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A Novel Method for the Synthesis of a C/D-Ring Synthon of Vitamin D Derivatives From Hyodeoxycholic Acid

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Abstract: A new C/D ring synthon of vitamin D is readily obtained from hyodeoxycholic acid via permanganate acid oxidation, Jones oxidation, elimination of an acetoxy group and a Norrish type II photochemical reaction, in 47% overall yield.

In recent years, the vitamin D research area has been stimulated by the discoveries that 1 α ,25-dihydroxyvitamin D_3, the active metabolite of vitamin D_3, in addition to the classical roles of regulating calcium and phosphorus metabolism,[1] has a much broader spectrum of activity than originally thought, such as promoting cell differentiation and inhibiting cell proliferation.[2,3] This biological significance and medical needs have led efforts toward the search for analogues which display potent cell differentiation and antiproliferation activity without the toxic hypercalcemia associated with the normal calcitropic effects of 1,25-dihydroxyvitamin D_3.[4]

The continual need for the synthesis of new analogues has resulted in an enhanced interest in the development of new synthetic strategies. Comparing the classical approaches, Lythoge's convergent methodology of coupling the A-ring with a C/D-ring fragment offers great flexibility.[5,6] A variety of efficient routes to A-ring synthons have been reported,[6,7] but the C/D-ring synthons used in most convergent total syntheses of vitamin D analogues were degraded from vitamin D_2 and D_3. A variety of C/D-ring synthons can also be prepared from the photochemical degradation of 5,6-seco-steroids derived from Δ^5-steroidal derivatives via a Norrish type II cleavage.[8,9,10] However, most of these are difficult to modify on the saturated side-chain. In this communication, we wish to report a novel method for preparing a new C/D-ring fragment from hyodeoxycholic acid, a readily available steroid.

As indicated in scheme 1, the compound **2** was obtained from hyodeoxycholic acid by a literature method[11,12] in 98% yield. Oxidation of **2** using $KMnO_4/H_2SO_4$ in CH_2Cl_2/acetone at room temperature afforded the 5,6-epoxide quantitatively, in which the 5 β , 6 β -isomer **3** is the predominant product.[13] Treatment of the crude epoxide with Jones reagent at 50℃ afforded the 5,6-seco-product **4** in 91% yield. It was observed that the Jones oxidation of **3** occurred in two steps. The intermediate 5-hydroxy-6-one could be obtained by controlling the amount of Jones reagent. Elimination of the acetoxy group with TsOH/t-BuOH gave the product **5** in 96% yield. Compound **4** was treated with CH_3OH/HCl in a preliminary study, but the yield of **5** was poor due to the addition of methanol to the double bond of **4**. When treating **4** with concentrated hydrochloric acid in t-BuOH, the addition product was avoided, however the 24-carboxylate group was partly hydrolyzed. Irradiation of **5** in cyclohexane/ethyl acetate using 400w high pressure mercury lamp[10] afforded the novel C/D-ring fragment **6** in

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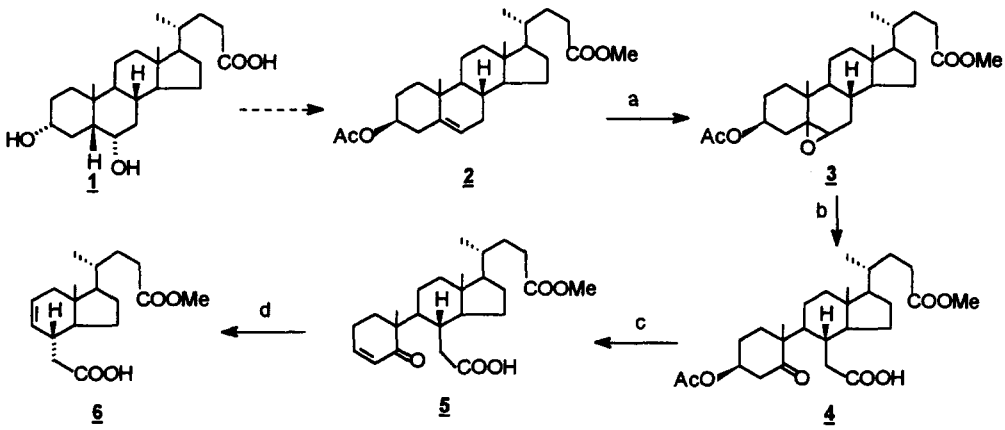
55% yield. Compound **6**, with two side chains, can be easily modified into various C/D-ring synthons with Barton free-radical chemistry. Further modifications of **6** are currently under investigation.



a. $KMnO_4$, H_2SO_4, CH_2Cl_2/acetone, r.t. b. Jones regent, acetone 50℃. c. TsOH/t-BuOH, Under reflux
d. Cyclohexane/ethyl acetate, hv.

Scheme 1

In summary, a new C/D-ring synthon of vitamin D is readily prepared from hyodeoxycholic acid in 7 steps and 47% overall yield.

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14. **2**: ^{1}HNMR($CDCl_3$, 400MHz) δ 0.69(s, 3H, 18-CH_3), 0.91(d, 3H, J=6.0Hz, 21-CH_3), 1.01(s, 3H, 19-CH_3), 2.03(s, 3H, CH_3CO), 3.66(s, 3H, OCH_3), 4.62(m, 1H, 3 α -H), 5.41(m, 1H, 6-H). **3**: ^{1}HNMR($CDCl_3$, 400MHz) δ 0.64(s, 3H, 18-CH_3), 0.91(d, 3H, J=6.0Hz, 21-CH_3), 1.00(s, 3H, 19-CH_3), 2.02(s, 3H, CH_3CO), 3.07(d, 1H, J=2.4Hz, 6 α -H), 3.66(s, 3H, OCH_3), 4.78(m, 1H, 3 α -H). **4**: ^{1}HNMR($CDCl_3$, 400MHz) δ 0.68(s, 3H, 18-CH_3), 0.91(d, 3H, J=6.0Hz, 21-CH_3), 1.03(s, 3H, 19-CH_3), 2.02(s, 3H, CH_3CO), 3.66(s, 3H, OCH_3), 5.39(m, 1H, 3 α -H), 8.42(br, 1H, COOH). **5**: ^{1}HNMR($CDCl_3$, 400MHz) δ 0.68(s, 3H, 18-CH_3), 0.92(d, 3H, J=6.0Hz, 21-CH_3), 1.09(s, 3H, 19-CH_3), 5.88(d, 1H, J=9.6Hz, 1H, 4-H), 6.77(m, 1H, 3-H), 8.75(br, 1H, COOH). **6**: ^{1}HNMR($CDCl_3$, 400MHz) δ 0.70(s, 3H, 7a-CH_3), 0.93(d, 3H, J=6.4Hz, 1'-CH_3), 1.05-1.50(m, 6H, 2-H, 3-H & 2'-H), 1.60-2.00(m, 3H, 1-H, 3a-H & 1'-H), 2.10-2.30(m, 4H, 3'-H & -CH_2COOH), 2.10-2.48(m, 3H, 4-H & 7-H), 3.67(s, 3H, OCH_3), 5.53(d, J=10.0Hz, 1H, 5-H), 5.61(m, 1H, 6-H), 8.67(w, 1H, COOH); ^{13}CNMR($CDCl_3$, 100MHz) δ 11.7, 17.9, 24.8, 27.6, 30.9, 31.0, 35.1, 35.9, 38.7, 41.5, 41.8, 50.9, 51.5, 55.8, 127.3, 128.7, 174.8, 179.0.