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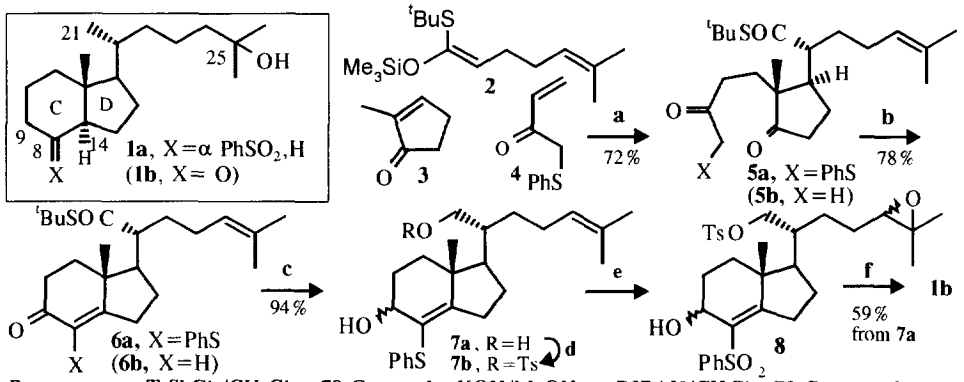
New Diastereoselective Approach to *trans*-Hydrindane Derivatives. Synthesis of a 8-Phenylsulphonyl-A,B-descholestane Derivative, a Precursor to 25-Hydroxyvitamin D_3

Karol Michalak, Wiaczesław Stepanenko, Jerzy Wicha*

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

Abstract: Six steps total synthesis of racemic **1a**, a CD rings - side chain fragment of 25-hydroxyvitamin D_3, is described.

We have recently developed[1] a synthesis of a racemic CD-rings side chain fragment **1b** of 25-hydroxyvitamin D_3, based upon a tandem Mukaiyama-Michael reaction of ketene acetal **2**, 2-methylcyclopent-2-en-1-one **3** and methyl vinyl ketone (MVK) or ethylene acetal of MVK. The synthesis was relatively short and efficient owing to the one-step construction of **5b** with the entire carbon skeleton of **1b**. However, to exercise the full potential of this convergent three-component approach to A,B-descholestane derivatives there were required (1) a more efficient reagent for termination of the conjugate addition sequence since MVK affords a considerable amount of side products and (2) a simple new method for transformation of α,β-unsaturated ketones related to **6b** into the respective *trans*-hydrindane derivatives. Now we report a synthesis of sulphone **1a**, which is another convenient precursor[2] to 25-hydroxyvitamin D_3, by the route that involves new solutions to both these problems.



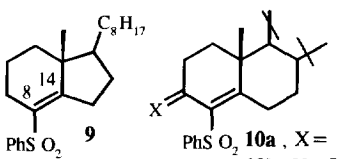
Reagents: **a** . $TrSbCl_6/CH_2Cl_2$, -78°C to rt; **b**. KOH/MeOH; **c**. DIBAH/CH_2Cl_2,-78°C-to rt; **d**. TsCl-DMAP-Et_3N/CH_2Cl_2, -20°C to O °; **e**. MCPBA/CH_2Cl_2, 0° to rt; **f**. $LiAlH_4$/THF, reflux.

It was found that treatment of ketene acetal **2** with enone **3** in the presence of a catalytic amount of $TrSbCl_6$ (CH_2Cl_2, -78°C) and then adding to the reaction mixture 1-thiophenylbut-3-en-2-one (**4**) as the second Michael

acceptor gave diketone **5a**. No products involving more than one structural unit of **4** could be detected. Usual cyclization of **5a** gave **6a**.

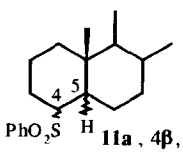
Reduction of **6a** with DIBAH afforded a mixture of diols **7a** (94%, 9β:9α = 78:22) which was tosylated to give the respective monotosylates **7b**. The double bond and sulphur moiety in **7b** were oxidized with MCPBA (3.7 equivalents) to give a mixture of epoxy sulphones **8**. This product, without isolation, was treated with an excess of $LiAlH_4$ to yield, after chromatography, sulphone **1a** (59% from **7a**) and a mixture of the corresponding 24 hydroxy derivatives (14%). Alternatively, the keto group in **6a** was reduced with $NaBH_4$-$CeCl_3$ and the product was further reduced with $LiAlH_4$ to give 9β-hydroxy **7a** (88% yield, contaminated with ca. 3% of the 9α epimer). This product was consecutively tosylated, oxidized with MCPBA and reduced to give **1a** in the essentially same overall yield.

The final step of the synthesis requires some comments. Reduction of vinylsulphone **9** with $LiAlH_4$ affording the corresponding 14α-H sulphone was reported recently by Clasby and Craig.[3] We commenced the present work on the premise that $LiAlH_4$ reduction of a similar vinylsulphones bearing in the α position the hydroxy (as **8**) or oxo group will be accompanied by deoxygenation. Model experiments using easily accessible cholestane derivatives were carried out to verify this assumption and, ultimately, to elucidate stereochemistry of the reduction. It was found that reduction of **10a**[4] with $LiAlH_4$ affords exclusively 5β-cholestane derivative **11a**. Similarly, reduction of the 3β-hydroxy vinylsulphone **10b** yielded **11a**. However, reduction of 3α-hydroxy derivative **10c** provided 5α-H sulphone **11b** in an excellent yield, showing that the stereochemistry of the double bond reduction is controlled by orientation of the hydroxy group. To our pleasant surprise the correlations observed on the model compounds were not relevant to the hydrindene derivatives. 9β-Hydroxy **8** compounds (epimers at C_{24}) were transformed with complete stereoselectivity (*vide supra*) into the *trans* product **1a**. Likewise, the 9α- hydroxy **8** (prepared from **6a** by a reaction sequence involving $NaBH_4$ - $CeCl_3$ reduction and inversion at C9 with DEAD, PPh_3 and BzOH by Mitsunobu) upon treatment with $LiAlH_4$ afforded **1a** (36% overall yield from **6a**).



9

10a , X= O
10b, X=β OH, H
10c , X=α OH, H



11a , 4β, 5β
11b, 4α, 5α

In conclusion, six steps synthesis of vitamin D precursor **1a** from ketene acetal **2**, methylcyclopentenone **3** and thiophenylmethyl vinyl ketone **4**, affording the final product in 31% overall yield from **2**, was developed. A striking difference in the steric course of $LiAlH_4$ reduction of the vinylsulphone moiety at the hydrindane and decaline rings junctions was observed.[5]

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