RELATIVE CONFIGURATION OF GLECHOMAFURAN ISOLATED FROM THE FRUITS OF *SMYRNIUM OLUSATRUM*

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ABSTRACT.—A furanogermacrane, 1β,10α,4α,5β-diepoxy-7,8-furanogermacrane (glechomafuran, **1**), was isolated from the fruit of *Smyrnium olusatrum* L. The relative configuration of this known compound of previously undetermined stereochemistry was established by X-ray diffraction studies. In addition, the ^{1}H-nmr assignments were revised, and the ^{13}C-nmr spectral data were obtained.

As part of our continuing phytochemical investigation of the genus *Smyrnium* L. (Umbelliferae) (1-7), we report here the isolation, new spectral data, and relative configuration of glechomafuran, a furanogermacrane of previously undetermined stereochemistry found in the roots of *S. olusatrum* (8) and the leaves of *Glechoma hederaceae* (Labiatae) (9). This compound, 1β,10α,4α,5β-diepoxy-7,8-furanogermacrane (**1**), was obtained here in large quantity from the fruit of this same *Smyrnium* species. Stahl and Datta (9) in 1972 first published the structural elucidation of glechomafuran without stereochemical assignments of the two epoxy functions. The mass spectrum of the same compound, under the name alexandrofuran, had been reported earlier without structural proof or reference to its botanical source (10).

Previous studies of the terpenoid constituents of the roots of *S. olusatrum* have yielded, in addition to compound **1**, the 1,10,4,5-diene analogue of **1**, a secofuranogermacrane, a furanoeremophilane, and several eremophilanolides (2,8). The roots of another *Smyrnium* species, *S. connatum*, provided only eremophilanolides (6). The facile auto-oxidation of furanoeremophilanes to their corresponding lactones (eremophilanolides) is well known (11,12). Similarly, we observed the conversion of **1** in solution (but not when crystallized) to several lactonic derivatives in accord with earlier observations that **1** yielded at least one sesquiterpene lactone (9). The oxidative transformation of **1** will be the subject of a future report.

The ms, ir, and ^{1}H-nmr spectra of the diepoxide **1** were identical to those reported in the literature for glechomafuran (9) as well as to the ms of alexandrofuran (10). The conformational flexibility of the ten-membered ring system has not allowed assignment of the stereochemistry of the two epoxy groups by spin-spin coupling constants. Therefore, the relative configurations of the four chiral centers were established by X-ray diffraction studies of **1**.

The correct relative configuration of **1** is shown in figure 1, a stereoscopic view that also includes the atom labeling scheme. It should be noted that, in the conventional two-dimensional representation of **1** (figure 2), the configurations at C-10 and C-5 are not reversed as these angles are actually re-entrant (see reference 13 for a discussion of the problem of two-dimensional representation of germacrane derivatives). Because there is no atom in the molecule that has a large anomalous scattering component for Mo radiation, the absolute configuration could not be established, and it may, in fact, be the opposite of that shown (1-R, 4-R, 5-R, 10-R, or 1-S, 4-S, 5-S, 10-S). The averages of the intramolecular bond distances are as follows: C(sp^2)-O 1.378(5), C(sp^3-O)

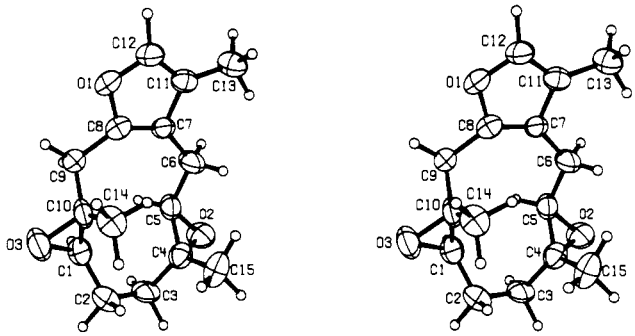

FIGURE 1. Stereoscopic representation of glechomafuran (**1**).

1.454(5), $C(sp^2)=C(sp^2)$ 1.327(6), $C(sp^2)$-$C(sp^2)$ 1.461(6), $C(sp^2)$-$C(sp^3)$ 1,502(6), $C(sp^3)$-$C(sp^3)$ 1.511(6), epoxide C-C 1.470(6)Å. These values are in good agreement with those found in the germacranolide melampodin, which contains a 2,3-epoxide (14). A complete structural description of the molecule, including atomic coordinates, structure factors, and a detailed analysis of the molecular geometry, will be published separately.

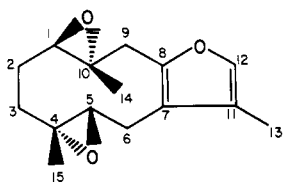

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FIGURE 2. Two-dimensional representation of **1**.

With the relative configuration of **1** established, spin decoupling experiments and inspection of Dreiding models permitted assignment of the ^{1}H-nmr signals (see Experimental section). Our assignments differ from those originally reported by Stahl and Datta (9). The homoallylic coupling characteristically observed in other furanosesquiterpenes (15) was found in **1** between H-9α and H-6β. Interestingly, in furanoeremophilanes, this long-range coupling occurs between H-9β and H-6α. This coupling in glechomafuran indicates that a near-90° angle is formed between the plane of the furan system and each of the two coupled protons, H-9α and H-6β. The spin-spin coupling to H-1 allowed the assignment of the H-2α and H-2β signals, although these two multiplets could not be fully resolved; indeed, in this molecule the only protons that could not be clearly distinguished were H-3α and H-3β.

The ^{13}C-nmr signal assignments given in the Experimental section were confirmed by single-frequency off-resonance decoupling (sford) experiments when possible. Therefore, even in this highly symmetrical molecule, all resonances could be unambiguously assigned, except for the two pairs C-4, C-10 and C-14, C-15.

EXPERIMENTAL

Air-dried fruits of *Smyrnium olusatrum* L. (1.4 kg), collected in the European section of Turkey near Istanbul (voucher No. ISTE 14970, deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul), were extracted; in a Soxhlet with petroleum (35-70°). The extract was evaporated to a small volume and allowed to stand overnight under refrigeration. Compound **1** precipitated from this concentrate as white crytals (5 g), which were filtered from the greenish, oily mother liquor. Recrystallization from petroleum yielded sharp melting crystals (mp, 115°: Lit. [9], 110°) ms identical to Lit. (10); ir (KBr) was identical for purposes of comparison with the spectrum reported by Stahl and Datta (9). ^{1}H-nmr (200 MHz,

$CDCl_3$, TMS): δ 7.08, br s, H-12; 3.41, d (J=17 Hz), H-9β; 3.20, dd (10, 2.5) H-5; 3.03, br d (18), H-6α; 2.86, dd (10.5, 2) H-1; 2.57 br d (17), H-9α; 2.36, ddd (18, 10, 1.5), H-6β; 2.31, m, H-3; 2.14, m ($J_{1,2\alpha}$=2), H-2α; 1.93, (3H), d (1.5), H-13; 1.49, m ($J_{1,2\beta}$=10.5), H-2β; 1.38, m, H-3′; 1.29, (3H), s, H-14[a]; 1.18, (3H),, s, H-15[a]. ^{13}C-nmr (22.6 MHz, $CDCl_3$, TMS): δ 146.5, s, C-8; 136.8, d, C-12; 121.9, s, C-7; 116, s, C-11; 68.1, d, C-1[b]; 61.5, d, C-5[b]; 61.1, s, C-4[c]; 59.7, s, C-10[c]; 38.2, t, C-9[b]; 36.5, t, C-6[b]; 24.6, t, C-3[b]; 23.9, t, C-2[b]; 17.3, q, C-14[d]; 16.3, q, C-15[d]; 8.6, q, C-13.

All X-ray measurements were made with an Enraf-Nonius CAD-4 automatic diffractometer using Mo Kα radiation. The space group is P2, with four molecules in a unit cell of dimensions: a=6.785(4), b=12.325(9), c=16.390(6)Å, and β=97.89(4)°. A total of 2789 independent reflections were collected, of which 1354 having I>3σ (I) were used in the least squares refinement of the 363 variables associated with the two crystallographically unique molecules in the asymmetric unit. The structure was solved by use of MULTAN (16) and refined to a final agreement factor of R=0.040. The hydrogens were fixed at ideal positions. There were no unusually high correlations between any of the refined variables.

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[a]Assignments may be interchanged.
[b]Assignments confirmed by SFORD experiments.
[c,d]Assignments may be interchanged.