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Allylic Hydroxylation of Vitamin D with Mercury(II)trifluoroacetate

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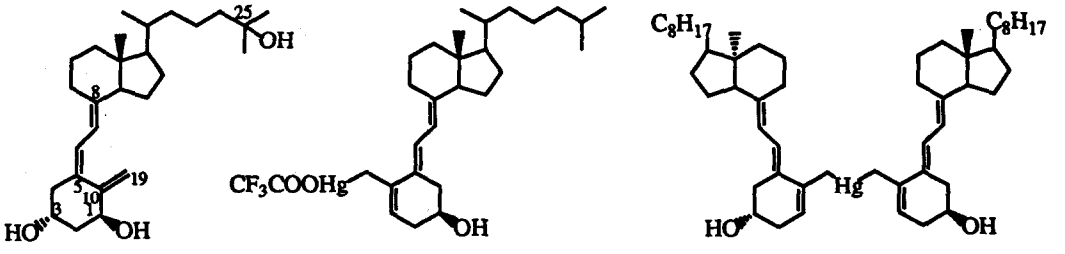
Abstract: *Treatment of vitamin D with $Hg(OCOCF_3)_2$ results in formation of the isovitamin D derivative **2**, which can be converted into C-1 hydroxylated 5E vitamin D derivatives.*

It is now well established that 1α, 25-dihydroxyvitamin D_3 **1** is the active form of vitamin D regulating the calcium homeostasis and in addition exhibits potent effects upon cell differentiation and cell proliferation.[1] Therefore the chemistry of vitamin D still is a field of continuous interest originated in the biological profile of the polar metabolites of this steroid hormone.

In our continuous search for selective transformations of the vitamin D triene moiety we turned our attention towards reacting vitamin D with various mercury salts. Mercury salts are well known to achieve allylic



1 **2** **3**

oxidation (Treibs reaction[2]), although not too many examples are known in the steroidal field due to the poor reactivity and forced reaction conditions of such reagents.[3] We wish to disclose our findings of the selective transformation of vitamin D into a C-19 functionalized isovitamin D derivative, which can be utilized for

introducing the C-1 hydroxyl group into the vitamin D skeleton.

Treatment of vitamin D with $Hg(OCOCF_3)_2$ in dry THF yields a single product quantitatively. The cross structure of the reaction product could be shown by NMR spectroscopy [4] to belong to the class of the 5E isovitamin D isomers,[5] as suggested by its UV-spectrum (λ_{max}=289, 292, 306 nm). The organomercurial compound proved to be stable in solution, but any attempt to isolate resulted in complete decomposition. Due to this fact and the nature of the reagent, there seemed to be no possibility to distinguish between the monomeric structure **2** or the potential dimeric structure **3** by ^1H- and ^{13}C-NMR spectroscopy or combustion analysis. Clear evidence for the actual structure came from its ^{199}Hg-NMR spectrum. The ^{199}Hg shift value of -1414 ppm is in the region of structures having allylic trifluoroacetoxy mercury moieties and establishes structure **2**[6] as the correct one (for comparison of ^{199}Hg shifts of selected organomercurials see Table 1)

Table 1. ^{199}Hg Chemical Shifts of Selected Organomercury Compounds

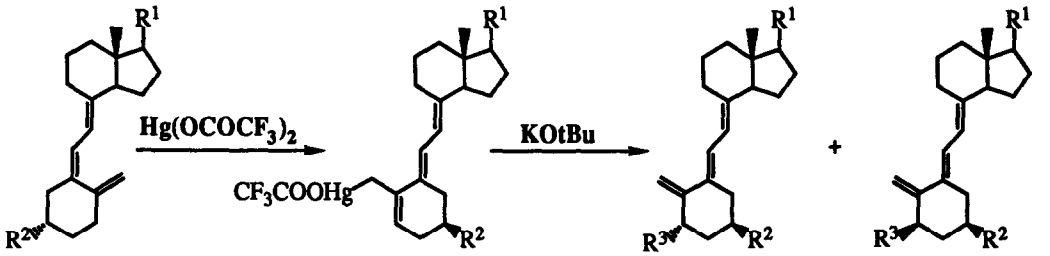
entry	ppm[a]
diallylmercury	-691
diphenylmercury	-795
allylmercuryacetate	-1388
allylmercurytrifluoroacetate	-1410
phenylmercuryacetate	-1466
phenylmercurytrifluoroacetate	-1514
mercuryacetate	-2383
mercurytrifluoroacetate	-2413
2	-1414

[a] 0.1 M in THF-d_8; 71.7 MHz; 300K; relative to external Me_2Hg[7]

This transformation constitutes the first example of a stable C-19 functionalized isovitamin D triene isomer generated under electrophilic reaction conditions, starting from 5Z vitamin D (for similar transformations by nucleophlic processes see[8]). Two features of this transformation are worth noting: first, the clean 5Z to 5E isomerization of the central double bond which arises from a delocalized carbocation between carbons 10 and 6 and which stabilizes by loss of a proton from C-1, thus clearly indicating that the attack of $Hg(OCOCF_3)_2$ proceeds via a stepwise ionic mechanism. Second, that this cation does not delocalize over the whole polyene system yielding C-19 *and* C-8 functionalised structures (a fact which was already demonstrated by us using NBS as the electrophile in aqueous solvent systems[9]).

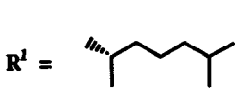
Upon treatment of a solution of the isovitamin D derivative with potassium-t-butoxide, a smooth C-1 hydroxylation occurs. The C-1 hydroxylated 5E vitamin D derivatives **6** and **7** are isolated in 48% yield as a 1 : 1 mixture. No preference in favour of the biologically important 1α stereoisomer was observed. Using 3-OH protected vitamin D (e. g. tBDMSi) and therefore forcing the flexible A-ring more towards a conformer having the C-3 substituent equatorial, a preference in favour of the 1α stereochemistry could be achieved. Thus, from

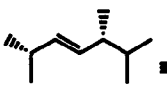
the reaction of **8** with mercurytrifluoroacetate and subsequently with potassium-t-butoxide a 1 : 5 mixture (by NMR) of **10** and **11** could be isolated. The crude reaction mixture of **10/11** was immediately silylated for simplifying the isolation of the 1α– derivative **12** (a strategy recently described by M. J. Calverley[10]) and the bis-silylated 1α, 5E-dihydroxyvitamin D_2 derivative **12**[11] (a key intermediate in the synthesis of various polar vitamin D metabolites and analogs) was obtained in an overall yield of 38% starting from **8**.



4 $R^1 = D_3$, R^2 = OH **5** $R^1 = D_3$, R^2 = OH **6** **7** $R^1 = D_3$, $R^2 = R^3$ = OH

8 $R^1 = D_2$, R^2 = OtBDMSi **9** $R^1 = D_2$, R^2 = OtBDMSi **10** **11** $R^1 = D_2$, R^2 = OtBDMSi, R^3 = OH





12 **13** $R^1 = D_2$, $R^2 = R^3$ = OtBDMSi

The mechanism of this transformation is not yet clear and needs further clarification. Simple molecular modelling[12] (note that the C-Hg-O moiety is linear) showed minimum conformations having a distance between the carbonyl oxygen of the trifluoroacetate and the sp^2- center at C-1 of ≤ 4.8Å, thus making an intramolecular process very unlikely. Therefore we favour at the moment an intermolecular SN´ process in which trifluoroacetate is the attacking nucleophile. The formed trifluoroacetates are hydrolysed immediately under the reaction conditions. In this sequence the trifluoroacetate anion is acting as the base in generating the organomercurial derivative **2** and as well as the nucleophile in the subsequent hydroxylation step.

In summary the above sequence describes an alternative route to the known allylic oxidation of 5E vitamin D with seleniumdioxide,[13] for introducing the biologically important hydroxyl function into the vitamin D molecule.

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6. NMR data of **2**: ^{1}H-NMR (400 MHz) THF-d_8: δ = 6.65 (d; J = 11 Hz, 1H, H-6), 6.01 (d; J = 11 Hz, 1H, H-7), 5.73 (dd; J = 6 Hz, 3 Hz, 1 H, H-1), 3.75 (m; 1H, H-3), 2.99 (d; J = 12 Hz, 1H, H-9ß), 2.88 (dd; J = 15 Hz, 4 Hz, 1H, H-4ß), 2.89 (AB-system, J = 10 Hz, 2H-19), 2.38 (td; J = 13 Hz, 5 Hz, 1H, H-2ß), 2.18 (dd, J = 14 Hz, 12 Hz, 1H, H-4α), ~2.09 (m; 1H, H-14), ~2.04 (m; 1H, H-2α), 1.93 (m; 1H, H-16), ~1.70 (m; 1H, H-9α), ~1.65 (m; 5H, 2H-11, H-15, 2H-23), 1.55 (m; 1H, H-25), ~1.40 (m; 4H, H-12, H-15, H-20, H-22), ~1.34 (m; 2H, H-16, H-17), ~1.17 (m; 2H, 2H-24), ~1.10 (m; 1H, H-12), 1.06 (m; 1H, H-22), 0.96 (d; J = 6 Hz, 3H, 3H-21), 0.88 (d, J = 6 Hz, 3H, 3H- 26), 0.87 (d; J = 6 Hz, 3H, 3H-27), 0.58 (s; 3H, 3H-18).
   ^{13}C-NMR THF-d_8: δ = 145.06 (C-5*), 136.83 (C-8*), 134.12 (C-10*), 125.90 (C-7), 120.44 (C-6), 117.40 (C-1), 67.12 (C-3), 57.75 (C-115), 57.61 (C-17), 46.85 (C-13), 41.61 (C-12), 40.47 (C-24), 37.17 (C-20), 37.13 (C-22), 36.60 (C-2), 36.51 (C-4), 29.97 (C-9), 28.95 (C-25), 28.51 (C-16), 26.86 (C-19), 24.79 (C-23), 24.45 (C-15), 23.15 (C-11), 23.11 (C-26), 22.89 (C-27), 19.29 (C-21), 12.36 (C-18).
7. Where data were available, the chemical shifts and line widths were in accordance width the values given in the literature; see: Webb, G. A. ed. *Ann. Rev. NMR Spec.* Vol. **10A**, p 69 (1980)
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