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REGIOSELECTIVE REACTIONS OF ABIETIC ACID METHYL ESTER†

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Abstract—Ozonolysis of abietic acid methyl ester **1** in the presence of mercuric acetate afforded the 13,14-seco-derivative in fair yield (50%). Selenium dioxide oxidation of **1** in *t*-butanol gave 9-α-hydroxy-abietic acid methyl ester **6**, dehydroabietic acid methyl ester **4** and its 7α-hydroxy-derivative **4b**.

The ring system of abietic acid, a main component of pine resin, can be a good starting material for the enantio-specific synthesis of natural products possessing biological activity.[1-4] Of particular interest is the case of plant hormones as the gibberellins and insect antifeedants as warburganal,[5] or grindalane diterpene acids.[6] A knowledge of possible regioselective reactions of abietic acid methyl ester **1** could open the way to new transformations of this skeleton and to new synthetic approaches to the desired products. The two double bonds present the most suitable point of attack if one wishes to perform some modifications to this molecule. It was considered of interest to investigate possible ways of carrying out selective reactions on either of the double bonds.

Another possibility consists of exploring reactions induced by the presence of the double bonds (e.g. allylic type reactions), since any function introduced in this manner could possibly be used later as a modifier of the reactivity of the diene system. The epoxidation and the ozonolysis of the title compound, are examples of the first approach. The reaction of methyl abietate **1** towards selenium dioxide was considered of interest as a reaction of the second type.

At the time these studies were initiated only one report[7] of regioselective reactions of this kind, carried out on a compound related to **1**, could be found in the literature; this is the formation of monoepoxide derivatives of abietic acid by treatment with peracetic acid in ethyl ether solution. Recently a regioselective osmylation on the double bond of ring C of abietic acid provides a new example[8] of this type of reaction. To our knowledge no attempt to prepare allylic derivatives of abietic acid methyl ester has been reported.

Ozonolysis of abietic acid methyl ester. The ester derivative was preferred to the original acid for ease of handling, particularly in chromatographic separations. The ozonolysis of diterpene acids has been previously investigated for the case of neoabietic acid and levopimaric acid,[9] and derivatives of dehydroabietic acid.[3, 10] Partial ozonolysis of one of the two double bonds has only been achieved in the case of neoabietic acid.[9] Short reaction times (25 min) and reductive work up are the conditions employed for this case.

In our approach it was postulated that certain cations such as Hg^{++}, Ag^{+}, etc. could effectively block one of the two double bonds in a selective manner, while the ozonolysis can take place on the other. This prediction was effectively materialized since the zononlysis of abietic acid methyl ester **1** in the presence of 1-equiv of mercuric acetate afforded, after reductive work up, the ketoalcohol **3** (Scheme).

Besides compounds **3**, **4** and **4a**, a compound was isolated to which was tentatively assigned structure **2**, considering its ^{1}H NMR spectrum (no signal corresponding to an olefinic proton) and the fact that when **2** was treated with zinc–acetic acid gave rise to compound **3**. Compound **2** was the major component of the ozonolysis mixture (50% yield) when short reduction times (up to four hours) were employed to destroy the intermediate ozonide. This product decomposed slowly on standing at room temperature and in the presence of air. In addition, it was difficult to isolate it in pure form since its chromatographic behaviour (column chromatography) was very similar to that of compound **4a**. Consequently, it was considered inconvenient to operate with compound **2**. Prolonged reduction with zinc–acetic acid reduced the amount of **2** in the ozonolysis mixture to negligible levels. The mixture of **3**, **4** and **4a** could be separated chromatographically. Compounds **4** and **4a** were identified by their spectral characteristics.

The ^{1}H NMR spectrum of **3** showed a broad singlet at δ 5.70 assigned to H-7 and a quartet with further coupling at δ 3.70 and 4.14 assigned to H-14 protons. The ^{13}C NMR spectrum of **3** showed its hemiketal nature since a carbon shift only assignable to a carbonyl group (178.6 ppm, C-18), and a hemiketal carbon signal at 103.8 ppm, assigned to C-13 were observed, also that while most of the remaining carbon atoms gave a single signal, some (C-11, C-14 and probably C-16 and C-17) gave duplicated signals, a result which was taken as an indication that compound **3** was actually formed by a mixture of the two epimeric ketals. The acetylation of **3**, under the usual conditions, gave the acetyl derivative **5**. The ^{1}H and ^{13}C NMR of compound 5 was fully consistent with the assigned structure (see Experimental and Table

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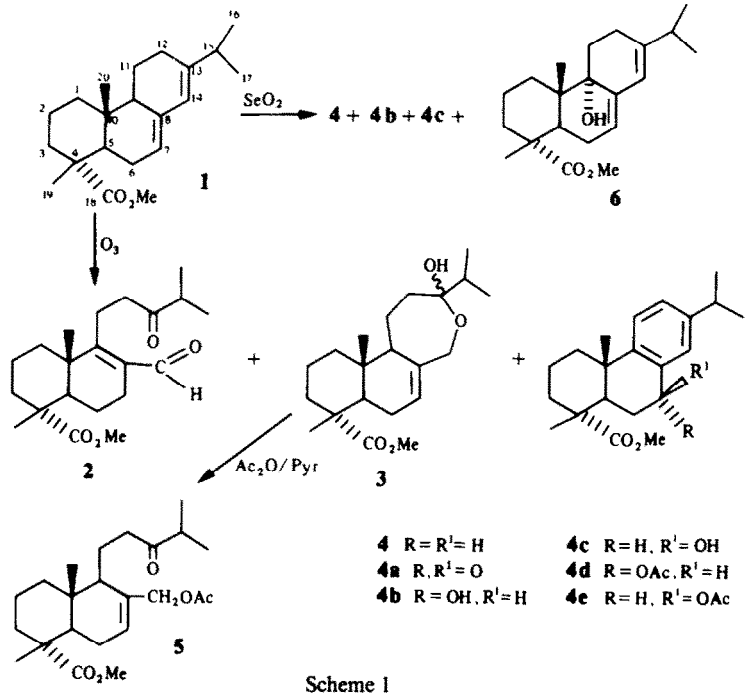

Scheme 1

1). An analog of synthon **5** has recently been transformed[8] into (–)-warburganal.

Epoxidation of compound **1**. Despite previous reports on the preparation of mono- and diepoxide derivatives of 1-abietic acid[7] we have been unable to prepare epoxide derivatives of **1**. The reaction of methyl abietate **1** with m-chloroperbenzoic acid in ethyl ether or chloroform solutions at low temperature (0–5°) afforded starting material only. Attempts to force the conditions, conducting the reaction in chloroform solution at reflux temperature during three hours gave mixtures of compounds **4** and **4a** as the only isolable products. Equally unsuccessful attempts were made using mixtures of hydrogen peroxide–acetic acid.

Oxidation with selenium dioxide of compound **1**. It was expected that the introduction of an allylic hydroxyl group in **1** would modify the reactivity of one of the double bonds of this molecule.[11, 4] According with the accepted mechanism,[12] one could predict that C-6, C-9, C-12 and C-15 could be possible oxidation sites. In fact, the isolated products showed (see Experimental) that the oxidation took place almost exclusively on C-9 and from the α-side of the molecule. The formation of the aromatic compounds **4b** and **4c** was interpreted as the result of an allylic rearrangement of the original alcohol **6** with concomitant aromatization of ring C. The assignment of configuration at C-7 for both epimers was based on considerations of the ^{1}H NMR data obtained with their acetylated derivatives. In the case of compound **4e**, the signal due to H-7 is clearly deshielded. **4c** is identical to the major porduct of the $NaBH_4$ reduction of compound **4a**.

Table 1. ^{13}C NMR data of compounds **4c**, **5** and **6** (ppm, $CDCl_3$, TMS as internal standard)[8]

C atom	4c	5	6	C atom	4c	5	6
1	37.9	37.9	30.2	11	124.0	19.9	26.6
2	18.4	18.0	18.0	12	125.0	40.9	23.2
3	36.4	36.8	36.7	13	146.1	213.8	144.3
4	47.3	46.4	46.4	14	125.7	67.4	120.4
5	43.4	44.4	37.4	15	33.6	40.6	34.7
6	32.8	25.3	25.8	16	24.0*	18.0*	21.4*
7	70.6	129.0	124.0	17	23.8*	17.8*	20.9*
8	137.3	133.5	136.2	18	178.4	178.6	178.8
9	146.3	51.6	72.8	19	16.4	16.7	17.2
10	37.5	36.3	39.6	20	25.4	13.6	16.6

*Interchangeable

The ^{1}H NMR spectrum of **6** showed signals at δ 5.75 (slightly broaden siglet) and 5.45 (triplet) assigned to H-14 and H-7 respectively. ^{13}C NMR data for this compounds (see Table 1) showed that the hydroxyl group was located on C-9. The α-configuration assigned to this substituent is in accord with mechanistic considerations and it is also sustained by the observation of the upfield shift shown by the signals due to C-1, C-5, and C-12 of compound **6** when they are compared with the published values,[13] for compound **1**.

Unfortunately, various attempts to epoxidize compound **6** with m-chloroperbenzoic acid led only to the isolation of products with an aromatic ring C. Table 1 collects the ^{13}C NMR data obtained for compounds **4c**, **5** and **6**. The assignments indicated for these compounds have been made taking into consideration the data published[13, 14] for compounds **1** and **4**.

EXPERIMENTAL

^{1}H NMR spectra and ^{13}C NMR spectra were measured at 90 and 22.5 MHz respectively in $CDCl_3$ solution with TMS as internal standard, unless otherwise stated. Assignments of ^{13}C NMR shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra.

General procedure for the ozonolysis of methyl abietate

A stream of ozone from a commercial ozonizer (1.5 l./min) was passed through a solution of methyl abietate (300 mg) in dry methanol (100 ml), which had been cooled to $-78°$, following the addition of mercuric acetate (300 mg) and acetaldehyde (1 ml). Dry N_2 was passed through the solution after 30 min, which was then poured on zinc dust (5g) and acetic acid (50 ml), and refluxed with stirring during 24 hr. Once cooled, the solids were filtered and most of the methanol distilled off under vacuum. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with aqueous $NaHCO_3$ until neutral, dried and evaporated to leave a syrupy residue which after chromatography on silica gel (20 g) using hexane:ethyl acetate 9:1 yielded **3** (150 mg), **4** (30 mg) and **4a** (30 mg). More polar compounds of unidentified nature were eluted from the column with ethyl acetate, and accounted for the remaining material. When shorter reduction times were used (4–8 hr) variable amounts of a substance, tentatively identified as ketoaldehyde **2**, were isolated.

Methyl dehydroabietate **4** and 7-keto-dehydroabietic acid methyl ester **4a** were identified by their spectral data, and comparison with authentic samples. The substance tentatively identified as the ketoaldehyde **2** (^{1}H NMR, δ :8.95, s, H-14; four methyl signals at 1.15, 1.10, 1.05 and 0.85; OMe group at 3.65) was partially transformed into the ketoalcohol **3**, by treatment with zinc dust and acetic acid.

The ketoalcohol **3** was isolated as a syrupy oil (150 mg), ^{1}H NMR (100 MHz) δ:5.70 (1H, $sW_{1/2}$, 8 Hz, H-7), 3.90 and 4.14 (2H, ABq, J 12 Hz with further allylic coupling J'1.5 Hz), four methyl signals at 1.23, 1.14, 1.06 and 0.80 (H-16, H-17, H-19 and H-20). ^{13}C NMR, ppm: 38.2 (C-1), 18.2 (C-2), 37.0 (C-3), 46.6 (C-4) 44.6 (C-5), 25.3 (C-6), 125.9 (C-7), 138.9 (C-8), 51.2 (C-9), 36.3 (C-10), 22.3 and 20.1 (C-11), 41.2 (C-12), 103.8 (C-13), 66.1 and 64.6 (C-14), 41.0 (C-15), 18.2 and 20.1 (C-16 and C-17), 178.6 (C-18), 16.8 (C-19) and 13.8 (C-20). The signals assigned to C-11, C-14, C-16 and C-17 are only tentative since the spectrum apparently showed duplicated signals for these carbon atoms.

Compound **3** was acetylated with Ac_2O/py at room temp. Evaporation of the solvents, under reduced pressure, provided a crude mixture, which after chromatography on silica gel (10 g) with hexane:ethyl acetate (9:1), yielded compound 5(110 mg), syrupy oil, ^{1}H NMR (270 MHz) δ: 5.80 (1H, m, H-7), 4.50 (2H, s, H-14), 2.55 (1H, m, H-15), 1.23 (3H, s, H-19), 1.09 and 1.08 (6H, d, d, J 7 Hz, H-16 and H-17), 0.81 (3H, s, H-20). 13C NMR, see Table 1.

Selenium dioxide oxidation of methyl abietate. Method A

Methyl abietate (**1**, 240 mg) was dissolved in t-butanol (4 ml) and SeO_2 (50 mg) was added to this solution. After 24 hr at room temperature with stirring, the reaction was worked up and the crude product was chromatographed on silica gel (10g) with hexane:ethyl acetate (9:1). Elution of this column afforded the following compounds: **4** (75 mg), a mixture of the two epimers of the methyl ester of 7-hydroxy-dehydroabietic acid (**4b** and **4c**), in approximate ratio 8:2 (45 mg), and the methyl ester of 9-α-hydroxy-abietic acid **6** (45 mg). The mixture of **4b** and **4c** was a thick oil, ^{1}H NMR, δ:7.10 (3H, complex signal, aromatic protons), 4.9 (0.2H, m, H-7α), 4.75 (0.8H, m, H-7β), five methyl signals at 1.25, 1.22, 1.20, 1.17 and 1.15, integrating for 12H. The major component was isolated through the preparation of their acetyl derivatives and further chromatography on silica gel (5g) with hexane:ethyl acetate (9:1). Compound 4d was an oil, ^{1}H NMR, δ:7.10 (3H, complex signal, aromatic protons), 5.20 (1H, m, H-7), three methyl signals at 1.30, 1.25 and 1.22, integrating for 12H. O–CO–CH_3 signal at 2.40 (3H, s).

Compound **6** was a thick oil, ^{1}H NMR, δ:5.75 (1H, s $W_{\frac{1}{2}}$ 4 Hz, H-14), 5.45 (1H, t, J 5 Hz, H-7), four methyl signals at 1.30, 1.06, 1.00 and 0.90, integrating for 12H, ^{13}C NMR, see Table 1.

Method B. Methyl abietate (250 mg) was dissolved in aceto-nitrile (5 ml), adding SeO_2 (50 mg) to the solution. Stirring during 24 hr and the usual work up afforded a crude product. Chromatography on silica gel (10 g) with hexane:ethyl acetate (9:1) allowed separation of a mixture of the two epimeric products **4b** and **4c** (6:4) (200 mg), judging from TLC and ^{1}H NMR of the mixture. Careful column chromatography of this mixture (hexane:ether 8:2, several developments) allowed separation of a pure sample of **4c**. The material was identical (TLC, various systems) to the major product of the $NaBH_4$ reduction of **4a**.

Acetylation, under the usual conditions, of **4b** and **4c**, and chromatography on silica gel (10 g) with hexane:ethyl ether = 7:3 of the resulting crude product yielded a pure sample of the 7β-acetoxyepimer (4e, 75 mg) as an oil, ^{1}H NMR, δ:7.10 (3H, complex signal, aromatic protons), 5.90 (1H, m, H-7), two methyl signals at 1.28 and 1.20, integrating for 12H, $OCOCH_3$ methyl signal at 2.00. Only minor amounts of 4 and 6 were isolated in this case. The 7α-acetoxy-epimer **4d** was not isolated in pure form, using this procedure.

Attempted epoxidation of methyl abietate. To methyl abietate (75 mg) in chlororoform solution (10 ml), and excess of m-chloro-perbenzoic acid (60 mg) was added at 0° for 24 hr. Control by TLC indicated no reaction had taken place. The usual work up allowed separation of the starting material, proved by ^{1}H NMR. At reflux and chromatographic separation on silica gel with hexane:ethyl acetate, the following substances were isolated: **4** (slightly contaminated by **1**) (32 mg), **4a** (25 mg), other unidentified more polar compounds (5 mg).

Using H_2O_2:AcOH as epoxidating agent and ethyl ether as the solvent no reaction was observed at 0–5° or room temperature. With H_2O_2:AcOH and acetic acid as solvent, a complex reaction took place, but no products were isolated.

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