Chemoenzymatic Synthesis of 3-Deoxy-D-*arabino*-heptulosonic Acid from Cycloheptatriene

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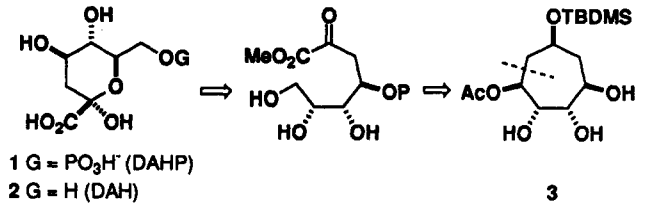
Received January 26, 1994

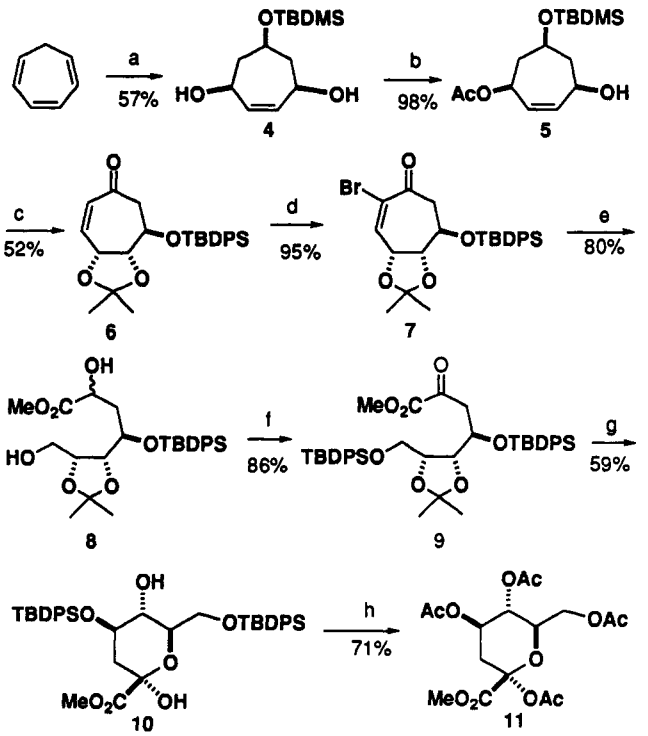
3-Deoxy-2-ulosonic acids occur as a variety of important natural products including sialic acids (*N*-acetylneuraminic acid and its derivatives),[1] 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) (1),[2] 3-deoxy-D-*manno*-octulosonic acid (KDO),[3] and 3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN).[4] These unusual carbohydrates have been the subject of synthetic studies by research groups throughout the world. Most approaches have been based on readily accessible carbohydrate precursors[5] such as D-glucose (DAH),[6,7] D-arabinose (KDO),[8] D-mannose (KDO),[9] D- or L-mannose (KDN),[5] and D-glyceraldehyde (KDO).[10] In fact, there are few exceptions[11] to carbohydrate-based chemical or enzymatic[12] syntheses. Furyl-substituted 1,4-dienes and optically pure α-selenated aldehydes have been recently reported as convenient starting materials for the synthesis of both *N*-acetylneuraminic acid (Neu5Ac) and KDO.[11a,b] The hetero Diels–Alder approach has also been demonstrated to be of utility.[11d]

DAHP[13] is recognized as an important intermediate in the shikimic acid biosynthetic pathway leading from D-glucose to aromatic amino acids.[2] We have described several chemoenzymatic syntheses of carbohydrates from cycloheptatriene.[14] In this paper we present a fully stereocontrolled total synthesis of the parent DAH (2) utilizing cycloheptatriene as a non-carbohydrate, achiral starting material.

Scheme 1



Scheme 2[a]



[a] (a) (i) HBF_4, Ph_3COH; (ii) Na_2CO_3, CH_3CN; (iii) $NaBH_4$, MeOH; (iv) TBDMSCl, imidazole, DMF; (v) $^1O_2$, CH_2Cl_2/MeOH; (vi) Zn/HOAC, CH_2Cl_2 (ref 14b); (b) *Pseudomonas cepacia* lipase (Amano PS-30), isopropenyl acetate (ref 14b and 15); (c) (i) TBDPSCl, imidazole, DMF; (ii) OsO_4, NMO, acetone, H_2O; (iii) dimethoxypropane, *p*-TsOH; (iv) KOH, MeOH; (v) MsCl, Et_3N, CH_2Cl_2; (vi) *p*-TsOH, MeOH; (vii) $(COCl)_2$, DMSO, Et_3N (ref 14c); (d) Br_2, TEA, CH_2Cl_2; (e) (i) $NaBH_4$, $CeCl_3$, MeOH, −78 °C; (ii) O_3, DMS, MeOH; (iii) $NaBH_4$; (f) (i) TPSCl, TEA, CH_2Cl_2; (ii) PDC/4-Å sieves, CH_2Cl_2; (g) TsOH, MeOH, 59%; (h) (i) TBAF, THF; (ii) Ac_2O/pyridine/DMAP. TBDMS = *tert*-butyldimethylsilyl. TBDPS = *tert*-butyldiphenylsilyl.

A simple retrosynthetic analysis shows that the title compound could be obtained from enantiopure monoacetate 3 (Scheme 1). Derivatives of the latter are readily available from monoacetate 5, which, in turn, has been prepared from cycloheptatriene, according to a previously reported reaction sequence which includes an enzymatic asymmetrization[14b,15] of the *meso*-diol 4 with *Pseudomonas cepacia* lipase in isopropenyl acetate (Scheme 2).

Monoacetate 5 was transformed into the α,β-unsaturated ketone 6,[14c] which, when treated with bromine and triethylamine, yielded the α-bromo enone 7. Luche reduction[16] of 7 gave a mixture of epimeric alcohols.

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Ozonolysis of this mixture in methanol:dichloromethane (1:1) followed by reductive workup with dimethyl sulfide[17] and immediate chemoselective reduction with sodium borohydride of the intermediate aldehyde gave ester 8, as a mixture of epimeric alcohols at C-2. Regioselective protection of the terminal hydroxyl group of 8 as the *tert*-butyldiphenylsilyl ether[18] and PDC oxidation[19] of the secondary alcohol yielded protected heptulosonic acid 9 possessing the desired *arabino* stereochemistry. Acid-catalyzed removal of the acetonide[20] gave cyclized DAH derivative 10 in 59% yield. Cleavage of the silyl ethers with tetrabutylammonium fluoride[21] yielded the methyl ester of DAH (2) which was characterized as its tetraacetate derivative 11. The acetylated 3-deoxy-*arabino*-heptulosonate (11) was found to be identical in all respects to the compound previously reported by Sugai *et al.*[5]

This synthesis of 3-deoxy-D-*arabino*-heptulosonic acid adds another example of our *de novo* approach to the synthesis of highly oxygenated natural products by chemoenzymatic strategies involving simple, cyclic hydrocarbons as starting materials.

Experimental Section

(4*R*,5*R*,6*R*)-2-Bromo-3,4-(isopropylidenedioxy)-5-[(*tert*-butyldiphenylsilyl)oxy]-2-cyclohepten-1-one (7). Enone 6[14c] (440 mg, 1 mmol) was dissolved in dichloromethane (10 mL) and the solution was cooled to 0 °C. Bromine (57 μL, 1.1 mmol) was added dropwise until the red color persisted. Triethylamine (701 μL, 5 mmol) was added. The mixture was kept at 0 °C for 5 min, evaporated to dryness, and chromatographed (10% EtOAc in petroleum ether) to yield 7 (390 mg, 75%) as a colorless oil: $[\alpha]^{20}_D$ −27.6 (*c* 0.75, $CHCl_3$); IR 3062, 2929, 2851, 2351, 2330, 1682, 1427, 1112, 1051, 702 cm^{-1}; ^1H NMR δ 7.90–7.70 (m, 4H), 7.60–7.30 (m, 6H), 7.12 (d, *J* = 6.0 Hz, 1H), 4.82 (dd, *J* = 5.1, 6.3 Hz, 1H), 4.29 (dd, *J* = 5.7 Hz, 1H), 4.12 (dd, *J* = 5.7, 8.1 Hz, 1H), 3.02 ($^1/_2$ABq, *J* = 16.5 Hz, 1H), 2.82 (d, $^1/_2$ABq, *J* = 8.7, 16.5 Hz, 1H), 1.40 (s, 3H), 1.31 (s, 3H), 1.04 (s, 9H); ^{13}C NMR δ 190.9, 143.1, 135.8, 134.8, 130.1, 130.0, 129.5, 127.9, 127.7, 126.8, 109.9, 79.7, 74.5, 68.8, 45.0, 26.9, 26.8, 26.6, 19.1.

Methyl 3-Deoxy-4,7-bis-*O*-(*tert*-butyldiphenylsilyl)-5,6-*O*-isopropylidene-D-*arabino*-heptulosonate (9). Bromo enone 7 (1.2 g, 2.4 mmol) was dissolved in methanol (24 mL) and $CeCl_3 \cdot 7H_2O$ (0.89 g, 2.6 mol) was added. The solution was stirred at rt for 10 min and cooled to −78 °C and $NaBH_4$ (90 mg, 2.4 mmol) was added. The reaction mixture was kept at −78 °C for 15 min; then excess borohydride was quenched with acetone. The solution was poured into diethyl ether (250 mL). The ether solution was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), NH_4Cl (50 mL), and brine (50 mL), dried with $MgSO_4$, filtered, and evaporated. Purification of the crude material by silica gel column chromatography with 20% EtOAc/petroleum ether as eluent gave 1.1 g (2.1 mmol, 90%) of a mixture (1:1) of epimeric alcohols.[22]

The mixture of alcohols was dissolved in methanol:dichloromethane (1:1, 18 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. Dimethyl sulfide (1.0 mL) followed by solid sodium borohydride (80 mg, 2.1 mmol) was added and the cooling bath was removed. After being stirred at room temperature for an additional 0.5 h, the reaction mixture was poured into diethyl ether (150 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), NH_4Cl (50 mL), and NaCl (50 mL). The combined aqueous phases were extracted with diethyl ether (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give an oil which was chromatographed on silica gel (30% EtOAc/petroleum ether) to give dihydroxy ester 8 (mixture of epimers at C-2) (722 mg, 1.7 mmol, 79% yield) as a clear oil.

The above mixture of diols (52 mg, 0.1 mmol), dissolved in dry dichloromethane (5 mL), was treated with *tert*-butyldiphenylchlorosilane (31 mg, 0.11 mmol) in the presence of triethylamine (29 μL, 2 mmol) at room temperature for 48 h. The mixture was diluted with diethyl ether (50 mL) and washed with saturated aqueous NH_4Cl (2 × 10 mL) and brine (10 mL) and then dried over $MgSO_4$. The solution was filtered and evaporated and the residue was purified by column chromatography (10% EtOAc in petroleum ether) to give 61 mg (0.08 mmol, 80%) of the terminal (*tert*-butyldiphenylsilyl)oxy derivative (mixture of C-2 epimers).[23]

The above mixture of epimeric alcohols (55 mg, 0.075 mmol) was dissolved in dry dichloromethane (8 mL) and treated with pyridinium dichromate (560 mg, 1.5 mmol) in the presence of freshly dried 4-Å molecular sieves (500 mg) for 16 h. Solids were filtered off and the solvent was evaporated. The oily material was purified by silica gel column chromatography (10% EtOAc/petroleum ether) to give DAH derivative 9 (47 mg, 0.064 mmol, 86%) as a colorless oil: $[\alpha]^{23}_D$ −2.94 (*c* 1.5, $CHCl_3$); ^1H NMR δ 7.80–7.60 (m, 4H), 7.55–7.45 (m, 4H), 7.40–7.30 (m, 12H), 4.55 (ddd, *J* = 4.2, 7.5, 11.7 Hz, 1H), 4.20 (dd, *J* = 5.4, 7.8 Hz, 1H), 4.13 (dt, *J* = 4.8, 6.9 Hz, 1H), 3.75 (s, 3H), 3.60 (d, $^1/_2$ABq, *J* = 7.2, 10.8 Hz, 1H), 3.42 (d, $^1/_2$ABq, *J* = 4.8, 10.5 Hz, 1H), 3.19 (d, $^1/_2$ABq, *J* = 6.9, 17.1 Hz, 1H), 3.12 (d, $^1/_2$ABq, *J* = 4.2, 17.1 Hz, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 0.97 (s, 9H), 0.95 (s, 9H); ^{13}C NMR δ 191.1, 160.9, 136.2, 136.0, 135.5, 133.1, 133.0, 129.6, 129.4, 129.2, 127.7, 127.3, 127.1, 108.2, 79.3, 77.6, 67.7, 63.1, 52.8, 43.7, 27.5, 27.0, 26.8, 25.0, 19.4, 19.0.

Methyl 3-Deoxy-4,7-bis-*O*-(*tert*-butyldiphenylsilyl)-D-*arabino*-heptopyranosulosonate (10). Keto ester 9 (19 mg, 0.026 mmol) was dissolved in dry methanol and a catalytic amount of *p*-toluenesulfonic acid was added. The mixture was stirred for 4 h, diluted with diethyl ether (50 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), NH_4Cl (10 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give 10 (10 mg, 0.014 mmol, 59%) as an oil: $[\alpha]^{20}_D$ +7.8 (*c* 0.5, $CHCl_3$); ^1H NMR δ 7.80–7.60 (m, 8H), 7.50–7.30 (m, 12H), 4.21–4.10 (m, 1H), 3.90–3.85 (m, 1H), 3.79 (s, 3H), 3.77–3.66 (m, 2H), 3.51–3.48 (m, 1H), 2.11 ($^1/_2$ABq, *J* = 12.3 Hz, 1H), 1.92 (d, $^1/_2$ABq, *J* = 4.8, 12.6 Hz, 1H), 1.09 (s, 9H), 1.05 (s, 9H); ^{13}C NMR δ 170.3, 136.1, 136.0, 135.8, 135.7, 135.6, 135.5, 133.8, 133.7, 129.8, 129.5, 127.8, 127.7, 127.6, 127.5, 94.9, 73.8, 72.6, 71.7, 63.6, 53.2, 38.4, 26.9, 26.7, 19.3.

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(22) A small sample of these epimeric alcohols was purified by silica gel chromatography. The faster moving isomer exhibited the following spectroscopic data: ^1H NMR δ 7.80–7.60 (m, 4H), 7.50–7.30 (m, 6H), 6.09 (d, *J* = 3.9 Hz, 1H), 4.72–4.64 (m, 1H), 4.28–4.02 (m, 3H), 2.10–1.95 (m, 2H), 1.35 (s, 3H), 1.27 (s, 3H), 1.09 (s, 9H); ^{13}C NMR δ 136.2, 136.1, 131.5, 129.9, 129.8, 127.7, 127.6, 109.0, 82.7, 74.0, 70.6, 69.1, 37.0, 27.1, 27.2, 25.0, 18.7. The slower moving isomer exhibited the following data: ^1H NMR δ 7.85–7.65 (m, 4H), 7.55–7.30 (m, 6H), 6.02 (d, *J* = 2.1 Hz, 1H), 4.80–4.70 (m, 1H), 4.37 (dd, *J* = 6.9 Hz, 1H), 3.84 (dd, *J* = 8.4 Hz, 1H), 3.70–3.55 (m, 1H), 2.03 (d, $^1/_2$ABq, *J* = 6.3, 14.1 Hz, 1H), 1.86 (d, $^1/_2$ABq, *J* = 4.5, 14.1 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.10 (s, 9H).

(23) A small sample of these epimeric alcohols was separated by silica gel chromatography. The faster moving isomer exhibited the following spectroscopic data: ^1H NMR δ 7.71 (dd, *J* = 7.6 Hz, 4H), 7.59 (dd, *J* = 6.9 Hz, 4H), 7.45–7.20 (m, 12H), 4.39 (bd, *J* = 10.8 Hz, 1H), 4.20–4.10 (m, 2H), 4.05 (dd, *J* = 5.4, 10.5 Hz, 1H), 3.73 (s, 3H), 3.45 (d, $^1/_2$ABq, *J* = 5.7, 11.4 Hz, 1H), 3.24 (d, $^1/_2$ABq, *J* = 6.3, 11.1 Hz, 1H), 2.50 (bs, 1H), 2.10–1.95 (m, 1H), 1.80–1.68 m, 1H), 1.26 (s, 3H), 1.05 (s, 3H), 1.00 (s, 9H); ^{13}C NMR δ 175.1, 136.1, 135.9, 135.6, 135.5, 133.7, 129.6, 129.4, 129.1, 127.6, 127.2, 127.0, 108.0, 79.7, 77.8, 68.8, 67.3, 63.0, 52.3, 38.5, 27.7, 27.1, 26.8, 25.1, 19.5, 19.1. The slower moving epimer exhibited the following spectroscopic data: ^1H NMR δ 7.80–7.75 (m, 4H), 7.60–7.45 (m, 4H), 7.40–7.20 (m, 12H), 4.57 (dd, *J* = 2.4, 9.0 Hz, 1H), 4.47 (dd, *J* = 5.1, 8.4 Hz, 1H), 4.26–4.10 (m, 2H), 3.64 (s, 3H), 3.49 (dd, $^1/_2$ABq, *J* = 7.2, 8.4, 10.8 Hz, 1H), 3.35 (d, $^1/_2$ABq, *J* = 4.8, 10.8 Hz, 1H), 2.57 (bs, 1H), 1.98 (dd, $^1/_2$ABq, *J* = 2.7, 5.4, 14.7 Hz, 1H), 1.86 (dd, $^1/_2$ABq, *J* = 3.0, 9.6, 14.7 Hz, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 1.06 (s, 9H); ^{13}C NMR δ 176.0, 136.3, 136.2, 135.5, 134.1, 133.2, 133.1, 131.8, 129.8, 129.6, 129.4, 129.3, 127.6, 127.3, 127.0, 107.7, 79.5, 77.3, 69.1, 66.6, 63.0, 52.4, 38.9, 27.9, 27.0, 26.7, 25.4, 19.4, 19.0.

Methyl 3-Deoxy-2,4,5,7-*O*-tetraacety-D-*arabino*-heptopyranosulosonate (11). Silyl-protected pyranoside **10** (20 mg, 0.028 mmol), dissolved in dry THF (2 mL), was treated with 1 M tetrabutylammonium fluoride in THF (60 μL, 0.06 mmol). The reaction mixture was stirred at rt for 15 min and then evaporated to dryness. The residue was passed through a silica gel column with 50% EtOAc in petroleum ether as eluent to give an oily residue which was dissolved in dry pyridine (1.5 mL) and treated with acetic anhydride (22.8 μL, 0.224 mmol) and a catalytic amount of DMAP to yield after chromatographic purification, the known tetraacetate (9 mg, 0.023 mmol, 82%) as an oil (spectroscopic and polarimetric data match those previous reported[5]): $[\alpha]^{20}_D$ +52 (*c* 1, $CHCl_3$) [lit.[5] $[\alpha]^{20}_D$ +54.0 (*c* 0.5, $CHCl_3$)]; ^{1}H NMR δ 4.35 (dd, *J* = 4.3, 12.4 Hz, 1H), 4.10 (dd, *J* = 2.3, 12.4 Hz, 1H), 4.06 (ddd, *J* = 2.3, 4.3, 10.2 Hz, 1H), 3.81 (s, 3H), 2.66 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.17 (s, 3H), 2.09 (dd, *J* = 11.4, 13.6 Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H); ^{13}C NMR δ 170.7, 170.3, 169.6, 168.4, 166.4, 97.3, 71.5, 68.4; 68.2, 61.7, 53.3, 35.6, 20.8, 20.7, 20.7, 20.6.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE 9223011).

Supplementary Material Available: ^{1}H NMR (300 MHz) of **7**, **9**, and **10**; ^{13}C NMR of **10** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see current masthead page for ordering information.