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Intramolecular Methylation of an Allyl Sulfone via Lithium Alkoxyaluminate; Application to the Enantioselective Synthesis of the CD Ring of Vitamin D_3

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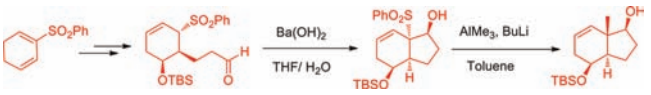
ABSTRACT



Alcohol-directed intramolecular methylation of an enantiopure allyl sulfone using $AlMe_3$ provides a *trans*-hydrindane CD ring alcohol. The substrate *cis*-CD ring allyl sulfone alcohol is prepared via intramolecular allyl sulfonyl anion addition to aldehyde using $Ba(OH)_2$.

$1\alpha,25(OH)_2D_3$ is the most biologically active metabolite of Vitamin D_3 and is involved in the regulation of calcium homeostasis and bone metabolism (Figure 1). In addition, it suppresses the growth of numerous human cancer cell lines by inhibiting cell cycle progression and inducing cell death. There has been enormous research on the development of analogs of Vitamin D_3 that are more potent than natural Vitamin D_3. CD ring modification has also made a substantial contribution to this area. A major problem in the *de novo* synthesis of steroidal CD rings has been the efficient construction of the enantiopure *trans*-hydrindane system.[1] It has also been reported that the *trans* Grundmann's ketone obtained from oxidative degradation of Vitamin D is less stable than the *cis* form by >0.76 kcal/mol.[2] The Hajos dione **2** produced by an organocatalytic reaction of 2-methylcyclopentane-1,3-dione with methyl vinyl ketone has been routinely used for the construction of the CD ring system.[1,3,4] The chemistry herein provides a complementary synthesis of the enantiopure *trans* CD ring from cyclohexadienyl sulfone **3**.

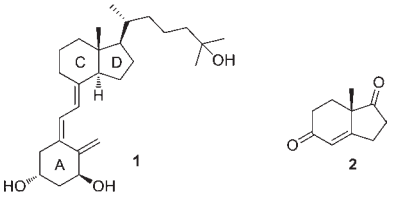


Figure 1. Structure of $1\alpha,25(OH)_2D_3$ **1** and Hajos dione **2**.

Alcohol-directed allylation of sulfone **4**[5] using 2.5 equiv of allyl magnesium bromide gave allyl sulfone **6** after TBS protection in 81% yield (Scheme 1). Selective hydroboration–oxidation of allyl sulfone **6** with 9-BBN afforded allyl sulfone **7** in 90% yield. Allyl sulfone **7** was oxidized using Dess-Martin Periodinane (DMP) to give aldehyde **8** in 92% yield.

Intramolecular sulfonyl anion addition to the aldehyde **8** using 5 equiv of $Ba(OH)_2$ gave the CD ring alcohol **9** in

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(6) $Ba(OH)_2$ and K_2CO_3 were found to be very selective for this transformation. Cs_2CO_3/ DMF/H_2O gives the product only in 32% yield, while DBU, LiHMDS, and KO-*t*Bu lead to no reaction.

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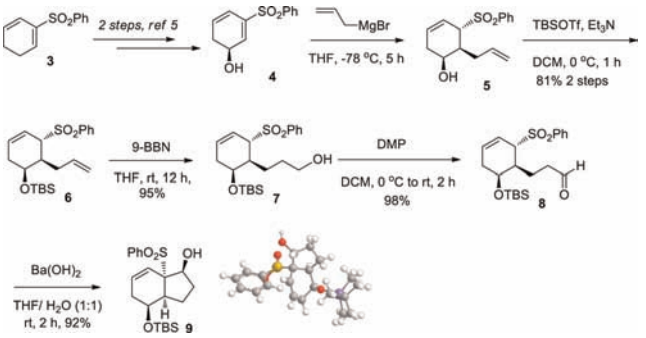
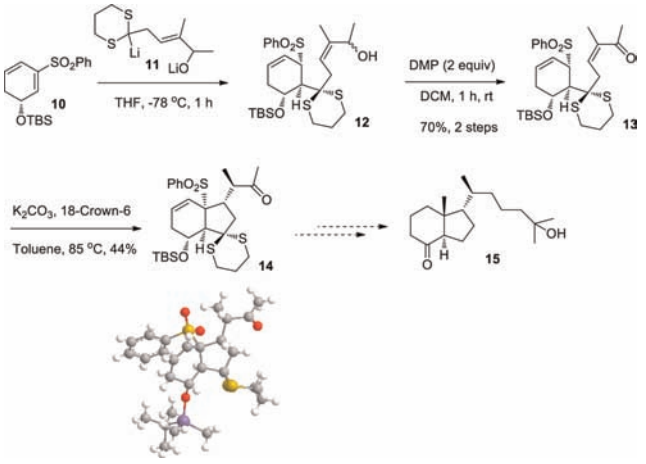
Scheme 1. Synthesis of CD Ring Alcohol **9** and Its X-ray



92% yield. K_2CO_3/18-Crown-6 could also be used for the above transformation which proceeded in 86% yield.[6] X-ray crystallography confirmed the stereochemistry of alcohol **9**. The competing enolization of aldehydes is a problem in these types of reactions, as most of the reactions have employed syringe pump techniques.[7] $Ba(OH)_2$ and K_2CO_3/18-Crown-6 have been found to be very mild and selective in this kind of transformation without employing syringe pump techniques.

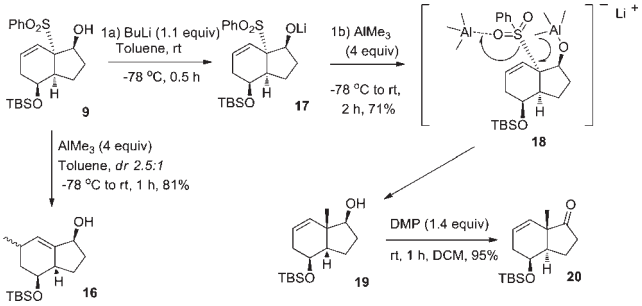
Scheme 2. Intramolecular Allyl Sulfone Addition to Enone and the X-ray of Ketone **14**



It was also found that K_2CO_3/18-Crown-6 affects intramolecular Michael addition of the allyl sulfone with enone **13** to provide CD ring ketone **14** in 44% yield (Scheme 2) which could potentially be used for the synthesis of Vitamin D_3 analogs.[8] The enone **13** was synthesized in 70% yield by reacting the dithiane dianion **11** with dienyl sulfone **10** followed by oxidizing the allyl alcohol using DMP.

To methylate and desulfonylate the allyl sulfone **9**, $AlMe_3$ was used. Aluminum reagents ($AlMe_3$, $AlCl_3$, $EtAlCl_2$, $MeAl(OTf)_2$) have been widely used for desulfonylating substrates to either trap the carbocation with nucleophiles or to effect elimination to generate an olefin.[9,10] In this study, $AlMe_3$ was found to be effective for activation of the allylic sulfone which was then intramolecularly methylated by the lithium alkoxyaluminate.

Scheme 3. Methylation of Allyl Sulfone **9**

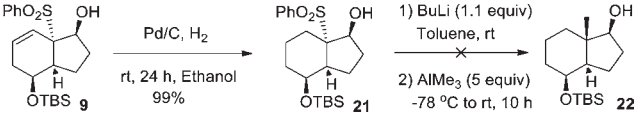


When CD ring alcohol **9** was treated with 1.1 equiv of BuLi and then subsequently with 4 equiv of $AlMe_3$, this led to installation of a methyl group at the quaternary carbon via displacement of phenyl sulfinate, to provide alcohol **19** in 71% yield. Oxidation of **19** using 1.4 equiv of DMP smoothly afforded ketone **20** in 95% yield. The mechanism of the phenyl sulfone substitution presumably involves the following: (1) deprotonation of the alcohol using BuLi, (2) formation of lithium alkoxyaluminate complex, (3) Lewis acid assisted desulfonylation using $AlMe_3$, and (4) intramolecular methylation (Scheme 3). Similar treatment of CD ring alcohol **9** with 4 equiv of $AlMe_3$ *in the absence of base* provided only S_E2' displacement of phenyl sulfinate to give alcohol **16** in 81% yield without any **19** being detectable.

BuLi/$AlMe_3$ was not able to substitute the phenyl sulfone when not activated by a double bond. Treatment of **21** under the same conditions employed for **9** returned **21** in >95% yield with no evidence for the formation of any **22** (Scheme 4). The test substrate sulfone **21** was prepared by hydrogenating allyl sulfone **9** using Pd/C in the presence of 1 atm of H_2.

In summary, we have reported a short synthesis of the *trans*-hydrindane CD ring of Vitamin D_3 from cyclohexadienyl sulfone. The synthesis features intramolecular allyl sulfone addition to aldehyde to construct the CD ring and

Scheme 4. Unreactivity of Dihydro Sulfone **21**



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(8) Three new stereogenic centers were created during the intramolecular allyl sulfone addition to enone. The methyl stereochemistry in the side chain could be anticipated because of the steric effects between the phenyl sulfone and the methyl group in the other diastereomer.

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alcohol directed $AlMe_3$ induced bridgehead methylation of allyl sulfones.

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

The authors declare no competing financial interest.