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Enantioselective Synthesis of 24,25-Dihydroxy Vitamin D_3 Northern Portion from (*S*)-3-Hydroxy-2,2-dimethylcyclohexane-1-one. Remote Asymmetric Induction in an Acid-catalysed Conjugate Addition

Wiaczesław Stepanenko and Jerzy Wicha*

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

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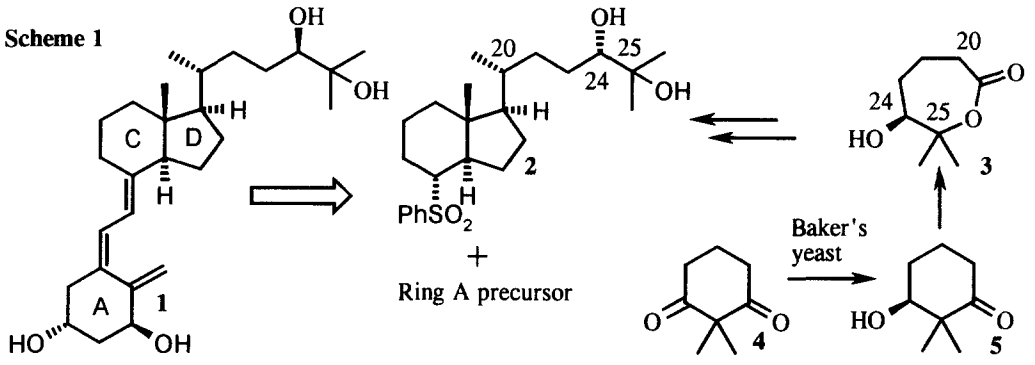
Abstract: Enantioselective synthesis of building blocks, **2** and **16**, for 24,25-dihydroxy- and 25-hydroxy vitamin D synthesis, respectively, from easily accessible optically active hydroxy ketone **5**, is described.

A great deal of attention has been given[1] to the partial synthesis of 24(*R*)- and 24(*S*)-hydroxy sterols and vitamin D derivatives following the isolation of natural biologically important compounds, such as 1α,24(*R*),25-trihydroxy vitamin D_3[2] (**1**, Scheme 1), cerebrosterol[3] and squalamine.[4] Some 24-hydroxy vitamin D analogues have been prepared and successfully used in therapy.[5] It was challenging to develop an approach to 24-hydroxy vitamin D derivatives by total synthesis, which would make available a greater variety of structures. To this end, dihydroxy sulfone **2** appeared to be an attractive building block since a method for its coupling with a proper ring A precursor is well known.[6] Now we present synthesis of **2** starting from 3(*S*)-hydroxy-2,2-dimethylcyclohexan-1-one **5**. Compound **5**(*S*) is easily accessible by Baker's yeast reduction of diketone **4** by the method of K. Mori and H. Mori.[7] Both enantiomers of **5** may be generated enantioselectively by reduction of dione **4** with the appropriate oxazaborolidine-borane reagents.[8]

Scheme 1



Oxidation of hydroxy ketone **5** (95% ee, prepared in ca. 50% yield from **4**) with MCPBA yielded lactone[9] **3** (Scheme 2). The latter, on treatment with 2-methyl-2-propanethiol and trimethyl aluminum, [10] gave the intermediate dihydroxy thioester which was transformed into the acetonide **6** without isolation. Compound **6** was allowed to react

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with lithium diisopropylamide to generate the corresponding enolate which was quenched with trimethylsilyl chloride. The resulting product was purified by Kugelrohr distillation to afford ketene acetal **7** as a mixture of (*E*) and (*Z*) isomers in a ratio of ca. 8:1 (by ^{1}H NMR).

With ketene acetal **7** in hand the stage was set for two tandem Mukaiyama-Michael conjugate additions according to the protocol previously developed in this laboratory.[11] On the grounds of Mukaiyama et al.[12] studies and our own experience it was anticipated that the reaction of **7** with 2-methylcyclopent-2-en-1-one **8** will occur predominantly with *lk* attack to yield **9** and will provide, after the consecutive addition of (thiophenyl)methyl vinyl ketone **10**, the product with the required relative configuration around C-13(*R**), C-17(*R**) and C-20(*R**).[13] With regard to the absolute configuration on the chiral centres involved, two extreme cases were considered. In the first instance, if the configuration of C-20 and C-17 is not influenced by the stereocentre at C-24, it is expected that the two diastereomers **11** and **12** should be formed in equal amount. On the other hand, the complete control of configuration at C-20 and C-17 by the stereocentre at C-24 would lead to exclusive formation of **11** or **12**. No literature precedent was available to assist us in prediction of the stereochemical outcome of the reaction.

The reaction of **7** with **8** in the presence of $TrSbCl_6$ (5 mol%, CH_2Cl_2, -78 °C) and then with **10** yielded a mixture (55% yield from **7**, after filtration of the crude mixture through a silica gel column) consisting of two components in a 3:1 ratio as found by HPLC.[14] The mixture resisted all attempts of chromatographic separation on silica gel. Fortunately, the major component crystallized and was isolated by recrystallization from methanol. Structure **11** was assigned to this product on the grounds of X-ray crystallographic analysis.[15] To the minor product, structure **12** was tentatively ascribed

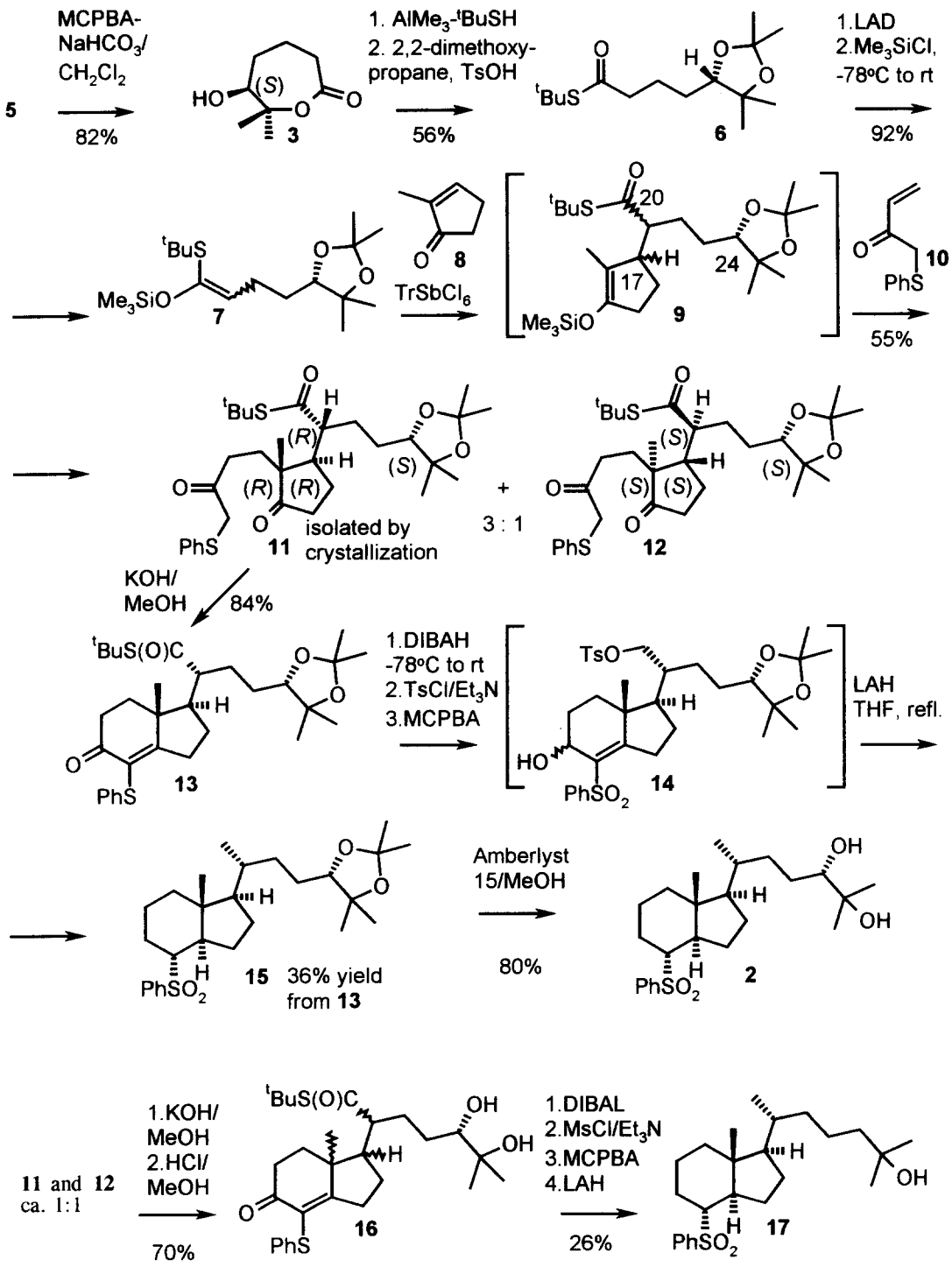
Ketone **13**, obtained from enantiomerically pure **11** in the usual way,[11] was first treated with DIBAL-H (CH_2Cl_2, -78 °C) to yield a mixture of the epimeric diols, subsequently the primary hydroxy group was esterified with *p*-toluenesulfonyl chloride and the sulfide moiety was oxidized to the sulfone. The intermediate **14** was filtered through silica gel to removed polar impurities and was then treated with an excess of lithium aluminum hydride in refluxing THF. The *trans* hydrindane derivative **15** was obtained in 36% overall yield from **13** along with small amounts of a side product arising from reductive opening of the dioxolane ring.[16] Removal of the acetal protective groups in **15** yielded the required diol **2**.

In parallel, the remainder after crystallization of **11**, consisting of **11** and **12** in a ratio of ca. 1:1, was subjected to the annulation reaction to give **13** and its counterpart resulting from **12**. This mixture was treated with methanolic HCl to cleave the acetonide moiety. The resulting mixture of keto esters **16** was reduced with DIBAL-H (CH_2Cl_2, -78 °C to rt) to the respective tetraols. Then the three step transformation involving mesylation (2 equiv. of MsCl, CH_2Cl_2, -10 °C, 30 min), MCPBA oxidation (in CH_2Cl_2 at rt) and reduction with an excess of lithium aluminum hydride (THF, reflux), all without isolation of the intermediates, afforded racemic[11b] **17** in 26% overall yield. These experiments confirmed structure **12**, assigned to the minor product of the conjugate addition reaction, and also provided a new synthetic approach to **17**, a common building block in synthesis of 1α,25-dihydroxy vitamin D_3.

It should be mentioned that the cyclic ketene acetal prepared from **5** by consecutive protection of the hydroxy group as triethylsilyl ether, Baeyer-Villiger oxidation with MCPBA, generation of the ester enolate (LDA) and quenching it with Me_3SiCl, gave on reaction with **8** and then with **10** the respective addition product in only ca. 12% yield (as a mixture of diastereomers in 1:1 ratio).

In conclusion, (1) an eight step enantioselective total synthesis of **2** from **5** was developed (along with rapid transformation of **13** into **17**, (2) it has been shown that the oxygen substituent at C-24 in **7** does not affect the topicity of the conjugate addition reaction **7** and **8**, and (3) an unprecedented remote asymmetric induction in acid-catalysed conjugate addition (**7** and **8**) has been observed.

Scheme 2


MCPBA-
NaHCO3/
CH2Cl2
82%
1. AlMe3-tBuSH
2. 2,2-dimethoxy-
propane, TsOH
56%
1.LAD
2.Me3SiCl,
-78°C to rt
92%
TrSbCl6
55%
isolated by
crystallization
3 : 1
KOH/
MeOH
84%
1.DIBAH
-78°C to rt
2.TsCl/Et3N
3.MCPBA
LAH
THF, refl.
Amberlyst
15/MeOH
80%
15 36% yield
from 13
11 and 12
ca. 1:1
1.KOH/
MeOH
2.HCl/
MeOH
70%
1.DIBAL
2.MsCl/Et3N
3.MCPBA
4.LAH
26%

Acknowledgements

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14. A Chiracel® OD-H analytical column, 0.46(I.D.)x25 cm with a precolumn 0.46x5 cm of Daicel Chemical Industries, Tokyo, Japan, was used.
15. X-ray measurements were performed in our Institute by Dr A. Kemme of the Latvian Institute of Organic Chemistry, Riga, Latvia. The details of the measurements will be presented in full paper.
16. A side product was isolated (16% yield) to which structure of 3-(5-Hydroxy-1-methoxymethyl-4-isopropoxy-5-methyl-hexyl)-6-hydroxy-3a-methyl-7-(phenylthio)-2,3,3a,4,5,6-hexahydro-1*H*-indene, was assigned.