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Stereoselective synthesis of (2*R*,3*S*,4*S*,5*R*)-*trans*-3,4-dihydroxy-5-(4-fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran and (2*R*,3*S*,4*S*,5*R*)-*trans*-5-ethynyl-2-(4-fluorophenoxymethyl)-3,4-*O*-isopropylidene tetrahydrofuran from mannose diacetonide☆

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Abstract—Stereoselective synthesis of pharmaceutically interesting chiral tetrahydrofurans starting from mannose diacetonide is reported. A 1,4-diol system derived from mannose diacetonide, through a Mitsunobu reaction was stereospecifically cyclized to give chiral tetrahydrofurans. Both the C-1 and C-4 centers of D-mannose are successfully exploited to install the requisite side chains.

1. Introduction

Currently significant effort is being directed in both the academic and industrial laboratories for the development of new anti-asthmatic agents with more efficacy and especially those that are orally active. Although several ground-breaking advances in understanding the pathology of asthma, and the subsequent discovery and synthesis of new drug targets have been reported,[1] the introduction of a completely safe and efficacious drug has remained elusive. Compounds, such as **1**, bearing a chiral tetrahydrofuran moiety, and several other 2,5-disubstituted tetrahydrofurans with biological activity have been found in nature or have been synthesized in the laboratory.[2] Pharmaceutical research aimed at the development of new drugs based on such chiral tetrahydrofurans has resulted in the synthesis[3] and testing of several analogues having potential 5-LO inhibitory activity.

To research further on the development of new chiral furans with potent activity, we report herein, starting

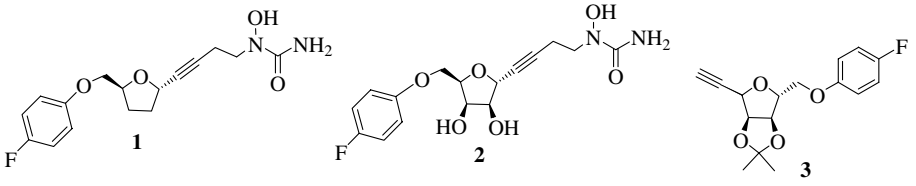

Figure 1.

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from mannose diacetonide, the first synthesis of **2** and **3**, which should be useful for building a library of compounds in this area (Fig. 1).

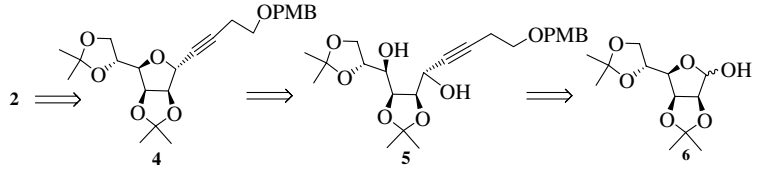
2. Results and discussion

Retrosynthetic analysis (Scheme 1) indicated that **2** could be synthesized from **4**, which in turn could be produced by a stereospecific cyclization of diol **5**. Furthermore, diol **5** should be obtainable from the easily accessible chiral starting material mannose diacetonide **6**. Thus, by making use of the lactol functionality in **6**, the diol for the cyclization could be made, while the C-2, 3 and 4 centers were retained in **2** and **3**.

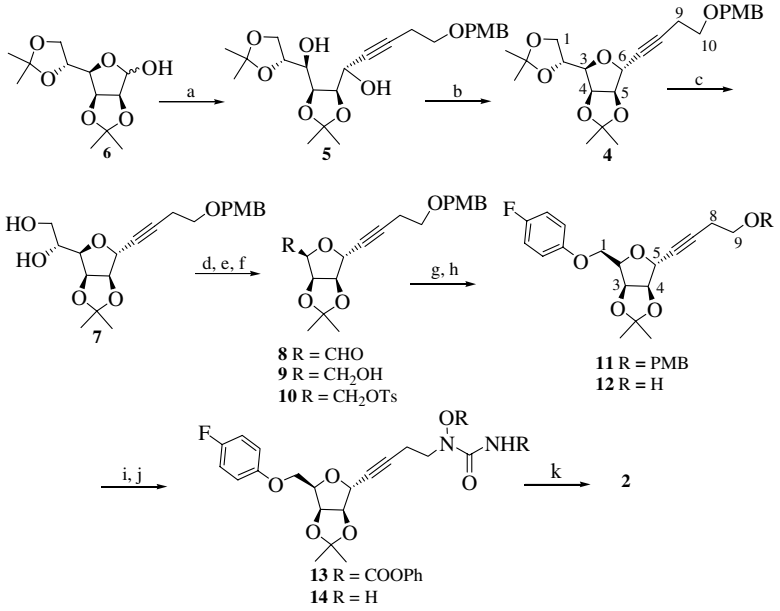
Accordingly, a reaction of the lithium anion of 1-(4-methoxybenzyloxy)-3-butyne (Scheme 2) [generated in situ on reaction of 1-(4-methoxybenzyloxy)-3-butyne **A**[4] and *n*-BuLi] in THF with **6** gave diol **5** (43%) in a 19:1 ratio.[5a,b] Diol **6**, on cyclization under Mitsunobu[6] reaction conditions (Ph_3P, DEAD) in dry THF, was found to be completely stereospecific[5c] and afforded **4** (93%), by an S_N2 mechanism. Acid (concd HCl) catalyzed deprotection of the acetonide group in **4** in aq MeOH at room temperature for 2 h furnished **7** (70%), which on oxidative cleavage with $NaIO_4$ and aq $NaHCO_3$ in CH_2Cl_2 gave aldehyde **8** (96%). Reduction of aldehyde **8** with $NaBH_4$ in MeOH afforded **9** in 60% yield. Tosylation of **9** with *p*-TsCl and Et_3N in CH_2Cl_2 in the presence of DMAP (cat) at room temperature afforded **10** (94%), which on reaction with 4-fluorophenol and NaH in DMF furnished **11** (75%). Oxidative deprotection of the PMB group in **11** using DDQ[7] in aq CH_2Cl_2 (1:19) at room temperature afforded **12** (69%), which was converted into the urea derivative in two steps.

Accordingly, alcohol **12** was treated with *N*,*O*-bis(phenyloxycarbonyl)hydroxylamine,[8] Ph_3P and DIAD in dry THF under Mitsunobu[6] conditions to give **13** in 99% yield, which on subsequent ammonolysis[8] with NH_4OH in MeOH afforded **14** in 66% yield. Finally, deprotection of the acetonide in **14** with catalytic concd HCl in MeOH at room temperature gave **2** in 78% yield, whose structure was ascertained by spectral analysis.

Having successfully completed the synthesis of dihydroxy tetrahydrofuran **2**, our focus was aimed at the development of a simple synthetic route for the acetylenic

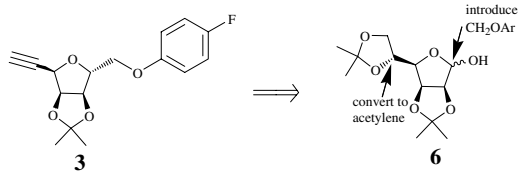


Scheme 1.



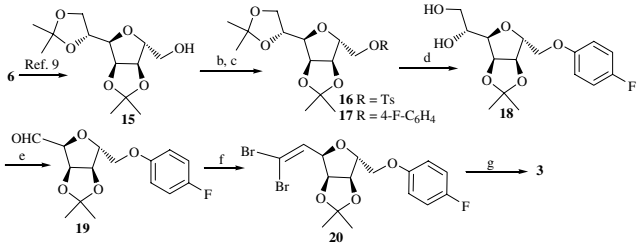
Scheme 2. Reagents and conditions: (a) 1-(4-methoxybenzyloxy)-3-butyne **A**, *n*-BuLi, −78 °C to rt, 1 h, 43%; (b) DEAD, Ph_3P, dry THF, rt, 1 h; 93%; (c) cat concd HCl, aq MeOH, rt, 2 h, 70%; (d) $NaIO_4$, aq $NaHCO_3$, CH_2Cl_2, rt, 5 h, 96%; (e) $NaBH_4$, MeOH, rt, 1 h, 60%; (f) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h, 94%; (g) 4-F–C_6H_4OH, NaH, DMF, 80 °C, 4 h, 75%; (h) DDQ, aq CH_2Cl_2, rt, 5 h, 69%; (i) DIAD, Ph_3P, PhCOONHCOOPh, dry THF, rt, 1 h, 99%; (j) NH_4OH, MeOH, rt, 3 h, 66%; (k) cat concd HCl, aq MeOH, 24 h, 78%.

system **3**, which would be useful for the synthesis of new chemical entities (NCEs). As shown in Scheme 3, from the retrosynthetic analysis, it was envisaged that **3** could be made from **6** by the transformations as indicated.



Scheme 3.

Accordingly, **6** (Scheme 4) on treatment with trimethyl sulfoxonium iodide in the presence of *t*-BuOK in DMSO afforded **15**.[9] Reaction of **15** with *p*-TsCl and Et_3N in CH_2Cl_2 gave **16**, which on etherification with 4-fluorophenol and NaH in dry DMF furnished **17** in 53% yield. Acetonide deprotection in **17** with catalytic concd HCl in aq MeOH at room temperature afforded diol **18**. Oxidative cleavage of **18** with $NaIO_4$ in the presence of aq $NaHCO_3$ in CH_2Cl_2 gave the corresponding aldehyde **19** (79%). Finally, aldehyde **19** on treatment with CBr_4 and Ph_3P in CH_2Cl_2 at room temperature afforded dibromo derivative **20**, which on *n*-BuLi induced double elimination gave **3** in 77% yield, whose structure was confirmed from a spectral study.



Scheme 4. Reagents and conditions: (a) $(CH_3)_3S^+OI^-$, *t*-BuOK, DMSO, rt, 1 h; (b) *p*-TsCl, Et_3N, CH_2Cl_2, rt, 8 h; 57%; (c) 4-F–C_6H_4OH, NaH, DMF, 80 °C, 5 h, 53%; (d) cat concd HCl, aq MeOH, rt, 2 h, 72%; (e) $NaIO_4$, aq $NaHCO_3$, CH_2Cl_2, rt, 5 h, 79%; (f) CBr_4, Ph_3P, CH_2Cl_2, rt, 30 min, 89%; (g) *n*-BuLi, THF, −78 °C to rt, 2 h, 77%.

3. Conclusion

In conclusion, mannose diacetonide **6** has been successfully utilized for the first, efficient synthesis of **2**, an analogue of **1**. Furthermore, a key acetylenic intermediate **3** was prepared from **6**, which is a very useful scaffold for the development of a variety of chiral tetrahydrofuran based NCEs and could lead to designed libraries of new glycosubstances of therapeutic importance.

4. Experimental section

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz) spectra were recorded in deuteriochloroform and DMSO-d_6 solutions 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. 4-(4-Methoxybenzyloxy)butyn-1-yl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside 4

To a stirred and cooled (−78 °C) solution of 1-(4-methoxybenzyloxy)-3-butyne **A** (0.365 g, 1.92 mmol) in dry THF (5 mL) under a nitrogen atmosphere, a solution of *n*-BuLi (1.37 mL, 1.92 mmol; 1.4 M hexane solution) was added and stirred for 30 min after which it was warmed to room temperature. A solution of **6** (0.5 g, 1.92 mmol) in dry THF (5 mL) was added dropwise at room temperature. After 1 h, the reaction mixture was quenched with NH_4Cl (5 mL) and extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford diol **5** (0.37 g) in 43% yield as a colourless syrup. $[\alpha]_D = -8.5$ (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.35, 1.40, 1.51 (4s, 12H), 2.48 (dt, 2H, $J = 6.9$, 2.3 Hz, H-9), 2.6–2.81 (br s, 2H, OH), 3.52 (t, 2H, $J = 6.9$ Hz, H-10), 3.7–3.76 (m, 1H, H-2), 3.78 (s, 3H, OCH_3), 3.9–4.1 (m, 3H, H-1, 3), 4.19–4.28 (m, 1H, H-5), 4.36–4.43 (m, 1H, H-4), 4.45 (s, 2H, OCH_2), 4.61–4.71 (m, 1H, H-6), 6.82, 7.21 (2d, 4H, $J = 8.8$ Hz, Ar–H). FABMS *m/z* (relative intensity): 473 (M^+ + Na, 26), 435 (14), 133 (24), 121 (100), 57 (36).

A solution of the above diol **5** (0.35 g, 0.78 mmol) in dry THF (5 mL) was treated with Ph_3P (0.813 g, 3.1 mmol) at room temperature. After 15 min, DEAD (0.04 g, 0.234 mmol) in THF (3 mL) was added dropwise and the mixture stirred for 1 h. The solvent was evaporated and the residue purified by column chromatography (silica gel, 10% EtOAc in hexane) to afford **4** (0.315 g) in 93% yield as a light yellow syrup. $[\alpha]_D = -11.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.39, 1.46, 1.47 (4s, 12H), 2.5 (dt, 2H, $J = 7.14$, 2.38 Hz, H-9), 3.54 (t, 2H, $J = 7.1$ Hz, H-10), 3.82 (s, 3H, OCH_3), 3.84–3.91 (m, 1H, H-3), 3.98–4.15 (m, 2H, H-1), 4.28–4.4 (m, 2H, H-2, 4), 4.49 (s, 2H, OCH_2), 4.64–4.82 (m, 2H, H-5, 6), 6.88, 7.26 (2d, 4H, $J = 8.8$ Hz, Ar–H). FABMS *m/z* (relative intensity %): 432 (M^+, 18), 431 (55), 417 (53), 343 (20), 121 (100).

4.2. 4-(4-Methoxybenzyloxy)butyn-1-yl 2,3-*O*-isopropylidene-α-D-mannofuranoside 7

A solution of **4** (0.3 g, 0.69 mmol) in aq MeOH (5:1, 6 mL) was treated with concd HCl (0.1 mL) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was treated with solid $NaHCO_3$ to neutralize the acid, filtered and washed with EtOAc (2 × 15 mL). The organic layer was dried over Na_2SO_4, evaporated and the residue obtained purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford **7** (0.19 g) in 70% yield as a pale yellow syrup. $[\alpha]_D = -10$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31,

1.4 (2s, 6H), 2.48 (dt, 2H, J = 6.97, 2.3 Hz, H-9), 3.52 (t, 2H, J = 6.97 Hz, H-10), 3.6–3.75 (m, 1H, H-2), 3.81 (s, 3H, OCH_3), 3.82–4.04 (m, 3H, H-1, 5), 4.46 (s, 2H, OCH_2), 4.65–4.76 (m, 2H, H-3, 4), 4.78–4.86 (m, 1H, H-6), 6.85, 7.22 (2d, 4H, J = 9.0 Hz, Ar–H). FABMS m/z (relative intensity %): 415 (M^+ + Na, 10), 121 (22), 95 (40), 69 (64), 55 (100).

4.3. 4-(4-Methoxybenzyloxy)butyn-1-yl-2,3-*O*-isopropylidene-α-D-lyxo-furanoside 9

A solution of **7** (0.17 g, 0.43 mmol) in CH_2Cl_2 (5 mL) containing saturated $NaHCO_3$ solution (0.1 mL) was treated with $NaIO_4$ (0.185 g, 0.86 mmol) portionwise at 0 °C and stirred at room temperature for 5 h. Solid Na_2SO_4 (0.5 g) was added, the mixture stirred for an additional 15 min, filtered and the solvent evaporated to afford 4-(4-methoxybenzyloxy)butyn-1-yl-2,3-*O*-isopropylidene-α-D-lyxo-pentadialdo-1,4-furanoside (**8**; 0.15 g) in 96% yield as a pale yellow syrup, that was immediately used for further reaction without additional purification.

To a stirred solution of the above alcohol **8** (0.15 g, 0.41 mmol) in MeOH (10 mL) $NaBH_4$ (0.015 g, 0.41 mmol) was added at 0 °C and stirred at room temperature for 1 h. MeOH was evaporated, residue dissolved in water (10 mL) and extracted with EtOAc (2 × 20 mL). The organic layer was washed with water (2 × 10 mL), dried over Na_2SO_4, evaporated and the residue obtained purified by column chromatography (silica gel, 25% EtOAc in hexane) to afford **9** (0.09 g) in 60% yield as a pale yellow syrup. $[\alpha]_D$ = +8.0 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.45 (2s, 6H), 2.48 (dt, 2H, J = 6.9, 2.32 Hz, H-8), 3.5 (t, 2H, J = 6.9 Hz, H-9), 3.81 (s, 3H, OCH_3), 3.84–3.93 (m, 2H, H-2, 3), 3.95–4.09 (m, 1H, H-4), 4.45 (s, 2H, OCH_2), 4.66–4.80 (m, 3H, H-1, 6), 6.85, 7.22 (2d, 4H, J = 8.8 Hz, Ar–H). FABMS m/z (relative intensity %): 385 (M^+ + Na, 4), 361 (4), 121 (50), 69 (74), 55 (100).

4.4. 4-(4-Methoxybenzyloxy)butyn-1-yl-2,3-*O*-isopropylidene-5-(*p*-toluenesulfonyl)-α-D-lyxo-furanoside 10

A solution of **9** (0.09 g, 0.25 mmol) and Et_3N (0.14 mL, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with *p*-TsCl (0.043 g, 0.25 mmol) and stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (2 × 15 mL), dried over Na_2SO_4, evaporated and the residue purified by column chromatography (silica gel, 15% EtOAc in hexane) to afford **10** (0.12 g) in 94% yield as a pale yellow syrup. $[\alpha]_D$ = −57 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22, 1.32 (2s, 6H), 2.35–2.53 (m, 5H, H-8, Ar–CH_3), 3.5 (t, 2H, J = 6.9 Hz, H-9), 3.8 (s, 3H, OCH_3), 4.05–4.2 (m, 2H, H-2, 3), 4.20–4.35 (m, 1H, H-4), 4.45 (s, 2H, OCH_2), 4.58–4.70 (m, 3H, H-1, 6), 6.85 (d, 2H, J = 8.8 Hz, ArH), 7.16–7.36 (m, 4H, Ar–H), 7.80 (d, 2H, J = 8.8 Hz, ArH). FABMS m/z (relative intensity %): 516 (M^+, 12), 515 (15), 155 (10), 121 (100), 91 (30).

4.5. 4-(4-Methoxybenzyloxy)butyn-1-yl-2,3-*O*-isopropylidene-5-(4-fluorophenyl)-α-D-lyxo-furanoside 11

A suspension of NaH (0.006 g, 0.28 mmol) in DMF (1 mL) at 0 °C was treated sequentially with a solution of 4-fluorophenol (0.031 g, 0.28 mmol) in DMF (2 mL) followed by a solution of **10** (0.12 g, 0.23 mmol) in DMF (2 mL) and stirred at 80 °C for 4 h. The reaction mixture was cooled to 0 °C, treated with a saturated solution of NH_4Cl (5 mL) and extracted with ether (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated to give **11** (0.08 g) in 75% yield as a pale yellow syrup. $[\alpha]_D$ = −35.8 (c 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.49 (2s, 6H), 2.50 (dt, 2H, J = 7.14, 2.8 Hz, H-8), 3.53 (t, 2H, J = 7.6 Hz, H-9), 3.81 (s, 3H, OCH_3), 3.98–4.36 (m, 3H, H-1, 2), 4.46 (s, 2H, OCH_2), 4.68–4.90 (m, 3H, H-3, 4, 5), 6.78–7.02 (m, 6H, Ar–H), 7.22 (d, 2H, J = 9.0 Hz, ArH).

4.6. 4-Hydroxybutyn-1-yl 2,3-*O*-isopropylidene-5-(4-fluorophenyl)-α-D-lyxo-furanoside 12

A mixture of **11** (0.08 g, 0.17 mmol) and DDQ (0.047 g, 0.21 mmol) in aq CH_2Cl_2 (10 mL; 1:19) was stirred at room temperature for 5 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (5 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with water (3 × 10 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 20% EtOAc in hexane) afforded **12** (0.04 g) in 69% yield as a pale yellow syrup. $[\alpha]_D$ = −18.5 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31, 1.46 (2s, 6H), 1.8–2.1 (br s, 1H, OH), 2.40–2.5 (m, 2H, H-8), 3.70 (t, 2H, J = 6.8 Hz, H-9), 4.04–4.36 (m, 3H, H-1, 2), 4.70–4.88 (m, 3H, H-3, 4, 5), 6.80–7.02 (m, 4H, Ar–H).

4.7. 4-*N*,*O*-Bis-(phenoxycarbonyl)hydroxylamine-1-butynyl-2,3-*O*-isopropylidene-5-(4-fluorophenyl)-α-D-lyxo-furanoside 13

To a stirred and cooled (0 °C) solution of **12** (0.3 g, 0.9 mmol), *N*,*O*-bis(phenoxycarbonyl)hydroxylamine (0.36 g, 1.35 mmol) and Ph_3P (0.37 g, 1.44 mmol) in CH_2Cl_2 (8 mL), DIAD (0.29 g, 1.44 mmol) was added dropwise. After stirring at room temperature for 1 h, the solvent was evaporated and residue purified by column chromatography (silica gel, 15% EtOAc in hexane) to afford **13** (0.5 g) in 99% yield as a pale yellow syrup. $[\alpha]_D$ = −3.5 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.49 (2s, 6H), 2.7–2.81 (m, 2H, H-8), 4.0–4.52 (m, 5H, H-1, 2, 9), 4.7–4.82 (m, 3H, H-3, 4, 5), 6.76–7.02 (m, 4H, Ar–H), 7.16–7.5 (m, 10H, ArH); FABMS m/z (relative intensity %): 614 (M^+ + Na, 7), 592 (M^+ + H, 35), 591 (M^+, 18), 576 ($M^+ - CH_3$, 7), 274 (100). HRMS: Calculated for $C_{32}H_{31}FNO_9$: 592.198285; found: 592.195641.

4.8. 4-*N*-Hydroxyureidyl-1-butynyl 2,3-*O*-isopropylidene-5-(4-fluorophenyl)-α-D-lyxo-furanoside 14

To a solution of **13** (0.5 g, 0.88 mmol) in MeOH (15 mL), NH_4OH (10 mL) was added and stirred at

room temperature for 3 h. MeOH was evaporated, diluted with water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and dried over Na_2SO_4. Evaporation of solvent and purification of residue by column chromatography (silica gel, 40% EtOAc in hexane) afforded **14** (0.218 g) in 66% yield as a pale yellow syrup. $[\alpha]_D$ = +65.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.46 (2s, 6H), 2.48–2.60 (m, 2H, H-8), 3.55–3.85 (m, 2H, H-9), 4.05–4.42 (m, 3H, H-1, 2), 4.72–4.90 (m, 3H, H-3, 4, 5), 5.31–5.52 (br s, 2H, NH_2), 6.80–7.05 (m, 4H, Ar–H); FABMS *m*/*z* (relative intensity %): 395 (M^+ + H, 5), 279 (7), 176 (5), 154 (13), 54 (14). HRMS: Calculated for $C_{19}H_{24}FN_2O_6$: 395.161840; found: 395.159948.

4.9. (2*R*,3*S*,4*S*,5*R*)-*trans*-3,4-Dihydroxy-5-(4-fluorophenoxymethyl)-2-(1-*N*-hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran 2

To a cooled (0 °C) and stirred solution of **14** (0.05 g, 0.126 mmol) in MeOH (9 mL) catalytic concd HCl (1 drop) was added followed by water (1 mL) and stirred at room temperature for 24 h. Solid $NaHCO_3$ was added to neutralize the reaction mixture and solvent evaporated. It was filtered and washed with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, EtOAc) to afford **2** (0.035 g) in 78% yield as a syrup. $[\alpha]_D$ = +14.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (DMSO, 200 MHz): δ 2.30–2.48 (m, 2H, H-2′), 3.80–4.15 (m, 4H, H-1), 4.18–4.31 (m, 2H, H-3, 4), 5.01–5.12 (m, 3H, H-5), 5.30 (d, 1H, *J* = 4.88 Hz, H-2), 6.30 (s, 2H, NH_2), 6.80–6.99 and 7.0–7.19 (2m, 4H, Ar–H), 9.38 (s, 1H, N–OH); FABMS *m*/*z* (relative intensity in %): 355 (M^+ + H, 7), 339 (5), 281 (9.5), 221 (12.9), 109 (100). Anal. Calcd for $C_{16}H_{19}FN_2O_6$: C, 54.24; H, 5.40. Found: C, 54.21; H, 5.38.

4.10. 3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-7-(*p*-toluenesulfonyl)-D-*glycero*-D-mannoheptitol 16

A solution of **15** (3.68 g, 13.4 mmol) and Et_3N (5.6 mL, 40.29 mmol) in CH_2Cl_2 (40 mL) at 0 °C, was treated with *p*-TsCl (3.83 g, 20.14 mmol) and stirred at room temperature for 8 h. Work-up and purification (silica gel, 15% EtOAc in hexane) as described for **10** afforded **16** (3.3 g) in 57% yield as a pale yellow syrup. IR (neat): 2950, 1580, 1210, 1175, 1005, 825 cm^{-1}; $[\alpha]_D$ = +9.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.27, 1.31, 1.37, 1.43 (4s, 12H), 2.48 (s, 3H), 3.75–3.88 (m, 2H, H-7), 3.90–4.10 (m, 3H, H-1, 3), 4.10–4.19 (m, 1H, H-6), 4.20–4.31 (m, 1H, H-2), 4.60–4.80 (m, 2H, H-4, 5), 7.33 (d, *J* = 8.7 Hz, 2H, Ar–H), 7.75 (d, *J* = 8.7 Hz, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 429 (M^+ + H, 38), 371 (12), 155 (30), 91 (46), 57 (100).

4.11. 3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-7-(4-fluorophenyl)-D-*glycero*-D-mannoheptitol 17

A solution of 4-fluorophenol (0.95 g, 8.44 mmol) in DMF (2 mL) was added to a suspension of NaH (0.611 g, 25.4 mmol) in DMF (3 mL) at 0 °C and then treated with a solution of **16** (3.3 g, 7.7 mmol) in DMF (5 mL) and stirred at 80 °C for 5 h. Work-up and purification (silica gel, 5% EtOAc in hexane) as described for **11** gave **17** (1.5 g) in 53% yield as a pale syrup. IR (neat): 2984, 1585, 1180, 1015, 835 cm^{-1}; $[\alpha]_D$ = −11.25 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40, 1.47, 1.56 (3s, 12H), 3.98–4.15 (m, 5H, H-1, 3, 7), 4.30–4.41 (m, 2H, H-2, 6), 4.81–4.95 (m, 2H, H-4, 5), 6.75–6.84 (m, 2H, Ar–H), 6.9–7.05 (m, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 369 (M^+ + H, 40), 311(30), 185 (26), 125 (100), 101 (100).

4.12. 3,6-Anhydro-4,5-*O*-isopropylidene-7-(4-fluorophenyl)-D-*glycero*-D-mannoheptitol 18

A solution of **17** (1.11 g, 3.01 mmol) in aq MeOH (5:1, 10 mL) was treated with concd HCl (0.2 mL) at 0 °C and stirred at room temperature for 4 h. Work-up and purification (silica gel, 50% EtOAc in hexane) as described for **7** afforded **18** (0.71 g) in 72% yield as a pale yellow syrup. IR (neat): 3241, 3010, 1572, 1150, 1030, 900 cm^{-1}; $[\alpha]_D$ = −11.33 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.55 (2s, 6H), 2.0 (br s, 2H, OH), 3.6–3.85 (m, 2H, 7), 3.92 (m, 1H, H-3), 4.0 (d, 2H, *J* = 4.54 Hz, H-1), 4.05–4.1 (m, 1H, H-2), 4.32–4.4 (m, 1H, H-6), 4.85–5.0 (m, 2H, H-4, 5), 6.73–6.85 (m, 2H, Ar–H), 6.9–7.05 (m, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 329 (M^+ + H, 8), 271(6), 109 (22), 69 (54), 57 (100).

4.13. (2*R*,5*R*) 5-(1,1′-Dibromoethylen-2-yl)–2-(4-fluorophenoxymethyl)-3,4-*O*-isopropylidene tetrahydrofuran 20

A solution of **18** (0.74 g, 2.25 mmol) in CH_2Cl_2 (10 mL) containing saturated $NaHCO_3$ solution (1.2 mL) was treated with $NaIO_4$ (0.48 g, 2.25 mmol) portionwise at 0 °C and stirred at room temperature for 5 h. Work-up and purification as described for **8** afforded 2,3-*O*-isopropylidene-5-(4-fluorophenyl)-D-*glycero*-D-lyxopentanedialdo-1,4-furanoside **19** (0.53 g) in 79% yield as a pale yellow syrup, which was used as such for further reaction immediately.

A solution of Ph_3P (2.32 g, 8.8 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of CBr_4 (1.03 g, 4.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C dropwise. After 15 min, a solution of **19** (0.53 g, 1.77 mmol) in CH_2Cl_2 (5 mL) was added and stirred at the same temperature for 30 min. The solvent was evaporated and the residue subjected to column chromatography (silica gel, 15% EtOAc in hexane) to afford **20** (0.69 g) in 89% yield as a pale yellow syrup. IR (neat): 2995, 1590, 1410, 1130, 890 cm^{-1}; $[\alpha]_D$ = −80 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34, 1.51 (2s, 6H), 3.91–4.11 (m, 2H), 4.29–4.35 (m, 1H), 4.74–4.91 (m, 3H, H-3, 4, 5), 6.58 (d, 1H, *J* = 7.5 Hz, H-6), 6.78–6.82 (m, 2H, Ar–H), 6.90–6.97 (m, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 453 (M^+ + H, 12), 147 (12), 125 (16), 95 (44), 81 (50), 69 (62), 59 (100).

4.14. (2*R*,3*S*,4*S*,5*R*)-*trans*-5-Ethynyl-2-(4-fluorophenoxymethyl)-3,4-*O*-isopropylidene tetrahydrofuran 3

A solution of **20** (0.65 g, 1.47 mmol) in THF (5 mL) was cooled to −78 °C and treated with *n*-BuLi (1.7 mL,

3.22 mmol; 2.0 M hexane solution). After 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. It was then quenched with NH_4Cl solution (5 mL) and extracted with EtOAc (2×25 mL), dried over Na_2SO_4 and evaporated. The residue obtained was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford **3** (0.32 g) in 77% yield as a pale yellow syrup. IR (neat): 3110, 2942, 1570, 1130, 830 cm^{-1}; $[\alpha]_D = -45.6$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.39, 1.59 (2s, 6H), 2.54 (d, 1H, $J = 1.5$ Hz, H-7), 4.0 (t, 2H, $J = 3.48$ Hz, H-1, 1′), 4.35 (m, 1H, H-2), 4.79–4.90 (m, 3H, H-3, 4, 5), 6.70–6.80 (m, 2H, Ar–H), 6.85–6.95 (m, 2H, Ar–H); FABMS *m*/*z* (relative intensity in %): 293 ($M^+ + H$, 10), 259 (50), 191 (10), 71 (20), 57 (100).

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