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Photochemical Synthesis of C/D-Ring Synthons of Vitamin D

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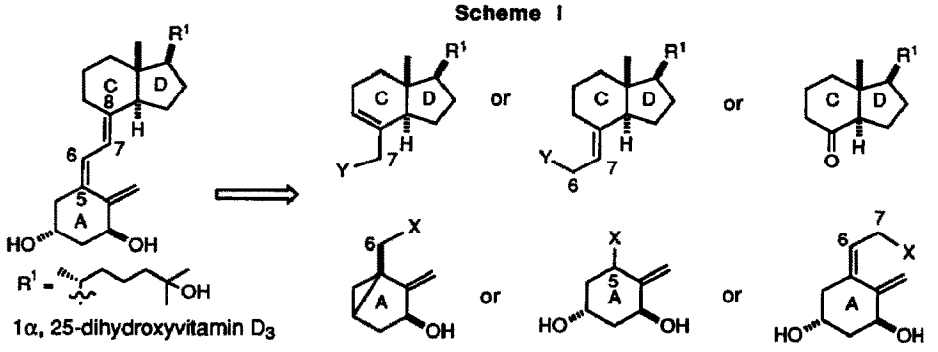
Abstract: Beginning with a steroid-5-ene, C/D-ring synthons of vitamin D are readily prepared via ozonization followed by a Norrish II photoelimination reaction.

Analogs of 1α-hydroxyvitamin D continue to display an increasing breadth of biological activities. In addition to its traditional role in calcium homeostasis,[1] the recent finding of therapeutic activity related to psoriasis,[2] to cellular differentiation of cancer cells,[3-5] including breast cancer,[6] and to alteration of the immune response of lymphocytes[7] are a few examples of other biological activities.

A drawback to the use of vitamin D analogs as therapeutic agents is that they produce hypercalcemia at microgram dosage per day. The continual need for the synthesis of new analogs calls attention to the development of new synthetic strategies. Current synthetic methodologies can be categorized into two classes. The classical approach involves photochemical ring opening of a steroidal precursor,[8] a route which does not function well in the presence of a 1α-hydroxy grouping in the required provitamin D. An alternate approach is based on the Lythgoe convergent methodology.[9] This approach offers great flexibility to include modified A-rings and C/D-ring synthons into the synthetic Scheme I. A wide variety of useful routes to ring A synthons have been reported, i.e., cyclohexane derivatives[10] and bicyclo[3.1.0]hexane derivatives.[11] Syntheses directed towards the C/D-ring unit[12] have not proved to be efficient processes. To date, degradation of vitamins D_2 and D_3 has been used to supply the C/D-ring units for most of the convergent total syntheses of vitamin D analogs. We wish to report a new, highly efficient process which yields a wide variety of highly fuctionalized C/D-ring synthons, starting with a variety of readily available steroidal olefins.

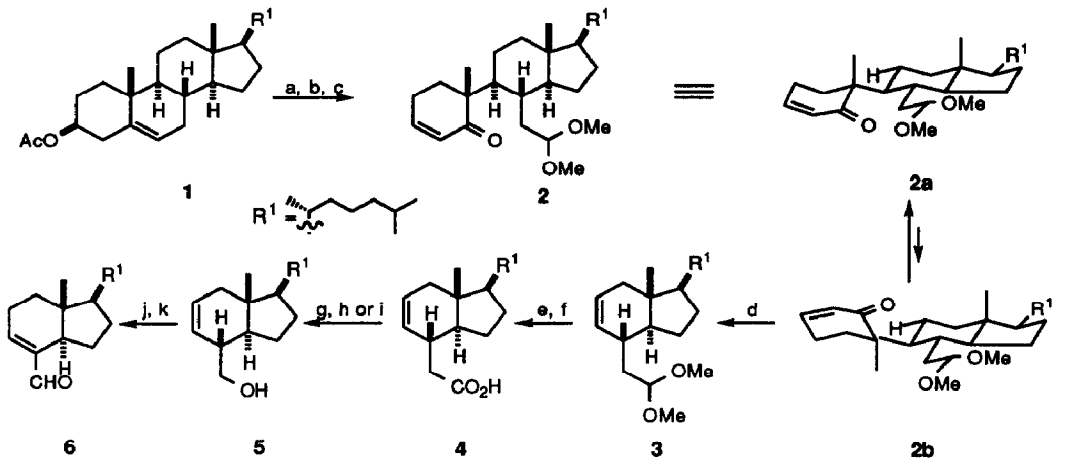
A variety of C/D synthons can be prepared from photochemical degradation of seco-steroids derived from Δ^5-steroidal olefin derivatives, a process known to give, in low yield, a C/D ring derivative from 5,6-seco-cholest-3-en-5-on-6-aldehyde via Norrish type II cleavage.[13] Modification of this Norrish type II reaction allowed synthetic access to a variety of ring C/D synthons in good yield as outlined in Scheme II. Ozonolysis of

Scheme I



cholesteryl acetate (**1**) in dichloromethane followed by reduction with dimethylsulfide, methyl acetal formation of the C-6 aldehyde with trimethyl orthoformate/methanol, and elimination of the acetoxy group with sodium methoxide gave **2** in 65% overall yield. Irradiation of **2** in hexane at room temperature using a

Scheme II

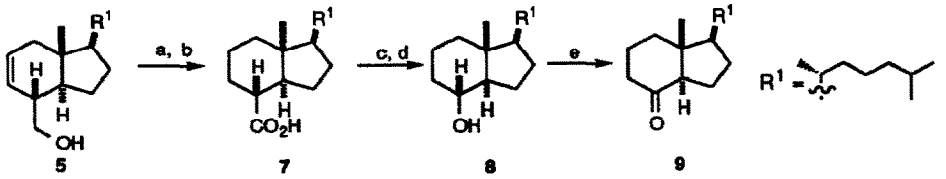


(a) O_3, CH_2Cl_2/CH_3OH (4:1); $(CH_3)_2S$ (b) $(CH_3O)_3CH/CH_3OH$ (7:3), *p*-Tos-OH (c) CH_3ONa, CH_3OH (d) hv, hexane (e) HCl, H_2O-THF (f) CrO_3-H_2SO_4, acetone (g) DCC, 4-DMAP, *N*-hydroxy-2-thiopyridone, CH_2Cl_2 (h) $(PhS)_3Sb$, CH_2Cl_2 (i) O_2, 2-methyl-2-propanethiol, CH_2Cl_2; $(CH_3)_2S$ (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (k) HCl, H_2O-THF

450 W Hanovia lamp with a Pyrex filter afforded **3** in 79% yield. It was noted that the photochemical degradation was more efficient when the reaction was carried out in refluxing octane, especially in experiments with a scale larger than 50 g. This observation can be explained by the γ-hydrogen abstraction which will occur only through the higher energy conformer **2b**.[14] The Barton decarboxylation-hydroxylation protocol was used to degrade the protected acetaldehyde side chain by one carbon.[15] Hydrolysis of acetal **3** with aqueous hydrochloric acid in tetrahydrofuran followed by Jones oxidation of the corresponding aldehyde gave **4** in 85% yield.[16] Treatment of acid **4** with *N*-hydroxy-2-thiopyridone, dicyclohexylcarbodiimide, and 4-dimethylaminopyridine followed by oxidative cleavage of the corresponding thiohydroxamate ester with antimony phenylsulfide or singlet oxygen afforded alcohol **5** in 85% and 88% yield, respectively.[17] Swern oxidation of **5** followed by isomerization of the resulting β,γ-unsaturated aldehyde gave the desired C/D-ring of vitamin D synthon aldehyde **6** in 43% yield. Structure of **5** was confirmed using the reaction sequence outlined in Scheme III. Hydrogenation of **5** using palladium on carbon as catalyst in methanol followed by Jones oxidation gave **7** in 86% yield. Oxidative cleavage of acid **7** to **8** was accomplished in 73% yield following a protocol similar for the conversion of **4** to **5**. Swern oxidation of **8** gave the known Grundmann's ketone (**9**) in 30% yield with 45% recovery of the starting alcohol **8**.[18]

Attention was next turned to the application of the current approach to other steroidal olefins to permit modification of side chain of C/D-ring synthons and the studies are outlined in Scheme IV. Olefin **10** and **11**

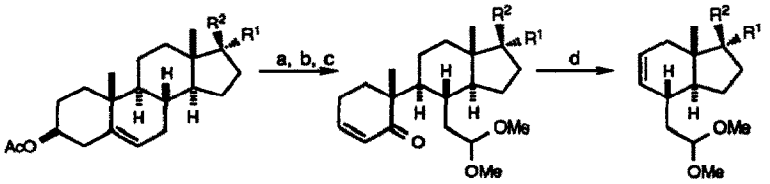
Scheme III



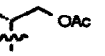
(a) H_2, Pd-C, MeOH (b) CrO_3-H_2SO_4, acetone. (c) DCC, 4-DMAP,*N*-hydroxy-2-thiopyridone, CH_2Cl_2. (d) O_2, 2-methyl-2-propanethiol, CH_2Cl_2; $(CH_3)_2S$. (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2

derived from stigmasterol[19] and 5-androsten-3β-ol-17-one 3-acetate, respectively, and 5-androsten-3β, 17β-diol diacetates (**12**) were converted to C/D-ring synthon **16, 17, 18** using the same approach outlined above with 38%, 42%, and 27% overall yield respectively. These C/D-ring synthons can also be further degraded by one carbon to derivatives related to aldehyde **6** and, in turn, to bisnor derivatives related to **9**.

Scheme IV



10, 11, 12 **13, 14, 15** **16, 17,18**

10, 13, 16 R^1 = H, R^2 = 

11, 14, 17 R^1 = OMe, R^2 = OMe

12, 15, 18 R^1 = H, R^2 = OAc

(a) O_3, CH_2Cl_2-CH_3OH (4:1); $(CH_3)_2S$ (b) $(CH_3O)_3CH/CH_3OH$ (7:3), *p*-Tos-OH
(c) CH_3ONa, CH_3OH (d) hv, hexane

In summary, the generality has been demonstrated for a facile and efficient route to C/D-ring synthons of vitamin D hormone. In addition, the units can serve as starting materials for many ring C substituted analogs

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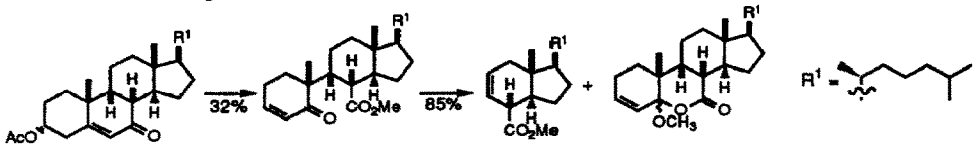

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