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Stereoselective syntheses of pharmaceutically relevant chiral tetrahydrofurans from (*S*)- and (*R*)-glyceraldehyde derivatives☆

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Abstract—A practically simple and flexible method of making chiral tetrahydrofurans of therapeutic relevance is reported from glyceraldehyde derivatives as chiral synthons. One of the stereocentres is derived from glyceraldehyde derivatives, while the other one is introduced by Sharpless asymmetric epoxidation using either (+)- or (−)-DIPT.

1. Introduction

Asthma is a chronic inflammatory disease complicated by periodic acute inflammatory changes. The role of leukotrienes, the metabolites of arachidonic acid that are produced by the action of the 5-lipoxygenase (5-LO) enzyme, in inflammatory and allergic responses, including arthritis, asthma, psoriasis and thrombotic diseases, is well recognized.[1,2] Blocking either the synthesis or function of leukotrienes (LTs) has been shown to confer therapeutic benefits on asthmatic patients. Chiral tetrahydrofurans are structural features in a variety of natural products,[3–5] while compounds **2a** and **3a** and their stereoisomers **1a** and **4a** (Fig. 1) have been investigated for their inhibitory action against 5-lipoxygenase.[6] Compound **2a** was found to be a potent and orally active leukotriene modulator that works by inhibiting the action of 5-lipoxygenase (5-LO) to block the generation of cysteinyl leukotrienes and LTB_4. Further studies on **3a** showed a high degree of potency, excellent oral bioavailability and exceptionally favourable safety profile[7] over **2a**. Synthetic routes for the preparation of **2** and **2a** and **3** and **3a** have been reported by us.[8] Herein, we report a flexible synthetic route for acetylenes **2** and **3** and their diastereoisomers **1** and **4**, from (*S*)- and (*R*)-glyceraldehyde derivatives.

2. Results and discussion

Retrosynthetic analysis (Scheme 1) indicates that **1**–**4** could be prepared from alcohols **5**–**8** derived from allylic alcohols **9** and **10**, while these could be envisaged from (*S*)- and (*R*)-glyceraldehyde derivatives **11** and **12**, respectively. Thus, of the two requisite stereogenic centres, one is obtained from either the (*S*)- or (*R*)-glyceraldehyde derivative, while the other is introduced on the allylic alcohol by the Sharpless asymmetric epoxidation method using (+) and (−)-DIPT. Thus the main strategy would be the synthesis of allylic alcohols **9** and **10** from glyceraldehyde derivatives and their conversion into chiral propargyl alcohols through the epoxy alcohols. Alcohols **5**–**8** in turn afforded the target acetylenic derivatives **1**–**4**.

2.1. Synthesis of allylic alcohol 9

Accordingly, the Wittig olefination of **11**[9] (prepared from L-ascorbic acid) with (carbethoxymethylene)triphenyl phosphorane in CH_2Cl_2 gave ester **13** (Scheme 2), which on catalytic hydrogenation with PtO_2 at room temperature afforded **14**[10] in quantitative yield. Ester **14** was reduced with LAH in THF to furnish the known alcohol **15**[11] (97%), which on oxidation with IBX in

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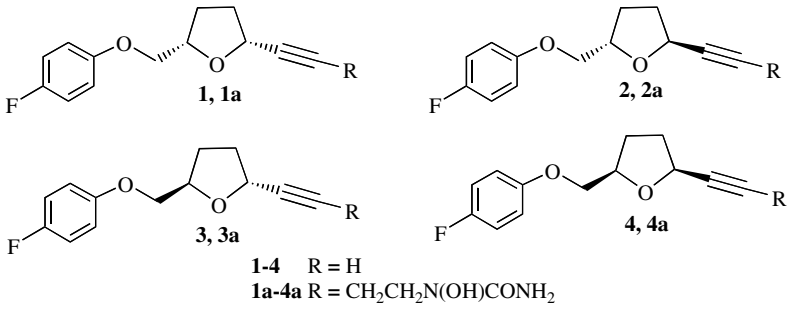
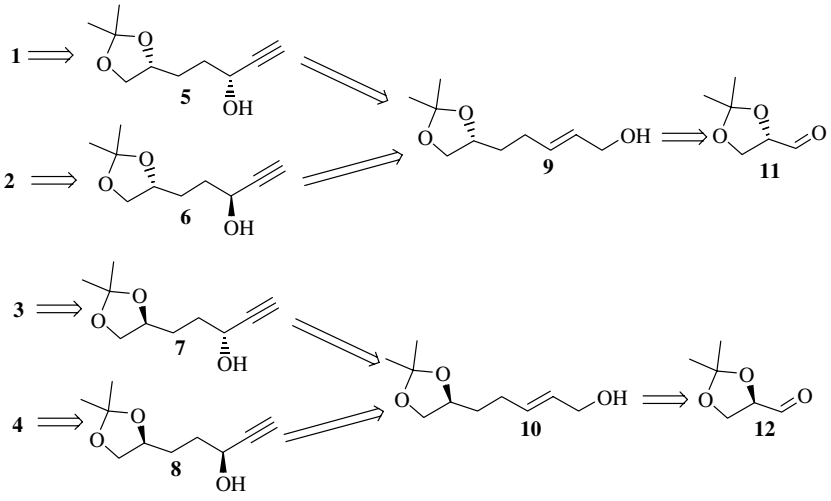
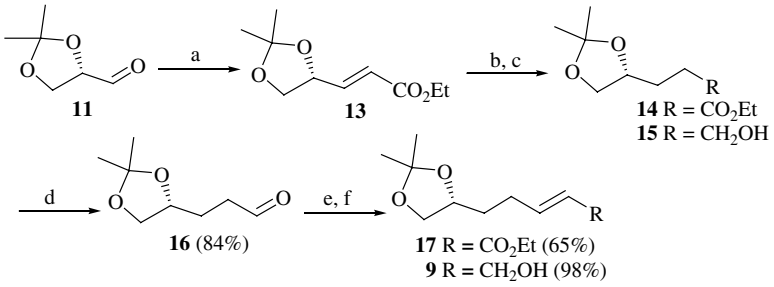


Figure 1.



Scheme 1.



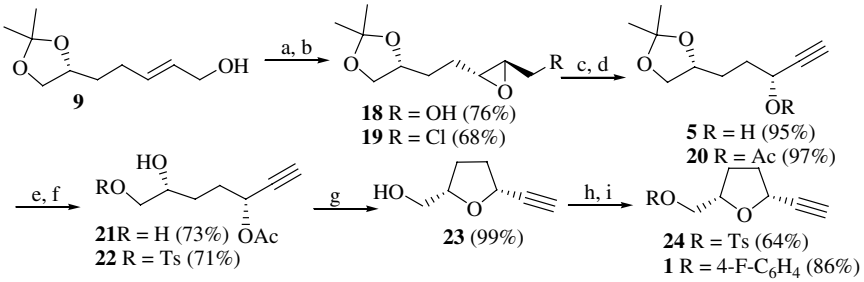
Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 9 h; (b) H_2, PtO_2, EtOAc, rt, 4 h; (c) $LiAlH_4$, dry THF, rt, 3 h; (d) IBX, dry DMSO, 0 °C to rt, 4 h; (e) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 6 h; (f) DIBAL-H, dry CH_2Cl_2, −20 °C, 2 h.

DMSO afforded aldehyde **16** (84%). Subjecting **16** to a Wittig olefination with (carbethoxymethylene)triphenyl phosphorane, in benzene at reflux, resulted in **17** (65%), which on selective reduction with DIBAL-H in CH_2Cl_2 at −20 °C furnished allylic alcohol **9** (98%).

2.2. Synthesis of (2*R*,5*S*)-*cis*-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 1

Sharpless asymmetric epoxidation[12] of **9** (Scheme 3) using (−)-DIPT, $Ti(O^iPr)_4$ and cumene hydroperoxide at −20 °C, furnished (2*R*,3*R*)-epoxide **18** (76%), which on subsequent reaction with Ph_3P in CCl_4 in the presence of $NaHCO_3$ (cat) at reflux, gave **19** (68%). The fragmentation[13] of chiral epoxy chloride **19** on treatment with LDA at −40 °C afforded **5** (95%), which on acetylation (Ac_2O, Et_3N) furnished the corresponding acetate **20** (97%). Hydrolysis of **20** with 60% aq AcOH at room temperature gave diol **21** (73%), which on tosylation (*p*-TsCl, Et_3N) in CH_2Cl_2, afforded monotosylate **22** in 71% yield.

Cyclization of tosylate **22** with K_2CO_3 in methanol at room temperature afforded the 2,5-disubstituted tetrahydrofuran **23** (99%), which on tosylation, and further treatment of **24** with 4-fluorophenol in the presence of NaH in DMF at 80 °C afforded **1** in 86% yield. Thus, making use of (*S*)-glyceraldehyde derivative **11** and Sharpless epoxidation with (−)-DIPT, the synthesis of (2*R*,5*S*)-isomer **1** was successfully achieved.



Scheme 3. Reagents and conditions: (a) (−)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, MS 4 Å, CH_2Cl_2, −20 °C, 3 h; (b) Ph_3P, cat $NaHCO_3$, CCl_4, reflux, 3 h; (c) LDA, dry THF, −40 °C, 3 h; (d) Ac_2O, Et_3N, CH_2Cl_2, rt, 30 min; (e) 60% aq AcOH, rt, 12 h; (f) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (g) K_2CO_3, MeOH, rt, 2 h; (h) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (i) 4-F-C_6H_4OH, NaH, DMF, 80 °C, 5 h.

2.3. Synthesis of (2*S*,5*S*)-*trans*-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran (2)

Similarly, Sharpless epoxidation of allylic alcohol **9** (Scheme 4) with (+)-DIPT gave (2*S*,3*S*)-epoxide **25** (72%), which was further converted into propargyl alcohol **6** (83%) through the corresponding chloride **26**. Acetylation of **6** furnished acetate **27** (91%), which on deprotection of the acetonide moiety in **27** and subsequent tosylation of **28** afforded **29** (89%). Treatment of **29** with K_2CO_3 in methanol gave tetrahydrofuran **30** (95%). Finally, tosylation of **30** followed by treatment of **31** with 4-fluorophenol in the presence of NaH at 80 °C gave **2**[8a] in 76% yield. In the ^1H NMR of *cis*-acetylene **1** the ArOCH_2-group resonated as two double doublets (δ 3.9, $J = 4.6$, 9.1 Hz and 4.06, $J = 5.9$, 9.1 Hz), while for *trans*-**2**, it resonated as a doublet at δ 3.9, $J = 5.8$ Hz, indicating a distinctive regiochemistry of the C-2 and C-5 positions of ring junction. No enhancement in the NOE was observed for **2**, which when irradiated, further indicates its *trans* geometry. HPLC (Chiralcel-OD; 1 cm ID/25 cm length; 10% *iso*-propanol in *n*-hexane; 1 mL/min) analysis of **1** and **2** confirmed their enantiomeric homogeneity.

2.4. Synthesis of allylic alcohol 10

Allylic alcohol **10** was prepared from aldehyde **12** (prepared from D-mannitol) following a similar sequence of reactions described for the preparation of **9**. Accordingly, **12** on two sequential Wittig olefinations (Scheme 5) and further reactions were converted into **10**.

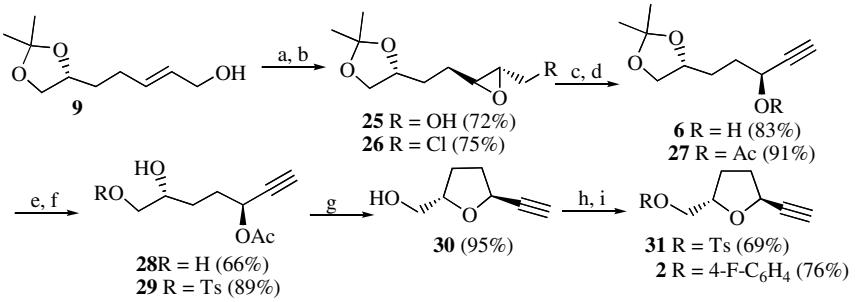
2.5. Synthesis of (2*R*,5*R*)-*trans*-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 3

As described in Scheme 3, **10** on Sharpless asymmetric epoxidation (Scheme 6) with (−)-DIPT gave epoxide **37** (69%). Fragmentation of **38** with LDA furnished **7** (80%), which on acetylation gave **39**. Acetonide deprotection in **39** followed by tosylation of diol **40** afforded **41** (71%). Cyclization of **41** with K_2CO_3 in methanol as described above afforded **42** in 75% yield. Finally, alcohol **42** on tosylation and subsequent etherification of **43** with 4-fluorophenol (NaH, DMF) at 80 °C afforded **3** in 82% yield.

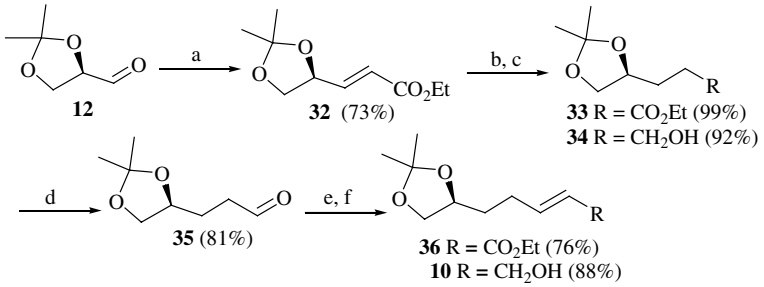
2.6. Synthesis of (2*S*,5*R*)-*cis*-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 4

Similar sequence of reactions as described for **3**, except for using (+)-DIPT for Sharpless epoxidation on allylic alcohol **10** (Scheme 7) afforded **4**. The ^1H NMR of **3** and **4** were found to be similar to that of **2** and **1**, respectively.

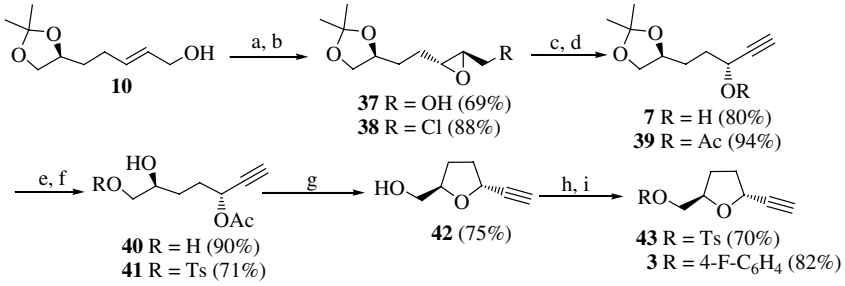
A possible plausible mechanism for the cyclization is shown in Scheme 8. Tosylate **22** on reaction with K_2CO_3 undergoes deacetylation as well as epoxide formation in situ, which on concomitant nucleophilic attack



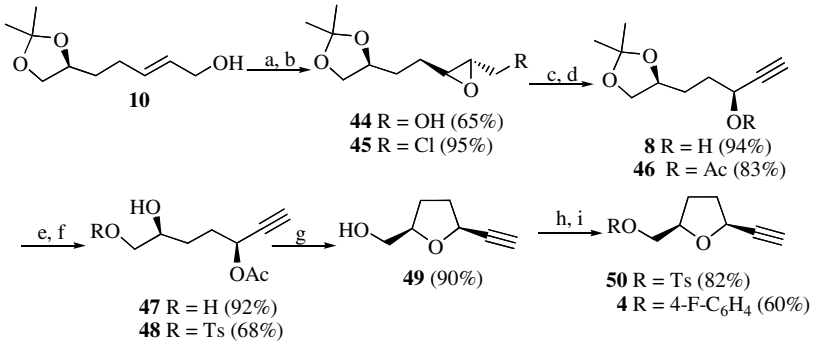
Scheme 4. Reagents and conditions: (a) (+)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, MS 4 Å, CH_2Cl_2, −20 °C, 3 h; (b) Ph_3P, cat $NaHCO_3$, CCl_4, reflux, 3 h; (c) LDA, dry THF, −40 °C, 3 h; (d) Ac_2O, Et_3N, CH_2Cl_2, rt, 30 min; (e) 60% aq AcOH, rt, 12 h; (f) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (g) K_2CO_3, MeOH, rt, 2 h; (h) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (i) 4-F-C_6H_4OH, NaH, DMF, 80 °C, 5 h.



Scheme 5. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 9 h; (b) H_2, PtO_2, EtOAc, rt, 4 h; (c) $LiAlH_4$, dry THF, rt, 3 h; (d) IBX, dry DMSO, 0 °C to rt, 4 h; (e) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 6 h; (f) DIBAL-H, dry CH_2Cl_2, −20 °C, 2 h.



Scheme 6. Reagents and conditions: (a) (−)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, MS 4 Å, CH_2Cl_2, −20 °C, 3 h; (b) Ph_3P, cat $NaHCO_3$, CCl_4, reflux, 3 h; (c) LDA, dry THF, −40 °C, 3 h; (d) Ac_2O, Et_3N, CH_2Cl_2, rt, 30 min; (e) 60% aq AcOH, rt, 12 h; (f) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (g) K_2CO_3, MeOH, rt, 2 h; (h) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (i) 4-F-C_6H_4OH, NaH, DMF, 80 °C, 5 h.



Scheme 7. Reagents and conditions: (a) (+)-DIPT, $Ti(O^iP)_4$, cumene hydroperoxide, MS 4 Å, CH_2Cl_2, −20 °C, 3 h; (b) Ph_3P, cat $NaHCO_3$, CCl_4, reflux, 3 h; (c) LDA, dry THF, −40 °C, 3 h; (d) Ac_2O, Et_3N, CH_2Cl_2, rt, 30 min; (e) 60% aq AcOH, rt, 12 h; (f) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (g) K_2CO_3, MeOH, rt, 2 h; (h) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (i) 4-F-C_6H_4OH, NaH, DMF, 80 °C, 5 h.

by an oxy-anion onto epoxide gives tetrahydrofuran **23**. As similar mechanism is also appropriate for the conversion of **29**, **41** and **48** into the corresponding THFs **30**, **42** and **49**.

3. Conclusion

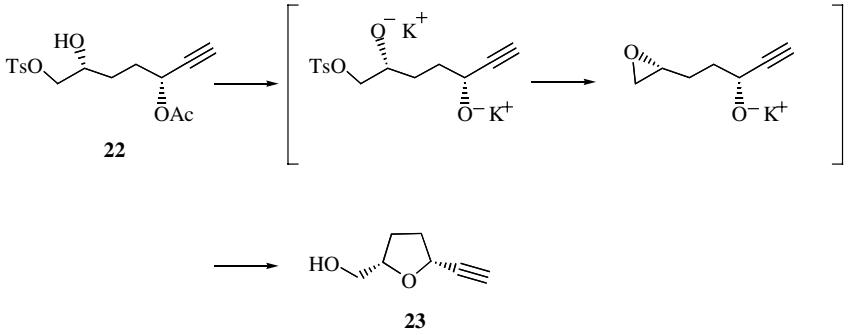
In conclusion, the four stereoisomeric acetylenes **1**–**4** were prepared from allylic alcohols **9** and **10** by a flexible approach using Sharpless asymmetric epoxidation using (−) and (+)-DIPT, respectively. The requisite allylic alcohols were in turn, prepared from the (*S*)- and (*R*)-glyceraldehyde derivatives. These acetylenes serve as advanced synthetic intermediates for the successful elaboration into several novel anti-asthmatic target molecules by attachment of the appropriate hydroxy urea derivatives.

4. Experimental

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz) spectra were recorded in deuteriochloroform solution with tetramethylsilane as an internal reference on Varian Gemini-200 MHz spectrometer. *J* values are given in hertz. Optical rotations were measured with a JASCO DIP-370 instrument, and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo.

4.1. Ethyl (2*E*,6*R*)-6,7-isopropylidenedioxy hept-2-enoate 17

A stirred solution of **15** (0.80 g, 5.0 mmol) in DMSO (5 mL) was treated with IBX (1.47 g, 5.26 mmol) in



Scheme 8.

portions, while maintaining the temperature below 0 °C and then stirred at room temperature for 4 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (20 mL), filtered through Celite and washed with EtOAc (3×30 mL). The organic layer was separated and washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Evaporation of the solvent gave (4*R*)-4,5-isopropylidenedioxy-1-pentanal **16** (0.663 g) in 84% yield as a yellow liquid, which was used in subsequent experiments without any further purification.

A solution of **16** (15 g, 94.9 mmol) in benzene (200 mL) was treated with (carbethoxymethylene)triphenyl phosphorane (39.6 g, 113.8 mmol) and heated at reflux for 6 h. The solvent was evaporated and the residue purified by column chromatography (silica gel, 10% EtOAc in hexane) to afford **17** (14 g) in 65% yield as a pale yellow liquid. $[\alpha]_D = -5.4$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3 (t, $2 \times 3H$, $J = 6.8$ Hz, CH_3), 1.34, 1.4 (2s, 6H), 1.61–1.7 (m, 2H, H-5), 2.2–2.42 (m, 2H, H-4), 3.5 (t, 1H, $J = 6.8$ Hz, H-7), 3.99–4.26 (m, 4H, H-6, 7′, OCH_2), 5.82 (td, 1H, $J = 2.25$, 15.75 Hz, H-2), 6.94 (dt, 1H, $J = 6.8$, 15.75 Hz, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0, 25.4, 26.7, 28.2, 31.9, 60.0, 69.0, 74.9, 108.7, 121.7, 147.7, 166.3; EIMS *m/z* (relative intensity): 213 ($M^+ - CH_3$, 9), 95 (40.2), 67 (25.3), 55 (53.7), 41 (100); HRMS: Calculated for $C_{11}H_{17}O_4$ ($M^+ - CH_3$): 213.112684; observed: 213.112732.

4.2. (2*E*,6*R*)-6,7-Isopropylidenedioxy hept-2-ene-1-ol 9

A stirred solution of **17** (13.87 g, 60.8 mmol) in dry CH_2Cl_2 (60 mL) was cooled to −20 °C and treated with a solution of DIBAL-H (17.27 g, 121.6 mmol; 2.5 M solution in hexane) dropwise. After 2 h, the reaction mixture was warmed to 0 °C and treated dropwise with MeOH (10 mL) to obtain a gelatinous cake. The mixture was diluted with CH_2Cl_2 (100 mL) and stirred for 15 min. A solution of Na–K tartrate (90 mL) was added dropwise and stirred for an additional 45 min. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (2×50 mL). The organic layer was washed with water (2×100 mL), brine (50 mL), dried over Na_2SO_4 and evaporated to give **9** (11 g) in 98% yield as a colourless liquid. $[\alpha]_D = -13.2$ (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.16, 1.2 (2s, 6H, $2 \times CH_3$), 1.46–1.74 (m, 2H, H-5), 1.79–1.98 (m, 1H, OH), 2.02–2.19 (m, 2H, H-4), 3.36–3.78 (m, 3H, H-6, 7), 4.02–4.12 (m, 2H, H-1), 5.61–5.71 (m, 2H, H-2, 3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.5, 28.0, 32.7, 62.8, 68.9, 75.1, 108.3, 129.8 (2C); EIMS *m/z* (relative intensity): 171 ($M^+ - CH_3$, 35.8), 93 (22.3), 67 (37.3), 55 (26.8), 43 (100); HRMS: Calculated for $C_9H_{15}O_3$ ($M^+ - CH_3$): 171.102120; observed: 171.102195.

4.3. Synthesis of (2*R*,5*S*)-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 1

4.3.1. (2*R*,3*R*,6*R*)-2,3-Epoxy-6,7-isopropylidenedioxyheptan-1-ol 18. To a stirred and cooled (−20 °C) suspension of molecular sieves (4 Å, 1.25 g) in CH_2Cl_2 (10 mL) under an N_2 atmosphere, (−)-DIPT (7.6 g, 32.4 mmol), $Ti(O^iPr)_4$ (7.68 g, 27.02 mmol) and cumene hydroperoxide (8.22 g, 54 mmol) were added sequentially. After 20 min, the resulting mixture was treated dropwise with a solution of **9** (5 g, 26.88 mmol) in CH_2Cl_2 (15 mL) and stirred for an additional 3 h. The reaction mixture was quenched with 10% NaOH solution saturated with NaCl (15 mL) and filtered through Celite. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 50% EtOAc in hexane) gave **18** (4.15 g) in 76% yield as a colourless liquid. $[\alpha]_D = +24.3$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.38 (2s, 6H, $2 \times CH_3$), 1.58–1.78 (m, 4H, H-4, 5), 2.84–3.01 (m, 2H, H-2, 3), 3.5 (t, 1H, $J = 6.1$ Hz, H-7), 3.6 (dd, 1H, $J = 4.7$, 11.75 Hz, H-1), 3.85 (dd, 1H, $J = 3.29$, 11.75 Hz, H-1′), 3.98–4.2 (m, 2H, H-6, 7′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.5, 26.8, 27.6, 29.6, 55.3, 58.3, 61.6, 69.1, 75.1, 108.8; EIMS *m/z* (relative intensity): 187 ($M^+ - CH_3$, 14.9), 144 (85), 101 (47.7), 83 (95), 43 (100); HRMS: Calculated for $C_9H_{15}O_4$ ($M^+ - CH_3$): 187.097034; observed: 187.096634.

4.3.2. (2*S*,3*R*,6*R*)-1-Chloro-2,3-epoxy-6,7-isopropylidenedioxy heptane 19. A stirred mixture of **18** (3.8 g, 18.8 mmol), Ph_3P (7.4 g, 28.3 mmol) and $NaHCO_3$ (0.6 g) in CCl_4 (50 mL) was heated at reflux for 3 h. The solvent was evaporated and the residue purified by column chromatography (silica gel, 20% EtOAc in hexane) to give **19** (2.8 g) in 68% yield as a colourless liquid. $[\alpha]_D = +8.2$ (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.31, 1.36 (2s, 6H, $2 \times CH_3$), 1.63–1.72 (m, 4H, H-4, 5), 2.8–2.9 (m, 1H, H-2), 2.91–3.02 (m, 1H, H-3), 3.32–3.68 (m, 3H, H-1, 7), 3.95–4.19 (m, 2H, H-6, 7′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.6,

26.9, 27.6, 29.6, 44.5, 57.0, 58.3, 69.2, 75.1, 109.1; EIMS *m/z* (relative intensity): 205 ($M^+ - CH_3$, 35.8), 145 (23), 83 (61), 72 (98), 43 (100); HRMS: Calculated for $C_9H_{14}ClO_3$ ($M^+ - CH_3$): 205.063147; observed: 205.062719.

4.3.3. (3*R*,6*R*)-3-Hydroxy-6,7-isopropylidenedioxy-hept-1-yne 5. To freshly prepared LDA [prepared from diisopropyl amine (4.6 g, 45.45 mmol) and *n*-BuLi (2.91 g, 45.54 mmol; 1.4 N hexane solution)] in THF (10 mL), a solution **19** (2.5 g, 11.36 mmol) in THF (20 mL) was added at −40 °C. After 3 h, the reaction was quenched with aq NH_4Cl solution (40 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with water (3 × 20 mL), brine (200 mL), dried over Na_2SO_4, concentrated in vacuo and the residue purified by column chromatography (silica gel, 15% EtOAc in hexane) to furnish **5** (2.0 g) in 95% yield as a pale yellow liquid. $[\alpha]_D = -3.0$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.39 (2s, 6H, 2 × CH_3), 1.64–1.94 (m, 4H, H-4, 5), 2.19–2.21 (br s, 1H, OH), 2.39 (d, 1H, $J = 2.3$ Hz, H-1), 3.5 (t, 1H, $J = 5.7$ Hz, H-7), 3.96–4.16 (m, 2H, H-6, 7′), 4.34–4.45 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4, 26.6, 28.8, 33.5, 61.3, 69.0, 72.7, 75.3, 84.7, 108.7; EIMS *m/z* (relative intensity): 169 ($M^+ - CH_3$, 22.3), 109 (20.8), 81 (37.3), 55 (35.8), 43 (100); HRMS: Calculated for $C_9H_{13}O_3$ ($M^+ - CH_3$): 169.086469; observed: 169.086140.

4.3.4. (3*R*,6*R*)-3-Acetoxy-6,7-isopropylidenedioxy-hept-1-yne 20. A solution of **5** (1.8 g, 9.8 mmol) and Et_3N (3.95 g, 39.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with Ac_2O (1.2 g, 11.7 mmol) and stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 10% EtOAc in hexane) gave **20** (2.15 g) in 97% yield as a yellow liquid. $[\alpha]_D = +37.5$ (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.39 (2s, 6H, 2 × CH_3), 1.64–2.0 (m, 4H, H-4, 5), 2.06 (s, 3H, CH_3), 2.4 (d, 1H, $J = 2.0$ Hz, H-1), 3.5 (t, 1H, $J = 5.7$ Hz, H-7), 3.95–4.13 (m, 2H, H-6, 7′), 5.31–5.41 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.8, 25.5, 26.8, 28.8, 30.7, 63.3, 69.1, 73.7, 75.1, 80.7, 108.9, 169.6; EIMS *m/z* (relative intensity): 211 ($M^+ - CH_3$, 29.8), 169 (11.9), 91 (22.3), 72 (23), 43 (100); HRMS: Calculated for $C_{11}H_{15}O_4$ ($M^+ - CH_3$): 211.097034; observed: 211.095947.

4.3.5. (3*R*,6*R*)-3-Acetoxy-6,7-dihydroxy-hept-1-yne 21. A solution of **20** (2 g, 8.8 mmol) in 60% aq AcOH (20 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution. It was extracted with EtOAc (3 × 50 mL), after which the organic layer was evaporated and the residue filtered through a small pad of silica gel with 50% EtOAc in hexane to afford **21** (1.2 g) in 73% yield as a colourless syrup. $[\alpha]_D = +53.2$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.5–1.7 (m, 2H, H-4), 1.75–2.05 (m, 2H, H-5), 2.14 (s, 3H, OAc), 2.45 (d, 1H, $J = 2.01$ Hz, H-1), 2.57 (br s, 2H, OH), 3.35–3.5 (m, 1H, H-7), 3.57–3.8 (m, 2H, H-6, 7′), 5.32–5.47 (m, 1H, H-3); CIMS *m/z* (relative intensity): 187 ($M^+ + H$, 74.6), 127 (59.7), 109 (35.8), 81 (56.7), 43 (100); HRMS Calculated for $C_9H_{15}O_4$ ($M^+ + H$): 187.097034; observed: 187.096547.

4.3.6. (3*R*,6*R*)-3-Acetoxy-6-hydroxy-7-*p*-toluenesulfonyloxy-hept-1-yne 22. A solution of **21** (1.1 g, 5.9 mmol) and Et_3N (1.19 g, 11.82 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, treated with *p*-TsCl (1.12 g, 5.91 mmol) and stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, evaporated and the residue obtained was purified by column chromatography (silica gel, 10% EtOAc in hexane) to furnish **22** (1.42 g) in 71% yield as a yellow syrup. $[\alpha]_D = +28.1$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35–1.68 (m, 3H, H-4, OH), 1.68–2.0 (m, 2H, H-5), 2.08 (s, 3H, CH_3), 2.4 (d, 1H, $J = 2.4$ Hz, H-1), 2.46 (s, 3H, Ar–CH_3), 3.79–4.06 (m, 3H, H-6, 7), 5.35 (td, 1H, $J = 4.8$, 7.2 Hz, H-3), 7.36 (d, 2H, $J = 7.2$ Hz, Ar–H), 7.8 (d, 2H, $J = 7.2$ Hz, Ar–H). FABMS *m/z* (relative intensity): 341 ($M^+ + H$, 13.8), 281 (50), 155 (54.1), 133 (52.7), 109 (100). HRMS: Calculated for $C_{16}H_{21}O_6S$ ($M^+ + H$): 341.105885; observed: 341.104916.

4.3.7. (2*R*,5*S*)-5-Ethynyl-2-(hydroxymethyl)tetrahydrofuran 23. To a solution of **22** (0.6 g, 1.76 mmol) in MeOH (10 mL) at room temperature, K_2CO_3 (0.536 g, 3.88 mmol) was added and the mixture stirred for 2 h. It was then treated with NH_4Cl solution (10 mL), MeOH evaporated and the residue extracted with EtOAc (3 × 20 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated. The residue obtained was purified by column chromatography (silica gel, 20% EtOAc in hexane) to furnish **23** (0.22 g) in 99% yield as a colourless liquid. $[\alpha]_D = +20.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.89–2.38 (m, 4H, H-3, 4), 2.4 (br s, 1H, OH), 2.46 (d, 1H, $J = 2.2$ Hz, acetylenic), 3.55 (dd, 1H, $J = 4.5$, 11.25 Hz, OCH_2), 3.72 (dd, 1H, $J = 4.0$, 11.25 Hz, OCH_2), 4.0–4.15 (m, 1H, H-2), 4.52–4.66 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.6, 29.6, 33.6, 64.6, 68.3, 73.0, 80.7; EIMS *m/z* (relative intensity): 125 ($M^+ - H$, 8), 95 (74.6), 67 (100), 53 (40), 41 (80); HRMS: Calculated for $C_7H_9O_2$ ($M^+ - H$): 125.060255; observed: 125.060322.

4.3.8. (2*R*,5*S*)-5-Ethynyl-2-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran 24. A solution of **23** (0.22 g, 1.75 mmol) and Et_3N (0.35 g, 3.5 mmol) in CH_2Cl_2 (5 mL) was treated with *p*-TsCl (0.354 g, 1.86 mmol) and stirred at room temperature for 8 h. It was worked-up and purified as described for **22** to give **24** (0.33 g) in 64% yield as a yellow syrup. $[\alpha]_D = +10.0$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.84–2.11 (m, 4H, H-3, 4) 2.32 (d, 1H, $J = 2.1$ Hz, acetylenic), 2.45 (s, 3H, CH_3), 3.92–4.2 (m, 3H, H-2, OCH_2), 4.48–4.58 (m, 1H, H-5), 7.34 (d, 2H, $J = 7.6$ Hz, Ar–H), 7.8 (d, 2H, $J = 7.6$ Hz, Ar–H); CIMS *m/z* (relative intensity): 281 ($M^+ + H$, 100), 109 (49.2), 117 (31.3), 81 (7.0), 43 (100); HRMS:

Calculated for $C_{14}H_{17}O_4S$ ($M^+ + H$): 281.084756; observed: 281.083610.

4.3.9. (2*R*,5*S*)-2-Ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 1. To a stirred suspension of NaH (0.032 g, 1.33 mmol) in DMF (3 mL), a solution of **24** (0.33 g, 1.1 mmol) in DMF (3 mL) was added and heated at 80 °C for 5 h. The reaction mixture was cooled to room temperature and treated with NH_4Cl solution. It was extracted with ether (2 × 10 mL) and the organic layer washed with water (2 × 10 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and purification of residue by column chromatography (silica gel, 7% EtOAc in hexane) afforded **1** (0.21 g) in 86% yield as a colourless liquid. $[\alpha]_D$ = +16.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.88–2.32 (m, 4H, H-3, 4), 2.41 (d, 1H, *J* = 2.3 Hz, acetylenic), 3.9 (dd, 1H, *J* = 4.6, 9.1 Hz, OCH_2), 4.06 (dd, 1H, *J* = 5.9, 9.1 Hz, OCH_2), 4.22–4.36 (m, 1H, H-5), 4.58–4.69 (m, 1H, H-2), 6.75–7.02 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.2, 33.1, 68.5, 71.2, 72.9, 76.3, 83.7, 115.4, 115.6, 115.8, 115.9, 154.9, 159.6; EIMS *m*/*z* (relative intensity): 220 (M^+, 10.4), 125 (14.9), 95 (94), 67 (100), 41 (59.7); HRMS: Calculated for $C_{13}H_{13}FO_2$ (M^+): 220.089958; observed: 220.089497.

4.4. Synthesis of (2*S*,5*S*)-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 2

4.4.1. (2*S*,3*S*,6*R*)-2,3-Epoxy-6,7-isopropylidenedioxyheptan-1-ol 25. To a stirred and cooled (−20 °C) suspension of molecular sieves (4 Å, 0.55 g) in CH_2Cl_2 (10 mL) under an N_2 atmosphere, (+)-DIPT (4.0 g, 17.41 mmol), $Ti(O^iPr)_4$ (4.12 g, 14.51 mmol) and cumene hydroperoxide (4.4 g, 29.0 mmol) were added sequentially. After 20 min, the resulting mixture was treated with a solution of **9** (2.7 g, 14.51 mmol) in CH_2Cl_2 (10 mL) and stirred for an additional 3 h. Work-up and purification as described for **18** gave **25** (2.1 g) in 72% yield as a colourless liquid. $[\alpha]_D$ = −26.9 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.38 (2s, 6H, 2 × CH_3), 1.58–1.79 (m, 4H, H-4, 5), 2.3–2.52 (br s, 1H, OH), 2.84–3.0 (m, 2H, H-2, 3), 3.5 (t, 1H, *J* = 6.1 Hz, H-7), 3.6 (dd, 1H, *J* = 4.5, 12.0 Hz, H-1), 3.85 (dd, 1H, *J* = 3.3, 11.2 Hz, H-1′), 3.98–4.2 (m, 2H, H-6, 7′); EIMS *m*/*z* (relative intensity in %): 187 ($M^+ - CH_3$, 7), 143 (27), 101 (25), 83 (63), 43 (100); HRMS: Calculated for $C_9H_{15}O_4$ ($M^+ - CH_3$): 187.097034; found: 187.097403.

4.4.2. (2*R*,3*S*,6*R*)-1-Chloro-2,3-epoxy-6,7-isopropylidenedioxy heptane 26. A stirred mixture of **25** (1.9 g, 9.4 mmol), Ph_3P (3.7 g, 14.1 mmol) and $NaHCO_3$ (0.3 g) in CCl_4 (25 mL) was heated at reflux for 3 h. Work-up and purification as described for **19** gave **26** (1.5 g) in 75% yield as a colourless liquid. $[\alpha]_D$ = +12.9 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.39 (2s, 6H, 2 × CH_3), 1.58–1.72 (m, 4H, H-4, 5), 2.8–2.9 (m, 1H, H-2), 2.91–3.02 (m, 1H, H-3), 3.32–3.68 (m, 3H, H-1, 7), 3.94–4.16 (m, 2H, H-6, 7a). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.5, 26.9, 28.1, 30.3, 44.9, 57.2, 57.2, 58.6, 69.2, 75.5, 109.1; EIMS *m*/*z* (relative intensity in %): 205 ($M^+ - CH_3$, 3), 127 (7), 101 (22), 72 (28), 43 (100).

4.4.3. (3*S*,6*R*)-3-Hydroxy-6,7-isopropylidenedioxy-hept-1-yne 6. To freshly prepared LDA [prepared from diisopropyl amine (2.3 g, 23.6 mmol) and *n*-BuLi (15.7 mL, 23.6 mmol; 1.5 N hexane solution)] in THF (6 mL), a solution of **26** (1.5 g, 5.9 mmol) in THF (10 mL) was added at −40 °C. After 3 h, it was worked-up and purified as described for **5** to furnish **6** (1.0 g) in 83% yield as a pale yellow liquid. $[\alpha]_D$ = −21.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34, 1.4 (2s, 6H, 2 × CH_3), 1.64–1.9 (m, 4H, H-4, 5), 2.49 (d, 1H, *J* = 2.3 Hz, H-1), 2.55–2.7 (br s, 1H, OH), 3.52 (t, 1H, *J* = 5.8 Hz, H-7), 3.98–4.16 (m, 2H, H-6, 7a), 4.35–4.49 (m, 1H, H-3). EIMS *m*/*z* (relative intensity in %): 169 ($M^+ - CH_3$, 25), 109 (25), 72 (33), 43 (100); HRMS: Calculated for $C_9H_{13}O_3$ ($M^+ - CH_3$): 169.086469; found: 169.086817.

4.4.4. (3*S*,6*R*)-3-Acetoxy-6,7-isopropylidenedioxy-hept-1-yne 27. A solution of **6** (1.0 g, 5.43 mmol) and Et_3N (2.74 g, 27.15 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with Ac_2O (0.665 g, 6.52 mmol) and stirred at room temperature for 30 min. Worked-up and purified as described for **20** to give **27** (1.1 g) in 91% yield as a yellow liquid. $[\alpha]_D$ = −51.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.39 (2s, 6H, 2 × CH_3), 1.46–2.01 (m, 4H, H-4, 5), 2.08 (s, 3H, CH_3), 2.41 (d, 1H, *J* = 2.3 Hz, H-1), 3.5 (t, 1H, *J* = 6.9 Hz, H-7′), 3.98–4.14 (m, 2H, H-6, 7′), 5.31–5.42 (m, 1H, H-3). EIMS *m*/*z* (relative intensity in %): 211 ($M^+ - CH_3$, 72), 169 (28), 109 (40), 72 (67), 43 (100); HRMS: Calculated for $C_{11}H_{15}O_4$ ($M^+ - CH_3$): 211.097034; found: 211.097445.

4.4.5. (3*S*,6*R*)-3-Acetoxy-6,7-dihydroxy-hept-1-yne 28. A solution of **27** (1.1 g, 4.86 mmol) in 60% aq AcOH (10 mL) was stirred at room temperature for 12 h. Work-up and purification as described for **21** afforded **28** (0.6 g) in 66% yield as a colourless syrup. $[\alpha]_D$ = −46.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.45–1.7 (m, 2H, H-4), 1.75–2.05 (m, 2H, H-5), 2.09 (s, 3H, –OAc), 2.4 (br s, 3H, H-1, OH), 3.32–3.5 (m, 1H, H-7), 3.52–3.8 (m, 2H, H-6, 7a), 5.3–5.44 (m, 1H, H-3); EIMS *m*/*z* (relative intensity in %): 155 ($M^+ - CH_3$, 3), 113 (3), 95 (60), 67 (63), 43 (100); HRMS: Calculated for $C_8H_{11}O_3$ ($M^+ - CH_3$): 155.070819; 155.071352.

4.4.6. (3*S*,6*R*)-3-Acetoxy-6-hydroxy-7-*p*-toluenesulfonyloxy-hept-1-yne 29. A solution of **28** (0.6 g, 3.22 mmol) and Et_3N (0.975 g, 9.66 mmol) in CH_2Cl_2 (10 mL) was treated with *p*-TsCl (0.737 g, 3.87 mmol) at 0 °C and stirred at room temperature for 8 h. Work-up and purification as described for **22** afforded **29** (0.94 g) in 89% yield as a colourless syrup. $[\alpha]_D$ = −37.2 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.51–2.0 (m, 5H, H-4, 5, –OH), 2.08 (s, 3H, CH_3), 2.4 (d, 1H, *J* = 2.3 Hz, H-1), 2.48 (s, 3H, Ar–CH_3), 3.8–4.06 (m, 3H, H-6, 7), 5.35 (td, 1H, *J* = 4.8, 7.2 Hz, H-3), 7.36 (d, 2H, *J* = 7.9 Hz, Ar–H), 7.8 (d, 2H, *J* = 7.9 Hz, Ar–H); FABMS *m*/*z* (relative intensity in %): 341 ($M^+ + H$, 18), 327 (33), 281

(51), 207 (61), 136 (54), 55 (100); HRMS: Calculated for $C_{16}H_{21}O_6S$ ($M^+ + H$): 341.105885; 341.104171.

4.4.7. (2*S*,5*S*)-5-Ethynyl-2-(hydroxymethyl)tetrahydrofuran 30. To a solution of **29** (0.9 g, 2.64 mmol) in MeOH (15 mL) at room temperature, K_2CO_3 (0.805 g, 5.83 mmol) was added and the mixture was stirred for 2 h. Work-up and purification as described for **23** furnished **30** (0.4 g) in 95% yield as a colourless liquid. $[\alpha]_D = -10.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.50–2.3 (m, 4H, H-3, 4), 2.4 (br s, 1H, OH), 2.42 (d, 1H, $J = 2.2$ Hz, acetylenic), 3.5 (dd, 1H, $J = 4.5$, 11.3 Hz, OCH_2), 3.75 (dd, 1H, $J = 3.3$, 11.35 Hz, OCH_2), 4.16–4.34 (m, 1H, H-2), 4.6–4.74 (m, 1H, H-5); EIMS *m*/*z* (relative intensity in %): 126 (M^+, 10), 95 (82), 67 (100), 53 (53), 41 (81); Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.60; H, 6.9.

4.4.8. (2*S*,5*S*)-5-Ethynyl-2-(*p*-toluenesulfonyloxymethyl)-tetrahydrofuran 31. A solution of **30** (0.33 g, 2.6 mmol) and Et_3N (0.263 g, 7.8 mmol) in CH_2Cl_2 (10 mL) was treated with *p*-TsCl (0.499 g, 2.6 mmol) at 0 °C and the mixture stirred at room temperature for 8 h. Work-up and purification as described for **22** gave **31** (0.59 g) in 69% yield as a colourless syrup. $[\alpha]_D = -7.0$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.64–2.0 (m, 4H, H-3, 4) 2.22 (d, 1H, $J = 2.1$ Hz, acetylenic), 2.35 (s, 3H, CH_3), 3.72–4.05 (m, 3H, H-2, OCH_2), 4.28–4.48 (m, 1H, H-5), 7.34 (d, 2H, $J = 7.6$ Hz, Ar–H), 7.8 (d, 2H, $J = 7.6$ Hz, Ar–H); EIMS *m*/*z* (relative intensity in %): 279 ($M^+ - H$, 30), 167 (75), 149 (100), 113 (25), 57 (19).

4.4.9. (2*S*,5*S*)-2-Ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 2. To a stirred suspension of NaH (0.041 g, 1.71 mmol) in DMF (3 mL), a solution of **31** (0.32 g, 1.1 mmol) in DMF (3 mL) was added and heated at 80 °C for 5 h. Work-up and purification as described for **1** afforded **2** (0.19 g) in 76% yield as a colourless liquid. $[\alpha]_D = -21.5$ (*c* 1.1, $CHCl_3$), $[\alpha]_D$[8a] $= -23.0$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.8–2.34 (m, 4H, H-3, 4), 2.38 (d, 1H, $J = 2.3$ Hz, acetylenic), 3.9 (d, 2H, $J = 5.8$ Hz, $-OCH_2$), 4.36–4.51 (m, 1H, H-2), 4.64–4.78 (m, 1H, H-5), 6.75–7.02 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.3, 33.4, 68.5, 70.6, 72.8, 76.3, 115.4, 115.5, 115.9, 154.9, 159.7; EIMS *m*/*z* (relative intensity in %): 220 (M^+, 21), 125 (10), 112 (30), 95 (100), 67 (78), 43 (61); HRMS: Calculated for $C_{13}H_{13}FO_2$ (M^+): 220.089958. Found: 220.090477.

4.4.10. Ethyl (2*EZ*,4*S*)-4,5-isopropylidenedioxy-2-pentenoate 32. A solution of **12** in CH_2Cl_2 (250 mL) was treated with (carbethoxymethylene)triphenyl phosphorane (61.9 g, 0.179 mol) below 10 °C and stirred at room temperature for 9 h. Work-up and purification as described for **13** afforded **32** (53 g) in 73% yield as a colourless liquid. $[\alpha]_D = +109.8$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.2 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.3, 1.35 (2s, 6H, $2 \times CH_3$), 3.48 (dd, 1H, $J = 6.1$ Hz, H-5), 4.05 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3), 4.25 (dd, 1H, $J = 8.0$ Hz, H-5a), 5.3–5.40 (m, 1H, H-4), 5.72 (dd, 1H, $J = 2.3$, 11.0 Hz, H-2), 6.72 (dd, 1H, $J = 6.1$, 12.2 Hz, H-3).

4.4.11. Ethyl (4*S*)-4,5-isopropylidenedioxy-1-pentanoate 33. A solution of **32** (50 g, 0.250 mol) in EtOAc (50 mL) was treated with PtO_2 (0.15 g) and subjected to hydrogenation at 40 psi for 4 h. Work-up and purification as described for **14** gave **33** (50 g) in 99% yield as a colourless liquid. $[\alpha]_D = +5.0$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.30 and 1.45 (2s, 6H, $2 \times CH_3$), 1.8–1.95 (m, 2H, H-3, 3′), 2.38–2.5 (m, 2H, H-2,2′), 3.52 (dd, 1H, $J = 7.1$ Hz, H-5), 4.0–4.2 (m, 4H, H-4, 5a, OCH_2CH_3).

4.4.12. (2*S*)-1,2-Isopropylidenedioxy-5-pentanol 34. A suspension of LAH (16.9 g, 0.44 mol) in THF (300 mL) at 0 °C was treated with a solution of **33** (90 g, 0.44 mol) in THF (200 mL). After 3 h, it was worked-up and purified as described for **15** to provide **34** (65.5 g) in 92% yield as a colourless liquid. $[\alpha]_D = +14.2$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.4 (2s, 6H, $2 \times CH_3$), 1.6–1.8 (m, 5H, H-3, 4, OH), 3.5 (t, 1H, $J = 8.3$ Hz, H-1), 3.6–3.7 (m, 2H, H-5), 4.0–4.18 (m, 2H, H-1′, 2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.5, 26.7, 28.9, 30.0, 62.2, 69.3, 76.3, 108.8; EIMS *m*/*z* (relative intensity in %): 145 ($M^+ - CH_3$); EI-HRMS: Calculated for $C_7H_{13}O_3$ ($M^+ - CH_3$): 145.086469: found: 145.086081.

4.4.13. Ethyl (2*E*,6*S*)-6,7-isopropylidenedioxy hept-2-enoate 36. A stirred solution of alcohol **34** (20 g, 0.125 mol) in DMSO (60 mL) at 0 °C was treated with IBX (38.5 g, 0.137 mol) in portions and allowed to stir at room temperature for 4 h. Work-up and purification as described for **16** gave (4*S*)-4,5-isopropylidenedioxy-1-pentanal **35** (16.0 g) in 81% yield as a light yellow liquid. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.35 (2s, 6H, CH_3), 1.6–2.1 (m, 2H, H-3), 2.6 (t, 2H, $J_{2,3} = 6.2$ Hz, H-2), 3.5 (t, 1H, $J_{4,5} = 6.2$ Hz, H-5), 3.98–4.2 (m, 2H, H-4, 5a), 9.8 (s, 1H, C*H*O).

A solution of aldehyde **35** (24 g, 0.15 mol) in benzene (250 mL) was treated with (carbethoxymethylene)triphenyl phosphorane (57.8 g, 0.167 mmol) and heated at reflux for 6 h. Work-up and purification as described for **17** afforded **36** (26.3 g) in 76% yield as a pale yellow liquid. $[\alpha]_D = +6.9$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (t, 3H, $J = 6.75$ Hz, CH_3), 1.32, 1.38 (2s, 6H, $2 \times CH_3$), 1.6–1.8 (m, 2H, H-5), 2.2–2.45 (m, 2H, H-4), 3.5 (t, 1H, $J = 6.75$ Hz, H-7), 3.95–4.25 (m, 4H, H-6, 7a, OCH_2), 5.8 (d, 1H, $J = 15.7$ Hz, H-2), 6.91 (dt, 1H, $J = 7.8$, 15.7 Hz, H-3); EIMS *m*/*z* (relative intensity in %): 213 ($M^+ - CH_3$, 65%), 125 (55%), 93 (20%), 81 (35%), 69 (100%).

4.4.14. (2*E*,6*S*)-6,7-Isopropylidenedioxy hept-2-ene-1-ol 10. A stirred solution of **36** (15 g, 65.7 mmol) in dry CH_2Cl_2 (80 mL) at −20 °C was treated with a solution of DIBAL-H (66 mL, 134 mmol; 2 M solution in hexane) dropwise. After 2 h, work-up and purification as described for **9** gave **10** (10.8 g) in 88% yield as a colourless liquid. $[\alpha]_D = +12.8$ (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.40 (2s, 6H, $2 \times CH_3$), 1.4–1.8 (m, 2H, H-5), 2.05–2.3 (m, 2H, H-4), 3.5 (t, 1H, $J = 7.95$ Hz, H-7), 3.95–4.2 (m, 4H, H-1, 6, 7′),

5.65–5.72 (m, 2H, H-2, 3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.60, 26.81, 28.26, 32.96, 63.20, 69.19, 75.38, 108.63, 129.68, 131.47; EIMS *m/z* (relative intensity in %): 171 ($M^+ - CH_3$, 45%), 101 (25%), 93 (50%), 67 (80%), 55 (50%), 43 (100%); EI-HRMS: Calculated for $C_9H_{15}O_3$ ($M^+ - CH_3$): 171.102120; found: 171.102318.

4.5. Synthesis of (2*R*,5*R*)-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 3

4.5.1. (2*R*,3*R*,6*S*)-2,3-Epoxy-6,7-isopropylidenedioxy heptan-1-ol 37. To a stirred and cooled (−20 °C) suspension of molecular sieves (4 Å, 3 g) in CH_2Cl_2 (10 mL) under an N_2 atmosphere, (−)-DIPT (28.7 g, 122 mmol) in CH_2Cl_2 (50 mL), Ti(O^{i}Pr)$_4$ (28.9 g, 122 mmol) and cumene hydroperoxide (31 g, 0.204 mmol; 80% solution in cumene) were added sequentially. After 20 min, the resulting mixture was treated with a solution of **10** (19 g, 102 mmol) in CH_2Cl_2 (50 mL). The reaction mixture, after 3 h, was worked-up and purified as described for **18** to furnish **37** (14.2 g) in 69% yield as a colourless liquid. $[\alpha]_D$ = +26.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34, 1.4 (2s, 6H, 2 × CH_3), 1.5–1.8 (m, 4H, H-4, 5), 2.35 (br s, 1H, OH), 2.85–3.0 (m, 2H, H-2, 3), 3.35–3.75 (m, 2H, H-1, 7), 3.75–3.90 (m, 1H, H-1), 3.98–4.18 (m, 2H, H-6, 7′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.59, 26.86, 28.25, 30.04, 55.81, 58.55, 61.75, 69.27, 75.71, 108.94; EIMS *m/z* (relative intensity in %): 187 ($M^+ - CH_3$, 20%), 143 (35%), 101 (50%), 83 (90%), 43 (100%); EI-HRMS: Calculated for $C_9H_{15}O_4$ ($M^+ - CH_3$): 187.097034; found: 187.096129.

4.5.2. (2*S*,3*R*,6*S*)-1-Chloro-2,3-epoxy-6,7-isopropylidenedioxy heptane 38. A stirred mixture of **37** (10.9 g, 53.9 mmol), Ph_3P (21.2 g, 80.9 mol) and $NaHCO_3$ (2 g) in CCl_4 (100 mL) was heated at reflux for 3 h. Work-up and purification was done as described for **19** gave **38** (10.4 g) in 88% yield as a colourless liquid. $[\alpha]_D$ = −17.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.4 (2s, 6H, 2 × CH_3), 1.62–1.72 (m, 4H, H-4, 5), 2.85–3.05 (m, 2H, H-2, 3), 3.4–3.6 (m, 3H, H-1, 7), 4.0–4.20 (m, 2H, H-6, 7′); EIMS *m/z* (relative intensity in %): 205 ($M^+ - CH_3$, 50%), 145 (10%), 101 (30%), 81 (40%), 72 (90%), 43 (100%).

4.5.3. (3*R*,6*S*)-3-Hydroxy-6,7-isopropylidenedioxy-hept-1-yne 7. To a solution of LDA [prepared from diisopropylamine (16.6 g, 160 mmol) and *n*-BuLi (109 mL, 0.165 mol; 1.5 N hexane solution)] in THF (50 mL), a solution of **38** (10.3 g, 47.1 mmol) in THF (25 mL) was added at −40 °C. After 3 h, work-up and purification as described for **5** gave **7** (6.9 g) in 80% yield as a yellow liquid. $[\alpha]_D$ = +23.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.36 (2s, 6H, 2 × CH_3), 1.62–1.88 (m, 4H, H-4, 5), 2.35 (d, 1H, *J* = 2.3 Hz, H-1), 3.5 (t, 1H, *J* = 4.7 Hz, H-7), 3.95–4.15 (m, 2H, H-6, 7′), 4.3–4.45 (m, 1H, H-3); EIMS *m/z* (relative intensity in %): 169 ($M^+ - CH_3$, 30%), 109 (15%), 82 (25%), 73 (40%), 44 (100%).

4.5.4. (3*R*,6*S*)-3-Acetoxy-6,7-isopropylidenedioxy-hept-1-yne 39. A solution of **7** (6.9 g, 37.5 mmol) and Et_3N (11.3 g, 112 mmol) in CH_2Cl_2 (50 mL) containing DMAP (catalytic) at 0 °C was treated with Ac_2O (5.7 g, 56.2 mmol) and stirred at room temperature for 30 min. Work-up and purification as described for **20** gave **39** (7.9 g) in 94% yield as a pale yellow liquid. $[\alpha]_D$ = +48.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34, 1.4 (2s, 6H), 1.6–2.05 (m, 4H, H-4, 5), 2.1 (s, 3H, OAc), 2.42 (d, 1H, *J* = 2.3 Hz, H-1), 3.52 (t, 1H, *J* = 5.8 Hz, H-7), 4.0–4.15 (m, 2H, H-6, 7′), 5.38 (dt, 1H, *J* = 5.7, 2.5 Hz, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.33, 25.20, 26.50, 28.53, 30.45, 62.87, 80.55, 108.40, 168.98. EIMS *m/z* (relative intensity in %): 211 ($M^+ - CH_3$, 21%), 109(16%), 91(20%), 43(100%); EI-HRMS Calculated for $C_{11}H_{15}O_4$ ($M^+ - CH_3$): 211.097034; found: 211.096451.

4.5.5. (3*R*,6*S*)-3-Acetoxy-6,7-dihydroxy-hept-1-yne 40. A mixture of compound **39** (7.9 g, 34.9 mmol) in 60% aq AcOH (60 mL) was stirred at room temperature for 12 h. Work-up and purification as described for **28** gave **40** (5.85 g) in 90% yield as a pale yellow liquid. $[\alpha]_D$ = +44.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45–1.62 (m, 2H, H-4), 1.7–2.0 (m, 2H, H-5), 2.05 (s, 3H, OAc), 2.45 (d, 1H, *J* = 1.5 Hz, H-1), 3.38 (dt, 1H, *J* = 6.5, 7 Hz, H-7), 3.5–3.8 (m, 2H, H-6, 7′), 5.35 (dt, 1H, *J* = 2.8, 5.1 Hz, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.87, 28.17, 30.73, 63.57, 66.55, 71.52, 73.91, 80.86, 170.04.

4.5.6. (3*R*,6*S*)-3-Acetoxy-6-hydroxy-7-*p*-toluenesulfonyloxy-hept-1-yne 41. A solution of **40** (5.9 g, 31.7 mmol) and Et_3N (6.38 g, 63.4 mmol) in CH_2Cl_2 (50 mL) at 0 °C was treated with *p*-TsCl (6.0 g, 31.5 mmol) and stirred at room temperature for 8 h. Work-up and purification as described for **22** gave **41** (7.65 g) in 71% yield as a yellow syrup. $[\alpha]_D$ = +35.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.5–1.65 (m, 2H, H-4), 1.7–2.1 (m, 2H, H-5), 2.10 (s, 3H, OAc), 2.4 (d, 1H, *J* = 2.2 Hz, H-1); 2.55 (s, 3H, Ar–CH_3), 3.8–4.05 (m, 3H, H-6, 7), 5.35 (dt, 1H, *J* = 1.1, 5.4 Hz, H-3), 7.35, 7.8 (2d, 4H, *J* = 7.9 Hz, Ar–H).

4.5.7. (2*R*,5*R*)-*trans*-5-Ethynyl-2-(hydroxymethyl)tetrahydrofuran 42. A solution of **41** (7.7 g, 22.6 mmol) in MeOH (50 mL) at room temperature was treated with K_2CO_3 (9.3 g, 67.3 mmol) and stirred for 2 h. Work-up and purification as described for **23** afforded **42** (2.14 g) in 75% yield as a colourless liquid. $[\alpha]_D$ = +8.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.98–2.35 (m, 4H, H-3, 4), 2.42 (d, 1H, *J* = 2.3 Hz, acetylenic), 3.6 (d, 2H, *J* = 4.7 Hz, OCH_2), 4.18–4.3 (m, 1H, H-2), 4.65–4.75 (m, 1H, H-5); EIMS *m/z* (relative intensity in %): 125 ($M^+ - H$, 10%), 95 (60%), 81 (35%), 67 (75%), 53 (65%), 43 (100%); EI-HRMS: Calculated for ($M^+ - H$) $C_7H_9O_2$: 125.060255; found: 125.060025.

4.5.8. (2*R*,5*R*)-*trans*-5-Ethynyl-2-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran 43. A solution of **42** (2.1 g, 16.6 mmol), Et_3N (6.06 g, 60 mmol) in CH_2Cl_2 (20 mL) was treated with *p*-TsCl (3.8 g, 20 mmol) and stirred at room temperature for 8 h. Work-up and purification as described for **22** gave **43** (3.26 g) in 70% yield as a yellow syrup. $[\alpha]_D$ = +5.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8–2.25 (m, 4H, H-3, 4), 2.35 (d,

1H, J = 2.2 Hz, acetylenic), 2.45 (s, 3H, Ar–CH_3), 4.0 (d, 2H, J = 4.6 Hz, OCH_2), 4.2–4.35 (m, 1H, H-2), 4.5–4.62 (m, 1H, H-5), 7.32 and 7.75 (2d, 4H, J = 9.0 Hz, Ar–H).

4.5.9. (2*R*,5*R*)-*trans*-2-Ethynyl-5-(*p*-fluorophenoxymethyl)-tetrahydrofuran 3. To a stirred suspension of NaH (0.55 g, 23.1 mmol) in DMF (10 mL) at 0 °C, 4-fluorophenol (1.74 g, 15.5 mmol) was added. After 15 min a solution of **43** (3.25 g, 11.6 mmol) in DMF (10 mL) was added and heated at 80 °C for 5 h. Work-up and purification as described for **1** afforded **3** (2.08 g) in 82% yield as a colourless liquid. $[\alpha]_D$ = +18.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.80–2.35 (m, 4H, H-3, 4′), 2.40 (d, 1H, J = 2.2 Hz, acetylenic), 3.95 (d, 2H, J = 5.4 Hz, OCH_2), 4.45 (quin, 1H, J = 4.3 Hz, H-2), 4.70–4.82 (m, 1H, H-5), 6.70–7.0 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.51, 33.09, 68.51, 70.53, 72.94, 77.01, 115.42, 115.64, 115.87, 116.10, 116.25, 154.89, 159.63; EIMS *m*/*z* (relative intensity in %): 220 (M^+, 20), 125 (10%), 112 (10%), 95 (100%), 81 (10%), 55 (20%), 67 (55%), 43 (80%); EI-HRMS: Calculated for (M^+) $C_{13}H_{13}FO_2$: 220.089958; found; 220.089897.

4.6. Synthesis of (2*S*,5*R*)-2-ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 4

4.6.1. (2*S*,3*S*,6*S*)-2,3-Epoxy-6,7-isopropylidenedioxy heptan-1-ol 44. To a stirred and cooled (−20 °C) suspension of molecular sieves (4 Å, 4 g), in CH_2Cl_2 (15 mL) under N_2 atmosphere, (+)-DIPT (18.1 g, 77.4 mmol) in CH_2Cl_2 (20 mL), $Ti(O^iPr)_4$ (19.1 mL, 64.54 mmol) and cumene hydroperoxide (19.6 mL, 103 mmol; 80% solution in cumene) were added sequentially. After 20 min, it was treated with a solution of **10** (12 g, 64.5 mmol) in CH_2Cl_2 (30 mL) dropwise and stirred for further 3 h at the same temperature. Work-up and purification as described for **18** furnished **44** (8.55 g) in 65% yield as a colourless liquid. $[\alpha]_D$ = −20.1 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.4 (2s, 6H, 2 × CH_3), 1.45–1.85 (m, 5H, H-4, 5, OH), 2.85–3.05 (m, 2H, H-2,3), 3.5 (t, 1H, J = 6.5 Hz, acetylenic), 3.65 (dd, 1H, J = 4.08, 12.2 Hz, H-1), 3.9 (dd, 1H, J = 3.06, 12.2 Hz, H-1′), 3.98–4.2 (m, 2H, H-6, 7′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.33, 26.31, 27.33, 29.87, 55.34, 58.41, 61.83, 69.12, 75.13, 100.84. EIMS *m*/*z* (relative intensity in %): 187 ($M^+ - CH_3$, 45%), 143 (15%), 101 (30%), 83 (95%), 43 (100%); EI-HRMS: Calculated for ($M^+ - CH_3$) $C_9H_{15}O_4$: 187.097034; found: 187.096927.

4.6.2. (2*R*,3*S*,6*S*)-1-Chloro-2,3-epoxy-6,7-isopropylidenedioxy heptane 45. A stirred mixture of **44** (6.0 g, 29.69 mmol), Ph_3P (9.69 g, 36.98 mmol) and $NaHCO_3$ (0.8 g) in CCl_4 (30 mL) was heated at reflux for 3 h. Work-up and purification as described for **19** gave **45** (6.1 g) in 95% yield as a colourless liquid. $[\alpha]_D$ = −10.2 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.4 (2s, 6H, 2CH_3), 1.6–1.82 (m, 4H, H-4, 5), 2.85–3.05 (m, 2H, H-2, 3), 3.35–3.55 (m, 2H, H-1, 7), 3.62 (dd, 1H, J = 4.5, 11.2 Hz, H-1′) 3.2–3.98 (m, 2H, H-6, 7′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.5, 26.8, 27.5, 29.5, 44.4, 57.1, 58.3, 69.1, 75.0, 108.8.

4.6.3. (3*S*,6*S*)-3-Hydroxy-6,7-isopropylidenedioxy-hept-1-yne 8. To a solution of LDA [prepared from diisopropylamine (11.8 g, 114.5 mmol) and *n*-BuLi (70 mL, 109 mmol; 1.5 N hexane solution)] in THF (100 mL), a solution of **45** (6.0 g, 27.4 mmol) in THF (20 mL) was added at −40 °C. After 3 h, work-up and purification as described for **5** furnished **8** (4.7 g) in 94% yield as a yellow liquid. $[\alpha]_D$ = +2.6 (*c* 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.4 (2s, 6H, 2 × CH_3) 1.6–198 (m, 4H, H-4, 5), 2.4 (d, 1H, J = 1.86 Hz, H-1), 3.5 (t, 1H, J = 6.9 Hz, H-7), 3.98–4.2 (m, 2H, H-6, 7′), 4.3–4.45 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.62, 26.84, 29.09, 33.85, 61.83, 69.24, 72.92, 75.55, 84.66, 109.01; EIMS *m*/*z* (relative intensity in %): 169 ($M^+ - CH_3$, 30%), 109 (25%), 81 (60%), 72 (25%), 55 (80%), 43 (100%); HRMS: Calculated for $C_9H_{13}O_3$ ($M^+ - CH_3$): 169.086469: found: 169.086063.

4.6.4. (3*S*,6*S*)-3-Acetoxy-6,7-isopropylidenedioxy-hept-1-yne 46. A solution of **8** (3.9 g, 21.7 mmol) and Et_3N (7.76 g, 76.9 mmol) in CH_2Cl_2 (40 mL) containing DMAP (catalytic) at 0 °C was treated with Ac_2O (3.65 mL, 38.48 mmol) and stirred at room temperature for 30 min. Work-up and purification as described for **20** gave **46** (4.15 g) in 83% yield as a pale yellow liquid. $[\alpha]_D$ = −30.5 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25, 1.35 (2s, 6H), 1.5–1.9 (m, 4H, H-4, 5), 2.02 (s, 3H, OCH_3), 2.35 (d, 1H, J = 2.3 Hz, H-1), 3.45 (t, 1H, J = 6.5 Hz, H-7), 3.9–4.1 (m, 2H, H-6, 7′), 5.25–5.4 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.54, 25.58, 26.89, 29.71, 30.88, 63.88, 69.12, 73.81, 75.99, 80.80, 108.93, 169.87.

4.6.5. (3*S*,6*S*)-3-Acetoxy-6,7-dihydroxy-hept-1-yne 47. A mixture of **46** (4.1 g) in 60% aq AcOH (20 mL) was stirred at room temperature for 12 h. Work-up and purification as described for **21** afforded **47** (3.1 g) in 92% yield as a pale yellow liquid. $[\alpha]_D$ = −49.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.5–1.65 (m, 2H, H-4), 1.75–2.10 (m, 2H, H-5), 2.10 (s, 3H, OAc), 2.45 (d, 1H, J = 2.7 Hz, H-1), 3.42 (dd, 1H, J = 6.3, 6.8 Hz, H-7), 3.55–3.78 (m, 2H, H-6, 7′), 5.38 (dt, 1H, J = 2.7, 5.0 Hz, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.87, 28.17, 30.73, 63.57, 66.55, 71.52, 73.91, 80.86, 170.04.

4.6.6. (3*S*,6*S*)-3-Acetoxy-6-hydroxy-7-*p*-toluenesulfonyloxy-hept-1-yne 48. A solution of **47** (4.3 g, 23.1 mmol) and Et_3N (4.65 g, 46.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C was treated with *p*-TsCl (4.4 g, 23.1 mmol) and stirred at room temperature for 8 h. Work-up and purification as described for **22** gave **48** (5.34 g) in 68% yield as a yellow syrup. $[\alpha]_D$ = −28.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.5–1.65 (m, 2H, H-4), 1.7–2.08 (m, 2H, H-5), 2.10 (s, 3H, OAc), 2.43 (d, 1H, J = 1.86 Hz, H-1) 2.55 (s, 3H, Ar–CH_3), 2.60 (br s, 1H, OH), 3.8–4.05 (m, 3H, H-6, 7, 7′), 5.35 (dt, 1H, J = 1.3, 6.9 Hz, H-3), 7.35, 7.80 (2d, 4H, J = 7.9 Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.87, 21.67, 27.92, 30.40, 63.25, 68.88, 73.83, 73.96, 127.95, 129.96, 145.12.

4.6.7. (2*S*,5*R*)-*cis*-5-Ethynyl-2-(hydroxymethyl)tetrahydrofuran 49. A solution of **48** (3.67 g, 10.77 mmol) in MeOH (50 mL) at room temperature was treated with K_2CO_3 (3.2 g, 23.18 mmol) and stirred for 2 h. Work-up and purification as described for **23** gave **49** (1.22 g) in 90% yield as a colourless liquid. $[\alpha]_D = -18.2$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.9–2.38 (m, 4H, H-3, 4), 2.45 (d, 1H, $J = 2.1$ Hz, acetylenic), 3.55 (dd, 1H, $J = 6.3$, 12.75 Hz, OCH_2), 3.72 (dd, 2H, $J = 3.8$, 12.75 Hz, OCH_2), 4.0–4.18 (m, 1H, H-2), 4.55–4.65 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.6, 29.64, 64.62, 68.33, 73.11, 80.7, 83.92; EIMS *m*/*z* (relative intensity in %): 125 ($M^+ - H$, 45%), 95 (15%), 81 (10%), 67 (80%), 53 (60%), 43 (100%); EI-HRMS: Calculated for ($M^+ - H$) $C_7H_9O_2$: 125.060255; found: 125.060105.

4.6.8. (2*S*,5*R*)-*cis*-5-Ethynyl-2-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran 50. A solution of **49** (1.3 g, 10.3 mmol) and Et_3N (5.2 g, 51.5 mmol) in CH_2Cl_2 (25 mL) was treated with *p*-TsCl (2.39 g, 12.57 mmol) and stirred at room temperature for 8 h. Work-up and purification as described for **22** gave **50** (2.36 g) in 82% yield as a yellow syrup. $[\alpha]_D = -12.9$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.8–2.25 (m, 4H, H-3, 4), 2.35 (d, 1H, $J = 2.2$ Hz, acetylenic), 2.45 (s, 3H, Ar–CH_3), 3.95–4.20 (m, 3H, H-2, OCH_2), 4.55–4.60 (m, 1H, H-5), 7.32 and 7.8 (2d, 4H, $J = 9.0$ Hz, Ar–H).

4.6.9. (2*S*,5*R*)-*cis*-2-Ethynyl-5-(4-fluorophenoxymethyl)tetrahydrofuran 4. To a stirred suspension of NaH (0.57 g, 23.86 mmol) in DMF (5 mL), a solution of **50** (3.34 g, 11.92 mmol) in DMF (5 mL) was added, followed by the addition of 4-fluorophenol (1.74 g, 15.5 mmol) in DMF (5 mL) and heated at 80 °C for 5 h. Work-up and purification as described for **1** gave **4** (1.57 g) in 60% yield as a colourless liquid. $[\alpha]_D = -15.1$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.0–2.35 (m, 4H, H-3, 4), 2.45 (d, 1H, $J = 2.2$ Hz, acetylenic), 3.92 (dd, 1H, $J = 4.5$, 9.0 Hz, OCH_2), 4.0 (dd, 1H, $J = 4.5$, 9.0 Hz, OCH_2), 4.35 (quin, 1H, $J = 4.6$ Hz, H-5), 4.65 (m, 1H, H-2), 6.85–7.05 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.24, 33.1, 68.45, 72.9, 79.9, 83.8, 71.28, 115.43, 115.52, 115.68, 115.89, 154.91, 159.66; EIMS *m*/*z* (relative intensity in %): 220 (M^+, 30), 112 (25%), 95 (100%), 67 (70%), 43 (30%); HRMS: Calculated for $C_{13}H_{13}O_2$ (M^+): 220.089958; found; 220.089905.

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