

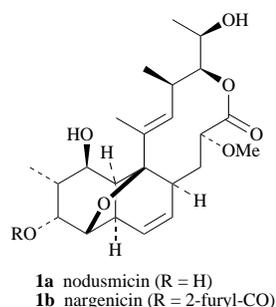
# Tandem Wittig–Diels–Alder reaction between sugar-derived phosphoranes and sugar aldehydes. An easy route to optically pure highly oxygenated decalins

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A highly oxygenated decalin system has been obtained by a tandem Wittig–Diels–Alder reaction of sugar derived phosphoranes with sugar aldehydes.

Several macrolide antibiotics with a decalin backbone—such as nodusmicin (**1a**, isolated from *Saccharopolyspora hirsuta*<sup>1</sup>) or structurally related nargenicins **1b**<sup>2</sup>—are active against Gram-

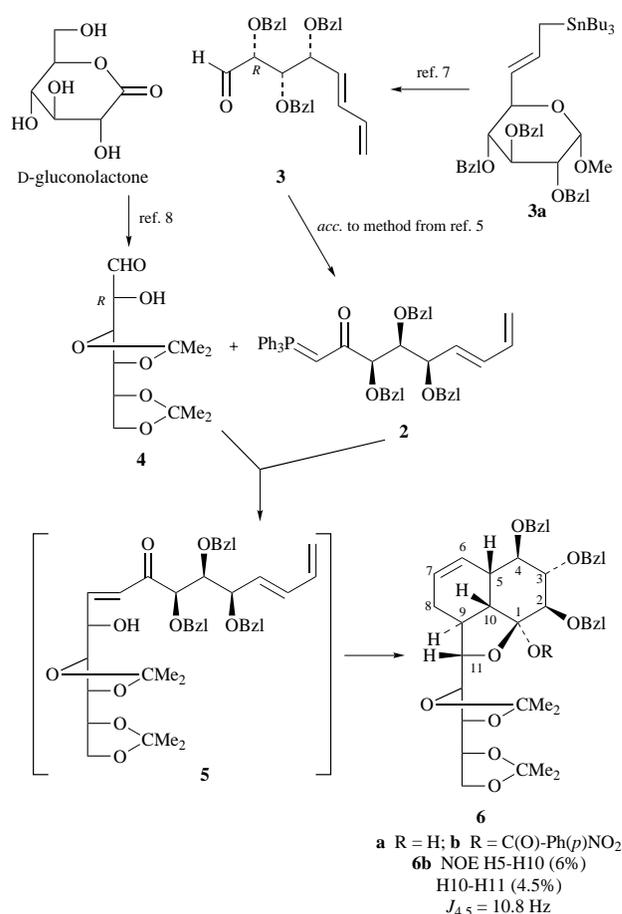


positive and drug-resistant bacteria. These antibiotics also exhibit low toxicity and substantial oral activity.<sup>2</sup> Several synthetic approaches, based on inter- and intra-molecular Diels–Alder methodology,<sup>3,4</sup> have been proposed for construction of such a system.

In this paper a convenient method leading to optically pure, highly oxygenated decalin derivatives is presented. It is based on the reaction of sugar-derived stabilized phosphoranes<sup>5</sup> with sugar aldehydes [methodology used for the synthesis of higher (C<sub>12</sub> to C<sub>21</sub>) carbon sugars<sup>6</sup>] followed by a [4 + 2] intra-molecular cyclization of the intermediate Wittig adduct as shown in Scheme 1.

Reaction of phosphorane **2** (readily available from diene aldehyde **3**, which was obtained from allyltin **3a** via a rearrangement–elimination reaction<sup>7</sup>) with an open-chain D-glucose derivative **4**<sup>8</sup> in boiling benzene led to a Wittig adduct **5** which, *in situ*, underwent [4 + 2] cyclization to give decalin **6** as a single stereoisomer (Scheme 1). The structure of this compound was assigned from high resolution NMR spectra and NOE experiments on its *p*-nitrobenzoyl derivative **6b**.

Reaction of phosphorane **2** with 2,3-*O*-isopropylidene-D-glyceraldehyde **7** at 140 °C (boiling xylene) afforded a mixture of stereoisomeric decalins from which the main stereoisomer **8** was isolated in 35% yield. When this reaction (**2** + **7**) was performed under high pressure (10 kbar) only one stereoisomer—the same as the main product from thermal reaction—of decalin **8** was isolated in 55% yield. Other sugar aldehydes with the opposite configuration at C<sub>a</sub> (methyl 2,3,4-tri-*O*-benzyl-6-aldehyde- $\alpha$ -D-glucopyranoside, **9**) afforded under high pressure conditions decalin **10**, but as an unseparable mixture of two

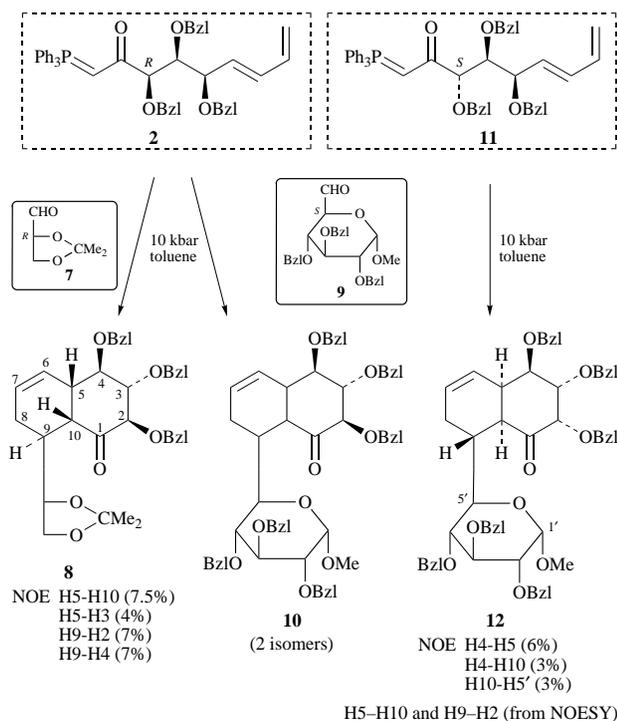


Scheme 1

stereoisomers. This may indicate that *R*-Wittig reagent **2** and *S*-aldehyde **9** are a mismatched pair. If so, aldehyde **9** should match with the isomeric *S*-phosphorane and give a single decalin. Indeed, the high pressure reaction of *S*-phosphorane **11** (prepared from the isomeric D-manno allyltin derivative<sup>7</sup> analogously to **2**) with **9** afforded decalin **12** as a single stereoisomer in 60% yield.

The tandem Wittig–Diels–Alder methodology presented in this paper opens a rather convenient route for the preparation of a highly oxygenated, optically pure decalin system. The possibility of the application of various diene–Wittig reagents (*e.g.* **2** or **11**, that can be readily prepared from appropriate sugar allyltins) and various sugar aldehydes makes this approach particularly interesting. Application of a high pressure technique improves the stereoselectivity of this process and gives chiral decalins in higher yields compared to thermal reactions.

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Scheme 2

## Experimental

All  $^1\text{H}$ - and  $^{13}\text{C}$ -resonances were assigned by 2D experiments. The configuration of **12** was proved also by NOESY spectroscopy.

### (3*R*,4*S*,5*R*)-3,4,5-Tribenzyloxy-2-oxonona-6,8-dienylidene-triphenylphosphorane **2**

Diene aldehyde **3**<sup>7</sup> (1.1 g, 2.49 mmol) was oxidized to an acid with Jones' reagent. To a solution of this crude acid (1.04 g, 2.26 mmol, 90%) in dry THF (10 ml), *N,N*-carbonyldiimidazole (1.1 equiv., 0.4 g) was added and after 15 min this solution of crude imidazolidine was added to a cooled ( $-78\text{ }^\circ\text{C}$ ) solution of  $\text{Ph}_3\text{P}=\text{CH}_2$  (4 equiv.; generated from  $\text{Ph}_3\text{PCH}_2\text{I}$  and BuLi for 2 h at  $-78\text{ }^\circ\text{C}$ ) in THF. After stirring for 30 min at  $-78\text{ }^\circ\text{C}$  the mixture was partitioned between water–benzene and the product **2** was purified by column chromatography to afford **2** (0.98 g, 1.37 mmol, 55%) [HRMS calcd. for  $\text{C}_{48}\text{H}_{46}\text{O}_4\text{P}$  ( $\text{M} + \text{H}^+$ ): 717.3134. Found: 717.3131]. Similarly, phosphorane **11** was prepared (HRMS: 717.3130).

### Synthesis of decalin **6** under atmospheric pressure

Phosphorane **2** (0.35 g, 0.49 mmol) and aldehyde **4**<sup>8</sup> (0.15 g, 0.58 mmol) in dry benzene (20 ml) were heated under reflux for 20 h. The product, decalin **6a**, was isolated by column chromatography (0.18 g, 0.26 mmol, 53%) [HRMS calcd. for  $\text{C}_{42}\text{H}_{50}\text{O}_9\text{Na}$  ( $\text{M} + \text{Na}^+$ ): 721.3352. Found: 721.3349]. *p*-Nitrobenzyl derivative **6b** (prepared from **6a** by the action of *p*-nitrobenzoyl chloride– $\text{Et}_3\text{N}$ –DMAP):  $\delta_{\text{H}}$  2.08 and 2.30 (2m, both H8), 2.32 (m, H9), 2.80 (m, H5), 3.13 (dd,  $J_{9,10}$  13.6,  $J_{5,10}$  6.8, H10), 3.55 (dd,  $J_{3,4}$  9.7,  $J_{4,5}$  10.8, H4), 3.90 (dd,  $J_{2,3}$  10.3, H3), 3.99 (d, H2), 5.81 (H6), 6.01 (H7);  $\delta_{\text{C}}$  27.2 (C8), 38.1 (C5),

38.6 (C9), 47.1 (C10), 83.5 (C3), 84.0 (C4), 86.0 (C2), 109.0 (C1), 126.7 (C6), 128.3 (C7).

### Reaction of stabilized Wittig reagents (**2** and **11**) with aldehydes under high pressure

A solution of the appropriate phosphorane (*ca.* 0.5 mmol) and aldehyde (*ca.* 0.6 mmol) in dry toluene (10 ml) was placed in a piston-type apparatus and kept under high pressure (*ca.* 10 kbar) for 2 d. Products were isolated by column chromatography.

**Decalin 8.** (Single isomer, 55%) [HRMS: calcd. for  $\text{C}_{36}\text{H}_{40}\text{O}_6\text{Na}$  ( $\text{M} + \text{Na}^+$ ): 591.2726. Found: 591.2762];  $\delta_{\text{H}}$  1.78 and 2.01 (2m, both H8), 2.19 (m, H9), 2.42 (m, H5), 2.56 (dd,  $J_{9,10}$  11.8,  $J_{5,10}$  5.6, H10), 3.68 (dd,  $J_{2,3}$  10.2,  $J_{3,4}$  9.1, H3), 3.82 (dd,  $J_{4,5}$  10.5, H4), 4.65 (d, H2), 5.75 (H6), 6.01 (H7);  $\delta_{\text{C}}$  27.2 (C8), 37.5 (C9), 38.6 (C5), 53.5 (C10), 83.3 (C4), 85.5 (C3), 85.6 (C2), 126.0 and 127.8 (C6,7), 207.0 (CO).

**Decalin 12.** (Single isomer, 60%) [HRMS: calcd. for  $\text{C}_{58}\text{H}_{60}\text{O}_9\text{Na}$  ( $\text{M} + \text{Na}^+$ ): 923.4135. Found: 923.4146]  $\nu_{\text{max}}/\text{cm}^{-1}$  1730;  $\delta_{\text{H}}$  2.06 and 2.39 (2m, both H8), 2.91 (m, H9), 2.98 (dd,  $J_{9,10}$  7.0,  $J_{5,10}$  6.4, H10), 3.03 (m, H5), 3.85 (dd,  $J_{2,3}$  2.9,  $J_{3,4}$  6.6, H3), 3.94 (dd,  $J_{4,5}$  4.3, H4), 4.40 (d, H2), 5.75 (m, H6,7);  $\delta_{\text{C}}$  28.0 (C8), 34.5 (C9), 37.0 (C5), 48.5 (C10), 78.1 (C4), 79.9 (C3), 81.0 (C2), 124.5 and 128.9 (C6,7).

**Decalin 10.** (50%) [HRMS: calcd. for  $\text{C}_{58}\text{H}_{60}\text{O}_9\text{Na}$  ( $\text{M} + \text{Na}^+$ ): 923.4135. Found: 923.4149]. Two major products were seen in the NMR spectra [ $^1\text{H}$ - 3.34, 3.49 (OMe) and  $^{13}\text{C}$ - 98.2, 97.7 ppm (C1 of glucose moiety)]. Signals at 3.10, 2.89 (H5 of both isomers), 34.4, 31.2 (C5), 2.64, 2.46 (H10), 49.9, 43.6 (C10), and 5.85–5.6 (H6,7), 129.8, 127.4, 126.2, 123.0 (C7,8) proved the decalin structure of both isomers of **10**.

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