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Stereoselective synthesis of the various isomers of 3,4-dideoxy furanoid sugar amino acids with methyl substitution at the C6 position☆

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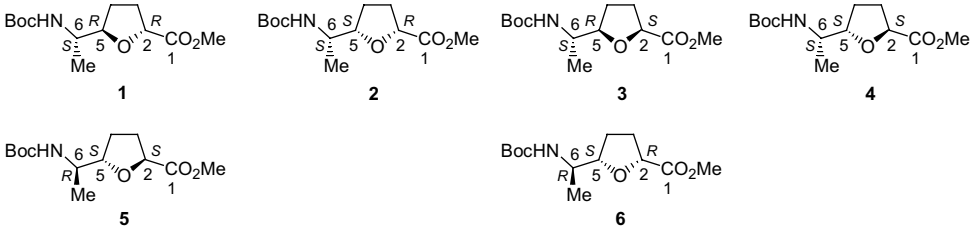
Abstract—Various isomers of C6-methyl-containing chiral 3,4-dideoxy furanoid sugar amino acids were synthesized following a common strategy, in which the C2 and C6 chiral centres were derived from the chiralities of the two starting materials, glyceraldehyde acetonide and *N*,*N*-dibenzylalaninal, respectively, and the C5 centre was fixed by standard diastereoselective transformations.

The advantage of sugar amino acids as potential combinatorial building blocks stems from the structural diversity of carbohydrate molecules.[1] Introduction of an additional combinatorial site in the C6 position can raise many fold the diversity of furanoid sugar amino acid-based molecular libraries.[2] Recently, we reported an efficient synthesis of C6-substituted furanoid sugar amino acids using chiral *N*,*N*-dibenzylaminoaldehydes and glyceraldehyde acetonide as starting materials.[3] The method was applied for the synthesis of a variety of 3,4-dideoxy furanoid sugar amino acids with 6-methyl, 6-benzyl, 6-isopropyl and 6-(CH_2OBn) substituents. It was envisaged that the method had the potential to lead to the synthesis of all the possible isomers of such C6-substituted furanoid sugar amino acids. To demonstrate the versatility of the method, we employed it successfully for the synthesis of six isomers of 3,4-dideoxy furanoid sugar amino acids with methyl substitution at the C6 position (**1**–**6**),[4] the results of which are presented in this communication. While the chiralities of the C2 and C6 centres were derived from the two chiral starting materials, glyceraldehyde acetonide and *N*,*N*-dibenzylalaninal, respectively, the third chiral centre at C5 position was fixed by standard stereoselective transformations. Diastereoselective addition of the acetylide derived from glyceraldehyde acetonide to the chiral amino aldehyde directly induced the requisite chirality in the C5 positions of **1**, **3**, **5** and **6**, which was inverted by an oxidation–reduction sequence to synthesize the other isomers **2** and **4**.

The outlines of the synthetic protocol for the first two compounds **1**–**2**, which were obtained from the L-alanine-derived amino aldehyde are shown in Scheme 1. Synthesis of compound **1** has already been reported by us.[3] The intermediate **9** from that synthesis constituted



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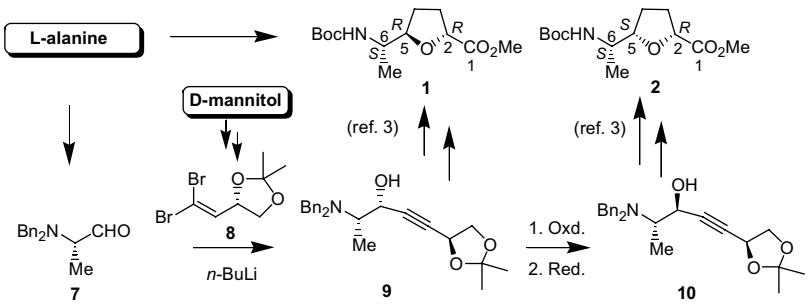
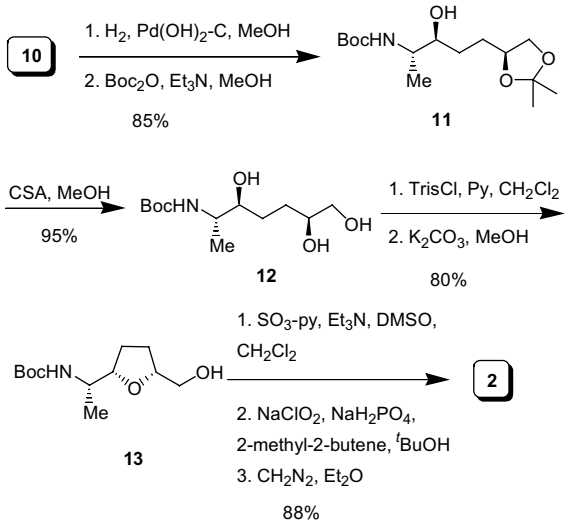


Scheme 1. Reagents and conditions for the conversion of **9** to **10**: (1) oxidation: SO_3-py, Et_3N, DMSO, CH_2Cl_2; (2) reduction: K-selectride, THF, −78 °C.

the starting material for the synthesis of isomer **2**. The stereochemistry of the C5 hydroxyl group of **9** was inverted by subjecting it to an oxidation–reduction sequence to give the isomeric product **10**.

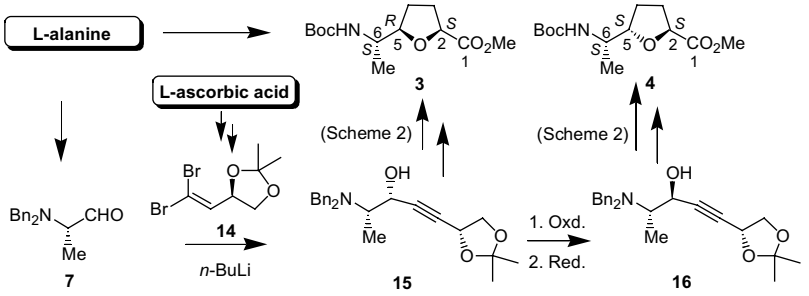
Oxidation of **9** using SO_3-py was immediately followed by the diastereoselective hydride reduction of the resulting unstable keto intermediate using K-selectride[5] to give compound **10**[6] with >98% diastereoselectivity and no trace of the other diastereomer. Compound **10** was then transformed into the furanoid 3,4-dideoxy sugar amino acid (2*R*,5*S*,6*S*)-**2** following the reported procedure (Scheme 2).[3]



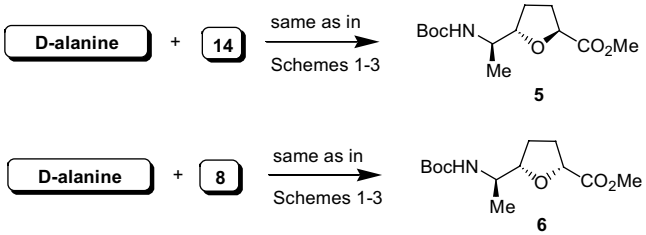
Scheme 2. Conversion of **10** to **2**.[3]

Hydrogenation of **10** 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, which was protected using Boc_2O to furnish **11** in 85% yield.[6] Treatment of **11** with acid deprotected the acetonide moiety giving the triol **12** in 95% yield. Selective sulfonylation of the primary hydroxyl group of **12** using 2,4,6-triisopropylbenzenesulfonyl chloride (TrisCl) gave a sulfonate intermediate that was treated with anhydrous K_2CO_3 to carry out an efficient intramolecular ring closure reaction via an epoxide intermediate to give the tetrahydrofuran **13** in 80% yield in two steps.[7] Finally, a two-step oxidation process converted the primary hydroxyl group of **13** into an acid that was treated with an excess of CH_2N_2 in ether to produce the final product **2**[8] in 88% yield.

For the synthesis of compounds **3**–**4**, as shown in Scheme 3, the same L-alanine-derived *N*,*N*-dibenzylamino aldehyde **7**, used in Scheme 1, was reacted with the Li-acetylide prepared from isomeric 3,4-*O*-isopropylidene-1,1-dibromobut-1-en-3,4-diol **14**. Compound **14**, an enantiomer of **8**, was prepared by known methods from L-ascorbic acid.[9] The adduct **15** was formed in 89% yield exclusively with no trace of the other diastereomer. Its C5-isomer, compound **16**, was next prepared in 82% yield from **15** by the same oxidation–reduction sequence used for the synthesis of **10**. The selectivity in this case was 90:10 in favour of the required isomer and the minor isomer could be separated easily by standard silica gel column chromatography after the cycloetherification step. Compounds **15** and **16** were next converted into (2*S*,5*R*,6*S*)-**3**[10] (51% overall yield from **15**) and (2*S*,5*S*,6*S*)-**4**[11] (52% overall yield from **16**), respectively, following the methods used in Scheme 2.



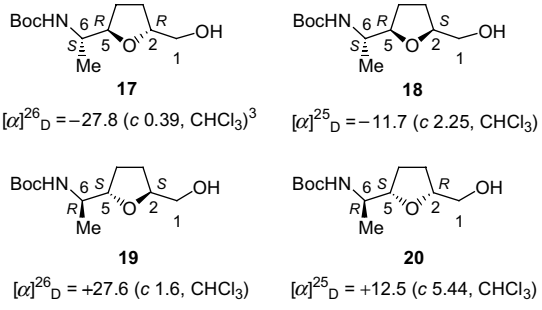
Scheme 3. Synthesis of **3** and **4**: Reagents and conditions for the conversion of **15** to **16**: (1) oxidation: SO_3-py, Et_3N, DMSO, CH_2Cl_2; (2) reduction: K-selectride, THF, −78 °C.



Scheme 4. Synthesis of **5** and **6**.

Similarly, starting from D-alanine and following the methods outlined in Schemes 1–3, the two other isomers of this C6-substituted 3,4-dideoxy furanoid sugar amino acid **5**[12] and **6**[13] were prepared as shown in Scheme 4.

Compounds **5** and **6** are enantiomers of **1** and **3**, respectively, having identical spectral data. The enantiomeric purities of these substrates were verified by measuring their specific rotations. In addition to the specific rotations of the final esters, they were also compared at the alcohol stage. Thus the intermediate **17** from **9**, en route to **1**, had a specific rotation equal, but opposite to that of intermediate **19** obtained during the synthesis of **5**. Similarly, the alcohol **18** prepared from **15**, en route to **3**, had an equal and opposite specific rotation to that of **20**, the precursor of **6**.



Thus, the present method, as depicted in Scheme 1–3, was employed successfully for the synthesis of various isomers of C6-substituted 3,4-dideoxyfuranoid sugar amino acids **1**–**6** in pure enantiomeric forms simply by altering the chiralities of the starting amino aldehydes and glyceraldehyde acetonides, but essentially following a common strategy.

Acknowledgements

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10. Selected physical data of **3**: R_f = 0.4 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{29}$ −20.1 (*c* 1.07, $CHCl_3$); IR (neat) ν_{max} 3350, 2977, 1745, 1709, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.01 (d, *J* = 5.2 Hz, 1H, NH), 4.42 (dd, *J* = 4.7, 8.3 Hz, 1H, C2H), 3.93 (m, 1H, C5H), 3.75 (m, 1H, C6H), 3.73 (s, 3H, CO_2Me), 2.21 (m, 1H), 2.07 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.43 (s, 9H, Boc), 1.19 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C ($CDCl_3$, 75 MHz): δ 173.49, 155.72, 84.09, 79.07, 76.57, 51.99, 48.89, 30.23, 28.41, 26.99, 16.27; MS (LSIMS) *m/z* (%) 274 (10) $[M+H]^+$, 174 (91) $[M+H-Boc]^+$.
11. Selected physical data of **4**: R_f = 0.4 (silica gel, 30% EtOAc in petroleum ether); IR (neat) ν_{max} 3395, 2975, 2928, 1712, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.0 (d, *J* = 4.5 Hz, 1H, NH), 4.5 (dd, *J* = 4.5, 7.8 Hz, 1H, C2H), 4.1 (m, 1H, C5H), 3.94 (m, 1H, C6H), 3.74 (s, 3H, CO_2Me), 2.22 (m, 1H), 2.02 (m, 2H), 1.78 (m, 1H), 1.43 (s, 9H, Boc), 1.2 (d, *J* = 6.8 Hz, 3H, CH_3); MS (EI) *m/z* (%) 173 (5) $[M-Boc]^+$.
12. Selected physical data of **5**: R_f = 0.4 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{29}$ +9.9 (*c* 1.01, $CHCl_3$); IR (neat) ν_{max} 3371, 2976, 1745, 1709, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.63 (d, *J* = 7.9 Hz, 1H, NH), 4.49 (dd, *J* = 4.9, 8.0 Hz, 1H, C2H), 4.1 (m, 1H, C5H), 3.72 (s, 3H, CO_2Me), 3.65 (m, 1H, C6H), 2.25 (m, 1H), 2.01 (m, 2H),

1.75 (m, 1H), 1.42 (s, 9H, Boc), 1.12 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C ($CDCl_3$, 75 MHz); δ 173.61, 155.36, 83.52, 79.28, 76.57, 51.99, 49.29, 29.9, 28.38, 27.48, 16.05; MS (LSIMS) m/z (%) 274 (7) $[M+H]^+$, 174 (42) $[M+H-Boc]^+$.

13. Selected physical data of **6**: R_f = 0.4 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{29}$ +20.7 (c 1.2, $CHCl_3$); IR (neat) ν_{max} 3350, 2977, 1745, 1709, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.01 (d, J = 3.7 Hz, 1H, NH), 4.42 (dd, J = 4.7, 8.3 Hz, 1H, C2H), 3.94 (m, 1H, C5H), 3.75 (m, 1H, C6H), 3.74 (s, 3H, CO_2Me), 2.22 (m, 1H), 2.07 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.43 (s, 9H, Boc), 1.19 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C ($CDCl_3$, 75 MHz): δ 173.49, 155.72, 84.09, 79.09, 76.57, 52, 48.92, 30.23, 28.41, 27, 16.28; MS (LSIMS) m/z (%) 296 (8) $[M+Na]^+$, 274 (14) $[M+H]^+$, 174 (98) $[M+H-Boc]^+$.