Pergamon

Tetrahedron, Vol. 53, No. 51, pp. 17417-17424, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10165-X

A Facile Approach for the Synthesis of *Pseudo*-Peptides Incorporating a (2*S*, 3*R*)-2-Amino-Cyclopropane Carboxylic Acid Residue.

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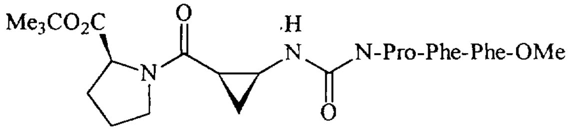
Abstract: The synthesis of a *pseudo*-tripeptide **9** and a *pseudo*-pentapeptide **1** incorporating the conformationally constrained β-amino acid (2*S*,3*R*)-2-amino cyclopropane carboxylic acid is reported. The key steps of the synthesis are the desymmetrisation of cyclopropane 1,2-dicarboxylic anhydride using (*S*)-proline t-butyl ester followed by a Curtius rearrangement. Subsequent trapping of the isocyanate with (*S*)-proline t-butyl ester or HN-(*S*)-Pro-(*S*)-Phe-(*S*)-Phe-OMe gave the desired *pseudo*-peptides. The stereochemistry of the desymmetrisation reaction was determined by X-ray crystallography of the amido-acid. © 1997 Elsevier Science Ltd.

INTRODUCTION

There is currently considerable interest in the synthesis of peptides incorporating conformational constraints.[1] Such compounds offer both enhanced biological activity and improved pharmokinetic properties due to reduced *in vivo* hydrolysis. Conformational constraints or conformation inducing groups are available for all of the main secondary structure elements commonly found in peptides and proteins. Thus α-helix inducers have been reported, as have β-sheet inducers and rigid analogues of both β- and γ-turns.[1,2] In particular, the use of non-peptidic units as β-turn mimetics has been the subject of considerable activity.[2] In this paper, we report the synthesis of peptide **1** which incorporates two unusual features designed to enhance *in vivo* stability and induce the formation of a β-turn.[3] The first of these features is the conformationally constrained β-amino acid (2*S*,3*R*)-2-amino cyclopropane carboxylic acid **2**, which was designed as a β-turn mimic,[4] and the second feature is the urea which replaces one of the amide bonds, and was designed both to limit *in vivo* hydrolysis, and to invert the direction of subsequent peptide chain growth so that the peptides on either side of the cyclopropane unit would be parallel to one another.

Cyclopropane containing amino acids are currently attracting much synthetic interest,[5] largely because α-amino cyclopropane carboxylic acid **3** is the biosynthetic precursor of ethene which is involved in the ripening of fruit.[6] The isomeric β-amino cyclopropane carboxylic acids have been the subject of far less investigation, since like other cyclopropanes bearing electron donating and electron withdrawing groups on adjacent ring atoms they are well known to undergo spontaneous ring opening.[7] This has hampered the preparation of peptides incorporating these and related[8] amino acids.



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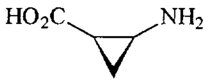

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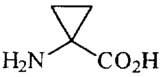

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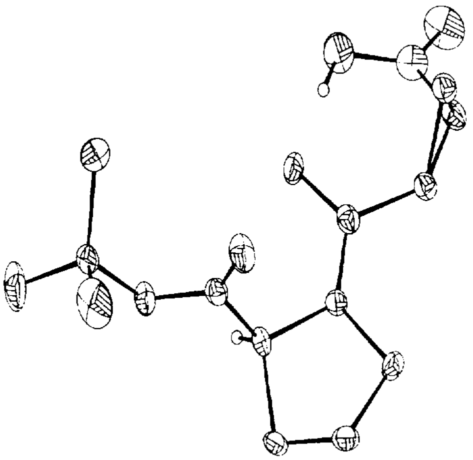
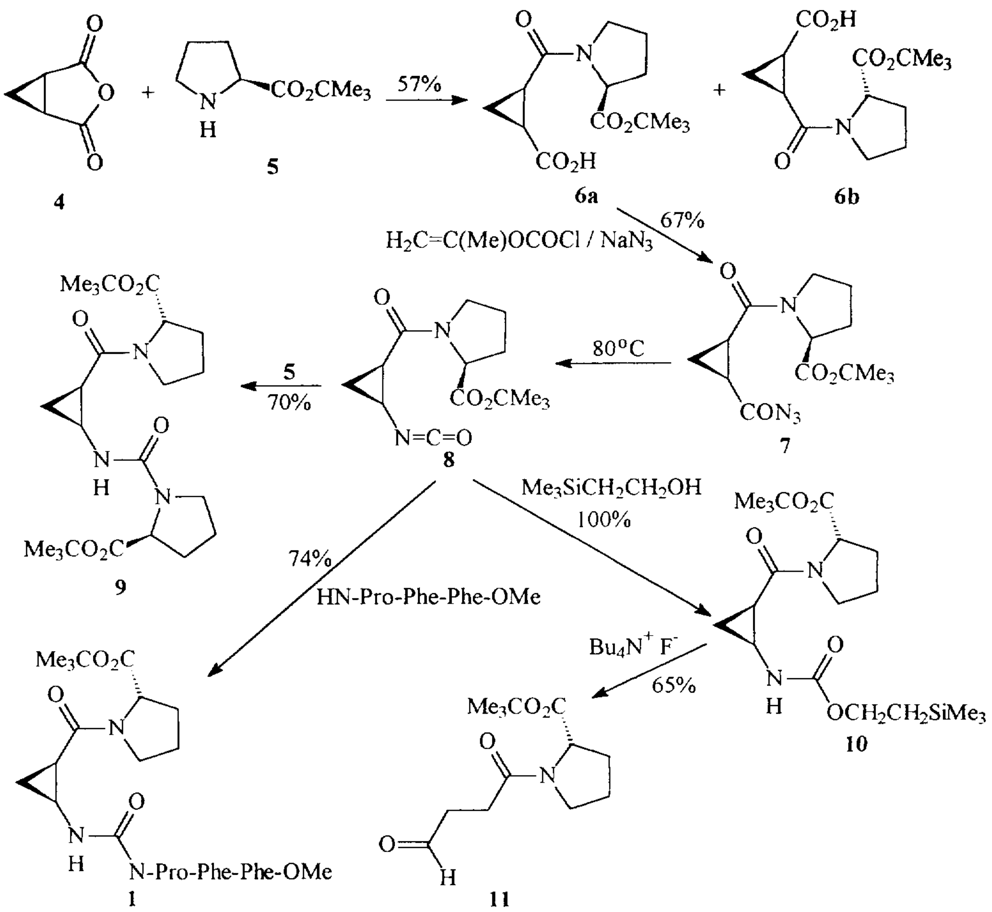
RESULTS AND DISCUSSION

Based on our previous work on the desymmetrisation of norbornane derived anhydrides using proline esters,[9] we reasoned that it should be possible to prepare peptides incorporating (2*S*,3*R*)-2-amino cyclopropane carboxylic acid from *meso*-anhydride **4** as shown in **Scheme 1**. Thus reaction of anhydride **4** with t-butyl (*S*)-prolinate[10] **5** gave amido acids **6a,b** as a 3:1 ratio of diastereomers from which the major diastereomer **6a** could be obtained as a crystalline solid in 40% yield simply by trituration with ether. The stereochemistry of the stereocentres within the cyclopropane ring of isomer **6a** could not be determined directly by X-ray crystallography[11] because of the absence of significant anomalous scatter in the molecule, but were deduced as 2*S*, 3*R* from the known absolute configuration of the proline stereocentre. An ORTEP representation of the crystal structure is shown in **Figure 1**. The crystal structure shows that an intramolecular hydrogen bond is formed between the carboxylic acid OH and the amide carbonyl, that the tertiary amide adopts an *s-trans* conformation whilst the t-butyl ester adopts an *s-cis* conformation.

Figure 1: ORTEP Diagram of Amido Acid **6a**





Scheme 1

The carboxylic acid of amide **6a** was transformed into the corresponding isocyanate **8** *via* a Curtius rearrangement.[12] Thus activation of the carboxylic acid as a mixed anhydride using isopropenyl chloroformate[13] followed by the addition of aqueous sodium azide gave acyl azide 7. The choice of isopropenyl chloroformate to activate the acid functionality was based on our previous work in the norbornane series,[9] where it was established that the by-product from the activating agent (acetone in this case) had to be non-nucleophilic in order to prevent competing ester formation. Simply heating acyl azide **7** in refluxing benzene resulted in smooth rearrangement to isocyanate **8**, a process which is well known to occur with retention of configuration at the migrating centre.

Isocyanate **8** was found to react with the amino group of amino esters and peptides to give peptide analogues incorporating a urea bond. Thus reaction of compound **8** with t-butyl (*S*)-prolinate gave *pseudo*-tripeptide 9, and reaction with the tripeptide HN-(*S*)-Pro-(*S*)-Phe-(*S*)-Phe-OMe gave *pseudo*-pentapeptide **1**. The ^{1}H and ^{13}C NMR spectra of compounds **1** and **9** were complicated due to the presence of rotamers about each of the proline amide bonds. Compounds **1** and **9** are the first examples of a new class of conformationally constrained peptide analogue, incorporating both a urea peptide bond isostere and a conformationally constrained (2*S*,3*R*)-2-amino cyclopropane carboxylic acid unit. The effect of the urea unit is to reverse the peptide chain direction, so that *pseudo*-peptides **9** and **1** have two *C*-termini and no *N*-terminus.

Finally, we attempted to convert isocyanate **8** into the corresponding amine so that peptide analogues incorporating a (2*S*,3*R*)-2-amino cyclopropane carboxylic acid but not a urea unit could be prepared. However, all attempts to directly hydrolyse **8** to the corresponding amine resulted only in decomposition. The isocyanate could however be converted into the corresponding urethane **10** simply by treatment with β-trimethylsilylethanol. Removal of the β-trimethylsilylethoxycarbonyl protecting group from compound **10** using tetra-n-butylammonium fluoride however resulted in concomitant ring opening of the cyclopropane ring and hydrolysis of the intermediate imine to give aldehyde **11** as the isolated product in line with literature precedent.[7]

CONCLUSIONS

It has been shown that the desymmetrisation of cyclopropane derived anhydride **4** by t-butyl (*S*)-prolinate **5** gives predominantly the (2*S*,3*R*)-diastereomer of amido-acid **6**, which can subsequently be transformed into conformationally constrained *pseudo*-peptides incorporating a (2*S*,3*R*)-2-amino cyclopropane carboxylic acid residue and a urea unit. Our work on the desymmetrisation of meso-anhydrides by amino acid derivatives is continuing, and further results will be reported in due course.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 250MHz on a Bruker AM250 spectrometer fitted with a ^{1}H-^{13}C dual probe, and were recorded at 293K in $CDCl_3$ unless otherwise stated. Spectra were internally referenced either to TMS or to the residual solvent peak, and peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination of these, broad (br), or multiplet (m). ^{13}C NMR spectra were recorded at 62.5MHz on the same spectrometer as ^{1}H NMR spectra, at 293K and in $CDCl_3$ unless otherwise stated. Spectra were referenced to the solvent peak, and are reported in ppm downfield of TMS. Superscripted 'a's indicate that the peak assignments may be interchanged. Infra red spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer, only characteristic absorptions are reported. Mass spectra were recorded by chemical ionisation (CI) with ammonia or electrospray (ES) on either a VG model 12-253 quadrupole spectrometer or a VG Quattro II triple quadrupole spectrometer. Only significant fragment ions are reported, and only molecular ions are assigned. High resolution mass measurements were made on a VG ZAB-E spectrometer. Optical rotations were recorded on an Optical Activity Ltd. Polar 2001 polarimeter, and are reported along with the solvent and concentration in g/100ml. Melting points are uncorrected.

Flash chromatography[14] was carried out on 40-60mm mesh silica, thin layer chromatography was carried out on aluminium backed silica plates (0.25mm depth of silica containing UV254), and the plates were visualised with u.v. light, and/or dodecaphosphomolybdic acid as appropriate. All yields refer to isolated, purified material, and are unoptimised. THF was dried by distillation from sodium immediately prior to use. Toluene and benzene were dried over sodium wire. Other solvents were used as supplied.

X-ray crystallographic measurements on **6a** were made at 150 K using a Delft Instruments FAST area detector diffractometer positioned at the window of a rotating anode generator using Mo-K_α radiation (λ = 0.71069 Å) by following previously described procedures.[15] Crystal data: $C_{14}H_{21}NO_5$ (FW 283.32); orthorhombic; space group $P2_12_12_1$; a = 6.2290(10), b = 10.4750(8) and c = 22.750(5) Å; V = 1484.4 Å^3; Z = 4; D_c = 1.268 Mg m^{-3}; λ(Mo-K_α) = 0.98 cm^{-1}; $F(000)$ = 608. The structure was solved by direct methods (SHELXS86),[16] and refined on F^2 by full-matrix least-squares (SHELXL93)[17] using all 2246 unique data corrected for Lorentz and polarisation factors but not for absorption. The structure was finally refined (185 parameters) to R [on F, $F_o > 4\sigma(F_o)$] and wR [on F^2, all data)] values of 0.0521 and 0.1199 respectively. Further details of data collection and structure refinement, atom coordinates, thermal coefficients, hydrogen atom parameters, and bond lengths and angles are available from the Cambridge Crystallographic Data Centre.[11]

Amido-acid **6a**

A solution of 3-oxabicyclo[3.1.0]hexane-2,4-dione, **4** (0.35g, 3.1mmol) and t-butyl (*S*)-prolinate **5** (0.5g, 3.1mmol) in dichloromethane (5ml) was stirred at room temperature for 18 hours. The reaction mixture was subsequently washed with 0.5M HCl (5ml), and water (2 x 5ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo* to leave 0.71g of a yellow oil. Trituration with Et_2O gave amido-acid **6a** (0.35g, 40%) as a white crystalline solid. m.p. 116-117°C; $[\alpha]_D^{22}$ -159.4 (c = 1, $CHCl_3$); υ_{max} 3500-2500 br, 1734 s, 1642 m, 1573 s and 1226cm^{-1} s; δ_H 1.48 (9H, s, $C(\underline{C}H_3)_3$), 1.5-2.4 (8H, br m, CH_2CH_2, $CHCH_2CH$), 3.7-3.9 (2H, m, NCH_2), 4.49 (1H, dd *J* 8.0, 3.2Hz, NCH); δ_C 15.67 (t, $CH\underline{C}H_2CH$), 20.91^a (d, $CH_2\underline{C}HCON$), 24.42^a (d, $CH_2\underline{C}HCO_2H$), 25.21 (t, $\underline{C}H_2CH_2$), 27.92 (q, $C(\underline{C}H_3)_3$), 29.1 (t, $CH_2\underline{C}H_2$), 47.91 (t, NCH_2), 61.05 (d, NCH), 81.99 (s, $\underline{C}Me_3$), 170.20, 171.97 and 172.41 (3s, 3 C=O); m/z (CI, NH_3): 301 (M + NH_4^+, 2), 284 (MH^+, 83), 228 (62), 172 (64), 70 (100); Found 284.1498 ($C_{14}H_{22}NO_5$ requires 284.1498).

Acyl azide **7**

Isopropenyl chloroformate (0.08ml, 0.77mmol) was added to a mixture of amido-acid **6a** (0.20g, 0.70mmol) and Et_3N (0.2ml) in dry THF (1ml) at -20°C. An aqueous solution of NaN_3 (0.12g, 1.85mmol) was added at -10°C. The temperature was gradually raised to room temperature, and stirring was continued for 1 hour. The reaction mixture was diluted with H_2O (5ml) and extracted with EtOAc (3 x 5ml). The combined organic phases were washed with Na_2CO_3 solution (5ml), water (5ml) and brine (5ml), dried ($MgSO_4$), filtered and concentrated to leave 0.15g (67%) of acyl azide **7** as a clear crystalline solid which was used without further purification. m.p. 60-61°C; $[\alpha]_D^{23}$ -19.5 (c = 1, $CHCl_3$); υ_{max} 3008 m, 2982 m, 2144 s, 1733 s, 1645 s, 1452 s and 1434cm^{-1} s; δ_H 1.2-2.3 (8H, br m, $CHCH_2CH$, and CH_2CH_2), 1.46 (9H, s, $C(\underline{C}H_3)_3$), 3.5-3.7 (2H, m, NCH_2), 4.38 (1H, dd *J* 8.4, 4.7Hz, NCH), δ_C 12.50 (t, $CH\underline{C}H_2CH$), 23.20^a (d, $CH_2\underline{C}HCON$), 24.69 (t, $\underline{C}H_2CH_2$), 24.86^a (d, $CH_2\underline{C}HCON_3$), 27.93 (q, $C(\underline{C}H_3)_3$), 29.24 (t, $CH_2\underline{C}H_2$), 47.1 (t, NCH_2), 59.57 (d, NCH), 81.28 (s, $\underline{C}Me_3$), 156.36, 165.89 and 171.35 (3s, 3 C=O); m/z (ES): 309 (MH^+, 51), 102 (100).

Isocyanate **8**

Acyl azide **7** (0.38g, 1.2mmol) was dissolved in anhydrous benzene (7ml), and heated under reflux for 2 hours. The solvent was evaporated *in vacuo* to leave 0.34g (100%) of isocyanate **8** as a clear oil which was pure enough to be used without purification. $[\alpha]_D^{22}$ -119.7 (c = 1, $CHCl_3$); υ_{max} 3017 m, 2982 m, 2268 s, 1735 s, 1637 s, 1450 s, 1219 and 1153cm^{-1} s; δ_H 1.1-1.3 (2H, m, $CHC\underline{H}_2CH$), 1.46 and 1.47 (9H, 2 s, $C(\underline{C}H_3)_3$), 1.6-2.5 (6H, m, $C\underline{H}CH_2C\underline{H}$ and $C\underline{H}_2C\underline{H}_2$), 3.4-4.0 (2H, m, NCH_2), 4.4-4.6 (1H, m, $CH_2C\underline{H}N$);

δ_C 13.69, 14.54 (t, $CH\underline{C}H_2CH$), 19.86, 20.57 (d, $CH_2\underline{C}HCON$), 24.47, 24.58 (t, $\underline{C}H_2CH_2$), 27.86, 27.90 (q, $C(\underline{C}H_3)_3$), 29.17, 29.32 (t, $CH_2\underline{C}H_2$), 30.21, 30.52 (d, $CH_2\underline{C}HNCO$), 47.0, 47.11 (t, NCH_2), 59.49, 59.90 (d, $CH_2\underline{C}HN$), 81.32, 82.25 (s, $\underline{C}Me_3$), 166.51, 166.99 and 171.31, 171.38 (2s, 2 C=O) The doubling of each peak was due to the presence of *s-cis* and *s-trans* rotamers about the proline amide bond and the N=C=O peak was not detected; m/z (CI, NH_3): 298 (M + NH_4^+, 21), 281 (MH^+, 37), 255 (100), 225 (40), 172 (32); Found 281.1501 ($C_{14}H_{20}N_2O_4$ requires 281.1501).

Pseudo-tripeptide **9**

Isocyanate **8** (0.25g, 0.9mmol) and t-butyl (*S*)-prolinate **5** (0.16g, 0.98mmol) were dissolved in dichloromethane (2ml) and stirred at room temperature for 18 hours. The reaction mixture was subsequently washed with 0.5M HCl (1ml), Na_2CO_3 (1ml), H_2O (1ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo* to leave 0.38g of a yellow / brown oil. This was subjected to flash chromatography (70% Hexane / 30% EtOAc) to give 0.28g (70%) of **9** (R_f = 0.09) as a yellow oil. $[\alpha]_D^{22}$ -43.6 (c = 1, $CHCl_3$); υ_{max} 3346 br, 2976 s, 1735 s, 1654 s, 1522 s and 1152cm^{-1} s; δ_H 1.1-1.3 (2H, m, $CHC\underline{H}_2CH$), 1.41 and 1.42 (18H, 2s, 2 CMe_3), 1.8-2.3 (9H, m, 2 $C\underline{H}_2C\underline{H}_2$ and $CH_2C\underline{H}CON$), 3.2-3.9 (5H, m, 2 NCH_2 and $CH_2C\underline{H}NH$), 4.2-4.4 (2H, m, 2 $CH_2C\underline{H}N$), 5.74 and 5.85 (1H, 2d *J* 8.3 and 8.4Hz, NH); δ_C (*only peaks corresponding to the major conformer are reported*) 13.31 (t, $CH\underline{C}H_2CH$), 19.01 (d, $CH_2\underline{C}HCON$), 24.17, 24.45, 29.22 and 29.82 (4t, 2 CH_2CH_2), 27.89 (q, $C(\underline{C}H_3)_3$), 27.97 (q, $C(\underline{C}H_3)_3$), 31.72 (d, $CH_2\underline{C}HNH$), 45.59 (t, NCH_2), 47.21 (t, NCH_2), 59.53 (d, $CH_2\underline{C}HN$), 59.69 (d, $CH_2\underline{C}HN$), 80.91 (s, $\underline{C}Me_3$), 81.14 (s, $\underline{C}Me_3$), 156.35 (s, NH-$\underline{C}$O-N), 170.08, 171.13 and 172.29 (3s, 3 C=O); m/z (CI, NH_3): 452 (MH^+, 100), 396 (12), 281 (10), 159 (42), 70 (42); Found 452.2761 ($C_{23}H_{38}N_3O_6$ requires 452.2761).

Pseudo-pentapeptide **1**

Triethylamine (1.05ml, 7.5mmol) was added to a cooled (0°C) suspension of isocyanate **8** (0.7g, 2.5mmol) and TFA. HN-Pro-Phe-Phe-OMe (1.14g, 2.75mmol) in CH_2Cl_2 (10ml). The reaction mixture was stirred at room temperature for 16 hours and subsequently washed with 0.5M HCl (7ml), aqueous saturated Na_2CO_3 (7ml) and water (7ml). The organic solution was dried ($MgSO_4$) and evaporated *in vacuo* affording 1.41g of an orange oil which was crystallised from EtOAc to give **1** (1.16g, 66%) as a white solid. Found: C, 62.6; H, 7.3; N, 9.7%; $C_{38}H_{49}N_5O_8$. 1.5 H_2O requires: C, 62.5; H, 7.2; N, 9.6% m.p. 64-66°C; $[\alpha]_D^{23}$ -94.5 (c = 1, $CHCl_3$); υ_{max} 3314 br 2978 m, 1737 s, 1638 s, 1529 s, 1454 s and 1153cm^{-1} s; δ_H 1.15-1.25 (2H, m, $CHC\underline{H}_2CH$), 1.42 (9H, s, $C(\underline{C}H_3)_3$), 1.50-2.24 (9H, m, 2 x CH_2CH_2 and $CH_2C\underline{H}CON$), 2.78-3.72 (9H, m, 2 x $PhCH_2$, $CH_2C\underline{H}NH$ and 2 x NCH_2), 3.62 (3H, s, OCH_3), 4.28-4.39 (2H, m, 2 x $CH_2C\underline{H}N$), 4.61-4.81 (2H, m, 2 x $PhCH_2C\underline{H}$), 6.17 (1H, d *J* 7.2Hz, NH), 7.11-7.34 (11H, m, 2 x ArCH and NH), 7.34 (1H, d *J* 6.8Hz, NH); δ_C (only peaks corresponding to the major conformer are reported) 14.06 (t, $CH\underline{C}H_2CH$), 18.05 (d, $CH_2\underline{C}HCON$), 24.23, 24.36, 29.18, and 29.25 (4 x t, 2 x CH_2CH_2), 27.90 (q, $C(\underline{C}H_3)_3$), 31.34 (d, $CH_2\underline{C}HNH$), 36.94 (t, $PhCH_2$), 37.67 (t, $PhCH_2$), 47.34 (t, NCH_2), 52.14 (q, OCH_3), 53.91 (d, $PhCH_2\underline{C}H$), 59.58 (d, $PhCH_2\underline{C}H$), 60.31 (d, $NCHCH_2$), 60.50 (d, $NCHCH_2$), 81.17 (s, $\underline{C}Me_3$), 126.55, 128.33, 128.40, 129.05, and 129.13 (5 x d, 2 x ArCH), 136.52 (s, ArC), 136.91 (s, ArC), 157.96 (s, $NH\underline{C}ON$), 170.26, 170.95, 171.14, 171.37 and 172.48 (5 x s, 5 xC=O); m/z (CI): 704 (MH^+, 3), 424 (100); Found 704.3660 ($C_{38}H_{50}N_5O_8$ requires 704.3659).

*Urethane **10***

β-Trimethylsilylethanol (0.17ml, 1.2mmol) and isocyanate **8** (0.30g, 1.07mmol) were refluxed in anhydrous benzene (5ml) for 24 hours. Solvent was subsequently removed at reduced pressure to afford 0.42g (100%) of **10** as a yellow oil which could be used without further purification. $[\alpha]_D^{22}$ -72.9 (c = 1, $CHCl_3$); υ_{max} 3358 m, 2954 s, 1718 s, 1636 s, 1527 s and 1250cm^{-1} s; δ_H -0.35 (9H, s, $SiMe_3$), 0.8-1.0 (2H, m, $C\underline{H}_2SiMe_3$), 1.0-1.4 (2H, $CHC\underline{H}_2CH$), 1.37 and 1.39 (9H, 2s, $C(\underline{C}H_3)_3$), 1.6-2.3 (5H, m, $CH_2C\underline{H}CON$ and CH_2CH_2), 3.2-3.4 (1H, m, $CH_2C\underline{H}NH$), 3.5-3.9 (2H, m, NCH_2), 4.0-4.2 (2H, m, OCH_2), 4.3-4.4 (1H, m, $CH_2C\underline{H}N$), 5.60 and 5.73 (1H, 2d *J* 8.1 and 8.0Hz, NH); δ_C -1.55 (q, $SiMe_3$), 12.57, 12.77 (t, $\underline{C}H_2SiMe_3$), 13.81, 13.82 (t, $CH\underline{C}H_2CH$), 17.98, 18.30 (d, $CH_2\underline{C}HCON$), 24.46, 24.54 (t, $\underline{C}H_2CH_2$), 27.80, 27.90 (q, $C(\underline{C}H_3)_3$), 29.08, 29.24 (t, $CH_2\underline{C}H_2$), 31.03, 31.27 (d, $CH_2\underline{C}HNH$), 47.06, 47.21 (t, NCH_2), 59.56, 59.86 (d, $CH_2\underline{C}HN$), 62.76, 62.87 (t, OCH_2), 81.11, 81.94 (s, $\underline{C}Me_3$), 157.32, 157.32 (s, NH-$\underline{C}$O-O), 169.07, 169.25 and 171.34, 171.54 (2s, 2 C=O) The doubling of each peak was due to the presence of *s-cis* and *s-trans* rotamers about the proline amide bond; m/z (CI, NH_3): 399 (MH^+, 100), 371 (14), 343 (11), 315 (23), 90 (29); Found 399.2315 ($C_{19}H_{35}N_2O_5Si$ requires 399.2315).

Aldehyde 11

Carbamate **10** (0.24g, 0.60mmol) was stirred with 1M tetra-n-butylammonium fluoride (1.75ml, 6.0mmol) in THF (5ml) at room temperature for 24 hours. Solvent was removed at reduced pressure and the residue was dissolved in dichloromethane (5ml). Water (5ml) was added and the layers were mixed by rapid stirring for approximately 15 minutes. The dichloromethane layer was extracted with saturated ammonium chloride solution and dried over $MgSO_4$. After filtration, solvent was evaporated *in vacuo* to afford a brown / black oil. Purification by flash chromatography using 95% EtOAc / 5% MeOH as eluent yielded 0.1g (65%) of aldehyde **11** (R_f = 0.46) as a clear oil. $[\alpha]_D^{22}$ -23.1 (c = 1, $CHCl_3$); υ_{max} 3424 br, 2956 s, 1716 s, 1646 m, 1456 m, 1367 m and 1154cm^{-1} s; δ_H 1.39 (9H, s, $C(\underline{C}H_3)_3$), 1.8-2.1 (4H, m, CH_2CH_2), 2.2-3.0 (4H, m, $C\underline{H}_2C\underline{H}_2CHO$), 3.4-3.6 (2H, m, NCH_2), 4.3-4.4 (1H, m, NCH), 9.85 (1H, s, CHO); δ_C 24.57 (t, $\underline{C}H_2CH_2$), 26.84 (t, $\underline{C}H_2CH_2CHO$), 27.94 (q, $C(\underline{C}H_3)_3$), 29.22 (t, $CH_2\underline{C}H_2$), 38.38 (t, $CH_2\underline{C}H_2CHO$), 46.94 (t, NCH_2), 59.54 (d, NCH), 81.22 (s, $\underline{C}Me_3$), 169.68 and 171.45 (2s, 2 C=O), 201 10 (d, CHO); m/z (CI, NH_3): 256 (MH^+, 100); Found 256.1549 ($C_{13}H_{22}NO_4$ requires 256.1549)

ACKNOWLEDGEMENTS

The authors thank Peboc Division of Eastman (UK) Ltd. and the EPSRC for a CASE award studentship to IGJ, and the staff of the EPSRC mass spectrometry service (University of Wales, Swansea) for low and high resolution mass spectra.

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(***Received in UK*** *15 September* 1997; *accepted* 9 *October* 1997)