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N-tert-BUTOXYCARBONYL-2-(*tert*-BUTYLDIMETHYLSILOXY)PYRROLE AS A GLYCINE ANION EQUIVALENT: A FLEXIBLE ENANTIOSELECTIVE ACCESS TO POLYHYDROXY-α-AMINO ACIDS

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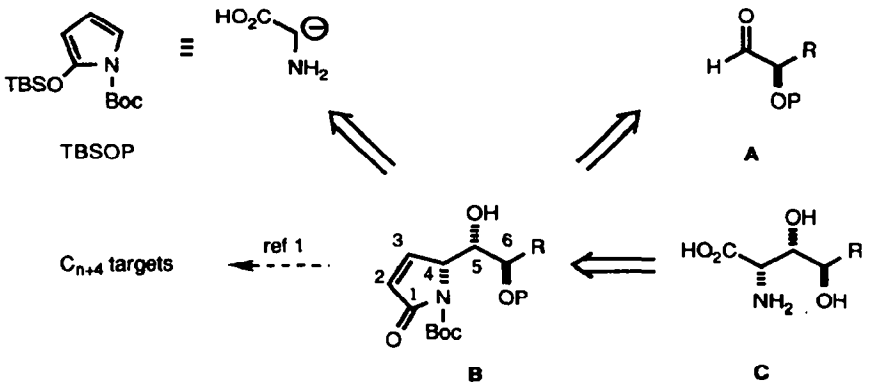
Abstract: An efficient stereoselective route to polyhydroxy-α-amino acids **7a-f** was developed by exploiting *N-tert*-butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole as a glycine anion equivalent.

We have introduced *N-tert*-butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)-pyrrole (TBSOP), readily available from pyrrole, to serve as a versatile four-carbon nucleophile for construction of biologically important nitrogen-containing polyhydroxylated compounds.[1] As shown in Scheme 1, under appropriate Lewis acid catalysis, its aldol addition reaction with n-carbon alkoxyaldehydes of type **A** allows the synthesis of enantiomerically pure α,β-unsaturated lactams **B**, which can further be elaborated into a variety of C_{n+4} multifunctional targets, including hydroxylated pyrrolidine,[1a,b] indolizidine,[1d] and γ-aminobutyric acid derivatives.[1c]

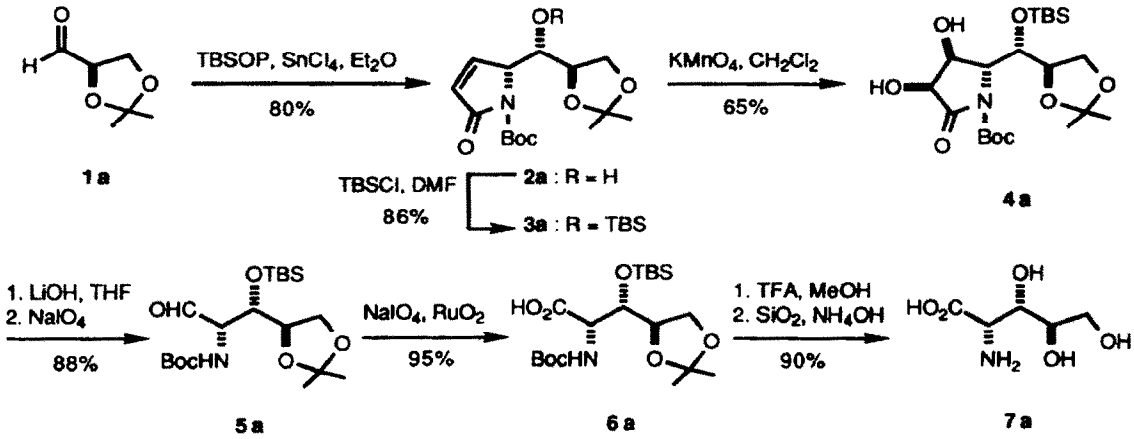


Scheme 1. Projected Synthesis of Hydroxylated α-Amino Acids.

This powerful synthetic tactic relies upon efficient chirality transfer during the aldehyde addition step with > 95% 4,5-*syn*-5,6-*anti* diastereoselectivity for a wide range of aldehydes, using $SnCl_4$ in diethyl ether as a promoter.[1] To allow access to enantiopure hydroxylated α-amino acids like **C**, a novel synthetic variation of the plan was envisaged, based upon oxidative extrusion of the C1 and C2 carbon atoms in the unsaturated

lactam **B**. Accordingly, TBSOP can be envisioned as a novel glycine anion equivalent.[2] This $C_{n+(4-2)}$ elongation reaction was now applied to short syntheses of stereochemically diverse polyhydroxy-α–amino acids, namely the non-natural polyoxamic acid analogues **7a**, **7b**, and **7f** and the higher homologues **7c**, **7d**, and **7e**.

Naturally occurring (+)-polyoxamic acid [(2*S*, 3*S*, 4*S*)-2-amino-3,4,5-trihydroxypentanoic acid][3] and certain synthetic congeners have generated widespread interest due to their potential biological activity and the synthetic challenge these highly functionalized non-proteinogenic α-amino acids represent.[4] Scheme 2 illustrates how (2*S*, 3*S*, 4*R*)-2-amino-3,4,5-trihydroxypentanoic acid (**7a**, 4-*epi*-polyoxamic acid) was constructed.

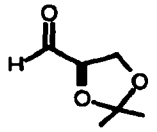
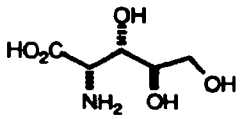
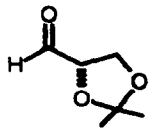
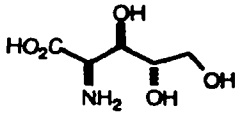
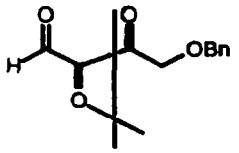
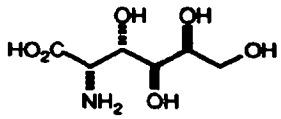
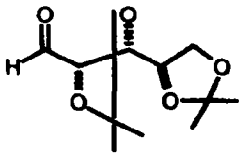
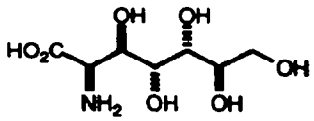
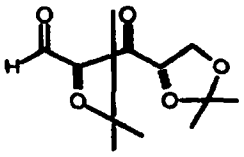
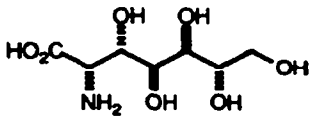
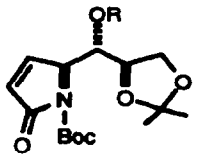
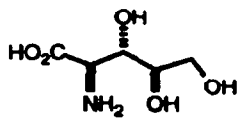


Scheme 2. Optimized Synthetic Protocol to 4-*epi*-Polyoxamic Acid **7a**.

According to an optimal protocol, crystalline lactam **2a**, easily available from **1a** with > 95% d.e. (80% yield) by following our existing synthesis, [1a,b] was first protected as *tert*-butyldimethylsilyl ether (**3a**, 86%) and then subjected to double bond dihydroxylation with the $KMnO_4$/18-crown-6/CH_2Cl_2 reagent system.[5] This gave saturated lactam **4a** as the sole stereoisomer in an acceptable 65% isolated yield. Hydrolytic lactam opening (LiOH, THF) and subsequent oxidative diol fission at the C2-C3 linkage ($NaIO_4$) provided protected 2-amino-2-deoxy-D-arabinose **5a** in 88% yield for the two consecutive reactions. Exposure of **5a** to $NaIO_4$/catalytic RuO_2 in CH_3CN-CCl_4-water-acetone solvent mixture [6] furnished protected amino acid **6a** almost quantitatively (> 95%), which was fully deprotected by 1:1 trifluoroacetic acid/methanol treatment to the trifluoroacetate salt of **7a**. Final chromatographic purification (SiO_2; CH_2Cl_2/MeOH/30% aq. NH_4OH, 5:5:2) provided pure aminoacid **7a** in 90% yield and 34% overall yield for the entire sequence from **1a**.

The same reaction protocol was successfully extended to other aldehydo-sugar derivatives **1b**-**1e** easily obtainable from common precursors by conventional procedures. Regardless of the aldehyde chirality and substitution, the desired amino acids **7b**-**7e** were obtained via the corresponding lactams and aminosugar intermediates in preparatively useful yields ranging from 25% to 34% for the complete sequences. The results are collected in Table 1.

Table 1. Synthesis of Hydroxylated Amino Acids **7a-7f**

Entry	Precursor	Product	Overall yield	$[\alpha]_D$
1	 **1a**	 **7a**	34	+5.0° (*c* 0.2, H_2O)
2	 **1b**	 **7b**	32	-4.8° (*c* 0.1, H_2O)
3	 **1c**	 **7c**	27	+10.2° (*c* 0.2, H_2O)
4	 **1d**	 **7d**	25	-16.0° (*c* 0.2, H_2O)
5	 **1e**	 **7e**	25	+16.4° (*c* 0.24, H_2O)
6	 **3f**	 **7f**	35	-2.7° (*c* 0.2, H_2O)

It is important to note that amino acids **7a-7e** (entries 1-5) invariably possess 2,3-*syn*-3,4-*anti* relationship, with their C2 and C3 chiralities strictly governed by the original chirality at C2 in the respective

aldehyde precursors: 2*S*-amino acids (L-series, entries 1, 3, and 5) correlate to 2*R*-aldehydes whereas 2*R*-compounds (D-series, entries 2 and 4) correlate to 2*S*-precursors.

Our approach could be directly applied to the synthesis of 2,3-*anti*-3,4-*anti* configured amino acids if it were possible to invert the stereochemistry at C4 in the lactam precursors. A well established way to achieve this with such α,β-unsaturated carbonyl compounds is base-promoted C4 epimerization. [1a,b] As an example, exposure of **3a** to Et_3N/DMAP in CH_2Cl_2 cleanly afforded epimer **3f** (Table 1, entry 6) in 70% yield, which was first converted to 2-amino-2-deoxy-D-ribose **5f** (not shown) and then to (2*R*, 3*S*, 4*R*)-2-amino-3,4,5-trihydroxypentanoic acid **7f** in a gratifying 35% yield from its lactam precursor.

In summary, TBSOP has been used, as a glycine anion equivalent, to generate a variety of polyhydroxylated α-amino acids structurally related to natural polyoxamic acid with five (norvaline family), six (norleucine family), and seven carbon atoms. Substantial quantities of enantiomerically pure amino acids with 2,3-*syn*-3,4-*anti* and 2,3-*anti*-3,4-*anti* relative configurations have been prepared in a highly diastereoselective and predictable manner by this $C_{n+(4-2)}$ homologative approach. 2-Amino-2-deoxyaldoses of type **5** have been also obtained, as reaction intermediates, in useful protected forms. Although by this technique direct preparation of 3,4-*syn*-configured amino acids is precluded, [7] the conciseness and versatility of this approach should prove beneficial for many other synthetic objectives in the α-amino acid field.

Acknowledgment

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References and Notes

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7. Indirect access to 3,4-*syn*-configured amino acids could be pursued, in principle, via Mitsunobu-type configurational inversion at C3 in proper intermediates (*e.g.* **6**).

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