Synthesis of Mono-*O*-tritylraffinoses and Deca-*O*-acetylraffinoses

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Starting from raffinose (**1**), its 6″-*O*-trityl (**2**) and 6′-*O*-trityl derivative (**6**) have been prepared. Acetylation of **2** and **6** gave deca-*O*-acetyl-6″-*O*-tritylraffinose (**3**) and deca-*O*-acetyl-6′-*O*-tritylraffinose (**7**) respectively. Detritylation of **3** gave two products: 1′,2,2″,3,3′,3″,4,4′,4″,6′-deca-*O*-acetylraffinose (**4**) as a main product and 1′,2,2″,3,3′,3″,4,4′,6′,6″-deca-*O*-acetylraffinose (**5**) as a minor product, which were successfully separated by a column chromatography. On the other hand, detritylation of **7** gave 1′,2,2″,3,3′,3″,4,4′,4″,6″-deca-*O*-acetylraffinose (**8**) as a sole product. Their structures were established by NMR spectra, together with a chemical evidence.

Tri-*O*-tritylraffinose has been described by Josephson[1] in 1929, but mono-*O*-tritylraffinose has never been described in a literature. In connection with our previous studies on sucrochemistry,[2-6] mono-*O*-trityl derivatives of raffinose have been prepared in our laboratory. By acetylation and subsequent detritylation, mono-*O*-tritylraffinose was readily converted to deca-*O*-acetylraffinose, which is an attractive key compound for a synthesis of a tetrasaccharide. For instance, a naturally occurring tetrasaccharide: stachyose will be prepared from 1′,2,2″,3,3′,3″,4,4′,4″,6′-deca-*O*-acetylraffinose (**4**), since α-D-galactopyranosyl group is linked to the 6″-*OH* of raffinose in this tetrasaccharide.

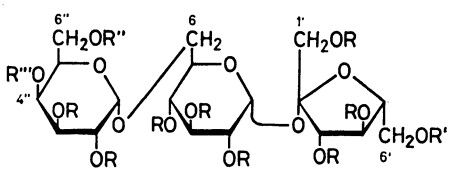
Results and Discussion

A reaction between raffinose (**1**) and trityl chloride in pyridine afforded a mixture of mono-, di-, and tri-*O*-tritylraffinoses. The di- and tri-*O*-tritylraffinoses are considerably less soluble in cold water, compared to the mono-*O*-tritylraffinoses. The mono-*O*-tritylraffinoses were able to be separated from the others by means of this solubility difference in an aqueous solution. The mono-*O*-tritylraffinoses thus obtained consisted of two components of 6″-*O*-trityl (**2**) and 6′-*O*-tritylraffinose (**6**). After acetylating, the intact mixture of **2** and **6** revealed two peaks in a ratio of 4: 1 on a high performance liquid chromatogram. The major component was assumed to be deca-*O*-acetyl-6″-*O*-tritylraffinose (**3**) and the minor component was assumed to be deca-*O*-acetyl-6′-*O*-tritylraffinose (**7**), since in the case of sucrose,[7] the hydroxyl group on C-6 of the D-glucopyranosyl moiety is most reactive and the hydroxyl group on C-1′ of the D-fructofuranosyl moiety is least reactive among the three primary hydroxyl groups against tritylation.

Compounds **2** and **6** were successfully separated by a column chromatography, and subsequently acetylated to give **3** and **7** respectively.

The assumed structure of **3** was confirmed by the following evidence. The ^{1}H NMR spectrum of **3** revealed the signals of the two methylene groups (4 protons) in a region between δ 2.9 and 3.9. These signals were regarded as two AB parts of ABM-systems, and each of them consisted of eight-line-signals. The signal pattern in a lower field was almost superposable on the signal pattern of the bridge methylene protons (C-6) of raffinose undecaacetate (**9**). The signal pattern in a higher field was coincident in the chemical shifts and coupling constants with that of the methylene protons of methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-α-D-galactopyranoside (**10**). Therefore, the signal pattern was attributable to the methylene protons on C-6″ of **3**, on which the trityloxyl group was attached (Fig. 1).

The structure of **7** was deduced from carbon-13 nuclear magnetic resonance (^{13}C NMR) spectrum of its detritylation product. That is, detritylation of **7** with



1: R=R′=R″=R‴=H **2**: R=R′=R‴=H,R″=Tr
3: R=R′=R‴=Ac,R″=Tr **4**: R=R′=R‴=Ac,R″=H
5: R=R′=R″=Ac,R‴=H **6**: R=R″=R‴=H,R′=Tr
7: R=R″=R‴=Ac,R′=Tr **8**: R=R″=R‴=Ac, R′=H **9**: R=R′=R″=R‴=Ac

Ac: $COCH_3$, Tr: $C(C_6H_5)_3$

Scheme 1.

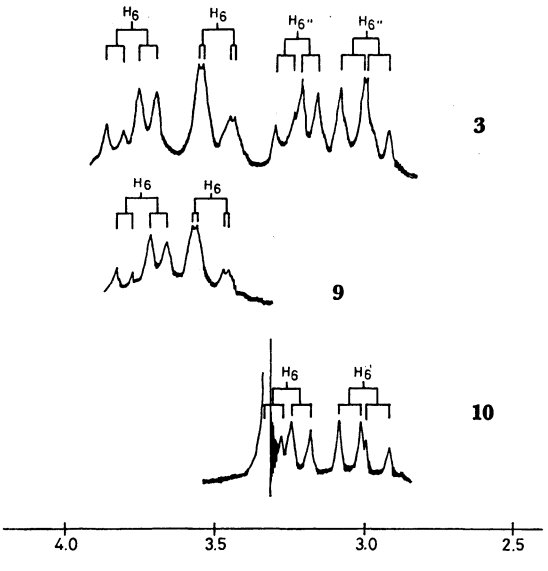


Fig. 1. ^{1}H NMR signals of *O*-methylene groups of **3**, **9**, and **10**.

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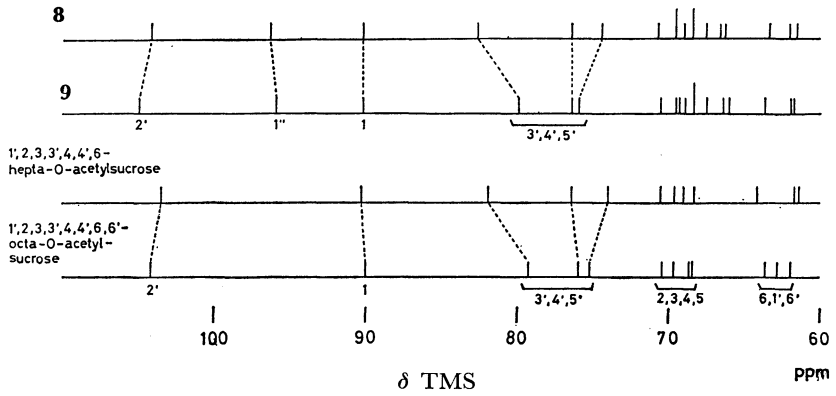
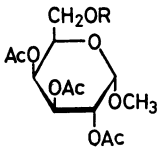


Fig. 2. Correlation map of ^{13}C NMR spectra of **8**, **9**, 1,2,3,3',4,4',6-hepta-*O*-acetylsucrose,[8] and 1',2,3,4,4',6,6'-octa-*O*-acetylsucrose.[12]

hydrogen bromide in glacial acetic acid gave 1',2,2'',3,-3',3'',4,4',4'',6''-deca-*O*-acetylraffinose (**8**) as a sole product. ^{13}C NMR spectrum of **8** revealed the signals of the three methine carbons of C-3', 4' and 5' in the D-fructofuranosyl moiety in a region between 74 and 82 ppm, which were shifted remarkably from the signals of the corresponding three methine carbons of **9** and were almost the same as those revealed by these carbons of 1',2,3,3',4,4',6-hepta-*O*-acetylsucrose[8] (Fig. 2).

On the other hand, detritylation of **3** with hydrogen bromide in glacial acetic acid under ice cooling gave a mixture of two products. These products were separated by a column chromatography, and the major component was assumed to be 1',2,2'',3,3',3'',4,4',4'',6'-deca-*O*-acetylraffinose (**4**). The minor component was assumed to be 1',2,2'',3,3',3'',4,4',6',6''-deca-*O*-acetylraffinose (**5**).

To establish the structure of **4**, a deuteration technique for an individual acetyl group[9] was applied. When ^1H NMR spectrum of a deuterioacetyl derivative of **4** was compared with the spectrum of **9**, it was readily observed that an intensity of the signal (6 protons) at δ 2.05 in the spectrum of **9** was reduced to one half (3 protons) in the spectrum of the deuterioacetyl derivative. The missing half of the signal was attributed to the acetoxyl group on C-6'' of **9**, since the acetoxyl group on C-6 of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside[11] (**12**) revealed its signal at δ 2.04. Furthermore, this assignment of the signal of **12** was achieved by comparing the ^1H NMR spectrum of methyl 2,3,4-tri-*O*-acetyl-6-*O*-trideuterioacetyl-α-D-galactopyranoside (**11**) with that of **12**. Therefore, the structure of **4** was reasonably established.



10: R=Tr **11**: R=$COCD_3$ **12**: R=Ac
Ac: $COCH_3$, Tr: $C(C_6H_5)_3$

Scheme 2.

Meanwhile, **5** might be formed from **4** by an acetyl group migration from 4''-*OH* to 6''-*OH* during a course of the reaction, and this has been verified by the fact that detritylation of **3** in an aqueous acetic acid solution at elevated temperature yielded **5** as a main product.

Experimental

General Methods. Raffinose was purchased from a commercial source. Melting points were determined in capillary tubes and are uncorrected. Solutions were evaporated under diminished pressure below 40 °C. Optical rotations were measured on a Japan Spectroscopic DIP-SL polarimeter. ^1H NMR spectra were recorded on a Varian A-60D spectrometer at 60 MHz or a Varian XL-100 spectrometer at 100 MHz. ^{13}C NMR spectra were recorded by the Fourier transform technique on a Varian CFT-20 spectrometer at 20 MHz. In both spectra, deuteriochloroform was used as a solvent and tetramethylsilane was used as an internal standard, and the peak positions are given in δ values. A high performance liquid chromatogram was obtained on a Varian Model 8520 liquid chromatograph equipped with a MicroPak Si-10 column using dichloromethane as an eluting solvent. Acetylation was carried out with acetic anhydride in pyridine in the usual manner. TLC was performed on Wakogel B-10 (Wako Pure Chemical Co., Ltd.) plates, and silica gel (Wakogel C-300) was employed for a column chromatography. Elemental analyses were performed by Mr. Saburo Nakada.

6''-O-Tritylraffinose (2) and 6'-O-Tritylraffinose (6). After drying over phosphorous pentoxide at 50 °C for several days, raffinose (**1**, 7.45 g, 14.8 mmol) was treated with trityl chloride (7.00 g, 25.1 mmol) in dry pyridine (60 ml) for 64 h under mild stirring at ambient temperature. The reaction mixture was poured into ice cold water (1 l), and an insoluble matter was filtered off. The filtrate was evaporated to one tenth of the original volume to give 2.74 g of amorphous precipitates which were collected by filtration. The product consisted mainly of mono-*O*-tritylraffinoses. The product was fractionated on a column using 4: 9: 4: 1 (v/v) acetone–chloroform–methanol–water as an eluant, and each fraction was monitored on TLC in the same solvent system.

The fractions which showed a single spot at R_f 0.40 were combined and evaporated. The residue was recrystallized from ethanol to give 1.04 g (9.4%) of **2**, mp 221—222 °C, $[\alpha]_D^{21}$ +70.9° (*c* 1.03, pyridine).

Found: C, 59.66; H, 6.17%. Calcd for $C_{37}H_{46}O_{16}$: C, 59.51; H, 6.21%.

The fractions having a single spot at R_f 0.31 were combined

and evaporated to give 0.19 g (1.7%) of **6** as a glassy solid, $[\alpha]_D^{21}$ +88° (*c* 0.5, pyridine).

*1′2,2,″3′,3″,4′,4″,6′,-Deca-*O*-acetyl-6″-*O*-tritylraffinose (3).* Compound **2** (1.04 g) was acetylated, and the product was recrystallized from isopropyl alcohol to give 1.07 g (66%) of **3**, mp 96—98 °C, $[\alpha]_D^{22}$ +73.8° (*c* 0.84, chloroform). ^{1}H NMR: δ 1.87 (s, OAc), 1.95 (s, 3, OAc), 2.04 (s, 12, 4OAc), 2.09 (s, 6, 2OAc), 2.12 (s, 3, OAc), 2.15 (s, 3, OAc), 4.77 (dd, 1, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10.5 Hz, H-2), 5.72 (d, 1, H-1).

Found: C, 58.64; H, 5.80%. Calcd for $C_{57}H_{66}O_{26}$: C, 58.66; H, 5.70%.

*1′,2,2″,3,3′,3″,4,4′,4″,6″,-Deca-*O*-acetyl-6′-*O*-tritylraffinose (7).* Compound **6** (186 mg) was acetylated, and the product was recrystallized from isopropyl alcohol to give 187 mg (64%) of **7**, mp 96—97.5 °C, $[\alpha]_D^{23}$ +98.1° (*c* 1.05, chloroform). ^{1}H NMR: δ 1.78 (s, 3, OAc), 1.88 (s, 3, OAc), 1.96 (s, 3, OAc), 2.02 (s, 6, 2OAc), 2.04 (s, 3, OAc), 2.09 (s, 9, 3OAc), 2.14 (s, 3, OAc), 4.70 (dd, 1, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 10.5 Hz, H-2), 5.04 (dd, 1, $J_{3,4}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz, H-4), 4.65 (d, 1, H-1).

Found: C, 58.43; H, 5.75%. Calcd for $C_{57}H_{66}O_{26}$: C, 58.66; H, 5.70%.

Detritylation of 3. To a solution of **3** (1.12 g) in glacial acetic acid (10 ml), a 0.5 ml portion of glacial acetic acid saturated with hydrogen bromide was added under ice cooling with agitation. After two min, the mixture was quenched into ice cold water, and the solution was extracted with chloroform repeatedly. The chloroform solution was washed with sodium hydrogencarbonate solution and water. After drying over sodium sulfate, the solution was evaporated to give 1.05 g of a crude product, which showed two spots on TLC at R_f 0.54 (major component) and 0.50 (minor component) in 20: 1 (v/v) chloroform–ethanol with a ratio of approximately 4: 1.

The major component: 1′,2,2″,3,3′,3″,4,4′,4″,6′-deca-*O*-acetylraffinose (**4**, 110 mg, 12%) was obtained from the mixture by a column chromatography with 1: 5 (v/v) acetone–benzene as an eluant. The amorphous product of **4** had $[\alpha]_D^{23}$ +101.8° (*c* 0.56, chloroform). ^{1}H NMR: δ 1.97 (s, 3, OAc), 2.00 (s, 3, OAc), 2.05 (s, 3, OAc), 2.08 (s, 3, OAc), 2.10 (s, 6, 2OAc), 2.12 (s, 3, OAc), 4.80 (dd, 1, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10.5 Hz, H-2), 5.06 (dd, 1, $J_{1'',2''}$ 5.0 Hz, $J_{2'',3''}$ 10.5 Hz, H-2″), 5.10 (dd, 1, $J_{3,4}$ 10.0 Hz, $J_{4,5}$ 10.0 Hz, H-4), 5.24 (d, 1, H-1″), 5.26 (dd, 1, $J_{3'',4''}$ 4.5 or 3.5 Hz, $J_{4'',5''}$ 3.5 or 4.5 Hz, H-4″), 5.66 (d, 1, H-1).

Found: C, 49.31; H, 5.69%. Calcd for $C_{38}H_{52}O_{26}$: C, 49.35; H, 5.67%.

Compound **4** (45 mg) was acylated with acetic anhydride-d_6 in pyridine to give 46 mg of 1′,2,2″,3,3′,3″,4,,4′,4″,6′-deca-*O*-acetyl-6″-*O*-trideuterioacetylraffinose as a glassy solid, $[\alpha]_D^{20}$ +88.9° (*c* 2.07, chloroform). ^{1}H NMR: δ 1.955 (s, 3, OAc), 2.015 (s, 3, OAc), 2.055 (s, 3, OAc), 2.10 (s, 6, 2OAc), 2.105 (s, 3, OAc), 2.11 (s, 3, OAc), 2.12 (s, 3, OAc), 2.135 (s, 3, OAc), 2.175 (s, 3, OAc).

The minor component: 1′,2,2″,3,3′,3″,4,4′,6′,6″-deca-*O*-acetylraffinose (**5**, 100 mg, 11%) was obtained by the column chromatography as described above. The amorphous product of **5** had $[\alpha]_D^{21}$ +101.0° (c 1.00, chloroform). ^{1}H NMR: δ 2.02 (s, 3, OAc), 2.06 (s, 3, OAc), 2.075 (s, 3, OAc), 2.095 (s, 6, 2OAc), 2.12 (s, 9, 3OAc), 2.15 (s, 3, OAc), 2.18 (s, 3, OAc), 3.50 (dd, 1, $J_{6''a,6''b}$ 10.0 Hz, $J_{6''a,5''}$ 1.3 Hz, H-6″a), 3.75 (dd, 1, $J_{6''b,5''}$ 5.0 Hz, H-6″b), 4.78 (dd, 1, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10 Hz, H-2), 5.66 (d, 1, H-1).

Found: C, 49.08; H, 5.50%. Calcd for $C_{38}H_{52}O_{26}$: C, 49.35; H, 5.67%.

Besides **4** and **5**, a mixture of **4** and **5** (340 mg, 38%) was recovered from the column.

Detritylation of 3 in 98% Acetic Acid. Compound **3** (120 mg) was heated in 98% acetic acid (5 ml) on a boiling water bath. After 70 min, the solution was evaporated, and the residue was purified by a column chromatography with 1: 5 (v/v) acetone–benzene as an eluant to give 48 mg (51%) of **5** as a main product.

Detritylation of 7. Compound **7** (166 mg) was detritylated with hydrogen bromide in glacial acetic acid under ice cooling as described in the case of **5**, to give 159 mg of a crude product. The product was purified by a column chromatography with 1: 5 (v/v) acetone–benzene as an eluant. The fractions that showed a single spot at R_f 0.53 on TLC in 20: 1 (v/v) chloroform–ethanol were combined and evaporated to give 107 mg (81%) of 1′,2,2″,3,3′,3″,4,4′,-4″,6″-deca-*O*-acetylraffinose (**8**) as a glassy solid, $[\alpha]_D^{21}$ +101.0° (*c* 1.00, chloroform). ^{1}H NMR: δ 1.97 (s, 3, OAc), 2.02 (s, 3, OAc), 2.08 (s, 6, 2OAc), 2.13 (s, 15, 5OAc), 2.20 (s, 3, OAc), 4.79 (dd, 1, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10.5 Hz, H-2), 5.70 (d, 1, $J_{1,2}$ 3.5 Hz, H-1).

Found: C, 48.84; H, 5.49%. Calcd for $C_{38}H_{52}O_{26}$: C, 49.35; H, 5.67%.

*Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-trityl-α-*D*-galactopyranoside (10).* Methyl α-D-galactopyranoside[10] (1.6 g) was treated with trityl chloride (6.5 g) in pyridine for 47 h, and subsequently acetylated in the conventional method. The product was purified by a column chromatography with 1: 40 (v/v) acetone–benzene to give 3.6 g of a crude product. Recrystallization from ethanol gave 2.9 g (63%) of **10**, mp 179—180 °C, $[\alpha]_D^{25}$ +69.2° (*c* 1.71, chloroform).

Found: C, 68.39; H, 6.09%. Calcd for $C_{32}H_{34}O_9$: C, 68.31; H, 6.09%.

*Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-trideuterioacetyl-α-*D*-galactopyranoside (11).* Compound **10** (0.5 g) was detritylated with hydrogen bromide in glacial acetic acid under ice cooling analogously as described above and the product was purified by a column chromatography with 1: 5 (v/v) acetone–benzene to give 0.24 g (86%) of methyl 2,3,4-tri-*O*-acetyl-α-D-galactopyranoside as a glassy solid, $[\alpha]_D^{20}$ +56.8 °C (*c* 0.67, chloroform).

The product (60 mg) was acylated with acetic anhydride-d_6 in pyridine, and the product was purified by a column chromatography to give 62 mg (91%) of **11** as a glassy solid, $[\alpha]_D^{20}$ +130 °C (*c* 1.6 chloroform).

^{1}H NMR: δ 1.97 (s, 3, OAc), 2.07 (s, 3, OAc), 2.13 (s, 3, OAc), 3.40 (s, 3, OCH_3).

^{1}H NMR spectrum of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside (**12**) was determined by Rathbone and his coworkers[11] [δ 1.97 (s, 3, OAc), 2.035 (s, 3, OAc), 2.07 (s, 3, OAc), 2.13 (s, 3, OAc), 3.40 (s, 3, OCH_3)].

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