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A new approach to a vitamin D ring C/D building block from the Hajos dione, involving epoxide opening at the more substituted carbon atom

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Abstract—A new approach to a *trans*-hydrindane building block for 1α,25-dihydroxyvitamin D_3 (calcitriol) synthesis from the Hajos dione has been developed. The α,β-unsaturated carbonyl group in the Hajos dione has been protected and the carbonyl group in the five-membered ring has been used for the side chain attachment. Key steps in the six-membered ring transformation include: reduction of the carbonyl group, stereoselective epoxidation of the double bond in the allylic alcohol, opening of the epoxide at the more substituted carbon atom and regioselective deoxygenation.
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A great deal of attention has been devoted to the total synthesis of 1α,25-dihydroxy vitamin D_3 (**1**, calcitriol, Fig. 1) and its analogues.[1–3] Hajos dione **2** available from L-proline-catalyzed annulation of 2-methylcyclopentadione with methyl vinyl ketone[4,5] provided a convenient starting material for the steroid skeleton construction. Several methods for the transformation of **2** into the *trans*-hydrindane alcohols **3a** and **4a**, which are key intermediates in vitamin D synthesis,[6–8] have been developed.[9,10] However, stereoselective saturation of the double bond at the hydrindane ring junction and transposition of the oxygen function remain operationally difficult or ineffective processes. We recently reported[11] a new approach to *trans*-hydrindane systems using stereoselective epoxidation and the Hutchins reagent[12] ($NaBH_3CN$–$BF_3{\cdot}Et_2O$) for epoxide ring opening at the more substituted carbon atom. We now present a simple and efficient approach to advanced intermediates **3** and **4** starting from **2** towards calicitriol synthesis.

When dione **2** was allowed to react consecutively with different batches of bis-*O*-(trimethylsilyl)ethylene glycol and TMSOTf[13] following the reported procedure[14,15] (DCM, −78 °C), mono-ketal **5** (Scheme 1) was formed

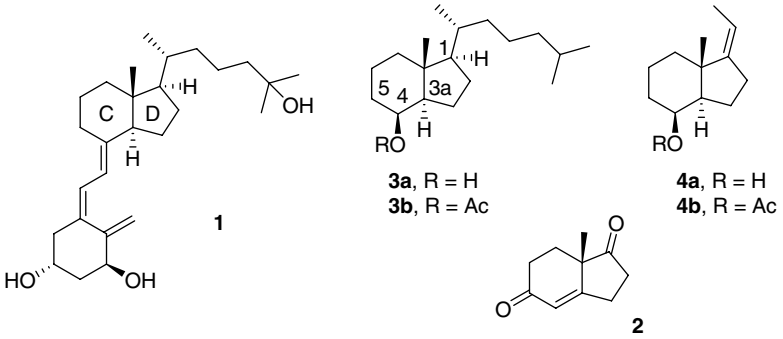

Figure 1.

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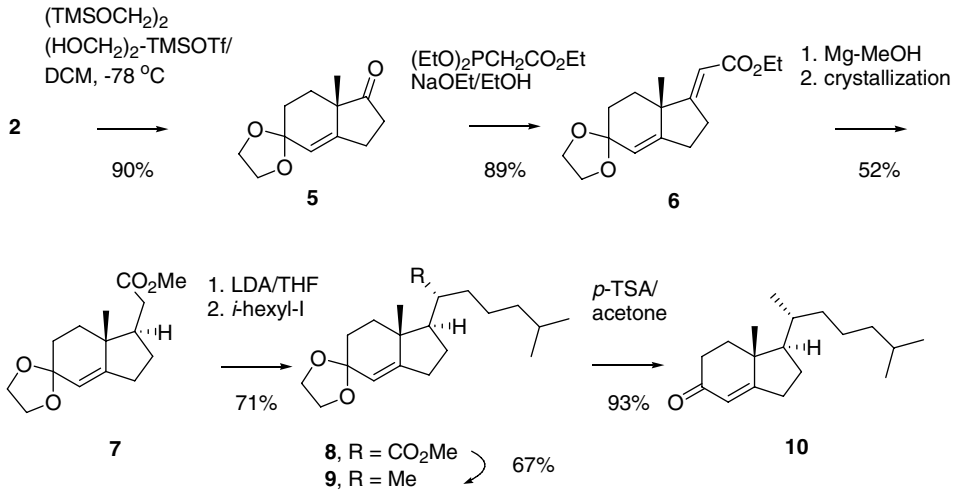


Scheme 1.

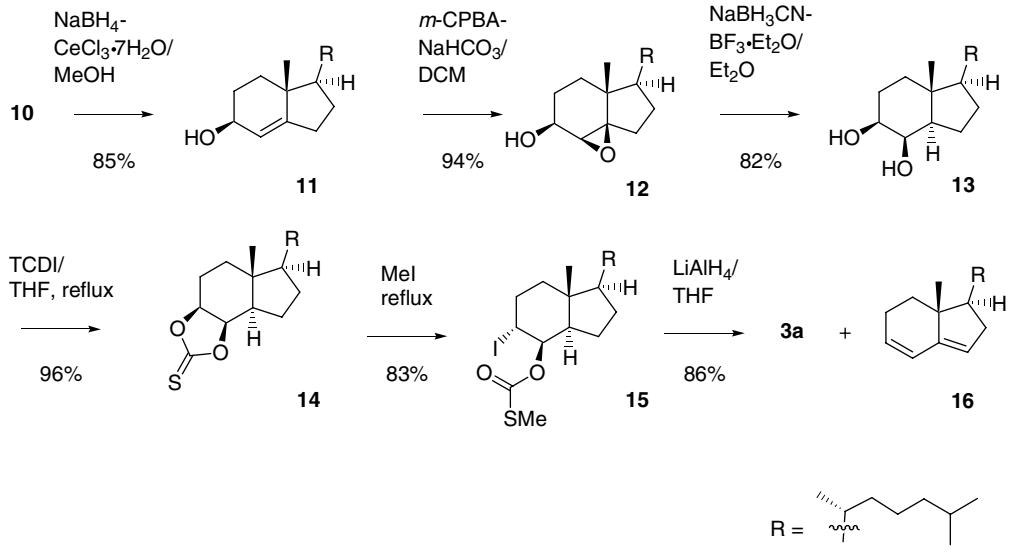
in irreproducible yields. The starting material was recovered unchanged when pure $TMSOCH_2CH_2OTMS$ and TMSOTf were used. It was found that the presence of the mono-silylated ethylene glycol derivative ($TMSOCH_2CH_2OH$) or ethylene glycol was necessary for the reaction to occur. In practice, to a solution of **2** in DCM at −78 °C, freshly distilled $TMSOCH_2CH_2OTMS$ (2.5 equiv) along with ethylene glycol (0.5 equiv) and TMSOTf were added. After the reaction was complete, pyridine was added and product **5** was isolated in 90% yield. The reaction was amenable to multi-gram scale-up.

Reaction of **5** with triethylphosphonoacetate and sodium ethoxide in ethanol gave *E*-unsaturated ester **6**, which was subsequently reduced with magnesium in methanol.[16] Surprisingly, a mixture of two products was formed (in a ratio of 5:1 by ^1H NMR, 79% yield), which could not be separated by chromatography. Crystallization from hexane gave the required ester **7** in 52% yield from **6**. The other product was proved to be the 1α-isomer of **7**.[17]

Intermediate **7** was alkylated with 1-iodo-4-methylpentane and the resulting derivative **8** was further transformed into **9** in the usual way[18] (in 67% overall yield from **8**). Hydrolysis of the acetal protecting group gave the known[19,20] α,β-unsaturated ketone **10**.

Enone **10** was reduced[21] and the resulting allylic alcohol **11** (Scheme 2) was oxidized with 3-chloroperoxybenzoic acid to give epoxide **12**. Treatment of **12** with $NaBH_3CN–BF_3{\cdot}Et_2O$[12] in ether gave diol **13** as the only product in 82% yield.

Diol **13** was treated with thionocarbonyl-1,1′-diimidazole (TCDI) to give the thionocarbonate **14**, quantitatively. Reaction of **14** with methyl iodide[22,23] at 44 °C in a sealed ampoule protected from light afforded iodohydrin **15**, which, without purification, was subjected to reduction with lithium aluminium hydride to afford alcohol **3a** in 86% yield, along with a small amount of diene **16** that could be removed either by crystallization or by filtration through silica gel.

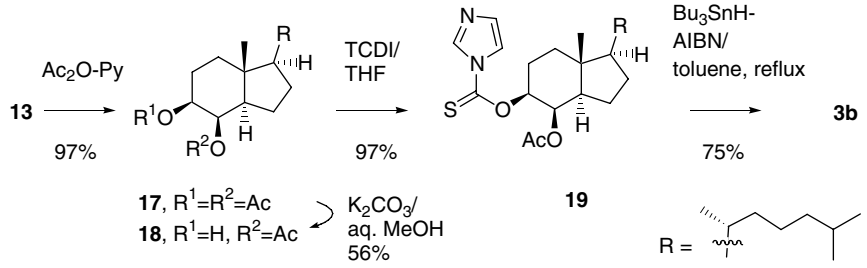


Scheme 2.

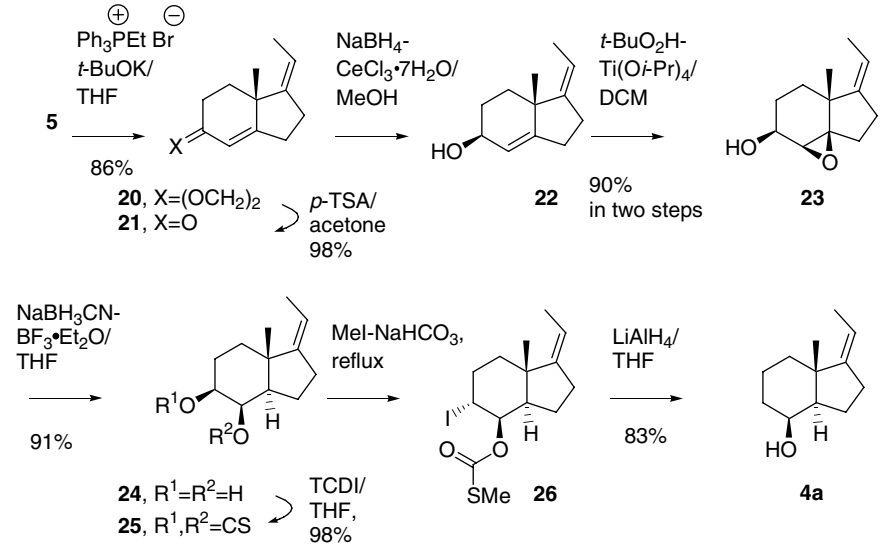
An alternative approach to **3b** from diol **13** involved the Barton–McCombie[24] deoxygenation reaction. The intermediate thionoimidazolide derivative **19** was prepared as outlined in Scheme 3. In the optimized procedure, a toluene solution of **19** containing ca. 10 mol % of AIBN was slowly added via a syringe pump to a refluxing dilute solution of tri-*n*-butyltin hydride in toluene (ca. 0.06 M) to give **3b** in a satisfactory 75% yield from **19**. However, dilution of the reaction hampered large-scale preparation and tedious chromatographic purification of the product was required.

The synthesis of the versatile vitamin D analogue precursors **4** from mono-ketal **5** is outlined in Scheme 4. Wittig olefination of **5** gave[25] *Z*-ethylidene derivative **20** in 86% yield, contaminated with less than 5% of the *E*-isomer (by ^{1}H NMR) and, after hydrolysis, enone **21**. Enone **21** was reduced to alcohol **22**, which was subsequently epoxidized selectively at the allylic alcohol using the Sharpless[26,27] procedure [*tert*-BuO_2H–Ti(O*i*-Pr)$_4$] to give **23** in 90% yield (from **21**). Reduction of **23** with Hutchins' reagent smoothly provided diol **24**. Diol **24** was treated with TCDI in THF to give cyclic thionocarbonate **25**, which was purified by chromatography. The product consisted of the double bond isomers in the ratio, ca. *E*/*Z* 5/95.

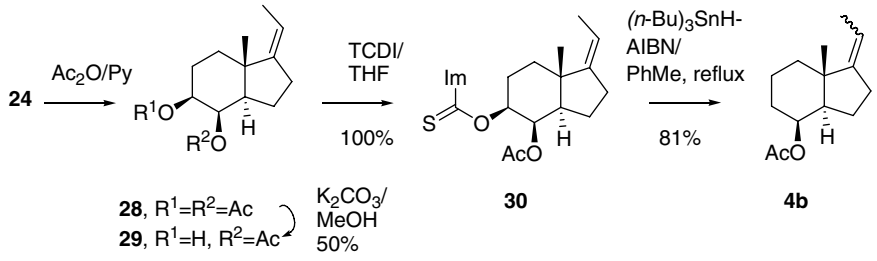
Heating **25** with methyl iodide at reflux resulted in the opening of the thionocarbonate ring to give **26**. However, the iodohydrin derivative **26** was accompanied by a considerable amount of side products resulting (presumably) from the ethylenic bond isomerization or migration. After some experimentation it was found that addition of powdered $NaHCO_3$ and copper



Scheme 3.



Scheme 4.



Scheme 5.

turnings to the reaction mixture effectively halted any side reactions and **26** was obtained almost quantitatively (*E*/*Z* 5/95). Finally, reduction of **26** with lithium aluminium hydride in THF gave **4a**.

In the complementary approach to **4b** (Scheme 5), hydrolysis of diacetate **28** was somewhat less selective than in the previously discussed sequence (Scheme 3), giving mono-acetate **29** in 50% yield. Thionoimidazolide **30** was prepared in the usual way, and on reduction with tri-*n*-butyltin hydride in the presence of AIBN gave acetate of **4b**. Reduction was accompanied by extensive double bond isomerization. Under optimized conditions, product **4b** was obtained in 81% yield (after chromatography) as a mixture of *E* and *Z* isomers in a ratio of 1:5, respectively.

In conclusion, a simple and efficient approach to advanced intermediates **3** and **4** in vitamin D synthesis from Hajos dione **2** have been developed. The *trans*-hydrindane ring system was established through hydroxyl group directed double bond epoxidation of allylic alcohols **11** or **22** and the Hutchins reduction of the corresponding epoxides. For removal of the C-5 hydroxy groups in diols **13** or **24**, two methods were applied: (1) opening of cyclic thionocarbonates **14** or **25** with methyl iodide and then lithium aluminium hydride reduction of the respective iodohydrin derivatives and, (2) tri-*n*-butyltin hydride reduction of thionoimidazolides **19** or **30**. The former method provided the products in higher yields and allowed problems with scaling-up and removal of tin-containing residues to be avoided.

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