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Enantioselective Synthesis Of Bis-α-Amino Acid Esters *Via* Asymmetric Phase-Transfer Catalysis.

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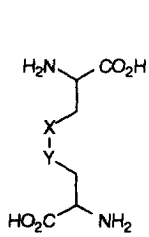
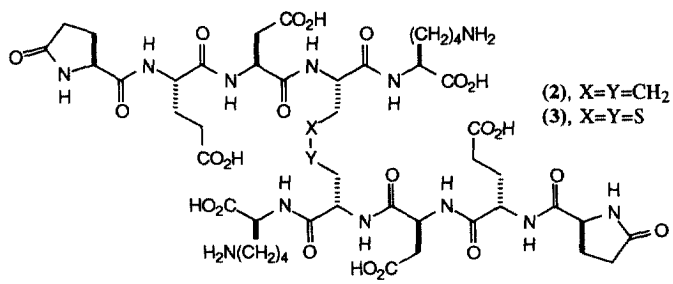
Abstract: Application of *N*-anthracenylmethyl dihydrocinchonidinium bromide quaternary ammonium phase-transfer catalysts to the enantio- and diastereoselective synthesis of a series of bis-α-amino acid esters is reported. Under liquid-liquid phase-transfer conditions the target amino acid esters are obtained with high enantiomeric excess (≥95%e.e.) *via* alkylation of two molecules of a benzophenone-derived glycine-imine with an appropriate dibromide.

Bis-α-amino acids of the general type **1** represent an interesting class of molecules. Naturally-occurring examples such as the dityrosines[1,2] and *meso*-diaminopimelic acid[3] appear to act as cross-linking agents that help stabilise structural polymer elements in plant and bacteria. In addition, isodityrosine[2] is a key structural subunit in a large class of bio-active peptides which include the potent ACE inhibitor K-13[4] and the anti-tumour antibiotic deoxybouvardin.[5] Unnatural bis-α-amino acids have also proved of interest as components for the synthesis of novel analogues of biologically-active peptides.[6] In particular compounds of type **1** have found application as replacements for cystine (**1**, X=Y=S)[7] as exemplified by SK&F 107647 **2**[8] a synthetic hematoregulatory nonapeptide whose structure was based on the known hemoregulatory peptide HP-5b **3**.[9] Consequently there is significant interest in synthetic methods that allow rapid access to structures of type **1**.



(1)



(2), X=Y=CH_2
(3), X=Y=S

As part of a study into the use of *Cinchona* alkaloid derivatives as chiral control elements for synthesis[10] we recently reported a series of asymmetric phase-transfer catalysts and demonstrated that they can be utilised in the enantioselective synthesis of α-amino acids *via* the alkylation of glycine imines under liquid-liquid phase-transfer conditions.[11,12,13] Here we report preliminary results on the application of these catalysts to enantioselective synthesis of a range of bis-α-amino acids.

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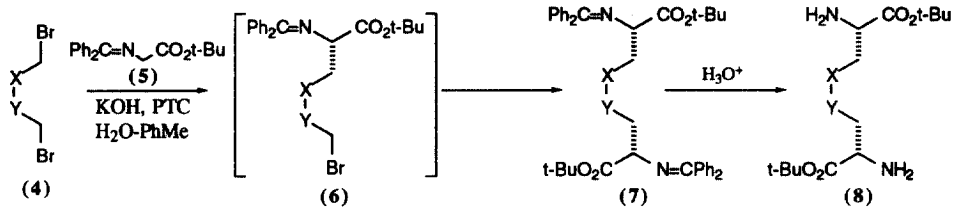
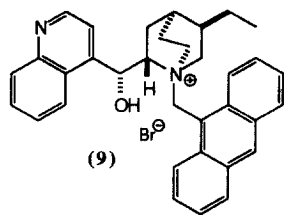
In principle the synthesis of bis-α-amino acid derivatives **7** possessing the natural L-configuration at both chiral centres can be achieved in one step *via* the asymmetric phase-transfer catalysed alkylation of an appropriate dihalide **4** with two mole equivalents of glycine imine **5** (scheme 1). In order for this approach to be successful we require that both alkylation steps proceed with high efficiency and high stereoselectivity.

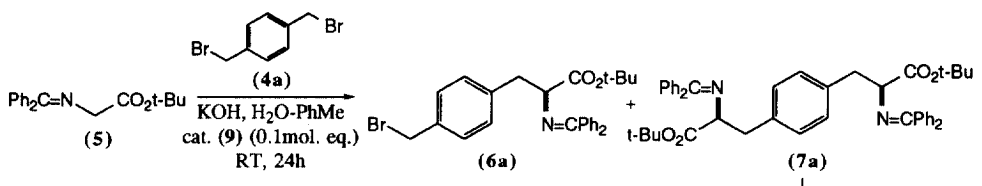


Scheme 1

Based on our earlier studies[10] we selected *N*-anthracenylmethyl dihydrocinchonidinium bromide **9** as the catalyst[14] of choice since, under the desired reaction conditions, this gave high enantioselectivity (up to 94% e.e.) for the alkylation reactions involving imine **5**.



Initial investigations using dibromide **4a**, demonstrated that either mono-alkylated **6a** or di-alkylated **7a** product could be obtained depending upon the reaction conditions employed (scheme 2). With excess dibromide (5 mol. eq.) the monoalkylated product **6a** was obtained in good yield whereas use of stoichiometric quantities of dibromide (0.5 mol. eq.) gave the desired dialkylated product **7a**. Hydrolysis of the imine function then provided the bis-α-amino acid ester **8a**[15] in good overall yield. We found that product **8a** was obtained with good diastereoisomeric excess (72% d.e.) and high enantiomeric excess (≥ 95%).[16] This suggests that each alkylation event proceeds with *ca.* 86% stereoisomeric excess which is similar to the level previously observed using these reaction conditions.[10]



Mol. Eq. (4a)	Ratio (6a) : (7a)
0.5	1 : 10
3.0	3 : 1
5.0	10 : 1

55% overall yield, 72% d.e., ≥95% e.e.[16]

Scheme 2

Once we had established that the target bis-α-amino acids could be prepared using this methodology we investigated its application to dihalides **4b-d** (table 1).

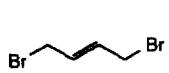
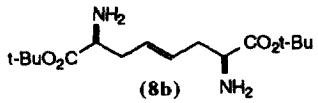
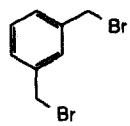
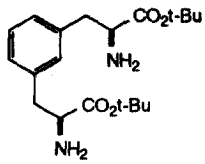
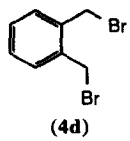
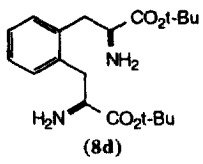
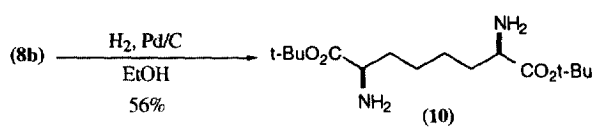
Dibromide	Bis-α-Amino Acid Ester	% d.e[16]	% e.e[16]	Overall Yield (%)
 (4b)	 (8b)	82	≥95	49
 (4c)	 (8c)	70	≥95	52
 (4d)	 (8d)	75	≥95	48

Table 1

As can be seen, in all cases the desired bis-α-amino acid esters were obtained in good overall yield and with high enantiomeric excess demonstrating that this approach is compatible with a variety of dihalide substrates. It also appears that the stereoselectivity of the second alkylation event is relatively insensitive to the proximity of the initially formed chiral centre (compare **8a**, **8c**, **8d**). Since it should be possible to prepare the enantiomeric series of amino acid derivatives using catalysts derived from cinchonine[10,17] this represents a rapid and versatile approach to this class of structures.

As might be expected, **8b** also serves as a direct precursor for the corresponding saturated bis-(amino acid) **10**, the transformation being readily achieved *via* hydrogenation over Pd/C (scheme 3).



Scheme 3

In conclusion, we have demonstrated that the asymmetric phase-transfer alkylation of glycine imine **5** can be used as an efficient highly enantioselective approach to bis-α-amino acid esters. In addition, by controlling the stoichiometry of the reaction it is also possible to access the mono-alkylated materials with good selectivity. Extension of this methodology to more complex bis-α-amino acids is reported in the accompanying paper.

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16. Enantiomeric and diastereoisomeric excesses were determined to ±5% by conversion of the amino acid *tert*-butyl esters into the corresponding *N*-benzoyl derivatives ($PhCOCl$, Et_3N, CH_2Cl_2) followed by HPLC analysis (Chiralcel OD-H, 30%ethanol-70%hexane, 232nm). In all cases the stereochemically enriched samples were compared with statistical mixtures generated using tetrabutylammonium bromide as the PTC for alkylation.
17. Preliminary studies have demonstrated that the enantiomer of **8a** can be prepared in ≥95% e.e. using *N*-anthracenylmethyl cinchoninium bromide as the PTC.