Double stereodifferentiation in aldol reactions of pyroglutamic urethane esters[1]

Bernard A. Starkmann and Douglas W. Young*

Sussex Centre for Biomolecular Design and Drug Development, CPES, University of Sussex, Falmer, Brighton, UK BN1 9QJ

Received (in Cambridge, UK) 11th January 2002, Accepted 1st February 2002
First published as an Advance Article on the web 20th February 2002

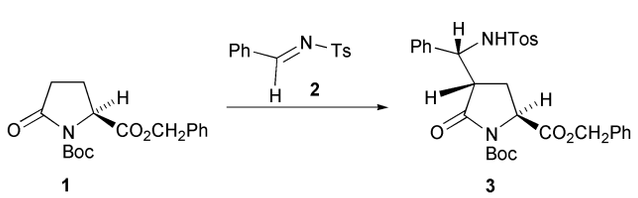
Aldol condensation of the (2*S*)-pyroglutamate urethane ester **4** with (*R*)-glyceraldehyde acetonide **8** and with (*S*)-Garner aldehyde **14** gives excellent stereoselectivity at both of the chiral centres created in each of the reactions. The reactants therefore seem to be matched pairs, as the corresponding reactions with (*S*)-glyceraldehyde acetonide **10** and (*R*)-Garner aldehyde **16** are less stereoselective. Stereoselectivity was not so impressive in the aldol condensation between the bromide **20** and the aldehyde **8**.

Introduction

Naturally-occurring proteinogenic and non-proteinogenic amino acids and unnatural amino acids have been the subject of intense research interest in recent years. This has led to the elaboration of new methods for the synthesis of these biologically important compounds. The cyclic amido acid, pyroglutamic acid, has been identified by several groups, including our own, as an ideal template for the stereospecific synthesis of amino acids.[2] Our interest in the mechanism and stereochemical course of biological reactions and in protein conformation led us to use this template to synthesise stereospecifically labelled amino acids,[3,4] homochiral non-proteinogenic amino acids,[5,6] and homochiral amino acids designed as glutamate antagonists[7] and as potential anti-bacterial drugs.[8]

Results and discussion

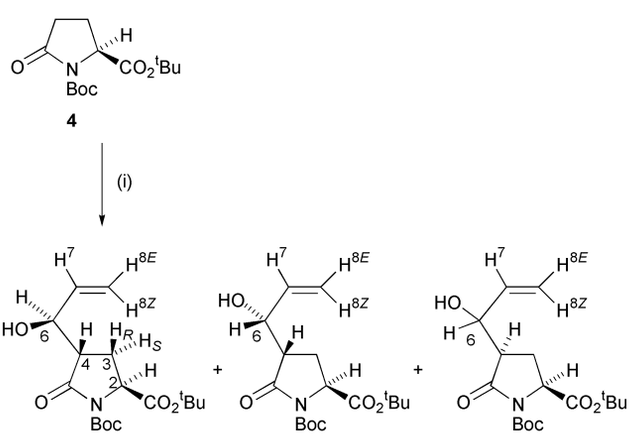
Baldwin investigated the application of the aldol condensation to pyroglutamic urethane esters in 1989.[9] He obtained reasonable yields of mixtures of diastereoisomers at the two centres created in the reaction, although no comment was made concerning the stereochemistry of the individual products. In 1991, we reported our results on the reaction of the pyroglutamate urethane benzyl ester **1** with imines in which we achieved a remarkable degree of stereoselectivity at the two new chiral centres created in the reaction.[10] The first of these centres, C-4 of pyroglutamate, was generated uniquely in one configuration due to the reaction occurring entirely at the less hindered face of the pyroglutamate ring. The second chiral centre was created with a high degree of stereoselectivity and in reaction with the aldimine **2** shown in Scheme 1, the (2*S*,4*S*,6*R*)-epimer **3** was



Scheme 1

the major product. This contrasted with a subsequent report on the aldol reaction between protected pyroglutamic esters with aromatic aldehydes by Dikshit and Panday.[11] They showed a facial selectivity of only 3 : 1 in favour of the less hindered face of the pyroglutamate moiety and made no comment on the stereochemistry of the second centre created in the reaction. Later studies by this group[12] achieved 4α-selectivity by use of a titanium enolate but again there was no indication of the degree of stereoselectivity at the second centre created in the reaction. A further study has reported aldol condensations with the enolate of a protected pyroglutamic ester in the presence of $Et_2O{\cdot}BF_3$ when unspecified diastereoisomeric mixtures of hydroxyalkylated products were obtained.[13]

As our initial studies[10] had given such impressive stereoselectivity in this type of reaction and the use of protected pyroglutamates in the synthesis of compounds with multiple chiral centres was appealing, we decided to investigate the aldol condensation reaction of protected pyroglutamic esters with chiral aldehydes. Before commencing this study we decided to reinvestigate the best yielding of Baldwin's aldol reactions,[9] that of acrolein with *tert*-butyl *tert*-butoxycarbonylpyroglutamate **4** using LiHMDS as base. We obtained a mixture of three diastereoisomers in 92% yield, as shown in Scheme 2. A mixture of



Scheme 2 (i) LiHMDS–$H_2C{=}CHCHO$ (96% – **5**–**6**–**7** ratio 10 : 6 : 9.

two compounds **5** and **6** could be separated from the third **7**. The ratio of (**5** and **6**) to **7** was 1.8 : 1, and that of **5** to **6** was 1.6 : 1 as judged by integration of signals in the ^{1}H-NMR spectrum. The stereochemistry at C-4 of the major isomer **5** was judged to be (4*S*) using NOE experiments (Fig. 1). The proton at 1.61 ppm was assigned as H-3*S* by its enhancement on irradiating the signal for H-2 at 4.41 ppm, and irradiation of

DOI: 10.1039/b200443g

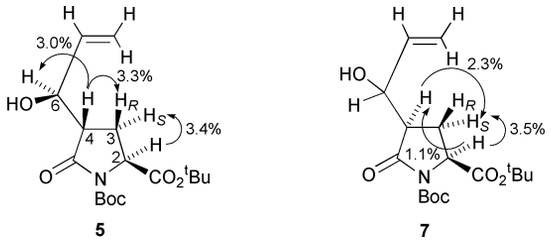
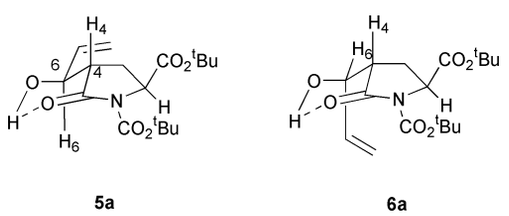


Fig. 1 Results of NOE experiments on the products **5** and **7**.

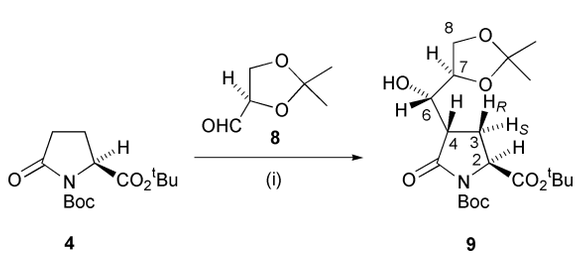
H-4 at 2.83 ppm gave an enhancement to H-3*R* at 1.86 ppm. The isomer **6** was deemed to have the same (4*S*) stereochemistry as the coupling constants of the appropriate hydrogens were similar to those of the corresponding hydrogens in isomer **5**.

These isomers must, therefore, be epimeric at C-6. We were not able to assign stereochemistry to this centre in these compounds from the ^{1}H-NMR spectra, even if we assumed the hydrogen bonded conformations **5a** and **6a**, since, although the coupling constant, $J_{4,6}$ was 7.9 Hz in the spectrum of the major isomer **5** which might imply these hydrogens to be *trans* diaxial as in **5a**, a sizeable NOE between these hydrogens was more in keeping with them being *gauche* as in **6a**. The coupling constant $J_{4,6}$ for the minor epimer **6** was 2.5 Hz. The minor isomer **7** from the reaction was shown to have (*R*)-stereochemistry at C-4, since H-3*S* at 2.4 ppm, defined by an NOE on irradiation of H-2 at 4.38 ppm, also showed an NOE when H-4 at 2.66 ppm was irradiated as shown in Fig. 1. There was also a small NOE to H-4 on irradiation of H-2.



5a **6a**

For our first reaction of the protected pyroglutamate **4** with a chiral aldehyde we chose D-(*R*)-glyceraldehyde acetonide **8**.[14] This was reacted with the anion of the protected pyroglutamate **4**, prepared using either LDA or LiHMDS in THF–HMPA, as shown in Scheme 3. A single product **9** was obtained from these



Scheme 3 (i) **8**–LDA or LiHMDS (75%).

reactions in 74% (LDA as base) and 76% (LiHMDS as base) yields respectively and its spectra indicated that it was a single diastereoisomer. NOE experiments (Fig. 2) defined the centre at

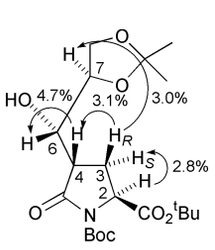
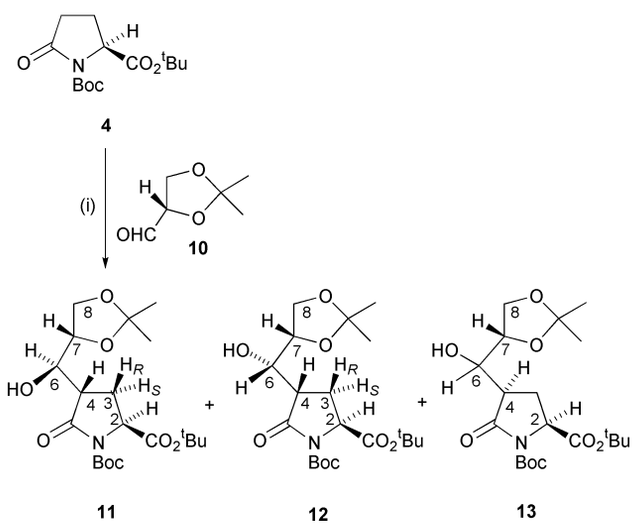


Fig. 2 Results of NOE experiments on the product **9**.

C-4 as (4*S*), with irradiation of H-2 at 4.39 ppm causing NOE to H-3*S* at 2.45 ppm, and irradiation of H-3*R* at 1.96 ppm causing NOE H-4 at d 2.94 ppm. Reaction had therefore occurred from the less hindered side of the molecule, a fact which was confirmed by an X-ray crystal structure[1] which showed that the other chiral centre created in the reaction had (6*S*) stereochemistry. A coupling constant, $J_{4,6}$, of 2.5 Hz suggested a *gauche* relationship between these hydrogens in solution and the X-ray crystal structure[1] indicated that this was so in the solid state, although the distance between the 6-OH and the C-5 carbonyl group was larger than hydrogen bonding difference. When HMPA was omitted from the reaction, a crystalline product running as a single spot on TLC was obtained in 67% yield. The NMR spectra indicated that this was a mixture containing the product **9** and a minor diastereoisomer in a ratio of *ca.* 12.5 : 1. The signals of the minor isomer in the NMR spectrum were not well enough resolved for us to speculate on its stereochemistry.

When L-(*S*)-glyceraldehyde **10**[15] was used in the aldol condensation with the protected pyroglutamic acid **4** using LiHMDS in THF–HMPA, the product proved to be a mixture of three diastereoisomers as shown in Scheme 4. These were



Scheme 4 (i) **10**–LiHMDS (66% [1 : 1 ratio of **11** : **12**, with **13** = minor isomer]).

chromatographically separated into a major fraction (66%) containing two diastereoisomers **11** and **12** in a 1 : 1 ratio and a minor fraction **13**. The major fractions were separated by crystallisation. The X-ray crystal structure of the major isomer **11** indicated that it was the (2*S*,4*S*,6*R*,7*S*)-isomer.[1] The relevant coupling constants in the second major isomer **12** indicated that it also had a *trans*-relationship between the substituents at C-2 and C-4. This was confirmed by NOE data (Fig. 3), since irradiation of H-2 at 4.45 ppm caused enhancement of H-3*S* at 2.5 ppm, and irradiation of H-4 at 2.7 ppm caused an NOE to H-3*R* at 2.01 ppm. The second major isomer was therefore the (2*S*,4*S*,6*S*,7*S*)-isomer **12**. The minor isomer had coupling constants in keeping with it being one of the *cis*-diastereoisomers

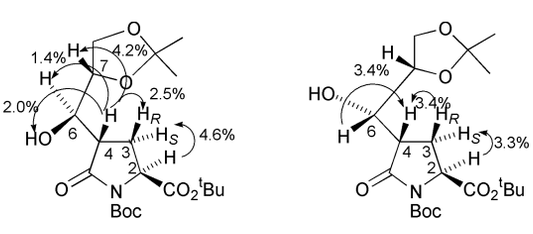
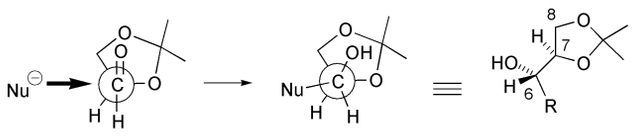


Fig. 3 Results of NOE experiments on the products **11** and **12**.

13. In an attempt to improve the diastereoselectivity in this reaction, the pyroglutamate **4** was reacted with $TiCl_4$ and diisopropylethylamine in dichloromethane at −78 °C followed by addition of the aldehyde **10**. The product, obtained in 88% yield, was predominantly a 1 : 1 mixture of the two *trans* isomers **11** and **12** containing a very small amount of the *cis*-diastereoisomer **13**. Use of $ZnBr_2$ in the reaction failed to give better stereoselectivity.

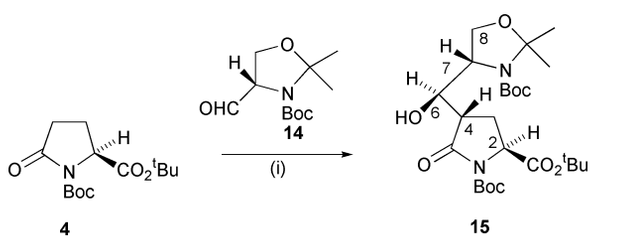
The reaction of the protected pyroglutamate **4** with the D-(*R*)-aldehyde **8** is evidently a good example of double stereodifferentiation[16] in which the enolate of **4** and the aldehyde **8** are a matched pair, leading to the formation of the observed single diastereoisomer **9**. This is not the case for reaction of the enolate of the pyroglutamate **4** with the enantiomeric aldehyde **10** where we have a mismatched pair. The stereochemistry in **9** is that expected of Felkin Ahn control as shown in Scheme 5 or of chelation to the β-oxygen group in **8**.



8a **9a** **9**

Scheme 5

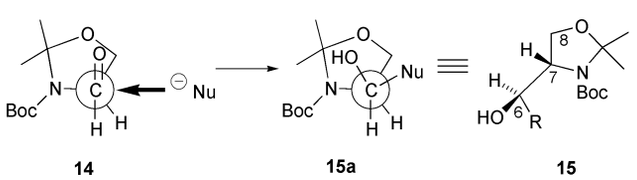
Our interest in analogues of L,L-diaminopimelic acid as potential antibacterial drugs[8] made the reaction of the protected pyroglutamate **4** with the (*S*)-"Garner" aldehyde **14**[17] of interest. This was carried out in THF–HMPA in the presence of LiHMDS as shown in Scheme 6. The ^{1}H-NMR spectrum of the



4 **15**

Scheme 6 (i) **14**–LiHMDS (58%).

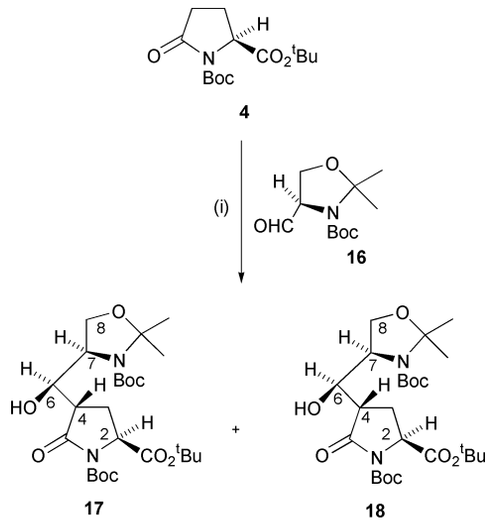
product was complicated by rotational isomerism but variable temperature ^{1}H-NMR spectroscopy showed that the reaction had predominantly given one diastereoisomer together with a small amount of a minor isomer. The products were obtained in a ratio of 19 : 1. The coupling constants in the ^{1}H NMR spectrum indicated that both isomers had *trans*-stereochemistry with respect to the centres C-2 and C-4 of the pyroglutamate ring and the fact that $J_{4,6}$ was 9.2 Hz in the major isomer suggested an *anti*-relationship between these protons in a hydrogen bonded model. Thus the predominant product appeared to have the (2*S*,4*S*,6*R*,7*S*)-stereochemistry of compound **15**. This is the product expected of Felkin Ahn control as shown in Scheme 7.



14 **15a** **15**

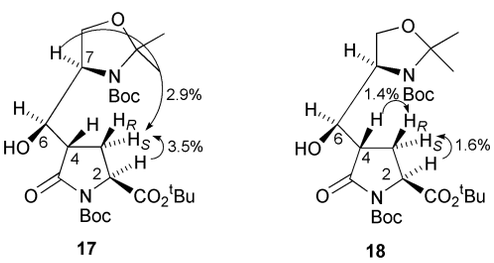
Scheme 7

When the (*R*)-Garner aldehyde **16** was used in this reaction, the major isomer **17** was obtained in 64% yield together with a 21% yield of a minor isomer **18** (Scheme 8). The ^{1}H NMR spectra of these compounds was not complicated by rotational isomerism, as had been the case with compound **15** and NOE experiments (Fig. 4) and coupling in the ^{1}H-NMR spectrum



4 **16** **17** **18**

Scheme 8 (i) **16**–LDA or LiHMDS (64% **17** + 21% **18**).

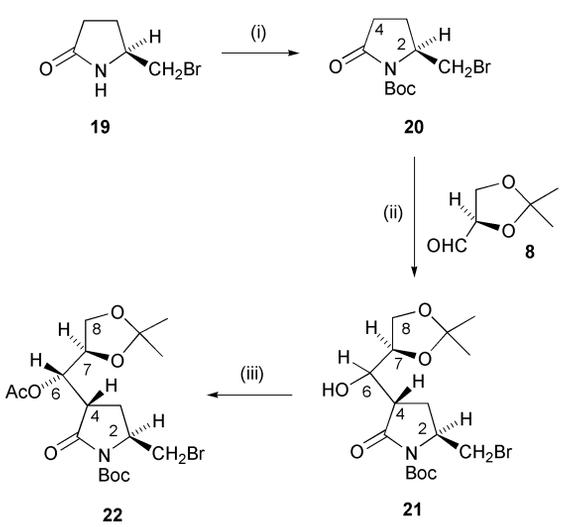


17 **18**

Fig. 4 Results of NOE experiments on the products **17** and **18**.

suggested that both isomers had *trans*-stereochemistry with respect to the substituents on the pyroglutamate ring. $J_{4,6}$ for the minor isomer was 9.4 Hz, suggesting an *anti* relationship between H-4 and H-6 in a hydrogen bonded ring and $J_{4,6}$ for the major isomer was 2.2 Hz suggesting *gauche* relationship between these hydrogens. X-Ray crystal structure analysis[1] confirmed that the major isomer had (2*S*,4*S*,6*S*,7*R*) stereochemistry as shown in **17**. This was again in keeping with a Felkin Ahn model and it seemed that reaction of the enolate of **4** with the (*S*)-aldehyde **14** represented reaction of a matched pair whereas reaction of this enolate with the (*R*)-aldehyde **16** represented reaction of a mismatched pair.

Much of the early synthetic work using pyroglutamate as a homochiral synthon was conducted using derivatives of pyroglutamic acid in which the C-2 ester functionality had been reduced. It was, therefore, of interest to see whether the



19 **20** **8** **22** **21**

Scheme 9 (i) Boc_2O–DMAP–CH_3CN, 0 °C (66%); (ii) **8**–LiHMDS (80%); (iii) Ac_2O–pyridine–DMAP (62% **22** + 7% diastereoisomer).

excellent stereoselectivity obtained for the matched pairs above might apply to the protected bromide **20** which we prepared from bromide **19**.[18] When the anion of bromide **20** was prepared using LiHMDS–THF–HMPA and reacted with aldehyde **8**, a mixture of stereoisomers **21** was obtained which were derivatised as their acetates. The ratio of diastereoisomeric acetates in the crude mixture was estimated to be 1.4 : 1 by ^{1}H NMR spectroscopy and, on flash chromatography, the major isomer **22**, obtained in 62% yield, was shown by X-ray crystallography[1] to be the (2*S*,4*S*,6*S*,7*R*) isomer (Scheme 9). The stereochemistry of the new centres in this isomer was the same as was found for the sole product **9** from the corresponding reaction using the anion of the pyroglutamic urethane ester **4**, although the degree of stereoselectivity was evidently of a different order.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotation measurements (in units of 10^{-1} deg cm^2 g^{-1}) were obtained on a Perkin Elmer PE 241 polarimeter, using a 1 dm path length micro cell. IR spectra were recorded on a Perkin Elmer 1710 Fourier transform instrument. UV spectra were recorded on ATI Unicam UV2–100 and Philips PU8720 UV–VIS Fourier transform scanning spectrophotometers. ε values are given in dm^3 mol^{-1} cm^{-1}. Microanalyses were performed at the Wellcome Research Laboratories, Beckenham and at Glaxo-Wellcome, Stevenage. ^{1}H NMR spectra were recorded on Bruker WM 360 (360 MHz), Bruker DPX 300 (300 MHz) and Bruker AMX 500 Fourier transform instruments. ^{13}C NMR spectra were recorded on Bruker DPX 300 (75.48 MHz) and Bruker AMX 500 (125.76 MHz) Fourier transform instruments. INEPT and DEPT experiments were used to help assign ^{13}C resonances where necessary. Residual undeuteriated solvent peaks were used as internal references. All *J* values are given in Hz. Mass spectra were recorded on Kratos MS80RF and Fisons Instruments VG Auto Spec double focusing spectrometers by Mr A. M. Greenway and Dr A. Abdul-Sada. Accurate mass measurements were carried out by the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea. Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh) – Art. 9385 and Sorbsil C60 40/60 A. Petroleum ether refers to the fraction of alkanes of bp 40–60 °C.

tert-Butyl(2*S*,4*RS*)-*N*-*tert*-butoxycarbonyl-4-[(1*RS*)-1-hydroxyprop-2-enyl]pyroglutamate (5, 6 and 7)

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (1.034 g, 3.62 mmol) was dissolved in tetrahydrofuran (20 ml) under argon with stirring and the solution was cooled to −78 °C. Lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 4.53 ml, 4.53 mmol) was added and the mixture was stirred for 1 h at −78 °C. Acrolein (0.27 g, 4.82 mmol) was added dropwise to the reaction mixture and stirring was continued for a further 4 h at low temperature. Saturated aqueous ammonium chloride (10 ml) was added and the mixture was allowed to warm to room temperature. The product was extracted with diethyl ether (3 × 20 ml). The extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the crude product as a yellow viscous oil. The crude product was a mixture of three diastereoisomers which were purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant. The *trans* products, *tert-butyl (2S,4S)-N-tert-butoxycarbonyl-4-[(1R)-1-hydroxyprop-2-enyl]pyroglutamate* **5** and *(2S,4S)-N-tert-butoxycarbonyl-4-[(1S)-1-hydroxyprop-2-enyl]pyroglutamate* **6**, were obtained as a clear colourless oil (0.515 g, 42%) as a 1.6 : 1 mixture which could not be separated; (*m*/*z* (FAB, PEG/3-NBA) Found 342.1918, $C_{17}H_{28}NO_6$ (M + H) requires 342.19166); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 342 [M + H]$^+$ and 364 [M + Na]$^+$; ν_{max} (film)/cm^{-1} 3491 (br, OH), 1789 (urethane) and 1740 (ester); δ_H (**5**) (500 MHz, $C_6{}^2H_6$) 5.75 (1H, ddd, $J_{7,8Z}$ 16.9, $J_{7,8E}$ 10.5, $J_{7,6}$ 7.9, H-7), 5.36 (1H, dt, $J_{8Z,7}$ 16.9, $J_{8Z,8E}$ 1.2, H-8*Z*), 5.09 (1H, dt, $J_{8E,7}$ 10.5, $J_{8E,8Z}$ 1.2, H-8*E*), 4.41 (1H, dd, $J_{2,3S}$ 9.8, $J_{2,3R}$ 1.3, H-2), 4.32 (1H, br s, OH), 4.23 (1H, t, $J_{6,7} = J_{6,4}$ 7.9, H-6), 2.83 (1H, ddd, $J_{4,6}$ 7.9, $J_{4,3R}$ 8.8, $J_{4,3S}$ 11.6, H-4), 1.86 (1H, ddd, $J_{3R,3S}$ 11.8, $J_{3R,4}$ 8.8, $J_{3R,2}$ 1.3, H-3*R*), 1.61 (1H, ddd, $J_{3R,3S}$ 11.8, $J_{3S,4}$ 11.6, $J_{3S,2}$ 9.8, H-3*S*), 1.51 (9H, s, $OC(CH_3)_3$) and 1.39 (9H, s, $OC(CH_3)_3$); δ_C (**5**) (125.76 MHz, $C_6{}^2H_6$) 174.5 (CON), 170.4 (ester), 150.1 (urethane), 137.4 (C-7), 116.5 (C-8), 83.1 ($OC(CH_3)_3$), 81.9 ($OC(CH_3)_3$), 73.5 (C-6), 58.0 (C-2), 46.9 (C-4), 27.9 ($OC(CH_3)_3$), 27.7 ($OC(CH_3)_3$) and 24.7 (C-3); δ_H (**6**) (500 MHz, $C_6{}^2H_6$) 5.63 (1H, ddd, $J_{7,8Z}$ 16.0, $J_{7,8E}$ 10.6, $J_{7,6}$ 4.4, H-7), 5.43 (1H, dt, $J_{8Z,7}$ 16.0, $J_{8Z,8E}$ 1.5, H-8*Z*), 5.09 (1H, dt, $J_{8E,7}$ 10.6, $J_{8E,8Z}$ 1.5, H-8*E*), 4.87 (1H, br s, H-6), 4.54 (1H, dd, $J_{2,3S}$ 9.9, $J_{2,3R}$ 2.1, H-2), 3.31 (1H, br s, OH), 2.73 (1H, ddd, $J_{4,6}$ 2.5, $J_{4,3R}$ 9.4, $J_{4,3S}$ 11.2, H-4), 2.44 (1H, ddd, $J_{3S,3R}$ 12.3, $J_{3S,4}$ 11.2, $J_{3S,2}$ 9.9, H-3*S*), 1.81 (1H, ddd, $J_{3R,3S}$ 12.3, $J_{3R,4}$ 9.4, $J_{3R,2}$ 2.1, H-3*R*), 1.50 (9H, s, $OC(CH_3)_3$) and 1.42 (9H, s, $OC(CH_3)_3$); δ_C (**6**) (125.76 MHz, $C_6{}^2H_6$) 173.4 (CON), 171.1 (ester), 150.2 (urethane), 138.7 (C-7), 114.9 (C-8), 82.8 ($OC(CH_3)_3$), 81.5 ($OC(CH_3)_3$), 69.4 (C-6), 58.2 (C-2), 48.0 (C-4), 27.9 ($OC(CH_3)_3$), 27.8 ($OC(CH_3)_3$) and 21.7 (C-3).

The *cis* product, *tert-butyl (2S,4R)-N-tert-butoxycarbonyl-4-[(1R or 1S)-1-hydroxyprop-2-enyl]pyroglutamate* **7** was obtained as a clear colourless oil (0.027 g, 2%); $[\alpha]_D^{27.5}$ −18.2 (*c* 2.0, $CHCl_3$); (*m*/*z* (FAB, PEG/3-NBA) Found 341.181903, $C_{17}H_{27}NO_6$ ([M]$^+$) requires 341.183838); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 342 [M + H]$^+$ and 364 [M + Na]$^+$; ν_{max} (film)/cm^{-1} 3496 (br, OH), 1785 (urethane) and 1742 (ester); δ_H (500 MHz, C^2HCl_3) 5.76 (1H, ddd, $J_{7,8Z}$ 17.2, $J_{7,8E}$ 10.4, $J_{7,6}$ 6.9, H-7), 5.33 (1H, dt, $J_{8Z,7}$ 17.2, $J_{8Z,8E}$ 1.2, H-8*Z*), 5.25 (1H, dt, $J_{8E,7}$ 10.4, $J_{8E,8Z}$ 1.2, H-8*E*), 4.38 (1H, dd, $J_{2,3S}$ 8.9, $J_{2,3R}$ 6.9, H-2), 4.31 (1H, dd, $J_{6,7}$ 6.9, $J_{6,4}$ 8.2, H-6), 4.02 (1H, br s, OH), 2.66 (1H, ddd, $J_{4,6}$ 8.2, $J_{4,3R}$ 8.5, $J_{4,3S}$ 10.0, H-4), 2.40 (1H, ddd, $J_{3S,3R}$ 13.6, $J_{3S,4}$ 10.0, $J_{3S,2}$ 8.9, H-3*S*), 1.66 (1H, ddd, $J_{3R,3S}$ 13.6, $J_{3R,4}$ 8.5, $J_{3R,2}$ 6.9, H-3*R*), 1.52 (9H, s, $OC(CH_3)_3$) and 1.49 (9H, s, $OC(CH_3)_3$); δ_C (125.76 MHz, C^2HCl_3) 175.1 (CON), 170.0 (ester), 149.1 (urethane), 136.7 (C-7), 118.0 (C-8), 84.0 ($OC(CH_3)_3$), 82.4 ($OC(CH_3)_3$), 73.9 (C-6), 58.0 (C-2), 47.1 (C-4), 27.9 ($OC(CH_3)_3$), 27.9 ($OC(CH_3)_3$) and 24.2 (C-3).

tert-Butyl (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-[(1*S*,2*R*)-2,3-*O*-isopropylidene-(1,2,3-trihydroxypropyl)]pyroglutamate (9)

Method A. Butyllithium (2.5 M in hexane, 0.312 ml, 0.78 mmol) was added dropwise to a stirred mixture of tetrahydrofuran (10 ml), HMPA (1.1 ml) and diisopropylamine (0.119 ml, 0.85 mmol) under argon at −78 °C. After 30 min a solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (0.203 g, 0.71 mmol) in tetrahydrofuran (4 ml) was added dropwise under argon and stirring at −78 °C was continued for 30 min. A solution of freshly prepared D-(*R*)-glyceraldehyde acetonide **8**[14] (0.177 g, 1.36 mmol) in tetrahydrofuran (5 ml) was added dropwise under argon and stirring was continued for 1 h at −78 °C. Saturated aqueous ammonium chloride (5 ml) was added at −78 °C and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with diethyl ether (3 × 15 ml). The combined organic extracts were washed with water (15 ml) and 10% aqueous sodium chloride and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude product as a pale yellow oil which was purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant. A clear colourless oil was obtained which crystallised on standing overnight to give *tert-butyl (2S,4S)-N-tert-butoxycarbonyl-4-[(1S,2R)-2,3-O-isopropylidene-(1,2,3-trihydroxypropyl)]pyroglutamate* **9** as a colourless crystalline solid (0.217 g, 74%); mp 136.0–138.0 °C; $[\alpha]_D^{19}$ −43.1 (*c* 1.0, $CHCl_3$) (Found: C, 58.05;

H, 8.1; N, 3.4. $C_{20}H_{33}NO_8$ requires C, 57.8; H, 8.0; N, 3.4%); *m/z* [+ve FAB (3-NBA/CH_2Cl_2)] 416 ([M + H]$^+$), 438 ([M + Na]$^+$) and 853 ([2M + Na]$^+$); ν_{max} (KBr)/cm^{-1} 3467 (br, OH), 1795 (imide/urethane), 1736 (ester) and 1716; δ_H (300 MHz, C^2HCl_3) 4.39 (1H, dd, $J_{2,3S}$ 10.1, $J_{2,3R}$ 1.2, H-2), 4.13 (1H, dd, $J_{6,7}$ 8.2, $J_{6,4}$ 2.5, H-6), 4.04 (1H, dd, $J_{8A,8B}$ 5.5, $J_{8A,7}$ 8.3, H-8A), 3.92 (1H, dd, $J_{8B,8A}$ 5.5, $J_{8B,7}$ 13.3, H-8B), 3.87 (1H, m, H-7), 3.01 (1H, br s, OH), 2.94 (1H, ddd, $J_{4,3S}$ 11.0, $J_{4,3R}$ 9.1, $J_{4,6}$ 2.5, H-4), 2.45 (1H, ddd, $J_{3S,4}$ 11.0, $J_{3S,3R}$ 10.3, $J_{3S,2}$ 10.1, H-3*S*), 1.96 (1H, ddd, $J_{3R,3S}$ 10.3, $J_{3R,4}$ 9.1, $J_{3R,2}$ 1.2, H-3*R*), 1.43 (9H, s, $OC(CH_3)_3$), 1.42 (9H, s, $(OC(CH_3)_3)$, 1.33 (3H, s, CH_3) and 1.26 (3H, s, CH_3); the broad OH signal at δ 3.01 ppm disappeared upon addition of $C^2H_3O^2H$; δ_C (75.47 MHz, C^2HCl_3) 175.2 (CON), 170.9 (ester), 149.6 (urethane), 110.0 (C-9), 83.9 ($OC(CH_3)_3$), 82.8 ($OC(CH_3)_3$), 76.3 (C-7), 70.3 (C-6), 67.7 (C-8), 58.5 (C-2), 45.4 (C-4), 28.4 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 27.2, 25.7 (C-10/C-11) and 22.1 (C-3).

The structure of this compound was confirmed by **single crystal X-ray diffraction analysis**, reported in our preliminary communication[1] and atomic coordinate data were lodged with the Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW at that time. They are available on request from the Director of the CCDC at the above address, quoting CCDC no 165619 (ref code QODPAA).

Method B. *tert*-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (0.200 g, 0.70 mmol) was dissolved in a mixture of tetrahydrofuran (10 ml) and HMPA (1.1 ml) under argon with stirring. The solution was cooled to −78 °C and LiHMDS (1.0 M in tetrahydrofuran, 0.77 ml, 0.77 mmol) was added. The reaction was stirred for 45 min at −78 °C and a solution of freshly prepared (D)-*R*-glyceraldehyde acetonide **8**[14] (0.219 g, 1.68 mmol) in tetrahydrofuran (10 ml) was added dropwise under argon. Stirring was continued at −78 °C for 1.3 h. Saturated aqueous ammonium chloride (8 ml) was added and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with diethyl ether (3 × 15 ml). The organic extracts were washed with water (15 ml) and 10% aqueous sodium chloride (15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product **9** as a clear colourless oil (0.273 g, 94%) which crystallised on standing overnight. Purification by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant, gave the product as a white crystalline solid (0.217 g, 74%) identical in all respects with the product from Method A.

Method C. *tert*-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (0.201 g, 0.70 mmol) was dissolved in tetrahydrofuran (10 ml) under argon with stirring. The solution was cooled to −78 °C and LiHMDS (1.0 M in tetrahydrofuran, 0.77 ml, 0.77 mmol) was added. The reaction was stirred for 30 min at −78 °C and a solution of freshly prepared (D)-(*R*)-glyceraldehyde acetonide **8**[14] (0.205 g, 1.56 mmol) in tetrahydrofuran (10 ml) was added dropwise under argon. Stirring was continued at −78 °C for 1.2 h. Saturated aqueous ammonium chloride (8 ml) was added and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with diethyl ether (3 × 15 ml). The organic extracts were washed with water (15 ml) and 10% aqueous sodium chloride (15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as a pale yellow oil. Purification by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant, gave a white crystalline solid (0.194 g, 67%) which was an inseparable mixture of two diastereoisomers of **9**. The ratio of the two diastereoisomers, obtained from the integration in the ^{1}H NMR spectrum, was approximately 1.5 : 1. The major diastereoisomer *tert-butyl (2S,4S)-N-tert-butoxycarbonyl-4-[(1S,2R)-2,3-O-isopropylidene-(1,2,3-trihydroxypropyl)]pyroglutamate* **9** had the same spectral characteristics as the single diastereoisomeric product of Method A. The minor diastereoisomer **9b** was not separable from **9** and most of the signals in the ^{1}H NMR spectrum, both in C^2HCl_3 and $C_6{}^2H_6$, were obscured by those of the major diastereoisomer **9**. The signals in the ^{1}H NMR spectrum which were identified as being those of the minor diastereoisomer were as follows: δ_H (360 MHz, C^2HCl_3) 4.39 (0.4H, t, $J_{6,7} = J_{6,4}$ 8.0, H-6), 4.28 (0.4H, d, $J_{OH,2}$ 2.3, OH), 2.98 (0.4H, dd, H-4), 2.59 (0.4H, m, H-3*S*), 1.95 (0.4H, m, H-3*R*), 1.44 (1.2H, s, CH_3) and 1.37 (1.2H, s, CH_3).

tert-Butyl (2*S*,4*RS*)-*N*-*tert*-butoxycarbonyl-4-[(1*RS*, 2*S*)-2,3-*O*-isopropylidene-(1,2,3-trihydroxypropyl)]pyroglutamate (11, 12 and 13)

Method A. *tert*-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (0.292 g, 1.02 mmol) was dissolved in tetrahydrofuran (15 ml) and HMPA (1.65 ml) under argon with stirring. The solution was cooled to −78 °C and LiHMDS (1.0 M in tetrahydrofuran, 1.12 ml, 1.12 mmol) was added. The reaction was stirred for 35 min at −78 °C and a solution of freshly prepared L-(*S*)-glyceraldehyde acetonide **10**[15] (0.266 g, 2.05 mmol) in tetrahydrofuran (3.5 ml) was added dropwise under argon. Stirring was continued for 1 h at −78 °C. Saturated aqueous ammonium chloride (8 ml) was added and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with diethyl ether (4 × 15 ml). The organic extracts were washed with water (2 × 15 ml) and 10% aqueous sodium chloride (15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as a clear pale yellow oil (0.386 g, 91%) which partially crystallised on standing overnight. This was a mixture of three diastereoisomers **11**, **12** and **13** together with unreacted starting material **4**. Purification by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant, partially separated these components. The major diastereoisomers *tert-butyl (2S,4S)-N-tert-butoxycarbonyl-4-[(1R and 1S,2S)-2,3-O-isopropylidene-(1,2,3-trihydroxypropyl)]pyroglutamate* **11** and **12**, both of which were *trans*-diastereoisomers, were separated from one another by recrystallisation from diethyl ether which provided two distinct crystalline forms which were separated manually. The (2*S*,4*S*,6*R*,7*S*) diastereoisomer **11** was clear colourless solid needle crystals; mp 170.0–171.5 °C; $[\alpha]_D^{20}$ +3.4 (*c* 1.0, $CHCl_3$) (Found: C, 57.7; H, 8.1; N, 3.3. $C_{20}H_{33}NO_8$ requires C, 57.8; H, 8.0; N, 3.4%); *m/z* [+ve FAB (3-NBA/CH_2Cl_2)] 416 ([M + H]$^+$), 438 ([M + Na]$^+$) and 853 [2M + Na]$^+$; ν_{max} (KBr)/cm^{-1} 3432 (br, OH), 1782 (imide/urethane), 1735 (ester) and 1720; δ_H (500 MHz, $C_6{}^2H_6$) 4.63 (1H, d, $J_{OH,6}$ 2.2, OH), 4.35 (1H, dd, $J_{2,3S}$ 9.7, $J_{2,3R}$ 1.2, H-2), 4.04 (1H, dd, $J_{8A,8B}$ 8.8, $J_{8A,7}$ 5.7, H-8A), 3.99 (1H, dd, $J_{8A,8B}$ 8.8, $J_{8B,7}$ 6.2, H-8B), 3.83 (1H, m, $J_{7,6}$ 8.4, $J_{7,8A}$ 5.7, $J_{7,8B}$ 6.2, H-7), 3.39 (1H, dt, $J_{6,7} = J_{6,4}$ 8.4, $J_{6,OH}$ 2.2, H-6), 2.79 (1H, m, $J_{4,3S}$ 12.1, $J_{4,3R}$ 8.6, $J_{4,6}$ 8.4, H-4), 2.15 (1H, ddd, $J_{3R,3S}$ 11.9, $J_{3R,4}$ 8.6, $J_{3R,2}$ 1.2, H-3*R*), 1.77 (1H, ddd, $J_{3S,4}$ 12.1, $J_{3S,3R}$ 11.9, $J_{3S,2}$ 9.7, H-3*S*), 1.42 (9H, s, $(OC(CH_3)_3)$, 1.27 (9H, s, $(OC(CH_3)_3)$, 1.27 (3H, s, CH_3) and 1.18 (3H, s, CH_3); the O*H* signal at δ 4.63 ppm disappeared upon addition of $C^2H_3O^2H$; δ_C (75.48 MHz, $C_6{}^2H_6$) 175.6 (CON), 170.7 (ester), 150.4 (urethane), 109.7 (C-9), 83.3 ($OC(CH_3)_3$), 82.1 ($OC(CH_3)_3$), 78.7 (C-7), 74.4 (C-6), 68.1 (C-8), 58.5 (C-2), 46.0 (C-4), 28.1($OC(CH_3)_3$), 27.9 ($OC(CH_3)_3$), 26.9, 25.6 (C-10/C-11) and 26.2 (C-3).

The structure of this compound was confirmed by **single crystal X-ray diffraction analysis**, reported in our preliminary communication[1] and atomic coordinate data were lodged with the Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW at that time. They are available on request from the Director of the CCDC at the above address, quoting CCDC no 165618 (ref code QODNUS).

The (2*S*,4*S*,6*S*,7*S*) diastereoisomer **12** was very fine white needle crystals; mp 160.0–163.0 °C; $[a]_D^{28}$ −24.9 (*c* 1.0, $CHCl_3$) (Found: C, 57.8; H, 8.2; N, 3.2. $C_{20}H_{33}NO_8$ requires C, 57.8; H, 8.0; N, 3.4%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 416 ($[M + H]^+$), 438 ($[M + Na]^+$) and 853 ($[2M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3434 (br, OH), 1785, (imide/urethane), 1726 (ester) and 1711; δ_H (300 MHz, C^2HCl_3) 4.45 (1H, dd, $J_{2,3S}$ 9.8, $J_{2,3R}$ 1.4, H-2), 4.22 (1H, ddd, $J_{7,6}$ 5.6, $J_{7,8A}$ 6.6, $J_{7,8B}$ 6.4, H-7), 4.10 (1H, dd, $J_{6,7}$ 5.6, $J_{6,4}$ 3.5, H-6), 4.03 (1H, dd, $J_{8A,8B}$ 8.3, $J_{8A,7}$ 6.6, H-8A), 3.82 (1H, dd, $J_{8A,8B}$ 8.3, $J_{8B,7}$ 6.4, H-8B), 2.70 (1H, ddd, $J_{4,3S}$ 11.3, $J_{4,3R}$ 9.0, $J_{4,6}$ 3.5, H-4), 2.56–2.44 (1H, br s, OH), 2.50 (1H, ddd, $J_{3S,4}$ 11.3, $J_{3S,3R}$ 10.3, $J_{3S,2}$ 9.8, H-3*S*), 2.01 (1H, ddd, $J_{3R,3S}$ 10.3, $J_{3R,4}$ 9.0, $J_{3R,2}$ 1.4, H-3*R*), 1.49 (9H, s, $OC(CH_3)_3$), 1.47 (9H, s, $OC(CH_3)_3$), 1.43 (3H, s, CH_3) and 1.35 (3H, s, CH_3); the broad OH signal at δ 2.56–2.44 ppm disappeared upon addition of $C^2H_3O^2H$; δ_C (75.48 MHz, C^2HCl_3) 173.8 (CON), 171.0 (ester), 149.6 (urethane), 110.3 (C-9), 83.9 ($OC(CH_3)_3$), 82.8 ($OC(CH_3)_3$), 77.9 (C-7), 69.9 (C-6), 66.4 (C-8), 58.3 (C-2), 45.8 (C-4), 28.4 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 26.8, 25.6 (C-10/C-11) and 23.1 (C-3).

The minor (2*S*,4*R*,6*R*,7*S*) diastereoisomer **13**, was not separable from the unreacted starting material **4** and some of the signals in the ^1H NMR spectrum in deuteriated chloroform were obscured by those of the starting material **4**. The signals in the ^1H NMR spectrum which were identified as being those of the minor diastereoisomer **13** were δ_H (360 MHz, C^2HCl_3) 4.41 (1H, dd, $J_{2,3S}$ 8.9, $J_{2,3R}$ 7.2, H-2), 4.14–3.94 (5H, m, OH, H-6, H-8A, H-8B and H-7), 2.95 (1H, ddd, $J_{4,3R}$ 9.9, $J_{4,3S}$ 9.0, $J_{4,6}$ 3.0, H-4), 2.42 (1H, m, H-3), 2.12 (1H, m, H-3), 1.50 (9H, s, $OC(CH_3)_3$), 1.47 (9H, s, $OC(CH_3)_3$), 1.39 (3H, s, CH_3) and 1.32 (3H, s, CH_3).

Method B. *tert*-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (0.348 g, 1.22 mmol) was dissolved in anhydrous dichloromethane (8 ml) under argon with stirring. The solution was cooled to −78 °C and $TiCl_4$ (1.0 M in CH_2Cl_2, 1.34 ml, 1.34 mmol) was added, followed after 5 min by dropwise addition of *N*,*N*-diisopropylethylamine (0.189 g, 1.46 mmol). The reaction mixture turned deep purple in colour and was stirred for 4.5 h at −78 °C. A solution of freshly prepared L-(*S*)-glyceraldehyde acetonide **10**[15] (0.221 g, 1.7 mmol) in dichloromethane (6 ml) was added dropwise under argon. Stirring was continued at −78 °C for 2.2 h. Saturated aqueous ammonium chloride (8 ml) was added and the reaction mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with dichloromethane (5 × 15 ml). The organic extracts were washed with water (15 ml) and 10% aqueous sodium chloride (2 × 15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as a clear pale orange oil (0.448 g, 88%) which crystallised on standing overnight. This was a mixture of each of the two *trans*-diastereoisomers **11** and **12** in a (1 : 1) ratio, together with a trace amount of the *cis*-diastereoisomer **13**. We did not attempt to separate the diastereoisomeric components of the crude product mixture and they were identified by comparison of the ^1H NMR spectrum of the crude product with the ^1H NMR spectra obtained from the purified diastereoisomers, described in method A above.

tert-Butyl (2*S*,4*S*,6*R*)-*N*-*tert*-butoxycarbonyl-4-[(4*S*)-2,2-dimethyl-3-*tert*-butoxycarbonyloxazolidin-4-ylhydroxymethyl]-pyroglutamate (15)

tert-Butyl *N*-*tert*-butoxycarbonyl-(2*S*)-pyroglutamate **4**[3] (0.506 g, 1.77 mmol) was dissolved in a mixture of tetrahydrofuran (15 ml) and HMPA (1.65 ml) under argon with stirring. The solution was cooled to −78 °C and LiHMDS (1.0 M in tetrahydrofuran, 1.95 ml, 1.95 mmol) was added. The reaction was stirred for 1 h at −78 °C and a solution of (4*S*)-2,2-dimethyl-4-formyl-3-*tert*-butoxycarbonyloxazolidine **14**[17] (0.448 g, 1.95 mmol) in tetrahydrofuran (4 ml) was added under argon. Stirring was continued at −78 °C for 2.2 h. Saturated aqueous ammonium chloride (8 ml) was added and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the mixture was extracted with diethyl ether (4 × 15 ml). The organic extracts were washed with water (2 × 15 ml) and 10% aqueous sodium chloride (15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the crude product as a clear pale yellow oil which crystallised as a pale yellow crystalline solid. Flash column chromatography on silica gel, using petroleum ether–ethyl acetate (3 : 2) as eluant gave the product *tert-butyl (2S,4S,6R)-N-tert-butoxycarbonyl-4-[(4S)-2,2-dimethyl-3-tert-butoxycarbonyloxazolidin-4-ylhydroxymethyl]-pyroglutamate* **15** as a white chalky solid (0.527 g, 58%) shown by ^1H NMR spectroscopic analysis in $(C^2H_3)_2SO$ at 343 K (70 °C) to contain 5% of the 6*S* diastereoisomer and a small amount of starting material **4**. We were unable to separate the 19 : 1 mixture of diastereoisomers by flash column chromatography on silica gel but could remove the starting material by recrystallisation from diethyl ether. The product was a white amorphous solid, mp 156.5–159.0 °C and 162.0–163.0 °C (Found: C, 58.15; H, 8.4; N, 5.4. $C_{25}H_{42}N_2O_9$ requires C, 58.35; H, 8.2; N, 5.4%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 515 ($[M + H]^+$) and 537 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3485 (br, OH), 1768 (imide/urethane), 1741 (ester) and 1700. We were able to assign the signals for the major diastereoisomer **15** δ_H (500 MHz, $(C^2H_3)_2SO$, 343 K) 5.16 (1H, d, $J_{OH,6}$ 5.8, OH), 4.40 (1H, dd, $J_{2,3S}$ 9.7, $J_{2,3R}$ 2.1, H-2), 4.18 (1H, t, $J_{7,6} = J_{7,8A} = J_{7,8B}$ 5.6, H-7), 4.12 (1H, dd, $J_{8A,8B}$ 8.9, $J_{8A,7}$ 1.7, H-8A), 3.82 (1H, dd, $J_{8B,8A}$ 8.9, $J_{8B,7}$ 5.6, H-8B), 3.70 (1H, dd, $J_{6,7}$ 5.6, $J_{6,4}$ 9.2, H-6), 2.79 (1H, m, $J_{4,3S}$ 3.6, $J_{4,3R}$ 10.0, $J_{4,6}$ 9.2, H-4), 2.36 (1H, m, H-3*S*), 1.98 (1H, ddd, $J_{3R,3S}$ 11.2, $J_{3R,4}$ 10.0, $J_{3R,2}$ 2.1, H-3*R*), 1.44–1.40 (27H, 3 × s, $OC(CH_3)_3$), and (6H, 2 × s, $C(CH_3)_2$); the OH signal at δ 5.16 ppm disappeared upon addition of ^2H_2O.

(4*R*)-2,2-Dimethyl-4-formyl-3-*tert*-butoxycarbonyloxazolidine (16)

Compound **16** was prepared using the method for the L (4*S*)-isomer[17] in 82% yield, $[a]_D^{26.5}$ +97.4 (*c* 1.34, $CHCl_3$) (lit.[19] $[a]_D$ +95 (*c* 1.34, $CHCl_3$)).

tert-Butyl (2*S*,4*S*,6*R* and 6*S*)-*N*-*tert*-butoxycarbonyl-4-[(4*R*)-2,2-dimethyl-3-*tert*-butoxycarbonyloxazolidin-4-ylhydroxymethyl]pyroglutamate (17 and 18)

tert-Butyl (2*S*)-*N*-*tert*-butoxycarbonylpyroglutamate **4**[3] (0.485 g, 1.70 mmol) was dissolved in a mixture of tetrahydrofuran (15 ml) and HMPA (1.65 ml) under argon with magnetic stirring. The solution was cooled to −78 °C and LiHMDS (1.0 M in tetrahydrofuran, 1.87 ml, 1.87 mmol) was added. The reaction mixture was stirred for 80 min at −78 °C and a solution of (4*R*)-2,2-dimethyl-4-formyl-3-*tert*-butoxycarbonyloxazolidine **16** (0.410 g, 1.79 mmol) in tetrahydrofuran (4 ml) under argon was added. Stirring was continued at −78 °C for 2.5 h. Saturated aqueous ammonium chloride (8 ml) was added and the mixture was allowed to warm to room temperature. Water (20 ml) was added and the mixture was extracted with diethyl ether (3 × 20 ml). The organic extracts were combined, washed with water (2 × 20 ml) and 10% aqueous sodium chloride (20 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the crude product as an orange oil which foamed under high vacuum. Purification by gravity elution on silica gel, using petroleum ether–ethyl acetate (2 : 1) as eluant, separated the two diastereoisomeric products **17** and **18**.

The minor diastereoisomer **18** crystallised as a white crystalline solid (0.186 g, 21%); mp 164.0–165.0 °C; $[a]_D^{27}$ +16.2 (*c* 1.0, $CHCl_3$) (Found: C, 58.3; H, 8.4; N, 5.3. $C_{25}H_{42}N_2O_9$ requires C, 58.35; H, 8.2; N, 5.4%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 515 ($[M + H]^+$) and 537 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3504 (br, OH), 1766 (imide/urethane), 1744 (ester) and 1694; δ_H (500 MHz, C^2HCl_3, ^2H_2O) 4.39 (1H, d, $J_{2,3S}$ 9.6, H-2), 3.92 (1H,

dd, $J_{7,8A} = J_{7,8B}$ 7.7, $J_{7,6}$ 1.4, H-7), 3.59 (2H, dd, $J_{8A,8B}$ 4.1, $J_{8A,7} = J_{8B,7}$ 7.7, H-8), 3.50 (1H, td, $J_{6,7}$ 1.4, $J_{6,4}$ 9.4, H-6), 2.70 (1H, dt, $J_{4,3S} = J_{4,3R}$ 9.6, $J_{4,6}$ 9.4, H-4), 2.21 (1H, dd, $J_{3R,3S}$ 12.9, $J_{3R,4}$ 9.6, H-3*R*), 1.91 (1H, dt, $J_{3S,3R}$ 12.9, $J_{3S,4} = J_{3S,2}$ 9.6, H-3*S*) and 1.44–1.35 (27H, 3 × s, $OC(CH_3)_3$) and (6H, 2 × s, $C(CH_3)_2$); the OH signal, previously seen at δ_H 5.25 ppm, disappeared upon addition of ^2H_2O; δ_C (75.48 MHz, C^2HCl_3) 178.1 (CON), 170.3 (ester), 156.6 (urethane), 149.1 (urethane), 126.3 (C-9), 84.5 ($OC(CH_3)_3$), 83.1 ($OC(CH_3)_3$), 80.2 ($OC(CH_3)_3$), 73.9 (C-7), 64.1 (C-8), 58.3 (C-2), 52.3 (C-6), 43.2 (C-4), 31.5 (C-10 and C-11), 28.6 ($OC(CH_3)_3$), 28.2 ($OC(CH_3)_3$), 28.2 ($OC(CH_3)_3$) and 25.5 (C-3).

The major diastereoisomer **17** crystallised as clear colourless crystals (0.558 g, 64%); mp 170.0–171.0 °C; $[\alpha]_D^{27.5}$ −16.7 (*c* 1.0, $CHCl_3$) (Found: C, 58.3; H, 8.3; N, 5.4. $C_{25}H_{42}N_2O_9$ requires C, 58.35; H, 8.2; N, 5.4%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 515 ($[M + H]^+$) and 537 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3504 (br, OH), 1774 (imide/urethane), 1734 (ester) and 1696; δ_H (500 MHz, C^2HCl_3) 5.40 (1H, d, $J_{OH,6}$ 7.6, OH), 4.42 (1H, dd, $J_{2,3S}$ 9.7, $J_{3,3R}$ 1.0, H-2), 4.28 (1H, dd, $J_{7,8A} = J_{7,8B}$ 2.4, $J_{7,6}$ 10.1, H-7), 4.08 (1H, dd, $J_{8A,8B}$ 11.6, $J_{8A,7}$ 2.4, H-8A), 3.62 (1H, dd, $J_{8B,8A}$ 11.6, $J_{8B,7}$ 2.4, H-8B), 3.49 (1H, tt, $J_{6,7}$ 10.1, $J_{6,OH}$ 7.6, $J_{6,4}$ 2.2, H-6), 2.91 (1H, td, $J_{4,3S} = J_{4,3R}$ 11.2, $J_{4,6}$ 2.2, H-4), 2.51 (1H, dt, $J_{3S,3R}$ 10.3, $J_{3S,4}$ 11.2, $J_{3S,2}$ 9.7, H-3*S*), 2.22 (1H, ddd, $J_{3R,3S}$ 10.3, $J_{3R,4}$ 11.2, $J_{3R,2}$ 1.0, H-3*R*) and 1.47–1.35 (27H, 3 × s, $OC(CH_3)_3$ and 6H, 2 × s, $OC(CH_3)_2$); the OH signal at δ 5.40 ppm disappeared upon addition of ^2H_2O; δ_C (75.48 MHz, C^2HCl_3) 177.5 (CON), 171.1 (ester), 156.2 (urethane), 149.6 (urethane), 126.3 (C-9), 84.2 ($OC(CH_3)_3$), 82.6 ($OC(CH_3)_3$), 79.7 ($OC(CH_3)_3$), 68.1 (C-7), 62.0 (C-8), 58.7 (C-2), 53.4 (C-6), 45.5 (C-4), 31.6 (C-10 and C-11), 28.7 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$) and 22.0 (C-3).

The structure of this compound was confirmed by **single crystal X-ray diffraction analysis**, reported in our preliminary communication[1] and atomic coordinate data were lodged with the Cambridge Crystallography Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW at that time. They are available on request from the Director of the CCDC at the above address, quoting CCDC no 165621 (ref code QODPII).

(5*S*)-5-Bromomethyl-*N*-*tert*-butoxycarbonylpyrrolidin-2-one (20)

(5*S*)-5-Bromomethylpyrrolidin-2-one (**19**)[18] (3.552 g, 19.95 mmol) was dissolved in acetonitrile (80 ml) under argon with stirring. The solution was cooled to 0 °C in an ice bath and 4-dimethylaminopyridine (0.244 g, 2.0 mmol) was added followed by a solution of di-*tert*-butyl dicarbonate (5.66 g, 25.93 mmol) in acetonitrile (30 ml). The mixture was allowed to warm to room temperature and stirred for 45 h. Removal of the solvent *in vacuo* gave a brown oil which was purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant. *(5*S)-5-Bromomethyl-N-tert-butoxycarbonylpyrrolidin-2-one (**20**) was obtained as a crystalline white solid (3.637 g, 66%); mp 69.0–70.0 °C; $[\alpha]_D^{22.5}$ −79.4 (*c* 3.0, $CHCl_3$) (Found: C, 43.3; H, 5.8; N, 5.2. $C_{10}H_{16}BrNO_3$ requires C, 43.2; H, 5.8; N, 5.0%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 278 and 280 $[M + H]^+$; ν_{max} (KBr)/cm^{-1} 1746 and 1708 (imide/urethane); δ_H (360 MHz, C^2HCl_3) 4.41 (1H, m, H-2), 3.63 (2H, m, CH_2Br), 2.71 (1H, dt, $J_{4S,4R}$ 18.0, $J_{4S,3S} = J_{4S,3R}$ 10.1, H-4*S*), 2.46 (1H, ddd, $J_{4R,4S}$ 18.0, $J_{4R,3R}$ 10.1, $J_{4R,3S}$ 3.2, H-4*R*), 2.21 (1H, m, H-3*S*), 2.05 (1H, m, H-3*R*) and 1.54 (9H, s, $(OC(CH_3)_3)$; δ_C (62.9 MHz, C^2HCl_3) 173.6 (CON), 149.6 (urethane), 83.5 ($OC(CH_3)_3$), 57.4 (C-2), 34.7 (CBr), 31.2 (C-4), 27.9 ($OC(CH_3)_3$) and 21.7 (C-3).

(3*S*,5*S*)-5-Bromomethyl-*N*-*tert*-butoxycarbonyl-3-[(1*S*,2*R*)-2,3-*O*-isopropylidene-(1,2,3-trihydroxypropyl)]pyrrolidin-2-one (21)

(5*S*)-5-Bromomethyl-*N*-*tert*-butoxycarbonylpyrrolidin-2-one (**20**) (0.563 g, 2.02 mmol) was dissolved in a mixture of tetrahydrofuran (13.5 ml) and HMPA (1.5 ml) under argon with magnetic stirring. The solution was cooled to −78 °C and LiHMDS (1.0 M in tetrahydrofuran, 2.22 ml, 2.22 mmol) was added. The reaction mixture was stirred for 40 min at −78 °C and a solution of freshly prepared D-(*R*)-glyceraldehyde acetonide **8**[14] (0.557 g, 4.28 mmol) in tetrahydrofuran (10 ml) under argon was added. Stirring at −78 °C was continued for 40 min, saturated aqueous ammonium chloride (8 ml) was added and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with diethyl ether (3 × 15 ml). The organic extracts were combined and washed with water (15 ml) and 10% aqueous sodium chloride (15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a clear yellow oil which was a mixture of diastereoisomers. Purification by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 1) as eluant, gave *(3S,5S)-5-bromomethyl-N-tert-butoxycarbonyl-3-[(1S,2R)-2,3-O-isopropylidene-(1,2,3-trihydroxypropyl)]pyrrolidin-2-one* (**21**) as a clear colourless oil which partially crystallised as a white solid on standing (0.660 g, 80%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 408 and 410 ($[M + H]^+$) and 430 and 432 ($[M + Na]^+$); δ_H (360 MHz, C^2HCl_3) 4.39–3.52 (8H, m, H-2, H-7, H-6, H-8A, H-8B, CH_2Br and OH), 3.14–1.93 (3H, m, H-4, and 2 × H-3) and 1.53–1.32 (15H, 6 × s, $OC(CH_3)_3$, and $C(CH_3)_2$).

(3*S*,5*S*)-5-Bromomethyl-*N*-*tert*-butoxycarbonyl-3-[(1*S*,2*R*)-1-acetoxy-2,3-*O*-isopropylidene-(1,2,3-trihydroxypropyl)]-pyrrolidin-2-one (22)

(3*S*,5*S*)-5-Bromomethyl-*N*-*tert*-butoxycarbonyl-3-[(1*S*,2*R*)-2,3-*O*-isopropylidene-(1,2,3-trihydroxypropyl)]pyrrolidin-2-one **21** (0.402 g, 0.98 mmol) was dissolved in anhydrous pyridine (6 ml) under argon with stirring. Acetic anhydride (1.082 g, 10.60 mmol) and DMAP (0.215 g, 1.76 mmol) were added and the solution was stirred at room temperature for 21 h, during which time the colour of the reaction mixture changed from colourless to dark orange. Water (15 ml) was added and the product was extracted with diethyl ether (3 × 15 ml). The organic extracts were combined and washed with water (4 × 15 ml), 10% aqueous sodium chloride (15 ml), saturated aqueous copper sulfate (3 × 15 ml), water (2 × 15 ml) and 10% aqueous sodium chloride (15 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a viscous yellow oil which was a mixture of two diastereoisomers. Further purification of the mixture by flash column chromatography on silica gel, using petroleum ether–ethyl acetate (3 : 2) as eluant, allowed these to be partially separated. The major diastereoisomer, *(3S,5S)-5-bromomethyl-N-tert-butoxycarbonyl-3-[(1S,2R)-1-acetoxy-2,3-O-isopropylidene-(1,2,3-trihydroxypropyl)]pyrrolidin-2-one* (**22**) was a white crystalline solid (0.276 g, 62%); mp 130.0–131.5 °C; $[\alpha]_D^{29}$ −52.3 (*c* 1.0, $CHCl_3$); (*m*/*z* (FAB, PEG/3-NBA) Found 452.1118, $C_{18}H_{29}{}^{81}BrNO_7$requires 452.11069); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 450 and 452 ($[M + H]^+$) and 472 and 474 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 1793 (imide/urethane), 1771 (acetate) and 1745 (ester); δ_H (300 MHz, C^2HCl_3) 5.39 (1H, dd, $J_{6,7}$ 6.3, $J_{6,4}$ 3.0, H-6), 4.40 (1H, m, H-2), 4.20 (1H, m, $J_{7,6}$ 6.3, $J_{7,8A} = J_{7,8B}$ 6.3, H-7), 4.07 (1H, dd, $J_{8A,8B}$ 8.6, $J_{8A,7}$ 6.3, H-8A), 3.85 (1H, dd, $J_{8A,8B}$ 8.6, $J_{8B,7}$ 6.3, H-8B), 3.62 (2H, m, H-1), 3.18 (1H, m, $J_{4,6}$ 3.0, H-4), 2.29 (2H, m, H-3), 2.06 (3H, s, $OCOCH_3$), 1.55 (9H, s, $OC(CH_3)_3$), 1.44 (3H, s, CH_3) and 1.35 (3H, s, CH_3); δ_C (75.47 MHz, C^2HCl_3) 172.8 (CON), 170.1 ($OCOCH_3$), 150.0 (urethane), 110.3 (C-9), 84.4 ($OC(CH_3)_3$), 75.7 (C-7), 71.9 (C-6), 67.1 (C-8), 56.3 (C-2), 43.5 (C-4), 34.6 (CBr), 28.4 ($OC(CH_3)_3$), 26.9, 25.5 (C-10 and C-11), 24.2 (C-3) and 21.4 ($OCOCH_3$).

The structure of this compound was confirmed by **single crystal X-ray diffraction analysis**, reported in our preliminary communication[1] and atomic coordinate data were lodged with the Cambridge Crystallography Data Centre, University

Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW at that time. They are available on request from the Director of the CCDC at the above address, quoting CCDC no 165620 (ref code QODPEE).

The minor diastereoisomer was a clear colourless oil which crystallised on long standing as a white crystalline solid (0.030 g, 7%); *m*/*z* [+ve FAB (3-NBA/CH_2Cl_2)] 450 and 452 ([M + H]$^+$) and 472 and 474 ([M + Na]$^+$); δ_H (360 MHz, C^2HCl_3) 5.44 (1H, dd, $J_{6,7}$ 3.2, $J_{6,4}$ 4.9, H-6), 4.50 (1H, m, H-2), 4.19 (1H, m, H-7), 4.02 (1H, dd, $J_{8A,8B}$ 9.5, $J_{8A,7}$ 6.9, H-8A), 3.79 (2H, m, H-1), 3.69 (1H, dd, $J_{8B,8A}$ 9.5, $J_{8B,7}$ 2.2, H-8B), 2.97 (1H, m, $J_{4,6}$ 4.9, H-4), 2.37, 2.11 (2H, m, H-3), 2.11 (3H, s, $OCOCH_3$), 1.55 (9H, s, $(OC(CH_3)_3)$), 1.45 (3H, s, CH_3) and 1.34 (3H, s, CH_3).

Acknowledgements

We thank the EPSRC for a studentship (to B.A.S.) and the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea for accurate isotopic mass measurements.

References

1 Part of this work has been reported in preliminary form in P. B. Hitchcock, B. A. Starkmann and D. W. Young, *Tetrahedron Lett.*, 2001, **42**, 2381. The X-ray structures reported in that publication have been lodged in the Cambridge Crystallographic Database and have been assigned the numbers noted in the experimental section.
2 C. Nàjera and M. Yus, *Tetrahedron: Asymmetry*, 1999, **10**, 2245.
3 R. A. August, J. A. Khan, C. M Moody and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1996, 507.
4 X. Durand, P. Hudhomme, J. A. Khan and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1131.
5 (*a*) C. M. Moody and D. W. Young, *Tetrahedron Lett.*, 1993, **34**, 4667; (*b*) C. M. Moody and D. W. Young, *Tetrahedron Lett.*, 1994, **35**, 7277; (*c*) C. M. Moody and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3519.
6 (*a*) C. M. Moody, B. A. Starkmann and D. W. Young, *Tetrahedron Lett.*, 1994, **35**, 5485; (*b*) J. Feeney, J. E. McCormick, C. J. Bauer, B. Birdsall, C. M. Moody, B. A. Starkmann, D. W. Young, P. Francis, R. H. Havlin, W. D. Arnold and E. Oldfield, *J. Am. Chem. Soc.*, 1996, **118**, 8700.
7 (*a*) A. N. Bowler, P. M. Doyle and D. W. Young, *J. Chem. Soc., Chem. Commun.*, 1991, 314; (*b*) A. Dinsmore, P. M. Doyle and D. W. Young, *Tetrahedron Lett.*, 1995, **36**, 7503; (*c*) A. N. Bowler, A. Dinsmore, P. M. Doyle and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1297; (*d*) A. Dinsmore, P. M. Doyle, P. B. Hitchcock and D. W. Young, *Tetrahedron Lett.*, 2000, **41**, 10153.
8 M. Steger and D. W. Young, *Tetrahedron*, 1999, **55**, 7935.
9 J. E. Baldwin, T. Miranda, M. Moloney and T. Hokelek, *Tetrahedron*, 1989, **45**, 7459.
10 (*a*) A. N. Bowler, P. M. Doyle, P. B. Hitchcock and D. W. Young, *Tetrahedron Lett.*, 1991, **32**, 2679; (*b*) A. N. Bowler, P. M. Doyle, P. B. Hitchcock and D. W. Young, *Tetrahedron*, 1997, **53**, 10545.
11 D. K. Dikshit and S. K. Panday, *J. Org. Chem.*, 1992, **57**, 1920.
12 D. K. Dikshit and S. N. Bajpai, *Tetrahedron Lett.*, 1995, **36**, 3231.
13 J. Ezquerra, C. Pedregal, B. Yruretagoyena, A. Rubio, M. C. Carreño, A. Escribano and J. L. G. Ruano, *J. Org. Chem.*, 1995, **60**, 2925.
14 D. Y. Jackson, *Synth. Commun.*, 1988, **18**, 337.
15 (*a*) C. Hubschwerlen, *Synthesis*, 1986, 962; (*b*) C. Hubschwerlen, J.-L. Specklin and J. Higelin, *Org. Synth.*, 1995, **72**, 1.
16 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
17 A. McKillop, R. J. K. Taylor, R. J. Watson and N. Lewis, *Synthesis*, 1994, 31.
18 R. B. Silverman and M. A. Levy, *J. Org. Chem.*, 1980, **45**, 815.
19 P. Garner and J. M. Park, *Org. Synth.*, 1992, **70**, 18.