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Asymmetric synthesis of amino sugars. Part 1: Stereoselective synthesis of (2*S*,3*S*,4*R*,5*S*)-2-amino-1,3,4,5,6-hexanepentol derivatives and their conversion to L-mannosamine derivatives

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Abstract

A novel approach for asymmetric synthesis of amino sugars is developed, starting from readily available chiral building blocks **1** and 2,3-*O*-isopropylideneglyceraldehyde **2**, via the Julia olefination and subsequent dihydroxylation as key steps.

Keywords: amino sugar; L-mannosamine; Julia olefination; dihydroxylation.

Amino sugars are constituents of various biologically active compounds such as anticancer antibiotics[1] and biopolymers[2] and consequently these molecules have been the targets of syntheses for many years. The traditional methods have involved carbohydrates as principal intermediates and usually required multistep synthetic transformations. Recently, several groups have focused on the asymmetric synthesis of amino sugars from non-carbohydrate precursors.[3,4] Among the methods available, the common approaches are direct amination of carbocycles,[5a–c] transformation of isoxazolines[5d–f] and 2-thiazolyl *N*-alkylhydroxylamines,[5g,h] the use of hetero Diels–Alder reactions,[5i,j] [3+2] cycloaddition of nitrones with vinylene carbonate[5k] and the utilization of readily available natural products such as amino acids[5l,m] and lactic acid[5n–p] as chiral pool materials for the construction of amino sugar skeletons. One of the most interesting methodologies is the transformation of serine and threonine into various types of amino sugars.[5q] However, some of these reactions suffer from complete lack of enantioselectivity, lengthy reaction sequences and limited versatility.

We describe here a novel and potentially versatile methodology for asymmetric synthesis of amino sugars either in the D- or L-configuration based on the transformation of the readily available chiral building blocks **1**[6] and **2** into a fully protected derivative of 2-amino polyol **3** (Fig. 1).

Starting from either (*R*)- or (*S*)-**1** and either (2*R*)- or (2*S*)-2,3-*O*-isopropylideneglyceraldehyde **2** and using the Julia olefination process followed by dihydroxylation, one can obtain a priori any one

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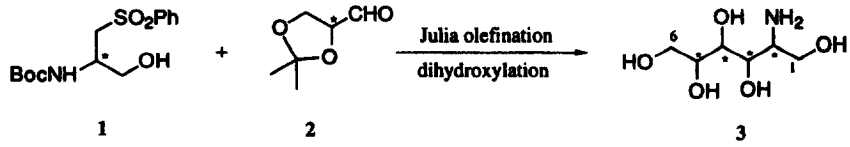
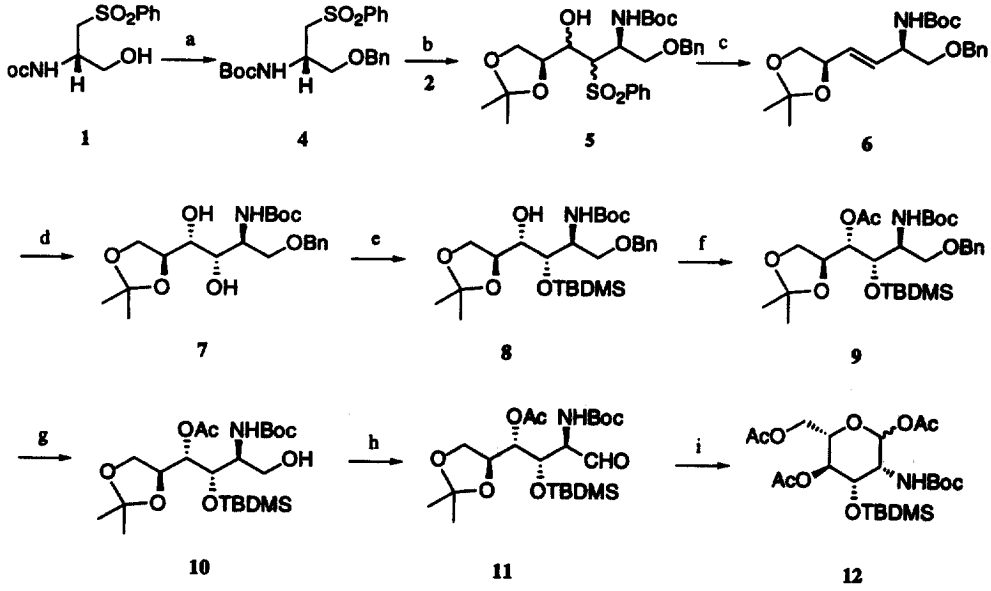


Figure 1.

of four diastereomers of the 2-amino hexanepentol derivative **3** as a major compound with the four asymmetric centers of desired stereochemistry at C-2, C-3, C-4 and C-5. This depends on three factors: the absolute configuration of **1** and **2**, the stereochemistry of the newly created olefin bond (*E* or *Z*) and the course of stereoselection during dihydroxylation. Intramolecular cyclization between C-1 and the OH function at C-5 of 2-aminopolyol **3** provides four 2-amino sugars in pyranose-form: L- or D-mannosamine and L- or D-glucosamine. Likewise, the cyclization between C-1 and the OH function at C-4 affords the furanose-form of these amino sugars. In order to demonstrate our novel approach in this preliminary communication, we have chosen L-mannosamine as a target molecule which is difficult to obtain in enantio- and diastereomerically pure form.[7] The synthesis of 1,4,6-tri-*O*-acetyl-2-*N*-(*tert*-butoxycarbonyl)amino-2-deoxy-3-*O*-*tert*-butyldimethylsilyl-L-mannopyranose **12** is shown in Scheme 1.

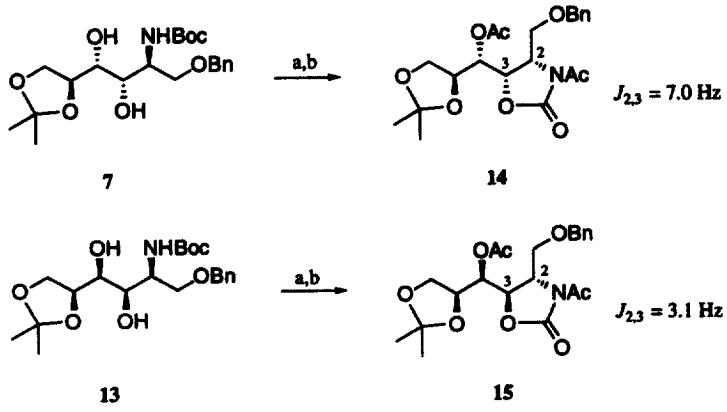


Scheme 1. Reagents and conditions: (a) NaH, THF, 0°C, 30 min, BnBr, Bu_4NI, 0°C, 24 h, 86%; (b) 2 equiv. BuLi, THF, (2*S*)-2,3-*O*-isopropylideneglyceraldehyde **2**, –78°C, 2 h, then rt, 1 h, 85%; (c) 6% Na–Hg, Na_2HPO_4, MeOH, 0°C, 3 h, 80%; (d) OsO_4, NMO, ^tBuOH:H_2O (1:4), rt, 2 h, 95%; (e) TBDMSCl, imidazole, DMF, rt, 24 h, 95%; (f) Ac_2O, Et_3N, DMAP, 50°C, 8 h, 80%; (g) H_2 (1 atm), 10% Pd/C, EtOAc, rt, 6 h, 98%; (h) Py·SO_3, Et_3N, DMSO, 0°C, 2 h, 90%; (i) HCl, MeOH, rt, 8 h, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 80%

Coupling of the dilithiate of **4**, prepared from (*S*)-**1**,[8] with (2*S*)-2,3-*O*-isopropylideneglyceraldehyde **2**[9,10] afforded a diastereomeric mixture of β-hydroxysulfone **5** in good yield.[11] Treatment of the β-hydroxysulfone **5** with 6% Na–Hg furnished the olefin **6** in 80% yield as a mixture of *E*- and *Z*-isomers (4:1) which were easily separated by column chromatography. Dihydroxylation of the *E*-olefin **6** was first investigated using the Sharpless chiral reagent AD-mix-β.[12] After 48 h, 40% conversion of the olefin to a mixture of diols **7** and **13** was attained with a 9:1 ratio, respectively.[13] On the contrary, application of the osmium-catalyzed procedure without any chiral auxiliary[14] afforded a mixture of diols **7** and **13**

in 95% yield with a 77:23 ratio, respectively. These diols are easily separable by preparative column chromatography.

The stereochemistry of diols **7** and **13** was assigned by NMR studies of *N,O*-bisacetyl oxazolidinone **14** and **15**[15] obtained from **7** and **13**, respectively, by treatment with NaH followed by acetylation. The $J_{2,3}$ coupling constants are 7.0 Hz for the 2,3-*anti*-isomer **14** and 3.1 Hz for the 2,3-*syn*-isomer **15**. These values are in agreement with corresponding data for related compounds[5g,16] and are also consistent with the dihedral angles determined from molecular mechanics calculations (approximately 10° for **14** and 115° for **15**). Furthermore, an intense NOE observed between H-2 and H-3, and between H-1 and H-4 in 2D NOESY experiments for oxazolidinone **14** is in accordance with the stereochemistry depicted in Scheme 2.



Scheme 2. Reagents and conditions: (a) NaH, THF, 50°C, 2 h, 80%; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%

The protection of the hydroxy functionalities of the diol **7** was found to be more difficult than expected. Attempts to obtain 3,4-*O*-bis protected diols were successful only in the case of acetyl and isopropylidene protecting groups. The presence of an acetyl group at the C-3 position of diol **7** resulted in undesired α,β-elimination during the oxidation of the C-1 primary alcohol to an aldehyde (step h). Fortunately, 3-*O*-mono TBDMS ether **8** was obtained in 95% yield by employing conventional conditions (TBDMSCl, imidazole, DMF, rt, 24 h). Subsequent acetylation at the C-4 position of **8** furnished the fully protected 2-amino hexanepentol **9** which was subjected to hydrogenolysis to give α-amino alcohol **10**. Oxidation of this amino alcohol by Py·SO_3 in DMSO[17] provided the desired α-amino aldehyde **11** in 90% yield. Hydrolysis of acetonide **11** in MeOH in the presence of a catalytic amount of HCl followed by acetylation afforded the fully protected L-mannosamine **12** as a mixture of α- and β-anomers approximately in 2:1 ratio, respectively, and in 80% yield.[18]

In summary, we have demonstrated an efficient methodology for the construction of amino sugars with good stereochemical control as exemplified by the synthesis of an enantiopure L-mannosamine derivative. Further applications of this new approach to the synthesis of other amino sugars of both L- and D-configurations are in progress.

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15. The signals due to H-2 and H-3 in the ^{1}H NMR ($CDCl_3$) spectra of **14** and **15** are as follows. Compound **14**: δ 4.69 (dd, $J_{3,4}$=$J_{2,3}$=7.0 Hz, 1H, H-3), 4.59 (ddd, J=7.0, 4.8, 2.0 Hz, 1H, H-2). Compound **15**: δ 4.66 (dd, $J_{3,4}$=4.7 Hz, $J_{2,3}$=3.1 Hz, 1H, H-3), 4.45–4.55 (m, 1H, H-2).
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18. Compound **12**: IR (neat) 3449, 3031, 2959, 1748, 1714, 1504, 1392, 1369, 1233, 1165, 1140, 1059, 967, 840 cm^{-1}; ^{1}H NMR (250 MHz, $CHCl_3$) δ 6.15 (br. s, α-anomer H-1) and 5.85 (d, $J_{1,2}$=2.4 Hz, β-anomer H-1), 1H; 5.05–4.8 (m, α-H-4 and β-H-4, α-NH and β-NH), 2H; 4.45–4.30 (m), 4.28–4.10 (m), 4.04 (dd, J=12.3, 2.5 Hz), 3.95–3.85 (m), 3.82–3.75 (m), 5H; 2.14 (s), 2.10 (s), 2.09 (s), 2.08 (s), 9H; 1.44 (s), 9H; 0.89 (s), 0.86 (s), 9H; 0.12 (s), 0.10 (s), 0.09 (s), 6H; ^{13}C NMR (62.9 MHz, $CHCl_3$) δ 170.8, 170.6, 169.8, 169.6, 169.2, 168.4 (CH_3CO); 155.7 (Me_3COCO); 92.3 (C-1, α-anomer), 91.6 (C-1, β-anomer), 80.2 (Me_3COCO, α), 80.0 (Me_3COCO, β), 72.9 (C-3-β or C-5-β interchangeable attribution), 70.1 (C-3-α or C-5-α), 69.3 (C-3-β or C-5-β), 68.8 (C-3-α or C-5-α), 68.4 (C-4-β), 68.1 (C-4-α), 62.9 (C-6-β), 62.3 (C-6-α), 53.9 (C-2-β), 51.1 (C-2-α), 28.3 (Me_3COCO), 25.0 (Me_3CSiMe_2), 21.0 and 20.8 (CH_3CO), 17.9 (Me_3CSiMe_2), –4.8 (Me_3CSiMe_2, β), –5.0 (Me_3CSiMe_2, α); MS (CI) *m/z* 537 [M+NH_4], 436.