

Short Note

## (–)-5-[(4*R*,5*R*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4,7-dihydro-1,3-dioxepine

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**Abstract:** The synthesis of (–)-5-[(4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4,7-dihydro-1,3-dioxepine is reported. Product characterization was carried out by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS, elemental analysis and optical rotation.

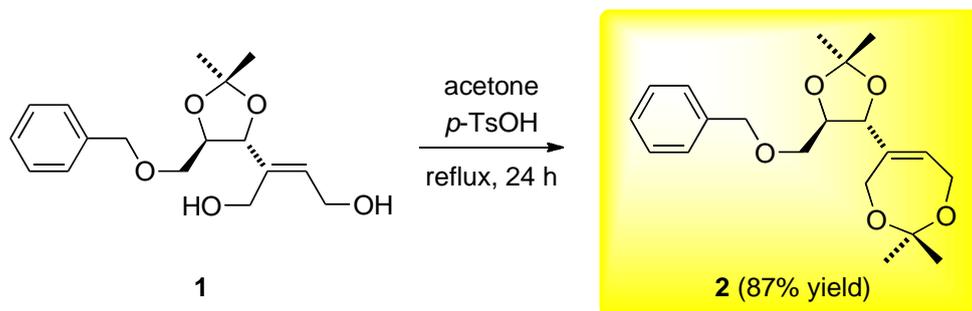
**Keywords:** polyoxygenated compounds; acetonide; allylic diol

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Acetals are frequently used as protecting groups for carbonyl groups in organic synthesis mainly due to their stability towards hydrolysis by bases [1]. As well as being remarkable synthetic building blocks, cyclic acetals are also important in nature. For instance, the most stable form of glucose in solution is its cyclic hemiacetal, maltose is an acetal made from two glucose units, and acetaldehyde diethyl acetal is an important flavouring compound in distilled beverages [2]. Pharmaceutical industry has also commercialized a number of bioactive acetonide-containing bioactive products such as fluocinolone acetonide or triamcinolone acetonide, which are potent corticosteroids primarily used in dermatology to reduce skin inflammation [3].

Herein, we report the synthesis of (–)-5-[(4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4,7-dihydro-1,3-dioxepine (**2**) by refluxing the corresponding allylic diol **1** in acetone for 24 h (Scheme 1). Chiral precursor **1** was prepared by reduction of the appropriate butenolide as reported previously [4].

Scheme 1.



## Experimental

### General

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 25 °C on a Bruker Avance 500 spectrometer in  $\text{CDCl}_3$  as solvent, and chemical shifts are reported relative to  $\text{Me}_4\text{Si}$  ( $\delta = 0$ ). Low- and high-resolution mass spectra were obtained by using a Micromass VG Autospec spectrometer. Elemental analysis was performed on a Fisons Instrument EA 1108 CHNS-O analyzer. Infrared spectra were recorded on a Bruker IFS 55 spectrophotometer on compounds dispersed on a NaCl disc. Optical rotations were determined for solutions in chloroform with a Perkin Elmer 343 polarimeter using a sodium lamp (589 nm). Thin-layer chromatography was carried out on Merck aluminium sheets coated with silica gel 60 F<sub>254</sub>. Compounds were visualized by use of 254 nm UV light and/or phosphomolybdic acid 20 wt.% solution in ethanol with heating. All solvents were purified by standard techniques [5]. Flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM). Anhydrous magnesium sulfate was used for drying solutions.

**Synthesis of (–)-5-[(4*R*,5*R*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4,7-dihydro-1,3-dioxepine (**2**):** To a stirred solution of allylic diol **1** (308 mg, 1.0 mmol) in acetone (25 mL), *p*-toluenesulfonic acid (*p*-TsOH) (3 mg, 0.017 mmol) was added at room temperature. The reaction mixture was refluxed for 24 h, until the TLC analysis showed that no starting material was present. The solvent was concentrated and the residue diluted with  $\text{Et}_2\text{O}$  (30 mL) and washed with a 5% solution of  $\text{NaHCO}_3$ . The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered, concentrated, and the residue purified by silica gel column chromatography, eluting with  $\text{AcOEt}$ :*n*-hexane 10:90. Product **2** (303 mg, 87% yield) was obtained as a colourless oil:  $[\alpha]_{\text{D}}^{25} = -12.3$  (*c* 0.70,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm = 1.43 (s, 12H), 3.56 (dd, *J* = 5.2, 10.6 Hz, 1H), 3.63 (dd, *J* = 3.1, 10.6 Hz, 1H), 3.95 (ddd, *J* = 3.1, 5.2, 8.6 Hz, 1H), 4.22–4.30 (m, 4H), 4.36–4.40 (m, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 5.61 (m, 1H), 7.28–7.37 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm = 23.8 (q), 26.9 (q), 60.0 (t), 60.8 (t), 69.4 (t), 73.5 (t), 78.4 (d), 80.1 (d), 102.1 (s), 109.2 (s), 127.6 (d), 127.7 (d), 128.3 (d), 128.5 (d), 137.3 (s), 137.9 (s); FT-IR (thin film)  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ )

2987, 2933, 2862, 1373, 1218, 1088, 870, 738; MS (EI+)  $m/z$  (relative intensity %) 348 ( $M^+$ , 1.3), 333 ( $[M-CH_3]^+$ , 1.2), 290 (4.7), 2.75 (2.4), 260 (4.2), 91 (100); HRMS (EI+) exact mass calculated for  $C_{20}H_{28}O_5$  ( $M^+$ )  $m/z$  348.1931, found  $m/z$  348.1937. Elemental analysis calculated for  $C_{20}H_{28}O_5$ : C, 68.94; H, 8.10; found: C, 68.74; H, 7.68.

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### References and Notes

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