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Synthesis of C6-substituted 3,4-dideoxy furanoid sugar amino acids

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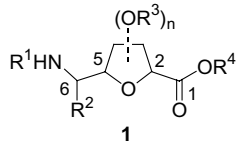
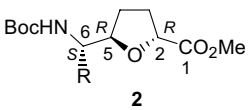
Abstract—A variety of chiral 3,4-dideoxy furanoid sugar amino acids have been synthesized, which were substituted at C6 with different alkyl groups, such as methyl, benzyl, isopropyl and hydroxymethyl synthesized from their corresponding *N*,*N*-dibenzylaminoaldehydes.

Introduction of a stereogenic centre at the C6 position of the amino terminus of furanoid amino acids gives rise to an additional combinatorial site in these multifunctional building blocks **1** that will not only help to induce desired secondary structure in peptides, but will also allow to mimic the side chains of natural amino acids influencing the hydrophobicity/hydrophilicity of the resulting peptidomimetic molecules.[1] Development of a robust synthetic strategy to construct these molecules in enantiomerically pure form will allow their application as dipeptide isosteres in peptidomimetic studies. C7-Substituted pyranoid sugar amino acids based on a tetrahydropyran framework have already been developed.[2] Compounds with a methyl at C6 of 3,4-dideoxy furanoid sugar amino acids have also been synthesized and used in peptidomimetic studies by Koert et al.[3] However, the reported procedures suffer from poor diastereoselectivity leading to mixtures of isomers. Herein, we describe an alternate method for the synthesis of C6-substituted furanoid sugar amino acids. The process, which uses chiral *N*,*N*-dibenzylaminoaldehydes and glyceraldehyde acetonide as starting materials, is applied to the synthesis of a variety C6-substituted 3,4-dideoxy furanoid sugar amino acids, (2*R*,5*R*,6*S*)-6-amino-2,5-anhydro-3,4,6-trideoxy-aldonic acids **2** with 6-methyl (**a**), 6-benzyl (**b**), 6-isopropyl (**c**) and 6-(CH_2OBn) (**d**) substituents.



1

R^1, R^3, R^4 = protective groups;
R^2 = alkyl or aryl substituents; n = 0-2



2

a: R = Me; **b**: R = CH_2Ph
c: R = $CHMe_2$; **d**: R = CH_2OBn

The synthesis is outlined in Scheme 1. One of the starting materials in this scheme was the commercially available (*S*)-*N*,*N*-dibenzylaminoaldehyde[4] **3a** (R = Me) that could also be prepared from L-Ala.[5] The second starting material used was 3,4-*O*-isopropylidene-1,1-dibromo-but-1-en-3,4-diol **4**[6] prepared from (*R*)-glyceraldehyde acetonide, which could be made easily in large quantities by oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol using $NaIO_4$.[7] Treatment of **3a** at −78 °C with the Li-acetylide, prepared in situ by reacting **4** with *n*-BuLi in dry THF at −78 °C for 30 min and subsequently at room temperature for an additional 30 min, gave the expected adduct **5a**[8] as the major product in 81% yield with excellent diastereoselectivity and, as expected, with a 5*R* stereochemistry.[4a,9]

Hydrogenation of **5a** using 20% $Pd(OH)_2$–C as a catalyst in MeOH reduced the triple bond and at the same time also deprotected NBn_2 to give a free amine,[10] which was reprotected using Boc_2O to furnish **6a** in 85% yield.[8]

Treatment of **6a** with acid deprotected the acetonide moiety giving the triol **7a** in 95% yield. Selective sulfonylation of the primary hydroxyl group of **7a** using 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl) gave a sulfonate intermediate that was treated with anhydrous K_2CO_3 to carry out a facile intramolecular ring closure reaction via an epoxide intermediate to get the tetrahydrofuran framework of **8a** in 72% yield in two steps.[11] Finally, a two-step oxidation process converted the

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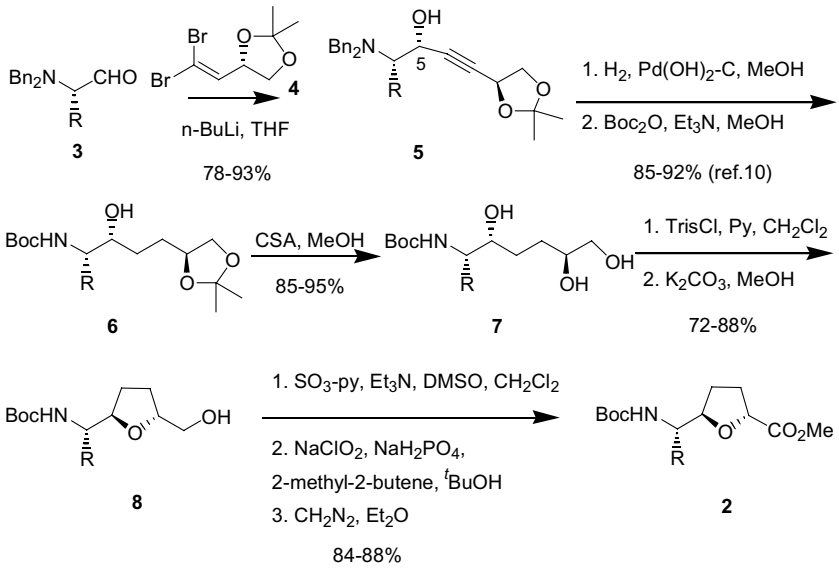

[**a**: R = Me; **b**: R = CH_2Ph; **c**: R = $CHMe_2$; **d**: R = CH_2OBn]

Scheme 1.

primary hydroxyl group of **8a** into an acid that was treated with an excess of diazomethane in ether to get the final product **2a**[12] in 84% yield.

Similarly, starting with *N*,*N*-dibenzylphenylalaninal **3b**, *N*,*N*-dibenzylvalinal **3c** and *N*,*N*,*O*-tribenzylserinal **3d** compounds **2b**, **2c** and **2d**, respectively, were synthesized following Scheme 1.[12]

Acknowledgements

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References

1. For reviews on sugar amino acids see: (a) Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *J. Chem. Sci.* **2004**, *116*, 187–207; (b) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514; (c) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421–435; (d) Chakraborty, T. K.; Jayaprakash, S.; Ghosh, S. *Comb. Chem. High Throughput Screening* **2002**, *5*, 373–387; (e) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253; (f) Peri, F.; Cipolla, L.; Forni, E.; La Ferla, B.; Nicotra, F. *Chemtracts Org. Chem.* **2001**, *14*, 481–499.
2. (a) Raunkjær, M.; El Oualid, F.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Org. Lett.* **2004**, *6*, 3167–3170; (b) Mazur, A. W.; Kulesza, A.; Mishra, R. A.; Cross-Doersen, D.; Russell, A. F.; Ebetino, F. H. *Bioorg. Med. Chem.* **2003**, *11*, 3053–3063; (c) Kulesza, A.; Ebetino, F. H.; Mishra, R. K.; Cross-Doersen, D.; Mazur, A. W. *Org. Lett.* **2003**, *5*, 1163–1166.
3. (a) Vescovi, A.; Knoll, A.; Koert, U. *Org. Biomol. Chem.* **2003**, 2983–2997; (b) Schrey, A.; Vescovi, A.; Knoll, A.; Rickert, C.; Koert, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 900–902; (c) Schrey, A.; Osterkamp, F.; Straudi, A.; Rickert, C.; Wagner, H.; Koert, U.; Herrschaft, B.; Harms, K. *Eur. J. Org. Chem.* **1999**, 2977–2990.
4. (a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162; (b) Reetz, M. T.; Drewes, M. W.; Schwickardi, R. *Org. Synth.* **1998**, *76*, 110–115.
5. (a) Chakraborty, T. K.; Dutta, S. *Synth. Commun.* **1997**, *27*, 4163–4172; (b) O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 4271–4274; (c) Beaulieu, P.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635–3645.
6. Gung, B. W.; Kumi, G. *J. Org. Chem.* **2003**, *68*, 5956–5960.
7. (a) Schmid, C. R.; Bryant, J. D. *J. Org. Chem.* **1991**, *56*, 4056–4058; (b) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056–4058.
8. All new compounds were characterized by IR, ^1H and ^{13}C NMR and mass spectroscopic studies.
9. For recent reports on the diastereoselective nucleophilic addition to *N*,*N*-dibenzylaminoaldehydes see: (a) Fukuzawa, S.; Miura, M.; Saitoh, T. *J. Org. Chem.* **2003**, *68*, 2042–2044; (b) Goff, N. L. C.; Audin, P.; Paris, J.; Cazes, B. *Tetrahedron Lett.* **2002**, *43*, 6325–6328.
10. During the hydrogenation of **5d**, selective deprotection of NBn_2 could be achieved by carefully monitoring the reaction and allowing it to run for a shorter period of time than other substrates. The rate of deprotection of NBn_2 was found to be much faster than that of OBn group giving a modest 58% yield of **6d**.
11. Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T. *Org. Lett.* **2002**, *4*, 2977–2980.
12. Selected physical data of **2a** (R = Me): R_f = 0.4 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{27}$ = –9.1 (*c* 0.98, $CHCl_3$); IR (neat) ν_{max} 3438, 3385, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.67 (d, *J* = 6.6 Hz, 1H, NH) 4.54 (dd, *J* = 5.2, 8.1 Hz, 1H, C2H), 4.15 (m, 1H, C5H), 3.74 (s, 3H, CO_2Me), 3.71 (m, 1H, C6H), 2.28 (m, 1H), 2.03 (m, 1H), 1.72 (m, 2H), 1.44 (s, 9H, Boc), 1.14 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C ($CDCl_3$, 75 MHz): δ 173.56, 155.35, 83.48, 79.22, 76.57, 51.92, 49.27, 29.84, 28.34, 27.43, 16.04; MS (LSIMS) *m/z* (%) 274 (24) $[M+H]^+$. Selected physical data of **2b** (R = Bn): R_f = 0.45 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{27}$ = +4.6 (*c* 0.98, $CHCl_3$); IR (KBr) ν_{max} 3369, 1831, 1669, 1508 cm^{-1}; ^1H NMR ($CDCl_3$ 200 MHz): δ 7.26 (m, 5H, Ph), 4.6 (m, 1H), 4.38 (br s, 1H,

NH), 4.07 (m, 1H), 3.87 (m, 1H), 3.75 (s, 3H, CO_2Me), 2.99 (m, 1H), 2.99 (m, 1H), 2.79 (m, 1H), 2.32 (m, 1H), 2.02 (m, 2H), 1.83 (m, 1H), 1.34 (s, 9H, Boc); ^{13}C ($CDCl_3$, 75 MHz): δ 173.53, 155.36, 137.52, 129.55, 128.19, 126.18, 81.74, 79.18, 76.56, 54.1, 51.8, 37.02, 29.67, 28.16, 27.81; MS (LSIMS) *m*/*z* (%) 350 (16) $[M+H]^+$.Selected physical data of **2c** (R = $CHMe_2$): R_f = 0.45 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{27} = -11.0$ (*c* 0.68, $CHCl_3$); IR (neat) ν_{max} 1523, 1354 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.51 (m, 1H), 4.3 (d, *J* = 10.2 Hz, 1H, NH), 4.03 (m, 1H), 3.72 (s, 3H, CO_2Me), 3.46 (m, 1H, C5H), 2.4–1.7 (m, 5H, C3H, C4H and C7H), 1.43 (s, 9H, Boc), 0.97–0.83 (m, 6H, 2 Me); ^{13}C ($CDCl_3$, 75 MHz): δ 173.71, 156.11, 80.78, 79.14, 76.58, 57.87, 51.79, 29.52, 28.31, 28.16, 19.97, 15.66; MS (LSIMS) *m*/*z* (%) 302 (34) $[M+H]^+$. Selected physical data of **2d** (R = OBn): R_f = 0.4 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{27} = -40.4$ (*c* 0.67, $CHCl_3$); IR (neat) ν_{max}3119, 1401 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28 (m, 5H, Ph), 4.96 (br s, 1H, NH), 4.49 (m, 3H), 4.27 (m, 1H), 3.7 (m, 5H), 3.54 (m, 1H), 2.27 (m, 1H), 2.04–1.86 (m, 3H), 1.4 (s, 9H, Boc); ^{13}C ($CDCl_3$, 75 MHz): δ 173.54, 155.63, 138.18, 128.26, 127.5, 79.93, 79.36, 76.56, 73.23, 63.43, 53.25, 51.81, 30.05, 29.64, 28.3, 27.63; MS (LSIMS) *m*/*z* (%) 380 (32) $[M+H]^+$.