Generation of Threonine- and Azathreonine *N*-Carboxy Anhydrides from α-Hydroxy *β*-Lactams Promoted by 2,2,6,6-Tetramethylpiperidinyl-1-oxyl (TEMPO) in Combination with Sodium Hypochlorite

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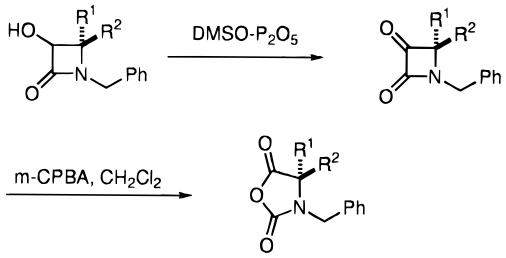
A versatile one-pot oxidation−Baeyer−Villiger reaction sequence applied to α-hydroxy *β*-lactams and promoted by 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) leads to α-amino acid *N*-carboxy anhydrides. The examples reported constitute the first application of TEMPO in a Baeyer−Villiger reaction and provide a way for peptide coupling from non α-amino acid precursors.

Despite the importance of nonproteinogenic α-amino acids for the design and preparation of bioactive peptides,[1] virtually all of the studies on this topic have dealt with the synthesis of the amino acid as a free form rather than with the generation of simultaneously *N*-protected and CO_2H-activated species.[2] Recently, we undertook a study on this subject and found, Scheme 1, that the Baeyer−Villiger rearrangement of α-keto *β*-lactams led to α-amino acid *N*-carboxy anhydrides (NCAs), allowing for the first time a synthesis of dipeptide fragments without prior construction of each individual nonproteinogenic α-amino acid.[3] This reaction has successfully been applied to the construction of threonine-,[4] α-branched threonine-,[5] and azathreonine[6]-derived NCAs, as well as to the synthesis of arylalanine- and homoarylalanine-NCAs.[7] In an effort to further enhance the utility of our procedure, we have investigated a more direct access to this particular class of mixed anhydrides and found that stable free nitroxide radicals, such as 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO),[8] in combination with a solution of commercial bleach, is exceedingly effective in promoting the oxidation of α-hydroxy *β*-lactams with concomitant Baeyer−Villiger rearrangement of the resulting intermediate α-keto *β*-lactams.

Scheme 1



The approach to both threonine- and azathreonine-NCAs from their corresponding α-hydroxy *β*-lactams illustrates the above unprecedented use of TEMPO to promote Baeyer−Villiger oxidations.[9] The former approach employs chiral α-oxy aldehyde-derived imines and, the latter, chiral α-amino imines as readily available starting materials, both of which possess the required structural subunits of the desired amino acids and, at the same time, provide the corresponding NCA precursors in high diastereoselectivities. For example, Scheme 2, using the standard [2 + 2] cycloaddition reaction of a (benzyloxy)ketene,[10] generated from (benzyloxy)acetyl chloride and triethylamine, with imine **1a** afforded a mixture of **2a** and its diastereomer in a ratio of 83:17, from which **2a** was separated by column chromatography in 59% yield. The same reaction carried out on imine **1b** gave, however, the *β*-lactam **2b**[10b] in 85% yield as a single diastereomer as established by NMR analysis of the reaction crude. Both *β*-lactam products were then submitted to hydrogenolysis to give α-hydroxy *β*-lactams **3a** and **3b** in 84% and 92% yield, respectively. Our finding is that treatment of each α-hydroxy *β*-lactam with a solution of commercial bleach and a catalytic amount of TEMPO afforded NCAs **5a** and **5b** in almost theoretical yields. In order to avoid a possible epimerization of the

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(1) For comprehensive reviews, see: (a) Degrado, W. F. *Adv. Protein Chem.* **1988**, *39*, 51. (b) Toniolo, C. *Int. Pept. Protein Res.* **1990**, *35*, 287. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (d) Liskamp, R. M. J. *Recuil. Trav. Chim. Pays-Bas* **1994**, *113*, 1. (e) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.

(2) For reviews, see: (a) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1993. (b) α-Amino Acid Synthesis; O'Donell, H. J., Ed.; Tetrahedron Symposia-in-print, *Tetrahedron* **1988**, *44*, 5253. (c) Shioiri, T.; Hamada, Y. *Heterocycles* **1988**, *27*, 1035. (d) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238. (e) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. (f) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (g) Bailey, P. D.; Clayson, J.; Boa, A. N. *Contemp. Org. Synth.* **1995**, *2*, 173. (h) Hegedus, L. S. *Acc. Chem. Res.* **1995**, *28*, 299.

(3) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123. For another approach to achieve this goal see, refs 2d and 2h.

(4) Palomo, C.; Aizpurua, J. M.; Cabré, F.; García, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1994**, *35*, 2721.

(5) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; García, J. M. *J. Chem. Soc.; Chem. Commun.* **1995**, 2327.

(6) Palomo, C.; Aizpurua, J. M.; Cabré, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.* **1994**, *35*, 2725.

(7) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Maneiro, E.; Odriozola, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1505.

(8) (a) Bobbit, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509. (b) Yamaguchi, M.; Miyagawa, T.; Takata, T.; Endo, T. *Pure Appl. Chem.* **1990**, *62*, 217. (c) Anelli, P. L.; Montanari, F.; Quici, S. *Organic Syntheses;* Wiley: New York, 1993; Collect. Vol. 8, 367.

(9) For a recent review on Baeyer−Villiger oxidations, see: Krow, G. R. *Org. React.* **1993**, *43*, 251.

(10) For a recent review, see: (a) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams;* Georg, G. I., Ed.; VCH: New York, 1993, p 295. See also: (b) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Kamijo, H.; Harada, Y.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853.

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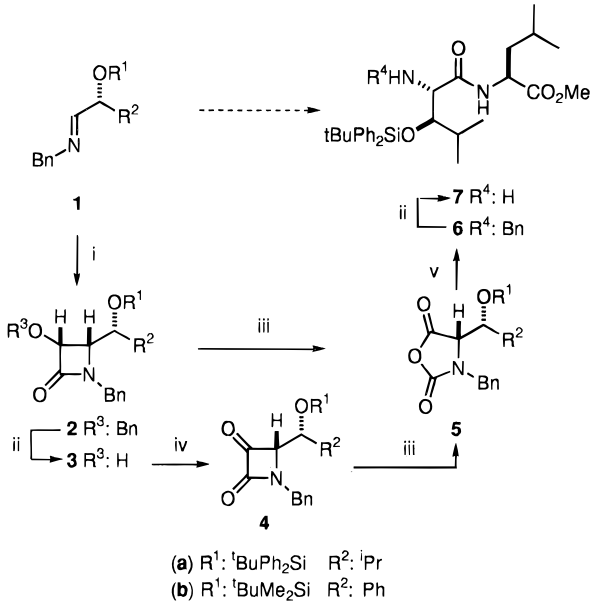
Scheme 2[a]

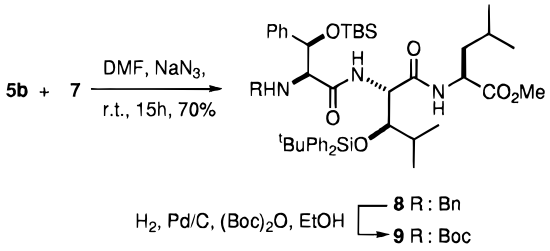


[a] **Reagents and Conditions: i** $BnOCH_2COCl$ (2 eq.), NEt_3, CH_2Cl_2, -78°C→r.t., 20h; **ii** H_2 (1atm.), Pd/C, EtOH, 15h; **iii** 1M NaOCl, TEMPO (cat.), $NaHCO_3$, KH_2PO_4-K_2HPO_4 KBr,(pH: 6.9),CH_2Cl_2, r.t., 20m.; **iv** P_2O_5-DMSO, r.t.(ref. 3) **v**(*S*)-H_2N-CH(CH_2CHMe_2)CO_2Me, CH_2Cl_2, r.t.,15h.

resulting NCA,[11] the pH of fresh commercial bleach (12.7) is adjusted to neutrality by first adding sodium hydrogen carbonate and then a solution of phosphate buffer. Reactions are performed at 0 °C using a twofold excess of 1 M aqueous sodium hypochlorite and a catalytic amount of TEMPO and are generally complete in a few minutes. Without the catalyst, the oxidation process did not take place and the starting α-hydroxy-*β*-lactams were recovered unchanged after 24 h at room temperature. On the other hand, by using equimolar amounts of aqueous sodium hypochlorite in combination with TEMPO, the reaction can be stopped at the first oxidation stage and the corresponding α-keto *β*-lactam **4** can be isolated in good yield albeit, in some instances, contaminated with the respective NCA. To confirm the effectiveness of TEMPO in the induction of the Baeyer−Villiger rearrangement, each α-keto *β*-lactam **4** was treated with a twofold excess of 1 M aqueous sodium hypochlorite. Under these conditions and without the catalyst, reactions were sluggish and incomplete after 2−3 h of stirring at room temperature. As expected, when the reactions were carried out in the presence of a catalytic amount of TEMPO, the corresponding NCAs **5** were produced almost instantaneously.

With the above NCAs in hand, the facile synthesis of dipeptides was anticipated.[12] For instance, **5a** coupled efficiently with (*S*)-leucine methyl ester in methylene chloride to give the dipeptide **6** in 95% yield. Further hydrogenolysis of **6** with hydrogen over 10% Pd on charcoal led to **7** in 85% yield. However, in contrast with the easy reaction of NCAs with α-amino esters to form dipeptides, the additional elongation to tripeptides met with difficulties. For example, the NCA **5b** was surprisingly resistant to ring opening by dipeptide **7** under the former conditions. Fortunately, we found that changing the solvent to DMF combined with the addition of NaN_3, effectively enhanced peptidic coupling. This was illustrated, Scheme 3, by the synthesis of the tripeptide product **8**, which was then converted into **9** under standard conditions. The synthesis of compound **9**, a fragment of the macrocyclic peptide lactone antibiotic lysobactin,[13] by using simultaneously *N*-protected and CO_2H-activated species of threonines **5** obtained from non α-amino acid precursors, is only an example of the utility of this methodology.

Scheme 3



The effectiveness of TEMPO in promoting the direct cycloexpansion of α-hydroxy *β*-lactams to α-amino acid *N*-carboxy anhydrides is further exemplified by the synthesis of NCAs formally derived from the nonproteinogenic α-aminopyrrolidine- and α-aminopiperidine-2-acetic acids. The latter is an amino acid related to the antitumor agent 593A.[14] Accordingly, the reaction of (benzyloxy)ketene, generated as above, with both prolinal imine **10a** and 2-piperidinecarbaldehyde imine **10b** furnished the corresponding *β*-lactams **11a** and **11b** as oils after purification by column chromatography (Scheme 4). In both cases, single diastereomers were detected by NMR analysis, and they were isolated in 75% and 70% yields, respectively. The sense of the asymmetric induction for these cycloadditions was in good agreement with the stereochemistry observed for a closely related reaction[15] and was confirmed by the single crystal X-ray analysis of **12a**.[16] Finally, removal of the benzyloxy protecting group in both **11a** and **11b** gave α-hydroxy *β*-lactams **12a** and **12b** in almost quantitative yields. Subsequent exposure of each α-hydroxy *β*-lactam to a

(11) To ensure the optical purity of these NCAs, both **4a** and **4b** were opened by methanol under reflux conditions followed by *N*-debenzylation and subsequent acylation of the resulting α-amino acid esters with Mosher acid chloride and triethylamine (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543). In each case a single set of signals was obtained in their ^1H, ^{13}C, and ^{19}F NMR spectra.

(12) For a comprehensive review on NCAs, see: Kricheldorf, H. R. α-Amino Acid N-Carboxy Anhydride and Related Heterocycles; Springer-Verlag: Berlin, 1987.

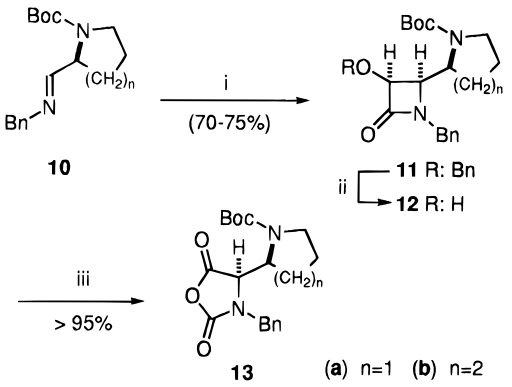
(13) (a) Tymiak, A. A.; McCormick, T. J.; Unger, S. E. *J. Org. Chem.* **1989**, *54*, 1149. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Odriozola, B.; Maneiro, E.; Miranda, J. I.; Urchegui, R. *J. Chem Soc., Chem. Commun.* **1996**, 161.

(14) (a) Pettit, G. R.; Von Dreele, R. B.; Herlad, D. L.; Edgar, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 6742. (b) Fukuyama, T.; Frank, R. K.; Jewell, C. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 2122. (c) Golding, B. T.; Smith, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 702.

(15) Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, B.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.

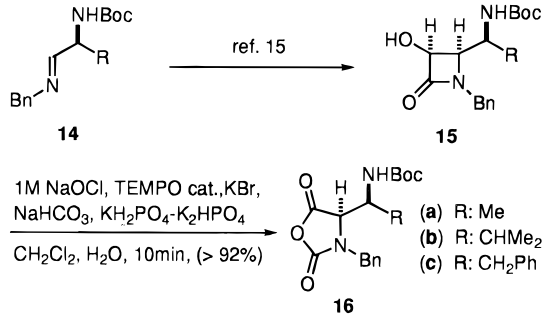
(16) Crystal data for compound **12a**: $C_{19}H_{26}N_2O_4$, M_r = 346.42, monoclinic, space group $P2_1$, a = 10.186(2), b = 6.225(5), c = 15.447-(2) Å, b = 107.83(1)°, V = 932.5(8) Å^{-3}, Z = 2, d_{calc} = 1.234 g cm^{-3}, T = −100 °C, Mo Kα radiation, λ = 0.71069 Å, μ = 0.087 mm^{-1}. The structure was solved by direct methods and refined on F by full-matrix least-squares methods to give R = 0.0513, wR = 0.0460, S = 1.686 using 1635 observed reflections with $I > 2\sigma(I)$ from the 2460 collected with 5° < 2θ < 55°. The enantiomorph was fixed by the known *S* configuration at C5 in the pyrrolidine ring. The atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 4[a]



[a] **Reagents and Conditions: i** $BnOCH_2COCl$ (2 eq.), NEt_3, CH_2Cl_2, -78°C→r.t., 20h; **ii** H_2, Pd/C, EtOH, 15h; **iii** 1M NaOCl, TEMPO (cat.), $NaHCO_3$, KH_2PO_4-K_2HPO_4 (pH: 6.9), CH_2Cl_2

Scheme 5



phosphate buffer solution of commercial bleach and a catalytic amount of TEMPO, as above, provided NCAs **13a** and **13b** in yields of up to 95%.

This one-pot oxidation−Baeyer−Villiger sequence could also be extended to 3-hydroxy β-lactams **15a**, **15b**, and **15c**, which are readily available from **14**,[15] to give NCAs **16a**, **16b**, and **16c** in 96%, 92%, and 97% yields, respectively, and without affecting the NH group (Scheme 5). In every case, no epimerization occurred at the α-position of the corresponding amino acid-derived NCA, as judged by both NMR and HPLC analysis of the crude reaction products. Once again, this oxidation process met with failure when carried out in the absence of TEMPO. Coupling reactions of these azathreonine NCAs with α-amino acid esters is expected to give dipeptide segments incorporating differently N-protected α,β-diamino acid residues which would be suitable for the design of new peptidomimetic drugs.[1] Additional attractive attributes of this approach include an easy availability of the starting α-hydroxy β-lactams,[10,15] and an expanded scope of the β-lactam chemistry.[17]

In summary, the results presented here set the basis for further studies on Baeyer−Villiger rearrangements promoted by oxammonium salts and open the way for a concise large scale production of α-amino acid *N*-carboxy anhydrides from non α-amino acid precursors.

(17) For the use of β-lactams in amino acid and natural product synthesis, see: (a) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755. (b) Ojima, I. In *The Organic Chemistry of β-Lactam Antibiotics;* Georg, G. I., Ed.; VCH: New York, 1992; p 197. (c) Ojima, I. *Acc. Chem. Res.* **1995**, 383. (d) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (e) Reference 2h.

Experimental Section

General. Commercially available compounds were used in this work without further purification or were prepared following literature procedures. *N,N*-dimethylformamide was purified by distillation on calcium hydride. Dichloromethane was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled.

General Procedure for the Synthesis of 3-Benzyloxy β-Lactams 2 and 11. A solution of (benzyloxy)acetyl chloride (2.21 mL, 14 mmol) in dry methylene chloride (10 mL) was added dropwise to a stirred solution containing the corresponding imine (7.0 mmol) and triethylamine (3.27 mL, 23.6 mmol) in dry methylene chloride (25 mL) under a nitrogen atmosphere at −78 °C. The resulting mixture was stirred overnight under nitrogen, and the temperature of the bath was allowed to rise from −78 °C to room temperature. The mixture was washed with water (25 mL), 0.1 N HCl (25 mL), and a saturated solution of $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give the corresponding crude β-lactam, which was further purified by column chromatography.

General Procedure for the Synthesis of 3-Hydroxy-β-Lactams 3 and 12. To a solution of 3-(benzyloxy)azetidin-2-one (7 mmol) in ethanol (40 mL) was added 10% palladium on charcoal (1.5 g), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature for 15 h. Then, the suspension was filtered through a pad of Celite and evaporated to yield the corresponding 3-hydroxyazetidin-2-one, which was purified by column chromatography and further crystallization.

(3*R*,4*R*)-1-Benzyl-4-[(1*R*)-1-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropyl]-3-hydroxyazetidin-2-one (3a). The general procedure was followed starting from **2a**. Yield 84%. Mp: 80−82 °C (hexane). $[\alpha]^{25}_D = -15.9°$ ($c = 1.1$, CH_2Cl_2). IR (KBr) ν 3303 cm^{-1} (OH); 1730 cm^{-1} (CO). ^1H NMR ($CDCl_3$, δ) 7.80−7.66 (m, 3H); 7.09−7.49 (m, 12H); 4.93 (d, 1H, $J = -15.0$ Hz); 4.68−4.65 (m, 1H); 4.25 (t, 1H, $J = 4.2$ Hz); 4.14 (d, 2H, $J = -15.0$ Hz); 3.60 (t, 1H, $J = 4.8$ Hz); 1.78−1.67 (m, 1H); 1.18 (s, 9H); 0.83 (d, 3H, $J = 6.8$ Hz); 0.58 (d, 3H, $J = 6.8$ Hz). ^{13}C NMR ($CDCl_3$, δ) 171.9, 136.6, 135.0, 134.4, 130.4, 129.4, 129.0, 128.3, 76.2, 74.2, 56.7, 46.6, 33.2, 28.2, 20.2, 18.4, 16.6. Anal. Calcd for $C_{30}H_{37}NO_3Si$ (487.69): C, 73.87; H, 7.64; N, 2.87. Found: C, 74.02; H, 7.66; N, 2.89

(3*R*,4*R*)-1-Benzyl-4-[[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]benzyl]-3-hydroxyazetidin-2-one (3b). The general procedure was followed starting from **2b**. Yield 92%. Mp: 90 °C (hexane). $[\alpha]^{25}_D = -54.4°$ ($c = 1$, CH_2Cl_2). IR (KBr) ν 3314 cm^{-1} (OH); 1729 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, δ) 7.40−7.12 (m, 10H); 5.10 (d, 1H, $J = 7.3$ Hz); 4.85 (d, 1H, $J = -14.5$ Hz); 4.58 (d, 1H, $J = 4.9$ Hz); 4.22 (d, 1H, $J = -14.5$ Hz); 3.71 (dd, 1H, $J = 7.3$ Hz, $J = 4.9$ Hz); 0.91 (s, 9H); 0.08 (s, 3H); −0.20 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 170.4, 141.4, 135.6, 128.7, 128.4, 128.1, 128.0, 127.7, 127.4, 75.7, 75.3, 62.9, 45.5, 25.9, 18.1, −4.3, −4.6. Anal. Calcd for $C_{23}H_{31}NO_3$ (397.57): C, 69.41; H, 7.86; N, 3.52. Found: C, 70.25; H, 7.89; N, 3.55.

(3*S*,4*R*)-1-Benzyl-4-[[(1*S*)-*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]-3-hydroxyazetidin-2-one (12a). The general procedure was followed starting from **11a** (8.72 g, 20 mmol). Yield 4.84 g (70%). Mp: 223−224 °C (MeOH). $[\alpha]^{25}_D = -1.7°$ ($c = 1$, CH_2Cl_2). IR (KBr) ν 3238 cm^{-1} (OH); 1710 cm^{-1} (C=O), 1674 cm^{-1} (C=O). ^1H NMR (DMSO-d_6, 90 °C, δ) 7.43−7.19 (m, 5H); 5.96 (d, 1H, $J = 7.3$ Hz); 4.76 (dd, 1H, $J = 4.9$ Hz, $J' = 7.3$ Hz); 4.70 (d, 1H, $J = 15.0$ Hz); 4.27 (m, 1H); 3.96 (d, 1H, $J = 15.0$ Hz); 3.48 (m, 1H); 3.42 (dd, 1H, $J = 4.9$ Hz, $J' = 9.0$ Hz); 3.07 (m, 1H); 1.86−1.68 (m, 4H); 1.51 (s, 9H). ^{13}C NMR (DMSO-d_6, 90 °C, δ) 169.3, 154.7, 136.7, 128.9, 128.4, 127.7, 79.2, 75.9, 59.2, 57.4, 46.3, 44.5, 28.7, 28.2, 23.1. Anal. Calcd for $C_{19}H_{26}N_2O_4$ (346.42): C, 65.87; H, 7.56; N, 8.08. Found: C, 65.67; H, 7.59; N, 8.05.

(3*S*,4*R*)-1-Benzyl-4-[(1*S*)-*N*-(*tert*-butoxycarbonyl)piperidin-2-yl]-3-hydroxyazetidin-2-one (12b). The general procedure was followed starting from **11b** (1.5 g, 3.3 mmol). Yield 1.07 g (90%). Mp: 160−162 °C (Et_2O). $[\alpha]^{25}_D = -19.1°$ ($c = 1$, CH_2Cl_2). IR (KBr) ν 3439 (OH); 1725 (C=O), 1686

(C=O). ^{1}H NMR (DMSO-d_6, 90 °C, δ) 7.37−7.11 (m, 5H); 5.99 (d, 1H, J = 6.5 Hz); 4.84 (t, 1H, J = 5.8 Hz); 4.67 (d, 1H, J = 15.4 Hz); 4.48 (m, 1H); 3.96 (dd, 1H, J = 4.7 Hz, J' = 10.7 Hz); 3.82 (m, 1H); 4.74 (d, 1H, J = 15.4 Hz); 2.5 (m, 1H); 1.7 (m, 1H); 1.61−1.35 (m, 4H); 1.45 (s, 9H); 1.26 (m, 1H). ^{13}C NMR (DMSO-d_6, 90 °C, δ) 168.6, 153.6, 135.6, 128.0, 127.1, 126.8, 78.3, 74.9, 53.9, 50.7, 43.5, 39.4, 27.7, 24.8, 24.5, 18.4. Anal. Calcd for $C_{20}H_{28}N_2O_4$ (360.45): C, 66.64 H, 7.83; N, 7.77. Found: C, 66.76; H, 7.65; N, 7.59.

General Procedure for the Preparation of α-Amino Acid *N*-Carboxy Anhydrides. To a magnetically stirred solution of 3-hydroxyazetidin-2-one (3 mmol) in 15 mL of dichloromethane were added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (6 mg, 0.03 mmol) and a solution of potassium bromide (36 mg, 0.3 mmol) in water (0.15 mL) at room temperature. The solution was cooled to −5−0 °C (ice−salt bath) and aqueous sodium hypochlorite (Aldrich, 23,930-5) (30 mL) buffered at pH 6.9 (1.8 g of sodium hydrogen carbonate for 84 mL of a 0.25 M buffer solution phosphate) was added, keeping the temperature of the reaction mixture between 10 and 15 °C. The mixture was stirred for a further 10 min. Workup[8c] afforded the corresponding α-amino acid *N*-carboxy anhydrides.

(4*S*)-3-Benzyl-4-[(1*R*)-1-[(*tert*-butyldiphenylsilyl)oxy]-2-methylpropyl]oxazolidine-3,5-dione (5a). The general procedure was followed starting from **3a**. Yield: 95%. Mp: 168−170 °C (EtOH). $[\alpha]^{25}_D$ = +31.8° (c = 1, CH_2Cl_2). IR (KBr) υ 1839 cm^{-1} (C=O), 1764 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.72−7.66 (m, 4H); 7.51−7.26 (m, 2H); 7.04−7.01 (m, 9H); 4.58 (d, 1H, J = −15.6 Hz); 4.23 (d, 2H, J = −15.6 Hz); 4.07 (d, 1H, J = 3.6 Hz); 3.83 (dd, 1H, J = 3.7 Hz, J = 4.8 Hz); 1.77−1.71 (m, 1H); 1.05 (s, 9H); 0.77 (d, 3H, J = 6.6 Hz); 0.52 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, δ) 167.0, 152.7, 136.1, 136.0, 134.4, 132.8, 132.4, 130.2, 130.0, 129.0, 128.4, 127.9, 127.8, 127.7, 75.6, 61.5, 46.8, 30.5, 26.8, 20.1, 19.6, 18.0. Anal. Calcd for $C_{30}H_{35}NO_4Si$ (501.60): C, 71.83; H, 7.05; N, 2.72. Found: C, 72.08; H, 7.16; N, 2.67.

(4*S*)-3-Benzyl-4-[(1*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-benzyl]oxazolidine-3,5-dione (5b). The general procedure was followed starting from **3b**. Yield 96%. Oil. $[\alpha]^{25}_D$ = −53.2° (c = 1, CH_2Cl_2). IR (KBr) υ 1810 cm^{-1} (C=O), 1763 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.45−7.12 (m, 9H); 6.52−6.49 (m, 1H); 5.28 (d, 1H, J = 1.7 Hz); 4.90 (d, 1H, J = −14.9 Hz); 4.11 (d, 1H, J = 1.7 Hz); 3.42 (d, 1H, J = −14.9 Hz); 0.99 (s, 9H); −0.02 (s, 3H); −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 167.5, 152.9, 139.1, 133.7, 128.7, 128.6, 128.4, 128.2, 128.0, 125.8, 72.9, 65.1, 46.7, 25.7, −4.4, −5.8.

(4*R*)-3-Benzyl-4-[(2*S*)-*N*-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]oxazolidine-2,5-dione (13a). The general procedure was followed starting from **12a**. Yield 98%. Oil. $[\alpha]^{25}_D$ = −33.4° (c = 0.9, CH_2Cl_2). IR (KBr) υ 1840 cm^{-1} (C=O), 1776 cm^{-1} (C=O), 1691 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.37−7.29 (m, 5H); 4.73 (d, 1H, J = 4.1 Hz); 4.57 (d, 1H, J = −15.8 Hz); 4.47 (d, 1H, J = −15.8 Hz); 4.06 (m, 1H); 3.35 (m, 1H); 1.99 (m, 1H); 1.71−1.51 (m, 3H); 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 167.3, 153.6, 151.8, 134.8, 128.1, 128.0, 127.3, 79.0, 60.2, 55.5, 46.5, 45.9.

(4*R*)-3-Benzyl-4-[(2*S*)-*N*-(*tert*-butoxycarbonyl)piperidin-2-yl]oxazolidine-2,5-dione (13b). The general procedure was followed starting from **12b**. Yield 96%. Oil. $[\alpha]^{25}_D$ = −19.3° (c = 1, CH_2Cl_2). IR (KBr) υ 1840 cm^{-1} (C=O), 1774 cm^{-1} (C=O), 1687 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.38−7.28 (m, 5H); 4.65 (d, 1H, J = 6.6 Hz); 4.64 (d, 1H, J = −15.8 Hz); 4.36 (m, 1H); 4.35 (d, 1H, J = −15.8 Hz); 3.77 (m, 1H); 2.83 (m, 1H); 1.73 (m, 1H); 1.53−1.30 (m, 5H); 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 167.5, 153.7, 151.7, 134.7, 128.0, 127.2, 127.1, 79.4, 59.7, 51.3, 45.9, 40.3, 38.9, 27.5, 22.8, 17.8.

(4*R*)-3-Benzyl-4-[(1*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-ethyl]oxazolidine-2,5-dione (16a). The general procedure was followed starting from **15a**. Yield 96%. Oil. $[\alpha]^{25}_D$ = −24.3° (c = 0.8, CH_2Cl_2). IR (KBr) υ 3160 cm^{-1} (C=O), 1788 cm^{-1} (C=O), 1725 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6, 90 °C, δ) 7.41−7.38 (m, 5H); 6.75 (s_b, 1H); 4.70 (d, 1H, J = −15.8 Hz); 4.51 (d, 1H, J = −15.8 Hz); 4.41 (d, 1H, J = 3.6 Hz); 4.02−3.93 (m, 1H); 1.41 (s, 9H); 1.07 (d, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6, 90 °C, δ) 167.3, 152.4, 135.2, 128.6, 127.9, 127.8, 78.7, 62.7, 46.4, 46.1, 28.1, 15.6.

(4*R*)-3-Benzyl-4-[(1*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-methylpropyl]oxazolidine-2,5-dione (16b). The general procedure was followed starting from **15b**. Yield 92%. Oil. $[\alpha]^{25}_D$ = −41.4° (c = 1.2, CH_2Cl_2). IR (KBr) υ 3355 cm^{-1} (C=O), 1795 cm^{-1} (C=O), 1730 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6, 90 °C, δ) 7.44−7.39 (m, 5H); 6.84 (s_b, 1H); 4.70 (d, 1H, J = −15.8 Hz); 4.56 (d, 1H, J = −15.8 Hz); 4.39 (d, 1H, J = 3.2 Hz); 3.94−3.89 (m, 1H); 1.62−1.53 (m, 1H); 1.45 (s, 9H); 0.85 (d, 3H, J = 6.6 Hz); 0.67 (d, 3H, J = 6.4 Hz). ^{13}C NMR (DMSO-d_6, 90 °C, δ) 167.5, 152.6, 135.3, 128.9, 128.4, 128.0, 127.8, 78.7, 63.0, 46.8, 38.2, 28.1, 24.2, 22.7, 20.7.

(4*R*)-3-Benzyl-4-[(1*S*)-1-[(*N*-(*tert*-butoxycarbonyl)amino]benzyl]oxazolidine-2,5-dione (16c). The general procedure was followed starting from **15c**. Yield 97%. Oil. $[\alpha]^{25}_D$ = −29.8° (c = 1.2, CH_2Cl_2). IR (KBr) υ 3150 cm^{-1} (N−H), 1825 cm^{-1} (C=O), 1750 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6, 90 °C, δ) 7.41−6.96 (m, 10H); 6.85 (s_b, 1H); 4.76 (d, 1H, J = −15.9 Hz); 4.60 (d, 1H, J = −15.9 Hz); 4.43 (d, 1H, J = 2.9 Hz); 4.19−4.02 (m, 1H); 2.76−2.50 (m, 2H); 1.32 (s, 9H). ^{13}C NMR (DMSO-d_6, 90 °C, δ) 167.6, 152.6, 137.3, 135.3, 128.9, 128.8, 128.4, 128.3, 128.0, 127.9, 126.3, 78.7, 62.2, 52.6, 46.8, 36.1, 28.0.

General Procedure for the Preparation of Peptides from α-Amino Acid *N*-Carboxy Anhydrides. To a solution of the NCA (1 mmol) and the ω-amino ester (1 mmol) in dimethylformamide (5 mL) was added NaN_3 (65mg, 1 mmol), and the mixture was stirred at room temperature for 15 h. Then, diethyl ether (10 mL) was added and the organic layer was washed with a satured solution of $NaHCO_3$ (3 × 8 mL). Drying and evaporation afforded the corresponding peptide which was purified by column chromatography.

***β*(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-(*R*)-Leu-(*S*)-Leu-(OMe) (7).** The general procedure was followed starting from NCA **5a** and (*S*)-leucine methyl ester to afford *N*-benzyl-*β*(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-(*R*)-Leu-(*S*)-Leu-(OMe) (**6**) which was purified by column chromatography (silica, eluant: AcOEt/hexanes 1/30). Yield 90%. Oil. $[\alpha]^{25}_D$ = −7.5° (c = 1, CH_2Cl_2). IR (KBr) υ 3350 cm^{-1} (NH), 1743 cm^{-1} (C=O), 1676 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.69−7.61 (m, 4H); 7.43−7.21 (m, 6H); 7.15−7.11 (m, 5H); 4.51−4.45 (m, 1H); 3.56 (t, 1H, J = 4.9 Hz); 3.70 (d, 1H, J = −12.5 Hz); 3.67 (s, 3H); 3.23 (d, 1H, J = 4.9 Hz); 1.82−1.77 (m, 1H); 1.55−1.40 (m, 3H); 1.00 (s, 9H); 0.85 (d, 6H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, δ) 173.1, 136.0, 135.8, 133.4, 133.0, 129.7, 128.2, 128.1, 127.5, 127.4, 126.9, 79.0, 64.8, 52.7, 52.1, 50.4, 41.2, 32.2, 27.2, 24.8, 22.8, 22.0, 18.9, 18.8, 17.8. Compound **6** was hydrogenolyzed following the General Procedure for the synthesis of 3-hydroxy *β*-lactams, to afford the title compound **7**. Yield 82%. Oil. $[\alpha]^{25}_D$ = −52.8° (c = 1, CH_2Cl_2). IR (KBr) υ 3850 cm^{-1} (NH), 1743 cm^{-1} (C=O), 1672 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.63−7.52 (m, 4H); 7.31−7.20 (m, 6H); 4.38−4.33 (m, 1H); 3.99 (dd, 1H, J = 2.6 Hz, J = 5.6 Hz); 3.53 (s, 3H); 3.69−3.36 (m, 1H); 1.55−1.40 (m, 4H); 1.00 (s, 9H); 0.94 (d, 3H, J = 6.6 Hz); 0.94 (d, 3H, J = 6.6 Hz); 0.91 (d, 3H, J = 6.8 Hz); 0.86 (d, 3H, J = 7.1 Hz); 0.69 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, δ) 173, 172, 135, 135, 133, 132, 129, 129, 127, 127, 76.9, 55.1, 52.1, 51.1, 41.2, 32.5, 27.1, 24.8, 22.7, 22.3, 19.7, 19.3, 18.3.

***N*-(*tert*-Butoxycarbonyl)-*β*(*R*)-[(*tert*-butyldimethylsilyl)oxy]-(*R*)-Phe-(*β*(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-Leu-(*S*)-Leu-(OMe) (9).** The general procedure was followed starting from NCA **5b** and dipeptide **7** to afford *N*-benzyl-*β*-(*R*)-[(*tert*-butyldimethylsilyl)oxy]-(*R*)-Phe-*β*(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-Leu-(*S*)-Leu-(OMe) (**8**) which was purified by column chromatography (silica, eluant: AcOEt/hexanes 1/8). Yield 65%. Oil. $[\alpha]^{25}_D$ = −26.9° (c = 1, CH_2Cl_2). IR (KBr) υ 3481−3349 cm^{-1} (NH), 1743 cm^{-1} (C=O), 1662 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, δ) 7.76 (d, 1H, J = 6.9 Hz); 7.85−7.79 (m, 4H); 7.77−7.08 (m, 16H); 5.41 (d, 1H, J = 3.2 Hz); 4.68−4.63 (m, 2H); 4.23 (dd, 1H, J = 2.5 Hz, J = 6.3 Hz); 3.76 (s, 3H); 3.44 (d, 1H, J = 12.2 Hz); 3.32 (d, 1H, J = 12.2 Hz); 3.28 (d, 1H, J = 3.2 Hz); 1.99−1.90 (m, 1H); 1.64−1.49 (m, 3H); 1.22 (s, 9H); 0.93 (d, 3H, J = 5.9 Hz); 0.91 (d, 3H, J = 5.9 Hz); 0.86 (s, 9H); 0.76 (d, 3H, J = 6.8 Hz); 0.67 (d, 3H, J = 6.9 Hz); −0.06 (s, 3H); −0.18 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 172.9, 172.3,

170.2, 142.9, 139.1, 136.2, 136.0, 133.5, 132.4, 129.8, 129.6, 128.4, 128.2, 128.1, 127.6, 127.4, 126.9, 126.0, 77.6, 73.5, 68.2, 55.5, 53.2, 52.1, 50.8, 41.7, 31.8, 27.3, 25.9, 24.7, 22.7, 21.9, 19.7, 19.6, 18.1, −4.8. To a solution of compound **8** (1 mmol) in ethanol (6 mL) were added 10% palladium on charcoal (0.2 g) and di-*tert*-butyl dicarbonate (1.5 mmol), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature for 15 h. After usual purification, the title compound **9** was obtained. Yield 78%. Oil. $[\alpha]^{25}_D = -20.4°$ (c = 1, CH_2Cl_2). IR (KBr) υ 3461−3370 cm^{-1} (NH), 1743 cm^{-1} (C═O), 1662 cm^{-1} (C═O). ^{1}H NMR ($CDCl_3$, δ) 7.81−7.66 (m, 6H); 7.46−7.23 (m, 10H); 6.98 (d, 1H, J = 8.1 Hz); 5.54 (d, 1H, J = 2.2 Hz); 5.37 (d, 1H, J = 9.4 Hz); 4.60 (dd, 1H, J = 2.1 Hz, J = 6.8 Hz); 4.57−4.52 (m, 1H); 4.37−4.30 (m, 2H); 3.74 (s, 3H); 2.04−1.93 (m, 1H); 1.74−1.45 (m, 3H); 1.29 (s, 9H); 1.06 (s, 9H); 0.91 (d, 6H, J = 5.7 Hz); 0.88 (s, 9H); 0.74 (d, 3H, J = 7.8 Hz); 0.64 (d, 3H, J = 5.8 Hz); 0.00 (s, 3H); −0.13 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 172.7, 170.0, 169.7, 156.1, 141.2, 136.1, 136.0, 133.3, 129.9, 128.1, 127.6, 126.0, 80.3, 77.0, 76.4, 73.0, 61.8, 55.2, 52.1, 51.0, 41.3, 32.0, 28.1, 27.3, 25.9, 24.7, 22.6, 22.1, 19.7, 18.8, −4.7, −4.8

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Supporting Information Available: Physical data (^{1}H-NMR spectra) for **5b**, **13a**, **13b**, **16a**, **16b**, **16c**, **6**, **7**, **8**, and **9** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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