Pergamon

Tetrahedron Letters 41 (2000) 2385–2388

TETRAHEDRON LETTERS

Asymmetric synthesis of 1α,25-dihydroxyvitamin D_3 A-ring precursor starting with 5-*tert*-butyldimethylsiloxy-2-cyclohexenone

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Received 13 December 1999; revised 17 January 2000; accepted 21 January 2000

Abstract

The A-ring precursor of 1α,25-dihydroxyvitamin D_3 [(*E*)-**4**] has been prepared starting from the (5*S*)-*tert*-butyldimethylsiloxy-2-cyclohexenone [(*S*)-**1**] via eight steps in 19% overall yield, where a catalytic osmium dihydroxylation which sets the stereochemistry of the hydroxyl group at C_1 and a regioselective protection of the hydroxy group as a TBS-ether are the key steps.

Keywords: asymmetric synthesis; hydroxylation; selective protection; vitamins.

The 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] We have recently reported an enantioselective synthesis of palitantin where an impressive, highly diastereoselective cat. OsO_4–NMO dihydroxylation of **1** was the key step.[1d] With these results in hand, we became interested in the A-ring precursor of 1α,25-dihydroxyvitamin D_3 which appeared to be an attractive target for the further utilization of **1**, together with its diastereoselective dihydroxylation reaction.

1α,25-Dihydroxyvitamin D_3 [1,25-$(OH)_2$-VD_3], which plays an important role in human physiology, has attracted substantial interest in its pharmacology and therapeutic potential. The chemical synthesis of 1,25-$(OH)_2$-VD_3 and its analogues, therefore, has been the subject of much research over a period of 15 years because organic synthesis is the only means to supply sufficient quantities and to create more effective compounds.[2] One of the most useful methods for producing 1,25-$(OH)_2$-VD_3 and its various analogues employs a Horner–Wittig olefination between the (*Z*)-allylic phosphine oxide **2** (A-ring portion) and the bicyclic ketone **3** (C,D-ring portion) as shown in Scheme 1. The Hoffmann–La Roche group prepared **2** starting from carvone via α,β-unsaturated ester (*E*)-**4** which, in turn, was converted

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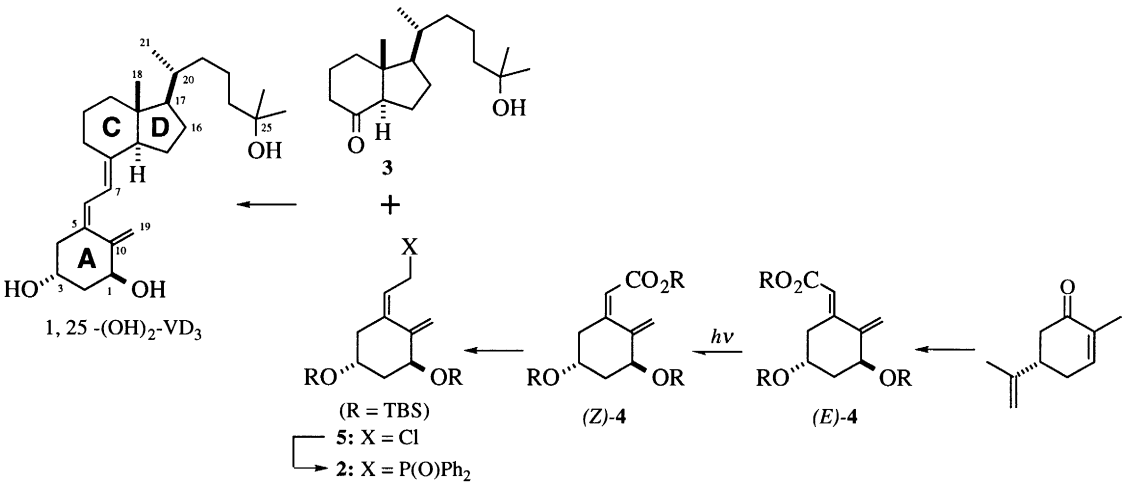
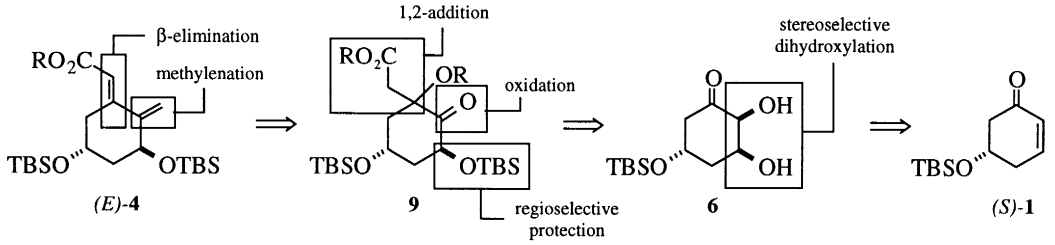
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00169-6

into (*Z*)-**4** by photoisomerization and then to the allylic chloride **5**.[3] This synthetic method remains one of the most efficient syntheses of **2**, and further effort has been devoted to the synthesis of **4**.[4]



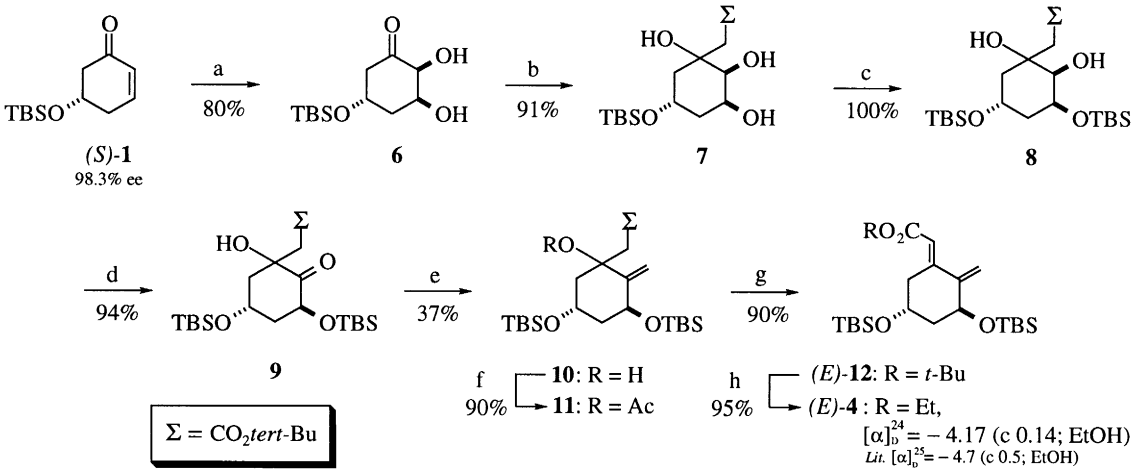
Scheme 1. The Hoffmann–La Roche protocol for synthesis of 1,25-$(OH)_2$-VD_3 from carvone

Here we report the synthesis of (*E*)-**4** from (*S*)-**1** according to the retrosynthetic approach illustrated in Scheme 2. We anticipated that a 1,2-addition of the enolate of acetate on **6**, prepared by a stereoselective dihydroxylation of **1**, and the following regioselective monoprotection of the less embedded hydroxy group and oxidation of the remaining secondary alcohol might afford the ketone **9**. The conversion of **9** to (*E*)-**4** was expected to be carried out by a Wittig-type methylenation and the following β-elimination of the protected tertiary alcohol.



Scheme 2. Retrosynthetic analysis of (*E*)-**4** from (*S*)-**1**

As previously reported, the dihydroxylation of (*S*)-**1** with catalytic osmium tetroxide–NMO gave **6** exclusively in 80% yield[1d] (Scheme 3). The compound **6** was subjected to the Reformatsky reaction ($Zn/BrCH_2CO_2$*tert*-Bu) to give the 1,2-addition product **7** very efficiently when trimethyl borate–THF was used as the solvent.[5] Under these conditions, **7** was obtained in 91% yield in which one diastereomer was produced highly predominantly. The treatment of **7** with TBSCl/imidazole at rt yielded, to our satisfaction, the exclusive monoprotected bis-TBS-ether **8** quantitatively. Regiospecific oxidation of the secondary alcohol under the Swern conditions using 1.1 equiv. of oxalylchloride gave the ketone **9** in 94% yield.[6] The methylenation reaction of **9**, according to the Nozaki protocol[7] using the 'aged' $Zn–CH_2Br_2–TiCl_4$ reagent,[7b] afforded the expected product **10** in 37% yield (checked by NMR) which contained an unseparable by-product in 7% yield, which, presumably, was produced by the conversion of the tertiary OH group of **9** to H. Other methylenation conditions (olefination using Cp_2TiCH_2, or PPh_3CH_2, or Peterson methylenation) did not afford good results.[8]



Scheme 3. Reagents and conditions: (a) OsO_4 (5 mol%)–NMO (2.5 equiv.), acetone–water, rt, 24 h; (b) Zn (5 equiv.), $BrCH_2CO_2t$-Bu (4 equiv.), $(MeO)_3B$–THF, rt→reflux→rt; (c) TBSCl (1.2 equiv.), imidazole, DMF, rt, 12 h; (d) Swern oxidation [oxalylchloride (1.1 equiv.)]; (e) 'aged' Zn–CH_2Br–$TiCl_4$ (4 equiv.), THF, rt, 4 h; (f) Ac_2O, $Sc(OTf)_3$ (10 mol%); (g) $Pd(PPh)_4$ (20 mol%), Et_2NH (10 equiv.), THF, rt, 15 h; (h) (1) TMSOTf (30 equiv.), 2,6-lutidine (40 equiv.), THF, reflux, 2 h; (2) EtI (3 equiv.), K_2CO_3 (4 equiv.), DMF, rt, 1 h

Protection of the tertiary alcohol moiety of **10** as acetate (in neat acetic anhydride for 12 h at rt in the presence of 10 mol% amounts of $Sc(OTf)_3$)[9] and the separation of the aforementioned by-product by column chromatography afforded pure **11** in 90% yield (based on **10**, and thus, 33% yield from **9**). The β-elimination of **11** yielding **12** was found to be troublesome and, unexpectedly, that became the major problem to be resolved for the completion of the synthesis. Standard procedures (DBU, *p*-TSA) met with utter failure, presumably due to conformational reasons; under these conditions, the target compound could not be detected despite variations of the solvent, temperature and/or reaction time which resulted in the clean recovery of the starting material or in its decomposition when conditions that were too harsh were used. After numerous unfruitful attempts, such as the β-elimination of **11** under basic conditions using MeONa, DMAP, LDA, KHMDS/toluene (the last yielded the corresponding spiro-Robinson annelation product cleanly), or under acidic conditions using PPTS, CSA or Lewis acids (all recovered the starting material), we finally found that the conversion of **11** to (*E*)-**12** was effectively achieved by treatment with Et_2NH in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF (rt, 15 h) which yielded, after hydrolysis, the desired α,β-unsaturated ester (*E*)-**12** in 90% isolated yield.[10] Finally, in order to reach the known (*E*)-**4**, we saponified (*E*)-**12** by treatment with TMS–triflate[11] and reacted the corresponding carboxylic acid with ethyl iodide; thus, the target (*E*)-**4** was obtained in 95% yield and showed identical physical and spectroscopic data to those previously reported.[4]

Acknowledgements

G.H. thanks the Japan Society for the Promotion of Science for financial support.

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