

Short Communication

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

Wolfgang Reischl

Institut für Organische Chemie, Universität Wien, A-1090 Wien, Austria

Summary. The title compound was prepared in three steps from 25-hydroxyvitamin D₃. 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 D₃ metabolite.

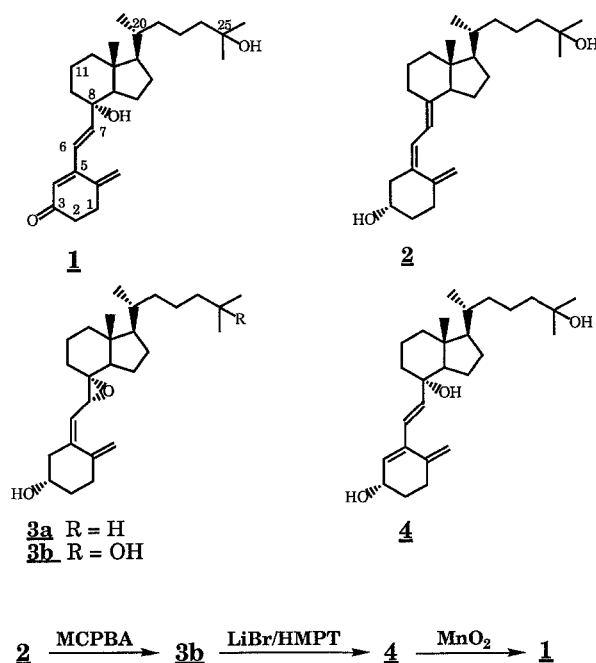
Ein bequemer Zugang zu 8*R*,25-Dihydroxy-9,10-seco-4,6,10(19)-cholestatrien-3-on (Kurze Mitt.)

Zusammenfassung. Die Titelverbindung wurde in drei Stufen, ausgehend von 25-Hydroxyvitamin D₃ dargestellt. Der Schlüsselschritt ist die Transformation von **3b** nach **4** mit Hilfe des LiBr/*HMPT*-Komplexes.

Current interest in the metabolism of vitamin D₃ is focused on the ability of phagocytic cells to convert vitamin D₃ 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 D₃ from the murine myeloid leukemia cell line M1 [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 Li₂CO₃ 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 MnO₂ 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 proves to be a highly efficient and simple preparation of **1**. The intermediate **4** may be a vitamin D₃ analog in its own way of right.

Acknowledgment

25-Hydroxyvitamin D₃ was a gift of Hoffmann-LaRoche AG, Basel. Financial support was provided by Hochschuljubiläumsstiftung der Stadt Wien. Interest and support of this work by Prof. Dr. E. Zbiral is gratefully acknowledged.

Experimental Part [10]

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

0.038 g MCPBA (85%; 1.1 equ.) in 5 ml CH₂Cl₂/CHCl₃ (1:1) was slowly added to an ice-cooled solution of 0.069 g 25-hydroxyvitamin D₃ (**1**) (0.174 mmol) in 50 ml CH₂Cl₂/CHCl₃ (1:1). After complete conversion (DC) the organic solution was extracted three times with sat. aqueous NaHCO₃ solution, dried over Na₂SO₄ and concentrated. Chromatotron® separation of the residue (hexanes:ethylacetate = 1:1; 1 mm rotor) yielded 0.058 g **3b** (81%): [α]_D = +30.1 (*c* = 0.565, CHCl₃). *R_f* = 0.48 (ether). IR (CH₂Cl₂): ν = 3590, 3440, 2940, 2880, 1460, 1440, 1370, 1050, 1040, 960,

900 cm⁻¹. ¹H-NMR: δ = 0.68 (s; 3 H, 3 H-18), 0.93 (d; J = 6 Hz, 3 H, 3 H-22), 1.20 (s; 6 H, 3 H-26, 3 H-27), 3.88 (d; J = 8.5 Hz, 1 H, H-7), 3.98 (m; $w_{1/2}$ = 16 Hz, 1 H, H-3), 4.98 (s; 1 H, H-19), 5.05 (s; 1 H, H-19'), 5.23 (d; J = 8.5 Hz, 1 H, H-6). ¹³C-NMR: δ = 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 Li₂CO₃ was added. The heterogenous reaction mixture was refluxed for 10 min, cooled, extracted three times with water, dried over Na₂SO₄ 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 (CH₂Cl₂): ν = 3 680, 3 600, 3 400, 2 940, 2 880, 1 600, 1 470, 1 440, 1 380, 1 260, 1 040, 980, 910 cm⁻¹. ¹H-NMR: δ = 0.66 (s; 3 H, 3 H-18), 0.89 (d; J = 6 Hz, 3 H, 3 H-21), 1.19 (s; 6 H, 3 H-26, 3 H-27), 4.39 (m; $w_{1/2}$ = 16.3 Hz, 1 H, H-3), 4.94 (s; 1 H, H-19), 5.03 (s; 1 H, H'-19), 5.87 (br. s.; 1 H, H-4), 6.11 (d; J = 15.8 Hz, 1 H, H-7), 6.37 (d; J = 15.8 Hz, 1 H, H-6). ¹³C-NMR: δ = 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): $\lambda_{\max}$ (ϵ) = 247 (9 700) nm.

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

A suspension of 0.120 g MnO₂ 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 MnO₂ 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 (CH₂Cl₂): ν = 3 600, 3 490, 3 030, 2 940, 2 860, 1 665, 1 520, 1 460, 1 380, 1 225, 1 210, 1 190, 1 090, 1 025, 910 cm⁻¹. ¹H-NMR: δ = 0.66 (s; 3 H, 3 H-18), 0.90 (d; J = 6 Hz, 3 H, 3 H-21), 1.21 (s; 3 H, 3 H-18), 2.61 (m; 4 H, 2 H-1, 2 H-2), 5.39 (s; 1 H, H-19), 5.42 (s; 1 H, H'-19), 6.05 (s; 1 H, H-4), 6.48 (AB-system; J = 16 Hz, H-6, H-7). ¹³C-NMR: δ = 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): $\lambda_{\max}$ (ϵ) = 294 nm (15 400).

References

- [1] Koeffler H. P., Norman A. W. (1988) Vitamin D. Molecular, Cellular and Clinical Endocrinology. De Gruyter, Berlin-New York, p. 263
- [2] Norman A. W. (1979) Vitamin D: The Calcium Homeostatic Steroid Hormone. Academic Press, New York
- [3] Cohen M. S., Gray T. K. (1984) Proc. Natl. Acad. Sci. USA **81**: 931
- [4] Okabe T., Ishizuka S., Fujisawa M., Watanabe J., Takaku F. (1984) Biochem. Biophys. Res. Commun. **123**: 822
- [5] Hayashi T., Yamada S., Miyaura C., Tanaka H., Yamamoto K., Abe E., Takayama H., Suda T. (1987) FEBS Letters **218**: 200
- [6] Yamada S., Yamamoto H., Takayama H., Hayashi T., Miyaura C., Tanaka H., Abe E., Suda T. (1987) J. Biol. Chem. **262**: 12939
- [7] Rickborn B., Gerkin R. M. (1971) J. Am. Soc. Chem. **93**: 1693
- [8] A full account on opening reaction of vitamin D oxiranes will be published in due course

- [9] Kratky C., Reischl W., Zbiral E. (1984) *Monatsh. Chem.* **115**: 1453; Nakayama K., Yamada S., Takayama H., Nawata Y., Itaka Y. (1984) *J. Org. Chem.* **49**: 1573
- [10] ¹H- and ¹³C-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)

Received September 9, 1989. Accepted October 2, 1989