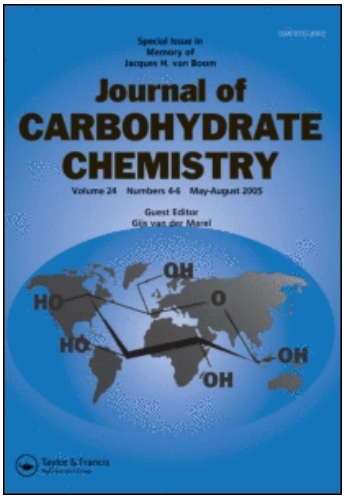

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SYNTHESIS OF THE TRISACCHARIDE REPEATING UNIT OF THE K-ANTIGEN FROM *KLEBSIELLA* TYPE-63

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ABSTRACT

The benzyl substituted ethyl thioglycoside of L-fucose was found to be a more reactive donor compared to 2-*O*-benzyl substituted *p*-tolyl thioglycoside of D-galactose. Using the benzyl substituted ethyl thioglycoside of L-fucose (**8**), as a donor and the suitably substituted *p*-tolyl thioglycoside of D-galactose (**7**) as acceptor, the *p*-tolyl thioglycoside of the disaccharide, **9**, was prepared. This disaccharide donor was allowed to react with a suitably protected galactopyranosyluronic acid acceptor, **16**, to give the trisaccharide repeating unit of the K-antigen from *Klebsiella* type 63 .

INTRODUCTION

Many bacterial antigens are polysaccharides which constitute an important class of biopolymers exhibiting a broad range of biological activity and specificity.[1] The polysaccharide from *Klebsiella* type 63 (K-63) has a trisaccharide repeating unit (**I**)[2] the structure of which is the same as the repeating unit of the K-antigen from *E. coli* type 42.[3] While most *Klebsiella* antigens contain D-glucuronic acid, this trisaccharide contains a D-galacturonic acid moiety and has only α-glycosidic linkages. It is therefore important to synthesize the repeating unit of the K-63 antigen so that immunochemical work may

be conducted involving the *Klebsiella* K-63 and *E. coli* K-42 immune systems. We now report the synthesis of the trisaccharide repeating unit of the K-antigen from *Klebsiella* type 63 in the form of its methyl ester methyl glycoside.

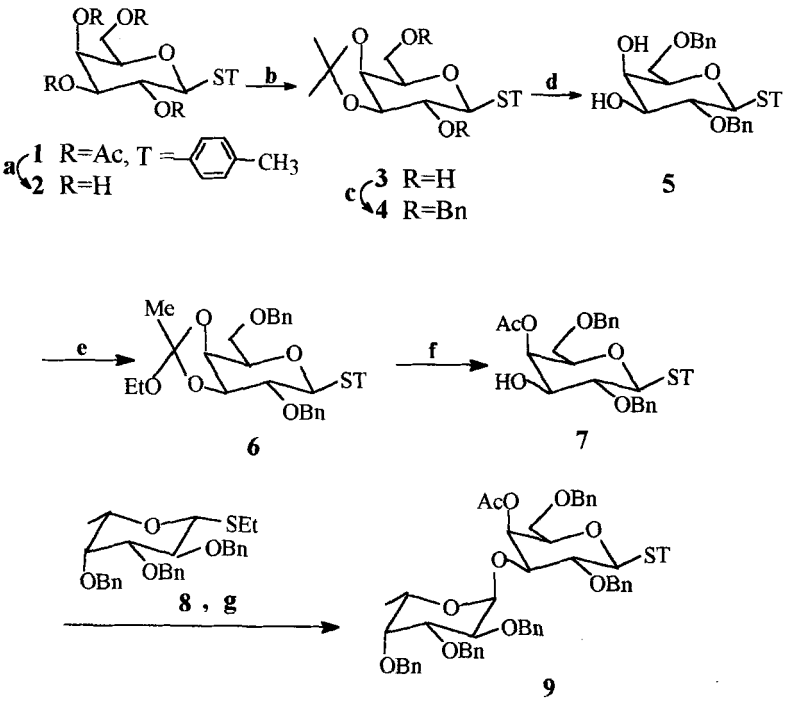
$$\rightarrow 3)\text{-}\alpha\text{-D-Galp}(1\rightarrow 3)\text{-}\alpha\text{-D-GalpA}(1\rightarrow 3)\text{-}\alpha\text{-L-Fucp}(1\rightarrow$$

I

RESULTS AND DISCUSSION

p-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**1**) was prepared from β-D-galactose pentaacetate using boron trifluoride diethyl etherate and *p*-thiocresol according to the method described by us previously.[4] Compound **1** was de-*O*-acetylated with sodium methoxide and the resulting *p*-tolyl 1-thio-β-D-galactopyranoside **2** on treatment with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid using *N,N*-dimethylformamide as a solvent gave the 3,4-isopropylidene compound **3** in 75% yield. Benzylation of **3** followed by removal of the isopropylidene group[5] from the resulting 2,6-di-*O*-benzyl derivative (**4**) afforded **5** in 80% yield. Treatment of **5** with triethyl orthoacetate and 10-camphorsulfonic acid and cleavage of the resulting orthoester **6** with 50% aqueous CF_3COOH using acetonitrile as solvent gave the 3-OH derivative **7** in 90% yield (Scheme 1).

In another experiment the suitably protected ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**8**) was obtained from L-fucose using the same reaction procedure as utilized by Lonn.[6] The ethyl thioglycoside donor **8** (0.3 mmol) was reacted with the *p*-tolyl thioglycoside **7** (0.2 mmol) as an acceptor in presence of *N*-iodosuccinimide (0.22 mmol) and trifluoromethanesulfonic acid (0.1 mmol)[7,8] using dichloromethane as a solvent at 0 ^{0}C to afford the disaccharide donor **9** having the *p*-tolyl thioglycoside group intact (Scheme 1) in 66% yield. The reaction was highly stereoselective and there was no coupling involving two units of *p*-tolyl thioglycosides (**7**). Higher reactivity of the ethyl thioglycoside compared to the *p*-tolyl thioglycoside, due to the greater electron withdrawing capacity of the tolyl group, was probably responsible for the selectivity of the reaction. Such selectivities were also observed in some similar experiments in this

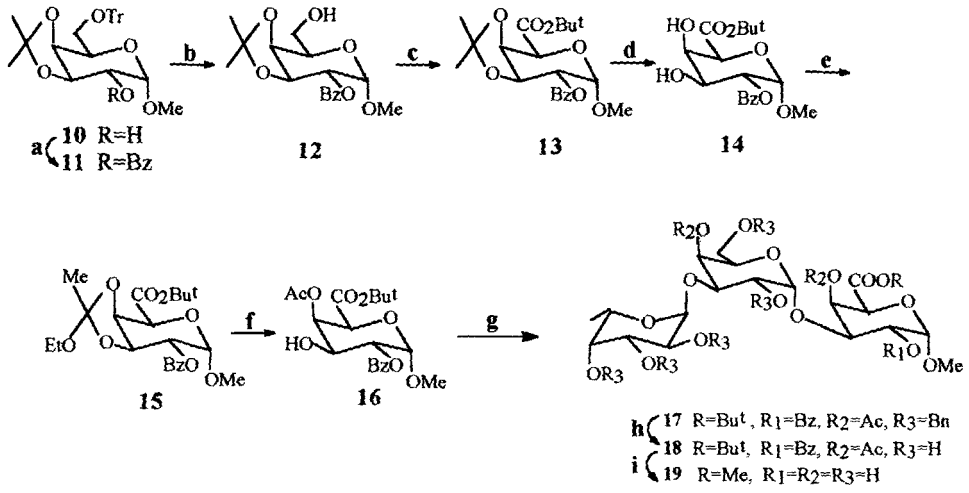


Reagents and conditions: a) 0.05M NaOMe, MeOH, 3 h, quantitative; b) 2,2-dimethoxypropane, *p*-TsOH(cat.), DMF, 25 ^{0}C, 2 h, 75%; c) NaH, BnBr, DMF, 5 h, 84%; d) MeOH-EtOAc (1:1, v/v), 0.1M *p*-TsOH, 25 ^{0}C, 2 h, 80%; e) triethyl orthoacetate, 10-camphorsulfonic acid, 15 min, 25 ^{0}C; f) CH_3CN, 50% aq CF_3COOH, 0 ^{0}C, 10 min, 90%; g) NIS/TfOH, CH_2Cl_2, 0 ^{0}C, 45 min, 66% .

Scheme 1

laboratory;[9] for example, when ethyl thioglycoside of tetra-*O*-benzyl galactose was allowed to react with *p*-tolyl 4-*O*-acetyl-2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside, the product was *p*-tolyl (2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside in 75% yield. Such chemoselective glycosylation strategy supports the active and latent glycosylation chemistry described previously.[10-12] The α-configuration of the newly formed glycosidic linkage was confirmed from its ^{13}C NMR signal at δ 99.2 and ^{1}H NMR signal at δ 5.34 (J = 2.0 Hz).

In a separate experiment, methyl 3,4-*O*-isopropylidene-6-*O*-trityl-α-D-galacto-pyranoside (**10**)[13] was benzoylated and the resulting 2-*O*-benzoate **11** was hydrogenolysed



Reagents and conditions: a) Pyridine, BzCl, 0 ^{0}C, 1 h, quantitative; b) EtOH, 10% Pd-C, 25 ^{0}C, 24 h, 82%; c) pyridine-CrO_3 , CH_2Cl_2-DMF (4:1, v/v), *t*-BuOH-Ac_2O, 25 ^{0}C, 10 h, 75%; d) 1:1 MeOH-EtOAc, 0.1M *p*-TsOH, 25 ^{0}C, 2 h, 78% ; e) triethyl orthoacetate, 10-camphorsulfonic acid, 25 ^{0}C, 15 min; f) CH_3CN, 50% aq CF_3COOH, 0 ^{0}C, 10 min, 85%; g) **9**, Et_2O-CH_2Cl_2 (14:1, v/v), MeOTf, 25 ^{0}C, 12 h, 77% ; h) AcOH, 10% Pd-C/H_2, 25 ^{0}C, 48 h; i) 0.1M NaOMe, MeOH, 25 ^{0}C, 4 h, 63%.

Scheme 2

to remove the trityl group[14] giving **12** in 82% yield. Oxidation of the primary hydroxyl group of **12** with pyridine-CrO_3-*t*-BuOH-Ac_2O[15] as solvent afforded the galacturonic acid derivative **13** in 75% yield. Removal of isopropylidene group from **13** gave the 3,4-dihydroxy compound **14** which was converted to the 4-*O*-acetate **16** via the orthoester **15** as described for the preparation of **7** from **5**. The *p*-tolyl thioglycoside donor **9** (180 mg, 0.21 mmol) was reacted with the acceptor **16** (70 mg, 0.17 mmol) in presence of methyl triflate[16] to afford the trisaccharide **17** in 77% yield (Scheme 2).

Hydrogenolysis of **17** with Pd-C in glacial acetic acid for 48 h gave **18** which on treatment with sodium methoxide in methanol afforded **19** in 63.4% yield. The structure of **19** was confirmed by its ^{1}H and ^{13}C NMR spectra . The ^{13}C NMR spectrum gave signals for 20 carbons and showed the presence of $COOCH_3$, OCH_3 , CCH_3 together with peaks at δ 101.4, 100.2 and 95.7 for three anomeric carbon atoms corresponding to α-fucosidic,

α-galactosidic, α-galacturonosidic moieties respectively, the *t*-butyl ester group being transesterified to the methyl ester group.[17]

In conclusion we have established the directive influence of ethyl thioglycoside as a donor in the presence of a *p*-tolyl thioglycoside, so that only the former compound acts as the donor in a mixture of the two. Similar strategy may be useful in the synthesis of complex oligosaccharides. The target K-63 trisaccharide was synthesized in four steps using the protected monosaccharide synthons **7, 8** and **16**. This trisaccharide, which is also the same as the antigen from *E. coli* type K-42, will be useful for important immunochemical work.

EXPERIMENTAL

General. All reactions were monitored by TLC on silica gel G (E. Merck). Column chromatography was performed using 100-200 mesh silica gel (SRL, India). The weight of silica taken for individual separation was approximately 10 to 25 times that of the weight of crude reaction mixture, depending on the extent of separation. All solvents were dried and/or distilled before use, and all evaporations were conducted below 50 ^{0}C under diminished pressure unless otherwise stated.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured at 24 ^{0}C with a Perkin-Elmer 241MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded (internal standard tetramethylsilane) with a Jeol FX100 and Bruker 300 MHz spectrometer, using $CDCl_3$ as the solvent unless stated otherwise. The organic extracts were dried over anhydrous Na_2SO_4.

***p*-Tolyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (1).** A solution of D-galactose pentaacetate (2g, 5.12 mmol) and *p*-thiocresol (770 mg, 6.15 mmol) in CH_2Cl_2 was cooled in an ice bath. Boron trifluoride diethyl etherate (1.90 mL, 15.8 mmol) was added and the mixture was stirred at room temperature for 6 h. The mixture was then diluted with CH_2Cl_2 (3 X 25 mL) and washed with 5% aqueous NaOH and water respectively. The organic layer was dried, filtered and then concentrated. Column chromatography of the resulting syrup with 6:1 toluene-EtOAc gave pure **1** (2.25g, 96.6%) which was crystallized from hot EtOH: mp 112-114 ^{0}C; $[\alpha]_D$ + 5.15^0 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.43-7.10 (m, 4H, $SC_6H_4CH_3$), 5.10 (d, 1H, $J_{1,2}$ = 7.0 Hz, H-1), 2.33 (s, 3H, $SC_6H_4CH_3$), 2.10-1.98 (4s, 12H, 4OAc).

Anal. Calcd for $C_{21}H_{26}O_9S$: C, 55.49; H, 5.76. Found : C, 55.60; H, 5.62.

***p*-Tolyl 2,6-Di-*O*-benzyl-1-thio-β-D-galactopyranoside (5).** To a solution of *p*-tolyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**4**) (500 mg, 0.99 mmol) in 1:1 MeOH-EtOAc (10 mL), *p*-TsOH (170 mg) was added. The mixture was stirred at 25 ^{0}C for 2 h when the reaction was found to be complete (TLC). The reaction was quenched with Et_3N and the mixture was concentrated. The syrupy product was chromatographed with 6:1 toluene-EtOAc to afford **5** (370 mg, 80%) as a syrup: $[\alpha]_D$ -30.1^0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.48-7.06 (m, 14H, aromatic protons), 4.94 (d, 2H, $J_{1,2}$ = 10 Hz, H-1), 2.30 (s, 3H, $SC_6H_4CH_3$).

***p*-Tolyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside (7).** A mixture of **5** (350 mg , 0.75 mmol), triethyl orthoacetate (0.3 mL , 1.88 mmol), and a catalytic amount of 10-camphorsulfonic acid was stirred at 25 ^{0}C until the mixture became homogeneous (~ 20 min). TLC (10:1 toluene-EtOAc) showed the absence of the starting material. The solvents were removed at 30 ^{0}C under reduced pressure. A solution of the intermediate, **6**, in CH_3CN was cooled in an ice bath and aq 50% CF_3COOH (0.5 mL) was added. After 5 min when a single spot was observed on TLC (10:1 toluene-EtOAc), the solution was concentrated under reduced pressure. The syrupy product thus obtained was chromatographed with 6:1 toluene-EtOAc to give 7 (350 mg, 91%): $[\alpha]_D$ -27.4^0 (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.48-7.04 (m, 14H, aromatic protons), 4.96 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 2.30 (s, 3H, $SC_6H_4CH_3$), 2.06 (s, 3H, OAc).

Anal. Calcd for $C_{29}H_{32}O_6S$: C, 68.47; H, 6.34. Found : C, 68.60; H, 6.25.

***p*-Tolyl *O*-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside (9).** A mixture of ethyl thioglycoside donor, **8**[6] (0.145 g, 0.3 mmol), *p*-tolyl thioglycoside acceptor, 7 (100 mg, 0.2 mmol) and 4A molecular sieve in CH_2Cl_2 was stirred for 6 h at 25 ^{0}C. The mixture was then cooled to 0 ^{0}C and *N*-iodosuccinimide (50 mg, 0.22 mmol) and trifluoromethanesulfonic acid (9 μL, 0.1 mmol) were added. Stirring was continued for 45 min at 0 ^{0}C. The solution was then diluted with CH_2Cl_2, filtered and washed successively with M Na_2CO_3, M $Na_2S_2O_3$ and water respectively. The organic layer was dried (Na_2SO_4) and concentrated to a syrup. Column chromatography with 8:1 toluene-EtOAc gave **9** (122 mg, 66%) as a syrup: $[\alpha]_D$

-25.9^0 (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.46-7.04 (m, 29H, aromatic protons), 5.34 (d, 1H, $J_{1',2'}$ = 2.0 Hz, H-1'), 5.32 (d, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 4.94 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 2.30 (s, 3H, $SC_6H_4CH_3$), 2.04 (s, 3H, OAc), 1.14 (d, 3H, $J_{5',6'}$ = 6.0 Hz, H-6'); ^{13}C NMR ($CDCl_3$) δ 170.4 ($COCH_3$), 138.7-127.0 (aromatic carbons), 99.2 (C-1'), 88.5 (C-1), 79.0, 78.3, 77.9, 77.5, 76.4, 75.8, 75.2, 74.7, 73.5, 73.1, 72.5, 70.4, 68.5, 67.2 (C-6), 21.0 ($COCH_3$), 20.8 ($SC_6H_4CH_3$), 16.6 (C-6').

Anal. Calcd for $C_{56}H_{60}O_{10}S$: C, 72.70; H, 6.53. Found: C, 72.52; H, 6.60.

Methyl 2-*O*-Benzoyl-3,4-*O*-isopropylidene-α-D-galactopyranoside(12). A solution of methyl 2-*O*-benzoyl-3,4-*O*-isopropylidene-6-*O*-trityl-α-D-galactopyranoside (**11**) (1g, 1.72 mmol), prepared from methyl 3,4-*O*-isopropylidene-6-*O*-trityl-α-D-galacto-pyranoside (**10**)[13] in EtOH (15 mL) was stirred with 10% Pd-C (350 mg) under hydrogen at 24 ^{0}C for 2 days, then filtered through Celite and concentrated under reduced pressure. Column chromatography with 4:1 toluene-EtOAc gave **12** (480 mg, 82.4%).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found : C, 60.20; H, 6.65.

Methyl (*t*-Butyl 2-*O*-benzoyl-3,4-*O*-isopropylidene-α-D-galactopyranosyl-uronate) (13). A mixture of chromium(VI) oxide (425 mg, 4.25 mmol) and pyridine (0.7 mL, 8.5 mmol) in CH_2Cl_2-DMF (4:1) (12 mL) was stirred in a flask for 15 min at 25 ^{0}C. Compound **12** (360 mg, 1.06 mmol) in CH_2Cl_2-DMF (4:1) (2.5 mL) was then introduced into the flask followed by the addition of acetic anhydride (0.8 mL, 8.4 mmol) and *tert*-butyl alcohol (2.0 mL, 21.3 mmol) and the mixture was stirred for 10 h at 25 ^{0}C. Ethanol (2 mL) was then added and stirring was continued for an additional period of 30 min. The mixture was then diluted with EtOAc and filtered through Celite. The filtrate was concentrated under reduced pressure to a syrup. Column chromatography of the product with 4:1 toluene-EtOAc gave pure **13** (325 mg, 75%): $[\alpha]_D$ + 80.37^0 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.03-7.40 (m, 5H, aromatic protons), 5.03 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 3.40 (s, 3H, OCH_3), 1.53 [s, 9H, $COO(CH_3)_3$], 1.53 and 1.26 [2s, 6H, $C(CH_3)_2$].

Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found : C, 61.70; H, 6.85.

Methyl (*t*-Butyl 4-*O*-acetyl-2-*O*-benzoyl-α-D-galactopyranosyluronate) (16). Treatment of **13** (235 mg, 0.58 mmol) with 1:1 MeOH-EtOAc (5 mL) and *p*-TsOH (85 mg) as described for the preparation of **5** , gave methyl (*t*-butyl 2-*O*-benzoyl-

α-D-galactopyranosyluronate) (**14**) (165 mg, 78.3%). Treatment of **14** with triethyl orthoacetate followed by opening of the resulting orthoester **15** with 50% aq CF_3COOH as described for the preparation of **7** gave **16** as amorphous solid (155 mg, 84.3%): $[\alpha]_D$ + 92.4^0 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.03-7.46 (m, 5H, aromatic protons), 5.16 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 3.43 (s, 3H, OCH_3), 1.45 [s, 9H, $COO(CH_3)_3$].

Anal. Calcd for $C_{20}H_{26}O_9$: C, 58.52; H, 6.38. Found : C, 58.60; H, 6.25.

Methyl *O*-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)-*O*-(4-*O*-acetyl-2,6-di-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-(*t*-butyl 4-*O*-acetyl-2-*O*-benzoyl-α-D-galacto-pyranosyluronate) (17). A mixture of *p*-tolyl thioglycoside **9** (194 mg, 0.21 mmol), **16** (70 mg, 0.17 mmol) and 4A molecular sieve (0.5 g) in 14:1 Et_2O-CH_2Cl_2 (2 mL) was stirred for 6 h at 25 ^{0}C. Methyl triflate (95 μL, 0.83 mmol) was then added and the mixture was stirred for 12 h. The reaction was quenched with Et_3N, filtered through Celite and the filtrate was concentrated to a syrup. Column chromatography with 8:1 toluene-EtOAc gave **17** as syrup (160 mg, 77%): $[\alpha]_D$ + 49.8^0 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.07-7.24 (m, 30H, aromatic protons), 5.27 (d, 1H, $J_{1'',2''}$ = 3.5 Hz, H-1''), 4.90 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1'), 4.78 (d, 1H, $J_{1,2}$ = 3.0 Hz, H-1), 3.40 (s, 3H, OCH_3), 2.06 and 1.96 (2s, 6H, 2OAc), 1.46 [s, 9H, $COO(CH_3)_3$].

Anal. Calcd for $C_{69}H_{78}O_{19}$: C, 68.41; H, 6.49. Found : C, 68.35; H, 6.55.

Methyl *O*-(α-L-Fucopyranosyl)-(1→3)-*O*-(α-D-galactopyranosyl)-(1→3)-(methyl α-D-galactopyranosyluronate) (19). A solution of **17** (160 mg, 0.132 mmol) in glacial acetic acid (5 mL) was stirred with 10% Pd-C (150 mg) under hydrogen at 24 ^{0}C for 2 days, then filtered through Celite and concentrated under reduced pressure. The product (**18**) was debenzoylated with 0.1 M NaOMe according to Zemplén[18]. The residue was purified by column chromatography using 3:2 $CHCl_3$-MeOH to give **19** (45 mg, 64.2%): $[\alpha]_D$ + 61.2^0 (*c* 2.4, MeOH); ^1H NMR (D_2O) δ 5.06 (d, 1H, $J_{1'',2''}$ = 2.0 Hz, H-1''), 5.04 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 4.82 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 3.70 (s, 3H, $COOCH_3$), 3.30 (s, 3H, OCH_3), 1.09 (d, 1H, $J_{5'',6''}$ = 7.0 Hz, H-6''); ^{13}C NMR (D_2O, internal standard dioxane) δ 171.7 (*C*$OOCH_3$), 101.4 (C-1''), 100.2 (C-1'), 95.7 (C-1), 78.0, 74.0, 72.4, 71.5, 70.9, 70.1, 69.9, 68.4, 68.0, 67.7, 67.0, 66.6, 61.5 (C-6'), 56.2 ($COOCH_3$), 53.5 (OCH_3), 15.9 (C-6'').

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