Pergamon

*Tetrahedron Letters*, Vol. 37, No. 31, pp. 5589-5592, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01132-X

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

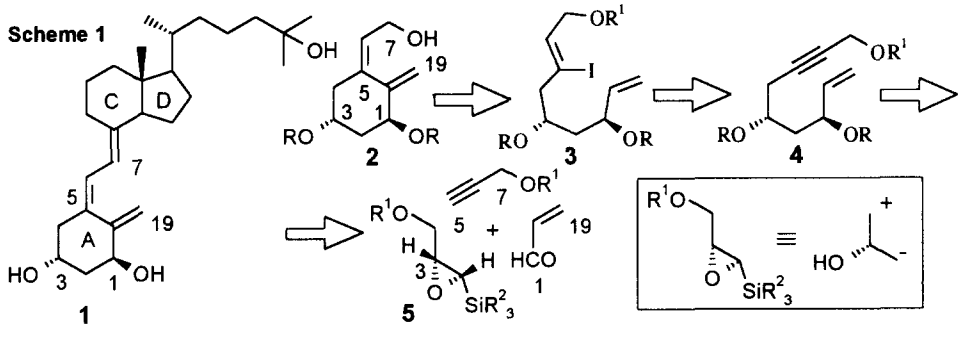
**Barbara Achmatowicz, Paweł Jankowski and Jerzy Wicha***

Institute of Organic Chemistry, Polish Academy of Sciences, POB 58, 01-224 Warsaw 42, Poland

***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 silylgycidol **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**.

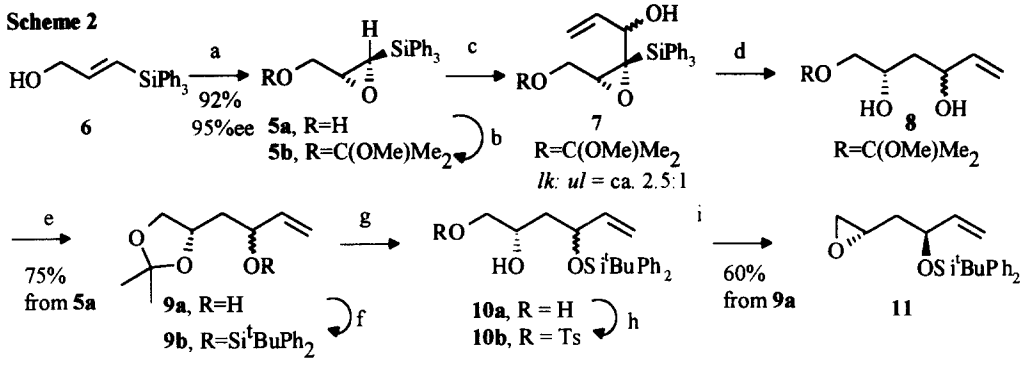
The key intermediate *anti* **10a** was also prepared diastereoselectively from L-(+)-malic acid *via* its easily accessible[12] derivative **12** as shown in Scheme 3. Ester **12** was transformed into the cyclopropanol derivative **13** in excellent yield by the method of Kulinkovich and coworkers[13] [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]

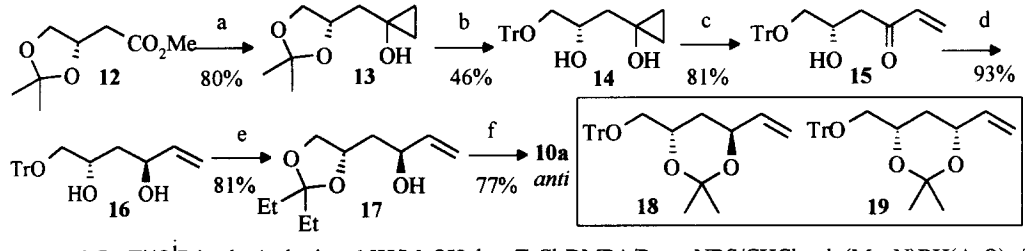
In conclusion, (triphenylsilyl)glycidol **5a** was used as the optically - active precursor of the A ring fragment in 1α,25-dihydroxyvitamin D synthesis. To the best of our knowledge, this is the first application of easily accessible optically active silylglycidols in the target-oriented synthesis.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

**Scheme 2**



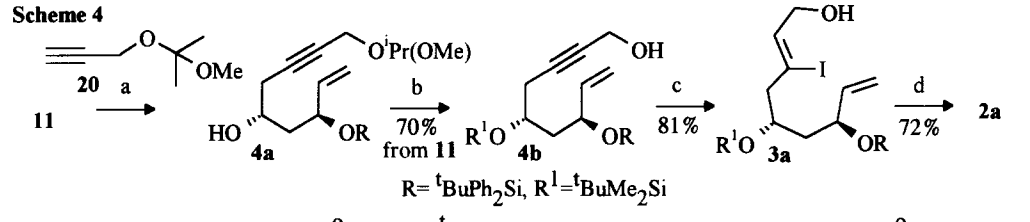
a. D-(-)DIPT cat.-Ti(O$^i$Pr)$_4$ cat. - TBHP, crystallization; b. 2-methoxypropene, PPTS; c. BuLi and then acrolein; d. $Bu_4NF$/THF, rt then Red-Al; e. PPTS/benzene; f. $^t$BuPh$_2$SiCl-imidazole/DMF; g. 80% AcOH; h. TsCl/Py and chromatography; i. 10%KOH/MeOH.

**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$^o$C to rt; b. $^t$BuMe$_2$SiCl-imidazole/DMF; c. Red-Al/THF, -78$^o$C and then $I_2$; d. Pd(OAc)$_2$-PPh$_3$-$Et_3N$/toluene, 95$^o$C.

**Acknowledgement**. We thank Professor M. Vandewalle for providing us with an unpublished procedure for the reductive iodination of a **4b** analogue. Support from the Committee of Scientific Researches, Republic of Poland (Grant No 3 T09A 007 10), is gratefully acknowledged.

## REFERENCES

1 For recent reviews, see: Bouillon, R.; Okamura, W. H. Norman, A. W. *Endocrine Rev.* **1995**, *16*, 200-257. Calvarley, M. J.; Jones, G. "Vitamin D" in "*Antitumor Steroids*" Blickenstaff R. T. Ed. AP, 1992, pp193-270.

2. For recent reviews, see: Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383-1398. Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877-1952.

3. Lythgoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449-475. Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945-2948.

4. S. Marczak, K. Michalak, J. Wicha *Tetrahedron Lett.* **1995**, *36*, 5425-5428. S. Marczak, J. Wicha, *Tetrahedron Lett.* **1993**, *34*, 6627-6630.

5. For recent relevant work, see: a. Vrielynck, S.; Vandewalle, M.; Garcìa, A. M.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1995**, *36*, 9023-9026. b. Dauben, W. G.; Lewis, T. A. *Synlett* **1995**, 857-858. c. Dauben, W. G.; Hendricks, R. T.; Pandy, B.; Wu, S. C. *Tetrahedron Lett.* **1995**, *36*, 2385-2388. d. Huang, P.-q.; Sabbe, K.; Pottie, M.; Vandewalle, M. *Tetrahedron Lett.* **1995**, *36*, 8299-8302. e. Fernández, S.; Ferrero, M.; Gotor, V.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 6057-6061. f. Linclau, B.; Vandewalle, M. *Synlett* **1995**, 1063-1064. f. Moriarty, R. M.; Kim, J.; Brumer III, H. *Tetrahedron Lett.* **1995**, *36*, 51-54.

6. Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646-4648.

7. Raubo, P.; Wicha, J. *Tetrahedron:Asymmetry* **1995**, *6*, 577 - 586.

8.a. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. b. Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 667-671. c. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

9. Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042-4050.

10. Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293-313.

11. Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719-2722.

12. Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83-95. Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389-1392.

13. Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Prityckaya, T. S. *Zh. Org. Chim.* **1989**, *25*, 2244-2245. Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234. Corey, E. J.; Rao, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345-9346.

14. DePuy, C. H.; Van Lanen, R. J. *J. Org. Chem.* **1974**, *39*, 3360-3365, see also: Savchenko, A. I.; Sviridov, S. V.; Kulinkovich, O. G. *Zh. Org. Chem.* **1994**, *30*, 333-335.

15. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578 and references cited therein.

16. Lavalleè, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedrn Lett.* **1986**, *27*, 679-682.

17. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948.

18. a. Takahashi, T.; Nakazawa, M. *Synlett* **1993**, 37-39. b Takahashi, T.; Nakazawa, M.; Sakamoto, Y.; Houk, K. N. *Tetrahedron Lett.* **1993**, *34*, 4075-4078. c. Tazumi, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1903-1904. See also: d. Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240-3241. e. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693-3694.f. Yamamoto, Y. *Angew. Chem. Intern. Ed.* **1986**, *25*, 947-959.

19. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595-3694. See also: Corey, E. J.; Ketzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245-4247.

20. a. Nagasawa, K.; Zako, H.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937-4940. b. Mascareñas, J. L.; Garcia, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 4365-4368. c Chen, C.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 1945-1948. d. Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943-7954. e. Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523-2529. f. Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369-13376.

(*Received in UK* 10 *May* 1996; *revised* 4 *June* 1996; *accepted* 7 *June* 1996)