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The first total synthesis of telephiose A

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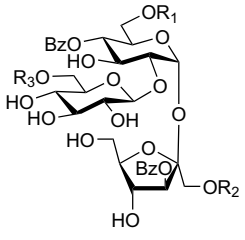
Abstract—The first total synthesis of telephiose A (**1**), a novel trisaccharide ester having two acetyl groups and two benzoyl groups, was achieved by using glucosyl donor **6** and disaccharide acceptor **12**. The crucial key step was the stereoselective construction of the β-D-glucosidic linkage featuring the neighboring group participation of the 2-*O*-*N*-phenylcarbamoyl group (of donor **6**), which can be selectively deprotected in the presence of acetyl and benzoyl groups. Donor **6** was prepared from D-glucose in eight steps (33% yield), whereas acceptor **12** was prepared from sucrose in six steps (35% yield). Precursors **6** and **12** were reacted in subsequent reactions (five steps) to afford **1** in 22% yield.

Three new oligosaccharide esters (telephiose A–C, Fig. 1) have been isolated from *Polygala telephioides WILLD*, a plant, that is, widely distributed in southern China and employed as a detoxification agent for heroin poisoning in China. The structures of the esters have been recently characterized using spectroscopic studies.[1] Due to our interest in the detoxification activities and the structures of these partially acylated oligosaccharide esters, we decided to undertake the total synthesis of telephiose A (**1**) via a key step in the stereoselective construction of the β-D-glucosidic linkage via neighboring group participation of 2-*O*-acyl type protecting group, which could be deprotected in the presence of acyl groups of the glucosyl donor.



Telephiose A (**1**) : $R_1 = R_2 = Ac$, $R_3 = H$
B : $R_1 = H$, $R_2 = R_3 = Ac$
C : $R_1 = R_2 = R_3 = H$

Figure 1. The structures of telephioses.

In a previous Letter,[2] we reported on the construction of four types of glycosidic linkages via a universal glucosyl donor that involves the neighboring group participation of an *N*-phenylcarbamoyl (Car) group and the S_N2 displacement reaction at *C*-2. The Car group is stable from pH 1 to 12 in aqueous solutions,[3] and because of the difficulty in the deprotection, the Car group has yet to be widely employed for the protection of hydroxyl groups. To the best of our knowledge, the Car protecting group has not been employed in the synthesis of complex natural products, which often require delicate chemical differentiation of various protecting groups under mild conditions. We have successfully developed a novel deprotection procedure that does not affect acyl, silyl, methoxymethyl, benzylidene acetal, and isopropylidene acetal protecting groups,[4] and therefore, has allowed the Car group to become a valuable tool in natural products syntheses.

Herein, we describe the practical synthesis of telephiose A (**1**) from D-glucose and D-sucrose featuring the properties of the Car group.

As shown in Scheme 1, glucosyl donor **6** was prepared from D-glucose in eight steps. Initially, phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**2**)[5] was prepared from D-glucose in four steps (61% yield). Treatment of **2** with methoxymethyl chloride (MOM–Cl,

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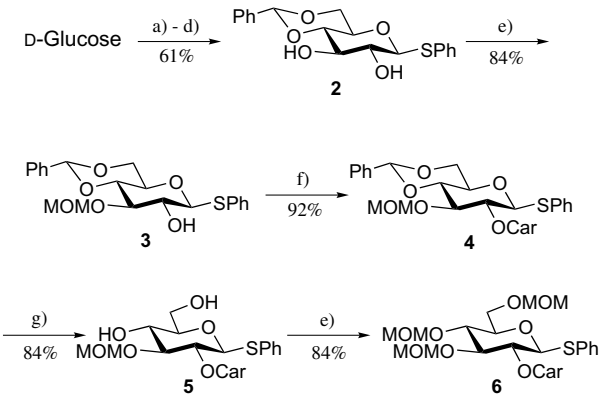
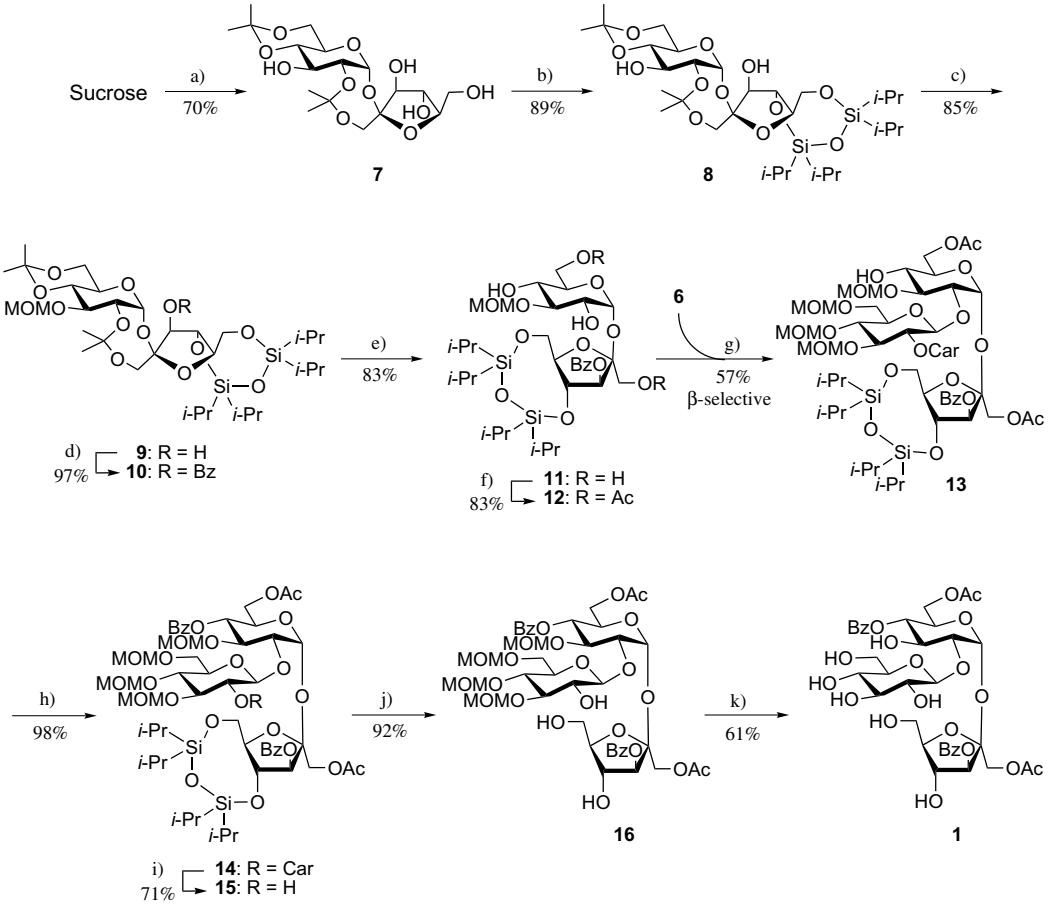


Scheme 1.[9] Reagents and conditions: (a) Ac_2O, AcONa; (b) PhSH, $BF_3{\cdot}Et_2O/(ClCH_2)_2$; (c) NaOMe/MeOH; (d) $PhCH(OCH_3)_2$, *p*-TsOH/DMF; (e) MOM–Cl, *i*-Pr_2NEt/CH_2Cl_2; (f) Ph–NCO/Py; (g) 70% aq AcOH.

1.5 equiv) and *N*-ethyldiisopropylamine (1.2 equiv) in CH_2Cl_2 at 0 °C for 12 h afforded **3** (84% yield), which was reacted with phenyl isocyanate (2.0 equiv) in pyridine with stirring for 5 h at rt. Upon the addition of MeOH, the reaction mixture was removed by evaporation, and the crude product was recrystallized to give the corresponding 2-*O*-Car derivative **4** in 92% yield. Acid hydrolysis of **4** using 70% aq AcOH at 60 °C for 1 h gave 4,6-diol derivative **5**, which was then treated with MOM–Cl (2.5 equiv) and *N*-ethyl-diisopropylamine (2.5 equiv) in CH_2Cl_2 for 4 h to afford glucosyl donor **6**[6] in 71% yield (two steps).

On the other hand, as showed in Scheme 2, acceptor **12** was prepared from sucrose in six steps. Following Mannzo's procedure,[7] sucrose, acetone dimethylacetal (10 equiv), and cerium(IV) ammonium nitrite (0.2 equiv) were reacted to afford 2,1′:4,6-di-*O*-isopropylidene-sucrose (**7**) in 70% yield. The selective protection[8] of the 4′,6′-OH groups of **7** involved the addition of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.2 equiv) (in three portions) to a mixture of **7** and imidazole (1.0 equiv) in pyridine at 0 °C. After maintaining the reaction mixture for 8 h, and upon the disappearance of **7** (determined by TLC), MeOH was added to the reaction mixture. Typical work up procedures, followed by purification using silica gel column chromatography afforded **8** in 89% yield. Purified **8** was reacted with MOM–Cl (1.2 equiv) and *N*-ethyldiisopropylamine (1.2 equiv) in CH_2Cl_2 at rt for 6 h to give 3-*O*-methoxymethyl derivative **9** (85% yield), which was treated with benzoyl chloride (2.0 equiv) in pyridine to afford



Scheme 2.[9] Reagents and conditions: (a) $Ce(N_2H_4)_2(NO_3)_6$, $(CH_3)_2C(OCH_3)_2$/DMF; (b) [[$(CH_3)_2CH]_2SiCl$]–O–[$ClSi[CH(CH_3)_2]_2$], imidazole/DMF; (c) MOM–Cl, *i*-Pr_2NEt/CH_2Cl_2; (d) BzCl, Py; (e) 0.1 M HCl–MeOH; (f) AcCl, Py; (g) NIS, TMSOTf, MS4A/CH_2Cl_2; (h) BzCl, Py; (i) Bu_4NNO_2/DMF; (j) TBAF/THF; (k) 90% AcOH aq.

the corresponding 3′-*O*-benzoate derivative as an oil (97% yield); the structure of **10** was confirmed using ^{1}H NMR spectroscopy [downfield shift of H-3′(fruc) and elemental analysis. Direct mono-benzoylation of **10** gave 3-*O*-benzoate (glc) instead 3′-*O*-benzoyl (glc) derivative, by the way. Selective hydrolysis of **10** at rt using 0.1 M HCl–MeOH, followed by neutralization using Dowex (OH^- form), afforded de-*O*-isopropylidene **11** (83% yield), which was treated with acetyl chloride (1.5 equiv) in pyridine at 0 °C for 30 min to afford 6,1′-di-*O*-acetate **12** as an oil[6] (83% yield). The structure of **12** was confirmed using ^{1}H NMR spectroscopy [downfield shift of H-6 and H-1′] and elemental analysis.

Using donor **6** and disaccharide acceptor **12**, telephiose A (**1**) was synthesized as follows: to a stirred mixture of **6** (1.0 equiv), **12** (0.9 equiv), and MS 4A in CH_2Cl_2 (after stirring for 30 min under argon at rt) was added (dropwise) dry *N*-iodosucinimide (1.5 equiv), followed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.3 equiv) at −40 °C. Upon disappearance of the starting material using TLC (1 h), the reaction mixture was neutralized with Et_3N, filtered, diluted with $CHCl_3$, and washed with aq $NaHCO_3$, aq $Na_2S_2O_3$, brine, and water. The organic layer was dried over anhydrous $MgSO_4$, removed by evaporation, then purified using silica gel column chromatography to give trisaccharide **13** as an oil [^{1}H NMR, $J_{1,2} = 9.7$ Hz, H-1 (β-linkage)] (57% yield). In addition to the main product, the formation of a small amount of a side product, the 4-*O*-glucoside (10%), was observed. Benzoylation of the 4-OH group of **13** with benzoyl chloride (1.5 equiv) in pyridine gave **14** (98% yield), which was confirmed using ^{1}H NMR spectroscopy [down field shift of H-4 (glc)] and elemental analysis. The 2-*O*-*N*-phenylcarbamoyl group of **14** was removed using Bu_4NNO_2 (3.0 equiv) in DMF at 90 °C for 12 h under argon to give **15** as an oil (71% yield), which was treated with Bu_4NF (TBAF) in THF to afford de-*O*-silylated **16** as an oil (92% yield). Deprotection conditions of the MOM groups using 90% aq AcOH at rt resulted in a mixture of **1** (yield 61%) and a side product (cleavage of the fructosyl linkage, ca. 20%). Purification using silica gel column chromatography ($CHCl_3$–MeOH) afforded pure **1**; the optical rotation values and ^{1}H NMR data are in good agreement with those reported.[1,6]

Herein, we described the first total synthesis of telephiose A using a glucosyl donor (based on D-glucose) and a disaccharide acceptor (based on sucrose). Our synthetic methodology illustrates the usefulness of a Car protecting group in the synthesis of oligosaccharide esters.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.138.

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6. IR (KBr, neat), ^{1}H NMR, and other physical data of compound **6**, **12**, and **1**.
Compound **6**: mp 173.5–174.0 °C (hexane–EtOH); $[\alpha]_D^{25}$ +20.8 (*c* 0.7, $CHCl_3$); ν_{NH} 2928 cm^{-1}, $\nu_{C=O}$ 1738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.05 (5H, m, Ph), 6.83 (1H, s, –NH–), 5.15 (1H, dd, $J_{2,1} = 9.7$ Hz, $J_{2,3} = 9.2$ Hz, H-2), 4.82, 4.72 (2H, each d, $J_{AB} = 7.4$ Hz, CH_2OCH$_3$), 4.74, 4.68 (2H, each d, $J_{AB} = 7.8$ Hz, CH_2OCH$_3$), 4.72, 4.67 (2H, each d, $J_{AB} = 6.2$ Hz, CH_2OCH$_3$), 4.68 (1H, d, H-1), 3.84 (1H, dd, $J_{6a,5} = 2.2$ Hz, $J_{6a,6b} = 11.5$ Hz, H-6a), 3.73 (1H, dd, $J_{6b,5} = 5.1$ Hz, H-6b), 3.68 (1H, dd, $J_{3,4} = 9.7$ Hz, H-5), 3.57 (1H, dd, $J_{4,5} = 9.2$ Hz, H-4), 3.41 (1H, ddd, H-5), 3.36, 3.33, 3.30 (9H, each s, OCH_3). Anal. Calcd for $C_{25}H_{33}NO_9S$ (523.60): C, 67.86; H, 5.34; N, 2.39. Found: C, 67.91; H, 5.54; N, 2.37.
Compound **12**: $[\alpha]_D^{26}$ −15.0 (*c* 0.7, $CHCl_3$); IR (KBr, neat) $\nu_{C=O}$ 1732 cm^{-1}, 1738 cm^{-1}, 1746 cm^{-1}, ν_{OH} 3455 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08–7.27 (5H, m, Ph), 5.61 (1H, d, $J_{3',4'} = 8.6$ Hz, H-3′), 5.52 (1H, d, $J_{1,2} = 3.4$ Hz, H-1), 4.76 (1H, dd, $J_{6a,5} = 8.6$ Hz, $J_{6a,6b} = 8.3$ Hz, H-6a), 4.71, 4.58 (2H, each d, $J_{AB} = 6.9$ Hz, CH_2OCH$_3$), 4.43 (1H, d, $J_{1a',1b'} = 12.0$ Hz, H-1a′), 4.32 (1H, d, H-1b′), 4.31 (1H, dd, $J_{6b,5} = 9.5$ Hz, H-6b), 4.06–4.05 (2H, m, H-4′, H-5′), 3.94–3.90 (2H, m, H-6a′, H-3), 3.56–3.50 (2H, m, H-5, H-6b′), 3.41 (3H, s, OCH_3), 3.39–3.32 (2H, m, H-2, H-4), 2.08 (6H, s, COC$H_3 \times 2$), 1.12–0.95 (24H, m, TIPDS); Anal. Calcd for $C_{37}H_{60}O_{16}Si_2$ (817.03): C, 54.39; H, 7.40. Found: C, 54.51; H, 7.64.
Telephiose (**1**): [Synthetic]: colorless syrup; $[\alpha]_D^{24}$ −14.8 (*c* 0.36, MeOH) ^{1}H NMR (600 MHz, Pyridine-d_5) δ 8.31–7.41 (10H, m, Ph), 6.30 (1H, d, $J_{1,2} = 3.9$ Hz, H-1 (Glc1)), 6.28 (1H, d, $J_{3,4} = 8.9$ Hz, H-3 (Fruc)), 5.69 (1H, dd, $J_{4,3} = 9.9$ Hz, $J_{4,5} = 9.9$ Hz, H-4 (Glc1)), 5.17 (1H, dd, $J_{4,5} = 8.0$ Hz, H-4 (Fruc)), 5.14 (1H, d, $J_{2,3} = 12.2$ Hz, H-2 (Fruc)), 5.09 (1H, d, $J_{1,2} = 8.0$ Hz, H-1 (Glc2)), 4.87 (1H, m, H-5 (Glc1)), 4.69 (1H, m, H-5 (Fruc)), 4.62 (1H, m, $J_{1,2} = 12.2$ Hz, H-1 (Fruc)), 4.59 (1H, dd, $J_{3,2} = 9.9$ Hz, H-3 (Glc1)), 4.54–4.48 (3H, m, H-6 (Glc1), H-6′ (Glc1), H-6 (Glc2)), 4.47 (1H, dd, $J_{5,6} = 6.4$ Hz, $J_{6,6'} = 12.3$ Hz, H-6 (Fruc)), 4.38 (1H, dd, $J_{5,6} = 3.2$ Hz, H-6′ (Fruc)), 4.30 (1H, dd, $J_{5,6'} = 5.8$ Hz, $J_{6',6} = 12.1$ Hz, H-6′(Glc2)), 4.17–3.98 (4H, m, H-4 (Glc2), H-3 (Glc2), H-2 (Glc2), H-2 (Glc1)), 3.93 (1H, m, H-5 (Glc2)), 2.10, 1.91 (6H, each s, COC$H_3 \times 2$).
[Natural]: syrup; $[\alpha]_D^{24}$ −11.0 (*c* 0.45, MeOH) ^{1}H NMR (300 MHz, Pyridine-d_5) δ 8.26–7.40 (10H, m, Ph), 6.31 (1H,

d, $J_{1,2} = 3.7$ Hz, H-1 (Glc1)), 6.30 (1H, d, $J_{3,4} = 8.6$ Hz, H-3 (Fruc)), 5.67 (1H, dd, $J_{4,3} = 9.8$ Hz, $J_{4,5} = 9.8$ Hz, H-4 (Glc1)), 5.15 (1H, dd, $J_{4,5} = 7.9$ Hz, H-4 (Fruc)), 5.12 (1H, d, $J_{2,3} = 12.2$ Hz, H-2 (Fruc)), 5.08 (1H, d, $J_{1,2} = 7.9$ Hz, H-1 (Glc2)), 4.87 (1H, m, H-5 (Glc1)), 4.68 (1H, m, H-5 (Fruc)), 4.60 (1H, m, $J_{1,2} = 12.2$ Hz, H-1 (Fruc)), 4.59 (1H, dd, $J_{3,2} = 9.8$ Hz, H-3 (Glc1)), 4.51-4.50 (3H, m, H-6 (Glc1), H-6′ (Glc1), H-6 (Glc2)), 4.43 (1 H, dd, $J_{5,6} = 6.4$ Hz, $J_{6,6'} = 12.4$ Hz, H-6 (Fruc)), 4.37 (1H, dd, $J_{5,6} = 3.4$ Hz, H-6′ (Fruc)), 4.31 (1H, dd, $J_{5,6'} = 5.8$ Hz, $J_{6',6} = 11.9$ Hz, H-6′ (Glc2)), 4.13–4.03 (4H, m, H-4 (Glc2), H-3 (Glc2), H-2 (Glc2), H-2 (Glc1)), 3.91 (1H, m, H-5 (Glc2)), 2.07, 1.89 (6H, each s, $COCH_3 \times 2$).

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9. For experimental procedure and their physical data of compounds **3**–**5**, **7**–**11**, and **13**–**16**, see Supplementary data at doi:10.1016/j.tetlet.2007.03.138.