A Novel Method for the Asymmetric Synthesis of α,β-Diamino Acids by a Glucose-Mediated Stereoselective *Strecker* Reaction

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A novel method for the asymmetric synthesis of α,β-diamino acids by using the 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl group (Piv_4Glc) as chiral auxiliary was developed (*Table* and *Scheme*). The reaction was promoted by $CuBr \cdot Me_2S$ as *Lewis* acid, and high yields and good diastereoselectivities were achieved.

1. Introduction. – Optically active α,β-diamino acids [1] have received much synthetic attention over the years because of the ubiquitous nature of α,β-diamino acids as key structural fragments in a variety of peptides, peptide antibiotics, and other biologically active compounds. For example, (2*S*)-2,3-diaminopropanoic acid occurs as a component of the neurotoxin (2*S*)-2-(oxalylamino)-3-aminopropanoic acid (= 3-amino-*N*-(carboxycarbonyl)-L-alanine) [2], capreomycin [3], and the antifungal dipeptides Sch37137 and A19009 [4]. Furthermore, (2*S*,3*S*)-2,3-diaminobutanoic acid is present in a variety of peptide antibiotics such as aspartocin [5], glumamycin [6], lavendomycin [7], cirrariomycin [8], *etc.*; and (2*S*,3*R*)-2,3-diamino-4-phenylbutanoic acid is the non-leucine part of aminodeoxybestatin [9]. The (2*R*,3*S*)-2,3-diamino-3-phenylpropanoic acid has been considered as an alternative side chain of the anticancer drug taxol [10].

As a consequence of the essential role played by these α,β-diamino acids in biological systems and their utility as synthetic building blocks, a range of useful methodologies for the asymmetric synthesis of these compounds have been reported. Recent important methods include catalytic asymmetric hydrogenation [11], enantioselective diamination of α,β-unsaturated acid derivatives [12], application of an asymmetric *Strecker* reaction [13], catalytic enantioselective aza-*Henry* reaction [14], and the application of *Sharpless* asymmetric aminohydroxylation to α,β-unsaturated esters and subsequent functional-group manipulation [15]. In addition, functional-group transformations from natural, optically active α-amino acids such as L-aspartic acid [16], L-serine [17], and D- or L-threonine [18] have also been applied to the synthesis of 2,3-diamino acids.

Our considerable current research interest is focussed on the asymmetric synthesis by using *N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)aldimine as a chiral template,

which is enlightened by the work of *Kunz* and co-workers [19]. As a continuation of our studies of the glucose-mediated stereoselective *Strecker* synthesis, a general synthetic protocol involving α-amino aldehydes, 2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosylamine, and trimethylsilanecarbonitrile (Me_3SiCN) was developed for the asymmetric synthesis of α,β-diamino acids.

2. Results and Discussion. – The initial investigation employed (dibenzylamino)aldehydes in the reactions, but the yields of the reaction were very low. The results seemed to indicate that the dibenzyl-protected amino group of the α-aminoaldehyde was probably far too highly sterically hindered. For this reason, we attempted to protect the aminoaldehydes with the (*tert*-butoxy)carbonyl (Boc) group, and high yields and good diastereoselectivities were achieved.

The starting *N*-Boc-phenylalaninals were prepared from phenylalanine by *tert*-butoxycarbonylation, formation of the *N*-methoxy-*N*-methylamide, and reduction using the known procedure [20]. The α-aminoaldehydes reacted with 2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosylamine (**1**) in CH_2Cl_2 in the presence of 4Å molecular sieves to give the corresponding imines **3a** and **3b** (*Table*) in high yields. After filtration, the crude products were used in further reactions. Next we examined the nucleophilic addition of Me_3SiCN to the aldimines **3a** and **3b** in CH_2Cl_2. The reaction employed $CuBr \cdot Me_2S$ as promoter to activate the C=N group since our previous studies [21] have shown that $CuBr \cdot Me_2S$ is the most efficient *Lewis* acid in this reaction. The reactions were completed within 6 h and afforded α,β-diaminonitriles **4a** and **4b**, respectively (*Table*). The diastereoselectivities of the addition of Me_3SiCN to aldimines **3a** and **3b** were 96% and 82% de, respectively, which were determined by HPLC. The absolute configurations of **4a** and **4b** were determined in further experiments.

The α,β-diaminonitriles **4a** and **4b**, which were prepared by stereoselective *Strecker* reaction, were precursors of the corresponding diastereoisomerically pure α,β-diamino acids: hydrolysis of the α,β-diaminonitriles in acidic medium (*Scheme*) afforded the α,β-diamino acids as the bis-hydrochlorides **5a** and **5b**, respectively.

Scheme. *Hydrolysis of the α,β-Diaminonitriles.* The reaction was carried out by bubbling anhydrous HCl gas through the solution.

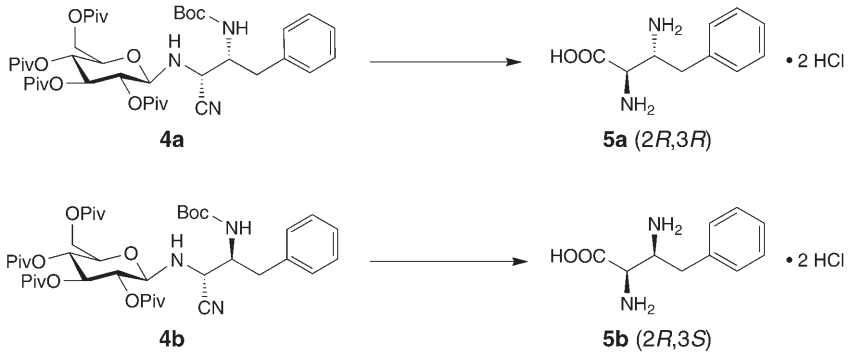
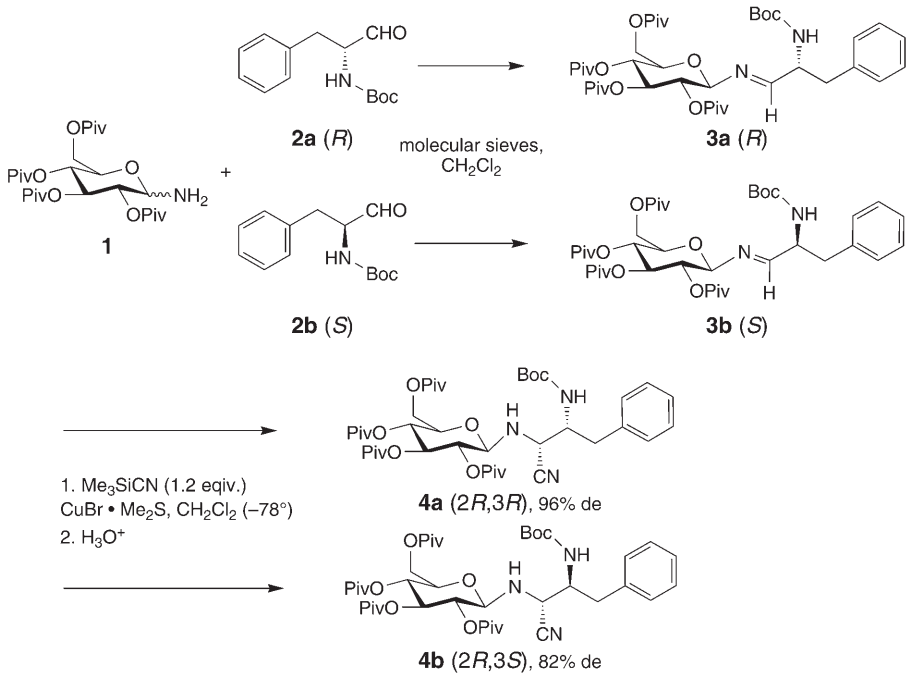


Table. *Asymmetric* Strecker *Reaction of Aldimines* **3a** *or* **3b** *with* Me_3SiCN



Entry	Substrate	Product	Yield[a]) [%]	de[b]) [%] (config)[c])	$[\alpha]_D^{20}$	δ(C) [ppm][d])
1	**3a**	**4a**	0.703 g (91%)	96 (2*R*,3*R*)	– 19.3[e])	117.673
2	**3b**	**4b**	0.692 g (89%)	82 (2*R*,3*S*)	– 4.3[f])	117.628

[a]) Isolated yields over two steps from **1**, after column chromatography (silica gel). [b]) Diastereoisomer excess determined by HPLC. [c]) The absolute configurations of **4a** and **4b** were confirmed after their hydrolysis to **5a** and **5b**, respectively, by comparison of the optical rotation with the literature values [16]. [d]) For CN. [e]) $c = 1.0$, $CHCl_3$. [f]) $c = 1.2$, $CHCl_3$.

The absolute configurations of **5a** and **5b**, which were established by comparison of their optical rotation with the literature values [16] (see *Exper. Part*), are (2*R*,3*R*) and (2*R*,3*S*), respectively. These results, which are consistent with our previous work [21], suggest the operation of a double stereo-differentiation effect, and the Piv_4Glc group plays a significant role in controlling the diastereoselective addition of cyanide to the aldimine. On the basis of the presented results, we propose the key transition state shown in *Fig. 1* ([21]) for this reaction. Therein, Cu^I is coordinated to both the N-atom of the imine and one of the O-atoms of the 2′-*O*-pivaloyl group. This complexation decreases the electron density at the C-atom of the C=N moiety and leads to the attack of CN^-.

In the present case, chelation cannot occur between the C=N moiety and the N-atom of the amino group at the stereogenic C(α) center. Therefore, the stereogenic C(α) of aldimines **3** controls the stereoselectivity slightly according to *Cram*'s rule

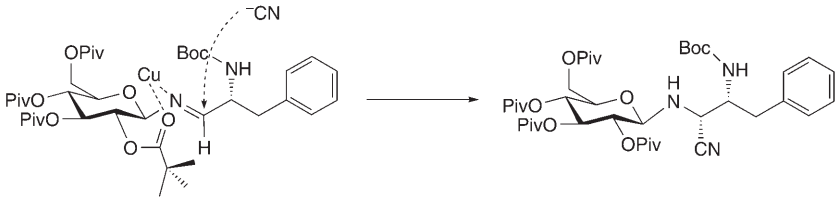


Fig. 1. *Proposed transition-state of the* Strecker *reaction*

(*Fig. 2*), *i.e.*, *si*-face addition of CN^- to aldimine **3a** and *re*-face addition of CN^- to aldimine **3b**. So, **3a** would be considered as a 'matched pair', while **3b** would be the 'mismatched pair'. However, the effect of the *Cram* control is weak, and mainly the Piv_4Glc group controls the asymmetric induction. Further work is currently going on to extend our synthetic protocol.

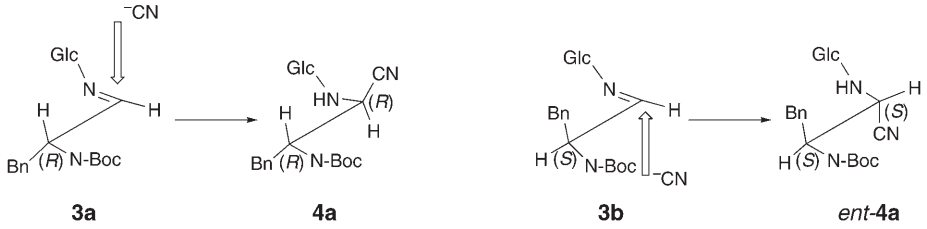


Fig. 2. Cram *model of the nucleophilic addition*

3. Conclusions. – We have developed a novel and efficient method for the asymmetric synthesis of α,β-diamino acids in which enatiomerically pure α-amino-aldehydes are efficiently transformed, in good yield and high diastereoselectivity, to α,β-diamino acids *via* the glucose-mediated asymmetric *Strecker* reaction.

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Experimental Part

General. Most chemicals are commercially available, and were purchased in reagent-grade quality; CH_2Cl_2 was freshly distilled from CaH_2 prior to use. *N*-Boc-Protected α-aminoaldehydes were prepared as previously described [20]. TLC: precoated silica gel *60* F_{254} plates (*Merck*). Column chromatography = CC. M.p.: *X4-Data* microscopic melting-point apparatus; uncorrected. IR Spectra: *Nicolet NEXUS-470-FT-IR* spectrometer; KBr pellets; in cm^{-1}. NMR Spectra: *Bruker Avance-DRX-500* spectrometer; δ in ppm rel. to $SiMe_4$, *J* in Hz. ESI-MS: *Bruker Esquire-3000-plus* spectrometer; in *m*/*z*.

Imines **3a** *and* **3b**: *General Procedure 1* (*GP 1*). A mixture of 2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosylamine (**1**; 0.515 g, 1.0 mmol) [21], α-aminoaldehyde (0.249 g, 1.0 mmol), and 4Å molecular sieves (1.00 g) in CH_2Cl_2 (10 ml) was stirred at r.t. for 5 h (TLC control). After filtration, the resulting soln. of imine **3a** or **3b** was ready for further reactions (without purification).

*3-{[(*tert*-Butoxy)carbonyl]amino}-2-(2,3,4,6-tetra*-O*-pivaloyl-β-*D*-glucopyranosyl)amino]nitriles* **4a** *and* **4b**: *General Procedure 2* (*GP 2*). To a soln. of Me_3SiCN (0.140 g, 1.2 mmol) and $CuBr \cdot Me_2S$ (0.206 g, 1.0 mmol) in CH_2Cl_2 (10 ml) at $-78°$, a soln. of the appropriate imine **3** (1.0 mmol) in CH_2Cl_2

(3 ml) was added dropwise. Then, the temp. was slowly raised to 0°, and the mixture was stirred for *ca.* 6 h (TLC control). After completion of the reaction, the mixture was quenched with 2M aq. HCl (10 ml) and washed with sat. aq. $NaHCO_3$ soln. (3 × 10 ml) and H_2O (10 ml). The org. layer was dried ($MgSO_4$) and concentrated. The crude product was purified by CC (silica gel, petroleum ether/AcOEt 8:1): diaminonitrile **4a** or **4b** as white solid.

*(2*R*,3*R*)-3-{[(*tert*-Butoxy)carbonyl]amino}-4-phenyl-2-[(2,3,4,6-tetra*-O*-pivaloyl-β-*D*-glucopyranosyl)amino]butanenitrile* (**4a**). Prepared according to *GP 2:* **4a** (0.703 g, 91% from **1**). White solid. M.p. 102–104°. $[\alpha]_D^{20} = -19.3$ ($c = 1.0$, $CHCl_3$). IR (KBr): 3444, 2977, 2247, 1744, 1631, 1481, 1460, 1146, 1033, 762, 700. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.22–7.34 (*m*, 5 H); 5.35 (*t*, $J = 9.6$, 1 H); 5.11 (*t*, $J = 9.6$, 1 H); 4.88 (*t*, $J = 9.6$, 1 H); 4.71 (*d*, $J = 6.8$, 1 H); 4.18–4.24 (*m*, 3 H); 4.02–4.05 (*m*, 1 H); 4.00 (*d*, $J = 4.4$, 1 H); 3.68 (*dd*, $J = 3.6$, 6.0, 1 H); 2.90 (*d*, $J = 7.2$, 2 H); 2.62 (*s*, 1 H); 1.67 (*s*, 1 H); 1.12–1.54 (*m*, 45 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.0; 177.5; 177.0; 176.4; 135.9; 129.0; 128.8; 127.2; 117.7; 87.3; 80.5; 73.4; 72.3; 70.3; 67.7; 61.6; 50.7; 38.8–38.1; 28.2–26.9. HR-MS: 774.4536 ($[M + H]^+$, $C_{41}H_{64}N_3O_{11}^+$; calc. 774.4541).

*(2*R*,3*S*)-3-{[(*tert*-Butoxy)carbonyl]amino}-4-phenyl-2-[(2,3,4,6-tetra*-O*-pivaloyl-β-*D*-glucopyranosyl)amino]butanenitrile* (**4b**). Prepared according to *GP 2:* **4b** (0.692 g, 89% from **1**). White solid. M.p. 109–112°. $[\alpha]_D^{20} = -4.3$ ($c = 1.2$, $CHCl_3$). IR (KBr): 3450, 2977, 2245, 1744, 1631, 1481, 1460, 1146, 1036, 760, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.21–7.33 (*m*, 5 H); 5.34 (*t*, $J = 9.6$, 1 H); 5.10 (*t*, $J = 9.6$, 1 H); 4.87 (*t*, $J = 9.6$, 1 H); 4.72 (*d*, $J = 6.8$, 1 H); 4.17–4.23 (*m*, 3 H); 4.02–4.04 (*m*, 1 H); 3.99 (*d*, $J = 5.2$, 1 H); 3.67 (*dd*, $J = 3.2$, 6.4, 1 H); 2.89 (*d*, $J = 7.2$, 2 H); 2.62 (*s*, 1 H); 1.82 (*s*, 1 H); 1.11–1.53 (*m*, 45 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.0; 177.5; 176.9; 176.3; 135.9; 129.0; 128.8; 127.1; 117.6; 87.2; 80.4; 73.3; 72.3; 70.3; 67.7; 61.6; 50.7; 38.8; 38.7; 38.6; 38.0; 28.1; 27.2; 27.1; 27.0. HR-MS: 774.4539 ($[M + H]^+$, $C_{41}H_{64}N_3O_{11}^+$; calc. 774.4541).

2,3-Diamino-4-phenylbutanoic Acid Dihydrochlorides **5a** *and* **5b**: *General Procedure 3* (*GP 3*). Anh. HCl gas was bubbled through a soln. of **4** (0.660 g , 1.0 mmol) in formic acid (20 ml) for 24 h at r.t. Then, the soln. was concentrated and filtered over silica gel (20 g), eluting with light petroleum ether/AcOEt 1:1. The silica gel (containing the product) was dried, and repeatedly extracted with 2N aq. HCl (400 ml). The combined acidic soln. was concentrated to *ca.* 10 ml, diluted with conc. HCl (10 ml), and heated to 80° for 48 h. After evaporation, 2,3-diamino-4-phenylbutanoic acid dihydrochloride **5a** or **5b** was obtained.

*(2*R*,3*R*)-2,3-Diamino-4-phenylbutanoic Acid Dihydrochloride* (**5a**). Prepared according to *GP 3:* **5a** (0.226 g, 99%). White crystalline solid. M.p. 171–172°. $[\alpha]_D^{20} = -1.8$ ($c = 1.04$, MeOH) ([16]: $[\alpha]_D^{20} = -1.8$, $c = 1.3$, MeOH). IR (KBr): 3478–2500 (br.), 1685, 1629, 1496, 1456, 1401. ^{1}H-NMR (500 MHz, D_2O): 7.22–7.37 (*m*, 5 H); 4.08 (*d*, $J = 5.2$, 1 H); 3.99 (*m*, 1 H); 3.19 (*dd*, $J = 14.4$, 5.2, 1 H); 2.97 (*dd*, $J = 14.5$, 10.2, 1 H). ^{13}C-NMR (125 MHz, D_2O): 167.1; 133.6; 129.4; 128.9; 127.6; 55.2; 52.9; 35.5. HR-MS: 98.0632 ($[M + 2\,H]^{2+}$, $C_{10}H_{16}N_2O_2^{2+}$; calc. 98.0606).

*(2*R*,3*S*)-2,3-Diamino-4-phenylbutanoic Acid Dihydrochloride* (**5b**). Prepared according to *GP 3*: *anti*-**5b** (0.223 g, 98%). White crystalline solid. M.p. 206–208°. $[\alpha]_D^{20} = -18.7$ ($c = 0.34$, MeOH) ([16]: $[\alpha]_D^{20} = -18.8$, $c = 1.4$, MeOH). IR (KBr): 3450–2500(br), 1687, 1631, 1496, 1456, 1401. ^{1}H-NMR (500 MHz, D_2O): 7.15–7.26 (*m*, 5 H); 4.21 (*d*, $J = 3.2$, 1 H); 4.07 (*d*, $J = 10.8$, 1 H); 3.08 (*dd*, $J = 13.6$, 3.2, 1 H); 2.82 (*dd*, $J = 13.8$, 11.6, 1 H). ^{13}C-NMR (125 MHz, D_2O): 166.4; 132.8; 128.7; 128.4; 127.5; 61.0; 52.8; 35.7. HR-MS: 98.0627 ($[M + 2\,H]^{2+}$, $C_{10}H_{16}N_2O_2^{2+}$; calc. 98.0606).

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