

Enantioselective Synthesis of (*S*)- γ -Acetylenic γ -Aminobutyric Acid (GABA) and (*S*)-*trans*- γ -Butenynyl GABA

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The enantioselective syntheses of (*S*)- γ -acetylenic γ -aminobutyric acid (GABA) (**1**) and the (*E*)-butenynyl analogue (**2**) by phthalimide displacement of the homochiral prop-2-ynylic alcohols (**6**) and (**11**) [generated from the acetals (**3**) and (**9**), respectively], are reported.

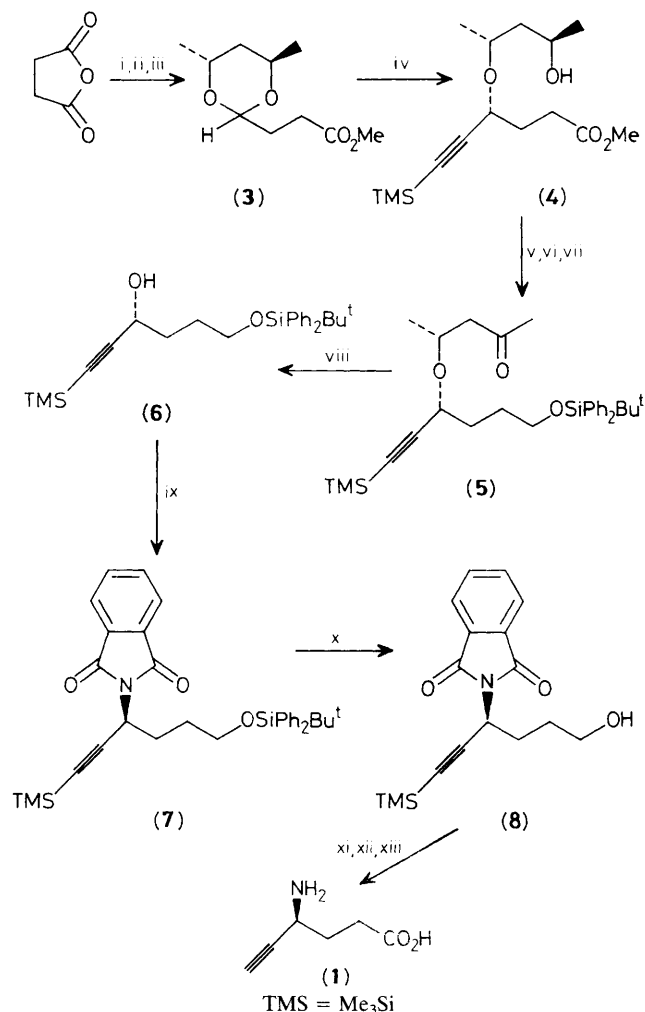
γ -Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system, and deficiencies of brain GABA have been linked to a number of neurological disorders. It has been shown that inhibition of the enzyme catalysing the breakdown of GABA, GABA-T (E.C. 2.6.1.19) raises brain GABA levels and hence prevents these disorders.¹ A number of unsaturated analogues of GABA, including γ -allenyl,² γ -vinyl, and γ -acetylenic GABA,³ have been synthesised and shown to act as mechanism-based inhibitors of GABA-T. Resolution of (+)- γ -acetylenic GABA afforded (*S*)-(+)- γ -acetylenic GABA (**1**), which has been shown to be the enantiomer responsible for the inhibition of mammalian GABA-T.⁴ However, no enantioselective syntheses of these compounds have been reported, nor have enyne or diyne analogues of GABA (which also

have the potential to act as mechanism-based inhibitors of GABA-T^{1,5}) been made. In this Communication we report the first enantioselective synthesis of (*S*)- γ -acetylenic GABA (**1**) and of (*S*)-*trans*- γ -butenynyl GABA (**2**).

There are few synthetic methods which are generally applicable to prop-2-ynylic and allylic amines.⁶ Our approach utilises the chiral acetal methodology of Johnson⁷ to generate homochiral propynylic alcohols, followed by displacement of the alcohol with inversion using phthalimide.

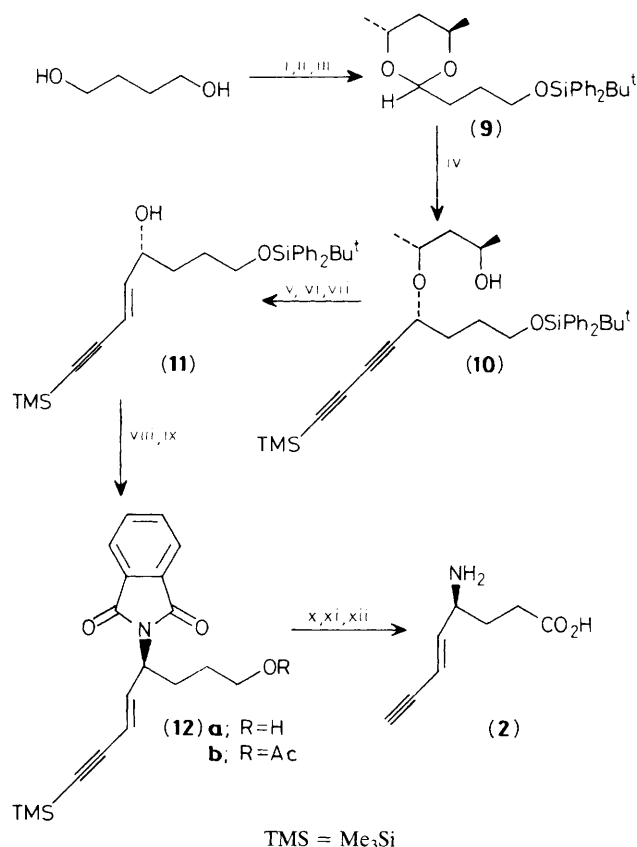
(*S*)- γ -Acetylenic GABA was prepared as shown in Scheme 1. The required chiral acetal (**3**)† {[α]_D²⁵ +10.98° (*c* 12.7 in CHCl₃)} was prepared from succinic anhydride in four steps.

† Satisfactory spectroscopic data, and microanalyses or high resolution mass spectra were obtained for all new compounds.



Scheme 1. Reagents and conditions: i, MeOH, then SOCl₂, reflux (86%); ii, H₂, 10% Pd/C, 2,6-lutidine (43%); iii, (2*R*,4*R*)-pentane-2,4-diol, toluene-*p*-sulphonic acid (TsOH), benzene, reflux, 3 h (96%); iv, BTMSA (5 equiv.), TiCl₄ (2 equiv.), CH₂Cl₂, 4 Å molecular sieves, -78 °C, 20 min (78%); v, LiAlH₄, Et₂O, -72 °C room temp., 6 h (96%); vi, Bu^tPh₂SiCl, imidazole, dimethylformamide (DMF), room temp., 15 h (80%); vii, PCC, NaOAc, 3 Å molecular sieves, CH₂Cl₂, room temp., 15 h (90%); viii, DBU (2 equiv.), benzene, 50 °C, 13 days (72%); ix, Ph₃P, phthalimide, diethyl azodicarboxylate (DEAD), tetrahydrofuran (THF), room temp., 19 h (79%); x, HF-pyridine (3 equiv.), THF, room temp., 19 h (79%); xi, (COCl)₂, dimethyl sulphoxide (DMSO), Et₃N, CH₂Cl₂, -78 °C, then Jones reagent (2 equiv.) (67%); xii, H₂NNH₂·H₂O, EtOH, reflux, 10 min (91%); xiii, TBAF·3H₂O, THF, -10 °C, 20 min (50%).

Coupling with bis(trimethylsilyl)acetylene (BTMSA)⁷ gave the propynyl ether (4) {[α]_D²⁵ +11.2° (c 14.1 in CHCl₃); diastereoisomeric excess (d.e.) >95% as determined by capillary g.c. and ¹H n.m.r.}. In order to prevent lactonisation when the chiral auxiliary was removed, the methyl ester was next reduced and the resulting alcohol protected as the *t*-butyldiphenylsilyl ether. Oxidation of the secondary alcohol using pyridinium chlorochromate (PCC)⁸ gave ketone (5) {[α]_D²⁵ +15.0° (c 5.9 in CHCl₃)}; treatment of this ketone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) removed the chiral auxiliary *via* β-elimination to give the propynyl alcohol (6) {[α]_D²⁵ -5.7° (c 0.525, CHCl₃)}. The use of DBU for the deprotection is noteworthy, as other previously reported procedures resulted in concomitant desilylation of the acetylene.^{7,9} Mitsunobu^{10,11} inversion of the alcohol (6) with



Scheme 2. Reagents and conditions: i, NaH, Bu^tPh₂SiCl, THF, room temp., 3 h¹⁶ (99%); ii, (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C (92%); iii, (2*R*,4*R*)-pentane-2,4-diol, TsOH, benzene, reflux, 3 h (99%); iv, BTMSBD (3 equiv.), TiCl₄ (2 equiv.), CH₂Cl₂, 4 Å molecular sieves, -80 °C, 2 h (51%); v, LiAlH₄, Et₂O, -78 °C to room temp., 5 h (73%); vi, PCC, NaOAc, 3 Å molecular sieves, CH₂Cl₂, room temp., 15 h (89%); vii, DBU (2 equiv.), benzene, 40 °C, 14 days (66%); viii, Ph₃P, phthalimide, DEAD, THF, room temp., 18 h (46%); ix, HF-pyridine (3 equiv.), THF, room temp., 19 h (67%); x, (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, then Jones reagent (2 equiv.) (47%); xi, H₂NNH₂·H₂O, EtOH, reflux, 10 min (94%); xii, TBAF·3H₂O, THF, -10 °C, 20 min (61%).

phthalimide gave (7) {[α]_D²⁵ -1.5° (c 3.54 in CHCl₃); enantiomeric excess (e.e.) >95% as shown by chiral shift studies}. Desilylation of the primary alcohol using HF-pyridine gave (8). Again, the acetylene was not deprotected during this reaction. The primary alcohol was then oxidised to the carboxylic acid (Swern,¹² followed by Jones¹³ reagent) which was treated with hydrazine hydrate¹¹ to remove the phthalimide. Desilylation of the acetylene using tetra-*n*-butylammonium fluoride trihydrate (TBAF·3H₂O) yielded (*S*)-γ-acetylenic GABA (1), ‡ m.p. 180 °C (decomp.) {lit.⁴ 200 °C (decomp.)} [α]_D²⁵ +31.4° (c 1.422 in H₂O) (lit.¹⁴ +30.0°, c 1.28 in H₂O; lit.⁴ +35.6°, c 1.03 in H₂O).

Conjugated analogues of (1) are accessible *via* a related strategy, as illustrated for the synthesis of (*S*)-*trans*-γ-

‡ Spectral data for (1): ν_{max}(KBr) 3290 (C≡C-H), 3100–2500 (br. NH₃⁺), 2210 (C≡C) 2130, 1980, 1640–1500 (amino acid) cm⁻¹; δ_H (CD₃OD, 250 MHz) 1.91–2.08 (2H, m), 2.30–2.56 (2H, m), 3.13 (1H, d, *J* 2.2 Hz), 4.09 (1H, br. t, *J* 6 Hz); δ_H (D₂O, 250 MHz) 1.99–2.30 (2H, m, ABX), 2.43 (2H, octet, *J* 7 Hz), 3.34 (1H, s), 4.17 (1H, m, ABX, *J*_{AX+BX} 14 Hz); δ_C (D₂O) 31.9, 35.8, 45.1, 79.7, 79.9, 183.5. Found: *M*⁺+H, 128.0712. C₆H₁₀NO₂ requires *M*⁺+H, 128.0712; *m/z* 128 (*M*⁺+H, 100%) 111 (20), 102 (52), 84 (64), 73 (48), 54 (29), 45 (20) (chemical ionisation, C.I.).

butenynyl GABA (**2**) (Scheme 2). The acetal (**9**) $\{[\alpha]_{\text{D}}^{25} + 6.9^\circ$ (c 2.438 in CHCl_3) $\}$ was obtained in three steps from butan-1,4-diol. Coupling to bis(trimethylsilyl)butadiyne (BTMSBD)¹⁵ as before afforded the propynyl diyne ether (**10**) $\{[\alpha]_{\text{D}}^{25} + 10.7^\circ$ (c 0.717 in CHCl_3); d.e. >96%. Reduction using LiAlH_4 gave a *trans*-enyne; oxidation of the secondary alcohol followed by treatment with DBU yielded the required homochiral *trans*-allylic enyne alcohol (**11**) $\{[\alpha]_{\text{D}}^{25} - 7.8^\circ$ (c 5.3 in CHCl_3) $\}$. Phthalimide inversion followed by *O*-desilylation gave the alcohol (**12a**) $\{[\alpha]_{\text{D}}^{25} - 45.1^\circ$ (c 1.824 in CHCl_3) $\}$ whose acetate (**12b**) exhibited an e.e. greater than 95% as shown by chiral shift studies. The alcohol (**12a**) was then converted into the target (*S*)-*trans*- γ -butenynyl GABA (**2**) $\{[\alpha]_{\text{D}}^{25} + 30.1^\circ$ (c 0.515 in H_2O) $\}$ in three steps using the methods described above.

In addition to the high enantioselectivity of the above syntheses, the selective *O*-desilylation of silyl ethers in the presence of ethynyl silanes and the stereoselective reduction of the ether (**10**) with LiAlH_4 are noteworthy.

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§ Spectral data for (**2**): ν_{max} (KBr) 3400–3100 (CO_2H), 3150 (C–H), 2350 ($\text{C}\equiv\text{C}$), 1500–1700 (amino acid) cm^{-1} ; δ_{H} (CD_3OD , 250 MHz) 1.79–2.02 (2H, m), 2.29–2.40 (2H, m), 3.80 (1H, m), 5.87 (1H, dd, J 16.0, 2 Hz), 6.09 (1H, dd, J 16.0, 8.1 Hz). Found: $M^+ + \text{H}$, 154.0868. $\text{C}_8\text{H}_{12}\text{NO}_2$ requires $M^+ + \text{H}$, 154.0868; m/z 154 ($M^+ + \text{H}$, 60%) 137 (56), 136 (100) (C.I.).

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