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A new approach to the stereoselective synthesis of conveniently protected α-allyl substituted amino acids; chiral key compounds in the synthesis of constrained peptide isostere constituents

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Abstract: Enantiomerically pure α-allyl-*N*-Boc-aminoamides were prepared by Curtius rearrangement of α,α-dialkyl chiral 2-cyanoesters obtained by the diastereoselective allylation of chiral 2-cyanoesters according to a modification of our previously described procedure. © 1997 Elsevier Science Ltd. All rights reserved.

Recently there has been a growing interest in the development of nonpeptidal mimics because these compounds, when rationally designed, can be used instead of bioactive peptides and can minimise the undesired effects observed in the original peptide.[1] In this field, conformational constraints play an important role in increasing the selectivity of the peptidomimetic with bioreceptors in relation to that of the flexible peptide. *N*-Methyl amino acids, α,α-dialkyl amino acids, proline residues and dipeptide lactam derivatives are common examples of moieties that can be incorporated to influence the local conformation of the peptide.

In this sense, α-allyl-substituted amino acid derivatives have proven to be useful intermediates in the synthesis of 2-substituted prolines,[2] useful secondary structure-inducing non-proteinogenic amino acids,[3] γ- and δ-lactam constrained peptide isosteres,[4] and pyrrolinone based peptidomimetics[5] (Figure 1).

Existing approaches for the synthesis of this class of amino acid generally involve (a) asymmetric alkylation of a glycine anion equivalent with reactive allyl halides,[6] (b) Claisen rearrangement of *N*-acyl amino acid allyl esters,[7] or (c) asymmetric allylation of chiral *N*-alkylidenesulfinamides.[8]

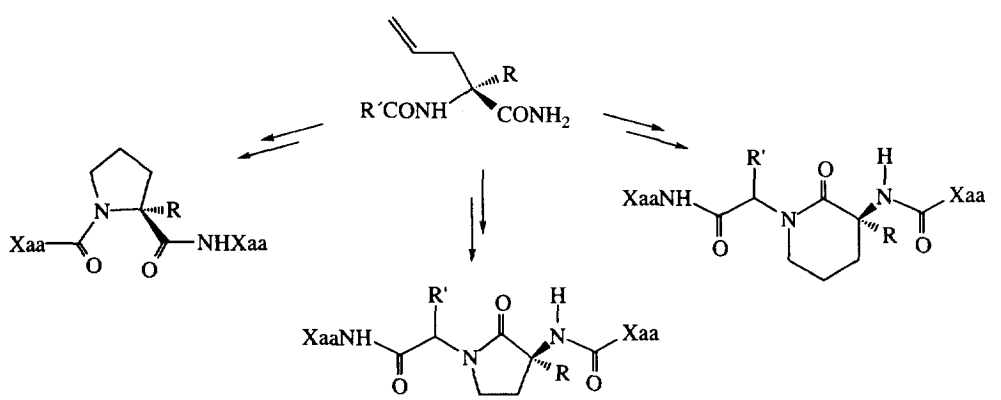

Figure 1.

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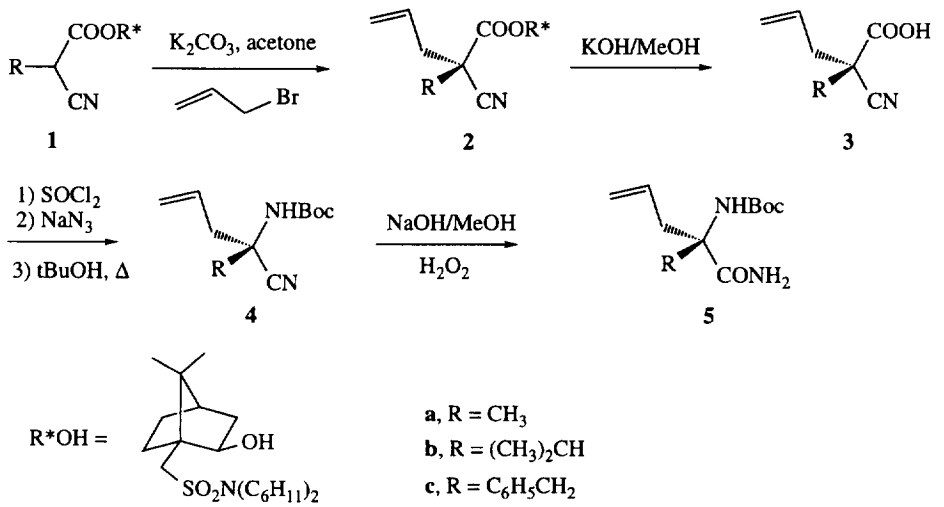
Table 1. Yields obtained in the synthesis of compounds **2**, **3**, **4** and **5**

Substrate	Yield of 2 (d.r.)	Isolated yield of 2	Yield of 3	Yield of 4	Yield of 5
1a	99 (75/25)	55	98	70	98
1b	97 (95/5)	66	99	63	91
1c	99 (92/8)	65	98	98	87



Scheme 1.

As part of our research program directed towards the design and synthesis of novel constrained amino acids, we have developed an efficient method for the preparation of α,α-dialkyl amino acids based on the diastereoselective alkylation of α-cyanoesters with reactive alkyl halides. This method has been successfully applied to the synthesis of enantiomerically pure α-allyl-*N*-Boc-aminoamides **2a–c**.

In the procedure which we reported previously, lithium enolates, formed by the treatment of (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyanoacetates with LDA at −78°C in an anhydrous medium under argon, were treated with the corresponding alkyl halide (10 mol per mol) in the presence of HMPA (carcinogenic!). This reaction afforded the corresponding alkylated compound with, in most cases, a high yield and a good diastereoselectivity.[9] We report here that treatment of a solution of the chiral cyanoester **1a–c** and allylbromide (2 mol per mol) in acetone with potassium carbonate at room temperature cleanly affords the corresponding alkylated compound. This reaction also gives a high yield and very good diastereoselectivity in the case of compounds **2b** and **2c** (Table 1) and, in addition, these new conditions are more convenient for large scale work (Scheme 1).

The major diastereoisomer can be easily isolated from diastereomeric mixtures by crystallisation from methanol or hexane in satisfactory yields. Diastereomerically pure compounds **2a–c** were hydrolysed under basic conditions to afford chiral 2-alkyl-2-cyano-4-pentenoic acid **3a–c** as single enantiomers in very high yields. Treatment of compounds **3a–c** with thionyl chloride followed by sodium azide yielded the corresponding acylazides which were not isolated. The Curtius rearrangement of the acylazides in the presence of *tert*-butanol gave 2-alkyl-2-*tert*-butoxycarbonylamino-4-

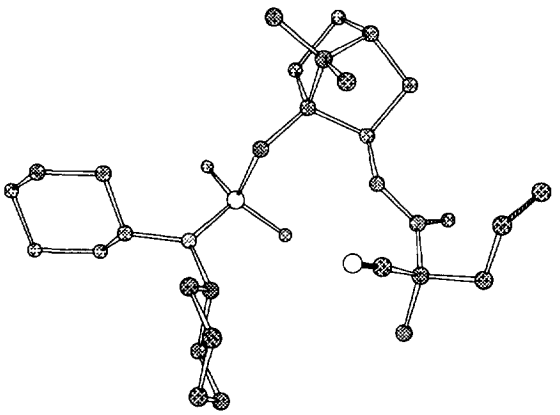


Figure 2.

pentenonitriles **4a–c** in the yields shown in Table 1. Higher yields can be obtained in the Curtius type rearrangement using methanol instead of *tert*-butanol to trap the intermediate isocyanate, but the resulting Moc protecting group requires stronger acid or basic hydrolysis conditions to be removed. Finally, when compounds **4a–c** were treated with hydrogen peroxide under basic conditions, the cyano group was easily converted to the amide group to afford the desired target compounds in very high yields.

The absolute stereochemistry of the newly formed stereogenic centre from the allylation reaction of compounds **1a–c** was previously determined on the basis of the CD curves of 2-propyl-2-alkyl-azetidinones obtained from them.[10] This has since been confirmed by single X-ray analysis of compound **2a** and the structure is represented in Figure 2. This assignment clearly demonstrates that the attack of the electrophile occurs from the $C_{\alpha\text{-Re}}$ side of the *Z*-enolate intermediate, opposite to the 10-(dicyclohexylsulfamoyl) group, which is in accordance with our previously proposed model.[11]

In summary, key intermediates **5** can be efficiently prepared by a relatively simple method from (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyanoacetates by stereoselective allylation, followed by Curtius rearrangement of the carboxylate moiety and partial basic hydrolysis of the nitrile to give the amide.

Experimental

Apparatus

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 FT IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 spectrometer in deuterochloroform using the residual solvent signal as the internal standard; chemical shifts (δ) are given in parts per million and the coupling constants (*J*) in Hertz. Elemental analyses were performed with a Perkin–Elmer 2400 analyser. Optical rotations were measured on a Perkin–Elmer 241-C polarimeter at 25°C.

Chemicals

Starting materials **1a–c** were obtained according to our previously described procedure.[10] All solvents were dried prior to use. All reagents were purchased from The Aldrich Chemical Co. and used as received. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulfuric acid/ethanol (2/1/100). Flash column chromatography was performed using silica-gel (Kiesegel 60).

General procedure for the enolate allylation of compounds ***1a–c***

Potassium carbonate (3.45 g, 25 mmol) was added to a well stirred solution of the corresponding (2*RS*)-(1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyanoacetate **1a–c** (5 mmol) and allylbromide (1.21 g, 10 mmol) in dry acetone (60 ml). The resulting mixture was stirred at room temperature for 24 h, filtered and the solid residue washed with ether. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ether, washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyano-4-pentenoate **2a–c** as a mixture of diastereoisomers (see Table 1). Recrystallization from methanol (**2a** and **2b**) or hexane (**2c**) afforded diastereoisomerically pure compounds as white solids in the yield indicated in Table 1.

(2S)-(1S,2R,4R)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-methyl-4-pentenoate ***2a***

Mp 154°C; $[\alpha]_D$=−64.5 (c=1 in $CHCl_3$); IR (Nujol) 2247, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.05 (s, 3H), 1.62 (s, 3H), 1.00–2.05 (m, 27H), 2.45 (dd, 1H, J=13.8 Hz, J=7.2 Hz), 2.60 (d, 1H, J=13.5 Hz), 2.63 (dd, 1H, J=13.8 Hz, J=7.2 Hz), 3.20–3.36 (m, 2H), 3.40 (d, 1H, 13.5 Hz), 4.98 (dd, 1H, J=7.8 Hz, J=2.7 Hz), 5.16–5.28 (m, 2H), 5.74–5.90 (m, 1H); $_{13}C$ NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.3, 22.9, 25.2, 26.2, 26.4, 27.0, 30.7, 32.2, 33.4, 39.3, 42.6, 43.5, 44.4, 49.3, 49.8, 53.7, 57.4, 80.4, 119.9, 120.9, 130.7, 167.8; Anal. Calcd. for $C_{29}H_{46}N_2O_4S$: C, 67.14; H, 8.94; N, 5.40; S, 6.18. Found: C, 67.03; H, 8.85; N, 5.33; S, 6.27.

(2R)-(1S,2R,4R)-10-(Dicyclohexylsulfamoyl)isobornyl 2-cyano-2-isopropyl-4-pentenoate ***2b***

Mp 162°C; $[\alpha]_D$=−77.8 (c=1 in $CHCl_3$); IR (Nujol) 2249, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.02 (s, 3H),1.09 (d, 3H, J=6.6 Hz), 1.14 (d, 3H, J=6.6 Hz), 1.00–2.05 (m, 27H), 2.23 (m, 1H, J=6.6 Hz), 2.50 (dd, 1H, J=13.5 Hz, J=6.9 Hz), 2.56 (d, 1H, J=13.2 Hz), 2.61 (dd, 1H, J=13.5 Hz, J=6.9 Hz), 3.22–3.34 (m, 2H), 3.38 (d, 1H, 13.2 Hz), 4.89 (dd, 1H, J=7.8 Hz, J=2.7 Hz), 5.12–5.26 (m, 2H), 5.72–5.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 19.7, 20.0, 20.4, 25.2, 26.2, 26.4, 27.0, 30.6, 31.9, 33.6, 34.4, 39.7, 40.4, 44.3, 49.3, 49.5, 53.3, 54.5, 57.2, 81.2, 118.0, 120.8, 131.0, 167.6; Anal. Calcd. for $C_{31}H_{50}N_2O_4S$: C, 68.09; H, 9.22; N, 5.12; S, 5.86. Found: C, 68.16; H, 9.31; N, 5.04; S, 5.93.

(2R)-(1S,2R,4R)-10-(Dicyclohexylsulfamoyl)isobornyl 2-benzyl-2-cyano-4-pentenoate ***2c***

Mp 157°C; $[\alpha]_D$=−76.3 (c=1 in $CHCl_3$); IR (Nujol) 2240, 1737 cm^{-1}; ^{1}NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.05 (s, 3H), 0.90–2.15 (m, 27H), 2.28 (dd, 1H, J=13.8 Hz, J=6.3 Hz), 2.53 (dd, 1H, J=13.8 Hz, J=8.4 Hz), 2.63 (d, 1H, J=13.5 Hz), 3.13 (d, 1H, J=13.8 Hz), 3.20–3.40 (m, 2H), 3.38 (d, 1H, J=13.8 Hz), 3.45 (d, 1H, J=13.5 Hz), 5.00 (dd, 1H, J=8.4 Hz, J=2.7 Hz), 5.10–5.21 (m, 2H), 5.66–5.82 (m, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0, 20.3, 25.2, 26.3, 26.4, 27.0, 30.9, 32.2, 33.4, 39.4, 40.0, 41.4, 44.5, 49.2, 49.4, 49.8, 54.0, 57.5, 80.8, 118.9, 120.9, 127.7, 128.5, 130.5, 130.8, 133.9, 167.4; Anal. Calcd. for $C_{35}H_{50}N_2O_4S$: C, 70.67; H, 8.47; N, 4.71; S, 5.39. Found: C, 70.91; H, 8.65; N, 4.61; S, 5.63.

General procedure for the hydrolysis of compounds ***2a–c***

The corresponding (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl 2-alkyl-2-cyano-4-pentenoate **2a–c** (3 mmol) was added to a 10% solution of KOH in methanol (20 ml) and the reaction mixture was heated under reflux for 6 h. The resulting solution was cooled and the solvent evaporated. The residue was diluted with water (15 ml) and washed with ether. The aqueous layer was then acidified and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding 2-alkyl-2-cyano-4-pentenoic acid **3a–c** in the yield shown in Table 1.

(2S)-2-Cyano-2-methyl-4-pentenoic acid ***3a***

Oil; $[\alpha]_D$=+4.4 (c=0.5 in $CHCl_3$); IR (Nujol) 3500–2500, 2252, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62 (s, 3H), 2.52 (dd, 1H, J=13.8 Hz, J=7.5 Hz), 2.69 (dd, 1H, J=13.8 Hz, J=7.2 Hz),

5.23–5.30 (m, 2H), 5.45 (brs, 1H), 5.75–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 41.8, 43.9, 118.9, 121.4, 130.1, 173.5; Anal. Calcd. for $C_7H_9NO_2$: C, 60.48; H, 6.42; N, 10.08. Found: C, 60.63; H, 6.65; N, 10.33.

(2R)-2-Cyano-2-isopropyl-4-pentenoic acid ***3b***

Oil; $[\alpha]_D=-17.2$ (c=1 in $CHCl_3$); IR (Nujol) 3500–2500, 2250, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (d, 3H, J=6.7 Hz), 1.13 (d, 3H, J=6.7 Hz), 2.19 (m, 1H, J=6.7 Hz), 2.52 (dd, 1H, J=13.7 Hz, J=7.9 Hz), 2.65 (dd, 1H, J=13.7 Hz, J=6.6 Hz), 5.19–5.26 (m, 2H), 5.73–5.85 (m, 1H), 8.84 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.6, 19.0, 34.5, 39.3, 56.2, 117.2, 120.9, 130.6, 173.8; Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.86; H, 7.61; N, 8.04.

(2R)-2-Benzyl-2-cyano-4-pentenoic acid ***3c***

Mp 95°C; $[\alpha]_D=-19.5$ (c=1 in $CHCl_3$); IR(Nujol) 3500–2500, 2245, 1710 cm^{-1}; ^{1}H NMR($CDCl_3$, 300 MHz) δ 2.60 (dd, 1H, J=13.8 Hz, J=7.1 Hz), 2.73 (dd, 1H, J=13.8 Hz, J=7.5 Hz), 3.10 (d, 1H, J=13.6 Hz), 3.22 (d, 1H, J=13.6 Hz), 5.20–5.32 (m, 2H), 5.75–5.90 (m, 1H), 7.20–7.35 (m, 5H), 9.04 (brs, 1H); ^{13}C NMR($CDCl_3$, 75 MHz) δ 41.1, 42.1, 51.7, 117.7, 121.6, 128.1, 128.7, 129.9, 130.0, 133.5, 173.4; Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.60; H, 6.15; N, 6.46.

General procedure for the Curtius rearrangement of compounds ***3a–c***

Thionyl chloride (5 ml) was added to the corresponding 2-alkyl-2-cyano-4-pentenoic acid **3a–c** (2 mmol) and the reaction mixture was stirred at room temperature for 2–8 h. The excess thionyl chloride was removed under reduced pressure and the oily residue was dissolved in acetone (4 ml). A solution of sodium azide (260 mg, 4 mmol) in water (1 ml) was added to the residue and stirring was continued for 1h. The acetone was removed *in vacuo* and the aqueous layer was extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in a mixture of toluene (20 ml) and *tert*-butanol (10 ml) and the resulting solution was heated under reflux for 2–4 h. The solvents were evaporated *in vacuo* and the crude product was purified by flash chromatography (eluent ether/hexane 1/3) to afford the corresponding 2-alkyl-2-*tert*-butoxycarbonylamino-4-pentenonitrile **4a–c** in the yield given in Table 1.

*(2S)-2-*tert*-Butoxycarbonylamino-2-methyl-4-pentenonitrile* ***4a***

Mp 54°C; $[\alpha]_D=-38$ (c=0.5 in $CHCl_3$);IR (Nujol) 3301, 2238, 1681 cm^{-1}; ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.63 (s, 3H), 2.50–2.54 (m, 2H), 4.65 (brs, 1H), 5.20–5.35 (m, 2H), 5.75–5.90 (m, 1H); ^{13}C NMR($CDCl_3$, 75 MHz) δ 25.2, 28.2, 43.8, 49.7, 81.3, 120.3, 121.9, 130.2, 153.6; Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.01; H, 8.25; N, 13.56.

*(2R)-2-*tert*-Butoxycarbonylamino-2-isopropyl-4-pentenonitrile* ***4b***

Oil; $[\alpha]_D=-43.1$ (c=1 in $CHCl_3$); IR (Nujol) 3343, 2239, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (d, 3H, J=6.8 Hz), 1.09 (d, 3H, J=6.8 Hz), 1.45 (s, 9H), 2.37 (m, 1H, J=6.8 Hz), 2.60 (dd, 1H, J=14.4 Hz, J=7.9 Hz), 2.76 (dd, 1H, J=14.4 Hz, J=6.5 Hz), 4.58 (brs, 1H), 5.18–5.26 (m, 2H), 5.77–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.8, 17.3, 28.3, 33.3, 38.0, 58.9, 81.1, 118.9, 120.8, 130.9, 153.7; Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.76. Found: C, 65.23; H, 9.51; N, 11.53;.

*(2R)-2-Benzyl-2-*tert*-butoxycarbonylamino-4-pentenonitrile* ***4c***

Oil; $[\alpha]_D=-6.5$ (c=0.99 in $CHCl_3$); IR (Nujol) 3342, 2241, 1711 cm^{-1}; ^{1}H NMR($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 2.48 (dd, 1H, J=14.1 Hz, J=8.2 Hz), 2.65 (dd, 1H, J=14.1 Hz, J=6.3 Hz), 3.23 (d, 1H, J=13.7 Hz), 3.32 (d, 1H, J=13.7 Hz), 4.60 (brs, 1H), 5.20–5.35 (m, 2H), 5.80–5.97 (m, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR($CDCl_3$, 75 MHz) δ 28.4, 41.3, 42.3, 54.3, 81.7, 119.7, 122.0, 127.9, 128.7, 130.6, 130.7, 133.6, 153.8; Anal. Calcd. for $C_{17}H_{22}N_2O_2$: c, 71.30; H, 7.74; N, 9.78. Found: C, 71.38; H, 7.60; N, 9.71.

General procedure for the basic hydrolysis of compounds ***4a–c***

A 1 M aqueous solution of NaOH (5 ml) was added to a solution of the corresponding 2-alkyl-2-*tert*-butoxycarbonylamino-4-pentenonitrile **4a–c** (1 mmol) in ethanol (10 ml). A 30% solution of H_2O_2 (20 ml) was then added dropwise and the resulting mixture was stirred at room temperature for 1–12 h. The reaction mixture was concentrated *in vacuo*, diluted with water (15 ml) and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluent ether/hexane 3/1) to afford the corresponding 2-alkyl-2-*tert*-butoxycarbonylamino-4-pentenamide **5a–c** in the yield given in Table 1.

*(2S)-2-*tert*-Butoxycarbonylamino-2-methyl-4-pentenamide* ***5a***

Mp 118°C; $[\alpha]_D$=−44 (c=0.5 in $CHCl_3$); IR(Nujol) 3416, 3303, 3221, 1687, 1658 cm^{-1}; ^1H NMR($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.55 (s, 3H), 2.53 (dd, 1H, J=13.7 Hz, J=7.7 Hz), 2.69 (dd, 1H, J=13.7 Hz, J=7.3 Hz), 4.93 (brs, 1H), 5.10–5.20 (m, 2H), 5.28 (brs, 1H), 5.67–5.82 (m, 1H), 6.41 (brs, 1H); ^{13} C NMR($CDCl_3$, 75 MHz) δ 23.3, 28.3, 41.8, 58.9, 80.3, 120.1, 132.3, 154.8, 176.4; Anal. Calcd. for $C_{11}H_{20}N_2O_3$: C, 57.88; H, 8.83; N, 12.27. Found: C, 58.03; H, 8.85; N, 12.33.

*(2R)-2-*tert*-Butoxycarbonylamino-2-isopropyl-4-pentenamide* ***5b***

Oil; $[\alpha]_D$=−79.2 (c=1 in $CHCl_3$); IR (Nujol) 3432, 3389, 3184, 1700, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 6H, J=6.9 Hz), 1.41 (s, 9H), 2.46 (m, 1H, J=6.9 Hz), 2.70–2.75 (m, 2H), 5.10–5.15 (m, 2H), 5.18 (brs, 1H), 5.68–5.83 (m, 1H), 6.06 (brs, 2H): ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.2, 17.3, 28.4, 32.8, 35.9, 65.8, 79.8, 119.0, 133.7, 155.2, 174.8: Anal. Calcd. for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.78; H, 9.31; N, 11.07.

*(2R)-2-Benzyl-2-*tert*-butoxycarbonylamino-4-pentenamide* ***5c***

Oil; $[\alpha]_D$=−5.8 (c=1.05 in $CHCl_3$); IR (Nujol) 3392, 3196, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.55–2.65 (m, 2H), 3.20–3.30 (m, 2H), 5.07–5.17 (m, 3H), 5.60–5.85 (m, 2H), 6.25 (brs, 1H), 7.10–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 40.2, 40.3, 63.0, 80.0, 119.8, 126.9, 128.2, 130.4, 132.2, 135.9, 154.6, 175.0; Anal. Calcd. for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.95; H, 7.91; N, 9.28.

Single crystal X-ray diffraction analysis of ***2a***[12]

Crystallographic measurement was carried out at ambient temperature on a 4-circle Siemens P4 diffractometer using graphite monochromated molybdenum $K\alpha$ X-radiation (λ=0.71069 Å). One equivalent set of data was collected in the range $4° < 2\theta < 50°$ using $\omega/2\theta$ scans. No significant variation was observed in the intensity of the three standard reflections. Lorentz and polarisation corrections were applied to the data-set. The structure was solved by direct methods using SIR92[13] and was refined by full-matrix least squares (based on F^2) using SHELXL-93[14] which used all data for refinement. The weighting scheme was $\omega=[\sigma^2(F_o^2)+(0.0583P)^2+0.7368P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions.

$C_{58}H_{82}N_4O_8S_2$ (two independent molecules per asymmetric unit) 0.44×0.34×0.32 mm, M_t=1027.43, monoclinic, space group $P2_1$ a=11.848(5), b=10.817(5), c=23.466(5) Å, β=90.550(5), V=3007.26(2) Å^3, Z=2, ρ_{calc}=1.135 g cm^{-3}, $F(000)$=1108, μ=1.41 cm^{-1}. 4668 independent reflections measured. Final R=0.0770, ωR=0.2070 for all independent reflections, R=0.0493, ωR=0.1094 for 3444 observed reflections with $F_0 > 4\sigma F_0$.

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