Production of carbohydrate building blocks from red seaweed polysaccharides. Efficient conversion of galactans into *C*-glycosyl aldehydes†

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Agarans and carrageenans are abundant natural polysaccharides which are obtained on a large scale by water extraction from a variety of red seaweeds. These galactans, in addition to being valuable products for the pharmaceutical and food industries, are low cost starting materials for the preparation of useful and rare carbohydrate-based building blocks whose access by total synthesis is difficult and expensive. The semisynthesis of two sets of *C*-glycosyl aldehydes with L- and D-configuration from agarose and kappa-carrageenan respectively is described. Succinctly, the partial acid-catalyzed mercaptolysis of the two galactans under mild conditions afforded agarobiose and carrabiose (β-D-Gal*p*-(1→4)-3,6-anhydro-*aldehydo*-L- and D-galactose, respectively) derivatives. Complete depolymerization of agarose and kappa-carrageenan under harsher conditions produced 3,6-anhydro L- and D-galactose aldehyde derivatives. Chain shortening of these products *via* alditol formation and oxidative carbon-carbon bond cleavage furnished *C*-formyl α-L- and α-D-threofuranosides. The above *C*-glycosyl aldehydes were all prepared on a meaningful preparative scale starting from gram quantities of galactans. Finally, a new procedure for the preparation of the 2,3-*O*-benzyl L-threofuranose was established by Baeyer-Villiger oxidation of the benzylated *C*-formyl α-L-threofuranoside here prepared from agarose.

Introduction

Proteoglycans, glycoproteins, and glycolipids are important mediators in specific cell-cell and cell-extracellular matrix interactions. The carbohydrate domain (mono- and oligosaccharide units) acts as an information carrier[1] while it is responsible for many functions performed by these glycoconjugates, such as neuronal development,[2] tumor growth and metastasis,[3] inflammation,[4] viral and bacterial infection,[5] immune response,[6] and fertilization.[7] Hence, the development of synthetic strategies toward natural oligosaccharides and their mimetics plays a pivotal role in biomedicinal chemistry.[8] Carbohydrate-based building blocks (CBBs) are key molecules for the synthesis of glycomimetics. The glycidic portion may act not only as a mimetic of particular biological motifs[9] but also as a valuable scaffold[10] by virtue of its rich stereochemistry, rigid conformation, and ease of functionalization. In particular, CBBs constituted of unusual sugar residues and holding suitable chemical functionalities have been demonstrated to be ideal substrates for the production of chemical libraries as sources of molecular diversity.[11] In this context, the great relevance of the sulfate group in bioactive sulfated carbohydrates has been recently recognized.[12] This chemical functionality appears to be involved in many recognition processes at the molecular level and participate in the development of a variety of diseases. The regiochemistry of sulfate derivatization onto the carbohydrate moiety as well as the configuration of the carbon atom bearing the sulfate group are crucial for the biological function of the whole molecule. Accordingly, several sulfated glycomimetics have been prepared.[13] Also, the synthesis of CBBs that display a chiral hydroxylated tetrahydrofuran moiety in their structure has attracted considerable attention[14] due to their potential use in the preparation of bioactive compounds such as antibiotics, nucleoside, and nucleotide analogues.[15]

In parallel, synthetic organic chemists have widely recognized the great potential of carbohydrates as chiral ligands and auxiliaries and, more recently, as organocatalysts in stereoselective transformations.[16] However, in many cases the scope of carbohydrate-based strategies in the above mentioned areas is limited by the availability of CBBs at low cost and in sufficient amount. Moreover only the more abundant enantiomeric form is easily accessible. Therefore, the development of efficient routes to CBBs with both natural and non-natural stereochemistry is of great relevance. Natural polysaccharides may constitute valuable and low cost starting materials for the preparation of CBBs. Remarkably, galactans from red seaweeds are interesting biopolymers that are constituted of alternating (1→3)-linked β-D-galactopyranose and (1→4)-linked α-D-galactopyranose units, some which are sulfated at specific positions. Depending on the configuration of the 4-linked units, galactans can be classified as agarans (L-enantiomer) or carrageenans (D-enantiomer).[17] Frequently, 4-linked units in galactans are displayed in the 3,6-anhydro form. Agarose **1** ([→3)-β-D-Gal*p*-(1→4)-3,6-anhydro-α-L-Gal*p*-(1→]$_n$) and kappa-carrageenan **2** ([→3)-β-D-Gal*p*-4-sulfate-(1→4)-3,6-anhydro-α-D-Gal*p*-(1→]$_n$) are representative examples of this sub-class of galactans (Fig. 1).[17a,c] Agarans and

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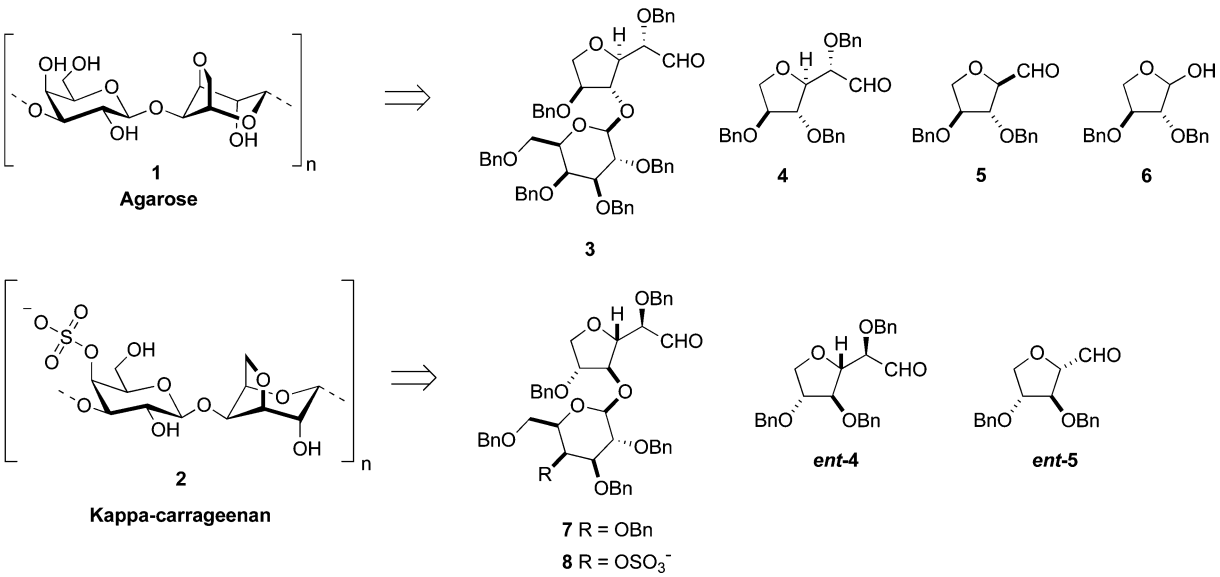


Fig. 1 Carbohydrate building blocks prepared from agarose **1** and kappa-carrageenan **2**.

carrageenans are valuable products for the pharmaceutical and food industries because they are used as gelling-stabilizing agents and consumer products (*e.g.* gel matrices for chromatography, microbial and cell culture, and other biochemical assay supports).[18] Hence, because of their broad use these galactans are produced on a large scale. They are, therefore, low cost starting materials for the production of useful and valuable CBBs.[19]

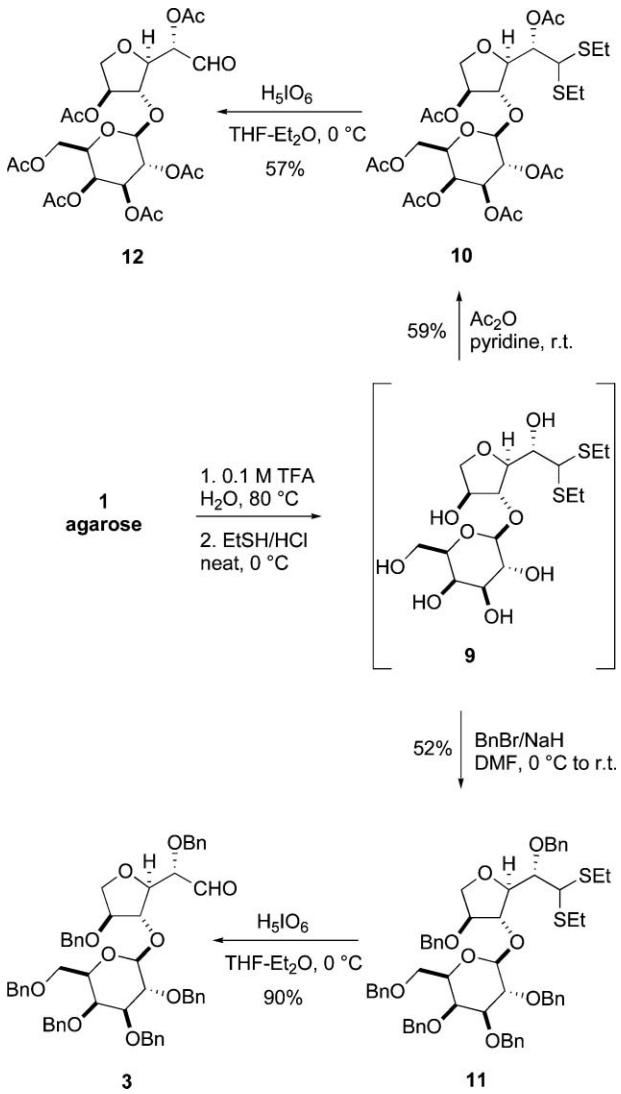
We would like to report in this paper the preparation of CBBs **3–5** from agarose **1**, and **7**, **8**, ***ent*-4** and ***ent*-5** from kappa-carrageenan **2**. These compounds constitute a set of *O*-benzyl protected aldehydes displaying a threofuranosyl unit in either the D or L enantiomeric form, and eventually bearing the sulfate group in their structure (Fig. 1). Another common feature of these derivatives is the presence of a hydrolytically and enzymatically stable carbon-carbon bond at the anomeric position of the threofuranose moiety. The synthesis of the rare sugar L-threose **6** from **5** is also reported. The main interest in the production of preparative amounts of **6** lies in its use as a starting material for non-natural nucleotide synthesis and the subsequent generation of (2′,3′)-α-L-threose nucleic acid (TNA) sequences.[20] In fact, TNAs are capable of giving Watson-Crick base pairing with complementary DNA or RNA sequences. Proposals about the role of TNA as a progenitor of RNA have been recently advanced.[21]

Results and discussion

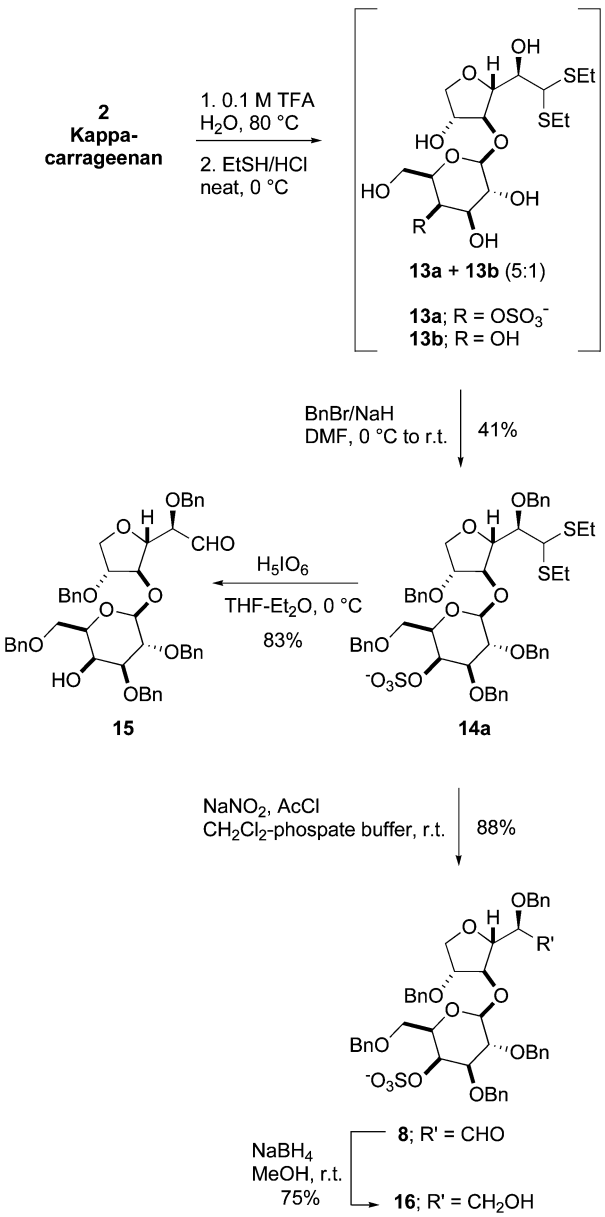
A. Semisynthesis of agarobiose derivative 3 and carrabiose derivatives 7 and 8

Early studies on the elucidation of galactan's structure were troublesome because of the high instability of the 3,6-anhydrogalactose unit under the harsh acidic conditions that were used for the hydrolysis of the polysaccharide backbone.[22] However, approaches based on HCl-promoted mercaptolysis proved to be successful in producing analytical samples and preparative amounts of dithioacetal derivatives of the anhydro unit of galactans. However, these methods involve time consuming reactions and laborious purifications steps.[22] Hence, to overcome these limitations and produce multigrams of the target CBB **3**, we submitted commercial agar (5 g scale), which is a source of agarose **1**,[23] to mild TFA (trifluoroacetic acid)-promoted hydrolysis according to the procedure of Stevenson and Furneaux[23] (Scheme 1). This procedure mainly afforded a reducing disaccharide intermediate (not shown) *via* selective 3,6-anhydro-α-galactosidic bond cleavage. This crude material was treated with ethanethiol (EtSH) and concentrated HCl to give crude agarobiose dithioacetal **9**. Flash chromatography of a portion (100 mg) of this material allowed the isolation of pure **9**,[24] which was characterized as the peracetylated derivative **10**.[24] Crude dithioacetal **9** was then perbenzylated under standard conditions (NaH/BnBr, DMF, 0 °C to r.t., 1 h) to give disaccharide **11** in 52% isolated yield (from agarose **1**; 5 g scale). Carbonyl group unmasking of dithioacetal **11** was carried out under oxidative conditions using periodic acid,[25] thus avoiding dithioacetal cleavage by harmful mercuric salts. This transformation was performed at 0 °C in THF-Et_2O and produced the aldehyde **3** in 90% yield and almost pure form as judged by ^{1}H NMR and TLC analyses. The formation of a single product indicated that the configuration at the C2 stereocenter of the epimerizable **3** remained unaltered in the course of the oxidation of **11**. The preparation of peracetylated aldehyde **12** was also investigated. Acetylation on a multigram scale of the crude extract containing **9** proceeded readily under standard conditions (Ac_2O/pyridine) and afforded the derivative **10** in 59% isolated yield. Unfortunately, the conversion of **10** to **12** by the above periodic acid method generated a complex reaction mixture, from which aldehyde **12** was isolated in 57% yield and 80% purity as established by ^{1}H NMR analysis.

The procedure depicted in Scheme 1 was then applied to kappa-carrageenan **2** depolymerization.[26] Accordingly, the two-step mercaptolysis of **2**[27] (5 g scale) produced a crude residue which contained a mixture of 4′-sulfated disaccharide **13a** and free-hydroxy disaccharide **13b** in 5:1 ratio (Scheme 2). This ratio was estimated after the isolation of pure **13a** and **13b** by analytical



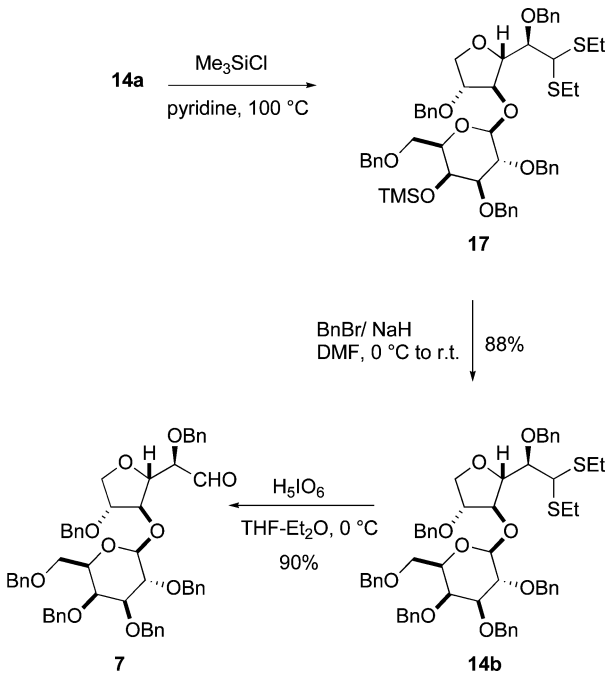
Scheme 1 Semisynthesis of CBB **3** derived from agarose **1**.



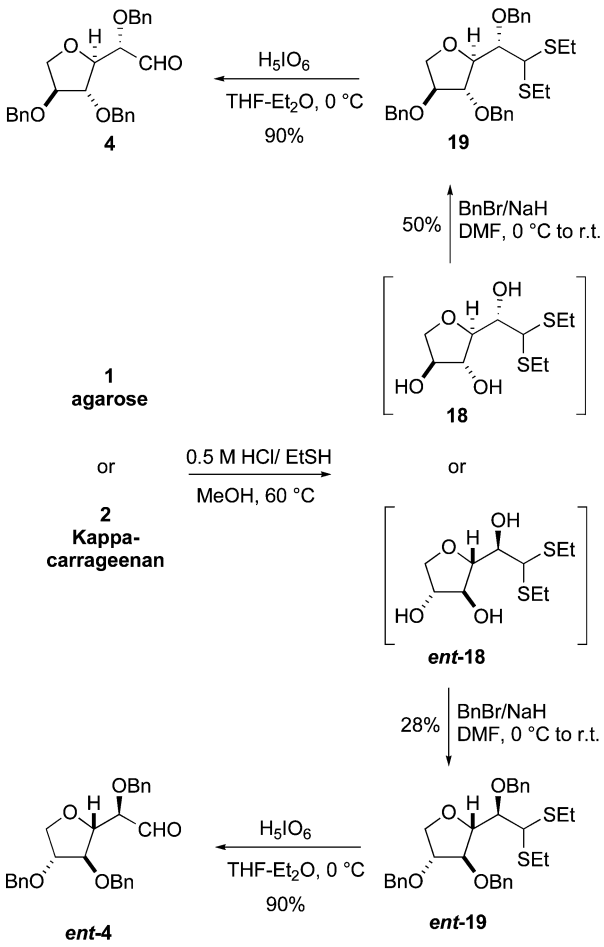
Scheme 2 Semisynthesis of CBB **8** derived from kappa-carrageenan **2**.

flash chromatography and acetylation of the above crude material (see Experimental Section). The presence of a sulfate group at C4′ of **13a** was confirmed by ESI MS (negative-ion mode) and ^{1}H NMR analyses. The MS spectrum showed an intense peak at m/z 509 ([M – H]$^-$), while the NMR spectrum displayed the H4′ signal shifted significantly downfield to 4.65 ppm. This result unequivocally excluded sulfate group hydrolysis or migration during the mercaptolysis of **2**.

The crude material containing **13a** and **13b** was benzylated under standard conditions to give the sulfated disaccharide **14a** in 41% isolated yield from **2** (3 g scale) along with the perbenzylated disaccharide **14b** (7%). Unfortunately, unmasking of the latent formyl group of **14a** by periodic acid oxidation resulted in the concomitant loss of the sulfate group and isolation of aldehyde **15** (83% yield). This unsatisfactory outcome was confirmed by ^{1}H NMR analysis of the 4′-trichloroacetyl carbamate derivative of **15** which was generated in the NMR tube by using trichloroacetyl isocyanate as a derivatizating agent (see Experimental Section). Moreover, the TLC profile of the unmasking reaction indicated that the sulfate group removal occurred before the formyl group formation. Fortunately enough, this problem was solved by applying different oxidizing conditions. Accordingly, treatment of **14a** with sodium nitrite and acetyl chloride in dichloromethane and phosphate buffer at room temperature[28] afforded the target aldehyde **8** in a rewarding 88% isolated yield (Scheme 2). The ^{1}H NMR spectrum of **8** (DMSO-d_6) at room temperature revealed the presence of the aldehyde and its hydrated form, whereas at higher temperatures (120–160 °C) partial epimerization at the C2 stereocenter and loss of sulfate group were observed. Hence, aldehyde **8** was conveniently converted into the corresponding alcohol **16** and this was fully characterized (Scheme 2). At this stage, we were also interested in preparing the benzylated disaccharide aldehyde **7**, *i.e.* using the minor product that resulted from the benzylation-oxidation sequence of the crude extract containing **13a** and **13b** (see Scheme 2 and Experimental Section). To this end, we envisaged the desulfation of **14a** and subsequent *O*-benzyl protection as an alternative route to **7** (Scheme 3). While several reagents have been reported for the desulfation of carbohydrates



Scheme 3 Semisynthesis of CBB **7** from sulfated intermediate **14a**.



Scheme 4 Semisynthesis of CBBs **4** and ***ent*-4** from galactans.

and polysaccharides,[29] chlorotrimethylsilane (CTMS) was selected in this endeavor. Accordingly, treatment of **14a** with CTMS in pyridine at 100 °C afforded the 4′-*O*-TMS protected disaccharide **17** in 78% isolated yield (column chromatography). It is worth noting that this compound constitutes a valuable CBB in its own right because the orthogonal protection of the 4′-hydroxy group of the β-Gal*p* unit provides easy access to other classes of carbohydrate molecules (library from library approach). The conversion of disaccharide **17** into CBB **7** proceeded readily as depicted in Scheme 3. The one-pot base (NaH)-promoted TMS group removal and Bn group installation afforded the intermediate **14b** (88%), which in turn was submitted to the optimized unmasking protocol with periodic acid to give the target aldehyde **7** (90%).

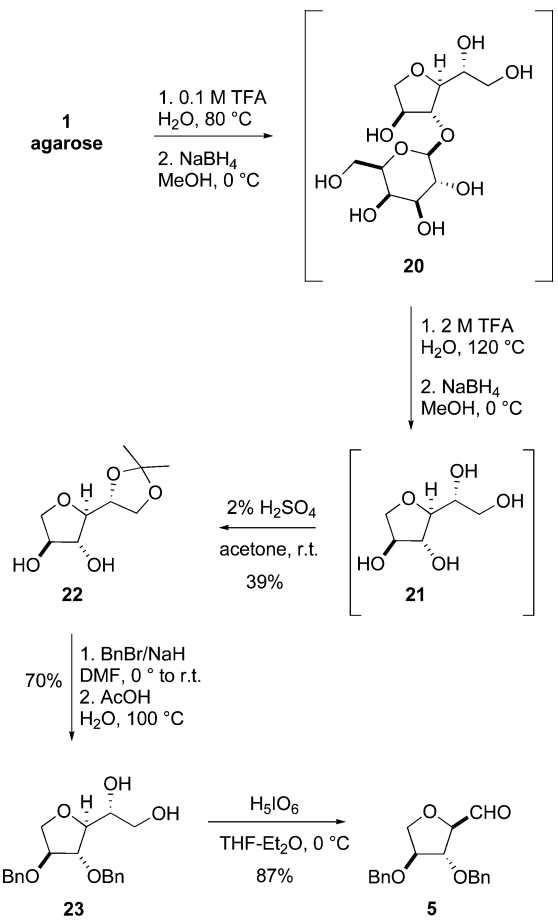
B. Semisynthesis of 3,6-anhydro L- and D-galactose aldehydes 4 and *ent*-4

Agarose **1** and kappa-carrageenan **2** were also considered as starting materials for the preparation of aldehydes **4** and ***ent*-4**, respectively. The approach toward these compounds required the complete mercaptolysis of **1** and **2**, *i.e.* acidic cleavage of both α- and β-galactosidic bonds followed by dithioacetal formation of the resulting 3,6-anhydro-galactose units. Previous studies were reported as early as in the 1960s dealing with the complete depolymerization of galactans[22,30] by the use of concentrated HCl and ethanethiol. However, in order to make the process developed by Hama and co-workers[30] operatively simple, we introduced an important modification, namely the use of a lower excess of stinky EtSH. Hence, agarose **1**[23] and kappa-carrageenan **2**[26,27] (6 g scale) were separately heated at 60 °C for 17 h in a mixture of HCl/MeOH/EtSH (Scheme 4). After neutralization (NaOH), diethyl ether extraction of the reaction mixtures afforded crude extracts containing monosaccharide dithioacetals **18** and ***ent*-18**. Acetylation of a portion of each extract furnished the peracetylated derivatives of these products (56% and 30% overall yields from **1** and **2**, respectively; see Experimental Section), thereby allowing us to evaluate the chemical efficiency of the optimized mercaptolysis procedure. The substantially different yields of **18** and ***ent*-18** are likely to be due to the lower hydrolysis rate of kappa-carrageenan **2** in comparison with agarose **1**. It is well known that the presence of sulfate groups in carrageenan's[23,31] backbone confers stability to both α- and β-glycosidic bonds through steric and electronic interactions. In addition, the observed low solubility of kappa-carrageenan **2** in the MeOH/EtSH mixture likely contributed to decreasing the polysaccharide hydrolysis rate. As a continuation of the synthetic plan, the crude extracts containing **18** and ***ent*-18** were perbenzylated under standard conditions to give **19** and ***ent*-19**. These intermediates were converted into the target 3,6-anyhdro-L-galactose **4** and 3,6-anhydro-D-galactose ***ent*-4** aldehydes by the optimized periodate-based formyl unmasking sequence described above (Scheme 4).

C. Semisynthesis of *C*-formyl α-L- and α-D-threofuranosides 5 and *ent*-5, and Protected L-Threofuranose 6

The development of efficient syntheses of *C*-formyl glycosides[32] and their elaboration into bioactive *C*-oligosaccharides and *C*-glycoconjugates[33] have been actively pursued in one of our laboratories over the course of the last two decades. Therefore,

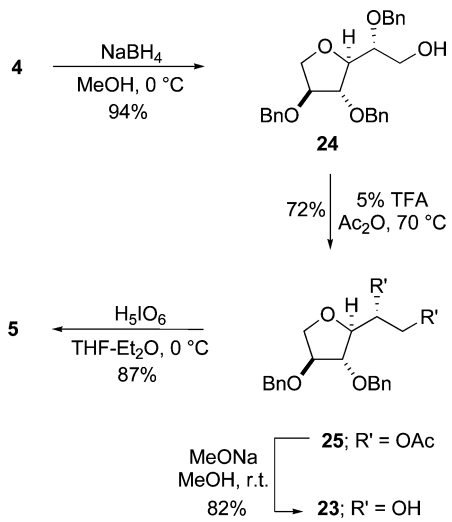
the preparation of hitherto unreported *C*-glycosyl aldehyde **5** and its enantiomer ***ent*-5**, featuring the rare threofuranosyl moiety, was established as a further goal of this study. To this aim we planned transforming agarose **1** and kappa-carrageenan **2** into alditols and elaborating these intermediates into **5** and ***ent*-5** *via* orthogonal manipulation of the hydroxyl groups (Scheme 5). The strategy was initially tested starting from agarose **1**.[23] This polysaccharide (10 grams) was submitted to the double hydrolysis/reduction protocol that was previously optimized on an analytical scale for the quantitative determination (GC-MS analysis) of the monosaccharide composition in galactans.[23] Accordingly, the mild acid hydrolysis of **1** by TFA at 80 °C resulted in selective α-galactosidic bond cleavage to give a crude mixture that was mainly constituted of the reducing disaccharide displaying the 3,6-anhydro-galactose residue as the terminal unit (not shown). The subsequent reduction of the above mixture by $NaBH_4$ in MeOH afforded the crude alditol disaccharide **20**, which in turn was submitted to a second hydrolysis step under harsher conditions (TFA, 120 °C) to promote the β-galactosidic bond cleavage. This reaction sequence afforded the 3,6-anhydro-L-galactitol **21**.[34] A second reductive step ($NaBH_4$) was also performed to convert D-galactose into D-galactitol (not shown) and thus facilitate the isolation of **21**. A suitable work-up of the complex reaction mixture by the use of ionic resins was then optimized (see Experimental Section) to remove inorganic salts and D-galactitol from **21**.



Scheme 5 Semisynthesis of CBB **5** *via* orthogonal protection of alditol intermediate **21**.

The satisfactory outcome of the whole procedure was confirmed by acetylation of a portion (100 mg) of the crude residue and recovery of acetylated **21** in 60% overall yield from agarose **1** (see Experimental Section). At this stage, the conversion of crude **21** into the target *C*-formyl α-L-threofuranoside **5** proceeded rapidly through selective 1,2-*O*-isopropylidene protection, 4,5-*O*-benzylation, acetonide removal, and final oxidation with periodic acid (24% overall yield from **1**; Scheme 5).

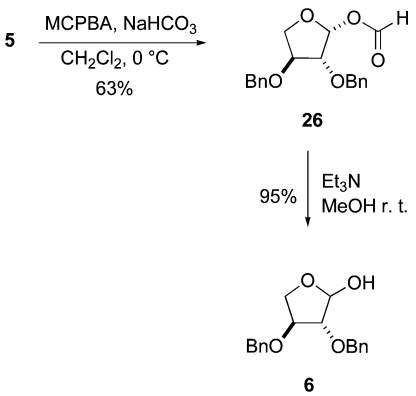
The numerous steps and the laborious purification of **21** prompted us to investigate a more efficient entry to **5** *via* a one-carbon chain-shortening of **4**. This approach involved the selective C2 debenzylation of protected alditol **24** as the key step (Scheme 6). This intermediate was readily prepared in almost quantitative yield by $NaBH_4$ reduction of aldehyde **4**. Methods for the regioselective deprotection of carbohydrate molecules are important tools to access derivatives that display free hydroxy groups in definite positions. Numerous reports dealing with this issue have been reported over the years.[35] Hence, after some experimentation that involved the screening of several acid catalysts, we found TFA was the optimal one to promote the selective C2 acetolysis of **24**. This transformation was effectively performed at 70 °C by using a mixture of acetic anhydride and 5% TFA. Column chromatography of the resulting crude material afforded the diacetyl intermediate **25** as the main product in 72% isolated yield. As previously postulated in similar studies on the selective deprotection of pentofuranoses,[35a] a chelation effect of the Lewis basic endocyclic oxygen and C2 benzylic oxygen atom on H^+ ions could be at the origin of the observed regioselectivity. Afterwards, deacetylation of **25** under standard conditions (NaOMe/MeOH) afforded the diol **23** (82%), which in turn was effectively oxidized with periodic acid to give the target *C*-formyl α-L-threofuranoside 5 in 87% yield. The same strategy was employed for the synthesis of the enantiomeric C-formyl α-D-threofuranoside ***ent*-5** starting from ***ent*-4** (see Experimental Section).



Scheme 6 Semisynthesis of CBB **5** *via* selective debenzylation of intermediate **24**.

As already mentioned, L-threofuranose derivative **6** is also a valuable CBB, mainly because of its utilization in non-natural nucleotide synthesis and TNA sequence generation.[20] This rare sugar is commercially available (Carbosynth: $400/g) and several

procedures for its production have been reported in the literature.[21c,36] We envisaged the Baeyer-Villiger oxidation of *C*-formyl α-L-threofuranoside **5** as a new route to **6** (Scheme 7). Indeed, *m*-chloroperbenzoic acid (MCPBA) promoted the cleavage of the anomeric carbon-carbon bond of **5** to give the *O*-formyl protected β-L-threofuranose **26** in 63% isolated yield. The β-configuration at the anomeric position of **26** was tentatively assigned by NMR analysis on the basis of the absence of NOE on H3 upon H1 irradiation. The removal of the formyl protective group from **26** was carried out under mild basic conditions (Et_3N), thus affording the target L-threofuranose derivative **6** in almost quantitative yield.



Scheme 7 Semisynthesis of threofuranose derivative **6** from CBB **5**.

Conclusions

In conclusion, we have reported a convenient utilization of natural polysaccharides of marine origin through their transformation into potentially valuable carbohydrate-based building blocks which may serve as starting materials in *C*-glycoside synthesis. The utility of these semisynthetic methods is demonstrated by their being effective for the production of orthogonally functionalized building blocks which are hardly accessible by total synthesis. It is noteworthy that the opposite stereochemistry of the 3,6-anhydro-galactose moiety that distinguishes the backbone of agarose from kappa-carrageenan enables access to products which belong to L- and D-series of carbohydrates. This great potential offers a wide range of opportunities for studies in glycobiology and applications in biomedicinal chemistry. The use of the herein described CBBs for the synthesis of dihydropyrimidine-based artificial *C*-nucleosides will be the subject of a forthcoming publication.

Experimental section

Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring either with sulfuric acid (conc. H_2SO_4/EtOH 1:9) or 0.5% orcinol in conc. H_2SO_4/EtOH 1:20. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Peaks assignments were aided by ^{1}H–^{1}H COSY and gradient-HMQC experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. ESI MS analyses were performed in negative-ion mode with samples dissolved in a mixture of MeCN/H_2O 1:1. Commercial agar,[23] a source of agarose **1**, was purchased from Oxoid Limited (Hampshire, UK). Kappa-carrageenan **2** was obtained from red algae *Kappaphycus alvarezii* as described.[26] Derivatives **6**,[37] **18**,[22b,30] and **21**[38] are known compounds and their spectroscopic data were identical to those reported. Derivatives **9**,[24] **10**,[24] **13b**,[22c] **peracetylated-13b**,[22d] and ***ent*-18**[22a] are known compounds but only their optical rotation values are reported.

β-D-Galactopyranosyl-(1→4)-3,6-anhydro-L-galactose diethyl dithioacetal (9)

Commercial agar (5 g)[23] was first dissolved in hot (~90 °C) H_2O (450 mL) and then 1M TFA solution (50 mL) was added in one portion. The resulting mixture was heated at 80 °C for 3 h, cooled to room temperature, diluted with H_2O (500 mL), and then concentrated under vacuum. The resulting residue was dissolved in water (90 mL), diluted with *i*-PrOH (90 mL), and then filtered through a glass-sintered filter. The filtrate was concentrated and coevaporated with toluene three times to give a brown-yellow solid (4.85 g). This material was dissolved in 37% HCl (7.2 mL) and EtSH (3.2 mL) at 0 °C. The resulting mixture was then stirred at 0 °C for 1h, neutralized with 1M NaOH solution, and kept under a nitrogen flow to remove unreacted EtSH. The mixture was then concentrated under vacuum to give a solid residue, which was suspended in MeOH (100 mL), and filtered through a glass-sintered filter. The filtrate was concentrated to afford a crude material (5.01 g) containing the dithioacetal derivate **9**. A small amount of this crude material (100 mg) was eluted from a column of silica gel with 7:1 AcOEt-MeOH to give **9** (60 mg, 59% from starting agar)[23] as a white amorphous solid. $[\alpha]_D = -16.4$ (*c* 0.7, MeOH) (lit.[24] $[\alpha]_D = -20.9$ (*c* 1.4, MeOH)); $R_f = 0.16$ (7:1 AcOEt-MeOH). ^{1}H NMR (CD_3OD): $\delta = 4.41$ (d, 1 H, $J_{1',2'} = 7.5$ Hz, H-1′), 4.34 (dd, 1 H, $J_{2,3} = 3.5$, $J_{3,4} = 4.0$ Hz, H-3), 4.29-4.26 (m, 2 H, H-4, H-5), 4.00 (d, 1 H, $J_{1,2} = 8.5$ Hz, H-1), 3.93 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 9.5$ Hz, H-6a), 3.86-3.84 (m, 2 H, H-2, H-4′), 3.80-3.70 (m, 3 H, H-6b, H-6a′, H-6b′), 3.55-3.50 (m, 2 H, H-5′, H-2′), 3.47 (dd, 1 H, $J_{2',3'} = 10.0$, $J_{3',4'} = 3.5$ Hz, H-3′), 2.80-2.61 (m, 4 H, SCH_2CH_3), 1.25, 1.24 (2 t, 6 H, $J = 7.5$ Hz, SCH_2CH_3). ^{13}C NMR: $\delta = 103.0$, 86.1, 83.9, 75.8, 75.6, 73.8, 73.4, 73.0, 71.2, 68.9, 61.3, 54.4, 24.8, 24.6, 13.7, 13.6. MALDI-TOF MS: 453.1 (M^+ + Na). Anal. Calcd for $C_{16}H_{30}O_9S_2$ (430.13): C, 44.64; H, 7.02; S, 14.90. Found: C, 44.72; H, 7.00; S, 14.99.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-acetyl-3,6-anhydro-L-galactose diethyl dithioacetal (10)

A mixture of crude material (125 mg) containing compound **9**, pyridine (2.2 mL), and Ac_2O (2.0 mL) was stirred at room temperature for 12 h, then concentrated, and coevaporated with toluene three times. The resulting residue was eluted from a column of silica gel with 1:1 cyclohexane-AcOEt to give **10** (120 mg, 59% from starting agar)[23] as a colorless syrup. $[\alpha]_D = -7.4$ (*c* 0.8, $CHCl_3$) (lit.[24] $[\alpha]_D = -11.8$ (*c* 1.0, $CHCl_3$)); $R_f = 0.28$ (1:1 cyclohexane-AcOEt). ^{1}H NMR: $\delta = 5.39$ (dd, 1 H, $J_{3',4'} = 3.5$, $J_{4',5'} = 1.0$ Hz, H-4′), 5.35 (dd, 1 H, $J_{1,2} = 9.2$, $J_{2,3} = 2.7$ Hz, H-2), 5.18 (dd, 1 H, $J_{1',2'} = 8.0$, $J_{2',3'} = 10.5$ Hz, H-2′), 5.02 (dd, 1 H, H-3′), 5.00

(m, 1 H, H-5), 4.59 (d, 1 H, H-1′), 4.47 (dd, 1 H, $J_{3,4}$ = 5.0 Hz, H-3), 4.22 (dd, 1 H, $J_{5',6b'}$ = 7.2, $J_{6a',6b'}$ = 11.0 Hz, H-6b′), 4.12 (dd, $J_{5',6a'}$ = 6.0 Hz, H-6a′), 4.06 (d, 1 H, H-1), 4.00-3.94 (m, 3 H, H-5′, H-6b, H-6a), 3.89 (dd, 1 H, $J_{4,5}$ = 1.5 Hz, H-4), 2.78-2.58 (m, 4 H, SCH_2CH_3), 2.14, 2.13, 2.08, 2.06, 2.04, 1.97 (6 s, 18 H, $COCH_3$), 1.26, 1.23 (2 t, 6 H, J = 7.5 Hz, SCH_2CH_3). ^{13}C NMR: δ = 170.3, 170.2, 170.1, 169.9, 169.4, 101.6, 86.0, 83.0, 79.5, 72.5, 71.1, 70.9, 70.6, 68.6, 66.9, 61.0, 52.0, 25.0, 24.8, 20.8, 20.7,20.6, 20.5, 20.4, 14.2, 14.1. MALDI-TOF MS: 721.3 (M^+ + K). Anal. Calcd for $C_{28}H_{42}O_{15}S_2$ (682.20): C, 49.26; H, 6.20; S, 9.39. Found: C, 49.39; H, 6.25; S, 9.31.

The above described procedure was repeated starting from 2.50 g of the crude material containing **9** to give 2.40 g of **10**.

2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-L-galactose diethyl dithioacetal (11)

To a cooled (0 °C), stirred mixture of the crude material (4.17 g) containing compound **9** (~2.51 g, 5.84 mmol) and DMF (80 mL) was added portionwise NaH (2.80 g, 70.1 mmol of a 60% suspension in mineral oil) and, after 30 min, benzyl bromide (5.4 mL, 45.5 mmol). The mixture was stirred at room temperature for 40 min, then treated with MeOH (10 mL), stirred for an additional 10 min, diluted with H_2O (100 mL), and extracted with Et_2O (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 5:1 cyclohexane-AcOEt to give **11** (5.1 g, 52% from starting agar)[23] as a white amorphous solid. $[\alpha]_D$ = −3.4 (*c* 0.9, $CHCl_3$); R_f = 0.19 (5:1cyclohexane-AcOEt).^{1}H NMR: δ = 7.40-7.20 (m, 30 H, Ph), 4.94, 4.89, 4.84, 4.78 (4 d, 5 H, J = 11.5 Hz, PhCH_2), 4.72 (s, 2 H, PhCH_2), 4.57, 4.43, 4.39, 4.37 (4 d, 5 H, J = 11.5 Hz, PhCH_2), 4.35 (d, 1 H, $J_{1',2'}$ = 7.5 Hz, H-1′), 4.33-4.28 (m, 2 H, H-3, H-4), 4.12 (d, 1 H, $J_{1,2}$ = 5.9 Hz, H-1), 4.07 (m, 1 H, H-5), 3.95 (dd, 1 H, $J_{5,6b}$ = 3.0, $J_{6a,6b}$ = 9.5 Hz, H-6b), 3.90 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, H-4′), 3.86 (dd, 1 H, $J_{2,3}$ = 4.5 Hz, H-2), 3.80 (dd, 1 H, $J_{5,6a}$ = 5.0 Hz, H-6a), 3.76 (dd, 1 H, $J_{2',3'}$ = 9.5 Hz, H-2′), 3.57 (dd, 1 H, $J_{5',6b'}$ = 7.5, $J_{6a',6b'}$ = 9.0 Hz, H-6b′), 3.51 (dd, 1 H, $J_{5',6a'}$ = 5.0 Hz, H-6a′), 3.48-3.43 (m, 2 H, H-5′, H-3′), 2.70-2.50 (m, 4 H, SCH_2CH_3), 1.27, 1.23 (2 t, 6 H, J = 7.5 Hz, SCH_2CH_3). ^{13}C NMR: δ = 138.6, 138.4, 138.3, 137.8, 137.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 102.6, 84.3, 83.0, 82.0, 81.9, 79.2, 75.1, 74.8, 74.6, 73.5, 73.2, 72.8, 71.4, 71.2, 68.3, 53.3, 26.0, 25.3, 14.4, 14.3. MALDI-TOF MS: 1009.3 (M^+ + K). Anal. Calcd for $C_{58}H_{66}O_9S_2$ (970.41): C, 71.72; H, 6.85; S, 6.60. Found: C, 71.60; H, 6.88; S, 6.69.

2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-*aldehydo*-L-galactose (3)

To a cooled (0 °C), stirred mixture of **11** (582 mg, 0.60 mmol), THF (1.2 mL), and Et_2O (3 mL) a solution of H_5IO_6 (274 mg, 1.20 mmol) in THF (0.6 mL) was added dropwise. The resulting mixture was warmed to room temperature, stirred for 20 min, diluted with 1M phosphate buffer (25 mL), and extracted with Et_2O (80 mL). The organic phase was washed with 10% aqueous Na_2SO_3 solution (2 × 25 mL), dried (Na_2SO_4), and concentrated to give **3** (467 mg, 90%) as a white amorphous solid at least 95% pure as established by ^{1}H NMR analysis. An analytical sample of **3** was obtained by flash chromatography with 3.3:1 cyclohexane-AcOEt as the eluent. $[\alpha]_D$ = −28.8 (*c* 2.4, $CHCl_3$); R_f = 0.26 (3.3:1cyclohexane-AcOEt).^{1}H NMR: δ = 9.67 (d,1 H, H-1), 7.38-7.18 (m, 30 H, Ph), 4.93, 4.86, 4.77 (3 d, 3 H, J = 12.0 Hz, PhCH_2), 4.73 (s, 1 H, PhCH_2), 4.70 (d, 2 H, J = 12.0 Hz, PhCH_2), 4.61, 4.51 (2 d, 2 H, PhCH_2), 4.42-4.30 (m, 6 H, PhCH_2, H-4, H-3), 4.21 (dd, 1 H, $J_{1,2}$ = 1.0, $J_{2,3}$ = 3.0 Hz, H-2), 4.11 (m, 1 H, H-5), 4.09 (d, 1 H, $J_{1',2'}$ = 8 Hz, H-1′), 3.97 (dd, 1 H, $J_{5,6b}$ = 4.0, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.83 (dd, 1 H, $J_{5,6a}$ = 5.0 Hz, H-6a), 3.80 (dd, 1 H, H-4′), 3.77 (dd, 1 H, $J_{2',3'}$ = 10.0 Hz, H-2′), 3.47 (dd, 1 H, $J_{5',6b'}$ = 6.5, $J_{6a',6b'}$ = 9.5 Hz, H-6b′), 3.40 (dd, 1 H, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.37 (dd, 1 H, $J_{5',6a'}$ = 6.0 Hz, H-6a′), 3.27 (ddd, 1 H, H-5′). ^{13}C NMR: δ = 202.5, 138.6, 138.3, 138.2, 137.8, 137.6, 137.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 104.0, 84.9, 83.8, 83.4, 82.2, 81.9, 79.1, 75.1, 74.5, 73.5, 73.4, 73.3, 73.0, 72.9, 71.5, 71.4, 69.2. MALDI-TOF MS: 887.4 (M^+ + Na). Anal. Calcd for $C_{54}H_{56}O_{10}$ (864.39): C, 74.98; H, 6.53. Found: C, 74.87; H, 6.57.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-acetyl-3,6-anhydro-*aldehydo*-L-galactose (12)

To a cooled (0 °C), stirred mixture of **10** (409 mg, 0.60 mmol), THF (1.2 mL), and Et_2O (3 mL) a solution of H_5IO_6 (274 mg, 1.20 mmol) in THF (0.6 mL) was added dropwise. The resulting mixture was warmed to room temperature, stirred for 20 min, diluted with 1M phosphate buffer (25 mL), and extracted with $CHCl_3$ (80 mL). The organic phase was washed with 10% aqueous Na_2SO_3 solution (2 × 25 mL), dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:2 cyclohexane-AcOEt to give aldehyde **12** (197 mg, 57%) at least 80% pure as established by ^{1}H NMR analysis. ^{1}H NMR: δ = 9.58 (s, 1 H, H-1), 5.41 (d, 1 H, $J_{2,3}$ = 3.5 Hz, H-2), 5.39 (dd, 1 H, $J_{3',4'}$ = 3.5, $J_{4',5'}$ = 1.0 Hz, H-4′), 5.18 (dd, 1 H, $J_{1',2'}$ = 8.0, $J_{2'3'}$ = 10.5 Hz, H-2′), 5.02 (dd, 1 H, H-3′), 5.00 (ddd, 1 H, H-5), 4.65 (d, 1 H, H-1′), 4.38 (t, 1 H, $J_{3,4}$ = 4.0 Hz, H-3), 4.20-4.14 (m, 2 H, H-4, H-6a′), 4.09 (dd, 1 H, $J_{5',6b'}$ = 6.5, $J_{6a',6b'}$ = 11.5 Hz, H-6b′), 3.99 (dd, 1 H, $J_{5,6b}$ = 2.0, $J_{6a,6b}$ = 10.5 Hz, H-6b), 3.93 (dd, 1 H, $J_{5,6a}$ = 4.5 Hz, H-6a), 3.92 (ddd, 1 H, H-5′), 2.25, 2.18, 2.12, 2.09, 2.04, 2.00 (6 s, 18 H, $COCH_3$). ^{13}C NMR: δ = 195.9, 170.4, 170.3, 107.2, 170.0, 169.4, 101.3, 84.1, 82.1, 78.6, 76.4, 71.4, 71.1, 70.6, 68.5, 67.0, 61.4, 61.4, 20.9, 20.6, 20.5. MALDI-TOF MS: 615.6 (M^+ + Na).

4-*O*-Sulfonato-β-D-galactopyranosyl-(1→4)-3,6-anhydro-D-galactose diethyl dithioacetal (13a) and β-D-galactopyranosyl-(1→4)-3,6-anhydro-D-galactose diethyl dithioacetal (13b)

Kappa-carrageenan[26] **2** (5 g) was first dissolved in hot (~90 °C) H_2O (450 mL) and then 1M TFA solution (50 mL) was added in one portion. The resulting mixture was heated at 80 °C for 3 h, cooled to room temperature, diluted with H_2O (500 mL), and then concentrated under vacuum. The resulting residue was dissolved in water (90 mL), diluted with *i*-PrOH (90 mL), and then filtered through a glass-sintered filter. The filtrate was concentrated and coevaporated with toluene three times to give a brown-yellow solid (4.60 g). This material was dissolved in 37% HCl (5.3 mL) and EtSH (3.5 mL) at 0 °C. The resulting mixture was then stirred at 0 °C for 1h, neutralized with 1M NaOH, and kept under a nitrogen flow to remove unreacted EtSH. The mixture was then concentrated under vacuum to give a solid residue, which was suspended in MeOH (100 mL), and filtered through a glass-sintered

filter. The filtrate was concentrated to afford a crude material (5.00 g) containing the dithioacetal derivates **13a** and **13b**. A small amount of the above crude material (250 mg) was eluted from a column of silica gel with 14:2:1 AcOEt-MeOH–H_2O and then with 10:2:1 AcOEt-MeOH-H_2O to give firstly **13b** (25 mg, 10% from starting kappa-carrageenan)[27] as a white amorphous solid. $[\alpha]_D = 7.4$ (*c* 0.8, MeOH) (lit.[22c] $[\alpha]_D = 14.0$ (*c* 2.0, H_2O)); $R_f = 0.30$ (14:2:1 AcOEt-MeOH-H_2O). ^{1}H NMR (CD_3OD): $\delta = 4.42$-4.37 (m, 2 H, H-5, H-3), 4.34 (d, 1 H, $J_{1',2'} = 7.5$ Hz, H-1′), 4.16 (dd, 1 H, $J = 3.0$ and 5 Hz, H-4), 4.00 (d, 1 H, $J_{1,2} = 8.5$ Hz, H-1), 3.95 (dd, 1 H, $J_{5,6b} = 5.5$, $J_{6a,6b} = 9.5$ Hz, H-6b), 3.82-3.75 (m, 4 H, H-2, H-4′, H-6b′, H-6a), 3.70 (dd, 1 H, $J_{5',6a'} = 4.5$, $J_{6a',6b'} = 11.5$ Hz, H-6a′), 3.56 (ddd, 1 H, H-5′), 3.54 (dd, 1 H, $J_{2',3'} = 9.5$ Hz, H-2′), 3.47 (dd, 1 H, $J_{3',4'} = 3.5$ Hz, H-3′), 2.80-2.60 (m, 4 H, SCH_2CH$_3$), 1.28, 1.27 (2 t, 6 H, $J = 7.5$ Hz, SCH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 104.0$, 87.8, 76.2, 75.8, 73.8, 73.2, 72.1, 71.2, 69.1, 61.5, 54.2, 24.8, 24.6, 13.8, 13.7. MALDI-TOF MS: 453.2 (M^+ + Na). Anal. Calcd for $C_{16}H_{30}O_9S_2$ (430.13): C, 44.64; H, 7.02; S, 14.90. Found: C, 44.73; H, 7.08; S, 14.85.

Eluted second was **13a** (147 mg, 48% from starting kappa-carrageenan)[27] as a white amorphous solid. $[\alpha]_D = 7.5$ (*c* 1.2, MeOH); $R_f = 0.27$ (10:2:1 AcOEt-MeOH-H_2O).^{1}H NMR (CD_3OD): $\delta = 4.65$ (dd, 1 H, $J_{3',4'} = 3.5$ Hz, H-4′), 4.40-4.35 (m, 2 H, H-3, H-5), 4.36 (d, 1 H, $J_{1',2'} = 7.5$ Hz, H-1′), 4.14 (dd, 1 H, $J =$ 3.0 and 4.5 Hz, H-4), 4.00 (d, 1 H, $J_{1,2} = 8.5$ Hz, H-1), 3.94 (dd, 1 H, $J_{5,6b} = 5.5$, $J_{6a,6b} = 9.5$ Hz, H-6b), 3.80-3.70 (m, 5 H, H-5′, H-2, H-6a, H-6b′, H-6a′), 3.62 (dd, 1 H, $J_{2',3'} = 10.0$ Hz, H-3′), 3.53 (dd, 1 H, H-2′), 2.80–2.61 (m, 4 H, SCH_2CH$_3$), 1.25, 1.24 (2 t, 6 H, $J = 7.5$ Hz, SCH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 105.1$, 88.9, 84.4, 77.4, 76.8, 76.0, 74.4, 73.0, 62.3, 55.8, 26.0, 25.7, 14.9, 14.8. ESI MS: 509.4 (M – H).

2,3,6-Tri-*O*-acetyl-4-*O*-sulfonato-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-acetyl-3,6-anhydro-D-galactose diethyl dithioacetal (peracetylated-13a) and 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-acetyl-3,6-anhydro-D-galactose diethyl dithioacetal (peracetylated-13b)

A mixture of the crude material (200 mg) containing compounds **13a** and **13b**, pyridine (2.2 mL), and Ac_2O (2.0 mL) was stirred at room temperature for 12 h, then concentrated, and coevaporated with toluene three times. The resulting residue was eluted from a column of silica gel with 1:1 cyclohexane-AcOEt and then with 10:1 AcOEt-MeOH to give firstly **peracetylated-13b** (31 mg, 10% from starting kappa-carrageenan)[27] as a colorless syrup. $[\alpha]_D = -2.6$ (*c* 0.6, $CHCl_3$) (lit.[22d] $[\alpha]_D = -4.0$ (*c* 1.2, $CHCl_3$)); $R_f = 0.3$ (1:1 cyclohexane-AcOEt). ^{1}H NMR: $\delta = 5.39$ (dd, 1 H, $J_{3',4'} =$ 3.5 Hz, H-4′), 5.31 (ddd, 1 H, H-5), 5.20 (dd, 1 H, $J_{1',2'} = 8.0$ Hz, $J_{2',3'} = 10.5$ Hz, H-2′), 5.12 (dd, 1 H, $J_{1,2} = 9.5$, $J_{2,3} = 2.5$ Hz, H-2), 5.02 (dd, 1 H, H-3′), 4.63 (d, 1 H, H-1′), 4.38 (dd, 1 H, $J_{3,4} =$ 5.0 Hz, H-3), 4.13 (dd, 1 H, $J_{5',6b'} = 4.5$, $J_{6a',6b'} = 11.0$ Hz, H-6b′), 4.11 (dd, 1 H, $J_{5',6a'} = 7.0$ Hz, H-6a′), 4.05 (d, 1 H, H-1), 4.02 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 10.5$ Hz, H-6a), 3.98-3.92 (m, 3 H, H-4, H-6b, H-5′), 2.78-2.60 (m, 4 H, SCH_2CH$_3$), 2.21, 2.17, 2.12, 2.10, 2.05, 2.00 (6 s, 18 H, COCH$_3$), 1.28, 1.27 (2 t, 6 H, $J = 7.5$ Hz, SCH$_2$CH_3). ^{13}C NMR: $\delta = 170.7$, 170.5, 170.3, 169.8, 101.9, 86.0, 82.5, 79.0, 72.7, 72.3, 71.2, 71.0, 68.7, 67.1, 61.3, 52.3, 25.3, 25.0, 21.2, 21.0, 20.9, 20.8, 14.6, 14.4. MALDI-TOF MS: 721.2 (M^+ + K). Anal. Calcd for $C_{28}H_{42}O_{15}S_2$ (682.20): C, 49.26; H, 6.20; S, 9.39. Found: C, 49.18; H, 6.26; S, 9.30.

Eluted second was **peracetylated-13a** (164 mg, 48%) as a colorless syrup. $[\alpha]_D = 17.9$ (*c* 2.0, MeOH); $R_f = 0.23$ (10:1 AcOEt-MeOH). ^{1}H NMR (CD_3OD): $\delta = 5.32$ (ddd, 1 H, H-5), 5.19 (dd, 1 H, $J_{1',2'} = 8.0$, $J_{2',3'} = 10.5$ Hz, H-2′), 5.17 (dd, 1 H, $J_{1,2} = 7.8$, $J_{2,3} = 4.0$ Hz, H-2), 4.92 (dd, 1 H, $J_{3',4'} = 3.5$ Hz, H-3′), 4.83 (dd, 1 H, H-4′), 4.71 (d, 1 H, H-1′), 4.40 (dd, 1 H, $J_{6a',6b'} = 12.0$, $J_{5',6a'} =$ 4.5 Hz, H-6a′), 4.31 (t, 1 H, $J = 4.0$ Hz, H-3), 4.23 (dd, 1 H, $J_{5',6b'} =$ 7.5 Hz, H-6b′), 4.13 (dd, 1 H, $J_{3,4} = 4.0$ Hz, H-4), 4.09 (d, 1 H, H-1), 4.00 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 10.5$ Hz, H-6a), 3.99 (ddd, 1 H, H-5′), 3.86 (dd, 1 H, H-6b), 2.80-2.60 (m, 4 H, SCH_2CH$_3$), 2.14, 2.11, 2.10, 2.06, 2.05 (5 s, 15 H, COCH$_3$), 1.29, 1.27 (2 t, 6 H, $J = 7.5$ Hz, SCH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 172.6$, 172.0, 171.7, 171.2, 102.9, 86.6, 84.1, 80.0, 74.1, 73.5, 73.0, 72.8, 70.2, 64.6, 53.0, 26.1, 26.0, 21.0, 20.9, 14.8, 14.6. ESI MS: 719.8 (M – H).

2,3,6-Tri-*O*-benzyl-4-*O*-sulfonato-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-D-galactose diethyl dithioacetal (14a)

Treatment of the crude material (3.0 g) containing **13a** (~1.77 g, 3.32 mmol) and **13b** (~298 mg, 0.69 mmol) as described for the preparation of **11** gave after column chromatography (10:1 AcOEt-MeOH) derivative **14a** (2.78 g, 41% from starting kappa-carrageenan)[27] as a yellow amorphous solid. $[\alpha]_D = 30.7$ (*c* 1.0, MeOH); $R_f = 0.50$ (10:1 AcOEt-MeOH). ^{1}H NMR (CD_3OD): $\delta = 7.50$-7.20 (m, 25 H, Ph), 4.97 (d, 1 H, $J = 11.5$ Hz, PhCH_2), 4.91 (dd, 1 H, $J_{3',4'} = 2.0$ Hz, H-4′), 4.81, 4.73, 4.70, 4.65, 4.56 (5 d, 5 H, $J = 11.5$ Hz, PhCH_2), 4.55-4.52 (m, 2 H, H-1′, H-4), 4.52, 4.49, 4.48 (3 d, 4 H, $J = 11.5$ Hz, PhCH_2), 4.35 (dd, 1 H, $J_{2,3} =$ 5.5, $J_{3,4} = 3.0$ Hz, H-3), 4.29 (ddd, 1 H, H-5), 4.00 (d, 1 H, $J_{1,2} =$ 5.0 Hz, H-1), 3.99 (dd, 1 H, H-6b), 3.90 (dd, 1 H, $J_{5',6a'} = 4.5$, $J_{6a',6b'} = 10.5$ Hz, H-6a′), 3.89 (dd, 1 H, $J_{5,6a} = 4.5$, H-6a), 3.88 (dd, 1 H, H-2), 3.81 (dd, 1 H, $J_{5',6b'} = 7.5$ Hz, H-6b′), 3.66 (dd, 1 H, H-5′), 3.57-3.54 (m, 2 H, H-2′, H-3′), 2.60-2.40 (m, 4 H, SCH_2CH$_3$), 1.09, 1.05 (2 t, 6 H, $J = 7.5$ Hz, SCH$_2$CH_3). ^{13}C NMR (CD_3OD): $\delta = 139.0$, 138.6, 138.5, 138.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.4, 127.3, 127.2, 103.2, 86.1, 84.3, 83.7, 81.3, 79.8, 78.6, 74.9, 74.7, 73.6, 73.1, 73.0, 71.7, 71.5, 71.3, 70.3, 53.3, 25.5, 25.3, 13.7, 13.5. ESI MS: 960.1 (M – H).

2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-D-galactose diethyl dithioacetal (14b). Route A (Scheme 2)

Treatment of crude material (3.0 g) containing **13a** (~1.77 g, 3.32 mmol) and **13b** (~298 mg, 0.69 mmol) as described for the preparation of **11** gave after column chromatography (5:1 cyclohexane-AcOEt) derivative **14b** (469 mg, 7% from starting kappa-carrageenan)[27] as a colorless syrup. $[\alpha]_D = 7.1$ (*c* 0.5, $CHCl_3$); $R_f = 0.41$ (5:1 cyclohexane-AcOEt). ^{1}H NMR: $\delta = 7.40$-7.20 (m, 30 H, Ph), 4.93, 4.89, 4.79, 4.72, 4.71, 4.68, 4.61 (7 d, 8 H, $J = 12.0$ Hz, PhCH_2), 4.52-4.45 (m, 4 H, H-4, H-1′, 2 PhCH_2), 4.38 (t, 1 H, $J_{2,3} = 4.5$ Hz, H-3), 4.50 (s, 2 H, PhCH_2), 4.28 (m, 1 H, H-5), 4.03 (d, 1 H, $J_{1,2} = 5.5$ Hz, H-1), 4.02 (dd, 1 H, H-6b), 3.91 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 10.0$ Hz, H-6a), 3.88 (dd, 1 H, $J_{3',4'} = 3.0$ Hz, H-4′), 3.84 (t, 1 H, H-2), 3.78 (dd, 1 H, $J_{1',2'} = 8.0$, $J_{2',3'} = 9.5$ Hz, H-2′), 3.54 (dd, 1 H, $J_{5',6b'} = 9.0$, $J_{6a',6b'} = 10.5$ Hz,

H-6b′), 3.48-3.42 (m, 3 H, H-6a′, H-5′, H-3′), 2.70-2.50 (m, 4 H, SCH_2CH_3), 1.19, 1.16 (2 t, 6 H, $J = 7.5$ Hz, SCH_2CH_3). ^{13}C NMR: δ = 138.7, 138.6, 138.5, 138.2, 137.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 127.3, 103.2, 85.0, 84.2, 83.8, 82.2, 81.3, 79.1, 75.0, 74.6, 74.5, 73.4, 73.3, 73.2, 73.1, 71.7, 71.2, 68.4, 53.2, 25.6, 25.4, 14.4, 14.2. MALDI-TOF MS: 993.4 (M^+ + Na). Anal. Calcd for $C_{58}H_{66}O_9S_2$ (970.41): C, 71.72; H, 6.85; S, 6.60. Found: C, 71.84; H, 6.80; S, 6.69.

Route B (Scheme 3)

To a cooled (0 °C), stirred solution of **17** (476 mg, 0.50 mmol) was added portionwise NaH (40 mg, 1.00 mmol of a 60% suspension in mineral oil) and, after 30 min, benzyl bromide (77 µL, 0.65 mmol). The mixture was stirred at room temperature for 40 min, then treated with MeOH (1 mL), stirred for an additional 10 min, diluted with H_2O (20 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 5:1 cyclohexane-AcOEt to give **14b** (427 mg, 88%).

2,3,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-*aldehydo*-D-galactose (15)

Treatment of **14a** (196 mg, 0.20 mmol) as described for the preparation of **3** gave **15** (128 mg, 835) at least 95% pure as established by ^{1}H NMR analysis. ^{1}H NMR (acetone-d_6): δ = 9.63 (d, 1 H, H-1), 7.50-7.20 (m, 25 H, Ph), 4.83, 4.77, 4.76, 4.74, 4.66, 4.63, 4.56 (7 d, 7 H, $J = 12.0$ Hz, $PhCH_2$), 4.54-4.50 (m, 4 H, 3 $PhCH_2$, H-4), 4.52 (d, 1 H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.31 (ddd, 1 H, H-5), 4.21 (t, 1H, $J = 4.5$ Hz, H-3), 4.17 (dd, 1 H, $J_{2,3} = 5.0$ Hz, H-2), 4.13 (dd, 1 H, $J_{3',4'} = 3.5$ Hz, H-4′), 3.96 (dd, 1 H, $J_{5,6b} = 2.0$, $J_{6a,6b} = 10.0$ Hz, H-6b), 3.87 (dd, 1 H, $J_{5,6a}$ = 4.5 Hz, H-6a), 3.76 (dd, 1 H, $J_{5',6a'} = 5.0$, $J_{6a',6b'} = 10.0$ Hz, H-6a′), 3.64 (dd, 1 H, $J_{5',6b'} = 3.0$ Hz, H-6b′), 3.64 (ddd, 1 H, H-5′), 3.62 (dd, 1 H, $J_{2',3'} = 9.5$ Hz, H-2′), 3.52 (dd, 1 H, H-3′). ^{13}C NMR (acetone-d_6): δ = 201.4, 139.6, 139.2, 139.0, 138.8, 138.3, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.5, 103.7, 84.2, 83.9, 83.6, 82.6, 81.4, 78.8, 74.8, 73.6, 73.1, 72.9, 72.0, 71.4, 70.9, 69.6, 66.2.

The 4′-trichloroacetyl carbamate derivative of **15** was generated in the NMR tube by adding trichloroacetyl isocyanate (5 µL) to a $CDCl_3$ solution of **15** (10 mg).

2,3,6-Tri-*O*-benzyl-4-*O*-sulfonato-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-D-*aldehydo*-galactose (8)

To a cooled (0 °C), stirred solution of sodium nitrite (104 mg, 1.50 mmol) in CH_2Cl_2 (4.0 mL) AcCl (107 µL, 1.50 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min, and then a solution of **14a** (492 mg, 0.50 mmol) in CH_2Cl_2 (3.0 mL) was slowly added. The mixture was stirred at 0 °C for an additional 5 min, then diluted with 1M phosphate buffer (pH = 7.0) (2.0 mL), stirred at the same temperature for 1 h, and then extracted with Et_2O (80 mL). The organic phase was washed with 1M phosphate buffer (pH = 7.0) (3 × 25 mL), concentrated, and eluted from a column of silica gel with 15:1 AcOEt-MeOH to give aldehyde **8** and its hydrate form (385 mg, 88%) as a colorless syrup. R_f = 0.34 (15:1 AcOEt-MeOH). ^{1}H NMR (DMSO-d_6) selected data: δ = 9.55 (s, 1 H, CHO). ESI MS: 853.3 (M – H).

2,3,6-Tri-*O*-benzyl-4-*O*-sulfonato-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-D-galactitol (16)

To a stirred solution of aldehyde **8** (88 mg, 0.10 mmol) in MeOH (5.0 mL) $NaBH_4$ (8 mg, 0.20 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 1 h, diluted with AcOH (0.50 mL), stirred for an additional 10 min, concentrated, and then eluted from a column of silica gel with 15:1 AcOEt-MeOH to give **16** (66 mg, 75%) as a white amorphous solid. $[\alpha]_D$ = 38.5 (*c* 0.8, acetone); R_f = 0.20 (15:1AcOEt-MeOH).^{1}H NMR (CD_3OD): δ = 7.50-7.10 (m, 25 H, Ph), 4.97 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.85 (dd, 1 H, $J_{3',4'} = 3.0$ Hz, H-4′), 4.73, 4.70, 4.64 (3 d, 3 H, $J = 12.0$ Hz, $PhCH_2$), 4.60 (s, 1 H, $PhCH_2$), 4.55, 4.53, 4.51, 4.45 (4 d, 5 H, $J = 12.0$ Hz, $PhCH_2$), 4.35 (dd, 1 H, $J_{3,4}$ = 4.0 Hz, H-4), 4.31 (d, 1 H, $J_{1',2'} = 7.5$ Hz, H-1′), 4.21 (ddd, 1 H, H-5), 3.98 (t, 1 H, H-3), 3.94 (dd, 1 H, $J_{6a,6b} = 10.0$ Hz, H-6b), 3.88 (dd, 1 H, $J_{5',6a'} = 4.5$, $J_{6a',6b'} = 10.5$ Hz, H-6a′), 3.81 (dd, 1 H, $J_{5,6a}$ = 4.5 Hz, H-6a), 3.78 (dd, 1 H, $J_{5',6b'} = 7.5$ Hz, H-6b′), 3.69 (dd, 1 H, $J_{1a,2} = 3.5$, $J_{1a,1b} = 10.0$ Hz, H-1a), 3.65 (ddd, 1 H, H-2), 3.60 (dd, 1 H, $J_{1b,2} = 5.5$ Hz, H-1b), 3.55 (dd, 1 H, $J_{2'3'} = 9.5$ Hz, H-2′), 3.51 (ddd, 1 H, H-5′), 3.45 (dd, 1 H, H-3′). ^{13}C NMR (CD_3OD): δ = 140.2, 140.0, 139.7, 139.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.9, 128.6, 128.5, 128.4, 104.2 86.1, 85.5, 84.6, 80.8, 79.9, 79.7, 76.2, 74.7, 74.3, 74.0, 73.0, 72.3, 72.2, 71.5, 62.8. ESI MS: 855.8 (M – H).

2,3,6-Tri-*O*-benzyl-4-*O*-trimethylsilyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-D-galactose diethyl dithioacetal (17)

A mixture of **14a** (659 mg, 0.67 mmol), chlorotrimethylsilane (4.3 mL, 33.5 mmol), and pyridine (10 mL) was warmed to 100 °C, stirred at this temperature for 3 h, cooled to room temperature, concentrated, and coevaporated with toluene three times. The resulting residue was eluted from a column of silica gel with 8:1 cyclohexane-AcOEt to give **17** (498 mg, 78%) as a colorless syrup. $[\alpha]_D$ = 18.6 (*c* 0.6, $CHCl_3$); R_f = 0.28 (8:1 cyclohexane-AcOEt).^{1}H NMR: δ = 7.40-7.20 (m, 25 H, Ph), 4.86, 4.79, 4.71, 4.70, 4.68, 4.67 (6 d, 6 H, $J = 11.5$ Hz, $PhCH_2$), 4.51-4.46 (m, 4 H, 3 $PhCH_2$, H-4), 4.44 (d, 1 H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.42 (d, 1 H, $J = 11.5$ Hz, $PhCH_2$), 4.40 (t, 1 H, H-3), 4.29 (ddd, 1 H, H-5), 4.06 (dd, 1 H, $J_{3',4'} = 3.0$ Hz, H-4′), 4.04 (d, 1 H, $J_{1,2} = 6.0$ Hz, H-1), 4.03 (dd, 1 H, H-6b), 3.92 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 10.0$ Hz, H-6a), 3.82 (dd, 1 H, $J_{2,3} = 4.5$ Hz, H-2), 3.66 (dd, 1 H, $J_{2',3'} = 9.5$ Hz, H-2′), 3.60 (dd, 1 H, $J_{5',6a'} = 9.0$, $J_{6a',6b'} = 10.0$ Hz, H-6a′), 3.44 (dd, 2 H, H-5′, H-6b′), 3.28 (dd, 1 H, H-3′), 2.70-2.51 (m, 4 H, SCH_2CH_3), 1.19, 1.16 (2 t, 6 H, $J = 7.5$ Hz, SCH_2CH_3), 0.10 (s, 9 H, $SiCH_3$). ^{13}C NMR: δ = 138.7, 138.4, 138.3, 138.2, 137.9, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 103.4, 84.9, 84.0, 81.3, 81.1, 78.6, 74.8, 74.5, 73.6, 73.5, 71.7, 71.2, 68.7, 68.5, 53.2, 25.6, 25.5, 14.4, 14.2, 0.6; MALDI-TOF MS: 975.3 (M^+ + Na). Anal. Calcd for $C_{54}H_{68}O_9S_2Si$ (952.41): C, 68.03; H, 7.19; S, 6.73; Si, 2.95. Found: C, 68.12; H, 7.10; S, 6.84; Si, 2.90.

Compound **17** easily decomposes by loss of TMS group when it is stored at room temperature.

2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,5-di-*O*-benzyl-3,6-anhydro-*aldehydo*-D-galactose (7)

Treatment of **14b** (427 mg, 0.44 mmol) as described for the preparation of **3** gave **7** (342 mg, 90%) as a colorless syrup at

least 95% pure as established by ^{1}H NMR analysis. An analytical sample of **7** was obtained by flash chromatography with 3.3:1 cyclohexane-AcOEt as the eluent. $[\alpha]_D = 6.3$ (*c* 1.0, $CHCl_3$).^{1}H NMR: $\delta = 9.59$ (d, 1 H, $J_{1,2} = 1.0$ Hz, H-1), 7.40-7.20 (m, 30 H, Ph), 4.94, 4.81, 4.76, (3 d, 3 H, $J = 12.0$ Hz, PhCH_2), 4.73 (s, 3 H, PhCH_2), 4.72, 4.64, 4.55, 4.54, 4.45 (5 d, 5 H, $J = 12.0$ Hz, PhCH_2), 4.40-4.38 (d, 2 H, H-4, PhCH_2), 4.31 (d, 1 H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.26 (m, 1 H, H-5), 4.18 (dd, 1 H, $J_{2,3} = 5.5$, $J_{3,4} = 3.5$ Hz, H-3), 4.04 (dd, 1 H, H-6b), 4.01 (dd, 1 H, H-2), 3.90 (dd, 1 H, H-4′), 3.88 (dd, 1 H, $J_{5,6a} = 4.0$, $J_{6a,6b} = 10.0$ Hz, H-6a), 3.77 (dd, 1 H, $J_{2',3'} = 9.5$ Hz, H-2′), 3.56 (dd, 1 H, $J_{5',6b'} = 5.5$, $J_{6a',6b'} = 9.0$ Hz, H-6b′), 3.49 (dd, 1 H, $J_{5',6a'} = 5.5$ Hz, H-6a′), 3.47-3.42 (m, 2 H, H-5′, H-3′). ^{13}C NMR: $\delta = 202.0$, 138.8, 138.6, 138.1, 138.0, 137.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 103.8, 84.2, 83.5, 83.4, 82.4, 82.1, 79.3, 75.4, 74.8, 73.7, 73.5, 73.3, 73.2, 72.5, 71.2, 68.7. MALDI-TOF MS: 887.3 (M^+ + Na). Anal. Calcd for $C_{54}H_{56}O_{10}$ (864.39): C, 74.98; H, 6.53. Found: C, 74.89; H, 6.59.

3,6-Anhydro-L-galactose diethyl dithioacetal (18)

A mixture of commercial agar[23] (6.0 g), EtSH (9.0 mL), 37% HCl (3.0 mL), and MeOH (48 mL) was warmed to 60 °C and stirred at this temperature for 17 h. The mixture was then cooled to room temperature, neutralized with 1M NaOH solution, and kept under a nitrogen flow to remove unreacted EtSH. The mixture was then concentrated under vacuum to give a solid residue, which was suspended in H_2O (80 mL) and then extracted with Et_2O (5 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude extract (3.18 g) containing the dithioacetal derivative **18**. A small amount of the crude extract (140 mg) was eluted from a column of silica gel with 1:3.3 cyclohexane-AcOEt to give **18** (94 mg, 56% from starting agar).[23] $[\alpha]_D = -14.9$ (*c* 0.4, MeOH); $[\alpha]_D = 10.0$ (*c* 1.0, H_2O); (lit.[22b] $[\alpha]_D = 14.4$ (*c* 1.2, H_2O); $R_f = 0.28$ (1:3.3 cyclohexane-AcOEt). ^{1}H NMR (acetone-d_6): $\delta = 4.21$ (t, 1 H, H-3), 4.11 (t, 1 H, H-4), 4.02 (ddd, 1 H, H-5), 3.97 (d, 1 H, $J_{1,2} = 8.5$ Hz, H-1), 3.87 (dd, 1 H, $J_{5,6a} = 4.0$, $J_{6a,6b} = 9.5$ Hz, H-6a), 3.74 (dd, 1 H, $J_{5,6b} = 2.0$ Hz, H-6b), 3.72 (dd, 1 H, $J_{2,3} = 2.5$ Hz, H-2), 2.75-2.60 (m, 4 H, SCH_2CH$_3$), 1.21, 1.20 (2 t, 6 H, $J = 7.5$ Hz, SCH_2CH_3). ^{13}C NMR (acetone-d_6): $\delta =$ 85.5, 79.2, 77.3, 73.7, 73.6, 54.7, 24.9, 24.8, 14.2, 14.1. MALDI-TOF MS: 307.1 (M^+ + K). Anal. Calcd for $C_{10}H_{20}O_4S_2$ (268.08): C, 44.75; H, 7.51; S, 23.89. Found: C, 44.87; H, 7.48; S, 23.81.

3,6-Anhydro-D-galactose diethyl dithioacetal (*ent*-18)

Treatment of kappa-carrageenan[26] (6.0 g) as described for the preparation of **18** gave a crude extract (2.60 g) containing the dithioacetal derivative ***ent*-18**. A small amount of the crude extract (240 mg) was eluted from a column of silica gel with 1:3.3 cyclohexane-AcOEt to give ***ent*-18** (102 mg, 30% from kappa-carrageenan).[27] $[\alpha]_D = 14.6$ (*c* 0.4, MeOH); $[\alpha]_D = -10.6$ (*c* 1.1, H_2O); (lit.[22a] $[\alpha]_D = -10.0$ (*c* 1.0, H_2O)). Anal. Calcd for $C_{10}H_{20}O_4S_2$ (268.08): C, 44.75; H, 7.51; S, 23.89. Found: C, 44.82; H, 7.45; S, 23.94.

2,4,5-Tri-*O*-acetyl-3,6-anhydro-L-galactose diethyl dithioacetal (peracetylated-18)

Treatment of crude extract (200 mg) containing **18** as described for the preparation of **peracetylated-13a** gave after column chromatography (3:1 cyclohexane-AcOEt) **peracetylated-18** (198 mg, 56% from starting agar).[23] $[\alpha]_D = 9.0$ (*c* 2.5, $CHCl_3$); $R_f = 0.30$ (3:1 cyclohexane-AcOEt).^{1}H NMR: $\delta = 5.40$ (dd, 1 H, $J_{1,2} = 8.0$, $J_{2,3} = 4.0$ Hz, H-2), 5.19 (ddd, 1 H, $J_{4,5} = 1.5$, $J_{5,6b} = 2.5$, $J_{5,6a} = 5.0$ Hz, H-5), 5.03 (ddd, 1 H, $J_{3,4} = 4.0$ Hz, H-4), 4.47 (t, 1 H, H-3), 4.12 (d, 1 H, H-1), 4.11 (dd, 1 H, $J_{6a,6b} = 11.0$ Hz, H-6b), 4.00 (dd, 1 H, H-6a), 2.81-2.63 (m, 4 H, SCH_2CH$_3$), 2.19, 2.12, 2.11 (3 s, 9 H, COCH3), 1.29, 1.26 (2 t, 6 H, $J = 7.5$ Hz, SCH_2CH_3). ^{13}C NMR: $\delta = 170.1$, 170.0, 82.5, 78.9, 78.2, 72.5, 72.1, 52.0, 25.1, 24.7, 20.9, 20.8, 14.3, 14.1. MALDI-TOF MS: 433.1 (M^+ + K). Anal. Calcd for $C_{16}H_{26}O_7S_2$ (394.11): C, 48.71; H, 6.64; S, 16.26. Found: C, 48.80; H, 6.61; S, 16.20.

2,4,5-Tri-*O*-acetyl-3,6-anhydro-D-galactose diethyl dithioacetal (peracetylated-*ent*-18)

Treatment of crude extract (200 mg) containing ***ent*-18** as described for the preparation of **peracetylated-13a** gave after column chromatography (3:1 cyclohexane-AcOEt) **peracetylated-*ent*-18** (126 mg, 30% from starting kappa-carrageenan).[27] $[\alpha]_D = -9.4$ (*c* 2.3, $CHCl_3$). MALDI-TOF MS: 417.1 (M^+ + Na). Anal. Calcd for $C_{16}H_{26}O_7S_2$ (394.11): C, 48.71; H, 6.64; S, 16.26. Found: C, 48.79; H, 6.69; S, 16.20.

2,4,5-Tri-*O*-benzyl-3,6-anhydro-L-galactose diethyl dithioacetal (19)

Treatment of crude extract (2.31 g) containing **18** (~1.56 g, 5.81 mmol) as described for the preparation of **11** gave after column chromatography (15:1 cyclohexane-AcOEt) **19** (2.80 g, 50% from starting agar)[23] as a colorless syrup. $[\alpha]_D = -29.3$ (*c* 0.6, $CHCl_3$); $R_f = 0.17$ (15:1 cyclohexane-AcOEt).^{1}H NMR: $\delta =$ 4.83, 4.62, 4.56, 4.51, 4.48, 4.47 (6 d, 6 H, $J = 12.0$ Hz, PhCH_2), 4.30 (t, 1 H, $J_{2,3} = 5.0$ Hz, H-3), 4.14-4.09 (m, 2 H, H-4, H-5), 4.02 (dd, 1 H, $J_{5,6b} = 2.5$, $J_{6a,6b} = 10.0$ Hz, H-6b), 3.99 (d, 1 H, $J_{1,2} = 5.5$ Hz, H-1), 3.91 (dd, 1 H, $J_{5,6a} = 4.5$ Hz, H-6a), 3.76 (t, 1 H, H-2), 2.73-2.53 (m, 4 H, SCH_2CH$_3$), 1.21, 1.18 (2 t, 6 H, $J = 7.5$ Hz, SCH_2CH_3). ^{13}C NMR: $\delta =$ 138.3, 137.8, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 84.2, 83.6, 81.9, 74.7, 71.8, 71.4, 71.3, 53.1, 25.6, 25.5, 14.4, 14.3. MALDI-TOF MS: 561.2 (M^+ + Na). Anal. Calcd for $C_{31}H_{38}O_4S_2$ (538.22): C, 69.11; H, 7.11; S, 11.90. Found: C, 69.02; H, 7.18; S, 11.99.

2,4,5-Tri-*O*-benzyl-3,6-anhydro-D-galactose diethyl dithioacetal (*ent*-19)

Treatment of crude extract (2.20 g) containing ***ent*-18** (~943 mg, 3.52 mmol) as described for the preparation of **11** gave after column chromatography (15:1 cyclohexane-AcOEt) ***ent*-19** (1.77 g, 28% from starting kappa-carrageenan)[27] as a colorless syrup. $[\alpha]_D = 28.9$ (*c* 0.5, $CHCl_3$); $R_f = 0.17$ (15:1 cyclohexane-AcOEt). MALDI-TOF MS: 561.6 (M^+ + Na). Anal. Calcd for $C_{31}H_{38}O_4S_2$ (538.22): C, 69.11; H, 7.11; S, 11.90. Found: C, 69.22; H, 7.04; S, 11.98.

2,4,5-Tri-*O*-benzyl-3,6-anhydro-*aldehydo*-L-galactose (4) and 2,4,5-Tri-*O*-benzyl-3,6-anhydro-*aldehydo*-D-galactose (*ent*-4)

Treatment of **19** or ***ent*-19** (1.22 g, 2.26 mmol) as described for the preparation of **3** gave **4** or ***ent*-4** (0.94 g, 95%) as a colorless syrup

at least 95% pure as established by ^{1}H NMR analysis. Analytical samples of each aldehyde were obtained by flash chromatography with 5:1 cyclohexane-AcOEt as the eluent. **4**: $[\alpha]_D = -24.4$ (*c* 1.0, $CHCl_3$); $R_f = 0.26$ (5:1 cyclohexane-AcOEt). ^{1}H NMR: $\delta = 9.68$ (d, 1 H, $J_{1,2} = 1.4$ Hz, H-1), 7.40-7.20 (m, 15 H, Ph), 4.74, 4.56, 4.48, 4.45, 4.43 (5 d, 6 H, $J = 12.0$ Hz, PhCH_2), 4.17-4.10 (m, 2 H, H-5, H-3), 4.07-4.01 (m, 2 H, H-4, H-6b), 3.97 (dd, 1 H, $J_{2,3} = 5.0$ Hz, H-2), 3.88 (dd, 1 H, $J_{5,6a} = 4.8$, $J_{6a,6b} = 10.5$ Hz, H-6a). ^{13}C NMR: $\delta = 202.0$, 137.5, 137.0, 128.5, 128.4, 128.3, 128.2 127.8, 127.7, 83.4, 83.0, 82.6, 82.3, 73.2, 71.9, 71.9, 71.1. MALDI-TOF MS: 471.3 (M^+ + K). Anal. Calcd for $C_{27}H_{28}O_5$ (432.19): C, 74.98; H, 6.53. Found: C, 75.00; H, 6.54. ***ent*-4**: $[\alpha]_D = 24.6$ (*c* 1.0, $CHCl_3$). MALDI-TOF MS: 471.8 (M^+ + K). Anal. Calcd for $C_{27}H_{28}O_5$ (432.19): C, 74.98; H, 6.53. Found: C, 75.04; H, 6.59.

1,4-Anhydro-D-galactitol or 3,6-Anhydro-L-galactitol (21)[34]

Commercial agar (10 g)[23] was first dissolved in hot (~90 °C) H_2O (900 mL) and then 1M TFA solution (100 mL) was added in one portion. The resulting mixture was heated at 80 °C for 3 h, cooled to room temperature, diluted with H_2O (800 mL), and then concentrated. The resulting residue was coevaporated with toluene three times to give a syrup. This material was dissolved in H_2O (100 mL), cooled to 0 °C and then $NaBH_4$ (1.90 g, 50.0 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 1 h, diluted with AcOH (~4.0 mL, pH ~4.0), stirred for an additional 10 min, and concentrated. The residue was coevaporated with MeOH (3 × 50 mL) to give a yellow syrup containing disaccharide **20**. This crude material was dissolved in 2M TFA solution (250 mL) and the resulting mixture was heated at 120 °C for 3 h, cooled to room temperature, diluted with H_2O (300 mL), and then concentrated. The resulting residue was coevaporated with toluene three times to give a syrup. This material was dissolved in H_2O (100 mL), cooled to 0 °C and then $NaBH_4$ (1.90 g, 50.0 mmol) was added in one portion. The resulting mixture was then stirred at room temperature for 1 h, diluted with AcOH (~ 4.0 mL, pH~4.0), stirred for an additional 10 min, and concentrated to give a syrup. This material was suspended in MeOH (30 mL) and acetone (100 mL), and then filtered through a glass-sintered filter. The filtrate was concentrated to afford a residue that was diluted with H_2O (30 mL) and treated with Dowex 1 × 8 OH^- form (64.8 g). The resulting mixture was stirred for 10 min, filtered through a glass-sintered filter, and washed thoroughly with H_2O. The combined filtrates were then treated with Amberlite IR120 H^+ form (64.8 g), stirred for 10 min, filtered through a glass-sintered filter, and washed thoroughly with H_2O. The combined filtrates were concentrated to give a crude material (3.36 g) mainly constituted of the anhydro alditol **21**. ^{1}H and ^{13}C NMR (D_2O) data of **21** were consistent with those previously reported.[38]

1,2,4,5-Tetra-*O*-acetyl-3,6-anhydro-L-galactitol (peracetylated-21)

Treatment of the crude material (185 mg) containing **21** as described for the preparation of **peracetylated-13a** gave after column chromatography (20:1 CH_2Cl_2-acetone) **peracetylated-21** (261 mg, 60% from starting agar).[23] $[\alpha]_D = 28.0$ (*c* 1.7, $CHCl_3$); $R_f = 0.28$ (20:1 CH_2Cl_2-acetone).^{1}H NMR: $\delta = 5.38$ (ddd, 1 H, $J_{1a,2} = 4.0$, $J_{1b,2} = 7.0$, $J_{2,3} = 5.0$ Hz, H-2), 5.16 (ddd, 1 H, $J_{5,6a} = 4.5$, $J_{5,6b} = 3.5$ Hz, H-5), 5.11 (dd, 1 H, $J_{3,4} = 3.0$ Hz, H-4), 4.37 (dd, 1 H, $J_{1a,1b} = 12.0$ Hz, H-1a), 4.18 (dd, 1 H, H-1b), 4.06 (dd, 1 H, $J_{6a,6b} = 11.0$ Hz, H-6a), 4.00-3.94 (m, 2 H, H-6b, H-3), 2.15, 2.13, 2.11, 2.08 (4 s, 12 H, $COCH_3$).^{13}C NMR: $\delta = 170.8$, 170.4, 170.0, 82.3, 78.2, 78.1, 72.3, 70.0, 63.0, 21.2, 20.9. MALDI-TOF MS: 355.1 (M^+ + Na). Anal. Calcd for $C_{14}H_{20}O_9$ (332.11): C, 50.60; H, 6.07. Found: C, 50.72; H, 6.10.

1,2-*O*-Isopropylidene-3,6-anhydro-L-galactitol (22)

A mixture of crude material (2.0 g) containing compound **21** (~1.39 g, 8.50 mmol), acetone (200 mL), and 98% H_2SO_4 (4.0 mL) was stirred at room temperature for 24 h, diluted with H_2O (100 mL), cooled to 0 °C, neutralized with Na_2CO_3 salt, and then concentrated. The resulting residue was suspended in acetone (100 mL), filtered through a glass-sintered, concentrated, and eluted from a column of silica gel with 20:1 CH_2Cl_2-acetone to give **22** (1.13 g, 39% from starting agar)[23] as a colorless syrup. $[\alpha]_D = -27.7$ (*c* 2.4, $CHCl_3$), $R_f = 0.20$ (20:1 CH_2Cl_2-acetone).^{1}H NMR: $\delta = 4.28$ (ddd, 1 H, $J_{1a,2} = 7.5$, $J_{1b,2} = 6.5$, $J_{2,3} = 2.5$ Hz, H-2), 4.14 (dd, 1 H, H-4), 4.07 (dd, 1 H, $J_{1a,1b} = 8.5$ Hz, H1b), 4.03 (dd, 1 H, $J_{5,6a} = 3.5$, $J_{6a,6b} = 9.0$ Hz, H-6a), 4.00 (m, 1 H, H-5), 3.98 (dd, 1 H, H-1a), 3.88 (dd, 1 H, H-6b), 3.79 (dd, 1 H, H-3), 1.40, 1.35 (2 s, 6 H, CMe_2). ^{13}C NMR: $\delta = 109.6$, 84.3, 79.1, 77.1, 76.2, 74.0, 65.7, 25.6, 25.3. MALDI-TOF MS: 243.1 (M^+ + K). Anal. Calcd for $C_9H_{16}O_5$ (204.10): C, 52.93; H, 7.90. Found: C, 52.88; H, 7.98.

4,5-Di-*O*-benzyl-3,6-anhydro-L-galactitol (23). Route A (Scheme 5)

Treatment of **22** (742 mg, 3.63 mmol) as described for the preparation of **11** gave after column chromatography (5:1 cyclohexane-AcOEt) 1,2-*O*-isopropylidene-4,5-di-*O*-benzyl-3,6-anhydro-L-galactitol intermediate (1.40 g, 100%) as a colorless syrup. $[\alpha]_D = -10.0$ (*c* 0.4, $CHCl_3$); $R_f = 0.16$ (5:1 cyclohexane-AcOEt).^{1}H NMR: $\delta = 7.40$-7.20 (m, 10 H, Ph), 4.56 (d, 2H, $J =$ 12 Hz, PhCH_2), 4.49, 4.47 (2 d, 2 H, $J = 12$ Hz, PhCH_2), 4.24 (ddd, 1 H, $J_{1b,2} = 6.5$, $J_{1a,2} = 7.0$ Hz, H-2), 4.10-4.05 (m, 2 H, H-5, H-6b), 3.91-3.76 (m, 5 H, H-6a, H-1b, H-3, H-4, H1a), 1.43, 1.35 (2 s, 6 H CMe_2).^{13}C NMR: $\delta = 137.4$, 137.2, 128.3, 127.8, 127.7, 127.6, 109.4, 84.5, 84.2, 82.8, 75.9, 71.7, 71.2, 71.1, 65.3, 26.4, 25.0.

A mixture of the above benzylated intermediate (1.00 g, 2.60 mmol), AcOH (16 mL), and H_2O (4 mL) was warmed to 100 °C, stirred at this temperature for 1 h, cooled to room temperature, concentrated, and coevaporated with toluene three times. The resulting residue was eluted from a column of silica gel with 1:2 cyclohexane-AcOEt to give **23** (626 mg, 70%) as a colorless syrup. $[\alpha]_D = -22.6$ (*c* 1.0, $CHCl_3$); $R_f = 0.28$ (1:2 cyclohexane-AcOEt).^{1}H NMR: $\delta = 7.40$-7.30 (m, 10 H, Ph), 4.57 (d, 1 H, PhCH_2), 4.54 (d, 3 H, PhCH_2), 4.15 (m, 1 H, H-4), 4.09-4.04 (m, 2 H, H-5, H-6b), 3.95 (dd, 1 H, $J_{2,3} = 4.0$, $J_{3,4} = 3.5$ Hz, H-3), 3.89 (dd, 1 H, $J_{5,6a} = 4.0$, $J_{6a,6b} = 10.5$ Hz, H-6a), 3.77 (m, 1 H, $J_{1a,2} =$ 4.5, $J_{1b,2} = 5.0$ Hz, H-2), 3.68 (dd, 1 H, $J_{1a,1b} = 11.0$ Hz, H-1b), 3.64 (dd, 1 H, H-1a). ^{13}C NMR: $\delta = 137.6$, 137.4, 128.8, 128.4, 128.2, 128.0, 85.2, 84.4, 82.6, 72.3, 72.0, 71.5, 64.6. MALDI-TOF MS: 383.1 (M^+ + K). Anal. Calcd for $C_{20}H_{24}O_5$ (344.16): C, 69.75; H, 7.02. Found: C, 69.63; H, 7.09.

Route B (Scheme 6)

Metallic sodium (61 mg, 2.65 mmol) was carefully added to MeOH (5 mL). The resulting mixture was stirred at room temperature under nitrogen until complete consumption of metallic sodium, and then a solution of **25** (570 mg, 1.33 mmol) in MeOH (15 mL) was slowly added. The mixture was stirred at room temperature for an additional 30 min, neutralized with Amberlite IR120 (H^+ form, 5.0 g), filtered through a glass-sintered filter, and washed thoroughly with MeOH. The combined filtrates were concentrated, and eluted from a column of silica gel with 1:2 cyclohexane-AcOEt to give **23** (380 mg, 83%).

4,5-Di-*O*-benzyl-3,6-anhydro-D-galactitol (*ent*-23)

Metallic sodium (61 mg, 2.65 mmol) was carefully added to MeOH (5 mL). The resulting mixture was stirred at room temperature under nitrogen until complete consumption of metallic sodium, and then a solution of ***ent*-25** (570 mg, 1.33 mmol) in MeOH (15 mL) was slowly added. The mixture was stirred at room temperature for an additional 30 min, neutralized with Amberlite IR120 (H^+ form, 5.0 g), filtered through a glass-sintered filter, and washed thoroughly with MeOH. The combined filtrates were concentrated, and eluted from a column of silica gel with 1:2 cyclohexane-AcOEt to give ***ent*-23** (380 mg, 83%) as a colorless syrup. $[\alpha]_D = 22.4$ (*c* 1.2, $CHCl_3$). MALDI-TOF MS: 367.5 (M^+ + Na). Anal. Calcd for $C_{20}H_{24}O_5$ (344.16): C, 69.75; H, 7.02. Found: C, 69.82; H, 7.08.

3,4-Di-*O*-benzyl-2,5-anhydro-*aldehydo*-L-lyxose (5) and 3,4-di-*O*-benzyl-2,5-anhydro-*aldehydo*-D-lyxose (*ent*-5)

Treatment of **23** or ***ent*-23** (623 mg, 1.81 mmol) as described for the preparation of **3** gave **5** or ***ent*-5** (492 mg, 87%) as a colorless syrup at least 95% pure as established by ^{1}H NMR analysis. Analytical samples of each aldehyde were obtained by flash chromatography with 3.3:1 cyclohexane-AcOEt as the eluent. **5**: $[\alpha]_D = 19.6$ (*c* 1.8, $CHCl_3$); $R_f = 0.20$ (3.3:1 cyclohexane-AcOEt).^{1}H NMR: $\delta = 9.63$ (d, 1 H, $J_{1,2} = 1.0$ Hz, H-1), 7.40-7.20 (m, 10 H, Ph), 4.66, 4.54, 4.44 (d, 3 H, $J = 12.0$ Hz, PhCH_2), 4.40 (s, 1 H, PhCH_2), 4.37 (s, 1 H, H-2), 4.22 (s, 1 H, H-3), 4.16 (dd, 1 H, $J_{4,5b} = 1.0$, $J_{5a,5b} = 10.0$ Hz, H-5b), 4.12 (dd, 1 H, $J_{4,5a} = 3.0$ Hz, H-5a), 4.04 (ddd, 1 H, H-4). ^{13}C NMR: $\delta = 203.0$, 137.1, 137.0, 128.6, 128.5, 128.1, 128.0, 127.7, 87.0, 84.6, 80.5, 72.7, 71.8, 70.9. MALDI-TOF MS: 351.1 (M^+ + K). Anal. Calcd for $C_{19}H_{20}O_4$ (312.14): C, 73.06; H, 6.45. Found: C, 73.09; H, 6.46. ***ent*-5**: $[\alpha]_D = -19.3$ (*c* 1.5, $CHCl_3$). MALDI-TOF MS: 351.8 (M^+ + K). Anal. Calcd for $C_{19}H_{20}O_4$ (312.14): C, 73.06; H, 6.45. Found: C, 73.11; H, 6.48.

2,4,5-Tri-*O*-benzyl-3,6-anhydro-L-galactitol (24) and 2,4,5-tri-*O*-benzyl-3,6-anhydro-D-galactitol (*ent*-24)

To a cooled (0 °C), stirred solution of aldehyde **4** or ***ent*-4** (886 mg, 2.05 mmol) in MeOH (10 mL) $NaBH_4$ (156 mg, 2.40 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 1 h, diluted with AcOH (1 mL), stirred for an additional 10 min, concentrated, and then eluted from a column of silica gel with 1.6:1 cyclohexane-AcOEt to give **24** or ***ent*-24** (837 mg, 94%) as a colorless syrup. **24**: $[\alpha]_D = 8.5$ (*c* 1.4, $CHCl_3$); $R_f = 0.34$ (8:5 cyclohexane-AcOEt). ^{1}H NMR: $\delta = 7.40$-7.25 (m, 15 H, Ph), 4.71, 4.68, 4.54, 4.53, 4.51, 4.50 (6 d, 6 H, $J = 12.0$ Hz, PhCH_2), 4.16 (dd, 1 H, $J_{3,4} = 4.5$ Hz, H-4), 4.09 (dd, 1 H, H-6b), 4.07 (m, 1 H, H-5), 4.03 (t, 1 H, H-3), 3.88 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 10.5$ Hz, H-6a), 3.76 (dd, 1 H, $J_{1a,2} = 6.0$, $J_{1a,1b} = 12.5$ Hz, H-1a), 3.72-3.67 (m, 2 H, H-2, H-1b). ^{13}C NMR: $\delta = 138.2$, 137.5, 137.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 84.8, 83.8, 83.0, 78.1, 72.6, 71.9, 71.4, 71.3, 61.8. MALDI-TOF MS: 457.2 (M^+ + Na). Anal. Calcd for $C_{27}H_{30}O_5$ (434.21): C, 74.63; H, 6.96. Found: C, 74.66; H, 6.98. ***ent*-24**: $[\alpha]_D = -8.3$ (*c* 2.4, $CHCl_3$). MALDI-TOF MS: 457.5 (M^+ + Na). Anal. Calcd for $C_{27}H_{30}O_5$ (434.21): C, 74.63; H, 6.96. Found: C, 74.55; H, 7.01.

1,2-Di-*O*-acetyl-4,5-di-*O*-benzyl-3,6-anhydro-L-galactitol (25) and 1,2-di-*O*-acetyl-4,5-di-*O*-benzyl-3,6-anhydro-D-galactitol (*ent*-25)

A mixture of **24** or ***ent*-24** (800 mg, 1.80 mmol) in Ac_2O-TFA 20:1 (42 mL) was heated at 70 °C for 8 h, then cooled to room temperature, and then coevaporated with toluene three times. The resulting brown syrup was eluted from a column of silica gel with 3:1 cyclohexane-AcOEt to afford **25** or ***ent*-25** (570 mg, 72%) slightly contaminated by uncharacterized byproducts. ^{1}H NMR: $\delta = 7.40$-7.20 (m, 10 H, Ph), 5.33 (ddd, 1 H, $J_{1a,2} = 7.0$, $J_{1b,2} = 4.0$ Hz, H-2), 4.54, 4.52, 4.51, 4.45 (4 d, 4 H, $J = 12.0$ Hz, PhCH_2), 4.32 (dd, 1 H, $J_{1a,1b} = 12.0$ Hz, H-1b), 4.15 (dd, 1 H, H-1a), 4.09-4.01 (m, 2 H, H-5, H-6b), 3.98-3.93 (m 2 H, H-3, H-4), 3.90 (dd, 1 H, $J_{5,6a} = 4.5$, $J_{6a,6b} = 10.5$ Hz, H-6a), 2.06, 2.05 (2 s, 6 H, $OCCH_3$). ^{13}C NMR: $\delta = 170.5$, 170.4, 137.5, 137.3, 128.4, 128.0, 127.9, 127.8, 84.4, 82.7, 82.2, 72.1, 71.6, 71.4, 70.5, 63.0, 20.9, 20.7. MALDI-TOF MS: 467.5 (M^+ + K).

Formyl 2,3-di-*O*-benzyl-β-L-threose (26)

To a cooled (0 °C), stirred mixture of aldehyde **5** (210 mg, 0.67 mmol), CH_2Cl_2 (5 mL), and $NaHCO_3$ (146 mg, 1.74 mmol), *m*CPBA (324 mg, 1.88 mmol) was added in one-portion. The resulting mixture was stirred at 0 °C for 30 minutes, diluted with CH_2Cl_2 (40 mL), then washed with brine (15 mL) and saturated aqueous $NaHCO_3$ solution (3 × 15 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 6.7:1 cyclohexane-AcOEt to give **26** (138 mg, 63%) as colorless syrup. $[\alpha]_D = -12.9$ (*c* 0.9, $CHCl_3$); $R_f = 0.43$ (6.7:1 cyclohexane-AcOEt).^{1}H NMR: $\delta = 8.10$ (s, 1 H, CHO), 7.41-7.29 (m, 10 H, Ph), 6.32 (s, 1 H, H-1), 4.69, 4.59, 4.53, 4.51 (4 d, 4 H, $J = 12.0$ Hz, PhCH_2), 4.34 (dd, 1 H, $J_{3,4a} = 5.5$, $J_{4a,4b} = 9.5$ Hz, H-4a), 4.17 (ddd, 1 H, H-3), 4.15 (s, 1 H, H-2), 4.05 (dd, 1 H, $J_{3,4b} = 4.5$ Hz, H-4b).^{13}C NMR: $\delta = 159.9$, 137.2, 137.0, 128.5, 128.1, 128.0, 127.9, 127.8, 100.4, 86.0, 81.7, 73.2, 72.1. MALDI-TOF MS: 351.1 (M^+ + Na). Anal. Calcd for $C_{19}H_{20}O_5$ (328.13): C, 69.50; H, 6.14. Found: C, 69.62; H, 6.05.

2,3-Di-*O*-benzyl-L-threose (6)

A mixture of **26** (138 mg, 0.42 mmol), MeOH (10 mL), and Et_3N (10 μL) was stirred at room temperature for 30 minutes, and then concentrated to give crude **6** (120 mg, 95%) at least 95% pure as established by ^{1}H NMR analysis. An analytical sample of **6** was obtained by column chromatography with 3.3:1 cyclohexane-AcOEt as the eluent. Analytical and spectroscopic data of **6** were consistent with those previously reported.[37]

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