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Control of Stereoselectivity in Samarium Metal Induced Cyclopropanations. Synthesis of 1,25-Dihydroxycholecalciferol†

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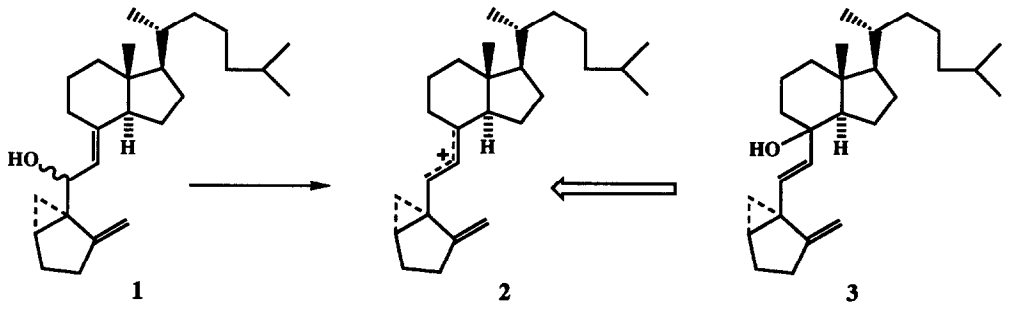
Summary: 1,25-Dihydroxycholecalciferol (**23**) was synthesized from A-ring precursor **18** and Windaus-Grundmann ketone **19** via cyclovitamin D **21**. Key reactions include highly stereoselective(**5** to **6**) and stereospecific(**13** to **14**) cyclopropanations.

It was recently proposed by Professor S. Wilson that the allyl cation intermediate **2** in the Mazur solvolysis of cyclovitamin D_3 (**1**) to vitamin D_3[1] should also be accessible from the regioisomer **3**.[2] Compound **3** could be formed by addition of an acetylene substituted with a cyclopropyl ring A precursor to the Windaus-Grundmann ketone, followed by reduction of the propargylic to allylic alcohol.

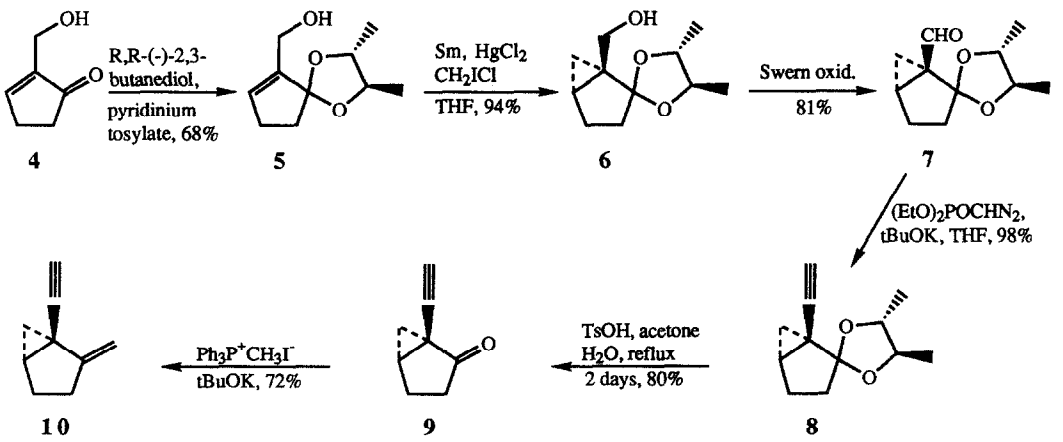


1 **2** **3**

This idea was pursued by Wilson in model systems[2] where simpler ketones such as cyclohexanone were coupled with a cyclopropyl acetylenic ring A precursor bearing an additional 1α-hydroxy group. The results of those studies demonstrated the potential of the approach for the synthesis of 1α-hydroxy vitamin D analogs. We describe, herein, our own efforts in this area, which include two asymmetric syntheses of the acetylenic ring A precursor and which culminate in the synthesis of 1,25-dihydroxy vitamin D_3 (**23**).

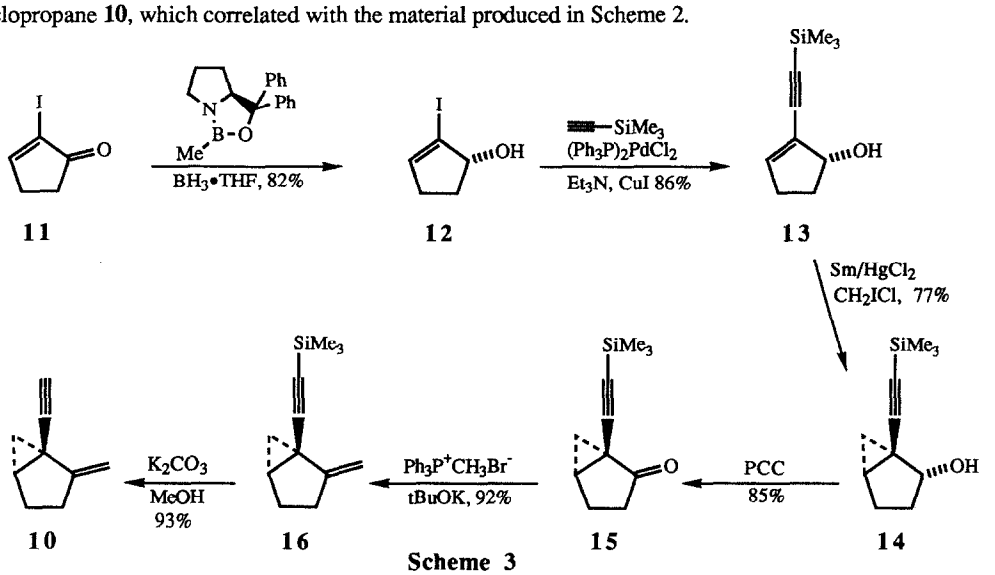
Two stereogenic centers of the 1α-desoxy ring A precursor **10** were formed by a diastereoselective cyclopropanation of the allylic alcohol-ketal **5** (Scheme 2). The desired chirality was generated under the influence of the two stereogenic centers on the (R, R)-2,3-butanediol ketal using Molander's cyclopropanation conditions (ICH_2Cl, Sm(Hg))[3]. The diastereoselectivity of this reaction, (**5**→**6**), was estimated to be 95:5 by nmr and 97:3 by capillary GC[4]. In this approach to **10**, introduction of the acetylene side chain was completed by reaction of the aldehyde **7** with diethyldiazomethylphosphonate to give **8** in high yield. Hydrolysis of the chiral ketal and Wittig olefination provided cyclopropane **10**.

† *Dedicated to the memory of our colleague, Dr. Enrico Baggiolini.*

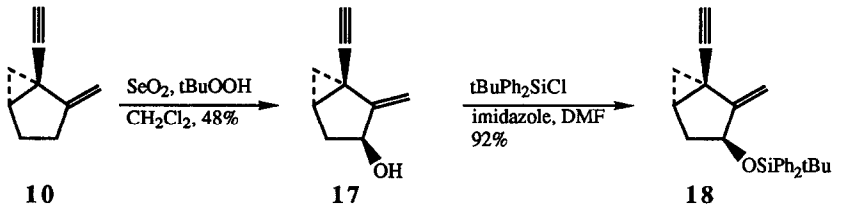


Scheme 2

In the second approach to compound **10**, the acetylene side chain in **13** was formed by a $(Ph_3P)_2PdCl_2$–CuI catalyzed[5] coupling of the allylic (1R)-2-iodo-cyclopenten-1-ol **12** with trimethylsilylacetylene (Scheme 3). Compound **12** (96% ee after recrystallization) was obtained by diborane reduction of the corresponding ketone **11** using Corey's chiral oxazaborolidine catalyst[6]. In this case the samarium amalgam mediated cyclopropanation[3] was directed entirely by the allylic hydroxy group to generate the cyclopropyl alcohol **14** stereospecifically. Wittig olefination of the corresponding ketone **15** followed by desilylation gave the cyclopropane **10**, which correlated with the material produced in Scheme 2.

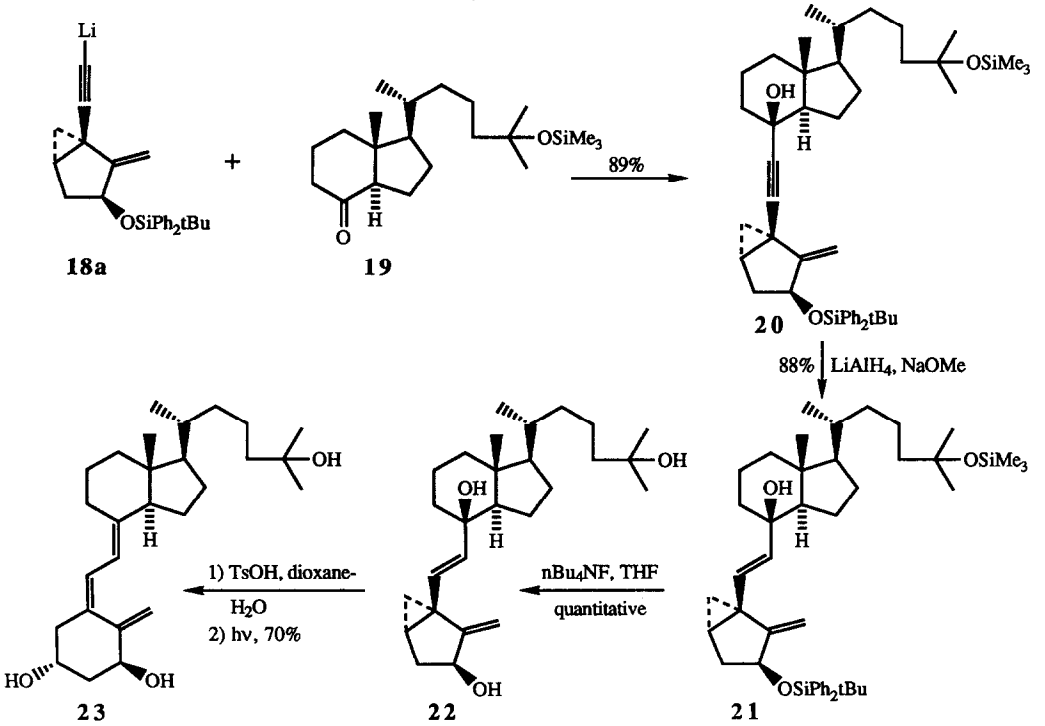


Scheme 3



Scheme 4

The allylic hydroxylation of **10** was best carried out using an excess of t-butyl hydroperoxide in dichloromethane in the presence of a catalytic amount of selenium dioxide (Scheme 4). The product, obtained in 54% yield, was a 5:1 mixture of the desired β-hydroxy allyl alcohol **17** and its α-hydroxy epimer, which were separated easily by silica gel chromatography. Silylation of **17** provided the key ring A precursor **18** which would be used for the coupling to the 25-trimethylsilyloxy Windaus-Grundmann ketone **19** in the final phase of the 1,25-dihydroxycholecalciferol (**23**) synthesis.



Scheme 5

Formation of the anion **18a** was conducted at –30°C with **18** in THF and an equimolar amount of n-butyllithium in the course of 15 min (Scheme 5). After warming the acetylide solution to room temperature, a solution of the ketone **19**[7] in THF was added, whereupon the propargylic alcohol **20** was formed rapidly as a single diastereomer. Subsequent reduction of **20** with lithium aluminum hydride gave cleanly the trans allylic alcohol **21**. Quantitative removal of the silyl groups was achieved with tetrabutylammonium fluoride. The stage was now set for the critical solvolytic unravelling of the dihydroxy ring A-vitamin D triene system. This acid catalyzed process proceded with the expected stereospecific attack of water at C_3 to yield a 63:37 mixture of 1,25-dihydroxycholecalciferol (**23**) and its C_5–C_6 trans isomer. Without separation, this olefin mixture was photoisomerized in t-butylmethyl ether in the presence of 9-acetoxyanthracene to give **23** in 70% yield, mp 118-119°C (methyl formate) $[\alpha]_D^{25}$ + 47.98° (ethanol *c* 0.5)[7].

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4. The absolute configuration of **6** was proven by p-bromobenzoylation and ketal hydrolysis. An x-ray crystallographic analysis of the resultant keto ester, mp 65-66°C, $[\alpha]_D^{25}$–20° (*c* 0.5, hexane) confirmed the [(1**S**)–*cis*]–configuration.
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