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Efficient modification of steroid 20*S*-hydroxy functionality for industrial preparation of 1α,25-dihydroxy-22-oxavitamin D_3, Maxacalcitol

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Abstract—A one-pot modification method of steroid 20*S*-hydroxy functionality involving sequential alkylation and reductive cleavage of epoxy bond has been established for the industrial preparation of a medicinally important 1α,25-dihydroxy-22-oxavitamin D_3 **2** (22-oxa-calcitriol), Maxacalcitol.

Discovery of a broad spectrum of biological activities of the vitamin D metabolite,[1] 1α,25-dihydroxyvitamin D_3 (Calcitriol) **1**, other than originally thought in regulating calcium and phosphorus metabolism stimulated synthetic study toward new vitamin D analogues with useful pharmacological properties.[2] Intending to obtain new vitamin D_3 analogues having therapeutic potential, we have been concentrating our efforts on the modification study, which led us to the discovery of a clinically useful Calcitriol analogue 1α,25-dihydroxy-22-oxavitamin D_3 **2** (22-oxa-calcitriol)[3,4] and named it Maxacalcitol. Although our compound **2** is a simple analogue of Calcitriol **1** whose 22-methylene functionality is replaced merely by an oxygen atom, it exhibits enhanced differentiation-inducing and antiproliferation activities,[5] compared to **1**. On the basis of this discovery, we developed a new antihyperparathylidism injection[6] and an antipsoriatic ointment[7] both of which consist of **2** as an active component (Fig. 1).

The compound **2** has so far been produced starting from the 20*S*-hydroxysteroid **4**, which was readily synthesized in a multi-kg scale from readily accessible 17-ketosteroid **3** in two steps. The secondary alcohol **4** was first coupled with *N*,*N*-dimethylacrylamide by Michael reaction to give the β-alkoxyamide **5**, which afforded the key intermediate tertiary alcohol **7** in the following two steps via the ketone **6** on sequential twice cerium-mediated Grignard reactions. Since the transformation of **7** to Maxacalcitol **2** could be readily carried out in a sequence of four steps of reactions in quite similar way[3c,8] that employed in the synthesis[2] of Calcitriol **1**, the most critical point is the Michael addition step[3c] to generate the β-alkoxyamide **5** (Scheme 1). The key Michael reaction generally proceeds smoothly, but it was found to be very capricious as it requires an excess Michael acceptor (5 equiv), which often results in a

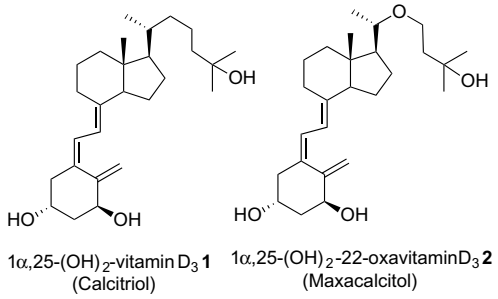

Figure 1.

Keywords: Vitamin D_3; Steroid; Williamson reaction; Michael reaction; One-pot reaction; L-Selectride.
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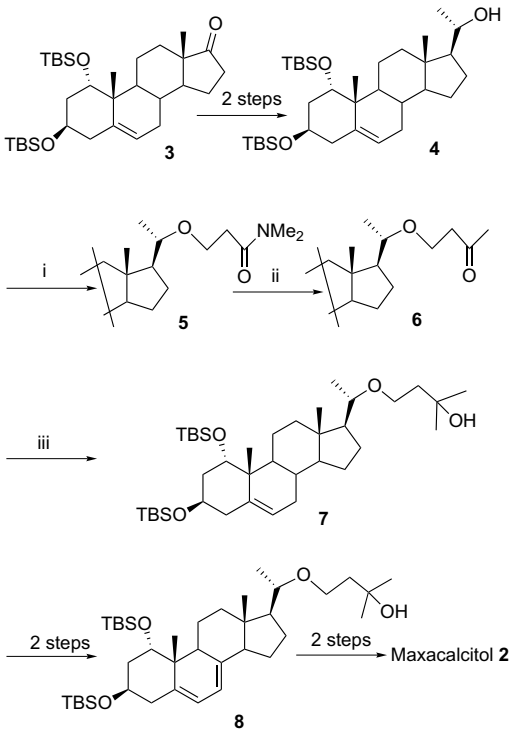
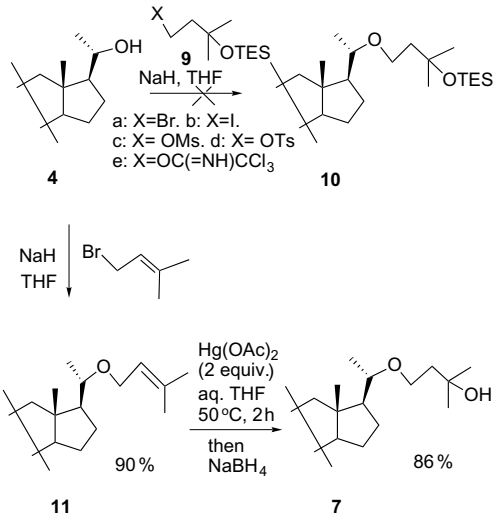


Scheme 1. Reagents and conditions: (i) *N*,*N*-dimethylacrylamide (5 equiv), NaH (1.5 equiv), THF (~87%); (ii) MeMgCl (4 equiv), $CeCl_3$ (4 equiv), THF; (iii) MeMgCl (4 equiv), $CeCl_3$ (4 equiv), THF (~78%, two steps).

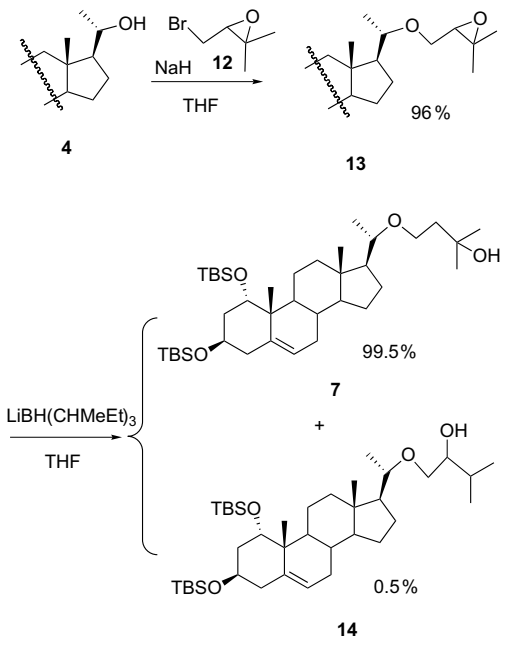


Scheme 2.

formation of a complex mixture depending on a subtle change in the reaction conditions. Moreover, inevitable use and unavoidable disposal of the cerium reagent in the later two stages as well as concomitant retro-Michael reaction during these two stages prevented efficient industrial production of Maxacalcitol. We, therefore, explored an alternative route capable of producing the key ether intermediate **7** in a more readily and straightforward way and, here, we wish to report the development of a highly efficient one-pot construction of the key intermediate **7** starting with the same steroid precursor **4** used in the previous synthesis.

Although we have so far recognized the difficulty in modification of 20*S*-hydroxy functionality in this kind of steroids,[3] we first examined etherification of the 20*S*-alcohol **4** extensively by standard Williamson reaction[9] with a series of alkylating agents **9a–d** carrying protected tertiary alcohol in THF and other solvents such as DMF and toluene in the presence of sodium hydride. Under these conditions, virtually no expected alkylation reaction occurred. Moreover, the alkylation did not take place when the trichloroacetimidate **9e** was used in the presence of an acid catalyst.[10] On the other hand, alkylation of the alcohol **4** with less hindered and more reactive prenyl bromide proceeded readily under basic conditions to give the prenyl ether **11** in excellent yield. However, discrimination of the two trisubstituted olefin functionalities in the molecule was found to be difficult under both hydration and oxidative conditions. For example, the reaction of the prenyl ether **11** with *m*-chloroperbenzoic acid (MCPBA) proceeded in a nonregioselective manner to yield a mixture of three possible epoxides besides the unchanged starting material **11**. We could only succeed in carrying out regioselective hydration in a satisfactory yield when the diolefin **11** was subjected to the oxymercuration–reduction conditions[11] in which more than an equimolar amount of unacceptable mercury salt was inevitable. Thus, the diolefin **11**, on treatment with 2 equiv of mercury(II) acetate in warm aqueous THF, followed by sodium borohydride, furnished regioselectively the key tertiary alcohol **7** in 86% yield to leave the other olefin functionality in the molecule intact (Scheme 2).

To alleviate use of the mercury salt in introduction of the requisite tertiary hydroxy functionality, we chose the epoxy-bromide **12** as the alkylating agent to obtain the epoxy-ether **13**, from which we expected the key tertiary alcohol **7** through regioselective epoxy-bond cleavage. Since the epoxy-bromide **12** resembles prenyl bromide sterically and electronically taking into account its size and its sp^2 like character of the epoxy functionality,[12] we could readily assume that it should react with the secondary alcohol **4** to afford the epoxy-ether **13**. Among the conditions examined, the desired product **13** was obtained in 96% yield from the alcohol **4** on treatment with 1.3 equiv of the epoxy-bromide **12**, readily prepared from 2-methyl-3-buten-2-ol with potassium hypobromite,[13] in THF at reflux for 2 h in the presence of 2 equiv of sodium hydride. With respect to the reductive cleavage of the epoxy linkage of **13**, we found, after extensive examination, that the desired reaction did occur with lithium tri(2-butyl)borohydride[15] (L-Selectride®) in THF to give regioselectively the tertiary alcohol **7** in excellent yield though the most of aluminum and boron hydride reagents[14] furnished a mixture of the tertiary **7** and the secondary **14** alcohols. Reductive cleavage of epoxy linkage with L-Selectride was precedented, but it was incidentally observed when L-Selectride was used for the demethylation[15] of a methyl aryl ether carrying epoxy linkage. Thus, exposure of the epoxide **13** to



Scheme 3.

5 equiv of L-Selectride® in THF at room temperature for 2.5 h afforded the key tertiary alcohol **7** selectively in 99.5% yield accompanied by 0.5% of the secondary alcohol **14**. During these two-step sequence virtually pure products were obtained without performing any chromatographical purification (Scheme 3).

Having established the optimal conditions for the transformation of the 20*S*-alcohol **4** into the key tertiary alcohol **7** through a two-step sequence involving Williamson synthesis and reductive epoxy-linkage cleavage, we further sought the conditions making this two-step sequence into a one-pot operation to increase synthetic efficiency. As described we have visualized it in a 2 kg scale synthesis: thus, to a solution of the secondary alcohol **4** (2.0 kg, 3.35 mol) in THF (8 L) was added NaH (95%, 179.5 g, 7.11 mol) portionwise with stirring at room temperature so as to control evolution of hydrogen in an appropriate rate. After having ceased the evolution of hydrogen, to the resulting suspension was added the bromide **12** (762 g, 4.62 mol) dropwise at the same temperature with stirring and the mixture was refluxed for 3 h. After cooling to room temperature, to this mixture was added L-Selectride® (1 M in THF, 9.9 L, 9.9 mol) dropwise and the mixture was refluxed for 3 h. The mixture was then cooled to −10 °C and treated sequentially with 3 N NaOH (8 L) and 35% H_2O_2 (10 L) and the stirring was continued for 2 h at room temperature. To this mixture was then added aqueous $Na_2S_2O_3$ (7 kg in 20 L) at the same temperature and, after stirring for 1 h, the mixture was extracted with AcOEt (8 L) and separated. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (6 L) and brine (2×6 L), and evaporated under reduced pressure to leave a colorless solid. The solid was dissolved in refluxing methanol (14 L) and to this solution, after cooling to 25 °C, was added water (6 L) with stirring to form a suspension, which was cooled to −5 °C and the stirring was continued for 1 h at the same temperature. Then the suspension was centrifuged and a colorless crystalline solid collected was dried at 50 °C to leave the tertiary alcohol **7** (2.1 Kg, 97.3%), as colorless granules, mp 130 °C, accompanied by 0.5% of the secondary alcohol **7**, the latter of which was detected by HPLC analysis and was removed during the later stage of the transformation into Maxacalcitol **2**. The key intermediate **7** for industrial synthesis of Maxacalcitol **2** is currently synthesized by employing the present method.

In summary, we have developed an efficient one-pot conversion method of the steroid 20*S*-alcohol **4** into the tertiary alcohol **7**, the key industrial intermediate of medicinally important 1α,25-dihydroxy-22-oxavitamin D_3 **2** (Maxacalcitol), via a sequence involving Williamson synthesis and regioselective cleavage of epoxy linkage.

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