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Note

Synthesis of 7-*O*-galloyl-D-sedoheptulose

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Abstract—A facile synthetic approach to 7-*O*-galloyl-D-sedoheptulose (**1**), a natural product with notable immunosuppressant activity, was developed. The starting material, 2,7-anhydro-D-sedoheptulose (**2**), was converted in three steps into 1,3,4,5-tetra-*O*-benzyl-D-sedoheptulose (**5**), a key intermediate that allows specific functionalization at C-7 of the sedoheptulpyranose. After regioselective esterification of **5** with 3,4,5-tri-*O*-benzylgalloyl acid, followed by catalytic debenzylation (Pd–C), **1** was obtained in an overall yield of 60%. The spectroscopic data and TLC behavior of **1** were found to be identical to that of the natural product.

Keywords: Sedoheptulose; D-Altro-hept-2-ulose; 7-*O*-Galloyl-D-sedoheptulose; 2,7-Anhydro-D-sedoheptulose; Acetolysis; Galloylation

7-*O*-Galloyl-D-sedoheptulose (**1**) is a natural product that was first isolated by Zhang et al. from the water extract of the fruit of *Cornus officinalis* Sieb et Zucc.[1] In traditional Chinese medicine, the fruit of *C. officinalis* is considered to have beneficial effects on liver and kidney functions. It has been reported that oral administration of water extracts of *C. officinalis* fruits could suppress type II collagen-induced arthritis and the production of collagen II-specific antibodies in rats,[2] as well as attenuate dextrane induced nephropathy in mice.[3] Compound **1** was isolated in our laboratory by bioassay-guided fractionation. It showed notable suppressant effects on the antibody production response in the plaque-forming cell assay. The antibody production response was reduced by 96% at 40 μg/mL concentration when the compound was tested in vitro, and by 47% when it was orally administered to mice at a dose of 40 mg/kg d for 7 days. These results inspired us to synthesize this compound and related derivatives for further pharmacological investigations. Sedoheptulose (systemic name D-altro-hept-2-ulose) normally occurs in nature in the form of its phosphate esters. These perform vital functions during the photosynthesis of plants and in the sugar metabolism of animal tissues. Other derivatives of sedoheptulose have rarely been reported except for **1**[1] and 1,7-di-*O*-galloyl-D-sedoheptulose[4] from *C. officinalis*, and 7-*O*-caffeoyl-D-sedoheptulose from *Nyssa sylvatica*.[5] Synthetic studies on these compounds have not been reported. The structure of **1** is simple. The major problem to be overcome in the synthesis of **1** is to selectively protect the multiple hydroxyl groups to ensure the specific galloylation at the 7-OH of the sugar. This problem was solved by using 2,7-anhydro-D-sedoheptulose (**2**), a commercially available form of sedoheptulose, as the starting material. The bicyclic skeleton of **2** simplified the procedure of hydroxyl protection. After fully protecting the free hydroxyls of **2** and opening the 2,7-anhydro ring, functional groups can be specifically introduced at C-7.

The synthesis of **1** (Scheme 1) started with perbenzylation of **2**. Treatment of **2** with sodium hydride (1.5 equiv per hydroxyl group), followed by benzylation with benzyl bromide (1.1 equiv per hydroxyl group) in the presence of a catalytic amount of tetra-butylammonium iodide (TBAI) (0.1 equiv),[6] gave the desired 1,3,4,5-tetra-*O*-benzyl-2,7-anhydro-D-sedoheptulose (**3**) in excellent yield (96%).

In order to open the anhydro ring of **3**, Lewis acids such as Me_3SiI[7] and anhydrous $ZnCl_2$,[8] as well as the ion-exchange resin Dowex 50-W (H^+),[9] were tested as catalysts. The reaction conditions and results are

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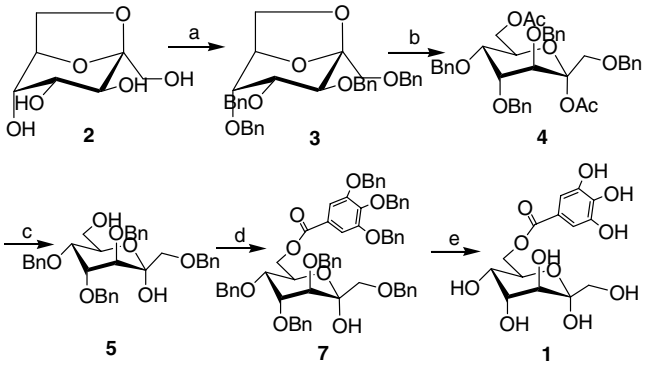

Scheme 1. Reagents and conditions: (a) DMF, NaH, TBAI, BnBr, 0 °C → rt, overnight, 96%; (b) Ac_2O, $BF_3{\cdot}Et_2O$, −30 °C, 75 min, 85%; (c) K_2CO_3, MeOH, pH = 10, rt, 1 h, 100%; (d) 3,4,5-tri-*O*-benzyl-galloyl acid (**6**), DMAP, DCC, Py, 0 °C, 48 h; rt, 48 h, 80%; (e) 10% Pd–C, EtOAc–EtOH, rt, 7 h, 98%.

summarized in Table 1. It was found that the internal acetal could not be opened by Me_3SiI, and the reactions catalyzed by $ZnCl_2$ and Dowex 50-W led to decomposition of **3** and a very low yield (<10%) of the expected product. It was known that the internal acetal in protected anhydro sugars undergoes effective acetolysis in the presence of TFA/Ac_2O[10] or $BF_3{\cdot}Et_2O$/Ac_2O.[11] We found that the TFA/Ac_2O-mediated reaction gave a very low yield of the ring-opened product (<10%), whereas the $BF_3{\cdot}Et_2O$/Ac_2O-catalyzed reaction proceeded quite quickly at 0 °C; however, the benzyl protecting groups were partially exchanged by acetyl groups. The exchange was found to occur at first in position 1, and then in the other positions successively. By lowering the reaction temperature to −30 °C and controlling the amount of $BF_3{\cdot}Et_2O$ to 0.25–0.35% of the quantity of **3**, the acetylation occurred only on C-7 and C-2 and a good yield (>85%) of 1,3,4,5-tetra-*O*-benzyl-2,7-di-*O*-acetyl-D-sedoheptulose (**4**) was achieved.

The acetyl groups of **4** were removed by stirring a methanol solution of **4** containing a small amount of water. The solution was adjusted to pH 10–11 with potassium carbonate at rt, and a quantitative yield of the deacetylated product 1,3,4,5-tetra-*O*-benzyl-D-sedoheptulose (**5**) was obtained. The pH must be strictly controlled, since side products are obtained when the pH is over 11.

Reaction of **5** with 3,4,5-tri-*O*-benzyl-galloyl acid (**6**) in the presence of DCC and DMAP in anhydrous pyridine afforded 1,3,4,5-tetra-*O*-benzyl-7-*O*-(tri-*O*-benzyl-galloyl)-D-sedoheptulose (**7**) in 80% yield. Since the primary hydroxyl 7-OH is more susceptible than the semi-acetal hydroxyl at C-2 toward esterification, and the bulky benzyl groups adjacent to C-2 possibly hinder the acylation of 2-OH, the galloylation of **5** proceeds regioselectively and gives **7** as the main product. The structure of **7** was confirmed by ^1H NMR, ^{13}C NMR, ^1H–^1HCOSY, and HMBC spectra. The C-2 signal could be observed at 98.0 ppm in the ^{13}C NMR spectrum. The ^1H NMR spectrum shows a singlet at 5.68 ppm that integrates to one H and is exchangeable in D_2O. This signal is correlated with C-2 in the HMBC spectrum, suggesting that there is a free hydroxyl at C-2 and that the galloyl is linked to C-7 of the protected sedoheptulose. The low-field shift of the H-7 signal from 3.80 to 4.24 ppm also indicates the galloylation of 7-OH.

The final removal of the benzyl protecting groups on both sugar moieties and the galloyl group by hydrogenolysis in the presence of a catalytic amount of 10% Pd/C afforded the desired compound **1**. In aqueous solution, 7-*O*-galloyl-D-sedoheptulose was found to exist in three tautomeric forms (see Fig. 1), and the proportion of β-F, α-F, and α-P was estimated to be 57:24:19 according to the intensities of their C-2 signals at 102.4 ppm, 105.3 ppm, and 98.5 ppm in the ^{13}C NMR spectrum. The ^{13}C and ^1H NMR data of **1** are identical to those of the natural 7-*O*-galloyl-D-sedoheptulose reported in the literature.[1]

1. Experimental

1.1. General methods

Melting points were determined with an X4 melting point apparatus (uncorrected, Beijing science and technology company). Optical rotations were measured with a PE-243 polarimeter. IR spectra were measured with a Nicolet Manga spectrometer (Micronicolet, America). ^1H and ^{13}C NMR spectra were recorded with a Mercury 400 spectrometer for solutions in $CDCl_3$ or DMSO-d_6.

Table 1. Reaction conditions and results of the ring-opening reaction of **3**

Entry	Acidic media	*T* (°C)	Time (h)	Yield[a] (%)
1	Me_3SiI (1.1 equiv) in $CHCl_3$	0	0.4	N[b]
2	CF_3COOH in Ac_2O	−15	0.6	10
3	CF_3COOH in Ac_2O	0	1.0	9
4	Anhydrous $ZnCl_2$ in Ac_2O/HOAc (2:1)	0	3.0	5
5	Dowex 50-W(H^+) in Ac_2O	80	4.0	8
6	$BF_3{\cdot}Et_2O$ in Ac_2O	0	0.4	52
7	$BF_3{\cdot}Et_2O$ in Ac_2O	−30	1.25	87

[a] Isolated yield of **4**.
[b] No ring-opening product was found.

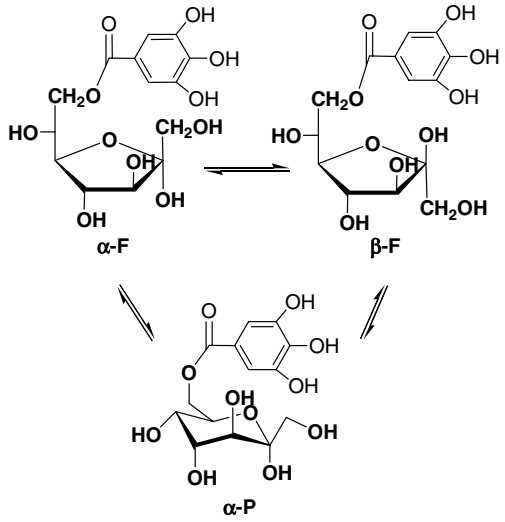

Figure 1. Tautomeric forms of 7-*O*-galloyl-D-sedoheptulose in aqueous solution.

Chemical shifts were given in ppm downfield from internal Me_4Si. ESI-MS spectra were obtained with an API3000 spectrometer (ABI, America), HRESI-MS was obtained with a Micromass LCT. The progress of reactions were monitored by TLC on GF_{254} plates (Haiyang Chemical Factory, Qingdao, China). Column chromatography was performed on silica gel H (100–200 or 200–300 mesh, Haiyang Chemical Factory, Qingdao, China) and Sephadex LH-20 (Amersham Pharmacia Biotech, Sweden). The solvent systems indicated are volume–volume ratios. Components were detected by spraying the plates with 20% concd H_2SO_4 in EtOH and heating. Solutions were concentrated below 40 °C under reduced pressure.

1.2. 1,3,4,5-Tetra-*O*-benzyl-2,7-anhydro-D-sedoheptulose (3)

To a suspension of NaH (6.2 g, 258.33 mmol, washed three times with cyclohexane before use) in DMF (60 mL) was added 2,7-anhydro-D-sedoheptulose **2** (5 g, 26.04 mmol) portionwise over 30 min at 0 °C under nitrogen. The mixture was stirred at rt for 2 h. TBAI (1 g, 2.71 mmol) was added to the thick mixture, followed by the dropwise addition of BnBr (14 mL, 118.11 mmol) over 45 min. The reaction mixture was stirred overnight until it turned clear. The solvent was removed under reduced pressure and the residue was evaporated in vacuo to dryness. The remaining solid was triturated with Et_2O (3×50 mL). The combined Et_2O extract was washed with water (200 mL) and brine (200 mL) and dried over Na_2SO_4. After removal of Et_2O, the product was purified by column chromatography (silica gel, 3.5:1 cyclohexane–EtOAc) to give **3** (13.8 g, 96%) as a colorless syrup. $[\alpha]_D$ +5.7 (*c* 0.7, $CHCl_3$); R_f 0.45 (3.5:1 cyclohexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.41 (m, 20H, 4Ph*H*), 4.52–4.87 (m, 8H, 4PhCH_2), 4.64 (m, 1H, H-6), 4.06 (d, 1H, $J = 8.7$ Hz, H-3), 3.92 (d, 1H, $J = 10.6$ Hz, H-1), 3.73–3.79 (m, 2H, H-4, H-7), 3.65 (m, 1H, H-5), 3.57 (d, 1H, $J = 7.6$ Hz, H-7), 3.52 (d, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.4 (4Ph, C-1), 138.0, 137.9, 137.8, 127.4–128.4 (m), 108.0 (C-2), 79.6 (C-3), 78.7 (C-4), 75.2 (2Ph*C*H$_2$), 74.2 (C-5), 73.6 (Ph*C*H$_2$), 72.3 (Ph*C*H$_2$), 71.6 (C-6), 68.9 (C-1), 65.9 (C-7); ESI-MS (*m*/*z*): 570 (M+NH_4^+), 575 (M+Na^+), 591 (M+K^+); HRESI-MS: Calcd for $C_{35}H_{40}NO_6$: 570.6952; found: 570.6946 (M+NH_4^+).

1.3. 1,3,4,5-Tetra-*O*-benzyl-2,7-di-*O*-acetyl-D-sedoheptulose (4)

A suspension of **3** (5 g, 9.06 mmol) in cold Ac_2O (30 mL, −30 °C) was stirred for 10 min under nitrogen. $BF_3{\cdot}Et_2O$ (98 μL) was added into the mixture and stirred at −30 °C for a further 75 min, then quenched with Et_3N (1 mL), diluted with toluene (5 mL), and concentrated in vacuo. Column chromatography (silica gel, 4:1 cyclohexanes–EtOAc) yielded pure **4** (5.04 g, 85%) as a colorless syrup. $[\alpha]_D$ +27 (*c* 0.6, $CHCl_3$); R_f 0.45 (4:1 cyclohexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13–7.33 (m, 20H, 4Ph*H*), 4.30–4.63 (m, 11H, H-6, H-7 and 8PhCH_2), 4.29 (m, 1H, H-3), 3.99 (d, 1H, $J = 10.6$ Hz, H-1), 3.92 (d, 1H, H-1), 3.73–3.78 (m, 2H, H-4, H-5), 2.00 (s, 3H, CH_3), 1.93 (s, 3H, CH_3); ESI-MS (*m*/*z*): 677 (M+Na^+), 693 (M+K^+); HRESI-MS: Calcd for $C_{39}H_{42}NaO_9$: 677.7352; found: 677.7349 (M+Na^+).

1.4. 1,3,4,5-Tetra-*O*-benzyl-D-sedoheptulose (5)

A suspension of **4** (9 g, 13.76 mmol) in MeOH–H_2O (95:4, 99 mL) was adjusted to pH 10–11 with anhydrous K_2CO_3 under stirring, and then stirred for 1 h at rt and filtered thereafter. The filtrate was evaporated under reduced pressure to dryness at 30 °C. The residue was purified by column chromatography (silica gel, 2:1 cyclohexanes–EtOAc) to afford **5** (7.84 g, 100%) as a colorless syrup. $[\alpha]_D$ +14 (*c* 0.5, $CHCl_3$); R_f 0.45 (2:1 cyclohexane–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.36 (m, 20H, 4Ph*H*), 5.78 (s, 1H, C$_2$–O*H*), 4.41–4.83 (m, 8H, 4PhCH_2), 4.44 (s, 1H, C$_7$–O*H*), 4.22 (m, 1H, H-4), 4.13 (dt, 1H, $J = 2.8$, 9.8 Hz, H-6), 3.89 (dd, 1H, $J = 12.1$, 3.6 Hz, H-7), 3.80 (dd, 1H, H-7), 3.75 (d, 1H, $J = 10.1$ Hz, H-1), 3.60 (d, 1H, $J = 2.2$ Hz, H-3), 3.50 (dd, 1H, $J = 2.2$, 9.8 Hz, H-5), 3.36 (d, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8 (4Ph C-1), 137.6 (2C), 136.6, 127.4–128.4 (m), 97.9 (C-2), 73.6–73.8 (4Ph CH_2), 73.1 (C-5), 71.8 (C-3), 71.7 (C-4), 71.5 (C-6), 67.5 (C-1), 62.1 (C-7); ESI-MS (*m*/*z*): 588 (M+NH_4^+), 593 (M+Na^+), 609 (M+K^+); HRESI-

MS: Calcd for $C_{35}H_{42}NO_7$: 588.7105; found: 588.7112 ($M+NH_4^+$).

1.5. 3,4,5-Tri-*O*-benzyl-galloyl acid (6)[12]

A mixture of gallic acid (20 g, 11.76 mmol) and anhydrous K_2CO_3 (134 g, 97.10 mmol) in DMF (100 mL) was stirred at rt for 1 h until the solids dissolved. BnBr (88 mL) was added dropwise into the solution over 30 min at 40 °C under nitrogen. The reaction mixture was stirred for 3 h at 40 °C and then filtered. The filtrate was evaporated to dryness in vacuo. The residue was dissolved in aqueous ethanol (50%, 400 mL) containing 5 M NaOH and refluxed for 3 h. The solution was diluted with H_2O (100 mL), adjusted to pH 2 with concd HCl and stirred for 0.5 h at rt. The precipitate was collected and recrystallized from methanol to afford needles of **6** (42.9 g, 83%): mp 119–120 °C; IR γ_{max}^{KBr} cm^{-1}: 3398, 1747 (C=O), 1675, 1573, 1499, 1427, 1330, 1127, 763, 729, 690; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.23–7.49 (m, 17H, Ar-H), 5.18 (s, 4H, 2 PhCH_2), 5.04 (s, 2H, PhCH_2); ESI-MS (*m*/*z*): 441 ($M+H^+$), 458 ($M+NH_4^+$).

1.6. 1,3,4,5-Tetra-*O*-benzyl-7-*O*-(tri-*O*-benzyl-galloyl)-D-sedoheptulose (7)

A mixture of **5** (2.4 g, 4.21 mmol), **6** (2.2 g, 5 mmol), DCC (1.3 g, 6.31 mmol) and DMAP (5.1 mg, 0.04 mmol) in anhydrous pyridine (22 mL) was stirred at 0 °C for 48 h and then at rt for 48 h. The soln was filtered and the filtrate was evaporated under reduced pressure to dryness. The residue was purified by column chromatography (silica gel, 5:1 cyclohexane–EtOAc) to give pure **5** (3.34 g, 80%) as a colorless syrup. $[\alpha]_D$ +25.7 (*c* 0.7, $CHCl_3$); R_f 0.45 (5:1 cyclohexane–EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.13–7.40 (m, 37H, Ar-H), 5.68 (s, 1H, C_2–OH), 5.01–5.12 (m, 6H, 3PhCH_2), 4.36–4.70 (m, 8H, 4PhCH_2), 4.55 (m, 1H, H-6), 4.53 (m, 1H, H-5), 4.38 (m, 1H, H-4), 4.24 (d, 1H, $J = 11.8$ Hz, H-7), 3.85 (m, 1H, H-3), 3.80 (d, 1H, H-7), 3.73 (d, 1H, $J = 9.8$ Hz, H-1), 3.40 (d, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9 (C=O), 152.3 (2C galloyl C-3 and C-5), 142.1 (galloyl C-4), 136.6–137.9 (m), 127.6–128.6 (m), 108.9 (2C galloyl C-2 and C-6), 98.0 (C-2), 75.0 (PhCH_2), 73.9 (C-5), 73.9 (PhCH_2), 73.8 (PhCH_2), 73.7 (PhCH_2), 73.2 (C-3), 72.0 (C-4), 71.4 (C-6), 71.3 (PhCH_2), 70.8 (2C, 2PhCH_2), 65.8 (C-1), 64.3 (C-7); ESI-MS (*m*/*z*): 1015 ($M+Na^+$); HRESI-MS: Calcd for $C_{63}H_{60}NaO_{11}$: 1016.1337; found: 1016.1330 ($M+Na^+$).

1.7. 7-*O*-Galloyl-D-sedoheptulose (1)

A suspension of **7** (2 g, 2.02 mmol) and 10% Pd–C (800 mg) in EtOAc–EtOH (1:1, 20 mL) was stirred at rt while H_2 was bubbled through (20 mL/min) for 7 h. After removing the Pd–C by filtration, the filtrate was concentrated under reduced pressure at 30 °C and the residue was purified by column chromatography (Sephadex LH-20, MeOH) to give pure **1** (0.72 g, 98%) as a colorless syrup. $[\alpha]_D$ +7.2 (*c* 0.2, MeOH); R_f 0.7 (4:1:5 *n*-butanol–HOAc–H_2O, upper layer); ^1H NMR (400 MHz, 1:1 Me_2CO-d_6-D_2O) δ: 7.02 (s, 2H, galloyl-H), 4.33 (m, β-F-H-4), 4.28 (m, α-F-H-7), 4.25 (m, β-F-H-7), 4.12–4.16 (m, α-F-H-4, α-P-H-6, β-F-H-3), 3.99–4.00 (m, β-F-H-6, α-F-H-6, α-P-H-4), 3.85 (m, α-P-H-3), 3.83 (m, α-P-H-5), 3.77 (m, β-F-H-5), 3.52–3.57 (m, α-F-H-1, α-P-H-7), 3.42 (s, β-F-H-1), 3.41 (s, α-P-H-1); ^{13}C NMR (100 MHz, 1:1 Me_2CO-d_6-D_2O) δ: 167.3 (C=O), 145.1 (2C, galloyl C-3, C-5), 138.5 (galloyl C-4), 120.3 (galloyl C-1), 109.4 (2C, galloyl C-2, C-6), 105.3 (α-F-C-2), 102.4 (β-F-C-2), 98.2 (α-P-C-2), 82.0, 81.1 (β-F-C-5), 76.9, 76.4 (β-F-C-3), 76.0 (β-F-C-4), 71.5, 70.5 (β-F-C-6), 69.5, 68.1, 67.2, 65.7 (β-F-C-7), 64.8, 64.2, 63.9 (α-P-C-1), 63.2 (α-F-C-1), 62.9 (β-F-C-1); ESI-MS (*m*/*z*): 385 ($M+Na^+$); HRESI-MS: Calcd for $C_{14}H_{18}NaO_{11}$: 385.2759; found: 385.2751 ($M+Na^+$).

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