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A synthesis of 17-*epi*-calcidiol

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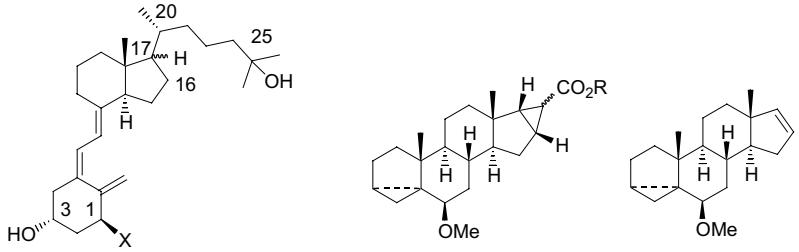
Abstract—The first synthetic approach to 17-*epi*-calcidiol **4** and congeners is presented. Key steps of the synthesis involve Pd-catalyzed reaction of the androst-16-ene derivative **6** with alkyl diazoacetates producing the respective cyclopropane derivatives **5**, and lithium in liquid ammonia reduction of **5** leading to 17α-pregnane-20-carboxylic acid derivatives **9**. The side chain was attached to ester **19** in a known manner.

Calcitriol **1** (Fig. 1), the hormonally active metabolite of calciol (vitamin D_3), shows a broad spectrum of biological activities.[1] Its prime function consists in providing adequate calcium and phosphorus concentration in circulating fluids to support skeletal mineralization. Non-calcemic activities of **1** proved useful in controlling various human diseases, including skin and immune system metabolic disorders. Calcidiol **2** is the biosynthetic precursor of calcitriol showing similar but weaker biological activities. Several synthetic analogues of calcitriol are presently available as drugs or have been accepted for advanced clinical trials[2] and have stimulated the search for new structures having improved therapeutic properties.[3] In continuing our work on synthesis and biological evaluation of calcitriol stereoisomers[4] we were interested in epimers of the natural products, 17-*epi*-calcitriol **3** and 17-*epi*-calcidiol **4**. It was reasoned that **4** will be accessible from alkyl 16α,20-cyclo-17α-pregnane-21-carboxylates **5** by reductive fission of the C16–C20 bond, followed by side chain elaboration. Intermediates **5**, in turn, would be obtained by diastereoselective cyclopropanation of the easily available androstane derivative **6**. In the present communication we report the first synthesis of 17-*epi*-calciol derivatives and, en route, the synthesis of some 17-*epi*-cholesterol derivatives.

The starting material for the synthesis, **6**, was prepared by reduction of 17-iodo-3α,5-cyclo-5α-androst-16-ene[5] with sodium in ethanol. To a solution of **6** in



1, 17α-H, X = OH, Calcitriol
2, 17α-H, X= H, Calcidiol
3, 17β-H, X = OH, 17-epi-Calcitriol
4, 17β-H, X = H, 17-*epi*-Calcidiol

5 **6**

Figure 1. Structures of calcitriol (1α,25-dihydroxy vitamin D_3) **1**, calcidiol **2**, their 17-*epi*-analogues **3** and **4**, and the respective synthetic precursors.

Keywords: Vitamin D synthesis; Cyclopropanation; Alkyl diazoacetates; Lithium in liquid ammonia.
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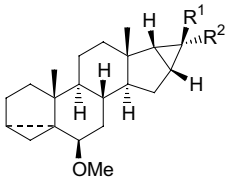
dichloromethane (DCM) containing palladium(II) acetate,[6] a solution of *tert*-butyl diazoacetate in DCM was slowly added[7] by means of a syringe pump. A product was obtained to which structure **5a** (Scheme 1) was assigned on the basis of its ^{1}H and ^{13}C NMR spectra. Product **5a** was contaminated with side products derived from the diazoester (ca. 5%) and could not be purified by column chromatography. Treatment of **5a** with sodium methoxide in methanol at reflux followed by chromatography afforded pure methyl ester **5d** in a 93% yield from **6**.

Palladium-catalyzed reaction of **6** with ethyl diazoacetate (commercial reagent) provided a mixture of cyclopropane derivatives **5b** and **5c** differing in configuration at C20, in a ratio of ca. 7:1 (by ^{1}H NMR). This mixture was subjected to methanolysis to give a single isomer **5d** in 89% yield from **6**. Similarly, **6** and methyl diazoacetate gave **5d** and **5e** in a ratio of 7:1. Treatment of *tert*-butyl ester **5a** (ca. 90% pure) with lithium in liquid ammonia[8–10] afforded a mixture of products. A neutral fraction, isolated in ca. 50% yield, was reduced with $LiAlH_4$ to give a mixture of alcohols that were identified as **7** (36% yield) and **10** (11% yield). The acid fraction contained mainly compound **12**. No product of alternative fission of the C17–C20 bond was detected. It was subsequently found that reduction of methyl (**5d**) or ethyl esters (mixture **5b** and **5c**) also proceeded virtually regioselectively; moreover with these esters only small amounts of acid **12** were formed.[11] In the most efficient procedure developed (Scheme 1), methyl ester **5d** was treated with Li in liquid ammonia containing *tert*-butyl alcohol and THF at reflux temperature to give a mixture of alcohol **7**, aldehyde **8** and alcohol **10** with the cyclopropane ring retained, in nearly quantitative yield. Since chromatographic separation of the undesired component of the mixture (**10**) was problematic, the whole reduction product was oxidized[12] with DMSO in the presence of $Py{\cdot}SO_3$ and the resulting mixture of aldehydes was further oxidized with potassium permanganate in *tert*-butanol in the presence of NaH_2PO_4 to give a mixture of carboxylic acids **9** and **12**. At this stage, acid **9** was easily purified by chromatography on silica gel. Crystalline **9** was obtained in 76% overall yield from **5d**.

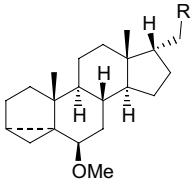
Alkylation of methyl ester **13** (obtained by esterification of **9** with diazomethane) was carried out via an earlier developed method.[13] It was rewarding to learn that the reaction affords the diastereomerically pure product (as an oil) in nearly quantitative yield. Several derivatives of this product were examined in the search for a crystalline material suitable for single crystal X-ray analysis. The structure was eventually solved[14] for acid **17** prepared as showed in Scheme 2. It revealed that the product **14** with the (20*S*) configuration was formed. X-ray analysis also confirmed the assumed stereoselectivity in the cyclopropanation reaction and the regioselectivity of the reductive cleavage of the cyclopropane ring (Fig. 2).

The side chain was attached to **14** in a known manner,[15] as illustrated in Scheme 2. Ester **14** was reduced to alcohol **15**. The respective tosylate **16** was allowed to react with the lithium derivative of 3-methyl-1-butyn-3-yl 2-tetrahydropyranyl ether, and the product **20** was subjected to catalytic reduction followed by removal of the protective groups. 25-Hydroxy-17-*epi*-cholesterol **18** was obtained in over 70% yield from **14**.

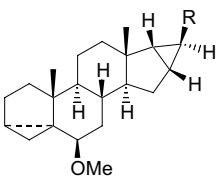
Acetate **19** was subjected to a bromination–dehydrobromination procedure[16] to give 17-*epi*-7-dehydrocholesteryl acetate **22** in ca. 40% yield. This product was hydrolyzed and the crude diol **23** was dissolved in a mix-



5a, $R^1 = COO^tBu$, $R^2 = H$
5b, $R^1 = COOEt$, $R^2 = H$
5c, $R^1 = H$, $R^2 = COOEt$
5d, $R^1 = COOMe$, $R^2 = H$
5e, $R^1 = H$, $R^2 = COOMe$

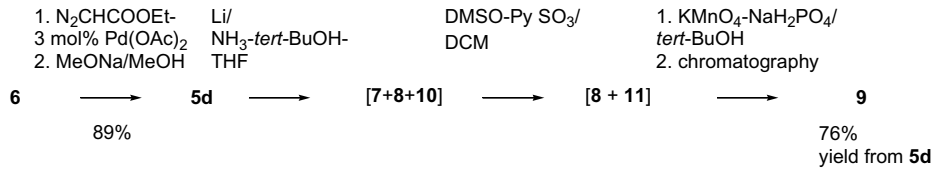


7, $R = CH_2OH$
8, R = CHO
9, $R = CO_2H$

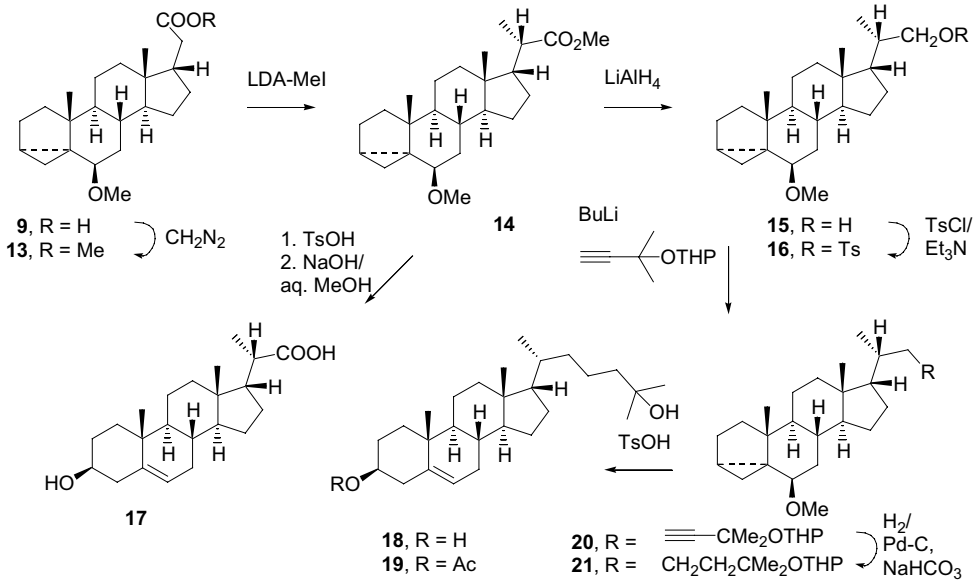


10, $R = CH_2OH$
11, R = CHO
12, $R = CO_2H$

Practical synthetic approach to intermediate **9**:



Scheme 1. 16α,17α-Cyclopregnan-20-oic acid derivatives obtained by palladium-catalyzed reaction of ene **6** with alkyl diazoacetates, and their reduction products.



Scheme 2. Synthesis of the 17-*epi*-cholesterol derivatives **18** and **19**.

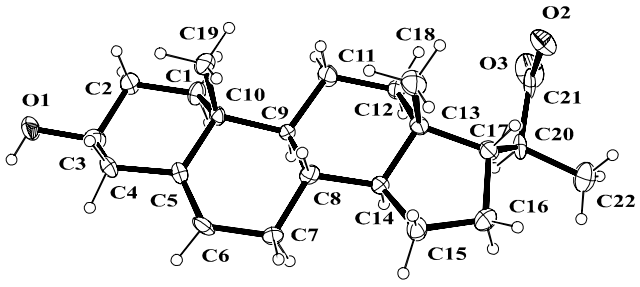


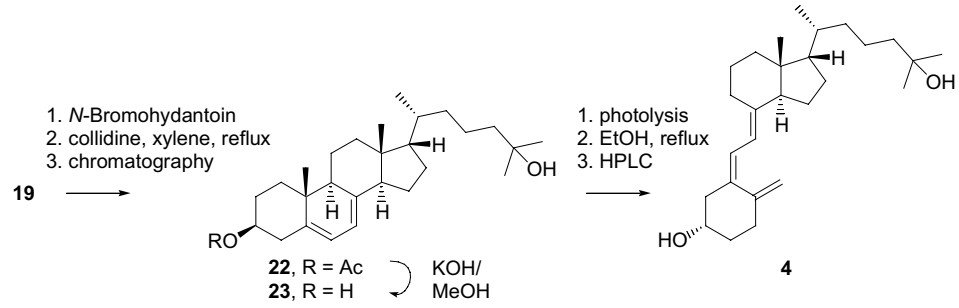
Figure 2. ORTEP plot of the X-ray structure of **17**.

ture of diethyl ether and toluene, and irradiated with a medium-pressure mercury lamp until ca. 50% of the substrate was consumed (HPLC). Then, the solvent was removed under reduced pressure and the crude product was dissolved in ethanol and heated under reflux for 6 h. The resulting product was chromatographed on a preparative HPLC column to give 17-*epi*-calcidiol **4** (Scheme 3).

The transformation of **4** into **3** and the biological activity of these compounds will be reported in due course.

Spectroscopic and analytical data of selected new compounds: Methyl 3α,5:16α:20(*S*)-bicyclo-5α,17α-pregnane-21-oate (**5d**) ^{1}H NMR (200 MHz, $CDCl_3$): 0.41 (dd, $J = 8.1$, 5.1 Hz, 1H, C4–Ha), 0.62 (t, $J = 5.1$ Hz, 1H, C4–Hb), overlapping 0.5–0.7 (m, 1H), 0.90 (s, 3H, C18–H), 1.00 (s, 3H, C19–H) overlapping 0.7–1.9 (m, 18H) 2.73 (t, $J = 2.6$ Hz, 1H, C6–H), 3.29 (s, 3H, OMe), 3.6 (s, 3H, COOMe); ^{13}C NMR (50 MHz): 13.02, 19.20, 19.66, 20.13, 21.32, 22.37, 24.82, 25.07, 27.04, 28.98, 33.16, 35.08, 35.20, 35.31, 38.32, 41.07, 43.51, 47.16, 48.61, 51.41, 56.53, 82.09, 174.58; HRMS: calcd for $C_{23}H_{34}O_3$: 358.25080; found: 358.25175.

Methyl 6β-methoxy-3α,5-*cyclo*-23,24-bisnor-5α,17α-cholane (**14**) ^{1}H NMR (200 MHz, $CDCl_3$): 0.42 (dd, $J = 8.1$, 5.1 Hz, 1H), 0.63 (t, $J = 4.9$ Hz, 1H,), 0.84 (s, 3H, C–19H), 1.00 (s, 3H, C–18H), 1.09 (d, $J = 6.8$ Hz, 3H, C–21H) overlapping, 0.7–2.1 (m, 19H), 2.28 (dq, $J = 10.5$, 6.8 Hz, 1H, C–20H), 2.76 (t, $J = 2.8$ Hz, 1H, C–6H), 3.31 (s, 3H, OMe), 3.65 (s, 3H, COOMe); ^{13}C NMR: 13.77, 17.88, 19.90, 22.12, 23.45, 25.59, 26.44, 26.49, 31.26, 34.00, 34.75, 35.86, 42.09, 36.29, 44.04, 44.32, 48.37, 51.07, 52.01, 52.62, 57.15, 82.94, 178.6; HRMS: calcd for $C_{24}H_{38}O_3$: 374.28210; found: 374.28173.



Scheme 3. Synthesis of 17-*epi*-calcidiol **4**.

17α-Cholesteryl acetate (**19**): ^{1}H NMR (500 MHz, $CDCl_3$) 0.77 (s, 3H, C–18H), 0.82 (d, $J = 6.5$ Hz, 3H, C–21H), 1.02 (s, 3H, C–19H) and 1.21 (s, 6H, C–26 and C–27H) overlapping 1.10–1.80 (m, ca. 24H), 1.80–1.90 (m, 2H), 2.03 (s, 3H, COMe), 2.29–2.35 (m, 2H), 4.56–4.64 (m, 1H, C–3H), 5.36–5.39 (m, 1H, C–5H), ^{13}C (125 MHz) 16.98, 19.29, 21.07, 21.04, 22.12, 22.27, 26.28, 27.79, 29.26, 29.27, 32.33, 32.45, 33.01, 38.12, 38.37, 43.52, 44.24, 50.13, 52.65, 52.85, 71.03, 73.97, 122.63, 139.61, 170.49. Elemental analysis: calcd for $C_{29}H_{48}O_3$ (444.69): C, 78.33, H, 10.88%; found: C, 78.37, H, 10.74%.

(5*Z*,7*E*)-3*S*-9,10-*seco*-17α-Cholesta-5,7,10(19)-trien-3β-ol (**4**): λ (EtOH) 264 nm; ^{1}H NMR (500 MHz, $CDCl_3$) 0.63 (s, 3H, C–18H), 0.86 (d, $J = 6.6$ Hz, 3H, C–21H), 1.21 (s, 6H, C–26 and C–27H) and 1.54 (s, H_2O) overlapping 1.05–1.75 (m, ca. 24H), 1.89–1.96 (m, 1H), 2.11–2.21 (m, 2H), 2.25–2.31 (m, 1H), 2.55–2.59 (m, 1H), 2.81–2.85 (m, 1H), 3.90–3.97 (m, 1H, C–3H), 4.82 (d, $J = 2.6$ Hz, 1H, C–19H*E*), 5.05 (dt, $J = 1.3$, 2.6 Hz, 1H, C–19H*Z*), 6.05 (dt, $J =$ ca. 1, 11.3 Hz, 1H, C–7H), 6.23 (d, $J =$ 11.2 Hz, 1H, C–6H); EI MS 400 (26) M^+, 382 (19) $(M-18)^+$, 367 (20) (M−18−15), 349 (17), 271 (18) (M−side chain), 253 (18) (217 − H_2O), 211 (15), 176 (22), 161 (18), 158 (60), 136 (100) (C1–C8 fragment), 118 (98) (136−H_2O); HR MS calcd for $C_{27}H_{44}O_2$: 400.3341; found: 400.3338.

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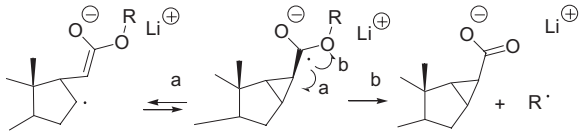
11. With ester **5a** cleavage of the C–O bond (path b) is preferred over cleavage of the C–C bond (path a), presumably due to the stability of the *tert*-butyl radical.



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14. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 242072. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge BC2 1EZ, UK [fax. +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].
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