Chiral relay auxiliary for the synthesis of enantiomerically pure α-amino acids

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Chiral auxiliary (3*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione employs a chiral relay network based on non-stereogenic *N*-benzyl protecting groups to enhance diastereocontrol during enolate alkylation.

The structural diversity of non-proteinogenic α-amino acids is reflected by the large number of different methods which have been developed for their asymmetric synthesis.[1] Those approaches that are based on chiral auxiliaries generally rely on alkylation of a masked glycine enolate where diastereofacial selectivity is controlled by an attached homochiral residue.[2] Schöllkopf's auxiliary **1** derived from *O*-methylation of diketopiperazine (DKP) **3** has been widely used in this area but there are problems associated with its use for synthesis (Scheme 1).[3] It is a volatile oil which is difficult to prepare, it exhibits poor diastereoselectivities with a linear or β-branched electrophiles and is also susceptible to acid catalysed hydrolysis.[4] It is known that *N*,*N*′-dialkylpiperazine-2,5-diones are robust, highly crystalline compounds[5] and we wished to exploit these characteristics to create a new chiral auxiliary **4** for the synthesis of enantiomerically pure α-amino acids.

Molecular modelling studies[6] revealed that enolate **5** derived by deprotonation of **4** adopts a conformation which enables the stereochemical information of the (3*S*)-isopropyl group to be relayed through space *via* non-stereogenic benzyl protecting groups. The ring system of enolate **5** is essentially planar with its isopropyl group fixing the conformation of the proximal N4 benzyl *anti*, which in turn directs the distal N1 benzyl group *syn* to the isopropyl group. This arrangement effectively blocks the *Si* face of enolate **5** towards alkylation at C6 (Fig. 1). We predicted that the proximity of the N1 benzyl group to C6 would result in significantly higher alkylation diastereoselectivities for DKP **4** than would be achieved for either Schöllkopf's auxiliary **1** or *N*,*N*′-dimethylated DKP **2** where, in both cases, the stereofacial control is only provided by the C3 isopropyl group.

Highly crystalline (3*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **4** ($[\alpha]_D^{23}$ −53.7, *c* 1.0 in $CHCl_3$)‡ was prepared in 85% yield by dropwise addition of *p*-methoxybenzyl chloride to cyclo-[L-Val-Gly] **3**[4] and sodium hydride in DMF (Scheme 1). Enantiomerically pure (3*S*)-*N*,*N*′-dimethyl-3-isopropylpiperazine-2,5-dione **2** ($[\alpha]_D^{23}$ +84.4, *c* 1.0 in $CHCl_3$)‡ was prepared in a similar manner using methyl iodide as the electrophile (Scheme 1). The enantiomeric purities of both **2** and **4** were confirmed by comparison of their ^{1}H NMR spectra with authentic racemic materials in the presence of chiral shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[7]

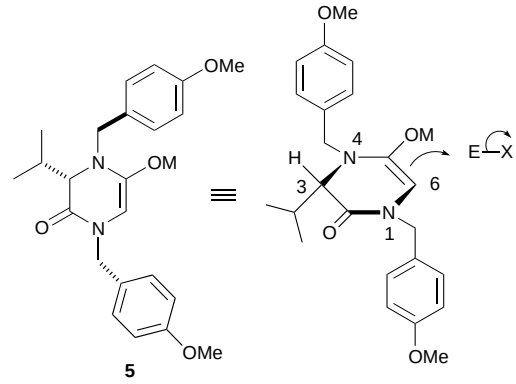
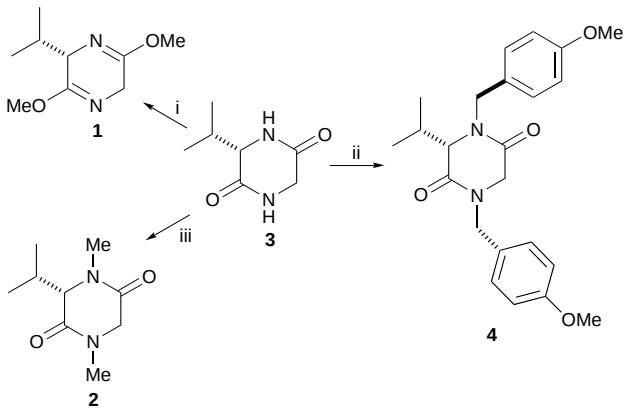
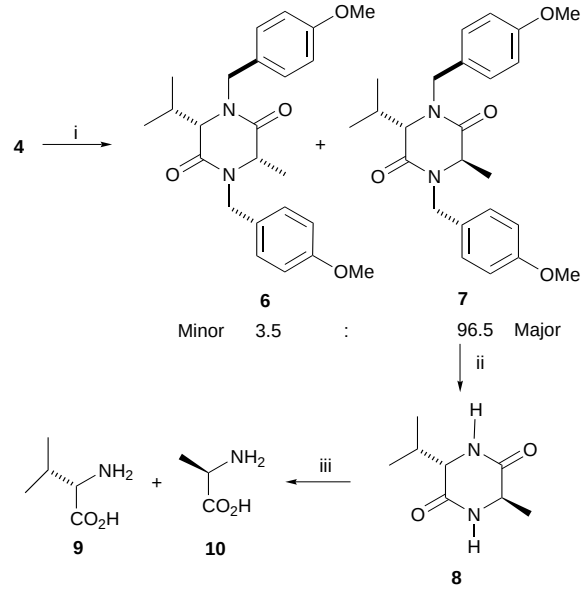


Fig. 1 Electrophile attacks *anti* to both the C3 isopropyl and N1 protecting group

DKP **4** was deprotonated with one equivalent of lithium hexamethyldisilazide in THF at −78 °C followed by addition of four equivalents of methyl iodide to afford a mixture of C6-methylated diastereoisomers **6** and **7** in 93% de (Scheme 2). The diastereoisomers were separated by chromatography [silica, diethyl ether–hexane (1 : 1)] and the configuration of the major diastereoisomer confirmed as *trans*-**7** by direct compar-

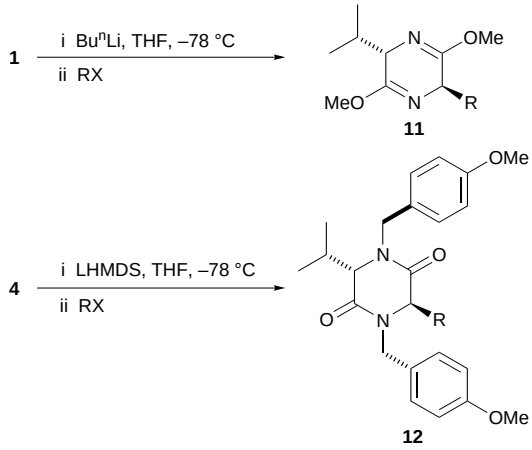


Scheme 1 *Reagents and conditions*: (i) $Me_3O^+BF_4^-$, CH_2Cl_2; (ii) NaH, *p*-methoxybenzyl chloride, DMF; (iii) NaH, MeI, DMF



Scheme 2 *Reagents and conditions*: (i) LHMDS, THF, −78 °C; 10 equiv. MeI; (ii) CAN, CH_3CN–H_2O; (iii) 6 M HCl, Dowex 50-XH

Table 1 Comparison of diastereoselectivity and yield for alkylation of auxiliaries **1** and **4**[a]



	De (%)		Yield (%)		
Electrophile RX	**11**	**12**	**11**	**12**	$[\alpha]_D^{23}$ **12** ($CHCl_3$)‡
Methyl iodide	50	93	54	72	+22.5 (*c* 0.98)
Benzyl bromide	91[b]	98	81[b]	88	+58.6 (*c* 0.99)
Allyl bromide	74	94	83[c]	63	+25.8 (*c* 0.99)
Prop-2-ynyl bromide	52[c]	89	70[d]	74	+14.6 (*c* 0.98)
Ethyl iodide	*d*	90	*a*	78	+46.1 (*c* 1.00)
Isopropyl iodide	*d*	96	*a*	90	0 (*c* 1.00)

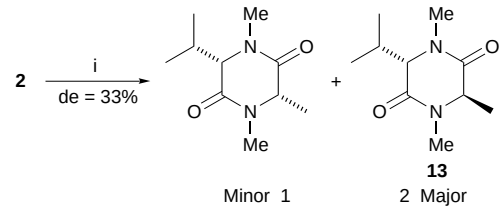
[a] Ref. 13. [b] Ref. 3. [c] Ref. 11. [d] Ref. 12.

ison with an authentic sample prepared *de novo* by *N*-*p*-methoxybenzylation of the piperazine-2,5-dione **8** derived from L-valine **9** and D-alanine **10**.

Deprotection of *trans*-methylated auxiliary **7** was easily achieved *via* oxidative removal of the *p*-methoxybenzyl groups using cerium ammonium nitrate in CH_3CN–H_2O[8] followed by acid catalysed hydrolysis of **8** to afford a mixture of (*S*)-valine **9** and (*R*)-alanine **10**. This mixture was separated by ion exchange chromatography[9] to afford enantiomerically pure (*R*)-alanine, **10** ($[\alpha]_D^{23}$ −14.0, *c* 0.6 M in 1 M HCl)[10]‡ in 86% yield (Scheme 2).

Alkylation of **4** with a range of electrophiles afforded highly crystalline *trans*-alkylated products **12** in > 90% de (Table 1). Simple recrystallisation of the crude reaction product afforded the major *trans*-diastereoisomer pure in good yield. The non-basic character of enolate **5** is particularly noteworthy since reaction with electrophiles that are prone to β-elimination (ethyl iodide or isopropyl iodide) occurred in excellent yield.

It is clear that the alkylation diastereoselectivities observed for the new piperazine-2,5-dione auxiliary **4** compare favourably with those obtained using Schöllkopf's auxiliary **1** (Table 1). Evidence to suggest that the benzylic *N*,*N*′-protecting groups are directly responsible for the improved performance of **4** was obtained by methylating *N*,*N*′-dimethylated piperazine-2,5-dione **2** in which the *N*-methyl groups do not have the capacity to enhance the stereoselectivity *via* the proposed relay mechanism. DKP **2** was methylated under identical conditions



Scheme 3 *Reagents and conditions*: (i) LHMDS, THF, −78 °C; 10 equiv. MeI.

described for **4** to afford *trans*-(3*S*,6*R*)-6-methyl-**13** as the major diastereoisomer in a much reduced 33% de (Scheme 3).

The results obtained for methylation of the enolates of **2** and **4** are clearly consistent with the proposed chiral relay network operating to enhance the diastereoselectivity observed for alkylation of enolate **5**. Further investigations are currently underway to apply the proposed chiral relay concept to enhance stereocontrol in other scenarios.

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Notes and References

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‡ Given in 10^{-1} deg cm^2 g^{-1}.

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13 All new compounds were fully characterised.

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