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An efficient enantioselective synthesis of 1α,25-dihydroxyvitamin D_3 A-ring synthon

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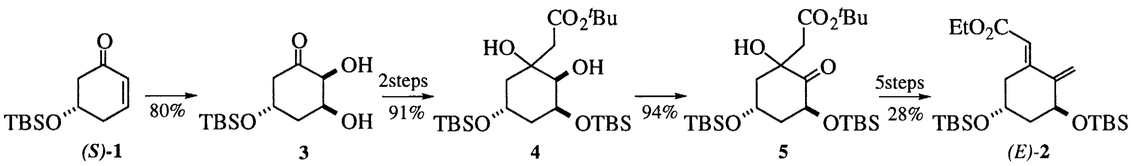
Abstract

The asymmetric synthesis of the A-ring of 1α,25-dihydroxyvitamin D_3, (*Z*)-**2**, from 5-*tert*-butyldimethylsiloxy-2-cyclohexenone [(*S*)-**1**], is described where an intramolecular lactonization using cat. scandium triflate is the key reaction.

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.[1] As reported in the preceding paper,[2] we have succeeded in synthesizing the A-ring precursor of 1α,25-dihydroxyvitamin D_3, (*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,[3] (*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 1α,25-dihydroxyvitamin D_3 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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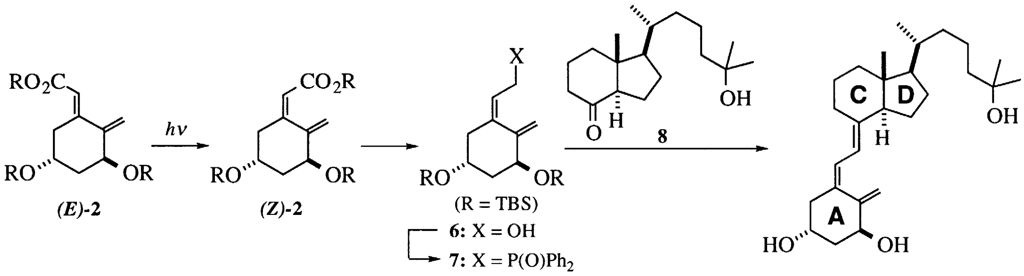
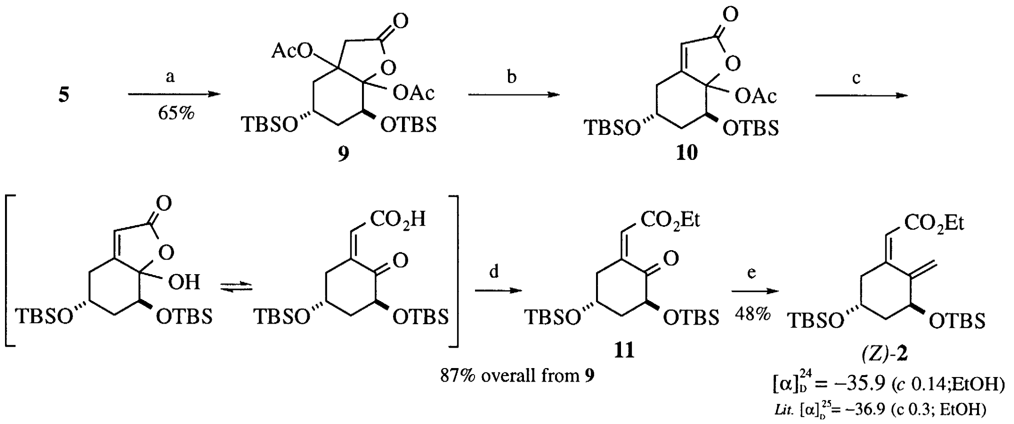


Scheme 2.

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 $Sc(OTf)_3$ (3 mol%)[4] 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 β-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 CH_2Cl_2 at rt for 0.5 h gave **10** smoothly. Saponification of **10** with K_2CO_3/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**[5] was achieved by using the Tebbe reagent in 48% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) Ac_2O (neat), 3 mol% $Sc(OTf)_3$ (0.25 M in MeCN), rt, 12 h; (b) DBU (1.5 equiv.), CH_2Cl_2, rt, 30 min; (c) K_2CO_3 (20 equiv.), MeOH, rt, 1 h; (d) C_2H_5I (3 equiv.), K_2CO_3 (5 equiv.), DMF, rt, 4 h; (e) Tebbe reagent (1.1 equiv.), 1 mol% Pyr, THF, rt 20 min

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