Reductive Cleavage of the 9,10-Bond in 11-Oxygenated Steroids: a New Method for the Partial Synthesis of the Vitamin D Skeleton

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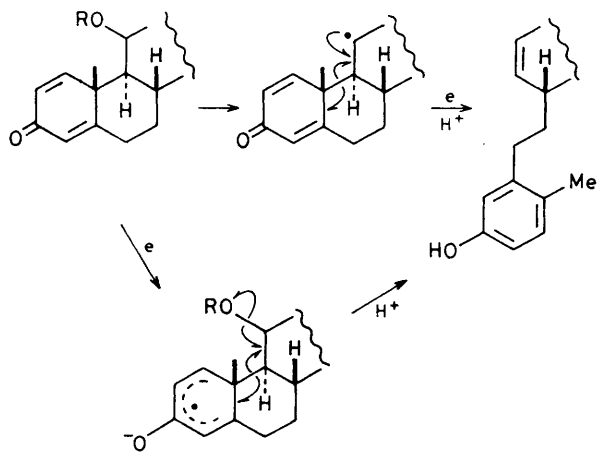
11-Oxygenated steroids with a ring A dienone system are reduced in non-protic media with cleavage of the 9,10-bond, and the resulting 9,10-secosteroids (**2**) or (**5**) were converted into 9,10-secocholesta-1,3,5(10)-triene-3-ol (**12**), an unknown isomer of cholecalciferol (vitamin D_3).

Of the numerous chemical and biochemical transformations of steroids, the conversion of the intact steroid carbon skeleton into 9,10-secosteroids is the important key to the partial synthesis of vitamin D structures.[1] The classical method is the photochemical ring B homoannular diene (usually ergosterol or 7-dehydrocholesterol) conversion, first into pre-

vitamin D, thence to *cis*-D_3 and *trans*-D_3, with concomitant photochemical equilibration to tachysterol and thermal equilibration to lumisterol.[2,3] The other method of synthesizing vitamin D compounds is through total synthesis. The exemplary methods developed by Lythgoe successfully illustrate this approach.[4] Another, less well known way, involves a series of microbiological oxidations that result in 9α-hydroxylation, dehydrogenation of ring A to the dienone oxidation level, followed by a vinylogous retro-aldol reaction to give the vitamin D carbon skeleton with the A-ring aromatized.[5]

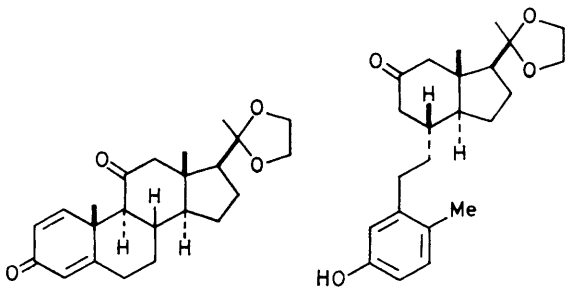


Scheme 1

Here we report an entirely new approach to this area that takes advantage of the readily available 11-oxygenated steroids, and the possibility of either a radical, or radical-anion fragmentation of the 9,10-bond to give the basic vitamin D system, with the appended A-ring aromatized (Scheme 1).

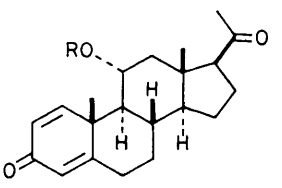
We considered that a 3,11-diketo-1,4-diene steroid would be capable of reduction using a dissolving metal procedure, with rupture of the 9,10-bond. Exposure of pregna-1,4-diene-3,11,20-trione 20-ethyleneacetal (**1**) to Li–NH_3 (no proton source) gave the 9,10-secosteroid (**2**) (70%),[6] m.p. 139—141 °C, $[\alpha]_D^{25}$ + 12.1° (*c* 2.0, $CHCl_3$), whereas the methanesulphonate of 11α-hydroxypregna-1,4-diene-3,20-dione, under the same reduction conditions gave a complex mixture with no evidence of the 9,10-secosteroid system. Treatment of 11α-hydroxypregna-1,4-diene-3,20-dione (**3**) with CS_2–1,5-diazabicyclo[4.3.0]non-5-ene(DBN)–dimethylformamide(DMF)–MeI gave the 11α-xanthate (**4**),[7] which on treatment with Bu^n_3SnH–azobisisobutyronitrile (AIBN) (catalytic amount of the latter) in toluene heated at reflux for 40 h gave the 9,10-secosteroid (**5**) (25%), m.p. 153 °C, $[\alpha]_D^{25}$ −18.1° (*c* 2.4, $CHCl_3$), and the reduction product pregna-1,4-diene-3,20-dione (25%). Treatment of (**4**) with Li–NH_3 gave a complex mixture containing neither (**5**) nor the pregnadienedione, whereas when (**4**) was treated with SmI_2 in tetrahydrofuran (THF) at 20 °C for 5 min the 9,10-secosteroid (**5**) was formed in 88% yield.[8] It should be noted that when similar reductions were carried out on 1,2-dihydro, or 6,7-dehydro derivatives of (**4**), no cleavage of the 9,10-bond was observed.

Treatment of (**2**) with Me_2SO_4–K_2CO_3–acetone at 20 °C, followed by Wolff–Kishner reduction, and mild acid hydrolysis,

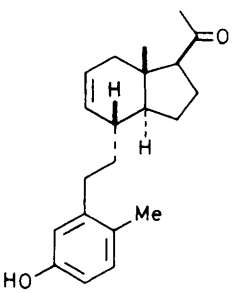


(**1**)

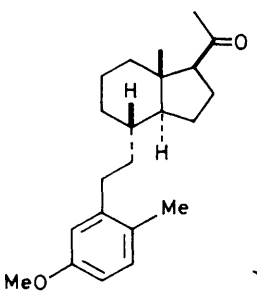
(**2**)



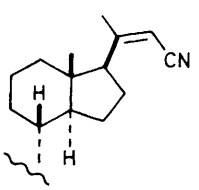
(**3**) R = H
(**4**) R = CS_2Me



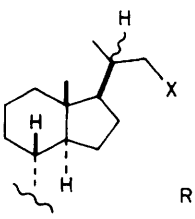
(**5**)



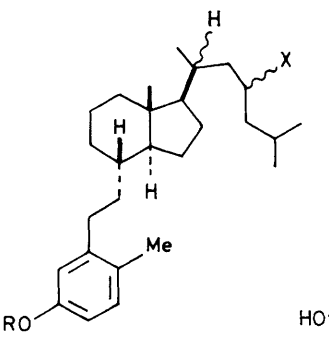
(**6**)



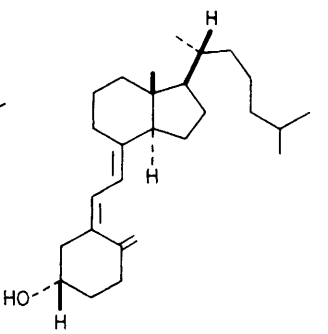
(**7**)



(**8**) X = CN
(**9**) X = CHO



(**10**) R = Me, X = OCS_2Me
(**11**) R = Me, X = H
(**12**) R = H, X = H



(**13**)

gave (**6**), $[\alpha]_D^{25}$ + 28° (*c* 2.42, $CHCl_3$). Methylation of (**5**) with Me_2SO_4–NaH–THF–imidazole at 20 °C, followed by hydrogenation, also gave (**6**), thus confirming the structure of (**5**) as a 9,10-secosteroid.

Conversion of (**6**) into 9,10-secocholesta-1,3,5(10)-triene-3-ol (**12**), a previously unknown isomer of cholecalciferol (**13**) was carried out in the following manner. Treatment of (**5**) with $(EtO)_2P(O)CH_2CN$–NaH–$CH_2(OMe)CH_2OMe$ gave (**7**) (86%) $[\alpha]_D^{25}$ −49.4° (*c* 5.0, $CHCl_3$), which was hydrogenated (10% Pd–C) to give (**8**) (90%) as a mixture (*ca.* 1 : 1) of epimers at C-20. The separated C-20 epimers (h.p.l.c.) were individually treated with di-isobutylaluminium hydride at −78 °C to give the aldehydes (**9**). Treatment of (**9**) with Bu^iMgBr–Et_2O, followed by conversion of the resulting alcohols into their respective xanthates (**10**) (77%) (CS_2–DBN–DMF–MeI), and deoxygenation with Bu^n_3SnH–AIBN(catalytic amount)–toluene at reflux,[7] provided (**11**)(95%). Exposure of (**11**) to BBr_3–CH_2Cl_2 at 0 °C completed the sequence to give (**12**) (76%) {$[\alpha]_D^{25}$ −15.95° (*c* 4.8, $CHCl_3$) for the 20*S* unnatural isomer; $[\alpha]_D^{25}$ −2.19° (*c* 4.19, $CHCl_3$) for the 20*R* natural isomer}. The overall yield of (**12**) from (**1**) is 13.7%.† Interestingly, treatment of (**13**) with $RhCl_3$–EtOH in a sealed tube at 100 °C did not give any (**12**).[9]

This method of cleaving the 9,10-bond in 11-oxygenated steroids should find applications in the synthesis of vitamin D_3 analogues. The natural isomer (**12**) (20*R*) exhibited modest stimulation of intestinal calcium absorption, and bone calcium mobilization, whereas the unnatural isomer (**12**) (20*S*) did not.

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† All new compounds gave satisfactory ^1H n.m.r. and i.r. spectra, and microanalytical data.

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