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AN ASYMMETRIC SYNTHESIS OF A 1α,25-DIHYDROXYVITAMIN D3 A-RING SYNTHON

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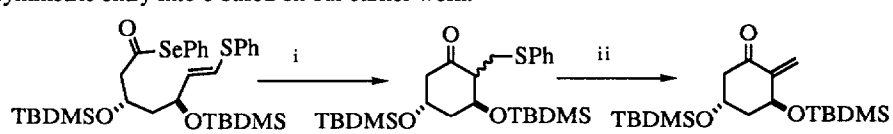
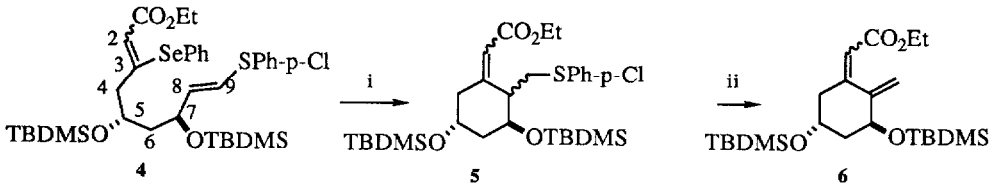
Summary : An efficient asymmetric synthesis of the A-ring of 1α,25-dihydroxyvitamin D3 from α–bromoacrolein is described. The key steps of the synthesis are the Evans type syn-selective asymmetric aldol reaction of bromoacrolein with the boron enolate of 3-chloroacetyl-4(S)-isopropyl oxazolidinone and ring closure by Heck type reaction of a vinyl bromide onto an α,β-unsaturated ester in the exo-mode.

Recently we have reported on two radical cyclization approaches to the A-ring of 1α,25-dihydroxyvitamin D3; a molecule which continues to attract much attention owing both to the challenge inherent in its synthesis and to its newly expanded spectrum of biological activity.[1] Our first approach involved preparation of the racemic selenoester (**1**) and its reaction with tributyl tin hydride to give **2** followed by peracid oxidation and syn elimination to the α-methylenecyclohexanone (**3**) (Scheme 1).[2] Our second approach, involving radical cyclization of **4** to give **5** followed again by controlled oxidation and syn elimination giving eventually the standard A-ring synthon (**6**) (Scheme 2), evolved out of difficulties encountered in the addition of the two carbon chain to **2** or **3**.[3] In this Letter, prompted by the recent report of a closely analogous method,[4] we report on an efficient asymmetric entry into **6** based on our earlier work.



i) Bu_3SnH, AIBN, 80 °C, 92%; ii) Magnesium monoperoxyphthalate, 0 °C; Δ, 80 °C, 60%

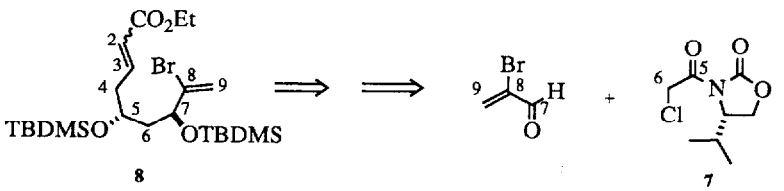
Scheme 1



i) Bu_3SnH, AIBN, 80 °C, 67%; ii) Magnesium monoperoxyphthalate, 0 °C; Δ, 80 °C, 60-80%

Scheme 2

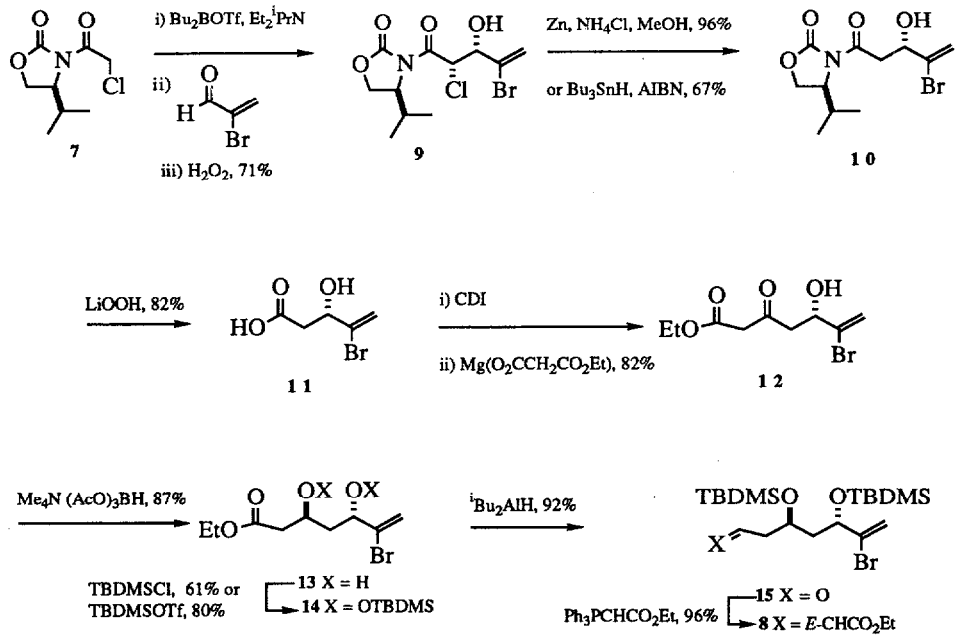
The development of an asymmetric variant of the method, outline in Scheme 2, suffered from two principal problems. Firstly, the low yield in the formation of the vinyl selenide moiety[3] has so far proven insurmountable. Secondly, our intention had been to introduce the appropriate chirality at an early stage of the synthesis by means of an Evans type aldol reaction[5] of the chloroacetyloxazolidinone (**7**)[6] with either β-phenyl-thioacrolein or the more crystalline β-4-(chlorophenylthio)acrolein. Unfortunately, in our hands, such unsaturated aldehydes give poor results with the Evans methods.[7] In view of these difficulties an alternative cyclization was envisaged in which a radical at C-8 would attack, in the favorable 6-exo-trig mode, onto an α,β-unsaturated ester with the synthesis of the radical precursor (**8**) being initiated by an Evans type aldol reaction of **7** with α-bromoacrolein as outlined in Scheme 3.



Scheme 3

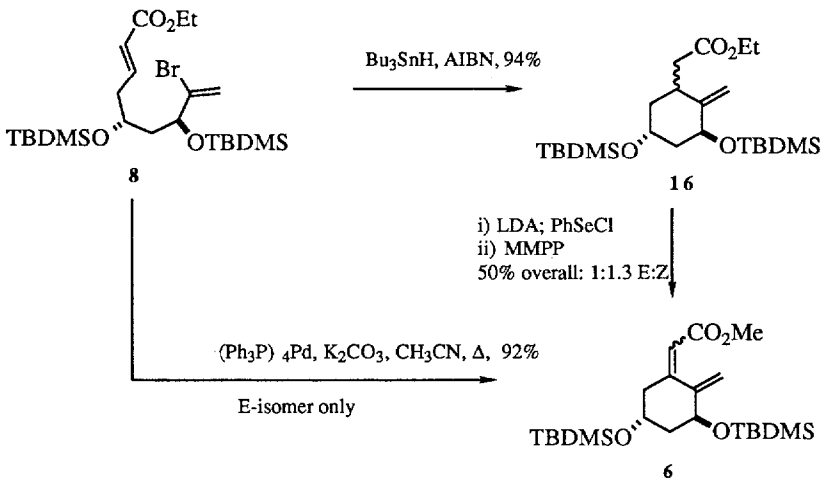
In the event , reaction of the boron enolate prepared from chloroacetyloxazolidinone **7** (dibutylboron triflate and Hunig's base, at -78 °C) with α-bromoacrolein[8] gave the crystalline aldol (**9**) as a single diastereoisomer in 71% yield.[9] The extraneous chlorine atom was then removed reductively, to give **10** in 96% yield, by stirring with zinc and ammonium chloride in methanol overnight at room temperature. Interestingly, the same transformation could be achieved, in 67% yield, by heating to reflux in benzene with tributyltin hydride and azoisobutyronitrile. Saponification to the acid (**11**) was achieved in 82% yield by stirring with lithium hydroperoxide and two carbon homologation by reaction with carbonyl diimidazole and subsequently with magnesium monoethylmalonate giving **12** in 82% yield. Reduction of this β-hydroxyketone by the Evans

protocol with tetramethylammonium triacetoxyborohydride[10] gave the diol (**13**) in 87% yield as a 13:1 anti:syn mixture. This mixture was silylated under standard conditions to **14** (The minor syn diastereoisomer was conveniently removed by chromatography at this stage). Dibal reduction of **14** took place uneventfully in 92% yield giving **15** which was homologated in 96% yield by means of the Wittig reaction to the cyclization precursor (**8**) (Scheme 4).



Scheme 4

The cyclization of **8** to **16** was achieved in 94% yield by treatment with tributyltin hydride and AIBN in benzene at reflux. The product (**16**), obtained as an unassigned 1.2:1 mixture of stereoisomers at the newly formed stereo center. Dehydrogenation of **16** to **6** was achieved in around 50% by sequential reaction with LDA, phenylselenyl chloride and magnesium monoperoxyphthalate. In this manner **6** was obtained as an approximately 1:1.3 E:Z mixture. In a more efficient procedure the bromide (**8**) was cyclized to E-**6** directly by heating to reflux in acetonitrile with a catalytic quantity of (Ph3P)4Pd and K_2CO_3 in 92% yield (Scheme 5). The obtention of the E-isomer in the conversion of **8** to **6** is of no consequence as it has been amply demonstrated[11] that photo-equilibration favors the required Z-isomer.[12]



Scheme 5

Acknowledgements: We thank the University of Illinois at Chicago for support ; Mr A. Papadatos for extensive exploratory reactions and Mr M. Bruncko for assistance with the dehydrogenation of **16**.

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12. All new compounds gave spectroscopic and microanalytic or high resolution data in accordance with the assigned structrues. The spectral data and optical rotation of **6** were in agreement with the literature values (ref 11).

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