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SYNTHESIS AND REARRANGEMENT OF HOMOSERINE DERIVATIVES

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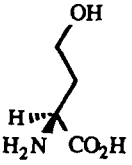
Abstract: Two new syntheses of L-homoserine and its derivatives are described and a rearrangement which converts an L-homoserine derivative into a protected L-azetidine carboxylic acid is discussed.

L-homoserine (1), L-azetidine carboxylic acid (2) and their derivatives are important amino acids both chemically[1] and biologically.[2] We now give full experimental details of two stereospecific synthesis of L-homoserine and its derivatives from the inexpensive amino acids L-aspartic acid[3] and L-methionine[4] respectively, and also we describe a novel rearrangement which converts an L-homoserine derivative into a protected L-azetidine carboxylic acid.



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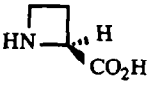

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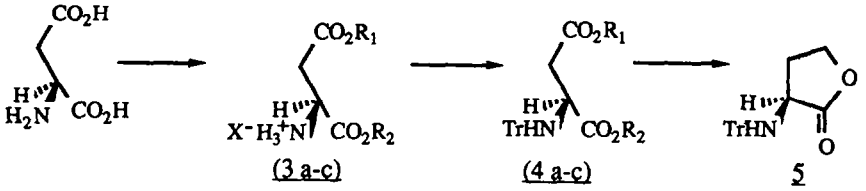
L-Aspartic acid was converted into its dibenzyl ester[5] (3a) and then into N-trityl L-aspartic acid dibenzyl ester[6] (4a). Treatment of diester (4a) with DIBAH in toluene gave N-trityl-L-homoserine lactone (5) in 50-60% yield. In our communication on this sequence,[3] the ^{1}H n.m.r. spectrum of (5) was fully assigned based on the absence of coupling between two of the protons. However after publishing that paper we were informed of deuterium labelling experiments which disagreed with the assignment given,[7] we hence performed a series of n.o.e. experiments on (5) (Table 1) which showed that the correct assignments are as shown in Figure 1. Lactone (5) could be deprotected with trifluoroacetic acid to give L-homoserine lactone as its hydrochloride (Scheme 1).



(3 a-c) (4 a-c) 5

a. R_1=Bn, R_2=Bn, X=TsO
b. R_1=Me, R_2=Me, X=Cl
c. R_1=Me, R_2=^{t}Bu, X=Cl

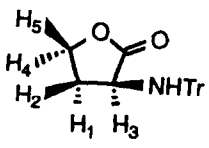


Figure 1

Scheme 1

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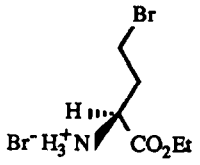
n.o.e. (%) (δ_H) Irradiate (assignment) (δ_H)	1.2 H_1	1.6 H_2	3.4 H_3	3.8 H_4	4.1 H_5
1.2 H_1		23	9	6	-1
1.6 H_2	16		0	0	5
3.4 H_3	7	0		3.5	0
3.8 H_4	5	0	3		27
4.1 H_5	0	9	0	35	

Table 1

The nature of the esters in compound (4) appears to be unimportant since both the dimethyl ester (4b) and mixed diester (4c) were reduced to lactone (5). The diester (3c) was synthesised in two steps by treatment of L-aspartic acid with methanolic hydrogen chloride to give C4-methyl L-aspartate hydrochloride,[9] followed by isobutene and concentrated sulphuric acid, rather than the four steps required by the literature method.[9] N-trityl compounds only could be reduced; starting material was obtained with a t-butyloxycarbonyl (Boc),[10] benzyloxycarbonyl (Z)[11] or tosyl group on nitrogen. When the solvent was changed to tetrahydrofuran, no reduction of diester (4a) occurred.

We envisaged that acid (2) should be available from lactone (5). The lactone ring was opened with hydrogen bromide in ethanol which proceeded with loss of the trityl group to give the unstable bromo amino ester hydrobromide (6), which was converted into the known, stable N-tosyl derivative (7)[12] for characterisation.



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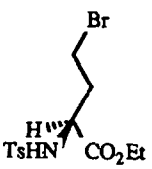

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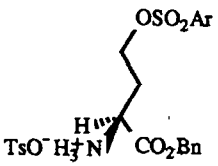
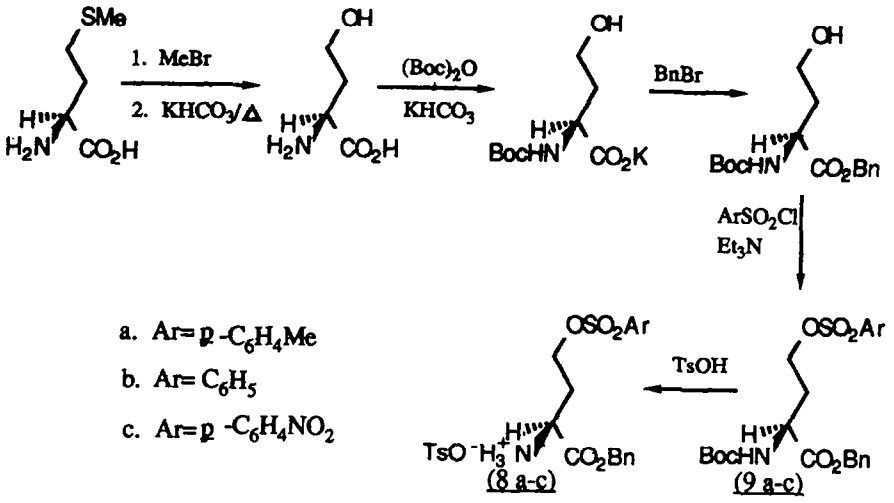


(8 a-c)

a. Ar= p -C_6H_4Me
b. Ar= C_6H_5
c. Ar= p -$C_6H_4NO_2$

Treatment of bromo ester (6) with sodium hydride in dimethylformamide however gave only an unidentified white solid and none of the desired L-azetidine carboxylic acid ethyl ester could be isolated. It was felt that a better leaving group was required, so O-tosyl L-homoserine benzyl ester (8a) was synthesised. This synthesis proceeded via a route developed separately by two of us.[4]

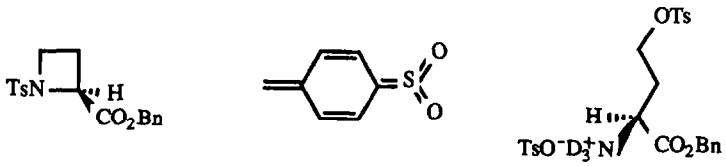
In this way L-methionine was converted into the potassium salt of N-Boc L-homoserine. Reaction with benzyl bromide gave N-Boc L-homoserine benzyl ester as an impure oil which could not be purified without extensive lactonisation. However reaction with p-toluenesulphonyl chloride gave the stable N-Boc O-tosyl L-homoserine benzyl ester (9a). Deprotection with p-toluenesulphonic acid gave ammonium salt (8a) as a white solid (Scheme 2).



Scheme 2

Treatment of (8a) with diisopropylethylamine in dichloromethane did not give the expected L-azetidine carboxylic acid benzyl ester, but gave N-tosyl L-azetidine carboxylic acid benzyl ester (10) as an unstable oil in 40% yield.

To investigate the mechanism of this rearrangement, the benzenesulphonyl derivative (8b) was synthesised by an analogous route to (8a). It could not be rearranged even under more forcing conditions than (8a), since only recovered starting material was obtained after refluxing (8b) with diisopropylethylamine in dichloromethane for 10 days and refluxing (8b) with sodium hydride in dimethylformamide caused decomposition.



10 11 12

It was felt that sulphene (11) might be an intermediate in this reaction, although it had not previously been detected under such mildly basic conditions.[12] Hence the deuterated derivative (12) was synthesised from (8a) by treatment with acetic acid-d_1, but rearrangement under the conditions described above gave no deuterium incorporation into the tosyl methyl group of azetidine (10).

The mechanism of this reaction must at some stage involve S-O bond cleavage of the sulphonate ester. This is known to be quite common for aryl sulphonates but not to occur as readily with alkyl or nitro-aryl sulphonates.[13] Hence we attempted to synthesise the mesylate analogous to (9) and the p-nitro derivative (9c). However both of these compounds were found to be unstable to chromatography, preventing us from further investigating the mechanism of this reaction.

EXPERIMENTAL

Melting points were determined with a Buchi 510 capillary apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter. I.R. spectra were recorded on a Perkin-Elmer 681 spectrophotometer; broad (br), weak (w), medium (m), and strong (s) bands are reported. ^1H *n.m.r.* spectra were recorded on Bruker AM 500 MHz, WH 300 MHz, or AM 250 MHz spectrometers using the residual solvent peak as internal standard and are in $CDCl_3$ unless

otherwise stated. ^{13}C n.m.r. spectra were recorded at 62.85 MHz on a Bruker 250 spectrometer using $CDCl_3$ = 77.0 p.p.m. as internal reference. Multiplicities are recorded as br (broad peak), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dt (double triplet) etc. Mass spectra were recorded on VG Analytical Ltd. ZAB1F or MM30F Mass spectrometers [for Ammonia Desorption Chemical Ionisation (DCI), positive argon Fast Atom Bombardment (FAB), or Field Desorption (F.D)]. Microanalyses were performed by Mrs. V. Lamburn, Dyson Perrins Laboratory, University of Oxford. All solvents were distilled before use, THF was distilled over sodium benzophenone. All chromatography was done on silica gel using the technique of flash chromatography[15] unless otherwise stated.

N-Trityl L-homoserine lactone (5)

To diester (4a)[5,6] (1.1 g, 2.0 mMol) in sodium dried toluene (30 ml) at -78°C was added 1.5 M DIBAH (1.5 ml, 1.1 eq.) in toluene. After stirring for 2 hours at -78°C, the solution was warmed to 0°C over 3 hours and stored at 4°C for 18 hours. Aqueous ammonium chloride was added and the product extracted into ethyl acetate, dried, ($MgSO_4$) and the solvents evaporate in vacuo. The crude product was chromatographed (CH_2Cl_2) to give (5) as a white foam. Yield 680 mg (60%); mp 179°C (lit.,[16] 180-181°C); (Found: C,80.55; H,6.2; N,3.9. $C_{23}H_{21}NO_2$ requires: C, 80.5; H,6.1; N,4.0%); $[\alpha]_D^{25}$ -102° (lit.,[16] -95°) (c 2.0 in $CHCl_3$); ν_{max}. ($CHCl_3$) 3050 m, 1775 s, 1170 s, and 705 cm^{-1} s; δ_H 1.2 (1H, ddd, CH_2), 1.6 (1H, ddd, CH_2), 2.9 (1H, br s, exchanges with D_2O, NH), 3.4 (1H, dd, NCH), 3.8 (1H, ddd, OCH_2), 4.1 (1H, pseudo t, OCH_2), and 7.2-7.7 (15H, m, ArH); δ_C 32.5 (t, CH_2), 53.3 (d, NCH), 65.3 (t, OCH_2), 71.2 (s, NC), 126.7, 128.2, and 128.8 (d, ArC), 145.6 (s, ArC), 178.2 (s, CO_2); m/z (F.D) 343 (M^+).

L-Homoserine lactone hydrochloride

To protected lactone (5) (500 mg, 1.5 mMol) in CH_2Cl_2 (5 ml) was added 90% aqueous trifluoroacetic acid (1 ml, excess). The resulting red solution was stirred at RT for 0.5 hours. The product was extracted into 2N HCl, thoroughly washed with CH_2Cl_2 and the water removed in vacuo with ethanol, giving 260 mg of product as a white solid. Yield 200 mg (97%); mp 199-200°C; $[\alpha]_D^{25}$ -4.2° (c 3.0 in EtOH); ν_{max} (nujol) 3600-2000 br, 1785 s, and 1200 cm^{-1} s; δ_H (DMSO-d_6) 2.2-2.4 (1H, m, CH_2), 2.5-2.6 (1H, m, CH_2), 4.2-4.4 (2H, m, OCH_2) 4.4-4.5 (1H, m, NCH), 8.9 (3H, br s, NH_3).

N-Trityl L-aspartic acid dimethyl ester (4b)

To (3b)[17] (5.0 g, 25 mMol) in CH_2Cl_2 (50 ml) was added triethylamine (7.5 ml, excess) followed by trityl chloride (7g, 25 mMol). The mixture was stirred at RT for 18h, filtered, washed with ammonium chloride and sodium carbonate solutions, dried ($MgSO_4$) and the solvent evaporated in vacuo to give a red oil which was purified by dry flash chromatography[18] (1:1 hexane/CH_2Cl_2 - CH_2Cl_2) to give (4b) as a colourless oil which slowly crystallized. Yield 7.9 g (78%); mp 71°C; (Found: C, 74.6; H,6.2; N,3.5. $C_{23}H_{23}NO_4$ requires: C,74.4; H,6.2; N,3.5%); $[\alpha]_D^{25}$ +9.04° (c 6.5 in $CHCl_3$); ν_{max} (neat) 3310 w, 3050 w, 2950 w, and 1740 cm^{-1} s; δ_H 2.6 (1H, dd, J 14.7, and 7.0 Hz, CH_2), 2.7 (1H, dd, J 14.7, and 5.4 Hz, CH_2), 3.0 (1H, d, J 10.1 Hz, NH), 3.3 (3H, s, C1-OCH_3), 3.7 (3H, s, C4-OCH_3), 3.8-3.9 (1H, m, NCH), 7.2-7.6 (15H, m, ArH), δ_C 40.0 (t, CH_2), 51.5 (q, C1-OCH_3), 51.6 (q, C4-OCH_3), 53.5 (d, NCH), 71.0 (s, NC), 126.4, 127.7, and 128.6 (d, ArCH), 145.5, (s, ArC), 170.7 (s, C1-CO_2), 173.7 (s, C4-CO_2); m/z (F.D) 403 (M^+).

L-Aspartic acid C1-t-butyl C4-methyl diester hydrochloride (3c)

Conc. H_2SO_4 (8 ml) was added dropwise to THF (30 ml) at 0°C in a pressure bottle. L-aspartic acid C4-methyl ester hydrochloride[7] (6.5g, 35.4 mMol) was then added followed by isobutene (30 ml). The bottle was sealed and the contents stirred at RT for 18 hours. The bottle was carefully opened and the contents poured into saturated aqueous sodium carbonate (100 ml). The products were extracted with ether (3x 100 ml), dried ($MgSO_4$) and the ether concentrated to ca. 50 ml in vacuo. HCl gas was bubbled through the solution, the resulting solid (3c) was filtered and recrystallized from EtOAc/Et_2O. Yield 3.5 g (42%); mp 143-144°C (lit.,[8] 144-146°C); ν_{max} (nujol) 2500-3500 br, and 1740 cm^{-1} s; δ_H 1.5 (9H, s, $C(CH_3)_3$), 3.7 (2H, pseudo q, J 18 Hz, CH_2), 3.8 (3H, s, OCH_3), 4.4 (1H, br, NCH); m/z (DCI) 204 (MH^+), 148, 102.

N-Trityl L-Aspartic acid C1-t-butyl C4-methyl diester (4c)

The method was as for diester (4b), using (3c) (2g, 8.4 mMol). The crude product was chromatographed (CH_2Cl_2) to give (4c) as a colourless oil. Yield 750 mg (20%); ν_{max} (neat) 3060 w, 2980 w, 1740 s, and 1155 cm^{-1} s; δ_H 1.2 (9H, s, $C(CH_3)_3$), 2.4 (1H, dd, J 14.9, and 7.3 Hz, CH_2), 2.5 (1H, dd, J 14.9, and 4.3 Hz, CH_2), 3.0 (1H, d, J 8.5 Hz, NH), 3.55-3.65 (1H, m, CH), 3.7 (3H, s, OCH_3), 7.1-7.6 (15H, m, ArH); δ_C 27.7 (q, $(CH_3)_3$), 40.1 (t, CH_2), 51.4 (q, OCH_3), 53.9 (d, CH), 71.3 (d, CN), 81.1 (s, CMe_3), 126.4, 127.8, and 128.7 (d, ArCH), 145.9 (s, ArC), 171.2 (s, C1-CO_2), 172.4 (s, C4-CO_2); m/z (FAB) 446 (MH^+), 444.

N-Tosyl L-aspartic acid dibenzyl ester

To diester (3a)[5] (15 g, 33 mMol) in THF (50 ml) was added Et_3N (20 ml, excess) followed by p-toluenesulphonyl chloride (6.3 g, 33 mMol). The solution was stirred at RT for 18 hours, the THF evaporated in vacuo and the products partitioned between CH_2Cl_2 and dilute HCl. The organic phase was washed with saturated aqueous sodium carbonate, dried and the solvent removed in vacuo. Recrystallization from ethanol gave the product as white crystals. Yield 14.3 g (93%); mp 79-80°C; (Found: C,64.21; H,5.52; N,3.02. $C_{25}H_{25}NO_6S$ requires: C,64.51; H,5.38; N,3.01%); $[\alpha]_D^{25}$ +34.9° (c 9.3 in $CHCl_3$); ν_{max} ($CHCl_3$) 3290 m, and 1740 cm^{-1} s; δ_H 2.4 (3H, s, CH_3Ph), 2.9 (1H, dd, J 17.1, and 4.9 Hz, CH_2), 3.0 (1H, dd, J 17.1, and 4.4 Hz, CH_2), 4.2 (1H, dt, J 8.0, and 4.5 Hz, NCH), 5.0 (2H, s, CH_2Ph), 5.05 (2H, s, CH_2Ph), 5.7 (1H, d, J 8.0 Hz, NH), 7.1-7.5 (12H, m, ArH), 7.7 (2H, d, J 8.3 Hz, ArH o-to SO_2); δ_C 21.1 (q, CH_3Ph), 37.6 (t, CH_2), 52.0 (d, NCH); 66.5 (t, CH_2Ph), 67.4

(t, CH_2Ph), 126.8, 127.8, 127.9, 128.0, 128.1, 128.2, 129.3, and 129.5 (d, ArCH), 134.5, 135.0, 136.7, and 143.2 (s, ArC), 169.5 (s, CO_2), 169.6 (s, CO_2); m/z (DCI) 485 ($M+NH_4^+$), 468 (MH^+), 332, 91.

Ethyl 2-amino 4-bromo L-butyrate hydrobromide (6)

HBr gas was passed through a solution of lactone (5) (1 g, 3 mMol) in ethanol (5 ml) for 1 hour. The solution was then stirred at RT for 18 hours and the ethanol removed in vacuo. The product was washed with hexane to remove trityl bromide, giving a brown oil (6) which was too unstable to further purify. Yield 260 mg (30%); ν_{max} (neat) 3400 br, 2900 br, 1745 s, and 1230 cm^{-1} m; m/z (DCI) 210 and 212 (MH^+), 136, 138, 116.

Ethyl N-tosyl 2-amino 4-bromo L-Butyrate (7)

To hydrobromide (6) (110 mg, 0.4 mMol) in CH_2Cl_2 (5 ml) was added p-toluenesulphonyl chloride (88 mg, 0.4 mMol) and triethylamine (2 ml, excess). The solution was stirred at RT for 18 hours and the CH_2Cl_2 evaporated in vacuo. The product was chromatographed (10% EtOAc/CH_2Cl_2) to give 180 mg of product (7) which was recrystallized from ether by addition of hexane. yield 140 mg (95%); δ_H 1.1 (3H, t, J 7.3 Hz, CH_3), 1.6-1.8 (2H, m, CH_2Br), 2.0-2.4 (2H, m, CH_2), 2.4 (3H, s, CH_3Ph), 3.5 (1H, t, J 6.5 Hz, NCH), 4.0 (2H, q, J 7.3 Hz, OCH_2), 5.3 (1H, br, NH), 7.3 (2H, d, J 8.3 Hz, ArH m-to SO_2), 7.7 (2H, d, J 8.3 Hz, ArH o-to SO_2); m/z (DCI) 381 and 383 ($M+NH_4^+$), 364 and 366 (MH^+), 273, 198.

L-homoserine

L-Methionine (7.5 g, 50 mMol) was dissolved in water (500 ml) and methanol (50 ml) in a pressure bottle. The solution was cooled with ice/salt and methyl bromide (100 ml, excess) was added. The bottle was sealed and the solution stirred at RT for 24 hours. The bottle was opened, excess methyl bromide was allowed to evaporate and the solution was concentrated to 200 ml in vacuo, using ethanol to azeotrope the water. Potassium hydrogen carbonate (5 g, 50 mMol) was added and the aqueous solution refluxed for 5 hours with evolution of dimethyl sulphide. The resulting cooled solution contained L-homoserine and was used without further purification.

N-Boc potassium L-homoserine

To the aqueous solution of L-homoserine obtained above was added dioxan (200 ml), potassium hydrogen carbonate (5 g, 50 mMol) and di-t-butyl carbonate (12 g, 55 mMol). The solution was stirred at RT for 18 hours and the solvents removed with ethanol in vacuo. The resulting white solid was used without further purification.

N-Boc L-homoserine benzyl ester

The N-Boc potassium L-homoserine obtained above was dissolved in DMF (50 ml) and benzyl chloride (6 ml, 52 mMol) was added. The solution was stirred at RT for 48 hours and the DMF was removed with xylene in vacuo. The products were partitioned between CH_2Cl_2 and aqueous sodium carbonate solution. The organic phase was washed with water, dried ($MgSO_4$) and evaporated in vacuo to give a yellow oil which could not be purified and slowly lactonised at 4°C.

N-Boc O-tosyl L-homoserine benzyl ester (9a)

N-Boc benzyl L-homoserine (1 g) obtained above was dissolved in CH_2Cl_2 (10 ml) and p-toluenesulphonyl chloride (0.9 g, excess) was added, followed by triethylamine (2 ml, excess). The solution was stirred at RT for 3 hours, washed with aqueous citric acid and aqueous sodium carbonate, dried ($MgSO_4$) and evaporated to give a yellow oil which was chromatographed (3% EtOAc/CH_2Cl_2) to give a colourless oil (9a). Yield 550 mg (30% from L-methionine) (Found: C,59.5; H,6.4; N,2.7. $C_{23}H_{29}NO_7S$ requires: C,59.6; H,6.3; N,3.0); $[\alpha]_D^{\beta}$° +5.29° (c 12.3 in $CHCl_3$); ν_{max} 3380 m, 3020 w, 2980 m, and 1720 cm^{-1} s; δ_H 1.4 (9H, s, $C(CH_3)_3$), 2.0-2.4 (2H, m, CH_2), 2.45 (3H, s, CH_3Ph), 4.0-4.2 (2H, m, CH_2OTs), 4.3-4.4 (1H, m, NCH), 5.1 (2H, s, CH_2Ph), 5.1-5.3 (1H, br, NH), 7.2-7.4 (7H, m, ArH), 7.7 (2H, d, J 8.4 Hz, Ar o-to SO_2); δ_C 21.4 (q, CH_3PH), 28.1 (q, $(CH_3)_3$), 31.3 (t, CH_2), 50.5 (d, NCH), 64.7 (t, CH_2OTs), 66.2 (t, CH_2Ph), 79.9 (s, CMe_3), 127.8, 128.2, 128.3, 128.4, and 129.7 (d, ArCH), 132.6, 135.0, and 144.7 (s, ArC), 155.0 (s, NCO_2), 171.3 (s, CO_2); m/z (F.D) 464 (MH^+).

O-Tosyl L-homoserine benzyl ester tosylate (8a)

To (9a) (500 mg, 1.1 mMol) in ethanol (2 ml) was added p-toluenesulphonic acid monohydrate (240 mg, 1.2 mMol). The ethanol was evaporated in vacuo, replenished, evaporated and the resulting oil was crystallized under high vacuum for 18 hours. The resulting solid (8a) was used without further purification. Yield 560 mg (95%); ν_{max} 3700-2500 br, and 1745 cm^{-1} s; δ_H 2.2 (2H, q, J 6.2 Hz, CH_2), 2.4 (6H, s, 2x CH_3Ph), 3.3 (1H, t, J 1.6 Hz, NCH), 4.2 (2H, t, J 6.1 Hz, CH_2OTs), 5.1 (3H, br s, NH_3), 5.2 (2H, dd, J 6.7 and 3.4 Hz, CH_2Ph), 7.2 (2H, d, J 8.1 Hz, ArH m-to SO_2), 7.3 (5H, s, ArH), 7.4 (2H, d, J 8.4 Hz, ArH m-to SO_2), 7.7 (2H, d, J 8.1 Hz, ArH o-to SO_2), 7.75 (2H, d, J 8.4 Hz, ArH o-to SO_2); m/z (DCI) 364 (MH^+), 192, 102, 91.

N-Tosyl L-azetidine carboxylic acid benzyl ester (10)

To tosyl derivative (8a) (100 mg, 0.3 mMol) in CH_2Cl_2 (5 ml) was added diisopropylethylamine (2 ml, excess). The solution was stirred at RT for five days, washed with aqueous sodium carbonate, dried ($MgSO_4$) and evaporated in vacuo to give a yellow oil. Chromatography (5% MeOH/CH_2Cl_2) gave (10) as a colourless oil. Yield 15 mg (40%); $[\alpha]_D^{\beta}$ -13.5° (c 8.8 in $CHCl_3$), ν_{max} (neat) 3030 w, 2920 w, 1745 s, and 1145 cm^{-1} s; δ_H 1.6-1.8 (1H, m, CH_2), 2.1-2.3 (1H, m, CH_2), 2.4 (3H, s, CH_3Ph), 3.5 (1H, dd, J 8.9, and 4.6 Hz, NCH), 4.1-4.3 (2H, m, CH_2OTs), 5.1 (2H, s, CH_2Ph), 7.1-7.5 (7H, m, ArH), 7.8 (2H, d, J 8.3 Hz, ArH o-to SO_2); δ_C 21.5 (q, CH_3Ph), 33.2 (t, CH_2), 50.9 (d, NCH), 66.9 (t, CH_2N), 67.1 (t, CH_2Ph), 127.9, 128.2, 128.4, 128.6, and 129.8 (d, ArCH), 135.4, 140.1, and 144.7 (s, ArC), 173.9 (s, CO_2); m/z (DCI) 363 ($M+NH_4^+$), 192, 102, 91.

N-Boc O-benzenesulphonyl L-homoserine benzyl ester (9b)

The method was as for (9a), using N-Boc L-homoserine benzyl ester (3 g) and benzenesulphonyl chloride (3 ml, excess). The product was purified by chromatography (3%-EtOAc/CH_2Cl_2) to give (9b) as a colourless oil. Yield 1.5 g (30% from L-methionine); (Found: C,58.5; H,5.89; N,3.4. $C_{22}H_{27}NO_7S$ requires: C,58.8; H,6.0; N,3.1%); ν_{max} (nujol) 3380 m, 1750 s, and 1710 cm^{-1} s; δ_H 1.4 (9H, s, $(CH_3)_3$), 2.0-2.2 (1H, m, CH_2), 2.2-2.4 (1H, m, CH_2), 4.0-4.2 (2H, m, CH_2OSO_2), 4.3-4.4 (1H, m, NCH), 5.1 (2H, s, CH_2Ph), 5.2 (1H, d, J 7.2 Hz, NH), 7.3-7.9 (10 H, m, ArH); δ_C 28.1 (q, $(CH_3)_3$), 31.4 (t, CH_2), 50.6 (d, NCH), 66.4 (t, CH_2OSO_2), 67.3 (t, CH_2Ph), 80.0 (s, $OCMe_3$), 125.9, 127.7, 128.2, 128.3, 128.4, and 129.1 (d, ArCH), 133.7, and 135.0 (s, ArC), 155.0 (s, NCO_2), 171.2 (s, CO_2).

O-Benzenesulphonyl benzyl L-homoserine tosylate (8b)

The method was as for (8a) using (9b) (0.33 g, 0.7 mMol). Yield 0.42 g (99%); ν_{max} (nujol) 3400 w, and 1740 cm^{-1} s; δ_H 2.0-2.2 (2H, m, CH_2), 2.3 (3H, s, CH_3Ph), 4.0-4.2 (3H, m, NCH and CH_2OSO_2), 5.0 (2H, dd, J 16.2 and 12.5 Hz, CH_2Ph), 7.0-8.0 (14 H, m, ArH), 8.4 (3H, br s, NH_3).

Prep. and rearrangement of deuterated derivative (12)

To (8a) (100 mg, 0.2 mMol) was added acetic acid d_1, the solution was stirred at RT for 10 minutes and the acid was evaporated *in vacuo* with toluene. The process was repeated three times to give (12). (12) was then cyclised as above, except that after two days di-t-butyl carbonate (100 mg, 0.24 mMol) was added and the solution stirred at RT for a further 24 hours. The solution was washed with 10% aqueous citric acid and with saturated sodium carbonate solution, dried ($MgSO_4$) and evaporated to give a yellow oil which was chromatographed (CH_2Cl_2 then 3% MeOH/CH_2Cl_2) to give (9a) and (10). ^1H NMR showed no deuterium incorporation into the tosyl methyl group of either product.

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