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Preliminary Communication

Stereocontrolled Total Synthesis of 1α,25-Dihydroxyergocalciferol*

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A stereocontrolled total synthesis of the vitamin D_2 metabolite 1α,25-dihydroxyergocalciferol (*1*), which involves a coupling of the previously described A ring synthon *2* with the appropriately functionalized C—D moiety *3*, is described. In the key step, stereochemical control is achieved by taking advantage of the thermal reversibility of a [3 + 2]-cycloaddition of methyl β,β-dimethylacrylate and the C—D C-23 nitrone *4* to effect conversion to the C-24S isoxazolidinecarboxylic acid methyl ester *5a*, which is readily transformed by reduction followed by elimination of the nitrone function into the necessary C—D precursor.

The discovery of the importance of metabolism in the activation of vitamin D_3[1,2] has stimulated a renaissance of research in this area. While it is well known that the vitamin D endocrine system controls calcium absorption, serum levels of calcium and phosphorus, and bone resorption and mineralization, the precise roles of the various metabolites have yet to be uncovered. Since the naturally occurring metabolites can be isolated only in extremely minute amounts, considerable interest in their synthesis, as well as in preparing new analogs, has been generated.

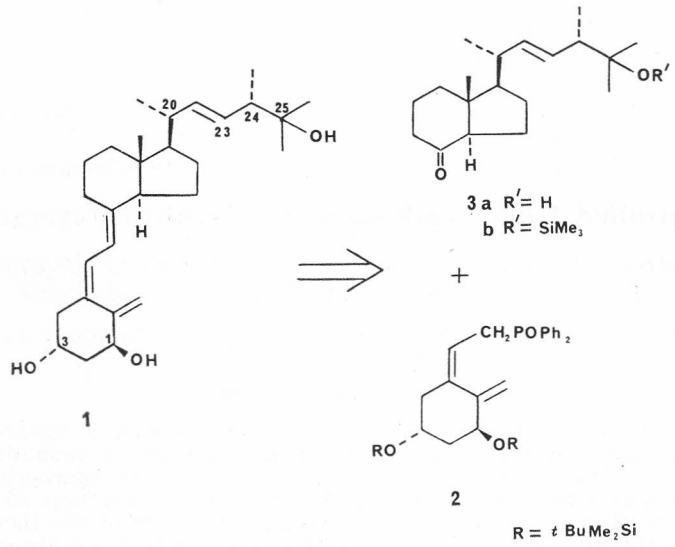
While it is believed that vitamin D_2 (ergocalciferol) metabolism[3] parallels that of vitamin D_3 (cholecalciferol), little is known about the biological activity of the various metabolites in man. We undertook the synthesis of 1α,25-dihydroxyergocalciferol[3] in order to make the substance available for biological studies, being particularly interested in uncovering any therapeutic utility.

The use of a convergent total synthesis as the method of choice for preparing the 1α-hydroxylated vitamin D derivatives and analogs has already been well demonstrated in the synthesis of 1α,25-dihydroxycholecalciferol[4], 1α,25S,26-trihydroxycholecalciferol[5], and calcitriol lactone[6], as well as several other derivatives and analogs.

Thus, total synthesis (Scheme 1) of 1α,25-dihydroxyergocalciferol (*1*) requires the preparation of the suitably protected C—D synthon *3* for coupling with the anion of the 1α-hydroxylated A ring synthon *2* (Scheme 1). Since *2* was already on hand[4], major synthetic efforts were directed at the ketone *3*. The side chain (commencing at C-20) bears five contiguously functionalized

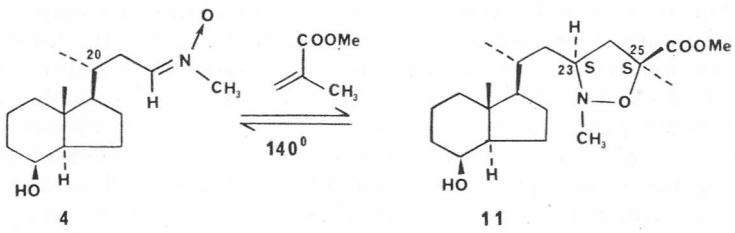
* Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.

Scheme 1



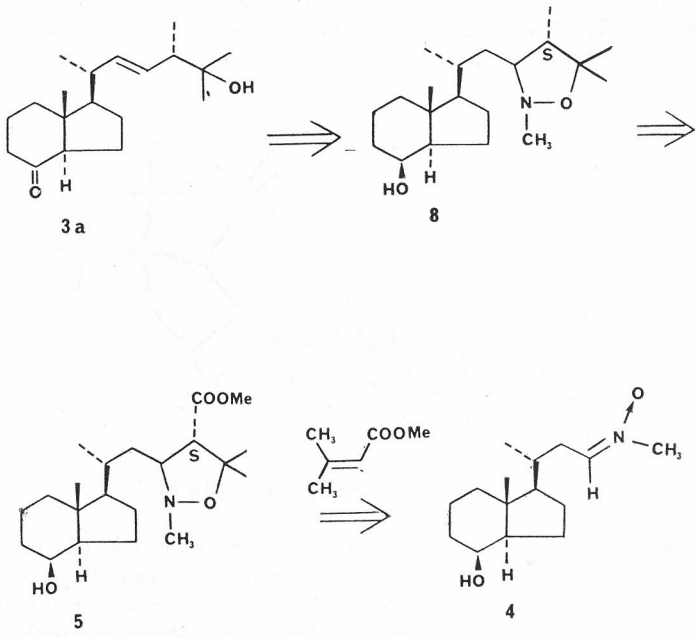
carbon atoms with the chiral centers in a 1,4-relationship. It was our intention to generate the remote C-24 chiral center by chiral induction under the influence of the pre-existing asymmetry at C-20. The approach to this side chain was patterned after our successful stereocontrolled total synthesis of 1α,25S,26-trihydroxycholecalciferol[5]. The key step in that synthesis was the [3 + 2]-cycloaddition of the C-23 nitrone *4* and methyl methacrylate to produce the 23*S*,25*S* isomer *11* with effective control of the stereochemistry at C-25 by taking advantage of the thermal reversibility of the regioselective cycloaddition (Scheme 2).

Scheme 2



Consequently, in a retrosynthetic analysis (Scheme 3) we envisioned that the C—D synthon *3* would be accessible from the trimethylisoxazolidine *8* which, in turn, would stem from a [3 + 2]-cycloaddition with the previously described C-23 nitrone *4*.[5] However, in order to control the regiochemistry and stereochemistry of the olefin cycloaddition, 2-methyl-2-butene was not considered as a satisfactory substrate. Thermodynamic control of the 1,3--dipolar cycloaddition dictated the use of a suitable acrylate ester. To this end, methyl β,β-dimethylacrylate was chosen as the dipolarophile which would

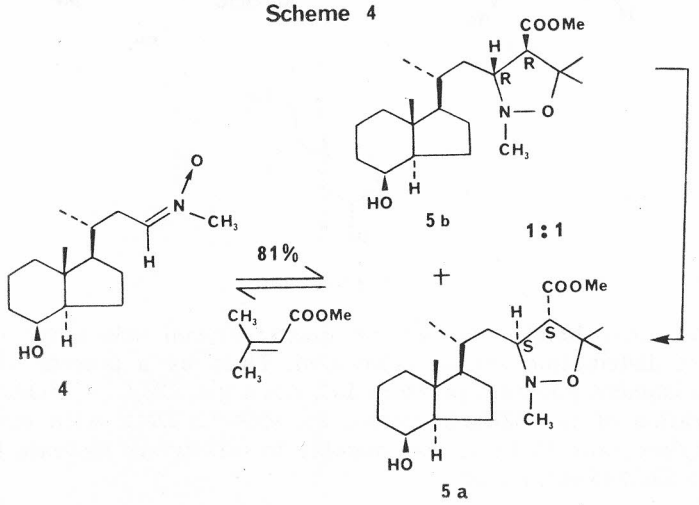
Scheme 3



produce, with predictable regiochemistry[7], 5 and furnish the complete carbon skeleton of the side chain. The C-24 ester group would serve as the progenitor of the methyl function. Elimination of the nitrogen function would lead to the Δ^{22} double bond.

Execution of this approach proceeded without incident. The Z-nitrone 4[5] underwent a smooth cycloaddition with methyl β,β-dimethylacrylate[8] (Scheme 4) under equilibrating conditions (overnight at 150 °C in xylenes) to give es-

Scheme 4



sentialy only two readily separable adducts, 23*S*,24*S* ester 5*a*[9] (41% yield) and 23*R*,24*R* ester 5*b* (40% yield).

The structure of 5*a* was established as 23*S*,24*S* by X-ray crystallographic analysis (Figure 1). The structure of the 23*R*,24*R* ester 5*b* was deduced from the very similar NMR spectrum.[10]

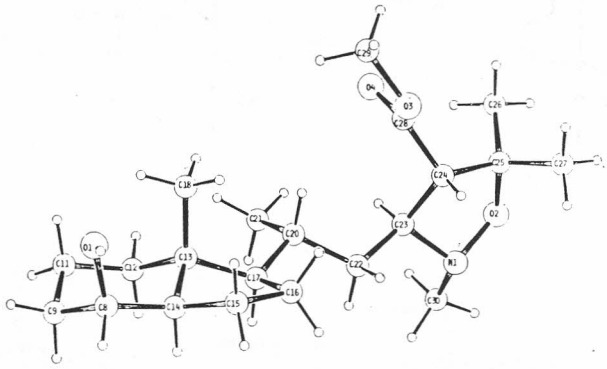


Figure 1. A perspective drawing of 5*a*.

The regiochemistry was as expected. High stereoselectivity, the result of almost exclusive endo addition to the *Z*-nitrone[5], can be rationalized from a comparison of the endo and exo transition states (Figure 2). Steric hindrance between C-23 and C-24 substituents in the exo transition state is much more severe and, consequently, this mode of addition is unfavorable.

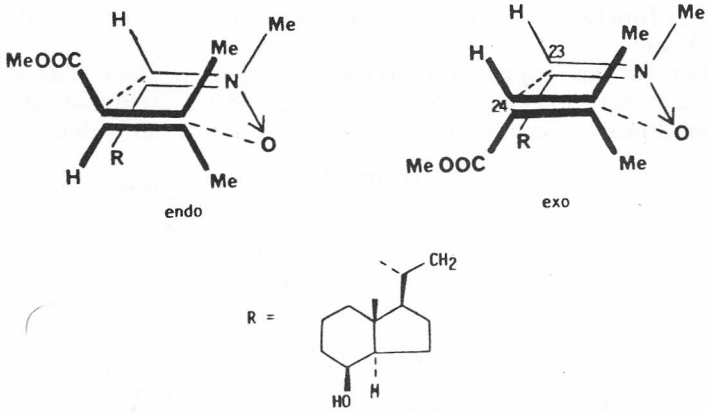
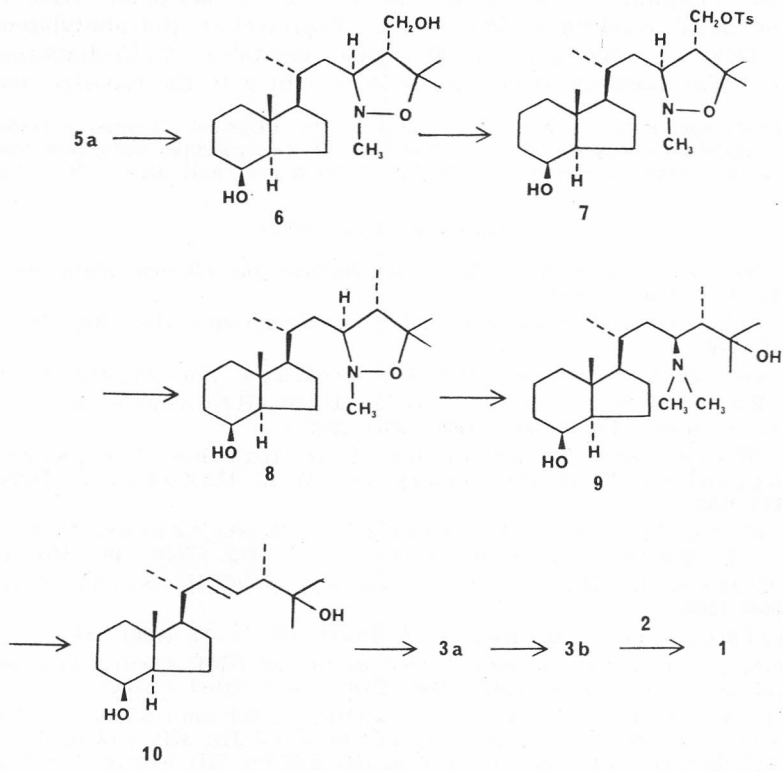


Figure 2.

On the other hand, although no diastereofacial selectivity is achieved, the product distribution can be controlled. Thus, by a process of separation of the two isomers (medium pressure LC, silica gel, CH_2Cl_2—EtOAc, 3 : 1), and re-equilibration of the 23*R*,24*R*-isomer 5*b*, (160 °C, DMF with excess methyl β,β-dimethylacrylate, 17 h), it was possible to effectively increase the production of the 23*S*,24*S*-isomer 5*a*.

Conversion of the ester group to the C-24 methyl group (Scheme 5) was accomplished by the lithium aluminum hydride reduction to alcohol *6* (90% yield), which on treatment with tosyl chloride in pyridine for 48 hrs at room temperature, gave the 28-monotosylate 7 (90% yield). The low reactivity of the axial 8-hydroxyl function made it unnecessary to protect this group during the entire side chain synthesis. Reduction of the tosylate (LAH, THF, reflux) gave trimethylisoxazolidine *8* (88% yield).

Scheme 5



Excession of the nitrogen function was achieved by cleavage of the isoxazolidine ring (1. MEI, 2. Zn/aq. HOAc) to give aminodiol *9* (89% yield) followed by a Hofmann degradation (1. MeI, 2. t-BuOK/t-BuOH, reflux, 5 hr), which regiospecifically afforded the trans Δ^{22}-diol *10* (78% yield). The *trans*--double bond was indicated by NMR, which showed a multiplet at δ 5.32 with $J = 16$ Hz for the C_{22}—C_{23} proton coupling, and was unequivocably confirmed by the X-ray crystallographic analysis (Figure 3).

The secondary C-8 alcohol was oxidized (pyridinium chlorochromate, methylene chloride, room temperature, 3 hrs) to hydroxyketone *3a* (93% yield), which was converted to the silyl ether *3b* (*N*-trimethylsilylimidazole,

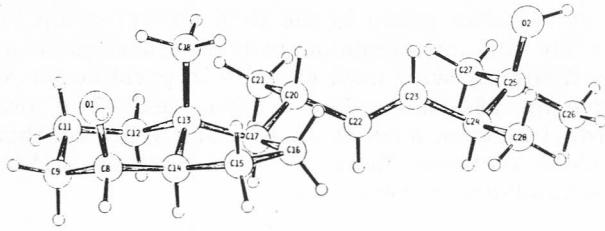


Figure 3. A perspective drawing of *10*.

84% yield). Coupling of the CD ketone *3b* and the phosphine oxide *2* anion under the usual conditions[4] followed by deprotection (tetrabutylammonium fluoride, THF, r. t., 23h) gave, in 80% yield, crystalline 1α,25-dihydroxyergocalciferol *1*. The mass spectrum was in agreement with the reported data.[3]

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9. Satisfactory combustion analyses as well as IR and NMR spectra were observed. Physical properties and proton NMR ($CDCl_3$) are listed below:

   1: m. p. 165—167 °C, $[\alpha]_D^{52}$ + 47.2° (c 0.2, EtOH), λ_{max} 265 nm (16,700); *m/e* 428; NMR δ 0.55 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 1.03 (d, J = 7 Hz, 3H), 1.13 (s, 3H), 1.17 (s, 3H), 4.25 (bm, 1H), 4.45 (bm, 1H), 4.98 (s, 1H), 5.32 (m, 3H), 6.02 (d, J = 12 Hz, 1H), 6.3 (d, J = 12 Hz, 1H).

   3a: m. p. 101—102 °C, $[\alpha]_D^{25}$ — 6.89° (c 0.5, EtOH); NMR: δ 0.64 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 1.06 (d, J = 7 Hz, 3H), 1.13 (s, 3H), 1.16 (s, 3H), 5.33 (m, 2H).

   5a: m. p. 80—81 °C (hexanes), $[\alpha]_D^{25}$ + 102.6° (c 1.05, $CHCl_3$), *m/e* 367; NMR δ 0.89 (s, 3H), 0.92 (d, J = 6 Hz, 3H), 1.17 (s, 3H), 1.44 (s, 3H), 2.67 (s, 3H), 2.78 (d, J = 8 Hz, 1H), 3.07 (m, 1H), 3.71 (s, 3H), 4.08 (m, 1H).

   5b: oil, $[\alpha]_D^{25}$ — 10.8° (c 0.591, $CHCl_3$) *m/e* 367; NMR δ 0.94 (s, 3H), 0.96 (d, J = 6 Hz, 3H), 1.18 (s, 3H), 1.45 (s, 3H), 2.62 (s, 3H), 2.88 (d, J = 8 Hz, 1H), 3.25 (m, 1H), 3.72 (s, 3H), 4.08 (m, 1H).

   6: m. p 153 °C (CH_3CN), $[\alpha]_D^{25}$ + 106.4° (c 1.07, $CHCl_3$), *m/e* 339; NMR δ 0.95 (s, 3H), 0.95 (d, J = 6 Hz, 3H), 1.31 (s, 3H), 1.37 (s, 3H), 2.36 (m, 1H), 2.65 (s, 3H), 3.74 (d, J = 6 Hz, 2H), 4.09 (m, 1H).

   7: m. p. 114—115 °C (hydrate from hexanes); $[\alpha]_D^{25}$ + 53.3° (c 0.99, $CHCl_3$); *m/e* 493; NMR: δ 0.84 (d, J = 7 Hz, 3H), 0.86 (s, 3H), 1.17 (s, 3H), 1.32 (s, 3H), 2.47

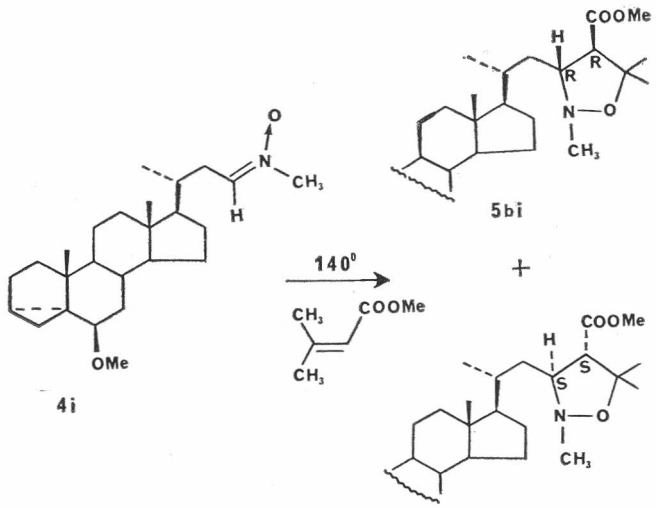
(s, 3H), 2.59 (s, 3H), 3.96 (dd, $J = 4$, 10Hz, 1H), 4.09 (m, 2H), 7.37 (d, $J = 8$ Hz, 2H), 7.79 (d, $J = 8$ Hz, 2H).

8: oil, *m/e* 328; NMR: δ 0.95 (s, 3H), 0.96 (d, $J = 6$ Hz, 3H), 1.02 (d, $J = 7$ Hz, 3H), 1.11 (s, 3H), 1.27 (s, 3H), 3.26 (m, 1H), 3.65 (s, 3H), 4.09 (m, 1H).

9: m. p. 180—181 °C (EtOAc), $[\alpha]_D^{25} + 4.79°$ (c 1.04, $CHCl_3$); NMR: δ 0.83 (d, $J = 7$ Hz, 3H), 0.94 (s, 3H), 0.94 (d, $J = 6$ Hz, 3H), 1.12 (s, 3H), 1.18 (s, 6H), 2.61 (dd, $J = 8$, 11 Hz, 1H), 4.09 (m, 1H).

10: m. p. 103—104 °C (hexanes), $[\alpha]_D^{25} + 2.01$ (c 1.05, $CHCl_3$); NMR: δ 0.95 (s, 3H), 1.00 (d, $J = 7$ Hz, 3H), 1.01 (d, $J = 6$ Hz, 3H), 1.13 (s, 3H), 1.17 (s, 3H), 4.09 (m, 1H), 5.31 (m, 2H).

10. We also carried out this cycloaddition using the i-steroid nitrone *4i* as a model.[11]



The structures of the two crystalline products *5ai* and *5bi* were established by X-ray.

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IZVOD

Stereo-kontrolisana totalna sinteza 1α,25-dihidroksi-ergokalciferola

Andrew D. Batcho, John F. Sereno, Enrico G. Baggiolini, Bernard M. Hennessy i Milan R. Uskoković

Opisana je stereohemijski kontrolisana totalna sinteza metabolita vitamina D_2, 1α,25-dihidroksi-ergokalciferola (*1*), koja se sastoji u kuplovanju ranije opisanog sintrona prstena A *2* i podesno funkcionalisanog C—D dela molekula *3*. U ključnoj fazi, stereohemijska kontrola postignuta je korišćenjem termičke reverzibilnosti [3 + 2]-cikloadicije metil-β,β-dimetil-akrilata i C—D C-23 nitrona *4*; postali metil--estar C-24S-izoksazolidin-karbonske kiseline *5a*, redukcijom a zatim eliminacijom nitronske funkcije, lako se transformiše u željeni C—D prekusor.