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Synthesis of (S)- and (R)-*tert* Leucine Enabling Direct Coupling with α–Amino Acid Esters via β–Lactam-Derived α–Amino Acid N-Carboxy Anhydrides.

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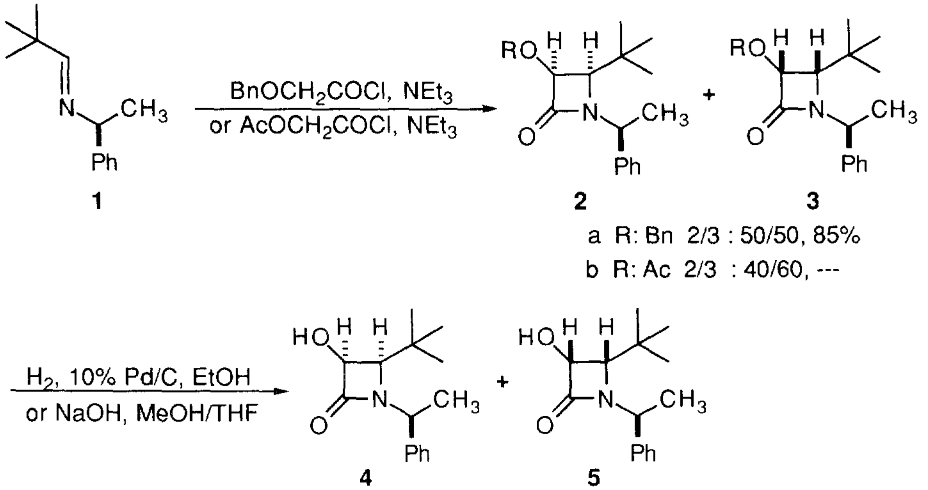
Abstract: (3S, 4R)- and (3R, 4S)-3-hydroxy-4-*tert*-butyl β–lactams on exposure to 1M NaOCl and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) afforded α–amino acid N-carboxy anhydrides formally derived from both (S)- and (R)-*tert*-leucine amino acids. © 1997 Published by Elsevier Science Ltd.

Besides the increased interest in both (S)- and (R)-tert-leucine and the corresponding amino alcohols as building blocks in asymmetric synthesis, the importance of this non-proteinogenic amino acid as a component of therapeutic pseudopeptides, HIV-protease inhibitors and pharmaceutically active substances, including anticancer agents, has also been increasingly recognized in recent years.[1] In general, owing to its bulky, inflexible and hydrophobic *tert*-butyl side chain, this amino acid, when incorporated into peptides, provides a useful starting point for conformational studies and/or new bioactive targets. As a result, several chemical and chemoenzymatic syntheses of this amino acid have been reported[1,2]. Nevertheless, on the basis of the above considerations, it would still be more desirable if the synthesis of this amino acid could be combined directly with a peptide coupling reaction. A recent report from this laboratory has addressed this issue and a practical one-pot conversion of α–hydroxy β–lactams into α–amino acid N-carboxy anhydrides (NCAs) has been developed[3]. Herein we report on the application of this approach into a practical method for the direct incorporation of both (S)- and (R)-tert leucine into short peptide segments.

As Scheme 1 illustrates, the preparation of the required α–hydroxy β–lactams involved cycloaddition reactions of α–hydroxyketene equivalents, generated from the corresponding acid chlorides and triethylamine, with the imine **1** derived from pivalaldehyde and α–methylbenzylamine. Although stereocontrol has rarely been found in [2+2] cycloadditions involving this amine as the source of chirality[4], we elected to use this approach on the basis of previous studies made by Thomas[5] at the Upjohn Company, and independently by Teutsch[6] at Roussel Uclaf. These authors suggested that due to the ready availability of both enantiomers of α–methylbenzylamine, this approach to β–lactams could be one of the most appropriate routes for scaling-up.

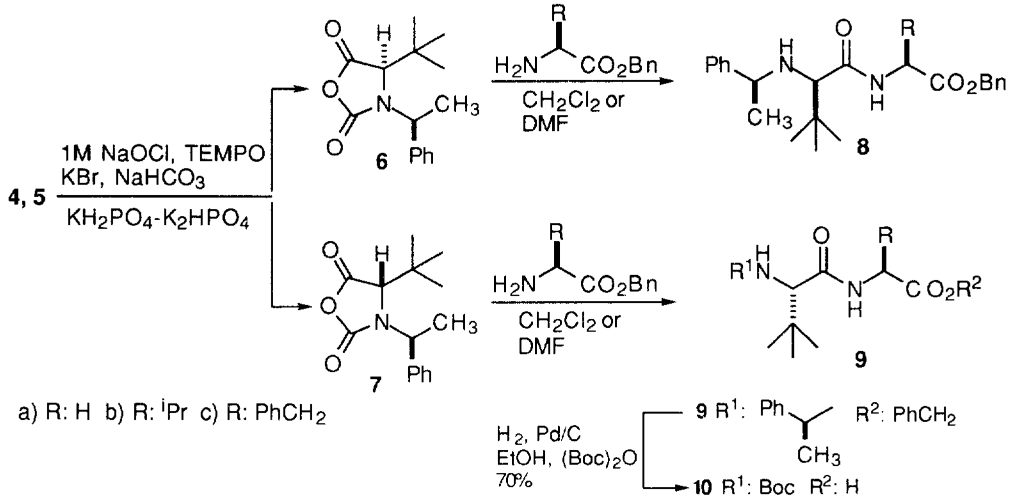
In addition, taking into account that the anticipated diastereomers could easily be separated by simple crystallizations and/or preparative HPLC, the approach would also permit access to both (S)- and (R)-*tert*-leucine derivatives in a concise and practical fashion.



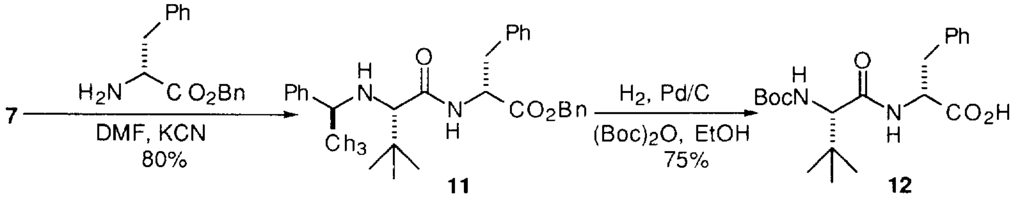
Scheme 1

Indeed, the reaction of benzyloxyketene with **1**, Scheme 1, in methylene chloride as solvent provided a mixture of **2a**/**3a** without any diastereoselectivity. However, two succesive crystallisations of the crude reaction mixture from methylene chloride/hexane gave diastereomerically pure **3a** in 30% isolated yield, which was then transformed into the α–hydroxy β–lactam **5** in almost quantitative yield. On the other hand, analysis of the mother liquors revealed additional **3a** along with **2a** which were not separated, instead the crude mixture was subjected to hydrogenolytic cleavage of the benzyloxy protecting group to give the corresponding diastereomeric α–hydroxy β–lactams **4**/**5** in 95% combined yield[7]. Alternatively, the reaction of acetoxyacetyl chloride and the imine **1** in the presence of triethylamine furnished **2b**/**3b** in a 40:60 ratio[8], which was directly subjected to saponification with NaOH in MeOH/THF to give **4**/**5** in 85% overall yield. Both compounds were then separated by preparative HPLC, using EtOAc/hexane as eluant, in yields of 30% and 50% respectively[9]. The relative cis-stereochemistry of both **4** and **5** was established on the basis of their coupling constants between the C3 and the C4 protons ($J_{3,4}$= 5.1-5.2 Hz) and their absolute configurations (relative to the known absolute configuration of **1**) by a single crystal X-ray analysis of the 3-benzyloxy β–lactam **3a**[10].

With both β–lactams **4** and **5** in hand, the synthesis of their corresponding NCAs **6** and **7**, Scheme 2, was then addressed. For instance, **4** on treatment with NaOCl and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) in a phosphate buffer solution afforded, within about 2 min., the NCA **6** [m.p.: 116-118°C, $[\alpha]_D^{25}$= -22.0 (c= 1.0, CH_2Cl_2)] in quantitative yield. Similarly starting from **5**, **7** [m.p.: 131-133°C, $[\alpha]_D^{25}$= +63.0 (c= 1.0, CH_2Cl_2)] was also produced in quantitative yield and almost instantaneously. The absence of epimerization at the C4 position of these NCAs was determined primarily by their ^{1}H-NMR spectra and subsequently by coupling each NCA with glycine benzyl ester in methylene chloride as solvent. The HPLC analysis of both reaction crudes of the resulting **8a** and **9a** showed the presence of only one diastereomeric dipeptide product, thus indicating that no loss of optical purity had occurred during the NCA formation and coupling steps. On the other hand, when the coupling reaction of both NCAs, **6** and **7**, was tested with (S)-valine benzyl ester under the same conditions as above, only small amounts of the expected dipeptide products **8b** and **9b** were formed, as judged by ^{1}H-NMR analysis of the corresponding products. The same trend was also observed in the coupling of both **6** and **7** with the less hindered (S)-phenylalanine benzyl ester. Nevertheless, after attempts to solve this limitation, we found that both α–amino acid esters could be coupled efficiently with these NCAs by performing the reaction in DMF as solvent and in the presence of KCN. Under these conditions, dipeptides **8b**, **9b**, **8c** and **9c** were obtained in good yields[11]. Compound **9b** was then converted to the N-Boc derivative **10**, suitable for further coupling steps at the C-terminal amino acid (S)-valine. It should be mentioned that in the absence of KCN the coupling reactions did not proceed to completion and low conversion, typically 20-30%, were observed after 24hr of stirring at room temperature. On the other hand, to ensure that no epimerization occurred at the α–center of the starting α–amino acid esters during coupling reactions, the NCA **7**, Scheme 3, was coupled with (R)-phenylalanine benzyl ester to give dipeptide **11** whose HPLC chromatogram revealed the virtual absence of epimeric **9c**. Compound **11** was isolated in 70% yield after crystallisation from CH_2Cl_2/hexane and then transformed into the N-Boc derivative **12** for subsequent couplings.



Scheme 2



Scheme 3

In summary, the results presented here open the way for a concise large scale production of both (S)- and (R)-*tert*-leucine α–amino acid N-carboxy anhydrides from non α–amino acid precursors and thereby facilitate their direct coupling with α–amino acid esters.

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7 From the mixture of **4/5**, an additional crop of **5** could be isolated by successive crystallizations from methylene chloride/hexane, thus increasing the overall yield of **5** to 37%. Representative data: Compound **4**: m.p.: 102-104°C, $[\alpha]_D^{25}$= -9.3 (c=1.0, CH_2Cl_2), ^{1}H-NMR($CDCl_3$) δ 3.31 (d, 1H, J=5.2 Hz, C_4H) 4.83 (t, 1H, J=5.1 Hz, C_3H); Compound **5**: m.p.: 141-143°C, $[\alpha]_D^{25}$= +203.6 (c=1.0, CH_2Cl_2), ^{1}H-NMR($CDCl_3$) δ 3.45 (d, 1H, J=5.1 Hz, C_4H) 4.95 (t, 1H, J=5.2 Hz, [C_3H).

8 The ratio of isomers was easily determined on the basis of their ^{1}H-NMR spectra. Thus, the proton at the C_4 position in **2b** shows as a doublet at 3.41 ppm, while the corresponding one in **3b** appears at 3.58 ppm.

9 Preparative HPLC was performed on a Lichrosorβ–Si60 7μM column with flow rates of 10 ml/min. (EtOAc/Hex., 40:60) and using a UV detector (254 nm). Retention times: **4**, 32.55 min. and **5**, 38.74 min.

10 The X-ray data have been deposited at Cambridged Crystallographic Data Center.

11 Compound **8b**: yield, 72%; oil, $[a]_D^{25}$= -4.2 (c=1.0, CH_2Cl_2); **8c**: yield, 85%; m.p.: 96-97°C, $[a]_D^{25}$= +13.0 (c=0.8, CH_2Cl_2); **9b**: yield, 75%; m.p.: 104-106°C, $[a]_D^{25}$= -82.0 (c=1.0, CH_2Cl_2); **9c** yield, ; 80% : m.p.: 102-103°C, $[a]_D^{25}$= -92.3 (c=1.0, CH_2Cl_2) **10**: yield,70%; m.p.: 111-112°C, $[a]_D^{25}$= -9.2 (c=0.7, MeOH); **12**: yield, 75%; oil, $[a]_D^{25}$= +0.7 (c=0.7, MeOH).

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