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A Novel Synthesis of an A-Ring Precursor to 1α-Hydroxyvitamin D

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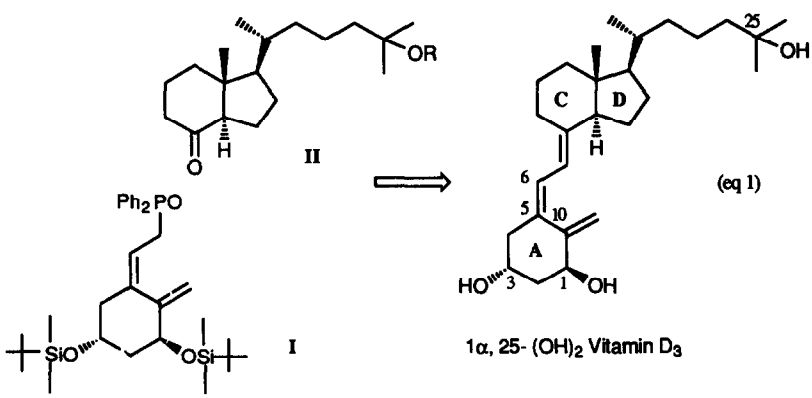
***Abstract** : A novel synthesis of the known, 1α-hydroxyvitamin D A-ring precursor **10**, in racemic form, is described based upon (i) the stereoselective cycloaddition of allene-dienophile **2** onto 3-trimethylsilyloxyfuran **1** to give **3**, and (ii) the samarium iodide induced reductive opening of the oxygen bridge in **4** to yield hydroxyketone **5**, as key-steps.*

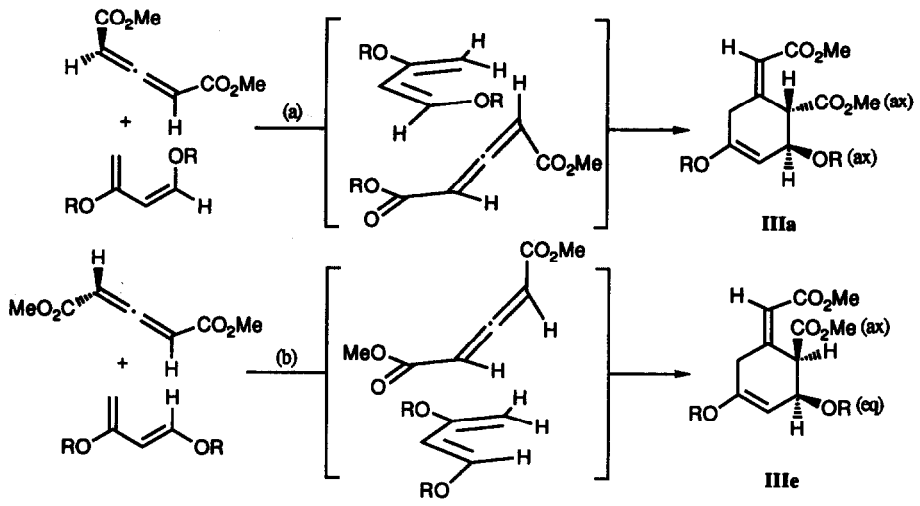
Since the discovery of 1α,25-dihydroxyvitamin D_3 as the active metabolite of the vitamin many synthetic efforts have been produced in this area.[1,2] The more recent discovery of a much expanded spectrum of biological activities has further initiated an impressive search for analogues with potential therapeutic activity.[3,4]

Basic strategies for the construction of the 1α-hydroxylated vitamin D skeleton include : (i) partial syntheses involving the introduction of the 1α-hydroxy group onto the vitamin D structure or the photochemical cleavage of an adequately functionalized 7-dehydrocholesterol derivative, followed by the spontaneous rearrangement of the resulting previtamin triene to vitamin D;[5] (ii) total syntheses which mostly involve the coupling of an A-ring precursor with the CD-ring part of the vitamin D skeleton, hence offering the advantages of convergency and flexibility.[6] Most popular among the latter is the Wittig-Horner reaction of the lithium carbanion derived from phosphine oxide **I** (equation 1),[7] based upon the original approach of Lythgoe and co-workers.[8] In this paper we wish to describe a novel stereoselective synthesis of (±)-**10**, a known precursor of **I**.[9]



(eq 1)

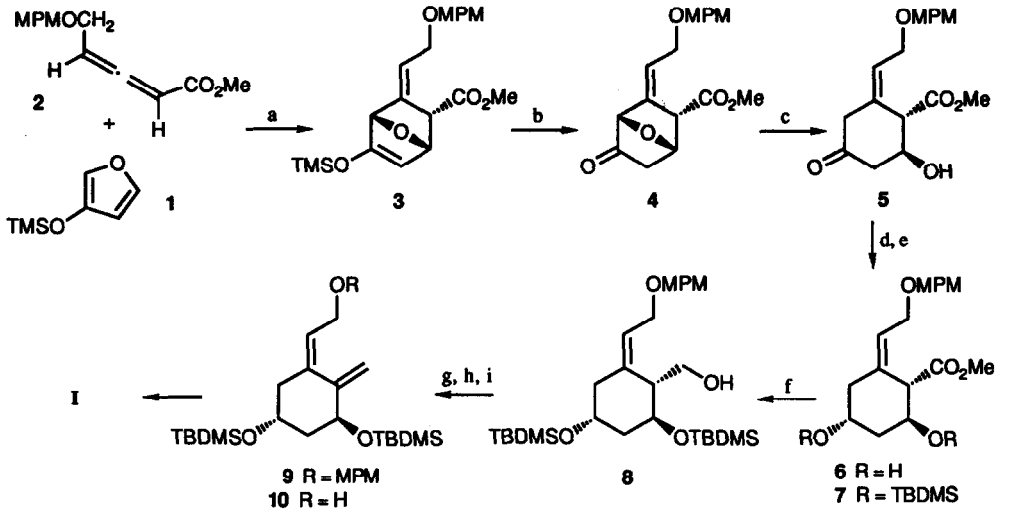
Central in the strategy stands the stereoselective cycloaddition between a 1,3-disubstituted allene and a 1,3-dioxydiene to give an adequately functionalized, full A-ring skeleton possessing all the required stereochemical features, in particular the (Z)-configuration at $\Delta^{5,6}$ and the 1α-configuration at C-1.



Scheme 1

As shown in scheme 1 obtention of the latter configuration can involve the combination of either (a) the (M)-allene with the (Z)-diene to give **IIIa**, or (b) the (P)-allene with the (E)-diene to give **IIIe**. In both cases the shown stereochemical features, i.e., the relative configuration at stereocenters C-1 and C-10, and the (Z)-configuration at the $\Delta^{5,6}$-bond, result from the preferred endo-addition to the least hindered side of the allene.[10] In both cases we note that the absolute configuration at C-1 is determined by the chirality of the allene (via C-10). The further obtention of the *trans*-relation between the protected hydroxy groups in **10** will result from an internal assisted hydride reduction requiring the axial orientation of the hydroxygroup at C-1 (vide infra); this orientation, however, would be available in **IIIa**, but not in **IIIe**, since it was anticipated that the severe allylic strain caused by the substituent at C-6 would dominate the ring conformation by enforcing the methoxycarbonyl group at C-10 in the axial position.[11] Following the above consideration a diene of the (Z)-type is thus required. Because of our longstanding interest in the use of furan as a diene in (intramolecular) Diels-Alder reactions,[12] we decided to investigate the potential of 3-trimethylsilyloxyfuran in the present context.[13,14] The resulting route is shown in scheme 2.

The cycloaddition between the known 3-trimethylsilyloxyfuran (**1**)[15] and an excess of the p-methoxyphenylmethyl protected methyl 5-hydroxypenta-2,3-dienoate (**2**)[16] leads smoothly (4 days, r.t., ether) to adduct **3** and, after methanol work-up, to bicyclic ketone **4** in 53 % isolated yield.[17] Only one diastereomer was detected, the moderate yield being due to the slow decomposition of the allene. The shown configuration in **4** is substantiated by the vicinal coupling J(1,10) = 5.7 Hz.[10,18] The subsequent crucial reductive opening of the oxygen bridge in **4** was realized in good yield (56 % isolated **5** with 22 % of starting material)[17] with samarium(II)iodide (THF MeOH, -78°C),[19] followed by careful low temperature acid quenching (2 equivs of acetic acid in THF, -90°C). Under these conditions no double bond isomerization is observed. The *trans*-diaxial conformation of **5** follows from the vicinal coupling J(1,10) = 3.8 Hz). The subsequent reduction of the hydroxy ketone **5** with aluminum hydride (THF, -78°C) led stereoselectively to the *trans*-diol **6** (62 % yield together with some starting material)[17] presumably via prior complexation with the axially oriented 1α-hydroxy group.[20] The equatorial orientation of the 3-hydroxy group follows from ^{1}H NMR analysis.[17]



(a) Et_2O, r.t., 4 days; (b) MeOH, r.t., 10 min (53 %); (c) SmI_2, THF, -78°C, 10 min; CH_3COOH, THF, -90°C (56 %); (d) AlH_3, THF, -78°C, 70 min (62 %); (e) t.butyldimethylsilyltriflate, 2,6-lutidine, CH_2Cl_2, r.t., 105 min (71 %); (f) LAH, THF, r.t., 30 min (70 %); (g) o-nitrophenyl selenocyanate, n.Bu_3P, THF, r.t., 2 h (55 %); (h) H_2O_2, CH_2Cl_2, r.t., 18 h (70 %); (i) DDQ, H_2O, CH_2Cl_2, r.t. (50 %).

Scheme 2

After protection of the diol (t-butyldimethylsilyltriflate, dichloromethane; 71 % yield),[21] the ester in **7** was reduced (lithium aluminum hydride, THF, r.t.; 70 % yield), and the resulting primary alcohol **8** dehydrated ((i) : *o*-nitrophenyl selenocyanate; (ii) : hydrogen peroxide)[22] to **9**. Eventual deprotection (DDQ, dichloromethane-water)[23] led to the alcohol **10**, the structure of which was fully confirmed by spectral comparison with authentic (+)-**10**.[24]

The practical importance of the above route mainly resides in the possibility of including modifications which could be useful for the preparation of 1α-hydroxylated A-ring analogues. Obviously, a further requirement is the elaboration of the enantioselective version which is presently under development.[25]

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