Stereoselective Synthesis of Differentially Protected *anti*-α,β-Diamino Acid Derivatives using Arylthionitrooxiranes

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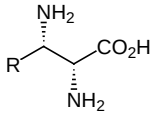
Abstract: Epoxidation of 1-tolylthio-1-nitroalkenes containing an allylic *Z*- or Fmoc-protected amino group yields the corresponding *syn*-epoxides which, although they cannot be isolated, can be trapped with aqueous ammonia to give stereoisomerically pure *anti*-α,β-diamino acid derivatives.

Key words: amino acids, amino aldehydes, epoxides, epoxidation, stereoselective synthesis

α,β-Diamino acids **1** and **2** are of interest as components of natural products,[1,2] pharmaceutical leads[3] and as metal-complexing agents. Routes for the synthesis of 2,3-diaminobutanoic acid derivatives have used threonine or *allo*-threonine.[4,5] More general methods that rely on the use of the chiral pool,[6-11] chiral reagents[12,13] or asymmetric catalysts[14-16] have extended the range of targets that are accessible. A useful summary of other routes has been assembled.[11] One route that does not appear to have been widely applied is the Strecker reaction in which an amino aldehyde is converted into the corresponding homologous α,β-diamino acid. Two examples that proceed with modest stereoselectivity have been described.[3,17] We now report such a route which allows the synthesis of a variety of stereoisomerically pure *anti*-α,β-diamino acid derivatives.



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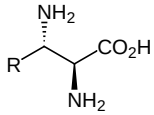
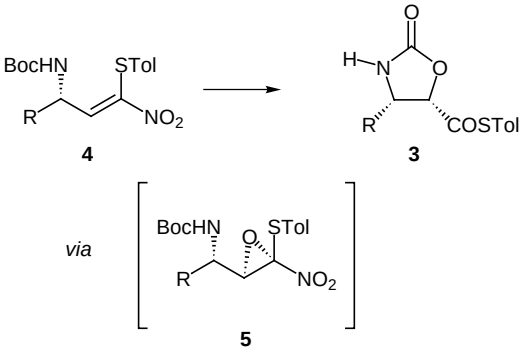


2

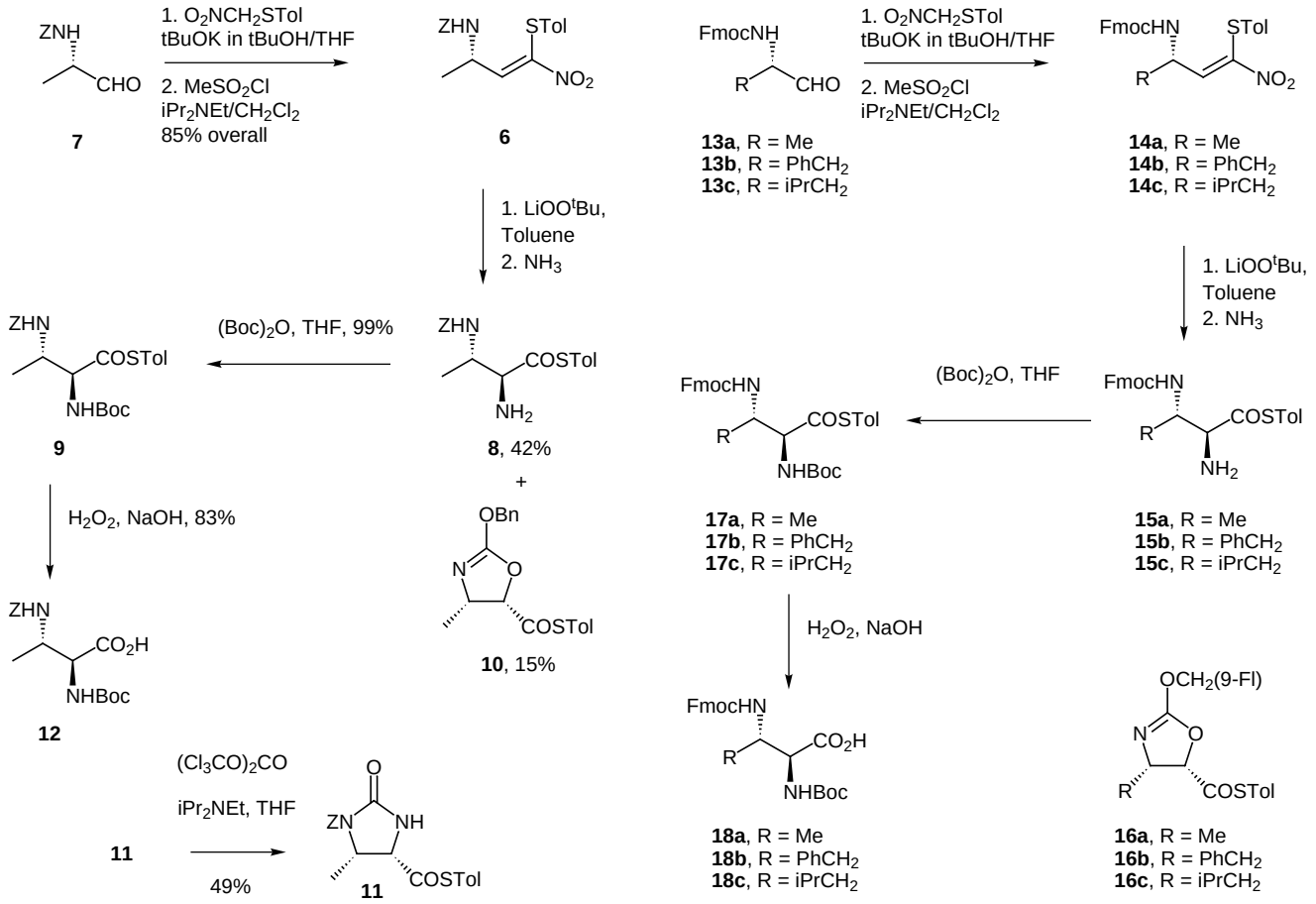
We have reported that it is possible to prepare *anti*-α-hydroxy-β-amino acid derivatives as the *cis*-oxazolidinones **3** by nucleophilic epoxidation of the Boc-protected γ-amino (tolylthio)nitroalkenes **4**,[18] via the inferred intermediacy of the corresponding *syn*-epoxides **5**. Attempts to isolate and characterise the *syn*-epoxides **5** were unsuccessful. Although this process provided convenient access to *anti*-α-hydroxy-β-amino acid derivatives, the instability of the epoxides **5** appeared to prohibit their use in a ring-opening reaction with aqueous ammonia, a process that we had previously developed for the synthesis of α-amino-β-hydroxy acid derivatives.[19]



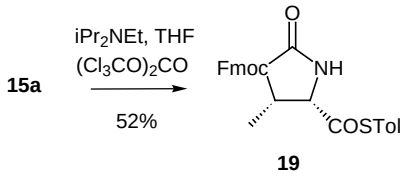
Results and Discussion

We judged that the instability of the *syn*-epoxides **5** was principally due to the ease of cyclisation of the *tert*-butyl carbamate, either as a result of steric factors, or the intrinsically greater nucleophilicity of this group due to the stability of the electrofugal *tert*-butyl cation. It seemed appropriate to choose *Z*-protection for the amino group, and we therefore prepared the alkene **6** from (*p*-tolylthio)nitromethane and the corresponding protected alaninal derivative **7** (Scheme 1). Treatment of the alkene **6** in toluene with lithium *tert*-butylperoxide,[20] followed by work-up and treatment with aqueous ammonia,[19] gave the monoprotected diamino thioester as a single diastereoisomer **8**, which could be converted into the corresponding diprotected derivative **9**. The by-product isolated in the reaction with ammonia was the oxazoline **10**. There was no evidence for the formation of the other diastereoisomer in this process, but the moderate yield means that we cannot exclude its formation to a minor extent.

The relative stereochemistry of the diamino thioester **8** was established by conversion into the corresponding cyclic urea **11** using bis(trichloromethyl)carbonate. The magnitude (9.0 Hz) of the coupling constant between the two ring protons allowed us to establish that the cyclic urea was *cis*-fused, and therefore that the precursor protected α,β-diamino acid derivative **8** was *anti*. The enantiomeric purity of the diamino acid derivative **9** was established by hydrolysis of the thioester to the carboxylic acid **12**, which exhibited a melting point and specific rotation that compared well with literature values.[21]



Scheme 1



Scheme 2

The encouraging results obtained for the *Z*-protected amino aldehyde, encouraged us to apply the same process to the Fmoc-protected analogue, **13a**. This compound was converted into the corresponding alkene **14a**, and epoxidation followed by treatment with ammonia gave the corresponding monoprotected diamino thioester *anti* **15a** (along with the corresponding oxazoline **16a**). Protection then gave the doubly protected derivative **17a**, which could be converted into the corresponding acid **18a** (Scheme 2).[22] Treatment of **15a** with bis(trichloromethyl)carbonate gave the *cis*-cyclic urea **19**, whose stereochemistry was again inferred from the large coupling constant (9.0 Hz) between the two ring protons (Scheme 2). We were pleased to find that the overall yields were higher, and the reaction less sensitive to the speed with which the crude epoxide was subjected to ammonia treatment. This encouraged us to explore the further application of this process, and we have therefore carried out an analogous series of reactions on the Fmoc-protected aldehydes **13b** and **13c** derived from phenylalanine and leucine, respectively, to give the protected diamino acids **18b** and **18c**.[22,23] The results were broadly comparable, although the yield for the formation of the amino thioester **15b** derived from phenylalanine was lower than for the other two examples (Table).

Table

Alkene	Yield, %	Diamino Thioester	Yield, %	Oxazoline	Yield, %	Protected Diamino Thioester	Yield, %	Protected Diamino Acid	Yield, %
14a	80	**15a**	55	**16a**	10	**17a**	98	**18a**	91
14b	69	**15b**	35	**16b**	*	**17b**	97	**18b**	63
14 c	75	**15c**	57	**16c**	*	**17c**	99	**18c**	90

* Not isolated

In conclusion, we have shown that an appropriate choice of N-protecting group allows α-amino aldehydes to be converted into stereoisomerically pure *anti*-α,β-diamino acid derivatives **12** and **18** in which the two amino groups are orthogonally protected as a natural conseqeunce of the reaction sequence.

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(21) Data for **12**: mp 106-107 °C, (lit.,[4] 112-113 °C); $[\alpha]_D^{18}$-20.6 (*c* 0.97 in MeOH), [lit.,[4] $[\alpha]_D^{26}$−21.0 (*c* 0.3 in MeOH); δ_H (500 MHz; $(CD_3)_2SO$) 1.09 (3H, d, *J* 6.5), 1.45 (9H, s,), 3.98-4.01 (1H, m), 4.18-4.21 (1H, m), 5.05 & 5.10 (2H, AB system, *J* 12.5), 7.00-7.02 (1H, m), 7.30 (1H, br d, *J* 7.3), 7.36-7.43 (5H, m); δ_C (125 MHz; $(CD_3)_2SO$) 16.3, 28.3, 47.8, 57.0, 65.3, 78.4, 127.6, 127.8, 128.4, 137.3, 155.5, 156.3, 172.2. [lit.,[4] δ_C (125 MHz; $(CD_3)_2SO$) 16.2, 28.2, 47.4, 57.2, 65.2, 78.3, 127.5, 127.7, 128.4, 137.2, 155.4, 155.7, 172.2].
(22) **General procedure for the synthesis of *N,N'*-protected α,β-diamino acids 12 and 18**: *n*-Butyllithium (2.5M solution in hexanes, 160 μL, 0.4 mmol, 1.2 equiv.) was added dropwise, at -78 °C under nitrogen, to a solution of *tert*-butylhydroperoxide (3.82M solution in toluene, 130 μL, 0.5 mmol, 1.5 equiv.) in toluene (10 mL), and left to stir for 15 min. The alkene **6** or **14** (0.33 mmol) in toluene (5 ml) was added dropwise at -78 °C and the reaction stirred for 2 h at this temperature before quenching with saturated aqueous NH_4Cl solution (10 mL) and allowing to warm to room temperature. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 10 mL). The combined organic portions were washed with 10% aqueous sodium sulphite, brine, then dried ($MgSO_4$) and filtered.The filtrate was cooled to 0 °C and aqueous ammonia (14.7 M, 115 μL, 1.67 mmol, 5 equiv.) was added dropwise and the reaction was left to stir for 15 h at 0 °C. The reaction mixture was filtered using a phase separator paper and absorbed on silica, and the solvent was removed under reduced pressure. A quick purification by flash chromatography (petrol:diethyl ether 1:6) gave the amines **8** and **15**.
Di-*tert* butyl dicarbonate (44 mg, 0.2 mmol, 1.05 equiv.) in THF (2 mL) was added to a solution of the free α-amino thioester **8** or **15** (1.9 mmol) in THF (10 mL). The mixture was refluxed for 15 h then cooled to room temperature and the solvent was removed under reduced pressure. Purification by flash chromatography (petrol:ethyl acetate 5:1) gave the *N,N'*-diprotected α,β-diamino acid derivatives **9** and **17**.
Aqueous hydrogen peroxide (30 w/w, 45 μL, 0.4 mmol, 4 equiv.) was added dropwise at 0 °C to a solution of the thioester **9** or **17** (0.1 mmol) in THF (5 mL) and the resulting solution was stirred for 15 min. at 0 °C. Aqueous sodium hydroxide (0.22M, 1.4ml, 0.3 mmol, 3 equiv.) was added dropwise and the reaction stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue taken up in water (15 mL) and diethyl ether (15mL). The organic layer was removed and the aqueous layer extracted with diethyl ether (2 × 10 mL). The aqueous layer was carefully acidified to pH 3 with 1 M HCl and extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude acids **12** and **18**.
(23) Data for **18a**: mp 102-103 °C; $[\alpha]_D^{18}$-26.1 (*c* 0.18 in MeOH); δ_H (500 MHz; $(CD_3)_2SO$) 1.02 (3H, d, *J* 7.0), 1.37 (9H, s), 3.93-3.96 (1H, m), 4.14 (1H, dd, *J* 8.5, 6.5), 4.16-4.20 (2H, m), 4.25-4.29 (1H, m), 6.96 (1H, d, *J* 8.5), 7.28 (1H, m), 7.28-7.33 (2H, m), 7.39 (2H, t, *J* 7.5), 7.66-7.88 (2H, m), 7.87 (2H, d, *J* 7.3); δ_C (125 MHz; $(CD_3)_2SO$) 16.3, 28.2, 46.7, 48.6, 58.5, 65.2, 78.1, 120.1, 125.2, 127.0, 127.6, 140.7, 143.3, 154.8, 155.9, 172.2.
Data for **18b** mp 107-108 °C; $[\alpha]_D^{18}$-17.8 (*c* 0.14 in MeOH); δ_H (500 MHz; $(CD_3)_2SO$) 0.86 (3H, d, *J* 6.5), 0.92 (3H, d, *J* 6.5), 1.10-1.15 (1H, m), 1.44 (9H, s), 1.55-1.60 (1H, m), 1.61-1.64 (1H, m), 3.98-4.03 (1H, m), 4.21 (1H, dd, *J* 8.5, 6.0), 4.26-4.35 (3H, m), 6.94 (1H, d, *J* 8.5), 7.30 (1H, d, *J* 9.0), 7.35-7.40 (2H, m), 7.47 (2H, t, *J* 7.5), 7.74 (1H, d, *J* 7.5), 7.77 (1H, d, *J* 7.5), 7.95 (2H, d, *J* 7.7); δ_C (125 MHz; $(CD_3)_2SO$) 21.1, 23.5, 24.1, 28.2, 38.2, 46.8, 49.7, 57.5, 65.4, 78.2, 120.1, 125.3, 127.0, 127.6, 140.7, 143.7, 155.7, 155.8, 172.2.
Data for **18c**: : mp 99-100 °C; $[\alpha]_D^{18}$-13.3 (*c* 0.16 in MeOH); δ_H (500 MHz; $(CD_3)_2SO$) 1.46 (9H, s), 2.76-2.86 (2H, m), 4.09-4.27 (5H, m), 6.94-6.99 (1H, m), 7.19-7.21 (1H, m), 7.24-7.40 (7H, m), 7.44-7.48 (2H, m), 7.68 (2H, t, *J* 6.5), 7.93 (2H, d, *J* 7.5); δ_C (125 MHz; $(CD_3)_2SO$) 28.2, 36.8, 46.6, 54.3, 57.3, 65.5, 78.1, 120.0, 125.4, 125.9, 127.6, 127.9, 128.1, 129.2, 137.5, 140.6, 143.7, 155.5, 155.6, 172.6.

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