

# Stereoselective conjugate addition of organocuprates to a dehydroalanine derived diketopiperazine

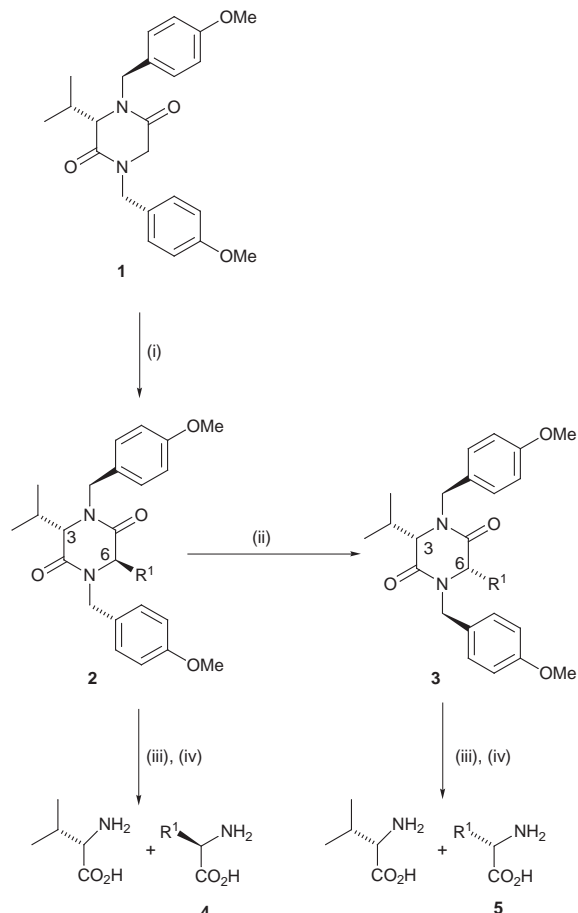
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An asymmetric synthesis of homochiral  $\alpha$ -amino acids has been developed which is based on the conjugate addition of organocuprates to the dehydroalanine equivalent (3*S*)-*N,N'*-bis(*p*-methoxybenzyl)-3-isopropyl-6-methylenepiperazine-2,5-dione **1**.

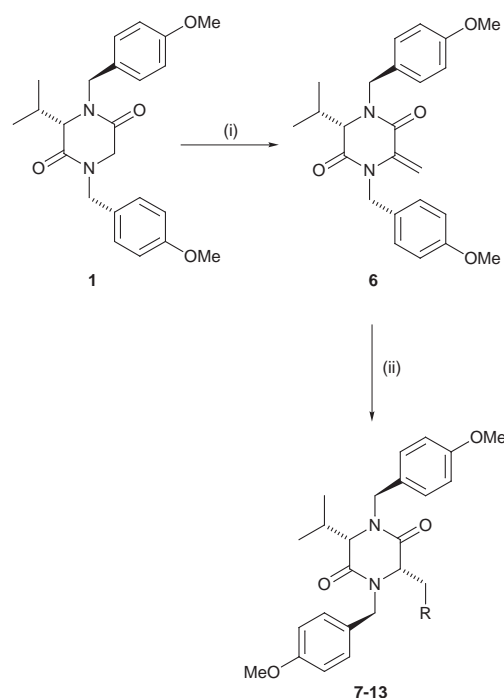
A large number of different methods have been developed for the asymmetric synthesis of non-proteinogenic  $\alpha$ -amino acids.<sup>1</sup> We have recently reported on a new diketopiperazine (DKP) based auxiliary, (3*S*)-*N,N'*-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **1**, the enolate of which adopts a conformation which ensures that alkylation with a range of electrophiles affords *trans*-(3*S*,6*R*)-DKPs in excellent de. The high des are the result of a chiral relay effect deriving from the conformation of the two *N*-*p*-methoxybenzyl protecting groups as illustrated in all the Schemes. Subsequent deprotection of the resultant DKPs **2** affords the desired (*R*)- $\alpha$ -amino acids **4** in good yield.<sup>2</sup> (*S*)- $\alpha$ -Amino acids **5** may also be prepared from DKP **1** using an epimerisation strategy where diastereoselective reprotonation of the enolates derived from DKPs **2** with 2,6-di-*tert*-butylphenol affords *cis*-(3*S*,6*R*)-DKPs **3** in excellent de (Scheme 1).<sup>3</sup> We now report that *cis*-(3*S*,6*S*)-DKPs **3** may also



**Scheme 1** Reagents and conditions: (i) 1.1 equiv. LHMDS, THF,  $-78^\circ\text{C}$ ; 2 equiv.  $\text{R}^1\text{X}$ ; (ii) *n*-BuLi, THF,  $-78^\circ\text{C}$ ; 2,6-di-*tert*-butylphenol; (iii) CAN,  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ ; (iv) 6 M HCl; Dowex 50-XH.

be prepared using methodology that relies on the 1,4-conjugate addition of organocuprates to the dehydroalanine equivalent **6**.<sup>4</sup>

DKP **1** in THF at  $-78^\circ\text{C}$  was deprotonated with *n*-BuLi, quenched with paraformaldehyde and the crude reaction mixture refluxed for 1 hour to afford the Michael acceptor (3*S*)-*N,N'*-bis(*p*-methoxybenzyl)-3-isopropyl-6-methylenepiperazine-2,5-dione **6** in 92% yield. Addition of preformed lithium diphenylcuprate to DKP **6** in THF at  $-78^\circ\text{C}$ , followed by quenching with aqueous ammonium chloride, afforded *cis*-(3*S*,6*S*)-benzylated DKP **7** ( $[\alpha]_{\text{D}}^{23} = -235.5$ , *c* 1.0,  $\text{CHCl}_3$ ) in greater than 95% de (Scheme 2).<sup>5</sup> The versatility of this



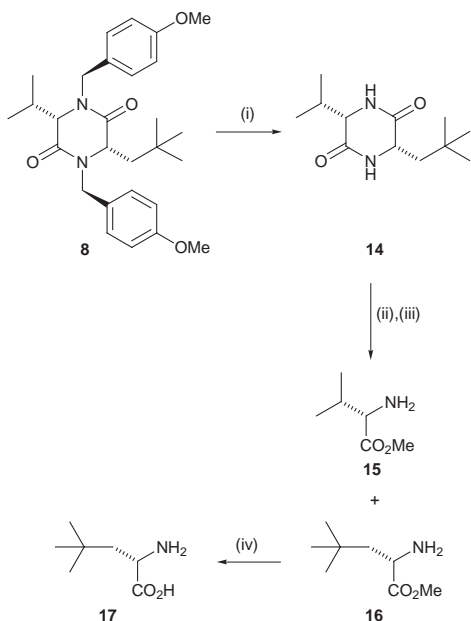
**Scheme 2** Reagents and conditions: (i) 1.1 equiv. *n*-BuLi, THF,  $-78^\circ\text{C}$ ; 2 equiv.  $(\text{CH}_2\text{O})_n$ ;  $\Delta$ ; (ii) organocuprate, THF,  $-78^\circ\text{C}$ ;  $\text{NH}_4\text{Cl}_{(\text{aq})}$ .

conjugate addition methodology was further demonstrated by the addition of a range of organocuprates to DKP **6** to afford *cis*-(3*S*,6*S*)-DKPs **8-13** in >95% de, all of which were purified to homogeneity via column chromatography (Table 1).

DKP **8** was N-deprotected by oxidative removal of the *p*-methoxybenzyl groups with ceric ammonium nitrate in  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  (3:1) and purified by chromatography over alumina, to afford DKP **14**. This DKP **14** was hydrolysed by refluxing in 6 M HCl, and the resultant mixture of  $\alpha$ -amino acids converted to their methyl esters **15** and **16** by treatment with HCl and MeOH. The volatile free amine of valine methyl ester was removed by fractional distillation under high vacuum,<sup>6</sup> followed by hydrolysis of methyl ester **16** to afford homochiral (*S*)- $\gamma$ -methylleucine **17** ( $[\alpha]_{\text{D}}^{23} = +15.7$ , *c* 1.0,  $\text{CH}_3\text{CO}_2\text{H}$  [lit.,<sup>7</sup>  $[\alpha]_{\text{D}}^{23} = +14.9$   $\text{CH}_3\text{CO}_2\text{H}$ ]) in 80% yield from DKP **8**. The enantiomeric excess of **17** was confirmed to be

**Table 1** Yields and des observed for formation of DKPs 7–13 via addition of organocuprates to DKP 6

R	Cuprate conditions	Isolated yield of homochiral DKP (%)	$[\alpha]_D^{23}$ (c 1.0, CHCl <sub>3</sub> )
7	Ph 2 PhLi, 2 CuCN	88	-235.5
8	<sup>t</sup> Bu 2 <sup>t</sup> BuMgCl, 2 CuCN	90	-198.6
9	Cy 2 CyMgBr, 2 CuCN	92	-159.4
10	<sup>n</sup> Bu 2 <sup>n</sup> BuLi, 2 CuCN	91	-186.7
11	Me 2 MeLi, 2 CuCN	91	-178.2
12	Vinyl 2 VinylMgBr, 2 CuCN	87	-137.8
13	<sup>i</sup> Pr 2 <sup>i</sup> PrMgBr, 2 CuCN	88	-225.3



**Scheme 3** Reagents and conditions: (i) CAN, CH<sub>3</sub>CN–H<sub>2</sub>O (3:1); (ii) 6 M HCl, Δ; (iii) (a) 2 M HCl, MeOH, (b) K<sub>2</sub>CO<sub>3</sub>(aq.), (c) separate by distillation; (iv) 2 M HCl, Δ; Dowex 50X8-200.

>99% ee by chiral HPLC analysis of its *N*-benzyloxycarbonyl derivative over a CYCLOBOND I™ stationary phase using CH<sub>3</sub>CN:TEAA (88:12) as eluant.

In conclusion, addition of organocuprates to Michael acceptor DKP 6 provides simple access to *cis*-(3*S*,6*S*)-DKPs 5 which are readily deprotected to afford homochiral (*S*)-α-amino acids in good yield.

## Experimental

### Selected data for DKP 6

Mp = 88–90 °C,  $[\alpha]_D^{23} = -129.4$  (c 2.3, CHCl<sub>3</sub>), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 0.90 (3H, d, *J* 6.8), 1.04 (3H, d, *J* 6.8), 2.24 (1H, m), 3.78 (3H, s), 3.80 (3H, s), 3.89 (1H, d, *J* 7.5), 3.93 (1H, d, *J* 14.7), 4.58 (1H, d, *J* 14.8), 5.02 (1H, d, *J* 1.1), 5.13 (1H, d, *J* 14.7), 5.40 (1H, d, *J* 14.8), 5.81 (1H, d, *J* 1.1), 6.80–6.89 (4H, m), 7.15–7.20 (4H, m); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>), 17.4, 19.4, 32.7, 46.9, 48.0, 55.3, 64.5, 104.4, 114.3, 114.4, 128.7, 129.9, 137.7, 159.3, 159.9, 164.7.

### (3*S*,6*S*)-*N,N'*-Bis(*p*-methoxybenzyl)-3-isopropyl-6-(2',2'-dimethylpropyl)piperazine-2,5-dione 8

<sup>t</sup>BuMgCl (1.6 mL, 2 M solution in Et<sub>2</sub>O) in THF (1.6 mL) was added to a rapidly stirred suspension of anhydrous copper cyanide (138 mg, 1.52 mmol) in THF (5 mL) at –78 °C, and the reaction warmed to –30 °C to afford a homogeneous solution. The solution was recooled to –78 °C, BF<sub>3</sub>·OEt<sub>2</sub> (0.204 mL, 1.92 mmol) added and the reaction stirred for 10 minutes at –78 °C. DKP 6 (600 mg, 1.47 mmol) was then added, the reaction mixture stirred at –78 °C for 2 hours, quenched with NH<sub>4</sub>Cl solution, extracted with ether, dried (MgSO<sub>4</sub>), and the solvent removed in vacuum. The crude reaction mixture (>95%

de) was purified by recrystallisation from ether–petrol (1:1) to afford DKP 8 (632 mg, 1.36 mmol) in 90% yield.  $[\alpha]_D^{23} = -198.6$  (c 1.0, CHCl<sub>3</sub>); mp = 112–114 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 1.02 (9H, s), 1.12 (3H, d, *J* 6.7), 1.17 (3H, d, *J* 6.7), 1.58 (1H, dd, *J* 14.4, 2.2), 1.99 (1H, dd, *J* 14.4, 8.0), 2.16 (1H, m), 3.59 (1H, d, *J* 6.9), 3.66 (1H, d, *J* 15.0), 3.73 (1H, d, *J* 14.6), 3.80 (6H, s), 3.83 (1H, dd, *J* 8.0, 2.2), 5.32 (1H, d, *J* 15.0), 5.42 (1H, d, *J* 14.6), 6.78–6.84 (4H, m), 6.98–7.02 (2H, m), 7.04–7.09 (2H, m); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) 20.0, 20.6, 29.7, 30.8, 33.8, 45.9, 49.6, 50.0, 65.8, 114.4, 128.0, 128.3, 129.1, 129.3, 159.4, 159.5, 167.1, 168.9.

### (3*S*,6*S*)-3-Isopropyl-6-(2',2'-dimethylpropyl)piperazine-2,5-dione 14

To a solution of DKP 8 (500 mg, 1.22 mmol) in water (3 mL) and acetonitrile (9 mL) was added ceric ammonium nitrate (4.0 g, 7.32 mmol {6 equiv.}) in one portion. The resultant suspension was stirred at room temperature for one hour, neutral alumina added (*ca.* 1 g), the solvent removed *in vacuo*, and the crude residue applied to a column of neutral alumina (gradient elution with EtOAc–EtOH 1:1→1:4) to afford DKP 14 (255 mg, 1.13 mmol) in 92% yield.  $[\alpha]_D^{23} = -53.0$  (c 0.94, AcOH); mp = 205 °C (subl.); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) 0.82 (3H, d, *J* 8.1), 0.88 (9H, s), 0.92 (3H, d, *J* 8.1), 1.37 (1H, dd, *J* 14.1, 7.5), 1.84 (1H, dd, *J* 14.1, 3.4), 2.04 (1H, m), 3.52 (1H, dd, *J* 4.53, 3.0), 3.72 (1H, ddd, *J* 6.7, 3.0, 3.0), 7.92 (1H, s), 8.08 (1H, s); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) 17.7, 18.8, 29.4, 30.4, 31.2, 48.0, 52.0, 59.8, 167.8, 169.8.

### (*S*)-γ-Methylleucine 17

A solution of DKP 14 (219 mg, 0.97 mmol) was refluxed in 6 M HCl (20 mL) overnight, the solvent removed *in vacuo* and the residue heated in methanol–HCl (sat.) for a further hour. The solvents were removed to afford a residue which was neutralised with NaHCO<sub>3</sub> (aq.), extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>), and the solvents again removed *in vacuo* to afford a mixture of crude α-amino acid methyl esters 15 and 16. The more volatile valine methyl ester 15 was removed *via* distillation at room temperature (0.1 mmHg), and the residual 16 hydrolysed in 2 M HCl under reflux, to afford (*S*)-γ-methylleucine 17 as its HCl salt. Subsequent desalting using Dowex 50X8-200™ ion exchange resin afforded (*S*)-γ-methylleucine 17 (129 mg, 0.912 mmol) in 94% yield.  $[\alpha]_D^{23} = +15.7$  (c 1.0, CH<sub>3</sub>CO<sub>2</sub>H), [lit.,<sup>7</sup>  $[\alpha]_D^{23} = +14.9$  (c 1.0, CH<sub>3</sub>CO<sub>2</sub>H)]; <sup>1</sup>H NMR (200 MHz, D<sub>2</sub>O) 0.75 (9H, s), 1.39 (1H, dd, *J* 14.9, 7.4), 1.70 (1H, dd, *J* 14.9, 4.8), 3.48 (1H, dd, *J* 7.1, 4.8).

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## Notes and references

- R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989; R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1540.
- S. D. Bull, S. G. Davies, S. W. Epstein and J. V. A. Ouzman, *Chem. Commun.*, 1998, 659.
- S. D. Bull, S. G. Davies, S. W. Epstein and J. V. A. Ouzman, *Tetrahedron: Asymmetry*, 1998, **9**, 2795.
- Similar approaches have been adopted by Seebach *et al.* who employed a racemic methylene imidazolidinone auxiliary in a diastereoselective butylcuprate addition (D. Seebach, H. M. Bürger and C. P. Schickli, *Liebigs. Ann. Chem.*, 1991, 669) and by Hegedus *et al.* who used optically active carbamatoacrylates (P. A. Lander and L. S. Hegedus, *J. Am. Chem. Soc.*, 1994, **116**, 8126).
- The stereochemistry of *cis*-(3*S*,6*S*)-benzylated DKP 7 was assigned by comparison with an authentic sample prepared *de novo* from (*S*)-phenylalanine and (*S*)-valine as described in reference 3.
- D. Deng, U. Groth and U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, 1981, **21**, 798; U. Schöllkopf, *Pure Appl. Chem.*, 1983, **55**, 1799; U. Schöllkopf, U. Busse, R. Lonsky and R. Hinrichs, *Liebigs. Ann. Chem.*, 1986, 2150.
- J. Pospicek and K. Blaha, *Collect. Czech. Chem. Commun.*, 1987, 514.

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