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Stereochemistry and oxidative degradation of a dimeric thymol derivative from *Arnica sachalinensis*

Claus M. Passreiter,[a,*] Horst Weber,[b] Dieter Bläser[c] and Roland Boese[c]

[a]*Institut für Pharmazeutische Biologie Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, Geb. 26.23, D-40225 Düsseldorf, Germany*

[b]*Institut für Pharmazeutische Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany*

[c]*Institut für Anorganische Chemie, Universität Essen, Universitätsstrasse 3-5, D-45117 Essen, Germany*

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Abstract—Recently we described a dimeric thymol derivative **1** with a novel spiro[benzofuran-3(2*H*),2′-pyrano[2,3-*b*]benzofuran] ring system isolated from *Arnica sachalinensis* (Asteraceae), but the stereochemistry of this compound remained unclear. Attempts to simplify the structure by oxidation of the hemiacetal to the lactone only resulted in the formation of degradation products. Therefore we produced suitable crystals to perform X-ray analysis, which finally showed that **1** consisted of a mixture of two enantiomers with the following configuration: 8*R*,8′*S*,9*S*,9′*S* and 8*S*,8′*R*,9*R*,9′*R*.

1. Introduction

Recently, we reported the structure elucidation of a dimeric thymol derivative **1** from *Arnica sachalinensis* (Asteraceae) containing a new spiro[benzofuran-3(2*H*),2′-pyrano[2,3-*b*]-benzofuran] ring system.[1] Unfortunately, there was no evidence for the stereochemistry of **1** from its NMR spectra. *cis*-Annelation of the hydrated pyrano[2,3-*b*]benzofuran was only assumed because there is no example in the literature for a *trans*-configuration, but the stereochemistry at both C-8′ and C-9′ remained completely unclear. The unconventional numbering of **1** used in our previous publication is following the standard used for the related monoterpene thymol and is subsequently also used in this paper.[1]

All possible stereoisomers of **1** were analyzed by molecular modeling using quantum chemical AM1 computations.[1] The calculated energy values for each isomer did not show one favorite isomer and the configuration of **1** still remained unclear. Therefore, we tried to simplify the structure of **1** by oxidation of C-9′ in order to investigate a possible anisotropic influence of the γ-lactone moiety in **4** (Scheme 1) by means of NMR spectroscopy, which would possibly give more information about the correct stereochemistry of the remaining stereogenic centers in **1**. In the meantime we continued our attempts to obtain crystals suitable for X-ray analysis.

2. Results and discussion

Due to the small available amount of **1**, we concentrated on those reagents commonly used for oxidation of hemiacetals to lactones. Most of them (especially the mild ones) failed to give any reaction product. Only if vigorous conditions (alkaline ferricyanide at 20°C or potassium dichromate in dilute sulfuric acid at 70°C) were used the diketone **3** was found as the only reaction product (Scheme 1). Bromine in aqueous sodium carbonate (2%), often used in sugar-chemistry to oxidize cyclic hemiacetals to lactones, only led to a complex mixture of mono- and polybrominated products, as seen from the mass spectra. Dried lead(IV)-oxide in ether/acetone at room temperature reacted slowly with **1** and gave a mixture of three compounds, which were separated by means of CC. Besides the diketone **3** and some starting material we isolated a small amount of a new compound **2**, which on further oxidation with ferricyanide or dichromate led to the stable diketone **3** as described above. Consequently **2** must be a precursor of **3** during oxidation of **1**. Although only a very small amount of **2** was available, the structure of this intermediate could be determined with a high degree of certainty by means of its mass and ^{1}H NMR spectra. The DCI (NH_3) mass spectrum of **2** led to the assumption that one carbon and two hydrogen atoms were eliminated from **1** during oxidation. In the ^{1}H NMR spectrum of **2** both H-9 and H-9′ were missing and only two exchangeable OH-protons were registrated between 5 and 6 ppm. Therefore it is very likely that oxidation of the cyclic hemiacetal to the lactone is accompanied by the oxidative elimination of the α-hydroxy-acetalic carbon (C-9) and that the pyrano[2,3-*b*]benzofuran moiety is subsequently cleaved (Scheme 1). However, the

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* Corresponding author. Tel.: +49-211-8114172; fax: +49-211-8111923; e-mail: passreit@uni-duesseldorf.de

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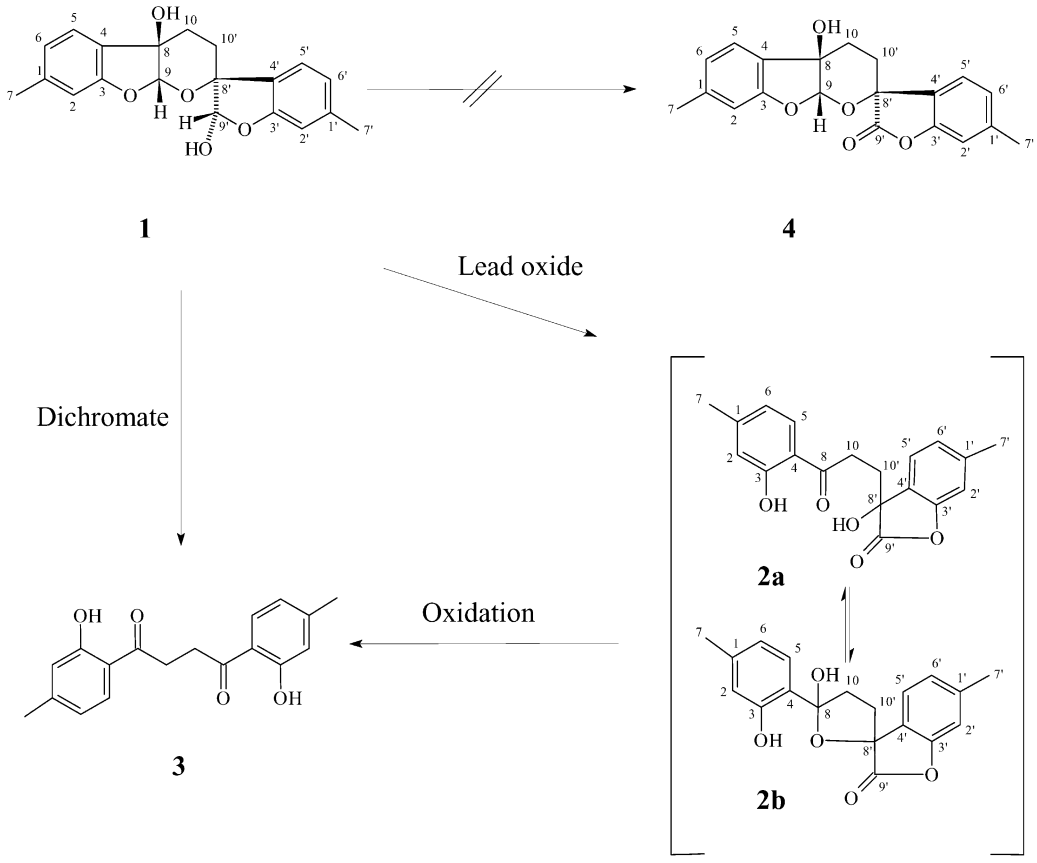

Scheme 1. Oxidation of **1**.

resulting intermediate **2** is not present as hydroxyketone **2a** but as its hemiketal tautomer **2b**, because there was no low-field shift found for an aromatic proton *ortho* to a carbonyl group.

Obviously it is impossible to produce the desired lactone **4** by use of the chosen reagents. Since both oxidation products **2** and **3** did not help to clarify the configuration of the parent compound **1**, we finally succeeded in preparing suitable crystals for X-ray analysis. These were obtained from a solution of microcrystalline **1** in hot acetonitrile, which was allowed to cool over a long period in an isolated vessel.

Thus, definite proof of the stereochemistry of **1** was furnished (Fig. 1): the pyrano[2,3-*b*]benzofuran-ring system was found to be *cis*-annelated as it was assumed. The tetrahydropyrane ring adopts a slightly distorted boat conformation as anticipated from our molecular modeling studies.[1] The configuration at C-8′ and C-9′ was found to be (*S*,*S*) or (*R*,*R*). Fig. 1 shows the *S*,*S*-enantiomer.

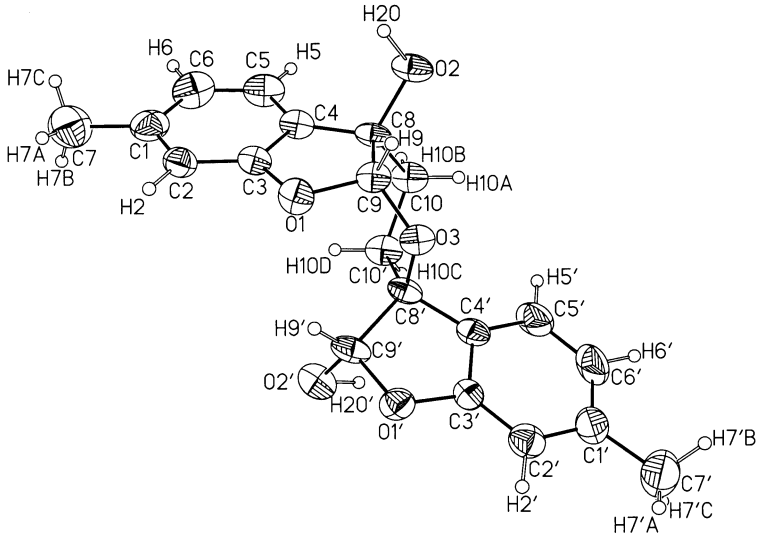

Figure 1. Ellipsoid presentation (50%) of the 8*R*,8′*S*,9*S*,9′*S*-enantiomer of **1**.

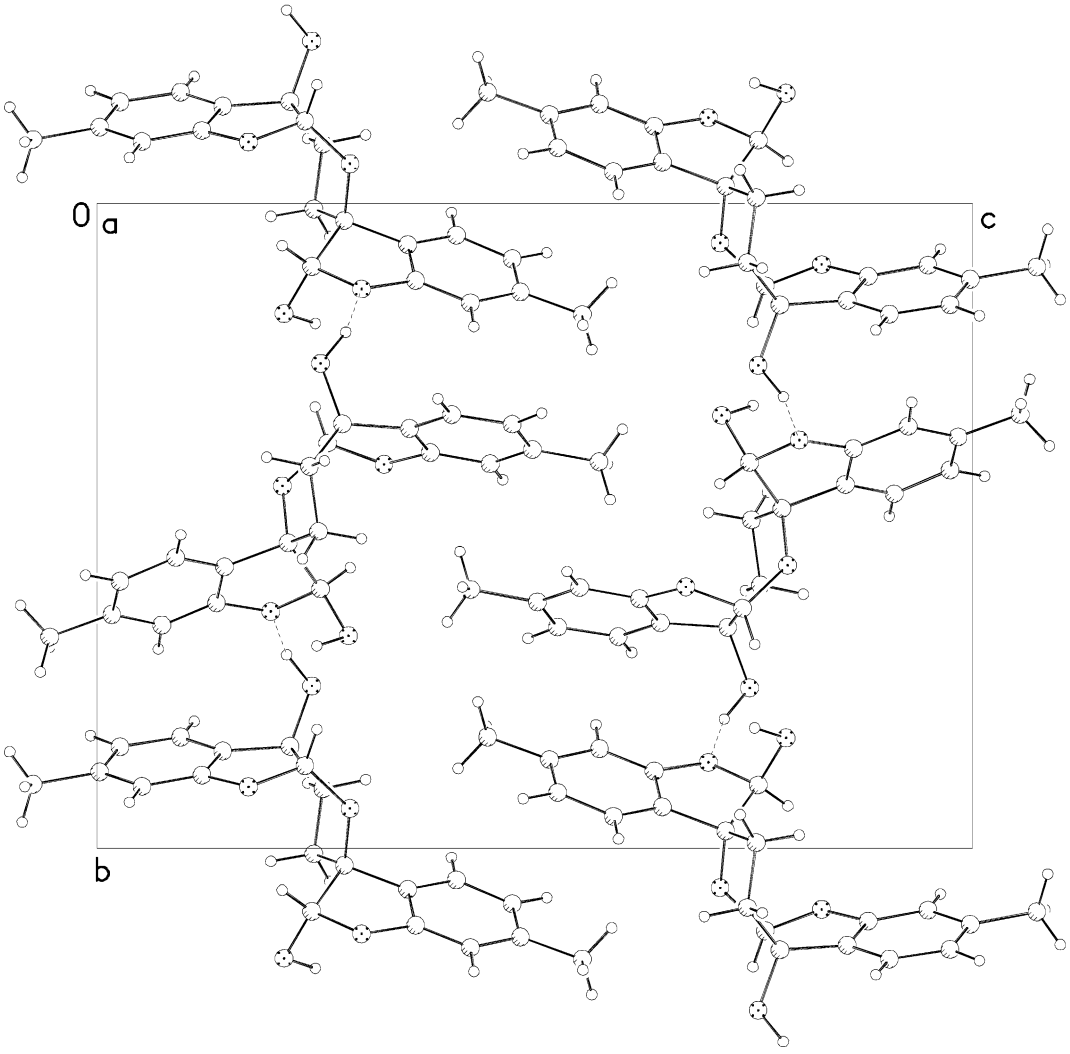

Figure 2. Interactions between 8*R*,8′*S*,9*S*,9′*S*-**1** and 8*S*,8′*R*,9*R*,9′*R*-**1** in the elementary cell.

According to the centrosymmetric space group **1** is a racemic mixture of (8*R*,8′*S*,9*S*,9′*S*)-**1** and its enantiomer (8*S*,8′*R*,9*R*,9′*R*)-**1** (both are shown in Fig. 2). Their hydroxy groups are involved in intermolecular O–H···O hydrogen bonds (numbering according to Fig. 1), on one side to the oxygen of the semiacetalic furan ring [O1′a···H20 1.89 Å, O1′a···H20–O2 159°, O1a···O2 2.83 Å], and on the other side to the hydroxy group of the other enantiomer [O2b···H20′ 1.93 Å, O2b···H20′–O2′ 147°, O2′···O2b 2.80 Å]; (*a* and *b* refer to symmetry operations $-x$, $y-0.5$, $0.5+z$ and $1-x$, $0.5+y$, $0.5+z$, respectively).

The two-dimensional network is also stabilized by C–H···π interactions of the aromatic rings with interplanar angles C1–C6/C1′a–C6′a and C1′–C6′/C1b–C6b 53.8° and C···H distances to the centers of the respective aromatic rings H2′a···cent(C1–C6) 2.72 Å and H5b···cent(C1′–C6′) 3.05 Å.[3,4]

Since crystal conformations often differ from those in solution we recorded a 2D-NOESY spectrum of **1** in acetone-d_6 to get information about the occurrence of possible NOE contacts. Beside of the expected cross peaks (methyl protons (H-7, H-7′) with H-2, H-6 and H-2′, H-6′, respectively) we found significant NOE contacts between H-5 and H-10B and H-5′ and H-10A, respectively. Thus, it could be clearly shown, that the slightly distorted boat conformation,[1] is present in solution as well as in the crystal structure. Moreover, due to the NOE contacts between H-5 and H-10B and H-5′ and H-10A we can now give the orientation of these protons. The high field signal (δ=2.18 ddd; H-10B) represents the equatorial proton at C-10, whereas the lower field multiplet (δ=2.33 m; H-10A) belongs to the axial oriented proton. Finally, with a clear assignment of these protons it was also possible to relate the protons at C-10′ to the corresponding signals. H-10C (δ=2.05 m) is equatorial, H-10D (δ=1.93 ddd) axial oriented (Fig. 1).[1]

3. Experimental

Microcrystalline **1** was isolated from *A. sachalinensis* (Regl.) A. Gray as described earlier.[1] Slow recrystallization from hot acetonitrile gave suitable crystals for X-ray analysis, mp 186°C.

Mass spectrometry. DCI (NH_3) recorded on a INCOS 50 spectrometer (Finnigan MAT, Bremen, Germany).

Nuclear magnetic resonance. Bruker ARX 500, 500 MHz, acetone-d_6.

X-Ray crystallographic analysis. Crystallographic structure determination of **1** at 233 K was performed on a Siemens SMART CCD-diffractometer, Mo Kα radiation, cell dimensions a=6.0563(6), b=14.210(2), c=19.306(2) Å, b=93.445(3)°, V=1658.5(3) Å^3, SG $P2_1/c$, Z=4, ρ=1.363 g cm^{-3}, $2\theta_{max}$=45.2°, 9477 reflections collected, 2184 unique, 1160 observed, $R1$=0.071, $wR2$=0.1423.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CSD 163496. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.1. Oxidation of 1

3.1.1. Potassium dichromate. 3.4 mg (0.01 mmol) of **1** were dissolved in 1 ml acetonitrile. 3 ml of dilute sulfuric acid (0.1%) and 5 ml of an aqueous solution of potassium dichromate (0.1%) were added and the mixture was stirred at 70°C for 1 h. After half of the solvent was evaporated, we obtained 2.4 mg of **3** as colorless needles, which were separated from the solution, washed with water and dried in vacuo.

3: DCI (NH_3): 316 $[M+NH_4]^+$, 299 $[M+H]^+$. ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 2.36 s (6H, 2×CH_3), 3.45 s (4H, 2×CH_2), 6.75 d (br.) (2H, 2×CH aromatic), 6.80 s (br.) (2H, 2×CH aromatic), 7.77 d (2H, 2×CH aromatic), 12.10 s (2H, 2×OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm): 203.53, 162.42, 148.13, 129.70, 120.37, 118.51, 117.05, 31.63, 21.97.

3.1.2. Lead(IV) oxide. 3.4 mg (0.01 mmol) of **1** were dissolved in 20 ml of a mixture of ether/acetone. 100 mg PbO_2, freshly prepared from $Pb(OAc)_4$,[2] was added and stirred at room temperature for 24 h. After filtration and evaporation in vacuo the residue was dissolved in ether and washed with water. The dried organic phase was chromatographed on a silica gel column using a mixture of petroleum ether/ethyl acetate (9:1) as eluent. We obtained three fractions: Fraction 1 contained **3**, whereas fraction 3 contained the rest of the educt **1**. From fraction 2 we isolated **2**, which was obtained in TLC-pure form after crystallization from *n*-hexane.

2: DCI (NH_3): 344 $[M+NH_4]^+$, 327 $[M+H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 2.34 s and 2.28 s (6H, H-7, H-7′), 2.49–2.39 and 2.02–1.94 (4H, H-10, H-10′), 5.82 s and 5.28 s (2×OH), 6.85–6.63 m (4H, H-6, H-6′, H-2, H-2′), 7.21 d (2H, H-5, H-5′).

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