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From cycloheptatriene to enantiopure sugars: synthesis of 2-deoxyhexoses

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Abstract

meso-Diol **3**, prepared from cycloheptatriene, was desymmetrized with *Pseudomonas cepacia* lipase and isopropenyl acetate to provide enantiopure **4**. The latter, through a series of stereocontrolled oxidation reactions, followed by ring cleavage by ozonolysis and oxidative cleavage of a terminal diol with periodate, provided of 2-deoxy-D-*xylo*-hexose (**1**) and 2-deoxy-D-*arabino*-hexose (**2**), which were characterized as the corresponding alditol pentaacetates.

Keywords: Lipase; Cycloheptatriene; Ozonolysis; Sodium metaperiodate; 2-deoxy-D-*xylo*-hexose; 2-deoxy-D-*arabino*-hexose

1. Introduction

Enzymes have proven to be practical and efficient tools for enantiocontrolled organic synthesis [1,2]. In the course of our studies on the enantioselective synthesis of polyoxygenated natural products, we have observed that lipases, in particular, offer wide opportunities for the generation of enantiopure intermediates from racemic alcohols and prochiral or *meso*-diols and/or the corresponding esters [3]. Enzymatic desymmetrization of *meso*-diols [4,5] opens access to complicated, stereochemically pure products including sugars [6]. This paper presents a part of our studies on the stereocontrolled synthesis of polyoxygenated compounds involving five-, six- and seven-membered polyenes as achiral starting materials.

2-Deoxyhexoses are currently of interest to many groups [7–13] for their biological activity [14–17], per se, and for use as analogs in the studies of various aspects of carbohydrate transport and metabolism [18–21]. In this note we describe the syntheses of 2-deoxy-D-*xylo*-hexose (**1**) and 2-deoxy-D-*arabino*-hexose (**2**) as examples of our cycloheptatriene-based approach to highly oxygenated natural products.

Scheme 1 shows synthetic and retrosynthetic links between these two sugars and cycloheptatriene.

Compound **4** was obtained in very high enantiopurity (>99% ee) from the *meso*-diol **3** by *Pseudomona cepacia* lipase-catalyzed desymmetrization in the presence of isopropenyl acetate according to the protocol previously described by us [6,22]. Protection of the allylic hydroxyl group of **4** as its benzyloxymethyl (BOM) ether, followed by alcoholysis of the acetate group and pyridinium dichromate (PDC) oxidation, afforded the

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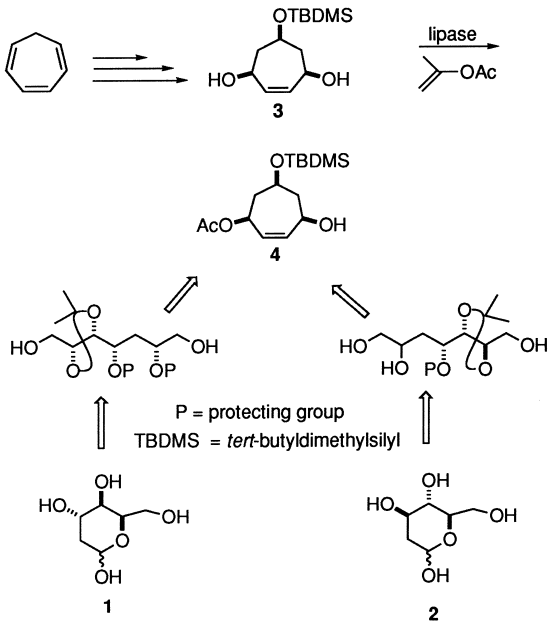
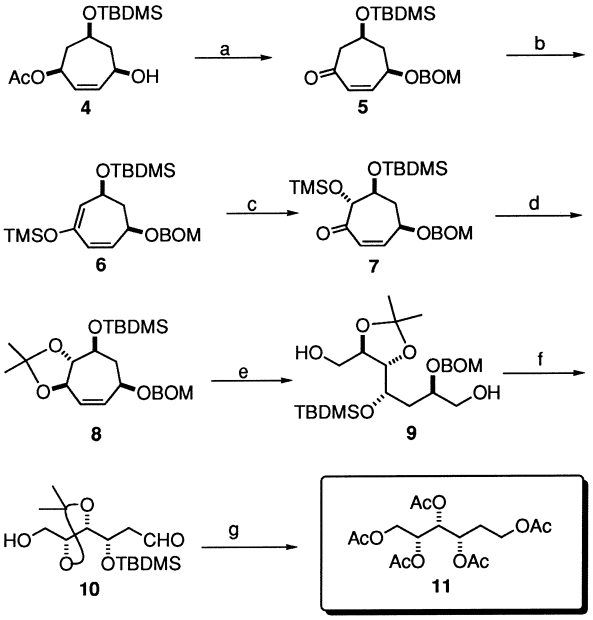


Scheme 1.

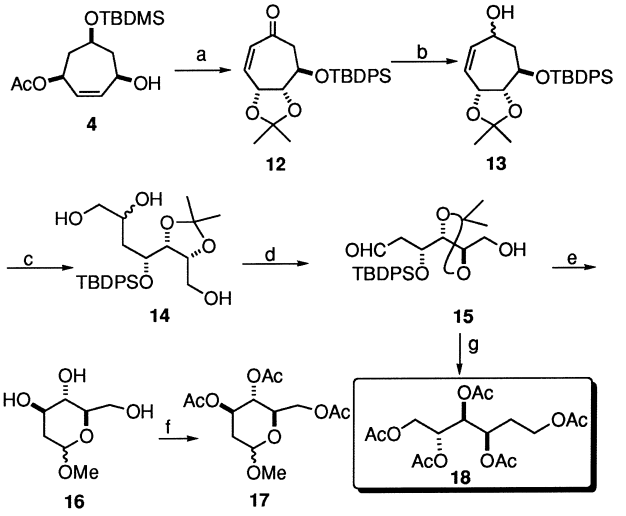
α,β-unsaturated ketone **5** [22] in ca. 90% overall yield (Scheme 2). Enone **5** was transformed into the silyloxydiene **6**, which upon treatment with *m*-CPBA (Rubottom procedure) [23] yielded α-oxygenated enone **7**. DIBAL-H reduction of **7** with removal of the Me_3Si group during workup resulted in a diol that was protected as its acetonide derivative **8**. Ozonolysis of **8**, followed by reductive workup afforded protected heptitol **9**, which, after hydrogenolytic removal of the BOM-ether with Degussa palladium catalyst [24] and cleavage of the resulting vicinal diol with $NaIO_4$ supported on silica gel [25], offered 2-deoxy-D-*xylo*-hexose as its open-chain, protected derivative **10**.

The free sugar exists as an anomeric mixture of both pyranose and furanose forms, and its 1,6-anhydro derivative is very easily formed [26]. For these reasons we decided to characterize this target by conversion to the known penta-*O*-acetyl 2-deoxy-D-*xylo*-hexitol (**11**) [27]. Sodium borohydride reduction of aldehyde **10**, followed by acidolysis and peracetylation of the resulting pentaol, afforded **11**, which was identical in all respects to the compound reported by Moore et al. [27].

2-Deoxy-D-*arabino*-hexopyranose ('2-deoxy-D-glucose', **2**) was synthesized using the same starting monoacetate **4** (Scheme 3). Protection of the allylic hydroxyl group as its *tert*-butyldiphenylsilyl (TBDPS) ether, *anti*-directed *cis*-hydroxylation [28,29] and protection of the resulting 1,2-diol, followed by chemoselective cleavage of the *tert*-butyldimethylsilyl ether and Swern oxidation of the thus formed alcohol, offered enone **12** in high (ca. 60%) yield [22]. DIBAL-H reduction of **12** gave a



Scheme 2. (a) i. BOMCl, 2-Pr_2EtN, CH_2Cl_2; ii. 0.05 N KOH, MeOH; iii. PDC, CH_2Cl_2; (b) TMSOTf, Et_3N; (c) *m*-CPBA, CH_2Cl_2; (d) i. DIBAL-H, Et_2O, −78 °C; ii. 2,2-dimethoxypropane, TsOH; (e) i. O_3, CH_2Cl_2, −78 °C, Me_2S; ii. $NaBH_4$, MeOH; (f) i. H_2, Pd/C, AcOEt; ii. $NaIO_4/SiO_2$, CH_2Cl_2; (g) i. $NaBH_4$, MeOH; ii. HCl (aq), MeOH; iii. Ac_2O–pyridine.



Scheme 3. (a) i. TPSCl, imidazole, DMF; ii. OsO_4, *N*-methylmorpholine *N*-oxide, THF–H_2O; iii. 2,2-dimethoxypropane, TsOH; iv. 0.05 N KOH, MeOH; v. MsCl, Et_3N, CH_2Cl_2; vi. pyridinium tosylate, MeOH; vii. PDC, CH_2Cl_2; (b) DIBAL-H, Et_2O; (c) i. O_3, −78 °C, Me_2S, ii. $NaBH_4$, MeOH; (d) $NaIO_4/SiO_2$, CH_2Cl_2; (e) i. Dowex-50 (H^+), MeOH; ii. Bu_4NF–THF; (f) Ac_2O–pyridine; (g) i. 6 N HCl, THF, ii. Ac_2O–pyridine.

1:1 mixture of diastereoisomeric allylic alcohols **13**. Ozonolysis of **13**, followed by reductive workup with sodium borohydride, afforded a mixture of triols **14** which, without separation, was subjected to one-carbon degradation at the vicinal diol functionality with the $NaIO_4/SiO_2$ system [25]. Our approach to the 2-deoxyglucose derivative **16** was executed starting from aldehyde **15**; the latter upon treatment with Dowex-50 resin in methanol and subsequent cleavage of the *tert*-butyldiphenylsilyl protection afforded crude methyl 2-deoxy-D-*arabino*-hexopyranoside (**16**). For analytical purposes this material was peracetylated to produce the desired triacetate **17** as a mixture of α- and β-anomers [31] 'enriched' with another major derivative (^{1}H NMR spectroscopy suggested the methyl furanoside). For this reason the aldehyde **15** was reduced with sodium borohydride in methanol, totally deprotected with 6 N hydrochloric acid in THF, and acetylated, to give penta-*O*-acetyl-2-deoxy-D-*arabino*-hexitol ('2-deoxy-D-glucitol pentaacetate') **18**. The latter was found to be identical to the literature compound in all respects [31].

2. Experimental

General.—Intermediates were characterized by clean ^{1}H and ^{13}C NMR spectra and by conversion to the known alditol acetates **11** and **18**. The structures of the latter were established by favorable comparison of optical rotation and NMR data with values in the literature.

*(2*R*,4*S*,5*R*,6*R*)-2-(Benzyloxymethoxy)-4-(*tert*-butyldimethylsilyloxy)-5,6-(isopropylidenedioxy)heptane-1,7-diol* (**9**).—Olefin **8** [22] (200 mg, 0.461 mmol) was dissolved in 1:1 methanol–dichloromethane (5 mL). A stream of ozone was passed through the solution at −78 °C until saturation was reached (blue color). The solution was flushed with oxygen until the blue color disappeared. Methyl sulfide (0.5 mL), followed by solid sodium borohydride (35 mg, 0.92 mmol), was added, and the cooling bath was removed. After stirring at room temperature for an additional 0.5 h, the reaction mixture was poured into diethyl ether (50 mL) and washed with satd aq solutions of $NaHCO_3$ (10 mL), NH_4Cl (10 mL) and NaCl (10 mL). The combined aqueous phases were extracted with diethyl ether (2×10 mL). The combined organic extracts were dried over $MgSO_4$, and solvent was removed under reduced pressure to give a clear oil that was chromatographed on silica gel (3:7 EtOAc–petroleum ether) to give **9** (178 mg, 0.379 mmol, 82% yield) as a clear oil: ^{1}H NMR ($CDCl_3$): δ 7.42–7.25 (m, 5 H); 4.89 (1/2 ABq *J* 7.01 Hz, 1 H); 4.78 (1/2 ABq *J* 7.06 Hz, 1 H); 4.74 (1/2 ABq *J* 11.8 Hz, 1 H); 4.60 (1/2 ABq *J* 11.8 Hz, 1 H); 4.10–3.42 (m, 8 H); 2.75 (bs, 2 H); 1.85 (dd1/2 ABq *J* 6.04, 12.32, 14.12 Hz, 1 H); 1.75 (dd1/2 ABq *J* 5.62, 7.63, 14.06 Hz, 1 H); 1.40 (s, 3 H); 1.38 (s, 3 H); 0.90 (s, 9 H); 0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 137.2; 128.7 (2C); 128.1 (2C); 128.0; 109.0; 95.1; 79.8; 79.2; 77.4; 70.2; 69.0; 65.6; 62.9; 35.5; 27.2; 26.0; 18.2; −4.3 −4.6

Penta-O-*acetyl-2-deoxy*-D-xylo-*hexitol* (**11**).—Diol **9** was dissolved in 80 mL of ethyl acetate, and Degussa 10% palladium catayst (50 mg) was added. The sample was hydrogenated at room temperature for 16 h. The catalyst was then filtered off and the solvent was evaporated under reduced pressure to yield the crude intermediate triol as a clear oil. Sodium periodate (162 mg, 0.757 mmol) dissolved in water (0.6 mL) was dropped into a vigorously stirred suspension of silica gel (4 g) in dichloromethane (15 mL) [24]. The crude triol (132 mg, 0.383 mmol) dissolved in dichloromethane (2 mL) was added, and the reaction mixture was stirred for 1 h. The reaction mixture was filtered, and the silica gel was washed with dichloromethane (2×20 mL). Combined filtrates were concentrated in vacuo, to give (3*S*,4*R*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-6-hydroxy-4,5-(isopropylidenedioxy)hexanal (**10**) (87 mg, 0.27 mmol, 72%) as a clear oil. The aldehyde was immediately carried forward to the next step.

Aldehyde **10** (87 mg, 0.27 mmol) was dissolved in 10 mL of methanol, and the solution was cooled to −20 °C. Sodium borohydride (21 mg, 0.54 mmol) was added, and the reaction mixture was maintained at −20 °C for 30 min. An excess of the hydride was then quenched with acetone, and the mixture was diluted with 50 mL of diethyl ether. The ether solution was washed with satd NH_4Cl (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude diol was dissolved in dry THF (10 mL) and treated with concentrated aqueous HCl (2 mL) for 16 h. The mixture was evaporated to dryness to give the crude pentaol, which was dissolved in dry pyridine (5 mL) and treated with acetic anhydride (5 mL) in the presence of the catalytic amount of DMAP. After 24 h stirring the reaction mixture was poured into diethyl ether (50 mL) and washed with 1 N HCl, (10 mL) satd aq $NaHCO_3$ (10 mL), and brine

(10 mL). The ether solution was dried over $MgSO_4$, filtered and evaporated to give crude pentaacetate **11**. The hexitol pentaacetate was purified by column chromatography using 20% EtOAc in petroleum ether as an eluent to yield 78 mg (76%) of optically [30] and spectroscopically [27] pure **11**: $[\alpha]_D^{20}$ −4.0 (*c* 1, $CHCl_3$), lit [30]. (for antipode) $[\alpha]_D^{20}$ +3.7 (*c* 4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.31–5.16 (m, 3 H); 4.34 (d1/2ABq, *J* 3.74, 12.2 Hz, 1 H); 4.05 (t, *J* 6.2 Hz, 2 H); 3.95 (d1/2ABq, *J* 5.6, 12.0 Hz, 1 H); 2.08 (s, 3 H); 2.064 (s, 3 H); 2.061 (s,3 H); 2.02 (s, 6 H); 1.90–1.76 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 170.9; 170.5; 170.2; 170.1; 170.0; 71.3; 69.4; 68.6; 62.0; 60.1; 29.9; 20.9 (2C); 20.8; 20.7; 20.6.

*(1*RS*,4*R*,5*S*,6*R*)-6-(*tert*-Butyldiphenylsilyloxy)-4,5-(isopropylidenedioxy)-2-cyclohepten-1-ol* (**13**).—Enone **12** [22] (200 mg, 0.459 mmol) was dissolved in dry diethyl ether (30 mL) and cooled under argon atmosphere to −78 °C. 1.5 M DIBAL-H in toluene (760 mL, 1.14 mmol) was added, and the reaction mixture was stirred for 15 min. An excess of the hydride was then quenched with methanol (1 mL), and satd aq sodium-potassium tartrate (20 mL) was added. The reaction mixture was vigorously stirred at room temperature until the alumina salts were completely dissolved. The phases were separated, and the etheral solution was washed with satd NH_4Cl (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The resulting colorless oil was purified with column chromatography (1:9 EtOAc–petroleum ether) to give 201 mg (95%) of **13** as a mixture of two diastereoisomers (2:1 ratio). **13a** (major): ^{1}H NMR ($CDCl_3$): δ 7.80–7.62 (m, 4 H); 7.52–7.30 (m, 6 H); 5.44 (s, 2 H); 4.74 (d, *J* 6.66 Hz, 1 H); 4.35 (dd, *J* 6.00, 4.52 Hz, 1 H); 4.21 (dd, *J* 6.60, 6.60 Hz, 1 H); 4.11 (ddd, *J* 8.71, 6.60, 1.82 Hz, 1 H); 2.01 (dd1/2ABq, *J* 4.80, 9.00, 13.80 Hz, 1 H); 1.87 (dd1/2ABq, *J* 1.81, 6.90, 13.82 Hz, 1 H); 1.36 (s, 3 H); 1.30 (s, 3 H); 1.09 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ 136.1; 136.0; 134.1; 133.6; 131.0; 129.8; 129.6; 129.0; 127.6; 127.4; 108.5; 82.1; 74.3; 69.4; 66.6; 39.2; 27.4; 27.0.; 25.3; 19.3. **13b** (minor): ^{1}H NMR ($CDCl_3$): δ 7.80–7.60 (m, 4 H); 7.50–7.30 (m, 6 H); 5.53 (s, 2 H); 4.82 (d, *J* 6.00 Hz, 1 H); 4.31 (dd, *J* 6.60, 6.60 Hz, 1 H); 3.89–3.68 (m, 2 H); 2.08–1.76 (m, 2 H); 1.67 (bs, 1 H); 1.35 (s, 3 H); 1.32 (s, 3 H); 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ 136.2; 135.9; 133.9; 133.5; 130.1; 129.8; 129.7; 129.6; 127.6; 127.4; 108.5; 82.6; 73.6; 70.6; 67.6; 39.7; 27.5; 27.0.; 25.2; 19.2.

Penta-O-*acetyl-2-deoxy*-D-arabino-*hexitol (2-deoxy*-D-*glucitol pentaacetate)* (**18**).—Enol **13** (201 mg, 0.459 mmol) was dissolved in a 1:1 methanol–dichloromethane mixture (6 mL). A stream of ozone was passed through the solution at −78 °C, until saturation was reached (blue color). The solution was flushed with oxygen untill the blue color disappeared. Methyl sulfide (0.5 mL), followed by solid sodium borohydride (87 mg, 2.3 mmol) was added, and the cooling bath was removed. After stirring at room temperature for additional 0.5 h, the reaction mixture was poured into diethyl ether (50 mL) and washed with satd aq solutions of $NaHCO_3$ (10 mL), NH_4Cl (10 mL), and NaCl (10 mL). The combined aq phases were washed with diethyl ether (2×10 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*RS*,4*R*,5*S*,6*R*)-4-(*tert*-butyldiphenylsilyloxy)-4,5-(isopropylidenedioxy)-1,2,7-heptanetriol (**14**) (216 mg, 0.456 mmol, 100% yield) as a clear oil that was immediately carried forward to the next step.

Sodium periodate (194 mg, 0.907 mmol) dissolved in water (1.5 mL) was added dropwise into a vigorously stirred suspension of silica gel (4 g) in dichloromethane (18 mL) [24]. Triol **14** (216 mg, 0.456 mmol) dissolved in dichloromethane (2 mL) was added, and the reaction mixture was stirred for 1 h. The reaction mixture was filtered, and the silica gel pad was washed with dichloromethane (2×10 mL). The combined filtrates were concentrated in vacuo to give crude (3*R*,4*S*,5*R*)-3-(*tert*-butyldiphenylsilyloxy)-6-hydroxy-4,5-(isopropylidenedioxy)hexanal (**15**) (148 mg, 0.34 mmol, 74%) as a colorless oil, which was used immediately in the next step.

Aldehyde **15** (148 mg, 0.335 mmol) was dissolved in 6 mL of absolute methanol and cooled to −20 °C. Sodium borohydride (25 mg, 0.67 mmol) was added, and reaction mixture was kept at −20 °C for 15 min. An excess of the hydride was then quenched with acetone (1 mL), and the mixture was diluted with 50 mL of diethyl ether. The ether solution was washed with satd aq NH_4Cl (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The crude diol was dissolved in dry tetrahydrofuran (10 mL) and treated with concentrated aqueous HCl (2 mL) for 16 h. The mixture was then evaporated to dryness, and the crude pentaol was dissolved in dry pyridine (4 mL) and treated with acetic anhydride (4 mL) in the

presence of a catalytic amount of DMAP. After stirring for 48 h the reaction mixture was poured into diethyl ether (50 mL) and washed with 1 N HCl (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL). After drying over $MgSO_4$, the etheral solution was filtered and evaporated to give crude pentaacetate **18**. The latter was purified by column chromatography using 2:8 EtOAc–petroleum ether as an eluent to give pure product **18** [31] (103 mg, 82%): $[\alpha]_D^{20}$ +36 (*c* 1.0, CH_2Cl_2); lit [31]. $[\alpha]_D^{25}$ +34.6 (*c* 0.1, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 5.33–5.20 (m, 2 H); 5.09 (ddd, *J* 2.71, 4.60, 8.00 Hz, 1 H); 4.20 (d1/2ABq, *J* 2.60, 12.59 Hz, 1 H); 4.11 (d1/2ABq, *J* 4.68, 12.49 Hz, 1 H); 4.02 (t, *J* 6.40 Hz, 2 H); 2.11 (s, 3 H); 2.034 (s, 3 H); 2.027 (s, 3 H); 2.024 (s, 3 H); 2.010 (s, 3 H); 1.90–1.75 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 170.7; 170.4; 170.1; 169.7 (2C); 70.5; 68.3; 67.6; 61.8; 60.2; 30.1; 20.7 (2C); 20.56 (3C).

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