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Synthesis of 16-Dehydro-20-Oxopregnanes from 17α,20-epoxy-23,24-dinorcholan-22-oic Acids. Highly Stereospecific Oxirane → Allyl Alcohol Isomerization of an Epoxycarboxylic Acid

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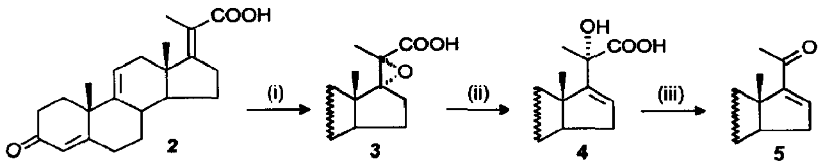
Abstract: A microbial degradation product of natural sterols was converted into traditional precursor of steroid syntheses by a simple sequence. The title isomerization, the key step, was investigated to demonstrate a concerted mechanism, in which a cyclic transition state, involving the oxirane oxygen, the β- and γ-carbon, the γ-proton to be removed and the catalyst coordinated by the carboxylate group, is postulated.

In the course of our studies on the synthetic routes towards anti inflammatory corticosteroids from 9α-hydroxy-3-oxo-23,24-dinorchola-4,17(20)-dien-22-oic acid (**1**), obtained efficiently by microbial partial side chain degradation of sitosterol[1], we reported the regio- and stereoselective epoxidation of unsaturated carboxylic acid **2**, dehydration product of **1**, into epoxy acid **3**[2]. We now report a simple sequence for the conversion of 17(20)-dehydro-23,24-dinorcholan-22-oic acids into 16-dehydro-20-oxopregnanes via (20*S*)-20-hydroxy-16-dehydro-dinorcholanoic acids, and our preliminary mechanistic study on the key step, a highly stereospecific oxirane → allyl alcohol isomerization.

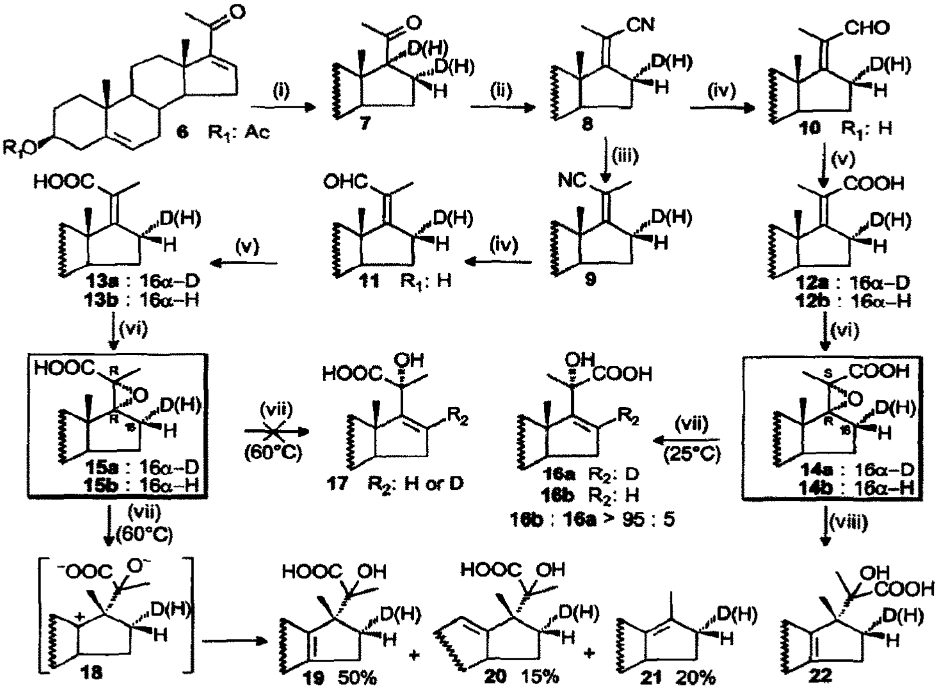


Scheme 1. Reagents: (i) 30% H_2O_2, Na_2WO_4, pyridine; (ii) $AlCl_3$, Et_3N, THF; (iii) CrO_3, AcOH.

In our synthetic approach the tungstate catalyzed epoxidation of dinorcholatrienoic acid **2** was applied[2]. To prevent the retropinacolinic rearrangement of the 13β-methyl group, a mild and simple catalytic process has been used for the isomerization of the oxidation product **3** into allylic alcohol **4**. When the triethylammonium salt of **3** was treated with 15 Mol% $AlCl_3$ in THF at 30°C, the allylic alcohol **4** was formed as a sole product[3]. During this isomerization, the 16-double bond is formed, and the simultaneous hydroxylation at its α-carbon promotes the removal of the carboxylic group. Accordingly, **4** could be easily decarboxylated oxidatively, conveniently with chromic acid to afford 16-pregnen-20-on **5**[4]. The overall yield of this transformation was 77%. We have also performed the analogous reactions in 3-oxo-Δ^4-, 3-oxo-$\Delta^{1,4,9(11)}$- and, applying periodate oxidation instead of chromic acid, in 3β-hydroxy-Δ^5-series with similar results. This simple sequence offers a novel route for converting 17,20-dehydrodinorcholanoic acids, the microbial degradation products of natural sterols into 16-dehydro-20-oxopregnanes, the traditional key intermediates of corticosteroid syntheses, obtained so far from steroidal sapogenines since R. E. Marker's pioneering work, and used recently again in corticoid syntheses as substrates for the elegant double hydroxylation process[5].

The oxirane → allyl alcohol isomerization, the key step of the above sequence was investigated in detail. Although aluminum compounds, e.g., aluminum isopropoxide[6] or aluminum amides[7] are well known catalysts or reagents for epoxide isomerization, no aluminum chloride was reported to have such a catalytic activity. Furthermore, we could find no data on oxirane → allyl alcohol isomerization of epoxy-carboxylic acids, especially under basic conditions.

As a part of our study on the oxidative decarboxylation of α,β-unsaturated carboxylic acids[8], we synthesized (17*R*,20*S*)- and (17*R*,20*R*)-epoxy-dinorcholanoic acids **14** and **15**, respectively, selectively deuterated at 16α-position. These two model compounds provided an outstanding opportunity to investigate the stereospecificity and mechanism of the title isomerization. The synthesis and investigation of epoxy acids **14** and **15** are summarized in **Scheme 2**:

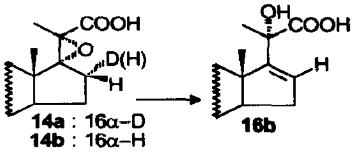


Scheme 2. Reagents: (i) D_2 (H_2), Pd(C); (ii) HCN; then $POCl_3$, pyridine; (iii) hν (254 nm), Ph_2CO, then chromatography; (iv) DIBALH; (v) $NaClO_2$; (vi) 30% H_2O_2, Na_2WO_4, pyridine; (vii) $AlCl_3$, Et_3N, pyridine; (viii) $Mg(ClO_4)_2$, EtOAc.

For the synthesis of epoxy acids **14** and **15**, aldehydes **10** and **11** were needed, which were obtained according to the literature using a somewhat modified procedure[9]. Accordingly, stereoselective cis-deuteration of **6** to dideutero-pregnenone **7**, followed by HCN addition and $POCl_3$ dehydration of the cyanohydrin led to the E-nitrile **8**, benzophenone sensitized photoisomerization of which and subsequent chromatography afforded Z-nitrile **9**. The E- and Z-aldehydes **10** and **11** were obtained by reduction of nitriles **8** and **9** with diisobutylaluminum hydride. For obtaining the target epoxy acids **14** and **15**, sodium chlorite[10] oxidation of aldehydes **10** and **11**, and subsequent tungstate catalyzed epoxidation[2] of the formed acids **12** and **13** was applied[11]. The benefit of our method, applying photoisomerization instead of the base catalyzed isomerization used in the original procedure[9] is the total retention of the C_{16} deuterium label[12]. Furthermore, the isomerization of the 17(20)-double bond during the conversion of nitriles **8** and **9**, into the corresponding acids **12** and **13** could be avoided by applying a very mild reduction-oxidation sequence.

At room temperature in THF, in the presence of $AlCl_3$, only the triethylammonium salt of epoxy acid **14a** isomerized into allylic alcohol **16b** , while **15a** remained unchanged even at reflux temperature for a week. **14a** also isomerized quantitatively and stereoselectively into **16b** in acetonitrile, in dimethyl formamide, in dimethyl sulfoxide or in pyridine. In the latter case the reaction rate accelerated considerably, and the reaction proceeded even in wet solvent. When pyridine was applied as solvent to isomerize epoxy acid **15**, at 60°C for 24 hours, instead of the allylic alcohol **17**, along with several minor components, only rearranged 18-nor steroids such as acids **19** and **20**, as well as olefin **21** were formed[13]. These three compounds (**19-21**) could be formed *via* carbonium ion **18**, deriving from the epoxide cleavage of **15** and subsequent **13** → **17** migration of the 13β-methyl group. **14** underwent similar rearrangement to give **22**, the 20-epimer of **19**, by simply drying its ethyl acetate solution over magnesium perchlorate[14]. In contrast with these retropinacolinic rearrangements of 17α,20-epoxy-dinorcholanoic acids in case of their 17β-epimers a D-homo rearrangement was observed[15].

Further information on the mechanism of the title isomerization was obtained by kinetic measurements (**Table 1**). Due to the high chemo- and stereoselectivity of the isomerization of **14**, and the characteristic 16-vinyl proton of the product **16b**, the reaction could be monitored easily by ^1H NMR[16]. The isomerization is first order with respect to substrate and zero order with respect to catalyst and base (over the equimolar concentration of the latter). Moreover, the isomerization shows a moderate kinetic isotope effect (k_H / k_D : 3.1) indicating a concerted mechanism. Interestingly, although the rate is independent of the base concentration, it does depend on its structure: applying N-methyl pyrrolidine (NMP), a weaker base, instead of triethylamine (Et_3N), the rate decreased to more than one third. On the other hand, the structure and the basicity of the base did not affect the kinetic isotope effect, which is indicative for an intramolecular process.



14a : 16α–D
14b : 16α–H
16b

Table 1. Investigation of the kinetics of the title isomerization

Substrate	base, mol%	$AlCl_3$, mol%	k, $x10^{-5}$ s^{-1}	k_H / k_D
14b	Et_3N, 133	15	23	3.14
14a	Et_3N, 133	15	7.2	
14a	Et_3N, 800	90	6.8	
14b	NMP, 133	15	7.2	3.19
14a	NMP, 133	15	2.3	

These results suggest a concerted mechanism, in which the cleavage of the epoxid ring and an intramolecular and stereoselective deprotonation of the 16-methylene group occur simultaneously with the assistance of the catalyst, an aluminum species, coordinated by the oxirane oxygen and the carboxylate group. This way the catalyst operates as a Lewis acid towards the oxirane oxygen and as a Brønsted base towards the proton to be removed. This mechanism is consistent with the results of the isomerization experiments of **15**, which undergoes a different rearrangement under identical conditions. Since in **15** the carboxylate group and C_{16} are anticlinal, the former can not coordinate the catalyst to the latter, therefore the C_{17}-O bond of the oxirane ring undergoes a heterolytic cleavage, which is not stabilised as allylic alcohol **17** by deprotonation at C_{16}, but rearranges into **18** trapped as retropinacolinic products.

In conclusion, the title isomerization yielding α-hydroxy-β,γ-unsaturated carboxylic acids was investigated on epoxy-dinorcholanoic acids to offer a novel route under mild basic condition, in a special arrangement of the substrate. Further examinations will be necessary to establish the limitations of this isomerization.

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3) Preparation of **4**: To a mixture of **3** (1782 mg, 5 mmol) and triethylamine (1 mL) in tetrahydrofuran (THF) (20 mL) a cold solution of $AlCl_3$ (100 mg, 7.5×10^{-4} M) in THF (1 mL) was added at 0°C. The solution was stirred for 3 days at 30 °C then cooled and poured into cold water (150 mL), the pH was adjusted to 3, the precipitate was filtered, washed and dried then recrystallized from CH_2Cl_2 to give **4** (1622 mg, 91%), mp 209-212°C; $[\alpha]_D$ +138° (c = 1, THF); IR (KBr) 3280 (br), 1750, 1665, 1605; ^{1}H NMR (250 MHz, DMSO-d_6, δ) 5.70 (m, 4-H, 16-H), 5.49 (dd, J = 5.8 and 1.8 Hz, 11-H), 1.48 (s, 21-H_3), 1.32 (s, 19-H_3), 0.90 (s, 18-H_3); ^{13}C NMR (DMSO-d_6, δ) 198.0 (s), 177.0 (s), 169.9 (s), 154.5 (s), 145.6 (s), 125.7 (d), 123.5 (d), 118.4 (d), 74.0 (s), 54.0 (d), 45.2 (s), 40.9 (s), 36.6 (t), 34.9 (d), 34.2 (t), 33.5 (t), 32.1(t), 31.7 (t), 31.3 (t), 27.0 (q), 25.9 (q), 16.6 (q). Multiplicity is based on DEPT spectra.

4) Preparation of **5**: To a solution of **4** (713 mg, 2 mmol) in THF (25 mL) and acetone (5 mL), CrO_3 (2.5 mL, 10% in acetic acid) was added. The reaction mixture was stirred for 1 hour at 5°C then diluted with CH_2Cl_2, washed with sodium sulphite and water, dried and evaporated to give **5** (505 mg, 81%), mp 200-204°C (methanol), $[\alpha]_D$ +235° (c = 1, chloroform) (Bernstein, S. et al. *J. Am. Chem. Soc* **1959**, *81*, 4956-4962: mp 204-207°C, $[\alpha]_D$ +237°).

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11) Overall yields of the preparation of epoxy acids **14** and **15** from **6** was 57% and 44%, respectively. During the synthesis, the deuterium content and position was monitored by ^{1}H NMR, ^{13}C NMR (in DEPT spectra and the sluggish relaxation of C-16) and by MS. The deuterium distribution was checked on acid **12** by ^{1}H NMR (400 MHz, pyridine-d_5, referenced on 8.95 ppm C_2-H of the solvent, δ) 5.42 (6-H), 3.85 (3-H), 3.15 (16β-H) and 3.00 (16α-H) showing 90% 16α-D in **12a**. Furthermore, according to ^{2}H NMR (61.4 MHz, pyridine-d_5) and MS data, 12% overdeuteration was observed at C_{21}.

12) The deuterium content of **13a** determined by MS is the same that of **8a** (d_0 10.7%, d_1 81.1%, d_2 8.2%).

13) To a solution of **15a** (400 mg, 1.11 mmol) and triethylamine (220 µL, 1.57 mmol) in 2 mL pyridine, 400 µL $AlCl_3$ solution (144 mg $AlCl_3$ in 2.5 mL dioxane) is added. The solution is stirred for 24 h at 60°C, then cooled and poured into cold water, the pH was adjusted to 3, extracted with a mixture of ethylacetate and dichloromethane, washed with water, dried, evaporated to give 397 mg crude product, which is purified on silica (benzene / ethylacetate / acetic acid 79:20:1 then 69:20:1). 16α-deutero-**19**: ^{1}H NMR (250 MHz, DMSO-d_6, δ) 5.32 (d, 6-H), 3.28 (m, 3-H), 1.17 (s, 21-H_3), 1.02 (s, 17-CH_3), 0.90 (s, 19-H_3); ^{13}C NMR (DMSO-d_6, δ) 177.5 (s), 141.8 (s), 138.7 (s), 137.8 (s), 120.4 (d), 78.2 (s), 70.1 (d), 55.6 (s), 48.7 (d), 41.9 (t), 36.6 (t), 36.3 (s), 33.2 (d, 16-CHD), 33.0 (d), 31.1 (t), 30.9 (t), 30.4 (t), 24.9(t), 23.0 (t), 21.7 (q), 21.6 (q), 18.2 (q). 16α-deutero-**20**: ^{1}H NMR (250 MHz, DMSO-d_6, δ) 5.47 (d, 12-H), 5.25 (d, 6-H), 3.28 (m, 3-H), 1.21 (s, 21-H_3), 1.08 (s, 17-CH_3), 0.87 (s, 19-H_3); It was important to distinguish **20** from its isomer **17**. Semiselective INEPT spectra (optimised to 7 Hz) verified structure **20** to show two doublets at 50.6 (C-9) and at 43.8 (C-14) as well as a singlet at 55.7 (C-17) when the signal at 5.47 ppm (12-H) was irradiated. 16α-deutero-**21**. ^{1}H NMR (250 MHz, $CDCl_3$, δ) 5.30 (d, 6-H), 3.48 (m, 3-H), 1.54 (s, 17-CH_3), 0.85 (s, 19-H_3); ^{13}C NMR (DMSO-d_6, δ) 140.1 (s), 130.4 (s), 127.5 (s), 121.5 (d), 71.7 (d), 54.3 (d), 48.8 (d), 42.2 (t), 41.2 (d), 37.2 (t), 36.9 (d, 16-CHD), 36.5 (s), 32.3 (t), 31.6 (t), 28.1 (t), 26.3 (t), 25.5 (t), 19.4 (q), 13.4 (q).

14) **22**: ^{1}H NMR (250 MHz, DMSO-d_6, δ) 5.32 (d, 6-H), 3.30 (m, 3-H), 1.30 (s, 21-H_3), 1.10 (s, 17-CH_3), 0.92 (s, 19-H_3); ^{13}C NMR (DMSO-d_6, δ) 177.4 (s), 141.8 (s), 138.7 (s), 137.7 (s), 120.3 (d), 78.3 (s), 70.1 (d), 55.7 (s), 48.3 (d), 41.9 (t), 36.6 (t), 36.2 (s), 33.7 (t), 32.7 (d), 31.0 (t), 30.6 (t), 30.1 (t), 24.5 (t), 22.9 (t), 22.0 (q), 21.1 (q), 18.2 (q).

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16) Isomerization kinetics was monitored by ^{1}H NMR (pyridine-d_5, referenced on 8.95 ppm C_2-H of the solvent, δ) at 5.63 (6-H) as well as at 6.13 and 6.18 (rotamers, 16-H), in a solution of **14** (27 mg, 7.5×10^{-5} mol), base (10^{-4} mol, Et_3N or NMP) and pyridine-d_5 (400 µL), and the reaction was started with an addition of $AlCl_3$ solution (27 µL, 1.125×10^{-6} mol). The k_D values are corrected by deuterium content at $C_{16\alpha}$ (91%, ref. 11)

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