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Site-Selective Modification of Vitamin D Analogue (Deltanoid) through a Resin-Based Version of Organoselenium 2,3-Sigmatropic Rearrangement

Wei-Ming Xu,* Jun He, Min-Qiang Yu, and Guo-Xiang Shen

College of Material Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, P. R. China
wmxu@zju.edu.cn

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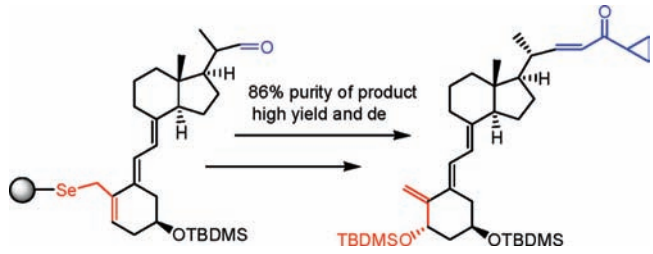
ABSTRACT



A site-selective modification of a vitamin D analogue (Deltanoid) through a two-step 2,3-sigmatropic rearrangement of organoselenium resin to prepare the key intermediate of calcipotriol has been developed. The polystyrene-supported selenium resins used here not only facilitate separation of product but also assist the crucial 2,3-sigmatropic rearrangement to introduce an important functional group (1α-hydroxyl) with high stereo- and regioselectivity.

Medicinal chemistry relies on the efficient generation of analogues of lead compounds. Natural products represent a special class of leads since they have survived eons of natural selection and generally evolved to perform a specific function.[1] As an effective approach, the application of solid-phase organic synthesis (SPOS) in the field of natural product-like synthesis[2] is of considerable significance in the discovery and development of new drug compounds. One of the key challenges in SPOS involves immobilizing the substrates onto the solid support, thus driving the demand for the development of new and innovative linkers.[3] Toward this end, there has been particular interest in developing linking strategies, whereby the loading and cleavage steps contribute to the complexity of the target structure rather than merely constituting extraneous manipulations.[3]

Since the discovery of the active hormone 1α,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$, calcitriol], synthetic organic chemists have altered the structure of 1,25$(OH)_2D_3$ in various ways with the goal of preparing vitamin D analogues as sensitive molecular biology probes and as new drugs having a favorable therapeutic index (i.e., high efficacy and low toxicity).[4] Considerable success has been achieved in the development of new deltanoid drugs. Among those currently in use as drugs for chemotheraphy of various human diseases and those currently in human clinical trials, most of the

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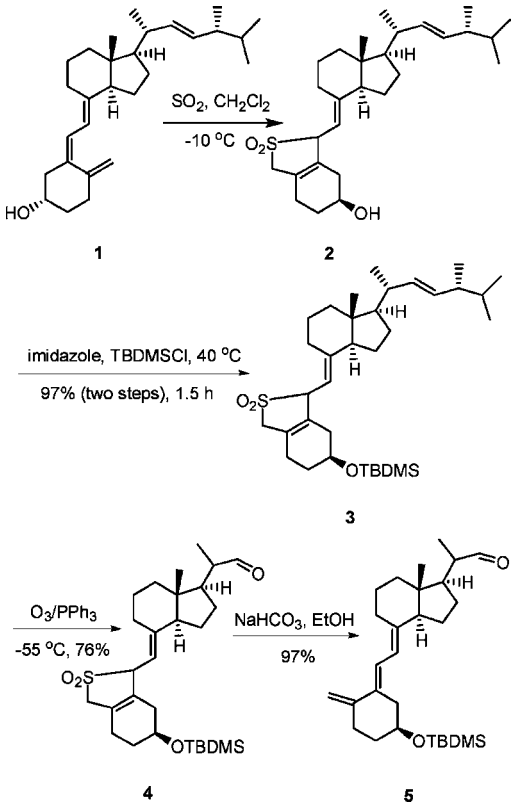
analogues used thus far are modified in the side chain along with a new 1α-hydroxyl compared with vitamin D_2.[5]

The major advantage of preparing new deltanoids from almost whole steroid precursors is that most of the deltanoid skeleton, including its absolute stereochemistry, is available without needing costly and time-consuming multistep syntheses.[6] Yet, natural products are difficult to modify efficiently by chemical methods because of their complexity and multifunctional nature.[7]

As part of our research program on the study of organoselenium resin,[8] we wish to report here a site-selective modification of modified vitamin D_2 through a two-step 2,3-sigmatropic rearrangement[9] to prepare the key intermediate of calcipotriol with evident advantages of easy operation for its odorlessness and high stereo- and regioselectivity of the product. Compared with the reported literature (during the allylic hydroxylation reaction, the ratio of two isomers was constant 6:1),[10] the high diastereomeric excess (de) values of 1α-hydroxyl in our reaction were proposed to be due to the steric course of organoselenium[11] and the intramolecular interaction between selenium and oxygen.[12]

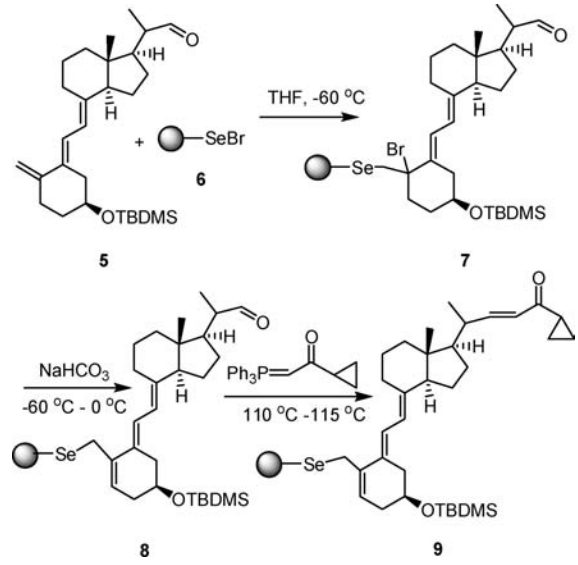
We began our efforts from vitamin D_2, which was converted to its SO_2-adducts, without further purification, directly followed by silylation with *tert*-butylchlorodimethylsilane (TBDMSCl) and ozonation with O_3. After flash chromatography, cheletropic extrusion of SO_2 in refluxing ethanol containing suspended $NaHCO_3$ gave substituted aldehyde **5**[13] (Scheme 1).

Scheme 1. Preparation of Substituted Aldehyde **5**



Aldehyde **5** was then treated with polystyrene-supported selenenyl bromide **6** (Br: 0.68 mmol/g, dark red resin, prepared as described in refs 3c and 8) to give the corresponding pale-green resin **7**, which was followed by elimination to give polystyrene-supported aldehyde **8** almost quantitatively. The characteristic IR −CHO stretch (1724 cm^{-1}) of resin **8** provides a convenient mode to monitor the progress of resin loading. Resin **8** reacted smoothly with cyclopropylcarbonylmethylenetriphenyl phosphorane to furnish resin **9**, and in this process the Wittig reaction was followed also using IR spectroscopy, which showed disappearance of the distinctive −CHO stretch and appearance of the distinctive −C═O stretches at 1686 and 1666 cm^{-1}. Upon further investigation, we found that it was necessary to keep the reaction temperature between 110 and 115 °C to ensure an adequate reaction rate and an acceptable product yield and purity of the final product (Scheme 2).

Scheme 2. Preparation of Resin **9**



In the field of synthetic organoselenium chemistry, 2,3-sigmatropic rearrangements of allylic selenides are one of the most fundamental reactions. Since the first 2,3-sigmatropic rearrangement of allylic selenide was reported in 1972,[14] the method has been widely studied due to this 1,3-allylic alcohol transposition which proceeds under very mild conditions.[15]

With resin **9** in hand, we first followed the conditions that Back and McPhee had devised[16] in the preparation of a natural product. Although the same strategy using organoselenium resin for 2,3-sigmatropic rearrangement to introduce a hydroxyl group on a different nature product can also be found,[17] an inseparable mixture was obtained in our reaction

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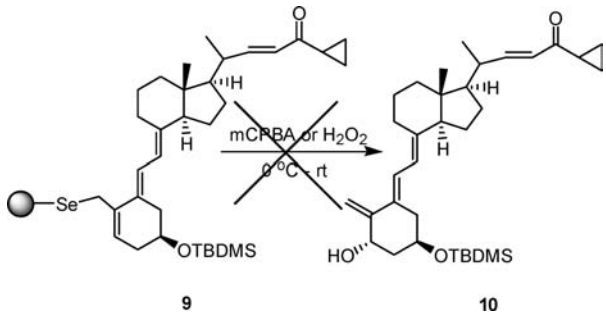
whether 3-chloroperoxybenzoic acid (mCPBA) or H_2O_2 is used as an oxidant (Scheme 3). Further investigation

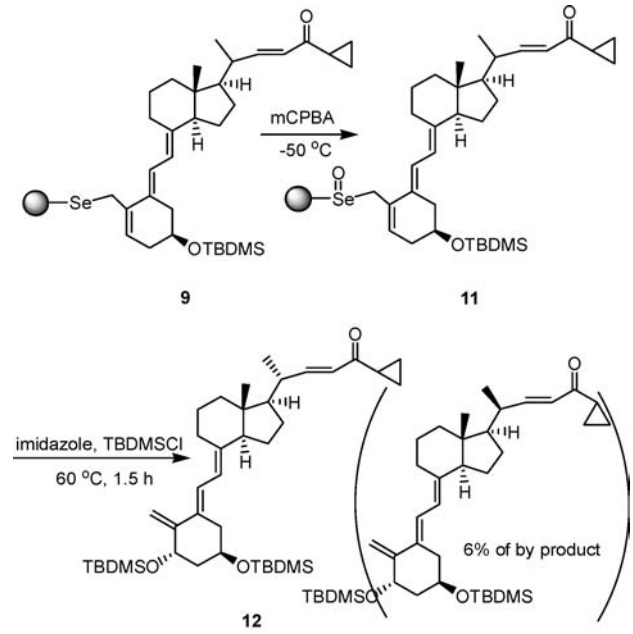
Scheme 3. General 2,3-Sigmatropic Rearrangement to Prepare the Key Intermediate of Calcipotriol



indicated that the assumed product (intermediate of calcipotriol) **10** could not stably exist in our oxidized system.

To solve this problem, we developed here a two-step 2,3-sigmatropic rearrangement: a typical 2,3-sigmatropic rearrangement involves an oxidation of selenides and a transfer of oxygen from the selenium atom to the carbon atom of an allylic selenoxide, then an allylic alcohol after hydrolysis. In our procedure, the intermediate selenoxide resin **11** was separated through filtration from the reaction mixture, which was then followed by hydrolysis and protection of the 1α-hydroxyl group with *tert*-butylchlorodimethylsilane (TBDMSCl) simultaneously (Scheme 4). To our surprise, key product **12** was obtained with 86% purity of the crude product and 64.5% of isolated yield according to resin **5**.[18] From the literature,[5] key product **12** can be smoothly followed by selective reduction, clean photoisomerization, and deprotection to give calcipotriol as a Psoriasis drug.

Scheme 4. Two-Step 2,3-Sigmatropic Rearrangement to Prepare the Key Intermediate of Calcipotriol



The purity of product **12** was 86%; and total isolated yield was 64.5% according to resin **5**

It is noteworthy that in our procedure the organoseleno species used here not only facilitate separation of the procedure but also assist the crucial 2,3-sigmatropic rearrangement to introduce an important functional group (1α-hydroxyl) with high stereo- and regioselectivity, which shows a wide range of activities, including cell-differentiating and antiproliferative activities among the hormonally active form of vitamin D_3. Furthermore, an efficient route, starting from vitamin D_2, to different kinds of vitamin D analogues is developed.

In conclusion, we have developed a site-selective modification of vitamin D analogue (Deltanoid) through a two-step 2,3-sigmatropic rearrangement of organoselenium resin to prepare the key intermediate of calcipotriol. Further detailed studies and application will be disclosed in due course.

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Supporting Information Available: Experimental procedures and IR, HPLC, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For the detailed processes, please see Supporting Information.