# A Modified Synthesis of the Antiosteoporosis Drug Alfacalcidol via a Key Photochemical Transformation of 1α-5,6-*trans*-Vitamin $D_3$

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**Abstract:** Alfacalcidol (1α-hydroxyvitamin $D_3$) is an important clinical drug for the treatment of osteoporosis. Its practical synthesis has been intensively pursued across academia. The difficulties of separating 5,6-*cis* and 5,6-*trans* isomers in the current process was avoided by photochemical transformation of the 5,6-*trans* isomer into the 5,6-*cis* isomer. Employing vitamin $D_3$ as a starting material, alfacalcidol was obtained by a five-step reaction sequence of esterification, cyclization, oxidation, solvolysis ring-opening, and subsequent photochemical reaction. The overall yield has been greatly improved from 17% to 31%.

**Key words:** antiosteoporosis drug, vitamin $D_3$, photochemical transformation

Alfacalcidol (1α-hydroxyvitamin $D_3$) is a drug for the treatment of parathyroid dysfunction, renal osteodystrophy, and osteoporosis caused by menopause.[1] It has been shown recently that 1α-hydroxyvitamin $D_3$ exhibits notable activities against some cancers.[2,3] Therefore an efficient synthesis of 1α-hydroxyvitamin $D_3$ is important in pharmaceutical industry with both clinical and industrial significance.

Currently, two approaches have been used for the industrial synthesis of 1α-hydroxyvitamin $D_3$, both using vitamin $D_3$ as a starting material.[4] Route one treated vitamin $D_3$ with sulfur dioxide to produce two cyclic adducts which are protected via a silyl group. These protected adducts undergo base-catalyzed sulfur dioxide removal and rearrangement to a single silyl 5,6-*trans*-vitamin $D_3$. Allylic oxidation then affords the corresponding 1α-hydroxy derivative, which is then deprotected to yield crystalline 1α-hydroxy-5,6-*trans*-vitamin $D_3$, photochemical isomerization of the 1α-hydroxy-5, 6-*trans*-vitamin $D_3$ may yield 1α-hydroxyvitamin $D_3$.[3,5] However, the use of sulfur dioxide as a solvent and the instability of the silyl compound have made syntheses by this process inefficient.

The second route, based on Mazur's observation on the vitamin–cyclovitamin conversion, devised by DeLuca and their collaborators, entails three main chemical operations: formation of cyclovitamin D, C-1 hydroxylation of the cyclovitamin D, and solvolysis of cyclovitamin D.[6] This method suffers from 5,6-*cis* and 5,6-*trans* isomers which are obtained with a molar ratio of 4:1 by solvolysis of cyclovitamin D. The isomers are hard to separate by column chromatography, even including preparative high-performance liquid chromatography (prep. HPLC).[7] At present, a Diels–Alder reaction was adopted to selectively remove the *trans* isomer.[8] With this method, a lot of intermediates become unusable, thus the overall yield is usually around 15%.

Our work has been concerned with the Mazur's solvolysis method, trying to overcome the separation issue of isomers. A photochemical reaction can be used to convert the 5,6-*trans* isomer into the targeted 5,6-*cis* isomer selectively; this replaces the previous Diels–Alder reaction (Scheme 1). Also, we have studied some important parameters in the 1α-hydroxy-vitamin $D_3$ synthetic process, such as solvent, temperature, and molar ratio of raw materials of esterification and cyclization reactions. In summary, an efficient procedure was reported here to produce the corresponding 1α-hydroxyvitamin $D_3$ from vitamin $D_3$ in 30% overall yield.

First, vitamin $D_3$ (**1**) was treated with *p*-toluenesulfonyl chloride in quantitative yield to the vitamin $D_3$ tosylate (**2**). Pyridine was reported to be used as solvent,[9] which is miscible with water and conjugated with the triene structure of the product to form π–π bond interaction. Thus tedious extraction and washing procedures were necessary for separation to avoid product loss with pyridine. In order to simplify the operating conditions and the posttreatment process, as well as to avoid product waste, dichloromethane was used as solvent to replace pyridine.[10] As a result, it significantly reduced pyridine hydrochloride waste and improved process economy. On the other hand, we selected 4-dimethylaminopyridine as catalyst, and the reaction temperature was changed from 4 °C to room temperature; and the reaction time was shortened from 48 hours to 6.5 hours. Compound **2** was obtained in ca. 100% yield.[11]

In the cyclization reaction, a large amount of sodium bicarbonate was used as catalyst.[12] This, however, made stirring difficult and subsequent filtration inconvenient, since it can hardly dissolve in the reaction system. In order to simplify operations and improve yield, we attempted to find out the optimal temperature and molar ratio of raw materials. Molar ratio of sodium bicarbonate and **2** was reduced from 18.3:1 to 3.6:1, which saved both sodium bicarbonate and filtration. At this molar ratio, the best reaction temperature is 63 °C, and the reaction time was shortened from 5.3 hours to 2.3 hours. Under optimized

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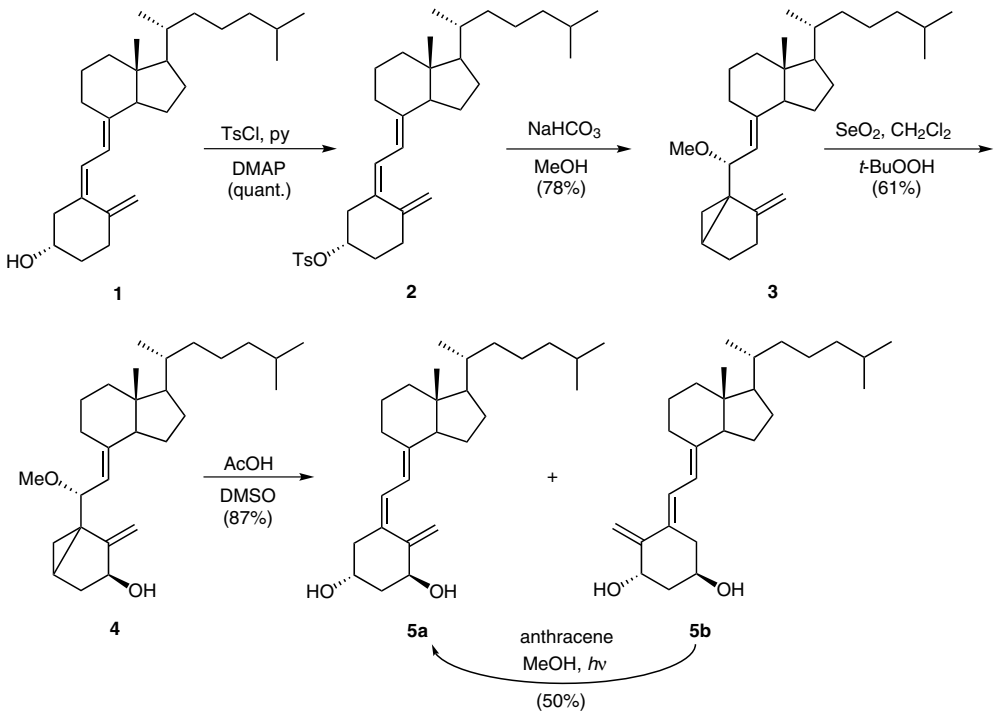


**Scheme 1** The synthetic route of alfacalcidol

conditions, the yield of 3,5-cyclovitamin $D_3$ (**3**) was improved from 73% to 78%.[13]

Selective oxidation of **3** was effected under *tert*-butyl alcohol peroxide and $SeO_2$, giving **4** as a yellowish oil in a yield of 61%, which was further solvolyzed under acetic acid and DMSO to give a mixture of **5a** and **5b**. The undesired byproduct of the solvolysis ring-opening reaction, 5,6-*trans*-isomer (**5b**),[14] which was formerly consumed and separated from 5,6-*cis*-1α-hydroxyvitamin $D_3$ (**5a**) by a selective Diels–Alder reaction with maleic anhydride as dienophile and further separation by column chromatography, was converted into **5a** by photochemical reaction employing anthracene as a photosensitizer.[15] 5,6-*trans*-1α-Hydroxyvitamin $D_3$ (**5b**) could be completely converted into 5,6-*cis*-1α-hydroxyvitamin $D_3$ (**5a**), and the total yield of the ring-opening and subsequent photochemical reaction [from 1α-hydroxy-3,5-cyclovitamin $D_3$ (**4**) to **5a**] came up to 66%. By this way, tedious procedure was simplified and loss of **5b** was reasonably avoided. To our satisfaction, the overall yield of the whole synthesis process is greatly improved from 17% to 31%.[16]

In conclusion, we have simplified the synthetic method of 1α-hydroxyvitamin $D_3$ with a higher yield. The tedious workup of the esterification reaction was simplified, and the reaction time was greatly reduced. The cyclization reaction was also improved with optimal temperature and molar ratio of raw materials and shorter reaction time. It is noteworthy that the previous Diels–Alder reaction used for separating the *cis*/*trans* mixtures was replaced by photochemical reaction. In this way, the loss of product was prevented and higher product yield was then achieved.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **Synthesis of Vitamin $D_3$ Tosylate (2)**
Vitamin $D_3$ (**1**, 1.00 g, 2.6 mmol), 4-dimethylaminopyridine (1.00 g, 8.2 mmol), and dry pyridine (1.55 mL), contained in a 25 mL round-bottom flask, was kept cool in an ice bath. A solution of freshly recrystallized *p*-toluenesulfonyl chloride (0.87 g, 4.6 mmol) in $CH_2Cl_2$ (8.5 mL) was added to it several times. The solution system was stirred and reacted until its color deepened to glassy yellow. It was kept airtight under argon protection and being stirred at r.t. away from light. After 6.5 h, the solution turned light red and colorless transparent needle crystals were formed at the bottom of the flask. The mixture was transferred into a 100 mL beaker and sat. $NaHCO_3$ (20 mL) was added in several times with stirring. Then the organic layer was washed with 3% HCl (3 × 30 mL), sat. $NaHCO_3$ (1 × 20 mL), and sat. NaCl (1 × 20 mL), dried over $MgSO_4$, and concentrated to 1.40 g of a white crystalline solid **2** in vacuo.

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(13) **Synthesis of 3,5-Cyclovitamin $D_3$ (3)**
To a stirring solution of anhydrous MeOH (150 mL) was added finely divided $NaHCO_3$ (2.00 g, 23.8 mmol) and vitamin $D_3$ tosylate (**2**, 3.50 g, 6.50 mmol). The mixture was heated to 63 °C under Argon protection for 2.3 h, cooled to r.t. and concentrated in vacuo. The residue was diluted with distilled $H_2O$ (70 mL) and was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with sat. brine (1 × 150 mL), dried over $MgSO_4$, and concentrated to a transparent yellowish oil in vacuo. Silica gel column chromatography in PE–EtOAc (19:1) yielded 2.01 g of colorless 3,5-cyclo-vitamin $D_3$ (**3**), which could be used for the next reaction without further purification.

(14) **General Procedure for 1α-Hydroxyvitamin $D_3$ 5a and 5b**
lα-hydroxy-3,5-cyclo-vitamin $D_3$ (**4**, 2.62 g, 6.3 mmol) was dissolved in DMSO (28.1 mL) and glacial acetic acid (22.4 mL). The mixture was heated to 50 °C under argon protection for 1 h and was then quenched by pouring the mixture over ice. The aqueous suspension was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then washed with sat. $NaHCO_3$ (3 × 100 mL) and sat. NaCl (3 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. Silica gel column chromatography in PE–EtOAc (4:6) afforded 2.20 g (87% yield) of a yellowish crystalline solid, which contained 5,6-*cis*-1α-hydroxyvitamin $D_3$ (**5a**) and 5,6-*trans*-1α-hydroxyvitamin $D_3$ (**5b**).

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(16) **Phototransformation of 5,6-*trans*-1α-Hydroxyvitamin $D_3$ (5b) to 5,6-*cis*-1α-Hydroxyvitamin $D_3$ (5a)**
A solution of of the crystalline solid (0.5 g, 1.2 mmol) from the last step in anhydrous MeOH (80 mL) containing anthracene (18.0 mg, 0.1 mmol) was thoroughly degassed. A medium-pressure 500 W ultraviolet lamp was placed such that the outside of the water-cooled jacket was 15 cm from the reaction vessel. Ice water was passed in the jacket of the quartz tube to keep the reaction cool. The mixture was irradiated for 4.0 h under argon protection at r.t., until all of **5a** was converted into **5b** and then concentrated in vacuo. The residue was eluted by PE–EtOAc (4:6) to separate **5a**, and further recrystallization from EtOAc and cyclohexane afforded 0.37 g (75% yield) of a white crystalline solid (**5a**)
**Analytcal Data**
IR (KBr): 3406, 1643, 1629, 1059, 909 $cm^{-1}$. $^1H$ NMR (500MHz, $CDCl_3$): δ = 0.55 (3 H, s, 18-$CH_3$), 0.87 (6 H, dd, $J_1$ = 2.3 Hz, $J_2$ = 6.6 Hz, 26-$CH_3$, 27-$CH_3$), 0.92 (3 H, d, $J$ = 6.5 Hz, 21-$CH_3$), 2.32 (1 H, dd, $J_1$ = 6.6 Hz, $J_2$ = 13.4 Hz, H-4β), 2.60 (1 H, dd, $J_1$ = 3.3 Hz, $J_2$ = 13.4 Hz, H-4α), 2.83 (1 H, dd, $J_1$ = 3.8 Hz, $J_2$ = 11.8 Hz, H-14), 4.24 (1 H, m, H-3α), 4.44 (1 H, dd, $J_1$ = 4.3 Hz, $J_2$ = 7.8 Hz, H-1β), 5.01 (1 H, s, H-19E), 5.33 (1 H, t, $J$ = 1.5 Hz, H-19Z), 6.02 (1 H, d, $J$ = 11.3 Hz, H-7), 6.39 (1 H, d, $J$ = 11.3 Hz, H-6).



 