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Note

Rhodinose derivatives suitable for the synthesis of anthracycline analogs

HASSAN S. EL KHADEM AND RICHARD C. CERMAK

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U.S.A.)

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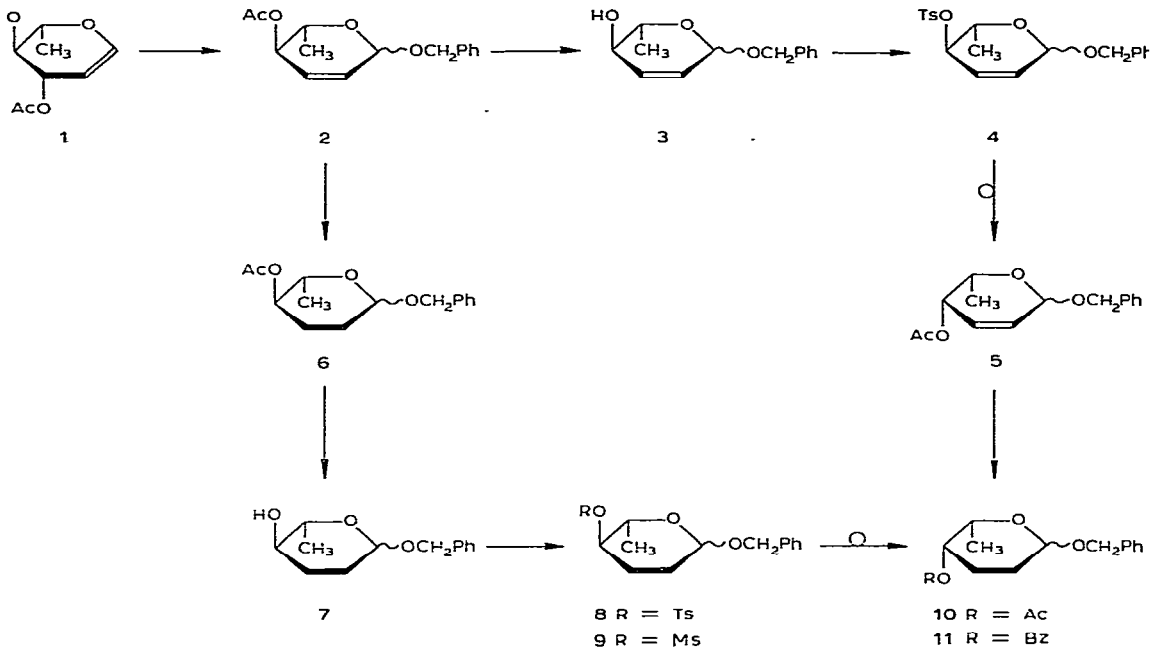
Rhodinose (2,3,6-trideoxy-L-*threo*-hexopyranose), identified as a component of the oligosaccharides present in the rhodomycin group of anthracycline antibiotics[1], has been synthesized by two low-yield methods. The first started with L-rhamnose[2] and involved an oxidation step to a 4-keto compound, and the second was a thirteen-step procedure starting with L-xylose[3].

The aim of the present work was to develop for the preparation of rhodinose derivatives a better procedure that could later be used for the synthesis of anthracycline analogs. The requisites for this procedure were that it (*a*) use readily accessible starting-materials, (*b*) involve a relatively small number of steps, and (*c*) afford the desired product in good yield.

Several procedures were tried, and route 1 (described next) seems to be best suited for the synthesis of the desired rhodinose derivative. This method is an improvement on route 2, developed earlier. Both synthetic routes start with 3,4-di-*O*-acetyl-L-rhamnal (**1**), a compound readily accessible from L-rhamnose by successive acetylation, halogenation, and treatment with zinc dust[4]. Compound **1** was treated with benzyl alcohol in the presence of BF_3 etherate; this caused migration of the double bond, affording benzyl 4-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hex-2-enopyranoside (**2**), a common starting-material for routes 1 and 2.

Route 1: Compound **2** was saponified, to give benzyl 2,3,6-trideoxy-L-*erythro*-hex-2-enopyranoside (**3**), which was tosylated and the 4-ester treated with acetate, to afford compound **5**. The latter was then catalytically hydrogenated, to give the desired benzyl 4-*O*-acetyl-2,3,6-trideoxy-L-*threo*-hexopyranoside (**10**).

Route 2: This procedure involved subjection of compound **2** to catalytic hydrogenation, to give benzyl 4-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hexopyranoside (**6**), which was then saponified to benzyl 2,3,6-trideoxy-L-*erythro*-hexopyranoside (**7**). In order to invert the configuration of C-4, compound **7** was first either tosylated or mesylated, to give sulfonate **8** or **9**, which was then treated with either acetate or benzoate, to give the desired benzyl rhodinoside, **10** or **11**. Product **10** was obtained from compound **2** in an overall yield of 55% by route 1, and 20% by route 2.



EXPERIMENTAL

General. — Melting points were determined with a Kofler block and are uncorrected. Optical rotations were measured with a Bendix series 1100 polarimeter. N.m.r. spectra were recorded with a Varian EM-360 spectrometer, with tetramethylsilane as the internal standard and CCl_4 as the solvent, unless otherwise indicated. Thin-layer chromatography was conducted on Eastman Kodak 13181 silica gel plates. Chromatographic columns were packed with Sargent-Welch SC 14608 silica gel (60–200 mesh). Microanalyses were performed by Mrs. S. Brotherton in the Department of Chemistry and Chemical Engineering Microanalysis Laboratory. Petroleum ether refers to the fraction boiling at 30–60°.

Benzyl 4-O-acetyl-2,3,6-trideoxy-L-erythro-*hex-2-enopyranoside* (**2**). — A solution of di-*O*-acetyl-L-rhamnal[4] (**1**) (5 g) in benzene (30 mL) was stirred at 0° with benzyl alcohol (5 g), and then treated with $BF_3 \cdot Et_2O$ (0.5 mL). T.l.c. in 8:1 (v/v) petroleum ether–ether indicated that the reaction was complete after 2 h. The mixture was stirred with saturated, aqueous K_2CO_3 (50 mL), extracted with chloroform (3 × 50 mL), and the extract dried (sodium sulfate), and evaporated. Distillation under diminished pressure removed the excess of benzyl alcohol, and then the product (**2**) was distilled at 120–130°/0.33 torr (yield 5.5 g, 90%). For analytical purposes, the sample was redistilled.

Anal. Calc. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found C, 68.29; H, 6.87.

Benzyl 2,3,6-trideoxy-L-erythro-*hex-2-enopyranoside* (**3**). — A solution of compound **2** (26.6 g) in 5:4:1 methanol–water–triethylamine (500 mL) was kept

for 6 h at room temperature, the methanol and triethylamine were removed by evaporation, and the resulting, aqueous solution was extracted with chloroform (3 × 100 mL). The extracts were combined, washed successively with saturated, aqueous $NaHCO_3$ (2 × 100 mL) and water (100 mL), dried (sodium sulfate), and evaporated to a syrup (yield 22.2 g, 99%), $[\alpha]_D^{21}$ −39° (*c* 1.3, chloroform), which, without further purification, was used in the next step.

*Benzyl 2,3,6-trideoxy-4-*O-p-*tolylsulfonyl-*L-erythro-*hex-2-enopyranoside* (**4**). — A solution of compound **3** (2.5 g) in pyridine (30 mL) was cooled to −10°, and *p*-toluenesulfonyl chloride (8.6 g) was added. After 24 h at −10°, ice was added, with vigorous stirring for 15 min. The solid that separated was filtered off, washed well with water, and then dissolved in chloroform. The solution was washed with saturated, aqueous sodium hydrogencarbonate, dried (sodium sulfate), and evaporated to a syrup that crystallized from diisopropyl ether (yield 3.6 g, 85%); m.p. 88–91°, $[\alpha]_D^{21}$ −86° (*c* 1.0, chloroform).

Anal. Calc. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.92. Found: C, 64.33; H, 6.25.

*Benzyl 4-*O-*acetyl-2,3,6-trideoxy-*L-threo-*hex-2-enopyranoside* (**5**). — A solution of compound **4** (7.0 g) in acetone was boiled under reflux with tetrabutylammonium acetate (11.2 g) for 18 h, cooled, and evaporated to a syrup; this was dissolved in chloroform (50 mL), and the solution was washed with water (2 × 50 mL), dried (sodium sulfate), and evaporated to a syrup. Separation of the desired product was achieved by column chromatography, with elution with toluene until the first fraction (a minor byproduct) had been collected, and then with diethyl ether to elute **5**. Evaporation of the ether eluate yielded crystals (3.53 g, 72%); m.p. 56–58°, $[\alpha]_D^{21}$ +100° (*c* 2.0, chloroform).

Anal. Calc. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.97; H, 7.04.

*Benzyl 4-*O-*acetyl-2,3,6-trideoxy-*L-threo-*hexopyranoside* (**10**). — *Method A.* A solution of compound **5** (4.53 g) in absolute ethanol was shaken for 30 min with 10% Pd–C (0.30 g) and hydrogen at 5 lb.in.$^{-2}$. The mixture was then filtered, the filtrate evaporated under diminished pressure, and the resulting syrup distilled (yield 3.24 g, 91%).

Method B. A solution of compound **8** (3.7 g) in *N,N*-dimethylformamide (30 mL) was boiled with tetrabutylammonium acetate (9.0 g) for 2 h under reflux. The product was separated on a column of silica gel eluted with 19:1 petroleum ether–ether, and evaporation of the eluate afforded a syrup (yield 0.80 g, 30%), $[\alpha]_D^{21}$ −76° (*c* 2.3, chloroform).

Anal. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.44; H, 7.49.

*Benzyl 4-*O-*acetyl-2,3,6-trideoxy-*L-erythro-*hexopyranoside* (**6**). — A mixture of compound **2** (5.58 g), absolute ethanol (20 mL), and 10% Pd–C (0.5 g) was shaken for 25 min with hydrogen at 70 lb.in.$^{-2}$, filtered, and the filtrate evaporated under diminished pressure to a syrup that was distilled at 104–108°/0.02 torr; yield 5.1 g (90%). The analytical sample was prepared by redistillation.

Anal. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; Found: C, 67.84; H, 7.73.

*Benzyl 2,3,6-trideoxy-*L-erythro-*hexopyranoside* (**7**). — Compound **6** (4.5 g) was treated with a catalytic amount of sodium methoxide in methanol (30 mL).

TABLE I

N.M.R. DATA FOR THE MONOSACCHARIDES PREPARED[a]

Compound No.	*δ (p.p.m.)*								
	H-1	*H-2,3*	*H-4*	*H-5*	*H-6*	*Ph*	*CH_2*	*Ac*	*Me*
2	4.85–5.05 (m)	5.73	4.85–5.05 (m)	4.9 (qq), $J_{4,5}$ 9.5, $J_{5,6}$ 7	1.1 (d), $J_{5,6}$ 7	7.26	4.6 (q)	1.97 (s)	—
4[b]	4.97	5.78	4.73 (m)	3.9 (qq), $J_{4,5}$ 9.5, $J_{5,6}$ 7	1.02 (d), $J_{5,6}$ 7	7.3–7.9 (m)	4.6 (q)	—	2.3
5	4.97, $J_{1,2}$ 2	5.94	4.80 (m)	4.15 (qq), $J_{4,5}$ 2.4, $J_{5,6}$ 7	1.09 (d), $J_{5,6}$ 7	7.3	4.6 (q)	2.00 (s)	—
6	4.77 (d), $J_{1,2}$ 2	1.75–1.93 (m)	4.3–4.5 (m)	3.76 (qq), $J_{4,5}$ 10, $J_{5,6}$ 7	1.1 (d), $J_{5,6}$ 7	7.3	4.53 (q)	1.96 (s)	—
8[b]	4.76	1.73–2.07 (m)	4.17 (m)	3.7 (qq), $J_{4,5}$ 10, $J_{5,6}$ 7	1.03 (d), $J_{5,6}$ 7	7.3–7.9 (m)	4.53 (q)	—	2.43
9[b]	4.8	1.7–2.2 (m)	4.2 (m)	3.83 (qq), $J_{4,5}$ 10, $J_{5,6}$ 7	1.23 (d), $J_{5,6}$ 7	7.38	4.57 (q)	—	2.98
10	4.75 (m)	1.5–2.0 (m)	4.75 (m)	3.92 (qq), $J_{4,5}$ 2, $J_{5,6}$ 7	1.00 (d), $J_{5,6}$ 7	7.3	4.5 (q)	2.02 (s)	—
11	4.87–5.10 (m)	1.6–2.27 (m)	4.87–5.10 (m)	4.05 (qq), $J_{4,5}$ 2, $J_{5,6}$ 7	1.13 (d), $J_{5,6}$ 7	7.37–8.2 (m)	4.57 (q)	—	—

[a]Key: coupling constants in Hz; d, doublet; m, multiplet; q, quartet; and qq, 2 quartets. [b]In $CDCl_3$.

T.l.c. in 10:1 (v/v) petroleum ether–ether showed the reaction to be complete in 1 h. Carbon dioxide was bubbled into the solution for 15 min, and the solution was evaporated under diminished pressure to a syrup; this was triturated with ether, the inorganic salts were filtered off, and the filtrate was evaporated under diminished pressure, to yield 3.5 g (92%) of **7** which was used directly for the following step.

*Benzyl 4-O-p-tolylsulfonyl-*L-erythro-*hexopyranoside* (**8**). — A solution of compound **7** (1.5 g) in pyridine (30 mL) was stirred at 0° with *p*-toluenesulfonyl chloride (2.6 g), and the mixture was kept overnight at room temperature. Ice–water (200 mL) was added, the mixture was extracted with chloroform (3 × 50 mL), and the extract was successively washed with saturated K_2CO_3 (100 mL) and water (100 mL), dried (Na_2SO_4), and evaporated under diminished pressure. The crystalline residue was co-evaporated with toluene, to remove pyridine, and recrystallized from diisopropyl ether (yield 2.2 g, 87%), m.p. 105–107°.

Anal. Calc. for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43. Found: C, 63.97; H, 6.52.

*Benzyl 2,3,6-trideoxy-4-O-(methylsulfonyl)-*L-erythro-*hexopyranoside* (**9**). — A solution of compound **7** (4.4 g) in pyridine (30 mL) was stirred at 0° with methanesulfonyl chloride (2.75 g). The mixture was then kept overnight at room temperature, and treated exactly as for compound **8**. The resulting syrup crystallized from aqueous ethanol; yield 4.3 g (72%). Recrystallization from cyclohexane–ether gave an analytical sample, m.p. 48–52°.

Anal. Calc. for $C_{14}H_{20}O_5S \cdot 0.5\ H_2O$: C, 54.35; H, 6.84. Found: C, 54.28; H, 6.96.

*Benzyl 4-O-benzoyl-2,3,6-trideoxy-*L-threo-*hexopyranoside* (**11**). — A solution of compound **8** (0.50 g) in *N,N*-dimethylformamide (50 mL) was boiled for 3 h under reflux with sodium benzoate (1.0 g). The mixture was cooled, water (50 mL) was added, and the mixture was extracted with diethyl ether (3 × 50 mL). The extracts were combined, washed with water (2 × 50 mL), dried (sodium sulfate), and evaporated to a syrup. Isolation of the desired product was achieved by chromatography on a column of silica gel eluted with 19:1 (v/v) petroleum ether–ether. The product was a syrup (0.13 g, 30%).

Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.43; H, 6.78.

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