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Asymmetric Synthesis of a Key 1α,25-Dihydroxy-Vitamin D3 Ring A Synthon

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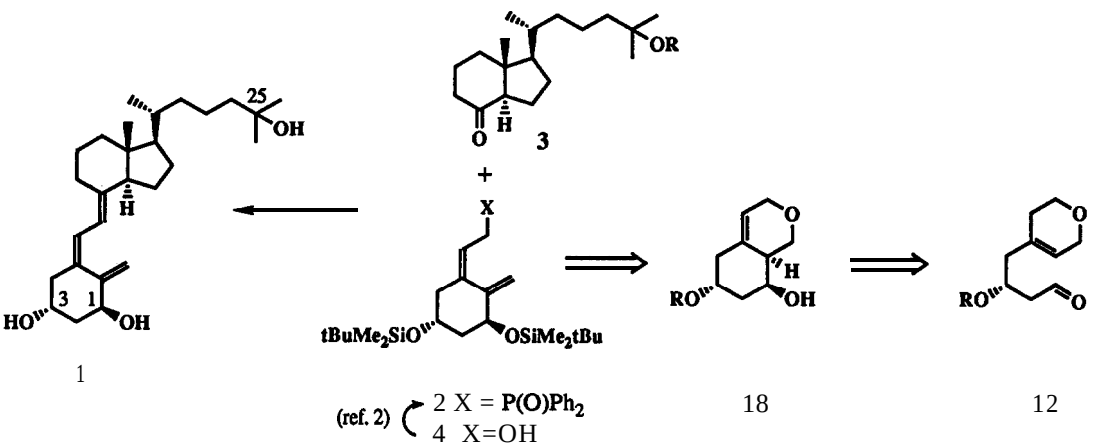
Summary: An efficient and highly stereoselective synthesis of the A-ring synthon 4 of 1,25(OH)$_2$-vitamin D$_3$ (1) is described The aldehyde 12, which was used for an intramolecular *ene* reaction to form the main framework 18, was obtained by two different asymmetric approaches starting from oleftn 6.

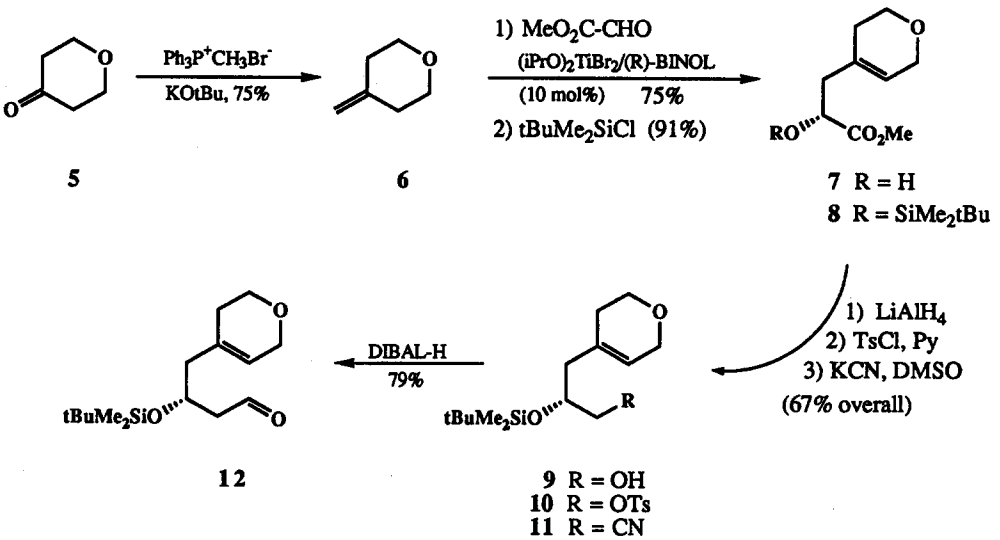
The ever growing volume of data regarding the biological activity of vitamin D$_3$ and its metabolites continues to stimulate vigorous research on the impact of these substances on basic cellular processes.* An essential component of such programs is access to the natural metabolites and especially their unnatural variants. In conjuction with our development of a ring A + CD approach to the vitamin D system, as exemplified in the formation of 1,25-(OH)$_2$-vitamin D$_3$ (1) by coupling the ring A unit 2 with the Windaus-Grundmann ketone derivative 3 (Scheme 1),[2] we have investigated alternate syntheses of the ring A synthon 4. In this letter we present a new synthesis of 4 which utilizes a highly stereoselective intramolecular *ene* reaction to set the proper configuration for both the hydroxyl group at Cl and for the Z double bond Two catalytic asymmetric routes to this *ene* reaction substrate (12) are described.



Scheme 1

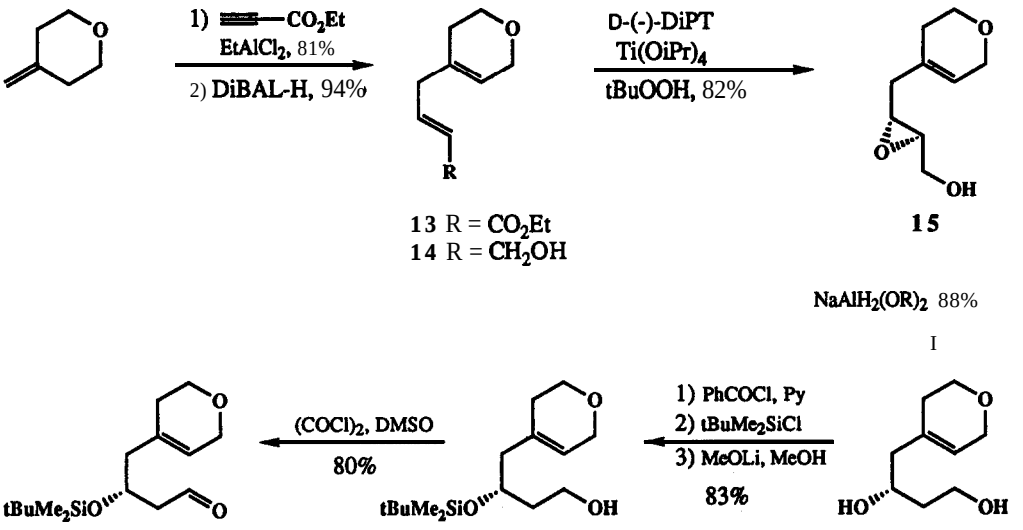
The fiit approach engaged the catalytic system introduced by Mikami et. al.[3] for the asymmetric *ene* reaction of methyl glyoxylate with olefins. Treatment of olefin 6, readily accessible from pyranone 5 (Ph$_3$P=CH$_2$), with methyl glyoxylate in the presence of 10 mol% of the Lewis acid obtained from

$TiBr_2(OiPr)_2$ and (R)-(+)-1,1'-bi-2-naphthol (CH_2Cl_2, -23 °C, 10 days[4]) afforded alcohol **7** with 94% ee[5] (Scheme 2). Support for the expectation that the newly formed stereogenic center in the product (**7**) had the required R-configuration, came from the nmr data for the MTPA ester of **7**.[6] A one carbon homologation of the silyl ether **8** (from **7**, $tBuMe_2SiCl$) was carried out by reduction of the ester to alcohol **9**, tosylation to form **10** and displacement by cyanide to generate nitrile **11**. Finally, reduction of nitrile **11** with DIBAL-H gave the requisite aldehyde **12** $[\alpha]_D^{25} = -8.4°$ (c=0.8, EtOH).



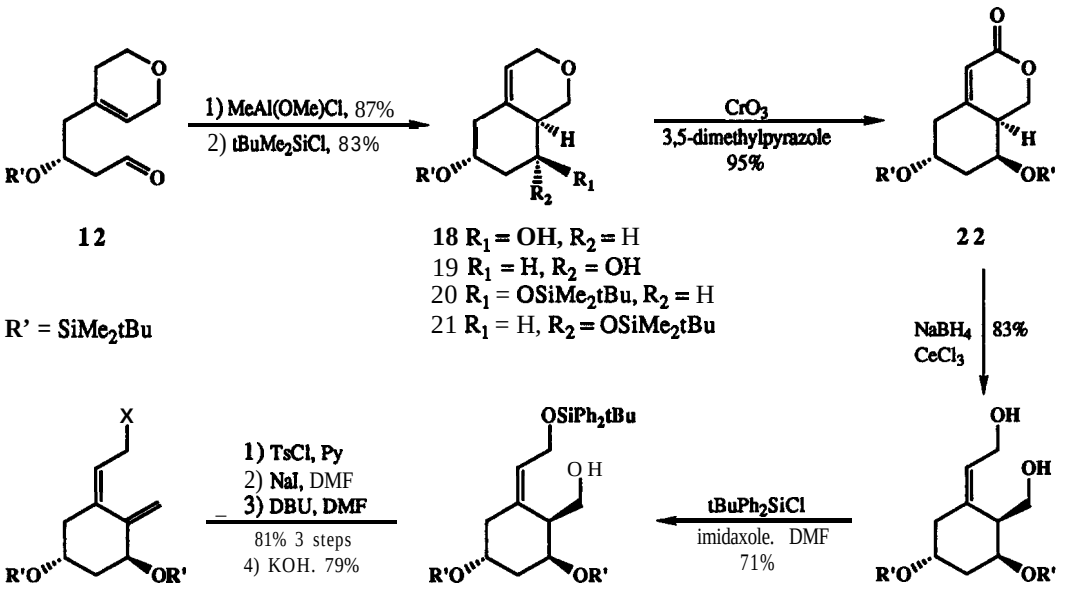
Scheme 2

The alternate route to aldehyde **12** was based on the catalytic asymmetric epoxidation of allylic alcohols as described by Sharpless and coworkers.[7] This approach also starts with olefin **6**, which underwent a smooth, albeit slow, *ene* reaction with ethyl propiolate in the presence of ethylaluminum dichloride (refluxing CH_2Cl_2, 6 days), to give the E-unsaturated ester **13** in good yield (Scheme 3). Reduction of **13** with DIBAL-H gave allylic alcohol **14**. Asymmetric epoxidation of **14** with t-BuOOH in the presence of D-(-)-diisopropyl tartrate/$Ti(OiPr)_4$ (CH_2Cl_2, -20 °C) provided epoxide **15** with 90% ee[8]. Regioselective reduction of the epoxide function in **15** with sodium bis(2-methoxyethoxy)aluminum hydride[9] in THF at 0 °C yielded exclusively the 1,3-diol **16**. A three step protocol, consisting of primary hydroxyl group benzoylation (PhCOCl, Py), silylation ($tBuMe_2SiCl$) and methanolysis of the benzoate (MeOLi, MeOH), was used to effectively situate the t-butyldimethylsilyl group at the secondary position of **16** to yield **17**. Swern oxidation of the primary hydroxyl group gave the desired aldehyde **12**, $[\alpha]_D^{25} = -8.0°$ (c = 1.0, EtOH).



Scheme 3

For the next stage of the synthesis, *ene* reaction chemistry was enlisted once again to effect the carbon-carbon bond formation. Exposure of akiehyde 12 to methoxymethylaluminum chloride[10] (4 equiv., CH_2Cl_2, -10 °C to +10 "C) gave a 10:1 mixture of the isomeric alcohols 18:19 in high yield(Scheme 4). This intramolecular *ene* reaction proceeded with extremely high stereoselectivity with respect to the newly formed center at the ring fusion since alcohols 18 and 19 are epirneric at the hydroxyl center only and no other diastereomers were observed.[11] Separation of the epimers was accomplished at the stage of the respective silyl ethers 20 and 21. Having served its purpose of providing a rigid framework around which controlled bond formation could take place, the pyran ring could now be cleaved. Allylic oxidation of 20 with CrO_3 and 3,5-dimethyl pyrazole[12] gave lactone 22 (mp 112-116 °C) which was smoothly reduced to diol 23 using $NaBH_4/CeCl_3$.[13] Differentiation of the two primary hydroxyl groups was accomplished by monosilylation with $tBuPh_2SiCl$ in DMF to give alcohol 24. Elimination of the primary hydroxyl was carried out by tosylation, tosylate displacement with iodide (NaI, DMF) followed by elimination with DBU in DMF (80 °C) to give olefin 25 in good overall yield. The final step entailed the selective removal of the $tBuPh_2Si$ ether in the presence of the secondary $tBuMe_2Si$ ethers and was brought about with 10% KOH in methanol (70 °C, 6 h), yielding allylic alcohol 4 in full accord, spectroscopically and analytically, with the previously prepared material. The transformation of 4 to 2 has been recorded previously.2



12

18 R_1 = OH, R_2 = H
19 R_1 = H, R_2 = OH
20 R_1 = $OSiMe_2tBu$, R_2 = H
21 R_1 = H, R_2 = $OSiMe_2tBu$

22

R' = $SiMe_2tBu$

25 X = $OSiPh_2tBu$
4 X=OH
2 X = $P(O)Ph_2$

24

23

Scheme 4

References and Notes:

† **On leave from the Institute of Organic** Chemistry, Poiiih Academy of Sciences, Warsaw, Poland.

1) For **recent developments** in this area see: **Proc.** Workshop Vitam. D. 8th (Vitamin. D: **Gene Regulation,** Structure-Function **Analysis,** and **Clinical** Application), W. de **Gruyter,** New York, 1991.

2) **Baggiolini, E. G.; Iacobelli,** J. A; **Hennessy,** B. **M.; Uskoković,** M. R.. ***J.*** Am. ***Chem. Soc.*****, 1982, *104*,** 2945; **Baggiolini, E. G.; Iacobelli,** J. **A.; Hennessy,** B. M.: Batcho, A. D.; **Sereno,** J. F.; **Uskoković,** M. **R., *J.*** Org. ***Chem.*****,** 1986.51, 3098; **Kiegiel, J.; Wovkulich,** P. M.; **Uskoković,** M. R., ***Tetrahedron Lett.*****, 1991, *32*, 6057.**

3) **Mikami,** K.; **Terada,** M.; Nakai, **T., *J.*** Am. ***Chem. Soc.*****,** 1990.112, 3949. **Mikami,** K.; **Terada,** M.; **Nakai, T., *J.*** Am. ***Chem. Soc.*****,** 1989, ***11*** I. 1940.

4) Olefii 6 **undergoes the *ene* reaction** at a much **slower** rate than the non-he **teroatom** containing **olefins** described in reference 3.

5) **The ee was determined by nmr of 7 in the presence of Eu(hfc)3 and supported by nmr of the MTPA ester.**

6) **The R-methoxytrifluoromethylphenylacetic** acid esters of 7 produced asymmetrically and in **racemic form** were prepared under standard conditions. Dale, J. A.; **Mosher,** H. S.; ***J.*** Am. ***Chem. Soc.*****,** 1973.95.512.

7) **Katsuki,** T.; **Sharpless,** K. B.; ***J.*** Am. ***Chem. Soc.*****, 1980, *102*, 5974;** Gao, Y.: Hanson. R. M.; **Klunder,** J. M.; Ko. S. Y.; **Masamune,** H.; **Sharpless,** K. B., ***J.*** Am. ***Chem. Soc.*****, 1987, *109*, 5765;** and references therein.

8) **The ee** was asses& by GC of the **corresponding** R-MTPA ester of 15.

9) **Ma,** P. **Martin;** V. S.; **Masamune,** S.; **Sharpless,** K. B.; **Viti,** S. M., ***J.*** Org. ***Chem.*****, 1982, *47*,** 1378; **Finan,** J. M.; Kishi, ***Y., Tetrahedron Lett.*****, 1982, *23*, 2719.**

10) **This catalvst was prepared fmm dimethylaluminum** chloride (1 **equiv.**) and methanol **(1 equiv.)** in **CH_2Cl_2** (0 **°C)** and has been utiiixed **in** a **similar ene** reaction leading to a total **synthesis of pravastatin,** cf. **Daniewski,** A. R.; Wovkulich, P. M.; Uskokovic. **M. R., *J.*** Org. ***Chem.*****, 1992, *57*,** 0000.

11) For **intramolecular ene** reactions of **this** type, we **previously** have not observed alcohols **epimeric** at only the hydroxyl center, see for example, Wovkulich. P. M.: Tang, P. C.: **Chadha,** N. K.: Batcho, A. D.; **Barrish,** J. C.; Uskokovic. M. R., ***J.*** Am. ***Chem. Soc.*****,** 1989,111. **2596; Barrish,** J. C.; Wovkulich, P. M.; Tang, P. C.: Batcho. A. D.: Uskokovic. M. R.. ***Tetrahedron Lett.*****, 1990, *31*, 2235; *see* also** Snider, B. B.; **Deutsch,** E. A., ***J.*** Org. ***Chem.*****,** 1983.48, 1822. Alcohol 19 could conceivably arise from **Oppenauer** processes cf. Snider, B. B.; Goldman, B. E., ***Tetrahedron*****, 1986, *42*, 2951.**

12) Salomond, W. G.; **Barta,** M. A.; Havens, J. L.: ***J.*** Org. ***Chem.*****,** 1978.43. 2057.

13) The bicyclic iactone related to 22 but epimeric at the ring fusion center has been reported previously, cf. Kobayashi, S.; Shibata, J.; **Shimada,** M.; **Ohno,** M., ***Tetrahedron Lett.*****,** 1990.31. 1577. Attempts to apply similar transformations to 22 were, however, **unproductive.**

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