Regioselective dehydration of axial and equatorial tertiary alcohols with α-methyl group in the cyclohexane ring by Swern's reagent

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Swern's reagent (a complex of oxalyl chloride with DMSO) was shown to dehydrate tertiary alcohols containing an α-methyl group in the cyclohexane ring. Dehydration of equatorial alcohols affords mixtures of isomeric compounds where isomers with an exocyclic double bond dominate, whereas isomers with an endocyclic double bond prevail in the products of dehydration of axial tertiary alcohols. Thus, Swern's reagent can serve as a chemical test to determine the configuration of tertiary alcohols containing an α-methyl group in cyclohexane ring. The composition of the products of dehydration of these alcohols with Swern's reagent is similar to that obtained by their dehydration with $POCl_3$ in pyridine.

Key words: Swern's reagent, phosphorus oxychloride, dehydration, cyclic tertiary alcohols, regioselectivity.

Previously, in the synthesis of 20-desoxoluteone,[1] we observed that the reaction of a tricyclic primary-tertiary diol (**1**) with a complex oxalyl chloride—DMSO (Swern's reagent)[2] involved regioselective dehydration of the tertiary hydroxyl group, along with the oxidation of the primary alcohol group into aldehyde, to give high yield of an unsaturated aldehyde (**2**) with an exocyclic double bond (Scheme 1).

The absence of published data on the dehydrating properties of Swern's reagent prompted us to investigate whether the dehydration of tertiary alcohols containing an α-methyl group in the cyclohexane ring is of a general character, to determine the pathway of dehydration of epimeric alcohols, and to check whether this reaction can serve as a chemical test for the determination of configuration of these alcohols. Barton's dehydration[3] is known to be used for this purpose. Tertiary equatorial alcohols with an α-methyl group in the cyclohexane ring yield a mixture of isomeric olefins in which isomers with an exocyclic double bond prevail, and epimeric alcohols with an axial hydroxy group afford mixtures of olefins with prevailing isomers with an endocyclic double bond.

Table 1. Composition of the products of dehydration of compounds **3**—**7**

Initial compound	Ratio of isomeric dehydration products containing exocyclic, tri-, and tetrasubstituted double bonds	
	Swern's reagent[a] [$(COCl)_2$—DMSO]	$POCl_3/C_5H_5N$[b]
3	65 : 17 : 18	72 : 13 : 15
4	64 : 23 : 13	70 : 14 : 16
5	75 : 20 : 5	—
6	73 : 20 : 7	55 : 36 : 9
7	Traces : (2—4) : (96—98)	Traces : (2—4) : (96—98)

[a] Reaction conditions: −60°C, 45 min, addition of NEt_3, 10 min; −60→20°C, 3—4 h. [b] The reaction temperature was 0 °C, 30 min; 0→−20 °C; −20 °C, 24 h.

In order to answer the above questions, we studied the reaction of Swern's reagent with compounds **3**—**7** containing the necessary structural fragment (Scheme 1). Bicyclohomofarnesane-8α,12-diol (**5**),[4] its 12-monoacetate (**3**),[5,6] methyl labdanolate (**4**),[7] and 8α-hydroxy-14,15,16-trinorlabdan-12-one (**6**)[8] are known compounds. 12-Monoacetate of bicyclohomofarnesan-8β,12-diol (**7**) was prepared by selective acetylation of the known diol (**8**)[9] with acetic anhydride in pyridine. Its structure was confirmed by analytical and spectral data (see Experimental). For comparison, we also studied the products of dehydration of compounds **3**—**7** by $POCl_3$ in pyridine.[3] The results are given in Table 1.

The yields of the products of dehydration of compounds **3**—**5** and **7** both with Swern's reagent and with $POCl_3$ in pyridine are rather high (84—92.5%). The yields of mixtures of ketones (**12**) upon dehydration of hydroxyketone **6** by both reagents are lower (76—79%), since in this case one more low-polarity reaction prod-

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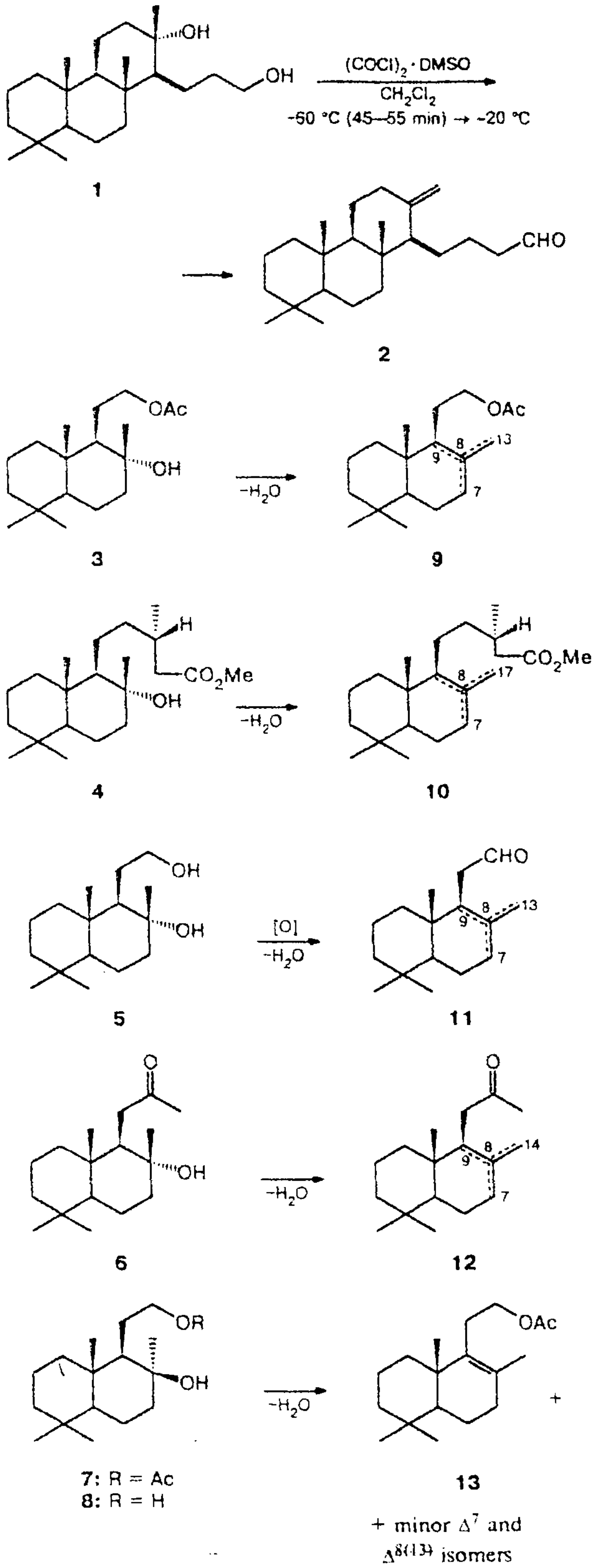
Scheme 1



uct, which we did not investigate,* is formed in a low yield.

The products of dehydration of compounds 3—7 were identified by comparison of their chromatographic and spectral data with those of the authentic samples previously synthesized by us.[6,8,10,11] Dehydration of diol 5 by POCl$_3$ in pyridine in known[12] to result in the corresponding tetrahydrofuran derivative. The isomeric composition of the products of dehydration of compounds 3 and 5—7 was determined by ^{1}H NMR spectroscopy. Attempts to use GLC for this purpose were unsuccessful. The composition of the products of dehydration of methyl labdanolate 4 by POCl$_3$ in pyridine (**10**) was determined after ozonolysis.[10]

One can see from the data in Table 1 that the dehydration of compounds 3—7 by Swern's reagent and by POCl$_3$ in pyridine affords products with very similar composition. In both cases, alcohols with an equatorial hydroxy group afford a mixture of isomers where the compounds with the exocyclic double bond prevail. On the contrary, dehydration of compound 7 with an axial hydroxy group in both cases affords a product which is almost pure Δ^8-isomer **13** with an endocyclic tetrasubstituted double bond.

The above data indicate that the ability of Swern's reagent to dehydrate tertiary alcohols is of a general character. The reaction occurs under considerably milder conditions than with POCl$_3$ in pyridine. In addition, Swern's reagent is a more effective dehydrating agent. For example, the dehydration of hydroxyacetate 7 containing an axial hydroxy group by POCl$_3$ in pyridine under standard conditions (see Experimental, method *B*) is incomplete even over a longer period of time. Swern's reagent has also other advantages as compared with the POCl$_3$—pyridine system: first, the two reactions, dehydration of a tertiary alcohol and oxidation of a primary or secondary alcohol into a carbonyl compound, can be carried out with primary-tertiary and secondary-tertiary diols, and second, Swern's reagent does not afford anhydro-compounds upon dehydration of 1,4- and 1,5-diols. Like the POCl$_3$—pyridine system, Swern's reagent can be used for the determination of configuration of a hydroxy group of cyclic alcohols containing an α-methyl group in the cyclohexane ring.

Experimental

Melting points were determined on a Boetius instrument. IR spectra were recorded in CCl$_4$ on a Specord 74 IR spectrophotometer. ^{1}H NMR spectra were obtained on Bruker AC-80 (80 MHz) and Bruker AC-200 (200 MHz) spectrometers in CDCl$_3$ with SiMe$_4$ as the internal standard. Column chromatography was carried out on 100/400 μm silica gel L and TLC was carried out on 5/40 μm silica gel LS containing 13%

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*This product might probably result from dehydration of the cyclic semiketal form of hydroxyketone **6**; the equilibrium between these forms can exist.

gypsum. Solutions of compounds in organic solvents were dried with anhydrous Na_2SO_4. Light petroleum with b.p. 50—70 °C was used.

12-*O*-Acetylbicyclohomofarnesane-8α,12-diol (7). Ac_2O (12.5 mL, 132.5 mmol) was added to a solution of diol **8** (5 g, 19.7 mmol) in dry pyridine (25 mL) at –20 °C. The reaction mixture was kept for 1.5 h at the same temperature, acidified with 10% H_2SO_4 (20 mL), and extracted with ether (3×20 mL). The combined ethereal extracts were washed with 10% H_2SO_4 (30 mL) and water (2×20 mL), dried, and concentrated *in vacuo* to yield 5.4 g (92.6%) of a crystalline product, m.p. 92.5—93.5 °C (light petroleum—diethyl ether, 8 : 2). Found (%): C, 72.75; H, 10.94. $C_{18}H_{32}O_3$. Calculated (%): C, 72.93; H, 10.88. IR, ν/cm^{-1} : 1025, 3515, 3595 (*tert*-OH); 1225, 1725 (OAc); 1355, 1375 (CMe_2). ^1H NMR, δ: 0.73 (s, 3 H, C(10)Me); 0.77 and 0.86 (both s, 3 H + 3 H, CMe_2); 1.05 (s, 3 H, C(8)Me); 1.99 (s, 3 H, OAc); 4.01 (m, 2 H, C(12)Me).

Dehydration of tertiary alcohols by Swern's reagent (*A*, general procedure).[2] A solution of $(COCl)_2$ (5.3 mmol) in CH_2Cl_2 (10 mL) was cooled to –60 °C, and a solution of DMSO (9.5 mmol) in CH_2Cl_2 (3.8 mL) was added. The mixture was stirred for 5 min at the same temperature, then a solution of an alcohol (1 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred for 45 min at the same temperature, then Et_3N (24 mmol) was added, and the mixture was stirred for 10 min (the temperature was gradually increased to room temperature). H_2O (25 mL) was added to the reaction mixture, and the mixture was extracted with ether (3×25 mL). The combined ethereal extracts were successively washed with water (2×25 mL), a solution of $NaHCO_3$ (25 mL), and water (2×25 mL), and dried. The solvent was distilled off *in vacuo*, and the residue was chromatographed on a SiO_2 column at a compound : adsorbent ratio 1 : 30. The reaction products were eluted with mixtures of light petroleum and diethyl ether.

Dehydration of tertiary alcohols by phosphorus oxychloride in pyridine (*B*, general procedure).[3] A solution of an alcohol (1 mmol) in dry pyridine (10 mL) was cooled to 0 °C, and $POCl_3$ (7 mmol) was added dropwise with stirring. The mixture was stirred at 0 °C for 30 min and kept at –20 °C for 24 h. Ice water (20 mL) was added, the mixture was extracted with ether (3×25 mL), and the combined ethereal extracts were worked up and chromatographed as described in procedure *A*.

Dehydration of 12-*O*-acetylbicyclohomofarnezan-8α,12-diol (3).[5,6] ***A*.** Starting from hydroxyacetate **3** (200 mg), 162 mg (86%) of a liquid mixture of acetates **9** was obtained. Found (%): C, 77.98; H, 10.92. $C_{18}H_{30}O_2$. Calculated (%): C, 77.63; H, 10.88. IR, ν/cm^{-1}: 890, 1640, 3065 ($C=CH_2$); 1675 (C=CH); 1235, 1735 (OAc). ^1H NMR, δ: 0.68, 0.80, 0.87 (all s, 9 H, $C(4)Me_2$, C(10)Me in the major $\Delta^{8(13)}$-isomer **9**); 2.05 (s, 3 H, OAc); 3.89, 3.99, and 4.19 (all m, 2 H, CH_2OAc); 4.55 and 4.84 (both s, $C=CH_2$); 5.42 (br.s, C=CH).

***B*.** Starting from hydroxyacetate **3** (200 mg), 158 mg (84%) of a mixture of unsaturated acetates **9** was obtained. The IR and ^1H NMR spectra of the reaction product are very close to the corresponding spectra of a mixture of acetates **9** obtained by procedure *A*.

Dehydration of methyl labdanolate (4). ***A*.** Starting from methyl labdanolate **4** (200 mg), 165 mg (87%) of a mixture of esters **10** was obtained. IR, ν/cm^{-1}: 885, 1640, 3090 ($C=CH_2$); 825, 1680 (C=CH); 1730 (CO_2Me). ^1H NMR, δ: 0.67, 0.80, 0.86 (all s, C(4)Me and C(10)Me in the major $\Delta^{8(17)}$-isomer **10**); 0.94 (d, 3 H, C(13)Me, J = 6 Hz); 1.66 (s, C(8)Me); 3.67 (s, 3 H, CO_2Me); 4.50 and 4.82 (both s, $C=CH_2$); 5.38 (br.s, C=CH).

***B*.** Earlier we carried out dehydration of methyl labdanolate **4** by $POCl_3$ in pyridine.[10] The yield of the dehydration product **10** was 92.5%.

Reaction of bicyclohomofarnesane-8α,12-diol (5) with Swern's reagent. Starting from bicyclohomofarnesol **5** (200 mg), 154 mg (84%) of a liquid mixture of isomeric aldehydes **11** was obtained using procedure *A*. IR, ν/cm^{-1}: 890, 1643, 3100 ($C=CH_2$); 1680 (C=CH); 1724, 2725 (CHO). ^1H NMR, δ: 0.71 (s, C(10)Me); 0.89 (s, $C(4)Me_2$ of the major isomer **11**); 4.39 and 4.82 (both s, 0.75 H + 0.75 H, $C=CH_2$); 5.47 (br.s, 0.2 H, C=CH); 9.53 (m, 0.05 H, CHO in Δ^8-isomer **11**); 9.63 (m, 0.75 H, CHO in $\Delta^{8(13)}$-isomer **11**); 9.84 (m, 0.2 H, CHO in Δ^7-isomer **11**). The product was identified by the comparison of its chromatographic and spectral data with those of the sample of a mixture of aldehydes **11** obtained by the known procedure.[11]

Dehydration of 8α-hydroxy-14,15,16-trinorlabdan-12-one (6). ***A*.** Starting from hydroxyketone **6** (200 mg), 19 mg of a low-polarity compound, which was not studied, and 147 mg (79%) of a liquid mixture of unsaturated ketones **12** were obtained. Found (%): C, 82.10; H, 11.20. $C_{17}H_{28}O$. Calculated (%): C, 82.26; H, 11.29. IR, ν/cm^{-1}: 880, 1635, 3080 ($C=CH_2$); 1705 (C=O). ^1H NMR, δ: 0.69, 0.80, and 0.87 (all s, $C(4)Me_2$ and C(10)Me in major $\Delta^{8(14)}$-isomer **12**); 2.15 and 2.20 (both s, 3 H, COMe); 4.33 and 4.73 (both s, $C=CH_2$); 5.44 (br.s, C=CH).

***B*.** Starting from hydroxyketone **6** (200 mg), 21 mg of a low-polarity product which was not studied, and 141 mg (76 %) of a liquid mixture of unsaturated ketones **12** were obtained. The spectral and chromatographic characteristics of the product were close to those of the product obtained by procedure *A*.

Dehydration of bicyclohomofarnezan-8α,12-diol 12-monoacetate (7). ***A*.** Dehydration of hydroxyacetate **7** (200 mg) by Swern's reagent afforded 157 mg (84%) of a liquid reaction product **13**, which appeared to be practically pure acetate of bicyclohomofarnes-8-en-12-ol (isomer with a Δ^8 double bond) containing only traces of isomer **13** with an exocyclic double bond and 2—4% of isomer **13** with a trisubstituted double bond, according to the ^1H NMR spectral data (obtained on a Bruker-AM 400 instrument (400 MHz)). IR, ν/cm^{-1}: 1235, 1735 (OAc). ^1H NMR, δ: 0.81 (s, 3 H, C(10)Me); 0.84 and 0.97 (both s, 3 H + 3 H, $C(4)Me_2$); 1.60 (s, 3 H, C(8)Me), 2.03 (s, 3 H, OAc); 3.98 (m, 2 H, CH_2OAc).

***B*.** Starting from hydroxyacetate **7** (200 mg), we obtained 129 mg of a product completely identical, according to chromatographic and spectral data, to the product obtained earlier by procedure *A*. A portion of the initial compound (28 mg, 14%) did not enter into the reaction under these conditions (procedure *B*). The yield of dehydration product **13** was 80% taking into account the unreacted initial compound.

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