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Syntheses of novel acarviosin analogs with anhydro or unsaturated sugar moieties

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ABSTRACT

A new class of pseudoacarviosins with 2,3-anhydro or unsaturated sugar moieties were synthesized efficiently. The designed target disaccharides were constructed by the glycosylation reactions using 2,3-anhydromonosaccharides as glycosyl donors. The glycosylation reactions were carried out in a highly stereoselective manner in most cases, especially when the preactivation protocol was used. The anhydrosugar units of disaccharides were kept intact during the deprotection operations of protective groups. Furthermore, the disaccharides containing anhydrosugar moieties were smoothly converted to the unsaturated disaccharides via the base-promoted rearrangement of sugar epoxides.

1. Introduction

Carbohydrate mimetics as inhibitors of carbohydrate-processing enzymes have been attractive target compounds for synthetic chemists and biochemists, not only because they can serve as useful biological tools for studying the biological functions of glycans[1] but also because they may have great potential as drugs to treat a variety of carbohydrate-mediated diseases[2], such as diabetes, obesity, lysosomal storage disorders, cancer, and viral infections.[3] For instance, acarbose **1** (Fig. 1), a potent α-glucosidase inhibitor, is a natural product, which is an orally active agent sold for the treatment of type II diabetes either on its own or in combination with other medications.[4] Inspired by the success of acarbose **1**, in order to obtain improved and more potent compounds, quite a few acarbose **1** analogs that exhibit very pronounced inhibitory effects on intestinal α-glucosidase have been reported and some of them have aroused medical interest in the treatment of diabetes and related disorders.[5,6] Namiki and co-workers reported the synthesis of a series of valienamine **2** analogs and some of them exhibited comparative inhibitory activities with acarbose **1**.[7] The Shing group reported an enantiospecific synthesis of a pseudoacarviosin showing to be a potent inhibitor of α-glucosidases.[8] Sabrina et al. prepared a series of 4-substituted 1,2,3-triazoles conjugated with sugars, some of which displayed up to 25-fold higher inhibitory potency than the complex oligosaccharide acarbose **1**.[9]

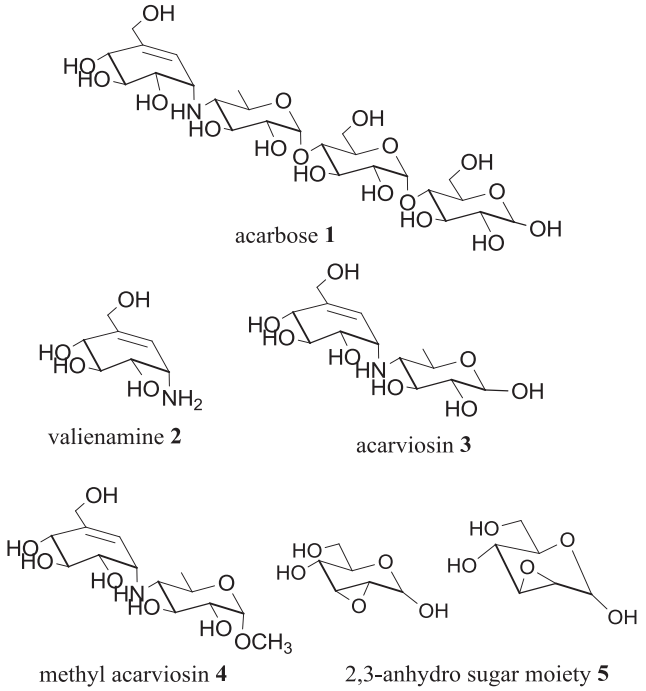

Fig. 1. Structures of acarbose, valienamine, acarviosin, methyl acarviosin, 2,3-anhydrosugar moiety.

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The strong inhibition of human amylases by acarbose **1** (micromolar Ki) is attributed to the valienamine ring.[10] However, valienamine **2** itself is only a weak α-glucosidase inhibitor.[11] The α-glucosidase inhibitory activity increases when it is linked to a mono- or tri-saccharide moiety as in acarviosin **3** and acarbose **1**, respectively.[12] Acarviosin **3** contains the valienamine unit connected to a 6-deoxy-D-glucose residue by 1,4-*N*-linkage. Moreover, methyl acarviosin **4**, obtained from the methanolysis of acarbose **1**, has been shown to exhibit stronger α-amylase inhibitory activity than acarbose **1**.[13] To search for new acarviosin analogs, we postulated that 2,3-anhydrosugar moiety **5** could mimic the structure of valienamine **2** due to some conformational similarity of the hexene ring to the anhydro pyranose ring, so disaccharides **6**–**8** (Fig. 2) were designed. On the other hand, it has been illustrated that *S*-linked glycosides, in which the interglycosidic oxygen atom is replaced by a sulfur atom, can be of enhanced utility and more stable to hydrolytic enzymes.[14] Thus, *S*-linked disaccharides **9** and **10** were designed. Compounds **11** and **12** were also designed to compare the effect of the substitution of 6-deoxy-α-D-glucoside with a 6-deoxy-α-D-galactoside on glucosidase inhibition. In addition, to mimic the planar structure in **4**, we designed unsaturated sugars **13** and **14**. So some new pseudoacarviosins **6**–**14**, which are novel molecules that have not been explored as glucosidase inhibitors, were designed. We describe herein the syntheses of these pseudoacarviosins.

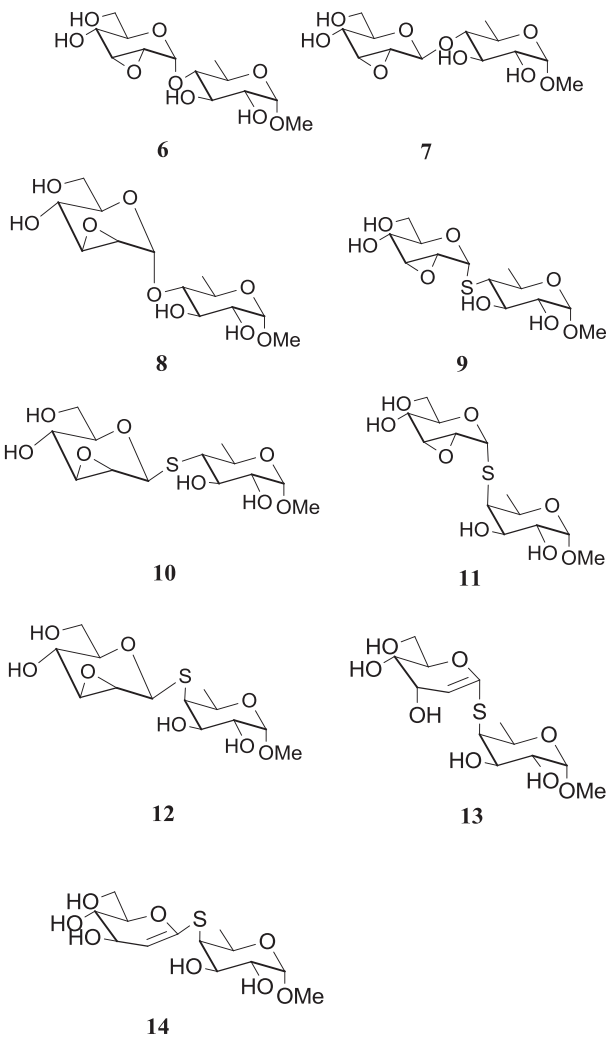
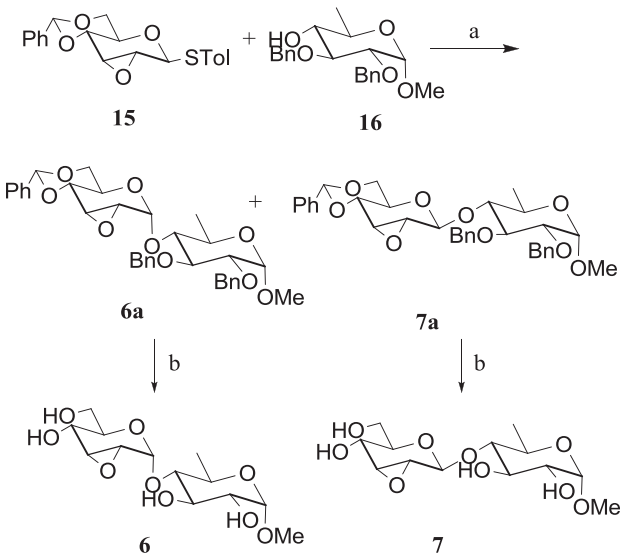


Fig. 2. Structures of the designed new acarviosin analogs.

2. Results and discussion

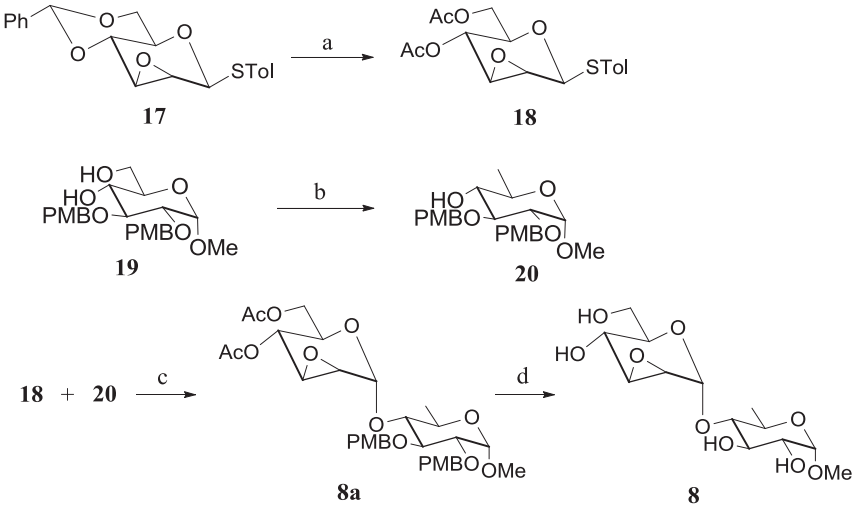
The synthesis of target compounds **6** and **7** was described in Scheme 1, starting from *p*-tolyl 2,3-anhydro-4,6-*O*-benzylidene-1-thio-β-D-allopyranoside (**15**) and methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (**16**), which were prepared according to the previous reports.[15,16] The acceptor **16** was glycosylated with donor **15** in dichloromethane at −40 °C by the standard protocol,[17] using *N*-iodosuccinimide (NIS)-silver triflate (AgOTf)[18] as promoter. The coupling product **6a** and its anomeric isomer **7a** were obtained in 35% and 42% isolated yields, respectively. Compounds **6a** and **7a** underwent hydrogenolysis over Pearlman's catalyst yielding the target compounds **6** and **7** smoothly. It is noteworthy that during the hydrogenolysis process, the anhydrosugar moiety in **6** and **7** was kept intact very well.



Scheme 1. Reagents and conditions: (a) NIS, AgOTf, −40 °C, 35% for **6a**, 42% for **7a**; (b) H_2, $Pd(OH)_2$, THF/EtOH, 85% for **6**, 87% for **7**.

The synthesis of compound **8** was described in Scheme 2. Thioglycoside **17**[15] was treated with *p*-toluenesulfonic acid in methanol followed by acetylation to provide **18** in 81% yield. Glucoside **19**[19] was selectively deoxygenated at the C-6 position by successive tosylation and $LiAlH_4$ reduction to give glycosyl acceptor **20**. The glycosylation of **18** and **20** afforded disaccharide **8a** in 67% yield in the form of pure α-anomer. It is noteworthy that no β-anomer was isolated in the glycosylation reaction. Comparing with the benzylidene-protected donor **15**, the glycosylation of di-acetyl-protected donor **18** showed excellent stereoselectivity, yielding the product with glycosidic bond trans to the epoxide ring. Treatment of **8a** with 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ) followed by deacetylation with potassium carbonate provided the target disaccharide **8** in 85% yield. Again, the anhydrosugar unit in compound **8** was kept intact.

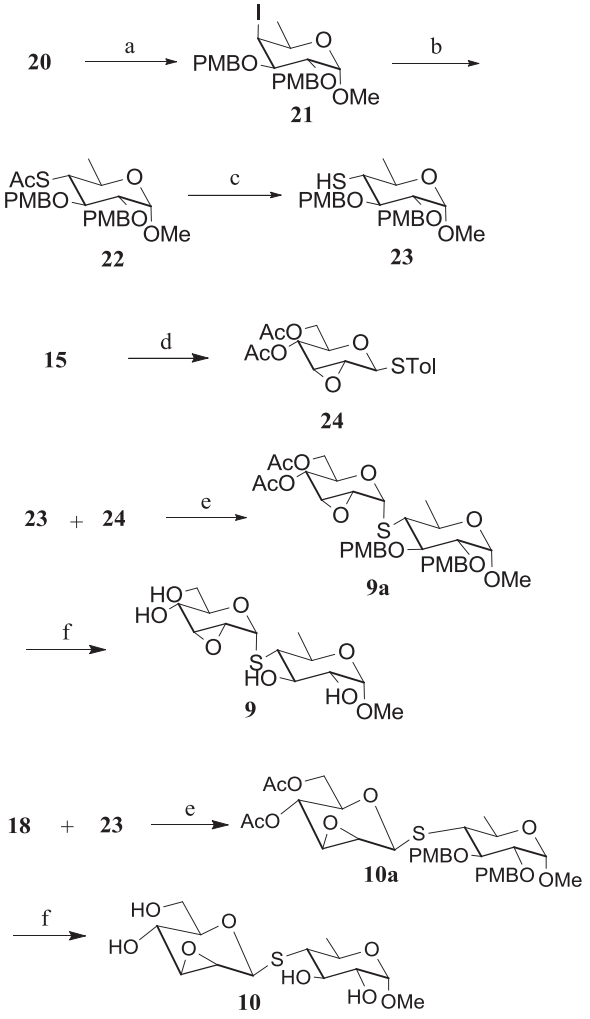
The synthesis of *S*-linked disaccharides **9** and **10** was shown in Scheme 3. Compound **20** was treated with triphenylphosphine and iodine in the presence of imidazole providing iodide **21** in 86% yield, which, on exposure to potassium thioacetate in DMF, afforded **22** in 67% yield. Treatment of **22** with potassium carbonate led to thioglycoside **23** in 75% yield. On the other hand, compound **15** was transformed to glycosyl donor **24** in the same manner as described in the preparation of **18**. With two building blocks **23** and **24** in hand, the glycosylation reaction was performed. Based on the glycosyl donor-preactivation protocol,[20] following the procedure



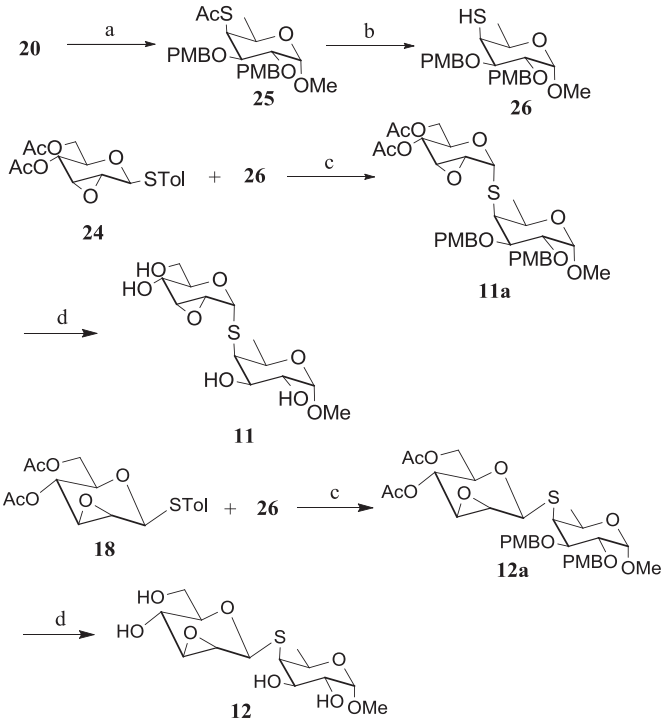
Scheme 2. Reagents and conditions: (a) TsOH, MeOH; then Ac_2O, Py, 81%; (b) TsCl, Py; then $LiAlH_4$, 67%; (c) NIS, AgOTf, −40 °C, 67%; (d) DDQ, CH_2Cl_2/H_2O; then K_2CO_3, MeOH, 85%.

developed by the Crich group[21] and modified by the Lowary group,[17] donor **24** was preactivated with diphenyl sulfoxide and triflic anhydride (Ph_2SO/Tf_2O)[22] in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP), which was followed by the addition of thiol **23**, affording disaccharide **9a** in the form of α-anomer in 81% isolated yield. Again, the anomeric isomer (β-anomer) was not obtained. Treatment of **9a** with DDQ followed by the addition of potassium carbonate provided the target product **9** successfully. In the same manner, compound **23** was glycosylated with **18** to provide disaccharide **10a** as the sole β-coupling product with high stereoselectivity. The deprotection of compound **10a** afforded **10**.

The synthesis of compounds **11** and **12** was shown in Scheme 4. Compound **20** was successively treated with triflic anhydride and potassium thioacetate to give **25** in 63% yield. Compound **25** was further treated with potassium carbonate in methanol to provide the galactose-type thiol **26** in 80% yield. The coupling reaction of **24** and **26** by the same protocol as described in the preparation of **9a** stereoselectively afforded *S*-linked disaccharide **11a** in 75% isolated



Scheme 3. Reagents and conditions: (a) I_2, PPh_3, Im, THF, 86%; (b) KSAc, DMF, 67%; (c) K_2CO_3, CH_3OH, 75%; (d) TsOH, MeOH; then Ac_2O, Py, 70%; (e) Ph_2SO/Tf_2O, TTBP, CH_2Cl_2, −78 °C, 81% for **9a**, 77% for **10a**; (f) DDQ, CH_2Cl_2/water; then K_2CO_3, MeOH, 81% for **9**, 72% for **10**.

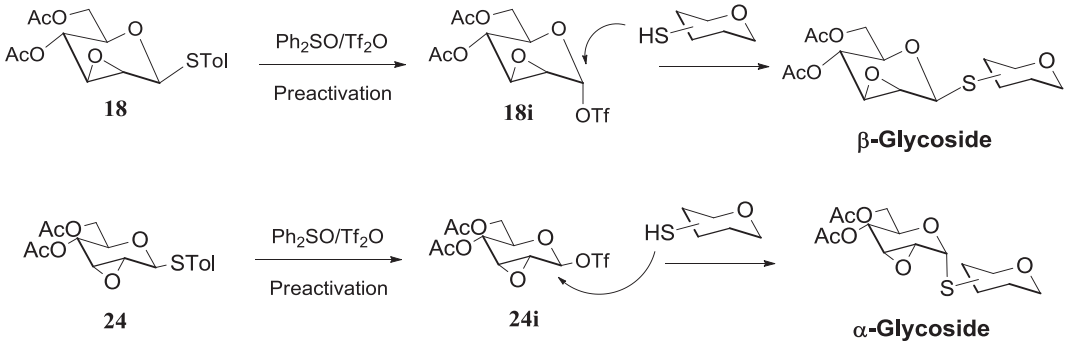


Scheme 4. Reagents and conditions: (a) Tf_2O, Py, CH_2Cl_2; then KSAc, DMF, 63%; (b) K_2CO_3, CH_3OH, 80%; (c) Ph_2SO/Tf_2O, TTBP, CH_2Cl_2, −78 °C, 75% for **11a**, 79% for **12a**; (d) DDQ, CH_2Cl_2/water; then K_2CO_3, MeOH, 75%.

yield. Finally, the *para*-methoxybenzyl (PMB) and acetyl groups in **11a** were removed to result in disaccharide **11** in 75% yield. On the other hand, the coupling reaction of **18** and **26** yielded the β-linked disaccharide **12a** as the sole coupling product, which underwent deprotection to provide **12** smoothly. Interestingly, it was found that in the preparation of *S*-linked disaccharides, when the 2,3-anhydro donor is allose-type, the exclusive coupling product is the α-glycoside; when the 2,3-anhydro donor is mannose-type, the exclusive product is the β-glycoside. This might be explained as the following: in the preactivation conditions, mannose-type donor **18** was preactivated to favorably produce the triflate intermediate **18i**, in which the glycosidic bond is trans to the epoxide ring, which was followed by an SN2-like attack from a glycosyl acceptor, affording the β-glycoside; whereas allose-type donor **24** was preactivated to dominantly form the glycosyl triflate **24i**, which was attacked by a glycosyl acceptor in the SN2-like manner, yielding the α-glycoside (Scheme 5). The excellent stereoselectivity highlights the importance of preactivation protocol to the stereochemistry outcomes toward glycosylations.

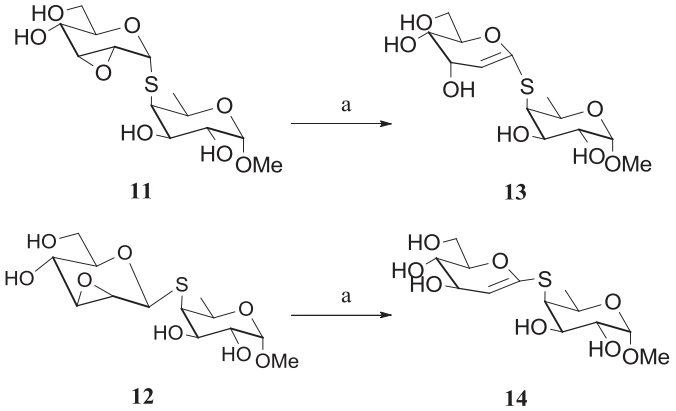
Distinguishing anomeric stereochemistry in 2,3-anhydroglycosides is essential to the structure assignments. In the case of *O*-linked glycosides, for 2,3-anhydrofuranosides, Lowary et al. have demonstrated that the magnitude of $^{1}J_{C\text{-}1',H\text{-}1'}$ is the only reliable method for establishing anomeric stereochemistry in the 2,3-anhydrosugar derivatives.[23a] For 2,3-anhydropyranosides, referring to the previous report,[23b] it was found that in the case of manno-type, the $^{1}J_{C\text{-}1',H\text{-}1'}$ of α-glycosides is about 170 Hz, whereas the $^{1}J_{C\text{-}1',H\text{-}1'}$ of β-glycosides is 160–165 Hz; in the case of allo-type, the $^{1}J_{C\text{-}1',H\text{-}1'}$ of α-glycosides is larger than that of β-glycosides, $\delta_{C1'}$ of α-glycosides (<95 ppm) is smaller than that of β-glycosides (about 100 ppm), and the $^{3}J_{H\text{-}1',H\text{-}2'}$ of α-glycosides (>2.5 Hz) is larger than that of β-glycosides (0.5 or 0 Hz). Based on these observations, the anomeric stereochemistry in these 2,3-anhydrosugar residues was determined. These NMR data for compounds **6a**, **7a**, and **8a** are presented in Table 1.

The assignments of anomeric stereochemistry in the *S*-linked 2,3-anhydroglycosides can be problematic due to the difference between the $^{1}J_{C\text{-}1',H\text{-}1'}$ values in the *O*- and *S*-series. Evidently, for



Scheme 5. Proposed mechanism for the stereoselective formation of *S*-linked disaccharides.

The synthesis of disaccharides **13** and **14** was displayed in Scheme 6. Previously, a method for rearranging 2,3-anhydromonosaccharides to unsaturated monosaccharides was developed by us.[15] The preparation of more complex unsaturated disaccharides by this protocol was attempted. Thus, when the anhydro disaccharide **11** was treated with *t*-BuOK in DMF at 50 °C, the rearranged product **13** was obtained smoothly in 75% isolated yield. In the same way, the base-promoted rearrangement of disaccharide **12** provided the target unsaturated sugar **14**.



Scheme 6. Reagents and conditions: (a) *t*-BuOK, DMF, 50 °C, 75% for **13**, 30% for **14**.

Table 1
The NMR parameters in compounds **6a**, **7a**, and **8a**[a]

Entry	Compound	Epoxide	$^{3}J_{H1',H2'}$ (Hz)	$^{1}J_{C1',H1'}$[b] (Hz)	Chemical shift of C-1′ (ppm)	Anomeric stereochemistry
1	**6a**	allo-	3.0	170.24	94.73	α
2	**7a**	allo-	0	168.19	97.70	β
3	**8a**	manno-	0	176.81	96.19	α

[a] Spectra measured in $CDCl_3$.
[b] Measured using HMBC experiments.

the β-anomer, the stereochemistry may be established unambiguously by the observation of nuclear Overhauser interactions between H-1′, H-4, and H-5′. Indeed, NOESY spectrum was used to confirm the configurations of **9a**–**12a**. For example, for **9a**, a strong NOE signal was observed between H-1′ and H-4, while no NOE signal was seen between H-1′ and the H-5′. These data are consistent with the α-stereochemistry in **9a**.

3. Conclusions

In summary, starting from readily available monosaccharides, nine new pseudoacarviosin analogs with 2,3-anhydro or unsaturated sugar moieties were designed and synthesized. The syntheses involved the glycosylation reactions by using 2,3-anhydromonosaccharides as glycosyl donors, and in most cases, the coupling reactions proceeded in a highly stereoselective manner, especially when the preactivation protocol was applied.

Furthermore, some 2,3-anhydrodisaccharides were able to undergo the base-promoted rearrangement to form unsaturated disaccharides. Due to the potential applications of these pseudoacarviosin analogs in drug discovery, the disclosed design strategy and synthetic approach may facilitate the construction of this type of pseudoacarviosins with biological importance.

4. Experimental section

4.1. Methyl 4-*O*-(2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranosyl)-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (6a) and methyl 4-*O*-(2,3-anhydro-4,6-di-*O*-benzylidene-β-D-allopyranosyl)-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (7a)

Compounds **15**[15] (25.0 mg, 0.069 mmol), **16**[16] (17.2 mg, 0.046 mmol), and 4 Å molecular sieves (400 mg) were dried overnight under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (5 mL); the mixture was cooled to −40 °C, and then NIS (16.6 mg, 0.074 mmol) and AgOTf (3.6 mg, 0.014 mmol) were successively added. After stirring for 20 min at −40 °C, the reaction mixture was warmed to −25 °C. Once the color of the reaction was changed to pink, it was cooled again to −40 °C. After another 30 min, the reaction mixture turned dark red and was neutralized by the addition of triethylamine. The mixture was diluted with CH_2Cl_2, filtered through Celite and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 20:1) to give **6a** (9.5 mg, 35% yield) as a colorless syrup and **7a** (11.1 mg, 42% yield) as a colorless syrup. For compound **6a**: $[\alpha]_D^{25}$ +70.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.60 (m, 2H), 7.26–7.48 (m, 13H), 5.54 (s, 1H, benzylidene), 5.35 (d, 1H, *J*=3.0 Hz, H-1′), 5.07 (d, 1H, *J*=11.5 Hz, −C*H*$_2$−), 4.74 (d, 1H, *J*=12.0 Hz, −C*H*$_2$−), 4.72 (d, 1H, *J*=11.5 Hz, −C*H*$_2$−), 4.65 (d, 1H, *J*=12.0 Hz, −C*H*$_2$−), 4.55 (d, 1H, *J*=3.5 Hz, H-1), 4.14 (dd, 1H, *J*=5.0, 10.3 Hz), 4.00–4.08 (m, 2H), 3.88 (dd, 1H, *J*=1.0, 9.0 Hz), 3.78–3.84 (m, 1H), 3.63 (t, 1H, *J*=10.0 Hz), 3.51 (dd, 1H, *J*=3.5, 9.5 Hz), 3.42 (d, 1H, *J*=4.0 Hz), 3.38 (s, 3H), 3.35 (t, 1H, *J*=9.5 Hz), 3.08 (dd, 1H, *J*=3.0, 4.0 Hz), 1.24 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.85, 137.94, 137.04, 129.22, 128.49, 128.46, 128.31, 128.14, 127.96, 127.60, 127.50, 126.22, 102.62 (benzylidene), 97.71 (C-1), 94.73 (C-1′), 81.84, 80.44, 79.89, 77.71, 75.57, 73.11, 68.64, 65.75, 60.25, 55.04, 53.07, 50.69, 17.60; HRMS (ESI) Anal. Calcd for $C_{34}H_{38}O_9Na$ [M+Na]$^+$ 613.2408, found 613.2417; $^1J_{C1,H1}$=174.17 Hz; $^1J_{C1',H1'}$=170.24 Hz. For compound **7a**: $[\alpha]_D^{25}$ +65.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.48 (m, 15H), 5.42 (s, 1H, benzylidene), 5.21 (s, 1H, H-1′), 4.93 (d, 1H, *J*=11.0 Hz, −C*H*$_2$−), 4.88 (d, 1H, *J*=11.0 Hz, −C*H*$_2$−), 4.77 (d, 1H, *J*=12.5 Hz, −C*H*$_2$−), 4.64 (d, 1H, *J*=12.0 Hz, −C*H*$_2$−), 4.52 (d, 1H, *J*=3.5 Hz, H-1), 3.95–3.98 (m, 2H), 3.86 (t, 1H, *J*=9.0 Hz), 3.73–3.79 (m, 1H), 3.59–3.64 (m, 1H), 3.50–3.52 (m, 2H), 3.36–3.41 (m, 6H), 1.30 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.24, 138.10, 137.03, 129.21, 128.42, 128.31, 128.26, 128.10, 127.88, 127.38, 127.16, 126.21, 102.54 (benzylidene), 97.90 (C-1), 97.70 (C-1′), 83.74, 80.10, 79.69, 77.34, 75.24, 73.43, 68.65, 66.03, 60.47, 55.48, 55.21, 51.30, 18.11; HRMS (ESI) Anal. Calcd for $C_{34}H_{38}O_9Na$ [M+Na]$^+$ 613.2408, found 613.2422; $^1J_{C1,H1}$=168.81 Hz; $^1J_{C1',H1'}$=168.19 Hz.

4.2. Methyl 4-*O*-(2,3-anhydro-α-D-allopyranosyl)-6-deoxy-α-D-glucopyranoside (6)

Compound **6a** (63 mg, 0.107 mmol) was dissolved in a mixture of THF and EtOH (20 mL, THF/EtOH=4:1), palladium hydroxide (10 mg) was added, and the mixture was stirred under H_2 atmosphere for 2 days. The mixture was filtered and concentrated to give disaccharide **6** (29 mg, 85% yield) as a colorless oil: $[\alpha]_D^{25}$ +110.6 (*c* 1.4, water); ^{1}H NMR (500 MHz, CD_3OD) δ 5.56 (d, 1H, *J*=3.5 Hz, H-1′), 4.59 (d, 1H, *J*=4.0 Hz, H-1), 3.84–3.86 (m, 1H), 3.64–3.77 (m, 5H), 3.56 (t, 1H, *J*=4.0 Hz), 3.37–3.39 (m, 4H), 3.31–3.33 (m, 2H), 1.24 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 101.14, 95.18, 81.35, 75.73, 73.94, 71.24, 67.23, 66.25, 62.27, 56.17, 55.50, 55.35, 18.58; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_9Na$ [M+Na]$^+$ 345.1156. Found 345.1160.

4.3. Methyl 4-*O*-(2,3-anhydro-β-D-allopyranosyl)-6-deoxy-α-D-glucopyranoside (7)

Compound **7a** (100 mg, 0.169 mmol) was dissolved in a mixture of THF and EtOH (25 mL, THF/EtOH=4:1), palladium hydroxide (10 mg) was added, and the mixture was stirred under H_2 atmosphere for 2 days. Filtration and concentration gave disaccharide **7** (47 mg, 87% yield) as a colorless oil: $[\alpha]_D^{25}$ +90.2 (*c* 1.4, water); ^{1}H NMR (500 MHz, CD_3OD) δ 4.93 (s, 1H, H-1′), 4.59 (d, 1H, *J*=4.0 Hz, H-1), 3.94 (dd, 1H, *J*=1.5, 9.5 Hz), 3.77 (dd, 1H, *J*=2.5, 12.0 Hz), 3.59–3.72 (m, 3H), 3.42–3.45 (m, 1H), 3.36–3.41 (m, 6H), 3.20 (dd, 1H, *J*=8.5, 9.5 Hz), 1.28 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 102.99, 101.58, 80.20, 72.57, 72.21, 71.57, 70.80, 70.55, 67.73, 66.21, 62.89, 55.71, 17.18; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_9Na$ [M+Na]$^+$ 345.1156. Found 345.1162.

4.4. *p*-Tolyl 2,3-anhydro-4,6-di-*O*-acetyl-1-thio-β-D-mannopyranoside (18)

Compound **17**[15] (2.08 g, 5.60 mmol) was dissolved in MeOH (60 mL) at 0 °C, and TsOH (0.29 g, 1.68 mmol) was added slowly. The mixture was stirred. After consumption of the starting material (3 h), triethylamine was added to neutralize the solution to pH 7, the mixture was then filtered and concentrated. The crude product was dissolved in pyridine (30 mL), and acetic anhydride (1.61 mL, 12.80 mmol) was added. The reaction mixture was stirred overnight. After consumption of the starting material, the mixture was concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 5:1) to give **18** (1.60 g, 81% yield) as white solids: $[\alpha]_D^{25}$ −45.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 2H, *J*=8.0 Hz), 7.13 (d, 2H, *J*=8.0 Hz), 5.17 (d, 1H, *J*=0.8 Hz), 4.93 (d, 1H, *J*=9.2 Hz), 4.17–4.19 (m, 2H), 3.57–3.60 (m, 1H), 3.41 (d, 1H, *J*=3.6 Hz), 3.27 (d, 1H, *J*=3.6 Hz), 2.35 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.59, 169.48, 138.12, 132.47, 129.79, 129.64, 82.97, 74.99, 63.33, 63.23, 54.11, 51.32, 21.11, 20.76, 20.72; HRMS (ESI) Anal. Calcd for $C_{17}H_{24}NO_6S$ [M+NH$_4$]$^+$ 370.1319. Found 370.1319.

4.5. Methyl 2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-α-D-glucopyranoside (20)

Compound **19**[19] (14.05 g, 32.33 mmol) and *p*-toluenesulfonyl chloride (12.30 g, 64.99 mmol) were added into pyridine (200 mL) at 0 °C. The mixture was stirred overnight allowing the reaction to be warmed up to room temperature. The reaction mixture was diluted with EtOAc. The organic phase was successively washed with 1 N HCl aqueous solution (three times), saturated $NaHCO_3$ aqueous solution, and brine, dried over Na_2SO_4. After removal of the solvent, the tosylated crude product was dissolved in THF (200 mL) and $LiAlH_4$ (3.60 g, 129.32 mmol) was added. The mixture was stirred at room temperature overnight, then heated under reflux for 2 h. After completion of the reaction, the mixture was quenched by the slow addition of ice, then filtered through Celite. The filtered cake was washed with EtOAc, and the resulting cloudy yellowish solution was filtered again through Celite. The combined organic solutions were successively washed with 1 N HCl aqueous solution, water, saturated $NaHCO_3$ aqueous solution, and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 5:1) to give **20** (9.01 g, 67% yield) as white solids: $[\alpha]_D^{25}$ +30.2

(*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.31 (m, 4H), 6.86–6.90 (m, 4H), 4.94 (d, 1H, *J*=11.2 Hz), 4.71 (d, 1H, *J*=11.6 Hz), 4.59–4.62 (m, 2H), 4.50 (d, 1H, *J*=3.6 Hz), 3.80 (s, 6H), 3.70–3.60 (m, 2H), 3.48 (dd, 1H, *J*=3.6, 9.6 Hz), 3.36 (s, 3H), 3.11 (t, 1H, *J*=9.2 Hz), 2.09 (s, 1H), 1.22 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.42, 159.37, 130.88, 130.15, 129.70, 129.64, 114.06, 113.86, 98.07, 80.84, 79.68, 75.27, 74.87, 72.64, 66.77, 55.25 (2C), 55.09, 17.63; HRMS (ESI) Anal. Calcd for $C_{23}H_{34}NO_7$ $[M+NH_4]^+$ 436.2330. Found 436.2340.

4.6. Methyl 4-*O*-(2,3-anhydro-4,6-di-*O*-acetyl-α-D-mannopyranosyl)-2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-α-D-glucopyranoside (8a)

Compounds **18** (30.0 mg, 0.085 mmol), **20** (23.8 mg, 0.057 mmol), and 4 Å molecular sieves (400 mg) were dried overnight under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (5 mL); the mixture was cooled to −40 °C, NIS (20.5 mg, 0.091 mmol) and AgOTf (6.9 mg, 0.027 mmol) were successively added. After stirring for 20 min at −40 °C, the mixture was warmed to −25 °C. Once the color of the reaction was changed to pink, it was cooled again to −40 °C. After another 30 min, the reaction mixture turned dark red and was then neutralized by the addition of triethylamine. The mixture was diluted with CH_2Cl_2, filtered through Celite, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 8:1) to give **8a** (24.6 mg, 67% yield) as a colorless syrup: $[\alpha]_D^{25}$ +10.0 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.29 (m, 2H), 7.22–7.24 (m, 2H), 6.85–6.88 (m, 4H), 5.52 (s, 1H, H-1′), 4.95 (d, 1H, *J*=11.0 Hz), 4.76 (d, 1H, *J*=10.0 Hz), 4.70 (d, 1H, *J*=11.5 Hz), 4.62 (d, 1H, *J*=11.0 Hz), 4.57 (d, 1H, *J*=11.5 Hz), 4.47 (d, 1H, *J*=3.5 Hz, H-1), 4.07 (d, 2H, *J*=4.0 Hz), 3.84–3.91 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.69 (dd, 1H, *J*=6.5, 9.5 Hz), 3.49 (dd, 1H, *J*=3.5, 9.5 Hz), 3.36–3.40 (m, 4H), 3.16 (d, 1H, *J*=4.0 Hz), 2.81 (d, 1H, *J*=3.5 Hz), 2.04 (s, 3H), 2.11 (s, 3H), 1.26 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.73, 169.48, 159.48, 159.30, 130.44, 129.99, 129.77, 129.53, 114.00, 113.89, 97.83 (C-1), 96.19 (C-1′), 81.31, 81.19, 80.19, 75.13, 72.86, 65.62, 65.02, 63.04, 55.29, 55.26, 55.20, 53.24, 49.15, 20.79, 20.72, 18.17. HRMS (ESI) Anal. Calcd for $C_{33}H_{42}O_{13}K$ $[M+K]^+$ 685.5117. Found 685.5117; $^1J_{C1,H1}$=167.09 Hz; $^1J_{C1',H1'}$=176.81 Hz.

4.7. Methyl 4-*O*-(2,3-anhydro-α-D-mannopyranosyl)-6-deoxy-α-D-glucopyranoside (8)

To a solution of compound **8a** (50 mg, 0.077 mmol) in CH_2C1_2 (1 mL) and water (9 mL) at room temperature was added 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (34 mg, 0.15 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (four times), and then dried (Na_2SO_4), concentrated. The crude product was dissolved in MeOH (20 mL), and K_2CO_3 (12.7 mg, 0.092 mmol) was added slowly. The mixture was stirred. After consumption of the starting material (5 h), to the reaction mixture was added acidic resin to neutralize the solution to pH 7. The mixture was filtered and concentrated. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc 1:10) to give **8** (21.0 mg, 85% yield) as a colorless oil: $[\alpha]_D^{25}$ +109.3 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, D_2O) δ 4.83 (s, 1H, H-1′), 4.65 (d, 1H, *J*=4.0 Hz, H-1), 4.17–4.19 (m, 1H), 3.94 (dd, 1H, *J*=6.8, 9.5 Hz), 3.89–3.92 (m, 2H), 3.78–3.83 (m, 3H), 3.76 (d, 1H, *J*=3.2 Hz), 3.66–3.73 (m, 2H), 3.34 (s, 3H), 1.27 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ: 100.92, 99.32, 87.28, 73.64, 73.48, 73.28, 67.22, 65.78, 62.35, 57.80, 55.59, 55.44, 18.01; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_9Na$ $[M+Na]^+$ 345.1156. Found 345.1159.

4.8. Methyl 2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-4-iodo-α-D-galactopyranoside (21)

Compound **20** (4.07 g, 9.54 mmol), I_2 (4.85 g, 19.08 mmol), PPh_3 (7.50 g, 29.16 mmol), and imidazole (1.95 g, 29.16 mmol) were added into THF (100 mL) at room temperature, and the ensuing mixture was stirred at 80 °C overnight. When the starting material disappeared, the reaction mixture was cooled to room temperature, diluted with toluene, and washed successively with saturated $NaHCO_3$, 5% sodium thiosulfate, and water. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 15:1) to give **21** (4.30 g, 86% yield) as a colorless oil: $[\alpha]_D^{25}$ +24.0 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.34 (m, 4H), 6.83–6.89 (m, 4H), 4.76 (d, 1H, *J*=12.0 Hz), 4.66 (d, 1H, *J*=11.2 Hz), 4.58 (d, 1H, *J*=12.0 Hz), 4.54 (d, 1H, *J*=12.0 Hz), 4.48 (d, 1H, *J*=4.0 Hz), 4.44 (d, 1H, *J*=2.8 Hz), 3.77–3.82 (m, 7H), 3.34 (s, 3H), 3.13–3.19 (m, 2H), 1.20 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.11, 159.04, 130.88, 130.33, 129.96, 129.62, 129.17, 113.63, 113.57, 98.92, 76.68, 75.39, 73.29, 70.74, 63.87, 55.14, 55.08, 55.07, 47.29, 22.90; HRMS (ESI) Anal. Calcd for $C_{23}H_{33}NO_6I$ $[M+NH_4]^+$ 546.1347. Found 546.1333.

4.9. Methyl 2,3-di-*O*-*p*-methoxybenzyl-4-acetylthio-6-deoxy-α-D-glucopyranoside (22)

Compound **21** (5.70 g, 10.80 mmol) and potassium thioacetate (4.90 g, 43.20 mmol) were dissolved in DMF (80 mL) at room temperature, and the mixture was stirred at 90 °C for 2 h. After the starting material was consumed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The water phase was extracted with ethyl acetate, and the combined organic phase was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 20:1) to give **22** (3.41 g, 67% yield) as a yellowish syrup: $[\alpha]_D^{25}$ +60.1 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.28 (m, 4H), 6.83–6.86 (m, 4H), 4.81 (d, 1H, *J*=10.8 Hz), 4.73 (d, 1H, *J*=11.6 Hz), 4.61 (d, 1H, *J*=10.4 Hz), 4.57 (d, 1H, *J*=12.0 Hz), 4.50 (d, 1H, *J*=3.2 Hz), 3.68–3.80 (m, 8H), 3.54 (dd, 1H, *J*=3.6, 9.2 Hz), 3.36–3.45 (m, 4H), 2.32 (s, 3H), 1.21 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.56, 159.31, 158.99, 130.83, 130.18, 129.76, 129.64, 129.20, 128.82, 127.78, 113.75, 113.51, 113.31, 98.34, 80.63, 77.60, 75.39, 72.87, 66.69, 55.23, 55.17, 55.15, 50.89, 30.56, 18.28; HRMS (ESI) Anal. Calcd for $C_{25}H_{36}NO_7S$ $[M+NH_4]^+$ 494.2207. Found 494.2213.

4.10. Methyl 2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-4-thio-α-D-glucopyranoside (23)

Compound **22** (1.60 g, 3.40 mmol) was dissolved in MeOH (35 mL) at room temperature, and potassium carbonate (0.56 g, 4.10 mmol) was added slowly. After consumption of the starting material (12 h), the reaction mixture was treated with acidic resin to neutralize the solution to pH 7. The mixture was filtered and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 10:1) to give **23** (1.10 g, 75% yield) as a yellowish syrup: $[\alpha]_D^{25}$ −26.7 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.34 (m, 4H), 6.85–6.89 (m, 4H), 4.89 (d, 1H, *J*=10.4 Hz), 4.73 (d, 1H, *J*=11.8 Hz), 4.72 (d, 1H, *J*=10.2 Hz), 4.60 (d, 1H, *J*=11.8 Hz), 4.53 (d, 1H, *J*=3.2 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.60–3.71 (m, 2H), 3.44 (dd, 1H, *J*=3.5, 9.4 Hz), 3.38 (s, 3H), 2.57–2.60 (m, 1H), 1.72 (d, 1H, *J*=6.0 Hz), 1.30 (d, 3H, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.41, 159.31, 130.68, 130.20, 129.83, 129.68, 113.85, 113.82, 98.39, 81.40, 80.54, 75.81, 72.73, 68.59, 55.27,

55.24, 48.16, 19.19; HRMS (ESI) Anal. Calcd for $C_{23}H_{34}NO_6S$ $[M+NH_4]^+$ 452.2101. Found 452.2112.

4.11. *p*-Tolyl 2,3-anhydro-4,6-di-*O*-acetyl-1-thio-β-D-allopyranoside (24)

Compound **15** (1.02 g, 2.80 mmol) was dissolved in MeOH (60 mL) at 0 °C, and TsOH (0.14 g, 0.84 mmol) was added slowly. After consumption of the starting material (3 h), triethylamine was added to neutralize the solution to pH 7, and then the reaction mixture was filtered and concentrated. The crude product was dissolved in pyridine (30 mL), and acetic anhydride (0.79 mL, 8.40 mmol) was added. The mixture was stirred overnight. After consumption of the starting material, the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 5:1) to give **24** (0.69 g, 70% yield) as white solids: $[\alpha]_D^{25}$ +23.5 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 2H, *J*=7.6 Hz), 7.14 (d, 2H, *J*=7.6 Hz), 5.14 (s, 1H), 4.93 (d, 1H, *J*=9.6 Hz), 4.15 (d, 2H, *J*=2.4 Hz), 3.81–3.83 (m, 1H), 3.64 (d, 1H, *J*=3.6 Hz), 3.97 (s, 1H), 2.36 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.54, 170.05, 138.83, 133.77, 129.65, 127.33, 79.77, 69.89, 66.58, 62.79, 58.46, 52.14, 21.10, 20.74, 20.69; HRMS (ESI) Anal. Calcd for $C_{17}H_{20}O_6SNa$ $[M+Na]^+$ 375.0873. Found 375.0871.

4.12. Methyl 4-*S*-(2,3-anhydro-4,6-di-*O*-acetyl-α-D-allopyranosyl)-2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-α-D-glucopyranoside (9a)

Compound **24** (25.0 mg, 0.071 mmol), TTBP (28.7 mg, 0.142 mmol), Ph_2SO (11.5 mg, 0.057 mmol), and 4 Å molecular sieves (400 mg) were dried for 3 h under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (5 mL), and the mixture was cooled to −78 °C. Tf_2O (10.8 μL, 0.064 mmol) was added, and the mixture was allowed to stir for 10 min. The mixture was then stirred for 20 min followed by the addition of **23** (49.0 mg, 0.142 mmol). After 2 h, the reaction was warmed to room temperature and triethylamine was then added. The reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 3:1) to give **9a** (37.0 mg, 81% yield) as a colorless syrup: $[\alpha]_D^{25}$ +11.8 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.30 (m, 4H), 6.85–6.88 (m, 4H), 5.66 (d, 1H, *J*=3.5 Hz, H-1′), 5.08 (dd, 1H, *J*=1.5, 9.8 Hz, H-4′), 5.02 (d, 1H, *J*=10.5 Hz, $-CH_2-$), 4.72 (d, 1H, *J*=12.0 Hz, $-CH_2-$), 4.68 (d, 1H, *J*=10.5 Hz, $-CH_2-$), 4.60 (d, 1H, *J*=12.0 Hz, $-CH_2-$), 4.53 (d, 1H, *J*=3.0 Hz, H-1), 4.14–4.19 (m, 2H, H-5′, H-6a′), 4.00–4.03 (m, 1H, H-6b′), 3.89 (t, 1H, *J*=10.0 Hz, H-3), 3.80 (s, 6H, $-OCH_3$, $-OCH_3$), 3.63–3.69 (m, 1H, H-5), 3.50 (dd, 1H, *J*=2.0, 4.0 Hz, H-3′), 3.46 (dd, 1H, *J*=3.5, 9.5 Hz, H-2), 3.37 (s, 3H, $-OCH_3$), 3.24 (t, 1H, *J*=4.0 Hz, H-2′), 2.60 (t, 1H, *J*=11.0 Hz, H-4), 2.10 (s, 3H, $-CH_3$), 2.04 (s, 3H, $-CH_3$), 1.34 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.56, 170.16, 159.37, 159.08, 131.04, 130.07, 129.67, 129.21, 113.81, 113.67, 98.21, 82.63, 80.64, 80.29, 75.94, 72.59, 66.99, 66.25, 64.82, 62.56, 56.64, 55.26, 55.21, 55.18, 52.46, 51.80, 20.75, 20.64, 19.26; HRMS (ESI) Anal. Calcd for $C_{33}H_{43}O_{12}S$ $[M+H]^+$ 663.2470. Found 663.2491.

4.13. Methyl 4-*S*-(2,3-anhydro-α-D-allopyranosyl)-6-deoxy-α-D-glucopyranoside (9)

Compound **9** was prepared from **9a** (40.0 mg, 0.060 mmol) in the same manner as described in the synthesis of compound **8** from **8a**, the product was purified by flash column chromatography on silica gel (MeOH/EtOAc 1:10) to give **9** (16.0 mg, 81% yield) as white solids: $[\alpha]_D^{25}$ +89.8 (*c* 1.4, water); ^1H NMR (400 MHz, D_2O) δ 5.64 (d, 1H, *J*=3.2 Hz, H-1′), 4.68 (d, 1H, *J*=3.6 Hz, H-1), 3.93 (d, 1H, *J*=9.2 Hz), 3.80 (dd, 1H, *J*=6.0, 10.8 Hz), 3.69–3.75 (m, 4H), 3.54–3.61 (m, 2H), 3.46 (dd, 1H, *J*=4.0, 9.6 Hz), 3.29 (s, 3H), 2.48 (t, 1H, *J*=10.8 Hz), 1.28 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (125 MHz, D_2O) δ 100.02, 78.93, 73.24, 73.01, 70.06, 67.82, 65.07, 61.08, 58.94, 56.76, 55.80, 53.47, 19.24; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_8SK$ $[M+K]^+$ 377.0662. Found 377.0671.

4.14. Methyl 4-*S*-(2,3-anhydro-4,6-di-*O*-acetyl-β-D-mannopyranosyl)-2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-α-D-glucopyranoside (10a)

Compound **10a** was prepared by the coupling reaction of **18** (26.0 mg, 0.076 mmol) and **23** (65.0 mg, 0.152 mmol) in the same manner as described in the synthesis of **9a**, the product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 3:1) to give **10a** (39.0 mg, 77% yield) as a colorless syrup: $[\alpha]_D^{25}$ +17.9 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.35 (m, 2H), 7.26–7.29 (m, 2H), 6.85–6.87 (m, 4H), 5.00 (s, 1H, H-1′), 4.85–4.89 (m, 2H, H-4′, $-CH_2-$), 4.78 (d, 1H, *J*=10.5 Hz, $-CH_2-$), 4.73 (d, 1H, *J*=12.0 Hz, $-CH_2-$), 4.59 (d, 1H, *J*=10.5 Hz, $-CH_2-$), 4.53 (d, 1H, *J*=3.5 Hz, H-1), 4.15 (dd, 1H, *J*=3.0, 12.3 Hz, H-6a′), 4.02 (dd, 1H, *J*=6.0, 12.0 Hz, H-6b′), 3.75–3.84 (m, 8H, H-3, H-5, $-OCH_3$, $-OCH_3$), 3.52 (dd, 1H, *J*=3.5, 9.0 Hz, H-2), 3.44–3.47 (m, 1H, H-5′), 3.37 (s, 3H, $-OCH_3$), 3.13–3.16 (m, 2H, H-2′, H-3′), 2.74 (t, 1H, *J*=10.5 Hz), 2.11 (s, 3H, $-CH_3$), 2.04 (s, 3H, $-CH_3$), 1.36 (d, 3H, *J*=6.5 Hz, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.57, 169.46, 159.39, 159.18, 130.89, 130.23, 129.66, 113.83, 113.66, 98.15, 81.07, 77.82, 77.60, 75.51, 75.12, 72.83, 67.51, 63.26, 62.94, 55.23, 53.93, 52.48, 51.82, 20.77, 20.67, 19.04; HRMS (ESI) Anal. Calcd for $C_{33}H_{43}O_{12}S$ $[M+H]^+$ 663.2470. Found 663.2478.

4.15. Methyl 4-*S*-(2,3-anhydro-β-D-mannopyranosyl)-6-deoxy-α-D-glucopyranoside (10)

Compound **10** was prepared from **10a** (80.0 mg, 0.121 mmol) in the same manner as described in the synthesis of compound **8** from **8a**, the product was purified by flash column chromatography on silica gel (MeOH/EtOAc 1:10) to give **10** (29.0 mg, 72% yield) as white solids: $[\alpha]_D^{25}$ +80.2 (*c* 1.4, water); ^1H NMR (400 MHz, D_2O) δ 5.18 (s, 1H, H-1′), 4.67 (s, 1H, H-1), 3.88 (dd, 1H, *J*=6.2, 10.9 Hz), 3.65–3.72 (m, 3H), 3.43–3.51 (m, 2H), 3.40 (d, 1H, *J*=3.9 Hz), 3.33 (d, 1H, *J*=3.9 Hz), 3.26 (s, 3H), 3.18–3.22 (m, 1H), 2.55 (t, 1H, *J*=10.6 Hz), 1.30 (d, 3H, *J*=6.2 Hz); ^{13}C NMR (125 MHz, D_2O) δ 99.91, 80.75, 78.69, 73.28, 70.03, 69.00, 62.19, 61.37, 57.99, 55.79, 54.45, 53.48, 18.90; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_8SK$ $[M+K]^+$ 377.0662. Found 377.0661.

4.16. Methyl 2,3-di-*O*-*p*-methoxybenzyl-4-acetylthio-6-deoxy-α-D-galactopyranoside (25)

Compound **20** (2.32 g, 5.54 mmol), Tf_2O (1.81 mL, 11.08 mmol), and pyridine (1.8 mL, 22.16 mmol) were dissolved in CH_2Cl_2 (15 mL) at −30 °C, and the mixture was stirred at room temperature for 2 h. After the starting material was consumed, the reaction mixture was diluted with ethyl acetate, and washed with $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product and potassium thioacetate (2.53 g, 22.16 mmol) were dissolved in DMF (80 mL) at room temperature, and the mixture was stirred at 90 °C for 2 h. After the starting material was consumed, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 20:1) to

give **25** (1.66 g, 63% yield) as a yellowish syrup: $[\alpha]_D^{25}$ +27.6 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.27 (m, 4H), 6.84–6.86 (m, 4H), 4.79 (d, 1H, *J*=11.7 Hz), 4.57 (ABq, 2H, *J*=11.2 Hz), 4.48–4.50 (m, 2H), 4.26 (d, 1H, *J*=3.4 Hz), 4.20 (d, 1H, *J*=6.4 Hz), 4.13 (dd, 1H, *J*=4.5, 10.0 Hz), 3.80 (s, 6H), 3.38 (dd, 1H, *J*=3.8, 10.0 Hz), 3.34 (s, 3H), 2.42 (s, 3H), 1.16 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.23, 159.26, 159.15, 130.59, 130.27, 129.59, 129.39, 113.74, 99.05, 75.95, 73.33, 71.51, 64.45, 55.37, 55.25, 51.02, 30.93, 17.70; HRMS (ESI) Anal. Calcd for $C_{25}H_{36}NO_7S$ $[M+NH_4]^+$ 494.2207. Found 494.2208.

4.17. Methyl 2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-4-thio-α-D-galactopyranoside (26)

Compound **25** (0.50 g, 1.05 mmol) was dissolved in MeOH (35 mL) at room temperature, and potassium carbonate (0.17 g, 1.26 mmol) was added slowly. After consumption of the starting material (12 h), the reaction mixture was treated with acidic resin to neutralize the solution to pH 7. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 8:1) to give **26** (0.36 g, 80% yield) as a yellowish syrup: $[\alpha]_D^{25}$ +4.1 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.32 (m, 4H), 6.84–6.89 (m, 4H), 4.77 (d, 1H, *J*=11.6 Hz), 4.57–4.62 (m, 3H), 4.52 (d, 1H, *J*=3.6 Hz), 4.13 (ddd, 1H, *J*=12.8, 6.4, 4.4 Hz), 3.96 (dd, 1H, *J*=4.4, 9.8 Hz), 3.90 (dd, 1H, *J*=3.6, 7.6 Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.41 (td, 1H, *J*=4.8, 1.6 Hz), 3.34 (s, 3H), 1.69 (d, 1H, *J*=4.8 Hz), 1.25 (d, 3H, *J*=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.19, 159.13, 130.59, 130.40, 129.61, 129.20, 113.74, 113.68, 98.95, 76.68, 74.59, 73.21, 71.54, 64.21, 55.19, 46.90, 18.43; HRMS (ESI) Anal. Calcd for $C_{23}H_{34}NO_6S$ $[M+NH_4]^+$ 452.2101. Found 452.2116.

4.18. Methyl 4-*S*-(2,3-anhydro-4,6-di-*O*-acetyl-α-D-allopyranosyl)-2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-α-D-galactopyranoside (11a)

Compound **11a** was prepared by the coupling reaction of **24** (24.0 mg, 0.069 mmol) and **26** (60.0 mg, 0.139 mmol) in the same manner as described in the synthesis of **9a**, the product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 5:1) to give **11a** (34.0 mg, 75% yield) as a colorless syrup: $[\alpha]_D^{25}$ +56.6 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.31 (m, 4H), 6.85–6.89 (m, 4H), 5.29 (s, 1H, H-1′), 4.93 (d, 1H, *J*=9.3 Hz), 4.79 (d, 1H, *J*=1.7 Hz), 4.76 (d, 1H, *J*=1.8 Hz), 4.61 (ABq, 2H, *J*=11.5 Hz), 4.52 (d, 1H, *J*=3.8 Hz, H-1), 4.13–4.19 (m, 2H), 4.04–4.11 (m, 2H), 3.91 (dd, 1H, *J*=3.8, 9.8 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.49–3.50 (m, 1H), 3.33–3.38 (m, 4H), 3.28 (d, 1H, *J*=3.6 Hz), 2.20 (d, 1H, *J*=3.6 Hz), 2.13 (s, 3H), 2.03 (s, 3H), 1.34 (d, 3H, *J*=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.40, 170.33, 159.31, 158.99, 130.78, 130.45, 129.72, 128.67, 113.79, 113.73, 98.77, 80.27, 77.16, 76.28, 73.19, 71.92, 66.49, 65.44, 64.91, 61.93, 56.84, 55.36, 55.24, 52.80, 52.73, 20.82, 20.71, 18.10; HRMS (ESI) Anal. Calcd for $C_{33}H_{43}O_{12}S$ $[M+H]^+$ 663.2470. Found 663.2480.

4.19. Methyl 4-*S*-(2,3-anhydro-4,6-di-*O*-acetyl-β-D-mannopyranosyl)-2,3-di-*O*-*p*-methoxybenzyl-6-deoxy-α-D-galactopyranoside (12a)

Compound **12a** was prepared by the coupling reaction of **18** (27.0 mg, 0.078 mmol) and **26** (67.0 mg, 0.155 mmol) in the same manner as described in the synthesis of **9a**, the product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 5:1) to give **12a** (41.0 mg, 79% yield) as a colorless syrup: $[\alpha]_D^{25}$ +24.5 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.31 (m, 4H), 6.84–6.87 (m, 4H), 5.34 (d, 1H, *J*=3.4 Hz, H-1′), 5.19 (dd, 1H, *J*=1.6, 9.9 Hz), 4.69–4.76 (m, 3H), 4.57 (d, 1H, *J*=11.7 Hz), 4.49 (d, 1H, *J*=3.7 Hz, H-1), 4.02–4.03 (m, 1H), 4.00–4.01 (m, 1H), 3.99–4.00 (m, 2H), 3.80 (s, 6H), 3.73 (d, 1H, *J*=2.0 Hz), 3.65 (t, 1H, *J*=4.0 Hz), 3.61 (d, 1H, *J*=3.9 Hz), 3.58 (d, 1H, *J*=3.7 Hz), 3.34–3.35 (m, 4H), 2.10 (s, 3H), 2.03 (s, 3H), 1.35 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.64, 169.48, 159.30, 159.21, 130.92, 130.59, 129.65, 129.17, 113.82, 113.76, 98.75, 79.11, 78.77, 74.92, 73.11, 73.02, 65.47, 63.20, 55.26, 54.06, 51.49, 51.44, 20.80, 20.75, 18.44; HRMS (ESI) Anal. Calcd for $C_{33}H_{43}O_{12}S$ $[M+H]^+$ 663.2470. Found 663.2478.

4.20. Methyl 4-*S*-(2,3-anhydro-α-D-allopyranosyl)-6-deoxy-α-D-galactopyranoside (11)

Compound **11** was prepared from **11a** (55.0 mg, 0.083 mmol) in the same manner as described in the synthesis of compound **8** from **8a**, the product was purified by flash column chromatography on silica gel (MeOH/EtOAc 1:10) to give **11** (21.0 mg, 75% yield) as white solids: $[\alpha]_D^{25}$ +99.0 (*c* 1.4, water); ^1H NMR (500 MHz, D_2O) δ 5.43 (d, 1H, *J*=3.5 Hz, H-1′), 4.75 (d, 1H, *J*=4.0 Hz, H-1), 4.33 (dd, 1H, *J*=6.5, 5.1 Hz), 4.05–4.08 (m, 2H), 3.88–3.92 (m, 2H), 3.79 (dd, 1H, *J*=4.0, 12.5 Hz), 3.79 (dd, 1H, *J*=4.0, 12.5 Hz), 3.67 (dd, 1H, *J*=1.5, 4.3 Hz), 3.56 (dd, 1H, *J*=4.0, 10.5 Hz), 3.42–3.39 (m, 4H), 1.42 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, D_2O) δ 100.15, 80.85, 70.27, 69.97, 69.77, 67.00, 65.06, 61.02, 58.60, 56.79, 56.25, 55.84, 17.74; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_8SK$ $[M+K]^+$ 377.0662. Found 377.0662.

4.21. Methyl 4-*S*-(2,3-anhydro-β-D-mannopyranosyl)-6-deoxy-α-D-galactopyranoside (12)

Compound **12** was prepared from **12a** (98.0 mg, 0.148 mmol) in the same manner as described in the synthesis of compound **8** from **8a**, the product was purified by flash column chromatography on silica gel (MeOH/EtOAc 1:10) to give **12** (37.0 mg, 75% yield) as white solids: $[\alpha]_D^{25}$ +77.0 (*c* 1.4, water); ^1H NMR (500 MHz, D_2O) δ 5.26 (s, 1H, H-1′), 4.74 (d, 1H, *J*=3.5 Hz, H-1), 4.34 (dd, 1H, *J*=5.5, 12.5 Hz), 4.12 (dd, 1H, *J*=4.0, 10.3 Hz), 3.81 (dd, 1H, *J*=2.5, 14.8 Hz), 3.76 (dd, 1H, *J*=4.0, 10.0 Hz), 3.69–3.71 (m, 1H), 3.59–3.62 (m, 3H), 3.45 (d, 1H, *J*=4.0 Hz), 3.58 (s, 3H), 3.28–3.32 (m, 1H), 1.35 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (125 MHz, D_2O) δ 100.18, 80.91, 80.79, 70.56, 69.78, 66.96, 62.35, 61.42, 57.79, 55.84, 55.62, 53.60, 18.31; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_8SK$ $[M+K]^+$ 377.0662. Found 377.0670.

4.22. Methyl 4-*S*-(1,2-dideoxy-D-*ribo*-hex-1-enopyranosyl)-6-deoxy-α-D-galactopyranoside (13)

To an ice-cooled solution of **11** (71.0 mg, 0.21 mmol) in DMF (5 mL) was added *t*-BuOK (40.0 mg, 0.63 mmol). The mixture was stirred at 50 °C for 5 h and then diluted with ethyl acetate. The solution was washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (methanol/ethyl acetate, 1:8, 1% TEA) to provide compound **13** (59.0 mg, 75% yield) as a colorless oil: $[\alpha]_D^{25}$ +19.3 (*c* 1.4, water); ^1H NMR (500 MHz, D_2O) δ 5.32 (d, 1H, *J*=6.0 Hz), 4.63 (d, 1H, *J*=4.0 Hz, H-1), 4.20–4.23 (m, 1H), 3.92–3.96 (m, 3H), 3.75–3.80 (m, 2H), 3.66 (dd, 1H, *J*=2.4, 12.2 Hz), 3.58 (dd, 1H, *J*=5.2, 12.4 Hz), 3.43 (dd, 1H, *J*=4.0, 10.4 Hz), 3.28 (s, 3H), 1.29 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, D_2O) δ 155.26, 102.99, 101.58, 70.27, 69.97, 69.77, 67.00, 65.06, 61.02, 58.60, 56.79, 56.25, 17.74; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_8SK$ $[M+K]^+$ 377.0662. Found 377.0660.

4.23. Methyl 4-*S*-(1,2-dideoxy-D-*arabino*-hex-1-enopyranosyl)-6-deoxy-α-D-galactopyranoside (14)

Compound **14** was prepared from **12** (71.0 mg, 0.21 mmol) in the same manner as described in the synthesis of compound **13** from

11, the product was purified by column chromatography (methanol/ethyl acetate, 1:9, 1% TEA) to provide compound **14** (21.3 mg, 30% yield) as a colorless oil: $[\alpha]_D^{25}$ −25.7 (*c* 1.4, water); ^{1}H NMR (500 MHz, D_2O) δ 5.13 (d, 1H, *J*=2.0 Hz), 4.61 (d, 1H, *J*=4.1 Hz, H-1), 4.53 (d, 1H, *J*=4.7 Hz), 4.21 (dd, 1H, *J*=1.4, 6.4 Hz), 3.97–4.01 (m, 1H), 3.67 (dd, 1H, *J*=2.3, 12.4 Hz), 3.62 (dd, 1H, *J*=4.1, 10.2 Hz), 3.58 (d, 1H, *J*=9.6 Hz), 3.45–3.49 (m, 2H), 3.25 (s, 3H), 3.14–3.19 (m, 1H), 1.22 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, D_2O) δ 155.38, 101.18, 97.86, 78.93, 70.56, 69.78, 66.96, 62.35, 61.42, 57.79, 55.84, 55.62, 18.31; HRMS (ESI) Anal. Calcd for $C_{13}H_{22}O_8SK$ $[M+K]^+$ 377.0662. Found 377.0660.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.09.037.

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