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Stereoselective synthesis of C-alkyl and functionalised C-alkyl glycosides using 'thiophene' as a masked C-4 synthon†

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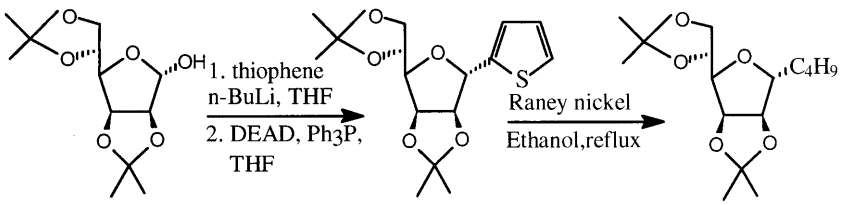
Abstract

Synthesis of C-alkyl and functionalised C-alkyl glycosides is achieved by desulphurisation of the corresponding thiophene glycosides, wherein 'thiophene' is utilised as a masked four-carbon synthon. Thiophene glycosides in turn were prepared from the corresponding sugar lactols.

1. Introduction

Stereoselective synthesis of C-glycosides[1] gains wide attention since they hold significant therapeutic[2,3] promise and usefulness in metabolic studies due to hydrolytic tolerance and as partial structures of several complex nucleosides[4] and natural products.[5] In particular, the utility of C-alkyl glycosides could be perceived as potential non-ionic detergents[6] in solubilisation and isolation of membrane proteins,[7] in addition to their unique liquid crystalline properties,[7] making them valuable synthetic targets. Alkyl glycosyl amino acids[8] as mimics of naturally occurring glycopeptides have enhanced the importance of these classes of compounds. In a continuation of our studies on the synthesis of C-glycosides[9,10] and C-saccharides[11] herein we describe the use of thiophene as a four-carbon masked synthon for the preparation of C-butyl glycosides (Eq. (1) and Table 1) and terminally functionalised C-alkyl mannosides (Scheme 1).



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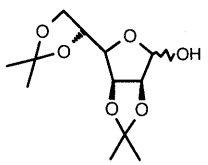
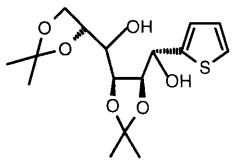
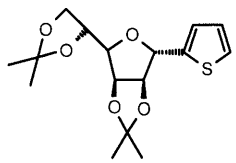
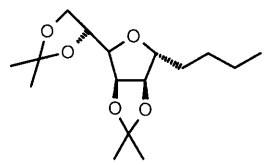
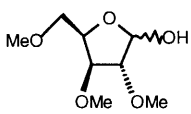
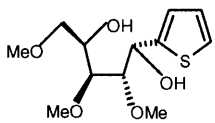
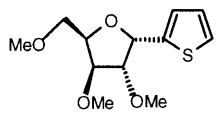
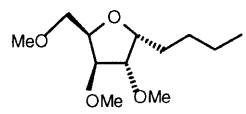
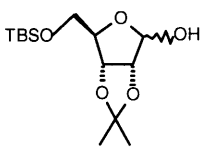
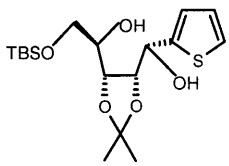
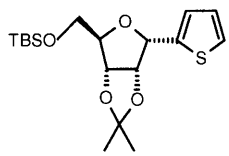
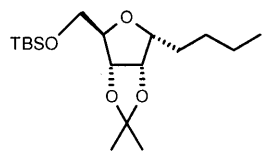
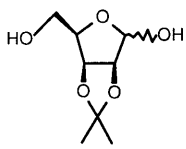
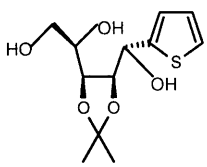
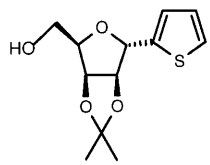
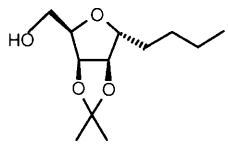
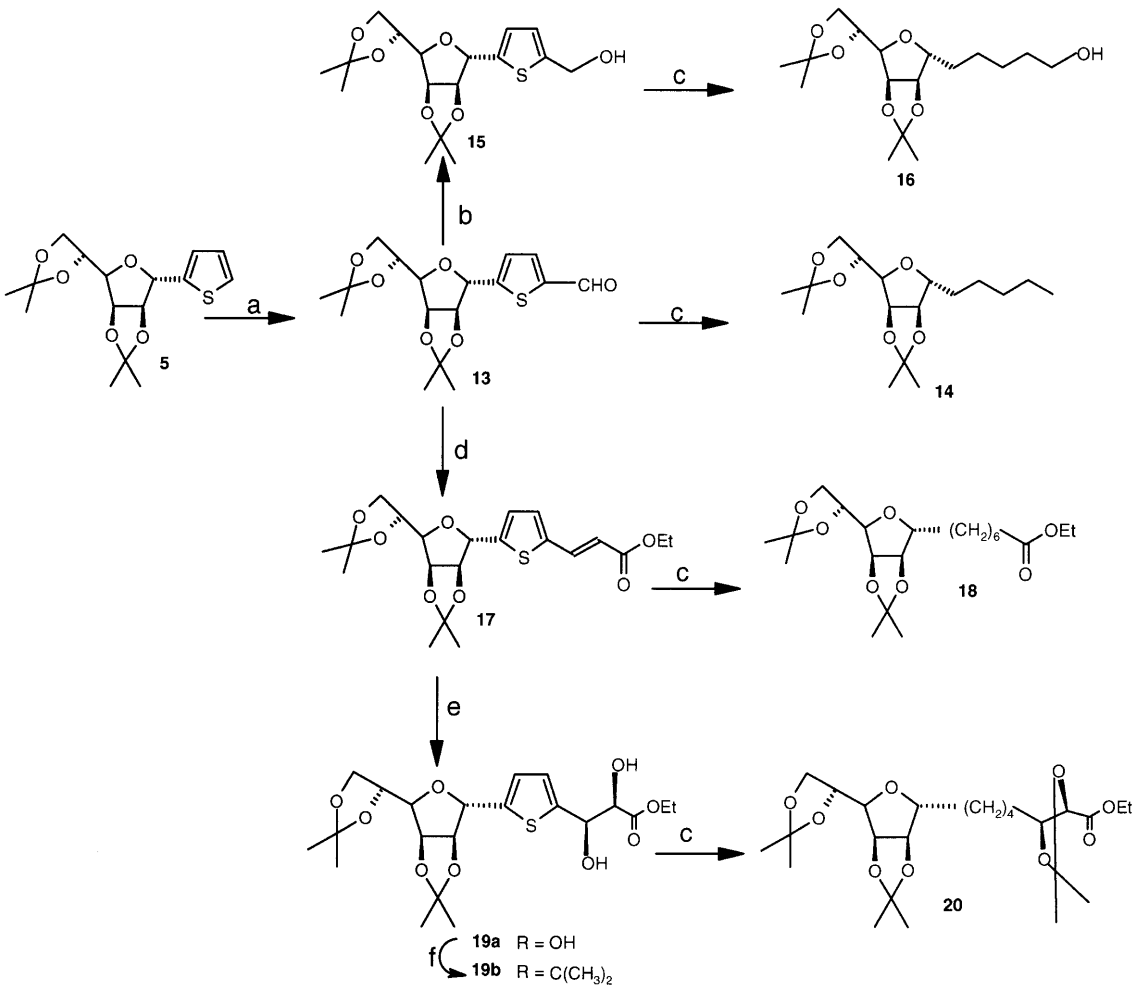
Not withstanding the importance of C-alkyl glycosides, to date, very few methods have been reported except the Wittig approach on lactol,[12] anomeric radical coupling,[13] electrochemical Kolbe coupling,[14] acetylenic alkylation followed by reduction,[15] etc., most of which lack versatility and generality.

Thiophene, as its 2-lithio derivative, is a useful C-4 synthon in C–C bond formation and readily undergoes reductive desulphurisation to release the butyl residue. Even though 2-C-thiophenyl glycosides are realised under Mitsunobu conditions,[16] interestingly this method was only restricted to ribose and deoxy ribose. The other methods[17,18] are too harsh to accommodate various acid sensitive protecting groups.

Table 1
Synthesis of C-*n*-butyl glycosides

No	Lactols	Diols	Thiphene glycosides	n-Butyl glycosides
1	 1	 **1a** (20:1)	 **5** (71%)	 **9** (55%)
2	 **2**	 **2a** (8:1)	 **6** (68%)	 **10** (67%)
3	 **3**	 **3a** (4: 3)	 **7** (51%)	 **11** (74%)
4	 **4**	 **4a** (8:1)	 **8** (69%)	 **12** (69%)



Scheme 1. Synthesis of functionalised C-alkyl mannosides. *Reagents*: (a) LDA, DMF, THF, –40°C→rt, 2 h; (b) $NaBH_4$, MeOH, rt, 30 min; (c) Raney nickel, EtOH, reflux, 2 h; (d) Ph_3P=CHCOOEt, benzene, rt, 2 h; (e) AD-mix-α, $MeSO_2NH_2$; (f) 2,2′-dimethoxypropane, PTSA, CH_2Cl_2, rt, 4 h

2. Results and discussion

Thus, the present study is mainly aimed at the synthesis of (a) 2-thiophenyl α-C-glycosides from a variety of sugar lactols and conversion into α-C-butyl glycosides and (b) conversion of 2-thiophenyl α-C-glycosides into functionalised C-alkyl glycosides.

2.1. Synthesis of C-butyl glycosides

Lactols **1**–**4** on reaction with thiophene (*n*-BuLi, THF, rt) afforded the diols **1a**–**4a** as diastereomeric mixtures (for ratios, see Table 1). Mitsunobu cyclisation[16] of **1a**, **2a** and **4a** with DEAD and Ph_3P in THF gave 2-thiophenyl α-C-glycosides **5**, **6**, and **8**, respectively, as major products, with no detectable amounts of β-isomers. However, in the case of the cyclisation of diol **3a**, even though the α-isomer **7** was obtained in 51% yield, it also gave the β-isomer in 37%

yield. The thus formed glycosides **5–8** clearly indicate that the cyclisation reaction essentially follows an S_N2 mechanism. The stereochemical outcome of this reaction was solely dependent on the *de* of the diols **1a–4a**. All new glycosides were fully characterised by spectral analysis. For instance, the formation of **5–8** as major α-C-glycosides was evidenced from ^{1}H NMR spectra. The α-anomeric configuration of **5** could easily be established from the multiplicity of the H-2′ proton which resonated at δ 4.95 as a doublet ($J=4.9$ Hz), **6** showed the H-2′ proton at δ 3.9 also as a doublet ($J=4.9$ Hz), while the same proton in compound **8** resonated at δ 5.0 as a doublet ($J=4.5$ Hz). However, **7** showed H-2′ at δ 4.7 as a double doublet ($J=3.6$ and 4.6 Hz) which could be reasoned only if the configuration is α. The anomeric stereochemistry in all cases of the major products was proved to be α unequivocally by taking into account the multiplicity of H-2′.

The glycosides **5–8** were finally subjected to reductive desulphurisation with Raney nickel in ethanol at reflux to afford the C-α-butyl glycosides **9–12**, respectively (Table 1, 55–74% yields).

2.2. Synthesis of functionalised C-alkyl mannosides

Having prepared several 2-thiophenyl-C-glycosides **5–8** and converted them to C-butyl glycosides, it was proposed to extend the methodology to prepare functionalised C-alkyl mannosides by making use of the C-5 centre of thiophene mannoside. Accordingly, mannoside **5** was formylated (LDA, DMF, −78°C) at C-5 of the thiophene ring to afford 5-formyl glycoside **13** in 74% yield, which was efficiently utilised for the preparation of several functionalised C-alkyl glycosides (Scheme 1), wherein the thiophene played the role as a latent C-4 fragment.

Firstly, **13** was subjected to reductive desulphurisation to afford C-pentyl mannoside **14** in 71% yield. The formation of the product **14** could be explained by the concomitant reduction of the aldehyde functionality along with desulphurisation. Alternatively **13**, on exposure to sodium borohydride, resulted in the reduction of the formyl functionality to afford the alcohol **15**. The structure of **15** was assigned by the chemical shift at δ 4.65 for the hydroxy methylene group, apart from the reassurance from the IR spectrum wherein the absence of the formyl functionality was observed. Subsequently **15**, when subjected to reductive desulphurisation with Raney nickel/ethanol, afforded C-4-hydroxy butyl mannoside **16** in 63% yield.

Similarly compound **13** was subjected to Wittig olefination with (carbethoxy methylene) triphenyl phosphorane in benzene at room temperature to afford **17** in 90% yield. The *trans*-geometry present in **17** could be confirmed from its ^{1}H NMR spectrum by the appearance of olefinic protons at δ 6.15 and 7.65 ($J=16.2$ Hz) besides the characteristic ethyl protons. Raney nickel reduction of **17** efficiently afforded the C-(carbethoxy) ethyl mannoside **18** in 73% yield. Likewise, **17** was subjected to Sharpless asymmetric dihydroxylation[19] (AD-mix-α, $CH_3SO_2NH_2$, aq. *t*-BuOH) to afford diol **19** (62%), which on further protection with dimethoxy propane (PTSA, MeOH) resulted in **19a** (80%). Reaction of **19a** with Raney nickel gave the mannoside **20**, with chiral dioxalanyl and ester groups.

Thus, the present study discloses a simple procedure for the synthesis of several 2-C-thiophenyl-α-glycosides and thence to C-butyl-α-glycosides; terminally functionalised C-alkyl-α-D-mannosides from the 5-C-formylated thiophenyl-α-D-mannoside **13**. In this report it is demonstrated that 'thiophene' could be used both as a masked C-4 synthon and also as a fragment suitable for further functionalisation. This protocol could be adopted as an alternative synthetic tool for the synthesis of several such glycosides.

3. Experimental

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were measured with a Varian Gemini spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in Hz. 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.

3.1. Synthesis of C-thiophenyl glycosides

3.1.1. 2-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)thiophene **5**

To a solution of thiophene (0.96 g, 11.5 mmol) in anhydrous THF (10 mL) was added *n*-BuLi (7.2 mL, 11.5 mmol, 1.6N hexane solution) dropwise during 5 min at 0°C and the solution was stirred at room temperature for 0.5 h. To the resultant solution was added a solution of **1** (1 g, 3.8 mmol) in dry THF (10 mL) dropwise during 5 min at 0°C. The reaction mixture was stirred at room temperature for 2 h and treated with aq. NH_4Cl solution (20 mL). The aqueous layer was separated, extracted with $CHCl_3$ (3×50 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (silica gel, EtOAc–hexane 1:4) gave 2-(2,3:5,6-di-*O*-isopropylidene-α-D-mannohexitol-1-yl)thiophene (**1a**; 0.920 g, 76%) as a syrup.

A mixture of **1a** (0.920 g, 2.6 mmol), Ph_3P (2.10 g, 8.0 mmol) in THF (10 mL) was stirred for 15 min and treated with a solution of DEAD (0.14 g, 0.80 mmol) in THF (10 mL) dropwise at 0°C. After stirring for 2.5 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc–hexane 1:10) to give **5** (0.9 g, 71.8%) as a liquid. $[\alpha]_D$ +18.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.20 (m, 1H, H-5), 7.00–6.90 (m, 2H, H-3,4), 5.20 (s, 1H, H-1′), 4.95 (d, 1H, $J_{2',3'}$=4.9 Hz, H-2′), 4.75 (dd, 1H, $J_{3',4'}$=6.75, $J_{3',2'}$=4.5 Hz, H-3′), 4.40–4.35 (m, 1H, H-5′), 4.10–3.95 (m, 2H, H-6′a,6′b), 3.80 (dd, 1H, $J_{4',5'}$=4.5, $J_{4',3'}$=7.0 Hz, H-4′), 1.50, 1.40, 1.35, 1.30 (4s, 12H); ^{13}C NMR (50 MHz): δ 142.1, 127.2, 127.0, 125.2, 112.8, 109.2, 86.6, 82.0, 81.2, 80.8, 73.1, 67.0, 26.7, 26.0, 25.1, 24.7; EIMS (*m*/*z*): 327 (M+1); analysis calculated for $C_{16}H_{22}O_5S$: C, 58.9; H, 6.8; found: C, 58.7; H, 6.8.

3.1.2. 2-(2,3,5-Tri-O-methyl-α-D-xylofuranosyl)thiophene **6**

A solution of thiophene (0.65 g, 7.8 mmol) in THF (10 mL) was treated with *n*-BuLi (4.8 mL, 7.8 mmol, 1.6N hexane solution) and **2** (0.5 g, 2.6 mmol) in THF (10 mL) sequentially as described for **1a** to give the product 2-(2,3,5-tri-*O*-methyl-α-D-xylopentitol-1-yl)thiophene (**2a**; 0.60 g, 87%) as a syrup.

A mixture of **2a** (0.60 g, 2.2 mmol) and Ph_3P (1.7 g, 6.5 mmol) in THF (10 mL) was treated with a solution of DEAD (0.11 g, 0.65 mmol) in THF (10 mL) as described for **5** gave **6** (0.38 g, 68%) as a liquid. $[\alpha]_D$ −53.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.20 (m, 1H, H-5), 7.00–6.90 (m, 2H, H-3,4), 5.30 (d, 1H, $J_{1',2'}$=4.6 Hz, H-1′), 4.40–4.25 (m, 1H, H-4′), 3.90 (d, 1H, $J_{2',1'}$=4.6 Hz, H-2′), 3.84 (br.d, 1H, $J_{3',4'}$=4.0 Hz, H-3′), 3.65–3.50 (m, 2H, H-5′a,5′b), 3.45, 3.4, 3.2 (3s, 9H, 3×OMe); analysis calculated for $C_{12}H_{18}O_4S$: C, 55.8; H, 7.0; found: C, 56.0; H, 7.8.

*3.1.3. 2-(2,3-*O*-Isopropylidene-5-*O*-tert-butyldimethylsilyl-α-D-ribofuranosyl)thiophene* **7**

A solution of thiophene (0.83 g, 9.8 mmol) in THF (10 mL) was treated with *n*-BuLi (6.1 mL, 9.8 mmol, 1.6N hexane solution) and **3** (1.0 g, 3.28 mmol) in THF (10 mL) sequentially. Usual work-up as described for **1a** gave 2-(2,3-*O*-isopropylidiene-5-*O*-*tert*-butyldimethylsilyl-α-D-ribopentitol-1-yl)thiophene (**3a**; 0.89 g, 74%) as a syrup.

A mixture of **3a** (0.15 g, 0.38 mmol) and Ph_3P (0.139 g, 0.38 mmol) in THF (10 mL) was treated with DEAD (0.67 g, 0.38 mmol) in THF (10 mL) as described for **5** gave **7** as a mixture of isomers in 92.8% overall yield (0.135 g). Chromatography (silica gel, EtOAc–hexane 1:9) of the residue gave first the α-isomer (0.075 g, 51% yield) as an oily compound. $[\alpha]_D$ −38 (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 7.25 (m, 1H, H-5), 7.00 (m, 1H, H-3), 6.90 (m, 1H, H-4), 5.10 (d, 1H, $J_{2',1'}=3.6$ Hz, H-1′), 4.70 (dd, 1H, $J_{2',3'}=4.6$ Hz, H-2′), 4.60 (m, 1H, H-3′), 4.20 (m, 1H, H-4′), 3.80–3.70 (m, 2H, H-5′a,5′b), 1.60, 1.40 (2s, 6H), 0.95 (s, 9H), 0.10 (s, 6H). The β-isomer (0.055 g, 37% yield) was eluted second as an oily compound. $[\alpha]_D$ −22 (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 7.30 (m, 1H, H-5), 7.02–6.90 (m, 2H, H-3,4), 5.49 (d, 1H, $J_{2',1'}=4.6$ Hz, H-1′), 4.95 (d, 1H, $J_{2',3'}=6.9$ Hz, H-2′), 4.75 (m, 1H, H-3′), 4.18 (m, 1H, H-4′), 3.85–3.75 (m, 2H, H-5′a,5′b), 1.60, 1.40 (2s, 6H), 0.95 (s, 9H), 0.10 (s, 6H); analysis calculated for $C_{18}H_{30}O_4SSi$: C, 58.3; H, 8.2; found: C, 58.1; H, 8.4.

*3.1.4. 2-(2,3-*O*-Isopropylidene-α-D-lyxofuranosyl)thiophene* ***8***

To a solution of thiophene (1.32 g, 15.78 mmol) in THF (10 mL) *n*-BuLi (9.8 mL, 15.78 mmol, 1.6N hexane solution) followed by **4** (1.0 g, 5.26 mmol) in THF (10 mL) was added and worked up as described for **1a** to give 2-(2,3-*O*-isopropylidene-α-D-lyxopentitol-1-yl)thiophene (**4a**; 0.78 g, 55.7%) as a thick syrup.

To a mixture of **4a** (0.78 g, 2.8 mmol) and Ph_3P (2.23 g, 8.5 mmol) in THF (10 mL) was added a solution of DEAD (0.16 g, 0.9 mmol) in THF (10 mL). Usual work-up as described for **5** gave **8** (0.50 g, 69%) as a liquid. $[\alpha]_D$ +19.6 (*c* 0.51, $CHCl_3$); ^{1}H NMR: δ 7.25 (m, 1H, H-5), 7.00–6.90 (m, 2H, H-3,4), 5.30 (s, 1H, H-1′), 5.00 (d, 1H, $J_{2',3'}=4.2$ Hz, H-2′), 4.80 (dd, 1H, $J_{3',2'}=4.2$, $J_{3',4'}=5.1$ Hz, H-3′), 4.15–4.05 (m, 2H, H-5′a,5′b), 3.92–3.82 (m, 1H, H-4′), 1.50, 1.30 (2s, 6H); FABMS (*m*/*z*): 255 (M−1); analysis calculated for $C_{12}H_{16}O_4S$: C, 56.2; H, 6.3; found: C, 57.3; H, 6.4.

3.2. Conversion of C-thiophenyl glycosides to C-butyl glycosides

*3.2.1. 1-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)butane* ***9***

A mixture of **5** (0.2 g, 0.6 mmol) and Raney nickel (0.12 mL) in ethanol (10 mL) was stirred at reflux for 4 h. After the completion of reaction (TLC analysis) the mixture was filtered over a bed of Celite and washed with ethanol (3×20 mL). Evaporation of solvent and purification of the residue by column chromatography on silica gel (EtOAc–hexane 1:49) gave **9** (0.09 g, 55%) as a liquid. $[\alpha]_D$ −9.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 4.65 (dd, 1H, $J_{1',CH_2}=3.6$, $J_{1',CH_2}=4.8$ Hz, H-1′), 4.40 (d, 1H, $J_{2',3'}=6.12$ Hz, H-2′), 4.30–4.20 (m, 1H, H-3′), 4.05–3.85 (m, 3H, H-5′, H-6′a,6′b), 3.60 (dd, 1H, $J_{4',3'}=7.7$, $J_{4',5'}=4.0$ Hz, H-4′), 1.50, 1.40, 1.20 (br.s, 9H), 1.30 (br.s, 9H), 0.90 (br.t, 3H, CH_3); analysis calculated for $C_{16}H_{28}O_5$: C, 64.0; H, 9.4; found: C, 63.5; H, 9.9.

*3.2.2. 1-(2,3,5-Tri-*O*-methyl-α-D-xylofuranosyl)butane* ***10***

A mixture of **6** (0.3 g, 1.1 mmol) and Raney nickel (0.18 mL) in ethanol (15 mL) was stirred at reflux for 4 h. Usual work-up as described for **9** gave **10** (0.17 g, 67%) as a liquid. $[\alpha]_D$ −66.2

(c 0.8, $CHCl_3$); ^1H NMR: δ 4.20–4.10 (m, 1H, H-1′), 3.95 (dt, 1H, $J_{3',4'}=3.6$, $J_{4',5'}=6.0$ Hz, H-4′), 3.72 (d, 1H, $J_{1',2'}=4.0$ Hz, H-2′), 3.60 (d, 1H, $J_{3',4'}=3.6$ Hz, H-3′), 3.50–3.40 (m, 2H, H-5′a,5′b), 3.40 (3s, 9H, 3×OMe), 1.60–1.50 (m, 2H, CH_2), 1.40–1.20 (m, 4H, 2×CH_2), 0.90 (t, 3H, $J=6.0$ Hz, CH_3); FABMS (m/z): 233 (M+1), FAB HRMS: calc. for $C_{12}H_{25}O_4$ (M+1) 233.175285. Observed 233.175774.

3.2.3. 1-(2,3-O-*Isopropylidene*-5-O-tert-*butyldimethylsilyl*-α-D-*ribofuranosyl*)*butane* **11**

A mixture of **7** (0.1 g, 0.27 mmol) and Raney nickel (0.06 mL) in ethanol (10 mL) was stirred at reflux for 4 h as described for **9**, and work-up after the completion of reaction (TLC analysis) gave **11** (0.067 g, 74%) as a syrup. $[\alpha]_D$ −17.5 (c 0.4, $CHCl_3$); ^1H NMR: δ 4.70 (d, 1H, $J_{2',3'}=4.6$ Hz, H-2′), 4.50 (dd, 1H, $J_{1',CH_2}=4.1$, $J_{1',CH_2}=5.0$ Hz, H-1′), 3.90 (br.t, 2H, H-3′,4′), 3.60 (2s, 2H, H-5′a,5′b), 1.60–1.50 (m, 2H), 1.40, 1.20 (2s, 6H), 1.30 (br.s, 4H), 0.90 (br.s, 9H), 0.10 (br.s, 6H); analysis calculated for $C_{18}H_{36}O_4Si$: C, 62.7; H, 10.5; found: C, 63.1; H, 10.9.

3.2.4. 1-(2,3-O-*Isopropylidene*-α-D-*lyxofuranosyl*)*butane* **12**

A mixture of **8** (0.1 g, 0.39 mmol) and Raney nickel (0.06 mL) in ethanol (15 mL) was stirred at reflux for 4 h as described for **9** to give **12** (0.62 g, 69%) as a liquid. $[\alpha]_D$ 3.60 (c 0.5, $CHCl_3$); ^1H NMR: δ 4.70 (br.d, 1H, H-1′), 4.40 (d, 1H, $J_{2',1'}=4.8$ Hz, H-2′), 4.10–4.00 (m, 1H, H-3′), 4.00–3.80 (m, 2H, H-5′a,5′b), 3.60–3.70 (m, 1H, H-4′), 1.50–1.40 (2s, 6H), 1.00–0.80 (br.t, 2H, CH_2); analysis calculated for $C_{12}H_{22}O_4$: C, 62.6; H, 9.6; found: C, 63.0; H, 10.0.

3.3. Synthesis of functionalised mannosides

3.3.1. 2-(2,3:5,6-*Di*-O-*isopropylidene*-α-D-*mannofuranosyl*)-5-*formylthiophene* **13**

A solution of **5** (1.0 g, 3.06 mmol) in THF (10 mL) was treated with freshly prepared LDA (0.65 g, 6.1 mmol) [prepared from diisopropylamine (1.54 mL, 14.0 mmol) and n-BuLi (4.6 mL, 7.38 mmol, 1.6N hexane solution)] dropwise at −40°C. After 40 min the reaction mixture was allowed to warm to −10 to 5°C, treated with DMF (0.22 g, 3.0 mmol) and stirred for 30 min. It was treated with aq. NH_4Cl solution (20 mL), extracted with $CHCl_3$ (3×50 mL) and dried (Na_2SO_4). The organic layer was evaporated under reduced pressure and the residue subjected to purification by column chromatography (silica gel, EtOAc–hexane 1:4) to afford **13** (0.70 g, 74%) as a syrup. $[\alpha]_D$ +31.5 (c 1.2, $CHCl_3$); ^1H NMR: δ 9.90 (s, 1H, CHO), 7.70 (d, 1H, $J_{3,4}=5.8$ Hz, H-4), 7.10 (d, 1H, H-3), 5.30 (s, 1H, H-1′), 5.00 (d, 1H, $J_{2',3'}=4.9$ Hz, H-2′), 4.80 (dd, 1H, $J_{3',2'}=4.2$ $J_{3',4'}=6.75$ Hz, H-3′), 4.50–4.40 (m, 1H, H-5′), 4.20–4.00 (m, 2H, H-6′a,6′b), 3.90 (dd, 1H, $J_{4'3'}=6.5$, $J_{4'5'}=4.5$ Hz, H-4′), 1.60, 1.50, 1.40 (3s, 12H); EIMS (m/z): 354; analysis calculated for $C_{17}H_{22}O_6S$: C, 57.6; H, 6.2; found: C, 57.8; H, 6.2.

3.3.2. 1-(2,3:5,6-*Di*-O-*isopropylidene*-α-D-*mannofuranosyl*) *pentane* **14**

A mixture of **13** (0.1 g, 0.2 mmol) and Raney nickel (0.06 mL) in ethanol (10 mL) was stirred at reflux for 4 h as described for **9** gave **14** (0.062 g, 71%) as a liquid. $[\alpha]_D$ +46.0 (c 0.5, $CHCl_3$); ^1H NMR: δ 4.75 (dd, 1H, $J_{1',CH_2}=5.23$, $J_{1',CH_2}=4.27$ Hz, H-1′), 4.50 (d, 1H, $J_{2',3'}=5.23$ Hz, H-2′), 4.40–4.20 (m, 1H, H-3′), 4.10–3.90 (m, 3H, H-5′,6′a,6′b), 3.60 (dd, 1H, $J_{3',4'}=2.85$, $J_{4',5'}=1.9$ Hz, H-4′), 1.50, 1.40, 1.20 (br.s, 9H), 1.30 (br.s, 9H), 0.90 (br.t, 3H), 0.88 (t, 3H); ^{13}C NMR (50 MHz): δ 112.5, 109.1, 89.3, 84.1, 80.8, 80.0, 73.5, 67.9, 31.5, 26.9, 26.26, 26.17, 25.67, 25.17, 22.6, 20.9, 14.2; analysis calculated for $C_{17}H_{30}O_5$: C, 64.9; H, 9.6; found: C, 64.9; H, 9.7.

3.3.3. 2-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-5-hydroxymethylthiophene ***15***

A solution of **13** (0.1 g, 0.2 mmol) in methanol (5 mL) was treated with $NaBH_4$ (0.012 g, 0.3 mmol) and stirred at room temperature for 1 h. The methanol was evaporated, the residue treated with CH_2Cl_2 (2×10 mL) and washed with water (2×10 mL). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography gave **15** (0.08 g, 80%). $[\alpha]_D$ +20.04 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 6.80, 6.70 (2br.d, 2H, H-3,4), 5.20 (s, 1H, H-1′), 4.90 (d, 1H, $J_{2',3'}=4.28$ Hz, H-2′), 4.75 (m, 1H, H-3′), 4.70 (s, 2H, -OCH_2), 4.30–4.45 (m, 1H, H-5′), 4.15–4.00 (m, 2H, H-6′a,6′b), 3.80 (dd, 1H, $J_{3',4'}=6.5$, $J_{4',5'}=4.5$ Hz, H-4′), 1.50, 1.40, 1.35, 1.30 (4s, 12H); FABMS (*m*/*z*): 355 (M−1); analysis calculated for $C_{17}H_{24}O_6S$: C, 57.3; H, 6.8; found: C, 57.3; H, 6.7.

3.3.4. 1-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)pentan-5-ol ***16***

A mixture of **15** (0.08 g, 0.2 mmol) and Raney nickel (0.04 mL) in ethanol (15 mL) was stirred at reflux for 4 h as described for **9** gave **16** (0.56 g, 75%). $[\alpha]_D$ −10.36 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 4.60 (dd, 1H, $J_{1',CH_2}=4.5$ Hz, $J_{1',CH_2}=5.2$ Hz, H-1′), 4.40 (d, 1H, $J_{2',3'}=5.0$ Hz, H-2′), 4.30 (m, 1H, H-3′), 4.00–3.80 (m, 3H, H-5′,6′a,6′b), 3.55–3.62 (m, 1H, H-4′), 3.52 (t, 2H, $J=6.75$ Hz, CH_2), 1.40, 1.30, 1.20, 1.10 (4s, 12H); ^{13}C NMR (50 MHz): δ 112.49, 109.05, 85.32, 84.09, 80.77, 79.98, 73.45, 66.99, 62.62, 32.54, 30.45, 29.61, 26.87, 26.08, 25.34, 25.13, 24.65; analysis calculated for $C_{17}H_{30}O_6$: C, 61.8; H, 9.1; found: C, 62.0; H, 9.2.

*3.3.5. 2-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-5-[(*E*)-2-ethoxycarbonyl-1-ethenyl]-thiophene* ***17***

A solution of **13** (0.44 g, 1.2 mmol) in benzene (15 mL) was treated with (carbethoxymethylene) triphenyl phosphorane (0.43 g, 1.2 mmol) at rt for 2 h. Benzene was distilled off and the residue purified by flash chromatography (EtOAc–hexane 1:9) to afford **17** (5,20 g, 98%) as a syrup. $[\alpha]_D$ +77.29 (*c* 0.74, $CHCl_3$); ^{1}H NMR: δ 7.65 (d, 1H, $J=16.2$ Hz, H-3″), 7.10 (d, 1H, $J=4.0$ Hz, H-4), 6.88 (d, 1H, $J=4.0$ Hz, H-3), 6.15 (d, 1H, $J=16.2$ Hz, H-2″), 5.20 (s, 1H, H-1′), 4.95 (d, 1H, $J_{2',3'}=6.9$ Hz, H-2′), 4.80 (dd, 1H, $J=4.5$, 6.9 Hz, H-3′), 4.45–4.30 (m, 1H, H-5′), 4.30–4.00 (m, 2H, H-6′a,6′b), 3.80 (dd, 1H, $J=4.5$, 9.0 Hz, H-4′), 1.60, 1.41, 1.35, (3s, 9H), 1.30–1.20 (m, 6H); ^{13}C NMR (50 MHz): δ 166.6, 145.5, 139.5, 136.6, 130.9, 125.2, 117.2, 113.1, 109.2, 86.5, 82.2, 81.6, 80.9, 73.1, 66.9, 60.6, 26.8, 26.0, 25.1, 24.7, 14.2; FABMS (*m*/*z*): 447 (M+Na); analysis calculated for $C_{21}H_{28}O_7S$: C, 59.4; H, 6.6; found: C, 59.6; H, 6.8.

3.3.6. Ethyl 7-(2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl) heptanoate ***18***

A mixture of **17** (0.5 g, 1.1 mmol) and Raney nickel (0.3 mL) in ethanol (10 mL) was stirred at reflux for 4 h as described for **9** to furnish **18** (0.34 g, 68%) as a liquid. $[\alpha]_D$ −17.20 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 4.77 (m, 1H, H-1′), 4.42 (d, 1H, $J=5.1$ Hz, H-2′), 4.40–4.30 (m, 1H, H-3′), 4.20–3.90 (m, 5H, H-5′,6′a,6′b, -OCH_2), 3.70–3.60 (dd, 1H, $J_{4',3'}=4.6$, $J_{4',5'}=6.9$ Hz, H-4′), 2.30 (t, 2H, $J=6.9$ Hz, -COCH_2), 1.50, 1.45, 1.38, 1.30 (4s, 12H), 1.27 (t, 3H, $J=6.75$ Hz, CH_3); ^{13}C NMR (50 MHz): δ 173.6, 112.4, 109.0, 85.2, 84.0, 80.7, 79.9, 73.4, 67.0, 60.1, 34.2, 30.4, 29.6, 28.8, 26.8, 26.0, 25.4, 25.1, 24.8, 24.6, 14.2; FABMS (*m*/*z*): 423 (M+Na); analysis calculated for $C_{21}H_{36}O_7$: C, 63.0; H, 9.1; found: C, 63.3; H, 9.1.

*3.3.7. 2-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)-5-[(4*R*,5*R*)-5-ethoxycarbonyl-1,3-dioxolane-4-yl]thiophene* ***19a***

A solution of AD-mix-α (0.183 g, 0.23 mL) in H_2O: *t*-BuOH (5 mL, 1:1) was treated with $MeSO_2NH_2$ (0.02 g, 0.23 mmol) and cooled to 0°C. A solution of olefin **17** (0.1 g, 0.23 mmol) in *t*-BuOH (2 mL) was added at once and the heterogeneous slurry was stirred for 24 h. Solid Na_2SO_4 (0.05 g) was added and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was extracted with EtOAc (3×10 mL), washed with brine (1×10 mL) and dried (Na_2SO_4). It was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, EtOAc–hexane 1:1) to give 2-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-5-[(4*R*,5*R*)-ethyl 2,3-dihydroxy propionate-3-yl]thiophene **19** (0.05 g, 52%) as a thick syrup.

To a solution of **19** (0.05 g, 0.11 mmol) in CH_2Cl_2 (5 mL), was added dimethoxy propane (0.01 mL, 0.11 mmol) and catalytic PTSA at room temperature. After the completion of the reaction, the reaction mixture was neutralised with aq. $NaHCO_3$ solution (three drops), extracted with $CHCl_3$ (2×10 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and the residue was purified chromatographically (silica gel, EtOAc–hexane 1:9) to give **19a** (0.042 g, 79%) as a liquid. $[\alpha]_D$ +29.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 6.92 (br.d, 1H, H-3), 6.80 (br.d, 1H, H-4), 5.30 (d, 1H, J=7.6 Hz, H-3″), 5.20 (s, 1H, H-1′), 4.95 (d, 1H, J=4.6 Hz, H-2′), 4.75–4.85 (m, 1H, H-3′), 4.00–4.50 (m, 6H, H-5′,6a′,6b′, H-2″, CH_3), 3.68 (dd, 1H, J=3.8, 6.3 Hz, H-4′), 1.42, 1.40, 1.32, 1.26, 1.22 (5s, 18H), 1.10 (br.t, 3H, CH_3); ^{13}C NMR (50 MHz): δ 170.0, 142.7, 141.2, 125.9, 124.9, 113.0, 111.9, 109.3, 86.6, 82.2, 81.5, 81.1 (2C), 73.3, 67.1, 61.7, 26.9 (2C), 26.2, 25.9, 25.2, 24.8, 14.2; analysis calculated for $C_{24}H_{34}O_9S$: C, 57.8; H, 6.9; found: C, 57.4; H, 6.8.

*3.3.8. Ethyl (2*R*,3*S*)-7-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-2,3-(isopropylidene)-dioxy heptanoate* ***20***

A mixture of **19a** (0.1 g 0.2 mmol) and Raney nickel (0.06 mL) in ethanol (10 mL) was stirred at reflux for 4 h as described for **9** and after usual work-up furnished **20** (0.07 g, 73.8%) as a liquid. $[\alpha]_D$ −0.70 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 4.77 (m, 1H, H-1′), 4.42 (d, 1H, $J_{2',3'}$=5.1 Hz, H-2′), 4.40–4.32 (m, 1H, H-3′), 4.32–4.20 (m, 2H, -CH_2), 4.18–3.90 (m, 5H, H-5′,6′a,6′b,2,3), 3.70–3.60 (dd, 1H, $J_{4',3'}$=4.6, $J_{4',5'}$=6.9 Hz, H-4′), 1.80–1.60 (m, 2H, -CH_2), 1.50, 1.45, 1.38, 1.30 (4s, 18H), 1.27 (t, 3H, J 6.9 Hz, CH_3); ^{13}C NMR (50 MHz): 172.1, 112.5, 110.8, 109.1, 85.4, 84.1, 80.8, 80.1, 79.1, 79.0, 73.5, 67.0, 60.5, 33.4, 30.5, 29.7, 27.2, 26.9, 26.1, 25.7, 25.4, 25.2, 24.7, 14.2; FABMS (m/z): 457 (M–CH_3); analysis calculated for $C_{24}H_{40}O_9$: C, 61.0; H, 8.5; found: C, 61.3; H, 8.6.

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