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A Radical Route to 2(S)-4-Exomethylene Proline

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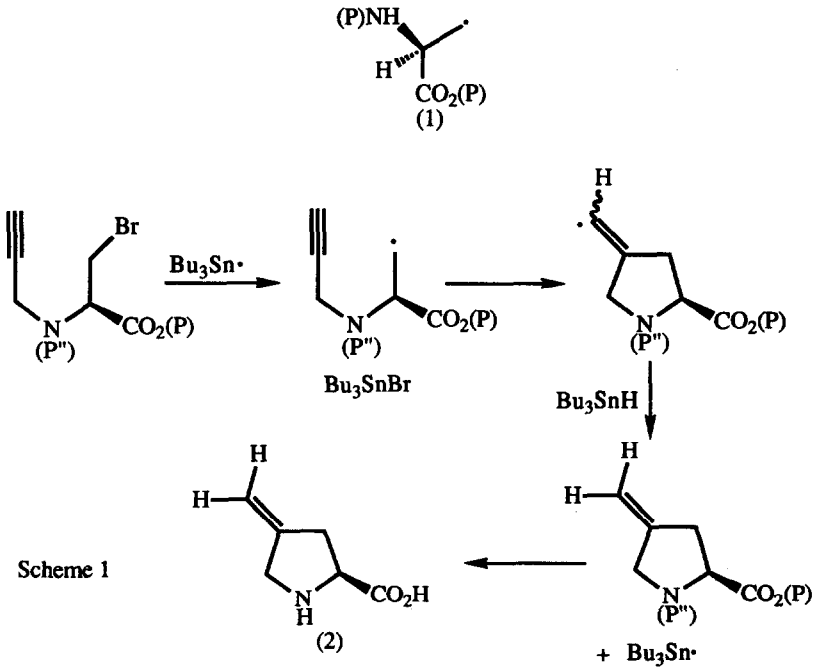
Abstract: A new route to 2(S)-4-Exomethylene proline via a favoured 5-Exo-dig radical cyclisation is described.

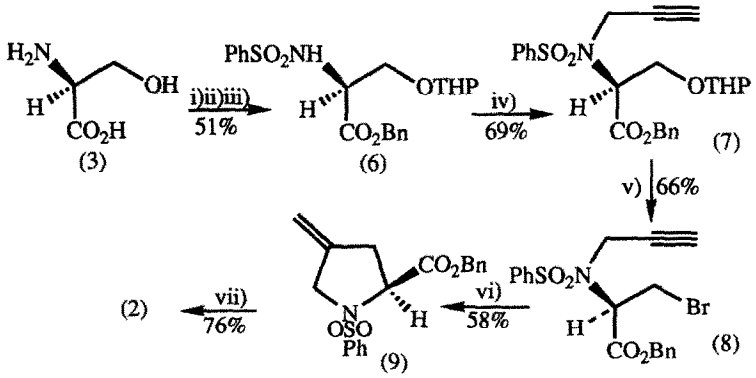
Recently we reported the use of a protected chiral alaninyl radical (1) as a new reagent for intermolecular carbon-carbon bond formation to provide functionalised α–amino acids[1]. Likewise the propensity of carbon radicals to undergo favoured ring closures is well documented,[2] and as such it seemed logical to extend our earlier studies on (1) by incorporating an intramolecular radicalphile. Thus 2(S)-4-exomethylene proline (2)[3], was chosen as a target to evaluate this proposal as illustrated in Scheme 1.



Scheme 1

Firstly 2(S)-serine (3) was sequentially triprotected as (6) and subsequently N-alkylated with propargyl bromide to provide (7). Treatment with triphenylphosphorous dibromide gave the bromide (8), the precursor for attempted intramolecular carbon based free radical ring closure. A solution of (8) in benzene heated under reflux

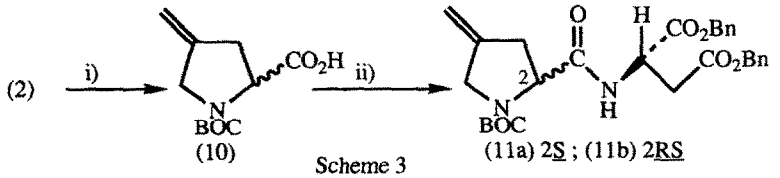
in the presence of tributylstannane (1.2 equiv) and A.I.B.N. (0.2 equiv) for eight hours gave solely an exomethylene product (9) without of any detectable directly reduced, non-cyclised product or product derived from an endo cyclization. Such a 5-Exo-Dig carbon based radical cyclization has precedent elsewhere[4] but has not been reported as a method for the synthesis of exomethylene pyrrolidine based natural products.[5] Deprotection of (9) was achieved smoothly with buffered sodium amalgam to afford 2(S)-4-exomethylene proline (2) as illustrated in Scheme 2.



i) $PhSO_2Cl$, Na_2CO_3; ii) BnBr, $NaHCO_3$; iii) dihydropyran, pyridinium toluene-4-sulphonate; iv) propargyl bromide, Cs_2CO_3; v) triphenylphosphorus dibromide; vi) AIBN, tri-*n*-butyl tin hydride; vii) K_2HPO_4, 6% sodium amalgam

Scheme 2

In order to substantiate that chiral integrity had been maintained throughout the route to 2(S)-4-exomethylene proline, (2) was N-protected as (10) then coupled to dibenzyl 2(S)-aspartate[6] to produce a single diastereomer of (11). Similar coupling with racemic (2), Scheme 3, gave a diastereomeric pair of amides (11) as illustrated in Fig (1).



Scheme 3

i) BOC_2O, triethylamine; ii) dibenzyl-(S)-aspartate toluene-4-sulphonic acid salt, triethylamine, 1-hydroxybenzotriazole, dicyclohexylcarbodiimide

In summary we have demonstrated a facile intramolecular ring closure of a functionalised alaninyl radical and have applied this new method to the synthesis of homochiral 2(S)-4-exomethylene proline (2) . Noteworthy is the exclusive 5-exo-dig nature of the ring closure and the mild manner of concomitant sulphonamide/benzyl ester cleavage.

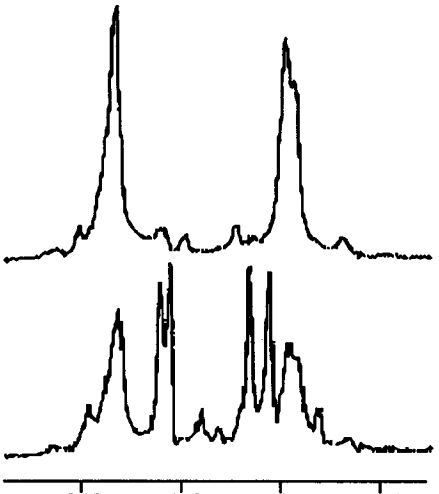


Figure 1

EXPERIMENTAL SECTION.

Standard experimental methods and techniques as reported elsewhere were employed[7].

N-Phenylsulphonyl-(S)-Serine (4)

The method of Rapoport[8] was followed to provide **N-Phenylsulphonyl-(S)-serine (4)** (7.8g, 64% yield) from (S)-serine; (5.3g, 50mmol); m.p. 221-222°C (decomp); [Lit.[8], 222-224°C]; $[\alpha]_D$ +9.18° (c=2, MeOH) Lit.[§] $[\alpha]_D$ +9.25° (c=2, MeOH); (Found C 44.26; H 4.48; N 5.69. $C_9H_{11}NO_5S$ requires C 44.08; H 4.52; N 5.71%).

N-Phenylsulphonyl-(S)-Serine benzyl ester (5)

N-Phenylsulphonyl-(S)-Serine (4) (9.0g, 36.7mmol) was added to added to water (30ml) and methanol (30ml) and the pH of the solution adjusted to 7 with $NaHCO_3$. The methanol and water were removed *in vacuo* to give a white solid which was dissolved in anhydrous DMF (50ml), benzyl bromide (7.53g, 44mmol, 1.2 equiv.) and a catalytic amount of potassium iodide (0.05g) added. The reaction mixture was stirred under nitrogen for 48 hours, the DMF was removed *in vacuo* and the residue partitioned between water (40ml) and ethyl acetate (20ml). The organic layer was removed and the aqueous phase extracted twice more with ethyl acetate (20ml). The combined organic layers were extracted with brine (20ml) then evaporated by rotory evaporator to give a slightly yellow solid which was recrystallised from ethyl acetate and petrol to give **N-Phenylsulphonyl-(S)-Serine benzyl ester (5)** (10.9g, 87% yield) a white solid; m.p.122-123°C; $[\alpha]_D$ -0.7° (c=1, $CHCl_3$); Rf 0.2 (SiO_2 plates, 1:1 ethyl acetate : petrol); (Found: C 57.33; H 5.15; N 4.15. $C_{16}H_{17}NO_5S$ requires C 57.30; H 5.10; N 4.18%); υ_{max} ($CHCl_3$) 3600 (br, m, OH str), 3330 (br, m, NH str), 1745 (s, C=O str), 1350cm^{-1} (s, SO_2N);

δ_H(200MHz; $CDCl_3$) 2.25 (1H, br, s, O<u>H</u>) 3.93 (2H, d, J 4, C<u>H</u>$_2$OH), 4.01-4.09 (1H, m, α proton), 5.03 (2H, s, C<u>H</u>$_2$Ph), 5.68 (1H, d, J 7.5, N<u>H</u>), 7.14-7.9 (10H, m, Ar<u>H</u>); δ_C(50.3MHz; $CDCl_3$) 59.30 (α carbon), 63.25 (<u>C</u>H$_2$OH), 67.28 (Ph<u>C</u>H$_2$), 127.94-130.54 (ArC), 133.99 (para $PhSO_2$), 137.12 (ipso $PhCH_2$), 142.49 (ipso $PhSO_2$), 171.53 (CO_2); m/z DCI/NH_3 353 (MNH_4^+, 100), 336 (MH^+, 17), 200 (22), 108 (46), 91 (57%).

N-Phenylsulphonyl-O-tetrahydropyranyl-(<u>S</u>)-Serine benzyl ester (6).

To N-Phenylsulphonyl-(<u>S</u>)-Serine benzyl ester **(5)** (4.00g, 11.9mmol) was added pyridinium paratoluenesulphonate (0.1 equiv, 0.30g, 1.19mmol) and anhydrous dichloromethane (30ml). The resulting solution was stirred for 10minutes and dihydropyran (1.10g, 13.1mmol, 1.1 equiv) was added, then the reaction mixture stirred for twelve hours at room temperature. The solvent was removed by rotory evaporator and the residue partitioned between ethyl acetate (20ml) and brine (10ml). The brine was extracted once more with ethyl acetate (10ml), the organic extracts combined and dried ($MgSO_4$). The solvent was removed by rotory evaporator to give a yellow oily residue which was purified by flash chromatography (SiO_2, 4:3:13-1:1:4 ethyl acetate : dichloromethane : petrol) to give a white solid which was recrystallised from ethyl acetate/petrol to give **N-Phenylsulphonyl-O-tetrahydropyranyl-(<u>S</u>)-serine benzyl ester (6)** (4.53g, 91% yield); m.p. 90.5-91.5°C; Rf 0.2 (SiO_2 plates, 1:4 ethyl acetate: petrol); (Found C 59.93; H 6.01; N 3.32. $C_{21}H_{25}NO_6S$ requires C 60.13; H 6.01; N 3.34%); υ_{max} ($CHCl_3$) 3370 (m, br, NH str), 1745 (s, C=Ostr), 1340 (s, SO_2N), 1155cm^{-1} (s, SO_2N); δ_H(200MHz; $CDCl_3$) major diastereomer 1.3-1.7 (6H, m, OTHP), 3.36-3.52 (2H, m, OTHP), 3.88 (2H, d, J 3.5, C<u>H</u>$_2$OTHP), 4.15-4.26 (1H, m, α proton), 4.40 (br, s, 1H, OC<u>H</u>O), 5.02 (2H, s, C<u>H</u>$_2$Ph), 5.84 (1H, d, J 9, N<u>H</u>), 7.21-7.88 (10H, m, ArH), minor diastereomer 1.3-1.7 (6H, m, OTHP), 3.58 (1H, dd, J 3.5, 13 C<u>H</u>$_2$OTHP), 3.67-3.8 (2H, m, OTHP), 4.08 (1H, dd, J 3.5 13, C<u>H</u>$_2$OTHP), 4.49 (1H, s, OC<u>H</u>O), 5.02 (2H, s, C<u>H</u>$_2$Ph), 5.61 (1H, d, J 9, N<u>H</u>), 7.21-7.9 (10H, m, ArH); δ_C(50.3MHz; $CDCl_3$) major diastereomer 18.79, 24.92, 29.96 (OTHP), 55.98 (α carbon), 62.11 (OTHP), 67.41 (<u>C</u>H$_2$OTHP), 68.95 (<u>C</u>H$_2$Ph), 99.27 (O<u>C</u>HO), 127.20-132.84 (ArC), 135.20 (ipso $PhCH_2$), 140.38 (ipso $PhSO_2$), 169.58 (CO_2), minor diastereomer 18.79, 24.92, 29.83 (OTHP), 55.98 (α carbon), 62.11 (<u>C</u>H$_2$OTHP), 67.41 (CH$_2$<u>C</u>H$_2$O), 67.89 (<u>C</u>H$_2$Ph), 98.67 (O<u>C</u>HO), 127.20-132.86 (ArC), 135.20 (ipso $PhCH_2$), 140.38 (ipso $PhSO_2$), 169.58 (CO_2) ; m/z DCI/NH_3 437(MNH_4^+, 38), 420 (MH^+,4), 353 (47), 91 ($C_7H_7^+$, 25), 85 (100%).

N-Phenylsulphonyl-N-propargyl-O-tetrahydropyranyl-(<u>S</u>)-serine benzyl ester (7)

To N-Phenylsulphonyl-O-tetrahydropyranyl-(<u>S</u>)-Serine benzyl ester **(6)** (1.70g, 4.05mmol) in anhydrous DMF (30ml) was added Cesium Carbonate (1.74g, 5.40mmol) under an argon atmosphere. After stirring for twenty minutes at room temperature, the mixture was cooled to 0°C and propargyl bromide (1.61g, 1.5cm^3 of 80% solution, 4.2 equiv.) was added. After 7 hours the DMF was removed *in vacuo* and the residue partitioned between water (30ml) and ethyl acetate (20ml). The aqueous phase was then adjusted to pH7, the organic phase removed and the aqueous phase extracted twice more with ethyl acetate (2x20ml). The combined organic extracts were washed with saturated brine (10ml). The organic layer was dried ($MgSO_4$) and the solvent removed by rotory evaporator to give a brown viscous oil which was purified by flash chromatography (SiO_2, 1: 9- 15: 85 ethyl acetate: petrol) to give an off-white coloured solid. Recrystalisation from ethyl acetate/hexane gave **N-Phenylsulphonyl-N-propargyl-O-tetrahydropyranyl-(<u>S</u>)-serine benzyl ester (7)** (1.28g, 69%) m.p.

85.5-86.5°C; (Found C 63.18; H 6.02; N 3.22. $C_{24}H_{27}NO_6S$ requires C 63.00; H 5.95; N 3.06%); R_f 0.4 (SiO_2 plates, 1: 4 ethyl acetate: petrol); υ_{max} ($CHCl_3$) 3285 (sh, m, C≡C str), 1745 (s, C=O str), 1350 (s, SO_2N), 1160cm^{-1} (s, SO_2N); δ_H (200MHz; $CDCl_3$) major diastereomer 1.35-1.7 (6H, m, OTHP), 2.08 (1H, t, J 1.5, C≡C<u>H</u>), 3.33-3.63 (2H, m, OTHP), 3.73-3.83 (m, 2H, C<u>H</u>$_2$OTHP), 4.14-4.47 (2H, m, NC<u>H</u>$_2$), 4.52 (1H, m, OC<u>H</u>O), 4.82-4.95 (1H, m, α proton), 5.08 (2H, m, C<u>H</u>$_2$Ph), 7.22-7.94 (8H, m, ArH), minor diastereomer 1.35-1.7 (6H, m, OTHP) 2.08 (1H, m, C≡C<u>H</u>), 3.73-3.83 (2H, m, OTHP), 4.14-4.47 (4H, m, C<u>H</u>$_2$OTHP, NC<u>H</u>$_2$), 4.65 (1H, m, OC<u>H</u>O), 4.82-4.95 (1H, m, α proton), 5.08 (2H, s, C<u>H</u>$_2$Ph), 7.22-7.63 (8H, m, ArH); δ_C(50.3MHz; $CDCl_3$) major diastereomer 18.46, 25.10, 29.81 (OTHP), 35.09 (N<u>C</u>H$_2$), 59.62 (α carbon), 65.51 (OTHP), 66.07 (<u>C</u>H$_2$OTHP), 67.19 (Ph<u>C</u>H$_2$), 72.25 (C≡<u>C</u>H), 79.39 (<u>C</u>≡CH) 99.02 (O<u>C</u>HO), 127.65-132.91 (ArC), 135.22 (ipso PhCH$_2$), 140.22 (ipso PhSO$_2$), 168.89 (CO_2), minor diastereomer 18.37, 25.10, 29.81 (OTHP), 35.45 (N<u>C</u>H$_2$), 58.75 (α carbon), 61.26 (O<u>C</u>H$_2$CH$_2$), 66.25 (<u>C</u>H$_2$OTHP), 67.19 (<u>C</u>H$_2$Bn), 71.71 (C≡<u>C</u>H), 79.71 (<u>C</u>≡CH), 99.38 (O<u>C</u>HO), 127.65-132.91 (ArC), 135.22 (ipso PhCH$_2$), 140.02 (ipso PhSO$_2$), 169.02 (CO_2); m/z DCI/NH_3 475 (MNH_4^+, 18), 391 (38), 374 (38), 202 (28), 102 (20), 91 ($C_7H_7^+$, 37), 85 (100%).

N-Phenylsulphonyl-N-propargyl-3-bromo-(<u>S</u>)-alanine benzyl ester (8)

Triphenylphosphorus dibromide (1.96g, 4.38mmol) was generated by the addition of bromine (0.77g, 4.38mmol, 2.5ml of 1:9 v/v stock solution of bromine : dichloromethane) to a solution of triphenyl phosphine (1.50g, 5.60mmol) in anhydrous dichloromethane (15ml) at 0°C. The mixture was stirred at room temperature for 20 minutes to give a colourless solution containing a white precipitate. N-Phenylsulphonyl-N-propargyl-O-tetrahydropyranyl-(<u>S</u>)-serine benzyl ester (**7**) (2.00g, 4.38mmol) was dissolved in anhydrous dichloromethane (10ml) and the resulting solution cooled to 0°C and transferred *via* a cannula into the triphenylphosphorus dibromide solution and the reaction was left to stir at 0°C for four hours. Almost all of the solvent was removed by rotory evaporator, hexane (10ml) added and the solution concentrated until a cloudiness appeared. The flask was scratched, seeded with triphenylphosphine oxide, sealed and placed in a refridgerator at -4°C for 30min, the precipitated triphenylphosphine oxide was filtered off, washed with 1:9 ethyl acetate:petrol, and the procedure repeated. Flash chromatograpy (SiO_2, 1:9-3:2 ethyl acetate:petrol) gave **N-Phenylsulphonyl-N-propargyl-3-bromo-(<u>S</u>)-alanine benzyl ester (8)** as a clear oil (1.23g, 66% yield); Rf 0.4 (SiO_2 plates, 1:4 ethyl acetate: hexane); $[\alpha]_D$ -28.7° (c=1, $CHCl_3$); (Found C 52.34; H 3.96; N 3.60. $C_{19}H_{18}BrNO_4S$ requires C 52.30; H 4.16; N 3.21%); υ_{max} (thin film) 3310 (sh, C≡C str), 1745 (s, C=O str), 1355 (s, SO_2N), 1165cm^{-1} (s, SO_2N). δ_H (200MHz; $CDCl_3$) 2.12 (1H, t, J 2, C≡C<u>H</u>), 3.62, 3.95 (2H, dd, J 8 12 , C<u>H</u>$_2$Br), 4.14 (2H, d, J 2, NC<u>H</u>$_2$), 4.93 (1H, t, J 8, α proton), 5.02-5.16 (2H, m, C<u>H</u>$_2$Ph), 7.22-7.62 (8H, m, ArH), 7.83-7.94 (2H, d, J 8.5, ArH); δ_C (50.3MHz; $CDCl_3$) 28.40 (<u>C</u>H$_2$Br), 34.36 (N<u>C</u>H$_2$), 60.57 (α carbon), 67.78 (Ph<u>C</u>H$_2$), 73.34 (C≡<u>C</u>H), 77.89 (CH$_2$<u>C</u>≡CH), 127.29-129.01 (ArC), 132.89 (para PhSO$_2$), 134.72 (ipso PhCH$_2$), 139.29 (ipso PhSO$_2$), 168.00 (<u>C</u>O$_2$); m/z DCI/NH_3 455/453 (MNH_4^+,24), 438/436 (MH^+,13), 373 (32), 356 (22), 300 (15), 216 (21), 108 (26), 91 (100%).

N-Phenylsulphonyl-4-exomethylene-(S)-proline benzyl ester (9)

N-phenylsulphonyl-N-propargyl-3-bromo-(S)-alanine benzyl ester (**8**) (1.23g, 2.81mmol) and A.I.B.N. (0.4 equiv.) were dissolved in degassed benzene (80ml). Tributyl tin hydride (0.93g, 3.37mmol, 1.2 equiv. 84%v/v solution) was added *via* a syringe and the reaction mixture was heated under reflux for ten hours. The reaction was allowed to cool and the benzene removed by rotory evaporator to give a brown oily substance which was partitioned between a 10% aqueous KF solution (10ml) and ether (10ml). This mixture was then stirred at room temperature for 30 minutes, during which time a white precipitate of tributyl tin fluoride developed which was filtered off through Celite. The filtrate was then stirred for a further thirty minutes and filtered again. The separated aqueous layer was then extracted again with ether (10ml), the organic layers combined and extracted with saturated brine (50ml) and dried ($MgSO_4$). Solvent removal afforded a yellow oil which was purified by flash chromatography (SiO_2, 150ml, 1:9-15:85 ethyl acetate:petrol) to give an off-white coloured solid which was recrystallised from ether / hexane to give **N-Phenylsulphonyl-4-exomethylene-(S)-proline benzyl ester (9)** (0.65g, 58%); m.p.55-56°C; Rf 0.6 (SiO_2 plates 3:7 ethyl acetate : petrol); $[\alpha]_D$ -29.9° (c=1, $CHCl_3$). (Found C 63.72; H 5.25; N 3.98. $C_{19}H_{19}NO_4S$ requires C 63.85; H 5.36; N 3.92%); υ_{max} ($CHCl_3$) 1750 (s, C=O str), 1358 (s, SO_2N), 1165 (s, SO_2N), 900cm^{-1} (m, C=CH_2); δ_H (200MHz; $CDCl_3$) 2.53-2.71 (1H, m, H3), 2.71-2.89 (1H, m, H3'), 4.05 (2H, s, H5), 4.03 (1H, dd, J 3.5, 9, H2), 4.96 (2H, m, C=CH_2), 4.94-5.04 (2H, m, CH_2Ph), 7.27-7.89 (10H, m, ArH); δ_C(200MHz;$CDCl_3$) 36.91 (C3), 51.65 (C5), 60.46 (C2), 67.08 (CH_2Ph), 108.86 (C=CH_2), 127.53-129.20 (ArC), 133.07 (para $PhSO_2$), 135.40 (ipso $PhCH_2$), 138.02 (ipso $PhSO_2$), 142.02 (C4), 171.28 (C1); m/z DCI/NH_3 375 (MNH_4^+,47), 358 (MH^+,100), 266 (22), 222 (78), 216 (40%)

4-Exomethylene-(S)-proline (2)

6% sodium amalgam (1.5g) was added to a stirred solution of K_2HPO_4 (0.70g, 4mmol) and N-Phenylsulphonyl-4-exomethylene-(S)-proline benzyl ester (**9**) (0.36g, 1.0 mmol) in anhydrous methanol (5ml) at 0°C. The reaction mixture was allowed to attain room temperature and stirred for a further hour, during which time the amalgam turned from solid to liquid. The reaction mixture was then filtered through Celite to remove any undissolved buffer and mercury.The methanol was removed by rotory evaporator and the residue partitioned between ethyl acetate (10ml) and distilled water (10ml). The separated aqueous layer was adjusted to pH 2 with 2N HCl and extracted twice more with ethyl acetate (2x10ml). The aqueous solution was the split into two 5ml aliquots, one of which was used in the preparation of (**10**) and the other desalted by ion exchange chromatography (Dowex 50X8 cation resin), after a prewash with 100ml of distilled water, the amino acid being eluted from the column by 1N NH_4OH. The first 20ml of basic eluant were taken, freeze dried to fine white needles of a substance which was recrystallised from wet methanol / ethyl acetate to give **4-exomethylene-(S)-proline (2)** (0.05g, 76% yield); m.p. 210-212°C; $[\alpha]_D^{20}$ -29.8° (c=0.9, 2N HCl) [Lit.,[3b] $[\alpha]_D^{25}$ -50.9 (c=0.44, H_2O)]; (Found C 56.53; H 6.85; N 11.42. $C_6H_9NO_2$ requires C 56.74; H 7.14; N 11.04%); υ_{max} (KBr disc) 3092 (s, br, NH str), 2379 (s, br, NH str), 1610 (s, CO str), 912cm^{-1} (m, C=CH_2); δ_H (200MHz; D_2O) 2.52, 2.76 (2H, AB part ABX, J_{AB} 17, J_{AX} =J_{BX} 9, H3), 3.76 (2H, m, H5), 4.03 (1H, t, br, J 9, H2), 4.92-5.12 (2H, m, C=CH_2); δ_C (50.3MHz; D_2O) 36.69 (C3), 49.32 (C5), 61.85 (C2), 110.90 (C=CH_2), 140.43 (C4), 174.81 (C1); m/z DCI/NH_3 130 (43), 128 (MH^+, 98), 112 (26), 84 (78), 82 (100%).

N-Boc-4-exomethylene-(S)-proline (10)

A 5ml aliquot of reaction product from the previous reaction was taken and the pH adjusted to 7 with solid K_2CO_3. Triethylamine (0.10g, 1.0mmol, 2 equiv.) and BOC anhydride (0.14g, 0.6mmol, 1.2 equiv.) were dissolved in tetrahydrofuran (5ml), the two solutions were mixed and stirred at room temperature for twelve hours. The tetrahydrofuran was removed by rotory evaporator and the remaining solution extracted with ethyl acetate (5ml). The aqueous layer was removed, acidified to pH 2 and extracted three times with ethyl acetate (5ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed by rotory evaporator to give a slightly yellow solid which was purified by flash chromatography (SiO_2, 6:1:13 ethyl acetate: Acetic acid: petrol) affording **N-Boc-4-exomethylene-(S)-proline (10)** (0.05g, 44% yield over two steps); m.p. 108-109 C; $[\alpha]_D$ -42.2° (c=1, $CHCl_3$); Rf 0.7 (SiO_2 plates, 8:1:9 ethyl acetate: acetic acid: petrol); (Found C 58.17; H 7.68; N 5.97. $C_{11}H_{17}NO_4$ requires C 58.13; H 7.54; N 6.16%); υ_{max} ($CHCl_3$) 2650 (br, s, CO_2H), 1755, 1725 (s, OCON, C=O str), 1695 (s, CO_2H str), 900cm^{-1} (s, C=CH_2); δ_H (200MHz; $CDCl_3$) 1.45 (9H, s, C$\underline{Me}_3$), 2.13-3.12 (2H, m, broadened, H3), 4.08 (2H, d, J 10.5, H5), 4.46 (1H, rotamer, d, J 7, H2), 4.50 (1H, rotamer, d, J 7, H2), 5.01 (2H, s, C=C$\underline{H}_2$), 9.38-9.68 (1H, br, s, $CO_2\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 28.1, 28.2 (C$\underline{Me}_3$), 35.3, 36.51 (C3), 50.57 (C5), 58.57, 58.78 (C2), 80.68, 81.06 ($\underline{C}Me_3$), 108.29 (C=$\underline{C}H_2$), 142.17, 142.98 (C4), 176.25 ($O_2\underline{C}N$), 178.6 (C1)

N-Boc-4-exomethylene-(S)-prolinyl dibenzyl-(S)-aspartate (11a)

To a mixture of N-Boc-4-exomethylene-(S)-proline **(10)** (0.02g, 0.09mmol), 1-hydroxybenzotriazole (0.01g, 0.09mmol) and dibenzyl-(S)-aspartate tosylate salt[6] (0.04g, 0.09mmol) dissolved in tetrahydrofuran (2ml) at 0°C was added triethylamine (0.09mmol, 0.12ml of a 1:9 v/v solution in tetrahydrofuran). The solution was stirred as dicyclohexylcarbodiimide (0.02g, 0.09mmol) in tetrahydrofuran (1ml) was added *via* a cannula, then the solution was stirred for one hour at 0°C and one hour at room temperature. The tetrahydrofuran was removed by rotory evaporator and the residual white solid was partitioned between ethyl acetate (2ml) and a 5% $NaHCO_3$ solution (1ml). Ethyl acetate (5ml) was added to the organic layer, which was dried ($MgSO_4$) and the solvent removed by rotory evaporator to yield a white solid which was **N-Boc-4-exomethylene-(S)-prolinyl-dibenzyl-(S)-aspartate (11a)**. After the extraction procedures an NMR was taken. The procedure was repeated using N-Boc-4-exomethylene-(RS)-proline derived from 4-exomethylene-(RS)-proline produced by the method of Burgstahler and Trollope[3a] to give N-Boc-4-exomethylene-(RS)-prolinyl-dibenzyl-(S)-aspartate **(11b)** as shown in fig 1. From comparison of these two spectra it is apparent that only one diastereomer was present in the material derived from the radical cyclisation. The relevant part of the spectrum is shown in Figure 1, for (11a) δ_H (500MHz; $CDCl_3$) 5.037-5.053 (2H, m, C$\underline{H}_2$Ph), 5.127-5.145 (2H, br, s, C$\underline{H}_2$Ph). For (11b) δ_H (500MHz; $CDCl_3$) 5.037-5.053 (2H, m, C$\underline{H}_2$Ph) 5.053-5.063 (2H, m, C$\underline{H}_2$Ph), 5.107-5.112 (2H, m, C$\underline{H}_2$Ph), 5.127-5.145 (2H, m, C$\underline{H}_2$Ph).

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