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

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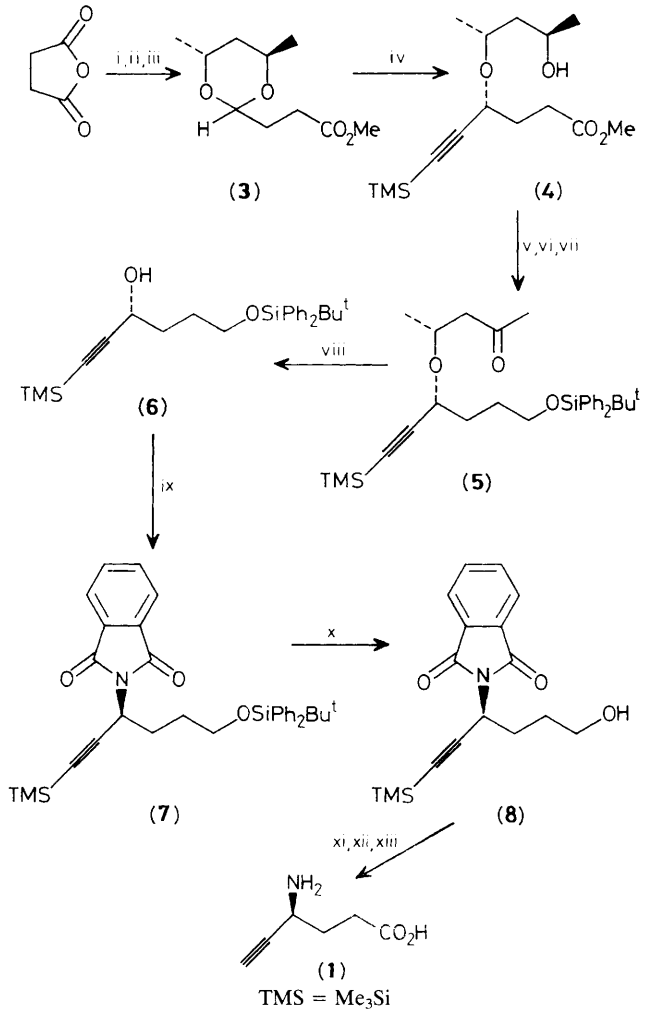
The enantioselective syntheses of (*S*)-γ-acetylenic γ-aminobutyric acid (GABA) (**1**) and the (*E*)-butenynyl analogue (**2**) by phthalimide displacement of the homochiral prop-2-ynylic alcohols (**6**) and (**11**) [generated from the acetals (**3**) and (**9**), respectively], are reported.

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-allenic,[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 Johnson[7] to generate homochiral propynylic alchols, followed by displacement of the alcohol with inversion using phthalimide.

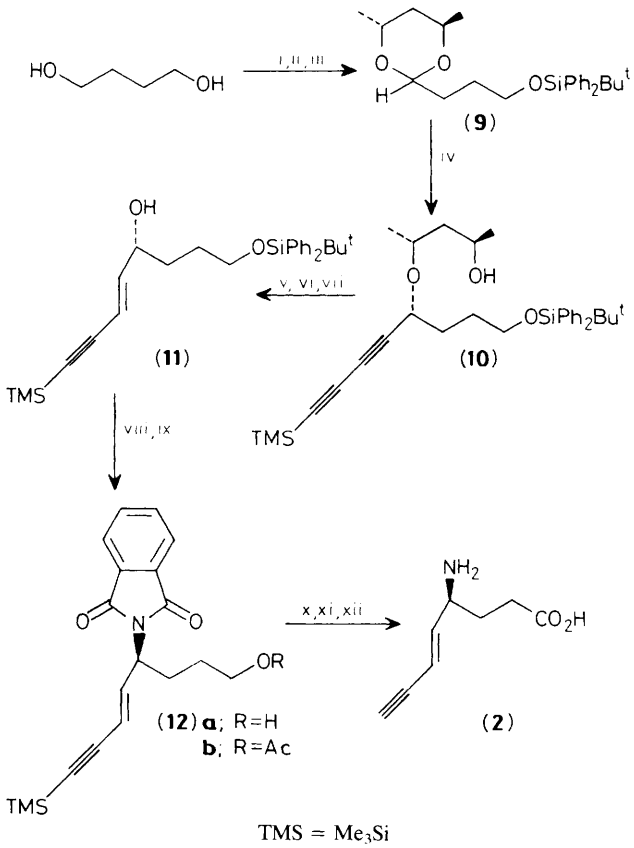
(*S*)-γ-Acetylenic GABA was prepared as shown in Scheme 1. The required chiral acetal (**3**)† {$[\alpha]_D^{25}$ +10.98° (*c* 12.7 in $CHCl_3$)} was prepared from succinic anhydride in four steps.

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



Scheme 1. *Reagents and conditions*: i, MeOH, then $SOCl_2$, reflux (86%); ii, H_2, 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.), $TiCl_4$ (2 equiv.), CH_2Cl_2, 4 Å molecular sieves, −78 °C, 20 min (78%); v, $LiAlH_4$, Et_2O, −72 °C room temp., 6 h (96%); vi, Bu^tPh_2SiCl, imidazole, dimethylformamide (DMF), room temp., 15 h (80%); vii, PCC, NaOAc, 3 Å molecular sieves, CH_2Cl_2, room temp., 15 h (90%); viii, DBU (2 equiv.), benzene, 50 °C, 13 days (72%); ix, Ph_3P, 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), Et_3N, CH_2Cl_2, −78 °C, then Jones reagent (2 equiv.) (67%); xii, $H_2NNH_2{\cdot}H_2O$, EtOH, reflux, 10 min (91%); xiii, TBAF·$3H_2O$, THF, −10 °C, 20 min (50%).

Coupling with bis(trimethylsilyl)acetylene (BTMSA)[7] gave the propynyl ether (**4**) {$[\alpha]_D^{25}$ +11.2° (*c* 14.1 in $CHCl_3$); 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**) {$[\alpha]_D^{25}$ +15.0° (*c* 5.9 in $CHCl_3$)}; 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**) {$[\alpha]_D^{25}$ −5.7° (*c* 0.525, $CHCl_3$)}. 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^tPh_2SiCl, THF, room temp., 3 h[16] (99%); ii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (92%); iii, (2*R*,4*R*)-pentane-2,4-diol, TsOH, benzene, reflux, 3 h (99%); iv, BTMSBD (3 equiv.), $TiCl_4$ (2 equiv.), CH_2Cl_2, 4 Å molecular sieves, −80 °C, 2 h (51%); v, $LiAlH_4$, Et_2O, −78 °C to room temp., 5 h (73%); vi, PCC, NaOAc, 3 Å molecular sieves, CH_2Cl_2, room temp., 15 h (89%); vii, DBU (2 equiv.), benzene, 40 °C, 14 days (66%); viii, Ph_3P, phthalimide, DEAD, THF, room temp., 18 h (46%); ix, HF–pyridine (3 equiv.), THF, room temp., 19 h (67%); x, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, then Jones reagent (2 equiv.) (47%); xi, $H_2NNH_2{\cdot}H_2O$, EtOH, reflux, 10 min (94%); xii, TBAF·$3H_2O$, THF, −10 °C, 20 min (61%).

phthalimide gave (**7**) {$[\alpha]_D^{25}$ −1.5° (*c* 3.54 in $CHCl_3$); 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 Jones[13] reagent) which was treated with hydrazine hydrate[11] to remove the phthalimide. Desilylation of the acetylene using tetra-n-butylammonium fluoride trihydrate (TBAF·$3H_2O$) yielded (*S*)-γ-acetylenic GABA (**1**),‡ m.p. 180 °C (decomp.) {lit.[4] 200 °C (decomp.)} $[\alpha]_D^{25}$ +31.4° (*c* 1.422 in H_2O) (lit.[14] +30.0°, *c* 1.28 in H_2O; lit.[4] +35.6°, *c* 1.03 in H_2O).

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. NH_3^+), 2210 (C≡C) 2130, 1980, 1640—1500 (amino acid) cm^{-1}; δ_H (CD_3OD, 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 (D_2O, 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 (D_2O) 31.9, 35.8, 45.1, 79.7, 79.9, 183.5. Found: M^++H, 128.0712. $C_6H_{10}NO_2$ 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**) {$[\alpha]_D^{25}$ +6.9° (*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**) {$[\alpha]_D^{25}$ +10.7° (*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**) {$[\alpha]_D^{25}$ −7.8° (*c* 5.3 in $CHCl_3$)}. Phthalimide inversion followed by *O*-desilylation gave the alcohol (**12a**) {$[\alpha]_D^{25}$ −45.1° (*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**)§ {$[\alpha]_D^{25}$ +30.1° (*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**): $\nu_{max.}$ (KBr) 3400—3100 (CO_2H), 3150 (C–H), 2350 (C≡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^++H, 154.0868. $C_8H_{12}NO_2$ requires *M*+H, 154.0868; *m/z* 154 (M^++H, 60%) 137 (56), 136 (100) (C.I.).

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