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Note

Synthesis of an L-quinovose-containing disaccharide

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Abstract

The synthesis of a versatile L-rhamnose monosaccharide synthon is described. This synthon is used in the synthesis of a disaccharide containing the rare sugar, 6-deoxy-L-glucose, linked to the 3-*C*-hydroxymethyl group of methyl 2,3-*O*-isopropylidene 3-*C*-(hydroxymethyl)-β-D-erythrofuranoside.

Keywords: L-Quinovose; 6-Deoxy-L-glucose; Rhamnosyl ulose; Apiose; 3-*C*-(hydroxymethyl)-β-D-erythrofuranose

Rhamnogalacturonan II is a complex oligosaccharide containing many unusual structural elements and rare monosaccharides.[1,2] One of the more complex structural elements is a fully substituted rhamnose monosaccharide, β-linked to 3-*C*-(hydroxymethyl)-β-D-erythrofuranose (β-D-apiose) (see Fig. 1), which is part of a side-chain structure of rhamnogalacturonan II. We have recently been directing our efforts at synthesizing this disaccharide, suitably protected for further elaboration into highly branched oligosaccharides. Efficient synthesis of this β-linked rhamnose disaccharide is very difficult, and we have tried various approaches to this problem. One approach we tried was the use of the ulosyl thioglycoside **7** as a glycosyl donor[3] together with the alcohol **8**[4] in dichloromethane. The resulting ulosyl disaccharide was then reduced, using sodium borohydride, to give the 2′-hydroxy disaccharide. The glycosylation reaction gave predominantly the unwanted α-linked product, which upon reduction of the carbonyl group at C-2′, gave the disaccharide **9** with an L-gluco configuration.

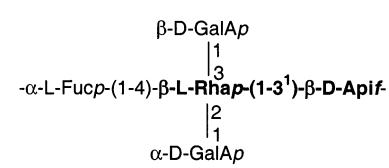

Fig. 1. Partial structure of one of the branched side chains found within the structure of rhamnogalacturonan II.

In separate experiments, the glycosylation reaction was also carried out using diethyl ether as the solvent; in addition, various reducing agents were used (sodium borohydride, L-selectride, LS-selectride and N-selectride). Similar results were obtained in all cases, with the major product having the α-gluco configuration, and about 10% of the reaction mixture contained a 1:1 mixture of co-eluting products that were determined to be the disaccharides

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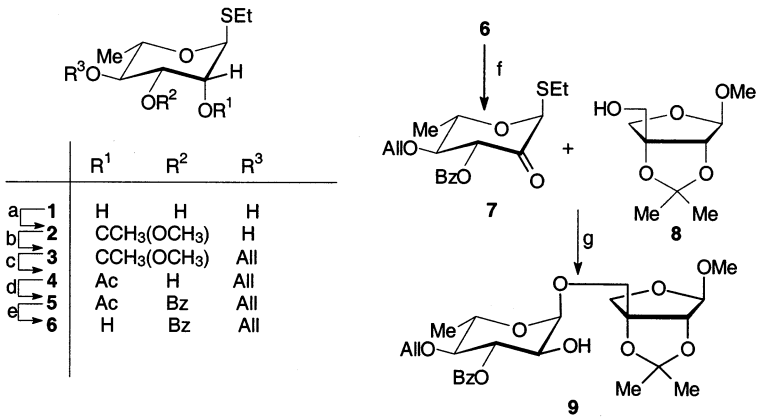

Scheme 1. (a) $CH_3C(OMe)_3$, PTSA, in DMF; (b) allyl bromide, NaH, in DMF; (c) 80% aq HOAc; (d) BzCl in pyridine; (e) HCl–MeOH; (f) pyridinium chlorochromate, CH_2Cl_2; (g) (i) triflic acid, *N*-iodosuccinimide in CH_2Cl_2 (ii) $NaBH_4$ in CH_2Cl_2–MeOH.

having the β-gluco and β-rhamno configurations. These results indicate that under the conditions that were used, the α-glycosidic bond was preferentially formed. We are continuing to work on this particular glycosylation, varying the nature of the rhamnosyl donor, in order to efficiently prepare the β-rhamnosyl linkage.

Although the desired β-rhamno linkage was not formed, this result is interesting in that it provides a route to introducing the rare monosaccharide 6-deoxy-L-glucose (L-quinovose) into an oligosaccharide synthesis (we were able to find only one reference in the literature to naturally occurring L-quinovose).[5] Situations where this would be useful are structural studies of oligosaccharides where structural modifications are introduced in order to elucidate the biological function of oligosaccharides. α-L-Quinovose could serve as a useful substitute for α-L-fucose or α-L-rhamnose.

Although we have previously cited the use of **5** in the literature,[6] its preparation was not published; in this work we wish to report the details of the synthesis of this useful synthon. Compound **5** was prepared in a series of reactions using the ethyl thioglycoside **1**[7] as a starting material. The orthoester of ethyl thioglycoside **1** was formed by treatment with trimethyl orthoacetate in *N*,*N*-dimethylformamide (DMF) and a catalytic amount of *p*-toluenesulfonic acid. The 4-hydroxyl group of the resulting orthoester **2** was then protected with an allyl group by treatment with allyl bromide in DMF to give **3**. Opening of the orthoester was achieved by treatment with 80% aq acetic acid to give the 2-*O*-acetyl derivative **4**. The free hydroxyl group of **4** was then benzoylated to give **5**. Compound **5** is a highly versatile synthon with hydroxyl groups at the 2-, 3- and 4-positions protected such that it allows for a variety of deprotection senarios following glycosylation. In addition, compound **5** can be prepared with a minimum of chromatography allowing for relatively easy scale-up (Scheme 1).

Removal of the acetyl group of **5** was achieved using methanolic HCl to give **6**.[8] The ^{1}H NMR spectrum of **6** showed that the signal for H-2 of the rhamnosyl residue had shifted to 4.28 ppm, from 5.45 ppm for compound **5**, consistent with deacetylation of the 2-position.

The resulting alcohol **6** was oxidized using pyridinium chlorochromate[9] to give the ulosyl derivative **7**. The ^{1}H NMR spectrum for **7** showed the loss of the signal for H-2 and the collapse of the signal for H-1 to a singlet, and the ^{13}C NMR showed a signal at 194.5 ppm that was attributed to the carbonyl carbon at C-2. These data are consistent with the oxidation of **6** to **7**.

Disaccharide **9** was synthesized by reaction of **7** with **8**[4] in dichloromethane using *N*-iodosuccinimide as a glycosylation promoter, with a catalytic amount of triflic acid. The unpurified product of this reaction was reduced using sodium borohydride to give **9** as the main product. The ^{1}H NMR signal for H-3′ of **9** had a $J_{3',2'}$ coupling constant of about 9.5

Hz consistent with an equatorial orientation of the hydroxyl at C-2′, indicating that the non-reducing monosaccharide had the gluco configuration. The one-bond $^{13}C-^{1}H$ coupling constant ($^{1}J_{^{13}C-^{1}H}$) for C-1′, measured from a ^{1}H-detected $^{13}C-^{1}H$ correlation spectrum of **9**, was found to be 172.8 Hz, a value characteristic of α-glycosidic linkages.[10]

1. Experimental

General methods.—^{1}H and ^{13}C NMR spectra were compiled with a Bruker AMX 300 spectrometer. All samples used $CDCl_3$ as a solvent with tetramethylsilane as an internal reference. Optical rotations were measured on an Autopol III polarimeter. Thin-layer chromatography (TLC) utilized Silica Gel-60 F_{254} (E. Merck), with detection by UV light and by charring with 5% sulfuric acid in EtOH. Medium-pressure column chromatography was performed with silica gel (E. Merck, 230–400 mesh).

Ethyl 2-O-acetyl-4-O-allyl-3-O-benzoyl-1-thio-α-L-rhamnopyranoside (**5**).—A sample of ethyl-1-thio-α-L-rhamnopyranoside (**1**)[7] (2.602 g, 12.50 mmol) was dissolved in *N*,*N*-dimethylformamide (52 mL) containing trimethyl orthoacetate (2.70 mL, 21.2 mmol). *p*-Toluenesulfonic acid (52 mg, 0.27 mmol) was added, and the mixture was placed under partial vacuum on a rotatory evaporator and heated to 50 °C. After 15 min triethylamine (0.40 mL) was added, and the solution was concentrated to a syrup. The syrup was dissolved in CH_2Cl_2 and washed with satd aq $NaHCO_3$ and water. The organic phase was dried and concentrated to give crude **2** as a syrup. The sample of crude **2** was dissolved in *N*,*N*-dimethylformamide (50 mL) and cooled to 0 °C under nitrogen, followed by the addition of NaH (2.11 g, 0.0703 mol, 80% dispersion in oil). After 15 min allyl bromide (4.60 mL, 52.8 mmol) was added. After 10 min the reaction was complete, and excess NaH was quenched by the addition of MeOH. The reaction mixture was evaporated to a syrup, which was then dissolved in CH_2Cl_2 and washed with water. The organic phase was dried and concentrated to give crude **3** as a syrup. Crude **3** was dissolved in 80% aq AcOH (100 mL) and stirred at rt for 30 min. The solution was then evaporated to dryness, and the residue was co-evaporated with EtOH (3 × 25 mL) to remove traces of AcOH. The resulting syrup **4** was then dissolved in pyridine (40 mL), and BzCl (4.15 mL, 35.8 mmol) was added. After 30 min the mixture was filtered through Celite, and the filtrate was evaporated to dryness. The syrupy residue was dissolved in CH_2Cl_2 and washed successively with satd aq $NaHCO_3$ and water. The organic phase was dried and evaporated to dryness to give **5** as a syrup. Crystallization from hexane gave pure **5** (2.455 g, 49.80%). The mother liquor was then purified by chromatography using silica gel (6:1 hexane–ethyl acetate) giving an additional sample of **5** (0.987 g, 20.0%); total yield 69.8%: mp 92.5–92.7 °C; $[\alpha]_D^{25}$ −77.2° (*c* 1.06, $CHCl_3$); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.00 (m, 2 H, aromatic), 7.58 (m, 1 H, aromatic), 7.45 (m, 2 H, aromatic), 5.80 (m, 1 H, $OCH_2CH{=}CH_2$), 5.48–5.43 (m, 2 H, H-2 and H-3), 5.22 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 5.07–5.21 (m, 2 H, $OCH_2CH{=}CH_2$), 4.22 (dq, 1 H, $J_{5,4}$ 9.3 Hz, H-5), 4.16 (m, 2 H, $OCH_2CH{=}CH_2$), 3.58 (m, 1 H, H-4), 2.65 (m, 2 H, SCH_2CH_3), 2.12 (s, 3 H, $OCOCH_3$) 1.39 (d, 3 H, $J_{6,5}$ 6.2 Hz, H_3-6), 1.31 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR (75.03 MHz, $CDCl_3$): δ 170.1 (*C*=O acetate), 165.4 (*C*=O benzoate), 134.7 ($CH_2CH{=}CH_2$), 133.4 (para aromatic), 130.1 (ipso aromatic), 129.8 (ortho aromatic), 128.7 (meta aromatic), 117.4 ($CH_2CH{=}CH_2$), 82.2 (C-1), 79.1 (C-4), 74.1 ($CH_2CH{=}CH_2$), 72.6, 72.5 (C-2,3), 68.6 (C-5), 25.7 (SCH_2CH_3), 21.1 ($OCOCH_3$), 18.1 (C-6), 15.1 (SCH_2CH_3). Anal. Calcd for $C_{20}H_{26}O_6S$: C, 60.89; H, 6.64. Found: C, 60.87; H, 6.64.

Ethyl 4-O-allyl-3-O-benzoyl-1-thio-α-L-rhamnopyranoside (**6**).—A sample of ethyl 2-*O*-acetyl-4-*O*-allyl-3-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**5**) (4.080 g, 10.34 mmol) was dissolved in 45 mL of methanolic HCl (prepared by dissolving 35 mL of acetyl chloride in 65 mL of MeOH). The solution was left stirring at rt for 8 h and then neutralized by adding solid $NaHCO_3$. The solution was filtered and evaporated to dryness. The residue was taken up in CH_2Cl_2 and washed with H_2O. The organic layer was dried over

Na_2SO_4, and the filtrate was evaporated to dryness. The crude syrup was purified by chromatography using silica gel (4:1 hexane–ethyl acetate) to give **6** (2.63 g, 72.2%); $[\alpha]_D^{25}$ −119° (*c* 0.789, $CHCl_3$); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.11 (m, 2 H, aromatic), 7.59 (m, 1 H, aromatic), 7.46 (m, 2 H, aromatic), 5.79 (m, 1 H, $OCH_2CH{=}CH_2$), 5.36 (dd, 1 H, $J_{3,4}$ 9.0, $J_{3,2}$ 3.0 Hz, H-3), 5.24 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 5.17, 5.07 (2m, 2 H, $OCH_2CH{=}CH_2$), 4.28 (br. m, H-2), 4.21 (dq, 1 H, $J_{5,4}$ 9.2 Hz, H-5), 4.15 (m, 1 H, $OCH_2CH{=}CH_2$), 3.63 (dd, $J_{3,4}+J_{4,5}$ 19.5 Hz, H-4), 2.73–2.54 (m, 2 H, SCH_2CH_3), 2.47 (br. s, 1 H, 2-OH), 1.37 (d, 3 H, $J_{6,5}$ 6.3 Hz, H_3-6), 1.30 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR (75.03 MHz, $CDCl_3$): δ 165.6 (*C*=O benzoate), 134.7 ($CH_2CH{=}CH_2$), 133.5 (para aromatic), 130.0 (ipso aromatic), 129.9 (ortho aromatic), 128.7 (meta aromatic), 117.5 ($CH_2CH{=}CH_2$), 84.1 (C-1), 78.9 (C-4), 75.2 (C-2), 74.1 ($CH_2CH{=}CH_2$), 71.4 (C-3), 68.4 (C-5), 25.3 (SCH_2CH_3), 18.1 (C-6), 15.1 (SCH_2CH_3). Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86; S, 9.10. Found: C, 61.31; H, 7.02; S, 8.73.

*Ethyl 4-*O*-allyl-3-benzoyl-1-thio-α-*L*-rhamnopyranosid-2-ulose* (**7**).—A sample of ethyl 4-*O*-allyl-3-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**6**) (0.8926 g, 2.533 mmol) was dissolved in CH_2Cl_2 (40.0 mL). Pyridinium chlorochromate (1.703 g, 7.899 mmol) was added to this solution, and the mixture was refluxed for 2.5 h. The reaction mixture was cooled and concentrated to a volume of about 10 mL. Silica gel (approx. 10 g) was added to the dark concentrate, and the mixture was placed on a rotary evaporator and evaporated to dryness. The silica gel mixture was loaded onto a silica gel column, and the mixture was purified by chromatography using 4:1 hexane–ethyl acetate as eluant. Compound **7** was obtained as a syrup (0.552 g, 62.2%); $[\alpha]_D^{25}$ −223° (*c* 2.34, $CHCl_3$); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.11 (m, 2 H, aromatic), 7.62 (m, 1 H, aromatic), 7.48 (m, 2 H, aromatic), 5.89–5.75 (m, 2 H, $OCH_2CH{=}CH_2$, H-3), 5.33 (s, 1 H, H-1), 5.26–5.11 (m, 2 H, $OCH_2CH{=}CH_2$), 4.48 (dq, 1 H, $J_{5,4}$ 9.5 Hz, H-5), 4.28–4.12 (m, 2 H, $OCH_2CH{=}CH_2$), 3.61 (dd, $J_{3,4}+J_{4,5}$ 19.2 Hz, H-4), 2.84–2.65 (m, 2 H, SCH_2CH_3), 1.44 (d, 3 H, $J_{6,5}$ 6.2 Hz, H_3-6), 1.34 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR (75.03 MHz, $CDCl_3$): δ 194.5 (C=O, C-2), 165.7 (*C*=O benzoate), 134.2 ($CH_2CH{=}CH_2$), 133.7 (para aromatic), 130.1 (ortho aromatic), 129.6 (ipso aromatic), 128.7 (meta aromatic), 118.1 ($CH_2CH{=}CH_2$), 85.8 (C-1), 82.5 (C-4), 78.4 (C-3), 74.0 ($CH_2CH{=}CH_2$), 69.0 (C-5), 26.3 (SCH_2CH_3), 17.8 (C-6), 15.2 (SCH_2CH_3). Anal. Calcd for $C_{18}H_{22}O_5S$: C, 61.69; H, 6.33; S, 9.15. Found: C, 61.73; H, 6.42; S, 8.78.

*Methyl 4-*O*-allyl-3-*O*-benzoyl-α-*L*-quinovopyranosyl-(1→3^1)-2,3-*O*-isopropylidene-3-*C*-(hydroxymethyl)-α-*D*-erythrofuranoside* (**9**).—A sample of ethyl 4-*O*-allyl-3-benzoyl-1-thio-α-L-rhamnopyranosid-2-ulose (**7**) (0.138 g, 0.394 mmol) was dissolved in CH_2Cl_2 (3.0 mL) followed by the addition of *N*-iodosuccinimide (0.0920 g, 0.409 mmol) and crushed 3 Å molecular sieves. To this solution a sample of methyl 2,3-*O*-isopropylidene-3-*C*-(hydroxymethyl)-α-D-erythrofuranoside (**8**)[4] (0.0389 g, 0.190 mmol) in CH_2Cl_2 (3.0 mL) was added, followed by the addition of triflic acid (15 μL of 10% triflic acid in diethyl ether). The reaction mixture was stirred at rt under an atmosphere of N_2. After 45 min triethylamine was added until the dark-colored solution turned yellow. The reaction mixture was filtered, and the filtrate was washed successively with satd aq $NaHCO_3$ and 10% $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The syrupy residue was taken up in 1:1 MeOH–CH_2Cl_2 (3.0 mL) and $NaBH_4$ (71 mg, 1.9 mmol) was added. After 10 min the reaction mixture was washed with aq HCl (1.0 M), dried over Na_2SO_4, and evaporated to dryness. The syrupy residue was purified by chromatography using 4:1 hexane–ethyl acetate as eluant. Compound **9** was obtained as a syrup (0.0425 g, 45.3%); $[\alpha]_D^{25}$ −108° (*c* 1.32, $CHCl_3$); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.09 (m, 2 H, aromatic), 7.58 (m, 1 H, aromatic), 7.46 (m, 2 H, aromatic), 5.73 (m, 1 H, $OCH_2CH{=}CH_2$), 5.41 (dd, 1 H, $J_{3',2'}+J_{3',4'}$ 18.9 Hz, H-3′), 5.11, 5.04 (2m, 2 H, $OCH_2CH{=}CH_2$), 4.96 (s, 1 H, H-1), 4.91 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.46 (s, 1 H, H-2), 4.11–4.07 (m, 2 H, $OCH_2CH{=}CH_2$), 4.07, 3.96 (2d, 2 H, $J_{4a,4b}$ 9.7 Hz, H-4_a, H-4_b), 4.01, 3.57 (2d, 2 H, $J_{5a,5b}$ 9.7 Hz, H-5_a, H-5_b), 3.84 (dq, 1

H, $J_{5',4'}$ 9.7 Hz, H-5′), 3.67 (br. m, 1 H, H-2′), 3.43 (s, 3 H, OCH_3), 3.21 (dd, 1 H, $J_{4',3'} + J_{4',5'}$ 18.6 Hz, H-4′), 1.50, 1.38 (2s, 6 H, C(CH_3)$_2$), 1.33 (d, 3 H, $J_{6',5'}$ 6.2 Hz, H_3-6′); ^{13}C NMR (75.03 MHz, $CDCl_3$): δ 166.4 (*C*=O benzoate), 134.5 ($CH_2CH{=}CH_2$), 133.2 (para aromatic), 130.4 (ipso aromatic), 129.9 (ortho aromatic), 128.6 (meta aromatic), 117.7 ($CH_2CH{=}CH_2$), 113.5 ($C(CH_3)_2$), 108.2 ($^1J_{^{13}C-^1H}$ 172.1 C-1), 100.3 ($^1J_{^{13}C-^1H}$ 172.8 C-1′), 90.1 (C-2), 87.9 (C-3), 81.4 (C-4′), 76.3 (C-3′), 74.1 ($CH_2CH{=}CH_2$, C-4), 72.0 (C-2), 69.6 (C-5), 67.6 (C-5′), 54.8 (OCH_3), 27.6, 25.5 (C(CH_3)$_2$), 18.0 (C-6′). Anal. Calcd for $C_{25}H_{34}O_{10}$: C, 60.72; H, 6.93. Found: C, 60.43; H, 7.09.

Acknowledgements

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