## Note

# Synthesis of a chiral polysubstituted *cis*-fused decalin containing an angular *C*-methyl group by an intramolecular Diels-Alder reaction

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Herczegh et al.<sup>1-3</sup> have observed exceptionally high diastereoselectivity in intramolecular Diels-Alder reactions of various nona-, deca-, and dodeca-trienes substituted in the linking chain and prepared from carbohydrates. In utilising this type of reaction in the carbohydrate field to construct chiral bicyclic and tricyclic systems related to natural products<sup>4,5</sup>, we have now prepared a chiral polyhydronaphthalene having an angular C-methyl group as found in many biologically important terpenes<sup>6</sup>.

Wittig reaction of 7-deoxy-1,2:3,4-di-O-isopropylidene- $\alpha$ -D-galacto-heptopyranos-6-ulose<sup>7</sup> (1), with methylenetriphenylphosphorane furnished 6,7-dideoxy-1,2:3,4-di-O-isopropylidene-6-C-methylene- $\alpha$ -D-galacto-hept-6-enopyranose (2, 72%). Conversion of 2 into the diethyl dithioacetal 3, followed by benzylation ( $\rightarrow$  4), and then mercury(II) salt-mediated hydrolysis afforded 2,3,4,5-tetra-O-benzyl-6,7-dideoxy-6-C-methylene-D-galacto-heptose (5, 43% from 2).

Treatment of **5** with allylidenetriphenylphosphorane afforded (5S,6R,7S,8R)-5,6,7,8-tetrabenzyloxy-9-methyldeca-1,3(E,Z),9-triene (**6**, 60%). HPLC and <sup>1</sup>H-NMR spectroscopy indicated a 3:2 ratio of the components but the identity of the preponderant could not be ascertained.



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Thermal intramolecular Diels-Alder reaction of **6** in toluene at 200° gave (<sup>1</sup>H-NMR data) a unique 1,2,3,4,5,8,9,10-octahydronaphthalene product to which the structure **7** was assigned. The <sup>1</sup>H-NMR spectrum of the product revealed H-1 to be axial ( $J_{1,2}$  10 Hz) and spin-decoupling experiments confirmed the *D*-galacto stereochemistry at C-1,2,3,4. The *cis* configuration of the ring junction, suggested by the chemical shift (14.0 ppm) of the <sup>13</sup>C resonance of the angular *C*-methyl group, was expected by the fact that *cis* isomers were obtained exclusively from closely related trienic systems<sup>3</sup> (the resonance would be expected to be at markedly higher field for the *trans* isomer). The chemical shift of the <sup>13</sup>C resonance of the C-19 angular methyl carbon is diagnostic for A/B-*trans* and A/B-*cis* steroidal compounds<sup>8</sup>. These results reduced the number of structural possibilities to **7** and the isomer **8**.

The choice between 7 and 8 was based on NOE data. Thus, pre-irradiation of the angular C-methyl group caused NOE of the resonance for H-8, but not of that for H-2 as would be expected in structure 8. Structure 7 may be favoured since there is only one 1,3-diaxial interaction (O-4/C-9), whereas there are two in 8 (O-4/Me-10 and O-3/C-6).

The question arises as to how the E,Z mixture of **6** could afford only one octahydronaphthalene product **7**. Herczegh et al.<sup>3</sup> found that pure deca-1,7*E*,9and -1,7*Z*,9-trienes gave the same bicyclic structure on intramolecular Diels-Alder reaction. Moreover, some *E*-triene was detected by chromatography as an intermediate when the *Z*-triene was subjected to the reaction, which indicated thermal isomerisation. The formation of **7** from **6** may be explained in the same way.

The character of the dienophile and the stereochemistry of the benzyloxy substituents appear not to affect the stereochemical outcome of the reaction. Thus, as found for the reaction  $6 \rightarrow 7$ , *cis* stereochemistry at the ring junction of the product was found by Herczegh et al.<sup>1-3</sup> where a monosubstituted dienophile and *O*-isopropylidene groups in the linking chain originating from D-glucose characterised the starting decatrienes<sup>3</sup>.

In view of the bulky O-benzyl substituents and the cis product formed, the transition state 9 is preferred for the E isomer of 6. For the Z isomer of 6, the strain in any reasonable transition state would make an intramolecular Diels-Alder reaction unlikely.



### EXPERIMENTAL

General procedures.—A Perkin–Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific optical rotations. The NMR spectra (internal Me<sub>4</sub>Si) were recorded for solutions in CDCl<sub>3</sub> (<sup>1</sup>H at 200 and 400 MHz, <sup>13</sup>C at 50.31 MHz) with a Bruker WP-200 spectrometer; <sup>13</sup>C chemical shifts for the resonances of aromatic carbons are not given. Microanalyses were performed by the Service Central de Microanalyse du C.N.R.S. Silica Gel 60 PF<sub>254</sub> (Merck) activated at 120° was used for TLC and column chromatography. The term "standard work-up" means that the organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered, and the solvent was evaporated under reduced pressure.

6,7-Dideoxy-1,2:3,4-di-O-isopropylidene-6-C-methylene-α-D-galacto-hept-6-enopyranose (2).—To a solution of methyltriphenylphosphonium bromide (28 g, 80 mmol) in tetrahydrofuran (50 mL) was added, dropwise at 0°, 1.6 M butyl-lithium in hexane (55 mL, 88 mmol), and the mixture was stirred for 1 h. A solution of 1 (9.0 g, 33.3 mmol) in tetrahydrofuran (250 mL) was then added rapidly at 0°, and the mixture was left to warm to room temperature during 1 h, then diluted with ether-acetone (4:1, 300 mL). After usual work-up, column chromatography (hexane-ethyl acetate, 8:1) of the product gave syrupy 2 (6.4 g, 72%),  $[\alpha]_D + 87^\circ$  (c 0.9, chloroform). Mass spectrum (CI): m/z 271 (M<sup>+</sup>+H). NMR data: <sup>1</sup>H, δ 5.61 (d, 1 H,  $J_{1,2}$  5 Hz, H-1), 5.11 (s, 1 H, H-8a), 5.00 (s, 1 H, H-8b), 4.64 (dd, 1 H,  $J_{2,3}$  8,  $J_{3,4}$  2.5 Hz, H-3), 4.36 (dd, 1 H,  $J_{4,5}$  2 Hz, H-4), 4.33 (dd, 1 H, H-2), 4.20 (bs, 1 H, H-5), 1.83 (s, 3 H, H-7,7,7), 1.53, 1.47, and 1.35 (3 s, 12 H, CMe<sub>2</sub>); <sup>13</sup>C, δ 140.7 (C-6), 111.4 (C-8), 108.8 and 107.9 (CMe<sub>2</sub>), 96.3 (C-1), 72.3, 70.8, 70.3, and 69.7 (C-2,3,4,5), 25.7, 25.6, 24.5, and 24.2 [2 C(CH<sub>3</sub>)<sub>2</sub>], 19.4 (C-7).

Anal. Calcd for C<sub>14</sub>H<sub>22</sub>O<sub>5</sub>: C, 62.20; H, 8.20. Found: C, 62.19; H, 8.05.

2,3,4,5-Tetra-O-benzyl-6,7-dideoxy-6-C-methylene-D-galacto-heptose diethyl dithioacetal (4).—To a stirred solution of 2 (990 mg, 3.67 mmol) in ethanethiol (1.83 mL, 24 mmol) was added, dropwise at 0°, concd HCl (1.06 mL) until a precipitate was formed. Stirring was continued at 0° for 30 min, the solution was left to warm to room temperature and then diluted with ice-water, and the precipitate was collected, washed until neutral, and dried. To a solution of the dry residue in tetrahydrofuran (30 mL) was added sodium hydride (1.08 g, 20 mmol), and the mixture was stirred for 30 min. Tetrabutylammonium iodide (15 mg, 0.04 mmol) and freshly distilled benzyl bromide (2.1 mL, 18 mmol) were added and stirring was maintained at room temperature for 15 h. After removal of the solvent and washing of the crude residue with pentane (100 mL), column chromatography (hexane-ethyl acetate, 60:1) gave 4 as a yellow oil (1.48 g, 47%),  $[\alpha]_D = 6^\circ$  (c 1.1 chloroform). Mass spectrum (CI): m/z 657 (M<sup>+</sup> + H). NMR data: <sup>1</sup>H,  $\delta$  5.20 (s, 1 H, H-8a), 5.10 (s, 1 H, H-8b), 4.00 (d, 1 H, J<sub>1,2</sub> 10 Hz, H-1), 1.80 (s, 3 H, H-7,7,7);  $^{13}$ C,  $\delta$  142.0 (C-6), 115.5 (C-8), 54.8 (C-1), 25.2 (2 CH<sub>3</sub>CH<sub>2</sub>S), 18.8 (C-7), 14.4 (2  $CH_3CH_2S$ ).

Anal. Calcd for  $C_{40}H_{48}S_2O_4$ : C, 73.13; H, 7.36; S, 9.76. Found: C, 73.36; H, 7.30; S, 9.46.

2,3,4,5-Tetra-O-benzyl-6,7-dideoxy-6-C-methylene-D-galacto-heptose (5).—To a stirred solution of 4 (430 mg, 0.66 mmol) in acetone-water (4:1, 15 mL) were added at room temperature, mercuric oxide (324 mg, 1.5 mmol) and mercuric chloride (820 mg, 1.5 mmol). The mixture was warmed up to 60° and stirring was continued for 30 min. The usual work-up gave syrupy 5 (330 mg, 91%),  $[\alpha]_D - 1^\circ$  (c 1.0, chloroform). Mass spectrum (CI); m/z 551 (M<sup>+</sup>+ H). NMR data: <sup>1</sup>H,  $\delta$  9.67 (s, 1 H, H-1), 7.33-7.21 (m, 20 H, 4 Ph), 5.14 (s, 1 H, H-8a), 5.08 (s, 1 H, H-8b), 4.73-4.00 (m, 12 H, 4 CHOR and 4 OCH<sub>2</sub>Ph), 1.73 (s, 3 H, H-7,7,7); <sup>13</sup>C (C<sub>6</sub>D<sub>6</sub>),  $\delta$  200.6 (C-1), 142.4 (C-6), 115.6 (C-8), 18.5 (C-7).

Anal. Calcd for C<sub>36</sub>H<sub>38</sub>O<sub>5</sub>: C, 78.55; H, 6.91. Found: C, 78.33; H, 7.12.

(5S,6R,7S,8R)-5,6,7,8-Tetrabenzyloxy-9-methyldeca-1,3(E,Z),9-triene (6).—To a stirred solution of allyltriphenylphosphonium bromide (570 mg, 1.5 mmol) in tetrahydrofuran (5 mL) was added, at  $-40^{\circ}$  during 1 h, 1.6 M butyl-lithium in hexane (1.1 mL, 1.65 mmol) and then a solution of 5 (270 mg, 0.49 mmol) in tetrahydrofuran (10 mL). The mixture was left overnight at room temperature. After the usual work-up, column chromatography (hexane-ethyl acetate, 15:1) of the crude product gave 6 (153 mg, 60%), isolated as a syrup. Mass spectrum (CI): m/z 575 (M<sup>+</sup> + H). <sup>1</sup>H-NMR data (product ratio 3:2): major product,  $\delta$  6.56 (m, 1 H, H-2), 6.14 (t, 1 H,  $J_{2,3} = J_{3,4} = 5$  Hz, H-3), 5.53 (t, 1 H,  $J_{4,5}$  5 Hz, H-4), 1.75 (s, 3 H, CMe);  $\delta$  3.72-5.24 (unassigned signals from both isomers).

(1R, 2S, 3R, 4S, 5S, 10R)-1,2,3,4-Tetrabenzyloxy-10-methyl-1,2,3,4,5,8,9,10-octahydronaphthalene (7).—A solution of **6** (230 mg,0.4 mmol) in anhydrous toluene (20 mL) was heated in a sealed tube at 200° for 3 h. The mixture was then filtered, and the solvent was evaporated to furnish a crude product (130 mg), the <sup>1</sup>H-NMR spectrum of which indicated only one product. HPLC (methanol-water, 4:1) of a small sample gave 7, isolated as a syrup,  $[\alpha]_D - 0.3^\circ$  (c 0.7, chloroform). Mass spectrum (CI): m/z 575 (M<sup>+</sup> + H). NMR data: <sup>1</sup>H,  $\delta$  7.30–7.10 (m, 20 H, 4 Ph), 5.65 (m, 1 H, H-7), 5.46 (d, 1 H,  $J_{6,7}$  10 Hz, H-6), 5.00–4.32 (m, 8 H, 4 CH<sub>2</sub>Ph), 3.93 (dd, 1 H,  $J_{1,2}$  10,  $J_{2,3}$  2 Hz, H-2), 3.78 (t, 1 H,  $J_{3,4}$  2 Hz, H-3), 3.55 (m, 2 H, H-1,4), 2.53 (bs, 1 H, H-5), 2.05 (m, 1 H, H-8ax), 1.88 (m, 1 H, H-8eq), 1.33 (m, 1 H, H-9eq), 1.10 (s, 3 H, Me-10), 0.85 (m, 1 H, H-9ax); <sup>13</sup>C,  $\delta$  139.1 and 138.9 (C-6,7), 85.6, 80.8, 79.7, and 76.3 (C-1,2,3,4), 76.0, 73.4, 73.2, and 72.8 (4 OCH<sub>2</sub>Ph), 41.3 (C-5), 38.9 (C-10), 35.1 (C-9), 22.7 (C-8), and 14.0 (CCH<sub>3</sub>).

Anal. Calcd for C<sub>39</sub>H<sub>42</sub>O<sub>4</sub>: C, 81.53; H, 7.32. Found: C, 81.38; H, 7.45.

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