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PAPER

Synthesis of apiose-containing oligosaccharide fragments of the plant cell wall: fragments of rhamnogalacturonan-II side chains A and B, and apiogalacturonan†

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Fragments of pectic polysaccharides rhamnogalacturonan-II (RG-II) and apiogalacturonan were synthesised using *p*-tolylthio apiofuranoside derivatives as key building blocks. Apiofuranose thioglycosides can be conveniently prepared by cyclization of the corresponding dithioacetals possessing a 2,3-*O*-isopropylidene group, which is required for preservation of the correct (3*R*) configuration of the apiofuranose ring. The remarkable stability of this protecting group in apiofuranose derivatives requires its replacement with a more reactive protecting group, such as a benzylidene acetal which was used in the synthesis of trisaccharide β-Rha*p*-(1→3′)-β-Api*f*-(1→2)-α-GalA*p*-OMe. The X-ray crystal structure of the protected precursor of this trisaccharide has been elucidated.

Introduction

Understanding the sequence of biochemical events leading to assembly of polysaccharides present in the plant cell wall[1] requires access to a variety of oligosaccharide substrates which can help to unravel the identity and specificity of the enzymes involved.[2] Among the plant cell wall polysaccharides, a family of pectins is characterized by its particular structural complexity. This family consists of several structurally unrelated macromolecules which may be covalently and non-covalently linked to each other, forming highly branched polysaccharide networks.[3] One of the major pectic polysaccharides is α-(1→4)-linked polygalacturonic acid (homogalacturonan or HG), which plays the role of a backbone to which a number of mono-, oligo- and poly-saccharides are attached in apparently random order. Most of the HG side chains are heterogeneous but there is one homogeneous and conserved structure, rhamnogalacturonan-II (RG-II), that is comprised of four discrete oligosaccharide chains attached to HG, as shown in Fig. 1A.[4]

The two most complex side chains of RG-II, A and B, have the same structure at the "reducing end", represented by disaccharide β-Rha*p*-(1→3′)-β-Api*f*, which in turn is attached to the HG backbone through a (1→2)-linkage. Apiofuranose[5] (Api*f*) is a branched pentose capable of borate diester formation[6] and serves as a point of cross-linking of RG-II molecules in the cell wall. This chemical event has important biological consequences: plant development is severely compromised in mutant plant lines with reduced ability to form such borate cross-links.[7] Apart from RG-II, apiofuranose occurs in other types of pectins that are characteristic for aquatic plants such as the sea grasses *Zosteraceae*[8] and duckweed *Lemna minor*.[9] In these cases β-apiofuranosyl residues are attached to either the 2 or 3 positions, or both positions, of selected GalA*p* residues of HG chains in the form of mono- or sometimes short oligo-saccharides (Fig. 1B).

Continuing our efforts in the chemical synthesis of RG-II fragments,[2b,10] we describe here the synthesis of trisaccharide fragment **1** of RG-II, which is common to both side chains A and B, and oligosaccharide fragments **2** and **4** related to apiogalacturonans (Fig. 2). In particular, this study addresses issues associated with the inherent chemical reactivity of furanosides and protecting group compatibility with 2,3-*cis*-configured furanoses.

Results and discussion

Synthesis of RG-II trisaccharide 1: first approach

Disaccharide thioglycoside donor. A key step common for synthesis of oligosaccharides **1–4** consists of the construction of β-D-apiofuranosyl linkages which requires suitable apiofuranosyl donors. As glycosyl donors, apiofuranose derivatives have been employed in the form of thioglycosides,[11] 1-*O*-acetates,[12] glycosyl bromide,[13] trichloroacetimidate[14] and 1,2-*O*-cyanoethylidene derivatives.[15] In our study we focused attention on thioglycosides as stable and versatile reagents which have been widely used for the synthesis of 1,2-*trans*-glycofuranosides.[16] In the initial approach to target trisaccharide **1**, disaccharide β-L-Rhap-(1-3′)-Apif, previously synthesised by us as protected methyl glycoside

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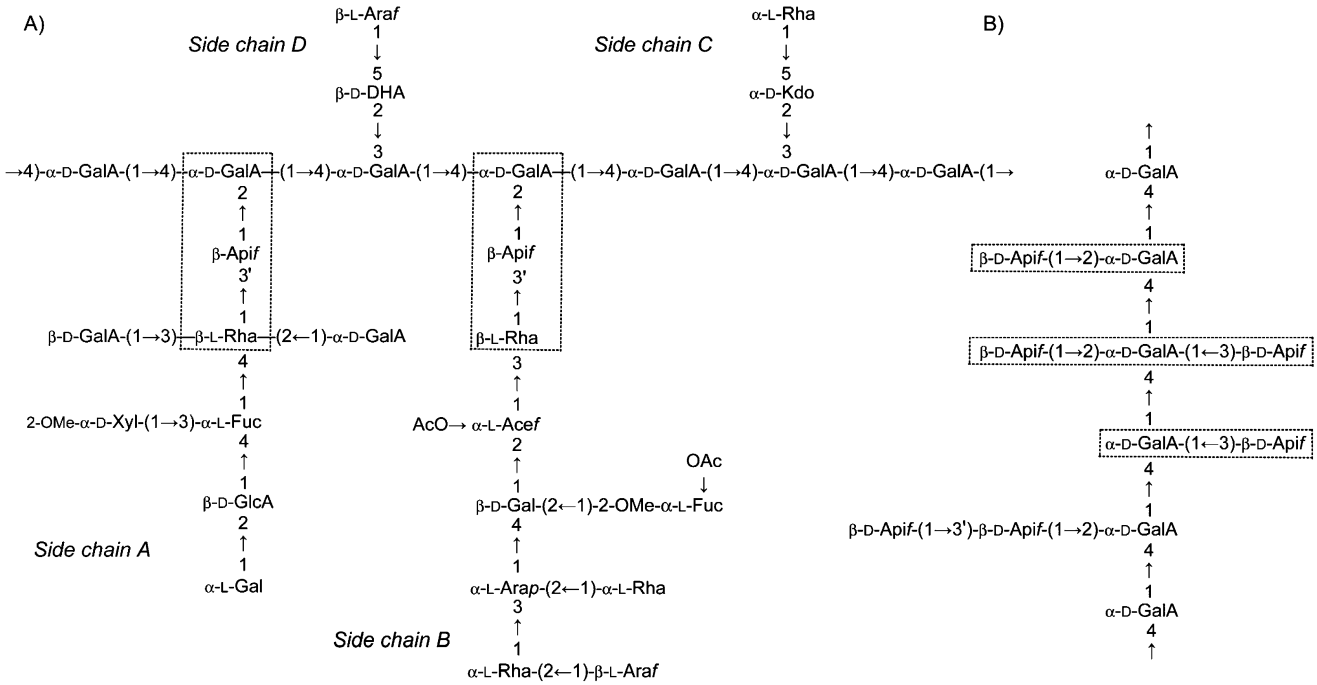


Fig. 1 (A) Structure of rhamnogalacturonan-II backbone and side chains A–D (the exact position of each side chain attachment is ambiguous[4e]). (B) Tentative structure of apiogalacturonan showing various types of branch point. The target fragments are shown in boxes.

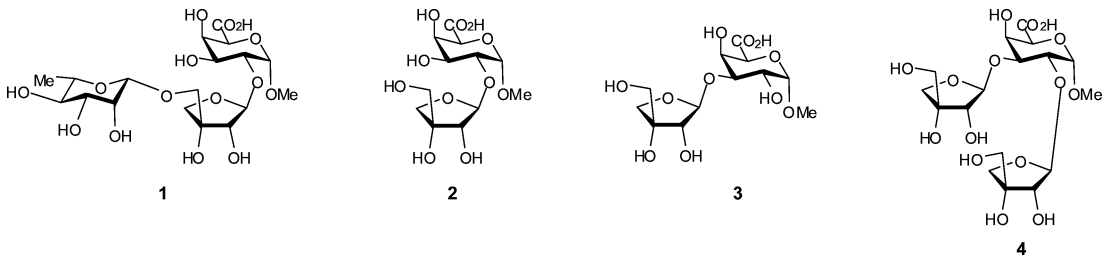
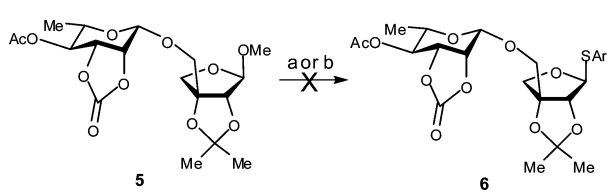


Fig. 2 Apiose-containing oligosaccharide fragments of pectic polysaccharides RG-II (**1** and **2**) and apiogalacturonan (**2**, **3** and **4**).

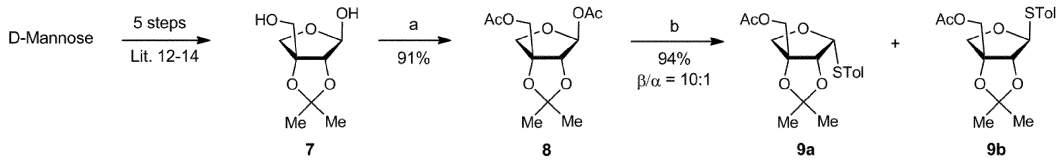
5,[17] was considered as a precursor for the disaccharide thioglycoside donor **6**. However, attempts to convert **5** into arylthio glycoside **6** (Scheme 1) under conventional (4-MeC_6H_4SH, $BF_3{\cdot}OEt_2$, 20 °C)[18] or more forceful (Me_3SiSPh, Me_3SiOTf)[19] conditions were largely unsuccessful and resulted in the decomposition of starting material. Therefore, methyl apiofuranoside, which has been used for the synthesis of disaccharide **5**, was not suitable for the preparation of trisaccharide **1** and building blocks based on other types of apiose derivatives needed to be designed.



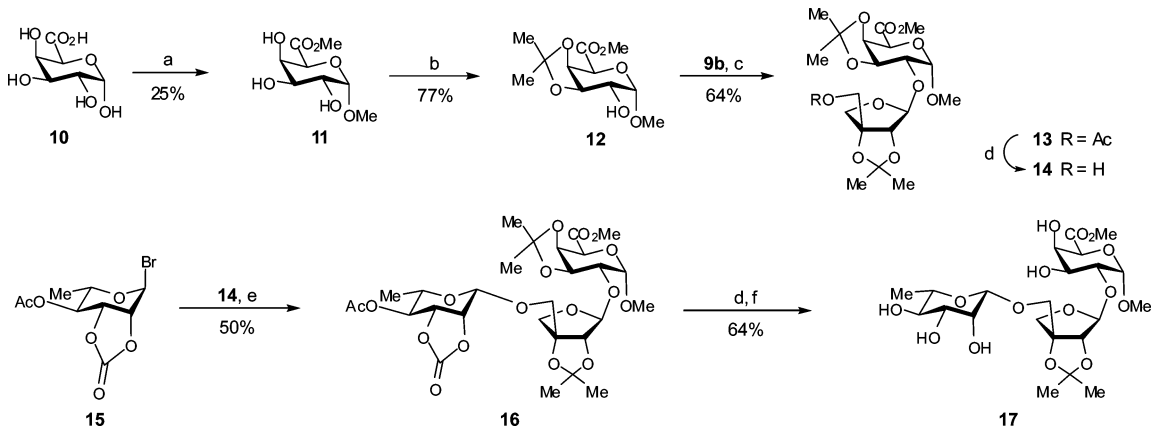
Scheme 1 Attempted synthesis of arylthio glycoside **6**. *Reagents and conditions*: (a) TolSH, $BF_3{\cdot}OEt_2$ for Ar = Tol; (b) Me_3SiSPh, Me_3SiOTf for Ar = Ph.

Sequential glycosylation. β-D-Apiofuranose derivatives are not readily available, mostly because of the rare natural occurrence of this branched-chain sugar and its ability to exist in four different cyclic forms, which complicates apiofuranose derivatisation.[5] The desired form of apiofuranose needs to have the correct (3*R*)-stereochemistry, as present in natural apiofuranosides. Such apiofuranose derivatives have been synthesised in the form of compounds with fixed 2,3-*cis*-configuration, for instance *O*-isopropylidene derivative **7**. Compound **7** can be prepared by a number of methods, including by protecting group manipulations of expensive 1,2:3,3′-di-*O*-isopropylidene-α-D-*erythro*-apiofuranose[11a] or by multistep procedures utilizing either D-mannose,[20] L-arabinose[21] or D-xylose[20c,22] as starting materials. We employed compound **7** as a precursor of the isomeric apiofuranosyl donors **9a** and **9b**, which were prepared from **7** in two successive steps, including acetylation and thioglycosidation with thiocresol in 86% overall yield (Scheme 2).

Galacturonide derivative **12**, having an unprotected 2-OH group, served as the "reducing" end building block for the target RG-II trisaccharide **1**. The former was prepared from readily accessible methyl (methyl α-D-galacturonopyranosid)uronate **11**[23]

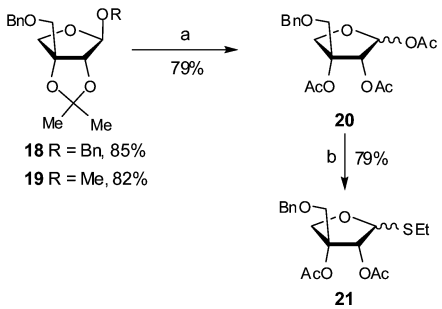


Scheme 2 Thioapiofuranoside donors **9a** and **9b**. *Reagents and conditions*: (a) Ac_2O, C_5H_5N; (b) *p*-MeC_6H_4SH, $BF_3{\cdot}OEt_2$, CH_2Cl_2.



Scheme 3 Synthesis of trisaccharide derivative **17**. *Reagents and conditions*: (a) MeOH–HCl, reflux 18 h; (b) $Me_2C(OMe)_2$, TsOH; (c) NIS–TfOH, CH_2Cl_2, –30 °C; (d) NaOMe, MeOH; (e) Ag_2O, MS 4 Å, CH_2Cl_2; (f) Amberlite IR120 (H^+).

by a known procedure[24] (Scheme 3). Glycosylation of **12** with *p*-tolylthio apiofuranoside **9b** in the presence of NIS–TMSOf as a promoter afforded disaccharide **13** in 80% yield. The lack of a participating group in the glycosyl donor did not interfere with expected 1,2-*trans*-glycosylation, which is generally a preferential stereochemical outcome of reactions with glycofuranosyl donors.[25] Disaccharide **13** was deacetylated to form glycosyl acceptor **14**, which was coupled with the 2,3-*O*-carbonate-protected rhamnopyranosyl bromide **15**[26] in the presence of molecular sieves and Ag_2O as an insoluble promoter to give fully protected trisaccharide **16** in 64% yield. This direct β-rhamnosylation technique,[26] applied in this case as well as in the synthesis of **5**,[17] proved to be practical for stereoselective glycosylation of reactive alcohols, although its efficiency was moderate. Deprotection of trisaccharide **16** was planned by sequential de-*O*-esterification and de-*O*-acetalation in basic and acidic conditions, respectively. The first stage of the deprotection of trisaccharide **16** proceeded as expected, but acid hydrolysis of isopropylidene groups catalysed by Amberlite IR120 (H^+) resin did not go to completion, leading instead to 2′,3′-mono-*O*-isopropylidene derivative **17** in 86% yield. Further attempts at the cleavage of the remaining *O*-isopropylidene group in **17** using more vigorous conditions involving 90% CF_3CO_2H in water were unsuccessful: either no changes of starting material were observed or decomposition occurred when slightly elevated temperature (30 °C) was applied. High resistance to hydrolysis of 2,3-*O*-isopropylidene acetals of *C*-3-branched furanoses, including molecules with apiofuranosyl[11b] and streptofuranosyl[27] residues, has been documented in the literature. It has also been observed that cleavage of the cyclic acetal in apiofuranosides **18** and **19** requires forcing hydrolysis conditions (80% HCO_2H, 60 °C, Scheme 4), which are accompanied by a complete cleavage of *O*-glycosidic linkages.[11a,15] Therefore, no further attempts to improve de-*O*-isopropylidenation conditions



Scheme 4 Ethyl thioapiofuranoside donor.[12a] *Reagents and conditions*: (a) 80% HCO_2H, 60 °C then Ac_2O, C_5H_5N; (b) EtSH, $SnCl_4$.

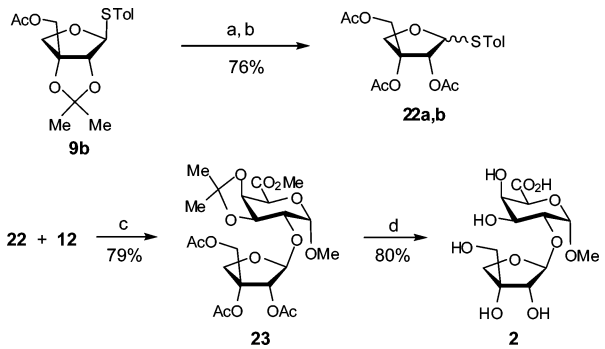
for compound **17** were made; rather a slightly different synthetic strategy was developed (*vide infra*).

Synthesis of apiogalacturonan fragments 2–4

The extreme stability of the *O*-isopropylidene group in positions 2,3 of the apiofuranose ring limits usability of this particular acetal as a protecting group in apiofuranose-containing oligosaccharide synthesis. Since presence of the 2,3-*O*-isopropylidene protecting group is essential for construction of initial building blocks such as acetal **7**, finding a practical alternative for the installation of isopropylidene protection at an earlier stage in the synthesis is complicated. Therefore, it is more practical to carry out the replacement of the 2,3-*O*-isopropylidene group with more easily cleavable protecting groups after the apiofuranose building block is already assembled. To preserve the (3*R*)-configuration of apiofuranose during the hydrolytic removal of the 2,3-*O*-isopropylidene group, the 3′-OH group has previously been protected with relatively stable benzyl ether.[15] Thus, the 3′-*O*-benzyl ether survives acid hydrolysis in benzyl or methyl apiofuranoside derivatives

18 and **19**, which have been used for preparation of triacetate **20** and its subsequent conversion to anomeric mixture of ethyl thioapiofuranosides **21** (Scheme 4).[11a]

We exploited the higher hydrolytic stability of *S*-glycosides compared to *O*-glycosides,[28] which made possible selective removal of the 2,3-*O*-isopropylidene group in thioapiofuranosides without affecting the (3*R*)-configuration and the cleavage of the *S*-glycosidic linkage. Thus, treatment of arylthio glycoside **9b** with 90% CF_3CO_2H followed by acetylation afforded triacetates **22** as a mixture of anomeric thioglycosides in a combined 76% yield over two steps (Scheme 5). Reversible anomerisation took place during the preparation of triacetates **22a,b** (Scheme 5), which were formed as a 1 : 4 mixture of α- and β-thioglycosides, even when anomerically pure 1,2-*trans*-glycoside **9b** was used as a starting material. This anomeric mixture of triacetates **22a,b** was used for glycosylation of the alcohol **12**, to afford exclusively β-apiofuranoside **23** in 79% yield. This reaction was promoted by NIS in the presence of $HClO_4$ on silica gel.[29] Similar results have been reported for coupling of **12** with ethyl thioglycoside **21** in the presence of NIS–AgOTf.[11c]



Scheme 5 Disaccharide **2**. *Reagents and conditions*: (a) 90% TFA, 20 °C, b) Ac_2O, DMAP, C_5H_5N; (c) NIS, $HClO_4/SiO_2$, –30 °C; (d) NaOMe, MeOH then NaOH, H_2O.

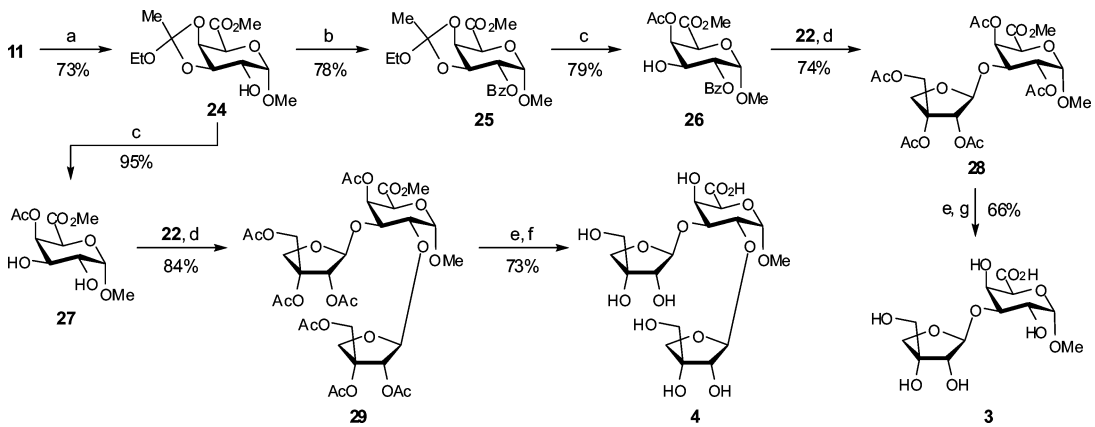
Glycosyl acceptors having unprotected 3-OH or both 2- and 3-OH groups in methyl (methyl α-D-galactopyranosid)uronate derivatives were also prepared and coupled with apiofuranosyl donor **22**. Synthesis of these glycosyl acceptors was carried out *via* the installation of the 3,4-*O*-[1-(ethoxy)ethylidene] group in compound **11**, followed by selective ring opening of the cyclic orthoester by careful hydrolysis of **24** or its 2-*O*-benzoate **25**, leading to diol **27** and alcohol **26**, respectively (Scheme 6). Glycosylation of compounds **26** and **27** with thioglycoside **22** under the same conditions as described for glycosylation of alcohol **12** led to di- and tri-saccharides **28** and **29**, in 74% and 84% yield, respectively. Ester protecting groups in **23** and **28** were cleaved under basic conditions to afford disaccharides representing fragments of apiogalacturonan **2** (Scheme 5), and **3** and **4** (Scheme 6).

Synthesis of RG-II trisaccharide 1: revised approach

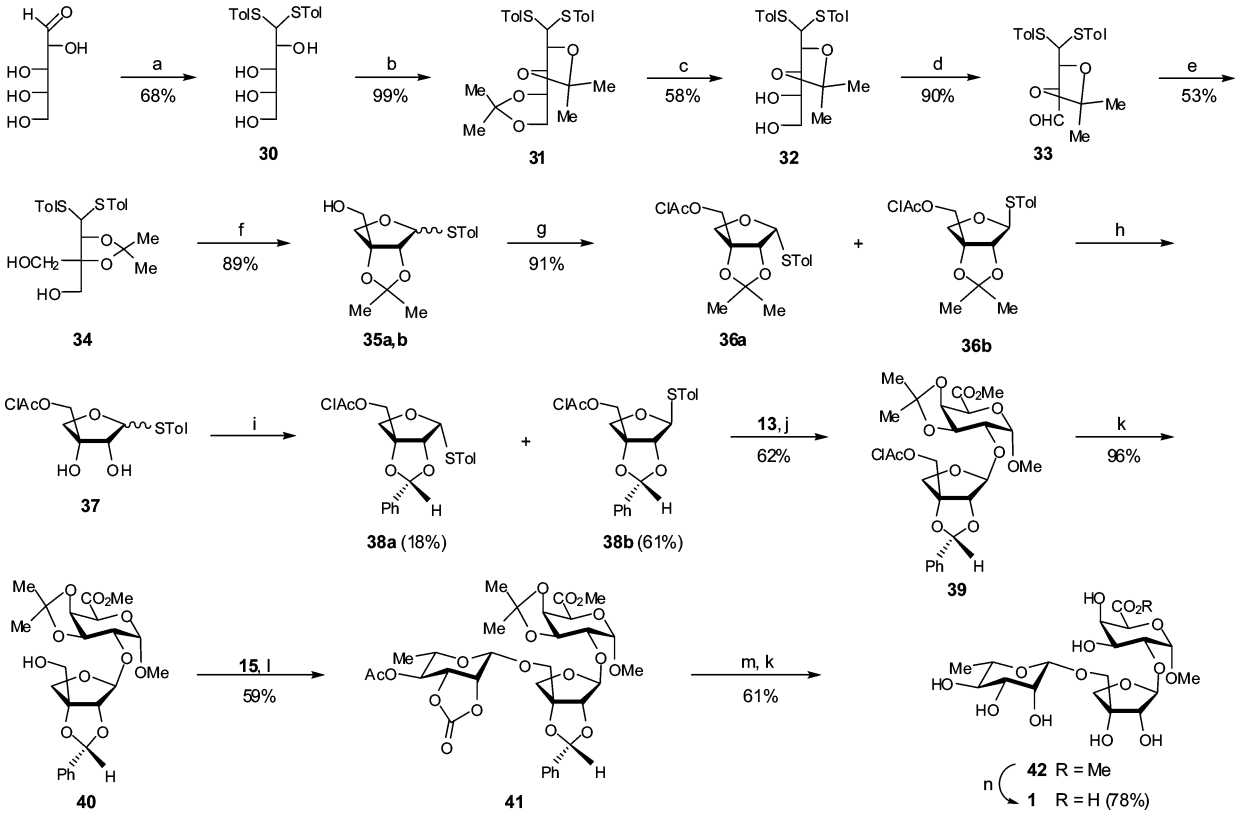
Revised thioapiofuranoside donor synthesis. Refinement of the reaction scheme leading to apiogalacturonan fragment **2** required additional levels of orthogonal protection for access to RG-II fragment **1**, given the internal apiose residue. This was achieved employing thioapiofuranoside **38**, which was equipped with cleavable 2,3-*O*-benzylidene and 3′-*O*-chloroacetyl protecting groups (Scheme 7). Although protecting groups other than the *O*-benzylidene group can be envisaged for blocking positions 2 and 3 in the apiofuranose residue (*e.g.* compound **21**[10a]), the benzylidene protection was preferred since it has potential advantages for the construction of larger RG-II fragments. In the synthesis of such fragments, benzylidene along with benzyl groups can be employed as permanent protecting groups which are orthogonal to temporary ester groups.

Synthesis of thioapiofuranosides **38a,b** was carried out starting from readily available L-arabinose dithioacetal by introduction of a *C*-3 branch point through a one-pot aldol–Cannizzaro reaction, followed by cyclisation of acyclic thioapiofuranoside **34**. Since aromatic thioglycosides possess higher hydrolytic stability than aliphatic analogues,[28] the dithioacetal precursor was prepared in the form of ditolylthio derivative **30**. The application of a similar approach to the preparation of apiose diethyldithio acetal has been reported.[30]

The reaction of L-arabinose with water-insoluble *p*-MeC_6H_4SH was carried out in 90% CF_3CO_2H according to a literature method.[31] This reaction gave crystalline dithioacetal **30** in 63% yield. *O*-Isopropylidenation of **30** led to dithioacetal **31**, which was hydrolyzed to 2,3-*O*-isopropylidene derivative **32** in 58% overall



Scheme 6 Synthesis of apiogalacturonan fragments. *Reagents and conditions*: (a) $MeC(OEt)_3$, TsOH, THF; (b) BzCl, C_5H_5N; (c) 80% AcOH; (d) NIS, $HClO_4/SiO_2$, MS 4 Å, –30 °C; (e) NaOMe, MeOH; (f) Et_3N–MeOH–H_2O; (g) NaOH, H_2O–MeOH.



Scheme 7 Trisaccharide fragment **1** of RG-II. *Reagents and conditions*: (a) *p*-MeC_6H_4SH, 90% TFA; (b) $Me_2C(OMe)_2$, Me_2CO, TsOH; (c) Py·HOTs, MeOH; d) $NaIO_4$ on SiO_2, CH_2Cl_2; (e) HCHO, NaOH, EtOH, H_2O; (f) NIS, CH_2Cl_2, –60 °C; (g) $CClCH_2COCl$, collidine, CH_2Cl_2; (h) 90% TFA; (i) $PhCH(OMe)_2$, CSA, toluene; (j) NIS, $HClO_4$ on SiO_2, CH_2Cl_2; (k) NaOMe, MeOH; (l) Ag_2O, MS 4 Å, CH_2Cl_2; (m) H_2–Pd/C, EtOAc; (n) Et_3N–H_2O–MeOH. ClAc = $ClCH_2CO$.

yield. It should be noted that while the former reaction was almost quantitative, in our hands the latter was accompanied by the undesirable cleavage of the 2,3-*O*-isopropylidene group, despite literature precedent for similar reactions with the diethyl dithioacetal analogue of **31**.[32] In order to improve the regioselectivity of the de-*O*-isopropylidenation of **31**, a very mild acid—pyridinium tosylate in MeOH[33]—was employed to catalyse the reaction, which was achieved in 58% yield.

In the following step, 4,5-diol **32** was oxidatively cleaved to afford aldehyde **33**—the precursor of the acyclic apiose derivative **34**. Complete insolubility of the starting diol **32** in water prevented application of conventional oxidation procedures for diols based on aqueous $NaIO_4$ treatment in homogeneous mixtures with organic solvents. To overcome the water solubility issue, periodate oxidation of vicinal diols was conducted in CH_2Cl_2 with the help of silica gel-supported $NaIO_4$.[34] Careful application of this procedure for oxidation of **32** allowed the synthesis of aldehyde **33** in 90% yield with over-oxidation of the substrate incorporating potentially vulnerable arylthio functionalities being avoided. The reaction was monitored by silica gel TLC, judged by the disappearance of the starting material. The product did not appear as a distinct spot, presumably because of the partial hydration of the aldehyde on the TLC plate. The NMR spectra of **34** clearly indicated the formation of an aldehyde, showing signals of the CHO group at δ_H 9.80 and δ_C 201.0 ppm in ^1H and ^{13}C NMR spectra, respectively. The aldol–Cannizzaro reaction of **33** with a slight excess of formaldehyde in the presence of NaOH gave 3-*C*-hydroxymethyl derivative **34** in 53% yield. Compound **34** is an acyclic derivative of apiose, which needs to be cyclized to form the furanose having the desired D-*erythro*-configuration *via* cleavage of one of the STol groups. Cyclization of dithioacetals leading to the formation of anomeric mixtures of corresponding thioglycosides is possible under the action of $HgCl_2$–HgO[35] or $CdCO_3$.[36] More recently such cyclization processes have been promoted with NIS–TfOH[37] or NIS[38] at low temperature. The latter method involving NIS as a thiophilic reagent was applied to synthesis of *p*-tolyl thioapiofuranosides **35a,b** from dithioacetal **34**, which proceeded in 89% yield.

The anomeric products ratio for the mixture of compounds **35a,b** was determined as $\alpha : \beta = 78 : 22$ using the H-1 and H-2 signal intensities in ^1H NMR spectra. Pure thioglycosides were easily isolated in the form of 3′-chloroacetates **36a** and **36b**, which were obtained by chloroacetylation of the mixture **35a,b**. Formation of α-thioapiofuranoside **35a** as the major product of cyclization was in accordance with the known, though not well understood, fact that cyclization of dithioacetals to thioglycosides proceeds with the predominant formation of 1,2-*cis*-thio glycofuranosides, which are apparently kinetic products of the reaction.[28,35] Cleavage of the isopropylidene acetal in compounds **36a** and **36b**, used as a mixture of thioglycosides, with 90% aq. TFA produced 2,3-diols **37a,b** as judged by near complete disappearance of *O*-isopropylidene group signals (δ 1.47 and 1.40 ppm) in the ^1H NMR spectrum. The crude

Table 1 Chemical shifts and coupling constants in ^{1}H NMR spectra (400 MHz, $CDCl_3$) of thioapiofuranosides **9a,b**, **22a,b**, **36a,b** and **38a,b**

Compound	H-1 ($J_{1,2}$)	H-2	H-3′a ($J_{3'a,3'b}$)	H-3′b	H-4a ($J_{4a,4b}$)	H-4b
9a	4.98 (3.9)	4.64	4.24 (11.7)	4.14	4.21 (10.2)	4.04
9b	5.60 (0)	4.54	4.41 (11.7)	4.29	4.17 (10.4)	4.03
22a[a]	5.66 (5.7)	5.58	4.59 (12.3)	4.34	4.27 (10.2)	4.21
22b[a]	5.32 (4.9)	5.21	4.54 (12.2)	4.37	4.27 (10.7)	4.10
36a	5.03 (3.9)	4.65	4.25 (11.7)	4.29	3.61 (10.3)	4.05
36b	5.60 (<0.1)	4.54	4.40 (10.8)	4.48	4.02 (10.4)	4.15
38a	5.07 (4.0)	4.80	4.41 (11.8)	4.47	3.64 (10.3)	4.30
38b	5.77 (<0.1)	4.62	4.51 (11.9)	4.60	4.22	4.22

[a] The assignment of the anomeric configurations of **22a** and **22b** is ambiguous and may be interchanged.

Table 2 Chemical shifts in ^{13}C NMR spectra (100 MHz, $CDCl_3$) of thioapiofuranosides **9a,b**, **22a,b**, **36a,b** and **38a,b**

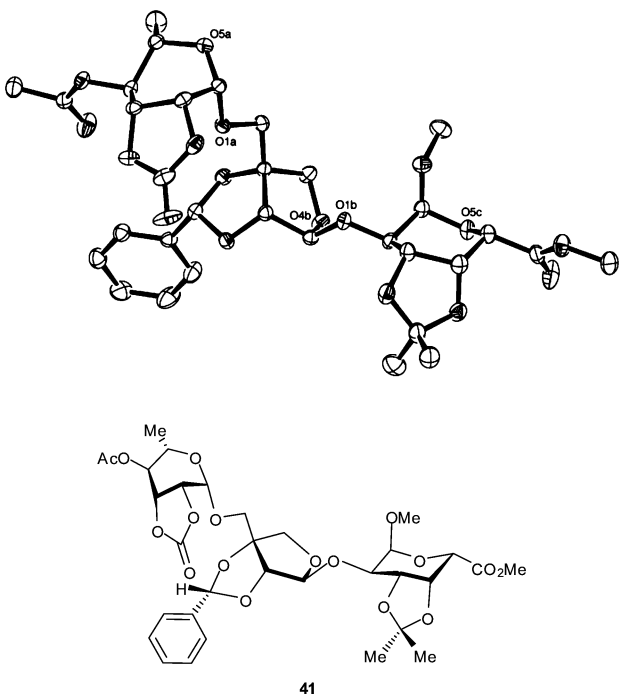
Compound	C-1	C-2	C-3	C-3′	C-4
9a	91.7	84.5	90.0	64.7	74.0
9b	93.3	87.7	90.5	65.1	73.6
22a	89.4	72.9	82.6	62.6	70.2
22b	90.7	75.9	83.6	62.6	72.6
36a	89.8	84.4	91.7	66.0	73.8
36b	93.3	87.6	90.3	66.5	73.5
38a	91.4	84.6	89.8	65.1	72.8
38b	92.6	87.7	90.3	65.4	72.6

mixture of **37a,b** was converted directly into 2,3-*O*-benzylidene compounds **38a** and **38b** by a camphorsulfonic acid-catalysed reaction with $PhCH(OMe)_2$. As expected from experience with thiofuranosides **22a,b**, noted earlier, deacetalation of individual samples of **36a** and **36b** with 90% TFA afforded anomeric mixtures of *p*-tolyl thioglycosides having approximately the same ~1 : 4 1,2-*cis*-/1,2-*trans*-glycoside ratio, as judged from ^{1}H NMR spectra.

Configurational assignment of thioapiofuranosides by NMR spectroscopy. The anomeric configuration assignment of thioapiofuranosides was made using the NMR spectral data for individual 3′-*O*-acylated compounds (Tables 1 and 2). Anomeric thioglycosides showed diagnostic differences between values of the $^3J_{H\text{-}1,H\text{-}2}$ coupling constant in ^{1}H NMR spectra of 2,3-*O*-isopropylidene derivatives: for 1,2-*trans*-thioglycosides the signal of H-1 appeared as a characteristic singlet whereas the corresponding signal of 1,2-*cis*-glycosides was in all cases a doublet with J ~ 4 Hz. It is well established[39] that $^3J_{H\text{-}1,H\text{-}2}$ coupling constants are usually 1–4 Hz larger for 1,2-*cis*- than for 1,2-*trans*-glycofuranosides, though absolute values of these coupling constants can be higher for *S*-glycofuranosides than for *O*-glycosides.[10d] Some deviation from typical patterns of $^3J_{H\text{-}1,H\text{-}2}$ values was observed in ^{1}H NMR spectra of a mixture of triacetates **22a,b**, where these coupling constants were 4.9 and 5.7 Hz and unambiguous assignment of α- and β-configuration for each component of the mixture was not possible. The configuration of benzylidene acetals **38a** and **38b** was tentatively assigned as (*S*), which proved consistent with subsequent X-ray crystallographic analysis (next section). The corresponding (*R*)-diastereoisomers were not purified as they were present only in minor quantities.

Sequential glycosylation to give trisaccharide 41. Coupling either **38a** or **38b** with methyl (galactopyranoside)uronate acceptor **12** promoted by NIS in the presence of cat. $HClO_4$ on SiO_2[29] at –40 °C led to 1,2-*trans*-linked disaccharide **39** in 62–70% yield as the only disaccharide product. Therefore 2,3-*O*-benzylidene-protected apiofuranose donors, as expected, can serve as stereoselective glycosylating agents. De-*O*-chloroacetylation of **39** afforded glycosyl acceptor **40**, which was β-rhamnosylated with 4-*O*-acetyl-2,3-*O*-carbonyl-α-L-rhamnopyranosyl bromide (**15**) in the presence of Ag_2O to afford protected trisaccharide **41** in 59% yield.

X-Ray crystal structure of trisaccharide 41. The structure of trisaccharide **41**, in particular the configuration of the β-rhamnopyranosidic and β-apiofuranosidic linkages, and the configuration of the benzylidene acetal protecting group, required additional confirmation which was obtained by X-ray crystallographic analysis (Fig. 3). Crystallographic data clearly demonstrated the *endo*-orientation of the phenyl group ((*S*)-configuration) of the benzylidene protecting group. They also revealed the anomeric configuration and conformations of individual monosaccharide components of the trisaccharide, each of which incorporates a five-membered ring protecting group. While a 3,4-*O*-isopropylidene protecting group doesn't affect the $^4C_1$



41

Fig. 3 ORTEP representation of the X-ray crystal structure of trisaccharide derivative **41**.

conformation of α-D-galactopyranosiduronic acid, the presence of a 2,3-*O*-carbonate group on a β-L-rhamnopyranosyl residue led to significant deviation from the normal $^4C_1$ chair conformation. In trisaccharide **41**, the rhamnopyranose ring approximates a $B_{1,4}$ boat conformation, which is different to the ^5H_O half-chair conformation found in the crystal structure of 3β-cholestanyl 4-*O*-acetyl-2,3-*O*-carbonyl-β-L-rhamnopyranoside.[40] The most obvious difference between conformations of the pyranose rings in these compounds is the orientation of the C1–O1 bond of the β-rhamnopyranosyl residue, which may be described as pseudo-axial for $B_{1,4}$ and pseudo-equatorial for ^5H_O conformations. However, the solution conformation of the β-rhamnopyranosyl ring of **41** appears different to either $B_{1,4}$ or ^5H_O, since values of the $^3J_{1,2}$ (~1 Hz) and $^3J_{2,3}$ (<3.7 Hz, see the ESI†) coupling constants in ^{1}H NMR spectra are smaller than the values of $^3J_{1,2}$ (>2 Hz) and $^3J_{2,3}$ (6–7 Hz) that can be expected for these conformations.

In the crystal structure of **41**, the five-membered furanose ring, the mobility of which is constrained by the cyclic acetal protecting group, adopts the E_O conformation. In the absence of such constraints in the crystal structure of benzyl (2,3,3′-tri-*O*-acetyl-β-D-apiofuranosyl)-(1→3)-(2,4-di-*O*-benzoyl-α-D-xylopyranoside)[11b] the apiofuranose ring has the E_2 conformation but both in this case and in the structure of **41** the C1–O1 bond is quasi-axial.

Deprotection to complete synthesis of target RG-II trisaccharide 42. The trisaccharide **41** was deprotected in a series of reactions starting with catalytic hydrogenolysis, which allowed removal of the benzylidene group, as confirmed by NMR spectroscopy and MS data. Mild acid hydrolysis of the isopropylidene group followed by standard Zemplen de-acetylation furnished methyl ester **42** in 61% overall yield. Finally, treatment of **42** with Et_3N in MeOH–H_2O[41] led to de-esterification of the GalA residue and formation of trisaccharide **1**.

Conclusions

The biosynthesis of complex pectic glycans remains a largely blank canvas. To date, few of the enzymes/genes required have been identified. In this study, we have elaborated methods for the chemical synthesis of apiofuranose building blocks and their use for the preparation of apiose-containing glycans. We have successfully completed the synthesis of di- and tri-saccharide fragments of RG-II side-chains A and B, and related apiogalacturonan structures. The biochemical evaluation of these materials will be reported in due course.

Experimental

All reagents were used as purchased without further purification. Reactions were carried out in dry solvents using septa and syringes for addition of reagents. Dry CH_2Cl_2 and MeCN were used freshly distilled from CaH_2. The SiO_2-supported $HClO_4$-catalyst (~0.5 mmol of the acid per 1 g of powder) was prepared using Merck silica gel (15–40 mkm) according to procedure reported in ref. 42 The SiO_2-supported $NaIO_4$ was prepared according to the method in ref. 34. TLC was performed on precoated aluminium plates (Silica Gel 60 F_{254}, Merck). Spots were visualized by exposure to UV light or by immersion into 5% ethanolic H_2SO_4 followed by heating to 150 °C. Solutions of reaction products were dried over $MgSO_4$ and solvents were evaporated under reduced pressure at 25–40 °C. Column chromatography was performed on a Biotage SP4 purification system using silica gel pre-packed cartridges. Gel permeation chromatography (GPC) was performed using Toyopearl HW-40S resin (80 × 1.5 cm column) using water as an eluent and a differential refractometer as a detector. Optical rotations were measured using a Perkin–Elmer 141 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded at 22 °C with a JEOL Lambda spectrometer at 400 and 100 MHz, respectively, using TMS (for solution in $CDCl_3$) or Me_2CO (δ 49.9, for solutions in D_2O) as internal standards. Resonance assignments were made with the aid of gCOSY and gHSQC experiments. High resolution electrospray ionisation mass spectra (HR ESI-MS) were obtained using positive ionization mode on a Finnigan MAT 900 XLT mass spectrometer or Thermofisher LTQ Orbitrap instrument.

p-Tolyl 3-*C*-acetoxymethyl-2,3-*O*-isopropylidene-1-thio-α-D-erythrofuranoside (9a) and *p*-tolyl 3-*C*-acetoxymethyl-2,3-*O*-isopropylidene-1-thio-β-D-erythrofuranoside (9b)

A mixture of 3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-D-erythrofuranoside (**7**)[20a] (2.00 g, 10.52 mmol) and Ac_2O (5.0 mL) in pyridine (10 mL) was stirred for 17 h at 22 °C, the reaction was quenched with MeOH (5.0 mL) at +5 °C, toluene (15 mL) was added and the mixture was concentrated. The operation was repeated several times and the residue was purified by chromatography. Fractions containing the major faster moving component were combined and concentrated to give diacetate **8**,[12a] as an oil, 2.34 g, 81%, R_f 0.42 (hexane–EtOAc 7 : 3), ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (1 H, s, H-1), 4.47 (1 H, s, H-2), 4.39 (1 H, d, *J* 11.7 Hz, H-3a), 4.25 (1 H, d, *J* 11.7 Hz, H-3b), 4.11 (1 H, d, *J* 10.3 Hz, H-4a), 3.97 (1 H, d, *J* 10.3 Hz, H-3b), 2.13 (3 H, s, Ac), 2.08 (3 H, s, Ac), 1.50 (3 H, s, C*Me*$_2$), 1.42 (3 H, s, C*Me*$_2$). Compound **8** (2.20 g, 8.02 mmol) and thiocresol (885 mg, 8.03 mmol) were dissolved in dry CH_2Cl_2 (20 mL), the solution was cooled to 0 °C, $BF_3{\cdot}OEt_2$ (0.4 mL, 3.65 mmol) was added and the mixture was stirred for 2 h at 22 °C. The solution was diluted with CH_2Cl_2 (100 mL), washed with satd $NaHCO_3$, concentrated and products were purified by chromatography. Compound **9b** was eluted first (1.80 g, 66%), R_f 0.42, then was eluted compound **9a** (160 mg, 6%), R_f 0.29 (hexane–EtOAc 80 : 20). Compound **9a**, $[\alpha]_D^{22}$ +43 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (2 H, d, *J* 8.1 Hz, SC$_6$*H*$_4$Me), 7.05 (2 H, d, *J* 8.1 Hz, SC$_6$*H*$_4$Me), 4.98 (1 H, d, 3.9 Hz, H-1), 4.64 (1 H, d, 3.9 Hz, H-2), 4.24 (1 H, d, *J* 11.7 Hz, H-3′a), 4.21 (1 H, d, *J* 10.2 Hz, H-4a), 4.14 (1 H, d, *J* 11.7 Hz, H-3′b), 4.04 (1 H, d, *J* 10.2 Hz, H-4b), 2.32 (3 H, s), 2.03 (3 H, s, Ac), 1.55 (3 H, s, C*Me*$_2$), 1.38 (3 H, s, C*Me*$_2$); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 170.6 (C═O), 137.6, 131.7, 129.9 (S*C*$_6$H$_4$Me), 115.3 (*C*Me$_2$), 91.7 (C-1), 90.0 (C-3), 84.5 (C-2), 74.0 (C-4), 64.7 (C-3′), 27.5 (×2, C*Me*$_2$), 21.0 (SC$_6$H$_4$*Me*), 20.6 (Ac);. ESI MS (+): *m*/*z* found 356.20 ([M + NH_4]$^+$); calcd for $C_{17}H_{26}NO_5S$ 356.15. Compound **9b**, $[\alpha]_D^{22}$ −282 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (2 H, d, *J* 8.1 Hz, SC$_6$*H*$_4$Me), 7.12 (2 H, d, *J* 8.1 Hz, SC$_6$*H*$_4$Me), 5.60 (1 H, s, H-1), 4.54 (1 H, s, H-2), 4.41 (1 H, d, *J* 11.7 Hz, H-3′a), 4.29 (1 H, d, *J* 11.7 Hz, H-3′b), 4.17 (1 H, d, *J* 10.4 Hz, H-4a), 4.03 (1 H, d, *J* 10.4 Hz, H-4b), 2.32 (3 H, s, SC$_6$H$_4$*Me*), 2.14 (3 H, s, Ac), 1.48 (3 H, s, C*Me*$_2$), 1.41 (3 H, s, C*Me*$_2$); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 170.6 (C═O),

138.0, 132.7, 130.0 (SC_6H_4Me), 115.3 (*C*Me_2), 91.7 (C-1), 90.0 (C-3), 84.5 (C-2), 74.0 (C-4), 64.7 (C-3′), 27.5 (CMe_2), 27.4 (CMe_2), 21.0 (SC_6H_4Me), 20.6 (Ac); HRMS (ESI+): *m/z* found 339.1263 ([M + H]$^+$); calcd for $C_{17}H_{22}O_5S{\cdot}H$ 339.1261.

Methyl (methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (12)

AcCl (11.2 mL) was carefully added to a stirred solution of galacturonic acid (**10**) (12.5 g, 64 mmol) in MeOH (750 mL) in order to generate 1 w/v% HCl solution. The mixture was refluxed for 18 h, neutralized with $PbCO_3$ (~21 g), the precipitate was filtered off and the solution was concentrated. Crystallization of the resulting residue from EtOH afforded compound **11**[23] (3.0 g, 21%) as a white powder. The mother liquor contained a mixture methyl (methyl galactopyranosid)uronates which was recycled as a starting material for preparation of compound **11**. Crystalline **11** (1.0 g, 4.5 mmol) was suspended in a mixture of DMP (10 mL) and acetone (10 mL), cat. CSA was added and the mixture was stirred for 4 h at 22 °C until starting material almost disappeared (TLC EtOAc–MeOH 9 : 1). The mixture was neutralized with Et_3N, concentrated and the residue was purified by chromatography followed by crystallization from hexane–EtOAc to give derivative **12** (910 mg, 77%); m.p. 112–114 °C; $[\alpha]_D^{22}$ +122 (*c* 1.0, H_2O); Lit.[43] m.p. 113–4 (pet. ether); $[\alpha]_D^{20}$ +117 (H_2O) ^{1}H NMR. (400 MHz, $CDCl_3$): δ 4.88 (1 H, d, *J* 3.9 Hz, H-1), 4.63 (1 H, d, *J* 2.5 Hz, H-5), 4.52 (1 H, dd, *J* 6.3 Hz, *J* 2.5 Hz, H-4), 4.33 (1 H, dd, *J* 10.4 Hz, 4.3 Hz, H-3), 3.93 (1 H, dd, *J* 5.8 Hz, 3.9 Hz, H-2), 3.81 (3 H, s, CO_2Me), 3.48 (3 H, s, OMe), 2.62 (1 H, br s, OH), 1.46 (3 H, s, CMe_2), 1.32 (3 H, s CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9 (C═O), 110.4 (Me_2C), 98.5 (C-1), 75.4 (C-5), 73.7 (C-4), 68.8 (C-3), 68.3 (C-2), 56.3 (CO_2Me), 52.6, O*Me*), 27.4 (Me_2C), 25.9 (Me_2C).

Methyl (3-*C*-acetoxymethyl-2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (13)

A mixture of **12** (170 mg, 0.65 mmol), NIS (150 mg, 0,67 mmol) and mol. sieves 4 Å (0.5 g) was stirred for 30 min at 22 °C, then the mixture was cooled to −40 °C and thioglycoside **9b** (170 mg, 0.50 mmol) in CH_2Cl_2 (4.0 mL) and TMSOTf (36 µL, 0.20 mmol) were sequentially added from separate syringes. The stirring continued for 1 h at −40 to −20 °C, before the reaction was quenched with Et_3N (0.4 mL). The mixture was filtered through a Celite pad, the filtrate was diluted with CH_2Cl_2 (50 mL) and washed with 10% $Na_2S_2O_3$ and satd $NaHCO_3$ solutions. Solvent was removed under reduced pressure and the residue was purified by chromatography to afford disaccharide **13** (190 mg, 79%), R_f 0.51 (hexane–EtOAc 70 : 30); $[\alpha]_D^{24}$ −1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (1 H, s, H-1 Api), 4.92 (1 H, d, *J* 3.5 Hz, H-1 GalA), 4.57 (1 H, d, *J* 2.8 Hz, H-5 GalA), 4.50– 4.45 (2 H, m, H-4 GalA, H-2 Api), 4.40 (1 H, d, *J* 11.6 Hz, H-H-3′a Api), 4.25 (1 H, dd, *J* 7.7 Hz, *J* 5.5 Hz, H-3 GalA), 4.19 (1 H, d, *J* 11.6 Hz, H-3′b Api), 3.97 (1 H, d, *J* 10.0 Hz, H-4a Api), 3.85–3.80 (4 H, m, H-4b Api, CO_2Me), 3.76 (1 H, dd, *J* 8.0 Hz, 3.5 Hz, H-2 GalA), 3.39 (3 H, s, OMe), 2.10 (3 H, s, Ac), 1.50 (3 H, s, CMe_2), 1.47 (3 H, s, CMe_2), 1.39 (3 H, s, CMe_2), 1.33 (3 H, s, CMe_2); ^{13}C NMR (100 MHz): δ 170.7 (CH_3CO), 168.5 (CO_2Me), 113.9 (Me_2C), 109.9 (Me_2C), 108.0 (C-1 Api), 99.9 (C-1 GalA), 89.9 (C-3 Api), 86.4 (C-2 Api), 75.8 (C-2 GalA), 75.1 (C-3 GalA), 74.5 (C-4 Api), 73.9 (C-4 GalA), 67.2 (C-5 GalA), 65.6 (C-3′ Api), 56.3 (O*Me*), 52.7 (CO_2Me), 28.3 (Me_2C), 27.7 (Me_2C), 27.2 (Me_2C).26.5 (Me_2C), 21.0 (*Me*CO); HRMS (ESI+): *m/z* found 494.2236 ([M + NH_4]$^+$); calcd for $C_{21}H_{32}O_{12}{\cdot}NH_4$ 494.2232.

Methyl (2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (14)

A solution of monoacetate **13** (186 mg, 0.39 mmol) in 0.1 M NaOMe in MeOH (2 mL) was kept for 1 h at 24 °C, carefully neutralized with Amberlite IR 120 (H^+) resin and concentrated. Purification of the residue by chromatography gave alcohol **14** as a white solid (164 mg, 97%); $[\alpha]_D^{22}$ +10 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (1 H, s, H-1 Api), 4.92 (1 H, d, *J* 3.6 Hz, H-1 GalA), 4.58 (1 H, d, *J* 2.9 Hz, H-5 GalA), 4.48 (1 H, dd, *J* 5.5 Hz, 2.9 Hz, H-4 GalA), 4.43 (1 H, s, H-2 Api), 4.27 (1 H, dd, *J* 7.9 Hz, 5.5 Hz, H-3 GalA), 3.96 (1 H, d, *J* 10.0 Hz, H-4a Api), 3.88 (1 H, d, *J* 10.0 Hz, H-4b Api), 3.80–3.71 (6 H, m, H-2 GalA, H-3′a and H-3′b Api, CO_2Me), 3.41 (3 H, s, OMe), 1.46 (s, 3 H, CMe_2), 1.43 (s, 3 H, CMe_2), 1.34 (s, 3 H, CMe_2), 1.28 (s, 3 H, CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (CO_2Me), 113.2 (Me_2C), 109.8 (Me_2C), 107.5 (C-1 Api), 99.6 (C-1 GalA), 91.9 (C-3 Api), 86.1 (C-2 Api), 75.0 (C-2 GalA), 74.8 (C-3 GalA), 74.3 (C-4 Api), 73.7 (C-4 GalA), 67.0 (C-5 GalA), 64.5 (C-3′ Api), 56.1 (O*Me*), 52.4 (CO_2Me), 27.9 (Me_2C), 27.4 (Me_2C), 27.2 (Me_2C), 26.2 (Me_2C). HRMS (ESI+): *m/z* found 435.1861 ([M + NH_4]$^+$); calcd for $C_{19}H_{30}O_{11}{\cdot}NH_4$ 435.1861.

Methyl (4-*O*-acetyl-2,3-*O*-carbonyl-β-L-rhamnopyranosyloxy-methyl)-(1→3)-*C*-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)-uronate (16)

A mixture of disaccharide **14** (130 mg, 0.30 mmol), Ag_2O (280 mg, 1.21 mmol) and molecular sieves 4 Å (1.0 g) in CH_2Cl_2 (6 mL) was stirred for 1 h in the dark at 20 °C and a solution of freshly prepared rhamnopyranosyl bromide **15**[26] (195 mg, 3.05 mmol) in CH_2Cl_2 (4 mL) was added over 1 h. After stirring the mixture in the dark for 5 h at 20 °C, it was treated with pyridine (0.3 mL), diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with 10% satd aq. $Na_2S_2O_3$, water, the organic layer concentrated and the residue was purified by chromatography to give trisaccharide **16** (85 mg, 44%), R_f 0.27 (toluene–EtOAc 50 : 50); $[\alpha]_D^{22}$ +31 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (1 H, dd, *J* 8.3 Hz, 4.6 Hz, H 4 Rha), 5.27 (1 H, s, H-1 Api), 5.16 (1 H, s H 1 Rha), 4.98 (1 H, d, *J* 3.4 Hz, H-1 GalA), 4.81–4.78 (2 H, m, H-2, H-3 Rha), 4.58 (1 H, d, *J* 2.6 Hz, H 5 GalA), 4.48 (1 H, dd, *J* 5.3 Hz, 2.6 Hz, H-4 GalA), 4.37 (1 H, s, H-2 Api), 4.26 (1 H, dd, *J* 7.6 Hz, 5.3 Hz, H-3 GalA), 4.10 (1 H, d, *J* 11.2 Hz, H-3′a Api), 4.01 (1 H, d, *J* 10.2 Hz, H-4a Api), 3.94 (1 H, d, *J* 10.2 Hz, H-3′b Api), 3.87 (1 H, d, *J* 11.2 Hz, H-4b Api) 3.84 (3 H, s, CO_2Me), 3.78–3.73 (2 H, m, H-2 GalA, H-5 Rha), 3.42 (3 H, s), 2.12 (3 H, s, OMe), 1.51 (3 H, s, Ac), 1.47 (s, 3 H, CMe_2), 1.40 (s, 3 H, CMe_2), 1.34 (s, 3 H, CMe_2), 1.30 (3 H, d, *J* 6.3 Hz, H-6 Rha); ^{13}C NMR (100.5 MHz): δ 169.3 (CH_3CO), 168.7 (CO_2Me), 153.6 (C═O), 114.1 (Me_2C), 110.0 (Me_2C), 108.2 (C-1 Api), 99.9 (C-1 GalA), 95.1 (C-1 Rha), 91.5 (C-3 Api), 86.3 (C-2 Api), 76.3 (C-2

GalA), 76.2 (C-2* Rha), 75.1 (C-3 GalA), 75.0 (C-4 Api), 74.0 (C-4 GalA), 72.6 (C-3* Rha), 71.4, 71.3 (C-3′ Api, C-4 Rha), 70.8 (C-5 Rha), 67.2 (C-5 GalA), 56.4 (O*Me*), 52.8 (CO_2*Me*), 28.4 (*Me*$_2$C), 27.7 (*Me*$_2$C), 27.4 (*Me*$_2$C), 26.6 (*Me*$_2$C), 21.0 (*Me* CO), 19.8 (C-6 Rha); HRMS (ESI+): *m*/*z* found 666.2605 ([M + NH_4]$^+$); calcd for $C_{28}H_{40}O_{17}\cdot NH_4$ 666.2604.

Methyl (β-L-rhamnopyranosyloxymethyl)-(1→3)-*C*-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (17)

A solution of trisaccharide **16** (65 mg, 100 μmol) in 0.1 M methanolic NaOMe solution (1 mL) was allowed to stand for 30 min at 22 °C, then neutralized with Amberlite IR-120 (H^+) resin, diluted with MeOH (6 mL) and an excess of the same resin was added. The mixture was stirred for 48 h at 22 °C, the resin was filtered off and the solvent was evaporated to give target trisaccharide **17** (50 mg, 91%); $[\alpha]_D^{25}$ +22.5 (*c* 1.6, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (1 H, s, H-1 Api), 4.94 (1 H, d, *J* 3.8 Hz, H-1 GalA), 4.61 (1 H, br s, H-1 Rha), 4.54 (1 H, d, *J* 1.3 Hz, H-5 GalA), 4.50 (1 H, s, H-2 Api), 4.26 (1 H, dd, *J* 1.5 Hz, *J* 3.4 Hz, H-4 GalA), 4.05 (1 H, d, *J* 11.0 Hz, H-3′a Api), 4.02 (1 H, d, *J* 10.7 Hz, H-4a Api), 3.96 (1 H, br d, *J* 3.3 Hz, H-2 Rha), 3.93 (1 H, d, *J* 10.7 Hz, H-4b Api), 3.89 (1 H, d, *J* 11.0 Hz, H-3′b Api), 3.86 (1 H, dd, *J* 3.4 Hz, *J* 10.3 Hz, H-3 GalA), 3.77 (1 H, dd, *J* 3.8 Hz, *J* 10.3 Hz, H-2 GalA), 3.72 (3 H, s, CO_2*Me*), 3.50 (1 H, m, H-3 Rha), 3.33 (3 H, s, OMe), 3.27–3.33 (2 H, m, H-4, H-5 Rha), 1.40 (3 H, s, *Me*$_2$C), 1.36 (3 H, s, *Me*$_2$C), 1.22 (1 H, d, *J* 6.5 Hz, H-6 Rha); ^{13}C NMR (100 MHz, D_2O): δ 171.6 (*C*O_2Me), 114.7 (Me$_2$*C*), 109.1 (C-1 Api), 100.6 (C-1 Rha), 99.5 (C-1 GalA), 91.5 (C-3 Api), 86.2 (C-2 Api), 75.6 (C-2 GalA), 75.0 (C-4 Api), 73.0 (C-2 or C-3 Rha), 72.6, 72.5 (C-4, C-5 Rha), 71.7 (C-3′ Api), 70.9 (C-3 or C-2 Rha), 70.8 (C-5 GalA), 70.4 (C-4 GalA), 68.2 (C-3 GalA), 55.9 (O*Me*), 53.3 (CO_2*Me*), 26.9 (*Me*$_2$C), 26.5 (*Me*$_2$C), 17.0 (C-6 Rha); HRMS (ESI+): *m*/*z* found 558.2393 ([M + NH_4]$^+$); calcd for $C_{22}H_{36}O_{15}\cdot NH_4$ 558.2392.

p-Tolyl 3-*C*-acetoxymethyl-2,3-di-*O*-acetyl-1-thio-α,β-D-erythrofuranoside (22a and 22b)

A solution of compound **9b** (570 mg, 1.68 mmol) in 90% CF_3CO_2H was allowed to stand at 20 °C, until TLC (EtOAc) indicated almost complete disappearance of the starting material (<1 h). The solution was concentrated *in vacuo* with toluene, the residues were dissolved in C_5H_5N (10 mL), Ac_2O (5.0 mL) and cat. DMAP were added and the mixture was kept for 18 h at 22 °C. After careful quenching of the reaction by addition of MeOH (5 mL) at 0 °C, the mixture was concentrated and the residue was purified by chromatography to give triacetate **22** (490 mg, 76%) as a mixture of α- and β-glycosides (**22a** : **22b** = 1 : 5, from ^{1}H NMR integration); R_f 0.27 (hexane–EtOAc 80 : 20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (2.4 H, m, SC_6H_4Me α and β), 7.11 (2.4 H, m, SC_6H_4Me α and β), 5.66 (0.2 H, d, *J* 5.7 Hz, H-1 α), 5.58 (0.2 H, d, *J* 5.7 Hz, H-2 α), 5.32 (1 H, d, *J* 4.9 Hz, H-1 β), 5.21 (1 H, d, *J* 4.9 Hz, H-2 β), 4.59 (0.2 H, d, *J* 12.3 Hz, H-3′a α), 4.54 (1 H, d, *J* 12.2 Hz, H-3′a β), 4.37 (1 H, d, *J* 12.2 Hz, H-3′b β), 4.34 (0.2 H, d, *J* 12.3 Hz, H-3′b α), 4.27 (1.2 H, d, *J* 10.7 Hz, H-4a β), 4.21 (0.2 H, br d, *J* 10.6 Hz, H4a α, H-4a β), 4.10 (1 H, d, *J* 10.6 Hz, H-4b β), 2.32 (3 H, s, SC_6H_4*Me* β), 2.31 (1 H, s, SC_6H_4*Me*, α), 2.17 (3 H, s, Ac, α), 2.10 (3 H, s, Ac β), 2.07 (3 H, s, Ac, α), 2.06 (3 H, s, Ac α), 2.04 (3 H, s, Ac β), 2.02 (3 H, s, Ac β).; ^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 169.9, 169.4 (Me*C*O), 138.8, 133.8, 132.9, 130.1, 128.5 (S*C*$_6$H$_4$Me), 90.7 (1α), 89.4 (1β), 83.6 (3β), 82.6 (3α), 75.9 (2β), 72.9 (2α), 72.6 (4β), 70.2 (4α), 62.6 (2 C, 3′α, 3′β), 21.5, 21.4 (SC$_6$H$_4$*Me*), 20.9 (2 C), 20.8 (*Me*CO); HRMS (ESI+): *m*/*z* found 400.1424 ([M + NH_4]$^+$); calcd for $C_{18}H_{22}O_7S\cdot NH_4$ 400.1424.

Methyl (3-*C*-acetoxymethyl-2,3-di-*O*-acetyl-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (23). A solution of thioglycoside **9b** (390 mg, 1.02 mmol) and alcohol **12** in CH_2Cl_2 (20 mL) was stirred with mol. sieves 4 Å (1.0 g) for 20 min at room temperature and the mixture was cooled to –40 °C. A solution of TMSOTf (18 μL, 0.10 mmol) in CH_2Cl_2 (0.18 mL) was added, the mixture was stirred for 30 min allowing the temperature to rise to –20 °C and then treated with Et_3N (0.2 mL). After dilution with CH_2Cl_2 and filtration through the Celite, $Na_2S_2O_3$ solution (10%) was added to the filtrate and the mixture was vigorously stirred for 30 min. The organic layer was separated and washed with aq. $NaHCO_3$ solution, dried and concentrated. Purification of the product by chromatography afforded disaccharide **23** (410 mg, 77%) as crystalline solid; R_f 0.36 (pet. ether–EtOAc 50 : 50); m. p. 146–148 °C; $[\alpha]_D^{22}$ –2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (1 H, s, H-2 Api), 5.23 (1 H, s, H-1 Api), 4.94 (1 H, d, *J* 3.6 Hz, H-1 GalA), 4.92 (1 H, d, *J* 12.3 Hz, H-3′a Api), 4.59 (1 H, d, *J* 2.8 Hz, H-5 GalA), 4.51 (1 H, d, *J* 12.3 Hz, H-3′b Api), 4.48 (1 H, d, *J* 2.8 Hz, H-4 GalA), 4.30 (1 H, dd, *J* 5.5 Hz, *J* 7.7 Hz, H-3 GalA), 4.17 (2 H, s, H 4a,b Api), 3.84 (3 H, s, OMe), 3.79 (dd, *J* 3.6 Hz, *J* 7.80 Hz, H-2 GalA), 3.43 (3 H, s, CO_2Me), 2.10 (3 H, s, Ac), 2.01 (3 H, s, Ac), 1.51 (3 H, s, *Me*$_2$C), 1.34 (3 H, s, *Me*$_2$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 169.8, 168.9, 168.4 (C═O), 109.9 (Me$_2$*C*), 105.8 (C-1 Api), 99.6 (C-1 GalA), 84.1 (C-3 Api), 76.2 (C-2 Api), 75.4 (C-2 GalA), 74.8 (C-3 GalA), 73.7 (C-4 GalA), 72.5 (C-4 Api), 67.1 (C-5 GalA), 63.0 (C-3′ Api), 56.2 (O*Me*), 52.5 (CO_2*Me*), 28.1 (C*Me*$_2$), 26.3 (C*Me*$_2$), 21.1, 20.7, 20.6 (C-Ac); HRMS (ESI+): *m*/*z* found 538.2133 ([M + NH_4]$^+$); calcd for $C_{22}H_{32}O_{14}\cdot NH_4$ 538.2130.

Methyl-(methyl 3,4-*O*-(1-ethoxyethylidene)-α-D-galactopyranosid)uronate (24)

A solution of triol **11** (2.22 g, 10.0 mmol), $(EtO)_3CMe$ (7.3 mL, 40 mmol) and cat. CSA in THF (20 mL) was stirred for 1.5 h at 22 °C. The reaction was quenched by addition of Et_3N (2 mL), the mixture was concentrated, redissolved in CH_2Cl_2, washed with satd $NaHCO_3$ and concentrated. The residue was purified by chromatography to give the orthoester **24** as a single diastereomer (2.12 g, 73%); R_f 0.33 (EtOAc–hexane 80 : 20); $[\alpha]_D^{20}$ +70 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (1 H, d, *J* 4.0 Hz, H-1), 4.74 (1 H, dd, *J* 6.9 Hz, 2.4 Hz, H-4), 4.67 (1 H, d, *J* 2.4 Hz, H-5), 4.56 (1 H, dd, *J* 6.9 Hz, 5.1 Hz, H-3), 4.02 (1 H, m, H-2), 3.83 (3 H, s, CO_2*Me*), 3.58–3.49 (5 H, m, OMe, O*C*H_2Me), 1.62 (3 H, s, C(OEt)*Me*), 1.22–1.16 (3 H, m, *J* 7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (*C*O_2Me), 122.1 (Me*C*OEt), 97.5 (C-1), 75.1 (C-3), 74.0 (C-4), 68.6 (C-5), 67.0 (C-2), 58.5 (*C*H_2Me), 56.0 (O*Me*), 52.4 (CO_2*Me*), 21.9 (*Me*COEt), 15.4 (CH$_2$*Me*); HRMS (ESI+): *m*/*z* found 293.1231 ([M + NH_4]$^+$); calcd for $C_{12}H_{20}O_8\cdot NH_4$ 293.1231.

Methyl (methyl 2-*O*-benzoyl-3,4-*O*-(1-ethoxyethylidene)-α-D-galactopyranosid)uronate (25)

Benzoyl chloride (0.81 mL, 7.00 mmol) was added to a solution of orthoester **24** (2.20 g, 5.56 mmol) in pyridine (10 mL) and the mixture was stirred for 17 h at 21 °C. After quenching the excess of BzCl with MeOH, the mixture was diluted with CH_2Cl_2 and washed with satd $NaHCO_3$, the organic layer was concentrated and the product **25** (1.73 g, 78%) was isolated by chromatography. R_f 0.30 (hexane–EtOAc 4 : 1); $[\alpha]_D^{20}$ +112.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (2 H, m, Ph), 7.56 (1 H, m, Ph), 7.40 (2 H, m, Ph), 5.17 (1 H, dd, *J* 7.4 Hz, 3.7 Hz, H-2), 5.10 (1 H, d, *J* 3.7 Hz, H-1), 4.79 (1 H, dd, *J* 6.0 Hz, 2.9 Hz, H-4), 4.67 (1 H, dd, *J* 7.4 Hz, *J* 6.0 Hz, H-3), 4.66 (1 H, d, *J* 2.9 Hz, H-5), 3.83 (3 H, s, CO_2Me), 3.56–3.47 (2 H, m, CH_2Me), 3.39 (3 H, s, OMe), 1.62 (3 H, s, EtOC*Me*), 1.15 (3 H, t, *J* 9.3 Hz, OCH_2Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (C═O), 165.9 (CO_2Me), 133.6, 130.1, 129.5, 128.6 (2C) (Ph), 122.0 (Me*C*OEt), 97.5 (C-1), 74.2, 74.0 (C-3, C-4), 71.2 (C-2), 67.4 (C-5), 58.8 (CH_2Me), 56.6 (OMe), 52.8 (CO_2Me), 23.0 (*Me*COEt), 15.5 (CH_2Me); HRMS (ESI+): *m*/*z* found 414.1763 ([M + NH_4]$^+$); calcd for $C_{19}H_{24}O_9{\cdot}NH_4$ 414.1759.

Methyl (methyl 4-*O*-acetyl-2-*O*-benzoyl-α-D-galactopyranosid)uronate (26)

A solution of orthoester **25** in 80% AcOH (20 mL) was kept for 30 min at 22 °C, then concentrated repeatedly with toluene to remove all solvents and the residue was crystallized from a toluene–hexane mixture to give acetate **26**, (1.25 g (79%), R_f 0.25 (hexane–EtOAc 60 : 40); m.p. 144.5–145 °C; $[\alpha]_D^{20}$ +141 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.01 (2 H, m, Ph), 7.54 (1 H, m, Ph), 7.43–7.38 (2 H, m, Ph), 5.67 (1 H, dd, *J* 3.6 Hz, *J* 1.4 Hz, H-4), 5.26 (1 H, dd, *J* 10.4 Hz, 3.7 Hz, H-2), 5.18 (1 H, d, *J* 3.7 Hz, H-1), 4.56 (1 H, d, *J* 1.4 Hz, H-5), 4.42–4.35 (1 H, m, H-3), 3.73 (3 H, s, CO_2Me), 3.40 (3 H, s, OMe), 2.93 (1 H, d, *J* 5.9 Hz, OH), 2.10 (3 H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.2, 166.8 (C═O), 133.7, 130.1, 129.5, 128.6 (Ph), 98.1 (C-1), 71.8 (C-4), 71.4 (C-2), 68.8 (C-5), 66.8 (C-3), 56.5 (O*Me*), 52.9 (CO_2Me), 20.9 (Ac); HRMS (ESI+): *m*/*z* found 369.1180 ([M + H]$^+$); calcd for $C_{17}H_{21}O_9$ 369.1180.

Methyl (methyl 4-*O*-acetyl-α-D-galactopyranosid)uronate (27)

A solution of orthoester **24** (430 mg, 1.47 mmol) in 80% AcOH (10 mL) was kept for 40 min at 22 °C, then concentrated repeatedly with toluene to remove solvents and the residue was purified by chromatography to give diol **27** as a white solid (370 mg, 95%), R_f 0.16 (EtOAc); $[\alpha]_D^{20}$ +200 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_2$, D_2O-exchange): δ 5.61 (1 H, d, *J* 3.4 Hz, H-4), 4.98 (1 H, d, *J* 3.8 Hz, H-1), 4.51 (1 H, s, H-5), 4.02 (1 H, dd, *J* 10.0 Hz, 3.4 Hz, H-3), 3.86 (1 H, dd, *J* 10.0 Hz, 3.8 Hz, H-2), 3.76 (3 H, s, CO_2Me), 3.48 (3 H, s, OMe), 2.11 (3 H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 168.0 (C═O), 99.8 (C-1), 71.2 (C-4), 68.6, 68.2, 67.9 (C-2, C-3, C-5), 55.8 (O*Me*), 52.2 (CO_2Me), 20.2 (Ac).

Methyl (3-*C*-acetoxymethyl-2,3,di-*O*-acetyl-β-D-erythrofuranosyl)-(1→3)-(methyl 4-*O*-acetyl-2-*O*-benzoyl-α-D-galactopyranosid)uronate (28)

Glycosyl acceptor **26** (258 mg, 0.70 mmol), glycosyl donors **22a,b** (250 mg, 0.96 mmol) and mol. sieves 4 Å (500 mg) were stirred with CH_2Cl_2 (15 mL) for 30 min, NIS (225 mg, 1.00 mmol) was added and the mixture was cooled to –40 °C. Fine powder of $HClO_4/SiO_2$ (50 mg) was added to the mixture by syringe through a wide bore needle and stirring continued for 1 h to allow the mixture to warm up to 20 °C. The reaction was quenched with Et_3N (0.4 mL), filtered through Celite, diluted with CH_2Cl_2 (20 mL) and vigorously stirred with aq. $Na_2S_2O_3$ (10%, 20 mL) for 30 min. The organic layer was separated, washed with satd aq. $NaHCO_3$, concentrated and dried. In order to facilitate the chromatographic purification, the residual alcohol was acetylated by treatment of the product mixture with Ac_2O–pyridine mixture (1 : 3, 10 mL) for 6 h at 22 °C, then the reaction was quenched with MeOH (3 mL) and concentrated with toluene. The residue was purified by chromatography to give disaccharide **28** (325 mg, 74%); R_f 0.38 (hexane–EtOAc 50 : 50), m.p. 151–152 °C; $[\alpha]_D^{22}$ 99 (*c* 1.1 $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (2 H, m, Ph), 7.58, (1 H, m, Ph), 7.46 (2 H, m, Ph), 5.79 (1 H, br d, *J* 2.2 Hz, H-4 GalA), 5.33 (2 H, dd, *J* 10.5 Hz, *J* 3.5 Hz, H-2 GalA), 5.28 (1 H, d, *J* 3.5 Hz, H-1 GalA), 5.26 (1 H, s, H-1 Api), 4.58 (1 H, br s, H-5 GalA), 4.50 (1 H, d, *J* 12.5 Hz, H-3′a Api), 4.45 (1 H, d, *J* 12.5 Hz, H-3′b Api), 4.33 (1 H, d, *J* 10.7 Hz, H-4a Api), 4.18 (1 H, d, *J* 10.7 Hz, H-4b Api), 3.77 (3 H, s, CO_2Me), 3.43 (3 H, s, OMe), 293 (3 H, s, Ac), 2.99 (3 H, s, Ac), 2.00 (3 H, s, Ac), 1.85 (3 H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.1, 169.7, 168.6, 167.8, 165.9 (C═O), 133.4, 129.9, 129.5, 128.5 (Ph), 107.5 (C-1 Api), 97.8 (C-1 GalA), 83.9 (C-3 Api), 76.3 (C-2 Api), 73.0 (C-4 Api), 72.0 (C-3 GalA), 70.8 (C-4 GalA), 70.5 (C-2 GalA), 68.7 (C-5 GalA), 63.0 (C-3′ Api), 56.2 (O*Me*), 52.5 (CO_2Me), 20.9, 20.5, 20.5, 20.0 (Ac); HRMS (ESI+): *m*/*z* found 644.2184 ([M + NH_4]$^+$); calcd for $C_{28}H_{34}O_{16}{\cdot}NH_4$ 644.2185.

Methyl (3-*C*-acetoxymethyl-2,3,di-*O*-acetyl-β-D-erythrofuranosyl)-(1→2)-[(3-*C*-acetoxymethyl-2,3-di-*O*-acetyl-β-D-erythrofuranosyl)-(1→3)]-(methyl 4-*O*-acetyl-α-D-galactopyranosid)uronate (29)

The title compound was synthesized by essentially the same method as disaccharide **28** using the following proportions of reagents: diol **27** (79 mg, 0.30 mmol), thioglycoside **22a,b** (250 mg, 0.65 mmol), mol. sieves 4 Å (500 mg), NIS (225 mg, 1.0 mmol), CH_2Cl_2 (15 mL), $HClO_4/SiO_2$ (50 mg). The product was purified by chromatography to give trisaccharide **29** (196 mg, 84%), R_f 0.41 (hexane–EtOAc 40 : 60); $[\alpha]_D^{20}$ +12.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (1 H, dd, *J* 3.6 Hz, 1.5 Hz, H-4 GalA), 5.34 (1 H, s, H-2 Api), 5.27 (1 H, s, H-1 Api), 5.21 (1 H, s, H-2 Api), 5.20 (1 H, s, H-1 Api), 4.98 (1 H, d, *J* 3.7, H-1 GalA), 4.86 (1 H, d, *J* 12.3 Hz, H-3′ Api), 4.575 (1 H, d, *J* 12.3 Hz, H-3′ Api), 4.570 (1 H, d, *J* 12.3 Hz, H-3′ Api), 4.48 (1 H, d, *J* 1.5 Hz, H-5 GalA), 4.41 (1 H, d, *J* 12.3 Hz, H-3′ Api), 4.31 (1 H, d, *J* 10.8 Hz, H-4 Api), 4.20–4.08 (4 H, m, H-3 GalA, H-4 Api × 3), 3.97 (1 H, dd, *J* 10.2 Hz, 3.7 Hz, H-2 GalA), 3.73 (3 H, s, CO_2Me), 3.42 (3 H, s, OMe), 2.11 (3 H, s, Ac), 2.09 (3 H, s, Ac), 2.08 (6 H, s, Ac), 2.07 (3 H, s, Ac), 2.03 (3 H, s, Ac), 2.02 (3 H, s, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 170.6, 170.1, 169.9, 169.9, 169.3, 169.1, 167.9 (C═O × 8), 107.4 (C-1 Api), 106.6 (C-1 Api), 99.8 (C-1 GalA), 84.1 (C-3 Api), 83.9 (C-3 Api), 76.2 (C-2 Api), 76.0 (C-2 Api), 74.5 (C-2 GalA), 73.2 (C-4 Api), 72.6 (C-3 GalA), 71.7 (C-4 Api), 70.8 (C-2 GalA), 68.5 (C-5 GalA), 63.5 (C-3′ Api), 62.7 (C-3′ Api), 56.0 (O*Me*), 52.4 (CO_2Me), 20.9, 20.9, 20.5, 20.4,

20.3, 20.2 (Ac × 7); HRMS (ESI+): *m/z* found 798.2660 ([M + NH_4]$^+$); calcd for $C_{32}H_{44}O_{22}{\cdot}NH_4$ 798.2662.

L-Arabinose di(*p*-tolyl) dithioacetal (30)

Powdered L-arabinose (13.95 g, 93.0 mmol) was added portion-wise to vigorously stirred solution of thiocresol (25.4 g, 204.6 mmol) in 90% CF_3CO_2H (55 ml), the mixture heated to 50–60 °C and stirring continually until the sugar was completely dissolved. The solution was allowed to stand for 30 min and concentrated under reduced pressure at 40 °C to give a viscous syrup which was crystallized after addition of EtOH (150 mL). The crystals were filtered off, washed extensively with EtOH and dried to afford dithioacetal **30** (24.0 g, 68%); m.p. 168.5–169.5 °C; $[\alpha]_D^{24}$ −34 (*c* 1.05, DMF); ^{1}H NMR (400 MHz, CD_3OD): δ 7.36–7.30 (4 H, m, SC_6H_4Me), 7.12–7.05 (4 H, m, SC_6H_4Me), 4.60 (1 H, d, *J* 7.7 Hz, H-1), 4.12 (1 H, dd, *J* 8.1 Hz, 1.9 Hz, H-3), 3.96 (1 H, dd, *J* 7.7 Hz, 1.9 Hz, H-2), 3.77 (1 H, dd, *J* 10.9 Hz, 3.1 Hz, H-5a), 3.72–3.64 (1 H, m, H-4), 3.62 (1 H, dd, *J* 10.9 Hz, 6.0 Hz, H-5b), 2.31 (3 H, s, SC_6H_4Me), 2.30 (3 H, s, SC_6H_4Me); ^{13}C NMR (100 MHz, CD_3OD): δ 138.7, 134.2 (2 C), 131.4, 130.2 (2 C) (SC_6H_4Me), 72.8 (C-4), 72.2, 71.6 (C-2 and C-3), 65.1 (C-1), 64.4 (C-5), 20.8 (2 C, SC_6H_4Me); HRMS (ESI+): *m/z* found 398.1461 ([M + NH_4]$^+$); calcd for $C_{19}H_{24}O_4S_2{\cdot}NH_4$ 398.1454.

2,3:4,5-Di-*O*-isopropylidene-L-arabinose di(*p*-tolyl) dithioacetal (31)

Tetraol **30** (15.0 g, 39.5 mmol) was dissolved in a mixture of 2,2-dimethoxypropane (20.0 mL) and acetone (90 mL) in the presence of CSA (0.6 g) which was stirred for 24 h at 22 °C. The solution was treated with Et_3N (10 mL), concentrated and dried to afford compound **31** (18.0 g, 99%) which was used in the next step without further purification. An analytical sample of **31** was obtained by chromatographic purification, R_f 0.67 (hexane–EtOAc 80 : 40); $[\alpha]_D^{24}$ 47 (*c* 1.3, $CHCl_3$); (400 MHz, $CDCl_3$): δ 7.37 (2 H, d, *J* 8.2 Hz, SC_6H_4Me), 7.30 (2 H, d, *J* 8.2 Hz, SC_6H_4Me), 7.08 (2 H, d, *J* 8.2 Hz, SC_6H_4Me), 7.06 (2 H, d, *J* 8.2 Hz, SC_6H_4Me), 4.70 (1 H, d, *J* 1.8 Hz, H-1), 4.32 (1 H, dd, *J* 7.5 Hz, *J* 1.8 Hz, H-2), 4.19 (1 H, dd, *J* 7.5 Hz, *J* 7.9 Hz, H-3), 4.12 (1 H, dd, *J* 8.4 Hz, *J* 6.1 Hz, H-5a), 4.00 (1 H, ddd, *J* 8.2 Hz, *J* 6.0 Hz, 5.8 Hz, H-4), 3.91 (1 H, dd, *J* 8.4 Hz, *J* 5.6 Hz, H-5b), 2.32 (3 H, s, SC_6H_4Me), 1.52 (2 H, s, CMe_2), 1.38 (2 H, s, CMe_2), 1.31 (1 H, s, CMe_2), 1.28 (2 H, s, CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 137.5, 132.5, 132.2, 131.6, 131.3129.9, 129.8 (SC_6H_4Me), 110.7 (CMe_2), 109.9 (CMe_2), 82.3 (C-2), 79.0 (C-3), 77.2 (C-4), 68.2 (C-5), 60.4 (C-1), 27.4, 27.2, 26.7, 25.5 (4 C, CMe_2), 21.4 (SC_6H_4Me); HRMS (ESI+): *m/z* found 478.2080 ([M + NH_4]$^+$); calcd for $C_{25}H_{32}O_4S_2{\cdot}NH_4$ 478.2080.

2,3-*O*-Isopropylidene-L-arabinose di(*p*-tolyl) dithioacetal (32)

A solution of compound **31** (8.2 g, 17.8 mmol) and pyridinium tosylate (4.5 g, 17.9 mmol) in MeOH (82 mL) was stirred at 55 °C and the progress of the reaction was monitored by TLC (hexane–EtOAc 3 : 2). After 18 h TLC indicated the presence of a major product (R_f 0.40), a minor product (R_f 0.50), unreacted **32** (R_f 0.90) and a polar material (R_f ~ 0). After quenching the reaction with pyridine (5 mL) and addition of toluene (100 mL), a white precipitate was filtered off. The filtrate was concentrated and the residue was purified by chromatography to give compound **32** (4.35 g, 58%); R_f 0.40 (hexane–EtOAc 3 : 2); $[\alpha]_D^{23}$ +76 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.31 (4 H, m, SC_6H_4Me), 7.07 (4 H, dd, *J* 7.7 Hz, *J* 0.7 Hz, SC_6H_4Me), 4.68 (1 H, d, *J* 2.6 Hz, H-1), 4.38 (1 H, dd, *J* 7.2 Hz, 2.6 Hz, H-2), 4.24 (1 H, dd, *J* 7.3 Hz, *J* 7.2 Hz, H3), 3.79–3.59 (3 H, m, H-4, H-5a, H-5b), 3.05 (1 H, br d, *J* 4.7 Hz, OH-4), 2.67 (1 H, br s, OH-5), 2.31 (6 H, s, SC_6H_4Me), 1.52 (3 H, s, CMe_2), 1.39 (3 H, s, CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 137.8, 133.0, 132.6, 1, 129.8, 129.7 (SC_6H_4Me), 110.2 (CMe_2), 81.4 (C-3), 78.4 (C-2), 72.9 (C-4), 63.9 (C-5), 61.6 (C-1), 27.3 (CMe_2), 27.0, (CMe_2), 21.1 (× 2, SC_6H_4Me); HRMS (ESI+): *m/z* found 421.1503 ([M + NH_4]$^+$); calcd for $C_{22}H_{28}O_4S_2{\cdot}NH_4$ 421.1502.

3-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-*glycero*-tetrose di(p-tolyl) dithioacetal (34)

Silica gel-supported $NaIO_4$ was prepared by addition of a hot (70 °C) solution of $NaIO_4$ (2.56 g, 12.0 mmol) in H_2O (6.1 mL) to silica gel (12.0 g, Fluorochem, 40–70 μkm) with vigorous swirling and shaking as described.[34] This mixture was added at room temperature to a vigorously stirred solution of diol **32** (3.69 g, 8.77 mmol) in CH_2Cl_2 (45 mL) containing Et_3N (1.2 mL) and stirring continued for 30 min at 22 °C. Silica gel was filtered off, washed with CH_2Cl_2 (50 mL) and at 22 °C combined filtrates were concentrated and dried to give crude 2,3-*O*-isopropylidene-L-*threo*-tetrodialdose di(*p*-tolyl)dithio acetal (**33**, 3.06 g), R_f 0.20–0.40 (hexane–EtOAc 80 : 20); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (1 H, d, *J* 1.2 Hz, CHO), 7.37 (m, 4 H, SC_6H_4Me), 7.12 (4 H, m, SC_6H_4Me), 4.65 (1 H, d, *J* 5.5 Hz, H-2), 4.50–4.44 (2 H, m, $CH(STol)_2$, H-3), 2.35 (6 H, s, SC_6H_4Me), 1.59 (3 H, s, CMe_2), 1.39 (3 H, s, CMe_2); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 200.9 (*C*HO), 138.6, 133.6, 133.5, 130.1 (SC_6H_4Me), 112.6 (CMe_2), 83.0 (C-2), 78.8 (C-3), 62.0 (C-1), 26.9, 26.6 (CMe_2), 21.4 (× 2, SC_6H_4Me). The product **33** was dissolved in EtOH (20 ml), 37% aq. CH_2O (2 mL) and a solution of NaOH (930 mg) in H_2O (14 mL) were added and the mixture was stirred for 17 h at 22 °C. The mixture was acidified by addition of AcOH and then concentrated to remove EtOH. The residue was suspended in CH_2Cl_2, washed with H_2O and satd NaCl solution, the organic layer was separated and the solvent was evaporated *in vacuo*. Purification of the residue by chromatography afforded compound **34** (1.76 g, 48%), R_f 0.30 (hexane–EtOAc 60 : 40); m.p. 86–89 °C (Et_2O–hexane); $[\alpha]_D^{20}$ +136 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (2 H, d, *J* 8.1 Hz, SC_6H_4Me), 7.35 (2 H, d, *J* 8.1 Hz, SC_6H_4Me), 7.13 (4 H, m, SC_6H_4Me), 4.55 (1 H, d, *J* 8.6 Hz, H-1), 4.18 (1 H, d, *J* 8.6 Hz, H-2), 3.85 (1 H, d, *J* 12.1 Hz, H-3′a), 3.82 (2 H, s, H-4a, 4b), 3.77 (1 H, d, *J* 12.1 Hz, H-3′b), 2.34 (6 H, s, SC_6H_4Me), 1.53 (3 H, s, CMe_2), 1.43 (3 H, s, CMe_2); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 138.7, 138.5, 134.7, 133.1, 130.0, 129.56 (SC_6H_4Me), 108.0 (CMe_2), 84.5 (C-3), 78.7 (C-2), 64.1 (C-3′), 62.5 (C-4), 28.3 (CMe_2), 26.4 (CMe_2), 21.2 (2 C, SC_6H_4Me); HRMS (ESI+): *m/z* found 421.1507 ([M + H]$^+$); calcd for $C_{22}H_{28}O_4S_2{\cdot}H$ 421.1502.

p-Tolyl 3-*C*-chloroacetoxymethyl-2,3-*O*-isopropylidene-1-thio-α-D-erythrofuranoside (36a) and *p*-tolyl 3-*C*-chloroacetoxy-methyl-2,3-*O*-isopropylidene-1-thio-β-D-erythrofuranoside (36b)

A solution of dithioacetal **34** (1.50 g, 3.57 mmol) in MeCN (30 mL) was cooled to −30 °C and NIS (800 mg, 3.57 mmol)

was added. The mixture was stirred and allowed to warm to 0 °C, and after 10 min the reaction was quenched with Et_3N (0.5 mL), the mixture was diluted with CH_2Cl_2 (40 mL) and washed with 10% $Na_2S_2O_3$ and satd $NaHCO_3$ solution. The organic layer was concentrated to give brown residue which was purified by column chromatography to give a mixture of *p*-tolyl 3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-1-thio-α,β-D-erythrofuranoside (**35a,b**, 940 mg); R_f 0.57 (minor spot) and 0.41 (major spot) (hexane–EtOAc 50 : 50); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (2 H, d, *J* 8.1 Hz, SC_6H_4Me α), 7.35 (0.46 H, d, *J* 8.0 Hz, SC_6H_4Me β), 7.10 (2.46 H, m, SC_6H_4Me α and β), 5.60 (0.23 H, s, H-1 β), 5.07 (1 H, d, *J* 3.8 Hz, H-1 α), 4.70 (1 H, d, *J* 3.8 Hz, H-2 α), 4.50 (0.23 H, s, H-2 β), 4.10 (0.23 H, d, *J* 10.6 Hz, H-4a β), 4.08 (1 H, d, *J* 10.3 Hz, H-4a α), 4.00 (0.23 H, d, *J* 10.6 Hz, H-4b β), 3.83 (0.48 H, br s, H-3′ β), 3.72 (2 H, m, H-3′ α), 3.62 (1 H, d, *J* 10.3 Hz, H-4b α), 2.31 (3 H, s, SC_6H_4Me α), 2.03 (0.69 H, s, SC_6H_4Me β), 1.62 (3 H, s, CMe_2 α), 1.48 (0.69 H, s, CMe_2 β), 1.45 (3 H, s, CMe_2 α), 1.41 (0.69 H, s, CMe_2 β); HRMS (ESI+): *m*/*z* found 314.1423 ([M + NH_4]$^+$); calcd for $C_{15}H_{20}O_4{\cdot}NH_4$ 314.1421. To a solution of a mixture of compounds **35a,b** (940 mg, 3.17 mmol) in CH_2Cl_2 (30 mL) collidine (0.5 mL, 3.49 mmol) and chloroacetyl chloride (0.28 mL, 3.50 mmol) were added successively at –40 °C. After stirring at 0 °C for 30 min the solution was washed with satd $NaHCO_3$, concentrated and the residue was purified by chromatography to give chloroacetate **36a,b** as a mixture of α- and β-thioglycosides (1.08 g, 81% overall, α : β ~ 67 : 33). Further chromatography purification afforded analytical samples of pure **36a** and **36b**. Compound **36a**: R_f 0.46 (hexane–EtOAc 80 : 20); $[\alpha]_D^{28}$ –255 (*c* 1.2 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (1 H, d, *J* 8.0 Hz, SC_6H_4Me), 7.09 (2 H, d, *J* 8.0 Hz, SC_6H_4Me), 5.03 (2 H, d, *J* 3.9 Hz, H-1), 4.65 (1 H, d, *J* 3.9 Hz, H-2), 4.29 (1 H, d, *J* 11.7 Hz, H-4a), 4.25 (1 H, d, *J* 11.7 Hz, H-4b), 4.05 (1 H, d, *J* 10.3 Hz, H-3′a), 4.04 (2 H, s, $ClCH_2$), 3.61 (1 H, d, *J* 10.3 Hz, H-3′b), 2.30 (MeC_6H_4S), 1.60 (CMe_2), 1.44 (CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C=O), 137.6, 131.7, 129.9 (SC_6H_4Me), 115.5 (CMe_2), 91.7 (C-3), 89.8 (C-1), 84.4 (C-2), 73.8 (C-4), 66.0 (C-3′), 40.5 (CH_2Cl), 27.5 (2 C, CMe_2), 20.9 (SC_6H_4Me); HRMS (ESI+): *m*/*z* found 390.1138 ([M + NH_4]$^+$); calcd for $C_{17}H_{21}ClO_5S{\cdot}NH_4$ 390.1136. Compound **36b**: R_f 0.36 (hexane–EtOAc 80 : 20); $[\alpha]_D^{28}$ +41 (c1.1 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (2 H, d, *J* 8.0 Hz, SC_6H_4Me), 7.11 (2 H, d, *J* 8.0 Hz, SC_6H_4Me), 5.60 (1 H, s, H-1), 4.54 (1 H, s, H-2), 4.48 (1 H, d, *J* 11.7 Hz, H-3′a), 4.41 (1 H, d, *J* 11.6 Hz, H-3′b), 4.15 (1 H, d, *J* 10.4, H-4a), 4.15 (2 H, s, $ClCH_2$), 4.02 (1 H, d, *J* 10.4, H-4b), 2.31 (2 H, s, SC_6H_4Me), 1.47 (3 H, s, CMe_2), 1.40 (3 H, s, CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (C=O), 138.2, 133.0, 130.0, 129.2 (SC_6H_4Me), 114.5 (CMe_2), 93.3 (C-3), 90.3 (C-1), 87.6 (C-2), 73.5 (C-4), 66.5 (C-3′), 40.6 (CH_2Cl), 27.5, 27.4 (CMe_2), 21.0 (SC_6H_4Me); HRMS (ESI+): *m*/*z* found 390.1138 ([M + NH_4]$^+$); calcd for $C_{17}H_{21}ClO_5S{\cdot}NH_4$ 390.1136.

p-Tolyl 3-*C*-chloroacetoxymethyl-2,3-*O*-(*S*)-benzylidene-1-thio-α-D-erythrofuranoside (38a) and *p*-tolyl 3-*C*-chloroacetoxymethyl-2,3-*O*-(*S*)-benzylidene-1-thio-β-D-erythrofuranoside (38b)

A mixture of glycosides **36a,b** (1.00 g, 2.68 mmol, α : β ~ 67 : 33) was dissolved in CF_3CO_2H (10 mL), H_2O (1.1 mL) was added and the solution was allowed to stand at 20 °C for 90 min before being concentrated with toluene (3 × 20 mL) at reduced pressure at 30 °C to give a yellow syrup containing a crude mixture of **37a,b**; selected ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (0.25 H, d, *J* 3.9 Hz, H-1 α), 5.38 (1 H, d, *J* 3.9 Hz, H-1 β). This product was dissolved in toluene (2.0 mL), $PhCH(OMe)_2$ (2.0 ml, 13.3 mmol) and a cat. amount of CSA were added, and the mixture was stirred for 17 h at 22 °C. The reaction was quenched with Et_3N (0.5 mL), the mixture was concentrated and the residue was purified by chromatography. The first eluted product was benzylidene derivative **38b** (690 mg, 61%) and the second was **38a** (200 mg, 18%). Compound **38a**: R_f 0.41 (hexane–EtOAc 9 : 1), $[\alpha]_D^{22}$ +16 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.58 (2 H, m), 7.50–7.35 (5 H, m), 7.13 (2 H, d, *J* 7.9 Hz, *Ph*CH), 6.06 (1 H, s, PhC*H*), 5.15 (1 H, d, *J* 3.9 Hz, H-1), 4.80 (1 H, d, *J* 3.9 Hz, H-2), 4.55 (1 H, d, *J* 11.9 Hz, H3′a), 4.43 (1 H, d, *J* 11.9 Hz, H-3′b), 4.30 (1 H, d, *J* 10.5 Hz, H-4a), 4.13 (2 H, s, CH_2Cl), 3.67 (1 H, d, *J* 10.5 Hz, H-4b), 2.33 (4 H, s, SC_6H_4Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C=O), 137.7, 135.5, 131.8, 131.3, 130.2, 129.9, 128.5, 127.4 (aromatics), 107.8 (Ph*C*H), 91.4 (C-1), 89.8 (C-3), 84.6 (C-2), 72.8 (C-4), 65.1 (C-3′), 40.4 (CH_2Cl), 21.0 (SC_6H_4Me); HRMS (ESI+): *m*/*z* found 438.1131 ([M + NH_4]$^+$); calcd for $C_{21}H_{21}ClO_5S{\cdot}NH_4$ 438.1136. Compound **38b**: R_f 0.49 (hexane–EtOAc 9 : 1), $[\alpha]_D^{20}$ –201 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.48 (2 H, m, aromatics), 7.40–7.34 (5 H, m, aromatics), 7.12 (2 H, d, *J* 8.3 Hz, aromatics), 5.93 (1 H, s, PhC*H*), 5.78 (1 H, s, H-1), 4.60 (1 H, s, H-2), 4.59 (2 H, d, *J* 11.8 Hz, H-3′a), 4.49 (1 H, d, *J* 11.8, H-3′b), 4.26–4.17 (2 H, m, H-4a,b), 4.15 (2 H, s, CH_2Cl), 2.32 (3 H, s, SC_6H_4Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (C=O), 138.3, 135.7, 133.0, 130.2, 130.1, 128.9, 128.6, 127.2 (Ph), 106.7 (Ph*C*H), 92.6 (C-1), 90.3 (C-3), 87.7 (C-1), 72.6 (C-4), 65.4 (C-3′), 40.6 (*C*H_2Cl), 21.0 (SC_6H_4Me); HRMS (ESI+): *m*/*z* found 438.1136 ([M + NH_4]$^+$); calcd for $C_{21}H_{21}ClO_5S{\cdot}NH_4$ 438.1136.

Methyl (2,3-*O*-(*S*)-benzylidene-3-*C*-chloroacetoxymethyl-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (39)

A solution of thioglycoside **38b** (700 mg, 1.67 mmol), glycosyl acceptor **12** (440 mg, 1.67 mmol) and mol. sieves 4 Å (1.4 g) in CH_2Cl_2 (45 mL) was stirred for 20 min at room temperature, NIS (395 mg, 1.7 mmol) was added and the mixture was cooled to –40 °C. A solution of TMSOTf (30 μL, 0.17 mmol) in CH_2Cl_2 (0.3 mL) was added to the mixture which was stirred for 30 min to allow temperature to raise to –20 °C, then treated with Et_3N (0.3 mL) and filtered through Celite. The filtrate was vigorously stirred for 30 min with aq. $Na_2S_2O_3$ solution (50 mL), the organic layer was separated and washed with aq. $NaHCO_3$ solution, dried and concentrated. Purification of the product by chromatography afforded disaccharide **39** (710 mg, 76%). R_f 0.55 (hexane–EtOAc 60 : 40); $[\alpha]_D^{21}$ +2 (*c* 0.8 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (1 H, m, Ph), 7.39 (1 H, m, Ph), 5.93 (1 H, s, C*H*Ph), 5.45 (1 H, s, H-1 Api), 4.98 (1 H, d, *J* 3.5 Hz, H-1 GalA), 4.61 (1 H, s, H-2 Api), 4.59 (1 H, d, *J* 2.7 Hz, H-5 GalA), 4.52 (2 H, broad s, H-3′a,b Api), 4.50 (1 H, dd, *J* 2.7 Hz, *J* 5.4 Hz, H-4 GalA), 4.27 (1 H, dd, *J* 5.4 Hz, *J* 8 Hz, H-3 GalA), 4.14–4.17 (3 H, m, H-4a Api, COCH_2Cl), 3.91 (1 H, d, *J* 10.1 Hz, H-4b Api), 3.84 (3 H, s, CO_2Me), 3.81 (1 H, dd, *J* 3.5 Hz, *J* 8 Hz, H-2 GalA), 3.43 (3 H, s, OMe), 1.51 (3 H, s, CMe_2), 1.34 (3 H, s, CMe_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 167.1 (C=O), 128.5, 127.1, 130.1 (Ph), 110.0 (Me_2C), 107.6 (C-1 Api), 106.4 (Ph*C*H), 99.7 (C-1 GalA), 89.5 (C-3 Api), 86.9 (C-2 Api), 75.9 (C-2 GalA), 74.8

(C-3 GalA), 73.7 (C-4 GalA), 72.9 (C-4 Api), 67.0 (C-5 GalA), 65.5 (C-3′ Api), 56.1 (OMe), 52.5 (CO_2Me), 40.5 (CH_2Cl), 28.0 (Me_2C), 26.2 (Me_2C); HRMS (ESI+): *m/z* found 557.1420 ([M + H]$^+$); calcd for $C_{25}H_{30}ClO_{12}$ 557.1421.

Methyl (2,3-*O*-(*S*)-benzylidene-3-*C*-hydroxymethyl-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (40)

A solution of disaccharide **39** (640 mg, 1.15 mmol) in 0.01 M MeOH (6 mL) was stirred for 10 min at 21 °C and then neutralized and concentrated. The residue was purified by chromatography (hexane–hexane 30 : 70→10 : 90) to give alcohol **40** (470 mg, 85%); R_f 0.20 (hexane–EtOAc 30 : 70); $[\alpha]_D^{22}$ –4 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (2 H, m, Ph), 7.40 (3 H, m, Ph), 5.91 (1 H, s, H-1 Api), 5.45 (1 H, s, C*H*Ph), 4.97 (1 H, d, *J* 3.5 Hz, H-1 GalA), 4.59 (1 H, d, *J* 2.7 Hz, H-5 GalA), 4.54 (1 H, d, *J* < 1 Hz, H-2 Api), 4.49 (1 H, dd, *J* 2.7, 5.4 Hz, H-4 GalA), 4.29 (1 H, dd, *J* 5.4, 7.6 Hz, H-3 GalA), 4.13 (1 H, d, *J* 10.1 Hz, H-4a Api), 3.82–3.98 (7 H, m, H-3′a, H-3′b, H-4b Api, H-2 GalA, CO_2Me), 3.43 (3 H, s, OMe), 1.52 (3 H, s, CMe_2), 1.34 (3 H, s, CMe_2), ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (CO_2Me), 136.1 (Ph), 130.0 (Ph), 128.5 (Ph), 127.1 (Ph), 109.9 (Me$_2C$), 107.2 (Ph*C*H), 106.2 (C-1 Api), 99.7 (C-1 Gal), 92.1 (C-3 Api), 86.7 (C-2 Api), 75.3 (C-2 GalA), 74.9 (C-3 GalA), 73.7 (C-4 GalA), 73.3 (C-4 Api), 67.1 (C-5 GalA), 63.7 (C-3′ Api), 56.1 (OMe), 52.4 (CO_2Me), 28.0 (CMe_2), 26.2 (CMe_2); HRMS (ESI+): *m/z* found 500.2129 ([M + NH_4]$^+$); calcd for $C_{23}H_{30}O_{11}\cdot NH_4$ 500.2126.

Methyl *C*-(4-*O*-acetyl-2,3-*O*-carbonyl-β-L-rhamnopyranosyloxymethyl)-(1→3)-(2,3-*O*-(*S*)-benzylidene-β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (41)

To a stirred solution of disaccharide **40** (470 mg, 0.98 mmol), bromide **15** (540 mg, 1.84 mmol) and mol. sieves 4 Å (2 g) in CH_2Cl_2 (10 mL) was added Ag_2O (460 mg, 2.0 mmol) and stirring was continued for 17 h at 21 °C. The mixture was filtered through Celite and the filtrate was diluted with CH_2Cl_2, washed successively with aq. $Na_2S_2O_3$ and water and concentrated. The product was purified by chromatography (hexane–EtOAc 80 : 20→20:80) to give compound **41** (403 mg, 59%). Crystals suitable for X-ray analysis were obtained by crystallization from hexane–CH_2Cl_2. Compound **41**, R_f 0.22 (hexane–EtOAc 30 : 70); m.p. 142–144 °C; $[\alpha]_D$ +16 (c 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (2 H, m, Ph), 7.38 (3 H, m, Ph), 5.92 (1 H, s, H-1 Api), 5.42 (1 H, s, C*H*Ph), 5.39 (1 H, dd, *J* 3 Hz, *J* 5.5 Hz, H-4 Rha), 5.15 (1 H, broad s, H-1 Rha), 5.02 (1 H, d, *J* 3.5 Hz, H-1 GalA), 4.79–4.75 (2 H, m, H-2, H-3 Rha), 4.60 (1 H, d, *J* 2.8 Hz, H-5 GalA), 4.52 (1 H, s, H-2 Api), 4.48 (1 H, dd, *J* 2.8 Hz, *J* 5.5 Hz, H-4 GalA), 4.28 (1 H, dd, *J* 5.5 Hz, *J* 7.8 Hz, H-3 GalA), 4.19 (1 H, d, *J* 3 Hz, H-3′a Api), 4.15 (1 H, d, *J* 2 Hz, H-4a Api), 3.95 (1 H, broad s, H-4b Api), 3.91 (1 H, d, *J* 3 Hz, H-3′b Api), 3.84 (1 H, s, CO_2Me), 3.72–3.82 (2 H, m, H-2 GalA, H-5 Rha), 3.43 (1 H, s, OMe), 2.08 (1 H, s, OAc), 1.51 (1 H, s, Me$_2$C), 1.33 (1 H, s, Me$_2$C), 1.31 (1 H, m, H-6 Rha); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 169.1 (Me*C*O), 168.4 (CO_2Me), 153.5 (Ph), 136.2 (Ph), 129.7 (Ph), 128.3 (Ph), 127.2 (Ph), 109.7 (Me$_2C$), 107.7 (Ph*C*H), 106.2 (C-1 Api), 99.6 (C-1 Gal), 95.1 (C-1 Rha), 91.0 (C-3 Api), 86.5 (C-2 Api), 76.1 (C-2 or C-3 Rha), 75.9 (C-2 GalA), 74.7 (C-3 GalA), 73.6 (C-4 GalA), 73.2 (C-4 Api), 72.2 (C-2 or C-3 Rha), 71.2 (C-4 Rha), 70.0 (C-5 Rha), 69.1 (C-3′ Api), 66.9 (C-5 GalA), 56.0 (OMe), 52.3 (CO_2Me), 27.9 (CMe_2), 26.1 (CMe_2), 20.5 (Ac), 19.2 (C-6 Rha); HRMS (ESI+): *m/z* found 714.2611 ([M + NH_4]$^+$); calcd for $C_{32}H_{40}O_{17}\cdot NH_4$ 714.2604.

Methyl *C*-(β-L-rhamnopyranosyloxymethyl)-(1→3)-β-D-erythrofuranosyl-(1→2)-(methyl α-D-galactopyranosid)uronate (42)

To a solution of the trisaccharide **41** (150 mg, 0.22 mmol) in EtOAc (4 ml) was added 10% Pd/C, the mixture was degassed and then stirred for 12 h at 35 °C under H_2. The catalyst was separated by filtration through a Celite pad, the filtrate was concentrated and the residue was purified by flash chromatography to afford methyl *C*-(4-*O*-acetyl-2,3-*O*-carbonyl-β-L-rhamnopyranosyloxymethyl)-(1→3)-(β-D-erythrofuranosyl)-(1→2)-(methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)-uronate (110 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (1 H, dd, *J* 8.6 Hz, 5.7 Hz, 4 Rha), 5.18 (1 H, d, *J* 1.5 Hz, H-1 Api), 5.02 (1 H, d, *J* 2.5 Hz, H-1 Rha), 4.96 (1 H, d, *J* 3.5 Hz, H-1 GalA), 4.85 (2 H, m, 2 Rha, H-3 Rha), 4.59 (1 H, d, *J* 2.8 Hz, H-5 GalA), 4.49 (1 H, dd, *J* 5.4 Hz, 2.9 Hz, H-4 GalA), 4.29 (1 H, dd, *J* 7.9 Hz, 5.4 Hz, H-3 GalA), 4.07–3.97 (2 H, m, H-2 Api, 4′a Api), 3.90 (2 H, s, H-3′a, H-3′b Api), 3.83 (3 H, s, CO_2Me), 3.77 (3 H, m, H-4′b Api, H-2 GalA, H-5 Rha), 3.42 (3 H, s, OMe), 2.12 (3 H, s, Ac), 1.51 (3 H, s, CMe_2), 1.31 (3 H, s, CMe_2), 1.24 (3 H, d, *J* 6.3 Hz, H-6 Rha). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (Me*C*O), 168.5 (CO_2Me), 110.1 (Me$_2C$), 109.8 (C-1 Api), 99.9 (C-1 Gal); 95.8(C-1 Rha), 78.7, 77.5, 76.5, 76.2, 74.9, 74.1, 73.8, 72.7, 72.4, 71.3, 70.3, 67.0, 56.2 (OMe), 52.5 (CO_2OMe), 28.01(CMe_2), 26.3 (CMe_2), 20.8 (Ac), 19.2 (C-6 Rha); MALDI TOF(+) MS, *m/z* found 631.08 ([M + Na]$^+$); calcd for $C_{25}H_{36}O_{17}\cdot Na$ 631.53. The latter compound was dissolved in 80% AcOH, the solution was heated for 25 min at 60 °C and concentrated. After drying the residue by repeated concentration of its solution in toluene *in vacuo*, the residue was dissolved in 0.05 M NaOMe in MeOH (1 mL) and the solution was stirred for 30 min at 22 °C. The mixture was carefully neutralised with Amberlite IR120 (H$^+$), the resin was removed and the solution was concentrated. The residue was redissolved in water, filtered through C18 cartridge and freeze-dried. Compound **42** (60 mg, 56%); $[\alpha]_D^{20}$ +61 (*c* 1.2, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.10 (1 H, d, *J* 3.0 Hz, H-1 Api), 4.94 (1 H, d, *J* 3.8 Hz, H-1 GalA), 4.56 (1 H, s, H-1 Rha), 4.55 (1 H, d, *J* 1.0 Hz, H-5 GalA), 4.26 (1 H, dd, *J* 3.3, 1.0 Hz, H-4 GalA), 4.02 (1 H, d, *J* 3.0 Hz, H-2 Api), 3.98–3.94 (2 H, m, H-2 Rha, H-3′a Api), 3.90–3.82 (3 H, m, H-3′b and H-4a Api, H-3 GalA), 3.75–3.70 (4 H, m, H-2 GalA, OMe), 3.67 (1 H, d, *J* 10.7, H-4b Api), 3.53–3.47 (1 H, m, H-3 Rha), 3.36–3.26 (5 H, m, H-4 and H-5 Rha, CO_2Me), 1.22 (3 H, *J* 5.4 Hz, H-6 Rha). ^{13}C NMR (100 MHz, D_2O): δ 171.1 (C-6 GalA), 110.2 (C-1 Api), 100.4 (C-1 Rha), 99.3 (C-1 GalA), 78.6 (C-3 Api), 77.4 (C-2 Api), 75.9, 73.8, 72.5, 72.2, 72.0, 71.3, 70.5, 70.3, 69.9, 67.8, 55.5 (OMe), 52.9 (CO_2Me), 16.7 (C-6 Rha); MALDI TOF(+) MS, *m/z* found 522.99 ([M + Na]$^+$); calcd for $C_{19}H_{32}O_{15}\cdot Na$ 523.44.

Methyl *C*-(β-L-rhamnopyranosyloxymethyl)-(1→3)-β-D-erythrofuranosyl-(1→2)-(α-D-galactopyranosid)uronic acid (1)

A solution of methyl ester **42** (23 mg, 46 μmol) in H_2O–MeOH–Et_3N (3 : 2 : 1, 10 mL) was kept for 17 h at 22 °C, diluted with water

(10 mL), concentrated *in vacuo*, and the residue was purified by GPC to give the title compound **1** (18 mg, 78%); $[\alpha]_D^{22}$ + 34 (*c* 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.12 (1 H, *J* 3.0 Hz, H-1 Api), 4.90 (1 H, *J* 3.8 Hz, H-1 GalA), 4.58 (1 H, s, H-1 Rha), 4.21 (dd, *J* 1.2 Hz, *J* 3.4 Hz, H-4 GalA), 4.13 (1 H, *J* 1.2 Hz, H-5 GalA), 4.00–3.96 (2 H, m, H-2 Rha, H-3′a Api), 3.90–3.84 (3 H, H-3′b and H-4a Api, H-3 GalA), 3.74 (1 H, *J* 3.8 Hz, *J* 10.2 Hz, H-2 GalA), 3.69 (1 H, *J* 10.8 Hz, H-4b Api), 3.50 (1 H, m, H-3 Rha), 3.34–3.27 (5 H, H-4 and H-5 Rha, OMe), 1.23, (3 H, d, *J* 5.9 Hz, H-6 Rha); ^{13}C NMR (100 MHz, D_2O): δ 175.6 (C═O), 110.2 (C-1 Api), 100.4 (C-1 Rha), 98.9 (C-1 GalA), 78.6 (C-3 Api), 77.4 (C-2 Api), 76.3 (C-2 GalA), 73.8 (C-3′ Api), 72.5 (C-3 Rha), 72.1, 72.0 (C-4 and C-5 Rha), 71.4 (C-4 Rha), 71.0 (C-5 GalA), 70.6 (C-4 GalA), 70.4 (C-2 Rha), 68.7 (C-3 GalA), 55.0 (OMe), 16.6 (C-6 Rha). HRMS (ESI+): *m/z* found 504.1922 ([M + NH_4]$^+$); calcd for $C_{18}H_{30}O_{15}\cdot NH_4$ 504.1923.

Methyl (3-*C*-hydroxymethyl-β-D-erythrofuranosyl)-(1→2)-(α-D-galactopyranosid)uronic acid (2)

A solution of disaccharide **29** (120 mg, 0.23 mmol) in 80% aq. AcOH was stirred for 30 min at 60 °C, the mixture was concentrated to dryness, the residue was dissolved in MeOH–H_2O (2 mL, 1 : 1) and conc. NaOH solution was added to pH 10. The mixture was stirred at 22 °C for 1 h, and then carefully neutralized with Amberlite IR120 (H^+) resin, the resin was removed and the solution was concentrated. The residue was purified by flash chromatography (H_2O–MeCN, 100 : 0→80:20) to give the title compound (63 mg, 80%); $[\alpha]_D^{20}$ + 24.5 (*c* 1.1, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.10 (1 H, d, *J* 3.0, H-1 Api), 4.90 (1 H, d, *J* 3.6, H-1 GalA), 4.22–4.18 (2 H, m, H-4, H-5 GalA), 3.95 (1 H, s, H-2 Api) 3.94 (1 H, d, *J* 8.3 Hz, H-4a Api), 3.85 (1 H, dd, *J* 11.4 Hz, 3.5 Hz, H-3 GalA), 3.82 (1 H, d, *J* 10.2 Hz, H-4b Api), 3.72 (1 H, dd, *J* 10.3 Hz, 3.6 Hz), 3.61–3.56 (2 H, m, H-3′a, H-3′b Api), 3.31 (3 H, s, OMe). ^{13}C NMR (100 MHz, D_2O): δ 176.7 (*C*O_2H), 111.2 (C-1 Api), 99.9 (C-1 GalA), 80.4 (C-3 Api), 78.0 (C-2 Api), 77.0 (C-2 GalA), 74.5 (C-4 Api), 71.9 (C-5 Gal), 71.3 (C-4 GalA), 69.3 (C-3 GalA), 64.5 (C-3′ Api), 56.0 (OMe). HRMS (ESI+): *m/z* found 363.0897 ([M + NH_4]$^+$); calcd for $C_{12}H_{20}O_{11}\cdot$Na 363.0898.

Methyl (3-*C*-hydroxymethyl-β-D-erythrofuranosyl)-(1→3)-(α-D-galactopyranosid)uronic acid (3)

A solution of disaccharide **28** (40 mg) in 0.05 M methanolic NaOMe (0.5 mL) was stirred for 3 h at 22 °C. The solvent was evaporated, the residue was dissolved in water (0.5 mL) and pH was adjusted to 10 by addition of 1 M NaOH solution. After 1 h at 22 °C the mixture was neutralised by careful addition of Amberlite IR120 (H^+) resin, the resin was filtered off of and the filtrate was concentrated. The residue was purified by GPC and freeze-dried to give disaccharide **3** (18 mg, 75%); $[\alpha]_D^{20}$ +72 (*c* 1.1, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.18 (1 H, d, *J* 3.2 Hz, H-1 Api), 4.79 (1 H, d, *J* 3.7 Hz, H-1 GalA), 4.33 (1 H, dd, *J* 3.2 Hz, *J* 1.3 Hz, H-4 GalA), 4.14 (1 H, d, *J* 1.3 Hz, H-5 GalA), 4.04 (1 H, d, *J* 10.3 Hz, H-4a Api), 3.99 (1 H, d, *J* 3.2 Hz, H-2 Api), 3.87 (1 H, dd, *J* 3.7 Hz, *J* 10.2 Hz, H-2 GalA), 3.82 (1 H, d, *J* 10.3 Hz, H-4b Api), 3.80 (1 H, dd, *J* 3.3 Hz, *J* 10.2 Hz, H-3 GalA), 3.61 (2 H, s, H-3′ Api), 3.33 (2 H, s, OMe). ^{13}C NMR (100 MHz, D_2O): δ 173.5 (*C*O_2H), 110.1 (C-1 Api), 99.3 (C-1 GalA), 79.4 (C-3 Api), 77.5 (C-3 GalA), 77.1 (C-2 Api), 73.7 (C-4 Api), 70.5 (C-5 GalA), 69.9 (C-4 GalA), 66.7 (C-2 GalA), 63.5 (C-3′ Api), 55.4 (OMe). HRMS (ESI+): *m/z* found 363.0897 ([M + NH_4]$^+$); calcd for $C_{12}H_{20}O_{11}\cdot$Na 363.0897

Methyl (3-*C*-hydroxymethyl-β-D-erythrofuranosyl)-(1→2)-[(3-*C*-hydroxymethyl-β-D-erythrofuranosyl)-(1→3)]-(α-D-galactopyranosid)uronic acid (4)

A solution of trisaccharide **29** (45 mg, 0.058 mmol) in 0.02 M methanolic NaOMe (0.5 mL) was kept for 1 h at 22 °C, diluted with MeOH and neutralised with Amberlite IR120 (H^+) resin. The resin was filtered off and the filtrate was concentrated to give methyl ester of **4** (26 mg, 93%); $[\alpha]_D^{20}$ – 20 (*c* 0.8, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.09 (1 H, d, *J* 2.9 Hz, H-1 Api), 5.06 (1 H, d, *J* 2.9 Hz, H-1 Api), 4.86 (1 H, d, *J* 3.7 Hz, H-1 GalA), 4.49 (1 H, br s, H-5 GalA), 4.30 (1 H, br d, H-4 GalA), 3.95–3.74 (6 H, H-4 Api, H-2 and H-3 GalA), 3.65 (3 H, s, OMe), 3.55–3.46 (4 H, m, H-3′ Api), 3.27 (3 H, s. CO_2Me). ^{13}C NMR (100 MHz, D_2O): δ 170.8 (*C*O_2Me), 110.2, 110.0 (C-1 Api), 99.1 (C-1 GalA), 79.55, 79.5 (C-3 Api), 77.1 (2 C, C-2 Api), 73.4, 74.4 (C-2 and C-3 GalA), 73.7 (2 C, C-4 Api), 70.1 (C-5 GalA), 69.8 (C-4 GalA), 63.65, 63.6 (C-3′ Api), 55.4 (OMe), 52.8 (CO_2*Me*). A solution of the methyl ester (26 mg, 0.054 mmol) in a mixture of H_2O–MeOH–Et_3N (3 : 2 : 1, 3 mL) was stirred for 24 h at 22 °C, then concentrated *in vacuo* and the residue was purified by GPC to give the title compound **4** (20 mg, 73%). ^{1}H NMR (400 MHz, D_2O): δ (400 MHz, D_2O) 5.11 (1 H, d, *J* 3.0 Hz, H-1 Api), 5.06 (1 H, d, *J* 2.8 Hz, H-1 Api), 4.79 (1 H, d, *J* 3.2 Hz, H-1 GalA), 4.23 (1 H, dd, *J* 2.7 Hz, *J* 1.2 Hz, H-4 GalA), 4.05 (1 H, d, *J* 1.2 Hz, H-5 GalA), 3.95 (1 H, d, *J* 10.2 Hz, H-4a Api), 3.90 (1 H, d, *J* 3.0 Hz, H-2 Api), 3.89 (1 H, d, *J* 10.2 Hz, H-4a Api), 3.88 (1 H, d, *J* 2.8 Hz, H-2 Api), 3.81–3.77 (2 H, m, H-2 and H-3 GalA), 3.76 (1 H, d, *J* 10.2 Hz, H-4b Api), 3.73 (1 H, d, *J* 10.2 Hz, H-4b Api), 3.53 (s, 2 H, H-3′ Api) 3.52 (4 H, s, H-3′ Api), 3.25 (3 H, s, OMe). ^{13}C NMR (100 MHz, D_2O): δ 173.8 (*C*O_2H), 110.2, 109.9 (C-1 Api), 98.8 (C-1 GalA), 79.6 and 79.5 (C-3 Api), 77.1 and 77.05 (C-2 Api), 76.3, 74.9 (C-2 and C-3 GalA), 73.7 and 73.6 (C-4 Api), 70.9 (C-5 GalA), 70.5 (C-4 GalA), 63.7 and 63.6 (C-3′ Api), 55.1 (OMe). HRMS (ESI+): *m/z* found 495.1319 ([M + Na]$^+$); calcd for $C_{17}H_{28}O_{15}\cdot$Na 495.1320.

Crystal structure analysis of protected trisaccharide 41

Crystal data: $C_{32}H_{40}O_{17}$, CH_2Cl_2, *M* = 781.6. Orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 11.2799(6), *b* = 15.1788(9), *c* = 21.4815(13) Å, *V* = 3678.0(4) Å^3. *Z* = 4, *D*c = 1.411 g cm^{-3}, *F*(000) = 1640, *T* = 140(1) K, μ(Mo-Kα) = 2.5 cm^{-1}, λ(Mo-Kα) = 0.71069 Å. Crystals are beautiful, colourless prisms. Intensity data were measured on an Oxford Diffraction Xcalibur-3 CCD diffractometer (Mo-Kα radiation, graphite monochromator). Total number of reflections recorded, to θ_{max} = 27.5°, was 49119 of which 8410 were unique (R_{int} = 0.045); 7002 were 'observed' with $I > 2\sigma_I$. Structure was determined by direct methods in SHELXS, and refined in SHELXL.[44] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in riding mode. Final *R*-values: wR_2 = 0.093 and R_1 = 0.049[44] for all data; R_1 = 0.037 for the 'observed' data.

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