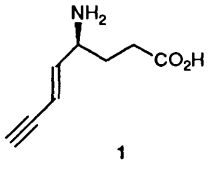
Enantioselective Synthesis of (*S*)-*trans*-γ-Butenynyl γ-Aminobutyric Acid (GABA)

Andrew B. Holmes,*[a] Alethea B. Tabor[a] and Raymond Baker[b]
[a] *University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK*
[b] *Merck, Sharp and Dohme Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK*

The enantioselective synthesis of (*S*)-*trans*-γ-butenynyl γ-aminobutyric acid (GABA) **1** by phthalimide displacement of the (*R*)-alcohol **9** (generated from the acetal **3**) is reported. Novel hydride reductions of the pentadiynylic ether **3** to the *trans*-enyne **5** are reported and discussed.

In a previous paper[1] we reported the first enantioselective total synthesis of (*S*)-γ-acetylenic GABA, a mechanism-based inhibitor of the enzyme GABA-T (E. C. 2.6.1.19).[2] The methodology used gave high enantiomeric excesses, and was designed to be flexible enough to be extended to the synthesis of polyunsaturated analogues of γ-acetylenic GABA. The synthesis of γ-allenic GABA[3] and 4-amino-7-fluorohepta-5,6-dienoic acid[4] have been previously reported, but no enyne or diyne analogues appear to have been made. Moreover, little methodology for the enantioselective synthesis of polyacetylenic or allylic enyne amines has been reported.[5] In this paper we report the first enantioselective synthesis of (*S*)-*trans*-γ-butenynyl GABA **1**.[6]



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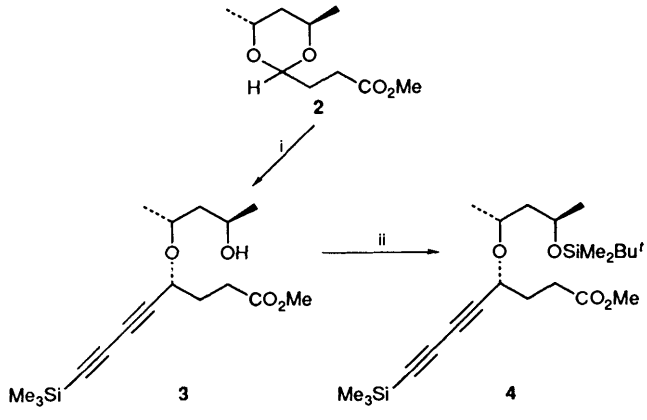
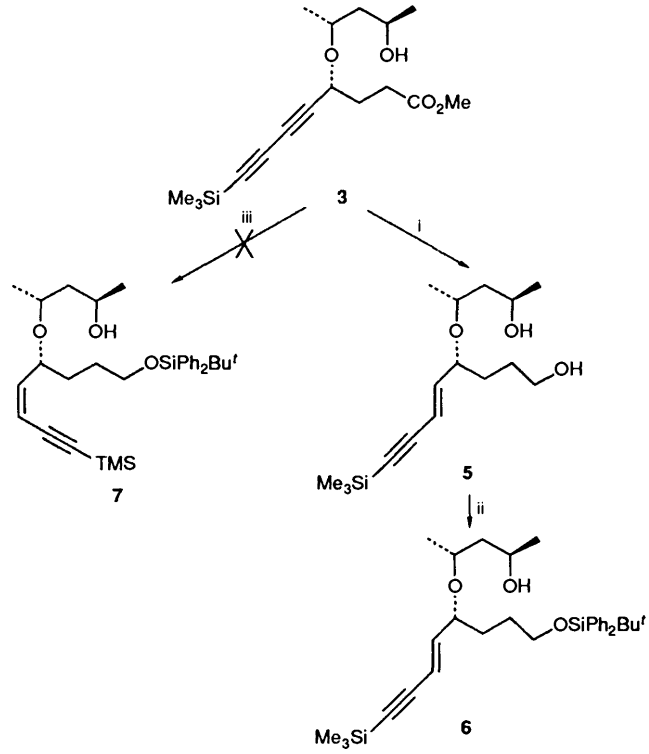
Our first route to the enantiomerically pure *cis*- and *trans*-butenynyl analogues of γ-vinyl GABA was planned through the common diyne precursor **3**. The acetal **2**[1] was coupled to bis(trimethylsilyl)butadiyne (BTMSBD)[7] using methodology analogous to that described by Johnson[8] (Scheme 1) to give the prop-2-ynyl ether **3**. The yield of this reaction was initially low, due to the formation of a number of unidentified by-products; however, when the temperature was maintained below −70 °C until after the reaction had been quenched, these by-products were not formed. Although TLC analysis showed that, under these conditions, the acetal was completely consumed, the yield from this reaction never exceeded 60%, probably because the diacetylene is susceptible to polymerisation by Lewis acids.



Scheme 1 *Reagents and conditions:* i, BTMSBD (6.7 equiv.), $TiCl_4$ (2.6 equiv.), CH_2Cl_2, 4 Å molecular sieves, −78 °C, 20 min (55%); ii, Bu^tMe_2SiCl, imidazole, DMF, room temp., 15 h

However, the diastereoselectivity of the reaction was very good; derivatisation of **3** to the more volatile silyl ether **4**, followed by gas chromatography (GC) analysis, showed the diastereoisomeric ratio to be about 97:3.

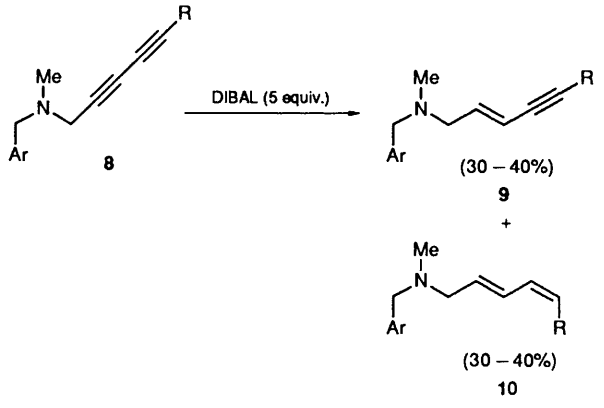
We had hoped to explore the possibility of synthesising both *cis*- and *trans*-isomers of γ-butenynyl GABA **1**, and wished at this stage to use metal hydride reagents to reduce both the ester and diyne functionalities of **3**. A number of reagents were first investigated with the aim of producing the *trans*-enyne. Surprisingly, the best results were obtained using a filtered solution of $LiAlH_4$ in ether[9] (LAH*) (Scheme 2), although this reagent is reported to give high *cis*-selectivity in reductions of prop-2-ynylic alcohols. The primary alcohol was then silylated to give **6**.



Scheme 2 *Reagents and conditions:* i, LAH* (see text[9]) (3.5 equiv.), Et_2O, reflux, 30 min (91%); ii, Bu^tPh_2SiCl, imidazole, DMF, room temp., 5 h (71%); iii, diisobutyl aluminium hydride (DIBAL) (2.5 equiv.), CH_2Cl_2–C_6H_6, 45 °C, 12 h

Attention was then turned to the simultaneous reduction of ester and acetylene to give a *cis*-enyne alcohol. As the reduction of acetylenes using diisobutyaluminium hydride (DIBAL) has been reported to produce *cis*-alkenes,[10] this appeared to be the reagent of choice. However, treatment of the ether **3** with

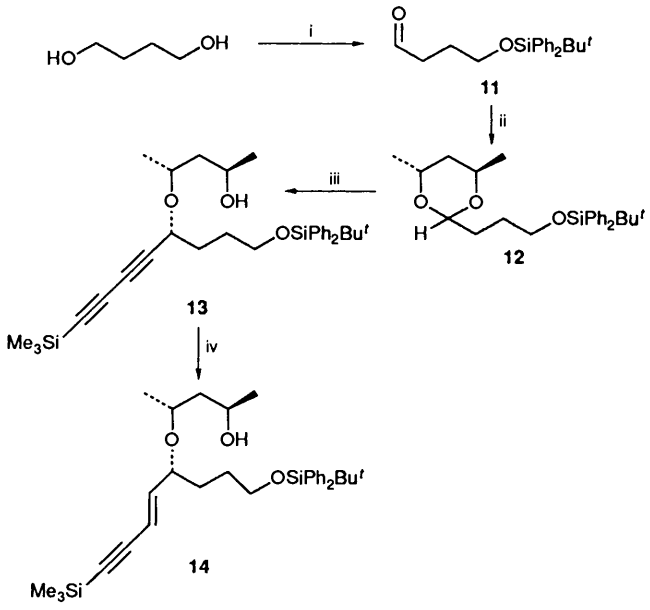
DIBAL (Scheme 2) proceeded sluggishly, even with an excess of reagent, and gave not **7**, but the *trans*-enyne alcohol **5** as evidenced by the 16 Hz vicinal coupling constant between the vinyl protons in the ^{1}H NMR spectrum. The reason for this *trans*-reduction was initially unclear. Extensive work by Eisch[11] and Utimoto and Nozaki[12] has shown that silylated or stannylated acetylenes are reduced by DIBAL to give exclusively *trans*-vinyl silanes. This was attributed to a low C=C rotational energy barrier induced by the adjacent Si or Sn, in the initially produced vinyl derivatives allowing stereomutation of the *cis*-adducts. When these reactions were repeated in the presence of tertiary amines,[11] or with ether as the solvent,[12] *cis*-vinyl silanes were exclusively produced, probably because co-ordination between these donor species and the aluminium stabilises the initially formed hydrometallation product. However, although we did not investigate the use of tertiary amines or donor solvents in the reaction of **3** with DIBAL, it seems unlikely that the trimethylsilyl group of **3** is close enough to the triple bond undergoing reduction to reduce significantly the rotational energy barrier of the intermediate vinyl alane. A more likely explanation for the low yield and unexpected stereochemical outcome of this reaction is provided by some recent work of Stütz[5a] in which the reduction of tertiary diacetylenic amines such as **8** by DIBAL was studied (Scheme 3). In this reduction the same slow reaction and low yield of the



Scheme 3

unexpected *trans*-enyne **9** were observed, and the *cis,trans*-diene **10** was also produced regio- and stereo-specifically. It is therefore possible that the DIBAL reduction of the diyne ether **3** is taking place *via* a similar mechanism. Although this is our preferred explanation for the observed stereochemistry we cannot rule out the alternative that thermal isomerisation of the initially produced (*Z*)-**5** to the (*E*)-isomer is occurring under the reaction conditions.

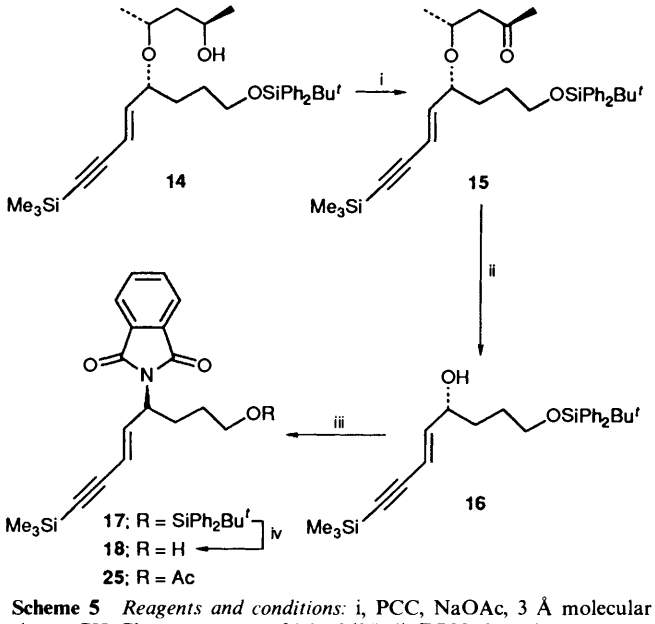
Having completed these metal hydride studies, we turned our attention to the synthesis of the *trans*-enyne **1** by a more direct route. The enantiomerically pure acetal **12** was readily synthesised in high yield from butane-1,4-diol (Scheme 4). We again found that the methodology described by Johnson[8] for the synthesis of enantiomerically pure propynylic alcohols could be extended to the synthesis of polyacetylenic propynylic alcohols; coupling of **12** to BTMSBD afforded the ether **13**. The assignment of the (*R*)-configuration to the propynylic alcohols **3** and **13** follows from the numerous examples reported by Johnson,[8] and in particular by analogy (consistent dextroratory values measured for the specific rotation of each compound) with the absolute configuration established for the reaction of the acetal **2** with bis(trimethylsilyl)acetylene, a reaction leading to the acetylenic analogues of **3** and **13** and producing eventually material of known absolute configuration, as described in the preceding paper.[1] Selective reduction of the diacetylenic ether



Scheme 4 *Reagents and conditions:* i, NaH, Bu^{t}Ph$_2$SiCl, tetrahydrofuran (THF), room temp., 3 h (99%);[13] then oxalyl chloride, dimethyl sulphoxide (DMSO), Et_3N, CH_2Cl_2, −78 °C (92%);[14] ii, (2*R*, 4*R*)-pentane-2,4-diol, toluene-*p*-sulphonic acid (TsOH), benzene, reflux, 3 h (99%); iii, BTMSBD (4 equiv.), $TiCl_4$ (2 equiv.), CH_2Cl_2, 4 Å molecular sieves, −78 °C, 2 h (51%); iv, $LiAlH_4$ (1 equiv.), Et_2O, −72 °C–room temp., 5 h (73%).

13 using $LiAlH_4$ gave exclusively the *trans*-enyne **14** presumably *via* complexation of AlH_4^- to the *ether* oxygen followed by intramolecular delivery of hydride in analogy to the mechanism proposed for reduction of prop-2-ynyl *alcohols*.[15]

The chiral auxiliary was then removed to expose the (*R*)-*trans*-allylic enyne alcohol, as shown in Scheme 5. Oxidation

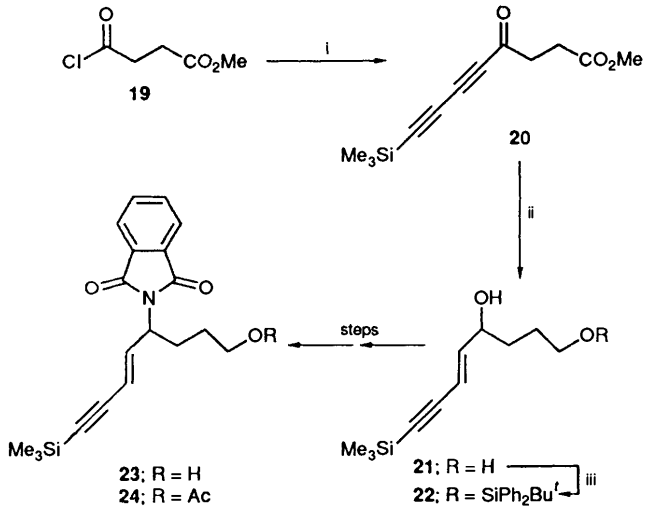


Scheme 5 *Reagents and conditions:* i, PCC, NaOAc, 3 Å molecular sieves, CH_2Cl_2, room temp., 21 h (96%); ii, DBU (2 equiv.), benzene, 50 °C, 12 d (66%); iii, Ph_3P, phthalimide, diethylazodicarboxylate (DEAD), tetrahydrofuran (THF), room temp., 3 d (46%); iv, HF–pyridine (3 equiv.), THF, room temp., 18 h (80%)

using pyridinium chlorochromate (PCC)[16] gave the ketone **15**; this was followed by β-elimination (deprotection) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the alcohol **16** with no loss of the acetylene protecting group.[1] Phthalimide displacement of the alcohol **16**, a reaction with numerous pre-

cedents for occurring with inversion of configuration under Mitsunobu conditions,[17,18] and in particular by analogy with the example reported in the previous paper,[1] afforded the phthalimide **17** whose absolute configuration can be confidently assigned as (*S*). Selective desilylation using HF–pyridine[1] afforded the primary alcohol **18**.

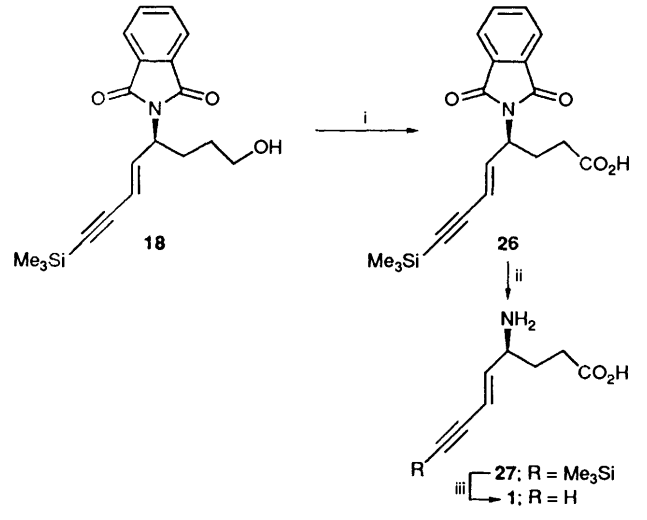
In order to establish the enantiomeric excess of the alcohol **18**, racemic material was also synthesised. The acid chloride **19**[19] was converted into the diol **22** as shown in Scheme 6, and the



Scheme 6 *Reagents and conditions:* i, BTMSBD (1 equiv.) $AlCl_3$ (1.5 equiv.) CH_2Cl_2, 0 °C, 5 h (29%); ii, $NaBH_4$ (3 equiv.), THF, H_2O, 0 °C, 20 min, then $LiAlH_4$ (1.5 equiv.), Et_2O, −20 °C, 18 h (88%); iii, Bu^tPh_2SiCl, imidazole, (DMF), room temp., 15 h (30%)

same sequence of phthalimide inversion and selective deprotection was carried out to give the racemic phthalimide derivative **23**. As a ^1H NMR chiral shift experiment using Eu-(+)-$(tfc)_3$ with **23** failed to shown any clear peak splitting, the material was converted into the acetate **24**. A ^1H NMR chiral shift experiment using Eu-(+)-$(hfc)_3$ showed a splitting of the double doublet at δ 5.7 (J 16, 1) into a quartet of doublets; this was not seen with the (*S*)-acetate **25**, indicating an enantiomeric excess of at least 95%.

The synthesis was completed as shown in Scheme 7. The primary alcohol **18** was oxidised to the acid **26** in a two-step procedure, then the phthalimide was removed using hydrazine



Scheme 7 *Reagents and conditions:* i, oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C,[8] then Jones reagent[16] (2 equiv.) (47%); ii, $H_2NNH_2{\cdot}H_2O$, EtOH, reflux, 30 min (94%); iii, TBAF·$3H_2O$, THF, −10 °C, 20 min (61%)

hydrate.[17] Desilylation of the enyne using tetrabutyl ammonium fluoride trihydrate (TBAF·$3H_2O$) yielded **1**.

In summary we have shown that the Lewis acid-catalysed opening of the enantiomerically pure acetals **2** and **12** with BTMSBD is an excellent route for the enantioselective synthesis of pentadiynyl ethers such as **3** and **13**, and that such compounds can serve as efficient precursors for the synthesis of the butenynyl analogue **1** of γ-vinyl GABA.

Experimental

Apparatus and equipment are described in the preceding paper.[1] Some small-scale chromatographic separations were carried out using a Harrison 7924 Chromatotron™, coated to a thickness of 1 mm with Merck 7749 silica. Gas Chromatography was carried out using a Carlo Erba 4130 instrument [S.G.E. BP5 (5% phenylmethylsiloxane as stationary phase) 25 m column, diameter 0.33 mm, carrier gas flow rate 2.0 cm^3 min^{-1}]; the retention times are given in min.

Methyl (4R)-4-[(1R,3R)-3-*Hydroxy*-1-*methylbutoxy*]-8-*trimethylsilylocta*-5,7-*diynoate* **3**.—BTMSBD (2.848 g, 14.7 mmol, 6.7 equiv.) was added to a solution of the acetal **2**[1] (444 mg, 2.2 mmol) in dichloromethane (30 cm^3) under argon over 4 Å sieves. The reaction was cooled to −74 °C and $TiCl_4$ (0.62 cm^3, 5.7 mmol, 2.6 equiv.) 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}; 30 cm^3) and water (2 × 30 cm^3). The organic layer was then dried over K_2CO_3 and the solvent was removed under reduced pressure to give a slightly yellow oil. This was purified by flash chromatography (9 cm, 30% EtOAc in toluene; R_F 0.36) and after removal of solvent the residue was distilled at reduced pressure to give the *ether* **3** (390.6 mg, 1.21 mmol, 55%) as a clear oil, b.p. 125–30 °C/0.1 mmHg, $[\alpha]_D^{22}$ +22.4 (*c* 0.767, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH), 2960, 2930, 2900 (CH), 2100 (C≡C) and 1730 (C=O); δ_H(250 MHz; $CDCl_3$) 0.16 (9 H, s), 1.14 (3 H, d, J 6.3), 1.25 (3 H, d, J 6.2), 1.48–1.60 (2 H, m), 1.99 (2 H, q, J 6.7), 2.43–2.50 (2 H, m), 3.33 (1 H, br s), 3.65 (3 H, s), 3.85–3.92 (1 H, m), 3.98–4.05 (1 H, m) and 4.26 (1 H, t, J 6.1); δ_C(100 MHz; $CDCl_3$) −0.5, 20.7, 23.8, 29.5, 31.0, 44.7, 51.7, 64.3, 67.6, 70.4, 73.6, 77.1; 87.2, 87.3 and 173.5; *m/z* (CI) 667 (22%), 666 (31, 2 M^+ + NH_4), 562 (27), 356 (22), 343 (24), 342 (100, M^+ + NH_4), 235 (28) and 221 (100) [Found (CI): M^+ + NH_4, 342.210 57. $C_{17}H_{32}NO_4Si$ requires M + NH_4, 342.21062].

A small sample of **3** was converted into the TBDMS derivative by stirring for 15 h in DMF with *tert*-butyldimethylsilyl chloride and imidazole. After work-up, the resulting *ether* **4** was analysed by GC (isothermal at 225 °C); this showed 2 peaks in the ratio 97:3 (retention times 13.5 and 11.2 min respectively), indicating a d.e. of 94%.

trans-4-(3-*Hydroxy*-1-*methylbutoxy*)-8-*trimethylsilyloct*-5-*en*-7-*yn*-1-*ol* **5**.—A solution of pentadiynyl ether **3** (355 mg, 1.10 mmol) in anhydrous ether (30 cm^3) was added to a filtered ethereal solution of $LiAlH_4$[9] (1.22 cm^3, standardised to 3.15 mol dm^{-3}; 3.84 mmol, 3.5 equiv.) over 4 Å sieves under nitrogen. The mixture was heated under reflux at 40 °C for 30 min, then cooled and poured into ice-cold saturated aqueous NH_4Cl solution (25 cm^3). The product was extracted with ethyl acetate (5 × 50 cm^3 portions); the combined ethyl acetate fractions were washed with brine (50 cm^3) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the *title*

compound as a colourless gum (297 mg, 91%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420 (OH), 2910 (CH), 2170 (C≡C) and 1605 (C=C); δ_H(250 MHz; $CDCl_3$) 0.18 (9 H, s), 1.14 (3 H, d, *J* 6), 1.15 (3 H, d, *J* 6), 1.4–1.7 (6 H, m), 2.8 (2 H, v br), 3.6 (2 H, m), 3.8 (1 H, m), 3.9 (1 H, br m), 4.1 (1 H, m), 5.68 (1 H, dd, *J* 16, 1) and 6.1 (1 H, dd, *J* 16, 7); δ_C(62.5 MHz; $CDCl_3$) −0.1, 20.8, 23.9, 28.1, 32.0, 44.6, 62.8, 64.5, 72.2, 77.9, 95.0 (weak), 103.6 (weak), 111.1 and 145.5; *m/z* (EI) 298 (M^+, 1%) 194 (52), 155 (75), 138 (22), 105 (27), 87 (27), 75 (85), 73 (100), 71 (36) and 69 (80) [Found (EI): M^+, 298.1981. $C_{16}H_{30}O_3Si$ requires *M*, 298.1964].

Preparation using DIBAL.[10] To a stirred solution of the ether **3** (222 mg, 0.69 mmol) in anhydrous dichloromethane (20 cm^3) and anhydrous benzene (8 cm^3) in a two-necked, 25 cm^3 round-bottomed flask equipped with septum cap and condenser under N_2 was added, dropwise over 10 min, a solution of DIBAL in hexane (1.71 cm^3 of a 1.0 mol dm^{-3} solution; 1.71 mmol, 2.5 equiv.) The septum cap was then replaced with a glass stopper and the mixture heated under reflux at 45 °C for 12 h. The flask was cooled in an ice-bath and the reaction was quenched by the dropwise addition of a mixture of MeOH (24 cm^3) and H_2SO_4 (1 mol dm^{-3}; 10 cm^3). The organic layer was then taken up in Et_2O (2 × 10 cm^3) and the combined organic layers were washed with water (10 cm^3), saturated aqueous sodium hydrogen carbonate (10 cm^3) and water (10 cm^3) and dried over $CaCl_2$. Removal of the solvent under reduced pressure gave a brown gum. TLC analysis (7% MeOH in CH_2Cl_2) showed 5 spots, of which one at R_F 0.38 predominated; this was isolated by flash chromatography (3 cm, 7% MeOH in CH_2Cl_2) to give a clear gum (67.5 mg, 0.23 mmol, 33%), spectroscopically identical to **5**.

(2R,4R)-trans-4-[(1R)1-(3-tert-*Butyldiphenylsilyloxypropyl*)-5-*trimethylsilylpent*-2-*en*-4-*ynyloxy*]*pentan*-2-*ol* **6**.—*tert*-Butyldiphenylsilyl chloride (0.29 cm^3, 1.1 mmol, 1.1 equiv.) was added to a solution of imidazole (150 mg, 2.2 mmol, 2.2 equiv.) in anhydrous DMF (10 cm^3) under N_2. A solution of the enyne ether **5** (297 mg, 0.998 mmol) in anhydrous DMF (6 cm^3) was then added and the mixture was stirred at room temperature for 5 h. The DMF was then removed under reduced pressure, and the mixture was purified by flash chromatography (5 cm column, 2% ethyl acetate in dichloromethane; R_F 0.35) followed by removal of the solvent under reduced pressure to give the *title compound* as a colourless oil (399 mg, 0.71 mmol, 71%), $[\alpha]_D^{22}$ −4.3 (*c* 0.62, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480 (OH), 2930, 2850 (CH), 2140br (C≡C), 1375 and 1005; δ_H(250 MHz; $CDCl_3$) 0.19 (9 H, s), 1.03 (9 H, s), 1.15 (3 H, d, *J* 6.2), 1.16 (3 H, d, *J* 6.3), 1.49–1.69 (6 H, m), 2.69 (1 H, br d, *J* 2.9), 3.61–3.86 (5 H, m), 5.65 (1 H, dd, *J* 1.0, 16.0), 6.07 (1 H, dd, *J* 6.9, 16.0), 7.34–7.42 (6 H, m) and 7.63–7.67 (4 H, m); δ_C(100 MHz; $CDCl_3$) −0.1, 20.6, 23.8, 26.9, 28.0, 31.8, 44.0, 53.4, 63.6, 64.4, 72.5, 78.4, 95.0, 104.0, 110.9, 127.6, 129.6, 133.9, 135.6 and 145.7; *m/z* (CI) 537 (M^+ + H, 1%), 433 (37), 274 (29), 196 (21), 177 (60), 147 (25), 122 (100), 120 (39), 90 (33) and 58 (24) [Found (CI): M^+ + H, 537.320 62. $C_{32}H_{49}O_3Si_2$ requires *M* + H, 537.320 40].

4-(tert-*Butyldiphenylsilyloxy*)*butanal* **11**.—Sodium hydride (0.8 g of a 60% dispersion in oil, 0.02 mol) was placed in a 500 cm^3 three-necked round-bottomed flask equipped with stirrer bar, septum cap and N_2 balloon, and was washed with hexane. The sodium hydride was then suspended in anhydrous THF (100 cm^3) and butane-1,4-diol (1.77 cm^3, 0.02 mol) was added. The mixture was stirred at room temperature for 1 h, after which time a large amount of an opaque white precipitate had formed.[13] *tert*-Butyldiphenylsilyl chloride (5.20 ml, 0.02 mol) was added dropwise over 30 min, and the mixture was stirred at room temperature for a further 1.5 h. The mixture was poured into ether (100 cm^3), washed with saturated aqueous K_2CO_3 (30 cm^3) and brine (30 cm^3), and the ethereal layers were combined and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 4-(*tert*-butyldiphenylsilyloxy)-butanol as a clear viscous oil (6.7 g, 0.02 mol, 100%), homogeneous by TLC (40% EtAOc in hexane, R_F 0.29). This material was then subjected to Swern[14] oxidation; a solution of oxalyl chloride (1.92 cm^3, 0.022 mol, 1.1 equiv.) in anhydrous CH_2Cl_2 (30 cm^3) was placed in a 250 cm^3 three-necked round-bottomed flask equipped with alcohol thermometer, N_2 balloon and septum cap. The mixture was cooled to −70 °C, and a solution of DMSO (3.41 cm^3, 0.048 mol, 2.4 equiv.) in anhydrous CH_2Cl_2 (20 cm^3) was 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 4-(*tert*-butyldiphenylsilyloxy)butanol (6.7 g, 0.02 mol) in anhydrous CH_2Cl_2 (20 cm^3) was added dropwise over 5 min, maintaining the temperature below −60 °C. The reaction then stirred at −70 °C for a further 15 min, then triethylamine (14.05 cm^3, 0.1 mol, 5 equiv.) was added dropwise over 5 min. The reaction mixture was warmed to room temperature and quenched by the addition of water (30 cm^3). Stirring was continued for 10 min, then the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 40 cm^3); the combined organic extracts were washed with HCl (1 mol dm^{-3}; 50 cm^3), water (40 cm^3), saturated aqueous sodium hydrogen carbonate (40 cm^3) and water (40 cm^3), and then dried over $MgSO_4$. The solvents were removed under reduced pressure to give a green-tinged viscous oil; this was purified by flash chromatography (40% EtOAc in hexane; R_f 0.52) to give the *aldehyde* (6.0 g, 0.018 mol, 92%) as a clear viscous oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2920 and 2850 (CH), 2730 (CHO), 1720 (C=O) and 1590 (Ar); δ_H(250 MHz: $CDCl_3$) 1.05 (9 H, s), 1.92 (2 H, quin, *J* 6), 2.56 (2 H, dt, *J* 2, 7), 3.71 (2 H, t, *J* 6), 7.34–7.47 (6 H, m), 7.64–7.69 (4 H, m) and 9.79 (1 H, t, *J* 2); *m/z* (CI) 327 (M^+ + H, 100%), 196 (30), 102 (57) and 71 (41) [Found (CI): M^+ + H, 327.1780. $C_{20}H_{27}O_2Si$ requires *M* + H, 327.1780].

4-[(4R,6R)-4,6-*Dimethyl*-1,3-*dioxan*-2-*yl*]-1-tert-*butyldiphenylsilyloxypropane* **12**.—To a solution of 4-(*tert*-butyldiphenylsilyloxy)butanal **11** (502 mg, 1.54 mmol) in dry benzene in a 25 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 (168 mg, 1.54 mmol, 1 equiv.) 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). After drying (K_2CO_3) the benzene was removed at reduced pressure to give the *acetal* **12** as a colourless oil (630 mg, 1.53 mmol, 99% from the aldehyde) (Found: C, 72.6; H, 8.5. $C_{25}H_{36}O_3Si$ requires C, 72.8; H, 8.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (H_2O), 2900, 2840, (CH), 1960, 1890, 1830, 1720w and 1580 (Ar); δ_H(250 MHz; $CDCl_3$) 1.12 (9 H, s) 1.23 (3 H, d, *J* 6.1), 1.35 (3 H, d, *J* 7.0), 1.70–1.81 (4 H, m), 1.75 (2 H, dt, *J* 13.0, 6.1, 13.0), 3.68–3.75 (2 H, br m), 3.95 (1 H, sextet of d, *J* 2.3, 5.7), 4.2 (1 H, quin, *J* 6.6), 4.90 (1 H, br m), 7.39–7.51 (6 H, m) and 7.69–7.80 (4 H, m); decoupling of the signal at δ 1.75 caused collapse of the signal at δ 3.95 to a quintet, (*J* 7) and collapse of the signal at δ 4.32 to a quartet, (*J* 7); decoupling of the signal at δ 1.25 caused collapse of the signal at δ 3.95 to a doublet of triplets, (*J* 13.0, 2.3); decoupling of the signal at δ 1.35 caused collapse of the signal at δ 3.95 to a quintet, (*J* 7) and collapse of the signal at δ 4.32 to a quartet, (*J* 7); δ_C(100 MHz; $CDCl_3$) 19.0, 21.7, 26.4, 26.7, 27.0, 31.5, 36.5, 63.5, 67.1, 67.5, 93.8, 128.0, 129.3, 133.7 and 135.3; *m/z* (EI) 412 (M^+, 1%), 411 (25), 397 (30), 319 (53), 311 (20), 269 (60), 199 (100), 139 (23) and 71 (60) [Found (EI): M^+, 412.2405. $C_{25}H_{35}O_3Si$ requires *M*, 412.2433].

(2R,4R)-4-[(1R)-1-(3-tert-*Butyldiphenylsilyloxypropyl*)-5-

trimethylsilylpenta-2,4-*diynyloxy*]*pentan*-2-*ol* **13**.—BTMSBD (1.182 g, 6.12 mmol, 4 equiv.) was added to a solution of the acetal **12** (630 mg, 1.53 mmol) in anhydrous dichloromethane (30 cm^3) under argon in a 50 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 −78 °C and $TiCl_4$ (3.17 cm^3 of a 1 mol dm^{-3} solution in dichloromethane; 3.17 mmol, 2 equiv.) added in one portion. The resulting brown solution was stirred at this temperature for 2 h, while being monitored by TLC (30% Et_2O in hexane; R_F of BTMSBD 0.67; R_F of **12** 0.46; R_F of **13** 0.19) until the starting acetal **12** had disappeared. A 1:1 mixture of anhydrous methanol and dichloromethane (10 cm^3) was then added slowly, keeping the temperature below −74 °C. During this time the colour changed through brown to green and then disappeared completely. The reaction mixture was warmed to room temperature and extracted with hydrochloric acid (1 mol dm^{-3}; 20 cm^3) and water (2 × 20 cm^3). The organic layer was then dried over K_2CO_3 and the solvent was removed under reduced pressure to give a slightly yellow oil; this was purified by flash chromatography (6 cm, 30% Et_2O in hexane) to give the *diyne* **13** as a colourless oil (411.9 mg, 0.78 mmol, 51%), $[\alpha]_D^{22}$ +10.7 (*c* 0.717, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (O–H), 2920, 2850 (CH), 2210w, 2100 (C≡C) and 1600 (Ar); δ_H(250 MHz; $CDCl_3$) 0.21 (9 H, s), 1.05 (9 H, s), 1.16 (3 H, d, *J* 6.2), 1.29 (3 H, d, *J* 6.3), 1.56 (2 H, dt, *J* 4.6, 1.1), 1.71 (2 H, m), 1.80 (2 H, m), 2.3 (1 H, br), 3.67 (2 H, t, *J* 6.0), 3.9 (1 H, m), 4.05 (1 H, m), 4.2 (1 H, t), 7.35–7.45 (6 H, m) and 7.65–7.69 (4 H, m); δ_C(100 MHz; $CDCl_3$) −0.5, 19.2, 20.7, 23.8, 26.9, 28.1, 32.6, 44.3, 63.4, 64.4, 68.8, 70.2, 73.6, 78.0, 86.7, 87.5, 127.6, 129.6, 133.8 and 135.6; *m*/*z* (CI) 552 ($M^+ + NH_4$, 14%), 448 (47), 431 (31), 180 (31), 177 (21), 122 (100), 120 (37) and 52 (25) [Found (CI): $M^+ + NH_4$, 552.3338. $C_{32}H_{50}NO_3Si_2$ requires $M + NH_4$, 552.3347].

(2R,4R)-trans-4-[(1R)-1-(3-tert-*Butyldiphenylsilyloxyprop*-*yl*)-5-*trimethylsilylpent*-2-*en*-4-*ynyloxy*]*pentan*-2-*ol* **14**.—To a suspension of $LiAlH_4$ (2 mg, 0.04 mmol, 1 equiv.) in anhydrous THF (1 cm^3) at room temperature was added the diyne ether **13** (20.6 mg, 0.039 mmol). The mixture was stirred at 40 °C for 2 h, while being monitored by TLC (2% EtOAc in CH_2Cl_2; R_F of **13** 0.39; R_F of **14** 0.34). A further 1 molar equiv. $LiAlH_4$ was then added, and the reaction mixture was stirred for a further 30 min; again 1 molar equiv. of $LiAlH_4$ was added. After 30 min, the reaction mixture was cooled to 0 °C, and water (0.01 cm^3), NaOH (5 mol dm^{-3}; 0.01 cm^3) and water (0.03 cm^3) were added sequentially. The mixture was then filtered through Celite, and the solvents were removed under reduced pressure to give the *enyne* **14** as a colourless gum (15.2 mg, 0.029 mmol, 73%), $[\alpha]_D^{22}$ −4.3 (*c* 0.62, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480 (OH), 2930, 2850 (CH), 2140br (C≡C), 1375 and 1005; δ_H(250 MHz; $CDCl_3$) 0.19 (9 H, s), 1.03 (9 H, s), 1.15 (3 H, d, *J* 6.2), 1.16 (3 H, d, *J* 6.3), 1.49–1.69 (6 H, m), 2.69 (1 H, br d, *J* 2.9), 3.61–3.86 (5 H, m), 5.65 (1 H, dd, *J* 1.0, 16.0), 6.07 (1 H, dd, *J* 6.9, 16.0), 7.34–7.42 (6 H, m) and 7.63–7.67 (4 H, m); δ_C(100 MHz; $CDCl_3$) −0.1, 20.6, 23.8, 26.9, 28.0, 31.8, 44.0, 53.4, 63.6, 64.4, 72.5, 78.4, 95.0, 104.0, 110.9, 127.6, 129.6, 133.9, 135.6 and 145.7 *m*/*z* (CI) 537 (M^+ + H, 1%), 433 (37), 274 (29), 196 (21), 177 (60), 147 (25), 122 (100), 120 (39), 90 (33) and 58 (24) [Found (CI): M^+ + H, 537.320 62. $C_{32}H_{49}O_3Si_2$ requires M + H, 537.320 40].

trans-(4R)-4-[(1R)-1-(3-tert-*Butyldiphenylsilyloxypropyl*)-5-*trimethylsilylpent*-2-*en*-4-*ynyloxy*]*pentan*-2-*one* **15**.—Pyridinium chlorochromate (PCC, 256 mg, 1.19 mmol) and sodium acetate (26 mg, 0.39 mmol) were suspended in dry dichloromethane (5 cm^3) with powdered 3 Å sieves and the alcohol **14** (410 mg, 0.73 mmol) was added in one portion in dry dichloromethane. The mixture was stirred at 25 °C for 21 h; dry ether (15 cm^3) was then added, and the mixture was chromatographed on a short Florisil column, eluting with dry ether (200 cm^3). The ether was removed at reduced pressure to give the *ketone* **15** as a slightly yellow oil (375 mg, 96%) which was homogeneous by TLC (10% MeOH in CH_2Cl_2; R_F 0.81), $[\alpha]_D^{22}$ +5.9 (*c* 3.08, $CHCl_3$) (Found: C, 72.1; H, 8.9. $C_{32}H_{46}O_3Si_2$ requires C, 71.9; H, 8.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2990, 2860 (C–H), 2150 (C≡C), 1960, 1895 (enyne), 1705 (C=O, ketone), 1620 (C=C) and 1595 (C_6H_5); δ_H(250 MHz; $CDCl_3$) 0.20 (9 H, s), 1.03 (9 H, s), 1.13 (3 H, d, *J* 6.2), 1.53–1.57 (4 H, m), 2.12 (3 H, s), 2.3 ($CH_XCH_AH_BC$=O, 1 H, dd, J_{AX} 5.8, J_{AB} 13.0), 2.5 (CH_X-CH_AH_BC=O, 1 H, dd, J_{BX} 6.6, J_{AB} 13.0), 3.63 (2 H, br m), 3.8 ($CH_XCH_AH_BC$=O, 1 H, m), 3.89 (1 H, q, *J* 6.2), 5.7 (1 H, dd, *J* 1.0, 16.0), 6.06 (1 H, dd, *J* 7.0, 16.0), 7.35–7.42 (6 H, m) and 7.63–7.67 (4 H, m); δ_C(100 MHz; $CDCl_3$) −0.1, 19.2, 21.5, 26.8, 28.2, 31.3, 31.8, 50.5, 63.6, 70.4, 78.6, 94.9 (weak), 103.1 (weak), 110.8, 127.6, 129.5, 133.9, 135.5, 145.8 and 207.4; *m*/*z* (CI) 552 (M^+ + NH_4, 20%) 453 (24), 452 (24), 451 (48), 450 (29), 449 (29), 433 (41), 415 (26), 344 (22), 327 (29), 274 (55), 216 (24), 196 (28), 177 (26), 120 (100) and 90 (52) [Found (CI): $M^+ + NH_4$, 552.333 28. $C_{32}H_{50}NO_3Si$ requires $M + NH_4$, 552.332 88].

trans-(R)-1-tert-*Butyldiphenylsilyloxy*-8-*trimethylsilyloct*-5-*en*-7-*yn*-4-*ol* **16**.—To a stirred solution of the enyne **15** (30.81 mg, 0.054 mmol) in anhydrous benzene (10 cm^3) under N_2 over 4 Å sieves at 6 °C (ice-bath) was added, dropwise with stirring over 10 min, DBU (9 mm^3, 0.06 mmol, 1.1 equiv.). The mixture was warmed to 50 °C and stirred at this temperature for 7 d, while being monitored by TLC (CH_2Cl_2; R_F of **15** 0.39; R_F of **16** 0.29). A further equivalent of DBU was then added and the mixture was heated at 50 °C for 7 d; a further equivalent was then added and the mixture heated at 60 °C for 5 d. The reaction was cooled to room temperature and diluted with dichloromethane (20 cm^3); the organic phase was washed with saturated aqueous ammonium chloride solution (15 cm^3) and water (2 × 15 cm^3). The aqueous extracts were washed with dichloromethane (20 cm^3), and the combined organic extracts were dried over magnesium sulphate. The solvents were removed under reduced pressure to give a brown gum, which was purified using the Chromatotron™ (CH_2Cl_2) to give the *alcohol* **16** as a colourless oil (16.0 mg, 0.036 mmol, 66%), $[\alpha]_D^{22}$ −7.8 (*c* 5.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420 (OH), 2910, 2840 (CH), 2120 (C≡C enyne), 1900, 1830, 1770, 1700 and 1600; δ_H(250 MHz; $CDCl_3$) 0.22 (9 H, s), 1.07 (9 H, s), 1.64–1.68 (4 H, m), 2.49 (1 H, br s), 3.69 (2 H, t, *J* 5.2), 4.20 (1 H, t, *J* 1.5), 5.77 (1 H, dd, *J* 1.4, 16.0), 6.23 (1 H, dd, *J* 5.5, 15.8), 7.36–7.45 (6 H, m) and 7.67–7.70 (4 H, m); δ_C(100 MHz; $CDCl_3$) −0.1, 19.1, 26.8, 28.2, 33.8, 63.7, 71.6, 94.9, 103.3, 109.6, 127.7, 129.7, 133.4, 135.5 and 146.9; *m*/*z* (CI) 468 ($M^+ + NH_4$, 1%), 212 (33), 138 (51) and 121 (100) [Found (CI): $M^+ + NH_4$, 468.2757. $C_{27}H_{42}NO_2Si_2$ requires $M + NH_4$, 468.2760].

(S)-trans-N{1-[3-(tert-*Butyldiphenylsilyloxypropyl*)]-5-*trimethylsilylpent*-2-*en*-4-*ynyl*}*phthalimide* **17**.—To a solution of the alcohol **16** (92.43 mg, 0.21 mmol), triphenylphosphine (58 mg, 1 equiv.) and phthalimide (33 mg, 1.1 equiv.) in anhydrous THF (5 cm^3) at room temperature was added diethylazodicarboxylate (0.04 cm^3, 1.2 equiv.). The reaction mixture was stirred at room temperature for 3 d, while being monitored by TLC (CH_2Cl_2; R_F of **16** 0.47; R_F of **17** 0.69). 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, and the filtrate was concentrated under reduced pressure to give a yellow oil. This was purified using the Chromatotron™ (1:1 hexane–CH_2Cl_2) to give the *phthalimide* **17** as a colourless viscous gum (55.32 mg, 0.10 mmol, 46%), $[\alpha]_D^{22}$ −29.2 (*c* 1.93, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2910, 2840 (C-H), 2150br (C≡C)

and minor bands, 1770 (C=O), 1700 (C=O), 1600w (C=C enyne) and 1580 (Ar); δ_H(250 MHz; $CDCl_3$) 0.18 (9 H, s), 1.04 (9 H, s), 1.41–1.66 (2 H, m), 2.03–2.22 (2 H, m), 3.66 (2 H, t, *J* 6.3), 4.75 (1 H, q, *J* 7.6), 5.70 (1 H, dd, *J* 15.9, 0.8), 6.56 (1 H, dd, *J* 15.9, 8.3), 7.25–7.43 (6 H, m), 7.62–7.74 (4 H, m) and 7.78–7.86 (4 H, m); δ_C(100 MHz; $CDCl_3$) −0.2, 19.1, 26.8, 28.3, 29.3, 53.0, 63.0, 95.9, 102.5, 112.9, 123.2, 127.6, 129.5, 131.8, 133.8, 134.0, 135.5, 141.2 and 167.7; *m/z* (CI) 597 ($M^+ + NH_4$, 13%), 274 (34), 196 (21), 156 (100), 151 (32), 147 (21), 140 (21), 139 (41), 138 (64), 134 (31), 126 (28), 125 (26), 124 (45), 122 (27), 113 (20), 112 (32), 111 (51), 110 (37), 109 (44), 108 (23), 98 (45), 97 (28), 96 (52), 95 (26), 94 (68), 91 (24), 90 (83), 85 (21), 84 (26), 83 (27), 78 (27), 74 (24), 73 (21), 72 (43), 70 (25), 60 (30), 59 (78), 58 (79) and 52 (94) [Found (CI): $M^+ + NH_4$, 597.298 93. $C_{35}H_{45}N_2O_3Si_2$ requires $M + NH_4$, 597.299 14].

(S)-N-[1-(3-*Hydroxypropyl*)-5-*trimethylsilylpent*-2-*en*-4-*ynyl*]*phthalimide* **18**.—To a solution of the phthalimide **17** (38.63 mg, 0.067 mmol) in THF at 0 °C was added HF–pyridine (0.05 cm^3, 2 equiv.). The reaction was stirred at room temperature for 3.5 h, while being monitored by TLC; a further portion of HF–pyridine (0.025 cm^3, 1 equiv.) was then added and the reaction was stirred for a further 18 h. After this time the starting material (1:1 EtOAc–hexane; R_F 0.70) had disappeared and another spot (R_F 0.34) had appeared. The reaction was then diluted with ethyl acetate (20 cm^3) and washed with water (15 cm^3). The aqueous layer was washed with ethyl acetate (20 cm^3), and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (3 × 5 cm^3) and brine (10 cm^3), and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromotography (1 cm, 1:1 EtOAc:hexane) gave the *alcohol* **18** as a white solid (18.24 mg, 0.054 mmol, 80%), $[\alpha]_D^{22}$ − 45.1 (*c* 1.82, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3470 (O–H), 2920sh and 2880sh (CH), 2160 (C≡C), 1775, 1705 (C=O) and 1610 (Ar); δ_H(250 MHz; $CDCl_3$) 0.14 (9 H, s), 1.46–1.63 (2 H, m), 1.79 (1 H, br s), 1.92–2.19 (2 H, m), 3.63 (2 H, t, *J* 6.4), 4.74 (1 H, q, *J* 7.6), 5.70 (1 H, dd, *J* 0.9, 16.0), 6.53 (1 H, dd, *J* 8.3, 16.0), 7.68–7.73 (2 H, m) and 7.78–7.84 (2 H, m); δ_C(100 MHz; $CDCl_3$) −0.3, 28.3, 29.4, 53.0, 62.1, 96.1, 102.3, 113.1, 123.3, 131.7, 134.1, 140.9 and 167.8; *m/z* (CI) 342 ($M^+ + H$, 100%), 230 (31), 195 (42) and 90 (71) [Found (CI): $M^+ + H$, 342.1492. $C_{19}H_{27}N_2O_3Si$ requires $M + H$, 342.1495].

The racemic compound **23** was prepared in the same way, starting from the alcohol **22**. When a chiral shift experiment was carried out using Eu-(+)-$(tfc)_3$, no clear splitting of the peaks was observed. The alcohols **18** and **23** were therefore converted into the acetates **25** and **24** respectively by treatment with acetic anhydride in neat pyridine; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2900, 2850 (CH), 2170w (C≡C), 1780, 1710 (C=O) and 1600 (Ar); δ_H(250 MHz; $CDCl_3$) 0.15 (9 H, s), 1.57–1.96 (4 H, m), 2.02 (3 H, s), 4.05 (2 H, t, *J* 6.5), 4.74 (1 H, q, *J* 8.2), 5.72 (1 H, dd, *J* 16.1, 0.6), 6.53 (1 H, dd, *J* 15.9, 8.5), 7.69–7.74 (2 H, m) and 7.78–7.83 (2 H, m). When a ^1H NMR chiral shift experiment was performed with the acetate **24** (2 mg) using Eu-(+)-$(hfc)_3$ (6 mg) in $CDCl_3$, the signal at δ 5.72 (C≡CC*H*=CH) was split into a quartet of doublets. This splitting was not observed when the same experiment was carried out with the enantiomerically pure acetate **25**, indicating an enantiomeric purity of >95:5.

(S)-trans-4-N-*Phthalimido*-8-*trimethylsilyloct*-5-*en*-7-*ynoic Acid* **26**.—A solution of oxalyl chloride (0.02 cm^3, 0.098 mmol, 1.1 equiv.) in anhydrous CH_2Cl_2 (30 cm^3) was placed in a 50 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 (0.03 cm^3, 0.113 mmol, 2.4 equiv.) in anhydrous CH_2Cl_2 (2 cm^3) was added dropwise over 5 min, while the temperature was maintained below −60 °C. The reaction mixture was stirred at −70 °C for 10 min, then a solution of the alcohol **18** (16 mg, 0.047 mmol) in anhydrous CH_2Cl_2 (10 cm^3) was added dropwise over 5 min, while the temperature was maintained below −60 °C. The reaction mixture was stirred at −70 °C for a further 15 min, then triethylamine (0.11 cm^3, 0.235 mmol, 5 equiv.) was added dropwise over 5 min.[14] The reaction mixture was warmed to room temperature and quenched by the addition of water (10 cm^3). Stirring was continued for 10 min, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3); the combined organic extracts were washed with HCl (1 mol dm^{-3}; 25 cm^3), water (20 cm^3), saturated aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3) and they were 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 0.46] as a clear viscous oil (8.13 mg, 0.024 mmol, 51%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2940 (C–H), 2900, 2880sh, 2740 (CHO), 2180w (C≡C), 1780, 1720 (C=O) and 1600 (Ar). The aldehyde (8.13 mg, 0.024 mmol) was then dissolved in acetone (5 cm^3) and the solution was cooled to −5 °C. Jones reagent[20] (0.3 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 0.46) and the appearance of **26** (R_F 0.13). The excess of oxidant was then quenched with excess propan-2-ol (5 cm^3), and the resulting green solution was poured into water (20 cm^3). The aqueous solution (pH 2) was 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 the *carboxylic acid* **26** (7.93 mg, 0.022 mmol, 47% over 2 steps), $[\alpha]_D^{22}$ −29.0 (*c* 0.80, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2600–3500 (CO_2H), 2910 and 2850 (CH), 2180w (C≡C), 1780 and 1270 (C=O) and 1600 (Ar); δ_H(250 MHz; $CDCl_3$) 0.15 (9 H, s), 1.20–1.40 (2 H, m), 2.16–2.47 (2 H, m), 4.77 (1 H, m), 5.72 (1 H, dd, *J* 15.9, 1.0), 6.54 (1 H, dd, *J* 16.0, 7.9), 7.74–7.76 (2 H, m) and 7.79–7.83 (2 H, m); δ_C(100 MHz; $CDCl_3$) −0.3, 26.9, 30.5, 52.3, 95.0, 102.1, 113.9, 123.4, 131.7, 134.2, 139.9, 167.7 and 176.7; *m/z* (CI) 373 ($M^+ + NH_4$, 60%), 356 (100, $M^+ + H$) and 90 (55) [Found (CI): $M^+ + H$, 356.1307. $C_{19}H_{22}NO_4Si$ requires $M + H$, 356.1296].

trans-(S)-4-*Amino*-8-*trimethylsilyloct*-5-*en*-7-*ynoic Acid* **27**.—To a solution of the phthalimide **26** (4.15 mg, 0.012 mmol) in ethanol (1 cm^3) was added $H_2NNH_2 \cdot H_2O$ (2 drops).[17] The mixture was heated at reflux for 30 min, then cooled to room temperature, and the ethanol was 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 *amine* **27** as a white solid (2.55 mg, 0.011 mmol, 94%), $[\alpha]_D^{22}$ +13.8 (*c* 0.26, MeOH); ν_{max}(KBr)/cm^{-1} 3400–2500 (CO_2H), 2910 (CH), 2380 (C≡C) and 1500–1700br; δ_H(250 MHz; CD_3OD) 0.16 (9 H, s), 1.75–1.86 (1 H, m), 1.89–2.04 (1 H, m), 2.21–2.42 (2 H, m), 3.79 (1 H, q, *J* 6.6), 5.90 (1 H, d, *J* 16.1) and 6.06 (1 H, dd, *J* 16.0, 7.9); *m/z* (CI) 208 ($M^+ - H_2O$, 35%) 90 (25), 58 (35), 45 (76) and 44 (100 [Found (CI): $M^+ + H$, 226.1263. $C_{11}H_{20}NO_2Si$ requires $M + H$, 226.1263].

trans-(S)-4-*Amino*-*oct*-5-*en*-7-*ynoic Acid* [(S)-trans-γ-*Butenynyl GABA*] **1**.—A solution of the silyl enyne **27** (2.55 mg, 0.011 mmol) in THF (0.5 cm^3) was added to TBAF·$3H_2O$ (7 mg, 2 equiv.) in damp THF (0.5 cm^3). The mixture was stirred at room temperature for 20 min, then diluted with water (2 cm^3) and extracted with ether (10 cm^3). The aqueous phase was then applied to a column of Dowex-50-X8-400 (1 cm diameter, 1 g resin, H^+ form) which was 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 (2 cm^3 fractions). TLC analysis showed the presence of the required amino acid in fractions 6–8 (MeOH; R_F 0.50) which were combined. The solvents were removed under reduced pressure (high vacuum pump and cold-finger Büchi rotavap™ to give the *butenynyl GABA* **1** as light brown needles (1.03 mg, 0.007 mmol, 61%), $[\alpha]_D^{22}$ +30.1 (*c* 0.515, H_2O); ν_{max}(KBr)/cm^{-1} 3400–3100 (CO_2H), 3150 (CH), 2350 (C≡C) and 1500–1700br (amino acid; δ_H(250 MHz; CD_3OD) 1.79–2.02 (2 H, m), 2.29–2.40 (2 H, m), 3.80 (1 H, m), 5.87 (1 H, dd, *J* 16.0, 2) and 6.09 (1 H, dd, *J* 16.0, 8.1); *m/z* (CI) 154 (M^+ + H, 60%); 137 (56) and 136 (100) [Found (CI): M^+ + H, 154.0868. $C_8H_{12}NO_2$ requires *M* + H, 154.0869].

trans-1-(3-tert-*Butyldiphenylsilyloxypropyl*)-5-*trimethylsilyl-pent-2-en-4-yn-1-ol* **22.**—To a suspension of finely powdered anhydrous $AlCl_3$ (1.07 g, 8 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (50 cm^3) at 0 °C was added freshly distilled 3-methoxycarbonylpropanoyl chloride **19**[19] (0.625 cm^3, 5.75 mmol) 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* a cannula to a solution of BTMSBD (1.12 g, 5.75 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C. The resulting brown mixture was stirred at 0 °C for 4 h, and washed with ice-cold HCl (2 mol dm^{-3}; 20 cm^3). The aqueous layer was extracted with ether (2 × 30 cm^3), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude diynol as a brown liquid (500 mg). This was purified by flash chromatography (5 cm, 10% hexane in CH_2Cl_2; R_F 0.53) to give *methyl 4-oxo-8-trimethylsilylocta-5,7-diynoate* **20** as a clear oil (394 mg, 1.67 mmol, 29%); ν_{max}($CHCl_3$)/cm^{-1} 2940 (CH) 2200, 2090 (C≡CC≡C) 1730 (C=O, ester) and 1670 (C=O, ketone); δ_H(90 MHz; $CDCl_3$) 0.15 (9 H, s), 2.6 (2 H, m), 2.8 (2 H, m) and 3.6 (3 H, s). The diyne (394 mg, 1.67 mmol) was then dissolved in THF (20 cm^3) and H_2O (10 drops) was added. The mixture was cooled to 0 °C and sodium borohydride (190 mg, 5.0 mmol, 3 equiv.) was added portion-wise 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 NH_4Cl (10 cm^3). The mixture was extracted with ether (3 × 10 cm^3), and the combined ether extracts were dried ($MgSO_4$) and then concentrated under reduced pressure to give the crude *methyl 4-hydroxy-8-trimethylsilylocta-5,7-diynoate* (379 mg). This was then added dropwise over 15 min to a stirred suspension of $LiAlH_4$ (91 mg, 1.5 equiv.) in anhydrous THF (15 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 mixture was then held at −20 °C on a cold plate for 18 h, after which it was quenched by pouring into ice-cold saturated aqueous NH_4Cl (25 cm^3). This mixture was extracted with EtOAc (6 × 10 cm^3). The combined organic layers were extracted with brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (2 cm, Et_2O, R_F 0.15) to give trans-8-*trimethylsilyloct-5-en-7-yn-1,4-diol* **21** (314 mg, 1.47 mmol, 88%); ν_{max}($CHCl_3$)/cm^{-1} 3400–3500 (OH), 2900 (CH), 2180 (C≡C) and 1590 (C=C); δ_H(90 MHz; $CDCl_3$) 0.15 (9 H, s), 1.6 (2 H, m), 1.8 (2 H, m), 3.5–3.9 (4 H, m), 4.1 (1 H, m), 5.7 (1 H, d, *J* 16) and 6.2 (1 H, dd, *J* 7, 16).

trans-8-Trimethylsilyloct-5-en-7-yn-1,4-diol **21** (314 mg, 1.47 mmol) was added to a solution of *tert*-butyldiphenylsilyl chloride (0.46 cm^3, 1.2 equiv.) and imidazole (261 mg, 2.6 equiv.) in dry DMF (10 cm^3). The mixture was stirred for 15 h at room temperature, then diluted with water (5 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 (10 cm^3), combined and dried ($MgSO_4$). The ether was removed under reduced pressure to give a colourless oil (300 mg). This was purified by flash chromatography (5 cm, 20% EtOAc in hexane; R_F 0.38) to give the *silyl ether* **22** (200 mg, 0.45 mmol, 30%), which was spectroscopically identical to compound **16** in all respects except optical rotation.

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