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Enantioselective Syntheses of a 1α-Hydroxyvitamin D Ring A Precursor from 3-(Triphenylsilyl)glycidol and from Malic Acid

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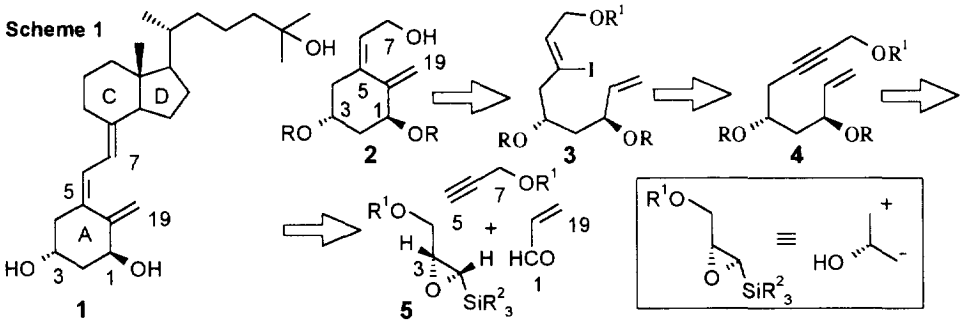
Abstract: Syntheses of the 1α-hydroxyvitamin D_3 A ring fragment **2** from (2*R*,3*R*) 3-(triphenylsilyl)glycidol **5a** and from L-(-)-malic acid are described. Copyright © 1996 Elsevier Science Ltd

Vitamin D and congeners have recently received a great deal of attention owing to a broad spectrum of biological activity and growing therapeutic applications.[1] The synthetic efforts in this field[2] are focused on 1α,25-dihydroxyvitamin D_3 (**1**, Scheme 1) and other derivatives that are functionalised, both in the ring A and in the side chain. Convergent synthesis based upon coupling of the pre-prepared ring A (**2**) and the corresponding ring CD-side chain fragments provides an attractive approach to compound **1** and to a variety of its analogues.[3] Recently,[4] we have described a short synthesis of a CD fragment. In this communication we present two alternative synthetic routes to the ring A fragment[5] (**2**), which completes the total synthesis of 1α,25-dihydroxyvitamin D_3 (**1**).

Scheme 1



The main feature of our synthetic plan consists in the use of optically - active 3-(trialkyl/arylsilyl)glycidol (**5**) as the precursor of the C_2-C_3-C_4 fragment. It was anticipated that deprotonation of silylglycidol **5** (with the hydroxy group protected) will generate an anion on the carbon bearing the silyl group,[6] which could be utilized for the attachment of acrolein (C_1-C_{10}-C_{19} fragment). On the other hand, conversion of the glycidol hydroxy group to a leaving group would allow for its substitution with an acetylenic anion (C_5-C_6-C_7 fragment). In this approach the silyl glycidol is used as a synthetic equivalent of a chiral carbinol flanked by electrophilic and nucleophilic carbons.

As the starting material we chose crystalline (triphenylsilyl)glycidol[7] **5a** (Scheme 2), which is easy to prepare in a highly pure enantiomeric form by Katsuki-Sharpless epoxidation of allylic alcohol **6**.[8] The hydroxy group in **5a** was protected with the methoxyisopropyl group to give **5b**. Treatment of the latter with *n*-butyllithium and then with an excess of acrolein afforded adduct **7** as a mixture of epimers in a ratio of 2.5:1 with the required *lk* isomer prevailing[9] (for the configuration assignment, see below). It is noteworthy that *n*-butyllithium is a sufficiently strong base to generate an anion from (triphenylsilyl)oxiranes, whereas *sec*-butyllithium was needed for deprotonation of (trialkylsilyl)oxiranes.[9,10]

The crude **7** was desilylated with Bu_4NF and the product was subjected to reduction with Red-Al,® which occurred with regioselective opening of the epoxide ring[11] affording **8** as a mixture of epimers.

Upon treatment with PPTS in benzene the methoxyisopropyl derivative **8** underwent intramolecular transketalization to give **9a** (75% overall yield from **5a**). The hydroxy group in **9a** was protected and the *tert*-butyldiphenylsilyl derivative **9b** was transformed into diol **10a** and then into monotosylate **10b**. The epimers were separated by an ordinary column chromatography of either diols **10a** or tosylates **10b**. The major tosylation product **10b** was treated with 10% KOH in methanol to give epoxide **11** in 60% overall yield from **9a**.

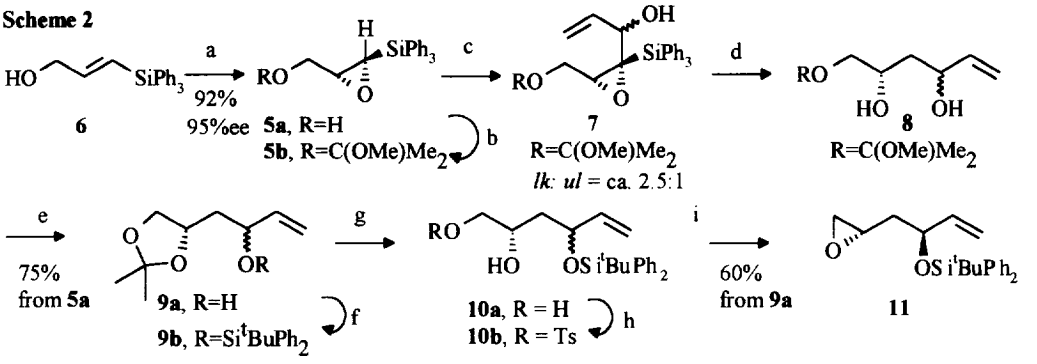
The key intermediate *anti* **10a** was also prepared diastereoselectively from L-(+)-malic acid *via* its easily accessible[12] derivative **12** as shown in Scheme 3. Ester **12** was transformed into the cyclopropanol derivative **13** in excellent yield by the method of Kulinkovich and coworkers[13] [ethylmagnesium bromide-$Ti(O^iPr)_4$]. Hydrolysis of the acetal group in **13** followed by protection of the primary hydroxy group in the intermediate triol gave the trityl derivative **14**. Cyclopropanol moiety in **14** was then subjected to bromonium ion induced rearrangement.[14] The resulting hydroxy ketone **15** was reduced[15] with $NMe_4BH(AcO)_3$ to give *anti* diol **16**. Subsequent hydrolysis of the trityl group in **16** and treatment of the intermediate triol with diethyl ketone in the presence of TsOH gave dioxolane **17** exclusively.[16] Finally, the allylic hydroxy group in **17** was protected with the *tert*-butyldiphenylsilyl chloride and then the diol system was liberated to give the product identical with the major isomer of **10a**.

It is well documented that reduction of β-hydroxy ketones similar to **15** with $NMe_4BH(AcO)_3$ affords the respective diols with the *anti* relative configuration of the hydroxy groups.[15] On these grounds *anti* configuration was assigned to **16** and consequently to the major isomer **10a**. These assignments were confirmed in the following way. The diol **16** was treated with acetone and TsOH to give 1,3-dioxane derivative **18** (98% yield). Its epimer **19** was obtained from the minor isomer of **10a** in an analogous way *via* the corresponding 1-O-trityl derivative (3 steps, 47% yield). ^{13}C NMR spectra of compounds **18** and **19** were investigated. The signals corresponding to the methyl groups occurred for **18** at 24.88 and 25.61 ppm, and for **19** at 19.73 and 30.00 ppm. These positions of resonance signals are in excellent agreement with the diagnostic values for derivatives of *anti* and *syn* 1,3-diols, respectively, given in the literature.[17]

Treatment of epoxide **11** (Scheme 4) with an anion generated from protected propargyl alcohol **20** and with $BF_3{\cdot}Et_2O$[18] afforded adduct **4a**. After routine operations with the protective groups, the derivative **4b** (70% yield from **11**) was reacted according to reported procedures[5a,19] with Red-Al® and then with I_2 to give vinyl iodide **3a**. Finally, **3a** was cyclized under conditions of the Heck reaction[20] to give the ring A fragment **2a**.[5a]

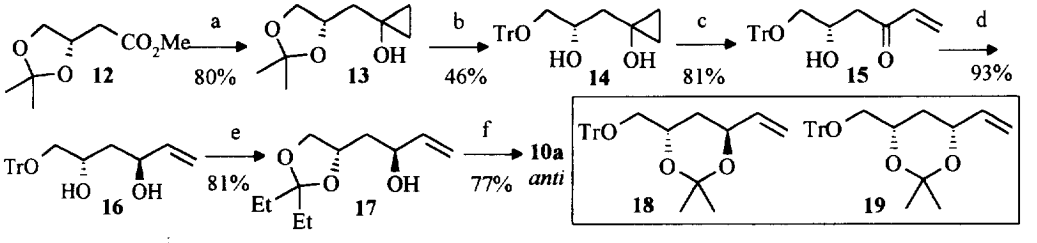
In conclusion, (triphenylsilyl)glycidol **5a** was used as the optically - active precursor of the A ring fragment in 1α,25-dihydroxyvitamin D synthesis. To the best of our knowledge, this is the first application of easily accessible optically active silylglycidols in the target-oriented synthesis. Malic acid was also used for stereocontrolled synthesis of the requisite *anti* 1,3-diols.

Scheme 2



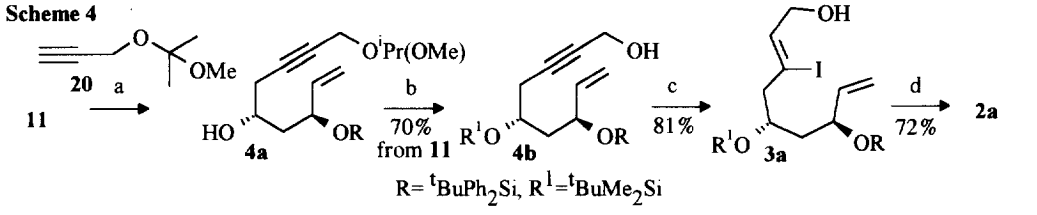
a. D-(-)DIPT cat.-Ti(O^{i}Pr)$_4$ cat. - TBHP, crystallization; b. 2-methoxypropene, PPTS; c. BuLi and then acrolein; d. Bu_4NF/THF, rt then Red-Al; e. PPTS/benzene; f. ^{t}BuPh$_2$SiCl-imidazole/DMF; g. 80% AcOH; h. TsCl/Py and chromatography; i. 10%KOH/MeOH.

Scheme 3



a. EtMgBr-Ti(O^{i}Pr)$_4$; b. Amberlyst-15H/MeOH then TrCl-DMPA/Py; c. NBS/$CHCl_3$; d. $(Me_4N)BH(AcO)_3$/AcOH. e. Amberlyst-15H/MeOH and then Et_2CO-TsOH; f. ^{t}BuPh$_2$SiCl/Py and then 80% AcOH.

Scheme 4



a. **20**, BuLi-BF_3·Et_2O/THF, -78°C to rt; b. ^{t}BuMe$_2$SiCl-imidazole/DMF; c. Red-Al/THF, -78°C and then I_2; d. $Pd(OAc)_2$-PPh_3-Et_3N/toluene, 95°C.

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