Synthesis of 2,3,5-Tri-O-benzyl-d-arabinitol 1,4-Cyclic Sulfate and Its Conversion into Potential Precursors of Shikimate Substrate Analogues

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A practical route to deoxycarbohydrates, which may serve as starting materials in the synthesis of shikimate substrate analogues is described. The deoxy derivatives ethyl 4,5,7-tri-O-benzyl-3-deoxy-d-arabino-2-heptulopyranosonate (10), 3,4,6-tri-O-benzyl-2-deoxy-α/β-d-arabino-hexopyranose (11) and 3,4,6-tri-O-benzyl-2-deoxy-d-arabino-hexono-1,5-lactone (12) were prepared from 2,3,5-tri-O-benzyl-d-arabinitol 1,4-sulfate (3b) by regioselective nucleophilic ring opening with 2-ethoxy carbonyl-2-lithio-1,3-dithiane (4), bis(methylthio)methyl lithium (5), and trimethylthio)methyl lithium (6), respectively, followed by consecutive hydrolysis of the resulting sulfates and unmasking of the alkylthio functions.

The production of plants and microorganisms of the aromatic amino acids phenylalanine, tyrosine and tryptophan is regulated by the shikimate pathway. The first metabolite in the pathway is the seven-carbon keto acid, 3-deoxy-d-arabino-heptulosonate 7-phosphate (DAHP), which is subsequently transformed to dehydroquinate (DHQ) by the enzyme dehydroquinase. Recent studies by Bartlett and Knowles nicely demonstrated that substrate analogues of DAHP are valuable tools to probe the enzyme-bond intermediates proposed to be involved in the five-step mechanistic pathway followed by DHQ synthase.

We earlier published that valuable derivatives of the unusual eight-carbon keto acid 3-deoxy-d-manno-2-octulosonic acid (KDO) were accessible by nucleophilic ring opening of a seven-membered open chain sugar cyclic sulfate. We now report that application of the cyclic sulfate principle gives an easy access to interesting precursors (i.e. compounds 10–12) of DAHP analogues.

The individual steps involved in the synthesis of 2,3,5-tri-O-benzyl-d-arabinitol 1,4-cyclic sulfate (3b), which is the key intermediate for the preparation of compounds 10–12, is outlined in Scheme 1. In the first step d-arabinitol is transformed under Fischer conditions to methyl α/β-d-arabinitofuranoside. Benzylxation of the latter gave, after purification by column chromatography, homogeneous 11 as a mixture of anomers. Acetolysis of 1 and subsequent reduction with sodium borohydride yielded, after column chromatography, 2,3,5-tri-O-benzyl-d-arabinitol 2. Transformation of 2 into the 1,4-cyclic sulfate 3b was easily accomplished according to a published two-step procedure. Thus, treatment of 2 with thionyl chloride in the presence of triethylamine gave the 1,4-cyclic sulfate 3a, which was oxidized with sodium periodate and catalytic ruthenium chloride hydrate to give the 1,4-cyclic sulfate 3b in 63% overall yield for the six steps.

The preparation of compounds 10–12 starting from the common intermediate 3b is illustrated in Scheme 2. For example, ethyl 4,5,7-tri-O-benzyl-3-deoxy-d-arabino-2-heptulopyranosonate (10) was prepared by the following typical sequence of reactions. In the first step, cyclic sulfate 3b was added to anion 4, prepared by treating ethyl 1,3-dithiane-2-carboxylate in tetrahydrofuran and a small amount of hexamethylphosphoric triamide with butyllithium. TLC analysis, after 16 h at 20°C, indicated complete conversion of 3b into the charged sulfate derivative 7a. Removal of the sulfate group in intermediate 7a was effected in situ by mild acidic hydrolysis to give, after silica gel chromatography, homogeneous 7b. Finally, unmasking of the dithioketal function in 7b with N-bromosuccinimide (NBS) afforded anomerically pure (α-form) 10 in 32% overall yield (based on d-arabinose). In a similar fashion (Scheme 2), the interesting derivatives 11 (α/β-mixture) and 12 could be prepared in a satisfactory overall yield.

Scheme 1

Scheme 2
Table. Compounds 7b–9b and 10–12 Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Rf</th>
<th>Molecular Formula* or Lit. mp (°C)</th>
<th>δ (CDCl3/TMS)</th>
</tr>
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<tbody>
<tr>
<td>7b</td>
<td>60</td>
<td>0.53 (C)</td>
<td>+12.8</td>
<td>C₃₅H₄₀O₈S₂ (516.8)</td>
<td>13.8 (CH₂CH₃), 24.6, 27.4, 27.8 (SCH₂CH₂CH₂S), 38.7 (C-3), 52.9 (C-2), 61.7 (CH₂CH₃), 71.1 (C-1), 71.2 (C-7), 72.7, 73.0, 73.4 (CH₂Ph), 75.3, 75.7 (C-4, 5), 127–129 (CH₃OMe), 137.2, 137.6, 138.2 (C=O), 170.5 (C-1)</td>
</tr>
<tr>
<td>8b</td>
<td>54b</td>
<td>0.65 (C)</td>
<td>+13.9</td>
<td>C₂₉Hₙ₆O₈S₂ (512.7)</td>
<td>13.1 (CH₂S), 35.3 (C-2), 51.0 (C-1), 71.2 (C-6), 71.0, 76.6, 76.9 (C-3, 4, 5), 73.1, 73.3, 73.5 (CH₂Ph), 126–129 (CH₃OMe), 137.8, 138.1 (C=O)</td>
</tr>
<tr>
<td>9b</td>
<td>60</td>
<td>0.67 (C)</td>
<td>+11.3</td>
<td>C₂₉Hₙ₆O₈S₃ (558.8)</td>
<td>13.0 (CH₂S), 37.9 (C-2), 71.1 (C-1), 71.3 (C-6), 72.6, 72.8, 73.5 (CH₃CH₃), 71.7, 74.6, 77.1 (C-3, 4, 5), 127–129 (CH₃OMe), 137.5, 137.6, 138.3 (C=O)</td>
</tr>
<tr>
<td>10</td>
<td>86</td>
<td>0.71 (B)</td>
<td>+25.4</td>
<td>C₃₀Hₙ₈O₇ (506.6)</td>
<td>13.9 (CH₂CH₃), 36.1 (C-3), 62.4 (CH₂CH₃), 68.9 (C-7), 71.7 73.2, 74.9 (CH₂Ph), 73.0, 77.5, 78.0 (C-4, 5, 6), 94.8 (C-2), 127–129 (CH₃OMe), 138.2, 138.4 (C=O), 169.8 (C-1)</td>
</tr>
<tr>
<td>11</td>
<td>84</td>
<td>97–99</td>
<td>0.19 (C)</td>
<td>+48.9</td>
<td>96–97²⁵</td>
</tr>
<tr>
<td>12</td>
<td>83⁶,a</td>
<td>82–83</td>
<td>0.71 (C)</td>
<td>+44.0f</td>
<td>82–83²⁶</td>
</tr>
</tbody>
</table>

a Satisfactory microanalyses obtained: C ± 0.21, H ± 0.19.
b Bis(methylthio)methyl lithium²³ was used as the nucleophile.
Substitution of 3b proceeded within 1 h.
c Tris(methylthio)methyl lithium²⁴ was used as the nucleophile.
Substitution of 3b proceeded within 0.5 h.
d 6 Mmol of NBS per mmol of 9b was used.

In conclusion, the cyclic sulfate approach described in this paper presents a convenient route to prepare precursors of shikimate substrate analogues.

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Optical rotations at the Na-D-line were obtained at 20 °C using a Perkin-Elmer 141 polarimeter. TLC analyses were performed on silica gel glass plates (Schleicher & Schüll, F 1500 LS 254) in the following solvent systems: A, petroleum ether (bp 40–60 °C)/Et₂O (1:1); B, CH₂Cl₂/acetone (95:5); and C, CH₂Cl₂/acetone (97:3). Compounds were visualized by UV light and by spraying with conc. sulfuric acid in MeOH (2:5, v/v) followed by charring at 140 °C for a few min. Column chromatography was performed on Merck silica gel (230–400 mesh, ASTM). Evaporation was carried out below 40 °C under reduced pressure (20 Torr or 1 Torr). H-NMR spectra were measured at 300 MHz using a Bruker WM-300 spectrometer, equipped with an ASPECT-2000 computer, operating in the Fourier transform mode. C-NMR spectra were measured at 50.1 MHz using a Jeol JNM-FX 200 spectrometer on line with a JEC 980 B computer. Chemical shifts are given in δ relative to TMS as internal standard.

Methyl 2,3,5-Tris(3-benzyl-α-β-α-arabinofuranoside (1):

D-Arabinose (5.5 g, 10 mmol) is added to a mixture of anhydrous MeOH (40 mL) and acetyl chloride (0.71 mL). After stirring for 12 h at 20 °C, the mixture is neutralized with NaOMe and concentrated. The sirup is dissolved in DMF (30 mL) and NaH (1.19 g, 80%, 1.3 equiv) and benzyl bromide (4.5 mL, 1.3 equiv) are added. After 2 h, MeOH (10 mL) is added, and the mixture is concentrated, redissolved in CH₂Cl₂ (100 mL), extracted with water (20 mL) and brine (20 mL), dried (MgSO₄), and evaporated. The residue is chromatographed on silica gel (elucent: petroleum ether (bp 40–60 °C)/Et₂O, 1:1) to give I; yield: 3.6 g (83%); Rₚ, 0.75 (A); [x]D²⁰ + 24.7° (c = 1, CHCl₃).

C₃₅H₄₀O₈S₂ calc. C 74.63 H 6.96
(434.5) found 74.57 6.91

C₃₅H₄₀O₈S₂ (516.8) δ (CDCl₃) = 13.8 (CH₂CH₃), 24.6, 27.4, 27.8 (SCH₂CH₂CH₂S), 38.7 (C-3), 52.9 (C-2), 61.7 (CH₂CH₃), 71.1 (C-6), 71.2 (C-7), 72.7, 73.0, 73.4 (CH₂Ph), 75.3, 75.7 (C-4, 5), 127–129 (CH₃OMe), 137.2, 137.6, 138.2 (C=O), 170.5 (C-1)
CH₂Cl₂ (100 mL) is added and the layers are separated. The organic layer is washed with brine (25 mL), dried (MgSO₄) and concentrated. The residue is filtered through a pad of silica gel (eluents CH₂Cl₂/acetone: 97:3) to afford 3b; yield: 2.84 g (84%); Rf 0.71 (CH₂Cl₂). [α]ᵢ²⁰ = +26.9° (c = 1, CHCl₃).

C₂₆H₂₃O₂S eal. C 64.45 H 5.82 (484.6) found 64.53 5.69

**Ethyl 4,5,7-Tri-O-benzyl-3-deoxy-α-arabinofuranose-2-ethylpyranoside (7b): Typical Procedure:**

Ethyl 2-ethoxycarbonyl-1,3-dithiane (1.3 mmol) is dissolved in dry THF (2.6 mL) and HMPT (0.8 mL). The temperature is lowered to −60 °C and BuLi (0.81 mL, 1.6 M) is added. After stirring for 1.5 h at −40 °C, cyclic sulfate 3b (484 mg, 1 mmol in THF) is added. The mixture is allowed to warm r.t. and stirred until TLC analysis, after 1 h at 20 °C, showed complete conversion of 3b. Conc. H₂SO₄ (50 mL) and water (18 mL) are added and the mixture is stirred for 2 h at 50 °C. The mixture is diluted with Et₂O, washed with sat. aq NaHCO₃ (2 × 5 mL) and water (5 mL), dried (Na₂SO₄), and concentrated. The resulting oil is chromatographed on silica gel (eluents: petroleum ether (bp 40–60 °C)/Et₂O, 1:1) to give 7b; yield: 357 mg (60%) (Table).

**Ethyl 4,5,7-Tri-O-benzyl-3-deoxy-α-arabinofuranose-2-ethylpyranoside (7b): Typical Procedure:**

To a cooled (0 °C) solution of compound 7b (1 mmol) in a mixture of MeCN (8 mL) and aq Et₃N/HCO₃ (2 mL, 0.25 M) is added NBS (4 mmol). After stirring for 5 min, the solution is poured into an aqueous mixture of NaHCO₃ and Na₂SO₄ (50 mL, 1:1, w/w, 10%) and diluted with CH₂Cl₂ (75 mL). The organic phase is washed with water (15 mL), dried (MgSO₄), and concentrated. The oil thus obtained is purified by silica gel column chromatography (eluents: petroleum ether (bp 40–60 °C)/Et₂O, 1:1) to afford 10; yield: 435 mg (86%) (Table).

1H-NMR (CDCl₃): δ = 1.31 (t, 3H, J = 7.1 Hz, CH₃CH₂), 2.10 (t, 1H, J₃,4,5 = 12 Hz, CH₂), 2.29 (dd, 1H, J₃,4,5 = 5.0 Hz, H-3e), 3.61 (dd, 1H, J = 9.2, 9.8 Hz, H-5), 3.66 (dd, 1H, J₄,5 = 1.8, J₃,4,5 = 11.1 Hz, H-7), 3.75 (dd, 1H, J₃,4,5 = 4.6 Hz, H-7), 4.04 (m, 2H, H-4, H-6), 4.66 (m, 2H, CH₂CH₂), 4.5–5.0 (m, 6H, CH₂Ph), 7.0–7.5 (m, 15H arom.).

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