Hokkaido Institute of Public Health
N-19, W-12, Kita-ku, Sapporo,
060, Japan

MAKOTO NISHIZAWA
TAKASHI YAMAGISHI

Received January 5, 1981

[Chem. Pharm. Bull. 29(4)1187—1188(1981)]

Synthesis of 25-Hydroxy-24-oxovitamin D_3, A New Metabolite of Vitamin D_3

The synthesis of 25-hydroxy-24-oxovitamin D_3 is described. The compound is identical in all respects with the natural product.

Keywords——vitamin D metabolite; synthesis; Moffatt oxidation; α-Sulphonyl-carbanion; epoxy alcohol; steroid

There has been considerable debate, in recent years, regarding the function of 24*R*,25-dihydroxyvitamin D_3,[1] one of the major metabolites of vitamin D_3.[2] Recently, we have isolated and identified a new metabolite of vitamin D_3, 25-hydroxy-24-oxovitamin D_3 (**1**), from chick kidney homogenate incubated with 25-hydroxyvitamin D_3 and suggested the metabolite to be derived from 24*R*,25-dihydroxyvitamin D_3.[3] In order to confirm the structure and to test the biological activity in detail, we carried out the synthesis of 25-hydroxy-24-oxovitamin D_3 and now report the first synthesis of the new metabolite (**1**).

The skeleton of the title compound was constructed from the C-22 steroid sulphone (**2**) which was obtained from ergosterol *via* the established route[4] and the epoxyalcohol (**3**)[5] prepared from commercially available 3-hydroxy-3-methyl-1-butene by epoxidation. The carbanion derived from the sulphone (**2**) (lithium diisopropylamide, tetrahydrofuran —20°) was reacted with the epoxide (**3**) at —20° to give the triol derivative (**4**) (Y: 85%)

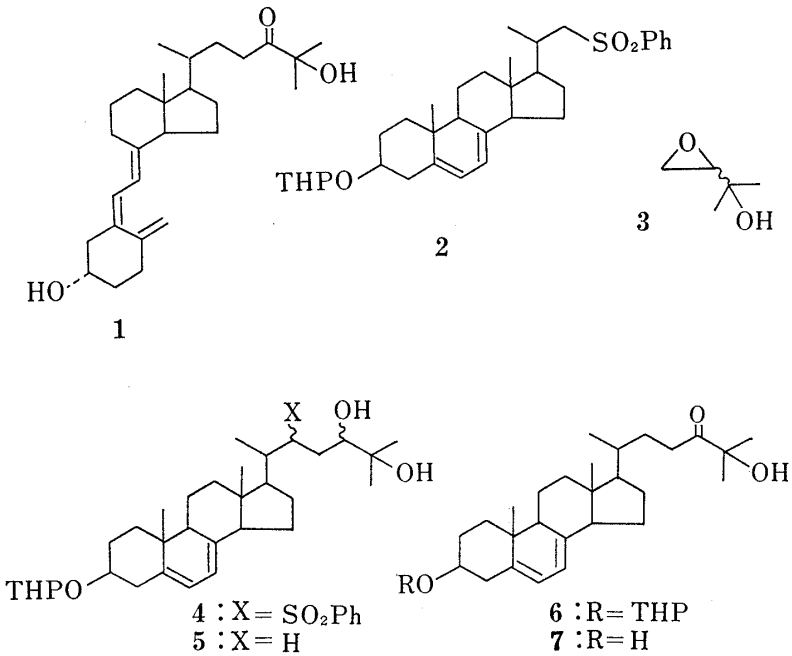

Chart 1

which upon treatment with amalgamated sodium (MeOH, Na_2HPO_4) afforded 24ξ, 25-dihydroxyprovitamin D (**5**) (Y: 93%). Oxidation of the 24-hydroxy group of **5** was performed in good yield (80%) by modified Moffatt oxidation[6] (DMSO, Et_3N, pyridine-SO_3) to yield the 24-oxo compound (**6**) (mp 133—135°), which by removal of the protecting group gave the desired provitamin D (**7**) [mp 161—163°; IR ($CHCl_3$): 3600, 3472, 1702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.63 (3H, s), 0.94 (3H, s), 1.38 (6H, s), 3.75 (1H, m), 5.40 (1H, d, J=5 Hz), 5.59 (1H, d, J=5 Hz); UV (EtOH): 272, 282, 294 nm; MS *m/e* 414, 381, 355]. The provitamin (**7**) was subjected to the standard method for the transformation into vitamin D, UV irradiation (separation of the irradiation mixture was performed using Sephadex LH-20 column) followed by thermal isomerization, to afford the vitamin D (**1**) [IR (KBr): 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.54 (3H, s), 1.38 (6H, s), 3.95 (1H, m), 4.84 (1H, bs), 5.08 (1H, bs), 6.17 (2H, ABq, J=11 Hz); MS: *m/e* 414, 271, 253, 136, 118; UV (EtOH): 265 nm]. The spectral properties of the vitamin D (**1**) thus synthesized were in complete agreement with those of the natural product.

The biological activity of the compound (**1**) is now under investigation and will be reported elsewhere.

References and Notes

1) M.T. Corvol, M.F. Dumontier, M. Garabedian, and R. Rappaport, *Endocrinology*, **102**, 1269 (1978); H.L. Henry and A.W. Norman, *Science*, **201**, 835 (1978); A. Ornoy, D. Goodwin, D. Noff, and S. Edelstein, *Nature* (London), **276**, 517 (1978); Y. Tanaka, H.F. DeLuca, Y. Kobayashi, T. Taguchi, N. Ikekawa, and M. Morisaki, *J. Biol. Chem.*, **254**, 7163 (1979); S. Okamoto, Y. Tanaka, H.F. DeLuca, S. Yamada, M. Ohmori, and H. Takayama, *Arch. Biochem. Biophys.*, **206**, 8 (1981).
2) M.F. Holick, H.K. Schnoes, H.F. DeLuca, R.W. Gray, I.T. Boyle, and T. Suda, *Biochemistry*, **11**, 4251 (1972).
3) Y. Takasaki, N. Horiuchi, N. Takahashi, E. Abe, T. Shinki, T. Suda, S. Yamada, H. Takayama, H. Horikawa, T. Masumura, and M. Sugahara, *Biochem. Biophys. Res. Comm.*, **95**, 177 (1980); Y. Takasaki, T. Suda, S. Yamada, H. Takayama, and Y. Nishii, *Biochemistry*, **20**, 1681 (1981).
4) H. Takayama, M. Ohmori, and S. Yamada, *Tetrahedron Lett*, **21**, 5027 (1980); D.H.R. Barton, T. Shioiri, and S.A. Widdowson, *J. Chem. Soc.* (*C*), **1971**, 1968.
5) G.P. Payne, *J. Org. Chem.*, **27**, 3819 (1962).
6) J.R. Parikh and W.E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).

Faculty of Pharmaceutical Sciences,
Teikyo University
Sagamiko, Kanagawa 199-01,
Japan

Sachiko Yamada
Masayuki Ohmori
Hiroaki Takayama*

Depart ment of Biochemistry,
Showa University Dental School
Hatanodai, Shinagawa, Tokyo 142,
Japan

Tatsuo Suda
Yoshiko Takasaki

Received February 10, 1981