A general route to protected quaternary α-amino acids from β-amino alcohols *via* a stereocontrolled radical approach

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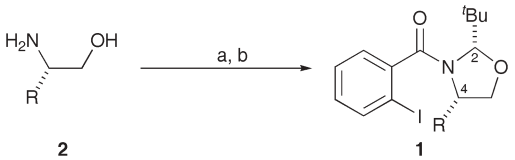
A radical-based approach facilitates the highly stereocontrolled functionalisation of β-amino alcohols, opening up a new, generally applicable methodology for the preparation of quaternary α-amino acids.

The significance of α,α-disubstituted (or quaternary) α-amino acids, particularly in the context of modification/optimisation of the activity of biologically active peptides and as enzyme inhibitors in their own right, has ensured their importance as synthetic targets. To date, the vast majority of asymmetric synthetic approaches to such compounds have relied upon the alkylation of enolate derivatives of existing amino acids,[1] particularly alanine. Stereocontrol has generally been achieved by the use of chiral auxiliaries, as typified by the Schöllkopf approach,[2] or exploitation of the principle of "self-regeneration of stereocentres (SRS)," championed by Seebach *et al.*[3] The sensitivity of many α-amino acid side-chains towards the strongly basic conditions required for quantitative enolate generation and the severe steric constraints associated with the efficient generation of quaternary centres under "anionic conditions", naturally impose serious restrictions on the amino acid substrates that can be employed. Reactions involving radical intermediates suffer from fewer such restrictions and so it is surprising that only a relatively small number of synthetic approaches to highly substituted amino acids use such methodology.[4]

Previously, we have shown that ethanolamine can be alkylated α-to nitrogen *via* racemic 1,3-oxazolidine intermediates using a radical chain sequence involving aryl radical generation, 1,5-hydrogen atom transfer and diastereoselective trapping of the α-aminoalkyl radical intermediate with acryronitrile or acrylate esters. After 1,3-oxazolidine hydrolysis, protected, alkylated ethanolamine derivatives were obtained.[5] Our goal has been to develop this approach into a generally applicable methodology for the synthesis of quaternary amino acids, allowing the derivatisation of a wider range of amine and amino acid derivatives. To this end, we describe herein, the efficient, stereocontrolled derivatisation of a number of "unactivated" β-amino alcohols.

The requisite radical reaction substrates **1** were prepared using a conventional two-step approach involving 1,3-oxazolidine formation from enantiomerically pure L-β-amino alcohols **2**,[6] followed by *N*-acylation for introduction of the 2-iodobenzoyl "protecting-radical-translocating (PRT)" group (Scheme 1 and Table 1). The



2 **1**

Scheme 1 Preparation of 1,3-oxazolidine radical precursors. Reagents and conditions: (a) ^{t}BuCHO, $MgSO_4$, $CHCl_3$, Δ; (b) 2-iodobenzoyl-chloride, pyridine, DMAP (cat.), R.T.

Table 1 Preparation of 1,3-oxazolidine radical precursors

Entry	R	Amino alcohol **2**	Product	Yield (%)[a]
1	CH_3	L-Alaninol	**1a**	66
2	$(CH_3)_2CH$	L-Valinol	**1b**	21
3	$(CH_3)_2CHCH_2$	L-Leucinol	**1c**	73
4	$PhCH_2$	L-Phenylalaninol	**1d**	87
5	$CH_3SCH_2CH_2$	L-Methioninol	**1e**	12

[a] Only single diastereoisomers isolated.

lower yields obtained with both L-valinol and L-methioninol (entries 3 and 5), can be attributed to the lower efficiency of the acylation step. In each case, only a single diastereoisomer of the product **1** could be obtained after chromatographic purification, the minor stereoisomer possibly being destroyed during the *N*-acylation procedure or by hydrolysis on silica gel.

X-Ray crystallographic analysis† of **1a** gave not only confirmation of the absolute and relative stereochemistry but also revealed the preferred rotameric structure of the amide bond, which provides much closer proximity of the future radical-bearing carbon atom of the PRT group (C9 in Fig. 1) to the key hydrogen atom at C-4 compared with that at C-2 (2.9 Å *vs.* 4.8 Å, Fig. 1). This amide geometry and resulting iodide placement are essential for regiospecific generation of the desired C-4 α-aminoalkyl radical, given that the rate of 1,5-hydrogen atom transfer is much faster than the rate of rotation around the C(O)–N bond.[7] NOESY studies also supported the C-2/C-4 *cis*-relative stereochemistry for L-phenylalaninol-derived product **1d** (entry 4). Unfortunately, crystallisation could not be induced in any of the other products and NOESY experiments proved inconclusive for determination of relative stereochemistry. Given that there is considerable literature precedent for the predominance of the thermodynamically favoured *cis*-product in the formation of such 1,3-oxazolidines[8,9] it was assumed that the remaining products possessed the same relative stereochemistry.

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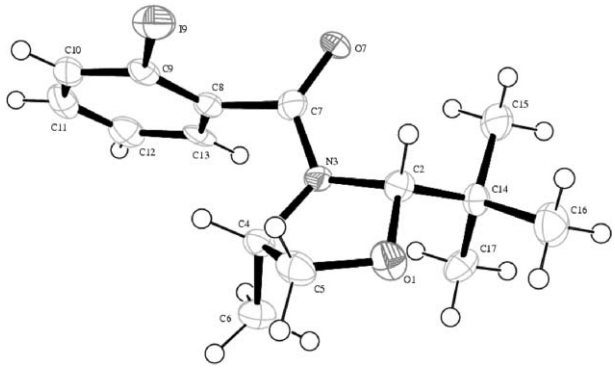
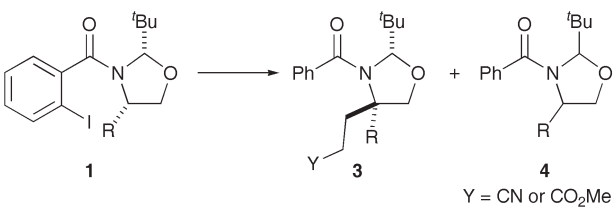


Fig. 1 ORTEP representation of **1a**; ellipsoids drawn at 30% probability level. (Note: The asymmetric unit of **1a** contains two independent molecules. For clarity, only one is shown.)



Scheme 2 Radical reactions of 1,3-oxazolidines. Reagents and conditions: Bu_3SnCl (0.15 equiv.), $NaBH_3CN$ (2 equiv.), acrylonitrile or methyl acrylate (5 equiv.), AIBN (4 × 0.2 equiv.), ^{t}BuOH, Δ.

Compounds **1a–e** were subjected to radical generating/trapping using *in situ* generation of tributyltin hydride (from 15 mol% tributyltin chloride and sodium cyanoborohydride) and acrylonitrile and methyl acrylate in 5-fold excess as the radicalphile (Scheme 2). The results from these experiments are summarised in Table 2. In all cases, a mixture of both trapped product **3** and reduced material **4** was obtained, with only a single diastereoisomer of **3** being detectable by ^{1}H NMR spectroscopy after chromatographic isolation. (The stereochemical integrity of the reduction product **4** was not determined.) The expected *trans*-relationship between the C-2 *tert*-butyl substituent and the newly added substituent at the quaternary C-4 centre was revealed by X-ray crystallographic analysis† of alaninol-derived product **3a** (Fig. 2).

For structures **3b** to **3i**, crystals suitable for X-ray analysis could not be obtained and peak overlap and line broadening in some key ^{1}H NMR signals from rotameric structures, precluded the use of NOESY experiments for determination of the relative

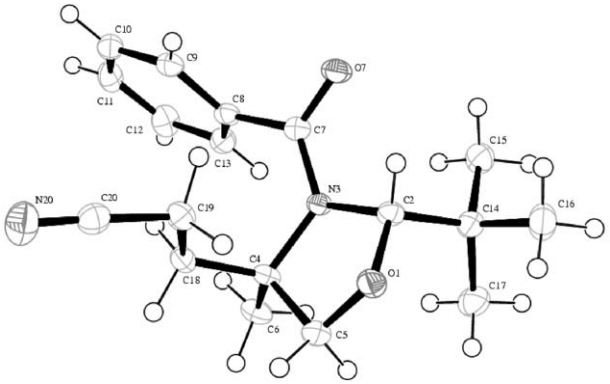
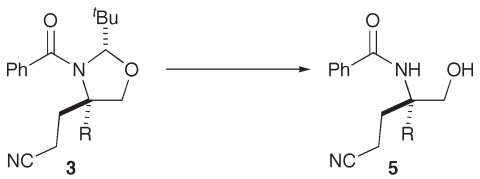


Fig. 2 ORTEP representation of **3a**; ellipsoids drawn at 30% probability level.



Scheme 3 Hydrolysis of functionalised 1,3-oxazolines. Reagents and conditions: CF_3CO_2H, CH_2Cl_2, R.T.

stereochemistry. There are however, many literature examples of closely related enolate alkylations of serine-derived 1,3-oxazolidines that occur predominantly on the opposite face of the heterocycle to the C-2 *tert*-butyl group,[3,10] hence it was thought reasonable to assume that the remaining radical-trapping products possessed the same relative stereochemistry as **3a**.

The proportion of reduction product **4** obtained was found to increase with the use of methyl acrylate rather than acrylonitrile as the radicalphile, a finding for which there is literature precedent.[11]

These results highlight the excellent efficiency of stereocontrolled quaternary centre generation under radical conditions and the successful result obtained with L-methioninol-derived 1,3-oxazolidine **1e**, shows the highly desirable tolerance for functionalised side-chains using this methodology.

Hydrolysis of acrylonitrile-derived products **3a–d** was carried out using trifluoroacetic acid in dichloromethane, in order to avoid simultaneous hydrolysis of the nitrile and amide (Scheme 3). Lower yields were obtained with more highly substituted 1,3-oxazolidines such as L-valinol-derived **3b** (Table 3) and further optimisation of this step is required.

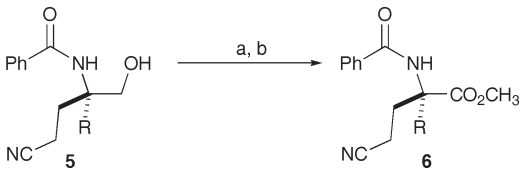
Table 2 Radical reactions of 1,3-oxazolidines

Entry	Substrate	R	Radicalphile	Product 3	Yield of **3**[a] (%)	Yield of **4** (%)
1	**1a**	CH_3	Acrylonitrile	**3a**	85	14
2	**1b**	$(CH_3)_2CH$	Acrylonitrile	**3b**	59	41
3	**1c**	$(CH_3)_2CHCH_2$	Acrylonitrile	**3c**	32	46
4	**1d**	$PhCH_2$	Acrylonitrile	**3d**	63	31
5	**1e**	$CH_3SCH_2CH_2$	Acrylonitrile	**3e**	50	34
6	**1a**	CH_3	Methyl acrylate	**3f**	48	23
7	**1b**	$(CH_3)_2CH$	Methyl acrylate	**3g**	38	36
8	**1c**	$(CH_3)_2CHCH_2$	Methyl acrylate	**3h**	34	28
9	**1d**	$PhCH_2$	Methyl acrylate	**3i**	22	18

[a] Only single diastereoisomers isolated.

Table 3 Results for hydrolysis of functionalised 1,3-oxazolidines

Entry	Substrate	R	Product	Yield (%)
1	**3a**	CH_3	**5a**	75
2	**3b**	$(CH_3)_2CH$	**5b**	24
3	**3c**	$(CH_3)_2CHCH_2$	**5c**	44
4	**3d**	$PhCH_2$	**5d**	21



Scheme 4 Oxidation/esterification of functionalised β-amino alcohols. Reagents and conditions: CrO_3, H_2SO_4, H_2O, $(CH_3)_2CO$; (b) $(CH_3)_3SiCHN_2$, C_6H_6, CH_3OH (4 :1 v/v).

Table 4 Results for β-amino alcohol oxidation/esterification

Entry	Substrate	R	Product	Yield (%)
1	**5a**	CH_3	**6a**	55
2	**5b**	$(CH_3)_2CH$	**6b**	70
3	**5c**	$(CH_3)_2CHCH_2$	**6c**	71
4	**5d**	$PhCH_2$	**6d**	52

The highly functionalised β-amino alcohols **5** thus obtained were oxidised efficiently to the corresponding *N*-benzoyl quaternary α-amino acids using Jones' reagent followed by treatment with (trimethylsilyl)diazomethane to give the methyl esters **6** as single enantiomers (Scheme 4). The yields given in Table 4 cover the combination of oxidation and esterification steps.

In summary, we have demonstrated a straightforward radical-based methodology for the asymmetric derivatisation of β-amino alcohols α-to nitrogen. The methodology represents a much-needed, versatile route to highly functionalised quaternary α-amino acids which will be applicable to a wide range of biologically important substrates. The carboxylic acid oxidation level of the nitrile and ester substituents, introduced *via* the acrylonitrile or methyl acrylate radicalphiles, allows the reported products **6** to be regarded as highly functionalised glutamic acid analogues.

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Notes and references

† Suitable crystals were selected and data collected on a Brüker Nonius KappaCCD Area Detector at the window of a Brüker Nonius FR591 rotating anode ($\lambda_{Mo\text{-}K\alpha}$ = 0.71073 Å) driven by COLLECT[12] and DENZO[13] software at 120 K. Structures were determined in SHELXS-97[14] and refined using SHELXL-97.[15]

Crystal data for **1a**: $C_{15}H_{20}INO_2$, M = 373.22, monoclinic, a = 12.7729(7) Å, b = 7.4551(4) Å, c = 17.0731(8) Å, β = 107.236(4)°, U = 1552.75(14) Å^3, T = 120(2) K, space group $P2_1$, Z = 4, μ(Mo-K$_\alpha$) = 1.597 mm^{-1}, 15953 reflections measured, 6846 unique (R_{int} = 0.0352) which were used in all calculations. Final R_1 = 0.0370, wR_2 = 0.0728 [$F^2 > 2\sigma(F^2)$], R_1 = 0.0526, wR_2 = 0.0787 (all data). Absolute structure parameter = 0.005(18).

Crystal data for **3a**: $C_{18}H_{24}N_2O_2$, M = 300.39, orthorhombic, a = 7.6733(6) Å, b = 13.630(2) Å, c = 15.8871(19) Å, U = 1661.6(3) Å^3, T = 120(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo-K$_\alpha$) = 0.079 mm^{-1}, 9839 reflections measured, 2926 unique (R_{int} = 0.0326) which were used in all calculations. Final R_1 = 0.0304, wR_2 = 0.0723 [$F^2 > 2\sigma(F^2)$], R_1 = 0.0345, wR_2 = 0.0751 (all data). CCDC 602435 and 602436. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604123j

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