Concise synthesis of α-alkyl α-amino acids and their incorporation into peptides *via* β-lactam-derived α-amino acid *N*-carboxy anhydrides

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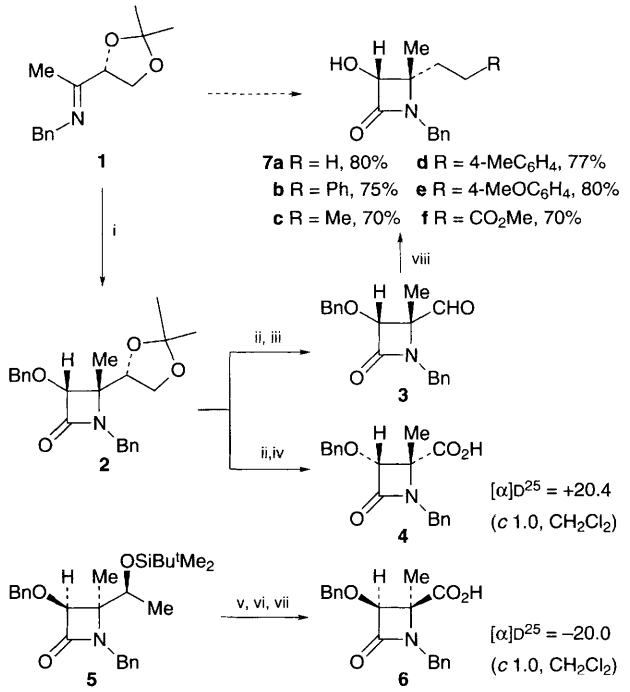
α-Hydroxy β-lactams in which C$_4$ exists as a quaternary carbon are transformed in a single one-pot operation into α,α-dialkyl α-amino acid *N*-carboxy anhydrides providing a new approach to conformationally restricted peptide segments from non α-amino acid precursors.

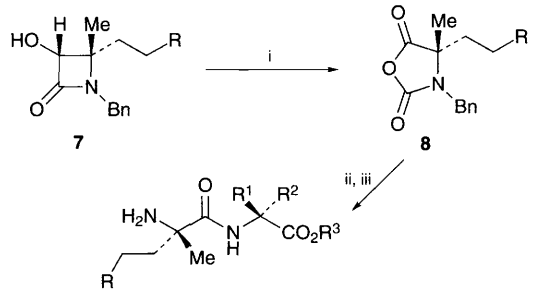
Despite the importance of α,α-disubstituted α-amino acids for the study and design of structurally defined peptides, peptidomimetics and, in general, potent bioactive targets,[1] the majority of the investigations on this topic have dealt with the synthesis of the α-branched α-amino acid itself rather than with the construction of activated species ready for subsequent peptide coupling steps.[2] Towards this goal Heimgartner[3] has developed the azirine–oxazolone method putting into practice the idea of amino group activation.† Here we report a complementary approach to α-branched α-amino acid derived peptides based on our recently reported β-lactam-derived α-amino acid *N*-carboxy anhydride (NCAs) procedures.[4] The key of our approach is based on the easy access to an array of enantiomerically pure 3-hydroxy-4,4-dialkyl-β-lactams from a readily available single 3-benzyloxy-4-alkyl-4-formyl β-lactam. By this means, simultaneously *N*-protected and CO$_2$H-activated forms of a wide variety of α,α-disubstituted α-amino acids would be readily accessible from non-α-amino acid precursors.

At the beginning of this work no general method for the synthesis of homochiral β-lactams with quaternary stereogenic centres at the C$_4$ position was available.[5] To close this gap, we have explored the cycloaddition of benzyloxyketene, generated from benzyloxyacetyl chloride and triethylamine, with the ketimine **1** incorporating a masked form of the required formyl group (Scheme 1). Using standard cycloaddition conditions the β-lactam **2** [syrup, $[\alpha]_D^{25}$ + 27 (*c* 1.0, Cl_2CH_2)] was formed as single stereoisomer[6] and in excellent yield. This was established by the chemical correlation between 4-carboxy-β-lactams **4** and **6** combined with X-ray analysis of **5**.‡ With β-lactam **3** in hand the synthesis of C$_4$-disubstituted α-hydroxy β-lactams **7** was easily performed by a Wittig reaction followed by hydrogenolysis of the benzyloxy protective group and simultaneous double bond reduction of the resulting alkenic intermediates. Yields were generally high for the two steps and no epimerization occurred at the α-position of the β-lactam ring as judged by both 300 MHz ^{1}H NMR and HPLC analysis of the crude reaction products.

Besides the intrinsic interest of these α-hydroxy β-lactams as cyclisized forms of α-hydroxy β-amino acids which, in turn, might be subsequently incorporated into peptides according to our procedure,[7] we also found that these compounds can be transformed into α-branched α-amino acid *N*-carboxy anhydrides (NCAs) and, hence, into α-branched α-amino acids ready for subsequent coupling steps. To illustrate this latter aspect, compounds **7a** and **7b** were subjected to treatment with twofold excess of a 1 mol dm^{-3} solution of commercial bleach and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl[8] (TEMPO) to produce in a single one pot operation the oxidation of the hydroxy group and concomitant Baeyer–Villiger



Scheme 1 *Reagents and conditions*: i, $BnOCH_2COCl$ (2 equiv.), NEt_3, CH_2Cl_2, −78 °C→ room temp., 20 h, 80%; ii, $HClO_4/H_2O$, THF, room temp., 2 h, 100%; iii, $NaIO_4$, Me_2CO/H_2O, room temp., 20 h, 90%; iv, $NaIO_4$, $KMnO_4$, Me_2CO/H_2O, room temp., 1 h, 70%; v, Bu_4NF 1.1 mol dm^{-3} THF, room temp., 2 h, 85%; vi, $(Cl_3CO)_2CO$/DMSO, NEt_3, CH_2Cl_2, −78 °C, 5 min, 88%; vii, $F_3CSO_3SiMe_3$, NEt_3, CH_2Cl_2, 0 °C, 3 h, then, O_3, CH_2Cl_2, −78 °C, 10 min, 70%; viii, Ph_3P=CHR, THF, refl., 1 h–8 h, then, H_2, 10% Pd/C (0.3 equiv.), EtOH, room temp., 14 h



Scheme 2 *Reagents and conditions*: i, 1 mol dm^{-3} NaOCl, TEMPO (cat.), KBr (cat.), $NaHCO_3$, CH_2Cl_2, room temp., 15–20 min; ii, (*S*)-PheOMe; (*S*)-ValOBn or AibOBn, DMF, KCN (1 equiv.), room temp., 24 h; iii, H_2, 10% Pd/C (0.3 equiv.), EtOH, room temp., 20 h

rearrangement of the resulting intermediate α-keto-β-lactam. In this way, NCAs **8a** [mp 57–58 °C, $[\alpha]_D^{25}$ −17.4 (*c* 1.0, Cl_2CH_2)] and **8b** [syrup, $[\alpha]_D^{25}$ +24.5 (*c* 1.0, Cl_2CH_2)] were obtained in 95 and 97% yields, respectively.§ As expected by earlier work in methods to couple hindered α-amino acids,[9] these NCAs were resistant to ring opening by both (*S*)-phenylalanine methyl ester and (*S*)-valine benzyl ester but, by addition of potassium cyanide, the coupling reaction proceeded cleanly to give, after hydrogenation over Pd on charcoal, dipeptides **9** and **10** in 73 and 71% yields respectively. Remarkably, the bulky Aib-benzyl ester (benzyl α-aminoisobutyrate) could also be efficiently coupled with **8c** to give the corresponding dipeptide product which upon *N,O*-didebenzylation afforded **11** [mp 194 °C dec., $[\alpha]_D^{25}$ +3.0 (*c* 0.5, MeOH)] in 70% yield. These results demonstrate the effectiveness of this new approach to α-branched α-amino acid peptides, and complement the well established azirine–oxazolone method.[10] Additional attractive features of this approach include an expanded scope of the β-lactam chemistry,[11] and its potential use for the incorporation of α-branched α-amino acids, with different *N*-alkyl substituents into peptides.

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Footnotes

† For an approach accomplishing the idea of carboxy group activation involving generation of aminoketenes as activated species of α-amino acids and subsequent coupling with α,α-amino acids, see ref. 2.

‡ *Crystal structure* of **5**: $C_{21}H_{35}NO_3Si$, M = 377.6; colourless quaderlike crystals, crystal dimension 0.30 × 0.30 × 0.25 mm, orthorhombic, $P2_12_12_1$, a = 7.589(1), b = 12.176(1), c = 25.204(3) Å, V = 2328.9(5) Å^3, T = 275(1) K, Z = 4, D_c = 1.08 g cm^{-3}, μ = 1.2 cm^{-1}, λ = 0.71069 Å, 3731 measured reflections, 3374 symmetry-independent reflections, 2398 observed [$I > 2\sigma(I)$], 235 refined parameters, Flack parameter 0.0 (4), R_1 = 0.052, wR_2 = 0.136, residual electron density 0.31 eÅ^3. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/58.

§ Without the catalyst, no oxidation was observed and the starting α-hydroxy-β-lactams were recovered unchanged. On the other hand, using equimolar amounts of aqueous sodium hypochlorite in combination with TEMPO, the reaction could be stopped at the first oxidation stage to give the corresponding α-keto-β-lactams, but the products were sometimes contaminated with the respective NCAs.

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