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A short formal synthesis of three epimers of penmacric acid

Dimpy Sikriwal [a], Ruchir Kant [b], Prakas R. Maulik [b], Dinesh K. Dikshit [a,*]

[a] Division of Medicinal and Process Chemistry, Central Drug Research Institute (C.S.I.R) Lucknow 226 001, India
[b] Division of Molecular and Structural Biology, Central Drug Research Institute (C.S.I.R) Lucknow 226 001, India

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ABSTRACT

An extremely short formal synthesis of three epimers of penmacric acid is accomplished starting from pyroglutamate in one or two steps. Stereochemical outcome in the reaction of Li and Ti enolates of pyroglutamate with imines is found to be dependent on both chelation and steric factors.

1. Introduction

Unnatural and non-proteinogenic amino acids have become very important and attractive synthetic targets due to their intrinsic biological activities and applications as conformational modifiers for physiologically active peptides. Pyroglutamic acid, due to its unique structural features, is utilized as a versatile chiral building block for the synthesis of several natural products, such as pyrrolidine alkaloids,[1] kainoids,[2] (−)-bulgecinine,[3] (−)-domic acid,[4] enantiomerically pure proline derivatives[5] and a wide variety of non-proteinogenic amino acids.[6] Penmacric acid (**1**) (Fig. 1) is an unusual amino acid isolated in 1975 independently by Welter et al.[7] and Mbadiwe[8] from the seeds of the leguminous tree *Pentaclethra macrophylla*, commonly known as 'pauco nuts' or 'owala seeds' that are usually used for food, dye and also find application for their medicinal value as *anti*-inflammatories.[9,10] The absolute configuration of penmacric acid was elucidated by ^{1}H NMR, ^{13}C NMR, CD and X-ray studies.[11] The first synthetic route for **1** using diastereoselective nucleophilic addition of bicyclic lactam enolate to *N*-tosyl imine, was reported by Moloney et al.[12] Recently, Naito et al. described the first total synthesis of **1** and its C-1′ epimer in 12 steps with an overall yield of 5.4 and 3.0%, respectively.[13] This was followed by an 11 step elegant synthesis starting from *N*-triisopropylsilylpyrrole.[14]

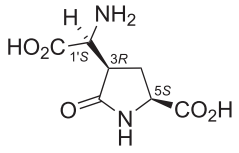

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Figure 1. Penmacric acid.

Pyroglutamic acid based strategies for the chiral synthesis of several complex molecules primarily take advantage of differential nature of the two carbonyls, the enolization of which is directed by the substitution on ring nitrogen.[15] Lithium enolates of *N*-urethane protected pyroglutamates react with various aldehydes to give a mixture of 4α- and 4β-products, with 4α-adduct predominating due to facial preference induced by the carboalkoxy group.[16] Titanium enolates, however, give almost exclusively the 4α-aldol adducts.[17] Similar facial preferences have been reported by Moloney et al.[12] for the aldol reaction of bicyclic lactam (Fig. 2). Extension of this strategy to penmacric acid synthesis using *N*-tosyl benzaldimine (**5**)[18] however proved unsuccessful as only 4α-products were obtained.[12] These results were in consonance with an earlier report that the reaction of pyroglutamate derived enolates with aldimine **5** provides only two diastereomeric 4α-products in 4:1 ratio.[19] We hypothesized that exclusive formation of 4α-adducts in the reaction of *N*-tosyl aldimine **5** might be due to steric bulk of *N*-tosyl group and its replacement with *N*-Boc might reduce this facial selectivity to provide direct access to penmacric acid (Fig. 2).

* Corresponding author. Fax: +91 522 2623405; e-mail address: dk_dikshit@cdri.res.in (D.K. Dikshit).

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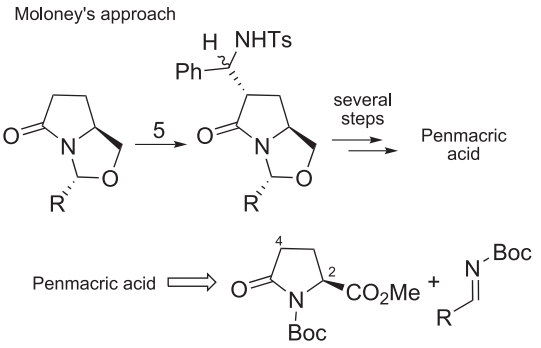


Figure 2. Reterosynthetic route towards penmacric acid (**1**).

Herein, we report the formal synthesis of three epimers[20] of **1** through reinvestigation of reactions between Li/enolate of methyl *N*-Boc pyroglutamate (**6**)[21] with different *N*-Boc imines (Fig. 3) in one or two steps. We also present the stereochemical outcome from the reaction between Ti/enolate of **6** with four imines **2**–**5**.

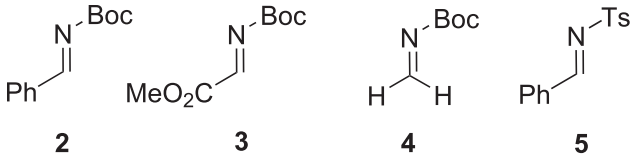


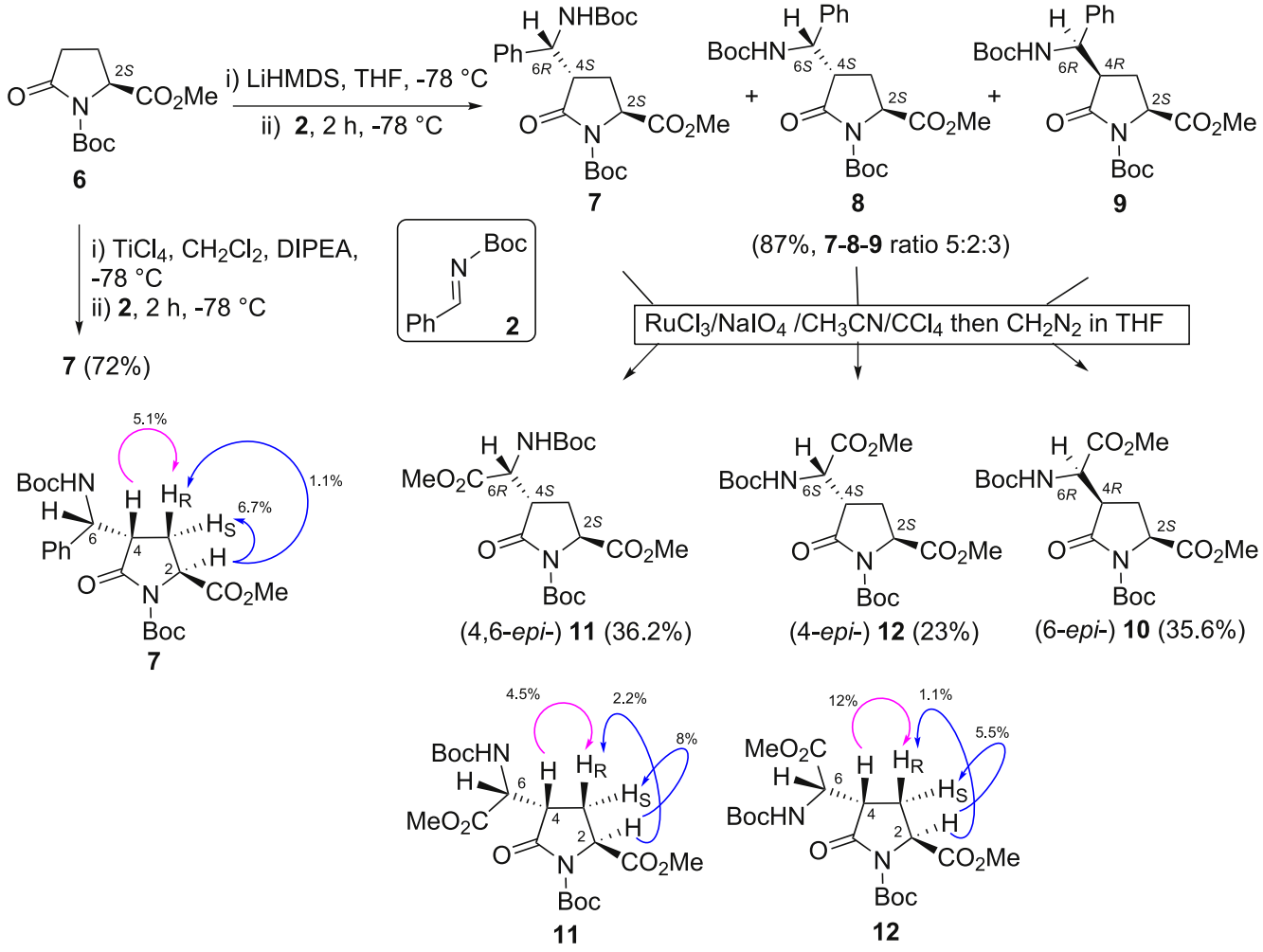
Figure 3. List of imines used.

2. Results and discussion

Reaction of methyl *N*-Boc pyroglutamate (**6**) derived lithium enolate with *N*-Boc benzaldimine (**2**)[22] at −78 °C gave a diastereomeric mixture of three products (**7**, **8** and **9**) in 5:2:3 ratio (Scheme 1), which were purified through flash chromatography and subsequent crystallisations. The (4*S*) stereochemical assignments at C-4 of **7** and **8** were made using NOE data (Scheme 1). Single-crystal X-ray analysis of **7** confirmed its (6*R*) stereochemistry at C-6 (Fig. 4).[23] Hence **8**, the other 4α-product, was assigned 2*S*,4*S*,6*S* configuration. The stereochemistry at C-4 of **9** was thus deductively assigned as (4*R*). $RuCl_3/NaIO_4$ oxidation of the phenyl group in **9** followed by esterification gave **10**, which was found to have spectral data identical to that of C6-epimer of penmacric acid ester as reported by Naito et al.[13] Similarly, 4,6-*epi*-, and 4-*epi*-penmacric acids (**11** and **12**) were prepared from **7** and **8**, respectively.

As titanium enolates are known to enhance the diastereoselectivity in aldol reactions,[17,24] direct chlorotitanium enolate of **6** was reacted with imine **2** at −78 °C for 2 h. In contrast to the results obtained with lithium enolate, only a single diastereomer **7** was obtained in excellent yield (Scheme 1).

Since carboxylate group is expected to be sterically less hindered than phenyl group, in order to achieve one step synthesis of penmacric acid we next studied the reaction of lithium enolate of **6** with methyl *N*-Boc-α-iminoacetate (**3**)[25] prepared in situ from methyl *N*-Boc-2-bromoglycinate where only 4α-adducts **11**[23] and **12** were obtained in 7:3 ratio (Scheme 2).



Scheme 1. Reaction of imine **2** with Li and Ti enolate of **6**.

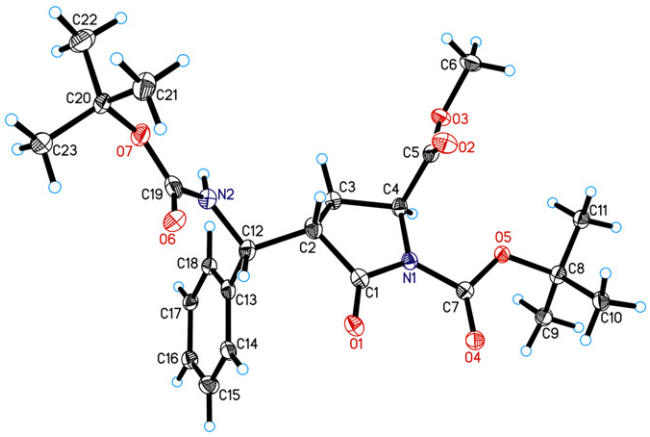
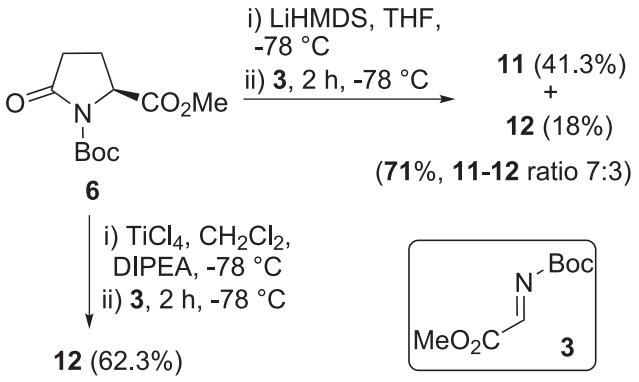
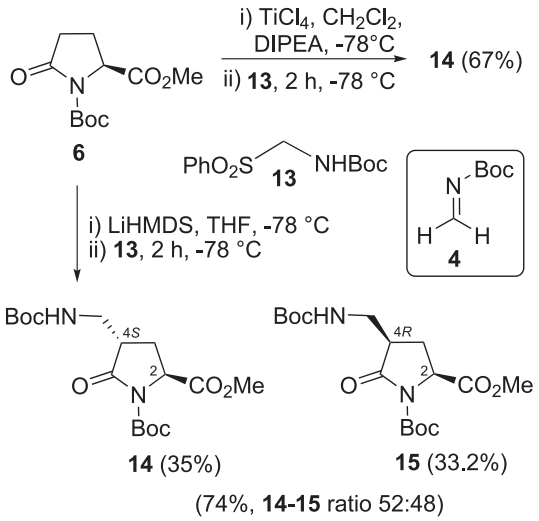


Figure 4. X-ray structure of compound **7**.



Scheme 2. Reaction of imine **3** with Li and Ti enolate of **6**.

The high *exo*-stereoselectivity observed in the reaction of **3** with lithium enolate of **6** is indeed surprising and the present unexpected *exo*-stereoselection in this reaction is still unexplained. Moreover, condensation of unsubstituted imine **4**, generated in situ from sulfone **13**, with lithium enolate of **6** was expectedly found to be non-stereoselective, giving an almost 1:1 ratio of 4α- and 4β-products **14** and **15**, respectively (Scheme 3) (Fig. 5).[26] In contrast to the results obtained with Li enolate, reaction of chlorotitanium enolate of **6** with imine **4** gave predominantly 4α-isomer **14** in 67% yield (Scheme 3). Incidentally, this also constitutes a one step synthesis of **14** and **15** as intermediates for (4*S*) and (4*R*) 4-aminomethyl glutamic acid, respectively serving as glutamate transport inhibitors, which were otherwise have been synthesized in multisteps.[26]



Scheme 3. Reaction of imine **4** with Li and Ti enolate of **6**.

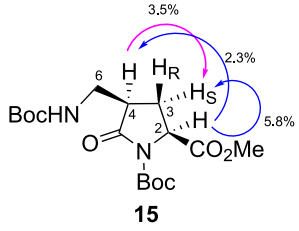


Figure 5. Key NOESY correlations for compound **15**.

High stereoselectivity (exclusive 6*S*) was also observed in the reaction of titanium enolate of **6** with imine **3**, where **12** was obtained as the sole product (Scheme 2). The attack of Ti/enolate to the *si*-face of imine in reaction could be rationalized through a more chelated intermediate (Fig. 6). It is pertinent to note that in absence of such chelation in *N*-tosyl aldimine **5**, its reaction with titanium enolate of **6** afforded a diastereomeric mixture of 4α-products (**16** and **17**) in a ratio of 65:35 similar to the results observed in case of Li/enolate (Scheme 4).[19,27]

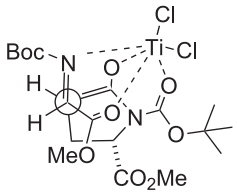
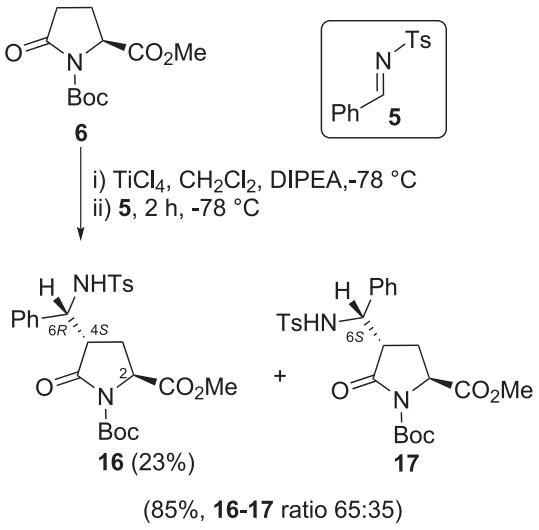


Figure. 6. Proposed transition state model.



Scheme 4. Reaction of imine **5** with Ti enolate of **6**.

3. Conclusion

In conclusion, we have accomplished a short formal synthesis of three epimers of penmacric acid, and have shown dependency of the stereochemical outcome in the reaction of imines with Li enolates of pyrogluatmate, to the steric bulk of substituents. On the other hand, chelation seems to be predominant factor in reaction with titanium enolates.

4. Experimental

4.1. General

All enolate reactions were done using flame-dried glassware under nitrogen atmosphere. THF was distilled from sodium/benzophenone ketyl immediately before use. Triethylamine, *N*,*N*-diisopropylethylamine and dichloromethane were distilled over calcium hydride. *N*-bromosuccinimide was recrystallised from water prior to use. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck pre-coated (Merch 60 F_{254}) silica gel plates using ninhydrine as visualizing agent. Purification was performed by flash chromatography using silica gel (230–400 mesh). NMR spectra were recorded either on a Bruker Advance-300 or Advance-400 spectrometers. Chemical shifts are reported as parts per million (delta) relative to TMS as internal standard. Mass spectra were recorded on LCQ Advantage MAX (ESI), JOEL JMS-600H (EI/HRMS) and Accu. TOF JMS T100 LC (DART/HRMS) mass spectrometer. IR spectra were recorded on a Perkin–Elmer FT-IR RXI spectrometer. Microanalytical data were obtained using Vario-EL-III elemental analyzer. Optical rotations were determined on an Autopol III polarimeter.

4.2. Methyl (2*S*,4*RS*,6*RS*)-*N*-*tert*-butoxycarbonyl-4-(*N*-*tert*-butoxycarbonylamidobenzyl)pyroglutamate (7, 8, 9)

4.2.1. Lithium enolate. Under nitrogen atmosphere and at −78 °C, LiHMDS (1.0 M in THF, 7.63 ml, 7.64 mmol) was added slowly to the magnetically stirred solution of methyl (2*S*)-*N*-*tert*-butoxycarbonypyroglutamate **6** (1.54 g, 6.36 mmol) in freshly distilled THF (30 ml), and the reaction mixture was stirred for 1 h at −78 °C. A solution of *N*-Boc aldimine **2** (1.69 g, 8.27 mmol) in tetrahydrofuran (20 ml) was added dropwise to the reaction mixture and stirring was continued for additional 2 h at −78 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride (15 ml), allowed to warm to room temperature, diluted with water (25 ml) and extracted with ethyl acetate (3×25 ml). The combined organic layer was washed with brine (25 ml), dried (Na_2SO_4) and concentrated in vacuo to give a mixture of three diastereoisomers **7**, **8** and **9** (2.48 g, 87%) as white foam, which was flash chromatographed on a silica gel column using ethyl acetate/hexane (30:70) as eluant to give a mixture of **7**, **8** (83:17) and pure **9** as clear viscous oil (0.68 g, 23.8%). Repeated recrystallisations of the mixture of **7** and **8** from diethyl ether gave a pure sample of **7** as distinct crystalline white solid (0.82 g, 29%) and **8** as clear viscous oil (0.19 g, 7.0%).

*4.2.1.1. Methyl (2S,4S,6R)-N-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylamidobenzyl) pyroglutamate (**7**).* Colourless crystalline solid: [found: C, 61.51; H, 7.12; N, 6.32. $C_{23}H_{32}N_2O_7$ requires C, 61.59; H, 7.19; N, 6.25%]; R_f (30% EtOAc/hexane) 0.35; mp 172–173 °C; $[\alpha]_D^{28}$ −10.3 (*c* 0.81, $CHCl_3$); ν_{max} (KBr) 2980, 1791, 1753, 1717, 1500, 1456, 1370, 1314, 1156, 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26–7.35 (5H, m, Ar*H*), 5.64–5.67 (1H, d, $J_{NH,6}$ 7.2 Hz, N*H*), 4.87–4.91 (1H, dd, $J_{6,NH}$ 7.2 Hz, $J_{6,4}$ 4.9 Hz, *H*-6), 4.46–4.49 (1H, d, $J_{2,3S}$ 8.6 Hz, *H*-2), 3.75 (3H, s, CO_2CH_3), 3.13–3.21 (1H, m, *H*-4), 2.14–2.26 (1H, m, *H*-3S), 2.03–2.10 (1H, m, *H*-3R), 1.48 (9H, s, $(CH_3)_3CO$), 1.39 (9H, s, $(CH_3)_3CO$); δ_C (75 MHz, $CDCl_3$) 172.6, 171.6, 155.7, 149.1, 140.3, 128.7, 127.6, 127.0, 84.0, 80.0, 56.9, 54.9, 52.7, 46.9, 28.3, 27.9, 26.1; MS (ESI) *m*/*z*: 471 $[M+Na]^+$; HRMS (DART): $[M+H]^+$, found 449.2271. $C_{23}H_{33}N_2O_7$ requires 449.2287.

Crystallographic data (excluding structure factors) for the compound **7** in this paper was deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 770723. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.2.1.2. Methyl (2S,4S,6S)-N-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylamidobenzyl) pyroglutamate (**8**).* Clear viscous oil; R_f (30% EtOAc/hexane) 0.35; $[\alpha]_D^{28}$ −47.7 (*c* 0.84, $CHCl_3$); ν_{max} (neat) 3021, 2366, 1787, 1751, 1710, 1492, 1370, 1313, 1217, 1157 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27–7.34 (5H, m, Ar*H*), 6.64 (1H, br, N*H*), 4.85–4.88 (1H, dd, $J_{6,4}$ 9.1 Hz, $J_{6,NH}$ 4.8 Hz, *H*-6), 4.09–4.12 (1H, d, $J_{2,3S}$ 8.4 Hz, *H*-2), 3.74 (3H, s, CO_2CH_3), 3.18–3.24 (1H, m, *H*-4), 2.06–2.12 (1H, m, *H*-3R), 1.91–2.00 (1H, m, *H*-3S), 1.45 (9H, s, $(CH_3)_3CO$), 1.39 (9H, s, $(CH_3)_3CO$); δ_C (75 MHz, $CDCl_3$) 173.8, 171.4, 155.0, 148.8, 138.3, 128.7, 128.0, 127.9, 83.9, 79.7, 57.0, 54.6, 52.7, 46.1, 28.3, 27.8, 25.1; MS (ESI) *m*/*z*: 471$[M+Na]^+$; HRMS (DART): $[M+H]^+$, found 449.2288. $C_{23}H_{33}N_2O_7$ requires 449.2287.

*4.2.1.3. Methyl (2S,4R,6R)-N-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylamidobenzyl) pyroglutamate (**9**).* Clear viscous oil; [found: C, 61.45; H, 7.26; N, 6.22. $C_{23}H_{32}N_2O_7$ requires C, 61.59; H, 7.19; N, 6.25%]; R_f (30% EtOAc/hexane) 0.31; $[\alpha]_D^{29}$ +22.5 (*c* 0.88, $CHCl_3$); ν_{max} (neat) 2923, 1788, 1751, 1709, 1497, 1455, 1370, 1313, 1217, 1157, 1028 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26–7.32 (5H, m, Ar*H*), 6.50 (1H, br, N*H*), 4.92–4.97 (1H, dd, *J* 8.8, 4.9 Hz, *H*-6), 4.39–4.45 (1H, dd (unresolved), *H*-2), 3.57 (3H, s, CO_2CH_3), 3.12–3.20 (1H, m, *H*-4), 2.36–2.47 (1H, m, *H*-3), 1.64–1.67 (1H, br m, *H*-3), 1.46 (9H, s, $(CH_3)_3CO$), 1.38 (9H, s, $(CH_3)_3CO$); δ_C (75 MHz, $CDCl_3$) 173.4, 171.1, 155.1, 148.8, 138.4, 128.7, 127.9, 127.0, 84.1, 79.7, 57.0, 54.6, 52.5, 46.9, 28.3, 27.9, 24.0; MS (ESI) *m*/*z*: 471 $[M+Na]^+$; HRMS (ESI): $[M+H]^+$, found 449.2315. $C_{23}H_{33}N_2O_7$ requires 449.2287.

4.2.2. Titanium enolate. A solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 1.16 ml, 1.16 mmol,) was added dropwise to a stirred solution of **6** (0.26 g, 1.07 mmol) in anhydrous CH_2Cl_2 (10 ml) at −78 °C under nitrogen, giving a yellow slurry. After 5 min, *N*,*N*-diisopropylethylamine (0.37 ml, 2.14 mmol) was added slowly over a period of 15 min. The resulting violet coloured solution was stirred at −78 °C under nitrogen for 1.5 h, a solution of *N*-Boc aldimine **2** (0.26 g, 1.28 mmol) in CH_2Cl_2 (5 ml) was added to it over a period of 10 min, and the stirring was continued at −78 °C for 2 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 ml), allowed to warm to room temperature, diluted with water (15 ml) and extracted with CH_2Cl_2 (3×10 ml). The combined organic extracts were washed with brine (2×10 ml), dried (Na_2SO_4) and concentrated in vacuo to give a white foam, which was purified using flash chromatography over a silica gel column using ethyl acetate/hexane as eluant (30:70) to give pure **7** as white crystalline solid (0.34 g, 72%).

4.3. General procedure for methyl (2*S*,4*RS*,6*RS*)-*N*-*tert*-butoxycarbonyl-4-(methoxycarbonyl-*N*-*tert*-butoxycarbonylaminomethyl)pyroglutamate (10, 11, 12)

To a stirred solution of **9** (0.22 g, 0.51 mmol) in a mixture of CH_3CN (4 ml) and CCl_4 (4 ml) was added a solution of $NaIO_4$ (1.14 g, 5.34 mmol) in water (7 ml) and the stirring was continued for additional 15 min. $RuCl_3 \cdot 3H_2O$ (10 mg, cat.) was added to it and the reaction mixture was vigorously stirred for 12 h. CH_2Cl_2 (15 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml) and dried (Na_2SO_4). The residue obtained after concentration was redissolved in THF (5 ml) to which a solution of diazomethane in ether was added with swirling. Water (15 ml) was added to it and extracted with ethyl acetate (3×15 ml). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give a colourless oil (0.094 g, 43%); purified by flash column chromatography on silica gel using ethyl acetate/hexane as eluant (45:65) to give **10** as viscous oil

(0.078 g, 35.6%), which was crystallised from diethyl ether to white solid after standing overnight.

*4.3.1. Methyl (2S,4R,6R)-N-tert-butoxycarbonyl-4-(methoxycarbonyl-N-tert-butoxycarbonylaminomethyl)pyroglutamate (**10**).* White solid; [found: C, 53.11; H, 7.09; N, 6.57. $C_{19}H_{30}N_2O_9$ requires C, 53.02; H, 7.02; N, 6.51%]; R_f (50% EtOAc/hexane) 0.4; mp 122–125 °C; $[\alpha]_D^{30}$ −7.7 (*c* 0.31, $CHCl_3$); ν_{max} (KBr) 2960, 2923, 1789, 1750, 1717, 1501, 1457, 1396, 1259, 1156, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.67 (1H, br, N*H*), 4.50–4.61 (2H, m, *H*-6+*H*-2), 3.80 (3H, s, CO_2CH_3), 3.77 (3H, s, CO_2CH_3), 3.04–3.12 (1H, m, *H*-4), 2.51–2.61 (1H, m, *H*-3), 2.04–2.13 (1H, br m, *H*-3), 1.50 (9H, s, $(CH_3)_3CO$), 1.45 (9H, s, $(CH_3)_3CO$); δ_C (100 MHz, $CDCl_3$) 171.1, 170.3, 169.5, 154.2, 147.9, 83.0, 79.3, 56.0, 51.9, 51.6, 51.5, 44.4, 27.1, 26.7, 23.0; MS (ESI) *m/z*: 453 $[M+Na]^+$; HRMS (DART): $[M-C_{10}H_{15}O_4]^+$, found 231.1008. $C_9H_{15}N_2O_5$ requires 231.0981.

*4.3.2. Methyl (2S,4S,6R)-N-tert-butoxycarbonyl-4-(methoxycarbonyl-N-tert-butoxycarbonylaminomethyl)pyroglutamate (**11**).* Colourless crystalline solid (36.2%); [found: C, 53.09; H, 7.12; N, 6.48. $C_{19}H_{30}N_2O_9$ requires C, 53.02; H, 7.02; N, 6.51%]; R_f (50% EtOAc/hexane) 0.62; mp 137–139 °C; $[\alpha]_D^{29}$ −65.0 (*c* 0.32 $CHCl_3$); ν_{max} (KBr) 3021, 2981, 1790, 1750, 1717, 1501, 1370, 1316, 1216, 1154 cm^{-1}; δ_H (400 MHz, C_6D_6) 5.37–5.39 (1H, d, $J_{NH,6}$ 8.9 Hz, N*H*), 4.65–4.57 (1H, dd, $J_{6,NH}$ 8.9 Hz, $J_{6,4}$ 2.6 Hz, *H*-6), 4.27–4.30 (1H, dd, $J_{2,3S}$ 10.8 Hz, $J_{2,3R}$ 2.6, *H*-2), 3.41–3.47 (1H, m, *H*-4), 3.29 (3H, s, CO_2CH_3), 3.22 (3H, s, CO_2CH_3), 1.98–2.07 (1H, m, *H*-3S), 1.63–1.68 (1H, m, *H*-3R); 1.36 (9H, s, $(CH_3)_3CO$), 1.34 (9H, s, $(CH_3)_3CO$); δ_C (100 MHz, C_6D_6) 171.5, 171.3, 170.7, 156.7, 150.2, 83.3, 80.0, 56.9, 52.6, 52.3, 51.9, 45.6, 28.2, 27.8, 25.0; MS (ESI) *m/z*: 453$[M+Na]^+$; HRMS (EI): $[M]^+$, found 430.1977. $C_{19}H_{30}N_2O_9$ requires 430.1951.

Crystallographic data (excluding structure factors) for the compound **11** in this paper was deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 770724. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.3.3. Methyl (2S,4S,6S)-N-tert-butoxycarbonyl-4-(methoxycarbonyl-N-tert-butoxycarbonylaminomethyl)pyroglutamate (**12**).* White foam (23%); R_f (50% EtOAc/hexane) 0.53; $[\alpha]_D^{27}$ +3.3 (*c* 0.56, $CHCl_3$); ν_{max} (KBr) 3020, 2979, 1789, 1749, 1718, 1501, 1370, 1316, 1216, 1154 cm^{-1}; δ_H (400 MHz, C_6D_6) 5.78 (1H, br, N*H*), 4.65–4.69 (1H, dd, $J_{6,4}$ 9.4 Hz, $J_{6,NH}$ 4.2 Hz, *H*-6), 4.42–4.45 (1H, dd, $J_{2,3S}$ 9.8 Hz, $J_{2,3R}$ 1.4 Hz, *H*-2), 3.26 (3H, s, CO_2CH_3), 3.20 (3H, s, CO_2CH_3), 2.95–2.99 (1H, m, *H*-4), 2.03–2.11 (1H, m, *H*-3S), 1.66–1.72 (1H, ddd, $J_{3R,3S}$ 10.5 Hz, $J_{3R,4}$ 9.2 Hz, $J_{3R,2}$ 1.4 Hz, *H*-3R); δ_C (100 MHz, C_6D_6) 172.1, 171.6, 171.1, 155.4, 150.3, 83.2, 79.8, 57.1, 53.3, 52.08, 52.05, 45.3, 28.3, 27.9, 25.0; MS (ESI) *m/z*: 453 $[M+Na]^+$; HRMS (EI): $[M]^+$, found: 430.1984. $C_{19}H_{30}N_2O_9$ requires 430.1951.

4.4. Methyl (2*S*,4*S*,6*RS*)-*N*-*tert*-butoxycarbonyl-4-(methoxycarbonyl-*N*-*tert*-butoxycarbonylaminomethyl) pyroglutamate (11 and 12)

4.4.1. Lithium enolate. *N*-bromosuccinimide (0.56 g, 3.16 mmol) was added to a stirred solution of methyl *N*-*tert*-butoxycarbonylglycinate[28] (0.57 g, 3.02 mmol) in CCl_4 (10 ml) under nitrogen atmosphere. The stirred solution was illuminated with 500 W lamp for 1 h, keeping the reaction mixture between 10–30 °C using a water bath. The resulting orange reaction mixture was then filtered and the filtrate was concentrated in vacuo to afford the crude methyl 2-bromo-*N*-*tert*-butoxycarbonylglycinate as yellow oil. To the crude bromide in THF (6 ml) at −78 °C under nitrogen was added anhydrous triethylamine (0.46 ml, 3.30 mmol) with stirring and the reaction mixture was stirred for 45 min at −78 °C to afford a crude imine **3**[25] solution. Meanwhile to a stirred solution of pyroglutamate **6** (0.67 g, 2.75 mmol) in THF (12 ml) was slowly added LiHMDS (1.0 M in THF, 3.44 ml, 3.44 mmol) at −78 °C and the reaction mixture was stirred for 1 h. The cold crude enolate solution was then quickly added to crude imine solution via cannula and stirred for another 2 h at −78 °C. Saturated aqueous ammonium chloride (6 ml) was added and the reaction mixture was allowed to warm to room temperature; water (15 ml) was added and was extracted with ethyl acetate (3×15 ml). The combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and concentrated in vacuo to give a mixture of two diastereoisomers (**11** and **12**) as yellow foam (0.84 g, 71%), which was purified by flash column chromatography on silica gel, using ethyl acetate/hexane (40:60) as eluant to afford **11** (0.48 g, 41.3%) as viscous oil (crystallised further from diethyl ether to a crystalline solid), and **12** as white foam (0.21 g, 18%).

4.4.2. Titanium enolate. Compound **6** (0.29 g, 1.21 mmol) was dissolved in anhydrous CH_2Cl_2 (10 ml) under nitrogen with stirring, cooled to −78 °C and $TiCl_4$ (1.0 M in CH_2Cl_2, 1.32 ml, 1.32 mmol) was added dropwise followed by slow addition of DIPEA (0.25 ml, 1.46 mmol) after 5 min., and the resultant deep violet enolate solution was stirred for 1.5 h at −78 °C. Meanwhile a fresh imine **3** solution (-78 °C) was prepared in anhydrous CH_2Cl_2 (6 ml) as described above, quickly added to enolate solution via cannula and the reaction mixture was stirred for another 2 h at −78 °C. The reaction mixture was then quenched with saturated aqueous ammonium chloride (10 ml), allowed to warm to room temperature, diluted with water (15 ml) and extracted with dichloromethane (3×15 ml). The combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and concentrated in vacuo to give the crude product as yellowish foam (0.37 g, 71.7%), which was purified by flash column chromatography on silica using ethyl acetate/hexane as eluant (40:60) to give **12** as a white foamy solid (0.32 g, 62.3%).

4.5. *tert*-Butyl phenylsulfonylmethylcarbamate (13)

A mixture of *tert*-butyl carbamate (1.5 g, 12.8 mmol) and benzenesulfinic acid sodium salt (4.20 g, 25.6 mmol) was suspended in a solution of methanol in water (1:2, 45 ml) followed by the addition of 30% aqueous formalin (2.56 ml, 25.6 mmol) and formic acid (98%, 1.5 ml). The reaction was allowed to stir for 3 days at room temperature during, which time the product precipitated as a white solid. The crystalline sulfone **13** was filtered off with suction, washed with water and diethyl ether, redissolved in dichloromethane, dried over Na_2SO_4 and concentrated under reduced pressure to afford the sulfone **13** (3.0 g, 86.4%). White solid; mp 155–157 °C; ν_{max} (KBr) 1703, 1477, 1448, 1421, 1364, 1291, 1142, 1087, 1007 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.91–7.94 (1H, d, *J* 7.4 Hz, Ar*H*), 7.53–7.68 (3H, m, Ar*H*), 5.42 (1H, br, N*H*), 4.52–4.54 (2H, d, *J* 7.0 Hz, CH_2), 1.26 (9H, s, $(CH_3)_3CO$); δ_C (75 MHz, $CDCl_3$) 154.0, 137.0, 134.2, 129.3, 129.1, 81.2, 62.2, 28.1; MS (ESI) *m/z*: 289 $[M+NH_4]^+$.

4.6. Methyl (2*S*,4*RS*)-*N*-*tert*-butoxycarbonyl-4-(*N*-*tert*-butoxycarbonylaminomethyl)pyroglutamate (14 and 15)

4.6.1. Lithium enolate. LiHMDS (1.0 M in THF, 6.14 ml, 6.14 mmol) was added dropwise to a solution of **6** (0.65 g, 2.672 mmol) in anhydrous THF (15 ml) at −78 °C under nitrogen atmosphere with stirring. The reaction mixture was stirred for 1.2 h, a solution of sulfone **13** (0.79 g, 2.93 mmol) in THF (15 ml) was added to it, and the stirring was continued for a further 2 h at −78 °C. The reaction was quenched with aqueous saturated ammonium chloride solution (15 ml), allowed to warm to room temperature, diluted with water (25 ml) and extracted with ethyl acetate (3×25 ml). The combined organic extracts were washed with brine (15 ml) and

dried (Na_2SO_4). Removal of the solvent in vacuo gave the product as a pale yellow foam (0.73 g, 74%), which was purified by flash column chromatography on silica gel using ethyl acetate/hexane (45:65) as eluant to give **14** (0.34 g, 35%) and **15** (0.33 g, 33.2%) as viscous oils, which crystallised to white solid on standing overnight.

*4.6.1.1. Methyl(2S,4S)-N-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylaminomethyl)pyroglutamate (**14**).* White solid; [found: C, 54.88; H, 7.45; N, 7.61. $C_{23}H_{32}N_2O_7$ requires C, 54.83; H, 7.58; N, 7.52%]; R_f (70% EtOAc/hexane) 0.5; mp 95–97 °C; $[\alpha]_D^{22}$ −40.2 (*c* 0.28, $CHCl_3$); ν_{max} (KBr) 2928, 1772, 1707, 1520, 1459, 1374, 1313, 1258, 1217, 1158 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.15 (1H, br, N*H*), 4.56–4.60 (1H, dd, $J_{2,3S}$ 8.9 Hz, $J_{2,3R}$ 1.7 Hz, *H*-2), 3.78 (3H, s, CO_2CH_3), 3.46–3.52 (1H, m, *H*-6), 3.30–3.36 (1H, m, *H*-6), 2.77–2.85 (1H, m, *H*-4), 2.06–2.23 (2H, m, *H*-3R+*H*-3S), 1.50 (9H, s, $(CH_3)_3CO$), 1.42 (9H, s, $(CH_3)_3CO$); δC (75 MHz, $CDCl_3$) 174.4, 171.6, 156.3, 83.9, 79.5, 57.0, 52.7, 42.7, 39.5, 28.3, 27.9, 25.6; MS (ESI) *m*/*z*: 395 $[M+Na]^+$; HRMS (DART): $[M+H]^+$, found 373.2010. $C_{17}H_{29}N_2O_7$ requires 373.1974.

*4.6.1.2. Methyl (2S,4R)-N-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylaminomethyl)pyroglutamate (**15**).* White solid; [found: C, 54.91; H, 7.53; N, 7.49. $C_{23}H_{32}N_2O_7$ requires C, 54.83; H, 7.58; N, 7.52%]; R_f (70% EtOAc/hexane) 0.43; mp 105–107 °C; $[\alpha]_D^{23}$ −44.1 (*c* 0.2, $CHCl_3$); ν_{max} (KBr) 3020, 1786, 1748, 1710, 1511, 1369, 1308, 1216, 1156 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.17 (1H, br, N*H*), 4.47–4.53 (1H, dd (unresolved), *H*-2), 3.77 (3H, s, CO_2CH_3), 3.46–3.52 (1H, m, *H*-6), 3.30–3.38 (1H, m, *H*-6), 2.70–2.80 (1H, m, *H*-4), 2.46–2.56 (1H, m, *H*-3S), 1.74–1.84 (1H, m, *H*-3R), 1.49 (9H, s, $(CH_3)_3CO$), 1.42 (9H, s, $(CH_3)_3CO$); δ_C (75 MHz, $CDCl_3$) 174.2, 171.7, 156.3, 149.2, 84.1, 79.6, 57.4, 52.6, 43.4, 40.3, 28.4, 27.9, 25.2; MS (ESI) *m*/*z*: 395 $[M+Na]^+$; HRMS (DART): $[M+H]^+$, found 373.1982. $C_{17}H_{29}N_2O_7$ requires 373.1974.

4.6.2. Titanium enolate. $TiCl_4$ (1.0 M in CH_2Cl_2, 3.3 ml, 3.3 mmol) was added dropwise to a solution of **6** (0.35 g, 1.43 mmol) in anhydrous CH_2Cl_2 (10 ml) at −78 °C under nitrogen atmosphere with stirring followed after 5 min by dropwise addition of DIPEA (0.62 ml, 3.59 mmol) resulting into a deep violet coloured solution. The reaction mixture was stirred for 1.5 h at −78 °C and a solution of sulfone **13** (0.42 g, 1.58 mmol) in CH_2Cl_2 (10 ml) was added (warm to dissolve). After stirring for 2 h at the same temperature, the reaction was quenched with aqueous saturated ammonium chloride solution (12 ml) and the mixture was allowed to warm to room temperature. Water (15 ml) was added and the product was extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo to yield the crude product **14** (0.43 g, 82%), which was purified by flash column chromatography on silica gel, using ethyl acetate/hexane (45:65) as eluant to give **14** (0.358 g, 67%) as clear oil, which crystallised on standing overnight.

4.7. Methyl (2*S*,4*S*,6*RS*)-*N*-*tert*-butoxycarbonyl-4-(*N*-*para*-toluenesulonylamidobenzyl)pyroglutamate (16 and 17)

Compounds **16** and **17** were obtained following the general procedure for **7**, **8** and **9**.

4.7.1. Titanium enolate. Purification by flash column chromatography on silica gel, using ethyl acetate/hexane (40:60) as eluant separated mixture of **16** and **17** (0.526 g, 85%) together with unreacted tosylamide. The major diastereoisomer **16** was separated and purified by repeated recrystallisation from diethyl ether, which provided distinct crystalline white solid **16** (0.142 g, 23%). The minor isomer **17** could not be obtained pure but the spectrum was obtained by subtraction from the mixture.

*4.7.1.1. Methyl (2S,4S,6R)-N-tert-butoxycarbonyl-4-(N-para-toluenesulonylamidobenzyl) pyroglutamate (**16**).* 0White crystalline solid; [found: C, 59.70; H, 5.99; N, 5.61. $C_{25}H_{30}N_2O_7S$ requires C, 59.75; H, 6.02; N, 5.57%]; R_f (40% EtOAc/hexane) 0.32; mp 171–175 °C; $[\alpha]_D^{28}$ +77.5 (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 2993, 1749, 1720, 1457, 1328, 1215, 1157, 1092 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.46–7.49 (2H, d, *J* 8.1 Hz, Ar*H*), 7.09–7.17 (7H, m, Ar*H*), 6.45–6.47 (1H, d, $J_{NH.6}$ 4.0 Hz, N*H*), 4.40–4.44 (1H, d, $J_{2,3S}$ 9.5 Hz, *H*-2), 4.33–4.36 (1H, dd, $J_{6,NH}$ 4.0 Hz, $J_{6,4}$ 6.9 Hz, *H*-6), 3.71 (3H, s, CO_2CH_3), 3.01–3.10 (1H, m, *H*-4), 2.35 (3H, s, PhCH_3), 2.00–2.12 (1H, m, *H*-3S), 1.78–1.85 (1H, m, *H*-3R), 1.74 (9H, s, $(CH_3)_3CO$); δ_C (75 MHz, $CDCl_3$) 173.0, 171.3, 148.8, 143.2, 137.2, 136.8, 129.3, 128.5, 128.1, 127.7, 127.4, 84.2, 59.0, 56.7, 52.7, 46.7, 27.9, 25.6, 21.5; MS (ESI) *m*/*z*: 525 $[M+Na]^+$; HRMS (DART): $[M-C_5H_{10}O_2]^+$, found 403.1281. $C_{20}H_{23}N_2O_5S_1$ requires 403.1327.

*4.7.1.2. Methyl (2S,4S,6S)-N-tert-butoxycarbonyl-4-(N-para-toluenesulonylamidobenzyl)pyroglutamate (**17** from **16**+**17**).* R_f (40% EtOAc/hexane) 0.32; ν_{max} (KBr) 2933, 1749, 1720, 1457, 1327, 1263, 1214, 1156, 1092 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42–7.45 (2H, d, *J* 8.2 Hz, Ar*H*), 7.00–7.17 (7H, m, Ar*H*), 6.75–6.78 (1H, d, $J_{NH.6}$ 9.1 Hz, N*H*), 4.63–4.68 (1H, dd, $J_{6,NH}$ 9.1 Hz, $J_{6,4}$ 4.8 Hz, *H*-6), 4.13–4.17 (1H, dd, $J_{2,3S}$ 9.1 Hz, $J_{2,3R}$ 2.3 Hz, *H*-2), 3.73 (3H, s, CO_2CH_3), 3.16–3.24 (1H, m, *H*-4), 2.30 (3H, s, PhCH_3), 1.79–2.12 (2H, m, *H*-3S+*H*-3R), 1.43 (9H, s, $(CH_3)_3CO$); δ_C NMR (75 MHz, $CDCl_3$) 173.6, 171.2, 148.6, 142.9, 137.7, 136.4, 129.2, 128.6, 128.0, 127.9, 126.9, 84.1, 57.7, 57.0, 46.5, 27.8, 24.7, 21.4; MS (ESI) *m*/*z*: 525 $[M+Na]^+$.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.102. These data include MOL files and InChIKeys of the most important compounds described in this article.

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