A Facile Access to Peptides Containing D-α-Methyl β-Alkylserines by Coupling of α-Branched Leuchs Anhydrides with α-Amino Esters

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A new one step synthesis of α,α-disubstituted α-amino acid N-carboxy anhydrides from α-hydroxy β-lactams and their coupling with α-aminoesters promoted by KCN is described.

Despite the importance of α-methyl-β-alkylserines for the study and design of new bioactive targets,[1] most of their reported syntheses involve reactions that are not extremely diastereoselective, particularly at the newly created β-stereogenic centre.[2] In concert with this problem, virtually all of the studies on the synthesis of α,α-disubstituted α-amino acids have dealt with the construction of the non-pro- teinogenic amino acid in its free form rather than the generation of simultaneously N-protected and CO₂H-activated species.[3] Therefore it would be a conceptually new approach to short peptide units if the synthesis of the α,α-disubstituted α-aminoacid framework could directly be combined with a peptide coupling reaction.[4] Herein we report that Baeyer–Villiger rearrangement of α-keto β-lactams with quaternary stereogenic centres at the C-4 position fulfils this requirement and provides α-branched Leuchs anhydrides (NCAs)[5] which, on coupling with α-amino esters, lead to a tactically new route to dipeptides containing α-methyl-β-alkylserine frameworks.
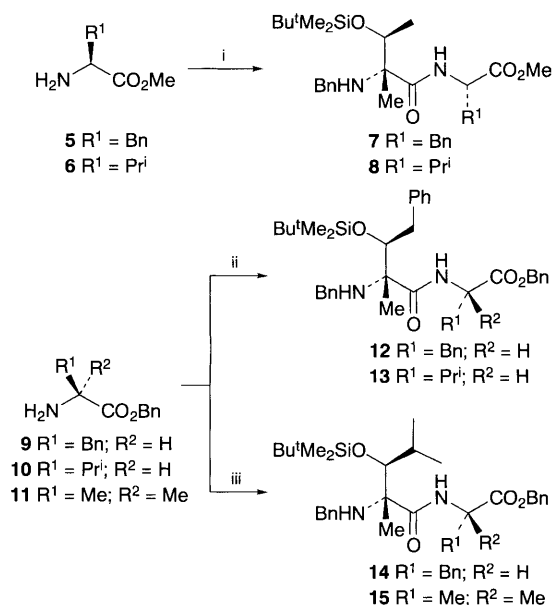
Our approach employs chiral α-alkoxyketone-derived imines as readily available starting materials,† incorporating the required structural subunit of the desired amino acid and, at the same time, providing chirality to the corresponding NCA precursor. In this way, NCAs with both L- and D-configurations would be readily available through this approach. Accordingly, using standard Bose's [2 + 2] cycloaddition[6] reaction of benzyloxyketene (Scheme 1), generated *in situ* from benzyl-oxyacetyl chloride and triethylamine, with ketimines **1a, b** and **c** and subsequent removal of the benzyloxy protective group, we found we could prepare α-hydroxy β-lactams **2** as single diastereoisomers. We devised this β-lactam route after the enolate–imine condensation pathway failed. We tentatively propose that this failure is caused, in part, by the intrinsic low reactivity of ketimines and, in part, by competitive α-deprotonations. The yields of these reactions were reasonably good (70–90% for the first step and almost theoretical for the hydrogenolysis) and no loss of enantiomeric purity was observed as judged by the Mosher esters prepared.‡[7] Further, the absolute configuration given for the adducts is based on a single crystal X-ray analysis of **2c** and the assumption of a uniform reaction mechanism.§ As expected,[8] these α-hydroxy
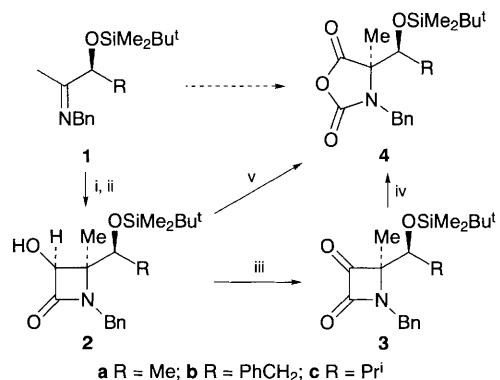
β-lactams were resistant to oxidation with usual oxidising agents, *i.e.* pyridinium dichromate (PDC), pyridinium chloro-chromate (PCC), Swern, but on treatment with P_2O_5 in Me_2SO produced the desired α-keto-β-lactams **3a–c** as pure isolated materials in 88, 92 and 80% yields respectively. At this stage, the next question was to establish whether Baeyer–Villiger rearrangement of these α-keto β-lactams would proceed regioselectively, and if so, whether the resulting α-branched NCAs could be coupled with α-amino esters.[9] Compounds **3a, b** and **c** upon exposure to MCPBA in methylene chloride at −40 °C exclusively afforded the NCAs **4a, b** and **c** in 90, 80 and 85% yields respectively. In each case, no other side-products were formed and the resulting NCAs were isolated in a fairly pure form after usual workup. Once we had proved that insertion of the oxygen atom took place exclusively between both carbonyl groups of α-keto β-lactams, a more direct access to these NCAs was investigated. We have found that **2a, b** and **c** on exposure to commercial bleach and a catalytic amount of tetramethylpiperidine-N-oxyl (TEMPO)[10] afforded the desired NCAs in yields up to 95% within about 5 min. Thus, a concise and practical synthesis of α-branched Leuchs anhydrides from non-α-amino acid precursors is provided for the first time.¶

Problems arose, however, in attempted coupling of these NCAs with α-amino esters where yields generally fell to 0–10%. Using potassium cyanide as additive, the corresponding coupling reaction proceeded to give the expected dipeptide fragments in excellent yields.‖ For example, (S)-phenylalanine methyl ester **5** underwent acylation by the NCA **4a** within *ca.* 24 h in the presence of 1 quiv. of KCN to give **7** in 87% isolated yield (Scheme 2). In the absence of this salt, only a trace of the expected coupling product was formed. For the α-amino ester **6**, virtually no conversion was observed without the additive, but in the presence of 1 equiv. of KCN, the coupling reaction

Scheme 1 *Reagents and conditions*: i, BnOCH₂COCl, NEt₃, CH₂Cl₂, −78 °C → room temp., 20 h, 70–90%; ii, NH₄HCO₂, Pd–C (10%), MeOH; iii, P₂O₅–Me₂SO room temp. 20 h; iv, MCPBA, CH₂Cl₂, −40 °C, 2 h; v, NaOCl, H₂O–CH₂Cl₂, TEMPO cat., 0 °C, 5 min

Scheme 2 *Reagents*: i, **4a**, KCN, DMF; ii, **4b**, KCN, DMF; iii, **4c**, KCN, DMF

proceeded smoothly to give the dipeptide **8** in 90% isolated yield. Under these conditions, both **9** and **10** reacted with NCA **4b** to give **12** $[\alpha]_D^{25}$ = +15.8 (c = 1.0, CH_2Cl_2) and **13** $[\alpha]_D^{25}$ = +19.9 (c = 1.0, CH_2Cl_2) in yields of 95 and 93% respectively. Similarly, **9** could be acylated by the highly hindered NCA **4c** to furnish **14** in 95% yield.** Remarkably, the bulky Aib-benzyl ester **11** could also be efficiently coupled with **4c** to afford the dipeptide product **15** $[\alpha]_D^{25}$ = +9.7 (c = 1.0, CH_2Cl_2) in 79% yield. In these latter cases, the presence of KCN was also crucial to achieve the coupling reaction and no detectable coproducts were formed. From these results it is clear that this simple and versatile procedure for the assembly of hindered α-amino acids will find further applications.

In conclusion, our strategy complements the existing available protocols to synthesise non-proteinogenic dipeptide units which, hitherto, are necessarily guided by the following steps: (*a*) the installation of an appropriate chiral auxiliary on a preselected substrate, (*b*) asymmetric reaction, (*c*) separation of diastereoisomers, (*d*) removal of the chiral auxiliary (*e*) protection of the existing or remaining functionalities, (*f*) activation of the carboxyl group and (*g*) coupling reaction. Consequently, suitably protected short peptide frameworks can now be synthesised without the requirements imposed by the conventional Leuchs procedure.

Footnotes

† These ketimines were prepared from the corresponding methylketones and benzylamine at −78 °C using $TiCl_4$, according to Weingarten's procedure. Otherwise, a loss of optical purity was observed in the formation of cycloadducts. See H. Weingarten, S. P. Chupp and W. A. White, *J. Org. Chem.*, 1967, **32**, 3246.

‡ In every case a unique signal set was observed in the ¹H, ¹³C and ¹⁹F NMR spectra. To ensure the validity of this optical purity assay, the racemic form of **2a** was prepared and acylated with (+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride and triethylamine in the presence of a catalytic amount of DMAP. In this case, two sets of signals were observed in the ¹H, ¹³C and ¹⁹F NMR spectra.

§The ORTEP diagram and the X-ray crystallographic data will be submitted in a separate communication.

¶ Selected data for **3a**: mp 49–50 °C, $[\alpha]_D^{25}$ −2.0 (c = 1.0, CH_2Cl_2); For **3b**: syrup, $[\alpha]_D^{25}$ = −39.4 (c = 1.0, CH_2Cl_2); For **3c**: mp 49–50 °C, $[\alpha]_D^{25}$ = +12.3 (c = 1.0, CH_2Cl_2); For **4a**: mp 110 °C; For **4b**: syrup, $[\alpha]_D^{25}$ = −52.3 (c = 1.0, CH_2Cl_2); For **4c**: 86–88 °C, $[\alpha]_D^{25}$ = −20.0 (c = 1.0, CH_2Cl_2)

‖ We speculate that, under these conditions, a reactive intermediate acyl cyanide could be formed. For a review on acyl cyanides, see S. Hünig and R. Schaller, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 36.

** Under these conditions no racemisation was observed as judged by ¹H NMR and HPLC analysis of the dipeptide products. The absence of racemisation in the starting proteinogenic α-amino esters employed for each coupling reaction was verified by the Mosher test after their exposure to KCN under the reaction conditions.

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