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Technical-Scale Homologation of a Cholanic Acid Derivative through the Barton Ester. A Practical Approach to 25-Hydroxy Vitamin D_3 and Congeners

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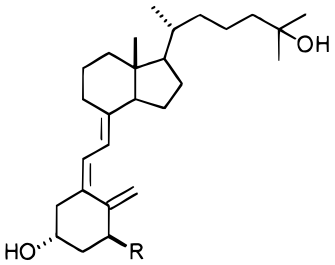
Abstract:

A novel method was developed of the homologation of a cholanic acid derivative using the Barton ester, as a practical approach to 25-hydroxy vitamin D and congeners. The method involves transformation of a cholanic acid derivative into a nor-bromide by using 2-mercaptopyridine *N*-oxide sodium salt and bromotrichloromethane and then alkylation of the bromide with dimethylmalonate followed by demethoxycarbonylation by Krapcho procedure. The major byproducts of the synthesis were isolated, and their structures were identified by spectroscopic and chemical methods. Our method is designed especially for the large-scale manufacturing of vitamin D compounds because it involves an intermediate that can be easily purified and it avoids the use of toxic and explosive diazomethane that is employed in the classical synthesis of vitamins D from natural steroids.

Introduction

Endogenous metabolites of vitamin D, such as 25-hydroxy vitamin D_3 (**1**) and 1α,25-dihydroxy vitamin D_3 (**2**) as well as their synthetic analogues, are well-established pharmaceuticals against a number of metabolic, bone, and dermatological diseases.[1] A series of compounds from this group is clinically tested against hyperproliferative diseases such as leukemia and some solid tumors.[2] There are reports on



1: R = H
2: R = OH

activity of the vitamin D derivatives as immunosuppressants.[2] Increase in manufacturing of these compounds on industrial scale seems likely in view of their present and expected applications. Despite of the advances in the total synthesis,[3] a large-scale preparation of vitamin D compounds from abundant natural steroids still remains technically and economically advantageous.[4]

In the classical synthesis of **1** developed by the Upjohn group,[5] cholenic acid was used as the starting material. A side chain was elongated by reacting of the corresponding acid chloride with diazomethane that yielded homocholenic acid ester (Arndt−Eistert homologation). With renewable supplies, cholenic acid still remains a convenient starting material for preparation of vitamin D derivatives.[6] However, the use of diazomethane in the synthesis causes serious health hazards and danger of explosion that hamper large-scale preparations. These obstacles in the scale-up of the synthesis stimulated our efforts to avoid the use of diazomethane in otherwise well-functioning reaction sequence. In the present paper we report a synthesis of methyl homocholenate from cholenic acid that involves Barton's radical chemistry.[7]

Results and Discussion

3-Acetyl cholenic acid (**3**) was transformed (Scheme 1) into acid chloride **4** using thionyl chloride under the standard conditions.[5] The crude chloride **4** was suspended in bromotrichloromethane (which served as a solvent and a radical quencher) and treated with 2-mercaptopyridine *N*-oxide sodium salt in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) according to the method of Barton and co-workers.[8] Under the carefully selected reaction and the product purification conditions, crystalline bromide **5** was obtained in 73% overall yield from chloride **4** on a 50 g scale. Although the yield and the product purity were rather satisfying, it was of interest to scrutinize the reaction concerning the side products.

Chromatography of the crude product allowed to isolate two side products accompanying bromide **5**. The less polar

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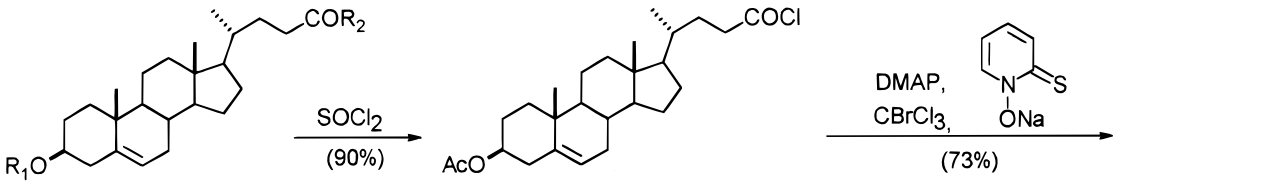
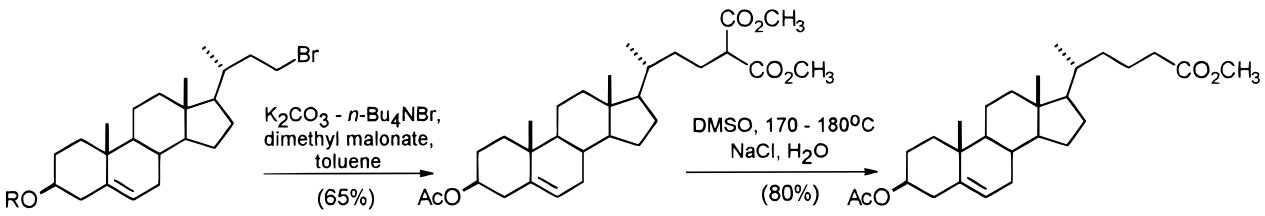
Scheme 1



3: R_1 = Ac , R_2 = OH
6: R_1 = Ac , R_2 = OCH_3
9: R_1 = H , R_2 = OH

4

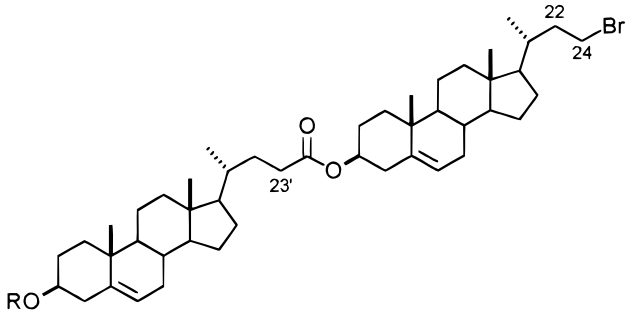


5: R = Ac
8: R = H

11

12

byproduct present in a trace amount was immediately identified as methyl 3β-acetoxy-5-cholen-24-oate (**6**). The major byproduct, formed in 1−3% yield, showed in its ^{1}H NMR (500 MHz) signals at 3.26 and 3.50 ppm (which could be assigned to the $-CH_2Br$ group) with the splitting pattern identical with that for the respective signals in the spectrum of bromide **5**. At 2.2 ppm it appeared as a five-line multiplet similar to the signal corresponding to C-23 proton in methyl cholenate **6**. There are two three-proton signals in the region of angular C-18 methyl group at 0.70 and 0.68 ppm. There are also two signals that could be attributed to protons of C-19 methyl group (1.016 and 1.020 ppm). Additionally, there is a three-proton singlet at 2.03, typical for acetate methyl. These data suggested a dimeric structure[9] for this byproduct, most likely that of bromide **7**. Indeed, liquid



7: R = Ac
10: R = H

matrix secondary ion mass spectrum confirmed the dimeric structure with the ion *m*/*z* 831 ($C_{49}H_{75}BrO_4$ + Na). The dimeric structure of **7** was also confirmed chemically, by the cleaving of the ester linkage C24′−C3. Alkaline hydrolysis of **7** resulted in hydroxy bromide **8** and hydroxy acid **9** along with some partially hydrolyzed product **10**. Ultimately, structure **7** was proven by single-crystal X-ray analysis.[10] It appears likely that the byproduct **7** was formed from the respective "dimeric" acyl chloride which was in turn generated from **4** in acid-catalysed transesterification. Formation of a "dimer" presumably takes place also in the Arndt−Eistert homologation of **4** in the Upjohn approach. Such a dimer is composed from a fragment containing five-carbon side chain (southern part) and a fragment with a six-carbon side chain (northern part). However, the byproduct could neither be separated nor detected by TLC at this stage because its migration was similar to that of the major product. This explains why 25-hydroxy vitamin D_3, prepared with the route involving diazomethane, requires tedious chromatographic purification in order to remove a contaminant which has been proved to be its 24-nor-analogue. Now, we postulate that the nor-analogue is generated from the southern part of the dimer.

Free radical quenchers, such as 2-nitroethylene or 2-nitro-3-phenylthioethylene, were recommended[11] for one-pot transformation of the Barton esters of cholanic acids into the respective cholestane derivatives. For economic reasons and to simplify the reaction conditions, we have chosen dimethyl malonate as a source of two carbon atoms. Thus, alkylation[12] of bromide **5** with dimethyl malonate afforded **11** (65% yield, after chromatography). Malonate **11** was dissolved in DMSO containing some sodium chloride and

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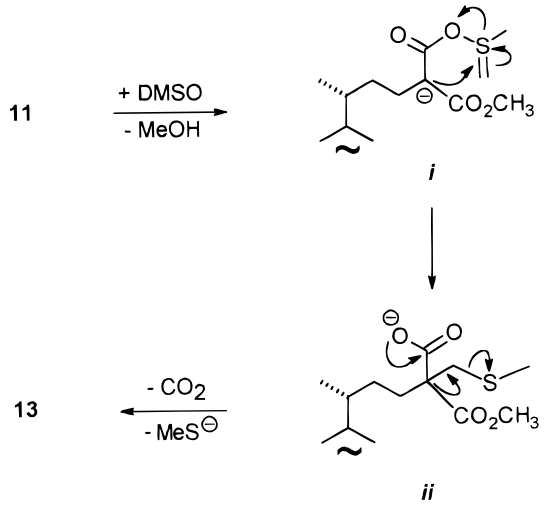
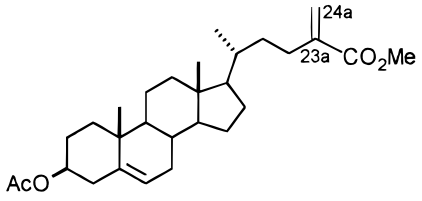
Scheme 2



heated under reflux. Demethoxycarbonylation[13] smoothly yielded the required ester **12** (80% yield, after chromatography and crystallization). Under the conditions of dealkoxycarbonylation, a trace product was formed. This product was separated by chromatography and identified as the 24-methylene derivative **13**. The origin of the methylene group



13

in **13** is not quite clear. One may postulate attack of dimethyl sulfoxide on the ester group that would generate ionic intermediate (***i***, Scheme 2) which would rearrange to ***ii*** and, then, undergo decarboxylation and elimination of methyl sulfide. To the best of our knowledge, no similar methylenation has been reported in the Krapcho procedure.

In summary, a new procedure for transformation of the cholenic acid derivative **3** into its one-carbon homologue **12** has been developed. It involves transformation of acid chloride **4** into bromide **5** by using 2-mercaptopyridine *N*-oxide sodium salt and bromotrichloromethane and, then alkylation of **5** with dimethylmalonate followed by dealkoxycarbonylation. Our new method meets the requirements of large-scale synthesis: it involves an intermediate that can be easily purified and avoids generation and use of toxic and explosive diazomethane.

Experimental Section

General Methods. Reagents and solvents were of reagent grade. They were used as received, unless otherwise noted. 2-Mercaptopyridine *N*-oxide sodium salt (anhydrous, 98%) was from Avocado Research Chemicals, Ltd. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1725X FT-IR spectrophotometer as films and are reported in wavenumbers (cm^{-1}). Ultraviolet (UV) spectrum of compound **13** was taken in ethanol on a Shimadzu Model 160A UV-vis spectrophotometer. Nuclear magnetic resonance (^1H NMR) spectra were recorded at 200 MHz on a Varian Gemini 2000 spectrometer and at 500 MHz on a Bruker AM 500 spectrometer in deuterated chloroform, and they are reported downfield from tetramethylsilane (TMS). Low- and high-resolution electron impact mass spectra (EIMS) and liquid matrix secondary ion mass spectrum (LSIMS) of **7** were recorded at 70 eV on an AMD Intectra GmbH Model 604 spectrometer. Column flash chromatography was performed on silica gel Si 60 (70−230 and 300−400 mesh, Merck), LiChroprep RP-18 (25−40 μm, Merck), and alumina (Brockmann grade I). High-performance liquid chromatography (HPLC) was carried out by using a Knauer Instrument Model 64, Hibar Si 60 column, 10 μm, 4 × 25 cm (Merck), Si 100 column, 10 μm, 10 × 25 cm and 22 × 25 cm (Solvay Duphar B.V.). Melting points were determined on a Buchi capillary instrument model 535 and are uncorrected. Optical rotations were measured with a Perkin-Elmer polarimeter model 241 in chloroform.

24-Bromo-23-nor-5-cholen-3*β*-ol acetate (5). Thionyl chloride[5] (10.4 mL, 14 mmol) was added in one portion at 0 °C to the solution of acid **3** (10 g, 24 mmol) in toluene (180 mL) containing pyridine (0.5 mL). The mixture was stirred at room temperature for 2.5 h (until none of the substrate was detected by TLC). The excess of thionyl chloride was removed by distillation with toluene under reduced pressure, and the solution was concentrated to dryness. Acyl chloride **4** thus obtained was used for the next step without further purification. 2-Mercaptopyridine *N*-oxide sodium salt hydrate (23 g, 150 mmol) was suspended in bromotrichloromethane (1000 mL). Some of the solvent was distilled off (ca. 50 mL) for azeotropic drying of the mixture. 4-(Dimethylamino)pyridine (2 g, 3.4 mmol) and acyl chloride **4** (50 g, 115 mmol) were added, and the mixture was gradually warmed and heated under reflux for 1.5 h.

CAUTION: Vigorous evolution of CO_2. The mixture was cooled to room temperature, the solid was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in a mixture of chloroform (60 mL), triethylamine (6 mL), and methanol (400 mL) on heating. The solution was cooled and kept at 4 °C for 2 h. The resulting precipitate was collected to give bromide **5** as a light brown powder (41 g). Filtration of this product in toluene (2 L) over the alumina (425 g) column gave bromide **5** as a white solid (37.8 g, 73%). An analytical sample was obtained by crystallization from ethyl acetate: $R_f = 0.56$ (hexane:ethyl acetate 1:9), mp 162−164 °C; $[\alpha]_D^{25} = -29.2$ (*c* 0.73); IR 2963, 1728, 1245, 1035; ^1H NMR (500 MHz) δ 0.70 (3H, s, 18-CH_3), 0.95 (3H, d, $J = 6$ Hz, 21-CH_3), 1.02 (3H, s, 19-CH_3), 2.03 (3H, s, COC*H*$_3$), 3.36 (1H, m, 23-CH), 3.50 (1H, m, 23-CH), 4.60 (1H, m, 3α-H), 5.37 (1H, br s, 6-H); EIMS *m*/*z* (rel intensity) 450 (M^+, 0.1), 390 (100), 375 (20), 346 (13), 282 (22), 269 (29), 255 (25), 213 (18), 147 (59); HRMS calcd for $C_{23}H_{35}Br$ [M^+ − AcOH (60)] 390.1919, found 390.1919. Anal. Calcd for $C_{25}H_{39}BrO_2$: C, 66.5; H, 8.7. Found: C, 66.7; H, 9.0%.

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Byproduct **7** (0.7 g, 1.7%) was isolated from crude bromide **5** by silica gel flash chromatography (2.4% of ethyl acetate in hexane): $R_f = 0.42$ (hexane:ethyl acetate 1:9). An analytical sample of **7** was obtained by crystallization from ethyl acetate: mp 215−217 °C; $[\alpha]_D^{25} = -33.6$ (*c* 0.2); IR 2945, 1732, 1250, 1239, 1163, 1031; ^{1}H NMR (500 MHz) δ 0.68, 0.70 (3H and 3H, s and s, 18-CH_3, 18′-CH_3), 0.94, 0.95 (3H and 3H, d, $J = 6$ Hz, 21-CH_3), 1.01, 1.02 (3H and 3H, s and s, 19-CH_3, 19′-CH_3), 2.03 (3H, s, COCH_3), 2.21 (2H, m, 23′-CH_2), 3.4, 3.5 (1H and 1H, m and m, 23-CH_2), 4.6 (1H, m, 3α-H), 5.37 (1H, br s, 6-H); EIMS *m*/*z* (rel intensity) 390 (100), 375 (21), 356 (41), 346 (14), 312 (8), 282 (19), 269 (22), 255 (26), 213 (14), 147 (47); LSIMS *m*/*z* 831 $(M + Na)^+$. Anal. Calcd for $C_{49}H_{75}BrO_4$: C, 72.8; H, 9.4; Br, 9.9. Found: C, 72.8; H, 9.4%.

Acetoxy ester **6**, isolated in trace amounts ($R_f = 0.38$, hexane:ethyl acetate 1:9), was found identical with an original sample.

Methyl 3*β*-Acetoxy-23a-carbomethoxy-23a-homo-5-cholen-24-oate (11). A solvent (50 mL) was distilled off from a mixture of bromide **5** (54 g, 120 mmol), dimethyl malonate (130 mL, 1.5 mmol), tetrabutylammonium bromide (6 g, 18.6 mmol), and potassium carbonate (90 g) in toluene (500 mL). The mixture was heated under reflux for 4 h. The solid was filtered off, and the filtrate was concentrated under reduced pressure to give malonate **11** (69 g) as a light brown powder. Filtration of this product through alumina (900 g) in 10% of ethyl acetate in toluene (1.8 L) gave malonate **11** as a white powder (40.4 g, 65%). An analytical sample was obtained by crystallization from hexane/ethyl acetate 1:1, mp 132−133 °C; $[\alpha]_D^{25} = -38.5$ (*c* 0.74); IR 2945, 1730, 1438, 1379, 1244, 1038; ^{1}H NMR (200 MHz) δ 0.67 (3H, s, 18-CH_3), 0.95 (3H, d, $J = 6$ Hz, 21-CH_3), 1.02 (3H, s, 19-CH_3), 2.03 (3H, s, COCH_3), 3.3 (1H, m, 23a-CH), 3.74 (6H, s, −COOCH_3), 4.60 (1H, m, 3α-H), 5.37 (1H, br s, 6-H); EIMS *m*/*z* (rel intensity) 442 (M − AcOH, 100), 427 (10), 411 (7), 321 (12), 255 (10), 213 (8), 147 (17); HRMS calcd for $C_{28}H_{42}O_4$ (M − AcOH) 442.3083, found 442.3103. Anal. Calcd for $C_{30}H_{46}O_6$: C, 71.7; H, 9.2. Found: C, 71.5; H, 9.3%.

Methyl 3*β*-Acetoxy-23a-homo-5-cholen-24-oate (12). A mixture of diester **11** (72 g, 143 mmol), sodium chloride (11 g, 188 mmol) and water (11 g, 611 mmol) in DMSO (1.2 L) was heated at 170−180 °C for 2.5 h. The mixture was poured into water (2 L) and left overnight. The precipitate was filtered off, rinsed with water, and dissolved in ethyl acetate. The solvent was removed and homoester **12** was obtained as yellow oil. Filtration over alumina (400 g) in toluene (2 L) gave homoester **12** (69 g) as a creamy-white solid. Crystallization from methanol/benzene (1:1) gave colorless crystals (66 g, 80%), mp 110−112 °C; $[\alpha]_D^{25} = -45$ (*c* 0.3) {ref 5, 110−112.5 °C, from methylene chloride-methanol; $[\alpha]^{25}{}_D = -45$ (c 1, $CHCl_3$)}; IR 2940, 1730, 1375, 1261, 1049; ^{1}H NMR (200 MHz) δ 0.68 (3H, s, 18-CH_3), 0.93 (3H, d, $J = 6$ Hz, 21-CH_3), 1.02 (3H, s, 19-CH_3), 2.03 (3H, s, COCH_3), 3.7 (3H, s, −COOCH_3), 4.6 (1H, m, 3α-H), 5.37 (1H, br s, 6-H); EIMS *m*/*z* (rel intensity) 384 ($M^+ - 60$, 100), 369 (17), 353 (5), 342 (3), 276 (8), 263 (22), 255 (17), 213 (10), 147 (19); HRMS calcd for $C_{26}H_{40}O_2$ (M − AcOH) 384.3028, found 384.3029. Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.6; H, 10.0. Found: C, 75.6; H, 10.2%.

Silica gel (300−400 mesh, 6 g) flash chromatography of an aliquot of mother liquors (300 mg) using ethyl acetate (0.4−3.6%) in hexane gave unchanged homoester **12** (61 mg) and eneester **13** (less polar byproduct, 32 mg) as a white solid: UV λ_{max} 208 nm; IR 2940, 1725, 1629, 1367, 1244, 1041; ^{1}H NMR (200 MHz) δ 0.68 (3H, s, 18-CH_3), 0.98 (3H, d, $J = 6$ Hz, 21-CH_3), 1.02 (3H, s, 19-CH_3), 2.03 (3H, s, COCH_3), 3.7 (3H, s, −COOCH_3) 4.6 (1H, m, 3α-H), 5.38 (1H, br s, 6-H), 5.5, 6.1 (1H and 1H, br s and br s, 26-CH_2); EIMS *m*/*z* (rel intensity) 396 ($M^+ - 60$, 100), 381 (15), 354 (3), 275 (12), 255 (14), 213 (10), 145 (13); HRMS calcd for $C_{27}H_{40}O_2$ (M − AcOH) 396.3028, found 396.3013.

Homoester **12** was obtained in a similar experiment using crude malonate **11** (without the alumina filtration) with an overall yield of 58% from bromide **5**.

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