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## An efficient enantioselective synthesis of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> A-ring synthon

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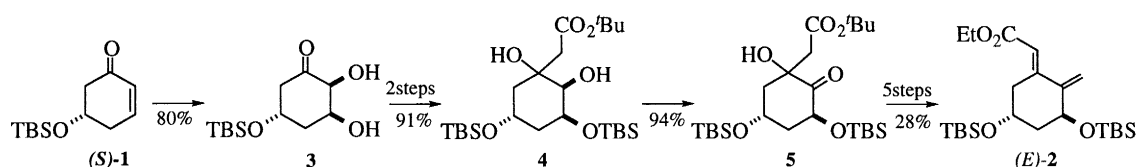
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### Abstract

The asymmetric synthesis of the A-ring of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, (*Z*)-**2**, from 5-*tert*-butyldimethylsiloxy-2-cyclohexenone [(*S*)-**1**], is described where an intramolecular lactonization using cat. scandium triflate is the key reaction. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:** asymmetric synthesis; cyclization; scandium and compounds; vitamins.

Optically active 5-*tert*-butyldimethylsiloxy-2-cyclohexenone [(*R*)- and (*S*)-**1**], prepared in our laboratory, has proved to be an efficient chiral building block in the synthesis of natural products.<sup>1</sup> As reported in the preceding paper,<sup>2</sup> we have succeeded in synthesizing the A-ring precursor of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, (*E*)-**2**, starting from (*S*)-**1** via the intermediates **3**, **4** and **5** (Scheme 1).

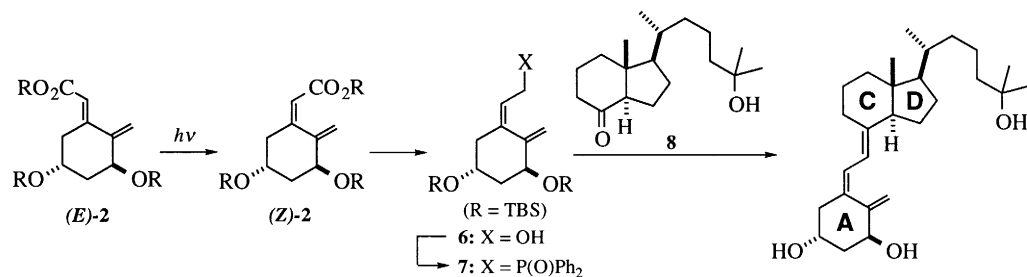


Scheme 1.

According to the protocol reported by the Hoffmann–La Roche group,<sup>3</sup> (*E*)-**2** can be converted to (*Z*)-**2**, to allylic alcohol **6** and then to (*Z*)-allylic phosphine oxide **7** (A-ring portion) which, in turn, affords 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> through Horner–Wittig coupling with the bicyclic ketone **8** (C,D-ring portion). As the isomerization of (*E*)-**2** to (*Z*)-**2** remains difficult to achieve without photoisomerization, we continued our efforts to prepare (*Z*)-**2** directly from (*S*)-**1**, and we report the results here (Scheme 2).

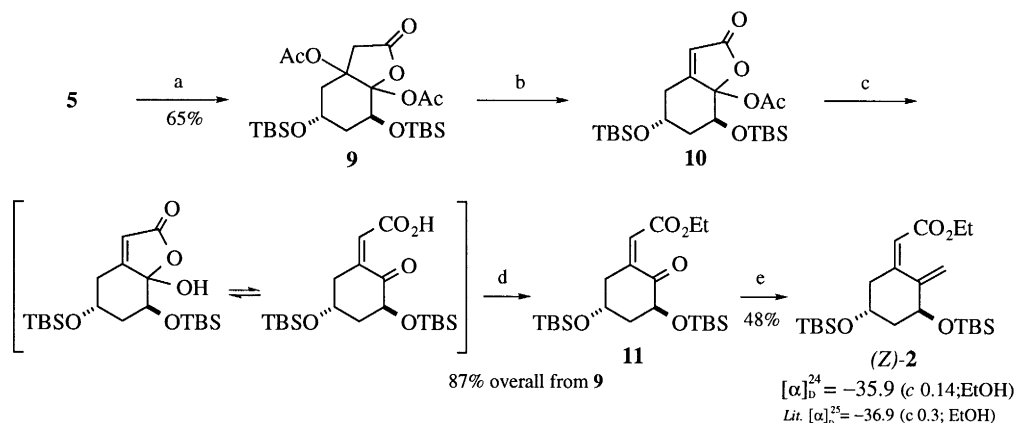
Initially, we investigated a lactonization of **4** which would enable the (*Z*)-geometry of the double bond, together with a selective protection of one hydroxy group in **4**. However, the lactonization under

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Scheme 2.

various conditions furnished only small amounts of the desired compound since the retroaldolization to **3** competed with the cyclization. During the course of this investigation, we fortunately found that treatment of **5** with neat acetic anhydride in the presence of catalytic amounts of  $\text{Sc}(\text{OTf})_3$  (3 mol%)<sup>4</sup> at rt for 12 h gave the bicyclic diacetate **9** cleanly in 65% yield and in a >95:<5 diastereoisomeric ratio. This unexpected result encouraged us to try to take advantage of the bicyclic moiety **9** where the  $\beta$ -elimination of the acetate group would fix the (*Z*)-geometry of the trisubstituted double bond. To our satisfaction, the reaction of **9** with DBU in  $\text{CH}_2\text{Cl}_2$  at rt for 0.5 h gave **10** smoothly. Saponification of **10** with  $\text{K}_2\text{CO}_3/\text{MeOH}$  at rt, followed by treatment with ethyl iodide in DMF for 4 h at rt, yielded **11** in 87% overall yield from **9**. Finally, the methylenation of **11** to (*Z*)-**2**<sup>5</sup> was achieved by using the Tebbe reagent in 48% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a)  $\text{Ac}_2\text{O}$  (neat), 3 mol%  $\text{Sc}(\text{OTf})_3$  (0.25 M in MeCN), rt, 12 h; (b) DBU (1.5 equiv.),  $\text{CH}_2\text{Cl}_2$ , rt, 30 min; (c)  $\text{K}_2\text{CO}_3$  (20 equiv.), MeOH, rt, 1 h; (d)  $\text{C}_2\text{H}_5\text{I}$  (3 equiv.),  $\text{K}_2\text{CO}_3$  (5 equiv.), DMF, rt, 4 h; (e) Tebbe reagent (1.1 equiv.), 1 mol% Pyr, THF, rt 20 min

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