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

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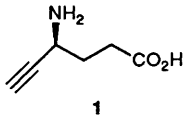
The enantioselective synthesis of (*S*)-γ-acetylenic γ-aminobutyric acid (GABA) **1** by phthalimide displacement of the (*R*)-prop-2-ynylic alcohol **12** (generated from acetal **4**) is reported.

γ-Acetylenic GABA, an unsaturated analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), functions as a mechanism-based inhibitor of the enzyme GABA-T (E. C. 2.6.1.19).[1]† As deficiencies of brain GABA have been shown to cause a number of neurological disorders, γ-acetylenic GABA has potential for therapeutic use.[2] The enantiomers of (±)-acetylenic GABA have been resolved, and it has been shown that the (*S*)-enantiomer **1** is responsible for the inhibition of mammalian GABA-T;[3] however, no enantioselective synthesis of this compound had previously been carried out. Furthermore, few approaches to the enantioselective synthesis of prop-2-ynylic and allylic amines are available.[4] In this paper we report the first enantioselective total synthesis of (*S*)-γ-acetylenic GABA **1**.[5]



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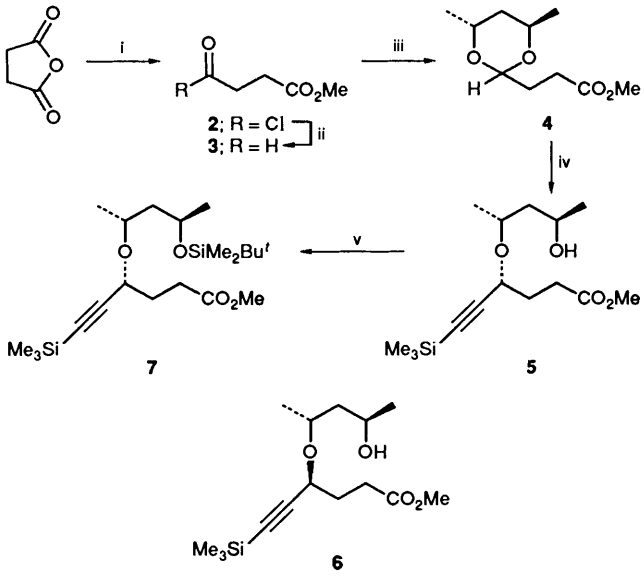
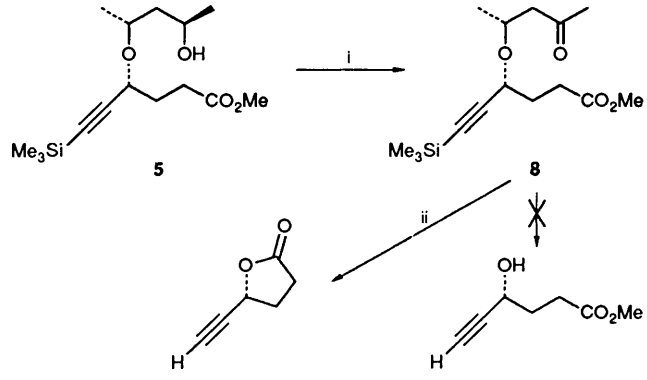
We decided to generate the stereogenic centre by using the chiral acetal methodology developed by Johnson[6] to form an enantiomerically pure propynylic alcohol, with the aim of converting this into the required enantiomerically pure amine with inversion using phthalimide. The required enantiomerically pure acetal **4** was synthesised from succinic anhydride *via* acid chloride **2**[7] followed by Rosenmund reduction[8] and acetalisation with (2*R*,4*R*)-pentane-2,4-diol (Scheme 1). This acetal was then coupled with bis(trimethylsilyl)acetylene (BTMSA) in the presence of $TiCl_4$ to give the prop-2-ynyl ether **5**; best yields were obtained when the temperature was kept below −70 °C both during the reaction and upon quenching. Under these conditions, no trace was seen by NMR spectroscopy of the opposite diastereoisomer **6**. A sample of **5** was converted into the silyl ether **7** and analysed by gas chromatography (GC); this indicated the diastereoisomeric ratio to be about 99:1.

Oxidation of the secondary alcohol using pyridinium chlorochromate (PCC)[9] gave the ketone **8** (Scheme 2); however, all attempts to remove the chiral auxiliary *via* base-catalysed retro-Michael reaction using KOH,[6] K_2CO_3[10] or piperidinium acetate[11] resulted in extensive decomposition. Use of the milder dibenzylammonium trifluoroacetate[12] resulted in lactone formation. The ester was therefore reduced, and the primary alcohol was selectively silylated (Scheme 3); oxidation with PCC gave the ketone **11**. Treatment of this ketone with the hindered base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the desired propynylic alcohol **12**. This deprotection represents an improvement on the methods using heterogeneous bases previously described,[6,10] as the acetylene is not desilylated during the process.



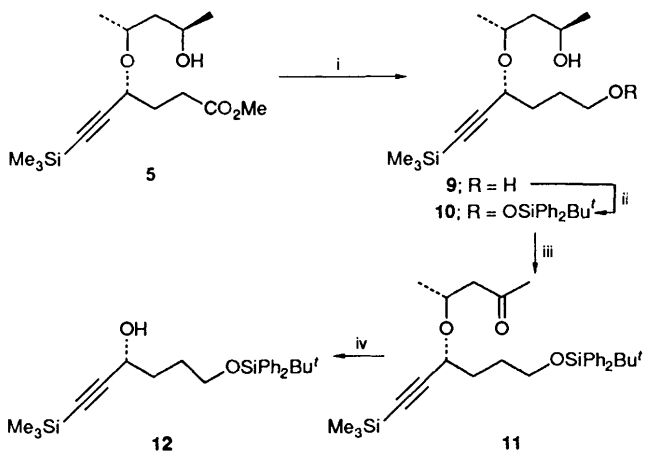
Scheme 1 *Reagents and conditions:* i, MeOH, then $SOCl_2$, reflux (86%); ii, H_2, 10% Pd–C, 2,6-lutidine (43%); iii, (2*R*,4*R*)-pentane-2,4-diol, toluene-*p*-sulphonic acid (TsOH), benzene, reflux, 2 h (96%); iv, BTMSA (5 equiv.), $TiCl_4$ (2 equiv.), CH_2Cl_2, 4 Å molecular sieves, −78 °C, 20 min (78%); v, Bu^tMe_2SiCl, imidazole, DMF



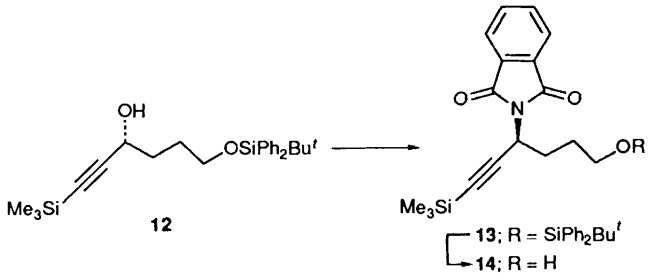
Scheme 2 *Reagents and conditions:* i, PCC, NaOAc, 3 Å molecular sieves, CH_2Cl_2, room temp., 15 h (81%); ii, dibenzylammonium trifluoroacetate, benzene, 60 °C

The alcohol **12** was then treated under Mitsunobu inversion conditions[13,14] to produce the phthalimide **13** (Scheme 4). Treatment of **13** using HF–pyridine[15] deprotected the alcohol cleanly and in good yield to give **14**; surprisingly, the silyl group on the acetylene remained intact, even after the addition of three equivalents of HF–pyridine. This reaction appears to be unprecedented.

† Vinyl GABA, a related analogue, is approved in the UK for treating refractory epileptic patients: see *FDC Reports*, 20th November 1989.

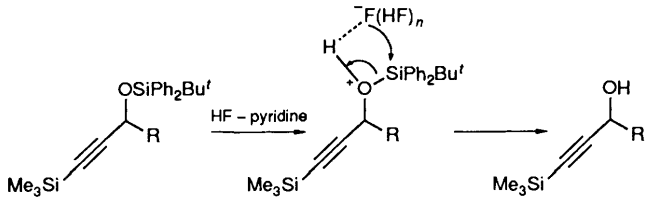


Scheme 3 *Reagents and conditions:* i, $LiAlH_4$, Et_2O, −72 °C–room temp., 5 h (96%); ii, Bu^tPh_2SiCl, imidazole, dimethylformamide (DMF), room temp., 15 h (44%); iii, PCC, NaOAc, 3 Å molecular sieves, CH_2Cl_2, room temp., 15 h (94%); iv, DBU (2 equiv.), benzene, 50 °C, 13 d (72%)



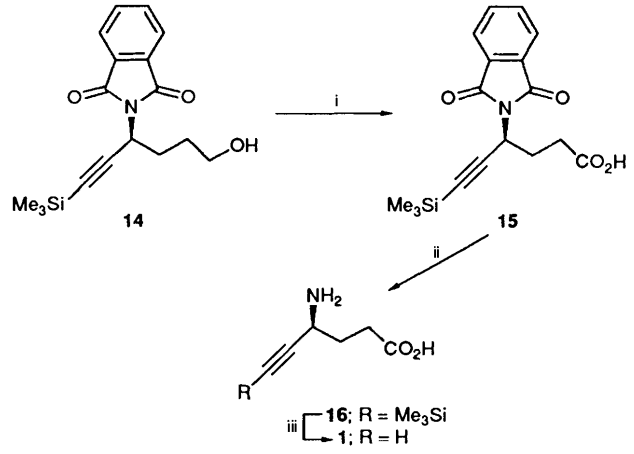
Scheme 4 *Reagents and conditions:* i, Ph_3P, phthalimide, diethylazodicarboxylate (DEAD), tetrahydrofuran (THF), room temp., 20 h (79%); ii, HF–pyridine (3 equiv.), THF, room temp., 8 h (70%)

Selective cleavage of trimethylsilyl ethers in the presence of (trimethylsilyl)acetylene groups has been reported previously using AcOH[16] and Amberlyst™ 15;[17] however, these methods failed when selective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers was attempted in the presence of ethynyl trimethylsilyl groups. The difference between these reactions and the reaction with HF–pyridine appears to lie in the nature of the nucleophile. With mild aqueous acid, the reaction takes place *via* a S_N2-Si[18] mechanism, *i.e.* preferential protonation of the oxygen followed by nucleophilic attack at silicon, displacing the prop-2-ynyl alcohol. With more hindered silyl ethers such as TBDMS or *tert*-butyldiphenylsilyl (TBDPS) ethers, nucleophilic attack is more difficult and forcing conditions have to be used, resulting in concomitant deprotection of the acetylene. Reaction with HF–pyridine, however, involves protonation by a poly(hydrogen fluoride) complex, which is also an excellent fluoride donor.[19] It is therefore probable that the selective cleavage of TBDPS ethers in the presence of the (trimethylsilyl)-acetylene group takes place *via* preferential protonation of the oxygen, followed by intramolecular delivery of F^- to the silicon (Scheme 5).



Scheme 5

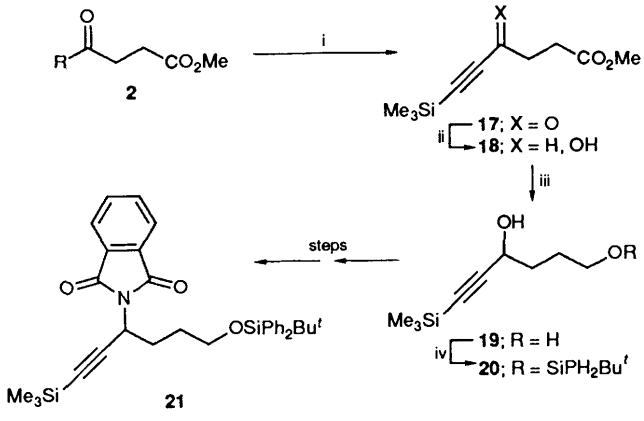
The synthesis was then completed as shown in Scheme 6. Conversion of the primary alcohol into the acid *via* a two-stage oxidation procedure (Swern,[20] followed by Jones reagent[21]) gave the most satisfactory yields. Deprotection of the amine using hydrazine hydrate[13] gave the free amine. The silyl group was then removed using tetrabutyl ammonium fluoride trihydrate (TBAF·$3H_2O$) in wet THF to give (*S*)-γ-acetylenic



Scheme 6 *Reagents and conditions:* i, oxalyl chloride, dimethyl sulphoxide (DMSO), Et_3N, CH_2Cl_2, −78 °C, then Jones reagent (2 equiv.) (67%); ii, $H_2NNH_2·H_2O$, EtOH, reflux, 30 min (91%); iii, TBAF·$3H_2O$, THF, 10 °C, 20 min (48%)

GABA **1**. Spectral data for this compound have not yet been published, but the optical rotation agrees well with the previously reported value.[3,32]

In order to determine the enantiomeric purity of key intermediates in this synthesis, it was necessary to synthesise racemic versions of these intermediates. The racemic alcohol **20** was first synthesised from the acid chloride **2** as shown in Scheme 7. However, derivatisation of **20** with camphanic acid chloride followed by attempts to separate the diastereoisomers by high pressure liquid chromatography (HPLC) failed. A ^1H NMR chiral shift experiment was performed with Eu-(+)-$(hfc)_3$, but no peak separation was obtained. The alcohol was therefore converted into the racemic phthalimide **21**, using the methodology outlined in Scheme 4. A ^1H NMR chiral shift experiment with **21** using Eu-(+)-$(hfc)_3$ showed a clear splitting of the signal at δ 5.07 ($R_2NCR'R''H$); this was not observed when the same experiment was carried out with **13**, indicating the enantiomeric purity of the latter to be >95:5.



Scheme 7 *Reagents and conditions:* i, BTMSA (1 equiv.) $AlCl_3$ (1.5 equiv.) CH_2Cl_2, 0 °C, 4 h (90%); ii, $NaBH_4$, THF, H_2O, −10 °C, 20 min (77%); iii, $LiAlH_4$, Et_2O, −20 °C, 5 h (77%); iv, Bu^tPh_2SiCl, imidazole, (DMF), room temp., 15 h (58%)

In summary, a novel and highly enantioselective route to (*S*)-γ-acetylenic GABA has been devised, using methodology that can be easily extended to afford a variety of unsaturated GABA analogues.

Experimental

Ether refers to diethyl ether; light petroleum (40–60) refers to the fraction boiling between 40 and 60 °C. IR spectra were recorded on a Perkin-Elmer 297 or 1310 spectrometer. ^{1}H NMR spectra were recorded on Varian EM-390 (90 MHz), Bruker WP-80 SY (80 MHz) and Bruker WM-250 (250 MHz) instruments, using either chloroform as reference or internal deuterium lock. ^{13}C NMR spectra were recorded on Bruker WM-250 (63 MHz) and Bruker WM-400 (100 MHz) instruments, using internal deuterium lock and proton decoupling. *J* Values are given in Hz. EI and FAB mass spectra were recorded using an AEI MS902 or MS 30 instrument; high resolution EI spectra were carried out on the MS30 instrument in conjunction with a DS50S data system. High resolution CI mass spectra were performed on a VG ZAB-E instrument at the SERC Mass Spectrometry Centre, University of Swansea (Dr. J. Ballantine and colleagues), using NH_3 as the carrier gas. Optical rotations were measured using a Perkin-Elmer 241 polarimeter; specific rotations are expressed in implied units of 10^{-1} deg cm^2 g^{-1} and the concentration is expressed in g cm^{-3}. M.p.s were determined using a Büchi 510 melting point apparatus and are uncorrected. TLC was carried out on pre-coated 0.25 mm thick Merck 60 F_{254} silica plates. Visualisation was by absorption of UV light, or by spraying with basic potassium permanganate solution. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh); the column diameter is given in cm. Analytical HPLC was carried out using a Gilson system (303 pump) with a Dynamax™ Si column, 4.6 mm × 25 cm; the retention times are given in min. Reagents were purified and dried where necessary by standard techniques; THF was dried from potassium in a recycling still.

Methyl 4-*Oxobutanoate* **3**.—2,6-Dimethylpyridine (2.89 cm^3, 0.025 mol) was added to a suspension of 10% Pd–C catalyst (0.37 g) in anhydrous THF (100 cm^3). The mixture was then prehydrogenated at atmospheric pressure for 2 h with stirring. Methyl 4-chloro-4-oxobutanoate **2**[7] (2.7 cm^3, 0.025 mol) was then added by syringe and hydrogen uptake continued until 500 cm^3 had been taken up. The solvent was removed under reduced pressure and dry ether (50 cm^3) added to the mixture of product and catalyst. The mixture was then filtered through a pad of Celite and the solution was concentrated to give a yellow oil. This was purified by Kugelrohr distillation to give the *title compound* as a colourless oil (1.247 g, 43%), b.p. 70–72 °C/13 mmHg (lit.,[23] 69–71 °C/15 mmHg); ν_{max}(CHCl$_3$)/cm^{-1} 2800m (CH), 2700m (CH) and 1700br; δ_H(250 MHz; CDCl$_3$) 2.5 (2 H, t, *J* 6), 2.7 (2 H, t, *J* 6), 3.5 (3 H, s) and 9.5 (1 H, s).

Methyl 4-[(4R,6R)-4,6-*Dimethyl*-1,3-*dioxan*-2-*yl*]*propanoate* **4**.—To a solution of methyl 4-oxobutanoate **3** (175 mg, 1.51 mmol) in dry benzene in a 2.5 cm^3 flask under nitrogen equipped with stirrer bead, lagged Dean–Stark head and condenser was added (2*R*,4*R*)-pentane-2,4-diol (158 mg, 1.52 mmol) and a trace of toluene-*p*-sulphonic acid. The mixture was heated under reflux for 2 h, then cooled to room temperature and washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and distilled water (2 × 20 cm^3), then dried (K_2CO_3). The benzene was removed at reduced pressure to give the *title compound* as a colourless oil (293 mg, 96% from the aldehyde); $[\alpha]_D^{22}$ +10.98 (*c* 12.7, CHCl$_3$) (Found: C, 59.2; H, 8.9. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%); λ_{max}(MeOH)/nm 210.5 (ε 320 dm^3 mol^{-1} cm^{-1}) and 273.3 (50); ν_{max}(CCl$_4$)/cm^{-1} 2970, 2940, 2860, 2710, 2610 and 1740; δ_H(250 MHz; CDCl$_3$) 1.12 (3 H, d, *J* 6.1), 1.27 (3 H, d, *J* 7.0), 1.68–1.86 (4 H, m), 2.37 (2 H, t, *J* 7.5), 3.60 (3 H, s), 3.90 (1 H, sextet of doublets, *J* 6.0, 2.4), 4.21 (1 H, quintet, *J* 6.7) and 4.84 (1 H, t, *J* 5.0).

Methyl (4R)-4-[(4R,3R)-3-*Hydroxy*-1-*methylbutoxy*]-6-*trimethylsilylhex*-5-*ynoate* **5**.—Bis(trimethylsilyl)acetylene (7.60 g, 44.6 mmol, 6 equiv.) was added to a solution of the acetal **4** (1.46 g, 7.20 mmol) in dichloromethane (70 cm^3) under argon in a 100 cm^3 three-necked flask fitted with an alcohol thermometer, septum cap, Ar balloon, stirrer bead and 4 Å sieves. The reaction was cooled to −74 °C and $TiCl_4$ (1.24 cm^3) was added in one portion. The resulting opaque yellow solution was stirred at this temperature for 20 min, then a 1:1 mixture of anhydrous methanol and dichloromethane (10 cm^3) was added slowly, keeping the temperature below −74 °C. During this time the colour changed through brown to green and then disappeared completely. The reaction was warmed to room temperature and extracted with hydrochloric acid (1 mol dm^{-3}; 40 cm^3) and water (2 × 40 cm^3). The organic layer was dried over K_2CO_3 and the solvent was removed under reduced pressure to give a slightly yellow oil: this was purified by Kugelrohr distillation to give **5** as a *colourless oil* (1.68 g, 5.6 mmol, 78%), b.p. 90–95 °C/0.1 mmHg, $[\alpha]_D^{22}$ +11.2 (*c* 14.1, CHCl$_3$) (Found: C, 60.3; H, 9.5. $C_{15}H_{28}O_4Si$ requires C, 60.0; H, 9.4%); ν_{max}(CHCl$_3$)/cm^{-1} 3540, 2970, 2940, 2900, 2170 and 1740; δ_H(90 MHz; CDCl$_3$) 0.05 (9 H, s), 1.05 (3 H, d, *J* 6), 1.15 (3 H, d, *J* 6), 1.45 (2 H, m), 1.9 (2 H, q, *J* 6), 2.35 (1 H, br s), 2.47 (2 H, dt, *J* 2, 7), 3.6 (3 H, s) and 3.75–4.3 (3 H, m); δ_C (62.5 MHz; CDCl$_3$) −0.25, 20.72, 23.81, 29.73, 31.21, 45.05, 51.50, 64.24, 67.88, 72.21, 90.42, 105.13 and 173.58; *m*/*z* (EI) 300 (M$^+$, 2%), 213 (20), 197 (36), 183 (24), 181 (31), 127 (59), 115 (24), 105 (36), 75 (49), 73 (100), 69 (92), 65 (45), 59 (27) and 55 (30); [Found (EI): M$^+$, 300.1747. $C_{15}H_{28}O_4Si$ requires *M*, 300.1757]. A small sample of **5** was converted into the TBDMS derivative by stirring for 15 h in DMF with *tert*-butyldimethylsilyl chloride and imidazole. After work-up and purification by Kugelrohr distillation, **7** δ_H(CDCl$_3$) −0.05 (6 H, s), 0.0 (9 H, s), 0.75 (9 H, s), 0.95 (3 H, d, *J* 6), 1.1 (3 H, s, *J* 6), 1.4 (2 H, m), 1.85 (2 H, q, *J* 6), 2.45 (2 H, t, *J* 6), 3.45 (3 H, s), 3.6–3.8 (2 H, m) and 4.0 (1 H, t, *J* 5) was analysed by GC (isothermal at 100 °C, then increasing in temperature by 10 °C min^{-1}); this showed 2 peaks in the ratio 98.9:1.1, retention times 9.8 and 10.2 min, indicating a d.e. of 98%.

Methyl (4R)-[(1R)-1-*Methyl*-3-*oxobutoxy*]-6-*trimethylsilylhex*-5-*ynoate* **8**.—To a suspension of PCC (814 mg, 3.78 mmol, 3.26 equiv.) and sodium acetate (28 mg) in dry CH_2Cl_2 (20 cm^3) in a 50 cm^3 round-bottomed flask equipped with stirrer, N_2 balloon and powdered 3 Å molecular sieves, was added a solution of the alcohol **5** (279.7 mg, 0.94 mmol) in dry CH_2Cl_2 (5 cm^3). The reaction was stirred at room temperature for 15 h, then the solvent was removed under reduced pressure and ether (20 cm^3) was added. The resulting suspension was applied to a Florisil column (2.5 × 4 cm) and eluted with ether (200 cm^3). The ether was removed under reduced pressure to give the *title compound* as a colourless oil (280 mg, 0.94 mmol, 81%) (Found: C, 60.3; H, 9.0. $C_{15}H_{26}O_4Si$ requires C, 60.4; H, 8.8%); ν_{max}(CHCl$_3$)/cm^{-1} 2930 and 2800sh (CH), 2180w (C≡C), 1730s (C=O), ester) and 1720s (C=O, ketone); δ_H(250 MHz; CDCl$_3$) −0.05 (9 H, s), 1.1 (3 H, d, *J* 5), 1.8 (2 H, q, *J* 5), 1.95 (3 H, s), 2.25 (2 H, t, *J* 5), 2.5 (2 H, d, *J* 7), 3.5 (3 H, s), 4.0 (1 H, m) and 4.05 (1 H, t); *m*/*z* (CI) 300 (M$^+$ + NH$_4$, 19%), 297 (26) and 197 (100). [Found (CI): M$^+$ + NH$_4$, 316.1935. $C_{15}H_{30}NO_4Si$ requires *M* + NH$_4$, 316.1926].

(4R)-4-[(1R,3R)-3-*Hydroxy*-1-*methylbutoxy*]-6-*trimethylsilylhex*-5-*yn*-1-*ol* **9**.—The ketone **5** (1.57 g, 5.24 mmol) in ether (5 cm^3) was added over 5 min to a stirred suspension of $LiAlH_4$

(483 mg, 2.4 equiv.) in anhydrous ether (10 cm^3) at −72 °C over 4 Å sieves under N_2. The mixture was then stirred at −72 °C for 30 min, then warmed to room temperature over 30 min and stirred for a further 4 h. It was then poured into ice-cold saturated aqueous NH_4Cl solution (30 cm^3) and extracted with ethyl acetate (6 × 30 cm^3). The combined organic layers were washed with brine (30 cm^3) and dried ($MgSO_4$); the solvents were removed under reduced pressure to give a yellow viscous oil. This was purified by Kugelrohr distillation to give the *alcohol* **9** as a colourless viscous oil (1.30 g, 5 mmol, 96%), b.p. 108–110 °C/0.5 mmHg (Found: C, 61.9; H, 10.5. $C_{14}H_{28}O_3Si$ requires C, 61.7; H, 10.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3440br (OH) 2900 (CH) and 2180w (C≡C); δ_H(250 MHz; $CDCl_3$) 0.10 (9 H, s), 1.11 (3 H, d, *J* 6.2), 1.23 (3 H, d, *J* 6.3), 1.50 (2 H, t, *J* 5.9), 1.64–1.71 (4 H, m), 3.25 (1 H, br s), 3.27 (1 H, br s), 3.58 (2 H, br m), 3.89 (1 H, sextet, *J* 6.2), 4.03 (1 H, sextet, *J* 6.2) and 4.1 (1 H, br t); δ_C (62.5 MHz; $CDCl_3$) −0.2, 20.7, 23.8, 28.2, 32.7, 44.9, 62.2, 64.1, 68.7, 73.0, 89.8 and 105.9; *m/z* (EI) 213 (M^+ − C_3H_7O, 15%), 168 (39), 162 (28), 124 (92), 99 (31), 77 (30), 75 (100), 73 (60) and 69 (51).

(2R,4R)-4-[4-tert-*Butyldiphenylsilyloxy*-1-(2-*trimethylsilylethynyl*)*butoxy*]*pentan*-2-*ol* **10**.—The alcohol **9** (1.01 g, 3.72 mmol) was added to a solution of *tert*-butyldiphenylsilyl chloride (1.16 cm^3, 1.16 mmol, 1.2 equiv.) and imidazole (660 mg, 9.7 mmol, 2.6 equiv.) in dry DMF (10 cm^3). The mixture was stirred for 15 h at room temperature, then diluted with water (30 cm^3) and extracted with ether (2 × 20 cm^3). The ethereal layers were extracted with saturated aqueous NH_4Cl (20 cm^3) and water (30 cm^3) and dried ($MgSO_4$). The ether was removed to give a colourless oil (2.32 g). This was purified by flash chromatography (0.5% MeOH in CH_2Cl_2; R_F 0.40) and then distilled under reduced pressure to give the *silyl ether* **10** (827 mg, 1.62 mmol, 44%), b.p. 188–192 °C/0.5 mmHg, $[\alpha]_D^{22}$ +5.73 (*c* 12.0, $CHCl_3$) (Found: C, 70.6; H, 9.1. $C_{30}H_{46}O_3Si$ requires C, 70.5; H, 9.1%); λ_{max}(cyclohexane)/nm 265 (ε 590) and 226 (3000); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490br (OH), 2860 (CH), 2170 (C≡C) and 1580 (Ph); δ_H(250 MHz; $CDCl_3$) 0.18 (9 H, s), 1.07 (9 H, s), 1.17 (3 H, d, *J* 6.2), 1.30 (3 H, d, *J* 6.4), 1.54–1.61 (2 H, m), 1.72–1.83 (4 H, m), 2.55 (1 H, br s), 3.70 (2 H, t, *J* 5.8), 4.01 (1 H, m), 4.10 (1 H, m), 4.19 (1 H, t, *J* 6.2), 7.34–7.43 (6 H, m) and 7.66–7.71 (4 H, m); δ_C(62.5 MHz; $CDCl_3$) −0.2, 19.2, 20.7, 23.8, 26.9 (strong), 28.35, 32.8, 44.7 (weak), 63.6, 64.4, 69.0, 73.0, 89.9 (weak), 106.1 (weak), 127.6, 129.5, 134.0 (weak) and 135.5 (strong).

(4R)-4-[4-tert-*Butyldiphenylsilyloxy*-1-(2-*trimethylsilylethynyl*)*butoxy*]*pentan*-2-*one* **11**.—The alcohol **10** (310 mg, 0.61 mmol) was added to a suspension of PCC (420 mg, 1.9 mmol, 3.2 equiv.), sodium acetate (15 mg) and 3 Å sieves in dry CH_2Cl_2 under N_2. The mixture was stirred for 15 hr at room temperature, then the CH_2Cl_2 was removed under reduced pressure and ether (50 cm^3) was added. The ethereal solution was applied to a Florisil column (2.5 × 4 cm) and eluted with ether (200 cm^3); the ether was removed under reduced pressure to give the *ketone* **11** (291 mg, 0.58 mmol, 94%) as a colourless oil, b.p. 160–165 °C/0.4 mmHg, $[\alpha]_D^{22}$ +15.0 (*c* 5.9, $CHCl_3$) (Found: C, 70.95; H, 9.0. $C_{30}H_{44}O_3Si_2$ requires C, 70.8; H, 8.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2970, 2940, 2900, 2870 (CH), 2170 (C≡C), 1720 (C=O) and 1600 (Ph); δ_H(250 MHz; $CDCl_3$) 0.19 (9 H, s), 1.07 (9 H, s), 1.29 (3 H, d, *J* 6.2), 1.69–1.78 (4 H, m), 2.14 (3 H, s), 2.40 (1 H, dd, *J* 5.5, 16.0), 2.75 (1 H, dd, *J* 7.1, 16.0), 3.69 (2 H, t, *J* 5.8), 4.12–4.17 (2 H, m), 7.34–7.43 (6 H, m) and 7.67–7.71 (4 H, m); δ_C(62.5 MHz; $CDCl_3$) −0.1, 19.2, 21.2, 26.8, 28.3, 31.1, 32.7, 50.5, 63.5, 69.1, 71.5, 89.7, 106.0, 127.6, 129.5, 133.9, 135.5 and 207.1.

(R)-6-tert-*Butyldimethylsilyloxy*-1-*trimethylsilylhex*-1-*yn*-3-*ol* **12**.—The ketone **11** (269 mg, 0.53 mmol) was dissolved in anhydrous benzene (20 cm^3) over 4 Å sieves and DBU (0.1 ml, 0.67 mmol, 1.3 equiv.) was added. The mixture was then heated at 60 °C for 13 d, cooled and extracted with saturated aqueous NH_4Cl (20 cm^3) and water (20 cm^3). The organic layer was dried over $MgSO_4$ and the benzene was removed under reduced pressure to give crude **12** as a colourless oil (224 mg). This was purified by flash chromatography [4 cm^3, 20% EtOAc in light petroleum (60–80); R_F 0.44] followed by Kugelrohr distillation to give the *alcohol* **12** as a colourless viscous oil (163 mg, 0.383 mmol, 72%), b.p. 135–138 °C/0.05 mmHg, $[\alpha]_D^{22}$ −5.7 (*c* 0.525, $CHCl_3$) (Found: C, 70.4; H, 8.3. $C_{25}H_{36}O_2Si$ requires C, 70.7; H, 8.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600 and 3350 (OH), 2910, 2840, 2160 (C≡C) and 1580 (Ph); δ_H(250 MHz; $CDCl_3$) 0.18 (9 H, s), 1.06 (9 H, s), 1.8–2.0 (4 H, m), 2.9 (1 H, d), 3.6–3.7 (2 H, m), 4.3 (1 H, m), 7.25–7.44 (6 H, m) and 7.66–7.70 (4 H, m); δ_C(62.5 MHz; $CDCl_3$) −0.1, 19.2, 26.8, 28.2, 35.0, 62.6, 63.9, 89.2, 106.8, 127.7, 129.7, 133.5 and 135.6; *m/z* (CI) 442 ($M^+ + NH_4$, 23%), 425 (100, M + H), 407 (26), 216 (55) and 196 (37) [Found (CI): $M^+ + NH_4$, 23%], 425 (100, M + H), 407 (26), 216 (55) and 196 (37) [Found (CI): M^+ + H, 425.2344. $C_{25}H_{37}O_2Si$ requires $(M + H)^+$, 425.2356].

(S)-N-[4-(tert-*Butyldiphenylsilyloxy*)-1-(2-*trimethylsilylethynyl*)*butyl*]*phthalimide* **13**.—To a solution of the alcohol **12** (1.46 g, 3.44 mmol), triphenylphosphine (971 mg, 1 equiv.) and phthalimide (559 mg, 1.1 equiv.) in anhydrous THF (30 cm^3) at room temperature was added diethylazodicarboxylate (0.68 cm^3, 1.2 equiv.). The reaction was stirred at room temperature for 20 h, then the solvent was removed under reduced pressure to give a yellow gum. The product was taken up in 1:1 ether–hexane and the solid triphenylphosphine oxide was removed by filtration; the precipitate was washed with several portions of 1:1 ether–hexane. The filtrate was concentrated under reduced pressure to give a yellow oil. This was purified by flash chromatography (6 cm, toluene; R_F 0.38) followed by distillation at reduced pressure (oil-pump) to give the *title compound* as a colourless viscous oil (1.50 g, 2.71 mmol, 79%), b.p. 190–195 °C/0.05 mmHg, $[\alpha]_D^{22}$ −1.5 (*c* 3.54, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2920, 2860 (CH), 2180 (C≡C), 1775 and 1710 (C=O); δ_H(250 MHz, $CDCl_3$) 0.15 (9 H, s), 1.04 (9 H, s), 1.65–1.85 (2 H, m), 2.05–2.20 (2 H, m), 3.68 (2 H, t, *J* 6.5), 5.07 (1 H, t, *J* 8), 7.33–7.41 (6 H, m), 7.62–7.67 (4 H, m), 7.70–7.73 (2 H, m) and 7.84–7.87 (2 H, m); δ_C(62.5 MHz; $CDCl_3$) −0.1, 19.2 (weak), 26.6, 29.4, 30.1, 42.3, 63.0, 88.5 (weak), 101.7 (weak), 123.4, 127.6, 129.6, 131.9 (weak), 133.8 (weak), 134.0, 135.5 and 166.9 (weak); *m/z* (CI) 571 [$(M + NH_4)^+$, 100%], 554 (21) and 476 (32) [Found (CI): M^+ + H 554.2548. $C_{33}H_{40}NO_3Si_2$ requires *M* + H, 554.2546]. The same procedures were carried out using the racemic alcohol **20** to give the racemic phthalimide **21**. When a ^1H NMR chiral shift experiment was performed with **21** (10 mg) using Eu-(+)-$(hfc)_3$ (6 mg) in $CDCl_3$, a clear splitting of the signal at δ 5.07 ($R_2NCR'R''H$) was seen. This splitting was not observed when the same experiment was carried out with **13** (10 mg), indicating the enantiomeric purity of this material to be >95:5.

(S)-N-[4-*Hydroxy*-1-(2-*trimethylsilylethynyl*)*butyl*]*phthalimide* **14**.—To a solution of the phthalimide **13** (98.9 mg, 0.179 mmol) in THF at 0 °C was added HF–pyridine (0.10 cm^3, 2 equiv.). The reaction was stirred at room temperature for 3.5 h, monitoring by TLC; a further portion of HF–pyridine (0.05 cm^3, 1 equiv.) was then added and the reaction stirred for a further 4 h. After this time the starting material (1:1 EtOAc–hexane; R_F 0.65) had disappeared and another spot (R_F 0.32) had appeared. The reaction was then diluted with ethyl acetate (20 cm^3) and washed with water (15 cm^3). The aqueous layer was then washed with ethyl acetate (20 cm^3) and the combined

organic layers were washed with saturated aqueous sodium hydrogen carbonate (3 × 5 cm^3) and brine (10 cm^3) and dried over $MgSO_4$. Removal of the solvents under reduced pressure followed by flash chromatography (1 cm, 1:1 EtOAc–hexane) gave the *title compound* as a white solid (39 mg, 0.13 mmol, 70%), $[\alpha]_D^{22}$ +4.25 (*c* 1.21, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3610 (OH) 2950, 2880 (CH), 2180 (C≡C), 1775 and 1710 (C=O phthalimide); δ_H(250 MHz; $CDCl_3$) 0.12 (9 H, s), 1.51–1.77 (3 H, m), 2.00–2.27 (2 H, m), 3.63 (2 H, t, *J* 6.4), 5.04 (1 H, t, *J* 7.3), 7.66–7.73 (2 H, m) and 7.78–7.86 (2 H, m); δ_C(62.5 MHz; $CDCl_3$) −0.2, 29.3, 29.9, 42.1, 61.7, 88.6, 101.5, 123.4, 131.7, 134.1 and 167.0; *m/z* (CI) 333 ($M^+ + NH_4$, 100%), 317 (25) and 316 (92) (Found: $M^+ + NH_4$, 333.1635. $C_{17}H_{25}N_2O_3Si$ requires *M* + NH_4, 333.1634).

(S)-4-*Phthalimido*-6-*trimethylsilylhex*-5-*ynoic Acid* **15**.—A solution of oxalyl chloride (0.06 cm^3, 0.22 mmol, 1.1 equiv.) in anhydrous CH_2Cl_2 (30 cm^3) was placed in a 100 cm^3 three-necked round-bottomed flask equipped with alcohol thermometer, N_2 balloon and septum cap. The mixture was then cooled to −70 °C and a solution of DMSO (0.1 cm^3, 0.48 mmol, 2.4 equiv.) in anhydrous CH_2Cl_2 (2 cm^3) added dropwise over 5 min, maintaining the temperature below −60 °C. The reaction was stirred at −70 °C for 10 min, then a solution of the alcohol **14** (63.9 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (10 cm^3) was added dropwise over 5 min, maintaining the temperature below −60 °C. The reaction mixture was then stirred at −70 °C for a further 15 min, then triethylamine (0.42 cm^3, 1.1 mmol, 5 equiv.) was added dropwise over 5 min. The reaction mixture was warmed to room temperature and quenched by the addition of water (10 cm^3). Stirring was continued for 10 min, then the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3): the combined organic extracts were washed with 1 mol dm^{-3} HCl (25 cm^3), water (20 cm^3), saturated aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3) and then dried over $MgSO_4$. The solvents were removed under reduced pressure to give the intermediate *aldehyde* [1:1 EtOAc–hexane (1 drop AcOH); R_F 0.50] as a clear viscous oil (54.9 mg, 0.176 mmol, 88%); $\nu_{max}(CCl_4)/cm^{-1}$ 2950, 2800 (CH), 2700 (CH, aldehyde), 2170 (C≡C), 1775 (C=O) and 1720 (C=O); δ_H(90 MHz $CDCl_3$) 0.1 (9 H, s), 2.0–2.7 (4 H, m), 5.0 (1 H, t, *J* 7), 7.6–7.9 (4 H, m) and 9.75 (1 H, s). The aldehyde (54.9 mg, 0.176 mmol) was then dissolved in acetone (5 cm^3) and cooled to −5 °C. Jones reagent[21] (0.26 cm^3, 2 equiv.), was then added dropwise over 10 min. This process was repeated at 10 min intervals until TLC analysis [1:1 EtOAc:hexane (1 drop AcOH)] indicated the disappearance of the starting material (R_F 0.50) and the appearance of **15** (R_F 0.21). The excess of oxidant was then quenched with excess of propan-2-ol (5 cm^3) and the resulting green solution was poured into water (20 cm^3). The aqueous solution (pH 2) was then extracted with ether (3 × 20 cm^3) and the combined organic layers were washed with brine (10 cm^3) and dried over $MgSO_4$. The solvents were removed under reduced pressure to give crude **15** (44.2 mg, 0.13 mmol, 67% over 2 steps). Recrystallisation from EtOAc–hexane gave the *acid* **15** as white cubes, m.p. 65–67 °C; $[\alpha]_D^{22}$ +5.1 (*c* 3.32, $CHCl_3$) (Found: C, 62.2; H, 5.9; N, 4.55. $C_{17}H_{19}NO_4Si$ requires C, 62.0; H, 5.8; N, 4.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3200–2800 (OH, acid), 2940, 2880 (CH), 2170 (C≡C), 1765, 1720 (C=O phthalimide, acid), 1600 and 1590 (Ar); δ_H(250 MHz; $CDCl_3$) 0.14 (9 H, s), 2.2–2.6 (4 H, m), 5.11 (2 H, t, *J* 7.5), 7.67–7.75 (2 H, m), 7.80–7.88 (2 H, m) and 8.6–8.8 (1 H, v br); δ_C(62.5 MHz; $CDCl_3$) −0.2, 28.2, 30.7, 41.4, 89.6 (weak), 100.3 (weak), 123.5, 131.7, 134.1, 166.8 and 178.2 (weak); *m/z* (CI) 347 ($M^+ + NH_4$, 100%), 330 (31, M + H), 90 (31) and 52 (22) [Found (CI): $M^+ + NH_4$, 347.1421. $C_{17}H_{23}N_2O_4Si$ requires *M* + NH_4, 347.1420].

(S)-4-*Amino*-6-*trimethylsilylhex*-5-*ynoic Acid* **16**.—To a solution of the acid **15** (71.8 mg, 0.22 mmol) in ethanol (5 cm^3) was added $H_2NNH_2 \cdot H_2O$ (10 drops). The mixture was heated at reflux for 30 min, then cooled to room temperature and the ethanol removed under reduced pressure to give a white solid. This was dissolved in MeOH–CH_2Cl_2–NH_3 (8:12:1), applied to a silica column (1 cm) and eluted with the same solvent system under gravity (R_F 0.57–0.67). This yielded the *title compound* as a white solid (40.5 mg, 0.2 mmol, 91%), $[\alpha]_D^{22}$ + 23.3 (*c* 1.58, MeOH); ν_{max}(KBr)/cm^{-1} 3020–2500 (CO_2H and CH), 2200 (C≡C, weak) and 1655 (C=O); δ_H(80 MHz; CD_3OD) 0.03 (9 H, s), 1.8–2.0 (2 H, m), 2.2–2.5 (2 H, m) and 4.1 (1 H, m); δ_C(62.5 MHz; CD_3OD) −2.2, 29.1, 32.5, 42.5, 91.3, 99.8 and 177.8; *m/z* (CI) 205 (50%), 202 (70) and 200 (100, M + H) (Found: M^+ + H, 200.110 28. $C_9H_{18}O_2NSi$ requires *M* + H, 200.110 24).

S-4-*Aminohex*-5-*ynoic Acid* (γ-*Acetylenic GABA*) **1**.—A solution of the amino acid **16** (10 mg, 0.05 mmol) in THF (0.5 cm^3) was added to TBAF·$3H_2O$ (32 mg, 2 equiv.) in THF (0.5 cm^3) and water (10 drops). The mixture was stirred at room temperature for 30 min, then diluted with water (2 cm^3) and extracted with ether (10 cm^3). The aqueous layer was then applied to a column of Dowex-50-X8-400 (1 cm diameter, 10 g resin, H^+ form) and eluted with water until the fractions were neutral. The amino acid was then removed from the column by elution with 10% NH_4OH in water. TLC analysis showed the presence of the required amino acid in fractions 6 to 10 (MeOH: R_F 0.48) which were combined. The solvents were removed under reduced pressure to give the *title compound* as a white solid (3.03 mg, 0.024 mmol, 48%), m.p. 170 °C (decomp.), $[\alpha]_D^{22}$ +31.4 (*c* 1.42, H_2O) (lit.[22] 30.0, *c* 1.28, H_2O; lit.[3] 35.6, *c* 1.03, H_2O); ν_{max}(KBr)/cm^{-1} 3290 (C≡CH), 3100–2500br (NH_3^+), 2210 (C≡C), 2130, 1980 and 1640–1500 (amino acid); δ_H(250 MHz; CD_3OD) 1.91–2.08 (2 H, m), 2.30–2.56 (2 H, m), 3.13 (1 H, d, *J* 2.2) and 4.09 (1 H, br t, *J* 6); δ_H(250 MHz; D_2O) 1.99–2.30 (2 H, m), 2.43 (2 H, octet, *J* 7), 3.34 (1 H, s) and 4.17 (1 H, ABX, J_{AX+BX} 14, J_1 6, J_2 9); δ_C(62.5 MHz; D_2O) 31.9, 35.8, 45.1, 79.7, 79.9 and 183.5; *m/z* (CI) 128 (M^+ + H, 100%), 111 (20), 102 (52), 84 (64), 73 (48), 54 (29) and 45 (20) (Found: M^+ + H, 128.0712. $C_6H_{10}NO_2$ requires *M* + H, 128.0712).

Methyl 4-*Oxo*-6-*trimethylsilylhex*-5-*ynoate* **17**.—To a suspension of finely powdered anhydrous $AlCl_3$ (4.72 g, 0.032 mol) in anhydrous CH_2Cl_2 (50 cm^3) at 0 °C was added freshly distilled methyl 3-chloroformyl propanoate **2** (2.5 cm^3, 0.023 mol) over 30 min. The reaction was stirred at 0 °C for 30 min, then the dark brown solution was filtered through Celite under N_2 and added over 1 h *via* cannula to a solution of bis-(trimethylsilyl)acetylene (5.1 cm^3, 0.023 mol) in CH_2Cl_2 (50 cm^3) at 0 °C. The resulting brown mixture was stirred at 0 °C for 4 h, then washed with ice-cold HCl (2 mol dm^{-3}; 50 cm^3). The aqueous layer was then washed with ether (2 × 75 cm^3); the combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure to give crude **17** as a brown liquid (3.13 g). This was purified by flash chromatography (CH_2Cl_2; R_F 0.3–0.52) and then distilled twice at reduced pressure to give the *title compound* as a clear oil, b.p. 100 °C/14 mmHg (4.4 g, 0.021 mol, 90%) (Found: C, 56.6; H, 7.7. $C_{10}H_{16}O_3Si$ requires C, 56.6; H, 7.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2960, 2910, 2860 (CH), 2150 (C≡C), 1740 (C=O), and 1680 (C=O); δ_H(250 MHz; $CDCl_3$) 0.12 (9 H, s), 2.5 (2 H, m), 2.77 (2 H, t, *J* 7) and 3.55 (3 H, s); δ_C(62.5 MHz; $CDCl_3$) −1.2, 27.3, 39.5, 51.5, 98.1, 101.2, 172.2 and 184.8.

6-*Trimethylsilylhex*-5-*yn*-1,4-*diol* **19**.—Methyl 4-oxo-6-trimethylsilylhex-5-ynoate **17** (3.685 g, 17 mmol) was dissolved in THF (100 cm^3) and H_2O (10 drops) added. The mixture was cooled to 0 °C and sodium borohydride (1.973 g, 52 mmol, 3

equiv.) was added portionwise over 10 min. When the effervescence had subsided, the reaction mixture was stirred at 0 °C for a further 10 min, then quenched with saturated aqueous ammonium chloride (50 cm^3). The mixture was then extracted with ether (3 × 50 cm^3); the combined ether extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude hydroxy ester **18** (2.80 g, 13 mmol, 77%); δ_H(90 MHz; $CDCl_3$) 0.15 (9 H, s), 1.9 (2 H, m), 2.4 (2 H, m), 2.7 (1 H, br s), 3.55 (3 H, s) and 4.3 (1 H, t, *J* 7). The crude hydroxy ester **18** was then added dropwise over 15 min to a stirred suspension of $LiAlH_4$ (0.497 g, 13 mmol, 1 equiv.) in anhydrous THF (50 cm^3) at −78 °C in a three-necked round-bottomed flask equipped with stirrer bar, septum cap, N_2 balloon and alcohol thermometer. The reaction was then held at −20 °C on a cold plate for 18 h, then quenched by pouring into ice-cold saturated aqueous ammonium chloride (50 cm^3). This was then extracted with EtOAc (6 × 25 cm^3). The combined organic layers were extracted with brine (50 cm^3) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give a yellow oil, homogeneous by TLC (Et_2O; R_F 0.30). This was purified by Kugelrohr distillation to give the *title compound* **19** as a colourless oil (1.84 g, 10 mmol, 77%), b.p. 100 °C/0.5 mmHg; ν_{max}($CHCl_3$)/cm^{-1} 3360br s (OH), 2910, 2880 (CH) and 2180 (C≡C); δ_H(250 MHz; $CDCl_3$) 0.13 (9 H, s), 1.73–1.78 (4 H, m), 3.44 (2 H, br s), 3.63 (2 H, sextet, *J* 4.7) and 4.38 (1 H, t, *J* 5.6); δ_C(62.5 MHz; $CDCl_3$) −0.2, 28.2, 34.6, 62.2, 62.3, 89.16 and 106.63; *m/z* (EI) 155 ($M^+ - CH_3OH$, 1%), 127 (63), 111 (41), 99 (67), 75 (100) and 73 (60); *m/z* (FAB) 187 [Found (EI): $M^+ - CH_3OH$, 155.0886. $C_8H_{15}OSi$ requires $M - CH_3OH$, 155.0892].

6-tert-*Butyldiphenylsilyloxy*-1-*trimethylsilylhex*-1-*yn*-3-*ol* **20**.—A solution of 6-trimethylsilylhex-5-yn-1,4-diol **19** (1.33 g, 7.15 mmol) in anhydrous DMF (20 cm^3) was added to imidazole (1.27 g, 18.7 mmol, 2.6 equiv.) in a 50 cm^3 round-bottomed flask equipped with stirrer bar and N_2 balloon. *tert*-Butyldiphenylsilyl chloride (2.24 cm^3, 8.6 mmol, 1.2 equiv.) was then added and the mixture stirred for 18 h at room temperature. The reaction was then quenched by the addition of MeOH (1 cm^3), followed by stirring for a further 20 min. Water (20 cm^3) was then added and the mixture extracted with ether (3 × 20 cm^3). The combined ethereal extracts were then washed with saturated aqueous ammonium chloride (20 cm^3) and brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a white gum. This was purified by flash chromatography (20% EtOAc in hexane, R_F 0.40) followed by Kugelrohr distillation to give the *title compound* as a colourless gum, b.p. 135–140 °C/0.05 mmHg (1.76 g, 4.15 mmol, 58%). This was spectroscopically identical to **12** in all respects except optical rotation.

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