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A (3+2)-Cycloaddition Approach to 1α, 2β, 25-Trihydroxyvitamin D3 A Ring Synthon

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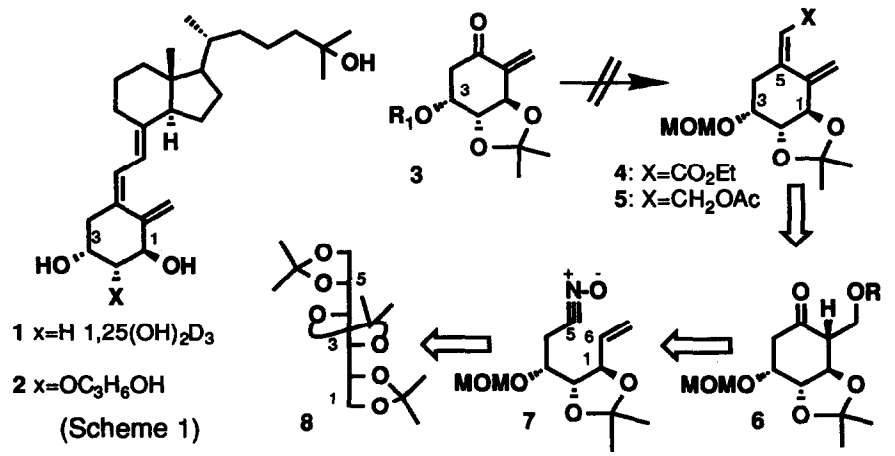
SUMMARY: Synthesis of a chiral A-ring model of 1α, 2β, 25-trihydroxyvitamin D3 by the nitrile oxide cycloaddition and its diastereoselectivity based on MM2 transition state model are described.

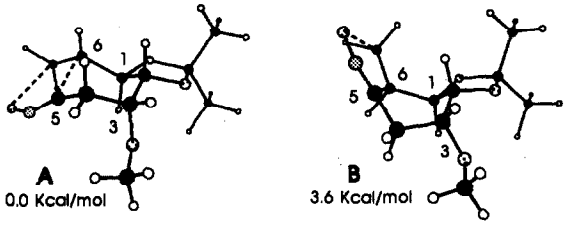
1α, 25-Dihydroxyvitamin D3 (calcitriol) (**1**) is well known as the hormonally active form of vitamin D3 whose physiological activities[1] include regulation of cell differentiation and proliferation, intestinal calcium absorption, bone mobilization and bone formation. These properties have stimulated significant efforts toward syntheses of various calcitriol analogues having modified side chains.[2] However, only a relatively restricted number of examples of modified A-ring derivative have been reported[3]. Recent *in vivo* studies[4] on regulatory activities for calcium metabolism of 1α, 25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D3 (ED-71) (**2**) showed better results than those of calcitriol **1**, suggesting its promising profile as a drug for therapy of osteoporosis. We report here the stereoselective synthesis of chiral trihydroxylated A-ring **5** as a synthetic intermediate for 1α,2β,25-trihydroxyvitamin D3.



The initial approach to the synthesis of 5*Z*-unsaturated ester **4** from the exocyclic enone **3** by Horner-Emmons reaction proved unworkable due to an easy β-elimination of the alkoxy group at C-3[5]. Peterson-type reaction of **3** with the lithium enolate of ethyl α-trimethysilylacetate (**13**) gave the 1,4-addition product[5]. Based on the stereoselectivity of model reactions[6], we anticipated, that the 1,2-addition of **13** to 2-alkoxymethylcyclohexanone

6 followed by Peterson-type elimination[7] should give the desired 5*Z*-unsaturated ester with a high stereoselectivity. In our synthetic plan (scheme 1), the ketone **6** is the key intermediate. Its 6-membered ring is constructed by the intramolecular nitrile oxide cycloaddition (INOC)[8] of **7**. Moreover, MM2 transition state models based on *ab-initio* calculations[9] (Fig.1) suggest that the (3+2)-cycloaddition of **7** should proceed with a high stereoselectivity to provide the C-6(R) chirality. 1.2,3.4,5.6-tri-O-isopropylidene-D-mannitol (**8**), having C_2 symmetry, is selected as the starting material in which the C-O chiralities at C-3,4,5 are directly used as the hydroxy groups at C-1,-2,-3 in **5**. The terminal olefin in **7** is constructed by thermolysis of the N.N-dimethylformamide cyclic acetal derived from the terminal 1,2-diols in **8**.

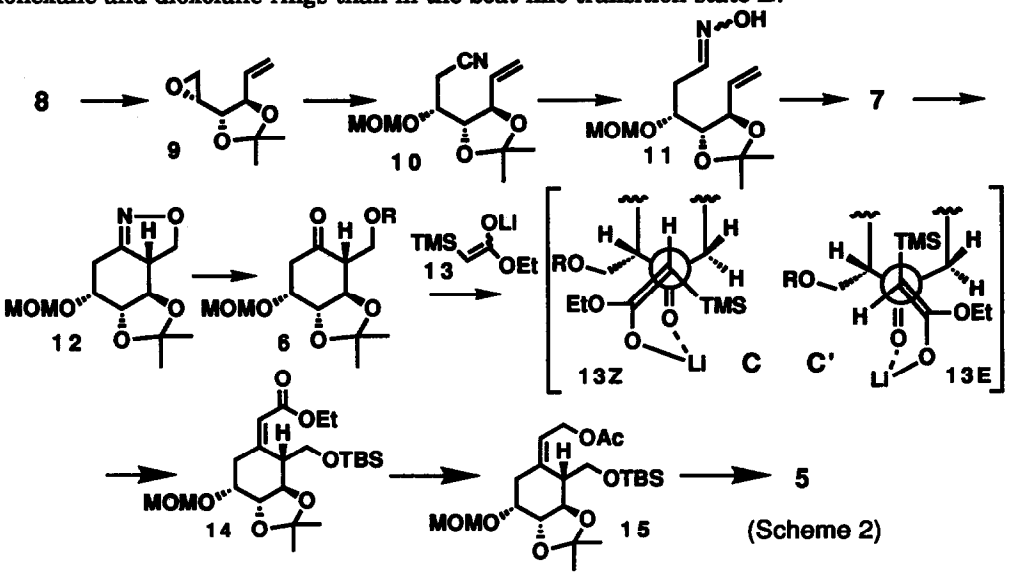
Molecular mechanics calculations[10] and MM2 transition state models[11] have proven useful for molecular modelings[12]; e.g. stereochemical predictions (or analyses) and designing the synthetic key intermediate. Here, MM2 transition state model calculations (rigid reactant model)[13] for the (3+2)-cycloaddition of **7** (MOM replaced by Me) was performed. In these calculations, the partial geometry of the reactive dipole and dipolarophile was frozen in the 3-21G transition state model geometry[9] of the HCNO-ethylene reaction. The forming cyclohexane ring has two possible conformations; chair and boat-like transition state structures A and B (Fig. 1). The methoxy group at C-3 was rotated with 120° resolution and two C-O bonds of the dioxolane ring and the alkoxy group were placed in the equatorial and axial orientation, respectively. These 12 conformations were fully optimized by using extended MM2 parameters[14] for INOC reactions. Figure 1 shows the lowest energy transition state structure A leading to the C-6(R)-isomer **12** and the preferred transition state structure B providing the C-6(S)-isomer. These calculations and a Boltzmann distribution based on the energy difference between A and B, predict an exclusive formation of C-6(R)-isomer **12**.



(Figure 1)

The epoxide **9** was prepared from a readily available tri-O-isopropylidene **8** by our previous procedure.[3c] Epoxide opening of **9** (KCN, $MgSO_4$ in aq. MeOH, 0°C; 91% yield) and protection of the alcohol ($MeOCH_2Cl$ / i-Pr_2NEt) afforded the nitrile **10** in 96% yield. Reduction of **10** with diisobutylaluminum hydride at -78°C and reaction of the resulting aldehyde with hydroxylamine hydrochloride gave the oxime **11** in 52% overall yield. Construction of the cyclohexanone ring from **11** was carried out by the Kozikowski method[8]. Oxidation of the oxime **11** to the nitrile oxide **7** with aq. NaOCl followed by spontaneous cycloaddition gave the isoxazoline **12** in 56% yield. None of the other stereoisomer of **12** was detected by HPLC analysis. This high diastereoselectivity can be explained by the transition state model **A**, in which π-orbitals of the alkene and nitrile oxide face each other on the same plane; parallel

plane approach of dipole and dipolarophile. The forming cyclohexane ring in the transition state exists in a chair-like conformation, which carries two equatorial C-O bonds, one equatorial C-C bond, one pseudo equatorial C=N bond, and one axial MOM group (see structure **A**, Fig 1 and structure **12**, Scheme 2). Thus overlapping of the dipole/dipolarophile orbitals in the chair-like transition state **A** requires less distortions of the forming cyclohexane and dioxolane rings than in the boat-like transition state **B**.



Reductive hydrolysis[15] of the isoxazoline ring in **12** with Raney Ni in the presence of $B(OH)_3$ under a hydrogen atmosphere in aq MeOH gave the 2-hydroxymethylcyclohexanone **6** (R=H) in 61% yield. Protection of the alcohol (*tert*-butyldimethylsilyl (TBS) chloride/NEt_3, DMPA) and 1,2-addition of the lithium enolate **13** (prepared from ethyl α-trimethylsilylacetate and lithium dicyclohexylamide at -78 °C in THF), to **6** (R=TBS) followed by Peterson elimination afforded the single stereoisomer **14** in 75% yield. This striking *Z*-selectivity may be explained as follows. Although the stereochemistry of the lithium enolate **13** was not clear, examination of molecular models revealed that the 1,2-addition of **13** can be achieved through gauche arrangements (**C** and **C'** in scheme 2) of the ketone **6** and *E*-, *Z*-enolate **13*E*** and **13*Z***. Reduction of the ester **14** with diisobutylaluminum hydride at -78°C and protection of the resulting alcohol with acetic anhydride gave the allylic acetate **15** in 47% yield. Deprotection of the TBS group (n-Bu_4NF/THF) in **15**, selenenylation of the resulting alcohol (o-$NO_2C_6H_4SeCN$, Bu_3P/THF), and syn-elimination of the o-nitrophenyl selenoxide (H_2O_2/THF) gave the diene **5** in 35% overall yield.

Thus an enantiospecific synthesis of a 1α,2β,25-trihydroxyvitamin D_3 A-ring synthon (**5**) was accomplished from D-mannitol derivative **8** by using (3+2)-cycloaddition of a nitrile oxide and Peterson-type reaction of a 2-alkoxymethylcyclohexanone. While our MM2

transition state model does not incorporate stereoelectronic effects at the allylic position, the desicribed calculations are shown to have predicting value in organic synthesis.

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