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An Expedited Approach to the Vitamin D *trans*-Hydrindane Building Block from the Hajos Dione

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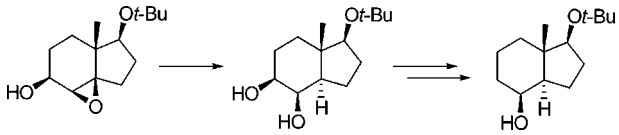
ABSTRACT



Efficient and operationally simple synthesis of the key *trans*-hydrindane alcohol building block for the synthesis of calcitriol (1α,25-dihydroxyvitamin D_3) has been developed. Epoxy alcohol prepared almost quantitatively from the Hajos dione was reduced at the quaternary carbon by the Hutchins procedure ($NaBH_3CN$–BF_3·Et_2O). The diol was selectively deoxygenized either using the Barton–McCombie reaction (with Bu_3SnH–AIBN) or via the respective iodohydrine (with $LiAlH_4$).

The syntheses of calcitriol (1α,25-dihydroxyvitamin D_3) **1** (Figure 1) and other derivatives of vitamin D_3 have received a great deal of attention[1] due to their application for treatment of various human metabolic diseases and their importance in biomedical research.[2] The Hajos dione[3] **3**, produced from L-proline-catalyzed annulation of 2-methylcyclopentane-1,3-dione with methyl vinyl ketone, presents a classic precursor to the calcitriol CD ring building block[4] **2**. However, methods currently available for saturation of the double bond in **3** or easily accessible derivatives as **4** and for transposition of the oxygen substituent from C-5 to C-4 suffer from serious drawbacks (e.g., catalytic hydrogenation of **3** or **4** affords predominantly *cis*-hydrindan derivatives).

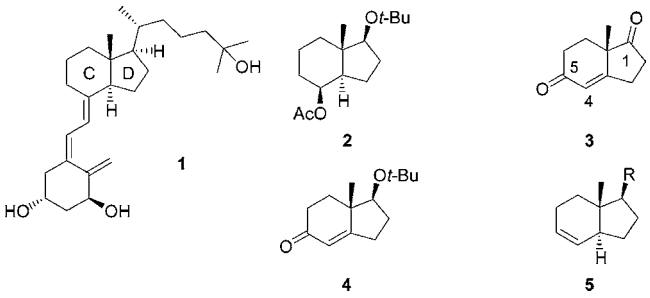


Figure 1. Structures of calcitriol **1**, the Hajos dione **3**, and selected synthetic precursors to the calcitriol CD ring system.

Reduction of the carbonyl group in **4** with the Luche reagent[5] affords the respective β-alcohol **6** (Scheme 1). Ingenious methods[6−8] have been developed for hydrogen

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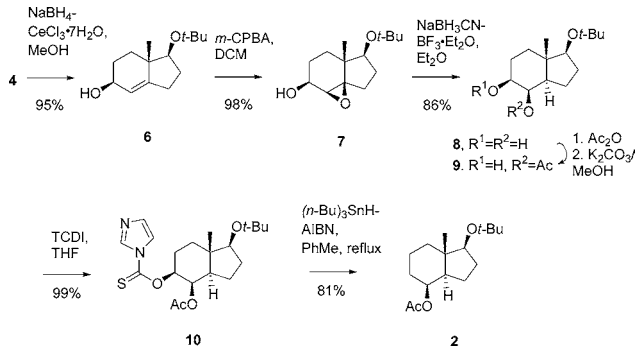
Scheme 1



atom delivery from the α-side in allylic alcohols related to **6** via "chirality transfer". All of these methods lead to olefins **5** which have a lack of regiocontrolling factors for further functionalization. Direct conjugate reduction of ketones **3** with DIBAL−cuprous iodide provides a short-step approach to functionalized *trans*-hydrindane derivatives,[9] but the fragile nature of the intermediate copper hydride species may obstruct large-scale preparations. More circumvent approaches to **2** starting from **3** or **4** have also been developed.[10] We wish now to present a facile and operationally simple method for transforming **4** into **2** via alcohol **6**, epoxide **7**, and diol **8**.

Allylic alcohol **6** was treated with *m*-CPBA to give *β*-epoxide **7** quantitatively. Reduction of the epoxide **7** with sodium cyanoborohydride−BF_3·Et_2O in THF according to the Hutchins protocol[11] afforded diol **8** in 77% yield. Use of Et_2O[12] as the solvent led to an increase of the product yield to 86%.[13] Diol **8** was transformed quantitatively into the diacetate which by controlled hydrolysis and chromatography afforded monoacetate **9** in 70% yield along with unchanged diacetate (7%), isomeric monoacetate (7%), and diol **8** (16%). The hydrolysis step was not optimalized extensively since all side products could be easily recycled.

The monohydroxy derivative **9** was esterified with thionocarbonyl-1,1′-diimidazole (TCDI) in THF at reflux, and the thionocarbonate **10** was reduced with tri(*n*-butyl)tin hydride−2,2′-azobis(2-methylpropanenitrile) (AIBN).[14] Chromatography then gave the known[4] derivative **2**. The best yields of **2** (80% in two steps) were obtained when a solution of **10** containing AIBN (ca. 20 mol %) was added slowly with a syringe pump to a dilute solution of Bu_3SnH (4 molar equiv) in toluene at reflux. At higher concentrations of tri(*n*-butyltin)hydride substantial amounts of the methoxy derivative **11** (Figure 2) were formed along with an unstable tin-containing derivative to which structure **12** was assigned (by ^{1}H NMR) and the alcohol **9**. Fragmentation of hemiacetal **12** provides a likely mechanism for reversion from **10** to the starting alcohol **9**. When the thionocarbamate **10** in toluene containing AIBN was added to neat Bu_3SnH at 120 °C, methoxy derivative **11** was obtained in 77% yield. Reduction of **10** in dilute solutions but at a lower temperature (80 °C) also gave considerable amounts of **11** and **12**. These results corroborate some earlier reported observations on tri-*n*-butyltin hydride reduction of xanthate esters.[15]

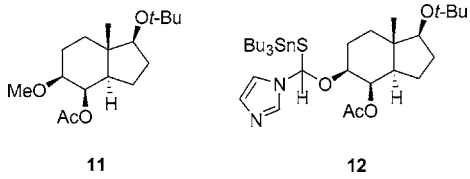


Figure 2. Structures of side products formed on tri(*n*-butyl)tin hydride−AIBN reduction of the imidazolylthionocarbonyl derivative **10**.

Although the overall yield of **2** compared rather well with those attainable by other methods, other approaches to selective removal of the C-5 hydroxyl group in diol **8** were examined.

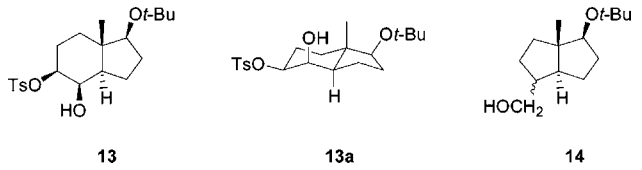


Figure 3. Structures of monotosylate **13** and of the product obtained on its reduction with $LiAlH_4$.

Monotosylate **13** (Figure 3) was obtained almost quantitatively by treating **8** with 1.5 molar equiv of tosyl chloride in pyridine. Upon reduction of tosylate **13** with $LiAlH_4$ in THF rearranged primary alcohol **14** was obtained. Antiperiplanar disposition of the C-3a−C-4 bond and the tosyloxy C−O bond explains the rearrangement (Figure 3, **13a**).

Diol **8** when treated with TCDI produced cyclic thionocarbonate **15** (Scheme 2) quantitatively. Reduction of **15** with tri-*n*-butyltin hydride−AIBN provided a complex mixture of products. Gratifyingly, treatment of **15** with methyl iodide[16] at 40 °C (sealed ampule) provided crystalline and stable iodohydrine derivative **16** (81% yield after chromatography). The structure of **16** was confirmed by narrow multiplets corresponding to equatorial protons at C-4 (*δ* 5.33 ppm) and C-5 (*δ* 4.63 ppm). An ^{1}H NMR spectrum of the

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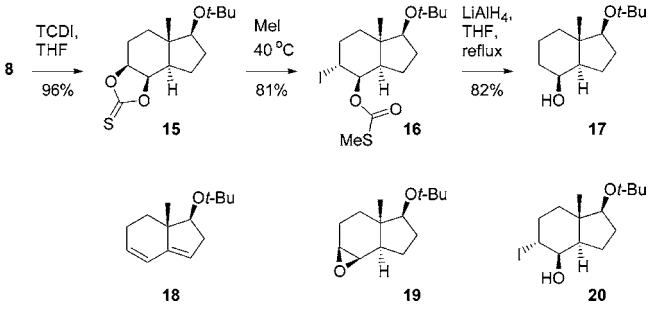
Scheme 2



crude reaction product showed traces of contamination, most likely the regioisomeric iodohydrine derivative.

Reduction of **16** with $LiAlH_4$ (4 molar equiv) in THF at reflux gave alcohol **17** in 80−85% yield along with some diene[17] **18**, which was easily removed by chromatography or by crystallization. It was found important that the solution of **16** in THF was added dropwise to a refluxing $LiAlH_4$ solution. Monitoring of the reaction by TLC suggested that intermediates, most likely epoxide **19** and iodohydrine **20** were involved. Indeed, careful reduction of **16** at a room temperature with $LiAlH_4$ (1 molar equiv) afforded a mixture of products from which epoxide **19** (27%), iodohydrine **20** (53%), and diene **18** (18%) were isolated by chromatography.

In summary, the synthetic route from α,β-unsaturated ketone **4** to monoacetate **2** via thionoimidazolyl acetate derivative (**10**) involved seven steps. The product was obtained in 44% yield (neglecting recovery of some diol **8**), which compares rather well to those attainable by other methods. The route via cyclic thionocarbonate (**15**) is one step shorter and provides the product **17** (alcohol) in 51% yield, which is self-indicative. The latter route also has other advantages; namely, no chromatographic purification of intermediates in all synthetic sequences was needed and only the final product (**17**) was briefly filtered through a silica gel column before crystallization.

Synthesis of other *trans*-hydrindane-based natural products by these methods is in progress.

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Supporting Information Available: Experimental procedures, compound characterization, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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