Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 239-244, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(94)00380-7

Asymmetric Synthesis of S-(+)-4-Amino-5-hexynoic Acid.

Helena McAlonan and Paul J. Stevenson*.

School of Chemistry. The Queens University of Belfast.
BT9 5AG. N. Ireland.

Abstract: 4-Amino-5-hexynoic acid is efficiently synthesised in eight steps (overall yield 10%) from commercially available (S)-glutamic acid. The key step was conversion of an aldehyde to an acetylene using diethylmethydiazophosphonate.

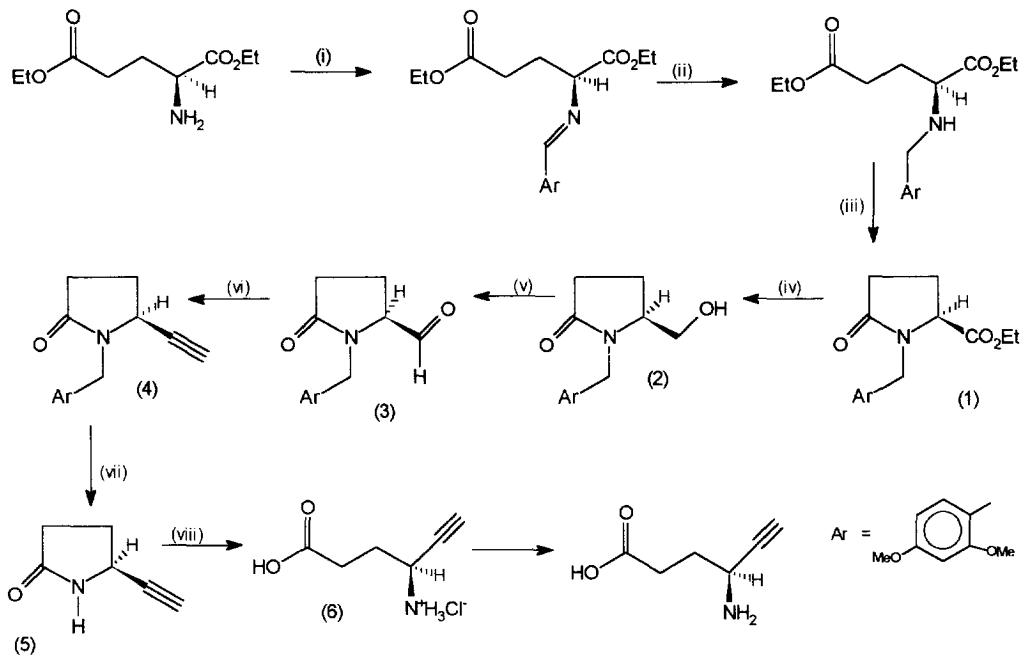
4-Aminobutanoic acid (γ-aminobutyric acid, GABA) is an important inhibitory neurotransmitter[1]. Low levels of GABA has been associated with a number of neurological disorders such as epilepsy, Huntingtons chorea and Parkinson's disease[2]. Since GABA cannot cross the blood brain barrier direct administration of GABA is ineffective for the treatment of these diseases[3]. The enzyme GABA aminotransferase efficiently metabolises GABA hence effectively decreasing its concentration. Selective inhibition of this metabolic pathway increases the levels of GABA in the central nervous system and has potential in the management of the above neurological disorders[4].

Recently it has emerged, that structural analogues of GABA bearing an unsaturated linkage on the carbon next to the carbon bearing the amino group are selective inhibitors of GABA transaminase[5]. Vigabatrin® (4-amino-5-hexenoic acid) is one such inhibitor, and is currently undergoing clinical evaluation. Although Vigabatrin® consists of racemic 4-amino-5-hexenoic acid, it is well documented that only the (S)-enantiomer is physiologically active. To this end, five asymmetric syntheses of (S)-4-amino-5-hexenoic acid have been published in the last ten years[6]. (R)-4-Amino-5-hexynoic acid is also a selective inhibitor of GABA aminotransferase, but the (S)-enantiomer inhibits both GABA aminotransferase and glutamic acid decarboxylase (an enzyme involved in the biosynthesis of GABA from glutamic acid)[7]. Therefore racemic 4-amino-5-hexynoic acid is not as effective an anticonvulsant agent as the (R)-enantiomer. A number of synthesises of racemic 4-amino-5-hexynoic acid exist and resolution procedures have been reported (albeit with very little experimental detail) to give the pure enantiomers[8]. In contrast to 4-amino-5-hexenoic acid, to date only one asymmetric synthesis of 4-amino-5-hexynoic acid has been reported. This was elegantly achieved by Holmes[9], the key step being the asymmetric synthesis of the corresponding propargyl alcohol, by a Lewis acid mediated reaction of a chiral acetal with trimethylsilylacetylene, followed by conversion of the alcohol to the amine. The chief drawback of this procedure is that the chiral auxiliary is expensive and many steps are required for its removal.

One conceptually simple approach to (S)-4-amino-5-hexynoic acid would involve the use of (S)-glutamic acid as the homochiral starting material and selectively converting one of the carboxy groups to an acetylene. Clearly this would require protection of the other carboxy group as well as protection of the amino group. **Scheme 1** outlines our approach in which one carboxy group is protected as the cyclic lactam and the amine nitrogen is protected as a 2,4-dimethoxybenzyl amide.

Hence treatment of (S)-diethylglutamate with 2,4-dimethoxybenzaldehyde gave an intermediate imine which was reduced with sodium borohydride in methanol to give a mixture of (S)-N-2,4-dimethoxybenzyldiethylglutamate and (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-carboethoxy-2-pyrrolidinone (**1**). Heating this mixture in boiling xylene for eight hours effected quantitative cyclisation of the amine to the lactam. The overall yield for these three steps was 72%. This simple procedure ensured protection of the amine nitrogen and differentiation between the two carboxy groups.

Reduction of the carboethoxy group in (**1**) with sodium borohydride in ethanol give the primary alcohol (**2**, 86%). Swern oxidation of (**2**) proceeded smoothly at -30°C to give aldehyde (**3**, 85%, crude). Attempted purification by flash chromatography resulted in complete decomposition, hence it was used immediately without purification for the next stage. Reduction of the aldehyde (**3**) back to the alcohol, followed by preparation of Mosher esters showed that no racemisation had taken place at any of the prior transformations. Although aldehyde (**3**) is unstable to silica gel, it is remarkably stable with respect to racemisation. When a sample of the aldehyde was allowed to stand neat at room temperature for three days, and then reduced back to the alcohol, examination of the Mosher esters by nmr spectroscopy revealed that no racemisation had taken place.



Reagents: (i) 2,4-Dimethoxybenzaldehyde. (ii) $NaBH_4$. (iii)Boiling xylene. (iv) $NaBH_4$. (v)Oxalyl chloride, DMSO, Et_3N. (vi) Diethylmethyldiazophosphonate, potassium t-butoxide. (vii)DDQ, water, chloroform. (viii)Hydrochloric acid.

Scheme 1

Conversion of the aldehyde (**3**) to the acetylene (**4**) was accomplished using diethylmethyldiazophosphonate[10] and Gilbert's procedure[11]. It has previously been reported that aldehydes with stereogenic centres α to a carbonyl group can be converted to acetylenes using Gilbert's procedure without racemisation[12]. Essentially using Gilbert's conditions, the aldehyde (**3**) was transformed to the acetylene (**4**, 64%).

Removal of the amide N-2,4-dimethoxybenzyl protecting group proved to be much more troublesome than initially anticipated. Trifluoroacetic acid led to decomposition of the acetylene (**4**). With aqueous ceric ammonium nitrate (CAN)[13], 2,4-dimethoxybenzaldehyde was isolated in quantitative yield but no acetylenic compound could be obtained. Finally, it was found that the protecting group could be removed using DDQ in wet boiling chloroform[14] to give the NH lactam (**5**, 54%).

The urea derivatives of 5-ethynyl-2-pyrollidinone (**5**) with (+) and (-)-methylbenzylisocyanate were made in order to determine the enantiomeric purity of (**5**)[15]. The proton nmr spectra of the two diastereoisomers were very different and hence could be used for the determination of the enantiomeric purity. In particular the nmr signals for the acetylenic hydrogens from the two diastereoismoers were used for the quantification. The ratio of diastereoismers was found to be 96:4, which means that 5-ethynyl-2-pyrollidinone (**5**) was formed with an ee of 92%. The strongly basic reaction conditions for converting the aldehyde to the acetylene had therefore resulted in some racemisation.

Finally, lactam (**5**) was hydrolysed to the amino acid hydrochloride salt by boiling it overnight in aqueous hydrochloric acid. Ion exchange chromatography on Dowex®50x8 give 4-amino-5-hexynoic acid (67%). Since both enantiomers of glutamic acid are commercially available and are relatively cheap this procedure makes available both enantiomers of 4-amino-5-hexynoic acid.

Experimental.

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalysis were obtained using a Perkin Elmer 2400 CHN elemental analyser. Infrared spectra were recorded on a Perkin Elmer 983G infra red spectrometer as potassium bromide (KBr) disks, or films (liquids). Mass spectra were recorded using Double Focussing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference. Nuclear magnetic resonance (nmr) spectra were recorded at 300MHz using a General Electric QE nmr spectrometer and at 500MHz using a General Electric Omega nmr spectrometer. Chemical shifts are given in parts per million (δ) down field from tetramethylsilane as internal standard and coupling constants are given in hertz. Unless otherwise stated, deuterochloroform was used as solvent. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Flash chromatography was performed using air pressure to maintain a flow rate at 5ml/min and silica refers to Silica Gel 60 (Merck 9385). Analytical thin layer chromatography (t.l.c.) was carried out on Merck $60F_{254}$ plates and were visualised using a Hanovia Chromatolite ultraviolet lamp or iodine. The term petroleum ether refers to that fraction of petroleum with a boiling point between 40°C and 60°C. All solvents were purified and dried according to standard procedures. Ether refers to diethyl ether.

(S)-1-(2,4'-Dimethoxybenzyl)-5-carboethoxy-2-pyrrolidinone (1).

A solution of (S)-diethylglutamate (3.21g, 15.8mmol) and 2,4-dimethoxybenzaldehyde (2.89g, 17.4mmol) in methylene chloride (40ml) was stirred at room temperature for four hours. Magnesium sulphate (5g) was then added and the mixture stirred for a further six hours. After filtration of the magnesium sulphate, the methylene chloride was removed under reduced pressure and dry methanol (50ml) was added to the yellow oil. This was cooled to 0°C and sodium borohydride (1.2g, 31.5mmol) was added in small portions over five minutes, followed by stirring at 0°C for a further 60 minutes. The methanol was then removed under reduced

pressure to give a mixture of N-2,4-dimethoxybenzyldiethylglutamate and (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-carboethoxy-2-pyrrolidinone (**1**). It proved impossible to purify N-2',4'-dimethoxybenzyldiethylglutamate as it had a strong tendency to cyclise to the corresponding lactam. Heating the crude reaction mixture in boiling xylene (20ml) overnight gave after concentration a red oil. Purification by flash chromatography give (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-carboethoxy-2-pyrrolidinone (**1**, 3.5g, 72 %) as a clear oil R_f =0.42 (ether): $[\alpha]_D$ = +34.6, (c 8.6, chloroform). $C_{16}H_{21}NO_5$ requires M^+ 307.142; Found 307.143; m/z (%) M^+ 307 (25.4), 151(100), 121(15.9); $\nu_{max.}$ 3475, 3037, 2999, 2838, 1742, 1695,1211, 1175, 1035cm^{-1}. δ(500MHz) 7.15(1H, d, J= 8.0Hz, C**H**CHCOMe), 6.42(1H, s, MeOCC**H**CMeO), 6.43(1H, d, J= 8.3Hz, CHC**H**COMe), 4.21(2H, q, J= 7.2Hz, OC**H**$_2$CH$_3$), 4.12 and 4.80(2x1H, 2xd, J= 14.4Hz, NC**H**$_2$Ar), 4.03(1H, dd, J= 9.4, 3.5Hz, C**H**CO$_2$Et), 3.76 and 3.80(2x3H, 2xs, 2xArOC**H**$_3$), 2.43(1H, dt, J= 17.1, 8.7Hz COC**H**H), 2.27(1H, ddt, J= 16.8, 9.9, 3.9Hz, NCOCH**H**), 2.15(1H, m, NCOCH$_2$C**H**H), 1.91(1H, ddt, J = 13.2, 9.5, 3.7Hz COCH$_2$CH**H**), 1.12(3H, t, J= 7.1Hz, C**H**$_3$CH$_2$O).

(S)-(+)-1-(2',4'-Dimethoxybenzyl)-5-hydroxymethyl-2-pyrrolidinone (2).

Sodium borohydride (0.39g, 10.24mmol) was added in small portions over 10 minutes to an ice cooled stirred solution of (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-carboethoxy-2-pyrrolidinone (3.0g, 10.24mmol) in ethanol (50ml). The resulting solution was stirred overnight at room temperature whereupon the solvent was removed under reduced pressure. Hydrochloric acid (5ml, 2M) was added to the residue and this was extracted with methylene chloride (3x50ml). The combined methylene chloride extracts were dried over magnesium sulphate and concentrated to give an off white solid. This was recrystallised from methanol to give (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-hydroxymethyl-2-pyrrolidinone (**3**, 2.32g, 85%) as white prisms mp 97-99°C. $[\alpha]_D$ = +77.84 (c 5.1, chloroform). Found C, 63.1; H, 7.2; N, 5.3; $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.1; m/z (%) M^+265(11), 151(100), 121(18), 91(7); $\nu_{max.}$ 3259, 2929, 1654, 1610, 1592, 1464, 1440, 1196, 825cm^{-1}; δ(500MHz) 7.20(1H, d, J= 8.1Hz, C**H**CHCOMe), 6.43(1H, d, J= 8.0Hz, CHC**H**COMe), 6.42(1H, s, MeOCC**H**COMe), 4.71 and 4.26(2x1H, 2xd, J= 15.0Hz, ArC**H**$_2$N), 3.79 and 3.81(2x3H, 2xs, 2x**OMe**), 3.80(1H, m, C**H**OH), 3.53(1H, d,d,d, J= 8.1, 3.4, 0.9Hz, C**H**N), 3.50(1H, dd, J= 11.9, 3.0, C**H**OH), 2.54(1H, ddd, J= 17.0, 9.7, 7.3Hz, COC**H**HCH$_2$), 2.34(1H, ddd, J= 16.9, 10.0, 5.6Hz, COCH**H**CH$_2$), 2.01(2x1H, 2xm, C**H**$_2$CH$_2$CO).

(R) and (S)-MTPA esters of (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-hydroxymethyl-2-pyrrolidinone were made by the standard procedure. One of the diastereotopic C**H**HOCO protons from each diastereoisomer were used to determine the enantiomeric purity of the samples. (R,S) isomer δ(500MHz) 4.56(1H, dd, J=11.5, 4.0Hz C**H**HOCO). (S,S) isomer δ(500MHz) 4.62(1H, dd, J= 11.6, 4.6Hz, C**H**HOCO).

(S)-1-(2',4'-Dimethoxybenzyl)-5-carboxaldehyde-2-pyrrolidinone (3).

DMSO (1.42ml, 19.9mmol) in dry methylene chloride (2ml) was added to a stirred solution of oxalyl chloride (6.5ml, 74mmol) in dry methylene chloride (22ml) at -55°C. (S)-(+)-1-(2',4'-Dimethoxybenzyl)-5-hydroxymethyl-2-pyrrolidinone (2.0g, 7.5mmol) in methylene chloride (8ml) was slowly added keeping the temperature below -50°C. This was stirred for forty minutes, followed by the addition of triethylamine (5.8ml, 41.8mmol). The mixture was then allowed to warm to room temperature where it was extracted with brine (3x75ml) followed by water (3x75ml). Drying over magnesium sulphate followed by removal of solvent give (S)-1-(2',4'-dimethoxybenzyl)-5-carboxaldehyde-2-pyrrolidinone **(3)** (1.7g, 85% crude) as a red oil. Attempted purification by flash chromatography lead to complete decomposition of the aldehyde. The crude product was used directly for the next stage. m/z(%)M^+ 263(7), 234(11), 151(100), 121(19), 101(19), 86(81). δ(300MHz)

9.44(1H, t, J= 1.1Hz, CO**H**), 7.19(1H, d, J= 8.1Hz, C**H**CHCOMe), 6.45(1H, d, J= 8.0Hz, CHC**H**COMe), 6.44(1H, s, COMeC**H**COMe), 4.33 and 4.70(2x1H, J= 14.3Hz, ArC$\mathbf{H_2}$N), 3.95(1H, ddd, J= 7.6, 1.5, 1.5Hz, CH_2C**H**N), 3.80 and 3.78(2x3H, 2xs, 2xO**Me**), 2.48(2x1H, 2xm, $CH_2\mathbf{CH_2}CO$), 2.18 and 1.90(2x1H, 2xm, $\mathbf{CH_2}CH_2CO$).

(S)-(+)-1-(2',4'-Dimethoxybenzyl)-5-ethynyl-2-pyrrolidinone (4).

Diethylmethyldiazophosphonate (1.48g, 8.3mmol) in dry THF (30ml) was added dropwise to a slurry of potassium tert butoxide (932mg, 8.3mmol) in dry THF (20ml) at -78°C and this was allowed to stir for ten minutes. (S)-1-(2',4'-Dimethoxybenzyl)-5-carboxaldehyde-2-pyrrolidinone (1.7g, 6.46mmol) in THF (20ml) was then added and this was stirred for a further 6h at -78°C. The reaction vessel was then stoppered and transferred to a fridge at -20°C for 10h. Saturated aqueous sodium bicarbonate solution (20ml) was then added and this was extracted with ether (3x20ml). The combined organic layers were dried over magnesium sulphate and concentrated to give a red oil. Flash chromatography (solvent ether) followed by recrystallisation from ethanol gave (S)-(+)-1-(2',4'-dimethoxybenzyl)-5-ethynyl-2-pyrrolidinone (**4**) (1.3g, 64%) as white prisms mp 87-88°C. R_f = 0.44(ether). $[\alpha]_D$ = +8.7, (c 9.0, chloroform). Found C, 69.2; H, 6.6; N, 5.3; $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.4; N, 5.4. m/z(%) 259(71), 149(100), 108(7); ν_{max} 3231 3003, 2940, 2964, 2847 1671cm^{-1}. δ(500MHz) 7.20(1H, d, J= 8.8Hz, C**H**CHCOMe), 6.43(1H, s, COMeC**H**COMe), 6.42(1H, d, J= 8.7Hz, CHC**H**COMe), 4.89 and 4.14(2x1H, 2xd, J= 14.7Hz, ArC$\mathbf{H_2}$N), 4.15(1H, ddd, J= 8.3, 4.1, 2.0Hz, NC**H**CH_2), 3.81 and 3.80(2x3H, 2xs, 2xO**Me**), 2.54 and 2.38(2x1H, 2xm, C$\mathbf{H_2}$CO), 2.39(1H, d, J= 2.2Hz, C**H**), 2.23 and 2.10(2x1H, 2xm, $\mathbf{CH_2}CH_2CO$).

(S)-(-)-5-Ethynyl-2-pyrollidinone (5).

(S)-(+)-1-(2',4'-Dimethoxybenzyl)-5-ethynyl-2-pyrrolidinone (700mg, 2.7mmol) and DDQ (675mg, 3.0mmol) in chloroform (20ml) containing three drops of water (~0.06ml) was boiled under reflux overnight. The solvent was removed under reduced pressure and the residue was dissolved in hot benzene. The insoluble material was removed by filtration. Concentration of the benzene solution gave a red oil. Flash chromatography, solvent ether gave 5-ethynyl-2-pyrollidinone as a pale yellow oil (216mg, 53%). R_f = 0.16(ether). Vacuum distillation give 5-ethynyl-2-pyrollidinone as colourless oil which slowly crystallised on standing m.p. 53-55°C lit mp for racemate 101-103[16]. $[\alpha]_D$ = -14.4, (c 5.3, $CHCl_3$); m/z(%) M^+ 109(65), 81(84), 80(74), 65(66), 54(100); ν_{max} 3279, 3219, 2943, 2927, 2115, 1692, 1507, 855cm^{-1}. δ(500MHz) 6.6(1H, s, N**H**), 4.37(1H, ddd, J= 7.3, 5.0, 2.0Hz, C**H**NH), 2.45(2x1H, 2xm, C$\mathbf{H_2}$CO), 2.38(1H, d, J = 2.2Hz, C**H**), 2.31 and 2.19(2x1H, 2xm, $\mathbf{CH_2}CH_2CO$).

Reaction of (S)-(-)-5-ethynyl-2-pyrollidinone with (R)-(+) and (S)-(-)-methylbenzylisocyanate.

Standard procedure[15] used to give nmr samples of two diastereoisomeric urea derivatives. With (R)-(+)-methylbenzylisocyanate δ(500MHz) 8.65(1H, d, J= 7.5Hz, N**H**), 7.2-7.4(5H, overlapping m, Ar**H**), 5.07(1H, quintet, J= 6.9Hz, NHC**H**CH_3), 5.02(1H, d, J= 8.4Hz, NC**H**-), 2.82(1H, ddd, J= 17.7, 11.6, 8.8Hz, COC**H**H), 2.54(1H, ddd, J= 17.6, 8.8, 1.7Hz, COCH**H**), 2.33(1H, d, J= 2.3Hz, C**H**), 2.28(ddd, J= 12.4, 8.6, 3.5Hz, $COCH_2$C**H**H), 2.15(1H, m, $COCH_2$CH**H**), 1.51(3H, d, J= 7.0Hz, CHC$\mathbf{H_3}$). With (S)-(-)-methylbenzylisocyanate δ(500MHz) 8.64(1H, d, J= 7.0Hz, N**H**), 7.2-7.4(5H, overlapping m, Ar**H**), 5.06(1H, quintet, J= 7.0Hz, NHC**H**CH_3), 4.97(1H, d, J= 8.8Hz, NC**H**-), 2.89(1H, ddd, J= 17.2, 11.6, 8.7Hz, COC**H**H), 2.53(1H, ddd, J= 17.5, 8.7, 1.9Hz, COCH**H**), 2.41(1H, d, J= 1.9Hz, C**H**), 2.24 and 2.15(2x1H, 2xm, $COCH_2$CH**H**), 1.52(3H, d, J= 7.0Hz, CHC$\mathbf{H_3}$).

The two samples showed a 96:4 and a 4:96 ratio of two diastereoisomers. Using the resonance for the acetylenic hydrogens at δ 2.33 and 2.41 these ratios could be accurately calculated. This translates to an ee of 92% for the pyrrolidinone (**5**).

(S)-(+)-4-Amino-5-hexynoic acid.

5-Ethynyl-2-pyrollidinone (21.2mg, 0.19mmol) in hydrochloric acid (5ml, 2M) was boiled under reflux for twelve hours. The excess hydrochloric acid was removed under reduced pressure to give a crude sample of 4-amino-5-hexynoic acid hydrochloride. Purification by ion exchange chromatography (stationary phase Dowex®50x8), solvent water followed by ammonium hydroxide gave 4-amino-5-hexynoic acid as a white solid (16.1mg, 67%) R_f = 0.7(methanol), mp 170°C (dec) lit value 170°C (dec)[9]. $[\alpha]_D$ = +32.0, (c 3.0, water). lit value +33[9], +35[8]. δ(D_2O, 300MHz) 4.18(1H, ddd, J= 8.5, 5.7, 2.5Hz, NC**H**), 3.02(1H, d, J= 2.2Hz, C**H**), 2.48(1H, dd, J= 15.8, 6.8Hz, COC**H**H), 2.41(1H, dd, J= 15.8, 7.8Hz, COCH**H**), 2.04 and 2.13(2x1H, 2xm, $COCH_2CH_2$). This spectrum was recorded within ten minutes of the sample been made up and the intensity of the signal for the acetylenic hydrogen was 71% of what it should of been. After one day at room temperature it had dropped to 8%, indicating that the acetylenic hydrogen was been slowly exchanged with deuterium.

Acknowledgement: We would like to thank the Department of Education for N. Ireland (DENI), for a studentship (H.McA.).

References and notes.

1a. Roberts, E.; Chase, T.N.; Tower, D.B. GABA in Nervous System Function; Raven Press, New York 1976.
b. Nanavati, S.M.; Silverman, R.B. *J. Med. Chem.*, **1989**, *32*, 2413-2420.
2. Grant, S.M.; Heel, R.C. *Drugs*, **1991**, *41*, 889-926.
3. Meldrum, B.S.; Horton, R.W. In *Epilepsy*; Harris, P.; Mawdsley, C.; Eds.; Churchill Livingston: Edinburgh, 1974, 55-64.
4. Silverman, R.B.; Nanavati, S.M. *J. Med. Chem.* **1990**, *33*, 931-936.
5a. Lippert, B.; Metcalf, B.W.; Jung, M.J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441-445.
b. Metcalf, B.W. *Biochem. Pharmacol.*, 1979, 28, 1705-1712.
6a. Wei, Z.; Knaus, E.E. *Tetrahedron* **1994**, *50*, 5569-5578.
b. Wei, Z.; Knaus, E.E. *Syn Lett.* **1994**, 345-6.
c. Kwon, T.W.; Keusenkothen, P.F.; Smith, M.B. *J. Org. Chem.*, **1992**, *57*, 6169-6179.
d. Mullins, M.J.; Woo, E.P. *U.S. Pat.* 4,912,232, March 27, 1990.
e. Frieben, W.; Gerhart, F. *UK Pat.* 2,133,002, July 18 1984.
7a. Burke, J.R., Silverman, R.B. *J. Amer. Chem. Soc.*, **1991**, *113*, 9329-9340.
b Palfreyman, M.G.; Schechter, P.J.; Buckett, W.R.; Tell, G.P. *J. Biochem. Pharmacol.*, **1981**, *30*, 817-824.
8. Jung, M.J.; Metcalf, B.W.; Lippert, B.; Casara, P. *Biochemistry*, **1978**, *17*, 2628-2632.
9. Holmes, A.B.; Tabour, A.B.; Baker, R. *J. Chem. Soc. Perkin 1*, **1991**, 3301-3306.
10. Regitz, M.; Liedheyenier, A.; Eckstein, U.; Martain, M.; Anschutz, W. *Annalen*, **1971**, *748*, 207-210.
11. Gilbert, J.C.; Weerasooniga, U. *J. Org. Chem.*, **1979**, *44*, 4997-4998.
12. Nakatsuka, M.; Ragan, J.A.; Sammakia, T.; Smith, D.B.; Uehling, D.E.; Schrieber, S. *J. Amer. Chem. Soc.*, **1990**, *112*, 5583-5601.
13. Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.*, **1983**, 1001-1002.
14. Mori, S.; Iwakura, H.; Takechi, S. *Tet Lett.*, **1988**, *29*, 5391-94.
15 Pirkle, W.H.; Robertson, M.R.; Hyun, M. *J. Org. Chem.*, **1984**, *49*, 2433-2437.
16. Kolb, M.; Barth, J. J.; Heydt, .; Jung, M.J. *J. Med. Chem.*, **1987**, *30*, 267-272.

(*Received in UK* 17 *October* 1994)