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Chemical Conversion of Vitamin D_3 To Its 1,25-Dihydroxy Metabolite

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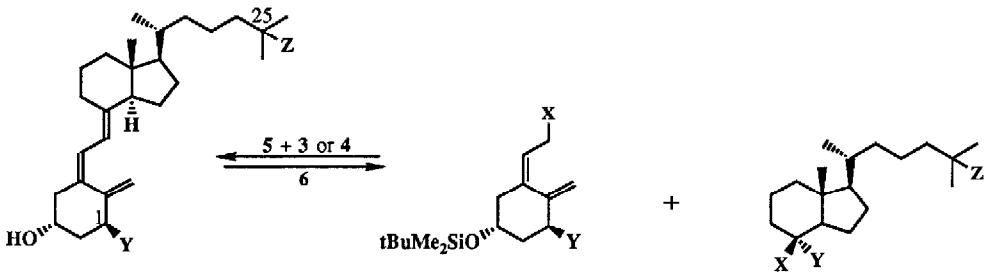
Summary. Vitamin D_3 (**6**) has been converted to the 1,25-dihydroxy vitamin D_3 metabolite (**1**) and the 1α-fluoro derivative **2** via a new process. The strategy involved the cleavage of the ring A portion from the CD portion in vitamin D_3 followed by the individual modification of each subunit to form **3**, **4**, and **5**. The subsequent recombination of **3** and **5** formed **1** while **4** and **5** produced **2**.

The natural 1,25-dihydroxy metabolite (**1**) of vitamin D_3 and its 1α-fluoro analog **2** exert a plethora of biological activities. These compounds are the subject of extensive pharmacological investigations, with 1,25-$(OH)_2D_3$ (**1**) already being a well established drug in the therapy of secondary hyperparathyroidism, osteodystrophy, renal failure, rickets, osteoporosis, psoriasis and hypertension.

The original approach to the synthesis of 1,25-$(OH)_2D_3$ (**1**), based on photolysis of 1,25-dihydroxy-cholesta-5,7-diene[1] has been recently supplanted in our laboratories by more effective total syntheses. We developed a total synthesis of 1,25-$(OH)_2D_3$ (**1**)[2] based on Lythgoe's concept[3] and more recently applied this method to the preparation of the 1α-fluoro analog **2**.[4] In this convergent approach a Wittig reaction of the ring A precursors **3** or **4** with the 25-hydroxy Windaus-Grunmann ketone **5** directly produces the vitamin D triene system of **1** or **2** in a very high yield (Scheme 1).



1 Y = Z = OH
2 Y = F, Z = OH
6 Y = Z = H Vitamin D_3

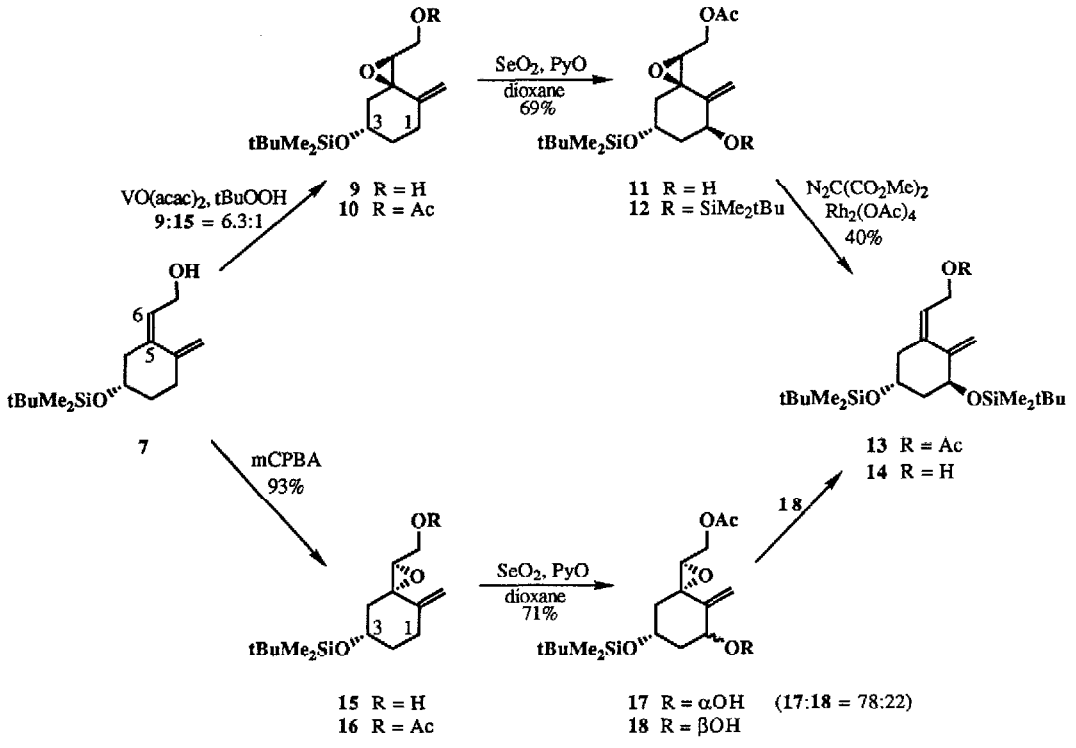
3 X = $POPh_2$, Y = $OSitBuMe_2$
4 X = $POPh_2$, Y = F
7 X = OH, Y = H

5 X + Y = O, Z = $OSiMe_3$
8 X = OH, Y = Z = H

Scheme 1

In order to prepare the intermediates **3**, **4**, and **5**, we considered as starting materials the ring A and the C,D-side chain fragments **7** and **8**, which were efficiently obtained from vitamin D_3 (**6**) by the three step oxidation procedure of Okamura.[5] Formation of the ring A precursors **3** and **4** would require stereoselective α or β hydroxylations at C1. Preliminary attempts to cleanly hydroxylate diene **7** or its esters with selenium dioxide were complicated by the reactivity of the 5,6 double bond. We anticipated, therefore, that protection of

the 5,6 bond as the corresponding epoxide would circumvent the problem.



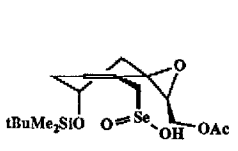
Scheme 2

By taking advantage of the dissimilar stereochemical requirements of the mCPBA vs the $VO(acac)_2$ based oxidations, either the α or β 5,6 epoxide could be obtained with a high degree of stereoselectivity (Scheme 2). Tertiary butyl hydroperoxide with $VO(acac)_2$ gave a 6.3:1 ratio of β and α epoxides **9** and **15** respectively (81% yield), while mCPBA produced the α epoxide **15** stereospecifically. The epoxide stereochemistry in each case was assigned on the basis of the nmr characteristics of the C3 proton. In **9**, the C3 proton is equatorial, appearing as a broadened singlet at 4.29 ppm. This corresponds to a chair conformation having an axial C3 oxygen, which was calculated to be about 3 Kcal/mol lower in energy than the alternate chair form. The epoxide **15** exhibits an axial C3 proton at 3.86 ppm (broad multiplet). This corresponds to the chair conformation having an equatorial C3 oxygen, and was calculated to be ca. 2 Kcal/mol lower in energy than the alternate conformation.

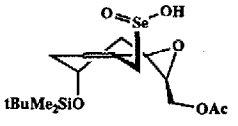
Although the novel hydroxylation procedure with SeO_2 and N-methylmorpholine N-oxide (NMO)[6] failed to generate the desired products, we found subsequently that replacement of NMO with pyridine N-oxide in dioxane produced a very effective reagent for these C1 hydroxylations. Starting from **10**, we obtained the 1β-hydroxy isomer **11** stereospecifically, while under the same conditions acetate **16** was converted to a 78:22 mixture of the 1α- and 1β- hydroxy isomers **17** and **18** respectively. The structure of **17** was confirmed by an x-ray crystallographic analysis. Interestingly, the x-ray structure shows **17** in the same chair conformation as

found in the starting material precursor **15** and correlates very closely to the minimized structure at the ring and epoxide atoms (< 0.1 Å) with a somewhat larger deviation at the C3 oxygen (≈ 0.3 Å).

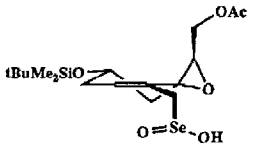
In an effort to uncover factors which may be responsible for the stereoselectivity of the hydroxylation, consideration was given to the putative selenium intermediates[7] **10Se$_\alpha$**, **10Se$_\beta$**, **16Se$_\alpha$**, and **16Se$_\beta$**. A simplified conformational analysis by MM2 suggested an 85:15 preference of **10Se$_\beta$** over **10Se$_\alpha$** and an 80:20 preference of **16Se$_\alpha$** over **16Se$_\beta$**, which would be in accord with the direction of the observed hydroxylations. While this simple analysis does not directly address aspects of the [2,3] rearrangement of the selenium intermediates to products, it may, nevertheless, have predictive value, as it does correlate well with the ratio observed for **16**, but only qualitatively for **10**.



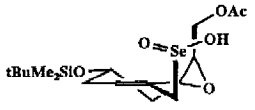
10Se$_\alpha$



10Se$_b$



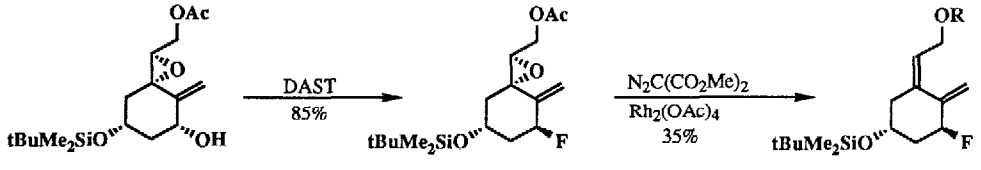
16Se$_\alpha$



16Se$_\beta$

Of the various epoxide deoxygenation methods which proceed with retention of the original geometry, only the method described by Ganem[8] was productive in our case. Regeneration of the 5,6 double bond was accomplished in modest yield on the silyl ether epoxides **12** and **18** (R = $SiMe_2tBu$) by treatment with dimethyldiazomalonate in the presence of a catalytic amount of rhodium (II) acetate. Acetate **13**, derived from the β-epoxide **12**, was hydrolyzed to allylic alcohol **14** and found to be identical to material synthesized previously by Baggiolini.[2] This compound was used for the preparation of our target diphenyl phosphine oxide **3**.[2]

The all-*cis* allylic alcohol **17** was effectively converted to the fluoride **19** by inversion of configuration with the DAST reagent (Scheme 4). Deoxygenation then regenerated the 5,6-*cis* double bond of the acetate **20**, which on hydrolysis produced the allylic alcohol **21**[4] precursor of the target molecule **4** previously described by us. With this we have completed the desired modifications of the ring A fragment of vitamin D_3.

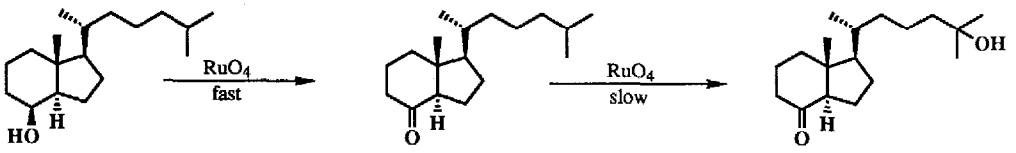


17 **19** **20** R = Ac
21 R = H

Scheme 4

Modification of the CD-side chain fragment **8** of vitamin D_3 to form the 25-hydroxy functionalized intermediate **5** (Scheme 4) required an effective and highly regioselective replacement of the tertiary hydrogen with a hydroxyl. Literature precedent for such a transformation is Mazur's 25-hydroxylation of a cholesterol

derivative using ozone on silica gel.[1c] In the optimized version of this process the 25-hydroxylated product was formed in 51% yield based on converted starting material at 11% conversion. We investigated the catalytic oxidation of the fragment **8** with RuO_4, a system recently described to preferentially hydroxylate the tertiary positions of various bicyclic and tricyclic alkanes.[9]



8 **22** **23**

Scheme 5

We observed a rapid oxidation of the hydroxy group in **8** to form the Windaus-Grundmann ketone **22**[10], which was then slowly hydroxylated at C25 to the desired **23** (Scheme 5). Under the best conditions established thus far, the use of 10% mol-equivalent of $RuCl_3$ and 3.5 mol-equivalent of $NaIO_4$ generated 22 in 13% yield and **23** in 44% yield. After separation by column chromatography, the intermediate **22** was recycled to produce additional 5% of **23**. In this way the desired 25-hydroxyketone **23** was obtained in a 49% overall yield from the vitamin D_3 fragment **8**.

In summary, we have established the feasibility of a conversion of vitamin D_3 (**6**) to the 1α,25 dihydroxy metabolite (**1**) and the 1α-fluoro analog (**2**) by employing a strategy, wherein the ring A and CD units were separated chemically, appropriately modified individually and the modified units then rejoined.[11]

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11) **9**: mp 61-61°C(pentane) $[\alpha]_D^{25}$ +3.39 (c 0.50, EtOH); ^{1}H-NMR(400mHz) δ 0.58 (s, 3H), 0.064 (s,3H), 0.90 (s, 9H), 1.46-1.60 (m, 3H), 1.80 (br d, J=13.5Hz, 1H), 2.08 (dd, J=2.4, 13 Hz, 1H), 2.28 (dm, J=13 Hz, 1H), 2.47 (tm, J=13 Hz, 1H), 3.16 (dd, J=4.3, 7.2 Hz, 1H), 3.52 (ddd, J = 5.0, 7.2, 12.2 Hz, 1H), 3.72 (ddd, J = 4.3, 7.7, 12.2 Hz, 1H), 4.29 (bs, 1H), 4.88 (nm, 2H); **11**: $[\alpha]_D^{25}$ -2.58 (c 0.43, EtOH); ^{1}H-NMR δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.47-1.56 (m, 2H), 2.07 (s, 3H), 2.10 (dd, J = 10.6, 13.1 Hz, 1H), 2.21-2.27 (m, 1H), 3.20 (dd, J = 5.0, 6.4 Hz, 1H), 4.00 (dd, J = 6.4, 12.0 Hz, 1H), 4.10 (dd, J = 5.0, 12.0 Hz, 1H), 4.29 (bs, 1H), 4.49 (bm, 1H), 5.10 (s, 1H), 5.25 (s, 1H); **15**: $[\alpha]_D^{25}$ -2.52 (c 0.48, EtOH); ^{1}H-NMR δ 0.063 (s, 3H), 0.068 (s, 3H), 0.88 (s, 9H), 1.38-1.49 (m, 1H), 1.54 (m, 1H, OH), 1.62 (dm, J = 13.5 Hz, 1H), 1.96 (m, 3H), 2.43 (m, 1H), 3.10 (t, J = 5.6 Hz, 1H), 3.60 (m, 2H), 3.86 (br m, 1H), 4.91 (m, 1H); **17** mp 65.5-66.0°C; ^{1}H-NMR δ 0.069 (s, 3H), 0.080 (s, 3H), 0.88 (s, 9H), 1.50 (q, J = 11.1 Hz, 1H), 1.60 (dm, J = 11 Hz, 1H), 2.02 (t, J = 11.3 Hz, 1H), 2.09 (s, 3H), 2.38, (m, 1H), 3.11 (dd, J = 5.1, 6.1 Hz, 1H), 3.90 (br m, 1H), 3.94 (dd, J = 6.1, 12.0 Hz, 1H), 4.07 (m, 1H), 4.09 (dd, J = 5.1, 12.0 Hz, 1H), 5.12 (s, 1H), 5.27 (s, 1H).

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