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Prostanoids: LXXV. Synthesis of 4-Hydroxy-2-octyl-2-cyclopentenone*

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Abstract—The title compound was synthesized by Ad_NE addition of *n*-octyl cuprate to 2,3-dichloro-4,4-ethylenedioxy-2-cyclopentenone, followed by alcoholysis and reduction with $NaBH_4$.

The present communication reports on the transformation of readily accessible 2,3-dichloro-2-cyclopentene-1,4-dione monoacetal **I** [1] into 4-hydroxy-2-octyl-2-cyclopentenone (**II**) as key intermediate in the cuprate synthesis [2, 3] of 9-LO E-prostanoids [4, 5], specifically of 9-LO PGE_1 (Scheme 1).

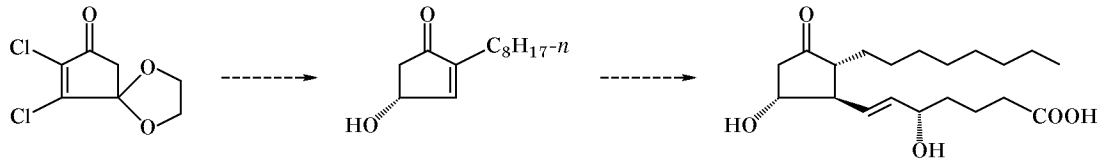
The structure of molecule **I**, as concerns its topology and functionalization pattern, is favorable for preparation of compound **II**, and some efforts are to be made to introduce *n*-octyl side chain. We have solved this problem through 1,4-addition to enone **I** of a cuprate reagent prepared from *n*-octylmagnesium bromide and copper(I) iodide. As a result of smooth Ad_NE reaction, substituted product **III** was obtained. Reduction of the ketone group in **III** with sodium tetrahydridoborate, followed by acid treatment of the reaction mixture, gave hydroxy ketone **IV** in an overall yield of 87%. However, our attempts to effect reductive dechlorination of **IV** with zinc in methanol led to isolation of an undesirable product, deoxycyclopentenone **V** (Scheme 2). We succeeded in obtaining the target product by changing the order of treatment of compoound **III** with reducing agents. When acetal **III** was treated first with zinc in methanol and mixed acetal **VI** thus obtained was then reduced with $NaBH_4$, the target 4-hydroxy-2-octyl-2-cyclopentenone (**II**) was synthesized in an overall yield of more than 20% (calculated on the initial dichlorocyclopentenone **I**).

EXPERIMENTAL

The IR spectra were measured from thin films on a UR-20 spectrometer. The ^1H and ^{13}C NMR spectra were taken on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent. The chemical shifts were measured relative to TMS.

2-Chloro-3-octyl-4,4-ethylenedioxy-2-cyclopentenone (III). To a solution of magnesium–cuprate reagent, prepared from 0.71 g (3.7 mmol) of CuI, 2.4 ml of a 1.68 N solution of $C_8H_{17}MgBr$ in Et_2O, and 5 ml of THF, we added with stirring at –10°C in an inert atmosphere a solution of 0.5 g (2.4 mmol) of enone **I** in 3 ml of THF. The mixture was stirred for 0.5 h at –10°C, decomposed with an aqueous solution of NH_4Cl, and extracted with methylene chloride (3 × 20 ml). The extracts were dried over

Scheme 1.



I **II** 9-LO PGE_1

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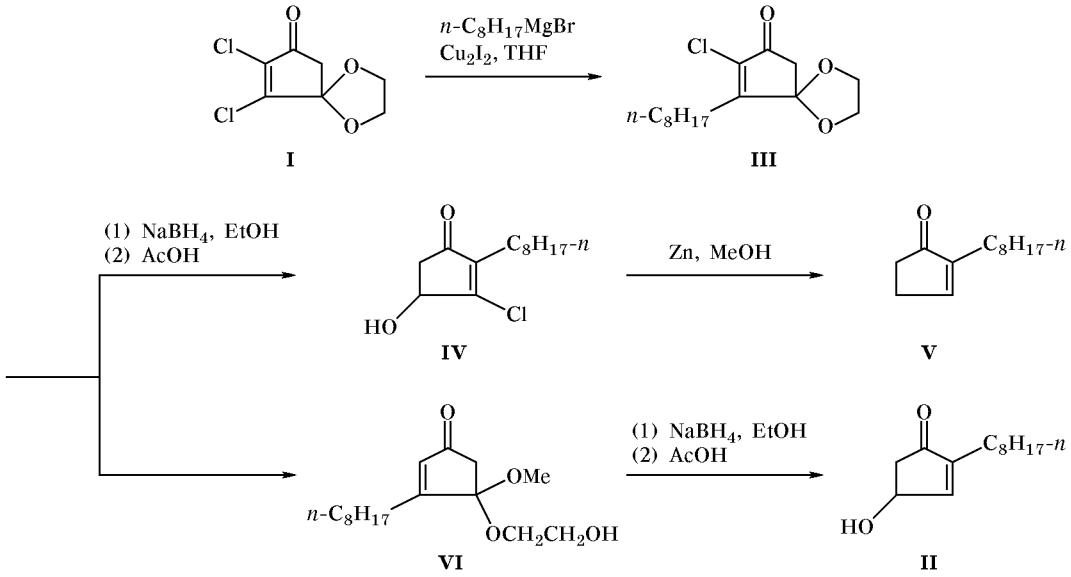
Scheme 2.



$MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel using pentane–ethyl acetate (1:1) as eluent. Yield 0.3 g (44%). IR spectrum, ν, cm^{-1}: 1650, 1750. ^1H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3), 1.20–1.45 m (10H, $5CH_2$), 1.55–1.75 m (2H, $C^{7'}H_2$), 2.35–2.45 m (2H, $C^{1'}H_2$), 2.66 s (2H, C^9H_2), 4.0–4.2 m (4H, $2CH_2O$). ^{13}C NMR spectrum, δ_C, ppm: 13.09 ($C^{8'}$), 22.55 ($C^{7'}$), 26.21 ($C^{1'}$), 27.23 ($C^{2'}$), 29.04 ($C^{5'}$), 29.10 ($C^{4'}$), 29.88 ($C^{3'}$), 31.73 ($C^{6'}$), 46.31 (C^9), 65.99 (CH_2O), 110.35 (C^5), 135.21 (C^7), 166.20 (C^6), 195.19 (C^8).

4-Hydroxy-2-octyl-3-chloro-2-cyclopentenone (IV). To a solution of 0.3 g of compound **III** in 10 ml of ethanol at 0°C we added 0.05 g of $NaBH_4$. The mixture was stirred for 1 h, and 0.5 ml of AcOH was added. The mixture was evaporated, the residue was dissolved in 10 ml H_2O, the product was extracted into methylene chloride (3 × 20 ml), the extract was dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel using pentane–ethyl acetate (4:1) as eluent. Yield 0.22 g (87%). IR spectrum, ν, cm^{-1}: 1620, 1720, 3400. ^1H NMR spectrum, δ, ppm: 0.82 t (3H, CH_3, J = 6.7 Hz), 1.1–1.5 m (12H, $6CH_2$), 2.2 t (2H, $C^{1'}H$), 2.43 d.d (1H, 5-H, ^2J = 18, ^3J = 2 Hz), 2.84 (1H, 5-H, ^2J = 18, ^3J = 6.3 Hz), 4.0–4.15 br.s (1H, OH), 4.73–4.83 m (1H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 13.94 ($C^{8'}$), 22.51 ($C^{7'}$), 23.09 ($C^{1'}$), 26.84 ($C^{2'}$), 29.04 ($C^{5'}$), 29.12 ($C^{4'}$), 29.36 ($C^{3'}$), 31.70 ($C^{6'}$), 44.40 (C^5), 70.63 (C^4), 142.98 (C^3), 164.10 (C^2), 201.70 (C^1).

2-Octyl-2-cyclopentenone (V). A mixture of 0.5 g of ketone **IV**, 5 g of zinc dust, and 0.5 g of NH_4Cl in 20 ml of MeOH was heated under reflux with stirring for 1 h. The mixture was cooled and filtered, and the filtrate was evaporated. The residue was dissolved in 10 ml of H_2O, and the solution was extracted with methylene chloride (3 × 20 ml). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to chromatography on silica gel using pentane–ethyl acetate (1:1) to isolate 0.21 g (53%) of compound **V**. R_f 0.26. IR spectrum, ν, cm^{-1}: 1640, 1730. ^1H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, J = 7 Hz), 1.2–1.4 m (10H, $5CH_2$), 1.4–1.55 m (2H, $C^{7'}H_2$), 2.10–2.20 m (2H, $C^{1'}H$), 2.35–2.45 m (2H, 4-H), 2.50–2.60 m (2H, 5-H), 7.25–7.35 m (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 14.14 ($C^{8'}$), 22.71 ($C^{7'}$), 24.83 ($C^{1'}$), 26.50 ($C^{2'}$), 27.81 ($C^{5'}$), 29.30 ($C^{4'}$), 29.42 ($C^{3'}$), 29.47 ($C^{6'}$), 31.93 (C^4), 34.67 (C^5), 146.65 (C^2), 157.31 (C^3), 210.17 (C^1).

4-(2-Hydroxyethyloxy)-4-methoxy-3-octyl-2-cyclopentenone (VI) was synthesized from acetal **III** by the procedure described above for ketone **V**. Yield 43%, oily substance. IR spectrum, ν, cm^{-1}: 1640, 1730, 3030, 3600. ^1H NMR spectrum, δ, ppm: 0.80 t (3H, CH_3, J = 7 Hz), 1.1–1.6 m (10H, $5CH_2$), 2.25–2.45 m (2H, $C^{1'}H$), 2.57 s (2H, 5-H), 2.65–2.80 br.m (1H, OH), 3.23 s (3H, OMe), 3.45–3.75 m (4H, $2CH_2O$), 5.95 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 13.99 ($C^{8'}$), 22.54 ($C^{7'}$), 26.79 ($C^{1'}$), 27.42 ($C^{2'}$), 29.09 ($C^{5'}$), 29.24 ($C^{4'}$), 29.35 ($C^{3'}$), 31.72 ($C^{6'}$), 43.33 (C^5), 51.25 (OMe), 61.67 (CH_2O), 65.54 (CH_2O), 107.04 (C^4), 130.76 (C^3), 177.0 (C^2), 202.55 (C^1).

4-Hydroxy-2-octyl-2-cyclopentenone (II) was synthesized by reduction of ketone **IV** with $NaBH_4$, following the procedure described above for the synthesis of ketone **IV**. Yield 72%, oily substance. IR spectrum, ν, cm^{-1}: 1640, 1730, 3030, 3600. ^1H NMR spectrum, δ, ppm: 0.84 t (3H, CH_3, J = 7 Hz), 1.15–1.35 m (10H, $5CH_2$), 1.35–1.5 m (2H, $C^{7'}H_2$), 2.05–2.2 m (2H, $C^{1'}H$), 2.27 d.d (1H, 5-H, J = 18.6, 6 Hz), 2.76 d.d (1H, 5-H, J = 18.6, 6 Hz), 3.05–3.30 br.m (1H, OH), 4.85–4.95 m (1H, 4-H), 7.1–7.15 (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 13.99 ($C^{8'}$), 22.55 ($C^{7'}$), 24.36 ($C^{1'}$), 27.36 ($C^{2'}$), 29.11 ($C^{5'}$), 29.24 ($C^{4'}$), 29.29 ($C^{3'}$), 32.10 ($C^{6'}$), 44.80 (C^5), 68.26 (C^4), 147.86 (C^2), 156.26 (C^3), 206.75 (C^1).

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