**Terpenoids from Achillea setacea**

Milka Todorova\textsuperscript{a}, Bernhard Vogler\textsuperscript{b} and Elena Tsankova\textsuperscript{a}\textsuperscript{,*}

\textsuperscript{a} Institute of Organic Chemistry with Center of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria. Fax: 003592 700 225.
\textsuperscript{b} Department of Chemistry, University of Hohenheim, 70593 Stuttgart, Germany

\* Author for correspondence and reprint requests

Z. Naturforsch. 55c, 840-842 (2000); received June 6/July 11, 2000

**Achillea setacea**, Guaianolides, Monoterpane Triol

The aerial parts of *Achillea setacea* afforded, in addition of a rare monoterpene triol and 12 known sesquiterpene lactones, a new guaianolide containing an endoperoxide ring. Its structure was elucidated by spectral methods.

**Introduction**

*Achillea setacea* Waldst. & Kit. is described as a white flowering diploid taxon occurring in central and south-east Europe, extending to western Asia (Richardson, 1976). This species belongs to the *Achillea millefolium* group (Richardson, 1976) which has received much attention for its medical properties. Thus, three antitumor sesquiterpenoids have been recently found in *A. millefolium* from Japanese origin (Tozyo et al., 1994). A number of sesquiterpene lactones, mainly of guaianolide type are isolated from different taxa of the *A. millefolium* group and they have been proved to be responsible for the anti-inflammatory activity of the plant infusions (Kastner et al., 1991; Kastner et al., 1993). So far, 11,13-dihydrosesachetalcarin, rupicolin-A and rupicolin-B are the only sesquiterpene lactones found in *A. setacea* (Zitterl-Eglseer et al., 1991). In the course of our study on the Bulgarian *Achillea* species used in the traditional medicine we investigated wild growing *A. setacea* and report now the isolation and identification of a rare monoterpene triol and 13 sesquiterpene lactones, among which the new endoperoxide guaianolide I.

**Experimental**

**Plant material**

The aerial parts of *A. setacea* were collected in flowering stage in July 1998 from the following locations: Vitosha mountain (sample 1), Pirin mountain (sample 2) and Golo bardo (sample 3). Voucher specimens (SOM 154209, SOM 154212 and SOM 154207) were deposited in the Herbarium of the Institute of Botany, Bulgarian Academy of Sciences, Sofia.

**Extraction and isolation**

The air-dried above ground parts of sample 1 (150 g) were extracted with CH\textsubscript{2}Cl\textsubscript{2} (2x500 ml) at room temperature. After evaporation of the solvent in vacuo and working up as described earlier (Todorova et al., 1998) a crude lactone fraction (2.7 g) was obtained. The latter was separated by column chromatography on silica gel (90 g) using solvent mixtures (CHCl\textsubscript{3}-MeOH) with increasing polarity. Selected fractions (IR control) were additionally purified by CC and prep. TLC on silica gel to give: siitennin (5 mg), 1β,10α-epoxy-3β, 9β- diacetoxy-11α,13-dihydrocostunolid (3 mg), rupicolin-A (10 mg) and rupicolin-B (12 mg), 1-desoxy-1α-peroxy-rupicolin-A (4 mg) and 1-desoxy-1α-peroxy-rupicolin-B (3 mg), 3α,4α-epoxyrupicolin-A (4 mg) and 3α,4α-epoxyrupicolin-B (5 mg), rupin A (8 mg), desacytel-1α,4c-dihydroxybisbispolicopeilde (7 mg), desacetyl-1α,4β-dihydroxybispolicopeilde (4 mg), 11,13-dihydrodesacetylcarinarin (5 mg), arteludovincinolide A (5 mg), 15S,2R,4S, trihydroxy-p-methanin (4 mg) and 8α-hydroxy-tanaparthin-α-peroxide (5 mg).

Crude lactone fractions (200 mg and 550 mg) were obtained from samples 2 (23 g) and 3 (600 g), respectively, using the procedure described above. TLC analyses were performed on TLC aluminum sheets, Silicagel 60, F254, Merck using CHCl\textsubscript{3}-MeOH (15:1 v/v) as a solvent system.

**8α-Hydroxy-tanaparthin-α-peroxide (1)**

Gum, CIMS (NH\textsubscript{3}) m/z (rel. int.): 312 [M+NH\textsubscript{4}]\textsuperscript{+} (100), 294 [M]\textsuperscript{+} (8). EIMS (70 eV) m/z (rel.int.): 294 [M]\textsuperscript{+} (0.5), 276 [M-H\textsubscript{2}O]\textsuperscript{+} (0.5), 262

---

This work has been digitalized and published in 2013 by Verlag Zeitschrift für Naturforschung in cooperation with the Max Planck Society for the Advancement of Science under a Creative Commons Attribution-NoDerivs 3.0 Germany License. On 01.01.2015 it is planned to change the License Conditions (the removal of the Creative Commons License condition "no derivative works"). This is to allow reuse in the area of future scientific usage.
IS, 2R, 4S-Trihydroxy-p-mentane (3)

Amorphous powder. EI-MS (70 eV) m/z (rel. int.): 170 [M-H$_2$O]$^+$ (20), 152 [170-H$_2$O]$^+$ (29), 134 [152-H$_2$O]$^+$ (18). $^1$H and $^{13}$C NMR: in Table I.

Results and Discussion

Air-dried plant material (sample 1, see Experimental) was extracted with dichloromethane and the crude extract was subjected to column chromatography separation to give the lactone containing fractions (IR control). Further rechromatography and purification afforded 14 individual compounds. By analogy of their spectral data to those reported, twelve were assigned as the following sesquiterpene lactones: sintenin (Goren et al., 1988), 1ß,10a-epoxy-3ß,9ß-diacetoxy-lla,13-di­hydro-costunolide (Milosavljevic et al., 1991), rupicolin-A and rupicolin-B (Irwin and Geissman, 1973), 1-desoxy-1a-peroxy-rupicolin-A and 1-desoxy-1a-peroxy-rupicolin-B (Bohlmann et al., 1980), 3a,4a-epoxyrupicolin-A and 3a,4a-epoxyrupicolin-B (Todorova et al., 1998), rupin A (Irwin and Geissman, 1973), desacytetyl-1a,4a-dihydroxy­bishospicepolide (Jakupovic et al., 1988), desacytetyl-1a,4ß-dihydroxy bishop-solicepolide (Milosavljevic et al., 1994), 11,13-dehydrodesacet­ylmatricarin (Ohno et al., 1980; Ognyanov and Todorova, 1983) and arteludovicinolide A (Bohl­mann and Zdero, 1982).

Compound 1 was isolated as colourless gum. The mass spectrum (EI) displayed a molecular ion peak at m/z 294 with very low intensity which corresponded to a molecular formula C$_{15}$H$_{18}$O$_6$. The other informative fragments were m/z 262 [M-O$_2$$^+$], 244 [262-H$_2$O]$^+$ and 226 [244-H$_2$O]$^+$.

The ‘H NMR spectrum (see Experimental) gave the clue to the structure of this compound, as it was very similar to that of tanaparthin-α-peroxide 2 (Bohlmann and Zdero, 1982), the stereochem­istry of which was determined unambiguously (Ja­kupovic et al., 1986). The observed chemical shifts of the signals for H-2, H-3, H-5 and H-6 (δ 6.24, 6.33, 2.73 and 3.70, respectively) are consistent with the α-orientation of the endoperoxide ring and the OH group at C-10. However, the presence of an additional OH group in 1 was required by both the MS and ‘H NMR data. The location of this OH group at C-8 and its α-orientation followed from the multiplicity of the H-8 signal (dddd) and the magnitude of the coupling constant J$_{8,7}$ = 8.3 Hz, as well as the downfield shift of the H-13’ signal to δ 5.99. Thus, the relative stereo­chemistry of the chiral centers in 1 was the same as that in 2. Therefore, compound 1 was identified as 8α-hydroxy-tanaparthin-α-peroxide.

Besides the sesquiterpene lactones described above, the polyoxygenated monoterpenes 3 was

Table I. NMR data of (3) in CDCl$_3$ (500/125.3 MHz).

<table>
<thead>
<tr>
<th>Position</th>
<th>H</th>
<th>C</th>
<th>HMQC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>71.62 s</td>
<td>H-5, H-6, H-10, H-2</td>
</tr>
<tr>
<td>2</td>
<td>3.5 brs</td>
<td>74.84 d</td>
<td>H-6, H-3’, H-10</td>
</tr>
<tr>
<td>3</td>
<td>2.01 ddd (14.5, 3.3)</td>
<td>33.77 t</td>
<td>H-7</td>
</tr>
<tr>
<td>3’</td>
<td>1.79 ddd (14.5, 3.0, 3.0)</td>
<td>75.31 s</td>
<td>H-5’, H-3’, H-7, H-8, H-9</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>29.58 t</td>
<td>H-7</td>
</tr>
<tr>
<td>5</td>
<td>2.07 ddd (13.8, 13.8, 4.0)</td>
<td>29.16 t</td>
<td>H-5, H-10</td>
</tr>
<tr>
<td>5’</td>
<td>1.87 ddd (13.8, 13.8, 3.0)</td>
<td>29.16 t</td>
<td>H-5, H-10</td>
</tr>
<tr>
<td>6</td>
<td>1.35 – 1.50 m</td>
<td>29.16 t</td>
<td>H-5, H-10</td>
</tr>
<tr>
<td>7</td>
<td>1.65 qui (6.8)</td>
<td>38.46 d</td>
<td>H-8, H-9</td>
</tr>
<tr>
<td>8</td>
<td>0.93 d (6.8)</td>
<td>16.62 q</td>
<td>H-7</td>
</tr>
<tr>
<td>9</td>
<td>0.93 d (6.8)</td>
<td>16.64 q</td>
<td>H-7</td>
</tr>
<tr>
<td>10</td>
<td>1.35 s</td>
<td>27.69 q</td>
<td>H-6</td>
</tr>
</tbody>
</table>
842 Notes

1  R=OH  3
2 R=H
Fig. 1. 1: 8α-hydroxy-tanaparthin-α-peroxide;
2: Tanaparthin-α-peroxide;
3: 1S, 2R, 4S-trihydroxy-α-p-methane.

also isolated as an amorphous powder. Its structure and relative stereochemistry was elucidated by MS and NMR data (1H-, 13C-NMR, COSY and NOESY). To the best of our knowledge, the monoterpene triol 1S,2R,4S-trihydroxy-α-p-methane

was isolated for the first time from an Indian plant belonging to the Rutaceae family (Thappa et al., 1976). As only selected NMR data are reported in this early publication, we present in Table I the thorough NMR properties of the rare monoterpene triol 3.

Finally, comparative analyses by TLC were performed on the crude lactone fractions obtained from the aerial parts of A. setacea collected from two other localities (samples 2 and 3, see Experimental) using the isolated terpenoids from sample 1 as references. The results revealed no differences in the composition of the investigated samples regarding the sesquiterpene lactones, thus demonstrating the homogeneity of the studied species.

Acknowledgements

The authors are grateful for the financial support of Project X-911 provided by the Bulgarian National Research Foundation.


