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Short Communication

A Convenient Preparation of 8*R*,25-Dihydroxy-9,10-seco-4,6,10(19)-cholestatrien-3-one*

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Summary. The title compound was prepared in three steps from 25-hydroxyvitamin D_3. The key-step in this sequence is the transformation of **3b** to **4** by means of the LiBr/*HMPT* complex.

Keywords. 8*R*,25-Dihydroxy-9,10-seco-4,6,10(19)-cholestatrien-3-one; 9,10-Seco-4,6,10(19)cholestatrien-3*S*,8*R*,25-triol; Vitamin D_3 metabolite.

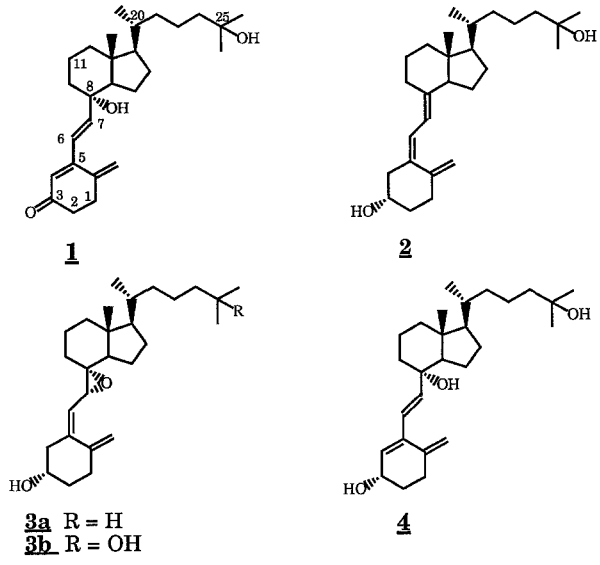
Ein bequemer Zugang zu 8*R*,25-Dihydroxy-9,10-seco-4,6,10(19)-cholestatrien-3-on (Kurze Mitt.)

Zusammenfassung. Die Titelverbindung wurde in drei Stufen, ausgehend von 25-Hydroxyvitamin D_3 dargestellt. Der Schlüsselschritt ist die Transformation von **3b** nach **4** mit Hilfe des LiBr/*HMPT*-Komplexes.

Current interest in the metabolism of vitamin D_3 is focused on the ability of phagocytic cells to convert vitamin D_3 into more polar derivatives, since vitamin D metabolites play a role in inducing cell differentiation [1], in addition to the classical role of vitamin D as the calcium homeostatic hormone [2]. Besides the well documented production of 19-nor-10-oxo-derivatives by e.g. blood leucocytes [3] or certain tissue macrophages [4] S. Yamada and coworkers reported **1** as a new metabolite of 25-hydroxyvitamin D_3 from the murine myeloid leukemia cell line M 1 [5]. In a subsequent paper full details of the isolation and the proof of structure of the new metabolite – 8*R*,25-dihydroxy-9,10-seco-4,6,10(19)-cholestatrien-3-one **1** – have been disclosed [6]. The present paper reports on a simple and convenient preparation of this metabolite.

During our systematic investigation on transformation of various vitamin D oxiranes into more polar *and* trien modified vitamin D analogs it was discovered that the LiBr/*HMPT* complex (a reagent usually used for oxirane-carbonyl rearrangement [7]) is capable of converting vitamin D oxiranes into allylic carbinols [8]. The oxirane **3b** is the starting material of choice since it was already demonstrated independently by us and others [9] that *MCPBA* treatment of vitamin

* Dedicated to Prof. Dr. Karl Schlögl on the occasion of his 65th anniversary



D produces regio- and stereoselectively the 7*R*,8*R* oxirane **3a**. The sequence for the preparation of **1** is outlined below.

The easily accessible **3b** was treated with 1.1 equivalent of the LiBr/*HMPT* complex in refluxing toluene. Some Li_2CO_3 was added to the reaction mixture as acid scavenger. No protective groups of the sensitive alcohol functions were used throughout this sequence. After work up and purification **4** was isolated in 76% yield. To complete the sequence the allylic secondary alcohol at C-2 was oxidized with MnO_2 in the usual way. The spectroscopic data of **1** produced by the above sequence are identical with the published ones [6].

In summary the above sequence proofs to be a highly efficient and simple preparation of **1**. The intermediate **4** may be a vitamin D_3 analog in its own way of right.

Acknowledgment

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Experimental Part [10]

7R-Epoxy-25-hydroxy-9,10-seco-5,7,9(10)-cholestrien-ol (**3b**)

0.038 g *MCPBA* (85%; 1.1 equ.) in 5 ml $CH_2Cl_2/CHCl_3$ (1 : 1) was slowly added to an ice-cooled solution of 0.069 g 25-hydroxyvitamin D_3 (**1**) (0.174 mmol) in 50 ml $CH_2Cl_2/CHCl_3$ (1 : 1). After complete conversion (DC) the organic solution was extracted three times with sat. aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. Chromatotron® separation of the residue (hexanes : ethylacetate = 1 : 1; 1 mm rotor) yielded 0.058 g **3b** (81%): $[\alpha]_D = +30.1$ ($c = 0.565$, $CHCl_3$). $R_f = 0.48$ (ether). IR (CH_2Cl_2): $\nu = 3590$, 3440, 2940, 2880, 1460, 1440, 1370, 1050, 1040, 960,

900 cm^{-1}. ^{1}H-NMR: $\delta = 0.68$ (s; 3H, 3H-18), 0.93 (d; $J = 6$ Hz, 3H, 3H-22), 1.20 (s; 6H, 3H-26, 3H-27), 3.88 (d; $J = 8.5$ Hz, 1H, H-7), 3.98 (m; $w_{1/2} = 16$ Hz, 1H, H-3), 4.98 (s; 1H, H-19), 5.05 (s; 1H, H-19'), 5.23 (d; $J = 8.5$ Hz, 1H, H-6). ^{13}C-NMR: $\delta = 145.3$ (C-10), 144.9 (C-5), 121.6 (C-6), 112.2 (C-19), 71.1 (C-25), 69.2 (C-3), 65.8 (C-8), 56.7 (C-14), 56.3 (C-17), 46.1 (C-4), 46.0 (C-24), 44.4 (C-13), 39.6 (C-12), 36.5 (C-22), 35.6 (C-20), 36.11 (C-9), 32.0 (C-1), 30.8 (C-2), 29.4 (C-21), 29.3 (C-26), 27.4 (C-16), 22.3 (C-11), 20.9 (C-23), 20.1 (C-15), 18.8 (C-21), 12.7 (C-18).

9,10-Seco-4,6,10(19)-cholestrien-3S,8R,25-triol (**4**)

To a solution of 0.045 g **3** (0.108 mmol) in 25 ml toluene 0.009 g LiBr, 1 equivalent of *HMPT* (1 *M* in toluene; 0.103 ml) and 0.003 g Li_2CO_3 was added. The heterogenous reaction mixture was refluxed for 10 min, cooled, extracted three times with water, dried over Na_2SO_4 and concentrated. Chromatotron® separation (hexanes : ethylacetate = 1 : 1; 1 mm rotor) gave 0.034 g of **4** (76%): $R_f = 0.29$ (hexanes : ethylacetate = 1 : 1). IR (CH_2Cl_2): $\nu = 3680$, 3600, 3400, 2940, 2880, 1600, 1470, 1440, 1380, 1260, 1040, 980, 910 cm^{-1}. ^{1}H-NMR: $\delta = 0.66$ (s; 3H, 3H-18), 0.89 (d; $J = 6$ Hz, 3H, 3H-21), 1.19 (s; 6H, 3H-26, 3H-27), 4.39 (m; $w_{1/2} = 16.3$ Hz, 1H, H-3), 4.94 (s; 1H, H-19), 5.03 (s; 1H, H'-19), 5.87 (br. s.; 1H, H-4), 6.11 (d; $J = 15.8$ Hz, 1H, H-7), 6.37 (d; $J = 15.8$ Hz, 1H, H-6). ^{13}C-NMR: $\delta = 142.3$ (C-5), 139.1 (C-10), 134.3 (C-6), 128.6 (C-7), 126.8 (C-4), 111.1 (C-19), 73.8 (C-8), 71.1 (C-25), 66.3 (C-3), 59.3 (C-17), 57.2 (C-14), 44.4 (C-13), 40.0 (C-12), 40.0 (C-24), 39.9 (C-9), 36.3 (C-22), 35.4 (C-20), 32.7 (C-2), 29.3 (C-26), 29.2 (C-27), 29.0 (C-1), 27.1 (C-16), 21.4 (C-23), 20.9 (C-11), 19.9 (C-15), 18.5 (C-21), 13.1 (C-18). UV (ethanol): λ_{max} (ε) = 247 (9700) nm.

8R,25-Dihydroxy-9,10-seco-4,6,10(19)-cholestatrien-3-one (**1**)

A suspension of 0.120 g MnO_2 in 15 ml hexanes was cooled to 0°C and 0.010 g of **3** (0.024 mmol) in 1 ml of hexanes was added. After 10 min the suspension was freed of MnO_2 by filtering through celite and the clear solution was concentrated. 0.008 g (81%) of **1** was isolated after Chromatotron® separation: $R_f = 0.29$ (hexanes : ethylacetate = 1 : 1). IR (CH_2Cl_2): $\nu = 3600$, 3490, 3030, 2940, 2860, 1665, 1520, 1460, 1380, 1225, 1210, 1190, 1090, 1025, 910 cm^{-1}. ^{1}H-NMR: $\delta = 0.66$ (s; 3H, 3H-18), 0.90 (d; $J = 6$ Hz, 3H, 3H-21), 1.21 (s; 3H, 3H-18), 2.61 (m; 4H, 2H-1, 2H-2), 5.39 (s; 1H, H-19), 5.42 (s; 1H, H'-19), 6.05 (s; 1H, H-4), 6.48 (AB-system; $J = 16$ Hz, H-6, H-7). ^{13}C-NMR: $\delta = 200.3$ (C-3), 153.3 (C-5), 142.5 (C-10), 140.4 (C-6), 125.6 (C-7), 124.0 (C-4), 116.6 (C-19), 74.5 (C-8), 71.1 (C-25), 59.8 (C-14), 57.2 (C-17), 44.4 (C-13), 40.3 (C-2), 39.7 (C-24), 39.7 (C-12), 38.1 (C-1), 36.2 (C-22), 35.4 (C-20), 32.2 (C-9), 29.4 (C-26), 29.2 (C-27), 27.3 (C-16), 21.3 (C-23), 20.8 (C-11), 20.0 (C-15), 18.4 (C-21), 13.3 (C-18). UV (ethanol): λ_{max} (ε) = 294 nm (15400).

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[10] ^{1}H- and ^{13}C-NMR: Bruker WM 250; IR: Perkin Elmer 377; MS: Varian Mat CH 7; UV: Perkin Elmer Lambda 5; preparative thin layer chromatography: Chromatotron®, Harrison Research, Palo Alto; rotors coated with silica gel 60 PF-254 (E. Merck)

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