

## Development of commercially applicable syntheses of Vitamin D derivatives

### Background:

Vitamin D derivatives have raised an increasing interest in the past years, because it has been realized that 1 $\alpha$ ,25-Dihydroxyvitamin D<sub>3</sub> (known as Calcitriol) plays a more important and diversified role as originally thought. The importance of Calcitriol is by far not limited to its classical role in calcium and phosphate metabolism. It has additionally been shown that Calcitriol and its derivatives are connected to the occurrence of various serious diseases, such as psoriasis, leukemia, AIDS und Alzheimer's disease, and contributes particularly to the prevention of cancer. Consequently, new Vitamin D derivatives will presumably be needed in the future as a prerequisite for drug discovery and development efforts to successfully explore new therapeutic rationales and disease prevention strategies.

Although a vast knowledge related to the synthesis of Vitamin D derivatives is known from the literature, the limited accessibility of compounds of particular interest in sufficient quantity and purity is still often a drawback in the drug discovery process and also in API production.

### Methods & Results:

With the aim to develop a versatile technology platform towards the synthesis of a wide variety of known and new Vitamin D derivatives, 3 distinguished representative processes for the synthesis of Calcitriol, and two alternative synthesis of 25-Hydroxy Vitamin D<sub>2</sub>, each in turn partly already known from the literature<sup>[1-3]</sup>, were developed, optimized and applied to production scale.

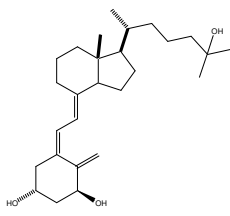


Figure 1. Calcitriol

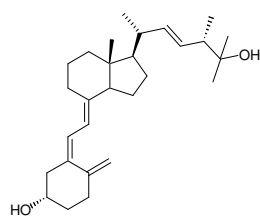
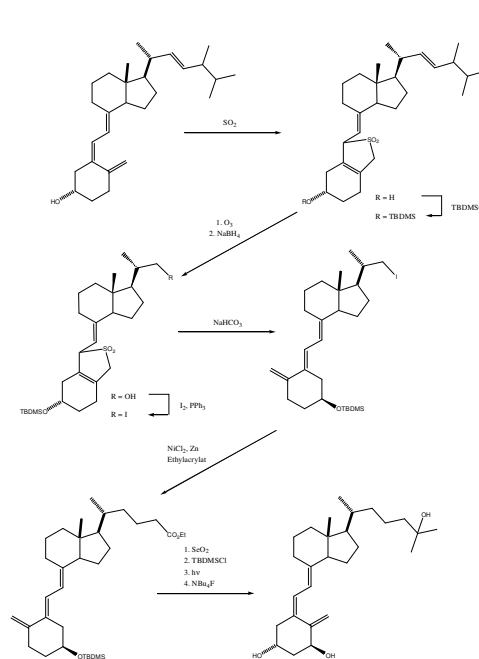
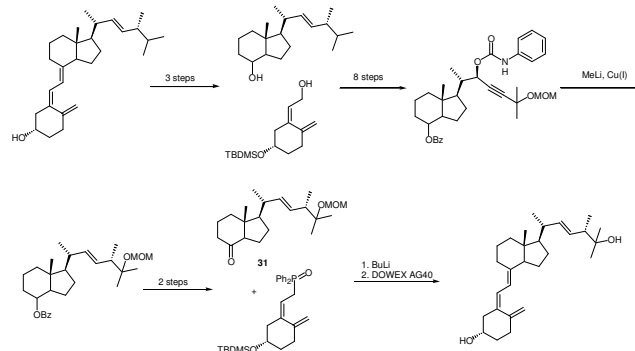


Figure 2. 25-Hydroxyvitamin D<sub>2</sub>

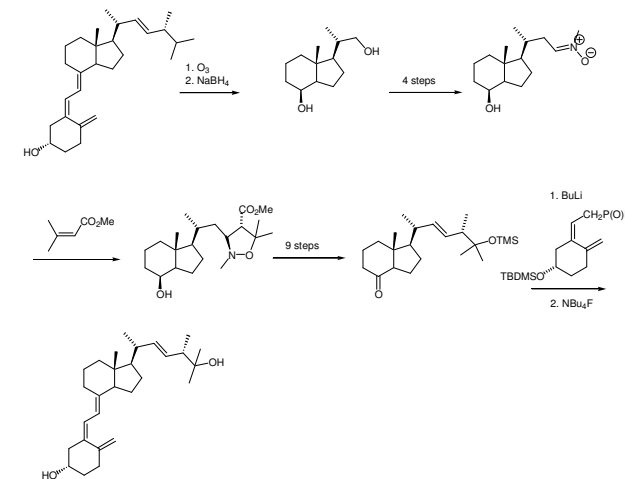
L. Kattner \*, R. Pfeifer, M. Behr, E. Rauch, N. Weber, P. Seck



Scheme 1. Synthesis of Calcitriol<sup>[1]</sup>. The (linear) synthesis, starting with Vitamin D<sub>2</sub>, has been proven as most productive concerning obtainable yields and purity.



Scheme 2. Synthesis of 25-Hydroxyvitamin D<sub>2</sub>, alternative 1<sup>[2]</sup>.



Scheme 3. Synthesis of 25-Hydroxyvitamin D<sub>2</sub>, alternative 2<sup>[3]</sup>.

Table 1. Comparison of different syntheses

Name	Steps	Yield %	Purity %
Calcitriol	11	5,3	93-99,3
25-Hydroxyvitamin D <sub>2</sub> alternative 1	17	1,7	85
25-Hydroxyvitamin D <sub>2</sub> alternative 2	15	1,5	>99

### Conclusion:

➤ By proving and optimizing procedures known from literature we have developed commercially applicable syntheses of Calcitriol and 25-Hydroxyvitamin D<sub>2</sub>, providing these compounds in g-quantities and high purity.

➤ The developed technology platform allows the synthesis of a wide variety of new Vitamin D derivatives in a building set fashion.

[1] a) *Org. Proc. Res. Dev.* **2002**, 6, 246.; (b) *J. Org. Chem.* **1995**, 60, 65741; c) *Chinese Chem. Lett.* **2002**, 13(12), 1158.

[2] *J. Org. Chem.* **1986**, 51, 1264.

[3] a) *J. Org. Chem.* **1986**, 51, 3098; b) *J. Org. Chem.* **2002**, 67, 1580; c) *Tetrahedron* **1984**, 40, 2296.