COMMUNICATION

Stereoselective conjugate addition of organocuprates to a dehydroalanine derived diketopiperazine

Steven D. Bull, Stephen G. Davies* and Michael D. O'Shea

The Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, UK OX1 3QY

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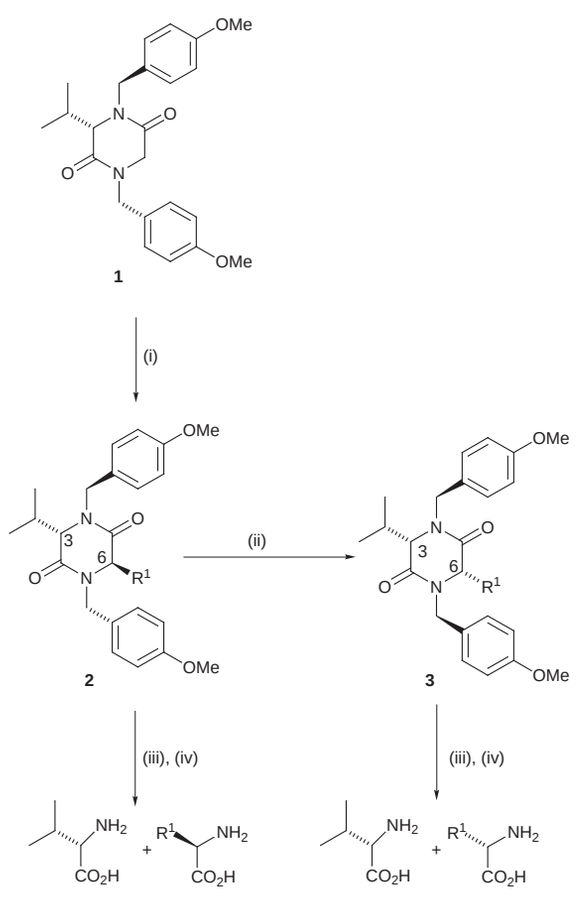
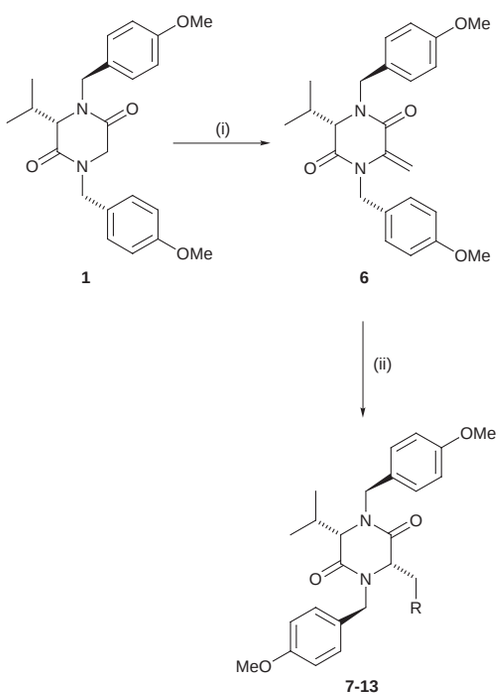
An asymmetric synthesis of homochiral α-amino acids has been developed which is based on the conjugate addition of organocuprates to the dehydroalanine equivalent (3*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropyl-6-methylenepiperazine-2,5-dione 6.

A large number of different methods have been developed for the asymmetric synthesis of non-proteinogenic α-amino acids.[1] 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*)-α-amino acids **4** in good yield.[2] (*S*)-α-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).[3] We now report that *cis*-(3*S*,6*S*)-DKPs **3** may also be prepared using methodology that relies on the 1,4-conjugate addition of organocuprates to the dehydroalanine equivalent **6**.[4]



Scheme 1 *Reagents and conditions*: (i) 1.1 equiv. LHMDS, THF, −78 °C; 2 equiv. R^1X; (ii) *n*-BuLi, THF, −78 °C; 2,6-di-*tert*-butylphenol; (iii) CAN, CH_3CN–H_2O; (iv) 6 M HCl; Dowex 50-XH.

DKP **1** in THF at −78 °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 diphenylcyanocuprate to DKP **6** in THF at −78 °C, followed by quenching with aqueous ammonium chloride, afforded *cis*-(3*S*,6*S*)-benzylated DKP **7** ($[\alpha]_D^{23} = -235.5$, *c* 1.0, $CHCl_3$) in greater than 95% de (Scheme 2).[5] The versatility of this



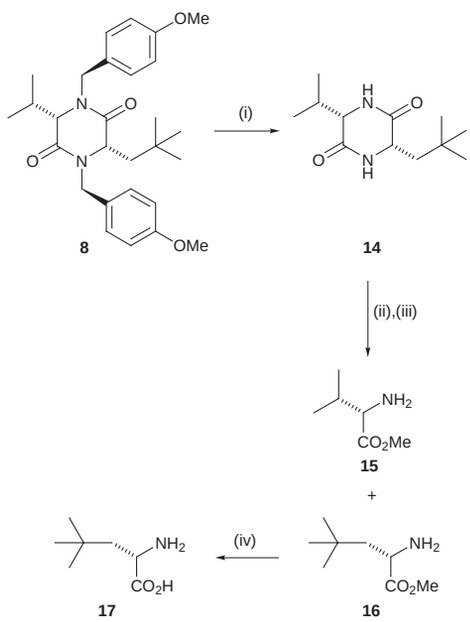
Scheme 2 *Reagents and conditions*: (i) 1.1 equiv. *n*-BuLi, THF, −78 °C; 2 equiv. $(CH_2O)_n$; Δ; (ii) organocuprate, THF, −78 °C; $NH_4Cl_{(aq)}$.

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 CH_3CN–H_2O (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 α-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,[6] followed by hydrolysis of methyl ester **16** to afford homochiral (*S*)-γ-methylleucine **17** ($[\alpha]_D^{23} = +15.7$, *c* 1.0, CH_3CO_2H [lit.,[7] $[\alpha]_D^{23} = +14.9$ CH_3CO_2H]) 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, $CHCl_3$)
7	Ph	2 PhLi, 2 CuCN	88	−235.5
8	^{t}Bu	2 ^{t}BuMgCl, 2 CuCN	90	−198.6
9	Cy	2 CyMgBr, 2 CuCN	92	−159.4
10	^{n}Bu	2 ^{n}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	^{i}Pr	2 ^{i}PrMgBr, 2 CuCN	88	−225.3



Scheme 3 *Reagents and conditions*: (i) CAN, CH_3CN–H_2O (3:1); (ii) 6 M HCl, Δ; (iii) (a) 2 M HCl, MeOH, (b) K_2CO_3(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_3CN: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, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (50 MHz, $CDCl_3$), 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

^{t}BuMgCl (1.6 mL, 2 M solution in Et_2O) 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_3·OEt_2 (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_4Cl solution, extracted with ether, dried ($MgSO_4$), 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, $CHCl_3$); mp = 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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.); ^{1}H NMR (500 MHz, DMSO-d_6) 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $NaHCO_3$ (aq.), extracted with CH_2Cl_2, dried ($MgSO_4$), 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_3CO_2H), [lit.,[7] $[\alpha]_D^{23}$ = +14.9 (*c* 1.0, CH_3CO_2H)]; ^{1}H NMR (200 MHz, D_2O) 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).

Acknowledgements

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Notes and references

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