Obviously the cyclization occurs under kinetically controlled conditions from a rapid epimerization equilibrium.

In summary, we have shown that aldol reactions of chelated amino acid ester enolates with chiral aldehydes give rise to polyhydroxylated amino acids and azasugars in a straightforward and highly stereoselective fashion.

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References and Notes

1 M. L. Sinnott, *Chem. Rev.* **1990**, *90*, 1171, and references cited therein.
2 A. B. Hughes, A. J. Rudge, *Nat. Prod. Rep.* **1994**, *11*, 135.
3 a) D. D. Schmidt, W. Frommer, L. Müller, E. Truscheit, *Naturwissenschaften* **1979**, *66*, 584; b) S. Murao, S. Miyata, *Agric. Biol. Chem.* **1980**, *44*, 219.
4 a) G. W. J. Fleet, N. G. Ramsden, D. R. Witty, *Tetrahedron* **1989**, *45*, 327; b) E. W. Baxter, A. B. Reitz, *J. Org. Chem.* **1994**, *59*, 3175; c) K. H. Park, Y. J. Yoon, S. G. Lee, *J.Chem. Soc. Perkin Trans. 1* **1994**, 2621. d) N. Asano, H. Kizu, K. Oseki, E. Tomioka, K. Matsui, *J. Med. Chem.* **1995**, *38*, 2349; e) Y.-M. Xu, W.-S. Zhou, *Tetrahedron Lett.* **1996**, *37*, 1461; f) L. Poitout, Y. Le Merrer, J.-C. Depezay, *Tetrahedron Lett.* **1996**, *37*, 1609.
5 L. E. Fellows, E. A. Bell, D. G. Lynn, F. J. Pilkiewicz, I. Miura, K. Nakanishi, *J. Chem. Soc., Chem. Commun.* **1979**, 977.
6 a) U. Fuhrmann, E. Bause, G. Legler, H. Ploegh, *Nature* **1984**, *307*, 755; b) A. D. Elbein, G. Legler, A. Tlusty, W. McDowell, R. Schwarz, *Arch. Biochem. Biophys.* **1984**, *235*, 579.
7 S. V. Evans, L. E. Fellows, T. K. M. Shing, G. W. J. Fleet, *Phytochemistry* **1985**, *24*, 1953.
8 a) R. C. Bernotas, B. Ganem, *Tedrahedron Lett.* **1985**, *26*, 4981; b) B. P. Bashyal, H.-F. Chow, L. E. Fellows, G. W. J. Fleet, *Tetrahedron* **1987**, *43*, 415; c) G. W. J. Fleet, L. E. Fellows, P. W. Smith, *Tetrahedron* **1987**, *43*, 979.
9 K. S. Manning, D. G. Lynn, J. Shabanowitz, L. E. Fellows, M. Singh, B. D. Shrire, *J. Chem. Soc., Chem. Comm.* **1985**, 127.
10 I. C. di Bello, P. Dorling, L. E. Fellow, B. Winchester, *FEBS Lett.* **1984**, *176*, 61.
11 a) S. Horii, H. Fukase, T. Matsuo, Y. Kameda, N. Asano, K. Matsui, *J. Med. Chem.* **1986**, *29*, 1038; b) P. B. Anzeveno, L. J. Creemer, J. K. Daniel, C.-H. R. King, P. S. Liu, *J. Org. Chem* **1989**, *54*, 2539.
12 a) M. J. Humphries, K. Matsumoto, S. L. White, K. Olden, *Cancer Res.* **1986**, *46*, 5215; b) J. W. Dennis, K. Koch, S. Yousefi, I. van der Elst, *Cancer Res.* **1990**, *50*, 1867.
13 a) F. M. Platt, G. R. Neises, R. A. Dwek, T. D. Butters, *J. Biol. Chem.* **1994**, *269*, 8362; b) T. M. Block, X. Lu, F. M. Platt, G. R. Foster, W. H. Gerlich, B. S. Blumberg, R. A. Dwek, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 2235.
14 A selection of recent syntheses: a) T. Kajimoto, L. Chen, K. K.-C. Liu, C.-H. Wong, *J. Am. Chem. Soc.* **1991**, *113*, 6678; b) R. H. Furneaux, P. C. Tyler, L. A. Whitehouse, *Tetrahedron Lett.* **1993**, *34*, 3609; c) P. A. Fowler, A. H. Haines, R. J. K. Taylor, E. J. T. Chrystal, M. B. Gravestock, *Carbohydr. Res.* **1993**, *246*, 377; d) L. Poitout, Y. Le Merrer, J.-C. Depezay, *Tetrahedron Lett.* **1994**, *35*, 3293; e) H.-J. Altenbach, K. Himmeldirk, *Tetrahedron: Asym.* **1995**, *6*, 1077; f) C. R. Johnson, A. Golebiowski, E. Schoffers, H. Sundram, M. P. Braun, *Synlett* **1995**, 313.
15 A selection of recent syntheses: a) A. P. Nin, O. Varela, R. M. de Lederkremer, *Tetrahedron* **1993**, *49*, 9459; b) C. Herdeis, E. Heller, *Tetrahedron: Asym.* **1993**, *4*, 2085.
16 a) U. Kazmaier, *Angew. Chem.* **1994**, *106*, 1046; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 998; b) U. Kazmaier, *Liebigs Ann. Chem.* **1997**, 285.
17 a) U. Kazmaier, R. Grandel, *Synlett* **1995**, 945; b) R. Grandel, U. Kazmaier, B. Nuber, *Liebigs Ann. Chem.* **1996**,1143.
18 T. Mukaiyama, K. Suzuki, T. Yamada, F. Tabusa, *Tetrahedron* **1990**, *46*, 265.
19 a) O. Mitsunobu, *Synthesis* **1981**, 1; b) J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris, S. M. Weinreb, *Tetrahedron Lett.* **1989**, *30*, 5709.
20 Selected chiroptical data $[\alpha]_D^{20}$: **6**: + 42.4 (c = 1.6, $CHCl_3$); **7**: +32.1 (c = 1.0, $CHCl_3$); **13**: + 42.6 (c = 0.7, $CHCl_3$); 1-*epi*-**13**: + 27.8 (c = 0.3, $CHCl_3$); **15**: -14.5 (c = 0.7, $CHCl_3$).
21 J. A. Marshall, S. Beaudoin, *J. Org. Chem.* **1994**, *59*, 6614.

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