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Deracemisation of α-amino acids — (*R*)- and (*S*)-phenylalanine from the same enantiomer of a homochiral auxiliary

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Abstract

Chiral auxiliary (3*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **1** was employed for the synthesis of both enantiomers of phenylalanine using a regioselective deprotonation/stereoselective reprotonation strategy. Modification of this approach enables the efficient deracemisation of (±)-phenylalanine.

A large number of chiral auxiliaries have been developed for the asymmetric synthesis of homochiral α-amino acids.[1] The majority of these auxiliaries rely on stereoselective alkylation of a chiral glycine enolate equivalent where subsequent cleavage of the major diastereoisomeric product affords the desired homochiral α-amino acid.[2] Although this methodology is ideally suited for the preparation of homochiral α-amino acids of known absolute configuration, situations often arise where both enantiomers of a given α-amino acid are required.[3] Although both enantiomers of an α-amino acid can be prepared separately via duplicate syntheses using the same auxiliary of opposite absolute configuration, this approach is inherently wasteful. An alternative approach involves the possibility of preparing both enantiomers from a single homochiral auxiliary via a stereodivergent strategy. We now report that homochiral auxiliary (3*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **1** can be used for the preparation of both enantiomers of phenylalanine using an epimerisation strategy which relies on the stereoselective reprotonation of enolate **5**.[4]

We have recently reported that diketopiperazine (DKP) **1** can be used for the asymmetric synthesis of homochiral α-amino acids in multigram quantities.[5] In a typical transformation, deprotonation of DKP **1** with LHMDS at −78°C followed by alkylation with benzyl bromide afforded *trans*-benzylated DKP **2** ($[\alpha]_D^{23}$=+58.6, *c* 1.0, $CHCl_3$) in 98% d.e. Homochiral DKP **2** was obtained by recrystallisation of the crude reaction mixture (ethyl acetate) and deprotected by successive treatment with ceric ammonium nitrate (CAN) and 6 M HCl to afford homochiral (*R*)-phenylalanine **3** ($[\alpha]_D^{23}$=+35.0, *c* 2.0, H_2O)[6] in 81% yield (Scheme 1). The uniformly high diastereoselectivity observed for alkylation of enolate **4** is

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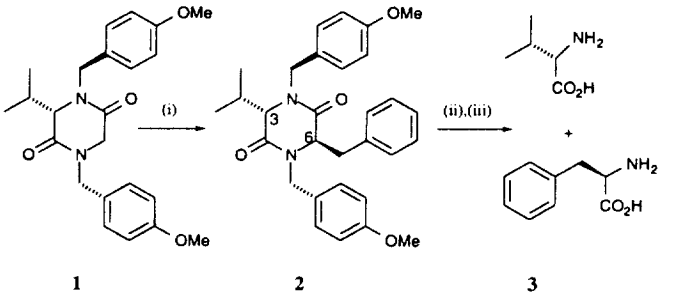
believed to be a result of its conformation whereby the stereochemical information of the isopropyl bearing stereogenic centre at C_3 controls the conformation of both *p*-methoxybenzyl protecting groups (Fig. 1).



Reagents and conditions: (i) 1.1 eq. LHMDS, THF, -78°C; 2 eq. BnBr;
(ii) CAN, CH_3CN/H_2O;(iii) 6M HCl, Dowex 50-XH.

Scheme 1.

Molecular modelling studies[7] and X-ray crystal structure analysis suggested that (3*S*,6*R*)-benzylated DKP **2** adopted a similar conformation to DKP **1**. It was proposed that the β-branched C_3 isopropyl group of **2** should provide sufficient steric bias to enable regioselective deprotonation of the DKP ring proton at C_6 to form enolate **5**. Subsequent reprotonation of this enolate **5** with a suitably hindered proton source should occur *trans* to both the C_3-isopropyl and the N_1-*p*-methoxybenzyl group to afford (3*S*,6*S*)-benzylated DKP **6** in high d.e.[8] Deprotection of DKP **6** under standard conditions would then afford (*S*)-phenylalanine *ent*-**3** directly from auxiliary **1** (Fig. 2).

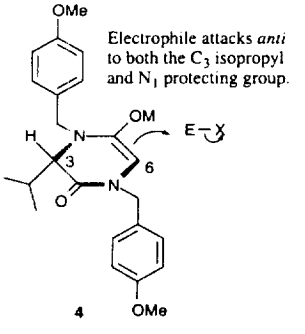


Fig. 1.

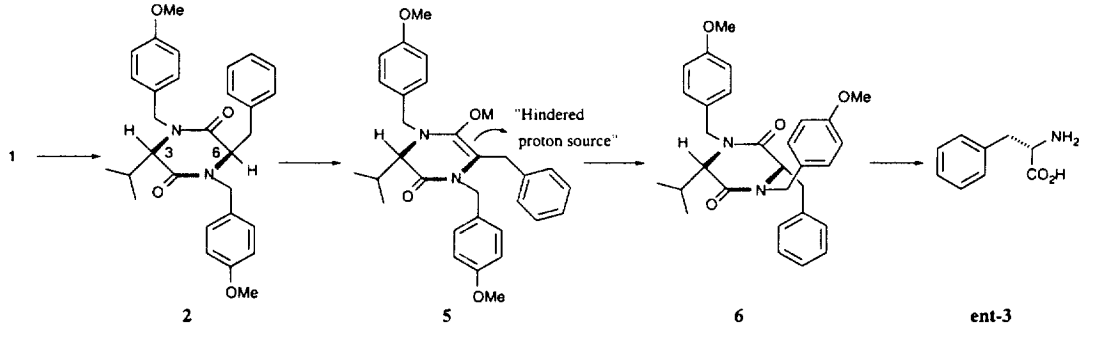
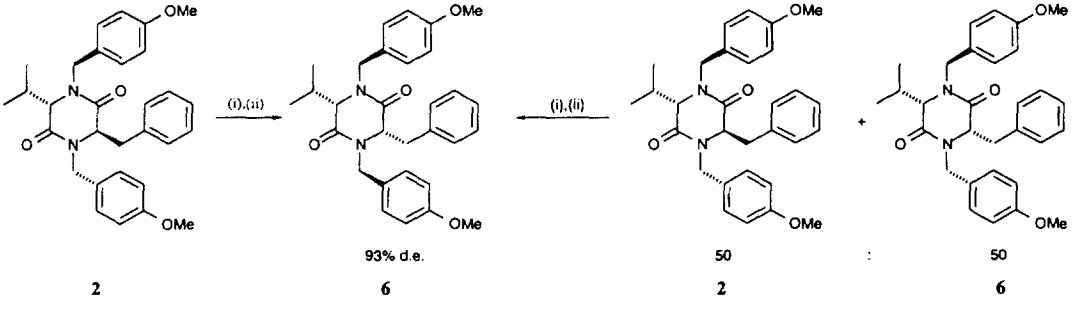


Fig. 2.

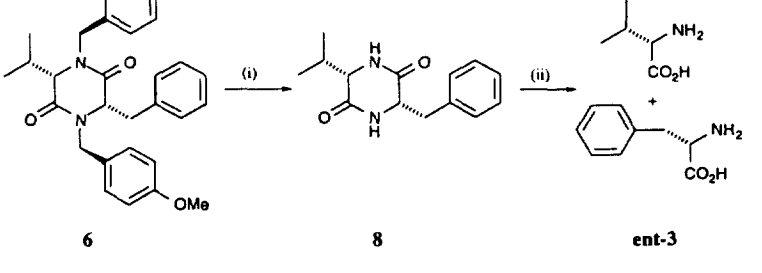
trans-(3*S*,6*R*)-6-Benzyl DKP **2** in THF at −78°C was treated with 2 equiv. of *n*-butyllithium and the reaction mixture quenched via addition of a solution of 2,6-di-*t*-butylphenol in THF at −78°C, to afford *cis*-(3*S*,6*S*)-benzylated **6** in 92% d.e. Subsequent purification of the crude reaction mixture by chromatography [petrol:ethyl acetate (50:50)], afforded pure DKP **6** ($[\alpha]_D^{23}=-235.5$, *c* 1.0, $CHCl_3$) in 93% yield. No evidence could be obtained for a competing deprotonation pathway at the C_3 centre since treatment of DKP **2** in THF at −78°C with 2.5 equiv. of *n*-BuLi, followed by quenching with MeOD, afforded DKP **6** with no deuterium incorporation at the C_3 centre.[9] The enantiomeric purity of DKP **6** was confirmed by comparison of its ^1H NMR spectra with that of an authentic sample of racemic (±)-**6** in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[10] Since the epimerisation protocol had clearly demonstrated the stereoselective conversion of *trans*-DKP **2** to *cis*-DKP **6** we were interested in determining whether this approach could be applied to the deracemisation of α-amino acids.[11] A 50:50 mixture of the epimeric DKPs **2** and **6** was prepared *de novo* from racemic phenylalanine and (*S*)-valine in 74% yield,[12] and the resulting mixture treated with 3.0 equiv. of *n*-BuLi at −78°C, followed by reprotonation with 2,6-di-*t*-butylphenol according to the general protocol described, to afford DKP **6** (93% d.e.). Purification by chromatography afforded homochiral diastereomerically pure DKP **6** in 87% isolated yield (Scheme 2).[13]



Reagents and conditions: (i) 2.eq *n*-BuLi, THF, -78°C; (ii) 2,6-di-*t*-butylphenol, THF, -78°C

Scheme 2.

Subsequent oxidative debenzylation of DKP **6** with ceric ammonium nitrate gave the parent *cis*-(3*S*,6*S*)-DKP **8** ($[\alpha]_D^{23}=-69.5$, *c* 1.0, H_2O) which was identical to the homochiral material prepared *de novo* by thermal cyclisation of dipeptide H_2N–(*S*)-Phe-(*S*)-Val–OMe, clearly demonstrating that no racemisation had occurred during deprotonation of DKP **2** with *n*-BuLi. *cis*-(3*S*,6*S*)-DKP-**8** was easily deprotected using 6 M HCl to give homochiral (*S*)-phenylalanine *ent*-**3** ($[\alpha]_D^{23}=-34.7$, *c* 2.0, H_2O)[5] in 70% yield.



Reagents and Conditions: (i) 3 eq. CAN, CH_3CN/H_2O (2:1); (iv) 2M HCl, Δ; Ion exchange chromatography.

In conclusion, the epimerisation protocol described for DKP **2** clearly demonstrates that both enantiomers of phenylalanine **3** and *ent*-**3** can be prepared from homochiral (*S*)-auxiliary **1**, and this approach

may be employed for the deracemisation of phenylalanine to (*S*)-phenylalanine. We are currently investigating the scope of this enolate reprotonation strategy for the deracemisation of other racemic α-amino acids and its use for the enantiospecific conversion of L- into D-α-amino acids (and *vice versa*).

Acknowledgements

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3. (*S*)-Penicillamine, for example, is used for the treatment of heavy metal poisoning while (*R*)-penicillamine causes atrophy and blindness; G. M. Coppola, K. M. Schuster, *Asymmetric Synthesis — Construction of Chiral Molecules using Amino Acids*, Wiley, New York, 1987.
4. For an excellent review on the enantiospecific reprotonation of prochiral enolates see: C. Fehr, *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2566.
5. S. D. Bull, S. G. Davies, S. W. Epstein, J. V. A. Ouzman, *Chem. Commun*, **1998**, 659.
6. The α-amino acids had identical specific rotations to authentic samples of homochiral phenylalanine and valine purchased from Aldrich chemical company.
7. Molecular modelling calculations were carried out using the MOPAC® (Chem 3D®) suite of Molecular Mechanics programs using PM3 parameters.
8. Juaristi and Seebach have employed a similar enolate reprotonation strategy to epimerise alanine derived imidazolidinone auxiliaries containing two stereogenic centres, although no d.e. values were reported for these transformations; E. Juaristi, J. L. Anzorena, A. Boog, D. Madrigal, D. Seebach, E. V. García-Baez, O. García-Barradas, B. Gordillo, A. Kramer, I. Steiner, S. Zürcher, *J. Org. Chem.*, **1995**, *60*, 6408.
9. Quenching enolate **5** with MeOD afforded deuterated *cis*-DKP (6D)-**6** in 87% d.e. The use of 2.5 equiv. of *n*-BuLi resulted in deuterium incorporation at both C_6 and one of the four *p*-methoxy benzylic protons. Partial incorporation of deuterium at the C_3 position of DKP **6** could only be achieved when 5 equiv. of *n*-BuLi and prolonged reaction times were employed.
10. Addition of 3 equiv. of this chiral solvating agent clearly resolved the benzylic hydrogens of racemic (±)-**6** in $CDCl_3$ at δ 5.17 and 5.38: W. H. Pirkle, P. E. Adams, *J. Org. Chem.*, **1980**, *45*, 4117.
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12. Synthesis of the epimeric mixture of DKPs **2** and **6** from racemic phenylalanine may be achieved via *p*-methoxybenzylation of the parent DKPs cyclo-(*SR*)-Phe-(*S*)-Val which are derived in a similar yield either via condensation of the Leuch's anhydride of (*S*)-valine with (±)-phenylalanine methyl ester according to the procedure described by S. D. Bull, S. G. Davies, W. O. Moss, *Tetrahedron: Asymmetry*, **1998**, *9*, 321; or via DCC coupling of *Z*-(*S*)-valine and (±)-phenylalanine methyl ester according to the method described by J. E. Rose, P. D. Leeson, D. Gani, *J. Chem. Soc., Perkin. Trans. 1*, **1995**, 157.
13. The high diastereoselectivity observed for reprotonation of enolate **5** is under kinetic control, since thermodynamic equilibration of *trans*-**2** or *cis*-**6** via treatment with sodium methoxide in methanol afforded a 60:40 ratio of *trans*-**2**:*cis*-**6**.