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Stereoselective synthesis of chiral tetrahydrofurans with potent 5-LO inhibitory activity☆

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Abstract—Chiral glyceraldehydes have been exploited for the design of convenient and scalable synthetic approaches to chiral tetrahydrofurans, which have potential as potent 5-lipoxygenase (5-LO) inhibitors. The synthesis of all four possible stereoisomers by a general methodology is reported; wherein the chirons derived from the glyceraldehyde derivatives on reaction with homopropargyl ether, cyclization and further reactions gave the targets.

1. Introduction

Bronchial asthma is characterized by both broncho constriction and airway inflammation, which leads to bronchial hyper responsiveness to various stimuli. Cysteinyl leukotrienes (LTs) have been implicated in bronchial constriction and submucosal odema of airways in asthmatics.[1] The relationship between inflammatory conditions and prostaglandins, thromboxanes and leukotrienes has been established.[1] Chiral tetrahydrofurans **1** and **3** have been explored for their action against 5-lipoxygenase (5-LO). These belong to the lignan family of 2,5-disubstituted tetrahydrofurans, with diverse substitution and a *trans*-juxtaposition of ring and substituents. Compound **1** is a highly selective and orally active leukotriene modulator that works by inhibiting the action of 5-lipoxygenase.[2,3] Previously we have reported several investigations aimed at optimizing the syntheses of the target molecules.[4] Herein, we report a flexible approach for the formal synthesis of **1** and **2** and the synthesis of **3** and **4** (Fig. 1) from (*S*)- and (*R*)-glyceraldehyde derivatives and homopropargyl alcohol (a C-4 synthon).

2. Results and discussion

Retrosynthetic analysis, as depicted in Scheme 1, suggests that **1**, **2**, **3** and **4** could be prepared from tetrahydrofurans **5**, **6**, **7** and **8**, which, in turn could be made from the propargylic carbinols **9** and **10** derived from **11** and **12**, respectively. Thus, the main strategy for the synthesis of **1**–**4** would be to convert **11** and **12** to diastereomeric carbinols, their cyclization and further transformations.

2.1. Synthesis of 1 and 2 from (*S*)-glyceraldehyde derivative 11

Accordingly, Wittig olefination of **11**[5] (Scheme 2) with (carbethoxymethylene)triphenyl phosphorane in MeOH gave **13** (85:15 *cis*:*trans*), which on hydrogenation with PtO_2 at room temperature furnished **14** in quantitative yield. Reduction of ester **14** with LAH in THF gave alcohol **15** (97%), which on iodoxybenzoic acid (IBX) oxidation in DMSO afforded aldehyde **16** (84%). Reaction of **16** with the lithium anion of 1-(4-methoxybenzyloxy)-3-butyne [prepared from 1-(4-methoxybenzyloxy)-3-butyne[6] and *n*-BuLi] in dry THF afforded **9** (55%) as an inseparable 1:1 mixture of diastereoisomers, which was used as such in further reactions. Carbinol **9** on treatment with Ac_2O and Et_3N in CH_2Cl_2 at room temperature furnished **17** (77%), which on hydrolysis with 60% aq AcOH at room temperature, afforded **18** (89%). Selective tosylation of diol **18** using *p*-TsCl and Et_3N in CH_2Cl_2 gave

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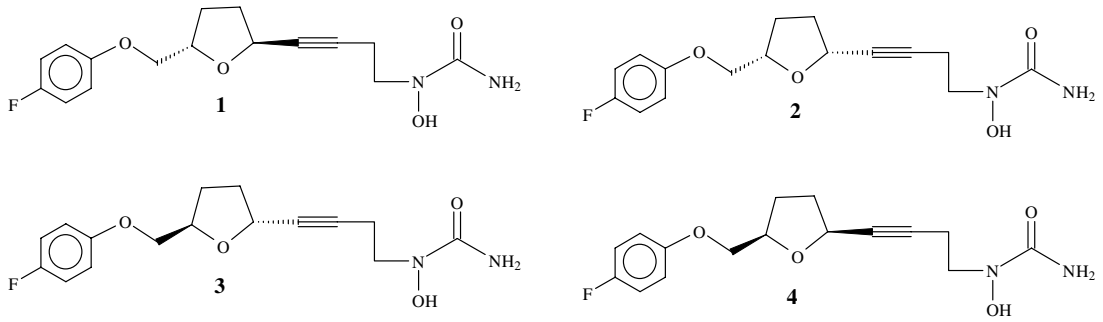
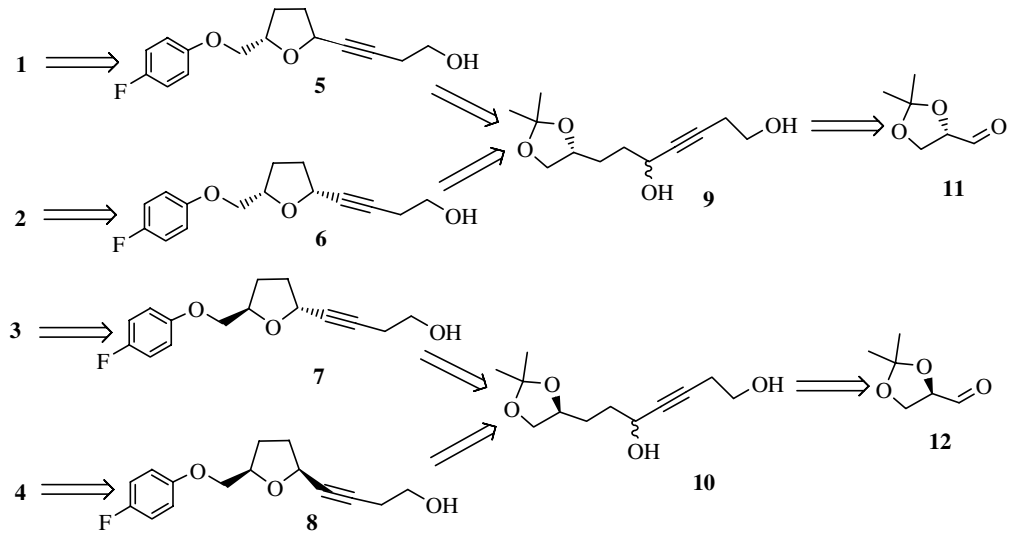


Figure 1.



Scheme 1.

monotosylate **19** (77%), which on treatment with K_2CO_3 in methanol at room temperature gave the desired tetrahydrofuran **20** as a diastereomeric mixture. Alcohol **20** was subjected to tosylation with *p*-TsCl and Et_3N to give **21** (78%), which on subsequent reaction with 4-fluorophenol and NaH in DMF at 80 °C furnished **22** (66%).

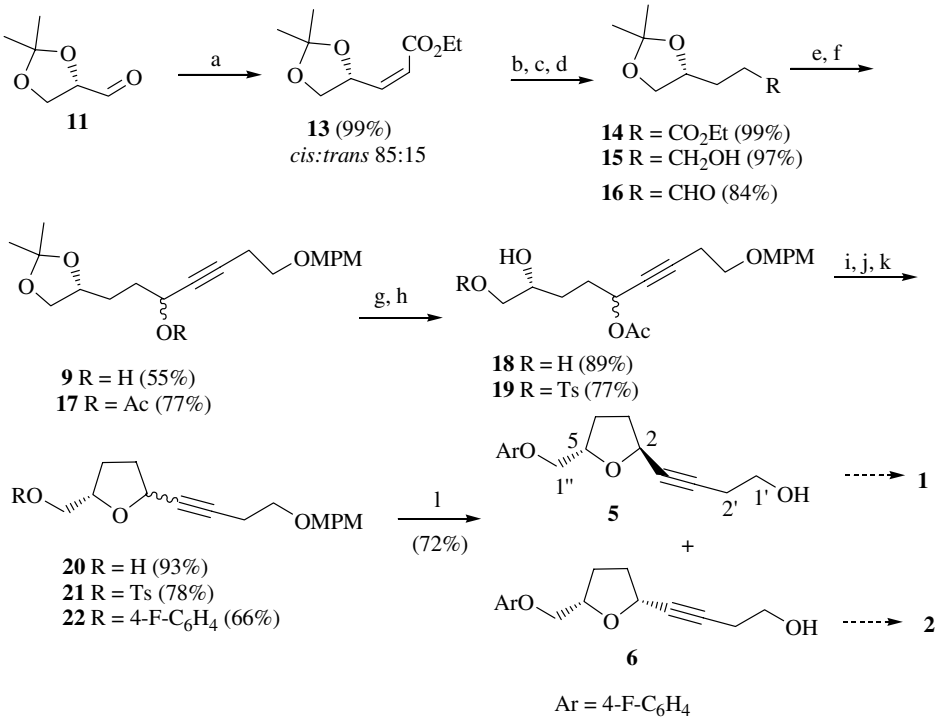
Treatment of tetrahydrofuran **22** with DDQ[7] in CH_2Cl_2–H_2O (19:1 ratio) afforded the corresponding hydroxy compounds **5** and **6**, separable by column chromatography (silica gel, finer than 200 mesh, 20% EtOAc in petroleum ether), in 72% overall yield (~1:1 ratio). The splitting pattern of the $-CH_2OAr$ group in the ^1H NMR of **5** and **6** was found to be distinctively different. For example, the methylene protons in *cis*-acetylene **6** resonated at δ 3.93 and 4.05 as double doublets, while for **5** (*trans*) the same protons appeared at δ 3.97 as a doublet. The conversion of these enantiomerically pure products **5** and **6** to targets **1** and **2**, is well established in the literature[4a] and formally completes the synthesis of **1** and **2**.

2.2. Synthesis of 3 and 4 from (*R*)-glyceraldehyde derivative 12

The synthesis of **3** and **4** was initiated from **12**. Thus, the known ester **23**,[8] prepared from **12** (Scheme 3), on catalytic hydrogenation and reduction afforded **25**. IBX oxidation of **25** gave **26** (84%), which on reaction with the lithium anion of 1-(4-methoxybenzyloxy)-3-butyne in THF gave **10** as an inseparable (1:1) mixture. Acetylation (Ac_2O, Et_3N) of **10** gave acetate **27**, which on acid hydrolysis (60% aq AcOH), afforded diol **28** (83%). Selective tosylation of **28** furnished **29** (81%), which on cyclization gave **30**. Reaction of **30** with *p*-TsCl and Et_3N, followed by further reaction of **31** with 4-fluorophenol and NaH in DMF furnished **32** (94%). Further, oxidative deprotection of PMB in **32** with DDQ afforded a separable mixture of **7** and **8** (79%; ~1:1 ratio). In the ^1H NMR of **8** and **7**, the methylene ($-CH_2OAr$) protons resonated at δ 3.99/4.11 as two double doublets and δ 3.94 (doublet), respectively, which is characteristic of *cis* and *trans* compounds. Reaction of **7** and **8** with *N*,*O*-bis-(phenoxycarbonyl)hydroxylamine[9] in the presence of Ph_3P and DIAD, under Mitsunobu[10] reaction conditions, furnished **33** and **34**, respectively. Finally, ammonolysis[9] of **33** and **34** with aq NH_4OH afforded targets **3** and **4**.

3. Conclusion

In conclusion, the synthesis of chiral furans **1**–**4** has been achieved from (*S*)- and (*R*)-glyceraldehyde derivatives



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, MeOH, 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) 1-(4-methoxybenzyloxy)-3-butyne, *n*-BuLi, −78 °C to rt, 2 h; (f) Ac_2O, Et_3N, CH_2Cl_2, rt, 0.5 h; (g) 60% aq AcOH, rt, 12 h; (h) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 10 h; (i) K_2CO_3, MeOH, rt, 3 h; (j) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (k) 4-FC_6H_4OH, NaH, DMF, 80 °C, 5 h; (l) DDQ, aq CH_2Cl_2 (19:1), rt, 5 h.

11 and **12**, respectively. The formal synthesis of **1** and **2**, and the total synthesis of **3** and **4** for a large scale preparation has been well established by a flexible approach from (*S*)- and (*R*)-glyceraldehyde derivatives and provides the data base for all four possible stereoisomers for their evaluation.

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*Z*,4*R*)-4,5-isopropylidenedioxy-2-pentenoate 13

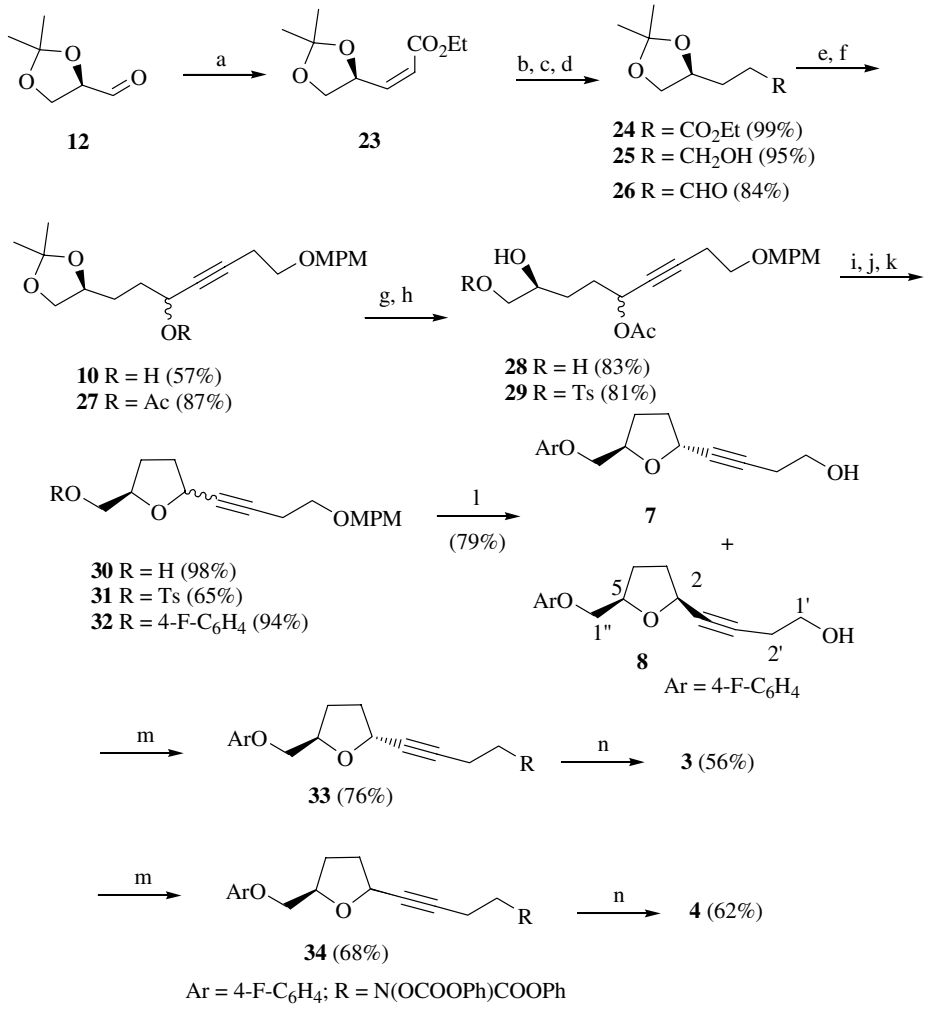
A solution of **11** (15 g, 115.4 mmol) in MeOH (150 mL) at 10 °C was treated with (carbethoxymethylene)triphenyl phosphorane (48.1 g, 138.4 mmol) in portions. After stirring at room temperature for 9 h, the solvent was evaporated and the residue purified by column chromatography (silica gel, 10% EtOAc in petroleum ether) to give **13** (23 g) in 99% yield (85:15 *cis*:*trans*) as a pale yellow liquid. Compound *cis*-**13**: $[\alpha]_D = -116.3$ (*c* 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.2 (t, 3H, *J* = 6.8 Hz, CH_3), 1.3, 1.35 (2s, 6H, CH_3), 3.5 (dd, 1H, *J* = 5.9 Hz, H-5), 4.07 (q, 2H, *J* = 6.8 Hz, –OCH_2), 4.27 (dd, 1H, *J* = 5.9 Hz, H-5a), 5.32–5.43 (m, 1H, H-4), 5.72 (dd, 1H, *J* = 2.2, 11.3 Hz, H-2), 6.27 (dd, 1H, *J* = 5.4, 11.3 Hz, H-3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.0, 25.2, 26.3, 60.1, 69.21, 73.3, 109.4, 120.5, 149.1, 165.3; EIMS *m*/*z* (relative intensity in %): 185 (M^+-CH_3, 15), 173 (6), 149 (23), 125 (20), 97 (45), 43 (100); HRMS: Calculated for $C_9H_{13}O_4$ (M^+-CH_3): 145.086469; Observed: 145.087162.

4.2. Ethyl (4*R*)-4,5-isopropylidenedioxy-1-pentanoate 14

A solution of **13** (23 g, 115 mmol) in EtOAc (50 mL) was treated with PtO_2 (0.100 g, 0.44 mmol) and hydrogenated till there was no additional consumption of hydrogen (4 h). The reaction mixture was filtered and concentrated to afford **14** (23 g) in 99% yield as a colourless liquid. $[\alpha]_D = -4.0$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, 3H, *J* = 6.8 Hz, CH_3), 1.29, 1.32 (2s, 6H, CH_3), 1.75–1.89 (m, 2H, H-3), 2.3–2.45 (m, 2H, H-2), 3.5 (t, 1H, *J* = 6.5 Hz, H-5), 3.92–4.15 (m, 4H, H-4, 5a, OCH_2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0, 25.4, 26.8, 28.6, 30.2, 60.1, 68.8, 74.7, 108.7, 172.6. EIMS *m*/*z* (relative intensity in %): 203 (M^++H, 23), 173 (16.4), 143 (13.4), 101 (100), 43 (97); HRMS: Calculated for $C_8H_{13}O_4$ (M^+-29): 173.081384; Observed: 1173.081619.

4.3. (2*R*)-1,2-Isopropylidenedioxy-5-pentanol 15

A suspension of LAH (4.93 g, 130.4 mmol) in THF (50 mL) was cooled to 0 °C and treated dropwise with



Scheme 3. 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) 1-(4-methoxybenzyloxy)-3-butyne, *n*-BuLi, −78 °C to rt, 2 h; (f) Ac_2O, Et_3N, CH_2Cl_2, rt, 0.5 h; (g) 60% aq AcOH, rt, 12 h; (h) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 10 h; (i) K_2CO_3, MeOH, rt, 3 h; (j) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; (k) 4-FC_6H_4OH, NaH, DMF, 80 °C, 5 h; (l) DDQ, aq CH_2Cl_2 (19:1), rt, 5 h; (m) DIAD, Ph_3P, PhCOONHCOOPh, dry THF, 0 °C to rt, 1 h; (n) NH_4OH, MeOH, rt, 3 h.

a solution of **14** (22 g, 108.9 mmol) in THF (75 mL). The reaction mixture was warmed to room temperature, allowed to stir for 3 h and then treated with a saturated solution of Na_2SO_4 (15 mL). After stirring for an additional 30 min, it was filtered through Celite and washed with EtOAc (3 × 75 mL). The combined organic layers were washed with NaCl solution (2 × 25 mL) and evaporated to give **15** (17 g) in 97% yield as a colourless liquid. $[\alpha]_D = -10.3$ (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.4 (2s, 6H), 1.6–1.75 (m, 4H, H-3, 4), 1.92 (br s, 1H, OH), 3.5 (t, 1H, $J = 6.1$ Hz, H-1), 3.6–3.72 (m, 2H, H-5), 3.98–4.16 (m, 2H, H-1a, 2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.6, 26.8, 29.0, 30.1, 62.4, 69.4, 75.9, 108.8; EIMS *m/z* (relative intensity in %): 145 (M^+-CH_3, 13.4), 85 (32), 72 (18), 57 (13.4), 43 (100); HRMS: Calculated for $C_7H_{13}O_3$ (M^+-CH_3): 145.086468; Observed: 145.087162.

4.4. (2*R*,5*RS*)-5-Hydroxy-1,2-isopropylidenedioxy-9-(4-methoxybenzyloxy)non-6-yne 9

A stirred solution of **15** (0.80 g, 5.00 mmol) in dry DMSO (5 mL) at 0 °C was treated with IBX (1.47 g, 5.25 mmol) in portions. The reaction mixture was stirred at room temperature for 4 h, treated with saturated aq $NaHCO_3$ solution (15 mL), filtered through Celite and washed with solvent ether (3 × 30 mL). Two layers were separated and the organic layer washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. Evaporation of solvent gave (4*R*)-4,5-isopropylidenedioxy-1-pentanal **16** (0.663 g) in 84% yield as a yellow liquid, which was used as such for further reaction.

A stirred solution of 1-(4-methoxybenzyloxy)-3-butyne (4.47 g, 23.50 mmol) in dry THF (10 mL) at −78 °C was treated with *n*-BuLi (16.78 mL, 23.5 mmol, 1.4 M hexane solution). After 30 min, a solution of **16** (3.10 g, 19.60 mmol) in THF (10 mL) was added dropwise at −78 °C and stirred at room temperature for 2 h. The reaction mixture was quenched with aq NH_4Cl solution (25 mL) and EtOAc (50 mL) then added and stirred for 10 min. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, evaporated and the residue purified by column

chromatography (silica gel, 25% EtOAc in petroleum ether) to furnish **9** (3.75 g) in 55% yield as a pale yellow syrup. $[\alpha]_D = -13.4$ (*c* 0.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.40 (2s, 6H, $-CH_3$) 1.60–1.87 (m, 5H, H-3, 4, –OH), 2.49 (dt, 2H, $J = 2.10$, 8.60 Hz, H-8), 3.44–3.58 (m, 3H, H-1, 9), 3.80 (s, 3H, Ar–OCH_3), 3.95–4.15 (m, 2H, H-1a, 2), 4.30–4.42 (m, 1H, H-5), 4.46 (s, 2H, –OCH_2–Ar), 6.85, 7.22 (2d, 4H, $J = 7.50$ Hz, Ar–H); FABMS *m/z* (relative intensity in %): 348 (M^+, 12), 347 (40), 289 (26), 189 (100); HRMS: Calculated for $C_{20}H_{27}O_5$ (M^+-H): 347.185849. Found: 347.185567.

4.5. (2*R*,5*RS*)-5-Acetoxy-1,2-isopropylidenedioxy-9-(4-methoxybenzyloxy)non-6-yne 17

A solution of **9** (3.50 g, 10.05 mmol) and Et_3N (4.18 mL, 30.16 mmol) in CH_2Cl_2 (20 mL) containing DMAP (0.1 equiv) at 0 °C was treated with Ac_2O (1.13 mL, 12.06 mmol) dropwise and stirred at room temperature for 30 min. The reaction mixture was treated with saturated aq NH_4Cl solution (20 mL), diluted with CH_2Cl_2 (50 mL) and the organic layer separated. It was washed with water (2×30 mL), brine (40 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 25% EtOAc in petroleum ether) gave **17** (3.02 g) in 77% yield as a pale yellow liquid. $[\alpha]_D = -12.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.25, 1.40 (2s, 6H, $-CH_3$), 1.45–2.00 (m, 4H, H-3, 4), 2.05 (s, 3H, –OAc), 2.46 (d, 2H, $J = 1.30$, 6.90 Hz, H-8), 3.30–3.82 (m, 6H, H-1, 9, Ar–OCH_3), 3.88–4.25 (m, 2H, H-1a, 2), 4.42 (s, 2H, –OCH_2–Ar), 5.29–5.45 (m, 1H, H-5), 6.84, 7.22 (2d, 4H, $J = 8.90$ Hz, Ar–H); FABMS *m/z* (relative intensity in %): 413 (M^++Na, 10), 389 (M^+-1, 15), 375 (M^+-CH_3, 20), 331 (10), 272 (10), 215 (15), 121 (100), 43 (15); HRMS: Calculated for $C_{22}H_{29}O_6$ (M^+-H): 389.196414. Found: 389.195793.

4.6. (2*R*,5*RS*)-5-Acetoxy-1,2-dihydroxy-9-(4-methoxybenzyloxy)non-6-yne 18

A mixture of **17** (1.60 g, 4.10 mmol) and 60% aq AcOH (15 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralized with solid $NaHCO_3$, saturated aq $NaHCO_3$ solution (pH 7) and extracted with EtOAc (3×50 mL). The combined organic layers were evaporated and the residue purified by filtration through a small pad of silica gel with 50% EtOAc in petroleum ether solvent system to afford diol **18** (1.28 g) in 89% yield as a pale yellow syrup. $[\alpha]_D = -10.2$ (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.50–2.00 (m, 4H, H-3, 4), 2.05 (s, 3H, –OAc), 2.50 (dt, 2H, $J = 1.20$, 6.80 Hz, H-8), 3.30–3.82 (m, 7H, H-1, 9, –OCH_3), 4.09 (t, 1H, $J = 6.50$ Hz, H-2), 4.45 (s, 2H, –O*C*H_2–Ar), 5.30–5.44 (m, 1H, H-5), 6.85, 7.22 (2d, 4H, $J = 9.00$ Hz, Ar–H); FABMS *m/z* (relative intensity in %): 373 (M^++Na, 40), 349 (M^+-H, 18), 335 (M^+-CH_3, 45), 290 (15), 241 (20), 121 (100), 91 (5), 69 (8), 55 (10); HRMS: Calculated for $C_{18}H_{23}O_6$ (M^+-CH_3): 335.149464. Found: 335.149249.

4.7. (2*R*,5*RS*))-5-Acetoxy-2-hydroxy-9-(4-methoxybenzyloxy)-1-(*p*-toluenesulfonyloxy)non-6-yne 19

A solution of **18** (1.00 g, 2.85 mmol) in CH_2Cl_2 (15 mL) containing Et_3N (1.59 mL, 11.40 mmol) was cooled to 0 °C and treated with *p*-TsCl (0.65 g, 3.41 mmol) and stirred at room temperature for 10 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (2×20 mL). The organic layer was dried over Na_2SO_4, evaporated and purified the residue by column chromatography (silica gel, 25% EtOAc in petroleum ether) to afford **19** (1.10 g) in 77% yield as a yellow syrup. $[\alpha]_D = -8.7$ (*c* 0.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.45–1.90 (m, 4H, H-3, 4), 2.04 (s, 3H, –OAc), 2.40–2.52 (m, 5H, H-8, $-CH_3$), 3.52 (t, 2H, $J = 6.97$ Hz, H-9), 3.80 (s, 3H, Ar–OCH_3), 3.82–4.18 (m, 3H, H-1, 2), 4.45 (s, 2H, –OCH_2–Ar), 5.32 (t, 1H, $J = 10.00$ Hz, H-5), 6.83, 7.22 (2d, 4H, $J = 7.44$ Hz, Ar–H), 7.32, 7.78 (2d, 4H, $J = 8.30$ Hz, Ar–H).

4.8. (2*S*,5*RS*)-2-(Hydroxymethyl)-5-(1-(4-methoxybenzyloxy-3-butyn-4-yl)tetrahydrofuran 20

A solution of compound **19** (1.45 g, 2.87 mmol) in MeOH (20 mL) at room temperature was treated with K_2CO_3 (0.87 g, 6.30 mmol) and stirred for 3 h. It was treated with aq NH_4Cl solution (20 mL), evaporated MeOH and the residue extracted with EtOAc (3×50 mL). The organic layer was washed with water (2×50 mL), brine (40 mL), dried over Na_2SO_4 and evaporated. The obtained residue was purified by column chromatography (silica gel, 25% EtOAc in petroleum ether) to afford **20** (0.776 g) in 93% yield as a colourless liquid. $[\alpha]_D = -19.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–2.25 (m, 4H, H-3, 4), 2.48 (dt, 2H, $J = 0.72$, 7.14 Hz, H-2″), 3.52 (t, 3H, $J = 7.39$ Hz, H-1′, 1″) 3.60–3.78 (m, 1H, H-1′a), 3.78 (s, 3H, Ar–OCH_3), 3.95–4.10, 4.10–4.25 (2m, 1H, H-2), 4.44 (s, 2H, –OCH_2–Ar), 4.50–4.61, 4.61–4.71 (2m, 1H, H-5), 6.82, 7.22 (2d, 4H, $J = 9.00$ Hz, Ar–H); FABMS *m/z* (relative intensity in %): 313 (M^++Na, 65), 289 (M^+-H, 100), 259 (20), 241 (30), 182 (30), 154 (75), 137 (95); HRMS: Calculated for $C_{17}H_{21}O_4$ (M^+-H): 289.143984. Found: 289.143748.

4.9. (2*S*,5*RS*)-5-(1-(4-Methoxybenzyloxy-3-butyn-4-yl)-2-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran 21

A solution of **20** (0.77 g, 2.65 mmol) and Et_3N (1.10 mL, 7.95 mmol) in CH_2Cl_2 (10 mL) was treated with *p*-TsCl (0.61 g, 3.20 mmol) and stirred at room temperature for 8 h. Work-up and purification as described for **19** gave **21** (0.92 g) in 78% yield as a light yellow syrup. $[\alpha]_D = +7.2$ (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.22 (m, 4H, H-3, 4), 2.28–2.35 (m, 5H, H-2″, Ar–CH_3), 3.50 (t, 2H, $J = 7.10$ Hz, H-1″), 3.80 (s, 3H, Ar–OCH_3), 3.98 (d, 1H, $J = 4.80$ Hz, H-1′), 4.00–4.12 (m, 1H, H-1′a), 4.15–4.22 (m, 1H, H-2), 4.44 (s, 2H, –OCH_2–Ar), 4.45–4.62 (m, 1H, H-5), 6.84, 7.22 (2d, 4H, $J = 8.80$ Hz, Ar–H), 7.30, 7.80 (2d, 4H, $J = 8.20$ Hz, Ar–H); FABMS *m/z* (relative intensity in %): 467 (M^++Na, 55), 444 (M^+, 65), 443 (M^+-H, 80), 413 (15), 336 (25), 255 (50), 214 (60).

4.10. (2*RS*,5*S*)-5-(4-Fluorophenoxymethyl)-2-(1-(4-methoxybenzyloxy)-3-butyn-4-yl)tetrahydrofuran 22

To a stirred suspension of NaH (0.13 g, 3.15 mmol, 60% w/w dispersion in miner oil) and 4-fluorophenol (0.29 g, 2.50 mmol) in DMF (5 mL), a solution of **21** (0.94 g, 2.10 mmol) in DMF (3 mL) was added and allowed to stir at 80 °C for 5 h. The reaction mixture was cooled to room temperature and treated with aq NH_4Cl solution (10 mL). It was extracted with solvent ether (3 × 20 mL) and the combined organic layers washed with water (2 × 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, 5% EtOAc in petroleum ether) afforded **22** (0.536 g) in 66% yield as a pale yellow liquid. $[\alpha]_D = -9.2$ (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–2.35 (m, 4H, H-3, 4), 2.50 (dt, 2H, *J* = 1.02, 6.70 Hz, H-2′), 3.52 (t, 2H, *J* = 7.10 Hz, H-1′), 3.80 (s, 3H, Ar–OCH_3), 3.81–3.95 (m, 2H, H-1″), 4.00–4.15 (m, 1H, H-5), 4.48 (s, 2H, –OCH_2–Ar), 4.55–4.65, 4.65–4.80 (2m, 1H, H-2), 6.70–7.00 (m, 6H, Ar–H), 7.20–7.25 (m, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 384 (M^+, 5), 383 (M^+-H, 20), 243 (100), 183 (25), 165 (20), 91 (10), 69 (25), 55 (32); HRMS: Calculated for $C_{23}H_{24}FO_4$ (M^+-H): 383.165863. Found: 383.164866.

4.11. (2*S*,5*S*)-*trans*-5-(4-Fluorophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)tetrahydrofuran 5 and (2*R*,5*S*)-*cis*-5-(4-fluorophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)-tetrahydrofuran 6

To a stirred solution of compound **22** (0.45 g, 1.17 mmol) in CH_2Cl_2–H_2O (19:1) (10 mL), DDQ (0.4 g, 1.75 mmol) was added at 0 °C and allowed to stir for 5 h at room temperature. Saturated aq $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, evaporated and residue purified by column chromatography (silica gel, finer than 200 mesh, 20% EtOAc in petroleum ether) to give **5** and **6** overall in 72% yield. First eluted was **6** (0.11 g) as a colourless syrup. $[\alpha]_D = +14.3$ (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.76–2.30 (m, 4H, H-3, 4), 2.45 (dt, 2H, *J* = 1.20, 6.75 Hz, H-2′), 3.70 (t, 2H, *J* = 6.40 H-1′), 3.93 and 4.05 (2dd, 2H, *J* = 6.40, 9.60 Hz, H-1″), 4.15–4.36 (m, 1H, H-5), 4.56–4.69 (m, 1H, H-2), 6.78, 7.02 (m, 4H, Ar–H); FABMS: *m*/*z* (relative intensity in %) 264 (M^+, 50), 153 (35), 139 (80), 95 (90), 77 (75), 55 (90), 43 (100); HRMS: Calculated for (M^+) $C_{15}H_{17}FO_3$: 264.116173. Found: 264.116018.

Second eluted was **5** (0.113 g) as a white solid, mp 73–76 °C; lit.[4a] 77–79 °C. $[\alpha]_D = -32.8$ (*c* 1.0, $CHCl_3$); lit.[4a] $[\alpha]_D = -34.0$ (*c* 1.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.64–2.40 (m, 4H, H-6, 7), 2.53 (dt, 2H, *J* = 1.48, 6.66 Hz, H-2′), 3.75 (t, 2H, *J* = 6.6 Hz, H-1′), 3.97 (d, 2H, *J* = 5.30 Hz, H-1″), 4.40–4.62 (m, 1H, H-5), 4.70–4.85 (m, 1H, H-2), 6.80, 7.08 (m, 4H, Ar–H); FABMS *m*/*z* (relative intensity in %): 264 (M^+, 68), 153 (25), 139 (78), 95 (80), 55 (90), 43 (100); HRMS: Calculated for $C_{15}H_{17}FO_3$ (M^+): 264.116173. Found: 264.117053.

4.12. Ethyl (4*S*)-4,5-isopropylidenedioxy-1-pentanoate 24

A solution of **23** (20.0 g, 0.10 mol) in EtOAc (75 mL) was treated with PtO_2 (0.10 g) and subjected to hydrogenation at 40 psi pressure for 4 h. Work-up as described for **14** afforded **24** (20.0 g) in 99% yield as a colourless liquid. $[\alpha]_D = +5.0$ (*c* 2.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.10 Hz, –CH_3), 1.30, 1.45 (2s, 6H, –CH_3), 1.80–1.95 (m, 2H, H-3), 2.38–2.50 (m, 2H, H-2), 3.52 (t, 1H, *J* = 7.10 Hz, H-5), 4.00–4.20 (m, 4H, H-4, 5a, –OCH_2–). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found : C, 58.99; H, 8.92.

4.13. (2*S*)-1,2-Isopropylidenedioxy-5-pentanol 25

A cooled (0 °C) suspension of $LiAlH_4$ (3.74 g, 0.099 mol) in dry THF (75 mL) was treated dropwise with a solution of **24** (20.00 g, 0.099 mol) in dry THF (100 mL). After 3 h, work-up and purification as described for **15** gave **25** (15.05 g) in 95% yield as a colourless liquid. $[\alpha]_D = +12.1$ (*c* 2.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.30, 1.40 (2s, 6H, –CH_3), 1.60–1.80 (m, 5H, H-3, 4, –OH), 3.50 (t, 1H, *J* = 8.30 Hz, H-1), 3.60–3.70 (m, 2H, H-5), 4.00–4.18 (m, 2H, H-1a, 2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5, 26.7, 28.9, 30.0, 62.2, 69.3, 76.3, 108.8; EIMS: 145 (M^+-CH_3); HRMS: Calculated for $C_7H_{13}O_3$ (M^+-CH_3): 145.086469. Found: 145.086081.

4.14. (2*S*,5*R*/*S*)-5-Hydroxy-1,2-isopropylidenedioxy-9-(4-methoxybenzyloxy)non-6-yne 10

A stirred solution of **25** (0.80 g, 5.0 mmol) in dry DMSO (5 mL) at 0 °C was treated with IBX (1.47 g, 5.25 mmol) and stirred at room temperature for 4 h. Work-up as described for **16** gave (4*S*)-4,5-isopropylidenedioxy-1-pentanal **26** (0.663 g) in 84% yield as a yellow liquid.

A stirred solution of 1-(4-methoxybenzyloxy)-3-butyne (1.0 g, 5.30 mmol) in dry THF (5 mL) at −78 °C was treated with *n*-BuLi (3.80 mL, 5.30 mmol; 1.4 M hexane solution). After 30 min, a solution of **26** (0.60 g, 3.80 mmol) in dry THF (5 mL) was added dropwise and stirred for 2 h at room temperature. Work-up and purification by column chromatography (silica gel, 25% EtOAc in petroleum ether) as described for **9** furnished **10** (0.75 g) in 57% yield as a pale yellow syrup. $[\alpha]_D = +11.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.40 (2s, 6H, –CH_3) 1.64–1.85 (m, 5H, H-3, 4, –OH), 2.50 (dt, 1H, *J* = 2.10, 8.60 Hz, H-8), 3.45–3.58 (m, 3H, H-1, 9), 3.80 (s, 3H, Ar–OCH_3), 3.98–4.18 (m, 2H, H-1a, 2), 4.32–4.44 (m, 1H, H-5), 4.46 (s, 2H, –OCH_2–Ar–), 6.85, 7.25 (2d, 4H, *J* = 7.50 Hz, Ar–H); FABMS *m*/*z* (relative intensity in %): 348 (M^+, 12), 347 (40), 289 (26), 189 (100); HRMS: Calculated for $C_{20}H_{27}O_5$ (M^+-H): 347.185849. Found: 347.185567.

4.15. (2*S*,5*RS*)-5-Acetoxy-1,2-isopropylidenedioxy-9-(4-methoxybenzyloxy)non-6-yne 27

A solution of **10** (0.70 g, 2.01 mmol) and Et_3N (0.84 mL, 6.03 mmol) in CH_2Cl_2 (10 mL) containing DMAP (0.1 equiv) at 0 °C was treated with Ac_2O (0.23 mL, 2.41 mmol) and stirred at room temperature for 30 min. Work-up and purification by column chromatography (silica gel, 5% EtOAc in petroleum ether) as described for **17** afforded **27** (0.68 g) in 87% yield as a pale yellow syrup. $[\alpha]_D = +9.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.36, 1.42 (2s, 6H, $-CH_3$), 1.60–2.00 (m, 4H, H-3, 4), 2.10 (s, 3H, –OAc), 2.51 (dt, 2H, $J = 2.17$, 8.20 Hz, H-8), 3.45–3.60 (m, 3H, H-1, 9), 3.82 (s, 3H, Ar–OCH_3), 3.96–4.14 (m, 2H, H-1a, 2), 4.48 (s, 2H, –OCH_2–Ar), 5.32–5.45 (m, 1H, H-5), 6.86, 7.25 (2d, 4H, $J = 7.60$ Hz, Ar–H); FABMS *m*/*z* (relative intensity in %): 413 (M^++Na, 4), 391 (6), 337 (19), 253 (10), 143 (100).

4.16. (2*S*,5*RS*)-5-Acetoxy-1,2-dihydroxy-9-(4-methoxybenzyloxy)non-6-yne 28

A mixture of **27** (0.80 g, 2.05) and 60% aq AcOH (8 mL) was stirred at room temperature for 12 h. Work-up and purification as described for **18** afforded **28** (0.595 g) in 83% yield as a syrup. $[\alpha]_D = +6.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.46–1.65 (m, 2H, H-3), 1.69–2.00 (m, 2H, H-4), 2.09 (s, 3H, –OAc), 2.02–2.26 (br s, 2H, –OH), 2.50 (dt, 2H, $J = 2.08$, 8.17 Hz, H-8), 3.30–3.46 (m, 1H, H-1), 3.46–3.78 (m, 4H, H-1, 2, 9), 3.80 (s, 3H, Ar–OCH_3), 4.45 (s, 2H, –OCH_2–Ar–), 5.30–5.42 (m, 1H, H-5), 6.82, 7.20 (d, 4H, $J = 7.20$ Hz, Ar–H); FABMS *m*/*z* (relative intensity in %): 335 (M^+-CH_3, 12), 215 (5), 183 (28), 154 (64), 107 (100); HRMS: Calculated for $C_{18}H_{23}O_6$ (M^+-CH_3): 335.149464. Found: 335.149249.

4.17. (2*S*,5*RS*)-5-Acetoxy-2-hydroxy-9-(4-methoxybenzyloxy)-1-(*p*-toluenesulfonyloxy)non-6-yne 29

A solution of **28** (0.60 g, 1.71 mmol) and Et_3N (0.72 mL, 5.14 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with *p*-TsCl (0.327 g, 1.71 mmol) and stirred at room temperature for 10 h. Work-up and purification by column chromatography (silica gel, 20% EtOAc in petroleum ether) as described for **19** afforded **29** (0.69 g) in 81% yield as yellow syrup. $[\alpha]_D = +10.6$ (*c* 0.45, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.52–1.98 (m, 4H, H-3, 4), 1.98 (s, 3H, –OAc), 2.41–2.56 (m, 5H, H-8, Ar–CH_3), 3.34–3.72 (m, 2H, H-9), 3.80 (s, 3H, –OCH_3), 3.94–4.2 (m, 3H, H-1, 2), 4.45 (s, 2H, Ar–OCH_2–), 5.26–5.42 (m, 1H, H-5), 6.82, 7.21 (2d, 4H, $J = 7.90$ Hz, Ar–H), 7.26–7.30 (m, 2H, Ar–H), 7.62–7.82 (m, 2H, Ar–H).

4.18. (2*R*,5*RS*)-2-(Hydroxymethyl)-5-(1-(4-methoxybenzyloxy)-3-butyn-4-yl)tetrahydrofuran 30

To a solution of **29** (0.80 g, 1.58 mmol) in MeOH (15 mL), K_2CO_3 (0.482 g, 3.49 mmol) was added and stirred at room temperature for 3 h. Work-up and purification by column chromatography (silica gel, 25% EtOAc in petroleum ether) as described for **20** gave **30** (0.451 g) in 98% yield as a yellow syrup. $[\alpha]_D = +23.3$ (*c* 1.85, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.87–2.26 (m, 4H, H-3, 4), 2.26–2.42 (br s, 1H, –OH), 2.49 (dt, 2H, $J = 1.15$, 7.69 Hz, H-2), 3.40–3.60 (m, 3H, H-1′, 1″), 3.62–3.78 (m, 1H, H-1a), 3.80 (s, 3H, –OCH_3), 3.98–4.12, 4.12–4.30 (2m, 1H, H-2), 4.48 (s, 2H, –OCH_2–), 4.52–4.62, 4.62–4.73 (2m, 1H, H-5), 6.86, 7.25 (2d, 4H, $J = 8.46$ Hz, Ar–H); FABMS *m*/*z* (relative intensity in %): 313 (M^++Na, 65), 289 (M^+-H, 100), 259 (20), 241 (30), 182 (30), 154 (75), 137 (95); HRMS: Calculated for $C_{17}H_{21}O_4$ (M^+-H): 289.143984. Found: 289.143748.

4.19. (2*R*,5*RS*)-5-(4-Methoxybenzyloxy)-3-butyn-4-yl)-2-(*p*-toluenesulfonyloxymethyl)tetrahydrofuran 31

A solution of **30** (0.45 g, 1.55 mmol) and Et_3N (0.65 mL, 4.65 mmol) in CH_2Cl_2 (10 mL) was treated with *p*-TsCl (0.32 g, 1.70 mmol). After 8 h, work-up and purification by column chromatography (silica gel, 25% EtOAc in petroleum ether) as described for **21** gave **31** (0.448 g) in 65% yield as a yellow syrup. $[\alpha]_D = -3.5$ (*c* 1.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.74–2.21 (m, 4H, H-3, 4), 2.39–2.49 (m, 2H, H-2″), 2.50 (s, 3H, Ar–CH_3), 3.50 (t, 2H, $J = 8.10$ Hz, H-1″), 3.79 (s, 3H, Ar–OCH_3), 3.97 (d, 1H, $J = 4.91$ Hz, H-1′), 4.02–4.15 (m, 1H, H-1′a), 4.20–4.30 (m, 1H, H-2), 4.44 (s, 2H, –OCH_2–Ar–), 4.50–4.60 (m, 1H, H-5), 6.82 (d, 2H, $J = 7.90$ Hz, Ar–H), 7.16–7.38 (m, 4H, Ar–H), 7.79 (d, 2H, $J = 7.90$ Hz, Ar–H); FABMS *m*/*z* (relative intensity in %): 467 (M^++Na, 2), 443 (M^+-H, 3), 121 (100), 107 (10), 91 (27), 55 (34); HRMS: Calculated for $C_{24}H_{24}O_6S$ (M^+-H): 443.152830. Found: 443.152732.

4.20. (2*RS*,5*R*)-5-(4-Fluorophenoxymethyl)-2-(1-(4-methoxybenzyloxy-3-butyn-4-yl)tetrahydrofuran 32

To a stirred suspension of NaH (0.04 g, 1.08 mmol, 60% w/w dispersion in mineral oil) in DMF (3 mL), a solution of **31** (0.40 g, 0.9 mmol) in DMF (3 mL) was added, followed by the addition of 4-fluorophenol (0.121 g, 1.08 mmol) in DMF (2 mL) and heated at 80 °C for 5 h. Work-up and purification by column chromatography (silica gel, 5% EtOAc in petroleum ether) as described for **22** afforded **32** (0.325 g) in 94% yield as a colourless syrup. $[\alpha]_D = +6.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.82–2.29 (m, 4H, H-3, 4), 2.42–2.58 (m, 2H, H-2′), 3.45–3.59 (m, 2H, H-1′), 3.81 (s, 3H, –OCH_3), 3.85–3.96 (m, 2H, H-1″), 4.00–4.14 (m, 1H, H-5), 4.47 (s, 2H, –OCH_2–Ar), 4.66–4.76, 4.76–4.82 (2m, 1H, H-2), 6.76–7.0 (m, 6H, Ar–H), 7.18–7.23 (m, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 384 (18), 383 (69), 369 (10), 313 (20), 121 (100); HRMS: Calculated for $C_{23}H_{24}FO_4$ (M^+-H): 383.165863. Found: 383.164866.

4.21. (2*R*,5*R*)-*trans*-5-(4-Fluorophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)tetrahydrofuran 7 and (2*S*,5*R*)-*cis*-5-(4-fluorophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)tetrahydrofuran 8

A mixture of **32** (0.30 g, 0.78 mmol) and DDQ (0.212 g, 0.937 mmol) in aq CH_2Cl_2 (10 mL, 1:19) was stirred at

room temperature for 5 h. It was worked-up and purified by column chromatography (silica gel, 200 mesh, 20% EtOAc in petroleum ether) as described for **5** and **6** to give **7** and **8** as a colourless syrup in 79% overall yield. First eluted was **8** (0.11 g) $[\alpha]_D = -12.8$ (*c* 0.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.88–2.38 (m, 4H, H-3, 4), 2.51 (dt, 2H, $J = 1.31$, 6.66 Hz, H-2′), 3.75 (t, 2H, $J = 6.66$ Hz, H-1′), 3.99, 4.11 (2dd, 2H, $J = 5.83$, 10.1 Hz, H-1″), 4.25–4.42 (m, 1H, H-5), 4.61–4.76 (m, 1H, H-2), 6.84–7.10 (m, 4H, Ar–H); FABMS *m*/*z* (relative intensity in %): 264 (M^+, 50), 153 (35), 139 (80), 95 (90), 77 (75), 55 (90), 43 (100); HRMS: Calculated for (M^+) $C_{15}H_{17}FO_3$: 264.116173. Found: 264.116018.

Second eluted was **7** (0.117 g) as a colourless syrup. Compound **7**: $[\alpha]_D = +31.9$ (*c* 0.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.78–2.38 (m, 4H, H-3, 4), 2.49 (dt, 2H, $J = 1.25$, 6.66 Hz, H-2′), 3.70 (t, 2H, $J = 7.50$ Hz, H-1′), 3.94 (d, $J = 5.0$ Hz, 2H, H-1″), 4.36–4.53 (m, 1H, H-5), 4.65–4.82 (m, 1H, H-2), 6.75, 7.05 (m, 4H, Ar–H); FABMS: 264 (M^+, 68), 153 (25), 139 (78), 95 (80), 55 (90), 43 (100); HRMS: Calculated for $C_{15}H_{17}FO_3$ (M^+): 264.116173. Found: 264.117053.

4.22. (2*R*,5*R*)-*trans*-5-(4-Fluorophenoxymethyl)-2-(1-*N*,*O*-bis(phenoxycarbonyl)hydroxylamino-3-butyn-4-yl)tetrahydrofuran 33

To a stirred solution of **7** (0.26 g, 1.0 mmol), *N*,*O*-bis-phenoxycarbonyl-hydroxylamine (0.409 g, 1.50 mmol) and Ph_3P (0.26 g, 0.99 mmol) in CH_2Cl_2 (10 mL), DIAD (0.30 g, 1.50 mmol) was added dropwise at 0 °C and stirred at room temperature 1 h. The reaction mixture was filtered through a silica gel column using CH_2Cl_2 as eluent and evaporated the solvent in vacuum to give **33** (0.39) in 76% yield as a pale yellow oil. $[\alpha]_D = +14.6$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.73–2.40 (m, 4H, H-3, 4), 2.70 (t, 2H, $J = 7.50$ Hz, H-2′), 3.88 (d, 2H, $J = 5.0$ Hz, H-1′), 4.0 (t, $J = 8.8$ Hz, 2H, H-1′), 4.30–4.52 (m, 1H, H-5), 4.62–4.80 (m, 1H, H-2), 6.70–7.02 (m, 4H, Ar–H), 7.10–7.55 (m, 10H, Ar–H); FABMS *m*/*z* (relative intensity in %): 520 (M^++H, 25), 519 (M^+, 10), 459 (48), 363 (10), 291 (30), 191 (100), 175 (60). Anal. Calcd for $C_{29}H_{26}FNO_7$: C, 66.92; H, 5.23. Found: C, 66.90; H, 5.22.

4.23. (2*S*,5*R*)-*cis*-5-(4-Fluorophenoxymethyl)-2-(1-*N*,*O*-bis(phenoxycarbonyl)hydroxylamino-3-butyn-4-yl)tetrahydrofuran 34

To a stirred solution of **8** (0.264 g, 1.00 mmol), *N*,*O*-bis(phenoxycarbonyl)hydroxylamine (0.409 g, 1.50 mmol), and Ph_3P (0.393 g, 1.50 mmol) in CH_2Cl_2 (10 mL) DIAD (0.30 g, 1.50 mmol) was added dropwise at 0 °C. After 1 h, it was worked-up as described for **33** to give **34** (0.352 g) in 68% yield as a pale yellow oil. $[\alpha]_D = -11.2$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.85–2.25 (m, 4H, H-3, 4), 2.70 (d, 2H, $J = 0.88$, 6.36 Hz, H-2′), 3.80–4.15 (m, 4H, H-1′, 1″), 4.15–4.35 (m, 1H, H-5), 4.52–4.68 (m, 1H, H-2), 6.72–6.98 (m, 4H, Ar–H), 7.08–7.48 (m, 10H, Ar–H); FABMS *m*/*z* (relative intensity in %): 518 (M^+−H, 55), 495 (15), 459 (28), 313 (90), 291 (75), 191 (40), 176 (32). Analysis for $C_{29}H_{26}FNO_7$: found: C, 66.85; H, 5.23.

4.24. (2*R*,5*R*)-*trans*-5-(4-Fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran 3

To a stirred solution of **33** (0.30 g, 0.572 mmol) in MeOH (10 mL), NH_4OH solution (10 mL) was added at room temperature. After 6 h, it was extracted with CH_2Cl_2 (3 × 20 mL) and washed with 5% NaOH solution (40 mL). The aqueous phase was cooled and acidified with concd HCl to pH 7–8. The resulting solid was filtered and washed with water. The crude product (solid) was dissolved in MeOH and heated at reflux with carbon (0.10 g) for 1 h. The solution was filtered and concentrated under vacuum to give **3** (0.104 g) in 56% yield as a gummy syrup. $[\alpha]_D = +43.9$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.90 (m, 1H, H-4), 1.90–2.12 (m, 1H, H-4a), 2.12–2.38 (m, 2H, H-3), 2.55 (dt, 2H, $J = 0.80$, 8.00 Hz, H-2′), 3.70 (t, 2H, $J = 6.40$ Hz, H-1′), 3.83–4.06 (m, 2H, H-1″), 4.4–4.55 (m, 1H, H-5), 4.68–4.80 (m, 1H, H-2), 5.30–5.50 (br s, 2H, $-NH_2$), 6.78–7.05 (m, 4H, Ar–H), 8.10–8.22 (br s, 1H, OH); IR (KBR): 3438, 3193, 2941, 1626, 1508 cm^{-1}; EIMS *m*/*z* (relative intensity in %): 323 (M^++H, 7), 280 (100), 264 (55). Anal. Calcd for $C_{16}H_{19}FN_2O_4$: C, 59.62; H, 5.94. Found: C, 59.57; H, 5.89.

4.25. (2*S*,5*R*)-*cis*-5-(4-Fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran 4

To a stirred solution of **34** (0.25 g, 0.48 mmol) in MeOH (5 mL), NH_4OH solution (10 mL) was added at room temperature and stirred for 6 h. Work-up as described for **3** gave a solid, which was dissolved in MeOH and heated at reflux with carbon (0.10 g) for 1 h, filtered and concentrated in vacuo to give **4** (0.096 g) in 62% yield. $[\alpha]_D = -51.0$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.80–2.35 (m, 4H, H-3, 4), 2.60 (dt, 2H, $J = 0.60$, 6.80 Hz, H-2), 3.60–3.90 (m, 3H, H-1′, 1″), 4.0 (dd, 1H, $J = 4.50$, 9.00 Hz, H-1′a), 4.24 (t, 1H, $J = 6.70$ Hz, H-5), 4.45–4.64 (m, 1H, H-2), 6.70–7.03 (m, 4H, Ar–H). EIMS *m*/*z* (relative intensity in %): 323 (M^++H, 10), 280 (100), 264 (65) Analysis for $C_{16}H_{19}FN_2O_4$: found: C, 59.58; H, 5.93.

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