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The Synthesis of (R)-(-) and (S)-(+)-Hydroxysaclofen

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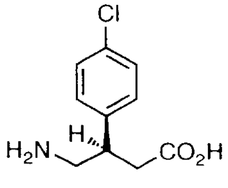
Abstract: 2-(4-Chlorophenyl)-3-hydroxypropene has been separately converted to both enantiomers of its epoxide. The epoxides were converted to (R)-(-) and (S)-(+)-hydroxysaclofen. Only the latter showed activity as a specific GABA$_B$ antagonist.

INTRODUCTION

The GABA$_B$ receptor in the peripheral and central nervous system is implicated in analgesia, muscle relaxation, hypertension, increased gastric motility, and inhibition of the release of corticotropin releasing hormone[1]. Until recently, (R)-(-)-baclofen (**1**) has been the only selective and therapeutically useful agonist[2], although a few analogues have lesser activity[3,4]. Phosphinic analogues of GABA bind effectively at the GABA$_B$ site, and act as agonists in functional tests[5-7]. The first specific antagonists for GABA$_B$ receptors were phaclofen (**2**), saclofen (**3**), and hydroxysaclofen (**4**), all of which were first synthesised in our laboratory, [8-10] and which provided the first physiological evidence for GABA$_B$ receptor mediated actions in the CNS[11].



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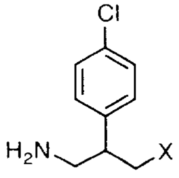

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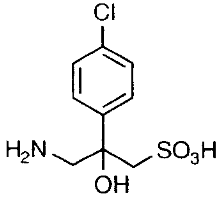
3 X = SO_3H



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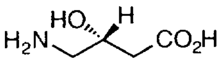

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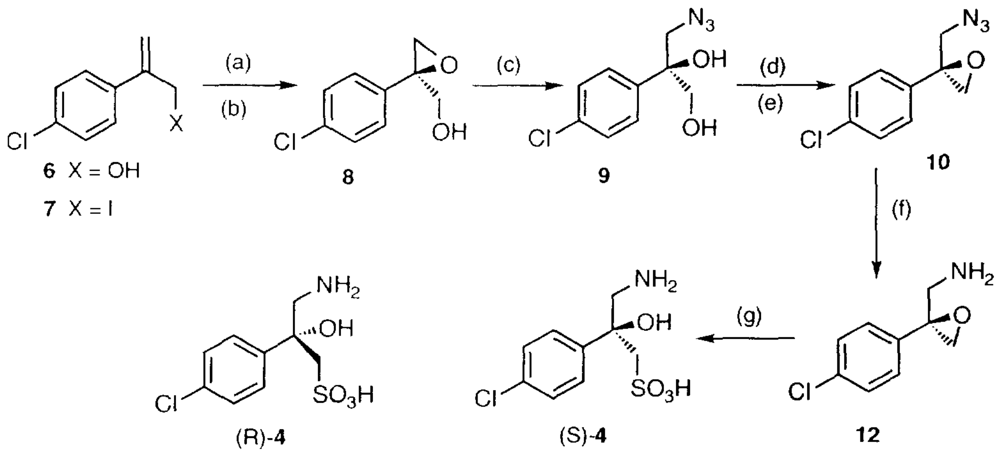
The widespread use of hydroxysaclofen[2,11], the observation that only (R)-(-)-baciofen binds to the GABA$_B$ receptor[12], and the higher activity of (R)-(-)-4-amino-3-hydroxybutanoic acid (**5**) than its enantiomer[13], have prompted us to synthesise both enantiomers of hydroxysaclofen in order to compare their physiological activity. Recently phaclofen,[14] hydroxysaclofen[15] and saclofen[16] have been resolved by the use of chiral analytical HPLC. In the case of phaclofen, the (R)-(-) enantiomer was shown to be responsible for its reactivity[14] : in the case of hydroxysaclofen, insufficient quantities were obtained to characterise their properties[15]. Only (R)-(-)-saclofen was active[16].

DISCUSSION

The allylic alcohol (**6**) was prepared by a modification of the general procedure of Barluenga[17]. In our hands, the reaction of the benzoyl chloride and chloroiodomethane is much cleaner when methyllithium, rather than butyllithium, is used. Even then, the alcohol (**6**) was invariably accompanied by the iodide (**7**) (5-12%) and methyl 4-chlorobenzoate (10-15%) which were readily removed by flash chromatography. Sharpless epoxidation[18] of (**6**) (Scheme 1) with diethyl D-(-)-tartrate gave the (R)-epoxyalcohol (**8**) in 67% yield after purification by flash chromatography. Both the racemic and optically derived acetates, and the racemic 2,4-dinitrobenzoate, were obtained as oils, but the 4-nitrobenzoate was highly crystalline. The acetate,[19,20] or preferably the 4-nitrobenzoate, could be used to determine the optical purity of samples by integration of either of the diastereotopic methylene proton resonances, or of the 4-chlorophenyl aryl resonances, respectively, in the 300 MHz ^1H NMR spectrum in the presence of the optically active NMR shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III). The epoxyalcohol was unsuitable due to line broadening. The product from the Sharpless epoxidation showed 86% e.e., but two recrystallisations of the nitrobenzoate derivative gave the (S)-enantiomer, judged to be greater than 98% optically pure by NMR shift experiments. Hydrolysis with potassium carbonate in methanol gave the optically pure epoxy alcohol (**8**). Ring opening of (**8**) with sodium azide in the presence of ammonium chloride[21] gave the azidodiol (**9**). The diol was converted slowly to the tosylate, which readily formed epoxide (**10**) on reaction with KOtBu in t-butyl alcohol. Reaction of the azido tosylate with sodium methoxide in methanol was not a satisfactory procedure, yielding a mixture of the desired epoxide (**10**) (59%) and the methyl ether (**11**)(41%). Attempts to directly displace the tosylate with sodium sulfite were totally unsuccessful.

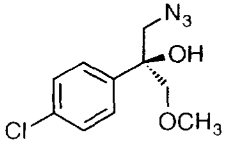


Scheme 1

(a) D-(-)-DET, $Ti(O\text{-}iPr)_4$, t-BuOOH, CH_2Cl_2, -20°; 67% (b) (i) $4\text{-}NO_2C_6H_4COCl$, NEt_3, CH_2Cl_2, 20°; 94% (ii) K_2CO_3, MeOH, 20°; 93% (c) NaN_3, NH_4Cl, $MeOH/H_2O$, 70°; 93% (d) TsCl, pyridine, 20°; 84% (e) KOtBu, THF/ t-BuOH, 20°; 92% (f) H_2/PtO_2, EtOH; 94% (g) $NaHSO_3$, $EtOH/H_2O$, 100°; 51%.

We hoped to obtain (**4**) directly from (**10**) by reaction with sodium hydrogensulfite, but found that direct reduction of the azide to amine was incomplete, and a number of products was formed. The amino-epoxide (**12**), derived from (**10**) by hydrogenation, was then converted to (S)-(+)-hydroxysaclofen (**4**) by reaction with sodium hydrogen sulfite in refluxing ethanol-water, and isolated as its hydrochloride, m.p. 260-263° $[\alpha]_D^{20}$ +19° (H_2O, c = 1.13). If sodium sulfite was used to open the epoxide (**12**), the product consisted of a mixture of hydroxysaclofen (60%) and its isomer (**13**) (40%). The latter probably arises by electron mediated reactions, or an S_N1 solvolysis reaction.

Our first approach to the synthesis of the (R)-enantiomer was to utilise the same optically pure (R)-epoxyalcohol (**8**), using the sulfite and azide nucleophiles in reverse order. However, although (**8**) appeared to react efficiently with sodium hydrogensulfite to give the dihydroxysulfonic acid (**14**), the extreme water solubility of the latter made isolation difficult, and only 10% of (**14**) could be isolated after lengthy continuous extraction with ethyl acetate. The original plan to convert (**14**) to its epoxide and open it with azide was therefore not pursued.



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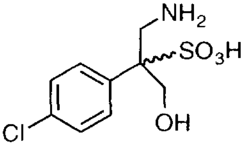

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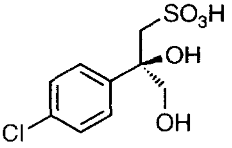

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The procedure summarised in Scheme 1 was duplicated using diethyl L-(+)-tartrate in the Sharpless procedure, which led to the (S)-epoxyalcohol. Each subsequent step proceeded in almost identical yield and with identical enantioselectivity to those depicted in Scheme 1, leading finally to the formation of (R)-(-)-hydroxysaclofen, the hydrochloride of which had m.p. 258-262°, and $[\alpha]_D^{20}$ -18° (H_2O, c = 1.08).

The absolute configuration of the enantiomers above follows directly from the rules enunciated by Sharpless[18], and secondly by comparison of the sign for the optical rotation of (**8**) with those of the des-chloro epoxyalcohol prepared analogously by Landro[22], the configuration of which was confirmed by conversion to a product of known absolute configuration . Both enantiomers have been tested as antagonists or agonists of baclofen and GABA at the $GABA_B$ receptor of isolated guinea pig ileum[23] and rat brain slices[24]. (R)-(-)-Hydroxysaclofen was completely inactive, while (S)-(+)-hydroxysaclofen was a potent and specific antagonist, with activity 2 to 3 times that of the racemate[25]. These results suggest that (S)-(4) maps on to (R)-(1) by replacing the hydrogen atom at the stereogenic centre with hydroxyl. Such a change would clearly not favour binding, and explains why both hydroxysaclofen and hydroxybaclofen[26] are about one third as active as saclofen[11,16,23] and baclofen , respectively. Although Krogsgaard-Larsen[27] has gone to some effort to map the weak, and non-specific $GABA_B$ receptor binders, (S)-(-)-5-amino-2-hydroxyvaleric acid, and (R)-(-)-4-amino-3-hydroxy-butyric acid, and this suggested the un-ionised phosphonic acid hydroxyl group of phaclofen may also overlay the hydroxyl groups of these compounds, we do not believe a hydroxyl group beta to an acid functionality in $GABA_B$ receptor binders plays a dominant role. This is born out by the large decrease in inhibition of GABA binding to cerebellar synaptic membranes on going from 3-aminopropanesulfonic acid to 3-amino-2-hydroxy-propanesulfonic acid[28].

EXPERIMENTAL

General : All solvents were dried by established procedures and distilled before use. Flash chromatography was performed according to the method of Still[29] with silica gel 60 (230-400 mesh). Infrared spectra of liquids were recorded neat, and of solids as nujol mulls. ^{1}H and ^{13}C NMR were obtained in $CDCl_3$, unless otherwise stated, on a Gemini 300 MHz spectrometer.

2-(4-Chlorophenyl)-3-hydroxypropene (6)

The allylic alcohol (**6**) was prepared by modifying the general procedure of Barluenga et al.[17] Methyl lithium (1.4 M in ether, 7.1 ml) was added dropwise over 0.25 h to a stirring mixture of lithium bromide (8.4 g, 96 mmol), 4-chlorobenzoyl chloride (5.6 ml, 44 mmol) and chloroiodomethane (7.05 ml, 96 mmol) in dry tetrahydrofuran (140 ml) at -80° under an atmosphere of nitrogen. After 1 h at -80°, the reaction mixture was warmed to room temperature and stirred overnight (ca. 14 h). Lithium iodide (5.9 g, 44 mmol) was added and the resultant mixture stirred for 40 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (20 ml) and the solvent evaporated. The residue was extracted with ether (2x100 ml). The combined organic extracts were washed successively with 0.5 M aqueous sodium thiosulphate (2x100 ml) and saturated aqueous sodium bicarbonate (100 ml), dried, and concentrated. The crude residue was purified by flash column chromatography on silica gel (light petroleum/ethyl acetate 4:1) to afford methyl 4-chlorobenzoate (0.93 g, 12%) as the first fraction, identified by comparison with an authentic sample.

The second fraction was 2-(4-chlorophenyl)-3-iodopropene (7), obtained as a pale yellow oil (0.83 g, 7%).^{1}H NMR δ 4.26 (s, 2H), 5.32 (s, 1H), 5.50 (s, 1H), 7.28-7.37 (m, 4H); ^{13}C NMR δ 74.49, 115.13, 127.41, 128.69, 133.57, 137.15, 143.09; Mass spectrum m/z (%) 154/152 (M-I+H, 36/100), 139/137 (90/50), 117/115 (22/49).

The third fraction was 2-(4-chlorophenyl)-3-hydroxypropene (**6**) (3.84 g, 52%), obtained as a colourless oil after distillation, b.p. 115°/ 0.1mm . Anal. $C_9H_{10}ClO$: C, 64.11; H, 5.38%. Found C, 64.32; H, 5.46 %; HRMS found ($M^{+\bullet}$), 168.0327. $C_9H_9{}^{35}ClO$ requires 168.0319; IR : 3350, 3089, 1631, 1594, 1493, 1398, 1091, 1044, 1012, 910, 834 cm^{-1}; ^{1}H NMR δ 2.05 (br s, 1H, OH), 4.48 (s, 2H), 5.35 (s, 1H), 5.45(s, 1H), 7.29-7.39 (m, 4H); ^{13}C NMR δ 64.90, 113.30, 127.41, 128.65, 133.77, 136.94, 146.14; Mass spectrum m/z (%) 170/168 (M, 21/66), 139/137 (52/94), 133(49), 127/125 (17/44), 103/101 (21/60).

Sharpless Epoxidation of (6)

The catalytic asymmetric epoxidation of (**6**) was carried out by the modified general procedure of Sharpless et al.[30]

Diethyl D-(-)-tartrate (0.639 g ; 0.528 ml, 3.09 mmol) and titanium tetraisopropoxide (0.666 g, 0.698 ml, 2.34 mmol) were added sequentially to a mixture of powdered activated 4 Å molecular sieves (1.90 g) and dry dichloromethane (61 ml) at 0° with stirring. The reaction mixture was cooled to -20°, tert-butyl hydroperoxide (4.2 M in dichloromethane, 14.7 ml, 61.80 mmol) was added dropwise over 0.25 h, and the resulting mixture was stirred at -20° for 0.75 h. Alkene (**6**) (4.0 g, 23.81 mmol) dissolved in dichloromethane (4 ml) was then added dropwise over 0.25 h. The reaction mixture was stirred for 7 h at -20°, and then kept for 36 h at -12°. The reaction mixture was warmed to 0°, water (14 mL) was added and the mixture was stirred for 1 h, and allowed to warm to room temperature. A 30% aqueous solution of sodium hydroxide saturated with sodium chloride (3 ml) was added, and after 1 h of vigorous stirring, the organic layer was separated. The aqueous layer was extracted with dichloromethane (4x30 ml). The combined organic layers were dried, filtered and concentrated.The residue was purified by flash column chromatography on silica gel (eluent : light petroleum/ethyl acetate 7:3) to afford the epoxy alcohol (**8**) as a colourless oil (2.94 g, 67%).

The crude epoxy alcohol was conveted to its 4-nitrobenzoate [4-nitrobenzoyl chloride (1.1 equiv.) and triethylamine (1.3 equiv.) in dichloromethane, 0.5 h, 0°]. Purification of the crude product by flash chromatography on elution with light petroleum/ethyl acetate (7:3), gave the ester (94%). Recrystallization from hot ethanol, gave the enantiomerically pure benzoate as white needles, m.p. 81-83°, 74%; $[\alpha]_D^{20}$ +3° (c = 0.95, $CHCl_3$); >98% enantiomeric excess by ^1H NMR analysis, with the chiral shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III)). Anal. $C_{16}H_{12}ClNO_5$: C, 57.58; H, 3.62; N, 4.19%. Found C, 57.66; H, 3.38; N, 4.21% ; HRMS found ($M^{+\bullet}$), 333.0417. $C_{16}H_{12}{}^{35}ClNO_5$ requires 333.0404. IR : 3115, 1719, 1605, 1527, 1495, 1411, 1308, 1277, 1120, 926, 873 cm^{-1}; ^1H NMR δ 2.88 (d, J = 5.1 Hz, 1H, H-3a), 3.21 (d, J = 5.1Hz, 1H, H-3b), 4.52 (d, J = 12.3 Hz, 1H, H-1a), 5.05 (d, J = 12.3 Hz, 1H, H-1b), 7.35-7.40 (m, 4H, ArH), 8.13 (d, J = 9.0 Hz, 2H, ArH), 8.27 (d, J = 9.0 Hz, 2H, ArH); ^{13}C NMR δ 53.61 (t), 57.78 (s), 67.10 (t), 123.66 (d), 127.52 (d), 128.91 (d), 130.85 (d), 134.39 (s), 134.82 (s), 135.10 (s), 150.77 (s), 164.19 (CO); Mass spectrum m/z (%) 335/333 (M, 2/7), 305/303 (12/43), 169/167 (4/17), 166 (55), 155/153 (13/19), 150 (100), 139/137 (91/88), 136 (30), 134 (25), 127/125 (25/61), 120 (44), 113/111 (10/26), 104 (90), 92 (40), 76 (80), 75 (82), 51 (60).

The nitrobenzoate was hydrolyzed at 20° with potassium carbonate in methanol for 10 minutes. The alcohol was purified by flash column chromatography on elution with 70% light petroleum in ethyl acetate, to yield the (R)-epoxyalcohol (**8**) (1.35 g, 93%) as a colourless oil, $[\alpha]_D^{20}$ +26° (c = 0.92, $CHCl_3$). HRMS found ($M^{+\bullet}$), 184.0288. $C_9H_9{}^{35}ClO_2$ requires 184.0291; IR : 3580, 3450, 3060, 2961, 1504, 1453, 1376, 1150, 1084, 1043, 861 cm^{-1}; ^1H NMR δ 2.11 (br s, 1H, OH, D_2O exchange), 2.76 (d, J = 5.2 Hz, 1H), 3.21 (d, J = 5.2 Hz, 1H), 3.90 (d, J = 12.6 Hz, 1H), 4.06 (d, J = 12.6 Hz, 1H), 7.30-7.35 (m, 4H); ^{13}C NMR δ 52.82 (t), 60.15 (s), 63.18 (t), 127.52 (d), 128.73 (d), 133.99 (s), 135.98 (s); Mass spectrum m/z (%) 186/184 (M, 5/12), 168/166 (18/21), 156/154 (57/100), 155/153 (49/22), 141/139 (38/96), 140/138 (18/38), 127/125 (55/85), 113/111 (23/27), 103/101 (15/34), 91 (70), 75 (39), 63 (24), 51 (48).

Use of diethyl L-(+)-tartrate as above gave (2S)-2-(4-chlorophenyl)-2,3-epoxypropan-1-ol in 66% yield, with an e.e.of 90% as determined above. The pure 4-nitrobenzoate derivative, m.p. 79-81°, had $[\alpha]_D^{20}$ -3° (c = 1.03, $CHCl_3$), and was hydrolyzed as above to give pure (2S)-2-(4-chlorophenyl)-2,3-epoxypropan-1-ol as a colourless oil, $[\alpha]_D^{20}$ -27° (c = 1.16, $CHCl_3$).

(2S)-3-Azido-2-(4-chlorophenyl)propan-1,2-diol (9)

A mixture of pure epoxyalcohol (**8**) (1.05 g, 5.71 mmol), sodium azide (1.85 g, 28.53 mmol) and ammonium chloride (0.67 g, 12.55 mmol) in methanol/water (5:1 v/v, 48 ml) was refluxed for 15 h. After cooling, the reaction mixture was concentrated. Water (15 ml) was added to the resultant residue and the mixture extracted with dichloromethane (4x20 ml). The combined organic extracts were dried, filtered, concentrated and flash chromatographed on silica gel (light petroleum/ethyl acetate 7:3) to give the diol (**9**) (1.20 g, 93%) as a pale yellow oil, $[\alpha]_D^{20}$ +40° (c = 0.89, $CHCl_3$). Anal. $C_9H_{10}ClN_3O_2$ requires : C, 47.48; H, 4.43; N, 18.46%. Found C, 47.43; H, 4.43; N, 18.52%; HRMS found ($M^{+\bullet}$ -CH_2OH), 196.0292. $C_8H_7{}^{35}ClN_3O$ requires 196.0278; IR : 3387, 2932, 2109, 1714, 1596, 1492, 1292, 1094, 1012, 829 cm^{-1}; ^1H NMR δ 2.50 (br s, 2H, OH, D_2O exchange), 3.60 (s, 2H), 3.75 (q, J = 13.5 Hz, 2H), 7.32-7.39 (m, 4H); ^{13}C NMR δ 57.77 (t), 67.49 (t), 76.49 (s), 126.93 (d), 128.70 (d), 133.96 (s), 139.62 (s); Mass spectrum m/z (%) 198/196 (M -CH_2OH, 5/12), 173/171 (42/69), 155/153 (34/55), 141/139 (60/77), 127/125 (46/100), 113/111 (39/77), 75 (55).

In the same way, (2R)-3-azido-2-(4-chlorophenyl)propan-1,2-diol was obtained as a pale yellow oil, $[\alpha]_D^{20}$ -42° (c = 0.88, $CHCl_3$).

(2S)-3-Azido-2-(4-chlorophenyl)-2-hydroxyprop-1-yl 4-toluenesulfonate

4-Toluenesulfonyl chloride (1.20 g, 6.30 mmol) was added in small portions over 0.25 h to an ice cooled mixture of (2S)-(**9**) (1.10 g, 4.85mmol) and pyridine (0.77 g: 0.78 ml, 9.70 mmol) in dry dichloromethane (15 ml) under nitrogen. The reaction mixture was stirred for 48 h at room temperature and the mixture was then poured onto ice water (15 ml). The aqueous phase was extracted with dichloromethane (3x20 ml) and the combined organic fractions were washed with 3M hydrochloric acid (4x50 ml) and brine (2x50 ml), then dried and concentrated. The crude residue was purified by silica gel flash chromatography (eluent:light petroleum/ ethyl acetate 7:3) to yield the tosylate as a colourless crystalline solid (1.56 g, 84%), m.p. 94-96°. $[\alpha]_D^{20}$ +18° (c = 1.01, $CHCl_3$); Anal. $C_{16}H_{16}ClN_3O_4S$: C, 50.33; H, 4.22; N, 11.00%. Found C, 50.38; H, 4.44; N, 11.0%; HRMS found ($M^{+\bullet}$ -CH_2N_3), 325.0274. $C_{15}H_{14}{}^{35}ClO_4S$ requires 325.0301; IR : 3520, 2118, 1597, 1489, 1357, 1330, 1307, 1266, 1175, 1068, 988cm^{-1}; ^{1}H NMR δ 2.46 (s, 3H), 2.90 (br s, 1H, OH, D_2O exchange), 3.57 (d, J = 12.7 Hz, 1H,), 3.62 (d, J = 12.7 Hz, 1H), 4.17 (d, J = 10.3 Hz, 1H), 4.22 (d, J = 10.3 Hz, 1H), 7.29 (s, 4H) ; 7.33 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.72 (q), 57.25 (t), 72.88 (t), 74.95 (s), 126.95 (d), 127.99 (d), 128.01 (d), 130.03 (d), 132.09 (s), 134.48 (s), 137.89 (s), 145.47 (s); Mass spectrum m/z (%) 327/325 (M -CH_2N_3, 19/52), 156/154 (26/35), 155(96), 141/139 (70/100), 127/125 (33/77), 113/111 (24/58), 91 (93), 75 (43), 65 (30), 51 (26).

(2S)-1-Azido-2-(4-chlorophenyl)-2,3-epoxypropane (10)

1.0 M Potassium tert-butoxide in t-butyl alcohol (3.5 ml) was added dropwise to a stirring suspension of the (2S)-tosylate (1.17 g, 3.07 mmol) in a mixture of dry t-butyl alcohol (15 ml) and tetrahydrofuran (15 ml), at room temperature under nitrogen. TLC analysis showed that the conversion was complete within 10 min. Water (10 ml) was added and the solution was stirred for 5 min. The reaction was concentrated, the residue suspended in water (10 ml) and extracted with ether (4x10 ml). The combined organic extracts were dried, concentrated and chromatographed on silica gel (eluent : light petroleum/ethyl acetate 7:3) to afford (**10**) (0.59 g, 92%) as a faint yellow oil, $[\alpha]_D^{20}$ +42° (c = 1.13, $CHCl_3$); Anal. $C_9H_8ClN_3O$: C, 51.57; H, 3.85; N, 20.04%. Found C, 51.48; H, 3.85; N, 20.11%; HRMS found ($M^{+\bullet}$), 209.0362. $C_9H_8{}^{35}ClN_3O$ requires 209.0356; IR : 2992, 2920, 2105, 1600, 1495, 1441, 1337, 1274, 1093, 1014, 871 cm^{-1}; ^{1}H NMR δ 2.79 (d, J = 5.1 Hz, 1H), 3.19 (d, J = 5.1 Hz, 1H), 3.55 (d, J = 13.6 Hz, 1H), 3.84 (d, J = 13.7 Hz, 1H), 7.30-7.35 (m, 4H); ^{13}C NMR δ 53.30 (t), 54.44 (t), 58.95 (s), 127.46 (d), 128.88 (d), 134.35 (s), 135.71 (s); Mass spectrum m/z (%) 211/209 (M, 7/22), 155/153 (31/73), 141/139 (55/99), 127/125 (66/100), 113/111 (29/68), 103/101 (11/39), 89 (89), 75 (83).

In the same way (2R)-3-azido-2-(4-chlorophenyl)propan-1,2-diol was converted into its toluenesulfonate, m.p. 95-97°, $[\alpha]_D^{20}$ -19° (c = 1.03, $CHCl_3$). This was then converted, as above, to the epoxide, (2R)-1-azido-2-(4-chlorophenyl)-2,3-epoxypropane, $[\alpha]_D^{20}$ - 41° (c = 1.20, $CHCl_3$).

(2S)-1-Amino-2-(4-chlorophenyl)-2,3-epoxypropane (12)

A mixture of the azide (**10**) (0.40 g, 1.91 mmol), ethanol (20 ml) and Adams' catalyst (100 mg) was

hydrogenated at 50 psi for 0.5 h. The crude product was passed through a short column of alumina, eluted with ethanol, to afford the amine as a colourless oil (0.33 g, 94%), $[\alpha]_D^{20}$ +5° (c = 1.31, $CHCl_3$), which was used in the next step without further purification. IR : 3372, 3056, 2924, 2855, 1600, 1493, 1399, 1300, 1176, 1013, 923 cm^{-1}; ^1H NMR δ 2.05 (br s, 2H, NH_2, D_2O exchange), 2.74 (d, J = 5.2 Hz, 1H), 3.01 (d, J = 14.2 Hz, 1H), 3.15 (d, J = 5.2 Hz, 1H), 3.39 (d, J = 14.25 Hz, 1H), 7.27-7.36 (m, 4H); ^{13}C NMR δ 45.82 (t), 53.74 (t), 55.42 (s), 127.53 (d), 128.77 (d), 133.71 (s), 137.14 (s).

The amine, (2R)-1-amino-2-(4-chlorophenyl)-2,3-epoxypropane, was obtained as above, $[\alpha]_D^{20}$ -4° (c = 1.35, $CHCl_3$).

Hydrochloride of (S)-(+)-Hydroxysaclofen (4)

A solution of the epoxyamine (**12**) (0.30 g, 1.64 mmol) and sodium bisulfite (0.51 g, 4.92 mmol) in ethanol/water (1:1 v/v, 60 ml) was refluxed for 24 h. The reaction mixture was concentrated and the residue was redissolved in water (15 ml). The aqueous phase was extracted with ethyl acetate (4x15 ml) to remove any unreacted (**12**), then acidified with concentrated hydrochloric acid and washed with ethyl acetate (4x15 ml). The aqueous fraction was concentrated to a white solid, which was extracted with boiling ethanol (4x15 ml), which gave the pure hydrochloride of (2S)-3-amino-2-(4-chlorophenyl)-2-hydroxypropanesulfonic acid (**4**) (0.212 g, 51% based on unrecovered (**12**)), m.p. 260-263° (dec), $[\alpha]_D^{20}$ +19° (c = 1.13, H_2O); IR : 3392, 3095, 2722, 1599, 1533, 1496, 1251, 1146, 1029, 831 cm^{-1}; ^1H NMR (D_2O) δ 3.46 (d, J = 13.3 Hz, 1H), 3.58 (d, J = 2.9 Hz, 2H) 3.63 (d, J = 13.3 Hz, 1H), 7.49-7.58 (m, 4H); ^{13}C NMR (D_2O) δ 48.57 (t), 58.07 (t), 72.32 (s), 127.51 (d), 129.01 (d), 133.91 (s), 138.40 (s).

R-(-)-Hydroxysaclofen (**4**) was obtained as above (49%), hydrochloride m.p. 258-262° (dec), $[\alpha]_D^{20}$ -18 (c = 1.08, H_2O).

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